Steroids and Related Natural Products. 69. Synthesis of 20(22)-Dihydro-23-deoxodigitoxigenin[1,2]

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A synthetic route from digitoxigenin to 20(22)-dihydro-23-deoxodigitoxigenin (**10a**) has been developed. Digitoxigenin was acetylated, dehydrated, and selectively hydrogenated to give 3β-acetoxy-5β,20ξ-card-14-enolide (**4**). Reduction with lithium aluminum hydride gave diol **5** which was cyclized to yield 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**). Introduction of the 14β-hydroxyl (**10a**) group was achieved by successive formation of the 14β-hydroxy-15α-bromo (**7**) and β-epoxide (**8**) derivatives followed by a reduction step.

The relationship of structure to cardiac activity in naturally occurring cardenolides has been receiving increased attention.[3] For example, the effect on activity with respect to type and number of glycoside units and location of certain oxygen functional groups on the steroid nucleus has been studied by Chen.[3] Less attention has been given to the lactone ring, but it is known[4] that a 20-fold decrease in cardiac activity results when the lactone ring of digitoxigenin is modified by hydrogenation. Thus, we undertook synthesis of 20(22)-dihydro-23-deoxodigitoxigenin (**10a**) to provide a model lacking the entire lactone π-bond system.

Digitoxin (**1a**) served as starting material and was hydrolyzed[5] in high yield to digitoxigenin (**1b**). Preparation of 3β-acetoxy-5β-carda-14,20(22)-dienolide (**2b**) was achieved as described by Engel.[6] Application of 5% palladium on calcium carbonate catalyst was successful in selective reduction of olefin **2b** to 3β-acetoxy-5β,20ξ-card-14-enolide (**4**, 86% overall yield from digitoxigenin). A second pathway to Δ^{14} olefin **4** which involved hydrogenation of the C-20(22) double bond in digitoxigenin (**1b**) to give dihydrodigitoxigenin (**3a**) followed by the preceding acetylation–dehydration sequence led to a 72% overall yield from digitoxigenin (**1b**).

Next, 3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**) was obtained (35% yield) by reduction of lactone **5** with lithium aluminum hydride. An attempt at reducing lactone **2b** directly to triol **5** with lithium aluminum hydride produced a complex mixture and was discontinued. Once alcohol **5** was in hand, cyclization to 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**) was explored. Gillis and Beck[7] reported high yields for diol → tetrahydrofuran cyclization using hot dimethyl sulfoxide. Another method frequently employed utilizes *p*-toluenesulfonyl chloride in pyridine.[8] The dimethyl sulfoxide method was evaluated first. In a series of accessory experiments redistilled dimethyl sulfoxide (from calcium hydride) was found acidic enough to cleave tetrahydropyranyl ethers. Later it was determined that neutral dimethyl sulfoxide was best obtained by passing through a column of basic alumina. When diol **5** was heated in neutral dimethyl sulfoxide at 150° for 5 hr, 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**) resulted in 45% yield. The same cyclization to tetrahydrofuran **6** was also realized in 34% yield by heating diol **5** in pyridine with *p*-toluenesulfonyl chloride.

The final sequence involved reintroduction of the 14β-hydroxyl group. Formation of the 14β-hydroxyl derivative of a Δ^{14} steroid usually involves preparation of the corresponding 14β,15β epoxide. Reduction of such 14,15 epoxides with lithium aluminum hydride readily gives the 14β alcohol.[9] Several methods for obtaining 14β,15β epoxides exist. Addition of hypobromous acid to the Δ^{14} position leads to 14β-hydroxy-15α-bromo derivatives which can be converted to β epoxides by base treatment.[9c,10] Another method involves oxidation of the Δ^{14} olefin with a peracid to give a 14α,15α epoxide followed by acid cleavage to a 14β,15α diol and treatment with a sulfonyl chloride to effect ring closure.[11] On one occasion[12] involving 14-dehydrobufalin, *m*-chloroperbenzoic acid was shown to give resibufogenin, the 14β,15β epoxide, rather than the 14α,15α epoxide expected from peracid treatment. However, in later experiments[2] with different specimens of *m*-chloroperbenzoic acid only the expected 14α,15α epoxide was obtained. Thus, treatment of 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**) with *m*-chloroperbenzoic acid afforded a 14,15 epoxide which showed a proton magnetic resonance chemical shift of 3 Hz upfield for the C-18 methyl resonance. Furthermore, lithium aluminum hydride reduction of this epoxide gave a C-14 alcohol which also showed an upfield shift of 7 Hz for the C-18 methyl group. Previously, studies of Δ^{14} steroids have shown that the C-18 methyl group is shifted up-

