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SYNTHETIC AND NATURAL PHENOLS

J.H.P. TYMAN

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52 **Synthetic and Natural Phenols** by J.H.P. Tyman

To: Experimenters in the chemistry of phenolic compounds who have gone before, those of today and others whose work has escaped mention.

PREFACE

The chemistry of phenols tends to be ignored in chapters in organic chemical textbooks and to be lost amongst the many classes of functional derivatives. This book is not intended however to provide such a text book approach but to give an account of developments in phenol chemistry in the last two and more decades. It assumes some familiarity with the chemistry of the phenolic ring.

In this sense it may well appeal more to postgraduates students in academic and industrial work. By no means all phenolic systems have been covered in detail, as for example phenolic propanoids, although most have been referred to at some stage amongst the fourteen chapters. The emphasis thoughout has been on synthesis, on what can be achieved by the use of phenolic intermediates and in the construction of phenolic end products.

The intention in many chapters has been to enable the reader to refer to the original literature wherever possible. Mechanistic aspects have not been depicted except in the first chapter. It is thought and hoped that many of the chapters provide a fund of tutorial material and problems for undergraduate studies and further, that these will encourage perusal of the literature. Relevant to this there are almost 2,000 references to applied and academic papers.

Phenols are ubiquitous substances and now it is more widely accepted that there are pros and cons concerned in their usage. The pros for compounds are well-known and are illustrated by perennial panaceas such as aspirin, paracetamol, codeine and many others. The cons are less obvious because they are also materials deeply involved in our standard of living and in most cases hazards involved have only recently come to light.

This authorship was commenced privately several years ago and progressed through different processing systems and equipment with improved printing facility. The author is glad to acknowledge advice on systems and procedures from Mr G Marshall of European Colour plc, from Dr E L Short and Mr N Taylor of Brunel University, help from Mr P Edaline, systems consultant and on approaches to graphics from Dr M Sharp. Some early assistance on tabular material and later on contents pages was very kindly rendered by Mrs M Westcot. I am indebted to the patience of my wife in tolerating the triangle involved in my associating with pc systems involved in the preparation of this book.

Thanks are due to Wiley-Interscience for the use of material in three Tables in Chapter 1 adapted from Kirk Othmer Encyclopedia of Chemical Technology, Addison Wesley Longman for the use of part of Fig. 9.7 from 'The Chemical Economy', the German Chemical Society for a picture of F F Runge, the Royal Society of Chemistry for a picture of A. Laurent, and Figs. 13.1 and 13.3, Dr J G Ohler for Table 13.4, the Society of Chemical Industry and HMSO for the use of Fig. 13.2, and Elsevier Science for material adapted in Tables 13.6, 13.7, 3.8, and 13.9.

CONTENTS

CHAPTER 1
HISTORICAL ASPECTS AND INDUSTRIAL SYNTHESES OF MONOHYDRIC AND DIHYDRIC PHENOLS

CHAPTER 2
RECENT ADVANCES IN THE SYNTHESIS OF MONOHYDRIC PHENOLS

CHAPTER 3
REACTIONS OF THE HYDROXYL GROUP IN MONOHYDRIC PHENOLS

CHAPTER 4
PHENOLIC ETHERS OF HYDROXY AROMATICS

CHAPTER 8
HALOGENO, NITRO, AMINO, AZO, SULPHO AND THIO DERIVATIVES OF PHENOLS

CHAPTER 9
DIHYDRIC PHENOLS

CHAPTER 10
POLYHYDRIC PHENOLS

CHAPTER 13
NON-ISOPRENOID ALKYLPHENOLS

CHAPTER 14
SYNTHESIS OF NATURAL PHENOLS (AND THEIR DERIVATIVES) OF PHARMACEUTICAL, MEDICINAL OR TECHNICAL INTEREST

ABBREVIATIONS

AIBN	2,2'-Azobisisobutyronitrile
Acac	Acetylacetonate
Aq	Aqueous
Atm	Atmosphere
Bn	Benzyl
BTAC	Behenyltrimethylammonium chloride
Bz	Benzoyl
CAN	Ceric ammonium nitrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAEC	2-Diethylaminoethylcellulose
DHP	Dihydropyran
DIBAL	Diisobutylaluminium hydride
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethyl formamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidionone
DMS	Dimethyl sulphide
DMSO	Dimethyl sulphoxide
ee	Enantiomeric excess
GLC	Gas/liquid chromatography
HMPT	Hexamethylphosphoric triamide
h	Hour
hv	Light
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
MCPBA	m-Chloroperbenzoic acid
MEM	Methoxyethoxymethyl
MnTddPP	Tetra 2,6-dichlorophenylporphyrin
mol	Mole
MOM	Methoxymethyl
MS	Mass spectrometry
$Ni(COD)_2$	Bis(cyclooctadienyl)nickel
NBS	N-bromosuccinimide
ODS	Octadecylsilane
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PPA	Polyphosphoric acid
psi	Pounds per square inch
py	Pyridine
Ref	Reference
RT	Room temperature

TBAF	Tetrabutylammonium fluoride
TBS	tert-Butyldimethylsilyl
TDI	Tolylene-2,5-diisocyanate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin layer chromatography
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMOF	Trimethyl orthoformate
TMS	Trimethylsilyl
TMSCI	Trimethylsilyl chloride
TMSI	Trimethylsilyl iodide
TSA	Toluene-4-sulphonic acid
TTN	Thallium trinitrate
Δ	Heat

CHAPTER 1

HISTORICAL ASPECTS AND INDUSTRIAL SYNTHESES OF MONOHYDRIC AND DIHYDRIC PHENOLS

1. Monohydric Phenols

1.1 Introduction

Although phenol and alkylphenols do occur widely in traces in living sources it has been commonly thought they are non-natural substances existent only in fossil fuels such as coal. The essential oil from tobacco leaves (*Nicotiana tabacum*, Solanaceae), from pine needles (*Pinus sylvestris*, Pinaceae) and mammalian urine from many species all contain phenol itself. The discovery of phenol is attributed to Runge in 1834 who isolated several components of coal tar including carbolic acid. Bearing in mind that a tonne of coal produces 0.400K of very impure phenol requiring careful fractionation this experimentation demonstrates considerable expertise. Friedlieb Ferdinand Runge (1795-1896), Fig.1, was a German chemist who was succesively a professor at Breslau (now Wroclaw) University prior to Ladenburg, an instructor at Berlin and director of a chemical factory at Oranienburg. Considered to be the originator of the paper chromatographic technique (ca.1850), he experimented with, apart from his coal tar researches, pyrrole, rosolic acid, (aurin), aniline, and a process for obtaining sugar from sugar beet although he does not seem to have used elemental analysis in studying organic compounds. August Laurent (1808-1853), Fig.2, who was also independently experimenting, around 1841, with phenol and its derivatives showed that the former was identical to Runge's carbolic acid and different from creosote discovered in wood tar by Reichenbach in 1834. Laurent used chemical analysis for the characterisation of compounds. He was a careful and systematic experimenter who, along with his coworker Charles Gerhardt appears to have been ostracised and neglected in his time although his contribution to chemistry was recognised posthumously.

Through researches in aromatic chemistry it was not long before synthetic phenol became available. Prior to work by Griess on aromatic diazo compounds published in 1860, Hunt (ref.1) had in 1849 obtained phenol from a diazonium salt produced by the reaction of aniline hydrochloride and siver nitrite. F.A. Kekule, (1829-1896), Fig.3, in 1867 (ref.2) described the 'recently completed' sulphonation of benzene and fusion of the sulphonic acid with alkali as a new

Fig.1.1 F. F. Runge
(1795-1867)

Fig.1.2 A. Laurent
(1808-1853)

Fig.1.3 F.A. Kekule
(1829-1896)

Fig.1.4 F. Raschig
(1863-1928)

route to phenol. Referring to the potential formation of phenol from the hydrolysis of aryl halides he commented that even by 'melting' of chloro or bromobenzene or their homologues with alkali, 'no conditions have ever been found in which this decomposition takes place'. Hardly surprisingly in the Dow and the Bayer processes some 60 years later, 360°C and 300 atmospheres proved necessary. A pioneer in the first stage of this process namely that of oxychlorination, a key step also in the modern process for vinyl chloride, was the industrial chemist Friedrich, ('Fritz') Raschig, (1863-1928), Fig.1.4, although the full implementation of his process only occurred in the mid thirties. This versatile chemist (ref.3) explored inorganic and organic chemistry alike and his researches resulted in a new process for hydrazine, developments in nitric acid chemistry, and the introduction of Raschig rings for gas absorption and fractionation columns. His technology for phenol has been largely superseded by the development of the cumene process currently the major synthetic route which emerged from academic and industrial origins. Another process deriving from an historical observation (ref.4) of the formation of phenyl benzoate by heating copper(II) benzoate, later in the 20th.century vigorously industrially developed, has also been displaced by the cumene route (refs.5,6) These various methodologies are discussed in greater detail in ensuing sections.
In 1865 just prior to Kekule's synthesis of phenol, Joseph Lister (1827-1912) was experimenting with carbolic acid as an aid to antiseptic surgery which he had pioneered. A mixture of crystallised carbolic acid and shellac (lac plaster) was employed in the finally adopted mode of application. The requirement of phenol for the manufacture of picric acid during the Boer war and other uses resulted in a demand which soon outstripped the resources of phenol/cresols available from coal distillation. Synthetic phenol thus became a potentially important intermediate. The lengthy processing involved in the separation of phenol and the isomeric cresols led to the desirability for specific syntheses. In 1978 of the world production of phenol only 3% came from coal sources by extraction of the mixed phenols (about 1.5% in coal tar) with 10% sodium hydroxide, acidification with carbon dioxide and separation. Phenolic compounds are also formed during catalytic cracking processes in the petroleum industry. There are historically six industrial processes for the production of synthetic phenol, variously from benzene and toluene, some of which are also applicable to the cresols and the dihydric phenols.

1.2 The Benzene Sulphonation Route for the Synthesis of Phenol

This, the oldest industrial method, was used by one company in the USA up to 1978 (ref.7), and in Italy and the former German Democratic Republic in more recent times. Benzene can be monosulphonated with 100% sulphuric acid in 100% excess at 65-100°C although it has been considered more economical to use less acid and remove the water formed azeotropically. The benzenesulphonic acid formed is converted to the sodium salt by neutralisation

with sodium sulphite. Fusion of the isolated anhydrous sodium salt by its introduction under the surface of fused sodium hydroxide at 300°C to 320°C gives sodium phenate which in concentrated aqueous solution with sulphur dioxide and some sulphuric acid yields free phenol. The separated crude product is purifed by steam distilation and the by-product sodium sulphite employed in the manufacture of cellulose. The fusion and extraction stages result in high labour and energy costs. The reaction stages and mechanism for the two stages appear to be as shown.

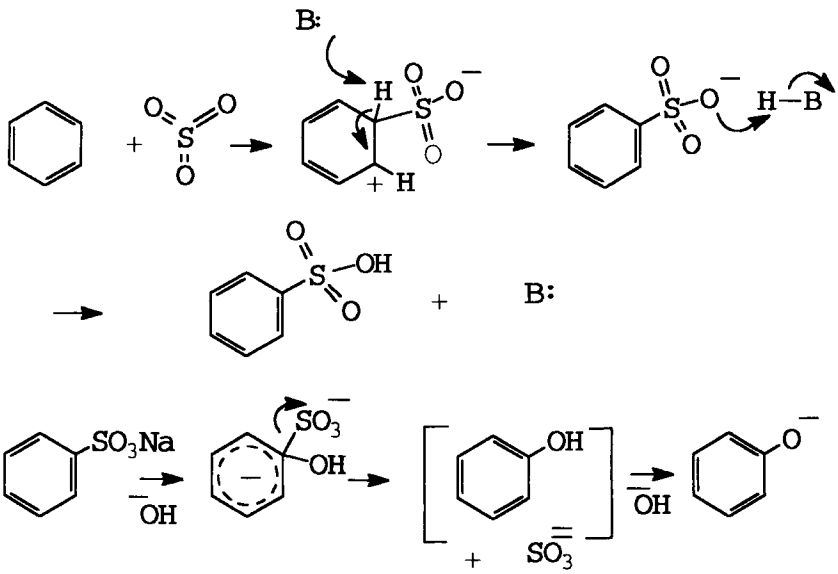
$$2C_6H_6 + 2H_2SO_4 \rightarrow 2C_6H_5SO_3H + 2H_2O$$

$$2C_5H_5SO_3H + Na_2SO_3 \rightarrow 2C_6H_5SO_3Na + SO_2 + H_2O$$

$$2C_6H_5SO_3Na + 4\,NaOH \rightarrow 2\,C_6H_5ONa + 2\,Na_2SO_3 + 2\,H_2O$$

$$2C_6H_5ONa + H_2O + SO_2 \rightarrow 2C_6H_5OH + Na_2SO_3$$

The mechanism is probably as follows.



Only one practical organic chemistry manual describes a laboratory method (ref.8).

1.3 The Chlorobenzene Process for the Synthesis of Phenol

A variety of modes of operation has evolved from the first process in 1924. In the Dow (1928) and Bayer methods, benzene is chlorinated at 25-50°C in the liquid phase in the presence of an anhydrous ferric chloride catalyst. By chlorination at or near the boiling point of benzene a mixture of monochlorobenzene (30-50%), and polychlorobenzenes (3-12%) is formed and unreacted benzene is recycled. The chlorobenzene is hydrolysed to sodium phenate with 10-15% sodium hydroxide solution at 300-390°C and 280-300 atmospheres (28-30 MPa). Diphenyl ether is formed as a by-product together with 2- and 4-hydroxydiphenyl and is returned to the first stage since under the reaction conditions it can be transformed into the two latter substances. The sodium phenate resulting is acidified with by-product hydrochloroic acid from the first stage chlorination and the phenol is purified as before by steam distillation. By-product sodium chloride is electrolysed to provide chlorine and sodium hydroxide for the next production cycle. Large scale operation is obligatory (100,000 tons per annum) for the Dow-Midland process to be economic and other drawbacks are the expense of chlorine, the high capital costs for the electrolysis and some engineering difficulties caused by the severe hydrolytic conditions. The yield of phenol is 90-95% based on chlorobenzene and although substantially displaced by the cumene process, the hydrolysis route accounts for a small proportion of world production. The mechanism of the hydrolysis may involve two simultaneous but different pathways, namely that of nucleophilic substitution and of intermediate benzyne formation, through evidence from chlorobenzene labelled with ^{14}C at the 1-position which yielded phenol substantially labelled in the 2-position. The stoichiometry is as follows

$$C_6H_6 + Cl_2 \rightarrow C_6H_5Cl + HCl$$

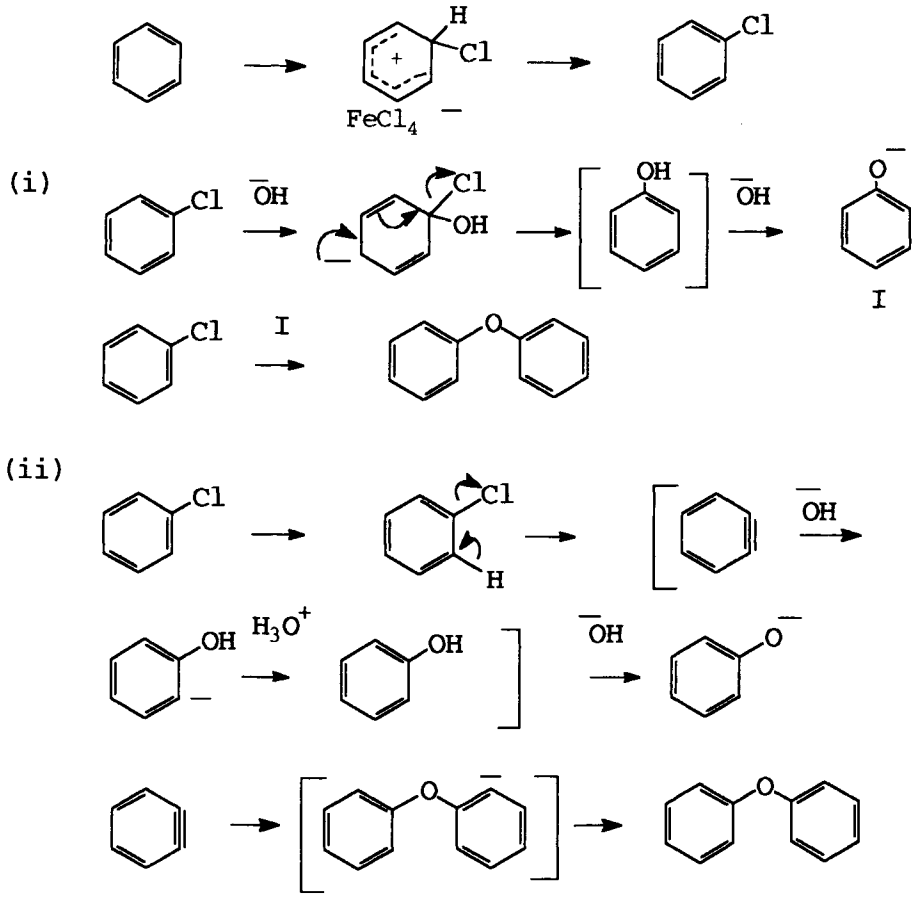
$$C_6H_5Cl + 2NaOH \rightarrow C_6H_5ONa + NaCl + H_2O$$

$$C_6H_5Cl + C_6H_5ONa \rightarrow C_6H_5OC_6H_5 + NaCl$$

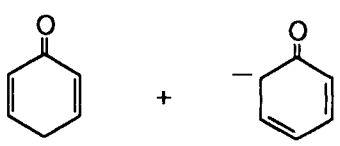
$$C_6H_5OC_6H_5 \rightarrow C_6H_5C_6H_4OH \text{ (4- and 2-)}$$

The mechanism at the two stages may be as shown.

$$Cl_2 + FeCl_3 \rightarrow Cl^+ + FeCl_4^-$$



2-Hydroxy and 4-hydroxydiphenyl can be considered to form by reaction of chlorobenzene, or benzyne, with the tautomeric forms shown.



1.4 The Raschig-Hooker Process for the Synthesis of Phenol

Some of the difficulties referred to in the previous process were overcome in the

Raschig process (refs.9,10,11) which was essentially a regenerative route introduced prior to World War II. Chlorobenzene, obtained by the oxychlorination of benzene with an air/chlorine mixture at 200-230°C in the presence of a catalyst containing cupric chloride, ferric chloride and alumina, was hydrolysed with steam under pressure at 400-450°C over a calcium phosphate catalyst. Alternatively a copper-promoted calcium phosphate/silica catalyst has been employed.

$$2C_6H_6 + 2HCl + O_2 \rightarrow 2C_6H_5Cl + 2H_2O$$

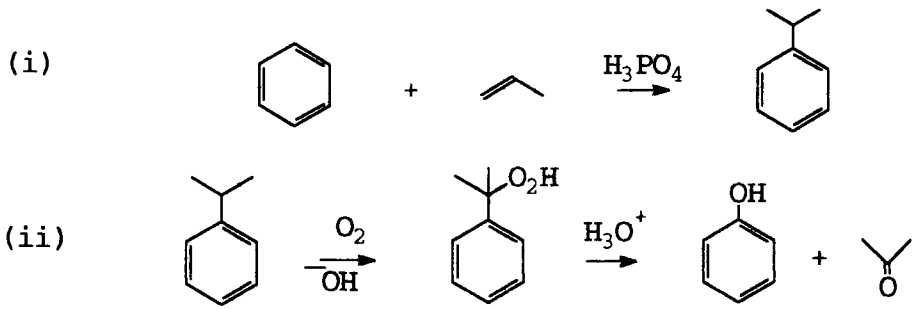
$$2C_6H_5Cl + H_2O \rightarrow 2C_6H_5OH + HCl$$

Conversion of benzene, effectively the only intermediate used, to chlorobenzene was kept low to avoid an exothermic reaction at the catalyst with formation of dichlorobenzenes which are present to only 6-10% in the product. In the hydrolysis frequent regeneration of the catalyst was found necessary to remove carbon. Although the selectivity of each step is high the conversion is only 10-15% with the consequence that large reactors are required with high capital costs. The high energy consumption and corrosion presented further problems. The method declined with the advent of aereal oxidative technology.

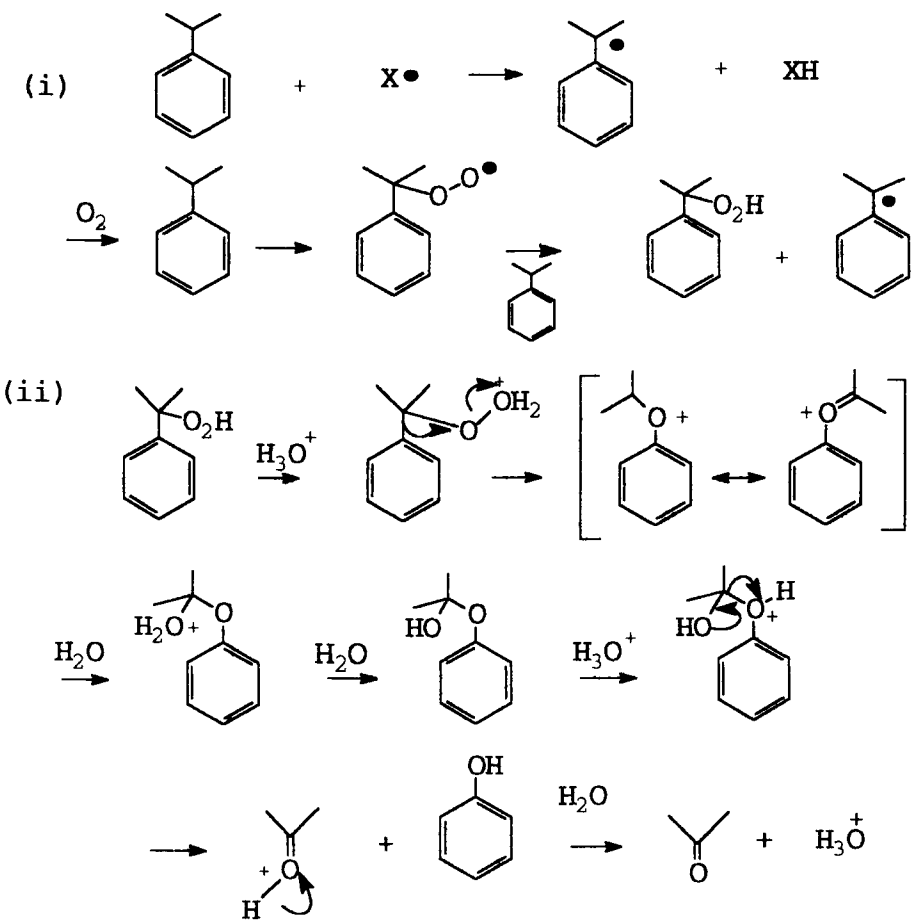
1.5 The Cumene Process for the Synthesis of Phenol

The cumene hydroperoxide process was developed from an earlier academic observation (ref.5) independently by the Distillers Co., Hercules Powder Co. and Allied Chemical Co.(refs.12,13), in the early 1950's and represented a completely new approach to phenol manufacture. The by-product acetone is of value, unlike the inorganic materials from the earlier processes and the success of the method is dependent on this. Benzene is alkylated with propene in the gas or liquid phase by a Friedel-Crafts reaction in the presence of phosphoric acid, sulphuric acid or aluminium chloride. Air or oxygen is used to oxidise cumene to its hydroperoxide at 80-130°C in the presence of alkali to neutralise acidic by-products and suppress its premature rearrangement. Cumene hydroperoxide which may be present to 30-40% in the final reactor and obtained in 90-95% conversion, is cleaved at 60-100°C with a non-oxidising inorganic acid such as sulphur dioxide and represents a 1,2-shift from carbon to oxygen. The acidic solution is neutralised, acetone is recovered by distillation, the other organic products are separated, washed and phenol is recovered by distillation. The yield is approximately 93% based on cumene and 84% on benzene, although a number of by-products, iso-propenylbenzene, cumylphenols, acetophenone, and dimethylphenylcarbinol are formed. The cumene process is highly favoured in the USA and in the UK where it is the

only major route to phenol. The overall reaction is as shown.

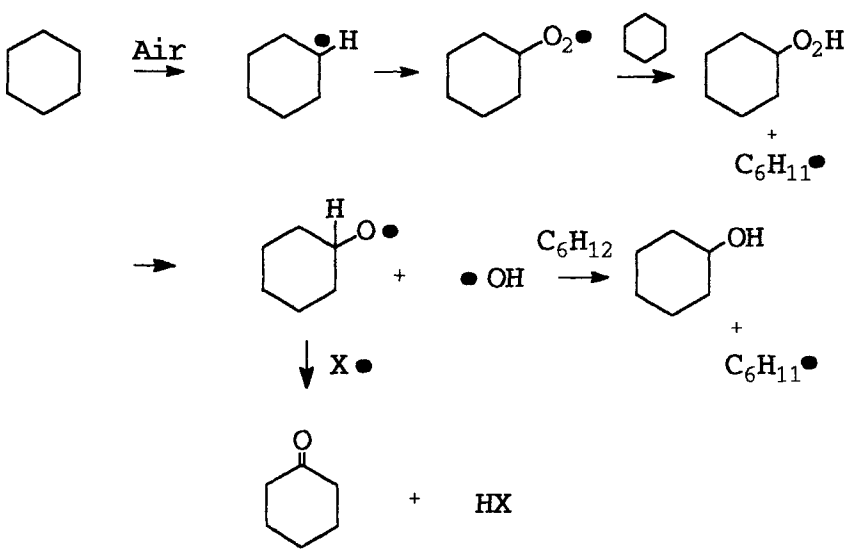


The first stage in the sequence of reactions proceeds by a free radical mechanism (refs.14,15), and the decomposition of the hydroperoxide by essentially an ionic pathway.



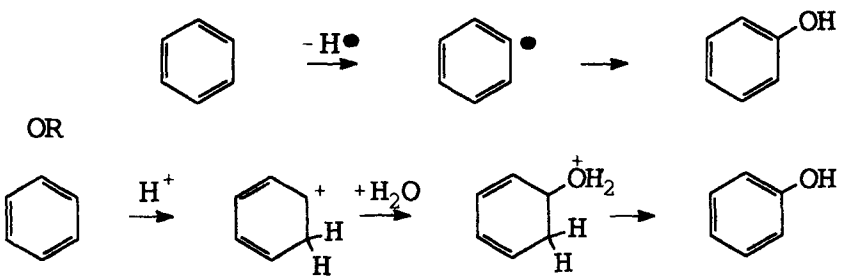
1.6 The Oxidation of Cyclohexane for the Synthesis of Phenol

The oxidation of cyclohexane introduced by Scientific Design (now Halcon International Inc.) (ref.16) for the production of cyclohexanol/cyclohexanone which are intermediates for 6,6 nylon manufacture, affords a route to phenol by dehydrogenation of the oxidation product. The oxidation of cyclohexane is effected with air at 150-160°C under pressure (8-9 atmospheres) in the presence of a cobalt octanoate or naphthenate catalyst and is more difficult than that of cumene because the methylene group involved is not benzylic in type. To prevent over-oxidation the conversion is restricted to approximately 10%. The oxidation product can be dehydrogenated to phenol at 400°C over a platinum-carbon or nickel-cobalt catalyst. By operation of the first stage of the oxidation process in the presence of boric acid side reactions are avoided, a considerably higher conversion is achieved and the product can be recovered after the dehydrogenation by an extractive distillation utilising the phenol/cyclohexanone azeotrope. The cyclohexanone route to phenol was used for a period by the Monsanto Co. but economically was less favourable than production from cumene.The probable course of the reactions is shown.



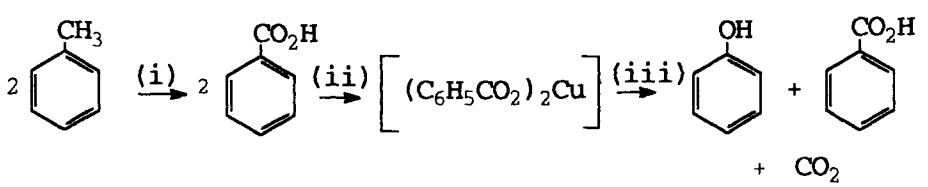
The most direct route to phenol, by the oxidation of benzene, has not yet achieved any commercial status through either a chemical or a biological method although plants are reputed to have been commissioned in various

countries. Small yields have generally been encountered although the formation of phenol in 40% yield was reported many years ago (ref.17) by the oxidation of benzene with air at 800°C in a reactor vessel coated with boric acid. No analogy exists in the case of benzene with the Hoechst-Wacker type oxidation used for ethene. Alternatively the hypothetical simple reaction indicated would provide the most rudimentary route.



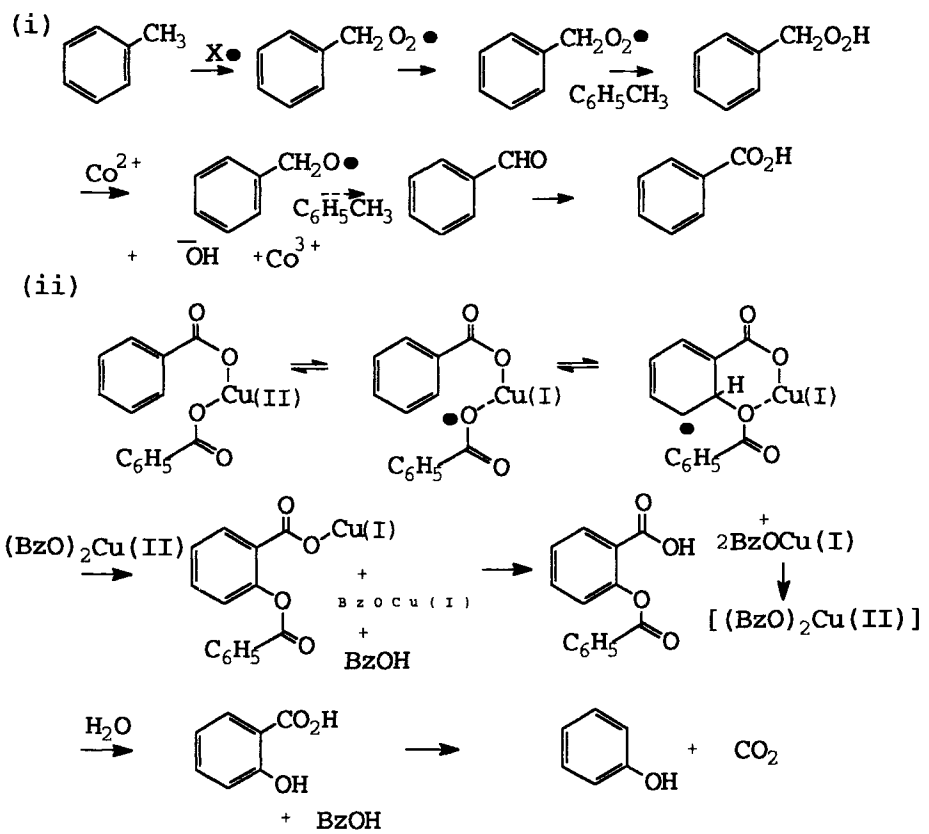
1.7 The Toluene-Benzoic route for the Synthesis of Phenol

The availability of abundant toluene from reforming operations has been the motivation for the Dow process (refs.18,19), introduced in 1961 for obtaining phenol by way of the intermediate formation of benzoic acid. Previously all processes had commenced with benzene. The technology stemmed from an early observation (in 1845) by German chemists that a neutral product, 'benzil', in reality phenyl benzoate, results from heating copper(II)benzoate.
The first stage oxidation of toluene by air to benzoic acid in the presence of cobalt salts at 110-125°C and 2 atmospheres pressure was first used in Germany during World War II. Oxidation by sulphur under autoclave conditions has also been an alternative approach for this step.



(i) Co^{2+}, air, 150°C (ii) air, steam, Cu^{2+} , Mg^{2+} (iii) Δ, 220-240°C

In the second stage the purified benzoic acid, molten or in a high boiling solvent containing a catalytic proportion of copper(II)benzoate together with magnesium benzoate as a promoter, is treated with steam and air at 220-250°C and phenol directly distilled from the mixture. A key stage is the conversion of copper(II)benzoate to 2-benzoyloxybenzoic acid and copper(I)benzoate which is then oxidised by air to copper(II)benzoate. The 2-benzoyloxybenzoic acid is hydrolysed to benzoic acid and salicylic acid which affords phenol with loss of carbon dioxide at the temperature of operation.
The mechanism of the first and second stages seems likely to be as shown although other pathways may also be feasible. By the use of basic copper salts of 2-alkylbenzoic acids and the use of high boiling solvents such as nitrobenzene, 6-alkylsalicylic acids are obtained (ref.20).



The yield of phenol from benzoic acid is approximately 85%. Although several plants mainly in the USA, Canada and the Netherlands operate this process the

technology is not as attractive as that developed in the cumene route. The comparative costs for the six processes for the production of phenol have been placed in the decreasing order (ref.10), benzene sulphonate route, chlorobenzene hydrolysis, toluene oxidation, Raschig oxy-chlorination, cyclohexane oxidation and cumene oxidation, the last route being universally favoured in the USA and the UK. Table 1.0 gives a comparison of the costs in the early seventies.

TABLE 1.0 COMPARATIVE COSTS OF SYNTHETIC PHENOL

Process	Benzene-Sulphonate	Chloro-benzene	Raschig	Cumene-hydroperoxide	Benzene-cyclohexane	Toluene Oxidn.
Net production Cost (£/ton)	81.7	78.3	57.1	45.7	51.5	59.5

(Adapted from Fig. 9.7, ref. 10, with permission)

1.8 The World-wide Production and some Uses of Phenol

Table 1.1 gives, for the year 1978, the annual synthetic capacity throughout the world.

TABLE 1.1 WORLD PRODUTION OF SYNTHETIC PHENOL

CONTINENT	COUNTRY	TONNES
North America	United States	1,589,000
	Canada	50,000
	Mexico	25,000
South America	Brazil	77/000
	Argentine	12,000
Western Europe	W. Germany (formerly)	420,000
	Italy	280,000
	UK	267,000
	France	175,000
	Benelux	140,000
Eastern Europe		>360,000
Asia	Japan	289,000
	Other	22,000
Australia		17,000

(Adapted from Table 4, 'Phenol', by C. Thurman, .Kirk-Othmer Encl. Chem. Tech., vol. 17, p376, 3rd Edn., 1982, by permision of Wiley-Interscience).

For the UK, the Annual Abstract of Statistics for 1993, has indicated an erratic production level for synthetic phenol in recent years, namely, 109,700(1981),140,000(1982), 143,200(1983), 184,400(1984), 117,500(1985) and 52,900(1986). The % distribution in the uses of phenol for the USA and the UK during the two previous decades has altered little and the % of principal applications is shown in Table 1.2 for the years 1970,1976 and 1978.

TABLE 1.2

MAIN USES OF PHENOL (%)

PRODUCT	STRUCTURE	1970(UK)	1976(W. EUROPE)	1978 (USA)
PF Resins	(1)*	45	35	48.1
Caprolactam	(2)	29	21	15.3
Bis-Phenol A	(3)	19	10	18.1
Alkylphenols (Nonylphenol and Miscellaneous+)	(4)	7	34	18.5

(* For the UK the quantity is 50,000 tonnes)

For Japan (1976) (PF) phenol-formaldehyde rsins were 54% and bis-phenol A, 29%.

+ The miscellaneous uses include adipic acid, salicylic acid, alkyl salicylates and others

(Adapted from Table 6, 'Phenol', by C. Thurman, Kirk-Othmer Encl. Chem. Tech., vol. 17, p380, 3rd. Edn., 1982, by permission of Wiley-Interscience).

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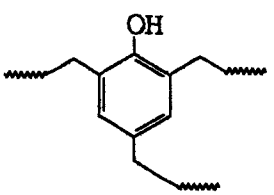

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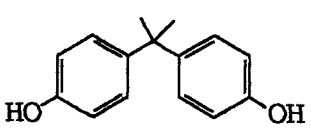

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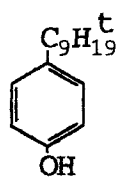


An extensive list of the physical properties of phenol and its homologues has

been given (ref.21). The parent compound, hydroxybenzene, has mp 40.9°C, bp 181.8°C and pK_A10 at 25°C.

1.9 The Synthesis of the Methylphenols (Cresols)

The cresols were traditionally obtained from the'cresylic acid' fraction (b.p. 170-230°C) obtained from the distillation products of coal. Fractionation gave o-cresol (2-methylphenol), b.p. 191°C, and a mixture of m-cresol, (3-methylphenol) (b.p. 203°C) and p-cresol, (4-methylphenol) (b.p. 202°C) which was chemically separated by sulphonation, fractional crystallisation and desulphonation. Another source of cresols is from catalytic cracking processes in the petroleum industry. A physical separatory method for the m-/p-mixture has been based on the formation of an addition compound of m-cresol with urea and for p-cresol an addition compound with anhydrous oxalic acid.
The formation of cresols (and xylenols) by Friedel-Crafts type alkylation in the reaction of phenol with methanol at 300-450°C over a solid catalyst usually a modified metal oxide is an important and well established synthetic route (ref.22) and typically can result in predominantly o/p substitution (o-cresol,54%, p-cresol,30%, and m-cresol,17%). Selectivity can be achieved with a magnesium oxide or metal oxide-iron oxide mixture to afford o-cresol and 2,6-xylenol (refs.23,24). The alkylation of phenol to give higher branched alkylphenols is described in a later chapter.
Partly on account of the protracted separation required for mixtures of m- and p-cresol various more selective synthetic strategies have been sought. Toluene with propylene by Friedel-Crafts alkylation affords a mixture of cymenes in which the m-/p- ratio is about 2:1.
4-Methylisopropylbenzene (p-cymene) and 3-methylisopropylbenzene can be converted to p-cresol and m-cresol respectively by the hydroperoxidation method used for phenol itself. Dealkylation of the di-tert-butylation product, 5-methyl-2,4-di-tert-butylphenol under acidic conditions affords another useful synthesis of m-cresol. Such methods are reminiscent respectively of the historical formation of the latter from thymol (6-isopropyl-3-methylphenol) and of o-cresol from carvacrol (2-methyl-5-isopropylphenol) by heating with phosphorus pentoxide.The sulphonation route has been employed for the production of p-cresol but the hydrolysis of chlorotoluenes or the oxydecarboxylation of the copper salts of the toluic acids have never found any permanent place in the production of the cresol isomers. 2-Chlorotoluene for example yields both o- and m-cresols by alkaline hydrolysis under pressure due to aryne formation.
Although cryogenic separation has made the xylene isomers readily available, their use has been directed substantially towards the benzene dicarboxylic acids rather than to the toluic acids, potential intermediates in the Dow technology, and furthermore, interest in the toluene/benzoic acid route for phenol itself has diminished considerably.

1.10 Uses of the Cresols

Compared with those for phenol the applications of the cresol isomers are more restricted and specialised. 2-Methylphenol is used for the selective herbicide 2-methyl-4-chlorophenoxyacetic acid (MCPA), the manufacture of the perfumery chemical coumarin, although it is relevant to mention that the 4-methyl analogue has recently been synthesised in 75% yield from the reaction of phenol and acetic anhydride (1:1) by passage through CeNaY zeolite at 380°C (ref. 25). 2-Methylphenol has been used for 2-hydroxy-3-methylbenzoic acid for certain chrome dyes and as a source of 4-methoxy-3-methylbenzoyl chloride for a member of an early group of optical bleaching agents based on 4,4'-diaminostilbene-2,2'-disulphonic acid prepared by the author (ref.26) and described later (ref.27). 3-Methylphenol has been employed for the antiseptic, 4-chloro-3-methylphenol and as the intermediate 3-methyl-6-tert-butylphenol for the synthesis of the nitro musk, musk ambrette (2,4-dinitro-3-methyl -6-tert-butylanisole). The most widely used cresol, 4-methylphenol, is an intermediate by reaction with isobutylene for the antioxidant BHT (2,6-di-tert-butyl-4-methylphenol), and for 4-methylphenyl methyl ether a perfumery chemical which is also used as an intermediate for its oxidation product, anisaldehyde (4-methoxybenzaldehyde), another important perfumery chemical.

2. Dihydric Phenols

2.1 Introduction

The discoveries of the isomeric dihydric phenols were as old as that of phenol itself. Catechol,(1,2-benzenediol, 1,2-dihydroxybenzene, o-dihydroxybenzene) was first obtained in 1839 essentially from the dry distillation of tannin. Resorcinol (1,3-dihydroxybenzene), was isolated in 1864 from the alkaline fusion of galbanum, and of asafoetida, resins , repectively from Iranian species of Ferula and *Narthex asafoetida.* In 1820 hydroquinone was recovered from the dry distillation of quinic acid although it was not investigated structurally until 1844 by Wohler.
Of the three isomers, catechol is the only member to occur naturally, namely in the leaves and branches of the oak and willow, in apples, onions, and crude sugar beet and in the tannin layer of mycorrhizas (ref.28). Its derivatives are widely distributed in higher plants. Hydroquinone occurs as the glucoside arbutin (4-hydroxyphenyl-D-glucopyranose) and resorcinol only in pyrolysis products in, for example, cigarette smoke.

2.2 The Synthesis of Catechol, Resorcinol and Hydroquinone

All the methods for the industrial synthesis of phenol with the exception of

oxydecarboxylation and oxidative chlorination have an application for the dihydric phenols. These procedures are mostly based on disubstituted benzenes although activated monosubstituted benzenes have extended the range of methods. Table 1.3 gives the type of process, the production level and the country of operation for the three isomers.

TABLE 1.3 THE PRODUCTION of DIHYDRIC PHENOLS (tonnes)

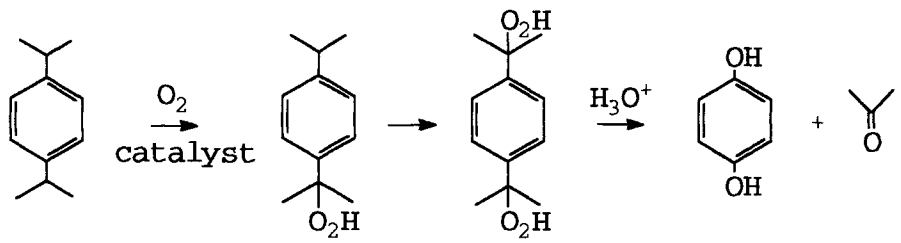
ISOMER	PROCESS	PRODUCTION	COUNTRY
Catechol	Hydrolysis of 2-chlorophenol	>20.000	-
	Hydroxylation of phenol		Fr,It.J
	Coal tar distillation		EEur,UK
Hydroquinone	Oxidation of aniline	>40,000	USA,WG,J
	Hydroxylation of phenol		UK,EEur,C
	From 1,4-di-iso-propylbenzene		Fr,It,J
Resorcinol	Benzene-1,3-disulphonic acid	30,000 to 50,000	USA,It,WG UK,PR J
	1,3-di-iso-Propylbenzene		J

(C,China, Fr,France, It, Italy, J, Japan, EEur, Eastern Europe, PR, Puerto Rico, WG, Western germany)

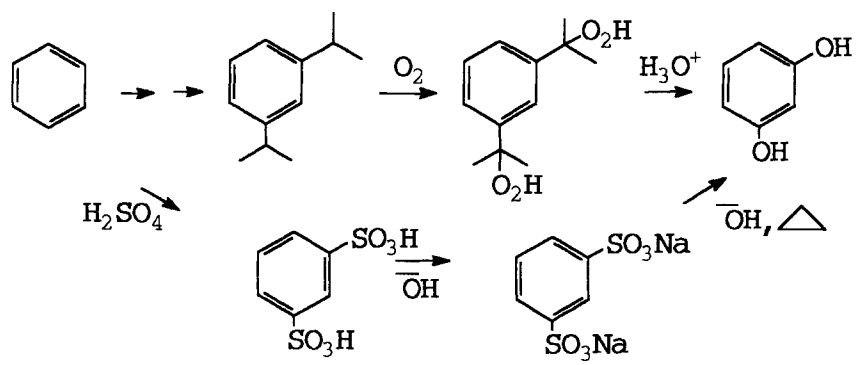
(Adapted from Table 3, 'Hydroquinone, Resorcinol and Catechol', by J. Varagnat, Kirk-Othmer Encl.,vol. 13, p47, 3rd. Edn., 1981, by permission of Wiley-Interscience).

The alkaline fusion of aryl 1,3-disulphonates and the acidic rearrangement of 1,3- and 1,4-bis-hydroperoxides of dialkylbenzenes are important methods for the production of the corresponding dihydric phenols.
Unlike the almost abandoned route for phenol from benzenesulphonic acid by alkaline fusion, resorcinol is manufactured substantially by this methodology which was first described in 1878. The yield of resorcinol on benzene-1,3-disulphonic acid is 94% (ref.29) after recovery from the acidified alkaline solution and purification by distillation. For catechol, the hydrolysis of 2-chlorophenol, originally an important route, was effected with a 300% molar excess of alkali at 190°C in the presence of a copper catalyst (usually a copper vessel). In the absence of copper the product contained a high proportion of resorcinol formed by the involvement of an aryne intermediate. For both resorcinol and for hydroquinone, the bis-hydroperoxidation of 1,3- and

1,4-di-isopropylbenzenes followed by acidic rearrangement is the preferred method although it is not applicable to catechol because of side reactions involving cyclisation.
The key stage is the alkylation of cumene. From its reaction in the liquid phase at 300°C in the presence of a silica/alumina catalyst with 3 moles of propene the 1,4-isomer required for hydroquinone is separated by fractionation (ref.30) and the mixture of 1,2- and 1,3-di-isopropylbenzenes together with the tri-isopropyl isomer equilibrated with benzene at 270°C with the same catalyst to enrich the proportion of the 1,3-compound required for the synthesis of resorcinol. The sequence of steps for hydroquinone is shown. By-product 4-isopropylphenol is mostly reoxidised and recycled giving a total yield of 71% based on di-isopropylbenzene (ref.31).

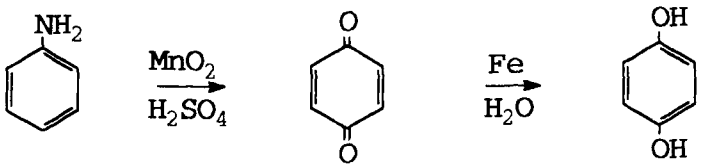


In a similar manner and yield, resorcinol is produced from the 1,3-isomer although the greater reactivity of the product towards condensation with the acetone by-product is an added complication. The route is shown together with older sulphonation method.

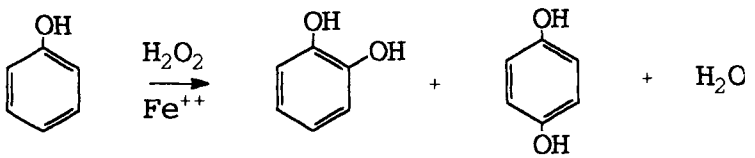


A well-tried route (ref.32) for hydroquinone deriving essentially from early organic chemistry (ref.33,34) is by the oxidation of aniline to 1,4-benzoquinone

and, after separation, reduction of this to the product by the Bechamp method.



The most recent processes particularly for the industrial synthesis of catechol and hydroquinone are by the direct hydroxylation of phenol at 80°C with 70% hydrogen peroxide solution in the presence of catalytic quantities of strong mineral acids, such as perchloric acid, with ferrous sulphate (Fenton's reagent) or cobaltous sulphate (ref.35). The organic products are solvent extracted and fractionated to separate the two products from the starting material. With a ferrous catalyst, resorcinol accompanies the two main products.



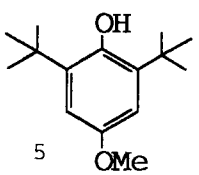
2.3 Uses of Dihydric Phenols

The dihydric phenols are speciality products widely used industrially and commercially. Hydroquinone and its relative, 4-methylaminophenol (metol) are the main chemicals used for development in black and white photography. Butylated hydroxyanisole, (BHA) mainly 2,6-di-tert-butyl-4-methoxyphenol (5), an important food antioxidant is synthesised from 2,4,6-tri-t-butylphenol by reaction in methanolic solution with chlorine to give 2,4,6-tri-t-butyl-4-methoxy-2,5-cyclohexa-2,5-dienone which is then dealkylated in acidic methanol.
Resorcinol is largely used as a 'phenol formaldehyde' resin for adhesive application in the rubber and tyre industry. Resorcinol or its formaldehyde reaction product can be used as accelerators for curing phenolic resins. The dihydric phenol is an intermediate for azo and triphenylmethane dyes, pharmaceuticals, antioxidants and other industrial chemicals. Two useful derivatives of resorcinol are the ultraviolet absorber, 2,4-dihydroxybenzophenone (6), available from the mild mono-benzoylation of

resorcinol and β-methylumbelliferone (7-hydroxy-4-methylcoumarin) (7), prepared from ethylacetoacetate and resorcinol in an acidic medium. This is extensively employed as an optical brightener in many consumer products such as soap. Fluorescein (8; X = H), is synthesised from phthalic anhydride and resorcinol, and its 2,7-dichloro derivative (8; X = Cl) has a wide application as a water dye marker on account of its intense fluorescence.

Catechol is an intermediate for the synthesis of racemic adrenaline which, although quite medicinally active, can be resolved (ref. 36) in 71% yield to afford the more active R(-) enantiomer, the natural form, which can also be derived quantitatively by asymmetric reduction (ref. 37) of the synthetic precursor, adrenalone as the hydrochloride by catalytic hydrogenation in methanol containing the rhodium complex of (R)-α[(S)-1',2-bis(diphenylphosphine)ferrocenyl]ethyl alcohol. Adrenalone is obtained by the acylation of catechol with chloroacetyl chloride to afford 3,4-dihydroxy-ϖ-chloroacetophenone followed by reaction with methylamine.

Catechol is also employed for the industrial antioxidant 4-tert-butylcatechol, and its monomethyl ether, guaiacol is used for the production of vanillin (10). This account is by no means a complete summary of the applications of the dihydric phenols more of which have been listed elsewhere (ref. 38).



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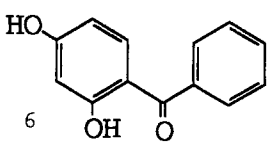

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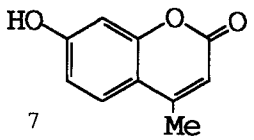

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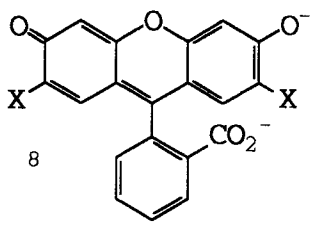

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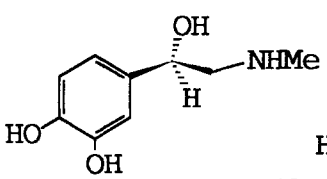

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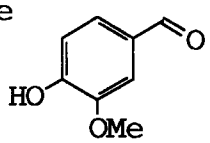

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3 General Summary

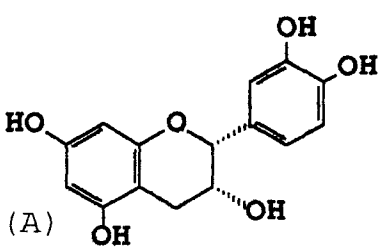
In conclusion it can be seen that the production of phenol, 4-methylphenol and the isomeric dihydric phenols, with the exception of catechol, is dominated by hydroperoxidation technology. The comprehensiveness and elegance of this methodology rests partly upon the simultaneous recovery of acetone and in the dihydric series upon the thermal equilibration step to obtain the stable but

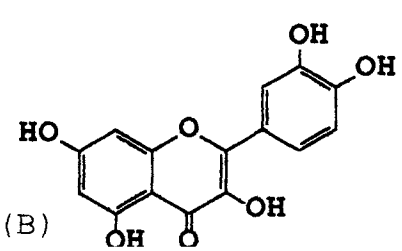
elusive 1,3-compound. Catalytic hydroxylation has an almost comparable applicability with the exclusion that it is not effective for the formation of 4-methylphenol from toluene on account of the greater reactivity of the benzylic group in contrast to the ring which is of course the inherent strategy of the cumene process.

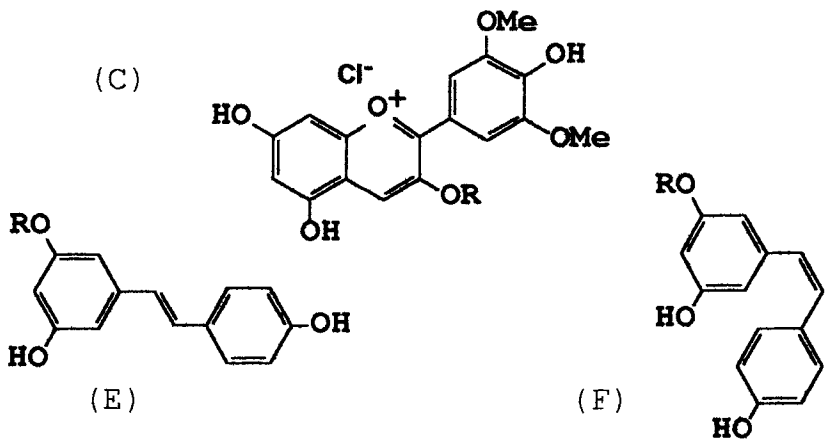
The current dominance of petroleum-derived intermediates for the synthesis of hydroxybenzenes in vast quantities may raise the question of the ultimate longevity of these fossil fuel sources. Replenishable raw materials of fatty or other origin could furnish useful C_2 and C_3 intermediates for cyclisations and dehydrogenations towards phenolic structures. Biological-type syntheses offer an alternative route as yet little explored.

However it has to be remembered that our knowledge of the long-term effects of the great range of present-day chemicals upon the living world and the environment are not known for certainty and the intermediates as well as products we regard as so vitally important may themselves be displaced with critical advances. In this connection it is noteworthy that nonylphenol and bisphenol A which are well-established intermediates for a number of highly efficacious consumer products have been shown in recent work by a number of independent world-wide research groups to have a profound and disturbing effect on the male reproductive systems of test groups of animals and thus by implication on human beings (ref. 39). The action is attributable to estrogenic mimicry and is also observed with non-phenols such as the plasticiser, butyl benzyl phthalate. The formerly used synthetic estrogen diethylstilbestrol has been linked to the ocurrence of certain cancers.

The potential longevity of man (ref.40) has been linked with the existence of radicals in the living system and paradoxically, natural and synthetic phenols, sometimes thought of as foreign and offensive to the living world, in their role often as highly effective antioxidants, probably still have a part to play in this complicated array. Many natural products notably fruit, wine and tea contain components such as (A), the flavonol, epicatechin, (B) the flavonoid, quercitin and (C; R = glucose)), the anthocyanin, malvidin-3-glucoside, which can have a beneficial influence, from the appropriate source of material, on the health of humanity (ref. 41). The reduction in coronary heart disease has been suggested (ref. 42) as attributable to resveratrol (E), trans-3,5,4'-trihydroxystilbene, while (F) the 3-glucoside, piceid, is the main component of 'Koji jon', a traditional Chinese medicine prepared from *Polygonum caspidatum*, and used for the treatment of atherosclerosis.







The familiar browning of cut friut and vegetables caused by the enzyme phenolase is another aspect of the close proximity of phenolic sysztems in daily life (ref.43). Dopamine [2-(3,4-dihydroxyphenyl)ethylamine] is the causative agent implicated in recent genetic researches examining reasons for human novelty-seeking (ref. 44).

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CHAPTER 2

RECENT ADVANCES IN THE SYNTHESIS OF MONOHYDRIC PHENOLS

2.1 Introduction

In the ensuing chapters some of the important advances during the previous decade in the chemistry of phenols (including reference to monocyclic bicyclic and polycyclic compounds), their substitution products and their reactions are considered. The format in a previous review (ref.1) has been adopted. Detailed reference to physical and spectroscopic properties or to kinetic studies has been excluded and the subject matter described is very largely of organic chemical interest. The present chapter is concerned with recent investigations in five preparative categories (i), the hydroxylation of arenes, (ii), the replacement of substituents by the hydroxyl group, (iii), the formation of phenolic rings by way of alicyclic precursors, (iv), the production of phenols from a single acyclic precursor, (v), the same methodology as in (iv) but involving two acyclic reactants as precursors.

Although this formal division into five aspects is convenient from the classification point of view, aromatic chemistry is still an area of both striking as well as more conventional developments and phenolic compounds and aromatic ethers (Chapter 4) have been in the forefront of recent novel synthetic methodology.

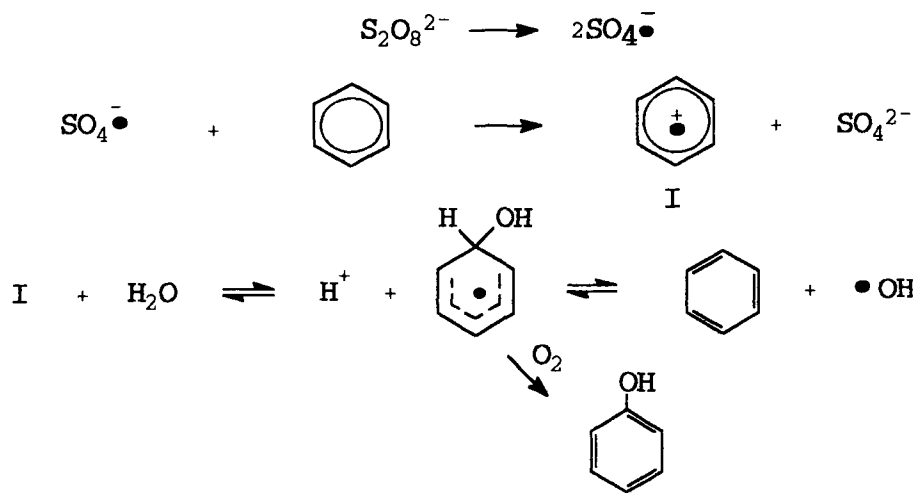
The synthetic material covered is in reality that of hydroxyaromatics and of some hydroxy heterocyclic compounds. Inevitably, synthetic routes to phenol are generally applicable to the mono and certain dialkyl derivatives but an attempt has been made to leave descriptions of recent methods for polyalkylphenols until Chapter 6 where also derivatives of the side chain in alkylphenols are discussed.

Palladium-catalysed substitution for the coupling of two different phenolic ethers by Suzuki (ref.2) or other procedures has extended the possibilities of the symmetrical Ullmann reaction. Transition metal complexation through the employment of chromium tricarbonyl (ref.3) has enabled orientation effect of groups in the ring to be selective and varied. Metallation reactions, an area first pioneered by A.I. Meyers with alkyllithiums, have been greatly extended by the coordination of the alkyllithium with a variety of directive groups in the aromatic ring resulting in o-lithiation and subsequent selective o-substitution by an incoming electrophile (ref.4).

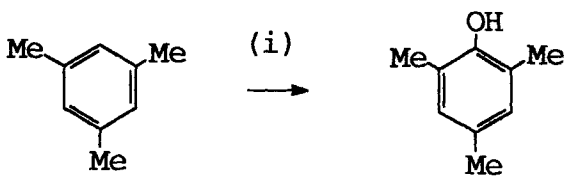
Organometallic chemistry has generally had a great influence in this whole area and the use of η^2 coordinated arenes, particularly osmium complexes, having enhanced electrophilic character has given remarkable results (ref.5). Fluoro compounds are of great interest in medicinal chemistry and improved techniques such as the use of acyl hypofluorite for the fluorinationn of phenolic ethers (ref.6) has superseded the Schiemann method. Aromatic chemistry is generally thought of as the province of electrophilic substitution with all its accompanying uncertain selectivity while the application of nucleophilic substitution requires the displacement of the right electronegative group, the right aprotic solvent (which is often toxic or expensive) or the employment of unduly drastic reaction conditions. The new approach of 'vicarious nucleophilic substitution', involving the displacement of hydrogen by the nucleophile and the use of mild and available reagents (ref.7), is applicable in phenolic and aromatic ether chemistry. Examples of the preceding innovations are given throughout the ensuing chapters and serve to illustrate that the phenolic and aromatic ether front is a very lively sector of the general changes coming about in aromatic chemistry.

2.2 The Hydroxylation of Arenes

The mechanism of the catalytic hydroxylation of aromatic hydrocarbons by hydrogen peroxide has been reviewed (ref.8). The hydroxylation of benzene or toluene by peroxydiphosphate (ref.9) and peroxydisulphate, (more commonly termed persulphate) (ref.10) in aqueous (0.05-1.0M) acid in the presence of Cu(II) has been found to be similar. Phenol (15.6%), diphenyl (5.2%), and 2- and 4-nitrophenols (11.7% and 5.6% respectively) resulted from a mixture of benzene and nitrobenzene in water at 80°C with peroxydisulphate.



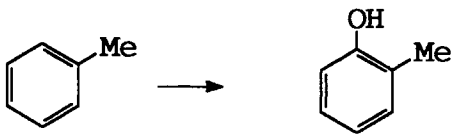
Without benzene or with its replacement by toluene or anisole no nitrophenols were formed and the preceding mechanism has been proposed in which hydroxyl radicals are removed from the system by the nitrobenzene. Various hypothetical schemes for the formation of phenol from benzene have been mentioned in Chapter 1.
By the action of peroxymonophosphoric acid in acetone on excess of mesitylene (1,3,5-trimethylbenzene) diluted in acetone at 25°C during 4 hours, mesitol resulted in 74% yield (ref.11).



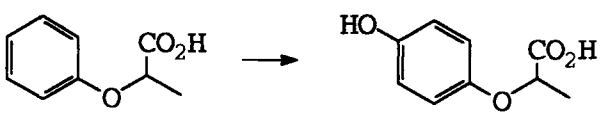
The photolysis of α-azohydroperoxides in acetonitrile solutions of arenes gives rise to a different isomeric mixture of phenols in the presence or absence of oxygen (ref.12).
An aqueous mixture of benzene, hydrogen peroxide, ferric nitrate and a catalytic proportion of hexadecyltrimethylammonium bromide at 35-50°C has been claimed to afford an 82% yield of phenol although this was only 8-10% without the phase-transfer catalyst (ref.13).

The use of a heterogeneous system under nitrogen consisting of a stirred suspension of silica gel with adsorbed ferric-catechol complex in benzene treated with 35% hydrogen peroxide has been reported to result after 2.5 hours in a 60% yield of phenol (ref.14). The formation of phenol in 56% yield resulted from a mixture of benzene and vanadium(V) catalyst in acetonitrile under nitrogen when reacted for 2 hours at ambient temperature (ref.15). More recent studies have involved the conversion of benzene in trifluoromethanesulphonic acid to phenol by the electroreduction of dioxygen (ref.16) and from generation

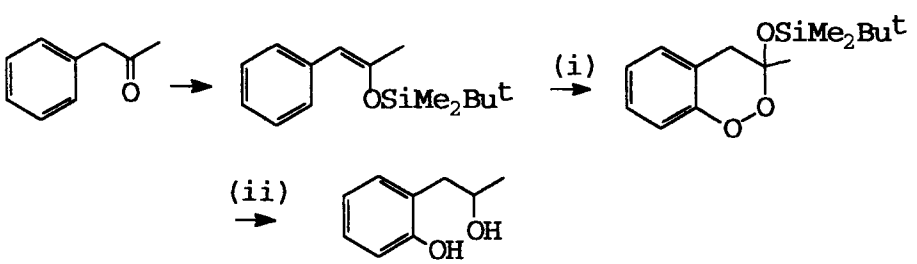
of the hydroxyl radical (ref.17). In the presence of trifluoromethanesulphonic acid diazonium fluoroborates are converted to phenyltriflates by thermal or photolytic decomposition (ref. 18). The electrophilic o-hydroxylation of toluene in trifluoromethanesulphonic acid has been described by the slow addition of sodium borate over 3-5 hours at -10°C, stirring of the mixture for 20 hours at that temperature, cooling to -78°C and finally quenching with ice and water. o-Cresol was obtained in 66% yield (65% ortho) and the procedure apparently has general applicability even to deactivated compounds (ref.19).



Regioselective 4-hydroxylation by a microbial organism, the fungus *Beauverya sulphurescens* has been described (ref.20).
Hydroxylation of 2-phenoxypropionic acid to give the 4-hydroxy compound, 2-(4-hydroxyphenoxy)propionic acid, in 97% yield has been effected microbiologically by the use of *Streptomyces hygroscopicus* in a solution containing glucose, corn steep liquor, potassium dihydrogen and dipotassium hydrogen phosphates over a period of 3-7 days at 28°C (ref.21).



Oxidation of more complex compounds resulting in, essentially, replacement of H by OH has received little attention. The transformation shown, effectively

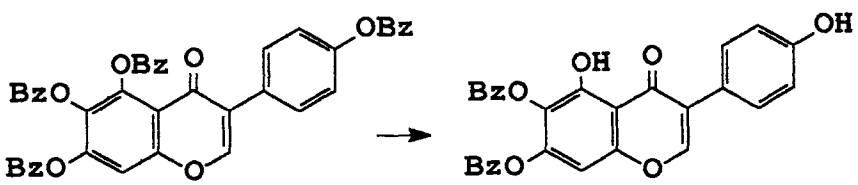


an o-hydroxylation, was achieved in 66% yield, (i) hν, O_2,(ii) $LiAlH_4$ (ref.22). An o-alkylphenol could be readily obtained from the hydroxy product. Other procedures are reminiscent of the oxidation of allylic systems with succssively, de- and re-aromatisation steps (ref.23). The methodology is related to that used for olivetol (5-pentyl-1,3-dihydroxybenzene) (ref.24).

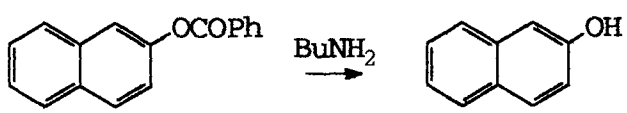
2.3 The Replacement of Substituents by the Hydroxyl Group

2.3.1 Phenolic esters to phenolic compounds

During recent years more attention has been given to the selective hydrolysis of phenolic esters. Thus, a stirred mixture of 5,6,7,4'-tetrabenzoyloxyflavone in dry pyridine, in the absence of light and moisture, with the reactants phenol and silver carbonate gave after 3 hours at ambient temperature, 5,6-dibenzoyloxy-7,4'-dihydroxyflavone (ref.25).



1-Naphthyl benzoate in benzene at ambient temperature stirred with 1-butylamine during 2.5 hours gave 1-naphthol in 97% yield, although alkyl and allylic benzoates were not hydrolysed under these conditions (ref.26).



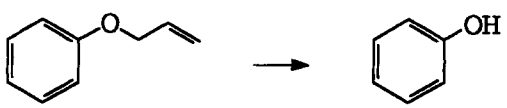
Ethyl phenyl carbonate was hydrolysed in 98% yield with sodium hydrogentelluride (prepared from Te powder and sodium borohydride *in situ*) in ethanol containing deoxygenated acetic acid as a buffer, by refluxing for 0.5 hour under nitrogen (ref.27).

$$PhOCO_2Et + NaHTe \rightarrow PhOH + EtOH$$

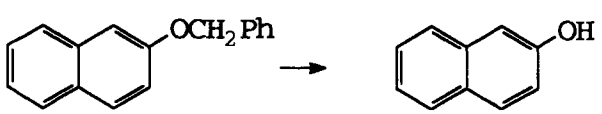
2.3.2 Phenolic ethers to phenolic compounds

Adddition of anisole in cyclohexane containing tetra-n-butylammonium iodide to a cooled suspension of aluminium iodide in cyclohexane and refluxing of the mixture for 20 mins. afforded phenol in quantitative yield (ref.28). Preferential cleavage can occur. The apparent mildness of the system, unlike that of $AlCl_3$ and BBr_3, recalls the use of BCl_3.

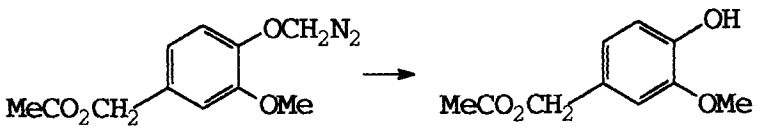
A molar solution of allyloxybenzene in acetonitrile has been converted to phenol in 87% yield by addition to a freshly-prepared solution of AlI_3 in acetonitrile followed by refluxing for 5 hours. Phenolic ethers were demethylated more rapidly than aliphatic ethers (ref.29). Further examples are given in Chapter 4.



An interesting debenzylation technique under essentially chemical conditions has been described having aspects of transfer hydrogenation. A mixture of 2-naphthylbenzyl ether, sodium formate and formic acid (1:1:4 molar) in methanol or ethanol refluxed for 0.5 hour with a little 10% Pd-C, afforded 2-naphthol in 79% yield (ref.30).



The protective azidomethyl group can be selectively chemically removed in the presence of methoxyl and ester groups. Thus the compound indicated in methanolic solution at 25°C with an equimolar proportion of stannous chloride gave the corresponding phenol in 82% yield (ref.31).



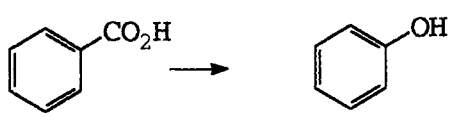
Demethylation has been effected microbiologically in 90% yield. Reduced nicotinamide adenine dinucleotide phosphate and the methyl ether were added to a cell-free extract of methane-grown *Methylosinus tricosporium* OB 3b and the mixture left in a shaker-incubator for 20 mins. at 30°C (ref.32).

2.3.3 Formation of phenols by replacement of boron, oxoalkyl, carboxy,formyl, nitro, triazeno, sulphonamido, halogeno and thallic group

A technique primarily for obtaining ^{17}O-radio-labelled phenol in 86% yield with 13.8% enrichment from phenylboronic acid in ether-ethanol (10:1) by brief exothermic reaction with ^{17}O KOOH (obtained by autoxidation of benzhydrol with ^{17}O-enriched O_2 and potassium tert-butoxide) followed by standing of the mixture for 1 hour has been reported (ref.33).

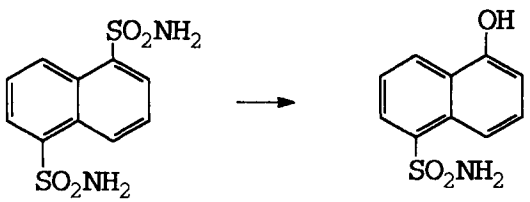
^{17}O- and ^{18}O-Labelled phenols have also been synthesised in 88% yield from the triazene, PhN=NNEt$_2$, by its dropwise addition in acetonitrile solution over 5 mins. to a boiling aqueous suspension of bio-rad AG 50W-X12 acid resin (ref.34).

Replacement of the carboxyl group has been effected catalytically as in the conversion of benzoic acid in a mixture of steam and air (1:38:0.6) to phenol over Cu-ZrO-K_2O on alumina at 280-300°C/ 90-100 psig. during 3 hours (ref. 35). The process is reminiscent of the pyrolysis of copper (II) benzoate.

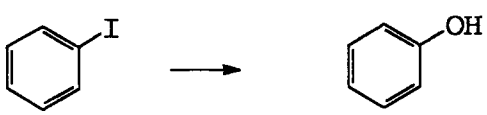


Nitrobenzenes (and naphthalenes) have been converted to the corresponding phenols by reaction with benzyl alcohol in tetramethylurea after a final debenzylation step (ref. 36).

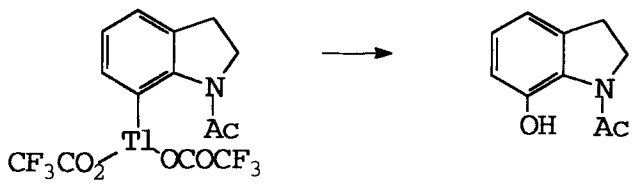
The 5-sulphonamido group of naphthalene-1,5-disulphonamide is hydrolysed in a Bucherer-type reaction with 20% aqueous sodium hydroxide in an autoclave at 220°C during 10-15 hours to give 1-hydroxynaphalene-5-sulphonamide in 88% yield (ref.37).



Iodobenzene has been found to give phenol in 61% yield by stirring at 180°C for 4 hours in a sealed reactor with 1 equivalent of potassium hydroxide and a little cuprous oxide in deionised water (ref.38).

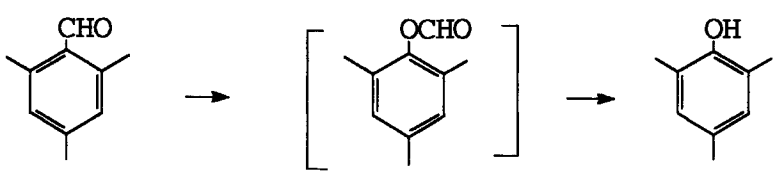


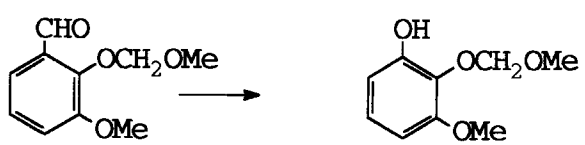
Very mild oxidative conditions, with copper sulphate, compared with those ordinarily used, sufficed for the conversion in 62% yield of (1-acetyl-2,3-dihydroindol-7-yl)thallium bis tri-fluoroacetate to 1-acetyl-7-hydroxyindoline in dimethylformamide/water (1:1) solution at 125°C during 6 hours (ref.39).



Phenols have been derived by the oxidation of aryltriethoxysilanes in methanol with 3-chloroperbenzoic acid at ambient temperature during 24 hours (ref.40), the first step consisting in the reaction of an aryl Grignard reagent with a tetrahalogenosilane.

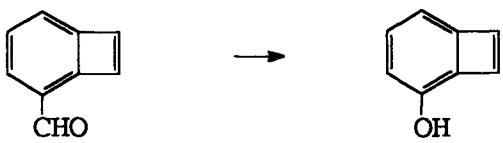
Baeyer-Villiger oxidations, perhaps more reminiscent of Dakin oxidations, have been used for transforming aldehydes and ketones to phenols. For aldehydes with alkyl groups or two or more alkoxy groups, excess 30% hydrogen peroxide added to a solution of the aldehyde containing a small proportion of bis(2,4-dinitrophenyl)selenide in dichloromethane followed by stirring at ambient temperature for 28 hours, removal of the catalyst and hydrolysis with methanolic potassium hydroxide gave the corresponding phenol in 91% yield in the examples shown (ref.41). Benzenoid aromatic ketones were not susceptible to attack.



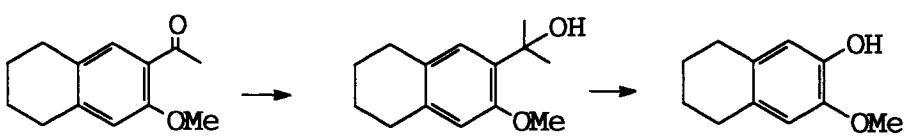


With hydrogen peroxide in acidic methanol, benzaldehyes have been converted directly to phenols without prior formation of the formate ester (ref.42). Upon treatment with 3-perchlorobenzoic acid in anhydrous dichloromethane at ambient temperature, naphthaldehydes have been transformed in 80-90% yields to the corresponding naphthyl formate. Non-aqueous work-up with anhydrous potassium fluoride was used for the first stage followed by selective cleavage

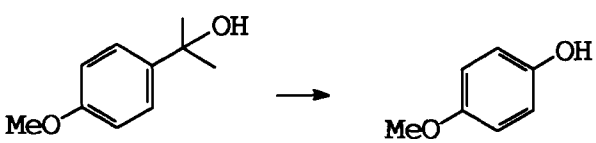
of the formate ester with alumina (activity I) (ref.43).
Also in the bicyclic series, 3-formylbenzocyclobutene when added to monoperoxyphosphoric acid in acetonitrile gave a 79% yield of 3-hydroxybenzocyclobutene (ref. 44).



By contrast with the conditions for aldehydes, ketones have been oxidised to phenols by methodology essentially that of the 'cumene-hydroperoxide' rearrangement. In the naphthalenic series, treatment of the derived t-alcohol shown with excess 90% hydrogen peroxide followed by stirring of the mixture with a little 4-toluenesulphonic acid for 6 hours at 22°C gave the phenolic product, 2-hydroxy-3-methoxy-5,6,7,8-tetrahydronaphthalene in 85% yield (ref.45).



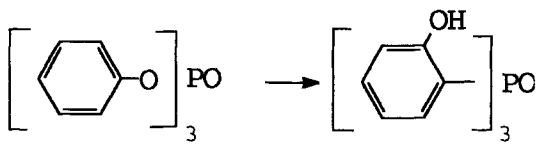
In the benzenoid series the t-alcohol illustrated, derived from a ketonic precursor, afforded 4-methoxyphenol in 93% yield by addition in THF solution at 0°C during 1 hour to a reagent prepared at 0°C during 30 minutes by the addition of excess BF_3 etherate to a suspension of $NaBO_3.4H_2O$ in THF (ref. 46)



Amongst the miscellaneous procedures by which phenols have been derived may be mentioned the catalytic reduction of a cumene nuclear hydroperoxide with hydrogen and Pd/Al_2O_3 under a slight pressure for 5 hours at less than

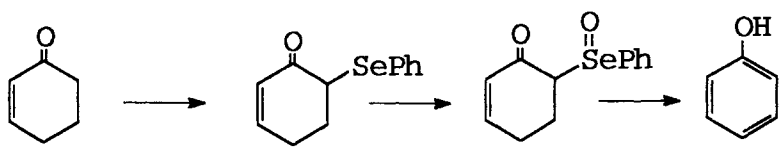
65°C (ref.47).

Rearrangement of triphenylphosphate in tetrahydrofuran, added to lithium di-isopropylamide in the same solvent at -78°C under nitrogen followed by further reaction during 4 hours has been reported to afford tri-(2-hydroxyphenyl)phosphine oxide in 87% yield (ref.48).

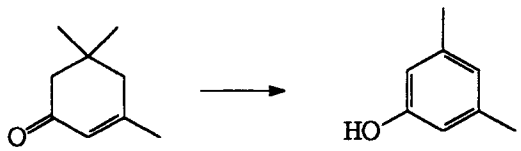


2.3.4 Conversion of cycloaliphatic compounds to phenols

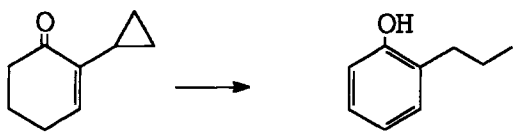
In this approach a number of monocyclic and bicyclic compounds have served as intermediate and models for the synthesis of phenols and naphthols. Cyclohex-2-enone in tetrahydrofuran containin lithium diethylamide at -78°C has been converted to the 6-phenylselenide by the action of phenylselenyl chloride on the anion.Treatment of the isolated product with 3-chloroperbenzoic acid in tetrahydrofuran (or with 30% hydrogen peroxid in THF) at -15°C for 0.5 hour followed by warming of the reaction mixture to ambient temperature gave phenol in an overall yield of 55% (ref.49). The method was not effective for 1-tetralone.



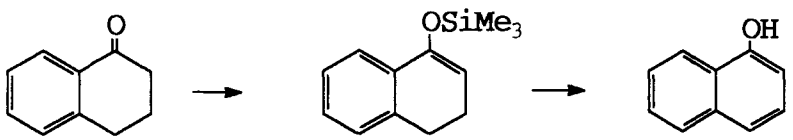
Very different catalytic conditions have been use for the conversion of isophorone in 87% yield to 3,5-xylenol by passage over Cr_2O_3-Al_2O_3 at 400-600°C (ref.50).



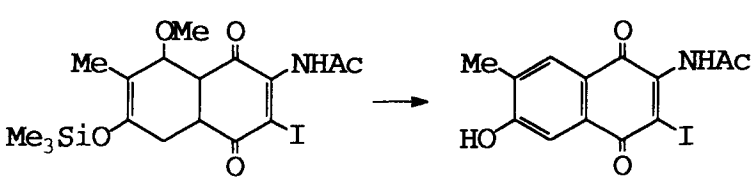
Thermal treatment of 2-cyclopropylcyclohex-2-enone afforded 2-n-propylphenol (ref.51).



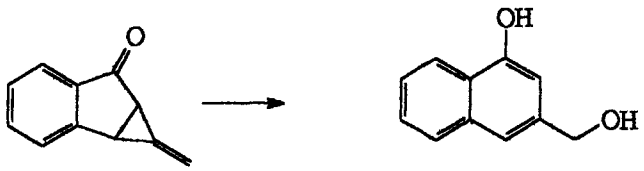
The enolic trimethylsilyl ether of 1-tetralone with 2,6-lutidine in dichloromethane upon dropwise addition at ambient temperature to a suspension of trityl perchlorate in the same stirred solvent followed by reaction for 1 hour afforded 1-naphthol in 93% yield (ref.52).



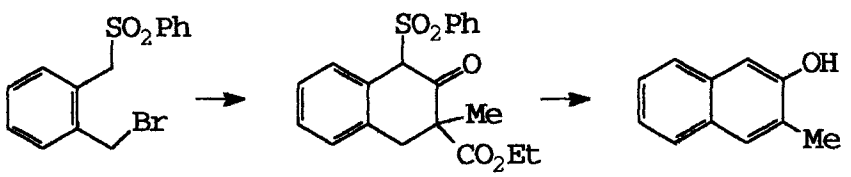
The bicyclic cyclohexenone shown, prepared by Diels-Alder addition from 2-acetamido-3-iodo-1,4-benzoquinone and 1-methoxy-2-methyl-3-trimethylsiloxy-1,3-butadiene by treatment with 2M hydrochloric during 20 mins. at ambient temperature and aeration gave the naphthoquinone in 78% yield (ref.53).



Certain bridged benzocyclohexanones can give 1-naphthols merely by thermal treatment as seen with 3,4-benzo-6-methylenebicyclo[3.1.0]hex-3-ene-2-one,in 1,2-ethanediol at 150°C for 1 hour, which gave 3-hydroxymethyl-1-naphthol in quantitative yield (ref.54). Irradiation was also effective.

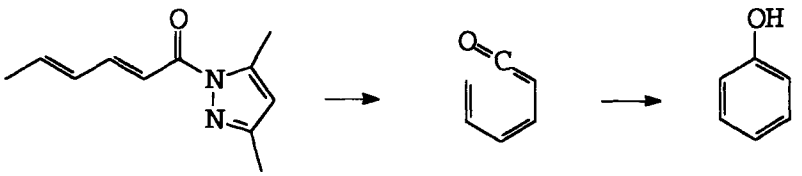


By contrast with the preceding, 2-naphthols can be obtained essentially from 1,2-xylylenedibromide as the starting material. Conversion to the phenyl-sulphonyl derivative followed by its addition in tetrahydrofuran solution to diethyl methylmalonate in tetrahydrofuran containing excess (6 mols.) sodium hydride and reaction during 0.5-1 hour, to complete cyclisation, afforded the tetralone shown in 80% yield. This upon desulphonylation and aromatisation produced 3-methyl-2-naphthol (ref.55).

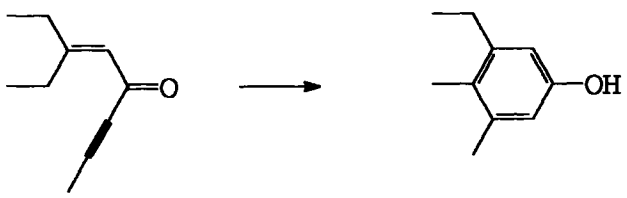


2.3.5 Formation of phenols from an acyclic precursor

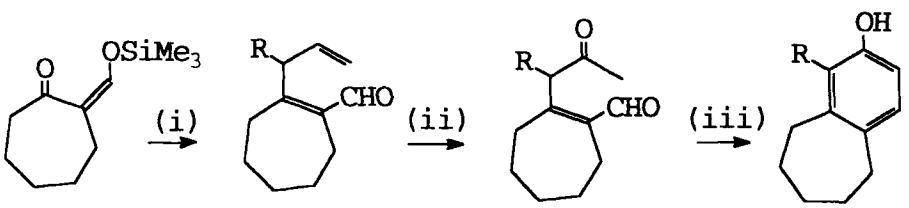
A review has appeared on this subject (ref.56). Remarkably little work has been reported on the conversion of C_6 acyclic intermediates and homologous substances to phenolic compounds although in the extant investigations in the last decade considerable ingenuity has been shown as in the following two thermal methods. Flash vacuum pyrolysis of 1-[(E,E)-hexa-2,4-diene-1-oxo]-3,5-dimethylpyrazole at 650°C or at 80°C under 10-3mm. Hg for 90 min. gave phenol in 93% yield by way of a reactive ketene intermediate (ref.57).



The eneynone, 3-ethyl-5-oxo-oct-3-ene-6-yne in toluene solution upon heating with collidine 4-toluenesulphonate at 250°C, formed 3,4-dimethyl- 5-ethylphenol in 82% yield (ref.58). Although strictly this synthesis is relevant to the preparation of alkylphenols, it is conceivable that the parent C_6 enynone, or a derivative,could be used for phenol itself.



Cycloheptanophenols have been formed from 1-formyl-2-(2-oxopropyl)-cyclohept-1-enes by the route shown. The 2-enol of 2-formylcycloheptanone as the trimethylsilyl ether reacted with an allylic Grignard reagent to afford, upon acidification, an intermediate which underwent 'Wacker' oxidation to a ketoaldehyde. Cyclisation of this with methanolic potassium hydroxide gave the product (ref. 59).



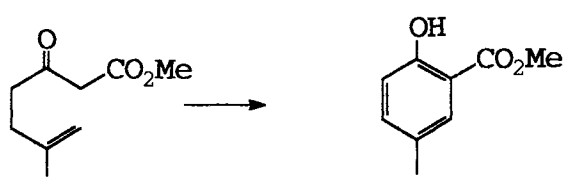
(i) CH_2=CHCH(R)MgCl;H_3O^+, (ii) O_2, $PdCl_2$, (iii) MeOH, KOH

Cyclisation of a stirred mixture of 3-methyl-6-(6-methyl-5-hepten-2-yl)-2,4-hexadienoic acid in refluxing acetic anhydride containing fused sodium acetate during 30 hours led to 5-methyl-2-(6-methyl-5-hepten-2-yl)phenyl acetate in 70% yield (ref.60).

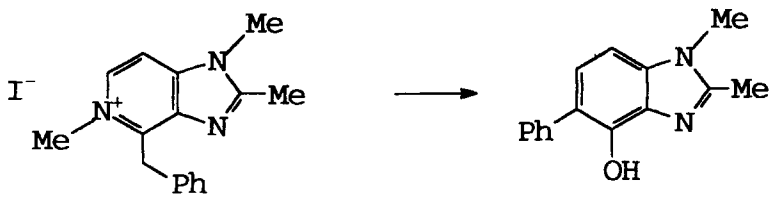
R = -CH(Me)CH_2CH_2CH=CMe_2

A structurally related acid, 3-methoxycarbonyl-5-methylhexa-3,5-dienoic acid in dichloromethane solution with N-methylmorpholine and diphenylphosphinic chloride in the same solvent at -23°C was stirred for 0.5 hour and triethylamine added to the mixture which was then allowed to reach ambient temperature over approximately 1.5 hours. Methyl 3-hydroxy-5-methylbenzoate was obtained in 50% yield (ref.61) by a process having some similarity to Horner-Emmons methodology.

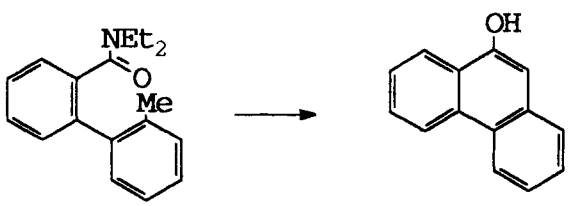
An oxidative procedure was adopted for the cyclisation of a β-keto ester, methyl 3-oxo-6-methylhept-6-enoate in acetic acid containing excess Mn(III) acetate and lithium chloride, initially at ambient temperature for 24 hours and finally at 100°C for a similar period with the addition of more lithium chloride. The product, methyl 5-methylsalicylate was produced in 71% yield (ref.62).



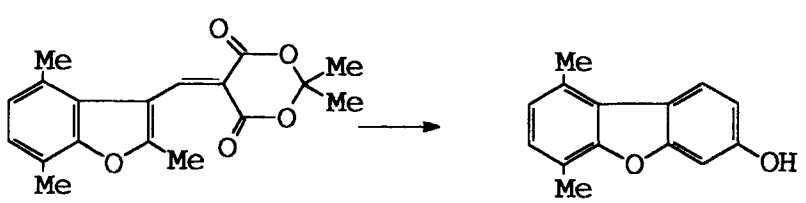
In both this and the preceding route hydrolysis and decarboxylation could be used to obtain 4-methyl and 3-methylphenol respectively. The bicyclic imidazole, 4-benzyl-1,2,5-trimethyl-1H-imidazo[4,5-c]pyridinium iodide upon heating with potassium hydroxide in ethanol/water (10:1) during 2 hours afforded 4-hydroxy-5-phenyl-1,2-dimethylbenzimidazole in 95% yield apparently by an alkylation/recyclisation (ref.63).



In the polycyclic field it has been reported that 2-methyldiphenyl-2'-N,N-diethylcarboxamide with excess lithium diethylamide in tetrahydrofuran at 0°C, by subsequently warming during 3 hours to ambient temperature gave 9-phenanthrol in 92% yield (ref.64).

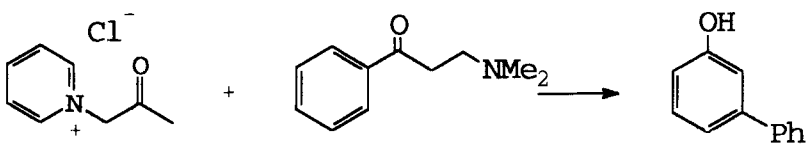


The 'Meldrum acid' condensate with 3-formyl-2,4,7-trimethylbenzofuran namely 5-(2,4,7-trimethyl-3-benzofurylidene)-2,2-dimethy-1,3-dioxan-4,6-dione by flash vacuum pyrolysis at 650 C and 0.02mm Hg in an open silica tube afforded 6,9-dimethyldibenzofuran-3-ol in 82% yield, (ref.65).

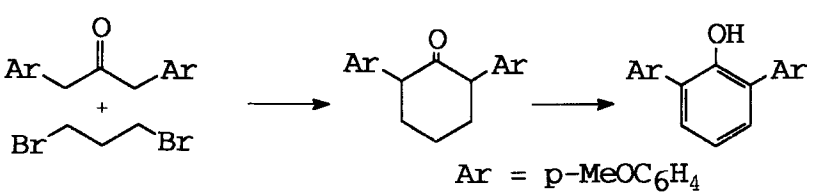


2.3.6 Formation of phenols from reactions of two acyclic precursors

A variety of approaches has been adopted in the following methods which involve comparatively unusual and neglected routes to phenols. Syntheses described in this section have been employed to obtain cycloaromatic structures and bicyclic heterocyclic compounds containing the phenolic group. Methods involving the use of noble and transition metal compounds have invariably produced polyalkylphenols and these procedures are more appropriately considered in Chapter 6 although it is clear that there is a considerable overlap between the synthesis of monoalkylphenols and polyalkyl compounds.
3-Phenylphenol resulted in 83% yield by reaction of the aminoketonic salt from chloroacetone and pyridine with the Mannich base from acetophenone, formaldehyde and dimethylamine in hot ethanol containing triethylamine (ref. 66).

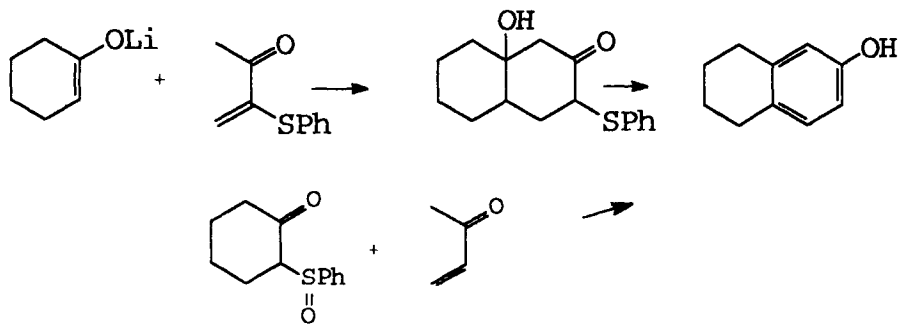


A double alkylation procedure followed by a dehydrogenation method has been employed for obtaining 2,6-diarylphenols. 1,3-Bis[4-methoxyphenyl]-2-propanone, tetrabutylammonium bromide together with 50% sodium hydroxide and chlorobenzene, treated dropwise with 1,3-dibromopropane at below 40°C followed by reaction over 16 hours afforded 2,6-bis(4-methoxyphenyl)cyclohexanone in 51% yield. Dehydrogenation with Pd-C gave the corresponding 2,6-diarylphenol (ref.67).

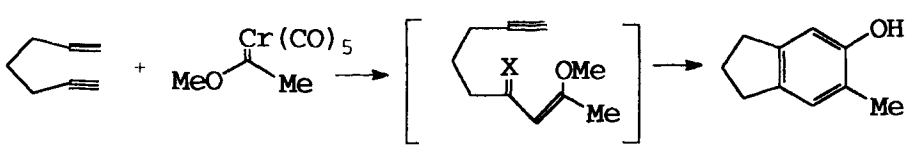


Diels-Alder and Michael addition reactions have been prominent. For the synthesis of 5,6,7,8-tetrahydro-2-naphthol, the lithium enolate of cyclohexanoe in tetrahydrofuran with 3-phenylthiobut-3-en-2-one at -70°C initially and then

at ambient temperature for 4.5 hours, gave the intermediate shown which by refluxing with 4-toluenesulphonic acid in benzene for 6.5 hours formed the product in 74% yield thus avoiding an unselective catalytic dehydrogenation stage (ref.68).



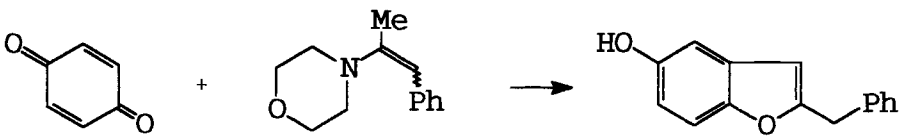
The presence of the SPh group would also enable alkyl derivatives to be obtained. A variation on this methodology is seen in the reaction at 0°C of the carbanion of 2-(phenylsulphinyl)cyclohexanone (obtained by the addition of NaOMe) with methyl vinyl ketone during 2 hours followed by further treatment with NaOMe and completion of the reaction over 31 hours at 25°C (ref.69).
By the use of cyclopentanone in a similar way the following compound could have been synthesised, although it was in fact derived by a totally different strategy. 1,6-Heptadiyne with a chromium carbene complex in deoxygenated tetrahydrofuran after heating at 70°C for 6.5 hours afforded 4,5-cyclopentano-2-methylphenol in 57% yield by a regiospecific double ring closure (ref.70).



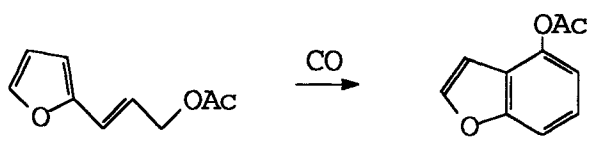
A related technique has involved the use of a substituted analogue, 4-alkyl-4-hydroxy-1,7-heptadiyne, to afford a 3-methyl-5-alkylphenol (ref.71) where the yields according to the type of alkyl group, R, were, with R = H, 35%, Me, 50%,

34%, i-Pr, 39% and t-Bu, 40%.
Similar diyne intermediates have been used by Volhardt and coworkers in an acylation/addition manner for steroid ring syntheses. Acetylenic precusors have also found a place in addition/acylation reactions. Propyne with 2,3-dimethylbut-3-en-oyl chloride gave 2,3,5-trimethylphenol and but-3-enoyl chloride with but-2-yne resulted in 2,3-dimethylphenol (ref. 72)..The outcome of using trimethylsilylacetylene in this reaction would be of interest.

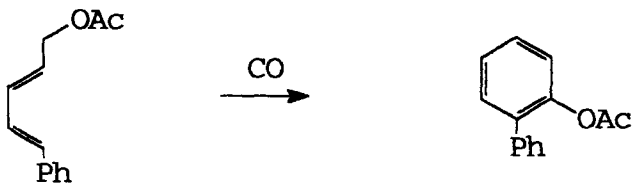
Enamines have enabled hydroxybenzofurans to be synthesised. 1,4-Benzoquinone in benzene treated with 2-(4-morpholino)-1-phenyl-1-propene at ambient temperature during 1 hour followed by hydrolysis of the intermediate with ethanolic hydrochloric acid gave 2-benzyl-5-hydroxybenzofuran in 46% yield, a compound relatively inaccessible by the standard intramolecular Claisen condensation (ref.73).



Palladium-catalysed insertion reactions have generally proved valuable for both bicyclic and tricyclic compounds. In this way 3-(2-furyl)allyl acetate with a little $PdCl_2(PPh_3)_2$ in benzene containing two proportions each of triethylamine and acetic anhydride in an autoclave pressured to 70Kg/cm^2 with carbon monoxide and heating of the mixture at 170°C followed by stirring for 1.5 hours, gave 4-acetoxybenzofuran in 85% yield (ref.74). In a similar way 7-acetoxybenzofuran was derived from 3-(3-furyl)allylacetate. By employing thiophene intermediates, the corresponding benzothiophenes were synthesised.



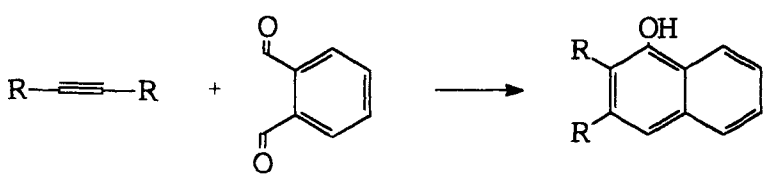
Dienoid systems have been investigated as in the insertion reaction of 5-phenylpenta-2,4-dienyl acetate with palladium(II)chloride bis(triphenylphosphine), together with 2 moles of acetic anhydride and 2.2 moles triethylamine heated for 3 hours at 140°C under carbon monoxide (50 ats), to afford a 69% yield of 2-phenylphenyl acetate (ref.75).



In a parallel way 1-acetoxydibenzofuran and 4- and 7-acetoxythianaphthenes were derived. Likewise 3-(2-naphthyl)allylacetate resulted in 4-acetoxy- phenanthrene in 73% yield (ref.76).

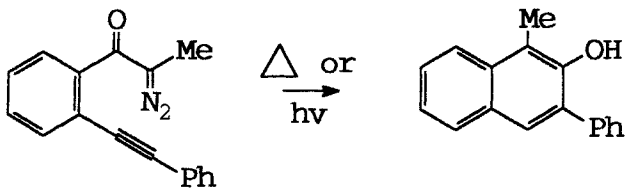
2.3.7 Formation of naphthols from benzenoid compounds and alkynes

1,2-Aryl dialdehydes were reacted with symmetrical dialkylacetylenes in the presence of a niobium(III) catalyst to afford 2,3-dialkyl-1-naphthols in high yield. With unsymmetrical acetylenes, the formation of two products is highly dependent upon the structure of the alkyl groups (ref.77).



In the case of 1-dodecyne, reaction with the same dialdehyde in the presence of niobium(V)chloride led to a variety of products, including 2-n-decylnaphthalene (23%), a minor proportion of 2-n-decyl-1-naphthol (14%), 2-n-decylnaphthalene-1,4-diol (2%) and 1-n-dodecene (ref.78).
The diazoketone shown upon irradiation, or thermal treatment, afforded a 2-naphthol derivative through intermediate formation of an arylketen (ref.79). By contrast,

reaction of the same diazoketone with ethyl vinyl ether in the presence of rhodium(II) acetate afforded an entirely different product.



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CHAPTER 3

REACTION OF THE HYDROXYL GROUP IN MONOHYDRIC PHENOLS

3.1 Introduction

The reactions of the phenolic hydroxyl group which have been included in this chapter comprise esterification with carboxylic acids and related reactants, with inorganic materials, with replacements producing nitrogen, sulphur and halogen-containing compounds, procedures for removal of the OH group and miscellaneous reactions.

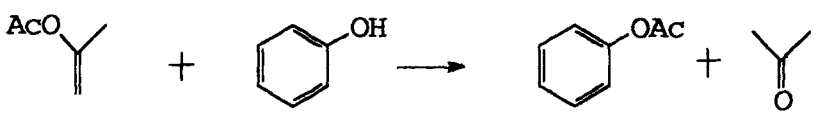
3.2 Phenolic Esters

3.2.1 From Alkane Carboxylic Acids and Related Reactants

Phenolic ester formation between a phenol and a higher carboxylic acid catalysed by a 4A molecular sieve has been described with a modification that after 1 hour at 120°C under nitrogen, boric oxide B_2O_3, was added, presumably to absorb water and the refluxing continued for 5 hours at 185°C (ref.1).

$$RCO_2H + PhOH \rightarrow RCO_2Ph \quad (R = C_8\text{-}C_{10})$$

Phenyl acetate results in nearly quantitative yield by the reaction of phenol with isopropenyl acetate in the presence of 0.2 equivalents of potassium carbonate (ref.2).



A stirred mixture of phenylmercuric acetate, peracetic and acetic acids together with iodobenzene at 75°C for 4 hours gave phenyl acetate in 75% yield. The corresponding tin, thallium, cadmium and lead compounds were reported to behave similarly (ref.3).

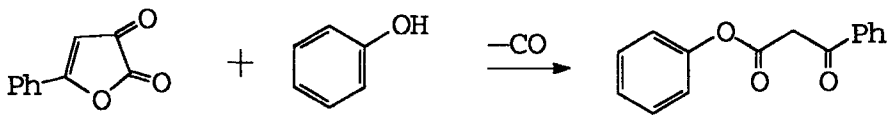
$$PhHgOAc + HOAc + HO_2Ac + PhI \rightarrow PhOAc$$

Phenol adsorbed on silica gel and treated at ambient temperature with a stream of ketene diluted with nitrogen gave an almost quantitative yield of phenyl acetate

(ref.4)

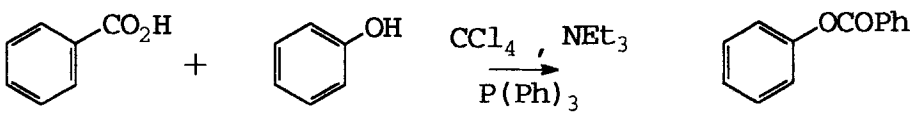
$$CH_2=C=O + PhOH \rightarrow PhOAc$$

Aryl esters of a 3-ketocarboxylic acid have been produced in 90% yield by the interaction of 5-phenyl-2,3-dihydrofuran-2,3-dione and phenol in benzene at 80°C for 2-3 hours (ref.5).



3.2.2 From Aromatic Acids and Other Reactants

Phenyl benzoate has been formed in 91% yield by the reaction of a stirred mixture of benzoic acid, phenol, carbon tetrachloride, triethylamine and triphenylphosphine in acetonitrile solution at ambient temperature for 3 hours (ref.6).



A benzene suspension of phenyl dichlorophosphite added with stirring and cooling to benzoic acid in pyridine during 2 hours gave, after treatment with excess phenol followed by refluxing of the mixture for 4-5 hours, phenyl benzoate in 85% yield (ref.7).

$$PhOH + PhCO_2H + PhOPCl_2 \rightarrow PhOCOPh$$

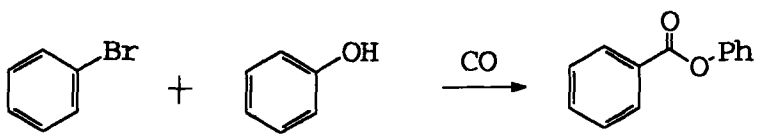
Diphenyl terephthalate was obtained with a conversion of 99.9% from a mixture of terephthalic acid, phenol, some tetra-n-butyl-1,3-diphenoxydistannoxane and platinum wire (pretreated with hydrogen) heated for 2 hours in an autoclave at 260°C under hydrogen (ref.8).

$$PhOH + C_6H_4(CO_2H)_2 \rightarrow C_6H_4(CO_2Ph)_2 + H_2O$$

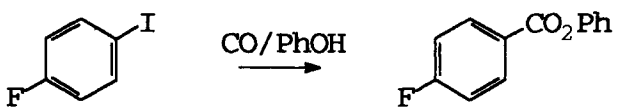
Amberlite IRA-400 (chloride form, P^+Cl^-) converted to the phenoxide form with 0.25M aqueous sodium phenoxide and reacted with a benzene solution of benzoyl chloride afforded phenyl benzoate in 95% yield. The resin was easily recycled by treatment with hydrochloric acid solution (ref.9).

$$P^+Cl^- \rightarrow P^+PhO^- \rightarrow PhOCOPh + P^+Cl^-$$

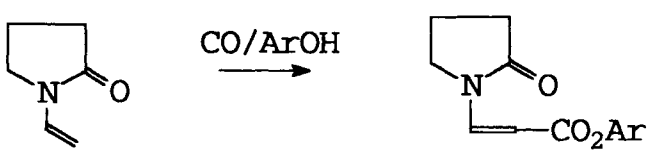
Aryl halides have been employed for ester formation in two related methods. Thus a mixture of phenol and bromobenzene reacted under a pressure of carbon monoxide (0.1-10.0 Kg/cm2) in the presence of a platinum metal catalyst and a base such as pyridine or triethylamine, afforded phenyl benzoate (ref.10).



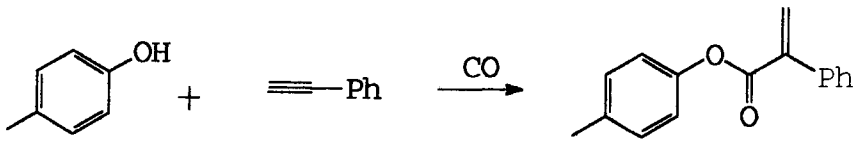
4-Fluoroiodobenzene with phenol and tri-n-butylamine and a catalyst, Ni(II) acetylacetonate in a stirred reactor under a CO pressure (50 Kg/cm2) at 200-220°C gave selectively a 91% yield of phenyl 4-fluorobenzoate (ref.11).



In a related manner but at ambient presure, unsaturated esters have been derived by, for example in 85% yield, the reaction of N-vinyl-2-pyrrolidinone with 2,6-dichlorophenol and CO in dichloromethane containing diisopropylamine and palladium chloride for 4 hours at ambient temperature (ref.12).



Phenylacetylene and 4 moles of 4-methylphenol in toluene together with a catalytic proportion of palladium(II) acetate when heated for 10 hours at 100 C under a 1 atmosphere pressure of carbon monoxide afforded in 83% yield the α-methylenic aryl ester shown (ref.13).

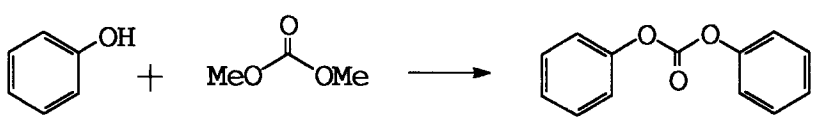


3.2.3 Formation of Diaryl Carbonates

Some novel procedures have been introduced for the synthesis of diaryl carbonates, substances of interest in polymer chemistry. Unsymmetrical compounds in the series have been obtained by the slow addition over 5 hours at 0°C of 4-methoxyphenol (ArOH) to a stirred suspension of N-(dichloromethylene)dimethyl ammonium chloride in dichloromethane followed by treatment of the mixture with phenol and continuation of stirring for 10 hours. 4-Methoxyphenyl phenyl carbonate was produced in 80% yield and by similar processes, thiocarbonates and carbamates were
derived (ref.14).

$$ArOH + Cl_2C{=}N^+Me_2Cl^- + PhOH \rightarrow ArOCO_2Ph$$

Transesterification of dimethyl carbonate by phenol, catalysed with dioctyl tin oxide and titanium tetra-isopropoxide, has been effected by passage of the mixture through 5A molecular sieve at 175-185°C under pressure (203 Bar). Unreacted starting materials were removed separately by heating at 185-195°C for 2 hours to give diphenyl carbonate in 85% yield (ref.15).



A similar technology for diphenyl carbonate with di(2,2,2-trifluoroethyl) carbonate and phenol in refluxing heptane containing sodium methoxide has been patented (ref.16).

$$2PhOH + CF_3OCO_2CF_3 \rightarrow PhOCO_2Ph + 2CF_3OH$$

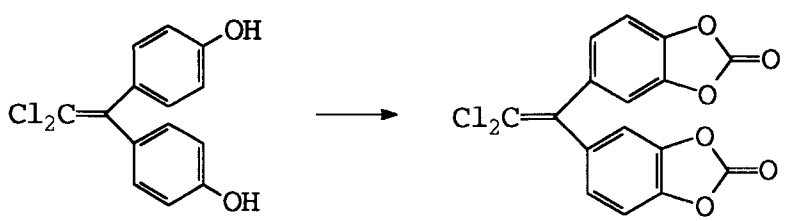
Phenyl chloroformate and phenol in 1,2-dichlorobenzene containing a little triphenylphosphine after reaction at 150°C until hydrogen chloride was no longer evolved, which was approximately 24 mins., gave an 84% yield of diphenyl carbonate (ref.17).

$$ClCO_2Ph + PhOH \rightarrow PhOCO_2Ph + HCl$$

In a further variation, a mixture of phenol and O-phenyl S-methyl thiocarbonate when refluxed for 1 hour in decane containing 15-20 weight% of sodium carbonate afforded diphenyl carbonate in 85% yield (ref.18).
Transesterification of phenol with 2-nitrophenyl carbonate in dichloromethane containing 1 mole % of 4-dimethylaminopyridine for 2 hours at 25°C afforded a quantitative yield of diphenyl carbonate (ref.19).

$$2PhOH + (2\text{-}NO_2C_6H_4O)_2CO \rightarrow PhOCO_2Ph + 2(2\text{-}NO_2C_6H_4OH)$$

The mixed allyl aryl carbonate, $CH_2{=}CHCH_2OCO_2Ph$, was formed when to a solution of phenol and bis(trichloromethyl) carbonate in dichloromethane pyridine was added dropwise with stirring for 1/2 hour and then allyl alcohol introduced followed by further pyridine and stirring of the mixture for 2 hours prior to aqueous quenching and work-up to give the product in high yield (ref.20).
Intramolecular rather intermolecular carbonylation involving formation of a cyclic carbonate with 67% conversion took place in the case of 1,1-dichloro-2,2-bis(4-hydroxyphenyl)ethene, in the presence of cupric bromide, N,N-diisopropylamine, and a catalyst, dibromo bis-(benzonitrile)palladium(II), in dichloromethane containing 4A molecular sieve, followed by saturation of the mixture with carbon monoxide, pressurisation with oxygen and carbon dioxide (each at 31psi) and completion of reaction by stirring at ambient temperature for 78 hours (ref.21).



3.2.4 Formation of Thionecarbonates, Thiolcarbonates, Xanthates, Chlorothioneformates, and Carbamates

A variety of these functional types have been made with phenolic precursors. Nucleophilic attack by carbon disulphide on an activated phenoxide has been employed for the first group. Sodium 4-bromophenoxide in acetonitrile containing cuprous chloride, stirred under nitrogen for 1 hour, treated with triethylamine during a further hour and finally reacted with carbon disulphide until the mixture became brown-coloured gave di-(4-bromophenyl)thionecarbonate in 98% yield (ref.22).

$$4\text{-}BrC_6H_4ONa \rightarrow \rightarrow (4\text{-}BrC_6H_4O)_2C{=}S$$

o-Aryl monothiolcarbonates have been obtained in 60% yield from a potassium phenolate in dioxan/dimethyl sulphoxide and carbon oxysulphide during 3 hours at ambient temperature followed by alkylation with a primary halide (PrI) as shown (ref.23).

$$ArOK + O{=}C{=}S + PrI \rightarrow ArOCOSPr$$

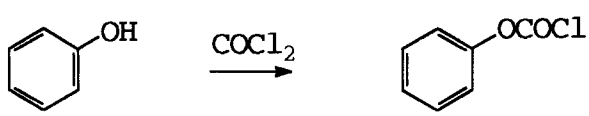
Aryl xanthates have been derived in 90% yield by a phase transfer-catalysed method. The phenol and iodomethane were added to the two-phase system of 50% aqueous sodium hydroxide containing tetra-n-butylammonium bisulphate and carbon disulphide and the mixture stirred vigorously for 0.5 hour (ref.24).

$$ArOH + CS_2 + MeI \rightarrow ArOCS_2Me$$

Chlorothioneformates, useful as general intermediates have been produced in 95% yield by the following technique. Sulphur dioxide was introduced at 0-10°C into a two-phase mixture of trichloromethyl thiol in carbon tetrachloride/water containing some potassium iodide and, after removal of the aqueous layer, 3-tert-butylphenol followed by 10% aqueous sodium hydroxide was added. Stirring of the mixture at ambient temperature and work-up gave the product apparently without formation of the thionecarbonate (ref.25).

$$3\text{-t-}BuC_6H_4OH + CCl_3SH \rightarrow 3\text{-t-}BuC_6H_4OCSCl$$

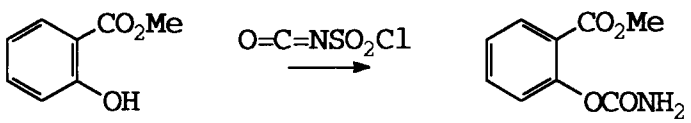
A number of developmental methodologies which are of interest in the herbicidal field have been examined for the formation of carbamates and related intermediates . Phosgene and phenol reacted in the presence of triphenylphosphine and a quaternary ammonium salt catalyst at 120-125°C over a total period of 10 hours gave phenyl chloroformate in 89% yield (ref.26).



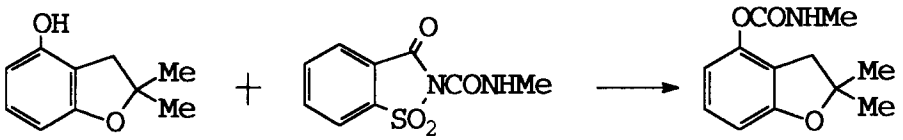
Vinyl isocyanate added slowly to 2-(1-methoxy-2-chloroethoxy)phenol (2-HOC_6H_4OR, R = $CH(OMe)CH_2Cl$) in toluene containing triethylamine and the reaction completed at 40-50°C during 1 hour afforded the corresponding vinyl carbamate in 57% yield. The technique is probably of general application and may have synthetic potential (ref.27).

$$2\text{-}ROC_6H_4OH + CH_2{=}CHNCO \rightarrow 2\text{-}ROC_6H_4OCONHCH{=}CH_2$$

A parent unalkylated compound in the series has been formed by adding chlorosulphonyl isocyanate in dichloromethane to methyl salicylate at 4-6°C, reacting for a further 3 hours at ambient temperature, removing the solvent and hydrolysing the intermediate at 5-10°C with cold water to give the product shown in 83% yield (ref.28).



Formation of the methylcarbamate of 2,3-dihydro-2,2- dimethyl-4-hydroxy benzofuran in 57% yield has been reported from the N-methylamido derivative of saccharin through nucleophilic substitution by the addition of triethylamine in aqueous acetone (1:2) at ambient temperature over 2 hours (ref.29).



Transesterification has been used for carbamate formation. Methyl N-methylcarbamate added to a mixture of phenol and a small amount of titanium(IV) ethoxide in 1,2-dichlorobenzene at 180°C with removal of methanol in a stream of nitrogen over 8 hours resulted in phenyl N-methylcarbamate in 100% conversion with 85% selectivity (ref.30).

$$MeOCONHMe + PhOH \rightarrow PhOCONHMe + MeOH$$

A stirred mixture of 1-naphthol and 2 moles of the same reagent treated dropwise with 2 moles of phosphorus oxychloride and reaction continued for 7 hours at 60°C afforded after work-up by quenching with ice-cold water an 88% yield of 1-naphthyl N-methylcarbamate (ref.31).

$$C_{10}H_7OH + MeOCONHMe \rightarrow C_{10}H_7OCONHMe + MeOH$$

3.2.5 Formation of phenolic esters with phosphorus acids and related compounds

In this group developments in the formation of aryl phosphites, aryl phosphates and structurally related compounds are considered.
Diaryl phosphites have been reported to form in nearly quantitative yield by the simultaneous addition of phosphorus trichloride and 38% hydrochloric acid (fuming HCl) to a two molar proportion of phenol, continuation of stirring for 2 hours and standing of the mixture during 8-10 hours (ref.32).
Triphenyl phosphite has been synthesised in 86% yield by the addtion of tris(dimethylamino)phosphine to 3 moles of phenol in the presence of imidazole in carbon disulphide/benzene and stirring of the mixture at ambient temperature for 24 hours. Mixed esters were obtained by interception of the intermediate (ref.33).

$$3PhOH + (Me_2N)_3P \rightarrow [PhOP(NMe_2)_2] \rightarrow \rightarrow (PhO)_3P$$

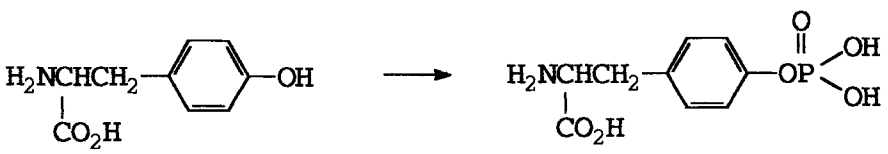
The formation of phosphorodichloroidites in 67% yield from phenols has been described, in particular from 2,6-di-tert-butylphenol with phosphorus trichloride in the presence of some 1,8-bis(dimethylamino)naphthalene by refluxing for a total period of 37 hours (ref.34).

$$2,6\text{-di-t-Bu}C_6H_4OH + PCl_3 \rightarrow 2,6\text{-di-t-Bu}C_6H_4OPCl_2 + HCl$$

By the dropwise addition of phosphorus oxychloride during 20 minutes to a heterogeneous mixture of aqueous sodium phenoxide and chloroform with the catalyst Aliquat 336 in a baffled mechanical agitated reactor followed by further stirring for 40 minutes, triphenyl phosphate was obtained in 89% yield (ref.35).

$$3PhONa + POCl_3 \rightarrow (PhO)_3P{=}O + 3NaCl$$

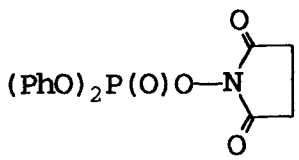
A related procedure giving a 90% yield has been described in which phosphorus oxychloride in chloroform was added to a stirred paste of chloroform, water and sodium phenoxide containing a catalytic quantity of polyethyleneglycol 400 (ref.36).
L-Tyrosine has been phosphorylated quantitatively by addition to a stirred mixture of phosphorus pentoxide and 85% orthophosphoric acid followed by heating at 80°C for 24 hours, after which water was introduced, the mixture was cooled, diluted with n-butanol and kept at 0°C for 3 hours to precipitate the product (ref.37).



Diphenyl phosphate and phenyl iodosoacetate have been reacted together in acetonitrile containing a little water at ambienttemperature for 24 hours to give hydroxy[bis(phenoxyphosphoryloxy]iodobenzene in 90% yield (ref.38).

$$PhI(OAc)_2 + (PhO)_2PO_2H \rightarrow PhI(OH)OPO(OPh)_2$$

One of the intermediate products from the reaction of phosphorus oxychloride with phenol, diphenyl chlorophosphate, $(PhO)_2POCl$, interacts with N-hydroxysuccinimide in dichloromethane at 15°C to afford the mixed ester shown (ref.39).



Thiophosphorus compounds and their reactions have been studied. Phenols such as 4-tert-butylphenol with red phosphorus and sulphur in equivalent amount heated from 150 to 220°C in 8.5 hours gave tri(4-tert-butylphenyl)thionophosphate in 93% yield (ref.40).

$$ArOH + P + S \rightarrow (ArO)_3P{=}S$$

The intermediate reaction product of stirred chloromethylthiophosphonyl dichloride in chloroform containing triethylamine was treated with iso-propylamine in chloroform at 5-10°C, then after 1 hour at ambient temperature followed by cooling to 2-4°C, 2-chloro-4-methylphenol (ArOH) and triethylamine were added and after reaction at 35-50°C for 1 to 1.5 hours the final product 2-chloro-4-methylphenyl, N-iso-propylamino (chloromethyl)thionophosphonate was isolated in 55% yield (ref.41).

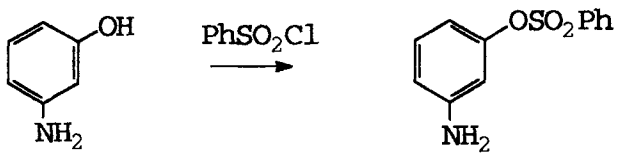
$$ClCH_2PSCl_2 + i\text{-}PrNH_2 + ArOH \rightarrow ClCH_2PS(OAr)(NHiPr)$$

The formation of an aroxylamine, O-phenylhydroxylamine, results from the addition of potassium phenoxide in dimethylformamide to mesityl sulphonylhydroxylamine in the same solvent at 0°C with subsequent stirring for 0.5 hour in 82% yield (ref.42).

$$ArOH + Me_3C_6H_2SO_2ONH_2 \rightarrow ArONH_2 + Me_3C_6H_2SO_3H$$

3.2.6 Formation of phenolic esters with sulphuric acid and related compounds

O-Sulphonation in 93% yield of 3-aminophenol in water/chlorobenzene containing sodium carbonate and some tri(C_8-C_{10})alkylmethylammonium chloride has been achieved with benzenesulphonyl chloride added over 2 hours at 35-40°C and pH control at 10.5-10.8 by means of sodium hydroxide solution (ref.43).



3-Hydroxybenzo[a]pyrene (ArOH) in dimethylformamide with sulphuric acid in the presence of dicyclohexylcarbodiimide at 0°C afforded an 85% yield of the corresponding sodium O-sulphate after neutralisation and purification on a DEAE column with methanolic elution (ref.44).

$$ArOH + H_2SO_4 \rightarrow [ArOSO_3H] \rightarrow ArOSO_3Na$$

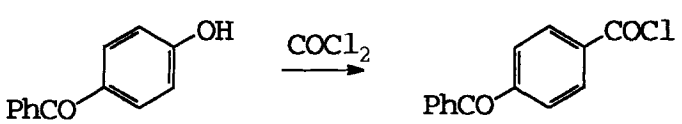
A 4-tosyl ester has been prepared in 70-80% yield from a phenol (human calcitonin) in 0.02M lithium carbonate at pH 10-11.5 by the use of the reagent 1-tosyl-4-dimethylaminopyridinium chloride added at 5°C (ref.45).

$$4\text{-}NMe_2C_5H_4N^+SO_2C_6H_4Me\ Cl^-$$

3.3 Replacement of the Hydroxyl Group

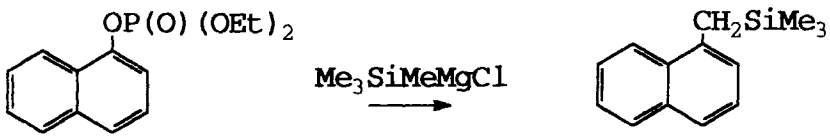
3.3.1 By substituents other than hydrogen

The hydroxyl group has been replaced by a variety of substituents in some unusual reactions. 4-Hydroxybenzophenone and benzyltriethylammonium chloride in o-xylene upon treatment under anhydrous conditions with phosgene at 95-120°C during 5.5 hours gave 4-chloroformylbenzophenone in 99% yield (ref.46).



1-Naphthyl diethyl phosphate stirred with trimethylsilylmethyl magnesium chloride in ether containing nickel acetoacetonate at ambient temperature during 10 hours

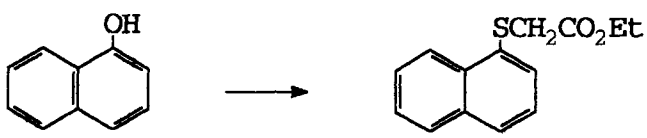
afforded 1-trimethylsilylmethylnaphthalene in 79% yield (ref.47)



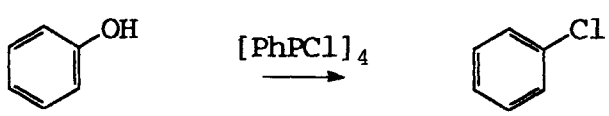
2-Methylphenol has been converted by way of the diethylaminothionecarbamate to the diethylaminothiol carbamate, (through the Newman-Kwart rearrangement), which in 80% acetic acid with excess chlorine gave 2-methylbenzene sulphonyl chloride in 95% yield, (characterised in 94% yield as the dimethylamide by reaction with 40% aqueous dimethylamine) (ref.48).

$$ArOH \rightarrow ArOCSNEt_2 \rightarrow ArSCONEt_2 \rightarrow ArSO_2Cl \rightarrow ArSO_2NMe_2$$

1-Naphthol with ethyl thioglycollate in benzene upon dropwise treatment with trifluoromethanesulphonic acid followed by stirring of the mixture at 50°C for 3 hours gave ethyl 1-thionaphthoxyacetate in 88% yield (ref.49).



An unusual replacement has been described in the conversion of phenol to chlorobenzene in 76% yield by addition at 70-80°C to molten tetrachlorophenylphosphorane (from chlorine and phenyldichlorophosphine at 70-80°C) and heating of the mixture to 160°C for 16 hours (ref.50).

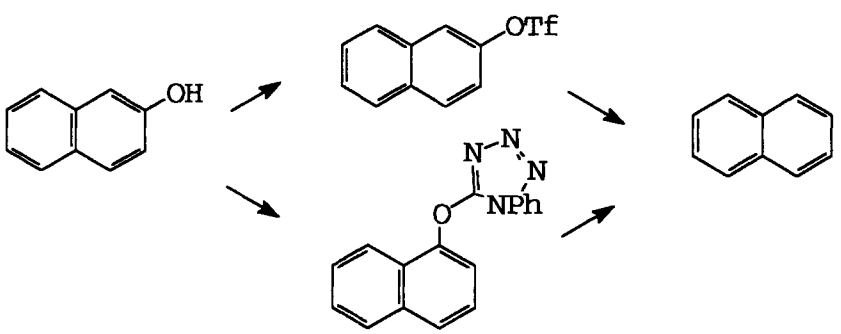


3.3.2 Replacement by Hydrogen

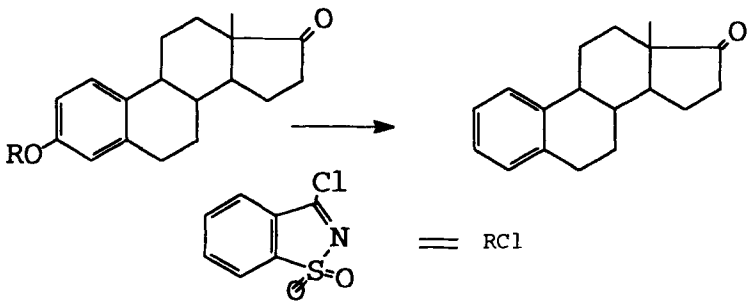
Several processes are available for the removal of the phenolic group (dehydroxylation). 2-Naphthyl triflate in dimethylformamide containing triethylamine, Pd(II) acetate and triphenylphosphine, after treatment with 99% formic acid and stirring of the mixture at 60°C for 1 hour under nitrogen furnished naphthalene in 91% yield (ref.51).

A 'transfer' hydrogenation modification has been described of a known dehydroxylation procedure (ref.52) in which the phenyl ether with 1-chloro-2-phenyltetrazole is used. The tetrazolyl ether stirred in benzene/ethanol/water (7:3:2) with 10% Pd-C was treated dropwise with 64% aqueous hydrazine, with TLC monitoring for completion of reaction, to give naphthalene in 82% yield (ref.53).

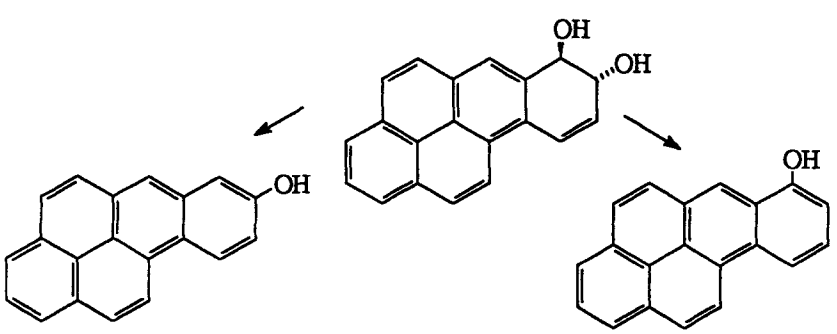
Both these procedures are depicted in the following scheme.



A superior method was used for the dehydroxylation of estrone in 96% yield by initial reaction with 3-chloro-1,2-benzoisothiazole-1,1-dioxide (RCl) in refluxing toluene containing triethylamine (yield 100%) followed by heating in benzene with aqueous sodium hypophosphite for 15 minutes in the presencs of 10% Pd-C (ref.54).



2-Naphthyl tosylate, formed from 2-naphthol and sodium hydride with tosyl chloride in THF, with nickel chloride hexahydrate in chloroform/methanol (1:1) by treatment with excess sodium borohydride at 0 C afforded a 96% yield of naphthalene although isolated keto and alkene groups were also susceptible (ref.55).
Dehydroxylation accompanied by ring reduction of 1,1-bis(4-hydroxyphenyl)-cyclohexane in ethylcyclohexane containing some ruthenium and Galleon earth took place when the mixture was heated under hydrogen (75Kg/cm2) for 2 hours at 120°C then for a similar time at 190°C to give a 99% yield of 1,1-dicyclohexylcyclohexane (ref.56).
Trans-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene under basic conditions with tetrabutyl- ammonium hydroxide in methanol followed by evaporation at 61°C under nitrogen gave an 89% yield of the 8-hydroxy compound while in methanolic phosphoric acid the 7-hydroxy compound resulted in 97% yield presumably due to the more stable allylic carbocation formed under these conditions while the more acidic benzyl group favoured the 8-isomer (ref.57).



The deoxygenation of a polyphenolic melanin precursor can be effected biologically and the role of NADPH in this has been studied (ref.58)

3.4 Miscellaneous Reactions

3.4.1 Protection of the Phenolic Group

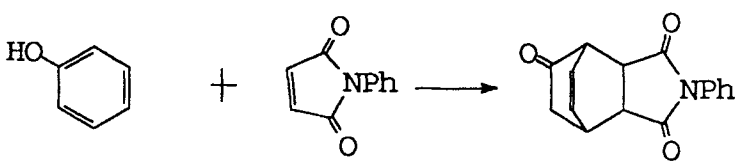
Although the esterifiction of phenols and also their etherification (considered in the next chapter) can be regarded as protective methods for the phenolic hydroxyl group there have been few developments in this aspect of phenolic chemistry. The definitive text on this topic remains relevant (ref,59).

It is interesting to note that 2-methyl and 2,6-dimethylphenol afford better protecting systems than 4-hydroxydiphenyl for phosphopeptide syntheses by solid phase techniques (ref.60).

The 2-bromophenyl group in a phosphoryl compound was selectively removed over 2 hours by treatment in pyridine/water (9:1) with copper(II) acetate without the nucleotide being affected (ref.61).

3.4.2 Diels-Alder Addition

It has been reported that a 2:1 mixture of phenol and N-phenylmaleimide heated at 170°C for 3 days afforded an adduct in 36% yield. It seems probable that this reaction depends on the formation of a keto tautomer (ref.62).

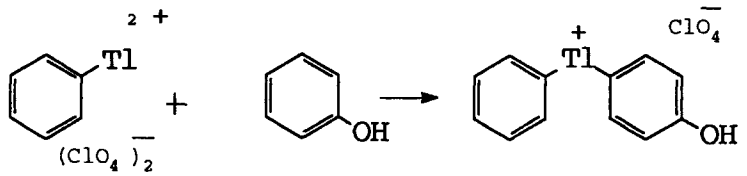


3.4.3 Deuteration

Phenol in 10% sodium deuteroxide in deuterium oxide upon treatment with Raney nickel-aluminium alloy and heating at100°C for 3 hours afforded a pentedeurated product in 86% yield (ref.63).

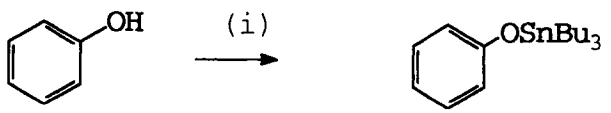
3.4.4 Reaction with organometallic reagents

Thallation in the 4-position of phenol was effected by its reaction in acetonitrile with [phenylthallium(III)(18-crown-6)] diperchlorate under reduced pressure for 4 days at 60°C in the dark to afford in 97% yield [phenyl(4'-hydroxyphenyl-thallium(18-crown-6)]perchlorate (ref.64).



18-crown-6

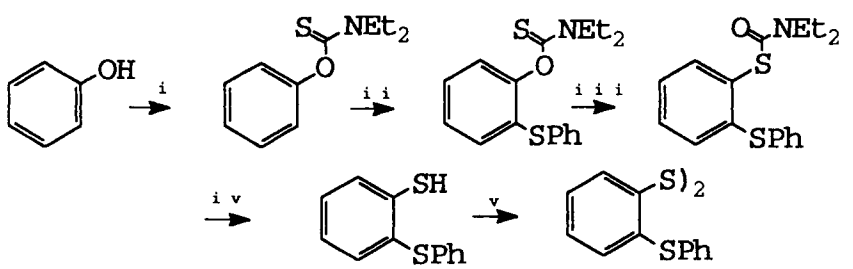
By contrast, tri-n-butyltin methoxide reacted at the hydroxyl group rather than the ring to afford tri-n-butyltin phenoxide in 100% yield by dropwise addition of the reagent under nitrogen to a refluxing solution of phenol in 1,2-dichloroethane and reaction over 2-3 hours (65).



(i) $MeOSnBu_3$,CH_2ClCH_2Cl

3.4.5 Thiophenol Derivatives

After conversion of phenol to O-phenyl diethylthiocarbamate, 2,2'-di(phenylthio)diphenyl disulphide has been obtained by the steps indicated (ref. 66).



(i) s-BuLi,Et_2NCSCl,TMEDA, (ii) $(PhS)_2$ (iii) Δ, 250°C (iv) MeOH, KOH (v) oxidn

A reaction involving sulphur chemistry although more relevant to section 3.2.6 is the finding that phenols react with 1-benzenesulphonylbenzotriazole in THF solution containing 1-methylimidazole at ambient temperature over 72 hours to give O-benzenesulphonyl deivatives in yields of 51-99% (ref.67).

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CHAPTER 4

PHENOLIC ETHERS OF HYDROXY AROMATICS

4.1 Introduction

During the preceding decade much has been published on the chemistry of phenolic ethers and for this reason this class of materials justifies separate consideration rather than review under the reactions of the phenolic group. In this account the preparations of ethers from monocyclic sources with a variety of alkylating agents and those from bicyclic/polycyclic sources are described. Syntheses of phenolic ethers from non-phenolic reactants and from open-chain precursors are considered next and subsequently the demethylation, demethyloxylation, substitution, coupling and other general reactions of aryl ethers.

4.2 Synthesis of Phenolic Ethers

4.2.1 From Phenolic Intermediates by Intermolecular Reactions

These procedures illustrate a remarkable range of reaction environments and 'leaving' groups, with the general feature that more drastic conditions, usually higher temperatures are necessary for less effective leaving groups or under circumstances where an S_N2 nucleophilic substitution reaction with a powerful nucleophile is inoperative. Table 4.1 (refs.1-9) lists a summary of the methylation conditions and yields in the preparation of phenyl methyl ether (anisole) from phenol. Table 4.2 (refs.10-16) shows a further number of phenyl ether syntheses which have involved excellent leaving groups, unusual bases, the use of crown ethers or calixarenes serving to render the phenoxide more 'naked'. Phase-transfer catalysis, accepted as a universal part of methodology, does not noticeably feature. Table 4.3 (refs.17-27) summarises a number of addition reactions used for the preparation of phenyl ethers (particularly refs.17,19) and a phase-transfer method (ref.25) enabling an ester functional group to be retained and in another case (ref.27) resulting in the formation of a methoxycarbonyl group. Table 4.4 (refs. 28-31) records a number of predictable transformations including that of a 1,3-benzodioxan, presumably by way of a hemiacetal, instead of acetaldehyde diphenylacetal. In the case of ref.29 the product is likely to be the *trans* compound. The reaction of α,β-unsaturated aldehydes is more complicated. Thus, 3-methylbut-2-enal with 2

TABLE 4.1 **THE SYNTHESIS OF ANISOLE AND A RELATED ETHER**

MATERIAL	METHYLATING AGENT	CONDITIONS	(ANISOLE)	YIELD%	REF
Phenol	MeOH	PhOH in MeOH at 1 ml/min. through a tubular reactor containing $Ce(SO_4)_2$-Al_2O_3 catalyst at 300° (50-55 psig).	conversion selectivity	38 95	1
Phenol	$(MeO)_2C=O$	PhOH/Me_2CO_3 (equimolar) vapour phase over Al_2O_3 at 239° with contact time 10.8 sec.	selectivity	74	2
4-Cresol	MeOH	4-MeC_6H_4OH/MeOH with argon over Zeosorb 13X/K catalyst at 4.36 l/h with contact time 1.34 sec. (catalyst from activation of Zeosorb-type mol. sieves at 450° for 1-2 h and exchanging 36.8% Na^+ with K^+ from 0.25 M KCL).	(4-Me anisole)	94.2	3
Phenol	Me_2O	Mixture of PhOH and acidic form of polystyrene sulphonic acid heated to 120°, treated with Me_2O over 2.5 h.	-		4
Phenol	MeOH	Phenol (94 g) and 60% benzene sulphonic acid, heated to 130°, diluted with xylene, refluxed, MeOH added, azeotropic water removal and reaction for 5 h, giving 75 g anisole.	conversion selectivity	69 95	5
Phenol	Me_2O	PhOH, Me_2O and BPO_4 in toluene (and a little H_2O) heated at 280° and 40 Atm. in autoclave for 48 h.		53	6
Phenol	Cl_3CCl_2Me	PhOH, Cl_3CCO_2Me, and catalytic amts. K_2CO_3 and 18-crown-6 heated to 150° and maintained until CO_2 and $CHCl_3$ evolution ceased (1-2 h).		96	7

TABLE 4.1 (contd.)

Phenol	$P(OMe)_3$	Phenol and trimethylphosphite in THF treated with diethyl azodicarboxylate, and solvent removed after 2h.	86	8
Phenol	Me_2SO_4	Phenol, in 1,4-dioxan, treated at 65° with powdered KOH, 1 equiv. Me_2SO_4 added (3 drops/5 min.) and reacted for 1.5 h.	90	9

TABLE 4.2 THE SYNTHESIS OF AROMATIC ETHERS

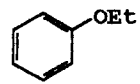
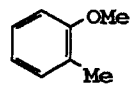
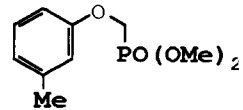
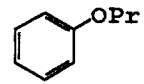
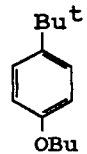
MATERIAL AGENT	METHYLATING	CONDITIONS	PRODUCT	YIELD (%)	REF.
Phenol	iodoethane	Catalytic quantity of dicyclohexyl 18-crown-6 and a copolymer of 2-vinylpyridine and styrene, together with ethyl iodide and aq. KOH added to PhOH in $CHCl_3$. Refluxed 6h to give phenetole.		97	10
2-Methylphenol	ethyl fluoro-sulphonate	To 2-methylphenol in aq. NaOH at 5-10° ethyl fluoro-sulphonate added with vigorous stirring and mixture heatedat 40° for 0.5h., to give 2-methylphenyl methyl ether.		69.7	11
3-Methylphenol	dimethyl 4-tosyloxy methylphosphonate	3-Methylphenol, NaH in DMSO and the phosphonate (5-10%XS) stirred 16h., to give dimethyl 3-methyl - phenoxymethylphosphonate.		95	11a
Phenol	1-iodopropane	PhOH, 1,8-diazabicyclo[5,4,0]undec-7-ene and C_3H_7I in ethanol refluxed for 3h., to give n-propyl phenyl ether.		76.0	12
4-Tert-butyl phenol	tri-n-butylamine	4-Tert-butylphenol (15g) and aq. NaOH, treated with tri-n-butylamine (18.5g) and $CHCl_3$ in benzene and mixture stirred and refluxed 2h, 4-tert-butylphenyl n-butyl ether and N,N-dibutylformamide (8.02g).		52.3	13

TABLE 4.2 (contd.)

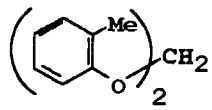
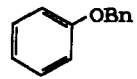
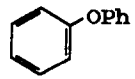
2-Methylphenol	CH_2Cl_2	Amberlite IRA-400 in the phenoxide form (capacity ca. 1 mmol phenoxide anion/g dry resin) in dichloromethane refluxed 12h , to give di(2-methylphenoxy)methane.		91	14
Phenol	$PhCh_2Br$	Phenol, benzyl bromide, KOH and a calixarene in CH_2Cl_2 stirred at 40° for 2 h. The calixarene (both hydrophilic and -phobic) gave reduced reaction times (cf polyethene glycol diethyl ether and quaternary NH_4 salts). Product benzyl phenyl ether.		100	15
Phenol	C_6H_5Cl	Phenol (686g), 85% KOH, NaOH and chlorobenzene (675g) heated with azeotropic removal of H_2O, CuCl added, mixture heated (N_2) for 4h to 175° to give diphenyl ether(613g).		60 (on chloro-benzene)	16

TABLE 4.3 SYNTHESIS OF AROMATIC ETHERS

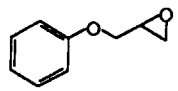
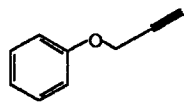
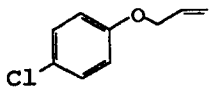
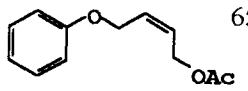
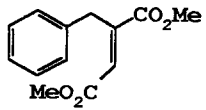
MATERIAL	ALKYLATING AGENT	CONDITIONS	PRODUCT	YIELD (%)	REF.
Phenol	epichlor hydrin	Phenol in epichlorohydrin with a little piperidine and mixture refluxed (2-18h) and mixture refluxed (2-18 h). Solvent replaced by THF, M NaOH added stirred (45-60°) for 10 min., then at ambient temp. for 0.5h., to give epoxymethyl phenyl ether.		85-90	17
"	"	Phenol with epichlorhydrin (8 mole) K_2CO_3 and n-$BuNOSO_3CH_2CH(OH)Me$ catalysts stirred at 75-80C (1.5h) to give product.	"	91	17a
Phenol	propargyl alcohol	Phenol and propargyl alc. added to stirred Ph_3P in benzene (N_2) at ambient temp. and then $EtO_2CN{=}NCO_2Et$ added slowly. Reaction for 18h., to give phenyl propargyl ether.		85	18
4-Chloro phenol	allyldiisobutyl telluronium bromide	4-Chlorophenol 1 moles of NaOH in THF then telluronium bromide added: mixture stirred (5h.) under N_2 to give allyl 4-chlorophenyl ether.		86	18a
Phenol	(Z)-1-hydroxy -4-acetoxybut -2-ene	Phenol (Z)-1-hydroxy-4-acetoxybut-2-ene some Bis[1,2-(diphenylphosphino) ethane] palladium(0) and KF/Al_2O_3 in the reacted at ambient temp. (argon) for 24h. gives the allyl ether (loss of AcOH), to give 4-acetoxybut-2-enyl phenyl ether.		65	19
Phenol	Dimethyl ethyne carboxylate	Phenol and dimethyl ethynedicarboxylate neutral, Al_2O_3 Woelin N super/ suspension in CH_2Cl_2 at ambient temp., solvent removed, at 40°, further drying (1 h.) in $CCl_4$and the mixture stirred vigorously at 30° for 5 h. to give dimethyl phenoxyfumarate.		91	20

TABLE 4.3 (Contd.)

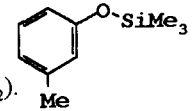
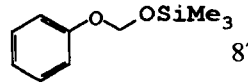
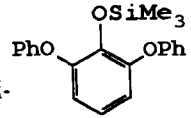
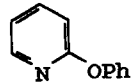
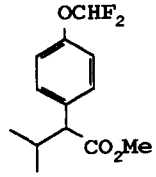
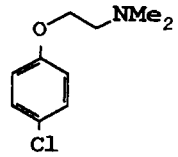
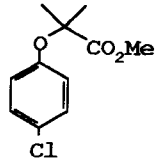
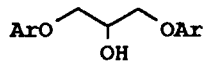
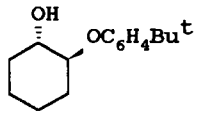
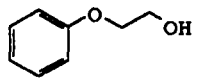
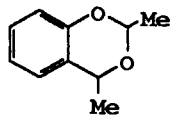
MATERIAL	ALKYLATING AGENT	CONDITIONS	PRODUCT	YIELD (%)	REF.
3-Methyl phenol	t rimethylsilyl richloroacetate ($Me_3SiO_2CCCl_3$)	rimethylsilyl trichloroacetate (XS) and 3-methylphenol stirred with K_2CO_3,and 18-crown-6(catalyst) and heated (150°) until CO_2 ceased. Product 3-methylphenyl trimethylsilyl ether (+ $CHCl_3$ + CO_2).		90	21
Phenol	chloromethyl trimethylsilane ($ClCH_2SiMe_3$)	Phenol in DMSO added to NaH in DMSO at 25° (8 h.). Then $ClCH_2SiMe_3$ and stirring continued (8 h.), and hydrolysed to give phenyltrimethylsilylmethyl ether		87	22
2,6-Diphenyl phenol	trimethylsilyl cyanide (Me_3SiCN)	2,6-diphenylphenol treated dropwise with trimethylsilylcyanide (HCN evolution!) and mixture (½h) at 100° to give 2,6-diphenyl-phenyltrimethylsilyl ether.		97	23
Phenol sulphide	2,2'-dipyridyl	XS phenol and 2,2'-dipyridyl sulphide heatedat 200° (1h) in a sealed tube to give phenyl 2-pyridyl ether.		72	24
Methyl 2-(4-hydroxy phenyl)-3 methylbutyrate	chlorodifluoro methane ($ClCHF_2$	The 4-phenol deriv. in acetone/isopropanol (1:1), and cat. benzyltriethylammonium chloride with H_2O stirred at 30-5°, 3 moles $ClCH_2F_2$ added (0.5h.). After 5 min. aq NaOH (1 mole), then 3 moles added (0.25h.) mixture stirred for 1h.		79	25

TABLE 4.3 (contd.)

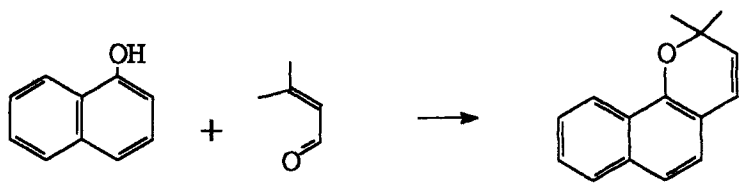
4-Chlorophenol	2-dimethylamino ethyl chloride* ($Me_2NCH_2CH_2Cl$)	4-Chlorophenol in methyl isobutylketone containing K_2CO_3 (stirred0.5h), then $Me_2NCH_2CH_2Cl$*(NB) added, and mixture refluxed (5h) to give 4-chlorophenyl 2-dimethylaminoethyl ether		54	26
4-Chloro phenol	1,1,1-trichloro-2-methylpropan--2-ol	To 4-chlorophenol and 1,1,1-trichloro-2-methyl-propanol (from Me_2CO) and $CHCl_3$ with KOH, caution) in MeOH, NaOHadded to give Me 2-(4-chlorophenoxy)-2,2-dimethyl acetate.		86	27

NB *This compound is an alkylating agent.

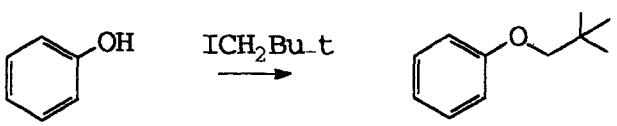
TABLE 4.4 SYNTHESIS OF AROMATIC ETHERS

PHENOL	ALKYLATING AGENT	CONDITIONS	PRODUCT	YIELD(%)	REF
2,4,6-Tri bromophenol (ArOH)	epichlor hydrin	Excess of the phenol and epichlorhydrin refluxed in 5% aq. NaOH, gave 1,3-bisaryloxy-2-hydroxypropane.		91	28
4-Tert-butyl phenol	cyclohexene oxide	Cyclohexene oxide and Na added to 4-tert-butylphenol at 210° under N_2 and reacted at 210° (½h) (presumably a trans product) to give 2-(4-tert-butylphenoxy)cyclohexanol.		92	29
Phenol	ethylene carbonate	Ethylene carbonate, phenol and imidazole heated (2 h) at 160° to afford 2-phenoxyethanol.		91	30
Phenol	acetaldehyde	Equimolar mixture phenol and K phenoxide in toluene treated with $TiCl_4$ in toluene at ambient temp., stirred and refluxed (0.5h) ;acetaldehyde in toluene added and reaction for 10 h, to give 4H-2,4-dimethyl-1,3-benzodioxin.		70	31

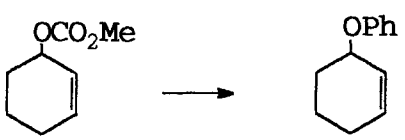
moles of 1-naphthol in 4-methylpyridine, when refluxed at 125°C for 8 hours, afforded 2,2-dimethyl-2H-naphtho[1,2-b]pyran in 86% yield (ref. 32).



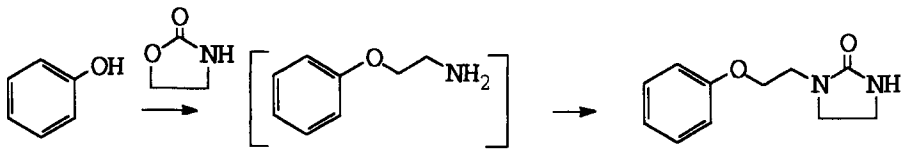
Although Table 4.2 lists a number of organic bases, relatively few inorganic analogues have been studied but the greater availability of, for example, caesium carbonate has enabled it to be employed in a practical synthesis of neopentyl phenyl ether in 94% yield from neopentyl iodide and phenol in diethyleneglycol dimethyl ether by heating at 150-180°C during 12 hours (ref. 33).



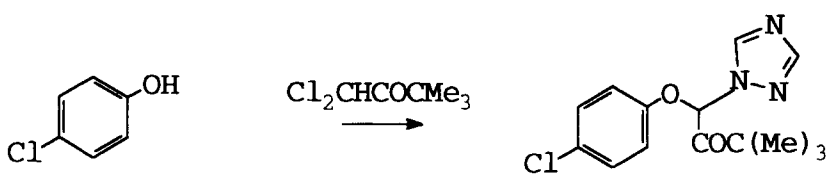
The conversion of the cyclohexenyl methyl carbonate shown, to an ether with loss of carbon dioxide in preference to trans-esterification was effected by heating with phenol and small quantities of $Pd_2(dba)_3$ and 1,4-bis(diphenylphosphino)butane in tetrahydrofuran at 60°C during 12 hours to give an 82% yield of cyclohex-2-enyl phenyl ether (ref.34).



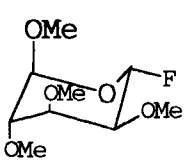
A 2-oxazolidone has been employed for ether formation with phenol in 2-(2-methoxyethoxy)ethanol solution by heating at 160-170°C during a prolonged period until carbon dioxide evolution ceased, to give mainly the imidazolone shown by way of the transient 2-aminoethylether formed in no more than 10% yield (ref.35), although thiophenols afforded good yields of the latter derivative.



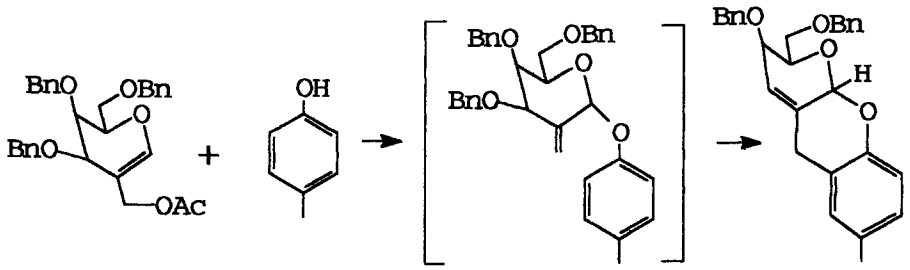
A double alkylation was effected in the reaction of 4-chlorophenol at 100°C for 10 hours with 1H-1,2,4-triazole and dichloromethyl tert-butylketone in benzene/methyl iso-propylketone (1:1) to give 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazin-1-yl)butan-2-one ('Tridimefon') indicated in 97% yield (ref.36).



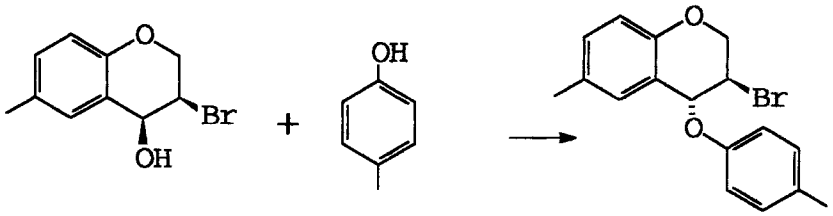
The glycosyl fluoride illustrated (from L-rhamnose) in dichloromethane reacted at -78°C with phenol (2 moles), bis-cyclopentadienylhafnium dichloride (3 moles) and silver perchlorate (3 moles) in dichloromethane containing powdered 4A molecular sieve during 45 minutes to give the O-phenoxy derivative without C-arylglycoside formation (ref.37).



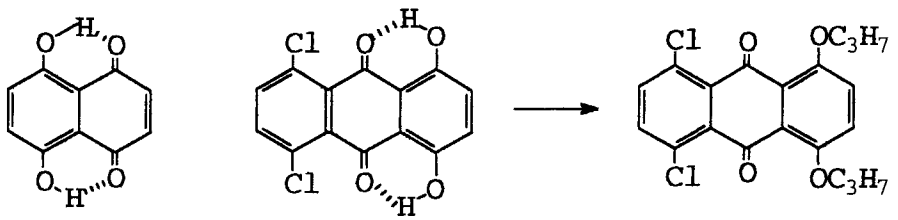
Glycoside formation followed by ring closure occurred with formation of a chroman in the reaction of the 3,4,6-tri-O-benzyl-2-C-acetoxymethylgalactal shown with 4-methylphenol in dichloromethane containing boron trifluoride-etherate at 0°C to afford the α-product in 70% yield by way of the C-2-methylene-O-glucoside which could be prepared separately and converted to the same pyranobenzopyran under similar conditions (ref. 38).



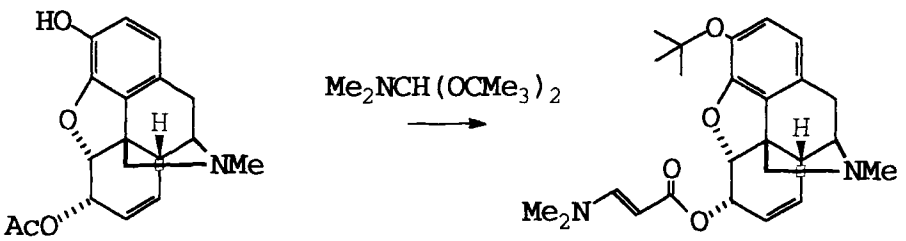
Formation of an ether at a benzylic position rather than at an alternative site by bromide ion displacement is seen in the reaction of either *cis* or *trans*-3-bromochroman-4-ols with 4-methylphenol in the presence of equimolar proportons of diethyl azodicarboxylate and triphenylphosphine in benzene solution over 8 hours at ambient temperature to result in the product illustrated in 84% yield (from the *cis* intermediate) (ref. 39).



Hydrogen-bonded naphthaquinonediols and anthraquinonediols which are ordinarily difficult to alkylate when potassium carbonate is employed, even with a high boiling point non-aprotic solvent, respond with a greatly improved yield with the more basic caesium salt. Thus, 1,4-dichloro-5,8-dihydroxy-9,10-anthraquinone refluxed under nitrogen in acetone/dimethyl formamide (40:13) containing anhydrous caesium carbonate with 2-iodopropane over 20 hours gave the 5,8-di-isopropoxy derivative shown in 83% yield (ref.40).



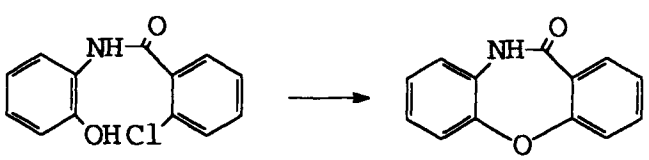
t-Butylation, normally effected with acid-stable molecules under acidic conditions, can be achieved if necessary in excess dimethylformamide as in the case of 6-O-acetylmorphine which gave the phenolic O-tert-butyl ether together with a condensation product at the acetoxy group in 59% yield as illustrated upon heating at 100-110°C for 30 min. with the di-tert-butyl acetal of dimethylformamide (ref.41).



O-Alkylation of 4-tert-butylcalix[b]arene has been carried out in 94% yield with triethyleneglycol monomethyl ether 4-tosylate (TsOR) in the presence of benzyltrimethylammonium chloride and potassium hydroxide in chloroform /dichloromethane/methanol solution after stirring for 24 hours at 40°C (ref.42). The synthesis of a number of naphthyl ethers or their further reaction products has been summarised in Table 4.5 (refs.43-46).

4.2.2 From Phenolic Intermediates and Derivatives by Intramolecular and Transetherification Reactions

As a step from the previous phenoxides towards less familiar examples, the intramolecular cyclisation of 2-(2'-chlorobenzamido)phenol may be mentioned. By formation of the phenoxide with potassium methoxide in warm quinoline containing methanol, followed by refluxing for a short period, dibenz[b,f]-[1,4]oxazepin-11(10H)-one, was obtained in 60% yield (ref.47).



A number of transetherifications have been summarised in Table 4.6 (refs.48-52) which also gives some examples of the conversion of acetates to ethers. The reaction of 1-acetoxy-2,3-diethyl-4-methoxynaphthalene in tetrahydrofuran

TABLE 4.5 SYNTHESIS OF NAPHTHYL ETHERS AND DERIVATIVES

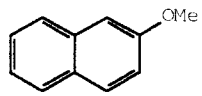
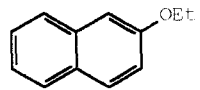
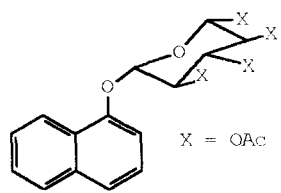
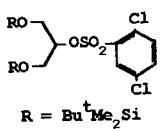
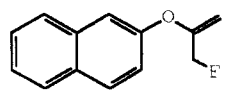
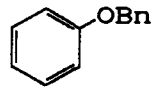
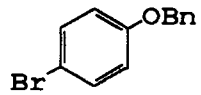
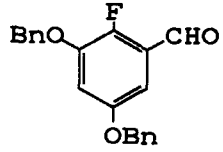
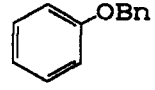
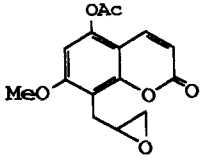
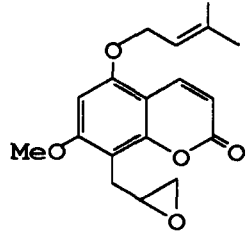
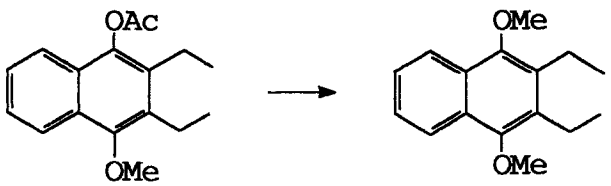
NAPHTHOL	ALKYLATING AGENT	CONDITIONS	PRODUCT	YIELD (%)	REF.
2-Naphthol	trimethylsilyl diazomethane (Me_3SiCHN_2)	2-Naphthol and ethyldiisopropylamine in acetonitrile/ methanol (9:1) stirred and treated with trimethylsilyl-diazomethane at ambient temp. for 15h., to give 2-methoxynaphthalene.		100	43
2-Naphthyl chloroacetate	ethyl iodide	2-Naphthylchloroacetate in DMF added methane at ambient temp.for 15 h.to suspension Na_2Te in DMF at ambient temp.(N_2), stirred 10 mins., ethyl iodide added and reaction continued for 2½h from 30° to 50°.		50	44
1-Naphthol	1-α-fluoro-2,3, 4,6-tetra-acetyl-D-glucopyranose	2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl fluoride, 1-naphthol and tertramethylguanidine in acetonitrile at ambient temp. gave the 1-naphthyloxy derivative in 90% yield(97% ß). Electron donating groups gave high ß-selectivity, absence of the base gave more α-isomer.		90	45
2-Naphthol		Sodium 2-naphthoxide (from NaH) in THF added to 1,3-bis(tert-butyldimethylsiloxy)propyl-2-yl 2,5-dichloro-benzensulphonate with 18-crown-6 at ambient, stirred and refluxed (14h) gave the bis(siloxy)prop-2-yl ether (99%)which with $MeSO_3F$ added to $(Bu)_4NF$ + 4A mol Sieve in THF for 18h at 50° afforded the product.		99 (and then 70)	46

TABLE 4.6 FORMATION OF ALKYL ETHERS FROM SILYL AND OTHER ETHERS

STARTING REACTANT	SUBSTITUTING REACTANT	CONDITIONS	PRODUCT	YIELD (%)	REF.
Trimethylsilyl phenylether	benzyl bromide	Trimethylsilyl phenyl ether, tris(diethylamino) sulphonium difluoro trimethylsiliconate and benzyl bromide in THF at -78° during 2h gave benzyl phenyl ether		67	48
Dimethyl, tert-butyl-silyl-4-bromo-	benzyl chloride	The siloxy compound and benzyl chloride treated with tetrabutylammonium fluoride 3 H_2O in THF and left at ambient temp. (for 16h) gave benzyl 4-bromophenyl ether		85	49
The bis(dimethyl tert-butyl-silyl) ether	benzyl bromide	The bis ether, anhydrous KF, benzyl bromide in DMF (argon) at 25° during 2h. gave 3,5-dibenzyloxy-2-fluorobenzaldehyde		92	50
Methylphenyl carbonate ($MeOCO_2Ph$)	benzyl chloride	Methyl phenyl carbonates with benzyl chloride and $(n\text{-}Bu)_4PBr$ heated at 150° (3h) gave benzyl phenyl ether		96	51
Prenyl chloride		The acetate shown in acetone containing potassium carbonate (with some, 18-crown-6), then after 1h reflux the prenyl chloride added and refluxing (½h) continued to give the 5-O-prenyl ether		74	52

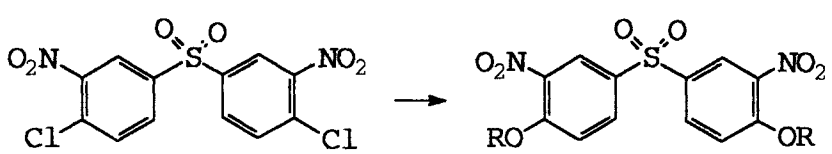
solution containing excess hexamethylphosphorictriamide with sodium hydride (2.2 moles) at 0°C for 1 hour followed by treatment with iodomethane and stirring of the mixture for 48 hours at 25°C gave 2,3-diethyl-1,4-dimethoxynaphthalene in 70% yield with substantial recovery of the starting material. Benzyl acetate afforded the benzyl methyl ether (ref.53).



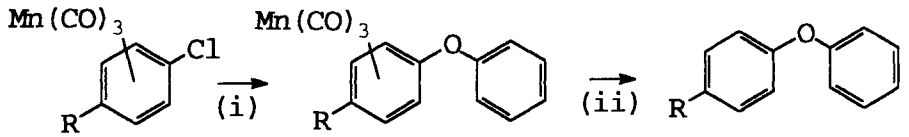
4.2.3 From Benzenoid Derivatives by Displacement of nitro, chloro and other groups

Nitro compounds activated by 2- or 4-groups such as nitro, cyano or alkoxycarbonyl, smoothly form ether derivatives by intermolecular or intramolecular pathways.

Activation by nitro groups results in a facile phase-catalysed reaction of 3,3'-dinitro- 4,4'-dichlorodiphenylsulphone with the phenoxide ion in the absence of an aprotic solvent (ref.54). Thus phenol, 2-naphthol, 4-ethylphenol, 4-phenoxyphenol and 3,5-dimethylphenol in aqueous NaOH-dichloromethane containing Bu_4NBr or Bu_4PBr gave 66-94% yields of the corresponding bis(4-aryloxy-3-nitrophenyl)sulphone, $[3,4\text{-}O_2N(RO)C_6H_3]_2SO_2$ (where R is phenyl, 2-naphthyl, 4-ethylphenol, 4-phenoxyphenyl and 3,4-dimethylphenyl) after 16 hours reaction at ambient temperature

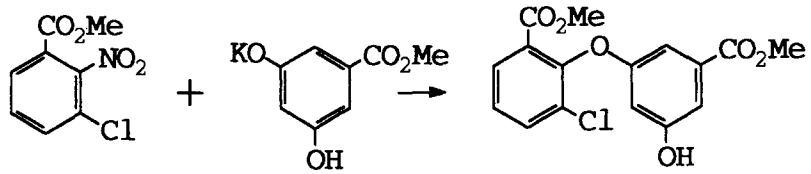


The reaction of nucleophiles with chloroarene-$Mn(CO)_3$ and fluoro arene-$Cr(CO)_3$ complexes has been employed for the synthesis of diaryl ethers and has been particularly applied (ref.55) to the selective arylation of polyfunctional phenols by reaction of the phenoxide formed from NaH in dimethylformamide with the 4-chlorotoluene-manganese tricarbonyl cation (as the hexafluorophosphate) in acetonitrile at ambient temperature over 18 hours.

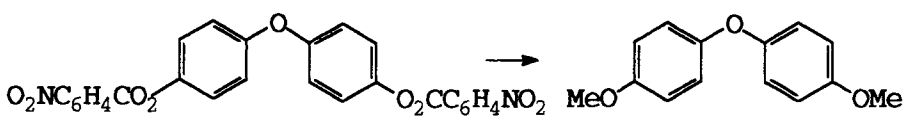


(R = H, Me) (i) PhONa, Me_2CO, 0°C (ii) MeCN, 50°C

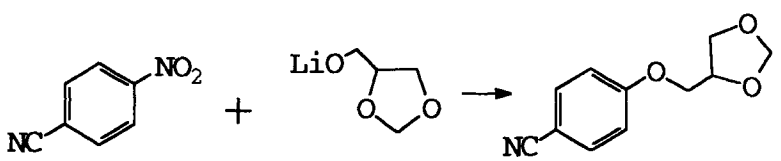
By contrast with the first example, the nitro group can sometimes be expelled. Thus, methyl 3-chloro-2-nitrobenzoate and the monopotassium salt of methyl 3,5-dihydroxybenzoate (1.5 moles) in refluxing dimethylformamide containing cupric oxide gave the diphenyl ether shown in 60% yield (ref.56) with displacement of the nitrite ion.



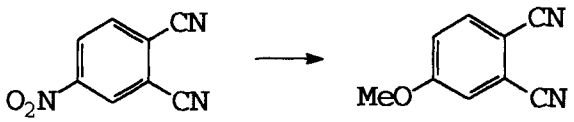
4,4'-bis(4-nitrobenzoyl)diphenylether afforded the corresponding bis(methoxy) compound in 91% yield by stirring with 20% methanolic sodium methoxide in dimethylsulphoxide at ambient temperature (ref.57).



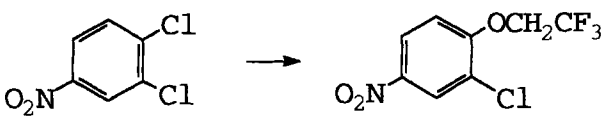
The cyano compound, 4-nitrobenzonitrile with the lithium alkoxide shown furnished an ether in 50% yield by stirring at 25°C for 18 hours (ref.58).



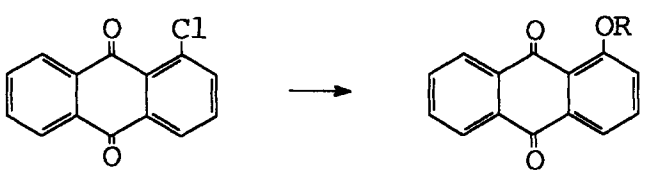
The use of the free alcohol in strong organic base solution for ether formation is illustrated in the reaction of 4-nitrophthalonitrile with methanol in dimethylformamide/1,8-diazobicyclo[5,4,0]undec-7-ene, heated during 24 hours at 60°C to give 4-methoxyphthalonitrile in 98% yield (ref.59).



The preparation of ethers selectively by displacement of the halide ion from nitrohalogenobenzenes is particularly successful as seen in the following examples. The sodium salt of 2,2,2-trifluoroethanol prepared in dimethylformamide by adding the alcohol to sodium hydride was treated with 3,4-dichloronitrobenzene and after stirring for 18 hours, 3-chloro-4-(2,2,2-trifluoroethoxy)nitrobenzene was formed in 58% yield (ref.60).

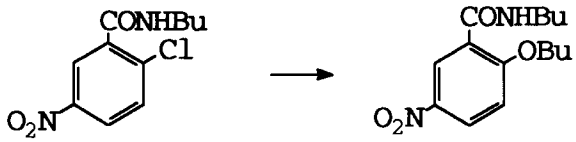


In the polycyclic series, although 1-chloroanthraquinone in tetrahydrofuran /hexadecanol containing sodium hydride did not form the hexadecyl ether, with ethylene glycol oligomers the corresponding ether was obtained, while a mixture of hexadecanol and ethylene glycol oligomer afforded the hexadecyl ether. It is concluded that ethylene glycol alkoxide is the more nucleophilic and equally that ethylene glycol alkoxide is a better leaving group than chloride under the experimental conditions used (ref.61).

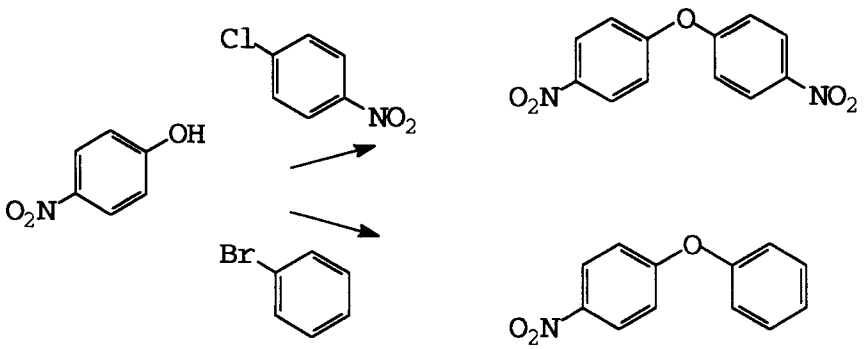


After conversion of 1-butanol to the sodium salt by addition to sodium hydride

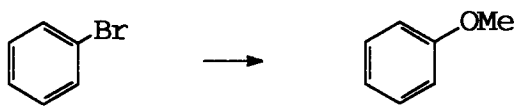
in toluene, 4-chloro-3-(N-butylamido)nitrobenzene with a little tetrabutylammonium bromide was introduced at ambient temperature and following reaction for 30 minutes, an 89% yield of 4-n-butoxy-3-N-butyl-amidonitrobenzene was isolated (ref.62).



In the presence of sodium tetraborate and nitrite in dimethylsulphoxide at 160°C during 10 hours, 4-nitrochlorobenzene with 4-nitrophenol afforded an 82% yield of bis(4-nitrophenyl)ether (ref.63).
Also in the diphenylether series, 4-nitrophenol in dry pyridine containing Cu(I)phenylacetylide after refluxing under nitrogen for 10 hours and then treatment with bromobenzene followed by further refluxing during 4 hours, furnished 4-nitrophenyl phenyl ether in 70-77% yield (ref.64).

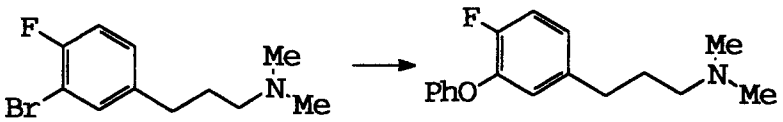


Bromobenzene in methanol containing sodium methoxide in the presence of the catalysts sodium formate and cuprous bromide gave anisole in 56% yield after refluxing at 70°C for 7 hours (ref.65).

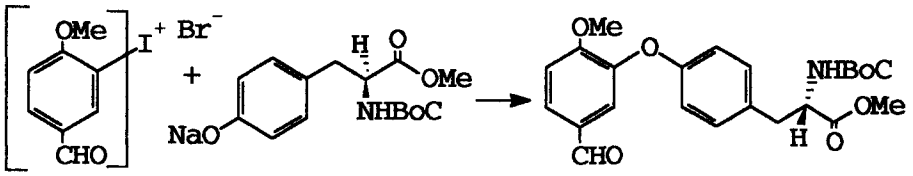


The bromo derivative [3-(3-bromo-4-fluorophenyl)propyl]dimethylamine, with

sodium phenoxide in 2,2'-diethoxydiethyl ether containing cuprous oxide stirred at 190°C during 24 hours afforded [3-(4-fluoro-3-phenoxyphenyl)propyl]-dimethylamine in 97% yield (ref.66).



The iodonium salt shown with N-protected O-methyl tyrosine (sodium salt) in dimethylformamide at 90-95°C gave the diaryl ether in 51% yield without racemisation, under these preferred milder conditions rather than by the Ullmann reaction (ref.67).



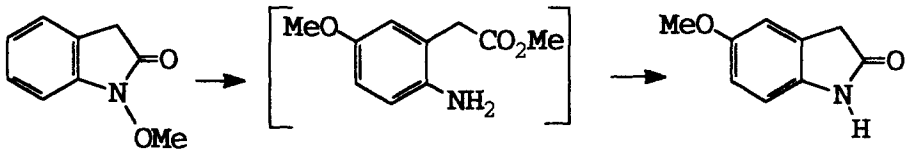
Triphenylbismuth diacetate in ethanol containing some cupric chloride afforded phenyl ethyl ether (ref.68).

$$Ph_3Bi(OAc)_2 + EtOH \rightarrow PhOEt$$

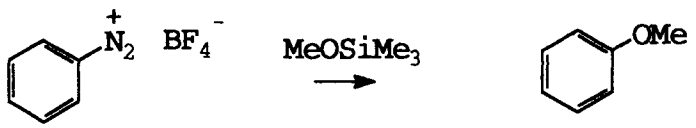
N-Phenyl-N'-4-toluenesulphonylhydrazine added portionwise over 30 minutes to a stirred solution of mercuric acetate in methanol at ambient temoerature and further reaction during 15 hours, gave anisole in excellent yield (ref.69).

$$PhNHNHSO_2C_6H_4Me + Hg(OAc)_2 + MeOH \rightarrow PhOMe$$

The unusual displacement of a hydrogen atom was found to take place with 1-methoxy-2-hydroxyindole in methanol containing conc. sulphuric acid to give 5-methoxy-2-hydroxyindole in 72% yield by refluxing for 1 hour, followed by concentration and basification with aqueous sodium hydroxide and then refluxing of a xylene solution for 7 hours (ref.70). A possible intermediate is shown although the reaction has some features of the Wallach rearrangement.

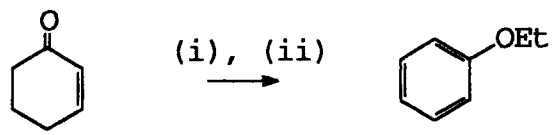


The classical diazonium salt route to phenolic ethers has been re-examined. The slow addition of methoxytrimethylsilane (4 moles) to benzenediazonium fluoroborate in ice-cold freshly distilled Freon-113 under nitrogen, warming of the mixture to 55°C with ultrasonic agitation (W-385 processor) and finally refluxing with continued sonication at the same temperature during 16 hours, afforded a 51% yield of anisole (ref.71).



4.2.4 From Alicyclic and Acyclic Precursors

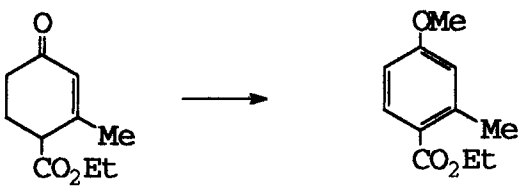
The simplest example of this type of transformation, a type of reversed Birch reduction, is the conversion of cyclohex-2-enone to phenyl ethyl ether in 93% yield by treatment with 2 equivalents of the ethoxy dichlorovanadium compound, $VO(OEt)Cl_2$ under an oxygen atmosphere which resulted in a faster reaction rather than with nitrogen or in a toluene solution (ref.72).



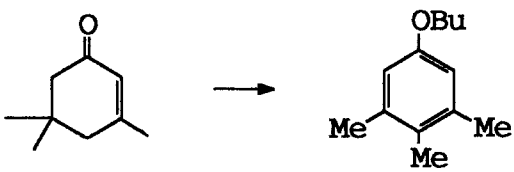
(i) $VO(OEt)Cl_2$ (ii) EtOH, O_2 , Δ

This type of procedure has been extended to carbonylethoxy derivatives as in the conversion of so-called 'Hagermann esters', such as in the example, to 3-methyl-4-ethoxycarbonylanisole in 90% yield by refluxing the starting material

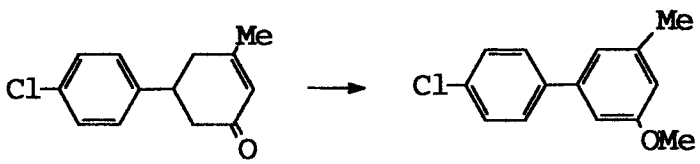
in methanol containing iodine for 30 mins. (ref.73).



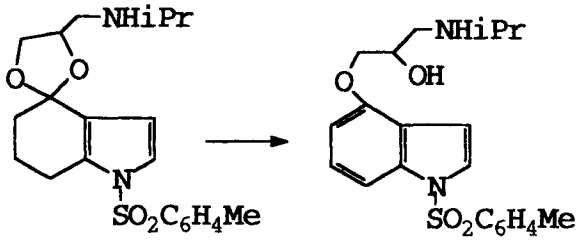
5-n-Butoxy-1,2,3-trimethylbenzene was formed in 90% yield from isophorone in n-butanol containing iodine and ceric ammonium nitrate after refluxing the mixture for 18 hours (ref.74).



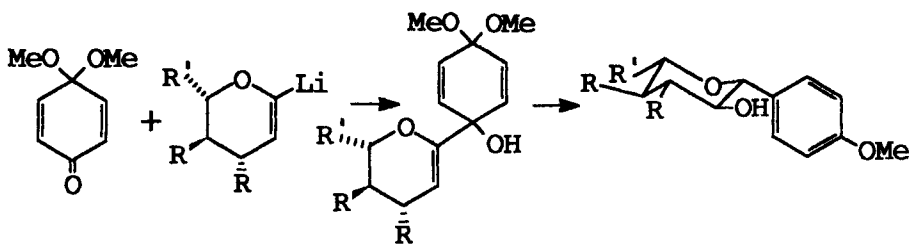
Substituted derivatives have been employed as for example in the conversion of 5-(4-chlorophenyl)-3-methylcyclohex-2-enone in methanol to 4-chloro-3'-methyl-5'-methoxydiphenyl in 86% yield by dropwise treatment with methanolic iodine followed by refluxing for 3 hours (ref.75).



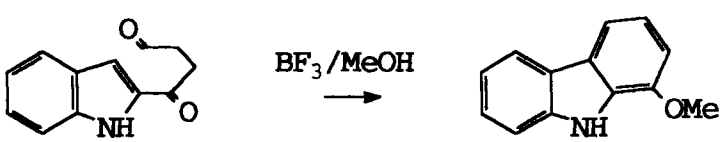
Dehydrobromination of a cyclohexanone ketal, 4'-isopropylamino-1-tosyl-4,5,6,7-tetrahydroindole-4-spiro-2'-(1',2')dioxalan has been used to make, in 72% yield, the substituted anisole shown by treatment in dichloromethane solution with bromine at -20°C followed by stirring at -20 to-10°C during 2 hours and at ambient temperature for 1 hour (ref.76).



The dimethyl ketal of the pyranylcyclohexadienone depicted in dichloromethane by treatment with $BH_3.Me_2S$ (1.3 moles) at ambient temperature followed by alkaline peroxidic work-up, gave a C-pyranylanisole in 50-60% yield, a reaction sequence having a potential for the synthesis of C-glycosides (ref.77).

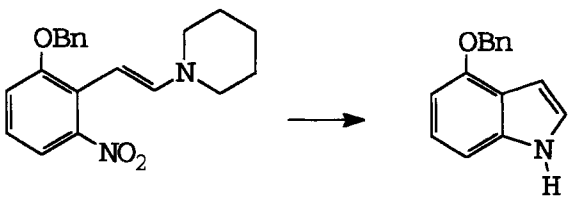


Intramolecular cyclisations have been used for a variety of complex anisole derivatives. Thus, 2-methoxycarbonylindole with butyrolactone or a 2-alkylbutyrolactone in the presence of NaOMe gave a derivative which after decarboxylation and oxidation with PCC resulted in 4-(2'-indolyl)-4-oxobutanal, or the corresponding alkyl analogue. 4-Methoxycarbazole was then obtained for the parent compound by treatment of the aldehyde with boron trifluoride/methanol at ambient temperature (ref.78) with yields generally in the range 61-83%.

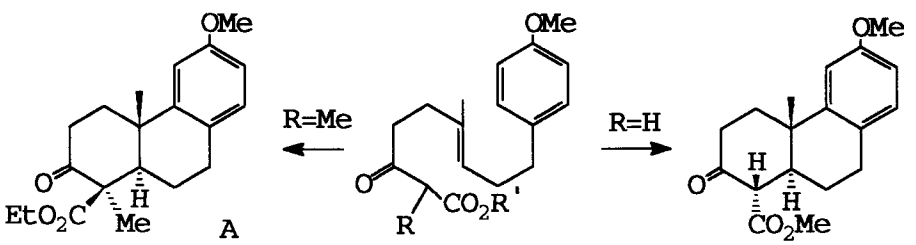


The benzyl ether, 2-benzyloxy-6-nitro-2'-piperidinostyrene was reductively

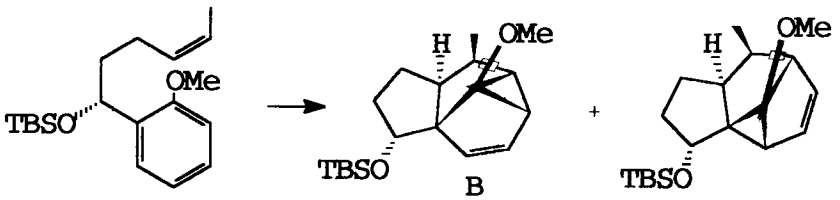
cyclised by addition to a suspension of nickel boride (prepared from nickel(II) acetate and sodium borohydride) in absolute ethanol and treatment of the refluxing mixture with ethanolic hydrazine over 15 minutes. Work-up after cessation of gas evolution gave a 90% yield of 4-benzyloxyindole (ref.79). No debenzylation occurred and the non-pyrophoric nature of the reagent are advantages of this method.



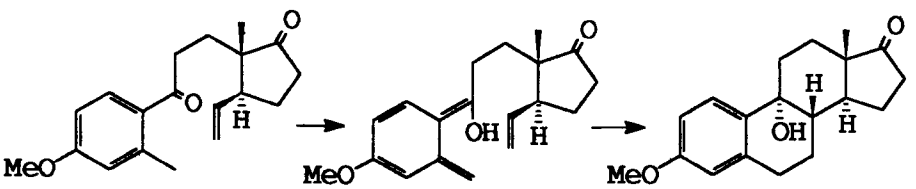
Manganese triacetate oxidation in acetic acid of an anisole having a 4-substituent with an E-configurational chain furnished a keto precursor (A) of racemic podocarpic acid by a methodology having generality for ring synthesis (refs.80,81). The stereochemistry at the carbon adjacent to the keto group in the product appeared to be dependent on the nature of R (H or Me) and possibly on the nature of alkyl group in the ester.



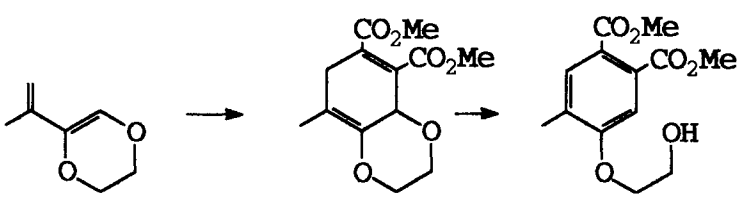
By contrast, and although an aspect of the reactions of anisoles rather of their synthesis it is noteworthy that in a photochemical transformation (with the use of a Vycor filter) of a 2-substituted anisole in pentane at ambient temperature, two isomeric cyclopentacycloheptanes were obtained in 63% yield, a useful step from component B for a synthesis of rudmollin, a substance with anti-leukaemic properties (ref.82).



Another photochemical cyclisation of an o-quinomethide derived from a 3-methylanisole derivative has afforded an intermediate, dehydration of which with oxalic acid followed by reduction led to a synthesis of racemic estrone (ref.83).

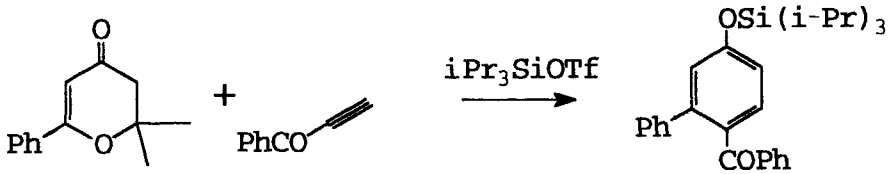


Purely acyclic intermediates have been utilised for the synthesis of phenolic rings. The Diels-Alder addition of dimethyl acetylenedicarboxylate to 5,6-dihydro-2-isopropenyl-1,4-dioxine in refluxing benzene during 6 hours gave 3,6-dihydro-5-methyl-3,4-ethanedioxy-1,2-di(methoxycarbonyl)benzene in 75% yield, treatment of which in tetrahydrofuran with DBU under reflux for 1-3 hours furnished, by aromatisation, a 2-hydroxyethoxyphthalate ester (ref.84).

