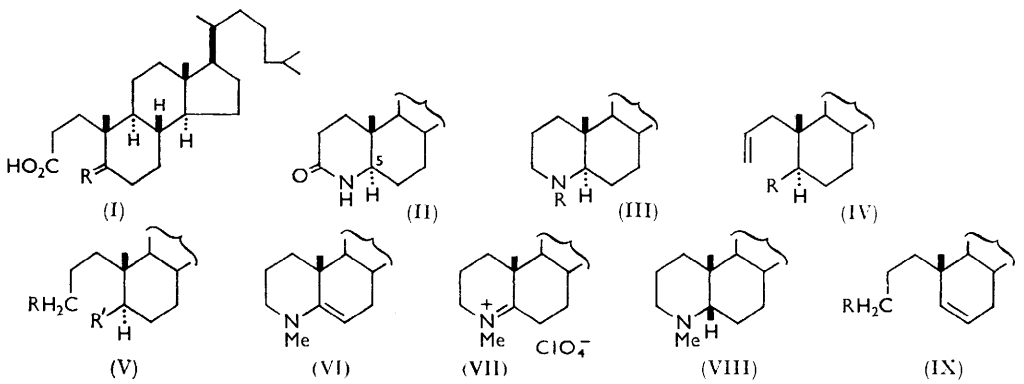
198. *Stereochemical Investigations of Cyclic Bases. Part V.* Exhaustive Methylation of* N-*Methyl*-4-*aza*-5α- *and* -5β-*cholestane, and the Reaction of the Methines with Acetic Acid: the Possibility of "* α′β *" Hofmann Elimination with Cyclic Ammonium Hydroxides.*

By J. McKenna and A. Tulley.

Bolt's aza-steriod,[1] m. p. 116—117°, has been shown to be 4-aza-5α-cholestane; from the *N*-methyl derivative the isomeric *N*-methyl-4-aza-5β-cholestane has been obtained by oxidation with mercuric acetate followed by catalytic hydrogenation of the perchlorate of the resulting enamine. Hofmann degradation of *N*-methyl-4-aza-5α- and -5β-cholestane yielded respectively 5β-dimethylamino-3,5-seco-A-norcholest-2-ene and 3-dimethylamino-3,5-seco-A-norcholest-5-ene. The latter methine was not cyclised in boiling acetic acid, but the former yielded the methoacetate of *N*,2ξ-dimethyl-3-aza-A-nor-5α-cholestane, from which the cyclic tertiary base was obtained by reduction of the related quaternary iodide with lithium aluminium hydride. The results are discussed and compared with those previously obtained with other cyclic bases, and the possibility of "α′β" Hofmann elimination arising in such systems is examined.

Increasing attention has recently † been given to aza-steroids in view of their general structural interest and possible therapeutic value. Some of them appear to be suitable for the study of ring-fission and other reactions in rigid heterocyclic systems. The synthesis and exhaustive methylation of *N*-methyl-4-aza-5α- and -5β-cholestane (III; R = Me and VIII respectively) are described in this paper, together with related work.



In 1938 Bolt [1] prepared the lactam (II) by reduction of the ketoxime (I; R = N·OH) with sodium and alcohol followed by acidification of the alkaline reduction mixture; whether this lactam was a derivative of 5α- or 5β-cholestane was not discussed but modern conformational theory indicates that the N–$C_{(5)}$ bond is probably equatorial, as it is in the A/B-*trans*-structure (II), and this assignment is confirmed by the degradative evidence discussed below. Bolt reduced his lactam to the secondary base (III; R = H) with sodium and pentanol; we have repeated this work, but find that the modern procedure using lithium aluminium hydride is preferable. Hofmann degradation of *N*-methyl-4-aza-5α-cholestane (III; R = Me) yielded 5β-dimethylamino-3,5-seco-A-norcholest-2-ene

* Part IV, *J.*, 1959, 137.

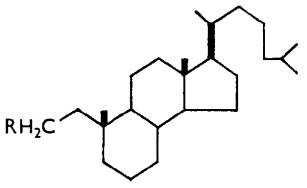
† Shoppee and Sly,[2a] for instance, have announced an extensive synthetical programme; these authors and, more recently, Mazur [2b] give references to earlier work. Most authors (including those named) have so far confined themselves to the more readily accessible aza-homo-steroids.

[1] Bolt, *Rec. Trav. chim.*, 1938, **57**, 905; U.S.P. 2,227,876/1941.

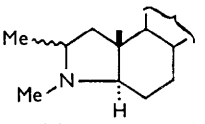
[2] (*a*) Shoppee and Sly, *J.*, 1958, 3458; (*b*) Mazur, *J. Amer. Chem. Soc.*, 1959, **81**, 1454.

(IV; R = NMe_2); the structure of this methine was deduced from its infrared absorption spectrum, from the difficulty in eliminating nitrogen from the dihydromethine (V; R = H, R′ = NMe_2) by further Hofmann degradation (equatorial dimethylamino-group [3,4]) and from the synthesis (following paragraph) of the other possible dihydromethine (V; R = NMe_2, R′ = H).

