reported by Wright,[7] its toxicity was antagonized by MVA only partially. Furthermore, it did not inhibit ergosterol synthesis in yeast, or cholesterol synthesis in growing mice, even at toxic concentrations.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. X.[1a] The Synthesis of 21-Deoxytriamcinolone

BY SEYMOUR BERNSTEIN,[1b] J. J. BROWN,[1b] L. I. FELDMAN[1c] AND N. E. RIGLER[1c]

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9α-Fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIId) was obtained by multi-stage syntheses starting from 4,9(11),16-pregnatriene-3,20-dione (VIa) and also from 16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (X). Microbiological dehydrogenation of compound XIId gave 21-deoxytriamcinolone (Ib). Reaction of ethyl oxalate with 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIb) gave a product which was converted into 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (XXI) and 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4,6-pregnadiene-3,20-dione (XXII).

It has been shown[2a] that triamcinolone, 9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione (Ia),[3] has high glucocorticoid activity and exhibits no sodium-retaining properties. Because of this, it was decided to prepare 21-deoxytriamcinolone, 9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (Ib), in order to investigate its possible biological activity.

The most obvious route paralleled that used in the preparation[2a,b,4] of compound Ia and involved the preparation of 4,9(11),16-pregnatriene-3,20-dione (VIa), a compound reported previously by Szpilfogel and Gerris.[5] The desired intermediate VIa was synthesized by four methods. In the first, cortisone 21-mesylate (IIa) was converted into 21-deoxycortisone (IIb)[6] by treatment with sodium iodide in acetic acid, and the bis-ethylene ketal III then was reduced with sodium borohydride in ethanolic sodium hydroxide[7] to give 3,20-bis-ethylenedioxy-5-pregnene-11β,17α-diol (IV). Reaction of the bis-ethylene ketal IV with thionyl chloride–pyridine,[4] followed by acid hydrolysis without characterization of the intermediate V, gave the triene VIa.

In the second, pregnane-3,11,20-trione was converted into 4,16-pregnadiene-3,11,20-trione (VII) by the method of Magerlein, Lyttle and Levin.[8] The triene VIa was obtained readily from the compound VII by a process similar to that outlined above. Thus, reduction of 3,20-bis-ethylenedioxy-5,16-pregnadien-11-one (VIII) gave 3,20-bis-ethylenedioxy-5,16-pregnadien-11β-ol (IX) which, on treatment with thionyl chloride followed by acid hydrolysis, gave the compound VIa. The intermediate 3,20-bis-ethylenedioxy-5,9(11),-16-pregnatriene (V) was not characterized.

In the third, the 21-mesyl derivative VIb of 21-hydroxy-4,9(11),16-pregnatriene-3,20-dione[4] was transformed into the triene VIa using sodium iodide in acetic acid.

In the last method, 16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (X), prepared[9,10] from 16α,-17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione[11] by formation of the 11α-mesyl derivative and then elimination of the elements of methanesulfonic acid using sodium acetate in acetic acid, was treated with chromous chloride[12] to give the triene VIa.

Oxidation of the triene VIa with osmium tetroxide in benzene and pyridine gave 16α,17α-dihydroxy-4,9(11)-pregnadiene-3,20-dione (XIa) in excellent yield. The acetate XIb formed 16α-acetoxy-9α-bromo-11β,17α-dihydroxy-4-pregnene-3,20-dione (XIIa) on treatment[13] with N-bromosuccinimide in aqueous dioxane containing perchloric acid. 16α-Acetoxy-9α-chloro-11β,17α-dihydroxy-4-pregnene-3,20-dione (XIIb) was obtained using 1,3-dichloro-5,5-dimethylhydantoin[14] under the same conditions. Attempts to convert the bromohydrin XIIa into 16α-acetoxy-9β,11β-epoxy-17α-hydroxy-4-pregnene-3,20-dione (XIII) using anhydrous potassium acetate in ethanol under reflux[2a,13] failed, probably due to the sensitivity of the D-ring side-chain toward base.[15–18]

(1) (a) Paper IX, S. Bernstein and R. Littell, *J. Org. Chem.*, **24**, in press (1959); (b) Organic Chemical Research Section; (c) Biochemical Research Section.

