

Stereochemical Studies. V.¹⁾ Intramolecular C-H Bond Insertion Reaction of Acyl Nitrene generated from optically Active Acyl Azide²⁾

SHIRO TERASHIMA, MUNEHICO NARA, and SHUN-ICHI YAMADA

Faculty of Pharmaceutical Sciences, University of Tokyo³⁾

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In order to determine the spin state of the acyl nitrene (VII) which is thought to intervene in the insertion reaction at the intramolecular aliphatic C-H bond, optically active (*R*)-5-methyl-6-phenylhexanoyl azide ((*R*)-XVII) was synthesized from ((*S*)(+)-2-methyl-3-phenylpropionic acid ((*S*)(+)-XVIII), and submitted to photochemical decomposition in methylene dichloride solution. (*S*)(-)-6-Benzyl-6-methyl-2-piperidone ((*S*)(-)-XIX) was obtained as a reaction product in a 4.3% yield with 98% retention of configuration.

These results show that the singlet state acyl nitrene (XXXVIII) produced from (*R*)-XVII by irradiation, had inserted into the intramolecular optically active C-H bond through the transition state (II), as in the intramolecular insertion reaction of alkoxy-carbonyl nitrene.

Independent synthesis of (*S*)(-)-XIX from (*R*)- α -methylphenylalanine ethyl ester ((*R*)(+)-XX), and preliminary experiments on racemic compounds are also reported.

Introduction

Many useful reactions are thought to proceed *via* nitrene intermediates.⁴⁾ Relationships between the spin states of these intermediates and the stereospecificity of nitrene reactions present very interesting problems.⁴⁻⁷⁾

A previous communication⁷⁾ reported that alkoxy-carbonyl nitrene(II) generated from thermal and photochemical decomposition of optically active alkyl azidoformate(I), inserted exclusively at the intramolecular aliphatic C-H bond in its singlet state, also that optically

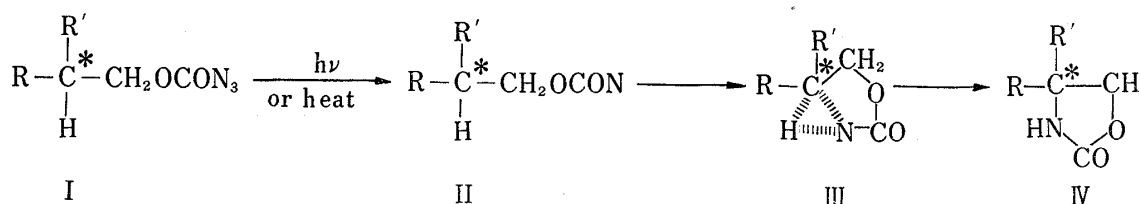


Chart 1

active 2-oxazolidinone(IV) was obtained through a transition state, such as III, with almost 100% retention of configuration. Lwowski⁵⁾ demonstrated that in the intermolecular reaction, the insertion reaction at the aliphatic C-H bond was observed only in the singlet state alkoxy-carbonyl nitrene. However, the nitrene species, which are formed from thermal

1) Part IV: K.K. Lee, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2540 (1969).

2) This work was the subject of a preliminary report. S. Yamada and S. Terashima, *Chem. Comm.*, **1969**, 511.

3) Location: *Hongo, Tokyo*.

4) R.A. Abramovitch and B.A. Davis, *Chem. Rev.*, **64**, 149 (1964).

5) W. Lwowski, *Angew. Chem.*, **79**, 922 (1967).

6) S. Yamada and S. Terashima, *Kagaku*, **23**, 1063 (1968).

7) S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1953 (1968).

decomposition of phenyl azide⁸⁾ and cyanogen azide,⁹⁾ are thought to insert at the aliphatic C-H bond, in both the singlet and triplet states.

When acyl azide(V), with a structure similar to that of alkyl azidoformate, is decomposed thermally, a normal Curtius rearrangement occurs and isocyanate(VI) is obtained as the rearranged product.¹⁰⁾ With photochemical decomposition, the formation of acyl nitrene (VII) is observed rather than the normal Curtius reaction.¹⁰⁾ The nitrene intermediate(VII), which is generated, shows nearly the same reactivity as that of alkoxycarbonyl nitrene.^{5,10)} Among the reactions of VII, intramolecular insertion reaction at the aliphatic C-H bond is of value, and has been frequently used with diterpenes and diterpene alkaloids.¹¹⁾ However, a precise examination of the reaction mechanism in this intramolecular reaction has never

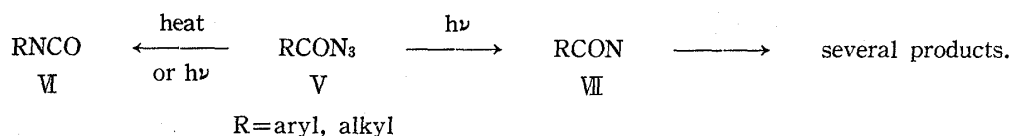


Chart 2

been done at the level of its spin state.¹²⁾ Based on the fact that acyl azide(VIII) on photochemical decomposition, afforded δ -lactam(X) in an amount two times that of γ -lactam(XI),⁵⁾ Lwowski⁵⁾ posited that the transition state in the formation of X should have a three membered ring system, such as XII. The same transition state was also proposed by Edwards, *et al.*¹³⁾ for the intramolecular δ -lactam formation observed after photochemical decomposition of hexanoyl azide. The transition state (XII) assumed by Lwowski⁵⁾ and Edwards,¹³⁾ should have the same characteristics as the transition state (III) seen in the intramolecular insertion reaction of II. If so, the intramolecular insertion reaction of VII at the aliphatic C-H bond should be a reaction of the singlet state nitrene, and should give an insertion product

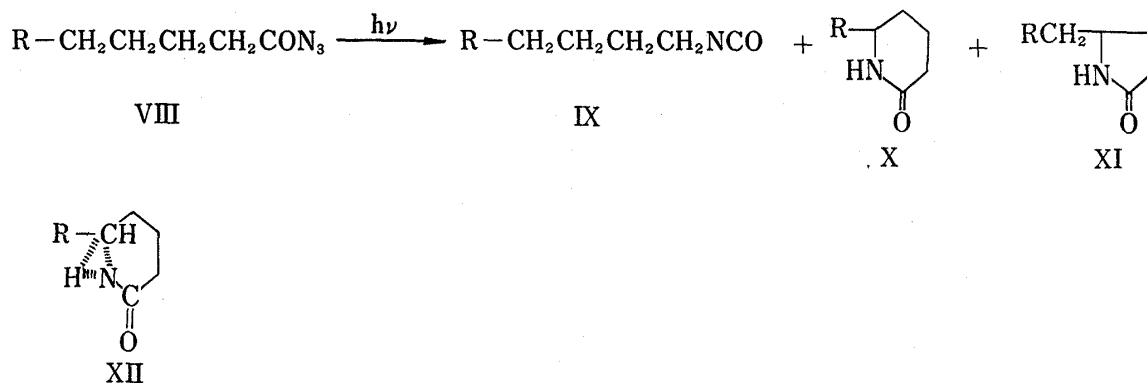


Chart 3

- 8) J.H. Hall, J.W. Hill, and J.M. Fargher, *J. Am. Chem. Soc.*, **90**, 5313 (1968).
- 9) J.G. Anastassiou, *J. Am. Chem. Soc.*, **88**, 2322 (1966); *idem, ibid.*, **89**, 3184 (1967).
- 10) G.T. Tissue, S. Linke, and W. Lwowski, *J. Am. Chem. Soc.*, **89**, 6303, 6308 (1967).
- 11) a) W. Antkowiak, J.W. ApSimon, and O.E. Edwards, *J. Org. Chem.*, **27**, 1930 (1962); b) W. Antkowiak, O.E. Edwards, and R. Howe, *Canad. J. Chem.*, **43**, 1275 (1965); c) S. Huneck, *Ber.*, **98**, 2305 (1965); d) J.W. ApSimon and O.E. Edwards, *Proc. Chem. Soc.*, **1961**, 461. *Idem, Canad. J. Chem.*, **40**, 896 (1962); e) A. Tahara, K. Hirao, and Y. Hamazaki, *Chem. Ind.*, **1965**, 850; f) W.L. Meyer and A.S. Levinson, *J. Org. Chem.*, **28**, 2859 (1963); g) R.F.C. Brown, *Austral. J. Chem.*, **17**, 47 (1964).
- 12) In ref. 11d, two possible mechanisms, *i.e.* a radical and an ionic one, were considered for the intramolecular insertion reaction. However, no definite conclusion could be reached. Subsequently, in ref. 13, δ -lactam formation *via* C-H bond insertion was assumed to be the reaction of a singlet state nitrene, without sufficient explanation.
- 13) I. Brown and O.E. Edwards, *Canad. J. Chem.*, **45**, 2599 (1967).

with almost 100% retention of configuration, if acyl azide having an optically active C-H bond at δ - or γ -position were used.

In order to clearly evaluate the spin state of VII in the intramolecular insertion reaction, photochemical decomposition of optically active acyl azide (XIV) carrying an optically active C-H bond at δ -position was examined. Optically active carboxylic acid (XIII), whose absolute configuration and optical purity are known, was chosen as substrate in the synthesis of XIV. δ -lactam (XV), an important and expected product of the photochemical reaction, was isolated from a reaction mixture and compared with an authentic sample prepared independently from α -alkyl- α -amino acid (XVI), whose absolute configuration and optical purity have been established. Based on obtained results, we undertook to evaluate the percent of retention for the configuration of XV prepared from XIV, and to elucidate the spin state of the acyl nitrene which might intervene in this intramolecular reaction.