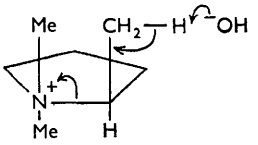
Leonard and his collaborators have extensively investigated [5] the oxidation of cyclic tertiary bases with mercuric acetate; this procedure, followed by hydrogenation of the resulting enamines or their salts is occasionally a useful method for effecting epimerisation at an asymmetric centre adjacent to the ring nitrogen atom.[6] Oxidation of *N*-methyl-4-aza-5α-cholestane with mercuric acetate gave *N*-methyl-4-azacholest-5-ene (VI) characterised as the perchlorate (VII): the assigned structures accord with the infrared and ultraviolet absorption spectra. Catalytic hydrogenation of the perchlorate in ethanol yielded a mixture of *N*-methyl-4-aza-5α- and -5β-cholestanes (III; R = Me; and VIII; respectively) which were readily separated by chromatography. Hofmann degradation of *N*-methyl-4-aza-5β-cholestane (VIII) yielded 3-dimethylamino-3,5-seco-A-norcholest-5-ene (IX; R = NMe_2) together with a little of the original cyclic tertiary base (VIII). The structure of the methine was shown by its infrared absorption spectrum, by the identity of the dihydromethine (V; R = NMe_2, R′ = H) with a specimen prepared independently from 3,5-seco-A-norcholestan-3-oic acid (X; R = CO_2H) and by further Hofmann degradation of the dihydromethine to 3,5-seco-A-norcholest-2-ene (IV; R = H).



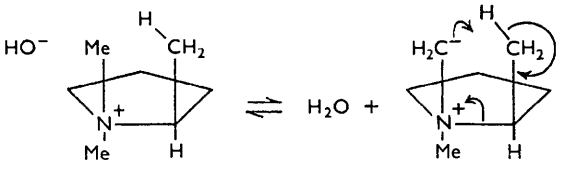
(X)



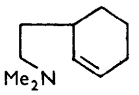
(XI)



(XII)



(XIII)



(XIV)

Catalytic hydrogenation of this unsaturated hydrocarbon gave 3,5-seco-A-norcholestane (V; R = R′ = H), which was also obtained as a terminal product of exhaustive methylation and catalytic hydrogenation from the isomeric aza-steroid (III; R = Me).

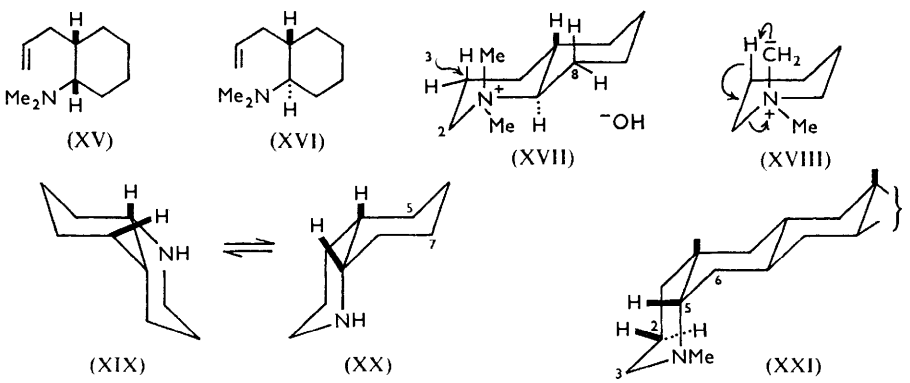
The methine (IV; R = NMe_2) was cyclised to a methoacetate in hot acetic acid, the reaction being very rapid at the boiling point of the solvent. The product was isolated as methiodide and converted by reduction with lithium aluminium hydride in tetrahydrofuran [7] into the related tertiary base * (XI), so formulated because it was not identical with the

* This base, m. p. 69—70°, appeared to be homogeneous, but there is a possibility that the methiodide is a mixture of 2-epimers. Different samples of methiodide gave different proportions of the base (XI) and the methine (IV; R = NMe_2) on treatment with lithium aluminium hydride, and the reason for this has not been examined.

[3] Haworth, McKenna, and Powell, *J.*, 1953, 1110; Gent and McKenna, *J.*, 1956, 573.
[4] Gent and McKenna, *J.*, 1959, 137.
[5] Leonard and Morrow, *J. Amer. Chem. Soc.*, 1958, **80**, 371, and numerous earlier papers in the same journal.
[6] Cf. Favre and Mariner, *Canad. J. Chem.*, 1958, **36**, 429.
[7] Cf. Cope and Bumgardner, *J. Amer. Chem. Soc.*, 1957, **79**, 960.

