US.Pat. 2,413,493

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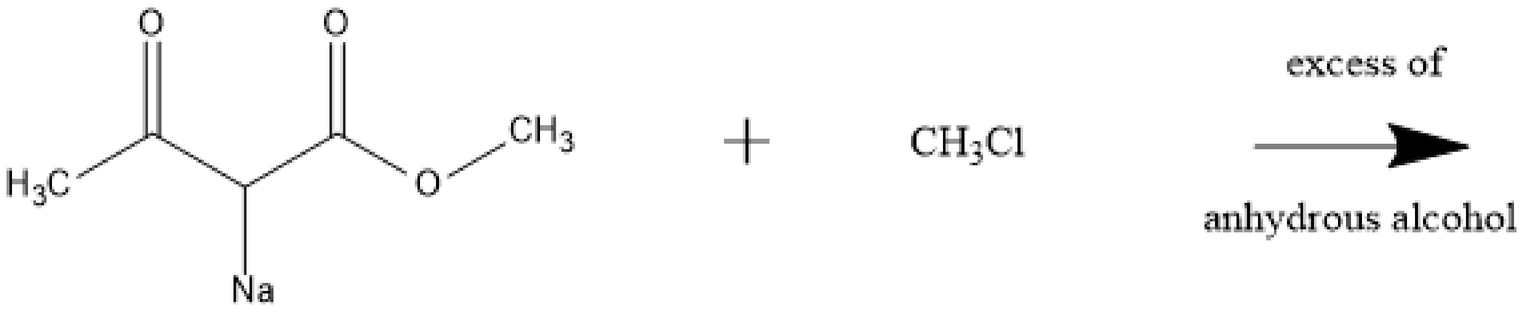
Patented Dec. 31, 1946

Synthesis of Isomer-Free Benzyl Methyl AcetoAcetic Methyl Ester

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(Amphetamine) ! 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 requred to secure the desired product. It has now been found that 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 derivate by reacting the ester with a methyl halide, such as the chloride. The methyl residue is joined to the active carbon so that subsquent benzylation can result only in the introduction of the benzyl group in proper place, and without the formation of isomers which is the characteristic of this reaction when benzylation first is carried out followed by methylation. The novel procedures will permit the securing of the desired product alpha-phenyl-beta-amino propane by reacting the sodium derivative of AcetoAcetic Ester first with methyl halide such as the methyl chloride and then reacting the sodium salt of the methyl derivative with benzyl chloride.

