Bufadienolides. 29. Synthetic Routes to Bufotalin[1]

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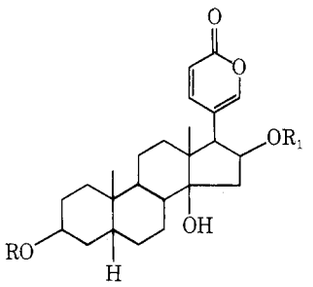
Two partial syntheses of bufotalin (**1a**) were developed as follows. The 16-ketone **3** was prepared from cinobufagin and the 14,15β-epoxide group was reduced with chromous acetate to yield β-hydroxy ketone **4** (61%) and α,β-unsaturated ketone **5** (27%). Selective reduction of β-ketone **4** with Urushibara nickel A afforded alcohol **1b**, which was acetylated to provide diacetate **1c**. Treatment of diacetate **1c** with hydrochloric acid in methanol gave bufotalin (**1a**) accompanied by lesser amounts of other hydrolysis products (**1b**, **1d**, and **6a**). In an alternative approach, α,β-unsaturated ketone **5** was first reduced with Urushibara nickel A to allylic alcohol **6a**. After acetylation (to **6b**) the olefin was subjected to reaction with hypoiodous acid or hypobromous acid and the resulting halohydrin (**7a** or **7b**) was treated with Urushibara nickel A. The product of hydrogenolysis was bufotalin 3β-acetate (**1c**).

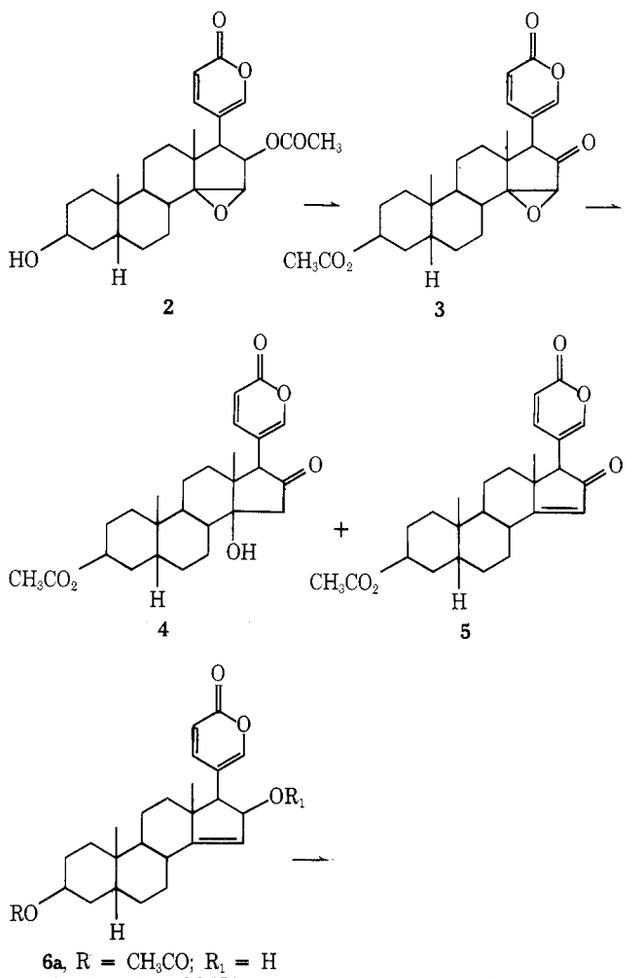
Bufotalin (**1a**) is one of the more widely known and thoroughly characterized constituents of the Chinese medicinal