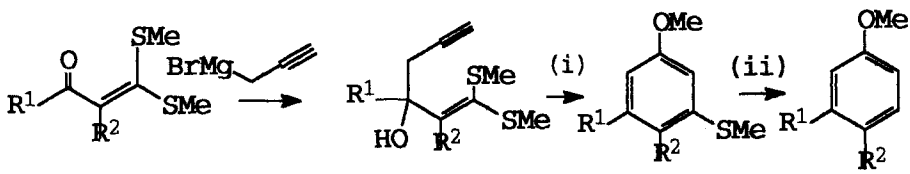


The pyran indicated, 2,3-dihydro-2,2-dimethyl-6-phenyl-4H-pyran-4-one and benzoylacetylene in chloroform containing 2.5 moles of 2,6-di-tert-butylpyridine underwent addition in the presence of excess triisopropylsilyl triflate by stirring

during 2 hours at 0°C and then for a further 2 hours at ambient temperature, to afford the silylether of a 4-benzoylphenol derivative in 90% yield (ref.85). The synthesis has wide applicability to substituted compounds and included in the work are procedures for obtaining the pyran intermediates from t-carbinol derivatives of benzoylacetylene.



The synthesis of 3,4-substituted anisoles [for example, R = R' = $(CH_2)_4$] has been effected in the manner shown by the reaction of propynylmagnesium bromide with a sulphur-containing α,β-unsaturated ketone derivative to afford an intermediate carbinol. Cyclisation of this with boron trifluoride-etherate in the presence of methanol occurred with loss of methylthiol and desulphurisation by means of Raney nickel gave the final product (ref.86). The same sulphur-containing intermediates have been used with aryl esters to derive 4-methoxy acetophenone (ref. 87,88). Carbonyl derivatives of phenols are considered in detail in Chapter 7.



(i) BF_3 Et_2O, MeOH (ii) Raney Ni

4.3 Reactions of Phenolic Ethers

4.3.1 Introduction

Since the alkyl group, usually the methyl, is used for the protection of the phenolic group, the reactions described in this section effectively extend the synthesis of phenols already described. Thus some of the syntheses from phenolic ethers in the last part of the preceding section would also appear to be equally an aspect of the reactions of phenolic ethers. The general reactions

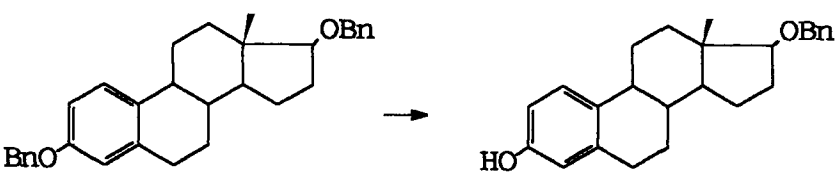
of phenolic ethers are considered now, comprising demethylation and dealkoxylation, substitution of the ether group, ring substitution, cyclisation of phenolic ether derivatives, carbonyl compounds of phenolic ethers, coupling of phenolic ethers, ring saturation and Diels-Alder reactions. The majority of the reactions are assisted by the the presence of the alkoxyl group while others arguably would occur in its absence. Such reactions show the ubiquitous nature of the methoxyl group in particular and of course with the availability of selective dealkylation methods it can be regarded as a functional peg for a variety of purposes leading to molecular fine tuning in structure/property studies.

4.3.2 Dealkylation and Dealkoxylation

A number of examples of dealkylations by chemical and catalytic methods are given in Table 4.7 (refs.89-93). A very general method for the cleavage of phenolic ethers consists in their reaction under reflux during 36 hours with an excess of 37% hydrobromic acid and a small amount of hexadecylammonium bromide. Phenyl n-pentyl ether gave phenol in 71% yield (ref.94).

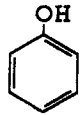
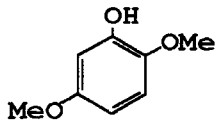
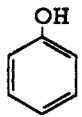
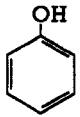
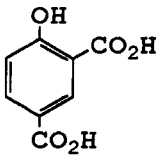
$$PhO(CH_2)_4CH_3 + HBr \rightarrow PhOH + CH_3(CH_2)_4Br$$

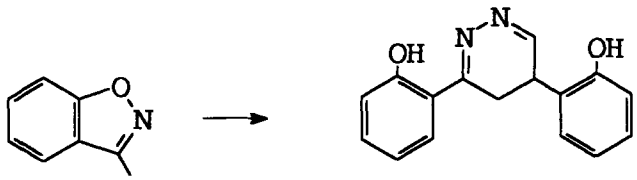
Selective cleavage, so often a prerequisite in synthesis, of an aryl benzyl ether was effected in 80% yield with the dibenzyl ether of estrane-3,17-diol in chloroform containing N,N-dimethylaniline by the addition of powdered aluminium chloride, stirring during 30 mins. at ambient temperature, and work-up following quenching with M hydrochloric acid (ref.95).



The heterocycle 3-methyl-1,2-benzisoxazole, whilst structurally distinct from the phenolic aryl ethers underwent cleavage at the O-N bond by slow addition in tetrahydrofuran to 1M lithium diethylamide at -75°C followed by isolation of crude 1,6-dihydropyridazine and its oxidation with manganese dioxide over 1 hour to give 3,5-bis(2-hydroxyphenyl)pyridazine in 61% yield (ref.96).

TABLE 4.7 DEALKYLATION OF PHENOLIC ETHERS

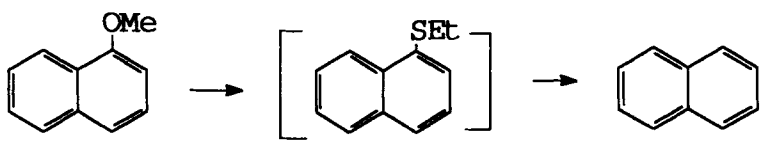
REACTANT	REAGENT	CONDITIONS	PRODUCT	YIELD%	REF.
Anisole	$BBr_3.Me_2S$	Anisole added to 1,2-dichloroethane complex containing boron tribromide dimethyl sulphide complex (N_2) and the mixture refluxed (12 h)to give phenol.		86	89
1,2-4-Trimethoxy benzene	N-methylaniline/ $NaH/(Me_2N)_3PO$	To N-methylaniline added first dropwise at 65° to stirred sodium hydride in xylene containing hexamethylphosphoramide (1 equiv.) after 1/4 h, 1,2,4-trimethoxybenzene in xylene and mixture at 85° (6 h) to afford 2,4-dimethoxyphenol.		90	90
I sopropyl phenyl ether	$NaI/SiCl_4$	To isopropyl phenyl ether and sodium iodide in dichloromethane/acetonitrile (1:1), silicon tetrachloride added and the mixture refluxed (14 h) to give phenol (acetals are also cleaved).		80	91
Phenylallyl ether	Bis(benzonitrile) palladium (II) chloride	A mixture of phenyl allyl ether palladium (II)and bis(benzonitrile) palladium (II) chloride in dry benzene refluxed (16-20h) to give phenol		85-93	92
2,4-Dicarboxy phenyl benzyl ether	10% Pd/C sodium hypophosphite	10% Pd-C and a solution of aqueous hypophosphite effected the transfer phenol hydrogenolysis of the benzyl ether in ethanol after rfluxing (2½h) to give 2,4-dicarboxyphenol (carbonate ethers also respond).		86-98	93



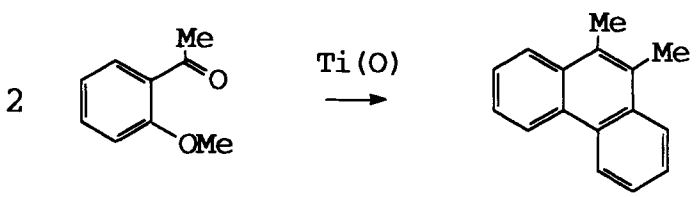
Oxidative cleavage of allyl phenyl ethers in dichloromethane containing some chromia-pillared montmorillonite, stirred initially for 30 mins., and then treated with 2 moles of an iso-octane solution of 2.8M tert-butyl hydroperoxide followed by reaction under nitrogen during 12 hours, afforded phenol in 80-90% yield in the case of allyoxybenzene in dichloromethane solution (ref.97). The oxidative aspect of the method, described as general for N-allyl and O-allyl ethers, appears in the conversion of 2-allyloxyoctane to octan-2-one

Dealkoxylations are less widely used but in recent years a number of new approaches have been adopted.

1-Methoxynaphthalene treated with aluminium chloride (2.5 equivs.) and ethanethiol (5 equivs.) in dichloromethane at ambient temperature for 5 hours gave naphthalene in 76% yield (ref.98). The method is also applicable to 1-naphthol and to 1-fluoronaphthalene in 87% yield in each case and is considered to proceed by way of the thioether.



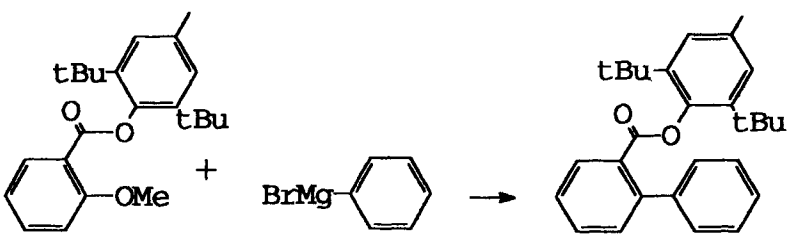
Demethoxylations involving intermolecular processes have been described, as in the reaction of 2-methoxyacetophenone in hot tetrahydrofuran containing Ti(O) (from titanium trichloride and lithium) to give 9,10-dimethylphenanthrene albeit in the relatively low yield of 36% (ref.99).



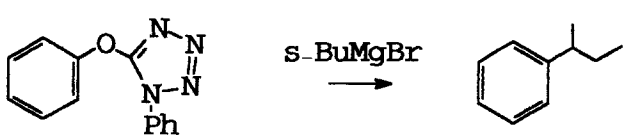
Dealkoxylation is also closely related to substitution of the phenolic ether group which is considered in the next section.

4.3.3 Substitution of the Phenolic Ether Group

Grignard reagents have been used traditionally as somewhat crude demethylating agents but in the following example demethoxylation was effected in preference to attack of the reagent at the hindered ester site. A 2:1 mixture of phenyl magnesium bromide and 2,6-di-tert-butyl-4-methylphenyl 2-methoxybenzoate in benzene/ether (2:1) during 6 hours at ambient temperature furnished the 2-phenyl derivative shown in 96% yield. The % yield was influenced by the degree of hindrance in the ester (ref.100). 2-Methylphenyl magnesium bromide has also been employed for the 2-methyl analogue of interest in synthetic work on cannabinoids (ref. 100a).

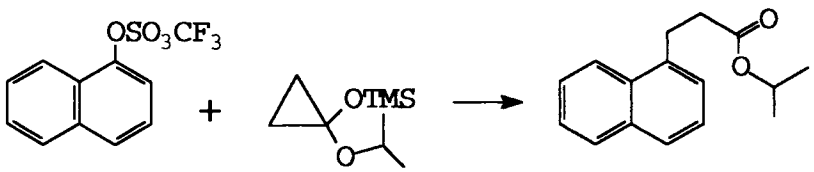


Conventionally phenyl tetrazolyl ethers have been employed for the removal of an OH group. Addition of a mixture of an ethereal solution of phenyl 5-(1-tetrazolyl)ether and a catalytic amount of dichloro[1,3-bis(diphenyl-phosphino)-propane]nickel(II) introduced dropwise into refluxing sec-butyl-magnesium chloride under nitrogen followed by reaction for 10 minutes afforded upon work-up,sec-butylbenzene in 77% yield (ref.101).

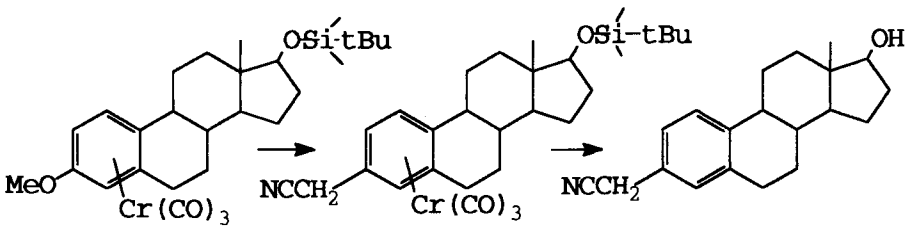


9-Methoxyanthracene in benzene with 1-butylthiol and a little methanesulphonic acid after refluxing for 15 hours gave 9-anthryl n-butyl sulphide in 85% yield (ref.102).

Replacement of the triflate group in 1-naphthyltriflate by reaction with 1-trimethylsiloxy,1-isopropoxycyclopropane (1.1 equivs.) in benzene containing the catalyst 1,4-bis(allylpalladium)triphenylphosphine, and sealing of the mixture in vacuo followed by heating for 6 hours, produced isopropyl 3-(1-naphthyl)-propionate in 89% yield (ref. 103).

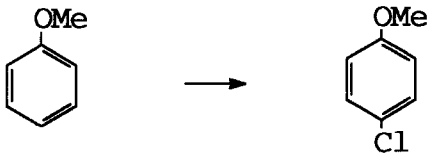


The method can be employed when the substrate contains aldehyde, keto, ester and nitro groups but fails with 4-methoxyphenyltriflate although it should have some potential for synthesis in the polycyclic area.
Removal of the methoxy group and its substitution by cyanomethyl in the protected estrone derivative shown in the form of the arene chromium tricarbonyl complex in tetrahydrofuran solution, was achieved in 46% yield by treatment at -78 C with lithioacetonitrile (from acetonitrile in tetrahydrofuran containing hexamethylphosphorictriamide and lithium di-isopropylamide at -78°C) followed by stirring for 4 hours at ambient temperature (ref.104).



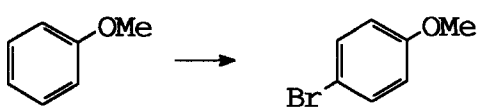
4.3.4 Substitution in the Aryl Ring of Phenolic Ethers

(i) Halogenation.
A variety of methods for the selective chlorination of anisole have appeared. A solution of anisole in chlorobenzene treated with cupric chloride supported on neutral alumina followed by vigorous stirring at 100°C for 3 hours afforded 4-chloroanisole in 98% yield with little of the 2-isomer (4-/2-: 32.3/1) (ref.105).



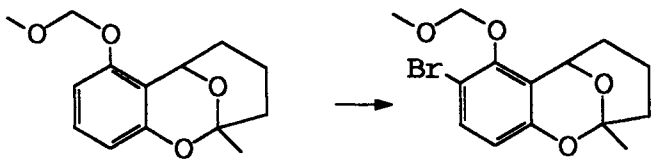
In another approach chlorine water on a reversed-phase HPLC column at ambient temperature was used (ref.106). Anisole and aluminium chloride added to stirred phenylselenyl chloride in dichloromethane at -70°C gave a 100% yield of 4-chloroanisole after the mixture had been reacted for 2 hours following attainment of ambient temperature. Benzene and chlorobenzene did not react under these conditions although N,N-dimethylaniline gave only the 4-chloro derivative (ref.107).
Benzyltrimethylammonium tetrachloroiodate was less effective although nevertheless a stable chlorinating agent which with anisole in acetic acid at 70°C during 24 hours afforded 4- and 2-chloroanisole (6:1) in 73% yield (ref.108).
Side-chain monochlorination, not evident in the preceding methods, was accomplished in 72% yield by reacting diphenoxymethane under nitrogen with chlorine in carbon tetrachloride containing azoisobutyronitrile (ref.109).

4-Bromoanisole has been derived regiospecifically in 98% yield by bromination of anisole in dichloromethane/methanol (5:2) with benzyl trimethylammonium bromide over 2 hours at ambient temperature (ref.110).

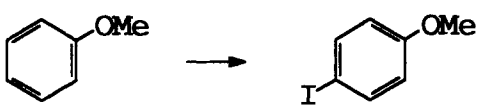


Anisole in dichloromethane added slowly to bromodimethylsulphonium bromide in the same solvent at ambient temperature with stirring over 8 hours furnished 4-bromoanisole in 94% yield.
Interestingly, phenols and amines responded similarly to these conditions although toluene and 4-substituted arenes did not (ref.111). Perbromination took place when phenol or diphenyl ether was stirred with a mixture of bromine and

aluminium at 35°C for 50 minutes followed by refluxing during 2 hours at 60°C (ref.112).
The curious tricyclic compound shown was brominated in the 2-position next to the methoxymethoxyl group by cyanogen bromide in ether solution to afford a 95% yield, after metallation with n-butyllithium in hexane solution over 3.5 hours at ambient temperature (ref.113).



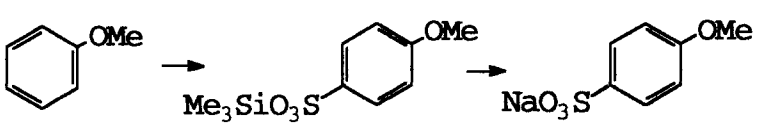
Iodination of anisole in acetic acid was achieved in 92% yield with benzyltrimethylammonium dichloroiodate in the presence of anhydrous zinc chloride over 3 hours at ambient temperature (ref.114).



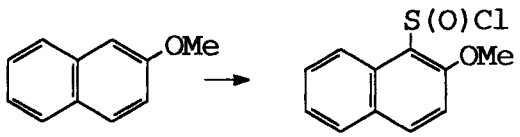
Alkoxybenzenes have also been iodinated with iodine- silver sulphate (ref.115).

(ii) Nitro, Sulphonic, Sulphur Derivatives, Thioalkyl, Hydroxyalkyl, and Acyl derivatives of Phenolic Ethers.

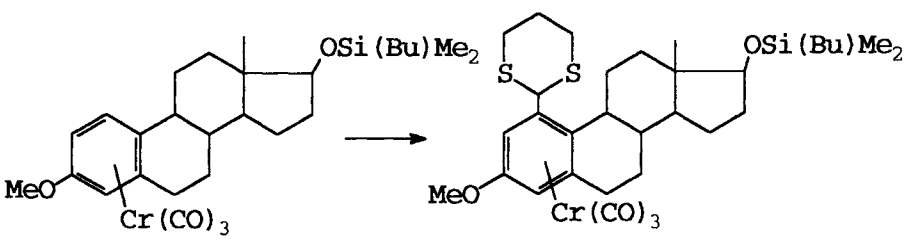
Although anisole is unreactive in the two-phase system of concentrated nitric acid-ether, 4-nitroanisole is mainly formed upon replacing the ether with other organic solvents such as alkanes and nitrobenzene (ref.116).
Anisole refluxed with bis(trimethylsilyl)sulphate over 4 hours (in a Dean-Starke apparatus) afforded, in 92% yield, the trimethyl silyl sulphonate derivative which was quantitatively transformed by aqueous ether to 4-methoxybenzene-sulphonate (ref.117).



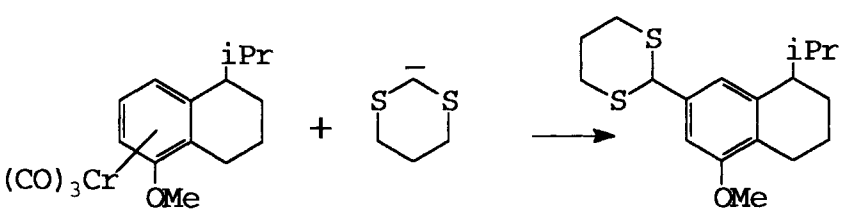
Solid powdered 2-methoxynaphthalene treated with thionyl chloride at ambient temperature and processed after 1 hour gave the 1-sulphinyl chloride in 91% yield, a route which presumably could be developed to obtain the sulphonic acid (ref.118).



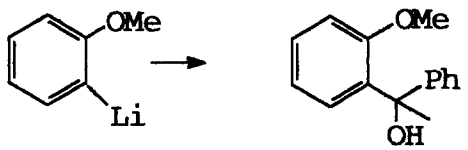
Substitution m- to the methoxy group, established earlier for arene/chromium tricarbonyl systems (ref.119), has been used to prepare the 1-(2-dithianyl) derivative of estrone (ref.120). A solution of 2-lithio-1,3-dithian in tetrahydrofuran at -78°C treated with the chromium tricarbonyl complex of HO-protected estrol (from the protected steroid with chromium hexacarbonyl by refluxing in 2-methylpyridine) in THF and, after 30 minutes at -30°C, working-up of the mixture by quenching with iodine, gave the product shown in 42% yield eligible for cleavage, alkylation or nucleophilic addition reactions.



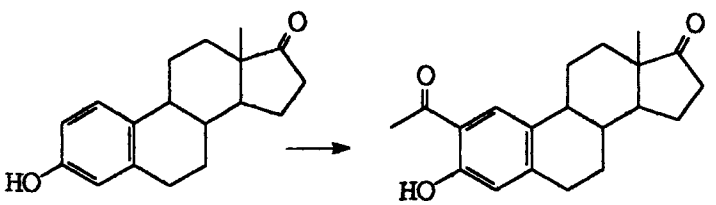
A similar oxidative nucleophilic strategy led to m-substitution of the methyl ether of the tetralin derivative shown in a yield of 60% (comprising 93% of the m-isomer). The carbanion of 1,3-dithian formed in tetrahydrofuran at -78°C from 1 mole of 1.6M n-butyllithium was treated with the chromium tricarbonyl complex (0.5 mole) in the presence of hexamethylphosphorictriamide and,



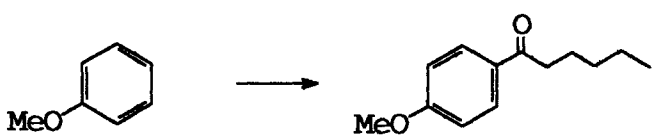
following reaction for 30 mins., work-up was effected by the addition of iodine in THF (ref.121).
o-Lithiated anisole prepared in tetrahydropyran solution by a sonication method upon quenching with acetophenone gave the carbinol indicated in 84% yield (ref.122).



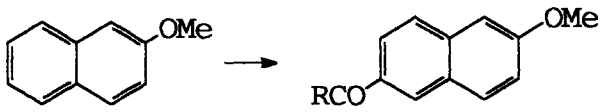
Acetylation at the 2-position in estrone methyl ether in chloroform solution occurred in 89% yield by the dropwise addition of acetyl mesylate followed by reaction over 9 hours at ambient temperature (ref.123).



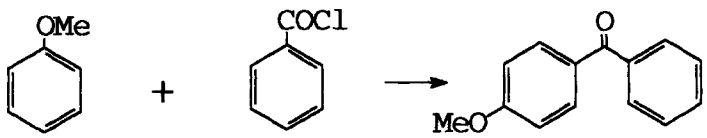
4-Methoxyphenyl n-pentyl ketone was formed in 85% yield by the addition of a mixture of anisole and caproic anhydride in dichloromethane to a suspension of lithium perchlorate (1 mole) and a small proportion of antimony pentachloride (allowed first to stir together for 1 hour) in dichloromethane, followed by refluxing for 30 mins., and work-up by quenching with aqueous sodium bicarbonate (ref.124).



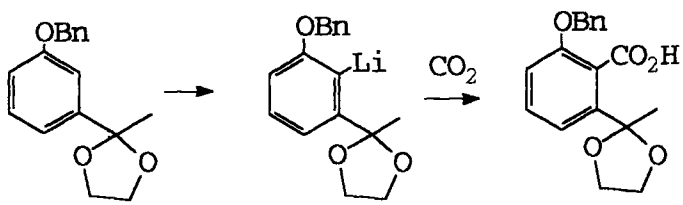
6-Acyl-2-methoxynaphthalenes have been prepared in a large-scale procedure which is dependent on the reversible acylation of 2-methoxynaphthalene to give the 'thermodynamic' product (ref.125).



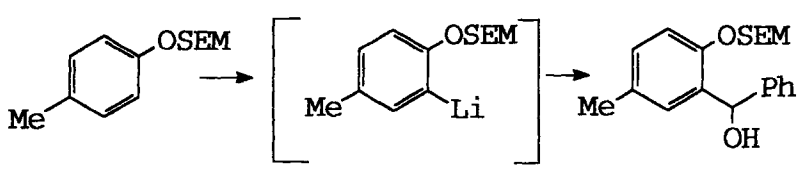
Friedel-Crafts acylation of anisole with benzoyl chloride (2 moles) by their addition together to a solution of anhydrous (5 mol%) cobalt(II) chloride in dry methyl cyanide afforded a 72% yield of 4-methoxybenzophenone (ref.126).



Carboxylation in the 2-position of the ketal of 3-benzyloxyacetophenone in hexane solution was effected in 75% yield by lithiation with 1.1 moles of a hexane solution of n-butyllithium at 0°C during 2 hours and addition of the reaction mixture to excess dry ice in hexane followed by aqueous work-up (ref.127).

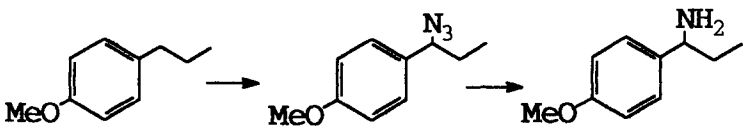


Lithiation in the 2-position of 4-methylphenyl 2-(trimethylsilyl)ethoxymethyl ether in diethyl ether solution by treatment with n-butyllithium at ambient temperature and reaction over 2.5 hours followed by the addition of benzaldehyde led upon work-up to α-[5-methyl-2-(2-trimethylsilyl)ethoxymethylphenyl]benzyl alcohol in an overall yield of 80% (ref.128).

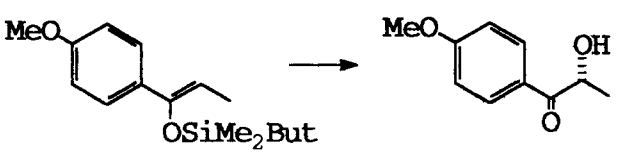


(iii) Reactions in the alkyl side-chain of C-alkyl Phenolic Ethers.

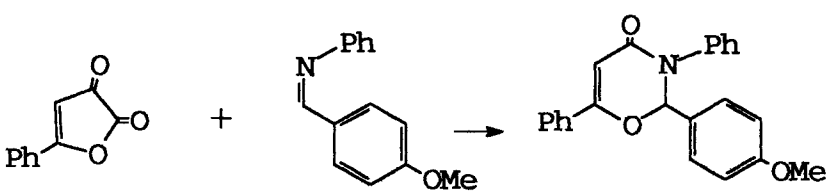
The benzylic position of 4-methoxy-n-propylbenzene has been substituted by the azido group in 97% yield through prolonged reaction over 5 days with excess trimethylsilylazide in chloroform containing 2,3-dichloro-5,6-dicyanobenzoquinone, followed by catalytic hydrogenation of the product in ethanol with 5% palladium-barium sulphate at ambient temperature and 1 atmosphere during 3.5 hours. 1-(4-Methoxyphenyl)propylamine was isolated as the hydrochloride in 60% yield (ref.129).



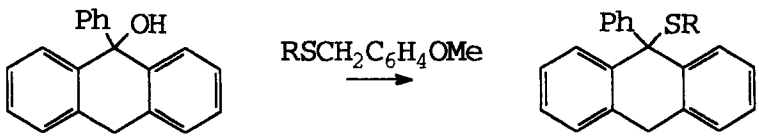
Asymmetric dihydroxylation of the side-chain of Z-1-(4-methoxyphenyl)-1-(tert-butyldimethylsiloxy)-1-propene to give (R)-1-hydroxyethyl 4-methoxyphenyl ketone in 94% yield (99% e.e.) was effected by addition of the alkene to a stirred mixture of osmium tetroxide, potassium ferricyanide, potassium carbonate, a 9-O-(9'-phenanthryl)ether (PHN) of dihydroquinidine and 1 mole of methanesulphonamide in aqueous tert-butanol (1:1), with reaction during 16 hours at ambient temperature. Then treatment with sodium sulphite prior to work-up to gave the product (ref.130). Other 'best ligands' were the 9-O-(4'-methyl-2'-quinolyl) ethers (MEQ) of dihydroquinine.



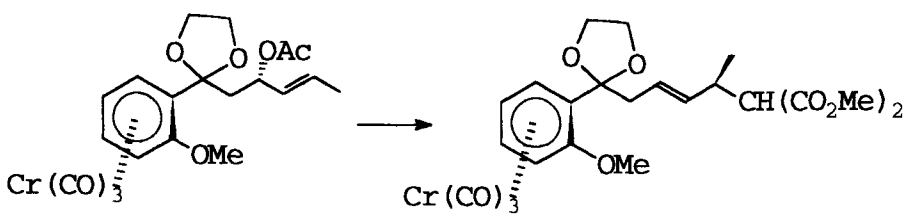
Addition to the side-chain of the aldimine from 4-anisaldehyde and aniline occurred in its reaction with the furan-2,3-dione shown with loss of carbon monoxide by heating in benzene during 2 hours to give 2-(4-methoxyphenyl)-3,6-diphenyl-2,3-dihydro-4H-1,3-oxazine-4-one in 93% yield (ref.131)



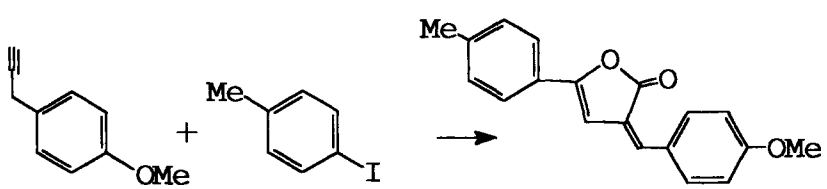
In a reaction at the benzylic group of 9-phenylxanthen-9-ol, the hydroxyl group was substituted by the uridine moiety with side formation of 4-methoxybenzyl acohol.
2'-Deoxy-2'-(4-methoxybenzylthio)uridine ($RSCH_2C_6H_4OMe$), in trifluoroacetic acid containing phenol was refluxed for 1 hour, and after removal of the solvent, the xanthen in glacial acetic acid was added and reacted at ambient temperature during 20 minutes to afford 2'-deoxy-2'-(9-phenylxanthen-9-ylthio)-uridine in 80% yield (ref.132).



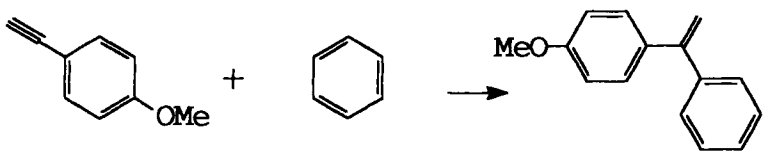
Asymmetric induction at an allylic centre in the side-chain of a phenolic ether in the form of its chromium tricarbonyl complex has been described. The chiral (E)-allyl acetate shown, in tetrahydrofuran containing 10 mol% $[PdCl(CH_2CH{=}CH_2]_2$-dppe, reacted with dimethyl sodiomalonate at ambient temperature during 16 hours to afford the (R) adduct in 95% yield (ref.133).



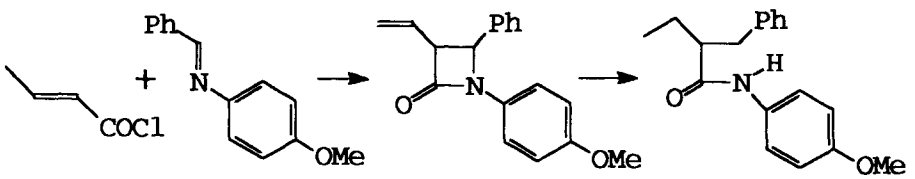
The terminal alkyne, 3-(4-methoxyphenyl)-1-propyne (1.2 moles) and 4-iodotoluene in benzene containing 2 moles triethylamine, catalytic amounts of palladium(II) acetate and triphenylphosphine when heated in an autoclave at 119°C for 4 hours under pressure with carbon monoxide (300psi.) afforded an 85% yield of the alkylidenebutenolide, 3-(4-methoxybenzylidene)-5-(4-methylphenyl)furan-2(3H)-one (ref.134).



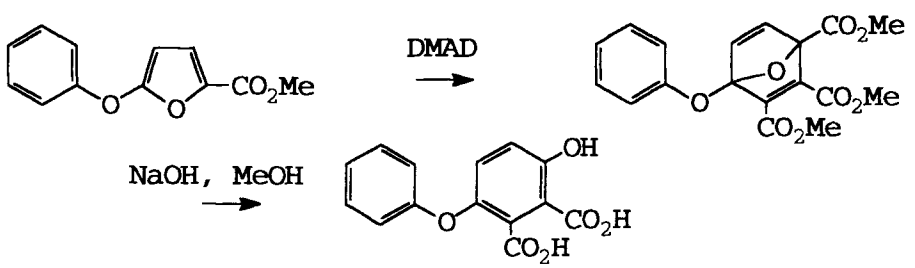
A related alkyne in benzene containing some rhodium trimethylphosphine carbonylchloride, $Rh(PMe_3)(CO)Cl$, when irradiated at 50°C through Pyrex with a 500 watt high pressure Hg arc lamp, reacted with the solvent to furnish the alkylidene derivative indicated in 95% yield (ref. 135).



By the use of a microwave oven it has been found that the α-vinyl-β-lactam illustrated, formed from a Schiff's base and but-2-enyl chloride in the presence of triethylamine, undergoes both hydrogenation and ring cleavage merely in 45 seconds at 110°C in ethanediol containing ammonium formate and 10% Pd-C (ref.136).

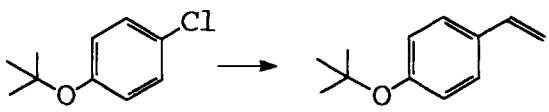


Diels-Alder addition of dimethyl acetylenedicarboxylate (DMAD) occurs to the dienoid side chain of 2-methoxycarbonyl-5-phenoxyfuran, formed itself from the 5-nitro analogue, to afford in toluene at 110°C, an adduct which undergoes base-catalysed aromatisation to yield a substituted diphenyl ether (ref.137).

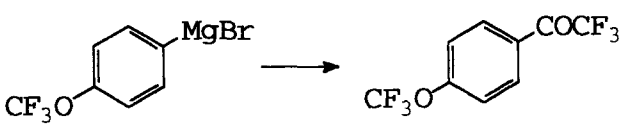


(iv) Displacement of Nuclear Chlorine, bromine or fluorine from a Phenolic Ether.

Conversion of 4-tert-butoxychlorobenzene in tetrahydrofuran to the Grignard reagent and reaction with vinyl chloride in the presence of a small proportion of dichloro[1,3-bis(diphenylphosphino)propane]nickel at 30-40°C over a total reaction time of 6.5 hours furnished 4-tert-butoxystyrene in 93% yield (ref.138).



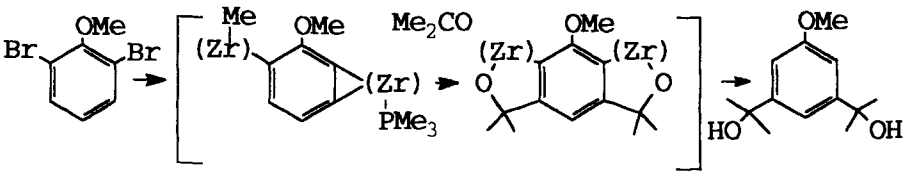
The Grignard reagent prepared from 4-bromophenyl trifluoromethyl ether in diethyl ether, with trifluoroacetic anhydride gave 4-trifluoromethoxy-trifluoroacetophenone (ref.139).



2-Fluoroanisole or 3-fluoroanisole with an n-alkyllithium in 2-4 molar excess in dry ethereal solution followed by quenching of the reaction mixture by addition to solid carbon dioxide and subsequent acidification with dilute hydrochloric acid afford the 6-n-alkyl-2-methoxybenzoic acid in moderate yield through intermediate formation of 2-anisyne. By contrast, 4-fluoroanisole gives mainly 2-methoxy-5-fluorobenzoic acid (ref.140).

The formation of 3,5-bis[(2-hydroxy-2-methyl)ethyl]anisole from 2,6-dibromo-anisole by way of a zirconocene intermediate has been reported (ref.141). A pentane solution of n-butyllithium (4moles) was added to 1 mole of 2,6-dibromoanisole in tetrahydrofuran containing 2 moles of methylzirconocene

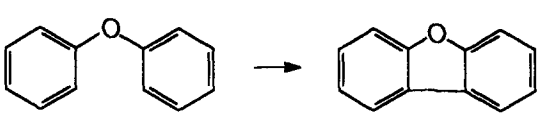
chloride at -78°C and after treatment of the mixture with trimethylphosphine during 16 hours at ambient temperature, acetone was added and hydrolysis gave the product shown in 66% yield.



Displacement of bromide ion from 2-bromophenoxy(dimethyl)chloro-methylsilane with sodium in refluxing toluene, until monitoring indicated completion of reaction, occurred with formation of 2,3-dihydro-1,3-benzoxasilole in 60% yield (ref.142).

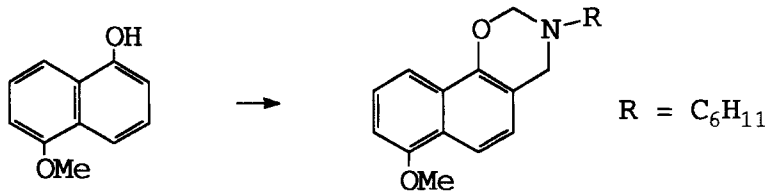
4.3.5 Cyclisation Reactions of Phenolic Ethers

Intramolecular cyclisations of phenolic ether derivatives often aided by an activating group at the 4-position have been used to obtain a variety of heterocycles.
Dihenyl ether in the presence of palladous and cuprous acetates in acetic acid and oxygen (300psig) at 140°C was oxidatively converted to dibenzofuran in high yield after heating for 3 hours (ref.143).

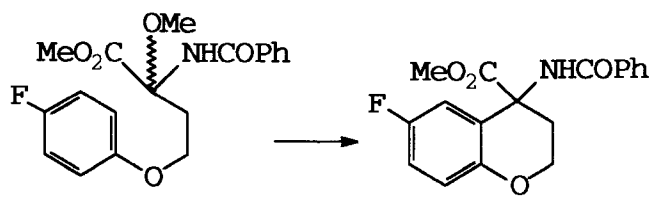


The reaction of 5-methoxy-1-naphthol with cyclohexylamine (1mole) and aqueous formalin (2moles) at ambient temperature gave 3-cyclohexyl-

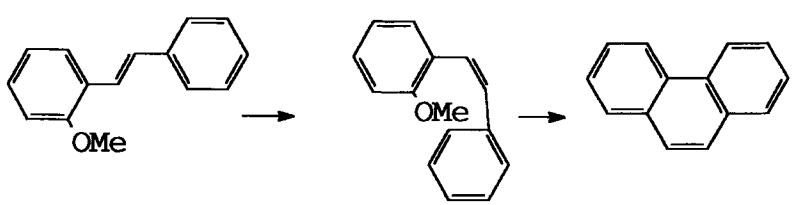
3,4-dihydro-7-methoxy-2H-naphtho[2,1,e][1,3]-oxazine in 80% yield (ref.144).



The fluorophenoxyl ether, methyl 2-benzoylamino-4-(4-fluorophenoxy)-2-methoxybutyrate with methanesulphonic acid (or boron trifluoride etherate in chloroform) at 0°C followed by warming to ambient temperature gave the pyran, methyl 4-benzoylamino-2,3-dihydro-6-fluoro-4H-benzopyran-4-carboxylate in 85% yield (ref.145).

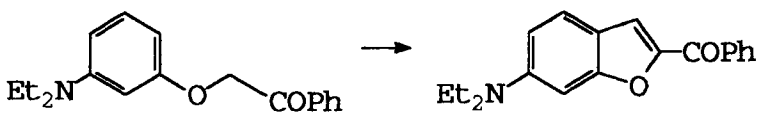


The loss of a methoxyl group from the ring of an aromatic ether occurred in the regioselective photocyclisation of 2-methoxystilbene to phenanthrene in a mixture of sulphuric acid and tert-butanol with elimination of methanol (ref.146). Phenanthrenes are also obtained by treatment of 2,2'-dialkoxystilbenes with low valent titanium. The same pathway is involved as in the reduction of 2-methoxyacetophenone to 9,10-dimethylphenanthrene referred to earlier (ref.99).

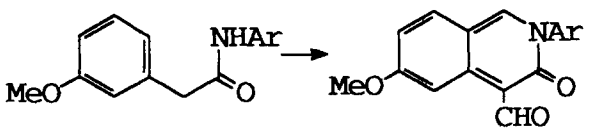


The cyclisation of intermediate formyl derivatives is shown by the two following examples. α-Aryloxyacetophenones which by direct dehydration with concentrated sulphuric acid afford 3-arylbenzofurans, give upon formylation and

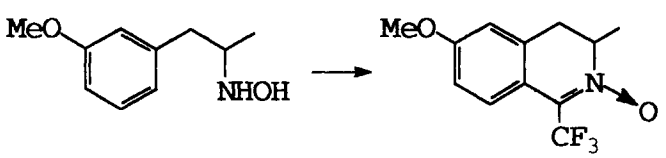
cyclisation, 2-benzoylbenzofurans. When formylated with dimethylformamide /phosphorus oxychloride (1:3) at 0°C during 30 minutes and then cyclised at 60°C for 10 hours α-(3-diethylaminophenoxy)acetophenone furnished 2-benzoyl-6-diethylaminobenzofuran in 78% yield (ref.147).



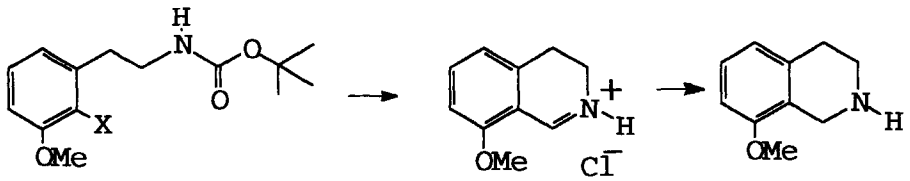
Addition of excess of the dimethylformamide/phosphorus oxychloride reagent to N-3-trifluoromethylphenyl 3-methoxyphenylacetamide (Ar = $-C_6H_4CF_3$) at 0°C during 15 minutes followed by cyclisation of the resulting diformyl derivative by heating at 75°C for 6 hours gave 4-formyl-6-methoxy-2-(3-trifluoromethyl-phenyl)-isoquinol-3-one in 60% yield (ref.148).



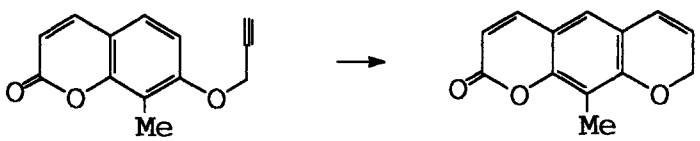
In a similar general way trifluoroacetyl derivatives have been cyclised. N-Hydroxy 1-(3-methoxyphenyl)-2-aminopropane in trifluoroacetic acid and trifluoroacetic anhydride upon refluxing for 15 hours afforded 6-methoxy-3-methyl-1-trifluoromethyl-3,4-dihydroisoquinoline-N-oxide in 86% yield (ref.149).



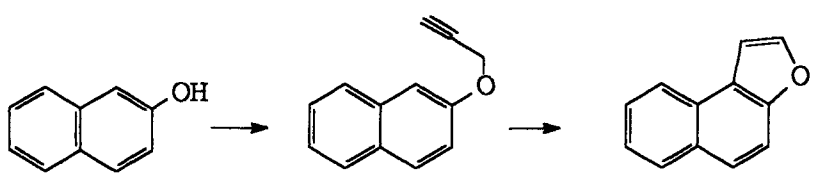
8-Methoxy-1,2,3,4-tetrahydroisoquinoline has been obtained through lithiation with butyllithium between the methoxyl group and the side-chain in N-pivaloyl 2-(3-methoxyphenyl)ethylamine (X = H), formylation with dimethylformamide to give the formyl compound (X = CHO), followed by cyclisation with 10% hydrochloric acid and finally reduction with sodium borohydride (ref.150).



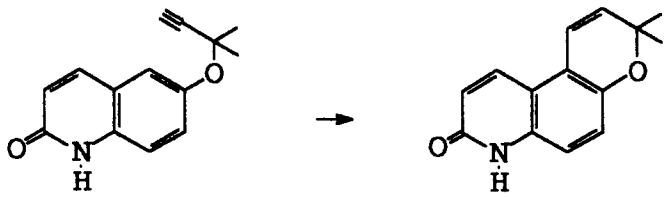
Pyran dervatives have been synthesised from the cyclisation of propynyl ethers. Thus 8-methyl-7-hydroxycoumarin was converted in 72% yield with 3-bromopropyne by refluxing in acetone containing potassium carbonate to 8-methyl-7-propynyloxycoumarin, which in boiling diethylaniline for 3 hours gave 10-methyl-2H,8H-benzo[1,2-b;5,4-b']dipyran-2-one in 48% yield (ref.151). When the 6-position was substituted, cyclisation proceeded at the 8-position.



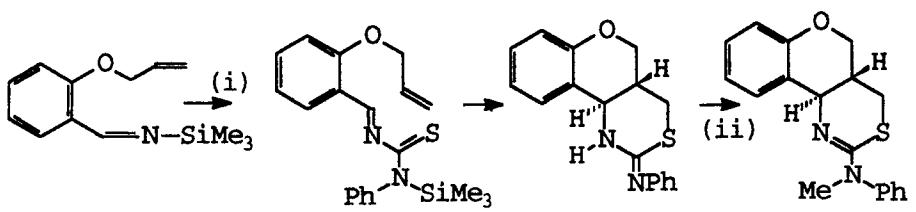
By contrast, the propynyl ether from 2-naphthol when refluxed in N,N-diethylaniline containing 1.4 moles caesium fluoride for 1 hour gave the naphthofuran shown in 88% yield (ref.152).



8-Hydroxyquinoline-2-one with 3-chloro-3-methylbutyne refluxed in acetone containing potassium iodide and carbonate during 20 hours gave the butynyl ether, cyclisation of which in hot dimethylaniline at 200°C for 2 hours furnished 3,3-dimethyl-3H-pyrano[3,2-f]quinoline-8(7H)-one (ref.153).

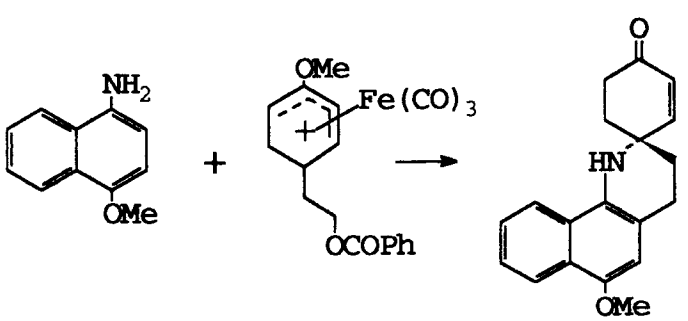


Cyclisation of the allyl ether shown having an azadiene and an alkene system occurred by an intramolecular Diels-Alder addition to afford a route to a tricyclic thiazine (ref.154). Cyclohexyl isothiocyanate has also been used in the initial step.

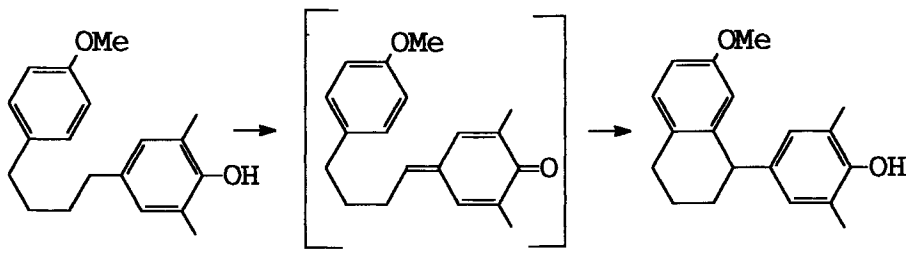


(i) PhNCS, toluene, 90°C; H_2O (ii) NaH, DMF, 25°C; MeI.

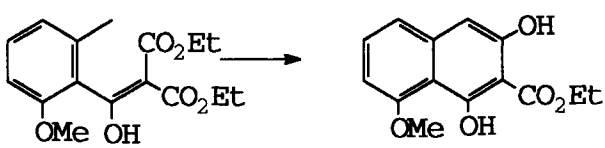
The previous cyclisations proceeded to o- and p-positions to the activating alkoxyl group whereas the influence of a metaltricarbonyl system in one of the reactants as in the following example may affect the orientation of the product. 4-Methoxy-1-aminonaphthalene with the tricarbonyl(η^5-4-methoxycyclohexadienylium)iron cation when refluxed in methyl cyanide afforded the spiro cyclohexeno product shown comprising a 9:1 ratio of regioisomers in 71% yield after decmplexation (ref.155).



Another cyclisation resulting in substitution m- to the methoxyl group is the intramolecular result of phenolic oxidation brought about by way of a quinone methide generated under biological conditions. The 4-hydroxydiarylalkane shown upon treatment with mushroom tyrosinase (E.C.1.14.18.1) in a phosphate buffer in methylcyanide (1:1) at pH 6.8 and reacted during 48-72 hours (with TIC monitoring) afforded a tetralin derivative (ref.156) in 50-60% yield.



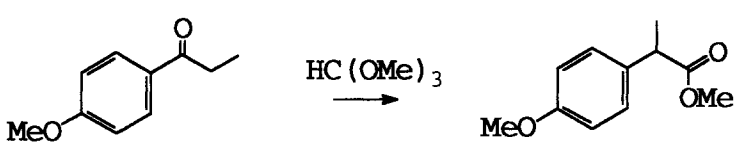
Cyclisation in 68% yield at the benzylic position occurred when the substituted benzoylmalonic ester indicated was treated with 4 proportions of lithium di-isopropylamide in tetrahydrofuran at -16°C to give in 68% yield ethyl 1,3-dihydroxy-8-methoxynaphthalene-2-carboxylate (ref.157).



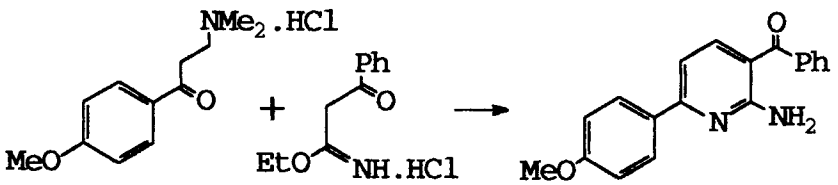
4.3.6 Reactions of Keto Derivatives of Phenolic Ethers

Certain of these reactions are also examples of side-chain substitution in phenolic ethers.

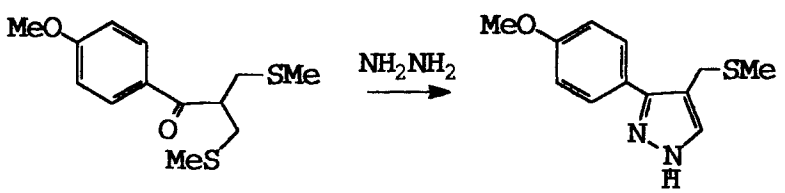
4-Methoxypropiophenone in methyl orthoformate containing iodine after reaction at ambient temperature for 20 hours has been reported to give methyl 2-(4-methoxyphenyl)propionate in 85% yield by a 1,2-aryl migration (ref.158).



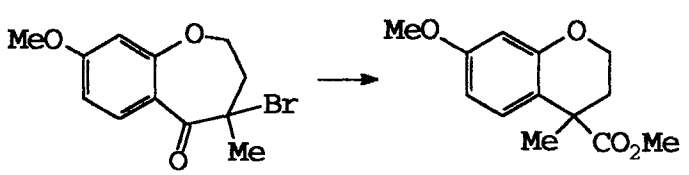
A number of heterocyclic systems are obtainable from methoxyphenyl and other substituted ethers of keto compounds.
Interaction of the Mannich base from 4-methoxyacetophenone, formaldehyde and dimethylamine over 2 hours in refluxing dimethylformamide with the iminoester hydrochloride of ethyl benzoylacetate, initially converted to the amidine with ammonium acetate, afforded 2-amino-6-(4-methoxyphenyl)pyrid-3-yl phenyl ketone in 66% yield (ref.159) the reaction proceeding essentially by Michael addition.



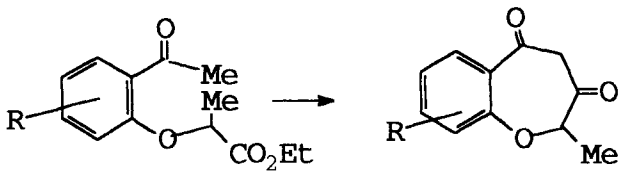
The reaction of hydrazine hydrate and the phenolic ether derivative shown in refluxng ethanol during 2 hours gave 4-methylthiomethyl 5-(4-methoxyphenyl)-pyrazole in 93% yield presumably by way of the hydrazone followed by loss of methylthiol (ref.160).



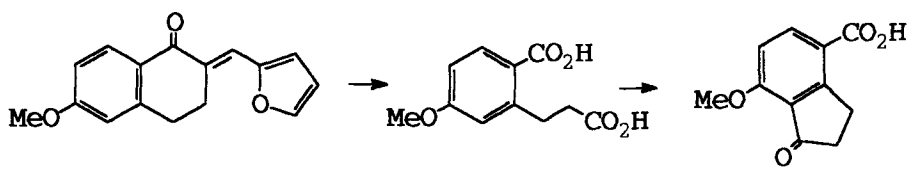
Benzopyrans have been synthesised from benzoxepine derivatives by way of the Favorsky rearrangement. The bromo compound shown, when added in methanol to a methanolic solution of zinc chloride at 115 C and then reacted with stirring for 17 hours afforded methyl 4-methyl-7-methoxychroman-4 -carboxylate in 61% yield (ref.161).



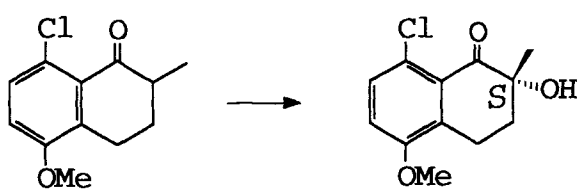
Chloro, bromo, dichloro, tert-butyl, and unsubstituted 1-benzoxepine-3,5(2H,4H)-diones have been synthesised from the corresponding ethyl 2-(2-acetophenoxy)propionates in good overall yields by the action of ethanolic sodium ethoxide (ref.162).



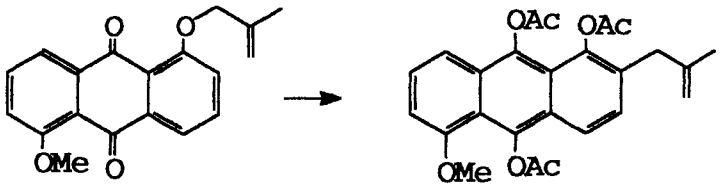
Ozonisation of 2-furfurylidene-6-methoxy-1-tetralone in ethyl acetete at -78°C, removal of excess ozone with nitrogen and treatment of the ozonide in glacial acetic acid with 30% hydrogen peroxide, afforded after 12 hours, 3-(2-carboxy-5-methoxyphenyl)propionic acid in 82% yield which after conversion to the acid chloride with thionyl chloride in dichloromethane at 5°C was cyclised in the presence of aluminium chloride at ambient temperature to 7-methoxy-1-oxo-indan-4-carboxylic acid (isolated as the methyl ester with diazomethane in 45% yield) (ref.163).



7-chloro-4-methoxy-2-methyltetral-1-one in toluene solution containing triethyl phosphite and 5 mole% of a chiral cinchonine catalyst added to 50% aqueous sodium hydroxide with oxygenation and vigorous stirring during 5 hours at ambient temperature gave a 95% yield of the 2(S)-hydroxy derivative with 79% enantiomeric excess. Cinchonidine and ephedrine afforded lower enantioselectivity (ref.164).



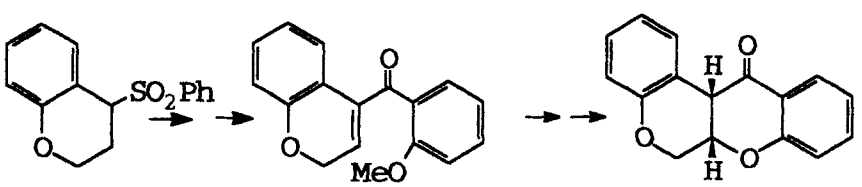
Claisen rearrangement accompanied by reductive acetoxylation of 1-isobutenyloxy-5-methoxy-9,10-anthraquinone has been reported in 86% yield by refluxing with acetic anhydride containing sodium acetate and zinc dust for 1 hour at 140°C (ref.165).



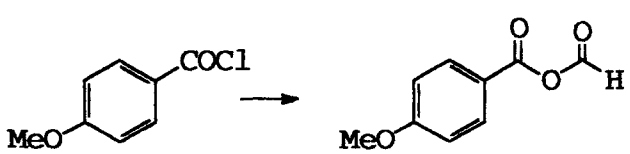
4.3.7. Reactions of Carboxy, Amido, Formyl and Nitro Derivatives of Phenolic Ethers

Some of these reactions also represent examples of side-chain substitution in phenolic ethers. .

2-Methoxybenzoyl chloride has been used to acylate the carbanion from 4-phenylsulphonylchroman furnishing the product shown which after conversion to the corresponding α,β-unsaturated ketone, demethylation with boron trichloride and cyclisation with ethanolic potassium acetate afforded a chromanochromanone related to the parent ring system of rotenone (ref.166)



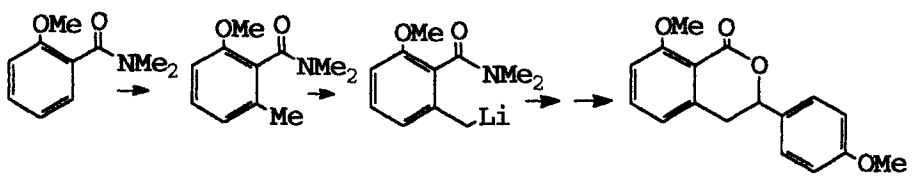
4-Methoxybenzoyl chloride has been found to give the mixed carboxy formic anhydride shown in 89% yield upon reaction, accompanied by vigorous stirring, with sodium formate in acetonitrile containing a 4-vinylpyridine-1-oxide copolymer (ref.167).



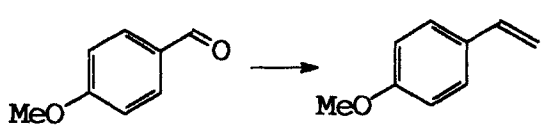
2-Aryloxybutyramides (effectively amido derivatives at the benzylic position in phenyl isopropyl ether) readily formed from 2-bromo-iso-butyramide and a variety of phenoxides in dioxane undergo the Smiles rearrangement in dimethylformamide containing 1,3-dimethyltetrahydropyrimidin-2(1H)-one (DMPU) solution and sodium hydride to form substiuted acetanilides with yields in the range 60-90%. Thence by hydrolysis aromatic amines are formed in good yields (ref.168).

$$ArONa \rightarrow ArOC(Me_2)CONH_2 \rightarrow ArNHCOC(Me_2)OH \rightarrow ArNH_2$$

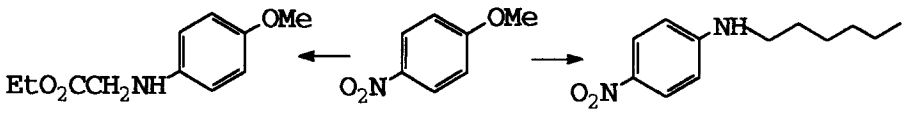
2-Methoxybenzamide after o-lithiation in tetrahydrofuran with sec-butyllithium containing tetra(N-methyl)ethylenediamine, methylation with excess iodomethane at -90°C, removal of excess reagent, followed by re-cooling of the mixture to -60°C to form the carbanion of the intermediate product with lithium diisopropylamide, and finally reaction with 4-methoxybenzaldehyde, afforded the isocoumarin derivative shown in 45% yield (ref.169) after work-up with aqueous ethanolic sodium hydroxide.



4-Methoxystyrene was produced in 84% yield from 4-methoxybenzaldehyde by reaction with methylenetrichloromolybdenum (obtained by the addition of of 2 moles of methyllithium to molybdenum pentachloride in tetrahydrofuran /ether (4:1) at -70°C) during 1-2 hours at -70°C followed by warming to 20°C over 15 hours (ref.170).

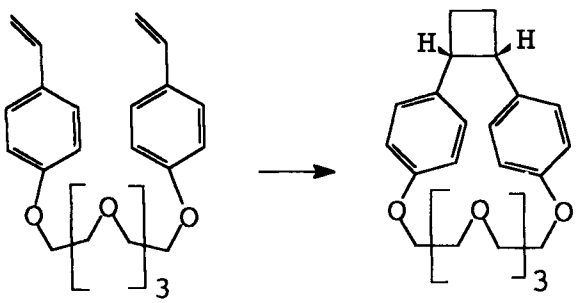


Ketones were unreactive in this interesting modification of the Wittig technique. In the photoreaction of 4-nitroanisole with n-hexylamine the methoxyl group is replaced while ethyl glycinate substitutes the nitro group the former being attributed to an $S_N2^3Ar^*$ process and the latter to the participation of a radical-ion pair (ref.171).

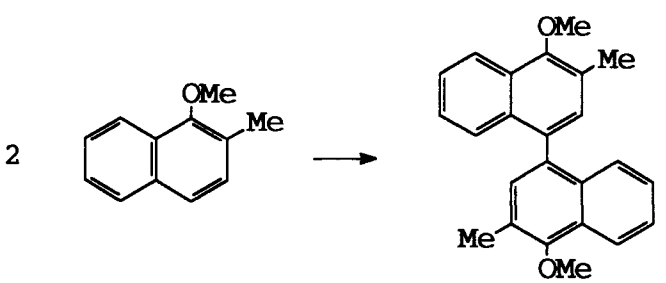


4.3.8. Phenolic Ether Coupling

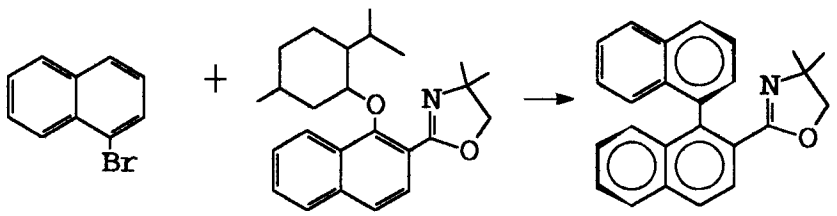
Coupling either at the ring or in the side-chain has been described under a variety of conditions.
The styrenoid crown ether indicated, with lithium borofluoride in methanol contained in a Pyrex tube, upon irradiation under nitrogen with a 400w high pressure mercury lamp furnished a cyclobutane derivative in 82% yield (ref.172).



1-Methoxy-2-methylnaphthalene, with cobalt trifluoride in trifluoracetic acid upon refluxing for 12 hours afforded in 88% yield the 4,4'-dinaphthyl shown, which was also obtained from oxidation with lead tetra-acetate, ferric chloride, thallium(III) trifluoroacetate and mercuric trifluoroacetate (ref.173).

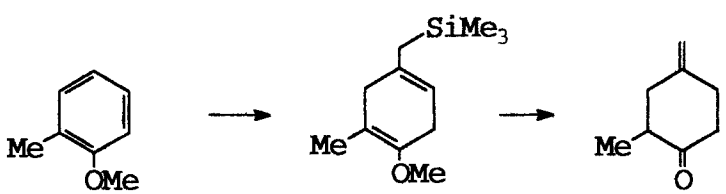


Coupling simulutaneously with asymmetric synthesis has been reported by the use of a chiral leaving group.
1-(1-Menthoxy)-2-oxazolinonaphthalene in tetrahydrofuran at -78°C added to 1-lithionaphthalene (formed from 1-bromonaphthalene in tetrahydrofuran at -78° to -42°C with sec-butyllithium) followed by stirring of the mixture for 1 hour afforded the 2-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-1,1'-binaphthyl, having 67% enantiomeric excess, in 80% yield (refs.174,175).



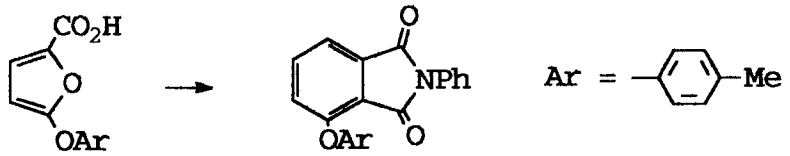
4.3.9. Ring Saturation of Phenolic Ethers

A Birch reduction of 2-methylanisole leading to methylenation has been described. The final step was effected by treatment of the intermediate, 3,6-dihydro-2-methyl-4-trimethylsilylmethylanisole with concentrated hydrochloric acid and aqueous tetrahydrofuran during 30 hours to give 4-methylene-2-methylcyclohexanone in 60% yield (ref.176).



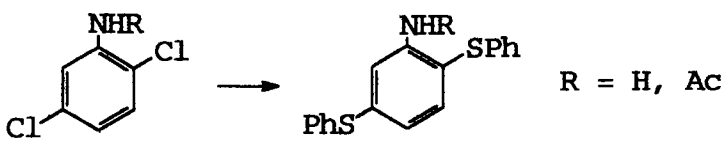
4.3.10. Diels-Alder Reactions of Phenolic Ethers

An additive reaction of a phenolic ether is shown in a one-pot syntheses in which decarboxlation also takes place. 5-(4-Methylphenoxy)-2-furoic acid and N-phenylmaleimide in chloroform containing 10mole% trifluoroacetic acid heated in a sealed thick-walled tube under nitrogen for 1-2 hours gave N-phenyl 3-(4-methylphenoxy)phthalimide in 95% yield accompanied presumably by loss of water from the reactants (ref.177). In a similar way 5-alkoxy and 5-arylthio-furan-2-carboxylic acids have been reacted.



4.3.11 Thiophenyl and Selenophenyl Ethers

The reactions of thiophenyl ethers (previously reviewed (ref.178) are of synthetic interest. Chlorobenzenes in N-methylpyrrolidinone containing sodium alkanethiolates are converted to the corresponding thioethers (ref.179). 2,5-Dichloroaniline in N-methylpyrrolidinone containing thiophenol and potassium carbonate when reacted during 18 hours at 190°C gave 5-chloro-2-phenylthioaniline in 90% yield, while 2,5-dichloroacetanilide with the same reagents afforded the corresponding monothiophenyl product in the same yield at 140°C (ref.180).



Methyl phenyl thioether with hexadecane in an aqueous culture medium of diammonium hydrogen phosphate, magnesium sulphate, traces of ferrous sulphate containing yeast extract after inoculation with Corynebacterium equi, FO 3730 and incubation during 3 days at 30°C, afforded (R)-methyl phenyl sulphoxide in quantitative yield (enantiomeric excess 75%) (ref.181).

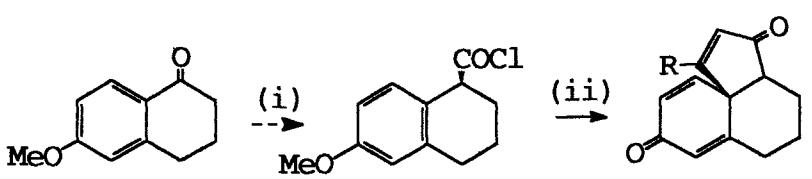
tert-Butyl phenyl thioether and dibromodioxan in dioxane after being stirred occasionaly at ambient temperature for 2 hours gave a 78% yield of diphenyl disulphide. By contrast, with primary or secondary alkyl compounds, bromination took place in the 4-position (ref.182).

In the selenium series, methyl phenylselenide in chloroform at 25°C upon portionwise treatment with 1 mole of 2-benzenesulphonyl-3-(4-nitrophenyl)oxaziridine and reaction for 1 min. only, gave the selenoxide in 97% yield (ref.183).

4.3.12 Hydroxylation of Phenolic Ethers and Cyclohexadienone formation

The oxidative coupling of phenolic ethers has been referred to. The hyroxylation of anisole, also of interest for obtaining monomethyl derivatives of hydroquinone and of catechol, albeit in low yields, has been investigated both with hydrogen peroxide and iodoxybebzene in dichloromethane/acetonitrile (1:1) containing imidazole and catalytic amounts of iron(III) and of manganese(III) porphorin derivatives (ref.184). Thus anisole (700parts), hydrogen peroxide (10parts), imidazole (10parts) and a manganese polyhalogenated porphyrin [termed Mn(TdCPP)Cl] (1part, at a concentration of 2mM) afforded 4-hydroxyanisole (47%), 2-hydroxyanisole (3.5%) and phenol (2%) the yields being based on the starting hydrogen peroxide employed.

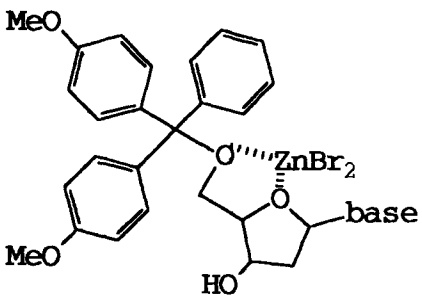
The transformation of 6-methoxytetral-1-one to the spiro cyclohexadienone structure depicted by way of the 1-chlorocarbonyl derivative has been described (ref.185). R = Ph and n-Pr.



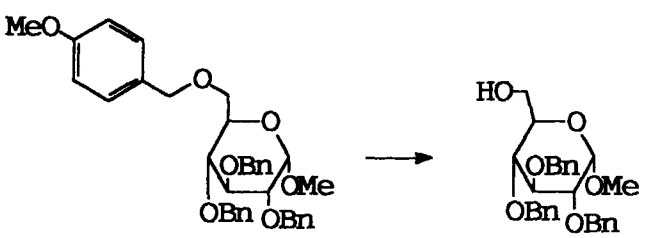
(i) Me_3SO^+, NaH; CrO_3,H_2SO_4,Me_2CO; $(COCl)_2$, DMF,(ii) RC=CH, $AlCl_3$, CH_2Cl_2

4.3.13 The Phenolic Ether Group used for Protective Purposes

The dimethoxy trityl group at the 5-position in the derivative shown was removed preferentially by addition of the compound to a suspension of zinc bromide in nitromethane and work-up after 1 minute to afford a quantitative yield (ref.186).



The 4-methoxybenzyl ether group in the compound shown was preferentially removed in dichloromethane solution containing anisole and stannous chloride upon treatment at ambient temperature with trimethylchlorosilane during 30 minutes to give the product in 87% yield (ref.187).



4.3.14 General Structural and Synthetic Interest in the Phenoxyl Group

Diaryl oxalates afford a convenient photolytic source of phenoxyl radicals (ref.188) The oxido grouping has been employed for imparting conformational immobility to a complex multi-ring structure in ligand binding studies (ref.189).

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CHAPTER 5

OXIDATION OF PHENOLS

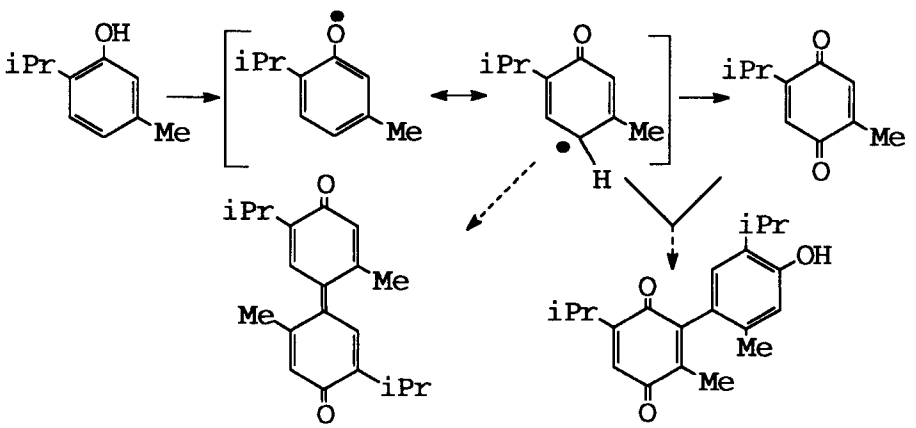
5.1 Introduction

The oxidation of phenols has many different aspects. In this account, oxidative coupling, the formation of cyclohexadienones, conversion to quinones and other carbonylic and transformation products (other than those obtained by electrophilic substitution or rearrangement of phenyl esters) are considered. Particular attention has been paid to work carried out in the last decade. An early review has described initial work (ref.1) and that carried out later is available in the same source (ref.1, Ch.2). To a certain extent this present chapter inevitably impinges on the chemistry of alkylphenols (Ch.6), although oxidation has been excluded in that section except in the case of hindered phenols which are only briefly referred to in the following examples.

5.2 Oxidative Coupling

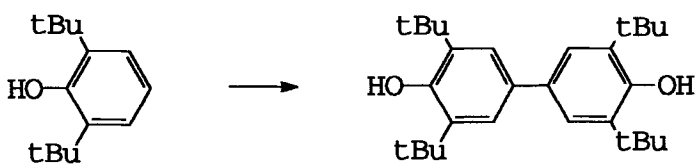
5.2.1 Phenols

Under mild conditions the oxidation of thymol has been studied extensively in

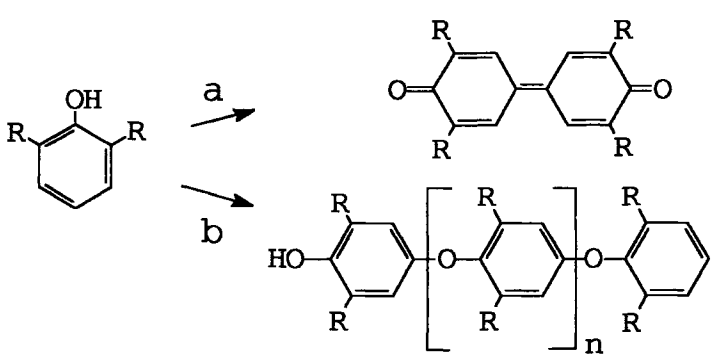


ethanolic solution at 60°C by dropwise addition to anhydrous cupric chloride and gassing of the stirred solution with oxygen over 48 hour to give the thymylthymoquinone shown (65%), the more completely oxidised diphenoquinone (10%) as well as some thymoquinone (25%) (ref.2). 2-Methylphenol under similar conditions afforded a cresylcresoquinone analogue of the major product from the oxidation of thymol. From 2,6-dimethylphenol and 2,6-di-tert-butylphenol 3,5,3',5'-diphenoquinones resulted as the major products in 51% and 70% yields respectively with, in the former case, some 2,6-dimethylbenzo-1,4-quinone (32%). The general mechanism shown on the preceding page seems operative although the phenylbenzoquinone pathway is speculative.

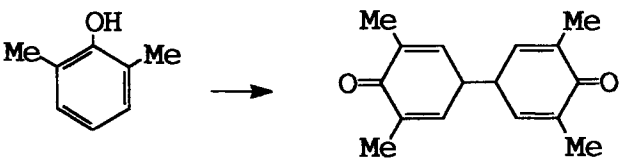
By contrast with the above conditions, the oxidation of 2,6-di-tert-butylphenol in 50% aqueous potassium hydroxide containing 50% aqueous methyl tri-n-butylammonium chloride in a sealed reactor at 200°C and 300 psig. for 1 hour with 50%hydrogen peroxide has been reported to give 4,4'-bis(2,6-di-tert-butylphenol) the precursor of the diphenoquinone in 97.5% yield (ref.3).



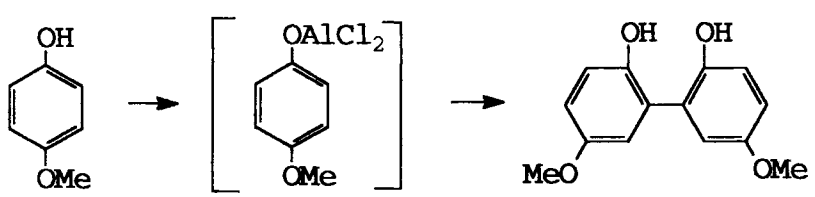
A comparison of phenolic coupling on solid potassium permanganate and on potassium manganate surfaces has been made to emulate the natural biological process (ref.4). Diphenoquinone formation in more than 90% yield was observed with the oxidation of 2,6-dimethyl, 2,6-di-isopropyl, and 2,6-di-tert-butyl phenol (R = Me,i-Pr,t-Bu) in chloroform solution on (a) solid potassium permanganate whereas under the same conditions (b) potassium manganate,



a milder oxidant, gave exclusively a poly(2,6-diaryl-1,4-phenyleneoxide). By the addition of powdered potassium hydroxide to the potassium permanganate system, the polyphenylene oxide (85%) and the diphenoquinone (15%) resulted. It has also been reported that solid iron(III) chloride is more effective for the oxidative coupling of phenols than when used in solution (ref.5).
Cobalt(III) acetate (2.5 moles) with 2,6-dimethylphenol in acetic acid reacted at 70°C during 5.5 hours afforded a 75% yield of 3,3',5,5'-tetra-methyl-4,4'diphenoquinone together with a 23% yield of 2,6-dimethyl-1,4-benzoquinone (ref.6).

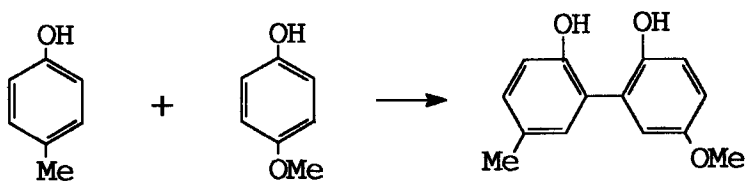


Biological methods have been extended by the use of mushroom tyrosinase which with 0.01M 2,6-dimethylphenol in stirred phosphate buffer (pH 6.8) gave after 9 hours the diphenoquinone in 96% yield. Dissolved oxygen was necessary for the oxidation. Only o-blocked electron-donating phenols were oxidised since 2,6-dichlorophenol proved unreactive in this system. The co-solvent acetonitrile afforded bis-phenols as by-products (ref.7).
The previous examples have invariably involved the 4-position but where this is substituted as in the case of 4-methoxyphenol, oxidative coupling can take place at the 2-position probably via an intermediate phenoxide ion without 1,4-benzoquinone formation. Thus 1 mole of aluminium chloride in nitromethane solution treated with 4-methoxyphenol and, after 1 hour, anhydrous ferric chloride in nitromethane gradually introduced, led after reaction during 5 hours and acidic work-up to 2,2'-dihydroxy-5,5'-dimethoxybiphenyl in 78% yield (ref.8).



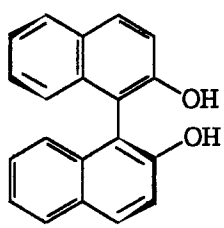
Oxidative cross-coupling has been effected moderately selectively. For example, by the addition of aluminium chloride in nitromethane to a nitromethane solution of 4-methylphenol and 4-methoxyphenol under nitrogen followed by gradual treatment with with dichlorodicyano-1,4-benzoquinone and reaction at ambient

temperature during 1 hour 2.2'-dihydroxy-5'-methyl-5-methoxybiphenyl was obtained in 70% yield (ref.9).

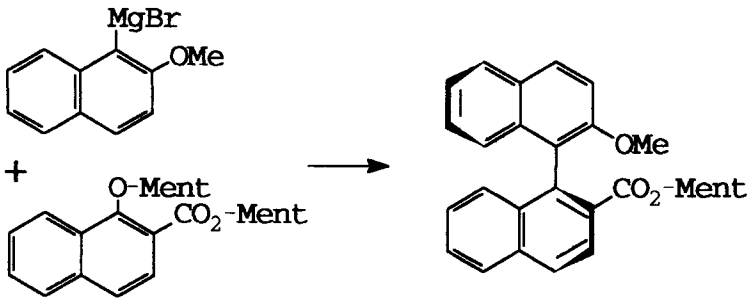


5.2.2 Naphthols

With the cupric chloride/oxygen system used for phenols, 2-naphthol in ethanol solution did not give a coupled product but only 4-ethoxy-1,2-naphthoquinone (65%) together with 1-chloro-2-naphthol (30%) was isolated. Finely powdered 2-naphthol with ferric chloride hexahydrate maintained at 50°C during 2 hours followed by acidic hydrolysis gave racemic 2,2'-dihydroxy-1,1'-binaphthyl, (1,1'-dinaphthalene-2,2'- diol) in 95% yield without quinone formation (ref.10). By the use of the S(+)-amphetamine copper(II) complex, the enantiomer S(-)-[1,1'-binaphthalene]-2,2'-diol has been synthesised in 85% yield and high optical purity (up to 95%) with 80% recovery of the amphetamine salt (ref.11).

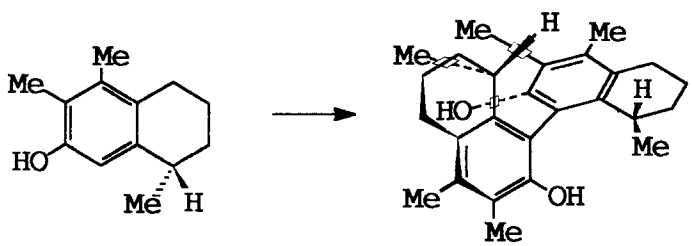


The absolute configuration of the monohydroxy analogue, 2-hydroxy-1,1'-binaphthyl reported (ref.12), has been revised to the R-(+) form.
Asymmetric cross coupling of the Grignard reagent from 2-methoxy-1-bromonaphthalene with menthyl 1-(-)menthoxy-2-naphthoate in ether/benzene (1:1) by reaction at ambient temperature for 3 hours followed by gentle refluxing for 2 hours, gave the product shown in 81% yield with an optical purity of 98% (ref.13).



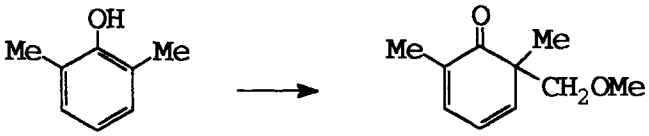
[(-)-menthol = ment]

Asymmetric oxidative dimerisation of S(+)-3,4,8-trimethyl-5,6,7,8-tetrahydro-2-naphthol in ether with potassium ferricyanide in aqueous 0.2M sodium hydroxide was effected by stirring at ambient temperature for 2 hours to afford the S,S-(+)-trans dimer in 62% yield (ref.14).

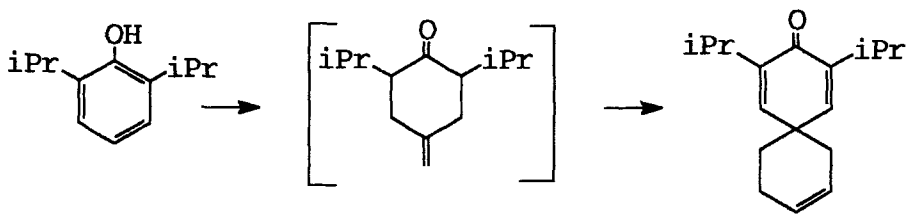


5.3 Formation of Cyclohexadienones

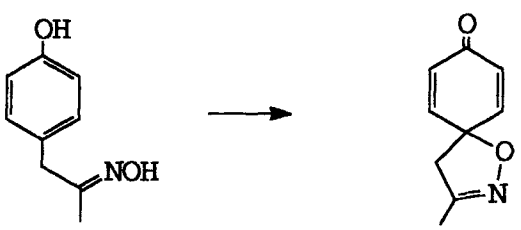
Cyclohexadienones can be considered structurally as hemi-quinones and they have been synthesised in recent years by a variety of simple approaches in which invariably a substituent becomes attached to the 2- or 4- position and the structure becomes locked. 2,6-Dimethylphenol in hexane or benzene converted at 0°C to the anion with n-butyllithium in hexane, gradually warmed to ambient temperature, stirred for 1 hour, and then alkylated at 0°C with chloromethyl methyl ether afforded after 2-4 hours reaction 2,6-dimethyl-6-methoxymethylcyclohexa-2,4-dienone in 85% yield without formation of the 2,5-isomer. Chloromethyl methyl thioether and 2-trimethylsilylethoxymethyl chloride were also used (ref.15).



2,6-di-isopropylphenol interacted with paraformaldehyde and 40% aqueous dimethylamine in isopropanol to give the expected 4-hydroxy-N,N-dimethylbenzylamine which, probably by way of the quinone methide, has been reacted then with buta-1,3-diene by heating in a pressure vessel at 200°C for 7 hours to give the spiro compound, 2,4-di-isopropylspiro[6,6]undeca-1,4,8- trien-3-one in 82% yield (ref.16).

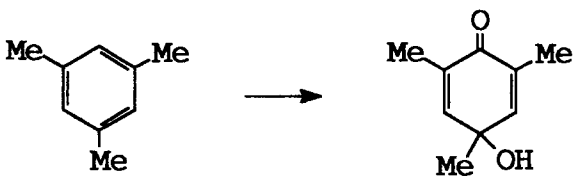


The oxime of 4-hydroxybenzyl methyl ketone by treatment in refluxing acetonitrile solution with phenyliodosodi(trifluoroacetate) afforded the spiro product 3-methyl-1-oxa-2-azaspiro[4.5]deca-2,6,9-trien-8-one in 63% yield (ref.17).

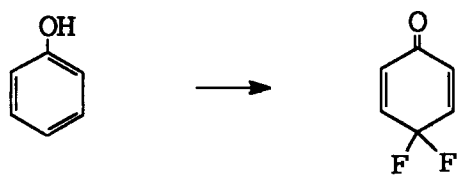


The cyclohexadienone formed from carvacrol, (5-isopropyl-2-methylphenol), by potassium periodate oxidation, or with iodic acid in ethanol, has been used to synthesise 3,10-dihydroxydielmentha-5,11-diene-4,9-dione, a monoterpene dimer from the plant, *Callitris macleayana* (ref.18).

The iodic acid oxidation of thymol and of isothymol also afforded similar compounds (ref.18).
A number of alternative routes have been investigated for the conversion of 2,4,6-trimethylphenol to a number of different cyclohexadienones. These are summarised in Table 5.1 (refs.19-24).
By contrast the electrolytic oxidation at 8°C and a current of 0.7A with a graphite anode and a stainless steel cathode of a solution of mesitylene in aqueous sulphuric acid/acetonitrile (4:1) gave, over 5.5 hours, a 43% yield of the same product, namely 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (ref.25) as obtained with the oxidants chlorine, manganese dioxide or sodium hypochlorite.



A number of halogenated cyclohexadienones have been prepared.
4,4-Difluorocyclohexa-2,5-dienone was obtained in 60% yield by the addition over 15 min. of phenol and lead dioxide to a stirred mixture at 35°C of 70% hydrogen fluoride in pyridine and dichloromethane followed by reaction for 30 min. (ref.26).



2,6-Dibromo-4-methylphenol in methanolic dichloromethane upon treatment with phenyliodosoacetate in dichloromethane at ambient temperature and reaction with stirring for 1 hour afforded 2,6-dibromo-4-methoxy-4-methylcyclohexa-2,5-dienone in 63% yield (ref.27).

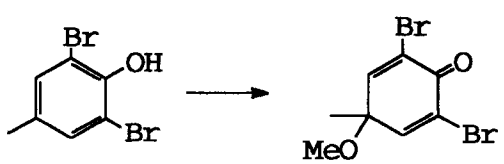
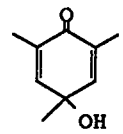
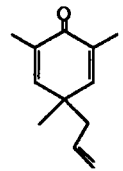
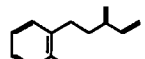
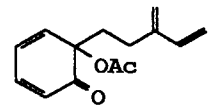
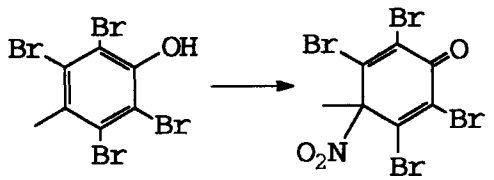


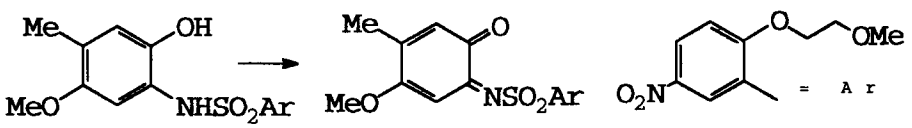
TABLE 5.1 CYCLOHEXADIENONES DERIVED FROM 2,4,6-TRIMETHYLPHENOL

REAGENT	CONDITIONS	PRODUCT	YIELD%	REF.
Chlorine	2,4,6-Trimethylphenol and sodium bicarbonate in carbon tetrachloride treated with Cl_2 at 0° (21 min.), filtered into aq. $NaHCO_3$, to give 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone.		70	19
Manganese dioxide	To manganese dioxide, aq. H_2SO_4 and diisopropyl ether, 2,4,6-trimethylphenol and diisopropyl ether added at 0°, then reacted at 0-5° for 5½h.	"	66	20
Sodium hypochlorite	16% Sodium hypochlorite (pH 12.5) added dropwise (15 min.) to 2,4,6-trimethylphenol in H_2O, and then reacted for 10 min.	"	65	21
Oxygen	2,4,6-Trimethylphenol in water pressurised to 30 kg/cm² with oxygen at 30° and stirring (4½h)	"	81	22
ß-Cyclodextrin and allyl bromide	A mixture of 2,4,6-trimethylphenol and ß-cyclodextrin (with all 1° OH groups substituted by N-methyl formamide) in 1% sodium hydride treated dropwise with allyl bromide and reacted 1h. to give 2,4,6-trimethyl--4-allylcyclohex-2,5-dienone.		88	23
Lead tetraacetate	The phenol,  , in acetic acid treated with lead tetraacetate to give 6-acetoxy,6-(3-methylenepent-4-enyl)-cyclohexa-2,4-dienone		50	24

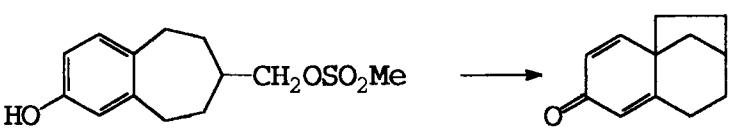
4-Methyl-4-nitro-2,3,5,6-tetrabromocyclohexa-2,5-dienone, a regiospecific nitrating agent was obtained in 88% yield by the addition at 100°C over 10 mins. of nitric acid (d 1.52) to 4-methyl-2,3,5,6-tetrabromophenol in acetic acid followed by reaction for 2 hours at 5°C (ref.28).



With an oxidisable group in the 2-position to the phenolic hydroxyl group an o-quinonimine structure can be derived as in the oxidation of 4-methoxy-2-([2-(2-methoxyethoxy)-5-nitrophenyl]sulphonamido)-5-methylphenol in acetone by manganese dioxide at ambient temperature over 3 hours to give 4-methoxy-N([2-(2-methoxyethoxy)-5-nitrophenyl]sulphonyl)-5-methyl-o-benzo quinonimine in 59% yield (ref.29).

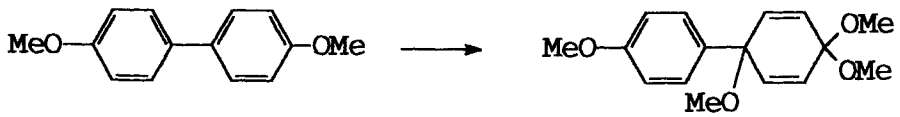


Production of an anionic centre by the use of potassium tert-butoxide in tert-butanol accompanied by an S_n2 intramolecular cyclisation has enabled a 2,5-cyclohexadienone to be used in a novel synthetic way as shown in the following reaction which after a 7 hour refluxing period gave 6,7,8,9-tetrahydro-4a,7-methano-4a,(H)-benzocyclohepten-2,(5H)-one in 57% yield (ref.30).

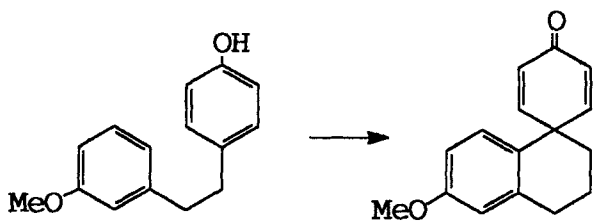


An electrolytic procedure facilitated the conversion of a 1% methanolic potasium hydroxide solution of 4,4'-dimethoxybiphenyl, in a single cell with a platinum

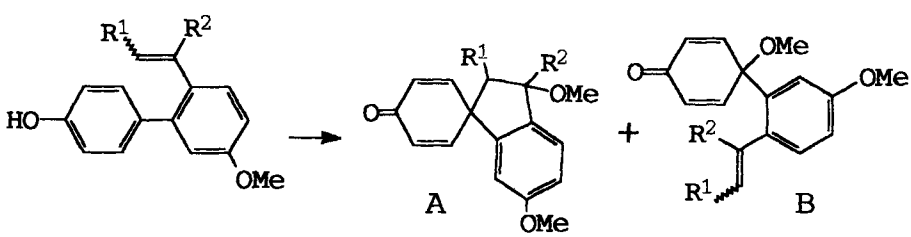
gauze anode and a constant current of 2A over 8 hours, to the dimethyl acetal of a cyclohexadienone system in 86% yield (ref.31).



Spiro-annulated 2,5-cyclohexadienones have been obtained by the oxidation of 4-phenylphenols with phenyliodosodiacetate. Thus 1-(4-hydroxyphenyl)-2-(3-methoxyphenyl)ethane in acetonitrile afforded the 1-spirotetralin compound illustrated upon refluxing with the reagent during 4 hours (ref.32). Unsubstituted, 4-methoxy and 3,4-dimethoxyphenyl analogues have also been synthesised.

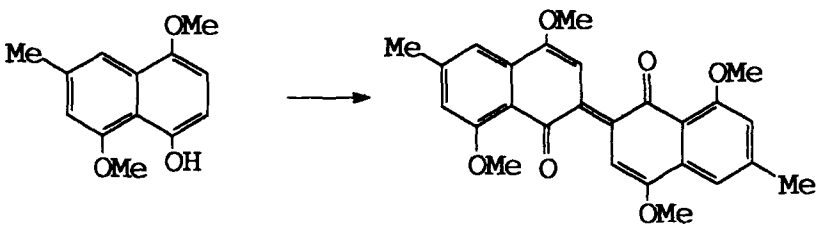


The structurally related spiroindane (A),(R = alkyl) together with the cyclohexadienylanisole (B) by-product, in proportion dependent upon the position of a methoxyl substituent, resulted from oxidation of 2'-alkenyl-4-phenylphenols by treatment with the same reagent in methanolic solution (ref.33). For example with a 4-methoxy group, as shown, A(56%) and B(34%) were produced while a 3-methoxy reactant afforded only B(63%).



Naphthalenic compounds such as 4,8-dimethoxy-6-methyl-1-naphthol can be oxidatively coupled essentially by way of a cyclohexadienone. The naphthol

shown in chloroform containing 0.2% triethylamine was oxidised with silver oxide and the extent of reaction monitored chromatographically until formation of 4,4',8,8'-tetramethoxy-6,6'-dimethyl-2,2'-dinaphthylidene-1,1'-dione was complete with a 95% yield (ref.34).



5.4 Quinone Formation

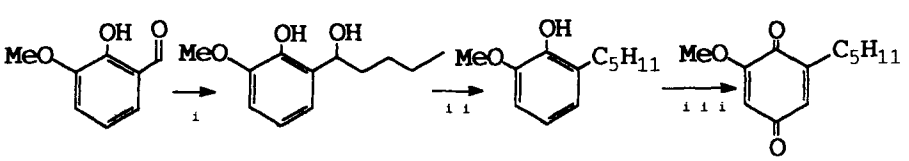
5.4.1 Benzoquinones

Under more drastic conditions than for formation of cyclohexadienones, 1,4-quinones are produced sometimes even when the the 4-position is substituted as in the case of 2,4,6-trichlorophenol which gives 2,6-dichloro-1,4-benzoquinone.

Table 5.2 (refs.35-44) summarises the conditions employed for a variety of alkyl-substituted phenols. In many cases homologous and other substituted compounds gave equally satisfactory results.

The compounds listed in the table all afforded high yields of 1,4-benzoquinones even in the examples of thymol, carvacrol and the 3- and 4-methylphenols. 1,4-Benzoquinones were derived from the oxidation of electron-rich methoxyarenes by magnesium monoperoxyphthalate with a water-soluble iron porphyrin as catalyst (ref.45).

Primin (2-methoxy-6-n-pentyl-1,4-benzoquinone) has been synthesised from the oxidation of 2-methoxy-6-n-pentylphenol with Fremy's salt (the Teuber reaction) by the route indicated (ref. 46).



(i) 2BuLi, H_3O^+ (ii) Pd-C, H_2 (iii) oxidn.

TABLE 5.2 FORMATION OF 1,4-BENZOQUINONES

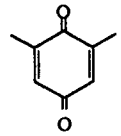
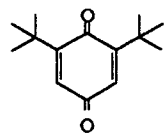
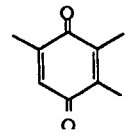
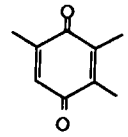
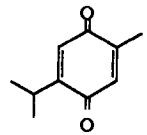
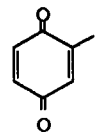
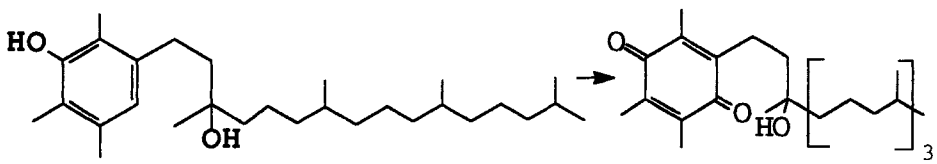
PHENOL	OXIDANT	CONDITIONS	PRODUCT	YIELD (%)	REF.
2,6-Dimethyl phenol	Jones reagent (chromic acid)	2,6-Dimethyl phenol in ether treated at 0° with Jones reagent over 2½h and stirred 24h. to give 2,6-dimethylbenzoquinone.		84	35
2,6-Dimethyl	Br_2/H_2O_2	2,6-Dimethylphenol and 0.55 equivs. bromine added to a solution of 60% hydrogen peroxide (2 equiv.) and conc. sulphuric acid in methanol, followed by refluxing (20 min.).	"	85	36
2,6-Di-tert butylphenol	Br_2/H_2O	2,6-Di-tert-butylphenol, 59% H_2O_2 and concentrated sulphuric acid in methanol treated with bromine (a catalyst) and the mixture refluxed 10 min. (I_2, HBr and HI can be used as catalysts) to give 2,6-di-tert-butylquinone.		92	37
2,6-Di-tert butylphenol	O_2/KOH, dimethyl sulphoxide	A mixture of 2,6-di-tert-butyl phenol and potassium hydroxide in dimethyl sulphoxide gassed with oxygen for 2 h.	"	68	38
2,3,6-Trimethyl phenol	$RuCl_3.3H_2O$/ H_2O_2	Acetic acid containing ruthenium trichloride trihydrate and 2,3,6-tri-methylphenol treated at ambient temperature with hydrogen peroxide,stirred continuously for 5 h. and finally sodium thiosulphate solution added to give 2,3,6-trimethylquinone.		90	39
2,3,6-Trimethyl	$RuCl_3.3H_2O$/ 30% H_2O_2	To a solution of 2,3,6-trimethylphenol and a little ruthenium chloride trihydrate in acetic acid 30% H_2O_2 (2 equiv.) added at ambient temperature during 5		90	40

TABLE 5.2 (contd.)

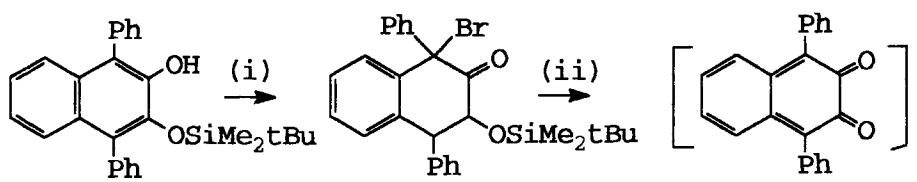
PHENOL	OXIDANT	CONDITIONS	PRODUCT	YIELD (%)	REF.
2,3,6-Trimethyl phenol	NPV_6Mo_6/C	Oxygen bubbled intp a stirred solution of 2,3,6-trimethylphenol and the vanadomolybdophosphate catalyst on active carbon in 1:2(AcOH-H_2O) at 60C for 5h. Catalyst reusable.		75	41
2,3,6-Trimethy phenol	60% H_2O_2 ($H_3PMo_{12}O_{40}$	The phenol and a little phosphomolybdic acid in acetic acid treated dropwise with 60% H_2O_2 followed by stirring for 5 h at 30° under N_2 to give 2,3,6-trimethylquinone.	"	78	42
2,3,6-Trimethyl phenol	tert-butyl hydroperoxide/ cuprous chloride	To stirred 2,3,6-trimethylphenol in acetic acid at acid at 23° containing a little cuprous chloride, a solution of tert-butylhydroperoxide in tert-butanol added dropwise and reaction completed in a further 20 mins.	"	95	43
Thymol (2-isopropyl-5-methylphenol)	oxygen	Cobalt (II) salicylaldehyde ethylene diamine added to thymol in dimethylformamide and the stirred mixture gassed with oxygen at ambient temp. for 3 h.		79	44
Carvacrol (2-methyl-5-iso-propylphenol)	"	alternatively Co(II) salen and O_2 treatment repeated for 6 h: work-up by ethereal extraction in presence of O.1M hydrochloric acid to afford 2-isopropyl--5-methyl-benzoquinone.	"	88	44
2-Methyl phenol	"	Similar conditions gave 2-methylbenzoquinone.		50	44
3-Methyl phenol		"			

By the use of iodoxybenzene in the presence of a small amount of trichloroacetic at ambient temperature o-quinones have been obtained (ref.47). Dimethyldioxirane oxidises phenols to o-quinones (ref.48) while catechols are cleaved to Z,Z-muconic acid (ref.49).
In the tocopherol series, 2,3,6-trimethyl-5-(3'-hydroxy-3',7',11',15'-tetramethyl - hexadecany)phenol in benzene was added to a slurry of Fremy's salt and aqueous sodium carbonate containing tri-caprylmethylammonium chloride in benzene to give, after 2.5 hours reaction tocopherylquinone in 93% yield (ref.50).



5.4.2 Naphthoquinones and Polycyclic Quinones

Some new reagents have been introduced for the preparation of 1,4- and 1,2-naphthoquinones. These have been summarised in Table 5.3 (refs.51-57). 2,3-Naphthoquinones have been generated by a non-oxidative route involving bromination with N-bromosuccinimide in the 1-position of the respective 2-keto tautomer as the mono t-butyldimethylsilyl derivative, treatment of the bromo compound with tetra-n-butylammonium fluoride and trapping of the product as a norbornadiene adduct, in a yield of 64% in the case of the 1,4-diphenyl member (ref.58).



(i) NBS, CH_2Cl_2, (ii) Bu_4NF, CH_2Cl_2, -50°C

2,7-Phenanthrenequinones have been produced from the coupling of cis-4,4'-dihydroxystilbenes, (in one example obtained through a Wittig reaction with 3,4,5-trimethoxybenzaldehyde and 2,3,4-trimethoxybenzylphosphoniumbromide), followed by selective demethylation and oxidation with the silver(I) cation, (Ag_2O) (ref.59).

TABLE 5.3 OXIDATION OF NAPHTHOLS TO NAPHTHOQUINONES

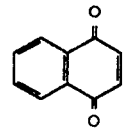
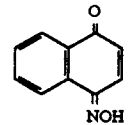
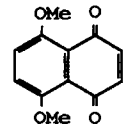
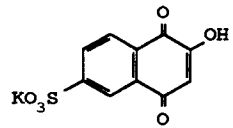
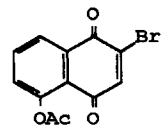
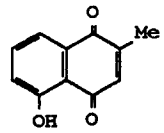
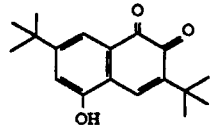
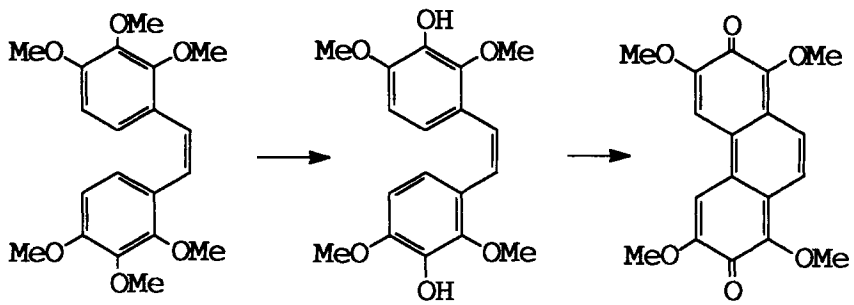
NAPHTHOL	OXIDANT	CONDITIONS	PRODUCT	YIELD (%)	REF
1-Naphthol	phenyl iodosotrifluoro acetate	1-naphthol in acetonitrile/water (2:1) added dropwise to phenyl iodosotrifluoro acetate (2:2 equivs.) in the same solvent at 0°, followed by stirring for 2 h		73	51
1-Naphthol	N-nitroso dimethylamine (Me_2NNO)	1-naphthol (1 mole) and N-nitrosodimethyl amine (1 mole) in dioxan irradiated through a pyrex filter gave 1,4-naphthoquinone mono-oxime		68	52
1-Hydroxy-5,8-dimethoxy naphthalene	Ammonium cerium (IV) nitrate	a 10% aqueous ammonium cerium (IV) nitrate was added dropwise to the stirred naphthol in acetonitrile (until a colouration remained) producing 5,8-dimethoxynaphth-1,4-quinone		68	53
Sodium 2-hydroxy naphthalene-6 -sulphonate	copper (II) acetate oxygen	Sodium 2-hydroxynaphthalene-6-sulphonate added to a stirred mixture of morpholine and copper (II) acetate in in methanol was gassed with oxygen at 20° to give the intermediate 4-morpholino-1,2-naphtholquinone-6-sulphonate in 83% yield. After addition to aq. potassium hydroxide followed by stirring of the mixture at 45C. the producyt was obtained.		76	54
1,5-Diacetoxy naphthalene	N-bromo succinimide	1,5-Diacetoxynaphthalene in warm acetic acid was added to an aqueous acetic acid solution of N-bromo-succinimide and the mixture stirred for 45 min. at 55-60°		90	55

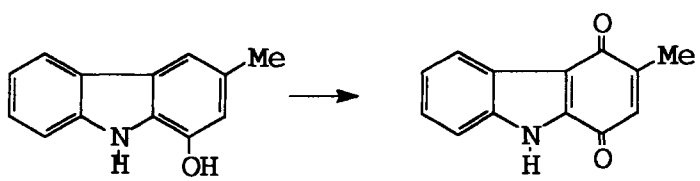
TABLE 5.3 (contd.)

NAPHTHOL	OXIDANT	CONDITIONS	PRODUCT	YIELD (%)	REF.
2-Methyl-5-acetoxy -1-naphthol	Fremy's salt	The required staerting material was prepd. from naphthalene-1,5-diol by the Mannich reaction to give the morpholinomethyl deriv. Selective 5-acetylation and reductive deamination with H_2/ Pd-Cgave 2-methyl-5-acetoxy-1-naphthol. Oxidation then afforded 5-hydroxy-2-methyl-naphthoquinone-1,4-quinone.		33 (from the diol)	56
1,5-Dihydroxy-3,7-di-tert-butyl naphthalene	$[Mo(O_2)_2O]Pyr.$	The molybdenum oxide pyridine complex was added to the naphthalene in dichloromethane at 0°, the mixture wasstirred for 44 h and then hydrolysed with acid to give the product.		73	57

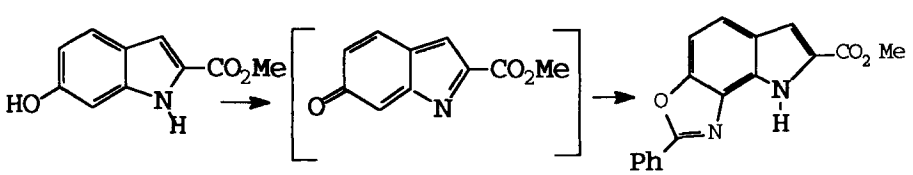


5.4.3 Bicyclic Heterocyclic Quinones

Specific oxidative treatments have enabled 1,4-quinone systems to be obtained. 1-Hydroxy-3-methylcarbazole in dichloromethane treated very briefly with pyridinium chlorochromate at ambient temperature afforded a 40% yield of 3-methylcarbazole-1,4-quinone (ref.60).

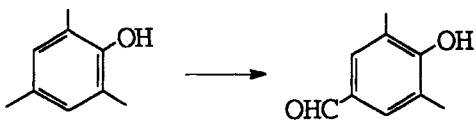


A hemiquinone intermediate rather than an o-quinone resulted from the oxidation of methyl 6-hydroxyindole-2-carboxylate in dimethoxyethane with activated manganese dioxide. By reaction with benzylamine in dimethoxyethane solution the intermediate formed methyl 2-phenylpyrrolo[2,3,e]-benzo-xazole-5-carboxylate in 61% yield (ref.61).

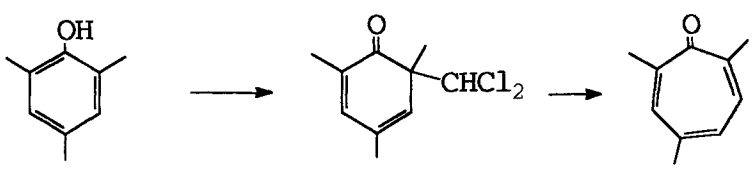


5.5 Other Carbonylic and Transformation Products

The versatility of the phenolic molecule towards oxidation is demonstrated by the formation of other oxidation derivatves than the coupling, quinone and cyclohexadienone series. 2,4,6-Trimethylphenol has been converted in 98% yield to 3,5-dimethyl-4-hydroxybenzaldehyde by aerial oxidation in dimethylformamide/methanol solution (1:5) containing cuprous chloride by passage of air through the solution during 8 hours (ref.62).

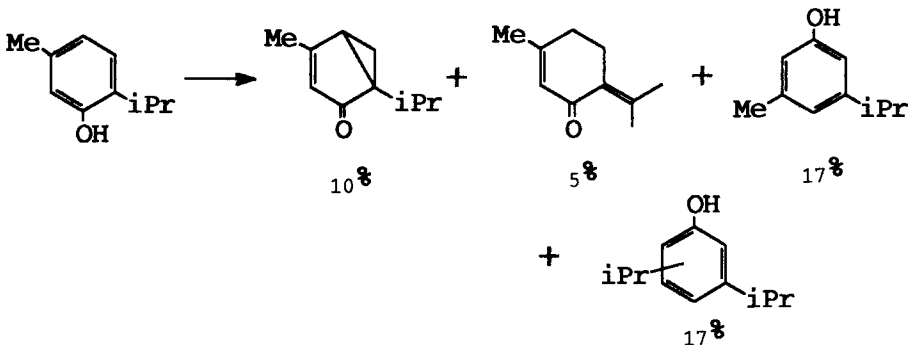


Formation of a trimethyltropone has been described by the transformation of the cyclohexadienone intermediate formed in the Reimer-Tiemann reaction in 59% yield from 2,4,6-trimethylphenol, chloroform and a little cetyltrimethylammonium bromide by treatment dropwise at 50°C over 10 mins. with aqueous sodium hydroxide. Refluxing of the cyclohexadienone for 4 hours with tributyltin hydride in benzene containing azoisobutyronitrile (AIBN) afforded 2,4,7-trimethyltropone in quantitative yield (ref.63).



The photochemical rearrangement products of thymol in tri-fluoromethanesulphonic acid by UV irradiation at 300nm during 40 hours at ambient temperature have been studied in detail and ten compounds isolated of which eight have been characterised. (ref.64). The conversion of the hydroxyl group in three of the products to a keto group is of interest in this section on oxidation. The irradiated acidic reaction mixture was quenched at 0°C in sodium hydrogen carbonate and dichloromethane and after isolation of the organic material it was separated chromatographically. In this one-step process one of the important products was umbellone (10%) formed by a regioselective type A rearrangement. Three other processes were suggested to be operative. Firstly, a C2-C3 migration (type A rearrangement) and ring-opening to give the principal product, 3-isopropyl-5-methylphenol (17%), secondly intermolecular

transalkylation giving three isomeric di-isopropylphenols (17%) and thirdly, formation of piperitone (5%) initiated by hydrogen abstraction.



Although outside the scope of the present chapter, another transformation of interest is the conversion of the fully hydrogenated product from phenol, namely cyclohexanol, to cyclohexanone in 100% yield by addition of a dichloromethane solution to bis(quinuclidine)bromine fluoroborate and silver fluoroborate in dichloromethane followed by reaction for 30 mins.at ambient temperature (ref.65).

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CHAPTER 6

ALKYL AND HINDERED PHENOLS

6.1 Introduction

Some of the preparative methods for alkyl phenols and their reactions are unique to this class and both therefore warrant separate treatment from the parent compound. These features are even more prevalent in the 'hindered phenols' a group of substances first synthesised less than half a century ago. In this account the synthesis of alkylphenols bearing purely methylenic side-chains in the benzenoid, naphthalenic and polycyclic series are considered first. Alkylphenols with side-chains containing oxy or alkoxycarbonyl groups are then reviewed, followed by mention of those containing Si, N or S in the side-chain and finally polycyclic types with saturated and unsaturated rings bearing hetero atoms. As before emphasis has been placed on developments in the last decade.
The reactions discussed fall into several categories. Intramolecular, intermolecular processes, those producing side-chains bearing oxy or carbonylalkoxy groups, cyclisations where the side-chain results in formation of a bicyclic compound and aspects of calixarene chemistry. In some cases synthetic and reaction chemistry overlap. For the majority of the reactions described the phenolic hydroxyl group provides an activating source and although a few would proceed in its absence, subsequent transformations on such a latent group extend the scope of synthesis.

6.2 Synthesis of Alkylphenols, Alkylnaphthols and Hydroxypolycyclic compounds with alkyl side-chains

6.2.1 Alkylphenols

A number of typical alkylations of various phenols are shown in Table 6.1 (refs.1-7). A novel feature of four of these procedures is the o-substitution which resulted. This feature, particularly where metallic systems are involved, reflects the tautomeric nature of phenols. While benzenoid intermediates represent the most obvious choice of starting material, the facile dehydrogenation of an alkylated cyclohexanone has also been used. Thus cyclohexanone and propanal (2 equivs.) heated at 150°C in the presence of bis-cyclopentadienyl zirconium dichloride afforded 2,6-di-n-propylphenol in 69% yield (ref.8).

TABLE 6.1 SYNTHESIS OF ALKYLPHENOLS WITH METHYLENIC SIDE CHAINS

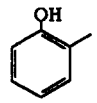
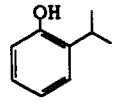
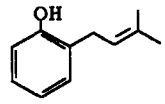
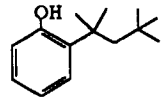
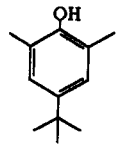
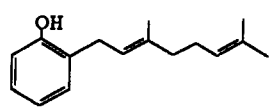
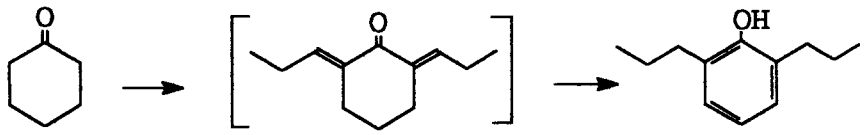
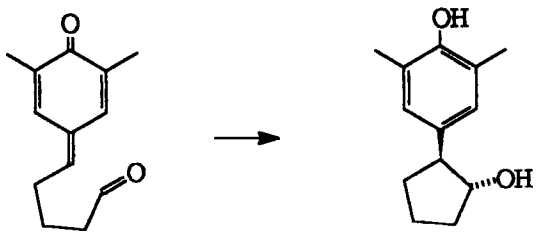
PHENOL	ALKYLATING AGENT	CONDITIONS	PRODUCT	YIELD (%)	REF
Phenol	di-iodo methane as (ethyl iodomethyl zinc)	To 1.2M diethylzinc in toluene which had first been added to a solution of diiodo methane in toluene at 0°, a solution of phenol in toluene was introduced. After 10 secs. the mixture was stirred at 0° for 5 min and refluxed for 1.5 h to give 2-methylphenol. $CH_2I_2 + El_2Zn \longrightarrow ElZnCH_2I$		50	1
Phenol	methanol	Molar mixture of phenol and methanol (2:1) heated at 425C with catalytic amount of 9.9 wt. % of Ga-modified TiO_2 (from $Ti(OiPr)_4$ and $Ga(NO_3)_3$ togive 2-methylphenol.	"	65	2
Phenol	propan-2-one	A mixture of propan-2-one and phenol (5:1) passed through a ZnO_2/Al_2O_3 catalyst held in a pyrex tube at 355° at 14 ml/min., followed by hydrogen at 100 ml/min. to give 2-isopropylphenol		92 (88% conversion)	3
Phenol	isoprene	To the phenol in benzene isoprene added slowly and freshly prepared MgI_2 in dry ether. Refluxed 3h. then worked up to give 2-prenylphenol. Naphthols gave 35% prenylnaphthols. all products were cyxlised tochromans with formic acid.		60	4
Phenol	2,2,4-trimethyl pent-4-ene	A mixture of phenol and 2,2,4-trimethylpent-4-ene (1:8 moles) was heated at 100-110° with a small amount of Al turnings until H_2 ceased to evolve, to give 2-(1,1,3,3-tetramethylbutyl)phenol		64	5

TABLE 6.1 (contd.)

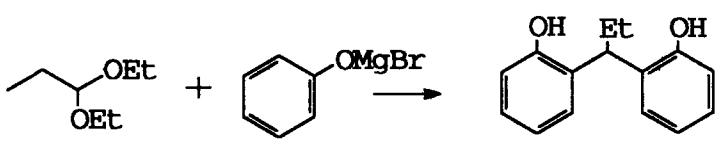
2,6-Dimethyl-phenol	tert-butyl bromide	To tert-butyl bromide was added 2,6-dimethylphenol in carbon tetrachloride containing silica gel and sodium carbonate and the mixture refluxed (24 h) to give 2,6-dimethyl-4-tert-butylphenol.		85	6
Phenol	(E) 3,7-dimethyl-octa-2,6-dienyl chloride	Potassium in small pieces was added under N_2 to phenol in xylene, the mixture refluxed for 3 h, powdered $ZnCl_2$ chloride added at ambient temp. and after 1 h, the halide in xylene introduced and the mixture refluxed (12 h) to afford (E)-2-(3,7-dimethylocta-2,6-dienyl)phenol.		86	7



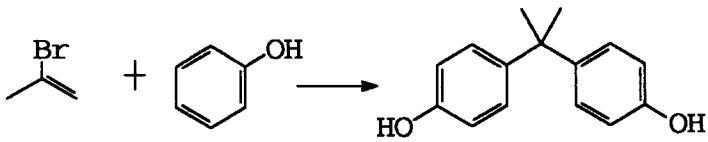
Cyclohexadienones, not unexpectedly, can been employed to obtain alkylphenolic systems. Thus a solution of the p-quinone methide depicted when slowly introduced in tetrahydrofuran solution over 2 hours into samarium(II) iodide at 35°C followed by work-up with sodium bicarbonate solution gave a 67% yield of (E)-2-(3,5-dimethyl-4-hydroxyphenyl)cyclopentanol. The SmI_2 was obtained by treating samarium during 1 hour with methylene diiodide in tetrahydrofuran at 0°C and reacting for a further hour (ref.9).



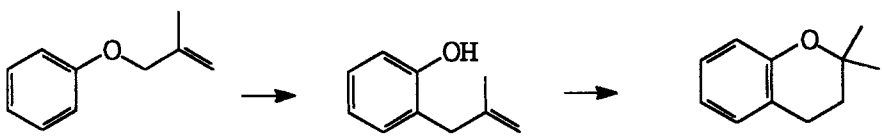
Acetals have been employed to derive 1,1-bis(2-hydroxyphenyl)alkanes. In this way propanal diethylacetal added to phenoxymagnesium bromide, prepared from phenol and ethylmagnesium bromide, gave 1,1-bis(2-hydroxyphenyl)propane in 70% yield after refluxing for 24 hours (ref.10). The enolic character of the phenoxy compound favours nucleophilic 2-substitution.



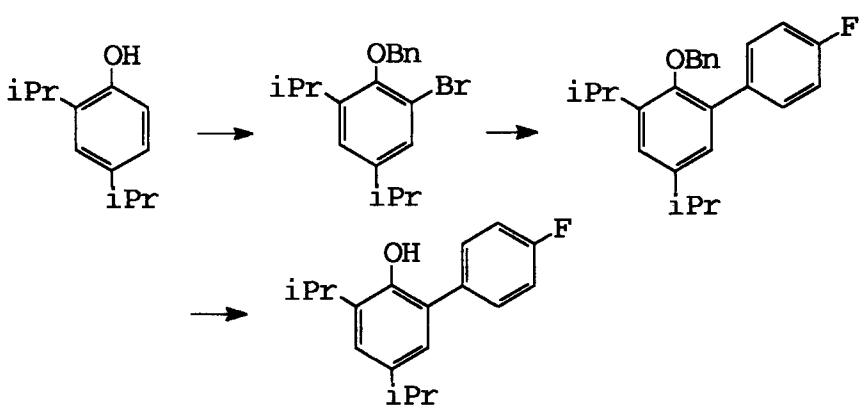
A double electrophilic alkylation was effected by the sequential addition of 2-bromopropene and tellurium tetrachloride to phenol at 0°C, succeeded by heating of the mixture at 50°C during 2 hours to afford an 82% yield of 2,2-bis(4-hydroxyphenyl)propane, ('bis phenol A') (ref.11).



The Claisen rearrangement of substituted allyl phenyl ethers in benzene solution to 2-allylphenols has been effected by montmorillonite clays employed in equal weight to the reactant (ref.12). A short reaction time at ambient temperature favours the allylphenol but longer period at a higher temperature results in formation of a chroman or, exceptionally, a coumaran.

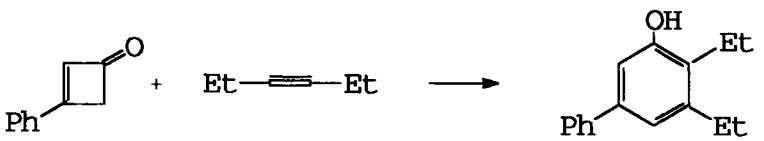


A variety of approaches involving addition reactions with organometallic reagents or transition metal mediation, usually involving two C3 components or (4+2) strategies, have been devised as seen in the following examples.
Grignard reagents have been used for the direct arylation of phenols (ref.13). Thus, 2,4-di-isopropylphenol was converted to the 6-bromo compound and benzylated. The Grignard reagent from this intermediate was reacted with 4-fluoroiodobenzene in tetrahydrofuran, containing tetra(triphenylphosphine) palladium, at 50°C during 1 hour and then at ambient temperature during 14 hours to afford 6-(4-fluorophenyl)-2,4-di-isopropylphenyl benzyl ether. the correspnding phenol was obtained upon hydrogenolysis with Pd-C in an overall yield of 83%.

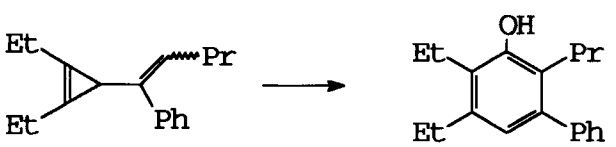


4-Bromofluorobenzene was an alternative reagent used in tetrahydrofuran solution containing Pd(II) acetate and triphenylphosphine and either reagent was considered to provide a superior phenylation technique to the use of Ph_3BiCl_2.

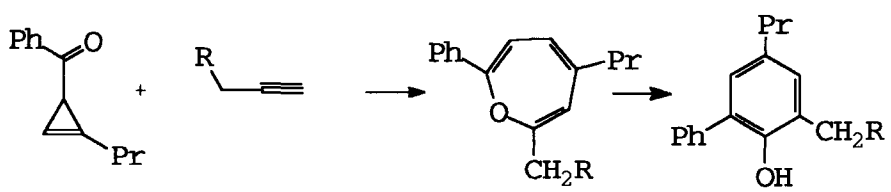
2,3-Diethyl-5-phenylphenol was obtained in 75% yield from 3-phenylcyclobutenone and 2 moles of 3-hexyne in diethyl ether (under argon at 0°C) containing 0.1mole $Ni(COD)_2$, [bis(1,5-cyclooctadiene)nickel], with the addition of a further 0.05 mole after 45mins. and subsequent reaction for 30mins (ref.14). This nickel(0)-promoted reaction is considered general for phenols.



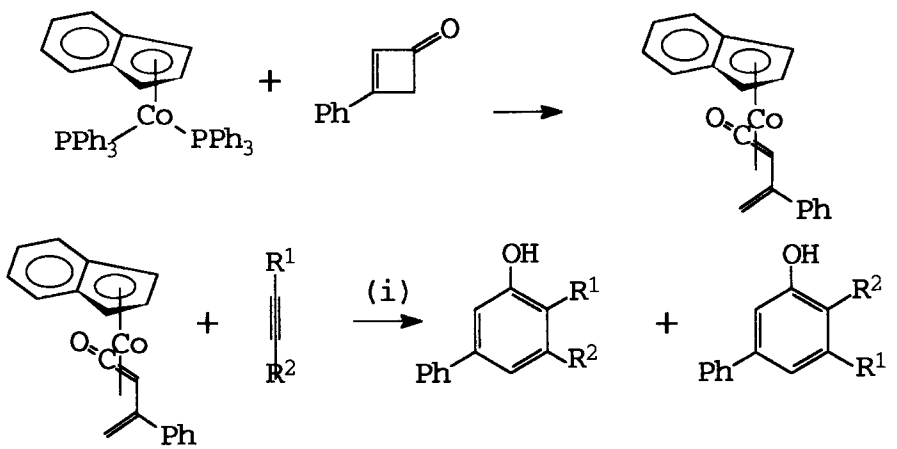
Several different organometallic reagents have been used for the synthesis of polysubstituted phenols. Thus the vinylcyclopropene depicted, underwent carbonylation and rearrangement in benzene solution, containing a little tetracarbonyldichlorodirhodium, with carbon monoxide at 80°C under 1 atmosphere pressure to afford 5,6-diethyl-3-phenyl-2-propylphenol in 82% yield (ref.15).



1-Hexyne (R = n-C_3H_7) and 3-benzoyl-2-propylcycloprop-1-ene in dichloromethane upon treatment with 10 mole% of the rhodium complex $[Rh(CO)_2Cl_2]_2$ formed an intermediate oxepin in 62% yield which by acidification with 1 drop of hydrochloric acid at 40°C afforded 2-n-butyl-4-propyl-6-phenylphenol



quantitatively (ref.16).
Cobalt complexes of vinylketene by reaction with alkynes in the presence of 2 moles of cyclooctadiene 100°C during 20 hours resulted in moderate yields of phenols (ref.17). This procedure represents the first synthesis of alkylphenols by the insertion of (η^5-indenyl)cobalt(I) into a cyclobutenone, the latter being prepared by analogy with a method for $cpCo(PPh_3)_2$. With symmetrical alkynes ($R^1 = R^2 = Et$) the yield was 65%, although with unsymmetrical compounds the two isomers shown were both produced in proportions dependent upon the substituent.



A variety of patented approaches, summarised in Table 6.2 (refs.18-20), have been used in the preparation of 2-benzylphenols.

6.2.2 Alkylnaphthols and Hydroxypolycyclic compounds with alkyl side-chains

Tetral-1-one by way of the benzoylated 2-formyl derivative, 2-benzoyloxymethylene-1-tetralone, has been converted in refluxing cyclohexene containing 10% palladium-charcoal to 2-methyl-1-hydroxy-naphthalene in 70% yield (ref.21).

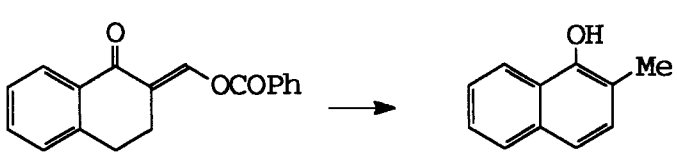
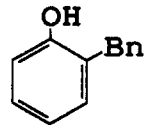
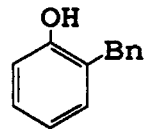
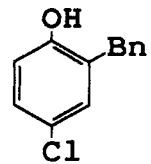
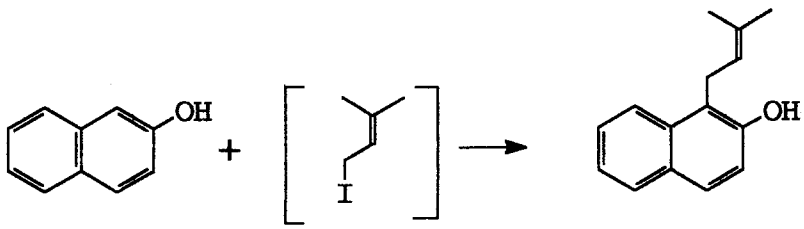


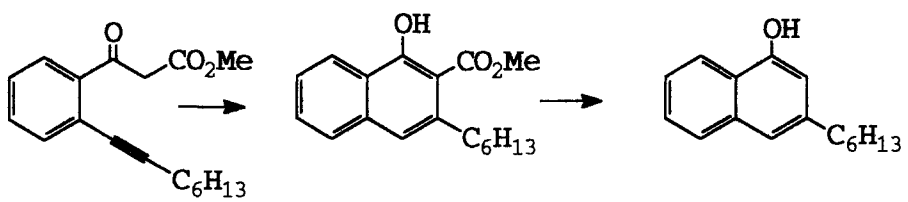
TABLE 6.2 SYNTHESIS OF BENZYLPHENOLS

PHENOL	BENZYLATING AGENT	CONDITIONS	PRODUCT	YIELD (%)	REF.
Phenol	dibenzyl ether	Phenol, dibenzyl ether and gamma alumina (95% alumina) were refluxed in toluene for 10h. to give 2-benzylphenol.		84	18
"	benzyl alcohol	To phenol and gamma alumina heated in an oil-bath, benzyl alcohol was added dropwise (during 40 mni.) and the mixture then heated at 200C for 2h. Magnesium oxide acted similarly to give 2-benzylphenol.		88.5	19
2-chloro-phenol	"	4-Chlorophenol and benzyl alcohol were heated with sodium-Y-zeolite at 200C for 3h. to give 2-benzyl-4-chlorophenol.		95	20

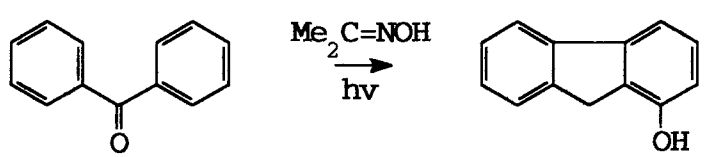
1-(isoPent-2-enyl)-2-naphthol has been synthesised in 60% yield by the sequential addition to 2-naphthol in dry acetonitrile of sodium iodide, isoprene and trimethylchlorosilane and reaction with stirring at ambient temperature during 1 hour (ref.22).



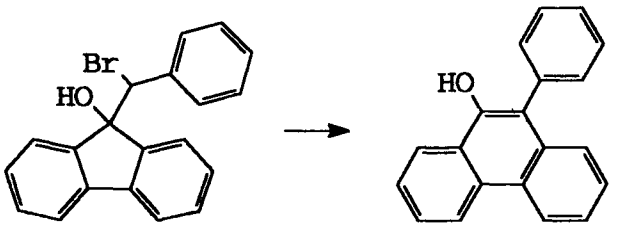
1-n-Hexyl-2-(2-methoxycarbonylacetyl)phenylacetylene in chloroform solution containing 1 mole of camphorsulphonic acid when refluxed for 8-12 hours afforded by intramolecular ring closure 2-methoxycarbonyl-3-n-hexyl-1-naphthol in 90% yield (ref.23). Hydrolysis and decarboxylation could serve as a route to 3-n-hexyl-1-naphthol and the method as a general route to alkyl analogues.



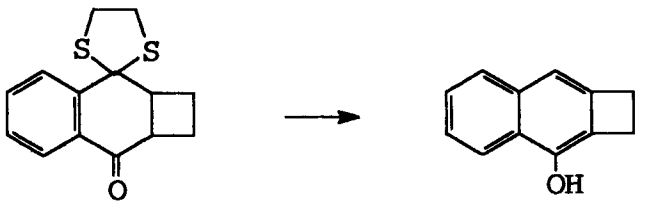
1-Fluorenol has been prepared in 60% yield by the photolysis during 12 hours of a dilute mixture of benzophenone and propanone oxime in methanol in a double-walled, internally-cooled pyrex tube (ref.24).



9-phenylphenanthrol was obtained from 9-(α-bromobenzyl)-9-hydroxyfluorene in 90% yield by addition of ethereal isopropylmagnesium bromide and nickel(II) acetylacetonate in benzene/ether (1:1) at -50°C followed by stirring for a further 2 hours (ref.25).



Desulphurisation of the dithioketal shown with W2 Raney nickel afforded 2,3-ethano-1-naphthol, an intermediate having synthetic potential through opening of the fused cyclobutane ring (ref.26).



6.3 Synthesis of Phenols and Naphthols with side-chains containing oxy or alkoxycarbonyl groups

Phenols substituted by the 2-hydroxymethyl group represent the monomers of phenol/formaldehyde polymers and their regio specific synthesis has received extensive experimental study. A number of preparations are lised in Table 6.3 (refs.27-33). The alkyl methyl ether of α-methylsalicyl alcohol [2-(1'-methoxyethyl)phenol] has been formed in a yield of 12% from a mixture of phenol and 1,1-dimethoxyethane (1:10) by passage at 250°C with helium as carrier gas through a fixed bed catalyst of an H-ZSM-5 zeolite (proton exchangeable) supported on glass wool with a contact time of 6.9 secs. (ref.34).

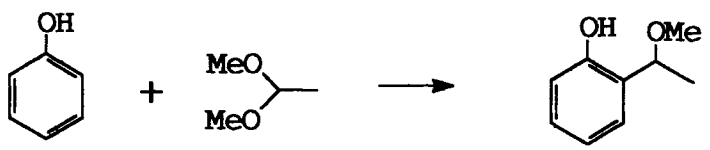


TABLE 6.3 SYNTHESIS OF OXYALKYL AND ALKOXYCARBONYLALKYL PHENOLS

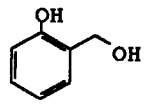
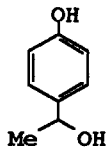
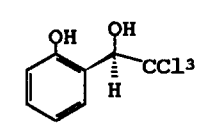
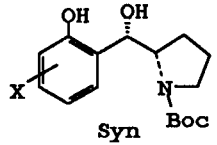
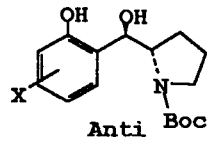
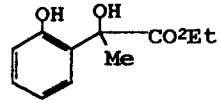
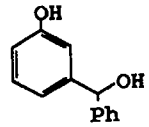
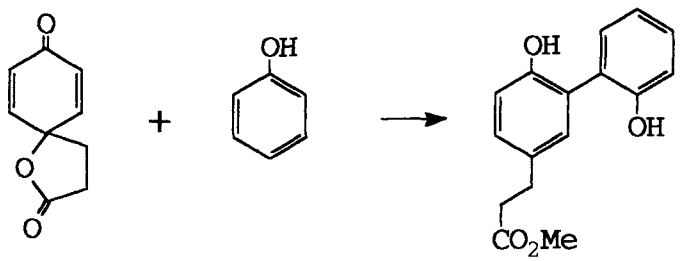
PHENOL	REAGENT	CONDITIONS	PRODUCT	YIELD (%)	REF.
Phenol	paraformaldehyde $(CH_2O)_n$	Phenol with excess paraformaldehyde and dimethoxy-ethane (1 equiv.) in xylene stirred thoroughly in a sealed reactor at 135° for 12 h to give salicyl alcohol.		72	27
Phenol	paraformaldehyde $(CH_2O)_n$	Phenol at 85° was treated with paraformaldehyde and after ½h, following the addition of powdered anhydrous aluminium phenoxide, reaction was continued for 3h. to afford salicyl alcohol.	"	91.5	28
Phenol	paraldehyde	Phenol and paradehyde heated to 150° in an autoclave, 4-H^+-y-zeolite added and heating continued for 3 h to afford 1-(4-hydroxyphenyl)ethanol		86 (60% conversion)	29
Phenol (as phenoxy menthoxy aluminium chloride)	trichloro acetaldehyde (chloral)	Phenol, (-) menthol and diethyl aluminium chloride were reacted in toluene to produce the required intermediate for the ensuing asymmetric synthesis. Addition of chloral and stirring for 24 h at 25°C gave the product. (-)-2-(2,2,2-trichloro-1-hydroxyethyl)phenol.		96 (33% ee)	30
A phenol (as the magnesium phenolate)	N-t-Boc-L-prolinal	2-tert-Butylphenol converted to the magnesio bromide with ethereal EtMgBr, solvent replaced by CH_2Cl_2 and equimolar N-tert-butoxycarbonyl L-prolinal added, mixture stirred 3h. to give the *syn* aldol.		65 (S,S) (*syn* 100:1)	31
A phenol (as titanium phenolate	"	3-Methoxyphenol in toluene with $Ti(OiPr)_4$.iIPrOH removed and replaced by $CH_2Cl_2$and N-tet-butoxy-carbonyl-L-prolinal in CH_2Cl_2 added. Reaction and stirring for 48h. togive the *anti* aldol.		51 (R,S) *anti* 88%	31

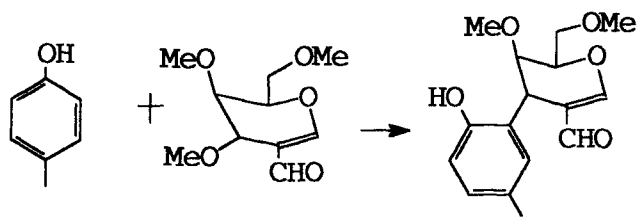
TABLE 6.3 (contd.)

Phenol (as the titanium phenolate	ethyl pyruvate	Phenol, and ethyl pyruvate were stirred in dichloromethane containing titanium tetrachloride at 0° for 3 h and then at ambient temp. for 5 h to give 1-ethoxycarbonyl, 1-(2-hydroxy-phenyl)ethanol		80	32
Phenol (as chromium tricarbonyl complex	benzaldehyde	Phenol chromium tricarbonyl complex, n-butyllithium (2.mols) tertramethylethylenediamine (3 mols.) in THF at 60C for 3h. Benzaldehyde added and after oxidative decomplexation by addn. of I_2 and camphor sulphonic acid in 10% HC/THF 1-(3-hydroxyphenyl)benzyl slcohol obtained.		64	33

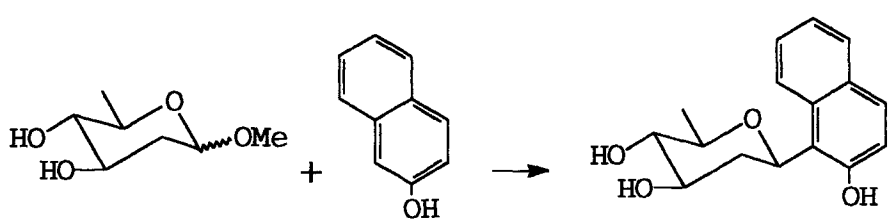
Conveniently included in this section, although an aspect of electrophilic substitution, is the synthesis of an unusual 5',2,2'-biphenyl. By treatment of phenol in nitromethane solution containing 1-oxaspiro[4,5]deca-6,9-diene-2,8-dione briefly during 2 mins. with stannic chloride, followed by refluxing the acidic product with 1% sulphuric acid in methanol for 1 hour, 2,2'-dihydroxybiphenyl-5'-(2-methoxycarbonylethyl)biphenyl has been obtained in 60% yield (ref.35). The reaction also occurred with phenolic ethers and its regiospecificity in the case of phenol may be attributable to hydrogen bonding.



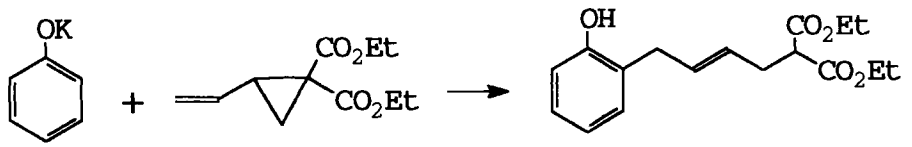
4-methylphenol with the glycal shown in dichloromethane by treatment with boron trifluoride-etherate and reaction for 48 hours at ambient temperature afforded a 50% yield of a substitution rather than a Michael addition product (ref.36).



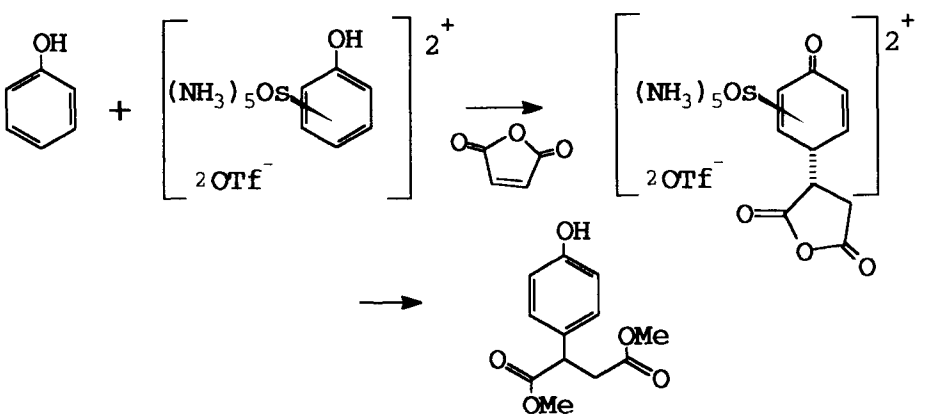
Phenols and naphthols have been reacted with unprotected methylglycosides. For example, 2-naphthol with the methyl glycoside illustrated in dichloromethane



upon treatment with 20 mole% trimethylsilyltriflate at 25°C during 1 hour gave the product shown in 98% yield although with the di-O-benzoyl derivative of the methylglycoside only a 57% yield resulted (ref.37).
In another reaction of a different type, probably involving anionic nucleophilic attack, potassium phenolate was treated first in toluene solution with stannic chloride in the same solvent at ambient temperature followed by refluxing for 15mins. Finally to the mixture at 80°C over 3 hours a toluene solution of diethyl 2-vinylcylopropane-1,1-dicarboxylate was introduced and reaction continued over a further 10 hours, to give ethyl 6-(2-hydroxyphenyl)-2-ethoxycarbonyl-4-hexenoate in 25% yield (85% based on recovered phenol) (ref.38).

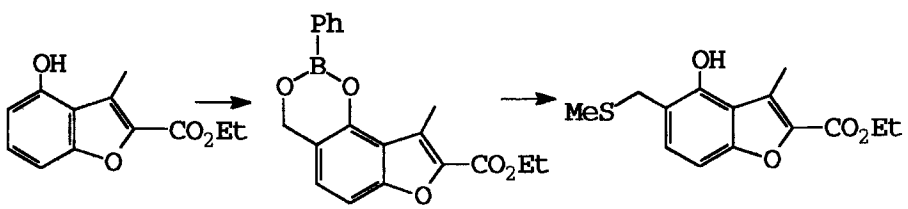


A transformation showing enhancement of the reactivity of phenol through transition metal complexation occurs in the reaction of $[Os(NH_3)_5(\eta^2\text{-phenol})](OTf)_2$ with maleic anhydride in acetonitrile over 20 hours at ambient temperature followed by recovery of the product, dimethyl (4-hydroxyphenyl)succinate in 85% yield by simple ethereal precipitation and removal of the osmium by refluxing in acidic methanol (ref.39). These last two examples illustrate the versatility of the appropriately modified phenolic structure to function either in a nucleophilic or in an electrophilic manner.

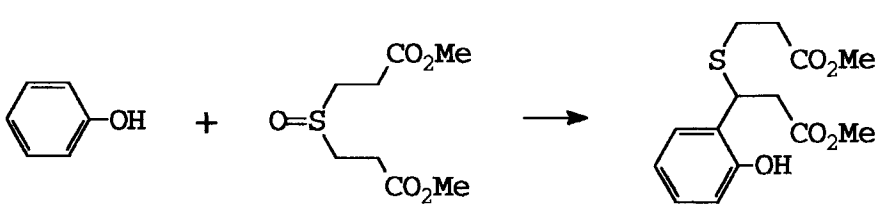


6.4 Synthesis of Phenols with side-chains containing Si, N or S atoms

Phenols with side-chains containing Si, N or S atoms (but rarely their combination) are comparatively easily synthesised and either provide valuable terminal products or intermediates for further reactions. This group includes the products of the Mannich reaction, compounds with silicon in place of carbon and a array of sulphur compounds some of which have been discussed in a previous review (ref.40).
Some of the reactions in this section are summarised in Table 6.4 (refs.41-44) with reference mostly to methylenic side chains.
A further method of methylthiomethylation is shown in the reaction of methanethiol with 9-methyl-2-phenyl-4H-1,3,2-di-oxaborin[6,5,e]benzofuran-8-carboxylate (derived from ethyl 4-hydroxy-5-hydroxymethyl-3-methylbenzofuran-2-carboxylate and phenylboronic acid) in dichloromethane at 0°C in the presence of aluminium chloride (4 equivs.) for 30 mins. followed by 30 mins. at ambient temperature and work-up with hydrochloric acid at 0°C, to furnish, in 56% yield, ethyl 4-hydroxy-3-methyl-5-methylthiomethyl-benzofuran-2-carboxylate (ref.45) by displacement of phenylborinic acid.

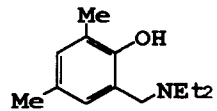
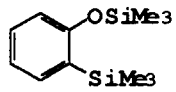
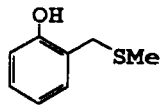
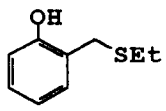


In a reaction related to that of phenol with dimethylsulphoxide, the same group of workers have treated dimethyl 3,3'-sulphinylpropionate in dichloromethane with a dichloromethane solution of thionyl chloride at -60°C. After 15 mins., phenol was introduced at -55°C, followed after 1 hour by triethylamine at -50°C, to afford upon work-up, dimethyl 3-(2-hydroxyphenyl)-3,3'-thiodi-propionate in 84% yield(ref 46).

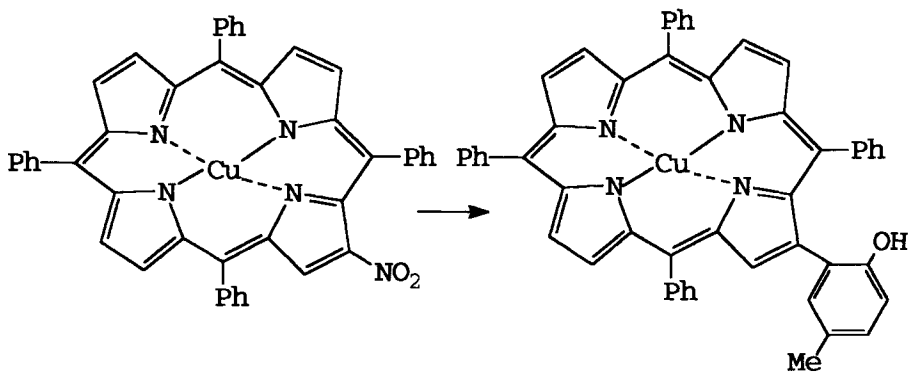


Sodium 4-methylphenoxide (7 equivalents) interacted with copper(II) chelated

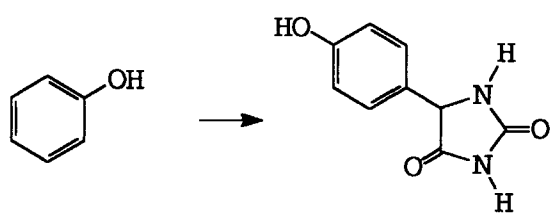
TABLE 6.4 PHENOLS WITH SIDE CHAINS CONTAINING N, Si, OR S

PHENOL	REAGENT	CONDITIONS	PRODUCT	YIELD (%)	REF.
2,4-Dimethyl phenol	Bis(diethylamino) methane	A mixture of the aminal and 2,4-dimethylphenol was treated in acetonitrile with sulphur dioxide (22 equivts.) at ambient temperature during 14h. to give 2-diethylamino-methyl-4,6-dimethylphenol.		72	41
Phenol 2-Bromo phenols 2-Hydroxy benzoic acid 2-Hydroxy acetphenone	Trimethyl chlorosilane	Phenol and tetrahydropyran (4mols.) were treated dropwise with tert-butyl lithium (1.74M) in hexane and after the mixture had been stirred at ambient temp.for 2h, trimethylsilylchlorosilane was added rapdily and stirring continued for a further 14h. to give 2-trimethyl-silylphenyl trimethylsilyl ether.		67	42
Phenol	Dimethyl sulphoxide and thionyl chloride	The reagent was prepared by treating thionyl chloride dropwise in dichloromethane at -60° under nitrogen with dimethyl sulphoxide in dichloromethane. After stirring (20 mins.), phenol in dichloromethane was added at -50°, stirring continued for 40 mins. (at -50°), triethylamine in CH_2Cl_2 added dropwise at -50° to -40°, mixture allowed to reach ambient temp. and poured into 1M HCl. $Me_2SO + SOCl_2 = [MeS^+Cl][SO_2Cl]^-$		78	43
Phenol	paraformaldehyde, ethanethiol	To molten phenol at 75C, 20% aqueous zinc acetate was added folowed by paraformaldehyde and EtSH and the mixture then heated to 135C and refluxed 6h. to give 2-ethylthiomethylphenol.		86	44

2-nitro-5,10,15,20-tetraphenylporphyrin in refluxing 4-methylphenol for 6 hours furnished copper(II) 2-(2-hydroxy-5-methylphenyl)-5,10,15,20-tetraphenyl-porphyrin in 86% yield through displacement of the nitro group (ref.47).



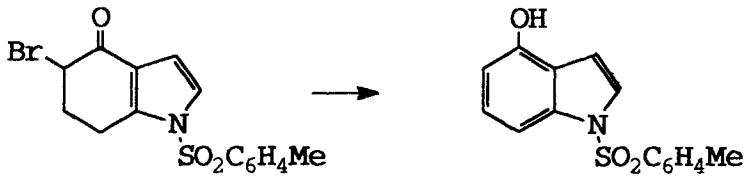
5-(4-Hydroxyphenyl)hydantoin was formed, with avoidance of the use of sodium cyanide, in 61% yield, by the addition of a mixture of phenol, urea, water and concentrated hydrochloric acid to stirred 50% aqueous methyl 2-hydroxy-2-methoxyacetate at 70°C followed by further reaction during 10 hours (ref.48).



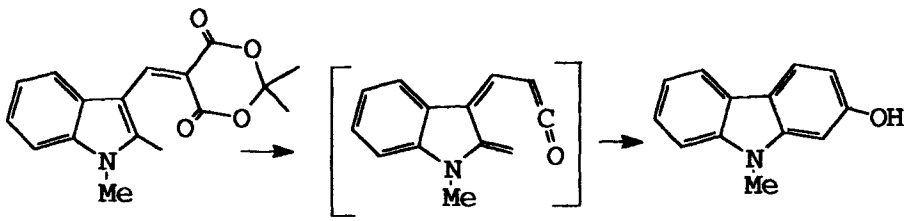
6.5 Synthesis of Polycyclic Phenols containing unsaturated and saturated rings bearing hetero atoms

A number of bicyclic and polycyclic phenols have been prepared invariably from cycloaliphatic intermediates and these have been classified in this section which essentially describes alkenylphenol derivatives.

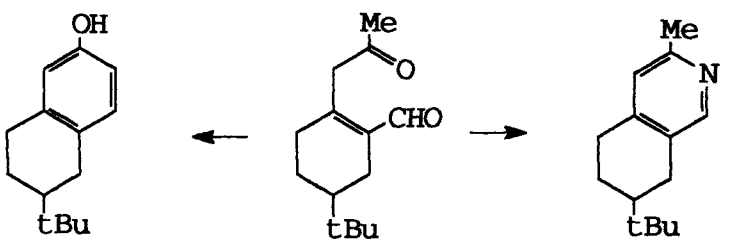
Dehydrobromination of 5-bromo-4-oxo-1-(4'-toluenesulphonyl)-4,5,6,7-tetra-hydroindole with lithium bromide in dimethylformamide at 150°C during 1 hour gave in 97% yield, 4-hydroxy-1-(4'-toluenesulphonyl)indole (ref.49).



Generation of the phenolic hydroxyl group via a reactive ketene intermediate is shown in the pyrolysis of the condensation product of 1,2-dimethyl-3-formylindole with Meldrum's acid at 600°C and 10-2mm.Hg to afford in 89% yield 9-methyl-2-hydroxycarbazole (ref.50).

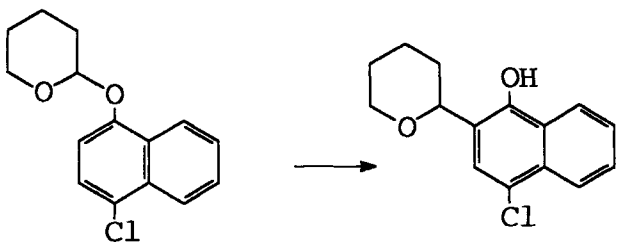


4-tert-Butyl-2-formylcyclohex-2-enylacetone, prepared by Wacker oxidation of the dienal precursor, gave by intramolecular Claisen condensation with ethanolic potassium hydroxide 4,5-(8-tert-butylcyclohexeno)phenol in 91% yield (ref.51). Treatment of the formyl compound with excess ammonium acetate and alternative ring closure afforded the tetrahydroisoquinoline indicated.

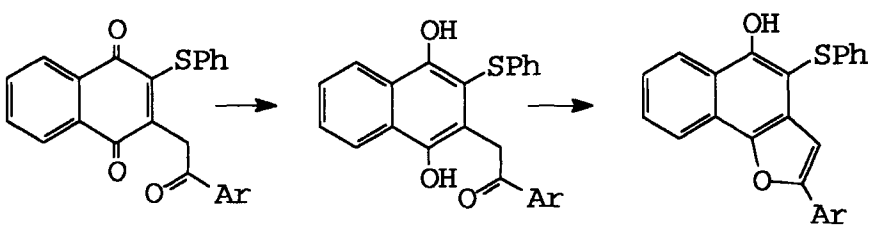


Rearrangement of certain naphthylethers has afforded 1-naphthols. Thus a solution of the tetrahydropyran-2-yl ether of 4-chloro-1-naphthol in dichloromethane added rapidly to boron trifluoride etherate (0.1 equiv.) in dichloromethane at 0°C followed by reaction for 1 hour gave 2-(2-tetrahydro-

pyranyl)-4-chloro-1-naphthol in 65% yield. O-Tetramethyl glucosides were rearranged in a similar fashion to the C-glucosides (ref.52).



6,7-Benzo-2-aryl-6-hydroxy-5-phenylthiobenzofurans have been obtained from 1,4-naphthoquinones. In this procedure reduction of an acetic acid solution of the 2-aroyl-3-phenylthio-1,4-naphthoquinone shown to the quinol analogue with stannous chloride dihydrate in conc. hydrochloric acid during 40 mins followed by cyclisation resulted in a 6,7-benzobenzofuran derivative in 82% yield (ref.53).

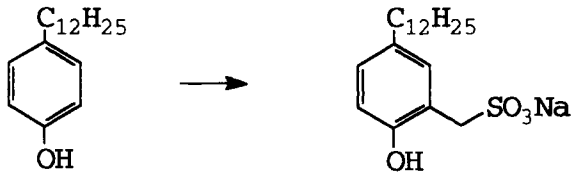


6.6 Reactions of Alkylphenols

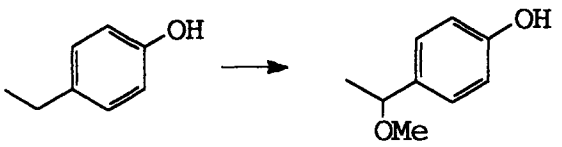
The reactions of alkylphenols show a remarkable variety of transformations no doubt partly attributable to the increased activation of the ring and opportunities for regiospecific procedures. In this section the range explored in recent years is divided into substitution, addition and intramolecular reactions in which a single benzenoid ring product results, intermolecular reactions where a bicyclic or more usually a polycyclic product is formed, and processes resulting in alkylphenols with a second chain containing hydroxy or alkoxycarbonyl groups leading sometimes to a cyclisation reaction. Finally the behaviour of the relatively recently investigated group of macrocyclic compounds, the calixarenes is listed.

6.6.1 Substitution, Addition and Intramolecular Reactions

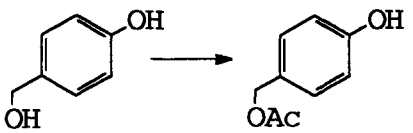
These processes can involve either the ring or the reactive benzylic position. C-Sulphomethylation of 4-dodecylphenol was effected by refluxing with sodium sulphite and aqueous formaldehyde for 20 hours under nitrogen (ref.54).



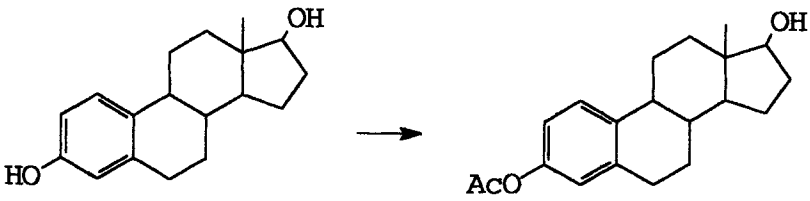
4-Ethylphenol and 2,3-dichloro-5,6-dicyanoquinone in equimolecular proportions in methanolic solution gave at ambient temperature 4-(1-methoxyethyl)phenol with a selectivity of 87%, and a conversion of 89% (ref.55).



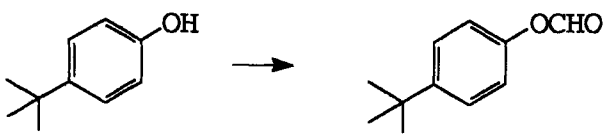
Preferential acetylation of the alcoholic hydroxyl group in 4-hydroxymethylphenol was achieved in 60% yield by the use of a little boron trifluoride etherate in acetic anhydride added dropwise to the phenolic alcohol in tetrahdrofuran at 0°C followed by reaction during 4 hours (ref.56).



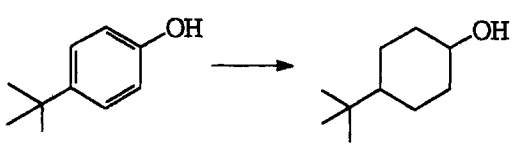
In diols containing both phenolic and alcoholic hydroxyl groups neutral conditions favour the acylation of the latter while the former are selectively acylated in the presence of triethylamine (ref.57) doubtless due to the more nucleophilic phenoxide ion so formed, which is the basis of the Chattaway procedure originated many years ago. This is exemplified in the preferential formation in 95% yield of the phenolic acetate of estradiol in isopropanol containing 2.9 moles of sodium hydroxide in concentrated solution followed by the addition of 2.9 moles of acetic anhydride and then by stirring of the mixture for 30mins. at ambient temperature with maintenance of the pH at 7.8 (ref.58).



Phenolic formates are generally troublesome to form but 4-tert-butylphenyl-formate resulted in 80% yield by the addition of dicyclohexyldiimide (1.4 moles) to a mixture of 4-tert-butylphenol and formic acid (1.2 moles) in dry dichloromethane followed by reaction during 20 hours at ambient temperature (ref.59).



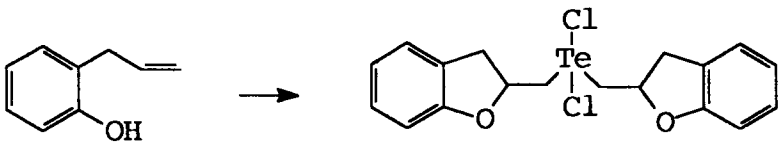
Ring reduction of 4-tert-butylphenol in butyl acetate was effected in 99% yield by heating with 50% nickel-aluminium oxide at 180-190°C (under 1-1.5Pa pressure) (ref.60) although the stereochemistry of the product was not disclosed.



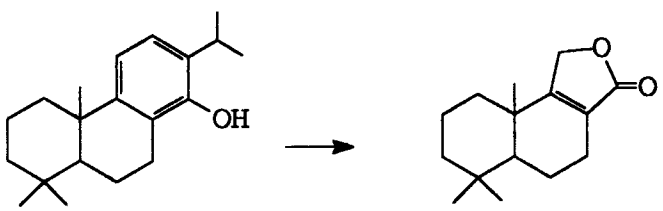
The use of a Raney nickel catalyst which may be of similar type, from the interaction of 50% nickel-aluminium alloy with water at 100°C has been described (ref.61) which was employed under atmospheric pressure and did not effect ring reduction.

A organotellurium reagent has been referred to in Chap.3, for the preparation of 4-chlorophenyl allyl ether. 2-Allylphenol in refluxing acetic acid containing tellurium oxide and lithium chloride during 1.5 hours afforded bis[1-(2,3-dihydrofuryl)methyl]tellurium dichloride in 78% yield rather than

2-methylbenzofuran (ref.62).

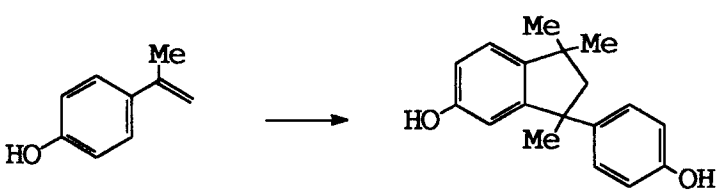


The angular methyl octahydrophenanthrene depicted, a 2-isopropylphenol derivative, upon ozonation at -78°C in dichloromethane/methanol for 22 hours, followed by warming to ambient temperature and finally treatment with sodium borohydride in aqueous ethanol over 2 hours, has been reported to result in a decalenofuranone in 49% yield (ref.63), apparently by preferred cleavage at the di- and trisubstituted double bonds.



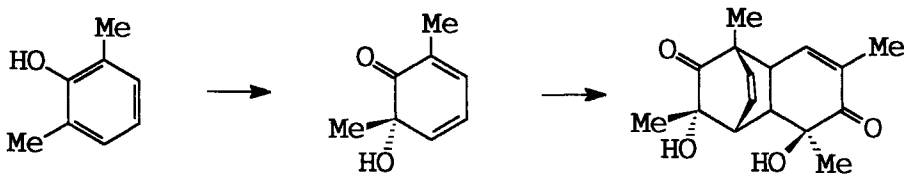
6.6.2 Intermolecular Reactions

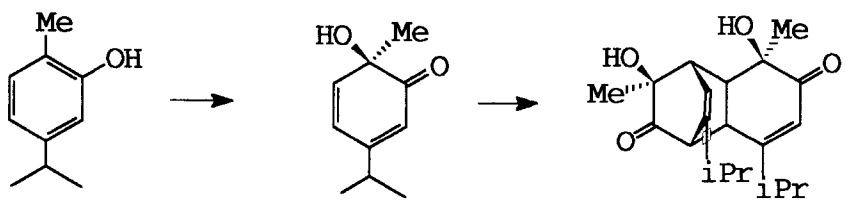
The possibility of the occurrence of unusual condensation reactions with alkylphenols might be anticipated from the increased activation of the ring. Amongst the first, dimerisation of the alkenylphenol shown may be mentioned. 4-iso-Propenylphenol in trifluoracetic acid at ambient temperature furnished after 5 mins., 1-(4-hydroxyphenyl)-1,3,3-trimethylindan-6-ol in acceptable yield (ref.64).



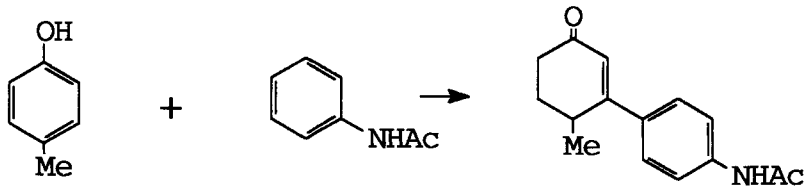
2,6-Xylenol afforded a dimeric product upon bacterial action resulting in

oxidation to a cyclohexadienone followed by [4+2] cycloaddition to give exo-3,10-dihydroxy-3,5,8,10-tetramethyltricyclo[6.2.2.$0^{2,7}$]dodeca-5,11-diene-4,9-dione (ref.65), a known natural product. Sodium periodate oxidation of 2,6-xylenol also gave the same product in racemic form. Carvacrol under similar conditions (chap. 5, ref.18) gives a related product, which has been formulated with the structure shown.



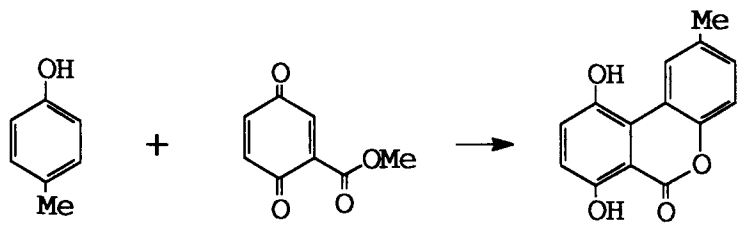


4-Methylphenol and acetanilide (3mols.) added to a mixture of hydrochloric acid and antimony pentafluoride at 0°C and then reacted during 90mins. have been reported to give in 87% yield an arylation product at the 2-position to the methyl group, namely 3-(4-acetylaminophenyl)-4-methyl-2-cyclohexen-1-one, a result ascribable to the m-directing oxonium ion intermediate formed from the phenol. The procedure can be regarded as an alternative to the use of chromium tricarbonyl adducts. Phenolic ethers responded to the conditions (ref.66).

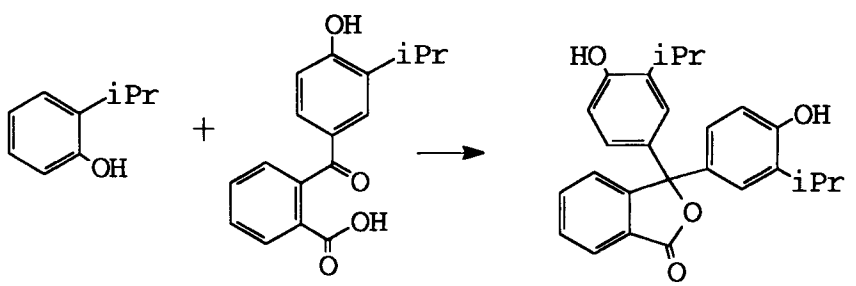


By contrast, 4-methylphenol in benzene or dichloromethane containing a little trifluoracetic acid reacts at the 2-position to the hydroxyl group with 2-methoxycarbonylbenzo-1,4-quinone over 4 hours at ambient temperature to

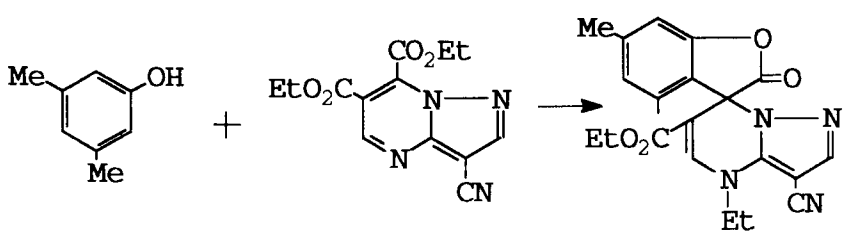
give 7,10-dihydroxy-2-methyl-6H-dibenzo[b,d]pyran-6-one in 78% yield (ref.67).



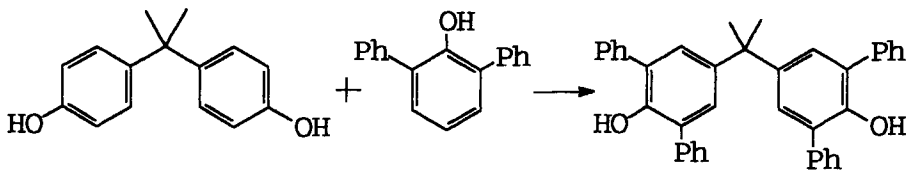
2-iso-Propylphenol and 2-(4-hydroxy-3-isopropylbenzoyl)benzoic acid in ice-cold ethereal solution treated dropwise with concentrated sulphuric acid during 5 mins. and reacted for a further 15 mins. afforded 3,3-bis(4-hydroxy-3-isopropyl-phenyl)phthalide in 76% yield presumably by way of the 3-monophthalide (ref.68).



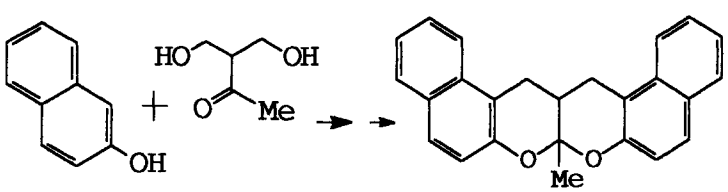
3,5-Dimethylphenol reacted with aromatic esters, for example the diethyl ester shown, which was first treated with dichloromethane containing triethyloxonium fluoroborate during 24 hours, and then allowed to react with the phenol for a further day at ambient temperature to give an N-ethylated spiro compound in 63% yield (ref.69).



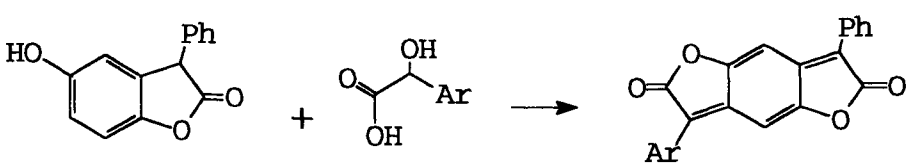
Transarylation has been observed in the reaction of 2,6-diphenylphenol (8 mols.) with 2,2-bis(4-hydroxyphenyl)propane ('bis-phenol A') in dry chloroform by treatment with methanesulphonic acid (5 mols.) followed by reaction for 4 hours at ambient temperature to afford 2,2-bis(4-hydroxy-3,5-diphenyl-phenyl)propane in 87% yield (ref.70)



A symmetrically-fused naphthopyran has been synthesised albeit in the low yield of 6.25% from 2-naphthol by way of prior 1-alkylation. Thus 4-hydroxy-3-hydroxymethylbutan-2-one added gradually during 3 hours to 2-naphthol in ethanol at 70°C containing amberlyst-15 and the mixture allowed to stand for 16 hours afforded the compound shown after removal of the resin (ref.71).

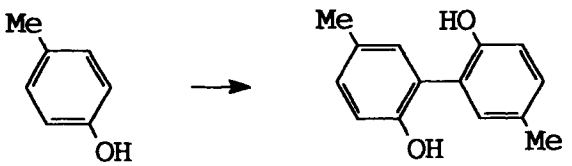


The hydroxybenzofuran derivative, 5-hydroxy-2-oxo-3-phenyl-2,3-dihydrobenzo-furan underwent 2-alkylation and ring closure with 4-(2-n-butoxyethoxy)mandelic acid in acetic acid at 110°C containing sulphuric acid during 9 hours, followed by oxidation by the addition of ammonium persulphate with further reaction at 110°C for 1 hour (ref.72).



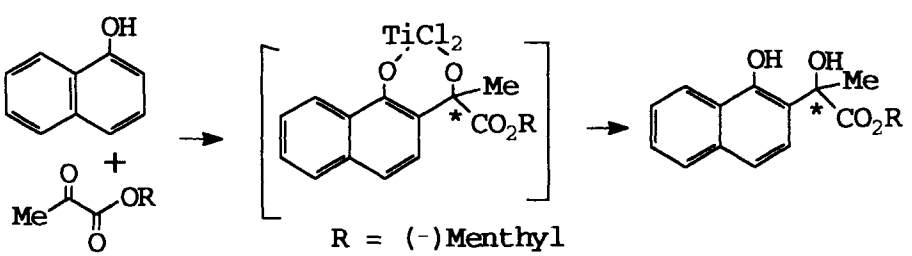
Ar = 4 - $(BuOC_2H_4O)C_6H_4$ -

Oxidative dimerisation of 4-methoxyphenol has been mentioned in the previous chapter. 4-Methylphenol in bromobenzene containing caesium carbonate, the only effective base for the reaction, was mixed with 10mole% of a rhodium complex at ambient temperature. Heating of the mixture at 90°C for 24 hours afforded a 51% yield of the coupled product, 2,2'-dihydroxy-5,5'-dimethylbiphenyl (ref. 73). The yield was improved by the addition of 2.2 moles of water.



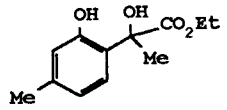
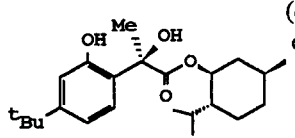
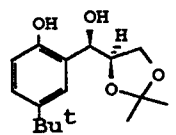
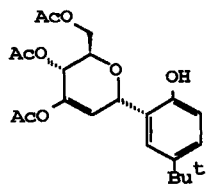
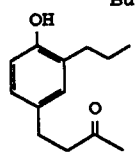
6.6.3 Reactions of alkylphenols producing side-chains having oxy or alkoxycarbonyl substituents.

On account of their increased ease of substitution, alkylphenols readily afford side-chains containing alkyl substituents having oxy, oxo or alkoxycarbonyl groups as shown by the examples given in Table 6.5 (refs.74-78). Frequently these reactions have been mediated by titanium tetrachloride or even by a phenoxymagnesium halide.
A number of asymmetric syntheses have been developed. Aldol-type asymmetric condensations have also been effected in the naphthol series. To 1-naphthol in dichloromethane at -60°C, titanium tetrachloride was added, followed after 15 mins. stirring by menthyl pyruvate introduced over 15 mins. Quenching gave menthyl (-)2-hydroxy-2-(1-hydroxy-2-naphthyl)propionate in 81% yield (diastereoisomeric excess 92%) (ref.79).

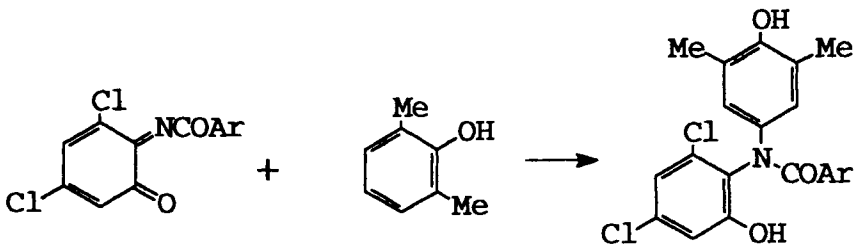


Side-chains containing amido groups have also been elaborated. 2,6-Dimethylphenol when added to a stirred methanolic suspension of the quinonemonoimine, N-(2,4-dichloro-6-oxo-2,4-cyclohexadien-1-ylidene)-4-nitro-

TABLE 6.5 REACTIONS OF ALKYLPHENOLS TO GIVE SIDE CHAINS WITH OXY,OXO, ALKOXYCARBONYL SUBSTITUENTS

PHENOL	REACTANT	CONDITIONS	PRODUCT	YIELD%	REF.
3-Methyl	Ethyl pyruvate	To 3-methylphenol in CH_2Cl_2 at 0C $TiCl_4$ was added and , after stirring for 30min. a soln of Et pyruvate in CH_2Cl_2 was slowly introduced and reaction contd. for 10 min. at 0C, to afford ethyl 1-(2-hydroxy-4-methylphenyl)-1-hydroxypropionate.		81	74
3-tert-Butyl	(+)-Menthyl pyruvate	To (+)-menthol in CH_2Cl_2 at -60C, $TiCl_4$ was added and after 20 min. a soln. of 3-tert-butylphenol in CH_2Cl_2, followed (2h) by (+)-menthyl pyruvate. The reaction was stirred for 3h. to give menthyl (2R)-(+)-(2-hydroxy-4-tert-butylphenyl)lactate.		67 (diastereoisomer excess 82%)	75
4-tert-Butyl	(R)-glyceraldehyde acetonide	4-tert-Butylphenol treated with ethereal EtMgBr then solvent changed to CH_2Cl_2, (R)-glyceraldehyde compd. in CH_2Cl_2 added at 0C and mixture ulrasonicated (5h) (50kHz), (Branson type 2200) to give the aldol.		70 (syn:anti 76:4)	76
"	3,4,6-Tri-O-acetyl-D-glucal	As before 4-tert-butylphenoxy magnesium bromide in CH_2Cl_2 treated dropwise with the glucal in CH_2Cl_2 at 0C and then in an ultrasonic bath over 6h at 22C to afford the 2-substituted phenol.		71 (alpha: beta 100: 1)	77
2-n-Propyl	But-3-ene-2-one	To 2-n-propylphenol and amberlyst-15 as a slurry in toluene at 20C the ketone in toluene was added (1h) and reaction contd. until complete by TLC to give 4-(3-oxobutyl)-2-n-propylphenol.		77	78

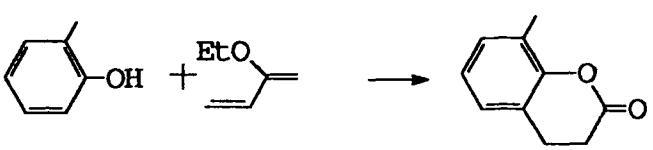
benzamide led to a 91% yield of N-(2,4-dichloro-6-hydroxyphenyl)-N-(4-hydroxy-3,5-dimethylphenyl)-4-nitrobenzamide after the mixture had been reacted overnight (ref.80). Quinone diimines in the same series also were also reacted with phenol.



Ar = $4\text{-}NO_2C_6H_4$-

6.6.4. Cyclisation Reactions of Alkylphenols having oxy, oxo or alkoxycarbonyl substituents in the side-chain

The cyclisation products discussed in this section proceed mechanistically by way of substituted alkyl side chains and are summarised in Table 6.6 (refs.81-87). The syntheses referred to in the table involve the reaction of phenol itself with a reactant to form an open-chain intermediate which was usually not isolated but processed to give the cyclised product isolated.
The preceeding cyclisations were generally effected at the final stage under acidic conditions. The ability of the phenolate anion to behave with carbanion character and consequently to participate in Michael addition is seen in the following example. 2-Methylphenol with some lithium hydride heated under reflux and then treated rapidly with ethyl acrylate (0.1 mole), after heating at 185°C during 24 hours, afforded an 58% yield of 8-methyldihydrocoumarin (ref.88) although under the same conditions methacrylates and 3,3-dimethylacrylates did not respond.



The ability of alkylphenols to form cyclohexadienones has been referred to in Chapter 5 and in the present context, the spiro compound, 2-tert-butyl-1,3-oxazaspiro[6.6]undeca-2,7,10-trien-9-one was formed in 75% yield upon

TABLE 6.6 CYCLISATION REACTIONS OF SUBSTITUTEDALKYL PHENOLS AND PHENOLIC ETHERS

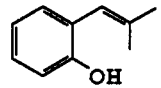
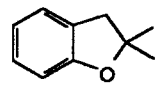
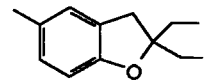
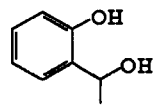
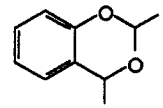
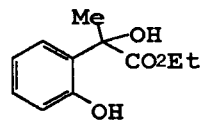
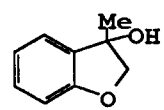
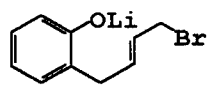
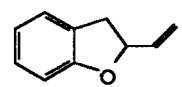
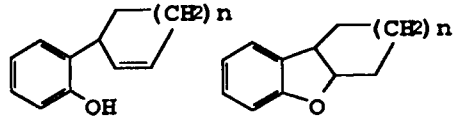
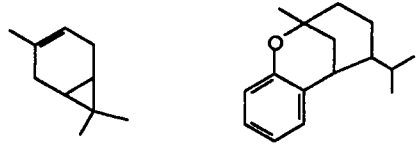
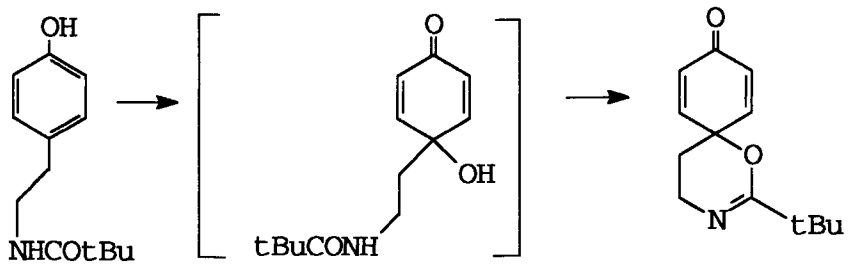
PHENOL	REACTANT	CONDITIONS	PROBABLE INTERMEDIATE	PRODUCT	YIELD%	REF.
Phenol	isoButanal	Phenol and isobutanal (1:10) passed through pyrex tube holding alumina at 300C to give 2,3-dihydro-2,2-dimethylbenzofuran			60	81
4-Methyl-phenol	2-Ethyl-butanal	4-Methylphenol and 2-ethylbutanal a small quantity of $SnCl_4$ refluxed with stirring for 15h. with removal of water to give 2,2-diethyl-5-methylbenzofuran.			44 (conversion 43%)	82
Phenol	Ethanal	Phenol and K phenolate (1:1) in toluene treated at ambient temp. with $TiCl_4$, mixture refluxed 30 min., cooled to ambient temp., ethanal (2 mols.) in toluene introduced and reaction contd. (10h) to give 5,6-benzo-2,4-dimethyl-1,3-dioxane.			70	83
phenol	Ethyl pyruvate	To Li phenolate in toluene, $AlCl_3$ was added at ambient temp. and the mixture refluxed 15 min., cooled and ethyl pyruvate introduced dropwise. The mixture was stirred at ambient temp. (4h.) to to give ethyl 1-hydroxy,1-(2-hydroxyphenyl)-propionate (45%). An ethanol solution added dropwise at 0C to $LiAlH_4$ in ether and reacted (1h) afforded 3-methyl-2,3-dihydrobenzofuran-3-ol.			98	84
Phenol	Butyllithium, 1,4-dibromo-2-butene	Phenol in toluene treated with BuLi (1.6M) in hexane and after15min, a toluene soln. of 1,4-di-brombutene introduced and the slurry refluxed to give 2-vinyl-2,3-dihydrobenzofuran			75 (95% based on phenol)	85

TABLE 6.6 (contd.)

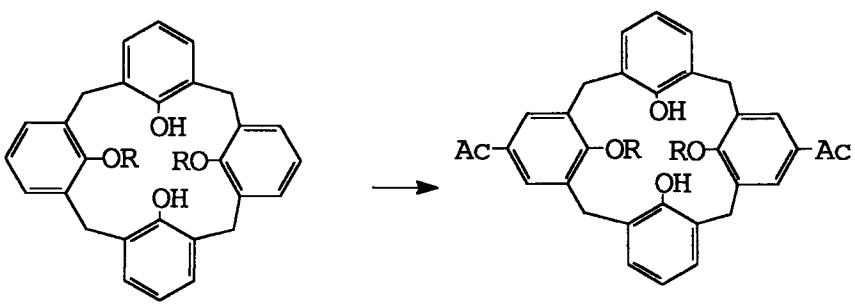
Phenol	1,3-Cyclo alkadiene	The 1,3-cycloalkadiene cooled to -5C was introduced toa soln. of aluminium in phenol and the mixture (at 10-12 atm.) stirred at 150-180C for 90 min. to give a 2,3-cyclo-2,3-dihydrobenzofuran.		73-86	86
Phenol	3-carene	Phenol, 3-carene and $Al(OPh)_3$ heated at 150-160C until monitoring indicated complete reaction.		75-80	87

addition of phenyliodosodi(trifluoroacetate) to a 2,2,2-trifluoroethanol solution of an N-tert-butyrotyramine derivative at ambient temperature, under nitrogen, followed by reaction during 30 mins.(ref.89). In water, ethanol or acetic acid the 4-hemiquinol, the ether or acetate resulted.



6.6.5. Calixarenes

Calixarenes a group of compounds first observed many years ago (ref.90) have been studied intensively only in the last few years. Their chemistry has been reviewed (ref.91,92). Calix[4]arene in dichloromethane was acetylated with acetyl chloride in the presence of aluminium chloride to give a 4,4'-diacetyl derivative in 63% yield without the formation of any O-acetyl isomers (ref.93).

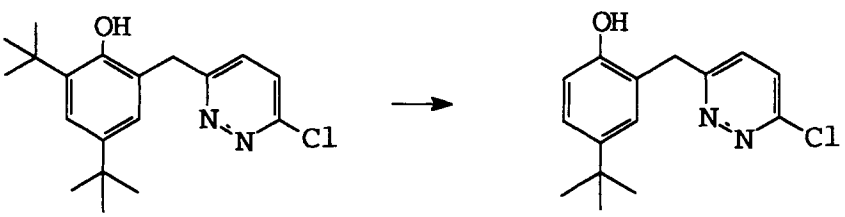


6.6.6. Cryptophenols and Hindered Phenols

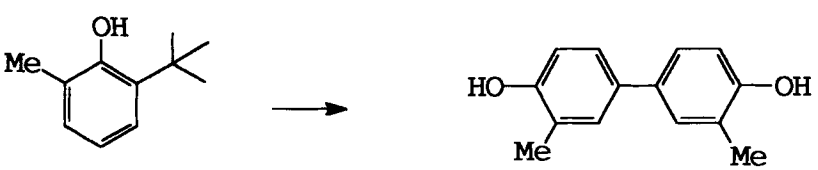
In this section the reactions of 2-tert-butylated and 2,6-di-tert-butylated phenols recently described are considered. The former, the cryptophenols are not completely hindered like the 2,6-di-tert-butylphenols although their reactions are different from those of 2-methylphenols. In both groups the reactions are comparatively straightforward and comprise substitution or oxidation either at the phenolic oxygen or at the carbon in the 4-position.