aza-steroid (III; R = Me) from which the methine had been derived, and from consideration of analogous cases where a pyrrolidine rather than a piperidine ring is formed.[8,9,10] Hofmann degradation of the new base (XI) gave back the methine (IV; R = NMe_2) apparently exclusively, in contrast to similar degradation of the aza-steroid (III; R = Me) when some of the original cyclic tertiary base is also formed by elimination of methanol from the quaternary hydroxide. An alternative method to chromatography for separation of the tertiary bases in the Hofmann mixture from the degradation of the aza-steroid (III; R = Me) consisted in treatment of the mixture with hot acetic acid, separation of the product into recovered cyclic base (III; R = Me) and metho-salt, and Hofmann degradation of this to the methine (IV; R = NMe_2). Some of this methine was also formed during reduction of the methiodide of the tertiary base (XI) with lithium aluminium hydride; a similar result has been observed with the methiodides of other 1,2-dimethylpyrrolidines.[10] The particular ease of Hofmann fission of 2-methylpyrrolidinium quaternary hydroxides was demonstrated in Part II [11] and discussed in terms of the *E*2 mechanism (as in XII) which seems appropriate for the spiro-quaternary hydroxides used in the investigation. Wittig [12] and Weygand's [13] " α'β " elimination mechanism, however (which requires presence of an ^+NMe group) has been shown [13] to be competitive with the *E*2 process above 100° in the degradation of ethyltrimethylammonium hydroxide, and could also readily operate (as in XIII) in the Hofmann fission of 1,2-dimethylpyrrolidinium methohydroxides (*e.g.*, the methohydroxide of the base XI).* The geometrical ideals for the *E*2 (*trans* coplanar H–C–C–N^+) and the α'β [*cis*-coplanar H–C–C–N^+–C(methyl)] mechanism, however, are quite distinct, so that more typically one mechanism or the other will be favoured with cyclic ammonium hydroxides.

The methine (IX; R = NMe_2) in contrast to its isomer (IV; R = NMe_2) did not cyclise on long boiling in acetic acid, although the base (XIV) with one methylene group less in the side chain does undergo this reaction.[9] These results accord with general geometrical considerations governing ring-closures.



The aza-steroids (VIII) and (III; R = Me) are analogues of *cis*- and *trans*-decahydro-1-methylquinoline, which yield the methines (XV) and (XVI) respectively, on Hofmann degradation.[9] As has been previously pointed out,[14] the direction of fission with the

* Trialkylcyclopentylammonium hydroxides could readily yield cyclopentenes by the same mechanism. Degradation [11] of cyclohexylcyclopentyldimethylammonium hydroxide yields cyclopentene rather than cyclohexene.

[8] Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115.
[9] Bailey, Haworth, and McKenna, *J.*, 1954, 967.
[10] Jewers and McKenna, unpublished work.
[11] Jewers and McKenna, *J.*, 1958, 2209.
[12] Wittig and Polster, *Annalen*, 1958, **612**, 102.
[13] Weygand, Daniel, and Simon, *Chem. Ber.*, 1958, **91**, 1691.
[14] McKenna, *Chem. and Ind.*, 1954, 406.

trans-quaternary hydroxide (XVII) is probably due to the necessarily equatorial attachment of the nitrogen atom to the six-carbon ring, but a suitable geometrical disposition of $N-C_{(2)}-C_{(3)}-H$ (*eq*) is available for the normal *E*2 process leading to the methine (XVI). A similar interpretation can be applied to the reaction of the A/B-trans-aza-steroid (III; R = Me) which affords the structurally analogous methine (IV; R = NMe_2). These methines do not appear to arise by the α′β process involving transfer (cf. XVIII) of the axial 3-hydrogen atom since, from a geometrical standpoint, fission of the bond between nitrogen and the adjacent bicyclic carbon atom [with transfer of hydrogen atom from position 8 in (XVII) or position 6 in the steroidal analogue] could take place equally readily, as could formation of an olefin by a similar mechanism on pyrolysis of an alicyclic equatorial steroidal quaternary ammonium hydroxide. The isomeric methines have not been observed, and only low yields of olefins are obtained from the alicyclic quaternary bases. In the latter case, however, where the alternative *E*2 mechanism is not favoured, the α′β mechanism may well operate: certainly, elimination of $^+NMe_3$ and (unactivated *) *cis*-β-hydrogen has been observed with some equatorial quaternary ammonium salts, a good example [4] being 5α-cholestan-6α-yltrimethylammonium hydroxide. The fission illustrated in (XVIII) may thus arise in a piperidine so substituted that the *E*2 mechanism cannot readily operate, but a similar reaction with a pyrrolidine system is probably ruled out by the geometry of the five-membered ring.

