Dinitrophenylhydrazone[19]: mp 162° (recrystallized from EtOH). *Anal.* Calcd. for $C_{14}H_{18}O_4N_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.90; H, 6.05; N, 18.06.

R(−)-**5c**: IR ν_{max}^{film} cm^{-1}: 1710 ($\nu_{C=O}$). NMR (in $CDCl_3$): 0.90 (3H, t, J=6.0 cps, $C\underline{H}_3CH_2CH_2$), 1.0—2.6 (13H, m, other protons). IR and NMR spectra of *R*(−)-**5c** prepared with *S*(−)-**2a** and *S*(+)-**2b** were identical when measured in the same states. ORD (c=2.610, MeOH) $[\alpha]^{20}(m\mu)^{20}$: −7.3° (700), −10.2° (589), −11.9° (550), −16.9° (500), −24.6° (450), −41.4° (400), −107° (350), −376° (305) (trough), 0° (289), +346° (274) (peak). Semicarbazone[19]: mp 130° (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{19}O_2N_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.80; H, 9.61; N, 21.48.

S(−)-**5d**: IR ν_{max}^{film} cm^{-1}: 1710 ($\nu_{C=O}$). NMR (in $CDCl_3$): 0.90 (6H, d, J=7.0 cps, $(C\underline{H}_3)_2CH$), 1.1—2.5 (10H, m, other protons). ORD (c=1.566, MeOH) $[\alpha]^{23}(m\mu)$: −14.0° (700), −21.7° (589), −27.4° (550), −35.0° (500), −47.8° (450), −79.8° (400), −179° (350), −575° (310) (trough), 0° (290), +575° (270) (peak). Semicarbazone[19]: mp 185° (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{19}ON_3$: C, 60.88; H, 9.71; N, 21.30. Found: C, 60.89; H, 9.70; N, 21.54.

S(−)-**5e**: IR ν_{max}^{film} cm^{-1}: 1716 ($\nu_{C=O}$), 1640 ($\nu_{C=C}$). NMR (in $CDCl_3$): 1.10—2.80 (11H, m, other protons), 4.91 (1H, d, J=1 cps $_{H}\!>\!C\!=\!C\!<^{H}_{H}$), 5.05 (1H, d, J=6 cps, $_{H}\!>\!C\!=\!C\!<^{H}_{H}$), 5.5—6.0 (1H, m, $-C\underline{H}\!=\!CH_2$). ORD (c=2.219, MeOH) $[\alpha]^{20}(m\mu)$: −3.6° (700), −4.5° (589), −6.3° (550), −9.0° (500), −14.9° (450), −27.0° (400), −76.5° (350), −302 (306) (trough), 0° (288), +306° (264) (peak). Semicarbazone[19]: mp 172° (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{17}ON_3$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.53; H, 8.63; N, 21.34.

Acknowledgement The authors are grateful to the members of the Central Analysis Room of this Faculty for elemental analyses and spectral data.

20) This ORD curve was measured for *R*(−)-**5c** prepared with *S*(−)-**2a**.

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Conversion of Digitoxigenin to Uzarigenin

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A great number of cardenolide aglycones have been found in nature, the majority of which belong to *cis*- or *trans*-A/B steroids.[2] There are several instances where both type cardenolides isomeric only at the C-5 position are known. Between 5β- and 5α-cardenolide, however, the former far predominates over the latter. It is to be desired, therefore, to devise a simple, convenient method of converting 5β-cardenolide to 5α-cardenolide. This paper describes the conversion of digitoxigenin (I) to uzarigenin (IIa), which represent 5β- and 5α-cardenolide respectively.

Previously[3] it was reported that 3-hydroxy-5β-steroids undergo epimerization at the C-5 position to provide 3-keto-5α-compounds on heating under reflux with freshly prepared Raney nickel in a solvent such as *p*-cymene. This procedure has been successfully applied to 5β-cholanoates for the preparation of 5α-cholanoates.[4–7] The attempt[8] to prepare IIa,

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on the other hand, by applying this procedure to I or 3-oxodigitoxigenin (V) failed owing to the alkalinity of Raney nickel. Recently[9,10] another procedure has been reported for the isomerization of the steroidal-type *cis*-A/B ring juncture to *trans*-A/B one, which is accomplished *via* treatment with 10% palladium-charcoal catalyst in refluxing triglyme (triethylene glycol dimethyl ether).

