for 5 h at room temperature. The resulting suspension was filtered, poured into H_2O, and extracted with ether. The organic phase was washed with H_2O and brine and dried. Removal of the solvent in vacuo afforded 383 mg (85%) of lactone **3**. After VPC purification on column A, **3** had the following spectral data: IR 2940 (s), 2870 (s), 1780 (s), 1455 (m), 1375 (m), 1160 (m), 1090 (m), 1030 cm^{-1} (m); NMR (60 MHz) δ 0.80–2.58 (m, 14 H), 3.95–4.40 (m, 2 H); for 220-MHz NMR data see Table I.

4-Cyclohexyldihydro-2(3*H*)-furanone (2). A suspension containing 15 mg (0.90 mmol) of lactone **8**, 6 mg of palladium on carbon (10%), and 6 ml of MeOH was stirred under a H_2 atmosphere for 4 h at room temperature. The suspension was then filtered, poured into H_2O, and extracted with ether. The organic phase was washed with H_2O and brine and dried. Partial removal of solvent in vacuo afforded an oily residue from which lactone **2** was isolated by preparative VPC employing column B. Lactone **2** had the following spectral data: IR 2940 (s), 2860 (s), 1780 (s), 1455 (m), 1175 (s), 1050 (m), 1020 cm^{-1} (s); for 220-MHz NMR data see Table I.

Photolysis of 2(5*H*)-Furanone (1) in Cyclohexane. A solution of 220 mg (2.62 mmol) of lactone **1**[13] in 250 ml of cyclohexane was flushed with N_2 for 20 min and then irradiated through Corex for 7 h under nitrogen. The photolysate was then concentrated in vacuo to afford 261 mg of an oily liquid which contained **2** and **3** in 13 and 16% yield, respectively. After VPC separation on column A, **2** and **3** were identical in all respects (e.g., VPC retention time, IR, 220-MHz NMR) with the authentic samples prepared above.

Photolysis of 2(5*H*)-Furanone (1) in Cyclohexane-d_{12}. A solution containing 15 mg of lactone **1** and 5g of cyclohexane-d_{12} was placed in a quartz test tube (1 × 20 cm) fitted with a nitrogen inlet. The solution was flushed with nitrogen for 30 min and then irradiated through Corex for 20 h under nitrogen. After 20 h, the progress of the reaction was monitored by VPC on column C; approximately 80% of **1** was comsumed. To the photolysis mixture was added an additional 15 mg of **1**, and the mixture was irradiated for 20 h and then monitored. This process was continued until 480 mg of **1** had been destroyed. At this point the excess solvent was removed by distillation and the residue purified by VPC to yield (400–600 μg) **2-*d*** and **3-*d***. The deuterium incorporation as determined by Fourier transform 220-MHz NMR is given in Table I. Model studies with α-deuterio-α-methyl-γ-butyrolactone indicate that deuterium was not lost during purification. Examination of the recovered solvent by NMR revealed negligible hydrogen incorporation.

Acknowledgments. It is a pleasure to acknowledge the support of this investigation by Research Corporation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. The 220-MHz NMR spectra were obtained at the Middle Atlantic Regional NMR Facility (NIH RR542) at the University of Pennsylvania.

Registry No.—**1**, 497-23-4; **7**, 21681-63-0; **8**, 30088-97-2; butyrolactone, 96-48-0; cyclohexanone, 108-94-1; cyclohexane-d_{12}, 1735-17-7.