(2) (a) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, THIS JOURNAL, **78**, 5693 (1956); *idem*, *ibid.*, **81**, 1689 (1959); S. Bernstein, *Rec. Prog. Hormone Res.*, **14**, 1 (1958); (b) R. W. Thoma, J. Fried, S. Bonnano and P. Grabowich, THIS JOURNAL, **79**, 4818 (1957), synthesized triamcinolone by a microbiological procedure starting from 9α-fluorohydrocortisone and 9α-fluoroprednisolone.

(3) The American Cyanamid Co.'s trade name for this compound is Aristocort.

(4) W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

(5) S. A. Szpilfogel and V. Gerris, *Rec. trav. chim.*, **74**, 1462 (1955).

(6) After completion of this work, A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 3091 (1958), described a preparation of 21-deoxycortisone from cortisone.

(7) The conditions (sodium borohydride in tetrahydrofuran containing aqueous sodium hydroxide) used by W. S. Allen, S. Bernstein and R. Littell, *ibid.*, **76**, 6116 (1954), to reduce the bis-ethylene ketal of cortisone to that of hydrocortisone failed with compound III.

(8) B. J. Magerlein, D. A. Lyttle and R. H. Levin, *J. Org. Chem.*, **20**, 1709 (1955).

(9) C. G. Bergstrom U. S. Patent 2,703,799, March 8, 1955.

(10) G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959).

(11) D. H. Peterson, P. D. Meister, A. Weintraub, L. M. Reineke, S. H. Eppstein, H. C. Murray and H. M. Leigh Osborn, *ibid.*, **77**, 4428 (1955).

(12) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

(13) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957).

(14) J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *ibid.*, **77**, 1068 (1955).

(15) H. Inhoffen, F. Blomeyer and K. Bruchner, *Chem. Ber.*, **87**, 593 (1954).

(16) K. Heusler and A. Wettstein, *ibid.*, **87**, 1301 (1954).

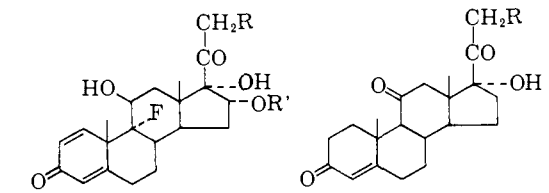
(17) G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.*, 4377 (1955).

(18) J. Romo and A. De Vivar, *J. Org. Chem.*, **21**, 902 (1956).

Under the same conditions, the acetate XIb gave a substance A, $C_{21}H_{28}O_4$, isomeric with the diol XIa. Substance A also was obtained by passing a solution of the diol XIa in chloroform through a column of alkaline alumina[17] and it was characterized as its acetate and isopropylidene derivatives. Recent work[19] on D-homoannulation of 16α,17α-dihydroxy-20-keto steroids suggests that substance A is 16α,17α-dihydroxy-17β-methyl-4,9(11)-D-homoandrostadiene-3,17a-dione (XIV).

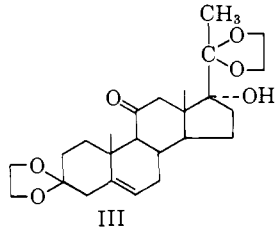
Our attention was now turned toward the use of an isopropylidene group to prevent D-homoannulation during the formation of the 9β,11β-epoxide. This required a later removal of this protective group. Surprisingly, in a model experiment, 16α,17α-isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione (XV) was very resistant toward mild acid hydrolysis,[20,21] the diol XIa being obtained in low yield only under fairly strong conditions. However, 9α-bromo-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIa) was prepared by the addition[13] of hypobromous acid to the compound XV and by a similar addition to the diol XIa followed by formation of the isopropylidene derivative of the intermediate 9α-bromo-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIIc). The bromohydrin XVIa readily yielded 9β,11β-epoxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVII) which was converted, in good yield, into 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIb) using anhydrous hydrofluoric acid in tetrahydrofuran–methylene chloride solution.[22] Acid hydrolysis of the compound XVIb furnished 9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIId) in low yield.