(i) 2-tert-Butylphenols

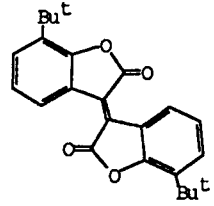
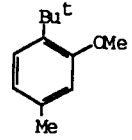
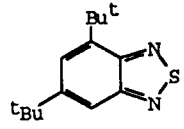
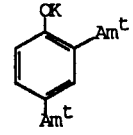
The reactions of this group either at the phenolic hydroxyl or at ring positions have been summarised in Table 6.7 (refs.94-97).
In the reactions described the tert-butyl group survives comparatively drastic conditions although as might be expected the use of aluminium chloride sometimes causes de-tert-butylation. The compound 2,4-di-tert-butyl-6-(5-chloro-pyridazin-2-yl)methylphenol in dichloromethane with aluminium chloride (3 equivs.), upon stirring at ambient temperature for 15 mins. followed by careful work-up of the mixture by quenching with water over 30 mins. gave the 4-mono tert-butyl product in 73% yield (ref.98).



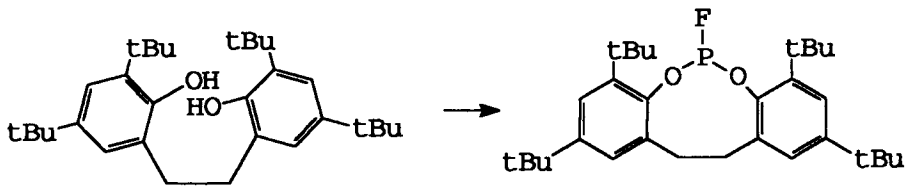
Loss of the tert-butyl groups occurred in the oxidative dimerisation of 2-methyl-6-tert-butylphenol in 54% yield finally to 3,3'-dimethyl-4,4'-dihydroxybiphenyl by heating with a catalytic quantity of ferric manganese naphthoate at 160°C during 6 hours in a stream of dry air to afford first a dimeric intermediate which after acidic washing in xylene solution was dealkylated by refluxing for 6 hours with 4-toluenesulphonic acid (ref.99).



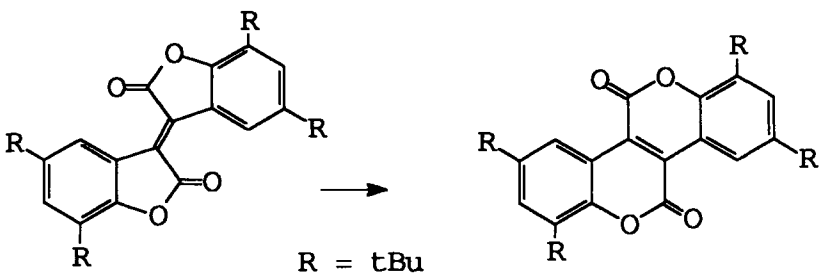
A nine-membered ring containing a dioxafluorophosphorus grouping was derived from the reaction of 2,2'-ethano-bis(4,6-di-tert-butylphenol) and phosphorus trichloride in dichloromethane by refluxing for 10 hours in the presence of a little pyridine with further successive additions of the trichloride and the introduction finally of hydrogen fluoride over 7 hours at the same temperature, followed after 30mins. by an ammoniated work-up to give

PHENOL	REACTANT	CONDITIONS	PRODUCT	YIELD%	REF.
-tert-Butyl	Trichlor-acetaldehyde	K 2-tert-butylphenoxide (preparted from the phenol (1 mole) and K pellets (1 mole) was treated treated in toluene with $AlCl_3$ and refluxed (N_2) for 10 min. After cooling CCl_3CHO in toluene added dropwise (15 min.) allowed to stand overnight and solvent removed to give the trichloromethylol deriv. Refluxed in decalin with basic alumina to give (E)-[3,3]-dibenzofuranylidene-7,7-ditert-butyl-2,2-dione.		58	94
-tert-Butyl--methyl	Chloromethane	A mixture of the phenol and a little polystyrene-bound phosphonium salt MeP^+Bu Cl-in CH_2Cl_2 was treated with sodium hydroxide, cooled, MeCl introduced. Reaction at ambient temp. with stirring (6h) to give 2-tert-butyl-5-methylphenyl methyl ether		94	95
2,4-di-tert-Butyl	N_4S_4	A mixture of the phenol and tetranitrogen tetrasulphide (1 mole) was refluxed in toluene (6h). Other phenols reacted similarly.		86	96
2,4-di-tert-Pentyl	Aqueous KOH	Aqueous potassium hydroxide added to the phenol in methsanol and the mixture sprayed into a drier and the solvents removed in N_2 at 110C to give the potassium salt in powder form.		100	97

2,2'ethano-bis(4,6-di-tert-butylphenyl)fluorophosphite (ref.100).



An isomerisation of the 2-tert-butyllactone derivative, tetra-tert-butylisoxindigo in refluxing pyridine/methanol (1:1) during 15 mins. has been observed to take place in 95% yield (ref.101).



(ii) 2,6-di-tert-Butylphenols

The reactions depicted in this section comprise substitutions at the phenolic hydroxyl or at the 4-position in the ring (some of which are described in Table 6.8 (refs.102-105) and oxidations.

Substitution at the phenolic hydroxyl and in the ring:
Ethyl 3,5-di-tert-butyl-4-hydroxybenzoate in acetonitrile containing sodium perchlorate and perchloric acid after pulse-electrolysis with a platinum-iridium anode at 1.5v gave ethyl 7-tert-butyl-2-methylbenzoxazole-5-carboxylate in 73% yield (ref.106).

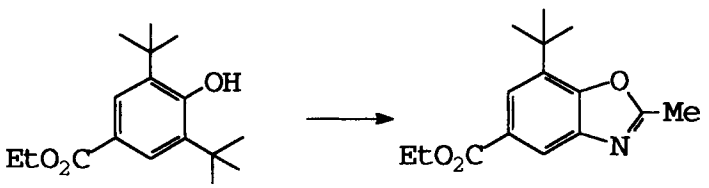
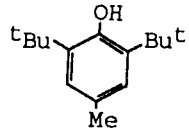
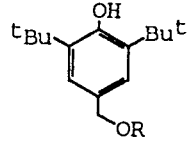
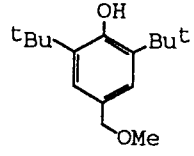
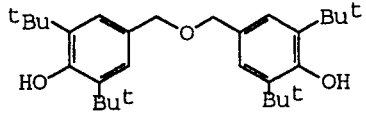
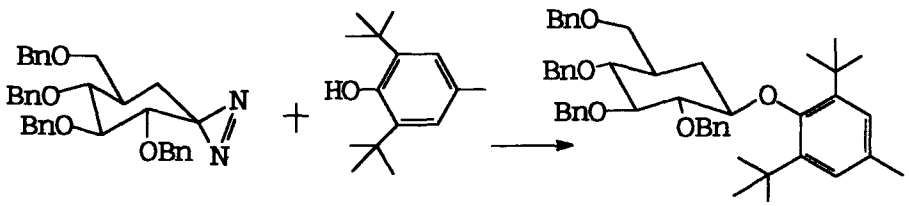


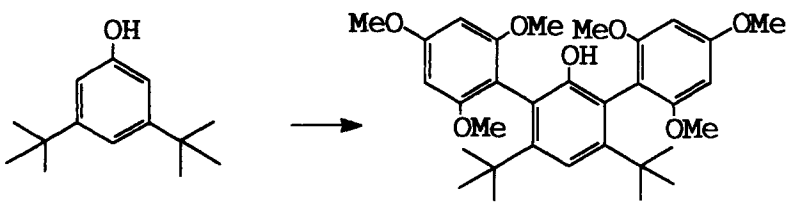
TABLE 6.8 REACTION OF 2,6-di-tert-BUTYLPHENOL AT THE 4-POSITION

REACTANT	CONDITIONS	PRODUCT	YIELD %	REF.
Paraformaldehyde	Paraformaldehyde (2 moles) and 2,6-di-tert-butyl-phenol and catalyst, 10% Pd-C and ytterbium chloride hydrogenated (7Kg/cm.^{2}) at ambient temp. to give 2,6-di-tert-butyl-4-methylphenol.		97	102
Paraformaldehyde, Alkanol, ROH	Paraformaldehyde, 2,6-di-tert-butylphenol and the alkanol (ROH) heated in the temp. range 70-150C under pressure (5-100Kg/cm.^{2}) for 1-10h. with a base (eg N,N-diethylbenzylamine) to the give 2,6-di-tert-butyl-4-alkoxymethylphenol		high	103
Paraformaldehyde, methanol, dimethylamine	2,6-di-tert-butylphenol in methanol was added dropwise (3h) to refluxing methanol containing paraformaldehyd and dimethylamine and the reaction continued for 4h at 15-20 psig.		high	104
Paraformmaldehyde	2,6-di-tert-butylphenol and paraformaldehyde refluxed in methanol containing triethylamine for 16h.		98	105

The O-glycoside of 2,6-di-tert-butyl-4-methylphenol has been produced in 75% yield by the addition of 1-azi-2,3,4,6-tetra-O-benzyl-1-deoxyglucopyranose in toluene to the phenol in toluene containing powdered molecular sieve 4A followed by reaction at 40°C during 1 hour (ref.107).



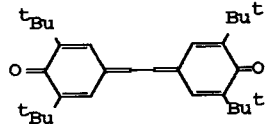
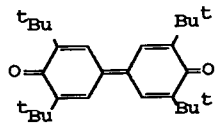
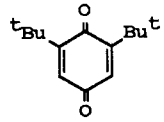
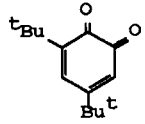
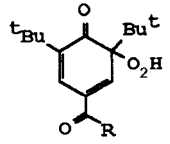
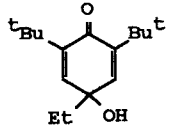
In the 3,5 isomer of this group of 2,6-di-tert-butyl compounds, 2,4,6-trimethoxyphenyllead triacetate can effect arylation, in pyridine solution containing some chloroform, through the process of 'ligand coupling' to give the crowded substitution product depicted (ref.108). Triphenylbismuth dichloride afforded the 2,6-diphenyl analogue.

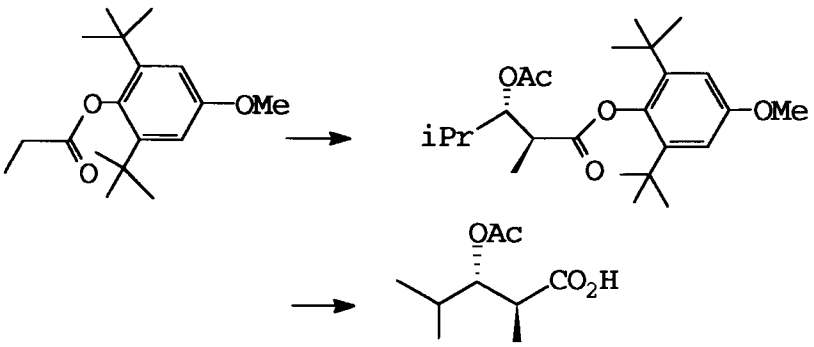


Oxidation Reactions:
A variety of oxidation products result from hindered phenols, ranging from cyclohexadienones to quinones as shown in Table 6.9 (refs.109-114).

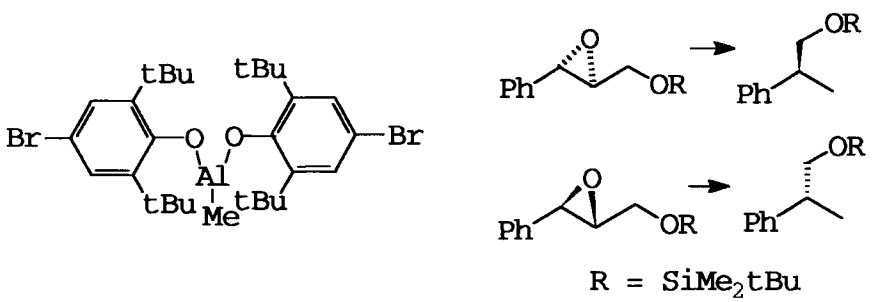
Other Applications of Hindered Phenols:
2,6-di-tert-Butyl-4-methoxyphenyl esters have been used for stereospecific aldol reactions. Thus the threo aldol obtained from the reaction of isobutanal and 2,6-di-tert-butyl-4-methoxyphenylpropionate, after acetylation was converted in acetonitrile solution with ceric ammonium nitrate during 30 mins. to the acetoxy acid which was hydrolysed with aqueous sodium hydroxide to give (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoic acid (ref.115).

TABLE 6.9 OXIDATION REACTIONS OF HINDERED PHENOLS

PHENOL	OXIDANT	CONDITIONS	PRODUCT	YIELD%	REF.
2,6-di-tert-Butyl-4-methylphenol	MnO_2	The phenol in benzene srirred with manganese dioxide on alumina at ambient temp. for 6h.to 3,5,3',5'-tetra-tert-butylstilbene-4,4'-quinone.		72	109
2,6-di-tert-Butyl-phenol	$BnMe_3NBr_3$	The phenol and aqueous sodim hydroxide added dichloromethane and then stirred at ambient temp. for 5h. to give 2,6,2',6'-tetratert-butyldipheno-quinone.		61	110
2,6-di-tert-Butyl phenol	O_2	The phenol and the chelate [N,N'-bis-(2'-pyridine-carboxamido)-1,2-benzene]cobalt(II)-water in acetonitrile at ambient temp. with oxygen for for 5h. to give 2,6-di-tert-butylbenzo-1,4-quinone.		96	111
2,4-di-tert-Butyl-phenol	O_3	The phenol in acetone/dichloromethane/water (1:1:2) containing sodium bicarbonate treated ozone to give the 4,6-di-tert-butylbenzo-1,2-quinone.		72	112
4-Acyl-2,6-di-tert-butylphenol	O_2	The acyl compound and bis(salicylidene)-propanediaminecobalt(II) (1.1equiv.) in dichloromethane at ambient temp. gassed with oxygen for 4h. to give 4-acyl-2,6-di-tert-butyl-6-hydroperoxy-2,4-cyclohexadiene.		98	113
2,6-di-tert-Butyl 4-ethylphenol	O_2	The phenol in ethanol treated with aqueous KOH abnd gassed wth oxygen at 0-5C for 12h. Then diluted with water and the 4-hydroperoxide reduced.		82	114

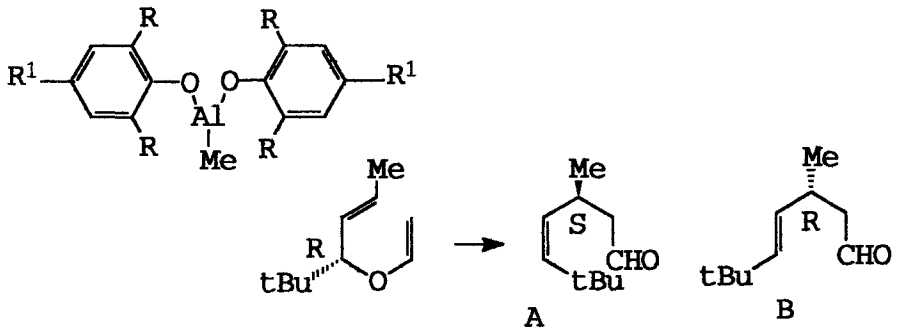


A methylaluminium phenoxide derived from 2,6-di-tert-butyl-4-bromophenol can function as a catalyst in the stereoselective anti-migration of the dimethyl-t-butylsiloxy group in the epoxides illustrated to afford siloxyaldehydes in high yields (ref.116).

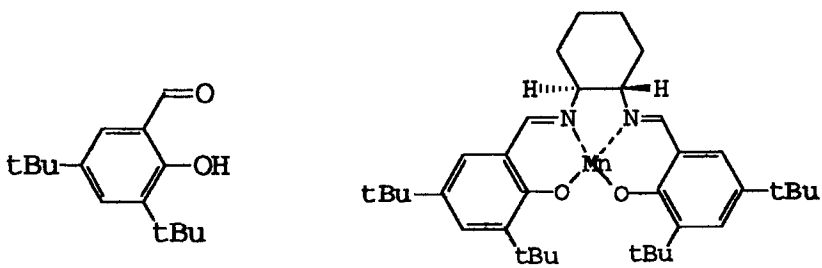


Methylaluminium bis(2,6-di-t-butyl-4-methylphenoxide) complexes with methyl ethyl ether in preference to diethyl ether and adsorbed on silanized silica gel can chromatographically separate tetrahydrofuran from diethyl ether (ref.117). The analogue from 2,6-diphenylphenol can complex gaseous formaldehyde and prevent its polymerisation (ref.118).

It can exert a different type of control on the course of the Claisen rearrangement of the vinyl ether shown. Thus, the E-isomer results in 74% yield (B:A, 98:2) from the use of methylaluminium bis(2,6-diphenylphenoxide (R^1 = H) while the bis(2,6-di-t-butyl-4-bromo) analogue (R^1 = Br) in the series affords the Z-compound in 90% yield (B:A, 16:84) (ref.119). An extensive study has been made by the authors on many structural analogues in this work.



2,4-Di-t-butyl-6-formylphenol has been employed as the manganese derivative shown with readily available trans-1,2-diaminocyclohexane, which can be easily resolved, for highly enantioselective epoxidation (for example of Z-1-phenylprop-1-ene) when employed in catalytic amounts with sodium hypochlorite solution as oxidant (ref.120).



By the reaction of 2,6-di-t-butyl-4-formyl phenol with pyrrole in the presence of propionic acid (ref.121), a phenolic porphyrin, 5,10,15,20-tetrakis(3,5-di-t-butyl-4-hydroxyporphyrin has been synthesised. This compound forms stable phenoxyl radicals in deoxygenated as well as in oxygen-rich basic solutions the redox behaviour of which has been extensively studied (ref. 122).

Deoxygenation Reaction:

Highly hindered phenols can be deoxygenated through hydrogenation of their triflates (ref.123).

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CHAPTER 7

CARBONYL DERIVATIVES OF PHENOLS

7.1 Introduction

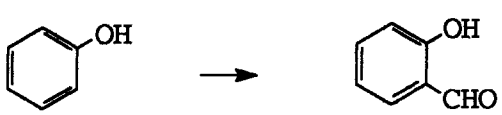
In this chapter the preparations and reactions of carbonyl derivatives are considered with reference to phenolic aldehydes, phenolic ketones, acids and esters in which the carbonyl group is directly attached to the ring rather than as a substituent in an alkyl side-chain. Developments in the last one and half decades are considered. The range of synthetic methods is not as extensive as with phenol anf the alkylphenols but catalytic procedures are prevalent and several ingenious alkylations and acylations of intermediate anions have been found. Some mention is made of the related groups, the amides and nitriles. Progress in all these areas and in the synthesis of certain bicyclic and polycyclic members with the same range of functional groups has been summarised. These sections are followed by an account of the reactions of this whole group of compounds. While it could be said that certain of the reaction could occur in the absence of the phenolic hydroxyl group the latter of course at the minimum provides a functional handle for structure/activity studies in many different areas. In the array of carbocyclic and heterocyclic compounds which can be derived often very easily, the remarkable synthetic potential of the phenolic ring system is again demonstrable.

7.2 Synthesis of Phenolic Carbonyl Compounds

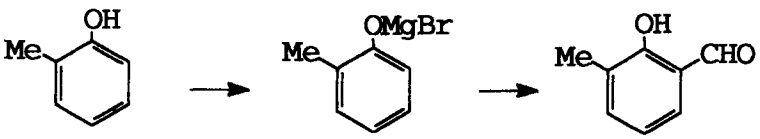
7.2.1 Phenolic Aldehydes

(i) 2-Hydroxy aldehydes

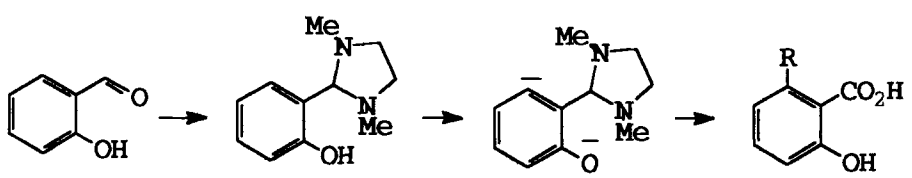
Improvements in the regiospecific synthesis of salicyl aldehyde have been made by the same group who earlier (ref.1) devised a novel route to saligenin. Salicylaldehyde can be obtained in 99% yield by the reaction of phenol in



toluene solution containing stannic chloride and tri-n-butylamine by stirring for 20 mins. followed by addition of paraformaldehyde and heating of the mixture for 8 hours at 100°C (ref.2).
In a method which avoids the use of hexamethylphosphoric triamide (as in the procedure described in ref.1), 3-methylsalicylaldehyde has been prepared from 2-methylphenoxymagnesium bromide, obtained by initial treatment of the phenol in benzene with ethylmagnesium bromide, followed by addition of 1.5 moles of triethylamine and 2.5 moles of paraformaldehyde. The mixture was then refluxed for 2.5 hours and acidification afforded the product in 75% yield (ref.3).



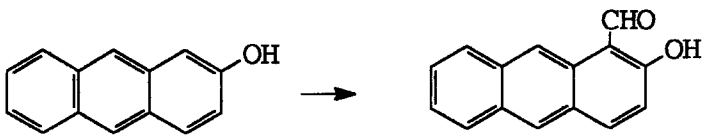
In an alternative approach, phenol and hexamethylenetetramine in ethanol afforded salicylaldehyde in 97% yield by refluxing for 3.5 hours and a further 1.5 hours after the addition of water (ref.4).
It has been found that N,N'-dimethylethylenediamine adducts of salicylaldehydes metalate ortho to the modified formyl group and use has been made of this in the preparation of 6-alkyl and 6-substitutedalkyl salicylaldehydes (ref.5) with the synthetic objective of the antifeedant, panacene in view. Thus for example salicylaldehyde with N.N'-dimethylethylenediamine gave 2-(2-hydroxyphenyl)-1,3-dimethylimidazolidine which, by treatment with n-butyl-lithium in diethyl ether containing tetramethylethylenediamine (TMEDA), gave the dianion. Reaction with a variety of electrophiles gave acceptable yields after removal of the protective group with 2M hydrochloric acid. The yields (R,%) were (Me,95; Et,54; PhCHOH,47; TMS,76).



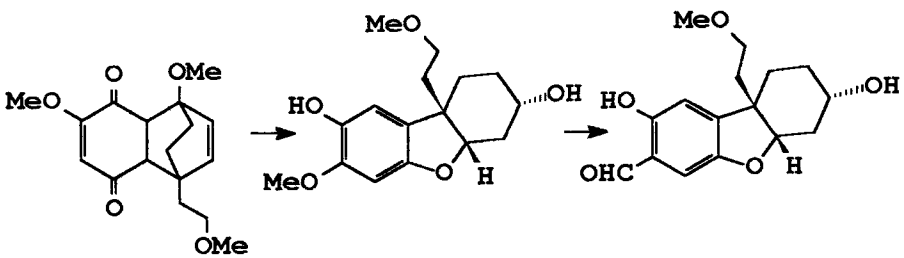
In basic methodology reminiscent of the formation of anisaldehyde from 4-methoxytoluene and also an aspect of phenol oxidation (Chap. 5), 2-cresol in methanol containing sodium hydroxide and a catalytic quantity of tetrakis(2,4-dimethoxyphenyl)porphyrinatoiron(III) chloride and cupric nitrate trihydrate afforded a 78% yield of salicylaldehyde after oxygenation with oxygen

at 70°C during 30 hours (ref.6).

In the polycyclic field, 2-hydroxyanthracene and ethyl N-phenylformidate, PhN=CHOEt (2 moles) furnished 2-hydroxy-1-anthraldehyde in 60% yield when heated together with continuous removal of ethanol, followed by hydrolysis of the resultant Schiff's base in acetic acid containing hydrochloric acid (ref.7).



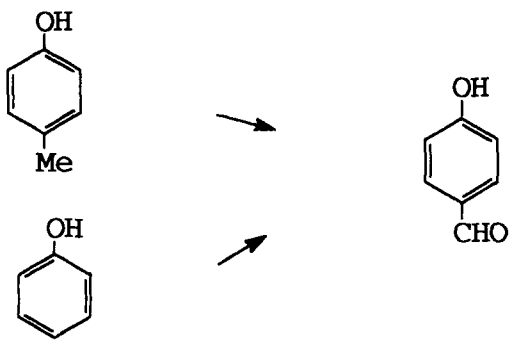
An abnormal Reimer-Tiemann reaction has been observed in which dichlorocarbene attack at the 2-position to the phenolic hydroxyl group was sterically blocked resulting instead in displacement of the methoxyl group at the adjoining position (ref.8). The hexahydrodibenzfuran depicted was obtained by the Diels-Alder reaction of 2-methoxybenzo-1,4-quinone and 1-methoxy-4(2-methoxyethyl)cyclohexa-1,3-diene followed by acidic rearrangement at ambient temperature.



(ii) 4-Hydroxyaldehydes

2,3-Dichloro-5,6-dicyanobenzoquinone has been employed to oxidise 4-methylphenol stirred in methanolic solution at ambient temperature over 1.5 to 2 hours to give an 84% yield of 4-hydroxybenzaldehyde (ref.9). This is an all-

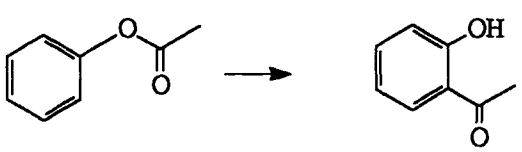
organic procedure unlike the traditional oxidation method based on inorganic reagents such as manganese dioxide.
In an interesting modification of the Reimer-Tiemann reaction the dropwise addition of chloroform to a mixture of phenol and α-cyclodextrin in 10% aqueous sodium hydroxide at 60°C and reaction over 10 hours afforded 4-hydroxybenzaldehyde in 46% yield (ref.10). Both these methods are shown below



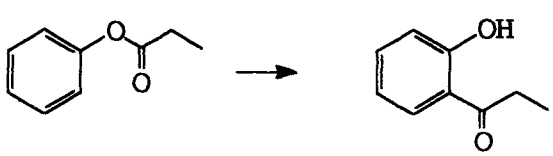
7.2.2 Phenolic Ketones

(i) 2-Hydroxyaryl alkyl ketones

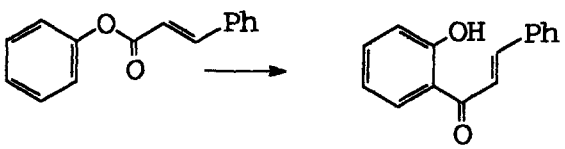
A Fries rearrangement of phenyl acetate with zirconium tetrachloride in benzene, toluene or xylene in the temperature range 120-170°C has been reported to give 2-hydroxyacetophenone in high yield (ref.11).



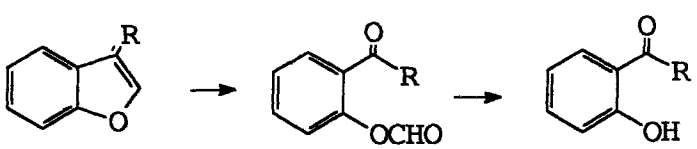
Phenyl propionate has been converted to 2-propionylphenol in 62% yield by



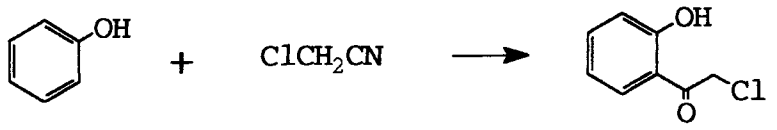
dropwise addition over 1 hour to a solution of titanium tetrachloride in o-dichlorobenzene, followed by heating of the mixture at 150°C for 1 hour and work-up by quenching in dilute hydrochloric acid (ref.12).
A photochemical rearragement of phenyl acetate in hexane solution containing powdered potassium carbonate by irradiation at ambient temperature with a 125 watt medium pressure mercury lamp during 12 hours furnished a 74% yield of 2-hydroxyacetophenone although in the absence of the base the yield dropped to 13% (ref.13).
A rapid photochemial method, described as higher-yielding than the conventional Fries rearrangement for phenyl cinnamate, in which a 10^{-4}M solution as micelles in 10^{-2}M aqueous sodium dodecylsulphate was stirred for 10-12 hours and then irradiated at 254nm for 6 hours under nitrogen in the quartz well of an annular photoreactor (model APQ 40, with a 16w low-pressure mercury lamp), produced a 70% yield of 2-cinnamoylphenol (with 90% conversion) (ref.14).



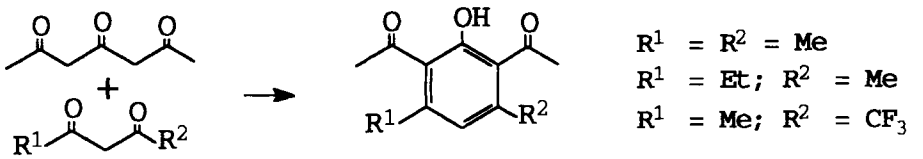
Amongst the methods for 2-hydroxycarbonyl compounds alternative to Fries rearrangement may be instanced the ozonolysis of appropriate benzofurans. 3-Cyclohexylbenzofuran in dichloromethane with a saturated solution of ozone in the same solvent at -78°C after stirring for 10mins. and warming to ambient temperature over 1 hour, followed by treatment with dimethyl sulphide during 1 hour, afforded cyclohexyl 2-(formyloxy)phenyl ketone (R = C_6H_{11}) in 86% yield readily transformed quantitatively with methanolic sodium hydroxide to cyclohexyl 2-hydroxyphenyl ketone (ref.15).



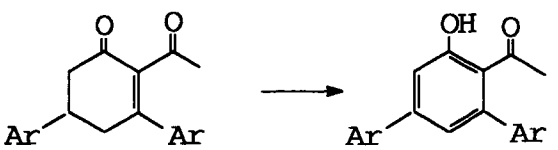
In the presence of both aluminium chloride and boron trifluoride, chloromethyl cyanide reacts with phenols to give exclusively 2-chloroacylphenols whereas the Houben-Hoesch reaction predominantly results in 4-hydroxy ketones (ref.16).



Open-chain precursors have been employed to produce diacylphenols substitututed in the 3- and 5-positions although the yields are moderate (ref.17) due to self-reaction rather than cross-reaction of the components.

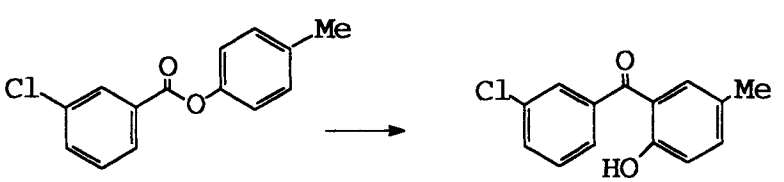


Aromatisation of 2-acyl-3,5-diarylcyclohex-2-enones by treatment with bromine in chloroform and warming of the solution until the evolution of hydrogen bromide ceased followed by work-up after cooling, by addition of diethyl ether, affords another procedure to the corresponding 2-acylphenols (ref.18).

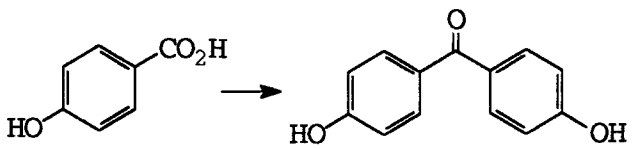


(ii) 2-and 4-Hydroxybenzophenones

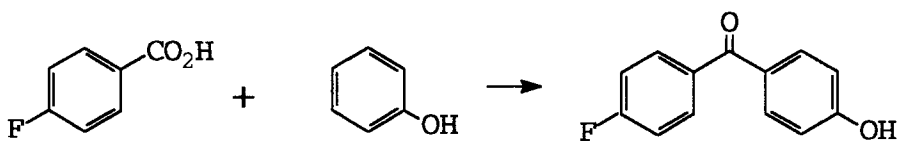
4-Methylphenyl 3-chlorobenzoate has been catalytically rearranged in refluxing nitrobenzene solution containing Nafion-H during 12 hours to give 3-chloro-2'-hydroxy-5'-methylbenzophenone in 71% yield (ref.19).



4-Hydroxybenzophenones have been derived by various intermolecular acylations. Thus 4-hydroxybenzoic acid and phenol with a catalytic amount of 98% methanesulphonic acid afforded, after 4.5 hours at 80°C, 4,4'-dihydroxybenzophenone in 51% yield (ref.20).

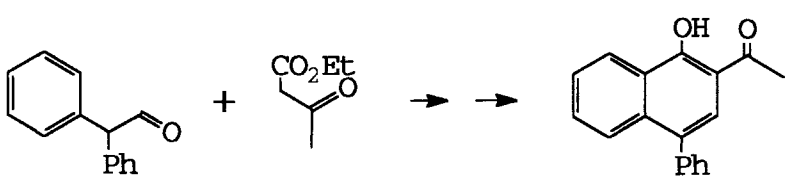


In a similar way 4-fluorobenzoic acid and phenol at -1°C with trifluoromethanesulphonic acid followed by reaction at ambient temperature overnight gave 4-hydroxy-4'-fluorobenzophenone in 59% yield (ref.21).



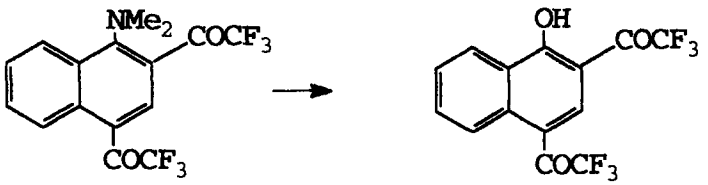
(iii) Polycyclic Hydroxyketones

The Knoevenagel reaction has been used to obtain 2-acetyl-4-phenyl-1-naphthol and the 2-benzoyl analogue (ref.22). Thus, diphenylacetaldehyde with ethyl acetoacetate or the benzoylacetate in toluene containing piperidine, benzoic acid and excess of a molecular sieve (type 4A, 4-8 mesh beads) gave upon work-up the afore-mentioned compounds respectively. By the use of ethyl malonate under similar conditions, 2-ethoxycarbonyl-4-phenyl-1-naphthol was obtained in 55% yield but an 87% yield of this compound resulted from 3,3-diethoxycarbonyl-1,1-diphenylpropene by heating in the presence of a molecular sieve although the saturated propane analogue did not respond.

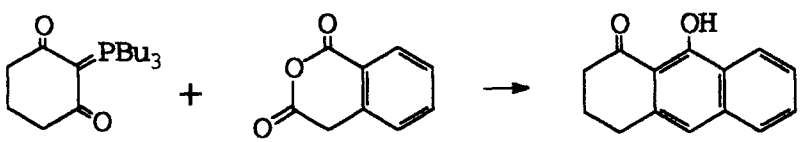


Nucleophilic displacement of the dimethylamino group in N,N-

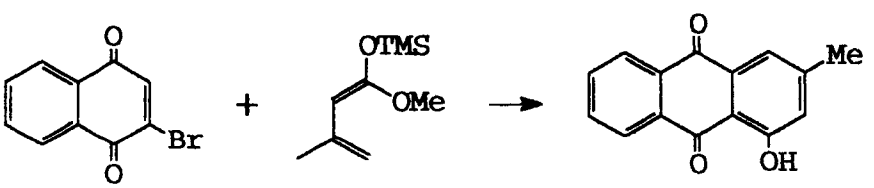
dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine by the hydroxide, alkoxide (or thioalkyl) ions leads smoothly to 1-hydroxy-2,4-bis(trifluoroacetyl)naphthalene and the corresponding ether and thioether analogues respectively (ref.23). For example, 1-dimethylaminonaphthalene initially upon treatment with trifluoroacetic anhydride in pyridine at room temperature furnished the 2,4-bis(trifluoroacetyl) derivative which with aqueous acetonitrile at 85°C over 40 hours gave 2,4-bis(trifluoroacetyl)-1-naphthol.



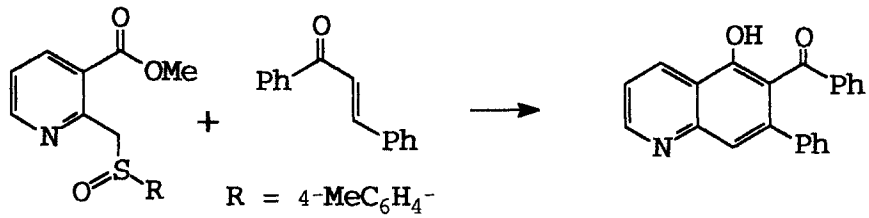
An ingenious synthesis, albeit in low yield, of 1-oxo-1,2,3,4-tetrahydro-9-hydroxyanthracene has been achieved from a phosphoran and a ketene formed as an intermediate. The phosphoran with homophthalic anhydride (3.3mols.) and trimethylsilane (3mols.) upon themolysis in toluene at 150°C for 40 hours in a sealed tube gave the product in 23% yield (ref.24).



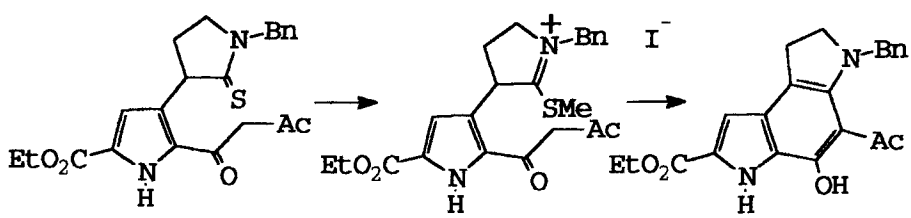
Pachybasin, 2-methyl-4-hydroxyanthra-9,10-quinone has been obtained in 73% yield by Diels-Alder addition from 2-bromonaphthoquinone and the vinylketene mixed acetal, 1-trimethylsiloxy-1-methoxy-3-methylbuta-1,3-diene, by reaction in dichloromethane containing potassium carbonate, heating with sodium acetate and finally aromatisation of the crude product by refluxing in ethanol The diene was accessible from methyl senecioate (methyl 3-methylbut-2-enoate) by treatment with lithium diisopropylamide and trimethylchlorosilane (ref.25).



Substituted 2-methyl analogues were also obtained by the use of the appropriate diene.
In the heterocyclic field, 3-carbonylmethoxypyridine-2-(4-tolyl)methylsulphoxide indicated reacted with benzylideneacetophenone in 1,1-dimethoxyethane by Michael addition in the presence of potassium t-butoxide (2.5mols.), and then cyclisation, to afford a 72% yield of 6-benzoyl-5-hydroxy-7-phenylquinoline during 24 hours at ambient temperature (ref.26).



In another approach methylthiol as a leaving group has been used to obtain a tricyclic derivative of 2-hydroxyacetophenone.
Following formation of the S-Me derivative of ethyl 4-(1-benzyl-2-thia-oxopyrrolidin-3-yl)-5-(1,3-dioxobutyl)pyrrole-2-carboxylate with methyl iodide, the mixture was heated in a sealed Pyrex tube under nitrogen at 80°C for 15 hours to produce ethyl 5-acetyl-6-benzyl-4-hydroxy-3,6,7,8-tetra-hydrobenzo-[1,2-b:4,3-b']dipyrrole-2-carboxylate in 97% yield (ref.27)

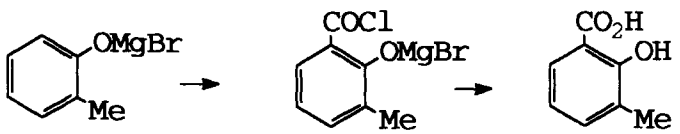


7.2.3. Phenolic Acids

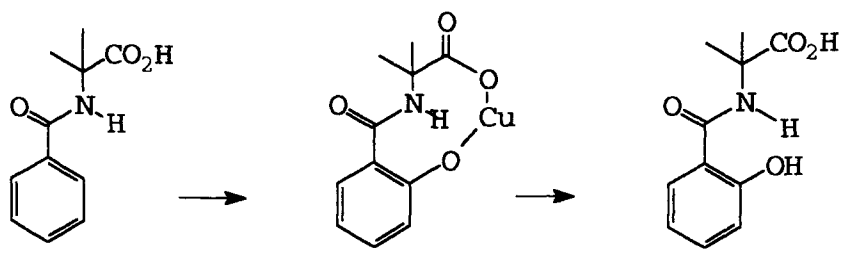
(i) 2-Hydroxy, 4-Hydroxy and Hydroxynaphthoic acids

A range of procedures for obtaining phenolic acids has become available in recent years involving either o-hydroxylation or carboxylation. A general method for obtaining salicylic acids without substituents reactive towards ethylmagnesium bromide has been devised.
Thus 2-methylphenoxymagnesiobromide, obtained from 2-methylphenol in ethereal solution under nitrogen with ethylmagnesim bromide was recovered in

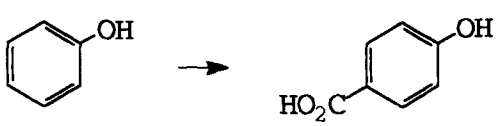
powdered form by high vacuum treatment during 3 hours, suspended in carbon disulphide and the mixture treated rapidly with phosgene in carbon disulphide, allowed to react for 15 mins., and then quenched with 10% aqueous ammonium chloride to give 3-methylsalicylic acid in 55% yield (ref.28).



By contrast, N-benzoyl-2-methylalanine in trimethylamine oxide upon oxidation with oxygen in the presence of copper(0) afforded an intermediate copper(II) salt which was hydrolysed with 0.5M hydrochloric to afford salicylic acid in the form of the corresponding amide in quantitative yield (ref.29). Aryl carbonates were produced when the phenoxide was poorly coordinated

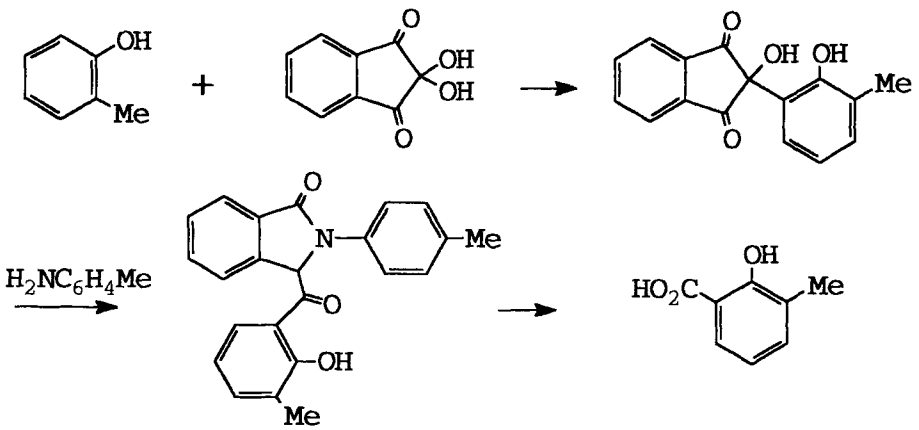


In the reworking of an old method, 4-hydroxybenzoic acid has been derived in high yield by the copper-catalysed carboxylation of phenol in alkaline solution with carbon tetrachloride (ref.30). The author recalls preparing 4-hydroxy-3-methylbenzoic acid precisely by this route in 1947.

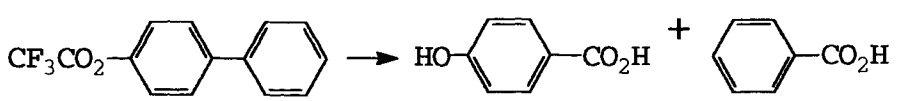


A novel electrophiic substitution, based on the reaction of ninhydrin in refluxing acetic acid over 2 hours with 2-methylphenol, afforded 2-hydroxy-2-(2-hydroxy-3-methylphenyl)indane-1,3-dione in 78% yield. With 4-methylaniline in refluxing acetic acid for 12 hours, 3-(2-hydroxy-3-methyl-

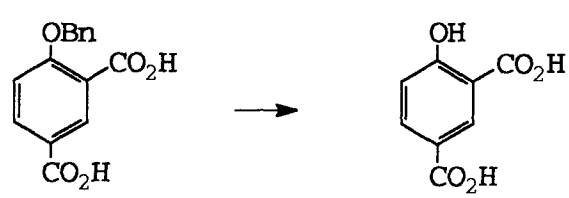
benzoyl)-2-(4-tolyl)-1-oxo-1,3-dihydroisoindole was formed in 70% yield which was then hydrolysed during 5 mins. with 2M sodium hydroxide to give 3-methylsalicylic acid after acidification. The overall yield was 55% (ref.31).



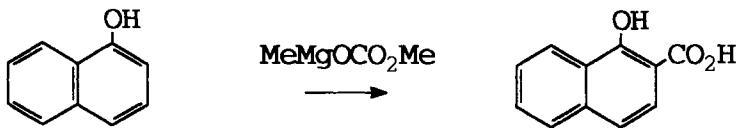
4-Phenylphenyl trifluoracetate in carbon tetrachloride upon treatment with ruthenium tetroxide (from ruthenium dioxide and sodium periodate) in carbon tetrachloride during 1 hour gave by cleavage a 9:1 mixture of 4-hydroxybenzoic and benzoic acid in 55% yield. Protection of the OH group is necessary to avoid fragmentation of the phenolic ring (ref.32).



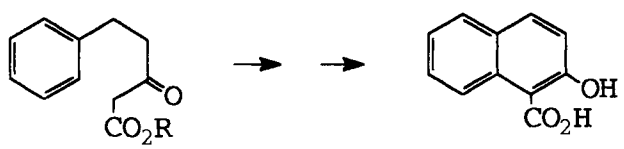
Transfer hydrogenation has been employed to effect debenzylation. In this way the benzyl ether of 2,4-dicarboxyphenol in ethanol solution with 10% palladium-carbon, and aqueous sodium hypophosphite after refluxing for 2



hours furnished the phenolic acid in 95% yield. In related compounds carbonyl, halogen, carboxyl and amide groups remained unaffected (ref.33).
1-hydroxy-2-naphthoic acid has been derived from 1-naphthol and 1.8M methoxymagnesium methyl carbonate in dimethylformamide under pressure (500psi.) at 180°C during 6 hours in a static system in 96% yield. Phenol itself did not react although catechol afforded dihydroxyisophthalic acid (ref.34).



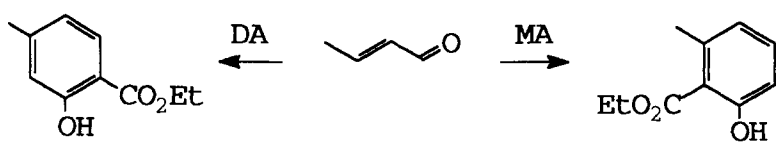
The oxidative cyclisation of alkyl 5-aryl-3-oxonaphthoates results in the formation of 2-hydroxy-1-naphthoic acid (ref.35).



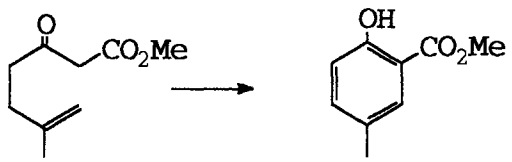
7.2.4. Phenolic Esters

(i) Alkyl 2-hydroxybenzoates

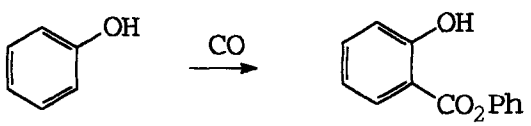
A variety of novel procedures has been developed for the synthesis of phenolic esters in the last decade.
Intermolecular reactions involving non-aromatic precursors have been used to furnish salicylate esters. ,β-Unsaturated aldehydes have been reacted with the dianion (DA) of ethyl acetoacetate to afford 4-substituted salicylates in good yield (ref.36). 6-Methylsalicylates result from the addition of the monoanion (MA) at C2 (ref.37).



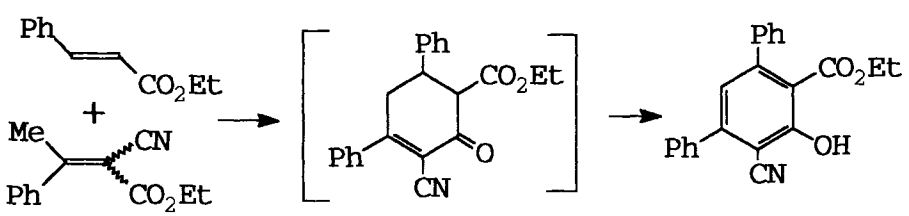
Methyl 5-methylsalicylate has been obtained in 71% yield by intramolecular cyclisation of the open-chain ketoester, methyl 6-methylene-3-oxoheptanoate in acetic acid containing 4 equivs. manganese(III) acetate dihydrate and 4 equivs. lithium chloride at ambient temperature during 24 hours followed by heating of the crude product with lithium chloride at 100°C for 24 hours (ref.38).



A mixture of phenol and dichloro bis(benzonitrile)palladium(II) in dichloromethane under carbon monoxide treated and stirred with diisopropylamine during 3 hours furnished phenyl salicylate in 53% yield (ref.39).

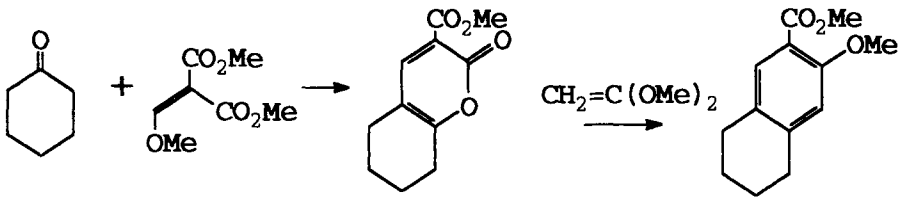


The intermolecular Michael addition of ethyl 2-cyano-3-phenyl-2-butenoate and ethyl cinnamate in benzene containing sodium hydride and a little dry ethanol followed by aromatisation of the intermediate by refluxing for 1 hour gave after acidification ethyl 3-cyano-4,6-diphenyl-2-hydroxybenzoate in 52% yield (ref.40).

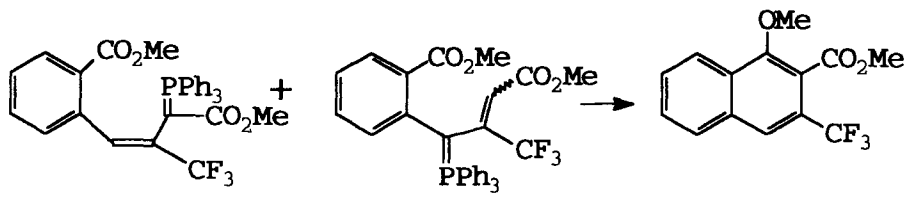


A variation on the Michael addition is shown by the formation of methyl 3-methoxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate from the anion of cyclohexanone and dimethyl methoxymethylenemalonate and reaction of the pyrone intermediate with dimethoxyethene. Cyclohexanone in tetrahydrofuran was added to lithium diisopropylamide in the same solvent at -78°C and after stirring for 1.75 hours the mixture at -30°C was treated dropwise with a solution of dimethyl methoxymethylene malonate in tetrahydrofuran over 15 mins., and

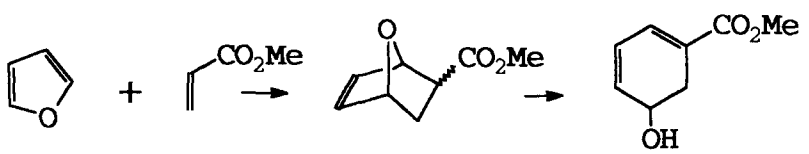
stirred for 2.75 hours to give an α-pyrone intermediate (formed in 84% yield). After the introduction of dimethoxyethene (5.5 moles) in toluene, and reaction by warming at 95°C during 15 mins. the final product was obtained in 78% yield (ref.41).



Methyl 1-methoxy-3-trifluoromethylnaphthalene-2-carboxylate was formed in 90% yield, with loss of triphenylphosphine oxide, by heating the isomeric benzylidenephosphorans shown (of unspecified stereochemistry) in dry xylene solution in a sealed tube at 250°C during 10 hours (ref.42).

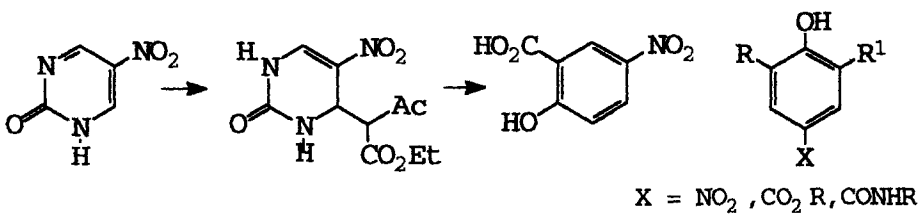


The dihydroaromatic compound, methyl 3-methoxycarbonylcyclohexa-3,5-dienol has been prepared by the Diels-Alder addition of furan and methyl acrylate in the presence of zinc iodide at 40°C during 48 hours to give first the adduct shown in 55% yield. A solution of this in tetrahydrofuran added dropwise to lithium bis(trimethylsilyl)amide at -78°C with subsequent warming to ambient temperature after 1.5 hours gave the cyclohexadiene product in 85% yield. This should be readily dehydrogenated to methyl 3-hydroxybenzoate (ref.43).

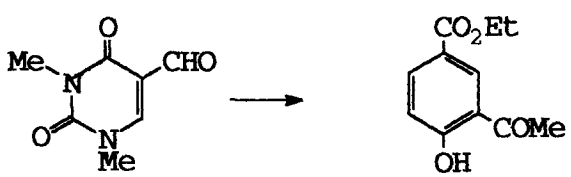


(ii) Alkyl 4-Hydroxybenzoates

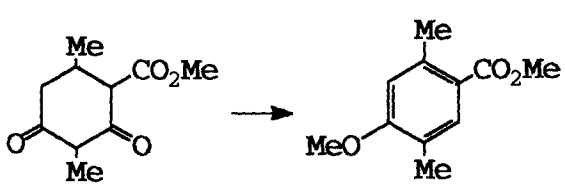
Pyrimidines, appropriately substituted, acting as protected malonaldehydes can function as quasi aromatic intermediates in Claisen methodology to give quite acceptable yields of certain 2-hydroxybenzoic acid and 4-hydroxyphenyl compounds by reaction with β-ketoesters and with ketones, $RCH_2COCH_2R^1$ respectively (ref.44). Thus 5-nitro-2-hydroxypyrimidine with ethyl acetoacetate in ethanol containing a catalytic quantity of hydrochloric acid afforded an adduct which with sodium hydroxide at ambient temperature, followed by acidification gave 2-hydroxy-5-nitrobenzoic acid in an overall of 43% yield. Other appropriate starting materials with ketones (R,R^1= alkyl) gave alkyl 4-hydroxybenzoates (X = CO_2R).



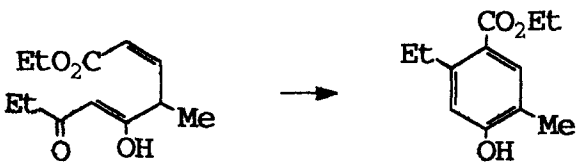
In a similar way by reaction in ethanolic sodium ethoxide the dioxo compound, 5-formyl-1,3-dimethyluracil gave with acetylacetone the 4-substituted phenol, ethyl 3-acetyl-4-hydroxybenzoate in 55% yield (ref.45).



Aromatisation, dehydration and methylation of methyl 3,6-dimethyl-dihydroresorcylate(2,5-dimethyl-4-methoxycarbonylcyclohexane-1,3-dione)was

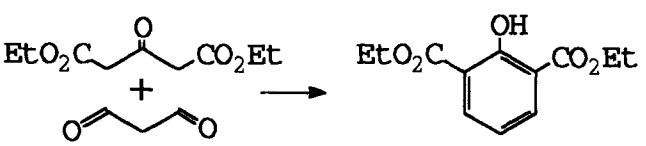


effected by treatment in methanolic solution with thionyl chloride and copper oxide, stirring and continuous introduction of air during 5 hours at 50°C to give in 84% yield the O-methyl ether of methyl 4-hydroxy-3,6-dimethyl benzoate (ref.46).
Ethyl 4-hydroxy-3-methyl-6-ethylbenzoate has been prepared in 80% yield by the cyclisation of ethyl 4-methyl-5,7-dioxo-2(Z)-non-2-enoate in 0.18M ethanolic sodium ethoxide during 1 hour (ref.47).

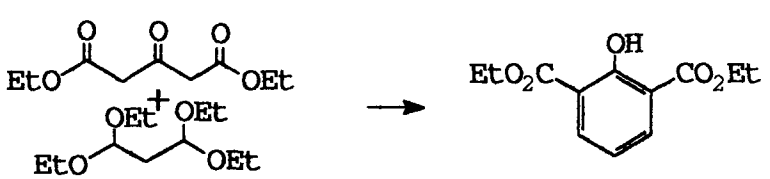


(iii) Dialkyl Hydroxyphenyldicarboxylates

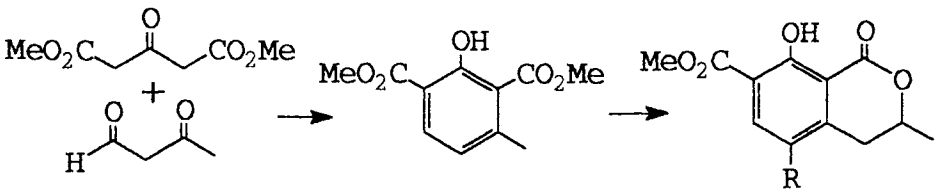
A number of syntheses of hydroxyphthalate, isophthalate and terephthalate systems have been devised. The double Claisen condensation of malondialdehyde with diethyl 3-oxoglutarate which results in 2,6-diethoxycarbonylphenol, represents the simplest approach to this type of structure although the moderate yield of 41% is the lowest of a series with different substituents based on this methodology (ref.48).



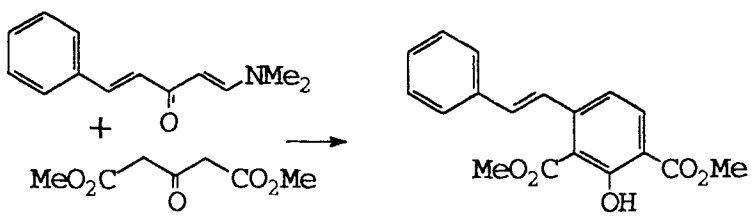
A variation on this approach in which malonaldehyde tetraethylacetal and an 0.5 molar solution of diethyl 3-oxoglutarate in dichloromethane were treated with 1 mole of a molar solution of titanium tetrachloride in dichloromethane and



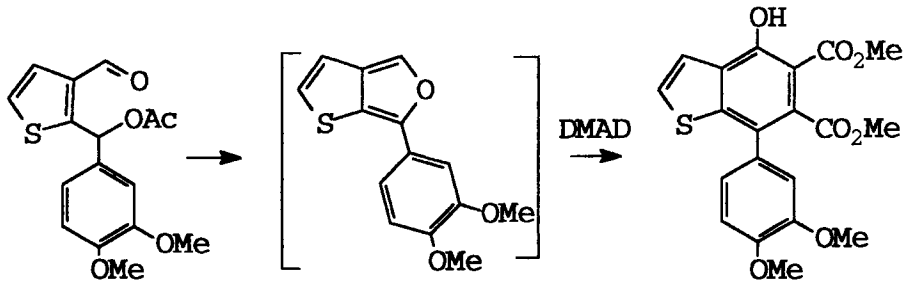
reacted during 1 hour led to a 58% yield of 2,6-di(ethoxycarbonyl)phenol (ref.49).
Ethyl formylacetate and diethyl 3-oxoglutarate have afforded modest yields of 2,6-di(methoxycarbonyl)-3-methylphenol otherwise difficult to obtain which has been used in a synthesis of the aromatic acidic moiety of ochratoxin from *Aspergillus ochraceus*. 2,6-Di(methoxycarbonyl)-3-methylphenol with lithium diisopropylamide in tetrahydrofuran containing hexamethylphosphorictriamide and reaction with ethanal followed by final acidification gave a lactone (R = H) which with sulphuryl chloride and hydroysis of the ester by lithium hydroxide, afforded 3-methyl-5-chloro-8-hydroxyisocoumarin-7-carboxylic acid (R = Cl) in an overall yield of 20% from the starting two esters (ref.50).



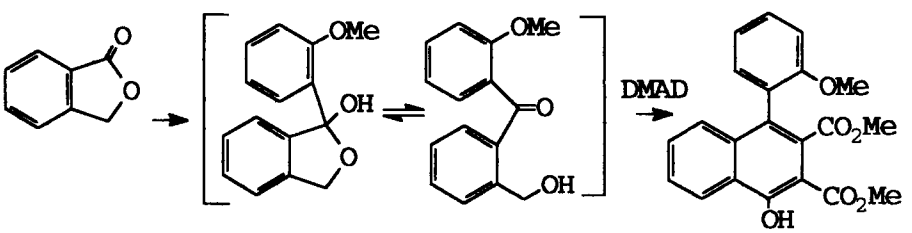
A mixture of dimethyl 3-oxoglutarate and 5-dimethylamino-1-phenyl-1,4-pentadiene-3-one in dioxan containing acetic acid and potassium fluoride upon refluxing overnight underwent Michael addition and afforded dimethyl 2-hydroxy-4-(2-phenylethenyl)-1,3-benzenedicarboxylate in 63% yield (ref.51).



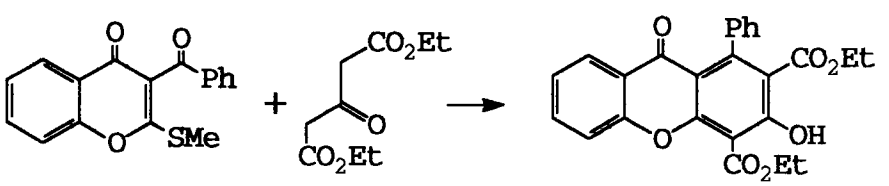
The Diels-Alder addition of 2-(α-acetoxy-3,4dimethoxybenzyl)-3-formylthiophene with dimethyl acetylenedicarboxylate (DMAD) by refluxing during 1 hour in benzene containing a small amount of trifluoroacetic acid furnished a 3-hydroxy-4,5-thienophthalate in 88% yield (ref.52). The formation of dimethyl 3-hydroxy-6-phenoxyphthalate by the Diels-Alder addition of 5-phenoxyfuryl-2-methanol with dimethyl acetylene dicarboxylate has been referred to earlier (ref.137, Chap.4) in the chemistry of phenolic ethers and indicates the dual classification possible with polyfunctional compounds.



A dimethyl 1-naphthol-2.3-dicarboxylate compound has been synthesised from phthalide. Thus 2-methoxyphenyllithium, prepared from 2-bromoanisole and n-butyllithium, was reacted with phthalide in tetrahydrofuran solution at -78°C during 30 minutes and after the reaction mixture had attained ambient temperature during a further 30 minutes, 4 moles of dimethyl acetylene (DMAD) in dichloromethane were introduced. Following completion of reaction overnight, and removal of excess reagent, the crude product was aromatised by refluxing for 4 hours with a benzene solution of toluenesulphonic acid to afford dimethyl 1-hydroxy-4-(2-methoxyphenyl)naphthalene-2,3-dicarboxylate (ref.53).



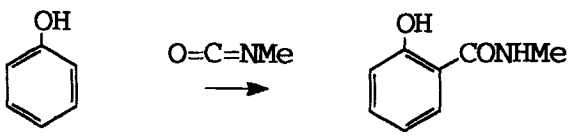
In the polycyclic field, 3-benzoyl-2-methylthiochromone with diethyl 3-oxoglutarate underwent Michael addition and Claisen condensation initially in tetrahydrofuran containing potassium tert-butoxide during 5 mins. followed by desulphurisation at ambient temperature during 1 hour to afford, after acidification diethyl 3-hydroxy-1-phenylxanthon-2,4-dicarboxylate (ref.54).



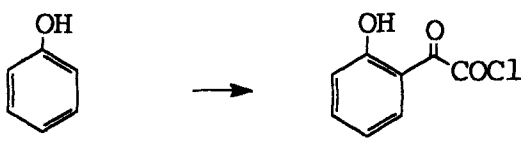
7.2.5. Phenolic nitriles, Amides, Ketoacids and Phthalides

A number of derivatives of 2-hydroxybenzoic acid have been derived by novel routes. 2-Hydroxybenzonitrile has been synthesised from 6-chloro-6-cyano-2-cyclohexenone by a brief treatment with triethylamine during 10 mins. to give 2-cyanophenol in nearly quantitative yield (ref. 55).

The reaction of phenol in benzene added to boron trichloride (1 mole) in dichloromethane at -10°C followed by slow treatment at 0°C with methyl isocyanate in benzene and refluxing of the mixture for 4 hours afforded, after quenching with sodium hydroxide solution, 2-hydroxy-N-methylbenzamide in 73% yield (ref.56).

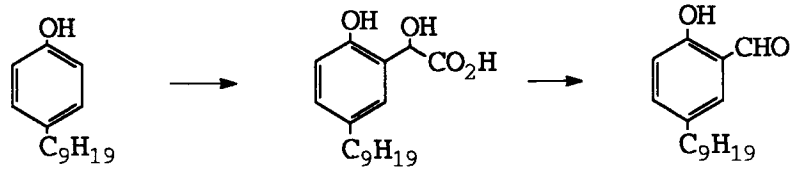


A further example of the regiospecific synthetic utility of phenoxy magnesiumbromide is illustrated by the following reaction. Phenoxymagnesium bromide in toluene, prepared in the usual way from phenol and ethylmagnesium bromide in toluene, treated dropwise with oxalyl chloride in toluene over 20 mins. and then reacted at ambient temperature for 7 hours, gave, after work-up by acidification, 2-hydroxyphenylglyoxylic acid in 44% yield (ref.57).

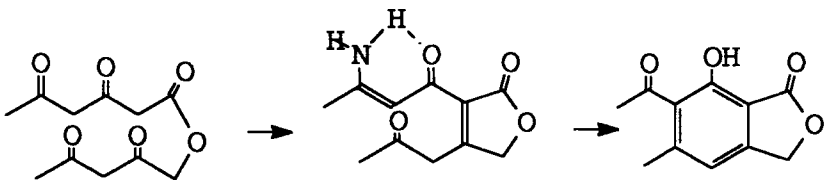


An alternative aldehyde synthesis based on the initial formation of a glyoxylic acid has been achieved by the use of glyoxylic acid itself with 4-t-nonylphenol and boric acid. Thus by way of a final oxidative decarboxylation on the

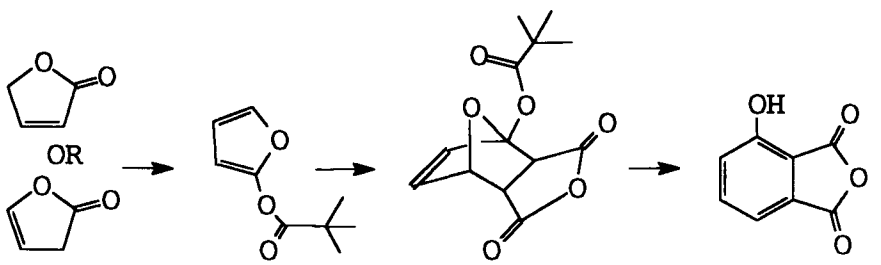
intermediate, the important aldehyde, 5-t-nonylsalicylaldehyde, of value as its oxime in the commercial extraction of copper, is derived (58).



2-Hydroxyphthalide derivatives have been formed from open-chain precursors via an enaminoketone derived with ammonia in which process either terminal keto system appears open to reaction. Prior formation of the five-membered lactone ring apparently occurs (ref.59).



2-Hydroxyphthalic anhydride ring formation by the Diels-Alder reaction of 2-pivaloyloxyfuran and maleic anhydride, giving the exo adduct, followed by aromatisation with concentrated sulphuric acid has been described ref.60) in



an 64% overall yield. The initial mixture of butenolides reacted with pivaloyl chloride in triethylamine to give 2-pivaloyloxyfuran in 75-95% yield. The Diels-Alder addition afforded an 89-92% yield while the final step proceeded nearly quantitatively in 98% yield.

7.3 Reactions of Phenolic Carbonyl Compounds

7.3.1 Phenolic Aldehydes

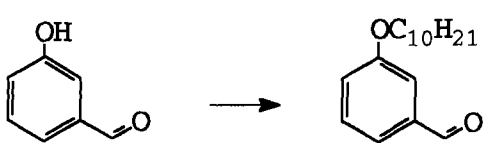
The reactions of the phenolic aldehydes may be conveniently grouped under etherification of the phenolic hydroxyl group, replacement of the aldehyde group and condensation reaction of the latter.

(i) Etherification

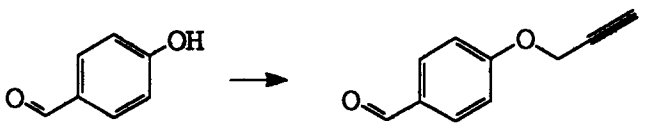
2-Methoxymethoxybenzaldehyde was formed in 90% yield by the gradual treatment of salicylaldehyde, methylal and dimethylformamide in toluene with phosphorus oxychloride at 65°C during maintenance of a gentle reflux, which was continued after completion of the addition for 2 hours followed by work-up by pouring the mixture into ice-cold sodium hydroxide solution (ref.61).

By passage of difluorochloromethane through an aqueous solution of salicylaldehyde in sodium hydroxide at 60°C, 2-difluoromethoxybenzaldehyde was formed in 90% yield (ref.62).

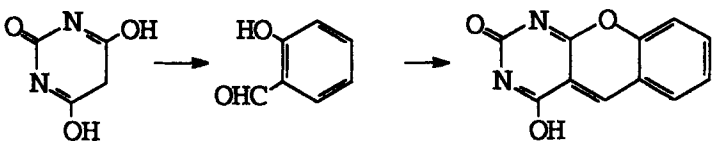
3-Hydroxybenzaldehyde, 1-bromodecane and caesium carbonate in dimethylformamide when reacted at 80°C during 16 hours gave the



corresponding ether in 96% yield. It was also obtainable under phase transfer conditions with 1-chlorodecane and potassium hydroxide solution (ref.63). 4-Hydroxybenzaldehyde in acetone containing calcium carbonate and, reportedly, ferrous chloride, upon refluxing with propargyl bromide (2-bromoprop-1-yne) during 4 hours afforded 4-propargyloxybenzaldehyde in 68% yield although this was much lower in the absence of the iron compound (ref. 64).



Salicylaldehyde in aqueous solution upon addition to an aqueous solution of barbituric acid afforded a precipitate after stirring for 5-10 mins. which in hot acetic acid/acetic anhydride (9:1) gave in 50% yield 2H-chromeno[2,3-d]-pyrimidine-2,4(3H)-dione (ref.65).

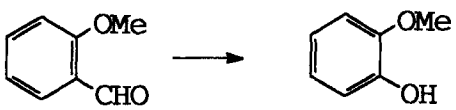


(ii) Replacement of the aldehyde group

Dakin reaction conditions have been used on 2-hydroxyisophthaldehyde in 85% aqueous potassium hydroxide added over 45 mins. to a cooled solution of 26% hydrogen peroxide at 5-10°C with continued stirring for 2.5 hours, to furnish pyrogallol in 64% yield (ref.66).

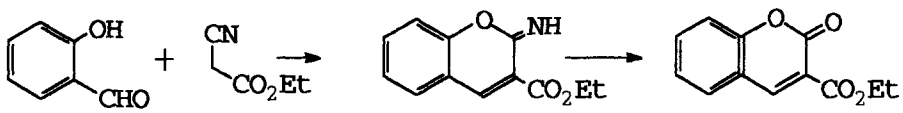
By contrast, acidic conditions for the transformation of 2-methoxybenzaldehyde in methanol containing 31% hydrogen peroxide and a little sulphuric acid were used at ambient temperature during 24 hours to give a 94% yield of 2-

methoxyphenol (ref.67).

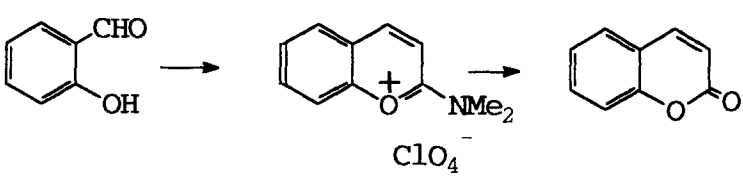


(iii) Reactions of the formyl group

This category comprises essentially Claisen or Knoevenagel reactions followed invariably by cyclisation. For example, a stirred mixture of 2-hydroxybenzaldehyde and ethyl cyanoacetate was treated at ambient temperarure with a 3:1 mixture of aluminium phosphate /alumina during 1 hour to give ethyl, 3-ethoxycarbonyl-2-iminobenzopyran, hydrolysis of which with dilute hydrochloric acid at 60°C afforded 3-ethoxycarbonylcoumarin (ref. 68).

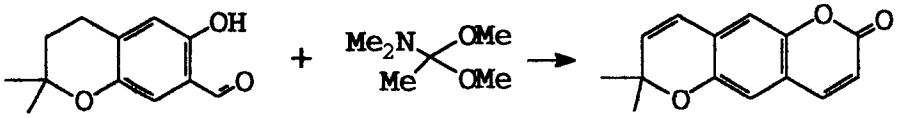


Coumarin was synthesised by the addition of 2-hydroxybenzaldehyde to a stirred mixture of phosphorus oxychloride and N,N-dimethylacetamide at ambient temperature followed by heating at 60-70°C to give the 2-dimethylaminobenzopyrylium salt which was isolated in 98% yield after quenching the reaction mixture in ice and treatment with perchloric acid. Hydrolysis of this at 100°C with 20% sodium carbonate solution until dimethylamine ceased to be evolved afforded coumarin quantitatively (ref.69).

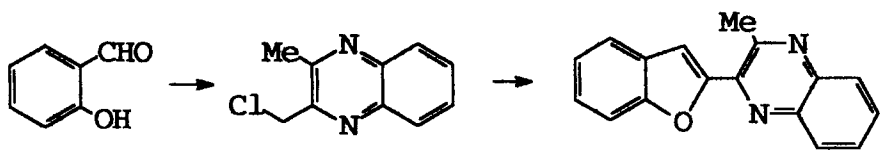


An alternative approach dispensing with the need for phosphorus oxychloride consisted in using the dimethyl acetal of N,N-dimethylacetamide. With this reagent, 6-hydroxy-7-formyl-2,2-dimethyl-2H-chromen in dry ether by refluxing for 6 hours, cooling and acidifying with 10% hydrochloric acid gave the pyranocoumarin, 7,7-dimethyl-2(7H)-benzo-[1,2-b,4,5-b']bipyranone in 64% yield

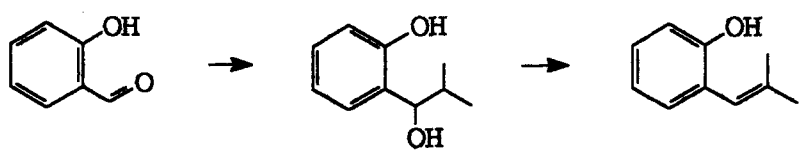
(ref.70).



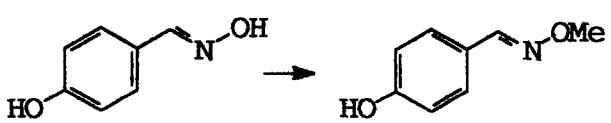
Preliminary ether formation followed by cyclisation to a benzofuran was achieved by reaction of 2-hydroxybenzaldehyde with a 2-halogeno-methyl-3-methylquinoxaline and treatment of the product, 2-(3-methyl-2-quinoxalinylmethoxy)benzaldehyde in ethanol with potassium hydroxide under reflux for 3 hours, to afford in 92% yield, 2-(3-methylquinoxalin-2-yl)benzofuran (ref.71). Alkylation occurs rather than condensation of the 3-methyl group with the o-formyl group.



2-iso-butenylphenol was obtained in 85% yield by heating a suspension of the secondary alcohol, derived by a Grignard reaction with 2 moles of iso-propylmagnesium bromide on 2-hydroxybenzaldehyde, in hexane in a sealed tube at 170°C until completion of dehydration (ref.72).



In the 4-hydroxybenzaldehyde series, the O-methyl ether of the oxime, 4-hydroxybenzaldehyde oxime hydrate (92% pure) was derived in 63% yield rather than the phenolic methyl ether by alkylation in aqueous sodium hydroxide

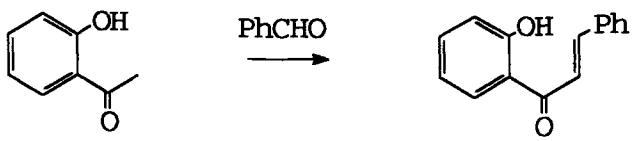


by the addition of dimethyl sulphate thus avoiding the use of valuable alkoxylamines (ref.73).

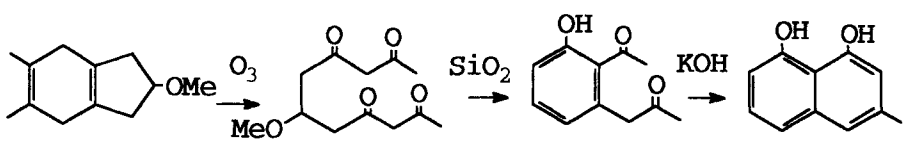
7.3.2 Phenolic Ketones

(i) 2- and 4-hydroxyacetophenone

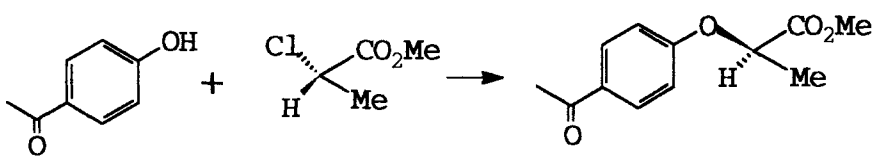
The addition of a little barium hydroxide to 2-hydroxyacetophenone and benzaldehyde in 96% ethanol followed by refluxing of the reaction mixture during 4 hours afforded the chalcone (benzylidene 2-hydroxyacetophenone) in 89% yield without the need for protection of the phenolic hydroxyl group and unaccompanied by impurities (ref.74).



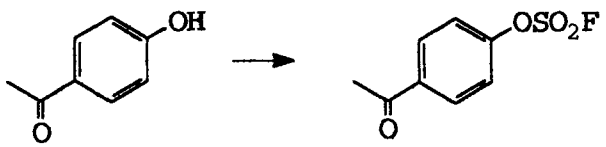
The 2-hydroxyacetophenone derivative depicted, formed spontaneously from a tetraketone precursor in the presence of silica, itself derived in turn by ozonolysis of 3,6-dihydroindan-1-one acetal, has been regiospecifically recyclised with potassium hydroxide to 1,8-dihydroxy-3-methylnaphthalene (ref.75).



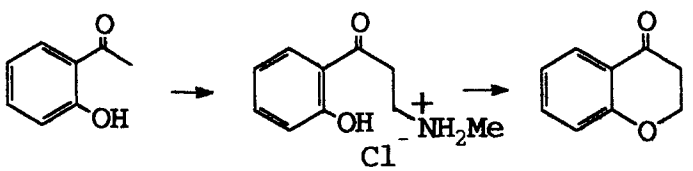
Etherification of 4-hydroxyacetophenone in dimethyl sulphoxide containing potassium carbonate by the slow addition of methyl (S)-2-chloropropionate over 30 mins. and reaction with stirring during 6 hours at ambient temperature (with introduction of more potassium carbonate over a further 5 hours) gave methyl (R)-2-(4-acetylphenoxy)propionate (enantiomeric excess, 86%).



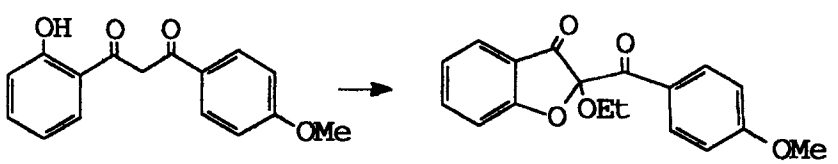
Racemisation was suppressed by effecting the reaction at less than 50°C (ref.76).
4-Hydroxyacetophenone in dichloromethane suspension after the addition of 1 mole proportion of diisopropylamine at -78°C during 20 mins. was then treated dropwise during 10 mins. with 1 mole of fluorosulphonic anhydride and following reaction for 30 mins. succeeded by aqueous work-up, 4-acetylphenyl fluorosulphonate was obtained in 95% yield (ref.77).



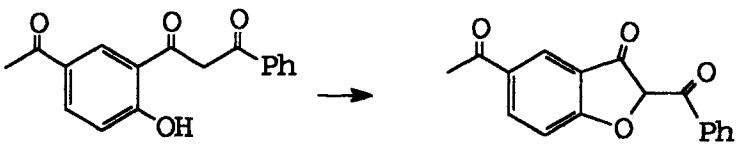
Difficulties in the synthesis of 4-chromanones by the condensation of 2-hydroxyacetophenone with formaldehyde and methylamine can be overcome through isolation of the Mannich base hydrochloride and its cyclisation with potassium hydroxide (ref.78).



The action of ethanolic thallic nitrate on the diketone, 2-hydroxy-ω-(4-methoxybenzoyl)acetophenone, at ambient temperature during 20 mins. gave by oxidation the cyclic product, 2-ethoxy-2-(4-methoxybenzoyl)-3(2H)benzofuranone in 66% yield (ref.79).

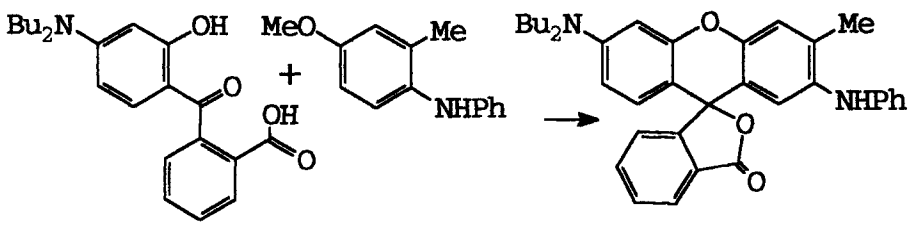


A 4-aceto analogue of the preceeding diketone in methanolic solution containing 5 moles potassium hydroxide by treatment at 0-5°C with excess phenyliodosodiacetate, stirring for 1 hour and then at ambient temperature during 2 hours afforded an 82% yield of the benzofuranone shown (ref.80).

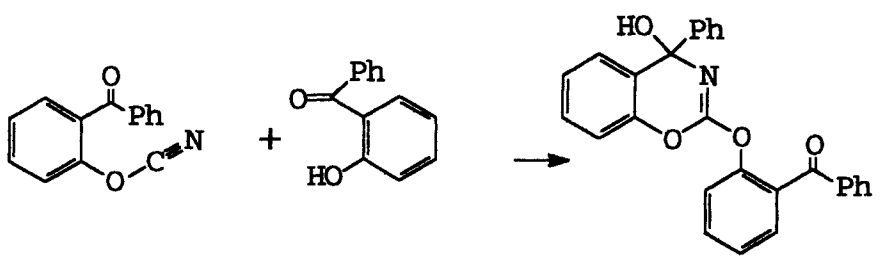


(ii) 2- and 4-Hydroxybenzophenones

The substituted 2-hydroxybenzophenone, 2-(2-hydroxy-4-di-n-butylamino)-benzoylbenzoic acid underwent reaction with 4-methoxy-2-methyldiphenyl-amine in concentrated sulphuric acid at 10-15°C during 20 hours followed by work-up in alkaline solution and a final treatment by refluxing in hot toluene for 2 hours to give 2-anilino-3-methyl-6-dibutylaminofluoran in 88% yield (ref.81).



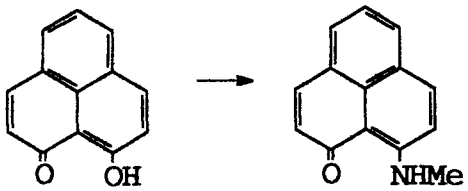
2-Hydroxybenzophenone, introduced into a mixture of its O-cyanide derivative in ether containing finely powdered potassium hydroxide with vigorous stirring and reaction at ambient temperature during 1 hour led to 2-(2-benzoylphenoxy)-4-hydroxy-4-phenyl-4H-1,3-benzoxazine in 73% yield (ref.82).



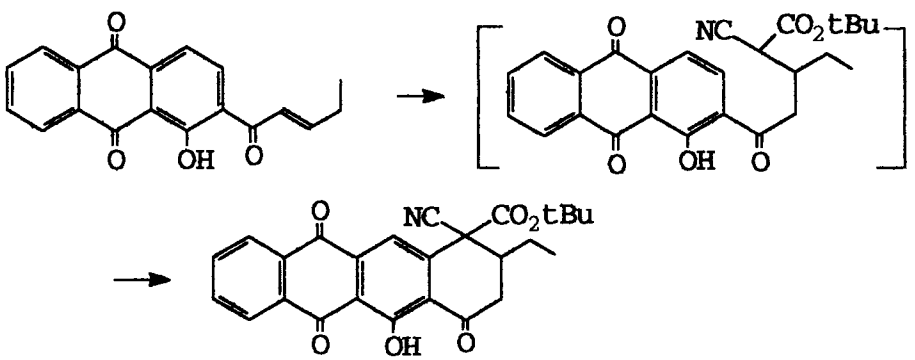
(iii) Phenolic polycyclic ketones and quinones

A vigorously stirred mixture of 9-hydroxy-1-oxophenalene and 40% aqueous methylamine heated at 125°C under pressure (150psi) for 1 hour in a Monel

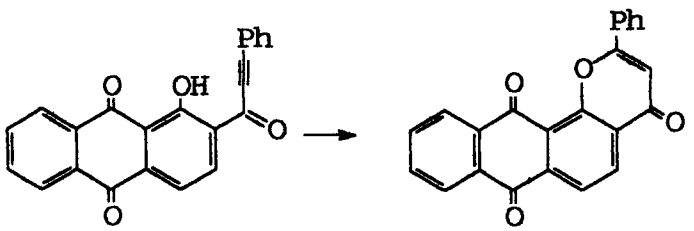
metal bomb gave 9-methylamino-1-oxophenalene in 83% yield (ref.83).



A double Michael addition has been observed in the intermolecular reaction of the α,β-unsaturatedacylanthraquinone, 1-hydroxy-2-(1-oxopent-2-enyl)anthraquinone illustrated with tert-butyl cyanoacetate followed by an intramolecular cyclisation of the product. The whole sequence was conducted at ambient temperature during 6 hours in dimethylformamide to give a substituted benzohydroxyanthraquinone in 75% yield (ref.84).

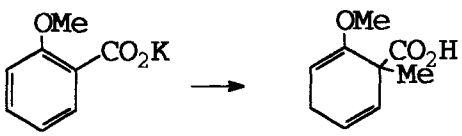


In the same series, 1-hydroxy-2-(3-phenylprop-2-ynol)anthraquinone when stirred in piperidine for 1/2 hour at 20°C and then added as a concentrate from chloroform extraction to silica gel followed by work-up afforded 2-phenyl-4H-anthra[1,2b]pyran-4,7,12-trione in 82% yield (ref.85).

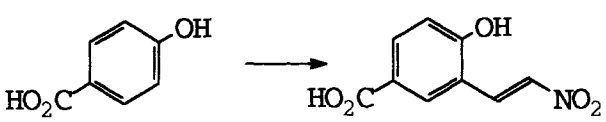


7.3.3 Phenolic Acids and Nitriles

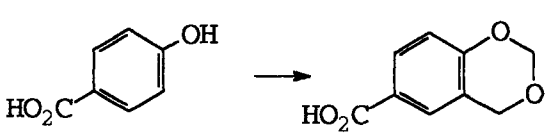
Salicylic acid O-methyl ether has been submitted to the Birch reduction and the product methylated. This sequence is reminiscent of the synthesis of 3,5-dimethoxy-n-pentylbenzene (olivetol dimethylether) in which the pentylated intermediate carboxylic acid was then oxidatively decarboxylated (ref.86).
Thus to 2-methoxybenzoic acid in tetrahydrofuran treated with potassium tert-butoxide followed by tert-butanol and 100% ammonia at -70°C, potassium metal in small pieces was added until the blue colour persisted. After this had been discharged by the addition of a drop of 1,3-pentadiene, the dihydro reduction product was methylated with methyl iodide in tetrahydrofuran and after work-up, 2-methoxy-1-methyl-cyclohexa-2,5-diene-1-carboxylic acid isolated in 84% yield (ref.87).



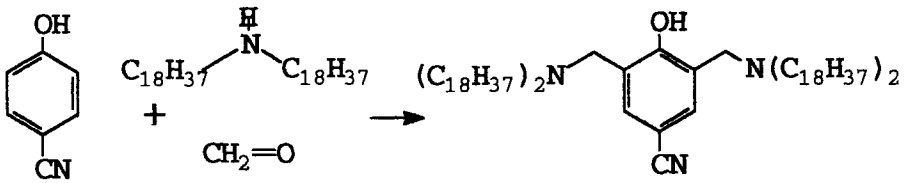
A combined Reimer-Tiemann formylation and Claisen condensation procedure with nitromethane has been described for 4-hydroxybenzoic acid constituting o-2-nitrovinylation. 4-Hydroxybenzoic acid and β-cyclodextrin in 20% aqueous sodium hydroxide treated sequentially with a little copper powder and carbon tetrachloride were reacted at 60°C during 10 hours with chloroform introduced dropwise. After a further 10 hours, and at ambient temperature, nitromethane was added and the mixture worked-up following 10 hours reaction to give 4-hydroxy-3-(2-nitrovinyl)benzoic acid in 87% yield (ref.88).



Methylolation and cyclic acetal formation has been observed in the reaction of 4-hydroxybenzoic acid with formaldehyde. A mixture of 4-hydroxybenzoic acid



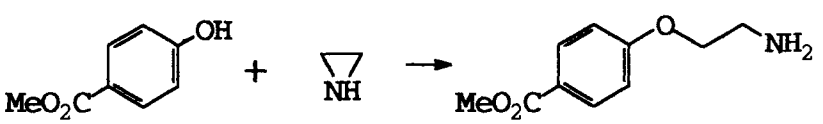
and paraformaldehyde in 1,2-dimethoxyethane was treated with Nafion-501 (or less effectively with Amberlite IRA 120) and reaction continued with stirring at 70°C for 25 hours to afford 6-carboxy-1,3-benzodioxin in 80% yield (ref.89). 4-Hydroxybenzonitrile underwent a double Mannich reaction with 3 moles each of di-n-octadecylamine and paraformaldehyde by refluxing in toluene over 24 hours to give 2,6-di(di-n-octadecylaminomethyl)phenol in 95% yield (ref.90). The authors suggest that this behaviour can be expected with electron-withdrawing substituents in the 4-position while, by contrast, monoaminomethylation occurs with electron-donating groups.



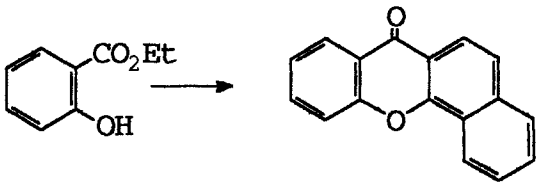
7.3.4 Phenolic Esters

The hydrolysis of alkyl salicylates often a prolonged process under alkaline conditions can be effected in quantitative yield with trifluoroacetic acid. Thus methyl 2-hydroxybenzoate in trifluoroacetic acid (10 moles) sealed in a thick glass tube, after heating at 100°C for 13 hours, gave 2-hydroxybenzoic acid in 100% yield (ref.91).

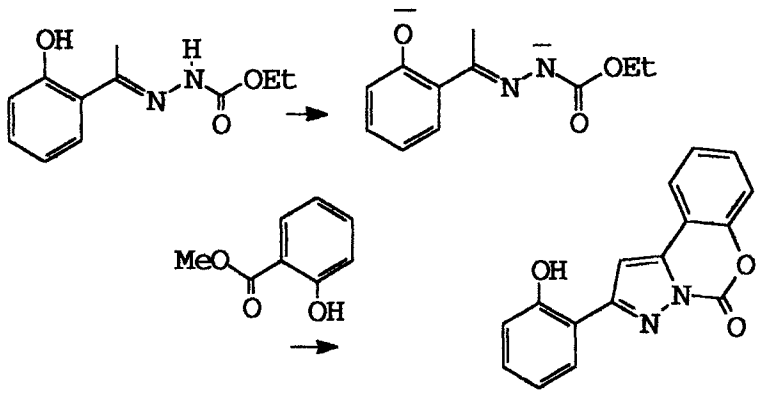
Methyl 4-hydroxybenzoate in dioxan reacted at the phenolic group with a solution of aziridine (ethyleneimine) in dioxan added over 30 mins. at 50°C and subsequently for 3 hours at 90°C to furnish 2-(4-methoxycarbonyl phenoxy)ethylamine in 53% yield (ref.92).



Benzo[b]xanthone formation in 74% yield occurred readily in the reaction of ethyl salicylate and 1-naphthol at elevated temperature in refluxing diphenyl ether during 8 hours (ref.93).



A pyrazolobenzoxazine derivative has been synthesised from an alkoxycarbonylhydrazone of 2-hydroxyacetophenone by further reaction with methyl salicylate. Thus, the hydrazone in tetrahydrofuran was first treated with excess lithium diisopropylamide in THF at 0°C to generate a dianion which was then reacted with methyl salicylate. Acidification of the mixture after 2 hours followed by refluxing afforded the product in 86% yield (ref. 94).



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CHAPTER 8

HALOGENO, NITRO, AMINO, AZO, SULPHO and THIO DERIVATIVES OF PHENOLS

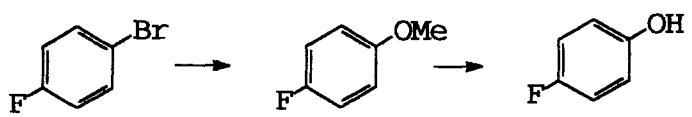
8.1 Introduction

This chapter describes the preparative advances achieved in the last one and half decades in the chemistry of halogeno, nitro, aminophenols, and of thiophenols resulting from substitution in the phenolic ring. As with previous chapters naphthols are included in the review of procedures. Certain of the methods relate to the use of phenolic ethers and although these might strictly have been discussed in Chapter 4 the comparative results from the use of phenols and their ethers in the preparation of, for example, fluoro phenolic compounds seem to justify their inclusion in this section. The use of simple chlorophenols in pharmaceutical products such as 2,4,6-trichlorophenol (TCP) and 2,4-dichloro-3,5-dimethylphenol (a component of 'Dettol') is perhaps legendary and illustrates the continuing role of 'single step' products obtained from phenols. The reactions of each group in the title are summarised after each section concerned with synthesis and include many examples in benzenoid, bicyclic polycyclic and heterocyclic chemistry.

8.2 Synthesis of Halogenophenols and Derivatives

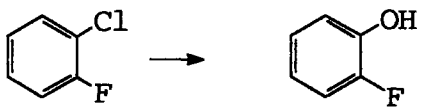
8.2.1. Fluorophenols

4-Fluorophenol has been synthesised from 4-bromofluorobenzene by initial refluxing with 28% methanolic sodium methoxide containing a little cuprous iodide for 9 hours to give 4-fluoroanisole in 83% yield which with hot 47% hydrobromic acid for 10 hours gave 92% 4-fluorophenol (ref.1).

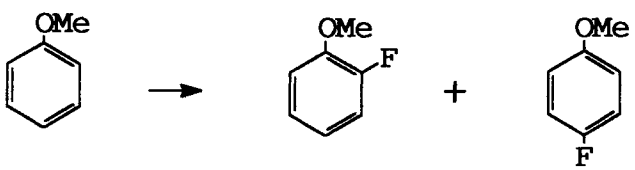


2-Fluorophenol has been derived in a yield of 67% (60% conversion) by heating a mixture of 2-chlorofluorobenene and cupric oxide with 1M dipotassium

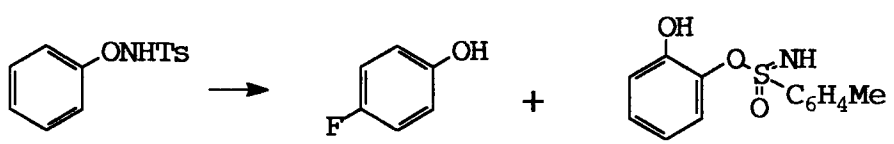
hydrogen phosphate for 24 hours in a sealed Parr reactor at 250°C (ref.2).



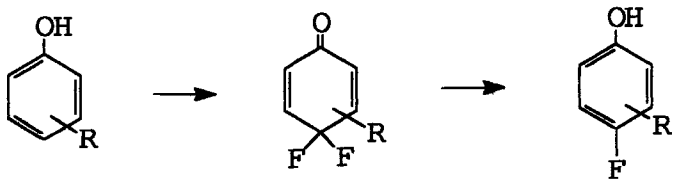
An alternative synthesis of 2-fluorophenol, requiring an additional demethylation step, is seen in the following regiospecific fluorination of anisole with acetyl hypofluorite. A cold chloroform or Freon solution of anisole was added to a solution of acetyl hypofluorite (prepared by the passage of fluorine 5-8% diluted with nitrogen through a suspension of sodium acetate in Freon/acetic acid (9:1 at -70°C for a few seconds) resulting in 2-fluoroanisole in 85% yield accompanied by 10% of the 4-fluoro isomer with 75% conversion (ref.3).



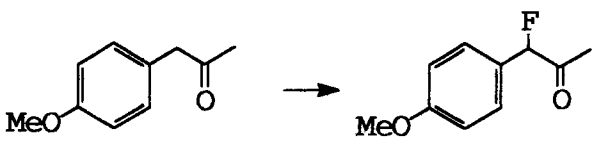
By the solvolysis of N-tosyl-O-phenylhydroxylamine, prepared in 75-85% yield from phenoxylamine (Chap. 3) by reaction with 4-toluenesulphonyl chloride in pyridine, 4-fluorophenol resulted regiospecifically in 38% yield accompanied by an imino compound (34%) arising from the reagent which was used at ambient temperature and consisted of a solution of hydrogen fluoride in THF (5:1) (ref. 4).



4,4-Difluorocyclohexa-2,5-dienone, or its alkyl derivatives, prepared by the reaction in dichloromethane solution of the fluoride ion of hydrogen fluoride/base complexes (e.g., hydrogen fluoride/pyridine, 7:3 W/W) with aryl cations resulting from chemical (for example, lead dioxide) or anodic oxidation of phenol, furnished 4-fluorophenol, or its corresponding alkyl derivatives, in quantitative yield by hydrogenation in methanol solution containing 10% Pt-C and (ref.5). .



By contrast with the o-fluorination in ref.3, side-chain fluorination at the reactive benzylic position occurred without nuclear substitution when 4-methoxyphenylpropan-2-one in acetonitrile containing triethylamine was electrolysed in an undivided cell between platinum electrodes to give a 69% yield of the derivative (ref.6).



8.2.2 Chlorophenols

A range of selective procedures has been introduced for the formation of monochloro and dichlorophenols from phenolic intermediates in the great majority of which free chlorine has not been used. For the monochlorination of phenol and acylphenols these methods have been summarised in Table 8.1 (refs.7-13).

For the synthesis of dichloro and polychlorophenols the chlorination of a less chlorinated precursor has been the method of choice, doubtless because the presence of one or two chlorine atoms partially deactivates the ring. The preparations of some compounds in this class are listed in Table 8.2 (refs.14-17).

A number of other strategies have been devised for the synthesis of polychlorophenols containing other functional groups.

2,5-dichlorothiophene has been ring-expanded to a dichlorophenolic derivative by way of a bicyclic intermediate. Ethyl 2-diazoacetoacetate was introduced dropwise into a solution of 2,5-dichlorothiophene in toluene containing rhodium(II) acetate and the mixture stirred for 20 hours at ambient temperature toproduce1,3-dichloro-6-acetyl-6-ethoxycarbonyl-2-thiabicyclo-[3,10]hex-3-ene in 67% yield, which upon refluxing in toluene for 38 hours was transformed into ethyl 2,4-dichloro-5-hydroxy-6-methylbenzoate with a yield of 86% (ref.18).

TABLE 8.1 SYNTHESIS OF MONOCHLOROPHENOLS

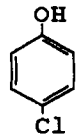
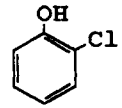
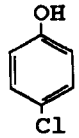
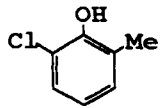
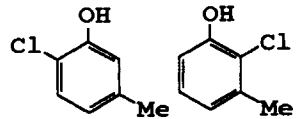
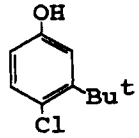
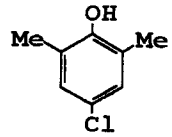
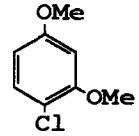
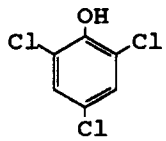
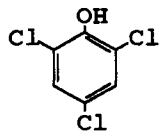
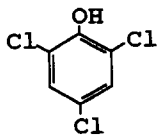
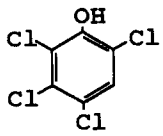
PHENOL	CJLORINATING	CONDITIONS	PRODUCT	YIELD%	REF.
Phenol	Phenylselenyl chloride	Phenol in dichloromethane was treated with phenylselenyl chloride (slight excess) and stirred at ambient temp. to give 4-chlorophenol.		50	7
Phenol	2,3,4,5,6,6-hexa-chlorocyclohexa--2,4-diene-1-one	Phenol and the chloinating agent in carbon tetra-chloride irradiated at -50C during 10h. with a 100watt Hanovia Hg lamp to give 2-chloro-phenol.		92	8
Phenol	2,3,4,4,5,6-hexa chloro isomer	With this isomer in dimethylformamide for 72h. at ambient temp. 4-chlorophenol was formed.		72	8
2-Methyl-phenol	N-chloro bis(2-chloro-ethyl)amine	2-Methylphenol, the chlorinating agent and silica in carbon tetrachloride stirred at 25C to afford 6-chloro and 4-chloro isomers (4:1).		100	9
3-Methyl-phenol	N,N-Dichloro-tert-butylamine	3-Methylphenol in carbon tetrachloride treated dropwise at ambient temp. with chlorinating agent to give o/p isomers (18:1). 0- comprising some 2-chloro and 6-chloro-3-methylphenol.		62	10
3-tert-Butyl-phenol	Copper(II) chloride dihydrate	3-tert-Butylphenol and $CuCl_2$ dihydrate in refluxing acetic acid and reaction during 20h.		71 (selectivity 79%	11

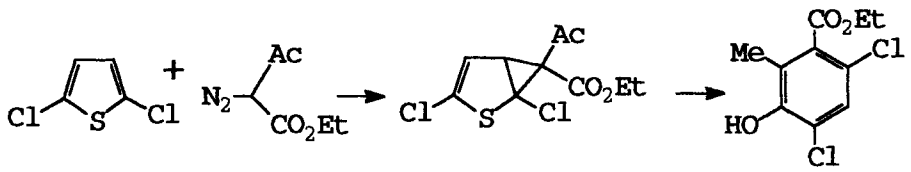
TABLE 8.1 (contd.)

2,6-Dimethl-phenol	Benzyl trimethyl ammonium tetrachloro iodate	The halogenating agent was added to 2,6-dimethyl phenol in dichloromethhane and the mixture stirred at ambient temp. for 1 min. to give 4-chloro-2,6-dimethylphenol		91	12
Phenol ethers (and some phenols)*	Potassium chloride and 3-chloro-perbenzoic acid with 18-crown-6 ether	A suspension of KCl (59 mmol), 18-crown-6(264mg) (1 mmol) and the phenol ether in dichloromethane (35 ml) cooled to 0C and with stirring treated with 3-chlorobenzoic acid (2.59g; 12mmol). Reaction stirred 15 mnn. and workred up with sodium bisulphite to give 4-chloro-1,3-dimethoxybenzene.		65	13

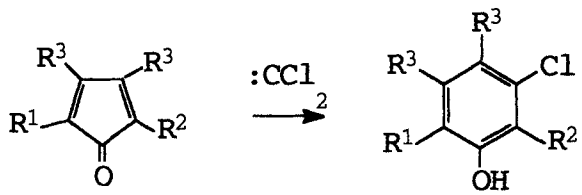
* This method has also been used for the iodination of phenols and for the bromination of anisole to give 4-bromoanisole (87%), of 1,3-dimethoxybenzene to give 4-bromo-1,3-dimethoxybenzene (80%).

TABLE 8.2 SYNTHESIS OF POLYCHLOROPHENOLS

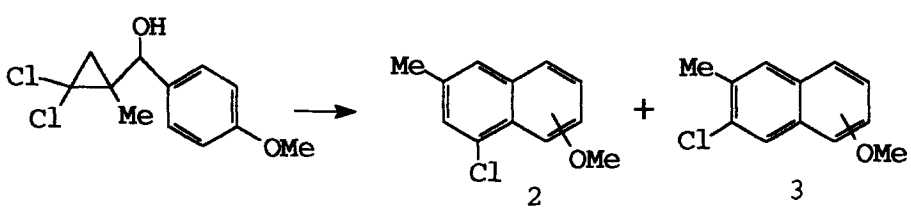
PHENOL	CHLORINATING AGENT	CONDITIONS	PRODUCT	YIELD%	REF.
2,4-Dichlor phenol	Chlorine	A mixture of 2,4-dichlorophenol and 2,6-dichlorophenol and diisopropylamine at 70C was treated with chlorine during 38 min. 94% of the 2,6-dichlorophenol was unaffected. The product was 2,4,6-trichlorophenol.		100	14
2,6-Dichloro-phenol	"	2,6-Dichlorophenol containing a little tetra n-butylammonium chloride was treated with chlorine at 70C to give 2,4,6-trichloro-phenol.		97	15
2,6-Dichlor-phenol	"	2,6-Dichlorophenol and a little trifluoro-methan sulphonic acid weretreated with chlorine at 70C during 54 min.		100	16
2,4,6-Trichloro-phenol	"	2,4,6-Trichlorophenol and a little zirconium tetrachloride was treated with chlorine at 80C. with aluminium chloride the yield was 70%		89	17



The reaction of the cyclopentadienone shown, having alkyl or aryl substituents, (R^3 = Ar; R^1 = R^2 = alkyl, aryl) with dichlorocarbene afforded a polysubstituted 3-chlorophenol in yields of 55-89% dependent on the groups present (ref.19).



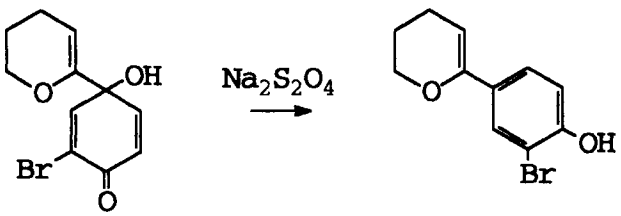
1- or 2-Chloronaphthyl methyl ethers have resulted from the acid treatment of aryl-(gem-dihalogenocyclopropyl)methanols (ref.20) which were preliminary model compounds in the course of work directed to the synthesis of lignan structures. Thus, methyl methacrylate after conversion to the gem-dichloro derivative with dichlorocarbene, generated by a phase transfer method, was reacted with 4-methoxyphenyllithium to provide 4-methoxyphenyl-(2-gem-dichloro-1-methylcyclopropyl-1)methanol. This, upon acidic rearrangement in the presence of boron trifluoride afforded the naphthol methyl ether depicted (2) in 66% yield as the 1-methoxy or 2-methoxy isomer unaccompanied by (3)



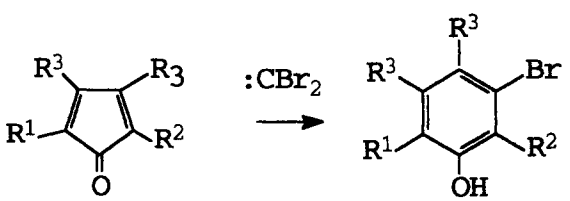
8.2.3. Bromophenols

Considerable attention has been directed to regiospecific monobromination in which bromine has been used often in conjunction with another component.

These reactions have been summarised in Table 8.3 (refs.21-28) and often indicate the known more selective nature of bromination compared with chlorination.
A 2-bromophenol derivative has been obtained in 90% yield from the reductive aromatisation of 2-bromo-4-hydroxycyclohexa-2.5-dienones by treatment over 2 hours with sodium hydrosulphite in tetrahydrofuran/water (3:1) (ref.29).



Due to their activation the preparation of nuclear monobromo methylphenols can be unexpectedly complicated. The use of polybromophenols to obtain simpler phenols such as 4-bromo-3-methylphenol, 3-bromo and 3,5-dibromo-4-methylphenol, 3-bromo and 3,5-dibromo-2-methylphenol from the corresponding methylphenols, by the action of 55% hydriodic acid, has been described (ref.30).
As with the synthesis of chlorophenols, methods are available for bromophenols from non-aromatic precursors. The substituted cyclopentadienone shown reacts with dibromocarbene to give a substituted 3-bromophenol (ref.20).



Claisen condensations have been used historically for constructing phenolic rings from non-aromatic precursors as in the reaction of bromomalonaldehyde

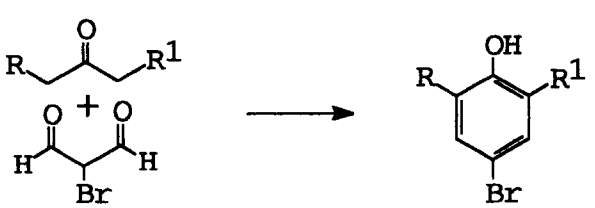


TABLE 8.3 SYNTHESIS OF BROMOPHENOLS

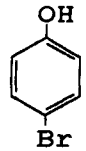
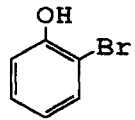
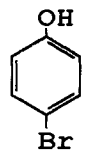
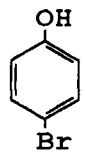
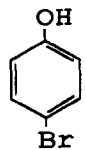
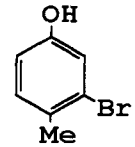
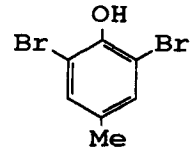
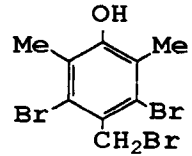
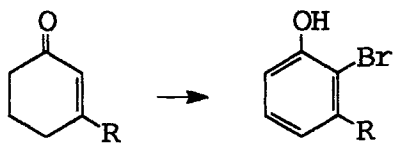
PHENOL	BROMINATING AGENT	CONDITIONS	PRODUCT	YIELD%	REF.
Phenol	Bromine	Phenol in ethyl acetate was added dropwise to a solution of bromine (orBrCl) in ethyl acetate at 0-5C during 90min. to 2h. and excess halogen removed by sodium bisulphite to give 4-bromophenol.		99 (98% 4-Br)	21
Phenol	Bromine	Bromine (2 moles) in carbon tetrachloride was added to a stirred solution of 2,2'-(azo-2-phenoxypropane) and phenol in acetonitrile at ambient temp. and the mixture worked up after a few mnis. to give 2-bromophenol.		68 (98%)	22
Phenol	Large excess of bromine/ phenol (7:1)	Identical conditions to the preceding preparation. The product was 4-bromophenol.		88 (exclusive)	22
Phenol	Tetra n-butyl ammonoium tribromide	The reagent was added to a stirred solution of phenol in chloroform at ambient temp. and stiring contd. for 2min. to give 4-bromophenol. Phenol ethers and esters do not react		95	23
Phenol	Bis(dimethyl-acetamido) hydrogen tribromide	Phenol in acetonitrile with the reagent afforded 4-bromo-phenol. 4-methylphenol gave 2-bromo-4-methylphenol (92%).		92	24
Phenol	Bromo dimethyl sulphonium bromide	Reagent prepared from Me_2S and Br_2 togive $Me_2S^+Br\ Br.^-$ Phenol in CH_2Cl_2 at ambient temp. and reagent stirred 4h. Chlorinastion also with chloro analogue, $Me_2S^+Cl\ Cl^-$		85	25

TABLE 8.3 (contd.)

4-Methyl phenol	Bromine	4-Methylphenol in HF/ antimonypentafluoride treated with bromine and worked up after 1h. to give 3-bromo-4-methylphenol.		85	26
4-Methyl phenol	Benzyl trimethyl ammonium tribromide	The reagent (2.1 moles) was added at ambient temp. to a soln. of 4-methylphenol in dichloro-methane/methanol (5:2) and stirred for 1h until the orange colour disappeared to give 2,6-dibromo-4-methylphenol.		93	27
2,4,6-trimethyl phenol	Bromine	Bromine was added to the trimethylphenol in bromochloromethane at 19-23C and the mixture heated at 66-68C for 2h. to give 3,5-dibromo-2,6-dimethyl-4-bromomethylphenol.		91	28

and diethyl acetonedicarboxylate to give the 4-bromophenol derivative shown ($R = R^1 = CO_2Et$) (ref.31).
In more recent years the dehydrogenation of cyclohexenones and their alkyl derivatives has been developed. The cyclohexenones shown with bromine and sodium hydroxide afford otherwise relatively inaccesible 2-bromophenol derivatives in moderate yields of 10-60% (ref. 32).



8.2.4. Iodophenols

Iodo compounds ordinarily somewhat intractable to synthesise become more accessible in the phenolic series due to the strong activating effect of the hydroxyl group. Both elemental iodine and the element in conjunction with a second component have been employed in synthetic methodology. The monoiodination and polyiodination of phenols have been listed in Table 8.4 (refs.33-36).
The examples given in the table are based on chemical oxidation. By contrast, anodic oxidation of iodine in trimethyl orthoformate provides the iodonium ion which is effective for the iodination of appropriate substituted benzenoid compounds (ref.37) and has been considered superior to the iodonium ion developed in acetonitrile solution. Thus the addition of the anolyte (4 moles) from trimethyl orthoformate (TMOF), elemental iodine and lithium perchlorate trihydrate, by anodic oxidation at ambient temperature in a divided electrolytic cell equipped with a ceramic diaphragm and platinum electrodes, to anisole (1 mole) in TMOF afforded iodoanisoles in 69% yield, in the proportions, 4-iodomethoxybenzene (87%), and the 2-iodo isomer (13%) with none of the 3-isomer.

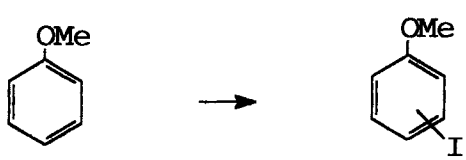
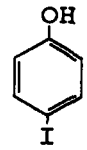
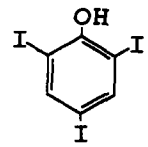
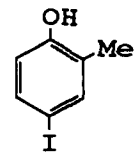
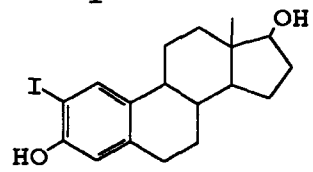


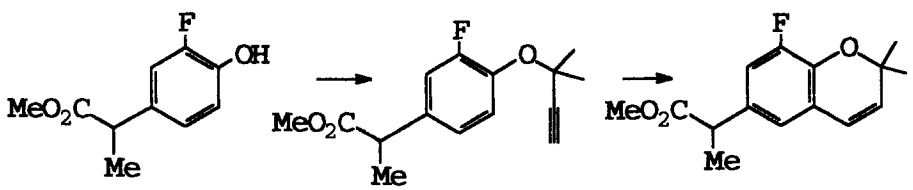
TABLE 8.4 SYNTESIS OF IODOPHENOLS

PHENOL	IODINATING AGENT	CONDITIONS	PRODUCT	YIELD%	REF.
Phenol	Iodine/ Sodium iodide	A mixture of phenol and cyclodextrin in 20% sodim hydroxide at 2C was treated with iodine in 10% sodium iodide solution and stirred 1h. to give 4-iodophenol.		96	33
Phenol	Benzyl trimethyl ammonium dichloro iodate	Benzyl trimethyl ammonium dichloro iodate (3.1 moles) and sodium bicarbonate were stirred at ambient temp. with a solution of phenol in dichloromethane/methanol (2.5:1) for 7h. to give 2,4,6-triiodophenol.		72	34
2-Methyl phenol	Sodium hypochlor-ite/sodium iodide	A soln. of 2-methylphenol in methanol was treated with sodium iodide (1 mole) and sodium hydroxide (1 mole), cooled to 0C sodium hypochlorite was added at 0-3C during 45min. After addition of aqueous sodium thiosulphate, 4-iodo-2-methylphenol was isolated		-	35
Estradiol	copper(II) acetate/ iodine	Estradiol was heated at 55C with copper(II) acetate monohydrate and iodine in acetic acid for 2h. to give 2-iodoestradiol.		-	36

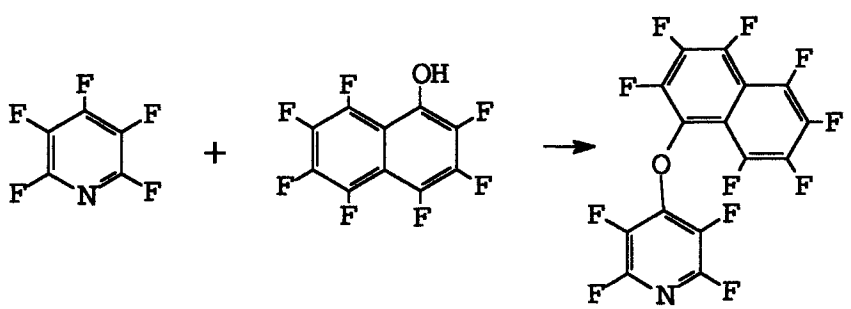
8.3 Reactions of Halogenophenols

8.3.1. Fluorophenols

The reactions of halogenophenols are discussed in this section dealing with fluoro, chloro, bromo and iodophenols. Certain of these reactions would of course take place in the absence of the halogen substituent and it is perhaps remarkable that many of the cyclisations described occur despite the deactivating influence of that group.
Methyl 2-(3-fluoro-4-hydroxyphenyl)propionate in dimethylformamide containing potassium iodide and carbonate when treated slowly with 3-chloro-3-methyl-1-butyne gave the corresponding ether by reaction at 75°C during 18 hours in 75% yield. Cyclisation of this was effected in N,N-dimethylaniline by refluxing at 215°C for 3 hours to give an 80% yield of methyl 2-(2,2-dimethyl-8-fluoro-1,2-benzopyran-6-yl)propionate (ref.38).



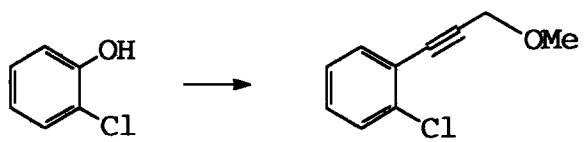
Perfluoro-1-naphthol was added to dimethylformamide containing graphite into which a little potassim fluoride had been intercalated and after the mixture had been stirred for 5-10 mins. a dimethylformamide solution of pentafluoropyridine was introduced.



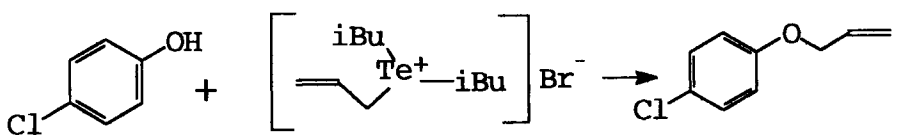
The mixture was then heated at 80°C for 5 hours to give perfluoro-1-naphthyl perfluoro-4-pyridyl ether depicted in 71% yield (ref.39).

8.3.2. Chlorophenols

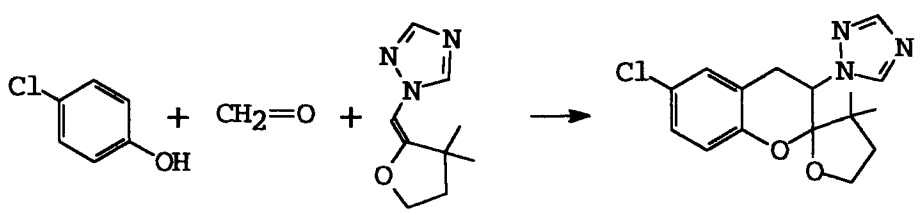
A variety of electrophilic substitution and nucleophilic displacement reactions are found with chlorophenols. 2-Chlorophenol with propargyl methyl ether in dimethylformamide containing triethylamine, a litle dichloro-bis(triphenyl-phosphine)palladium(II) and $CHF_2CF_2OCF_2CF_2SO_2F$, when heated under nitrogen in a closed screw-cap pyrex tube at 80°C during 19 hours and then quenched with 0.5M hydrochloric acid gave the C-alkyl product indicated in 63% yield, rather than the O-alkyl ether (ref.40).



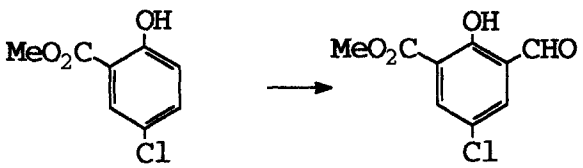
By contrast, 4-chlorophenol underwent etherification when reacted in tetrahydrofuran solution containing 1 mole of sodium hydroxide with allyldiisobutyltelluronium bromide under nitrogen during 5 hours to give allyl 4-chlorophenyl ether in 86% yield (ref. 41).



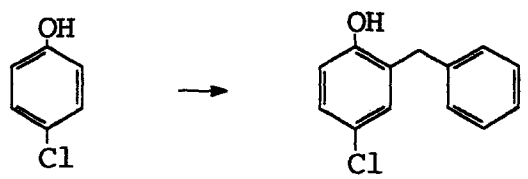
Both enamine condensation and cyclisation occurred with 4-chlorophenol in the following reaction. A mixture of 1-(3,3-dimethyltetrahydro-2-furfurylidene)-1,2,4-triazole, paraformaldehyde and trifluoracetic acid with 2-chlorophenol upon heating to 100°C during 22 hours afforded the spirocoumarin, 6'-chloro-3,3-dimethyl-3'-(1,2,4-triazol-1-yl)-spiro(tetrahydrofuryl)-2,2'-chroman in 82% yield (ref.42), the reaction being aided by further addition of paraformaldehyde and heating for 20 hours.



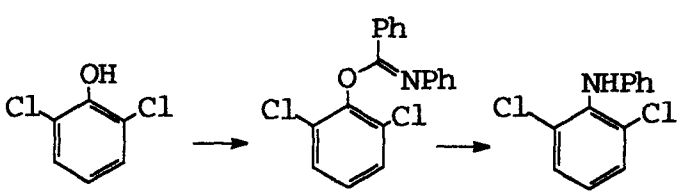
Application of the Duff reaction to methyl 5-chlorosalicylate containing methanesulphonic acid by the portion-wise addition of hexamethylenetetramine, maintenance of the reaction mixture initially at 80-90°C and finally at 130°C for 5 hours, followed by acidic hydrolysis, furnished the 3-formyl derivative in 77% yield (ref.43).



Friedel-Crafts type alkylation of 4-chlorophenol was effected with benzyl alcohol in the presence of Na-Y-zeolite at 200°C during 3 hours to give 2-benzyl-4-chlorophenol in 95% yield (ref.44).

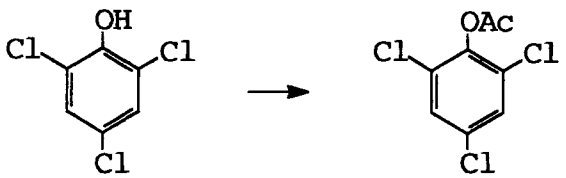


A procedure ultimately representing an aspect of the Beckmann displacement of the hydroxyl group by the phenylamino group commenced with the reaction of 2,6-dichlorophenol in methanolic sodium methoxide and N-phenylbenzimidoyl chloride in isopropyl ether during 1.5 hours to give 2,6-dichlorophenyl N-phenylbenzimidate in 92% yield. The remaining steps consisting of Beckmann rearrangement and hydrolysis proceeded smoothly resulting in N-phenyl 2,6-dichloroaniline (ref.45).

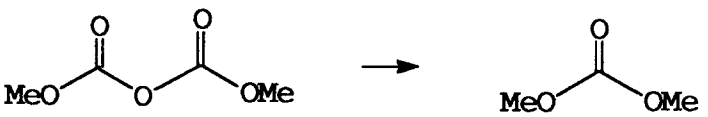


2,4,6-Trichlorophenol was acetylated by a phase transfer-type procedure in which ice-cold aqueous sodium hydroxide and tetra-n-butylammonium bromide

were added to the phenol in dichloromethane at 0°C followed, dropwise by acetic anhydride, and with vigorous stirring of the mixture for 5 mins. to afford after further reaction during 5 mins., 2,4,6-trichlorophenyl acetate in 86% yield (ref.46).

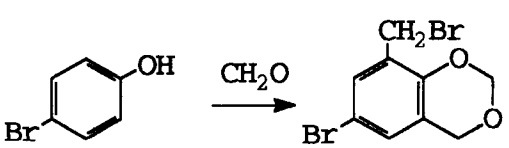


2,4,6-Trichlorophenol has been employed in the transformation of dimethyl pyrocarbonate to dimethyl carbonate in nearly theoretical yield accompanied by loss of carbon dioxide upon heating in dimethyl sulphoxide or dimethylformamide containing some titanium(IV) methoxide (ref.47).



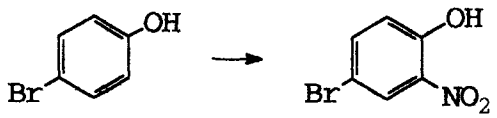
8.3.3. Bromophenols

Reactions studied have mainly included electrophilic substitutions and procedures for the removal of the bromo groups. Some ring contraction reactions have been observed with polysubstituted compounds.
The reaction of 4-bromophenol with formaldehyde resulting finally in the introduction of three methylene groups has been reported by the use of formalin solution and fuming hydrobromic acid (46%) to give 6-bromo-8-bromomethyl-1,3-benzodioxan in 92% yield (ref.48).



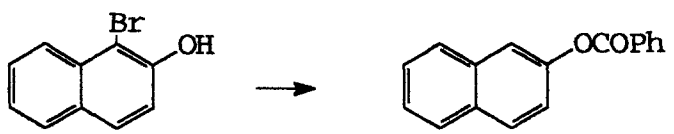
Electrophilic substitution processes, effected either in solution or the vapour phase, by the use of reagents supported appropriately have been examined increasingly in recent years. 4-Bromophenol in dichloromethane containing 1

equivalent of silica gel impregnated with nitric acid upon shaking at ambient temparature for 3 mins. produced 2-nitro-4-bromophenol in 88% yield. By contrast phenol gave a 1:1 mixture of 2-nitro and 4-nitrophenol. The reagent resulted in much reduced reaction times compared with ferric nitrate supported on clay (ref.49). Phenolic ethers also respond to the modified conditions.

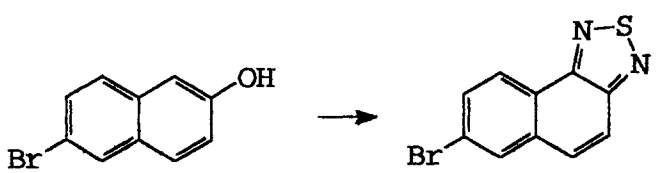


Processes for the removal of bromo groups have generaly consisted in the use of lithium aluminium hydride and of catalytic reduction and there is interest in alternative selective procedures.
2,4-Dibromophenol in dichloromethane containing ethanethiol and aluminium chloride after stirring of the reaction mixture (under nitrogen) at ambient temperature for 17 hours gave phenol in 84% yield (ref.50).

1-Bromo-2-naphthol with benzoic acid, triphenylphosphine and triethylamine when heated for 3 hours at 150°C afforded a 70% yield of 2-naphthyl benzoate (ref.51).

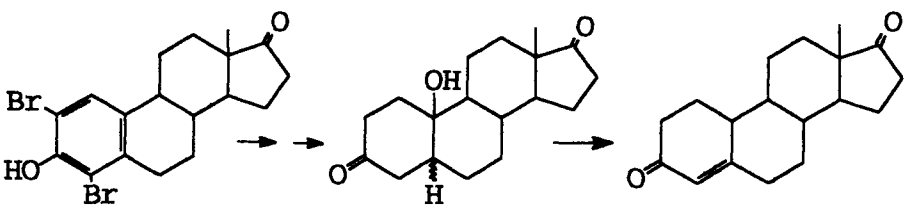


6-Bromo-2-naphthol and nitrogensulphide (N_4S_4) in 1:2 molar proportions in

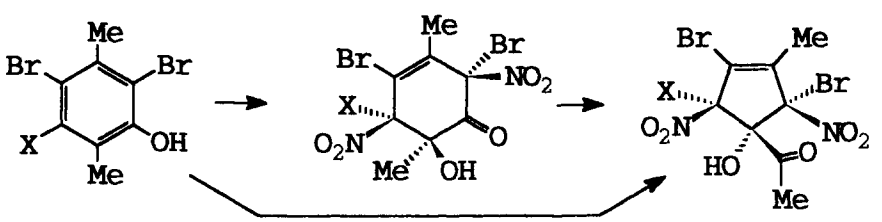


refluxing toluene gave after 48 hours a benzothiadiazole, naphtho-[1,2,-c]-[1,2,5]thiadiazole, in 96% yield (ref.52). Nitrogen sulphide is an orange red crystalline solid obtained by the action of dry ammonia on a solution of sulphur shloride and chlorine in benzene. It is explosive on percussion and is decomposed by cold water.

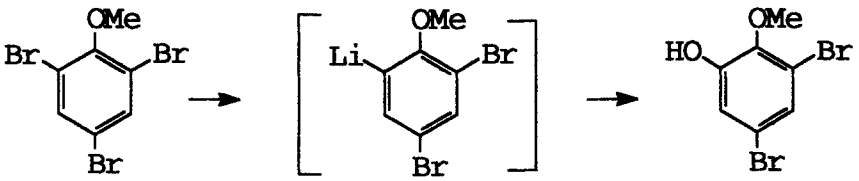
Debromination of an aryl ring in the steroid series accompanied by ring saturation has been described. 2,4-Dibromoestrone in acetic acid/chloroform with 70% nitric acid (2.5 moles) at ambient temperature during 2 hours gave a dibromo oxidised intermediate in 90% yield which upon facile hydrogenation in ethanol with a palladium-carbon catalyst, regulated with pyridine, gave after absorbtion of 4 moles of hydrogen, the hydroxy ketone indicated, in 92% yield (ref.53). Dehydration gave the corresponding 4-en-3-one.



2,4-Dibromo-3,6-dimethylphenol (X = H) upon nitration in acetic acid gave the cyclohexenone shown while 2,4,5-tribromo-3,6-dimethylphenol (X = Br) afforded the bromo analogue. By aqueous nitration of either compound a ring-contracted product was obtained which also resulted through Favorsky rearrangement from the tribromo compound by treatment with aqueous sodium carbonate (ref.54).

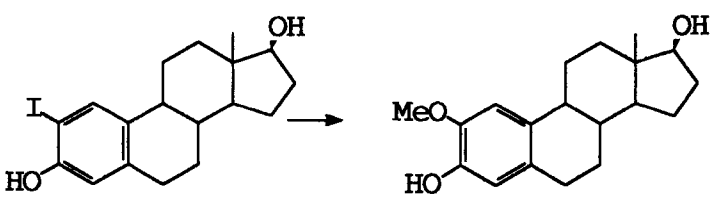


Selective metal-halogen exchange has been described with the methyl ether, 2,4,6-tribromoanisole, derived from the corresponding phenol or from bromination of anisole. By treatment with 1 mole of butyllithium the 2-monolithio derivative resulted, which with trimethyl borate followed by oxidation with peracetic acid afforded 3,5-dibromo-2-methoxyphenol in 87% yield, whereas with 2 moles of butyllithium the 2,6-dilithio derivative was obtained which upon similar work-up gave 4-bromo-2,6-dihydroxyanisole in 91% yield (ref.55).

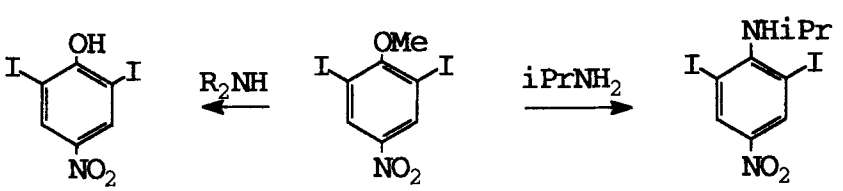


8.3.4. Iodophenols

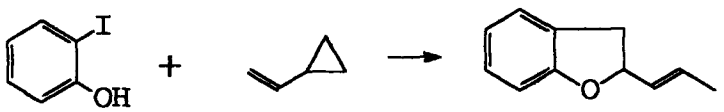
In this group the main reactions studied have been displacement of either iodine atoms or of adjoining substituents.
To complement the reaction in the bromo series previously described, a solution of 2-iodoestradiol in dimethylformamide containing copper(II) chloride and methanolic sodium methoxide upon refluxing for 5 mins. gave the corresponding 2-methoxy compound in 95% yield (ref.56).



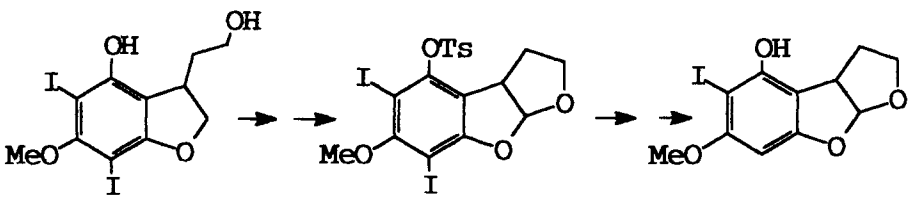
By contrast, 2,6-diiodo-4-nitromethoxybenzene in ethanol solution underwent displacement of the methoxy group by dropwise treatment at 0°C with excess isopropylamine followed by completion of reaction at ambient temperature during 2 hours to afford, in 70% yield, N-isopropyl 2,6-diiodo-4-nitroaniline. Secondary amines resulted simply in dealkylation to give the corresponding phenol (ref.57), a difference probably due to the influence of a differing degree of steric hindrance.



2-(Prop-1-enyl)-2,3-dihydrobenzofuran has been synthesised in 70% yield from 2-iodophenol, vinylcyclopropane, tetra-n-butylammonium chloride and a little palladium(II) acetate in dimethylformamide containing potassium acetate by reaction at 80°C for 72 hours (ref.58).

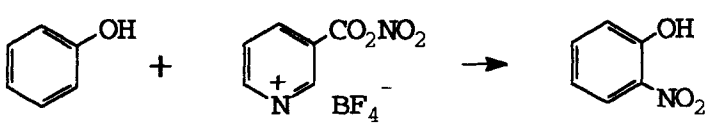


Selective complexation of iodophenols with β-cyclodextrin under aqueous conditions has been investigated for separation purposes (ref.59).
The regiospecific deiodination of diiodophenols in the dihydrobenzofuran series by n-butyllithium has been used as an important step in the synthesis of aflatoxin B_2 (ref.60). Thus, 3-(2-hydroxyethyl)-4-hydroxy-5,7-diiodo-6-methoxy-dihydrobenzofuran as the phenate formed with sodium hydride has been selectively deiodinated at the 7-position by means of butyllithium.

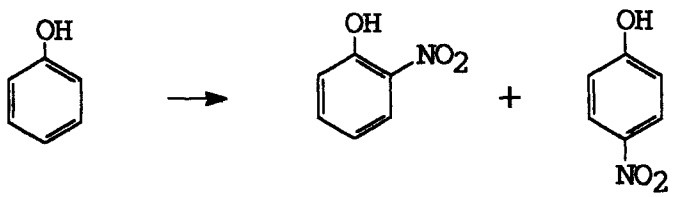


8.4. Synthesis of Nitrophenols

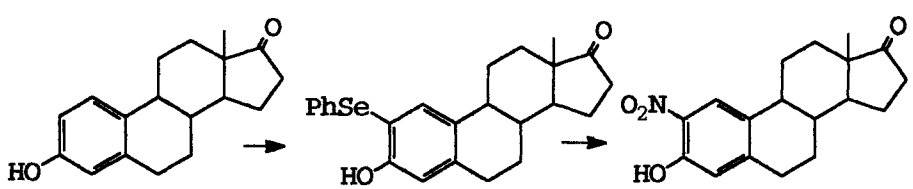
The finding of regiospecific routes to the nitrophenols is an important development in an area which has consistently presented difficulty in this respect.
The zwitterion, N-dodecylpyridinium-3-carboxylate converted in an acetonitrile suspension with an acetonitrile solution of nitronium tetrafluoroborate to the 'nitro ester', upon treatment with phenol gave 2-nitrophenol in 95% yield (ref.61).



It seems possible that other well-known nitro esters might also be effective. Indirect nitration of phenol in ether/water (1:1) by the addition of sodium nitrate and concentrated (11M) hydrochloric acid and stirring of the mixture at ambient temperature for more than 12 hours gave the isomeric 2- and 4-nitrophenols in 65% yield with the ratio 3:2 respectively (ref.62). Although this percentage of products is the same as in standard laboratory methods the conditions are essentially milder.

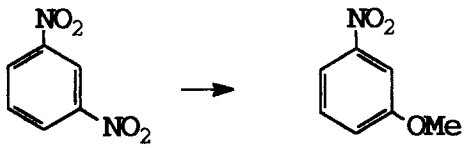


4-Methylphenol in ethanolic solution treated with ferric nitrate nonahydrate (1 equiv.) and heated briefly for 30 sec. afforded an 83% yield of 4-methyl-2-nitrophenol. Under similar conditions 4-chlorophenol gave 4-chloro-2-nitrophenol (88%), 4-bromophenol gave 4-bromo-2-nitrophenol (64%) and 2-chlorophenol, a mixture of 2-chloro-4-nitrophenol (56%) and 2-chloro-6-nitrophenol (35%). Aluminium, chromium and copper(II) nitrates were also used (ref.63).
2-Nitroestrone has been obtained in 79% yield by the addition of estrone to molar proportions of benzeneselenyl chloride and silver nitrate in acetonitrile followed by reaction with stirring for 3 hours at ambient temperature (ref.64).

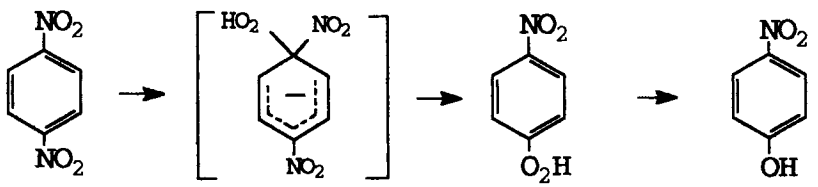


Although there are several routes to both 3-nitrophenol and to 3-nitroanisole, 1,3-dinitrobenzene is clearly an attractive intermediate. 3-Nitrophenol effectively, has been obtained as the methyl ether by treatment of a solution of 1,3-dinitrobenzene and Aliquat 336 in chlorobenzene with sodium methoxide, followed by heating the stirred mixture at 80°C during 2 hours (ref.65). In an alternative approach with the very weak nucleophile methanol, 1,3-dinitrobenzene at 180°C and under pressure (initially 3 Kg/cm2) in the presence of carbon dioxide after 20 hours gave 3-nitroanisole in 38% yield with a conversion of 40% (ref.66). Water under similar conditions would probably

afford the phenol.

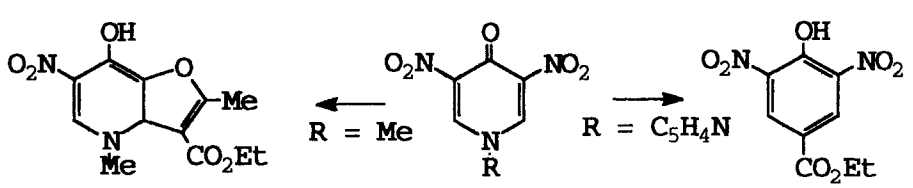


In the reaction of 1,4-dinitrobenzene with basic hydrogen peroxide, hydroperoxynitrobenzene, by way of the Meisenheimer complex, is formed more rapidly than 4-nitrophenol (ref.67)

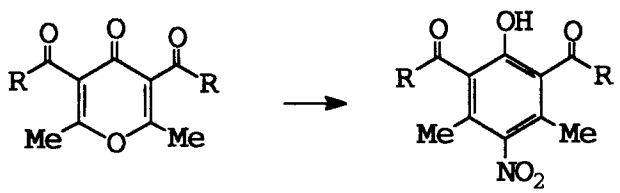


Non-aromatic precursors have been employed for the synthesis of nitrophenols since the application of nitromalonaldehyde in early work, by for example its reaction with 3-pentanone to give 4-nitro-2,6-dimethyl phenol in 94% yield (ref.68).

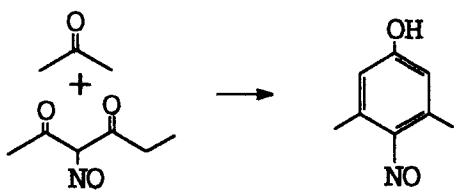
Six-membered ring heterocycles, for example N-2-pyridyl, N-6-methylpyridyl and N-4-pyridyl-2,6-dinitro-4-pyridones have been used with the ethyl acetoacetate anion in pyridine solution at 65-70°C during 5 hours for the synthesis of ethyl 3,5-dinitro-4-hydroxybenzoate in yields of 65-72% (ref.69), whereas the N-Me analogue afforded a furopyridone. The starting materials were obtained by reacting the sodium salt of 4-hydroxypyridine with the appropriate 2-bromopyridine and the required dinitro compound was then formed by nitration with fuming nitric acid. The process of using dinitropyridones can be compared with that of using formylpyrimidones for phenolic carbonyl compounds discussed in Chapter 7.



The pyrones (R = alkyl) indicated reacted with nitromethane to give 4-nitro-3,5-di methyl-2,6-diacylphenols in yields of 77-80% (ref.70).



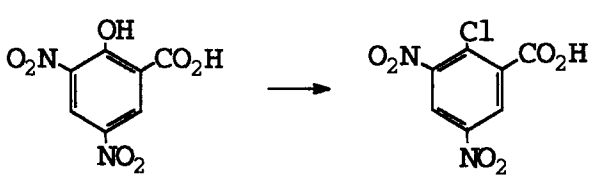
4-Nitrosophenols have been synthesised from propanone and its derivatives by condensation with 3-nitrosopentane-2,4-dione in moderate to good yields (ref.71). The products are a source of a variety of further compounds.



8.5. Reactions of Nitrophenols and their Derivatives

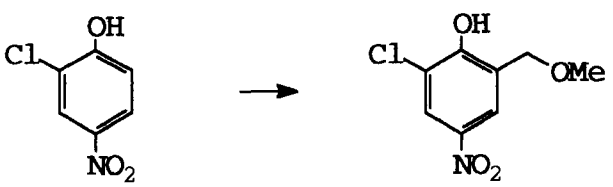
The reactions in this group comprise substitution of the nitro or the hydroxyl group, etherification of the latter and condensation reactions in the aromatic ring.

In the category of hydroxyl replacement, 2-hydroxy-3,5-dinitrobenzoic acid added slowly to phosphorus oxychloride/dimethylformamide (1:1) followed by completion of reaction at ambient temperature during 2 hours produced 2-chloro-3,5-dinitrobenzoic acid in a yield of 90% (ref.72).

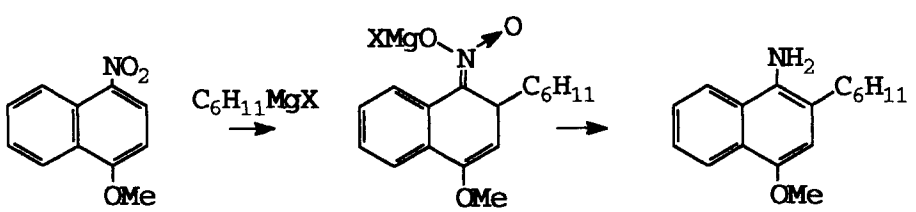


3-Nitrophenyl trifluoromethyl ether has been derived in 62% yield from a vigorously stirred mixture of 3-nitrophenol, anhydrous carbon tetrachloride and antimony pentafluoride together with a little antimony pentachloride by heating at 150°C for 5.5 hours (ref.73).

Methoxymethylation of 2-chloro-4-nitrophenol with paraformaldehyde and methanol occurred by the addition of concentrated sulphuric acid over 35mins. followed by reaction at 90-95°C during 4 hours. Dropwise treatment with methanol and continuation of refluxing for 2.5 hours resulted in a 93% yield of 2-chloro-6-methoxymethyl-4-nitrophenol (ref.74).

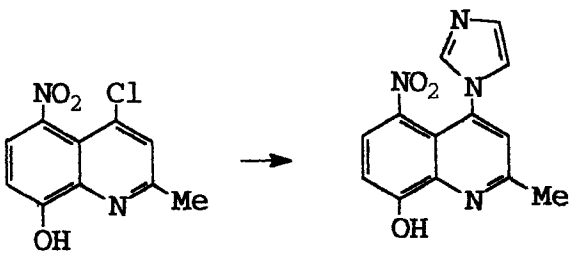


2-Alkylation and reduction of the nitro group to the amino has been observed in the methyl ether of 4-hydroxy-nitronaphthalene. Cyclohexylmagnesium chloride in tetrahydrofuran added dropwise but rapidly at 0°C to the compound in tetrahydrofuran followed successively by tert-butanol and phosphorus trichloride in tetrahydrofuran with completion of the reaction at ambient temperarure during 3 hours gave after acidification with hydrochloric acid,

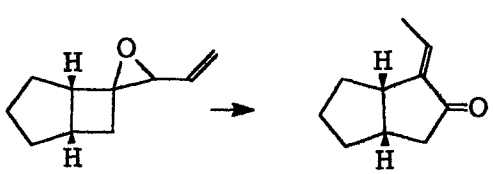


2-cyclohexyl-4-methoxynaphthylamine in 70% yield (ref.75).

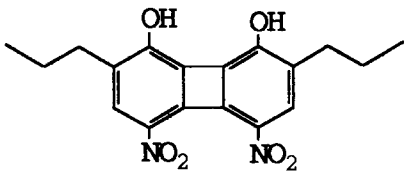
By treatment of the ice-cold intermediate nitronate salt with tris(dimethylamino) phosphine and reaction for 48 hours, the corresponding 1,2-dihydro-1-oxime was obtained in 51% yield. Quenching with methanolic hydrochloric acid led to 2,3-dihydro-1,4-naphthalenedione monooxime (ref.75).
4-Chloro-2-methyl-5-nitro-8-hydroxyquinolineunderwentnucleophilicsubstitution by imidazole in the presence of phenol by refluxing at 200°C during 24 hours to give a 40% yield of 4-(1-imidazyl)-2-methyl-5-nitro-8-hydroxyquinoline (ref.76).



Phenol has been classically employed as a solvent in the attachment of alkylamino side chains in the synthesis of antimalarial drugs such as 'chloroquine' and of 'mepacrine' and it seems probable that an easier reaction could result from the use of the aprotic N-methylpyrrolidinone which has been examined in nucleophilic substitutions (ref.77).
4-Nitrophenol (1 mole) together with 5 mol.% palladium tetra(triphenyl phosphine) in tetrahydrofuran has been employed catalytically for the rearrangement at ambient temperature during 2 hours of an epoxide to an alkylidenecyclopentanocyclopentanone in 90% yield (ref.78). Analogues with an epoxide ring having a tertiary migrating group reacted swiftly.



The 4,4'-dinitro-1,1'-dihydroxy-2,2'-di-n-propyldiphenylene compound depicted functions as a catalyst for the Diels-Alder reaction by binding the carbonyl group of the dienophile through hydrogen bonds (ref.79).

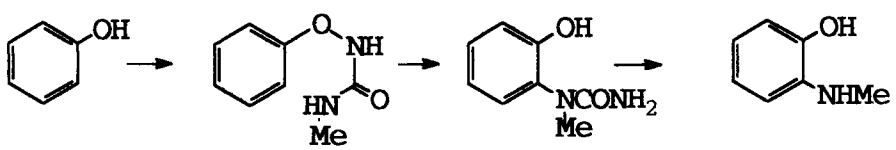


8.6. Synthesis of Aminophenols

Syntheses from benzenoid compounds, saturated sources such as cyclohexenones and cyclohexanediones, heterocycle sources and preparations by way of C_2-C_4 intermediates have been employed for obtaining aminophenols.

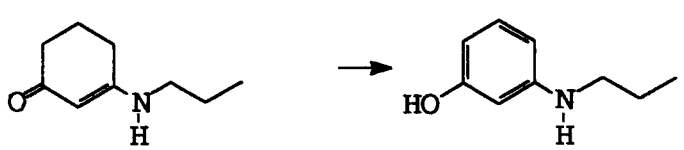
8.6.1. Benzenoid Intermediates

Anilines have been hydroxylated with hydrogen peroxide in superacid, HF/SbF_5, the substituting species being $H_3O_2^+$ (ref.80). Thus, aniline afforded the hydroxyanilines, 2-hydroxy (29%), 3-hydroxy (51%) and 4-hydroxy (20%).
A novel neighbouring group has been introduced in which N-methyl-N'-phenoxyurea in dichloromethane after treatment at 0°C with trifluoroacetic acid was reacted to give N-(2-hydroxyphenyl)-N-methylurea in 85% yield, from which 2-N-methylaminophenol was obtained (ref.81).

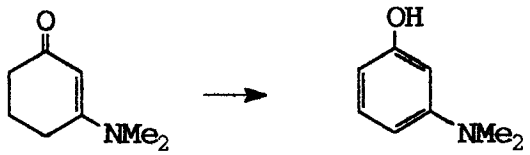


8.6.2. Aminocyclohexenone, aminodienone and cyclohexanedione intermediates

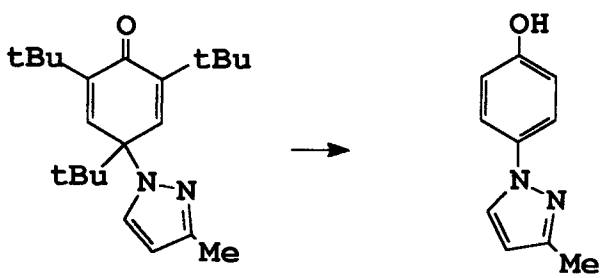
3-Propylaminocyclohex-2-enone gave 3-propylaminophenol in 78% yield by refluxing for 10 hours in acetonitrile containing mercuric acetate (ref.82).



A related compound 3-dimethylaminocyclohex-2-enone in aqueous solution has been dehydrogenated by dropwise addition, vaporisation and passage with nitrogen and hydrogen (3:1) over a palladium-potassium-charcoal catalyst at 300°C to produce 3-dimethylaminophenol in 98% yield (ref.83).

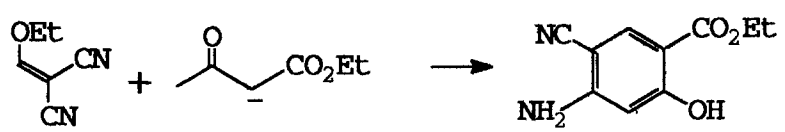


Cyclohexane-1,3-diones generally, for example the parent compound, dihydroresorcinol, available from rhe hydrogenation of resorcinol, have been aromatised by various techniques including the use of mercuric acetate in the presence of secondary amines to afford yields of 3-substituted aminophenols in the range 32-79% (ref.84).
The cyclohexadienone shown has been de-tert-butylated and transformed into N-(4-hydroxyphenyl)pyrazole in 99% yield by refluxing in 85% orthophosphoric acid for 4 hours (ref.85). The method would appear to have potential for the preparation of the 2-isomer.



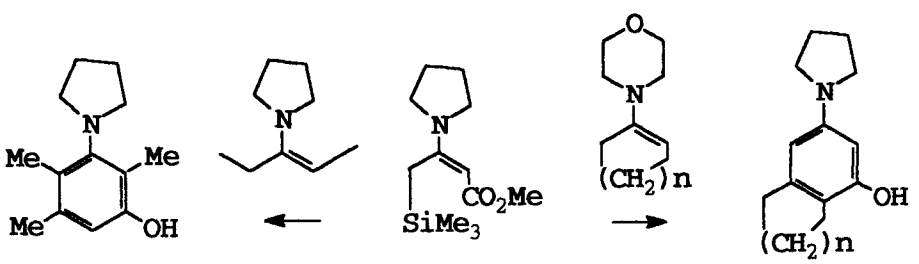
8.6.3. The use of C_3 Intermediates

3-Aminophenols in particular have been synthesised by this type of route. Appropriate ethoxymethylene compounds having cyano or carbonylmethoxy groups have been condensed with β-ketoesters, malononitrile or cyanoacetic

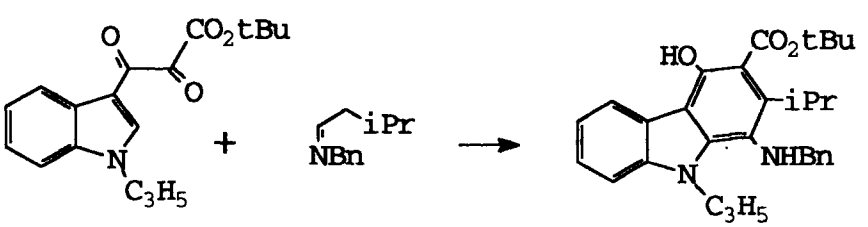


esters to afford substituted aminophenols with good yields. In the example, ethoxymethylenemalononitrile has been reacted with the anion of ethyl acetoacetate, by Michael addition, cyclisation and acidification, to finally afford ethyl 4-amino-5-cyano-2-hydroxybenzoate (refs.86,87) but the process is general.
Enamines had been used in earlier work for the synthesis of substituted 3-aminophenols (ref.88) although their dimerisation with loss of NHR^1R^2 as depicted, can be a complication (ref.89).

Nevertheless this can be circumvented if a silyl group (R = Me_3Si) is present in the enamine derived, in the example, from pyrrolidine (ref.90). The direction of cyclisation, in dichloromethane containing titanium(IV) chloride, is dependent on the structure of the co-reacting enamine so that enamines from symmetrical dialkylketones give 5-alkylaminophenols whereas those from cyclic ketones (in the example shown, a morpholino compound) afford the 5,6-cyclo series (n = 2-5).



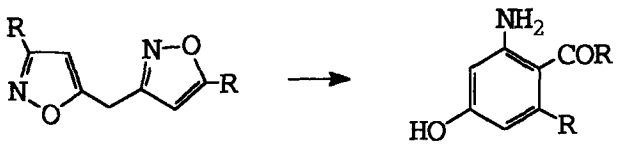
More complex substituted 4-aminophenols have been constructed from aldimines and diketones as in the case with an N-allylindole-3-diketoester



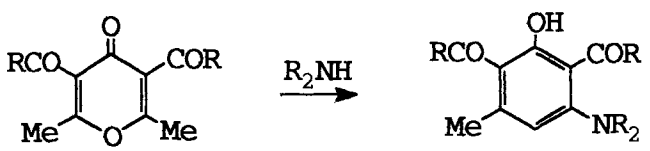
where a large excess of the formylimino compound (2 moles) reacted with the 1,2-diketoester in benzene solution at 50-60°C until completion of reaction, to furnish the product in 63% yield (ref.91).

8.6.4. Heterocycle Intermediates

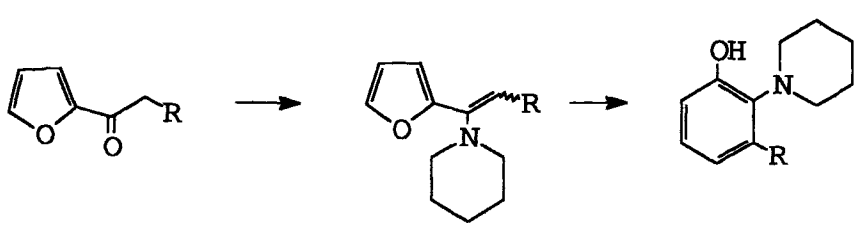
Heterocycles have been employed for the synthesis of 3-aminophenols in earlier work as in the use of the 'masked' dioxazole shown (*R* = alkyl) (ref.92).



The facile rearrangement of the acylpyrone depicted can be effected in good yield through ring opening followed by recyclisation (ref.93).

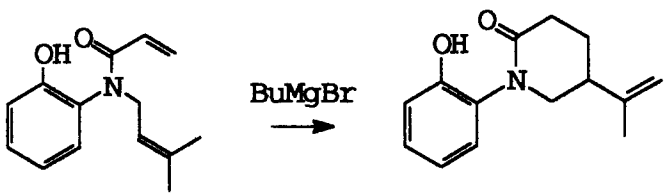


In a comparable way 2-aminophenols can be prepared in variable yields from 2-acylfuranones and a cyclic amine, such as piperidine in the example given, although morpholine pyrrolidine served equally well (ref.94). These phenolic structures are now accessible by more well-known methods.



The side-chain substituents in the 2-aminophenol shown have been intereacted to afford a 2-oxopiperidino derivative. After the addition of ethereal butylmagnesium bromide to the 2-N-prenyl,N-acryloyl derivative in tetrahydrofuran at -78°C, solvent removal and refluxing of the magnesio

complex in xylene for 6 hours, the product was isolated in 85% yield (ref.95).

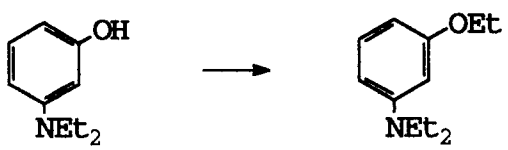


8.7. Reactions of Aminophenols

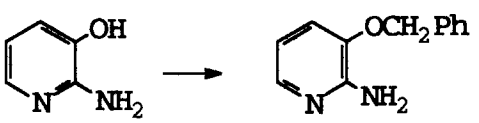
A range of reactions at the hydroxyl group, the amino group or through substitution in the ring are shown by aminophenols. Some of these transformations are described in this section.

8.7.1. O-Alkylation and Acetylation

The O-alkylation of 3-diethylaminophenol has been effected in 97.5% yield from the phenol in methyl iso-butyl ketone containing powdered potassium carbonate by stirring for 30mins. and after the addition of ethyl bromide, reacting for 3 hours in an autoclave initially at 115-120°C and finally at 140-142°C during 5 hours under 5 bar to give 3-diethylaminophenyl O-ethyl ether (ref.96).

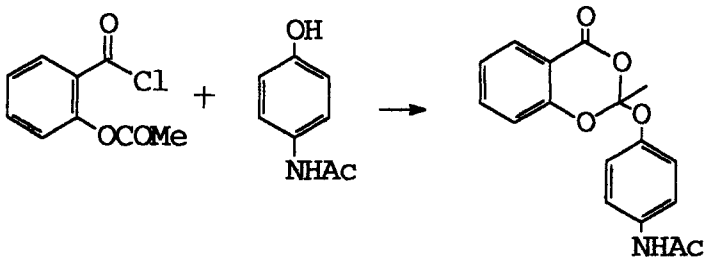


The selective O-benzylation can be noted in passing, of what might be termed an 'azaaminophenol', namely 2-amino-3-hydroxypyridine which took place in 91% yield by reaction with benzyl chloride during 16 hours at ambient temperature in 40% sodium hydroxide/dichloromethane (1:1) in the presence of some Adogen 464 (ref.97).

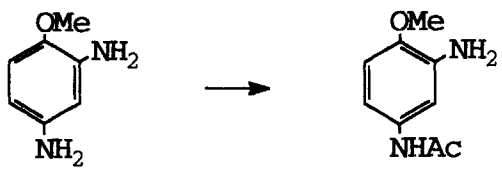


4-Acetylaminophenol and O-acetylsalicoyl chloride in chloroform solution treated

with pyridine and allowed to react at 20-25°C during 12 hours gave 2-methyl-2-(4-acetylaminophenoxy)-1,3-benzodioxan-4-one in moderate yield (ref.98).

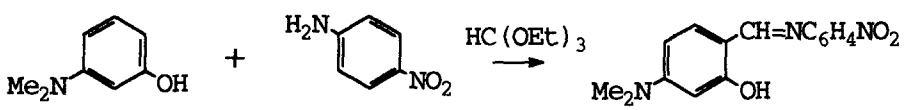


Specific N-acetylation has been effected by the sequential addition of magnesium oxide and acetic anhydride to 2,4-diaminoanisole in methanol solution at 0-5°C during 2 hours to give an 80% yield of 3-amino-4-methoxyacetanilide (ref.99).



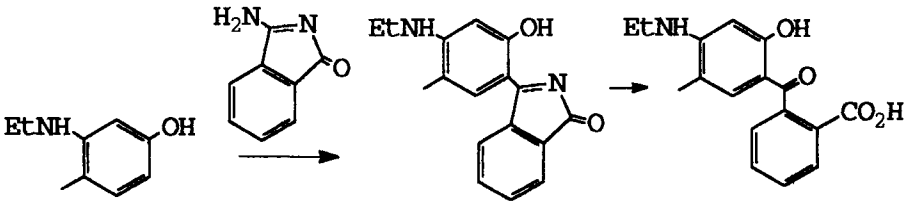
8.7.2. Ring Substitution and C-acylations

Formylation of 3-aminophenols leading to intermediates for the synthesis of coumarins and other carbonyl derivatives has been described. Nuclear formylation of 3-dimethylaminophenol with ethyl orthoformate in the presence of 4-nitroaniline by boiling for 5 mins. resulted in formation of 2-hydroxy-4-dimethylaminobenzylidene-4-nitroaniline in 88% yield (ref.100).



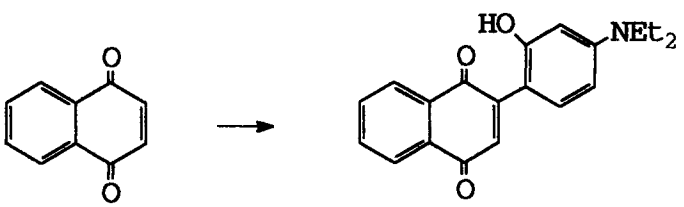
3-Ethylamino-4-methylphenol in dimethylformamide at 120°C treated gradually with 3-amino-1-oxoisoindoline hydrochloride and then reacted in the hot for 1 hour afforded a 94% yield of 3-(4-ethylamino-2-hydroxy-5-methylphenyl)-1-oxoisoindolinone, hydrolysis of which by refluxing with 20%

aqueous sodium hydroxide gave 2-(4-ethylamino-2-hydroxy-5-methylbenzoyl)-benzoic acid in 78% yield (ref.101).



o-Directed metallation followed by carbonation has given an efficient route to 6-hydroxyanthranilic acid from 3-aminophenol (ref.102). The amino group was first protected by reaction in sodium bicarbonate solution with pivaloyl chloride and then the phenate from sodium hydroxide solution with chloromethyl methyl ether. The isolated doubly protected derivative was lithiated at the 2-position with butyllithium, carbonated and finally hydrolysed with methanolic hydrochloric acid.

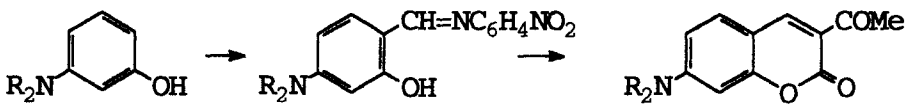
Oxidative arylation of 1,4-naphthoquinone with 3-diethylaminophenol was effected by stirring an acetic acid solution of the mixture containing cupric acetate monohydrate at 50°C for 7 hours to afford 2-[2-hydroxy-4-(diethylamino)phenyl]-1,4-naphthoquinone in 71%yield (ref.103).



8.7.3 Formation of 7-Alkylaminocoumarins from 3-alkylaminophenols and their derivatives

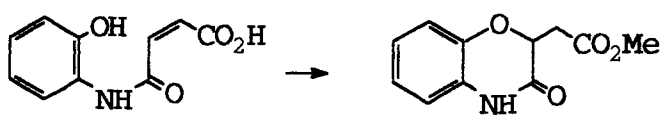
A variety of methods for the synthesis of this group of highly fluorescent substances having a range of industrial uses has been described. For example,

the 3-pyrrolidino analogue of the dimethylamino derivative described in ref.84, and formed in a similar way, has been used for this purpose. 3-Pyrrolidinylphenol was formylated with ethyl orthoformate and the 4-nitrobenzylidene derivative (as described in ref.100) reacted with ethyl acetoacetate in the presence of piperidine. After heating of the mixture for 30 mins., 7-pyrrolidino-3-acetylcoumarin was obtained in 94% yield (ref.104).

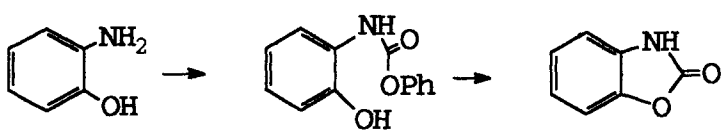


(R_2N = Pyrrolidino)

The general procedures for obtaining a variety of coumarins and some pyrans have been summarised in Table 8.5 (refs.105-109).
2-Aminophenols are valuable precursors of heterocycles. For example a benzoxazole has been obtained from an N-acyl, 2-aminophenol derivative in the following way. 2-Hydroxymaleanilic acid refluxed with triethylamine in methanol for 3 hours afforded a nearly quantitative yield of methyl [3,4-dihydro-1,4-benzoxazin-3(2H)-one-2-yl]acetate (ref.110).



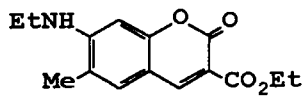
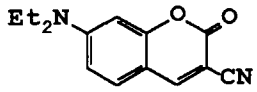
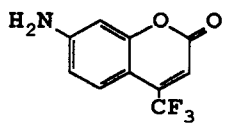
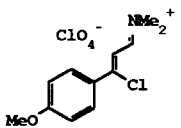
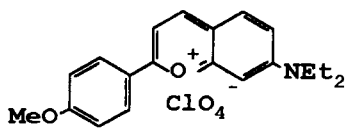
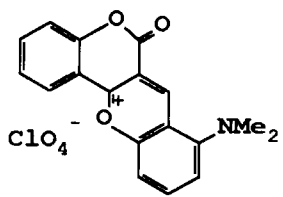
Benzoxazolin-2(3H)-one has been derived from 2-aminophenol in 83% yield by firstly reaction at 25-30°C during 30 mins. with 1 mole of phenyl chloroformate in methanol/water (1:1) containing sodium bicarbonate and then cyclisation of the intermediate N-phenoxycarbonyl compound with 1 mole of aqueous sodium hydroxide followed by acidification (ref.111).



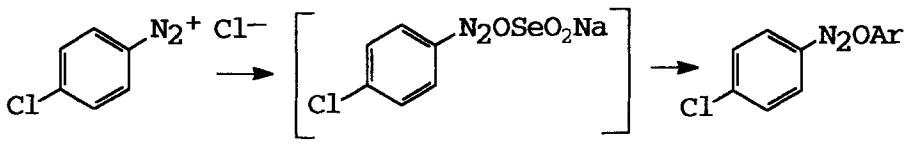
8.8. Hydroxy Azo compounds and their derivatives

The role of phenols in the chemistry of diazonium salts and their coupling products is an important one which is so well established that it may well be

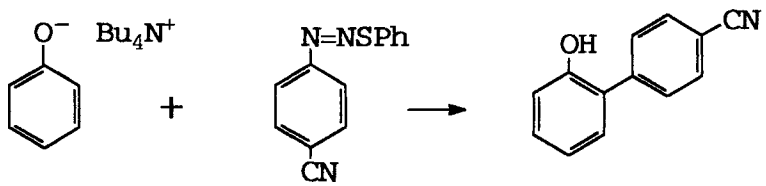
TABLE 8.5 SYNTHESIS OF COUMARINS FROM 3-AMINOPHENOLS

PHENOL	REACTANT	CONDITIONS	PRODUCT	YIELD%	REF.
3-Ethylamino-4-methylphenol	Diethyl ethoxy-methylenemalonate	The two reactants in THF containing titanium tetrachloride refluxed 24h. to give 7-ethylamino-3-ethoxycarbonylcoumarin.		81	105
3-Diethylamino-phenol	2-Chloro-1-cyano-acrylonitrile	The two reactnts initially in diethyl ether at ambient temp.during 1h followed by evapn. of solvent and reflusing of the residual material (6h) in aqueuous ethanol to give 7-diethylamino-3-cyanocoumarin.		56	106
3-Aminophenol	Ethyl 4,4,4-trifluoro-acetoacetate	The two reactants in ethanol containing zinc chloride refluxed (12h) gave 7-amino-4-tri-fluoromethylcoumarin.		75	107
3-Diethylamino phenol		The two reactants boiled for 1h in glacial acetic acid gave the flavylium salt.		41	108
3-Dimethylamino phenol	4-chloro-3-formyl coumarin	The two reactants and 70% perchloric acid gave dimethylaminocoumarino[4,3-b]benzo pyrylium perchlorate		60	109

forgotten. Nevertheless developments have taken place. Diazonium aryl ethers have been prepared by the addition of aqueous sodium selenite to an aqueous solution of a diazonium salt at 0°C to -5°C succeeded by an aqueous solution of the sodium salt of 4-chlorophenol in water at pH 7-8. The mixture was stirred for 5 hours and the precipitated product, obtained in 64% yield, collected by filtration after a further 7 hours (ref.112).

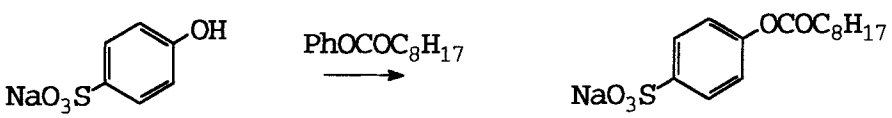


Diaryl formation has been effected by displacement of the phenylthioazo group. 4-Cyanophenylazophenylsulphide in dimethylsulphoxide was added to a solution of tetra-n-butylammonium phenoxide in the same solvent and after reaction at ambient temperature for 2 hour and acidification of the mixture 2-(4-cyanophenyl)phenol and 4-(4-cyanophenyl)phenol (in 3:1 proportion) were isolated in 60% yield (ref.113).



8.9. Phenolsulphonic acids

Sodium 4-hydroxybenzenesulphonate dihydrate has been used to transacylate phenyl nonanoate. The sodium sulphonate in octane/hexadecane was treated with phenyl nonanoate, the octane removed by distillation and the mixture refluxed at 180-200°C during 4 hours when most of the hexadecane was also removed to give the product in 87% yield (ref. 114).

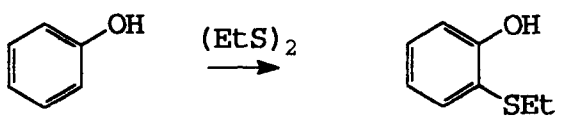


An alternative acylation procedure carried out in the absence of solvent was

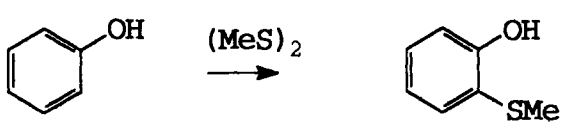
effected with a fatty acid anhydride. Nonanoic acid and excess acetic anhydride were refluxed together for 8 hours after which the acetic anhydride excess and acetic acid formed were removed in vacuo, sodium phenolsulphonate and some sulphuric acid were added and the mixture was then heated for 4 hours at 90-100°C to give sodium nonanoyloxybenzene sulphonate in 96% yield (ref.115).

8.10. Thio derivatives of Phenol

Sulphur halides and dialkyl disulphides have been used to obtain a variety of arylthio and alkylthio derivatives of phenols generally by electrophilic substitution. For example, phenol was treated with zirconium tetrachloride, heated to 156°C under nitrogen, kept at this temperature overnight and after reduction of this to 100°C, diethyldisulphide was added. The mixture was heated to remove ethanethiol and the product, 2-(ethylthio)phenol, isolated in 41% yield (ref. 116).

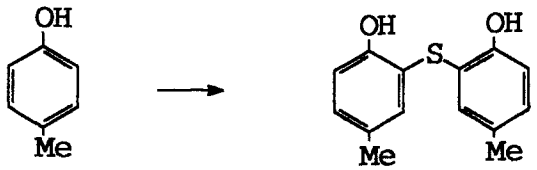


A unique feature of these substitution reactions is that they lead to o-products. An aluminium salt has been used to effect this type of reaction. A little aluminium (10-20mesh) was stirred and heated at 130-150°C with phenol under a nitrogen atmosphere until hydrogen evolution ceased. After the addition of dimethyldisulphide at 100°C the mixture was refluxed for 18 hours during which methanethiol was formed and after 3 hours at 185°C the product 2-(methylthio)phenol was isolated in 41% yield (ref.117).

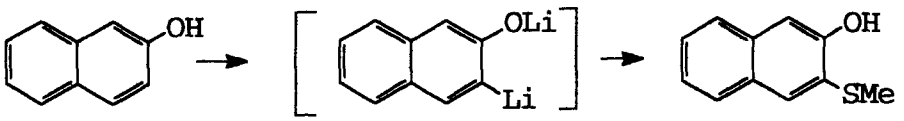


In the phenylthio series, 4-alkylphenols are widely used to produce the so-called thio bisphenols, the higher alkyl members of which are important industrial chemicals discussed further in Chapter 13. For 4-methylphenol and such higher members, Lewis acids are generally employed and milder conditions with sulphur dichloride. Thus, a mixture of 4-methylphenol in hexane containing a small proportion of zinc chloride was kept at 0-10°C during the addition of sulphur dichloride in 1 hour. Reaction was continued for 2 hour and the product

isolated by filtration in 87% yield (ref.118).



All these procedures in the benzenoid series are based on electrophilic substitution while with napthalene compounds nucleophilic substitution has been employed as seen in the following examples. 2-Naphthol in anhydrous tetrahydropyran was treated rapidly over 2 mins. with butyllithium (2 moles) in pentane at 20-25°C. The solution was stirred for 4 hours, cooled to 0°C and after the addition of dimethyldisulphide in tetrahydropyran, the mixture was stirred for 2.5 hours to complete reaction to afford, after acidic work-up, 2-hydroxy-3-(methylthio)naphthalene in 83% yield (ref.119).

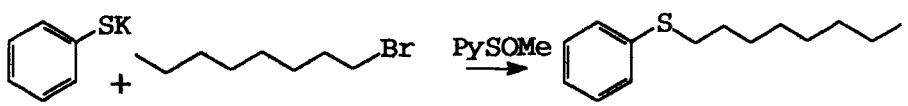


8.11. Thiophenols and derivatives

Thiophenols can be readily derived from phenolic sources by a number of processes (ref, 120). They are reactive and are susceptible to a variety of reactions either at the sulphur atom or the ring.

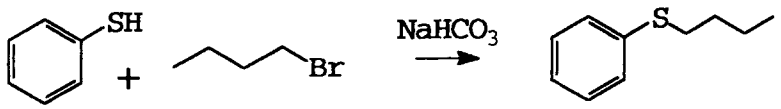
8.11.1. Thioether formation

n-Octyl phenyl thioether has been obtained in 98% yield during 2 mins. at ambient temperature from 1-bromooctane and potassium thiophenoxide in xylene containing 4 moles of methyl 2-pyridylsulphoxide as aprotic solvent (ref.121).

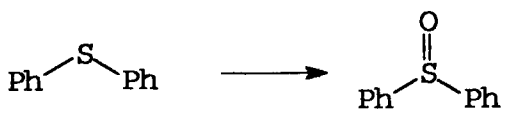


The phase transfer method did not succeed well when applied to the

preparation of n-butyl phenyl thioether and more drastic thermal conditions proved necessary. Thus a mixture of thiophenol and 1-bromobutane pumped through a column containing a solid bed of sodium bicarbonate and a small proportion of carbowax 6000 at 170°C and 20mm Hg afforded the product in 71% yield (with a conversion of 95%) (ref.122).



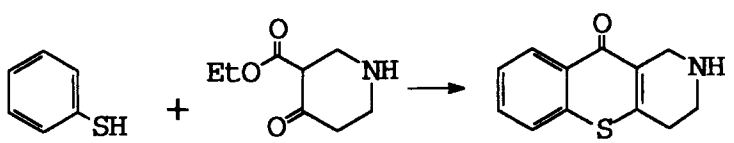
Diphenyl thioether and (meso-tetraphenylporphyrinato)iron(III) chloride supported on silica, by treatment with 1 mole of iodosobenzene at ambient temperature, gave with stirring during 3 hours under nitrogen, diphenylsulphoxide in 74% yield with 7% of the corresponding sulphone, formation of which was suppresed by adsorption of the main product on the silica (ref.123).



The method of ref.122 was also effective for phenols and would undoubtedly be favourable for the preparation of ethers of long-chain phenols which react only moderately well under phase transfer conditions.

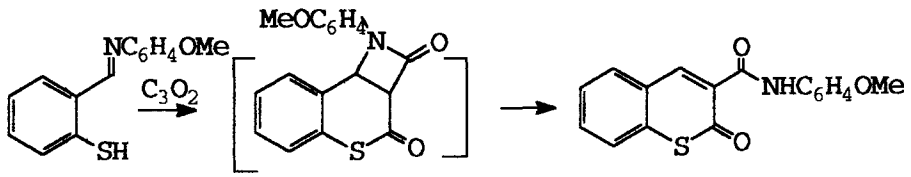
8.11.2. Substitution in the ring

Substitution o- to the thiol group occurs and can be used for heterocycle formation as in the synthesis of the tetrahydropyridothiochromone shown. A mixture of ethyl 4-oxopiperidine-3-carboxylate hydrochloride was added slowly to stirred polyphosphoric acid at 100°C, and after 4 hours reaction at

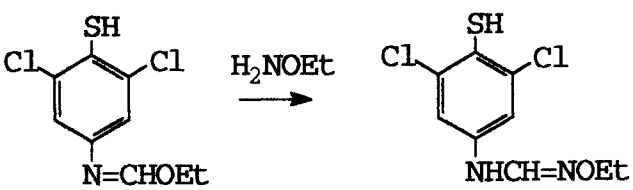


this temperature the product was isolated by quenching in water and

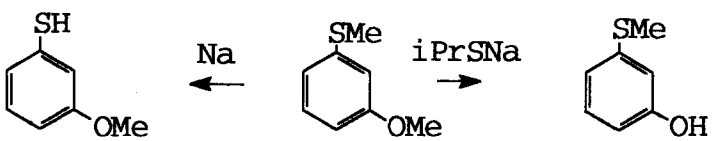
basification to pH 8.0, in 54% yield (ref.124)
A cyclic thiocoumarin derivative was prepared from 4-methoxybenzylidene thiosalicylaldehyde in a novel use of the three C unit of carbon suboxide. 2-[(4-methoxphenylimino)methyl]thiophenol suspended in ether was treated at -10°C with ethereal carbon suboxide during 30 mins. and after stirring at 0°C for 2 nours and completion of reaction over 3-4 days the product, thiocoumarin-3-(N-4-methoxyphenyl)amide, was obtained in 51% yield (ref.125) by way of a postulated lactam.



An ether of an of a oxime of a formylamino derivative apparently difficult to prepare in the usual way was obtained indirectly by way of an iminoether, ethyl N-(3,5-dichloro-4-mercaptophenyl)-N-ethoxyformamidine in high yield (ref.126).

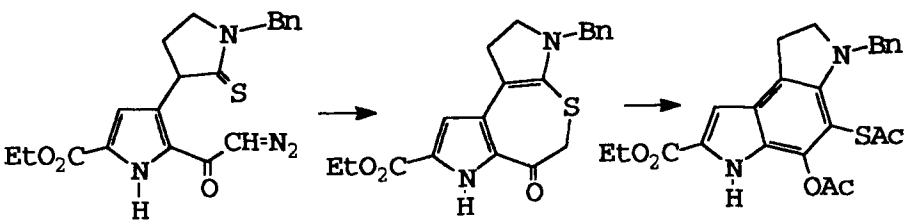


The preferential dealkylation of a combined thio and O-alkyl ether was selectively chemically achieved either at the O or the S atom by appropriate choice of reagent. Sodium iso-propylthiolate at 120°C added to 3-(methylthio)anisole in hexamethylphosphorictriamide in a nitrogen atmosphere followed after 2.5 hours by acidification gave 3-(methylthio)phenol in 88% yield, while sodium alone in hexamethylphosphorictriamide resulted in selective S-dealkylation (ref.127).

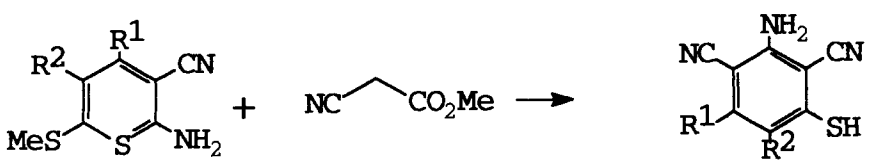


8.11.3 The use of Heterocyclic Intermediates for obtaining Thiophenol Derivatives

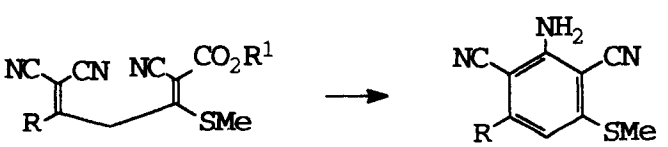
Unlike the synthesis of phenols from non-aromatic sources that of thiophenol by similar methodology is virtually unknown. The synthesis shown of the diacetate of a tricyclic compound containing an o-substituted thiophenol system would appear to be applicable to the simpler central portion and to bicyclic analogues. Ethyl 4-(1-benzyl-2-thioxo-pyrrolidin-3-yl)-5-(diazoacetyl)-pyrrole - 2-carboxylate in dichloromethane was treated with boron trifluoride etherate in the same solvent and after 15 mins. the intermediate shown resulted which in a sealed tube (under vacuum) with acetic acid/acetic anhydride (3:1) at 132°C during 90mins. produced by a Pummerer rearrangement, ethyl 4-acetoxy-5-(acetylthio)-6-benzyl-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrole-2-carboxylate in 88% yield (ref.128).



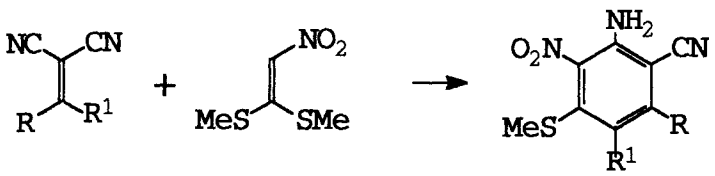
Aminothiophenols have been synthesised from acyclic precursors with yields in the range 83-92%. By the reaction of the substituted thiabenzene shown with cyanoacetic esters, 3-amino-2,4-dicyano-5,6-dialkylthiophenols ($R^1 = R^2$ = alkyl) have resulted (ref.129).



S-Me derivatives have been obtained by analogous routes in yields of 72-77% (ref.130).



and in the following way (ref.131) in yields of 76-79%.



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CHAPTER 9

DIHYDRIC PHENOLS

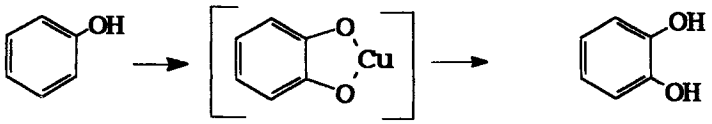
9.1 Introduction

In this chapter the recent advances during the previous one and a half decades in the chemistry of dihydric phenols are reviewed covering 1,2-dihydroxybenzenes (catechols), 1,3-dihydroxybenzenes (resorcinols) and 1,4-dihydroxybenzenes (hydroquinones). Some reference has been made to dihydric phenols and their industrial synthesis and applications in Chapter 1. Catechol itself occurs naturally in several plants, hydroquinone apparently only as the O-monomethyl-O-glycosyl derivative, arbutin, while resorcinol is found solely in the form of its derivatives which are very widely distributed as monocyclic, bicyclic and polycyclic compounds. The monomethyl ether and dimethyl ether derivatives of catechol and resorcinol are particularly widespread and in this account regiospecific procedures for obtaining the parent monoalkyl and monoacyl compounds are described as well as recent procedures for dialkyl compounds.
Reference is also made to dihydroxynaphthalenes and to dihydroxy compounds in the polycyclic series. In all these classes the methods of synthesis of dihydroxyarenes and simple derivatives are discussed. The major section of this chapter is concerned with the reactions of dihydric phenols, their monoalkyl ether and acyl and dialkyl ether derivatives. Although the enhanced reactivity in the dihydroxy series enables a wide variety of bicyclic and polycyclic oxygen and nitrogen ring compounds to be synthesised, the demands of regiospecificity are increased. The large number of examples indicate that dihydric phenols and their derivatives lie at the heart of the organic synthesis of many bicyclic and polycyclic systems. While it might be argued that in certain cases the reaction in question would proceed anyway in the absence of the additional hydroxyl group, its presence confers utility in the area of structure/activity studies.

9.2 Synthesis of Dihydric Phenols

9.2.1. 1,2-Dihydroxybenzenes (Catechols) and their Derivatives

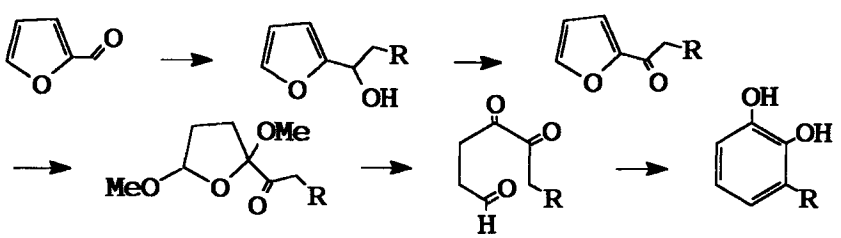
There has been considerable interest in the hydroxylation of phenol through a variety of approaches. The oxygenation of phenol in acetonitrile in the presence of cuprous chloride in catalytic quantities gave, after work-up by acidification, catechol in yields of 70-90% (ref.1) by way of a copper (II) intermediate.



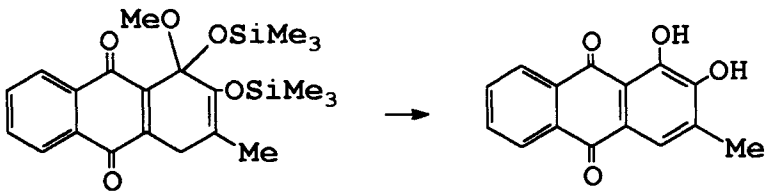
By the use of hydrogen peroxide a similar transformation has been effected (ref.2).

1,2-Cyclohexane derivatives have been employed as in the case of 3-phenylcyclohexane-1,2-dione which by refluxing with 4-toluenesulphonyl chloride, potassium carbonate and a small proportion of azoisobutyronitrile for 12 hours under argon gave a 45% yield of 3-phenylcatechol. Catechol itself was obtained in a similar yield (ref.3).

