

tion 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 ammonia 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. This amine can also be synthesized by forming benzyl methyl acetoacetic ethyl ester and then cleaving this product with sodium methylate solution to form methyl acetate and benzyl methyl acetic acid methyl ester. The methyl acetate is separated as a constant boiling mixture, after distilling off with the excess methanol. The benzyl methyl acetic acid methyl ester is hydrolyzed with sodium hydroxide solution to form a sodium salt of benzyl methyl acetic acid. The free acid is liberated, then dried and converted to its chloride by means of thionyl chloride. The chloride is converted to benzyl methyl acetamide by reaction with anhydrous ammonia in ether as a solvent. The amide is then converted to alpha-phenyl-beta-amino propane by means of the Hofmann reaction above described.

In the preparation of the alpha-phenyl-beta-amino propane, the following detailed steps were taken and a detailed preparation of the several intermediates identified in the equations hereinabove set out are given.

Methyl methyl aceto acetate

4440 grams of methyl acetate, containing 2% methyl alcohol, was weighed into a 12-liter flask provided with a reflux condenser. 230 grams of sodium metal, in the form of small pieces (approximately $\frac{1}{2}$ " x $\frac{1}{2}$ "'), 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 then 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 dissolve 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 the benzol.

Methyl benzyl methyl aceto acetate

750 grams of methyl methyl aceto acetate, as formed above, 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 were required for the addition, and the temperature was held be-

tween 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.

Methyl benzyl acetic acid

855 grams of methyl benzyl methyl aceto acetate from the above run was refluxed with a sodium methylate solution (17 grams Na in 321 cc. methanol) for 3 to 4 hours, and then the constant boiling mixture of methyl acetate-methanol was slowly distilled off in the course of another $1\frac{1}{2}$ hours. The resulting benzyl methyl acetic acid methyl ester was then saponified by the addition of 120 grams of NaOH in the form of 30% aqueous solution. The sodium salt was given two extractions, using 200 cc. of xylol each time. The methyl benzyl acetic acid was liberated from the sodium salt by the addition of 50% H₂SO₄ solution. The oil was washed with water, the water washes were combined, extracted with xylene, and then added to the methyl benzyl acetic acid. The xylene was distilled from the acid under vacuum. A yield of 567 grams of methyl benzyl acetic acid was obtained. B. P. 150–155° C. at 8 mm.

Methyl benzyl acetyl chloride

502 grams of thionyl chloride was weighed into a 2-liter 3-neck flask provided with a thermometer, agitator, dropping funnel and reflux condenser. 472 grams of the above described methyl benzyl acetic acid was then added over a period of one hour. The temperature during addition varied between 30–40° C. The excess thionyl chloride was then distilled off, and the acid chloride vacuum distilled. Yield: 420 grams of methyl benzyl acetyl chloride. B. P. 118–120° C. at 15 mm.

Methyl benzyl acetamide

420 grams of methyl benzyl acetyl chloride, formed as above, was converted to the amide by adding the chloride slowly to 4260 cc. of benzol, saturated with NH₃ at 200° C., the NH₃ always being in excess. After all of the chloride was in the reaction product was heated on a steam bath to 62° C., and the separated out ammonium chloride filtered off. The filtrate was then cooled to 10° C., and the crystals of the benzyl methyl acetamide filtered and dried. Yield: 336 grams methyl benzyl acetamide. Upon recrystallization from benzol there was obtained 286 grams of amide having a M. P. of 108.4° C.

Beta-amino propyl benzene

230 grams of methyl benzyl acetamide, prepared as above, 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