1a, R = H; R_1 = $COCH_3$
b, R = CH_3CO; R_1 = H
c, R = R_1 = $COCH_3$
d, R = R_1 = H

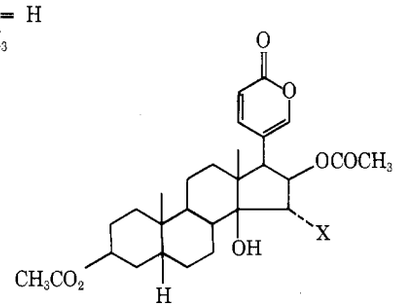
preparation, Ch'an Su. This common toad venom component has been shown to be a potent cytotoxic agent (KB, ED_{50} 0.026)[3] and to exhibit cardiac activity.[4] In prior studies we have reconfirmed the structure of bufotalin (**1a**)[5] and employed this interesting substance as starting material for partial syntheses of cinobufagin (**2**)[6] and bufotoxin.[7] As the next step in an effort to extend our earlier total synthesis of bufalin[8] to bufotalin it became necessary to explore preparation of this bufadienolide from cinobufagin (**2** → **1a**). Two usable synthetic routes from cinobufagin to bufotalin were uncovered and are herein summarized.

Cinobufagin (**2**, KB, ED_{50} 0.011)[3] was isolated from Ch'an Su and converted to ketone **3** as previously described.[6] The last step in this transformation, namely oxidation of desacetylcinobufagin 3β-acetate to ketone **3**, was found easily reversible by sodium borohydride reduction. Interestingly, the 16β-alcohol was the major product. Next, ketone **3** was subjected to the chromium(II) acetate reduction reaction analogous to that employed as the key step in our recent synthesis of telocinobufagin.[9] Column chromatographic separation of the reduction product provided hydroxy ketone **4** (61%) and α,β-unsaturated ketone **5** (27%). The structural assignments of both products easily followed from the known course[10] of such reduction reactions combined with the results of mass, ultraviolet, and proton magnetic resonance measurements. Under a variety of conditions (hydrochloric acid, oxalic acid, acetic acid, and acidic exchange resin) hydroxy ketone **4** was easily dehydrated to olefin **5**. At this point reduction of hydroxy ketone **4** was found quite convenient using Urushibara nickel A.[8,11] After purification by chromatography and recrystallization diol **1b** was obtained to 70% yield. Gentle oxidation with the chromium trioxide–pyridine complex easily reversed the reduction step and ketone **4** was obtained in 63%



2 **3** **4** **5**

6a, R = CH_3CO; R_1 = H
b, R = R_1 = $COCH_3$



7a, X = I
b, X = Br

yield. Lesser yields (56 and 47%, respectively) were obtained using *N*-bromoacetamide and chromium trioxide–acetic acid procedures.

Mild acetylation of diol **1b** afforded bufotalin acetate (**1c**). Once the structure of diacetate **1c** was confirmed by comparison with authentic bufotalin acetate the partial synthesis of bufotalin seemed close at hand. However, selective hydrolysis of bufotalin acetate proved more challenging than expected. Eventually, acid-catalyzed hydrolysis employing short (10 min) contact with hydrochloric acid in methanol or with an acidic ion exchange resin was found to produce bufotalin in somewhat less than 20% conversion. Application of a basic ion exchange resin or use of potassium bicarbonate was less effective. The major result of both the acid- and base-catalyzed hydrolysis reactions was simply a mixture of recovered starting material accompanied by diol **1b**, triol **1d**, and allylic alcohol **6a**. However, the yield of bufotalin could be substantially increased by recycling diol **1b** and triol **1d** through the acetylation sequence. Further, the yield of bufotalin was more directly increased by selective acetylation of triol **1d** employing acetic acid to afford bufotalin (**1a**) accompanied by bufotalin acetate (**1c**) and diol **1b**.

A second partial synthesis of bufotalin was developed utilizing olefin **5**. First, conditions were found for specific nickel-catalyzed reduction of the 16-carbonyl group of bufadienolide **5** to yield allylic alcohol **6a**. The structure and stereochemistry of alcohol **6a** were confirmed as follows. Bufotalin acetate was dehydrated[6] to olefin **6b**. Selective saponification of the 16β-acetate was performed in good yield using potassium bicarbonate as base. The product, allylic alcohol **6a**, was identical with the same substance obtained from cinobufagin. Mutually identical specimens were again obtained by acetylation of alcohol **6a** derived from cinobufagin and comparing the product with diacetate **6b** prepared from bufotalin acetate. In addition, allylic alcohol **6a** was easily oxidized by active manganese dioxide, chromium trioxide–pyridine complex, or chromium trioxide–acetic acid to ketone **5**.

