318. *Stereochemical Investigations of Cyclic Bases. Part VI.* Reduction Products of 3,4-Cyclopentenopyridine and their Hofmann Degradation: Cyclisation of the Derived Methines and Related Steroidal Bases in Hot Acetic Acid.*

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cis-1-Dimethylamino-2-vinylcyclopentane, derived from *cis*-3,4-cyclopentanopiperidine by Hofmann degradation, yields a 1,2-dimethylpyrrolidinium methoacetate on being heated in acetic acid, but the reaction is much slower than for the steroidal analogues, conessimethine and dihydroconessimethine, which cyclise readily to yield pyrrolidines with predominantly the less stable configuration at the asymmetric centre >CHMe developed on cyclisation. In agreement with Ayerst and Schofield [1] (but see Prelog and Metzler [2]) we find that reduction of 3,4-cyclopentenopyridine with sodium and alcohol gives an unsaturated mixture containing some *cis*-3,4-cyclopentanopiperidine. Hofmann degradation of this mixture is also described.

ACCORDING to Prelog and Metzler,[2] reduction of 3,4-cyclopentenopyridine (I) catalytically or with sodium and ethanol yielded respectively the *cis*- (II; R = H) and the *trans*-isomer (III) of 3,4-cyclopentanopiperidine.† We briefly record experiments which show that

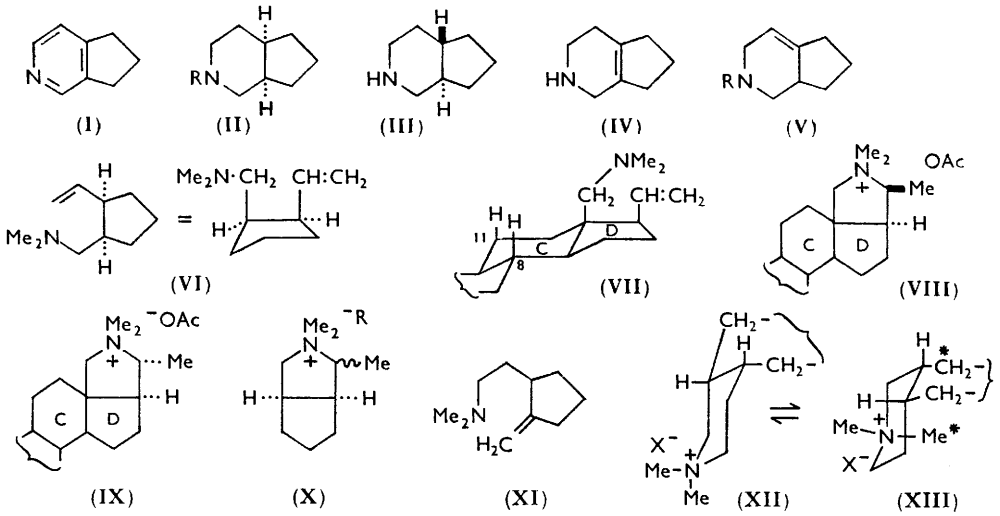
* Part V, *J.*, 1960, 945. Much of the experimental work in this paper is described by Jewers (Thesis, Sheffield, 1958).

† Where the formulæ of mono- and bi-cyclic bases represent one enantiomer, only the racemates were prepared.

[1] Ayerst and Schofield, *J.*, 1958, 4097.

[2] Prelog and Metzler, *Helv. Chim. Acta*, 1946, **29**, 1170.

while catalytic hydrogenation of the pyridine (I) yields a saturated base, reduction with sodium and ethanol affords a mixture of this with at least one unsaturated base, the latter being converted into the former by catalytic hydrogenation. During the course of our work Ayerst and Schofield [1] reached similar conclusions, the unsaturated base being formulated as (IV) or (V; R = H); there was some experimental evidence (not regarded



as conclusive) favouring (IV), although our infrared spectroscopic results favour the isomer (V; R = H) as the chief unsaturated component. Ayerst and Schofield synthesised the *cis*-isomer (II; R = H) and showed it to be identical with the product of catalytic hydrogenation of the pyridine (I), and they converted this isomer by Hofmann degradation into the methine (VI). We had also obtained this methine, together with a little recovered cyclic tertiary base (II; R = Me) by the same method; its infrared spectrum accords with formula (VI), but further investigation of its structure was rendered unnecessary by the work of Ayerst and Schofield. We also obtained a methine containing a conjugated diene system by Hofmann degradation of the unsaturated sodium–ethanol reduction product, and we have examined the cyclisation of the methines and related bases in hot acetic acid.