Since the yield of compound XIId by the above method was inadequate, another route for its preparation was sought. A convenient starting material appeared to be 16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (X), prepared as above. The compound X gave 9α-bromo-16α,17α-epoxy-11β-hydroxy-4-pregnene-3,20-dione (XVIIIa) and thence 9β,11β;16α,17α-bis-epoxy-4-pregnene-3,20-dione (XIX)[9] which was then converted into 16α,17α-epoxy-9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione (XVIIIb), the 16α,17α-epoxide being stable[21] to anhydrous hydrofluoric acid under the conditions used.[22] Treatment of the epoxide XVIIIb with chromous chloride[12] produced 9α-fluoro-11β-hydroxy-4,16-pregnadiene-3,20-dione (XX),[23] osmium tetroxide oxidation of which gave the compound XIId in excellent yield. The acetate XIIe was prepared. Microbiological dehydrogenation of XIId with *Nocardia corallina* gave the desired final product, 9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (Ib). The compound Ib was characterized as its acetate Ic and its isopropylidene derivative XXI.[10]

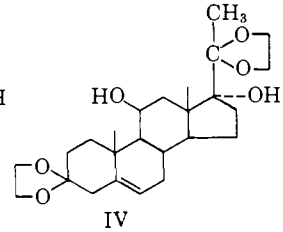


Ia, R = OH, R′ = H
Ib, R = H, R′ = H
Ic, R = H, R′ = Ac

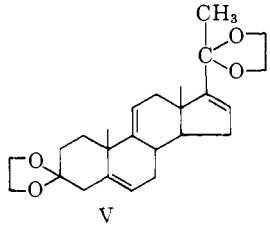
IIa, R = OSO_2CH_3
IIb, R = H



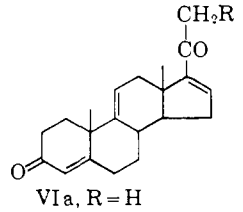
III



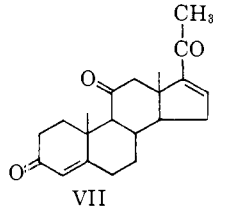
IV



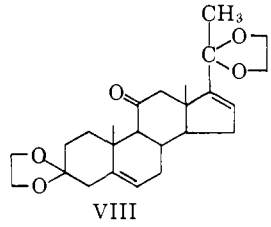
V



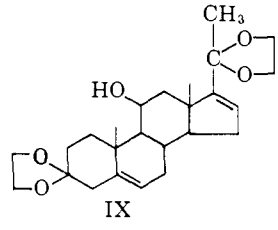
VIa, R = H
VIb, R = OSO_2CH_3



VII



VIII



IX

Finally, it has been shown[10] that treatment of 16α,17α-isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione (XV) with ethyl oxalate and sodium methoxide, with subsequent bromination, de-ethoxalylation and dehydrobromination, gives 16α,17α-isopropylidenedioxy-1,4,9(11)-pregnatriene-3,20-dione. Application of the same reaction sequence to the 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIb) gave two isomeric products $C_{24}H_{31}FO_5$, which were isolated by chromatography. One of these products was shown to be 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (XXI) and the other, which had an ultraviolet absorption maximum characteristic[24] of a $\Delta^{4,6}$-3-one,

(19) N. L. Wendler and D. Taub, *Chemistry & Industry*, 1237 (1957).

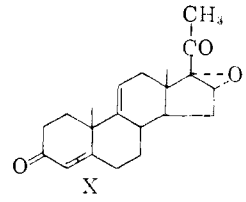
(20) G. Cooley, B. Ellis and V. Petrow, *J. Chem. Soc.*, 4373 (1955), and J. Fried, A. Borman, W. B. Kessler, P. Grabowich and E. F. Sabo, THIS JOURNAL, **80**, 2338 (1958), have reported the stability of certain 16α,17α-isopropylidenedioxy compounds to acid.