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(2) For part 68 of this series, see G. R. Pettit, Y. Kamano, F. Bruschweiler, and P. Brown, *J. Org. Chem.*, **36**, 3736 (1971).

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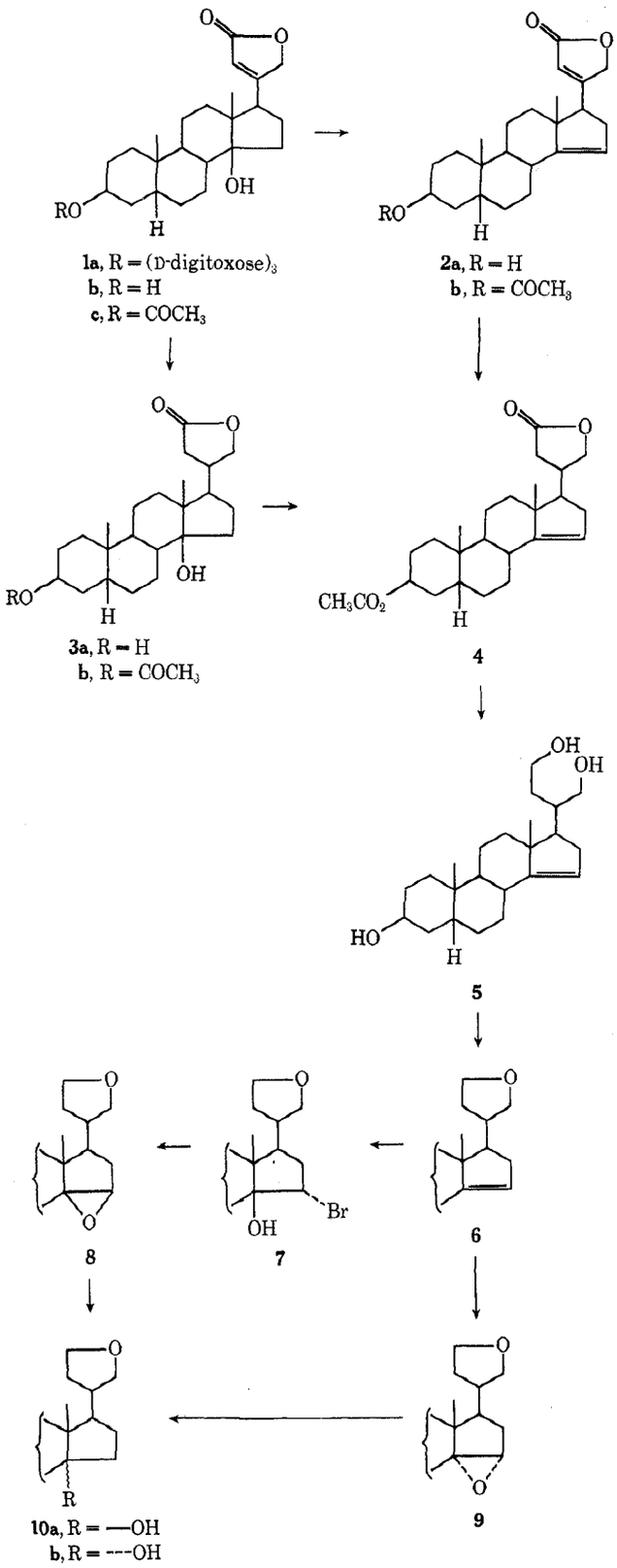

