Novel Heterocyclic Steroidal Amines

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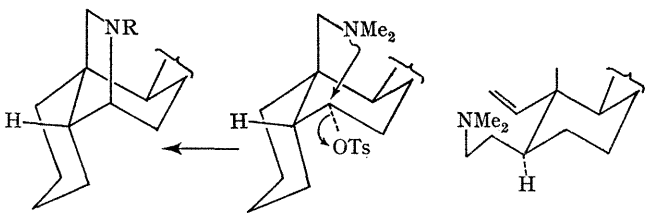
Summary Interrelated photochemical and thermal reaction sequences are outlined with novel stereochemical or other mechanistic features leading to derivatives of 6β,19-imino-5α- and -5β-cholestanes (I and II) and a range of aza-steroids such as (VIII) containing 2-methylpiperidine residues.

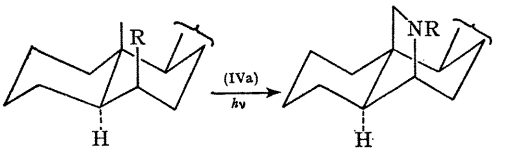
WE described previously[1] the cyclisation of a steroidal 19-dimethylamino-6β-tosylate to the methotosylate of a bridged heterocyclic system formulated as 6β,19-methylimino-5α-cholestane (Ib). The precursor 6α-alcohol had been prepared from the corresponding 5α-6-ketone by reduction with sodium and pentanol. It now appears that the equilibrium in alkaline solution between the 5α- and 5β-ketones may be markedly affected by the angular dimethylamino-*methyl* group, with the subsequent result that the tosylate cyclised actually had the 5β-configuration (III) leading to the methotosylate of the amine (IIb). However, the crystalline ketone, m.p. 59°, previously[1] described was apparently correctly formulated as the 5α-ketone, a balance of conformational and crystal-lattice forces being operative in the synthetical sequence. The amplitude of the o.r.d. Cotton-effect curve of a solution of the 5α-ketone in 0·5-N-alcoholic KOH increases nearly threefold in 24 hr. at room temperature, suggesting[2] substantial conversion into the 5β-isomer.



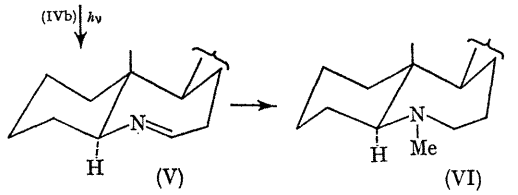
(II) a; R=H
b; R=Me (III) (IX)

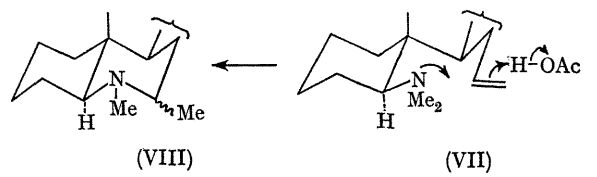
An unambiguous synthesis of the base (I; R = Me) has now been effected by photochemical cyclisation of the chloramine (IVa), previous difficulties[1] in handling this very unstable intermediate being successfully overcome by its isolation from solution in ether–cyclohexane by freeze-drying rather than evaporation, followed by photolysis at *ca.* 10° in trifluoroacetic acid. The methiodides from (Ib) and (IIb) have, respectively, m.p. 142—143°, N–CH_3 at τ 6·08 and 6·30; and m.p. 250—251°, N–CH_3 at τ 6·22 and 6·36 (n.m.r. spectra in $CDCl_3$ solutions).

Apart from 6-imino-5α-cholestane (*ca.* 40%) the chief nitrogeneous product (*ca.* 30%) from the photolysis of 6β-azido-5α-cholestane (IVb) in refluxing cyclohexane appears to be the aza-B-homocholestene (V) rather than the initially expected[3] heterocycle (Ia). Reductive methylation of (V) with formaldehyde and formic acid gives 6-methyl-6-aza-B-homo-5α-cholestane (VI) identical with an authentic specimen prepared from 5α-cholestan-6-one oxime by successive Beckmann rearrangement, reduction of the resultant lactam with lithium aluminium hydride, and *N*-methylation.



(IV) a; R=NMeCl
b; R=N_3 (I) a; R=H, b; R=Me





A group of related azahomocholestanes including (VI) has been converted into azacholestanes [*e.g.*, (VIII), as metho-acetate] by Hofmann degradation followed by subsequent cyclisation of the methines by heating (160 hr., reflux) in acetic acid[4,5] [*cf.* (VII)]. Of the range of methines examined (from syntheses starting with 5α-cholestan-3-, -4-, -6-, and -7-one oximes), only (IX) from 3-methyl-3-aza-A-homo-5α-cholestane failed to cyclise in acetic acid, but others did so even in hot ethylene glycol.[5] Such cyclisations in acetic or weaker acids are probably the synchronous processes represented, in contrast to the reactions with hydrogen bromide where the intermediate ε-bromoamine salt may be isolated [and sometimes even the free base, as from the methine (IX)]. The detailed mechanism of these reversed Hofmann eliminations is being studied.

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[2] *cf.* C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362; D. N. Jones and D. E. Kime, *J. Chem. Soc.* (C), 1966, 846.
[3] D. H. R. Barton and L. R. Morgan, jun., *J. Chem. Soc.*, 1962, 622; *cf.* D. H. R. Barton and A. N. Starratt, *ibid.*, 1965, 2444.
[4] J. McKenna and A. Tulley, *J. Chem. Soc.*, 1960, 945; K. Jewers and J. McKenna, *ibid.*, p. 1575.
[5] *cf.* H. Favre, R. D. Haworth, J. McKenna, R. G. Powell, and G. H. Whitfield, *J. Chem. Soc.*, 1953, 1115.