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Steroids and Related Natural Products. 94. Synthesis of Toad Venom Cardenolides[1]

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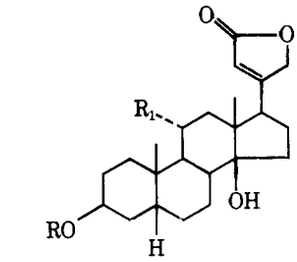
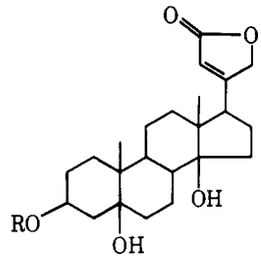
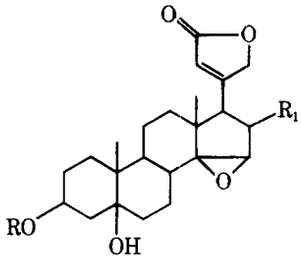
Some species of the milkweed butterfly family (Danaidae) have been found by Reichstein and colleagues to contain cardenolides.[3] The occurrence of such cardiac active plant constituents in these particular butterflies has been nicely correlated with their feeding habits which involve certain cardenolide containing plants (e.g., from the Asclepiadaceae family) and their need for an exogenous source of defensive substances. In 1970, Meyer and colleagues[4] reported the presence of seven cardenolides in the Chinese toad venom preparation Ch'an Su. The constituents included digitoxigenin (**1a**), sarmentogenin (**1b**), periplogenin (**2a**), and two previously unknown 14,15β-epoxycardenolides (**3a** and **3b**). Whether such cardenolides represent a normal biosynthetic pathway in venom production characteristic of certain amphibians of the Bufonidae family or instead are initially obtained by ingestion of Asclepiadaceae-type plant eating insects poses an interesting biochemical question. However, the discovery[4a] of two cardenolides bearing suberic acid ester groups (e.g., **1c**) in Ch'an Su and the more recent isolation[5] of sarmentogenin (**1b**), 3-suberoylarginine, and 3-pimeloylarginine esters from the skin of *Bufo vulgaris formosus*



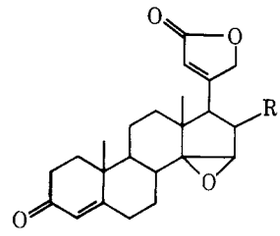
1a, R = R_1 = H
b, R = H; R_1 = OH
c, R = $CO(CH_2)_6CO_2H$; R_1 = H



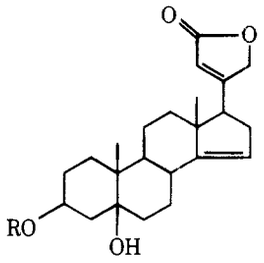
2a, R = H
b, R = $COCH_3$



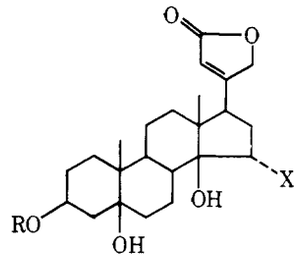
3a, R = R_1 = H
b, R = H; R_1 = $OCOCH_3$
c, R = $COCH_3$; R_1 = H



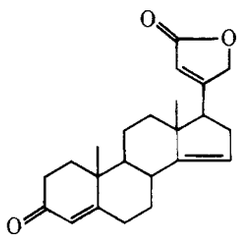
4a, R = H
b, R = $OCOCH_3$



5a, R = H
b, R = $COCH_3$



6a, R = H; X = I
b, R = H; X = Br
c, R = $COCH_3$; X = I
d, R = $COCH_3$; X = Br



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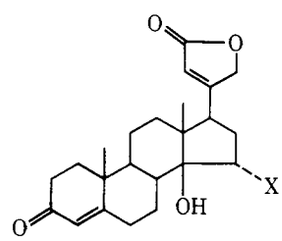

8a, X = I
b, X = Br

Boulenger suggests that cardenolide formation may reflect a normal biosynthetic avenue in toads of the genus *Bufo*.

