Cholestanes Containing an Oxygenated 14α-Methyl Group*

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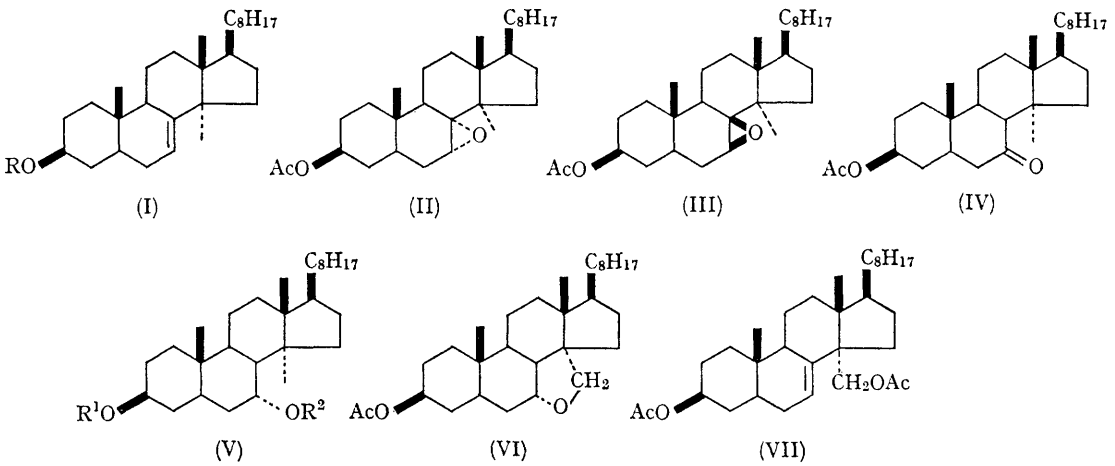
RECENTLY several laboratories have reported the synthesis of lanostane derivatives oxygenated at C-32.[1] Such compounds are of interest as possible intermediates in early stages of the biological conversion of lanosterol into cholesterol.[2] Our interest in this field stems from the possibility that defects or alternate pathways in sterol metabolism might produce 14α-methyl steroids, and has led to the synthesis of 14α-methyl hormones for biological evaluation.[3] The isolation of macdougallin (3β,6α-dihydroxy-14α-methyl-5α-cholest-8-ene) from natural sources[4] strengthened our earlier hypothesis, and the demonstration that 14α-methyl compounds could be converted into cholesterol *in vitro*[5] led us to investigate the mechanism of the demethylation reaction. In connection with this study we report a route (*cf.* ref. 1b) to cholestane derivatives bearing an oxygenated methyl group at C-14.

Epoxidation of 3β-acetoxy-14α-methyl-5α-cholest-7-ene[5,6] (I; R = Ac) with *m*-chloroperbenzoic acid in chloroform gave the 7α,8α-epoxide (II) m.p. 101—102°, $[\alpha]_D^{20}$ + 36°, n.m.r. δ 1·06 (14α-Me), 3·3 (7β-H); and a number of other products in lesser yield, including the 7β,8β-oxide (III) m.p. 124—125°, $[\alpha]_D$ + 6·5° and the 7-ketone (IV) m.p. 121—122°, $[\alpha]_D$ + 23°.

Reduction of 3β-acetoxy-7α,8α-epoxy-14α-methyl-5α-cholestane (II) with lithium in ethylamine[1b,7] followed by addition of methanol to the reaction mixture led to a mixture of 3β-hydroxy-14α-methyl-5α-cholest-7-ene (I; R = H) and 3β,7α-dihydroxy-14α-methyl-5α-cholestane (V; $R^1 = R^2 = H$), m.p. 168—169°, $[\alpha]_D$ − 25°. Acetylation of the diol with a mixture of acetic anhydride and pyridine (1 : 1) at 60° for 10 min. gave the 3β-monoacetate (V; R^1 = Ac, R^2 = H) m.p. 156—158°, $[\alpha]_D$ + 22°, which was easily separated from minor amounts of the 3β,7α-diacetate (V; $R^1 = R^2$ = Ac) m.p. 136—137°, $[\alpha]_D$ − 24·5°; by preparative thin-layer chromatography.

On refluxing with lead tetra-acetate in dry benzene for 24 hr., the monoacetate (V; R^1 = Ac; R^2 = H) was converted in good yield into cyclic ether (VI). The reaction product was crystallized from methanol to yield needles of (VI), m.p. 133—134°, $[\alpha]_D$ + 18·5°. The n.m.r. spectrum

* For the previous paper in this series, see G. R. Pettit and A. K. Das Dupta, *Canad. J. Chem.*, 1966, **44**, in the press.



showed two doublets centred at δ 3·32 (14α-CH_2; J = 7 c./sec.) and 3·98 (14α-CH_2; J = 7 c./sec.) (Fried[1b] gives δ 3·33 and 3·97 for a similar CH_2 in the corresponding 4,4-dimethyl derivative), and a peak at δ 4·03 (7β-H). Addition of iodine to the reaction mixture greatly reduced the yield of cyclic ether (VI), and the product could only be recovered by preparative thin-layer chromatography.[1b]

Cleavage of the ether linkage in (VI) was brought about by pyridine hydrochloride in refluxing acetic anhydride. Careful preparative thin-layer chromatography gave the unsaturated diacetate (VII) in low yield, m.p. 103—104°, $[\alpha]_D$ + 19°. The n.m.r. spectrum showed a pair of doublets centred at δ 3·76 (14α-CH_2; J = 12 c./sec.) and 4·64 (14α-CH_2; J = 12 c./sec.), and signals at δ 1·98 (14α-CH_2OAc), 2·04 (3β-OAc), and 5·24 (7β-H). Diacetate (VII) and several derivatives of the oxygenated-14α-methyl group are now being prepared for cholesterol biosynthesis studies.[5]

Satisfactory analytical data were obtained for all compounds mentioned. Optical rotations were determined in chloroform at 20°.

(*Received, August 18th,* 1966; *Com.* 609.)

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