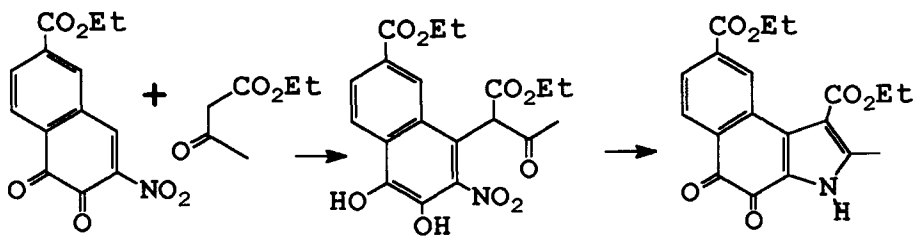
3-Alkylcatechols (R = n-C_3H_7 to $C_{17}H_{35}$) have been synthesised through ring-opening and re-cyclisation of 2-alkanoyl-2,5-dimethoxytetrahydrofurans (ref.4) by an adaptation of an earlier route. Furfural was reacted with RCH_2MgBr and the resultant carbinol upon oxidation with manganese dioxide and then electrochemical oxidation in methanolic solution afforded an acyldimethoxytetrahydrofuran. Ring-opening to an intermediate dioxoaldehyde followed by ring closure led to the product.



In the methylalizarin series a Diels-Alder adduct from naphtho-1,4-quinone and 1,2-bis(trimethylsiloxy)-1-methoxy-2-methylbuta-1,3-diene was converted by demethanolation and hydrolysis to afford 3-methyl-1,2-dihydroxyanthraquinone in 92% yield (ref.5).



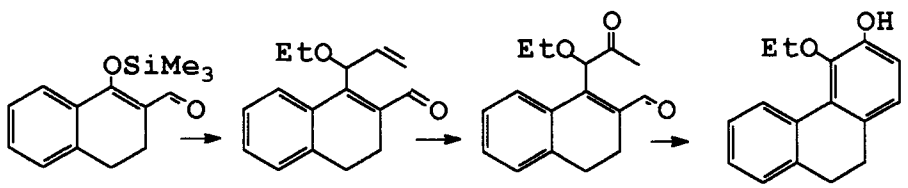
A Michael adduct, reminiscent in structure of the first intermediate in the Gates synthesis of morphine, has been obtained as a catechol derivative en route to conversion to an indole. 3-Nitro-6-ethoxycarbonyl-1,2-naphthoquinone with ethyl acetoacetate in dioxan containing zinc chloride was refluxed for 5-10 minutes, allowed to stand for 20 minutes, the nitro compound reduced with zinc dust to the amino compound which cyclised after a final oxidation step to an indole, 1,8-diethoxycarbonyl-4,5-dioxo-4,5-dihydro-3H-benz[e]-indole in an overall yield of 70% (ref.6).



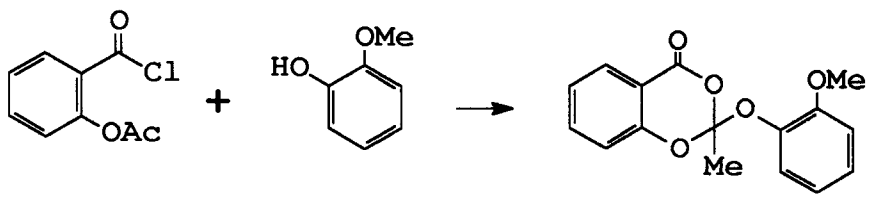
9.2.2. O-Derivatives of 1,2-dihydroxybenzene

Guaiacol (2-methoxyphenol) has been obtained in quantitative yield from catechol, sdium acetate and acetic acid by heating an aqueous methanolic solution in a sealed tube for 5 hours at 250°C (ref.7).

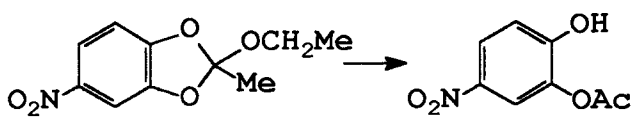
The zinc 'ate' complex from ethoxyallyllithium and zinc chloride reacted with the ketocarbonyl group of the trimethylsilyl ether of 2-formyl-3,4-dihydro naphthalene-2H-1-one and following a Wacker-type oxidation, afforded finally 4-ethoxy-3-hydroxy-9,10-dihydrophenanthrene in 66% overall yield (ref.8).



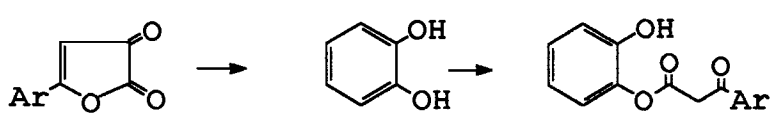
A mixed ether considered to comprise a 1,3-dioxan system has been derived in 58% yield from O-acetylsalicyloyl chloride and 2-methoxyphenol by refluxing in dichloromethane for 48 hours and isolation by neutralisation with ammonium hydroxide (ref.9).



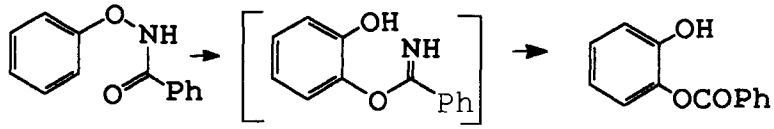
Selective O-acetylation in 97% yield has been observed in the treatment at 0°C of 2-ethoxy-2-methyl-5-nitro-1,3-benzdioxole in dichloromethane with an acetone solution of sodium iodide and with boron trifluoride etherate during 5 mins. to give 4-nitrocatechol-2-monoacetate (ref.10).



The mono O-4-methoxybenzoylacetyl derivative of catechol has been produced in 92% yield by refluxing 5-(4-methoxyphenyl)-2,3-dihydrofuran-2,3-dione with catechol in benzene during 3 hours, apparently with loss of carbon monoxide (ref.11).



Catechol monobenzoate has been synthesised effectively from phenol by treatment of O-phenyl-N-benzoylhydroxylamine in trifluoroacetic acid during 1 hour at 0°C with trifluoromethanesulphonic acid and allowing the mixture to react for a further hour (ref.12).

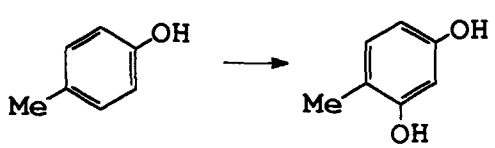


Monoethers of catechol have been prepared from 2,2,6-trichlorocyclohexanone by dehydrochlorination through treatment, for example, with alcohols such as ethanol and a base (ref.13).

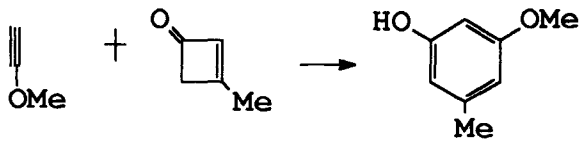
9.2.3. 1,3-Dihydroxybenzenes (Resorcinols) and their Derivatives

(i) Monocyclic Dihydroxy Compounds

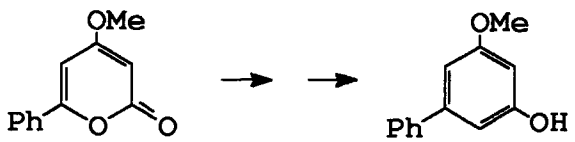
By the addition of hydrogen peroxide to a solution of 4-methylphenol in antimony pentafluoride/hydrogen fluoride (2:5) at -40°C and reaction with stirring during 30 mins., 4-methylresorcinol was formed in 78% yield (ref.14).



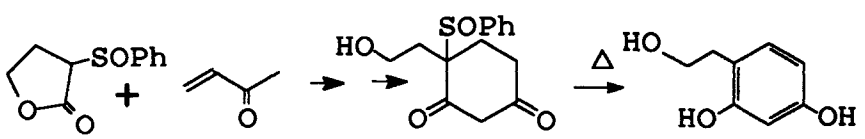
5-Methylresorcinol monomethylether (orcinol monomethylether) has been synthesised in 71% yield from 3-methylcyclobut-2-enone (2.5 moles) and 2-methoxyacetylene (1-1.2 moles) in the presence of 2,4,6-tri-tert-butylphenol (1.1 moles) by heating the mixture in a sealed tube at 80°C for 26 hours followed by treatment of the crude product with hot 10% methanolic potassium hydroxide during several hours (ref. 15).



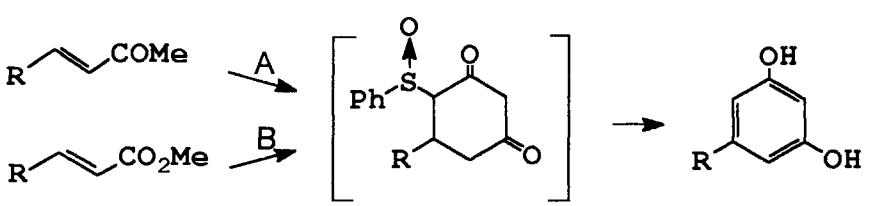
The 5-phenyl analogue has been obtained by a type of Horner-Emmons reaction. 4-Methoxy-6-phenyl-2-pyrone in tetrahydrofuran was added at -10°C to dimethyl methylphosphonate in tetrahydrofuran previously treated at -10°C with n-butyllithium in hexane and reacted for 30 mins. Further butyllithium was introduced and after reaction during 1 hour at ambient temperature and work-up by acidification, 5-phenylresorcinol monomethylether was isolated in 88% yield (ref.16).



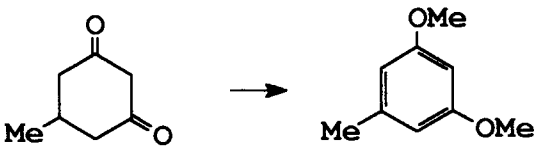
4-(2-hydroxyethyl)resorcinol has been prepared by the Michael addition of the carbanion from α-phenylsulphinyl-γ-butyrolactone with methyl vinyl ketone (but-1-en-3-one) followed by thermal treatment of the intermediate adduct (ref. 17).



Earlier syntheses had employed $PhSOCH_2CO_2Me$ (A) and RCH=CHCOMe, and $PhSOCH_2COMe$ (B) with $RCH=CHCO_2Me$, (R = alkyl or Ph) (ref.18).

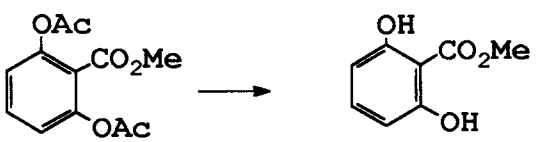


2-Substituted resorcinol dimethyl ethers have been synthesised by the removal of the 2-methoxyl group from 1,2,3-trimethoxybenzene by electron transfer from alkali metals and reaction with an electrophile (ref.19).
5-Methylresorcinol dimethyl ether has been prepared in 87% yield from 5-methyl-1,3-cyclohexanedione in methanolic solution by the addition of 2 moles of iodine, and stirring of the mixture until homogeneous, followed by refluxing under nitrogen for 30mins (ref.20).

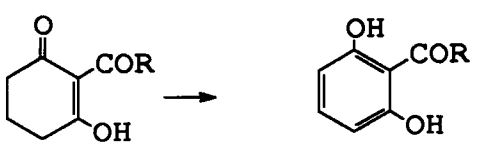


(ii) Carbonyl Derivatives of Resorcinols

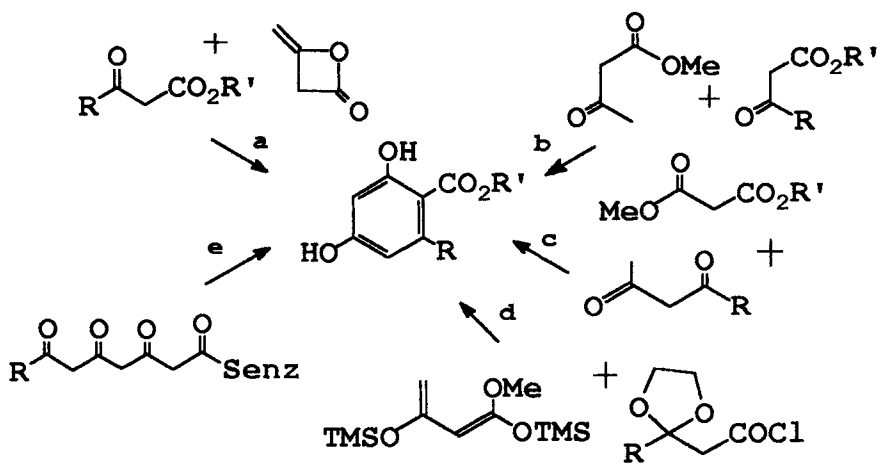
The facile decarboxylation of resorcinol carboxylic acids and notably of orsellinic acids in alkaline solution poses a problem during their syntheses in high yield. For this reason the synthesis of alkoxycarbonyl derivatives is usually adopted followed by acidic hydrolysis. The removal of the protective acetyl groups in the compound shown was effected preferentially without hydrolysis of the ester group. Methyl 2,6-diacetoxybenzoate in toluene saturated with water when added to a catalyst (prepared from 4-toluenesulphonic acid monohydrate and silica gel) and stirred at 86°C during 6 hours, afforded methyl 2,6-dihydroxybenzoate (ref.21).



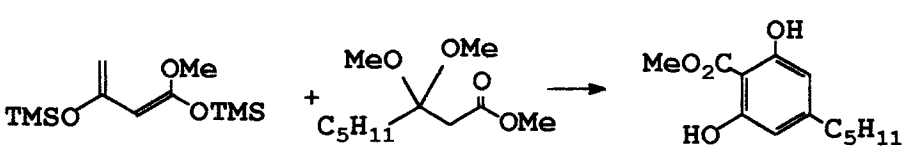
2-Acylresorcinols have been derived by the aromatisation of 2-acyl-3-hydroxy-cyclohex-2-en-1-ones (R = alkyl) through oxidation with mercuric acetate (ref.22).



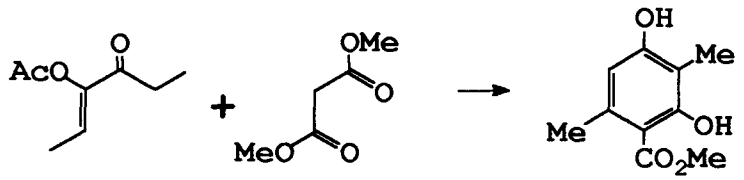
There has been considerable activity in the synthesis of orsellinic acids in the past decade. On account of their ready decarboxylation all these procedures also give access to 5-alkylresorcinols. These routes are summarised in the scheme shown. Homologous alkyl acetoacetates (R = R' = alkyl) with thallium ethoxide or sodium hydride followed by reaction with diketene (route a) afford the corresponding homologous alkyl orsellinates (ref.23). In a related method (route b) methyl orsellinate (R = Me) results from the interaction of the monoanion with the dianion of methyl acetoacetate (ref.24).
A closely related methodology (route c) involves the dianion from a diketone (R = Me) with the anion of dimethyl malonate (R' = Me) (ref.25). The bis-trimethylsilyl ether from methyl acetoacetate has been interacted with the ketalised acid chloride shown (R = C_5H_{11}) to furnish the methoxy carbonyl derivative of olivetol (route d) (ref.26). It was also found that pentane-2,4-dione with dimethyl malonate in the presence of sodium hydride afforded methyl orsellinate (ref.26). In a biomimetic approach (route e) a tetraketone has been enzymically cyclised to give the corresponding orsellinic acid (R'=H, R = alkyl) (ref. 27).



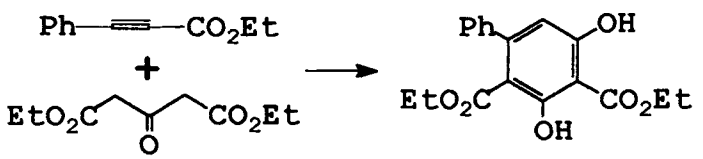
To contrast with the preceding strategies, 2-methoxycarbonylresorcinol compounds can be synthesised from the bis-trimethylsilyl derivative of methyl acetoacetate and the dimethyl acetal of methyl 3-oxooctanoate (ref.28).



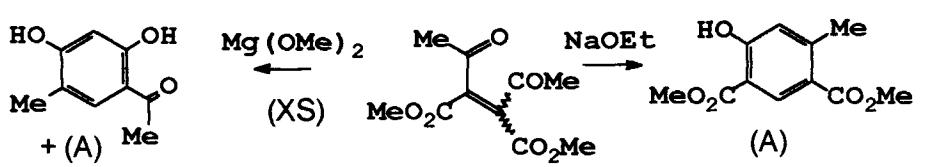
Methyl 2,4-dihydroxy-3,6-dimethylbenzoate has been obtained by Michael addition of the, α,β-unsaturated ketone shown, the enol acetate of hexane-3,4-dione, with the anion of dimethyl malonate (ref.29).



In the Michael addition procedure for orsellinic acid itself (ref.30) the dihydro intermediate was aromatised by a bromination/dehydrobromination step which was obviated in the preceding example by the incorporation of an acetoxy group. Complete aromatisation is also achieved by the use of an acetylenic intermediate as seen in the following case of the synthesis of 2,4-diethoxycarbonyl-3,5-dihydroxybiphenyl (ref.31).

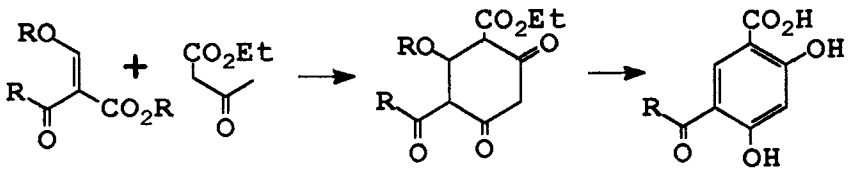


While the majority of the syntheses discussed have been directed to the orsellinic acids and their homologues, keto and cyano analogues have also been prepared in the monocyclic series. The ketoester shown afforded the salicylate upon cyclisation with sodium ethoxide or magnesium methoxide and none of the resorcinol although an excess of magnesium ethoxide gave a mixture of both products (refs. 32, 33, and 34).

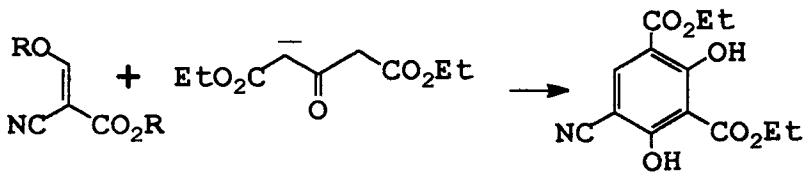


Substituted resorcinols can be prepared from alkoxymethylene intermediates

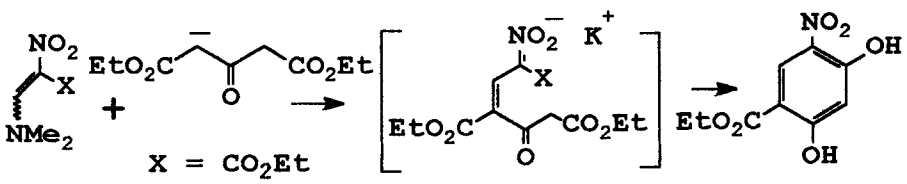
such as in the following (R = Me) (ref.35).



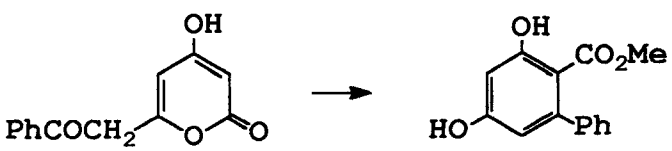
By contrast, earlier work showed that resorcinols with cyano groups resulted from alkoxymethylene compounds with cyano groups and diethyl acetone dicarboxylate (ref.36).



With a nitro substituent in the reactant ethyl 2-dimethylamino-1-nitroacrylate, diethyl acetonedicarboxylate produced the nitroresorcinol shown (ref. 37).



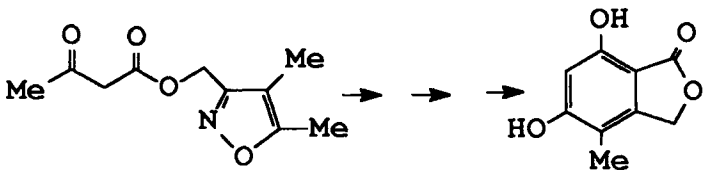
Lactones which have been used for the synthesis of phenolic compounds have also been similarly engaged for the preparation of resorcinols (refs.39,40,41),



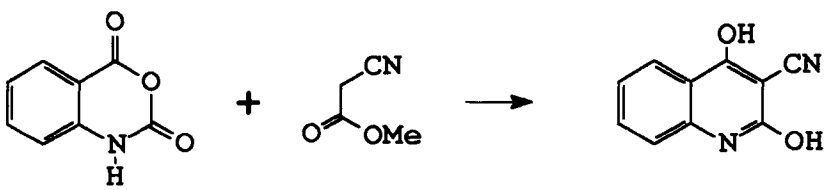
one of which shown (ref. 40) undergoes ring cleavage into a variety of related resorcinols, a procedure reminiscent of the classical conversion of dehydroacetic acid into 5-methylresorcinol (ref.38).

(iii) Bicyclic 1,3-Dihydroxy Compounds

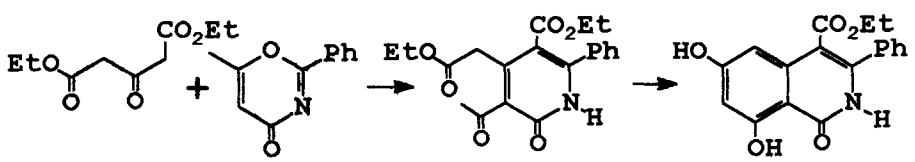
2,4-Dihydroxy-5-methylphthalide, a synthetic precursor for mycophenolic acid has been produced in an overall yield of 20% from the isoxazoline shown, used in a masked form, in three reaction stages (ref.42).



3-Cyano-2,4-dihydroxyquinoline has been simply obtained from isatoic anhydride by reaction with methyl cyanoacetate in dimethylformamide containing triethylamine by stirring at 25-30°C during 1 hour, followed by reaction at 78°C for 2 hours. The mixture was then heated with sodium hydroxide in an autoclave at 150°C (275psi.) for 3 hours to afford the product in 88% yield (ref.43)



4-ethoxycarbonyl-1,6,8-trihydroxy-3-phenylisoquinoline has been synthesised from diethyl acetonedicarboxylate and 6-methyl-1,3-oxazin-4-one in THF containing potassium t-butoxide by reaction at ambient temperature over 16 hours with formation of an intermediate 2-pyridone in 90% yield.



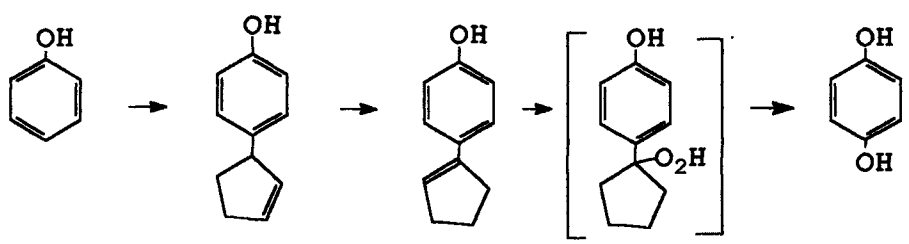
This upon treatment with ethanolic sodium ethoxide overnight and then acidification with hydrochloric acid gave the product in 96% yield (ref.44)

9.2.4. 1,4-Dihydroxybenzenes (Hydroquinones) and their Derivatives

(i) Monocyclic 1,4-Dihydroxy Compounds

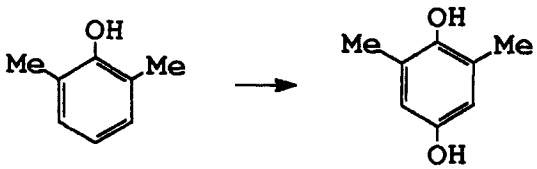
Classical diazotisation methods for substituted hydroquinones have been improved. Thus 2,3-dimethyl-4-aminophenol in 50% aqueous sulphuric acid solution containing acetone was treated dropwise with aqueous sodium nitrite at ambient temperature and the isolated diazonium salt together with sodium sulphate, after being washed with acetone, was suspended in 50% aqueous sulhuric acid and gradually added to a boiling mixture of the same acid and toluene to afford after cessation of nitrogen evolution and cooling of the mixture to 5°C, a 77% yield of 2,3-dimethyl-1,4-dihydroxybenzene (ref.45).

An autoxidative procedure has been described by the initial alkylation of phenol with cyclopentadiene in the presence of phosphoric acid at ambient temperature giving 4-(cyclopenten-2-yl)phenol, in more than 80% yield followed by isomerisation in 91% yield to the 1-isomer during 2 hours in refluxing benzene solution with a catalytic quantity of dichlorobis(benzonitrile)palladium(II). The conjugated product with 30% hydrogen peroxide and hydrochloric acid upon stirring at 50°C for 3 hours afforded 1,4-dihydroxybenzene in 92% yield accompanied by cyclopentanone (ref.46).

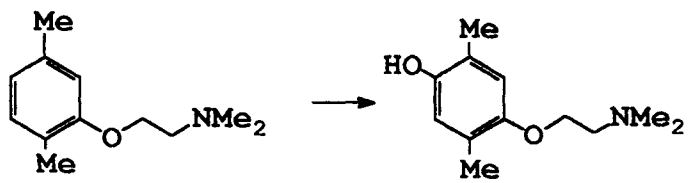


2,6-dimethylphenol has been converted to 2,6-dimethylhydroquinone. Thus the

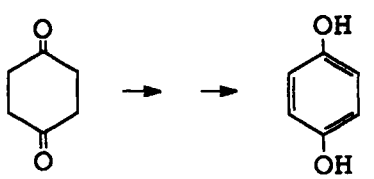
complex $[(Ce_2L)(DMSO)_5]2DMSO$, prepared from ammonium ceric nitrate $(NH_4)Ce(NO_3)_6$ and 4-tert-butylcalix(8)arene in DMSO, and 2,6-dimethylphenol in acetonitrile were treated with hydrogen peroxide at ambient temperature during 5 hours to give the hydroquinone in 44% yield (ref.47).



In an alternative procedure to autoxidation, mesitylene iodosoacetate has been used for the oxidation of 2-dimethylaminoethyl 2,5-dimethylphenyl ether to 2-dimethylaminoethyl 4-hydroxy-2,5-dimethylphenyl ether (ref.48). The starting phenol in acetic anhydride containing mesitylene iodosoacetate was treated slowly below 10°C with sulphuric acid and after a reaction time of approximately 18 hours the mixture was quenched at 0°C with water and, following a work-up involving addition of ether and cuprous chloride, the product was isolated in 61% yield.



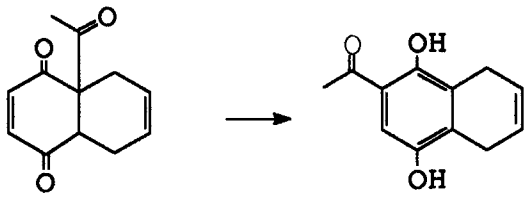
As with the similar formation of catechol and resorcinol, cyclohexane-1,4-dione can be converted into 1,4-dihydroxybenzene in high yield by treatment with acetic anhydride and inorganic acids (ref.49).



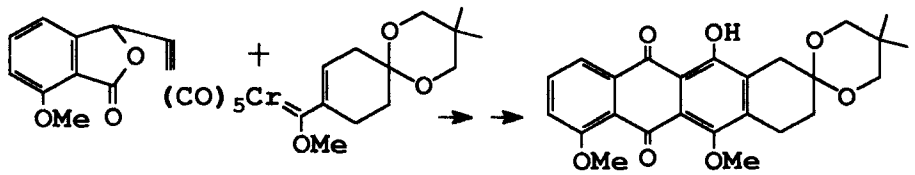
(ii) Bicyclic and Polycyclic 1,4-Dihydroxy Compounds

In the bicyclic series the Diels-Alder adduct of 2-acetyl-1,4-benzoquinone and

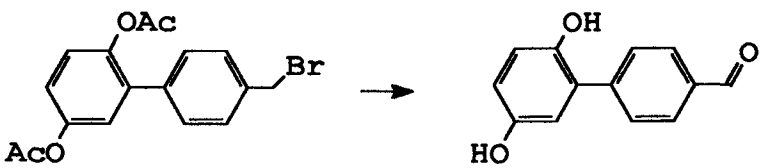
buta-1,3-diene in xylene solution containing a little pyridine upon heating at 140°C during 3 hours, isomerised in 85% yield to 2-acetyl-1,4-di-hydroxy-5,8-dihydronaphthalene (ref.50).



By the reaction in tetrahydrofuran at 45°C over 12 hours of 3-ethynylphthalide and a pentacarbonyl chromium carbene complex of the cyclohexenone ketal depicted, followed by treatment of the product with ferric chloride-dimethylformamide (2 moles) a 74% yield of an anthracycline-type structure was obtained (ref.51).

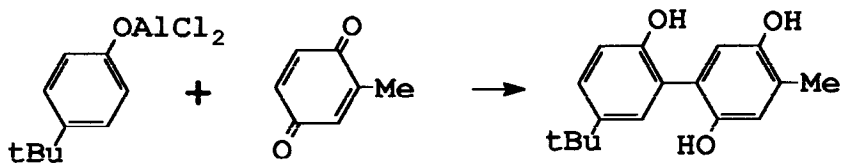


In the application of the Sommelet reaction to 4'-bromomethyl-2,5-diacetoxydiphenyl with hexamethylenetetramine in acetonitrile by refluxing for 6 hours (under nitrogen) followed by solvent removal and hydrolysis for 1 hour in aqueous methanol containing concentrated hydrochloric acid, 4'-formyl-2,5-dihydroxybiphenyl was obtained in 61% yield (ref.52).

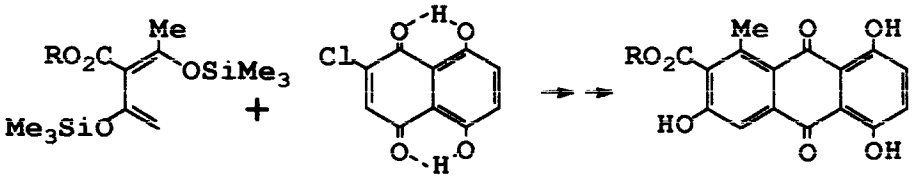


2,2',5'-Trihydroxybiphenyls have been synthesised by coupling benzo-1,4-quinones with phenolates. Thus the dichloroaluminium salt of 4-tert-butylphenol (formed by reaction of the phenol in carbon disulphide with aluminium chloride) upon addition to the 2-methyl-benzo-1,4-quinone/ aluminium chloride (1:2)

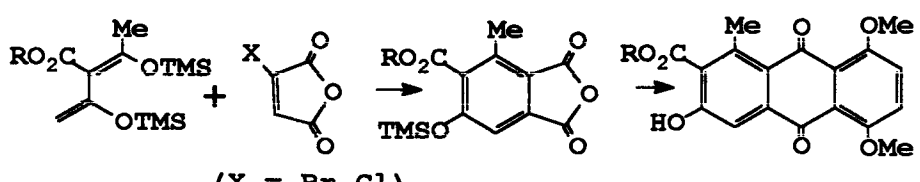
adduct in carbon disulphide and reacted over 4 hours at ambient temperature afforded after acidification, 5-tert-butyl-2,2',5'-trihydroxy-4'-methylbiphenylin 83% yield (ref. 53).



In the polycyclic field a number of anthraquinones with 1,4-dihydroxy groups have been synthesised by Diels-Alder reactions. 2-Chloronaphthazarin with the bis-trimethylsilyldiene shown, 2,4-bis-trimethylsiloxy-3-alkoxycarbonylpenta-2,4-diene (R = Me, Et, i-Pr) affords the corresponding alkyl 1-methyl-3,5,8-trihydroxy-anthraquinone-2-carboxylate (alkyl 6-deoxykermesates) in high yield (ref. 54).



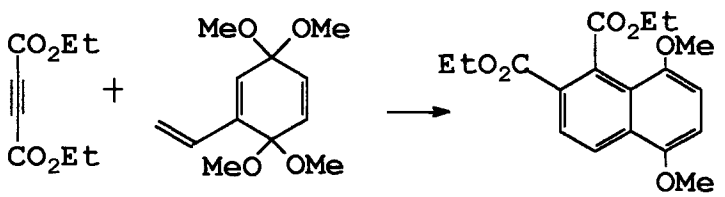
Similar structures can be realised in low yield from the Friedel-Crafts reaction of 1,4-dimethoxybenzene with substituted phthalic anhydrides (R = Me, Et, i-Pr), which were obtained by the appropriate Diels-Alder synthesis. The acylations were effected in the presence of boron trifluoride etherate as catalyst, followed by demethylation of the product (ref.55).



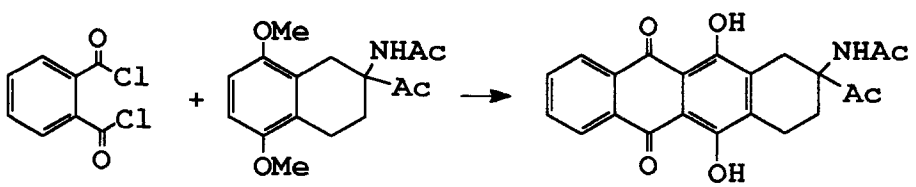
(X = Br, Cl)

The naphthalene derivative shown, a possible intermediate for synthesis in the polycyclic field has been obtained by the Diels-Alder reaction between a vinyl bis-ketal derivative of cyclohexa-2,5-diene-1,4-dione and diethyl acetylene-

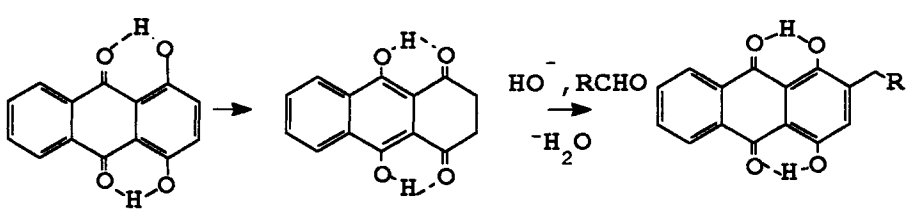
dicarboxylate (ref.56).



Tetracyclic structures emanate in the following way. A mixture of phthalic acid chloride and L-2-acetyl-2-amino-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene in dichloromethane treated during 3 hours at ambient temperature with aluminium chloride gave after solvent removal and work-up with aqueous oxalic acid, L-9-acetyl-9-acetylamino-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacene-dione in 90% yield (ref.57).



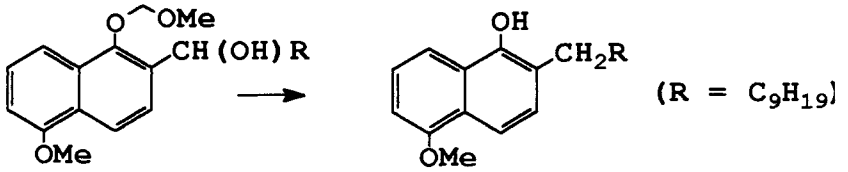
In the tricyclic anthraquinone series, 1,4-dihydroxy-9,10-anthraquinone in the leoco form undergoes aldol addition with an aldehyde followed by loss of water from the aldol intermediate and isomerisation to give the 2-alkyl derivative depicted (ref.58,59).



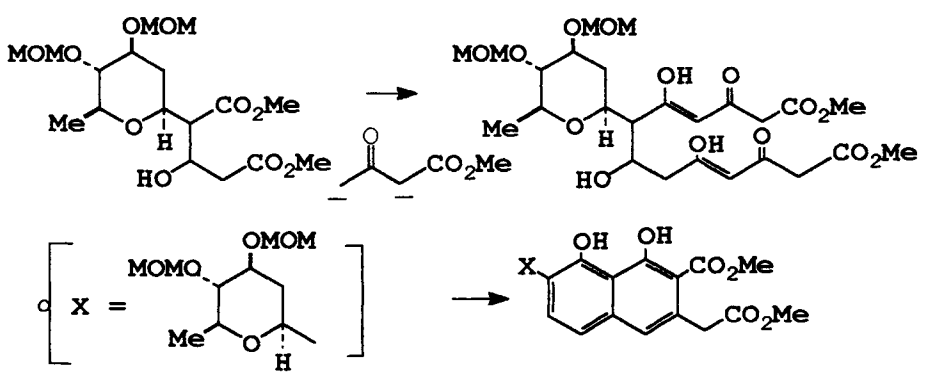
9.2.5 Polycyclic Dihydroxy Compounds

Several dihydroxy compounds lying outside the preceding three classes are described in this section. Selective removal of the methoxymethyl group by treatment of 2-(1-hydroxydecyl)-5-methoxy-1-methoxymethoxynaphthalene and

triethylamine in dichloromethane with trifluoracetic acid in dichloromethane at ambient temperature by stirring for 2 hours followed by quenching in sodium bicarbonate solution afforded 2-decyl-5-methoxy-1-naphthol (ref.60). There is a parallel with the previous example.



In continuation of studies on the aromatisation of synthetic polyketides, aryl C-glycosides in the 1,8-dihydroxynaphthalene series were obtained by an approach modelled on biomimetic lines. Thus diethyl 3-hydroxyglutarate (obtained from L-rhamnal) in tetrahydrofuran was added at 0°C under nitrogen to the lithium-sodium dianion of methyl acetoacetate (15 moles) in tetrahydrofuran/hexamethyl phosphoric triamide (1:1), the mixture was stirred at ambient temperature for 2.5 hours and after acidification the recovered crude diethyl 3,5,9,11-tetraoxo-tridecanedioate was refluxed for 2.5 hours in methanolic solution containing calcium acetate to afford the product shown in 40% yield as a single isomer, after O-acylation, purification and O-deacylation (ref.61). (MOM = methoxymethyl)



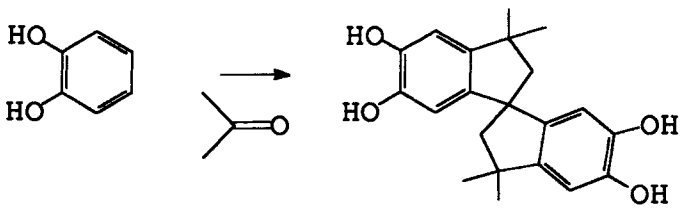
9.3 Reactions of Dihydric Phenols

9.3.1. 1,2-Dihydric Phenols (Catechols) and their Derivatives

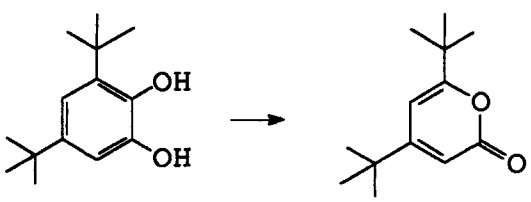
(i) 1,2-Dihydroxy Compounds

An unusual structure, 5,5',6,6'-tetrahydroxy-3,3,3',3'-tetramethyl-1,1'-spiro-

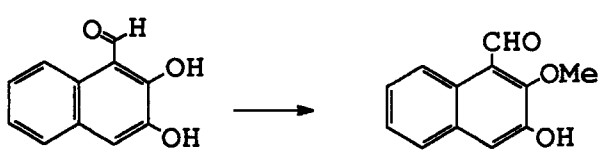
bis(indan) has been obtained with a yield of 87% in a remarkably simple manner from the reaction of catechol and acetone in glacial acetic acid containing hydrogen bromide (ref.62).



The majority of the reactions of catechols relate to their monoalkyl and dialkylethers (guaiacol and veratryl systems respectively) and remarkably few to the parent dihydric phenol which alone is prone to facile oxidation. 3,5-di-tert-Butylcatechol with a catalytic quantity of dichloro tris(triphenyl-phosphine)ruthenium(II) in 1,1,2,2-tetrachlorethane upon stirring in an oxygen atmosphere at ambient temperature for 15 hours furnished the corresponding 2H-pyran-1-one (ref.63).

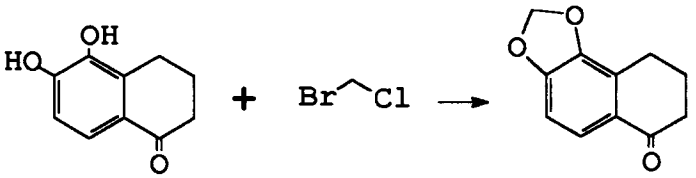


In the methylation of 2,3-dihydroxy-1-naphthaldehyde with iodomethane and potassium carbonate the 2-methyl ether is formed, a reaction attributable to the ionisation of the 2-hydroxyl group following the breaking of stabilising hydrogen-bonding and the adoption of the preferred conformation shown of the formyl group (ref.64).



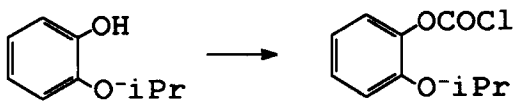
The methylenedioxy compound indicated was derived in 92% yield from 5,6-dihydroxy-1-tetralone in dimethylformamide containing caesium carbonate

by the addition of chlorobromomethane and heating of the mixture at 110°C during 2 hours (ref.65).

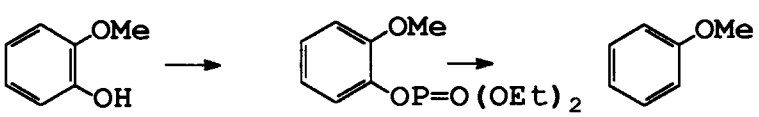


(ii)Mono O-derivatives of 1,2-Dihydroxy Compounds

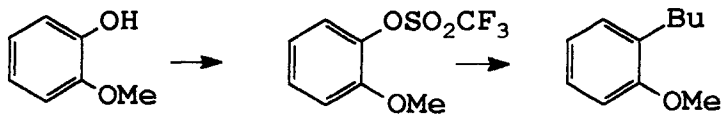
Reactions of the hydroxyl group in this group of compounds comprise chlorocarbonylation, its reduction, substitution by an alkyl group, and methylation, as shown in the following examples.
Moderately pure 2-isopropoxyphenol, containing a small amount of triphenylphosphonium choride, when gradualy treated at 118-150°C with phosgene afforded 2-isopropoxyphenyl chloroformate in 97% yield with recoverable starting material (ref.66).



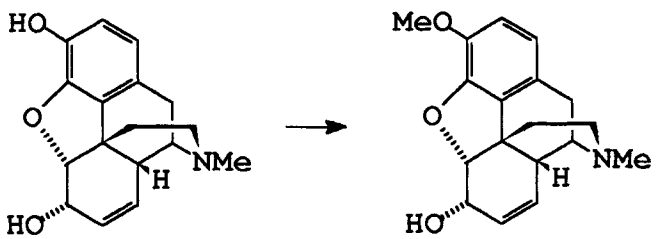
Electrochemical dehydroxylation of 2-methoxyphenol by way of the diethyl phosphate, prepared by standard procedures, in dimethylformamide containing tetraethylammonium 4-toluenesulphonate as supporting electrolyte in a divided cell (at -2.6 to -2.7 volts) gave anisole in 61% yield (ref.67).



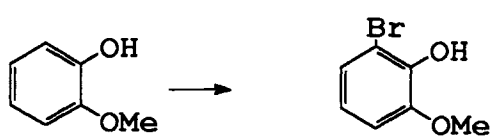
Replacement of the hydroxyl group in 2-methoxyphenol by an n-butyl group was achieved in the following way. To $Li_2Cu(CN)Bu_2$, prepared by dropwise addition of n-butyllithium in tetrahydrofuran at -78°C to cuprous cyanide in tetrahydrofuran and warming of the mixture to -20°C, 2-methoxyphenyl trifluoromethanesulphonate in tetrahydrofuran was gradually added after the reagent mixture had been recooled to -70°C. Reaction was completed over 40 hours at -20°C to afford 2-n-butylanisole in 50% yield (ref.68).



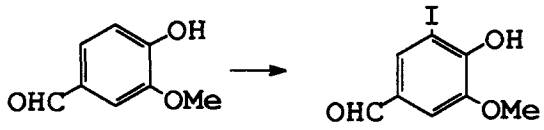
Morphine in toluene solution containing potassium carbonate and trimethylphenylammonium chloride followed by stirring of the mixture at 45-120°C during 25 hours gave, after removal of toluene, acidification to pH 5 and removal of dimethylaniline, codeine in 99% yield (ref.69). There is an element of rediscovery in this since the author recalls an exactly similar method being investigated successfully in 1945 by May and Baker Ltd. (now Rhone Poulenc).



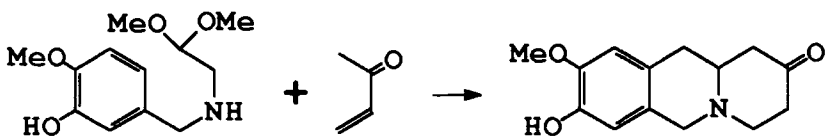
Reactions of the aromatic ring in dihydric phenols such as halogenation, cyclisation and oxidative dimerisation are exhibited in the following examples. Regiospecific halogenation of guaiacol has been effected. 2-Methoxyphenol in diisopropyl ether at 0°C upon dropwise treatment with N,N-dibromo-tert-butylamine in the same solvent and reaction for 3 hours gave after removal of excess reagent with aqueous sodium sulphite and dilute sulphuric acid, 6-bromoguaiacol in 75% yield (ref.70).



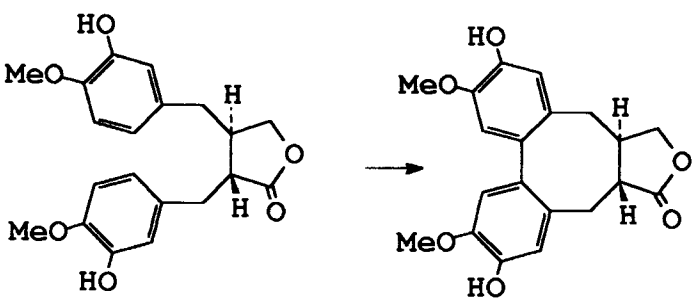
Iodination of vanillin (4-hydroxy-3-methoxybenzaldehyde) in dimethylformamide containing sodium iodide gave 5-iodovanillin in 94% yield by treatment of the solution at 25°C with chloramine T and stirring of the mixture for 1 hour (ref.71).



Reaction at the 4-position of a guaiacyl system through electrophilic substitution followed by a ring closure involving an enamine was achieved in the synthesis of 8-hydroxy-9-methoxy-4,6,11,11a-tetrahydro-1H-benzo[b]quinolizin-2(3H)-6-one in 68% yield from the acetal shown with methyl vinyl ketone in ether solution by interaction at ambient temperature during 24 hours (under nitrogen) followed by solvent removal and treatment with concentrated hydrochloric acid at 100°C for 30 mins (ref.72).



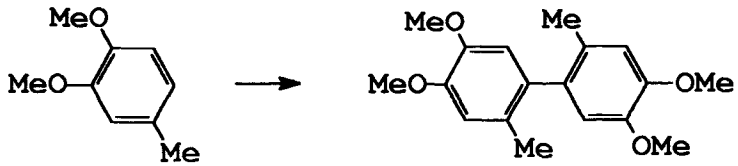
Oxidative dimerisation of a guaiacyl system, namely prestegane B, in dichloromethane containing boron trifluoride etherate was achieved in 80% yield by addition to a stirred suspension of ruthenium dioxide dihydrate in dichloromethane containing triflic acid/triflic anhydride (in the proportions 8:2:1) at 0°C followed by reaction for 3 hours (ref.73).



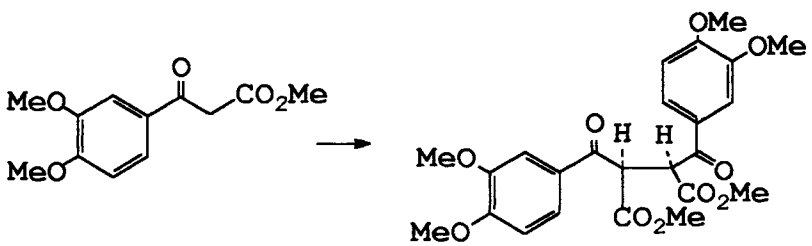
(iii) Di O-alkyl Derivatives of 1,2-Dihydroxy Compounds

Because of their interest as natural products 1,2-dimethylether derivatives from benzenoid and polycyclic compounds have been submitted to a variety of

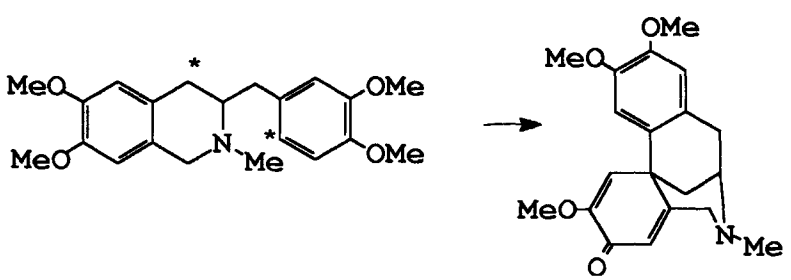
reactions including oxidative dimerisations, other intramolecular oxidative reactions, carboxylations, acylations and alkylations, miscellaneous cleavage reactions. They have been used to effect asymmetric syntheses.
In the area of oxidative dimerisation, a solution of 3,4-dimethoxytoluene in dichloromethane was added to silica gel impregnated with ferric chloride. After the solvent had been removed and the residue left for 1 hour, 2,2'-dimethyl-4,4',5,5'-tetramethoxybiphenyl was formed in 95% yield (ref.74).



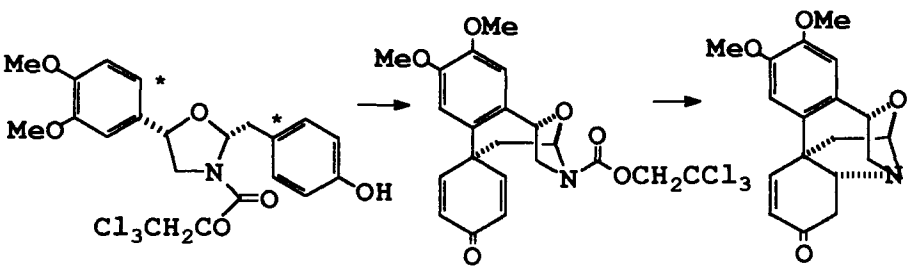
Oxidative dimerisation at the side-chain has been described as relevant to the synthesis of lignans (ref.75). Methyl 3,4-dimethoxybenzoylacetate in refluxing aqueous acetonitrile treated with potassium persulphate and a small amount of copper sulphate in an inert atmosphere produced after several hours (monitored by TLC), the dimer shown (racemate:meso; 3:1) in 58% yield.



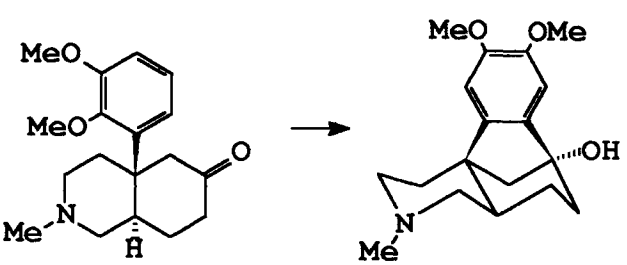
1,2-Dialkoxybenzenes and benzenecrown ethers when submitted to mixed anodic trimerisation afford triphenylenes which possess one or two complexing sites (ref.76). Intramolecular oxidative reactions familiar in the area of morphine



chemistry have been applied to 3-benzylisoquinolines (ref.77). Thus, in the example, 2-methyl-6,7-dimethoxy-3-(4'-veratryl)-1,2,3,4-tetrahydroisoquinoline in trifluoroacetic acid by dropwise treatment during 5 mins.under nitrogen at -15 to -10°C with vanadium oxyfluoride gave, in 85% yield, after reaction for 1 hour the six-membered ring spiro compound shown, reaction proceeding at the * positions rather than affording larger ring coupling products arising from ortho positions in the dimethoxybenzyl group.
Another spiro compound has been obtained from the oxazolidine illustrated by the use of essentially the same reagent (ref.78). N-3-trichloroethoxycarbonyl-(2R)-4-hydroxybenzyl-(5S)-3,4-dimethoxyphenyloxazolidine in dichloromethane upon treatment with vanadium oxyfluoride in trifluoroacetic/trifluoroacetic anhydride at -78 to-10°C afforded the para-para coupling product.

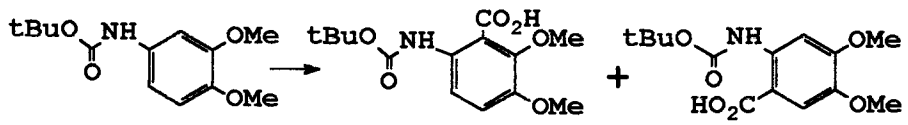


The trans oxazolidine did not react in the same way. Another intramolecular oxidation involving the 4-position of a veratryl system and the transformation of a carbonyl group into a tert-alcohol centre is shown in the conversion of trans-4a-(2,3-dimethoxyphenyl)-2-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydro-isoquinoline in ether at 0°C quantitatively into a tetracyclic structure by treatment with 75% sulphuric acid followed by quenching after 36 hours by diluting in ice/ammonia solution (ref.79).

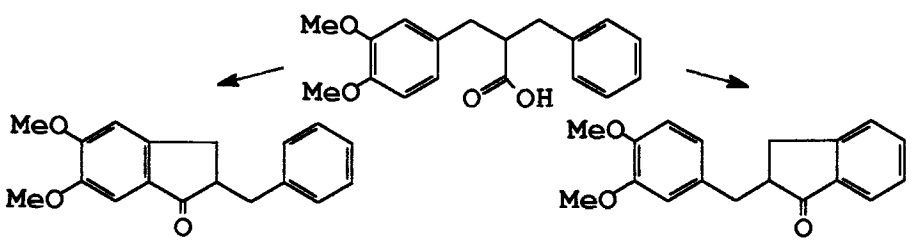


The tert-butyl carbamate ester of 4-amino-1,2-dimethoxybenzene (veratrylamine) was lithiated with n-butyllithium and carboxylated regiospecifically to afford a combined 70% yield of the 3- and the 5-carboxylic acids (20:1) while with

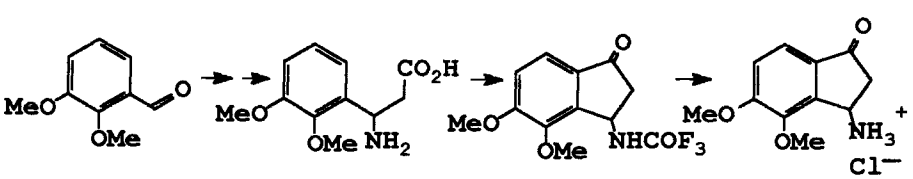
tert-butyllithium a mixture of the isomers (7:3, respectively) formed in 66% yield (ref.80).



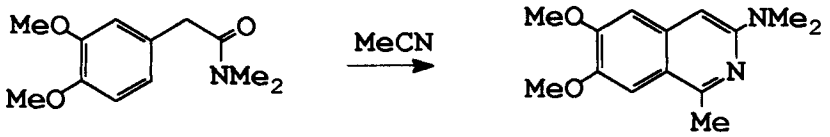
Acylation and alkylation reactions are illustrated in the following examples. Two modes of cyclisation of 2-(3,4-dimethoxybenzyl)-3-phenylpropionic acid in dichloromethane, after conversion to the acid chloride, have been described by reaction with oxalyl chloride in dimethylformamide during 12 hours (ref.81). After cooling of the starting solution to -15°C, aluminium bromide (in 100mole% proportion) in dichloromethane for 24 hours gave 2-benzyl-5,6-dimethoxyindane-1-one in 78% yield, while with 300 mole% reagent over a longer reaction period an 86% yield of 2-(3,4-dimethoxybenzyl)indan-1-one resulted. In the latter case some demethylation occurred.



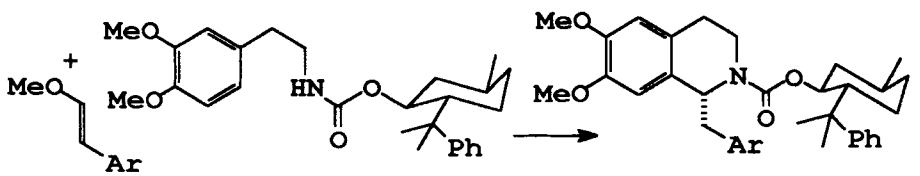
Indanone formation from the amino acid derivative shown in trifluoroacetic acid solution with 1 mole of trifluoroacetic anhydride occurred in 95% yield after refluxing for 3 hours (ref.82).



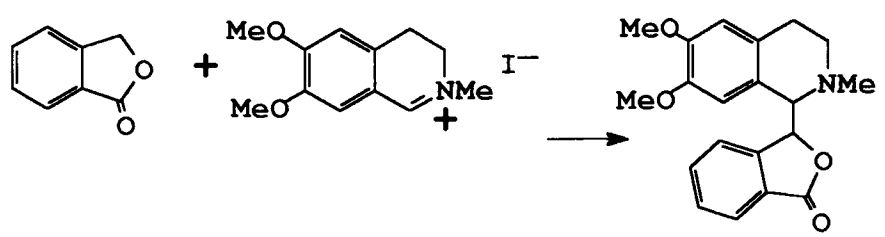
Reaction at the 4-position of a veratryl ring followed by cyclisation has been observed. To 2-(3,4-dimethoxyphenyl)-N,N-dimethylacetamide in acetonitrile, phosphorus oxychloride was added and after refluxing for 6 hours more reagent was introduced and refluxing extended for 2 hours producing a 56% yield of 3-dimethylamino-6,7-dimethoxy-1-methylisoquinoline (ref.83).



A 1-benzyl analogue of the preceeding structure was obtained by way of an asymmetric Pictet-Spengler ring closure of the chiral carbamate shown (a derivative of (-)-8-phenylmenthol) with an enol methyl ether of 3,4-dimethoxyphenylacetaldehyde by treatment at ambient temperature with phosphorus oxychloride and reaction during 3 hours resulting in a 68% yield (ref.84).

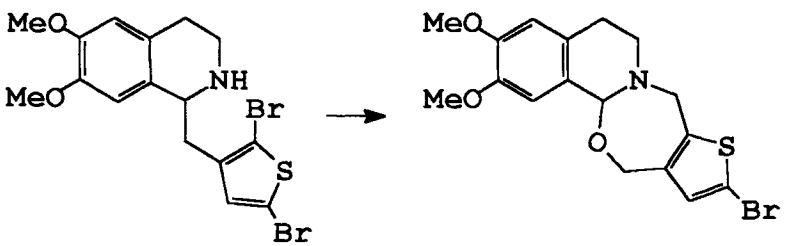


Alkylation at a benzylic position in the ring adjoining a veratryl system has been reported. The carbanion from phthalide in tetrahydrofuran by addition to lithium diisopropylamide in tetrahydrofuran at -70°C was reacted after 20mins. at -35°C by introducing the suspension into 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium iodide in the same solvent. After reaction with stirring at ambient temperature overnight, 6,7-dimethoxy-2-methyl-1-phthalidyl-1,2,3,4-tetrahydroisoquinoline was formed in 40% yield as a mixture of diastereoisomers (ref.85).

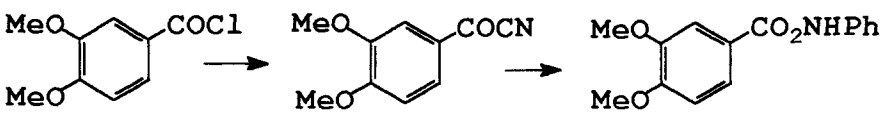


Reaction at nitrogen followed by cyclisation has also been reported in a dimethoxytetrahydroisoquinoline. The starting material illustrated upon reaction with 37% formalin solution in glacial acetic acid by refluxing for 1 hour was considered to have given the oxazepinoisoquinoline instanced (in 91% yield)

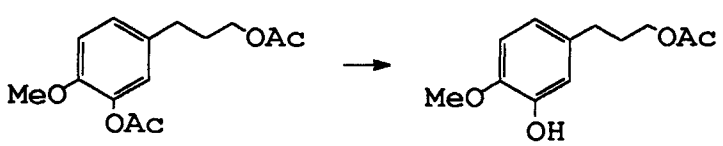
rather than the 1-benzyl compound (ref.86).



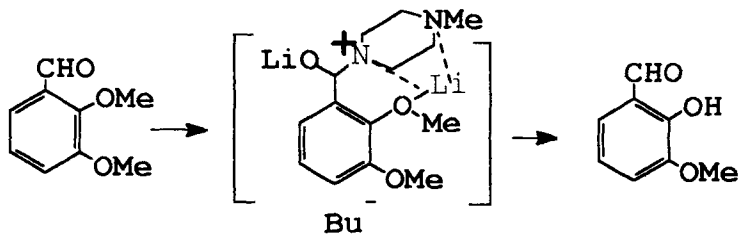
In the simple benzenoid compound 3,4-dimethoxybenzoylcyanide in ether, benzene, toluene or dichloromethane, reaction with phenylhydroxylamine occurred at ambient temperature to give O-(3,4-dimethoxybenzoyl)-N-phenylhydroxylamine in 90% yield accompanied by HCN evolution (ref.87).



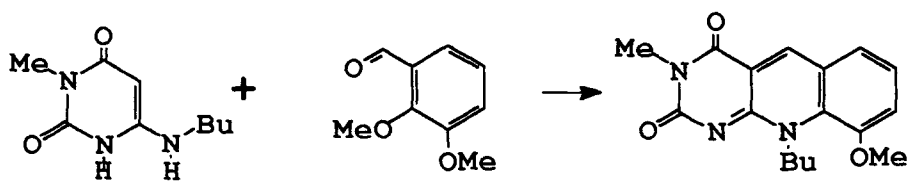
Several selective cleavage reactions (classed as miscellaneous reactions in the introduction to this section) have been described. Thus, preferential O-deacetylation of a phenyl acetate in the presence of an alkyl acetate occurred when 3-(4-acetoxy-3-methoxyphenyl)propylacetate was allowed to stand in pyrrolidine (or pyrrolidine in dichloromethane) at ambient temperature for 3 mins. followed by acidic quenching, to give 3-(3-methoxy-4-hydroxy)propylacetate in more than 80% yield (ref.88).



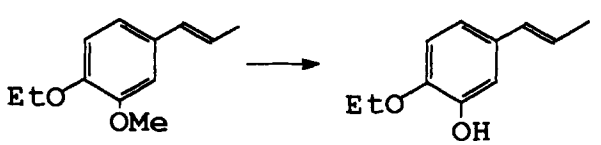
2,3-Dimethoxybenzaldehyde in toluene solution was regiospecifically demethylated by treatment initially during 20 mins. with lithium N-methylpiperazide (1 mole) at ambient temperature, followed by addition of butyllithium (1 mole) and warming to 65°C. TLC monitoring and acidic quenching afforded 3-methoxy-2-hydroxybenzaldehyde (o-vanillin) in 55% yield. Methoxyl and ethoxy groups responded but not tert-butoxy groups (ref.89).



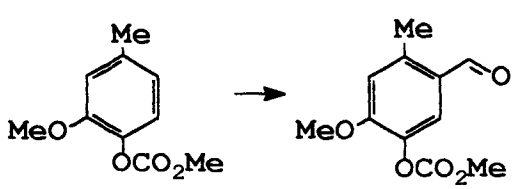
2,3-Dimethoxybenzaldehyde has been employed in the synthesis of deazaflavins (pyrimidoquinolines). Thus, 6-butylamino-3-methyluracil with the aldehyde in dimethylformamide suspension after being heated for 4 hours afforded in 70% yield, 10-butyl-9-methoxy-3-methyl-5-deazaflavin (ref.90).



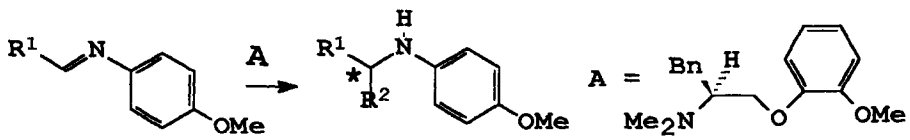
Preferential demethylation of the methoxyl group in O-ethylisoeugenol, giving a 60% yield of the phenolic compound shown, occurred upon addition to 1,2-dihydroxyethane containing potassium fluoride-alumina at 150°C with continued heating at 210°C during 5 hours (ref.91).



3-Methoxy-4-methoxycarbonyoxytoluene at 0°C in dichloromethane upon treatment with titanium tetrachloride and then dichloromethyl methyl ether both in CH_2Cl_2 over 30mins. by stirring for a few mins. with hydrochloric acid gave 6-formyl-4-methoxy-5-methoxycarbonyloxy-2-methylbenzaldehyde in 97% yield (ref.92).



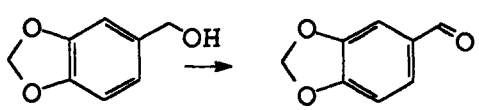
The reaction of methyllithium with the 4-methoxyphenylimine of 1-naphthaldehyde in the presence of a chiral ligand derived from a catechol dialkyl ether as an asymmetric controller (A) afforded the corresponding 1,2-addition product as an optically active amine in 70% ee (ref.93). A solution of methyllithium (R^2Li) (2.0 mmol) in diethyl ether was added at -100°C to a solution of the imine (R^1 = 1-Naph; 1.0 mmol) and ligand A (2.6 mmol) in toluene and the reaction mixture was then stirred for 1 hour at the same temperarture and finally quenched with water.



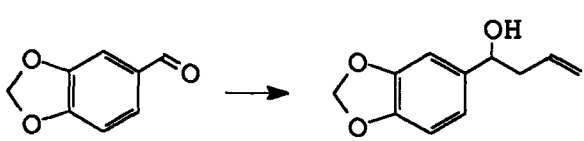
(iv) Methylenedioxy Derivatives of 1,2-Dihydroxy Compounds

In this quite important group, side-chain and etherification reactions are considered first in benzenoid compounds and then reactions of more complex methylenedioxy compounds.

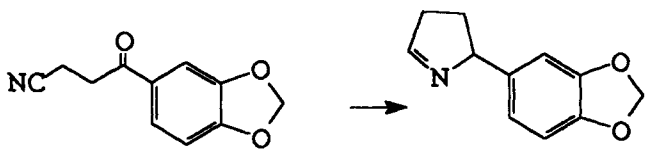
To 4-(dimethylamino)pyridinium chromate (5 mole), obtained from 4-dimethylaminopyridine and chromium trioxide in 1.65M hydrochloric acid, in dichloromethane solution 3,4-methylenedioxybenzyl alcohol was introduced in one portion. After stirring for 15 hours, 3,4-methylenedioxybenzaldehyde was isolated in 98% yield. The reagent is selective for allylic and benzylic alcohols (ref.94).



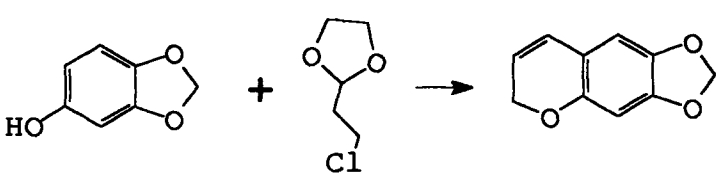
The reaction of allylic Grignard reagents with aldehydes to produce allylic carbinols does not always proceed smoothly. In the reaction of 3,4-methylene dioxybenzaldehyde with allyl alcohol (1.5-3.0 moles) at ambient temperature



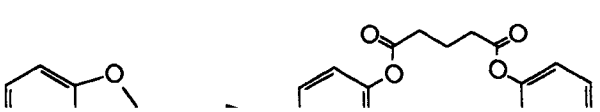
over 39 hours, catalysed by $Pd(Cl)_2(PhCN)_2$ in the presence of stannous chloride (3 moles) in 1,3-dimethylimidazolidine, the allylic alcohol was produced in 88% yield (ref.95). Charge reversal of the π-allylpalladium complex is facilitated in this system which is also applicable to ketones although with ketoaldehydes the formyl group reacts preferentially.
In the hydrogenation of 4-(3-cyano-1-oxopropyl)methylenedioxybenzene in methanol containing freshly-prepared Raney nickel for 8 hours at 100°C, ring closure afforded a 90% yield of 2-(benzo[1,2-d]-[1,3]dioxo-5-yl)pyrroline (ref.96).



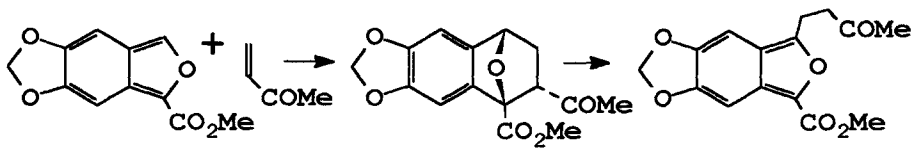
Etherification followed by a ring closure is shown in the succeeding example. To 4-hydroxymethylenedioxybenzene (sesamol) in tetrahydrofuran which had been treated at 0°C with potassium hydride in tetrahydrofuran and reacted at ambient temperature, tetra-n-butylammonium iodide and then a solution of 2-(2-chloroethyl)-1,3-dioxolane in tetrahydrofuran were added. After refluxing for 3 days, the intermediate ether-acetal, formed in 81% yield, was cyclised in benzene containing 4-toluenesulphonic acid by refluxing for 12 hours to furnish, after an alkaline work-up treatment, 6,7-methylenedioxy-2H-benzopyran in 60% yield (ref.97).



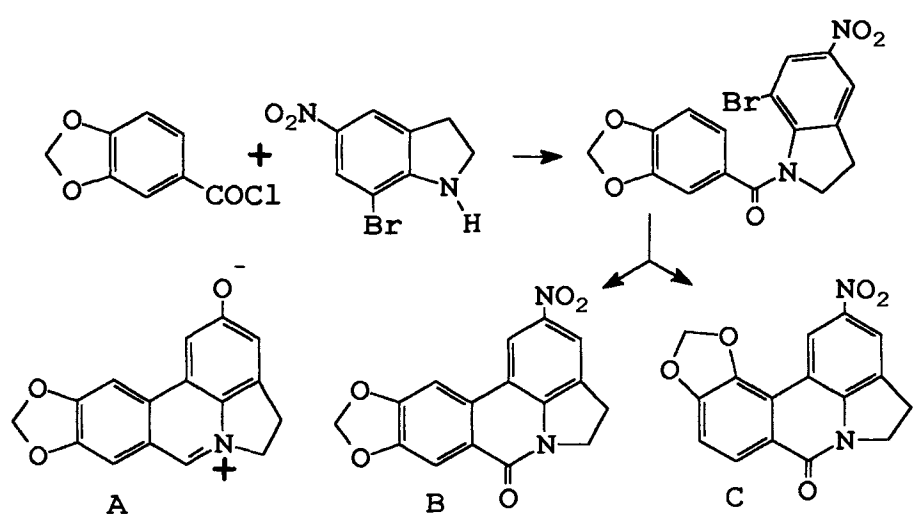
Methylenedioxybenzene (1,3-benzodioxole) in acetonitrile containing sodium iodide (2.5 moles) has been stated to give the crown ester, 8,9,19,20-tetrahydro-7H,18H-dibenzo[b,k]-1,7,10,16-tetraoxacyclooctadecane-6,10,17,21-tetraone in 51% yield by dropwise treatment with glutaroyl chloride (1.2 mole) initially at 0°C and subsequently by reaction at ambient temperature



during 24 hours (ref.98). By the use of 1,3-benzoxathioles and with magnesium bromide as catalyst, dithia analogues are obtained.
Reactions of more complex methylenedioxybenzene derivatives have been examined. The bicyclic compound shown, upon treatment with methyl vinyl ketone in dichloromethane afforded a regiospecific Diels-Alder adduct which, in the same refluxing solvent containing a catalytic quantity of methanolic sulphuric acid, produced a 95% yield of 1-carbonylmethoxy-3-(3-oxobutyl)-5,6-methylenedioxyisobenzofuran (ref.99).

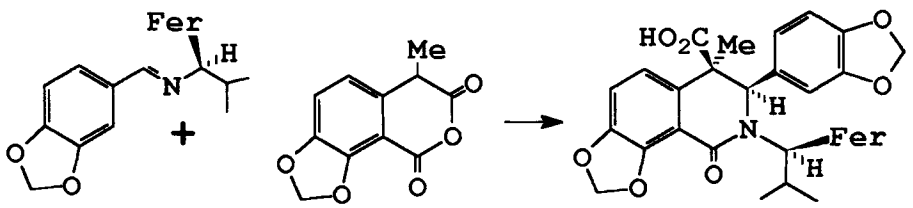


The benzoyldihydroindole shown formed by the reaction of 3,4-methylenedioxybenzoyl chloride and 7-bromo-5-nitrodihydroindole in pyridine at 100°C upon reaction at 155°C in dimethyl sulphoxide containing potassium carbonate and BTAC was cyclised to the isoquinolone derivatives (B) and (C) (1:1) in 27% yield. This ring closure was considered to proceed by way of a radical intermediate, (ref.100) and constituted a route to the alkaloid ungeremine (A) after three more steps on compound (B) consisting of the conversions, $-NO_2 \rightarrow -NH_2 \rightarrow N_2BF_4 \rightarrow OH$.

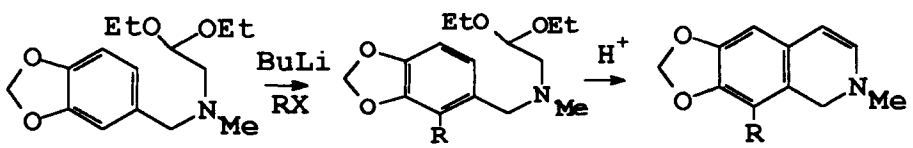


The methylenedioxy methylhomophthalic anhydride derivative shown, by interaction in refluxing benzene during 82 hours with the chiral azomethine

R(-)-N-piperonylidene-1-ferrocenyl-2-methylpropylamine afforded (3R,4R)(-)-N-[(R)-1-ferrocenyl-2-methylpropyl]-4-carboxy-3,4-dihydro-4-methyl-7,8-(methylenedioxy)-3-[3,4-(methylenedioxy)phenyl]-1(2H)-isoquinoline in 81% yield (ref.101). The ring system is present in the alkaloid (+)-corynoline.

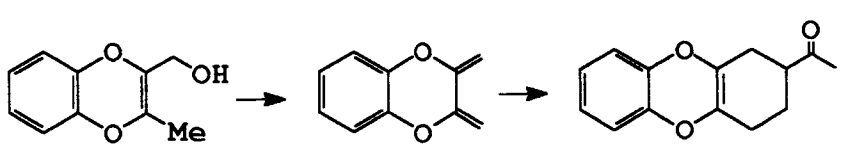


Regiospecific lithiation of the methylenedioxy benzylamine indicated followed by quenching with an electrophile (RX) gave a derivative which could be cyclised by acidic treatment to an 8-substituted isoquinoline (ref.102).



(v) Dioxin derivatives

The dioxin system (effectively a 1,2-ethenodioxy structure) is derivable from catechol and the Diels-Alder reaction shown between one such compound namely 2,3-dimethylene-2,3-dihydro-1,4-benzodioxin and methyl vinyl ketone at 70°C for 15 hours a reaction which has enabled a tricyclic compound in the series to be synthesised in 84% yield (ref.103).

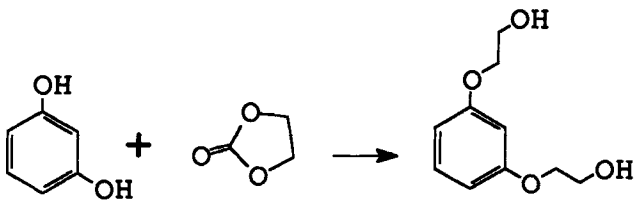


9.3.2. 1,3-Dihydric Phenols (Resorcinols) and their Derivatives

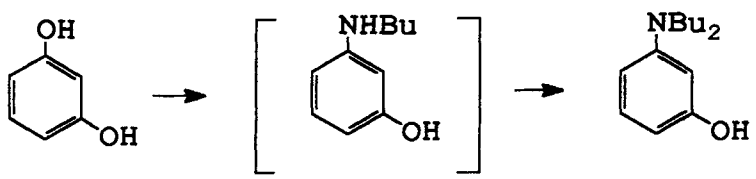
(i) 1,3-Dihydroxy Compounds

In this section the reactions of 1,3-dihydroxybenzene and its derivatives in

forming O-alkyl, C-acyl compounds, C-alkylation leading to bicyclic structures, substitution of the hydroxyl group and of the ring are discussed. The uses of resorcinol and its derivatives have been discussed at length (ref. 104)
In the first group, resorcinol has been reacted with ethylene carbonate (98% purity) in the presence of some triphenylphosphine by heating at 150-170°C for 4.5 hours with loss of carbon dioxide to afford a quantitative yield of the bis(2-hydroxyethyl) ether (ref.105).

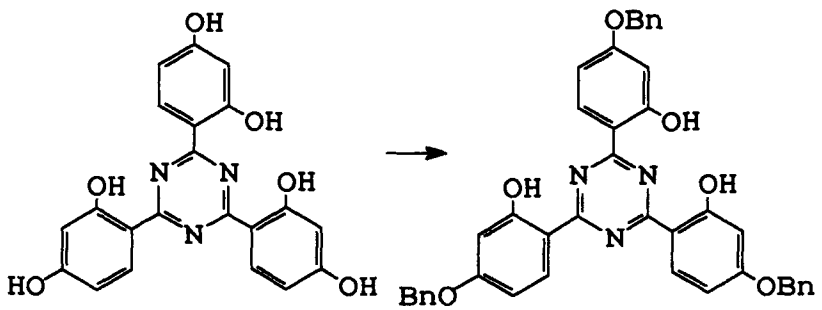


Replacement of an hydroxyl group in resorcinol, most probably through tautomerism and imine formation, has been effected by heating it in an autoclave with 1-aminobutane and a small amount of phosphoric acid at 200°C under pressure (13 bar) for 8 hours. Only the monobutylamino substitution product was obtained but by phase transfer catalysis on the reaction product, with a benzyltrimethylammonium salt, (formed *in situ* from a surfactant and potassium iodide), sodium hydroxide solution and 1-bromobutane for 20 hours at 60-80°C, 3-dibutylaminphenol was produced in 64% yield (ref. 106).



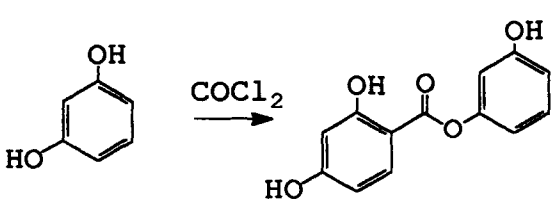
Selective methylation of 2,4-dihydroxyacetophenone in the 4-position has been effected in 90% yield by the addition of lithium carbonate (1.25 moles) and methyl iodide to a dimethylformamide solution and stirring of the suspension for 18 hours at 55°C (ref.107). The method is effective for the selective methylation

of phenolic OH groups having pK_a = or < 8 or in chelated phenolic/enolic instances where the pK_a is approx.10.
In a similar manner 2,4-dihydroxyacetophenone with benzyl tosylate and potassium carbonate in refluxing acetone during 2-3 hours afforded the corresponding 4-benzyl ether in 69% yield (ref.108).
Chelation of one hydroxyl group with a nitrogen atom enabled the other in the resorcinol, 2,4,6-tris(2,4-dihydroxyphenyl)-1,3,5-triazine to monobenzylate in each ring by heating at 65°C during 4 hours in the presence of sodium carbonate to afford the product in 95% yield (ref.109).

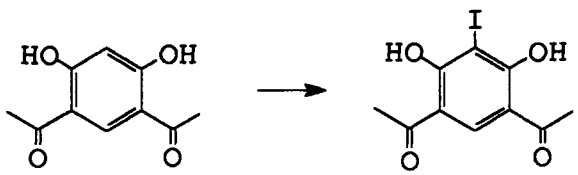


C-Acyl reactions of resorcinol are illustrated by that of resorcinol itself which in glacial acetic acid containing 5% hydrobromic acid gave 2,4-dihydroxyacetophenone whereas traditional reagents and catalysts caused over-reaction. Applied to resorcinol ethers, simultaneous ether cleavage occurred (ref.110).

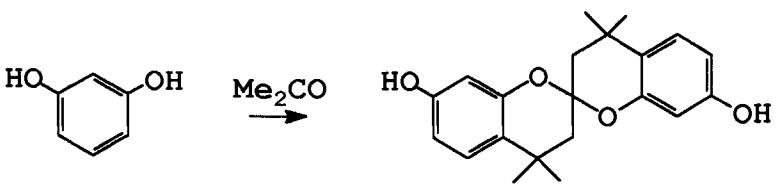
Equimolar proportions of resorcinol and phosgene in nitrobenzene at 100°C



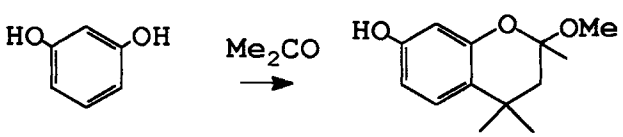
under nitrogen during 10 hours afforded after cooling and work-up a 73% yield of 3-hydroxyphenyl 2,4-dihydroxybenzoate (ref.111).
Iodination of 5-acetyl-2,4-dihydroxyacetophenone (4,6-diacetylresorcinol) was effected in methanol by the addition of phenyliodosodiacetate and potassium hydroxide to give a 75% yield of the monoiodo product shown (ref.112).



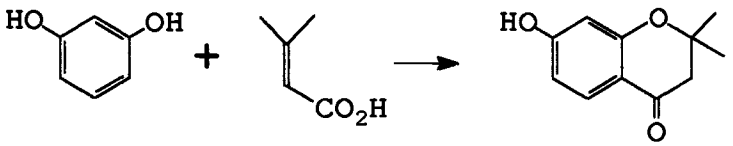
Examples of C-alkylation leading to bicyclic and tricyclic structures are shown in the following reactions. Resorcinol in dichloroethane containing concentrated aqueous sulphuric acid by dropwise treatment at 45°C with acetone during 30 minutes followed by stirring for 2 hours gave the spirochroman derivative in 30% yield (ref.113).



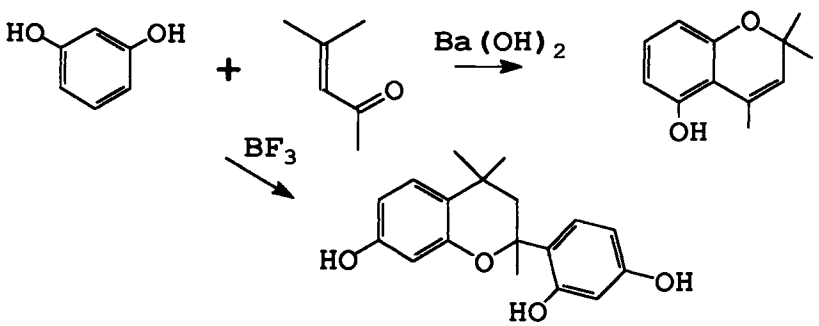
Contrasting with this finding, another group have isolated 7-hydroxy-2-methoxy-2,2,4-trimethylchroman in 17% yield through heating resorcinol with 4 moles of acetone in toluene containing methanol and a little concentrated sulphuric acid for 4 hours at 70°C in an autoclave (ref.114).



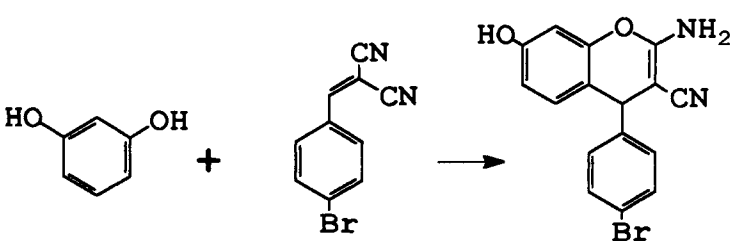
Resorcinol and 3-methyl-2-butenoic acid added simultaneously with rapid stirring to methanesulphonic acid and phosphorus pentoxide at 70°C, with continuance of stirring for 30 minutes, resulted in a 94% yield of 2,2-dimethyl-7-hydroxy-4-chromanone (ref.115).



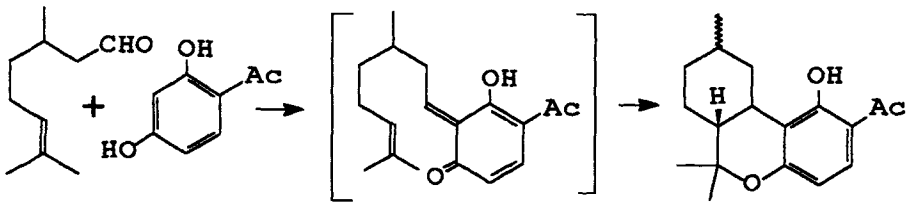
By contrast, the reaction of resorcinol with mesityl oxide (2-methylpent-2-ene-one) in the presence of barium hydrate at 150-170°C in vacuo (165-170mm Hg) with azeotropic removal of water during 5 hours has been claimed to afford a 34% yield of 2,2,4-trimethyl-5-hydroxy-2H-chromene rather than the 7-hydroxy isomer (ref.116).
Under acidic conditions a stirred mixture of resorcinol and mesityl oxide in carbon disulphide containing boron trifluoride etherate followed by refluxing for 5 hours resulted in two electrophilic substitutions and ring closure to furnish 2,4,4-trimethyl-2-(2,4-dihydroxyphenyl)-7-hydroxychroman in 77% yield (ref.117). Both these reactions are depicted in the scheme.



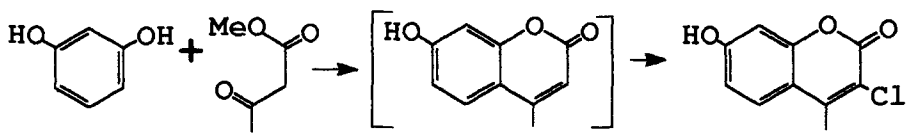
Under basic conditions a version of the Michael addition occurred followed by cyclisation in the reaction of resorcinol and 4-bromobenzylidenemalononitrile in ethanol containing morpholine with a brief heating period to produce a 70% yield



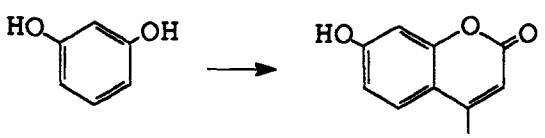
of 2-amino-4-(4-bromophenyl)-7-hydroxy-3-cyano-4H-chromene (ref.118). Resacetophenone (2,4-dihydroxyacetophenone) and citronellal in quinoline solution upon refluxing for 24 hours gave a 73% yield of the tetrahydrocannabinoid compound depicted which consisted of a major proportion (91%) of the equatorial isomer (ref. 119).



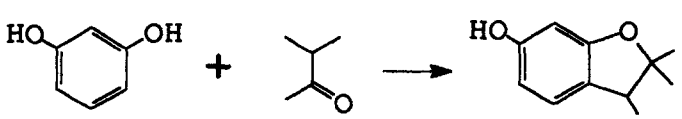
Resorcinol with methyl acetoacetate in octane containing a small proportion of sulphuric acid, a variant of the usual Pechmann conditions, upon refluxing for 5 minutes with removal of volatile material afforded 7-hydroxy-4-methylcoumarin which, without isolation, was converted to the 3-chloro derivative in 98% yield by the addition of acetic acid at 60°C followed by that of sulphuryl chloride at 80°C during 10 minutes and reaction for 2 hours (ref.120).



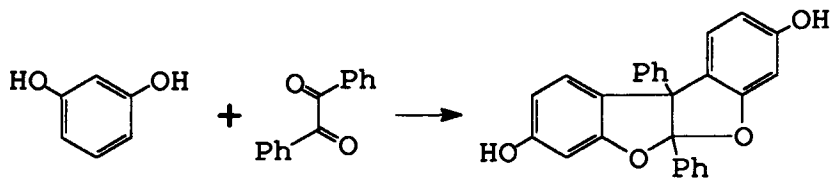
The use of Nafion-H in place of sulphuric acid in the reaction of resorcinol and ethyl acetoacetate gave a 90% yield of 7-hydroxy-4-methylcoumarin (ref.121).



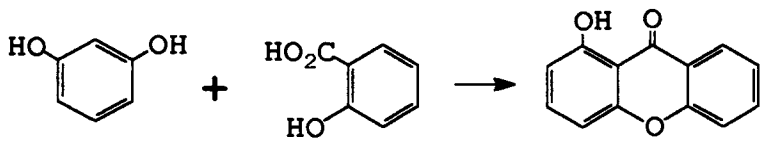
Resorcinol with isopropyl methyl ketone in the presence of the cation exchange resin Amberlyst 15 after reaction during 10 hours at 100°C gave a 66% yield of 6-hydroxy-2,2,3-trimethyl- 2,3-dihydrobenzofuran (ref.122).



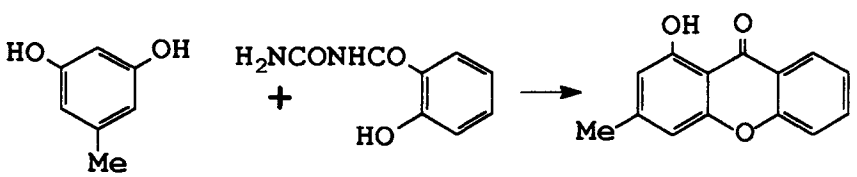
With a diketone such as benzil, resorcinol in xylene solution saturated with hydrogen chloride reacted at 50-60°C during 5-6 hours to give an 81% yield of 6,12-dihydro-3,9-dihydroxy-6,12-diphenylbenzofurano[2,3-b]benzofuran (ref.123).



1-Hydroxyxanthone has been synthesised in low yield from an equimolar mixture of resorcinol and salicylic acid by addition to an equimolar mixture of 85% orthophosphoric acid and phosphorus oxychloride which had been previously heated at 50°C for 1 hour and treated with freshly fused zinc chloride, the whole mixture being then reacted at 130°C for 4 hours. By this methodology higher reaction temperatures can be attained than with $POCl_3$ alone (b.p.110°C) (ref.124).

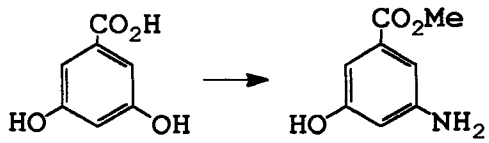


The methyl homologue, 1-hydroxy-3-methylxanthone, has been synthesised in 3 % yield from equimolar proportions of salicyloylurea and orcinol in the presence of orthophosphoric acid, phosphorus oxychloride and anhydrous zinc chloride by heating at 150°C for 5 hours (ref.125).

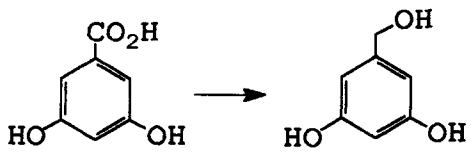


Water liberated in the reaction probably results in the emission of carbon dioxide and formatiom of ammonium phosphate.
The acetyl group in the 1,3-dicarbonyl system shown was removed by hydrolysing with 10% aqueous sodium carbonate during 2 hours giving the parent pyranobenzochromenone, 2,2,8-trimethyl-3,4-dihydro-2H,3H-benzo- [1,2-b:5,4-b']-dipyran-6-one in 55% yield (ref.126).

Substitution of an hydroxyl group in 3,5-dihydroxybenzoic acid can be achieved by heating with ammonium chloride and 28% aqueous ammonia in an autoclave at 180°C for 40hours. Following concentration and esterification of the residue by refluxing for 36 hours with methanol containing sulphuric acid a 75% yield of methyl 3-amino-5-hydroxybenzoate was obtained. The starting material probably reacts in the tautomeric form (ref.127).

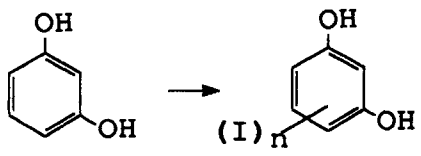


3,5-Dihydroxybenzyl alcohol has been employed as starting intermediate for the synthesis of new polymeric systems, dendritic macromolecules (fan-like structures) or molecules with controlled molecular architecture (ref.128). It is readily obtained by the lithium hydride reduction of 3,5-dihydroxybenzoic acid.



In a range of studies on carcerands and hemicarcerands involving resorcinol (and pyrogallol) structures some remarkable reactions have been effected on trapped molecules (ref.129).

Monosubstitution of dihydric and polyhydric phenols has never proved easy. In this

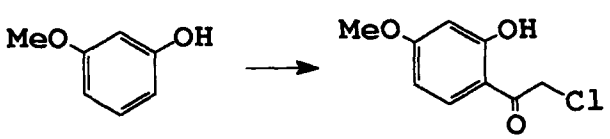


connection, the regioselective monoiodination of resorcinol (and phloroglucinol) has been described (ref.130) for obtaining 2-iodoresorcinol (77%), 4-iodo- (85%), as well as 4,6-diiodo- (90%), 2,3,6-triiodo- (57%), iodophloroglucinol (87%), diiodo- (56%), and triiodophloroglucinol (89%). Thus for example when resorcinol (2.58g) in ice-water (20ml) was treated with iodine (6.7g) and sodium bicarbonate (2.3g) and the crude product triturated with chloroform at -10°C, practically pure 2-iodoresorcinol was produced in 77% yield. 4-Iodoresorcinol was prepared from resorcinol (5.5g) in dry diethylether (50ml) with ICl (8.2g) in dry ether (100ml) over 30mins. initially at 0°C then the temperature was allowed to rise to 25°C during 1 hour. After treatment with aqueous sodium sulphite, the separated ether phase was chromatographed on silica gel with chloroform-acetic acid (9:1) to afford the product (85% yield).
1,3,5-Tris(1-quinolinyl)benzene has been utilised as a simple receptor for resorcinol through binding as a bidentate host molecule (ref.131).

(ii) Monoalkoxy Derivatives of 1,3-Dihydroxy Compounds

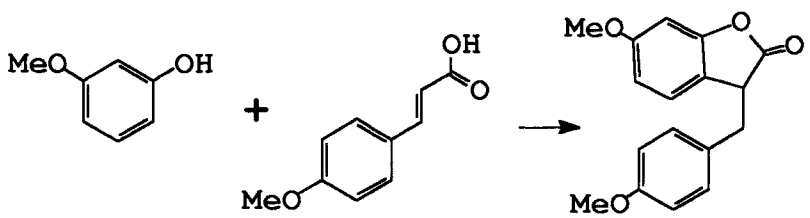
Due to their reactivity towards substitution under conditions in which phenol itself is unreactive, 1-hydroxy-3-alkoxybenzenes require milder catalysts than generally employed for the former. Resorcinol monomethyl ether in benzene containing benzoyl chloride upon addition to boron trichloride (1 mole) in benzene at -10°C followed by refluxing for 10 hours and aqueous work-up at ambient temperature, afforded 2-hydroxy-4-methoxybenzophenone in 85% yield (ref.132).

For the reaction of a cyanoalkyl compound more drastic conditions are required. A solution of resorcinol monomethyl ether, chloroacetonitrile and aluminium chloride in dichloroethane added with stirring to an ice-cold solution of boron trichloride and reaction at ambient temperature during 20 hours followed by acidification produced an 81% yield of 2-hydroxy-4-methoxychloroacetophenone (ref.133).

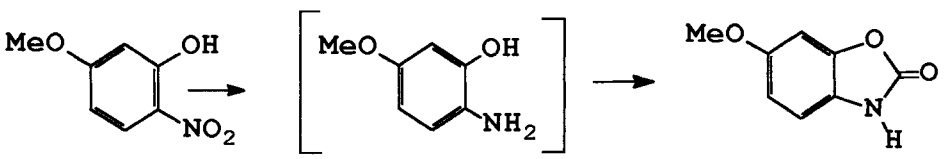


Bicyclic structures have readily formed from resorcinol mono methyl ether. The

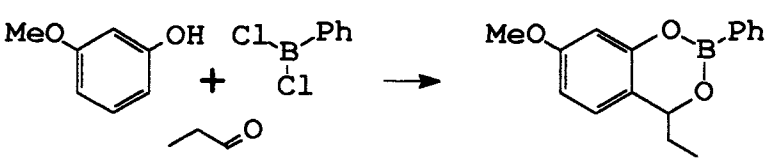
benzofuranone shown was formed in 89% yield by refluxing equimolar proportions of 4-methoxycinnamic acid and the monomethyl ether in trifluoroacetic acid for 3 hours (ref.134).



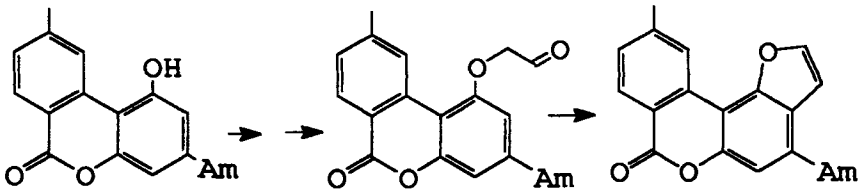
6-Methoxybenzoxazol-2-one was obtained from 5-methoxy-2-nitrophenol in 75% yield by hydrogenation in methanol containing palladium-carbon at normal pressure and temperature followed by treatment of the intermediate product with triethylamine and bis(trichloromethyl)carbonate (ref.135).



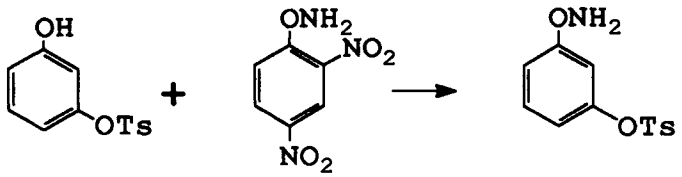
Resorcinol monomethyl ether (3-methoxyphenol) upon treatment initially at 0°C with dichlorophenylborane, triethylamine and 4-dimethylaminopyridine, and then with propanal afforded after reaction during one and a half hours a 98% yield of the 1,3,2-benzodioxaborin, (4-ethyl-7-methoxy-2-bora-1,3-dioxa-2-phenyl-1,2,3,4-tetralin) (ref.136).



4-Hydroxy-6-methyl-2-pentyl-9-oxo-10-oxa-phenanthrene with bromoacetaldehyde diethyl acetal in refluxing dimethylformamide containing potassium carbonate, after 30 minutes gave the corresponding acetal in 90% yield which by way of the aldehyde obtained upon acidic hydrolysis with 2M hydrochloric acid in 89% yield furnished with ethanolic 0.1M sodium hydroxide during 30 minutes the benzofuran shown in 91% yield (ref.137) a cyclisation attributable to the highly reactive 3-position in the phenanthrene.

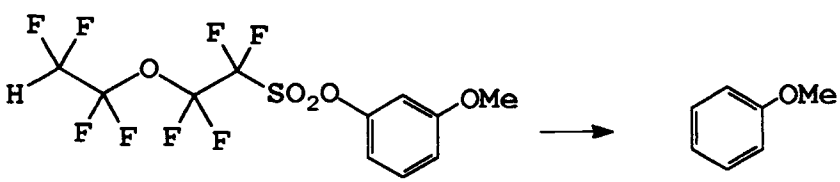


Reaction at the hydroxyl group occurred in 3-tosyloxyphenol in dimethylformamide solution by conversion to the phenoxide by slow addition of sodium hydride in dimethylformamide under nitrogen at 0°C and gradual introduction of 2,4-dinitrophenoxylamine in dimethylformamide during 2 hours. After reaction for 2 hours, 3-tosyloxyphenoxylamine was obtained in 83% yield (ref.138). This method represents a variation on the use of hydroxylamine with other systems.



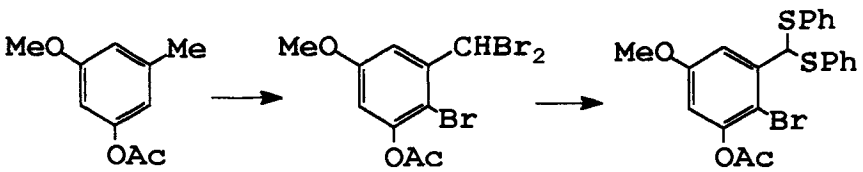
(iii) Mixed Unsymmetrical O-substituted Derivatives of 1,3-Dihydroxy Compounds

Synthetic uses have been made of resorcinol monomethyl ether derivatives to differentiate between the two functions. Dehydroxylation has been effected affording a route from dihydric to monohydric derivatives. 3-Methoxyphenyl 2-(1,1,2,2-tetrafluoroethoxy)-1,1,2,2-tetrafluoroethane sulphonate with tri-n-butyl amine and a small proportion of dichloro bis(triphenylphosphine)palladium(II) in dimethylsulphoxide by stirring at 110°C under nitrogen during 6 hours, afforded an 89% yield of anisole (ref.139).



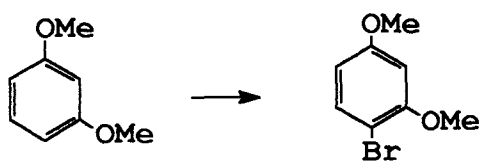
The mixed O-methyl, O-acetyl derivative from orcinol was reacted in refluxing

carbon tetrachloride containing some benzoyl peroxide with N-bromosuccinimide for 4-9 hours whilst being irradiated. The tribromide intermediate formed in 90% yield was added over 5 mins. in concentrated dimethylformamide solution to sodium thiophenoxide (from sodium hydride) in dimethylformamide at 5-10°C. After reaction with stirring for 5.5 hours and acid quenching the bis(phenylthio)methyl compound shown was formed in 85% yield. Conversion to a formyl derivative or alkylation of the carbanion are possible synthetic applications (ref.140).

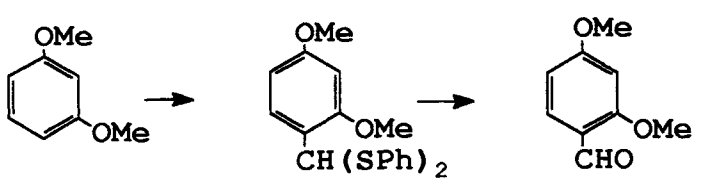


(iv) 1,3-Dialkoxy Derivatives of 1,3-Dihydroxy Compounds

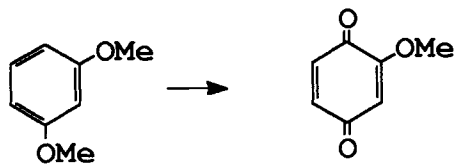
The reactions in this group comprise ring substitution and dealkylation of benzenoid compounds and syntheses with 1,3-dimethoxy compounds in the bicyclic and polycyclic series. The monosubstitution of polyalkoxy benzenes is generally not facile. Monobromination of 1,3-dimethoxybenzene in carbon tetrachloride was effected at 30°C during 2 hours with N-bromosuccinimide in the presence of acidic silica gel (type microbead 3A) in 99% yield without formation of dibromo compounds (ref.141). The evolution of HBr is avoided.



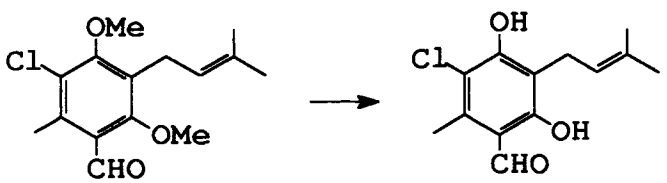
Mild monoformylation of 1,3-dimethoxybenzene took place in dichloromethane containing tris(phenylthio)methane by subsequent treatment over 1.5 hours at ambient temperature with dimethyl methylthiosulphonium fluoroborate and work-up by quenching with water to afford 2,4-dimethoxybenzaldehyde in 70% yield (ref.142).



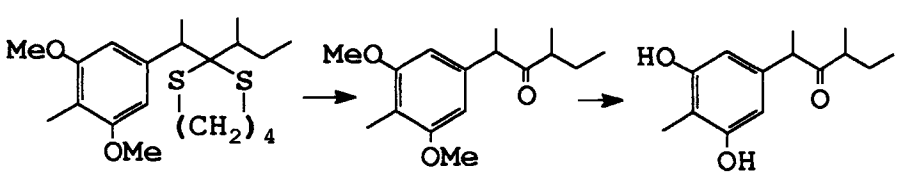
1,3-Dimethoxybenzene, magnesium monoperoxyphthalate and iron(III) meso-tetrakis-(2,3,5,6-tetrafluorophenyl)tetrasulphonatoporphyrin in the proportions (1:3:0.01) in acetonitrile/tartrate buffer (pH3) when kept at 20°C for 1 hour afforded 2-methoxybenzo-1,4-quinone in 95% yield (ref.143).



In dealkylation experiments although removal of methyl groups can be achieved readily by reagents such as lithium iodide in hot collidine (ref.144) milder conditions are frequently obligatory.
The iso-pentenyldimethoxy compound shown by treatment in dimethylformamide with bromomagnesium ethyl mercaptide was converted in 53% yield to the natural resorcinol,colletochlorin 2-(3-methylbut-3-enyl)-3-chloro-5-formyl-4-methylresorcinol (ref.145).

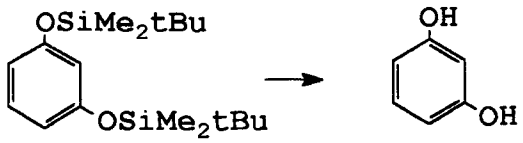


The dithian depicted underwent simultaneous demethylation and dethiolation in dichloromethane by treatment with methyl fluorosulphonate initially at 0°C and subsequently at ambient temperature for 3 hours to give the corresponding dihydroxyketone in 92% yield (ref.146).

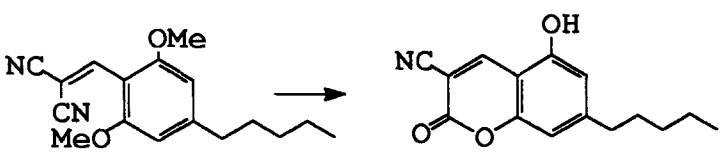


Resorcinol bis(tert-butyldimethylsilylether) underwent decomposition by treatment with tetrabutylammonium fluoride in tetrahydrofuran but was smoothly converted in 91% yield to 1,3-dihydroxybenzene after stirring at ambient temperature for 2 hours

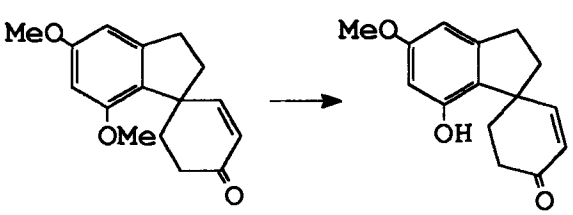
with potassium fluoride (4 moles) and 48% hydrogen bromide in dimethylformamide (ref.147).



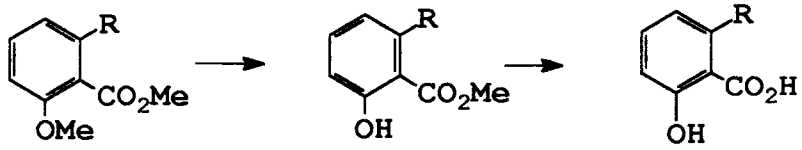
Coumarin ring formation presumably by way of an intermediate imide accompanied the demethylation of the dinitrile shown with aluminium chloride in chlorobenzene by refluxing for 3.5 hours to afford a 96% yield of 3-cyano-5-hydroxy-7-pentylcoumarin (ref.148).



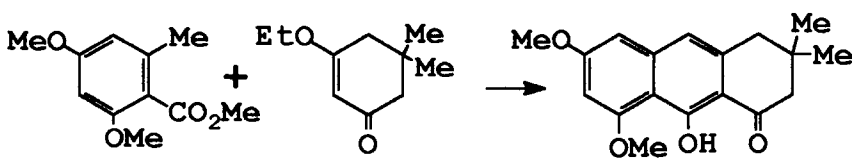
Partial demethylation occurred of the spiro cannabinoid compound illustrated by treatment in hexamethylphosphorictriamide with the lithium salt of 2-methylpropane-2-thiol in the same solvent at 70°C during 2 hours to give an 89% yield of (+)-dehydrocannabispiran. The lithium salt was prepared from lithium hydride and the thiol in oxygen-free hexamethylphosphoric triamide by reaction at 50°C during 5 hours (ref.149).



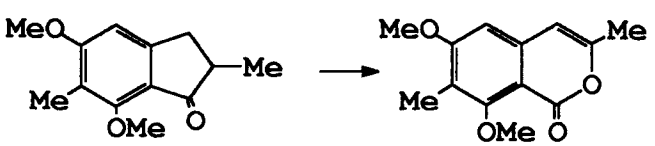
O-Methyl ethers of methyl 6-alkylsalicylates (R = n-alkyl) were smoothly demethylated by treatment with excess lithium 2-methylpropane-2-thiolate (prepared from t-butyl thiol and n-butyllithium) in dimethylformamide at ambient temperature during 1 hour to give the ester. This was hydrolysed by heating the mixture under reflux (ref.150). The method has applicability to alkyl dimethylorsellinates.



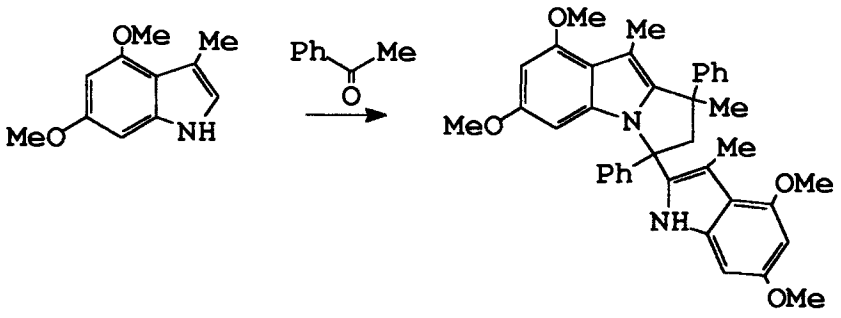
In the reactions of bicyclic and tricyclic 1,3-dimethoxy compounds, the following transformations have been described.
The carbanion of methyl dimethylorsellinate has been employed in a Michael addition followed by facile cyclisation to a tricyclic system. Methyl dimethylorsellinate in tetrahydrofuran was added to stirred lithium diisopropylamide in the same solvent at -78°C and after 10mins., 5,5-dimethyl-3-ethoxycyclohex-2-enone in tetrahydrofuran was introduced. The mixture was allowed to warm to ambient temperature and then gave 3,3-dimethyl-3,4-dihydro-9-hydroxy-6,8-dimethoxy-1-oxo anthracene in 64% yield (ref.151).



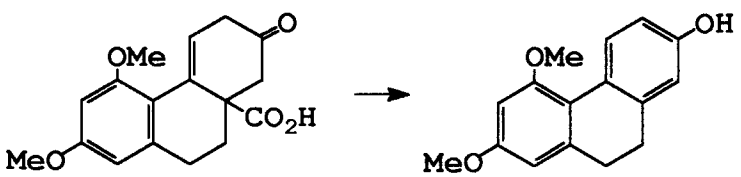
Isocoumarin formation from an indanone has been effected through involvement of an enol trifluoroacetate followed by ozonolysis.



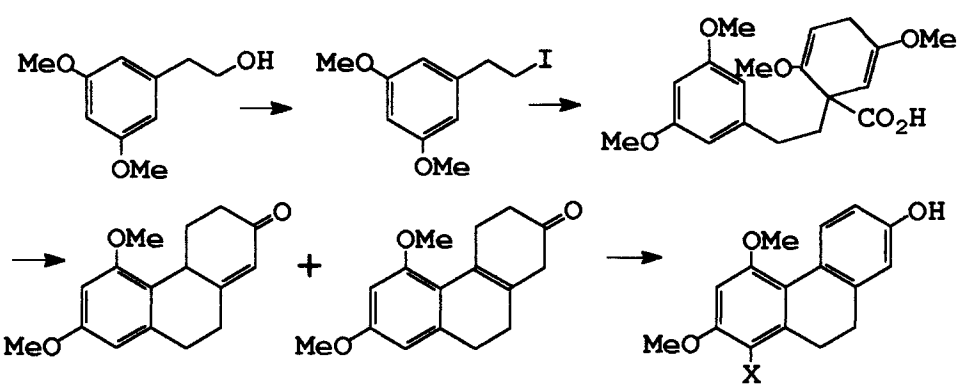
5,7-Dimethoxy-2,6-dimethylindan-1-one with trifluoroacetic anhydride at 20°C during 40mins. gave in 79% yield 1-trifluoroacetoxyindene which by ozonolysis at -78°C in ethyl acetate afforded after saturation with nitrogen and dimethyl sulphoxide treatment followed by stirring overnight a 75% yield of 6,8-dimethoxy-3,7-dimethylisocoumarin (ref.152).
In the reaction of 4,6-dimethoxy-3-methylindole with 2 moles of acetophenone in methanolic hydrogen chloride, the 2-position underwent substitution and the activated 7-position remaining unaffected, to give the ring annelated product indicated in 75% yield (ref.153).



Oxidative decarboxylation with aromatisation of the angular carboxy dimethoxy compound shown by treatment of a methanolic solution with a solution of methanolic cupric bromide followed by refluxing for 1.5 hours furnished a 76% yield of 5,7-dimethoxy-9,10-dihydro-2-hydroxyphenanthrene (ref.154).



An alternative reagent, namely pyridinium perbromide followed by butyllithium treatment has been used for this compound arising at an intermediate stage in a synthesis of the phytoalexin, orchinol. 2-(3,5-Dimethoxyphenyl)ethanol was converted with methyltriphenoxyphosphonium iodide in 93% yield to the iodide

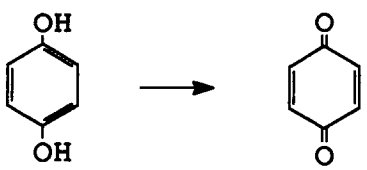


which was used to alkylate the carbanion obtained from the Birch reduction of 2,5-dimethoxybenzoic acid thus producing 1-[2-(3,5-dimethoxyphenyl)ethyl]-2,5-dimethoxy-2,5-cyclohexadiene-1-carboxylic acid in 75% yield. Treatment of this compound with 75% sulphuric acid resulted directly in the formation of two isomeric ketones which were dehydrogenated with pyridinium perbromide in acetic acid to give bromoorchinol (X = Br) from which orchinol (X = H) was derived by reaction with butyllithium and aqueous work-up (ref.155).

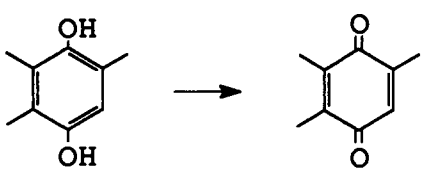
9.3.3 1,4-Dihydric Phenols (Hydroquinones) and their Derivatives

(i) 1,4-Dihydroxy Benzenoid Compounds

The reactions reviewed in this group consist of oxidation and substitution in the ring for the benzenoid series and a number of sequences involving polycyclic compounds which contain 1,4-dihydroxy systems.
Hydroquinone in isopropanol containing a small proportion of iodine by gradual addition of 35% hydrogen peroxide over 3 hours and subsequent reaction for the same period, furnished an 86% yield of 1,4-benzoquinone (ref.156).

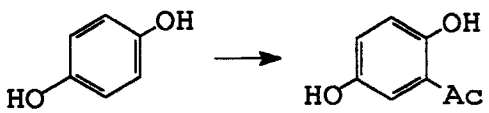


A quantitative yield of 2,3,6-trimethylbenzo-1,4-quinone was obtained from 2,3,6-trimethylhydroquinone and phenyl iodosodiacetate (1 mole) in methanol at ambient temperature. The reagent also has applicability to 4-alkylphenols and 4-unsubstituted phenols (ref.157).

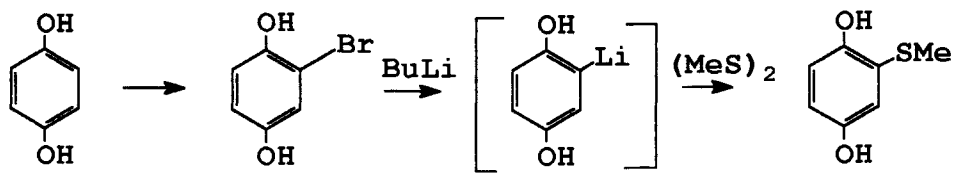


Reactions involving substitution in the ring are of two types, those consisting of attachment of a group to the ring and those where an alkoxyl group is formed and ring closure leads to a polycyclic compound.
2,5-Dihydroxyacetophenone was formed in 76% yield by the rapid addition of 1,4-dihydroxybenzene to a stirred mixture of acetic anhydride and zinc chloride

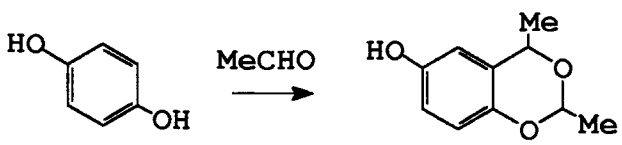
followed by slow heating to 145-150°C with maintenance of that temperature for 30mins. By the same procedure resorcinol and phloroglucinol gave both mono and diacetyl derivatives while phenol, catechol and pyrogallol produced monoacetyl compounds (ref.158).



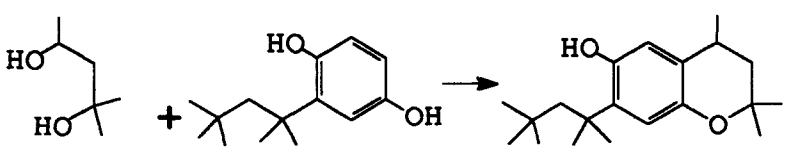
Although lithiation of hydroquinone had no useful outcome the 2-bromo derivative gave the 2-lithio intermediate by haloge-metal exchange and thence 2-methylthio-1,4-dihydroxybenzene by reaction with dimethyldisulphide, together with some hydroquinone by reduction (ref.159,160).



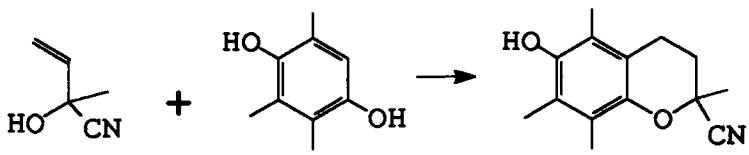
In the second group, 6-hydroxy-2,4-dimethyl-1,3-benzodioxane was synthesised in 72% yield by the addition of hydroquinone during 6-8 hours to a cold acetic acid solution of acetaldehyde containing concentrated hydrochloric acid and reaction at 0-5°C for 3 hours (ref.161), presumably by electrophilic substitution followed by cyclic acetal formation.



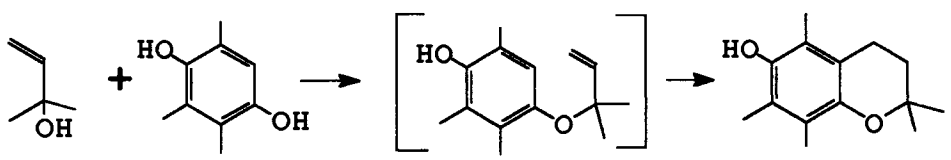
Chroman formation occurred in the reaction of 2-(2,2,4,4-tetramethyl)butylhydroquinone (from hydroquinone and diisobutylene) with



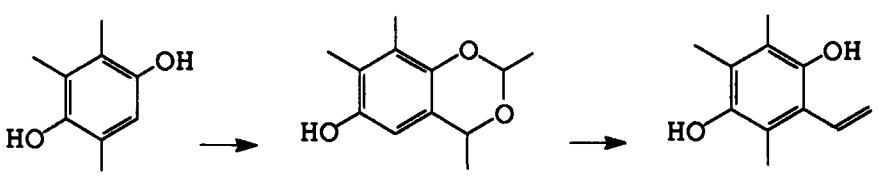
2-methyl-2,4-pentanediol in heptane containing amberlyst 15 by refluxing for 3 hours, to give the product shown in 71% yield (ref.162).
A similar ring structure resulted, with no evidence of five-membered ring formation, from the treatment of methyl vinyl ketone cyanohydrin and phosphoric acid in toluene/nitromethane during 1 hour with a suspension of 2,3,6-trimethyl hydroquinone and boron trifluoride in toluene at 0-5°C, followed by reaction at ambient temperature for 13 hours to give an 81% yield of 2-cyano-2,5,7,8-tetramethyl-6-hydroxychroman (ref.163).



The same phenol together with an equimolar proportion of the allylic tertiary alcohol, 3-hydroxy-3-methylbut-1-ene in a small volume of trifluoroacetic acid afforded after stirring at ambient temperature for 30 mins. a 63% yield of 6-hydroxy-2,2,5,7,8-pentamethylchroman (ref.164).

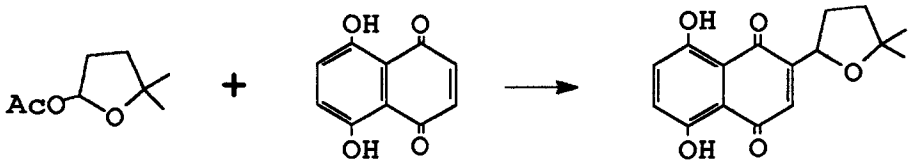


Trimethylhydroquinone in dichloromethane by reaction with acetaldehyde in dichloromethane saturated with hydrogen chloride at less than ambient temperature produced a 1,3-dioxan intermediate in 94% yield which upon vacuum pyrolysis at 460°C afforded 1,4-dihydroxy-2,3,5-trimethylvinylbenzene in 62% yield (ref.165).

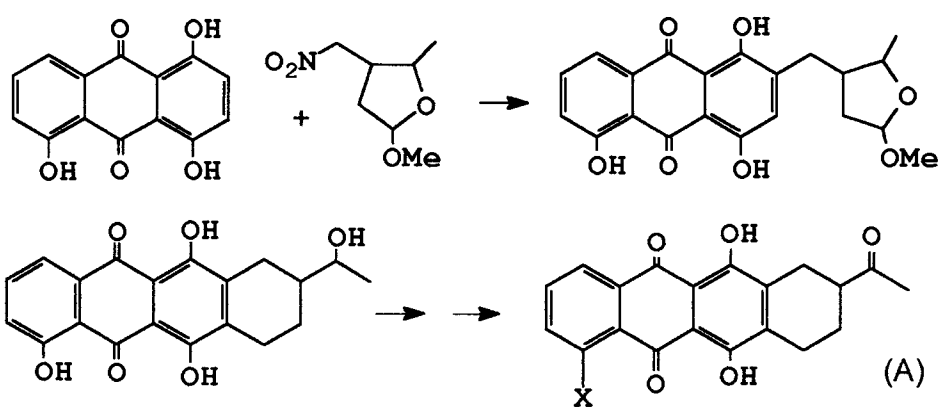


Bicyclic, tricyclic and polycyclic compounds containing 1,4-dihydroxy systems undergo reactions not shown by the parent compound, 1,4-dihydroxybenzene. Naphthazarin together with boron trifluoride etherate in acetic acid following a

refluxing period during 40 mins. was added gradually to tetrahydro-5,5-dimethyl-2-furylacetate and reacted over 5 hour at ambient temperature to afford 5,8-dihydroxy-2-(2,2-dimethyltetrahydrofuran-5-yl)-1,4-naphthoquinone in 56% yield (ref.166).

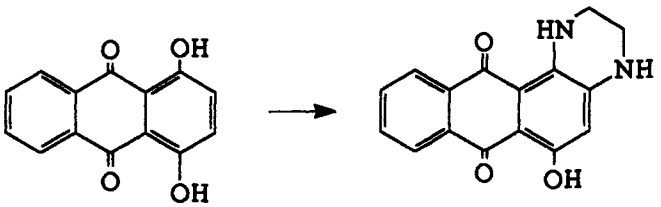


The above electrophilic substitution compares with the following under basic conditions. A carminomycine derivative has been synthesised from 5-hydroxyquinizarin and 2-methoxy-5-methyl-4-nitromethyltetrahydrofuran. Thus, the quinizarin (1 mol) in methanolic solution containing sodium methoxide (1.4 mol) upon refluxing with the nitroalkane (3 mol) until reaction was complete, produced the 7-substituted compound regiospecifically in 65% yield. The methoxyl group transformed to an hydroxyl with 1M hydrochloric acid and reductive/cyclisation led to a tetracyclic structure bearing an 8-(2-hydroxyethyl)- substituent. Oxidation with pyridinium chlorochromate afforded the keto compound (8,10-dideoxycarminomycine)(A, X = OH) and regiospecific methylation of this with diazomethane in dichloromethane afforded a daunomycinone derivative (A, X = OMe) (ref.167).

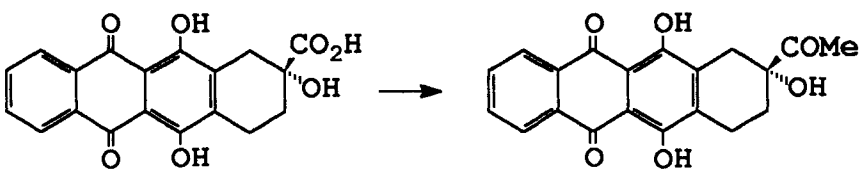


The required nitroalkane was synthesised from ethyl levulinate (ethyl 4-oxopentanoate) by formation of ethyl 4-oxopent-2-enoate by bromination/dehydrobromination, reduction with sodium borohydride in methanol to give initially ethyl 4-hydroxypent-2-enoate in 82% yield and Michael addition of methyl nitromethane (in 70% yield) from which 2-methoxy-5-methyl-4-

nitromethyltetrahydrofuran was obtained.
Related reactions of quinizarin itself have been reported involving 1,2-diaminoethane in pyridine containing cupric chloride over 24 hours at 30°C and resulted in a 98% yield of 6-hydroxy-1,2,3,4-tetrahydronaphtho [2,3-f]quinoxaline-7,12-dione (ref.168).

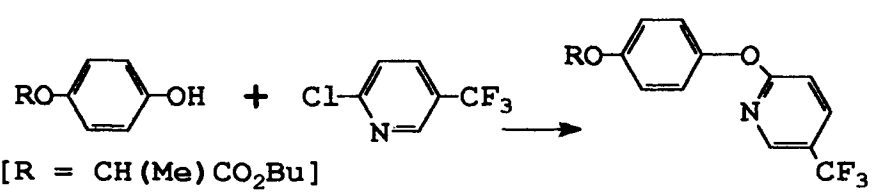


The reaction is described as general for α,ω-diaminoalkanes, $H_2N(CH_2)_nNH_2$.
In the tetracyclic series the transformation of a naphthacenecarboxylic acid into daunomycinone has been described. Racemic 2,5,12-trihydroxy-1,2,3,4-tetra hydronaphthacene-6,11-dione-2-carboxylic acid in tetrahydrofuran containing hexamethylphosphoramide after treatment during 18 hours at ambient temperature with N,N'-carbonyldiimidazole (2 moles) followed at -20°C by trimethylsilyltriflate and finally reaction with a large excess (14 moles) of ethereal methyl magnesium bromide at -40°C over 3 hours afforded, after acidic work-up, racemic 7-deoxy-4-demethoxydaunomycinone in 65% yield (ref.169).



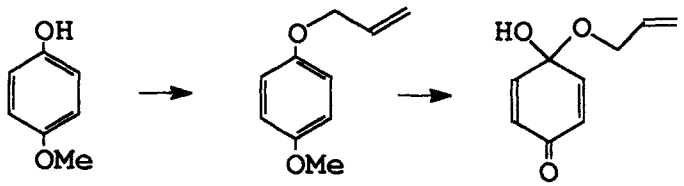
(ii) Monoalkoxy Derivatives of 1,4-Dihydroxybenzenes

Reactions of these compounds comprise those at the hydroxyl group and

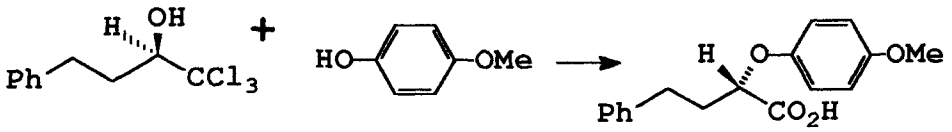


substitution in the ring. The mono ester, butyl 2-(4-hydroxyphenoxy)propionate, with

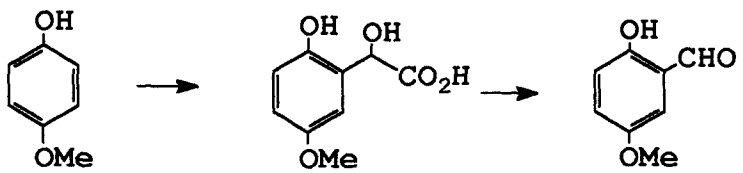
2-chloro-5-trifluoromethylpyridine in dimethylformamide containing potassium fluoride on alumina by heating at 120°C for 9 hours afforded the corresponding ether in 88% yield. The 5-nitro analogue reacts similarly (ref.170).
Allyl or propargyl ethers of 4-methoxyphenol upon anodic oxidation directly gave quinone monoketals (ref.171).



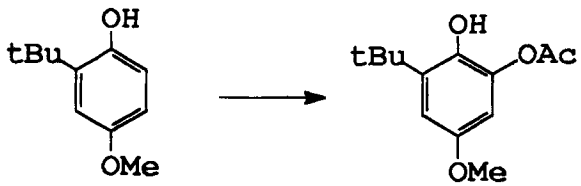
Etherification of 4-methoxyphenol occurred in its reaction with (R)-4-phenyl-1,1,1-trichloro-2-butanol in dimethoxyethane/water (3:2) by dropwise treatment with concentrated (10.7M) aqueous sodium hydroxide over 10mins. at 23°C followed by stirring for 12 hours to afford an 84% yield of (S)-2-(4-methoxyphenyl)-4-phenylbutanoic acid (ref.172).



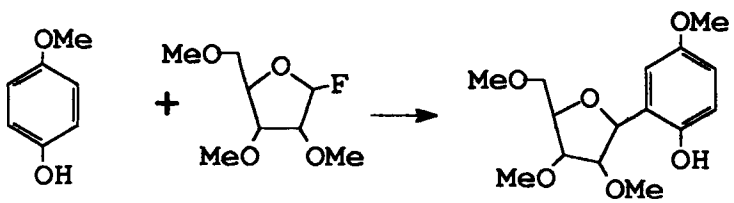
Substitution in the ring occurred when 4-methoxyphenol, glyoxylic acid and alumina were added to 2M sodium hydroxide and the mixture was stirred at ambient temperature for 12 hours giving a 75% yield of 2-hydroxy-5-methoxymandelic acid which upon oxidation gave 2-hydroxy-5-methoxybenzaldehyde (ref.173).



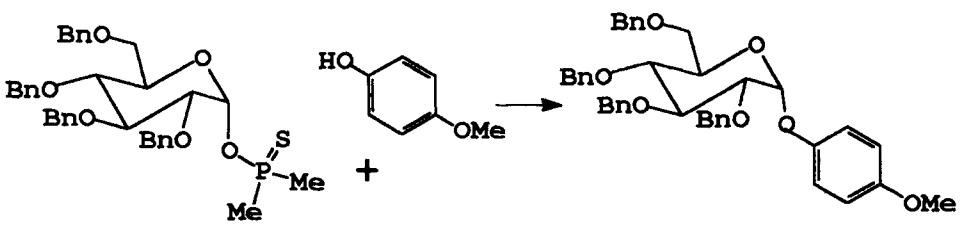
Although the corresponding 4-methyl and 4-phenyl analogues failed to similarly react, 2-tert-butyl-4-methoxyphenol in acetic acid containing copper(II) acetate when refluxed for 24 hours under argon afforded a 70% yield of 2-acetoxy-4-methoxy-6-tert-butylphenol (ref.174).



Addition of the fluorofuranoside shown in dichloromethane to a mixture of 4-methoxyphenol, cyclopentadienylhafnium dichloride, silver perchlorate and a powdered molecular sieve (type 4A) in dichloromethane initially at -78°C and finally at -20°C for 30 mins. gave after a further 30 min, the β-glycoside derivative in 70% yield (ref.175).

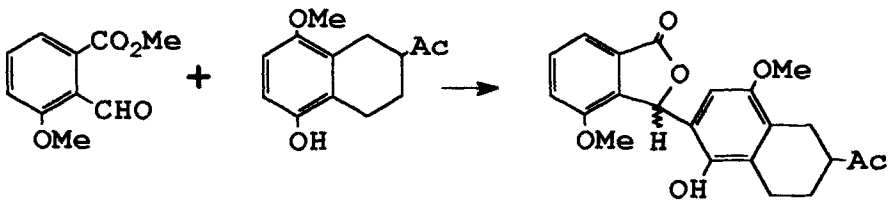


2,3,4,6-Tetra-O-benzylarbutin has been derived from the reaction of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl dimethylphoshinothiolate with 4-methoxyphenol in benzene containing a 4A molecular sieve upon treatment with siver perchlorate by reaction over 16 hours at ambient temperature. No C-glycosylation was detected and the product obtained in 79% yield comprised 65:35 proportions of α:β isomers (ref.176). By contrast phloroglucinol trimethyl ether gave a C-glycosylation product. A bicyclic compound, 6-acetyl-4-methoxy-5,6,7,8-tetrahydro-1-naphthol, with methyl



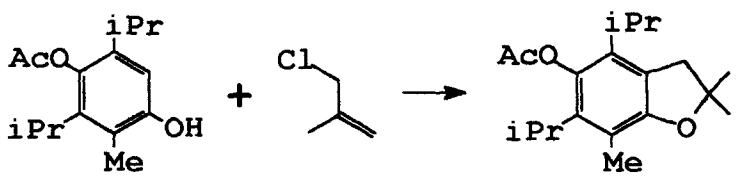
2-formyl-3-methoxybenzoate and phenylboronic acid in benzene containing a little propionic acid upon refluxing for 20 hours afforded an intermediate boronate which upon stirring during 20 hours in dichloromethane/2-methyl pentane-2,4-diol and a

small proportion of acetic acid furnished an 83% yield of 3-(2-acetyl-1,2,3,4-tetrahydro-5-hydroxy-8-methoxy-6-naphthyl)-4-methoxyphthalide. No competing reactions took place at the acetyl group (ref.177).

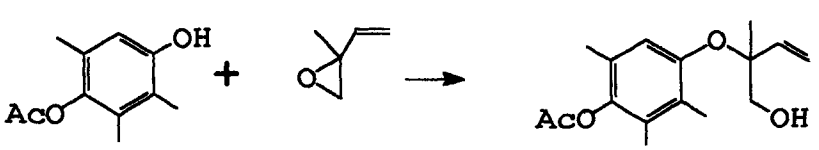


(iii) Mono O-Acyl derivatives of 1,4-Dihydroxybenzenes

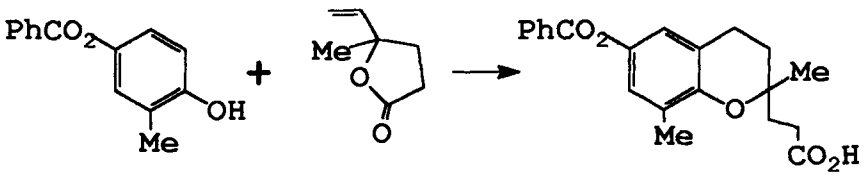
Most of the reactions in this section involve the formation of oxygen heterocyclic bicyclic compounds.
The highly substituted hydroquinone monoacetate shown with 3-chloro-2-methyl -1-propene in dichloromethane/acetic acid (10:1) containing zinc chloride after reaction with stirring during 6 hours at ambient temperature gave 2,2,7-trimethyl-4,6-diisopropyl-5-acetoxy-2,3-dihydrobenzofuran in 72% yield, a process doubtless facilitated by hydrogen chloride liberated at the C-alkylation stage (ref.178).



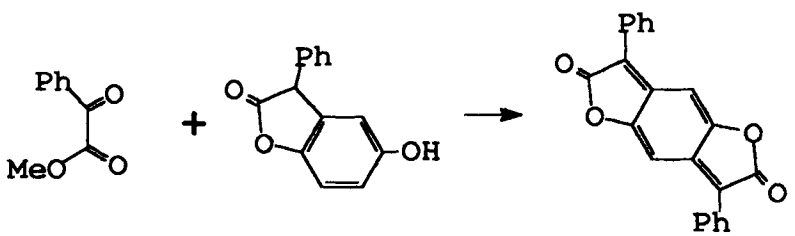
Cleavage of 3,4-epoxy-3-methyl-1-butene in its reaction with 2,3,5-trimethyl -4-acetoxyphenol at ambient temperature in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) occurred at the more highly-substituted side to give 2,3,6-trimethyl-4-(1-hydroxymethyl-1-methylallyloxy)-phenyl acetate without chroman formation (ref.179).



By contrast, in the reaction in refluxing dioxan of the substituted butyrolactone shown with 2-methyl-4-benzoyloxyphenol in the presence of boron trifluoride etherate until completion, 2-(6-benzoyloxy-3,4-dihydro-3,8-dimethylbenzopyran-2-yl)propionic acid was obtained (ref.180). Acylation was not observed.

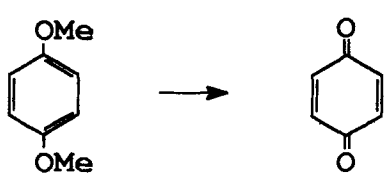


The lactone, 3-phenyl-5-hydroxy-2-oxo-2,3-dihydrobenzofuran when stirred with methyl phenylglyoxylate in the presence of 73% sulphuric acid at 120°C for 1 hour afforded after work-up the symmetrical derivative, 3,7-diphenyl-2,6-dioxo-2,6-dihydrobenzo[1,2-b:4,5-b']difuran (ref.181).



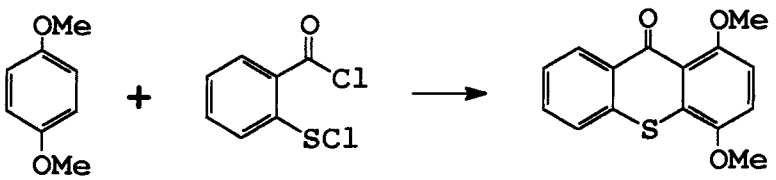
(iv) Dialkoxy Derivatives of 1,4-dihydroxybenzenes

Reactions of benzenoid and of polycyclic compounds are described in this section. 1,4-Dimethoxybenzene in benzene solution cooled in an ice-/water bath, upon treatment with a mixture of nitric acid-impregnated manganese dioxide and celite followed by ultrasonification (300w for 8 mins.) gave an 87% yield of benzoquinone (ref.182).



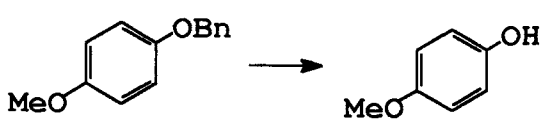
The activity of 1,4-dimethoxybenzene to electrophilic substitution is shown by the

formation of 1,4-dimethoxythioxanthone in 87% yield from the addition of 1,4-dimethoxybenzene to a solution of 2-chlorosulphenylbenzoyl chloride in 1,2-dichloroethane containing stannic chloride with continuance of reaction for 12 hours at ambient temperature (ref.183).



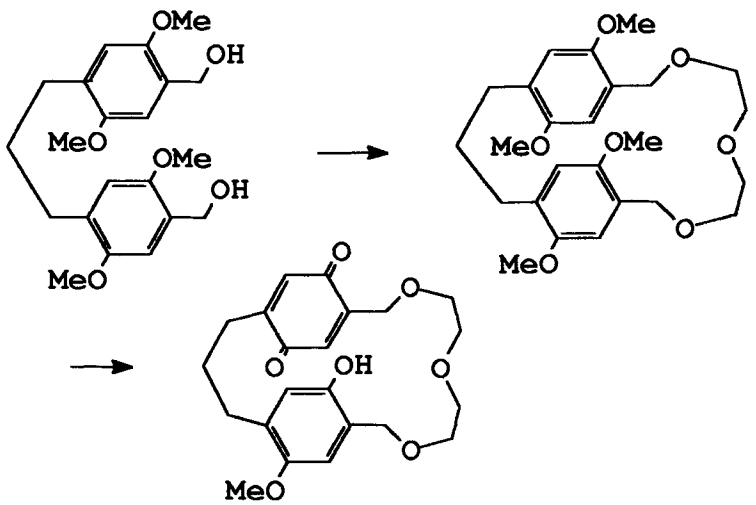
Preferential and selective O-deacetylation in the presence of other ester functions in a variety of compounds has been achieved in tetrahydrofuran solution containing 0.5M N-methyl 2-dimethyl aminoacetohydroxamic acid in a phosphate buffer (pH 7.6) by stirring at ambient temperature during 1 hour. Thus for example the acetate of2,5-dimethoxybenzaloxime and of ethyl 6-acetoxy-3-chlorocoumarin-4-carboxylate are susceptible to this reagent in 79% and 95% yields respectively to give the corresponding hydroxy compounds and as depicted for the latter case (ref.184).

Selective debenzylation of 4-methoxyphenyl benzyl ether in hexamethyl phosphorictriamide has been affected by addition of sodium metal and stirring of the mixture at 100°C under nitrogen during 3 hours to furnish a 93% yield of 4-methoxyphenol (ref.185).

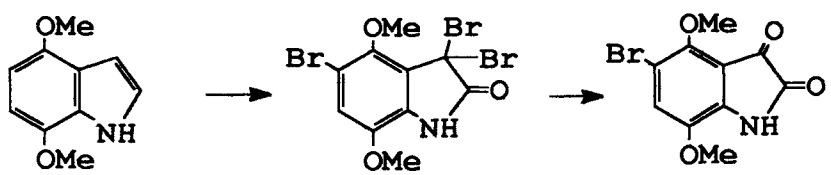


2,5-Disubstituted derivatives of 1,4-dimethoxybenzene in association with 1,4-benzoquinone analogues have been used for deriving crown ether systems (ref.186). Thus for example, 4,4'-trimethylene bis(2,5-dimethoxybenzyl alcohol) and diethylene glycol ditosylate with sodium hydride in tetrahydrofuran at high dilution gave a crown ether in 20% yield which by partial oxidation with ceric ammonium

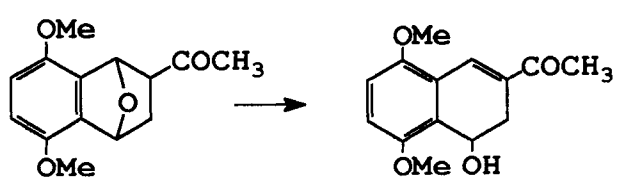
nitrate afforded a 42% yield of a monoquinone.



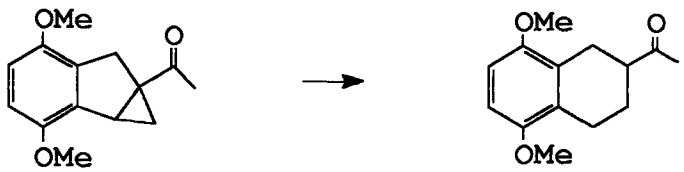
Amongst the reactions of polycyclic 1,4-dimethoxybenzenoid derivatives may be mentioned the following. 4,7-Dimethoxyindole by treatment at ambient temperature with N-bromosuccinimide (3 moles) in tert-butanol during 6 hours afforded a tribromo intermediate in 45% yield, hydrolysis of which with warm aqueous methanol resulted in 4,7-dimethoxy-5-bromoisatin in 98% yield (ref.187).



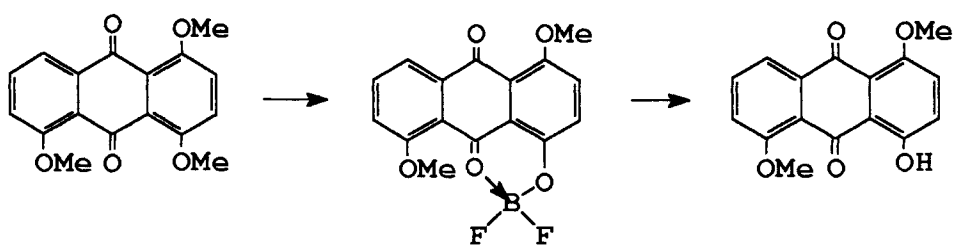
The 5,8-oxa-bridged compound shown was transformed into the 5,6-dihydro analogue in 90% yield by treatment with methanolic sodium methoxide (ref.188).



A 5-deoxy derivative of the above compound has been synthesised in 84% yield as an intermediate towards daunomycinone from the cyclopropane depicted by treatment at ambient temperature in acetic acid with a catalytic quantity of boron trifluoride etherate (ref 189).

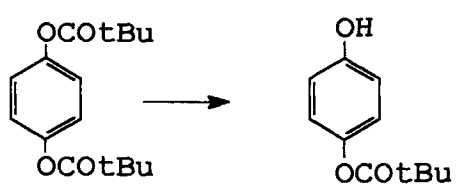


Demethylation normally effected with boron trichloride or tribromide has been realised with the trifluoride in a selective and partial manner. 1,4,5-Trimethoxyanthraquinone in refluxing benzene containing boron trifluoride etherate afforded after reaction during 30mins. an intermediate 4,10-chelated compound in 89% yield which with hot methanol at 50°C for 10mins. gave an 94% yield of 4-hydroxy-1,5-dimethoxyanthraquinone (ref.190).



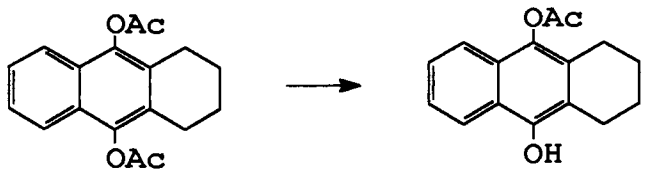
(v) Diacyl Derivatives of 1,4-dihydroxybenzenes

The bis-pivalyl ester of hydroquinone added to methanolic potassium hydroxide and reacted at ambient temperature for 15mins. gave the half-hydrolysed ester in 94% yield (ref.191).



Partial deacetylation of 9,10-bis-acetoxy-1,2,3,4-tetrahydroanthracene was effected

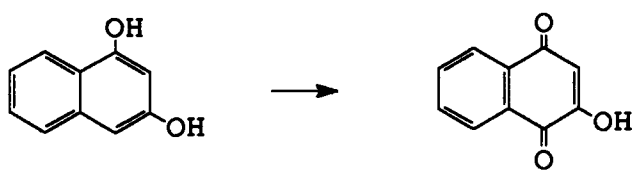
in 90% yield by stirring a solution in dimethoxyethane with a 10-fold excess of



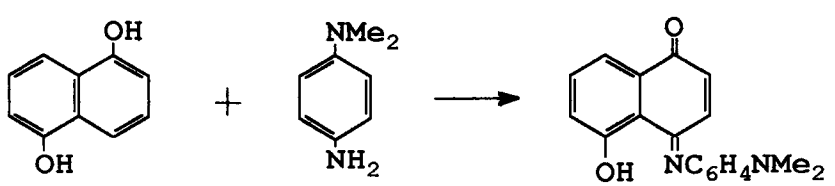
sodium borohydride for 30 hours at 60°C followed by acidic work-up, to give a 90% yield of 10-acetoxy-9-hydroxy-1,2,3,4-tetrahydroanthracene (ref.192).

9.3.4. Naphthalenic and Polycyclic Systems with Two Hydroxyl Groups

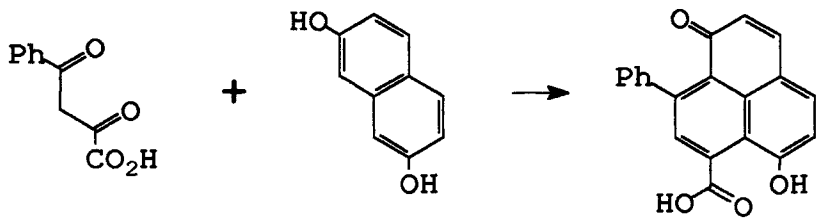
Naphthalenic diols may conveniently be classed as dihydric phenols and as such they have been used both synthetically, the synthesis of morphine by M. Gates in 1954 being an example of one application of 2,6-dihydroxynaphthalene. The reaction chemistry of 1,3- and 1,5-isomers has been studied more recently. Naphthalene-1,3-diol in pyridine added to a toluene suspension of solid potassium superoxide under argon followed after 5 mins. by quenching with water gave 2-hydroxy-1,4-naphthaquinone in 60% yield (ref.193).



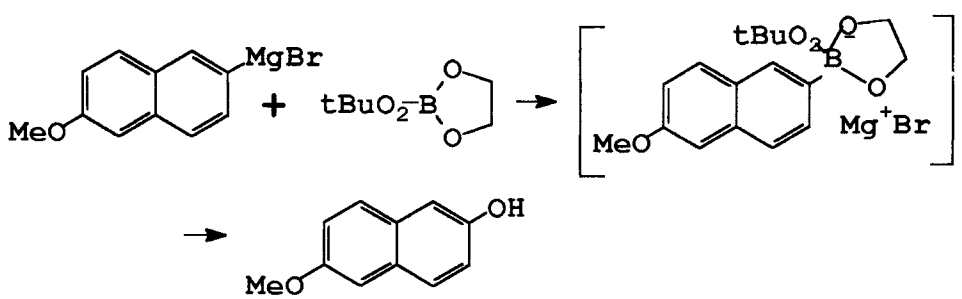
Naphthalene-1,5-diol and 4-dimethylaminoaniline in ethanol/water (1:1) stirred for 1 hour with 4 moles of potassium ferricyanide at ambient temperature and then diluted with water gave the quinoneimine shown in 85% yield (ref.194). The compound can be hydrolysed to juglone, 5-hydroxy-1,4-naphthoquinone.



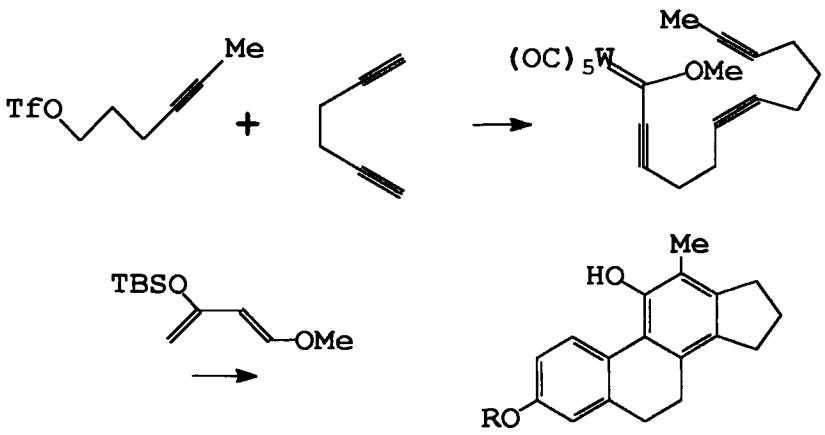
1-Hydroxy-5-methoxynaphthalene underwent a Mannich reaction with cyclohexyl amine and 2 moles of 35% formalin in methanol until reaction was complete leading to an 80% yield of 3-cyclohexyl-2,4-dihydro-7-methoxy-2H-naphth[2,1-e][1,3]oxazine although secondary amines afforded normal 2-dialkylamino methylation (ref.195). This reaction has been referred to in an earlier Chapter.
2,7-Dihydroxynaphthalene with 4-phenyl-2,4-dioxobutanoic acid upon addition to phosphorus oxychloride gave after reaction during 20 hours at ambient temperature, 6-hydroxy-1-oxo-9-phenyl-1H-phenalene-7-carboxylic acid (ref.196).



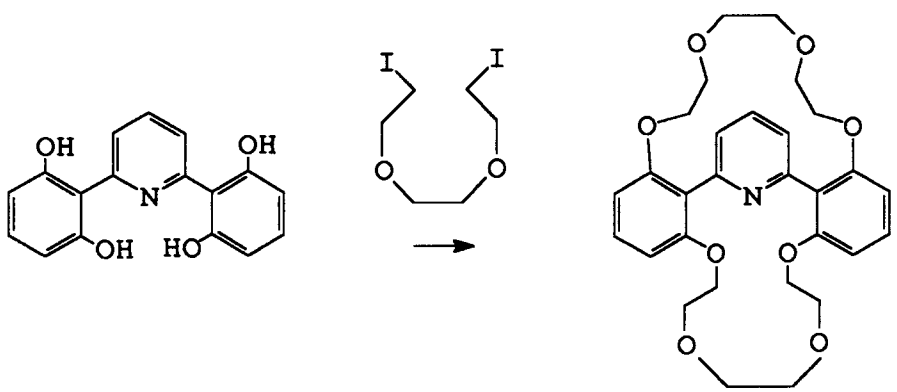
2-Bromo-6-methoxynaphthalene has been transformed in 91% yield to 2-hydroxy-6-methoxynaphthalene by conversion in tetrahydrofuran to the Grignard reagent. This solution was gradually added to 2-tert-butylperoxy-1,3,2-dioxaborolane, reacted at ambient temperature for 16 hours, refluxed for 3 hours and worked up by acidic treatment to afford the product (ref.197).



Electrocyclic ring closure combined with Diels-Alder addition has been employed to derive all four rings of the tetracyclic ring system in the steroids by means of a one pot synthesis (ref.198). Thus, from the triflate of hex-4-ynol and the readily available hexa-1,5-diyne a triyne intermediate was obtained which with chromium or tungsten hexacarbonyl formed a triyne carbene complex. This with a 1,3-dialkoxybuta-1,3-diene in acetonitrile with carbon monoxide (1 atmosphere) initially at ambient temperature and then at 110°C over 24 hours afforded a 62% yield of the two products shown [(1) R = TBS; (2) R = H, (1):(2) 5:2].



The incorporation of two aryl bridgeheads, both linked in turn through the 2,6-substitution of a pyridine nucleus has provided an intermediate which has been converted to a crown ether. Thus, 2,6-bis(2',6'-dimethoxyphenyl)pyridine after demethylation with boron tribromide or hydrogen bromide in 65% yield was reacted in dimethylsulphoxide containing potassium carbonate with the α,ω-diiodo derivative of triethylene glycol to afford a crown ether system in 22% yield (ref.199).



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CHAPTER 10

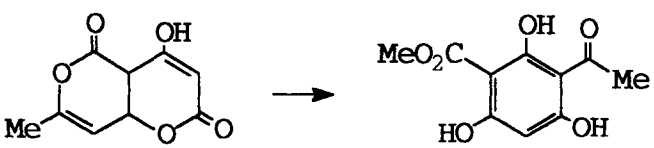
POLYHYDRIC PHENOLS

10.1 Introduction

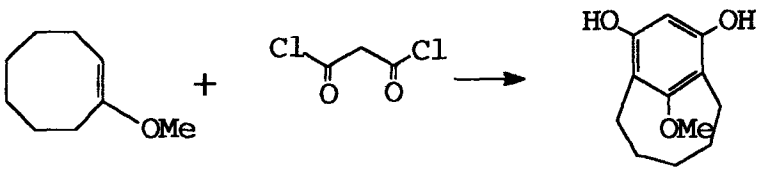
This chapter describes recent progress in the chemistry of 1,3,5-tri-hydroxybenzene(phloroglucinol), the 1,2,3-trihydroxy (pyrogallol) and 1,2,4-isomers and in polycyclic compounds in the series. Although the benzenoid members have a number of industrial uses, a variety of polycyclic systems are widely distributed naturally and the group has continued to attract interest because of the extensive number of complex derivatives possessing such polyhydroxy and methoxy substitution patterns. Developments particularly in the last decade are listed.

10.2 Synthesis of Trihydroxybenzenes and derivatives of tetrahydroxy benzenes

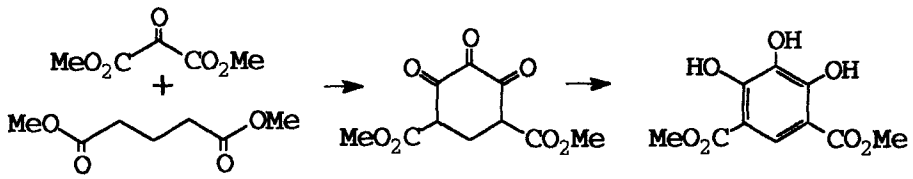
While no new synthetic methods for this group have appeared improvements in the synthesis of phloroglucinol and that of some of its derivatives have attracted attention. The classic route by way of trinitrotoluene, trinitrobenzoic acid, triaminobenzoic acid and its hydrolysis and decarboxylation has been challenged by methods based on the use of acyclic precursors.
In earlier work the α-pyrone shown upon treatment with magnesium methoxide afforded the C-methoxycarbonyl derivative of phloroacetophenone (ref.1).



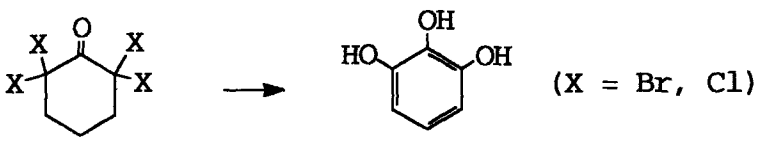
More recently, the reaction of malonyl chloride with the enol ethers of cyclic alkenes to give 4,6-alkano-1,3,5-trihydroxybenzene systems in variable yields (18-70%)(ref.2) has been investigated. For example, the enolic methyl ether of cyclooctene gives with malonyl chloride the phloroglucinol depicted by acylation at the double bond and allylic position.



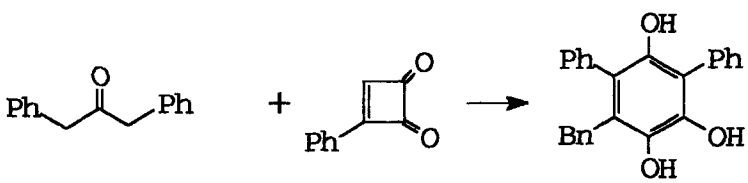
The traditional synthesis of 1,2,3-trihydroxybenzene by decarboxylation of gallic acid from natural sources has been superseded by the use of acyclic precursors. Dimethyl oxomalonate and dimethyl glutarate undergo cyclodehydration and tautomerism to give a diester product which uponhydrolysis decarboxylates to pyrogallol in about 65% yield (ref.3).



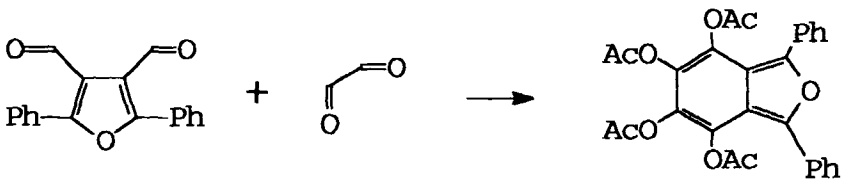
2,2',6,6'-Tetrahalogenocyclohexanones can also be dehydrohalogenated, hydrolysed and tautomerised to pyrogallol derivatives although the yields are only in the region of 20% (ref.4).



By comparison with its isomers, the synthesis of 1,2,4-trihydroxybenzene is straightforward by hydrolysis of the triacetate from the Thiele reaction on 1,4-benzoquinone, also a reaction of versatility for derivatives. Acyclic precursors can be used as in the synthesis of



2,6-diphenyl-5-benzyl-1,3,4-trihydroxybenzene from 1,3-diphenylacetone with 3-phenylcyclobutenedione (ref.5).
3,4,5,6-Tetraacetoxy-2,7-diphenylisobenzofuran has been synthesised from 3,4-diformyl-2,5-diphenylfuran and glyoxal by way of thermal cycloaddition and reductive acetylation with acetic anhydride (ref.6).

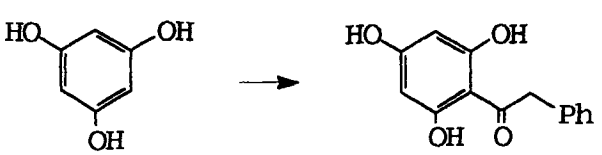


This chapter is mainly concerned with the reactions of the trihydroxy benzenes, of their alkoxy derivatives and finally with those of tetraalkoxy and polyalkoxy compounds.

10.3 Reactions of 1,3,5-Trihydroxybenzenes

10.3.1. Acylation

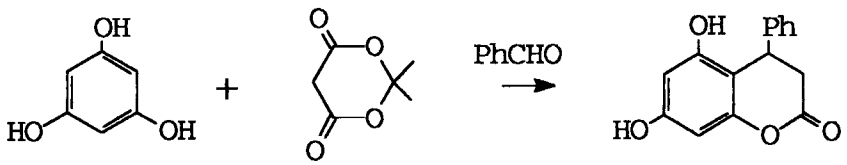
Coumarin, chromone and flavenol ring formation, as might be expected with this highly activated polyhydroxy system, represent the main development. A mixture of phloroglucinol and phenylacetonitrile together with a catalytic amount of boron trifluoride etherate saturated with dry hydrogen chloride over 6 hours at 0-5°C, followed by reaction at ambient temperature for 18 hours afforded a ketimine hydrochloride which upon aqueous hydrolysis gave an 82% yield of benzyl 2,4,6-trihydroxyphenyl ketone. Compared with these improved Hoesch conditions the use of zinc chloride or acid anhydrides was significantly inferior (ref.7).



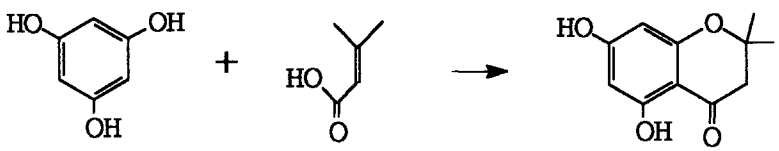
10.3.2. Bicyclic Compounds

4-Phenyl-5,7-dihydroxy-3,4-dihydrocoumarin was formed in 87% yield from phloroglucinol and Meldrum's acid in pyridine and addition after 10 mins. of benzaldehyde followed by stirring of the reaction mixture at 70-75°C for 1 hour

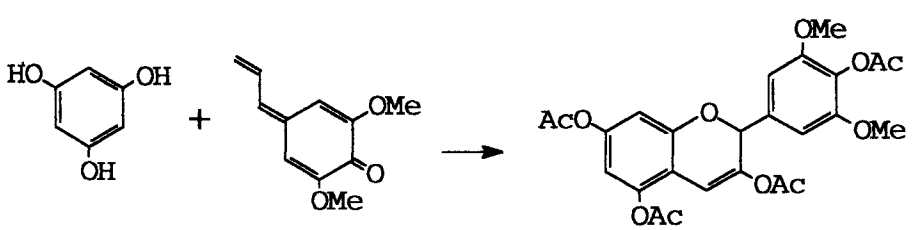
(ref.8).



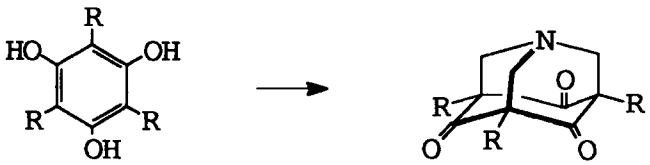
By contrast, reaction of phloroglucinol with 3,3-dimethylacrylic acid (3-methylbut-2-enoic acid) in the presence of anhydrous aluminium chloride and phosphorus oxychloride by agitation during 5 hours at ambient temperature gave a 90% yield of 2,2-dimethyl-5,7-dihydroxychroman-4-one (ref.9).



2-(4'-Acetoxy-3,5-dimethoxyphenyl)-5,7-diacetyl-3-acetoxyflav-3-ene has been synthesised from the quinonemethide shown by addition to a benzene/dimethyl formamide (25:1) solution of phloroglucinol followed by reaction for 2 mins. in the presence of a catalytic quantity of 4-toluenesulphonic acid to give initially the open chain C-alkylated intermediate in 48% yield. This was stirred for 48 hours at ambient temperature in benzene/acetone containing silver oxide and was then acetylated with acetic anhydride/pyridine (ref.10).

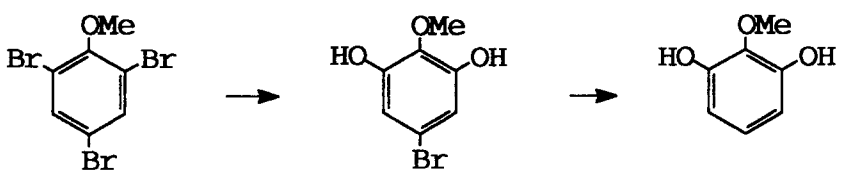


Trimethylphloroglucinol (R = Me) and hexamethylenetetramine after refluxing in methanol during several hours afforded the aminoalkylated tetracyclic product indicated containing three 3,5-dimethylpiperid-4-one rings in 80% yield (ref.11).



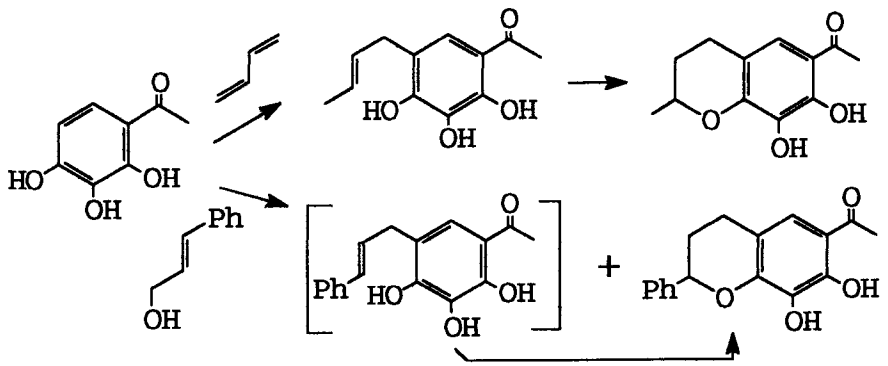
10.4 Reactions of 1,2,3-trihydroxybenzenes

The methylation of pyrogallol affords a mixture of products in which the 2-O-methyl ether would be expected to be a minor component. It is not irrelevant perhaps to this section to note that this compound, 2,6-dihydroxyanisole (2-O-methylpyrogallol) has been prepared regiospecifically. By treatment of 2,4,6-tribromoanisole with 2 moles of butyllithium, 2,6-dilithio-4-bromoanisole is formed in situ which with trimethyl borate followed by oxidation with peracetic acid afforded 4-bromo-2,6-dihydroxyanisole. Hydrogenation in the presence of Pd-C then gave the product in an overall yield of 91% (ref.12).

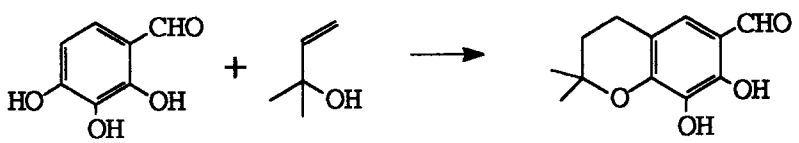


2,3,4-Trihydroxyacetophenone in xylene containing orthophosphoric acid was treated with buta-1,3-diene at 30-5°C during 2 hours and stirring continued for a further 15 hours to give the alkylated product 5-(but-2-enyl)-2,3,4-trihydroxyacetophenone and a small quantity of the final cyclised product 6-acetyl-7,8-dihydroxy-2-methyl-3,4-dihydro-2H-benzopyran more of which was obtained by heating the intermediate in orthophosphoric acid on a water bath (ref.13).

The 2-phenyl analogue of this compound, 6-acetyl-7,8-di hydroxy-2-phenyl-3,4-dihydro-2H-benzopyran has been prepared in 35% yield by the gradual addition over 6 hours of cinnamyl alcohol in benzene solution to a stirred suspension at 60°C of 2,3,4-trihydroxyacetophenone in orthophosphoric acid in benzene (2:5) with continuance of reaction for a further 12 hours. Some uncyclised material, 5-cinnamyl-2,3,4-trihydroxyacetophenone (25%) was cyclised by heating with phosphoric acid at 80°C at which temperature the starting material furnished only the cyclised product directly in 55% yield (ref.14).



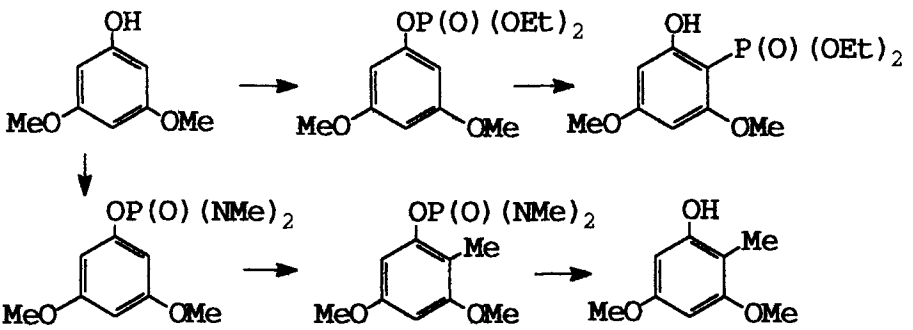
The corresponding aldehyde, 2,3,4-trihydroxybenzaldehyde in light petroleum solution containing 85% orthophosphoric acid by treatment with 2-methylbut-3-en-2-ol in light petroleum during 6 hours with continued reaction for 4 hours afforded the formyl compound, 6-formyl-7,8-dihydroxy-2,2-dimethyl-3,4-dihydro-2H-benzopyran in 75% yield (ref.15).



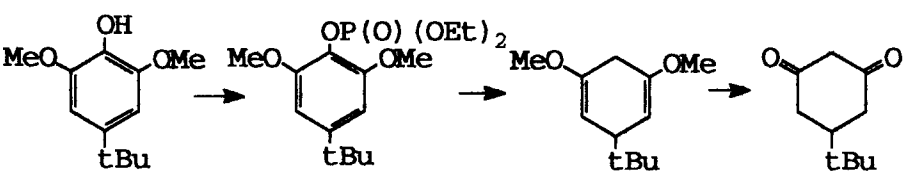
10.5. Reactions of Alkoxy Derivatives of 1,3,5-trihydroxybenzene

Mono and dialkoxy as well as diacyloxy derivatives of phloroglucinol have served as protected compounds in various syntheses. Rearrangement of diethyl 3,5-dimethoxyphenyl phosphate (derived from 3,5-dimethoxyphenol) in tetrahydrofuran added gradually at -78 C to lithium diisopropylamide in tetrahydrofuran during 15 mins. followed by stirring at 0°C for 30 mins.gave a 93% yield of diethyl 2,4-dimethoxy-6-hydroxyphenyl phosphonate (ref.16).
In another approach, the phosphorodiamidate group (prepared by a standard procedure on the phenol) has been used to direct and effect o-methylation of 3,5-dimethoxyphenol possibly partially by way of the C-phosphorodiamidate. To the O-phosphorodiamidate in tetrahdyrofuran, sec-butyllithium (1.2 moles) was added at -105°C over 1 hour and the product quenched with methyl iodide (1.5 moles) to give a 93% yield of 2-methyl-3,5-dimethoxyphenol after acidic hydrolysis of the bis(dimethylamino)phosphoryl group by refluxing with formic acid (ref.17). Both these sequences are shown starting in each case with 3,6-

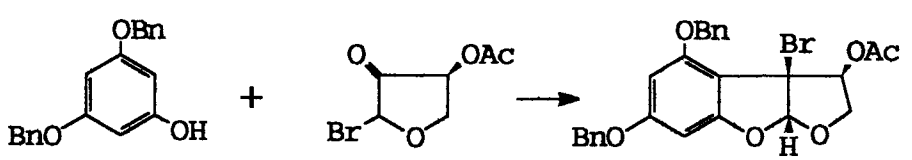
dimethoxyphenol.



Dehydroxylation of 4-tert-butyl-2,6-dimethoxyphenol was achieved in the following way. The phenol as its diethyl phosphate in tetrahydrofuran/t-butanol was added to 100% ammonia into which small pieces of lithium were introduced over 1 hour. Further lithium was added to maintain a blue colour whereby 3-tert-butyl-1,5-dimethoxy-1,4-cyclohexadiene was obtained in 82% yield (ref.18). Hydroysis of the enol ether with dilute acid afforded 5-tert-butylcyclohexane-1,3-dione.

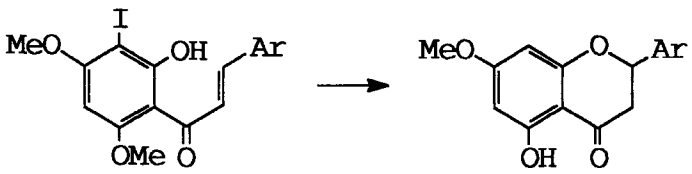


3,5-dibenzyloxyphenol after initial treatment with hydrogen bromide-saturated dichloromethane followed by addition over 5 mins. of 4-acetoxy-2-bromotetrahydrofuran-3-one in dichloromethane and reaction for 20 mins. at ambient temperature gave a 42% yield of 3-acetoxy-3a-bromo-4,6-bis (dibenzyloxy)-2,3,3a,8a-tetrahydrofuro[2,3-b]benzofuran (ref.19).

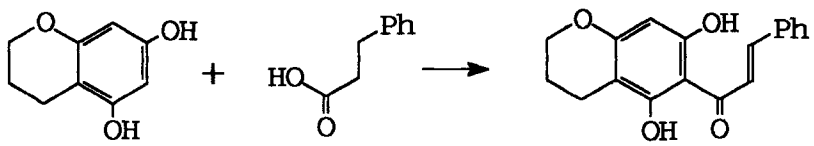


The flavone, 5-hydroxy-7,4'-dimethoxyflavone (Ar = 4-MeoC$_6$H$_4$) was formed in

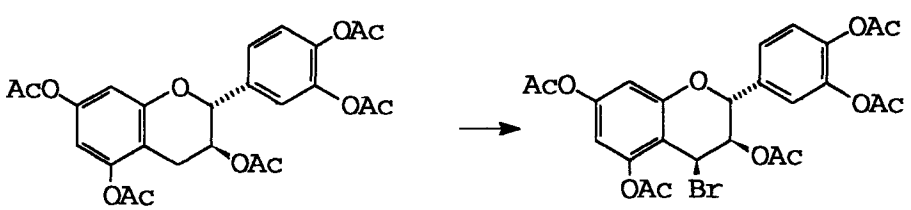
80% yield from 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone in dimethylformamide by treatment with nickel(II) chloride, zinc powder and potassium iodide followed by refluxing for 3 hours (ref.20).



6-Cinnamoyl-5,7-dihydroxychroman has been formed in 83% yield from 5,7-dihydroxychroman and cinnamic acid by treatment of the mixture with freshly fused zinc chloride and phosphorus oxychloride and reaction at ambient temperature for 24 hours (ref.21).



The benzylic position in the phloroglucinol moiety of (+)penta-O-acetylcatechin in hot carbon tetrachloride reacted in preference to the ring in bromination during 5 hours with N-bromosuccinimide plus a small quantity of benzoyl peroxide with a 50% yield (83% conversion) and formation of the β-product (ref.22).

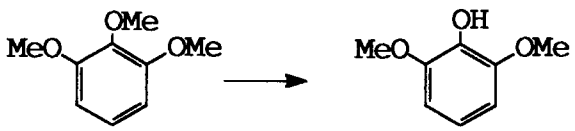


10.6. Reactions of Alkoxy Derivatives of 1,2,3-trihydroxybenzene

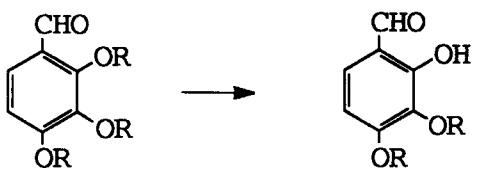
10.6.1. Reactions at Methoxyl Groups

Pyrogallol trimethyl ether was selectively demethylated in dichloromethane

containing boron trichloride by reaction at -10 to 0°C initially and for 3 hours at ambient temperature to give a 90% yield of 2,6-dimethoxyphenol (ref.23).

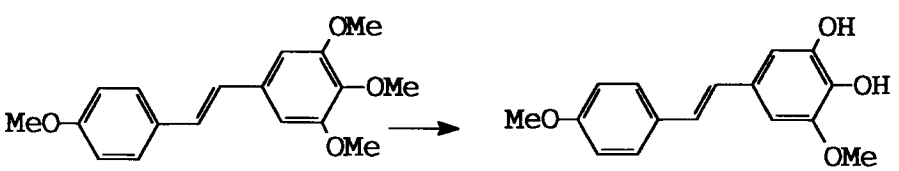


By contrast, 2,3,4-tris(2-ethylhexyloxy)benzaldehyde in 1,2-dichloroethane was monodealkylated selectively at the 2-position by the dropwise addition over 30 mins. of titanium tetrachloride at 8-12°C with continued stirring for a further 30 mins. and then at ambient temperature for 2 hours prior to quenching with dilute hydrochloric acid to afford 2-hydroxy-3,4-bis(2-ethylhexyloxy)benzaldehyde in 73% yield (ref.24).



[R = $CH_2CH(Et)Bu$]

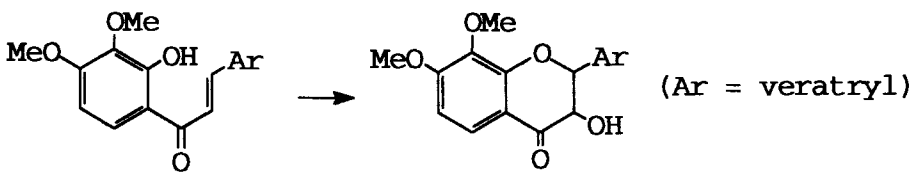
3,4,5,4'-Tetramethoxystilbene was selectively didemethylated in 80% yield to 3,4-dihydroxy-4',5-dimethoxystilbene by refluxing for 6.5 hours in benzene containing lithium aluminium hydride (ref.25).



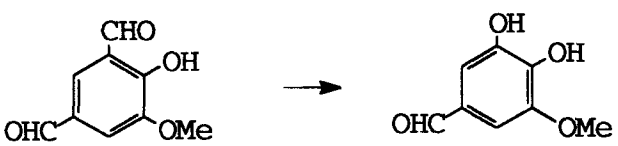
10.6.2. Reactions at the Side Chain Position

2-Hydroxy-3,4-dimethoxyacetophenone with benzaldehyde (1.5 moles) in ethanol containing 30% aqueous potassium hydroxide and a catalytic quantity of benzyltrimethylammonium chloride, the inclusion of which was essential, after being stirred at 30°C for 24 hours was cooled to 0°C and gassed with sulphur dioxide to give a 93% yield of benzylidene 2-hydroxy-3,4-dimethoxyacetophenone (ref.26).

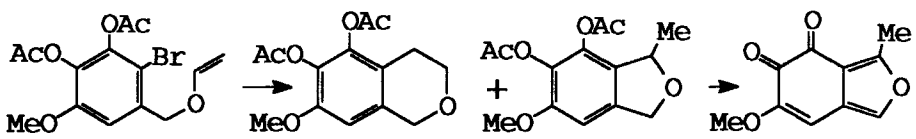
By treatment of structures such as the above with oxidising agents 3-hydroxyflavanones were prepared from 2-hydroxychalcones. Thus, 3,4-dimethoxybenzylidene 2-hydroxy-3,4-dimethoxyacetophenone in dioxan containing diethylamine treated with 30% hydrogen peroxide and the mixture left to complete the reaction gave a 63% yield of 2-(3,4-dimethoxyphenyl)-3-hydroxyflavone (ref.27).



The pyrogallol ring system was obtained by a Dakin reaction on 2-methoxy-4,6-diformylphenol which in 0.1M sodium hydroxide at 5°C was treated with a small quantity of copper sulphate pentahydrate followed over 1 hour by 10% hydrogen peroxide at 5-10°C. After 15 mins. reaction, work-up gave a 91% yield of 3-methoxy-5-formylcatechol (ref.28).

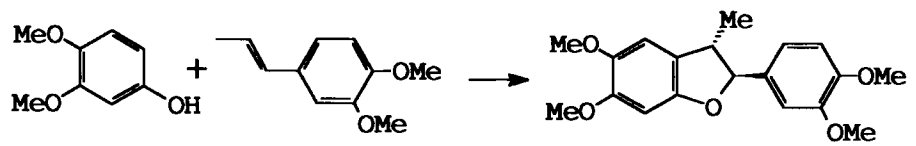


The diacetoxymonomethoxy vinyl ether derivative shown has been used in a radical cyclisation procedure with tributyltin hydride to furnish a mixture of cyclic ethers in 87% yield of which 70% comprises a five-membered ring compound. Hydrolysis and oxidation of this with dichlordicyanobenzoquinone resulted in 6-methoxy-3-methylisobenzofuran-4,5-dione, albidin, a red pigment from *Penicillium albidum* Sopp (ref.29).

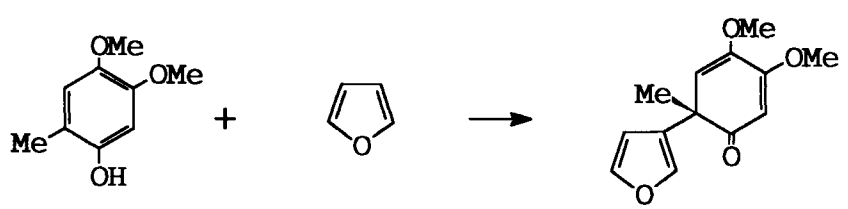


10.7. Reactions of Alkoxy Derivatives of 1,2,4-trihydroxybenzene

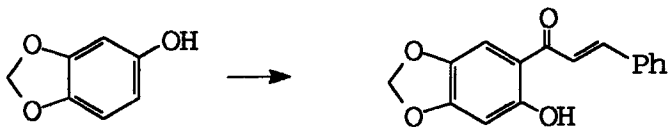
3,4-Dimethoxyphenol and (E)-3,4-dimethoxypropenylbenzene (4 moles.) in acetonitrile gave the trans-product shown in 65% yield upon treatment with phenyl iodosodi(trifluoroacetate) (ref.30) although the triacetate gave inferior yields.



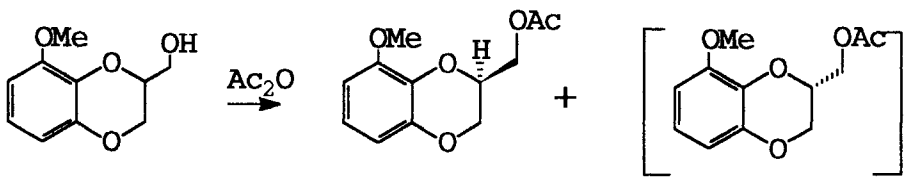
3,4-Dimethoxy-6-methylphenol and furan in acetic anhydride contaning tetra-n-butylammonium fluoroborate by electrolysis at 160-220mV with a current of 0.27mA/cm2 until 2F/mol. had been consumed gave the furylcyclohexadienone in the moderate yield of 32% (ref.31).



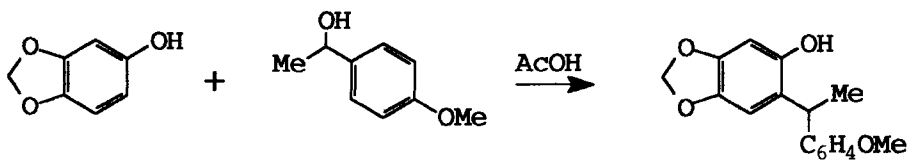
3,4-Methylenedioxyphenol in ethereal solution by conversion with ethyl magnesium bromide to the ethoxymagnesio derivative at ambient temperature and removal of solvent and its replacement with toluene, was acylated with cinnamoyl chloride by dropwise introduction of a toluene solution of the acid chloride and reaction at ambient temperature for 5 hours following which work-up by quenching with ammonium chloride solution, gave 2-hydroxy-4,5-methylenedioxychalcone in 70% yield (ref.32).



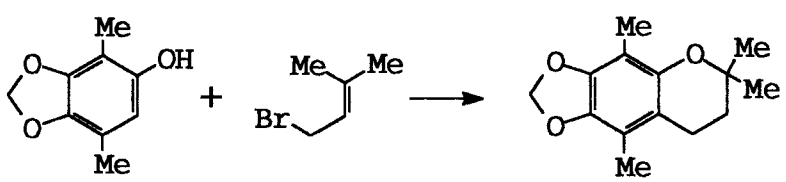
2-Hydroxymethyl-8-methoxy-1,4-benzodioxane in benzene containing acetic anhydride by treatment at ambient temperature with the enzyme, Amano P-30 afforded after work-up at 50% conversion (monitored by HPLC analysis) a 44% yield of (S)-2-hydroxymethyl-8-methoxy-1,4-benzodioxane (e.e.83%) (ref.33).



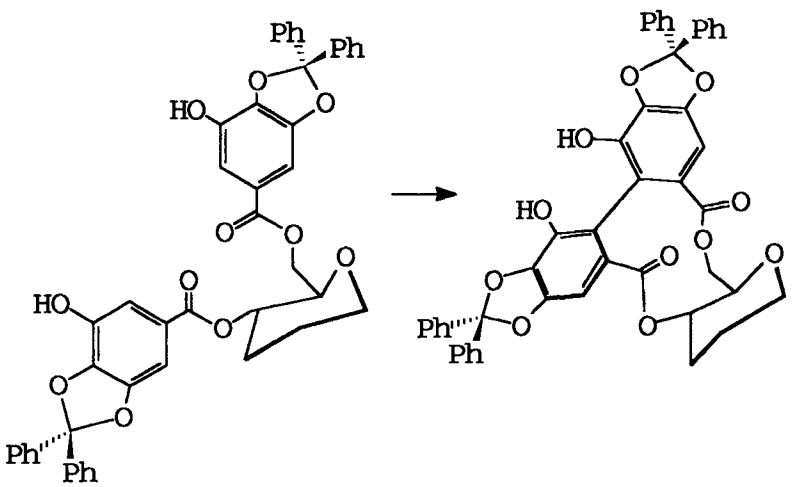
Alkylation of 3,4-methylenedioxyphenol with 1-(4-methoxyphenyl)ethanol in glacial acetic acid/water (6:1) was effected by refluxing for 7 hours to give a 97% yield of 3,4-methylenedioxy-6-[α-(4-methoxyphenyl)ethyl]phenol (ref. 34).



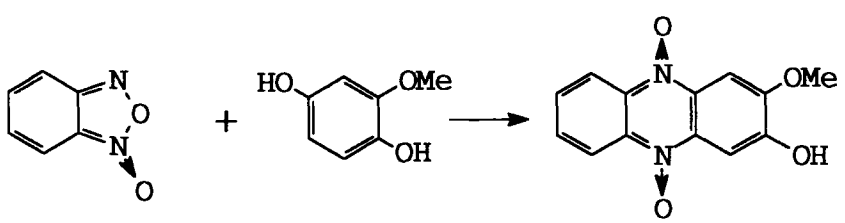
The 2,5-dimethyl analogue of the preceding phenol in benzene containing anhydrous zinc chloride was alkylated with 3-methylbut-3-enyl bromide at 60 C over 3 hours to give 2,2,5,8-tetramethyl-[1,3]dioxolo[6,7-d]chroman in 72% yield (ref.35).



