

213. Reduction of Amides with Lithium Aluminium Hydride.

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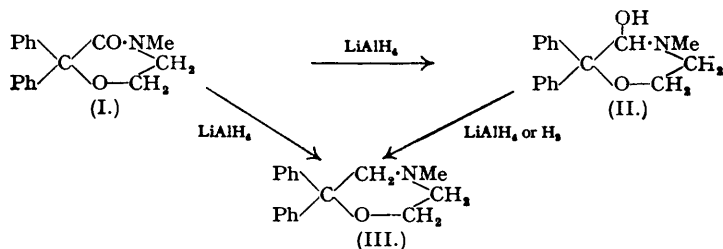
Reduction of 3-keto-4-methyl-2 : 2-diphenylmorpholine (I) with excess of lithium aluminium hydride gave a mixture of 4-methyl-2 : 2-diphenylmorpholine (III), the expected product, and 3-hydroxy-4-methyl-2 : 2-diphenylmorpholine (II).

Treatment of α -(2-dimethylaminoethoxy)- α : α -diphenylacetopiperidide (IV) with lithium aluminium hydride gave, besides the expected product 2-(2-dimethylaminoethoxy)-2 : 2-diphenyl-1-piperidinoethane (V), another substance which was shown to be 3-dimethylamino-1 : 1-diphenylpropanol (VII). The course of the rearrangement of the lithium aluminium hydride complex of (IV) to give (VII) has not been established but it has been shown that treatment of (2-diethylaminoethoxy)diphenylmethane ("Benadryl") (VI) with powdered sodium also gives (VII).

It has recently been reported (Galínovsky and Weiser, *Experientia*, 1950, **6**, 377) that lactams, generally, when treated with the calculated amount of lithium aluminium hydride, yield amino-aldehydes, while excess of the reagent gives the oxygen-free amines.

It was reported by Morrison, Königstein, and Cohen (*J.*, 1950, 2887) that 3-keto-4-methyl-2 : 2-diphenylmorpholine (I) was formed by the action of thionyl chloride on sodium α -(2-dimethylaminoethoxy)- α : α -diphenylacetate. Reduction of (I) with excess of lithium aluminium hydride would be expected to yield 4-methyl-2 : 2-diphenylmorpholine (III) (Uffer

and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397) which can be considered as a cyclic form of the well-known antihistaminic compound, "Benadryl," *i.e.* (2-diethylaminoethoxy)diphenylmethane. The product from the action of 2 moles of the hydride was found to be a mixture of (III) and 3-hydroxy-4-methyl-2 : 2-diphenylmorpholine (II).

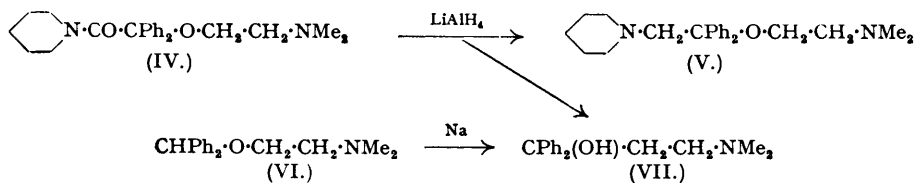


Catalytic hydrogenation of (II) gave (III), which was also formed in 88% yield by the further action of the hydride on (II). Condensation of (II) with nitromethane gave 4-methyl-3-nitromethyl-2 : 2-diphenylmorpholine, which on reduction with aluminium amalgam in moist ether yielded 3-aminomethyl-4-methyl-2 : 2-diphenylmorpholine. Hydrogenation of acetone in presence of the latter compound gave 4-methyl-2 : 2-diphenyl-3-isopropylaminomethylmorpholine.

The action of excess of lithium aluminium hydride on a number of amides structurally related to (I) was investigated, and in no case was there any evidence of formation of an aldehyde. The lactam, 1-methyl-3 : 3-diphenylpyrrolid-2-one, was reduced to 1-methyl-3 : 3-diphenylpyrrolidine. Open-chain amides such as the piperidides of diphenylacetic acid and benzoic acid were reduced to 1 : 1-diphenyl-2-piperidinoethane and 1-hydroxy-1 : 1-diphenyl-2-piperidinoethane, respectively.

