907. *Stereochemistry of the Hofmann–Freytag–Loeffler Reaction applied to* N-*Methyl*-2-*cyclopentylethylamine.*

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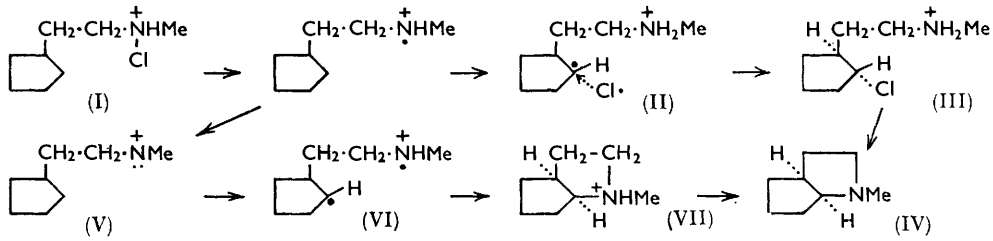
The reaction named in the title leads to *cis*-perhydro-1-methylcyclopenta-[*b*]pyrrole.

Radical intermediates generated from suitable amino-derivatives can abstract a hydrogen from the fourth carbon of the chain and then, by ring closure, yield pyrrolidine derivatives, a reaction used for building the *cis*-perhydrocyclopenta[*c*]pyrrole system [1-3] of natural bases such as conessine. It has been pointed out [1] that the cyclisation proceeds only if " an important conformational requirement " of the postulated transition state is satisfied. It was, therefore, of interest to see whether such a transformarion of *N*-methyl-2-cyclopentylethylamine affords the ismeric perhydrocyclopenta[*b*]pyrrole and, if so, with what stereochemistry. Should *cis*-fusion obtain, the method could be of use for synthesis of natural products such as solanidine.

Cyclopentylacetic acid was converted into its methylamide which on reduction with lithium aluminium hydride yielded *N*-methyl-2-cyclopentylethylamine. The *N*-chloro-amine (I) obtained therefrom by use of *N*-chlorosuccinimide was rearranged thermally or by ultraviolet irradiation in sulphuric acid to a tertiary base in 20% yield (as pure picrate). This was shown to be *cis*-perhydro-1-methylcyclopenta[*b*]pyrrole by independent synthesis.

[1] Barton and Morgan, *Proc. Chem. Soc.*, 1961, 206; *J.*, 1962, 622.
[2] Buchschacher, Kalvoda, Arigoni, and Jeger, *J. Amer. Chem. Soc.*, 1958, **80**, 2905; Buzzetti, Wicki, Kalvoda, and Jeger, *Helv. Chim. Acta*, 1959, **42**, 338.
[3] Corey and Hertler, *J. Amer. Chem. Soc.*, 1958, **80**, 2903; 1959, **81**, 5209; 1960, **82**, 1657; Schaffner, Arigoni, and Jeger, *Experientia*, 1960, **16**, 169.

According to the accepted mechanism [3,4] the Hofmann–Freytag–Loeffler reaction proceeds *via* the intermediate (II). This radical adds the chlorine atom preferentially on the side opposite to that shielded by the side chain, to give the *trans*-chloride (III) which on an internal S_N2 ring closure furnishes the *cis*-amine (IV).



On irradiating *N*-chlorodibutylamine in sulphuric acid, Wawzonek and Culbertson [5] isolated 4-chlorodibutylamine which was converted by alkali into 1-butylpyrrolidine in 64% yield. However, the yield of 1-butylpyrrolidine obtained by the direct Hofmann–Freytag–Loeffler reaction of *N*-chlorodibutylamine was as high as 78%. It seems, therefore, that part of the reaction proceeds by an alternative route in which 4-chlorodibutylamine is not an intermediate. This dichotomy may be of general occurrence and we propose an alternative mechanism which is similar to that suggested by Barton and Morgan [1] for photolysis of azides. The ion (V), having one electron in each of two vacant orbitals, can behave as a radical and may cyclise as shown. Owing to the relative stability of the *cis*-bicyclic transition state (VI ⟶ VII) the product is expected to have the observed stereochemistry.

Experimental

Ethyl α-Cyano-α-cyclopentylideneacetate.—Cyclopentanone (42 g.), ethyl cyanoacetate (68·5 g.), ammonium acetate (2 g.), and benzene (150 c.c.) were refluxed, with continuous removal of water, for 8 hr. while additional ammonium acetate (2 g. portions) was added twice at 2 hr. intervals. The cooled mixture was washed with water and the solvent removed. The residue gave a colourless oil (82 g.), b. p. 152—153°/15 mm., m. p. 54—56° (lit.,[6] b. p. 152—156°/18 mm., m. p. 55—57°).