According to The following Chemical Equations

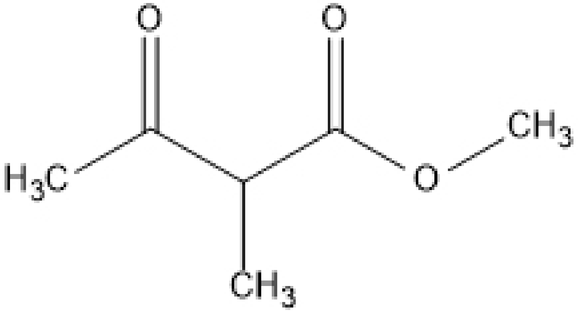


(1-methoxy-1,3-dioxobutan-2-yl)sodium

Methyl Acetoacetate Sodium

chloromethane

MethylChloride



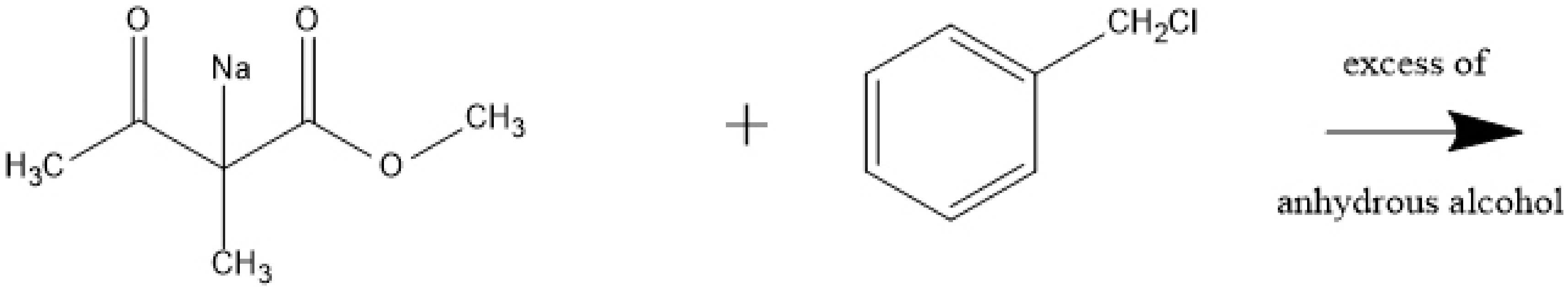
methyl 2-methyl-3-oxobutanoate

Methyl Methyl Acetoacetate

+

NaCl

Sodium Chloride

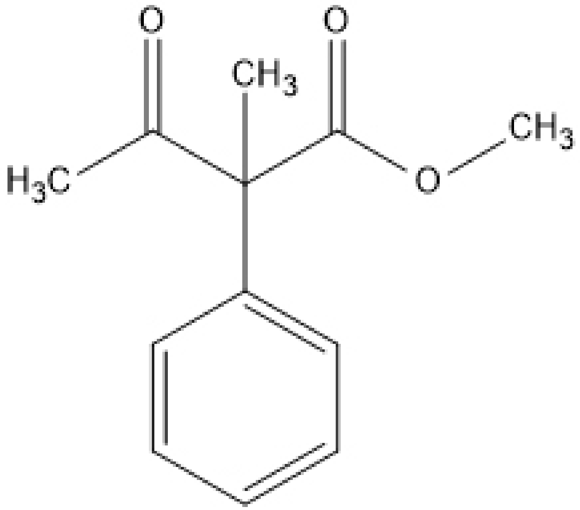


(1-methoxy-2-methyl-1,3-dioxobutan-2-yl)sodium

Methyl Methyl Acetoacetate Sodium

(chloromethyl)benzene

BenzylChloride



methyl 2-methyl-3-oxo-2-phenylbutanoate

Methyl Benzyl Methyl Acetoacetate

+

NaCl

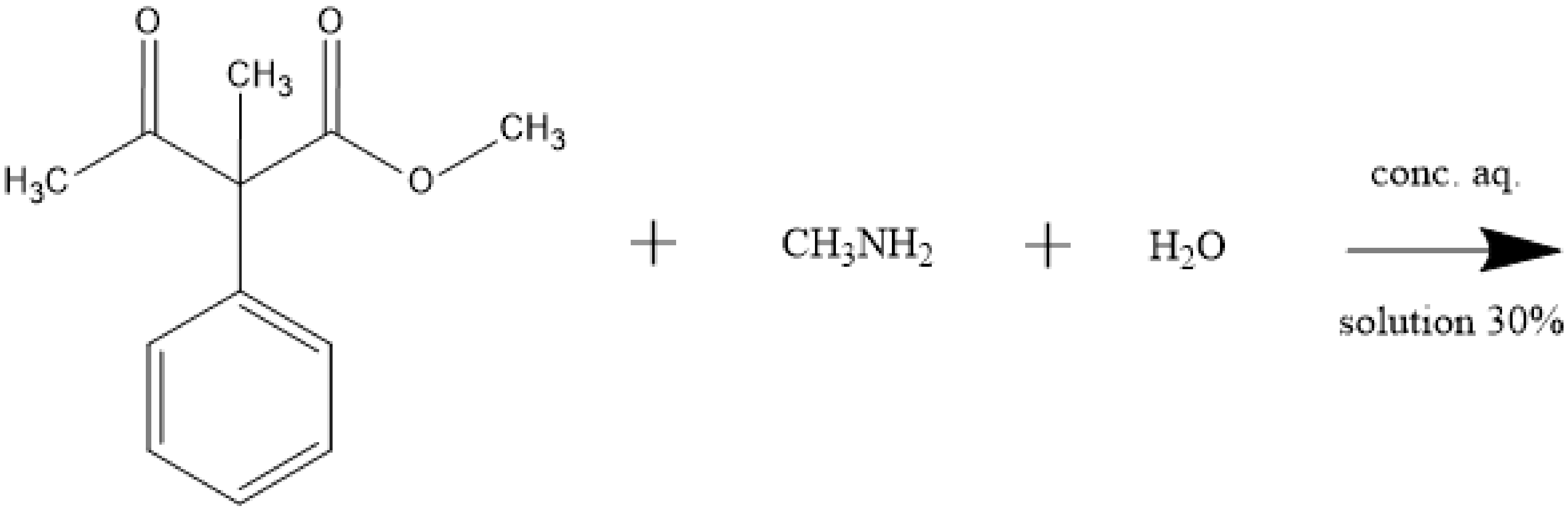
Sodium Chloride

Thus the correct acetoacetic ester derivative must be obtained, and from this product
alpha-phenyl-beta-amino-propane(Amphetamine)
can be secured.

It is found 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(Amphetamine) 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 sustitution 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(MethAmphetamine) derivative of alpha-phenyl-beta-amino propane(Amphetamine) could be formed.