After isolation of epoxycardenolides **3a** and **3b**, the Meyer group nicely assigned structures based on spectral evidence and analogous study of the compounds (**4a** and **4b**) resulting from a dehydration–oxidation sequence. In order to extend our cytotoxicity and antineoplastic evaluations of amphibian venom constituents we have completed a formal total synthesis of the toad venom cardenolide **3a** using periplogenin (**2a**) as relay. Our earlier synthesis of periplogenin (**2a**) from digitoxigenin (**1a**) was repeated to obtain sufficient starting material.[6] The subsequent route employed for obtaining epoxycardenolide **3a** was based on a series of reactions we developed previously for syntheses of bufotalin,[7a] marinobufotoxin,[7b] and bufalin.[7c] Thus, periplogenin (**2a**) was selectively dehydrated[7b] to 14-olefin **5a** which was converted[7c] to halohydrins **6a** and **6b**. Periplogenin acetate (**2b**) was analogously transformed via olefin **5b** to halohydrins **6c** and **6d**. Treatment of the halohydrins **6a** and **6b** or **6c** and **6d** with pyridine or basic aluminum oxide readily provided, respectively, the Ch'an Su constituent **3a** and acetate derivative **3c**. Epoxycardenolide **3a** was found to be identical with an authentic specimen obtained by the Meyer group[4] from Ch'an Su.

The stereochemical course of halohydrin addition to olefin **5** was conclusively established by selective reduction (Raney nickel)[7a] of the halohydrins represented by structure **6** to yield exclusively periplogenin (**2a**) and the corresponding acetate derivative **2b**. The very dependable stereochemical course of halohydrin reaction in this series was further demonstrated by conversion of 14-dehydrocanarigenone (**7**)[6] to the 3-oxo-4-ene **4a** by way of halohydrin **8**. Ketone **4a** was found identical with a specimen obtained by selective oxidation of epoxycardenolide **3a** followed by dehydration catalyzed by Amberlite CG-120 (H^+).

Experimental Section

The general experimental techniques in this study have been summarized in parts 93[1] and 91[6] of this series. The same procedures have been utilized for column and thin layer chromatography (on silica gel) and establishing the mutual identity of comparison specimens (e.g., infrared spectra in KBr).

14-Dehydroperiplogenin (5a). A mixture prepared from periplogenin (**2a**, 0.25 g), methanol (45 ml), and 35% hydrochloric acid (0.05 ml) was heated at reflux for 1.5 h, poured into ice–water, and extracted with chloroform. The solvent extract was washed with water and evaporated to dryness. The crude product was column chromatographed and the fraction eluted by *n*-hexane–acetone (5:1) was recrystallized from acetone–*n*-hexane to give 14-dehydroperiplogenin (**5a**, 0.13 g) as needles: mp 200–202 °C; λ_{max} (MeOH) nm (log ϵ) 217 (4.20); ν_{max} (KBr) 3500 (OH), 1798, 1777, 1726 (butenolide ring), 1630, 1623 (C=C), 1445, 1030, 898, 695 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 0.98 (3 H, s, 19-CH_3), 4.17 (1 H, broad s, 3α H), 4.76 (2 H, t, J = 2 Hz, 21-CH_2), 5.23 (broad s, 15-H), 5.89 (1 H, t, J = 2 Hz, 22-H); mass spectrum *m/e* 372 (M^+), 354 ($M^+ - H_2O$), 336 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.36; H, 8.70.

A 20-mg specimen of 14-dehydroperiplogenin was acetylated at room temperature with acetic anhydride (0.4 ml)–pyridine (0.28 ml) to give **14-dehydroperiplogenin acetate** (**5b**, 17 mg) as needles melting at 195–198°C (from acetone–*n*-hexane); λ_{max} (MeOH) nm (log ϵ) 217 (4.19); ν_{max} (KBr) 3480 (OH), 1784, 1752, 1730 (butenolide ring and ester CO), 1700, 1644, 1631 (C=C), 1450, 1255, 1245, 1240 (ester C–O), 1030, 890, 692 cm^{-1}; ^1h NMR (10% solution in $CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 1.01 (3 H, s, 19-CH_3), 2.09 (3 H, s, 3-$OCOCH_3$), 4.75 (2 H, t, J = 2 Hz, 21-CH_2), 5.05 (1 H, broad s, 3α H), 5.23 (1 H, broad s, 15α H), 5.88 (1 H, t, J = 2 Hz, 22-H); mass spectrum *m/e* 414 (M^+), 396 ($M^+ - H_2O$), 354 (M^+ – AcOH), 336 (M^+ – AcOH – H_2O).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.39; H, 8.25.