(21) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956), have reported the stability of 16α,17α-epoxides to hydrofluoric acid under the conditions used to open 9β,11β-epoxides.

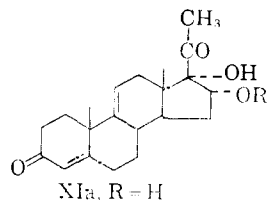
(22) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, THIS JOURNAL, **78**, 4956 (1956).

(23) The fluorohydrin is stable to these conditions in contrast to 9α-bromohydrocortisone acetate which gives 21-acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (ref. 13).

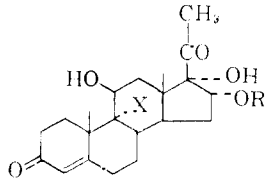
(24) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

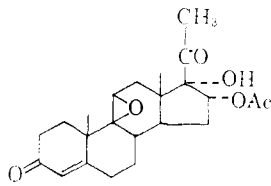


X



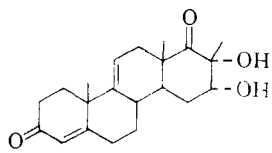
XIa, R = H
XIb, R = Ac



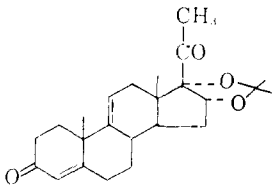


XIIa, R = Ac, X = Br
XIIb, R = Ac, X = Cl
XIIc, R = H, X = Br
XIId, R = H, X = F
XIIe, R = Ac, X = F

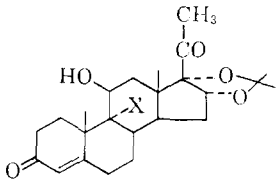
XIII



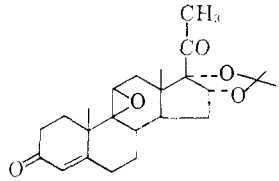
XIV



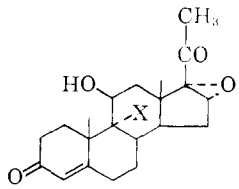
XV



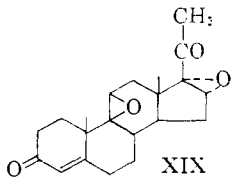
XVIa, X = Br
XVIb, X = F



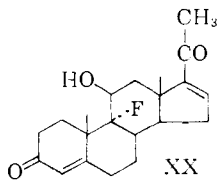
XVII



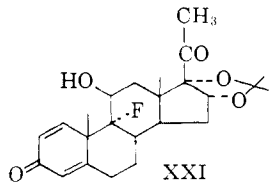
XVIIIa, X = Br
XVIIIb, X = F



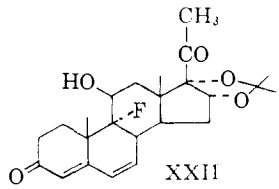
XIX



XX



XXI



XXII

to be 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4,6-pregnadiene-3,20-dione (XXII). It is likely that compound XXII was formed by a rearrangement[25,26] of the 2-bromo compound during the collidine treatment. However, it is possible that some 6-ethoxalyl compound was formed during the initial reaction giving rise to compound XXII. This was not investigated further.

Since the isopropylidene derivative XXI has been converted[10] into Ib by acid hydrolysis, the preparation of the former compound by the ethyl oxalate method constitutes a formal synthesis of 9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (Ib).

Bioassays.[27]—In the rat liver glycogen assay, 21-deoxytriamcinolone (Ib) possessed an activity of about four times that of hydrocortisone and exhibited no sodium retention properties.

Acknowledgment.—We wish to thank Mr. F. J. McEvoy, Mr. R. E. Schaub and Dr. M. J. Weiss for carrying out the experiments indicated. Mr. F. J. McEvoy supplied also the experimental details of the osmium tetroxide oxidations. Thanks are due also to Dr. P. Shu and Mr. C. Pidacks for the supply of 16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione and to Dr. J. H. Clark and his associates for the large-scale preparation of certain intermediates.

Experimental[28]

Optical Rotations.—The rotations are for chloroform solutions unless noted otherwise.