The methines (XV) and (IX; R = NMe_2) from *cis*-decahydro-1-methylquinoline and *N*-methyl-4-aza-5β-cholestane (VIII) respectively are not structurally analogous, unlike those just discussed from the corresponding *trans*-bases, and these diverse results are of some interest. *cis*-Decahydroquinoline, like *cis*-decalin, would be expected to exist as two readily interconvertible twin-chair conformations (XIX and XX), but the conformations of the metho-salts will probably be related to (XIX) since the bulky quaternary group will adopt the equatorial position with respect to the six-carbon ring.† Hence Hofmann pyrolysis of the *cis*-methohydroxide will yield the methine (XV). The only all-chair conformation for the *cis*-aza-steroid (VIII), however, is (XXI), where the $N-C_{(5)}$ bond is axial, and the molecular geometry is thus particularly suitable for *E*2 Hofmann fission leading to the methine (IX; R = NMe_2). The geometrical disposition of $N-C_{(3)}-C_{(2)}-H(\beta)$ would also be suitable for *E*2 fission to an isomeric methine of type (XV); this reaction, however, does not occur, probably because strain due to attachment of the quaternary group axial to ring B would not thereby be reduced, and because the developing double bond would be at $C_{(2)}-C_{(3)}$ in the partially opened aza-5β-cholestane framework, a position where it is certainly difficult to form a double bond in the normal 5β-cholestane nucleus.[17]

In this and several other laboratories steroidal amines have frequently been encountered as uncrystallisable oils. Some of the bases described in this paper (and some non-basic compounds in which ring A is opened) are oils, but three of the new amines, *viz.*, (III; R = Me), (V; R = H, R′ = NMe_2), and (XI) are crystalline.

* *cis*-Elimination of $^+NMe_3$ and a strongly activated β-hydrogen atom can readily occur, but probably by the *E*2 process.[15]

† For a detailed discussion of the special steric interactions which may arise in compounds containing *cis*-bicyclic systems see, *e.g.*, Dauben and his collaborators.[16] In the case of metho-salts related to the conformation (XX), the interactions arise between the axial *N*-Me group and the methylene groups (or more precisely the axial hydrogen atoms thereof) at $C_{(5)}$ and $C_{(7)}$. Examination of accurate scale models indicates that these interactions are reduced somewhat in metho-salts in an analogous conformation derived from *cis*-octahydro-*N*-methylindole (although these derivatives will also prefer a conformation with the quaternary group equatorial to the six-carbon ring). Hence the Hofmann degradation [9] of *cis*-octahydro-*N*-methylindole methohydroxide to the methine (XIV) may be yet another example of the ready *E*2 fission of an axial quaternary ammonium group, although the α′β mechanism with other conformations is also a possibility.

[15] See Weinstock and Bordwell, *J. Amer. Chem. Soc.*, 1955, **77**, 2706; Hodnett and Flynn, *ibid.*, 1957, **79**, 2300; ref. 13.

[16] Dauben, Tweit, and Mannarkantz, *J. Amer. Chem. Soc.*, 1954, **76**, 4420; Dauben and Jiu, *ibid.*, p. 4426.

[17] For a recent discussion see Turner, Meador, and Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.

Experimental

Optical rotations, except where otherwise stated, refer to chloroform solutions at room temperature (17—23°) at concentrations of 1—5%. Light petroleum refers to the fraction of b. p. 40—60°. Spence's alumina (Type H) activated at 160° for 10 min., and dry " AnalaR "-grade solvents were used for chromatography.

4-Aza-5α-cholestan-3-one.—The oxime [1] (0·84 g.) from 5-oxo-3,5-seco-A-norcholestan-3-oic acid [18] in boiling ethanol (20 c.c.) was reduced with sodium (1·8 g.). The reaction mixture was cooled, diluted with water, and acidified with acetic acid, and the white precipitate (0·78 g.) was separated into 4-aza-5α-cholestan-3-one (0·38 g.), m. p. 244—246°, and an acidic residue (0·40 g.), m. p. 160—170°. This residue appeared to be a mixture of keto- (m. p. 150°) and hydroxyimino-acid (m. p. 188°) and was converted by re-oximation into the pure hydroxyimino-acid (0·37 g.), m. p. and mixed m. p. 188°, from which more of the lactam was prepared in a second reduction. Bolt [1] records m. p. 253—255° for this lactam.

4-Aza-5α-cholestane.—(*a*) 4-Aza-5α-cholestan-3-one (0·55 g.) in boiling pentanol (45 c.c.) was reduced with sodium (2·2 g.), the mixture was poured into water, the pentanol was removed by steam-distillation, and the residue was extracted with ether. The extract yielded 4-aza-5α-cholestane which on recrystallisation from methanol formed irregular prisms (0·48 g.), m. p. 114—115°, $[\alpha]_D$ +40° (in $CHCl_3$), +46° (in pyridine) (Found: C, 83·9; H, 12·4; N, 3·5. Calc. for $C_{26}H_{47}N$: C, 83·6; H, 12·7; N, 3·7%). Bolt [1] gives m. p. 116—117°, $[\alpha]_D$ +48° (in pyridine) for this base.

(*b*) The lactam (0·1 g.) was reduced (Soxhlet method) with lithium aluminium hydride (0·1 g.) in ether (125 c.c.) for 48 hr. The basic product had m. p. 114—115°, undepressed with a sample prepared by method (*a*).

4-Aza-5α-cholestane hydrochloride was readily soluble in water and dilute hydrochloric acid, and separated from acetone-chloroform as irregular prisms, m. p. 246—250° (Found: N, 3·5; Cl, 8·9. $C_{26}H_{48}NCl$ requires N, 3·4; Cl, 8·7%).

