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: λ_{max} none; infrared spectrum, λ_{max} 3450 and 1095 cm.$^{-1}$; $[\alpha]^{25}D$ −23° (12.91 mg., chloroform, αD −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: λ_{max} 3545, 1710 and 1099 cm.$^{-1}$; $[\alpha]^{25}D$ +16° (12.26 mg., chloroform, αD +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: λ_{max} 241 mμ (ε 15,600); infrared spectrum: λ_{max} 3470, 1706, 1660 and 1630 cm.$^{-1}$ (identical in all respects with an authentic sample); $[\alpha]^{25}D$ +213° (11 mg., absolute alcohol; αD +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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CHEMICAL AND BIOLOGICAL RESEARCH SECTION
AMERICAN CYANAMID CO.
RESEARCH DIVISION
LEDERLE LABORATORIES
PEARL RIVER, NEW YORK

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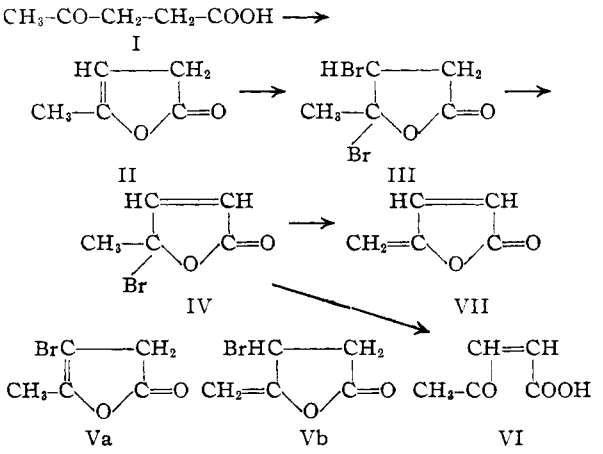
(2) See E. Shaw, THIS JOURNAL, **68**, 2510 (1946), for a review of the earlier synthetic work on protoanemonin.

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



The yields depend to some extent on the tertiary base and the solvent, as indicated in Table I.

TABLE I

Solvent	Base	Protoanemonin, %[a,b]
Ether	Triethylamine	44
Ether	Pyridine	23
Ether	Picoline, techn.	73
Ether	2,4,6-Collidine	24
Ether	Quinoline	76
Benzene	Quinoline	99
Chloroform	Quinoline	12
Carbon disulfide	Quinoline	66

[a] Yields are based on α-angelica lactone. [b] A second distillation lowers the yield about 15% due to partial polymerization. The dimer, anemonin, can be isolated from the residue.

Replacement of the tertiary bases by calcium oxide or potassium hydroxide (in benzene) gave unsatisfactory results; in the latter case 11% of impure protoanemonin was obtained.

The dichlorovalerolactone, unlike the dibromide, is difficult to prepare, as addition of chlorine to the α-angelica lactone (II) always is accompanied by substitution. The dichlorolactone yielded with tertiary amines only an unsaturated monochlorolactone, probably analogous to IV, which could not be isolated in a pure state, but was characterized by its hydrolysis to β-acetylacrylic acid (VI). Our attempts to convert the monochlorolactone at higher temperatures to VII resulted in complete polymerization of the protoanemonin formed.

Experimental

Preparation of Protoanemonin (VII).—α-Angelica lactone (22.8), which was prepared by the slow dehydration of levulinic acid[3] in 90% yield, was dissolved in 25 ml. of carbon disulfide; 27.2 g. of bromine was added dropwise at about −20°. After the solution had become colorless, the carbon disulfide was evaporated under reduced pressure in a water-bath and the residue diluted with 200 ml. of the solvent; a trace of hydroquinone was added to prevent polymerization. Two equivalents of the tertiary amine was added dropwise at about −20°. After the mixture had stood overnight at room temperature, the precipitated hydrobromide of the amine was separated by filtration and washed thoroughly with the solvent. The solvent was removed from the combined filtrates under reduced pressure and the residue distilled at 12 mm. The fraction boiling between 65 and 80° was collected in a trap cooled with Dry Ice and acetone. A subsequent vacuum distillation immediately following the first yielded a pure product, b.p. 68° (8 mm.). The protoanemonin was identified as the crystalline dimer, anemonin, m.p. 153.5°.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.17; double bonds, 2.00. Found: C, 61.66; H, 4.18; double bonds, 2.20.

Care is recommended in handling protoanemonin because of its vesicant properties. After the addition of a small amount of hydroquinone it can be stored unchanged in a refrigerator for several days. Without an inhibitor and at room temperature polymerization to anemonin begins very soon.

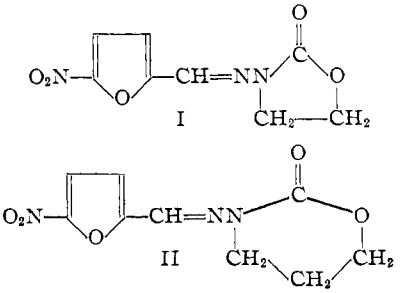
COLUMBUS 10, OHIO

Chemotherapeutic Nitrofurans. III.[1] N-(5-Nitro-2-furfurylidene)-3-aminotetrahydro-1,3-oxazine-2-one

BY K. HAYES

RECEIVED OCTOBER 16, 1954

The chemotherapeutic effectiveness of N-(5-nitro-2-furfurylidene)-3-amino-2-oxazolidone (I)[2,3] led to an interest in the preparation for microbiological testing of the six-membered ring analog, N-(5-nitro-2-furfurylidene)-3-aminotetrahydro-1,3-oxazine-2-one (II). This N-aminoheterocycle has not been prepared previously.



It was observed that 3-hydrazino-1-propanol[4] could be condensed and cyclized smoothly with diethyl carbonate in the presence of sodium methoxide to yield crude 3-aminotetrahydro-1,3-oxazine-2-one; when this was treated with 5-nitro-2-furaldehyde under acidic conditions it yielded II. The ultraviolet absorption characteristics of II are identical with those observed for the five-membered ring analog.[2]

Experimental

N-(5-Nitro-2-furfurylidene)-3-aminotetrahydro-1,3-oxazine-2-one.—A solution of 1.5 g. of sodium in 15 cc. of methanol was added to a mixture of 90 g. (1.0 mole) of 3-hydrazino-1-propanol and 150 g. (1.27 moles) of diethyl carbonate. The mixture was refluxed for two hours while the alcohol formed was removed continuously through a 20-inch Vigreux column. The oily residue was treated with 600 cc. of 3% hydrochloric acid and heated at 85° to hydrolyze the excess diethyl carbonate. A solution of 106 g. (0.75 mole) of 5-nitro-2-furaldehyde in 300 cc. of hot alcohol then was added. A yellow solid precipitated immediately. This was collected, after cooling, and washed by slurrying with two 200-cc. portions of alcohol and 200 cc. of ether; yield 110 g. (46%), m.p. 265–267°.

An analytical sample was prepared by recrystallizing twice from nitromethane and drying *in vacuo* at 56°. The material sublimes above 220° and melts at 267.5° (Fisher-Johns apparatus (cor.)); solubility in water 80 mg. per

(1) For the previous paper in this series see THIS JOURNAL, **77**, 2282, (1955).

(2) For the first paper in this series see G. Gever, *et al.*, *ibid.*, **77**, 2277 (1955).

(3) J. Yurchenco, *et al.*, *Antibiotics and Chemotherapy*, **3**, 1035 (1953).

(4) G. Gever, THIS JOURNAL, **76**, 1283 (1954).