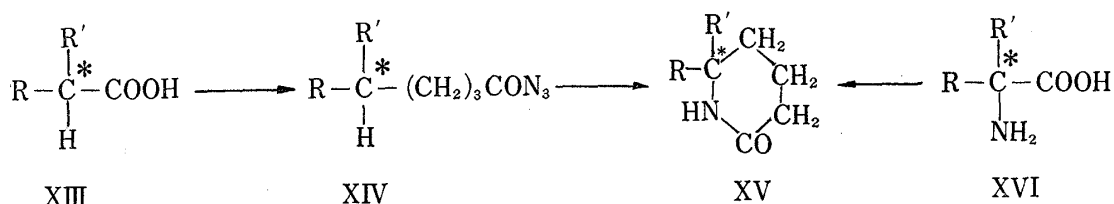


Chart 4

Results and Discussions

(*R*)-5-Methyl-6-phenylhexanoyl azide ((*R*)-XVII) was selected as substrate for the photochemical reaction, since this azide was an expected product of (*S*)(+)-2-methyl-3-phenylpropionic acid ((*S*)(+)-XVIII), whose absolute configuration and optical purity are known.¹⁴ Also, optically active 6-benzyl-6-methyl-2-piperidone (XIX), a product of the photochemical reaction, seemed to be easily obtainable from (*R*)(+)- α -methylphenylalanine ethyl ester ((*R*)(+)-XX),^{7,15} whose absolute configuration and optical purity are established.

First, preparation of optically active XIX from (*R*)(+)-XX was examined. Preliminary experiments on racemic compounds were studied in order to find the optimal working conditions. The chemical scheme used is shown in Chart 5.

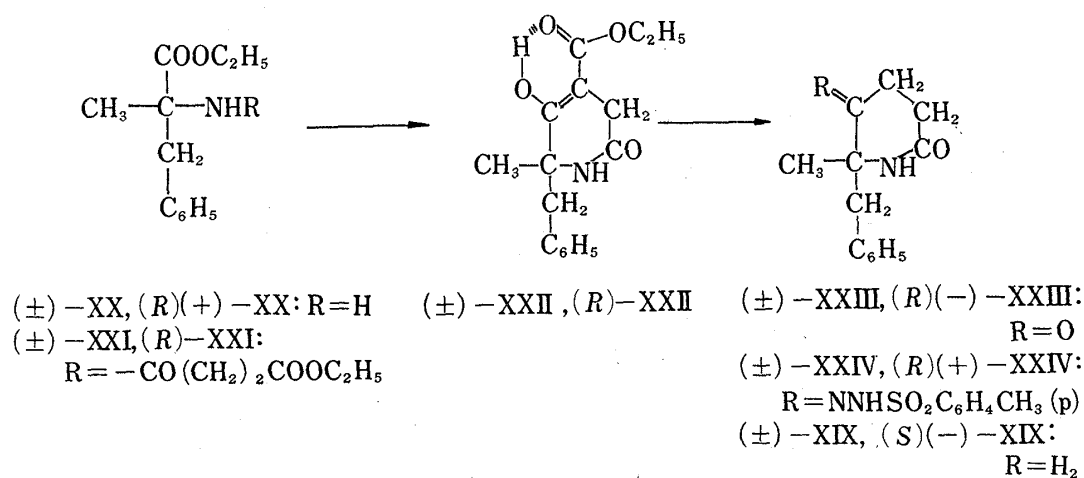


Chart 5

Acylation of (±)-XX^{7,15} with 3-ethoxycarbonylpropionyl chloride in the presence of triethylamine in chloroform solution gave (±)-ethyl 2-(3-ethoxycarbonyl)propionamido-2-

14) S. Yamada and S. Terashima, *Chem. Pharm. Bull.* (Tokyo), **16**, 1816 (1968).

15) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1138 (1966).

methyl-3-phenylpropionate ((±)-XXI) in a 96% yield. This was confirmed by spectral data and elemental analysis. The (±)-XXI obtained underwent Dieckmann condensation using sodium methoxide in benzene, affording (±)-6-benzyl-4-methoxycarbonyl-6-methyl-2,5-piperidinedione ((±)-XXII) in a 29% yield, based on (±)-XXI. Infrared (IR) spectra and the nuclear magnetic resonance (NMR) spectrum of this sample (IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1668 (hydrogen bonded COOCH_3 , $-\text{NHCO}-$), 1635 ($>\text{C}=\text{C}<$); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1665 (hydrogen bonded COOCH_3 , $-\text{NHCO}-$), 1635 ($>\text{C}=\text{C}<$); NMR (-2.22τ (1H, singlet, hydrogen bonded enol OH),¹⁶ 7.58τ (2H, quartet, $-\text{NHCOCH}_2-\text{C}=\text{C}-$)) clearly demonstrated that (±)-XXII existed exclusively in its enol form.¹⁶ The ester function of this compound was methyl, not ethyl ester, as clearly confirmed from the NMR spectrum and elemental analysis. Reflux of (±)-XXII with three equivalents of potassium hydroxide in aqueous 70% ethanol, followed by decarboxylation afforded (±)-6-benzyl-6-methyl-2,5-piperidinedione ((±)-XXIII) in a 42% yield. This was converted to (±)-*p*-toluenesulfonyl hydrazone ((±)-XXIV) in an 88% yield by treating it with *p*-toluenesulfonyl hydrazine in ethanol containing a catalytic amount of acetic acid.¹⁷ Reduction of (±)-XXIV with 10 equivalents of sodium borohydride in pyridine,¹⁸ followed by purification with silica gel column chromatography gave (±)-XIX, mp $96.5-98^\circ$, in a 31% yield. This (±)-XIX, was confirmed from its infrared spectrum, NMR spectrum, and by elemental analysis.

The same treatment of (R)(+)-XX^{7,19} ($\alpha_D^{25} +1.166^\circ$ ($l=0.1$, neat), optical purity 100%) as that of (±)-XX gave (R)(-)-XXIII, $[\alpha]_D^{25} -168^\circ$ (ethanol), in a 56% yield from (R)-XXII by way of (R)-XXI and (R)-XXII. The yield of (R)-XXI from (R)(+)-XX and that of (R)-XXII from (R)-XXI were 90 and 44%, respectively. (R)-XXI and (R)-XXII were identified with (±)-XXI and (±)-XXII using infrared spectra in chloroform solution. (R)(-)-XXIII was converted to (S)(-)-XIX, mp $89.5-90^\circ$, $[\alpha]_D^{18.5} -72.2^\circ$ (ethanol), by way of (R)(+)-XXIV, $[\alpha]_D^{25} +165^\circ$ (ethanol) in a manner similar to (±)-XIX from (±)-XXIII. The (S)(-)-XIX produced was confirmed from infrared spectrum, by gas chromatography, and by elemental analysis.

As cited above, (S)(-)-XIX, which was expected from the photochemical decomposition of (R)-XVII, was prepared. Then synthesis of (R)-XVII from (S)(+)-XVIII was undertaken.

Here too, preliminary examinations with racemic compounds were examined before optically active compounds were studied.

As shown in Chart 6, treatment of (±)-2-methyl-3-phenylpropanol^{7,14} ((±)-XXV) prepared from (±)-XVIII, with thionyl chloride and a catalytic amount of pyridine gave (±)-

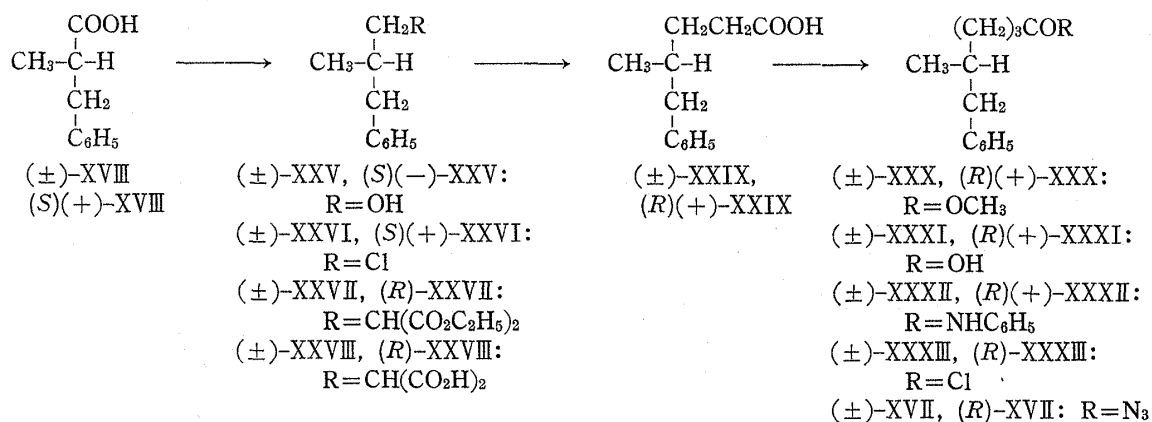


Chart 6

16) T. Shioiri, T. Takusagawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 467 (1969).

17) L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963).

18) cf. S. Yamada and T. Kunieda, *Chem. Pharm. Bull.* (Tokyo), **15**, 490 (1967).

19) According to the methods described in ref. 7, this ester was prepared from optically pure (R)(+)-N-acetyl- α -methylphenylalanine.

