Bufadienolides. 17. Synthesis of 14α- and 14β-Artebufogenin[1]

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Received November 24, 1972

Treatment of resibufogenin (**1***a*) or its acetate (**1***b*) with perchloric acid or hydrochloric acid gave 14α- and 14β-artebufogenin (**5***a* and **6***a*, or **5***b* and **6***b*), in addition to 15α-hydroxy-bufalin (**4***a* or *b*). Reaction of epoxide **1***b* with chloranil or boron trifluoride etherate easily afforded 14α- and 14β-artebufogenin acetate (**5***b* and **6***b*) in good yields. Analogous reaction of the isomeric 3β-hydroxy-14α,15α-epoxide **3***a* with perchloric acid, hydrochloric acid, or sulfuric acid again led to 14α- and 14β-artebufogenin (**5***a* and **6***a*) and the 14β,15α-dihydroxy-derivative **4***a*. Similar reaction with periodic acid gave **6***a* and **4***a*.

Lors du traitement de la résibufogénine (**1***a*) ou de son acétate (**1***b*) avec de l'acide perchlorique ou avec de l'acide chlorhydrique, on a obtenu l'artébyfagénine-14α et 14β (**5***a* et **6***a* ou **5***b* et **6***b*), en plus de l'hydroxy-15α bufaline (**4***a* ou **4***b*). La réaction de l'époxyde **1***b* avec du chloranil ou avec de l'éthérate de trifluorure de bore a produit aisément [l'acétate-14α et 14β d'arté bufogénine (**5***b* et **6***B*) avec d'excellents rendements. La réaction similaire de l'époxyde-14α,15α hydroxy-3β isomérique avec de l'acide perchlorique, de l'acide chlorhydrique ou de l'acide sulfurique a conduit de nouveau à l'artébufogénine-14α et 14β (**5***a* et **6***a*) et le dérivé dihydroxy-14β,15α (**4***a*). La réaction identique avec l'acide periodique a conduit aux produits **6***a* et **4***a*. [Traduit par le journal]

Can. J. Chem., 51, 1973 (1973)

In one of the early studies (1) which preceded the bufadienolide structural assignment, 14α-artebufogenin (**5***a*) was prepared from the 14β,-15β-epoxide, resibufogenin (**1***a*), by reaction with concentrated hydrochloric acid and later (2) using perchloric acid. Recently (3), we noted that a small amount of 14α-artebufogenin (**5***a*) could be isolated by column chromatography of 3β,14β-dihydroxy-15α-bromo-5β-bufa-20,22-dienolide (**2**) on alumina. Treatment of the 14α-isomer (**5***a*) with alumina (2) or hydrochloric acid (4) has afforded the epimeric 14β-artebufogenin (**6***a*). Also epimerization of the 14β-isomer (**6***a*) with acid (5) has afforded 14α-artebufogenin (**5***a*). A more direct route to 14β-artebufogenin (**6***a*) has not heretofore been reported.

In the present report we wish to describe new syntheses of 14α- and 14β-artebufogenin (**5***a* and **6***a*) from resibufogenin (**1**) and the isomeric (2) 14α,15α-epoxide **3**. The latter epoxide (**3**) was prepared from 14-dehydrobufalin by oxidation with meta-chloroperbenzoic acid (3)[3]. When 3β-hydroxy-14β,15β-epoxide **1***a* was treated with 70% perchloric acid in acetone (2) and the product carefully chromatographed, 14α-artebufogenin (**5***a*), 14β-artebufogenin (**6***a*), and 3β,-14β,15α-triol **4***a* were obtained in respectively 69 and ~9% yields. Analogous treatment of 3β-acetoxy-14β,15β-epoxide **1***b* gave 14α-artebufogenin acetate (**5***b*), 14β-artebufogenin acetate (**6***b*), 3-acetoxy-14β,15α-diol (**4***b*), and 14α-artebufogenin (**5***a*) (5) in respectively 73, 8, 12, and 8% yields.

Reaction of resibufogenin (**1***a*) with 2 *N* hydrochloric acid in acetone gave 14α-artebufogenin (**5***a*), 14β-artebufogenin (**6***a*), and 15α-hydroxybufalin (**4***a*) in 62, 23.5, and 6% yields. Extension of the reaction to 3β-acetate **1***b* gave the corresponding 3β-acetates, **5***b*, **6***b*, and **4***b* in 60, 22, and 10% yields. The higher yield of 14β-epimer (**6***a* or *b*) resulting from reaction with hydrochloric acid may have been due to the longer contact time. It should also be mentioned that certain etianic acid (7) and pregnane (8) 14β,15β-epoxides have been converted to 14β,15α-dihydroxy derivatives by treatment with perchloric acid.

