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Preparation of the 3-Ethylenedioxy Derivatives of 11-Ketoprogesterone, Dehydrocorticosterone Acetate and Cortisone Acetate

BY JAMES M. CONSTANTIN, ALFRED C. HAVEN, JR., AND L. H. SARETT

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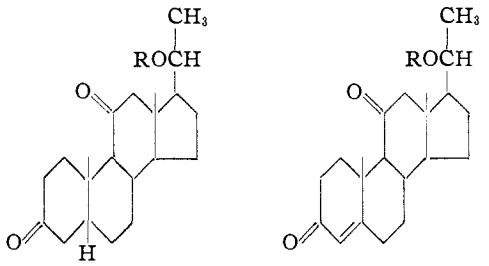
The preparation of the 3-ethylenedioxy derivative of 11-ketoprogesterone has been accomplished by two methods: from pregnane-20β-ol-3,11-dione, and from 11-ketoprogesterone by exchange dioxolanation using the ethylenedioxy derivative of mesityl oxide. The latter method has been applied to the preparation of the ethylenedioxy derivatives of dehydrocorticosterone acetate and cortisone acetate.

During the course of a program on the total synthesis of adrenocortical hormones a quantity of the 3-ethylenedioxy derivative of 11-ketoprogesterone (VI) was required for purposes of comparison and for related synthetic studies. A satisfactory procedure for the preparation of this compound started with pregnane-20β-ol-3,11-dione (II), a substance which is easily obtained[1] from the readily available pregnane-3α-ol-11,20-dione acetate.[2a,b]

Reaction of the hydroxydiketone (II) with bromine gave a crystalline 4-bromide which could be dehydrobrominated *via* the semicarbazide procedure[3] to Δ^4-pregnene-20β-ol-3,11-dione (IV). The same series of reactions could be conducted on the 20-benzoate of II, which was the immediate precursor of the free alcohol,[1] but in this case, the 4-bromide failed to crystallize; the usual recovery of starting material by reduction of the bromination mother liquors was thereby precluded, with attendant decrease in over-all yield.

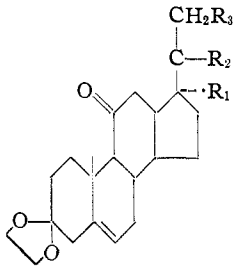
Reaction of the unsaturated ketone (IV) with ethylene glycol and *p*-toluenesulfonic acid was accompanied by the usual shift of the double bond to the 5,6-position.[4,5,6] (A corresponding shift appeared to have occurred with mesityl oxide—see Experimental.) The resulting unsaturated hydroxyketodioxolane (V) was smoothly oxidized with the chromium trioxide–pyridine complex[6] to Δ^5-3-ethylenedioxypregnene-11,20-dione (VI).

An alternate route to the 3-ethylenedioxy derivatives of 11-ketoprogesterone and other Δ^4-3-ketosteroids consisted of an exchange dioxolanation.[7] The dioxolane of mesityl oxide[8] was generally used during the present investigation although a critical comparison of the efficacy of this dioxolane as against others was not made. When this method was employed on 11-ketoprogesterone both the bis- and the desired 3-monoketal derivatives could be isolated; however, treating either dehydrocorticosterone acetate or cortisone acetate in the same manner readily afforded the 3-mono derivative (VII and VIII, respectively).[8a]



I, R = $C_6H_5CO^-$
II, R = H

III, R = $C_6H_5CO^-$
IV, R = H



V, R_1 = R_3 = H; R_2 = H, OH(β)
VI, R_1 = R_3 = H; R_2 = O
VII, R_1 = H, R_2 = O; R_3 = OAc
VIII, R_1 = OH(α); R_2 = O; R_3 = OAc

Acknowledgment.—We are indebted to Mr. Louis H. Peterson, Jr., for technical assistance. The microanalyses reported herein were performed by Mr. R. N. Boos and his associates. The infrared spectra were determined by Mr. R. W. Walker.

