Steroids and Related Natural Products. Part XCII.[1] Conversion of Canarigenone [14-Hydroxy-3-oxo-14β-carda-4,20(22)-dienolide] into Periplogenin [3β,5,14-Trihydroxy-5β,14β-card-20(22)-enolide] [2]

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Oxidation of canarigenone (IV) by peroxy-acid gave the 4β,5β-epoxide (V), which was reduced by chromium(II) acetate to the 5β-hydroxy-3-ketone (VI). Selective reduction of this with Urushibara nickel A led to periplogenin (Ia). The epoxy-ketone (V) was also prepared from canarigenin (VII). Since digitoxigenin (III) had previously been converted to canarigenin (VII) and canarigenone (IV) the synthetic route to periplogenin constituted a formal total synthesis.

CERTAIN plants of the *Apocynaceae* and *Asclepiadaceae* families are known to produce periplogenin [2] (Ia) and corresponding 3-glycosides. Members of this group of cardiac active cardenolides occur, for example, as the parent genin (Ia) and its D-cymarose glycoside in *Pentopetia androsaemifolia* Decne.[3] and *Strophantus eminii* Asch. and Pax.,[4] and as D-digitoxose and D-fucose glycosides in *S. Vanderijettii* Staner and *S. sarmentosus*.[5] However, such cardenolides occur with related substances as complex mixtures and their isolation and identification has been difficult. The isolation of periplogenin (Ia) from the Chinese toad venom preparation Ch'an Su provides a recent illustration.[6] To make periplogenin (Ia) available for biological evaluation, a convenient synthesis was required.

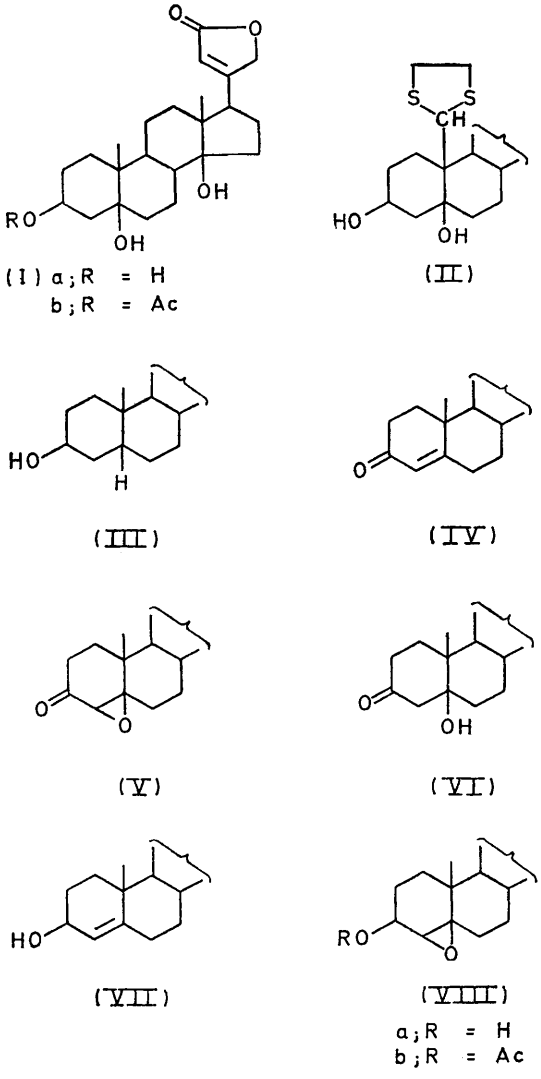
Speiser and Reichstein [7] have converted strophanthidin *via* the ethylene thioacetal derivative (II) into periplogenin (Ia), and this general approach offers a reasonable synthetic route. However our synthesis of the structurally analogous bufadienolide telocinobufagin [8] suggested that a shorter reaction pathway should be feasible, in which the readily available digitoxigenin (III) would be employed as both starting material and relay for formal total synthesis.