Thus, V was heated in boiling triglyme with 10% palladium-charcoal catalyst for three hours, affording a mixture of five compounds (V, VI, VII, IX, and X) including the starting material. The mixture was separated into four fractions by column chromatography and preparative thin-layer chromatography (TLC). A fraction containing V and 3-oxo-uzarigenin (VI) which were hardly separable was treated with sodium borohydride to give IIa, 3-epi-digitoxigenin (III) and I. IIa and its acetate (IIb) were identical with an authentic sample of uzarigenin and uzarigenin acetate, respectively. The estimated yield of IIa from V was about 3%.

The compound (VII) obtained in about 12% yield was found to be an isomer of V, whose nuclear magnetic resonance (NMR) spectrum exhibited signals at 3.22 ppm ascribable to the 17β-proton.[11] It was found to be identical with 3-oxo-17α-digitoxigenin (3-oxomenabegenin), which was prepared by chromium trioxide-pyridine complex oxidation of 17α-digitoxigenin (menabegenin) (IV) or by isomerization of V according to the procedure of Kuritzkes, *et al.*[12] The principal product (IX) obtained in about 18% yield gave a positive reaction for 3-oxo-Δ^4-steroids with isonicotinic acid hydrazide reagent (INAH test)[13] and its ultraviolet (UV), infrared (IR) and NMR spectra given in the "Experimental" below clearly indicated