Treatment[8] of olefin **6b** with hypoiodous acid or with hypobromous acid led respectively to halohydrins **7a** and **7b**. Hydrogenolysis of each halohydrin with Urushibara nickel A afforded bufotalin acetate (**1a**). As diacetate **1c** had already been used to obtain bufotalin (**1a**, see above) the alternative approach from cinobufagin was thereby complete.

The plausibility of extending prior total syntheses of 14-dehydrobufalin (16-desacetoxy-**6a**) or resibufogenin (16-desacetoxy-**2**) to bufotalin (**1a**) received much encouragement from successful completion of the preceding series of experiments. Presently we are attempting to complete the necessary connecting transformations.

Experimental Section

The bufotalin and cinobufagin employed in these experiments were both isolated from the Chinese medicinal preparation, Ch'an Su. Chromium(II) acetate was prepared essentially as described by Balthis and Bailar.[12]

General experimental procedures including materials and methods for thin layer chromatography (3:3:4 acetone–chloroform–hexane as solvent unless otherwise noted) and column chromatography (silica gel) have been summarized in the corresponding section of part 27 of this series.[9] As before, the mutual identity of synthetic with natural specimens was established by mixture melting point determination, comparison thin layer chromatography, and comparison infrared spectra.

All infrared spectra were obtained using potassium bromide pellets. Except for melting points (uncorrected) all instrumental measurements were obtained by Messrs. R. Scott and E. Kelley or Miss K. Reimer.

3β-Acetoxy-16-oxo-14β,15β-epoxy-5β-bufa-20,22-dienolide (3). Ketone **3** was prepared from cinobufagin (**2**) as described in part 21 of this series.[6] Reconversion of ketone **3** to its immediate alcohol precursor was conducted as follows. Sodium borohydride (48 mg) in dioxane (2.4 ml)–water (0.8 ml) was added to a solution of ketone **3** (50 mg, mp 226–228°) in dioxane (5 ml)–water (1.8 ml). After 2 hr at room temperature the mixture was poured into ice–water, acidified with dilute sulfuric acid, and extracted with chloroform. The combined extract was washed with water and concentrated to dryness. The residue (55 mg) was chromatographed on a column of silica gel. A fraction eluted by hexane–acetone (5:1) was recrystallized from methanol to provide 33 mg of 3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide as needles melting at 205–208°. The alcohol was identical with authentic specimens prepared from cinobufagin.[6]

Chromium(II) Acetate Reduction of 3β-Acetoxy-16-oxo-14β,15β-epoxy-5β-bufa-20,22-dienolide (3). Chromium(II) acetate (0.70 g) was added to a solution of ketone **3** (0.105 g) in ethyl alcohol (18 ml). After 1 hr at room temperature the mixture was diluted with chloroform and poured into ice–water. The chloroform layer was washed with water, dried, and concentrated to dryness and the residue (0.125 g) was separated by column chromatography with 5:1 hexane–acetone as eluent. Two significant fractions were obtained. The more polar fraction was recrystallized from methanol–hexane to provide 64 mg of **3β-acetoxy-14β-hydroxy-16-oxo-5β-bufa-20,22-dienolide (4)** as needles melting at 229–235°: tlc R_f 0.31; λ_{max} (CH_3OH) 296 nm (log ϵ 4.25); ν_{max} 3420 (OH), 1740, 1720, 1710 (conjugated C=O and ester C=O), 1630, 1535 (conjugated C=C), 1260, 1240 (ester C=O), 1030, 960, 830, 807, 748 cm^{-1}; pmr (10% deuteriopyridine) δ 0.96 (3 H, s, 18-CH_3), 1.11 (3 H, s, 19-CH_3), 2.09 (3 H, s, 3-OAc), 3.12 (1 H, s, 17α-H), 2.56 and 3.23 (2 H, q, J = 17 Hz, 15-CH_2), 5.24 (1 H, broad peak, 3α-H), 6.3 (1 H, d, J = 9.5 Hz, 23-H), 7.65 (1 H, d, J = 3 Hz, 21-H), 7.95 (1 H, dd, J = 9.5 and 3 Hz, 22-H); mass spectrum m/e 442 (M^+), 424 ($M^+ - H_2O$), 382 (M^+ – AcOH), 364 ($M^+ - H_2O$ – AcOH), 231, 213, and 203.