According to The following Chemical Equations



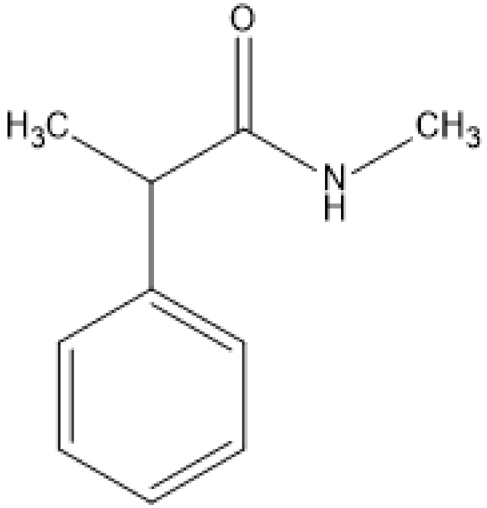
methyl 2-methyl-3-oxo-2-phenylbutanoate

Methyl Benzyl Methyl Acetoacetate

methanamine

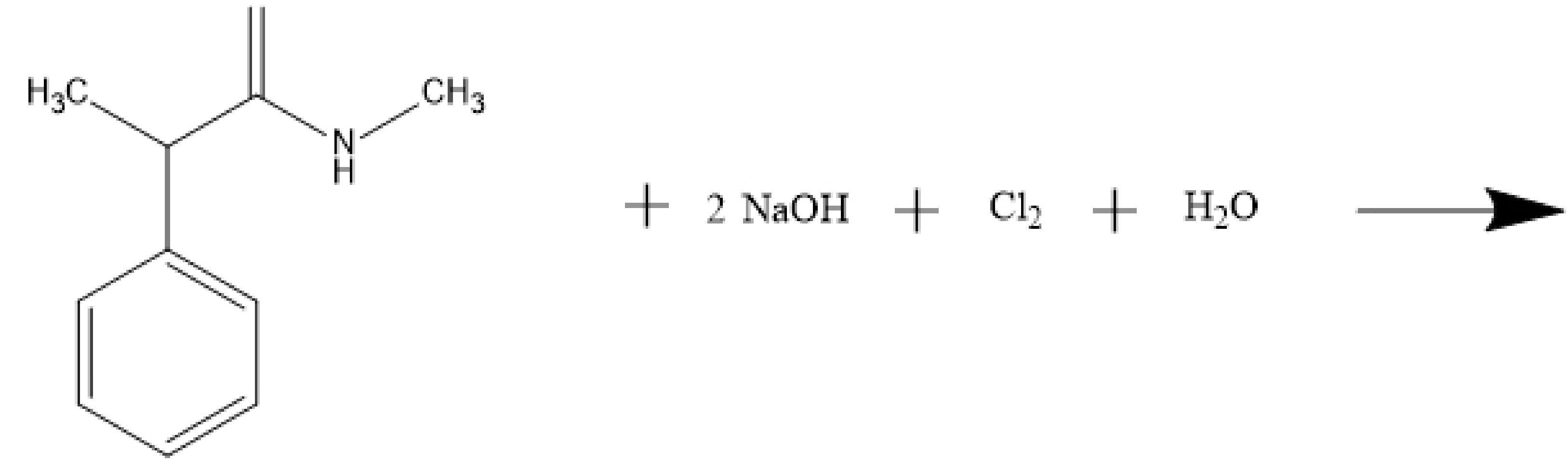
Methyl Amine

Water



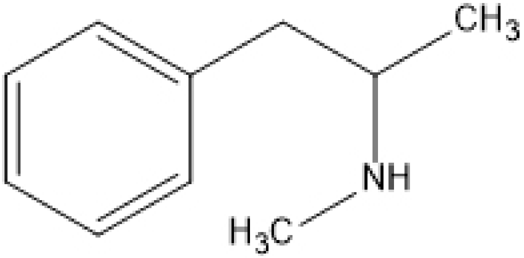
N-methyl-2-phenylpropanamide