Absorption Spectra.—The ultraviolet absorption spectra were determined in methanol unless noted otherwise. The infrared absorption spectra were determined in potassium bromide.

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

17α-Hydroxy-4-pregnene-3,11,20-trione (IIb).—A solution of methane-sulfonyl chloride (764 mg.) in pyridine (2 ml.) was added portionwise, with swirling, to a solution of cortisone (2 g.) in pyridine (6 ml.). The reaction mixture was kept at room temperature for 24 hours during which time a mass of crystals separated. The mixture was diluted with water (25 ml.) and the crude mesylate (IIa, 1.5 g.) was filtered off, dried in air, and then heated under reflux for 30 minutes in acetic acid (5 ml.) containing sodium iodide (1 g.). The cooled reaction mixture was diluted with water (50 ml.) and extracted with chloroform (3 × 30 ml.). The combined chloroform extracts were washed with aqueous sodium thiosulfate solution until free of iodine, water (60 ml.), and dried. Evaporation of solvent gave 17α-hydroxy-4-pregnene-3,11,20-trione as a brown solid which crystallized from ethyl acetate–petroleum ether (charcoal) as small prisms (700 mg.), m.p. 233–235°. A sample, recrystallized from chloroform–ethyl acetate, had m.p. 237.5–239.5°, $[\alpha]^{25}D$ + 189° (c, 0.965), λ_{max} 239 mμ (ϵ 15,300); ν_{max} 3500, 1700, 1660 and 1620 cm.$^{-1}$ [lit.[29] m.p. 238.5–239.5°, $[\alpha]^{25}D$ +181° (c 0.6923), λ_{max} 239 mμ (ϵ 15,500)].

(25) R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, THIS JOURNAL, **77**, 3166 (1955).

(26) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955).

(27) The assays were carried out by L. Bortle, E. Heyder, A. Monteforte, J. Perrine, E. Ross and Dr. I. Ringler of the Experimental Therapeutics Research Section of these laboratories. Adrenolectomized immature male rats were given a daily subcutaneous injection of steroid for 5 days, the rats being fasted for 15 hours prior to the last injection. The rats were anesthetized with sodium pentobarbital and their livers excised and saponified with aqueous potassium hydroxide solution (30%). Liver glycogen was measured by the anthrone method of S. Seifter, S. Dayton, B. Noric and J. Muntwyler, *Arch. Biochem.*, **25**, 191 (1950).

(28) Analyses were done by Mr. Louis M. Brancone and associates. Infrared and ultraviolet absorption spectra and optical rotations were done by Mr. William Fulmor and associates.

(29) P. D. Meister, D. H. Peterson, H. C. Murray, G. B. Spero, S. H. Eppstein, A. Weintraub, L. M. Reineke and H. Marian Leigh, THIS JOURNAL, **75**, 416 (1953).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.50; H, 8.28.

3,20-Bis-ethylenedioxy-17α-hydroxy-5-pregnen-11-one (III).—17α-Hydroxy-4-pregnene-3,11,20-trione (IIb, 5 g.), ethylene glycol (3 g.), *p*-toluenesulfonic acid monohydrate (100 mg.) and benzene (50 ml.) were heated under reflux for 3.5 hours, water formed during the reaction being removed by a Dean and Stark moisture trap. The red solution was cooled, chloroform (50 ml.) added, and the solution was washed with aqueous sodium hydrogen carbonate solution (50 ml., 10%), water (50 ml.), and dried. The brown solid obtained by removal of solvent was washed with a little ether and then crystallized from chloroform–methanol to give 3,20-bis-ethylenedioxy-17α-hydroxy-5-pregnen-11-one as needles (3 g.), m.p. 238–241°. The mother liquor afforded a further quantity (1 g.), m.p. 236–238°. The analysis sample had m.p. 238–241°, $[\alpha]^{25}D$ −15.8° (*c* 1.012); ν_{max} 3525, 1700, 1100 and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.32; H, 8.72.

In larger runs, an improved yield was obtained by heating the reactants under reflux for 16 hours.

