450. *The Clemmensen Reduction of Certain α-Amino-ketones and its Bearing on the Reduction of 1-Keto-octahydropyridocoline.*

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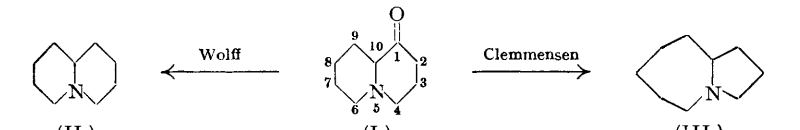
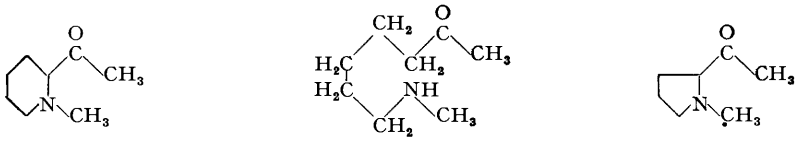
Continuing our study of the anomalous Clemmensen reduction of 1-keto-octahydropyridocoline (I), we have prepared 2-acetyl-1-methylpiperidine and, from an examination of its reduction and that of 2-acetyl-1-methylpyrrolidine under similar conditions, offer an explanation of the peculiar rearrangement of (I).

In previous communications it was shown that whereas the Wolff reduction of 1-keto-octahydropyridocoline (I) yielded norlupinane (II) (*J.*, 1936, 1429), reduction by the Clemmensen method was anomalous, yielding an isomeric " base B " (*J.*, 1931, 437), and all substituted 1-keto-octahydropyridocolines so far studied have behaved similarly (*J.*, 1937, 1518; 1938, 1183, 1318). Prelog and Seiworth (*Ber.*, 1939, **72**, 1638) have since synthesised *bicyclo*[5 : 3 : 0]-1-azadecane (III) and shown it to be identical with " base B."



(II.) (I.) (III.)



(IV.) (VI.) (V.)

In order to study this peculiar rearrangement further it was decided to prepare the simpler but analogous ketone, 2-acetyl-1-methylpiperidine (IV), and examine its reduction by the Clemmensen and Wolff methods. Later 2-acetyl-1-methylpyrrolidine (V) was also examined.

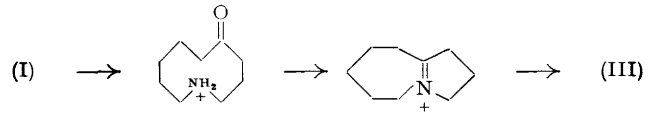
2-Acetylpyridine and its methosulphate could not be converted by fractional catalytic hydrogenation into the desired hexahydro-ketones, and (IV) was therefore prepared by complete hydrogenation of 2-acetylpyridine to 2-1′-hydroxyethylpiperidine, followed by *N*-methylation and oxidation with chromic acid, after the method of Hess and Corleis (*Ber.*, 1921, **54**, 3010). 2-Acetyl-1-methylpyrrolidine (V) has been prepared by a similar series of reactions. Hess, Merck, and Uibrig (*Ber.*, 1915, **48**, 1900) claimed to have obtained (V) by the action of formaldehyde on a hydrochloric acid solution of 2-1′-hydroxyethylpyrrolidine, but later stated that the base was more probably 5-methyl-3 : 4-trimethyleneoxazolidine. We have found that *N*-methylation of the above pyrrolidine alcohol by formaldehyde and formic acid proceeded normally to give *1-methyl-2-1′-hydroxyethylpyrrolidine*, chromic acid oxidation of which gave (V) identical with that described by H. King (*J.*, 1941, 337).

Wolff reduction of (IV) proceeded normally giving 1-methyl-2-ethylpiperidine. Clemmensen reduction, however, was anomalous, giving two products. One, a fully reduced secondary base, agreed in properties with the *N*-methylheptylamine described by von Braun (*Annalen*, 1911, **382**, 46) and its identity was confirmed by comparison of its derivatives with those of a synthetic specimen prepared from *methylheptylaniline*. 1 : 2-*Dimethylhexamethyleneimine* was also prepared, but no trace of it or of 1-methyl-2-ethylpiperidine could be isolated from the reduction mixture. The second product, a methyl ketone differing from the starting product, gave *N*-methylheptylamine on further reduction, and was shown by synthesis and comparison of derivatives to be *7-methylaminoheptan-2-one* (VI). This was readily prepared from the lactam of 5-methylaminohexoic acid and methylmagnesium iodide. Clemmensen reduction of (V) was also anomalous, yielding 1 : 2-dimethylpiperidine as sole product.