Synthesis of 3β,5β-Dihydroxy-14,15β-epoxycard-20(22)-enolide (3a). Method A. A solution of *N*-iodosuccinimide (30 mg) in acetone (3 ml)–water (3 ml) was added to 14-dehydroperiplogenin (**5a**, 30 mg) in acetone (4.5 ml). The mixture was stirred for 22 h at room temperature and a solution prepared from sodium sulfite (30 mg) and water (0.6 ml) was added. The solution was concentrated (to about one-third volume), poured into ice–water with stirring, and extracted with chloroform. The combined extract was washed with water, solvent was evaporated, and the crude iodohydrin (**6a**, 26 mg) was stirred in pyridine (2 ml) for 4 h at room temperature. Following removal of solvent the product was column chromatographed and the fraction eluted with *n*-hexane–acetone (5:1) was recrystallized from ethyl acetate–*n*-hexane to give **3β,5β-dihydroxy-14,15β-epoxycard-20(22)-enolide** (**3a**, 21 mg) as prisms melting at 217–220 °C.

When a 15-mg sample of the crude iodohydrin (**6a**, 15 mg), obtained as described above, was chromatographed on basic alumina with benzene–chloroform (19:1–9:1), the 14β,15β-epoxide (**3a**, 8.2 mg) was, after recrystallization, isolated as prisms melting at 217–219 °C.

Method B. Substitution of *N*-bromosuccinimide (15 mg) for *N*-iodosuccinimide in the method A reaction sequence with olefin **5a** (15 mg) led to 14 mg of the crude bromohydrin (**6b**). Conversion of the bromohydrin to 14β,15β-epoxide **3a** with pyridine provided an 8.4-mg (mp 216–219 °C) yield.

Method C. When *N*-bromoacetamide (15 mg) was substituted for *N*-iodosuccinimide or *N*-bromosuccinimide as described in method A or method B, olefin **5a** (15 mg) led to 16 mg of the crude bromohydrin (**6b**). Similar conversion of bromohydrin **6b** to 14β,15β-epoxide **3a** by use of pyridine as described in method A provided 8.7 mg of 14β,15β-epoxide **3a** (mp 217–220 °C): λ_{max} (MeOH) nm (log ε) 214 (4.19); ν_{max} (KBr) 3500 (OH), 3110, 3050 (CH), 1787, 1746 (butenolide ring), 1625 (C=C), 1445, 1170, 1135, 1030, 899, 697 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 1.00 (3 H, s, 19-CH_3) 3.47 (1 H, broad s, 15α-H), 4.16 (1 H, broad s, 3α-H), 4.76 (2 H, t, *J* = 2 Hz, 21-CH_2), 5.89 (1 H, t, *J* = 2 Hz, 22-H); mass spectrum *m/e* 388 (M^+), 370 ($M^+ - H_2O$), 352 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.23; H, 8.22.

The samples of 3β,5-dihydroxy-14,15β-epoxy-5β,14β-card-20(22)-enolide (**3a**) prepared by methods A–C were found to be identical with an authentic sample of the natural product (mp 200–221 °C, provided by Professor K. Meyer).

Synthesis of 3β-Acetoxy-5β-hydroxy-14,15β-epoxycard-20(22)-enolide (3c). Method A. Reaction of 14-dehydroperiplogenin acetate (**5b**, 25 mg) with hypoiodous acid prepared from *N*-iodosuccinimide (25 mg) was performed as described above for the preparation of iodohydrin **6a**. After treatment with pyridine and chromatographic purification (elution with 7:1 *n*-hexane–acetone and recrystallization from ethyl acetate–*n*-hexane) the crude iodohydrin acetate (**6c**, 23 mg) gave rise to 3β-acetoxy-5β-hydroxy-14,15β-epoxycard-20(22)-enolide (**3c**, 18 mg) as prisms melting at 217–220 °C.