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.49; H, 7.75.

The less polar fraction was recrystallized from methanol to yield 28 mg of **3β-acetoxy-16-oxo-5β-bufa-14,20,22-trienolide (5)** as needles melting at 211–214°: tlc R_f 0.43; λ_{max} (CH_3OH) 232 nm (log ϵ 4.25) and 295 (3.84); ν_{max} 1750, 1730, 1720, 1700 (conjugated C=O and ester C=O), 1640, 1610, 1538 (conjugated C=C), 1250, 1230 (ester C=O), 1030, 955, 905, 865, 750 cm^{-1}; pmr (10% solution in deuteriochloroform) δ 0.94 (3 H, s, 18-CH_3), 1.05 (3 H, s, 19-CH_3), 2.02 (3 H, s, 3-OAc), 3.12 (1 H, s, 17α-H), 5.06 (1 H, broad peak, 3α-H), 5.83 (1 H, s, 15-H), 6.25 (1 H, d, J = 10 Hz, 23-H), 6.96 (1 H, d, J = 3 Hz, 21-H), 7.22 (1 H, dd, J = 10 and 3 Hz, 22-H); mass spectrum m/e 424 (M^+), 409 ($M^+ - CH_3$), 396 (M^+ – CO), 381, 364 (M^+ – AcOH), 349, 335, 321, 255, 202.

Anal. Calcd for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.47; H, 7.69.

Dehydration of 3β-Acetoxy-14β-hydroxy-16-oxo-5β-bufa-20,22-dienolide (4). Method A. With Hydrochloric Acid. A solution prepared from hydroxy ketone **4** (40 mg), ethyl alcohol (2 ml), and 35% hydrochloric acid (0.1 ml) was heated at reflux for 15 min and poured into ice–water. A chloroform extract of the mixture was washed with water, dried, and evaporated to dryness. Column chromatographic separation (elution with 7:1 hexane–acetone) and recrystallization from methanol gave 34 mg of α,β-unsaturated ketone **5** as needles melting at 212–215°.

Method B. With Oxalic Acid. The preceding experiment was repeated using 30 mg of ketone **4**, 1.8 ml of methyl alcohol, and 10 mg of oxalic acid. In this example the mixture was heated at reflux for 30 min. Isolation of product as above led to 26 mg of ketone **5** melting at 210–213°.

Method C. With Acetic Acid. A solution of ketone **4** (15 mg) in acetic acid (1 ml) was heated at reflux for 15 min. Product was isolated as described in method A and found to weigh 12 mg (mp 210–213°).

Method D. With Amberlite CG-120 (H^+ Form). A mixture prepared from ketone **4** (25 mg), methyl alcohol (2 ml), and 0.125 g of Amberlite CG-120 (H^+ form) was stirred at room temperature for 8 hr. The solution was filtered and evaporated to dryness. The crude product was purified as indicated in method A to provide 19 mg of ketone **5** melting at 212–215°. Essentially the same yield (16 mg) of ketone **5** was obtained employing Dowex 50 W-X8 (H^+ form) and ethyl alcohol as solvent.

The specimens of ketone **5** obtained using methods A–D were mutually identical and identical with the specimen obtained by chromium(II) acetate reduction of ketone **3**.

3β-Acetoxy-14β,16β-dihydroxy-5β-bufa-20,22-dienolide (1b). Method A. Using Urushibara Nickel A. A large excess of freshly prepared Urushibara nickel A[11] was added to a solution of ketone **4** (40 mg) in ethyl alcohol (4 ml). The solution was heated at reflux 1 hr, filtered, and evaporated to dryness and the residue

(45 mg) was chromatographed on a column of silica gel. Elution with hexane–acetone (5:1 to 3:1) and recrystallization from acetone–hexane provided 28 mg of diol **1b** as needles melting at 255–256°.