Digitoxigenin [9] (III) was used to prepare canarigenone (IV) by the two steps previously described.[1] Treating the ketone (IV) with peroxy-acid gave the epoxy-ketone (V) in *ca.* 20% yields. The less direct procedure of reducing the ketone (IV) to canarigenin (VII) [1] and then proceeding with peroxy-acid oxidation and subsequent oxidation of the 3β-hydroxy-group to give the ketone (V) did provide *ca.* 70% conversion in the step leading to the epoxy alcohol (VIIIa) but offered no advantage on an overall yield basis. Application of the Robinson chromium(II) acetate reduction reaction [2,8] to the epoxy-ketone (V) provided an excellent route to the hydroxy-ketone (VI) (60% yield), accompanied by a lesser amount of canarigenone [1] (IV). The mixture was easily separable by column chromatography. The hydroxy-ketone (VI) was readily identified from spectral data and its dehydration, under mild conditions, to canarigenone (IV).

The simplest method developed for the final step, reduction of the ketone (VI) to periplogenin (Ia), involved use of hydrogen on a surface of finely divided nickel. Treatment of the hydroxy-ketone (VI) with

[1] Part CXI, Y. Kamano, G. R. Pettit, and M. Tozawa, *J.C.S. Perkin I*, preceding paper.
[2] A brief history of periplogenin chemical characterization studies was included in a preliminary report: Y. Kamano, G. R. Pettit, and M. Tozawa, *J. Org. Chem.*, 1974, **39**, 2319.
[3] E. Wyss, H. Jäger, and O. Schindler, *Helv. Chim. Acta*, 1960, **43**, 664.
[4] R. Zelnik and O. Schindler, *Helv. Chim. Acta*, 1957, **40**, 2110.
[5] H. Lichti, C. Tamm, and T. Reichstein, *Helv. Chim. Acta*, 1956, **39**, 1933; B. Fechtig, O. Schindler, and T. Reichstein, *ibid.*, 1960, **43**, 727.
[6] N. Höriger, D. Živanov, H. H. A. Linde, and K. Meyer, *Helv. Chim. Acta*, 1970, **53**, 2051.
[7] P. Speiser and T. Reichstein, *Helv. Chim. Acta*, 1949, **32**, 1368. Analogously, the 3β-acetate of strophanthidin was converted by way of the trimethylene thioacetal derivative into 3-*O*-acetyl periplogenin (A. Katz, *Helv. Chim. Acta*, 1958, **41**, 1399). A synthesis of periplogenin from 21-acetoxypregna-4,14-diene-3,20-dione has also been reported: R. Deghenghi, A. Philipp, and R. Gaudry, *Tetrahedron Letters*, 1963, 2045. *Cf.*, also footnote 33 in C. R. Engle and G. Bach, *Steroids*, 1964, **3**, 593.
[8] G. R. Pettit and Y. Kamano, *J. Org. Chem.*, 1974, **39**, 2632.
[9] Y. Kamano, M. Tozawa, and G. R. Pettit, *J. Org. Chem.*, 1975, **40**, 793.

Urishibara nickel A [10] or with Raney nickel (W-2) [11] led to good yields of periplogenin (Ia). The synthetic specimen of periplogenin was easily reoxidized by *N*-bromoacetamide or, for example, chromium trioxide–pyridine complex to the hydroxy-ketone (VI), and was



identical with a specimen of the natural product kindly provided by Professor T. Reichstein. The synthetic sample exhibited the wide and variable m.p. range (227—234°) noted for the natural product isolated in various laboratories.[12] We have also experienced such behaviour with the closely related telocinobufagin.[8]

EXPERIMENTAL

For general techniques see Part XCI.[1]

4β,5-*Epoxy*-14-*hydroxy*-3-*oxo*-5β,14β-*card*-20(22)-*enolide* (V).—Canarigenone (IV) (40 mg), prepared [1] from digitoxigenin (III), was dissolved in chloroform (3 ml), and *m*-chloroperbenzoic acid (28 mg) was added. After 1 h at room temperature, the mixture was diluted with chloroform and poured into ice–water. The organic layer was washed with water, dilute aqueous sodium thiosulphate, and water. Removal of solvent left a crude product (45 mg) which was chromatographed on a column of silica gel. Hexane–acetone (5 : 1) eluted the *epoxy-ketone* (V), prisms, m.p. 229—232° (from acetone–hexane) (Found: C, 71.45; H, 7.85. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%); $\nu_{max.}$ (KBr) 3 480 (OH), 1 780, 1 740, 1 710, 1 690 (butenolide ring and ketone), 1 210, 950, 910, 850, and 750 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 218 nm (log ε 4.23); δ (10% solution in $CDCl_3$) 0.89 (3 H, s, 18-H_3), 1.16 (3 H, s, 19-H_3), 2.80 (1 H, d, *J* 8 Hz, 17α-H), 3.05 (1 H, s, 4α-H), 4.80 and 5.10 (2 H, slightly doubled AB-type q, *J* 18 and 2 Hz, 21-H_2), and 5.90 (1 H, t, *J* 2 Hz, 22-H); *m/e* 386 (M^+) and 368 (M^+-H_2O).