2-methyl-3-phenylpropylchloride ((\pm)-XXVI)^{20,21} in an 86% yield. This was condensed with a sodium salt of diethyl malonate to give (\pm)-diethyl 2-methyl-3-phenylpropylmalonate ((\pm)-XXVII) in a 67% yield, based on (\pm)-XXVI. Hydrolysis followed by decarboxylation yielded (\pm)-4-methyl-5-phenylvaleric acid ((\pm)-XXIX).²² The yield of (\pm)-XXIX from (\pm)-XXVII was 94%. DL-XXIX was submitted to Arndt-Eistert synthesis according to the usual procedure.²³ The diazoketone derivative was decomposed in methanol under silver oxide catalysis. (\pm)-Methyl 5-methyl-6-phenylhexanoate ((\pm)-XXX), prepared in a 64% yield from the acid chloride of (\pm)-XXIX, was hydrolyzed with 2 equivalents of potassium hydroxide in aqueous 70% methanol, affording (\pm)-5-methyl-6-phenylhexanoic acid ((\pm)-XXXI) in a 78% yield. This was confirmed by conversion to its anilide ((\pm)-XXXII).

The above (\pm)-XXXI was treated with three equivalents of thionyl chloride to give (\pm)-5-methyl-6-phenylhexanoyl chloride ((\pm)-XXXIII) in a 93% yield. A mixture of (\pm)-XXXIII and 10 equivalents of sodium azide in methylene dichloride solution was stirred vigorously at -15° – 0° . After 4 hrs' stirring, the reaction mixture was examined using its infrared spectrum and showed the complete disappearance of acid chloride at 1800 cm^{-1} and the existence of acyl azide ((\pm)-XVII) at $2140, 1718\text{ cm}^{-1}$. This methylene dichloride solution was immediately used for photochemical decomposition.²⁴

Next, synthesis of (*R*)-XVII from (*S*)(+)-XVIII,^{14,25} $\alpha_D^{19} + 2.686^{\circ}$ ($l=0.1$, neat) (optical purity 100%),^{14,26} prepared by resolution of (\pm)-XVIII according to the method of Schrecker,²⁵ was examined.

The same treatment of (*S*)(+)-XXVI, $\alpha_D^{18} + 2.996^{\circ}$ ($l=0.1$, neat), obtained from (*S*)(+)-XVIII by way of (*S*)(–)-XXV, $\alpha_D^{18} - 1.370^{\circ}$ ($l=0.1$, neat) as that of (\pm)-XXVI, afforded (*R*)(+)-XXIX, $[\alpha]_D^{19} + 18.3^{\circ}$ (chloroform) through (*R*)-XXVII and (*R*)-XXVIII. The yield of (*R*)-XXVII from (*S*)(+)-XXVI and that of (*R*)(+)-XXIX from (*R*)-XXVII were 61 and 82%, respectively. The (*R*)(+)-XXIX was treated the same as (\pm)-XXIX giving (*R*)(+)-XXX, $\alpha_D^{18} + 0.690^{\circ}$ ($l=0.1$, neat), in a 69% yield based on (*R*)(+)-XXIX. Hydrolysis of (*R*)(+)-XXX, similar to that of (\pm)-XXX, gave (*R*)(+)-XXXI, $\alpha_D^{18} + 0.578^{\circ}$ ($l=0.1$, neat) in a nearly quantitative yield. This was also identified as (*R*)(+)-anilide (*R*)(+)-XXXII, $[\alpha]_D^{20} + 15.3^{\circ}$ (chloroform). (*R*)(+)-XXXI was converted to (*R*)-XVII by way of (*R*)-XXXIII. Stirring of the mixture of (*R*)-XXXIII with 10 equivalents of sodium azide in methylene dichloride solution was continued for 6 hr.²⁷ The methylene dichloride solution of (*R*)-XVII was directly submitted to the photochemical reaction.

Preliminary examination of the photochemical reaction was also done using (\pm)-XVII. Methylene dichloride solution of (\pm)-XVII was irradiated, using a 30W low pressure mercury lamp²⁸ at 5 – 10° , in a nitrogen atmosphere. After 30 hrs' irradiation,²⁹ the solution was

20) G. Baddeley and R. Williamson, *J. Chem. Soc.*, **1956**, 4647.

21) K.B. Wiberg and T.W. Hutton, *J. Am. Chem. Soc.*, **78**, 1640 (1956).

22) W.J. Horton, C.E. Hummel, and H.W. Johnson, *J. Am. Chem. Soc.*, **75**, 944 (1953).

23) J.F. Lane and E.S. Wallis, *J. Org. Chem.*, **6**, 443 (1941).

24) Isolation and purification of (\pm)-XVII were not attempted.

25) A.W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957).

26) The maximum optical rotation of (*S*)(+)-XVIII as found in the literature was; ref. 25, $[\alpha]_D^{22} - 24.56^{\circ}$ ($l=1$, neat), $d_4^{22} 1.065$. When this optical rotation was assumed to be 100% optically pure, (*S*)(+)-XVIII showing $\alpha_D^{19} + 2.686^{\circ}$ ($l=0.1$, neat) was calculated as 103% optically pure (see also ref. 14 footnote 27).

27) After 4 hrs' stirring, measurement of the infrared spectrum of the reaction mixture clearly disclosed a small absorption near 1800 cm^{-1} . This was considered to be presence of unreacted acyl chloride. Therefore, stirring was continued for two more hours.

28) A 30W low pressure mercury lamp with quartz protection tube manufactured by Riko Kagaku Co. Ltd. was used.

29) When the photolyzed solution was evaporated under reduced pressure below 30° after 20 hrs' irradiation, the infrared spectrum of the residual oil clearly showed some remaining (\pm)-XVII. The irradiation time was considered to be related to the condition of the UV lamp.

evaporated *in vacuo* to give a brown turbid oil. After the absence of acyl azide ((±)-XVII) in this oil was confirmed, using its infrared spectrum, purification with column chromatography using silica gel was performed which gave three fractions. Distillation of the first fraction under reduced pressure gave nearly pure (±)-4-methyl-5-phenylpentyl isocyanate ((±)-XXXIV) in a 28% yield. The small amount of impurity involved in (±)-XXXIV was identified from its NMR spectrum as (±)-methyl 4-methyl-5-phenylpentyl carbamate ((±)-XXXV). This (±)-XXXIV was confirmed by its conversion to (±)-N-(4-methyl-5-phenyl)pentyl-N'-cyclohexyl urea ((±)-XXXVII), as usual. Distillation of the second fraction *in vacuo* gave nearly pure (±)-XXXV in *ca.* 22% yield. This was confirmed using its infrared and NMR spectra. The third fraction was further purified by silica gel, column chromatography. Each fraction eluted from the chromatogram was examined using its infrared

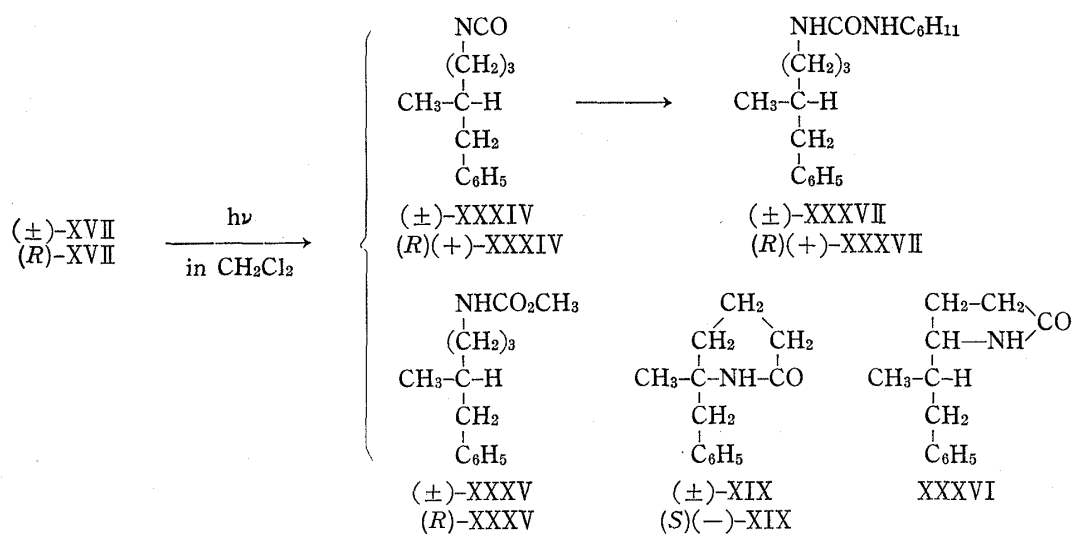


Chart 7

spectrum in a chloroform solution. This produced pure (±)-XIX in a 9.4% yield based on (±)-XXXIII, which was identified with the authentic sample prepared from (±)-XX using its infrared and NMR spectra, gas chromatography, and its mixed melting point measurement. A mixture of (±)-XIX and 5-(1-methyl-2-phenyl)ethyl-2-pyrrolidone (XXXVI)³⁰ contaminated with some impurities was also obtained in a fairly large amount, since their complete isolation was difficult with this chromatography. The structure of XXXVI³⁰ was deduced from the infrared spectrum of a mixture of (±)-XIX and XXXVI (IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1690, 1647), and from accumulated results of the photochemical decompositions of several acyl azides.^{4,5}

The same photochemical reaction was attempted on the methylene dichloride solution of (R)-XVII. In this case, irradiation was continued for 18.5 hr. A brown turbid oil, in which the absence of the azide function was confirmed *via* its infrared spectrum, was obtained. Similar treatment of this oil to that of (±)-XVII gave three fractions. (R)(+)-XXXIV, $[\alpha]_D^{20} +19.5^\circ$ (chloroform), identified as (R)(+)-XXXVII, $[\alpha]_D^{17} +16.3^\circ$ (chloroform), was obtained from the first fraction in a 23% yield, based on (R)-XXXIII. Identification, other than comparison of its infrared spectrum with that of the same fraction of the racemic compound, was not carried out with the second fraction. Further purification with column chromatography was made on the third fraction. Each fraction was examined using infrared spectra (in chloroform), gas chromatography, and thin-layer chromatography. They gave pure (-)-XIX, showing $[\alpha]_D^{17} -70.6^\circ$ (ethanol), in a 4.3% yield from (R)-XVII. Comparison of its

30) This XXXVI was considered a mixture of diastereoisomers, as this compound contained two asymmetric carbons. Precise examination was not undertaken because the formation of XXXVI had no importance in this report.

optical activity with that of the authentic sample, showed that (–)-XIX had (S)-configuration and was 98% optically pure. A mixture of (–)-XIX and XXXVI contaminated with a small amount of impurities was also obtained from this column chromatography.