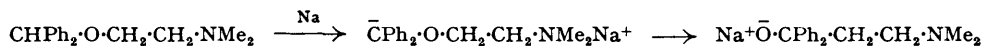
The reduction of the piperidide of α -(2-dimethylaminoethoxy)- α : α -diphenylacetic acid (IV) was then investigated, the products to be expected being either 2-(2-dimethylaminoethoxy)-2 : 2-diphenyl-1-piperidinoethane (V) or α -(2-dimethylaminoethoxy)- α : α -diphenylacetaldehyde. Treatment of (IV) with 1 mole of the hydride gave (V) (30% yield) and 3-dimethylamino-1 : 1-diphenylpropan-1-ol (32% yield), the latter being identified with the compound investigated by Morrison and Rinderknecht (*J.*, 1950, 1510).

It has also been observed that on heating a solution of (2-dimethylaminoethoxy)diphenylmethane (VI) in benzene with powdered sodium, the solution underwent a series of colour changes through blue, green, and yellow, finally becoming brown when cooled, and gave, as

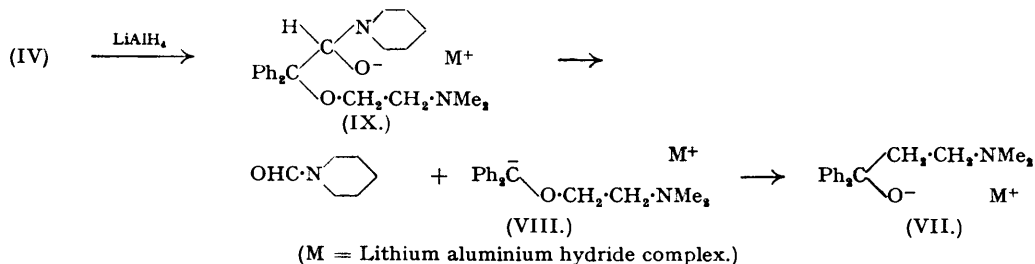


the only identified product, (VII) in at least 30% yield. This change from (VI) to (VII) is in accordance with the work of Schorigin (*Ber.*, 1923, **56**, 176; 1924, **57**, 1627, 1634; 1925, **58**, 2028; 1926, **59**, 2510) who showed that certain ethers when heated with sodium underwent, apart from a splitting of the molecule, a "carbinol rearrangement" to give an alcohol. We have not studied this reaction extensively but it would appear from the complete absence of any colour change that diphenylmethyl 3-piperidinopropyl ether is unaffected when heated with powdered sodium in toluene, indicating that the fission of the ether in the required manner is dependent on the tertiary amino-group in the β -position. Moreover, in conformity with Schorigin's observations, we have established that 2-dimethylaminoethyl diphenylmethyl thioether does not give a thiol corresponding to (VII), although there is evidence of the fission of the thioether.

If we formulate the reaction of sodium with (VI) as follows :



we can regard the reaction of lithium aluminium hydride with (IV) as taking the following course :



In the above mechanism of the reaction we have essentially the reductive cleavage of a C-C bond. As far as we are aware, only one other instance of such an action by lithium aluminium hydride has been reported, namely, the formation of 4-ketoquinolizidine from 3-carbethoxy-4-ketoquinolizidine (Boekelheide and Rothchild, *J. Amer. Chem. Soc.*, 1949, 71, 879).

It might be argued that the rearrangement of (VIII) to (VII) was very unlikely under the mild conditions employed, but it has been shown by Ziegler and Thielmann (*Ber.*, 1923, 56, 1741) that diphenylmethyl ethyl ether in ethereal solution is split by the action of potassium at room temperature into diphenylmethylpotassium and phenol. The only other product isolated from our reaction mixture was a very small amount of a base which gave a reineckate the m. p. of which was not depressed when mixed with piperidine reineckate. Further work will be necessary to determine definitely if piperidine is formed and also whether formaldehyde or formic acid is the other product of the reaction.

None of the new compounds described in this paper has been found to possess outstanding spasmolytic properties.

EXPERIMENTAL.