As Clemmensen reduction conditions had no effect on 1-methyl-2-1′-hydroxyethylpiperidine, (VI) is not produced by reduction to the alcohol followed by some type of " hydramine fission," but must be formed by preferential hydrogenolysis of the 1 : 2 N–C bond of (IV) (cf. the reduction of phenyl phenacyl sulphide, etc., von Braun and Weissbach *Ber.*, 1929, **62**, 2416). A normal Clemmensen reduction of the ε-amino-ketone (VI) then yields *N*-methylheptylamine. The anomalous Clemmensen reduction of (V) is also explained by a similar hydrogenolysis to

give 6-methylaminohexan-2-one, which, unlike (VI), spontaneously cyclises to 1 : 2-dimethyl-1 : 4 : 5 : 6-tetrahydropyridine (Lipp, *Ber.*, 1892, **25**, 2190; see also Adams and Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2588). This in its turn is reduced to 1 : 2-dimethylpiperidine by tin and hydrochloric acid (Lipp, *loc. cit.*), and would thus be easily reduced under the more vigorous Clemmensen conditions.

The Clemmensen reduction of (I) is more closely related to that of (V) than to that of (IV). Preferential hydrogenolysis of the 10 : 5 C–N bond yields as intermediate the γ-amino-ketone (VII) which, as with other γ-amino-ketones (Craig, *J. Amer. Chem. Soc.*, 1933, **55**, 295), immediately cyclises giving, in this case in acid solution, the quaternary ion (VIII) which is readily reduced to (III).



(VII.) (VIII.)

Experimental.

(All m. p.s are uncorrected.)

2-1′-*Hydroxyethylpiperidine.*—Catalytic hydrogenation of 2-acetylpyridine (10 g.) in acetic acid (50 ml.), by Hess and Corleis's method (*loc. cit.*) but with platinic oxide (150 mg.) and hydrogen at 100 lb./sq. in. during 12 hours, gave the alcohol as a colourless oil (8·95 g.), b. p. 101—102°/23 mm. (Found : C, 65·0; H, 11·2. Calc. for $C_7H_{15}ON$: C, 65·1; H, 11·7%). The *picrate* crystallised from alcohol–ether in yellow cubes, m. p. 115—117° (Found : C, 43·7; H, 5·5. $C_7H_{15}ON,C_6H_3O_7N_3$ requires C, 43·4; H, 5·1%).

1-*Methyl*-2-1′-*hydroxyethylpiperidine.*—The following method is an improvement on that described by Hess and Corleis (*loc. cit.*). 2-1′-Hydroxyethylpiperidine (12·1 g.) was heated for 18 hours on the water-bath under reflux with formic acid (12·5 ml.; 90%) and aqueous formaldehyde (12·0 ml.; 40%). The residue, after evaporation, was made alkaline with 40% sodium hydroxide solution, extracted with chloroform, dried, and distilled, giving the tertiary amino-alcohol (10·94 g.), b. p. 80—89°/18 mm. (Found : C, 66·7; H, 12·1. Calc. for $C_8H_{17}ON$: C, 67·0; H, 12·0%). The *picrate* formed large lemon-yellow prisms, m. p. 91—92°, from ethyl acetate–light petroleum (Found : C, 44·4; H, 5·7. $C_8H_{17}ON,C_6H_3O_7N_3$ requires C, 45·1; H, 5·4%), and the *picrolonate* bright yellow prisms, m. p. 174—175° from alcohol (Found : C, 52·9; H, 6·4. $C_8H_{17}ON,C_{10}H_8O_5N_4$ requires C, 53·0; H, 6·2%).

2-*Acetyl*-1-*methylpiperidine.*—Oxidation of the above alcohol as described by Hess and Corleis (*loc. cit.*) gave (IV) (57%), b. p. 77—79°/14 mm. (Found : C, 68·1; H, 10·7; N, 10·1. Calc. for $C_8H_{15}ON$: C, 68·0; H, 10·7; N, 9·9%). The picrate had m. p. 121—123° and the *picrolonate* formed yellow glistening plates, m. p. 179—181°, from alcohol (Found : C, 53·5; H, 6·0. $C_{18}H_{23}O_6N_5$ requires C, 53·3; H, 5·7%).

