*Anal.* Calcd. for $C_9H_{11}AsClNO_3$: N, 4.80; As, 25.69. Found: N, 4.72; As, 25.57.

**N-Acetyl-*p*-arsenosophenylalanine (X).**—Reduction of 3.3 g. (0.01 mole) of VII with sulfur dioxide gave 2.6 g. (88%) of X melting at 250–252°.

*Anal.* Calcd. for $C_{11}H_{12}AsNO_4$: N, 4.72; As, 25.21. Found: N, 4.62; As, 25.22.

**N-Benzoyl-*p*-arsenophenylalanine (XI).**—The corresponding arsonic acid V was reduced with sodium hydrosulfite.[10] A solution of 3.93 g. (0.01 mole) of V in 10 ml. of 2 *N* sodium hydroxide and 100 ml. of water was added to a solution of 50 g. of sodium hydrosulfite and 10 g. of magnesium chloride in 400 ml. of water. The mixture was stirred at 60° for 2 hours. Addition of dilute hydrochloric acid gave a yellow powder which was purified by solution in acetone and reprecipitation with water. For final purification, the material was dissolved in glacial acetic acid and precipitated with a large excess of dilute hydrochloric acid to give 2.15 g. (63%) of XI, m.p. 294–295°.

*Anal.* Calcd. for $C_{32}H_{28}As_2N_2O_6$: N, 4.08; As, 21.83. Found: N, 4.17; As, 21.65.

***p*-Arsenophenylalanine Hydrochloride (XII).**—Hydrolysis of XI with 6 *N* hydrochloric acid gave XII (79%), melting with decomposition at 282–285°.

*Anal.* Calcd. for $C_{18}H_{22}As_2Cl_2N_2O_4$: N, 5.08; As, 27.74. Found: N, 4.92; As, 27.98.

**N-Acetyl-*p*-arsenophenylalanine (XIII).**—The corresponding arsonic acid VII was reduced with sodium hydrosulfite to give 47% of product melting with decomposition at 272–277°.

*Anal.* Calcd. for $C_{22}H_{24}As_2N_2O_6$: N, 4.99; As, 26.65. Found: N, 4.86; As, 26.42.

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## Steroidal Cyclic Ketals. XIII.[1] The Conversion of 11-*epi*-Corticosterone into Corticosterone

BY SEYMOUR BERNSTEIN AND ROBERT H. LENHARD

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In Paper XI[2] of this series, there was described a procedure for the conversion of 11-*epi*-hydrocortisone *via* its bisethylene ketal into hydrocortisone. One of the features of this synthesis was that cortisone (free alcohol) was by-passed. Subsequently, this procedure was extended to the preparation of corticosterone (Va)[3] from the readily available 11-*epi*-corticosterone (I),[4] the details of which will be described here.

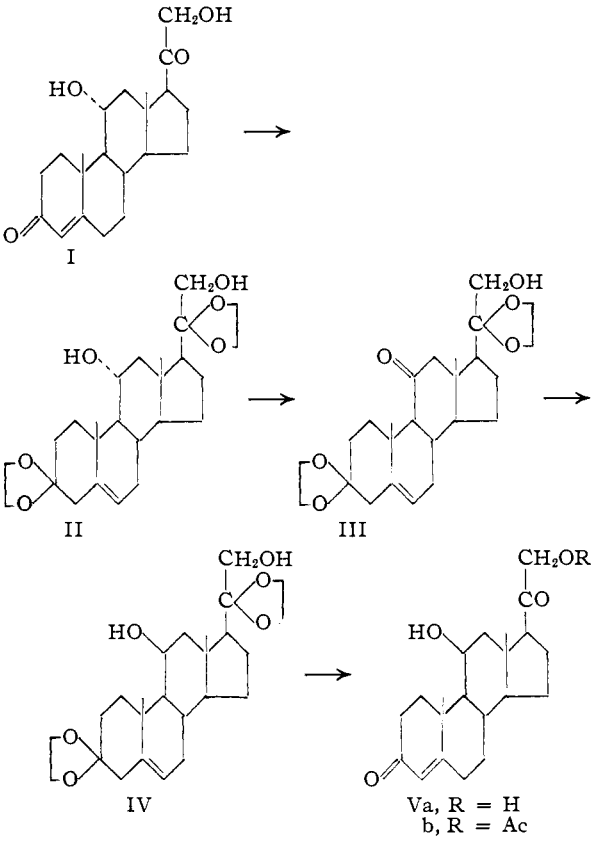
11-*epi*-Corticosterone (I) on ketalization (ethylene glycol, benzene and *p*-toluenesulfonic acid monohydrate) was converted in 37% yield into its 3,20-bisethylene ketal (II). Oxidation of the latter with chromic acid–pyridine complex[5] gave in 61% yield the 3,20-bisethylene ketal (III) of 11-dehydrocorticosterone.