N-Methyl-4-aza-5α-cholestane.—4-Aza-5α-cholestane was methylated in the usual way [19] with formaldehyde and formic acid, and the tertiary *base* was recrystallised from methanol as rectangular prisms, m. p. 70—71°, $[\alpha]_D$ +13° (Found: C, 83·8; H, 12·8; N, 3·4. $C_{27}H_{49}N$ requires C, 83·7; H, 12·7; N, 3·6%). Bolt [1] records m. p. 61—62° for a product obtained from the secondary aza-steroid and methyl iodide. The *hydrochloride* separated from acetone as prisms, m. p. 268—274° (Found: N, 3·2; Cl, 8·3. $C_{27}H_{50}NCl$ requires N, 3·3; Cl, 8·4%), and was insoluble in water and dilute hydrochloric acid. The *perchlorate*, which separated from ethanol in fine needles, had m. p. 248—250° (Found: C, 66·1; H, 10·0; Cl, 7·4. $C_{27}H_{50}NClO_4$ requires C, 66·6; H, 10·3; Cl, 7·3%). The *methiodide*, prepared from either the secondary or the tertiary base, separated from acetone in rectangular prisms, m. p. 284—286°, $[\alpha]_D$ +5° (Found: C, 63·3; H, 9·8; N, 2·4. $C_{28}H_{52}NI$ requires C, 63·5; H, 9·8; N, 2·6%). Reduction [7] of the methiodide (0·14 g.) with lithium aluminium hydride (0·25 g.) in dry tetrahydrofuran (125 c.c.) (Soxhlet procedure) yielded the tertiary base (0·10 g.), m. p. and mixed m. p. 70—71°.

Hofmann Degradation of N-Methyl-4-aza-5α-cholestane.—A solution of the foregoing methiodide (0·1 g.) in aqueous methanol was converted in the usual way into the methohydroxide, which was pyrolysed at 150—180° (bath-temp.)/0·002 mm. The distillate (0·06 g.) from this and similar experiments was treated in either of two ways.

(*a*) The pyrolysis distillate (0·06 g.) was dissolved in acetic acid (3 c.c.) and was refluxed for 3 hr. and then concentrated under reduced pressure. The residue was made strongly basic with concentrated aqueous potassium hydroxide and extracted with ether. The aqueous portion was treated with excess of potassium iodide and extracted with chloroform. The ether extract yielded *N*-methyl-4-aza-5α-cholestane (0·035 g.), m. p. and mixed m. p. 70—71° (from methanol). The chloroform extract contained *N*,2ξ-dimethyl-3-aza-A-nor-5α-cholestane methiodide (0·022 g.), hexagonal prisms (from acetone), m. p. 292—294°, which differed in its infrared spectrum from *N*-methyl-4-aza-5α-cholestane methiodide. (The cyclisation and the new methiodide are described more fully in a subsequent paragraph.) The new methiodide (0·037 g.) was converted into the methohydroxide which was pyrolysed to give 5β-dimethylamino-3,5-seco-A-norcholest-2-ene (0·019 g.) identical in specific rotation ($[\alpha]_D$ +27°) and infrared spectrum with the compound isolated by chromatography by method (*b*).

[18] Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579.
[19] Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.

(*b*) The pyrolysis distillate (0·1 g.) was chromatographed on alumina (3 g.). Elution with light petroleum followed by ether gave 5β-*dimethylamino*-3,5-*seco*-A-*norcholest*-2-*ene* (0·056 g.) as a colourless oil, $[\alpha]_D$ +27° (Found: C, 83·8; H, 12·8; N, 3·6. $C_{28}H_{51}N$ requires C, 83·8; H, 12·7; N, 3·5%); further elution with ether yielded *N*-methyl-4-aza-5α-cholestane (0·039 g.), m. p. and mixed m. p. 70—71° (from methanol). The methine was unsaturated to acid permanganate, and its infrared spectrum exhibited two strong bands at 910 and 988 cm.$^{-1}$ (–CH=CH_2).[20] Catalytic hydrogenation of the methine in acetic acid–ethanol in presence of a platinum catalyst resulted in the rapid uptake of one mol. of hydrogen, yielding 5β-*dimethylamino*-3,5-*seco*-A-*norcholestane*, which separated from acetone–methanol as prisms, m. p. 51—52°, $[\alpha]_D$ +11° (Found: C, 83·3; H, 13·1. $C_{28}H_{53}N$ requires C, 83·4; H, 13·2%). This base was saturated to acidic permanganate and exhibited no infrared band at 910 or 988 cm.$^{-1}$ (or elsewhere in the C–H deformation area). The *hydrochloride*, m. p. 198—200° (Found: Cl, 8·0. $C_{28}H_{54}NCl$ requires Cl, 8·1%), which was insoluble in water and dilute hydrochloric acid, and the *methiodide*, m. p. 170° (Found: I, 22·8. $C_{29}H_{56}NI$ requires I, 23·3%), were prepared.