Method B. Using Raney Nickel (W-2). The preceding experiment was repeated using 20 mg of ketone **4** and an excess of freshly prepared Raney nickel (W-2). The product weighed 11 mg and melted at 253–255°: tlc R_f 0.18; λ_{max} (CH_3CH_2OH) 295 nm (log ϵ 4.22); ν_{max} 3580, 3520 (OH), 1730, 1715, 1705, 1700, 1630, 1535, 1265, 1235, 1135, 1030, 950, 830, 745 cm^{-1}; pmr (10% solution in deuteriopyridine) δ 0.92 (3 H, s, 18-CH_3), 1.02 (3 H, s, 19-CH_3), 2.06 (3 H, s, 3-OAc), *ca.* 2.50 (*ca.* 2 H, broad d, J = 7 Hz, CH_2), 2.80 (1 H, d, J = 7 Hz, 17α-H), 4.81 (1 H, t, J = 7 Hz, 16α-H), 5.21 (1 H, broad peak, 3α-H), 6.28 (1 H, d, J = 10 Hz, 23-H), 7.47 (1 H, d, J = 3 Hz, 21-H), 8.45 (1 H, dd, J = 10 and 3 Hz, 22-H); mass spectrum *m/e* 444 (M^+), 426 ($M^+ - H_2O$), 408 ($M^+ - 2H_2O$), 400, 384, 366, 351, 348, 323, 261, 229, 214, 204.

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.14.

Oxidation of 3β-Acetoxy-14β,16β-dihydroxy-5β-bufa-20,22-dienolide (1b). Method A. Using Chromium Trioxide–Pyridine Complex. A 24-mg specimen of diol **1b** was treated with chromium trioxide (22 mg)–pyridine (2.2 ml) at 15–20° for 24 hr. Excess reagent was removed with methanol and the mixture was poured into ice–water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to a 44-mg residue which was chromatographed. The fractions eluted by 5:1 to 3:1 hexane–acetone recrystallized from methanol–hexane to afford hydroxy ketone **4** as needles (15 mg) melting at 228–233°.

When the oxidation was repeated employing 40 mg of diol **1b** in acetic acid (2.0 ml)–water (2 drops) with chromium trioxide (10 mg) at 0–5° for 20 hr two products were obtained, namely, 19 mg of hydroxy ketone **4** melting at 228–233° and 12 mg of α,β-unsaturated ketone **5** melting at 200–213° (from methanol). In each case the product was identical with the corresponding specimen prepared from ketone **3**.

Method B. Using *N*-Bromoacetamide. To a solution (at 10°) of diol **1b** (25 mg) in methanol (3 ml)–pyridine (1 ml)–water (0.1 ml) was added *N*-bromoacetamide (23 mg). The mixture was allowed to stand in the dark at 10–15° for 20 hr. After pouring the mixture into water and extraction with chloroform the combined extract was washed with water and evaporated to dryness. The crude product (28 mg) was purified as described in method A above to afford 14 mg of hydroxy ketone **4** melting at 229–233°.

3β,16β-Diacetoxy-14β-hydroxy-5β-bufa-20,22-dienolide (1c, Bufotalin Acetate). Selective acetylation of diol **1b** (30 mg) with acetic anhydride (0.5 ml)–pyridine (0.9 ml) was conducted at room temperature over 18 hr. The crude product (32 mg) was recrystallized from acetone–hexane to afford 25 mg of bufotalin acetate (**1c**) as prisms melting at 265–270°. The specimen of bufotalin acetate was identical with a sample prepared by analogous acetylation of natural bufotalin.

Bufotalin (1a). Method A. Hydrolysis with Hydrochloric Acid. A solution of bufotalin acetate (**1c**, 0.10 g) in methanol (4 ml) containing 35% hydrochloric acid (0.22 ml) was heated at reflux for 10 min. The reaction mixture was poured into ice–water and extracted with chloroform. The combined extract was washed with water and solvent was removed to give a 0.102-g residue. The mixture was separated by careful column chromatography. Successive elution with 19:1, 9:1, 7:1, 5:1, and 3:1 hexane–acetone mixtures and recrystallization of each fraction from acetone–hexane led to 15 mg of **bufotalin** (**1a**, needles melting at 215–220°), 12 mg of **3β-acetoxy-14β,16β-dihydroxy-5β-bufa-20,22-dienolide** (**1b**, needles melting at 253–255°), 10 mg of **desacetylbufotalin** (**1d**, prisms melting at 194–221°), 7 mg of **3β-acetoxy-16-hydroxy-5β-bufa-14,20,22-trienolide** (**6a**, prisms melting at 223–234°), and 35 mg of starting material (**1c**).