Experimental[9]

Δ^4-Pregnene-20β-ol-3,11-dione Benzoate (III).—A solution of 3.59 g. of pregnane-20β-ol-3,11-dione benzoate (I) in 36 ml. of glacial acetic acid and 0.72 ml. of water was treated with 1.32 g. of bromine in 16 ml. of glacial acetic acid and 3 drops of 1 *N* aqueous hydrobromic acid. When, after approximately ten minutes, the decolorization was complete, the reaction mixture was poured into 15 volumes of ice-water and stirred for 20 minutes. The suspension was filtered and the precipitate dissolved in ether. The ethereal solution was washed with saturated aqueous sodium bicarbonate, then with water, dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo*. After additional drying under high vacuum, 4.4 g. of amorphous 4-bromopregnane-20β-ol-3,11-dione benzoate was obtained.

(1) L. H. Sarett, THIS JOURNAL, **71**, 1165 (1949).

(2) (a) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 821 (1944); (b) A. Wettstein and Ch. Meystre, *ibid.*, **30**, 1262 (1947). See also V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **185**, 589 (1950).

(3) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **184**, 393 (1950). See also V. R. Mattox and E. C. Kendall, THIS JOURNAL, **70**, 882 (1948), and E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(4) E. Fernholz and H. E. Stavely, Abstracts, 102nd Meeting of the Am. Chem. Soc., Atlantic City, N. J., 39M (1941).

(5) R. Antonucci, S. Bernstein, D. Grancola, M. Heller, R. Lenhard, R. Littell, K. J. Sax and J. H. Williams, Abstracts, 4th Meeting-in-miniature of New York Section of Am. Chem. Soc., New York City, p. 36 (1952).

(6) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(7) *Cf.* H. J. Dauben, Jr., and B. Loken, Fourth Northwest Regional Meeting of Am. Chem. Soc., (C. and E. N. Reports, *Chem. Eng. News*, **29**, 2747 (1951)).

(8) E. J. Salmi and V. Ranniikko, *Ber.*, **72B**, 600 (1939).

(8a) NOTE ADDED IN PROOF.—Ethylenedioxy derivatives of similar ketopregnanes prepared by Salmi's method have recently been reported. *Cf.* E. Oliveto, T. Clayton and E. B. Hershberg, THIS JOURNAL, **75**, 486 (1953), also R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 73 (1953).

(9) All melting points were taken on the Kofler microhot stage.

The amorphous bromoketone was converted to the unsaturated semicarbazone and thence to the desired Δ^4-pregnene-20β-ol-3,11-dione benzoate essentially according to the procedure of Gallagher.[3] The crude unsaturated semicarbazone (6.15 g.) without further purification was dissolved in 100 ml. of 80% aqueous acetic acid and treated with 1.81 g. of recently distilled pyruvic acid. The reaction mixture was stirred overnight, poured into 400 ml. of water and extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate and filtered through 30 g. of acid-washed alumina. Evaporation of the chloroform eluate and recrystallization of the residue from methanol afforded 1.825 g. (50% from pregnane-20β-ol-3,11-dione benzoate[10]) of crude Δ^4-pregnene-20β-ol-3,11-dione benzoate, m.p. 213–220°. An analytical sample carefully chromatographed over acid-washed alumina and recrystallized from methanol melted at 233–234.5°, $(\alpha)^{25}D$ +131° (*c* 1.0 in chloroform); ultraviolet spectrum: λ_{max} 2320 Å., E_{mol} 25,000; infrared spectrum: maxima at 5.81, 5.89, 5.98 and 6.19 μ.

Anal. Calcd. for $C_{28}H_{34}O_4$: C, 77.39; H, 7.88. Found: C, 77.54; H, 7.99.

Δ^4-Pregnene-20β-ol-3,11-dione (IV). A. From 20-Benzoate.—To a solution of 210 mg. of Δ^4-pregnene-20β-ol-3,11-dione benzoate (III) in 20 ml. of warm methanol was added 1.12 g. of solid potassium hydroxide. The reaction mixture was refluxed for one hour, and then poured into 200 ml. of water. The aqueous suspension was extracted with ether, and the ether extract washed, dried and evaporated to dryness *in vacuo*. The crystalline residue (150 mg.) was recrystallized from benzene–petroleum ether to afford pure Δ^4-pregnene-20β-ol-3,11-dione, m.p. 200–202° (ultraviolet spectrum: λ_{max} 2380 Å., E_{mol} 16,570), identical with that obtained by method B.