field for an α-epoxide[13] and a 14α-hydroxyl group[14] and downfield for β substitution. Therefore, the upfield shifts serve to confirm that both substances were substituted on the D ring α side and were thus formulated as α epoxide **9** and 14α alcohol **10b**. The same result was obtained when 3β-acetoxy-14-dehydrodigitoxigenin (**2b**) was epoxidized by means of *m*-chloroperbenzoic acid. Support for this conclusion came from a shift in the C-18 methyl resonance of 2 Hz upfield and comparison of physical data with that reported by Meyer[10] for both the 14α,15α and 14β,15β epoxides of digitoxigenin.

Attention was next directed to a halohydrin approach to the 14β alcohol. Reaction of olefin **6** with *N*-bromoacetamide and perchloric acid in dioxane afforded the 14β-hydroxy-15α-bromo derivative **7**. Crude bromohydrin **7** was cyclized to β epoxide **8** employing methanolic potassium acetate. The β-epoxide configuration was confirmed by shift of the C-18 methyl resonance downfield 9 Hz. Reduction of epoxide **8** by means of lithium hydride gave 20(22)-dehydro-23-deoxodigitoxigenin (**10a**). The 14β-hydroxyl configuration was substantiated by a 5-Hz downfield shift of the 18-methyl group signal.

Experimental Section

All common reagents and solvents used were "Baker Analyzed," Mallinckrodt AR, or Matheson Coleman and Bell AR. Ligroin refers to Skellysolve B, bp 65–70°. Tetrahydrofuran, ether, benzene, *p*-dioxane, and pyridine were purified and redistilled. Dimethyl sulfoxide was purified by passing through a column of basic alumina. *N*-bromoacetamide was recrystallized and employed immediately. *m*-Chloroperbenzoic acid (from Aztec Chemical Co.) was purified by the method of Schwartz and Blumbergs.[15] The following materials were used as obtained from the sources indicated: 5% palladium on calcium carbonate, Englehard Industries; digitoxin, Centerchem, Inc.; lithium aluminum hydride, Ventron Corp.

Silica gel HF_{254} (E. Merck, Darmstadt, Germany) spread on microscope slides was used for thin layer chromatograms (tlc). The same silica gel on plates measuring 20 × 20 × 0.2 cm was used for preparative layer chromatograms (plc). Development of tlc plates was performed by charring with 2% ceric sulfate in 2 *N* sulfuric acid. Plc development was conducted under ultraviolet light and/or by spraying a thin strip down the side of the plate with 2% ceric sulfate in 2 *N* sulfuric acid and charring with a hot glass rod. Silica gel (E. Merck) for column chromatography was 0.05–0.20 mm in diameter (70–325 mesh). Chromatography columns were prepared using a slurry of silica gel in a solvent system of lesser polarity than that to be used for initial elution. If the mixture to be chromatographed was not soluble in this solvent system it was dissolved in chloroform, and silica gel (10% of the weight used for the column) was added. Removal of the chloroform *in vacuo* gave a silica gel powder coated with the mixture. Addition of the powder to the column gave a uniform band of adsorbed material.

Solvent extracts of aqueous solutions were dried over anhydrous magnesium sulfate. Solvents were concentrated *in vacuo*. Melting points were determined on a Kofler melting point apparatus and are uncorrected. All analytical samples were colorless. Elemental microanalysis were performed in the laboratory of Dr. A. Bernhardt, 5251 Elbach uber Engelskirchen, West Germany. Mass spectra were determined using an Atlas CH-4B mass spectrometer by Messrs. R. Scott or E. Bebee. Proton magnetic resonance spectra (pmr) were recorded by Miss K. Reimer using a Varian A-60 spectrometer (deuteriochloroform solution with tetramethylsilane as an internal standard unless stated otherwise). Infrared spectra (in potassium bromide) were determined (K. Reimer) with a Beckman IR-12 instrument.