$+$ $CH_3COONH_3CH_3$ $+$ CH_3OH



N-methyl-2-phenylpropanamide

Sodium HypoChlorite Solution

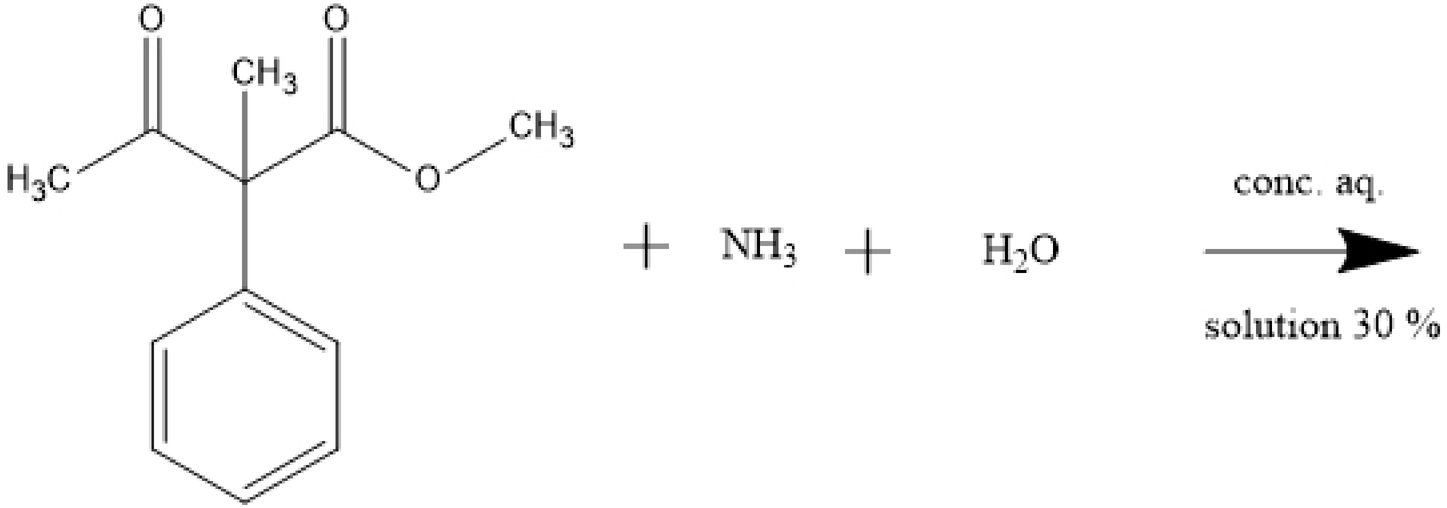


N-methyl-1-phenylpropan-2-amine

MethAmphetamine

$+ 2\ \mathrm{NaCl} + \mathrm{H_2O} + \mathrm{CO_2}$

Alpha-Phenyl-Beta-Amino Propane(Amphetamine) According to The following Chemical Equations