Reduction of III with sodium borohydride in a mixture of tetrahydrofuran and aqueous sodium hydroxide gave the bisethylene ketal (IV) of corticosterone. This product was not characterized because on recrystallization gels were obtained. Hydrolysis of the ketal groups with aqueous sulfuric acid in methanol gave corticosterone (Va) in 85% yield. The corticosterone (Va) so formed contained an insignificant trace amount of 11-*epi*-corticosterone (I), as shown by paper chromatographic analysis. Acetylation gave corticosterone 21-acetate (Vb).

From a preparative viewpoint it was found expedient to hydrolyze directly the crude reduction product III without recrystallization. This provided a 77% yield of corticosterone (Va) from II.

Although this four-step synthesis was performed in only a fair over-all yield of 17%, it represents a comparatively facile and convenient method for preparing corticosterone (Va).[6]

FLOW SHEET




### Experimental

**Melting Points.**—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

(1) Paper XII, W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

(2) W. S. Allen, S. Bernstein and R. Littell, *ibid.*, **76**, 6116 (1954).

(3) Corticosterone has been synthesized by chemical and biochemical methods: (a) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944); (b) O. Hechter, *et al.*, THIS JOURNAL, **71**, 3261 (1949); (c) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951); (d) F. W. Kahnt and A. Wettstein, *Helv. Chim. Acta*, **34**, 1790 (1951).

(4) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (July 8, 1952); J. Fried, *et al.*, THIS JOURNAL, **74**, 3962 (1952); S. H. Eppstein, *et al.*, *ibid.*, **75**, 408 (1953).

(5) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(6) After completion of this work, there appeared a publication by D. Taub, R. H. Pettebone, N. L. Wendler and M. Tishler, *ibid.*, **76**, 4094 (1954), in which corticosterone was prepared in 20–25% over-all yield from cortisone and hydrocortisone. In this connection, we wish to record here that the intermediate bisethylene ketal (IV) of corticosterone also may be prepared by selective hydrogenation of $\Delta^{5,16}$-pregnadiene-11$\beta$,21-diol-3,20-dione 3,20-bisethylene ketal with platinum oxide in absolute alcohol. The preparation of the $\Delta^{5,16}$-diene from either cortisone or 11-*epi*-hydrocortisone has been described already (W. S. Allen and S. Bernstein, *ibid.*, **77**, 1028 (1955); and references cited therein). Of these two pathways to corticosterone we prefer the one *via* 11-*epi*-corticosterone (I).

**Optical Rotations.**—The sample was dissolved in the stated solvent to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube at wave length 5893 Å. (D).

**Absorption Spectra.**—The ultraviolet spectra were determined in absolute alcohol with a Beckman spectrophotometer (model DU). The infrared spectra (pressed potassium bromide) were determined with a Perkin–Elmer spectrophotometer (model 21).

**Petroleum Ether.**—The fraction used was b.p. 60–70° (Skellysolve B).

*All evaporations were carried out under reduced pressure.*

**Bisethylene Ketal (II) of 11-*epi*-Corticosterone (Δ⁵-Pregnene-11α,21-diol-3,20-dione 3,20-Bisethylene Ketal).**—11-*epi*-Corticosterone (I, 2.0 g., m.p. 155–157°) in benzene (100 ml.) was treated with ethylene glycol (16 ml.) and *p*-toluenesulfonic acid monohydrate (60 mg.) in the manner previously described (3.5 hours reflux).[7] Two crystallizations of the crude product from acetone–petroleum ether gave 0.92 g., m.p. 228–232.5°, with previous softening (37% yield). Two further crystallizations gave pure II, 0.69 g., m.p. 231–234.5°, with previous softening; ultraviolet spectrum: $\lambda_{max}$ none; infrared spectrum, $\lambda_{max}$ 3450 and 1095 cm.$^{-1}$; $[\alpha]^{25}D$ −23° (12.91 mg., chloroform, $\alpha D$ −0.15°), $[M]D$ −100.

*Anal.* Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Found: C, 68.75; H, 8.94.

**Bisethylene Ketal (III) of 11-Dehydrocorticosterone (Δ⁵-Pregnene-21-ol-3,11,20-trione 3,20-Bisethylene Ketal).**—The bisketal (II, 0.47 g.) in pyridine (5 ml.) was added to a slurry of chromic anhydride (325 mg.) and pyridine (3.5 ml.). The reaction mixture, after standing for 16 hours at 25°, was poured into water and extracted with ethyl acetate. The extract was filtered through Celite for the removal of inorganic material. It was then washed, dried and evaporated to afford a white solid. Recrystallization of the crude product from acetone–petroleum ether gave 286 mg. of practically pure III, m.p. 203–206.5°, with previous softening (61% yield). Two additional crystallizations gave 257 mg. of pure product, m.p. 204.5–207°, with previous softening; infrared spectrum: $\lambda_{max}$ 3545, 1710 and 1099 cm.$^{-1}$; $[\alpha]^{25}D$ +16° (12.26 mg., chloroform, $\alpha D$ +0.10°), $[M]$ +69.

*Anal.* Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.21; H, 8.42.