3β-Acetoxy-5β,20ξ-card-14-enolide (4). Method A.—A solution of digitoxigenin **5** (**1b**, 3.6 g) in tetrahydrofuran (80 ml) containing suspended 5% palladium on calcium carbonate (0.40 g) was stirred under a hydrogen atmosphere (1 atm pressure) for 48 hr. The solution was filtered and solvent was removed *in vacuo*. A solution of the oily residue in ethyl acetate was passed through a short column of silica gel to yield 2.9 g (80%) of **3β,14-dihydroxy-5β,14β,20ξ-cardanolide (3a)**: mp 174–182°

(13) See, for instance, N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 13–32.

(14) See also Zürcher, ref 3.

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(lit.[16] 222–224°); ir 3420 (–OH), 1770 cm^{-1} (C=O); pmr δ 0.95 (s, 6 H, 18 and 19 methyl), 2.43 (br, 2 H, $-CH_2C=O$), 4.05 (br, 1 H, H-3), 4.38 (br, 2 H, $-CH_2O-$); mass spectrum *m/e* (rel intensity) 376 (M^+, 80), 358 (100), 341 (46), 246 (62), 203 (75), 182 (98).

A solution of crude alcohol **3a** (2.9 g, 7.7 mmol) in pyridine (25 ml)–acetic anhydride (13 ml) was allowed to stand at room temperature for 11 hr and poured onto crushed ice. The precipitate was collected, washed well with water, and dried to yield 3.2 g of crude acetate (**3b**). To a cold (ice bath) solution of the crude acetate in pyridine (25 ml) was added dropwise with stirring a solution of thionyl chloride (4 ml) in pyridine (8 ml). The reaction mixture was stirred for an additional 1 hr, stoppered, stored at −2° for 5 hr, and poured onto crushed ice. After 12 hr standing at room temperature the semicrystalline solid was collected and dissolved in chloroform (200 ml). The resulting solution was washed with water, 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, and water and dried, and the solvent removed *in vacuo*. The resultant solid was chromatographed (powder loading technique) on silica gel (70 g). Elution with ethyl acetate–ligroin ether (3:17) yielded 3.0 g (72% from **1b**) of **3β-acetoxy-5β,20ξ-card-14-enolide** (**4**). A small portion was recrystallized four times from ethanol–water to afford an analytical sample: mp 201–204°; ir 1770 (lactone C=O), 1730 (acetate C=O), 1640 cm^{-1} (C=C); pmr δ 0.92 (s, 18 methyl), 0.98 (s, 19 methyl), 2.03 (s, acetate), 3.90 and 4.40 (two broad multiplets each integrating for 1 H, $-CH_2O-$, chemically nonequivalent), 5.03 (br, 1 H, H-15), 5.13 (br, 1 H, H-3); mass spectrum *m/e* (rel intensity) 400 (M^+, 41), 340 (100), 325 (59), 315 (50), 314 (38), 255 (70).

Anal. Calcd for $C_{25}H_{36}O_4$ (400.5): C, 74.96; H, 9.06. Found: C, 75.05; H, 8.76.

Method B.—A solution of 3β-acetoxy-5β-carda-14,20(22)-dienolide[7] (**2b**, 3.8 g) in tetrahydrofuran (100 ml) containing suspended 5% palladium on calcium carbonate (0.38 g) was stirred under a hydrogen atmosphere (1 atm pressure) for 45 hr. The solution was filtered and solvent was removed *in vacuo* to yield 3.9 g (98%) of crude **3β-acetoxy-5β,20ξ-card-14-enolide** (**4**). A small amount was crystallized from ethanol–water, mp 192–198°, identical[17] with that obtained by method A.

