Rearrangement of Isodigitoxigenin†

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ONLY a small number of C-nor-steroids have been described[2] and steroids bearing a spiran nuclear ring system are rarely encountered.[1,3] We now report a unique rearrangement reaction of isodigitoxigenin which allows C-ring contraction and provides cardanolides bearing a spiro-C/D ring-juncture. The reaction is easily accomplished employing a two-step reaction sequence starting with digitoxigenin.

To summarize, digitoxigenin[4] was isomerized in methanol containing potassium hydroxide, as previously reported, to isodigitoxigenin[5] (I). Following acetylation of alcohol (Ia), ester (Ib) (0·67 g.) was heated in dry benzene (20 ml.) with toluene-*p*-sulphonic acid (0·15 g.) for approximately 25 hr. The product consisted mainly of C-nor-cardanolide (II) (*ca.* 50% yield as evidenced by thin-layer chromatography) and olefin (III) (m.p. 164—166°). The structure of cardenolide (III) was established by oxidation (ozone and subsequent methylation) to the methyl ketone (IV).[1] Isolation of isodigitoxigenin rearrangement product‡ (II) by preparative thin-layer chromatography and recrystallization from methanol provided needles melting at 195—196°; *M* (by mass spec.) 416, ^{1}H n.m.r. 0·98 (19-methyl), 1·35 (18-methyl), 2·00 (CH_3·CO), 2·67, 2·78, 2·88 (lactone CH_2), 4·92 (3α-H), and 5·83, 5·90 (·OCH·O·) δ. Further evidence in support of the structural assignment was obtained as follows. Lactone (II) (0·42 g.) was subjected to alcoholysis using toluene-*p*-sulphonic acid (0·01 g.) in refluxing

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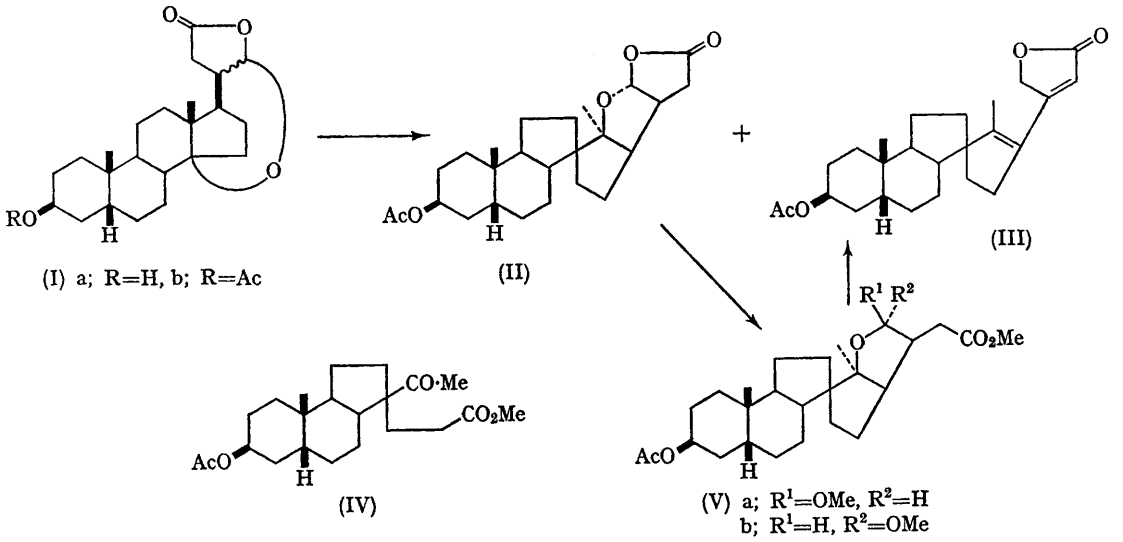
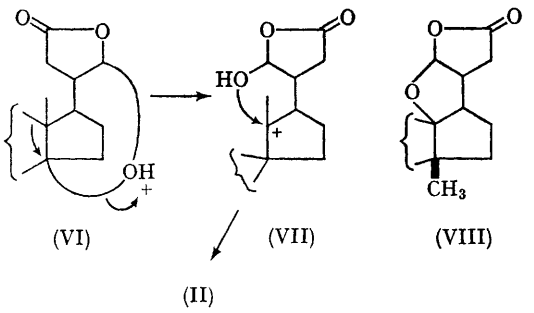
‡ All new compounds have been adequately characterized by elemental analyses and ^{1}H n.m.r. measurements (Varian A-60 spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard). Optical rotations were measured in chloroform solution. Acetylation reactions were conducted employing 1 : 1 acetic anhydride–pyridine at room temperature.