3,20-Bis-ethylenedioxy-5-pregnene-11β,17α-diol (IV).—3,20-Bis-ethylenedioxy-17α-hydroxy-5-pregnen-11-one (III, 10 g.), sodium borohydride (2.5 g.) and ethanol (500 ml.) were heated under reflux for 17 hours. The cooled reaction mixture was evaporated to dryness, water (300 ml.) added, and the mixture was extracted with chloroform (3 × 150 ml.). The combined chloroform extracts were washed with water (2 × 200 ml.) and dried. Removal of solvent followed by crystallization of the residue from chloroform–methanol, gave 3,20-bis-ethylenedioxy-5-pregnene-11β,17α-diol as needles (7 g.), m.p. 232–237°. A further quantity (2 g.), m.p. 231–236°, was obtained from the mother liquor. The analysis sample had m.p. 234–238°, $[\alpha]^{25}D$ −42.1° (*c* 2.017); ν_{max} 3600, 1100 and 1038 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55); C, 69.09; H, 8.81. Found: C, 68.95; H, 8.53.

3,20-Bis-ethylenedioxy-5,16-pregnadien-11-one (VIII).—4,16-Pregnadiene-3,11,20-trione (VII, 500 mg.),[8] ethylene glycol (500 mg.), *p*-toluenesulfonic acid monohydrate (10 mg.) and benzene (20 ml.) were heated under reflux for 18 hours, water formed during the reaction being removed by a Dean and Stark apparatus. The cooled solution was diluted with an equal volume of chloroform and was washed with sodium hydrogen carbonate solution (20 ml., 10%), water (20 ml.), and dried. Evaporation of solvent followed by crystallization of the residue from methanol gave the product as plates (250 mg.), m.p. 166–171°. Four crystallizations gave m.p. 186–188°, $[\alpha]^{25}D$ −14° (*c* 1.005); ν_{max} 1704, 1672, 1623, 1095, 1042 and 1031 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_5$ (414.52): C, 72.43; H, 8.27. Found: C, 72.69; H, 8.48.

3,20-Bis-ethylenedioxy-5,16-pregnadien-11β-ol (IX).—3,20-Bis-ethylenedioxy-5,16-pregnadien-11-one (VIII, 100 mg.), sodium borohydride (200 mg.), sodium hydroxide (25 mg.) and ethanol (5 ml.) were heated under reflux on the steam-bath for 17 hours. The cooled reaction mixture was diluted with water (25 ml.) and the solid which separated was extracted in ether (3 × 20 ml.). The combined ethereal extracts were washed with water (25 ml.), dried, so that removal of solvent and then crystallization of the residue from methanol yielded 3,20-bis-ethylenedioxy-5,16-pregnadien-11β-ol as needles (70 mg.), m.p. 178–180°. The analysis sample had m.p. 181–182°, $[\alpha]^{25}D$ −31.7° (*c* 1.042); ν_{max} 3550, 1625, 1100, 1045, and 1035 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_5$ (416.54): C, 72.08; H, 8.71. Found: C, 71.86; H, 8.93.

4,9(11),16-Pregnatriene-3,20-dione (VIa). A.—Thionyl chloride (4.7 ml.) was added dropwise, with swirling, to a solution of 3,20-bis-ethylenedioxy-5-pregnene-11β,17α-diol (IV, 8.2 g.) in pyridine (50 ml.) at −5 to −10°. The mixture was kept at −5° for 16 hours and then was poured, with stirring, into iced aqueous sodium hydrogen carbonate solution (400 ml., 10%). The solid was collected, washed with water, and crystallized from aqueous acetone (charcoal) from which 3,20-bis-ethylenedioxy-5,9(11),16-pregnatriene (V) was obtained as needles (4.4 g.), m.p. 140–142°. (Infrared and ultraviolet spectra indicated part-hydrolysis of the ketal groups.)