3β,21-Dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**).—To a stirred, ice-cold suspension of lithium aluminum hydride (1.0 g) in dry ether (200 ml) was added dropwise (under nitrogen) a solution of 3β-acetoxy-5β,20ξ-card-14-enolide (**4**, 2.5 g) in dry ether (100 ml). The mixture was stirred for an additional 1 hr, ethyl acetate (10 ml) was added, and the ice bath was removed. The resulting suspension was separated and the filtrate was evaporated to yield a very small amount of product. A solution of the product in ethyl acetate was used to extract the solid, recovered by filtration, in a Soxhlet extractor for 3.5 hr. Allowing the solution to stand overnight at room temperature produced 0.33 g of colorless crystals, mp 197–204°. Evaporation of the mother liquor *in vacuo* gave 1.70 g of residue which was chromatographed (powder leading technique) on silica gel (50 g) and eluted with ethyl acetate–ligroin (1:1) to yield 0.38 g of diol **5**. Another 0.09 g was obtained by an additional 20-hr extraction of the solid products. The total yield of **3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene** (**5**) was thus 0.80 g (35%). A small portion recrystallized twice from ethanol–water afforded an analytical sample as plates: mp 226–234°; ir 3360 (–OH), 1635 cm^{-1} (C=C); pmr (DMSO-d_6, external TMS) δ 0.97 (s, 18 methyl), 1.00 (s, 19 methyl), 3.80 (m, 2 H, $-CH_2O-$), 4.13 (m, 2 H, $-CH_2O-$), 4.27 (br, 1 H, H-3), 5.02 (br, 1 H, H-15); mass spectrum *m/e* (rel intensity) 362 (M^+, 3), 344 (21), 329 (8), 314 (7), 311 (7), 275 (21), 274 (84), 273 (82), 272 (100), 256 (30), 255 (82).

Anal. Calcd for $C_{23}H_{38}O_3$ (362.5): C, 76.20; H, 10.56. Found: C, 75.69; H, 10.60.

3β-Hydroxy-23-deoxy-5β,20ξ-card-14-enolide (**6**). **Method A.**—A mixture of 3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**, 0.38 g) and dimethyl sulfoxide (4 ml) was placed in an oil bath at 90°. After 5 hr no reaction was evident by tlc and the temperature was increased to 150°. Five hours later the reaction mixture was poured into saturated sodium chloride solution (60 ml) and extracted with chloroform. The combined extract was washed with water and dried and the solvent was removed *in vacuo* to yield 0.38 g of red oil which solidified on standing (overnight). The solid was combined with 0.22 g of red oil from another experiment, chromatographed (powder loading technique) on silica gel (20 g), and eluted with ligroin–ethyl acetate (9:1) to afford 0.26 g of **3β-hydroxy-23-deoxy-5β,20ξ-card-14-enolide** (**6**). Two recrystallizations from ethanol–water gave an analytical sample as microneedles: mp 162–165°; ir 3380 (–OH), 1645 (C=C), 1040 cm^{-1} (COC); pmr δ 0.95 (s, 18 methyl), 0.98 (s, 19 methyl), 3.00–3.92 (complex region, 4 H, $-CH_2OCH_2-$), 4.00 (br, 1 H, H-3), 5.05 (br, 1 H, H-15); mass spectrum *m/e* (rel intensity) 344 (M^+, 69), 329 (20), 326 (11), 311 (16), 275 (75), 274 (100), 273 (54), 272 (80), 259 (25), 257 (22), 256 (25), 255 (62), 241 (45).

Anal. Calcd for $C_{23}H_{36}O_2$ (344.5); C, 80.18; H, 10.53. Found: C, 79.92; H, 10.17.