**Bisethylene Ketal (IV) of Corticosterone (Δ⁵-Pregnene-11β,21-diol-3,20-dione 3,20-Bisethylene Ketal).**—The 11-one bisketal (III, 0.37 g.) in tetrahydrofuran (15 ml.) was treated with sodium borohydride (0.8 g.) and 2.5% aqueous sodium hydroxide (2 ml.). The mixture was refluxed for 16.5 hours, water was added, and the tetrahydrofuran was evaporated. The residual mixture was extracted with ethyl acetate, and the extract was washed, dried and evaporated to afford a gelatinous residue. Crystallization from acetone–petroleum ether gave 326 mg. of a gel which when dried melted at 154–158°, with previous softening and bubbles in the melt.

**Corticosterone (Δ⁴-Pregnene-11β,21-diol-3,20-dione) (Va).** A.—Compound IV (0.27 g.) in methanol (10 ml.) was treated with 8% (v./v.) sulfuric acid (1 ml.), and was refluxed for 30 minutes. The cooled solution was diluted with water, neutralized with sodium bicarbonate and was extracted with ethyl acetate. The washed and dried extract was evaporated, and the residue was crystallized from acetone–petroleum ether to give 0.18 g. (85% yield) of essentially pure V, m.p. 179.5–183°, with previous softening; ultraviolet spectrum: $\lambda_{max}$ 241 mμ (ε 15,600); infrared spectrum: $\lambda_{max}$ 3470, 1706, 1660 and 1630 cm.$^{-1}$ (identical in all respects with an authentic sample); $[\alpha]^{25}D$ +213° (11 mg., absolute alcohol; $\alpha D$ +1.17°); literature[8] m.p. 180–182° (cor.), $[\alpha]^{15}D$ +223 ± 3° (abs. alc.), $\lambda^{alc.}_{max}$ 240 mμ.

Paper chromatographic analysis of Va revealed the presence of a very minute trace of the 11α-epimer, 11-*epi*-corticosterone.

B.—In another run, the 11-one-bisketal (III, 0.63 g.) was reduced in the same manner as above, and the ethyl acetate extract was evaporated to give 0.63 g. of crude IV. The residue dissolved in methanol (10 ml.) was hydrolyzed by being refluxed for 30 minutes with 8% (v./v.) sulfuric acid (1 ml.). The addition of water to the cooled reaction mixture gave crystals which were collected, 0.36 g., m.p. 171–175°, cloudy melt with previous softening. The filtrate was saturated with salt, and was extracted with ethyl acetate. The washed and dried extract was evaporated, and the residue was crystallized from acetone–petroleum ether to give an additional 80 mg. of V, m.p. 175–177°. Both fractions were combined and recrystallized from acetone–petroleum ether to give 0.39 g. (78% yield from III) of pure V, m.p. 181–183.5°, with previous softening. Concentration of the mother liquors gave an additional 35 mg. of desired product, m.p. 173.5–178.5°, with previous softening.

**Corticosterone 21-Acetate (Δ⁴-Pregnene-11β,21-diol-3,20-dione 21-Acetate) (Vb).**—Compound Vb was prepared in the usual manner; m.p. 149.5–151° (recrystallized from aqueous acetone); literature m.p. 144–145°,[3a] m.p. 147–152°.[3c]

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(7) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(8) T. Reichstein, *Helv. Chim. Acta*, **20**, 953 (1937).

## An Improved Synthesis of Protoanemonin[1]

BY CHRISTOPH GRUNDMANN AND EHRENFRIED KOBER

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Protoanemonin (VII), which is a constituent of the essential oil of the buttercup and other ranunculaceae and which is of interest because of its antibiotic activity, was synthesized by Shaw[2] from β-acetylacrylic acid (VI); his yields (average 30%) were based on spectrophotometric determinations only. The older methods give only minute yields of protoanemonin. We have developed a convenient method for the preparation of protoanemonin from levulinic acid with a high yield.

Levulinic acid (I) is best converted to α-angelica lactone (II), by the procedure of Helberger, *et al.*[3] II accepts one mole of bromine readily to form the β,γ-dibromo-γ-valerolactone (III), which is dehydrobrominated, without further purification, with a tertiary base (2 moles) in an inert solvent. This reaction occurs stepwise; the first molecule of HBr is eliminated easily at room temperature, and at this stage an unsaturated monobromolactone can be isolated to which we ascribe structure IV. That IV is formed and not the other possible isomers, Va or Vb, is indicated by the prompt hydrolysis of IV, even with cold water, to β-acetylacrylic acid (VI). Under these conditions β-bromolevulinic acid, which would originate from Va or Vb, is stable and would not be converted to VI. When the mixture of IV and the tertiary amine is distilled *in vacuo*, the second molecule of HBr is split off with the formation of protoanemonin (VII)

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(2) See E. Shaw, THIS JOURNAL, **68**, 2510 (1946), for a review of the earlier synthetic work on protoanemonin.

(3) J. H. Helberger, S. Ulubay and H. Civelekoglu, *Ann.*, **561**, 215 (1949).