B. From Pregnane-20β-ol-3,11-dione.—One gram of pregnane-20β-ol-3,11-dione (II) was dissolved in 10 ml. of glacial acetic acid containing 0.2 ml. of water. Bromine (0.54 g.) and one drop of 40% hydrobromic acid were added. Decolorization was complete in four minutes. The reaction mixture was poured into 100 ml. of water and extracted twice with chloroform. The combined extracts were washed with aqueous sodium bicarbonate, filtered over sodium sulfate and concentrated *in vacuo* to an oil, which crystallized on trituration with ether, to give 0.94 g. of the desired α-bromoketone, m.p. 167–169° (dec.). A portion was recrystallized twice from chloroform–ether for analysis, m.p. 176–177° (dec.).

Anal. Calcd. for $C_{21}H_{31}O_2Br$: Br, 19.9. Found: Br, 20.6.

The dehydrobromination was effected according to the procedure given for the 20-benzoate (*vide supra*). The crude oily product thus obtained was crystallized by trituration with ether, giving material melting at 180–190°, in 56–58% yield. This was further purified by chromatography over acid-washed alumina. From 0.90 g. of crude crystalline Δ^4-ketone there was obtained 0.46 g. of pure IV, m.p. 197–201° and 0.24 g., m.p. 192–198°. The analytical sample, after two recrystallizations from ethyl acetate, melted at 200–202°, $[\alpha]^{24}D$ +189° (chloroform).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 8.86.

Δ^5-3-Ethylenedioxypregnene-20β-ol-11-one (V).—To a solution of 1.28 g. of Δ^4-pregnene-20β-ol-3,11-dione (IV) in 50 ml. of ethylene dichloride was added 11 ml. of ethylene glycol and 25 mg. of *p*-toluenesulfonic acid monohydrate. The reaction mixture was heated and the ethylene dichloride–water azeotrope distilled. Fresh ethylene dichloride was added as the azeotrope distilled until 200 ml. of distillate had been collected. The reaction mixture was cooled, extracted with 1% potassium carbonate and finally with water. The organic layer was dried and evaporated *in vacuo*. Chromatographic separation afforded 685 mg. of Δ^5-3-ethylenedioxypregnene-20β-ol-11-one and 440 mg. of starting material. After recrystallization from ether, the analytical sample melted at 184–186°, $[\alpha]^{25}D$ −21° (*c* 1.0 in chloroform); infrared spectrum: maxima at 2.80, 5.88 μ.

(10) It should be noted that this yield probably does not represent the optimum for this conversion.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.60; H, 8.86.

Δ^5-3-Ethylenedioxypregnene-11,20-dione (VI). A. From V.—To 5 ml. of cold pyridine was added portionwise 500 mg. of chromium trioxide. A solution of 500 mg. of Δ^5-3-ethylenedioxypregnene-20β-ol-11-one (V) in 5 ml. of pyridine was then added to the cooled suspension. The reaction mixture was stirred at room temperature overnight, then diluted with water and extracted with ether. The ethereal extract was washed thoroughly with water, dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo*. The crystalline residue (500 mg.) was recrystallized from methanol and from ether–petroleum ether to yield 370 mg. of the 3-ethylenedioxy derivative of 11-ketoprogesterone. An analytical sample recrystallized from ethyl acetate and from methanol melted at 170–173°, $[\alpha]^{25}D$ +52.5° (*c* 1.0 in chloroform); ultraviolet spectrum: no absorption; infrared spectrum: maxima at 5.85, 9.08 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.87; H, 8.58.

B. From 11-Ketoprogesterone.—A solution of 470 mg. of 11-ketoprogesterone (prepared by bromination and dehydrobromination of pregnane-3,11,20-trione according to the method of Gallagher),[3] in 3.5 ml. of dry tetrahydrofuran was treated with 1.2 ml. of the ethylenedioxy derivative of mesityl oxide (*vide infra*) and 0.31 ml. of a solution of 1.8 ml. of concentrated sulfuric acid in 36 ml. of tetrahydrofuran. The reaction was stirred at room temperature for 45 minutes, then the catalyst was neutralized with sodium methoxide in methanol. After dilution with ether, the organic solution was washed, dried, and evaporated *in vacuo*. The residual mixture (680 mg.) was dissolved in benzene–petroleum ether and carefully chromatographed over alkaline alumina. Both the 3,20-bis-dioxolane and the desired 3-monodioxolane were isolated, in addition to unreacted 11-ketoprogesterone; Δ^5-3,20-bis-ethylenedioxypregnene-11-one, m.p. 175–178° (recrystallized from ether-petroleum ether or from ethanol).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.21; H, 8.79.

