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3β-METHOXY-5α-CHOLESTANE-4β,5α-DIOL AND RELATED COMPOUNDS

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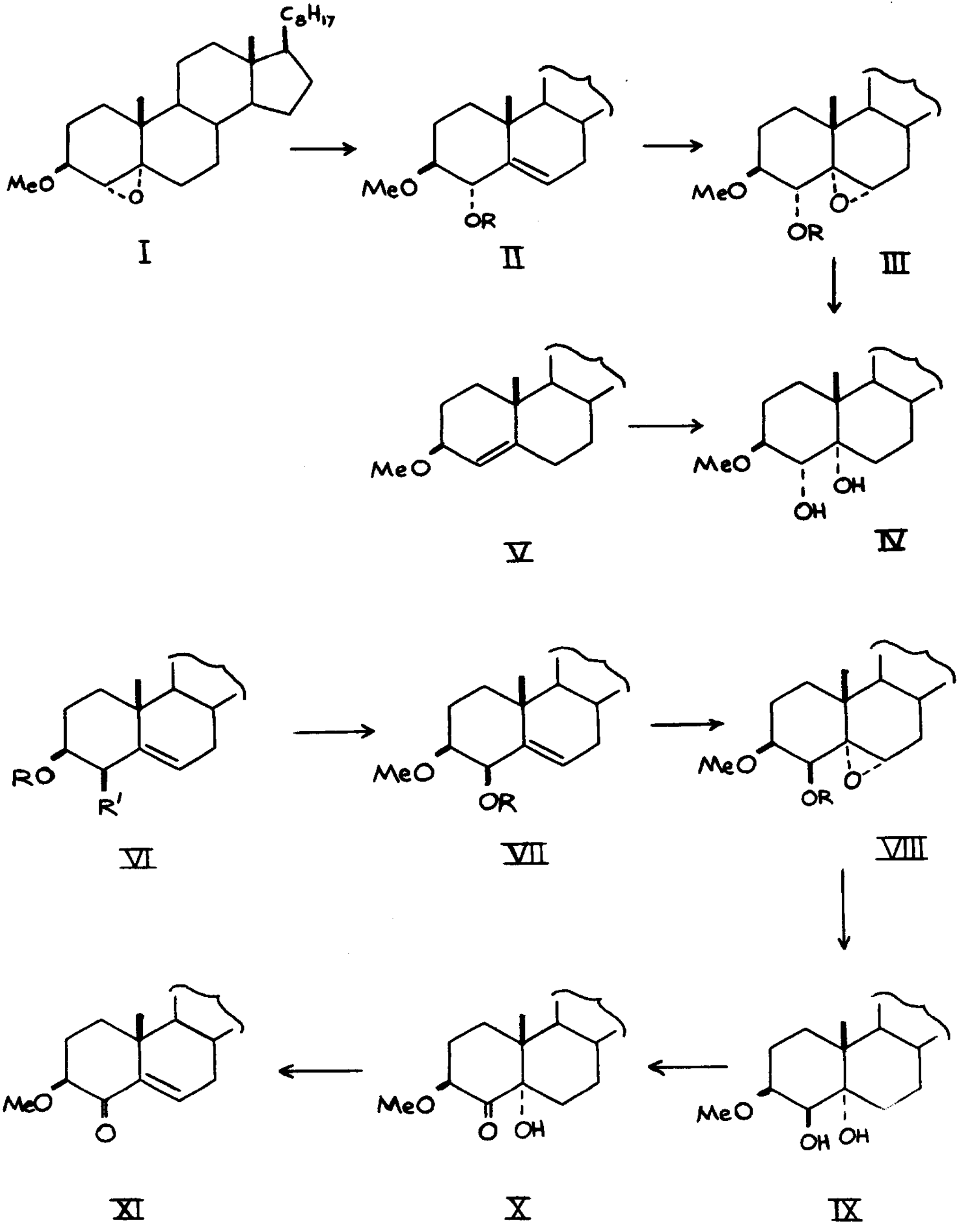
In connection with another project it recently became necessary for us to prepare 3β-methoxy-5α-cholestane-4β,5α-diol (IX). This structure has previously been assigned (1) to the compound of m.p. 172-3° and $[\alpha]_D$ -19° obtained by sulphuric acid-catalysed cleavage of 4α,5α-epoxy-3β-methoxycholestane (I). In our hands, repetition of this experiment afforded as the major product (75% yield) a compound with physical constants (m.p. 175-7°, $[\alpha]_D$ -15°) in reasonable agreement with those described in the literature.