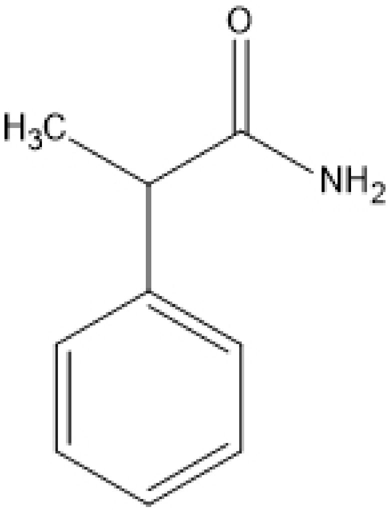


methyl 2-methyl-3-oxo-2-phenylbutanoate

Methyl Benzyl Acetoacetate

Ammonia

Water



2-phenylpropanamide

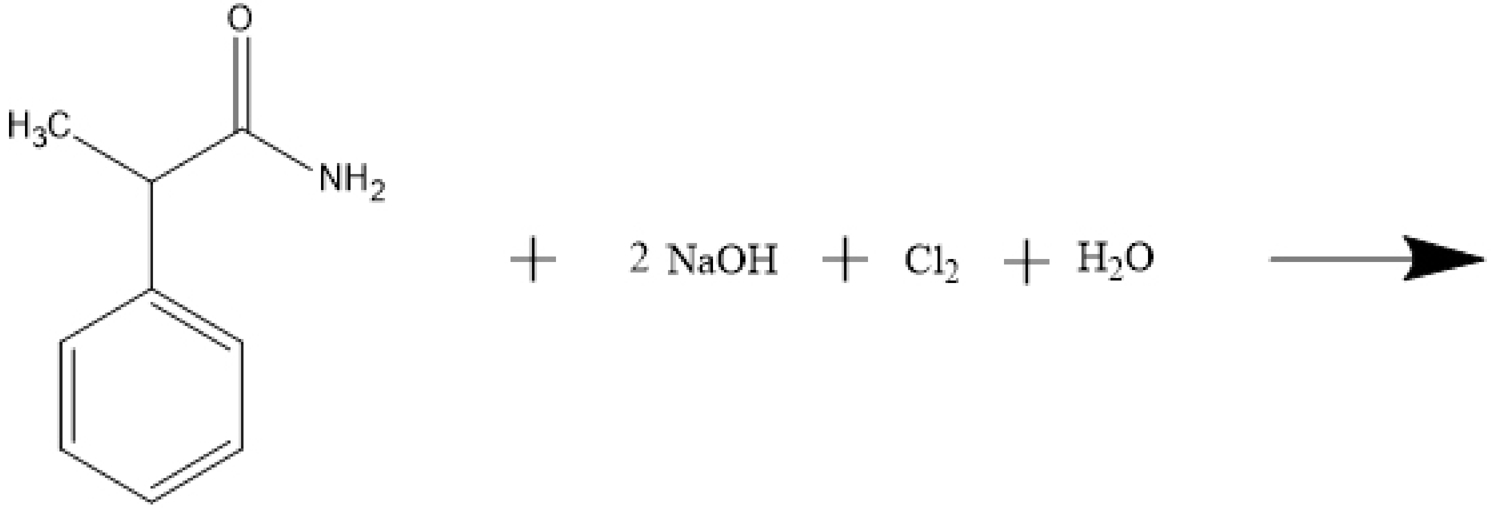
Hydratropamide

Methyl Benzyl Acetamide

+ CH_3OH

Methanol

+ $CH_3COONH_3CH_3$



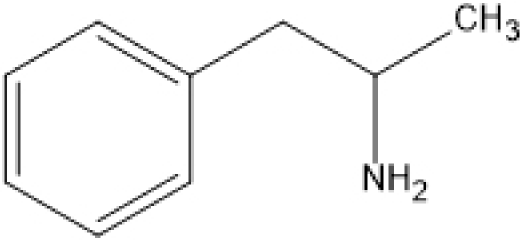
$+\ 2\ NaOH + Cl_2 + H_2O \longrightarrow$

2-phenylpropanamide

Hydratropamide

Methyl Benzyl Acetamide

Sodium Hypoclorite Solution



$+ \ 2\,NaCl + H_2O + CO_2$

1-phenylpropan-2-amine

Alpha-Phenyl-Beta-Amino Propane

Amphetamine

The use of a Hofmann reaction to specifically form alpha-phenyl-beta-amino propane(Amphetamine) by following the described procedure involving preliminary methylation of acetoacetic acid methyl ester, followed by benzylation of the methylated aceotoacetic ester results in the formation of the desired product without contamination with isomers. This step permits the use of cheaper raw materials with an accompanying advantage that the yields are higher. Briefly, the new process involves the methylation of acetoacetic acid methyl ester, and the substitution with benzyl compounds in the methyl acetoacetic acid methyl ester formed, to form benzyl methyl acetoacetic methyl ester.