4β,5-*Epoxy*-3β,14-*dihydroxy*-5β,14β-*card*-20(22)-*enolide* (VIIIa).—To a solution of canarigenin (VII) (0.10 g; prepared from digitoxigenin) [1] in chloroform (5 ml) was added *m*-chloroperbenzoic acid (50 mg). The mixture was kept at room temperature for 1 h, and the crude product was, isolated as described in the preceding experiment. Elution with 3 : 1 hexane–acetone gave the epoxy-alcohol (VIIIa) (78 mg), prisms, m.p. 220—224° (from methanol–hexane) (lit.,[13] 218—232°); $\nu_{max.}$ 3 540, 3 480, 3 440 (OH), 1 780, 1 738, 1 618 (butenolide ring), 1 249, 1 210 (C–O), 900, 858, and 755 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 217 nm (log ε 4.22); *m/e* 388 (M^+), 370 (M^+-H_2O), and 352 ($M^+-2\ H_2O$).

Acetylation of the alcohol (VIIIa) (25 mg) with acetic anhydride (0.3 ml)–pyridine (0.5 ml) and recrystallization of the product from chloroform–acetone–hexane yielded 3β-acetoxy-4β,5-epoxy-14-hydroxy-5β,14β-card-20(22)-enolide (VIIIb) (19 mg), prisms, m.p. 225—227° (lit.,[13] 225—229°); (Found: C, 69.8; H, 7.95. Calc. for $C_{25}H_{34}O_6$: C, 69.75; H, 7.95%); $\nu_{max.}$ (KBr) 3 500 (OH), 1 775, 1 735, 1 720, 1 690, 1 620 (butenolide ring and ester CO), 1 260, 1 220, 1 200 (C–O), 900, 860, and 750 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 218 nm (log ε 4.20); δ (10% solution in $CDCl_3$) 0.91 (3 H, s, 18-H_3), 1.05 (3 H, s, 19-H_3), 2.01 (3 H, s, 3-OAc), 2.77 (1 H, d, *J* 8 Hz, 17α-H), 3.19 (1 H, d, *J* 3.5 Hz, 4α-H), *ca.* 4.75 and 5.05 (3 H, slightly doubled AB-type overlapping with the 3α-proton signal at *ca.* 5.08 *J* 18 and 2 Hz, 21-H_2 and 3α-H), and 5.89 (1 H, t, *J* 2 Hz, 22-H); *m/e* 430 (M^+), 412 (M^+-H_2O), 370 (M^+-AcOH), and 352 ($M^+-AcOH-H_2O$).

Oxidation of the Epoxy-alcohol (VIIIa).—(A) *With chromium trioxide.* The epoxy-alcohol (20 mg) in pyridine (0.5 ml) was oxidized (room temperature, 18 h) with chromium trioxide (18 mg)–pyridine (0.2 ml) complex. The excess of reagent was removed with methanol and the mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water and concentrated to dryness. The residue was subjected to column chromatography on silica gel. Hexane–acetone (5 : 1) eluted the epoxy-ketone (V) (15 mg), m.p. 230—233° (from acetone–hexane).

In another experiment the epoxy-alcohol (80 mg) in acetic acid (1.0 ml) was oxidized with chromium trioxide (40 mg) in acetic acid (1.4 ml) containing 2 drops of water.

[10] K. Hata, 'Urushibara Catalyst,' University of Tokyo Press, Tokyo, 1971, p. 39. For a recent summary of experimental methods see K. Hata, I. Motoyama, and K. Sakai, *Org. Prep. and Procedures*, 1973, **4**, 179. See also Y. Kamano and G. R. Pettit, *J. Org. Chem.*, 1973, **38**, 2202.

