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SYNTHESIS OF ISOMER-FREE BENZYL METHYL ACETOACETIC METHYL ESTER

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No Drawing. Substituted for abandoned application Serial No. 410,575, September 12, 1941. This application June 3, 1943, Serial No. 489,500

4 Claims. (Cl. 260—476)

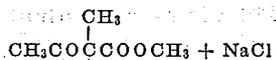
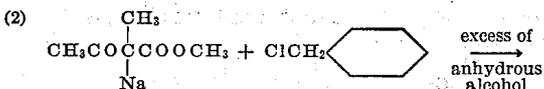
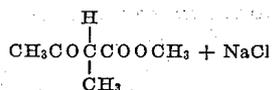
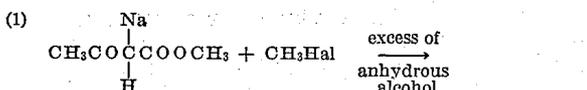
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This invention relates to improvements in the synthesis of isomer-free benzyl methyl acetoacetic methyl ester which is especially suited for use in the preparation of alpha-phenyl-beta-amino propane. This application is a substitute for our application Serial No. 410,575 filed September 12, 1941.

Hitherto, commercial synthesis of this amine involved several steps but with low yields and high material costs. The low yields are due, at least in part, to undesirable side reactions. In the prior art synthesis a multiplicity of reactions has been required to secure the desired product.

It has now been found that the prior art difficulties above enumerated may be essentially avoided by the controlled preparation of a suitable isomer-free intermediate derived from the acetoacetic ester. These conditions involve as a prerequisite the initial formation of a methyl derivative by reacting the ester with a methyl halide, such as the chloride. The methyl residue is joined to the active carbon so that subsequent benzylation can result only in the introduction of the benzyl group in the proper place, and without the formation of isomers which is the characteristic of this reaction when benzylation is first carried out followed by methylation.

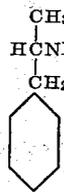
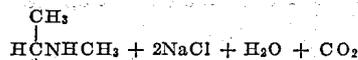
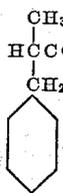
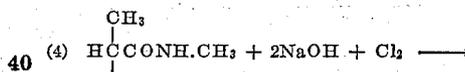
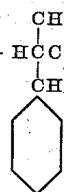
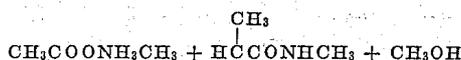
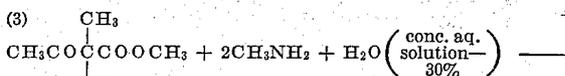
The novel procedures of the present invention will permit the securing of a desired product alpha-phenyl-beta-amino propane by reacting the sodium derivative of acetoacetic ester first with methyl halide such as methyl chloride and then reacting the sodium salt of the methyl derivative with benzyl chloride according to the following equations:



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that when the benzyl group is introduced into the acetoacetic ester molecule as a first step, the active hydrogen on the CH₂ group of the benzyl residue is substituted by the methyl group in the next step. In this manner an isomer of alpha-phenyl-beta-amino propane is arrived at. By reversing this procedure according to the present disclosure, and introducing the methyl group first, this methyl group must go on the active carbon of the acetoacetic ester. As a result, when the benzyl group is subsequently introduced into the molecule, there is but one substitution possible, and the correct derivative must be formed. The importance of the correct sequence of steps at this point in the general synthesis procedure is obvious, as the fundamental reactions and their general sequence is standard practice.

By a logical extension of the herein disclosed reaction, the methyl derivative of alpha-phenyl-beta-amino propane could be formed.



The use of a Hofmann reaction to specifically form alpha-phenyl-beta-amino propane by following the described procedure involving preliminary methylation of acetoacetic acid methyl ester, followed by benzylation of the methylated acetoacetic ester results directly in the formation of the desired product without contamina-

Thus the correct acetoacetic ester derivative must be obtained, and from this product alpha-phenyl-beta-amino propane can be secured. It is found