Hofmann Degradation of 5β-*Dimethylamino*-3,5-*seco*-A-*norcholestane*.—The foregoing methiodide (0·29 g.) was converted into the corresponding methohydroxide which was pyrolysed at 160° (bath)/0·001 mm. and the distillate (0·185 g.) was separated into basic and neutral fractions by careful treatment with hydrochloric acid. The basic product (0·13 g.), on recrystallisation from methanol, had m. p. 51—52°, undepressed on admixture with authentic 5β-dimethylamino-3,5-seco-A-norcholestane (Found: C, 83·5; H, 13·0; N, 3·8. Calc. for $C_{28}H_{53}N$: C, 83·4; H, 13·2; N, 3·5%); the hydrochloride, m. p. and mixed m. p. 198—200°, was also examined. The neutral product, 3,5-seco-A-norcholest-5-ene, was an oil, which gave a yellow colour with tetranitromethane and exhibited an infrared band at 726 cm.$^{-1}$ (*cis*- –CH=CH–).[20] Catalytic hydrogenation in acetic acid–ether in presence of a platinum catalyst gave an oil which gave no colour with tetranitromethane and was identical in infrared spectrum with synthetic 3,5-seco-A-norcholestane prepared as described below.

The neutral fraction in the Hofmann pyrolysis mixture could also be isolated by treatment of the mixture with methyl iodide, and separation of the petroleum-insoluble methiodide.

4-*Azacholest*-4-*ene Methoperchlorate* (VII).—A solution of mercuric acetate (0·8 g.) and *N*-methyl-4-aza-5α-cholestane (0·18 g.) in 20% aqueous acetic acid (5 c.c.) was heated to 100° and stirred mechanically. Mercurous acetate began to separate in a few minutes. After 2 hr. the mixture was cooled, mercurous acetate (0·236 g.) was separated by filtration and washed with alcohol, the combined filtrate and washings were saturated with hydrogen sulphide, and the resultant mercuric sulphide was removed in the centrifuge. The supernatant liquid was concentrated to 10 c.c. and basified with concentrated aqueous sodium hydroxide, and the precipitated base was extracted with ether and treated with alcoholic perchloric acid. The 4-*azacholest*-4-*ene methoperchlorate* so obtained separated from ethanol as irregular prisms (0·164 g.) (Found: N, 2·8; Cl, 7·7. $C_{27}H_{48}O_4NCl$ requires N, 2·9; Cl, 7·3%), m. p. 230—232° depressed to *ca.* 210° on admixture with *N*-methyl-4-aza-5α-cholestane perchlorate (m. p. 248—250°). The infrared spectrum of the unsaturated perchlorate showed a band at 1654 cm.$^{-1}$ ($^+$N=C stretching). The corresponding unsaturated base, *N*-methyl-4-azacholest-5-ene, was an oil which rapidly discoloured in the air and had bands at 793, 816, and 1634 cm.$^{-1}$ (>C=CH–),[21,22] and at 221 mμ (ε 8800).

N-*Methyl*-4-*aza*-5β-*cholestane*.—The unsaturated perchlorate (0·135 g.) in ethanol (15 c.c.) was hydrogenated at 38° in presence of platinum catalyst (0·01 g. of PtO_2); one mol. of hydrogen was rapidly absorbed. After 2 hr. the catalyst was filtered off, the filtrate was evaporated, the residue was treated with excess of sodium hydroxide, and the saturated basic oil (0·102 g.) liberated was extracted with ether and chromatographed on alumina (3 g.). Elution with light petroleum and ether gave a colourless oil (0·085 g.) followed by a crystalline solid (0·015 g.); separation of these components could readily be followed by infrared spectroscopic examination of the fractions from the column, the oil having a band at 1012 cm.$^{-1}$ and the solid one at 1024

[20] Bellamy, "The Infra-Red Spectra of Complex Molecules," 2nd edn., Methuen, London, 1958, pp. 34 *et seq.*

[21] Leonard, Miller, and Thomas, *J. Amer. Chem. Soc.*, 1956, **78**, 3463; Opitz, Hellmann, and Schubert, *Annalen*, 1959, **623**, 112.

[22] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2408.

cm.$^{-1}$ [possibly corresponding to C–N (*ax*) and C–N (*eq*) stretching frequencies respectively *]. The solid after recrystallisation from methanol had m. p. 70—71° alone or mixed with *N*-methyl-4-aza-5α-cholestane. The oily N-*methyl*-4-*aza*-5β-*cholestane* had b. p. 180° (bath)/0·001 mm., $[\alpha]_D$ +28° (Found: C, 83·7; H, 12·6. $C_{27}H_{49}N$ requires C, 83·7; H, 12·7%). The *hydrochloride* formed hexagonal prisms (from acetone), m. p. 238—240° (Found: N, 3·2; Cl, 8·4. $C_{27}H_{50}NCl$ requires N, 3·3; Cl, 8·4%). The *methiodide*, rectangular prisms from acetone, had m. p. 267—268° (Found: C, 63·3; H, 9·8. $C_{28}H_{52}NI$ requires C, 63·5; H, 9·8%).