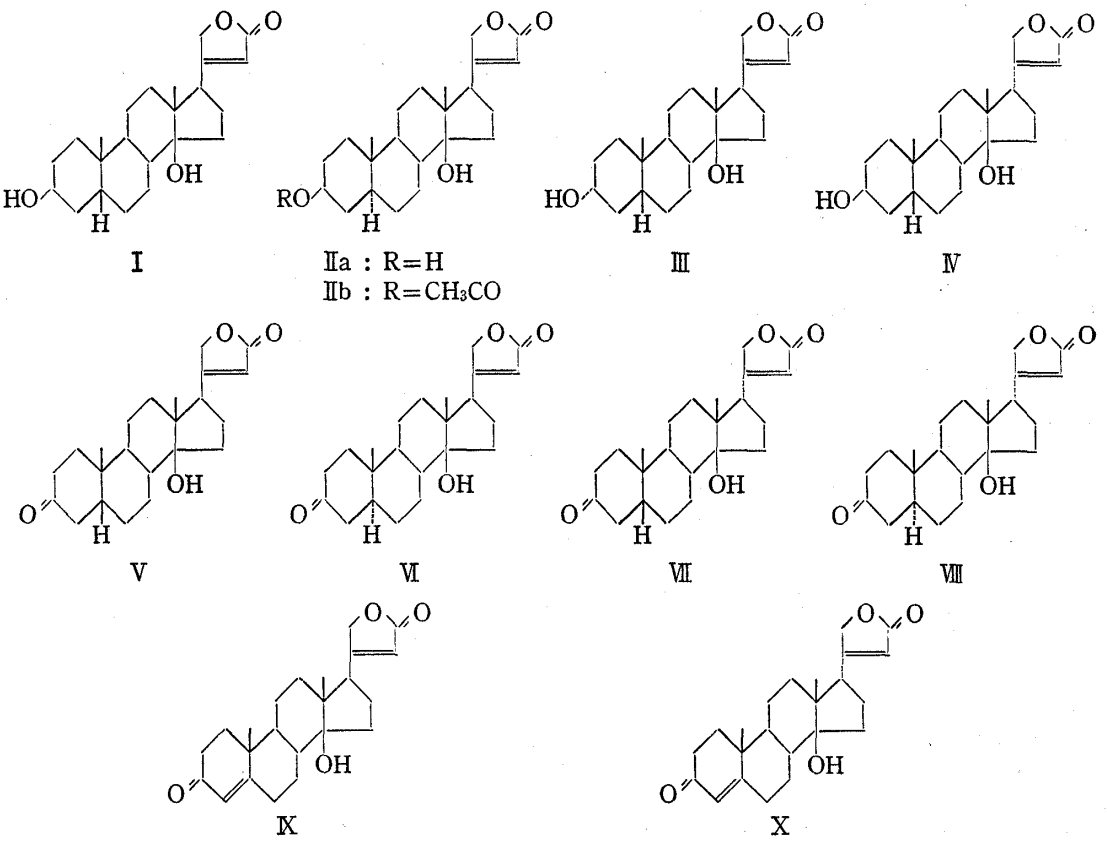

Chart 1

9) S.W. Pelletier, Y. Ichinohe, and D.L. Herald, Jr., *Tetrahedron Letters*. **1971**, 4179.
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the presence of the 3-oxo-Δ^4-grouping together with the butenolide in IX. By direct comparison with an authentic sample prepared from V by selenium dioxide oxidation according to the procedure as described by Satoh, *et al.*,[14] IX was identified as anhydroperiplogenone (14-hydroxy-3-oxo-14β-carda-4,20(22)-dienolide).[15] Similarly, based on the spectroscopic (UV, IR, NMR) data indicated in the "Experimental", the minor product (X) was reasonably presumed to be 17α-anhydroperiplogenone (14-hydroxy-3-oxo-14β,17α-carda-4,20(22)-dienolide). This compound was prepared by selenium dioxide oxidation of VII and found to be identical with X.

It was reported previously[16] that the transformation of 3-oxo-5β-steroids to 5α-compounds by heating with Raney nickel in boiling *p*-cymene proceeds by desaturation to 3-oxo-Δ^4-steroids. In view of the above result that the compound (IX) having 3-oxo-Δ^4-grouping predominates over the other ones produced in the epimerization reaction, IX was treated with palladium-charcoal catalyst in refluxing triglyme in the same manner with V. As expected, VI was obtained together with X and 3-oxo-17α-uzarigenin (VIII).[12] Treatment of VI with sodium borohydride gave IIa. The estimated yield (*ca.* 10%) of IIa from IX was fairly better than that from V.

Since the treatment of cardenolides with 10% palladium-charcoal catalyst in refluxing triglyme usually brought about the inversion of the butenolide at C-17 from β to α (V→VII, IX→X, VI→VIII), V was heated in boiling triglyme without the catalyst. It was found that the isomerization takes place regardless of the presence of the catalyst. The original procedure for the isomerization reported previously,[12] however, is far better than that described here. The mechanism of the isomerization[12] may be similar in both procedures.

Experimental[17]

Treatment of 3-Oxodigitoxigenin (V) with Palladium-Charcoal in Triglyme——To a solution of V (1 g) in triglyme (25 ml) was added 10% Pd-C (500 mg) and the solution was refluxed for 3 hr. After removal of the catalyst by filtration, the filtrate was diluted with CH_2Cl_2, washed with H_2O and dried over anhyd. Na_2SO_4. After usual work-up an oily residue obtained was chromatographed on a column of acid-washed alumina (70 g) and then submitted to preparative TLC using hexane–AcOEt (1: 3) as developing solvent. Four fractions (Fr. 1, 2, 3, 4) were obtained by eluting the adsorbents with CH_2Cl_2 corresponding to four spots (*Rf*: 0.57, 0.37, 0.34, 0.22).