In conclusion, the photochemical decompositions of (±)- and (R)-XVII in methylene dichloride afforded isocyanates ((±)-, and (R)(+)-XXXIV), δ-lactams ((±)-, and (S)(–)-XIX), γ-lactam (XXXVI), and moreover, carbamates ((±)-, and (R)-XXXV). These same results are found in many reports concerning photochemical decomposition of acyl azides.^{4,5,11} Formation of (±)- and (R)(+)-XXXIV is considered to be the result of a photo-induced Curtius rearrangement. It seems probable that (±)- and (R)-XXXV was formed due to the addition of methanol to (±)- and (R)(+)-XXXIV in the reaction medium. However, gas chromatographic analysis of the methylene dichloride used in the photochemical reaction clearly showed the absence of methanol in this solvent. Thus, the reason why such carbamates formed is still ambiguous.

Since (S)(–)-XIX was prepared in this photochemical reaction with 98% retention of its optical activity, this means that the acyl nitrene $\left(\text{VII: R} = \text{C}_6\text{H}_5\text{--CH}_2\text{--}\overset{\text{CH}_3}{\underset{\text{H}}{\text{C}}}\text{--}(\text{CH}_2)_3\text{--} \right)$ generated from (R)-XVII inserted at the intramolecular aliphatic C–H bond with 98% retention of configuration. As shown in Chart 8, two spin states, *i.e.* a singlet state (XXXVIII) and a triplet state (XXXIX) can be considered for VII similar to the case for II. However, since (S)(–)-XIX was obtained with almost 100% retention of configuration, it is evident that (S)(–)-XIX was exclusively formed from XXXVIII through a transition state (such as XL), since a fairly large amount of racemization is inevitable in the formation of (S)(–)-XIX from XXXIX, as was discussed in the intramolecular insertion reaction of II.⁷ Transition state (IL) seems to have the same nature as that considered for the insertion reaction of II at the intramolecular aliphatic C–H bond, and assumed by Lwowski⁵ and Edwards¹² to be XII.

Experimental³¹⁾

(±)-Ethyl 2-(3-Ethoxycarbonyl)propionamido-2-methyl-3-phenylpropionate ((±)-XXI)——A chloroform solution (50 ml) of 3-ethoxycarbonylpropionyl chloride (13.2 g, 0.0802 mole) was added to a mixture of (±)-XX (16.6 g, 0.0802 mole)^{7,15} and Et₃N (8.9 g, 0.088 mole) in chloroform (100 ml) under stirring and ice cooling. After stirring for 2 days, the pale yellow solution was successively washed with satd. NaHCO₃, H₂O, 10% AcOH, and H₂O, then dried over anhyd. Na₂SO₄. Filtration and evaporation *in vacuo* afforded crude (±)-XXI (25.7 g, 96%) as a yellow oil, which was immediately used for the Dieckmann condensation. The infrared spectrum of this oil was identical with that of the pure sample prepared below. Part of this oil was distilled under reduced pressure, followed by purification with silica gel column chromatography (solvent hexane:*i*-Pr₂O:CH₂Cl₂ = 1:1:1). Further distillation of the purified oil gave pure (±)-XXI as a viscous oil, bp 198–200° (0.25 mmHg). *Anal.* Calcd. for C₁₈H₂₅O₅N: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.71; H, 7.59; N, 4.45. IR $\nu_{\text{max}}^{\text{cap}}$ cm^{–1}: 3370, 1734, 1660, 1528, 1264. NMR (60 Mc, in CDCl₃, TMS as an internal standard): 8.77, 8.72 τ (6H, 2 triplets, $J = 7.2$ cps, 2 COOCH₂CH₃), 8.41 τ $\left(3\text{H, singlet, } \overset{\text{CH}_3}{\underset{|}{\text{C}}}\text{--} \right)$, 7.49 τ (4H, multiplet, –NH–CO–CH₂–CH₂–CO–), 6.67 τ (2H, quartet, $J = 23.2$ cps, C₆H₅–CH₂– $\overset{|}{\text{C}}\text{--}$), 5.90, 5.82 τ (4H, 2 quartets, $J = 7.2$ cps, 2 COOCH₂CH₃), 3.58 τ (1H, singlet, –NH–), 2.83 τ (5H, multiplet, C₆H₅–). (±)-6-Benzyl-4-methoxycarbonyl-6-methyl-2,5-piperidinedione ((±)-XXII)——A benzene solution (60 ml) of (±)-XXI (6.7 g, 0.020 mole) was added to a solution of sodium methoxide prepared from Na (0.7 g,

31) All melting and boiling points are uncorrected. IR spectra were measured using spectrometers; Models DS-402, DS-301, and IR-S, Japan Spectroscopic Co. Ltd., and Model EPI-510, Hitachi Co. Ltd. Measurements of NMR spectra were carried out with a spectrometer, Model 3H-60, Japan Electron Optics Lab. Optical activities were measured with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20. ORD curve measurements were performed with a spectrometer, Model ORD/UV-5, Japan Spectroscopic Co. Ltd. Gas chromatographic analyses were carried out with a Yanagimoto Gas Chromatograph, Model 550T.

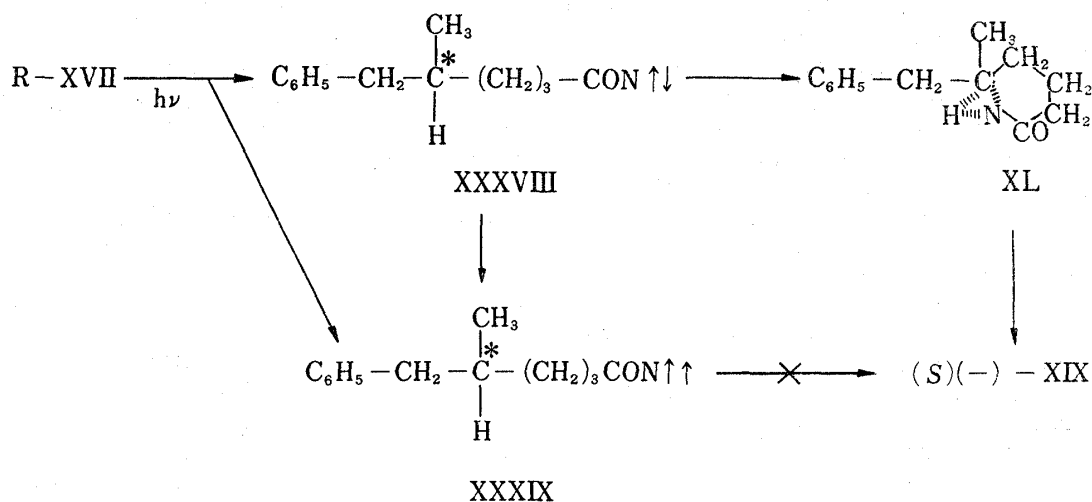


Chart 8

0.03 atom) and MeOH (12 ml) in benzene (60 ml). This was refluxed and stirred for 9 hr under a nitrogen stream. After cooling, H₂O (60 ml) was added to the reaction mixture to dissolve the precipitate. The aqueous layer was extracted. The organic layer was further extracted with H₂O (20 ml), after the addition of ether (20 ml). The combined aqueous layer was made acidic by adding conc. HCl. The oil which appeared was extracted with EtOAc. This EtOAc layer was washed successively with H₂O, satd. NaHCO₃, then with H₂O, and dried over anhyd. Na₂SO₄. Filtration and evaporation *in vacuo* gave a pale yellow solid, which was recrystallized from a mixture of CCl₄ (18 ml) and hexane (8 ml) to afford (±)-XXII (1.6 g, 29%) as pale yellow crystals, mp 156.5–159°. Several recrystallizations from the same solvent gave a pure sample as colorless prisms, mp 161.5–162.5°. *Anal.* Calcd. for C₁₅H₁₉O₄N: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.51; H, 6.25; N, 5.33. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3185, 3045, 1668, 1635, 1230. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3390, 1665, 1635.

NMR (60 Mc, in CDCl₃, TMS as an internal standard): 8.38 τ (3H, singlet, $-\overset{\text{CH}_3}{\underset{|}{\text{C}}}-$), 7.58 τ (2H, quartet, $J=21.0$ cps, $-\text{NH}-\text{CO}-\text{CH}_2-\overset{|}{\text{C}}-$), 7.00 τ (2H, quartet, $J=13.2$ cps, $\text{C}_6\text{H}_5-\text{CH}_2-\overset{|}{\text{C}}-$), 6.29 τ (3H, singlet, $-\text{COOCH}_3$), 2.85 τ (5H, singlet, C_6H_5-), 1.83 τ (1H, singlet, $-\text{NH}-$), -2.22τ (1H, singlet, hydrogen bonded enol OH).¹⁶ Two signals at 1.83 and -2.22τ disappeared after treatment with D₂O.