(26 hr.) methanol–water.[1] Following acetylation, acetals (Va) [0·26 g., m.p. 103—105°, ^{1}H n.m.r. 0·96 (19-methyl), 1·29 (18-methyl), 2·02 (CH_3·CO), 3·25 (acetal OCH_3), 3·66 (ester OCH_3), 4·80, 4·87 (·OCH·O·) and 5·05 (3α-H) δ], and (Vb) [oil, ^{1}H n.m.r. signal at 4·72 (·OCH·O·)] were isolated using preparative thin-layer chromatography. The stereochemical notations[6] at position C-21 of acetals (Va) (21*R*) and (Vb) (21*S*) seem consistent with their ^{1}H n.m.r. spectra. Treatment of acetal (Va) (0·24 g.) with toluene-*p*-sulphonic acid (0·05 g.) in refluxing benzene (2 hr.) provided c-nor-cardanolide (II) (0·069 g.) and diene (III) (0·035 g.). Analogous treatment of isomeric acetal (Vb) again afforded lactones (II) and (III).



Assuming a mechanistic pathway for rearrangement of isodigitoxigenin involving intermediates such as (VI) and (VII), the suggested c/D-spiro ring-system appears secure. A Westphalen-type rearrangement[7] involving the 18-methyl group would most likely terminate in 14β-bonding (VIII). Degradation of cardenolide (III) to ketone (IV) eliminates this possibility. The remarkable ease with which the isodigitoxigenin → c-nor-cardenolide rearrangement proceeds suggests that C-12 → C-14 methylene migrations may be reasonably general in scope and steroids similar to (II) and (III) may eventually be uncovered in natural sources. Also, biological evaluation of c-nor-cardenolides represents a completely unexplored but now readily accessible area.

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[3] *Cf.*, T. G. Halsall, Sir Ewart R. H. Jones, E. L. Tan, and G. R. Chaudhry, *J. Chem. Soc.* (*C*), 1966, 1374. One example of a spiro-c/D ring-juncture has been noted: A. Lardon and T. Reichstein, *Helv. Chim. Acta*, 1962, **45**, 943. Although a definite assignment was not made, Lardon and Reichstein's carefully considered structural suggestion receives support from the present study.
[4] N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, 1966, **22**, 3189.
[5] W. A. Jacobs and E. L. Gustus, *J. Biol. Chem.*, 1928, **78**, 573; O. Schindler and T. Reichstein, *Helv. Chim. Acta*, 1956, **39**, 1876.
[6] G. R. Pettit, *Experientia*, 1963, **19**, 124.
[7] A. Fischer, M. J. Hardman, M. P. Hartshorn, D. N. Kirk, and A. R. Thawley, *Tetrahedron*, 1967, **23**, 159; M. Mousseron-Canet and J. Brial, *Bull. Soc. chim. France*, 1966, 3867. Because of the C-12 → C-14 methylene migration noted above, we have begun reinvestigation of the classical Westphalen rearrangement involving, *e.g.*, 6β-acetoxy-3β-chloro-5α-hydroxycholestane (reported by A. Fischer and colleagues).