The 3,4-ketal of 3,4,5-trihydroxybenzoic acid (gallic acid) with benzophenone in the form of its 2,3-diacylpyranyl derivative upon treatment in dichloromethane and pyridine containing lead tetraacetate at 0°C afforded a coupled product (in diastereoisomerically pure form) at the 6,6'-positions of the adjoining aromatic rings in 79% yield (ref.36). One of four possible forms is shown.



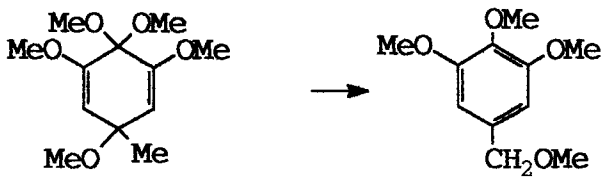
2-Methoxyhydroquinone with benzofurazan oxide in methanolic suspension by treatment with powdered sodium hydroxide and stirring of the mixture for 6 hours afforded a 78% yield, after work-up by acidification with acetic acid, of 2-hydroxy-3-methoxyphenazinedi-N-oxide (ref.37).



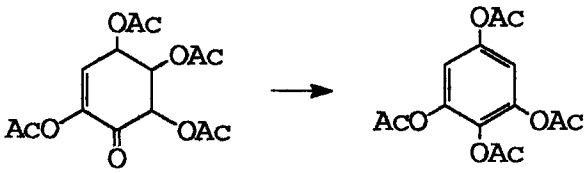
10.8 Reactions of Polyalkoxy and Tetraacylbenzenoid Compounds and Polyalkoxynaphthalenes

A methanolic solution of 1,3,5,6,6-pentamethoxy-3-methyl-1,4-cyclohexadiene upon treatment with a small proportion of concentrated sulphuric acid and

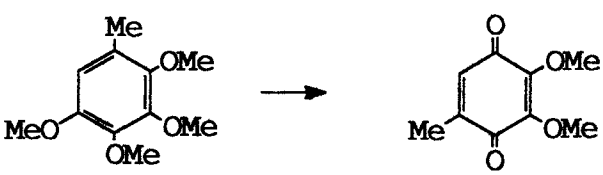
stirring of the mixture for 1 hour at ambient temperature gave a 97% yield of 3,4,5-trimethoxybenzyl methyl ether (ref.38).



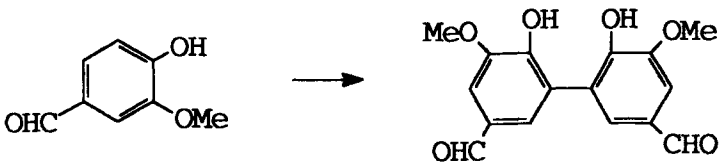
The tetraacetate of 1,2,3,5-tetrahydroxybenzene has been synthesised from the cyclohexenone shown (ref.39).



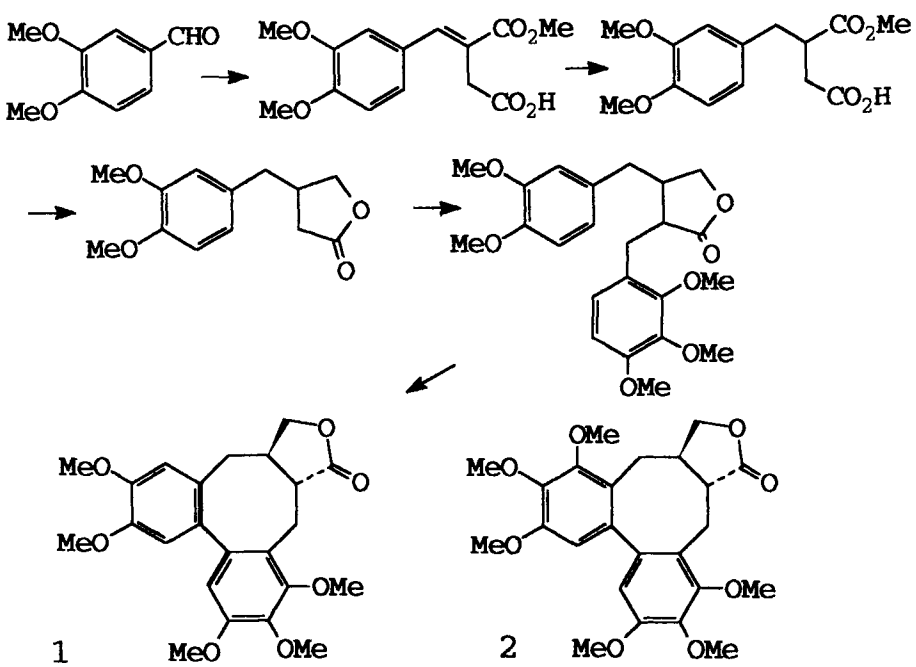
2,3,4,5-Tetramethoxytoluene in methanol containing sodium hydroxide was electrolysed at a platinum electrode in the anode compartment of a cell divided by glass filters at a current density of 10mA/cm.2 until 2.2F/mole current had passed at ambient temperature, to give a 90% yield of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (ref.40).



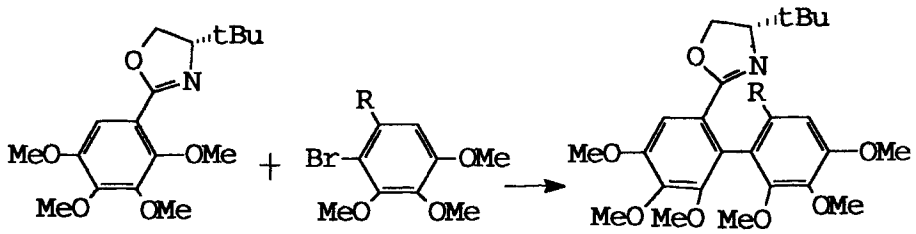
4-Hydroxy-3-methoxybenzaldehyde (vanillin) in acetonitrile containing potassium bicarbonate upon treatment with 1-oxo-2,2,6,6-tetramethylpiperidinium fluoroborate gave (dehydrovanillin), 2,2'-dihydroxy-3,3'-dimethoxy-5,5'-diformyl-biphenyl in 85% yield (ref.41).



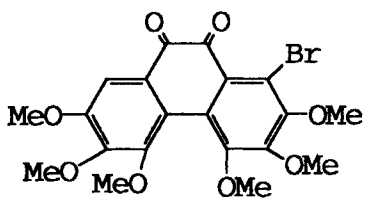
Diaryl oxidative coupling of polymethoxydibenzylbutanolides by means of ruthenium dioxide dihydrate in fluoroacetic acid containing trifluoroacetic anhydride and boron trifluoride etherate over 24 hours at ambient temperature has been used to obtain the pentamethoxy compound, neoisostegane (1) and the hexamethoxy analogue, steganolone (2) in racemic form in nearly quantitative yields. Both compounds are important lignan lactones which, from the same intermediates, resulted in only low yields with vanadium oxyfluoride. Thus for neoisostegnane, 3,4-dimethoxybenzaldehyde underwent the Stobbe reaction with dimethyl succinate, reduction gave methyl 3-(3,4-dimethoxyphenyl)-2-carboxymethylpropionate. Upon hydrolysis with potassium hydroxide and reduction by means of calcium borohydride, 3-(3,4-dimethoxybenzyl)butanolide resulted, alkylation of which with 2,3,4-trimethoxybenzyl bromide gave the required intermediate for oxidative coupling



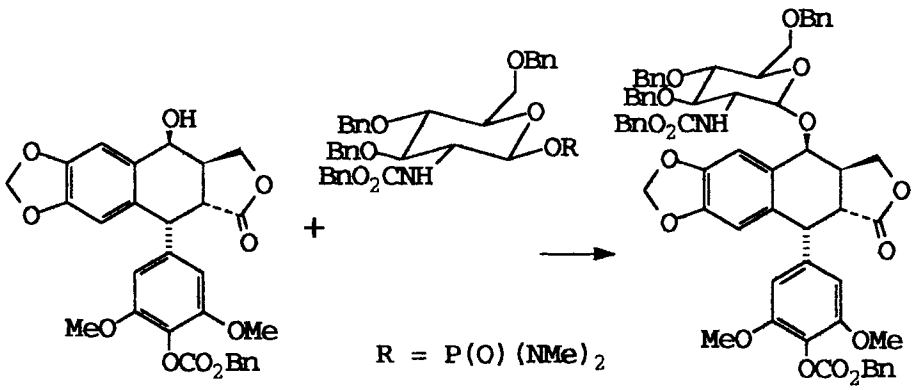
(ref.42).
The Grignard reagent from the 2,3,4-trimethoxybromobenzene shown (R = CH_2OSiMe_2tBu) by reaction with the chiral oxazinyl-2-yl tetramethoxy compound indicated by refluxing in tetrahydrofuran for between 48 and 60 hours afforded a hexamethoxybiphenyl derivative in 60% yield accompanied by methoxyl group



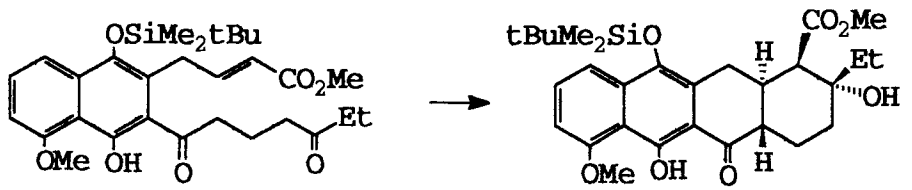
displacement with retention of configuration (S:R,>98%) (ref.43).
Only the less hindered keto group in the hexamethoxyphenanthrene quinone indicated, formed a ketal in 92% yield with 2,2-dimethyl-1,3-propanediol upon refluxing for 2-3 hours in benzene accompanied by azeotropic water removal in the presence of 4-toluenesulphonic acid (ref.44).



The polyoxy tetrahydronaphthalene (in the epipodophyllotoxin series) readily formed an O-glucoside in 74% yield with 3,4,6-tri-O-benzylglucosyl-2-benzyloxycarbonylamino-D-glucosephosphorodiamidate in dichloromethane containing boron trifluoride-etherate and 4A molecular sieve during 15mins. at -8°C (ref.45).

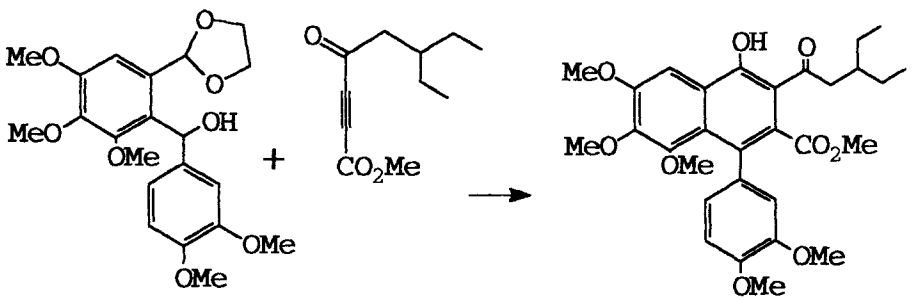


The naphthalene derivative, methyl 4-(1'-t-butyldimethylsilyloxy-4'-hydroxy-5'--methoxy-3'-(5''-oxoheptanoyl)naphth-2'-yl)-2-butenoate, in tetrahydrofuran added to a suspension of potassium hydride, Kryptofix 222 and hexamethylphosphorictriamide in tetrahydrofuran at -78°C and worked up after 3 hours at -78 to -50°C underwent a double condensation to give a 53% yield of methyl (6a-RS,9-RS,10-RS,10a-RS)-9-ethyl-12-t-butyldimethyl silyloxy-5,9-dihydroxy-4-methoxy-6-oxo-6,6a,7,8,9,10,10a,11-octahydronaphth-

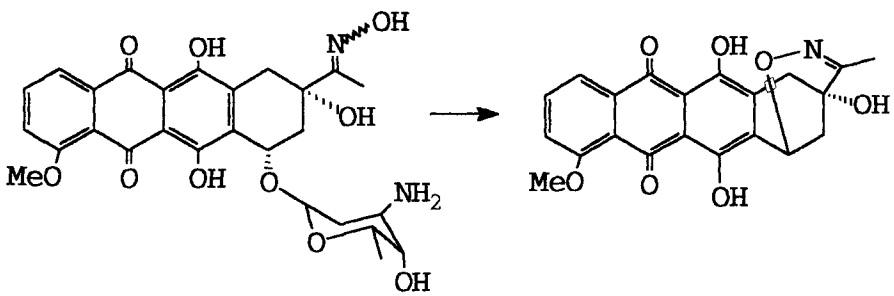


acene-10-carboxylate (ref.46).

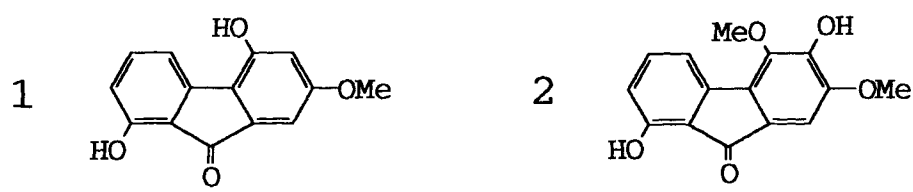
A polymethoxydiphenylmethane derivative underwent addition to an α-acetylenic ketone to afford essentially a 1-dimethoxyphenylpolymethoxy naphthalenic compound. Thus, a mixture of methyl 6-ethyl-4-oxooctyn-2-oate and the dioxyethano acetal of 2-(3,4-dimethoxy-α-hydroxybenzyl)-3,4,5-trimethoxybenzaldehyde in benzene containing 4-toluenesulphonic acid when refluxed for 1 hour gave a 30% yield of methyl 1-(3,4-dimethoxyphenyl)-3-(3-ethyl-1-oxopentyl)-4-hydroxy-6,7,8-trimethoxynaphthalene-2-carboxylate (ref.47).



Intramolecular molecular trapping led to the formation of 7,13-dideoxy-7,13-(epoxynitrilo)daunomycinone in 52% yield from the oxime shown in methanol containing 1M aqueous sodium hydroxide (deareated with argon) by the addition of the one electron reducing agent, meso-bi(3,5,5-trimethyl-2-oxo-morpholino-3-yl) and reaction for 1/2 hour at 30°C followed by admission of air to the mixture (ref.48).



The naturally-occurring polyhydroxyfluorenones (1) and (2) have been isolated from an orchid (ref.49).



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CHAPTER 11

BRANCHED ALKYLPHENOLS OF INDUSTRIAL INTEREST

11.1 Introduction

The chemistry of certain alkylphenols and that of hindered phenols has been discussed in chapter 6 where tabulated material has included introductory reference to compounds considered at length in the present chapter. Alkylphenols possessing longer alkyl chains which are sometimes mono- but usually multi-branched have achieved special industrial interest notably those with C_8 and C_9 alkyl groups in the 4-position such as 4-t-nonyl- and 4-t-octylphenol. In addition, 4-t-butylphenol has also attained a considerable level of commercial chemical interest and in recognition of the unique position of these types of compound their chemistry is now detailed.
Compounds considered have generally been derived from the reaction of alkenes and less commonly from dienes with phenols. In each group the structure, preparation and reactions are reviewed.

11.2 Synthetic Alkylphenols derived from Alkenes

(i) C_4, C_8 and C_9 Commercial Branched Chain Alkylphenols

Typically these compounds have their origin in alkenes possesssing a single double bond emanating from the petrochemical industry, such as propene, isobutene and their polymers, diisobutene and propene trimer. The uses of ethene to produce 4-ethylphenol and of propene to give 4-hydroxycumene are not reviewed here, reference having been made to the latter in the introductory chapter on the preparation of resorcinol and hydroquinone.
Some of the important structures arising, a brief note of their properties and some of their many uses are listed in Table 11.1 The C_4 and C_8 alkylphenols are pure compounds although the latter due to rearrangement can contain a small proportion of the 1,1,2,3-tetramethylbutyl isomer. By contrast the C_9 member is a mixture of several isomers as is the C_{12}, dodecylphenol a less well known material which is not listed in the Table. Nevertheless the vast number of uses of nonylphenol are partly attributable to this very lack of homogeneity. An extensive list of alkylphenols with their properties has been descrbed (ref.1)

TABLE 11.1

ALKYLPHENOLS FROM PHENOL AND 3-METHYLPHENOL

ALKENE	COMPOUND	Mp (C)	Bp(C) /at. pr.*	USES
ALKYLPHENOLS from PHENOL:				
iso-Butene	4-tert-Butylphenol	99	237	Resins with formaldehyde Antioxidant.
2,2,4-Trimethyl pent-1-ene and 2-ene	'Octylphenol'	83	290	Oil-soluble resins with formaldehyde Surfactants with oxirane.
Propene trimer	'Nonylphenol'	liquid	310	Surfactants with oxirane Phosphite as antioxidant.
Propene tetramer	'Dodecylphenol	liquid	334	Lubricating oil additive
ALKYLPHENOL from 3-METHYLPHENOL:				
iso-Butene	3-methylphenol	22	240	Synthesis of musk ambrette

(* 1 atmosphere = 101.3kPa)

(ii) Synthesis of Branched Chain Alkylphenols from Phenol

Type of Alkylating Agent

Alkylphenols of commercial significance are produced almost exclusively by the reaction of an alkene with a phenol, a methylphenol or a dimethylphenol rather than by the use of the corresponding alkyl chloride or alcohol although this type of procedure was formerly widely used (ref.2) and may indeed be applicable in cases where these two structures are more available than the alkene itself. The use of alcohols results in the formation of a mole of water which can obstruct the catalyst although paradoxically in certain patented procedures the admission of water is deemed necessary. Diisobutene (a mixture of 2,4,4-trimethylpent-1- and 2-enes) from iso-butene, propene trimer (a mixture of isomers, probably substantially tetramethyl C_5 and trimethyl C_6 isomers), propene tetramer (isomeric dodecenes) are readily available as well as heptenes by cross-polymerisation. On account of increasing interest in the biodegradability of industrial products, alkenes of more linear structure which meet this requirement have been used in recent practice as has been the case with the side-chain structures present in the alkylarylbenzene surfactants.

Structure and origin of the phenolic component

Phenol from the cumene process, 2-methylphenol, 3-methylphenol and 4-methylphenol from the alkylation of phenol with methanol and also, in the last exanple, from 4-methylcumene (cymene) constitute the main source of the monohydric phenols generally used.

Type of Catalyst employed for alkylations

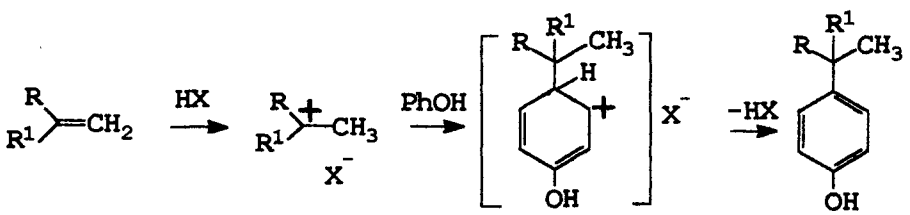
A variety of catalysts have been examined, comprising protonated acids including phosphoric acid on Fuller's earth, sulphuric acid on the same support, and cation exchange materials. Lewis acids such as aluminium chloride , boron trifluoride and its etherates, zinc chloride, silica/alumina, toluene-4-sulphonic acid and montmorillonite clays have found some application in numerous studies although generally the phosphoric acid system appears to be most favoured.

Reaction Conditions for the Synthesis of Branched Chain Alkylphenols

The alkene component A usually a C_4, C_8 or a C_9 compound or mixture of

isomers becomes converted to a carbocation $(HA^+)X^-$ by the action of the catalyst (HX), a proton source or Lewis acid to form a π complex which facilitates electrophilic addition by way of a σ complex to afford $(AAr^+OH)X^-$. This is then usually transformed to the final product AArOH with regeneration of the catalyst although loss of the alkylating component can also occur. The first and final stages in the sequence for 4-alkylation are depicted in the scheme of the general reaction where, R = H or Me, and $R^1 = C_nH_{2n+1}$. In the case of nonylphenol the technical product consists of 85-90% of the 4-alkyl compound 10-12% of the 2-alkyl and 5% of 2,4-dinonylphenol. Purer grades contain less than 5% of the 2-alkyl and none of the 2,4-dinonyl compound.

In one approach propene trimer was added to a solution of boron trifluoride in phenol and the mixture was introduced into heptane. The BF_3 evolved was absorbed in phenol for reuse (ref.3) and upon recovery of the heptane,



nonylphenol obtained containing approximately 10% of dinonylphenol. Entrainers other than heptane such as benzene could be employed although alkanes and cycloalkanes were preferred.

Boron trifluoride-dimethylether ($BF_3.Me_2O$) has been employed . Thus in a continous process phenol and nonene together with fresh and recovered catalyst were reacted at 80-5°C. Distillation gave nonylphenol and both recovered phenol and catalyst. In a similar way octene afforded octylphenol in 92.5% yield while di-isobutylene gave 94% (ref.4) .

Phenol containing zinc chloride catalyst has been treated with hydrogen chloride and then at 90°C, with nonene. After reaction, distillation afforded nonylphenol in high yield. The same process was applied to the synthesis of 4-tert-butylphenol (ref.5).

Processes involving silica/alumina (SiO_2/Al_2O_3) have been employed. In this way phenol containing 0.5% water and nonene were separately introduced into a reactor at 185°C, under pressure, holding the catalyst to give 4-nonylphenol (97%), 2-nonylphenol (2%) and 3-nonylphenol (1%) (ref. 6). In the absence of the catalyst the yields were lower.

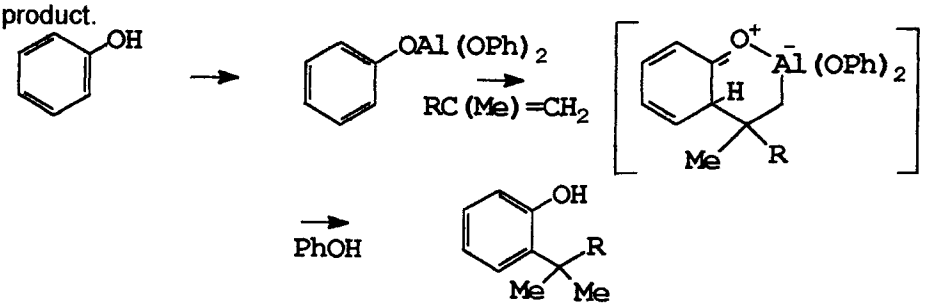
By contrast, with a cation exchange resin (KU-2), 2-alkylphenols reacted in p-

TABLE 11.2

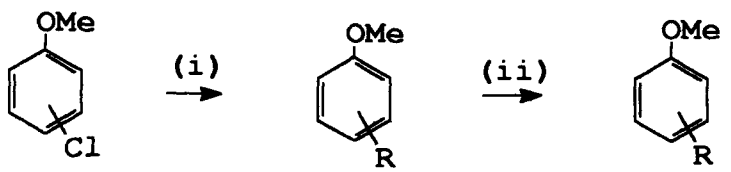
SYNTHESIS OF ALKYLPHENOLS (REACTANTS, CONDITIONS and CATALYSTS)

PHENOL(moles)	ALKENE(moles)	TEMP.(C)	CATALYST(moles)	PRODUCT(moles)	YIELD%	REF.
Dinonyl (0.5) + phenol (1.5)	-	160-170	Active clay	Nonylphenol (0.45)	45	9
Phenol (2.0)	Propene (0.95) trimer	45	BF_3 (0.1)	Nonylphenol (0.85)	89	3
Phenol (1.06)	Nonene (0.76)	70	$BF_3.Me_2O$ (0.14)	Nonylphenol (0.74)	98	4
"	Octene	"	"	Octylphenol	92.5	"
"	Diisobutene	"	"	"	94	"
Phenol (159.6)	iso-Butene (160.7)	90	$ZnCl_2$ (0.93) + HCl (6.68)	tert-Butylphenol (153.3)	96	5
Phenol (8.0)	1-Nonene (7.77)	90	$ZnCl_2$ (0.06)	Nonylphenol (7.02)	88	5
Phenol (1.0)	Propene (0.95) trimer	100	4-Toluenesulphonic acid H_2O (wt.% 0.1)	Nonylphenol	82	11
Phenol	Diisobutene	160	Montmorillonite clay	Octylphenol	98	8

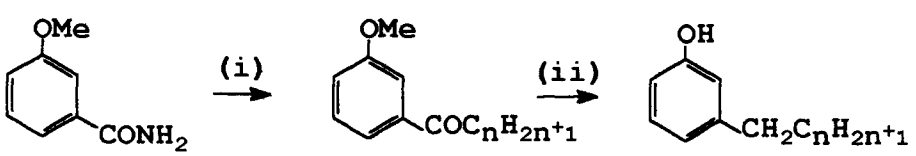
xylene at 140-3°C with alkenes to give 2,4-dialkylphenols indicating the far greater reactivity of the phenol compared with the solvent (ref.7).
Clays have found an application. For example, a mixture of phenol, di-isobutylene and 2% of an activated Montmorillonite clay catalyst, when held at 158-161°C, resulted in a 98% yield of 4-octylphenol as a white crystalline solid (ref. 8). Polyalkylphenols and phenol with an active clay at 160-170°C afford the monoalkylphenol (ref. 9). The pretreatment of a bentonite clay with an organic solvent and a strong acid (72% sulphuric acid) at 77°C has been described which results in a catalyst thirty times more active than an untreated one (ref. 10).
Organic sulphonic acids can be used instead of sulphuric acid. For example, phenol and a propene polymer having 9-24 C atoms react in the presence of 4-methylbenzenesulphonic acid monohydrate at 80-150°C to produce an 81.7% yield of 4-nonylphenol . 4-Dodecylphenol is obtained similarly (ref.11) .
In the generally preferred continuous alkylation process, phenol and the alkene react rapidly in the presence a Fuller's earth catalyst impregnated with phosphoric acid at 80-100°C. At the conclusion of the reaction, after filtration of the catalyst and neutralisation, fractionation affords the 4-alkylphenol with recovery of the 2-alkylphenol and unchanged phenol both of which are recycled.
All the alkylation methods referred to give substantially the 4-isomer, the 2-isomer only resulting if the 4-position is occupied. When the 2-alkylphenol is exclusively required the use of aluminiium phenoxide enables this regiospecificity to be achieved (ref. 12,13), although above 180°C dealkylation can take place with this reagent. The method has been referred to brielfly in Chapter 6. The reaction involves formation of a complex of aluminium phenoxide with the 1-alkene and electron donation from the the 2-position to the oxygen atom, attack by phenol with regeneration of aluminium phenoxide.
Table 11.2 shows and summarises some typical results referred to above and described in the literature for the 4-alkylphenols from the reaction of phenol with various alkenes .
Not mentioned in the table are the catalysts methanesulphonic acid, xylenesulphonic acid and certain modified zeolites all of which have found some application. Other alkenes include the pentenes and isomers of the compounds in the table such as non-1-ene. Of importance in industrial reaction conditions are procedures to avoid alkene/alkene side reactions and promote the desired alkene/phenol reaction, with temperature control to avoid dealkylation of the product.



With the exception of 4-(1,1,3,3-tetramethylbutyl)phenol prepared from di-isobutylene, all the multi-branched alkylphenols discussed consist of isomeric mixtures. In the pursuance of structure/property interests several studies have aimed to synthesise pure compounds. Thus by Wurtz-type methodology the reaction of the isomeric chloroanisoles with (i) alkyl iodides in ethereal solution in the presene of sodium and (ii) demethylation of the resultant alkylanisoles with aluminium bromide, a range of C_5, C_8 and C_9 alkylanisoles has been synthesised (ref. 14). Numerous other methods are available for the synthesis of the isomeric n-, iso-, sec- and tert-alkylphenols some of which are referred to in Chapter 13. Reaction of a mixture of the appropriate alkyl chloride and 2-, 3-, or 4-methoxybenzaldehyde by addition to lithium affords the benzylic alcohol in high yield which upon hydrogenolysis with Pd-C/H_2 gives the alkylbenzene methyl ether. Alternatively the Wittig reaction of the methoxybenzaldehyde with an alkylidenephosphoran results in an alkene and reduction then gives the saturated product. Demethylation can be effected with boron tribromide.



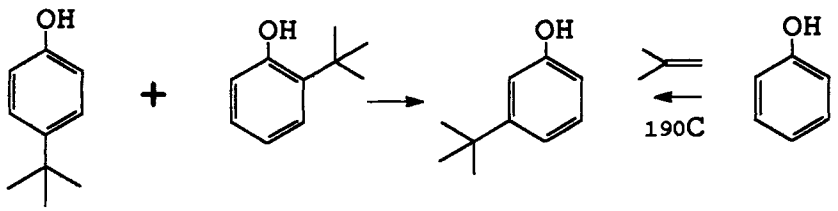
Another alternative approach primarily intended for the synthesis of 3-alkylphenols consisted in the reaction of (i) alkylmagnesiumbromides with 3-methoxybenzamide to afford the corresponding 3-methoxyphenyl n-alkylketone which was reduced (ii) by the Clemmensen method to the n-alkyl-3-methoxybenzene, demethylation of which with aluminium chloride was considered to give the 3-n-alkylphenol (ref. 15).



Friedel-Crafts conditions used at the demethylation stage may well result in some dealkylation in addition to demethylation as well as isomerisation of the side-chain.

Isomerisation Reactions

Although the thermodynamically more stable 3-tert-butylphenol can be synthesised by the reaction of phenol with iso-butene above 190°C over an activated silica/alumina clay catalyst (ref. 16), a preferred method is through isomerisation of the 2- or 4-isomer or of mixtures. Sec-amylphenols also afford 3-sec-amylphenol by thermolysis at 180-190°C (ref. 17).



Alkylation of Methyl and Dimethylphenols

The methylphenols (cresols and the dimethylphenols (xylenols) also respond to alkylation although this procedure is practically exclusively confined to the tert-butyl series. For example, the majority of compounds produced are hindered or crypto phenols the chemistry of which has been discussed in an earlier chapter. For these alkylations a small proportion of sulphuric acid is employed at moderate temperatures. When more valuable alkenes are involved and the objective is the yield of product, boron trifluoride is favoured as a catalyst.
It is of interest that mixtures of 3- and 4-methylphenols are usually employed for the preparation of the di-tert-butyl compounds, namely, 4-methyl-2,6-di-tert-butylphenol and 5-methyl-2,4-di-tert-butylphenol from the butylation reaction which is carried out at 40-50°C and atmospheric pressure with sulphuric acid (2%) as the catalyst. t-Butylation occurs ortho to the hydroxyl group. The products are separable by fractional distillation into the pure compounds. 2,4- and 2,5-Xylenols are employed as a mixture to provide, under the same reaction conditions, a source of the required 2,4-dimethyl-6-tert-butylphenol which has an important use as a stabiliser in petroleum fuels. The products from the reaction with iso-butene are procesed to remove alkali-soluble unchanged 2,5-xylenol together with the mono tert-butyl derivative and the alkali-insoluble 2,4-dimethyl-6-tert-butylphenol is recovered by distillation

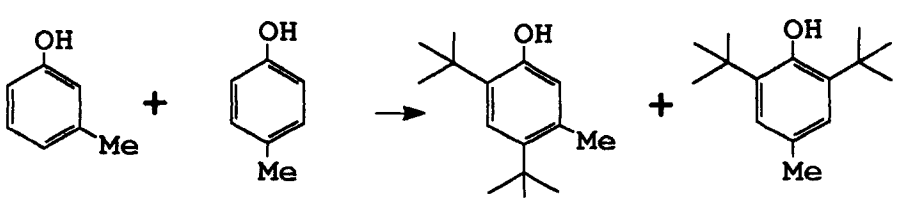
Structure and Reactivity

In all these alkylations of methylphenols and dimethylphenols the structure of

the products formed depends to a considerable extent on the positions of the methyl groups and on the size of the entering group, according to certain rules. Thus the tert-butyl group cannot enter the position between two 1,3-methyl groups (for example 1,3-dimethylbenzene gives with iso-butene, 5-tert-butyl-1,3-dimethylbenzene) or between a 1-methyl and a 3-hydroxyl group. Accordingly 3-methylphenol does not afford a 2-tert-butyl derivative and 3,5-dimethylphenol cannot be alkylated at all. The 1,1,3,3-tetramethylbutyl group will not react at positions unavailable to the tert-butyl group or any position adjacent to a methyl group. Thus, for these reasons 2,5-dimethylphenol cannot be reacted with these alkenes. In the case of the smaller iso-propyl group, the 2-position between a 1-hydroxyl and a 3-methyl is now accessible but not that between two 1,3-methyl groups. Therfore for example, 3,5-dimethylphenol gives on dialkylation with propene, 3,5-dimethyl-2,6-di-isopropylphenol. Although 3-methyl-5-iso-propylphenol (an important isomer of natural thymol, used for the preparation of the N-methylcarbamate, an insecticide), can be synthesised from iso-propylated 3-methylphenol with an activated clay above 250°C or with a molecular sieve (ref. 18), the separation of the required product is difficult and an alternative method has been proposed. This methodology (ref.19.) consists in reacting the mixture of iso-propylated 3-methylphenols with iso-butene in the presence of sulphuric acid whereby all the constituents except the required product form tert-butylated derivatives which are alkali insoluble. The alkali soluble 3-methyl-5-iso-propylphenol is then recovered free from impurities.

Dealkylation

A complication in the preparation of compounds having sec- and tert-alkyl groups in the 2- and in the 4-positions is their vulnerability to thermal dealkylation with acidic catalysts, particularly with 1% oleum in the range 160-200°C, and, as has been mentioned, to aluminium phenoxide when this is used at high temperature (ref.12). Indeed above 250°C all sec- and tert- groups are eliminated from alkylated phenols. The role of thermal dealkylation has been mentioned for the preparation of nonylphenol from dinonylphenol. In the case of 5-methyl-2,4-di-tert-butylphenol and 4-methyl-2,6-di-tert-butylphenol resulting from the tert-butylation of 3-methyl and 4-methylphenol mixtures, the former



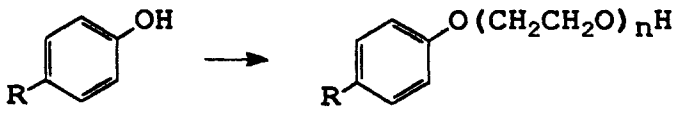
after isolation, upon heating with 1% oleum at 160-200°C loses the 4-butyl group preferentially, leaving 5-methyl-2-tert-butylphenol which can then be readily recovered. By contrast, when aluminium phenoxide was used at 180°C, the same compound gave a mixture of 5-methyl-2-tert-butylphenol and the normally inaccessible 3-methyl-4-tert-butylphenol which were separable by their differing solubility in aqueous alkali the latter being easily soluble. Zirconium phenoxide has been used as a more selective reagent (ref. 20).
Dealkylation procedures have been suggested for the recovery of phenol from undesired tert-butyl alkylation by-products and from iso-propyl compounds such as cumylphenol (4-iso-propylphenol) (ref. 21).
The removal of t-butyl groups has been used to selectively synthesise 4,4'-dihydroxybiphenyl. Thus 2,6-di-tert-butylphenol after oxidative conversion to 3,3',5,5'-tetra-tert-butyl-4,4'-biphenyl was dealkylated under acidic conditions with recovery of isobutylene (ref. 22).

11.3 Reactions of Synthetic Alkylphenols derived from Synthetic Alkenes

A vast literature exists on the reactions of C_4, C_8 and C_9 alkylphenols derived from commercial alkenes much of which is concerned with patented applications concerning polymeric systems. There is a significant difference of approach in the chemistry of the C_4 and C_8 series compared with the C_9. The former two are essentially pure organic compounds the derivatives of which have in almost all cases been characterised whereas the starting material in the case of t-nonylphenol is essentially a complex mixture which in no way makes the isolation of pure compounds easy or, in a commercial sense, desirable. In the present account some of the chemistry in the polymeric field is referred to but the main concern is with that resulting from the formation of ethers, organic and inorganic esters, condensation products, electrophilic substitution and the derivation of salts. As in the discussion of the reactions of phenols the array of reactions of nonylphenol in the technical literature can be considered under reactions of the hydroxyl group and substitution in the aromatic ring.

(i) Formation of Ethers

The most important group of compounds in this class is that of the polyethoxylates which result from the etherification of octylphenol (from diisobutene) and of nonylphenol (from propene trimer). In the presence of a basic catalyst polycondensation takes place and with an average addition of 8-9 oxirane units in both cases, the products obtained are highly effective surfactants of value as detergents, wetting agents, oil emulsifiers and agents for aiding emulsion polymerisation. In the following , R = t-C_8H_{17} or t-C_9H_{19}.

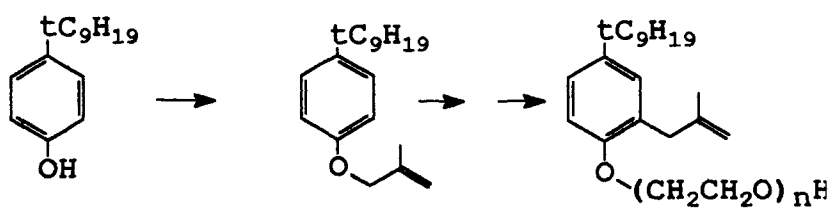


Mixed ethoxylate/propoxylates have also been prepared by the use firstly of ethylene oxide followed by that of propylene oxide. It has been claimed that the addition of such polycondensates to cement compositions extends their life through prevention of carbonation, and of both water and chloride ion penetration (ref. 23).

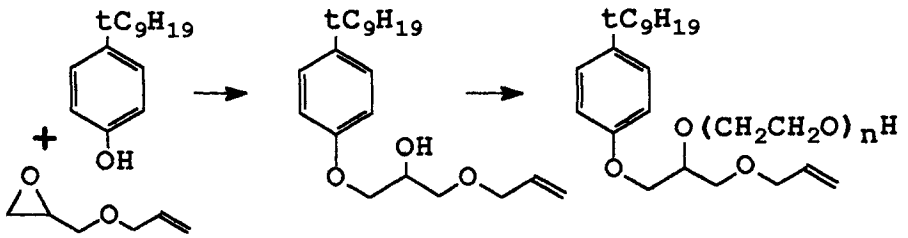
In recent years considerable attention has been given to the biodegradability of polyethoxylates and the role of their structure in this process. In consequence, there has been a move away from multi-branched alkyl side-chain in the starting alkylphenolic raw material towards more linear chains, a circumstance already adopted in the use of 'kerylbenzenes' for the manufacture of alkylaryl sulphonates. Another practice adopted has been that of sulphation of the terminal hydroxyl group in the polyalkoxylate. Recent studies on a comparison of ethoxylates derived from the natural alkenylphenol, cardanol and from nonylphenol have indicated a considerable difference in biodegradability (ref. 24).

Prior reaction of nonylphenol with a variety of different allylic, allylglycidyl and glycidylacrylate intermediates and glycidol itself has been used to provide structures, containing unsaturation in a side-chain, which were then ethoxylated. Vinylic polymerisation proceeding through the double bond in the side-chain could finally be employed to obtain further structurally modified products. The final products from these transformations almost certainly are mixtures.

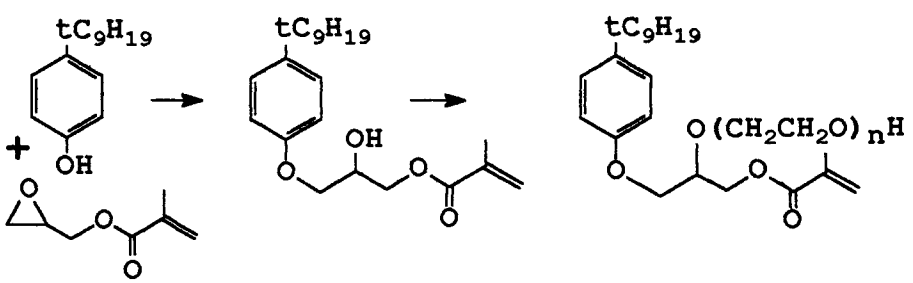
Thus, the O-methallyl ether of nonylphenol was rearranged by the Claisen reaction to afford an o-hydroxy C-methallyl compound, ethoxylation of which with excess ethylene oxide provided an intermediate for vinylic polymerisation with vinyl acetate in aqueous solution containing ammonium persulphate at 70°C (ref. 25).



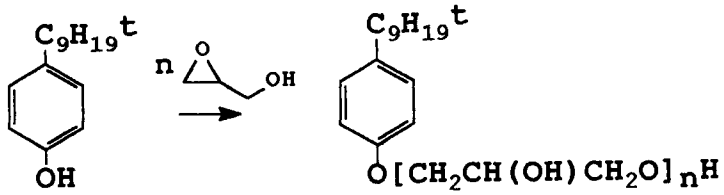
Glycidyl allyl ether has been treacted with nonylphenol in the presence of triethylamine at 80°C to give a ring-opened intermediate which after ethoxylation was employed in a polymerisation reaction, assisted by ammonium persulphate, with excess ethyl acrylate at 70°C. The emulsion when coated on glass, dried and briefly cured at 160°C gave a water-resistant film (ref. 26).



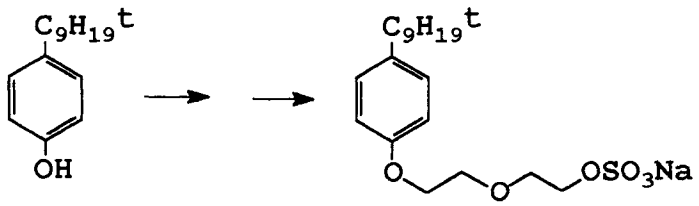
In a similar way styrene has been reacted with the vinyl group in such macromers leading to products with improved properties such as the contact angle with water and in their surface resistivity (ref. 27).
Glycidyl methacrylate has been reacted at 100°C during 5 hours with nonylphenol containing triethylamine. The ring-opened adduct was ethoxylated under basic conditions and then treated with sulphamic acid to give a terminal O-sulphate. This water-soluble product was an anionic surfactant containing a polymerisable acrylate group (ref.28). In the scheme the product prior to sulphation and formation of the terminal OSO_3H group is shown.



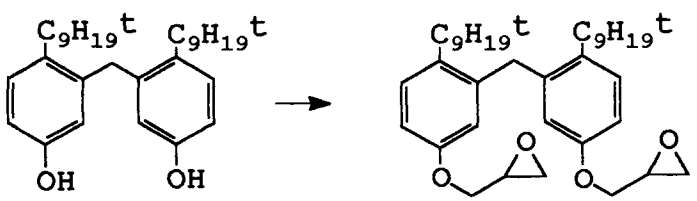
By the use of glycidol with nonylphenol the final product has proved of value as an emulsifier for stable aqueous acrylic polymers. Thus the reaction of excess glycidol with nonylphenol in toluene solution in the presence of ptassium hydroxide was described to give an hydoxypropoxylate (ref. 29). In the depicted reaction preferential etherification of the primary hydroxyl group takes place although it is probable that complex mixtures result in practice.



The ethoxylates having only two ethylene oxide units, for example, nonylphenol diglycol in the form of its O-sulphate has been employed as a surfactant in the aqueous suspension of weakly soluble azo dyes used for dyeing hydrophobic polyester fibres (ref. 30).



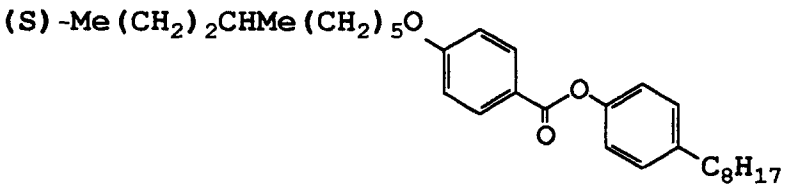
Ether derivatives of condensation products of nonylphenol have proved of value in several applications. Thus, methylene bis(nonylphenol) with epichlorhydrin afforded an intermediate which was used for example with diethanolamine in the presence of the basic catalyst, benzyldimethylamine, to furnish a ring-opened polyol of value in polyurethane coatings (ref.31).



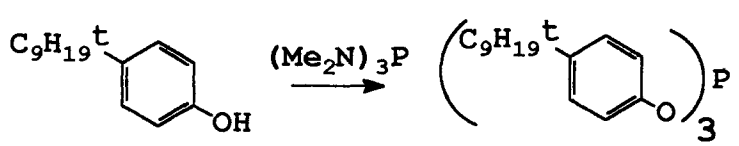
(ii) Formation of Esters

The formation of phenolic esters, including those of nonylphenol is much improved by the employment of phosphorous acid as a catalyst. Thus the octanoate ester was obtained in both high conversion and in 95% yield with octanoic acid whereas although sulphuric acid and boric acid afforded almost equal conversions, lower yields (72% and 75% respectively) resulted in both

cases (ref.32). Esters with aromatic acids can be synthesised from the appropriate acid chloride or by transesterification. For example, nonylphenyl benzoate can be derived and by Fries rearrangement with aluminium chloride 2-hydroxybenzophenone can be obtained, a compound of value as a uv absorber in thermoplastics and in packaging material.
Optically active esters of value in liquid crystal display device applications have been formed from 4-octylphenol with a chiral alkoxybenzoic acid .



By far the most significant applications of esters derived from nonylphenol have been with the phosphorus oxyacids, namely phosphorous and phosphoric acids, which afford a range of arylphosphites and arylphosphates respectively and with sulphuric acid resulting in the sulphate esters. The salts of these derivatives have found wide industrial usage.
Tris-4-nonylphenyl phosphite is an important additive useful as an antioxidant for rubber and in lubricating oil as for example in polyesters derived from neopentyl polyol (ref.33) in conjunction with a (C_8 or C_9) dialkyldiphenylamine. It has found a use as an additive in radiation-resistant polypropene compositions (ref. 34).
The synthesis of triarylphosphites has been referred to in a discussionof the reactions of phenols. For example, with phenols and tris(dimethylamino)-phosphine in solvents containing imidazole, high yields of triarylphosphites were obtained.

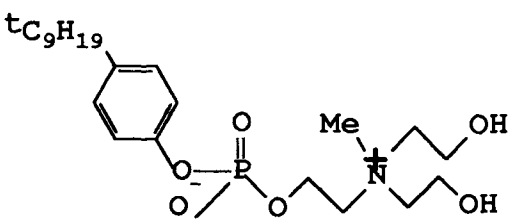


The triarylphosphates have an equally important place in industrial technology. The preparation of such materials on a manufacturing scale often follows on from the reaction stage of a phenol-aluminium chloride mixture with propene

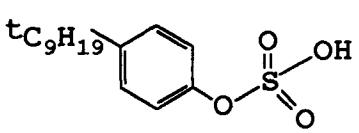
resulting in a mixture of propyl-, hexyl- and nonylphenols and other products which is treated with phosphorus oxychloride to give a corresponding random mixture of mono-, di- and trialkylphosphates (ref.35).
Phosphorylation by treatment of nonylphenol in concentrated phosphoric acid with phosphorus pentoxide has been described in the derivation of surfactants based on the phosphate group (ref. 36).
Frequently somewhat purer products are employed as for example in the case of mono- and di(nonylphenyl)phosphoric acid, used for the recovery of uranium from crude phosphoric acid (ref. 37).

$C_9H_{19}C_6H_4OP(O)(OH)_2$ $(C_9H_{19}C_6H_4O)_2P(O)(OH)$

Octylphenylphosphate and the nonylanalogue have also been employed in the extraction of gallium(III) from sulphuric acid solution (ref. 38).
Ethanophosphate esters of use in phospholipid-containing polypeptides as materials for artificial skin or for the slow release of pharmaceuticals, have been based on the use of ethanediol (ref.39). Nonylphenylphosphoric acid has been converted to a phospholipid-like structure. For example, nonylphenol reacted with 2-chloro-2-oxo-1,3-dioxa-2-phospholane in THF containing triethylamine and the resulting intermediate then treated with N-methyldiethanolamine in DMF at 70°C during 48 hours gave the product depicted which was of value as an intermediate for a biocompatible layer. Addition of a diisocyanate in the presence of 4-dimethylaminopyridine followed by polymerisation at 80-100°C afforded such a final product (ref. 40).

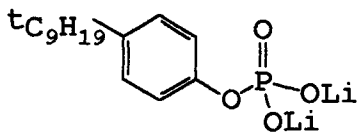


O-Sulphates derived from nonylphenol have been employed as corosion inhibitors in the electrolyte of batteries having zinc alloy anodes (ref. 41)



(iii) Formation and Usage of salts

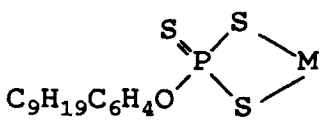
The salts of the inorganic esters of nonylphenol with phosphoric acid and sulphuric acid are frequently employed in a variety of applications. For example, the dilithio salt of nonylphenylphosphate has been employed as a component of lubricating greases (ref.42).



The tungsten salt resulting from treatment of nonylphenol with tungstic hexachloride has found an application as a catayst for the metathetical co-polymerisation of dicyclopentadiene and 5,5,6-trichloronorbornene (ref. 43).
Antimony and lead salts of alkyldithiophosphates are important additives for lubricating greases. In the nonylphenyl series such compounds are considered to have the 'dimeric' structure shown (where M = Pb and Sb) (ref. 44).

$$M[P(S)(OC_6H_4C_9H_{19})S_2]_2$$

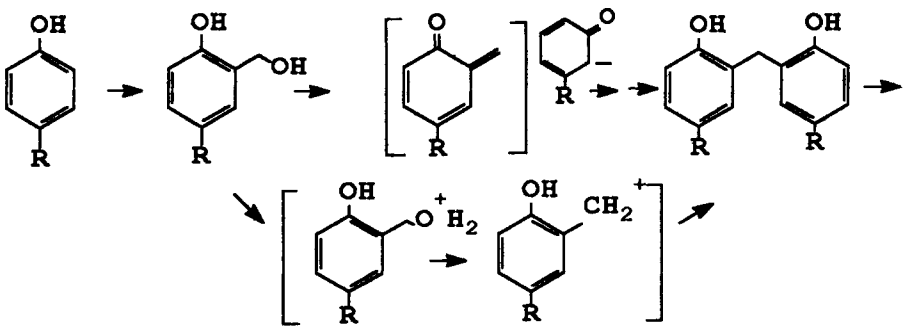
By contrast, the copper salt [M = Cu(II)] of the monomeric phosphorodithioate has been employed with 4-t-octyldiphenylamine as an antioxidant system and thermal stabiliser for lubricants and hydraulic fluids (ref.45).



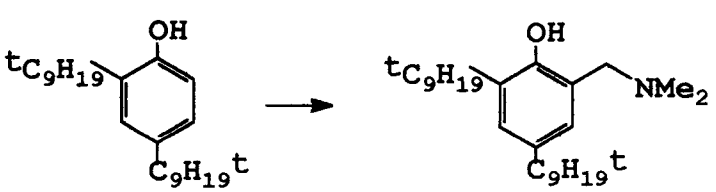
The barium salt of nonylphenol has found use as a additive component of mixtures employed as detergents for lubricating oils (ref.46).
Whereas the 1,1,3,3-tetramethylbutyl side chain structure in t-octylphenol derived from diisobutene is usually the sole contributor, that in t-nonylphenol comprises a complex but nevetheless extremely useful mixture. Recent work on the separation of the isomers present on a cross-linked methylsilcone column by capillary GLC (ref. 47) could be useful in indicating the connection between structure and the properties in this valuable technical product.

(iv) Condensation Products

The reactions in this group probably mainly involve nucleophilic additions, compared with nucleophilic substitutions in compounds of the ether series, since the phenoxide involved under basic conditions can be concluded to be reacting as a carbanion. It seems most likely that from an initially formed methylol, a quinone methide results to which the carbanion, from a phenoxide, then adds to afford first the dihydroxymethane shown which then reacts again to continue the sequence (R = C_9H_{19}, C_8H_{17}). In the reaction of formaldehyde with alkylphenols as well as nucleophilic addition in alkaline media, electrophilic substitution under acidic conditions can take place leading to the same product.

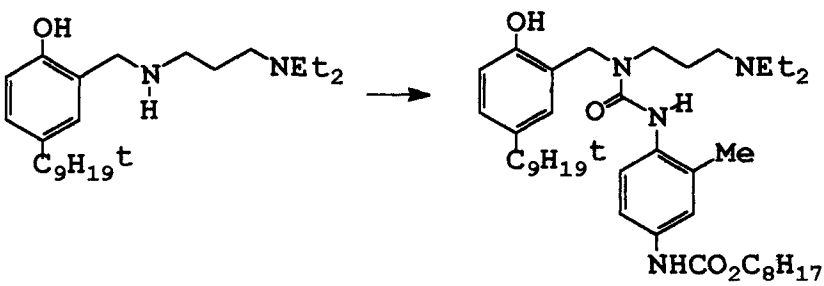


With a molar excess of formaldehyde and basic conditions, thermosetting resoles are formed while with an excess of the alkylphenol under acidic conditions the thermplastic novolaks result.
Cyclic compounds can also be formed and these compounds, the so-called calixarenes are discussed subsequently in section (v).
Another very useful reaction is that involving formaldehyde in Mannich reactions. These have usually consisted of complex mixtures in the case of polyamines such as diethylene triamine and simpler structures with secondary amines. Thus, cationic surfactants of some use as adhesion additives for bitumens, have been prepared from the residual phenols in the manufacture



of nonylphenol, (consisting of 20% nonyl and 50% dinonylphenol), by reaction with 37% aqueous formaldehyde and 30% dimethylamine during 5 hours at 60°C (ref. 48).

By the reaction of nonylphenol with equimolar proportions N,N-diethylamino-propylamine and paraformaldehyde in toluene solution accompanied by azeotropic removal of water a product resulted which was then treated with a molar proportion of tolylenediisocyanate partially 'blocked with 2-ethylhexanol. The final material seved as a cationic binder in self-crosslinking varnishes (ref. 49).

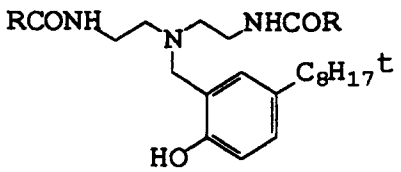


Complex mixtures of value as cationic binders for use in cathodic coatings have been derived from the reactions of substituted ureas, nonylphenol and formaldehyde. For example, the diketimine from diethylenetriamine and methyl isobutyl ketone (which served as a protective group in the first stsge of the process) by reaction with tolylene diisocyanate (semi-blocked with 2-ethylhexanol) afforded a urea. Treatment of the reaction mixture, presumably after removal of the ketonic group, with nonylphenol and aqueous formaldehyde gave a product which after solvent dilution was then reacted with bis-phenol A epoxy resin in diglyme solution (ref. 50). Such products can only be visualised as complex mixtures.

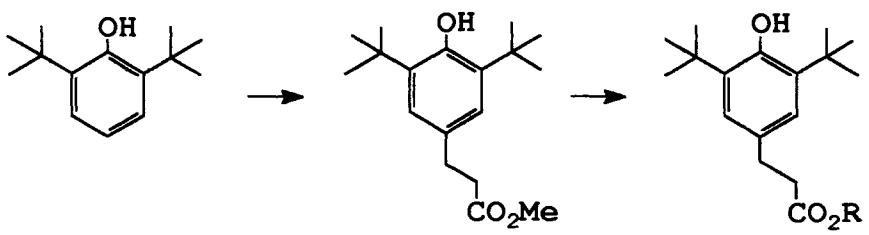
Compositions valuable as hardeners for epoxy resins by cross-linking have been derived by the reaction of dipropylene triamine with aqueous formaldehyde at 60°C acompanied by water removal, addition of a phenol such as nonylphenol and further reaction at the same temperature (ref. 51).

Other complex mixtures involving Mannich reaction products of use as anti-rust additives in lubricating oils have included the reaction of fatty acids (RCO_2H), nonylphenol, with diethylenetriamine or triethylenetriamine and aqueous formaldehyde. It would appear that the primary amine groups result in amide formation at 160-180°C and the residual secondary amine group then undergoes a Mannich reaction in the usual way with t-octylphenol and

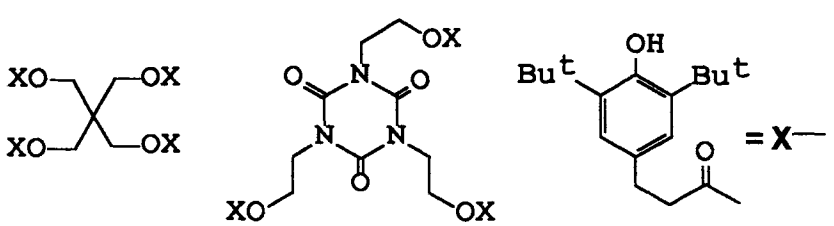
formaldehyde (ref.52).



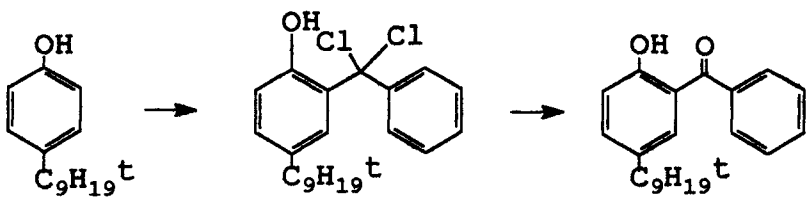
A series of compounds mostly having t-butyl groups, belonging to the group of crypto or hindered phenols and possessing a free 4-position, have been derived by reaction under basic conditions with acrylic esters. Thus 2,6-di-tert-butylphenol under basic conditions undergoes Michael addition with methyl acrylate to afford methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (ref.53).



By a variety of transesterification reactions, for example with octadecyl alcohol, (ROH), with pentaerythritol, or with 2,2'-dithioethylene glycol, products result known respectively as Irganox 1076, Irganox 1010 and 1035 respectively (Ciba-Geigy ltd.). and with N,N,N-tris-hydroxyethylcyanuric acid, Goodrite 3125 (B.F.Goodrich Chemical Co.). Pentaerythritol afforded a tetrakis ester and the tris-N-hydroxyethylcyanuric acid derivative shown gave a tris ester. All these higher molecular weight esters have been valuable as antioxidants for



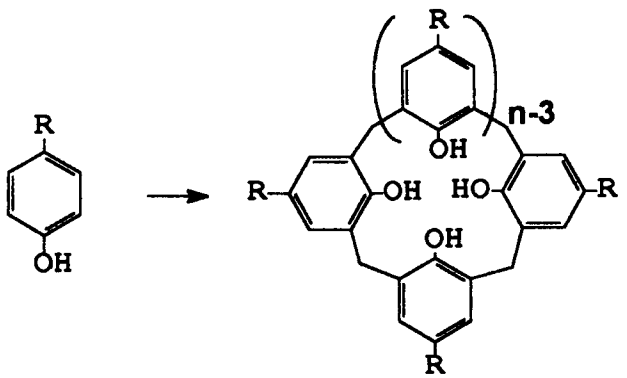
polyalkenes, plastics and synthetic rubbers.
A product having a different use, namely as the oxime in the extraction of copper(II) from dilute aqueous solution, is derived by the nucleophilic reaction of 4-nonylphenol, behaving as the 2-carbanion, with benzotrichloride in the presence of sodium hydroxide solution, to afford after hydrolysis of the intermediate dichloro compound, 2-hydroxy-5-nonylbenzophenone (ref.54), The oxime of this compound is similar in properties to the 5-dodecyl analogue known as Lix 64N (Henkel Co.). The Acorga series of metal extractants derived from 2-hydroxy-5-nonylsalicylaldehyde are more commercialy significant and are referred to later.



(v) Calixarenes and Other Methylene-bridged Oligomers

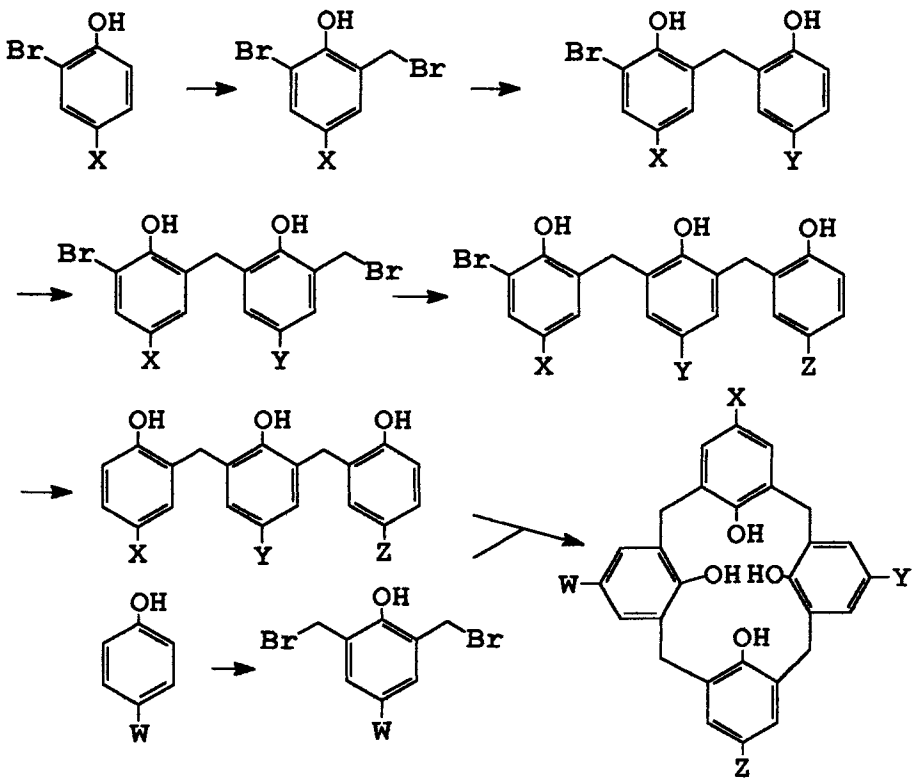
. A large number of monocyclic derivatives from 4-tert-butylhenol, 4-tert-octylphenol and 4-nonylphenol result by formal electrophilic substitution. Rather uniquely, as mentioned earlier, reaction with formaldehyde can be effected under either acidic or alkaline conditions (ref.55). From the initial monocyclic hydroxymethyl intermediate the products obtained are linear as opposed to cross-linked polymers and due to their lower molecular weight possess oil-solubility.. They have been extensively empoyed in surface compositions in conjunction with a triglyceride drying oil.
However it has been recognised in recent years that macrocyclic products, the calixarenes, (ref.56) also accompany the linear polymers under basic conditions, albeit in low yield but that also they can be formed in low yields in acidic media (ref.57). The four membered parent phenolic member, calix[4]arene was first noted, in alkaline reaction conditions, many yeas ago (ref.58). Although subsequently 4-t-octylphenol was found to give two products (ref.59) at first thought to be stereoisomeric cyclic tetramers, it was shown in later work that 4-t-butylphenol afforded not only cyclic compounds with methylene, but also dimethylene ether bridges (ref. 60).
In fact the composition of the products appears to depend on the reaction conditions. Nevertheless, from 4-tert-butylphenol well-defined preparative details now enable calixarenes with 4,5,6,7,8 phenolic units to be obtained. For the

compounds with 4,6,or 8 4-tert-butylphenol units, yields approaching 80% can be realised which can be duplicated on an industrial scale (60, 61). The structure shown represents the calix[4]arene from 4-t-butylphenol, R = t-Bu, n = 4.



Calixarenes have also been synthesised from 4-iso-propylphenol (ref.62), 4-t-pentylphenol (ref.63), n-octyl and n-dodecylphenol (ref.64). All these oligomers possess even-numbered rings which appear to be favoured, although both the reasons for this and indeed the mechanism of their formation are not yet unravelled. However small proportions of odd-nubered oligomers have been characterised (ref.65,66,67). Although n-nonylphenol in tetralin with formaldehyde in potassium hydroxide solution has been transformed into low yields of the calix[6]arene and calix[8]arene, namely (12%) and (10%) (ref.68), compounds in the branched chain t-nonyl series do not seem to have been synthesised probably because of the heterogeneity of the starting material.
The mixtures of oligomers resulting in formaldehyde reactions with 4-tert-butylphenols have been separated by HPLC (ref.57) and it is of interest to have available synthetic methods for individual reference oligomers. Work towards this originally (ref.69) has been developed (ref.70) whereby the 2-bromo or 2-chloro-4-alkylphenol derivative is first hydroxymethylated, and then a progressive sequential series of hydroxymethylations and condensations effected, the chlorine atom being finally removed and the relevant linear hydroxymethyl precursor cyclised under high dilution conditions to the oligomer required. With this somewhat laborious but obligatory technique calixarenes having up to seven units were derived in the 4-methyl and 4-tert-butyl series. A more streamlined and convergent approach has been put forward (ref. 71) and this type of methodology has been employed especially for calix[4]arenes having four different substituents in the 4-position. This simplified method consists in

the reaction of the appropriate selected trimer or dimer with the corresponding 2,6-bromomethyl-4-alkylphenol or 2,2'-bis(bromomethyl)dimer respectively (ref.72)

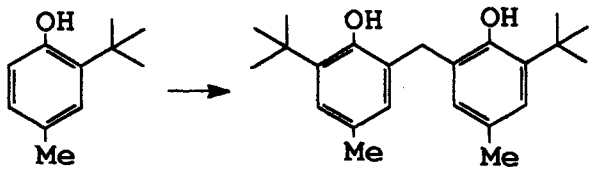


A variety of functional groups such as halogen, nitro and azophenyl substituents at the 4-position in the phenol can be introduced into the calixarene by this specific method and it gives also the opportunity for the synthesis of asymmetric compounds (ref.72,73). The structural substituent requirement is the presence of the four phenolic units (A,B,C, D) arranged ABCC, ABCD or simply a single 3-grouping (ref.74). Other structural variations can be incorporated such as a methylenic chain connecting two opposite 4-positions (ref.75) giving structures reminiscent of 'football crowns'. The dimethylene ether bridging unit has been another alternative to the methylene group (ref.76).

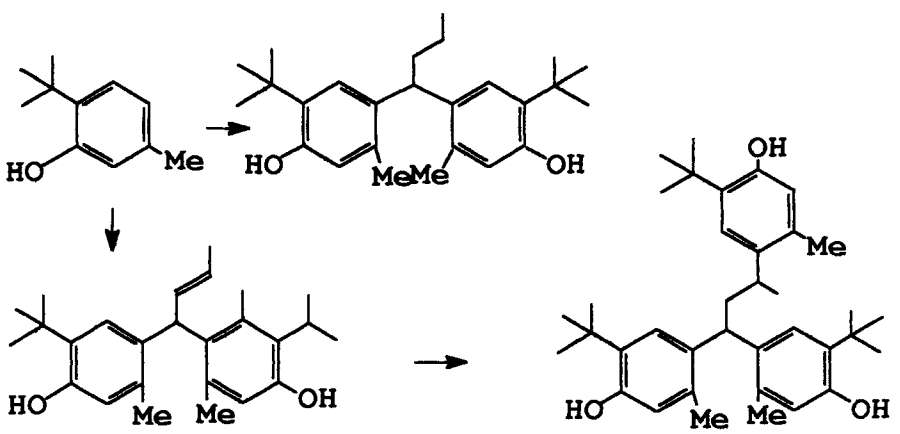
Single methylenic-bridged condensation products

With 2,4-dialkylphenols the condensation with formaldehyde is restricted to formation of the methylene-bridged product. Thus 2-tert-butyl-4-methylphenol

affords 2,2'-methylene-bis-(2-tert-butyl-4-methylphenol) (antioxidant CAO-5, Ashland Chemical Co.) which has an important use in rubber.



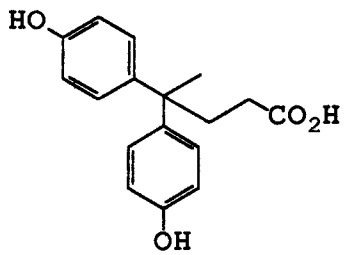
Several bis-phenols have branched alkyl bridging groups the most notable probably being bis-phenol A whch has been referred to earlier in Chapter 6. Although higher aldehydes are not usually employed on account of the adverse effect of a substituted bridge on the antioxidant properties, the product from 2-tert-butyl-5-methylphenol and butanal is an exception since 4,4'-butylidene-bis(2-tert-butyl-5-methylphenol) is a highly effective antioxidant. The same raw material upon condensation with but-2-enal under acidic conditions gives initially a butenylidene intermediate. The carbocation from this then undergoes reaction with another mole of the phenol to give the product, 1,1,3-tris-(5-tert-butyl-4-hydroxy-5-methyl)butane (Topanol CA)(ref.77). It is probably not coplanar.



2,6-Dialkylphenols are also employed. Thus, 2,6-di-tert-butylphenol with furfural affords a bisphenol with a furfuryl bridge (ref.78), again a compound with antioxidant uses.

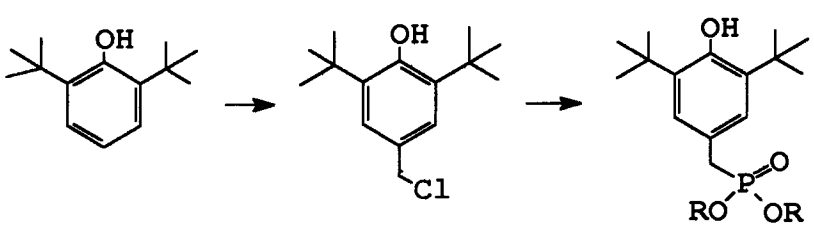
By contrast although alkylphenols do not appear to have been used, It is of interest that an alkylation rather than substitution and acylation products are formed in the reaction of phenol with levulinic acid (ref. 79). Thus in the

condensation of 4-oxopentanoic acid (levulinic acid) with phenol in the presence of conc. sulphuric acid containing phosphoric acid or hydrogen chloride 4,4-bis(4-hydroxyphenyl)pentanoic acid results in 77% yield while with polyphosphoric acid the same product is obtained together with phenyl levulinate.



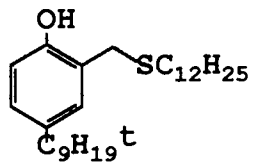
(vi) Products from Electrophilic and Nucleophilic Substitution

Whilst arguably, the formaldehyde condensation reactions in the preceding section are, under acidic conditions, electrophilic in type, a considerably wider range of compounds result from the commercially available C_4, C_8, and C_9 alkylphenols with a variety of reactants in other electrophilic substitution reactions. Thus 2,6-di-tert-butylphenol condensed with formaldehyde in hydrochloric acid gives 3,5-di-tert-butyl-4-hydroxybenzyl chloride which can be utilised in an Arbuzov reaction with trialkylphosphites to afford the dialkyl phosphonate depicted (ref. 80). The diethyl ester (Irganox 1222, Ciba-Geigy Ltd.) in this series is a significant stabiliser for polyester fibres in the prevention of photo and oxidative deterioration.

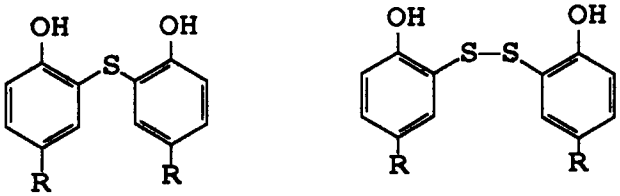


A related type of initial reaction has been employed in the thio series. For example, nonylphenol in toluene containing 4-toluenesulphonic acid and dodecylthiol upon treatment with aqueous formaldehyde and reaction at 135-140°C with azeotropic removal of water afforded a reaction product probably

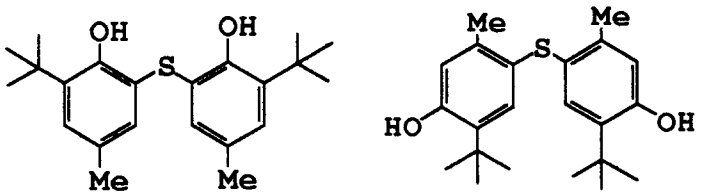
substantially a 2-dodecylthiomethyl substituted compound (ref. 81). 2,4-Dialkylphenols have also been employed giving products possessing auto-synergistic antioxidant properties.



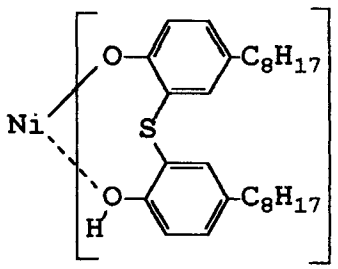
Bis-phenol monosulphides and disulphides resulting from the reaction of 4-alkylphenols with sulphur monochloride and with sulphur dichloride are of importance in the form of their calcium, barium, magnesium salts as lubricating oil additives although their place has been partly displaced by the alkoxyphosphorodithioates. Thus 4-tert-nonylphenol and 4-tert-octylphenol, afford 2,2'-thiobis products (R = t-C_9H_{19} and t-C_8H_{17} repectively (ref. 82).



2-tert-Butyl-4-methylphenol reacts similarly and the isomer 2-tert-butyl-5-methylphenol due to steric hindrance gives a 4,4'-thiobis final product (ref. 83) which is valuable as an antioxidant for polythene.



The bisphenol from 4-tert-octylphenol forms a nickel(II) complex which has useful properties as a light stabiliser (ref.84).



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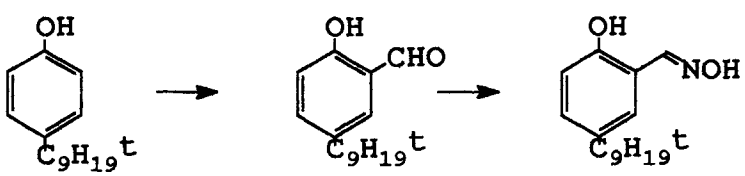
Formation of 4,4'-thiobis products is facile, by reaction of the alkylphenol in benzene with a benzene solution of sulphur mono or dichloride at 40-60°C during 2-3 hours followed by purifiction techniques to give the monosulphide or disulphide respectively (ref. 85).

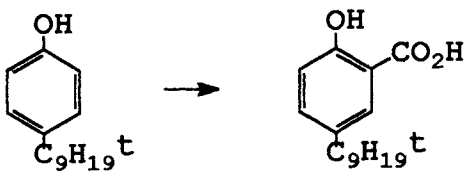
Simpler ring-substituted derivatives of nonylphenol and of octylphenol (1,1,3,3-tetramethyl)butylphenol) are also of considerable importance in many industrial operations.

One of the most important reagent for the extraction of copper(II) in hydrometallurgical operations has been 5-t-nonylsalicylaldoxime (Acorga reagent). Several syntheses are available for this compound one of which has been referred to in Chapter 7 on the phenolic carbonyl copounds. Another approach, although not proceeding by electrophilic substitution, has consisted in the initial reaction of nonylphenol in toluene containing potasium hydroxide to form the phenoxide accompanied by the azeotropic removal of water, after which stannic chloride, trioctylamine, further toluene and paraformaldehyde were introduced and reaction continued at 100°C during 22 hours (ref. 86).

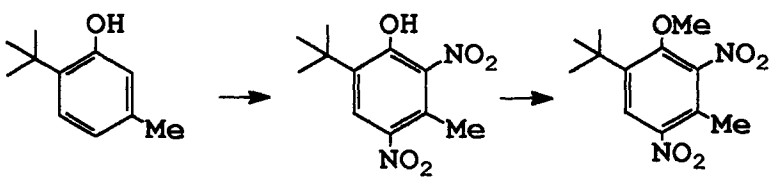


The product itself is useful as a perfumery. agrochemical and stabiliser chemical although its primary usage is in the form of the oxime. Analogues of the series are 2-hydroxy-5-t-nonylacetophenone (Shell SME as the oxime reagent) and 2-hydroxy-5-dodecylbenzophenone referred to earlier (LIX oxime reagent, Henkel). Both these ketoximes serve as copper extractants although less efficient than the aldoxime for this purpose. 2-Hydroxy-5-t-

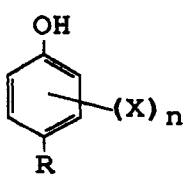
nonylacetophenone is readily synthesised by the Friedel-Crafts acetylation of nonylphenol or by the Fries rearrangement of the acetate while the synthesis of 2-hydroxy-5-nonyl and dodecylbenzophenones proceeds efficiently by the reaction of the appropriate phenoxide with benzotrichloride followed by hydrolysis and also as mentioned earlier by Fries methodology.
5-t-Nonylsalicylic acid has been synthesised by the Kolbe reaction. In one approach alkaline earth meta salts of nonylphenol in ethanediol at 160°C were treated with carbon dioxide during 2-3 hours (ref. 87).



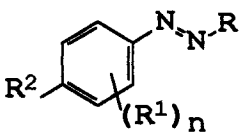
For the formation of nitro derivatives mild conditions are essential to avoid replacement of the branched alkyl group (ref. 88). The nitration of 6-tert-butyl-3-methylphenol and methylation of the product 6-tert-butyl-2,4-dinitro-3-methylphenol in xylene containing potassium carbonate with dimethyl sulphate offers an alternative to the classical route for musk ambrette. Hazards can be involved in this more well-known procedure consisting of the nitration of 6-tert-butyl-3-methylanisole (ref. 89) in acetic anhydride.



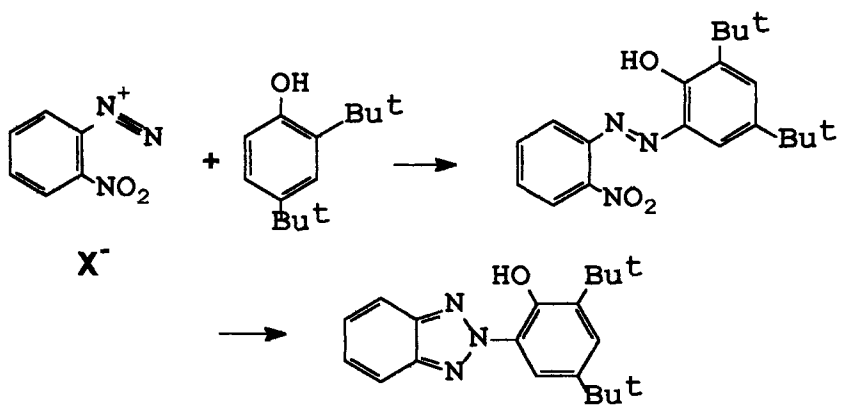
Halogenated derivatives of 4-t-pentylphenol and 2,4-di-t-pentylphenol have been used as solvent aids in silver halide colour photographic materials (ref.90).



In the structure depicted, R = a linear or branched alkyl chain, t-pentyl in the example, and X = is a halogen or R (n = 1-4).
Azo dyes derived from alkylphenols have been utilised in silver halide colour photographic compositions for obtaining improved sharpness (ref. 91). In the compound illustrated, R = a phenolic or alkylphenolic group having an hydroxyl substituent o- or p- to the azo group, R^2 = OH or NH_2 and R^1 = an organic group or atom.

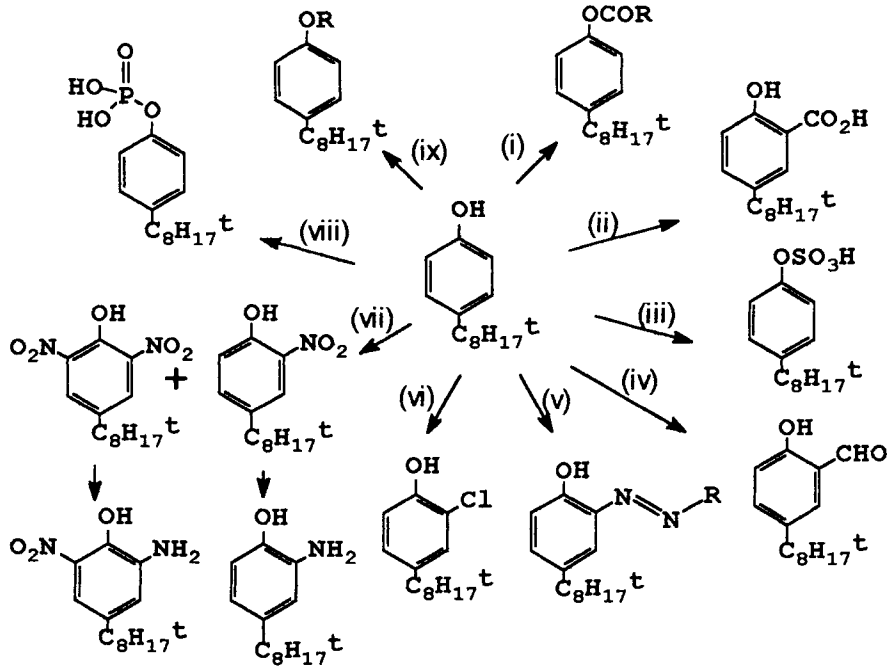


Bentriazoles formed from azo compounds obtained by coupling o-nitrodiazonium salts with alkylphenols have proved valuable as uv light stabilisers for use in polymers (ref.92).



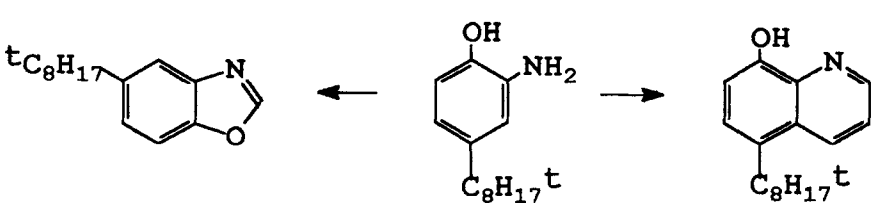
In general a much wider use has been made of electrophilic substitution reactions with t-octylphenol from the reaction of diisobutene with phenol and rather less applications in the field of polymer chemistry. Thus for example, esterification, nitration, phosphorylation, diazotisation, chlorination, sulphation, carboxylation, formylation and etherification have led to well-characterised derivatives (ref.93). Unlike t-nonylphenol, t-octylphenol [4-(1,1,3,3-tetra-methylbutyl)phenol] is a crystalline compound yielding characteristic crystalline derivatives as can be seen in the following instances. t-Nonylphenol by contrast is a mixture of sidechain isomers although predominantly a p-substituted compound. Its heterogeneity like that of many technical products undoubtedly enhances its physical properties in many of its industrial applications. Thus for

example 5-t-octylsalicylaldehydoxime, although not listed below, would probably be less effective than its mixed t-nonyl analogue for solvent extraction.



(i) RCOCl, Py., (ii) ArOK,CO_2(Kolbe);H_3O^+, (iii) H_2SO_4,(iv) $CHCl_3$,NaOH;H_3O^+, (v)ArN_2X, HO^-, (vi) SO_2Cl_2, (vii) HNO_3 ,(viii) $POCl_3$; H_2O, (ix) R_2SO_4, NaOH.

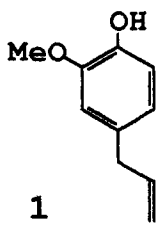
The scope of this extensively studied intermediate has included the preparation of a number of heterocyclic structures including quinolines, benzoxazoles, phenazines, phenoxazines and thiophenaazines (ref.94). Thus, 2-amino-4-t-octylphenol underwent the Skraup reaction by heating with glycerol containing ferrous sulphate to afford 5-t-octyl-8-hydroxyquinoline. 5-t-Octylbenzoxazole resulted by reaction of 2-amino-4-t-octylphenol in formic acid with zinc and hydrochloric acid.



Catechol and 4-t-octylcatechol with 2-amino-4-t-octylphenol by heating with hydrochloric acid at 220-230°C gave 4-t-octylphenoxazine and 4,9-di-t-octylphenoxazine respectively. 4-t-Octylcatechol with 1,2-diaminobenzene by prolonged heating at 260-280°C gave 3-t-octylphenazine.

11.4 Synthetic Alkenylphenols derived from Phenols and Dienes

A number of alkenylphenols of natural origin are of great importance in the perfume and flavour industries, such as eugenol (1), the principal component of oil of cloves, its semi-synthetic isomerisation product iso-eugenol (2), the phenolic ether, anethole (3) from fennel and oil of aniseed (umbelliferacae), and also of semisynthetic origin from chavicol (4). Their chemistry is not included in the present account which is devoted to less well-known substances.



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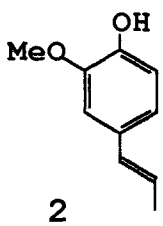

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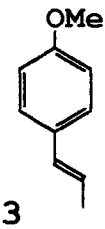

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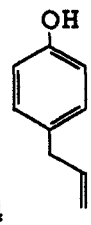


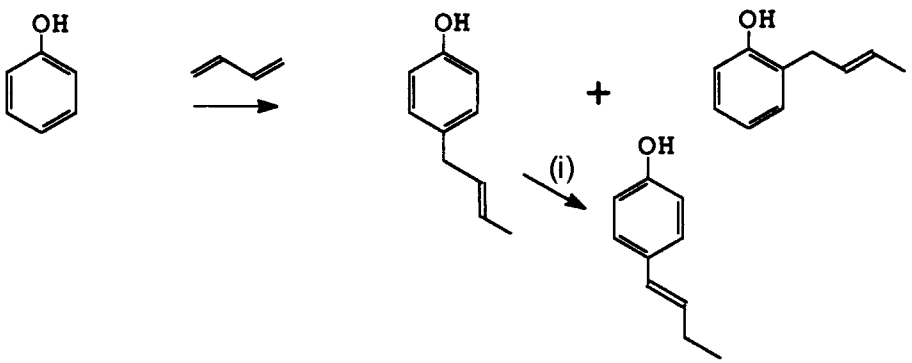
4

Dienes which have been reacted with phenols include buta-1,3-diene, isoprene (2-methylbuta-1,3-diene) and cyclopentadiene, all of which are perhaps more familiar in their reactions towards dienophiles in Diels-Alder additions. All are available from the petrochemical industry and their use in alkylations is an aspect of electrophilic substitution through carbocation addition. Because of their reactive nature, alkenylphenols during synthesis frequently undergo further transformations. Indeed this is an aspect of their reactions and reactivity which has been comparatively little studied although in previous chapters intermittent reference has been made in the case of certain specific structures.

The preparation of the compound, 2-vinylphenol, which could be regarded as a first member of the series is untypical. It has been synthesised by the decarboxylation of 2-hydroxycinnamic acid (ref. 95) which was considered the only convenient one of five procedures examined in the original work

Phenol in toluene containing H_3PO_4/BF_3 prepared by saturating 85% orthophosphoric acid with boron trifluoride, upon treatment with a toluene solution of butadiene followed by reaction at ambient temperature during 16 hours afforded a mixture of butenylphenols containing primarily 4-(but-2-enyl)phenol, 2-(but-2-enyl)phenol with small amounts of 2-ethylbenzofuran and 2-methylchroman (ref.96). An improved yield was obtained with phosphoric

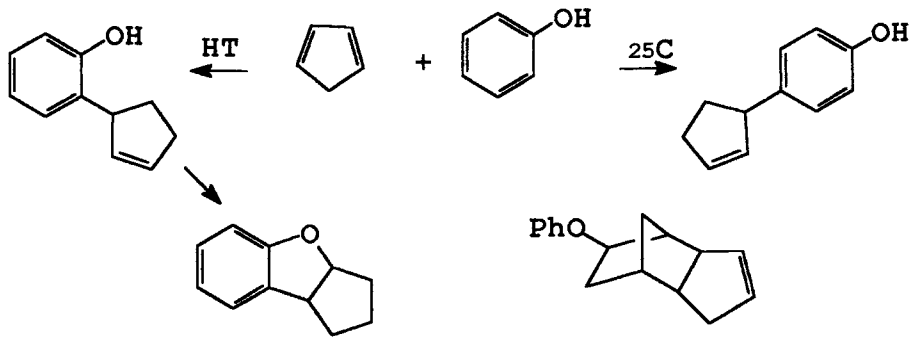
acid containing concentrated sulphuric acid and still better results with an equimolar proportion of reactants in the presence of 68% sulphuric acid, when monobutenylphenols (70%) were obtained (30% 4- and 60% 2-isomer). Inferior results accrued with all other catalysts. These included polyphosphoric acid, 2:1 polyphosphoric-85% phosphoric acids, $TiCl_4$-arenesulphonic acids, $ZnCl_2$-85% phosphoric acid. 4-(But-2-enyl)phenol upon refluxing with (i) palladium-carbon gave predominantly the corresponding but-1-enyl isomer and an unidentified dimeric product.



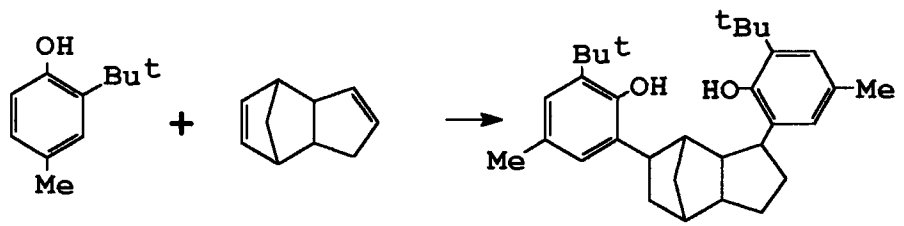
In a similar way phenol reacted with 2-methylbuta-1,3-diene (isoprene). This prenylation process is formally an aspect of the succeeding Chapter 12 and is discussed there along with other examples of the reaction chemistry of C_{10}, C_{15}, and C_{20} terpenoids with phenolic systems.

Cyclopentadiene with phenol gave either mainly 4-(cyclopent-2-enyl)phenol or the 2-isomer according to the experimenal conditions (ref.97). At 25°C in the presence of phosphoric acid the two reactants afforded the 4-isomer while under similar conditions but at higher temperatures (HT), the 2-isomer was formed. When 4-methylphenol reacted with cyclopentadiene at 25-50°C, 4-methyl-2-(cyclopent-2-enyl)phenol was produced.

By heating 4-(cyclopent-2-enyl)phenol with Pd-C, isomerisation afforded the 1-ene which upon hydrogenationn gave 4-cyclopentylphenol. After separation of 2-(cyclopent-2-enyl)phenol and 2,4-di(cyclopent-2-enyl)phenol from a reaction of phenol with excess of refluxing cyclopentadiene containing 85% phosphoric acid, the neutral fraction gave 2,3-cyclopentano-2,3-dihydrobenzofuran in low yield which was however derived in high yield from boiling an acetic acid solution of 2-(cyclopent-2-enyl)phenol with 48% hydrobromic acid. The higher boiling components of the neutral fraction were found to contain a phenoxy derivative of the dimer, dicyclopentadiene, namely phenoxydihydro-exo-dicyclopentadiene.



Phenols have also been reacted with the double bonds in dicyclopentadiene. Thus two moles of 2-tert-butyl-4-methylphenol in the presence of boron trifluoride gave a mixture of isomers (ref.98).



Higher molecular weight products can be formed by extended reaction of 4-methylphenol with dicyclopentadiene which in turn can then be reacted with isobutene (ref.99) to furnish complex mixtures which serve as excellent antioxidants for use in rubber.

An extensive study of the isomerisation of all the preceding allylphenols by heating methanolic solutions containing potassium hydroxide with removal of the methanol and continuation of refluxing during 100 hours afforded in every case moderate yields of the corresponding propenyl compound (ref.100). Although no isomerisation of the range of compounds in diethylene glycol containing 10% potassium hydroxide occurred during 1 hour at 165-170°C, heating for 4 hours at 200°C with an equal weight of the base afforded the conjugated phenol in each case with yields of 80% or more.

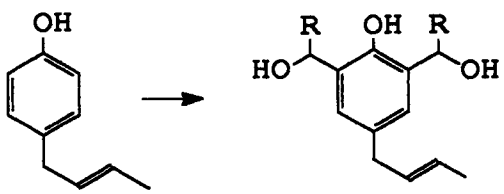
Several of the alkenylphenols referred to in the series discussed were found to possess interesting perfumery odours.

11.5 Reactions of Alkenylphenols

The reactions of the alkenylphenols resulting in the syntheses referred to have been studied with respect to the derivation of methylol compounds and the formation of unsaturated ethers.

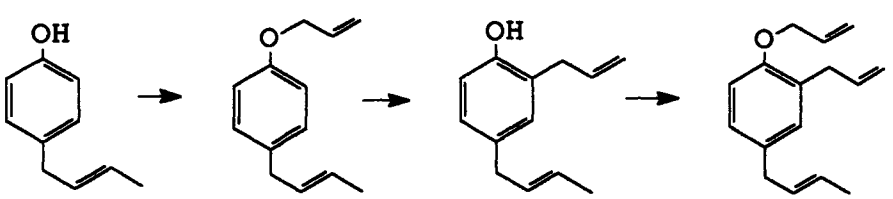
Methylol Derivatives

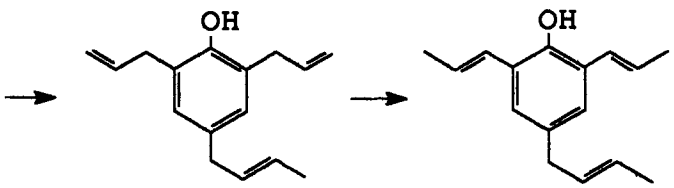
By the reaction of butenylphenols with aqueous formaldehyde under alkaline conditions dimethylol derivatives (R = H) were obtained (ref.101). Thus 4-(but-2-enyl)phenol in 10% aqueos sodium hydroxide treated with 37% aqueous formaldehyde and allowed to react during 48 hours afforded 2,6-dimethylol-4-(but-2-enyl)phenol. In a similar way 2,6-dimethylol-4-(cyclopent-2-enyl)phenol, 2,6-dimethylol-4-(3-methylbut-2-enyl)phenol and 2,6-dimethylol-4-isopentylphenol were derived. Ethanal and propanal gave analogues. These various monomers served as intermediates for polymeric systems.



Ethers derived from Alkenylphenols

4-(But-2-enyl)phenol readily formed an allyl ether in quantitative yield when its sodium salt was reacted with allyl chloride. This compound underwent Claisen rearrangement at 200°C to afford 2-allyl-4-but-2-enylphenol, the allyl ether of which, in turn, was rearranged to give 2,6-diallyl-4-but-2-enylphenol. Selective isomerisation of the allyl groups of this compound took place by heating at 110°C to afford 2,6-dipropenyl-4-but-2-enylphenol (ref.102).





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CHAPTER 12

PRENYLPHENOLS

12.1 Introduction

Isoprenoids have been an important class in biosynthetic studies on monoterpenoids, sesquiterpenes, diterpenes, tri- and tetraterpenoid compounds during the past four decades (ref.1). The potential interaction of the fundamental C_5 building blocks with other naturally-derived classes such as the polyketides at some stage must have been predictable in work on secondary metabolites yet comparatively few compounds having this dual origin have been isolated. However, the possible reaction of phenolic compounds with isoprenoids was only incidental at that time to the study of the latter. Although the natural formation of mixed systems by the reaction of phenols with C_5, C_{10}, C_{15} and C_{20} prenyl intermediates might be thought to be widespread, the present state of compositional studies reveals comparatively few substances in the prenylphenol class.

In this chapter the synthesis and reactions of prenylphenols will be discussed. Unlike the non-isoprenoid alkylphenols, considered in the next chapter, where the sidechains resemble those of the non-conjugated methylene group-interrupted fatty acids, the prenylphenol series possess double bonds more ideally placed for formation of bicyclic and polycyclic compounds. It is likely that the synthetic potential of this series for obtaining heterocycles apart form oxygen-ring compounds may not have yet been realised.

The first part of this account deals with the more recent chemistry of the alkenyl members typified by the C_5, isopentenylphenols, the C_{10}, dimethyloctadienyl-phenols, the C_{15}, farnesylphenols, and C_{20}, phytylphenols. The ubiquinones in the monocyclic and the naphthoquinone vitamins K_1 and K_2 in the bicyclic series are related chemically but are not discussed in this account.

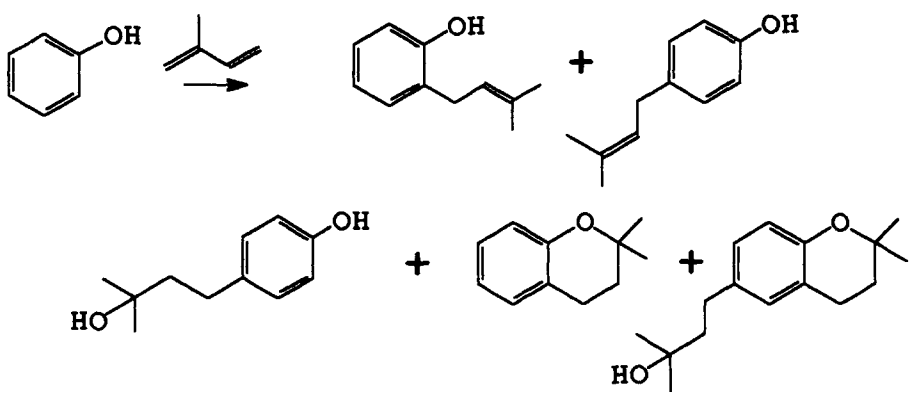
Under natural conditions the cyclisation of initially-formed C_5, C_{10} and C_{15} alkenylphenols can result in a profusion of oxygenated bicyclic and polycyclic structure which are invariably characterised by the presence of a 2,2-dimethyl substituted chroman ring although many compounds also contain a free prenyl group. A variety of typical classical compounds arising in this way are described initially followed by a summary of more recent work . In this the wide variety of biological properties is instanced which has come to light by the work of many different groups all over the world.

The chapter concludes with a review of the chemistry of the tocopherols and tocotrienols, groups of lipids which have generated a vast amount of work

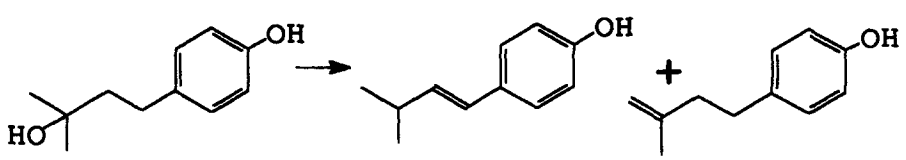
largely on account of the outstanding vitamin activity of these compounds. Earlier work on the synthesis of compounds with C_5, C_{10}, C_{15} and C_{20} prenyl sidechain was indeed complicated by their ready cyclisation to chroman, pyran or benzofuran structures but with improvements in methodology more specific routes were developed for prenylphenols the fundamental natural building blocks of the cyclic group. Some of these are described in the next two sections.

12.2 Synthesis of C_5, C_{10}, C_{15} and C_{20} prenyl monohydric phenols

In Chapter 6 the use of isoprene (Table 6.1) and of geranyl halides in reactions with naphthol and phenol respectively has been briefly referred to. In early work, isoprene with phenol in toluene containing 71% phosphoric acid, when reacted over 16 hours at ambient temperature (ref. 2) gave 4-(3-methylbut-2-enyl)phenol, the corresponding 2- isomer and 4-(3-methyl-3-hydroxybutyl)phenol in the phenolic products and in the neutral fraction, smaller proportions of 2,2-dimethylchroman and 6-(3-hydroxyisopentyl)-2,2-dimethylchroman. Hydrogenation of the unsaturated phenols afforded the respective 4- and 2-isopentylphenols.

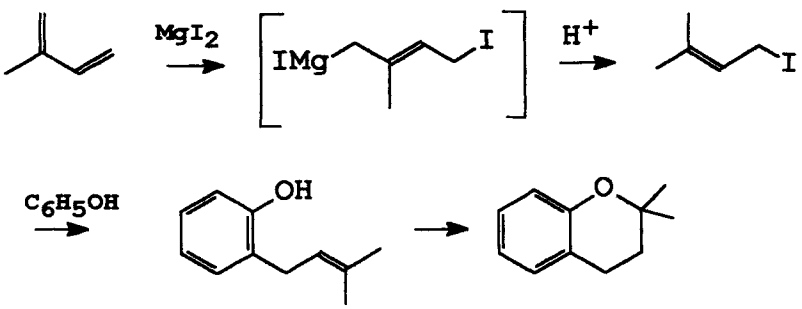


4-(3-Methylbut-2-enyl)phenol underwent hydration with aqueous phosphoric acid to give the 3-hydroxy analogue which by dehydration regenerated the alkene together with some of terminal alkene isomer.

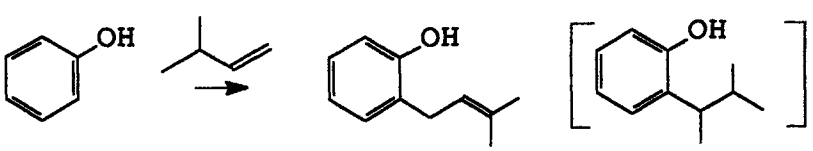


The use of isoprene with iodotrimethylsilane or hydrogen iodide has been

instanced (ref.3).
A simpler set of conditions has however been described (ref.4), which has been referred to in Chapter 6, consisting of the use of isoprene with the Lewis acid, magnesium iodide and diethyl ether, although both prenylphenols and some cyclised (2,2-dimethylchroman) products resulted with this system. It seems likely that the magnesium iodide undergoes addition to form a 1-iodomagnesio-4-iodo intermediate which is the effective reactant. The reagent was prepared by reacting magnesium turnings (1g) with iodine (5g) in dry diethyl ether (50ml) and following the exothermic reaction, the mixture was refluxed for 2 hours to give a colourless solution. In the general procedure, the phenol (0.5 mmol) in dry benzene (5 ml) was added to isoprene 1 ml) followed by the reagent (1 ml; 0.5 mmol) and the mixture then refluxed for 3 hours. Cold water quenching and final preparative TLC purification afforded the product. Thus phenol as shown gave 2-prenylphenol (60%), 1-naphthol gave 2-prenyl-1-naphthol (35%, together with a chroman, 35%) and 2-naphthol afforded the 1-prenyl isomer (35% accompanied by the isomeric chroman, 35%). The cyclised products are referred to again in a subsequent section.

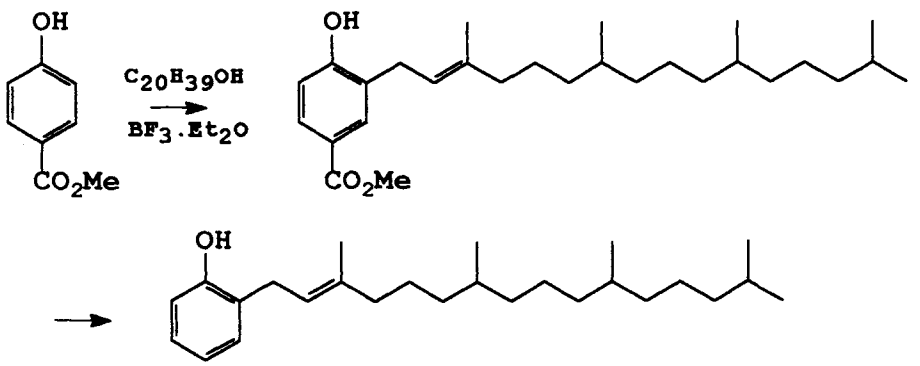


The preparation of 2-(3-methylbut-2-enyl)phenol by the acid-catalysed reaction of phenol with 3-methyl-1-butene has been reported (ref.5) although it would seem more probable that the product is 2-(1,2-dimethylpropyl)phenol.

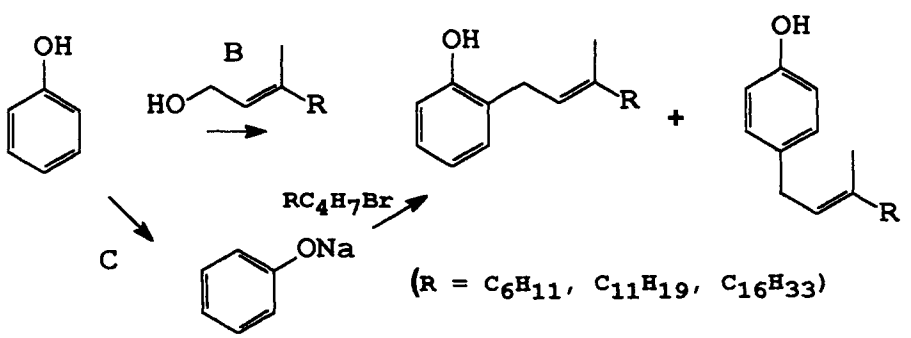


The reaction of phenol with natural C_{10} (and C_{15}) acyclic hydrocarbons such as the readily available myrcene, ocimene or alloocimene from the replenishable source pine oil, does not seem to have been examined in detail although the semi-synthetic 4- and 2-alkenylphenolic products obtained from it could be

anticipated to be more easily degradable than those currently derived from nonylphenol of petrochemical origin.
In a comprehensive study of 2-multiprenylphenols which are involved as biosynthetic precursors of ubiquiniones, three approaches were adopted (ref.6). In the first, to avoid 4-substitution found in acid-catalysed reaction of phenol, a blocking 4-methoxycarbonyl group was used. Thus reaction of methyl 4-hydroxybenzoate with phytol in dioxane containing boron trifluoride etherate at 50°C afforded a low yield of methyl 4-hydroxy-2-phytylbenzoate which upon hydrolysis and decarboxylation gave 2-phytylphenol.

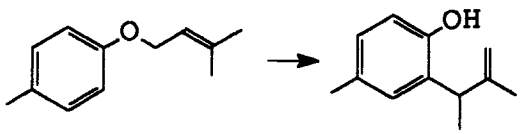


In the second approach (B), because of a low initial yield in the first method, the acid-catalysed reaction of the phenol in dioxane containing boron trifluoride etherate with the prenyl alcohol was used. In this way 2-geranyl, 2-farnesyl, 2-phytyl and 2-nonaprenylphenol were obtained in unstated yields, accompanied by the 4-isomer in each case. In the third strategy (C) the prenyl bromide was

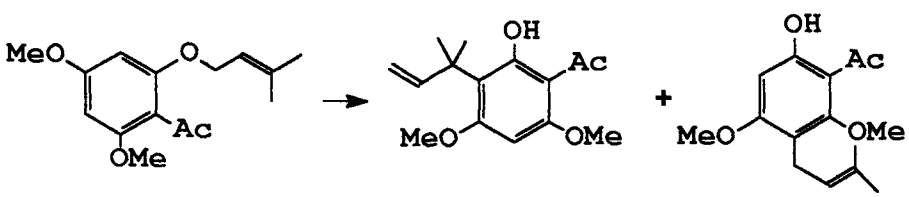


reacted with the sodium phenolate (formed wth sodium hydride) suspended in benzene. In each case the 2-prenylphenol resulted together with the O-prenyl

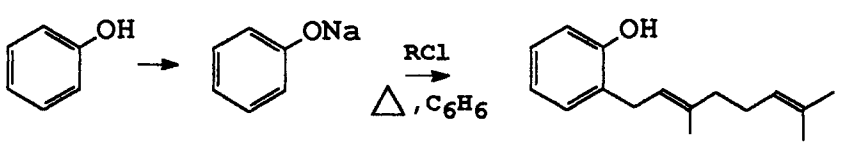
ether both in unrecorded yields.
The Claisen rearrangement has not proved of value for obtaining 2-(3-methylbut-2-enyl)phenol. Thus, 3-methylbuten-2-yl 4-methylphenyl ether at 220°C in dimethylpyridine gave an unstated yield of 4-methyl-2-(1,2-dimethylprop-2-enyl)phenol (ref. 7).



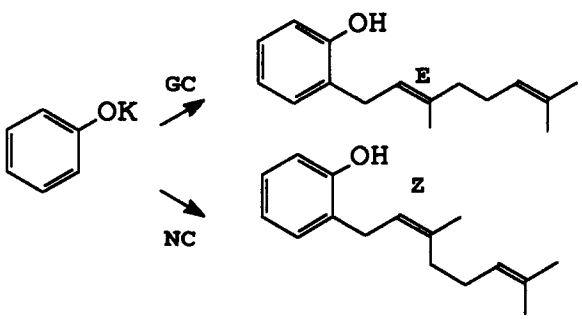
The more complex ether 3-methylbuten-2-yl 2-acetyl-3.5-dimethoxyphenyl ether upon refluxing in the same solvent for 5 hours gave two products in a total 70% yield (ref.8). The required 3-methylbuten-2-ol can be obtained from isobuten-1-ylmagnesium bromide by reaction with formaldehyde or by aluminium lithium hydride reduction of 3-methylbuten-2-oic acid while the chloride and bromide of 3-methylbuten-2-ol can be readily derived by reaction with thionyl chloride and phosphorus bromide respectively.



Claisen had reported that the proportion of C- to O-alkylation could be greatly enhanced by the use of sodium phenoxides in benzene suspension and indeed this method has been beneficially employed for o-C-isoprenylation. In a general procedure (ref.9), an ethereal solution of the phenol (0.05 mole), was treated with metallic sodium (0.2 mole) and after 1.5 hours the prenyl chloride (RCl) was introduced. Upon refluxing for 10 hours, removal of excess sodium and acidic work-up, monohydric phenols afforded yields from 66-90%. For example, 2-methylphenolwith3-methylbuten-2-ylchloridegave2-methyl-6-(3-methylbuten-2-

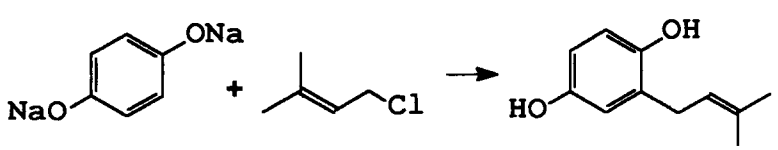


yl)phenol in 76% yield. Phenol reacted similarly with geranyl chloride as shown to give 2-geranylphenol in 90% yield.
By contrast these authors had found that Friedel-Crafts alkylation to be ineffective although another group employing Lewis acid systems was successful in effecting the o-prenylation of a a number of potassium phenolates (ref.10). The general reaction conditions consisted in the formation of the potassium phenolate in refluxing xylene solution with an equimolar proportion of potassium during 3 hours, introduction of a tenth molar proportion of zinc chloride at ambient temperature followed by refluxing for 1 hour. Addition of the prenyl chloride (1.5 moles) and reaction at reflux during 12 hours afforded after work up with ammonium chloride solution the product in excellent yield. Thus 2-geranylphenol, [(E)-2-(3,7-dimethyl-2,6-octadienyl)phenol] was obtained from geranyl chloride (GC) in 86% yield while neryl chloride (NC) gave the (Z)-isomer in 78% yield. Alkylphenols resulted in good yields of 2-prenylanalogues but deactivating groups (Cl, NO_2, Ac) produced somewhat lower yields.

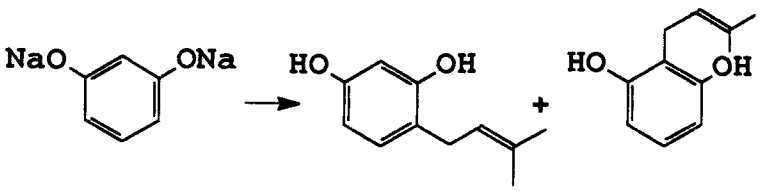


12.3 Synthesis of Prenyl Derivatives of Dihydric and Polyhydric Phenols

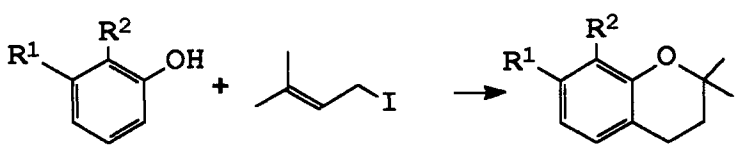
Probably because prenyl derivatives of dihydric phenols are more involved naturally and more reactive than those of the monhydric series as the precursors of many cyclic oxygen ring compounds they have attracted synthetic interest. Although the alkylation of hydroquinones affords good yields, the more reactive resorcinol series do not respond well and isomer formation occurs. Thus, (ref.9), hydroquinone as the disodium salt in hot benzene with 3-methylbuten-2-yl chloride gave 4-hydroxy-2-(3-methylbuten-2-yl)phenol in 66%



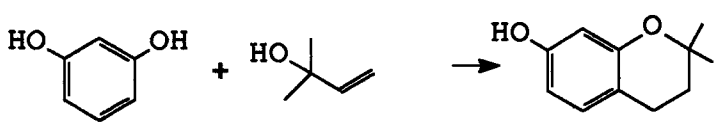
yield while the disodium salt of resorcinol with the same chloride afforded the 4- and the 2-substituted analogues in 16% and 27% yields respectively.



Although the dipotassium salt of hydroquinone in refluxing xylene with 3-methylbut-2-enyl bromide (ref.10) similarly gave 4-hydroxy-2-(3-methylbuten-2-yl)phenol in 50% yield, reactions were not described for the dipotassium salt of resorcinol with a prenyl chloride. The potassium salt of 3-methoxyphenol with allyl chloride gave 2-allyl-3-methoxyphenol in 42% yield.
No reactions were recorded for catechol and only for 2-methoxyphenol (ref. 6) which under acidic conditions gave with phytyl alcohol the 4- and 6-phytyl compounds and with base-catalysed conditions 2-methoxy-6-phytylphenol in low yield for both series.
The reaction of resorcinol with prenyl halides in ethereal solution containing alkali metals or alkaline earth metals or their hydroxides has been instanced among a range of other compounds (ref. 11). By contrast the reagent, isoprene-magnesium-diethyl ether (ref.4) with either resorcinol (R^1 = OH,R^2 = H) or catechol (R^1 = H, R^2 = OH) only afforded chroman products.



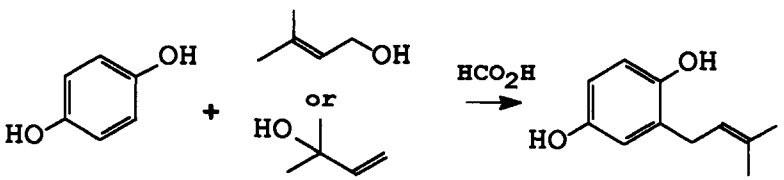
A report that 2-methylbuten-3-2-ol condensed with resorcinol in the presence of 85% phosphoric acid, possibly to simulate natural conditions, to give 4-prenylresorcinol (ref.12) could not be confirmed, the product isolated being 7-



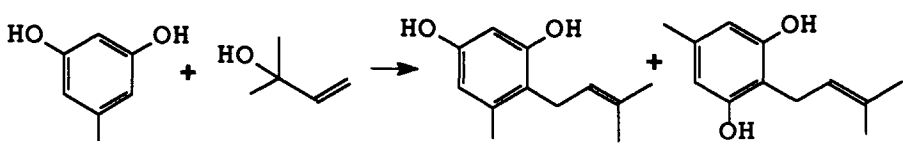
hydroxy-2,2-dimethylchroman (ref.13) and indeed strongly acidic conditions have been found inefficient for prenylation reactions (ref.14). It seems probable that

2- or 4-prenylresorcinols only survive in acceptable yields under basic reaction conditions.

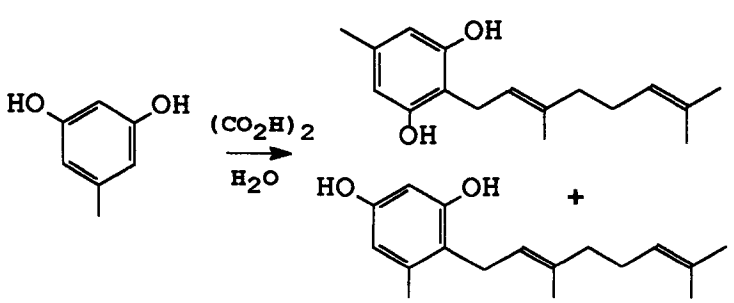
As with prenylphenols in the monohydric series mild acid-catalysed procedures have been developed for the prenylation of polyhydric phenols. Thus a variety of these compounds have been condensed with 3-methylbut-2-enol and with 2-methylbut-3-en-2-ol in dilute aqueous formic acid. Hydroquinone for example afforded isopentenylhydroquinone, 4-hydroxy-2-(3-methylbuten-2-yl)phenol (ref.15).



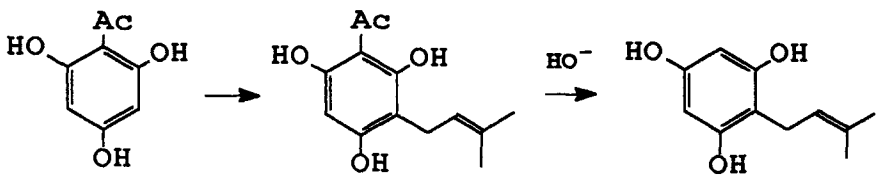
Orcinol upon treatment dropwise with 2-methyl-3-buten-2-ol in warm aqueous formic acid at 80°C and reaction for 1 hour afforded 5-methyl-4-(3-methylbuten-2-yl)resorcinol in low yield while from the filtrate of the reaction mixture, the isomeric compound, 5-methyl-2-(3-methylbuten-2-yl)resorcinol was isolated as well as a bis-prenyl compound by chromatographic purification (ref.16).



By reaction of geraniol with orcinol in 1% oxalic acid two isomeric monoprenyl compounds were obtained although with aqueous formic acid substantial amounts of cyclised products resulted.



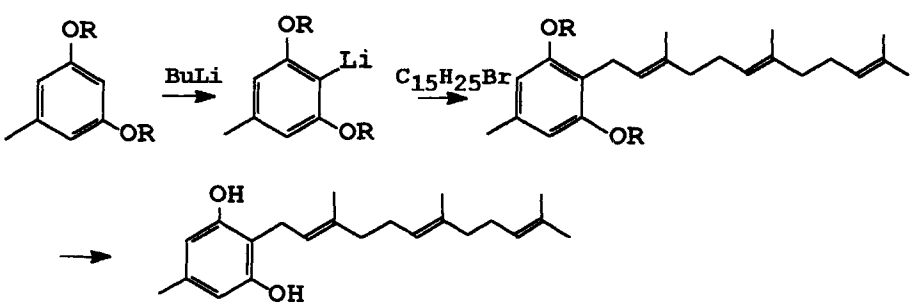
The monoprenyl derivative of phloroglucinol [2-(3-methylbut-2-enyl)phloroglucinol] was prepared in a circuitous maner from 3-methylbut-2-enylphloracetophenone, itself derived from prenylation of phloracetophenone, by boiling for 1 hour with an excess of 5% aqueous potassium hydroxide (ref. 17), to afford the product by 'ketonic' hydrolysis.



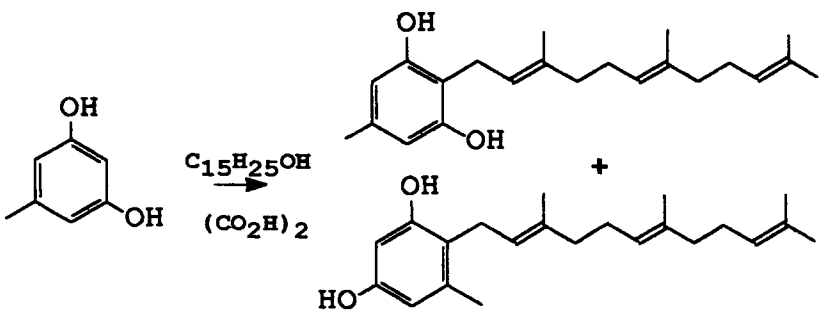
Attempts to prepare prenyl drivatives of pyrogallol under similar conditions to those used for orcinol were found to result in 2,2-dimethylchroman structures (ref. 13) which are descriobed in the next section.

All these easy condensations of 2-methylbut-3-ene-2-ol or 3-methylbut-2-enol (γ,γ-dimethylallyl alcohol) with mono- and dihydric pheniols under very mild acidic conditions do support the biogenetic theory of C-isopentenylation with γ,γ-dimethylallyl pyrophosphate (ref.1).

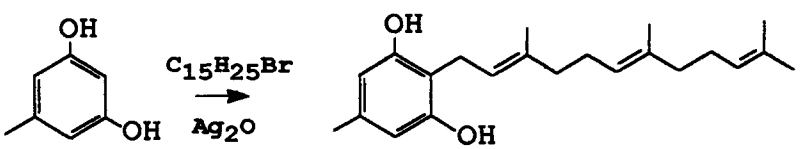
Although the main interest in obtaining prenyl derivatives of mono and dihydric phenols has been to study their cyclisation reactions, which are discussed in an ensuing section, grifolin and neogrifolin which are isomeric symmetrical and non-symmetrical farrnesyl derivatives respectively of orcinol have attracted synthetic interest. Grifolin, 2-farnesyl-5-methylresorcinol is an antifungal metabolite from *Grifola confluens* (ref. 18) and has been prepared in low yield from the reaction of 2-lihioorcinol bis(tetrahydropyranyl) ether (R = Thp) with farnesyl bromide (ref. 19) followed by acidic treatment to remove the protective groups. On account of the much easier availability of methyl ethers it was found that farnesyl bromide reacted with orcinol dimethyl ether (R = Me) in the presence of butyllithium to afford grifolin dimethyl ether although demethylation was less satisfactory (ref. 20).



Several alternative routes are available. In a biogenetic approach (ref. 21), farnesol with orcinol in 50% aqueous acetic acid or by prolonged reaction of the two reactants in methylene chloride containing 4-toluenesulphonic acid, low yields of grifolin were produced. In another method (ref.22) farnesol with excess orcinol in warm 1% aqueous oxalic acid resulted, after preparative chromatography, in a low yield of grifolin and a higher yield of neo-grifolin, a compond not isolated in the preceding methods.



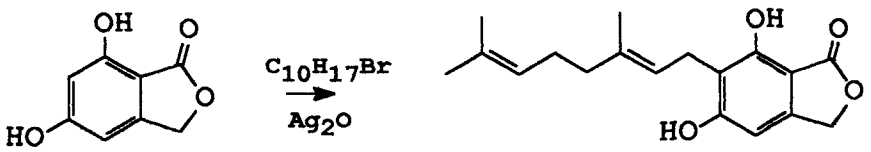
By the reaction of farnesyl bromide with excess orcinol in dioxane containing silver oxide followed by preparative chromatography a 15 % yield of grifolin was obtained containing only a small proportion of the isomer neogrifolin (ref. 23).



Grifolin, neogrifolin and 2,4-difarnesylorcinol have been synthesised in another procedure (ref. 24).

Interest in grifolin stems from its inhibition of Gram-positive bacteria such as *Staphylococcus aureus* whereas neogrifolin is considereably less effecrive. Neither compound is active against Gram-negative organisms and fungi. It is likely that the C_5 and C_{10} prenylphenols may also possess antibacterial action although this area does not seem to have been studied.

The synthesis of more complex natural prenyl structures is considered in a subsequent section. However it is worth noting at this juncture the studies made on the prenylation of 5,7-dihydroxyphthalide (ref. 25) to furnish analogues of mycophenolic acid. Thus for example prenylation was effected by reactiion of 5,7-dihydroxyphthalide (1 mole) in dioxane solution containing silver oxide (1.5 moles) at ambient temperature with geranyl bromide (1.3 moles) to afford 5,7-dihydroxy-6-geranylphthalide in 32% yield.



By the employment of other bromides O-desmethylmycophenolic acid was obtained. Thus, the C_7 bromoester methyl 6-bromo-4-methylhex-4-enoate, $BrCH_2CH=C(Me)CH_2CH_2CO_2Me$, was prepared from tritylgeraniol which was first converted in several steps to the terminal diol, Malaprade oxidation of which furnished 4-methy-6-trityloxylhex-4-enal. Mild oxidation to, the corresponding acid with silver oxide, formation of the methyl ester with diazomethane and derivation of the required allylic bromide by treatment of the alcohol, liberated from the trityl derivative, with carbon tetrabromide containing triphenylphosphine completed the synthesis.
Much of the interest in prenylphenols lies in their cyclisation and other transformation products and some of these reactions are described in the next section.

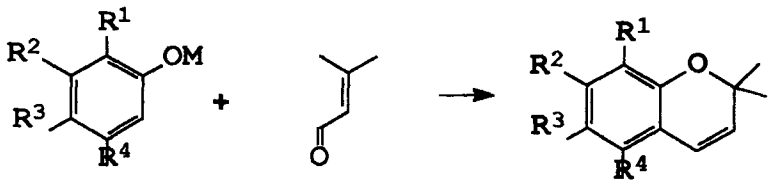
12.4 Cyclisation Products of C_5, C_{10}, C_{15} and C_{20} Prenyl Derivatives of Monohydric, Dihydric and Polyhydric phenols

Although many of the complex natural chromene, chroman, pyran and benzofuran structures clearly have arisen from reactive prenyl precursors which themselves have invariably not been isolated, certain prenyl derivatives of dihydric phenols have served as model compounds in cyclisation processes likely to be the pathways towards those naturally occurring compounds.
2-Prenylphenols and 2- and 4-prenylresorcinols and orcinols with C_5, C_{10}, and C_{15} side chains of the isopentenyl, geranyl and farnesyl type repectively have been examined in this connection.

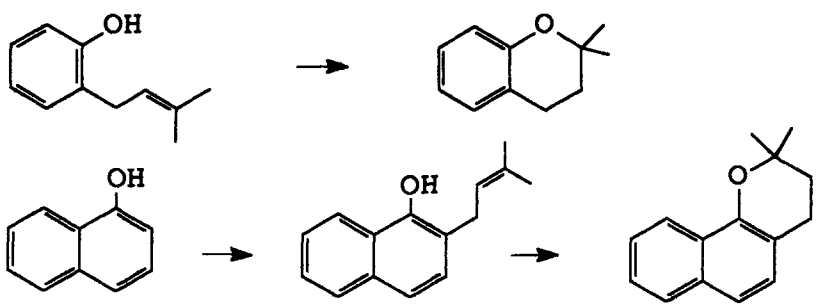
12.4.1 Prenyl Monohydric Phenols

Although strictly outside the reactions of prenylphenolic compounds the extensive work on the regiospecific general synthesis of chrom-3-enes (2H-benzo[b]pyrans), in particular 2,2-dimethylchromenes, from the reaction of metal phenoxides with 3-methylbut-3-enal is very noteworthy. In the general procedure a solution of titanium tetraethoxide (0.025 mol) in toluene was treated with the phenol (0.1 mol) in toluene and the ethanol formed removed by distillation over 2.5 hours following which the mixture was cooled to ambient temperature and 3-methylbut-2-enal (0.15 mol) in toluene introduced. After the addition of more toluene the mixture was refluxed for 8 hours and finally upon cooling, quenched with aqueous ammonium chloride. In this way, phenol ($R^1 = R^2 = R^3 = R^4 = H$)

gave 2,2-dimethylchrom-3-ene (yield 66%, 98% on phenol consumed) and 3-methoxyphenol (R^1 = R^3 = R^4 = H; R^2 = MeO) reacted to give 2,2-dimethyl-7-methoxychrom-3-ene (yield 70%, 96% on phenol consumed).

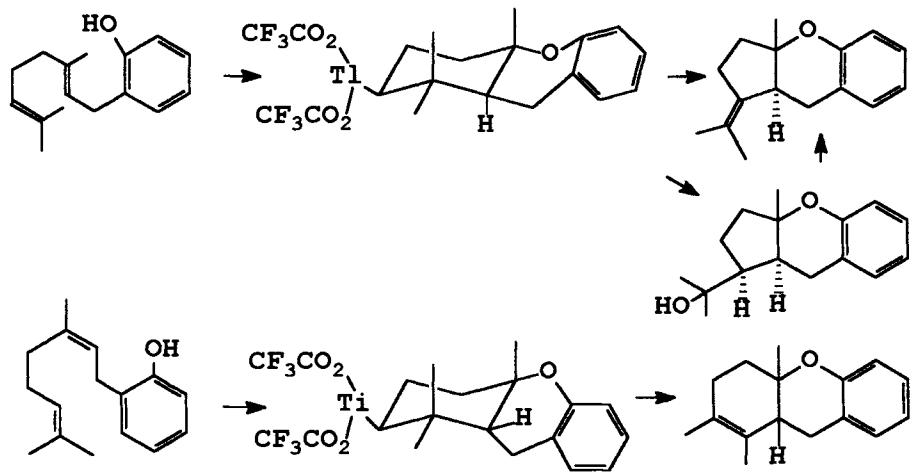


α,β-Unsaturated ketones also reacted in this methodology.
2-isoPrenylphenols obtained from isoprene, 2-methylbut-3-ene-2-ol or 3-methylbut-2-enol readily furnished 2,2-dimethylchroman products by cyclisation under mild conditions. Thus reaction with 90% formic acid (ref.4) at water-bath temperature over 1-2 hours followed by TLC purification afforded the chroman. For example, 2-isoprenyl-1-naphthol (ref. 4) and its isomer 1-isoprenyl-2-naphthol afforded chromans. Formation of the more stabilised carbocation of the 2-prenylphenol or naphthol and attack by the oxygen of the phenolic OH group results in production of the six- and not the five-membered ring.



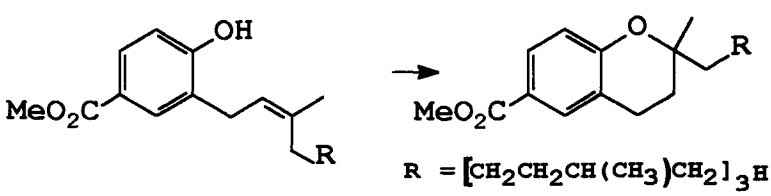
Under 'severe' acid-catalysed reactions of isoprene with phenols, chromans always accompanied the 2- and 4-alkenylphenols (ref. 2).
In the C_{10} series the cyclisation of 2-geranyl and of 2-nerylphenol have been studied under more selective conditions (ref.26). Thus treatment of 2-geranylphenol in dichloromethane with thallium(III) trifluoroacetate (TTFA) followed by reaction at ambient temperature and then hydrolysis with ethanolic sodium hydroxide afforded two tricyclic crystalline products in 38% and 35% yield respectively, the latter being transformed into the former upon dehydrationn with 4-toluene sulphonic acid.
By contrast, 2-nerylphenol under the same chemical conditions (but at -5°C) gave a single tricyclic product in 73% yield, the different pathway having its

origin it was believed in a conformational equilibration of the cis-fused intermediate involved.



2-Farnesylphenol underwent related conversions to those of 2-geranylphenol but in relatively poor yields.

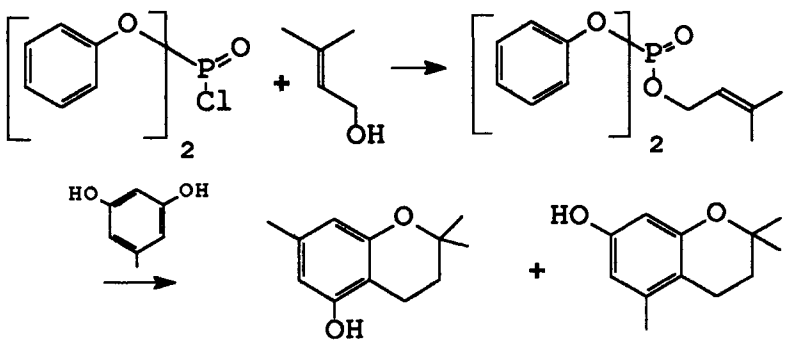
In the C_{20} series the 2-phytyl intermediate from the reaction of methyl 4-hydroxybenzoate with phytol, by treatment with hot methanolic hydrogen chloride afforded a chroman, namely 6-methoxycarbonyl-2-methyl-2-(4',8',12'-trimethyldecyl)chroman (ref. 6).



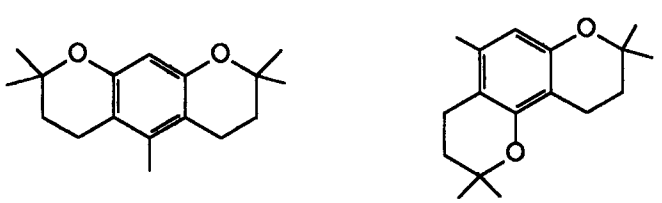
12.4.2 Prenyl Dihydric Phenols

In this group C_5, C_{10} and C_{15} prenyl derivatives of orcinol have featured widely although it is apprropriate to first mention C_5 compounds resulting from resorcinol. Isoprene reacted with resorcinol was found to give 2,2-dimethyl-7-hydroxychroman in 50% yield (ref.4) identical with the product from resorcinol and 2-methylbut-3-en-2-ol obtained in 55% yield (ref.13) by the use of 5% aqueous citric acid (containing ascorbic acid) by heating on a steam bath during 16 hours and with the Clemmensen reduction product of 7-hydroxy-2,2-dimethylchroman-4-one (ref. 27).

Reference has been made in the previous section to the isolation (ref.16) of the two isomeric C_5 prenylorcinols. Two of the twelve products from the reaction of orcinol with 2-methyl-3-buten-2-ol in aqueous formic acid were shown to be the isomeric chromans, 2,2-dimethyl-5-hydroxy-7-methylchroman and 2,2-dimethyl-7-hydroxy-5-methylchroman. which were identical with two compounds reported from the reaction of 3,3-dimethylallyl diphenyl phosphate with orcinol (ref. 28). The former was prepared from 3-methylbut-2-enol and diphenylphosphorochloridate. Upon heating with an excess of orcinol at 120°C during several hours it gave diphenyl hydrogen phosphate and the two chromans



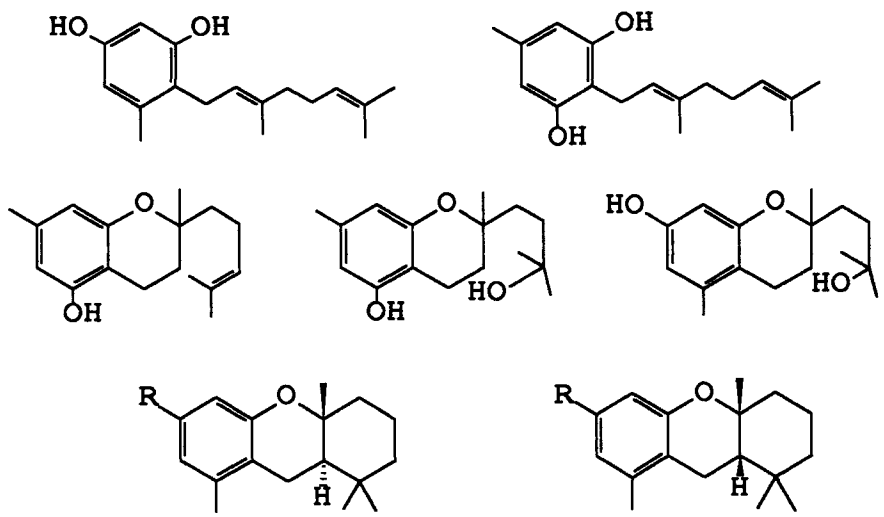
As found (refs.16,28), bis C_5 prenyl derivatives of orcinol can also give rise to isomeric tricyclic benzodipyrans such as the two compounds depicted. Certain of the remaining components of the reaction mixture could be isomeric mono O-prenyl C-prenyl compounds which in turn would be expected to afford 5- or 7-prenyl ethers of 2,2-dimethylchromans and the presence of C/O triprenylorcinols and their transformation products might be anticipated.



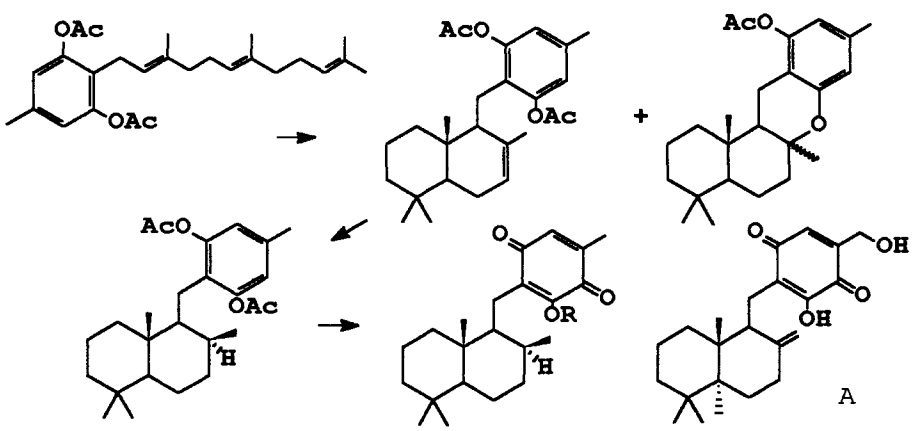
The products from the cyclisation of the two geranylorcinols in aqueous formic acid (ref. 16) have been studied and were found to consist of three chromans of the structure indicated.

In addition two tricyclic hexahydroxanthenes (R = Me) resulted having the structures shown from spectroscopic evidence on related *trans* and *cis*-fused

compounds (R = C_5H_{11}) obtained by the reaction of olivetol with geraniol in nitromethane containing 100% sulphuric acid (ref. 29). In all these cases the formation of six-membered ring products can be expected from the intermediacy

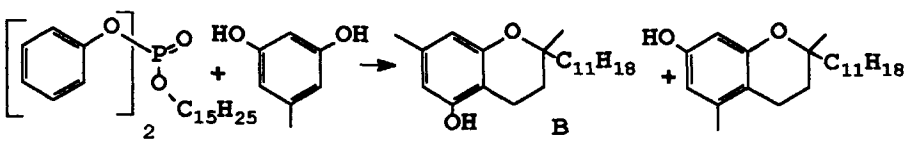


of the more stabilised carbocation intermediate.
The cyclisation of C-farnesylorcinols, in particular of grifolin diacetate has been studied (ref. 21) as a route to a derivative of the tricyclic compound, tauranin (A.)



Thus grifolin diacetate in benzene was treated dropwise with boron trifluoride - etherate at below 5°C and the solution then stirred for 72 hours. Column

chromatographic purification on silicic acid gave a less polar tetracyclic compound (10%) followed by several more polar substances which included a tricyclic compound (15%) having the skeletal structure of tauranin which was transformed to the tetracyclic compound by acidic treatment. Catalytic hydrogenation of the methyl-substituted double bond in the tricycle gave a 1:1 mixture of epimers, one of which separated by crystallisation, was hydrolysed by acid (R = H) and the product submitted to Fremy salt oxidation to afford a hydroxyquinone the monacetate (R = Ac) of which was identical with dihydrodeoxytauranin acetate.
Two simpler chromans obtained from orcinol and farnesyl diphenyl phosphate have been investigated (ref. 28). These have been assigned the structures shown and the less polar (B), having a more sterically hindered hydroxyl group, proved to be identical with an acid-catalysed rearrangement product of grifolin (ref. 30).

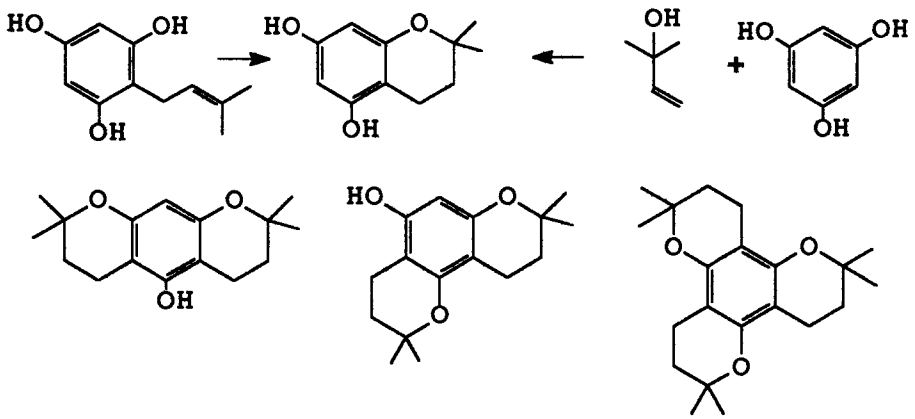


The C_{20} prenyl derivatives of hydroquinone and the methylhydroquinones are considered in a subsequent section devoted to the extensive chemistry of the tocopherols.

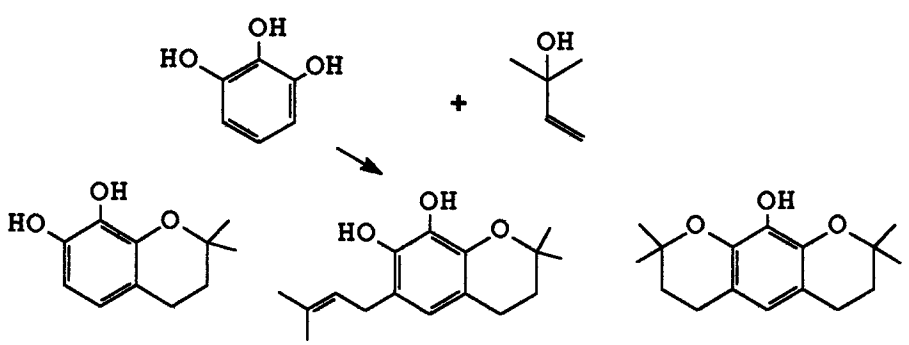
12.4.3 Prenyl Polyhydric Phenols

C_5 prenyl derivatives of phloroglucinol and of pyrogallol have been studied. The monoprenyl derivative of phloroglucinol referred to earlier and prepared by a deacetylation route, afforded a quantitative yield of 5,7-dihydroxy-2,2-dimethylchroman upon warming in 5% citric acid during 16 hours (ref. 13). Phloroglucinol itself was highly reactive towards 2-methylbut-3-ene-2-ol under the very mild conditions of warming with 5% aqueous citric acid and gave the same monochroman (18.5%) together with a compound (13%) (mp 161-162.5°C) considered to be the linear rather than the isomeric angular dichroman on the basis of NMR evidence and a positive response in the Gibbs test. By contrast, in the reaction of phloroglucinol hydrate and 3,3-dimethylallyl diphenyl phosphate (ref.28) during 8 hours at 100°C the symmetrical benzotripyran (26%) resulted and a compound (25%) (mp 157.5-158.5°C) considered to be the angular rather than the linear compound by analogy with earlier work (ref. 31) and possibly because of the accompanying symmetrical benzotripyran present in the reaction products. In their work (ref.28) on orcinol reacted with 3,3-dimethylallyl diphenyl phosphate leading to a tricyclic compound these authors did not distinguish between the formulation of the product as an angular

or a linear structure.



In the condensation of pyrogallol with 2-methylbut-3-ene-2-ol by warming in 5% aqueous citric acid the main fraction isolated proved to be 7,8-dihydroxy-2,2-dimethylchroman (25%) and a second oily fraction was obtained which appeared to be a mixture of 7,8-dihydroxy-2,2-dimethyl-6-prenylchroman and the linear dichroman since upon refluxing in ethanolic hydrochloric acid the latter was obtained in crystalline form, through cyclisation of the bicyclic to the tricyclic compound (15%).



12.5 Natural Prenyl Coumarins, Chromones and related Structures

Many natural isoprenoid oxygen ring products contain the intact C_5 prenyl group, and/or chroman, coumarin or coumaran rings derived from it. Fewer compounds have geranyl or farnesyl groups probably reflecting their reactivity towards cyclisation. The present section is a logical extension and proceeds from prenyl derivatives of monohydric to polyhydric phenols. Because prenyl

derivatives of the latter are invariably transformed to chromones these compounds represent an entry to more complex natural products. A selected range of monocyclic benzenoid, polycyclic chromans and chromenes, coumarins are now described. Several of these possess biological properties which has enhanced the study of their chemistry and that of analogues. For example, certain prenylchalcones have been found to have anti-feedant properties, the cabenegrins have been reported to be effective oral antidotes to snake and spider venoms, acronycine possesses anti-tumour activity, rotenone has well-known insecticidal activity and the precocenes have anti-juvenile hormone properties. It is convenient to summarise in the following Table 12.1, a selected number of structures deriving from might be termed the classical period of work on both chemistry and biosynthesis (ref. 32).

Table 12.2 summarises some more recently found prenylphenolic compounds from the classes referred to in the preceding Table some of which contain novel ring systems. The prolific range of biological properties in these oxygen ring compounds has undoubtedly prompted their close study as an aspect of the utilisation of natural organic resources. The chemistry of natural coumarins has been reviewed (ref.62).

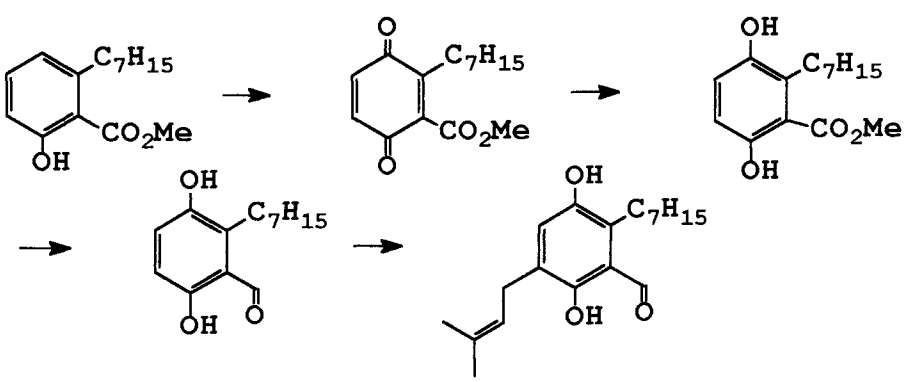
12.6 Synthesis of Prenyl Oxygen Ring Phenolic Compounds

The structures of the compounds listed in the Tables 12.1 and 12.2 have been revised from the original formulations in many cases. With the aid of MS and NMR spectroscopy they have been in most cases confirmed although the absolute configurations are not always known with certainty. In many instances the biological properties have been investigated and promising results frequently indicated with the consequence that the availability of the active component has become a matter of interest. As with many natural products the alternatives arise of either extraction and purification or total synthesis, with the further option of semi-synthesis of analogues in the case of compounds found to have worthwhile properties. Progress in synthesis has been spasmodic but in the last two decades considerable progrss has been made. In this section several syntheses are given of monocyclic bicyclic and polycyclic compounds which in effect extend the methods outlined in the initial sections on prenylation of phenols to more complex examples. In general a difficulty in preparative work has been the lack of regiospecificity in prenylations.
Nevertheless it is possible to summarise some preparative conclusions which appear to be generally useful.
(1) C-Prenylation is effected with 2-methylbut-3-en-2-ol and boron trifluoride etherate or zinc chloride.
(2) Both O- and C-prenylation result from the use of prenyl bromide with sodium methoxide /methanol.
(3) Regiospecific substitution is more prevalent at the 2-position with prenyl bromides in the presence of silver oxide in dioxan although the procedure is not

wholly specific.
(4) O-prenyl ethers result from phenolic hydroxyl groups under mild conditions with prenyl bromides in acetone containing potassium carbonate. Intramolecularly hydrogen-bonded hydroxyl groups react more slowly.
(5) As an alternative to prenyl alcohols and halides, α,β-unsaturated carbonyl compounds can be used. Resorcinols as dimetal salts then react at the 2-position whereas with the free resorcinol in pyridine solution, 4-substitution occurs.
(6) Chromene ring formation can be effected by oxidative cyclisation of 2-prenylphenols or by reaction of pyrano compounds with DDQ (dichlorodicyanobenzoquinone), by reduction of a chromone with a hydride followed by dehydration with a toluenesulphonic acid, and directly by the use of 1,1-dimethoxy-3,3-dimethyl-3-hydroxypropane.
(7) Chalcones can be easily converted to isoflavones rather than flavones by rearrangement with TTN (thallium trinitrate) followed by cyclisation.
In the following synthess the sequence of examples does not follow the type of compound as listed in Tables 1 and 2, but the methodology.

12.6.1 Monoprenyl Dihydric Phenols, Chalcones and Derivatives

As examples of functionalised compounds aurogalaucin (ref.35) and flavoglaucin provide a link with synthetic monoprenyl dihydric phenols of the type discussed in 12.4. Although these two compounds (Table 12.1) do not appear to have been synthesised a study of their biosynthesis (ref. 36) illustrates a potential laboratory route through oxidation of 7-heptylsalicylic acid, synthesised by standard methods (ref. 83), by procedures such as Teuber oxidation with Fremy's salt followed by reduction, conversion of the methoxycarbonyl to the formyl group by hydride reduction and oxidation of the benzylic alcohol and finally prenylation, which would probably be non-specific.



Ovalichalcone (ref.33, Table12.1) has been derived readily by the Claisen

TABLE 12.1 SOME NATURALLY-OCCURRING ISOPRENOIDS

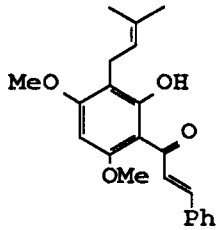
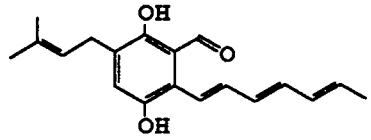
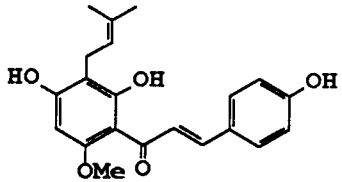
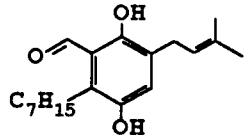
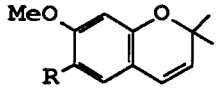
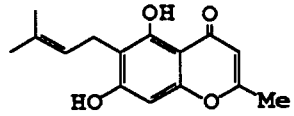
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
MONOCYCLIC COMPOUNDS							
Ovalichalcone		*Milletia ovalifia*	*33*	Auroglaucin		*Aspergillus* spp.	*35*
Xanthohumol		*Humulus lupulus*	34	Flavoglaucin		*Aspergillus* flavus	*36*
BICYCLIC and POLYCYLIC COMPOUNDS							
Precocenes 1,2 R = H, OMe		*Ageratum houstonianum*	37	Peucenin		*Peucedanum oreosselinum*	38

TABLE 12.1 (contd.)

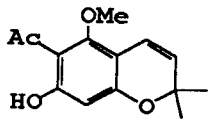
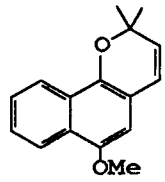
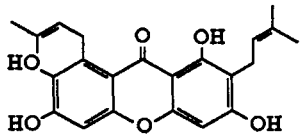
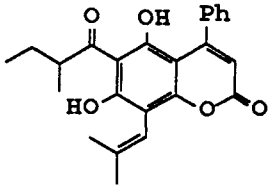
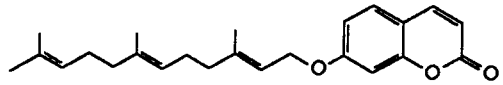
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
BICYCLIC and POLYCYCLIC CHROMONES							
Evodionol		*Medicosa cunninghasmii*	39	Lapachenole		*Tabebia avellanedae*	40
γ-Mangostin		*Hydnocarpus octandra*	41				
BICYCLIC and POLYCYCLIC COUMARINS							
Mammeins		(A/AB) *Mammea americana*	42	Umbelliprenin		*Ferula loccosii*	43

TABLE 12.1 (contd.)

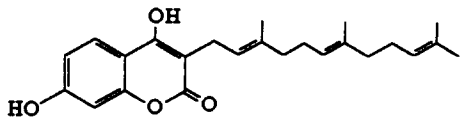
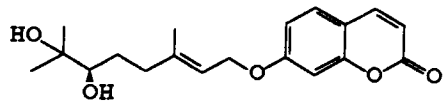
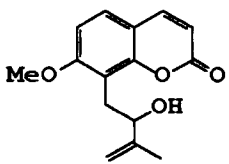
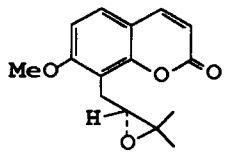
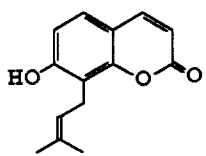
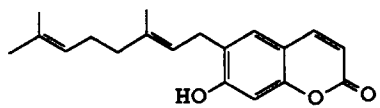
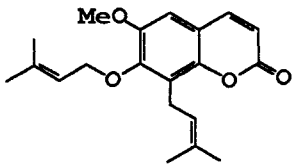
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
Ammoresinol		*Dorema ammoniacum*	44	(+)-(R)-Marmin (E form)		*Aegle marmelos*	45
Auraptenol		*Murraya spp.*	46	(+)-(R)-Meranzin		*Skimmia japonica*	47
Osthenol		*Apium graveolens*	48	Ostruthin		*Peucedanum ostruthium*	49

TABLE 12.1 (contd.)

COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
Braleyanin		*Flindersia brayleana*	50				

FURANOCOUMARINS

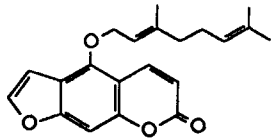
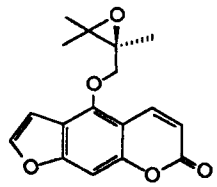
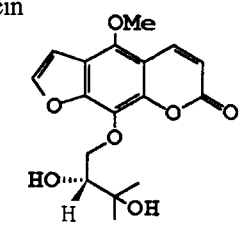
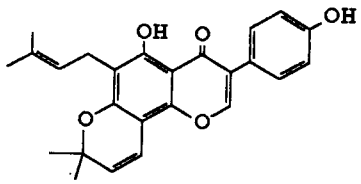
Bergamottin		Oil of Bergamot	51	(+)-(R)-Oxypeucedanin		*Peucedanum palustre*	52
(-)-(S)-Byakangelicin		*Ruta graveolens*	53				

TABLE 12.1 (contd.)

COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.

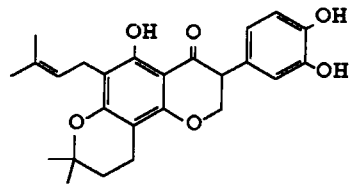
CHROMONOCHROMENES (ISIFLAVONES), CHROMONOCOUMARINS,-PYRIDINES, -PYRANS

Osajin



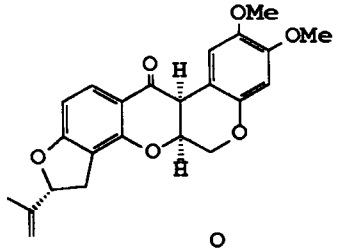
Erythrina variegata 54

Pomiferin



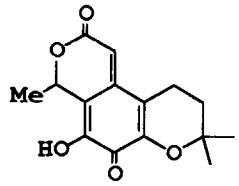
Maclura pomifera 55

(-)-Rotenone
6a(S),12a(S),5'(R)



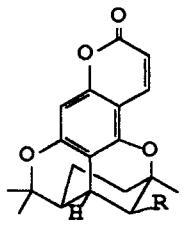
Derris elliptica 56

Fuscin



Oidiodendron fuscum 57

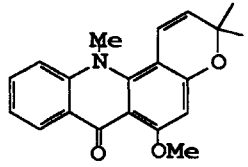
Deoxybruceol



R = H;
R = OH, (Bruceol)

Eriostemon brucei 58

Acronycine



Achronycine buerii 59

TABLE 12.1 (contd.)

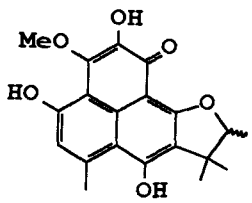
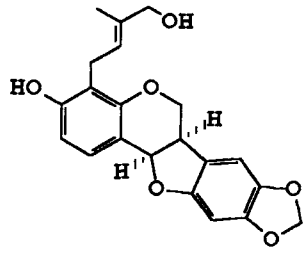
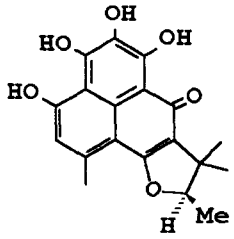
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
PHENALONES, FURANOPYRANS							
Herqueichrysin		*Penicillium herquei*	60	Cabenegrins		'Cabega de Negra'	61
Atrovenetin		*Penicillium atrovenetum*	60				

TABLE 12.2

FURTHER NATURALLY-OCCURRING PHENOLIC ISOPRENOIDS

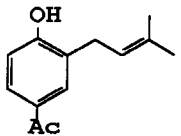
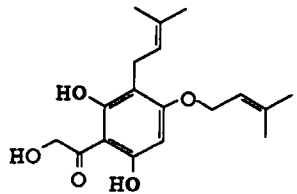
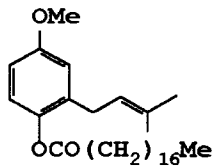
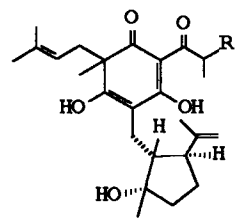
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
4-Acetyl-2-prenylphenol		*Artemesia campestris*	63	ω-2,6-Trihydroxy-3-prenyl-4-prenyloxy-acetophenone		*Evodia lunu-ankenda* (folk medicine)	64
4-Methoxy-2-prenyl-phenol (and stearoyl ester)		*Lactarius fuliginosus*	65	Chinensin I and II (anti-bacterial)	I ;R = Et II;R = Me 	*Hypericum chinensin*	66

TABLE 12.2 (contd.)

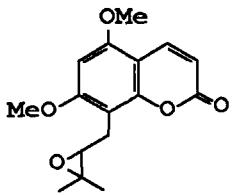
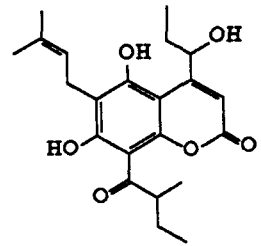
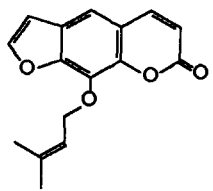
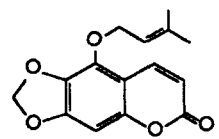
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
BICYLIC and POLYCYCLIC COUMARINS, CHROMONES, ISOFLAVONES, FLAVONES, TETRALONES							
Methoxy and dimethosy prenylcoumarins (Endangered species)		*Merillea caloxylon*	67	5,7-Dihydroxy-6,8-diprenylcoumarins (Fish poison)		*Kayea assamica*	68
Prenyloxycoumarins (Fungistats)		*Amyris barbata, brenesii, sylvatica*	69	6,7-Methylenedioxy-5-prenyloxycoumarins (Argentine folk medicine)		*Pterocaulon virgatum*	70

TABLE 12.2 (contd.)

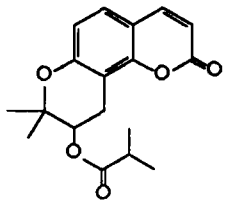
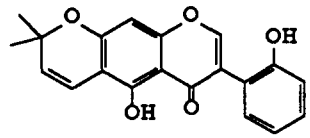
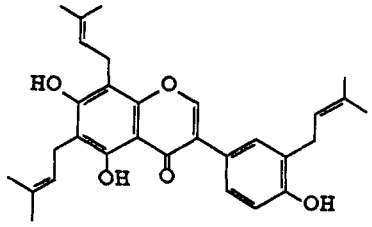
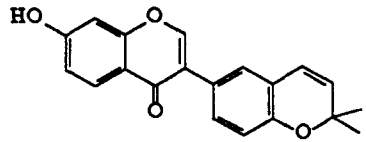
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
Dihydropyanocoumaruin (Insect repellent, folk medicine)		*Clausena anisata*	71	Pyranoisoflavones (antifungal)		-	72
Chromenoflavone (Antiinflammatory)		*Eucresta japonica*	73	Chromenochromone (isoflavone) (Antimicrobial, folk medicine)		*Erythrina eriotricha and sigmoidea*	74

TABLE 12.2 (contd.)

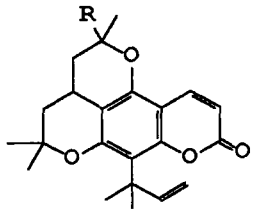
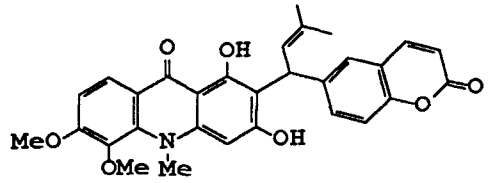
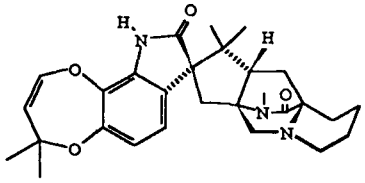
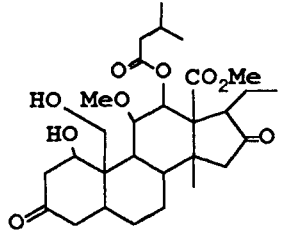
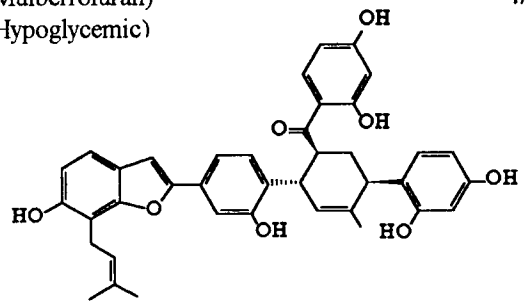
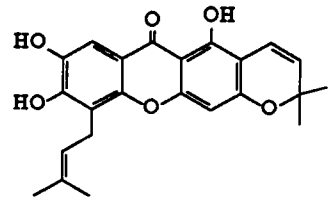
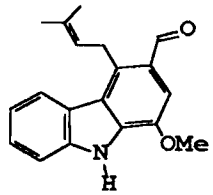
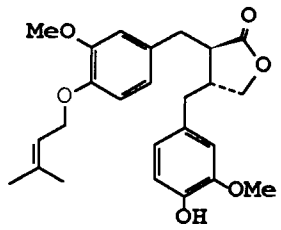
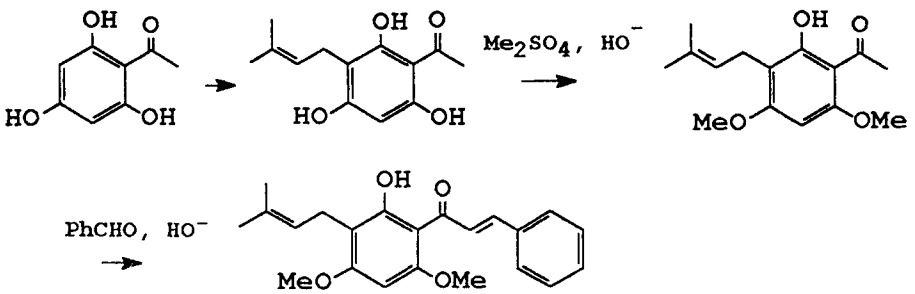
COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
Bipyranocoumarins	 R = HO-Coumarinic	Citrus spp.	75	Acridonocoumarin (Acrimarins)		*Citrus funakodo*	76
Complex alkaloidal (Mycotoxic) Marcfortine		*Penicillium brevicompactum*	77	Steroidal (Folk medicine abortion)	 Aromatisable ring A	*Marsdenia tinctoria*	78

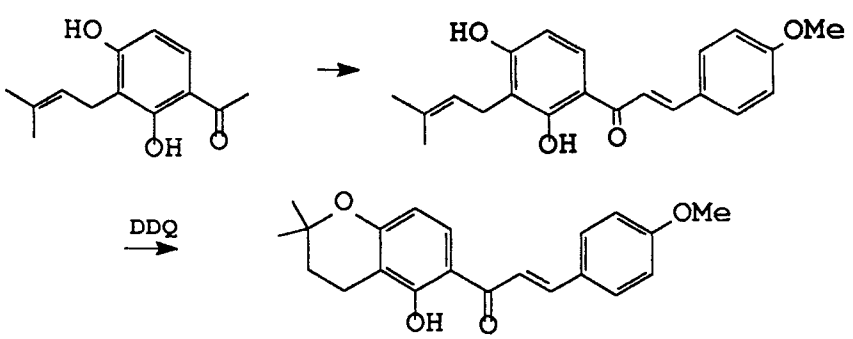
TABLE 12.2 (contd.)

COMPOUND	STRUCTURE	ORIGIN	REF.	COMPOUND	STRUCTURE	ORIGIN	REF.
Prenylbenzofuran (Mulberrofuran) (Hypoglycemic)		*Morus insignis*	79	Xanthones (Asian flok medicine)		*Calophyllum inophyllum*	80
Carbazole alkaloid		*Ekebergia senegalensis*	81	Lignan (Cytoxic)		*Haplophyllum thesioides*	82

condensation of benzaldehyde with 2,4-dimethoxy-6-hydroxy-5-C-prenylacetophenone obtained from the dimethylation of the two less hindered hydroxyl groups in the prenylphloroacetophenone which has been described earlier.

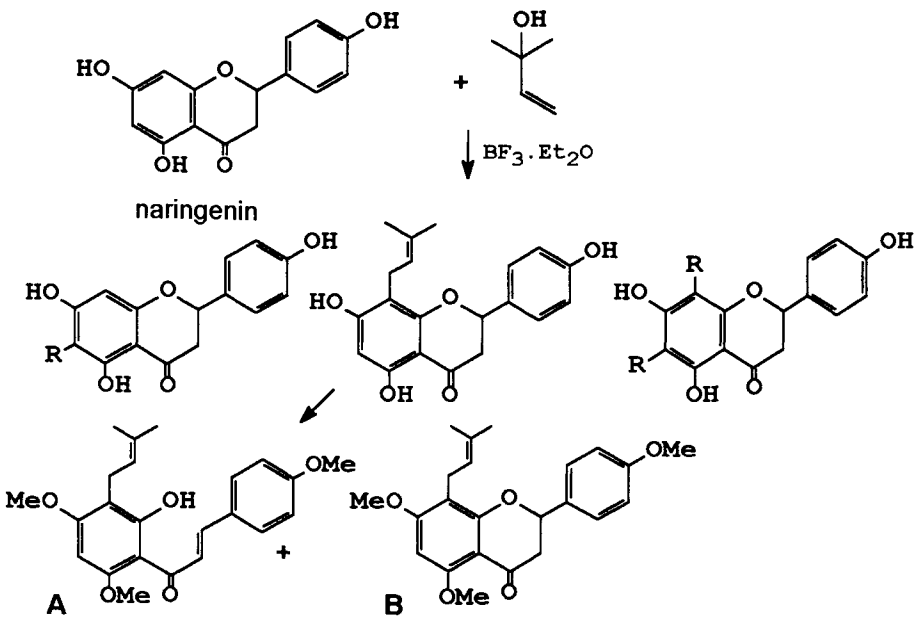


The synthesis of an analogue, a pyranochalcone isolated from a related species *Millettia pachycarpa,* which is described (ref.84) as an insect anti-feedant, commenced with the prenylation of 2,4-dihydroxyacetophenone with prenyl bromide in a basic medium to afford several products but primarily 2,4-dihydroxy-3-C-prenylacetophenone in 50% yield. Formic acid cyclisation gave a pyrone which was condensed with anisaldehyde. The resulting chalcone was oxidised in which reaction the non hydrogen-bonded hydroxyl group participated to obtain the final product. This was also be derived by the alternative of chalcone formation from 2,4-dihydroxyacetophenone followed by prenylation (non-specific) and finally DDQ oxidation.



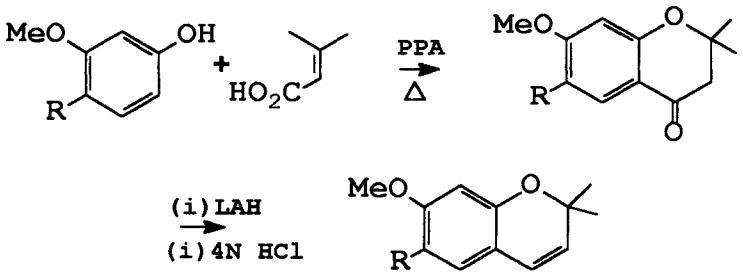
A dimethyl ether of xanthohumol has been prepared non-specifically (ref. 34) from the flavonoid naringenin reacted with 2-methylbut-3-en-2-ol in the presence of boron trifluoride etherate to afford the the 6-C-prenyl (R = prenyl), (some 6,8–di-C-prenyl, R = prenyl) and 8-C-prenyl derivatives. Methylation of the latter

with dimethyl sulphate in acetone containing potassium carbonate resulted in ring-opening to give xanthohumol dimethyl ether (A) and with ring retention, isoxanthohumol dimethyl ether (B). The requirement en route for the separation of mixtures from prenylation reactions, although sometimes giving simultaneous synthetic access to analogues, indicates their lack of specificity.

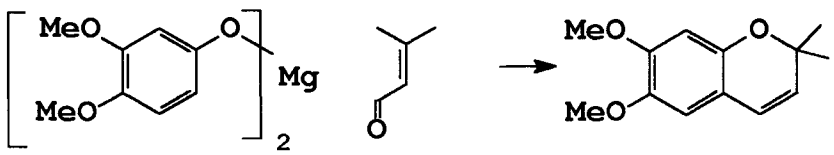


12.6.2 Chrom-3-enes

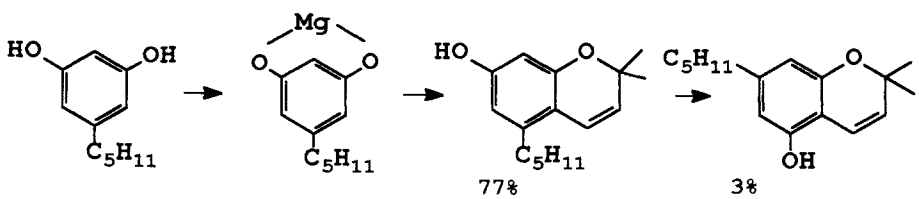
Considerable interest has followed from the early work on precocenes 1 and 2 (ref. 37), compounds having antijuvenile hormone activity and in consequence a number of syntheses have been developed. In the original work known methodology (ref. 85) was used. Thus, the reaction of 3-methoxyphenol and of 3,4-dimethoxyphenol (R = OMe) with 3-methylbut-2-enoic acid in the presence of polyphosphoric acid led to the respective 2,2-dimethylchromones which were reduced by lithium aluminium hydride and then dehydrated to afford the two final products. The procedure has been improved (ref. 86) by the reaction of resorcinol and of 3,4-dihydroxyphenol with the same acid in phosphorus oxychloride containing zinc chloride and 5% water to afford the respective chromones in 79-82% yield. Methylation with methyl iodide in DMF containing potassium carbonate gave the methyl ethers (R = OMe) which upon reduction in methanol with sodium borohydride gave the corresponding alcohols. Dehydration with 4M hydrochloric acid completed the syntheses.



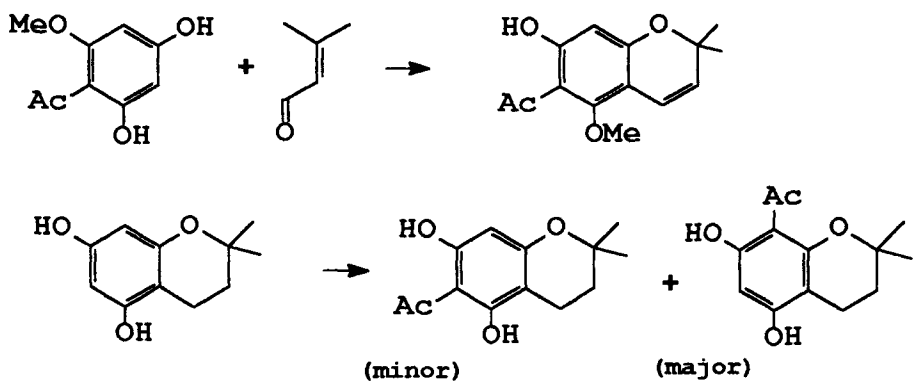
A direct procedure, partly based in earlier knowledge, giving the chrom-3-ene (2H-benzo[b]pyran) structure in one-step has been referred to earlier. In this method titanium or magnesium phenolates formed from the phenol with the metal ethoxide and removal of ethanol, are then reacted with α,β-unsaturated aldehydes or ketones in toluene solution at 110°C over 8 hours (ref. 40). In this way precocene 2 was derived from the reaction of the magnesium salt of 3,4-dimethoxyphenol with 3-methylbut-2-enal in 80% yield (98% based on the 3,4-dimethoxyphenol consumed). Tin(IV) and aluminium phenolates could also be employed and regiochemical control was high with more than 90% selectivity, through reaction at the 4-position in resorcinolic systems.



A further example is the reaction of the magnesium salt of olivetol with 3-methylbut-2-enal when the yield of the 4-substitited product was 77% and that of the 2- was 3%. By contrast in the reaction of resorcinols with α,β-unsaturated carbonyl compounds in pyridine solution 2-substitution occurs as will be seen in the synthesis of deoxybruceol in section 12.6.5.

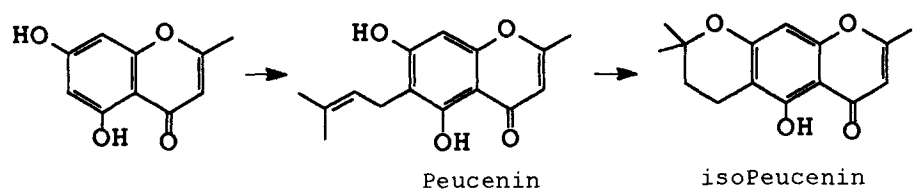


The method was applied to the synthesis of evodionol (Table 12.1) by the reaction of the methyl ether of phloroacetophenone shown, to give the chromene in 65% yield (95% on the intermediate used). In the much longer synthesis of evodionol (ref. 39), at the initial step by the Hoesch reaction on 2,2-dimethyl-5,7-dihydroxychroman, the desired 6-acetyl product was the minor one and following benzylation to give the 7-benzyloxy compound, methylation, hydrogenolysis and DDQ oxidation were the required remaining steps.



12.6.3 Chromones

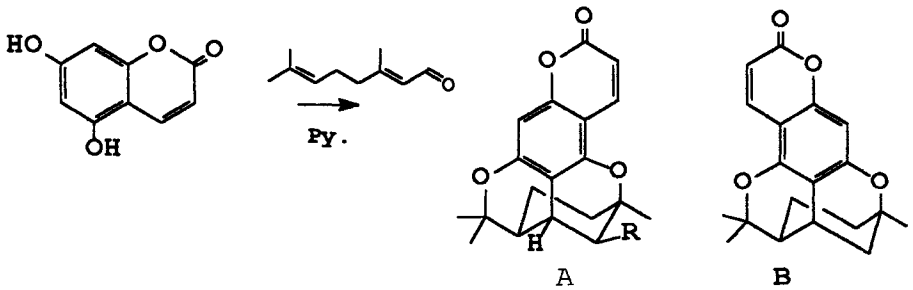
A number of these structures are widespread as illustrated by peucenin (Table 12.1, ref. 38). Nuclear prenylation of 5,7-dihydroxy-2-methylchromone by the unspecific procedure of prenyl bromide in methanolic sodium methoxide afforded peucenin, 5,7-dihydroxy-2-methyl-6-prenylchromone (15%), together with the 6,8-di-C-prenyl compound (21%) and 5-hydroxy-7-prenyloxychromone (1%). The cyclisation of peucenin by the standard procedure with formic acid gave isopeucenin.



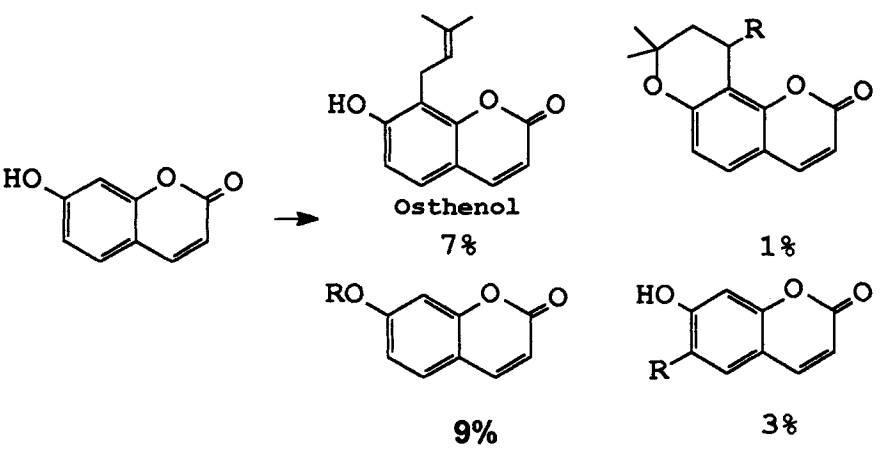
12.6.4 Coumarins

A large number of hydroxycoumarins contain C-prenyl members. An example of the selectivity and dependence on the reaction medium of the product formed

in the reaction of unsaturated aldehydes with resorcinols was referred to earlier, and is typified by the synthesis of racemic deoxybruceol (Table 12.1). The reaction of 5,7-dihydroxycoumarin (prepared from ethyl propiolate and phloroglucinol in 90 yield in acidic medium) in pyridine at 110°C containing an equimolar proportion of citral (ref. 57) afforded a low yield of racemic deoxybruceol (A; R = H; in bruceol R = OH). Although the required product was accompanied by a mixture of two monochromenes and a bischromene, the isomeric structure B was not formed.

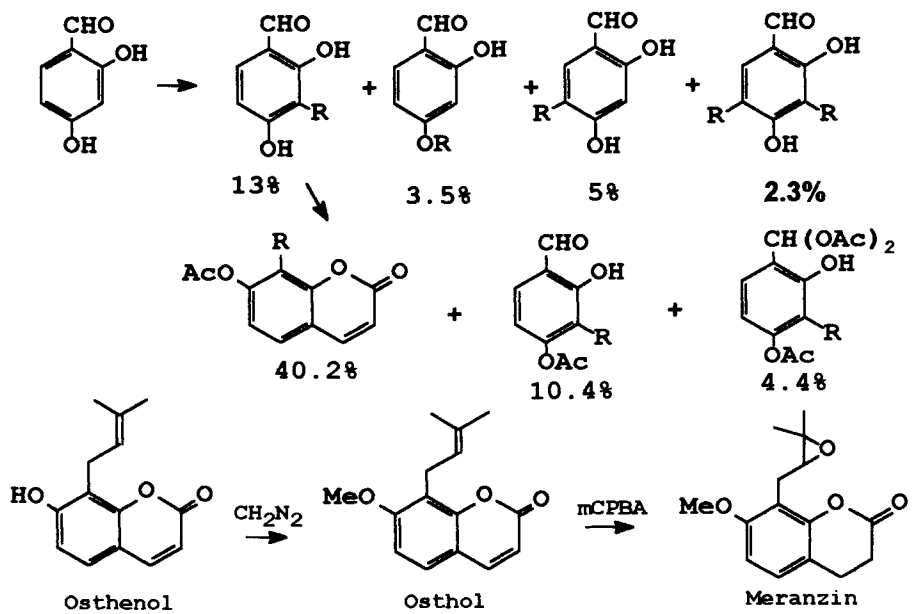


In the bicyclic series, the reaction (ref. 46) of umbelliferone (7-hydroxycoumarin) with prenyl bromide (RBr) in dioxan containing silver oxide afforded, osthenol, 7-hydroxy-8-prenylcoumarin (7%), (Table 12.2, ref. 47), 7-hydroxy-6-prenylcoumarin (3%), 7-prenyloxycoumarin (9%) and a prenyl derivative at the benzylic position of the pyrano cyclisation product of osthenol.

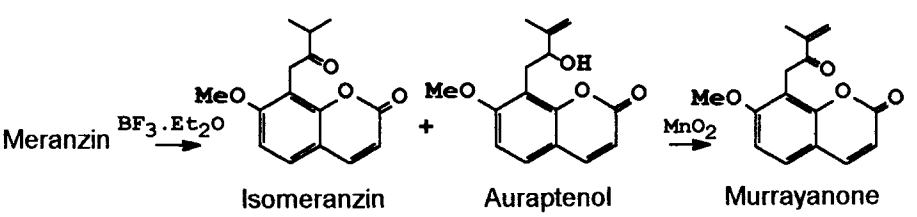


A more specific route (ref.46) to osthenol from which racemic meranzin, isomeranzin and auraptenol were obtained commenced with 2,4-dihydroxybenzaldehyde. By its reaction with 2-methylbut-3-en-2-ol in the

presence of boron trifluoride etherate 2,4-dihydroxy-3-prenylbenzaldehyde was obtained in low yield but rather better with prenyl bromide (RBr) in strongly alkaline solution. Coumarin ring formation resulting in osthenol acetate took place by reaction of 2,4-dihydroxy-3-prenylbenzaldehyde with acetiic anhydride/triethylamine. Hydrolysis with methanolic ammonia gave osthenol and methylation of this with diazomethane then gave osthol, 7-methoxy-8-prenylcoumarin which upon treatment with 3-chloroperbenzoic acid afforded racemic meranzin.

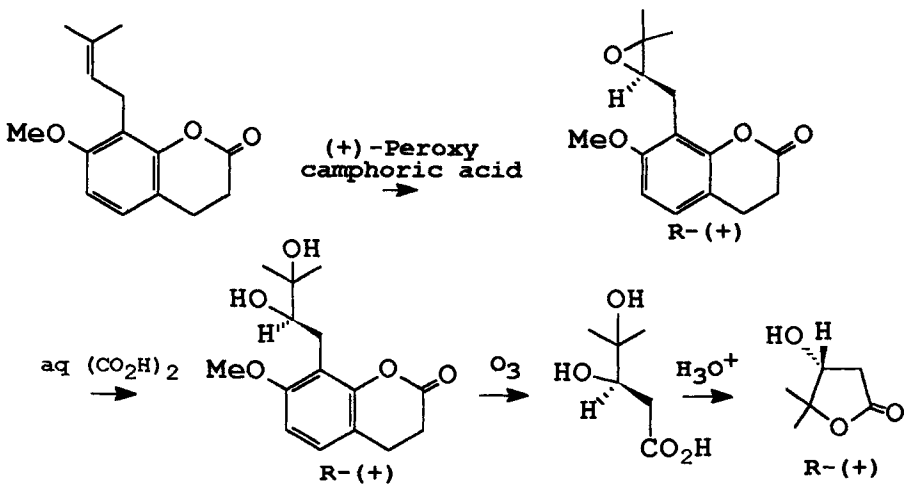


Acid-catalysed rearrangement of meranzin in DMSO containing boron trifluoride etherate at 100°C produced isomeranzin (30%) and racemic auroptenol, oxidation of which with manganese dioxide in benzene afforded murrayone.



An asymmetric synthesis of (+)-(R)-meranzin was effected in 84% yield by reaction of osthol (osthenol methyl etherl) with (+)-peroxycamphoric acid in

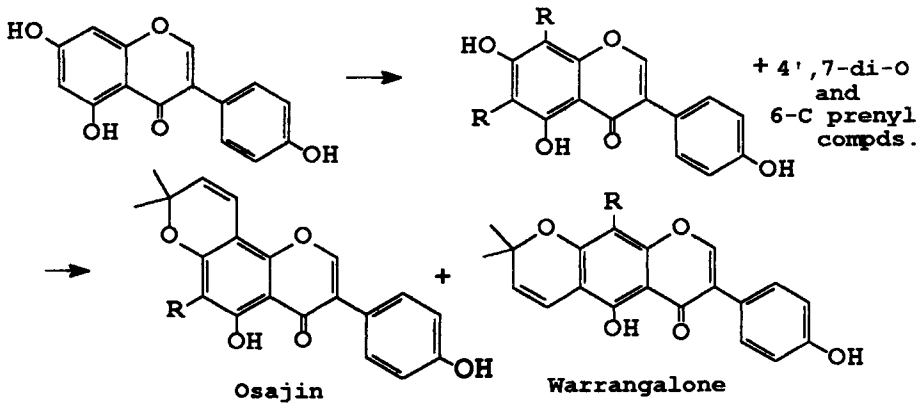
chloroform (ref. 60). The structure was proved by formation with aqueous oxalic acid of meranzin hydrate (meranzin diol), ozonolysis of which and lactonisation of the resultant hydroxy acid produced the (+)-hydroxylactone, 4-hydroxy-3-methylbutyrolactone of known R configuration.

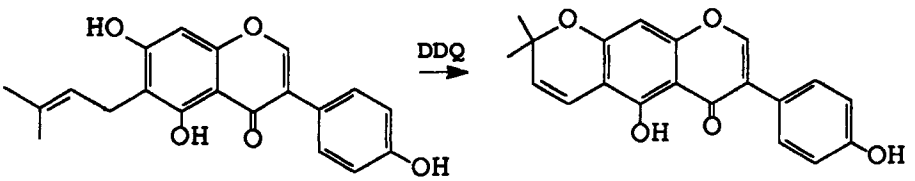


Although this also establishes the S-configuration of (-)- meranzin, this was synthesised by preparation of the tosyl derivative of the secondary OH group of meranzin diol and then formation of the epoxide.

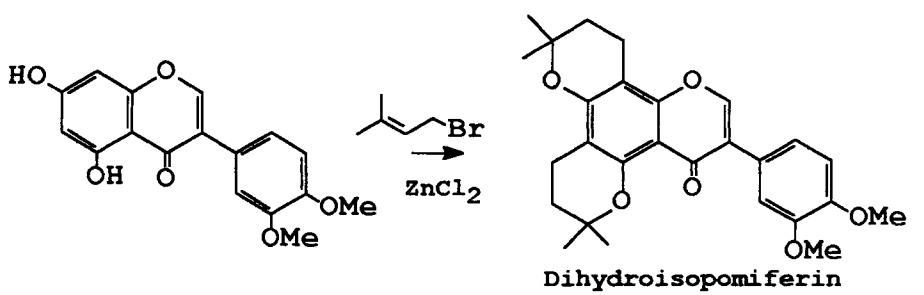
12.6.5 Isoflavones

Several prenylated isoflavones and their cyclisation products resulting in chromenoisoflavones such as osajin and pomiferin have been referred to in Table 12.1. The prenylation of genistein (4',5,7-trihydroxyisoflavone) a widely occurring isoflavone (ref.87) provides an appropriate semi-synthetic starting point for the synthesis of osajin (ref. 88) although as in many similar instances there is a lack of specificity at the iniitial stage. By the use of prenyl bromide (RBr) in methanolic sodium methoxide, 4',7-di-O-prenylgenistein, 6,8-di-C-prenylgenistein and 6-prenylgenistein were formed. Oxidative cyclisation of the 6,8-C-prenylated product with DDQ afforded the non-linear osajin and an isomeric linear compound, warrangalone through participation of the 7-hydroxyl non-hydrogen-bonded hydroxyl group. Only through formation of the 4',7-dimethyl ether of the 6-prenyl compound was it found possible to involve the 5-hydroxyl group in cyclisation with the 6-prenyl group. Hence cyclisation with DDQ of the 6-monoprenylgenistein involved the 7-hydroxyl group group and gave the linear compound alpinum isoflavone as shown in the seond scheme.