1-Methyl-3 : 3-diphenylpyrrolidine.—1-Methyl-3 : 3-diphenylpyrrolid-2-one (1.6 g.) in dry ether (20 ml.) was added to a stirred solution of lithium aluminium hydride (0.4 g.) in ether (30 ml.) in an atmosphere of nitrogen. The mixture was refluxed for 20 hours, and the cooled product decomposed by gradual addition of water, and then made acid with 2*N*-sulphuric acid. The acid layer was separated and made alkaline with 30% sodium hydroxide solution, the base taken up in ether, and the ethereal solution dried and concentrated. The residual oil (0.7 g.) on distillation gave the pure *pyrrolidine*, b. p. 140—142°/1 mm. (Found : C, 85.6; H, 8.3; N, 6.0. $\text{C}_{17}\text{H}_{19}\text{N}$ requires C, 86.1; H, 8.0; N, 5.9%). The *picrate*, recrystallised from alcohol, had m. p. 162—163° (Found : C, 59.3; H, 4.9; N, 12.3. $\text{C}_{23}\text{H}_{22}\text{O}_7\text{N}_4$ requires C, 59.2; H, 4.7; N, 12.0%).

3-Hydroxy-4-methyl-2 : 2-diphenylmorpholine (II).—A solution of 3-keto-4-methyl-2 : 2-diphenylmorpholine (5.9 g.) in dry ether (50 ml.) was added gradually to a stirred solution of lithium aluminium hydride (1.6 g.) in dry ether (200 ml.) under nitrogen, and the reaction mixture heated under reflux for 24 hours. The complex formed and the excess of hydride were then decomposed by addition of ice-cold water (30 ml.), and excess of 5*N*-sulphuric acid was added. The aqueous layer was separated, made alkaline, and extracted with ether. Drying and evaporation of the ethereal solution gave 5.0 g. of crude basic product. On recrystallisation from light petroleum (b. p. 60—80°), the *carbinolamine*, m. p. 97—99°, was obtained (1.9 g., 32%) (Found : C, 75.8; H, 6.8; N, 5.2. $\text{C}_{17}\text{H}_{19}\text{O}_2\text{N}$ requires C, 75.4; H, 7.1; N, 5.2%). The *hydrochloride* recrystallised from alcohol-ether had m. p. 194—195° (decomp.) (Found : Cl⁻, 11.8. $\text{C}_{17}\text{H}_{20}\text{O}_2\text{NCl}$ requires Cl⁻, 11.6%). The *picrate*, from alcohol, melted at 164—165° (Found : N, 11.6. $\text{C}_{23}\text{H}_{22}\text{O}_6\text{N}_4$ requires N, 11.25%).

4-Methyl-2 : 2-diphenylmorpholine (III).—(a) The light petroleum mother-liquors from recrystallisation of the above carbinolamine gave on concentration the *morpholine*, which was purified (m. p. 79—80°; 2.2 g., 39%) by recrystallisation from a small amount of light petroleum (b. p. 60—80°) (Found : C, 80.2; H, 7.6; N, 5.2. $\text{C}_{17}\text{H}_{19}\text{ON}$ requires C, 80.6; H, 7.5; N, 5.5%).

(b) 3-Hydroxy-4-methyl-2 : 2-diphenylmorpholine (2 g.), dissolved in ethanol, was hydrogenated by means of a 5% palladium-charcoal catalyst (0.3 g.), the theoretical amount of hydrogen being taken up in 5 hours. The residue remaining after distillation of the alcohol distilled at 140—150°/0.5 mm., and the solid distillate recrystallised from light petroleum (b. p. 40—60°) to give the pure *morpholine*, m. p. 79—80°. The *hydrochloride* melted at 266—268° (decomp.) (Found : C, 69.9; H, 6.8; N, 4.7; Cl⁻, 12.8. $\text{C}_{17}\text{H}_{20}\text{ONCl}$ requires C, 70.3; H, 6.9; N, 4.8; Cl⁻, 12.3%). The *picrate* melted at 233—234° (Found : N, 11.6. $\text{C}_{23}\text{H}_{22}\text{O}_6\text{N}_4$ requires N, 11.6%).

(c) Reaction of (II) (2 g.) in dry ether (30 ml.) with lithium aluminium hydride (0.3 g.) in dry ether (50 ml.) under nitrogen for 14 hours yielded (III) in 88% yield.