Reaction of 3β-acetoxy-14β,15β-epoxide **1***b* with chloranil in refluxing xylene or at room temperature with boron trifluoride etherate afforded only the 14α*H*-15-oxo- and 14β*H*-15-oxo-isomers (**5***b* and **6***b*). Best conversion was found using boron trifluoride etherate. Here 14β-artebufogenin was obtained in 60% yield and the 14α-epimer in 20% yield.

[1]For Parts 15 and 16 of this series (Steroids and Related Natural Products 71 and 72) see refs. 13 and 14, respectively.

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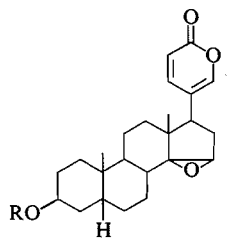
[3]A related study employing *p*-nitroperbenzoic acid has been described by Bingham *et al.* (6).



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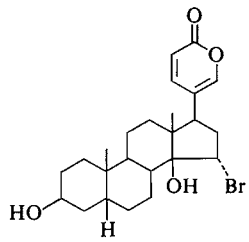

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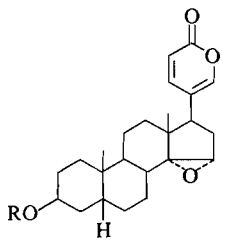

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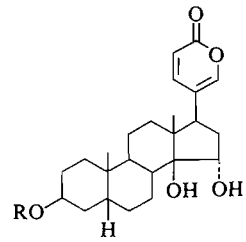

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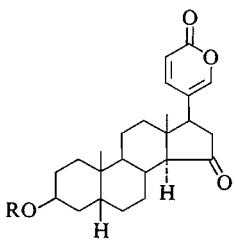

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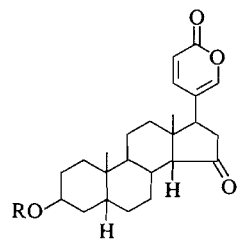
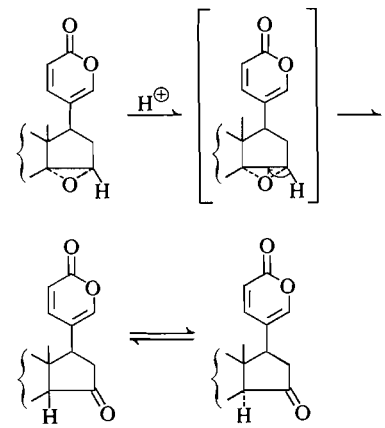


6
a R = H
b R = Ac

Application of the preceding reaction with 4 *N* hydrochloric acid to 3β-hydroxy- or 3β-acetoxy-14α,15α-epoxide **3***a* or *b* gave the 14α*H*-15-oxo- (**5***a* or *b*), 14β*H*-15-oxo- (**6***a* or *b*), and 14β,15α-dihydroxy derivatives (**4***a* or *b*) in respectively 26 or 21, 18 or 14, and 49 or 48% yields. With dilute sulfuric acid in acetone–water as acid catalyst detailed column chromatography of the product led to the 14α*H*- (**5***a* or *b*) and 14β*H*-isomers (**6***a* or *b*) as well as the 14β,15α-dihydroxy derivative (**4***a* or *b*) (3). Similar results were obtained by subjecting 3β-hydroxy-14α,15α-epoxide **3***a* to treatment with dilute perchloric acid in chloroform–acetone. However, reaction of α-epoxide **3***a* with periodic acid in chloroform–acetone gave 14β-artebufogenin (**6***a*) and 15α-hydroxy-bufalin (**4***a*) in 14 and 53% yields. Only a trace of 14α-artebufogenin was detected.

Mayo (9) has suggested that conversion of 14β,15β-epoxides to 14α*H*-15-oxo-derivatives using perchloric acid may be attributed to a 1,2-shift of the C-15 proton. An analogous mechanistic pathway may be operative in the acid-catalyzed reactions we have observed with resibufogenin (**1**) and the corresponding 14α,15α-epoxide **3** (see Scheme 1). In the latter



SCHEME 1

case, formation of 14α-artebufogenin is probably the result of epimerizing 14β-artebufogenin. The formation of 14β,15α-diols from 14α,15α-epoxides is analogous to observations made in several earlier studies (10) and we wish to thank a referee for providing this information.