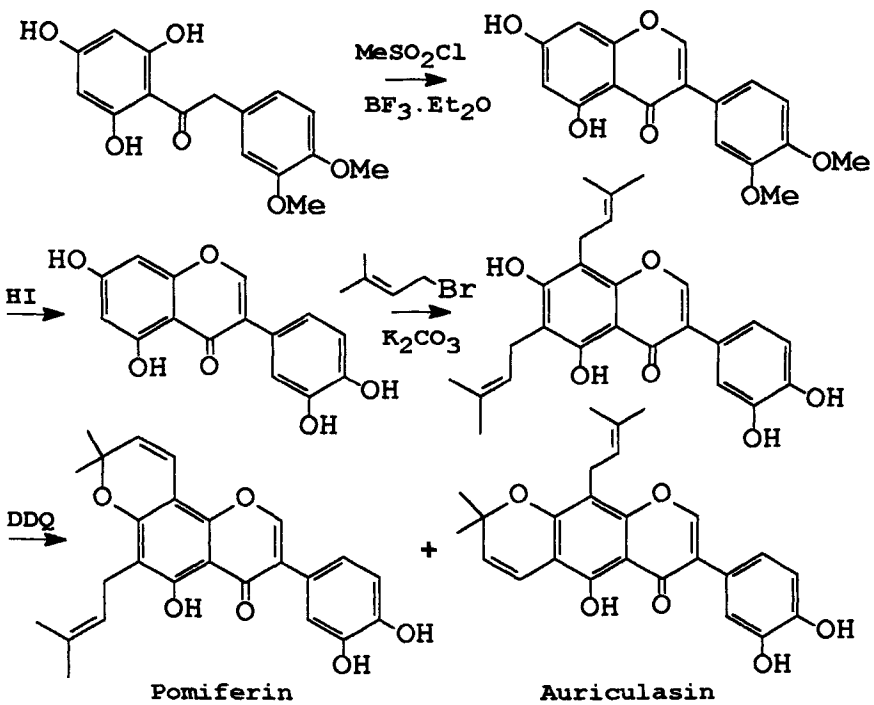


Firstly, the more hydroxylated compound, dihydroisopomiferin has been prepared as the dimethyl ether by a semi-synthetic route (ref. 89) from orobol dimethyl ether (5,7-dihydroxy-4',5'-dimethoxyisoflavone) by the drastic conditions of prenylation in benzene containing zinc chloride with prenylbromide.



Pomiferin itself (Table 12.1) has been obtained by a more selective synthetic route (ref. 54). In this, 2,4,6-trihydroxyphenyl 3,4-dimethoxybenzyl ketone was

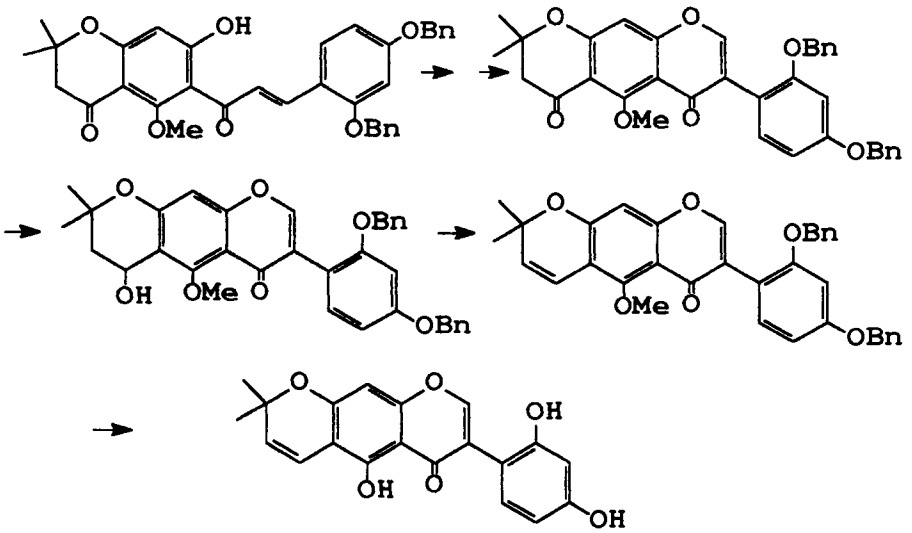
reacted with methanesulphonyl chloride in DMF containing boron trifluoride etherate to form the isoflavone system (ref.90). Demethylation with hydrogen iodide and C-prenylation in methanolic sodium methoxide afforded 6,8-di-C-prenylorobol as the major product which upon refluxing with DDQ in benzene afforded pomiferin together with the structural isomer auriculasin, through preferential involvement of the 7- and not the 5-hydrogen-bonded hydroxyl group.



Natural orobol was also converted to pomiferin and auriculasin (ref. 54). Thus prenylation with prenyl bromide and methanolic sodium methoxide afforded 6-C-prenyl and 6,8-di-C,C-prenylorobol. The latter when refluxed in benzene containing DDQ was converted to a mixture of pomiferin and auriculasin.

It is of interest to note in passing that In more recent work (ref.72), use has been made in synthesis of the transformation of chalcones to isoflavones with thallium(III) nitrate. Thus, 6-acetyl-2,2-dimethyl-7-hydroxy-5-methoxychromanone was converted to the chalcone with 2,4-dibenzyloxybenzaldehyde. The O-acetyl derivative by treatment with the thallium reagent followed by acidic cyclisation gave a bischromanone structure. Selective reduction of the least hindered carbonyl group in the bischromanone, acidic dehydration of the resultant alcohol and final debenzylation with boron trichloride gave the linear isoflavone,

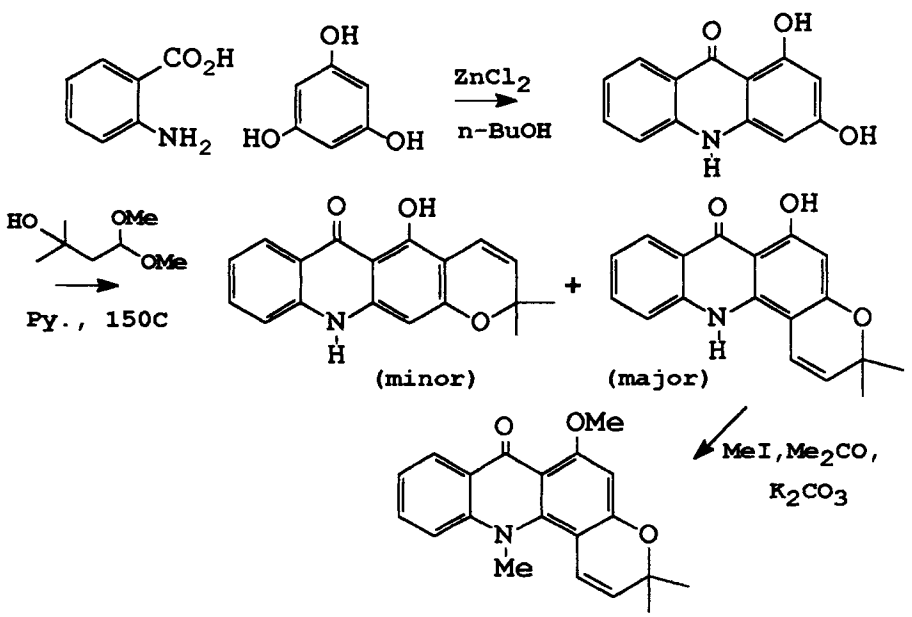
parvisoflavone.



Parvisoflavone B

12.6.6 Chromenoacridones

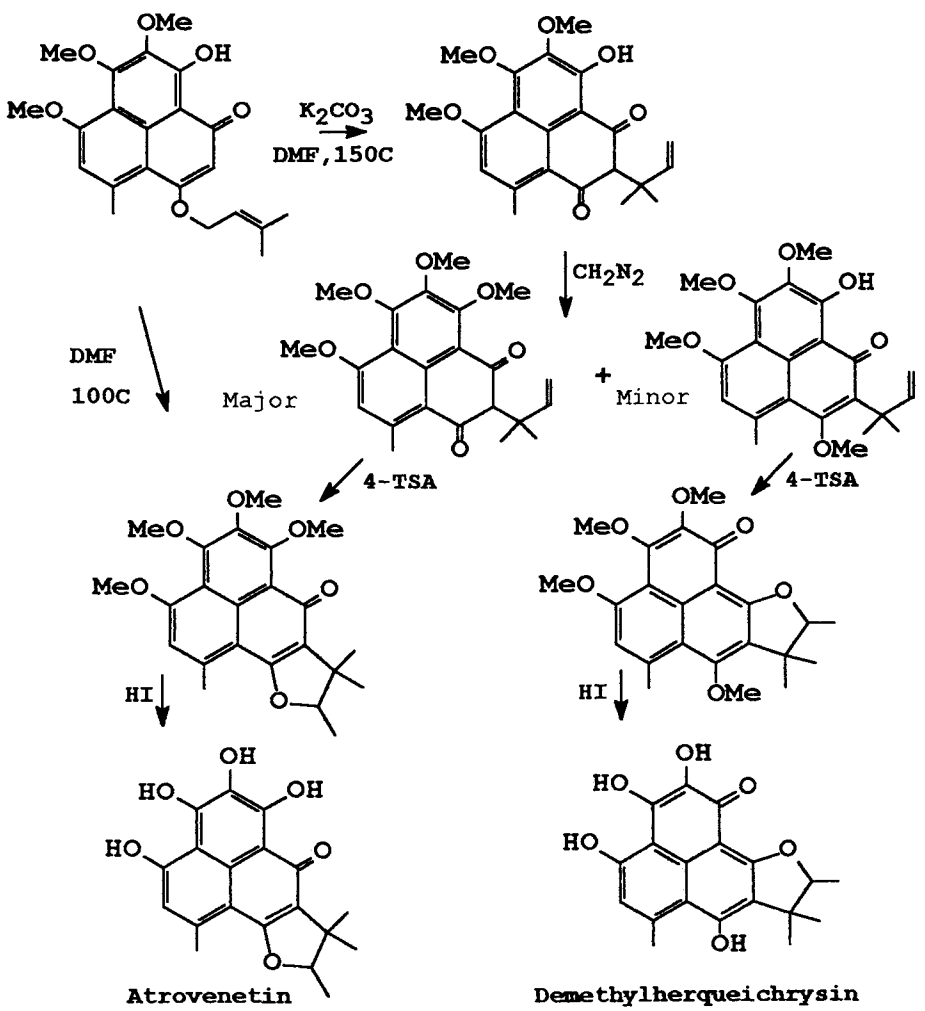
The alkaloid, acronycine, a pyrano[2,3-c]acridine (Table 12.1, ref.58), and the carbazole alkaloids (ref.81) contain cyclic systems derived from 2-hydroxy



groups adjacent to prenyl groups or free prenyl groups. The chemistry of the former has been studied in detail leading to a synthesis from 1,3-dihydoxyacridone which was prepared in 40% yield by heating anthranilic acid and phloroglucinol in n-butanol containing zinc chloride. Reaction of the acridone with 4,4-dimethoxy-2-methylbutan-2-ol in pyridine at 150°C led to a mixture of linear 2- (1 part) and angular 4-substituted (3 parts) products. Methylation of the latter with methyl iodide in acetone containing potassium carbonate, afforded the required N-methyl and O-methyl ether, acronycine.

12.6.7 Phenalenones

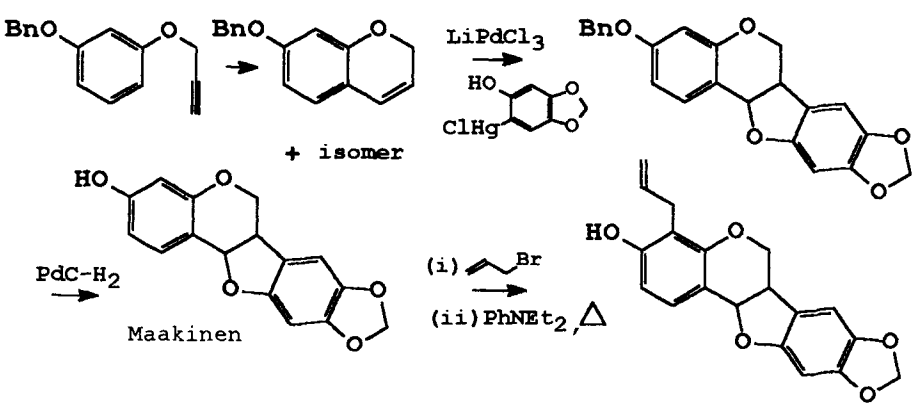
Atrovenetin, (Table 12.1), herqueichrysin are related phenalones (ref. 59) and are unusual in that they both contain a trimethylfurano moiety arising from an prenyl ether since there is no 2-hydroxyl group to form a chromene ring from an adjacent C-prenyl group. Synthetic work (ref.59) has led to members of the group by the Claisen rearrangement. Thus the prenyl ether of the phenalone intermediate in DMF at 100°C directly afforded atrovenetin trimethyl ether.



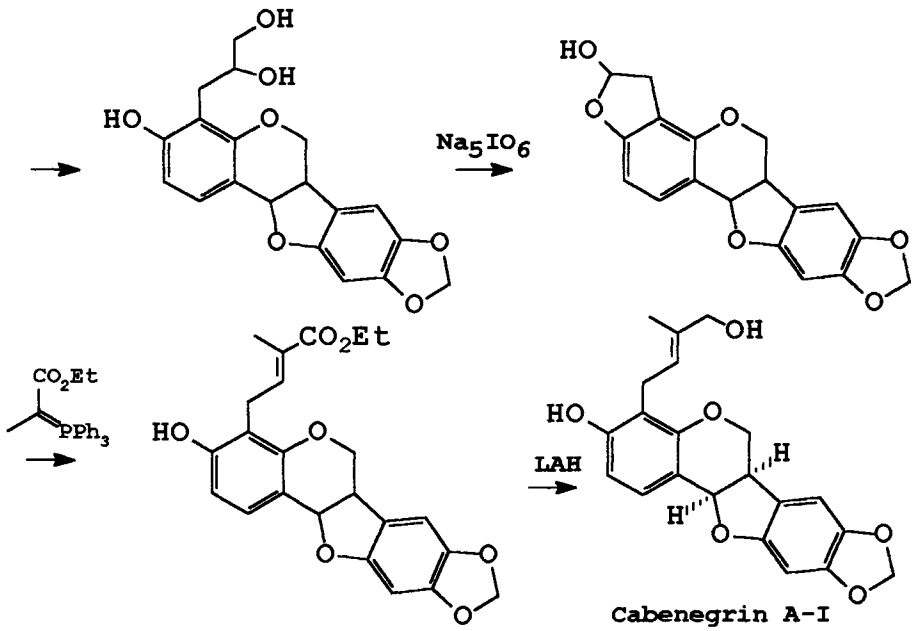
However in the same solvent containing potassium carbonate, to avoid cyclisation, from the same phenalenone trimethyl ether, a 2-(1,1-dimethyl)allyl-1,3-diketone resulted. Methylation of this trimethyl ether with diazomethane gave a major and a minor tetramethyl ether. The major product by acidic cyclisation with 4-toluenesulphonic acid and demethylation of the product with hydrogen iodide gave racemic atrovenetin and the minor product led by the same sequence of reactions to racemic demethylherqueichrysin.
The required starting material, 3,9-dihydroxy-6,7,8-trimethoxy-4-methyl-phenalenone, for the preceding synthesis was obtained in the following way from syringa aldehyde. This compound, 3,4,5-trimethoxybenzaldehyde was condensed with nitroethane to give 1,2,3-trimethoxy-5-(2-nitropropenyl)benzene which was then reduced with iron/hydrochloric acid to 3,4,5-trimethoxyphenylmethyl methyl ketone. By the Reformatsky reaction with zinc and ethyl bromoacetate this ketone afforded a hydroxy ester which by cyclisation with polyphosphoric acid was transformed into 4-hydroxy-5,6,7-trimethoxy-2-methylnaphthalene. Brief treatment of the fully methylated product with excess of malonic and polyphosphoric acids at 100°C gave 3-hydroxy-6,7.8.9-tetramethoxy-4-methylphenalenone in 73% yield. Selective hydrolysis of the 9-methoxy group with dilute hydrochloric acid gave the product.

12.6.8 Furanochromans (Cabenegrins A-I and A-II)

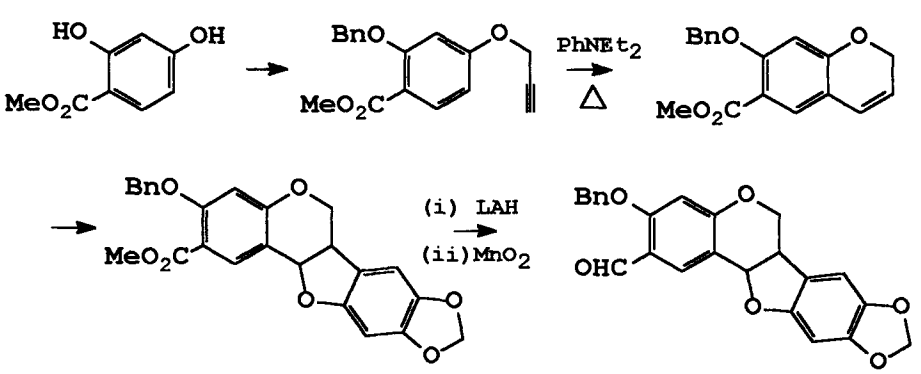
These two compounds (Table 12.1), which were considered to be potent antidotes towards snake and spider venoms, were extracted from the root of a South American plant of unidentified source but known as 'Cabeca de Negra'. Both compounds have been synthesised in racemic form (ref.91).
The propargyl ether of 3-benzyloxyphenol was cyclised in hot diethylaniline to 7-benzyloxychrom-3-ene which with 3-hydroxy-4-chloromercurimethylenedioxy benzene in acetonitrile containing lithium chloropalladite afforded acemic benzylmaakiain. Hydrogenolysis, formation of the allyl ether and its

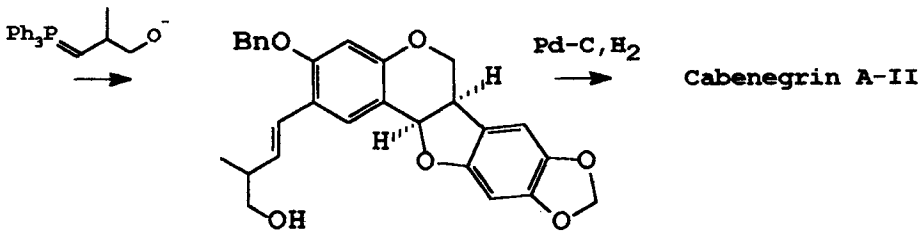


rearrangement gave the C-allyl compound, the vicinal diol from which afforded a hemiacetal upon Malaprade oxidation with sodium metaperiodate. Wittig reaction with α-ethoxycarbonylethyl triphenylphosphorane in DMSO at 110°C gave the E-ester which by lithium hydride reduction gave cabenegrin A-I



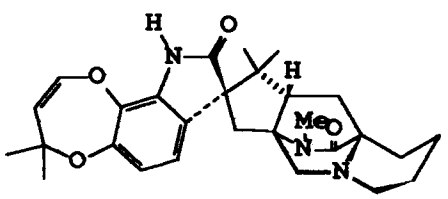
A similar series of reactions with 7-benzyloxy-6-methoxycarbonylchrom-3-ene with conversion of the ester to a formyl group followed by a Wittig reaction with a phosphorane derived from 3-bromo-2-methylpropanol and triphenylphosphine and a final hydrogenolysis produced racemic cabenegrin A-II.



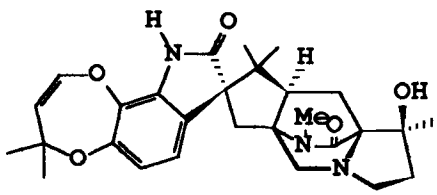


12.6.9 Cyclic Products from O-prenyl Ethers

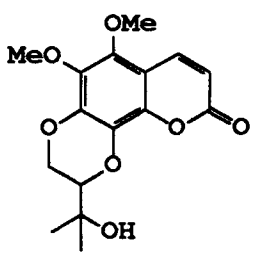
In the brevianamide series (ref.92) although brevianamide itself is non-phenolic, the related substances marcfortine and paraherquamide (ref.93) both contain 2,2-dimethyl-1,5-dioxacyclohept-3-eno rings attached at the 6,7-positions to the main pentacyclic structure. This structural feature arising from a 1,2-dihydroxy system is unusual in that prenyl groups invariably cyclise from a C-substituted position. Six-membered 1,4-dioxa rings occur in the purpurasols, highly oxygenated coumarins from *Pterocaulon purpurascens* (ref.94).



Marcfortine



Paraherquamide



Purpurasol

12.7 Tocopherols, Tocotrienols and Related Compounds

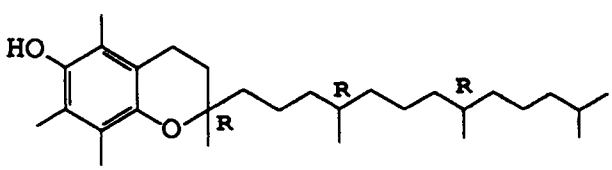
In this section the structures, nomenclature, synthesis and reactions of the tocopherols are discussed. α-Tocopherol, is a lipidic substance (ref.95) and is almost certainly the most important member of the group, generally referred to as vitamin E. The term α-tocopherol is now widely used instead of vitamin E although some consider the term vitamin E should be reserved for all tocol and tocotrienol derivatives qualitatively having the biological activity of α-tocopherol.

It is probably the most significant natural antioxidant for human beings in protecting the body from free radical degeneration, in preserving other lipidic vitamins such as vitamin A, being involved in cyclic squences with vitamin C and having an influence in reproductive systems. Although present in many natural articles of food, notably in oil seeds (ref. 96), the vagaries of diet, cooking practices and fashion may well lead to its insufficient presence and therefore consumption. It has been available in synthetic form for many years but despite this, research has continued to find alternative intermediates and to develop enantioselective syntheses.

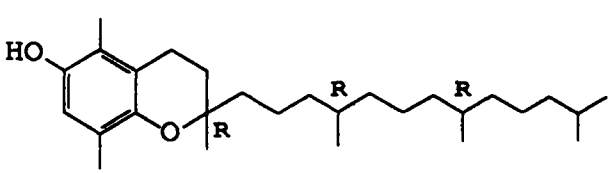
12.7.1 Structure of the Tocopherols and tocotrienols

The tocopherols, tocotrienols and plastoquinols are three natural structures related biosynthetically since all arise from homogentisic acid, 2,5-dihydroxyphenylacetic acid, the first group from its reaction with phytyl pyrophosphate followed by chroman ring formation, the second group from the tetraene analogue of phytol followed by chroman formation and the third group by C-monomethylation of the common initial intermediate (with decarboxylation in each case). Further biological methylation gives the dimethyl and trimethyl members in the tocopherol and tocotrienol series.
The tocopherols comprise four compounds all of which are methyl derivatives of tocol, 2-methyl-2-(4',8',12'-trimethyldecyl)-6-chromanol.

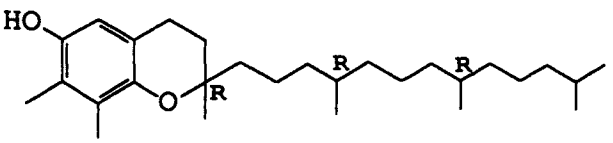
α-Tocopherol(2R,5,7,8-tetramethyl-2-(4'R,8'R,12'-trimethyldecyl)-6-chromanol, (5,7,8-trimethyltocol)



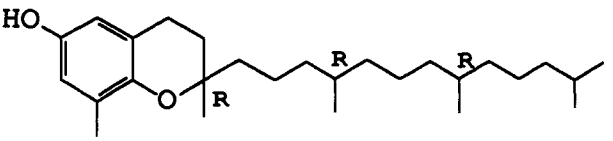
β-Tocopherol(2R,5,8-trimethyl-2-(4'R,8'R,12-trimethyldecyl)-6-chromanol (5,8-dimethyltocol)



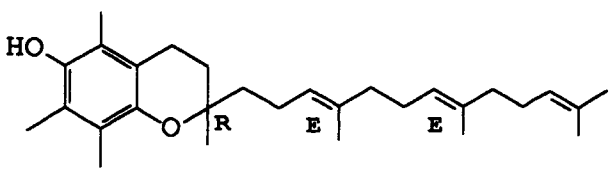
γ-tocopherol(2R,7,8-trimethyl-2-(4'R,8'R,12-trimethyldecyl)-6-chromanol (7,8-dimethyltocol)



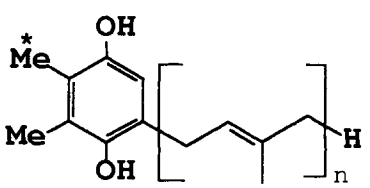
δ-tocopherol(2R,8-dimethyl-2-(4'R,8'R,12-trimethyldecyl)-6-chromanol
(8-methyltocol



Some years after the isolation of the four tocopherols the four tri-unsaturated analogues, the tocotrienols were discovered. They are 8-methyl, 5,8- and 7,8-dimethyl and 5,7,8-trimethyl derivatives repectively of tocotrienol, 2R-methyl-2-(4',8',12-trimethyldeca-3',7',11'-trienyl)-6-chromanol. α-Tocotrienol is shown.



A plastoquinol is depicted in which the methyl group (*) is that resulting from biological methylation.



12.7.2 Nomenclature and Relation of Structure and Biological Activity

In the case of the tocopherols the three chiral centres result in the potential existence of eight stereoisomer in each of the α, β, γ and δ compounds while similarly in the case of the tocotrienols all four members have the E-configuration and each has a chiral centre at the 2-position. The eight

stereoisomers of α-tocopherol have 2R4'R8'R, 2S4'S8'S, 2R4'S8'S, 2S4'R8'R, 2R4'S8'R, 2S4'R8'S, 2R4'S8'S, and 2R4'R8'S stereochemistry. α-Tocopherol is the (+)-enantiomer although for working purposes its optical activity is small (specific rotation in 2,2,4-trimethylpentane, 0.16°) and in consequence for stereochemical correlation work, oxidation products having much higher optical rotations have been used.

While there is no universally accepted scientific terminology for representation there is general agreement on a certain working nomenclature (refs. 97,98). Thus α-tocopherol, the natural stereoisomer is as stated earlier (RRR)-α-tocopherol, the 2-epimer is 2-epi-α-tocopherol and a mixture of (RRR) and (SRR)-α-tocopherols is 2-ambo-α-tocopherol. Synthetic α-tocopherol prepared from synthetic phytol or isophytol is called all-rac-α-tocopherol, since it is theoretically a mixture of (RRR) and (SSS). The mixture of reduction products of 5,7,8-trimethyltocotrienol is called 4'-ambo-8'-ambo-α-tocopherol since as a natural product, although it has a 2R centre, the stereochemistry from hydrogen addition at the 4- and 8- positions is probably substantially RS.

The above distinctions become important in the light of the relationship between measured biological activity and stereochemical structure and as a consequence of this quantification the methodologies of synthesis are of great interest.

Firstly the fully C-methylated natural compound, α-tocopherol has the highest activity and relative to this (1.0) the less methylated, although structurally related compounds are progressively less effective in the order, β(0.27), γ(0.13), δ(0.01). All-rac-α-tocopherol is less potent than the RRR form and generally racemic versions possess about three-quarters the activity of the respective pure stereochemical form which is rather more than expected on a molar basis and this aspect has been investigated.

Secondly ,the biopotency of all eight stereoisomers (whose purity was determined by careful GLC analysis) of α-tocopheryl acetate have been assessed by rat resorption-gestastion tests (ref. 99). With the parent (2R4R8R) at 100% activity, the relative values were (RRS) 90%, (RSS) 73%, (SSS) 60%, (RSR) 57%, (SRS) 37%, (SRR) 31% and (SSR) 21%. In all pairs of diastereoisomers, (RRR-SRR), (RRS-SRS), (RSR-SSR), and (RSS-SSS) the 2S form had a lower activity than the 2R form. Generally the 4-centre had a similar effect while the 8-centre had a minor influence. The observed activities of stereoisomer mixtures were considerably higher than the values expected from the calculated sums of activities of the individual stereoisomers indicating a synergistic effect.

Despite the favourable influence indicated from the use of mixtures rather than pure compounds there has been a strong organic endeavour to find selective procedures in synthetic work and to fully understand the relationshiop between structure and biological activity

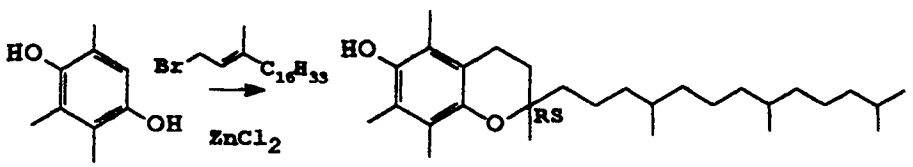
α-Tocopheryl acetate is an odourless, viscous slightly yellow oil and is the main commercial form ot vitamin E for use in food fortification, diet supplements, medicinal preparations and for domestic animals. By contrast tocopherols exist naturally in the free unesterified form. Cereal grain oils contain the highest

concentration of tocopherols generally as α,β,γ and δ mixtures; certain oils namely corn and wheat oils can contain 2g per kilo although in predominancy the α-form is highest only in safflower oil (90%), corn and soyabean oils (20%), the latter containing mainly the γ and δ forms and wheat oil the β form (65%).

12.8 Synthesis of Tocopherols and Tocotrienols

12.8.1 Industrial and Technical Synthesis

Several aspects of the organic chemistry of tocopherols and of tocotrienol will be discussed in the present section. These will cover the industrial synthesis of α-tocopherol, the synthesis of α-tocopherol stereoisomers, experimental approaches in alternative syntheses of tocopherols and the use of biological methods.
In the original synthesis of α-tocopherol, due to Karrer, 'dl-tocopherol' (present day, 2-ambo-α-tocopherol) was obtained by the reaction of phytyl bromide (from natural phytol) and trimethylhydroquinone in the presence of zinc chloride.



Little has been revealed of present industrial methods and strategy other than in the patent literature, except that methodologies have generally involved the use of either synthetic phytol or isophytol and the latter appears to be the preferred intermediate for the formation of all rac-α-tocopherol. Both these long chain alcohols stem from the extensive development of acetylene chemistry some decades ago by one of the major groups concerned Hoffmann La Roche, which led to syntheses of the C_{10} perfumery alcohols, vitamin A and the carotenoids. Thus although natural phytol ($C_{20}H_{39}OH$), [(E)3,7,11,15-tetramethyl-2-hexadecen-1-ol], is a somewhat rare commercial substance, although widely distributed in chlorophyll, the synthetic version and isophytol have become more available by standard synthetic methods. Thus from hexahydrofarnesol a C_{18} ketone, trimethyltridecyl methyl ketone can be derived by an ethyl acetoacetate synthesis and thence isophytol by reaction with sodium acetylide followed by reduction or directly by reaction of the ketone with vinylmagnesium bromide.
Since farnesol is not itself a common commodity the smaller molecules propanone and diketene can be employed as raw materials. ψ-Pseudoionone (C_{13}), available as an intermediate from the perfumery manufacture of the ionones by the employment of these C_3 and C_4 intermediates, affords a C_{15} acetylenic alcohol and thence after reduction and reaction with diketene a C_{18}

TABLE 12.3

SOME INDUSTRIAL REACTION CONDITIONS for THE SYNTHESIS of alpha-TOCOPHEROL

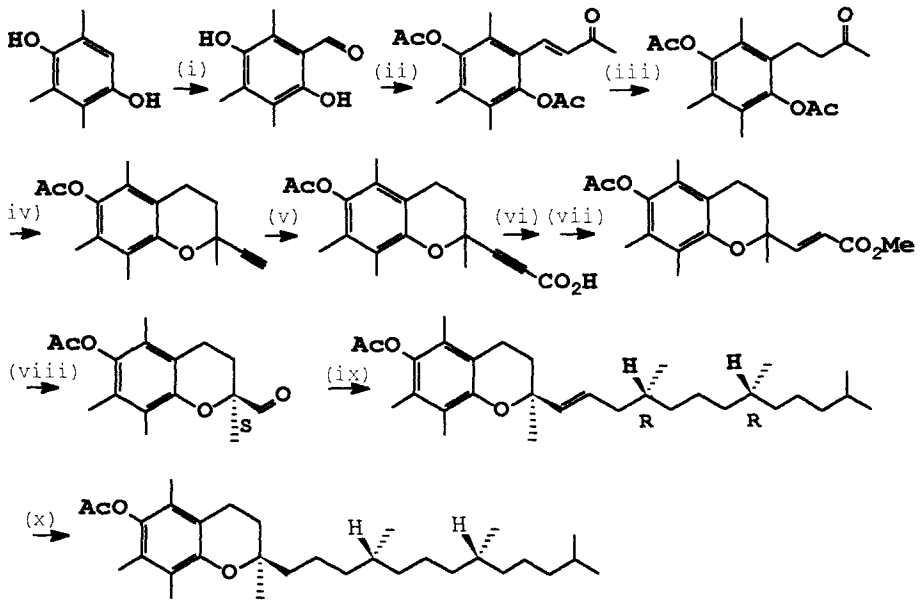
R M	CATALYST	SOLVENT	TIME (h)	TEMP (C)	YIELD %	REF.
RCl* ROH	Sn Powder	ligroin	3	Reflux	86	100
iROH	SiO_2-Al_2O_3	Tetrachlorethene	4	120	95	101
iROH	Zeolite with rare earth substn.	Toluene	6	reflux	86	102
iROH	Zinc chloride/C and/or BF_3	Toluene	6	reflux	97	103
iROH	Zinc chloride	Toluene	6	reflux	88	"
ROH	Zinc chloride	Butyl acetate	4	reflux	92	104
iROH	Zinc powder	Benzene	-	reflux	95	105
iROH	Pd-C,Hydrogen $ZnCl_2$, Zn Chloroacetic acid	iso-Propyl acetate	2	reflux	96	106

(* R = Phytyl ; iR = iso-Phytyl)

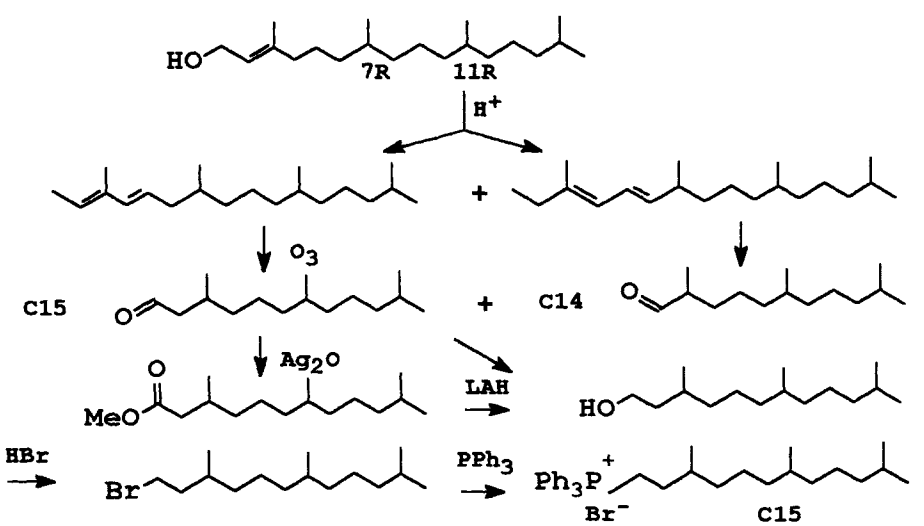
ketone which upon selective reduction at the C=C bonds and reaction of the ketone with sodium acetylide followed by partial reduction gives an alternative source of isophytol. To avoid the use of diketene, vinyl carbinols can also be transformed with ethyl acetoacetate to ketones possessing three more carbons by the Carroll reaction in which for example dimethyl vinyl carbinol (C_5) affords 'methyl heptenone', 6-methyl-5-hepten-2-one (C_8).
It appears probable that the relative biological activity of the final synthesised α-tocopherol and the cost of the particular synthesis would be intimately involved in a cost/benefit exercise in the choice between a synthetic route for the C_{20} intermediate or the use of natural phytol.
Since in most preparations described the origin of the phytol or isophytol was not given it is unclear whether the product was 2-ambo- (from natural phytol) or all rac-α-tocopherol (from isophytol). Table 12.3 summarises some typical conditions which have been described (R.M. = Raw material).
Syntheses have been carried out 'with best results' using phytol or isophytol and trimethylhydroquinone in carbon tetrachloride containing boron trifluoride or with zinc chloride and acid activators in toluene although no yields were quoted (ref. 107). However in another description details have been given of the use of boron trifluoride etherate (ref.108). Thus isophytol or phytol (29.6g; 0.1mol) was added to a mixture of trimethylhydroquinone (15.2g; 0.1mol), boron trifluoride (14.19g; 0.1mol) and zinc (1.31g) in hexane containing acetic acid (1g) and following a refluxing period of 2 hours, the water produced was removed azeotropically over a further 2 hours to give α-tocopherol (38.83g; 89%).
Acidic cyclisation has only been employed in conjunction with other materials such as silica/alumina but it would appear feasible to use a chiral organic sulphonic acid, for example (+)-camphor sulphonic acid in the reaction of natural phytol with trimethylhydroquinone to examine whether an asymmetric synthesis could be effected.

12.8.2 Synthesis of Stereoisomers of α-Tocopherol

Although the synthesis of 'dl-α-tocopherol' (ref.109) from natural phytol was in reality that of two epimers (2R,4'R,8'R and 2S,4'R,8'R), separated as derivatives with difficulty, the configuration of the C_{20} alcohol was only confirmed by synthesis 20 years later (ref.110) and in that year the first synthesis of the two tocopherol epimers was realised (ref. 111). A number of syntheses of 6-acetoxy-2-formyl-2,5,7,8-tetramethylchroman, a model compound for projected Wittig reactions, were devised one of which involved the key intermediate, 6-acetoxy-2-ethinyl-2,5,7,8-tetramethylchroman. By carbonation the acetylenic acid was prepared, the quinine salt of which was resolved and the enantiomeric acids converted by catalytic reduction (Lindlar), esterification and ozonolysis to the required enantiomers of the forgoing aldehyde. By reaction of 3R,7R-hexahydrofarnesyltriphenylphosphoniumbromide, prepared from 7R,11R-phytol, (as shown below the first scheme) with the S-(+)-aldehyde under Wittig conditions and subsequent reduction, (2R,4'R,8'R)-α-tocopherol was obtained.

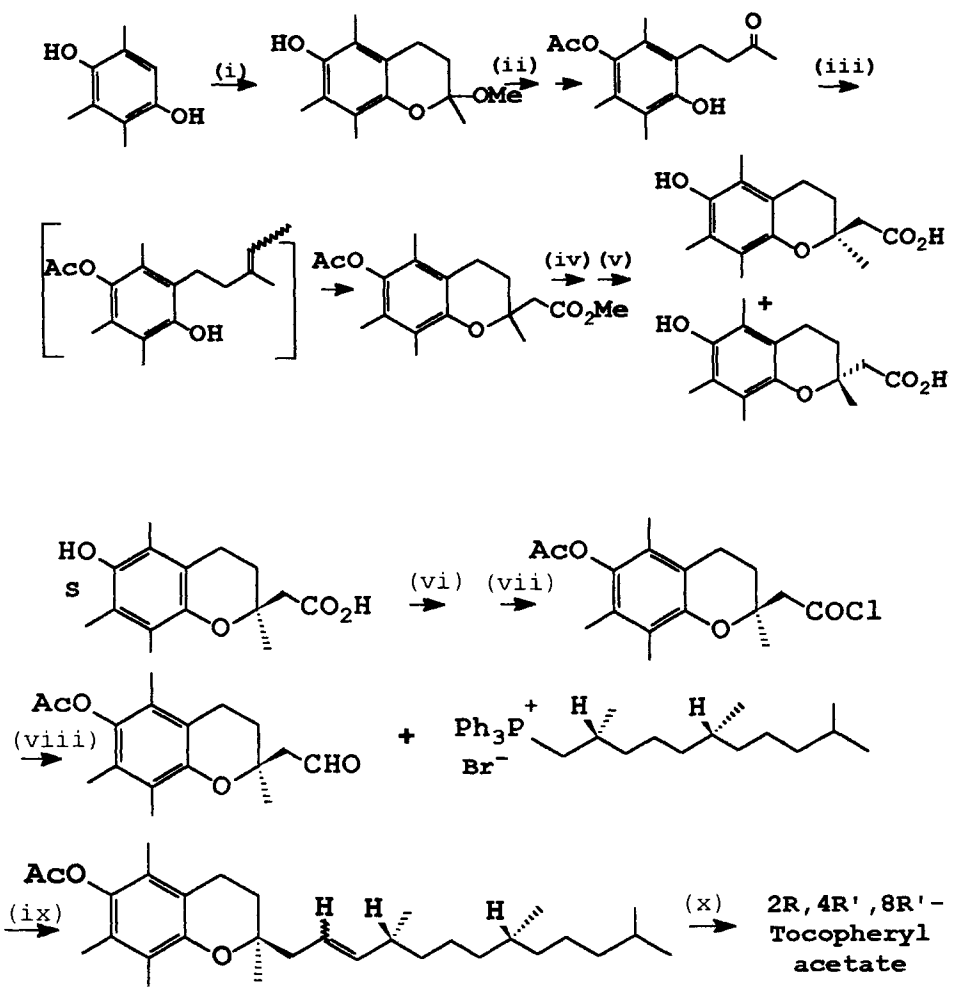


(i) Hexamethylenetetramine, (ii)Ac_2O; $MeCOCH{=}PPh_3$, (iii)Pd-C,H_2 (iv)$HC{\equiv}CMgBr;H_3O^+;Ac_2O$, (v) $EtMgBr;CO_2$;quinine resolution,(vi)Pd,H_2, (vii) MeOH,H^+, (viii)O_3, (ix) $C_{15}H_{31}P^+Ph_3Br^-$, PhLi (x) Pd-C,H_2



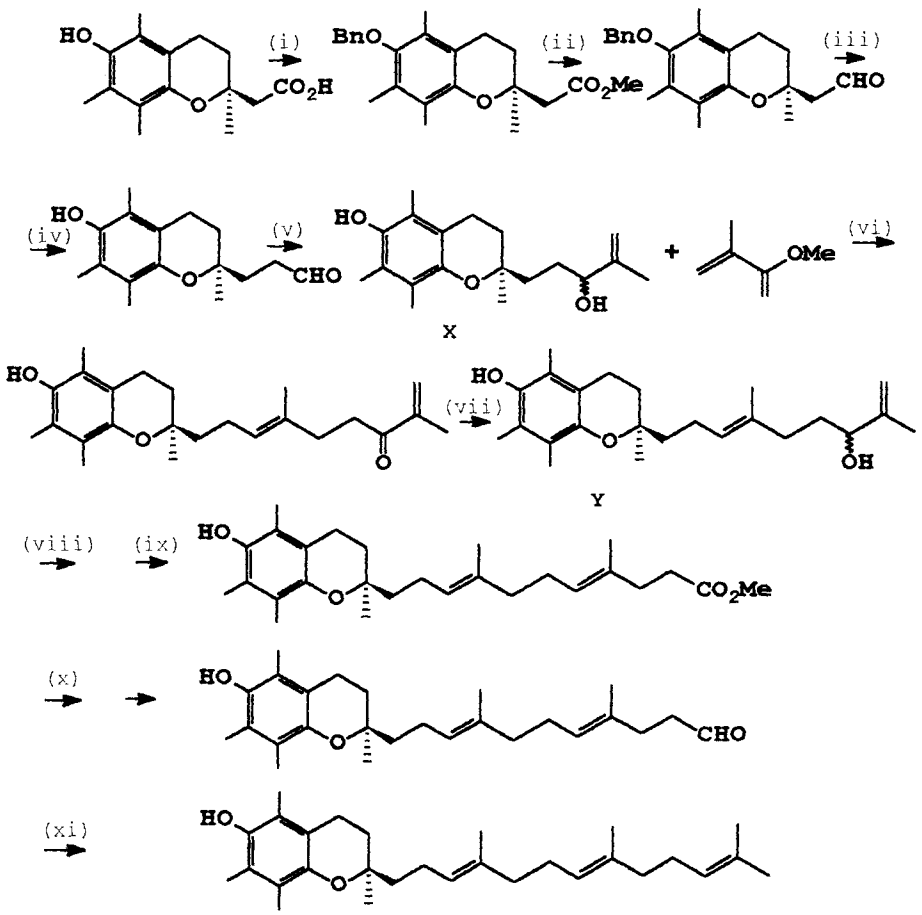
In a similar fashion the (R)-(-) aldehyde afforded the epimer 2S,4'R,8'R-α-tocopherol.

A related methodology (ref.112) was employed in which rather than a C_{15} farnesyl component a C_{14} compound was reacted with a chroman-2-acetaldehyde derivative. In this scheme the C_{14} aldehyde simultaneously formed at the ozonolysis stage in the previosly described synthesis was used. Thus, 2-carboxymethyl-6-hydroxy-2,5,7,8-tetramethylchroman, [(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)acetic acid] served as a source by resolution with (S)-α-methylbenzylamine of the two enantiomeric acids. The 2(S)-enantiomer was converted by way of the acid chloride to the aldehyde, a homologue of that employed by the Swiss workers in the foregoing method. The aldehyde was reacted with the triphenylphosphonium salt from the C_{14} bromide by the \Wittig reaction to afford 2R,4'R,8'R-α-tocopherol. A novel aspect of this approach was that it enabled a synthesis of 2R,3'E,7'E-α-tocotrienol to be achieved from the same carboxymethyl intermediate.



(i) $MeCOCH=CH_2$,MeOH,-H_2O, (ii) Ac_2O, (iii) $(MeO)_2P(O)CH^-CO_2Me$,(iv) HO^- ,(v)(S)-α-benzylamine, (vi) Ac_2O, (vii) $(COCl)_2$, (viii)Rosenmund, (ix) PhLi,(x) PtO_2,H_2.

The procedure adopted for the total synthesis of (2R,3'E,7'E)-α-tocotrienol was also based on the usage of the 'S-chromanylacetic acid' in the following way.

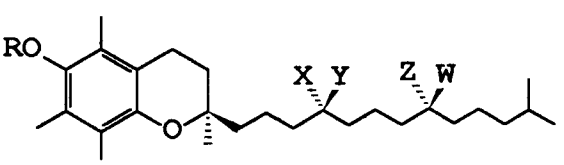


(i) MeI,$NaHCO_3$,DMF, (ii) BnCl,K_2CO_3,DMF, (iii) $(iC_4H_9)_2AlH$, -70C,(iv) $MeOCH=PPh_3$;H_3O^+; Pd-C,H_2, (v) isopropenylMgBr, (vi)2-OMe-3-Mebutadiene, $(CO_2H)_2$, Δ, (vii) $NaAlH_2(OEt)_2$, (viii) $MeC(OEt)_3$;HO^-, (ix) MeI,$NaHCO_3$,DMF, Ac_2O (x) $(iC_4H_9)_2AlH$; H_3O^+, (xi) $Me_2CH=PPh_3$.

The diastereomeric mixture X, having a C_6 sidechain, obtained by reaction of the preceding aldehyde with isopropenylmagnesium bromide was chain extended by the acidic cayalysed reaction of heating with 2-methoxy-3-methylbuta-1,3-diene. However when exactly the same process was tried with compond Y, the

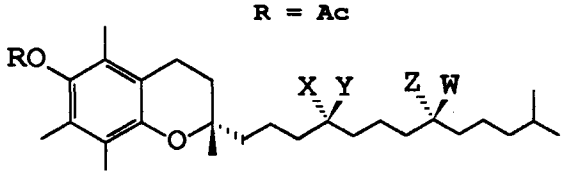
subsequent attempts to transform the C_{16} sidechain to that in tocotrienol led to a persistent impurity believed to be a terminal isopropenyl isomer. Accordingly Y was converted by triethyl orthoacetate under acidic conditions to give the ethyl ester corresponding to the methyl ester compound shown. The final steps then consisted in obtaining the methyl ester which was acetylated. This diester was reduced with diisobutylaluminium hydride. and Wittig reaction of the resultant aldehyde with isopropylidenetriphenylphosphorane afforded 2R,3'E.7'E-α-tocotrienol. Subsequent work by the American group (ref. 113) was directed to the total synthesis of the eight stereoisomers of α-tocopheryl acetate, that is in effect to the remaining six enantiomers to the two obtained at that time and just described in this account. Furthermore, a detailed chromatographic characterisation procedure was developed to assess the purity of both enantiomers and diastereoisomers. In this way structure/ biological activity studies in the vitamin E series were advanced. The configurations of the eight compounds, 1a, 1b, 1c, 1d in the (2-methylchromanyl), R series and 2a,2b,2c, and 2d in the (2-methylchromanyl) S series are shown.

	X	Y	Z	W	configuration
1a	Me	H	Me	H	2R, 4'R, 8'R
1b	H	Me	H	Me	2R, 4'S, 8'S
1c	Me	H	H	Me	2R, 4'R, 8'S
1d	H	Me	Me	H	2R, 4'S, 8'R
2a	H	Me	H	Me	2S,4'S, 8'S
2b	Me	H	Me	H	2S,4'R, 8'R
2c	H	Me	Me	H	2S, 4'S, 8'R
2d	Me	H	H	Me	2S, 4'R, 8'S



1a-d

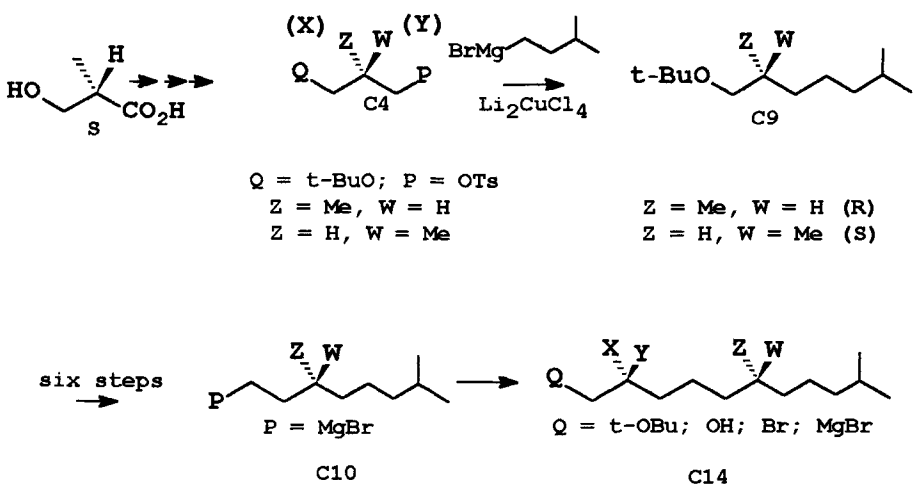
R = Ac



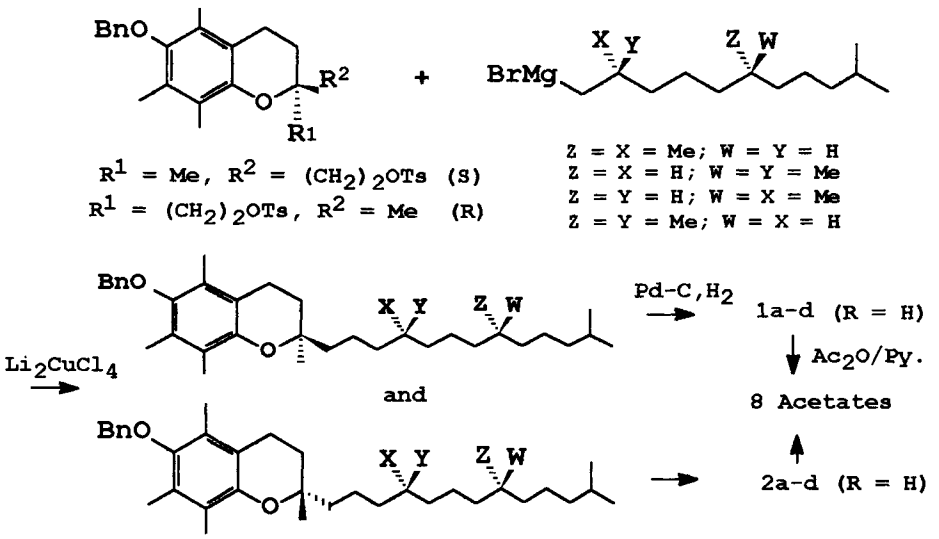
2a-d

In this work, the methodology rested upon the coupling of chiral units of

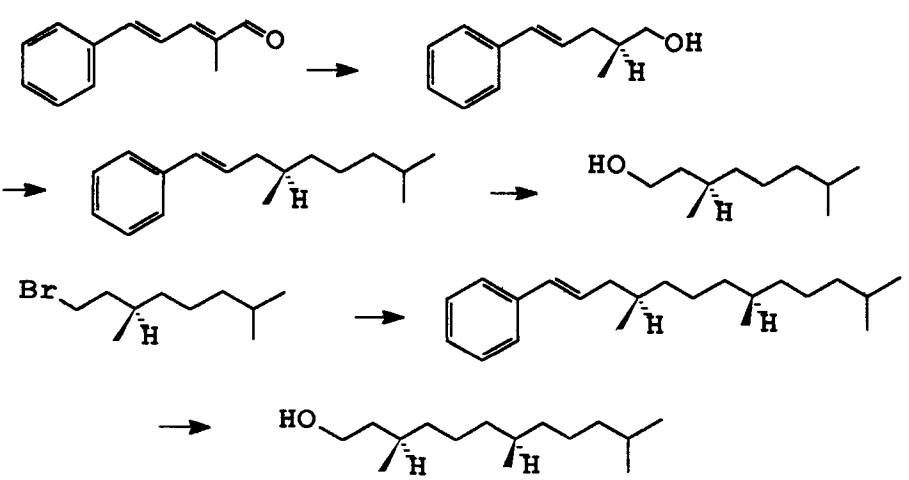
appropriate alkyl toluenesulphonates and alkyl magnesium bromides by the lithium cuprate (Li_2CuCl_4) procedure instead of by Wittig reactions. For this two enantiomeric chromanyl acetic acids described in the earlier work (ref. 112), were reduced to the corresponding ethanols and thence tosyl derivatives were formed which were reacted with the respective C_{14} Grignard reactant. Since phytol no longer served as the coupling component it was necessary to assemble the individual C_{14} side chains progressively by a novel method to obtain in turn the required chiral centres. For this purpose (+)-(S)-3-hydroxy-2-methylpropanoic acid was chosen, an intermediate derived in turn (ref. 114) by the bacterial oxidation of isobutyric acid. This versatile compound could serve as an R or an S C_4 source of compound simply by the sequence of reactions used on the HO or CO_2H groups although no detailed practical information has been described in ref. 113. The enantiomeric R acid could of course be used instead to create the respective stereoisomeric centres in the sidechain. The route using however solely the S-acid proceeded from the chiral C_4 (R or S) component by addition of isopentylmagnesium bromide to give a C_9 intermediate (R or S), addition of C_1 (formaldehyde) to the Grignard reagent of that compound and final reaction with the appropriate C_4 (R or S) to afford after further functional reactions the required C_{14} bromide. For the three stereoisomers 1a, 1d and 2c the natural C_{10} source (R)-pulrgone, by appropriate ring opening, circumvented the need for their particular totally convergent syntheses.



The tosyl derivative of the R and the S forms of 6-benzyloxy-2,5,7,8-tetramethylchroman-2-ethanol was then reacted with the respective C_{14} alkylmagnesium bromide and the final stereoisomer obtained as the acetate after catalytic hydrogenolysis and acetylation with acetic anhydride/pyridine in good yield in all cases.



Essentially, chiral C_{14} or C_{15} alcohols have been employed in the preceding methods described. Yet another variation in approach, that of biotransformation has been introduced (ref. 115) in which it was found that reduction with bakers' yeast of the the dienal, 2-methyl-5-phenylpenta-2,4-dienal gave 2-methyl-5-phenylpent-4-en-1-ol containing 87% of the (2S)-isomer (a masked C_5 chiral compound). Reaction of the 4-tosyl derivative with isopentylmagnesium bromide in THF containing lithium cuprate, Li_2CuCl_4 afforded an intermediate which upon ozonolysis at -30°C gave 3,7-dimethyloctan-1-ol predominantly as the (3R)-isomer. Conversion to the bromide with N-bromosuccinimide and triphenylphosphine, formation of the Grignard reagent followed by reaction again with the tosyl derivative of the masked C_5 compound and final ozonolysis gave the C_{15} alcohol, 3R,7R,11-trimethyldodecan-1-ol.

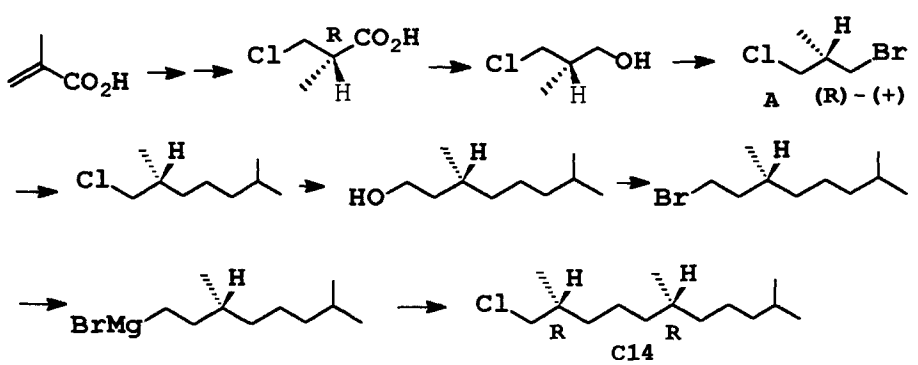


A related strategy afforded a C_{14} lower homologue and since both alcohols have been employd in the syntheses already described they provide alternative enantio-convergent syntheses of (2R,4'R,8'R)-α-tocopherol.
Finaly it is of interest that the acetonylidene diol shown has been both used for the chroman portion of 2R,4'R,8'R-α-tocopherol and also transformed into (3R)-(-)-linalool and thus affords a stereochemial correlation with this terpenoid (ref. 116).

(3R)-(-)-linalool

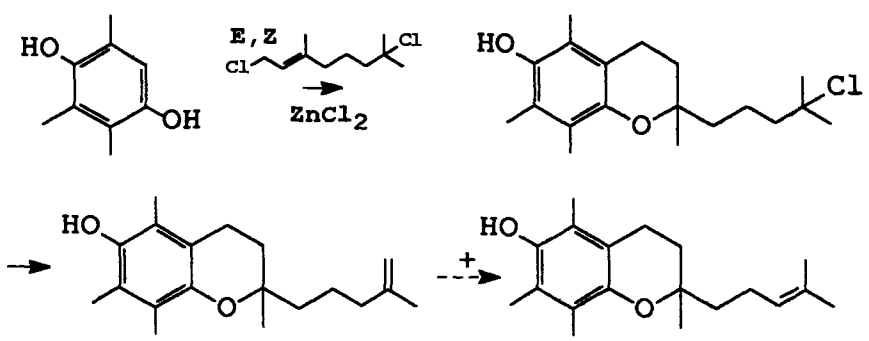
12.8.3 Alternative Synthetic Routes to α-Tocopherol

The purpose of synthesising the stereoisomers of α-tocopherol had been to aid structure/ biological studies about which little was known in the seventies. Fortuitously, the natural product was found from these investigations to be the most active member and although some consideration may have been given to its specific synthesis, rather than that of all racemic tocopherol or ambo tocopherol, more work was directed to finding if a viable route existed by employing alternative raw intermediates based either on petroleum or on replenishable natural products rather than on acetylene chemistry. This work has been oriented to the natural 2R,4'R,8'R product and all racemic and other diastereoisomeric mixtures through the use of other intermediates than phytol or isophytol.
In the first group, different routes to the C_{14} alcohol, 2R,6R,10-trimethylundecanol and its halides have been significant. Thus, readily available methacrylic acid was hydrochlorinated to afford racemic 3-chloro-2-methylpropionic acid and the (R)-(+)-isomer, obtained by resolution with (+)-ephedrine, reduced to the alcohol, and the bromide obtained with PBr_3 then reacted with isopentylmagnesium bromide to afford a C_9 halide. The Grignard



reagent after homologation with formaldehyde and formation of the bromide with PBr_3 was again reacted with the chiral C_4 chlorobromide to produce 1-chloro-2R,6R,10-trimethylundecane (ref. 117). The method relies essentially upon the relative reactivity of alkyl chlorides versus bromides and was conceived as a way around the need to use natural phytol. However although readily available materials are used and the resolution is ideally effected at an early stage in the synthesis the need to use a 'chromanyl-2-acetic acid' for completion of the route is a disadvantage.

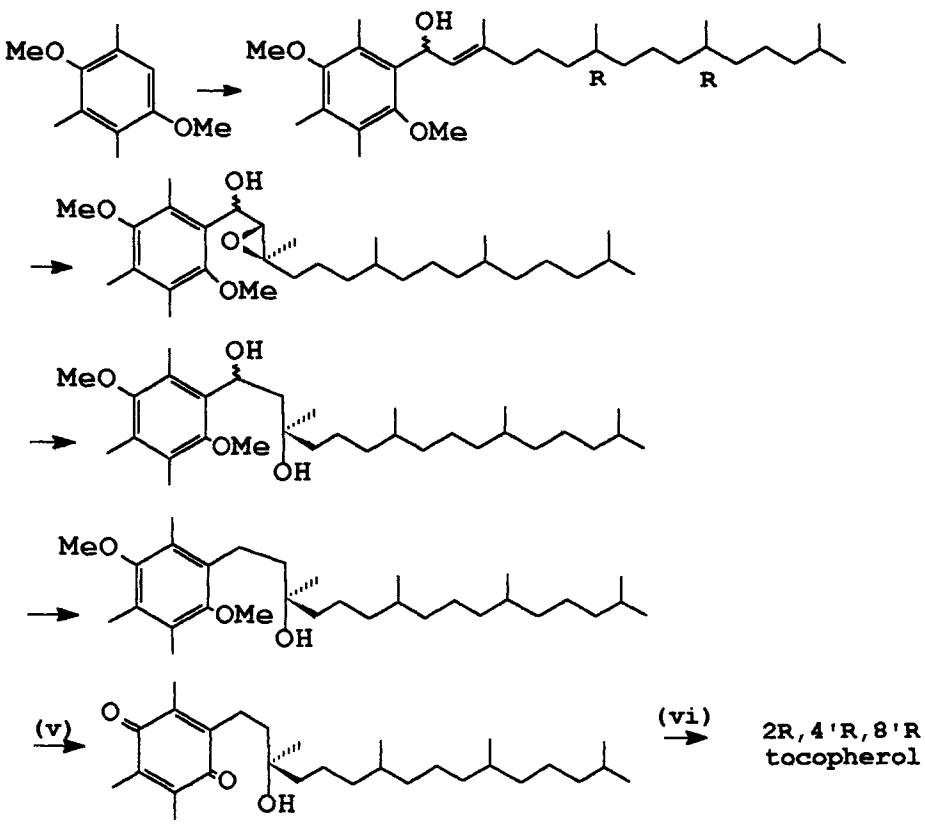
Terpenic-type intermediates of use in formation of the side-chain in tocopherols have been derived from myrcene (ref.118). Thus, a mixture of E- and Z-isomers from its hydrochlorination which resulted in a dichloroderivative containing primary and tertiary halide groups was reacted with trimethylhydroquinone in dioxane/dichloromethane containing zinc chloride, zinc and hydrogen chloride to afford an 89% yield of a chloro intermediate. Dehydrochlorination in methanol with sodium hydroxide afforded a mixture of pentenyl compounds which was isomerised with toluenesulphonic acid in refluxing benzene to 6-hydroxy-2,5,7,8-tetramethyl-2-(4-methyl-3-pentenyl)chroman. The elaboration of the side-chain to produce the tocopherol structure was not described and the synthesis is not stereospecific



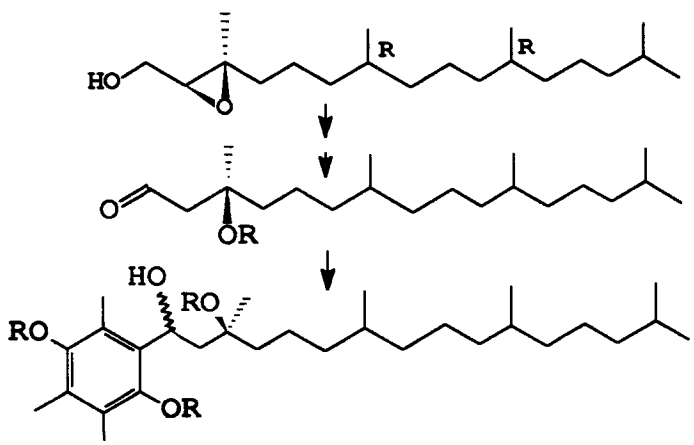
The use of terpenic raw materials such as geranylgeraniol has been reported in this case as a route to 'd-α-tocotrienol' (ref. 119) although with few details. In this procedure the 2,3 double bond of the C_{20} compound was epoxidised by a Sharpless-type method and following ring opening, conversion to the tosyl derivative of the 1° alcohol, introduction of a an isopropylthio group by displacement of the tosylate group, protection of the tertiary alcohol by acetylation, the monoacetyl trimethylhydroquinone moiety was reacted with the side chain component. Desulphurisation with Raney nickel, succeeded by treatment with lithium aluminium hydride, afforded a dihydroxy compound which by heating in benzene in the presence of toluenesulphonic acid underwent ring closure to afford 'd-α-tocotrienol.

More recent work has tended to concentrate on the usage of synthetic phytol or isophytol in the form of derivatives. In this second group of reactions intermediates such as the aldehyde phytal have been exploited. The importance of the 2R stereochemistry in tocopherol itowards imparting higher biological than manifested in the RS mixture has directed attention to more selective methodologies than achievable in the reaction of trimethylhydroquinone and the phytols.

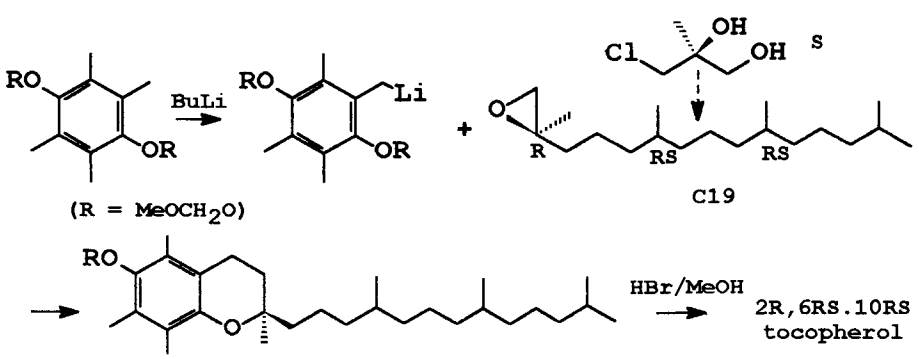
Thus, the aldol shown, which is susceptible to Sharpless-type epoxidation, has been obtained from phytal and the protected hydroquinone (ref.120). Formation of the epoxide presumably with a chiral peracid (or perhaps with a conventional peracid relying on the asymmetry of the substrate) and then cleavage reductively in t-butyl methyl ketone containing lithium aluminium hydride led to a diol. The benzylic hydroxyl group of this was hydrogenolysed to afford the hydroquinone dimethyl ether in 85% yield. Ceric ammonium nitrate (CAN) oxidation afforded the intermediate benzoquinone hydrogenation of which was reported to result in 2R,4'R,8'R-α-tocopherol by, presumably, avoidance of a racemisation step.



In related work (ref. 121), the Grignard reagent from a bromotrimethylhydroquinone derivative has been reacted with a phytal. For example, Sharpless enantioselective epoxidation of natural phytol in dichloromethane with ti(IV)isopropoxide/tert-butylhydroperoxide/ diethyl (+)-tartrate at -30°C gave the epoxide shown in 91% yield. Reduction with lithium aluminium hydride resulted in a quantitative yield of the (R)-alcohol which, protected at the t-alcohol position as the methoxymethyl derivative (R = CH_2OMe), was oxidised with pyridinium chlorohromate to a phytal derivative in 87% yield. The Grignard reagent from the bis(methoxymethyl) derivative of 2-bromo-3,5,6-trimethylhydroquinone reacted in high yield with this phytal drivative to give an aldol. Then, proceeding by the steps as described (ref. 120), similar products could result.

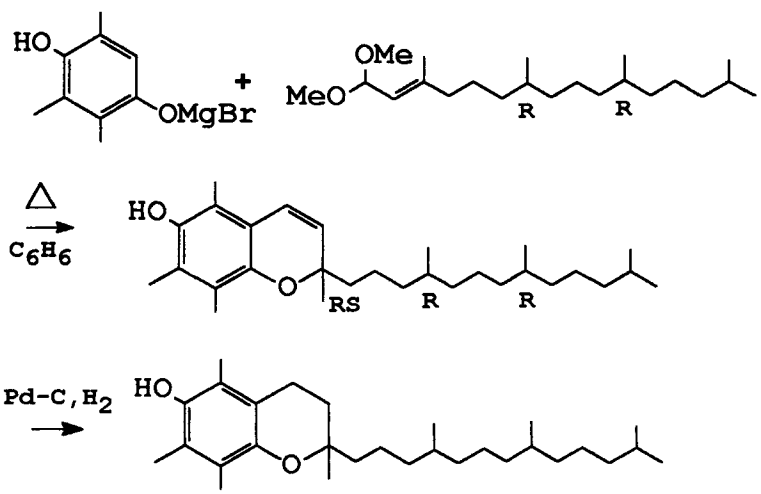


An epoxide have also served as an intermediate in more recent work (ref. 122) in which the purpose has also been to obtain the final product with the preferred 2R configuration although in this case the sidechain intermediate was a C_{19} compound of synthetic origin and the additional methylene group required was supplied by the use of tetramethylhydroquinone.



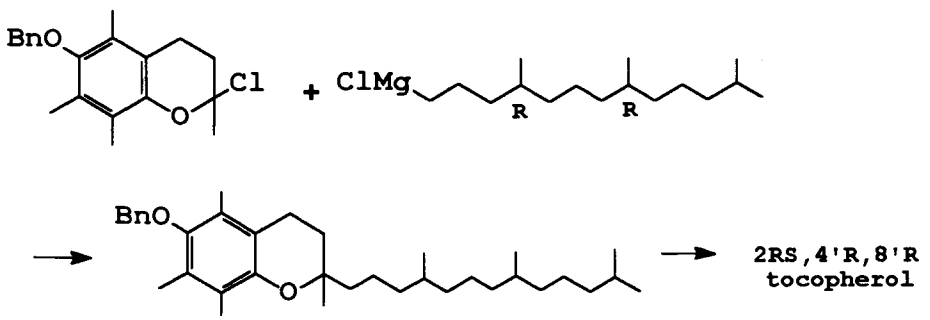
Thus tetramethylhydroquinone as the O-methoxymethyl derivative was lithiated with butyllithium in THF containing potassium butoxide and reacted with the terminal C_{19} epoxide having 2R,6RS,10RS stereochemistry, obtained in several steps from the diol, (S)-1-chloro-2,3-dihydroxy-2-methylpropane. After reaction at ambient temperature for 16 hours the open chain tert-methylcarbinol product resulting, with retention of configuration, was cyclised in methanolic hydrogen bromide to afford 2R,6RS10RS-α-tocopherol. This process avoids the synthesis of a C_{20} phytal and the need for the hydrogenolysis of a resultant benzylic alcohol.

Phytal dimethylacetal from natural phytol has been reacted with the magnesiobromo derivative of trimethylhydroquinone (the Casnati method, ref.40) in refluxing benzene to afford a modest yield of dehydro-2RS,4'R,8'R-α-tocopherol, hydrogenation of which afforded 2RS,4'R,8'R-α-tocopherol (ref.123). Several other α,β-unsaturated aldehyde acetals have been employed and this chromenylation procedure with 2,5-dimetylhydroquinone has also given β-tocopherol.

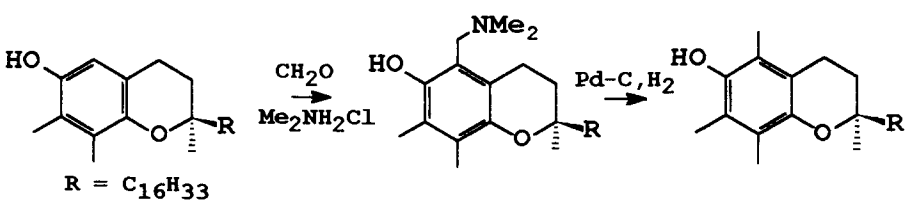


A range of tocopherols have been synthesised from methylbenzo-1,4-quinone, 2,6-dimethyl-1,4-benzoquinone and trimethylbenzo-1,4-quinone by cyclocondensation with phytol or isophytol (ref.124) under reductive conditions. Thus the respective benzoquinone in formic acid containing copper-zinc powder at 85°C was treated with isophytol and refluxed during 2 hours to afford racemic products with yields generally in excess of 70%. There is little relative novelty in this approach since the oxidative formation of the quinone from trimethylhydroquinone or other quinone used in this general method imposes a reductive step in the methodology.

A different strategy consisting of alkylation of the preformed chroman ring has been described (ref.125). Thus, 6-benzyloxy-2-chloro-2,5,7,8-tetramethylchroman was alkylated with the Grignard reagent from 1-chloro-4R,8R,12-trimethyltridecane and the product then hydrogenolysed to afford 2RS,4'R,8'R-α-tocopherol. A C_{16} intermediate is required and the synthesis of an unusual chroman.



Other aspects of the use of biological raw materials and biotechnological procedures have occurred in recent developments. Thus there has been interest in the transformation of β,γ and γ-tocopherols to the more biologically active α-compound. Soya sources predominantly contain β and γ-tocopherols which, due to their activated rings, although sterically hindered, undergo the Mannich reaction to afford nuclear dimethylaminomethyl derivatives. Hydrogenolysis of the Mannich bases in toluene solution at 200°C and 300psi with 5% Pd-C/H_2 greatly increased the α-tocopherol. For example after two such treatments an initial composition of 5.7%, α-, 40.6% β- and γ-, 19.4% δ- was transformed into 92.7%, α- , 0.4% β- and γ-, 0.4% δ-tocopherol (ref. 126).



The enzymic preparation of intermediates for the formation of the chroman ring in tocopherols has been investigated, notably the resolution of a racemic dioxolane derivative (ref.116) by selective hydrolysis with a carboxyesterase (ref. 127).

The potential manufacture of α-tocopherol by plant tissue culture of the bryophyte, *Marchantia polymorpha* A18, resulted in the formation of

0.1047g/100g dry tissue while *Carthamus tinctorius* (safflower) afforded 0.0184g (ref. 128) In another study (ref. 129) of the production of tocopherol from safflower by cell culture, it was found that its formation was stimulated by incorporating biosynthetic precursors such as phytol which increased the total content 18 fold. to 0.0636g/100g dry weight and the α- to 0.0288g/100g dry weight.

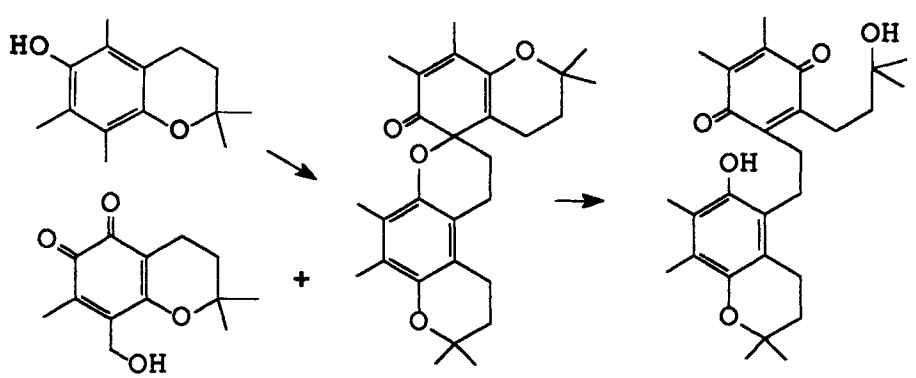
12.8.4 Reactions of Tocopherols

The *in vitro* oxidation products from tocopherol have been studied in detail although less is known about its *in vivo* metabolism. The oxidation of α-tocopherol is light-catalysed and accelerated by unsaturated fatty acids, metal salts and alkali. The structure of many of the products from chemical oxidation has been established (ref. 98). It is used in the form of the unnatural acetate in which form it may well be more chemically stable although the manifestation of antioxidancy requires the presence of the free phenol since its radical is stabilised by resonance and by steric effects with the participation of several contributory structures. It has been suggested, as mentioned earlier, that the activity of vitamins E and C are related synergistically and evidence from pulse radiolysis has supported this augmenting interaction on the effect of vitamin E (ref.130), depicted in the equation,

$$\text{Vitamin E radical} + \text{Vitamin C} \rightarrow \text{Vitamin E} + \text{Vitamin C radical}$$

Enzymic conditions by an NADH system could reform vitamin C. Although the biological activity, presumably its antioxidancy, is said to be preserved in the acetate this is almost lost in its ethers and thus the phenolic group is a vital functional group.

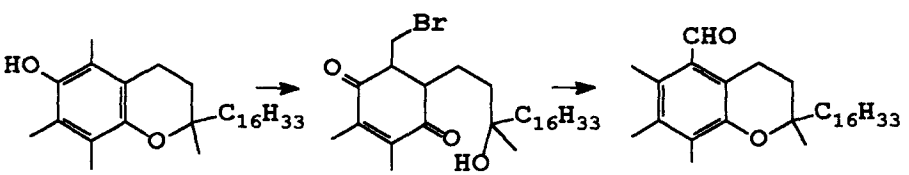
In recent quantitative work by HPLC related to the oxidation of α-tocopherol (ref. 131) the model compound 6-hydroxy-2,2,5,7,8-pentamethylchroman was found to result in new compounds, during attempts to synthesise the model oxidation analogue of tocored, 2,2,7,8-tetramethylchroman-5,6-dione and of tocopurple, 2,2,7-trimethyl-6-hydroxychroman-5,8-dione,



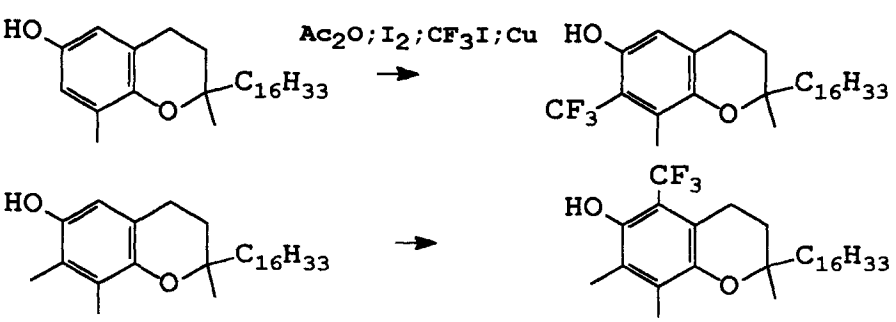
namely 8-hydroxymethyl-2,2,7-trimethylchroman-5,6-dione and 1,2-bis(2,2,7-trimethylchroman-5,6-dione-8-)ethane a dimer of the starting material. In TLC purification of the known spirodimer shown, an acid-catalysed decomposition was found to have occurred affording a polymethylated 1-(6-hydroxychroman-5-)2-(1,4-benzoquinone-3-)ethane derivative in which one of the chroman rings had suffered cleavage. These compounds indicate that there is still much to be found concerning α-tocopherol itself.

From studies with singlet oxygen (ref. 132) the formation of epoxides such as α-tocoquinone-2,3-oxide had been considered to be a main pathway of tocopherol oxidation. In more recent work on the products and relative reaction rates of tocopherol oxidation with singlet moleclar oxygen (ref.133), mixtures of quinones and quinone epoxides were found which were thought to result from the decomposition of the primary product, an hydroperoxydienone. In this study the relative efficiencies of the tocopherols towards singlet molecular oxygen was indicated to be in the order, (R)-(+)-α-, > β-, > γ-, > δ-, and the most useful member is the most vulnerable towards deterioration.

Reference has been made to an 8-hydroxymethyl product arising from oxidation studies and from this an 8-formyl compound might well be expected to arise. The 5-formyl compound has been synthesised by the oxidation of α-tocopherol with dioxane dibromide by way of a bromoquinone intermediate (ref. 134).



The susceptibility of tocopherol towards deterioration suggests that this might be circumvented or overcome by synthetic means to improve on the slight deficiencies of a natural product. Although the whole area of vitamins remains somewhat sacrosanct and molecular' tinkering' might be frowned on, a



remarkable situation compared with that in the pharmaceutical chemistry, the useful structure /activity studies in the 'hindered phenol' antioxidant series suggest a parallel. Trifluoromethyl derivatives of γ- and δ-tocopherols have been prepared, one of which is a 5-trifluoro analogue of α-tocopherol and the other a trifluoro relative of γ-tocopherol (ref. 135) and it would be of interest to know their relative stability and antioxidancy compared with the corresponding natural products.

From this overall view of prenyl derivatives of phenols which by no means embraces the whole picture it can be seen that they have many diverse functions. In conclusion the dual and perhaps ambiguous character of one simple prenylated compound has been instanced (ref. 136). Thus while various species of the genus *Stachyborus*, for example certain fungi, are pathogenic to both plants and animals (ref. 137), potentially useful antibiotic and antifungal compounds have also been reported from the genus (ref. 138) indicating the importance of specifc rather than general usage and knowledge.

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CHAPTER 13

NON-ISOPRENOID ALKYLPHENOLS

13.1 INTRODUCTION

Phenolic lipids can conveniently considered as compounds with a phenolic headgroup and an alkyl chain which can isoprenoid with regular branching as discussed in Chapter 12 or non-isoprenoid representing the types having n-alkyl or unsaturated side chains which are described in the present chapter. The unsaturated members tend to be more prolific and the non-conjugated methylene group characterises these compounds rather than conjugated unsaturation. In this structural feature they therefore resemble the unsaturated fatty acids. To date it would appear that the great majority of alkyl and alkenylphenols are non-isoprenoid in type although the tocopherol group in the isoprenoid series is very widespread in many natural seed species. Whereas the isoprenoid phenols arise from the reaction of a C_5, C_{10}, C_{15} or higher unsatuated pyrophosphate with a polyketide-derived phenol (ref.1), the non-isoprenoids can be thought of as of purely polyketide origin.

Members of this class are typified by saturated anacardic acid, (2-hydroxy-6-n-pentadecylbenzoic acid) which can be viewed as a fatty acid in which the carboxylic is now a carboxy phenolic or hydroxyphenolic group. The chemistry of these materials has been discussed in earlier reviews (ref. 2, 3) and the present review includes recent developments.

As well as occurring in the form of phenolic acids, alkylmonohydric, dihydric and polyhydric phenolic compounds are widespread. The polyhydroxy members seem to exist as such whereas in the phenolic isoprenoids, highly oxygenated members are sometimes quinonoid; for example bovinone, 2,5-dihydroxy-3-geranylgeranyl-1,4-benzoquinone (ref. 4) which has been isolated from a fungus of the *Boletus* species.

13.2 NOMENCLATURE

In a similar manner to the fatty acids, monohydric, dihydric and phenolic members invariably exists as a mixture of saturated, monoene, diene and triene constituents and rarely in the pure form as one of these four. In the nomenclature of this series a comprehensive system which takes account of the chain length, double bond position and its stereochemistry has not been widely agreed and accepted. Trivial and systematic names thus both abound and because of their dual functional nature as aromatic and acyclic these compounds have remained relatively unclassified. For example, cardanol is a well-known member consisting of saturated, monoene, diene

and triene constituents having predominantly a C_{15} chain with small amounts of homologues, particularly C_{17} present. In the technical literature cardanol is persistently described as having a pentadecadienyl chain simply because the unsaturation averages to that of a diene and the heterogeneity was not recognised analytically in early structural studies. In the nomenclature of these compounds (ref.3) a convenient strategy has been to term the saturated, monoene, diene, and triene constituents (15:0)-, (15:1)-, (15:2)- and (15:3)-cardanol respectively. A systematic name (IUPAC) for 'cardanol diene' which possesses the *cis*-configuration at the 8- and 11-positions is 3-[(ZZ)-pentadeca-8,11-dienyl]phenol. (15:0)-Cardol is n-pentadecylresorcinol and in IUPAC nomenclature is ideally 1,3-dihydroxy-5-n-pentadecylbenzene (15:0)-Anacardic acid becomes 2-hydroxy-6-n-pentadecylbenzoic acid rather than 6-n-pentadecylsalicylic acid while wth the lowest set of numbers and as a phenol it becomes 2-carboxy-3-n-pentadecylphenol.

13.3 TYPES OF NON-ISOPRENOID PHENOLIC LIPID

In the last decade increasing numbers of the class have been isolated from a wide variety of living sources. As a group the plant lipids represent a replenishable rather than a fossil-originated source. A new dimension of interest has been added to their chemistry as a resource of environmental interest through their biodegradability by comparison with their petrochemical counterparts (ref. 5). Speculation has turned on the probable life expectation of petroleum sources and of the desirability of conserving these for energy purposes rather than also for petrochemically-derived intermediates.

The phenolic lipids occur in many different botanical families, notably in the Anacardiaceae, and they exist in tropical, sub-tropical, temperate climates in certain trees, shrubs and plants. In addition they are found in some bacterial and antibiotic sources and in certain insects. As benzenoid derivatives they are conveniently ,although perhaps artificially, grouped for chemical purposes into phenolic acids, polyhydric, dihydric and monohydric phenols. Tables 13.1, 13.2 and 13.3 and the collections of formulae summarise some of the the information on these products. The structural types are extensive. For example, ω-phenylalkylphenols have been isolated from several different sources and included are certain bridged biphenyls from Grevillea and Betulaceae species.

13.3.1 Phenolic Acids

In this group (Table 13.1) the members are long chain salicylic and orsellinic acids usually having C_{13}, C_{15}, and C_{17} alkyl groups with saturated side chains, varying levels of unsaturation and in some cases hydroxy, acetoxy or oxo substituents in the chain. During the last decade several new anacardic acids have been isolated from the Anacardiaceae, Araceae and Myristaceae. A C_{15} orsellinic acid was first isolated from the seeds of *Ginkgo biloba* in the Ginkgoaceae (ref. 17). but they have now been isolated from members of the Compositae, Leguminoseae and in the fungal Merulius species of the Basidiomycetes. short chain length anacardic

TABLE 13.1 LONG ALKYLCHAIN PHENOLIC ACIDS (and DERIVATIVES)

BOTANICAL BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
ANACARDIACEAE						
Anacardium occidentale	Cashew nut i.e. cashew nut-shell liquid (natural CNSL)	Anacardic acids (C15) 4 constituents	(15:0)-Anacardic acid 2-Hydroxy-6-n-pentadecylbenzoic acid	1	2	Brazil, India Kenya,Nigeria
			2-Hydeoxy-6-[(z)-pentadec-8-enyl]-benzoic acid	2		Mozambique Tanzania
			2-Hydroxy-6-[(ZZ)-pentadec-8,11-dienyl] benzoic acid	3		Indonesia etc.
			2-Hydroxy-6-[(ZZ)-pentadec-8,11,14-trienyl] benzoic acid	4		
Anacardium giganteum (Hancock)	-	Anagigantic acid (C11)	2-Hydroxy-6-n-undecylbenzoic acid	cf.1	6	Brazil
Pentaspadon motleyi (Hook)	-	Pelandjauic acids (C17)	2-Hydroxy-6-[(Z)-heptadec-8-enyl]-benzoic acid	cf.2	7	Australia
			2-Hydroxy-6-[(ZZ)-heptadec-8,11-dienyl] benzoia acid	cf.3		
Pentaspadon officinalis (Holmes)	-	"	"			
Ozoroa mucronata	-	Anacardic acids (15:0) and (15:1)	2-Hydroxy-6-[(Z)-pentadec-10-enyl]-benzoic acid	cf.2	8	East Africa

TABLE 13.1 (contd.)

BOTANICAL BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
Pistacia vera	Pistachio	Anacardic acids (13:0),(15:0) ,(13:1)(15:1)	2-Hydroxy-6-[(Z)-tridec-8-enyl]- , and 2-Hydroxy-6-[(Z)-pentadec-8-enyl]-benzoic acids	cf.2	9	Iran
Spondias mombin	African Plum	Anacardic aid (17:3)	2-Hydroxy-6-[(ZZZ)-heptadec-8,11,14-trienylbenzoic acid	5	10	S. Africa
MYRISTICACEAE						
Kneama elegans	-	Anacardic acid (11:0),(13:0),(15:0) (15:1),(17:1)	2-Hydroxy-6-n-alkylbenzoic acid	cf.1		
		(10:0),(12:0),(12:1)	2-Hydroxy-6-(ω-phenyl)alkylbenzoic acid	6	11	USA
CHAENOMELES genus						
Lysimachia japonica	-	Orsellinic acid (13:0)	2,4-Dihydroxy-6-tridecylbenzoic acid	7	12	Japan
PLANT PATHOGEN						
Phoma	-	Oxooctyl resorcylic acid (8:0)	3,5-Dihydroxy-2-octanoylbenzoic aid	8	13	Russia

TABLE 13.1 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
BASIDOMYCETES						
Merulius spp.	Merulinic acids	Anacardic acid (15:1), (17:1)	2-Hydroxy-6-[(Z)-heptadec-10-enyl]-benzoic acid	cf.2	14	Europe
		Hydroxy deriv. (15:1)	2-Hydroxy-6-[(Z)-14-hydroxypentadec--8-enyl]benzoic acid	9		
		Orsellinic acids (15:1), (17:1)	2,4-Dihydroxy-6-[(Z)-pentadec-8-enyl]-benzoic acid	10		
			2,4-Dihydroxy-6-[(Z)-heptadec-10enyl]-benzoic acid	11		
ARACEAE						
Philodendron scandens	-	Anacardic acid	2-Hydroxy-6-[heptadecatrienyl]benzoic acid	cf.4	15	Scandinavia
GINKGOACEAE						
Gymnospermae	Gingo biloba (Maidenhair tree)	'Ginkgolic acid'	2-Hydroxy-6-[(Z)-pentadec-8-enyl]-acid	cf.2	16	China,Japan Europe
	Seeds	Orsellinic acid (15:1)	2,4-Dihydroxy-6-[(Z)-pentadec-8-enyl]-benzoic acid	cf.10	17	
COMPOSITAE						
Chrysanthemum frutescens	Marguerite	Frutesin and derivs. (C6)	Methyl 2-methoxy-6-(hexa-2,4-diinyl)-benzoate	12	18	

TABLE 13.1 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
		Demethyl-frutescin (C5)	Methyl 2-methoxy-6-(penta-2,4--diynyl)benzoate	13		Europe,North America
LICHENS						
Sphaerophorin cetraria	Depsides	Microphyllinic acid		14	19	World-wide
LEGUMINOSEAE						
Ononis viscosa		Side-chain methoxy,	*eg.* Methyl 2-hydroxy-4-methoxy-	15	55	Spain
Ononis pubescens		acetoxy and ketoderivs.	6-[(2R)-acetoxytridecyl]-	16	56	
Ononis viscosa subsp. brevifola		of C13, 15 orsellinic acid and methyl ester,	benzoate (structure 15)	17	57	
Ononis speciosa		and mono and dimethyl		18	58	
Ononis natrix		ethers		19		

TABLE 13.2 LONG ALKYLCHAIN DIHYDRIC PHENOLS

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
ANACARDIACEAE						
Anacardium occidentale	Cashew nut-shell liquid	Cardol (R = H) (4 constituents)	(5-Pentadecylresorcinol)			
			1,3-Dihydroxy-5-pentadecylbenzene	20	2	As for anacardium occidentale (Table 13.1)
			1,3-Dihydroxy-5-[(Z)-pentadec-8-enyl] benzene	21	20	
			1,3-Dihydroxy-5-[(ZZ)-pentadec-8,11-dienyl]benzene	22		
			1,3-Dihydroxt-5-[(ZZ)-pentadec-8,11,14 -trienyl]benzene	23		
		2-Methylcardol	As for cardol with R = Me in 20 to 23			
Mangifera indica	Mango latex	Cardol (17:1)	1,3-Dihydroxy-5-[(Z)-heptadec-12-enyl]-benzene	cf.21	21	India, Israel
	Mango peel	Cardol (15:0)	1,3-Dihydroxy-5-pentadecylbenzene	cf20	22	
Rhus vernicifera	Japanese lac Chinese lac	Urushiol	1,2-Dihydroxy-3-pentadecylbenzene	24	23	China, Korea, Japan
			1,2 -Dihydroxy-3-[(Z)-pentadec-8-enyl]-benzene	25		
			1,2-Dihydroxy-3-[(ZZ)-pentadec-8,11-dieenylbenzene	26		
			and 8(Z),11(E) analogue	27	24	
			1,2-Dihydroxy-3-[(ZEZ)-pentadec-8,11,14-trienyl]benzene	28	25	

TABLE 13.2 (contd)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
			1,2-Dihydroxy-3-[(ZZ)-pentadec-8,11,14]-benzene	29		
Rhus toxicodendron radicans	Poison ivy	Urushiol	As for Japanese lac except (27) absent		26	N. America
Rhus toxicodendron diversilobum	Poison oak	"	As for poison ivy		26	
Smoddingium argutum	-	-	Related to urushiol		27	S. Africa
Anacardium semecarpus	Indian marking nut	Bhilawainol	"			India
Melannorrhea usitata Wall	Burmese lac tree	Thitsiol	1,2-Dihydroxy-4-pentadecylbenzene (Constituents as for urushiol)	30	28	Burma
			1,2-Dihydroxy-4-heptadecylbenzene	cf.30	29	
			1,2-Dihydroxy-3-(10-phenyldecyl)benzene	31	30	
			1,2-Dihydroxy-3-(12-phenyldodecyl)benzene	32		
Gluta renghas	-	Glutarenghol	1,2-Dihydroxy-3-[heptadec-10-enyl]benzene (probably 10(Z))	25	31	
Semecarpus heterophylla	Renghas fruit	Renghol	As for glutarenghol		32	
Semecarpus vernicifera	Formosan lac	Laccol	As for glutarenghol, (probably 10Z,13Z)			
			1,2-Dihydroxy-3-[heptadec-10,13,16-trienyl]benzene	29	33	Taiwan
Rhus succedanea	Indochinese lac (Vietnamese lac)	-	-			Vietnam

TABLE 13.2 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
PROTACEAE						
Grevillea pyramidalis	-	(15:1)-Cardol	!,3-Dihydroxy-5-[(Z)-pentadec-10-enyl] benzene	cf.21	34	NW Australia
Grevillea banksii		C11,13 and15 Cardols (probably Z monoenes)	1,3-Dihydroxy-5-undecylbenzene	cf.20	35	"
			1,3-Dihydroxy-5-[(Z)-pentadec-8-enyl] benzene	cf.21	"	"
			1,3-Dihydroxy-5-[(Z)-pentadec-10-enyl] benzene	cf.21	"	"
Grevillea hilliana	-	-	Similar to G.banksii with C17,C19 analogues with unsatn at 10-position	cf.21	"	"
Grevillea pteridifolia	-	-	Similar to G. banksii but with (17:0)	"	"	"
Grevillea robusta	Grevillol	-	1,3-Dihydroxy-5-tridecylbenzene	cf.20	"	"
Grevillea striata	Striatol	C14 α,ω bis-phenylyetradecane	α,ω-Bis(3,5-dihydroxy-2-methyl) *tetradecane*	35	36	"
		Phenoliccyclo-phanes	-		36	"
Cardwellia sublimis *Hakea persihana* *Opisthiolepsis heterophylla*	-	-	Many related compomnents to 5-alkylresorcinols	-	35	"

TABLE 13.2 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
Persoona elliptica	Persoonol	-	1,3-Dihydroxy-5-[(Z)-undec-3-enyl]-benzene	cf.21	37	Australia
Hakea trifurcata	-	-	1,3-Dihydroxy-5-[(Z)-heptadec-8-enyl]-benzene	cf.21	38	"
Hakea amplexicaulis	-	-	1,3- Dihydroxy-5-[(ZZ)-heptadec-8,11-dienylbenzene	cf.22	39	"
Hakea saligna	-	Grevillol methyl ether	1,3-Dihydroxy-5-pentadecylbenzene (5-Undecylresorcinol)	cf.20		
			3-Hydroxy-5-methoxyundecylbenzene	33	40	India
		2-Methylgrevillol	1,3-Dihydroxy-2-methyl-5-undecyl benzene	34		
GRAMINAE						
Cereale secale	Rye	Homologousseries	1,3-Dihydoxy-5-alkylbenzenes, C15,17,19 21,23,25,27,29.	cf.20	41	Europe
			8(Z)-Monoenes corresponding to above	cf.21	42	"
			8(Z),11(Z)-Dienes corres. to above	cf.22	43	"
			1,3-Dihydroxy-5-(2-oxoalkyl)benzenes	36	44	"
						USA
Oryza sativa *Oryza glaberrima*	Rice root exudates	Alkenylresorcinols	1,3-Dihydroxy-5-(heptadec-12-enyl) benzenes	cf.21	45	Africa,India Taiwan, France
Hordeum distichon **(Triticale)**	Barley grains	-	1,3-Dihydroxy-5alkylbenzenes, C25,27,29, 31	cf.20	46	UK
Triticum vulgare	Wheat bran	Alkylphenols	1,3-Dihydroxyalkylbenzenes, C19,21	cf.20	47	USA

TABLE 13.2 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
Triticale	Wheat grains	5-Alkyl and alkenyl resorcinols	1,3-Dihydroxy-5-alkylbenzenes, C15,17,19,21,23,25 1,3-Dihydroxy-5-lkenylbenzenes C17,19,21,23,25	cf.20	40	
Sorghum bicolor	Sorghum (natural host)	-	5-Methoxy-3-[(ZZ)-pentadec-8,11,14-trienyl]-1,2,4-trihydroxybenzene	37		N. America
MYRISINACEAE						
Rapanea laetevirens	-	5-Alkyl and 5-alkenyl resorcinols	1,3-Dihydroxy-5-alkylbenzenes 1,3-Dihydroxy-5-alkenylbenzenes, C11,13,15	cf.20 cf.21	49	USA
ARACEAE						
Philodendron scandens	-	-	1,3-Dihydroxy-5-[(ZZZ)-heptadec-8,11,14-trienylbenzene	cf.23	50	Scabdinavia
GINGOACEAE						
Gymnospermae	Ginkgo biloba	Bilobol	1,3-Dihydroxy-5-[(Z)-pentadec-8-enyl]-benzene	cf.21	51	China, Japan Europe
MELASTOMACEAE						
Miconia spp.	Miconidin	-	1,4-Dihydroxy-2-methoxy-6-pentyl-benzene	38	52	Brazil
ZINGIBERACEAE						
Zingiber officinale Roscoe	Gingerol	-	1-Hydroxy-2-methoxy-4-[(5S)-hydroxy-3-oxodecyl]benzene	39	53	Japan

TABLE 13.2 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
	Shogaol	-	1-Hydroxy-2-methoxy-4-(3-oxodec-4-enyl)	40	53	
	Zingerone	-	1-hydroxy-2-methoxy-4-(3-oxobutyl)benzene	41		
COMPOSITAE						
Coryza podocephala	-	5-Alkylresorcinols and acetetes	1,3-ihydroxy-5-pentadecylbenzene, C16,17	cf.20	54	S. Africa
LEGUMINOSEAE						
Ononis viscosa	-	(C13 Orsellinic acid derivs) (Table 13.1) 5-Alkylresorcinols derivs.	eg. 1,3-Dihydroxy-5-(2-acetoxy-12-hydroxy-tridecylbenzene	42	55	Spain
Ononis viscosa sub sp. breviflora	-	5-Alkylresorcinols, (Orsellinic acida, and methyl esters, Isocoumarins)	eg. 1,3-Dihydroxy-5-(2,13-diacetoxytridecyl)-benzene, 1,3-Dihydroxy-5-(2-hydroxy-8-oxo-tridecylbenzene and 3-methoxy ether, 1,3-Dihydroxy-5-(2-hydroxy-8-oxotridecyl-benzene and 3-methyl ether	43 44	56	Spain
Ononis speciosa	-	(15:1)-cardol and derivs. Orsellinates (Table13,.1)	eg. 1,3-Dihydroxy-5-[(Z)-pentadec-8-enyl]-benzene and derivs.	45	57	Spain
Ononis natrix	-	5-Alkylresorcinols and derivs.	eg. 1-Hydroxy-3-methoxy-[(2R)-acetoxy-tridecyl]benzene and derivs.	46	58	Spain

TABLE 13.2 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
	-	(Orsellinates) (Table13.1)	eg. 1,3-Dihydroxy-5[(2R)-hydroxy-6-oxotridecyl]benzene	46a 47	58	Spain
ASTEROIDEAE						
Senecio johnstonii	-	Alkylresorcinol Prenyl 4-hydroxy acetophenone derivs.	1.3-Dihydroxy-5-penradecylbenzene	-	59	
CYSTOSEIRACEAE						
Cystophora torulosa	Brown algae	-	1,3-Dihydroxy-5-[(ZZZZ)-heptadec-5,8,11,14-tetraenyl]benzene	48	60	Australia
			1,3,5-Trihydroxy-2-[(ZZZZ)-octadec-1-oxo-6,9.12,15-tetraenyl]benzene	49		
Cystoseria spinosa (var. squarrosa)	"		Alkenylhydroquinone	-	61	Italy
Calocystis chlorophyceae	"	Alkylresorcinol	1,3-Dihydroxy-5-tridecylbenzene	-	62	Mediterr-anean
CHLOROPHYCEAE						
Botryococcus braunii	-	Phenolic ether lipids	Complex 21-monoether of 1,3-di-methoxy-4-hydroxy-5-(20,21-dihydroxy-nonaeicosanyl)benzene	50	63	Bolivia
BACTERIAL						
Mycobacterium leprae	-	α- and β-Leprosol	1-Hydroxy-3-methoxy-4,6-dimethyl-5-	51	64	Europe

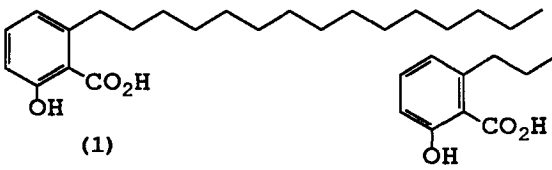
TABLE 13.2 (contd.)

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
	-	leprosol	heptadecylbenzene and C15 analogue			
			1,3-Dihydroxy-2,6-dimethylpentadecyl benzene	52		
Bacterium pseudomonas (sp. B-9004)	-	2,5-Dialkyl-resorcinol	1,3-Dihydroxy-5-hexyl-2-propylbenzene	53	65	Japan
Pseudomonas carbosydoflora		5-Alkylresorcinol	1,3-Dihydroxy-5-nonadecyl and hen-eicosylbenzene	-	66	Europe
Azobacter vinelandii		Alkylresorcinols	"		67	USA
			and monogalactoside of the above	-		
STREPTOMYCES	Panosialin	Alkylphenol sulphate	1,3-Dihydroxt-5-pentadecybenzene potassium disulphates (alsoisopenta decyl and isohexadecyl derivs.	-	68	
Streptomyces cyaneus	Adipostatins A,B	Alkylresorcinols	1,3-Dihydroxy-5-pentadecylbenzene (and isoppentadecyl analogue	54	69	Japan
Steraphylium majusculum	-	2,5-Dialkyl resorcinols	2-n-Butyl-1,3-dihydroxy-5-pentadecyl benzne	cf.53	70	USA
FUNGAL						
Verticicladiella spp.	-	5-Alkylresorcinol	Orcinol monomethyl ether and C2-C6 homologues	-	71	Canada
LEPIDOPTERA						
Anagasta kueniella	Insect source	-	2-[(Z)-Octadec-1-oxo--8enyl]-1,3-dioxocyclohexane and 4-hydroxyanalogue	54	72	W.Europe

TABLE 13.3 LONG ALKYLCHAIN MONOHYDRIC PHENOLS

BOTANICAL / BIOLOGICAL NAME	COMMON/ TRIVIAL NAME	MAIN COMPONENT	FORMULA	STRUCT-URE	REF.	COUNTRY OF ORIGIN
ANACARDIACEAE						
Anacardium occidentale	Cashew nut-shell liquid	Cardanol (C15) (4 constituents)	3-Pentadecylphenol 3-[(Z)-Pentadec-8-enyl]phenol 3-[(ZZ)-Pentadec-8,11-dienyl]phenol 3-[(ZZ)-Pentadec-8,11,14-trienyl]-phenol	57 58 59 60	12	As for Anacardium occidentale (Table 13.1)
Camnospermum auriculata	-	Camnospermanol	3-[(Z)-Nonade-2-oxo-9-enyl]phenol	61	73	Australia
GINKGOACEAE						
Gymnospermae	Ginkgo biloba	Ginkgol	3-[(Z)-Pentadec-8-enyl]phenol	cf.58	16	China, Japan Europe
BACTERIAL						
Cytophaga flexibacter elegans	Flexirubin	-	2-Dodecyl-3-hydroxy-5-methylphenyl 17-(4-hydroxy-3-methylphenyl)heptan-dec-2(E),4(E),6(E),8(E),10(E),14(E), 16(E)-oate	62	74	Europe
MYCOBACTERIAL						
Mycobacterium spp. eg. kansasii, bovis	Phenolic glyco-lipids	-	ω-[(4-Glycosyloxy)phenyl]phthiocerol	63	75	Worldwide

Long Alkylchain Phenolic Acids and Derivatives



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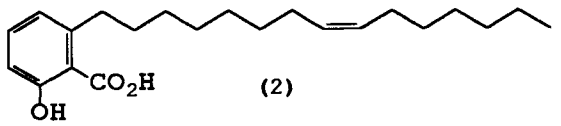

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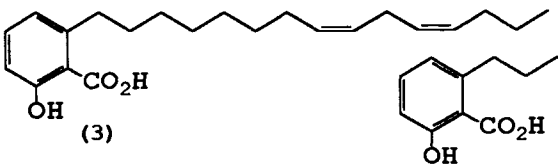

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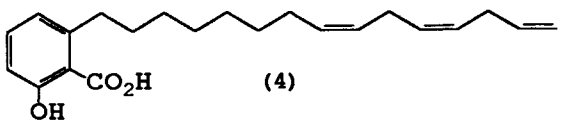

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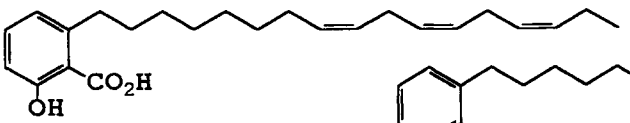

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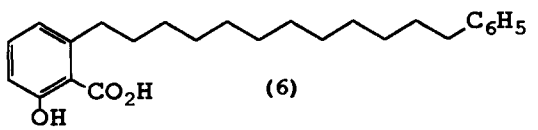

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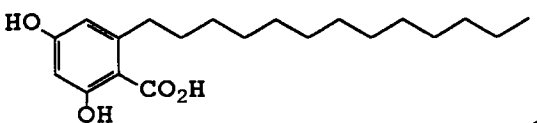

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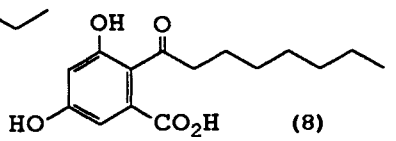

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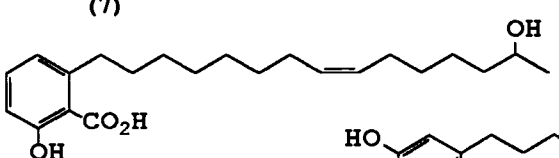

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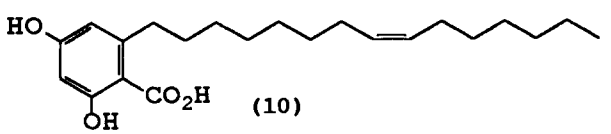

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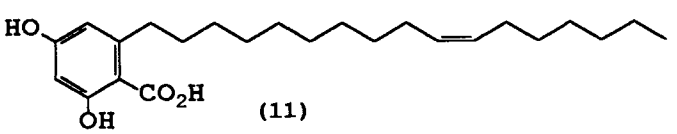

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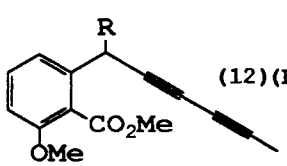
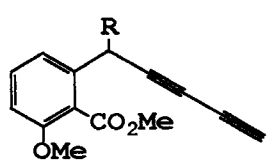


(12)(R = H,OAc)



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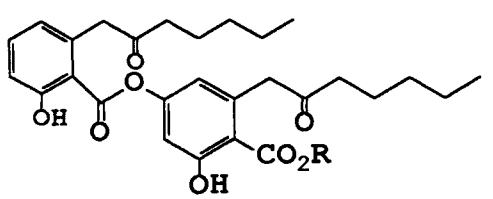

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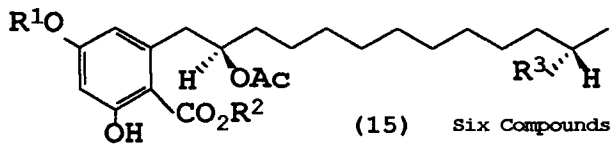
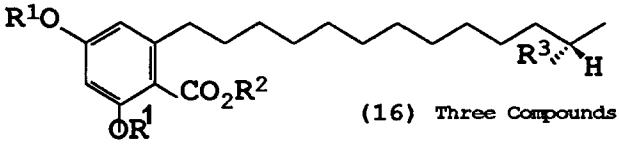


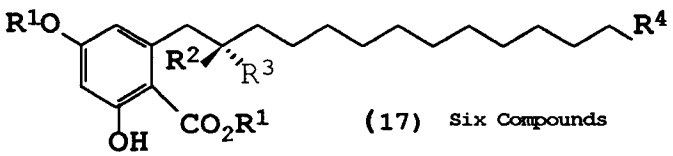
(15) Six Compounds

eg. R^1 = H,Me
R^2 = H,Me
R^3 = H,OAc



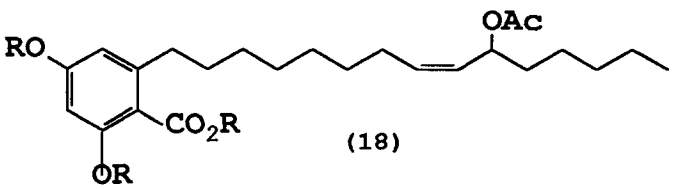
(16) Three Compounds

eg. R^1 = H,Me
R^2 = H,Me
R^3 = OMe



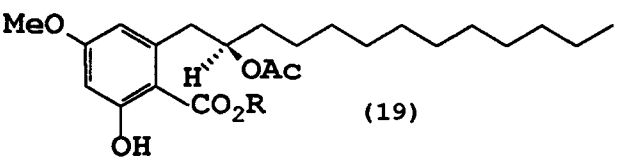
(17) Six Compounds

eg. R^1 = H,Me
R^2R^3 = O
R^2 = OAc, R^3 = H
R^4 = OH,H



(18)

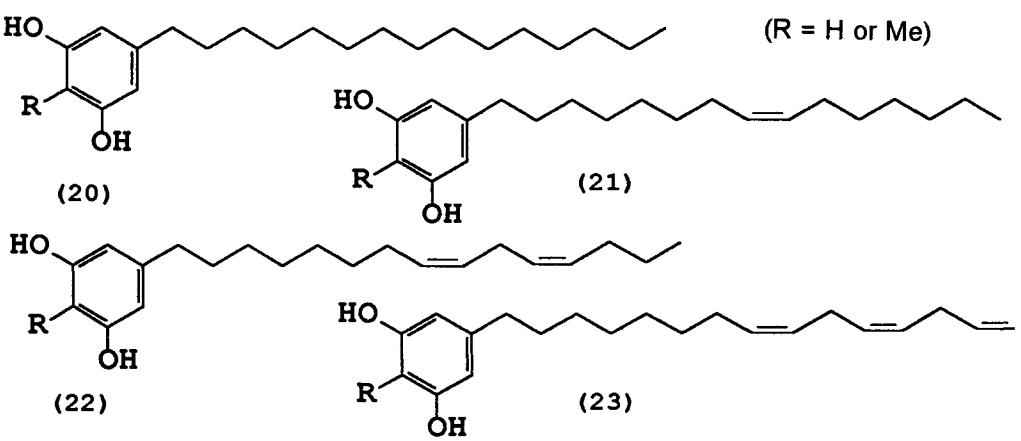
R = OH,OMe



(19)

R = H,Me

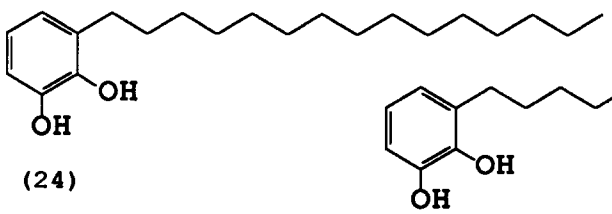
Long Alkylchain Dihydric and Polyhydric Phenols



(R = H or Me)

(20) (21) (22) (23)

(Contd.)



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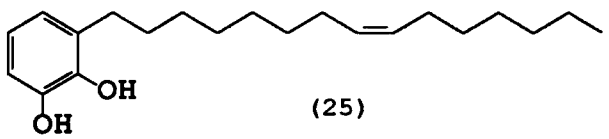

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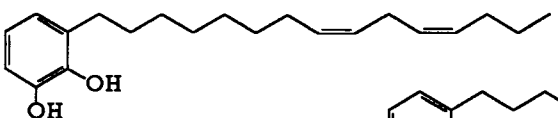

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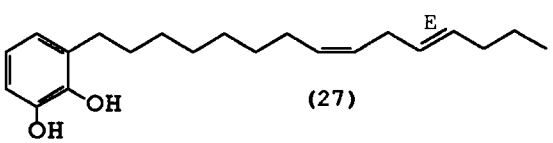

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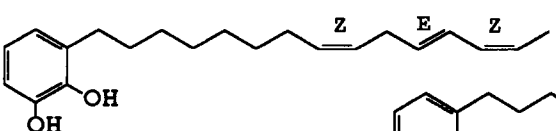

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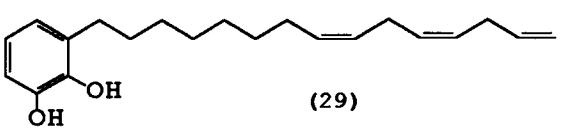

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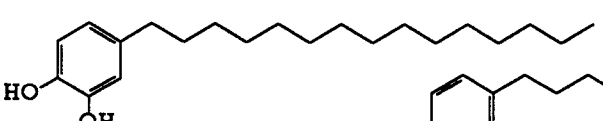

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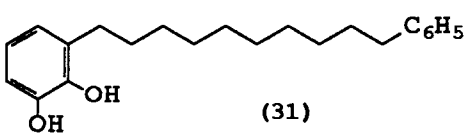

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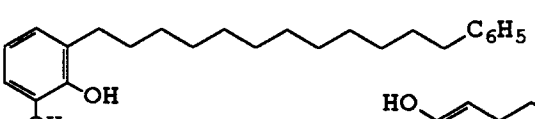

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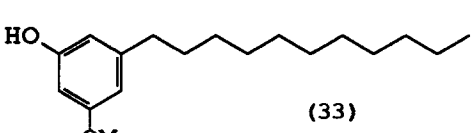

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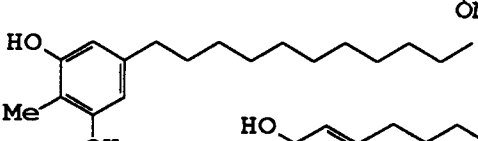

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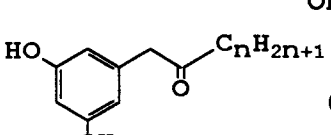

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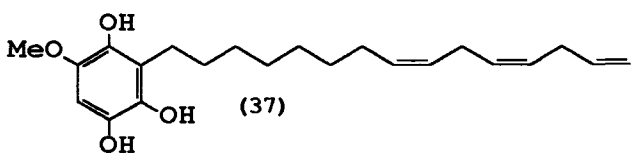

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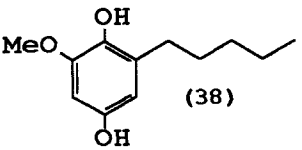

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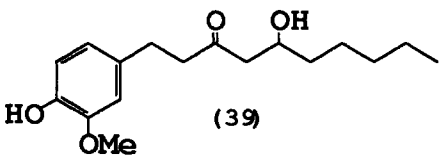

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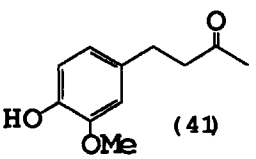

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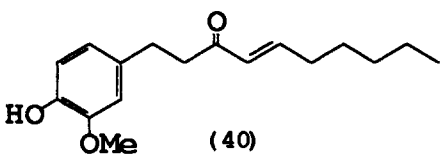

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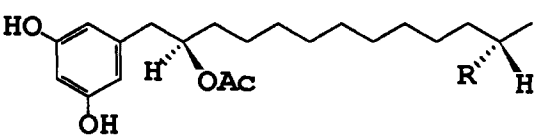
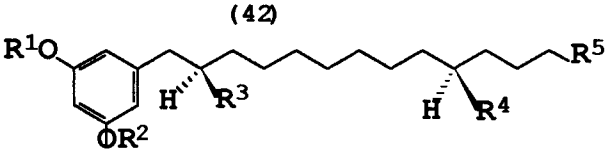


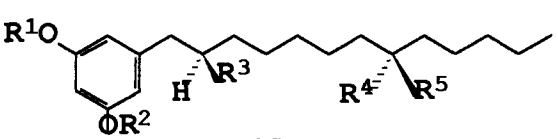
(42)

7 compounds
eg R = H,OH, OAc



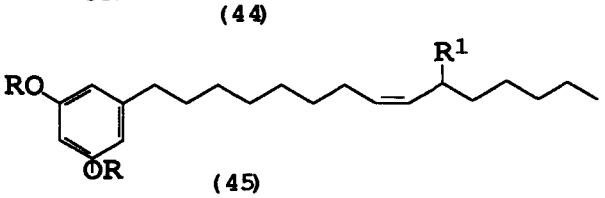
(43)

6 compounds
eg $R^1 = R^2 = OH$
$R^3 = OH; R^4 = H$
$R^5 = OAc$



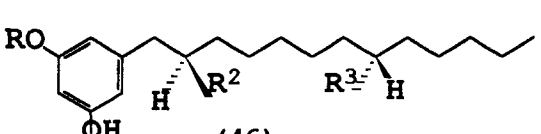
(44)

3 compounds
eg. $R^1 = R^2 = OH$
$R^3 = OAc$
$R^4R^5 = O$



(45)

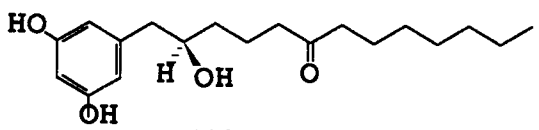
4 compounds
eg R = OH; R^1 = OAc



(46)

5 compounds
eg R = OMe; R^2 = OH
R^3 = OH

(Contd.)



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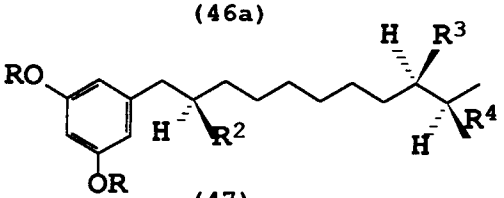
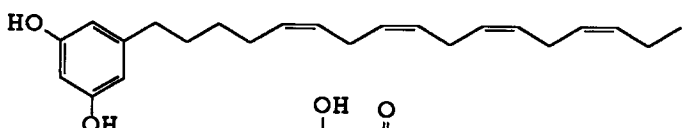


(47)

14 compounds



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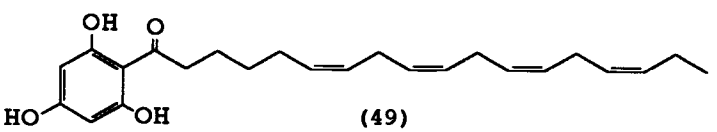

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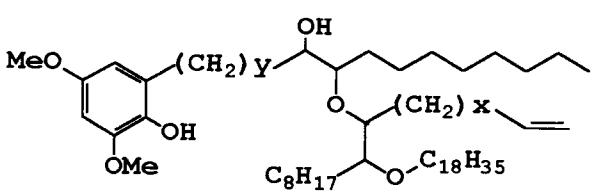
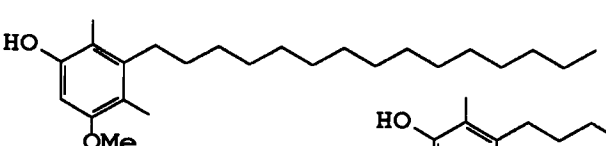


x = 17 (major)
y = 19 (major)

(50)



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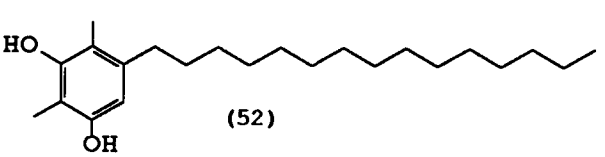

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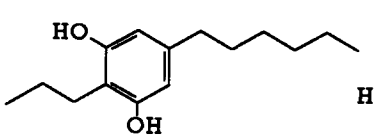

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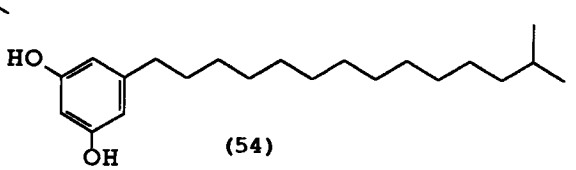

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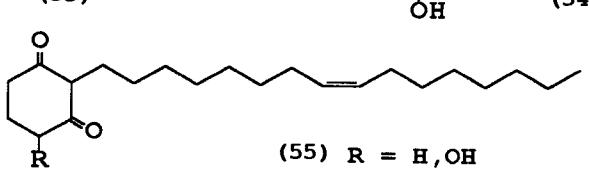
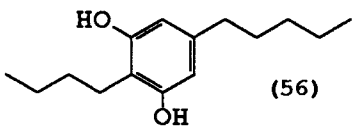


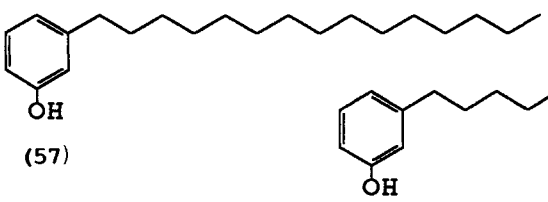
(55) R = H,OH

(Contd.)



(56)

Long Alkylchain Monohydric Phenols



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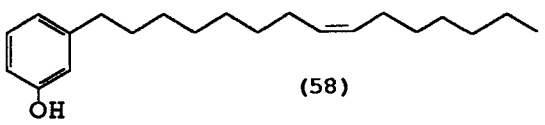

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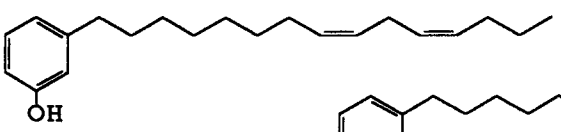

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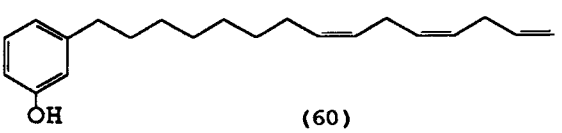

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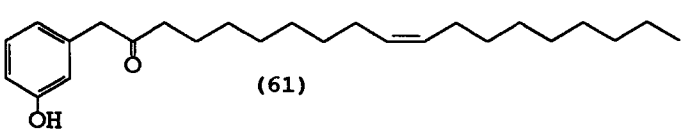

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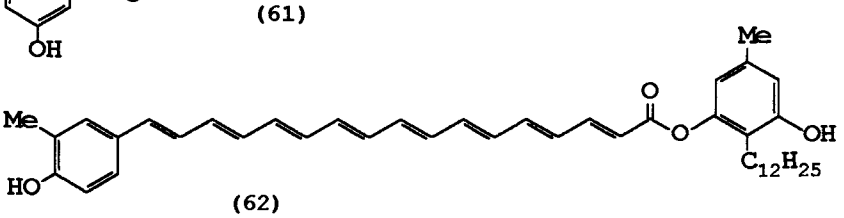

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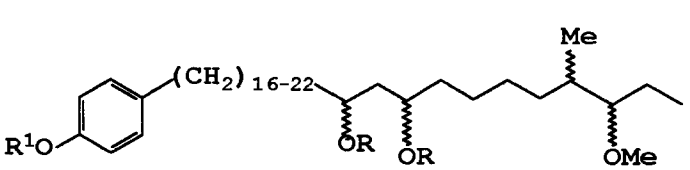
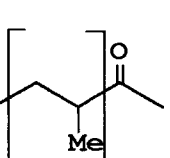


(63)

R = Me(CH$_2$)$_{16-20}$  (mycocerosate)

R^1 = oligosaccharide

acids, such as the C_1 and C_2 methyl esters have been found in beetle sources of the Coleoptera, *Chrysopeplus expolitus* (ref.76). Conjugated acetylenic C5 and C6 derivatives have been discovered in species from Compositae. The lichens contain as building units for the depsides a number of shorter side chain anacardic acids. Microphyllinic acid for example is an ester of 2-hydroxy-6-(2-oxoheptyl)benzoic acid with the corresponding orsellinic acid analogue.

13.3.2 Dihydric and Polyhydric Phenols and their Derivatives

This class some of which are listed in Table 13.2 comprises 1,2-dihydroxy 1,3-dihydroxy and 1,4-dihydroxybenzenes with alkyl, alkenyl and hydroxy, oxo, or acetoxyalkyl side chains. The group has a far wider distribution than the phenolic acids and monohydric phenols probably because the precursor orsellinic acids (see section on biosynthesis) are more readily decarboxylated than the anacardic acids. In recent years many more sources of 5-alkylresorcinols have been found. It is evident that they exist widely in the Graminae, for example in wheat, rye barley and rice root exudates. Thus in Canadian and US wheat between 317.5 and 655µg/g dry weight was detected although in wheat flour the values were 0.025-14.45µg/g dry weight (ref. 77). Their overall role has not yet been elucidated since they possess membrane disruptive properties (ref. 78), the anti-radical activity of all phenols, antagonism towards fat-synthesising enzymes (ref.69) and the ability to cause DNA scission (ref. 38). In the case of the alkenylbenzenetriol isolated from sorghum, this compound can act as a germination stimulant at extremely low concentrations for the undesirable witchweed, a parasitic plant for not only sorghum but also maize, millet rice and sugar cane.
Members of the plant families Anacardiaceae, Protaceae (many Grevillea types from Australia), Myrisinaceae, Araceae, Melastomaceae, Zingiberaceae, Compositae, Leguminoseae and Asteroideae all contain 5-alkyl and alkenylresorcinols. Numerous other living sources such as algae, various bacteria, antibiotic sources and fungi have been found to contain a variety of dihydric phenols. Very largely all these compounds are homologous variants of the cardols from cashew with C11, C13 C17 side chains. Increasingly, recent work particularly with alkylresorcinols has led to the isolation of a large group of compounds in the Compositae family having acetoxy, hydroxy, keto and methoxy substituents in the side chain (refs. 55-58). In the Rhus genus of the Anacardiaceae the urushiols in *Rhus vernicifera* and *Rhus Toxicodendron*, originaly studied in the extensive research of Majima (ref. 23) have been shown to be more complex and some structural modifications suggested for certain constituents (ref. 25). Japanese lac from *Rhus vernicifera* is probably the oldest known cultivated source of a phenolic lipid, since it has been employed before the 6th century. The structures and composition of lacs from other countries have been less studied. Alkylcatechols with a terminal phenyl group in the side chain bearing a superficial resemblance to flexirubin from bacterial sources, have been isolated from the Burmese lac tree (ref. 30). An unusual member of the catechol family is gingerol (ref. 53) from the rhizome of the ginger plant.
Highly unsaturated alkyl resorcinols and a phloroglucinol have been found in certain

brown algae (ref. 60). The latter is one of the few examples of an alternative biosynthetic pathway resulting in 2,4,6-hydroxy substitution rather than the usual 3-hydroxy or, 1,3-dihydroxy pattern. Comparatively few alkylhydroquinones have been located in natural sources. Miconidin (ref. 52) and the polyhydric compound from sorghum (ref. 48) are rare examples.

13.3.3 Monohydric Phenols and their Derivatives

Some of this group are listed in Table 13.3 All the members are 3-alkenylphenols sometimes, as with campnospermanol, containing a keto function in the side chain. The highly unsaturated substance flexirubin is a phenolic ester from a bacterial source. Complex phenolic ether compounds, essentially O-glycosyl derivatives of ω–(4-hydroxyphenyl)phthiocerol A have been isolated from mycobacterial sources (ref. 75).

Some of the phenolic lipids have the ability to cause allergenic reactions and to cause vesicant action (ref. 79, 80, 81), often manifested very specifically. It was partly these properties which led to Australian research into the structure of compounds isolated from a variety of Grevillia species through the clearance of rocket ranges and to American research with technical cashew nut shell liquid concerned with the problem of contamination from the handling of large imported containers. The effect is more pronounced with the urushiols and ground ivy in North America. Remarkably, the historical use of Japanese lacquer since the sixth century does not seem to have been impeded by this physiological action. More significantly, certain cardols have been reported to cause scission of DNA (ref. 38).

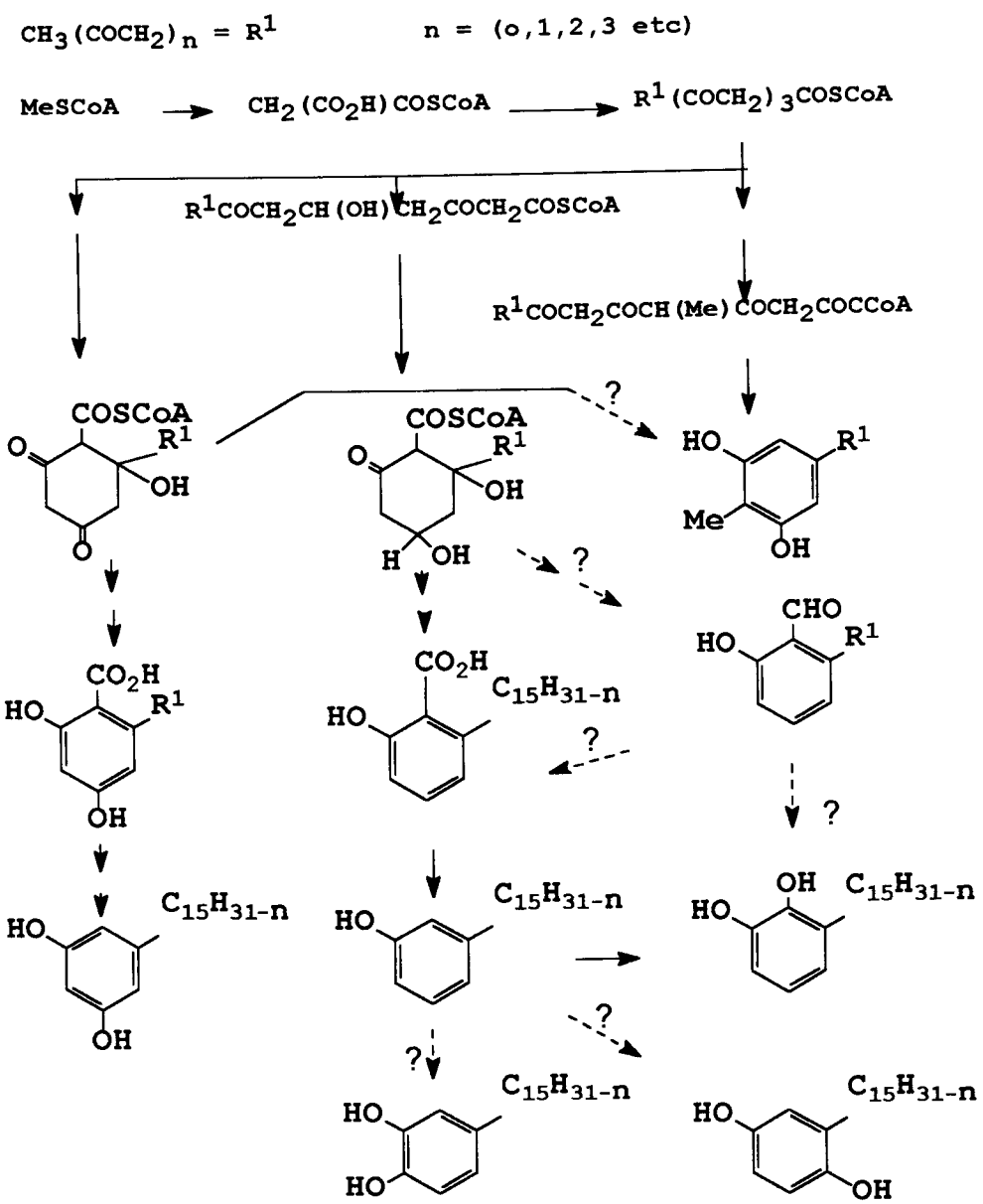
13.4 BIOSYNTHESIS

Early analytical work had suggested that the phenolic lipids of *Anacardium occidentale* arose through a polyketide pathway (ref. 82) and indeed the biosynthesis of C_{15} ginkgolic acid has been investigated by the ^{14}C acetate method (ref. 83) and a polyketide pathway based on malonylcoenzyme A has been established. The characteristic 1,3,5 substitution pattern of cardol in the cashew phenols had appeared likeky to have come about through a route involving Knoevenagel cyclisation (crotonic) giving an orsellinic structure rather than a Claisen type of intramolecular cyclisation, leading to a phloroacetophenone, both of which pathways have been discussed at length (ref. 84); and are fundamentally based on early theoretical speculations (ref. 85); the occurrence of both the resorcinol (48) and the phloroglucinol (49) indicates that in some species both mechanisms may operate. The subsequent finding of a C_{15} orsellininc acid in Ginkgo seeds (ref.17) substantiated the biosynthetic work and also readily accounts for the origin of bilobol through facile decarboxylation.

From the beginning It was feasible that the formation of the salicylic moiety in the C_{15} series was likely to be similar to that of 2-hydroxy-6-methylbenzoic acid (6-methylsalicylic acid) in *Penicillium grisofulvium* (ref.86) although, remarkably, the interesting case of *Anacardium occidentale* found no mention in one account (ref.

87) which was largely concerned with the C_1 series.
A full biosynthetic pathway has to account for the simultaneous formation of cardol, 2-methylcardol, anacardic acid, some cardanol and for the different unsaturation pattern of anacardic acid and cardanol which are similar with a relatively low 40% of triene compared with cardol and 2-methylcardol where the the triene constituent is more than 75%. Scheme 1 summarises known ring formation stages and speculative ones.

Scheme1



Although the mechanism of formation of unsaturation may well proceed as for the polyethenoid fatty acids, it is of interest that palmitoleic acid was not found to be incorporated (ref. 83). The conclusion was drawn that in the biosynthesis of anacardic acid, the side chain was in a different state of activation and/or site than in the case of the triacylglycerol lipids. Some of these of course are found in the oil in the cashew kernel.
The oxidative conversion of anacardic acid to urushiol has been proposed (ref. 85) although this conversion could not be realised *in vitro* (ref. 88). A 'biological' Dakin reaction on anacardic aldehyde seems possible although the hydroxylation of cardanol also appears feasible; it is of interest that cardanol has been found as a minor component in natural urushiol (ref. 89). The folding mechanism of the polyketide at the intramolecular cyclisation stage has been studied (ref. 90), portrayed schematically (ref. 91a) and enzymic pathways discussed (ref. 91b).
The nature of the side chain R' is shown as a polyketide although its transformation throughout, may accompany the reactions to give the final unsaturated phenolic natural products with a C_{15} side chain.

13.5 SYNTHESIS

Introduction

Synthesis has been useful in the chemistry of phenolic lipids for structural confirmation and in enabling structure/property correlations to be made by the general applicability of syntheses to a range of non-natural isomers. With the polyunsaturated constituents synthesis is valuable since either argentation chromatography or preparative HPLC have usually proved laborious on the natural products and on transformed isomeric compounds required for evaluatory purposes in structure/activity studies.
In the following sections the synthesis of saturated monohydric, dihydric phenols, phenolic acids and their unsaturated constituents is described.

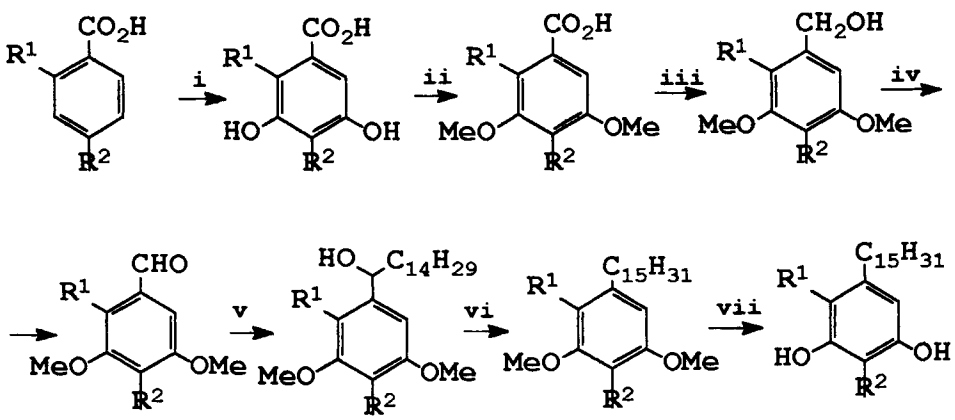
13.5.1 Saturated Side Chain Compounds

In early work substituted benzenoid intermediates were employed and subsequently, open-chain precursors in Diels-Alder reactions, Michael additions and organometallic procedures.

(i) Benzenoid intermediates

For a wide variety of (13:0), (15:0), (17:0) and higher alkyl substituted phenolic lipids a universally applicable method of preparation has been reaction of an OH-protected phenolic aldehyde with an even carbon number n-alkylmagnesium halide, followed by reduction (or dehydration and reduction) and removal of the protective group. This technique has been used with 3-methoxybenzaldehyde, 3,5-dimethoxybenzaldehyde or their isomers and further substituted versions.

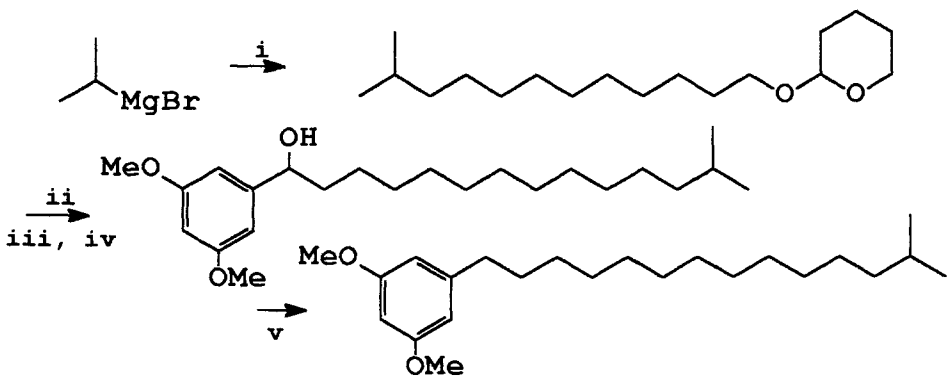
3-Pentadecylphenol (ref. 92), 1,2-dihydroxy-3-pentadecylbenzene (refs. 88, 93), 1,2-dihydroxy-4-pentadecylbenzene (refs.82,94), 1,3-dihydroxy-5-pentadecylbenzenes (ref. 95), 1,3-dihydroxy-5-nonadecyl and 5-heneicosylbenzenes (ref. 47), 1,3-dihydroxy-2-methyl-5-pentadecyl and 4-methyl-5-pentadecylbenzenes (ref. 82) and some non-natural isomers have been synthesised in this way (ref. 94). The processes are shown for 2-methyl (R^1=H, R^2=Me) and 4-methylcardol (R^1=Me, R^2=H) since the required benzaldehyde was not commercially available.



Reagents (i) H_2SO_4-SO_3 ; HO- ; (ii) Me_2SO_4, HO^-; (iii) $LiAlH_4$,THF; (iv) CrO_3Py. ; (v) $C_{14}H_{29}MgBr,N_2$;H_3O^+; (vi)Pd-C/H_2 ; (vii)Py.HCl.

Methylation has generally been used for HO-protection although benzylation has the advantage of the simultaneous removal of the benzyl and the hydroxyl group of the intermediate secondary alcohol at a catalytic hydrogenolysis stage. The Grignard reaction suffers from the defect of formation of Wurtz coupling products and the reagent can oxidise to the alcohol ROH (corresponding to the original halide RX) both of which complicate the purification of the secondary alcohol a process only efficiently achieved by chromatography. Although oxidation can be limited with a nitrogen atmosphere, the use of the alkyllithium through the device of addition of a mixture of the alkyl bromide and the aldehyde to finely-divided lithium suspended in tetrahydrofuran overcomes the Wurtz side reaction. This method is superior to the Grignard route and has been used for members of the cardanol, cardol and urushiol series (refs. 88, 96,97,98) and more recently for the higher chain length members found in rye phenols (ref. 99).

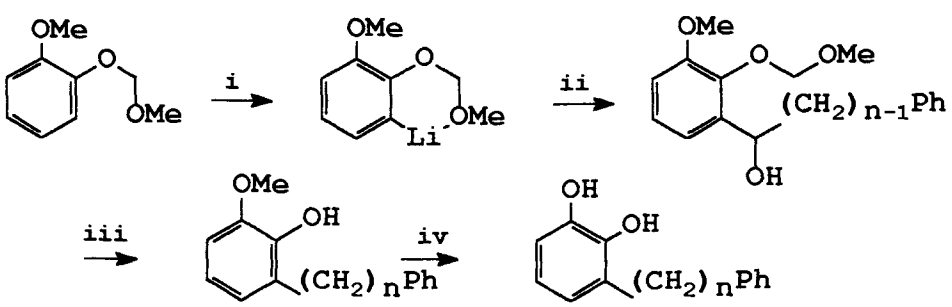
For obtaining branched chain members in the cardol series such as Adipostatin B, isotetradecyl bromide has been synthesised from isopropyl magnesium bromide and 11-bromundecanol (protected as the tetrahydropyranyl derivative) in the presence of lithium cuprate (Li_2CuCl_4). The usual reaction with 3,5-dimethoxybenzaldehyde followed by hydrogenolysis and demethylation afforded the required product (ref. 100).



Reagents (i) $Br(CH_2)_{11}OThp$, Li_2CuCl_4,THF; (ii) H_3O^+,MeOH ; (iii) PBr_3 ;(iv) iso-$C_{14}H_{29}Br$, $(MeO)_2C_6H_3CHO$, Li,THF;(v) Pd-C/H_2,EtOH.

The synthesis with aldehydes has not always proved amenable. Thus as an alternative 3,5-dimethoxybenzoyl chloride has been used for the preparation of 1,3-dihydroxy-5-tridecylbenzene (ref. 101) with an organocadmium reagent and a route was developed (ref. 102) from the diazoketone, by conversion to the phenacyl pyridinium perchlorate and reaction with undecyl iodide. 3,5-Dimethoxybenzoic acid has been employed for the synthesis of 1,3-dihydroxy-5-pentylbenzene (olivetol) (ref. 103) which has also been obtained by alkylation, from butyl-lithium and lithium 3,5-dimethoxybenzoate, followed by reduction of the intermediate ketone (ref. 104). A similar type of sequence for 1,3-dimethoxy-5-(7-hydroxyheptyl)benzene (ref. 105) has proved valuable. Alkylation of the ylid obtained from ethyl 3,5-dimethoxybenzoate and dimethylsulphoxide affords another route to 1,3-dihydroxy-5-alkylbenzenes (ref. 106).

3-(ω-Phenylalkyl)catechols, the phenolic lipids found in the sap of the Burmese lac tree, have been synthesised (ref.107) by the methodology of reacting ω-



phenyldodecanal with 3-lithio-2-methoxymethoxyanisole to form the benzylic alcohol which was then hydrogenolysed and demethylated to give the final product (n = 12).

Reagents (i) BuLi, Et_2O ; (ii) A ; (iii) Et_3SiH, CF_3CO_2H ; (iv) BBr_3 ,CH_2Cl_2.

The side chain component was synthesised from 1,12-dodecanediol (n = 12) by the following sequence.

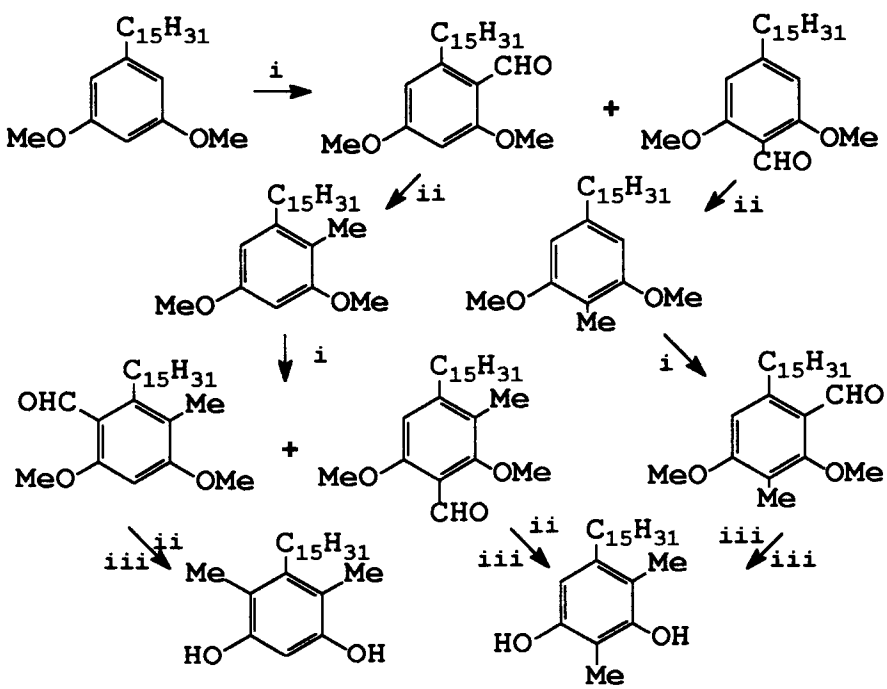
$$HO(CH_2)_nOH \xrightarrow[ii]{i} ThpO(CH_2)_{n-1}CHO \xrightarrow{iii}$$

$$ThpO(CH_2)_{n-1}CH(OH)Ph \xrightarrow[v]{iv}$$

$$\xrightarrow[v]{iv} HO(CH_2)_nPh \xrightarrow{ii} OHC(CH_2)_{n-1}Ph \quad (A)$$

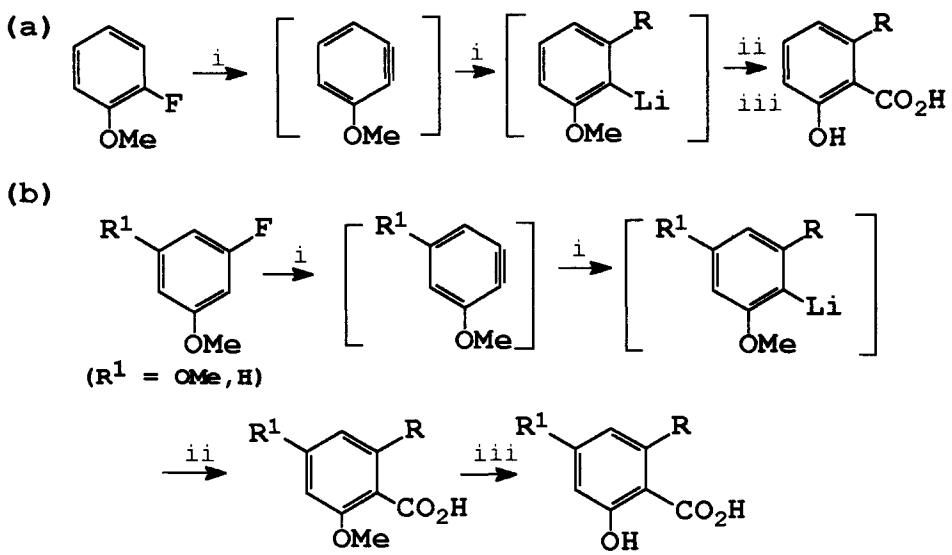
Reagents (i) $C_5H_{10}O$, 4-TSA, CH_2Cl_2 ; (ii) $(COCl)_2$, Me_2SO, CH_2Cl_2, Et_3N ;(iii) PhMgBr, Et_2O ; (iv) Et_3SiH, CF_3CO_2H ; (v) NaOH, MeOH.

For the synthesis of polymethyl phenolic lipids such as α-leprosol and its isomer



Reagents (i) $HCONMe_2$, $POCl_3$; (ii) N_2H_4, KOH, digol ; (iii) Py.-HCl.

it is more convenient to introduce the required methyl groups by succesive formylations followed by reduction as shown, rather than to use a complex substituted benzaldehyde in the Grignard reaction (refs. 64, 108).
(15:0)-Anacardic acid, 2-hydroxy-6-pentadecylbenzoic acid, has been synthesised by two routes. In the first, a less efficient procedure, phthalic anhydride was reacted with an organocadmium reagent to yield a 2-ketobenzoic acid (tautomeric with a 3-hydroxy-3-alkylphthalide) (ref.109), which was reduced by way of the 3-alkylphthalide to a 2-alkylbenzoic acid, the copper salt of which upon thermolysis yielded the 2-hydroxy-6-alkybenzoic acid (ref.110). The second selective method proceeded by reaction of 2-fluoro or 3-fluoroanisole and excess of an alkyl-lithium to give, after carbonation and demethylation, the 2-hydroxy-6-alkylbenzoic acid as depicted in (a) (ref. 111).
A related sequence (b) with 3,5-dimethoxyfluorobenzene gave an approach to orsellinic acids as their dimethyl ethers (ref. 112). Demethylation with boron trichloride afforded a monomethyl product, resulting from complexation of the methoxyl group adjacent to the carboxyl group, while the use of aluminium chloride in chlorobenzene gave the orsellinic acid.



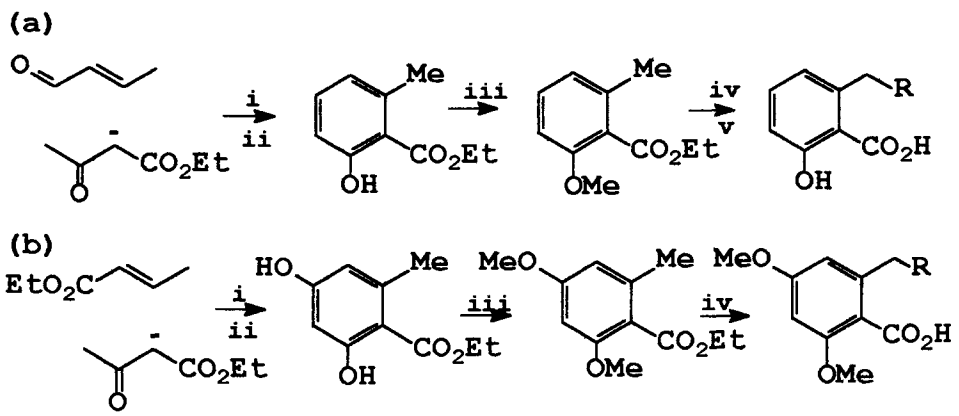
Reagents (i) RLi, THF ; (ii) CO_2 (solid), H_3O^+ ; (iii) (a) HI/P or BCl_3 ; (b) $AlCl_3$, ClC_6H_5.

The ease of decarboxylation of both orsellinic and anacardic acids as well as the reaction of the appropriate intermediate aryllithium with water followed by

demethylation, also affords a route to 1,3-dihydroxy-5-alkylbenzenes and 3-alkylphenols respectively.

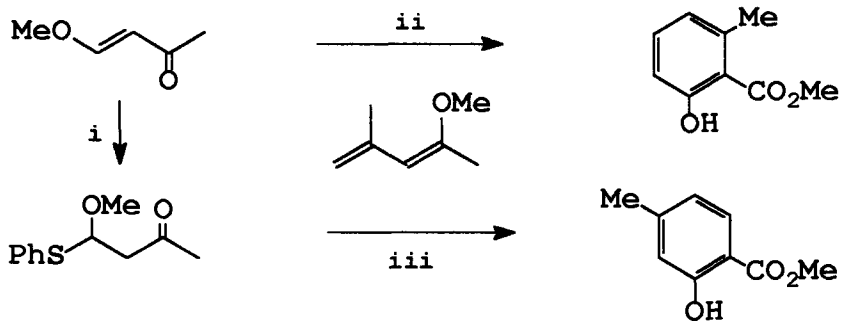
(ii) Acylic intermediates

The use of open-chain precursors for obtaining the benzenoid ring in anacardic and orsellinic acids has proved a fruitful approach. Ethyl 2-methoxy-6-methylbenzoate (synthesised through the Michael addition of ethyl acetoacetate with but-2-en-al, followed by cyclisation and aromatisation), has been alkylated in an aprotic solvent after formation of the carbanion with lithium di-isopropylamide (refs.113,114) to give the anacardic after hydrolysis and demethylation (a). In a similar way ethyl 2,4-dimethoxy-6-methylbenzoate (ethyl orsellinate), (formed from ethyl acetoacetate and ethyl crotonate followed by cyclisation aromatisation and methylation (ref. 115)), has been alkylated (ref. 116, 117). In this way the C_{15} orsellinic acid precursor [R = $C_{14}H_{29}$ in route (b)] of the component phenols in *Anacardium occidentale* has been synthesised (ref. 118) and the method indirectly affords another route to the cardol series.



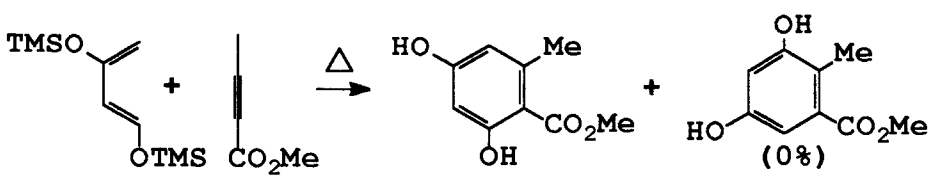
Reagents (a) EtOH, Δ ; H_3O^+ ; (ii) Br_2 , Δ ; (iii) Me_2SO_4, K_2CO_3, Me_2CO or PTC ; (iv) $LiNiPr_2$, RX, HMPA ; (v) HI/P or BCl_3.
(b) EtOH, Δ ; H_3O+ ; (ii) Br_2 ; Pd-C/H_2 , $CaCO_3$; (iv) as in (a).

Other routes to the parent orsellinic acid have been listed (ref. 119). Cycloaromatisation reactions have been employed for the synthesis of 2-hydroxy-6-methylbenzoic acid and for the 4-methyl isomer as shown in the scheme The syntheses which are claimed to be regiospecific involve two different pathways in the reaction of 4-methoxybut-3-en-2-one with the bis-trimethylsilyl ether of 1-methoxybuta-1,3-diene, dependent on the conditions used (ref. 120).

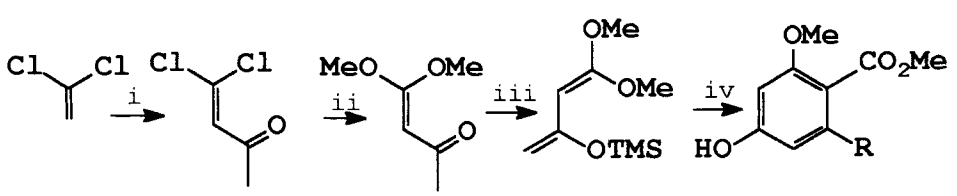


Reagents (i) PhSH, py. (ii) $TiCl_4$, $Ti(OiPr)_4$, CH_2Cl_2 (-40°C) ; (iii) $TiCl_4$, CH_2Cl_2 , (-78°C).

The Diels-Alder addition of 1-methoxybuta-1,3-diene and methyl but-2-en-oate followed by aromatisation has been described as specific for methyl 2-methoxy-6-methylbenzoate to the exclusion of the isomer, methyl 3-methoxy-2-methylbenzoate (ref. 121). Its application to higher homologues has been studied (ref. 122). More readily available dienes, for example 1,3-bistrimethylsiloxybuta-1,3-diene, have been used for the preparation of orsellinic

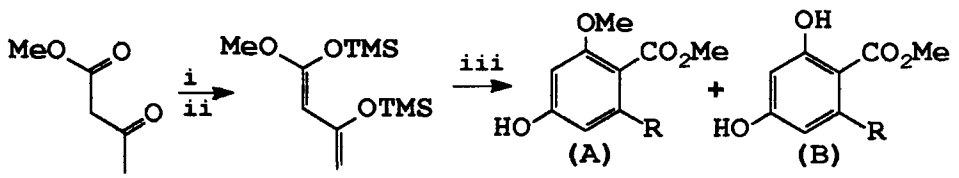


acid derivatives by reaction with methyl propiolate (ref. 123).
However, In related work (ref.114) with 1,1-dimethoxy-3-trimethylsiloxy-buta-1,3-diene and methyl octadec-2-ynoate (R = $C_{15}H_{31}$) , a very low yield resulted.



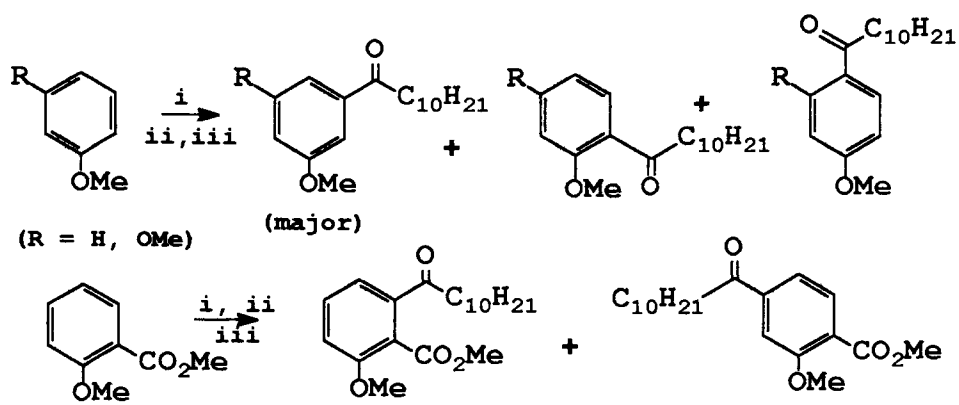
Reagents (i) AcCl, $AlCl_3$; (ii) NaOMe ; (iii) TMSCl, Et_3N, $ZnCl_2$; (iv) $C_{17}H_{31}CO_2Me$, Δ.

However, 1-methoxy-1,3-bistrimethylsiloxybuta-1,3-diene and the same dienophile afforded a mixture of products (A and B) in low yield. The final step for formation of the required anacardic acid, 2-methoxy-6-pentadecylbenzoic acid, was to be effected by catalytic hydrogenolysis of the unhindered hydroxy group by formation of the ether with 5-chloro-1-phenyltetrazole (refs.124,125).



Reagents (i) TMSCl, Et_3N, $ZnCl_2$; (ii) $LiNiPr_2$,TMEDA, TMSCl ;(iii) $C_{17}H_{31}CO_2Me$, Δ.

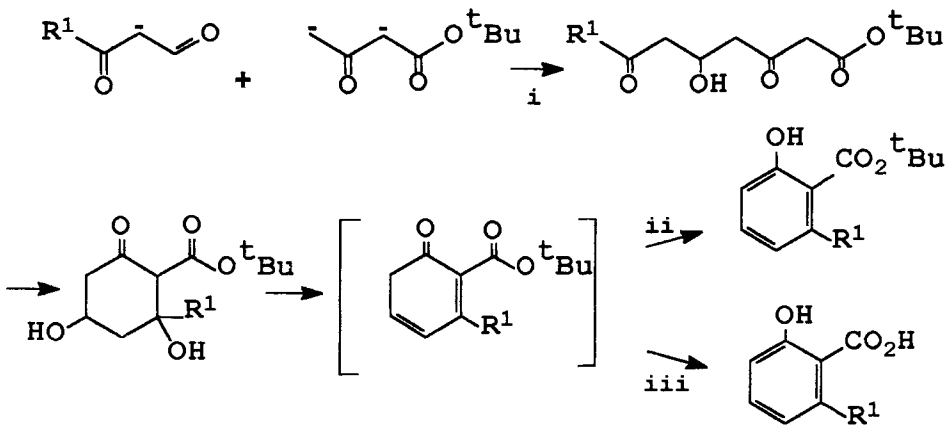
The finding (ref. 126) that methoxyarenes complexed with chromium hexacarbonyl, thus forming arene chromium tricarbonyls, then undergo 3- rather than the anticipated 2-/4- substitution with certain nucleophiles has a potential application in the synthesis of cardanols and cardols. The method has a number of variants (refs. 127, 128) and is shown in the following scheme. Salicylates formed two isomers.



Reagents (i) $Cr(CO)_6$, MeC_6H_5 ; (ii) $NCC^-(OTMS)C_{10}H_{21}$; (iii) oxidn., H_3O^+.

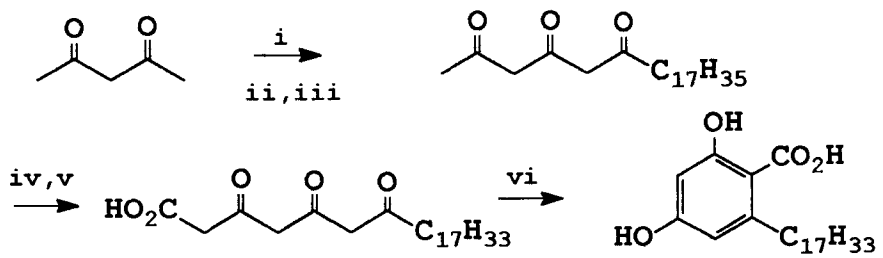
(iii) Biomimetic routes

The modelling of organic chemical methodology on biomimetic lines has been used for the synthesis of phenolic lipid structures. For example, a synthesis of 2-hydroxy-6-methylbenzoic acid has been effected from the dilithio salt of t-butylacetoacetate with the anion of formylacetone to give a tetraketide which was isolated as the cyclohexanone (ref. 129). Acidic dehydration and hydrolysis yielded an anacardic acid while alkaline treatment gave the t-butyl ester. The synthesis is shown in general form for a higher homologous member of the series.



Reagents (i) NaOAc, THF, 15°C ; (ii) aq. KOH ; (iii) HCl, dioxan.

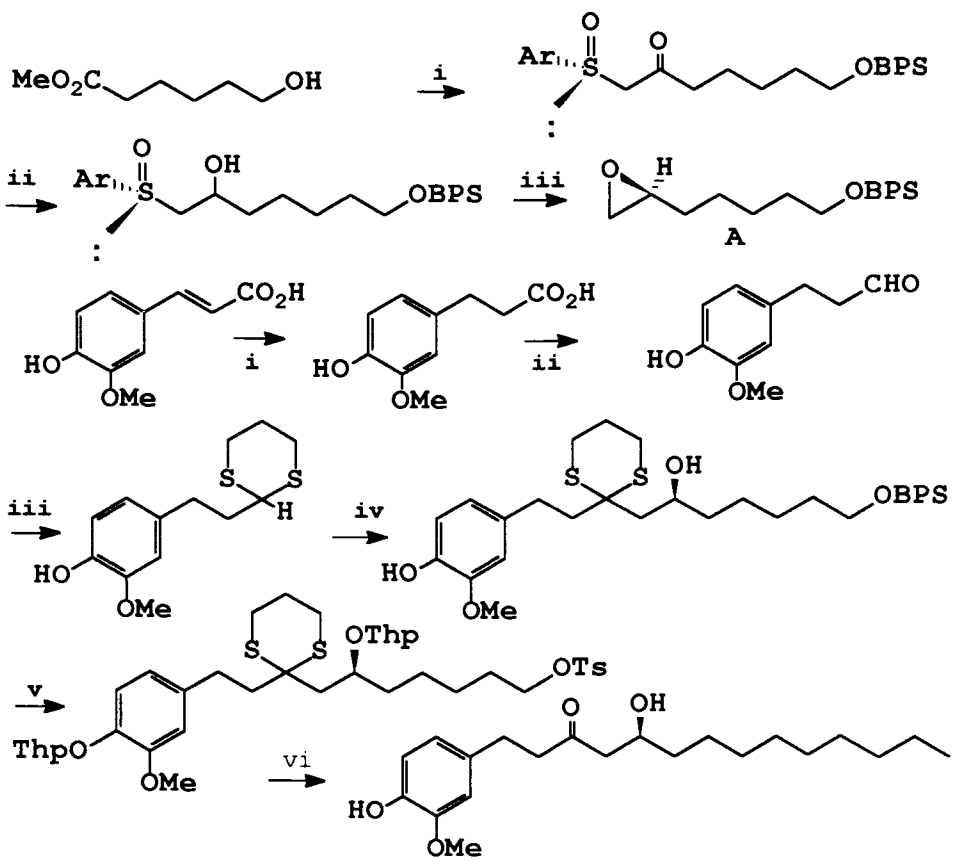
(17:1)-Orsellinic from the acids of the Merulius species has been synthesized (ref. 14) following an earlier established route (refs. 130, 131).



Reagents (i) $LiNH_2$; (ii) $C_{17}H_{33}CO_2Me$. THF ; (iii) Cu complex, purifn. ; (iv) $LiNiPr_2$ (v) CO_2 ; (vi) pH 5.

(iv) Oxo and hydroxy side chain substituted compounds

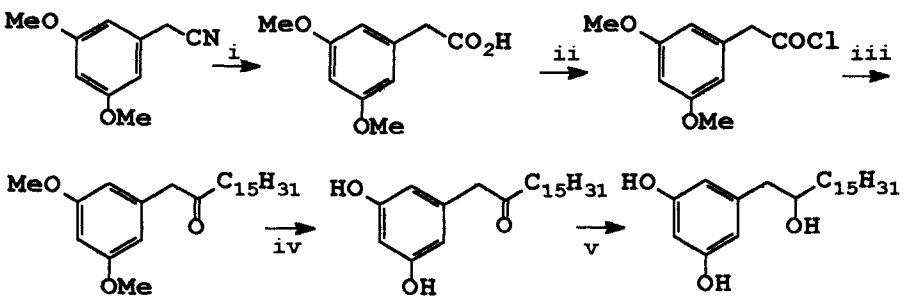
Apart from the hydroxy pentadecyl compounds reported in the orsellinic series (ref. 14), the long chain compounds constituting the gingerols, for example, 4-hydroxy-3-methoxy-(5'-hydroxy-3'-oxoalkyl)benzenes have attracted synthetic interest. Thus three members of the (+)-(S)-gingerol series, the C_{10} side chain compound, designated (+)(S)[6], and the homologous C_{12} and C_{14} compounds have been obtained from the ring opening of a chiral epoxide, itself asymmetrically synthesised from a chiral β-keto sulphoxide commencing with caprolactone. The epoxide was then reacted with the lithio salt of a dithiane (ref. 132) derived from 4-benzyloxy-3-methoxyhydrocinnamaldehyde. The synthesis of the C_{14} side chain member follows.



The details of reagents for the synthesis of the epoxide are given in (a) and the second stage for (+)(S)[10]-gingerol in (b). With (+)(S)[8]-gingerol, at vi, $Et_2CuCNLi_2$ was employed and with (+)(S)[6]-gingerol, the tosylate was reduced with LAH.

Reagents (a) (i) $tBuPh_2SiCl$, imidazole; LDA,(+)-R- MeC_6H_4SOMe (-50°C) ;(ii) DIBAL, THF(-78°C) ; (iii) TMSCl/Zn, THF ; Me_3OBF_4 , CH_2Cl_2 ;K_2CO_3, H_2O.
(b)(i) NaOH, Pd-C/H_2 ; MeOH/H+ ; NaH,BnBr,TBAI, THF; (ii) LAH ; CrO_3,Py., CH_2Cl_2 ; (iii) $HS(CH_2)_3SH$, $BF_3.Et_2O$; (iv) 2BuLi,TMEDA, DMPU, A ; (v) DHP, 4-TSA ; TBAF; 4-TsCl, py. ; (vi) $Bu_2CuCNLi_2$; MeI, $CaCO_3$MeCN ; EtOH, 4-TSA.

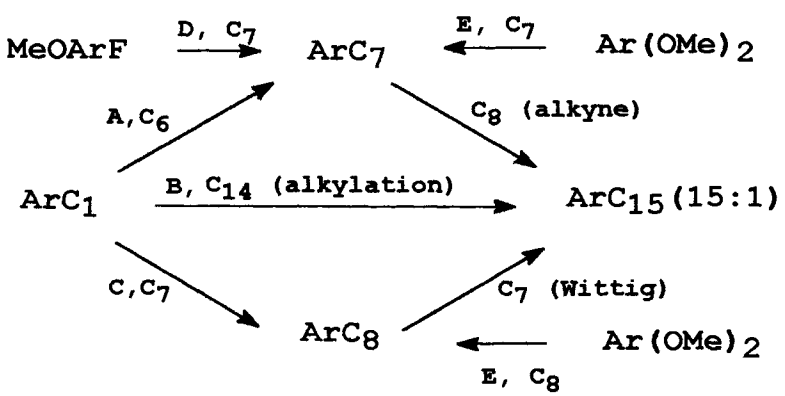
The synthesis of 5-(2-oxoalkyl)resorcinols which are present in *Cereale secale* has been simply effected by the reaction of 3,5-dimethoxyphenylacetyl chloride with a dialkyl cadmium reagent in the folowing way (ref. 99). The 2-hydroxy compound shown as the final product is also present in the phenolic lipids of rye.



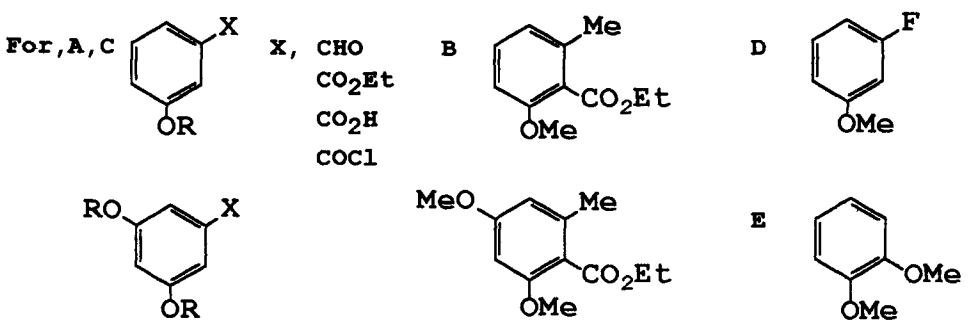
Reagents (i) KOH, EtOH ; H_3O^+ ; (ii) $SOCl_2$; (iii) $(C_{15}H_{31})_2Cd$, Et_2O ; H_3O^+ ; (iv) BBr_3 , CH_2Cl_2 ; (v) $NaBH_4$, MeOH.

13.5.2 Monoenes

For the synthesis of monoenes, three general methods may be employed involving,

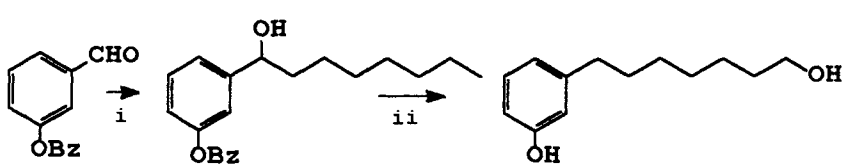


(a) acetylenic intermediates reducible to the Z or E-alkene by catalytic or chemical reduction respectively (ref. 133), (b) the Wittig reaction and its modifications with kinetic or thermodynamic control to produce the Z or E isomer (ref. 134) and (c) boration methodology with selective reagents (ref. 135). Many of the methods used for the synthesis of pheromones (mono, di and polyunsaturated compounds) have a relevance to the preparation of phenolic lipids. For most phenolic lipids (as for example in the cashew series) the first double bond is at the 8-position, and in the synthesis of the required intermediates the aryne and Wittig routes involve less readily available C_7 and C_8 reagents, while for the alkylation and alkyne routes more available C_6 compounds suffice. The following synthons with the routes A,B,C, D and E are applicable to an 8-monoene and appropriate modifications enable isomeric compounds to be synthesised.



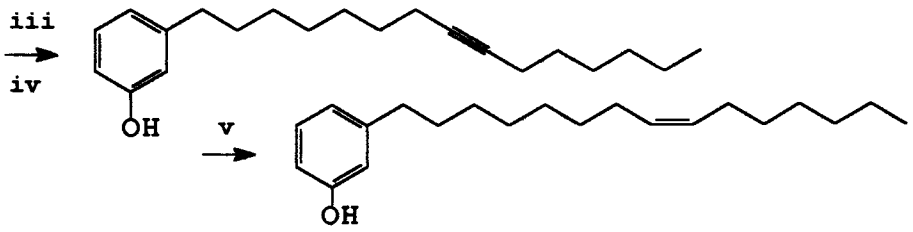
In earlier syntheses of the methyl ethers of (15:1)-cardanol (ref. 136) and urushiol (ref. 137) it is doubtful if the products were stereochemically pure. Nonetheless this work represents the first progress towards obtaining unsaturated methyl ethers of the phenolic lipids. Early difficulties centred on the lack of specificity in the reduction of the triple bond, in the removal of the protective group on the phenolic OH without affecting the double bond and, before kinetic and thermodynamic control was used, on lack of steric control in the Wittig reaction.

In the cardanol series, 3-benzyloxybenzaldehyde was used leading by way of a lithium or magnesium-based Grignard to a diol, selective hydrogenolysis of which gave 3-(7-hydroxyheptyl)phenol. The bromide of this was found to react satisfactorily



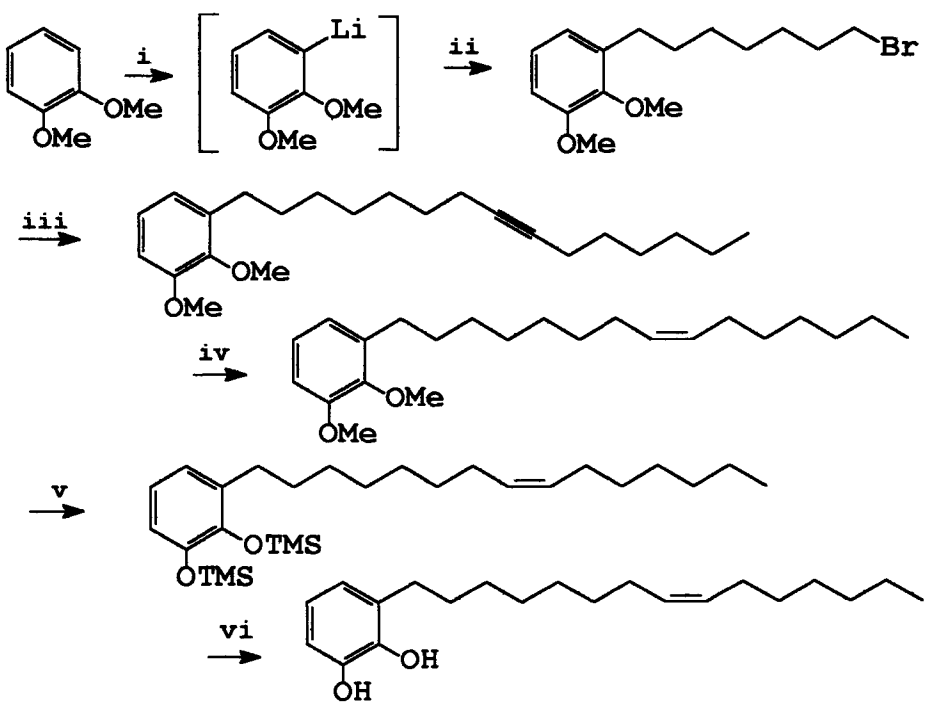
with lithium-1-octyne only in tetrahydrofuran containing hexamethylphosphoric triamide to give after selective catalytic hydrogenation with palladium-barium

sulphate, containing quinoline as a poison, (15:1)-cardanol (refs. 96,97).



Reagents Mg or Li, $Cl(CH_2)_6OThp$, THF ; 4-TSA,MeOH ; (ii) Pd-C,H_2 , EtOH, H^+ ; (iii) PBr_3 or HBr/H_2SO_4 ;(iv) Li-1-octyne, THF, HMPT ; (v) Pd-$BaSO_4$, quin.

In a similar way, 2,3-dimethoxybenzaldehyde with HO-protected 6-chlorohexan-1-ol and lithium afforded after acidic treatment 1,2-dimethoxy-3-(7-hydroxyheptyl)benzene. Demethylation and bromide formation with boron tribromide gave 1,2-dihydroxy-3-(7-bromoheptyl)benzene which interacted with lithium-1-octyne in tetrahydrofuran containing hexamethylphosphoric triamide to give after selective catalytic hydrogenation, (15:1)-urushiol (ref. 138). In a different approach this has been synthesised in moderate yield from 2,3-dimethoxyphenyllithium and 1,7-dibromheptane as shown in the following scheme (ref. 139)

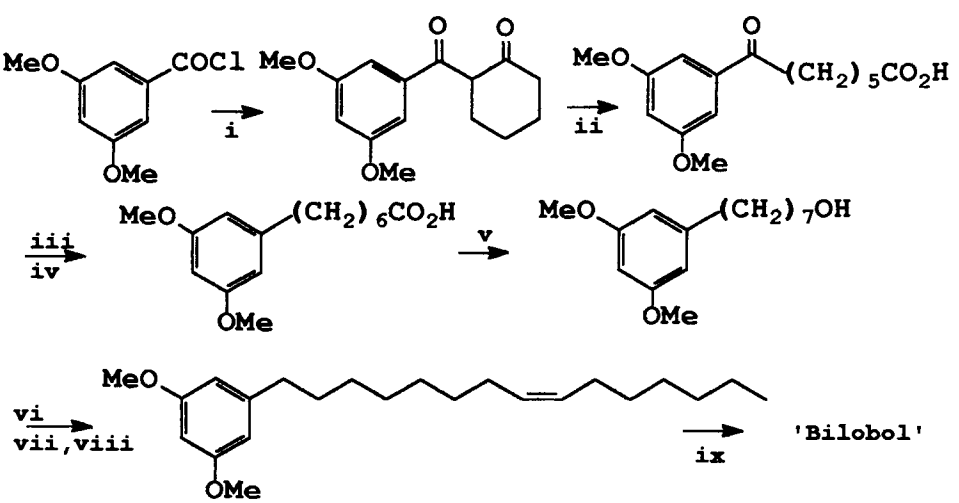


despite an earlier report (ref. 140) which could not substantiate a described synthesis (ref. 141) for (15:0)-urushiol based on the reaction of 1-bromopentadecane with 2,3-dimethoxyphenyllithium.

Reagents (i) BuLi, Et_2O, (ii) $Br(CH_2)_7Br$, THF ; BuLi, I-octyne, HMPT ; (iv) Pd-$BaSO_4$, H_2 , Py. ; (v) TMSI , Δ ; (vi) CF_3CO_2H , H_3O^+, THF.

The Wittig reaction has been employed (ref. 142) for 1,2-dimethoxy-3-(pentadec-1-enyl)benzene and for the C_{17} analogue. In either case the phosphonium salt of 2,3-dimethoxybenzylbromide was reacted with the appropriate aldehyde, giving an alkene of unassigned E or Z configuration. This was reduced to the saturated compound demethylation of which yielded (15:0) and (17:0)-urushiol respectively.

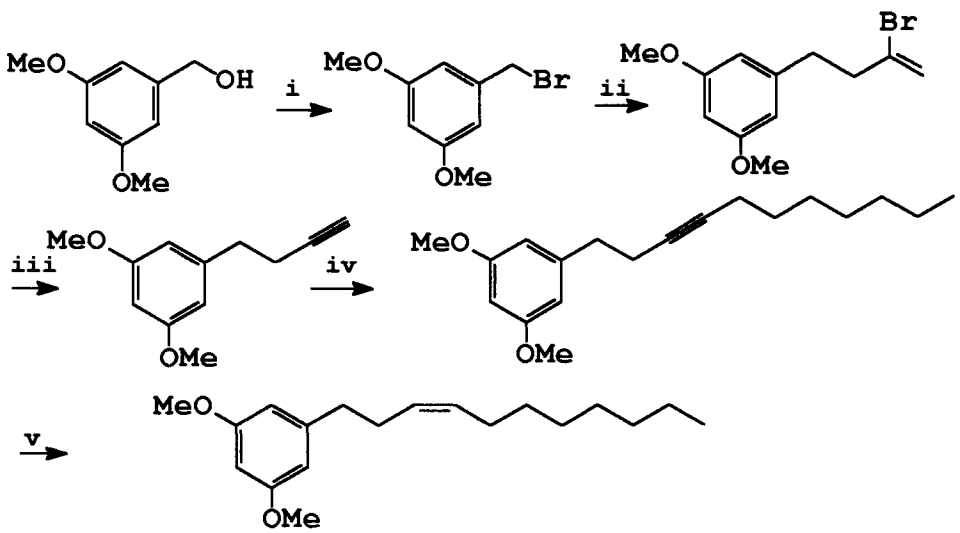
Cardol monoene, (15:1)-cardol, has been synthesised (ref. 105) from 3,5-dimethoxybenzaldehyde by reaction with OH-protected 6-chlorohexan-1-ol and lithium followed by catalytic hydrogenolysis of the acidified product to yield 1,3-dimethoxy-5-(7-hydroxyheptyl)benzene, the bromide of which with lithium-oct-1-yne gave the required alkyne. Selective catalytic hydrogenation and demethylation with lithium iodide in collidine yielded 1,3-dihydroxy-5-[(Z)-pentadec-8-enyl]benzene. An analogous route with HO-protected 9-chlorononan-1-ol and corresponding stages yielded the 10-(Z) isomer (ref. 143) isolated earlier (ref. 34) from *Grevillea pyramidalis*. Much ingenuity has been shown in methods for the formation of side-chains in the intermediates required for monoenes and an earlier synthesis of bilobol, (15:1)-cardol illustrates this (ref.35).



Reagents (i) Et_3N , 1-morpholinocyclohexene ; H_2O ; (ii) KOH, EtOH ; (iii)

N_2H_4 , digol ; (iv) Me_2SO_4 , Me_2CO , K_2CO_3 ; (v) CH_2N_2, LAH ; (vi) 4-TSCl, py. ; (vii) Hg(II)1-octyne, Li ; (viii) Pd-C, H_2 ; (ix) MeMgI, Et_2O

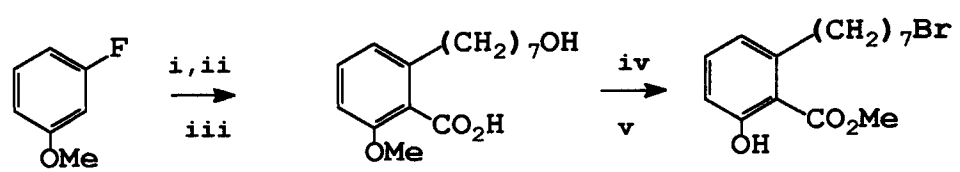
Persoonol dimethyl ether, the 3(Z)-alkene from *Persoona elliptica* has been synthesised (ref. 37) from 3,5-dimethoxybenzyl bromide by way of 4-(3,5-dimethoxyphenyl)but-1-yne which was alkylated with n-heptyl 4-toluenesulphonate followed by final reduction of the alkyne product as shown in the scheme This method of preparation of the butyne was probably obligatory because of the inapplicability of the alkylation technique with 2-(3,5-dimethoxyphenyl)ethyl bromide due to its facile dehydrobromination.

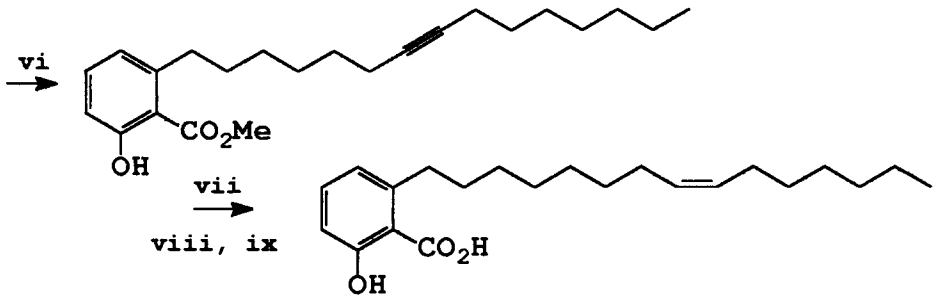


Reagents (i) PBr_3 ; (ii) Mg, 1,2-dibromoprop-2-ene , THF ; (iii) $NaNH_2$, Δ ; (iv) Hg(II) deriv. Li ; $TsOC_7H_{15}$; (v) Lindlar cat., MeOH, H_2 .

Reduction of the C11 alkyne with sodium/liquid ammonia afforded the non-natural E-isomer.

'Ginkgolic acid', (15:1)-anacardic acid has been synthesised by an aryne route

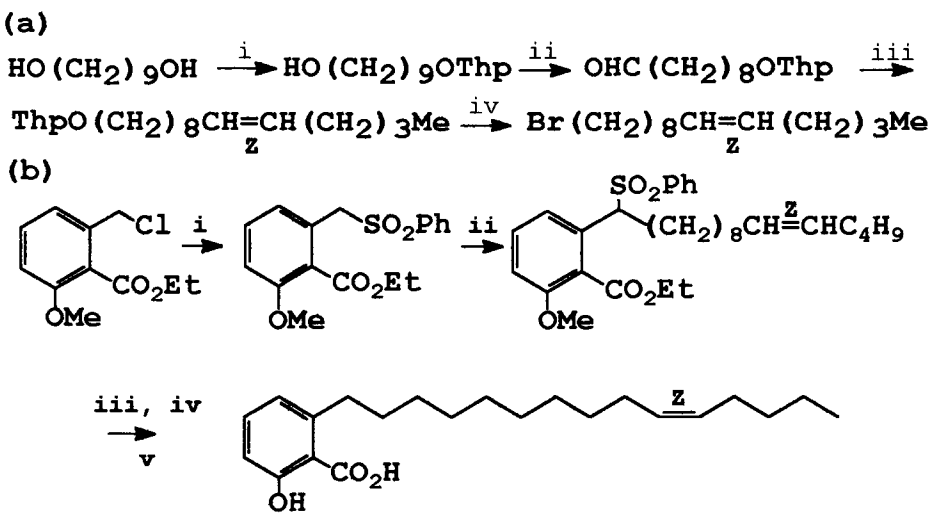




(ref. 144) starting from 3-methoxyfluorobenzene.