(±)-6-Benzyl-6-methyl-2,5-piperidinedione((±)-XXIII)—A mixture of (±)-XXII (0.97 g, 0.0035 mole) and KOH (0.56 g, 0.010 mole) in aqueous 70% EtOH (10 ml) was refluxed for 4 hr. After EtOH was distilled under reduced pressure, H₂O was added to the residual aqueous solution, which was then acidified (pH < 1) by the addition of 10% HCl. This was extracted with EtOAc. The combined EtOAc solution was washed with satd. NaCl, and dried over anhyd. Na₂SO₄. Filtration and evaporation produced an orange oil (0.76 g), which was purified using column chromatography (silica gel 50 g, solvent CHCl₃-AcOEt=1-1) giving crude (±)-XXIII (0.32 g, 42%) as a pale yellow solid, mp 145–146°. Several recrystallizations from CCl₄-hexane afforded pure (±)-XXIII as colorless needles, mp 146.5°. *Anal.* Calcd. for C₁₃H₁₅O₂N: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.69; H, 6.87; N, 6.51. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3210, 3090, 1730, 1680, 1616, 754, 704. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3405, 1732, 1670.

NMR (60 Mc, in CDCl₃, TMS as an internal standard): 8.51 τ (3H, singlet, $-\overset{\text{CH}_3}{\underset{|}{\text{C}}}-$), 8.50–7.25 τ (4H, multiplet, $-\text{COCH}_2\text{CH}_2\text{CO}-$), 6.97 τ (2H, quartet, $J=13.2$ cps, $\text{C}_6\text{H}_5-\text{CH}_2-$), 2.80 τ (5H, singlet, C_6H_5-), 2.30 τ (1H, singlet, $-\text{NH}-$). A signal at 2.30 τ disappeared after treatment with D₂O.

(R)(-)-6-Benzyl-6-methyl-2,5-piperidinedione(R)(-)-XXIII—The same treatment of (R)(+)-XX (bp 113–115° (6.5 mmHg), $\alpha_D^{25} +1.166^\circ$ ($l=0.1$, neat), 100% optically pure) (lit.,⁷) bp 119–122° (7 mmHg), $\alpha_D^{25} +1.182^\circ$ ($l=0.1$, neat)) (12.8 g, 0.0618 mole) as in the case of (±)-XX afforded crude (R)-XXI as a pale yellow oil (18.7 g, 90%), whose infrared spectrum in a film was identical with that of (±)-XXI. This (R)-XXI was submitted to Dieckmann condensation in a manner similar to (±)-XXI. It gave crude (R)-XXII as a brown caramel (6.8 g, 44%) after evaporation of the EtOAc extracts. Crude (R)-XXII was hydrolyzed with aqueous 70% EtOH solution (70 ml) of KOH (4.2 g, 0.072 mole), as described for (±)-XXII, to give a yellow solid (4.5 g). This was purified with column chromatography (silica gel 100 g, solvent CHCl₃:AcOEt=1:1), affording crude (R)(-)-XXIII (3.0 g, 56% based on (R)-XXII), mp 143.5–146.5°. Recrystallization from a mixture of CCl₄ (ca. 20 ml) and hexane (10 ml) gave (R)(-)-XXIII (2.2 g, 41%) as pale yellow prisms, mp 145.5–146.5°, $[\alpha]_D^{25} -168^\circ$ ($c=1.240$, EtOH). Two more crystallizations from CCl₄ afforded a pure sample as colorless prisms, mp 145.5–147.5°, $[\alpha]_D^{25} -169^\circ$ ($c=0.706$, EtOH). *Anal.* Calcd. for C₁₃H₁₅O₂N: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.61; H, 7.07; N, 6.83. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3220, 1727,

1673, 753, 735, 700. This infrared spectrum was different from that of (\pm)-XXIII. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3405, 1734, 1670. This infrared spectrum was identical with that of (\pm)-XXIII.

(\pm)-6-Benzyl-6-methyl-2,5-piperidinedione *p*-Toluenesulfonylhydrazone ((\pm)-XXIV)—An ethanolic solution (20 ml) of (\pm)-XXIII (1.0 g, 0.0046 mole) and *p*-toluenesulfonylhydrazine (0.85 g, 0.0046 mole) was refluxed for 3 hr with a catalytic amount of AcOH (5 drops).¹⁷ The reaction mixture was condensed to ca. 6 ml in a water bath. H₂O (10 ml) was added under ice cooling, affording a pale yellow oil. This oil was triturated, and was kept in an ice bath for 30 min after the addition of H₂O (5 ml). Filtration and drying *in vacuo* gave (\pm)-XXIV (1.11 g) as a white solid, showing a mp 163.5–166.5° (decomp.). More (\pm)-XXIV (0.48 g), mp 173.5–176.5° (decomp.), was obtained from the filtrate after it was kept overnight at room temperature. Total yield of (\pm)-XXIV was 88%. The two lots of (\pm)-XXIV were mixed, and recrystallized from a mixture of EtOH (10 ml) and H₂O (2 ml) producing (\pm)-XXIV (1.09 g, 60%) as nearly colorless prisms, mp 178–180° (decomp.). Three recrystallizations from EtOH gave a pure sample as colorless prisms, mp 178–178.5° (decomp.). Anal. Calcd. for C₂₀H₂₃O₃N₃·1/2 H₂O: C, 60.90; H, 6.14; N, 10.66. Found: C, 60.96; H, 6.24; N, 10.89. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3385, 1648, 1349, 1163.

(*R*)(+)-6-Benzyl-6-methyl-2,5-piperidinedione *p*-Toluenesulfonylhydrazone ((*R*)(+)-XXIV)—The same treatment of (*R*)(–)-XXIII (mp 145.5–146.5°, $[\alpha]_D^{25}$ –168° (c =1.240, EtOH)) (1.8 g, 0.0083 mole) as that of (\pm)-XXIII gave a pale yellow caramel after evaporation of the reaction mixture *in vacuo*. H₂O (20 ml) was added to the caramel, which was triturated to give crude (*R*)(+)-XXIV (3.3 g, quantitative yield) as a white powder, mp 128–132° (decomp.). Recrystallization from EtOH (18 ml) and H₂O (24 ml) afforded (*R*)(+)-XXIV as colorless plates (2.0 g, 62%), mp 128.5–132.5° (decomp.), $[\alpha]_D^{25}$ +175° (c =0.833, EtOH). Further recrystallization from the same solvent afforded pure (*R*)(+)-XXIV as colorless plates, mp 124–128.5° (decomp.), $[\alpha]_D^{25}$ +165° (c =0.573, EtOH). Anal. Calcd. for C₂₀H₂₃O₃N₃·1/3 H₂O: C, 61.34; H, 5.93; N, 10.95. Found: C, 61.33; H, 6.14; N, 10.95. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3360, 1660, 1348, 1165. This infrared spectrum was different from that of (\pm)-XXIV.

(\pm)-6-Benzyl-6-methyl-2-piperidone ((\pm)-XIX)—A mixture of (\pm)-XXIV (0.92 g, 0.0024 mole) and NaBH₄ (1.0 g, 0.026 mole) in pyridine (20 ml)¹⁸ was refluxed for 10 hr, then evaporated to dryness *in vacuo* giving an orange oil, to which was carefully added 10% HCl (20 ml). Heating of the acidic solution in a water bath was continued until gas evolution ceased. After cooling, the solution was extracted with CHCl₃. Its combined chloroform layers were successively washed with satd. NaHCO₃, and satd. NaCl, then dried over anhyd. Na₂SO₄. Filtration and evaporation *in vacuo* gave an orange oil (0.37 g), which was purified using column chromatography (silica gel 30 g, solvent AcOEt), affording (\pm)-XIX (0.15 g, 31%) as a pale yellow oil. This oil solidified after stimulation, and showed a mp of 90.5–94.5°. Three recrystallizations from hexane gave pure (\pm)-XIX as colorless prisms, mp 96.5–98°. Anal. Calcd. for C₁₃H₁₇ON: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.88; H, 8.36; N, 6.64. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3330, 3250, 1667,

755, 703. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3385, 1646. NMR (60 Mc, in CDCl₃, TMS as an internal standard): 8.81 τ (3H,

singlet, $\text{C}(\text{CH}_3)_2$), 8.26 τ (4H, multiplet, $-\text{C}-\text{CH}_2-\text{CH}_2-$), 7.73 τ (2H, multiplet, $-\text{CH}_2-\text{CO}-$), 7.22 τ (2H, singlet, C₆H₅–CH₂–), 3.60 τ (1H, singlet, $-\text{NH}-$), 2.78 τ (5H, singlet, C₆H₅–). A signal at 2.78 τ disappeared after treatment with D₂O. Gas chromatographic analysis of this sample showed a single peak whose retention time was 9.2 min (30% SE-30 on Diasolid L, 2.25 m, 222°). Thin-layer chromatography (silica gel, solvent AcOEt) exhibited a single spot whose *R_f* value was 0.35.

(*S*)(–)-6-Benzyl-6-methyl-2-piperidone (*S*)(–)-XIX)—The same treatment of (*R*)(+)-XXIV (mp 128.5–132.5° (decomp.), $[\alpha]_D^{25}$ +175° (c =0.833, EtOH)) (1.7 g, 0.0044 mole) as that of (+)-XXIV, followed by purification using column chromatography (silica gel 40 g, solvent AcOEt), gave (*S*)(–)-XIX (0.30 g, 33%) as a pale yellow oil. This solidified when kept at room temperature and showed a mp of 49–63°,³² $[\alpha]_D^{25}$ –70.5° (c =0.682, EtOH). Several recrystallizations from petr. ether gave pure (*S*)(–)-XIX as colorless needles, mp 89.5–90°,³² $[\alpha]_D^{18.5}$ –72.2° (c =0.544, EtOH). Anal. Calcd. for C₁₃H₁₇ON: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.62; H, 8.19; N, 6.96. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3240, 3190, 1664, 820, 757, 702. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3380, 1645. Infrared spectrum of (*S*)(–)-XIX was identical with that of (\pm)-XIX in chloroform solution, but differed from that of (\pm)-XIX in a solid state. Gas chromatographic analysis of this sample showed a single peak whose retention time (8.9 min) was identical with that of (\pm)-XIX (30% SE-30 on Diasolid L, 2.25 m, 222°). This (*S*)(–)-XIX was also identified with (\pm)-XIX using thin-layer chromatography.

