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THE STRUCTURE OF DIGACETIGENIN

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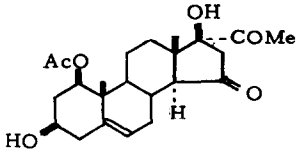
In 1964 we suggested[1] that digacetigenin, from D. purpurea, had the structure (I). The tertiary hydroxyl group was located at the 17β-position because of (a) the appearance of the 13β-methyl group signal in the n.m.r. spectrum at τ9.03, and (b) the facile dehydration to a Δ^{16}-15,20-diketone.[1,2]



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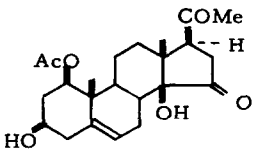

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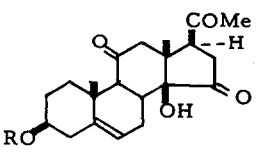
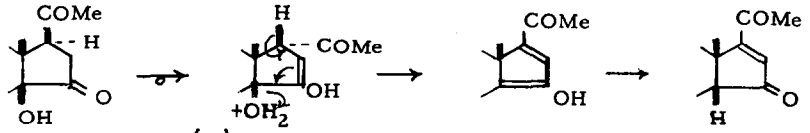


III

These facts are, however, readily accommodated by placing the tertiary hydroxyl group in digacetigenin at the 14β-position (II), and formulating the acid-catalysed dehydration reaction by the sequence:



Formula (II) accounts readily for a signal in the n.m.r. spectrum of digacetigenin, which we reported but were unable satisfactorily to identify.[1] At 60 Mc./sec., this signal for one proton appeared as a doublet of doublets centred at τ 6.85 (separations, 5 c./sec., and 9 c./sec.); at 100 Mc./sec. irradiation at τ 6.8 caused a multiplet at τ 7.45 to approximate to an AB system. Irradiation at τ 7.45 caused the signal at τ 6.85 to collapse to a singlet. These observations indicate the presence of an isolated ABX system readily assignable to the 17α-proton in (II) coupled with the 16-methylene protons.

"γ"-Digiprogenin, from D. purpurea, also undergoes ready acid-catalysed dehydration to a Δ^{16}-11,15,20-triketone[3,4]; one of us (C.W.S.) suggested application of

the above reaction mechanism to "γ"-digiprogenin in a letter of 22 April, 1966 to Dr. D. Satoh, whose reply of 2 May 1966 disclosed that he had independently developed the same mechanism for the transformation. Subsequently, Satoh[5] proved that "γ"-digiprogenin has the structure (III : R = H), and has subsequently informed us of the partial synthesis of 5,6-dihydro- -digiprogenin from hecogenin[6].

Deacetyldigacetigenin does not react with lead tetracetate[2] and cannot be a 1,2-glycol. It is stable to brief treatment with 2N-hydrochloric at 65°[1] and so cannot be a Δ^4-3β-ol, a conclusion confirmed by comparison of the position and profile of the n.m.r. signal for the vinyl proton (6-H, τ 4.56) with that of the vinyl proton in 3β-acetoxycholest-4-ene (4-H, τ 5.83) [cf. 6-H, τ 4.4 ± 0.1 in Δ^5-3β-ols[7] and their acetates[8]]. Since there is other good evidence[1,2] for the presence of a Δ^5-3β-ol grouping in digacetigenin, the possible locations for the secondary acetoxyl group are limited to positions 1, 7, 11, and 12

The n.m.r. signal for the proton attached to the carbon atom bearing the acetoxyl group in digacetigenin (an approximate quartet at τ 5.62, W_H 17 c./sec.)[1] is consistent only with an axial proton (coupled to two adjacent non-equivalent protons).

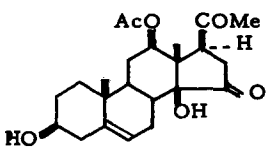
The profile and position of the axial 1α-proton signal for 1β-acetoxy-5α-cholestane (τ 5.2, W_H 12 c./sec.) is consistent[1] with the digacetigenin proton signal, but comparative studies with ruscogenin[9] exclude the 1β-position for the secondary acetoxyl group in digacetigenin.

