An Unusual Acid-catalysed Reaction of Steroidal 4,6-Diols with Acetone

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Summary The acid-catalysed reaction of 4α-methyl-5α-cholestane-4β,6α- and 6α-methyl-5α-cholestane-4α,6β-diol with acetone affords condensation products through the intermediacy of the appropriate methylene alcohol.

IT has been reported that whereas certain steroidal 12α,17α-diols can form acetonides,[1,2] 12α,17β-diols undergo acid-catalysed 1,5-hydride transfer to give 12α-isopropoxy-17-ketones if the 17-hydroxy-group is secondary,[3] and suffer dehydration if this group is tertiary.[1] We now report a novel condensation of acetone with two steroidal *trans*-4,6-diols under conditions for acetonide formation.[4]

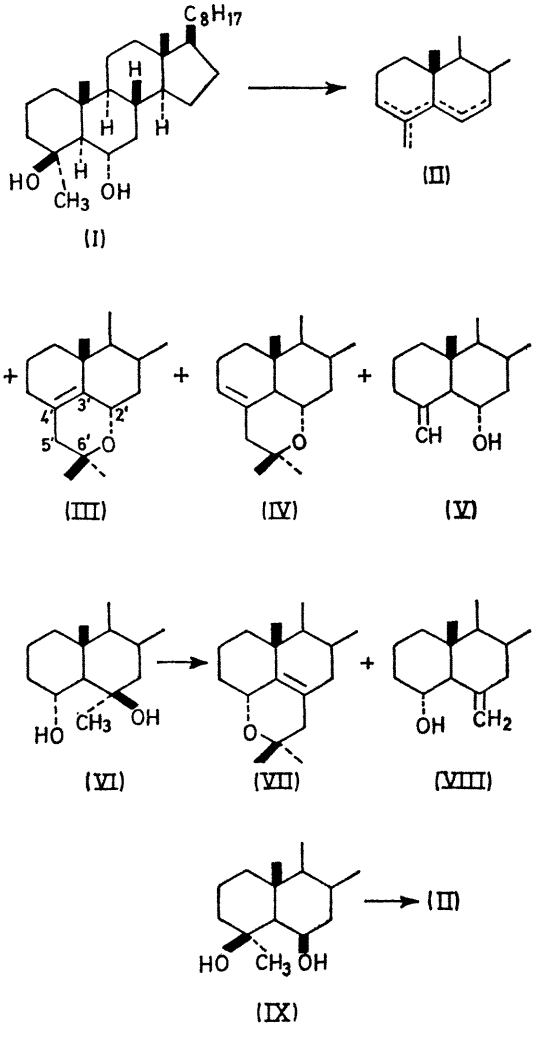
Treatment of 4α-methyl-5α-cholestane-4β,6α-diol[5] (I) with acetone containing 70% perchloric acid (0·5%) at 20° for 16 h, and careful chromatography of the product on silica gel gave an oily mixture of dienes (II) (7%), λ_{max} 239 nm. (Found: M^+, 382. Calc. for $C_{28}H_{46}$: M, 382); 2′βH-5′,6′-dihydro-6′,6′-dimethylcholest-4-eno[6,5,4-*b*,*c*]pyran (III)† (56%), m.p. 122—123°, $[\alpha]_D^{24}$ + 6° (*c* 0·5, $CHCl_3$); 2′βH-6′,6′-dimethyl-5α-cholest-3-eno[6,5,4-*b*,*c*]tetrahydropyran (IV) (13%), m.p. 70—73°, $[\alpha]_D^{24}$ + 31° (*c* 0·8, $CHCl_3$); and 4-methylene-5α-cholestan-6α-ol (V) (14%), m.p. 162—165°, $[\alpha]_D^{24}$ + 68° (*c* 0·7, $CHCl_3$), ν_{max} 3605 cm^{-1}. Despite careful examination of the crude product, no trace of an acetonide derivative was detected. The intermediacy of the olefinic alcohol (V) in the formation of the adducts was established by treatment of the pure compound (V) with 70% perchloric acid in acetone. After 2 h the presence of (III) and (IV) in the reaction mixture was demonstrated by comparative t.l.c. analysis.

The n.m.r. spectrum‡ of the major adduct (III) exhibited three-proton singlets at δ 0·65 (13-CH_3), 0·96 (10-CH_3), 1·12 and 1·18 (6′,6′-di-CH_3), and a broad, unstructured one-proton signal at δ 4·06 ($W_{\frac{1}{2}}$ 22 Hz, 6β-H). The unresolved nature of this signal is due to homoallylic coupling[6] with the 3α- and 5′α-protons, both of which are *trans*-1,4-diaxially disposed toward the 6β-proton, and perpendicular to the plane of the olefinic bond in the preferred conformation of the compound (III). This was demonstrated by irradiation at δ 4·06 which resulted in sharpening of signals in the lower-field region of the methylene envelope, particularly of the broad one-proton doublet (J_{gem} 16 Hz) at δ 2·15 due to the 5′α-proton. Conversely, irradiation at δ 1·92 or 2·15 resolved the 6-proton signal into a broad doublet ($J_{6\beta,7\alpha}$ *ca.*

† Satisfactory elemental and spectral analyses were obtained for all new compounds with the exception of (IV) which was available in insufficient quantity for complete characterisation.