Method B. The preceding reaction was repeated using 15 mg of olefin acetate **5b** and 15 mg of *N*-bromoacetamide. Alumina (basic) chromatographic treatment of the crude bromohydrin (**6d**, 14 mg) with benzene–chloroform (19:1) as eluent provided 7.8 mg of 14β,15β-epoxy acetate **3c** melting at 216–220 °C.

Method C. Alcohol **3a** (10 mg) was acetylated with acetic anhydride (0.014 ml)–pyridine (0.02 ml) and the product was isolated by column chromatography as described in method A. By this means 7 mg of 14β,15β-epoxy acetate **3c** was obtained which melted at 218–220 °C and was identical with the sample prepared by method A or method B; λ_{max} (MeOH) nm (log ε) 213 (4.18); ν_{max} (KBr) 3480 (OH), 3100, 3048 (CH), 1785, 1750, 1728 (butenolide ring and ester CO), 1700, 1642, 1626 (C=C), 1445, 1250, 1240 (ester C–O), 1170, 1135, 1030, 897, 695 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 0.95 (3 H, s, 18-CH_3), 1.02 (3 H, s, 19-CH_3), 2.08 (3 H, s, 3-$OCOCH_3$), 3.47 (1 H, broad s, 15α-H), 4.77 (2 H, a narrow quartet, *J* = 2.5 and 1.5 Hz, 21-CH_2), 5.24 (1 H, broad s, 3α-H), 5.88 (1 H, t, *J* = 2.5 Hz, 22-H); mass spectrum *m/e* 430 (M^+), 412 ($M^+ - H_2O$), 394 ($M^+ - 2H_2O$), 370 (M^+ – AcOH).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.77; H, 7.89.

Periplogenin (2a). The crude iodohydrin (**6a**, 21 mg) prepared from 14-dehydroperiplogenin (**5a**, 22 mg) and *N*-iodosuccinimide (22 mg) was treated[7c] with freshly prepared Raney nickel (approximately 0.8 g) for 4 h at 18–20 °C in a nitrogen atmosphere. The solution was filtered and the filtrate was concentrated to provide an 18-mg residue, which was subjected to column chromatography. The fraction eluted by 1:3 *n*-hexane–acetone was recrystallized from methanol to afford 11 mg of periplogenin (**2a**) melting at 226–232 °C.

By an analogous reduction reaction the crude bromohydrin (**6b**, 10 mg) prepared from 14-dehydroperiplogenin (**5a**, 12 mg) and *N*-bromoacetamide (12 mg) was treated (under nitrogen) with freshly prepared Raney nickel (ca. 0.5 g). By the same isolation procedure, 5 mg of periplogenin (**2a**, mp 226–231 °C) was obtained. The specimens of periplogenin (**2a**) obtained by both procedures were found identical with natural periplogenin.

Periplogenin Acetate (2b). A sample of the crude iodohydrin acetate (**6c**, 18 mg) prepared from 14-dehydroperiplogenin acetate (**5b**, 20 mg) and *N*-iodosuccinimide (20 mg) was converted to periplogenin acetate (**2b**, 10 mg, mp 230–238 °C) using Raney nickel (about 0.5 g, 4 h at 18 °C) as summarized above for obtaining periplogenin (**2a**).

With the same nickel (approximately 0.3 g) procedure, 8 mg of the crude bromohydrin acetate (**6d**, obtained using *N*-bromosuccinimide) provided 3.8 mg of periplogenin acetate (**2b**) melting at 230–237 °C.

Both samples of periplogenin acetate (**2b**) were found identical with an authentic sample.