Cyclisation of the methine (VI) is much slower than reaction of the structurally analogous steroidal bases, conessimethine and dihydroconessimethine [3] (each with partial structure VII), probably because the axial 8- and 11-hydrogen atoms in the bases (VII) prevent free rotation of the (axial)–CH_2·NMe_2 chain, thus keeping the basic and the unsaturated groups always close together. Cyclisation of the steroidal methines in acetic acid is now * shown to yield mainly the less stable [4] salts (VIII) rather than the more stable salts (IX); evidently there is little progress towards equilibration between methine and quaternary salts in the acid solution. Cyclisation of the methine (VI) gives no observable proportion of the methoacetate of the original piperidine (II; R = Me); the product is formulated as the pyrrolidinium isomer (X; R = OAc) in which the stereochemical arrangement around the >CHMe group is possibly as in the analogously prepared steroidal methoacetates (VIII). A general study of the cyclisation of methines to quaternary salts is in hand.

The formation of the methine (VI) rather than the isomer (XI) in the Hofmann degradation of the base (II; R = Me) is of interest. Hofmann fission of a piperidine ring

* It was not possible to determine this point conclusively in earlier work,[3] using only m. p.s of methiodides as criteria.

[3] Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115.
[4] Haworth and McKenna, *Chem. and Ind.*, 1957, 1510.

(in the normally more stable chair conformation) by the *E*2 process should involve anionoid attack preferentially on an equatorial rather than an axial β-hydrogen atom;[5] this will of course be available as part of any β-methylene group in the piperidine ring, but not necessarily in a β-methine group. When a piperidine ring in a chair conformation is *trans*-fused through adjacent carbon atoms to another small reduced ring, both angular hydrogen atoms (in absence of angular substitution) are axial; one is axial and one equatorial in the corresponding *cis*-systems, but in such systems the conformation (XII; axial angular β-hydrogen atom) for metho-salts is expected to be preferred to (XIII; equatorial angular β-hydrogen atom) because of steric interaction in the conformation (XIII) between the asterisked alkyl groups.†

King and Booth[7] obtained methines structurally analogous to (VI) on Hofmann degradation of *cis*- and *trans*-decahydroisoquinoline.

Experimental

Hofmann Degradation of cis-3,4-*Cyclopentanopiperidine.*—*cis*-3,4-Cyclopentanopiperidine[2] was characterised as the picrate, m. p. 142—143° (lit.,[1,2] m. p. 142—143°, 143—144°). Methylation with formaldehyde and formic acid gave the *N*-methyl derivative, b. p. 200° (bath)/760 mm., which afforded a picrate, yellow needles (from ethanol), m. p. 211—212° (lit.,[1] m. p. 210·5—211·5°) (Found: C, 48·8; H, 5·9; N, 15·5. Calc. for $C_{15}H_{20}O_7N_4$: C, 48·9; H, 5·5; N, 15·2%), *picrolonate*, yellow prisms (from ethanol), m. p. 178—180° (Found: C, 56·2; H, 6·1; N, 17·0. $C_{19}H_{25}O_5N_5$ requires C, 56·5; H, 6·2; N, 17·4%), and methiodide, prisms (from water or acetone), m. p. 248—250° (lit.,[1] m. p. 254—255°) (Found: C, 42·6; H, 7·5; N, 5·5. Calc. for $C_{10}H_{20}NI$: C, 42·7; H, 7·2; N, 5·0%). Pyrolysis of the related metho-hydroxide at 140—200° (bath-temp.) gave a distillate consisting largely of *cis*-1-dimethylaminomethyl-2-vinylcyclopentane (VI). This base exhibited two strong infrared bands at 907 and 993 cm.$^{-1}$ ($CH{:}CH_2$)[8] which were absent in the spectrum of the hydrogenated methine. The methine picrate was obtained as yellow needles (from ethanol), m. p. 121—122° (lit.,[1] m. p. 123·5—124·5°) (Found: C, 50·1; H, 5·7; N, 14·6. Calc. for $C_{16}H_{22}O_7N_4$: C, 50·2; H, 5·8; N, 14·7%). As shown below, the pyrolysis distillate also contained a little 1-methyl-*cis*-3,4-cyclopentanopiperidine.