This benzyl ester is then contacted with aqueous amonia for several days, with the results that a good yield of benzyl methyl acetamide is obtained. This acetamide is then converted by means of the Hofmann reaction to form alpha-phenyl-beta-amino propane(Amphetamine).

Experimental

Preparation
Of
Methyl Methyl Aceto Acetate

4440 grams of Methyl Acetate, containing 2 % Methyl alcohol, was weighted into a 12-liter flask provided with a reflux condenser. 230 grams of sodium metal, in the form of small pieces (aproximately 1/2” x 1/2”), was added to the Methyl Acetate at once. Heat was applied to bring the reaction mixture to refluxing temperature. After eleven hours all of the sodium dissolved. Excess Methyl Acetate was distilled from the reaction mixture until all of the constant boiling mixture with methanol distilled off. 5000 cc. of benzol was then added and distillation continued until the last of the Methyl Acetate was recovered.1200 grams of dimethyl sulphate was then added over a period of two hours at refluxing temperature. Refluxing was continued until reaction was neutral. The reaction mixture was then cooled to room temperature, and 1400 cc. of water added to the sodium methyl sulphate. The oil layer was separated, washed with two 1000 cc. portions of water and then fractionated. A yield of 882 grams of Methyl Methyl Aceto Acetate was obtained. B.P. 76,0-76,5 C at 20 mm. 1700 grams of Methyl Acetate was recovered as constant boiling mixture, balance was recovered with benzol.

Preparation
Of
Methyl Benzyl Methyl Aceto Acetate

750 grams of Methyl Methyl Aceto Acetate, and 1690 cc. of methanol were placed in a 3-liter 3-neck flask provided with a reflux. 125 grams of sodium metal was added, a liquid temperature of 50 C. being maintained. The solution of the sodium compound was then added to 657 grams of benzyl chloride contained in a 5-liter flask. Two hours where requred for the addition, and the temperature was held between 48-53 C. throughout. After several hours standing, allowing reaction to reach room temperature, a test portion indicated that the reaction was 99,5 % complete. Excess alcohol was then distilled off until a liquid temperature of 83 C. was reached. The reaction product was then cooled to 20 C., and 1400 cc. of water was added to dissolve out salt. The oil was shaken with 10 % caustic for 10 minutes and then washed with 500 cc. portions of water until neutral. The oil was then fractionated. 165 grams of benzyl chloride was recovered. A yield of 855 grams of Methyl Benzyl Methyl Aceto Acetate was obtained.

Preparation
Of
Methyl Benzyl Acetamide

100 grams of Methyl Benzyl Methyl Aceto Acetate is added to 400 cc. of 28-29 % aqueous NH4OH and allowed to stand for 7 days. A yield of 50 grams of Methyl Benzyl Acetamide was obtained.

Preparation Of Alpha-Phenyl-Beta-Amino Propane(Amphetamine)

230 grams of Methyl Benzyl Acetamide, and melting between 107-108,4 C., was added to sodium hypochlorite solution, made by Passing 109 grams of chlorine into a solution of 277 grams of sodium hydroxide in 453 cc. of water. The reaction mixture was held at 0 C. for one hour. It was then slowly heated to 18 C., at which point considerable heat was given off and the solid went into solution. The flask, at this stage, had to be immersed in a freezing bath to prevent the temperature from getting too high. After the temperature was under control, the solution was heated to 58 C. whereupon the rearrangement occurred. The heating was continued until 70 C. was reached. The solution was cooled, the oil layer separated and the solution extracted with benzene, using 60 cc. each time. The benzol solution was washed twice with 50 cc. portions of water and 148 grams of concentrated hydrochlric acid slowly added to it. The amine-hydrochloric acid solution was extracted twice with 30 cc. portions of benzol. The amine was then precipitated with sodium hydroxide solution (30 %). The water from the precipitated amine was extracted three times with 60 cc. portions of benzol. The benzol solution was washed twice with 100 cc. washes and then vacuum distilled. Yield: 131 grams of purified amine, B.P. 105 C./30 mm., 69,0 % of theory.

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The Suburb Gråbo to the only Town Visby In Gotland an Island In the Baltic Sea belonging to Sweden