Method B. Hydrolysis with Amberlite CG-120 (H^+ Form). A mixture prepared from bufotalin acetate (**1c**, 0.10 g), ethyl alcohol (12 ml)–water (3.5 ml), and 1 g of Amberlite CG-120 (H^+ form) was stirred at room temperature for 38 hr. The solution was filtered and solvent was removed. The crude product was separated as described in the preceding experiment (method A) and led to 14 mg of bufotalin (**1a**, mp 217–221°), 10 mg of diol **1b** (mp 255–256°), 9 mg of desacetylbufotalin (**1d**, mp 199–215°), 5 mg of olefin **6a** (mp 223–234°), and 43 mg of recovered starting material (**1c**).

Method C. By Hydrolysis with Amberlite CG-400 (OH^- Form). The procedure of method B was repeated with 40 mg of bufotalin acetate (**1c**), methyl alcohol (10 ml)–water (1 ml), and 0.20 g of Amberlite CG-400 (OH^- form). In this case the mixture was stirred at room temperature for 8 hr. Separation of the crude product (45 mg) gave 4.8 mg of bufotalin (**1a**, mp 215–220°), 11 mg of diol **1b** (mp 253–255°), 2.6 mg of triol **1d** (mp 195–222°), and 16 mg of starting material (**1c**).

Method D. Hydrolysis by Potassium Bicarbonate. Potassium bicarbonate (0.19 g) in water (6.5 ml) was added to a solution of bufotalin acetate (**1c**, 0.17 g) in methanol (14 ml) and the solution was allowed to stand at room temperature for 10 days. After acidification (to pH 3.0) with dilute sulfuric acid the mixture was extracted with chloroform and the extract was washed with water. Removal of solvent gave a 0.18-g residue which was separated as summarized in method A. By this means 10 mg of bufotalin (**1a**, mp 219–226°), 50 mg of diol **1b** (mp 254–257°), 8.5 mg of desacetylbufotalin (**1d**, mp 201–219°), and 79 mg of recovered bufotalin diacetate (**1c**) were obtained.

Acetylation of Desacetylbufotalin (1d). A solution of desacetylbufotalin (**1d**, 50 mg) in glacial acetic acid (1 ml) was heated at reflux for 1 hr. Solvent was removed and the residue was chromatographed. Elution with the solvent sequence 19:1, 9:1, 7:1, and 5:1 hexane–acetone led to 14 mg of bufotalin acetate (**1c**, mp 266–270°), 9 mg of bufotalin (**1a**, mp 217–220°), 12 mg of diol **1b** (mp 253–256°), and 10 mg of recovered desacetylbufotalin (**1d**).

3β-Acetoxy-16β-hydroxy-5β-bufa-14,20,22-trienolide (6a). Method A. Reduction with Urushibara Nickel A. A large excess of freshly prepared Urushibara nickel A[11] was added to a solution of ketone **5** (40 mg) in ethyl alcohol (4 ml). The mixture was heated at reflux for 1 hr and the solution was filtered. After removal of solvent the residue was chromatographed using 5:1 hexane–acetone as eluent. The principal fraction recrystallized from acetone–hexane to afford 20 mg of alcohol **6a** as prisms melting at 229–237°.

Method B. Reduction with Raney Nickel (W-2). The preceding reduction reaction was repeated employing 20 mg of ketone **5** and a large excess of freshly prepared Raney nickel (W-2). By this means an 8-mg specimen of alcohol **6a** melting at 227–235° was obtained.