Cyclisation of cis-1-*Dimethylamino*-2-*vinylcyclopentane and Steroidal Analogues in Acetic Acid.*—(*a*) The foregoing pyrolysis distillate (0·25 g.) in acetic acid (2 c.c.) was heated under reflux for 4 hr., the solution was made strongly basic with concentrated aqueous potassium hydroxide and extracted with ether, and the aqueous layer then treated with excess of potassium iodide and extracted with chloroform. The infrared spectra of the basic residue (60 mg.) from the ether extract and of the derived crude picrate, m. p. 109—112°, indicated that the residue consisted of uncyclised *cis*-1-dimethylaminomethyl-2-vinylcyclopentane (*inter al.* from the strong bands at 907 and 993 cm.$^{-1}$) with some 1-methyl-*cis*-3,4-cyclopentanopiperidine (II; R = Me) which had evidently been present in the original pyrolysis distillate and had been concentrated through cyclisation of most of the methine into methoacetate. Fractional crystallisation of the crude picrate from ethanol gave pure samples of the picrates of 1-methyl-*cis*-3,4-cyclopentanopiperidine and of *cis*-1-dimethylaminomethyl-2-vinylcyclopentane, m. p. 209—210° and 121—122° respectively, which were identified by mixed m. p.s and infrared spectra.

The chloroform extract yielded 1,2,2-*dimethyl*-cis-3,4-*cyclopentanopyrrolidine methiodide* (X; R = I) (0·30 g.) which separated from water as prisms, m. p. 280—282° (Found: C, 43·1; H, 7·2; I, 45·1. $C_{10}H_{20}NI$ requires C, 42·7; H, 7·2; I, 45·1%). The crude product had the

† If the Hofmann degradations were controlled inductively by the different degrees of alkylation at the β-carbon atoms, preferential attack at β-methylene groups would also be expected, but the importance of steric (including stereoelectronic) factors in controlling the Hofmann degradation of cyclic bases has been emphasised by results described in earlier papers of this series (cf. also ref. 6).

[5] McKenna, *Chem. and Ind.*, 1954, 406.
[6] Dauben, Tweit, and Mannerkantz, *J. Amer. Chem. Soc.*, 1954, **76**, 4420; Dauben and Jiu, *ibid.*, p. 4426.
[7] King and Booth, *J.*, 1954, 3798.
[8] Bellamy, "The Infra-Red Spectra of Complex Molecules," 2nd edn., Methuen, London, 1958, p. 34.

same m. p. and infrared spectrum as a twice recrystallised specimen, and this spectrum differed considerably (particularly in the 800—1000 cm.$^{-1}$ region) from that of the methiodide of the piperidine (II; R = Me).

(*b*) When a drop of a solution of conessimethine (20 mg.) in acetic acid (1 c.c.) was added to an excess of aqueous alkali there was an immediate heavy precipitate of the almost water-insoluble base. A similar test after refluxing of the solution for 2 min. yielded only a slight precipitate, and no uncyclised base was observable after 10 minutes' refluxing.

A solution of conessimethine (78 mg.) in acetic acid (2 c.c.) was refluxed for 30 min., cooled, treated with an excess of aqueous potassium hydroxide and potassium iodide, and extracted with chloroform. The monomethiodide mixture thus obtained was reduced with lithium aluminium hydride [9] (0·2 g.) in boiling tetrahydrofuran (30 c.c.) for 72 hr.; the resulting basic mixture was refluxed in acetic acid (2 c.c.) for 30 min., and the solution was cooled, basified with potassium hydroxide, and extracted with ether; the aqueous layer was then treated with an excess of potassium iodide and extracted with chloroform. The chloroform extract yielded a product (5 mg.) identical in infrared spectrum with the monomethiodide mixture obtained by cyclisation of conessimethine; this is a further example of partial Hofmann degradation during the reduction of a 1,2-methylpyrrolidinium methiodide with lithium aluminium hydride.[10] The ether extract yielded a basic mixture (65 mg.), $[\alpha]_D$ −8° (conessine and heteroconessine have $[\alpha]_D$ −1° and −25° respectively [3]) from which conessine, m. p. and mixed m. p. 122—124°, was obtained by several recrystallisations from acetone. Chromatography of the mother-liquors yielded a little crude heteroconessine, m. p. 117—119°, undepressed on admixture with an authentic specimen of m. p. 129—131° (conessine and heteroconessine show large depressions on admixture).

Dihydroconessimethine was also rapidly cyclised in boiling acetic acid; working up as above gave a monomethiodide which on methylation gave a dimethiodide identical in infrared spectrum with dihydroconessine dimethiodide; the spectrum of dihydroheteroconessine dimethiodide is slightly different. Reduction of the monomethiodide (0·20 g.) with lithium aluminium hydride in tetrahydrofuran again resulted in partial Hofmann fission (estimated 5 mg. of methine) but yielded mainly a mixture (115 mg.) of saturated bases, $[\alpha]_D$ +46°; this mixture was mainly dihydroconessine, pure samples of which (m. p. and mixed m. p. 104—105°) were readily obtained by recrystallisation from acetone or by chromatography. The tail fractions from these processes had a melting range of 85—90°, undepressed on admixture with either dihydroconessine (m. p. 104—105°, $[\alpha]_D$ +50°) or dihydroheteroconessine (m. p. 102—103°, $[\alpha]_D$ +17°).[11]

Heating conessimethine or dihydroconessimethine in neutral or alkaline solution or treating their dimethiodides with alkali in ethylene glycol has been shown [3] qualitatively to yield mainly the hetero-bases. In recent experiments the diacid non-m thine basic mixture obtained by heating conessine dimethiodide in alkaline glycol had $[\alpha]_D$ −20°; the corresponding fraction from dihydroconessine dimethiodide had $[\alpha]_D$ +24°.