Δ^5-3-Ethylenedioxypregnene-11,20-dione, m.p. 170–173°. No depression was observed upon admixture with a sample prepared by method A above. A mixture with the bis derivative melted at 145°.

Ethylenedioxy Derivative of Mesityl Oxide (2-Methyl-2-methallyl-1,3-dioxolane).—The dioxolane derivative of mesityl oxide was prepared essentially according to the method of Salmi and Rannikko,[8] and the crude dioxolane was fractionated at 16–17 mm. One fraction boiling at 48–49° at this pressure ($n^{25}D$ 1.4393) contained approximately 14% of mesityl oxide by ultraviolet absorption analysis. The desired dioxolane was obtained boiling at 49–53° (17 mm.), ($n^{25}D$ 1.4374) in approximately 50% yield. A final, careful fractionation yielded 35% of the pure ethylenedioxy derivative of mesityl oxide,[11] b.p. 58° (25 mm.), ($n^{24.5}D$ 1.4370).

The infrared spectrum of this material showed maxima at 11.17 and 6.08 μ with a weak band at 12.15 μ. The characteristic absorption of R_1R_2—C=CH_2 has been identified[12] at 11.23 and 6.09 μ (weak). The presence of such maxima requires the methallyl structure. The expected impurity (the isomeric 2-methyl-2-(2-methylpropenyl)-1,3-dioxolane) is also present as evidenced by the weak absorption band at 12.15 μ which is characteristic of the RR'C=CHR″ structure.[12]

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.78; H, 9.74.

3-Dioxolane of Dehydrocorticosterone Acetate (VII).—To a solution of 1.6 g. of dehydrocorticosterone acetate in 12 ml. of dry tetrahydrofuran and 3.2 ml. of the dioxolane of mesityl oxide was added 0.1 ml. of concentrated sulfuric acid. After 3.5 hours at room temperature the reaction mixture was neutralized with pyridine and treated with petroleum ether to complete the precipitation of the dioxolane deriva-

(11) The literature reports b.p. 155–156° (760 mm.), $n^{20}D$ 1.43963.

(12) (a) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1413 (1948); (b) R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 120 (1947); (c) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *Proc. Royal Soc. (London)*, **A196**, 195 (1949).

tive. The crude product was washed with petroleum ether and with water, and recrystallized from ethanol to yield 910 mg. of pure Δ^5-3-ethylenedioxypregnene-21-ol-11,20-dione acetate (VII), m.p. 193.5–194°, $[\alpha]^{25}D$ +52° (*c* 1.33 in chloroform); infrared spectrum: maxima at 5.71, 5.77 and 5.86 μ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.97. Found: C, 70.02; H, 7.65.

3-Dioxolane of Cortisone Acetate (VIII).—A mixture of 1.0 g. of cortisone acetate and 2.0 ml. of the dioxolane of mesityl oxide in 7.5 ml. of dry tetrahydrofuran was treated with 0.06 ml. of concentrated sulfuric acid and stirred at room temperature for two hours, then allowed to stand at 0° overnight. The acid catalyst was neutralized with pyridine, and sufficient petroleum ether added to complete precipitation of the ethylenedioxy derivative. The solution was filtered and washed with methanol and with water. The crude crystalline compound was recrystallized from pyridine, and traces of cortisone acetate removed by refluxing with methanol. Approximately 844 mg. of VIII which decomposed at 265–272° was obtained. Ultraviolet absorption analysis showed only a shoulder in the 2400 Å. region. A sample recrystallized for analysis from chloroform–petroleum ether decomposed variously over a five-degree range between 264° and 274°; $[\alpha]^{25}D$ +51.5° (*c* 0.815 in pyridine).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.25; H, 7.68. Found: C, 67.50; H, 7.49.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Mechanism of the Reduction of Steroidal Enol Acetates by Lithium Aluminum Hydride[1]