Method C. From Bufotalin Acetate (1c). Dehydration of bufotalin acetate (**1c**) was repeated as reported in Part 21.[6] The product, olefin **6b** (0.10 g), was dissolved in methyl alcohol (10ml) and a solution of potassium bicarbonate (0.10 g) in water (38 ml) was added. The saponification mixture was heated at 50° for 10 min and allowed to remain at room temperature for 4 days. Following acidification (to pH 3.0) with dilute sulfuric acid and extraction with chloroform the combined extract was washed with water and concentrated to dryness. The residue (97 mg) was chromatographed with 5:1 hexane–acetone as eluting solvent. The specimens of olefin **6a** prepared by methods A–C were found mutually identical. The major fraction was recrystallized from acetone–hexane to yield 67 mg of allylic alcohol **6a** as prisms melting at 228–237°: tlc R_f 0.31; λ_{max} (MeOH) 299 nm (log ϵ 4.22); ν_{max} 3520, 3480 (OH), 1750, 1720, 1710, 1690, 1635, 1538, 1260, 1230, 1030, 955, 910, 865, 750 cm^{-1}; pmr (10% solution in deuteriochloroform) δ 0.81 (3 H, s, 18-CH_3), 0.98 (3 H, s, 19-CH_3), 2.04 (3 H, s, 3-OAc), 2.53 (1 H, d, J = 8 Hz, 17-H), *ca.* 5.0 (1 H, broad m, 16α-H), 5.00 (*ca.* 2 H, m, 3α-H and 16α-H), 5.30 (1 H, broad s, 15-H), 6.30 (1 H, d, J = 11 Hz, 23-H), 7.33 (1 H, d, J = 3 Hz, 21-H), 7.86, (1 H, dd, J = 11 and 3 Hz, 22-H); mass spectrum *m/e* 426 (M^+), 408 ($M^+ - H_2O$), 366 (M^+ – AcOH), 348 ($M^+ - H_2O$ – AcOH), 241, 215, 202, 187.

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.2; H, 7.04. Found: 73.37; H, 8.03.

3β,16β-Diacetoxy-5β-bufa-14,20,22-trienolide (6b, 3β-Acetoxy-14-dehydrobufotalin). Alcohol **6a** (50 ml) was treated with acetic anhydride (0.7 ml)–pyridine (1.0 ml) at room temperature for 18 hr. The crude product (53 mg) recrystallized from acetone–hexane to give 44 mg of 3β-acetoxy-14-dehydrobufotalin as prisms melting at 204–106°. The diacetate was identical with an authentic sample prepared from natural bufotalin.

Oxidation of 3β-Acetoxy-16β-hydroxy-5β-bufa-14,20,22-trienolide (6a). Method A. With Manganese Dioxide. Active (freshly prepared) manganese dioxide (0.10 g) was added to a solution of allylic alcohol **6a** (20 mg) in chloroform (2.0 ml) and the mixture was stirred at room temperature for 8 hr. The solution was filtered and concentrated to dryness. The crude product was separated by preparative thin layer chromatography on silica gel using 3:3:4 acetone–chloroform–hexane as mobile phase. The zone corresponding to R_f 0.43 was eluted with 3:1 methylene chloride–methanol. The eluted fraction was recrystallized from methanol to provide 15 mg of ketone **5** as needls melting at 211–215°.

Method B. With Chromium Trioxide. The oxidation reaction described to method A directly above was repeated employing 30

mg of allylic alcohol **6a** and the chromium trioxide (30 mg)–pyridine (2 ml) reagent (room temperature, 18 hr). The yield of ketone **5** melting at 211–213° was 22 mg. The yield (20 mg) was somewhat less employing 2% chromium trioxide in acetic acid (room temperature, 4 hr).

Bufotalin Acetate (1c). Method A. From Iodohydrin 7a. A solution of *N*-iodosuccinimide (25 mg) in acetone (0.5 ml)–water (0.5 ml) was added to an acetone (4 ml) solution of 3β-acetoxy-14-dehydrobufotalin (**6b**, 25 mg). The mixture was stirred for 30 min and allowed to remain at room temperature for 20 hr. The mixture was then diluted with sodium sulfite (25 mg in 1 ml of water), poured into ice–water, and extracted with chloroform. The combined extract was washed with water and concentrated to dryness to yield 24 mg of iodohydrin **7a**. A solution of the crude iodohydrin in methylene chloride was allowed to react with excess Urushibara nickel A with stirring (nitrogen atmosphere) at room temperature for 4 hr. The solution was filtered, solvent was evaporated, and the residue was chromatographed. Elution with 9:1 hexane–acetone led to 19 mg of bufotalin acetate as prisms melting at 263–269°.