32) The infrared spectrum of this sample was identical with that of the analytical sample in a chloroform solution, but differed from the spectrum in a solid state. Two recrystallizations from petr. ether gave a sample with a mp of 63.5–66°. No change of its infrared spectrum in a solid state was observed. However, after three recrystallizations from the same solvent, the melting point of this sample rose to a mp of 88.5–90.5°. The infrared spectrum in the solid state became identical with that of the analytical sample. It seems probable that (*S*)(–)-XIX produced dimorphism.

ORD $[\alpha]_D^{21.5}$ ($c=0.544$, EtOH) ($m\mu$): -105° (700), -146° (589), -238° (500), -388° (400), -598° (350), -1046° (300), -2760° (250), -7300° (222, negative max.), -6200° (212).

(\pm)- and (S)(+)-2-Methyl-3-phenylpropionic Acid ((\pm)- and (S)(+)-XVIII)—In this case, (\pm)-XVIII was prepared from diethyl malonate by way of diethyl benzylmalonate (bp 158—162 (9 mmHg), 47%) (lit.,³³) bp 145—155° (5 mmHg), diethyl benzylmethylmalonate (bp 143—145° (5 mmHg), 99%) (lit.,³⁴) bp 127—133° (1.5 mmHg), and benzylmethylmalonic acid (mp 131—134°, 86%) (lit.,³⁴) mp 138—139.5°. Yield of (\pm)-XVIII from benzylmethylmalonic acid was 97%. This acid showed bp 145.5° (9 mmHg) (lit.,¹⁴) bp 137—137.5° (5.5 mmHg), lit.,³⁴) 118—122° (1 mmHg). DL-XVIII thus obtained was resolved according to the method of Schrecker²⁵) using (–)- α -phenethylamine (bp 68—70° (13 mmHg), α_D^{20} -3.953° ($l=0.1$, neat)) to give (S)(+)-XVIII, bp 142—144° (5 mmHg), α_D^{19} $+2.686^\circ$ ($l=0.1$, neat), $[\alpha]_D^{18}$ $+31.5^\circ$ ($c=5.810$, benzene), and $[\alpha]_D^{20}$ $+29.3^\circ$ ($c=5.346$, CHCl₃) (lit.,²⁵) bp 111° (0.22 mmHg), $[\alpha]_D^{22}$ -24.56° ($l=1$, neat), lit.,¹⁴) bp 146° (8.5 mmHg), α_D^{21} $+1.939^\circ$ ($l=0.1$, neat), $[\alpha]_D^{21}$ $+22.2^\circ$ ($c=4.946$, benzene)). This acid was assumed to be 100% optically pure.²⁰)

(\pm)- and (S)(–)-2-Methyl-3-phenylpropanol ((\pm)- and (S)(–)-XXV)—Reduction of (\pm)- and (S)(+)-XVIII with LiAlH₄ in ether, as described previously,⁷) gave (\pm)-XXV, bp 113° (10 mmHg) in a 90% yield (lit.,⁷) bp 111.5—113.5° (9 mmHg), and (S)(–)-XXV, bp 96—96.5° (7 mmHg), α_D^{18} -1.370° ($l=0.1$, neat), in a 91% yield (lit.,⁷) bp 110.5—111.5° (9 mmHg), α_D^{23} -0.964° ($l=0.1$, neat)), respectively. Both (\pm)- and (S)(–)-XXV were confirmed with authentic samples using infrared spectra.

(\pm)-2-Methyl-3-phenylpropyl Chloride ((\pm)-XXVI)—SOCl₂ (45.0 g, 0.378 mole) was added to a mixture of (\pm)-XXV (38.0 g, 0.253 mole) and pyridine (15 ml) over 30 min under stirring and ice cooling. Then, the whole was stirred at 70° for 3.5 hr. Excess SOCl₂ was distilled under reduced pressure, and the residue was extracted with ether. The ether layer was washed with 10% Na₂CO₃, and satd. NaCl, then dried over anhyd. Na₂SO₄. Filtration and evaporation, followed by fractional distillation, gave (\pm)-XXVI (36.7 g, 86%) as a colorless oil, bp 91.5—93° (8.5—9 mmHg) (lit.,²⁰) bp 101° (11 mmHg). IR ν_{\max}^{cap} cm⁻¹: 1605, 1498, 1454, 742, 700, 682.

(S)(+)-2-Methylpropylchloride ((S)(+)-XXVI)—Similar treatment of (S)(–)-XXV (bp 96—96.5° (7 mmHg), α_D^{18} -1.370° ($l=0.1$, neat)) (10.5 g, 0.0690 mole) to that of (\pm)-XXV afforded (S)(+)-XXVI (10.4 g, 90%), bp 85—86.5° (4 mmHg), α_D^{18} $+2.996^\circ$ ($l=0.1$, neat) (lit.,²¹) bp 109—110° (17 mmHg), $[\alpha]_D^{27}$ -23.79° ($l=1$, neat)). The infrared spectrum of this sample was identical with that of (\pm)-XXVI in the same state.

(\pm)-4-Methyl-5-phenylvaleric Acid ((\pm)-XXIX)—Diethyl malonate (37.2 g, 0.234 mole) was added to an ethanolic solution (240 ml) of NaOEt prepared with Na (4.2 g, 0.18 atom) and EtOH (240 ml). This was kept at room temperature for 45 min. The EtOH was then evaporated *in vacuo*. Addition of benzene (60 ml) and evaporation *in vacuo* was repeated three times producing a white solid, which was dissolved in dimethyl formamide (200 ml). (\pm)-XXVI (30.0 g, 0.179 mole) in dimethyl formamide (15 ml) was added to this dimethyl formamide solution. The whole was refluxed for 8.5 hr. After evaporation of dimethyl formamide *in vacuo* H₂O was added. The aqueous solution was neutralized by the addition of 10% HCl, then extracted with ether. The combined ether layers were successively washed with 10% HCl, satd. NaCl, 10% Na₂CO₃, and satd. NaCl, then dried over anhyd. Na₂SO₄. Filtration and evaporation gave an oil, which when submitted to distillation under reduced pressure gave (\pm)-XXVII (34.8 g, 67%) as a colorless oil, bp 161—162° (4 mmHg). IR ν_{\max}^{cap} cm⁻¹: 1740. A mixture of this (\pm)-XXVII and KOH (20.2 g, 0.360 mole) in aqueous methanol (MeOH (125 ml) and H₂O (50 ml)) was refluxed for 3 hr. The MeOH was distilled *in vacuo* over a water bath. After adding H₂O (100 ml), the whole was extracted with ether. The aqueous layer was acidified using conc. HCl, then extracted with ether. The ether layer was washed with satd. NaCl, and dried over anhyd. Na₂SO₄. Filtration and evaporation gave (\pm)-XXVIII (26.0 g) as a white solid, mp 108—110.5° (lit.,²²) 112.5—113.5°. IR ν_{\max}^{KBr} cm⁻¹: 1751, 1726. After being kept at 180—190° under reduced pressure (20 mmHg) for 15 min in a distillation flask, the whole was submitted to fractional distillation and gave (\pm)-XXIX (20.0 g, 94% from (+)-XXVII), bp 161° (5 mmHg), which solidified as colorless prisms, mp 44° (lit.,²²) mp 44—45.5°. IR ν_{\max}^{KBr} cm⁻¹: 1715, 744, 700. IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 1708.

(R)(+)-4-Methyl-5-phenylvaleric Acid ((R)(+)-XXIX)—The same treatment of (S)(+)-XXVI (bp 85—86.5° (4 mmHg), α_D^{18} $+2.996^\circ$ ($l=0.1$, neat)) (9.9 g, 0.059 mole) as that of (\pm)-XXVI gave (R)-XXVII as a colorless oil (10.6 g, 61%), bp 175—183° (7 mmHg). Hydrolysis and decarboxylation of (R)-XXVII in a manner similar to that for (\pm)-XXVII afforded (R)(+)-XXIX as a colorless oil (5.7 g, 82% based on (R)-XXVII), bp 167—169° (6 mmHg). This solidified when kept standing, mp 52—55.5°, $[\alpha]_D^{18}$ $+14.0^\circ$ ($c=2.394$, CHCl₃). Two recrystallizations from petr. ether gave pure (R)(+)-XXIX as colorless prisms, mp 55—56°, $[\alpha]_D^{19}$ $+18.3^\circ$ ($c=1.334$, CHCl₃). Anal. Calcd. for C₁₂H₁₆O₂: C, 74.97; H, 8.39. Found: C, 75.02; H, 8.26. IR ν_{\max}^{KBr} cm⁻¹: 1710, 744, 698. IR $\nu_{\max}^{\text{CHCl}_3}$ cm⁻¹: 1712. These infrared spectra were identical, respectively, with those of the authentic (\pm)-XXIX in the same states.

33) C.S. Marvel, *Org. Syn.*, Coll. Vol., 3, 705.

34) D.F. Detar and C. Weis, *J. Am. Chem. Soc.*, 79, 3045 (1957).

