C-Norcardenolides[1]

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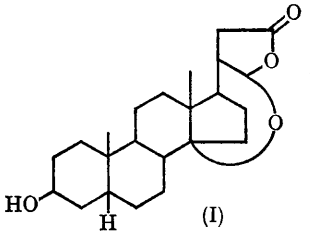
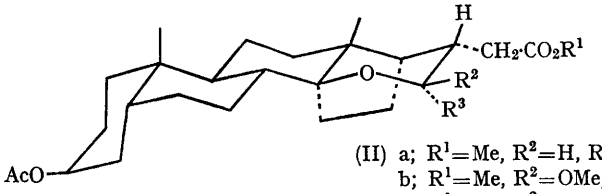
IN preceding contributions, we recorded new syntheses of cardenolides and isocardenolides.[2] We now report a convenient and unique route to the previously unknown c-norcardenolides.

Heating a solution of isodigitoxigenin (I) (0·5 g.)[3] in methanol (50 ml.) containing toluene-*p*-sulphonic acid (0·05 g.) and water (2·5 ml.) under reflux for 20 hr. gave acetals* (IIa) (0·22 g.), m.p. 194—196°, $[\alpha]_D$ −75°, n.m.r. 1·02 and 1·05 (angular CH_3), 3·32 (21α-OCH_3), 3·68 (22-$CO_2{\cdot}CH_3$), and 4·73 (21β-*H*; J = 5·5 c./sec.) δ and (IIb) (0·15 g.) m.p. 142—144°, $[\alpha]_D$ +9·03°, n.m.r. 1·08 and 1·12 (angular CH_3), 3·45 (21β-OCH_3), 3·68 (22-$CO_2{\cdot}CH_3$), and 4·23 (21α-*H*; J = 8 c./sec.) δ. The acetals were separated (after acetylation, 3 : 1 pyridine–acetic anhydride, room temperature) by column chromatography on basic alumina. Methanolysis of known[4] diacetate (IIc) also gave acetal (IIa). Further, acetals (IIa and IIb) were obtained as follows: isodigitoxigeninic acid (IIe),[3] obtained by hydrolysis of isodigitoxigenin (I) with aqueous potassium hydroxide in methanol was esterified (diazomethane). The ester was treated with methanol containing a trace of hydrobromic acid (to form the acetal) and then acetylated (3 : 1 pyridine–acetic anhydride, room temperature) to yield acetals (IIa and IIb). Oxidation of either acetal with CrO_3 in glacial acetic acid gave lactone (IId),[4] m.p. 137—138°, $[\alpha]_D$ −28°, n.m.r. 1·02 and 1·13 (angular CH_3), and 3·69 (22-$CO_2{\cdot}CH_3$) δ. Ease of oxidation in the case of acetal (IIa) compared to acetal (IIb) combined with a consideration of their H-20–H-21 n.m.r. coupling constants[5] support the assigned stereochemistry.

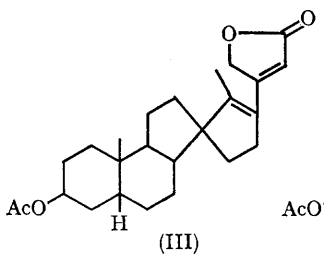
Heating (10 hr.) a solution of either acetal (IIa or IIb) (0·2 g) in benzene containing toluene-*p*-sulphonic acid (0·04 g.) under reflux for 10 hr. gave c-norcardenolide (III) (0·12 g.), m.p. 164—165°, $[\alpha]_D$ +36·35°, M (by mass spectrometry) 398, λ_{max} 288 mμ (ε 22,760), i.r. ($CHCl_3$) 5·58, 5·73, and 6·16 μ, n.m.r. 0·98 (19-CH_3), 1·82 (18-CH_3), 2·07 ($CH_3{\cdot}CO_2$), 5·1 (21-CH_2), and 5·82 (22-*H*) δ. Under the same reaction conditions digitoxigenin yields 14-dehydrodigitoxigenin as the almost exclusive product. The alternative structure (IV)



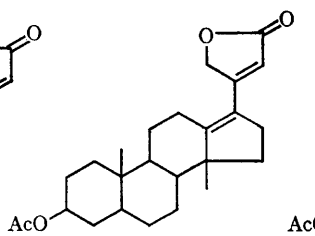
(I)



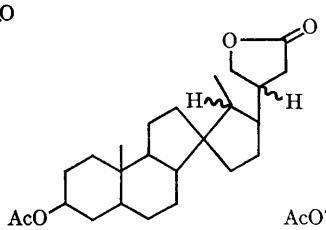
(II) a; R^1=Me, R^2=H, R^3=OMe
b; R^1=Me, R^2=OMe, R^3=H
c; R^1=Me, R^2=OAc, R^3=H
d; R^1=Me, R^2, R^3=O
e; R^1=H, R^2=OH, R^3=H



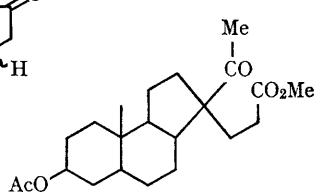
(III)



(IV)



(V)



(VI)

* All new compounds gave satisfactory elemental analyses. Optical rotations were measured in $CHCl_3$ and u.v. spectra in 95% ethanol solution. N.m.r. spectra were obtained with a Varian A-60 spectrometer ($CDCl_3$ as solvent and tetramethylsilane as internal standard).

was ruled out on the basis of hydrogenation and ozonolysis experiments. Hydrogenation (glacial acetic acid, 5% palladium–barium sulphate) of (III) gave a tetrahydro-lactone (V), m.p. 200—215°, $[\alpha]_D$ +18·8°, i.r. ($CHCl_3$) 5·65 and 5·8 μ, and n.m.r. 0·78 (18-CH_3 doublet, $J = 7$ c./sec.), 0·95 (19-CH_3), 2·07 (3β-acetate), 5·08 (3α-H) δ. Ozonolysis of olefin (III) at −70° in ethyl acetate, followed by an oxidation (hydrogen peroxide–hydrochloric acid–acetic acid)[6] and a methylation (diazomethane) step provided keto-ester (VI), b.p. 120—125°/0·1 mm. (sublimation temp.), i.r. (neat), 5·75 (ester), and 5·8 μ (CO·CH_3) and n.m.r. 0·94 (19-CH_3), 2·05 (3β-CH_3·CO_2), 2·14 (CO·CH_3), 3·67 (CO_2·CH_3) and 5·08 (3α-H) δ. The mass-spectral fragmentation patterns of (III) and (V) are also in accordance with the structure assigned.

The C-12 → C-14 methylene migration† is in contrast to the usual methyl group migration reported for Westphalen rearrangements[7] involving the steroid A/B-ring-functions.

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† A similar methylene migration has been suggested by Reichstein and his co-workers (ref. 8). The Westphalen rearrangement is being re-investigated by us in the light of these observations.

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