Method B. From Bromohydrin 7b. The procedure of method A was repeated employing 20 mg of olefin **6b** and 20 mg of *N*-bromosuccinimide. In this experiment the reaction time was 19 hr and 12 mg of bufotalin acetate (**1c**, mp 265–269°) was realized. The overall yield of bufotalin acetate was essentially unchanged using *N*-bromoacetamide in place of *N*-bromosuccinimide.

Method D. From 3β,14β,16β-Trihydroxy-5β-bufa-20,22-dienolide (1d). A 20-mg sample of triol **1b** obtained *via* the ketone **4** route (**4** → **1b** → **1c** → **1d**) was acetylated with acidic anhydride (0.28 ml)–pyridine (0.4 ml) at room temperature over 18 hr. The crude acetone (22 mg) was recrystallized from acetone–hexane to yield 17 mg of bufotalin acetate (**1c**) melting at 263–269°. The specimens of bufotalin acetate prepared by methods A–C were found mutually identical.

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Registry No.—**1a**, 471-95-4; **1b**, 4026-98-6; **1c**, 4029-69-0; **1d**, 465-19-0; **2**, 470-37-1; **3**, 36615-16-4; **4**, 35602-94-9; **5**, 51869-38-6; **6a**, 51869-39-7; **6b**, 36615-06-2; **7a**, 51869-40-0; **7b**, 51869-41-1; 3β-acetoxy-16β-hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide, 4026-96-4.

References and Notes

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Deoxygenation of 1,4-Epoxy-1,4-dihydronaphthalenes, a Possible Cheletropic Removal of Oxygen[1]

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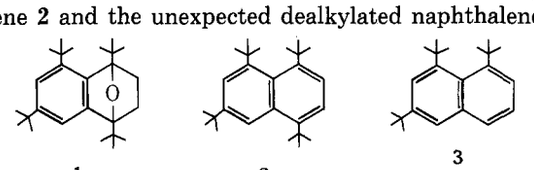
The one-step aromatization of benzyne–furan Diels–Alder adducts has been carried out in two ways. An apparent photochemical extrusion of atomic oxygen in triethylamine afforded a low yield of naphthalene. The use of naphthalene anion radical with substituted adducts proved to be a useful synthetic procedure.

In earlier work in our laboratory,[2] the acid-catalyzed dehydration of endoxide **1** afforded both the desired naphthalene **2** and the unexpected dealkylated naphthalene **3**.



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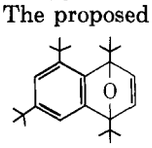
In addition, other dealkylations were observed, but the subject case was the most sensitive one. At the time, new routes to sensistive naphthalenes which would avoid acidic conditions were sought in our laboratory. One approach would be the direct deoxygenation of a benzyne–furan Diels–Alder adduct **4**. The proposed direct deoxygenation



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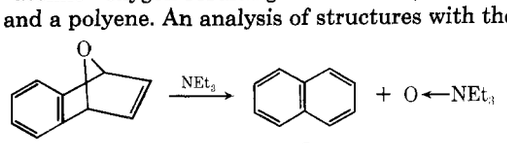
of endoxides such as **4** to form naphthalene **2**, is formally an *extrusion reaction*, examples of which are well known.[3] An approximate order of ease of extrusion is $N_2 > CO_2 > CO \geq$ "SO" $> SO_2 > O_2 \geq S > O$. Woodward and Hoffmann[4] describe a reaction and selection rules in which a tertiary amine reacts with a cyclic allyl ether so as to remove "atomic" oxygen resulting in the formation of an *N*-oxide and a polyene. An analysis of structures with the use



5 6

of models shows that the bridgehead protons of **5** obstruct the "linear" approach of the tertiary amine (one of the alkyl groups of the amine) so that oxygen abstraction cannot occur. Thus, a "nonlinear" disrotatory reaction requiring photochemical activation is predicted as necessary for our desired synthesis.[5]

The photolysis of 1,4-dihydronaphthalene-1,4-endoxide