3-Oxo-14,15β-epoxycarda-4,20(22)-dienolide (4a). Method A. A solution of *N*-iodosuccinimide (30 mg) in acetone (3 ml)–water (3 ml) was added to 30 mg of 14-dehydrocanarigenone [3-oxocarda-4,14,20(22)-trienolide **7**] in acetone (4.5 ml). The remaining reaction sequence and isolation procedure was completed (except for 18 h with sodium sulfite and 3 h with pyridine) as described above for obtaining epoxycardenolide **3a**. Recrystallization from ethyl acetate–*n*-hexane afforded 20 mg of 3-oxo-14,15β-epoxy-14β-carda-4,20(22)-dienolide (**4a**) as prisms melting at 236–240 °C. The product was identical with the sample prepared below from 3β,5β-dihydroxy-14,15β-epoxy-card-20(22)-enolide (**3a**).

Method B. The preceding reaction was repeated using 15 mg of olefin **7** and 15 mg of *N*-bromoacetamide. Analogous treatment of the crude bromohydrin (**8b**, 14 mg) with pyridine provided epoxide **4a** (6.6 mg) melting at 236–239 °C which was identical with the sample prepared below from diol **3a**.

When the crude bromohydrin (**8b**, 10 mg) obtained by similar treatment of olefin **7** (12 mg) with *N*-bromosuccinimide (12 mg), was chromatographed in benzene–chloroform (14:1) on basic alumina 4.7 mg of epoxide **4a**, mp 237–240C, was isolated.

Method C (From 3β,5β-Dihydroxy-14,15β-epoxycard-20(22)-enolide, 3a). Epoxy alcohol **3a** (18 mg) in pyridine (0.48 ml) was oxidized (room temperature, 16 h) with chromium trioxide (17 mg)–pyridine (0.18 ml) complex. Excess 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 crude epoxy ketone)16 mg) was employed in the following dehydration reaction without further purification.

A mixture prepared from the epoxy ketone (15 mg), 0.15 g of Amberlite CG-120 (H^+ form), and methanol (1.5 ml) was stirred at room temperature for 8 h. The solution was filtered and concentrated to dryness and the crude product was purified by column chromatography. The fraction eluted with 9:1 *n*-hexane–acetone was recrystallized from ethyl acetate–*n*-hexane to yield 9.2 mg of epoxide **4a** melting at 237–241 °C (lit[7b] mp 237–248 °C); λ_{max} (MeOH) nm (log ε) 227–230 (4.33); ν_{max} (KBr) 3100, 3048, (CH), 1780, 1735, 1715 (butenolide ring and saturated ketone), 1700, 1623 (C=C), 1445, 1170, 1120, 1022, 890, 858, 780, 750 cm^{-1}; ^1H NMR (10% solution in $CDCl_3$) δ 1.01 (3 H, s, 18-CH_3), 1.26 (3 H, s, 19-CH_3), 3.45 (1 H, broad s, 15α H), 4.78 (2 H, t, *J* = 2 Hz, 21-CH_2), 5.73 (1 H, broad s, 4-H), 5.88 (1 H, t, *J* = 2 Hz, 22-H); mass spectrum *m/e* 368 (M^+), 350 ($M^+ - H_2O$).

Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.95; H, 7.66. Found: C, 74.99; H, 7.63.

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Registry No.—**2a**, 514-39-6; **2b**, 13077-88-8; **3a**, 31655-31-9; **3c**, 31655-36-4; **4a**, 24366-48-1; **5a**, 60967-71-7; **5b**, 60967-72-8; **6a**, 60967-73-9; **6b**, 60967-74-0; **6c**, 60967-75-1; **6d**, 60967-76-2; **7**, 19637-08-2; **8**, 24366-46-9; *N*-iodosuccinimide, 516-12-1; *N*-bromosuccinimide, 128-08-5; *N*-bromoacetamide, 79-15-2.

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