Uzarigenin (IIa) and Its Acetate (IIb)——To a solution of the above Fr. 1 (261 mg) containing V and VI in MeOH (10 ml)–H_2O (2 ml) was added portionwise $NaBH_4$ (150 mg) under ice-cooling and the reaction mixture was allowed to stand at 0° for 30 min. After decomposing the excess reagent with AcOH, the resulting solution was extracted with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhyd. Na_2SO_4. After evaporation of the solvent the crystalline residue was recrystallized from MeOH to give III (65 mg) as colorless prisms, mp 290—298°, which was identical with an authentic specimen of 3-epi-digitoxigenin in the mixed melting point, TLC, and comparison of the IR spectrum. The combined mother liquor was submitted to preparative TLC using hexane–AcOEt (1: 3) as solvent. The adsorbent corresponding to the spot (*Rf*: 0.38) was eluted with CH_2Cl_2. Recrystallization of the eluate from MeOH–benzene gave IIa (22 mg) as colorless needles. mp 235—243°. Mixed mp on admixture with an authentic sample of uzarigenin showed no depression and IR spectra of the two samples were identical in all respects. IIa (9 mg) was acetylated in the usual way with Ac_2O and pyridine followed by recrystallization from acetone–

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16) M.N. Mitra and W.H. Elliott, *J. Org. Chem.*, **34**, 2170 (1969).
17) Melting points were determined on a Kofler block and are uncorrected. UV spectra were measured in 99% EtOH solution. IR spectra were determined in KBr disks on Hitachi EPI-S2 spectrophotometer. NMR spectra were measured at room temperature at 60 MHz, using Hitachi Model R-20A 60 MHz spectrometer. Chemical shifts are expressed in δ (parts per million) with tetramethylsilane as internal standard. The coupling constants (J) are expressed in cycles per second: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad singlet. TLC plates were prepared according to the Stahl's procedure using silica gel GF_{254} or HF_{254} (E. Merck AG) as adsorbents. Spots were revealed by heating plates at 110° for 10 min after spraying 95% H_2SO_4 or by Kedde reagent.

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hexane to yield IIb (8 mg) as colorless prisms. mp 260—268°. Mixed mp on admixture with an authentic specimen of uzarigenin acetate showed no depression and IR spectra of the two samples were entirely identical in every respect. From the eluate of the adsorbent corresponding to the spots (*Rf*: 0.33, 0.46) were obtained III (114 mg) and I (30 mg), respectively.

3-Oxo-17α-digitoxigenin (VII)——a) From Fr. 2: Recrystallization of Fr. 2 from acetone–hexane afforded VII (118 mg) as colorless prisms. mp 240—246°. $[\alpha]_D^{25}$ +51° (c=0.12, $CHCl_3$), IR ν_{max} cm^{-1}: 3550 (OH), 1795, 1750, 1630 (butenolide), 1700 (3C=O). NMR (5% solution in $CDCl_3$) δ: 1.03 (3H, s, 19-CH_3), 1.08 (3H, s, 18-CH_3), 3.22 (1H, t, J=8 cps, 17β-H), 4.78 (2H, d, J=1.5 cps, 21-CH_2), 5.90 (1H, m. 22-H). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.09; H, 8.89. It was identical with an authentic specimen of VII given below in the mixed melting point, TLC, and comparison of the IR spectrum.

b) From IV: A solution of IV (12 mg) in pyridine (1 ml) was added to a slurry of CrO_3 (50 mg) and pyridine (0.5 ml). The reaction mixture was allowed to stand at room temperature overnight, poured into ice-water, and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was subjected to preparative TLC using hexane–AcOEt (1: 3) as solvent. Elution of the adsorbent corresponding to the spot (*Rf*: 0.37) with CH_2Cl_2 and recrystallization of the eluate from acetone–hexane gave VII (9 mg) as colorless prisms. mp 235—243°.

c) From V: i) To a solution of V (20 mg) in dimethylformamide (6 ml) were added anhydrous AcONa (25 mg) and sodium tosylate (60 mg). The mixture was heated for 23 hr at 115°, and then poured into ice-water. The product was extracted with CH_2Cl_2. The organic layer was washed with 2% HCl, H_2O and dried over anhyd. Na_2SO_4. The solvent was evaporated and the oily residue was submitted to preparative TLC using hexane–AcOEt (1: 3) as solvent. Elution of the adsorbent corresponding to the spot (*Rf*: 0.37) with CH_2Cl_2 and recrystallization of the eluate from acetone–hexane gave VII (6 mg) as colorless leaflets. mp 245—248°. Elution of the adsorbent corresponding to the spot (*Rf*: 0.57) gave the starting material V (8 mg). ii) A solution of V (20 mg) in triglyme (1.5 ml) was refluxed for 3 hr. After work-up as described above the oily residue was submitted to preparative TLC to afford VII (2 mg), mp 238—244°, and V (13 mg).