BY WILLIAM G. DAUBEN AND JEROME F. EASTHAM

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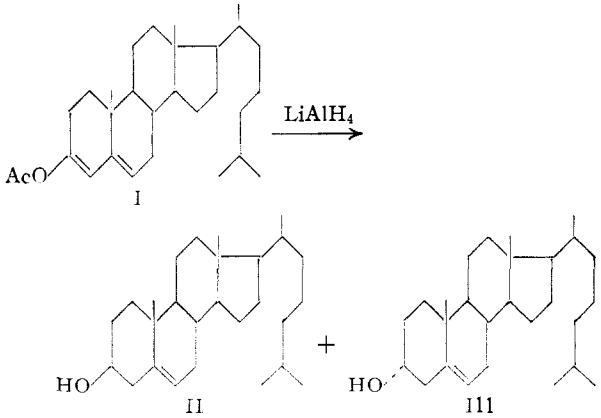
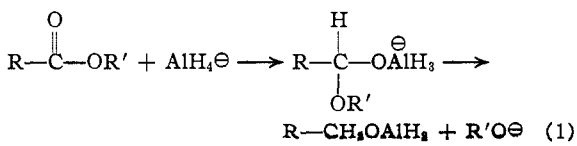
When steroidal enol acetates are reduced with lithium aluminum hydride, the products are epimeric saturated alcohols and starting ketone. It has been shown that the ketone cannot be the immediate precursor of the alcohols. The recovered ketone is a direct product of the reaction and is not formed by hydrolysis of unreacted enol acetate. The mechanism of the reduction is viewed as beginning with a nucleophilic attack of the aluminum hydride upon the carbonyl carbon atom. If the second attack by hydride is on the same carbon atom, as in a normal ester reduction, the products are ethoxide ion and the enolate ion of the ketone. This latter ion resists reduction under the conditions of the reaction and upon hydrolysis yields the starting ketone. Alternately, if the second attack by hydride is on the carbinol carbon atom of the double bond with concomitant formation of an organometallic bond, the complex, upon hydrolysis, yields saturated alcohols. Substantiation of these latter phases was obtained employing the deuterium tracer technique. Such a mechanism can account for the radically different product composition obtained upon reduction of the enol acetate as compared to the free ketone.

It has previously been reported[2] that when the enol acetate of cholestenone (I, 3-acetoxy-$\Delta^{3,5}$-cholestadiene) is reduced by lithium aluminum hydride, cholesterol (II) and epicholesterol (III) are the main products. This unique reaction has



been further investigated[3] to establish the fact that the second carbon–carbon double bond is not essential by a study of the reduction of the enol acetates of cholestanone and coprostanone. Again apparent carbon–carbon double bond reduction occurred. It was of interest, however, that the ratio of isomeric alcohols formed varied quite widely from that obtained by the direct reduction of the parent ketone and that in both cases an appreciable quantity of the ketone was recovered from the reduction of the ester. In order to gain further insight into the mechanism of this reaction, it has been investigated in more detail.

The first point to be considered is the isolation of the parent ketone from the reduction. It has been found that the same result was obtained when either a fivefold or a thirtyfold excess of lithium aluminum hydride was utilized or when the reaction time was varied from 1 to 24 hours.[2] Such results make it seem unlikely that the carbonyl compound could arise from unreacted enol acetate which would hydrolyze to the parent ketone upon decomposition of the reaction mixture with sodium hydrogen tartrate. A more plausible explanation would appear to be that this material arises from a moiety which is produced in the reaction but which is resistant to reduction and which upon acidification yields the ketone. Such a moiety could be the enolate ion of the ketone and such a species could arise in the reaction. In the reduction of esters with lithium aluminum hydride, the electrophilic carbonyl carbon atom is viewed as being the center for the first bimolecular attack by the anion, $AlH_4^{\ominus}$, with subsequent transfer of a hydride ion. A second hydride attack displaces the original



(1) This work was supported, in part, by a grant from the University of California Cancer Fund.

(2) W. G. Dauben and J. F. Eastham, THIS JOURNAL, **73**, 3260 (1951).

(3) W. G. Dauben, R. A. Micheli and J. F. Eastham, *ibid.*, **74**, 3862 (1952).