The Synthesis of 4α-Methylcholest-8(9)-en-3β-ol

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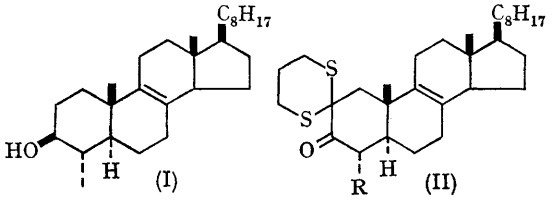
THE isolation from a transplantable, preputial tumour of a novel, steroidal metabolite which was characterised as 4α-methylcholest-8(9)-en-3β-ol (I) has been recorded,[1] together with evidence[2] that (I) is an intermediate in the biosynthesis of cholesterol from lanosterol. We now report the synthesis of this biologically significant steroid (I).



Thus, hydrogenation of 3β-acetoxycholesta-8(9),14(15)-diene[3] in alcohol with W-4 Raney nickel at atmospheric temperature and pressure during 90 min. gave 3β-acetoxycholest-8(9)-ene in 45% yield (contrast Barton and Cox,[4] and Gautschi and Bloch[5]). Oppenauer oxidation of the resultant cholest-8(9)-en-3β-ol gave cholest-8(9)-en-3-one,[6] which was converted by way of the 2-hydroxymethylene derivative into the 2,2′-spiro-dithian (II; R = H), m.p. 160°. Methylation of (II; R = H) with methyl iodide–potassium t-butoxide–benzene gave (II; R = Me), m.p. 141—143°, which was desulphurised with Raney nickel in ethanol to furnish a mixture of 4α-methylcholest-8(9)-en-3β-ol (I) and the corresponding 3α-ol, m.p. 107–108°. Separation by chromatography gave 4α-methylcholest-8(9)-en-3β-ol (I) which was identical (m.p., mixed m.p., mass spectrum, and g.l.c.) with a specimen from the preputial tumour. The acetate of synthetic (I) was identical (m.p., mixed m.p., and mass spectrum) with the acetate of natural (I).

Oxidation of (I) and of its 3α-epimer, by the Oppenauer procedure gave 4α-methylcholest-8(9)-en-3-one (70% yield), m.p. 113°, [α] + 44° which was reduced by sodium borohydride–methanol–benzene to (I), unaccompanied by the 3α-epimer.

Synthetic (I) exhibits an unusual degree of instability similar to that of the natural material.[1]

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All new compounds had the requisite spectral and analytical properties.

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