(±)-5-Methyl-6-phenylhexanoic Acid ((±)-XXXI)—A mixture of (±)-XXIX (15.0 g, 0.0780 mole) and SOCl_2 (27.8 g, 0.234 mole) was refluxed for 2 hr on an oil bath, and evaporated *in vacuo* under a nitrogen stream which gave an orange oil. This was submitted to fractional distillation and produced (±)-4-methyl-5-phenylvaleryl chloride (15.4 g, 94%) as a colorless oil, bp 110.5–113° (4 mmHg). An ether solution (50 ml) of the acid chloride was added to an ether solution (300 ml) of diazomethane, prepared from nitroso-methylurea (24.1 g, 0.234 mole) as usual, under stirring and ice cooling. Stirring was continued overnight at room temperature. The small amount of precipitate which appeared was filtered off. The ether solution was evaporated at room temperature under a nitrogen atmosphere giving a reddish brown oil. This was identified as the diazoketone by its infrared spectrum, IR $\nu_{\text{max}}^{\text{cap}}$ cm^{-1} : 2060, 1635. A catalytic amount of silver oxide was added to a methanol solution (100 ml) of this reddish brown oil, and the whole was stirred overnight at room temperature. Filtration and evaporation gave a red oil (14.9 g), which was purified with column chromatography (silica gel 150 g, solvent petr. ether: CHCl_3 = 1:1) giving a pale yellow oil (12.6 g). Fractional distillation of this oil gave (±)-XXX (11.1 g, 64% based on the acid chloride) as a colorless oil, bp 126–129° (3 mmHg). IR $\nu_{\text{max}}^{\text{cap}}$ cm^{-1} : 1740, 1196, 1165, 740, 700. Gas chromatographic analysis (30% SE-30 on Diasolid L, 2.25 m, 222°) of the (±)-XXX showed the presence of some impurities, whose retention times were 3.9 min and 4.7 min, respectively, as well as the large main peak with a retention time of 5.2 min.

A mixture of (±)-XXX (10.1 g, 0.046 mole) and KOH (5.6 g, 0.10 mole) in aqueous 70% MeOH (50 ml) was refluxed for 2 hr, and concentrated to *ca.* one third its original volume. H_2O (50 ml) was added, and the whole was extracted with ether. The aqueous layer was acidified by adding conc. HCl, and extracted with ether (50 ml \times 2). Ether extracts were washed with satd. NaCl, and dried over anhyd. Na_2SO_4 . Filtration and evaporation gave an oil, which was submitted to fractional distillation giving (±)-XXXI (7.4 g, 78%) as a colorless oil, bp 165–166° (6 mmHg). IR $\nu_{\text{max}}^{\text{cap}}$ cm^{-1} : 1706, 736, 700. The (±)-XXXI thus prepared was confirmed by conversion to its anilide ((±)-XXXII), mp 74–75.5°, colorless crystals (recrystallized from hexane–ether). Anal. Calcd. for $\text{C}_{19}\text{H}_{23}\text{ON}$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.74; H, 8.08; N, 5.09. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3245, 1670, 1603, 1531, 743. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3435, 3365, 1688, 1605, 1508.

NMR (60 Mc, in CDCl_3 , TMS as an internal standard): 9.14 τ (3H, doublet, $J=6$ cps, $\text{C}_6\text{H}_5\text{-CH}_2\text{-}\overset{\text{CH}_3}{\underset{|}{\text{CH}}}$), 8.0–9.0 τ (5H, multiplet, $\text{-}\overset{\text{CH}_3}{\underset{|}{\text{CH}}}\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO-}$), 7.4–8.0 τ (4H, multiplet, $\text{C}_6\text{H}_5\text{CH}_2\text{-}\overset{\text{CH}_3}{\underset{|}{\text{CH}}}\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CO-}$), 2.86 τ (10H, multiplet, $2\text{C}_6\text{H}_5$), 2.26 τ (1H, singlet, -CONH-). A signal at 2.26 τ disappeared after treatment with D_2O .

(R)(+)-5-Methyl-6-phenylhexanoic Acid ((R)(+)-XXXI)—(R)(+)-XXIX (mp 52.5–55.5°, $[\alpha]_D^{18} +14.0^\circ$ ($c=2.394$, CHCl_3)) (5.2 g, 0.027 mole) was treated in a manner similar to that of (±)-XXIX giving (R)(+)-XXX (4.1 g, 69% based on (R)(+)-XXIX) as a colorless oil, bp 137–143° (10 mmHg), $\alpha_D^{18} +0.690^\circ$ ($l=0.1$, neat). IR $\nu_{\text{max}}^{\text{cap}}$ cm^{-1} : 1744, 1196, 1167, 735, 698. After evaporation of excess SOCl_2 , the addition and evaporation of benzene (20 ml) was repeated twice producing the acid chloride as a pale yellow oil. This was treated with an ether solution of diazomethane, as described for the racemic compound.

The same treatment of the (R)(+)-XXX (3.5 g, 0.016 mole) prepared above as that of (±)-XXX gave (R)(+)-XXXI (3.3 g, quantitative yield) as a pale yellow oil, bp 158–160.5° (2 mmHg), $\alpha_D^{18} +0.578^\circ$ ($l=0.1$, neat), $[\alpha]_D^{18} +13.1^\circ$ ($c=5.596$, CHCl_3). IR $\nu_{\text{max}}^{\text{cap}}$ cm^{-1} : 1709, 732, 698. This infrared spectrum was identical with that of (±)-XXXI in the same state. (R)(+)-XXXI was also confirmed by its conversion to (R)(+)-anilide ((R)(+)-XXXII), colorless needles (recrystallized from *i*-Pr₂O), mp 91–92°, $[\alpha]_D^{20} +15.3^\circ$ ($c=0.666$, CHCl_3). Anal. Calcd. for $\text{C}_{19}\text{H}_{23}\text{ON}$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.27; H, 8.38; N, 5.19. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3340, 1664, 1601, 1532, 742. This infrared spectrum was different from that of (±)-XXXII in the solid state. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3430, 3360, 1687, 1604, 1506. This spectrum was identical with that of (±)-XXXII in the same state.

(±)-5-Methyl-6-phenylhexanoyl Azide ((±)-XVII)—A mixture of (±)-XXXI (5.4 g, 0.026 mole) and SOCl_2 (9.4 g, 0.079 mole) was refluxed for 2 hr, then evaporated under a nitrogen stream to give an oil, which was submitted to distillation *in vacuo* affording (±)-XXXIII (5.5 g, 93%) as a colorless oil, bp 131.5–137° (7–7.5 mmHg). IR $\nu_{\text{max}}^{\text{cap}}$ cm^{-1} : 1797. A mixture of (±)-XXXIII (2.0 g, 0.0089 mole) and NaN_3 (5.8 g, 0.089 mole) in methylene dichloride³⁵⁾ (50 ml) was stirred vigorously for 4 hr at -15° – 0° in an ice salt bath. Measurement of its infrared spectrum was preformed with methylene dichloride solution obtained by filtering the heterogeneous solution. IR $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ cm^{-1} : 2280 (very weak), 2140, 1718. This clear solution of acyl azide ((±)-XVII) showed no absorption near 1800 cm^{-1} and was immediately used for the following photochemical reaction.

(R)-5-Methyl-6-phenylhexanoyl Azide ((R)-XVII)—The same treatment of (R)(+)-XXXI (bp 158–160.5° (2 mmHg), $\alpha_D^{18} +0.578^\circ$ ($l=0.1$, neat)) (2.5 g, 0.012 mole) as that of (±)-XXXI gave (R)-XXXIII (2.3 g, 85%) as a colorless oil, bp 132–135.5°, IR $\nu_{\text{max}}^{\text{cap}}$ cm^{-1} : 1799. This infrared spectrum was identical with that of (±)-XXXIII in the same state. Similar treatment of (R)-XXXIII (2.3 g, 0.010 mole) to that of (±)-XXXIII afforded a methylene dichloride solution of (R)-XVII. Stirring at -15° – 0° was continued for 6 hr.²⁷⁾ The infrared spectrum of this solution showed no absorption near 1800 cm^{-1} , and was identical

with that of the racemic compound. IR $\nu_{\max}^{\text{CH}_2\text{Cl}_2}$ cm^{-1} : 2275 (very weak), 2140, 1716. This solution was used directly for photochemical decomposition.

Photochemical Decomposition of (\pm)-5-Methyl-6-phenylhexanoyl Azide ((\pm)-XVII)—The methylene dichloride solution of DL-XVII prepared above was added to methylene dichloride³⁵ (700 ml) cooled at *ca.* 5° and substituted with N₂. The whole was irradiated internally using a 30 W low pressure mercury lamp²⁸ for 30 hr²⁹ at 5–10°. Evaporation below 30° under a nitrogen stream gave a brown turbid oil (2.0 g), which showed no absorption near 2120 cm^{-1} based on measurement of its infrared spectrum in capillary. Purification of this oil with column chromatography (silica gel 50 g, solvent CH₂Cl₂) followed by evaporation of methylene dichloride gave three fractions; a brown oil (0.74 g) containing (\pm)-XXXIV (Fraction A), a brown oil (0.45 g) containing (\pm)-XXXV (Fraction B), and a brown oil (0.49 g) containing a mixture of (\pm)-XIX and XXXVI (Fraction C).