4-Methyl-3-nitromethyl-2 : 2-diphenylmorpholine.—A solution of the above carbinolamine (5.0 g.) in nitromethane (20 ml.) was heated under reflux for 1 hour. The solid product left on distilling off the nitromethane, recrystallised from alcohol, gave the *nitromethyl-morpholine*, m. p. 144—145° (5.3 g., 92%) (Found : C, 68.8; H, 6.45; N, 9.1. $\text{C}_{18}\text{H}_{20}\text{O}_2\text{N}_2$ requires C, 69.2; H, 6.4; N, 8.9%).

3-Aminomethyl-4-methyl-2 : 2-diphenylmorpholine.—A solution of the above nitromethylmorpholine (2 g.) in moist ether (150 ml.) was allowed to react with aluminium amalgam (prepared from foil, 2.5 g.) for 12 hours. The filtered ethereal solution was dried and concentrated to give a viscous oil, b. p. 156—160°/0.2 mm. The *dihydrochloride* melted at 200—203° (63%) (Found : C, 58.1; H, 7.2; N, 7.85; Cl⁻, 18.9. C₁₈H₂₄ON₂Cl₂ requires C, 57.7; H, 6.75; N, 7.9; Cl⁻, 20.0%).

4-Methyl-2 : 2-diphenyl-3-isopropylaminomethylmorpholine.—Hydrogenation of acetone (1 ml.) in presence of the above aminomethylmorpholine (2 g.) in ethanol (50 ml.) with reduced platinum oxide (0.1 g.) yielded the isopropylamine as an oil, b. p. 180—184°/0.3 mm. (68%). The *dihydrochloride* had m. p. 242—244° (decomp.) (Found : C, 63.4; H, 8.1; N, 7.4; Cl⁻, 17.2. C₂₁H₃₀ON₂Cl₂ requires C, 63.5; H, 7.6; N, 7.1; Cl⁻, 17.8%).

1 : 1-Diphenyl-2-piperidinoethane.—*Diphenylacetopiperidide* was prepared from diphenylacetyl chloride (1.5 g.) and piperidine (1.1 g.) in dry ether and obtained as a crystalline solid, m. p. 107—108°, from light petroleum (b. p. 60—80°) (Found : N, 5.0. C₁₉H₂₁ON requires N, 5.0%). This piperidide (1.3 g.) was reduced with lithium aluminium hydride (0.2 g.) to give the base as an oil which was converted into the *hydrochloride*, m. p. 145—147° (0.95 g., 65%) (Found : N, 4.6; Cl⁻, 11.05. C₁₉H₂₄NCl requires N, 4.3; Cl⁻, 11.7%).

1-Hydroxy-1 : 1-diphenyl-2-piperidinoethane.—By the action of phenylmagnesium bromide [from bromobenzene (20 g.) and magnesium (3.1 g.)] on 1-ethoxalylpiperidine (6 g.) in ethereal solution, *α-hydroxy-α : α-diphenylacetopiperidide* was obtained as a crystalline solid (68%), m. p. 121—122°, from light petroleum (b. p. 60—80°) (Found : N, 4.2. C₁₉H₂₁O₂N requires N, 4.75%). This piperidide (3.0 g.) was treated with lithium aluminium hydride (0.45 g.) as described above. On decomposition of the lithium aluminium complex with dilute sulphuric acid, *1-hydroxy-1 : 1-diphenyl-2-piperidinoethane hydrogen sulphate* (54.5%, 2.1 g.) separated; recrystallised from alcohol-ether, it had m. p. 165—166° (Found : N, 3.7; S, 8.9. C₁₈H₂₃O₂NS requires N, 3.7; S, 8.4%). On working up of the filtrate from this sulphate in the usual way, the *base* was isolated in 21% yield (0.6 g.) as a solid, m. p. 65—66°, from benzene-light petroleum (b. p. 40—60°) (Found : N, 5.0. C₁₉H₂₃ON requires N, 5.0%).

Reaction of Lithium Aluminium Hydride with α-(2-Dimethylaminoethoxy)-α : α-diphenylacetopiperidide.—The piperidide (4.5 g.) was allowed to react with lithium aluminium hydride (0.75 g.) in ether (120 ml.) for 16 hours. The basic product was isolated in the usual manner and found to be easily separated into two substances, one soluble and the other insoluble in light petroleum (b. p. 40—60°). The former was purified *via* its picrate, m. p. 180°, which was decomposed with a solution of lithium hydroxide. The regenerated base in ether was treated with an alcoholic solution of hydrogen chloride to give solvated *2-(2-dimethylaminoethoxy)-2 : 2-diphenyl-1-piperidinoethane hydrochloride*, m. p. 221—222° (28%) (Found : C, 63.1; H, 8.3; N, 6.1; Cl⁻, 15.5. C₂₃H₃₄ON₂Cl₂·C₂H₆O requires C, 63.7; H, 8.5; N, 5.9; Cl⁻, 15.1%).