Method B.—A solution of 3β,21-dihydroxy-20ξ-(β-hydroxyethyl)-5β-pregna-14-ene (**5**, 0.64 g) and *p*-toluenesulfonyl chloride (1.0 g) in pyridine (20 ml) was heated (steam bath) in a stoppered flask for 1.5 hr. Pyridine was removed by azeotroping with benzene. The residual oil in chloroform was washed with cold 2 *N* hydrochloric acid, saturated sodium bicarbonate solution, and water and dried, and the solvent was removed *in vacuo* to yield 0.85 g of brown oil. The oil was chromatographed (powder loading technique) on silica gel (50 g) and product was eluted with ligroin–ethyl acetate (9:1) to yield 0.21 g (34%) of **3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide** (**6**). Crystallization from ethanol–water afforded microneedles, mp 165–170°, identical[17] with the product from method A.

3β,14-Dihydroxy-23-deoxo-5β,14α,20ξ-cardanolide (**10b**).—To a solution of 3β-hydroxy-23-deoxy-5β,20ξ-card-14-enolide (**6**, 200 mg) in chloroform (15 ml) was added (small portions) *m*-chloroperbenzoic acid (0.17 g). After 0.5 hr the reaction mixture was washed with 5% sodium hydroxide solution and water and dried, and the solvent was removed *in vacuo* to yield 0.20 g of foamy solid. Chromatography (powder loading technique) on silica gel (5 g) and elution with ligroin–ethyl acetate (4:1) yielded 0.10 g of 3β-hydroxy-14,15α-epoxy-23-deoxo-5β,14α,20ξ-cardanolide (**9**). A portion recrystallized twice from ethyl acetate–hexane led to pure needles of 14α,15α epoxide **9**: mp 164–166°; ir 3380 (–OH), 3025 (epoxide CH), 1040 cm^{-1} (COC); pmr δ 0.88 (s, 18 methyl), 0.98 (s, 19 methyl), 3.35 (d, $J < 1$ Hz, H-15), 2.96–3.98 (complex, $-CH_2OCH_2-$), 4.07 (br, H-3); mass spectrum *m/e* (rel intensity) 360 (M^+, 61), 345 (87), 343 (23), 327 (24), 316 (80), 301 (23), 290 (57), 289 (95), 275 (28), 271 (23), 250 (45), 215 (47), 149 (100).

To a stirred suspension of lithium aluminum hydride (0.9 g) in refluxing dry ether (70 ml) was added (dropwise under nitrogen) a solution of α epoxide **9** (68 mg) in dry ether (50 ml). The solution was heated (reflux) for 24 hr and diluted with water (cautiously at first). The phases were separated, the organic layer was washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, and water and dried, and the solvent was removed *in vacuo* to yield 60 mg of clear oil. Following combination with 25 mg of crude product from a previous experiment and purification by plc (1:1 ligroin–ethyl acetate mobile phase), 52 mg of **3β,14-dihydroxy-23-deoxo-5β,14α,20ξ-cardanolide** (**10b**) was obtained as a pale yellow solid. Two recrystallizations from acetone–hexane gave an analytical sample as needles: mp 188–192°; ir 3490 (–OH), 1035 cm^{-1} (COC); pmr δ 0.82 (s, 3 H, 18 methyl), 0.98 (s, 3 H, 19 methyl), 3.05–3.98 (complex, 4 H, $-CH_2OCH_2-$), 4.08 (br, 1 H, H-3); mass spectrum *m/e* (rel intensity) 362 (M^+, 13), 344 (56), 329 (52), 326 (52), 311 (34), 275 (43), 274 (74), 273 (43), 272 (55), 255 (45), 250 (67), 241 (31), 215 (30), 203 (55), 183 (30), 177 (65), 168 (50), 164 (100).

Anal. Calcd for $C_{23}H_{38}O_3$ (362.5): C, 76.20; H, 10.56. Found: C, 75.55; H, 10.75.