Reduction of 3,4-*Cyclopentenopyridine with Sodium and Ethanol, and Hofmann Degradation of the Products.*—The pyridine (6 g.) in boiling ethanol (300 c.c.) was reduced by addition of sodium (24 g.). The basic product yielded a picrate, m. p. 156°, evidently identical with that obtained by Prelog and Metzler [2] (m. p. 158°) and by Ayerst and Schofield [1] (m. p. 153—154°). The crude reduction product was methylated with formaldehyde and formic acid; the resulting mixture of tertiary bases was unsaturated and had a moderately strong infrared band at 796 cm.$^{-1}$ [>C:CH as in formula (V; R = Me)?].[8] The tertiary basic mixture remained unsaturated on attempted reduction with sodium and ethanol, but catalytic hydrogenation in ethanol in presence of Adams catalyst gave a saturated product; the infrared spectrum of this product lacked the band at 796 cm.$^{-1}$ and was identical with that of 1-methyl-*cis*-3,4-cyclopentanopiperidine. Some of this saturated base was already present in the original tertiary basic mixture, which yielded the *cis*-1-methyl picrate, m. p. and mixed m. p. 211—212°; the tertiary base recovered from this picrate was also identified as 1-methyl-*cis*-3,4-cyclopentanopiperidine by its infrared spectrum. The tertiary basic mixture also yielded 1-methyl-*cis*-3,4-cyclopentanopiperidine picrolonate, m. p. and mixed m. p. 178—180°, by way of the picrate (m. p. 211—212°), but this picrolonate is rather readily soluble in ethanol and direct treatment of the

[9] Cf. Cope and Bumgardener, *J. Amer. Chem. Soc.*, 1957, **79**, 960.
[10] McKenna and Tulley, *J.*, 1960, 945.
[11] The optical rotations quoted are given by Favre and Mariner, *Canad. J. Chem.*, 1958, **36**, 429.

tertiary basic mixture with ethanolic picrolonic acid gave the *picrolonate*, m. p. 200—202° (Found: C, 56·5; H, 5·9; N, 17·1. $C_{19}H_{23}O_5N_5$ requires C, 56·9; H, 5·7; N, 17·5%), of an unsaturated base as yellow needles. The same salt was obtained by converting the picrate, m. p. 156°, of the unsaturated secondary base into its base, methylation, and treatment of the tertiary base with picrolonic acid. Ayerst and Schofield have described a picrate, m. p. 151—152°, of an unsaturated tertiary base. Dr. Schofield kindly provided us with a sample of this picrate, which we have converted into the picrolonate, m. p. 200—202°, through the unsaturated tertiary base, which has the infrared band at 796 $cm.^{-1}$ mentioned above. A picrate of presumed identical structure (no mixed m. p. depression) but slightly higher m. p. (155—157°) was prepared by Ayerst and Schofield [1] by synthesis, starting from *N*-methylcyclopent-1-enylacetamide. We have compared the infrared spectra (potassium bromide discs) of samples of each picrate provided by Dr. Schofield, and find them identical.

Hofmann degradation of the mixture of cyclic tertiary bases (*via* the mixed methiodides) gave a mixture of methines, b. p. 200—210° (bath), which had strong bands at 892, 907, 980, and 993 $cm.^{-1}$; the second and fourth of these correspond to bands of the methine derived from *cis*-3,4-cyclopentanopiperidine in the starting mixture. The methine mixture also exhibited a peak at 241 mμ in ethanol or ethanolic hydrochloric acid (conjugated diene). Separation of the methines by fractional crystallisation of the picrates or fractional cyclisation in acetic acid was only partly successful (it is of interest that the cyclisation rates were comparable), but an apparently homogeneous *methiodide*, m. p. 166° (Found: C, 45·0; H, 7·1; I, 43·2. $C_{11}H_{20}NI$ requires C, 45·1; H, 6·8; I, 43·4%), was isolated as plates (from acetone); the corresponding methochloride had $\lambda_{max.}$ 241 mμ (ε 17,000).

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