[11] *E.g.* see G. Bach, J. Capitaine, and C. R. Engle, *Canad. J. Chem.*, 1968, **46**, 733; G. R. Pettit and E. Van Tamelen, *Org. Reactions*, 1962, **12**, 356.

[12] *E.g.* W. A. Jacobs and A. Hoffmann, *J. Biol. Chem.*, 1928, **79**, 519.

[13] L. Sawlewicz, H. A. Linde, and K. Meyer, *Helv. Chim. Acta*, 1968, **51**, 1353.

In this case the mixture was stirred for 2 h at 15—20 °C. The epoxy-ketone (V) (52 mg; m.p. 230—233°) was isolated as just described.

(B) *With* N-*bromoacetamide*. To a solution of the alcohol (VIIIa) (20 mg) in methanol (1.8 ml)–acetone (1.8 ml) was added a solution of *N*-bromoacetamide (25 mg) in methanol (0.4 ml)–water (0.08 ml). Before isolation of the product, the mixture was kept at 20 °C for 22 h. Here, the yield of epoxy-ketone (V), m.p. 227—230°, was 12 mg. The specimens prepared by methods (A) and (B) were identical.

5,14-*Dihydroxy*-3-*oxo*-5β,14β-*card*-20(22)-*enolide* (VI).—Freshly prepared chromium(II) acetate [14] (0.28 g) was added to a solution of the epoxy-ketone (V) (70 mg) in ethanol (7 ml). The reduction was performed at room temperature during 30 min. After dilution with chloroform, the mixture was poured into ice–water and the chloroform layer was washed with water. Removal of solvent gave a residue (78 mg) which was chromatographed on a column of silica gel. Hexane–acetone (5 : 1) was eluted canarigenone (IV) (19 mg) m.p. 257—261° (from methylene chloride–acetone). Hexane–acetone (3 : 1) eluted the *hydroxy-ketone* (VI) (42 mg), prisms, m.p. 235—239° (from chloroform–methanol) (Found; C, 71.3; H, 8.25. $C_{23}H_{32}O_5$ requires C, 71.15; H, 8.25%); t.l.c. (1 : 9 methanol–chloroform) R_F 0.33, (1 : 9 hexane–ethyl acetate) R_F 0.18; $\nu_{max.}$ (KBr) 3 510, 3 480, 3 420 (OH), 1 780, 1 750, 1 740, 1 730, 1 710, 1 688 (butenolide ring and ketone), 1 030, 960, 920, 860, and 740 cm^{-1}; δ (10% solution in $CDCl_3$) 0.93 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 2.78 (1 H, m, 17α-H), 4.78 and 5.06 (2 H, slightly doubled AB-type q, *J* 18 and 2 Hz, 21-H_2), and 5.88 (1 H, t, *J* 2 Hz, 22-H); *m/e* 388 (M^+) 370 (M^+-H_2O), and 352 ($M^+-2\ H_2O$).

Dehydration of the Hydroxy-ketone (VI).—(*A*). *With oxalic acid*. The hydroxy-ketone (VI) (15 mg), oxalic acid (10 mg), and methanol (1.5 ml) were heated at reflux for 15 min, poured into ice–water and extracted with methylene chloride. The combined extract was washed with water and evaporated. The residue was separated by preparative t.l.c. on silica gel (3 : 3 : 4 acetone–chloroform–hexane). The zone corresponding to R_F 0.22 was eluted with 4 : 1 chloroform–methanol. Recrystallization from methylene chloride–acetone yielded canarigenone (IV) (12 mg), prisms, m.p. 255—259°.

(B) *With Amberlite* CG-120 (H^+ *form*). The hydroxy-ketone (VI) (30 mg), Amberlite CG-120 (H^+ form) (0.15 g), and ethanol (3 ml) were stirred at room temperature for 6 h. The solution was filtered and evaporated and the residue was purified by preparative t.l.c. as in method (A) to give canarigenone (IV) (25 mg), m.p. 260—263°, was obtained.

The specimens prepared by methods (A) and (B) were identical with an authentic sample prepared from digitoxigenin.