We have previously obtained both 14-dehydrobufalin and resibufogenin (**1***a*) by total synthetic routes (3). Thus, the reactions described above leading to 14α- and 14β-artebufogenin complete total syntheses of these substances.

Experimental

The general experimental techniques have been summarized in the experimental introduction of ref. 3. Authentic specimens of alcohols **4***a* and *b* and the artebufogenins were prepared as previously described (3, 11). The identity of each product was confirmed by results of chromatographic and spectral comparisons with the respective authentic sample. All melting points were observed using a micro hot-stage apparatus (Reichert, Austria) and are uncorrected. Column chromatography refers to the dry method using silica gel (12). All solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate. The identity of each product was established by mixture melting determination and i.r. spectral comparison with an authentic sample.

Epoxide Ring Opening with 3β-Hydroxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (Resibufogenin, 1a)

Method A. With Perchloric Acid

To a solution of epoxide **1***a* (115 mg) dissolved in acetone (6 ml), 0.05 ml of 72% perchloric acid was added and the mixture was allowed to stand for 30 min at room temperature. The mixture was poured into ice–water and extracted with chloroform. The extract was washed with water, and concentrated *in vacuo* to dryness. The residue (99 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone 5:1 and 3:1 gave 14α-isomer **5***a* (79 mg), m.p. 265–267° as colorless prisms from acetone, 14β-isomer **6***a* (11 mg), m.p. 128–130° as colorless prisms from methanol, and diol **4***a* (11 mg), m.p. 272–273° as colorless needles from acetone.

Method B. With Hydrochloric Acid

Hydrochloric acid (4 ml of 2 *N*) was added to a solution of **1***a* (100 mg) in acetone (12 ml) and the mixture was allowed to stand for 24 h at room temperature. The mixture was poured into ice–water and extracted with chloroform. The extract was washed with water and solvent evaporated. The residue (97 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (5:1) gave **5***a* (62 mg, m.p. 266–267°), **6***a* (24 mg, m.p. 127–129°), and **4***a* (6 mg, m.p. 271–273°).

Epoxide Ring Opening with 3β-Acetoxy-14β,15β-epoxy-5β-bufa-20,22-dienolide (Resibufogenin Acetate, 1b)

Method A. With Perchloric Acid

To a solution of **1***b* (75 mg) in acetone (5 ml), 0.05 ml of 70% perchloric acid was added and the mixture was allowed to stand for 30 min at room temperature. The residue (71 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone, 19:1, 9:1, and 5:1, provided **5***b* (55 mg), m.p. 221–223°, **6***b* (6 mg), m.p. 233–235°, **4***b* (9 mg), m.p. 271–273°, and **5***a* (6) (6 mg), m.p. 263–265° all as colorless prisms from acetone.

Method B. With Hydrochloric Acid

In the manner described above (**1***a*, method B) β-epoxide **1***b* (50 mg) in acetone (5 ml) was treated with 2 ml of 2 *N* hydrochloric acid. The product (48 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone 19:1, 9:1, and 5:1 afforded **5***b* (30 mg, m.p. 222–223°), **6***b* (11 mg, m.p. 232–234°), and **4***b* (5 mg, m.p. 269–272°).

Method C. With Chloranil

Chloranil (40 mg) was added to a solution of **1***b* (22 mg) in xylene (5 ml), and the mixture was heated at reflux for 45 min. After dilution with benzene, the mixture was poured into water. The benzene layer was washed with water, dilute sodium bicarbonate, and water, and evaporated to dryness. The residue (30 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1) afforded **5***b* (11 mg, m.p. 223–225°) and **6***b* (8 mg, m.p. 223 ~ 234°).

Method D. With Boron Trifluoride Etherate

Freshly distilled boron trifluoride etherate (0.2 ml) was added to a solution of **1***b* (20 mg) in benzene (2 ml)–ether (1 ml), and the mixture was allowed to stand for 10 min at room temperature. After dilution with benzene, the mixture was poured into ice–water. The benzene–ether layer was washed with water, dilute sodium bicarbonate solution, and water, and evaporated *in vacuo* to dryness. The residue (23 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1) gave **5***b* (11 mg, m.p. 222–224°) and **6***b* (4 mg, m.p. 232–235°).