3β,14-Dihydroxy-23-deoxo-5β,14β,20ξ-cardanolide (**10a**).—To a cold (ice bath) solution of 3β-hydroxy-23-deoxo-5β,20ξ-card-14-enolide (**6**, 150 mg) in *p*-dioxane (15 ml)–water (2 ml) was added with stirring 5 drops of 0.39 *M* perchloric acid. The slushlike mixture was elevated from the ice bath until it was just slightly cloudy, 120 mg of *N*-bromoacetamide was added, and the flask was reimmersed in the ice bath. After 40 min, ice–water (50 ml) was added and the resultant mixture was extracted with ethyl acetate. The combined extract was washed with 5% sodium bicarbonate solution and water and dried, and the solvent was removed *in vacuo* (minimum heat) to yield 0.23 g of crude bromohydrin **7** as an orange oil. The oil

(16) B. T. Brown and S. E. Wright, *J. Pharm. Pharmacol.*, **13**, 262 (1961).

(17) The samples gave identical infrared, nuclear magnetic resonance, and mass spectra and exhibited identical R_f values on thin layer chromatograms.

was dissolved in 5% potassium acetate in methanol (25 ml) and heated (reflux) with stirring for 11 hr. The solution was poured into saturated aqueous sodium chloride (100 ml) and extracted with chloroform. The combined extract was dried and solvent was removed *in vacuo* to yield 161 mg of yellow solid. Purification by plc (4:1 benzene–acetone mobile phase) provided 100 mg of pale yellow oil which solidified on standing. A second plc purification (2:1 benzene–acetone mobile phase) afforded 51 mg of β epoxide **8**: pmr δ 1.00 (s, 19 methyl), 1.10 (s, 18 methyl), 3.37 (d, $J < 0.5$ Hz, 1 H, H-15), 2.95–3.97 (complex, $-CH_2OCH_2-$), 4.08 (br, 1 H, H-3).

To a stirred suspension of lithium aluminum hydride (400 mg) in refluxing tetrahydrofuran (40 ml) was added (dropwise) a solution of the β epoxide **8** in tetrahydrofuran (10 ml, under nitrogen). After 3 hr the solution was cooled (ice bath), a few drops of water were added, and then the solution was filtered at room temperature. Solvent was removed and the residue was dissolved in chloroform. The solid products were extracted with chloroform and the extract was washed with water, dried, and evaporated to yield 44 mg of crude product. The solid was combined with 20 mg of crude product from a previous experiment and purified by plc (2:1 benzene–acetone mobile phase) to give 44 mg of clear oil. A second plc purification (3:2 benzene–acetone mobile phase) gave 25 mg of **3β,14-dihydroxy-23-deoxo-5β,14β,20ξ-cardanolide** (**10a**) as a colorless solid. Several recrystallizations from ethanol–water afforded an analytical specimen as needles: mp 163–173°; ir 3420 (–OH), 1040 cm^{-1} (COC); pmr δ 0.95 (s, 19 methyl), 1.02 (s, 18 methyl), 3.10–3.95 (complex, $-CH_2OCH_2-$), 4.08 (br, 1 H, H-3); mass spectrum *m/e* (rel intensity) 362 (M^+, 9), 344 (65), 329 (34), 326 (24), 311 (23), 275 (26), 274 (100), 273 (34), 272 (61), 259 (17), 258 (18), 257 (31), 256 (23), 255 (35), 250 (11), 241 (16).

Anal. Calcd for $C_{23}H_{38}O_3$ (362.5): C, 76.20; H, 10.56. Found: C, 76.41; H, 11.22.

Registry No.—**3a**, 32970-98-2; **4**, 32970-99-3; **5**, 32971-00-9; **6**, 32971-01-0; **8**, 33020-99-4; **9**, 32971-02-1; **10a**, 32971-04-3; **10b**, 32971-04-3.