The profile and position of axial 7α-proton signal observed at 60 Mc./sec. for 7β-acetoxycholest-5-en-3β-ol, an apparent doublet, τ 4.96, with separation 8.5 c./sec., is different from the corresponding digacetigenin proton signal. Further, we find that partial alkaline hydrolysis of digacetigenin 3-acetate to deacetyldigacetigenin 3-acetate, followed by Jones oxidation yields a triketone, m.p. 134-135°, M = 402 (mass spectrometry), $\nu_{max.}^{CCl4}$ 3300 (OH), 1746 (15-CO), 1730 (Ac), 1708 (new CO), and 1694 $cm.^{-1}$ (20-CO), with no intense absorption in the ultraviolet at ~240 mμ, in which the new carbonyl group is not conjugated with the Δ^5-double bond. These observations exclude the 7β-position for the secondary acetoxyl group in digacetigenin.

The profile and position of the axial 11β-proton signal (which is coupled to three adjacent protons) in a number of 11α-acetoxysteroids[1,10] (τ 4.8 - 4.9) is inconsistent with the digacetigenin proton signal. Further, if digacetigenin were an 11α-acetoxy compound, our triketone, m.p. 134 - 135°, should be, but is not, identical with "γ"-digiprogenin 3-acetate[3] (III : R = Ac). These considerations exclude the 11α-position for the secondary acetoxyl group in digacetigenin.

The profile and position of the axial 12α-proton four-line signal observed for 12β-acetoxy-5β-pregnane (τ 5.3) cf.[10] is somewhat similar to the digacetigenin proton signal, which appears as a multiplet, looking like an apparent quartet and collapsing to

a singlet by suitable irradiation in both 60 and 100 Mc./sec. spectra. Formulation of digacetigenin as 12β-acetoxy-3β, 14β-dihydroxypregn-5-ene-15, 20-dione (IV) is consistent with the production of the non-conjugated 12, 15, 20-triketone (V), m.p. 134 - 135°, and also explains the formation of the rearrangement product[1,2; cf.11] (VI), $C_{21}H_{28}O_4$, m.p. 125 - 135°, $\lambda_{max.}^{EtOH}$ 252 mμ (log ε 4.05)[1], $\lambda_{max.}$ 252 mμ (log ε 4.03)[2], in the n.m.r. spectrum of which a signal for an angular methyl group has disappeared and been replaced by a signal of area for three protons at τ 7.71 [-CMe=C-][1], and there is a multiplet at τ 6.8 attributable to the 16-methylene protons.



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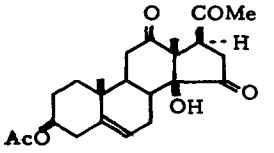

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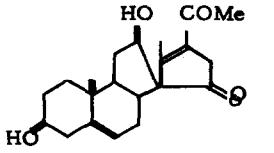
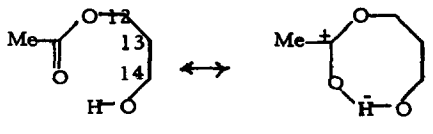


VI

Finally, formula (IV) suggests an explanation for the very facile hydrolysis of the secondary 12β-acetoxyl group with methanolic potassium hydrogen carbonate at 20°[1,2]. In C/D-cis-steroids ring C is probably a boat (with ends at C-12 and C-8) and ring D is essentially planar; a Dreiding model of this conformation shows that the carbonyl oxygen atom of the 12β-acetoxyl group and the hydrogen atom of the 14β-hydroxyl group can readily undergo hydrogen-bonding to give a strainless eight-membered ring (VII). Digacetigenin 3-acetate (cf. IV) shows in its infrared spectrum[1] a band at $\nu_{max.}^{CCl_4}$ 3320 cm.$^{-1}$ which indicates the presence of a hydrogen-bonded hydroxyl group. Such hydrogen-bonding would permit facilitation of hydrolysis of the 12β-acetoxyl group by specific basic catalysis (VIII), or more probably, by general basic catalysis (IX) leading to formation of methyl acetate[cf.12].



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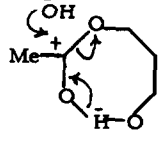

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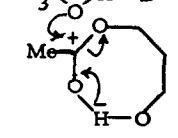

IX

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