Microanalysis, however, indicated a molecular formula of $C_{28}H_{48}O_2$ rather than $C_{28}H_{50}O_3$, and the spectrosopic and chemical properties of the compound showed that it is to be formulated as 3β-methoxycholest-5-en-4α-ol (II; R = H). Thus, in its n.m.r. spectrum, the presence of a trisubstituted double bond could be inferred from the appearance of a signal at τ 4.25 due to the vinyl proton at C_6. Both the alcohol (II; R = H) and the derived acetate (II; R = Ac) underwent epoxidation with m-chloroperbenzoic acid to afford the oxides (III; R = H) and (III; R = Ac) respectively. The α- configuration of the oxirane group in each of these compounds followed from their n.m.r. spectra (2). In both cases the signal due to the 6β-hydrogen atom was a doublet (J = 4·5 c.p.s.), exhibited by the alcohol (III; R = H) at τ 6·78 and by the acetate (III; R = Ac) at τ 7·02. The appearance of a doublet (J = 10·0 c.p.s.) at τ 4·61 in the spectrum of (III; R = Ac) due to the C_4-hydrogen atom established that the 4-acetoxyl group is equatorial and therefore α-oriented. Confirmation of these assignments was obtained by reduction of the oxides (III; R = H) and (III; R = Ac) with lithium aluminium hydride to afford, in each case, 3β-methoxy-5α-cholestane-4α,5α-diol (IV), identical with the material obtained by hydroxylation of 3β-methoxycholest-4-ene (V) with osmium tetroxide.

3β-Methoxy-5α-cholestane-4β,5α-diol (IX) was eventually prepared, starting from either 3β-methoxycholest-5-en-4β-ol (VII; R = H) or its acetate (VII; R = Ac). A mixture of (VII; R = H) and (VII; R = Ac) is obtainable by oxidation of 3β-methoxycholest-5-ene (VI; R = Me, R' = H) with selenium dioxide in acetic acid (1); however, the configuration at C_4 of these compounds had not previously been defined unambiguously. In the present work, the alcohol (VII; R = H) was obtained also by selective methylation of cholest-5-en-3β,4β-diol (VI; R = H, R' = OH) (3) with methyl iodide and silver oxide, thus establishing the correctness of the previous assignment. Epoxidation of the olefins (VII; R = H) and (VII; R = Ac) with m-chloroperbenzoic acid gave respectively the oxides (VIII; R = H) [n.m.r: doublet (J = 3 c.p.s.) at τ 6·65 (4α-H); doublet (J = 4 c.p.s.) at τ 6·92 (6β-H)] and (VIII; R = Ac) [n.m.r: doublet (J = 3 c.p.s.) at τ 5·59 (4α-H); doublet (J = 3 c.p.s.) at τ 6·95 (6β-H)]. Reduction of either of these epoxides with lithium aluminium hydride afforded the required diol (IX), m.p. 158-60°, $[\alpha]_D$ + 18°. Subsequently, this material was also obtained in very small yield by chromatography of the mother liquors remaining after crystallisation of the major product


C8H17
MeO
O
I
MeO
OR
II
MeO
OR
O
III
MeO
V
MeO
OH
OH
IV
RO
R'
VI
MeO
OR
VII
MeO
OR
O
VIII
MeO
OH OH
IX
MeO
O OH
X
MeO
O
XI

(II; R = H) arising from the sulphuric acid-catalysed cleavage of the oxide (I).

Oxidation of either of the diols (IV) or (IX) with chromium trioxide gave 5α-hydroxy-3β-methoxy-5α-cholestan-4-one (X) as a stable crystalline compound, m.p. 178-179·5°, $[\alpha]_D$ + 7·0°, $\nu_{max.}$ (CCl_4) 1730 cm.$^{-1}$. This is clearly not identical with the unstable gummy solid [$\nu_{max.}$ ($CHCl_3$) 1705 cm.$^{-1}$], previously formulated as (X) (1). Dehydration of the ketol (X) with thionyl chloride and pyridine yielded 3β-methoxycholest-5-en-4-one (XI), m.p. 112-15°, $[\alpha]_D$ -85°, $\nu_{max.}$ (CCl_4) 1703 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 243 mμ (log ε 3·86) [lit. (1) m.p. 118-19°, $[\alpha]_D$ -85°, $\nu_{max.}$ (CCl_4) 1685 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 241 mμ (log ε 3·78)], which was also obtained by oxidation of 3β-methoxycholest-5-en-4α-ol (II; R = H) with chromium trioxide. The unusually high frequencies of the carbonyl infrared absorption of the ketones (X) and (XI) may be attributed to the presence of an equatorial methoxyl group α- to the carbonyl function (4).

Satisfactory analyses and spectra were recorded for all the new compounds described.

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