Photochemical Addition of Acetone to D-Glucal Triacetate and Subsequent Oxetane Ring Cleavage[1]

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3,7-Anhydro-1-deoxy-2-*C*-methyl-2-*O*-methyl-D-*glycero*-D-*ido*-octitol (**3**) and 3,7-anhydro-1,2-dideoxy-2-methylene-D-*glycero*-D-*ido*-octitol (**4**) are obtained from acid-catalyzed methanolysis of 5,6,8-tri-*O*-acetyl-2,4:3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**1**), obtained from ultraviolet irradiation of 3,4,6-tri-*O*-acetyl-D-glucal in acetone. Oxetane ring opening in benzene affords **4**. Ethanolysis of **1** yields the 2-*O*-ethyl derivative **5** in addition to **4**. Saturation of the methylene group in **4** followed by acetylation yields crystalline 4,5,6,8-tetra-*O*-acetyl-3,7-anhydro-1,2-dideoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**10**). Benzylidenation of deacetylated **1** gives the 2,4:6,8-di-*O*-benzylidene derivative **6**.

Cycloaddition of carbonyl compounds to olefins leading to oxetane ring formation in the presence of ultraviolet irradiation has been extensively examined in aliphatic and aromatic compounds.[2-4] We have examined the photoaddition of acetone to 3,4,6-tri-*O*-acetyl-D-glucal and also have characterized the products obtained from opening of the produced oxetane ring.

Ultraviolet irradiation of 3,4,6-tri-*O*-acetyl-D-glucal in acetone at 10–15° for 5 hr gives 5,6,8-tri-*O*-acetyl-2,4:3,7-dianhydro-1-deoxy-2-*C*-methyl-D-*glycero*-D-*ido*-octitol (**1**) as the major product in 33% yield. The oxetane ring is thought to be formed through a stable biradical intermediate.[2] It is expected that carbon–oxygen bond formation at C-2 of the glucal predominates over its formation at C-1, because a carbon radical at C-1 has higher stability than a radical at C-2 of the sugar. Attachment at C-2 would be expected to position the oxygen trans to the acetoxy group at C-3. The dimethyl radical group presumably joins with the radical at C-1 to develop a ring of minimum strain resulting in the formation of the D-*glycero*-D-*ido*-octitol derivative. The gross structure of **1** may be assigned with the aid of nmr spectroscopy.[4] The signal of H-4 in the oxetane ring gives a quartet at τ 5.42 with $J_{4,5} = 3.5$ Hz and $J_{3,4} = 5.5$ Hz. Irradiation of the H-4 proton signal collapses the quartet ($J_{4,5} = 3.5$; $J_{5,6} = 9$ Hz) at τ 4.87 into a doublet with 9-Hz coupling constant. A triplet at τ 5.22 is due to H-6 and the signal of H-3 is superimposed in the τ 5.60–6.15 region which integrates for four protons.

Acid-catalyzed ring opening of oxetane rings has been reported.[2] However, deacetylation of **1** with 0.1 *N* sodium methoxide followed by deionization with excess Amberlite IR-120H at 25° for 16 hr affords a mixture of **3** and **4**, separated by column chromatography, in 45 and 10% yield, respectively. The oxetane ring of **2** is acid labile and is opened on a silica gel column eluted with chloroform–methanol, giving a mixture containing **3** and **4** in 10% yield. Compounds **3** and **4** can also be obtained by refluxing **1** in methanol in the presence of IR-120H; the yields of **3** and **4** are 41 and 14%, respectively. Treatment of **1** with IR-120H resin in benzene gives a 33% yield of the methylene derivative **4**. Ethanolysis of **2** at 25° in the presence of IR-120H resin for 16 hr provides a 34% yield of the methylene derivative **4** and a 21% yield of **5**. When direct ethanolysis is performed on **1** under reflux, the main product is the unsaturated octitol **4** (40%), while the *O*-ethyl derivative **5** is isolated in only 9% yield. Reaction of **2** with benzaldehyde and zinc chloride gives the 2,4:6,8-di-*O*-benzylidene compound **6** which is further characterized as its acetate **7**.

The nmr spectra of **4** and **8** permit assignment of structures. The methylene signals of **4** appear at τ 4.75, while these signals disappear in the reduction product **8**. In the nmr spectrum of **8**, resonance for the methine proton (H-2) appears as a multiplet around τ 8.20. The nmr spectrum of **3** demonstrates

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