Fraction A: This brown oil was submitted to fractional distillation under a nitrogen stream giving crude (\pm)-XXXIV (0.51 g, 28% based on DL-XXXIII), as a pale yellow oil, bp 129–131° (8 mmHg). IR ν_{\max}^{cap} cm^{-1} : 2280, 735, 698. NMR (60 Mc, in CCl₄, TMS as an internal standard): 9.14 τ (3H, doublet, $J=6.0$ cps,

$\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}- \end{array}$), 8.0–9.0 τ (5H, multiplet, $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NCO} \end{array}$), 7.18–7.85 τ ($\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}_6\text{H}_5-\text{CH}_2-\text{CH}- \end{array}$), 6.80 τ (2H, triplet, $J=6.0$ cps, $-\text{CH}_2\text{CH}_2-\text{NCO}$), 6.40 τ (very small signal, COOCH_3 of (\pm)-XXXV), 2.82 τ (5H, multiplet, C_6H_5). (\pm)-XXXIV was confirmed by its conversion to (\pm)-XXXVII *via* treatment with cyclohexylamine. (\pm)-XXXVII, obtained as colorless needles from recrystallization with *i*-Pr₂O, showed a mp of 99.5–101.5°. *Anal.* Calcd. for C₁₉H₃₀ON₂: C, 75.45; H, 10.00; N, 9.26. Found: C, 75.66; H, 9.84; N, 9.13. IR ν_{\max}^{KBr} cm^{-1} : 3360, 1617, 1572. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3430, 1666, 1524.

Fraction B: This oil was also submitted to distillation under reduced pressure. A colorless oil, which was distilled up to 126° (0.035 mmHg) (bath temperature 163–171°), was collected. The yield of (\pm)-XXXV was 22% based on (\pm)-XXXIII at the stage before distillation. *Anal.* Calcd. for C₁₄H₂₁O₂N: C, 71.45; H, 9.00; N, 5.95. Found: C, 70.66; H, 8.84; N, 6.20. IR ν_{\max}^{cap} cm^{-1} : 3365, 1712, 1530, 1268, 776, 735, 697.

NMR (60 Mc, in CDCl₃, TMS as an internal standard): 9.16 τ (3H, doublet, $J=6.0$ cps, $\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}_6\text{H}_5-\text{CH}_2-\text{CH}- \end{array}$), 8.0–9.0 τ (5H, multiplet, $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}- \end{array}$), 7.2–8.0 τ ($\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}_6\text{H}_5-\text{CH}_2-\text{CH}- \end{array}$), 6.65–7.2 τ (2H, multiplet, $-\text{CH}_2-\text{CH}_2-\text{NH}-$), 6.40 τ (3H, singlet, COOCH_3), 5.20 τ (1H, singlet, $-\text{NH}-$), 2.86 τ (5H, singlet, C_6H_5).

Fraction C: This fraction was further purified with column chromatography (silica gel 80 g, solvent AcOEt). Each fraction eluted from the column was examined by its infrared spectrum in CHCl₃ solution. This showed two fractions, one of which contained a mixture of (\pm)-XIX and XXXVI (0.12 g) as a pale yellow oil. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3430, 3390, 1690, 1647. This mixture showed four peaks as the results of gas chromatographic analysis (30% SE-30 on Deasolid L, 2.25 m, 222°), whose retention times were 5.8, 6.3, 8.9 and 12.5 min. The peak with the retention time of 8.9 min was identified with authentic (\pm)-XIX. From another fraction, pure (\pm)-XIX (0.17 g, 9.4% based on (\pm)-XXXIII) was obtained as a pale yellow oil, which solidified and showed a mp of 92.5–95.5°. This (\pm)-XIX showed no depression (mp 91.5–95°) on measuring the mixed melting point with authentic (\pm)-XIX (mp 96.5–98°). IR ν_{\max}^{KBr} cm^{-1} : 3320, 3250, 1666, 755, 702. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 3390, 1642. These infrared spectra were identical with those of the authentic sample in the same states. The NMR spectrum of this sample was also identical with that of the authentic one. Gas chromatographic analysis (30% SE-30 on Diasolid L, 2.25 m, 222°) showed a single peak whose retention time (9.4 min), was identical with that of authentic (\pm)-XIX. This sample was further identified with the authentic one by thin-layer chromatography (silica gel, solvent AcOEt). Three recrystallizations from hexane produced an analytical sample as colorless prisms, mp 96.5–97.5°. *Anal.* Calcd. for C₁₃H₁₇ON: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.58; H, 8.25; N, 6.88. This sample was further confirmed by its infrared spectra and by measurement of its mixed melting point.

Photochemical Decomposition of (*R*)-5-Methyl-6-phenylhexanoyl Azide ((*R*)-XVII)—Irradiation, with a 30 W low pressure mercury lamp²⁸ on the methylene dichloride solution of (*R*)-XVII prepared above similar to that of the solution of (\pm)-XVII, was continued at 5–10° for 18.5 hr.²⁹ Evaporation below 30° under a nitrogen stream gave a brown turbid oil (2.3 g). This showed no absorption near 2120 cm^{-1} based on measurement of its infrared spectrum in a film. This oil was purified *via* column chromatography in a manner similar to that for the racemic compound, giving three fractions; a brown oil (0.74 g) involving (*R*)(+)-XXXIV (Fraction A), a brown oil (0.9 g) containing (*R*)-XXXV (Fraction B), and a yellow oil (0.56 g) containing a mixture of (*S*)(–)-XIX and XXXVI (Fraction C).

Fraction A: This brown oil was submitted to fractional distillation in a nitrogen atmosphere and gave

35) Gas chromatographic analysis (30% SE-30 on Diasolid L, 2.25 m, 52°) of this solvent showed a complete absence of methanol.

(*R*)(+)-XXXIV (0.48 g, 23% based on (*R*)-XXXIII) as a pale yellow oil, bp 121–123° (2 mmHg), $[\alpha]_D^{20} +19.5^\circ$ ($c=2.492$, CHCl_3). IR $\nu_{\text{max}}^{\text{vap}}$ cm^{-1} : 2265, 735, 698. This infrared spectrum was identical with that of (\pm)-XXXIV in the same state. The (*R*)(+)-XXXIV was converted to (*R*)(+)-XXXVII *via* treatment with cyclohexylamine, as was the racemic compound. (*R*)(+)-XXXVII showed mp 81.5–83° (colorless needles recrystallized from *i*-Pr₂O), $[\alpha]_D^{17} +16.3^\circ$ ($c=0.184$, CHCl_3).³⁶ Anal. Calcd. for C₁₉H₃₀ON₂: C, 75.45; H, 10.00; N, 9.26. Found: C, 75.22; H, 9.87; N, 9.18. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3365, 1622, 1578. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3440, 1666, 1534. These infrared spectra were identical with those of DL-XXXVII in the same states. ORD $[\text{M}]^{17}$ ($c=0.184$, CHCl_3) ($m\mu$): +32.9° (700), +49.3° (589), +72.1° (500), +118° (400), +243° (350), +289° (300), +471° (272).

Fraction B: No identification, other than the comparison of its infrared spectrum in capillary with that of the same fraction from the racemic compound, was done.

Fraction C: This fraction was further purified by column chromatography (silica gel 80 g, solvent AcOEt). Fractions eluted from the column were examined using infrared spectra (in chloroform solution), gas chromatography (30% SE-30 on Diasolid L, 2.25 m, 222°), and thin-layer chromatography (silica gel, solvent AcOEt), giving three fractions. These were a crude mixture of (*S*)(–)-XIX and XXXVI (0.15 g), in which the presence of (*S*)(–)-XIX was confirmed using gas chromatography, (*S*)(–)-XIX contaminated with a small amount of impurities (0.04 g), and pure (*S*)(–)-XIX (0.09 g, 4.3% based on (*R*)-XXXIII). The infrared spectrum of the first fraction is as follows; IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420, 3385, 1688 (shoulder), 1643. The last fraction solidified on stimulation and showed a mp of 84.5–87.5°. No depression (mp 85.5–89.5°) was observed on measurement of mixed melting point with authentic (*S*)(–)-XIX (mp 89.5–90.5°). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3240, 3195, 1666, 1601, 820, 757, 704. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3385, 1646. These spectra were superimposable on those of authentic (*S*)(–)-XIX. Gas chromatographic analysis (30% SE-30 on Diasolid L, 2.25 m, 222°) showed a single peak whose retention time was identical with that of authentic (*S*)(–)-XIX (retention time, 10.2 min). This sample showed a single spot (*R*_f value 0.40) on thin-layer chromatography (silica gel, solvent AcOEt), whose *R*_f value was also identical with that of the authentic sample. $[\alpha]_D^{17} -70.6^\circ$ ($c=0.572$, EtOH). ORD $[\text{M}]^{19.5}$ ($c=0.572$, EtOH) ($m\mu$): –103° (700), –142° (589), –209° (500), –376° (400), –573° (350), –995° (300), –2660° (250), –6780° (223, negative max.), –6570° (217). Optical purity was calculated as 98% based on the assumption that (*S*)(–)-XIX, showing $[\alpha]_D^{18.5} -72.2^\circ$ ($c=0.544$, EtOH), is optically pure. The percent of retention of configuration in this photochemical reaction was 98%. Two recrystallizations from petr. ether gave pure (*S*)(–)-XIX as colorless needles, mp 89.5–90.5°. The mixed melting point with the authentic (*S*)(–)-XIX (mp 89.5–90.5°) was mp 89.5–91°. Anal. Calcd. for C₁₃H₁₇ON: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.66; H, 8.18; N, 6.78. This sample showed the same infrared spectra as those of the authentic (*S*)(–)-XIX in the solid state and in a chloroform solution. $[\alpha]_D^{21.5} -76^\circ$ ($c=0.108$, EtOH).³⁶ ORD $[\text{M}]^{21.5}$ ($c=0.108$, EtOH) ($m\mu$): –113° (700), –154° (589), –225° (500), –398° (400), –621° (350), –995° (300), –2680° (250), –7610° (223).

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36) This optical activity was calculated from the ORD Chart.