Reagents (i) $Li(CH_2)_7OThp$; (ii) CO_2 ; (iii) H_3O^+ ; (iv) BBr_3 , CH_2Cl_2 , (-78°C) ; (v) CH_2N_2 ; (vi) Li 1-octyne, HMPT , THF ; (vii) Pd-$BaSO_4$, H_2 , quin. ; (viii) HO^- ; (ix) H_3O^+.

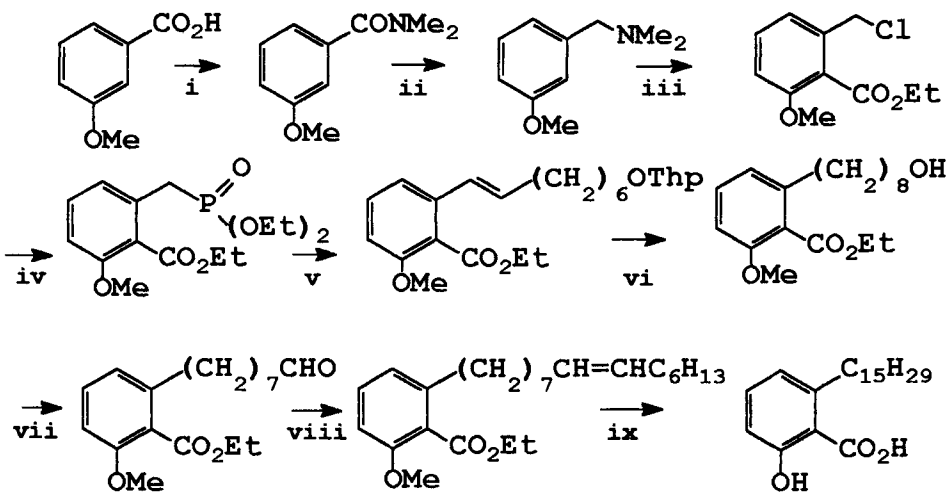
Alkylation routes have been used for the monoenes in this group. Thus, ethyl 2-methoxy-6-methylbenzoate as the carbanion (formed from lithium di-isopropylamide) has been alkylated with (Z) 1-bromotetradec-7-ene in the presence of hexamethylphosphoric triamide. Demethylation with lithium t-butylthiolate yielded (15:1)-anacardic acid (ref. 114). A more activated benzyl group having an adjacent sulphur atom was used for a synthesis of the 10(Z)-isomer of ginkgolic acid in the following way (ref. 8).



Reagents (a) (i) $C_5H_{10}O$, 4-TSA ; (ii) PCC ; (iii) $Me(CH_2)_3CH_2P^+Ph_3Br^-$,BuLi

;(iv) 4-TSA MeOH ; PBr_3 .
(b) $PhSO_2Na$; (ii) $LiNiPr_2$, $Br(CH_2)_8CH{=}CHC_4H_9$; (iii) Na/Hg ;(iv) HO^- , DMSO ; (v) EtSNa , DMF ; H_3O^+ .

(The Julia synthesis (ref.145) could be an alternative approach for isomers, through employing the phenylsulphonyl group α to a potential double bond). Another route for the 8(Z)-monoene but this time involving two Wittig reaction stages (ref. 8) is shown in the following route.



Reagents (i) $SOCl_2$; Me_2NH ; (ii) LAH ; (iii) BuLi, $ClCO_2Et$; (iv) $PO(OEt)_3$; (v) KOtBu, HMPA ; $OHC(CH_2)_6OThp$; (vi) 4-TSA , Pt-C/H_2 ; (vii) $(COCl)_2$, DMSO , Et_3N ; (viii) $C_6H_{13}CH{=}PPh_3$; (ix) HO^- , DMSO ; EtSNa , DMF ; H_3O^+ .

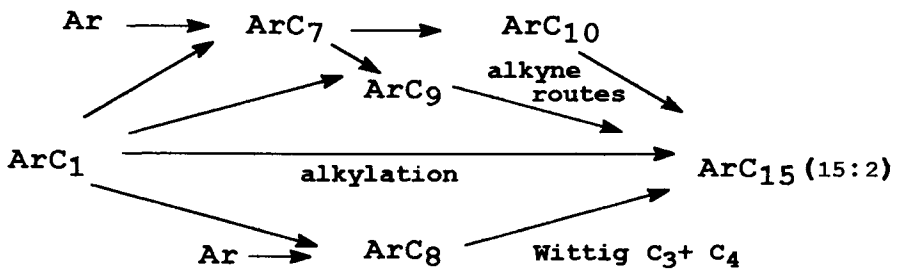
The phosphonate used in the Horner-Emmons reaction in the precediing synthesis was also converted, by reaction with tetradecanal, to the 1(E)-alkene which was then hydrogenated, hydrolysed and demethylated to give (15:0)-anacardic acid. Wittig methodology has been used for the synthesis of the 8-monenes of the C_{17} urushiol and thitsiol series, the synthon route being ArC_1-->ArC_8-->ArC_{17}. The strategy has also been generalised with the same ArC_8 intermediate (an 8-aryloctanal) for the synthesis of C_{15} 8,11-dienes described in 13.5.3 (iii) (ref. 152).

13.5.3 Dienes

(i) Synthon Approaches

Considerable advances have been made in the synthesis of the polyunsaturated

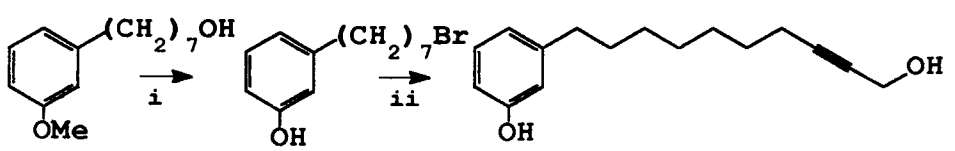
phenolic lipids. The increase in unsaturation confers more pronounced physiological properties and the role of stereochemical configuration is also a matter of some interest in polymer chemistry.
In the cardanol, cardol, urushiol and anacardic acid series, all of which have 8,11-unsaturation, two alternative synthons namely C_5 and C_6 units may be involved in alkyne routes for the formation of the second double bond. A summary is shown of alkyne, Wittig, and alkylation routes.

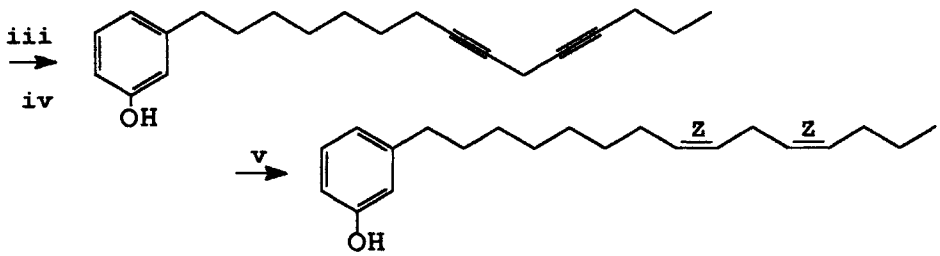


In procedures based on alkyne chemistry directed towards compounds with unsaturation commencing at the 8-position, the ArC_7 intermediates are the same essentially as used for monoene syntheses, while the ArC_9 unit contains a terminal alkyne grouping and the ArC_{10} is an aryl dec-2-yn-1-ol. In the cardanol and cardol series this latter synthon was obligatory since it was found that in the formation of 3-(non-8-ynyl)phenol from 3-(7-bromoheptyl)phenol and lithium acetylide a partial isomerisation occurred (refs. 146, 147) giving the 2-yne.

(ii) Acetylenic Routes

(15:2)-Cardanol, 3-[(ZZ)-pentadec-8,11-dienyl]phenol was obtained therefore by the ArC_7-->ArC_{10}-->ArC_{15} sequence as shown in the scheme (ref. 96). It was found unnecessary to protect the phenolic OH group in the latter stages. However, it was essential to use an HO-protected prop-2-yn-1-ol (as the ethyl vinyl ether adduct) to avoid interaction of the ArC_7 bromide with the OH group resulting in formation of an acetylenic ether although it has been stated that the dianion from prop-2-yn-1-ol only reacts at the 'hard' centre (C-nucleophile) rather than the 'soft' centre (O-nucleophile) (ref. 148).



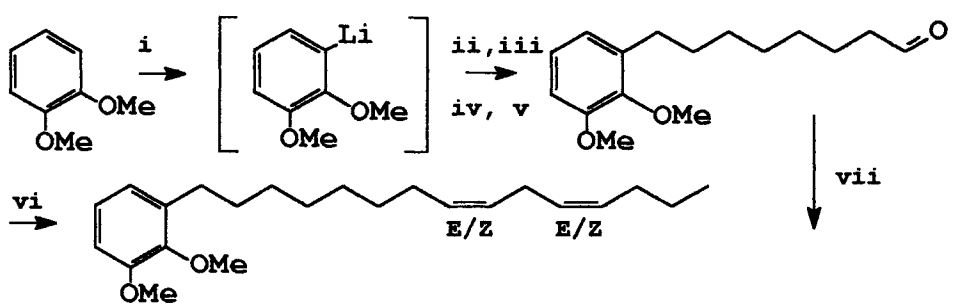


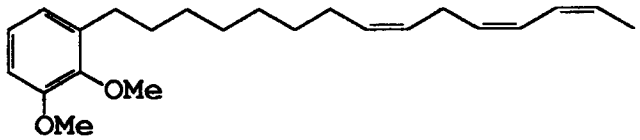
Reagents (i) BBr_3 , CH_2Cl_2 , (-78°C) (ii) $LiC{\equiv}CCH_2OCH(Me)OEt$; MeOH ;(iii) PBr_3 , Py. ; (iv) $BrMgC{\equiv}CC_3H_7$, CuCl , THF ;(v) Pd-$BaSO_4$ / H_2, quin.

Reaction of the ArC_{10} unit with 1-pentynylmagnesium bromide occurred smoothly in tetrahyrofuran containing cuprous chloride without formation of allenic impurities. An analogous type of route was used for the synthesis of 1,3-dimethoxy-5-[(ZZ)-pentadec-8,11-dienyl]benzene, (15:2)-cardol dimethyl ether (ref. 105). For the synthesis of (15:2)-urushiol, 1,2-dihydroxy-3-[(ZZ)-pentadec-8,11-dienyl]benzene and its dimethyl ether, 7-(2,3-dimethoxyphenyl)heptyl bromide and the corresponding 2,3-dihydroxy compound, obtained by demethylation with boron tribromide, have been used (ref. 149).

(iii) Wittig Routes

Alternatively, Wittig methodology has been invoked for the synthesis of 1,2-dimethoxy-3-[pentadec-8,11-dienyl]benzene athough the configurational specificity was not mentioned (ref. 150,151). 8-(2,3-Dimethoxyphenyl)octan-1-al, obtained either from ozonolysis of the natural product, or formed from 2,3-dimethoxyphenyllithium and the hemidiethyacetal of 1,6-diformylhexane followed by hydrogenolysis, was reacted with the bisphosphoran from 1,3-dibromopropane and then butanal.

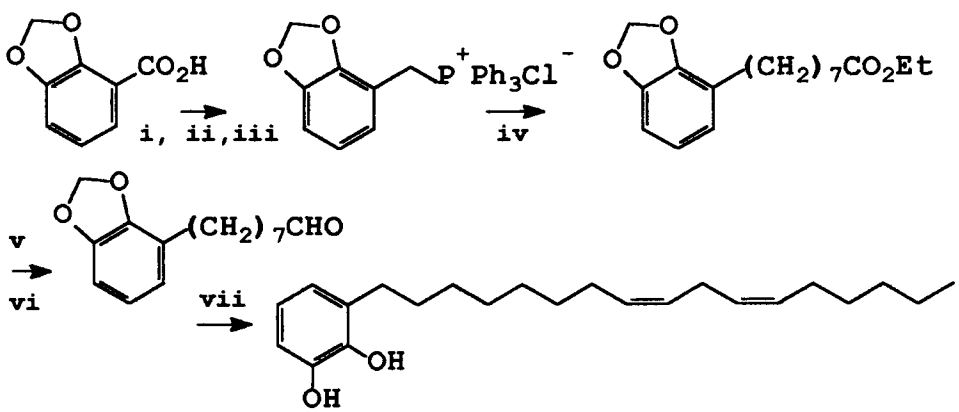




But-2-enal under similar conditions was stated to give the 8,11,13-triene dimethyl ether by reaction of the same bisphosphoran with 8-(2,3-dimethoxyphenyl)octanal and but-2-enal.

Reagents (i) Li, THF : (ii) $OHC(CH_2)_6CH(OEt)_2$; (iii) NH_4Cl ; (iv) Pd-C/ H_2 ; (v) H_3O^+ ; (vi) $Ph_3P{=}CHCH_2CH{=}PPh_3$; C_3H_7CHO ; (vii) $Ph_3P{=}CHCH_2CH{=}PPh_3$; $MeCH{=}CHCHO$

The Wittig reaction has been used in other methodological advances in regiospecific syntheses of urushiols and thitsiols (ref.152), such as 1,2-dihydroxy-3-[(ZZ)-heptadeca-8,11-dienyl]benzene and 1,2-dihydroxy-4-[(ZZ)-heptadeca-8,11-dienyl]benzene respectively. The synthon sequence was ArC_1–>ArC_8–>ArC_{17} diene which is shown for the urushiol compound as follows starting with 2,3-methylenedioxybenzoic acid.



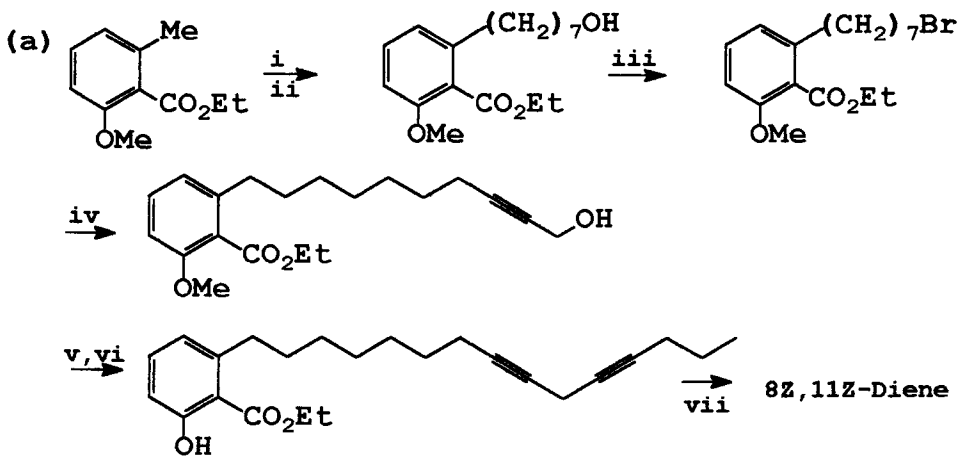
The thitsiol, 1,2-dihydroxy-4-[(ZZ)-heptadeca-8,11-dienyl]benzene was similarly derived from 3,4-methylenedioxybenzoic acid.

Reagents (i) LAH, Et_2O ; (ii) $SOCl_2$, Py. : (iii) PPh_3 , MeC_6H_5 ; (iv) BuLi , THF, $OHC(CH_2)_5CO_2Et$; Pd-C/ H_2 ; (v) LAH, Et_2O ; (vi) PCC, CH_2Cl_2 ; (vii) $I^- P^+Ph_3(CH_2)_2CH{=}CH(CH_2)_4Me$, BuLi , THF ;(viii) AcOH, H_2O , Δ .

The C_9 reactant used for step (vii) was synthesised from lithio-1-heptyne by reaction with oxirane followed by catalytic reduction to the Z-alkene, non-3-enol, and conversion to the 1-iodide by reaction with chlorotrimethylsilane in acetonitrile containing lithium iodide.

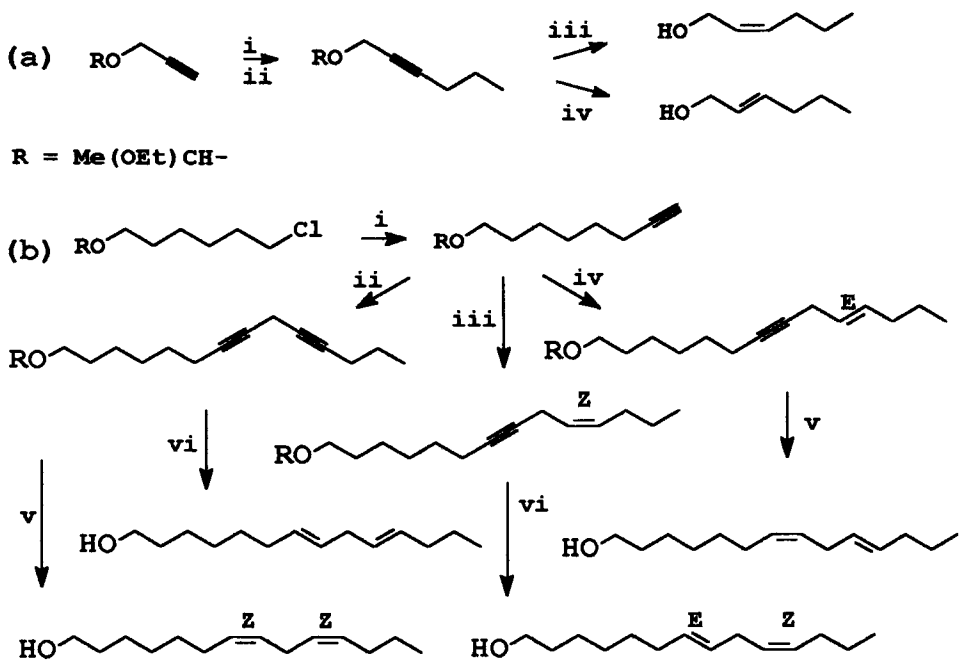
(iv) Alkylation Route

For the anacardic acid series, the synthon sequence, ArC_7--> ArC_{10}--> ArC_{15}, depicted in route (a), was obligatory since in the approach starting with the terminal alkyne ArC_9 intermediate, attempts to form the alkynylmagnesium bromide, resulted in a competing reaction of ethyl magnesium bromide with the ethoxycarbonyl group in the ring giving a ketone. The alkylation route (b) based on the use of ethyl 2-methoxy-6-methylbenzoate with 1-bromotetradec-7,10-diyne (obtained by a procedure described in the scheme following the one below) was also effective (refs. 114, 117). The C14 bromide required was obtained from the alcohol by reaction with chlorotrimethylsilane in acetonitrile containing lithium bromide (ref. 153).



Reagents (a) (i) $LiNiPr_2$, $Cl(CH_2)_6OCH(Me)OEt$; (ii) 4-TSA, MeOH ; (iii) PBr_3 Py. ; (iv) $LiC{\equiv}CCH_2OCH(Me)OEt$, HMPT , THF; 4-TSA, MeOH ; (v) PBr_3 , py. ; (vi) $BrMgC{\equiv}CC_3H_7$, CuCl , THF ; (vii) Pd-$BaSO_4$ / H_2 , quin.
(b) $LiNiPr_2$, $HC{\equiv}C(CH_2)_6Br$; (ii) EtMgBr ; (iii) $LiNiPr_2$, $Br(CH_2)_6C{\equiv}CCH_2C{\equiv}CC_3H_7$, HMPT (iv) Pd-$BaSO_4$ / H_2 , quin.

The strategy involving the use of a C_{14} intermediate has been examined with the four stereoisomeric dienes, namely the 8(E), 11(E); 8(E), 11(Z); 8(Z), 11(E) and 8(Z),11(Z) compounds, and their derivation is shown in the reactions depicted. This work (refs. 154, 155, 156) is incomplete but considerable progress has been made. Because of the ready availability of the intermediates 1,6-hexanediol and prop-2-yn-1-ol, the Wittig reaction requiring a C_7 or C_8 component has been less attractive. The synthesis of E and Z hex-2-enol is given in route (a) and their use in obtaining the required C_{14} stereoisomers in route (b).



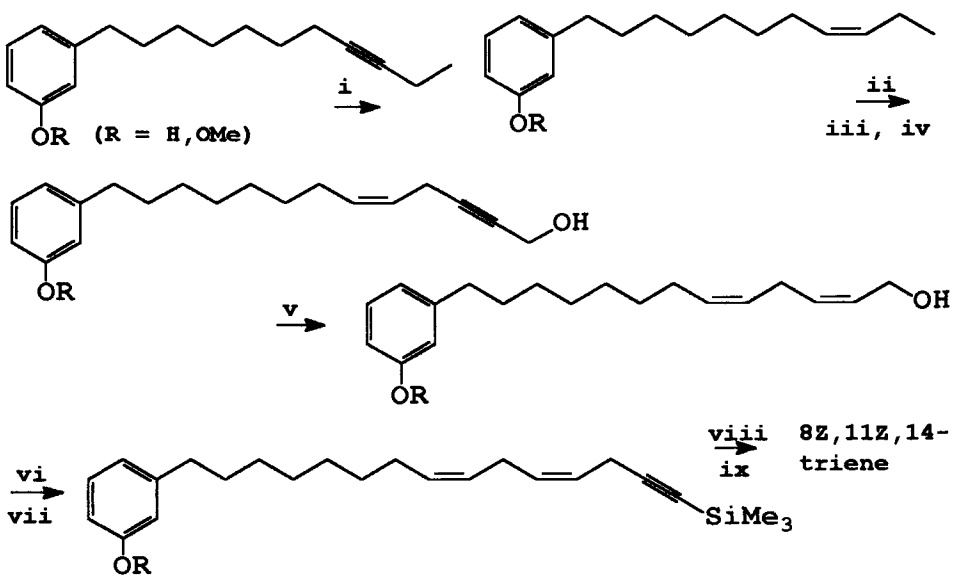
Reagents (a) (i) $LiNH_2$, C_3H_7Br ; (ii) 4-TSA, MeOH ; (iii) Pd-C/ H_2 , quin. ; (iv) Li/ NH_3 .
(b) (i) $LiC{\equiv}CH$, HMPA, THF; (ii) EtMgBr, CuCl , $BrCH_2C{\equiv}CC_3H_7$;
(iii) EtMgBr, CuCl , (Z) $BrCH_2CH{=}CHC_3H_7$; (iv) ditto,with (E)-alkene ; (v) Pd-$BaSO_4$, quin. ; (vi) Li, NH_3 .

13.5.4 Trienes

(i) Synthons

Whilst it might be thought that synthesis of trienes would be a natural extension of the corresponding diene approach shown in 13.5 (i), the desired unsaturated C_5 intermediate, pent-1-yne-4-ene simply having the required vinylic group, this method proved to be non-specific since at the catalytic hydrogenation stage this group was as susceptible to reduction as an internal alkyne triple bond with catalysts then available. In this respect the synthesis of phenolic lipids presents a more intractable problem than that of the polyethenoid fatty acids. Model experiments with nona-5-yne-8-ene readily demonstrated this difficulty. A modified synthon appoach was adopted, namely ArC_7-->ArC_{10}-->ArC_{13}-->ArC_{15}, as shown for the synthesis of (15:3)-cardanol (ref. 3).

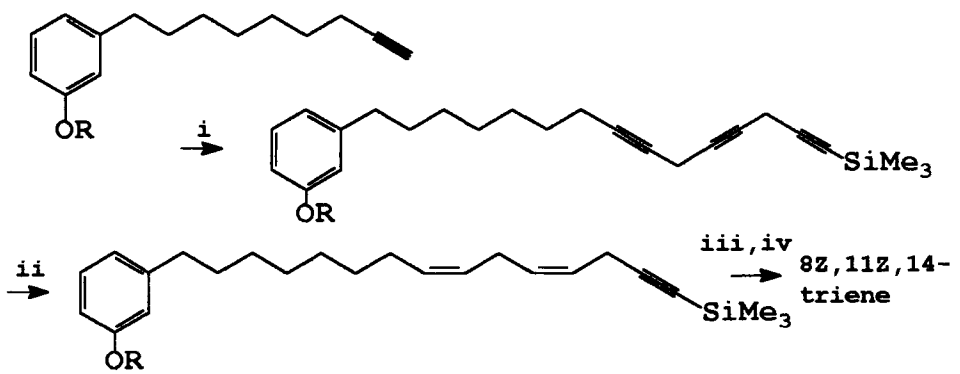
(ii) Acetylenic routes



Reagents (i) Pd-C/ H_2 , quin. ; (ii) PBr_3 , py. ; (iii) $BrMgC{\equiv}CCH_2OThp$, CuCl, THF ;4-TSa, MeOH ; (v) Pd-C/ H_2 , quin. ; (vi) PBr_3 , Py. ; (vii) $BrMgC{\equiv}CSiMe_3$, CuCl, THF ; (viii) $AgNO_3$; (ix) Pd-$BaSO_4$, quin.

The availability of the $SiMe_3$ group to protect the terminal alkyne group in a C_5 intermediate such as 1-trimethylsilylpenta-1,4-diyne or 1-bromo-6-trimethylsilylhexa-

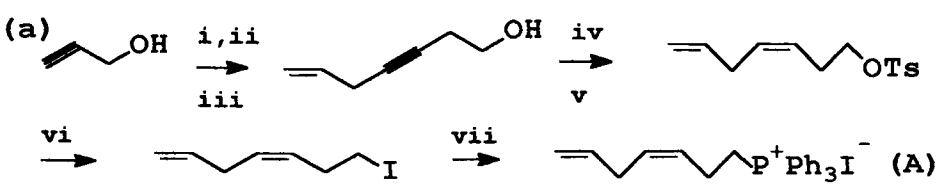
-2,5-diyne offered possibilities since in the presence of this terminal grouping, reduction was found to occur preferentially at an internal alkyne (ref. 157) thus enabling the original diene synthon strategy to be extended to the triene series in the following way (ref. 158).

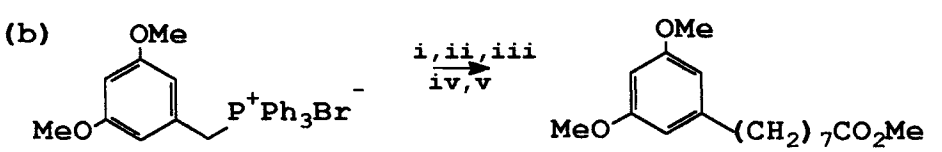


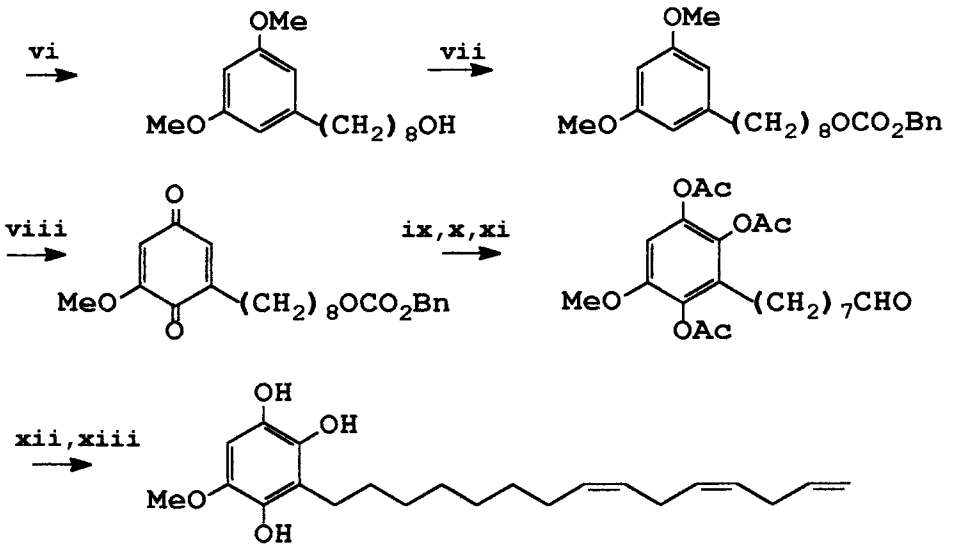
Reagents (i) EtMgBr , CuCl, $BrCH_2C{\equiv}CCH_2C{\equiv}CSiMe_3$; (ii) Pd-$BaSO_4$ / H_2. quin. ;(iii) Pd-$BaSO_4$ /H_2 , quin. ; (iv) $AgNO_3$.

(iii) Wittig Routes

There has been a significant development towards the regiospecific synthesis of a triene by means of the Wittig reaction. The germination stimulant 5-methoxy-3-[(ZZ)-pentadeca-8,11,14-trienyl]-1,2,4-trihydroxy-benzene, exuded by *Sorghum bicolor* for the seeds of *Striga asiatica*, (a parasite of the legumes, sorghum, maize and millet), has been synthesised (ref. 159). The approach involved the synthon sequence ArC_8--> ArC_{15}, the C_7 component (route a) being prepared by the allylation of 3-butyn-1-ol and its attachment in route (b).

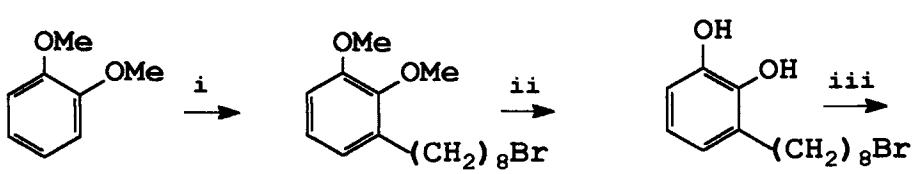


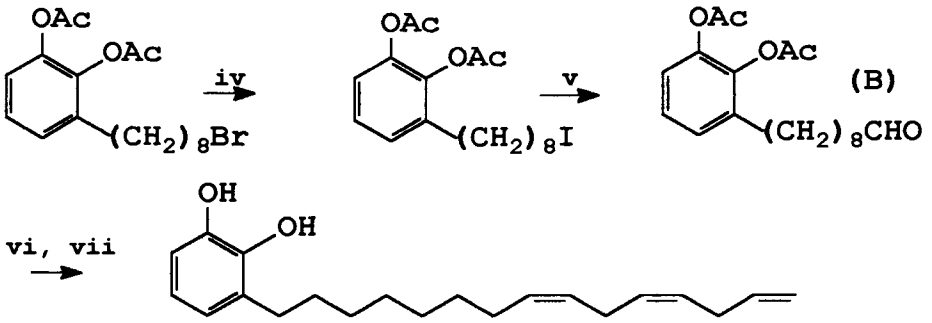




Reagents (a) (i) 4-TSA, DHP ; (ii) EtMgBr, CuCl , CH_2=$CHCH_2Br$; (iii) 4-TSA, MeOH ; (iv) Pd-$BaSO_4$/ H_2 , py. ; (v) 4-TsCl, py. ; (vi) NaI, Me_2CO ; (vii) $P^+Ph_3I^-$.
(b) BuLi, THF; (ii) $OHC(CH_2)_5CO_2Et$; (iii) NaOH, H_2O, MeOH ; (iv) Pd-C/ H_2 ; (v) MeOH, H^+ ; (vi) LAH, Et_2O ; (vii) $ClCO_2Bn$, py. ; (viii) CrO_3, AcOH, H_2O ; (ix) AcOH, H_2SO_4 ; (x) PCC, NaOAc, CH_2Cl_2 ; (xi) BuLi, THF, HMPT, (A) ; LAH, THF.

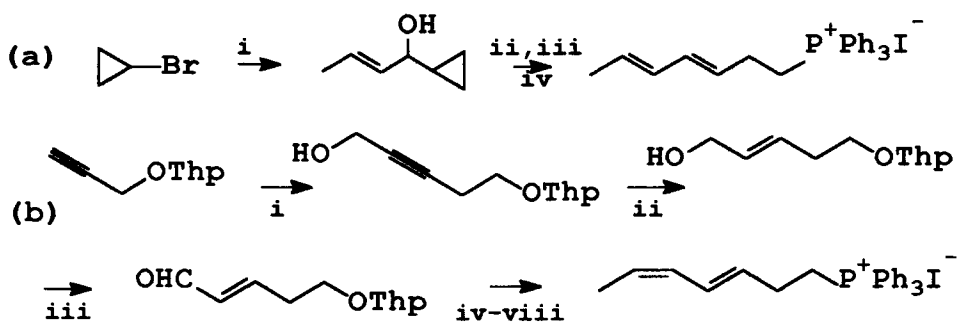
The same intermediate (A) has led to the synthesis of urushiols by Japanese workers and with 3-(8-oxooctyl)veratrole has been employed firstly for the synthesis of the dimethyl ethers of 3-[(8Z,11Z,14)-pentadecatrienyl- and 3-[(8Z,11E,13E)-pentadecatrienylurushiol (ref.160). Secondly a related procedure (ref. 161), has been used for the free phenol, 8(Z),11(Z),14-urushiol by way of the diacetate of the ArC_8 intermediate employed earlier, (ref. 150, 151) namely 3-(8-oxooctyl)catechol diacetate. This was prepared by the modified synthetic route depicted rather than by semi-synthesis from a natural product.





Reagents (i) BuLi, $Br(CH_2)_8Br$; (ii) BBr_3 ; (iii) Ac_2O, py. iv) NaI ; (v) DMSO ; (vi) (A), BuLi ; (vii) LAH , tBuOH.

In addition to reaction of the C_8 intermediate (B) with [(3Z,6)-heptadienyl]-triphenylphosphonium iodide to give 3-[(8Z,11Z,14)-pentadecatrienyl]catechol, the other main constituent of 'urushiol', namely 3-[(8Z,11E,13Z)]-pentadecatrienylcatechol has been obtained by reaction of (B) with [(3E,5Z)-heptadienyl]triphenylphosphonium iodide. Route (b) gives the synthesis of the latter compound (ref. 160). It incorporates the apparently successful and key reduction of an internal alkyne in the presence of a terminal vinyl group. Route (a) depicts the scheme for the isomer [(3E,5E)-heptadienyl]phosphonium iodide. Both were reacted with (B) as for the 8Z,11Z,14-compound.

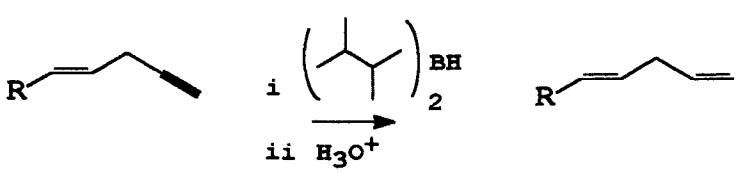


Reagents (a) (i) Mg, MeCH=CHCHO , (ii) HBr, CH_2Cl_2 ; (iii) NaI ; (iv) PPh_3 .
(b) (i) EtMgBr, CH_2O ; (ii) LAH ; (iii) PCC ; (iv) $EtP^+Ph_3Br^-$, BuLi ; (v) H_3O^+ ; (vi) CBr_4 , PPh_3 ; (vii) NaI ; (viii) PPh_3 , MeCN.

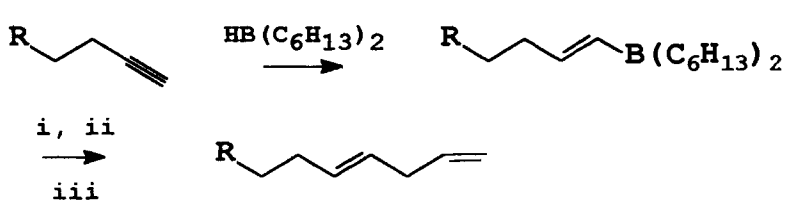
(iv) Boration Methodology

For the alkylation route, applicable particularly to the anacardic and orsellinic acid series, the synthesis of the C_{14} side chain intermediate lends itself to obtaining not only the 8(Z),11(Z),14-triene but also the other three stereoisomers. Although terminal trimethylsilylation affords some steric control in the final stage of selective catalytic hydrogenation, advances in boration methodology have also enabled a greater range of graded selectivity to be introduced (ref. 135).
With hydride reagents such as 'dibal', Z-alkenes can be selectively obtained from alkynes in the phenolic lipid series (ref. 162), and related series of boron reagents greatly supplement the chemical methods of selective reduction and alkylation. This selectivity has been achieved by the use of less reactive dialkylboranes such as bis(3-methyl-2-butyl)borane (di-isoamylborane), bis(2,3-dimethyl-2-butyl)borane (thexylborane), 9-borabicyclo[3.3.1]nonane (9-BBN) and dicyclohexylborane. Some applications in the polyethenoid field have been summarised (refs. 135, 163) and the synthesis of alkenyl compounds generally reviewed (ref. 164). By the use of dibromoborane dimethylsulphide, an internal alkyne can be reduced selectively (ref. 165) as for example in the following way (R = n-alkyl).

With bis(di-isoamyl) borane reduction of a terminal alkyne is selectively effected as shown (ref. 166).

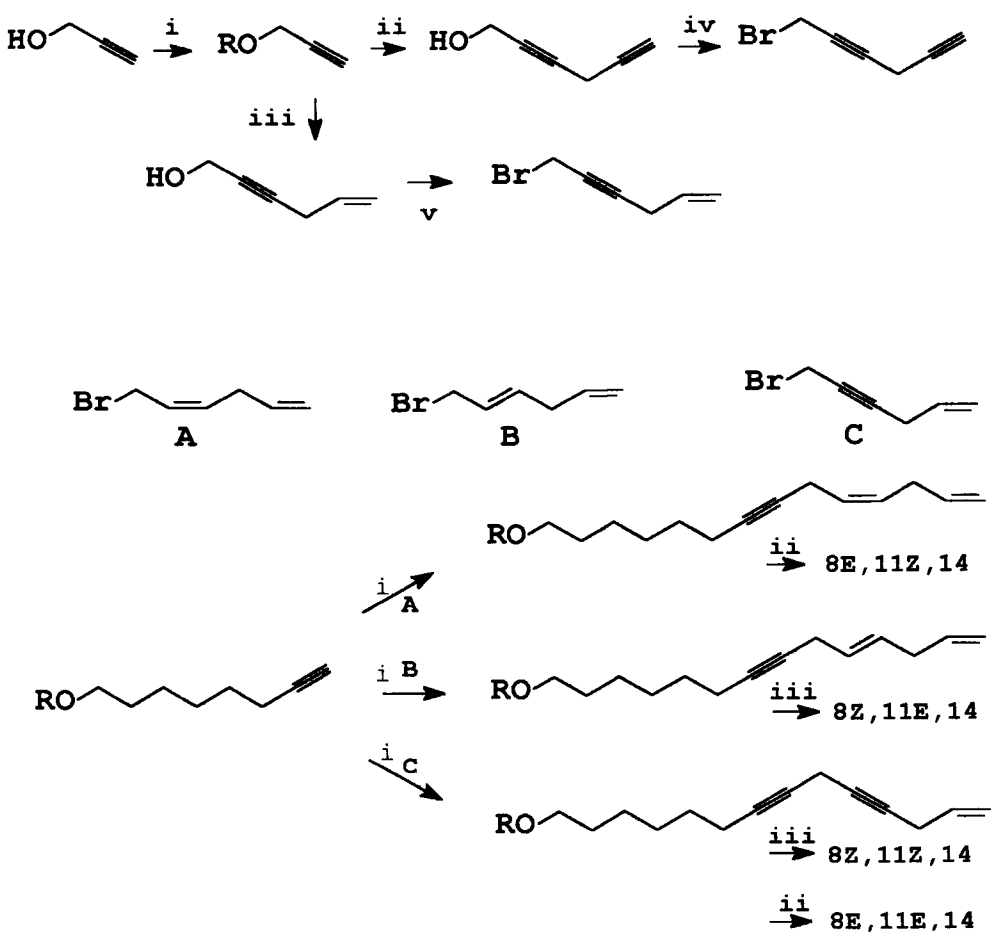


Selective alkylations can be achieved by the use of an intermediate involving bis (cyclohexyl) borane, as follows.



Reagent (i) NaOMe ; (ii) $CuBr.SMe_2$ (-15°C) ; (iii) CH_2=$CHCH_2Br$.

The 9-BBN reagent can be used similarity.
In the triene series for the synthesis of the stereoisomers of (15:3)-anacardic acid, namely the 8(Z),11(Z),14; 8(E),11(E),14; 8(Z),11(E),14; and 8(Z),11(E),14 compounds by the alkylation of the ArC_1 intermediate (ethyl 2-methoxy-6-methybenzoate) with a C_{14} component these boration methods have been of value as an addition to selective catalytic hydrogenation and the use of terminal trimethylsilylation (ref. 167). At this stage for synthetic purposes the selective reductive use of boration methods has been mainly exploited. The chief use of combined addition/alkylation procedures is for obtaining 8(E), and 11(E) isomers. For this, the sequence of synthons, for the side chain has to follow the different series, Ar_9-->ArC_{12}-->ArC_{15}.
The following scheme summarises some of the methods used to construct the C_{14} side chain component. The required C_6 synthons were prepared by route (a) which led to compound C. Catalytic reduction of this with Pd-$BaSO_4$ in the presence of quinoline gave compound A and chemical reduction afforded compound B. The usage of A,B and C is depicted in route (b).

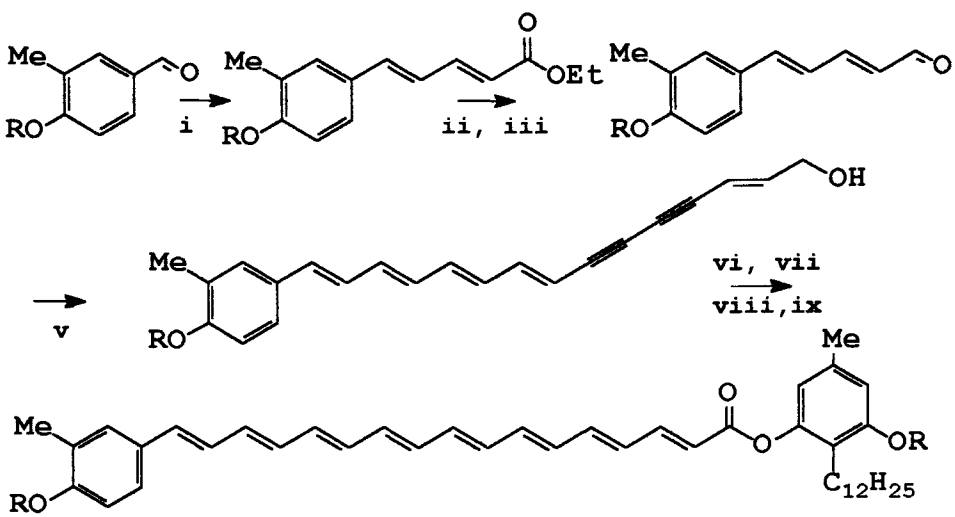


Reagent (a) (i) CH_2=CHOEt, 4-TSA ; (ii) EtMgBr, CH_2=$CHCH_2Br$; (iii) 4-TSA MeOH ; (iv) TMSCl, LiBr; (v) PBr_3 , py.
(b) (i) EtMgBr, CuCl, THF, A, B or C ; (ii) Li, NH_3 ; (iii) Pd-$BaSO_4$ / H_2 , quin.

Since cardanols can be obtained from anacardic acids and cardols from orsellinic acids, the methods outlined have a general applicability to a range of phenolic lipids. Reference has been made largely to the phenols of the Anacardiacae but the methods are likely to be applicable to other phenolic systems, and those with methylene-interrupted structures at different side-chain positions. Alkynes and phosphorans have both proved invaluable in synthetic studies but attention should be drawn to the very elegant use of allenic compounds in the polyethenoid (arachidonic) series (ref. 168) which has a potential application with phenolic lipids. Methods for the synthesis of leukotrienes are also relevant for the methylene group-interrupted structures of phenolic lipids (169).

13.5.5 Polyenes

There seems to be no inherent reason why the preceding methods should not be applicable to tetraenes and higher members of the non-conjugated phenolic lipids. So far no such syntheses have been described although in the conjugated series the highly unsaturated compound flexirubin has been obtained as shown (ref. 74)



Reagent (i) $Ph_3P^+CH_2CH$=$CHCO_2Et$ X^-, BuLi ; (ii) LAH ; (iii) MnO_2 ; (iv) $Ph_3P^+CH_2CH$=$CHC{\equiv}CH$ Br^- , (from CH_2=$CHCH(OH)C{\equiv}CH$), Buli ; (v) NaOBr, $BrC{\equiv}CCH$=$CHCH_2OH$; (vi) MnO_2 ; (vii) $Ph_3P^+CH_2CO_2C_6H_2(Me)(OMe)C_{12}H_{25}$ Br^- ,BuLi ; (viii) Pd-$BaSO_4$ /

H_2 ; (ix) I_2 (isomerisation).

13.6 INDUSTRIAL PHENOLIC LIPIDS

13.6.1 Cashew Phenols (Anacardiaceae) and Lacs (Rhus species)

Anacardiaceae

The cashew tree, *Anacardium occidentale* is an unusual member of the species in that it is a source of phenolic acids, mono and dihydric phenols and has attracted great technical interest. To a lesser extent urushiol from Rhus species has many technical applications in the far East. The chemistry of these groups has been reviewed with respect to their structural elucidation (ref. 2). The phenolic lipid cashew nut-shell liquid, (CNSL), is a semi-synthetic by-product of industrial processing which is directed primarily to produce the cashew kernel (refs.170, 171). Although originally indigenous to Brazil and first described in 1558 by the French monk A. Thevet, the cashew tree is now grown in many parts of the equatorial and sub-equatorial regions, including areas such as Thailand, Indonesia and Australia. Wide aspects of the cultivation of the cashew have been discussed (ref.172). The unusual nature of the raw cashew nut, an external seed of the cashew apple, is shown in Fig. 1. It is kidney-shaped and approximately 2-3 cm in length. The shell comprises some 50% of the weight of the raw nut, the kernel represents 25% and the remaining 25% consists of natural cashew nut shell liquid. This is a reddish brown liquid comprising the anacardic acids (Table 13.1) the cardols (Table 13.2) a smaller proportion of 2-methylcardols, cardanols (Table 13.3) and polymeric material.

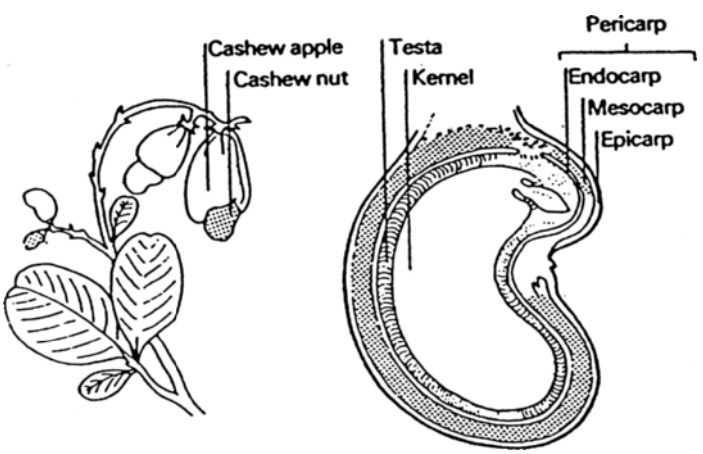


Fig 1. A cashew branch and cross-section of a cashew nut

(Adapted from ref. 2 by kind permission of the Roy. Soc. Chem.)

TABLE 13.4 ESTIMATED WORLD PRODUCTION of RAW CASHEW NUTS (1000tons) of MAJOR and SOME MINOR PRODUCERS

YEAR	WORLD	MOZAMBIQUE	TANZANIA	INDIA	BRAZIL	KENYA	MADAGASCAR
1955	125	54	18	47	2	2	-
1960	160	63	37	50	2	5	-
1965	280	119	65	50	4	8	-
1970	370	115	110	95	31	13	1
1975	470	166	115	110	44	22	5
1980	535	145	122	130	84	30	10
1985	750	215	135	130	207	35	15
1990	910	235	222	130	229	40	20
1995	1,000	255	240	140	260	45	25
2000	1,120	300	250	150	284	50	30
2,005	1,260	350	280	175	290	50	40

(By kind permission of J.G. Ohler, ref.172, Royal Tropical Institute)

TABLE 13.5 CHANGES in WORLD CASHEW NUT PRODUCTION (tons)

	1970	1980	1990
Africa	319,000	157,000	114,800
Asia	61,000	145,700	229,500
Latin America	27,500	87,000	127,000
Total	**407,000**	**390,200**	**471,300**

The kernel itself contains a rich source of protein and a glyceride oil having chiefly the components fatty acids palmitic and oleic acids. In world production the % of cashew is comparable to that of hazel and almond nuts. Table 4 gives projected estimates of the world production of cashew from figures available in 1978-9 (ref. 172).
A rather more conservative estimate of the trend in world cashew nut production has been made (ref. 173) which takes account also of the drop in African production in the early eighties and the rise in Latin American output. These figures are shown in Table 5.

Rhus species

13.6.2 Extraction

Although the production of lacs from *Rhus vernicifera* and relatives is a smaller volume industry on account of the fact that the product is solely the latex, the current production of 'urushi' is probably more than 3,000 tonnes in China and less in Japan and other Far Eastern countries. The industry is of great antiquity and has probably been in operation for the past 40,000 years. In more recent years the production of *Anacardium occidentale* has been introduced in Hainan the only warm enough region in that country suitable for its cultivation.

(i) Industrial Processes

The phenolic lipids of *Anacardieum occidentale* have been commercially exploited (ref.174) and those in *Rhus vernicifera* to a lesser extent. Most of the technical cashew nut shell liquid (CNSL) which results from industrial processing is and has been employed as a phenolic source for formaldehyde polymerisation the products from which in compounded form have been the basis for friction dusts widely used throughout the world in vehicle brake and clutch linings (ref.175). Urushiol has had use over many centuries in the art of Japanese lacquering (ref. 176) and in more recent years has been sometimes supplemented with CNSL. Chemical uses are referred to later.

(ii) Cashew Processing

The primary objective in cashew processing has been to recover the desirable kernel. The by-product, technical cashew nut-shell liquid, later became of interest as a raw material for friction dusts with superior properties to previous materials which were based on composites of phenol/formaldehyde resins with highly unsaturated glyceride oils. Because of its intractability the cashew nut has been termed in Mozambique, the devil's nut Most CNSL world-wide is now extracted or 'cracked' by an automated process (refs. 170, 177), the 'hot CNSL bath' method, developed comparatively recently, in which raw humidified cashew nuts are submerged in technical CNSL on a slowly-travelling conveyer belt and heated to

180-190°C. The scheme used is illustrated in fig 2. (ref. 171).

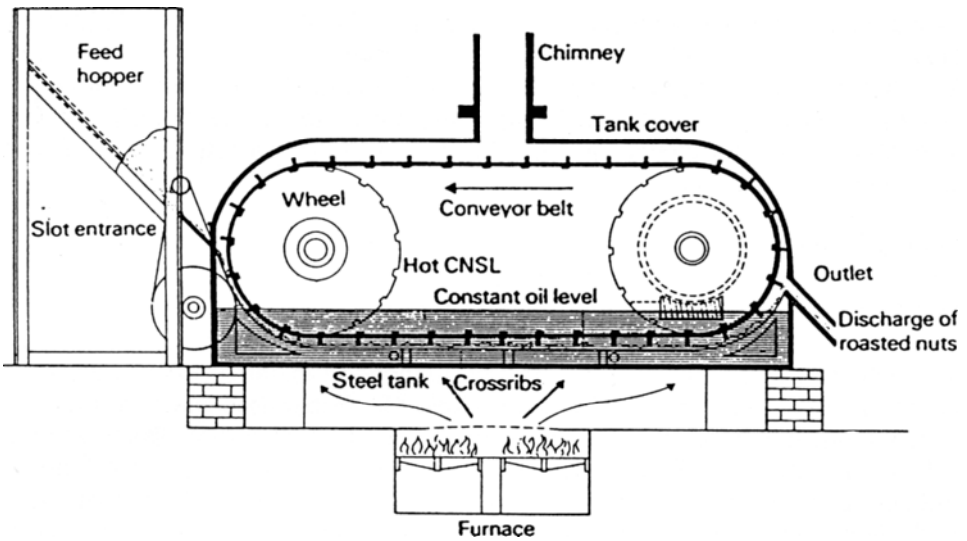


Fig. 2. An early hot CNSL plant for processing cashews (adapted from ref. 171 by permission of HMSO and Society of Chemical Industry)

The anacardic acids in the natural CNSL of the raw nut shell are decarboxylated and the resultant cardanol liberated supplements the hot technical CNSL in the bath through the bursting of the outer shell and, after an ideally short period, flows continuously out of the system. The spent processed nuts with the inner shell still intact also pass out of this system and after removal of the superficial CNSL by centrifugation or adsorption are shelled by an automatic procedure in Brazilian and East African technology or manually in Indian practice.

The removal of the inner shell has to be accomplished with retention of the intact kernel. In the original Sturtevant-Tropical Products Institute process for the removal of the inner shell, the brittle semi-shelled nut is projected against a hard steel plate and the kernel separated centrifugally from shell fragments. In the Oltremare process the shell is cut and the two halves removed while in labour-intensive India a manual light hammering method is employed in which the recovery of intact kernels is actually higher than by other methods. Although Table 5 indicates, from the tonnage of raw nuts cultivated, that the theoretical yield of natural CNSL would be expected to be in excess of 100,000 tonnes, availability of technical CNSL from hot oil bath and other processing methods falls far short of this. The world production for 1976 was 25,189 tons, Brazil and Mozambique contributing 10,670 and 8,300 tonnes respectively, while in 1990 the total was 32,426 tonnes, the bulk of which, 26,304 tonnes, came from Brazil. Generally it is considered that the yield from hot oil bath processing is probably only 40% of the theoretically available (that

is 10% on the weight of the nut). The process requires skilled operation and excessive heating can result in thermal polymerisation and an unacceptable product (ref. 178).
In recent years cold cutting of cashews has been examined (ref. 179). By cooling, preferably to sub zero temperatures, the cashew can be embrittled and cracked during which however the kernel is generally also fractured and is carefuly removed. Solvent extraction of the residual comminuted shell affords natural CNSL in yields of between 20-25%. By catalytic decarboxylation of this natural CNSL at a lower temperature to avoid polymerisation (ref. 180) technical CNSL can be recovered in nearly theoretical yield (25%) compared with approximately 10% by the hot oil bath process. The two separate stages involved are offset by the considerably greater yield recovered but the very low yield of whole kernels removes any commercial viability at the present time. A further development, suggested some years ago, has been supercritical fluid extraction of natural CNSL and the usage of undecarboxylated natural CNSL (ref. 117). Indeed in the case of Indian raw cashews supercritical CO_2 extraction afforded 18.7% phenolic lipids (ref.181) and CO_2 extraction in conjunction with the cosolvent isopropanol has also been used (ref. 182).
Alternative procedures to simplify the production of kernels and CNSL separately could lie in biological methods designed either to obtain a non-porous shell for recovery of the kernel or a kernel-less nut for obtaining CNSL. Genetic methods to modify a species and its secondary metabolic products have been discussed (ref. 183).

(iii) Urushiol processing

The recovery of the sap from the tree *Rhus vernicifera* to obtain urushiol has been described in the classical process (ref. 184, 185) and with regard to recent developments (ref. 186). It is a totally different operation from that with *Anacardium occidentale*, and not unlike that in the process for natural rubber. The name derives from 'kiurushi', the Japanese word for 'sap' which is a primary product of the tree. Much less of this very ancient material is now processed in the original region of Sendai, Japan and the main industry is based in China with some in Korea and Japan. In northern Vietnam and Taiwan, a source of lac is *Rhus succedanea* and in Thailand and Burma, *Melanorrhoea usitata*.

13.6.3 Separation of Phenolic Lipids

Cashew Phenols

In general phenolic lipids have been separated from natural sources for compositional studies and structural determination by solvent extraction and chromatographic techniques. The individual component phenols of the major phenolic lipid (CNSL) from *Anacardium occidentale* have assumed some significance in certain chemical applications and detailed purification processes

have been developed. Although for some industrial uses the mixture of phenols in the natural or technical product is quite satisfactory, in surface coatings and in synthetic chemical applications the dark colour of technical CNSL is unacceptable. and is desirably removed or the use of the separated component phenols may prove necessary. The dark colour is partly ascribable to brown impurities dissolved from the shell by the solvent action of the phenols during processing. A number of distillation, chemical/distillation, physical and chromatographic methods have been introduced.

(i) Molecular Distillation

Molecular distillation with a multi-stage still provides the only type of distillation method suitable for the separation of the cardanol and cardol (no separation of the three unsaturated constituents was observed) (ref. 187). With a ten-stage laboratory rotary molecular still technical CNSL afforded a 60% yield of almost colourless cardanol devoid of cardol. Conventional fractional distillation and spinning band techniques are ineffective since the prolonged heating involved merely causes extensive polymerisation and a poor throughput. By the use of wide-bore equipment and short-path stills excellent recoveries may be made by conventional high-vacuum distillation giving products substantially free of colour although the extent of separation of the two main phenols is by no means complete as in molecular distillation.

(ii) Organic Base addition and Vacuum Distillation

For the separation of cardanol and cardol without resorting to molecular distillation it is possible to use a combined chemical purification/vacuum distillation technique. The addition of a selected amine to technical CNSL resulted in preferential interaction with the more acidic cardol and considerably purer cardanol was then recovered by high vacuum distillation of the reaction mixture (ref. 188). Typically, technical CNSL containing cardanol (86.9%), cardol (10.3%) and 2-methylcardol (2.3%) upon treatment with diethylenetriamine (0.5mole) and reaction for 24 hours at ambient temperature gave by vacuum distillation a 62.3% recovery of a product containing cardanol (97.9%) and cardol (2.0%).

(iii) Selective Mannich reaction and Vacuum Distillation

Selective reaction of cardol in preference to cardanol under Mannich reaction conditions with diethylenetriamine (or 4-aminobutane) and aqueous formaldehyde in methanolic solution resulted in the separation, as a lower layer, of the cardol in the form of a low polymeric Mannich base. Recovery of cardanol from the upper layer and high vacuum distillation afforded pure material containing only traces of 2-methylcardol (ref. 189). Thus technical CNSL (1 mole; average mol. wt. 303g) with 40% aqueous formaldehyde (1.2 mole; CH_2O) and diethylenetriamine (0.125 mole) in methanol (1250ml) afforded after 30mins a dark methanol-insoluble lower

layer and a lighter upper layer which after solvent recovery and work-up gave cardanol (63% yield) containing a trace of cardol, some 2-methylcardol, which does not undergo the Mannich reaction, some oligomeric and coloured impurities. High vacuum distillation furnished cardanol substantially pure containing traces of 2-methylcardol.

(iv) Phase Separation of cardanol and cardol

The desirability of having a non-distillation method for larger scale work which would separate the dihydric from the monohydric phenols and permit the recovery of both cardanol and cardol rather than the loss of the latter as a Mannich base product has led to a phase separation method (ref. 190, 191). In this, technical CNSL is distributed between the two immiscible phases of a diol and light petroleum. As a result cardanol enters the upper petroleum phase while cardol and 2-methylcardol are found in the lower diol phase. In this way a highly selective procedure with butane-1,4-diol or pentane-1,4-diol afforded cardanol of greater than 99% purity.

13.6.4 Chromatographic Separation of Cardanol and Cardol

Although for large scale use, distillation processes are obligatory, flash chromatographic methods laboratory methods have been developed to facilitate rapid separation of the component phenols in technical CNSL (ref. 192). Combined flash chromatography with TLC, HPLC (ref. 193), medium pressure chromatography with uv detection and dry-packed columns (ref. 194) have all proved highly effective for the separation of the major and minor components of this material. Silica gel type 60 with solute/adsorbent ratios 1:5-1:6, by stepwise elution with light petroleum (60-80°C) and diethyl ether, enabled batches of up to 250g of technical CNSL to be processed. Smaller batches permitted the reuse of chromatographic columns.

(i) Anacardic Acid

For the recovery of anacardic acid, natural CNSL is required since technical CNSL only contains traces of this phenolic acid. Precipitation of its metal salts constitutes the most specific method, a procedure which was indeed used by the first investigator of the composition of the natural product (ref. 195). For convenience, ice-cold dilute nitric acid can be used for the regeneration stage provided adequate cooling is maintained. Lead nitrate rather than the insoluble sulphate is then formed. 4-Toluenesulphonic acid is an alternative acid for use in this method.
With modifications, the phase separation method method has an application in the recovery of anacardic acid from natural CNSL to avoid metal salt precipitation procedures.

(ii) Urushiol

The sap from *Rhus vernicifera* by extraction with light petroleum affords urushiol a mixture which is considerably more sensitive to oxidative deterioration and polymerisation than the cashew phenols since it is both a catechol and even more highly unsaturated. The composition of the sap is to some extent dependent on the source but typically it contains urushiol (55-65%), water (20-30%), glycoprotein (2-3%), polysaccharides (5-7%) and laccase (< 1%) (ref. 196).

(iii) Unsaturated Constituents of Phenolic Lipids

All the preceeding adsorption methods yield the component phenols without any significant separation of the unsaturated constituents. Such separations are intrinsically more difficult and have been more successful by partition chromatographic methods. Low temperature fractional crystallisation (ref. 197) of the anacardic acids from acetone solution, a technique widely applied in the classical work on the composition of fatty acid mixtures (ref. 198), gave the three constituents together however with mixed intermediate fractions. Cardanol has been separated on alumina only after methylation and this procedure represents the first chromatographic work (ref. 199). Argentation thin layer chromatography enabled all the constituents of anacardic acid, cardanol, cardol and 2-methylcardol to be completely separated (ref. 200, 201). A similar approach has been used with urushiol (ref. 89). Argentation TLC separation of the constituents of the component phenols of *Anacardium occidentale* can be smoothly effected with the centrifugal technique by means of 'Chromatotron' equipment (ref. 202). Improvements in flash chromatographic procedures have resulted in larger scale operations (ref. 192) although developments in preparative high performance liquid chromatography have also led to considerable advances. The constituents of anacardic acid (ref. 203) and of the other cashew phenols have been separated (ref. 204) in this way. A recycling technique termed R HPLC has been used for the recovery of cardanol (ref. 205). Preparative HPLC is probably the least complicated procedure for use in the urushiol series (ref. 25) .

13.6.5 Quantitative Analysis

(i) Gas-Liquid Chromatography (GLC), Thin layer chromatography(TLC), Mass Spectrometry (MS) and Chromatographic/Spectroscopic Methods.

CNSL used in polymerisation with formaldehyde as for example in friction dusts may not require elaborate analysis. Nevertheless interest in the industrial chemical uses of phenolic lipids has led to a study of quantitative methods of analysis by a variety of chromatographic methods. For cashew phenols these were first based on GLC. Thus the (15:3), (15:2), (15:1) and (15:0) constituents of methyl anacardate, cardol and cardanol have been separated by GLC on PEGA columns (ref.206), the free phenols (anacardic acid as methyl anacardate) by GLC on SE30 (ref.207) and the hydrogenated anf fully methylated phenols on Dexsil and PEGA columns (ref.208). A further number of stationary phases have been investigated

(ref.209) and by the use of an internal standard the polymeric material and component phenols of natural and technical CNSL determined quantitarively by the procedure of using relative response factors (ref.210). Thin layer chromatography-mass spectrometry (TLC/MS) without the need for derivatisation (except for methyl anacardate to avoid decarboxylation) has been employed for quantifying the unsaturated constituents of the component phenols in natural (ref. 211) and technical CNSL (ref.212). TLC-UV spectrophotometry 'on the plate' although requiring laborious calibration has proved a remarkably straightforward technique (ref.213). The composition of urushiol has been investigated by GLC of the methylated and trimethylsilylated material (ref. 89) and by MS (ref.214). Trimethylsilylated natural and technical CNSL have been examined quantitatively (ref.215). TLC methods for phenols (ref. 216), quantitative procedures for natural CNSL (ref. 217) and for technical CNSL and urushiol (ref. 218) have been reviewed.

(ii) High Performance Liquid Chromatographic (HPLC) Methods

Although GLC methods have undoubtedlty been useful the most effective analysis for both technical and natural CNSL has been by HPLC (refs. 219,220) which has the advantage that no derivatisation is required and further, that peaks for formerly unobserved oligomeric materials can now be obtained. By the use of an internal standard the non-volatile polymeric material in technical and in natural cashew nut-shell liquid can also be determined and a total analysis of these products obtained.

With the aid of gradient elution, a reversed phase partition method and an internal standard, considerable progress has been made in the quantitative determination of each constituent of the main component phenols present in technical CNSL and in natural cashew-nut shell liquid provided that relative molar response (RMR) factors are used. A typical quantitative HPLC analysis of the technical material indicated cardanol (67.8%), cardol (18.2%), 2-methylcardol (3.3%), minor constituents (3.3%) and polymeric material (7.4%).

The % distribution of the unsaturated constituents of cardanol and cardol by HPLC analysis is shown in Table 6.

Fig. 3 illustrates the type of chromatogram observed by reversed-phase HPLC on Spherisorb ODS (5µm) with gradient elution (ref.219).

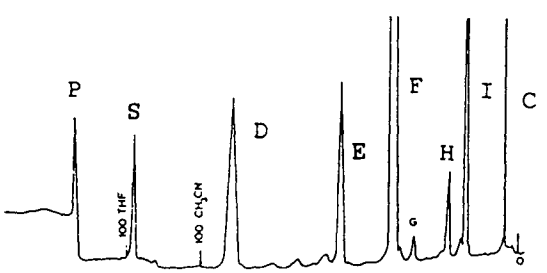


Fig.3, C,Int.std., D, (15:1)-cardanol, E,(15:2)-cardanol, F, (15:3) cardanol ,G, (15:1)-cardol, H, (15:2)-cardol,I (15:3)-cardol, P,polymer,(15:0)-cardanol

TABLE 13.6 % COMPOSITION of the CONSTITUENTS of CARDANOL and CARDOLin TECHNICAL CNSL by HPLC ANALYSIS (RMR = relative molar response)

CNSL TYPE	CARDANOL				CARDOL			
	(15:3)	(15:2)	(15:1)	(15:0)	(15:3)	(15:2)	(15:1)	(15:0)
(RMR)	1.296	1.297	1.305	1.294	0.993	1.003	0.997	-
New	33.4	12.3	19.3	2.9	13.6	3.5	1.1	
Distilled	32.6	16.0	30.1	3.8	7.7	2.4	1.0	
Old blend	22.5	12.5	25.1	3.1	6.6	2.6	1.1	

TABLE 13.7 %COMPOSITION of NATURAL CNSL by DIFFERENT CHROMATOGRAPHIC TECHNIQUES

METHOD	ANACARDIC ACID	CARDOL	2-METHYLCARDOL	CARDANOL
HPLC	71.65	22.3	1.10	5.1
TLC/UV	71.4	20.3	3.25	5.1
GLC	71.5	22.3	2.75	3.0

TABLE 13.8 %COMPOSITION of UNSATURATED CONSTITUENTS of ANACARDIC ACID in NATURAL CNSL by DIFFERENT TECHNIQUES

METHOD	SOURCE MATERIAL	TRIENE	DIENE	MONOENE
TLC/UV	Anacardic acid	45.1	16.3	38.7
GRAVIMETRY	"	44.1	17.4	38.4
GLC	Methyl anacardate	42.1	18.0	39.9
MS	"	44.1	17.4	38.4

TABLE 13.9 SEPARATION of THE CONSTITUENTS of URUSHIOL in *Rhus vernicifera* from HUPEI (CHINA)

STEREOCHEMISTRY	CONSTITUENTS	MASS	%APPROX
C_{15} 3-Substituted compounds			
8Z, 11E, 13Z	triene	314	64.1
8Z, 11Z, 14	"	314	-
8Z, 11E, 13E	"	314	trace
8Z, 11Z	diene	316	2.9
8Z, 11E	"	316	0.85
8Z	monoene	318	23.0
C_{17} 3-Substituted compounds			
10Z, 13E, 15Z	triene	342	0.6
10Z, 13Z, 16	"	342	trace
10Z, 13Z	diene	344	1.3
10Z	monene	346	0.2
C_{15} 4-Substituted compounrds			
8Z, 11E, 13Z	triene	342	1.2
8Z, 11Z, 14	"	342	-

Adapted from, J. Chromatogr., 294, 1984, 179.

For natural CNSL from different regions the % composition of the components, anacardic acid, cardol and 2-methylcardol by HPLC has been found to vary although all were produced from *Anacardium occidentale* (ref. 221).
The % unsaturated constituents also show small variations and generally it appears that the % of highly unsaturated constituents is higher in Brazillian CNSL and the % polymer lower than from other sources.

(iii) Comparisons of Analytical Methods

Although HPLC analysis affords by virtue of its partition nature a very detailed analysis of natural and technical CNSL, it is of interest to compare compositional results obtained by other methods. By contrast, GLC is less detailed and TLC as an adsorption process, operating through functional groups, affords a very direct uncomplicated indication of the main components present. Not all areas in the world producing CNSL have access to HPLC or even GLC analytical procedures and other chromatographic techniques may in those circumstances be obligatory. Tables 7 and 8 show respectively the % composition of the main components and of the unsaturated constituents of anacardic acid in natural CNSL by several different techniques.
Thus while HPLC gives a detailed picture of the composition of both natural and of technical CNSL, these complex products contains many minor materials of a homologous or different structural type which would be most easily identified by HPLC/MS or HPLC combined with another spectroscopic technique. Developments in ^{1}H and ^{13}C high resolution NMR spectroscopy and in FTIR may enable the analysis of the constituents of each component phenol to be extended to the technical and natural products. Observations have been made on the mixed unsaturated constituents by ^{1}H NMR and ^{13}C studies (refs.201, 222).
In this connection reversed-phase preparative HPLC with UV spectroscopic detection (254nm) of fractions has proved of particular use for the separation on Develosil ODS-5 of the stereoisomers in urushiol with eluent MeCN-H_2O-$MeCO_2H$ (ref.25) and these results are summarised in Table 9 (the % results are based on peak areas). The isolated comounds were identified by MS and ^{1}H NMR. Extensive work by Japanese groups on several other different chromatographic procedures has been described including the argentation HPLC of urushiol diacetate.

(iv) Orientation of Ring Substituents, Structure of the side chain and Configuration of double bonds

A prerequisite for quantitative analysis is a knowledge of the structure of phenolic lipids. An extensive amount of the work leading to the present accepted structures has been carried out with the phenols from *Anacardium occidentale* and the Rhus genus has been summarised in an earlier review (ref. 2) and more recently (ref.3). .A diagnostic of great importance in determining the position of substituents in monoalkyl phenolic lipids was the finding in mass spectroscopy (ref. 223) that in

3-alkylphenols the ratio of the M^+ to the $(M+1)^+$ peak was significantly greater than that in the 2- and 4-alkyl isomers. For 1,4-dialkylresorcinol compounds (ref. 65) the method was ambiguous and reliance was placed on other procedures. The formation of quinones from 1,2- and 1,4-dihydroxyphenolic lipids has proved valuable as for example with micondin (ref. 52) by the formation of the known 1,4-benzoquinone, primin and in structural verification by an improved synthesis (ref. 224). Generally saturated side chain compounds can be readily identified from MS and ^1H or ^{13}C NMR spectral information and the extensive literature available. Most problems arise with respect to unsaturated compounds. Frequently, chemical techniques to find positions of unsaturation have proved useful.

For many years it had been assumed that the side-chain in phenolic lipids such as the cashew phenols from *Anacardium occidentale* was dienoid but the detection of a mono and a diolefin (ref. 225), the separation on alumina of cardanol methyl ether (ref. 199) into its (15:1), (15:2) and (15:3)-constituents and their characterization by ozonolysis clearly showed the heterogeneity of the methylated natural product. The component phenols were separated later by argentation TLC (refs. 200, 201). The original assignment of double bonds to the 8-position in the (15:1) constituent and the 8,11- and 8,11,14-positions in the (15:2) and (15:3)-constituents respectively rests on ozonolysis in which heptanal, butanal and formaldehyde were isolated. In the case of cardol the 8-(3,5-dimethoxyphenyl)octan-1-al found analytically from its three constituents was synthesised (ref. 226). ^1H NMR spectroscopy has enabled the double bond assignment in the three unsaturated constituents of each component phenol to be verified (ref. 201,82) from the chemical shifts of the $ArCH_2$,$=HCCH_2CH=$, $=HCCH_2-$, and $-CH=CH_2$ groups. Technical CNSL contains minor isomeric constituent probably as a result of thermal isomerisation during industrial processing. By dihydroxylation of each double bond under mild conditions with performic acid, followed by hydrolysis, cleavage with potassium periodate and conversion of the resultant mixed aldehydes to their 2,4-dinitrophenylhydrazones it can be shown by partition TLC that in addition to heptanal, butanal and formaldehyde small proportions of other aldehydes are present (ref. 227).

GLC retention data proved useful in showing that *Rhus vernicifera* (from Japan) contains a small proportion of the 8,11,14-triene (ref. 89) in addition to the main 8,11,13- constituent. In *Rhus toxicodendron* the unsaturation is found at the 8; 8,11; and 8, 11,14-positions as in the cashew phenols (ref. 228).

A chemical/chromatographic method has been used to determine the first double bond position in the unsaturated anacardic acid constituents of *Pistacia vera* (ref. 9). The isolated constituent was methylated, dihydroxylated with performic acid, hydrolysed to remove some formate ester, oxidised with potassium periodate in acidic solution and the aldehydes formed reduced with sodium borohydride to the primary alcohols (refs. 226). The retention time of the aromatic product methyl 2-methoxy-6-(8-hydroxyoctyl)benzoate (C8 side chain) was compared with those of the C1, C3, C7 and C10 synthetic analogues and from the linear plot of retention time against methylenic carbon chain length, the double bond could be readily assigned to the 8-position. Nevertheless mostly on account of limited sample availability and the time involved in purely synthetic verification,

chemical/spectroscopic methods have become widely used. Dihydroxylation of double bonds, followed by ketalisation with acetone and mass spectroscopy of the derivatives has been used to assign double bond position in the thitsiol series (ref. 214) and in recent work with the resorcinols from *Cereale secale* (ref. 99) Mass spectroscopy has been useful for the detection of traces of C17 homologous compounds accompanying the C15 side chain components in the great majority of phenolic lipids (ref. 214). Derivatisation at the double bond through methoxy mercuration (and demercuration) to give a mixture of monomethoxy derivatives, dimethoxylation, methoxybromination, dithiomethylation and epoxidation have all been used with the polyethenoid fatty acids to given materials for mass spectroscopic study by directing fragmentation to the original site of unsaturation (ref. 229). Alternatively the carboxyl group has been derivatised with nitrogen functionality to afford compounds for similar specific fragmentation purposes (ref. 230). These procedures have a potential applicability to phenolic lipids.
The preceeding chemical and MS methods give information on the position of double bonds but not on their stereochemistry or indeed, if existent, their chirality (refs. 14,53). Infrared spectroscopy has been valuable. Thus In the early work on the configuration of the double bond in (15:1)-cardanol an initial *trans* assignment was later corrected when the natural product was found to possess an ir absorption band at 960cm^{-1} (10.4μ) characteristic of a *cis*-configuration (ref. 2). The *cis* (Z) configuration of the unsaturated constituents of phenolic lipids from *Anacardium occidentale* is clearly demonstrable by the J constants in the ^{1}H NMR spectra of the olefinic bonds (refs. 199,220) in the ^{13}C spectra (222, 231). The Z-configuration in phenolic lipids seems almost universal but (E) isomers sometimes co-exist as seen with urushiol constituents

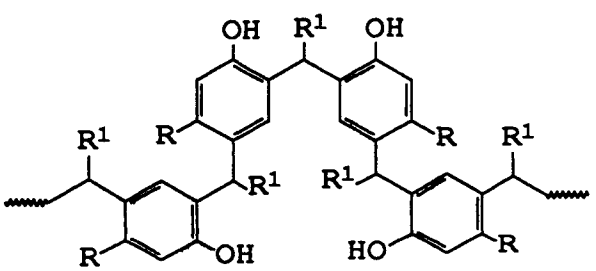
13.7 UTILISATION OF PHENOLIC LIPIDS

Technical CNSL has had extensive uses many of which have been summarised in the early patent literature (ref. 232), much of it the work of the Harvel Corporation. The lacs, used traditionally for many centuries (ref.185), have been studied in new areas largely due to their increased avaliability in China and other Far Eastern countries rather than primarily in Japan. The chief markets for CNSL are the USA, UK and Japan in all areas of its technology. Although the largest existing use of technical CNSL still remains in friction dusts (ref.177), both early (refs. 233, 234). and other recent applications in surface coatings and polymeric applications (refs. 235, 236) have been reviewed. Chemical uses of individual phenolic lipids have attracted interest probably because of the development of methods for their separation and the potential use of cardanol as a replacement for alkylphenols of petrochemical origin. Developments in the polymeric and chemical utilisation of CNSL, and of cardanol and cardol are discussed first in this section, followed by those in lac usage. To some extent the chemistry of CNSL and cardanol overlap as does that of polymer formation and chemical synthesis in for example the work on phosphorylation. The objective of specificity in synthesis namely in reactions of the phenolic hydroxyl group and of the side chain is not always achievable and the

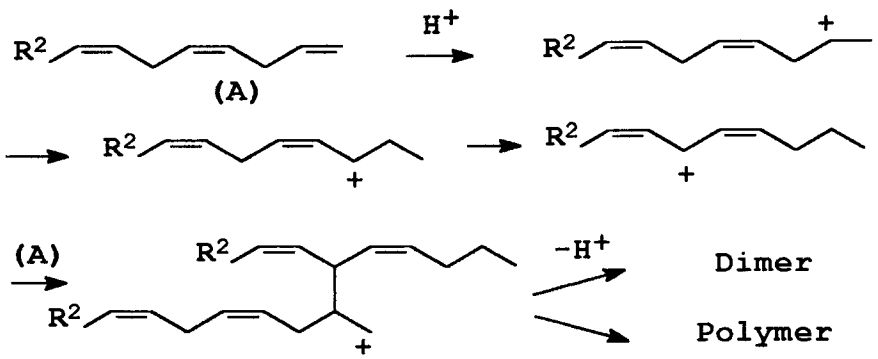
following account describes both types.

13.7.1 Polymer Applications of CNSL, Cardanol and Cardol

In the friction dust area where a vast patent literature exists only a few examples of which can be quoted from 'the prior art' the technology of this aspect of tribolgy has been in continuous development particularly with regard to improved methods of formation of CNSL-formaldehyde resins to avoid the need for the comminution at the final stage, in the formulation of asbestos-free products (refs. 237, 238), noise-free (ref.239), in the incorporation of thermally-stable polymers such as polyimides (Kevlar, Aramid) (refs. 240, 241) and in the usage of glass fibres, acrylic fibres and a wide range of inorganic materials. Thus fibrous material of various origins, thermosetting resins and friction controllers could be the basis of a friction material which typically comprises a mixture of an acrylic fibril (5 parts), phenolic resin (15 parts), cashew dust (10 parts), calcium carbonate (57 parts), graphite (5 parts), powdered aluminium (3 parts) and glass fibre (5 parts), a composition which was then press moulded at 150-160°C and heated fo a further period (ref. 242). Although the detailed composition of CNSL can now be found by HPLC analysis, for the production of friction dusts it is frequently assessed by much less sophisticated practical tests which are aimed at indicating the approximate level of polymer and triene present. For example, the viscosity and time of polymerisation with diethyl sulphate have been commonly-used criteria. The chemistry of the polymerisation processes occurring in the side-chain and at the phenolic ring have been discussed (ref. 2). The polymerisation processes employed for obtaining CNSL/aldehyde polymers vary and the patent literature abounds with different recipes. Sometimes partial oligomerisation of the unsaturated side chain with a proton source such as an dialkyl sulphate is a first step after which the product is reacted with formaldehyde so that a complex mixture results to which probably both novolak and resol structures contribute. Furfuraldehyde is also used and, for example, one reaction formulation consists of CNSL (100 parts), furfural (30 parts) and phenolsulphonic acid (2 parts). Reaction with an aldehyde, R^1CHO takes place at o- and p- positions but not between the OH group and the side chain (R) and a hypothetical structure is shown

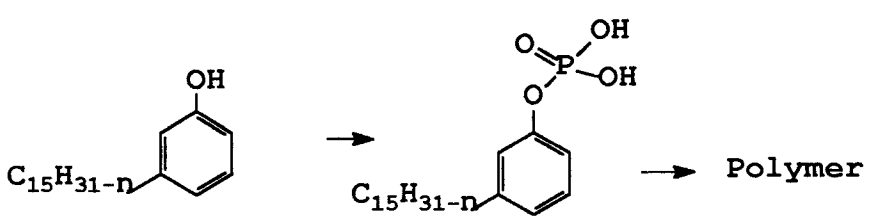


The oligomerisation stage with an acidic catalyst is likely to involve the reactive terminal double bond of the side chain in cardanol and formation of an allylic carbocation (ref. 2). It has been studied by initiation with boron trifluoride etherate (ref. 243) and the effect of temperature, ratio of catalyst to cardanol and duration of reaction time on its dimerisation examined (ref.244). In the following scheme R^2 represents for example $HOC_6H_4(CH_2)_7$-



The cardol present in CNSL, if in high proportion can lead to an exothermic reaction with formaldehyde and also It appears desirable for the phenolic components to have a high proportion of triene in order for the first acid-catalysed side chain oligomerisation stage to proceed. CNSL-formaldehyde polymers have greater flexibility than those from phenol-formaldehyde, due to internal plasticising, they are also more soluble in solvents, and due to their hydrophobicity they have resistance to water penetration, and hence acidic and alkaline media. For some applications highly methylolated cardanol is useful and this can be formed with formaldehyde, by the use of adipic or succinic acid as catalysts, and subsequently rapidly cured with hexamine (ref. 245).

There has been great interest in thermally stable materials having ablative and fire-retardant applications. Phosphorylated CNSL has been prepared many years ago (ref.246) but phosphorylated cardanol prepolymers, containing the dihydrogenphosphate group, have been obtained from CNSL by phosphorylation with orthophosphoric acid and dimeric products by simultaneous phosphorylation and oligomerisation (ref. 247).

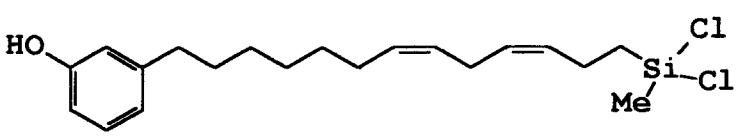


By reaction of phosphorylated materials with aldehydes, amines or with isocyanates highly thermally stable products have been then produced. TGA studies have indicated their superior properties compared to conventional cardanol/formaldehyde resins of the novolac type. It was also found that a phosphorylated CNSL polymer had improved adhesive properties when compared with conventional CNSL/formaldehyde resins (ref.248) and certain compounded products had wear, fade and frictional properties comparable to those of conventional PhOH/formaldehyde/copolymer brake linings (ref.249). The phosphorylated product from CNSL and its bromination derivative possessed good fire-retardant characteristics (ref. 250). Phosphorus derivatives of cardanol and of 3-pentadecylphenol have been studied by reaction with phosphorus oxychloride and its thio analogue (ref. 251).

The resins in the friction dust area tend to be rigid and the flexibility and plasticity associated with the long alkyl chain of phenolic lipids have been used in natural rubber vulcanisation by for example incorporating crosslinking with phosphorylated cardanol (ref. 252). Unpolymerised CNSL phenols have been used in natural or diene rubber compositions for tyre treads to give an improved dynamic elastic modulus but with the same hardness as formulations without the phenolic addition (ref. 253).

In recent years there has been activity generally in the production of safe plastic foams and in this connection certain flame retardant phenolic resin foams formulated from resols containing phenolic resin oligomers involving CNSL have been found to be free of harmful gases on combustion (ref. 254).

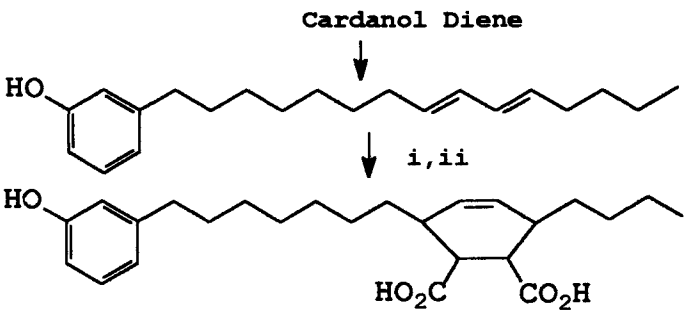
Reactions specificaly involving the side chain to increase the functionality of cardanol have been examined in recent years. For example, CNSL and cardanol have found an application in polysiloxane chemistry and a significant development has been the hydrosilation of cardanol with $MeHSiCl_2$ followed by hydrolysis leading to the incorporation of O-Si-C bonds (ref.255). Other double bonds may be involved than the terminal one.



The method was extended to novolak and resol cardanol/formaldehyde copolymers. HO-protected phenolic lipids have also been reacted. Thus, cardanol methyl ether and esters have been hydrosilated with $HSiCl_3$ and then reacted with methanol to afford methoxysilyl products useful as coupling agents for phenolic resins in sand cores (ref. 256).

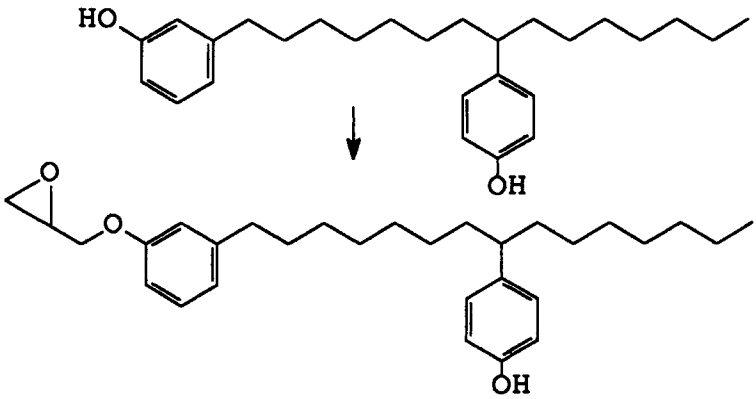
Other inorganic compounds have also found an application. CNSL has long had an indigenous use as a wood preservative and the employment of boric acid and of arsenic oxide to enhance this action has been studied (ref. 257). It seems most likely that the products are oligomers, hydrogen-bonded (in the case of boric acid)

with the inorganic additive in the matrix rather than being involved in chemical reaction.
Various titanate compounds have been employed with cardanol probably forming di, tri and tetra-substituted derivatives which were found to be useful for viscosity reduction in organic/inorganic systems, as aqueous emulsifying agents and in the processing of calcium carbonate-filled PVC (ref.258).
Co-polymerisation reactions of CNSL with styrene and with alkyd resins have for many years been aspects of its utilisation. Synthetic work to incorporate structural groups in the side chain and in the ring have aimed to produce new monomers. The oligomerisation of cardanol is likely to proceed through a Diels-Alder reaction involving prior formation of a conjugated structure. The isomerisation of cardanol under basic conditions as used for the transformation of eugenol to isoeugenol (ref. 259) and characterisation of the product have been described (ref. 260). In the scheme the initial movement of the 11- double bond is depicted although it seems probable that conjugation with the ring would probably occur. Reaction of the conjugated material with maleic anhydride led to a polyfunctional adduct, in high yield, available for intra or intermolecular polyester formation and for alkyd resins. The initial materials may also be converted to water soluble substances by salt formation and coatings derived from them were found to possess improved flexibility, hardness compared with conventional cardanol-based products.

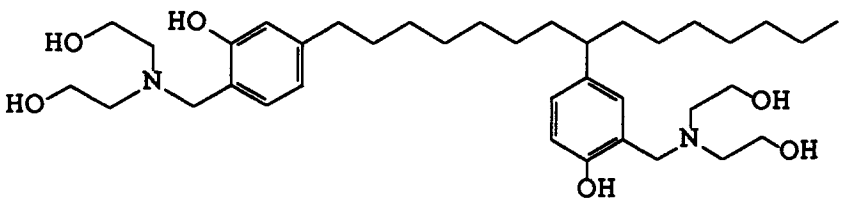


Although only cardol in CNSL has bifunctionality, attempts have been made to modify cardanol to the same effect. Thus reaction of (15:1)-cardanol with phenol in the presence of boron trifluoride afforded the 1,8-bis(hydroxyphenyl)pentadecane structure (ref. 261). Reaction then with a molar proportion of epichlorhydrin and polymerisation resulted in final products considered to be superior in properties to and cheaper than those derived from bisphenol A. The corresponding fully saturated 'cardbisphenol' compound has been converted to a water soluble bis Mannich base by reaction with diethanolamine and formaldehyde (ref. 262) of value for cathodic electrodeposition. In another case of a related bis diethanolamino product, it was found necessary to react the hydroxyl groups with the monoisocyanate resulting from treatment of tolylenediisocyanate (TDI) with a molecular proportion of cardanol (ref. 263) in order to obtain a suitable binder for

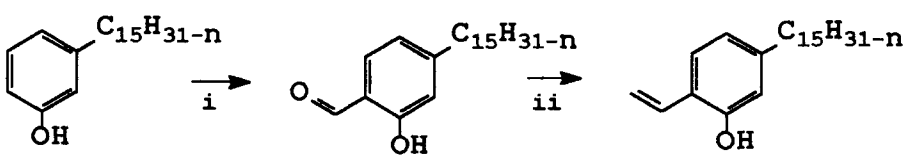
use in a electrodeposited paint formulation. The first stage in the process giving the monomer is shown.



The structure of the Mannich base obtained from 'cardbisphenol' is likely to be as depicted.

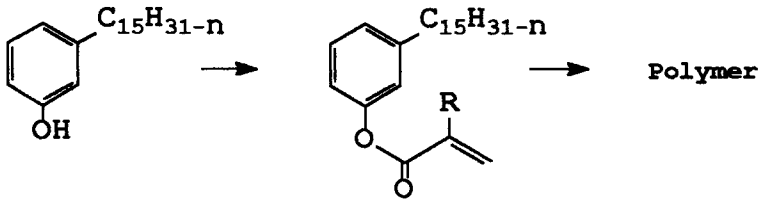


The introduction of a vinyl group into the benzenoid ring of cardanol to impart triple functionality, consisting of the vinylic double bond, the hydroxyl group and the unsaturated side chain has been effected from the 6-formyl derivative of cardanol (ref. 264).

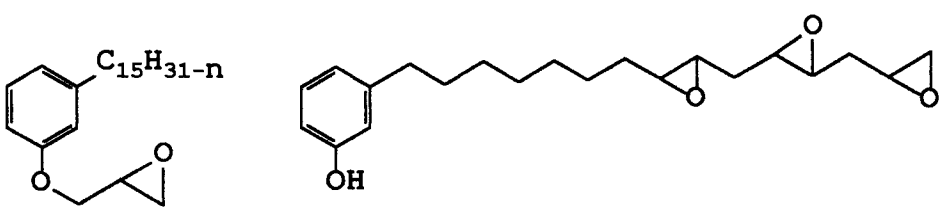


Reagents (i) EtMgBr , CH_2O , THF, HMPT ; (ii) $Ph_3P{=}CH_2$.

Copolymerisation reactions do not always succeed in the presence of phenols. Cardanol, converted to the acrylate (R = H) by reaction with acryloyl chloride, has been co-polymerised in the presence of benzoyl peroxide with methyl methacrylate leading to a product with improved thermal stability compared with polymethyl methacrylate alone (ref. 265). In a similar way an acrylate and a methacrylate (R = Me) have been synthesised from 3-pentadecylphenol. Polymerisation yielded moderately high molecular weight compounds of potential interest as pressure-sensitive adhesives (ref. 266).



A very important area in the application of CNSL is concerned with epoxy compounds and derived resins, synthesised traditionally from unsaturated 'cardbisphenol' (ref. 267), from CNSL/aldehyde condensation products or CNSL by reaction of the phenolic group with epichlorhydrin giving a range of proprietary 'cardolite' products (for example cardolite 513 is 3-pentadecenylphenoxy-methyloxirane) (ref.268). More recently the epoxidation of the side chain in cardanol in acetic acid with 30% hydrogen peroxide to give mono, di or triepoxides has been used to obtain a variety of monomers still having phenolic functionality (refs. 269,270). The former and a fully epoxidised derivative of (15:3)-cardanol are depicted.

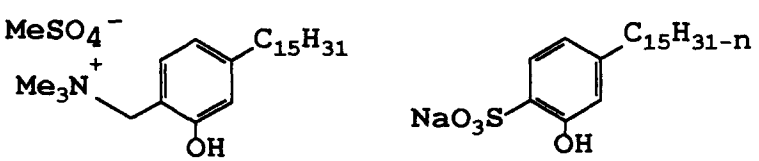


The addition of epoxidised CNSL to the glass fibre reinforced diglycidyl ether of bisphenol A resulted in the formation of laminates with increased chemical resistance, tensile and flexural strength although impact and hardness decreased (ref.271). Adhesives containing monoepoxy cardanol, a difunctional epoxycardanol and a trifunctional novolak of epoxycardanol together as diluents were found to impart improved thermal transfer to electronic components bonded on circuit boards

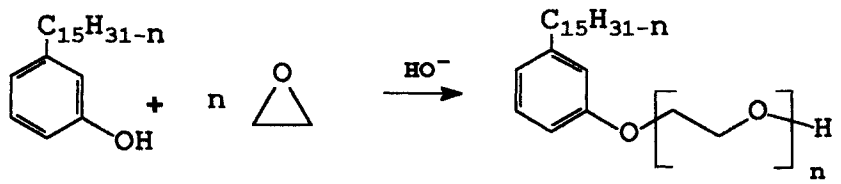
(ref. 272). Proprietary cardolite epoxy compounds have been incorporated in formulations for extremely tough thermosetting bismaleimide resins useful in aerospace applications (ref. 273). Mannich bases from complex amines with cardanol are valuable in the curing of epoxy resins (ref. 274).
The rocket fuel blend of cardanol (20 parts), norbornadiene (40 parts) and carene (40 parts) exhibit synergistic spontaneous ignition with an oxidiser such as red fuming nitric acid (ref. 275) and copolymerisation has been found to be one of the pre-ignition reactions (ref. 276).
An inherent problem in the usage of phenolic lipids, particularly in surface coatings, is the discolouration which can impair products. Apart from colourants arising from the solvent action of CNSL on the shell in the industrial process, the dihydric phenols in CNSL notably the minor component 2-methylcardol (ref. 200) more than cardol appear to be the cause of this deterioration rather than the monohydric member, cardanol. The usage of purer cardanol, or the less unsaturated material by semi-hydrogenation or chemical reduction, as well as the incorporation of an antioxidant are methods for colour stabilisation (ref. 277). Antioxidant applications and pharmaceutical uses of CNSL and its component phenols are referred to in the next section.

13.7.2 Non-Polymeric Applications of CNSL and its Component Phenols

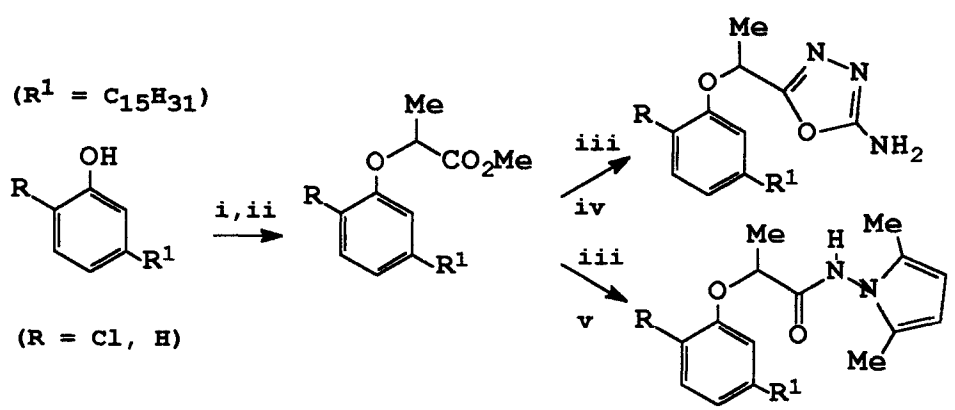
The development of improved separational processes for obtaining pure (mixed) cardanol and cardol from technical CNSL has encouraged experimentation in chemical instead of polymer uses for these component phenols as well as for anacardic acid, by extraction from natural CNSL. Some of the earlier chemistry has been reviewed (ref. 2). Most of the more recent uses particularly for cardanol, but also cardol and anacardic acid, stem from the conception of their semi-synthetic applications as readily available replenishable resources (refs. 278, 279). As with CNSL, the reactions considered in this section are concerned with the hydroxyl group of the side chain and substitution in the ring.
Although it might be thought that its C15 side chain would make cardanol an ideal candidate for surface active agents comparatively few developments have materialised. The use of CNSL as a potential source of surfactants and additives has been briefly reviewed (ref. 280). The Mannich reaction of cardanol with dialkylamines and formaldehyde (ref. 281) and the formation of cationics such as 3-pentadecyl-6-dimethylaminomethyl methosulphate has been described (ref. 2).



The synthesis of anionics is complicated in the case of unsaturated cardanol (ref. 282) by polymerisation reactions although the use of chlorosulphonic acid in chloroform at ambient temperature affords an unstable surface active product which probably contains side chain products and the phenol sulphate as well as the sulphonic acid.
Sodium anacardate is an excellent 'soap' the water solubility of which has been used in a subsequent reaction (ref. 283). There has been, following work on the preparation of cardanol polyethoxylate (ref.284,285,286), by the reaction of cardanol with ethylene oxide at 180°C in the presence of a catalytic amount of potassium hydroxide, considerable interest in its ready biodegradability compared with that of ethoxylates derived from t-nonylphenol (ref.287). The individual ethoxylate oligomers were synthesised having values of n = 1 to 6 to identify the oligomers present in cardanol polyethoxylate and the ready biodegradation of cardanol and to a lesser extent that of of cardol polyethoxylates quantitatively established in comparison with that of t-nonylphenol polyethoxylate which remained comparatively undegraded.



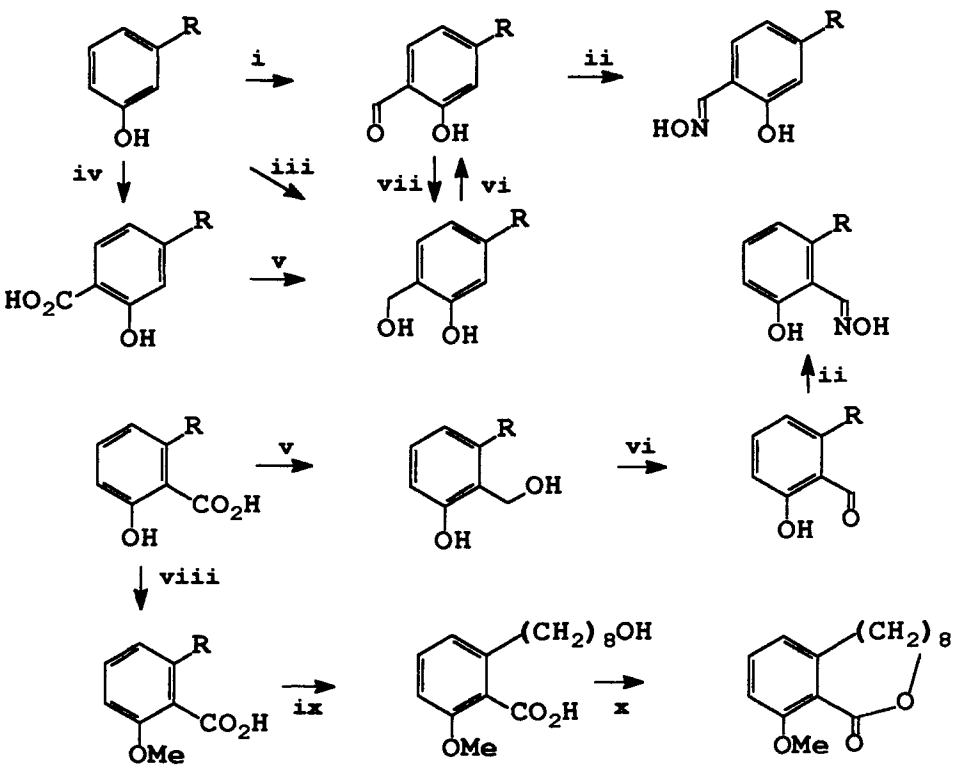
Drug analogues have previously been derived from saturated cardanol (ref. 2). In more recent work 3-pentadecylphenol and its 6-chloro derivative have been reacted with 2-chloropropionic acid and the derived methyl ester then converted to the hydrazide, reaction of which with cyanogen bromide afforded an aminooxadiazole while acetonylacetone gave a 2,5-dimethylpyrrole derivative (ref. 288).



Reagents (i) $ClCH(Me)CO_2H$, HO^- ; (ii) MeOH, HCl ; (iii) N_2H_4 ; (iv) CNBr ; (v) $MeCO(CH_2)_2COMe$

A range of compounds were screened for antiinflammatory properties and for hypotensive and motor activity.

Ring-substituted derivatives have been widely examined. Thus, the selective o-formylation of mixed cardanol (R = $C_{15}H_{31-n}$) was effected either through the reaction of the aryloxy magnesium bromide derivative with paraformaldehyde in tetrahydrofuran containing hexamethylphosphoric triamide (ref.279) or by reaction with paraformaldehyde in the presence of tri-n-butylamine and tin(IV) chloride (ref.289). Conversion of the resultant 'isoanacardic aldehyde' obtained to the oily aldoxime (ref.290) afforded an excellent chelatant for the solvent extraction of copper (II), having similar properties to current commercial reagents such as compounds of the Acorga series (ICI plc), derived from petrochemical sources (ref. 291). A similar reagent can also be derived from natural anacardic acid by way of the corresponding aldehyde, anacardic aldehyde, (ref. 88). 3-Pentadecylphenol was



also used.

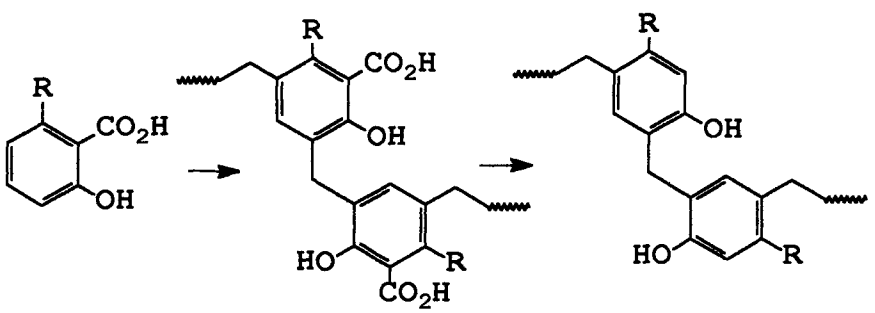
Reagents (i) CH_2O , Bu_3N , $SnCl_4$; (ii) H_2NOH_2Cl , py. ; (iii) CH_2O , HO^- ; (iv) Kolbe ; (v) LAH ; (vi) PCC ; (vii) $NaBH_4$; (viii) Me_2SO_4 , K_2CO_3 , Me_2CO ; HO^- ; (ix) $KMnO_4$; (x) High diln., H_3O^+.

Anacardic acid after methylation and conversion (ref. 226) to 2-methoxy-6-(8-hydroxyoctyl)benzoic acid has been transformed, as depicted iin the preceding scheme, to a compound at first considered to be a dimer but later concluded to be a twelve-membered lactone related to lasiodiplodin (ref. 292).

Reduction of isoanacardic aldehyde gave a methylol which could also be synthesised directly from cardanol together with formation of some of the 4,6-bis-methylol. The monomethylol compound 'isoanacardic alcohol' was an effective solvent extractant for the borate anion (ref. 279, 293). The isomeric compound, anacardic alcohol (ref. 88) was similarly obtained from anacardic acid (ref. 180). This In conjunction with the teriary amine Aliquat 336 was highly effective for the solvent extraction of the borate anion (ref. 293). Both these substances were comparable in properties to the 2,6-bis(hydroxymethyl) derivatives of 4-t nonylphenol and to 4-t octyl-2-chloro-6-hydroxymethylphenol (ref. 294).

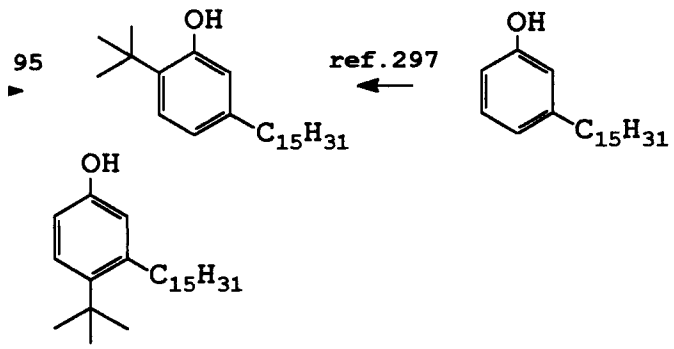
By Kolbe carbonation of cardanol in diglyme containing potassium hydroxide (ref. 283) (and of technical CNSL itself) 'isoanacardic' acid was obtained. This was also another source of both the methylol and aldehyde, namely isoanacardic alcohol and isoanacardic aldehyde repectively. These transformations are illustrated in the preceding scheme.

Natural CNSL itself (from solvent extraction), rich in anacardic acid has been initially reacted in aqueous systems in concentrated basic solution with paraformaldehyde and after addition of composite material has been heated and cured, during which process some decarboxylation of the anacardic acid polymer occurred, as shown in the scheme, to afford a particle board product (ref. 283) having excellent mechanical properties and resistance to water penetration. The customary use of organic solvents was avoided in this process.

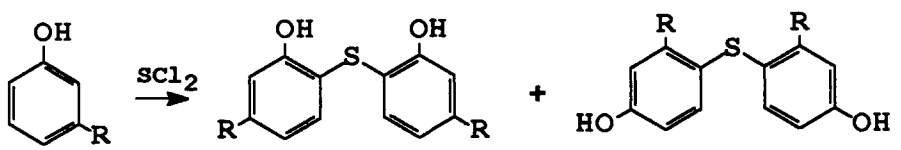


Antioxidants derived from cardanol such as 2-pentadecyl-1,4-dihydroxybenzene have been referred to (ref. 2). Hindered phenols are generally more efficient and

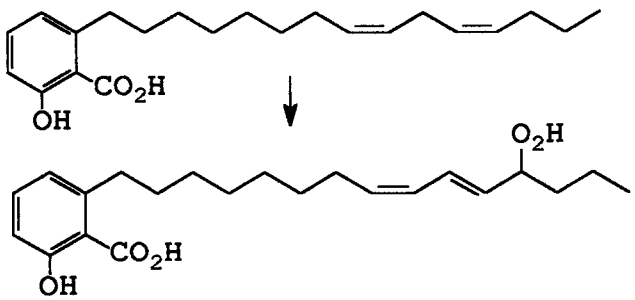
in the cardanol series, 6-t-butyl-3-pentadecylphenol (ref.295) has been prepared in good yield by the reaction of saturated cardanol in benzene solution with isobutylene containing sulphuric acid The 4-isomer has been prepared by the interaction of the saturated phenol (and the mixed phenol) with an acidic catalyst and a zirconium halide (ref. 296). In an alternative synthesis of the 6-isomer, t-butyl methyl ether has been reacted with 3-pentadecylphenol in dichloromethane containing tin(IV) chloride (ref. 297).



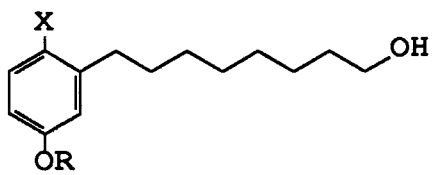
Traditionally in the petroleum industry antioxidants and anticorrosive agents have been obtained by the sulphurisation of 4-t-nonylphenol whereby the sulphur enters the 2,2'-positions. By contrast two isomeric products were obtained from 3-pentadecylphenol by reaction in benzene with sulpher dichloride. Both these, the 4.4' and 2,2' thiobiscompounds, were examined as magnesium salts for their anti-corrosive properties and, unusually, the isomer possessing the S atom in the 4,4'-position to the hydroxyl groups had superior properties (ref. 298).



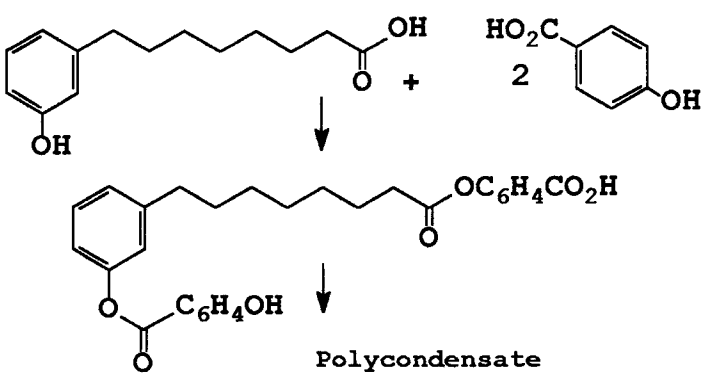
Reactions of the side chain have included hydroxylation (ref.226), halogenation, (ref. 299) isomerisation (ref.260) pyrolysis (ref. 300) and cleavage. In this CNSL was cracked with or without a catalyst (for example silica-alumina-zirconia) at 500-550oC and the products fractionated to give low molecular weight phenols, 24%, (150-220) higher molecular weight phenols (310-350) and hydrocarbons. Regiospecific hydroperoxidation of (15:2)-anacardic acid was effected with soya bean lipoxygenase to form 2-hydroxy-6-[12-hydroperoxy-(8Z,10E)-pentadecadienyl]-benzoic acid (ref. 301).



Oxidative cleavage of cardanol methyl ether has led to 8-(3-methoxyphenyl)octanoic acid, 8-(3-methoxyphenyloctaldehyde and the corresponding alcohol (ref. 226). A range of substituted 8-aryloctanoic acids have been prepared having chloro, bromo and nitro groups (X) as well as different alkoxyl substituents (R) (ref.302). Complete removal of the sidechain of cardanol methyl ether by way of a benzylic hydroperoxide, as for cumene hydroperoxide, to afford 3-methoxyphenol would appear to be possible.



A thermotropic liquid-crystalline polyester has been derived from the polycondensation of 8-(3-hydroxyphenyl)octanoic acid, prepared by the phase



transfer-catalysed oxidation of cardanol, with 4-hydroxybenzoic acid (ref. 303). The individual phenolic lipids and also technical CNSL have found pharmaceutical, applications, antioxidant use and shown to possess enzyme inhibitory action. Thus the antimicrobial activity of all the constituents of CNSL towards four typical microorganisms has been examined (ref. 304). Antifungal activity of cardanol derivatives has been studied by microcalorimetry (ref. 305). Cardol has been reported to possess antifilarial (anthelmintic) activity (ref. 306), skin-lightening activity (ref. 307), and all the phenolic lipids have been reported to relieve acne (ref. 308). They have been reported to be effective inhibitors in dentifrices of *Streptococcus mutans* (ref.309). A combination of 6.25μg/mL of anacardic acid and 0.78μg/mL of totarol was found to be inhibitory to the growth of two strains of methicillin-resistant *Staphyloccus aureus* (MRSA) while anacardic acid was bactericidal against MRSA at any stage of growth (ref. 310).
Antioxidants for food and cosmetics can it is claimed be selected from the components of natural or technical CNSL (ref. 311). The constituents of *Anacardium occidentale* have been described as inhibitory towards the enzymes α-glucosidase, invertase and aldose reductase (ref. 312). 5-isopentadecylresorcinol (isocardol) and cardol itself have similar antagonistic activity to α-glucosidase (ref. 69). Anacardic acid, notably the triene, has been reported as a molluscicide and the activity has been attributed to the carboxyl group and the unsaturation (ref. 313). There is little doubt that the full chemical potential of this readily available and replenishable group of biodegradable natural and semi-synthetic products has yet to be developed as it has already in the area of polymeric applications.

13.7.3 Utilisation of Lacs

A number of applications of commercial lacs and of separated urushiol have been referred to (ref. 2). As with the phenolic lipids of *Anacardium occidentale* a great deal of work has been carried out particularly in Japan and China to diversify the uses of lacs from *Rhus vernicifera*. It is widely employed in artistic decoration, building materials, textile equipment and furniture. The industrial utilisation of polyketide natural products including the phenolic lipid urushiol has been reviewed (ref. 314). The great number of uses largely comprise polymerisation reactions and some non-polymeric processes, some of both of which are described in the next sections.

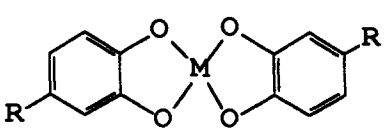
13.7.4 Polymer Applications of Lacs and of Urushiol

Although they have been incorporated in paints for their durable, hard, bright, anticorrosive and adhesive films, industrial applications of lacs and of urushiol have been limited because of their high viscosity, low drying rate, requiring a regulated temperature and humidity, their suseptibility to an alkaline environment and the contact sensitivity of human skin.
The gelation of formaldehyde condensates of urushiol has been studied (ref.315), and their etherification products with epichlorhydrin examined in the production of

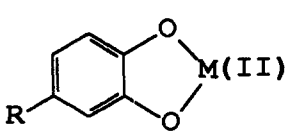
light-colured varnishes (ref. 316). Epoxidation of the side chain and coplymerisation reactions have been examined (ref. 317) for upgrading lacquers. Two component polyurethane and lac compositions gave coatings which were more stable than those prepared from the lac alone (ref. 318). The simulation of the action of laccase in the polymerisation of urushiol has been investigated with the use of Cu(II) complexes (ref. 319).

13.7.5 Non-Polymeric uses of Urushiol

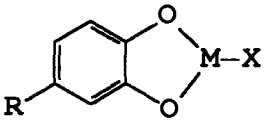
To aid chemical uses, the separation of urushiol on cation exchange resins has been employed (ref. 320). Recent work has concentrated on the preparation of various salts from Al, Sb (ref.321), Ti (IV), Fe(II) and Cu(II) (ref. 322). Aluminium compounds possessed good thermal stability, antimony compounds flame-retardant properties and titanium componds excellent anticorrosion action. 2:1 Complexes



(M = Ti)

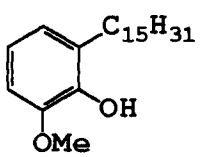


(M = Cu)



(M = Al)

would seem to be capable of existing as cis and trans forms.
The hydroxylation of benzene with hydrogen peroxide in the presence of urushiol and Fe(III), both probably in complexed form, afforded a 45% yield of phenol (ref. 323).
Not only a wide range of cations complex with the catechol system of urushiol but the borate anion also undergoes quite strong association. Thus urushiol together with Aliquat 336 was valuable for the solvent extraction of this anion probably through the formation of 1:1 and 2:1 chelates (ref.293).
The cleavage of urushiol by catechol-2,3-dioxygenase has been studied (ref. 324) and the oxidation of anacardic aldehyde to urushiol with manganeses dioxide (ref. 325), an alternative to the Dakin reaction descibed some years ago (ref. 88).
Experiments on the methylation of urushiol (refs. 88,89) indicate that the 3-hydroxyl group reacts preferentially under mild conditions. Hydrogenated urushiol, 1,2-dihydroxy-3-pentadecylbenzene, reacted similarly to form 1-methoxy-2-hydroxy-3-



pentadecylbenzene a compound having properties approaching those of the 'hindered' phenols. As with cardanol, urushiol can form a dimer and the crosslinking reactions of its diacetate have been studied (ref. 326).
The oxidation of 3-pentadecylcatechol in various solvents has been studied under aerobic conditions (ref. 327). The enzymic, thermal and oxidative reactions leading to the polymerisation of urushiol have been examined (ref. 328). Many other papers presented at the 1993 symposium on oriental lacs have been concerned with the same problem.
The removal of urushiol, when regarded as an offensive chemical, can be simply effected by the use of hypochlorites (ref. 329). In a rather more subtle way the induction of tolerance to 'poison ivy' urushiol has been established by epicutaneous applications of the analogue 5-methyl-3-n-pentadecylcatechol (1,2-dihydroxy-4-methylpentadecylbenzene) (ref. 330).
To conclude on the question of physiological effects, some apparent benefits of certain natural phenols were mentioned in Chapter 1. However, recently a number of synthetic phenols have been implicated as environmentally persistent and weakly to markedly estrogenic in their action. In consequence it has been suggested that they may be the etiological agents in several human disorders (ref. 331). The relative biodegradability (ref. 285) which appears in certain cases to favour natural compared with synthetic phenolic compounds may be a useful environmental factor .

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CHAPTER 14

SYNTHESIS OF NATURAL PHENOLS (and their Derivatives) OF PHARMACEUTICAL, MEDICINAL OR TECHNICAL INTEREST

14.1 Introduction

Many of the phenolic compounds described in the preceding chapters have had or indeed still have a pharmaceutical, medicinal or technical application while probably the vast majority may well have never been screened for such purposes. It is very likely that they have been prepared partly for the aesthetic pleasure of molecular construction. The laboratory synthesis of natural phenolic compounds like that of other classes has traditionally been the terminal step following isolation and structural determination. However although total synthesis has generally constituted an academic goal, very few complex molecules have been commercially produced by synthesis and in a large number of cases reliance has been placed on isolation of the product from natural sources or alternatively on semi-synthesis (ref.1). With advances in molecular biology, the genetically-engineered synthesis of modified natural products and biotechnical approaches towards known materials both based on biosynthetic pathways are likely to become increasingly and widely adopted (see e.g. ref. 58 and references therein).

In the case of the classical synthesis of phenolic compounds it is remarkable that in one text on natural products (ref. 2) one quarter of the compounds discussed are concerned with phenols or their methyl ethers. In another general account of organic synthesis (ref. 3) concerned with a vast array of structural types, phenolic systems comprise between 10 and 15% while in a more recent account of synthesis (ref. 4) again of natural products of all types, more than 115 compounds from 613 listed have phenolic or phenolic ether structures. This is a consequence of the prevalence of polyketide biosynthesis in natural product systems (ref. 5).

In the present chapter firstly some examples are given of a number of phenolic natural products which have engaged the attention of a great number of natural product investigators and resulted in unprecedented synthetic achievements and advances in organic synthetic methodology. From this vast group a small number of compounds have reached a high level of industrial importance. They range from the steroidal hormone estrone, the analgesic/opiate morphine, the tetracycline antibiotics, to the colourant carminic acid, to quote but a few. A considerably greater number have been medicinally or technically examined for

other attributes and subsequently passed into history. The compounds which have proved of immense significance to humanity are generally obtained by extraction from natural sources of from semi-synthesis in very few steps from a related structure of natural occurrence. Although all the compounds mentioned could be recovered from natural sources, to attempt to do so solely would be unadventurous and such natural recovery might be construed from a very short-sighted view as invalidating synthesis. However the history of man's advances in all areas of endeavour has been to to equal nature, to then advance on the natural situation, and to devise new systems unknown in the natural world.

The progressive march of synthesis up to the time of the Woodward-Eschenmoser achievement with vitamin B_{12} (ref 2), which at that time seemingly eclipsed earlier attainments, has in turn been surpassed by the synthesis of palytoxin (ref.6) and perhaps of other molecules. Although in practical terms advances in biological chemistry and the technique of semi-synthesis may bypass total multi-stage synthesis or even eventually result in its extinction in 'dinosaur' fashion, the academic challenge to construct molecules is likely to remain purely for the scientific and intellectual endeavour involved. Nevertheless, smaller molecules are within the bounds of economic viability and as advances continue, the multistage approach may be confined to 'single pot' success with conventional reagents or by means of enzymic systems. In an age when many living organisms are threatened with extinction a justification of total synthesis could be that microorganisms may conceivably also suffer the same fate leading to the extinction of a given natural product. In this event synthesis could prove an unexpected saving factor.

As must be apparent from earlier chapters in this book, phenolic systems abound in nature perhaps as a consequence of the ease of biosynthesis of polyketides and the innumerable ways in which these intermediates under enzymic influence can react with others or cyclise to multi-ring systems. A vast number of the resultant compounds have physiological effects although it is a large step before their biological evaluation and subsequently a giant leap before commercialisation if indeed valuable remedial properties are revealed. Beneficial effects may be bound up with folk medicine as in the case of Chinese natural products, with Ayurvedic practice in India or from an extensive knowledge of indigenous species having medicinal use. Despite the existence of a myriad of organic compounds having potential medical applications it has been observed that remedial health practice may revolve around the general employment of little more than ten major materials or compositions and of course a great number of specialised products comprising the remainder. Although phenolic compounds and their derivatives namely monomethyl, methylenedioxy, dimethyl and polymethyl ethers represent a small part of this whole, their abundance is striking.

Academic chemists will probably always have a fascination for the construction of organic molecules without too much concern as to whether they have have any use since the desire affords its own aesthetic satisfaction. The enormous step to 'industrialise' a natural product may thus not be seen as a prime initial

TABLE 14.1 SOME NATURAL PHENOLIC COMPOUNDS

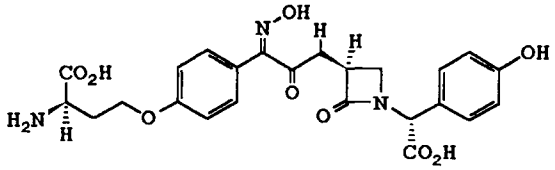
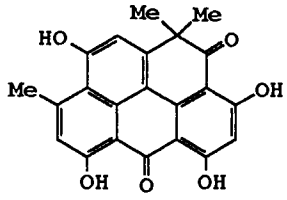
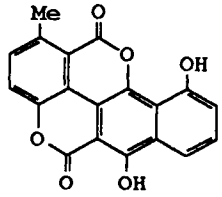
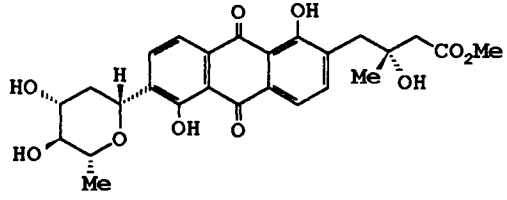
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Nocardicin A (Gram -ve bact.)		*Nocardia uniformis*	7
Resistomycin		*Streptomyces resistomycificus*	9
Chartreusin aglycone (Gram +ve bact.)		*Streptomyces chartreusin*	8
Vineomycin B_2 (antitumour)		*Streptomyces mateuris vineus*	10

TABLE 14.1 (contd.)

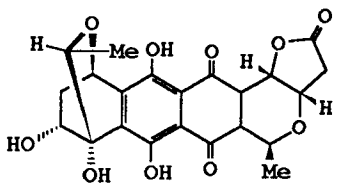
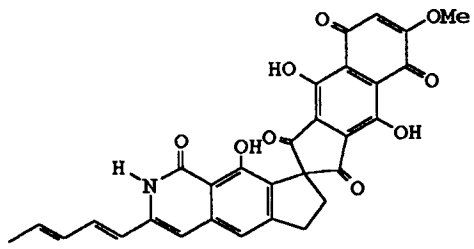
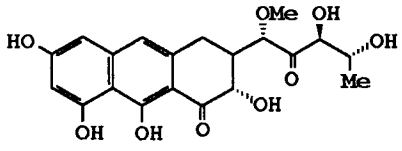
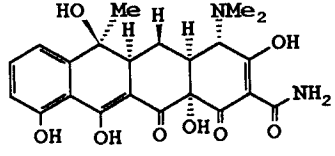
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Granaticin A (Gram +ve bact.)		*Streptomyces oliveacus*	11	Fredericamycin (anticancer)		*Streptomyces griseus* (FCRC-48)	12
Olivin (antitiumour)		Aglycone of olivomycins	13	Terramycin (Broad spectrum)		*Streptomyces aureofaciens*	14

TABLE 14.1 (contd.)

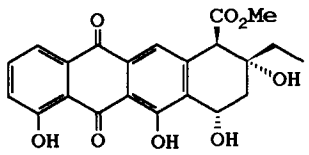
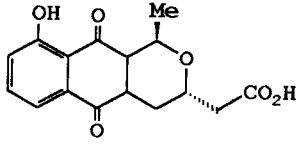
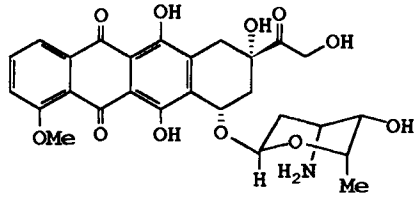
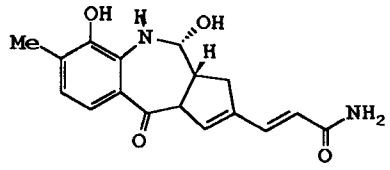
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Aklavinone (Antitumour)		*Actinomyces spp.*	15
Nanaomycin (Antibiotic)		*Streptomyces rosa*	17
Adriamycin (Anticancer)		*Streptomyces peucetius*	16
Anthramycin (Antibiotic)		*Streptomyces refuineus* var. *thermotolerans*	18

TABLE 14.1 (contd.)

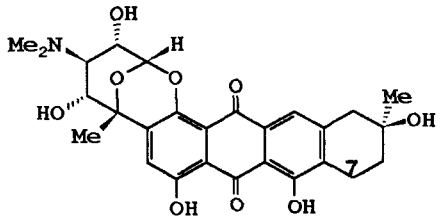
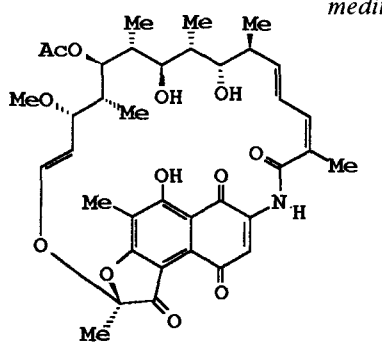
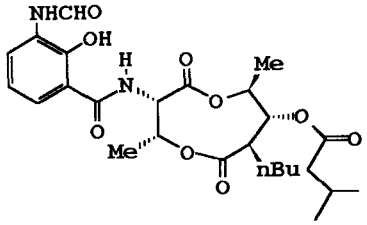
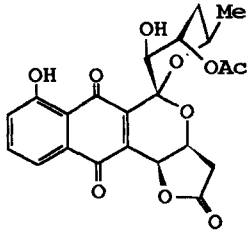
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
7-Deoxynogarol (Antitumour)		Nogalomycin	19
Rifamycin S		*Nocardia mediterranei*	21
Antimycin (Antifungal) toxic		*Streptomyces spp.*	*20*
Griseusin A		*Streptomyces griseus*	22

TABLE 14.1 (contd.)

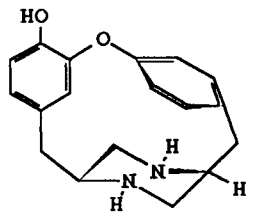
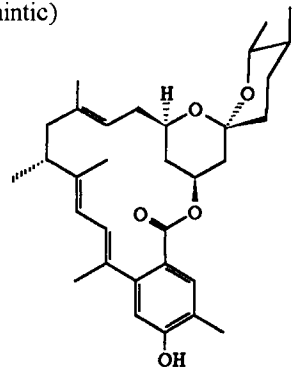
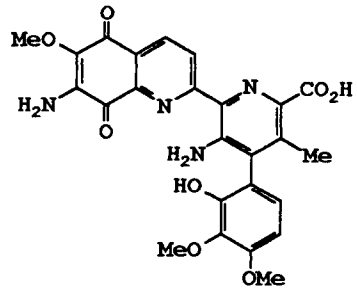
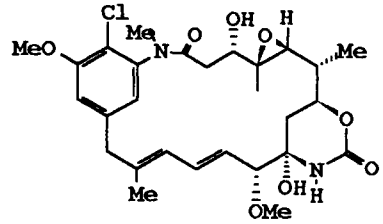
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Piperazinomycin		*Streptoverticillium olivoreticuli sub spp. neienactius*	23
Milbemycin β_3 (Anthelmintic)		*Streptomyces spp.*	25
Streptonigrin (antitumour)		*Streptomyces flocculus*	24
Maytansinol (Antileukaemic)		*Putterlickia*	26

TABLE 14.1 (contd.)

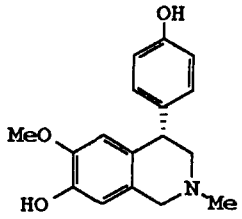
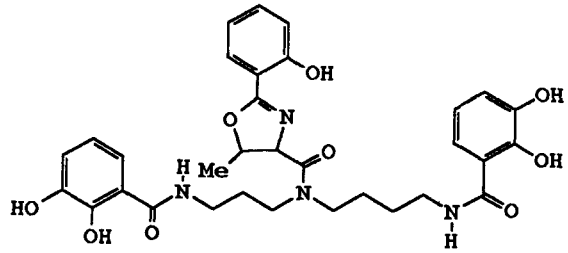
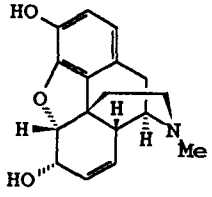
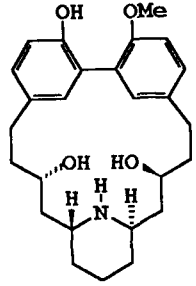
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
ALKALOIDS							
Cheryline		*Crinum moorei*	27	Parabactin (Siderophore)		*Paracoccus dentrificans*	28
Morphine (Opiate)		*Papaver somniferum*	29	Lythranidine		*Lythrum anceps*	30

TABLE 14.1 (contd.)

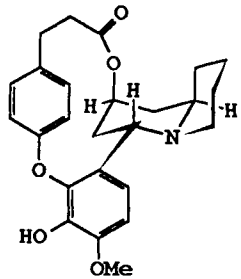
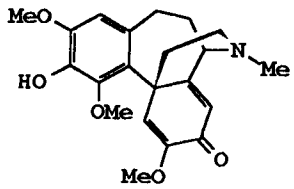
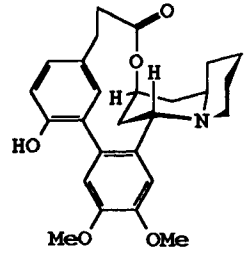
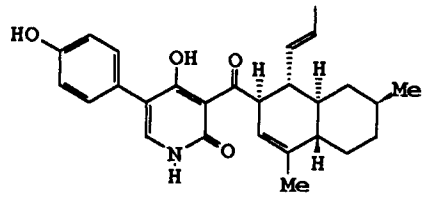
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Lagerine		Lythraceae	31
Anthrocymbine		*Colchicum autumnale*	33
Decamine (Early 1600's medicinal)		Lythraceae	32
Ilicicolin (Antifungal)		*Cylindrocladum ilicicola*	34

TABLE 14.1 (contd.)

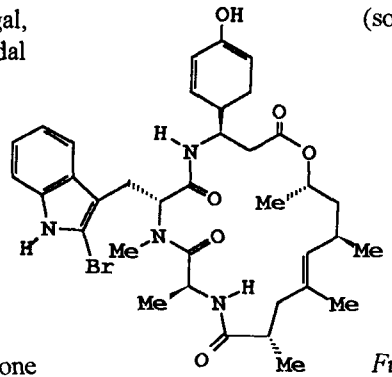
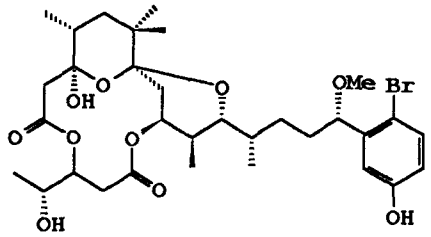
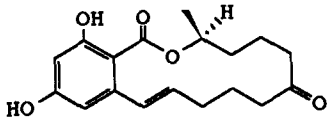
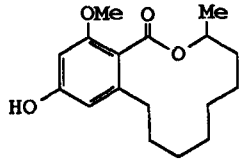
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
MACROLIDES							
Jasplakinolide (Antifungal, insecticidal		*Jaspis spp.* (soft-bodied sponge	35	Aplisiatoxin		*Stylocheilus longicanda*	36
Zearalenone (Estrogenic mycotxin)		*Fusarium graminearum*	37	Lasiodiplodin (Plant growth inhibitor)		*Lasiodiplodin theobromae*	38

TABLE 14.1 (contd.)

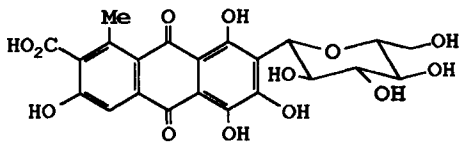
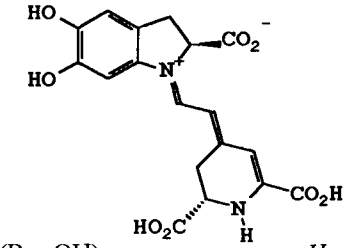
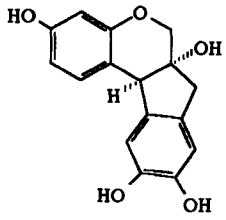
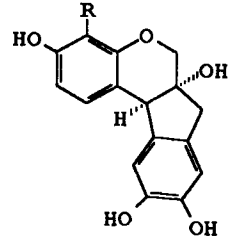
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
COLOURANTS and PIGMENTS							
Carminic acid (Cochineal)		*Dactylopius coccus* Costa	39	Betanidin (Aglycone of Betanin)		*Beta vulgaris*	40
Brazilin (Dye)		*Caesalpina braziliensis*	41	Haematoxylin (R = OH) (Logwood)	 (rel. confgn.)	*Haematoxylon campechianum*	41

TABLE 14.1 (contd.)

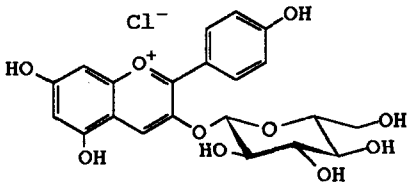
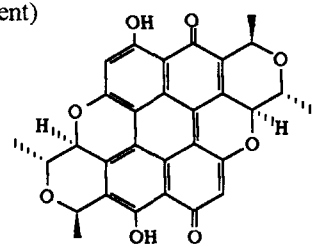
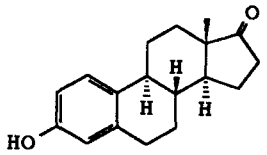
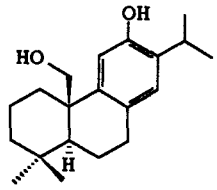
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Callistephin chloride (Red aster pigment)		*Callistephus chinensis*	42	Erythroaphins (Black pigment)	 (1R,3R,3aR,8R,10R,10aR)-form Erythroaphin fb	*Aphis fabae*	43
STEROID, DITERPENE, POLYPHENOL, PHENOL DIMER, TERPENE, HYDROXYQUINONE, MACROCYCLIC COMPDS.							
Estrone (Estrus hormone		*Homo sapiens*	44	Pisiferol		*Chaemaecyparis pisifera*	45

TABLE 14.1 (contd.)

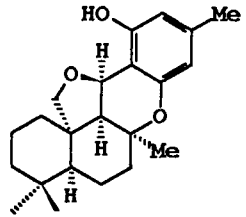
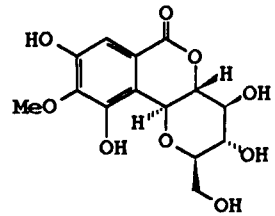
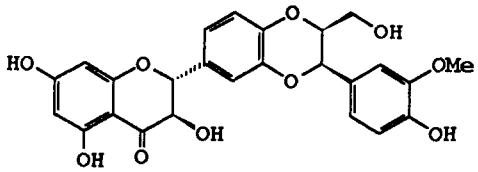
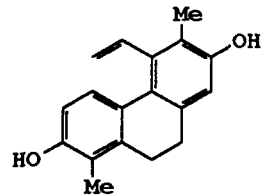
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Siccanin (Antifungal)		*Helmnithosporum siccans*	46	Bergenin		*Peltoboykinia spp. and Bergenia. crassifolia*	47
Silybin		*Silybum marianum*	48	Juncusol (antileukaemic)		*Juncus roemerianus*	49

TABLE 14.1 (contd.)

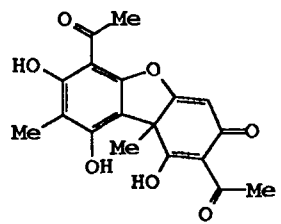
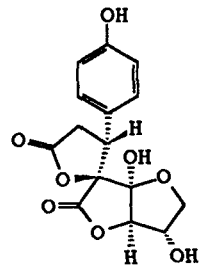
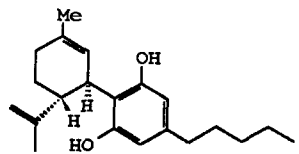
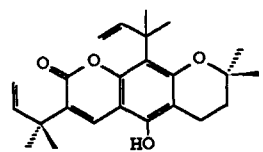
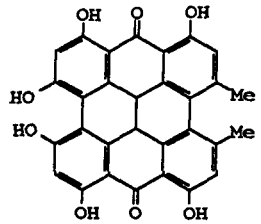
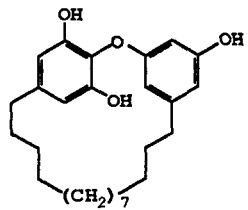
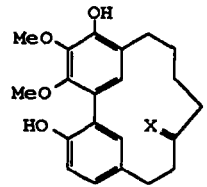
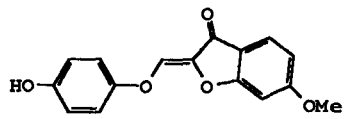
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Usnic acid (Lichen)		*Letharic vulpina*	50	Dilaspirolactone (anticoagulant)		*Viburnum dilatatum*	51
Cannabidiol (Euphoriate)		*Cannabis sativa*	52	Clausarin (Antibacterial)		*Clausena pentaphylla*	53

TABLE 14.1 (contd.)

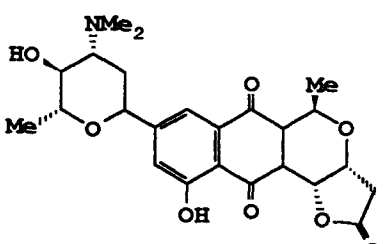
COMPOUND/ (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Hypericin (Irrirant)		*Hypericum perforatum*	54
Robustol		*Grevillea robusta*	56
Myricanol (Folk medicine)	 X = H,OH Myricanol X = O Myricanone	*Myrica nagi*	55
Chalaurenol (Plant metabolite)		*Amorpha fruticosa*	57

activity. In the industrial context it is the lot of few organic products from the vast number examined to reach commercialisation although witnesses from outside invariably appear to conceive this as the goal of chemists generally. It is appropriate to describe the chemical achievements involved in the cases of a few selected compounds

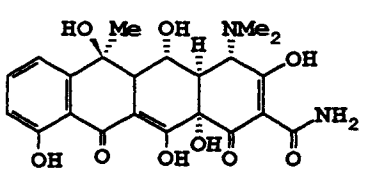
14.2 Some Examples of 'Classical'Phenolic Natural Products

Firstly It is of interest to assemble the structures of some of the compounds comprising a few examples of the great variety of phenolic systems which have engaged chemical attention over the last half century. An equal number of naturally occurring phenolic methyl ethers, partially methylated polyhydric phenols and methylenedioxy systems exist, arising by biological alkylation, and they demonstrate the significance of the phenolic group in nature. However they are not included in this account although this in no way diminishes from their importance as natural products. Thus only phenolic compounds are included in Table 14.1 which lists some antibiotics, alkaloids, macrolides, colourants and finally certain steroid, diterpene compounds, polyphenols, phenolic dimers, hydroxyquinones and macrocycles. The classification is arbitrary as for example in the case of ilicicilin, eligible for various classes, and it might equally have been grouped under oxygen heterocycles, nitrogen heterocycles, terpenoids or macrocyclic compounds. The structures, the botanical origin and physiological activity where known are given in the table.

All the compounds shown in Table 14.1 have been synthesised and in the majority of instances the biosynthesis has been elucidated. In the case of the antibiotic metabolites mederrhodin (1), oxytetracycline (2) and also granaticin (ref.11) together with the compounds frenolicin B and actinorhodin, a detailed study has revealed the organisation and complete sequence of genes involved in the biosynthesis from a polyketide and the factors controlling the programming of the polyketide chain assembly (refs. 58,59). These fundamental advances herald a general methodologyfor biologically producing new natural and unnatural products (ref.60).



(1) Mederrhodin



(2) Oxytetracycline

Table 14.1 depicts both 'classical' compounds such as the anthocyanin

callistephin (ref.42), erythroaphin fb (ref.43) morphine (ref.29) and estrone (ref.44) to quote a few and a large group of antibiotics (refs.7 to 26) and alkaloids (refs 27 to 34) the structural elucidation and synthesis of which represents a great expansion of interest and success achieved mostly in the last two decades. Comparatively few of the compounds listed have become well known through medicinal or other usage although organic chemical methodology, separatory methods and spectroscopy have been considerably advanced by the extensive world-wide studies in their structural elucidation and synthesis. An armoury of compounds is available for structure/property studies, through semi-synthesis and/or biotechnological processs based on a knowledge of biosynthetic pathways. This intense endeavour has scarcely abated and Table 14.2 illustrates topical interest in which phenolic compounds are involved as exemplified by contributions made to the last two IUPAC series of symposia concerned with the chemistry of natural products generally. For many of the compounds an emphasis has frequently been placed on physiological properties particularly medicinal utliity. In the present summary an arbitrary grouping has been adopted broadly based on classifying compounds as O- or C-glucosides, nitrogen heterocyces, oxygen heterocycles, flavonoids and a group of less well-defined structures comprising some highly novel compounds.

14.3 Topical Natural Phenolic compounds

In the first entry, aquayamycin is one of a group of antibiotics including ravidomycin and kidamycin of polyketide origin having a C-glycosidic structure. Others are mederrhodin (1), vincomycin B_2 methyl ester (Table14.1) and the second entry, gilvocarcin M with its relative gilvocarcin V which has a vinyl in place of the methyl group. Many of these aryl C-glycosides have biological activity notably antitumour properties. Entry 3 relates to the preparation of a fluoro analogue of the O-aminoglycosidic anthracycline series with enhanced intercalation properties at specific DNA sites. Knipholone (entry 4) is a major pigment found in the genus *knipholia* and is the first example in which an anthraquinone is attached to an acetylphloroglucinol methyl ether. The dynemycins A, M and H are based on 1-amino-4,5,8-trihydroxyanthraquinone and entry 5 relates to studies which have established that the biosynthesis of compound A involves two heptaketide chains which form the bicyclic enediyne and the anthraquinone moieties.

In the nitrogen heterocycle group, diazonamide (entry 6), an indolyl bis-oxazole natural product and its relative moroidin an indolylhistidinyl compound are both macrobicylic compounds with peptidic linking groups. Numularin (entry 7) is one of five new types of 1,2,3,4-tetrahdroisoquinoline alkaloid isolated from plants of the *Berberis* genus. A number of bis-benzylisoquinoline alkaloids having a diaryl ether bridge including the phenolic (+)-berbamunine (entry 8) and its enantiomer (-)-magnoline have been recovered from a Chilean *Berberis* source. Pyoverdin (entry 9) is characteristic of the chromphore grouping in the siderophores which result when members of the fluorescent group of

TABLE 14.2 FURTHER TOPICAL NATURALLY-OCCURRING PHENOLS

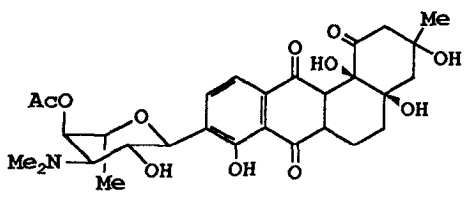
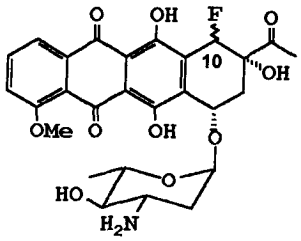
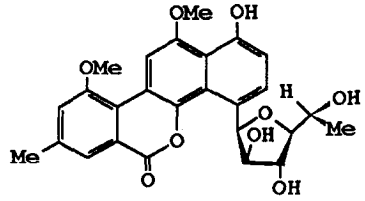
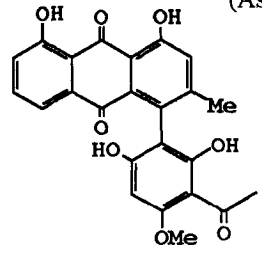
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Aquayamycin (1) ('Biol. activity')		*Streptomyces misawanensis*	61
Anthracycline (3) (Antitumour)			63
Gilvocarcin M (2) (antitumour)			62
Knipholone (4)		*Knipholia foliosa* (Asphodelaceae)	64

TABLE 14.2 (contd.)

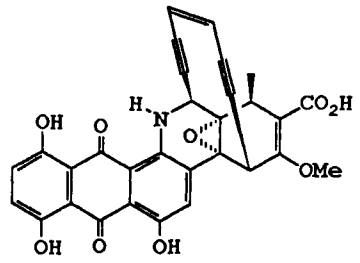
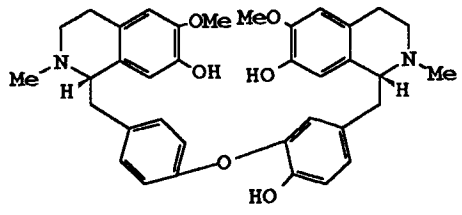
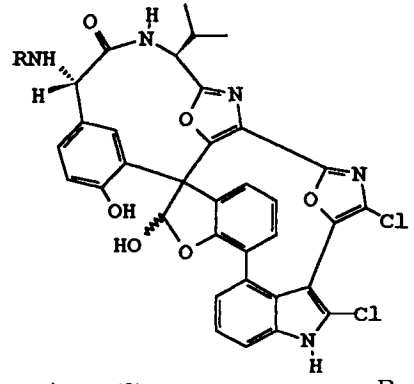
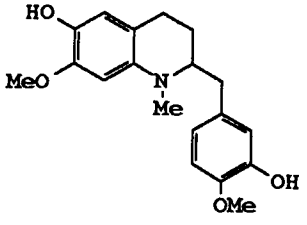
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Dynemycin (5) (Antibiotic)			65
Numularin (7)		Berberis alkaloid	67
Diazonamide (6) (Marine ascidian)		*Diazona chinensis*	66
Berbamunine (8)		Berberis alkaloid	68

TABLE 14.2 (contd.)

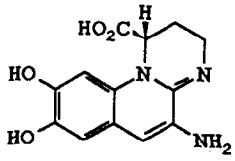
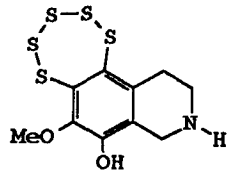
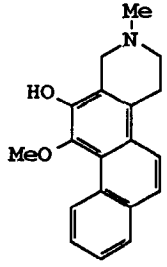
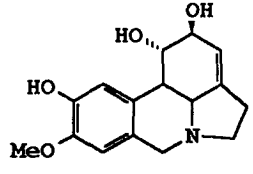
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Pyoverdins (9) (Siderophores)		*Pseudomonas sp.*	69	Polythioisoquinoline (10) (Antibiotic)		*Lissoclinum perforatum*	70
Annoretine (11) (Antitumour)		*Annona montana*	71	Pseudolycorine (12) (Pharmacological activity)		*Narcissus dubuis*	72

TABLE 14.2 (contd.)

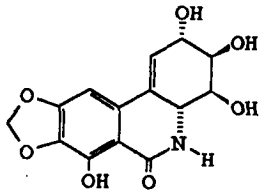
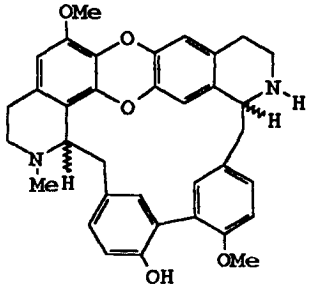
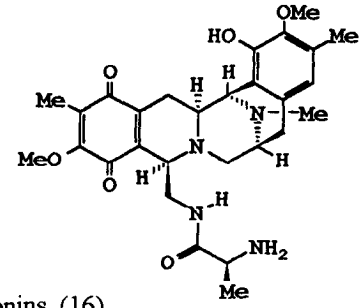
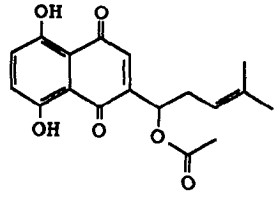
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Narciclasine (13) (Antitumour)		*Amaryllidaceae*	73
Tiliarine (15) (Indian medicinal)		*Tiliacora racemosa*	75
Safracin (14) (Antitumour)		*Pseudomonas fluorescens*	74
Acylshikonins (16) (Inhibitor of DNA topoisomerase)		*Lithospermum erythrorhizon*	76

TABLE 14.2 (contd.)

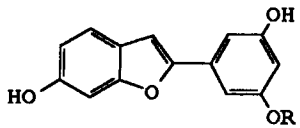
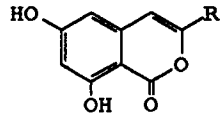
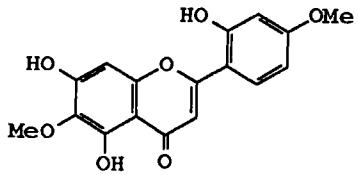
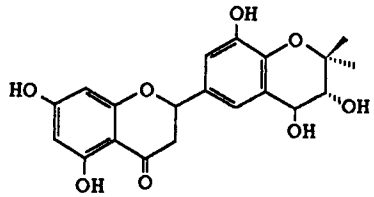
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Moracin (17) (Hypoglycemic)	 R = Beta-D-Glucopyranosyl	*Morus insignis*	77	isoCoumarins (18) (Phytotoxic)	 R = Me, CH_2OH, $CH_2CH(OH)Me$	*Ceratocystis fimbriata*	78
Benzopyranones (19) (Folk medicine)		*Tamarix dioica*	79	Sigmoidin G (20) (Muscle relaxant)		*Erythrina sigmoidea*	80

TABLE 14.2 (contd.)

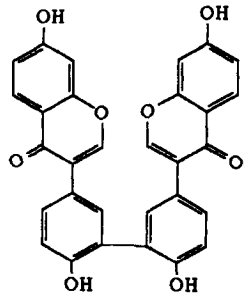
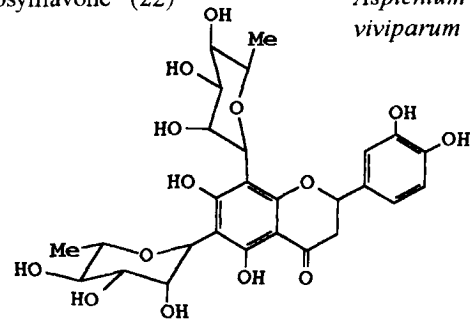
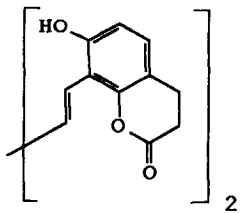
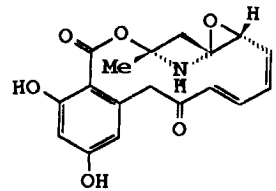
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Kuduisoflavone A (21) (Antibacterial)		*Pueraria lobata*	81	Di-C-Glycosylflavone (22)		*Asplenium viviparum*	82
Citrumarin B (23)		Citrus plant roots	83	Monocillin I (24) (Mycotoxin)		-	84

TABLE 14.2 (contd.)

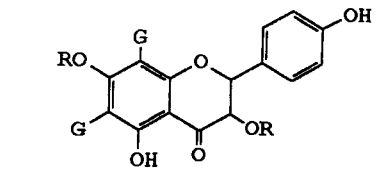
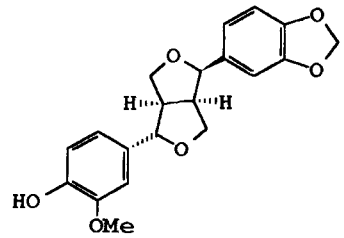
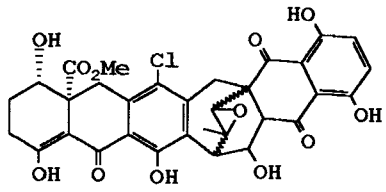
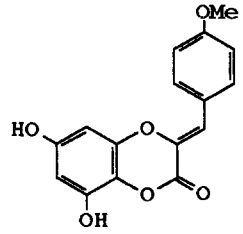
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
O-Glycosylflavonoid (25)	 R = Rhamnose; G = glucose	*Lagonychium farcatum*	85	Lignans (26) (Anticancer)		*Knema austrosiamensis*	86
Betiocolin I (27) (Toxin)		*Cercospora beticola*	87	Yurenolide (28) (Phytoalexin)		*Lilium maxiowiczii*	88

TABLE 14.2 (contd.)

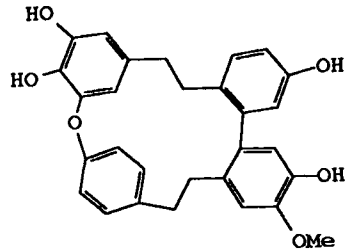
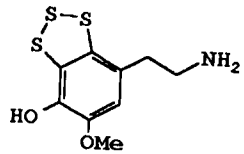
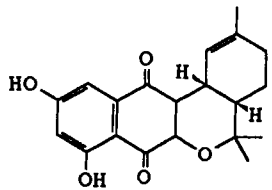
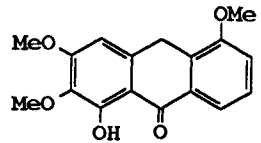
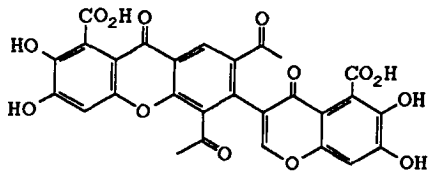
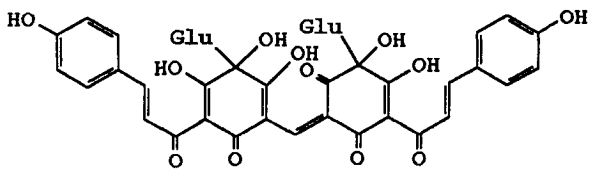
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Plagiochin B (29) (Liverwort)		*Plagiochila acantophylla*	89	Lissoclinotoxin (30) (Antimicrobial)		*Lissoclinum perforatum*	90
Naphthgeranine (31) (Antibiotic)		-	91	Xanthones (32)		*Halenia corniculata*	92

TABLE 14.2 (contd.)

COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Xanthones (33) (CDbinding activity)		*Penicillium glabrum*	93
Carthamin (35) (Colourant)		*Carthamus tinctorius*	95

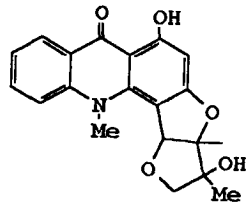
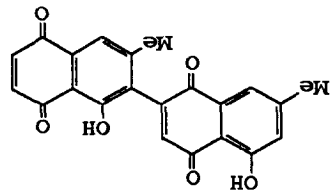
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Rutagravine (34) (Antimicrobial)		*Ruta graveolens*	94
Diosporin (36) (Antiprotozoal)		*Diospyros* and *Euclea sp.*	96

TABLE 14.2 (contd.)

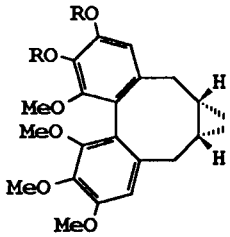
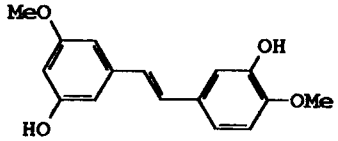
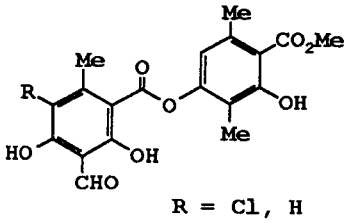
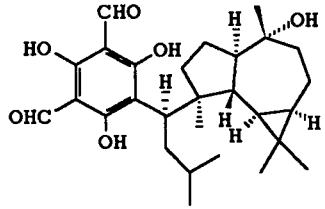
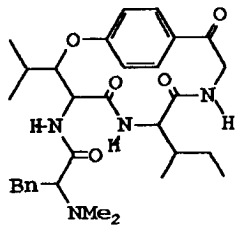
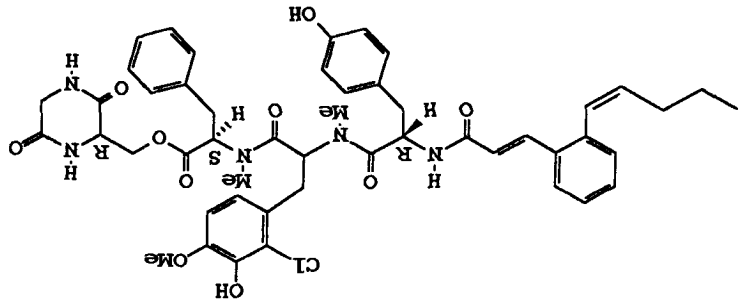
COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Schizandrin (37)		*Schizandra chinensis*	97	Stilbenes (38) (Dihydro compd. antileukaemic)		*Pices abies*	98
Oakmoss (39) (Allergenic)		*Evernia prunastri*	99	Macrocalpals (40) (HIV-RTase inhibitors)		*Eucalyptus globulus*	100

TABLE 14.2 (contd.)

COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.	COMPD. (ENTRY) (BIOL. ACTIVITY)	STRUCTURE	OCCURRENCE	REF.
Peptide alkaloid (41) (Asian medicine)		*Antidesma tetrandrum*	101	Phenolic peptide (42)		Microbial meabolite	102

Pseudomonas are cultivated in an iron-deficient medium. Marine invertebrates are a source of compounds with biological activity and the pentathianyltetrahydroisoquinoline depicted in entry 10 is an example of a metabolite isolated from a tunicate. The methanolic extract of stems and leaves of *Annona montana,* a small evergreen tree indigenous to the West Indies, Brazil and Taiwan has antitumour activity attributable to alkaloidal components including the novel compound annoretine (entry 11) and other known alkaloidal constituents. *Narcisus dubius* of the Amarillidaceae a family familiar for the pharmacological activity of its members afforded three structurally related alkaloids including pseudolycorine (entry 12), by methanolic extraction and chromatographic purification. Highly oxygenated alkaloids such as the phenolic narciclasine (entry 13) isolated from bulbs of the *Narcissus* genus have antitumour activity through the inhibition of protein synthesis. An enantiospecific approach to the synthesis of the phenanthridone structure has been originated. (-)-Safracin A (entry 14) is structurally related to the saframycins and to the ecteinascidins from a tunicate *Ecteinascidia turbinata* which has potent *in* vivo antitumour activity. Following determination of the absolute configurtion of the former, a total synthesis is being approached. From the common Indian medicinal plant *Tiliacora racemosa*, nine bioactive alkaloids of the bis-benzylisoqunoline group have been isolated, three of which are known and six, including tiliarine (entry 15), are novel. The natural acetoxyshikonin, 2-(1-acetoxy-4-methylpent-3-enyl)naphthoquinone (entry 16) proved to be the most active, when compared with a synthetic acyloxy homologous series, in its inhibitory effect on the enzyme DNA topoisomerase.

In the oxygen heterocycle series, from sixteen natural sources screened by using their hypoglycemic activity during isolation, two new compounds, moracin-3'-O-β-D-glucoside (entry 17) and mulberrofuran were characterised. From the fungus *Ceratocystis fimbriata* which afflicts the coffee tree and also related species which attack other trees, recalling also the incidence of Dutch elm disease caused by a relative *Ceratocystis ulmi*, a phytotoxic isocoumarin (entry 18) has been chacterised. Several *Tamarix* species are familiar in folk medicine for their curative properties towards a variety of ailments and five new highly oxygenated flavones, typified by entry 19, have been identified from *Tamarix dioica*. Although *Erythrina* species are more familiar as sources of physiologically active alkaloids they also produce flavonoids as secondary metabolites. Thus the novel sigmoidin G (entry 20) as well as the known sigmoidin C and senegalensin has been derived from *Erythrina sigmoidea.* Three new dimeric isoflavones including the symmetrical kudzuiisoflavone A (entry 21) have been produced from *Pueraria lobata* under special cultivation conditions which elicited and induced bis-benzopyranone formation and not that of pterocarpan phytoalexins. A bis-C-glycosylflavonoid, identified as the new product, luteolin 6,8-di-C-rhamnoside (entry 22), has been obtained from a fern source of the *Asplenium* genus. The citrus root is a source of both acridone alkaloids and coumarins and recent work has shown the presence of four biscoumarins including citrumarin B (entry 23). Monocillin I, a mycotoxin having

a structure (entry 24) reminiscent of zearalenone although more highly substituted, is a macrolide which has been synthesised with modifications and improvements on the original method. A series of flavonoid glycosides in which the members have an O-rhamnoside, or a further O-rhamnoside, O-robinoside or O-rutinoside substituent and each also has two C-glucoside residues (entry 25) has been isolated from certain Egyptian plants of the leguminoseae type. The barks of trees of the *Knema* species (myristicaceae) reputedly used as ingredients in Thai folk medicine for the treatment of cancer, contain lignans and isocoumarins as well as anacardic acid derivatives and cardanols (chap. 13). Thus for example the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignan, (+)-xanthoxylol (entry 26) has been isolated although the South American *virola* species has been a previously described source. A series of compounds termed beticolins all of which have as one structural element a 1,4-dihydroxybenzene ring from the mycelium of the source *Cercospora beticola* are toxins manifesting various biological effects. All are closely related structurally and that of beticolin I is shown (entry 27). Phytoalexins are antimicrobial compounds that are synthesised *de novo* by plants infected by microorganisms and they constitute a growing number of compounds which are often associated with particular plant families. Yurenelide, a novel phyoalexin compound having a 3-benzylidene-1,4-dioxin-2(3H)-one structure (entry 28) has been isolated from a lilliaceae species. Liverwort species are a source of macrocyclic bis(bibenzyls) typified by the plagiochins which have one Ar-O-Ar and one Ar-Ar bond. Plagiolin A (entry 29) is one of five related compounds some of which exhibit cytotoxic activity towards P-388 murine leukemia. The 1,2,3-trithian, lissoclinotoxin A (entry 30), isolated from the tunicate, *Lissoclinum perforatum* shows potent antimicrobial and antifungal activity. Naphthgeranine A (entry 31) is one a group of structurally similar pyranonaphthoquinone antibiotics, isolated as microbial metabolites, the synthesis of which has been studied from 3,5,7-trihydroxynaphth-1,4-quinone by reaction with citral under mildly acidic conditions (cf. examples in Chap. 12). *Halenia corniculata* is a Mongolian variety of the *Halenia* genus of which more than 80 species are known. New xanthones such as 1-hydroxy-2,3,4,5-tetramethoxyxanthone (entry 32) and 2,3,4,5-tetramethoxy-1-O-primeverosyloxyxanthone are among six related structures isolated for the first time. Fermentation of *Penicillium glabrum* resulted in the known polyketide metabolites citromycetin and anhydrofulvic acid and and several novel xanthones (entry 33) believed to have been formed by the dimerisation of two C_{14} polyketides such as for example the citromycetin precursor polivione. Rutagravine (entry 34) an antimicrobial alkaloid is a member of a new class possessing a difuranoid structure derivable in racemic form from rutacridone, an isopropenylfurano precursor, by oxidative cyclisation through formation of an intermediate diol. The synthesis of carthamin (entry 35), the red colouring material of the flowers of safflower, has been studied from 2,3,4,6-tetrahydroxyacetophenone by C-glucosylation at the 3-position, methylation, formation of a chalcone-type intermediate with 4-hydroxybenzaldehyde and a projected methylenation step. Diosporin, (entry 36),

a bisnaphthoquinone with antiprotozoal and antitumour activity and its synthetic analogues have been extensively bioassayed. Schizandrin, (entry 37) a hexamethoxy compound (R = OMe) and its bismethylenedioxy analogue, gomisin, have been synthesised in chiral form from a phenolic tetramethoxy precursor (R = H) commencing with a Stobbe condensation of 3,4,5-trimethoxybenzaldehyde and diethyl succinate. Hydroxylation of the double bond of highly methoxylated stilbenes from *Picea abies* with catalysis by means of the reagent, $TiCl_4$-$NaBH_4$ has led to derivatives (entry 38) with antileukemic activity. The allergenic activity attributed to aldehydic constituents of oakmoss (entry 39) from *Evernia prunastri* or *furfuraceae* can be reduced by reaction with aminoacids. *Eucalyptus* species have afforded a great variety of natural products and in the case of the leaves and calices of *Eucalyptus globulus,* five new macrocalpals (entry 40) which have inhibtory activity towards HIV-RTase have been isolated and characterised. A cyclopeptidic alkaloidal derivative of 4-hydroxyacetophenone (entry 41) has been isolated from an Asian medicinal plant. Microbial metabolites which can influence lipid biosynthesis have been found, such as pepticinamin, (entry 42) which possesses a peptide chain having three C-4-hydroxybenzylpeptide substituents.

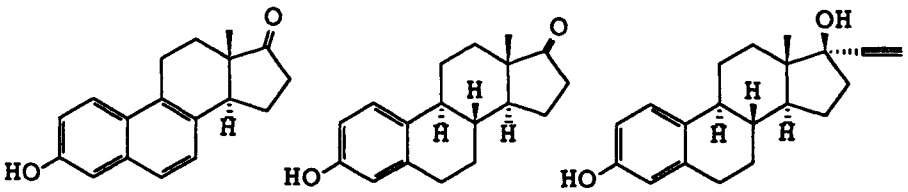
14.4 Syntheses of Selected Natural Phenolic Compounds

In the final part of this chapter attention will be given to describing the syntheses of five compounds listed in Table 14.1, four of which are probably widely known worldwide, at least in formulated products, although the fifth is by contrast relatively unknown except to those concerned with macrolide antibiotics. Of the first four only one, namely estrone has been obtained on an industrial scale by total synthesis, the other three, repectively morphine, carminic acid and terramycin are obtained by biological or extractive processes while the fifth maytansinol, a phenolic methyl ether,of great initial promise as an antileukaemic substance is unlikely to reach commercial utilisation. It is included to show the significance of the synthetic chemical methodology involved. A justification of these syntheses is probably superfluous since the activity involved is a result of human curiosity, enquiry and the inevitable search for knowledge; and has been said of climbing mountains, it is done 'because they are there'.

14.5 Synthesis of Estrone

The classical work of Butenandt and Doisy on the isolation of the estrognic hormone, estrone in 1929 from pregnancy urine was aided by much preliminary biological work, the introduction of important bioassay methods by Allen and Doisy in 1923 and Ascheim and Zondek and the involvement of the company Schering AG. The structure was elucidated through the work of several different groups on the synthesis of numerous degradation products. Estrone and its derivatives from such natural sources were soon introduced into therapy. The first synthesis of a steroid, namely the naphthalenic relative equilenin (3)

(ref.103) was a step which was followed by the more difficult construction of estrone itself by Anner and Miescher which was published in 1948 (ref.104). (+)-Estrone (4, and Table 14.1) was also obtained, by a route very similar to used for equilenin, and the synthesis of stereoisomers was described (ref. 105). The natural product appeared to be the most desirable target molecule of the sixteen possible stereoisomers and from that time strenuous endeavours have now resulted in a large number of alternative syntheses.
This synthetic work became of added interest not only through the useful



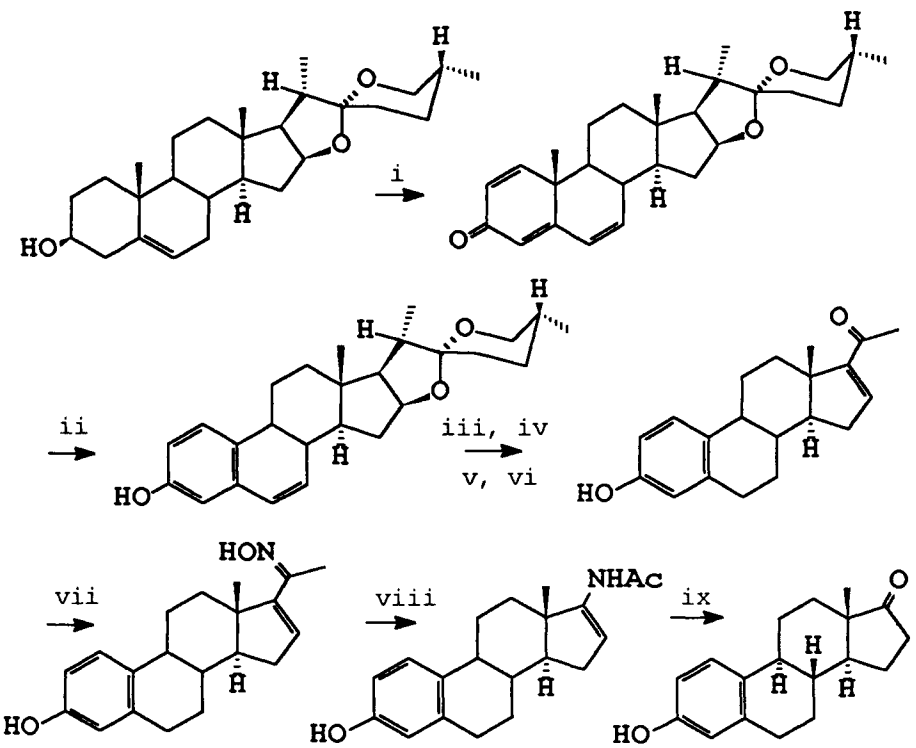
(3) (4) (5)

therapeutic properties of estrone irself but because of its value as a route to 19-norsteroids of value as oral contraceptives, the most popular form of contraception in the USA and the third in the world generally (ref.106). They were developed in the sixties and still represent a large volume of commercial pharmaceutical activity. Ethynyl estradiol (5), a compound first made in 1938 is very much more active than estrone and is widely used as the estrogenic component in combination with progestins in such products. Norhisterone and norethynodrel are important carbonyl compounds. obtained by the key reaction, the Birch reduction of estrone methyl ether. Estrogens in more recent years have been primarily employed in hormone replacement therapy (HRT) as it has become termed, now often adopted in the postmenopausal phase. There has been interest also in the retardation of osteoporosis by the use of estrogens but side effects and other issues (ref. 107) have led to a diminution in their recommendation. The soluble sodium estrone O-sulphate is also used in estrogen replacement therapy and various mixtures of compounds in the preparation Premarin. This is related to equilenin, containing for example 17α-dihydroequilenin and 17α-estradiol which have been derived from pregnant mares's urine, a source reminiscent of the initial work on the isolation of steroidal hormones. Intense interest and commercial demands in this whole area have on the one hand led to an array of synthetic pharmaceuticals structurally dissimilar to estrone and on the other to a whole variety of total synthetic strategies directed at estrone itself as a primary target. Because of their relative simplicity semi-synthetic routes have from the beginning also been highly attractive and in fact the industrial routes of choice. These have entailed the examination of many different natural products resources in preference to waste metabolic sources.

14.5.1 Semi-Syntheses of Estrone

An inherent problem in the transformation of plant steroids to nor-steroids (compounds lacking the C_{19} methyl group) is the removal of the unactivated 19-methyl group and the formation of the required aromatic ring since this was always an absent stuctural feature in those natural product. Early work was concerned with the use of diosgenin (ref. 108) and the derivation of a dienone ring (ref. 109) which was then thermally aromatised (ref, 110).

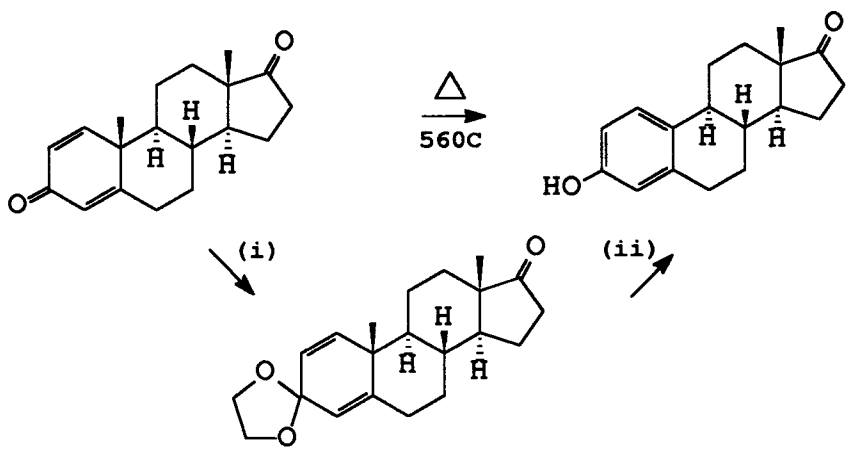
Reagents (i) Oxidn., (ii) 600C, heat min.oil, (iii) Pd-C, H_2 , (iv) Ac_2O, H^+,



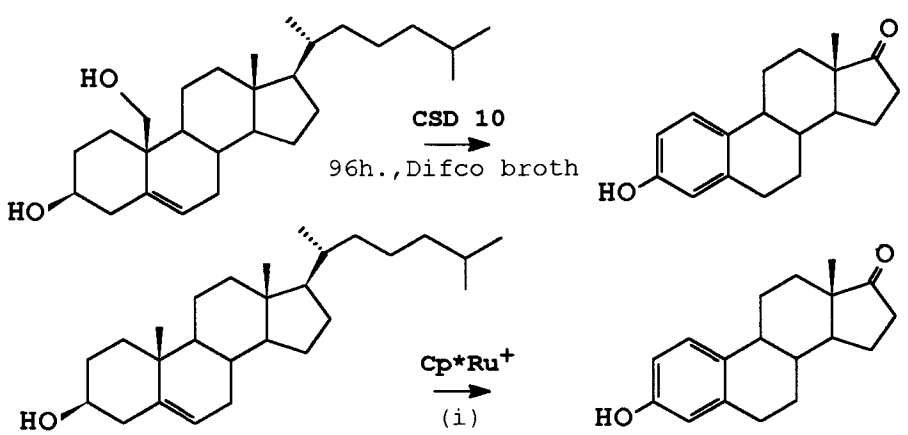
(v) CrO_3, AcOH, (vi) HO^-, (vii) H_2NOH HCl, Py. (viii) $AcNHPhSO_2Cl$, Py. 20C, (ix) H_3O^+

Subsequently readily available cholesterol has been degraded microbiologically to androst-1,4-diene-3,17-dione which is then ketalised with ethanediol to form regiospecifaically the 3-ketal, aromatisation of which occurs upon mild reaction with lithium in THF containing diphenyl/diphenylmethane Reaction takes place by way of the radical anion obtained from the lihium and diphenyl and diphenylmethane quenches the methyllithium arising from the leaving angular

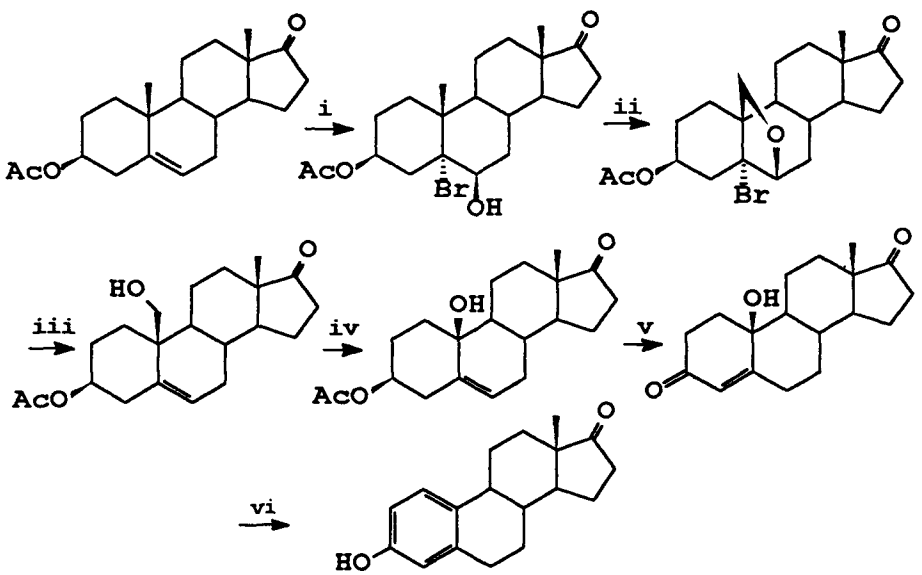
methyl group. Acidic hydrolysis affords estrone (ref. 111), Phytosterols also furnish appropriate raw materials for microbiological degradation.
Thermal aromatisation has been applied to the androst-1,4-diene-3,17-dione to obtain estrone, as in the early diosgenin work, namely through the Inhoffen approach, by passage of the dienone in mineral oil through a hot tube at 560°C.
Reagents (i) Ethane diol, 4-TSA, (ii) Li,biphenyl, THFreflux,$(Ph)_2CH_2$; H_3O^+



The microbial conversion of 19-hydroxycholesterol, obtained chemically in three steps from cholestery acetate, to estrone by incubation with the microorganism CSD-10 afforded estrone in a single step in 72% yield (ref.112) following



experiments with *Nocardia restrictus* (ref. 113).
A one-step chemical procedure (i, in the scheme) has proved valuable. Thus cholesterol and its oxidation product, dehydroisoandrosterone have been selectively aromatised by reaction with the electrophilic ruthenium complex (Cp^*Ru^+), η^5-cyclopentadienyl Ru^+, obtained by protonation in THF of $[Cp^*Ru(OMe)_2]_2$ (1 mol) with triflic acid, CF_3SO_3H (2 mol). The addition of cholesterol (2 mol) in THF during 40 hours at 120°C (or in dichloromethane at 90°C) afforded estrone in 48% yield with evolution of methane (ref. 114).
In early work directed towards 19-norsteroids, derivatives of the 19-methyl group have been obtained (ref.115) and the group then removed to effect aromatisation. This method for obtaining the 19-hydroxy derivative proved valuable for many subsequent workers.
Thus it has been used as the first stage to obtain the starting material for the microbiological method with CSD-10 and simplified in more recent work leading to a synthesis of estrone in four steps from 3β-acetoxy-19-hydroxyandrost-5-en-17-one (ref.116). Cholesteryl acetate was transformed by standard methods to the required androstane compound shown in the following scheme, which with hypobromous acid followed by lead tetraacetate and zinc reduction (cf. ref. 115) afforded the 19-hydroxy derivative. This with thallium nitrate in dioxan underwent loss of formaldehyde and hydration with water to afford the 19-nor-10β-alcohol in 70% yield. The diol obtained by saponification was converted by Oppenauer oxidation with N-methylpiperid-4-one as hydride aceptor (ref. 117) and afforded a 78% yield of the enone which was transformed almost quantitatively into



estrone by treatment with 4-toluenesulphonic acid.

Reagents (i) NBA, 0.5M $HClO_4$,dioxan, (ii) $Pb(OAc)_4$, I_2 ,$CaCO_3$, C_6H_{12}, hv, (iii) Zn, AcOH,H_2O, (iv) Aq.$HClO_4$, $Tl(NO_3)_3 3H_2O$, dioxane, (v) $Al(i\text{-}OPr)_3$, Oppenauer, (vi) 4-TSA,Et_2O

There is little doubt that semi-synthetic and biological strategies towards estrone are highly attractive. The toxicity of thallium compounds and the use of lead tetraacetate represent drawbacks in the chemical procedures compared with biological approaches. The availability of microbiological methods for transforming cholesterol (and sitosterol) into androstanes enhances the latter methodology (ref. 118).

14.5.2 Total Syntheses of Estrone

The desire for a total synthetic route to estrone has inspired a great range of organic methodologies over a period of nearly half a century. It is only relatively recently that biological methods leading to the aromatisation of ring A have been found and thus total synthetic approaches have tended to dominate the scene. An important early finding referred to earlier was that certain steroids lacking the 19-methyl group, for example norprogesterone, were very physiologically active compared with their 19-methyl analogues. The discovery of the Birch reduction of phenolic ethers, which when applied to estradiol methyl ether led to 19-nortestosterone, although not an oustanding compound compared to testosterone itself, enhanced interest in the search for syntheses which would make a range of structures accessible. Both industrial and academic laboratories have contributed in synthetic activity towards to produce routes, in earlier work, to the racemic product and in more recent enantioselective approaches to obtain the natural (+) form. Following the first synthesis of estrone (ref. 104) which was foreshadowed by earlier work (ref. 119) ensuing years were very much preoccupied with the synthesis of its eight possible racemates and the confirmation of their structures (ref. 120) as well as with improving synthetic methodology. The trans-anti-trans natural form was only equalled in activity by one diasteroisomer and the racemate of the former was the obvious target molecule for future synthetic work.

Synthetic work up to the early seventies has been reviewed (ref. 121). Notable advances at that time were the routes based on 6-methoxytetralone and its reaction with vinylmagnesium bromide and thence with 2-methylcyclopentane-1,3-dione (ref. 122), and the use of 3-(3-methoxyphenyl)propyl vinyl ketone with the same dione (ref. 123). Some of the strategies in ring formation towards the four ring structure ABCD in estrone are depicted in Fig. 14.1 which shows a number of classical retrosynthetic schemes. Although there was a precedent for the use of 1-vinylnaphthalenic compounds from the early work of Dane on Diels-Alder reactions of cyclopentenone, the early work on the synthesis of equilenin and the first synthesis of estrone employed lengthy stepwise approaches very different from later developments which were presaged by others (ref. 119).

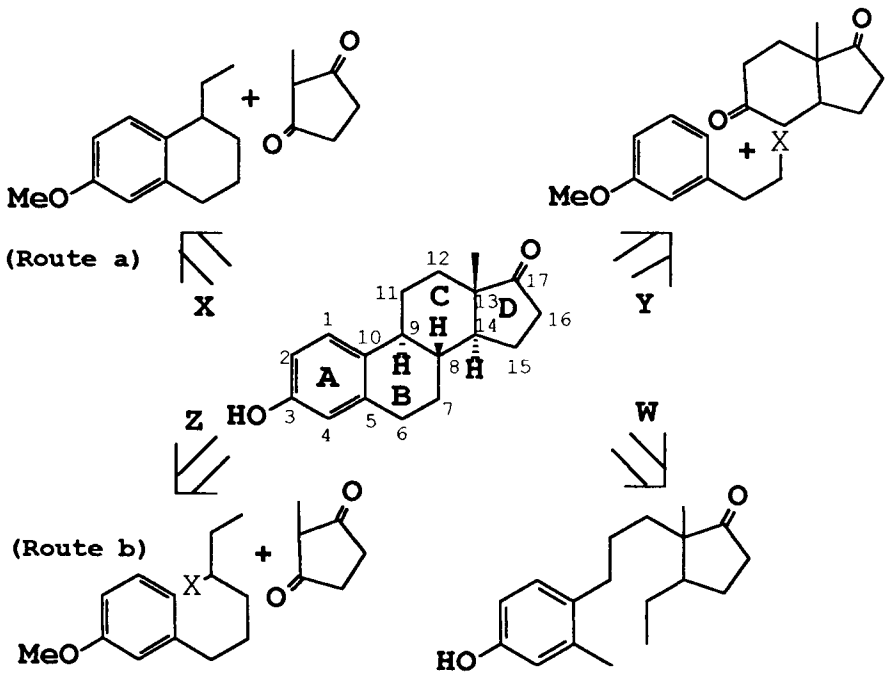
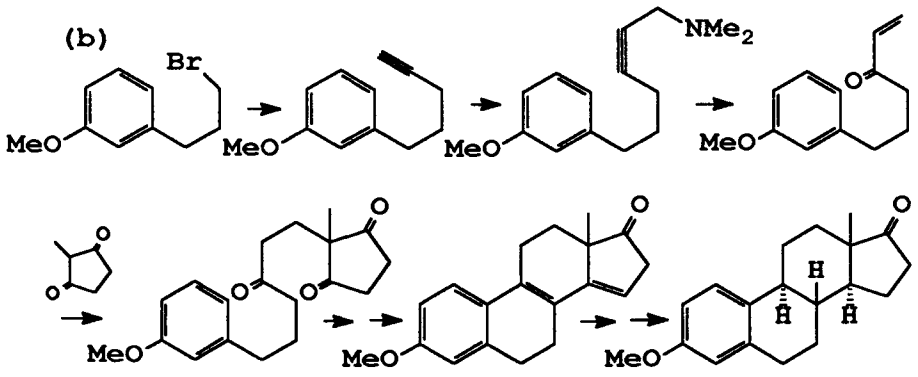


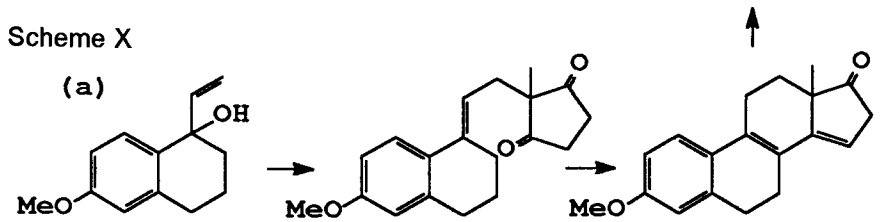
Fig. 14.1 Some Retosynthetic Schemes for Estrone

Fig. 14.1 depicts four approaches X,Y,Z and W of several possible which emphasise the convergent nature of syntheses towards estrone which characterises work during the last three decades by comparison with earlier work which tended to be linear or stepwise in strategy. In the scheme X (AB→ABD→ABCD) in which the disconnections are at C12-C13 and C8-C14, the bicyclic component, typically has been a 2-vinyltetralin (ref.122). The availability of vinylmagnesium bromide, a reagent which eluded Grignard, has facilitated this pathway. In scheme Z (A→AD→ABD→ABCD) the disconnections are the same together with C9-C10 and the strategy has been effected with the aryl component 3-(3-methoxyphenyl)propyl vinyl ketone (X = O) by Michael addition with methylcylopentane-2,5-dione (ref. 123). Strategy Y (A→ ACD→ABCD) proceeds by disconnections at C7-C8 and C9-C10 and as will be seen susequently uses the aryl component 3-bromoacetylanisole. The modes of synthesis in X, Y and Z employ Michael addition reactions, alkylations and ring formation at C8 and C10, often at activated positions by electrophilic attack. In Scheme W (A→AD→ABCD) where the most novel disconection is at C6-C7, a new methodology was introduced comprising the formation of a quinone methide (sometimes from a benzocyclobutene) and electrocyclic formation of ring B by means of a vinyl group attached to the cyclopentanone ring. This methodology D→ABCD) has been exploited by formation of ring A from a C_6 diyne. Aspects of the more recent approaches Y and W are shown in the following sections.