Clemmensen Reduction of (IV).—(IV) (3·45 g.), amalgamated zinc (45 g.), and hydrochloric acid (75 ml.) were heated under reflux for 64 hours, the mixture was reduced to small volume, made alkaline, and distilled in steam. The initial steam-distillate (*A*) (30 ml.) contained a sparingly soluble basic oil, the later distillate (*B*) contained no oil but was strongly basic and gave a positive iodoform reaction. The dried ethereal extract of *A*, on distillation, gave *N*-methylheptylamine (0·52 g.), b. p. 166—168° (Found : C, 75·1; H, 15·3. Calc. for $C_8H_{19}N$: C, 74·4; H, 14·9%). The *picrolonate* formed pale yellow plates or prisms (from alcohol or water), m. p. 174° not depressed by an authentic specimen (Found : C, 54·8; H, 7·0. $C_8H_{19}N,C_{10}H_8O_5N_4$ requires C, 54·9; H, 6·9%). The picrate, obtained from ether, had m. p. 96—97° not depressed by an authentic specimen. Acidification and evaporation of *B* gave a hygroscopic hydrochloride from which a colourless basic oil (0·92 g.), b. p. 90—105°/20 mm. (bath temp.), was obtained by addition of alkali and distillation of the dried extract. This oil gave the reactions of a methyl ketone and was shown by comparison of derivatives to be 7-methylaminoheptan-2-one (VI). The *picrolonate* formed yellow prisms, m. p. 134—135°, from alcohol or water (Found : C, 53·3; H, 6·1. $C_8H_{17}ON,C_{10}H_8O_5N_4$ requires C, 53·0; H, 6·2%), and the *semicarbazone hydrochloride* very fine colourless prisms, m. p. 162—165°, from alcohol (Found : C, 45·7; H, 8·5. $C_9H_{20}ON_4,HCl$ requires C, 45·5; H, 8·9%).

Clemmensen Reduction of (VI).—(VI) (0·5 g.), amalgamated zinc (10 g.) and hydrochloric acid (25 ml.) were heated under reflux for 48 hours and the mixture was worked up as above, giving *N*-methylheptylamine (97 mg.) (picrolonate, m. p. 173°) and unreduced (VI) (236 mg.) (picrolonate, m. p. 134°).

Wolff Reduction of (IV).—(IV) (0·4 g.) and hydrazine hydrate (3 ml.) were heated under reflux for 18 hours, and the hydrazone was extracted with ether, dried, and heated in a sealed tube with sodium (0·5 g.) dissolved in alcohol (3 ml.) at 170—175° for 18 hours. The mixture was diluted with water, acidified, evaporated to small bulk, made alkaline with potassium carbonate, and extracted with ether. Addition of the dried ethereal solution to picric acid (0·65 g.) in ether gave 1-methyl-2-ethylpiperidine picrate (0·52 g.) which crystallised from water in needles, m. p. 173° (Found : C, 47·2; H, 5·7. Calc. for $C_8H_{17}N,C_6H_3O_7N_3$: C, 47·1; H, 5·6%).

N-*Methylheptylamine.*—Heptyl bromide (2·0 g.) and methylaniline (4·0 g.) were heated at 100° for 40 hours, the residue was made alkaline with excess of sodium hydroxide and extracted with ether, and the dried extract was distilled, giving *methylheptylaniline* (1·7 g.), b. p. 278—280°, as an almost colourless oil (Found : C, 81·5; H, 10·7. $C_{14}H_{23}N$ requires C, 81·9; H, 11·3%). The *picrate* formed

bright yellow prisms, m. p. 75°, from alcohol–water (Found : C, 55·7; H, 5·8. $C_{14}H_{23}N,C_6H_3O_7N_3$ requires C, 55·3; H, 6·0%). Sodium nitrite (0·37 g.) in water (1 ml.) was added during 20 minutes to a cooled solution of the above oil (0·6 g.) in hydrochloric acid (1·1 ml.) and water (1·1 ml.), giving the green nitroso-compound hydrochloride. This was separated after 1 hour and boiled under reflux, for 4 hours with 10% sodium hydroxide (20 ml.), the mixture distilled in steam, the distillate extracted with ether, and the dried extract distilled, to give *N*-methylheptylamine (0·13 g.), b. p. 75—85°/45—50 mm. (bath temp.). The picrate, m. p. 97°, as described by von Braun (*loc. cit.*), and the picrolonate, m. p. 174—175°, were identical with those described above.