Epoxide Ring Opening with 3β-Hydroxy-14α,15α-epoxy-5β-bufa-20,22-dienolide (3a)

Method A. With Perchloric Acid

To a solution of α-epoxide **3***a* (0.20 g) in chloroform (3 ml) – acetone (12 ml), 0.1 ml of 72% perchloric acid solution was added and the mixture was allowed to stand for 48 h at room temperature. After isolation in the manner described above, the product (0.22 g) obtained was chromatographed on a column of silica gel. Elution with ligroin–ether, 5:1 and 3:1, gave **6***a* (57 mg, m.p. 128–130°, prisms from methanol), **5***a* (6 mg, m.p. 266–267°, prisms from acetone), and **4***a* (110 mg, m.p. 271–273°, needles from acetone).

Method B. With Hydrochloric Acid

A solution of α-epoxide **3***a* (70 mg) in chloroform (3 ml) – acetone (12 ml) was treated with 1.5 ml of 4 *N* hydrochloric acid with stirring for 24 h at room temperature. Extraction with chloroform and separation as described above gave the product (68 mg), which was chromatographed on a column of silica gel. Elution with ligroin–ether, 5:1 and 3:1, provided **6***a* (15 mg, m.p. 127–130°), **5***a* (13 mg, m.p. 266–268°), and **4***a* (34 mg, m.p. 272–273°).

Method C. With Sulfuric Acid

To a solution of **3***a* (100 mg) in chloroform (15 ml) – acetone (6 ml) – water (1 ml) was added 1.5 ml of 2 *N* sulfuric acid and the mixture was allowed to stand for 48 h at room temperature. The mixture was poured into water and extracted with chloroform. The extract was washed with water and evaporated (*in vacuo*) to dryness. The product (98 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone, 5:1 and 3:1, provided **6***a* (18 mg, m.p. 127–130°), **5***a* (4 mg, m.p. 265–268°), and **4***a* (7 mg, m.p. 215–218°).

Method D. With Periodic Acid

To a solution of **3***a* (80 mg) in chloroform (3 ml) – acetone (12 ml) – water (0.2 ml), 60 mg of periodic acid dihydrate was added and the mixture was allowed to stand for 18 h at room temperature. The mixture was poured into water, extracted with chloroform, and the extract was washed with water, and evaporated (*in vacuo*) to dryness. The product (56 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (3:1) gave **6***a* (11 mg, m.p. 125–129°) and **4***a* (42 mg, m.p. 271–273°). On t.l.c. (solvent: acetone–chloroform–cyclohexane (3:3:4), silica gel plate developed with concentrated sulfuric acid), the mother liquor of recrystallized **6***a* showed a spot corresponding to **5***a*.

Epoxide Ring Opening with 3β-Acetoxy-14α,15α-epoxy-5β-bufa-20,22-dienolide (3b)

Method A. With Hydrochloric Acid

A solution of α-epoxide **3***b* (0.10 g) in acetone (10 ml) – water (0.1 ml) was stirred with 2 ml of 4 *N* hydrochloric acid for 24 h at room temperature. Following initial separation as described above, the product (99 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1 and 5:1) provided **6***b* (26 mg, m.p. 234–235°), **5***b* (14 mg, m.p. 221–222°), and **4***b* (43 mg, m.p. 280–282°).

Method B. With Sulfuric Acid

To a solution of **3***b* (100 mg) in acetone (20 ml) – water (0.5 ml), 2.5 ml of 1 *N* sulfuric acid solution was added and the mixture was allowed to stand for 48 h at room temperature. The solution was poured into water and extracted with chloroform. After isolation (see above) the product (98 mg) was chromatographed on a column of silica gel. Elution with ligroin–acetone mixture (9:1 and 3:1) provided **5***b* (6 mg, m.p. 221–223°), **6***b* (14 mg, m.p. 234–236°), and **4***b* (62 mg, m.p. 280–283°).

Method C. With Boron Trifluoride Etherate

A solution of **3***b* (20 mg) in 4 ml of benzene–ether (1:1) was treated with freshly distilled boron trifluoride etherate for 10 min at room temperature. Isolation of product was performed as described above and provided 21 mg, which was chromatographed on a column of silica gel. Elution with ligroin–acetone (9:1) gave **6***b* (12 mg, m.p. 232–234°) and **5***b* (4 mg, m.p. 222–225°).

The present investigation was supported by Public Health Service Research Grants CA-10612-04, CA-11451-03, and CA-10115-04 from the National Cancer Institute.

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