Hofmann Degradation of N-*Methyl*-4-*aza*-5β-*cholestane*.—The foregoing methiodide (0·245 g.) was converted into methohydroxide which was pyrolysed at 150—200° (bath)/0·005 mm. and the distillate (0·186 g.) was chromatographed on alumina (6 g.), elution being with light petroleum and ether. The first compound eluted (0·027 g.) was identified as *N*-methyl-4-aza-5β-cholestane by its infrared spectrum. The second compound (0·132 g.) was an oil, b. p. 180° (bath)/0·001 mm., $[\alpha]_D$ +5°, unsaturated to acid permanganate, $\nu_{max.}$ 725 cm.$^{-1}$ (*cis*- CH=CH–);[20] it is formulated as 3-*dimethylamino*-3,5-*seco*-A-*norcholest*-5-*ene* (Found: C, 83·4; H, 12·5. $C_{28}H_{51}N$ requires C, 83·8; H, 12·7%). Catalytic hydrogenation in ethanol in the presence of a platinum catalyst gave 3-dimethylamino-3,5-seco-A-norcholestane, $[\alpha]_D$ +27°, identical in infrared spectrum with a sample independently synthesised (next paragraph); the hydrochloride, m. p. and mixed m. p. 227—229° (depressed to 176—178° on admixture with the hydrochloride, m. p. 198—200°, of the other dihydromethine, 5β-dimethylamino-3,5-seco-A-norcholestane), and the methiodide, m. p. and mixed m. p. 266—268°, were also identical in infrared spectra with the salts of the authentic tertiary base.

3-*Dimethylamino*-3,5-*seco*-A-*norcholestane from* 3,5-*Seco*-A-*norcholestan*-3-*oic Acid*.—(*a*) The acid, m. p. 137°, $[\alpha]_D$ +24° (0·4 g.), and urea (0·4 g.) were heated together[24] at 150—180° (bath) with intermittent stirring for 7 hr., ammonia being evolved at first. The product was taken up in ether and washed with sodium hydroxide and then with water, and the ether was evaporated. The residual 3,5-*seco*-A-*norcholestan*-3-*amide* (0·33 g.), recrystallised from ether–light petroleum, had m. p. 139—140° (depressed to 124—128° on admixture with the acid, m. p. 137°), $[\alpha]_D$ +30° (Found: C, 80·1; H, 12·2; N, 3·9. $C_{26}H_{47}ON$ requires C, 80·2; H, 12·1; N, 3·6%). The infrared spectrum was that of an amide. Reduction of the amide (0·1 g.) with lithium aluminium hydride (0·2 g.) in ether (50 c.c.) for 48 hr. gave 3-*amino*-3,5-*seco*-A-*norcholestane*, b. p. 190° (bath)/0·005 mm., $[\alpha]_D$ +36° (Found: C, 83·1; H, 13·1. $C_{26}H_{49}N$ requires C, 83·2; H, 13·1%). The *hydrochloride* had m. p. 255—256° (Found: C, 75·4; H, 11·9; Cl, 8·7. $C_{26}H_{50}NCl$ requires C, 75·8; H, 12·2; Cl, 8·6%). Methylation with formaldehyde and formic acid gave 3-*dimethylamino*-3,5-*seco*-A-*norcholestane*, b. p. 190° (bath)/0·005 mm., $[\alpha]_D$ +27° (Found: C, 83·2; H, 13·0. $C_{28}H_{53}N$ requires C, 83·4; H, 13·2%). The *hydrochloride* had m. p. 227—229° (Found: N, 3·2; Cl, 8·1. $C_{28}H_{54}NCl$ requires N, 3·2; Cl, 8·1%), and the *methiodide* had m. p. 266—268° (Found: N, 2·8; I, 23·5. $C_{29}H_{56}NI$ requires N, 2·6; I, 23·3%).

(*b*) Methylation of 3,5-seco-A-norcholestan-3-oic acid with diazomethane gave the *methyl ester* as an oil, b. p. 178° (bath)/0·005 mm., which slowly crystallised at 0°, $[\alpha]_D$ +23° (Found: C, 80·2; H, 12·1. $C_{27}H_{48}O_2$ requires C, 80·2; H, 11·9%). This compound has been previously prepared by Tschesche,[25] but without characterisation. Treatment of the ester in an autoclave with excess of dimethylamine at 130° for 24 hr. gave NN-*dimethyl*-3,5-*seco*-A-*norcholestan*-3-*amide* as an oil, $[\alpha]_D$ +24° (Found: C, 80·7; H, 11·8. $C_{28}H_{51}ON$ requires C, 80·6; H, 12·2%), which had an infrared spectrum with the appropriate (amide) characteristics. Reduction of this amide with lithium aluminium hydride in ether gave 3-dimethylamino-3,5-seco-A-norcholestane, $[\alpha]_D$ +27° (Found: C, 83·1; H, 12·8. Calc. for $C_{28}H_{53}N$: C, 83·4; H, 13·2%), which agreed in infrared spectrum with the base prepared by method (*a*).