7-*Methylaminoheptan*-2-*one* (VI).—The lactam of 5-methylaminohexoic acid (3·8 g.) in ether (30 ml.) was added to the Grignard reagent prepared from magnesium (0·8 g.) and methyl iodide (4·8 g.) in ether (40 ml.). After 3 hours the mixture was heated under reflux for ½ hour and kept overnight. Excess of 10% sulphuric acid was added to decompose the white complex, the aqueous layer separated made, alkaline, and extracted with ether, and the dried extract distilled and refractionated, to give the *ketone* (VI) (1·4 g.), b. p. 93—95°/16 mm. (Found : C, 67·1; H, 12·1. $C_8H_{17}ON$ requires C, 67·0; H, 12·0%). The picrolonate, m. p. 135°, and the semicarbazone hydrochloride, m. p. 163°, were identical with those described previously.

1 : 2-*Dimethylhexamethyleneimine*.—Lithium aluminium hydride (0·4 g.) in ether (20 ml.) was added to the lactam of 5-aminoheptoic acid (1·02 g.) in ether (30 ml.). After 3 days the complex was decomposed by 10% sulphuric acid, the aqueous layer was made alkaline and distilled in steam, and the distillate acidified with hydrochloric acid, evaporated to dryness, and recrystallised from acetone to give 2-methylhexamethyleneimine hydrochloride (0·53 g.), m. p. 156°, as colourless needles. The base from 0·5 g. of this hydrochloride was heated on the water-bath with formic acid (2 ml.) and aqueous formaldehyde (1·5 ml.; 40%) for 16 hours and worked up in the usual way, to give 1 : 2-dimethylhexamethyleneimine (210 mg.), b. p. 80—90°/50 mm. (bath temp.). The *picrate* formed light-yellow flat prisms, m. p. 233°, from alcohol (Found : C, 47·4; H, 6·0. $C_8H_{17}N,C_6H_3O_7N_3$ requires C, 47·2; H, 5·7%), and the *picrolonate* yellow needles, m. p. 162—164°, from alcohol (Found : C, 54·8; H, 6·7. $C_8H_{17}N,C_{10}H_8O_5N_4$ requires C, 55·2; H, 6·45%).

1-*Methyl*-2-1′-*hydroxyethylpyrrolidine*.—2-1′-Hydroxyethylpyrrolidine (1·8 g.), formic acid (4 ml.; 90%) and aqueous formaldehyde (4 ml.; 40%) were heated on the water-bath for 10 hours, hydrochloric acid (1·6 ml.) was added, the solution evaporated to dryness, made alkaline with 40% sodium hydroxide, and extracted with chloroform, and the extract dried and distilled, giving the tertiary *amino-alcohol* (1·6 g.), b. p. 70—72°/10 mm. (Found : C, 64·9; H, 11·2. $C_7H_{15}ON$ requires C, 65·1; H, 11·7%). The *picrate* formed bright yellow plates, m. p. 110—111°, from ethyl acetate or water (Found : C, 43·7; H, 5·2. $C_7H_{15}ON,C_6H_3O_7N_3$ requires C, 43·5; H, 5·0%).

2-*Acetyl*-1-*methylpyrrolidine* (V).—The above alcohol (0·6 g.) in acetic acid (18 ml.) was warmed to 70°, and chromic acid (0·9 g.) in water (0·9 ml.) and acetic acid (2·5 ml.) added dropwise during ½ hour. After a further 20 minutes at 80—90° hydrochloric acid (1·5 ml.) was added, the acetic acid removed, the residue made alkaline with potassium carbonate and extracted with ether, and the extract dried and distilled, giving the ketone (V) (170 mg.), b. p. 50—55°/9 mm. (bath temp.), as a colourless unstable oil. The picrate formed yellow plates on precipitation from ether but recrystallised from water in yellow prisms, m. p. 117—118° (Found : C, 43·5; H, 4·3. Calc. for $C_7H_{13}ON,C_6H_3O_7N_3$: C, 43·8; H, 4·5%).

Clemmensen Reduction of (V).—(V) (90 mg.), amalgamated zinc (2 g.), and hydrochloric acid (4 ml.) were boiled under reflux for 40 hours, the mixture was made alkaline with 10% sodium hydroxide solution and steam-distilled into dilute hydrochloric acid which was subsequently evaporated to dryness, made alkaline, and extracted with ether. The dried extract was added to picric acid (180 mg.) in ether, giving 1 : 2-dimethylpiperidine picrate (85 mg.), m. p. 240° after recrystallisation from water, not depressed by an authentic specimen (Found : C, 45·6; H, 5·2. Calc. for $C_7H_{15}N,C_6H_3O_7N_3$: C, 45·5; H, 5·3%).

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