Periplogenin (Ia), [3β,5,14-*Trihydroxy*-5β,14β-*card*-20(22)-*enolide*].—(A) *Reduction by Raney nickel*. A large excess of freshly prepared Raney nickel (W-2) [11] was added to a solution of the hydroxy-ketone (VI) (50 mg) in ethanol (5 ml). The mixture was heated at reflux for 1 h and filtered. Removal of solvent left a residue (55 mg) which was chromatographed on a column of silica gel. Hexane–acetone (1 : 3) eluted periplogenin (Ia) (41 mg), m.p. 227—234° (from methanol) (see Discussion section), identical with an authentic specimen (m.p. 210—235°) of natural periplogenin (Ia) generously provided by Professor T. Reichstein.

(B) *Reduction with Urushibara nickel A*. The preceding experiment was repeated with the hydroxy-ketone (VI) (30 mg) and a large excess of freshly prepared Urushibara nickel A.[10] In this case preparative t.l.c. [acetone–chloroform–hexane (4 : 3 : 3)] led to periplogenin (Ia) (26 mg), m.p. 225—231°, identical with the specimen prepared by method A.

Synthetic periplogenin (Ia) (28 mg) was treated with acetic anhydride (0.4 ml)–pyridine (0.6 ml) for 18 h at room temperature. Recrystallization of the crude acetate from acetone–hexane gave 3-*O*-acetylperiplogenin (Ib) (23 mg), m.p. 233—241° (lit.,[15] 231—239 and 235—245°), t.l.c. (1 : 9 methanol–chloroform) R_F 0.40, (1 : 9 hexane–ethyl acetate) R_F 0.24; $\nu_{max.}$ (KBr) 3 480, 3 410 (OH), 1 780, 1 740, 1 710, 1 690, 1 625 (butenolide ring and ester CO), 1 250, 1 210, 950, 860, 818, and 735 cm^{-1}; *m/e* 432 (M^+), 414 (M^+-H_2O), 396 ($M^+-2\ H_2O$), 372 (M^+-AcOH), and 354 ($M^+-AcOH-H_2O$).

Natural periplogenin (5 mg) was acetylated (see above) to give 3-*O*-acetylperiplogenin (Ib) m.p. 229—237°, identical with the foregoing sample.

Selective Oxidation of Periplogenin (Ia).—(A) *With chromium trioxide*. A solution of periplogenin (Ia) (20 mg) in pyridine (0.5 ml) was added to the freshly prepared complex from chromium trioxide (20 mg) and pyridine (0.2 ml). After 24 h at room temperature, the mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water, dilute hydrochloric acid, and water. Removal of solvent left a residue (22 mg) which was subjected to preparative t.l.c. on silica gel (1 : 9 methanol–chloroform). Elution of the zone corresponding to R_F 0.29 with 3 : 1 methylene chloride–methanol and recrystallization from chloroform–methanol afforded the hydroxy-ketone (VI) (14 mg), m.p. 233—238°.

Use of chromium trioxide (10 mg) in acetic acid (7 ml) (room temperature, 2 h) similarly gave the hydroxy-ketone (VI) (12 mg), m.p. 230—237°.

(B) *With* N-*bromoacetamide*. Periplogenin (Ia) (20 mg) in methanol (2 ml)–acetone (1 ml), was treated with *N*-bromoacetamide (22 mg) in methanol (0.4 ml)–water (0.1 ml) for 42 h at 20 °C. The mixture was poured into ice–water and extracted with methylene chloride. The extract was washed with water, dilute aqueous sodium sulphite and water, and evaporated. The residue was purified by preparative t.l.c. as in method (A) to give the hydroxy-ketone (VI) (11 mg), m.p. 231—237°.

The product from both methods identical with the hydroxy-ketone (VI) prepared from canarigenone.

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[14] C. H. Robinson and R. Henderson, *J. Org. Chem.*, 1972, **37**, 565; see also J. H. Balthis and J. C. Bailar, *Inorg. Synth.*, 1939, **1**, 122.

[15] P. Speiser and T. Reichstein, *Helv. Chim. Acta*, 1947, **30**, 2143; A. Lardon, *ibid.*, 1950, **33**, 639.