Hofmann Degradation of 3-*Dimethylamino*-3,5-*seco*-A-*norcholestane*.—Pyrolysis of 3-dimethylamino-3,5-seco-A-norcholestane methohydroxide (from 0·09 g. of methiodide) at 180—200° (bath)/0·001 mm. gave a distillate (0·056 g.) which was separated by treatment with hydrochloric acid into 3-dimethylamino-3,5-seco-A-norcholestane (0·03 g. of hydrochloride, m. p.

* Acyclic amines exhibit a C–N stretching band in the region 1020—1220 cm.$^{-1}$. In polycyclic systems the stretching frequencies of C–X bonds are usually higher for an equatorial than for an axial substituent X,[23] and we have found (unpublished results) the same to be true for a number of pairs of epimeric alicyclic steroidal tertiary amines.

[23] Barton and Cookson, *Quart. Rev.*, 1956, 64.

[24] Cf. Cherbuliez and Landolt, *Helv. Chim. Acta*, 1946, **29**, 1438; preparation of the amide by the acid chloride route was less satisfactory.

[25] Tschesche, *Annalen*, 1932, **498**, 185.

227—229°) and 3,5-seco-A-norcholest-2-ene (0·025 g.), b. p. 190—200° (bath)/0·005 mm., $[\alpha]_D$ +22°, the infrared spectrum of which showed strong bands at 906 and 992 cm.$^{-1}$ ($-CH=CH_2$).[20] Catalytic hydrogenation in acetic acid–ether in presence of a platinum catalyst gave 3,5-*seco*-A-*norcholestane*, b. p. 180° (bath)/0·001 mm., $[\alpha]_D$ +20° (Found: C, 86·4; H, 13·4. $C_{26}H_{48}$ requires C, 86·7; H, 13·3%), saturated to tetranitromethane and identical in infrared spectrum with the reduction product from 3,5-seco-A-norcholest-5-ene described above.

Cyclisation of 5β-*Dimethylamino*-3,5-*seco*-A-*norcholest*-2-*ene in Acetic Acid.*—A solution of the methine (0·061 g.) in acetic acid (3 c.c.) was refluxed and tested from time to time for residual uncyclised base by addition of a drop to aqueous alkali. Only a little methine remained after 5 min. and none after 20 min. In another experiment a solution of the methine (0·097 g.) in acetic acid (5 c.c.) was refluxed for 3 hr., cooled, treated with excess of concentrated aqueous potassium hydroxide and potassium iodide, and extracted three times with chloroform; the extract on evaporation gave a quantitative yield of *N*,2ξ-dimethyl-3-aza-A-norcholestane methiodide (or a mixture of 2-epimers), hexagonal prisms (from acetone), m. p. 292—294° (Found: N, 2·9; I, 24·3. Calc. for $C_{28}H_{52}NI$: N, 2·6; I, 24·0%). The methiodide (0·116 g.) was treated with lithium aluminium hydride (400 mg.) in boiling tetrahydrofuran (50 c.c.) for 72 hr. and the oily basic product (0·078 g.) was separated by chromatography into 5β-dimethylamino-3,5-seco-A-norcholest-2-ene (0·009 g.; first fraction) identified by its infrared spectrum (bands at 910 and 990 cm.$^{-1}$) and reaction with acid permanganate, and N,2ξ-*dimethyl*-3-*aza*-A-*norcholestane* (0·059 g.; second fraction), prisms (from acetone), m. p. 69—70°, depressed to 52—56° on admixture with *N*-methyl-4-aza-5α-cholestane (m. p. 70—71°), $[\alpha]_D$ +16° (Found: C, 83·5; H, 12·6; N, 3·8. $C_{27}H_{49}N$ requires C, 83·7; H, 12·7; N, 3·6%). This base was more readily isolated from the basic mixture from the reduction process by treatment of the mixture with hot acetic acid to cyclise the methine fraction; after appropriate treatment the cyclised methiodide (or methiodide mixture), m. p. and mixed m. p. 285—290°, was also obtained in such experiments.

When 5β-dimethylamino-3,5-seco-A-norcholest-2-ene (0·042 g.) was treated with acetic acid (3 c.c.) at 70° for 22 hr., none of the methine acetate remained. The cyclised product was isolated as before as methiodide (0·051 g.) which on reduction with lithium aluminium hydride in tetrahydrofuran gave a basic mixture (0·033 g.) affording by chromatography the methine (0·020 g.) and *N*,2ξ-dimethyl-3-aza-A-norcholestane (0·012 g.), m. p. 69°, undepressed on admixture with a specimen obtained from a cyclisation in boiling acetic acid.

Attempted Cyclisation of 3-*Dimethylamino*-3,5-*seco*-A-*norcholest*-5-*ene.*—The methine (0·070 g.) in acetic acid (4 c.c.) was refluxed for 6 hr., and the solution was cooled, treated with excess of potassium hydroxide and potassium iodide, and extracted with ether followed by chloroform. Evaporation of the ether yielded the methine (0·066 g.) (Found: C, 84·0; H, 12·8. Calc. for $C_{28}H_{51}N$: C, 83·8; H, 12·7%), identical in infrared spectrum and specific rotation with the starting product. No methiodide was obtained from the chloroform extract.

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