‡ All n.m.r. spectra were recorded at 100 MHz in $CDCl_3$ using $(CH_3)_4Si$ as internal standard.

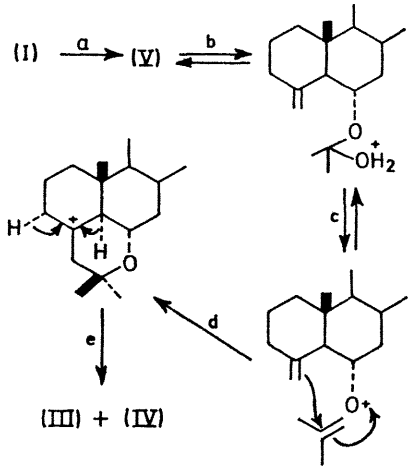
11 Hz) thereby establishing the retention of configuration at that position. By contrast the 6β-proton of the minor adduct (IV) exhibited a clear sextet at δ 3·54 (*J* 10 and 4 Hz) [*cf.* starting material[5] (I)], together with a signal at δ 5·27 ($W_{\frac{1}{2}}$ 8 Hz) for 3-H, and three-proton singlets at



δ 0·66 (13-CH_3), 0·87 (10-CH_3), 1·10 and 1·19 (6′,6′-di-CH_3). The structure of the olefinic alcohol (V) was conclusively established by n.m.r. signals at δ 0·64 (3H, s, 13-CH_3), 0·70 (3H, s, 10-CH_3), 3·79 (1H, sext., *J* 10 and 5 Hz, 6β-H), 4·65 and 4·98 (each 1H, s, $W_{\frac{1}{2}}$ 2·5 Hz, 4 =CH_2).

The isomeric diol[5] (VI), upon similar treatment with 70% perchloric acid in acetone at 20° for 90 h, gave 2′βH-5′,6′-dihydro-6′,6′-dimethylcholest-5-eno[4,5,6-*b*,c]pyran (VII) (15%), m.p. 145—148°, $[\alpha]_D^{24}$ 0° (*c* 0·2, $CHCl_3$), δ 0·67 (3H, s, 13-CH_3), 0·96 (3H, s, 10-CH_3), 1·12 and 1·20 (each 3H, s, 6′,6′-di-CH_3), and 4·06 (1H, $W_{\frac{1}{2}}$ 20 Hz, 4β-H); and 6-methylene-5α-cholestan-4α-ol (VIII) (61%), m.p. 156—161°, $[\alpha]_D^{24}$ − 3° (*c* 0·7, $CHCl_3$), ν_{max} 3608 cm^{-1}, δ 0·64 (3H, s, 13-CH_3), 0·68 (3H, s, 10-CH_3), 3·85 (1H, sext., *J* 10 and 5 Hz, 4β-H), 4·63 and 4·90 (each 1H, s, $W_{\frac{1}{2}}$ 2·5 Hz, 6 =CH_2), as the only isolable products. The 4α-methyl-4β,6β-diol[5] (IX) under similar reaction conditions, rapidly formed diene mixtures (II) *via* a transient intermediate (probably an olefinic alcohol), but no adducts were detected in the final product.

The probable sequence of events in these reactions is illustrated for (I) (Scheme). Rapid elimination (a) of the



SCHEME

4β-hydroxy-group (as evidenced by t.l.c. monitoring) is followed by formation (b) of the protonated acetone hemiacetal which undergoes loss of water (c) to give an oxonium ion.[3] This species is ideally orientated for nucleophilic attack (d) by the methylene group; subsequent or synchronous elimination (e) of the 5α- or 3α-proton leads to (III) or (IV), respectively. The reactions (V) → (III) + (IV) and (VIII) → (VII) were followed by g.l.c. analysis (3 m × 5 mm 1% OV-17 on Gas-chrom Q 60—80 mesh, 250°) and as was suggested by the preparative results, the latter reaction proceeded much more slowly. There is no obvious explanation for this difference.

The inability of the 4β,6β-diol (IX) to form an acetonide or related adduct is attributable to the intervention of highly favoured diaxial elimination of the secondary hydroxy-group compared to the slow formation of an acetone hemiacetal.

(*Received, May 4th*, 1971; *Com.* 702.)

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