Synthesis and Configuration at C-15 of the Epimeric 5α-lanost-8-en-3β,15-diols

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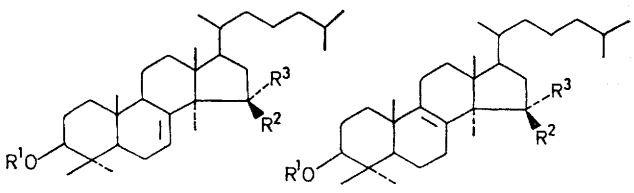
Summary Reduction of 3β-hydroxy-5α-lanost-7-en-15-one gives a mixture of the epimeric Δ^7-3β,15α- and Δ^7-3β,15β-diols; their 3β,15-diacetate derivatives undergo nuclear double bond rearrangement in the presence of HCl to yield the corresponding Δ^8-3β,15-diols after hydrolysis.

THE early part of the biosynthetic sequence in which cholesterol is formed from 4,4,14α-trimethyl sterols may involve the intermediacy of a 15-hydroxy steroid.[1] We now describe the synthesis of two such potential cholesterol precursors, 5α-lanost-8-en-3β,15α-diol (**8**) and 5α-lanost-8-en-3β,15β-diol (**9**).

3β-Hydroxy-5α-lanost-7-en-15-one (**1**) was synthesised from cholesta-5,7-dien-3β-ol.[2] Reduction of the 15-ketone (106 mg) with $LiAlH_4$ in ether gave two diols which were separated from each other by chromatography on a column of alumina. The 15α-OH configuration was assigned to the more polar diol (**3**) (58 mg, m.p. 184—185°, $[\alpha]_D^{22}$ + 19·3°) and the 15β-OH configuration to the less polar (**4**) (31 mg, m.p. 154—155°, $[\alpha]_D^{22}$ − 23·8°), on the basis of the following evidence.

(a) The C-18 methyl protons of (**3**) and (**4**) resonated at τ 9·37 and τ 9·11 respectively whilst those of the C-15 unsubstituted compound (**2**) resonated at τ 9·36. This large downfield shift of the C-18 methyl signal in the less polar diol is consistent with the 15β-configuration of the hydroxyl group.[3] The broad multiplet centred at τ 5·87 in the spectrum of (**3**) is also in closer agreement with values reported for a C-15βH^{3b} than is the multiplet centred at τ 6·05 observed in the spectrum of (**4**).

(b) Although (**3**) formed a diacetate (**5**) with pyridine and acetic anhydride at 30°, the diacetate (**6**) of (**4**) was obtained only after refluxing with acetic anhydride in the presence of sodium acetate. In this respect, the difficulties encountered in acetylating a steroidal 15β-OH have been reported previously.[4]



(c) The retention time of (**3**) during g.l.c. was greater than that of (**4**) and the same behaviour was observed of the respective ditrimethylsilyl ethers and diacetate derivatives. It has been reported that the trimethylsilyl ethers of 15α-hydroxy derivatives of 5α-androstanediols have longer retention times than their 15β-hydroxy epimers.[5]

(d) In all the cases studied, the $\Delta[M]_D$ contributed to a steroid by a 15-hydroxy group is positive when the substituent is α-orientated and negative when β-orientated.[3b] In the present case, using the enol (**2**) as the parent compound, the $\Delta[M]_D^{22}$ values for the 15-hydroxyl group of (**3**) and (**4**) were +36·8° and −154·6° respectively.

The mass spectra of the ditrimethylsilyl ethers of (**3**) and (**4**) each showed a molecular ion at *m/e* 588.

Nuclear double bond rearrangement from Δ^7 to Δ^8 in each epimer was achieved by formation of the respective 3β,15-diacetate followed by the passage of dry HCl gas through a chloroform solution of the diacetate for 6 h. Each Δ^8-diacetate (**10**) and (**11**) was separated from its corresponding Δ^7 precursor by argentation chromatography. Alkaline hydrolysis of (**10**) gave (**8**) m.p. 178—179°, $[\alpha]_D^{22}$ + 65·4° (*c* 1·0), τ 9·29 (s, C-18H), 6·81 (m, 3α-H) and 5·82 (m, 15β-H). Hydrolysis of (**11**) gave (**9**), the C-18 methyl protons of which resonated at τ 9·00. This larger downfield shift is again consistent with the β-configuration of the 15-hydroxy group.[3] The difficulty encountered in forming derivatives of the 15β-hydroxy group was again encountered on formation of the ditrimethylsilyl ethers of (**8**) and (**9**). After a few hours in the presence of *N,O*-bis-(trimethylsilyl)-acetamide (**8**) was completely converted and gave only one peak on g.l.c., M^+, *m/e* 588. However, even after two weeks under the same conditions, (**9**) showed the presence of two components, one corresponding to the ditrimethylsilyl ether and the other to the monotrimethylsilyl ether.

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