Cyclopentylacetic Acid.—The foregoing ester (75 g.) in ethanol (100 c.c.) was hydrogenated over 30% palladium–charcoal (0·7 g.). The catalyst and the solvent were removed and the residue was refluxed for 20 hr. with concentrated hydrochloric acid, affording cyclopentylacetic acid (40 g.), b. p. 118—120°/12 mm., n^{19}_D 1·4527 (lit.,[6] b. p. 119—120°/13 mm., n_D^{20} 1·4522).

N-*Methylcyclopentylacetamide.*—To an ice-cold solution of methylamine (28 g.) in dry ether (200 c.c.) was slowly added cyclopentylacetyl chloride [6] (27 g.) in ether (20 c.c.). The mixture was left at room temperature for 1 hr. The organic layer was washed with water, dried, and evaporated. The residue afforded the *amide* (22 g.), b. p. 148—150°/13 mm. (Found: C, 68·3; H, 10·6. $C_8H_{15}NO$ requires C, 68·0; H, 10·7%).

N-*Methyl-2-cyclopentylethylamine.*—To a stirred slurry of lithium aluminium hydride (9·7 g.) in dry ether (120 c.c.) was dropwise added a solution of *N*-methylcyclopentylacetamide (18 g.) in ether (250 c.c.). The mixture was refluxed with stirring for 8 hr. The excess of hydride was decomposed by water at 0° while stirring was continued. The solid was removed and extracted with ether. The ether solutions were washed with water, dried, and evaporated. The residue on fractionation gave a colourless base (11 g.), b. p. 60—61°/8 mm., n_D^{37} 1·4355, whose *picrate* separated from ethanol as needles, m. p. 121—121·5° (Found: C, 47·2; H, 5·65; N, 16·05. $C_{14}H_{20}N_4O_7$ requires C, 47·1; H, 5·7; N, 15·7%).

[4] Wawzonek and Culbertson, *J. Amer. Chem. Soc.*, 1960, **82**, 441; 1959, **81**, 3367.
[5] Archer, B.P. 632,094/1949.
[6] Burschkies and Scholl, *Arch. Pharm.*, 1943, **281**, 328.

Hofmann–Freytag–Loeffler Reaction of N-*Methyl-2-cyclopentylethylamine.*—(*a*) *N*-Methyl-2-cyclopentylethylamine (2·2 g.) and *N*-chlorosuccinimide (2·6 g.) were shaken in ether (180 c.c.) at 20° for 40 min. Dilution with light petroleum (100 c.c.; b. p. 40—60°) gave a white solid which was removed. The filtrate was washed thrice with water. A portion (20 c.c.) of the solution, on iodometric titration (sodium thiosulphate) showed 85% conversion into chloroamine. The remaining solution was cooled to 5° and extracted with 90% sulphuric acid (2 × 30 c.c.). To the combined acid extracts was added a crystal of ferrous sulphate and the whole was kept at 65—75° for 50 min., then diluted with ice (250 g.) and made basic with concentrated sodium hydroxide solution. From this mixture 1200 c.c. of liquid were steam-distilled into 10% hydrochloric acid (200 c.c.). The excess of acid was removed under reduced pressure, and the residue was made alkaline and extracted with ether. The ether extract was washed with water and the solvent removed. The residue was shaken for 40 min. with potassium hydroxide (8 g.), water (22 c.c.), and benzenesulphonyl chloride (8·2 g.), then acidified with concentrated hydrochloric acid and extracted with ether. The aqueous layer was made basic and the organic material taken up in ether, washed with water, and dried. This ethereal solution was concentrated to 10 c.c. and picric acid in dry ether was added to it till it was acidic. A yellow precipitate (1·15 g.) separated which on crystallisation from benzene (85% recovery) gave cis-*perhydro*-1-*methylcyclopenta*[b]*pyrrole picrate* as needles, m. p. 218—219°. Recrystallised from benzene this had m. p. 219—219·5° (Found: C, 47·6; H, 5·05. $C_{14}H_{18}N_4O_7$ requires C, 47·45; H, 5·1%).

(*b*) A sulphuric acid solution of *N*-chloro-*N*-methyl-2-cyclopentylethylamine (from the base, 1·0 g.) was irradiated with a mercury lamp for 6 hr. Working up as above yielded the same picrate (0·50 g.), m. p. and mixed m. p. 218—219°.

cis-*Perhydrocyclopenta*[b]*pyrrole.*—Attempts to form this parent base from *N*-2-bromoethylphthalimide and ethyl 2-oxocyclopentanecarboxylate by Belleau's method [7] gave only tars. The compound, b. p. 162—165° (picrate, m. p. 110—111°), was obtained as described by Booth *et al.*[8]

When this base (1·85 g.), 40% aqueous formaldehyde (2·5 c.c.), and formic acid (4·5 c.c.) had been refluxed for 4 hr., basification and extraction with ether, etc., gave the methyl derivative whose picrate, crystallised from benzene, had m. p. and mixed m. p. 217—218°.

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[7] Belleau, *Canad. J. Chem.*, 1957, **35**, 651.
[8] Booth, King, Mason, Parrick, and Whitehead, *J.*, 1959, 1050.