Scheme Z



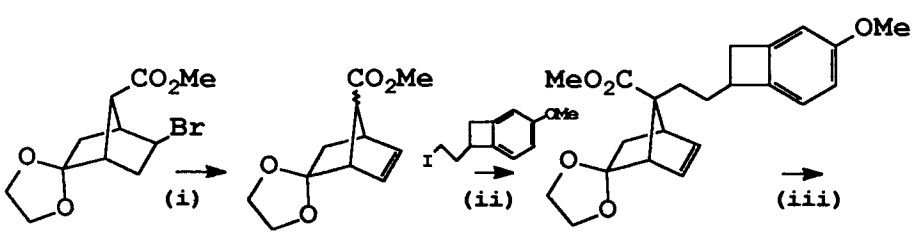
Scheme X

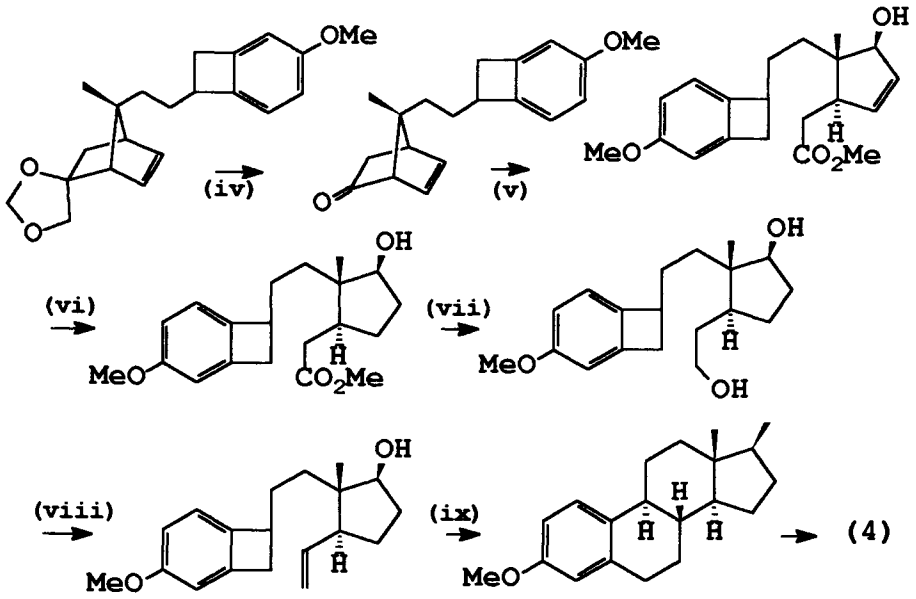


14.5.3 Syntheses of Estrone requiring a Resolution Stage

Based on the use of 4-methoxybenzocyclobutene-1-carboxylic acid, racemic homoestrone has been synthesised (ref. 124). A strategy based on boron annulation led not directly to estrone but to a synthesis of norpregnenolone which was then degraded by standard procedures to afford estradiol derivatives (ref. 125).

Benzocyclobutene derivatives have also been used to alkylate a bicyclo[2.2.1] heptane which after transformation to the appropriate vinyl derivative has been thermolysed to yield the the tetracyclic structure of estradiol methyl ether (ref. 126) which latter upon oxidation with Jones' reagent and demethylation ot the



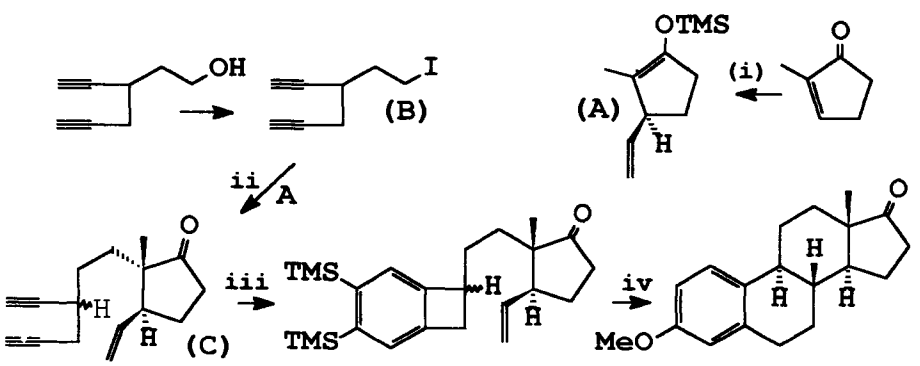


Reagents (i) DBU, DMF,reflux, (ii) LDA, 0C, (iii) LAH, THF, 60C; MsCl, Py. ; $LiEt_3BH$,THF; Pd-C,H_2 (iv) H_3O^+, (v) 10% aq.NaOH, H_2O_2, THF;CH_2N_2 (vi) PtO_2,H_2, (vii) LAH,THF,(viii) 2-$NO_2C_6H_4SeCN$, Bu_3P,THF;50%H_2O_2,THF,(ix)1,2-$Cl_2C_6H_4$,Δ

product with boron tribromide afforded estrone.

By the use of the chiral bromo precursor of the bicycloheptane (at step i) an asymmetric synthesis of estrone was envisaged by the authors.

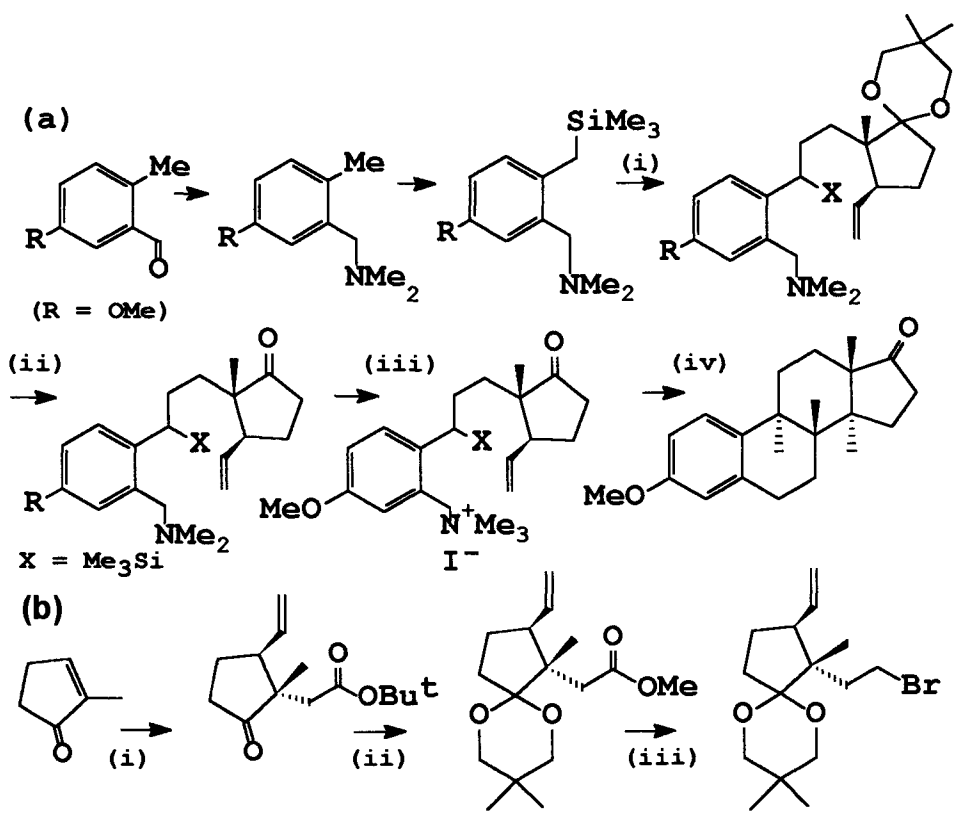
In a highly novel approach an alkylation reaction of a diyne with a vinylcyclopentene derivative has given an intermediate which by cobalt-mediated



cyclisation has afforded the required tetracyclic structure of estrone in one step (ref. 127) as depicted in the scheme shown. The benzobutene intermediate had also been the objective of the synthesis by Kametani (ref.124) but the hydrolysis of a precursor unexpectedly failed to produce the desired compound. The starting material was readily derived from trilithio-1,5-hexadiyne and oxirane and the resultant alcohol afforded the required iodide (B) by reaction of its 4-tosyl derivative with sodium iodide. The product (C) was the major one of three products formed.

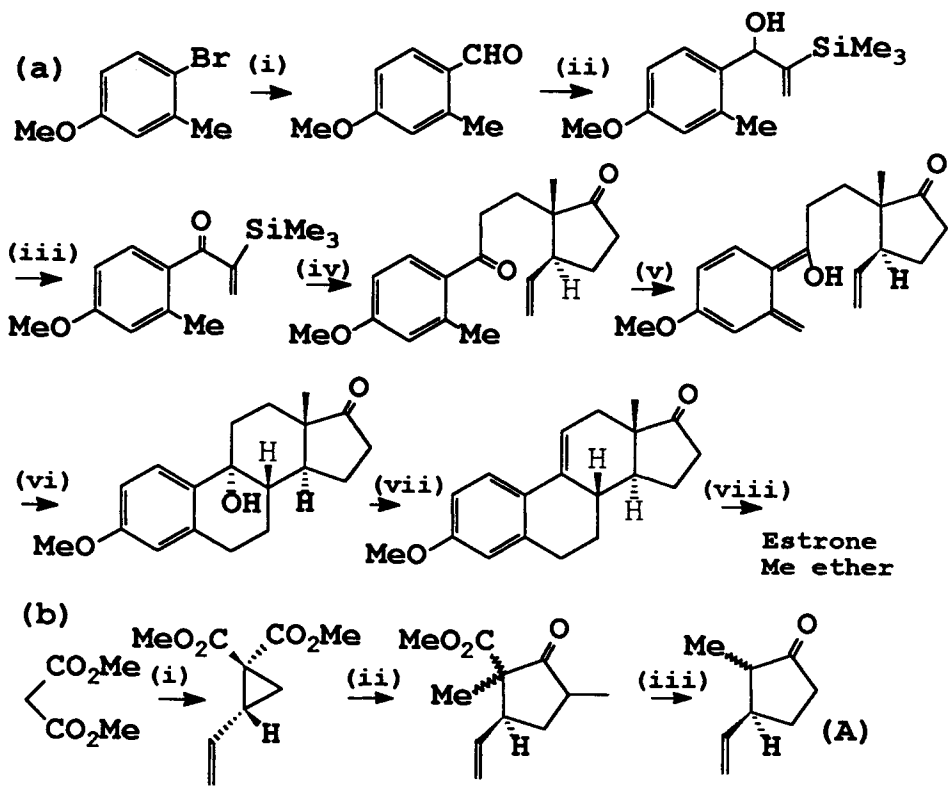
Reagents (i) 2 CH_2=CHMgBr, CuI; TMSCl, (ii) A,$LiNH_2$,NH_3,THF,B,(iii) $(HOCH_2)_2$,H^+; BTMSA,$CpCo(CO)_2$;cat. CF_3CO_2H,AcOH,H_2O, 0C,(iv) $Pb(O_2CCF_3)_4$

Quinodimethanes have been employed in a stereoselective synthesis (ref. 128) of estrone. A silicon-stabilised benzylic carbanion was obtained, avoiding lithiation of the methoxy-substituted ring, from the intermediate [2-[(trimethylsilyl)methyl]-5-methoxybenzyl]dimethylamine and after alkylation with the requisite cyclopentano component, generation of the quinodimethane structure with CsF afforded racemic estrone methyl ether.



Reagents (a) (i) BuLi,THF,ketal from route b, -75C,(ii) H_3O^+, (iii) MeI, (iv)CsF,MeCN.
(b) (i) CH_2=CHMgBr,CuI,THF; $BrCH_2CO_2Bu$-t,HMPA (ii)MeOH/HCl, $HOCH_2CMe_2CH_2OH$,4-TSA, (iii)LAH;TsCl,Py.;LiBr/DMF

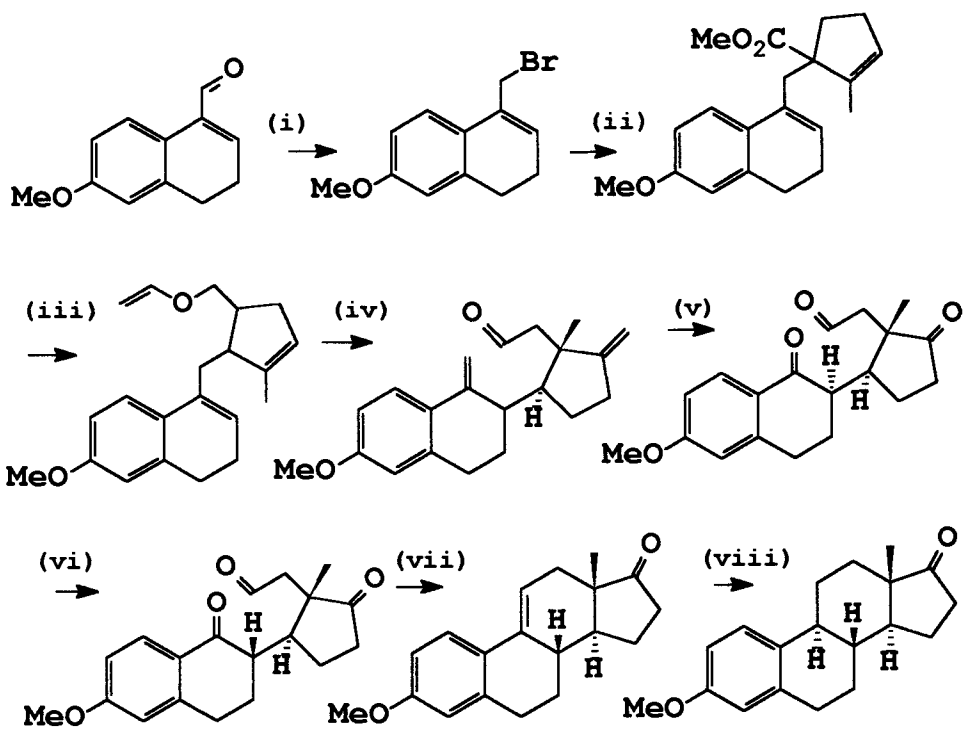
A photochemical route to racemic estrone commencing with 2-bromo-5-methoxytoluene depended upon the generation of a quinodimethane intermediate incorporating an enolic component (ref. 129). Subsequently the method was adapted to furnish an asymmetric synthesis of (+)-estrone as described in the ensuing section. The cyclopentanone component was derived by the reaction of dimethyl malonate with E-1,4-dibromobut-2-ene to give racemic dimethyl 2-vinylcyclopropane-1,1-dicarboxylate which was then transformed by reaction with dimetyl methylmalonate followed by hydrolysis into racemic 2-methyl-3-vinylcyclopentanone.



Reagents (a)(i) Mg; DMF,THF,-20°C,(ii) CH_2=C(Br)$SiMe_3$,THF,0°C,(iii)2-phase chromic oxidn.,(iv)A, $NaOBu^t$,Et_2O,(v)(vi)hυ,py.,(viii) $(CO_2H)_2$,(viii) redn. (b) (i)E-$BrCH_2CH$=$CHCH_2Br$,MeOH,

NaOMe, (ii)$MeCH(CO_2Me)_2$,NaOMe, (iii) HO^-, $-CO_2$

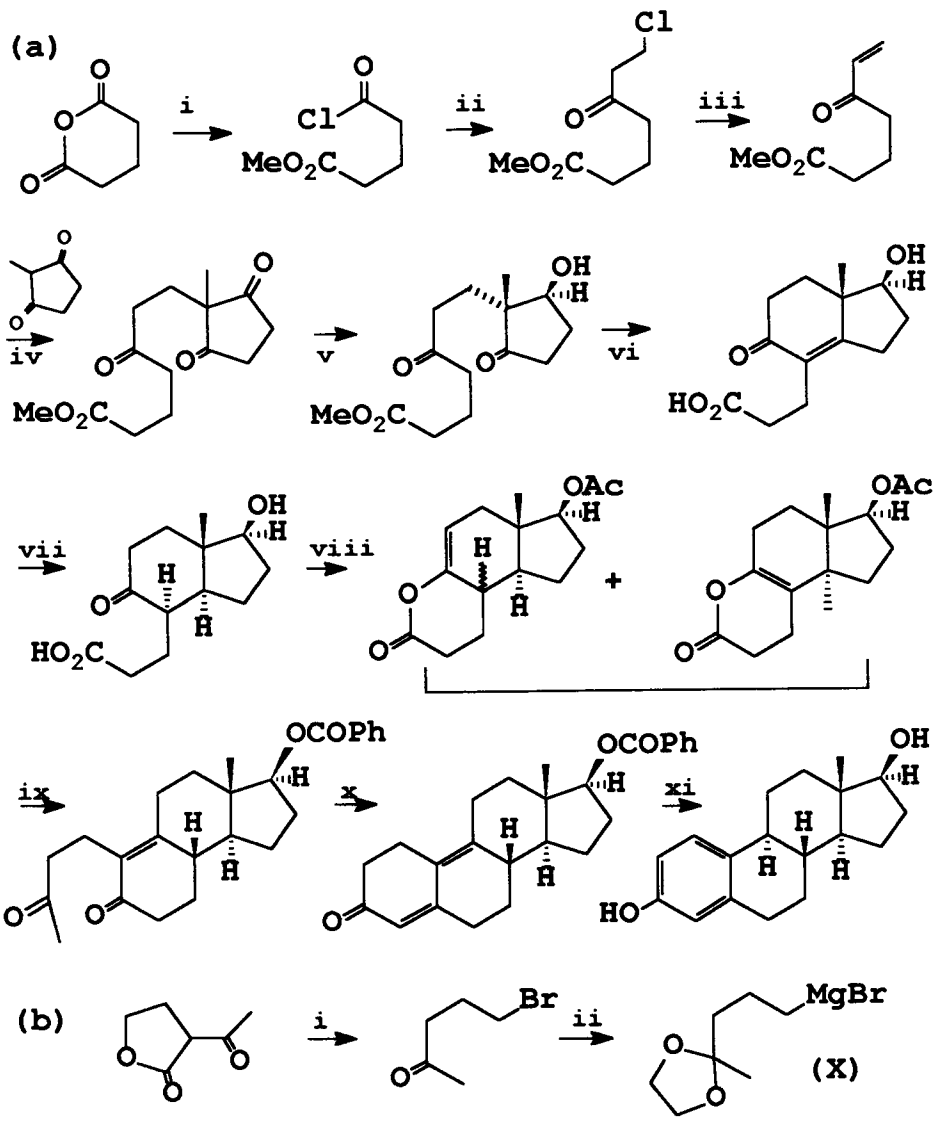
An ingenious approach to racemic estrone has used two reactions in a combined tandem Cope-Claisen rearrangement (ref. 130). 1-Bromomethyl-3,4-dihydro-6-methoxynaphthalene is used to alkylate 1-methoxycarbonyl-2-methylcyclopent-2-ene and the ester group in the product converted to a vinyloxymethyl substituent. Thermolysis afforded a mixture of diastereoisomeric aldehydes (2:1) containing a majority of the trans compound. Ozonolysis and epimerisation at the 8-position succeeded by McMurry coupling gave the required tetracyclic structure from which racemic estrone methyl ether was obtained.



Reagents (i) LAH, Et_2O; $MeSO_2Cl$, Et_3N,;LiBr, Me_2CO,(ii) 2-Me-2-cyclopent-1-CO_2Me,LDA,THF,-70C,(iii) LAH; $Hg(OAc)_2$,CH_2=CHOEt; (iv)$_\Delta$,370C, (v) O_3,CH_2Cl_2, -50C,(vi)NaOMe,MeOH, (vii) $TiCl_3$,Zn/Ag,DME,(viii)K/NH_3;CrO_3

The preceding approaches depict essentially laboratory scale syntheses. In the early stages of interest in the anticipated large scale demand for estrone, several industrial syntheses were developed by a number of different groups all of which differed at the time from other approaches in commencing with ring

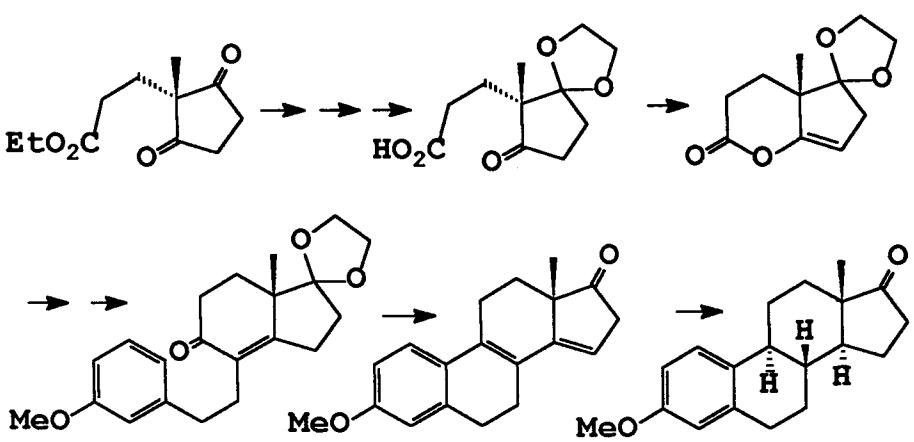
D. for the good reason that a resolution near to the first stage is the least wasteful. A commercial synthesis of estradiol (ref. 131,132) from Roussel-Uclaf, which partly owed something to earlier work by the Ciba group (ref.133), started from glutaric anhydrode and a microbial resolution was effected at the first possible reaction stage, namely step v, in which also simultaneous reduction of a keto group occurred. In the last stages, either estradiol or 19-nortestosterone can be derived.



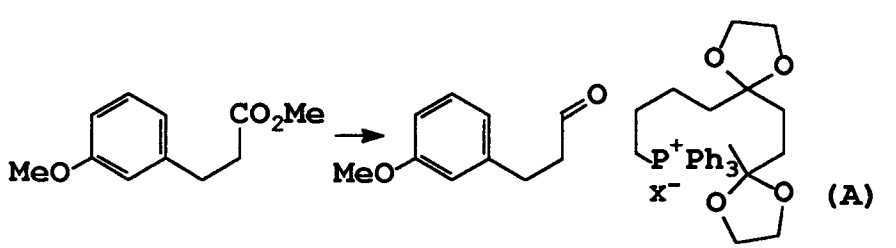
Reagents (a) (i) $SOCl_2$, MeOH, (ii) $CH_2{=}CH_2$, $AlCl_3$ (iii)Et_3N, (iv)MePh,Py.

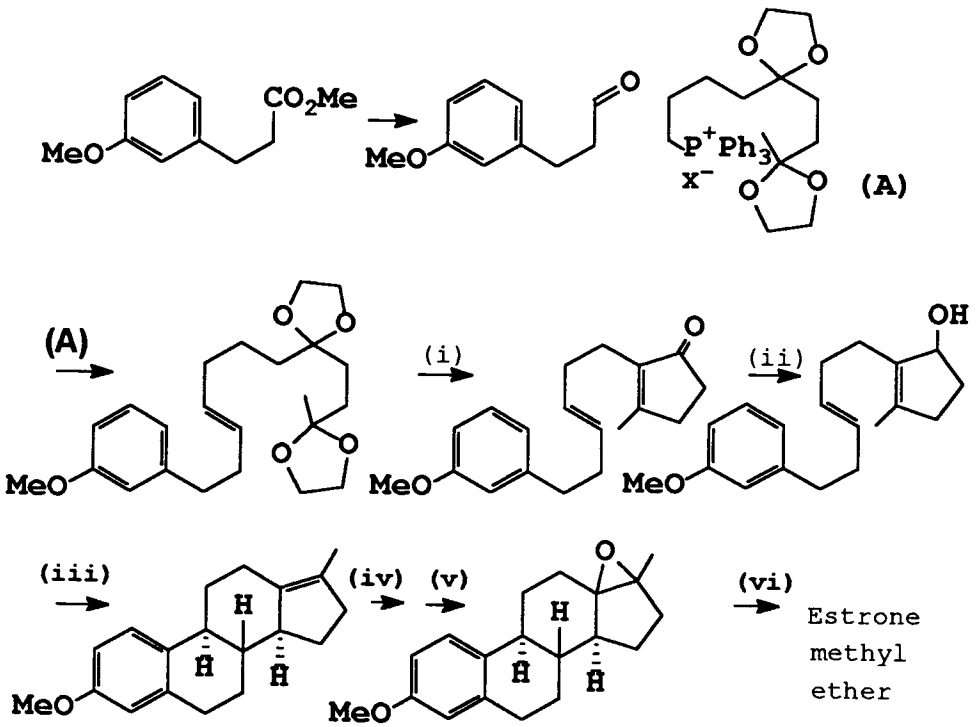
glutaric anhyd.,(v) *Rhyzopus arrhizus*,(vi) HCl,(vii) Pd-C,H_2, (viii) NaOAc/Ac_2O, (ix)X,THF;KOH/MeOH; AcOH/H^+;PhCOCl, (x) $KOBu^t$, (xi) Pd-C,H_2. (b) (i) HBr, (ii) $(HOCH_2)_2$,4-TSA; Mg

A number of variations of the scheme were also introduced. In a later development (ref. 134) a route was evolved having a resolution at the second step and which utilised, at the final stage, the reductive methodology of another group (ref. 123) and the final product was estrone or estradiol methyl ether as required. Thus, 2-methylcyclopentane-1,3-dione was converted by Michael reaction with ethyl acrylate to 2-methyl,2-(2-ethoxycarbonyl)- ethylcyclopentane-1,3-dione which was monoketalised, hydrolysed and the acidic product resolved with cinchonine to afford the isomer with the same relative configuration at the 2-position as in (+)-estrone. After formation of the lactone from the ketoacid, Grignard reaction with 1 mole of 3-(3-methoxyphenyl)propyl magnesium bromide gave the dione which was cyclised under Knoevenagel conditions to the tricyclic α,β-unsaturated ketone from which the required tetracyclic structure of the product was obtained through reaction with polyphosphoric acid. Successive catalytic and chemical reduction afforded the final product.



Cationic cyclisation of an hydroxyalkene produced by way of 3-methoxyhydrocinnamaldehyde and its Wittig reaction with the





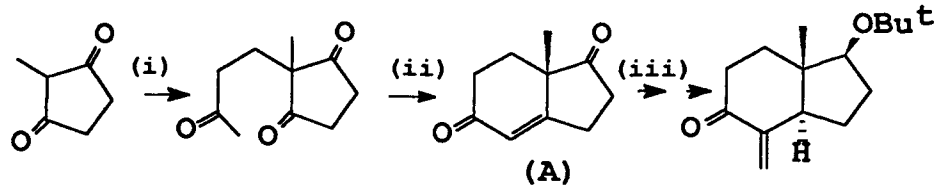
Reagents (i) HCl,EtOH;0.1M NaOH,(ii) $NaAlH_2(OR)_2$,THF,(iii) $SnCl_4$,$EtNO_2$,-70C, (iv)$TsNCl_2$, H_2O/DME, (v) Me_4NOH,(vi)$BF_3.Et_2O$

triphenylphosphoran from the phosphonium salt (A) of the diketal of 1-bromo-2,5-dioxononane, followed by deketalisation, Claisen condensation. and four further novel steps has been effected by Johnson and coworkers (ref. 135). whose classical work on steroids had spanned nearly 40 years. The dioxononane component was synthesised from 2-methylfuran and 1,4-dibromobutane by ring-opening of the product.

14.5.4 Enantioselective Syntheses of (+)-Estrone

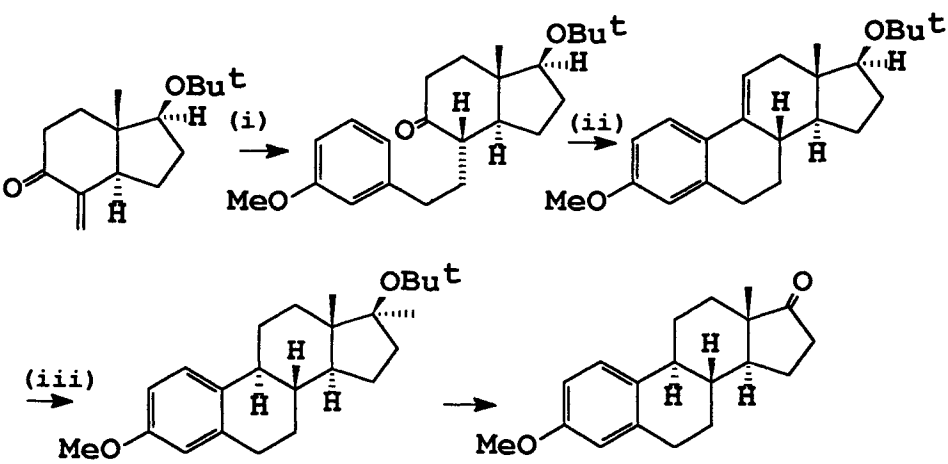
The general interest in asymmetrivc synthesis has led to its application to enantioselective synthetic methodology in the steroid series notably for obtaining (+)-estrone. The wish to be independent of natural chiral compounds employed in semi-synthetic routes has stimulated work with a wide range of chiral reactants. All the routes are characterised by the use of a chiral component in the first step of the synthesis and throughout the succeeding stages enantioselectivity generally prevailed. Earlier work has been reviewed (ref. 136). In the early syntheses the general approach had been AB → ABD → ABCD (Torgov) or AD → ACD → ABCD (Smith) where D was the prochiral 2-

methylcyclopentane-1,3-dione. An important development in this methodoogy was the asymmetric synthesis of a bicyclic ketoindanone (A) in the presence of L-proline from the diketone depicted (ref.137) since this made available the CD ring for subsequent attachment of rings A and B.



Reagents (i) CH_2=CHCOMe, base, (ii) L-proline,(iii) $NaBH_4$;Me_2C=CH_2, H_3PO_4,MeMgcarbonate,DMF;Pd-$BaSO_4$,H_2;HCHO,DMF

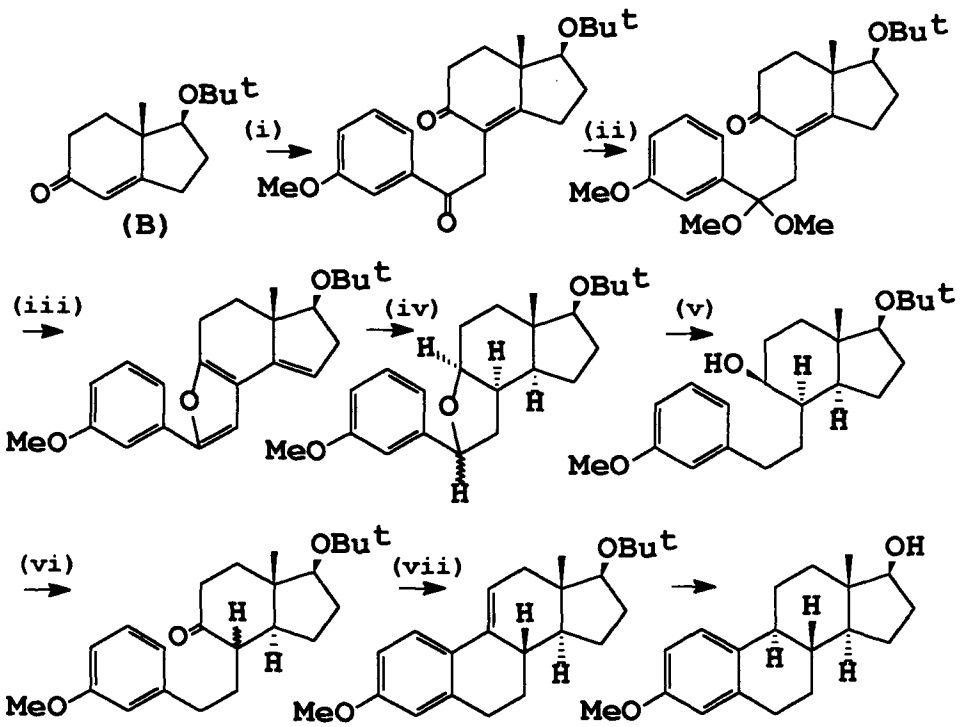
Equally, derivatives of this compound, notably an α-methylenic ketone (ref.138) have led to simplifications by the Hoffmann-La Roche group in the synthesis of (+)-estrone methyl ether (ref. 139). For example 3-methoxybenzyl chloride (ref. 140) was reacted with this α-methylenic compound, readily available from A, and afforded in the presence of Cu(I) a 1,4-addition product in 88% yield with little accompanying 1,2-addition. Electrophilic cyclisation with methanolic HCl afforded the tetracyclic product by way of the protonated ketone in 77% yield. Hydrogenation, in which some 9β epimer also resulted, followed by treatment of the crude product with trifluoroacetic acid and Jones oxidation gave estrone methyl ether in 63% yield.



Reagents (i) 3-OMe$C_6H_4CH_2$Cl,Mg,THF, (ii) aq.HCl,MeOH,(iii) Pd-C,H_2,EtOAc,(iv) CF_3CO_2H; Jones oxidn.

In a synthesis from the Schering group, the α,β-unsaturated ketone B (ref. 138) gave with 3-methoxyphenacyl bromide in THF containing sodium hydride the α-

alkylation product in 84% yield which was transformed in 4 high yielding steps to the same ketonic precursor as in the previous synthesis and thence to estradiol methyl ether (ref. 141).

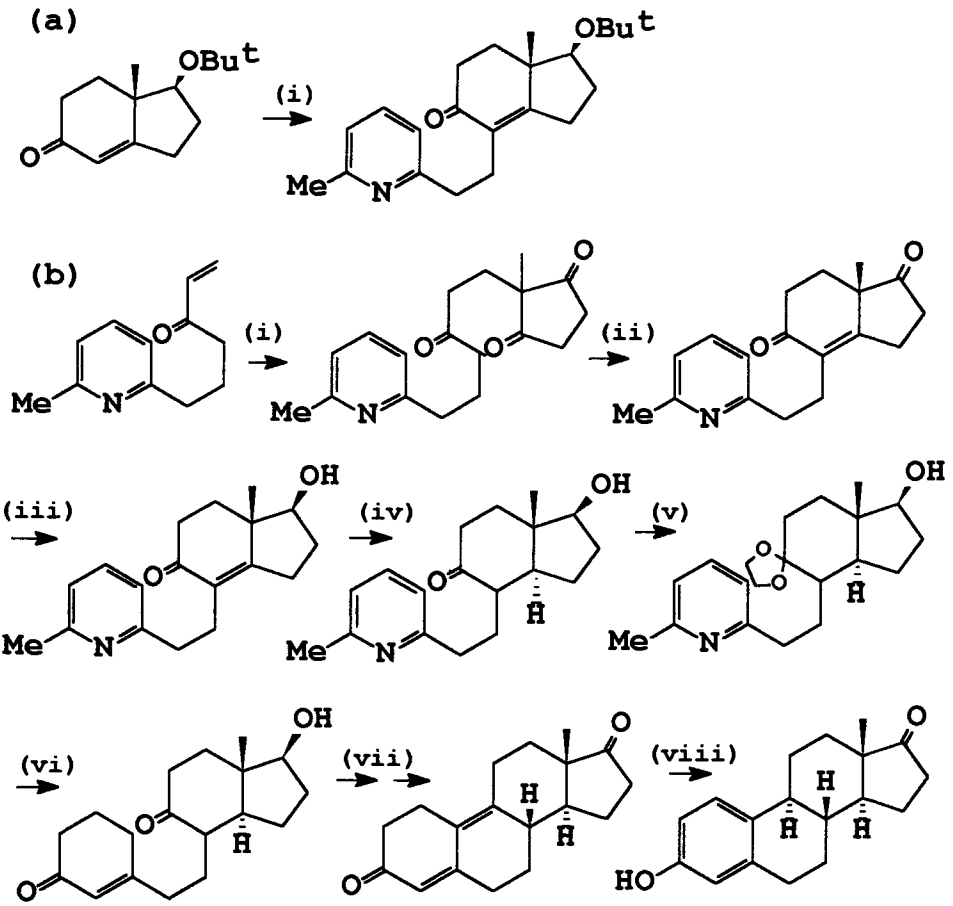


Reagents (i) NaH,THF, (ii) $HC(OMe)_3$, 4-TSA, (iii) H^+, (iv)(v) Pd-C,H_2,MeOH, (vi) Jones oxidn. Me_2CO, (vii)MeOH,HCl, (viii)Pd-C,H_2; HCl,dioxane

The continous search for high yielding syntheses and the elusive 100% yield has inspired several quite distinct novel enantioselective approaches to (+)-estrone following the outstanding industrial work of the sixties and early seventies.

The bicyclic indanedione used by the previous groups has been reacted with 6-methyl-2-vinylpyridine in a ingenious methodology (ref. 142) in which the pyridine ring is finally converted in high yield to a carbocyclic ring by Birch reduction (route a). The prefered and higher yielding pathway (route b) was found after extensive work to be reaction of 2-methylcyclopentane-1,3-dione with the vinyl 6-methypyridylpropyl ketone depicted to give the prochiral dione which was asymmetrically cyclised in the presence of L-phenylalanine to afford a chiral pyridylethylindandione. Two advantages of this strategy were the access to norsteroids and thence (+)-estrone directly with avoidance of demethylation.

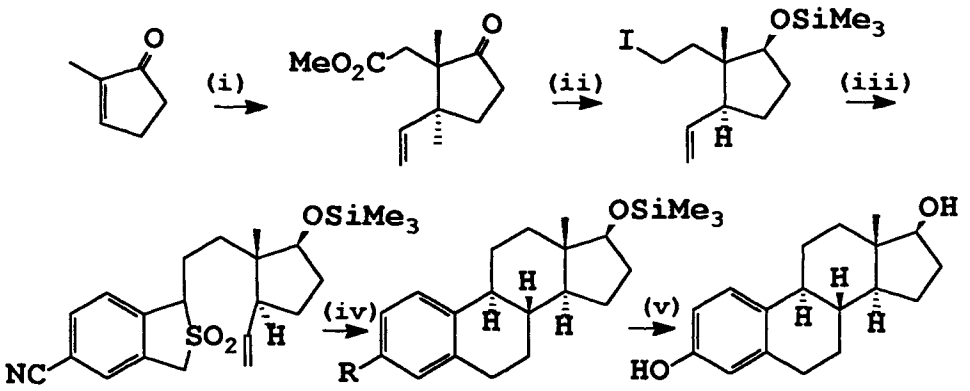
The starting material was readily synthesised from monolithio 2,6-dimethylpyridine and 1-chloro-3,3-diethoxypropane, hydrolysis, reaction with vinyl magnesium bromide and oxidation.



Reagents (a)(i)KOAm^t; H_3O^+. (b) Michael addn., base, (ii) L-phenylalanine ,1MHClO$_4$, MeCN, (iii),(iv)(v)Pd-C, H_2, $(HOCH_2)_2$,Et_3N,(vi) EtOH,Et_2O,Na,NH_3;HO^-,(vii) Jones oxidn.;4-TSA,AcOH,(viii) Ac_2O, AcBr,CH_2Cl_2; aq.K_2CO_3 ;H_3O^+.

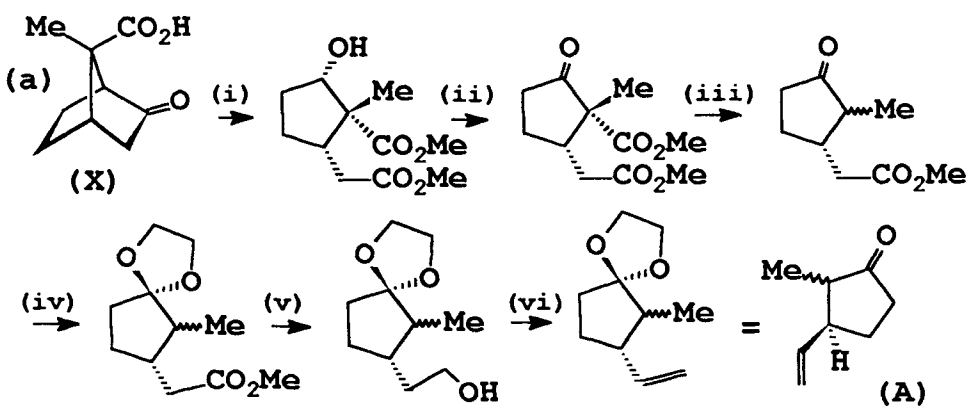
A synthesis of (+)-estradiol from an alkyl 1,3-dihydrobenzo[c]thiophene-2,2-dioxide involving o-quinodimethane formation by thermal extrusion of SO_2 and subsequent cycloaddition has been achieved in an overall yield of 50% (ref. 143). Thus a chiral cyclopentanone component (ref. 144) was used to alkylate the appropriate benzothiophene dioxide and the required tetracyclic stucture obtained directly with avoidance of the customary hydrogenation. It was found desirable at the alkylation stage to enhance deprotonation at C1 by having a cyano group in the benzenoid ring. The cyanotetracycle (R = CN) was reacted

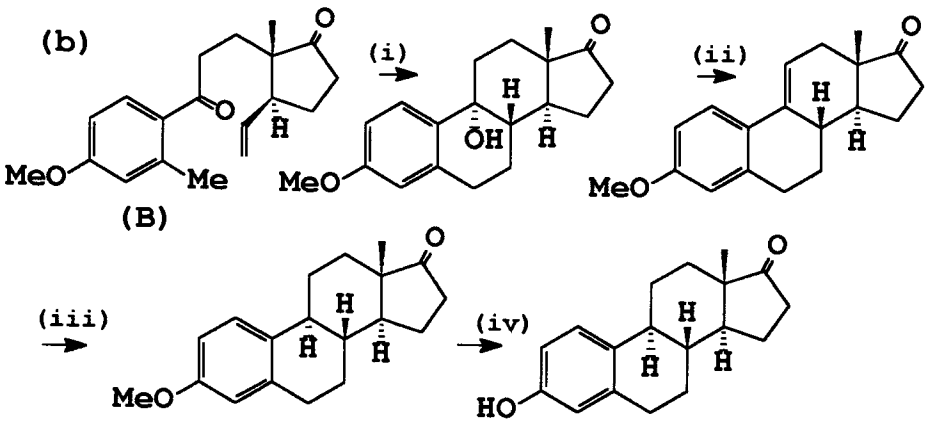
with methyllithum to form upon hydrolysis the acetyl derivative which upon Baeyer-villiger oxidation afforded (+)-estradiol.



Reagents (i) Bu^{t}C≡C(Li)CuCH=CH_2,THF,-20°C; $BrCH_2CO_2Me$, HMPT;HO^- ; resoln.(+)-ephedrine,(ii) routine steps (iii)5-cyano-1,3- di-hydrobenzothiophene-2,2-dioxide, NaH,THF HMPT, (iv)Δ, 1,2,4-trichloroC_6H_3, (v)MeLi, -20°C;CF_3CO_2H,CH_2Cl_2HCl,MeOH.

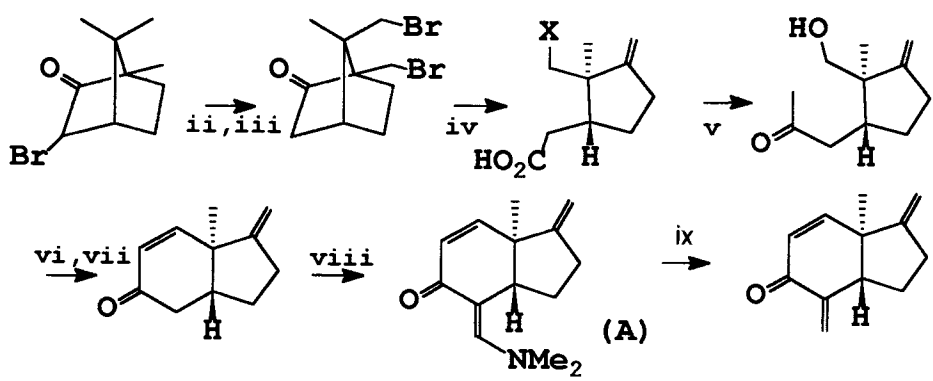
The photochemical procedure, referred to in the previous section, by the Quinkert group (ref.129) has been adapted to afford an asymmetric total synthesis (ref. 145) for which the chiral ring D component (A) has been derived by three distinct methodologies, two of which involved conventional optical resolution and the third used asymmetric induction. In the route shown, the tricyclic ketone (X) was obtained from the racemate by resolution with (+)-1-phenylethylamine.

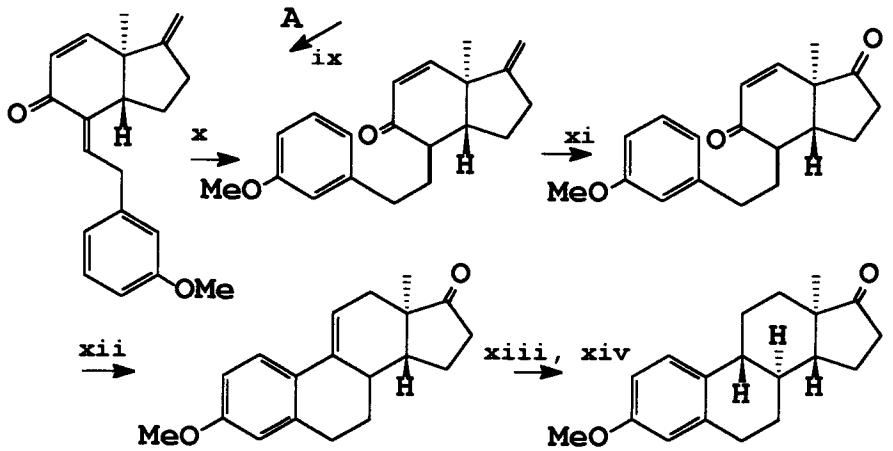




Reagents (a) (X) obtd. by resoln.,(i) ring-opening (ii) PCC (Iii)HO^-, $-CO_2$,(iv)MeOH, H^+ ; $(HOCH)_2$, H^+, (v) LAH, (vi) $-H_2O$;H_3O^+
(b)B obtained as in ref.129 but with use of (A) and remaining stages to estrone the same.

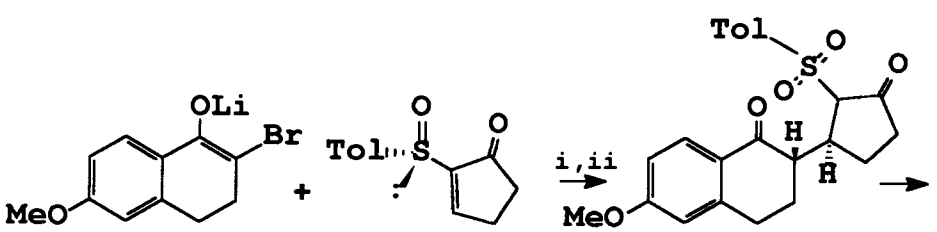
(+)-3-Bromocamphor has been employed as the chiral starting material in an enantiospecific synthesis (ref. 146) which involved the formation of an indanone (CD moiety) related structurally to that used by Hoffmann-La Roche and led finally to (-)-estrone. Attempts to alkylate the α,β-unsaturated ketone with 2-(3-methoxyphenyl)ethyl iodide failed, not surprisingly, due to an elimination rather than the desired substitution reaction and accordingly the use of an α-methylenic derivative of the ketone and 3-methoxybenzyl chloride were obligatory. By the use of (-)-3-bromocamphor, which is readily available from (-)-borneol by oxidation to (-)-camphor and bromination, natural (+)-estrone could be obtained.

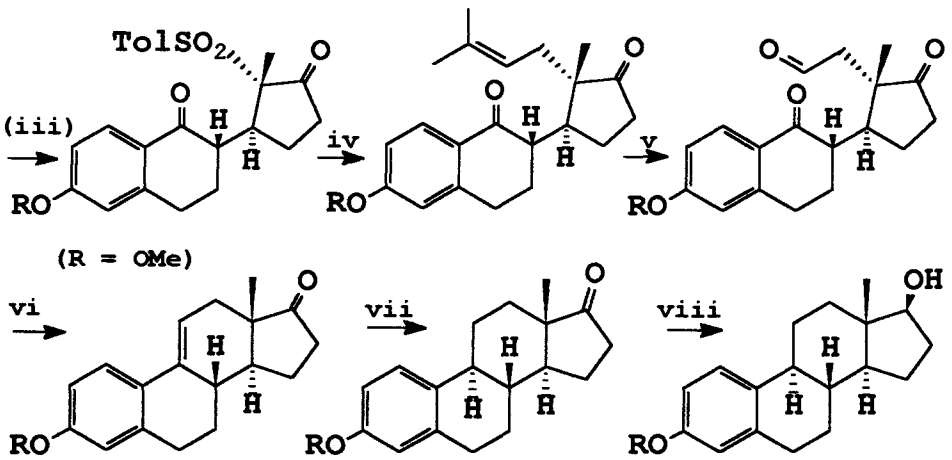




Reagents (i)Br_2 on camphor (ii)(iii) Br_2, $ClSO_3H$,5 days, (iii) Zn/AcOH, 0°C, (iv)KOH/DMSO/H_2O, (v) MeLi,THF, (vi)PDC/CH_2Cl_2,(vii) 2M NaOH/MeOH, 0°C;MsCl/Et_3N/DMAP;DBU, (viii) $(Me_2N)_2CHOBu^t$, Δ , (ix)3-$MeOC_6H_4CH_2MgCl$,Et_2O, (x) Li/NH_3,Et_2O, (xi) O_3, CH_2Cl_2;Me_2S,(xii) HCl/AcOH (xiii) Pd-C,H_2 , (xiv)BBr_3,CH_2Cl_2.

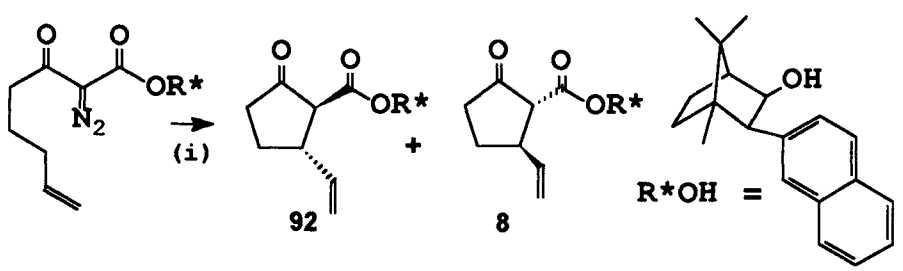
The chiral sulphoxide, (S)-(+)-2-(4-tolylsulphinyl)-2-cyclopentenone, has been used as a ring D component to effect an asymmetric Michael addition with 91-94% diastereoselectivity by reaction in the chelated form with the α,α-disubstituted lithium enolate from 2-bromo-6-methoxytetral-1-one; while the (R)-(-) antipode reacts in a non-chelated form with the α-monosubstituted lithium enolate of 6-methoxytetralone (ref. 147). This synthesis makes use of earlier experience in the use of α-mono and α,α-disubstituted lithium enolates in the ethyl acetoacetate series with the non-chelated and chelated forms respectively of a β-ketosulphoxide (ref. 148). Eight futher steps were involved to produce (+)-estrone methyl ether in an overall yield of 6.3%.

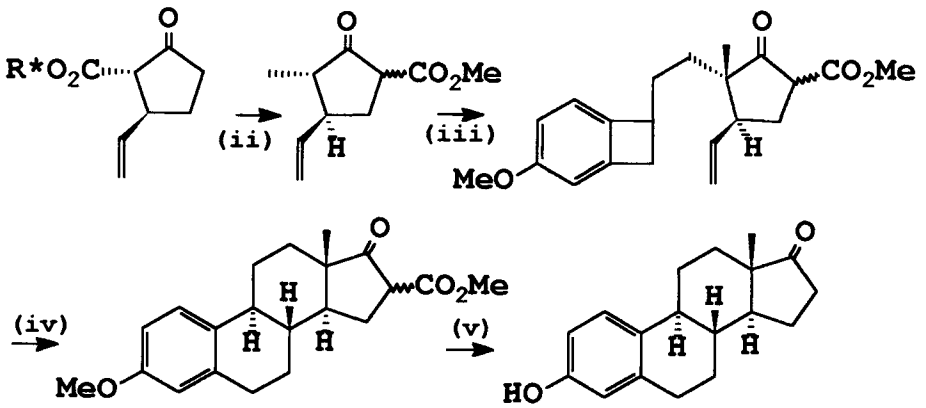




Reagents (i) ($Me_3Si)_2NH$, BuLi, -78°C,THF; MCPBA, (ii) $KOBu^t$, $HOBu^t$, (iii)NaH,MeI, (iv) Me_2CuLi, $Me_2C{=}CHCH_2Br$, (v) O_3, MeOH, Me_2S, (vi) $TiCl_3$, Zn/Ag, (vii) CF_3CO_2H, Et_3SiH ,(viii) $NaBH_4$

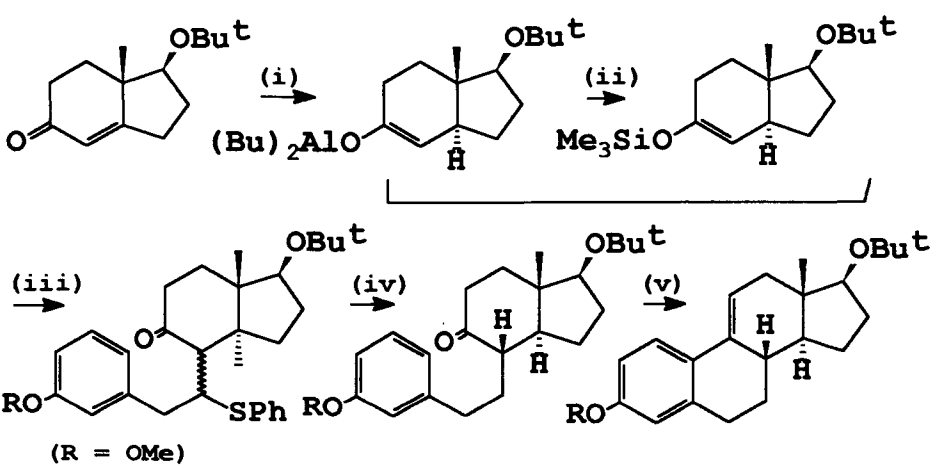
Other ways of obtaining ring D in optically active form have been elaborated. Thus functionalised cyclopentanone derivatives of high optical purity have been obtained from naphthylbornyl α-diazo-γ-alkylacetoacetates through diastereoselective intramolecular C-H insertion (ref.149). The required 3-vinyl cyclopentanone member of the series was derived from 1-naphthylbornyl 2-diazo-3-oxo-oct-7-eneoate with a diastereoselectivity of 92:8 in reasonable yield. This cyclopentanone ester upon methylation and reaction with sodium methoxide under retro Dieckmann conditions and then alkylation with 2-(4-methoxybenzocyclobutenyl)ethyl iodide underwent inversion at the C-Me position. Thermolysis afforded (+)-estrone (with 91% ee) effectively in four steps from the diazo ester.

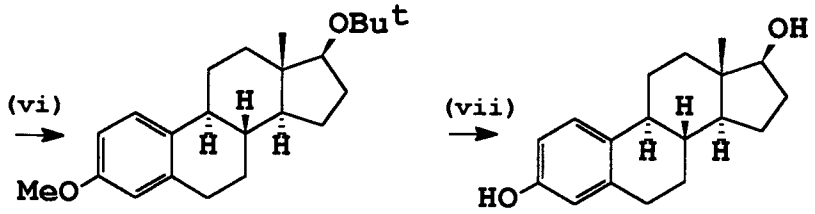




Reagents (i) $Rh_2(OAc)_4$, CH_2Cl_2 ,RT, (ii)MeI, $KOBu^t$,THF;NaOMe,xylene, Δ, (iii) LDA,THF, 40°C, (iv NaCl,H_2O,Me_2SO, (v)1,2-$Cl_2C_6H_4$,Δ

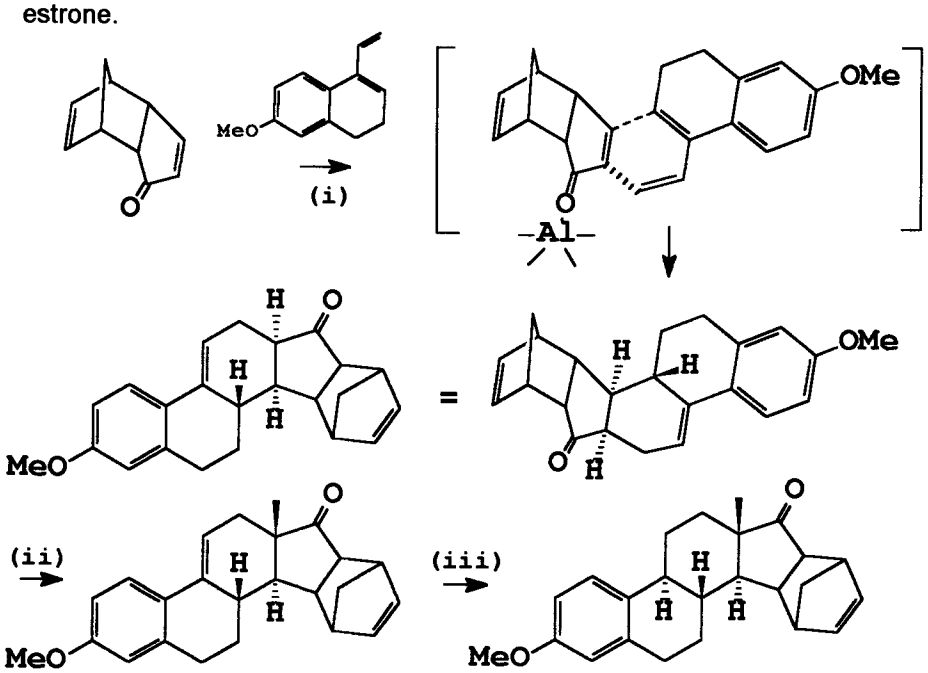
The alkylation of the α,β-unsaturated ketone, representing the component for rings DC, with β-iodo or bromoethylaryl components to obtain the intermediate ACD structure had been found to be ineffective, perhaps not surprisingly bearing in mind classical work on nucleophilic substitution. Another way around this has been to employ α-chloro-α-thiophenylalkanes, in particular α-chloro-β-(3-methoxyphenyl)ethyl phenyl sulphide which with Lewis acids behaves as a strong electrophile towards trimethylsilylenol ethers (ref.150). Thus initial reductive treatment and trapping of the enolate by timethylsilylation afforded a reaction product which was reacted with the aforesaid component to furnish a mixture of epimers. Desulpurisation yielded the desired stereochemistry and the remaining steps were accomplished as in previous syntheses to afford (+)-estradiol-3-methyl-17-t-butyl diether.

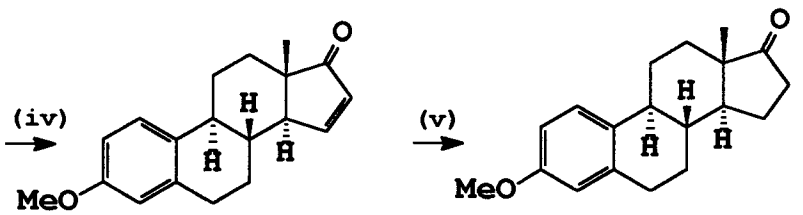




Reagents (i) Bu^{t}Cu, DIBAH,HMPT,THF, -78°C (ii)TMSCl, Et_3N,(iii)$ZnCl_2$, 3-$MeOC_6H_4CH_2CH(Cl)SPh$, (iv)Raney Ni,(v)HCl/MeOH,(vi)PdC, H_2, (vii) CF_3CO_2H

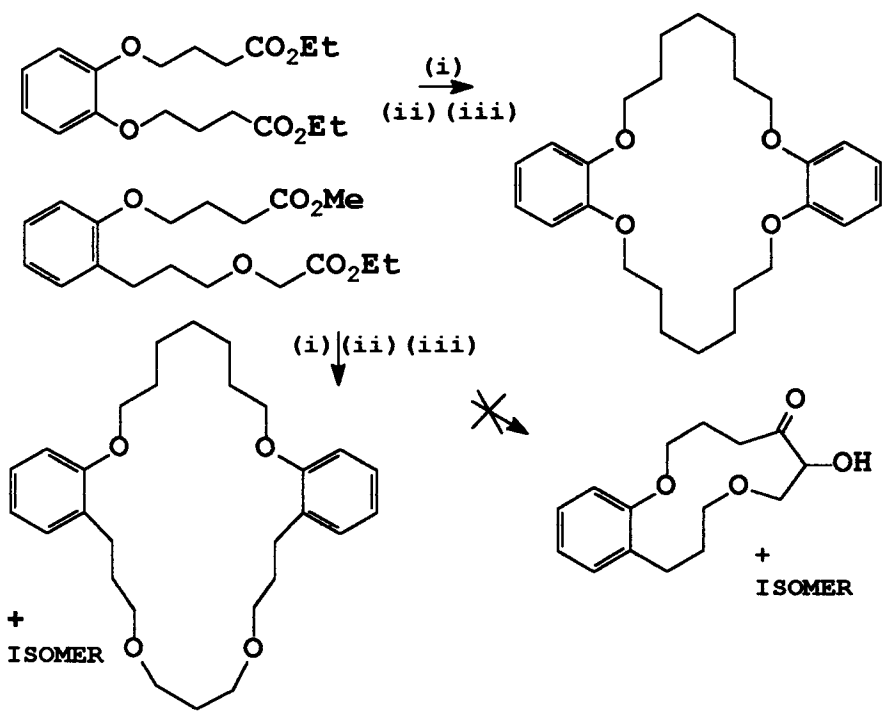
A very concise and remarkable stereocontrolled synthesis has been achieved in six steps to afford (+)-estrone in an overall yield of 28% by using Diels-Alder cycloaddition at the first and cycloreversion at the final stage (ref.151). For example (-)-dicyclopentadienone readily obtainable from dicyclopentadiene by way of lipase-mediated asymmetric resolution (ref. 152) was reacted with 6-methoxy-1-vinyl-3,4-dihydronphthalene, a compound first used in exploratory steroid work more than fifty years ago, in the presence of diethylaluminium chloride to give a single *exo* adduct which was sterically favoured as opposed to the electronically favoured *endo* isomer. Methylation afforded the methyl derivative (60%) with a trans C/D ring structure together with a minor amount (21%) of the enolic methyl ether. Thermolysis gave 15,16-dehydro estrone methyl ether which was chemically reduced and demethylated to produce (+)-estrone.





Reagents (i) Et_2AlCl, CH_2Cl_2,-20°C, (ii) $KOBu^t$,MeI,DME,0°C,(iii) Et_3SiH,CF_3CO_2H,CH_2Cl_2,RT, (iv) Ph_2O, Δ, (v)Pd-C,H_2,EtOH

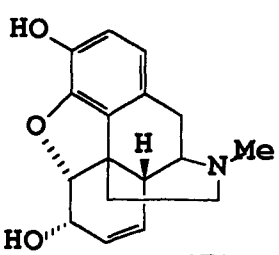
Although it would appear that semi-synthetic and biological methods might be preferred commercial routes to (+)-estrone, certain high-yielding total synthetic methods are highly significant in that they are potential competitors in a situation where the availabiity of starting materials can be a key factor. More especially they have enormously advanced organic chemical methodology and the understanding of stereoselective procedures. The synthesis of analogues has also has also been of organic chemical importance and occasionally has resulted in a completly different outcome (ref. 153). Thus in attempts to form dioxa analogues having an acyloin group in the peripheral structure of estrone, intermolecular Dieckmann cyclisation occurred rather than intramolecuklar acyloin condensation of the diesters shown giving finally a type of crown ether.



Reagents (i)Na,Xylene,Δ , (ii)HO^-, EtOH, (iii)N_2H_4 ,KOH,$(HOCH_2)_2$

14.6 Syntheses of (-)-Morphine

The opiates, morphine (7 and Table14.1) and codeine (8) are alkaloids of economic significance along with cocaine, caffeine and nicotine. Although more than 95% of the opium used for legal medical and scientific purposes comes from India, the USA the largest producer of alkaloids from opium had reduced its usage to little more than 200 tons in 1988 probably due to progress in structure/activity studies, leading to the development of more specific synthetic analgesic compounds free of side effects and addictive properties alongside the continued traditional use of the harmless derived phenolic methyl ether, codeine. This has a continuous popularity in a variety of freely available pharmaceutical preparations as an analgesic and anti-tussive agent. Thus as opium contains approximately 20% morphine, small amounts of codeine and a smaller proportion of thebaine (9) which has no medicinal value, of the 50 tons of morphine recovered in 1988, 90% was employed in making codeine and some 10% for the alleviation of pain in the terminally ill.



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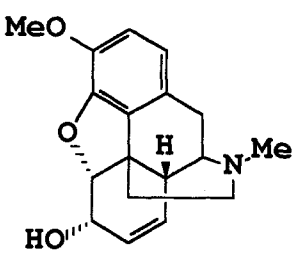

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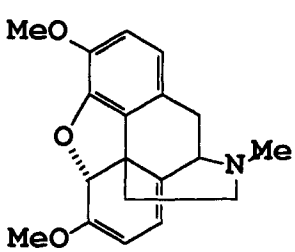


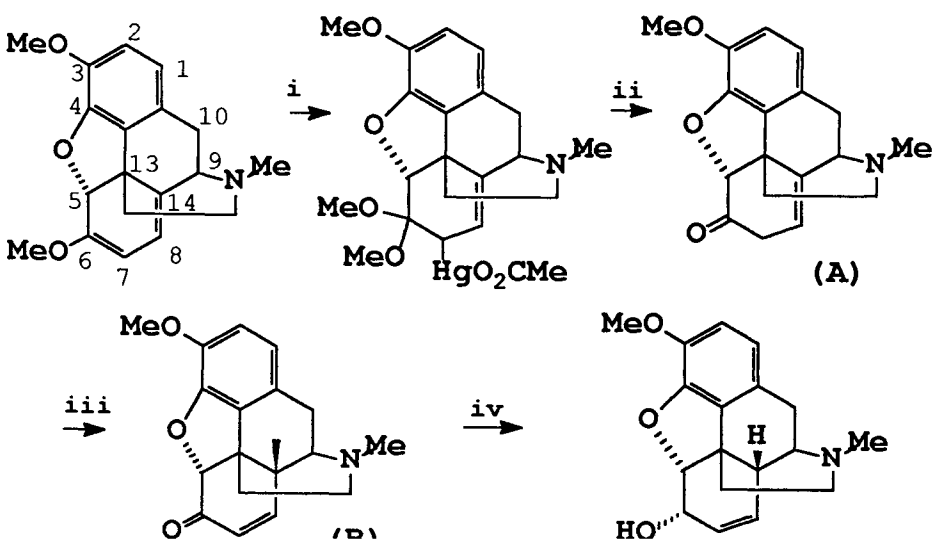
(9)

The chemistry of morphine is in some ways synonymous with the history and progress of organic chemistry itself from the extraction in 1803 by Seturner (ref. 154), its structural elucidation spanning a 100 years culminating in the Robinson-Gulland formula (ref.155) and the full details of its synthesis in 1956 and thereby that of codeine (ref. 156). Since that time twelve syntheses have been described all of which have enomously extended synthetic methodology although the recovery of the alkaloid from opium remains the commercial method of choice. Great endeavours have been and continue to be made to modify the morphine molecule by semi-synthetic routes, some of which have been referred to (ref.1), in the hope of obtaining analogues possessing the analgesic without the addictive properties of the alkaloid. Indeed the significance of morphine as an analgesic cannot be overlooked despite its addictive nature and side effects such as depression of the central nervous system, slowing of respiration and nausea. Accordingly much work has been devoted to improving the isolation process for obtaining morphine from crude opium, which in poppy straw or the dried exudate can reach 20%. As with many industrial processss

operations are cloaked in secrecy but particularly so in this instance where illicit procedures, as with cocaine, have an immense value. Nevertheless traditional methods tend to prevail and prior art remains (ref. 157). Aqueous extraction, concentration, precipitation in the presence of ethanol with ammonium hydroxide and crystallisation as the sulphate separates morphine from its relatives codeine and thebaine.

14.6.1 Semi-synthetic Aspects of the Morphine Alkaloids

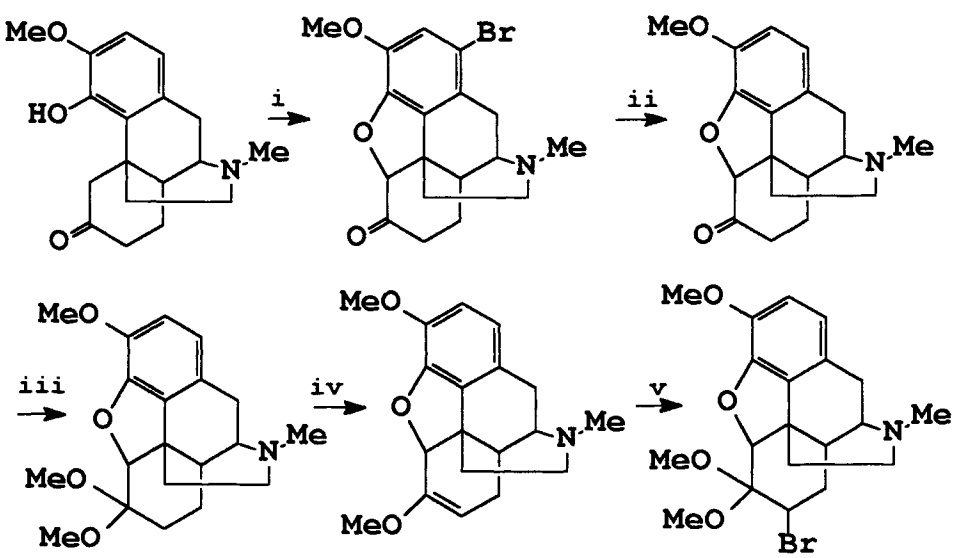
A conceived shortage of legally produced opium in the seventies (ref. 158) and the diversion of the potentially available morphine to illicit heroin production appeared to jeopardise the availability of the widely medicinally used codeine. Thebaine a very minor component of opium from *Papaver somniferum* is however the major component of *Papaver bracteatum* which has been extensively considered as a source for the production of codeine (ref. 159,160, 161). Thus there has been interest both in the improved conversion of thebaine to codeine and also in that of the latter to the still widely-prescribed morphine. An alternative botanical source could be seen as a way of monitoring the narcotic drug situation. In one process for the conversion of thebaine to codeine a yield of 74% was claimed (ref. 162) but an improved process has been developed (ref. 163). In this, thebaine is oxymercurated with mercuric acetate and the intermediate 7- and 14-acetoxymercurineopinone dimethylketals hydrolysed with 3N acetic acid or reduced with sodium borohydride and then hydrolysed to give mainly neopine (A). Isomerisation under acidic or alkaline conditions leads to a mixture of codeinone (B) with neopinone which is transformed to the former with anhydrous HCl or HBr followed by elimination of hydrogen halide from the intermediate 8-halodihydrocodeinone. Finally, sodium borohydride treatment affords codeine in an overal yield of 85% from thebaine.

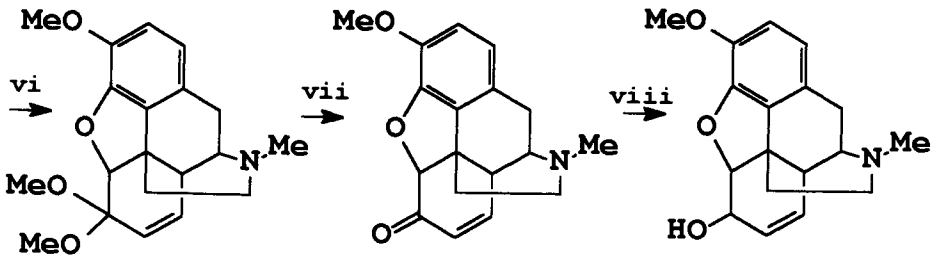


Reagents (i) $Hg(OAc)_2$,MeOH,(ii)AcOH or $NaBH_4$;3M HCO_2H, (iii)3M HCO_2H and HCl, CH_2Cl_2, HO^-,(iv) $NaBH_4$, MeOH

Codeine has been demethylated either by reaction with boron tribromide in chloroform at ambient temperature in 91% yield (ref. 164) or by treatment with sodium propylmercaptide in DMF at 125°C in 80% yield (ref.165) to give morphine, both procedures representing considerable improvements on the former method with pyridine hydrochloride (ref. 166).

Dihydrothebainone has constituted the target molecule in the majority of the synthetic approaches to morphine from the first synthesis (ref. 156) onwards although the final steps in that approach were only effected in low yield. In the light of the possible realisation of a viable commercial synthesis of morphine there has been interest in the development of a high yielding pathway from dihydrothebainone. Thus for example a practical synthesis has been described in which the 4,5-oxide ring is constructed by bromination, treatment with sodium hydroxide in a two phase aqueous chloroform system to form a mixture of 1-bromo and 1,7-dibromodihydrocodeinone which was converted to dihydrocodeinone by catalytic debrominationation. Ketalisation and elimination of methanol afforded the enol ether, which by reaction with methyl hypobromite, produced 7-bromodihydrocodeinone dimethyl ketal. Treatment of this with potasium tert-butoxide in DMSO at 60°C gave codeinone dimethyl ketal. and then hydrolysis and borohydride reduction furnished codeine in an overall 70% yield (ref. 167).



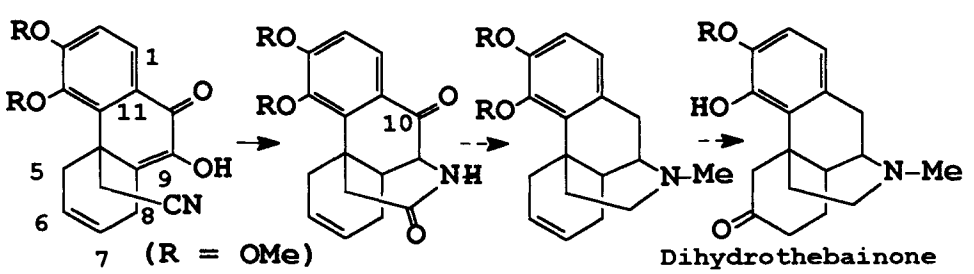


Reagents (i) $2Br_2$,AcOH; $CHCl_3$, HO^-, (ii)AcOH, NaOAc,Pd-C,H_2, (iii) $H(OEt)_3$, MeOH, H^+,(iv) 4-TSA,$CHCl_3$, (v)HBr-H_2O, (vi) $KOBu^t$,DMSO, (vii) 3M AcOH, (viii) $NaBH_4$,MeOH

For the preparation of codeine from morphine a number of methylation procedures are available among which the use of trimethylammonium salts is customary and has been referred to in Chap. 4.

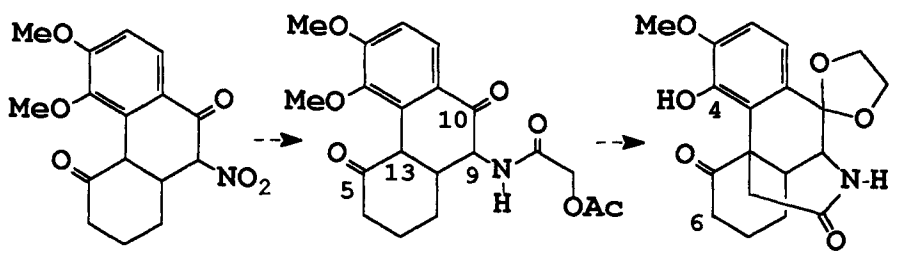
14.6.2 Total Syntheses of Morphine

Natural sources remain the only commercial supply of morphine more than forty years after the first synthesis was described. There has been, as seen in the previous section, activity to perfect semi-synthetic routes from the physiologically inactive thebaine to (-)-codeine one of the most important analgesic-antitussive agent worldwide. The possibility of shortages of opiates perhaps through potential international action and also the aim to make the legal production of these medicinal alkaloids independent of natural resources have both served as a spur to synthetic endeavours. It has even been proposed that a possible solution to the world drug problem could lie in the cessation of the planting of *Papaver somniferum* and reliance placed on a totally synthetic supply.
The earlier work on the the synthesis of opium alkaloids has been summarised (ref. 168) but the strategies in two can be briefly summarised. In the first synthesis of morphine (ref. 169) an early stage consisted of a Diels-Alder reactionof5,6-dimethoxy-4-cyanomethylnaphtho-1,2-quinoneandbuta-1,3-diene to form the phenanthrene shown, a reaction which had been used

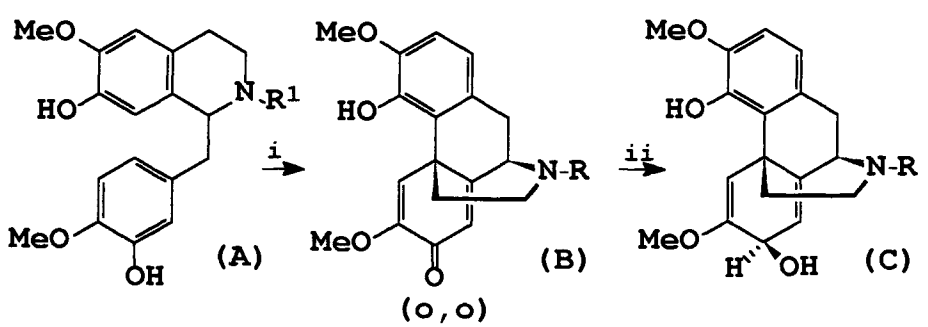


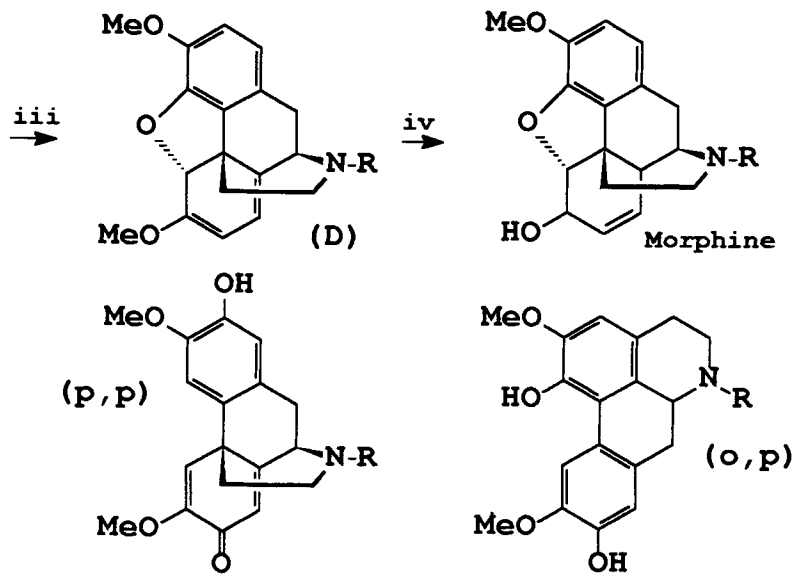
earlier with the didesmethoxy compound and R = $CH(CO_2H)_2$ (ref. 170). The six-membered nitrogen ring was then constructed by an unusual reductive cyclisation of the cyanomethyl group with the 9-carbonyl substituent and after N-methylation, hydroxylation of the 6,7-double bond fortunately occurred at the 6-position. Oxidation afforded dihydrothebainone (D). The oxide ring resulted in low yield by the reaction of the phenoxide ion in the 5-bromoketone, a type of reaction which was later developed in greatly improved yield (ref. 156). Optical resolution was caried out on the unsaturated precursor of the 6-hydroxy compound.

By contrast, the succeeding synthesis described (ref. 171), employed the Michael addition of 2-(2,3-dimethoxyphenyl)cyclohex-2-enone with ethyl nitroacetate and cyclisation to effect formation of a phenanthrene ring. The nitrogen ring was constructed by acylation of the 9-amino group with acetylglycolyl chloride and ring closure to the reactive benzylic position was accomplished with acetate ion as the leaving group. The 4-hydroxyl group was fortuitously liberated during formation of the nitrogen ring, an oximino group was introduced at the 6-position, Wolff-Kishner reduction removed the 5- and 10-carbonyl groups, and hydrolysis of the oxime liberated the 6-carbonyl group. Thenceforward lithium aluminium hydride reduction of the lactam and simultaneously of the 6-carbonyl group, N-methylation, and oxidation of the 6-hydroxy group to restore the carbonyl group gave dihydrothebainone, which was resolved and, as with the Gates synthesis was the basis for the final steps.



Both the preceding syntheses were multi-step procedures with a classical approach and subsequent work turned towards strategies modelled on biogenetic lines via for example the oxidative coupling of a phenolic



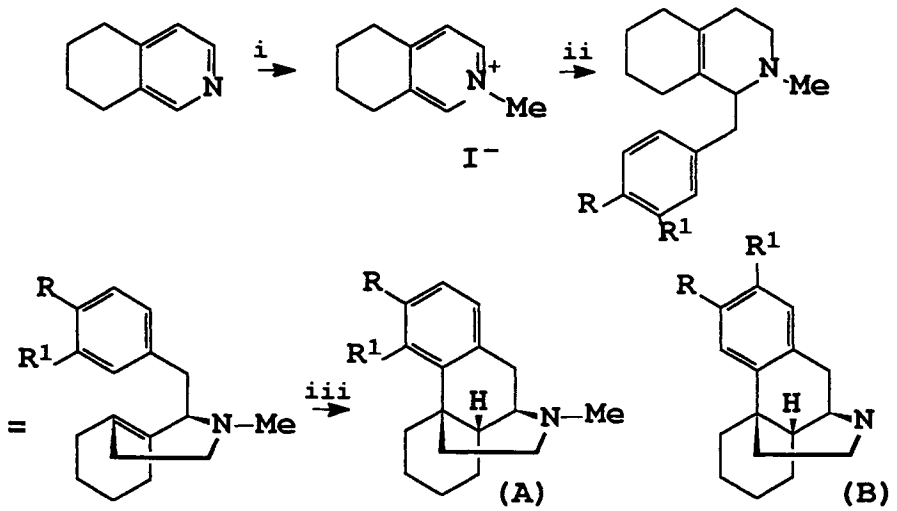


Reagents(ref.175) (i) $ClCO_2Et$, $K_2CO_3CH_2Cl_2$,(ii)LAH,THF,(iii) M HCl,1h,RT

benzyltetrahydroisoquinoline derivative (ref. 155, 172). Although the biosynthetic pathway ref. 173) has been elucidated from the oxidation of reticuline to salutaridine, thence through thebaine to morphine (ref. 174) as shown (R = R^1 = Me), in the sequence A,B,C,D the yield of the desired ortho,ortho coupling product (B) was very low at the initial stage (i) with the oxidant potassium ferricyanide (ref. 174). Numerous unsuccessful attempts to avoid the ortho,para and para,para coupling products shown have been made, but remarkably, the ethoxycarbonyl derivative (A; R^1 = CO_2Et) of racemic N-norreticuline afforded with thallium tristrifluoroacetate at step (i) the corresponding salutaridine derivative (B; R = CO_2Et) in 23% yield (ref. 175) which was then transformed via (C; R = Me) to racemic thebaine (D; R = Me) by the known remaining steps (ii),(iii) (ref. 176, 177).

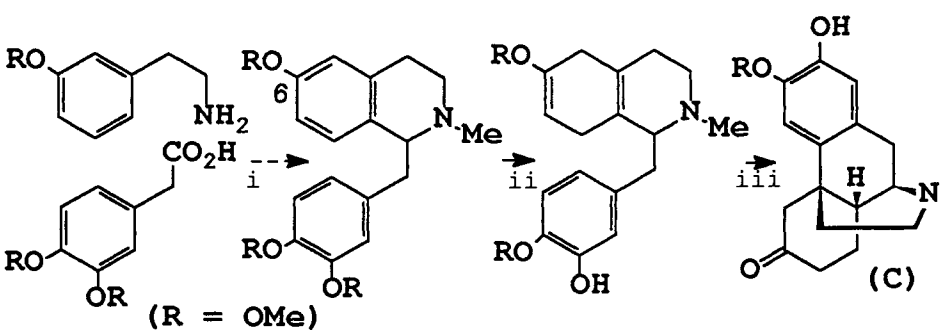
The potential usefulness of benzylhydroquinolines had been achieved earlier in the first synthesis of the carbon skeleton of the morphine alkaloids (ref. 178) by applying the Bogert-Cook synthesis of hydrophenathrenes to a suitably substituted compound which was readily synthesised for example from tetrahydrquinoline methiodide and 4-methoxybenzyl chloride. Reduction gave the octahydro compound and cyclisation with hot hydrochloric or hydrobromic acids gave a base (A = B; R = OMe,R^1 = H), the methoxy derivative of the parent 'N-methylmorphinan' together with a small proportion of an isomer (at C_{14}), isomorphinan. Upon resolution of the major product the (-) enantiomer was found to be an active analgesic, later known pharmaceutically as levorphanol which was found to be longer acting than morphine with fewer side effects

although equally addictive. Attempts to apply this reaction to the benzyl compound (R = R^1 = OMe) led to the morphinan A (R = OMe, R^1 = OH) as the minor product, the major one being the structural isomer B.



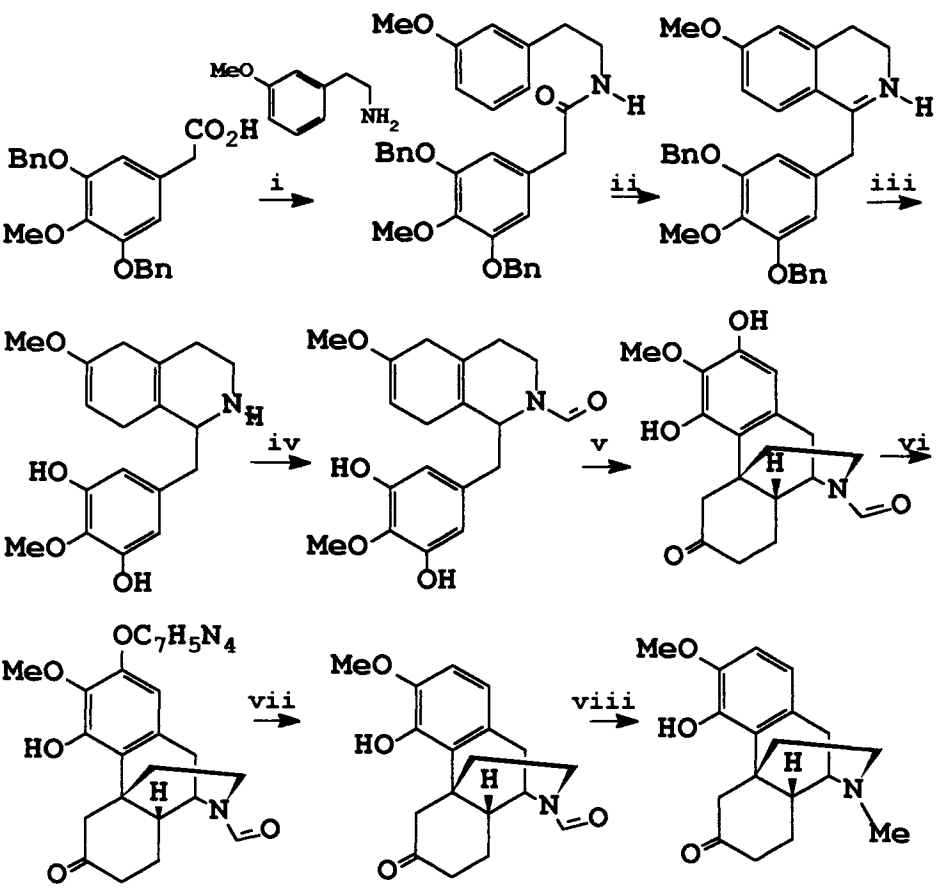
Reagents (i) MeI, (ii) (R^1 = H),4-$OMeC_6H_4CH_2MgCl$;Pd-C,H_2,(iii)HBr

With the related 6-methoxy compound shown the cyclisation to a morphinan with hydrochloric acid proceeded to the unwanted product C in 37% yield and the desired one in only a 3% yield (ref. 179). The same precursor, synthesised from 2-(3-methoxyphenyl)ethylamine and 3,4-dimethoxyphenylacetic acid by amide formation and ring closure by the Bischler-Napieralski cyclisation, followed by reduction, methylation and Birch reduction, was used by others with similar results (ref. 180). The route constitutes a synthesis of morphine by the use of the final steps of earlier work (refs. 169,171), albeit in low yield, although in considerably fewer steps than the earlier syntheses.



Reagents (i) △ ; PCl_5 ; Pd-C,H_2 ; MeI (ii)Na,NH_3,Bu^tOH, (iii) 10%HCl,△

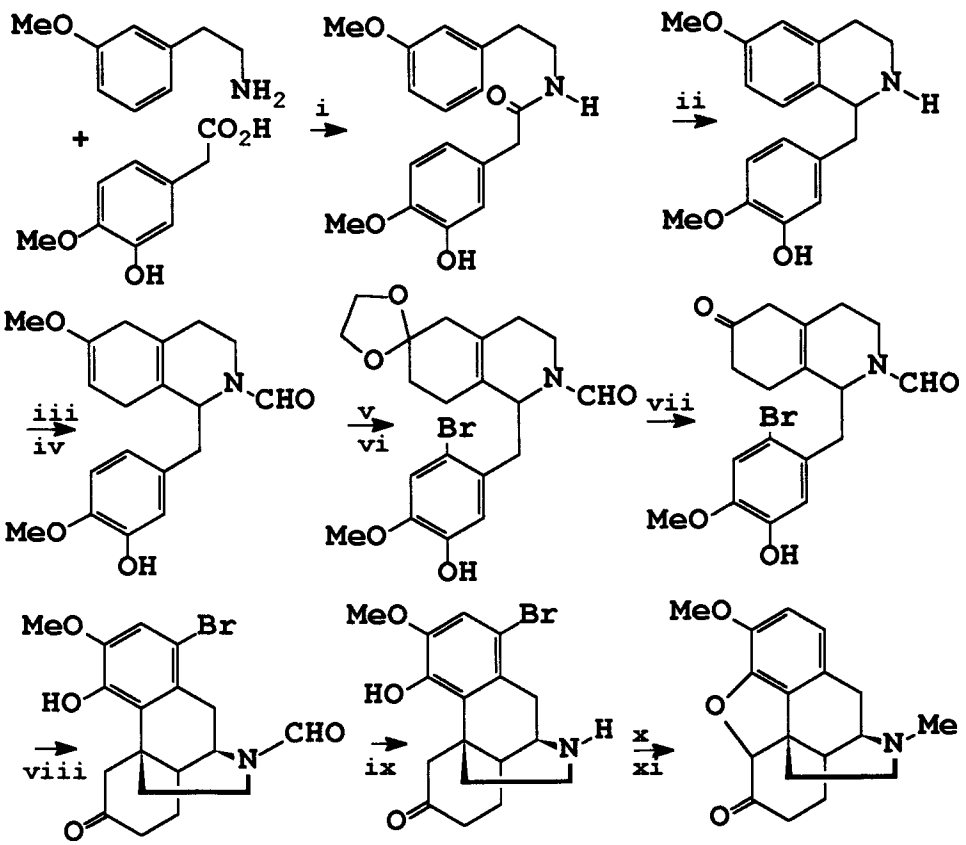
Although the perhaps inevitable 3,4-substituted compound rather than the desired 2,3- had resulted in the electrophilic cyclisation described, some time elapsed before experimentation took place towards directing the cyclisation to the desired position by the use of a blocking 4-methyl substituent in the benzyl group (ref. 181) (by the use of 4,5-dimethoxy-5-methylphenylacetic acid for the first step) a procedure which led to a 'methylmorphinan' in 85% yield. Subsequently in order to obtain a system in which the cyclisation was both directed and the blocking group was removable, a 3-hydroxy substitiuent was employed in the benzyl group (ref. 182) to provide an intermediate in which



either of two o-positions was available for the cyclisation stage. By this device racemic dihydrotebainone was obtained the transformation of the (-)form of which to morphine had already been described originally (ref.169) and in improved manner (ref.167) as discussed earlier. In the present synthesis the racemic tetrahydroisoquinoline obtained at step(iii) was resolved with (-)-malic acid and the enantiomers of the base then isolated.

Reagents (i) Δ, (ii) PCL_5,Bischler-Napieralski, (iii)Li,NH_3,Bu^tOH,(iv) HCO_2Et, (v)80% H_2SO_4 /Et_2O, (vi) 5-chlorotetrazole, (vii)Pd-C,base,(viii)HCl/MeOH ; CH_2O, Pt-C,H_2

Despite this success the authors had earlier envisaged using a 2-bromo substituent instead of a 2-methyl group and indeed this had been claimed in the patent literature (ref. 183). However although attempts both by the Dutch group and others (ref. 184) to duplicate this work had been abortive, a later reexamination of this strategy led to short successful syntheses of racemic dihydrothebainone, dihydrocodeinone and nordihydrocodeinone with the remarkably good yields of 37%, 29% and 30% repectively (ref.185). The same benzyltetrahydroisoquinoline employed by previous workers was reduced by the Birch reaction, N-formylated and the liberated carbonyl group ketalised. Selective bromintion with N-bromoacetamide introduced a bromo substituent in p-position to the hydroxyl group. Grewe cyclisation afforded a bromomorphinan accompanied by formation of a small amount of the α,β-conjugated isomer of the precursor which could not be cyclised [this conjugated material was in fact the same product with which cyclisation had been attempted unsuccessfully by



DeGraw (ref.184) and explains their failure]. Hydrolysis of the formyl group, bromination, alkaline treatment to effect oxide ring formation and finally hydrogenation in the presence aqueous formaldehyde afforded racemic dihydrocodeinone.

Reagents (i) Δ, 200°C, (ii) P_2O_5 /H_3PO_4 ;$NaCNBH_3$, MeOH,(iii)Li,NH_3,THF, Bu^tOH , (iv)PhOCHO.EtOAc, (v) $(HOCH_2)_2$,$MeSO_3H$,THF,RT, (vi) MeCONHBr,THF,(vii) HCO_2H,H_2O,(viii)CF_3SO_3H,NH_4F HF,(ix) MeOH,conc.HCl (x) Pd-C,H_2, AcOH ,(xi)Pd-C,H_2,CH_2O

By resolution of the benzyltetrahydroisoquinoline or preferably asymmetric reduction with a chiral borohydride of the precursor the chiral members of the series should be accessible bearing in mind the the efficient transformations already acomplished (ref. 167). In the light of potential shortages (ref. 186) and avoidance of dependence upon the sole natural commercial sourse, this synthetic strategy represents a practical approach to the medical opiates. Fig. 14.2 shows a partial retrosynthetic analysis for the three routes A, B,and C discussd and reveals many unexplored possibilities for the synthesis of morphine. Continued attempts have been made to find new routes to its ring sytem. Thus a photocyclisation of an aryloxyenone (Fig.14.2, scheme type D) (ref. 187), a methodology based upon the use of a metallated enamine (ref. 188), and a route employing a vanillin derivative and its reaction with a 2-allylcyclohex-2-ol have been described, the last two of which gave racemic morphine (ref. 189).

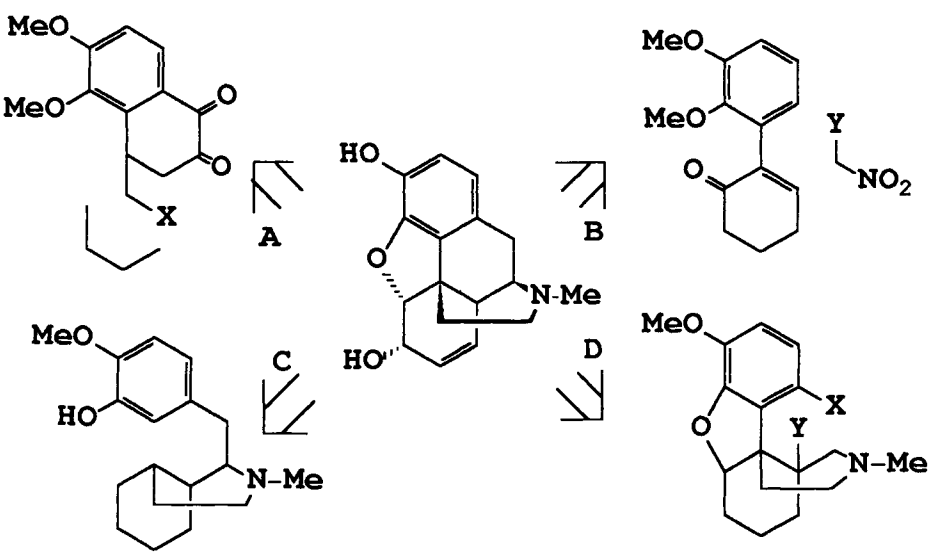
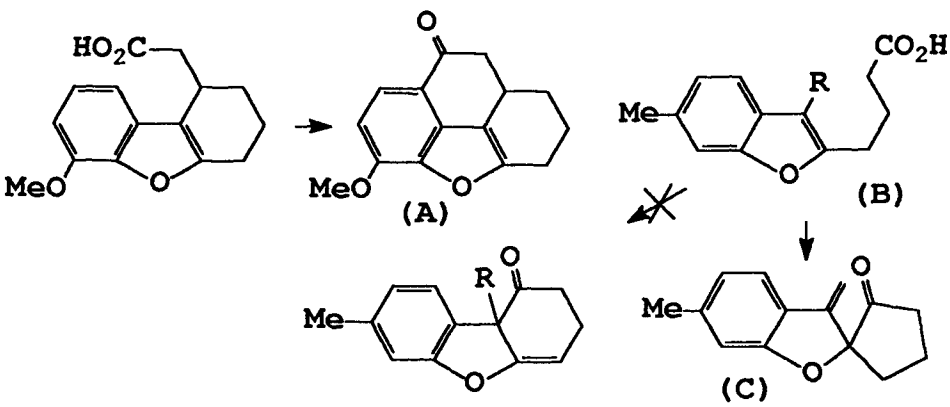


Fig.14.2 Partial Retrosynthetic Schemes for the Morphine Structure

The generally depicted structure for morphine is however a less satisfactory representation for retrosynthetic analysis than the absolute configuration which more truly indicates the steric problems to be surmounted.
Many more syntheses directed to the tetracyclic structure of morphine than those briefly listed here have been undertaken in the preceding fifty years. Sometimes unexpected results have materialised as in the novel formation of the phenanthrylene oxide (A) related to morphenol (ref. 190) and a spiro methylenic compound (C) which resulted from the cyclisation of a related acid (B; R = Me) (ref. 190, 191). Ozonation of the methylene group in this compound gave a structure related to the griseofulvin series. With a 3-(2-dimethylamino)ethyl grouip (B; R = $CH_2CH_2NMe_2$) the formation of the corresponding phenthrylene oxide had been the hoped-for outcome.



14.7 Chemistry and Synthesis of Carminic Acid

14.7.1 Introduction

Carminic acid (Table14.1, ref.39) is the colourant principle, often present to the extent of 22%, in cochineal an ancient colouring material which consists itself substantially of the dried crushed bodies of female insects of the species *Dactylopius Coccus* Costa of the Coccidae family. These are parasites which live on various cacti such as *Opuntia* and *Nopalea cochinellifera* indigenous to Peru, Mexico and the Canary Islands. Carminic acid is a glycoside and its aglycone kermesic acid which is also a pigment has an independent existence in *Kermes illicis*. Cochineal was used for many centuries in the Americas prior to its introduction to Europe through Spanish influence. Although it was expensive it gradually displaced the then used red dyes madder (alizarin) and kermes since it was found that with metal salts such as aluminium and tin compounds, crimson, scarlet and pink hues could be obtained on wool or silk.

Its influence diminished with the advent of the synthetic azo dyes through the discovery of diazotisation and coupling. However the brilliance of natural cochineal particularly for ceremonial uniforms ensured that it was in turn never completely replaced by the azo colours.
Both carminic aid and kermesic acid are members of the polyhydroxyquinone series which are mostly based on 1-methyl-3,6,8-trihydroxyantraquinone (deoxyerythrolaccin) (ref. 192) and have been termed the lac pigments. The natural occurrence of these compounds was considered to be only in coccid insects until they were isolated later from higher plants such as *Aloe saponaria* Haw (ref. 193).
Apart from its use as a valuable mordant dyestuff for textiles, cochineal (EEC 120) is still used as a colourant in cosmetics, foods, aperitifs and beverages (ref. 194) and is one of the several permitted natural colourants which includes for example β-carotene, betanidin from *Beta vulgaris*, curcumin from *Curcuma longa*, certain anthocyanins and chlorophyll complexes to quote a few structures. Commercial interest in natural products such as cochineal and carminic acid has been reactivated by the increasing pressures to avoid synthetic azo colours, their association with potential carcinogenic attributes and the increasing popularity of 'green' issues. Carminic acid is reputed to possess some anticancer activity (ref. 195,196) and is a distant structural relative of the antibiotics, carminomycin and carminomycinone.
Carminic acid or carmines have replaced the simple extracts of cochineal from antiquity since the modern products are metal-chelated forms tailored to produce the maximum colour yield, high pigmentation properties and enhanced photostability. Hot aqueous extraction in the country of importation, control of the proteinaceous material, of the pH and the incorporation of appropriate metal ions are aspects of the prior art which are shrouded in secrecy. However national interests in the indigenous countries compete with developed practices producing changes in the manufacturing situation. The practice of harvesting has however probably changed little over centuries and fully matured female insects the size of a small finger nail are collected by hand and the wax covering (coccerin) is removed. Approximately 150 kgs. of cochineal are produced from 1 acre planted with *Opuntia* and 100,000 insects are said to be required to produce 1 kg. The raw material is either stove or air dried for export purposes.

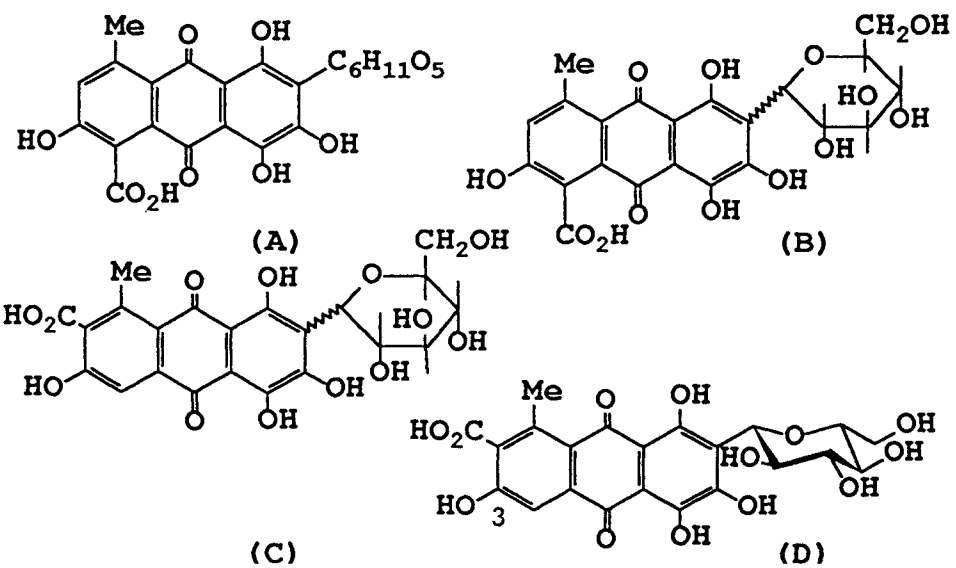
14.7.2 Structure of Carminic acid

Carminic acid was first obtained in crystalline form in 1858 (ref. 197) but its structure proved difficult to elucidate and was not finally established until 1965 through the work of two different groups while stereochemical detail was added in 1981. Some of the earlier work has been summarised (ref.198).
From classical degradative work on both carminic and kermesic acids (ref. 199, 200) the former was recognized as an anthraqinone resembling the latter and it was formulated (ref.201) as structure (A). This early work led to the surmise

that the side chain was of carbohydrate origin although its remarkable resistance to both acidic and enzymic hydrolysis defied understandng until it was suggested in 1924 (ref.202) that carminic acid contained an open chain C-glycosidic structure an idea which was later dismissed in a review (ref. 203). Nevertheless following work on barbaloin it was proposed 30 years later (ref. 204) from studies with periodic acid on the fully methylated anthraquinone moiety that a cyclic C-glucose unit (B) rather than an open chain form was indeed present at the 7-position in carminic acid. At that time carminic acid and barbaloin (from bitter aloes) were the only known C-glycosides.

The structure of the anthraquinone component, kermesic acid, was accepted for many years until the position of the carboxyl group was questioned (ref. 205) following inconsistencies with the later degradation of analogues and certain of the early work was reinterpreted. Accordingly the carboxyl group was reassigned to the 2-position giving the structure (C) which although it was not obvious at that time is also more likely on a biogenetic basis from the involvement of a coiled polyketide comprising 8 acetate units. Unaware at the time of the Dutch work, another group (ref. 206) arrived at the same conclusion and demonstrated from ^{1}H NMR work chemical studies (ref. 207) and later synthetic work that kermesic acid was 3,5,6,8-tetrahydroxy-1-methylanthra-9,19-quinone and certainly contained no acetyl group as had been surmised by Dimroth.

The β-linkage of the glucose component in carminic acid was established (ref. 208) from the ozonation of carminic acid which allowed the side chain to be removed and afford a known meso product after esterification to form the methyl ester, acetylation, hydride reduction of the methoxycarbonyl group and deacetylation. An α-glucosidic bond would have given a chiral degradation product. That the aglycone of carminic acid is indubitably kermesic acid was confirmed by its degradative formation from the former (ref. 209).

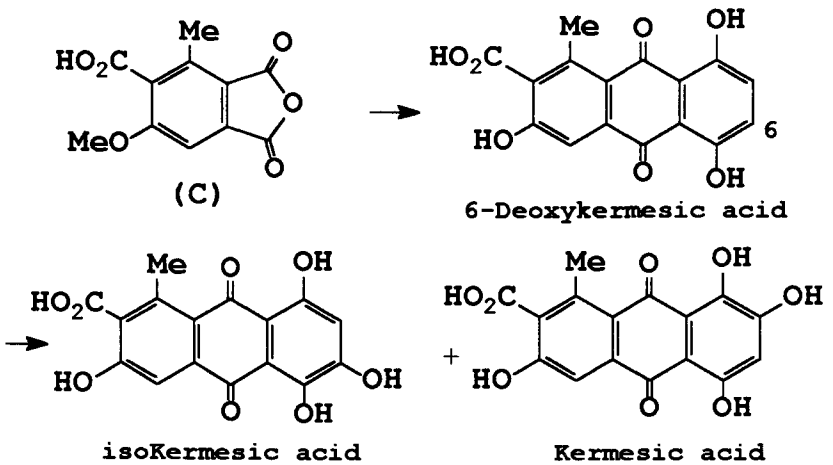


Thus carminic acid can be represented by structure (D) as 7-β-D-gluco-pyranosyl-3,5,6,8-tetrahydroxy-1-methylanthra-9,10-quinone-1-carboxylic acid, a formulation substantiated by its ^{1}H NMR and ^{13}C NMR spectra (ref. 210). By contrast, the detailed structure of the metal chelates of carminic acid is not known for certain (ref. 211) with regard to the possible competing role of the two chelating functions, namely the salicylic and the alizarin centres.

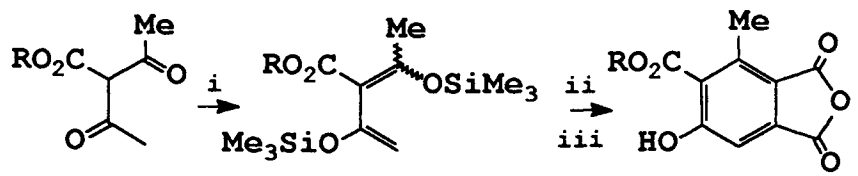
14.7.3 Synthesis of Carminic acid

Synthesis has usually followed on from full structural elucidation although from the commercial viewpoint the apparent abundant natural source, in the present case of cochineal, would not be a spur towards this objective. However experience in a number of areas shows that the availability and price of natural products are capricious matters subject to a number of vagaries including human factors as well as variations of nature. A spiralling price of cochineal in the mid eighties made total synthesis appear a more viable commercial proposition than purely an academic goal.

Carminic acid is now one of a great number C-glycosides and increasing pharmaceutical interest has led to the extensive study of their chemistry and methodologies for their synthesis (refs. 212, 213). Initially it appeared feasible to attempt the simplest strategy, namely the C-glycosylation of kermesic acid the synthesis of which had been accomplished by several different groups. In the first of these (ref. 214), experimental details of which have not been published, the condensation of coccinellic anhydride methyl ether (C) with 2-methoxy-1,4-dihydroxybenzene in a sodium/aluminium chloride melt led to isokermesic rather than kermesic acid. The subsequent use of 1,4-dihydroxy benzene to give 6-deoxykermesic acid followed by Thiele acetoxylation and hydrolysis afforded a mixture in which it was stated (ref.214) that the desired product kermesic acid predominated.

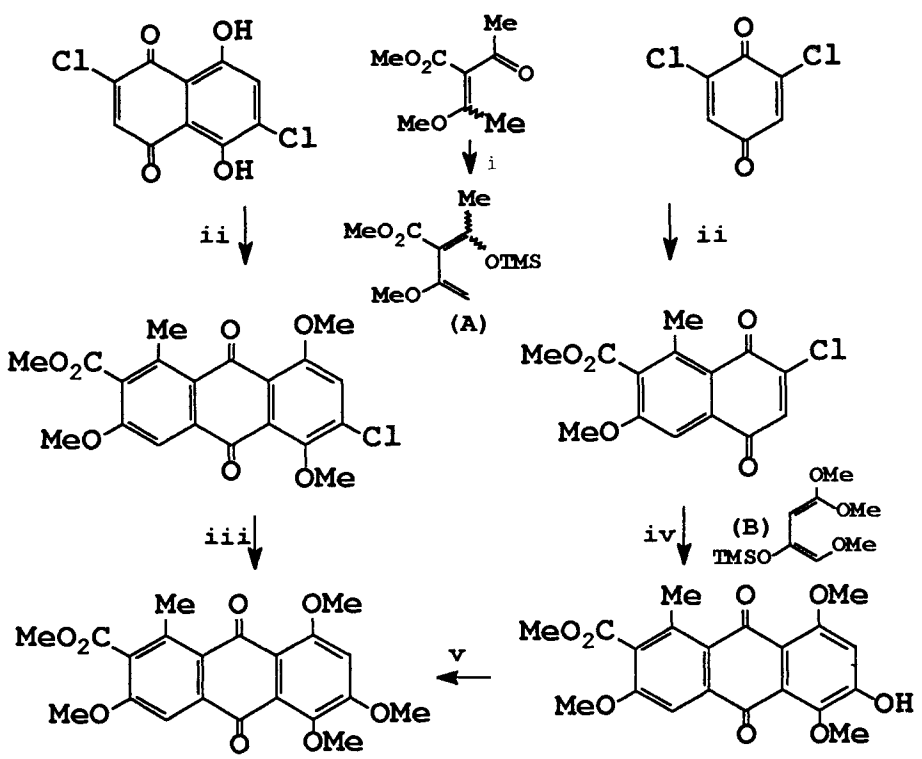


In our own work (ref.39) the methyl, ethyl and benzyl esters of coccinellic anhydride methyl ether were prepared by the Diels-Alder reaction of 2-chloro and 2-bromomaleic anhydride with 3-alkoxycarbonyl-2,4-bistrimethylsiloxypenta-1,3-diene (R = Me,Et,Bn) rather than by the lengthy procedure used formerly (ref. 214). Nevertheless the Friedel-Crafts reaction of these esters with 1,4-dihydroxybenzene to afford finally 6-deoxykermesic acid could not be effected.



Reagents (i) TMSCl, Et_3N, (ii) 2-Clmaleicanhydride, PhMe,Δ (iii)H_3O^+

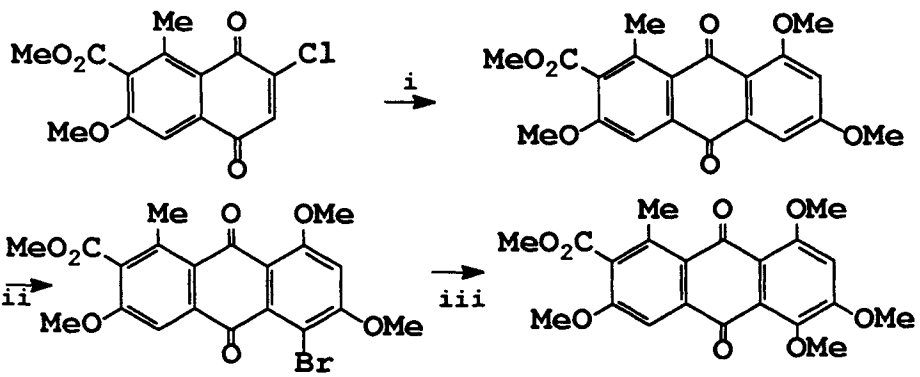
Regiospecific syntheses of kermesic acid were developed both based primarily on the Diels-Alder reaction. In the first (ref. 215) methyl diacetylacetate was converted to to the enol methyl ether which was silylated to give 4-methoxy-3-methoxycarbonyl-2-trimethylsiloxypenta-2,5-diene (A). Diels-Alder addition to 2,6-dichloronaphthazarin afforded, after methylation and nucleophilic displacement of



chloride, methyl tetra-O-methylkermesate. This compound was also obtained by the Diels-Alder reaction of 2,6-dichlorobenzo-1,4-quinone with the same diene to give a bicyclic compound which was then submitted to a further Diels-Alder reaction with 1,1,4-trimethoxy-3-trimethylsiloxybuta-1,3-diene (B), obtained from 1,1-dimethoxyethene by acylation with methoxyacetyl chloride followed by trimethylsilylation. Methylation gave the product.

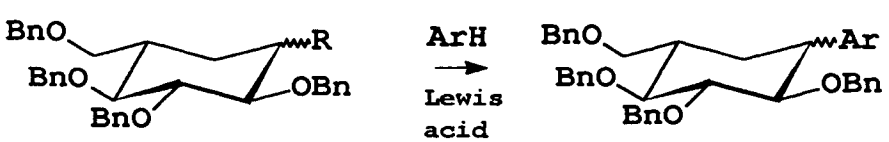
Reagents (i) TMSCl, Et_3N,$ZnCl_2$,(ii) A,PhMe,Δ, (iii) NaOMe,DMF,(iv)B, PhMe,Δ , (v) DMS, K_2CO_3, PhMe

In a second synthesis (ref. 216), the same bicyclic chloroquinone was reacted with 1,1-dimethoxyethene to afford a 3,6,8-trimethoxy tricyclic compound which upon monobromination and displacement of the bromine with methoxide gave methyl tetra-O-methylkermesate. Demethyation with aluminium chloride and hydrolysis of the methyl ester gave kermesic acid.



Reagents (i) $2(MeO)_2C{=}CH_2$,DMF,Δ, (ii)Br_2,AcOH, NaoAc,(iii)NaOMe,DMF

In the synthesis of aryl C-glycosides, the direct formation of a C-C bond of an arene to the anomeric centre, has been achieved by a great variety of methodologies, including Friedel-Crafts reactions, organometallic approaches, with metal phenolates and by means of aldol-type condensations in each category of which many different individual procedures have been employed. For example, in the first group 1-α or β-substituted derivatives of 2,3,4,6-tetra-O-benzyl-D-glucopyranose with groups (R) such as 2-thiopyridyl (ref. 217), trichloroacetamidate (ref. 218), trifuoroacetate (ref. 219), 4-nitrobenzoate (ref. 220), 3,5-dinitrobenzoate (ref. 221), fluoride (ref. 222), chloride (ref.223) and bromide (ref. 224) have been used with a reactive methoxyarene, ArH and a



Lewis acid catalyst to afford in the majority of cases a high proportion of the β-anomer.

Synthon analysis reveals four possibilities A, B, C and D as illustrated in Fig.14.3,(glu = D-glucose). Route A involving an octaketide may well represent the biogenetic pathway to carminic acid by way of an anthrone precursor and its subsequent hydroxylation at the 5-position. Higher polyketides have been prepared (ref. 225) and this type of approach has been used for a non-glucosidic anthraquinone, emodin (ref. 226). With route B although one of the components is available from kermesic acid syntheses the unequivocal synthesis of a 2-glucosylbuta-1,3-diene proved elusive (ref. 227) and progress has so far only been realised with simpler examples (ref. 228). While in the case of route C involving the preparation of a C-glycoside of 5,8-dimethoxytetral-1-one or its 7-chloro analogue through the use of an enamine (ref. 229) or the trimethylsilyl ether of an enol (ref. 230), preliminary work with tetralone itself proved inefficient (ref. 227). By contrast with the availability of kermesic acid, route D appeared more attractive than the foregoing proposals.

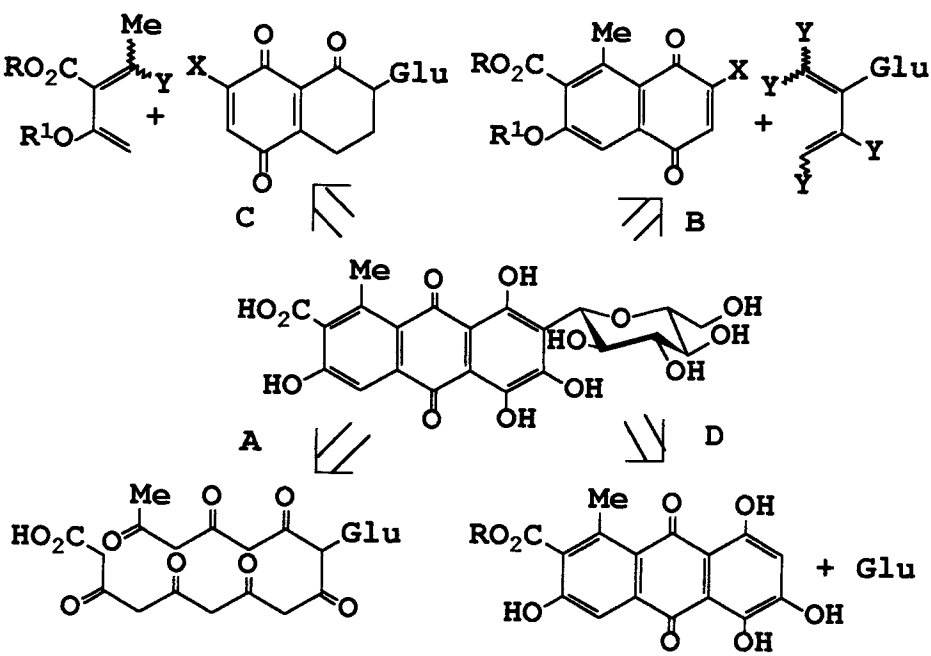


Fig.14.3 Retrosynthetic Schemes for Carminic acid

However, under a variety of conditions with a range of glucose derivatives, methyl tetra-O-methylkermesate, or its analogue with a 5,6-methylenedioxy group, failed to form a C-glycoside possibly due to steric hindrance at the 7-position.

Alternative strategies which in themseves might also be subject to steric limitations were to formylate at the 7-position and assemble a C_6 side chain by

either a Wittig reaction and Sharpless epoxidation or through a Danischefsky sequence involving a Diels-Alder reaction (ref. 231). However this approach appeared unnecessarily complicated. and to overcome the problem of steric hindrance, attention was turned to the use of 5,6-dideoxykermesic acid in which it was proposed to form the 8-O-glucoside and rearrange this to the 7-C-glucoside by an isomerisation which had been effected in the naphthol series (ref. 232) and finally to dihydroxylate at the 5,6-positions. Nevertheless a more available candidate was at hand with 6-deoxykermesic acid, although regiospecificity of glucosylation at the 7-position would be required. The hoped-for product would then be 6-deoxycarminic acid, a known degradation product of carminic acid capable of reconversion to that compound (ref. 201).

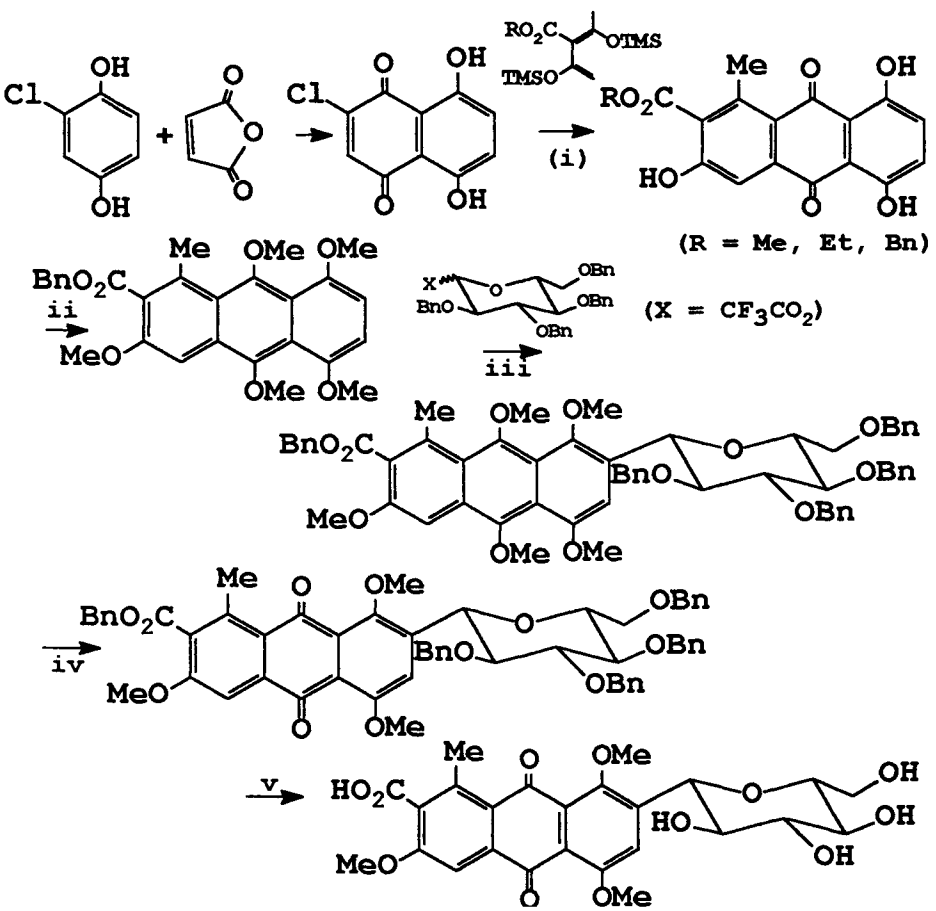
6-Deoxykermesic acid has a structural resemblance to 1,4-dihydroxyanthra-9,10-quinone (quinizarin) which in the *leuco* form will undergo an aldol type condensation, a reaction first described many years ago (ref. 233) and employed to attach a C_5 open chain sugar to the latter (ref. 234). By analogy, glucose protected in the open chain form and 6-deoxykermesic acid were potential reactants for a possible regiospecific aldol reaction with subsequent conversion of the side chain to the required cyclic form (ref. 235). Although experimental conditions were found with a number of simple aldehydes for aldol reaction to take place regiospecifically at the 7-position, penta-O-benzyl-D-glucose afforded very low yields. It was desirable to consider the synthesis of carminic acid by a different approach through glucosylation of an appropriate activated derivative of 6-deoxykermesic acid with a protected cyclic glucose derivative under Friedel-Crafts conditions.

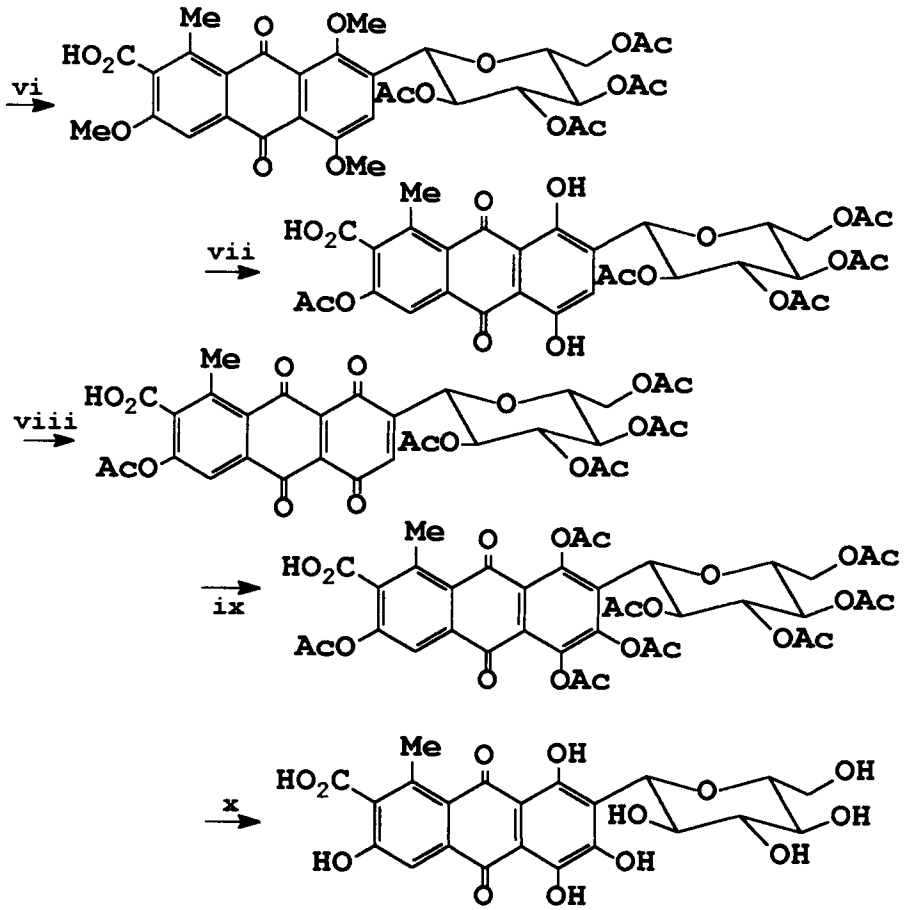
6-Deoxykermesic was first prepared by a improved procedure in view of the failure, referred to earlier, to duplicate the reported reaction (ref.214) of cochinellic anhydride derivatives with 1,4-dihydroxy or 1,4-dimethoxybenzene by a Friedel-Crafts reaction.

In a different approach it was found that (E) and (Z) 3-alkoxy-2,4-bis(trimethylsiloxy)penta-1,3-dienes (the methyl, ethyl and benzyl esters were used) were more easily prepared dienes than monotrimethylsilyl enolic methyl ethers such as compound A used in the first synthesis of kermesic acid due to the unwanted occurrence of C- as well as O-methylation in the methylation of methyl diacetylacetate.

2-Chloronaphthazarin, a hydrogen-bonded compound, equally represented as either 2-chloro-1,4-dihydroxynaphtho-5,8-quinone or 2-chloro-5,8-dihydroxynaphtho-1,4-quinone can be prepared from chloromaleic anhydride and hydroquinone or from maleic anhydride and 2-chlorohydroquinone by Friedel-Crafts acylation. It reacted only at the chlorine-containing ring by Diels-Alder addition with 3-alkoxy-2,4-bis(trimethylsilyl)penta-1,3-diene to afford alkyl 3,5,8-trihydroxy-1-methylanthra-9,10-quinone-2-carboxylates in high yield. Hydrolysis readily gave 6-deoxykermesic acid. Methylation of benzyl 3,5,8-trihydroxy-1-methylanthraquinone-2-carboxylate gave the corresponding trimethyl ether and reductive methylation then resulted in benzyl 3,5,8,9,10-pentamethoxyanthraquinone-2-carboxylate. With 2,3,4,6-tetra-O-benzyl-α-1-

trifluoroacetyl-D-glucopyranose, C-glycosylation took place regiospecifically at the 7-position although with other glucose derivatives there was no reaction. Oxidation with Jones reagent restored the 9,10-quinone and hydrogenolysis of this tetra-O-benzyl compound afforded the parent C-glycoside. Acetylation of the glucosidic hydroxyl groups and demethylation of the 3,5,8-dimethoxy compound followed by acetylation yielded 6-deoxycarminic acid as the heptaacetate which was identical with the product of degradation of carminic The hydrogenolysed product was mildly acetylated, demethylated and converted to the 3-acetoxy derivative under conditions whereby the hydrogen-O-acetyl, 3-acetoxy derivative, conditions under which the strongly hydrogen-bonded 5,8-dihydroxy system remained unaffected. Oxidation with lead tetraacetate gave the sensitive 5,8,9,10-bisquinone which underwent Thiele acetoxylation to give carminic acid octaacetate identical with natural carminic acid octaacetate (ref. 39). Hydrolysis, in the case of the methyl and the ethyl esters, with hydrochloric acid afforded carminic acid. Improvements in the synthesis of 6-deoxykermesic and kermesic acids have been made (ref. 236)





Reagents (i)PhMe,E and Z-'bisTMSdiene',Δ, THF,H_2O ,(ii)Me_2SO_4,K_2CO_3, Me_2CO; $(NBu)_4Br$,$Na_2S_2O_4$,HO^-,Me_2SO_4,(iii)2,3,4,6-tetra-O-Bn-D-glucose,$(CF_3CO)_2O$,CH_2Cl_2(iv) PCC, (v)Pd-C,H_2,H^+,THF, air,(vi)Ac_2O,py.DMAP,CH_2Cl_2, (vii) BBr_3,CH_2Cl_2,-80°C to 0C; Ac_2O,100°C, 1h,(viii)$Pb(OAc)_4$, Ac_2O,(ix)H_2SO_4 ,(cat.),Ac_2O, (x)EtOH,HCl

14.8 Chemistry and Synthesis of Tetracyclines

14.8.1 Introduction

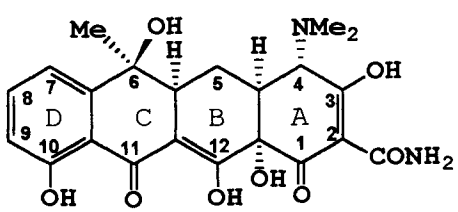
The tetracyclines are a small group within and arising from the antibiotics (ref. 237) which in themselves can be defined as substances produced by microorganisms capable in low concentrations of inhibiting the growth of bacteria or other microorganisms. The microorganisms involved in producing antibiotics are vast in number and include bacteria, fungi and algae; they are found in

marine organisms such as sponges and soft corals (ref.238) and can occur in terrestrial plants (ref. 239). More than 10,000 antibiotics are known although barely two-thirds of these have been structurally elucidated and of these only some 200 with appropriate *in vivo* activity and low toxicity have become commercially viable for human and animal use. Some appear to function by inhibition of bacterial cell wall biosynthesis, inhibition of protein, RNA or DNA synthesis and membrane damage. There is physical evidence that antibiotics such as the tetracyclines (ref. 240) in crude form were known in folk medicine and in antiquity. The pioneer antibacterial work of Pasteur and later of Fleming is renowned worldwide although systematic chemical investigation was not widespread, apart from early work by Raistrick, until the chemistry of penicillin was examined after 1939 in World War II. The term antiobiotic dates from 1942 and a chemical clasification now comprises aminoglucosides (eg. streptomycin), ansamacrolides sometimes called ansamycins (eg. the maytansinoids), β-lactams (eg. penicillins, cephalosporins), chloramphenicol, glycopeptides (eg. vancomycin), lincomycins, macrolides (eg amphotericin), polyethers sometimes referred to as ionophores (eg. monensin) and tetracyclines. The members of this last group contain a phenolic group like a number of antibiotics, eg. rifamycin S and the dihydric phenol, mycotrienol II, although the tetracyclines are also amphoteric.

The tetracyclines are a small group of antibiotics which are nevertheless of world-wide importance commercially since although having a relatively small share of the market (6% in 1989) compared with penicillins (14%) and cephalosporins (48%), some, eg. chlorotetracycline are effective orally with broad spectrum activity against both gram-positive and gram-negative bacteria; some are active against tickettsia and large viruses of the lymphogranuloma type. Chlorotetracycline was the first member to be discovered and was isolated from the soil organism, *Streptomyces aureofaciens* (ref. 241). Novel tetracyclines continue to be found as for example from a culture broth of a new species of Actinomadura, *Actinomadura brunnea* (ref. 242). The biosynthesis of tetracyclines has been investigated (ref. 243).

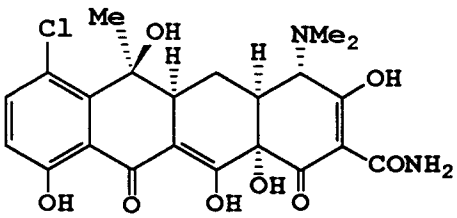
The tetracyclines are all structurally related by their having a naphthacene ring system and they differ only in the pattern of substituent groups.

The structure of seven important tetracyclines, namely tetracycline (1), chlorotetracycline(7-chlorotetracycline)(2), oxytetracycline (3) [5-hydroxytetracyline, trade name terramycin (ref.13,Table14.1], demeclocycline (4)

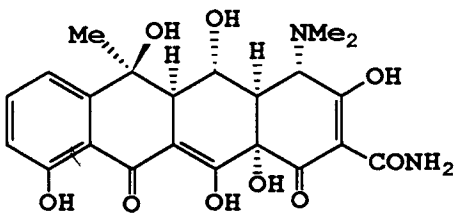


(1)

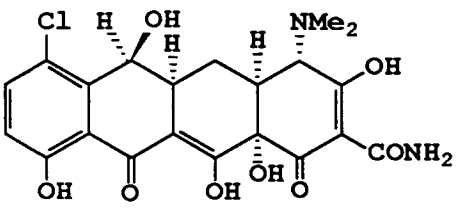
Tetracycline



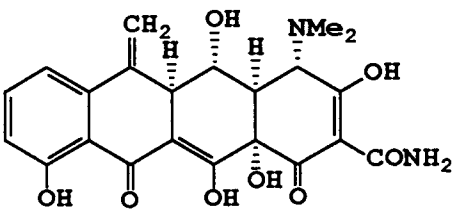
Chlorotetracycline (2)



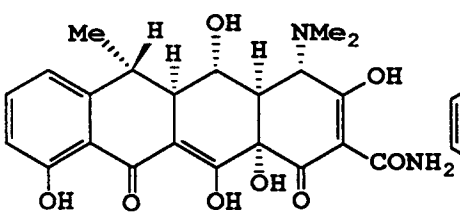
Oxytetracycline (3)



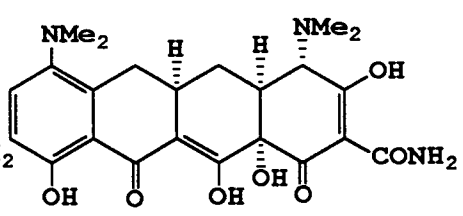
Demeclocycline (4)



Methacycline (5)



Doxycycline (6)



Minocycline (7)

(6-demethyl-7-chlorotetracycline, methacycline(5), (6-demethyl-6-deoxy-5-hydroxy-6-methylenetetracycline, doxycycline (6), (6α-deoxy-5-hydroxytetracycline and minocycline (7), (6-demethyl-6-deoxy-7-dimethylaminotetracycline are shown.

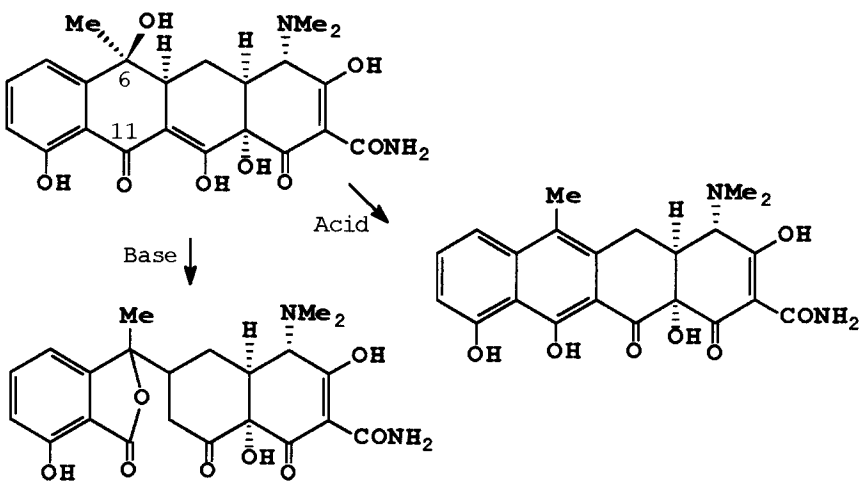
The usual ring numbering is shown and the parent compound tetracycline (1) is 4α-dimethylamino-1,4,4aα,5,5aα,6,11,12a-octahydro-3,6β,10,12,12aα-pentahydroxy-6α-methyl-1,11-dioxonaphthacene-2-carboxamide, although the trivial or generic name tetracycline is clearly preferable. A wide variety of trade names abound.

The determination of the structure of oxytetracycline involving at that time only degradative evidence, uv and ir spectroscopy was achieved in 1953 (ref. 244). Fermentation methods are employed as with most antibioics and selected strains of *Streptomyces* are cultivated to secure optimum growth and maximum formation of the product in a bioreactor at constant temperature in a sterile nutrient medium containing a carbon and a nitrogen source together with

inorganic salts, control of pH, aeration and agitation (ref. 245). Thus chlorotetracycline (2) is produced from *Streptomyces aureofaciens*, oxytetracycline (3) arises from the actinomycete *Streptomyces rimosus,* tetracycline (1) can be obtained by direct fermentation or by semi-synthesis through reductive dechlorination of (2) (ref.246) and 6-demethylchlorotetracycline (4) was obtained later as a metabolite of a mutant strain of *Streptomyces aureofaciens.* Compounds 5,6 and 7, the most recently introduced tetracyclines are formed by chemical operations. Such semi-synthetic transformations have proved important in the production and chemistry of tetracyclines.

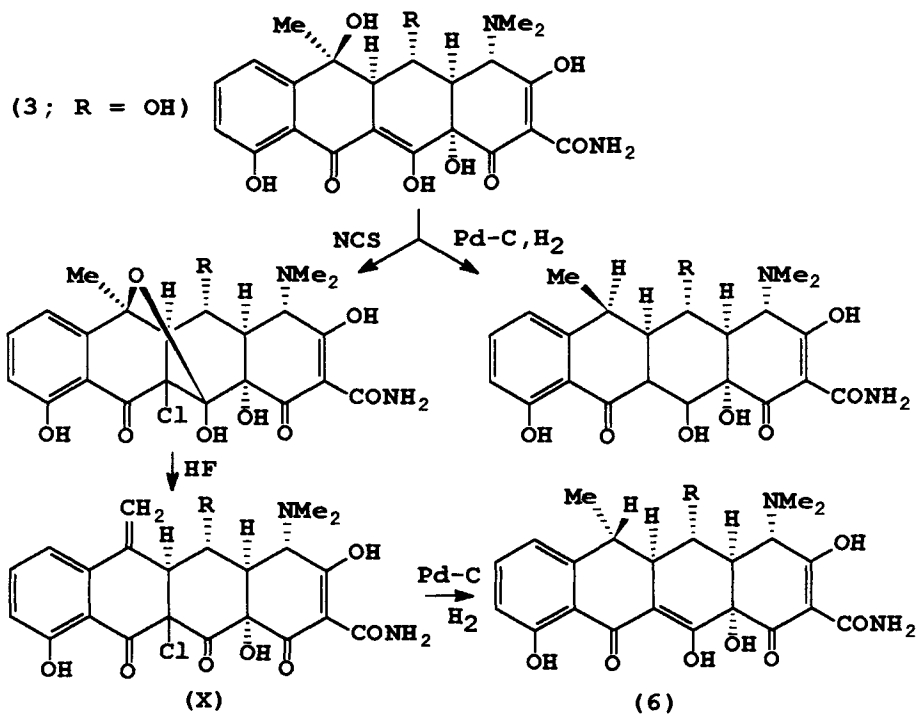
14.8.2 Semi-Synthesis of Tetracylines

Although the original tetracyclines brought in a new approach through their oral use as agents against a broad range of gram-positive and gram-negative bacteria, their instability towards acids resulting in dehydration of the 6-position leading for example in the case of tetracycline to anhydrotetracycline and with bases causing cleavage betwen the 11 and 12- positions were disadvantages. Greater stability was found in 6-demethyltetracycline (ref.247) and (4) its 7-chloro analogue.

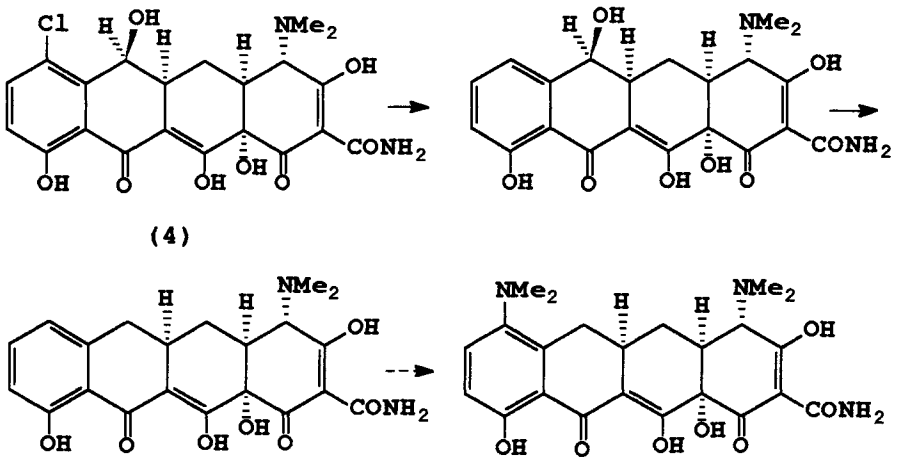


In this complex system of functional groups, once termed 'a diabolical concatenation' (ref. 248), structure/activity relationships indicate firstly that functional groups at positions 5,6 and 7 may be dispensed with without drastically affecting antibacterial properties, secondly the natural configurations at C-4 and C-5a are necessary and thirdly, loss of hydrogen from C-5a and C-11a causes loss of activity. The C11,C12 diketone system is thought to be vital (ref. 249) and the preservation of the BCD chromphores important. o-Substitution of the phenolic group is deleterious.

Structural susceptibilities and structure/activity studies have both inspired a large amount of semi-synthetic work to find more stable compounds without loss of antibacterial activity. The less active 6β methyl isomer of doxycycline (6) has been derived from oxytetracycline (3; R = OH) by catalytic reduction.. Treatment of (3) with N-chlorosuccinimide followed by hydrofluoric acid gave the chloro compound (X) which upon catalytic reduction afforded doxycycline (6), the 6α compound together with the less active 6β isomer (refs.250, 251) by saturation of the methylene group and removal of chlorine from (X). Reductive treatment of (X) with sodium hydrosulphite produced methacycline (5). The corresponding 5-deoxy analogues have likewise been derived by using tetracycline (3; R = H) in the same reaction sequences.



6-Deoxytetracyclines have enhanced chemical stability with maintenance of biological activity. and the former property enables the C7 and C9 positions to undergo electrophilic substitution. Thus 6-demethyltetracycline obtained by catalytic hydrogenolysis of (4), by further reduction afforded 6-deoxy-6-demethyltetracycline whcih underwent typical phenolic substitution reactions at the 7- and 9- positions (ref. 252), for example by way of the nitrate ion or with N-bromosuccinimide. Reduction and alkylation or reductve alkylation give routes to the 7-dimethyamino compound, minocycline (7) by means of selective reactions outlined in previous chapters.

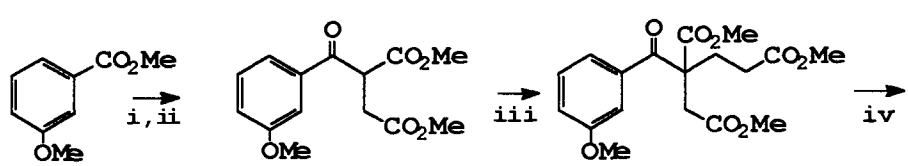


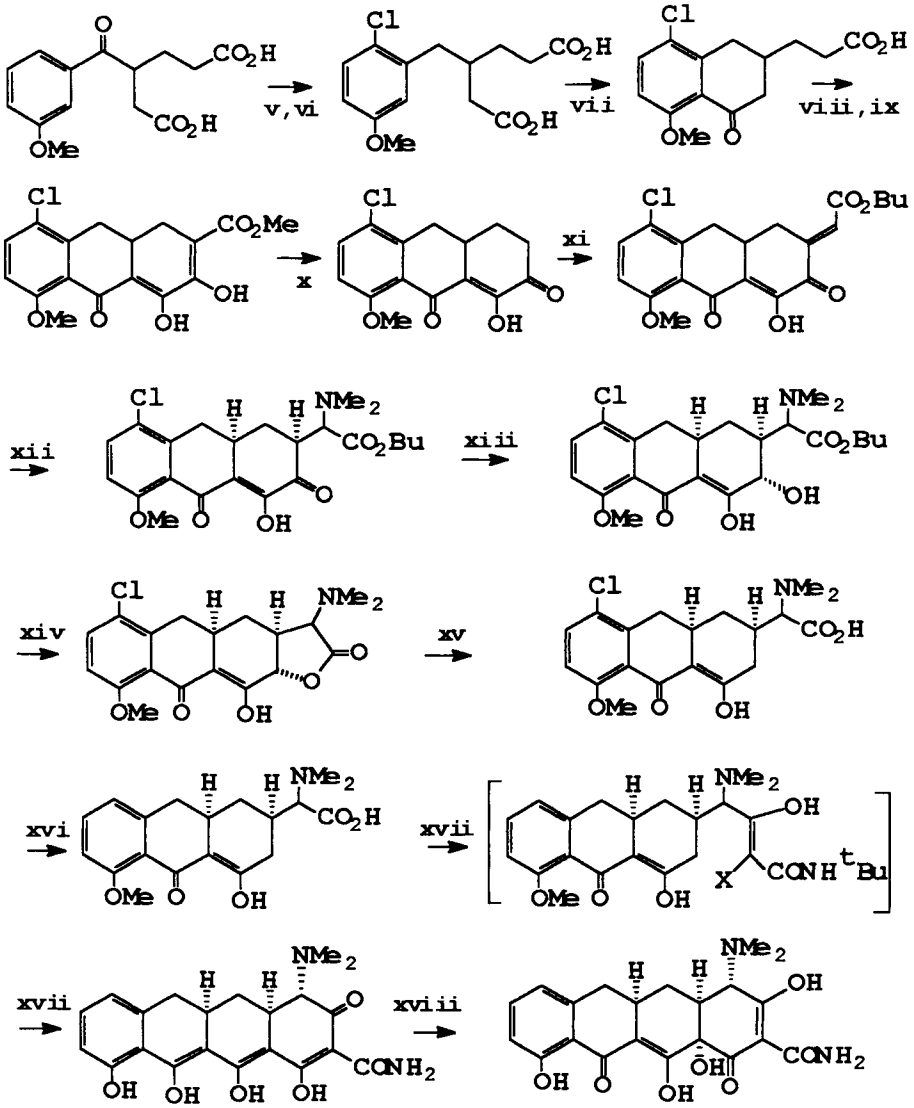
(4)

6-Deoxy-7-demethyl-6α-fluorotetracycline and the corresponding 6β- isomer have been synthesised and exhibit high activities compared to the parent tetracyclines. Acquired resistance to tetracyclines has been an impediment to their clinical use and in this context semi-synthetic studies which have already been very extensive have resulted in the introduction of valuable compounds such as minocycline.

14.8.3 Total Syntheses of Tetracyclines

The tetracycline molecules provide an illustrious but stern challenge towards synthesis and the results and achievements possess a classical quality and character in the annals of organic chemistry. Although the successes in synthetic work, as in much of natural product chemistry, have not displaced commercial fermentation-derived products, the gain to synthetic methodology in general has been immense and of value in numerous unrelated areas. Retrosynthetic analysis reveals several potential strategies but it is of interest that all of those given here proceed from the aromatic D ring. The first synthesis of racemic 6-demethyl-6-deoxytetracycline was described in 1962 (ref. 253) and published in full later (ref. 254). The sequence of ring formation was D→DC→DCB→DCBA and the synthesis commenced with methyl 3-methoxybenzoate.

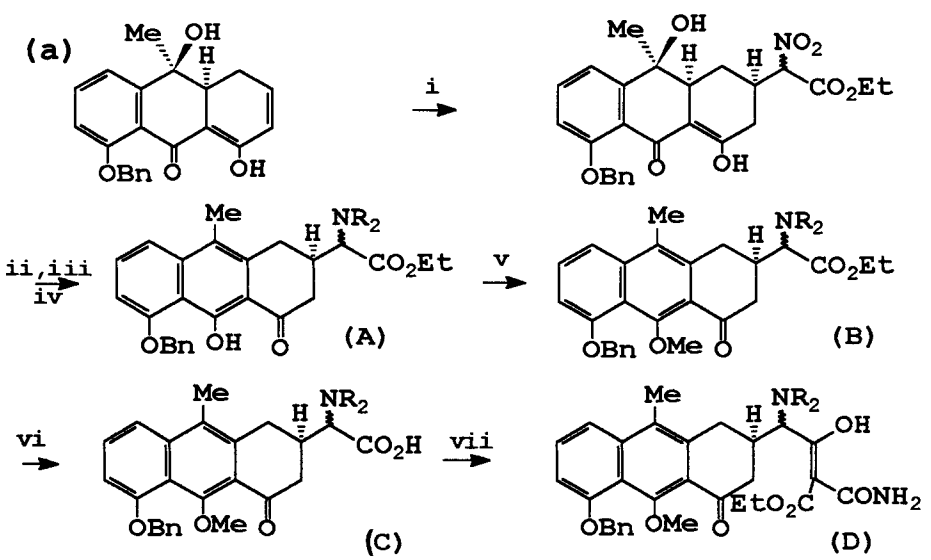


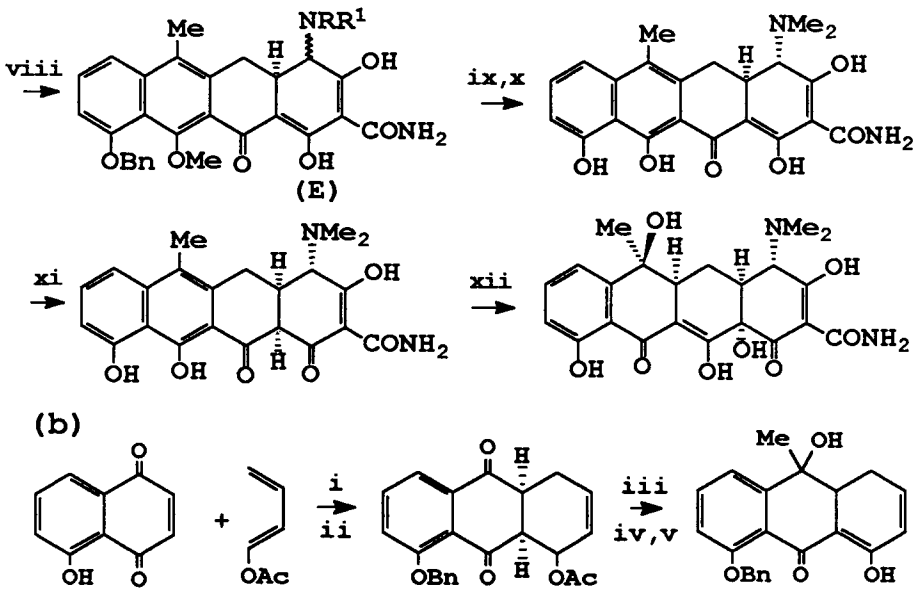


Reagents (i) $MeCO_2Me$,DMF,2NaH, (ii) $ClCH_2CO_2Me$, DMF,(iii)40%Triton ,MeOH,CH_2=$CHCO_2Me$,(iv)AcOH,H_2O, H_2SO_4, (v)MeOH,H_3O^+; Pd-C,AcOH,H_2;15% NaOH,(vi)AcOH,(cat.I_2),Cl_2,(vii) HF,(viii) MeOH,$CHCl_3$, H_3O^+,(ix) $(CO_2Me)_2$,DMF,NaH,MeOH,(x)AcOH ,HCl, (xi)$OHCCO_2Bu^n$, PhMe, $Mg(OMe)_2$,(xii)Me_2NH(liq.),N_2, (xiii) $NaBH_4$,DME,-70°C;AcOH, (xiv)4-TSA,PhMe, (-H_2O),(xv) HCO_2H, Zn,(xvi)Pd-C,EtOH,Et_3N,H_2, (xvii) $ClCO_2iC_3H_7$,Et_3N; Mg saltof $EtO_2CCH_2CONHBu^t$, MeCN, (X = CO_2Et); NaH, DMF,Δ ; HBr, (xviii)O_2, $CeCl_3$

A key step in the synthesis was the introduction at step (xvii) (X = CO_2Et) of the reagent ethyl N-t-butylmalonamate and its reaction with the mixed anhydride of the amino acid component obtained by reaction with iso-propyl chloroformate in the presence of triethylamine. The compound at this stage was 6-demethyl-6,12a-dideoxytetracycline and its oxygenated product, with A/B rings cis, 6-demethyl-6-deoxytetracycline is significant as one of the simplest product which retains full biological activity. The final racemic product possessed half the activity of its optically active counterpart and thus the unnnatural stereoisomer must be presumed inactive.

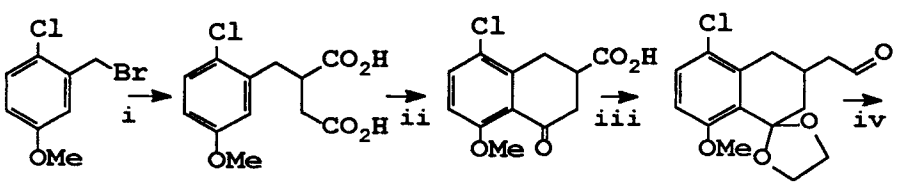
The synthesis of racemic 12a-deoxy-5a,6-anhydrotetracycline was described (ref. 255) during the period of work by the American group. Since the (-)-component of the racemic product had been 12a-hydroxylated (ref. 256) to afford 12a-hydroxy-5a,6-anhydrotetracycline which itself had previously been transformed into tetracycline (ref. 257), the authors refer to this work as the first total synthesis of a naturally occurring tetracycline. The naphthacene derivative synthesised by the Russian group, a known degradation product of tetracycline (ref. 258), can also be converted by an alternative route of 12a-hydroxylation, photooxidation and further steps (ref. 259) to tetracycline. The sequence (a) of ring formation steps was DC→DCB→DCBA and the starting point for the Russian work was juglone, 2-hydroxynaphtho-5,8-quinone which was transformed in several stages (b) (ref. 260) to give the initial DCB intermediate in the scheme shown (a) commencing with a Michael addition reaction. The Diels-Alder adduct obtained from juglone amd 1-acetoxybutadiene was a major product and the minor product was the same isomer used as the acetate by Muxfeldt and coworkers (ref.261) in their synthesis of racemic oxytetracycline (terramycin) which is depicted later. The mode of fomation of ring D was very similar to that used by the American group.

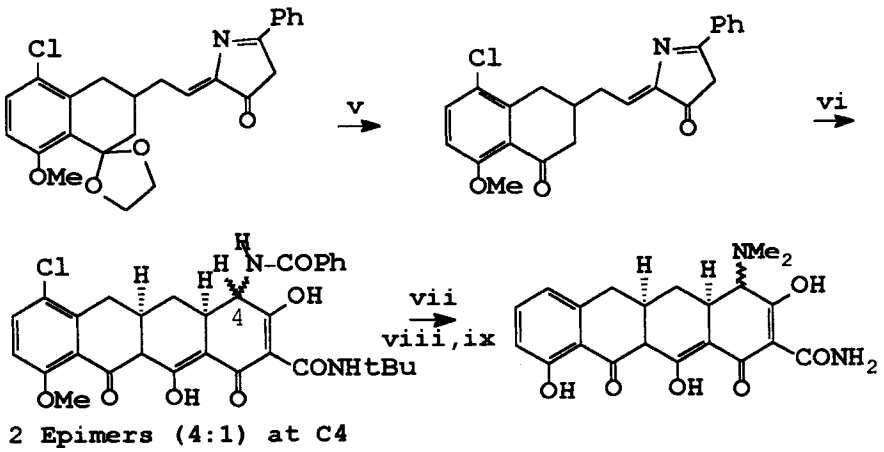




Reagents (a)N^+Me_4 $O_2NC^-HCO_2Et$,THF, (ii)EtOH,HCl;(A;R = H)Zn,AcOH; (iii)(iv) [A;R_2 = phthal,$(CO)_2C_6H_4$],THF, (v) (B; R_2 = phthal)MeI ,Ag_2O,(vi) (C; R_2 = phthal),aq.KOH,THF;diglyme,Δ,(-H_2O),(vi) (D; R_2 = phthal),(vii) PCl_5, DMF; EtOMgCH(CO_2Et)$CONH_2$,THF, (viii)(E; R =H,R_1 = $COC_6H_4CO_2H$), $MeSOCH_2Na$,DMSO,(ix)HBr, AcOH, (x) MeI,THF, (xi),(xii)known steps (ref.258)
(b) (i) Δ,(ii) $PhCH_2Cl$, Me_2CO,K_2CO_3,(iii) MeMgI,THF, (iv)HO^- ,(v)CrO_3,H_3O^+, Me_2CO

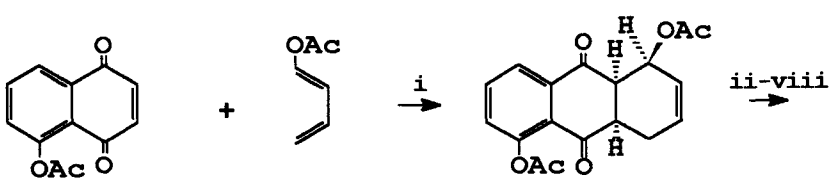
6-Deoxy-6-demethyltetracycline as a mixture (4:1) of two epimers at C4 has also been synthesised by an alternative remarkably short strategy which for the first time enabled the tetracyclic structure to be available in larger quantities (ref. 262). The synthesis begins with 2-bromomethyl-1-chloro-4-methoxybenzene (ref. 263), prepared by the bromination of 3-methyl-4-chloroanisole (with NBS), in order to obtain a DC tetralone and in a final step the assembly of a DC intermediate through the use of hippuric acid and a Michael addition of the DC bicyclic intermediate with methyl N-t-butyl-3-oxoglutaramate readily available from methyl 3-oxoglutarate followed by ring closure to afford the DCBA structure.

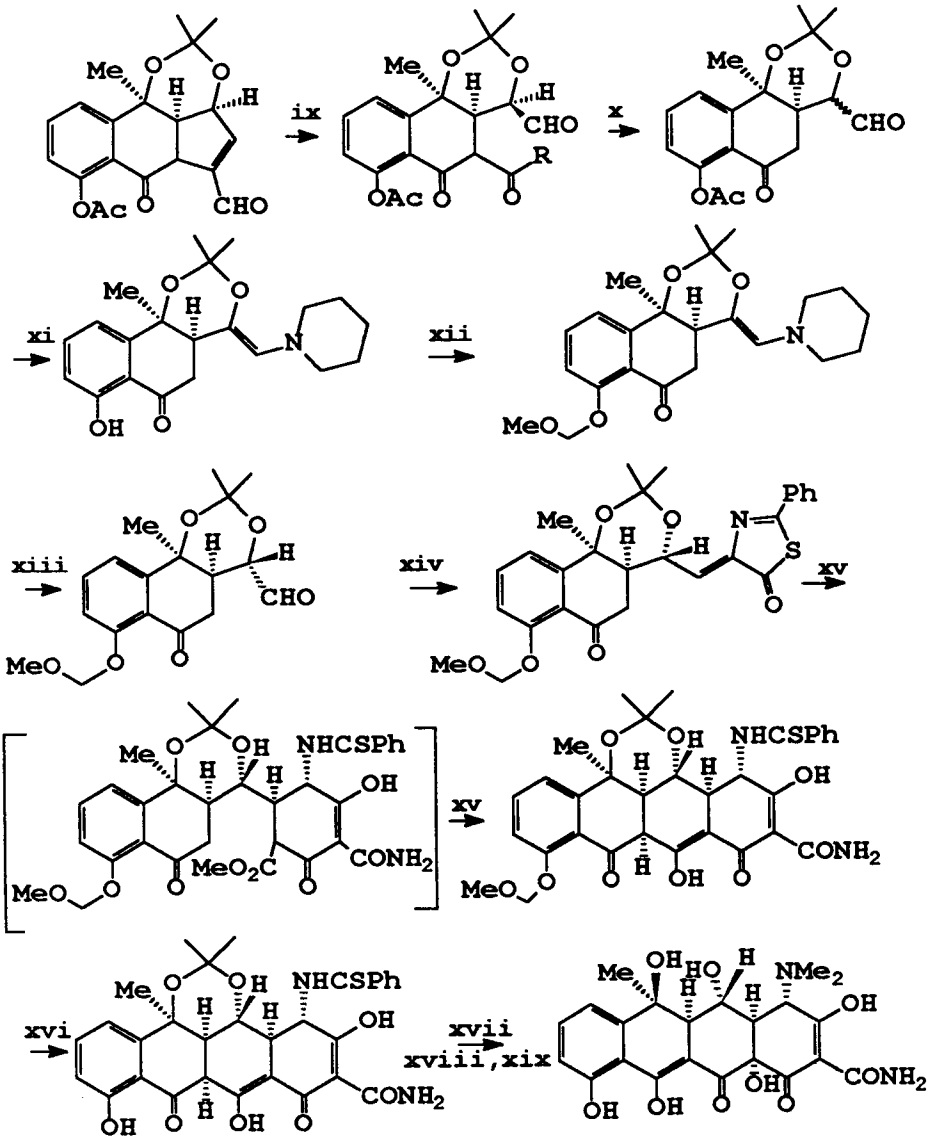




Reagents (i) $MeO_2CCH(CO_2Me)CH_2CO_2Me$,NaOMe,MeOH; HO^-, -CO_2,(ii)PPA, (iii)$(HOCH_2)_2$,4-TSA; (iv)$PhCONHCH_2CO_2H$,Ac_2O, $Pb(OAc)_2$,(v)THF,HCl, (vii)$MeO_2CCH_2COCH_2CONHBu^t$,THF,2NaH,35°C,(viii) Meerwein reagent;aqAcOH;HBr,AcOH,100°C,(ix)Pd-C, H_2,CH_2O,Et_3N

Oxidation of the final product at the 12a position with oxygen in the presence of platinum afforded essentially the same racemic product as in the Woodward synthesis. Resolution of either product, with or without an hydroxyl group at position 12a proved difficult due to rapid equilibrationa at the chiral centre, C4. The Muxfeldt group subsequently disclosed a preliminary account of a synthesis of racemic oxytetracycline (terramycin) (ref. 261) which was considered to the basis for a general method. Later, various refinements were incorporated and full experimental details recorded (ref. 264). The synthesis is depicted in the following scheme and starts from the major product of the Diels-Alder addition of acetyljuglone with 1-acetoxybuta-1,3-diene. The racemic oxytetracycline obtained was found to be half as active as the natural product from *Streptomyces rimosus* (ref. 265) and again illustrates that the unnatural enantiomer is biologically inactive. In view of this an enantioselective synthesis would be an appopriate objective if total synthesis became a viable commercial goal. Resolution at an early stage, for example of 5-chloro-8-methoxytetral-1-one-2-carboxylic acid obtained in the synthesis described (ref. 262) would be an approach.





Reagents (i)PhH,Δ, (ii) MeMgI,PhMe, (iii) aq. KOH, (iv)Me_2CO, $CuSO_4$, (v)Ac_2O, (vi)OsO_4,THF,$KClO_3$,H_2O(vii) Me_2CO,$Pb(OAc)_4$,(viii) xylene,DBU,AcOH,$C_5H_{11}N$,(ix) (R = CHO),O_3,$CHCl_3$ (x)aq. Na_2CO_3,(xi) PhH,$C_5H_{11}N$,-H_2O, (xii) THF, NaH, $ClCH_2OMe$,(xiii) SiO_2, (xiv)THF,2-Phthiazolinone,Pb(OH)OAc,(xv) $MeO_2CCH_2COCH_2CONH_2$,THF,-78°C,BuLi; bu^tOH, $LiOBu^t$, (xvi)aq.AcOH, (xvii)THF,DMF,$P(OEt)_3O_2$,(xviii) MeOH, HCl, (xix)MeI,THF,HCl; THF,EtN-iPr_2, DMS

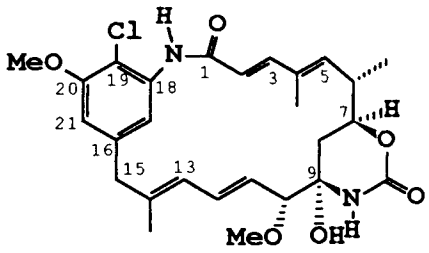
An important step in the preceding synthesis was the finding that the mixture of aldehyde epimers produced at step (x) was most easily transformed into the desired one through enamine formation and cleavage.
The methodology of synthesis in the tetracycline series has been investigated in great detail in a series of ten papers (ref. 266) in which to quote a few aspects, Michael type cyclisations for formation of ring B, its formatiom through 1,3-dipolar additions, photocyclisation of ring B, oxidation and reduction of potential ring A precursors, the synthesis of 6-methylpretetramid and 12aα-hydroxylation were studied.

14.9 Chemistry and Synthesis of Maytansinoids and Maytansides

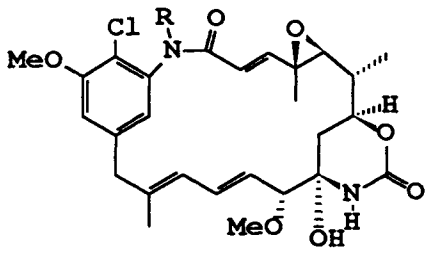
Introduction

The ansa macrolides have been referred to in the previous section and are antibiotics possessing an aliphatic bridge attached to two non-adjacent positions on the phenolic or phenolic ether ring. Of the two groups, one compises compounds having a naphthoquinonoid nucleus eg rifamycin S (ref.21,Table14.1); the other contains compounds based on a benzenoid ring and a typical example is the maytansinoid family (ref. 267) which were the first ansa macrolides to be found in plants. In general natural phenolic ethers are as abundant as free phenols in the form of monomethyl, dimethyl, polymethyl and methylendioxy members and the maytansinoids and the maytansides both contain an aromatic monomethyl ether group.
The maytansinoids possess an N-containing ester group at C3 as for example maytansine and all are derivatives of the parent alcohol maytansinol. Certain of the maytansinoids termed ansa mitocins are also esters of maytansinol in which the acyl group is derived from a branched chain carboxylic acid. The maytansides lack this ester group and are typified by maysine and maysenine.
Maytansine was recognised as the key member of a new and unusual class of natural product (ref. 268). It was first isolated from from *Maytenus ovatus* Loes. (ref. 269) and its structure was established by X-ray crystallography (ref. 269, 270) after which that of other members was deduced by NMR studies (ref. 271). The absolute configuration of maytansine is 3(S), 4(S), 5(S), 6(R), 7(S), 10(R) and 2'(S). Normaytansine has been isolated from *Maytenus buchananii* and others occur in which the ester chain from C3 is linked to the nitrogen atom to form overall a bicyclic system. A further large group of maytansinoids is associated with the nocardia microorganism, all of which possess, as with the maytansides, a C-4,C-5 epoxide ring (ref. 272). The parent alcohol of the series is maytansinol. Because of its biological interest maytansine and certain relatives have been separated by preparative liquid chromatography from the Indian source *Maytenus rothian* (ref. 273) in order to obtain larger amounts.
The maytansinoids have antitumour activity particularly against certain types of leukemia, such as P 388 lymphocytic leukemia, B 16 melanocarcinoma and Lewis lung carcinoma, while certain semi-synthetic esters derived by acylating

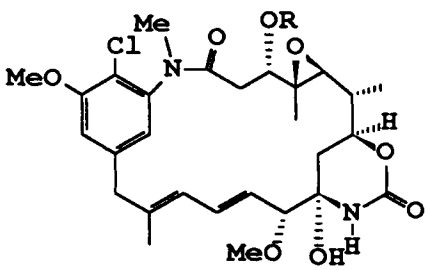
the C3 hydroxyl group in maytansinol have shown good antileukemic properties (ref. 274). By contrast the maytansides and maytansinol do not have antitumour activity showing that an ester group at C-3 is vital.

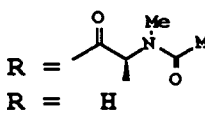


Maysenine



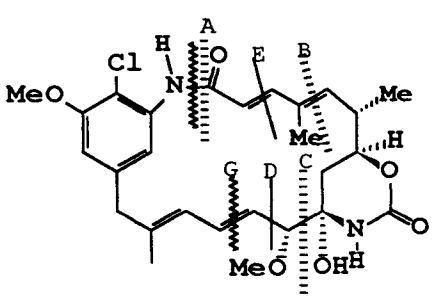
Maysine R = Me
Normaysine R = H





R = (Maytansine)
R = H (Maytansinol)

The promising properties, of potential clinical interest, found with certain members of the maytansinoids, such as remakable antitumour activity, led to total syntheses by several different groups. Maytansine was the first type of macrocyclic amide to be synthesised by a Corey group (ref.275) and the strategy adopted was to synthesise the target molecule maytansinol the conversion of which to maytansine had been effected (ref. 276). Several other groups have achieved success as for example that of Meyers in the synthesis of racemic N-methylmaysenine (ref.277), racemic maysine (ref. 278) and racemic maytansinol (ref. 279) while the first two compounds in this trio have also been obtained by a different approach in studies by Isobe (ref. 280). Disconnections for retrosynthetic analysis by the three groups are indicated for maysenine.



Disconnections

Corey A B C

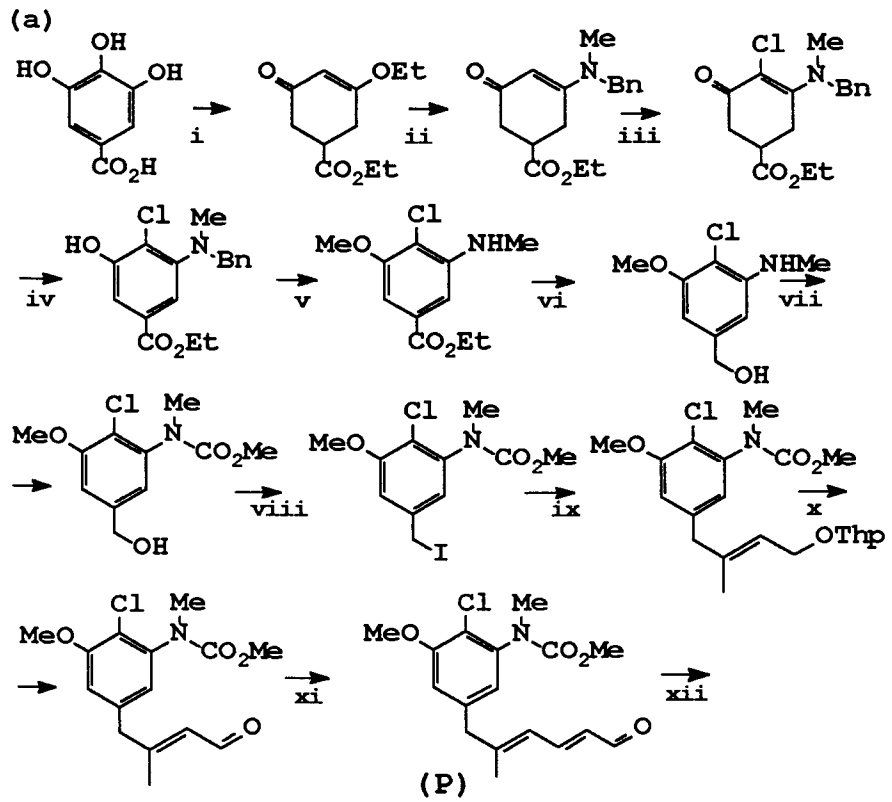
Meyers D E

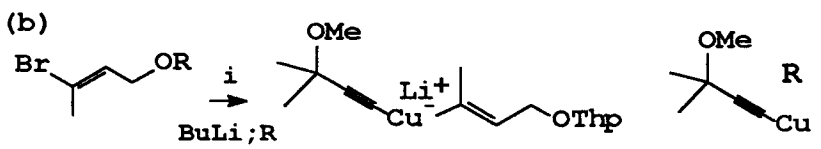
Isobe A G

The success of the synthesis in the work by the Corey group was dependent upon methodology achieved in the preparation of several key intermediates for maytansine, a dithian (ref. 281) and a benzenoid dienal (refs. 282,283) conceived from the disconnections A,B and C.

The synthesis of racemic N-methylmaysenine (ref.284) and the first chiral synthesis of (-)-N-methylmaysenine (ref.285) made use of these accomplishments and led to the total synthesis of maytansine (ref.275).

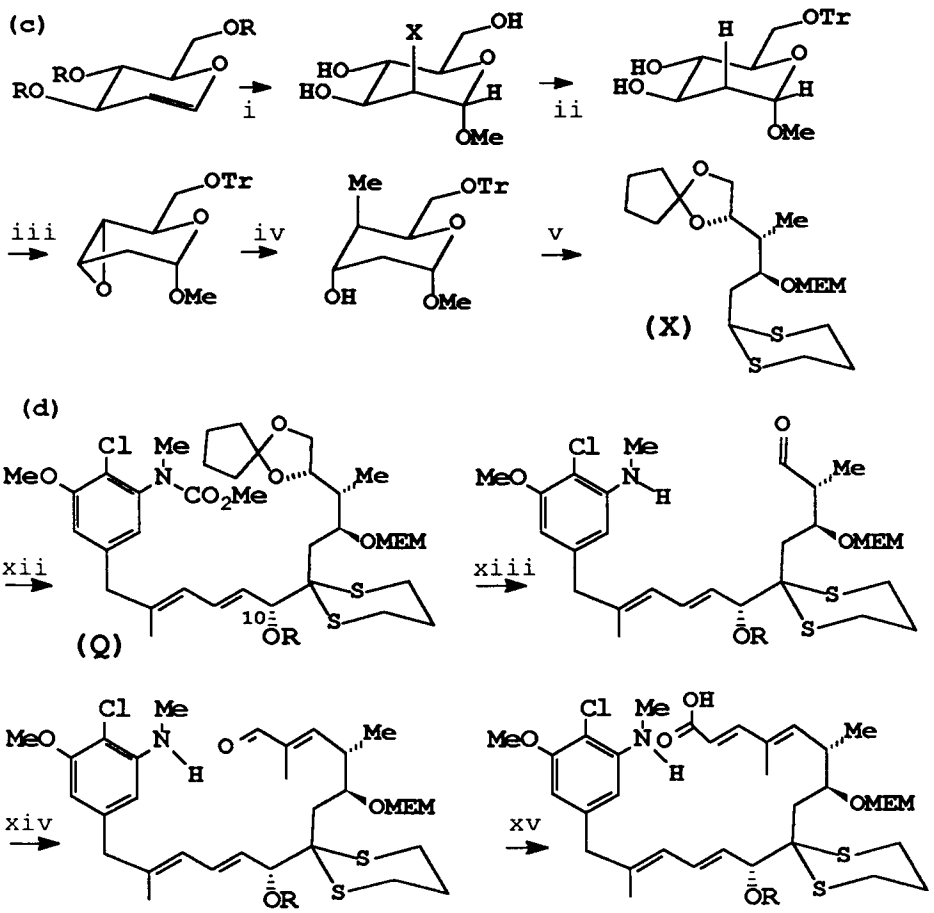
The synthon resulting from disconnections A and C was first synthesised (refs. 282, 283) as an aryldienal compound (P) commencing with gallic acid by Birch reduction, transformation of the ethoxyl group to a basic substituent and the ethoxycarbonyl to a dienal structure in the following way (route a). The attachment of the C_4 chain to the benzyl iodide at step ix was effected with the intermediate obtained by (route b).

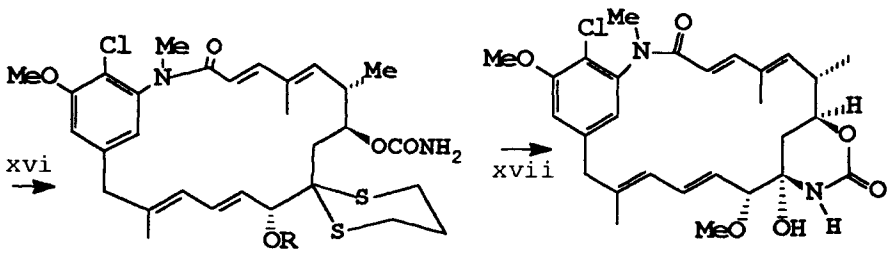




Reagents (a) (i)Birch redn. (ii) $PhCH_2NHMe$,Δ (iii)Bu^tOI,$CHCl_3$, -50°C(ivLiNEt$_2$,THF,-78°C;PhSeBr,THF,(v)MeI,K_2CO_3, Me_2CO;Pd-C,H_2,EtOH,(vi)LAH,THF,-5°C,(vii) $ClCO_2Me$, K_2CO_3, Me_2CO; HO^-,MeOH, (viii)$MeSO_2Cl$,Et_3N,THF; NaI, DME,(ix) reagent from route (b)i,THF,-78°C, (x)4-TSA, MeOH;MnO_2,CH_2Cl_2,(xi)$Me_3SiCH_2CH{=}NBu^t$,Et_2O,-78°C; AcOH,NaOAc,25°C,(xii)reaction in the next section (b)(i) (R = Thp), BuLi,THF,-105°C;R,THF:-78°C,(R from 3-MeO-2-Me-1-butyne, BuLi,CuI

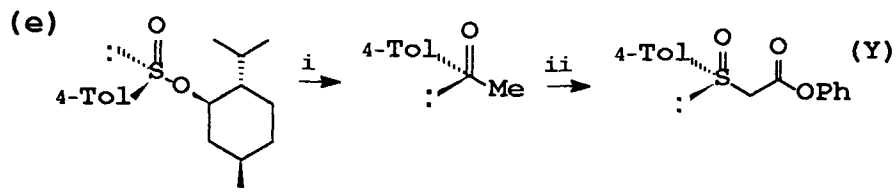
For the synthesis of (-)-N-methylmaysenine, the synthon resulting from disconnections B and C was in practice a chiral C_6 compound obtained from tri-O-acetyl-D-glucal which was transformed to an open chain dithian reactant X as shown in route (c). Reaction of X with the aryldienal P (step xii) led to Q which was then chain extended successively by C_3 and then C_2 to afford the two rings in the maysenine ring structure as shown in route (d).

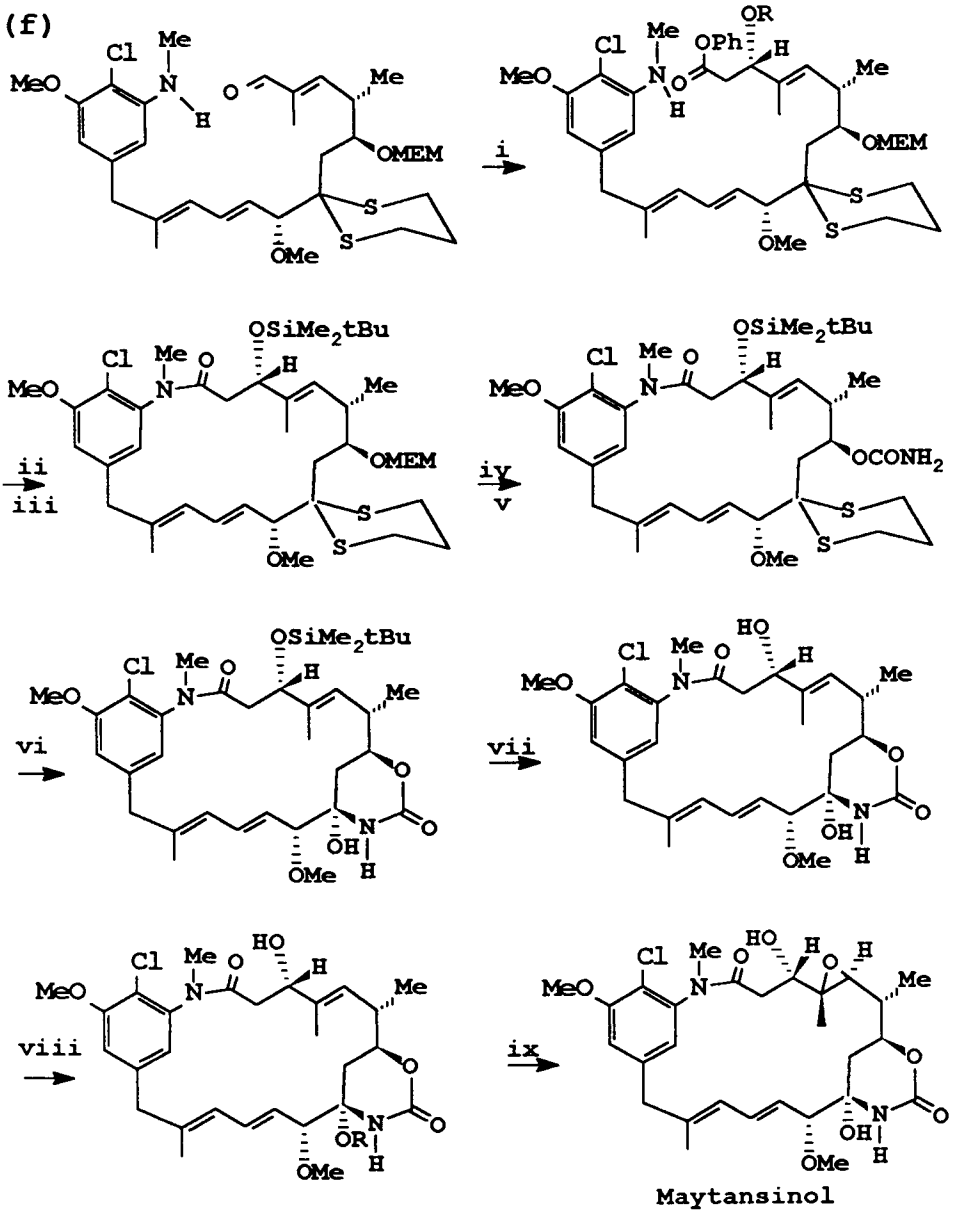




Reagents (c) (i) MeOH,NaOMe; $Hg(OAc)_2$(X = HgOAc,R = H) ; MeOH, NaCl ;$NaBH_4$, iPrOH;12MHCl (X = R = H),(ii) TrCl, Py.(ii)(X = H, R = Tr,(iii) 4NaH,HMPT,THF,$iPrC_6H_4$ SO_2-imidazole,-25°C, (iv) MeLi, CuI, PhMe,Et_2O,-78° C,(v)$HS(CH_2)_3SH$, $CHCl_3$,12M HCl ; 1-$EtOC_5H_7$, BF_3Et_2O ; 2-$MeO(CH_2)_2OCH_2Cl$(MEMCl), $EtiPr_2N$
(b)(xii)(Q, R = H, C10 epimers,1:1) P, X, BuLi, TMEDA,THF, -78°C; (Q, R = Me), NaH,MeI, (xiii) LiSMe,DMF; $HClO_4$ aq MeCN, (xiv) $MeC(Me_3Si)LiCH{=}NBu^t$, -110°C; SiO_2;C_5H_5NHCl, CH_2Cl_2 (Z →E),(xv)$MeO_2CCHLiP{=}O(OMe)_2$,THF; Bu_4NOH,aq. THF, (xvi)Bu_4N salt,$Me_3C_6H_2SO_2Cl$, iPr_2EtN,C_6H_6, 40°C ; 2M H_2SO_4 ,PhMe ; $ClCO_2C_6H_4NO_2$,py. ;conc.NH_3 Bu^tOH,(xvii) $HgCl_2$, $CaCO_3$, aq.MeCN, 27°C.

In the total synthesis of racemic N-methylmaysenine the synthon component from disconnections B and C had been derived (ref. 281) from cis–2-butene-1,4-diol by conversion to the dimethylacetonide by reaction with 2,2-dimethoxypropane followed by five further reactions although all the remaining reactions with the aryldienal and the C_3 and C_2 chain extentions were basically the same as in the synthesis of the (-) enantiomer.
For the synthesis of the 4,5-epoxy derivative, namely maysine and for that of the 3-hydroxy-4,5-epoxy derivative, maytansinol required for maytansine a number of further problems had to be surmounted. The aldehyde from step xiv (R = Me) resulting from the deketalisation of Q (R = Me) and C_3 chain extension was the starting point. A new chiral centre, to avoid epimer separation, was introduced by the use of the reagent, (R)-(+)-4-tolyl phenoxycarbonylmethyl sulphoxide prepared by route (e). The synthesis of maytansinol is shown in (f).





Reagents (e) (i)MeMgI, THF,-30°C,(ii) $LNiPr_2$, $ClCO_2Ph$,THF,
(f) (i) (Y), Bu^tMgCl,THF,-78°C ; Al/Hg, aq.THF,(R = H),
(ii) Bu^tMe_2SiCl, imidazole,THF,25°C ; LiOH,DME, 27°C,
(iii)cyclisation as for N-Me maysenine (iv)MEMremoval,
iPrSH,CH_2Cl_2 ,-78°C, BF_3Et_2O,5min.,Bu_4NOH,aq.PhH,27°C;
$AgNO_3$, 2,6-$Me_2C_5H_3N$,aq.THF,(v)$ClCO_2C_6H_4$4-NO_2,py.,27°C

(v)15M NH_4OH,aq.Bu^tOH, (vi)$HgCl_2$,$CaCO_3$,aq.MeCN,25°C; iPr_2EtN, (vii) MeCN,HF,H_2O,(23:1:1),0°C,(viii)(R = Me),0.1%4-TSA,MeOH, (ix) Bu^tO_2H, VO(IV)$(CHAc_2)_2$,2,6-$Me_2C_5H_3N$,PhMe, PhH,25°C,(R = Me);hydrolysis,(R = H).

The conversion of maytansinol 9-O-methyl ether to maytansine as the 9-O-methyl ether was effected with the imidazolide of N-acetyl-N-methylalanine in DMF-DME in the presence of imidazole during 75 hours at 45°C. Hydrolysis of the 9-O-methyl ether with 1% pyridinium chloride in aqueous THF gave a nearly theoretical yield of maytansine thus completing a highly memorable synthesis. Although promising initial clinical studies were reported (ref. 287) in the use of maytansine as a chemotherapeutic agent, advanced trials appear not to have been significant. Nevertheless organic synthetic methodology has been advanced in many diverse ways much of which has not been described in detail in this account but elsewhere (refs. 288,289). Semi-synthetic work has been carried out (refs.271, 290) and bearing in mind the much enhanced activity often found with parent phenols compared with their corresponding methyl ethers, demethylation of the aryl methyl ether in the maytansinoid series could be worth examination.

Many different aspects of phenolic chemistry have been presented in this account some positive in effect and others appparently less so. The impact of the chemistry of not just phenolic but all chemical compounds on humanity is sometimes, even frequently, misunderstood and the words of a great playwright are relevant (ref. 291). One objective in scientific work is to understand the natural world and to then improve and develop it; but human life is itself experimental and the outcome uncertain.

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SUBJECT INDEX