The substance insoluble in the light petroleum was recrystallised from light petroleum (b. p. 60—80°) and had m. p. 163—164°, not depressed when mixed with an authentic specimen of 3-dimethylamino-1 : 1-diphenylpropan-1-ol, m. p. 164—165° [Found : C, 79.8; H, 8.85; N, 5.7%; *M* (Rast), 230. Calc. for C₁₇H₂₁ON : C, 80.0; H, 8.2; N, 5.7%; *M*, 255]. The identity of the substance was further established (cf. Morrison and Rinderknecht, *loc. cit.*) by preparation and mixed m. p. determinations of the hydrochloride, m. p. 204—205° (Found : C, 69.2; H, 7.2; N, 4.7; Cl⁻, 11.8. Calc. for C₁₇H₂₂ONCl : C, 70.0; H, 7.55; N, 4.7; Cl⁻, 12.2%), and of the *picrate*, m. p. 151—152° (Found : N, 11.7. C₂₃H₃₄O₈N₄ requires N, 11.3%).

The alkaline aqueous phase, after the normal ether-extraction of these two basic products, was distilled into dilute hydrochloric acid, and this acid solution concentrated to dryness. The hydrochloride left (0.4 g.) was converted into the *reineckate*, which melted at 256—257° undepressed when mixed with *piperidine reineckate*, m. p. 258—259° (Found : C, 26.8; H, 4.3; N, 23.8. C₉H₁₇N₇S₄Cr requires C, 26.8; H, 4.2; N, 24.2%).

Action of Sodium on (VI).—A solution of (VI) (4 g.) in toluene (100 ml.) was heated under reflux with powdered sodium (0.4 g.) in an atmosphere of nitrogen with stirring for 8 hours, the solution undergoing the colour changes described on p. 953. On working up of the reaction mixture in the usual way for basic material, a solid, m. p. 164—165°, was isolated in 30% yield and was shown by mixed m. p. determination to be (VII) (Found : C, 80.05; H, 8.5. Calc. for C₁₇H₂₁ON : C, 80.0; H, 8.2%). The hydrochloride melted at 204—205° undepressed when mixed with an authentic specimen of the hydrochloride of (VII). The quaternary salt prepared from a benzene solution of the above carbinol and allyl bromide was shown to be identical with *allyldimethyl-(3 : 3-diphenyl-3-hydroxypropyl)ammonium bromide*, m. p. 229°, prepared from (VII) (Found : C, 63.9; H, 7.0; N, 3.7; Br⁻, 21.2. C₂₀H₂₈ONBr requires C, 63.8; H, 6.9; N, 3.7; Br⁻, 21.7%).

Action of Sodium on 2-Dimethylaminoethyl Diphenylmethyl Sulphide.—The sulphide was prepared as described in Example I of U.S.P. 2,483,671. A solution of it (7.0 g.) in toluene (50 ml.) was added with stirring to powdered sodium (0.65 g.) in toluene (75 ml.) in an atmosphere of nitrogen. The mixture was gradually heated to boiling, and a red colour slowly developed, becoming a deep vivid crimson after 30 minutes. Heating was continued for a further two hours. The toluene solution was then cooled and carefully treated with water, and the aqueous extract treated with excess of mercuric chloride solution. Decomposition of the mercury salt (8.6 g.) by suspension in 20% hydrochloric acid (50 ml.) and passage of hydrogen sulphide, filtration from mercuric sulphide, and concentration of the mother-liquor gave a small amount (0.6 g.) of a very deliquescent, white, crystalline solid, m. p. 144—147°, which from analysis and properties would appear to be essentially 2-dimethylaminoethanethiol hydrochloride (Found : N, 9.4; S, 20.1. Calc. for C₁₁H₁₂NSCl : N, 9.9; S, 22.6%). From the toluene solution 2.3 g. of the hydrochloride of the sulphide were recovered.