Anhydroperiplogenone (IX)——Recrystallization of the above Fr. 3 from acetone–hexane gave IX (179 mg) as colorless leaflets. mp 227—234°. UV λ_{max} mμ (log ε): 241 (4.13),[18] IR ν_{max} cm^{-1}: 3500 (OH), 1775, 1740, 1665, 1655, 1615 (butenolide and 3-oxo-Δ^4). NMR (5% solution in $CDCl_3$) δ: 0.94 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 2.83 (1H, m, 17α-H), 4.91 (2H, bs, 21-CH_2), 5.78 (1H, bs, 4-H), 5.92 (1H, bs, 22-H). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.42; H, 8.17. It stained yellow in INAH test. It was identical with an authentic sample of anhydroperiplogenone prepared from V according to the procedure reported earlier[14] in the mixed melting point, TLC, and comparison of the IR spectrum.

17α-Anhydroperiplogenone (X)——a) From Fr. 4: Recrystallization of Fr. 4 from acetone–hexane gave X (27 mg) as colorless leaflets. mp 228—230°. $[\alpha]_D^{25}$ +146° (c=0.10, $CHCl_3$), UV λ_{max} mμ (log ε): 240 (4.11),[19] IR ν_{max} cm^{-1}: 3550 (OH), 1795, 1745, 1655, 1620 (butenolide and 3-oxo-Δ^4). NMR (5% solution in $CDCl_3$) δ: 1.11 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 3.23 (1H, t, J=8 cps, 17β-H), 4.80 (2H, d, J=1.5 cps, 21-CH_2), 5.78 (1H, bs, 4-H), 5.92 (1H, t, J=1.5 cps, 22-H). *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.62; H, 8.32. It gave a positive INAH test.

b) From VII: To a solution of VII (20 mg) in *tert*-BuOH (3.4 ml)-AcOH (0.6 ml) was added SeO_2 (5 mg) and the solution was refluxed for 3 hr under nitrogen. After filtration of deposited selenium, the filtrate was diluted with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$, H_2O and dried over anhyd. Na_2SO_4. After usual work-up the oily residue was submitted to preparative TLC using hexane–AcOEt (1: 3) as solvent. Elution of the adsorbent corresponding to the spot (*Rf*: 0.22) with CH_2Cl_2 and recrystallization of the eluate from acetone–hexane afforded X (9 mg) as colorless leaflets. mp 227—229°. Mixed mp on admixture with the sample described above showed no depression and IR spectra of the two samples were identical in all respects.

Treatment of Anhydroperiplogenone (IX) with Palladium-Charcoal in Triglyme——To a solution of IX (85 mg) in triglyme (5 ml) was added 10% Pd-C (80 mg) and the solution was refluxed for 3 hr. After working up in the way described above, the oily residue was submitted to preparative TLC using hexane–AcOEt (1: 3) as developing solvent. The adsorbent corresponding to the spot (*Rf*: 0.57) was eluted with CH_2Cl_2. Recrystallization of the eluate from CH_2Cl_2–hexane afforded VI (10 mg) as colorless prisms. mp 260—268°. Treatment of VI (8 mg) with $NaBH_4$ in the way described above gave IIa (6 mg), mp 240—245°. The adsorbent corresponding to the spot (*Rf*: 0.37) was eluted with CH_2Cl_2. Recrystallization of the eluate from acetone–hexane yielded VIII (14 mg) as colorless leaflets. mp 255—262°. IR spectrum of VIII was identical with that of 3-oxo-17α-uzarigenin reported previously[12] in all respects. From the eluate of the adsorbent corresponding to the spots (*Rf*: 0.35, 0.22) were obtained IX (11 mg) and X (10 mg).

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18) Difference between IX and V.
19) Difference between X and VII.

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