A solution of the triene (V, 4 g.) in hot acetic acid (25 ml.) was diluted with hot water (15 ml.) and the solution was heated on the steam-bath for 1 hour. The solid obtained by addition of water (150 ml.) and then filtration was washed with water and crystallized from aqueous acetone to give 4,9(11),16-pregnatriene-3,20-dione as plates (2.5 g.), m.p. 204–207°. The pure compound had m.p. 208–210°, $[\alpha]^{25}D$ +237° (*c* 1.002), λ_{max} 238 mμ (ε 26,100); ν_{max} 1678, 1661, 1612 and 1592 cm.$^{-1}$ [lit.[5] m.p. 199–201°, $[\alpha]D$ +196° (acetone), λ_{max} 239 mμ (ε 22,200)].

Anal. Calcd. for $C_{21}H_{26}O_2$ (310.42): C, 81.25; H, 8.44. Found: C, 81.09; H, 8.60.

B.—3,20-Bis-ethylenedioxy-5,16-pregnadien-11β-ol (IX, 150 mg.) was treated with thionyl chloride and then acetic acid as above. The product (VIa, 25 mg.) had m.p. 203–206° undepressed on mixing with VIa above and was shown to be identical by the infrared spectrum.

C.[30]—Methanesulfonyl chloride (0.12 ml.) was added to an ice-cold solution of 21-hydroxy-4,9(11),16-pregnatriene-3,20-dione (450 mg.) in pyridine (4.5 ml.) and the mixture was kept at −5° for 20 hours. The reaction mixture was diluted with iced water (25 ml.), extracted with ether (3 × 25 ml.), and the combined ethereal extracts were dried. Evaporation of solvent (bath temperature, 45–50°) gave the mesylate VIb as a gum (320 mg.) from which traces of pyridine were removed by addition of toluene and then evaporation (bath temperature, 45–50°).

A solution of sodium iodide (9 g., oven-dried) in acetic acid (100 ml.) was added to a solution of the above crude mesylate (3.84 g.) in acetic acid (40 ml.) and the mixture was heated under reflux for 20 minutes. The cooled solution was poured into a solution of sodium thiosulfate (40 g.) in water (540 ml.), and the solid which separated was collected, washed with water, and dried. This material (2.63 g., m.p. 185–189°), in benzene, was chromatographed on silica gel, and elution with an ether–benzene mixture (3:1) yielded a white solid (1.71 g.) which crystallized from acetone–petroleum ether as plates (1.54 g.), m.p. 204–208°. Recrystallization gave m.p. 208–210°, $[\alpha]^{25}D$ +234° (*c* 0.586), λ_{max} 239 mμ (ε 25,800).

D.[31]—Chromous chloride in acetic acid (160 ml., 0.43*N*) was added to a solution of 16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (X, 9 g.)[10] in acetic acid (160 ml.), the operation being conducted in an atmosphere of carbon dioxide. After 30 minutes at room temperature, the mixture was diluted with methylene chloride (200 ml.) and iced water (200 ml.) and the aqueous layer was extracted further with methylene chloride (3 × 160 ml.). The combined extracts were washed with water, dried and evaporated. Acetone (200 ml.) containing hydrochloric acid (0.5 ml., d. 1.19) was added to the residue and the mixture was heated on the steam-bath for 1 hour. Concentration of the solution to about 75 ml. caused crystals (5.8 g., m.p. 204–206°) to separate. Further concentration of the filtrate followed by the addition of petroleum ether gave more product (1.11 g.), m.p. 200–205°. Recrystallization from acetone–petroleum ether gave the product as plates, m.p. 207–209°, $[\alpha]^{25}D$ +214° (*c* 0.5%, methanol), λ_{max} 238 mμ (ε 20,000).

16α,17α-Dihydroxy-4,9(11)-pregnadiene-3,20-dione (XIa).—A solution of osmium tetroxide (10 g.) in benzene (200 ml.) was added dropwise (1 drop per second) with stirring to a solution of 4,9(11),16-pregnatriene-3,20-dione (VIa, 11.6 g.) in benzene (340 ml.) and pyridine (6 ml.). When addition was complete, stirring was continued for 1 hour. Methanol (380 ml.), followed by a solution of sodium sulfite (54 g.) and potassium hydrogen carbonate (54 g.) in water (560 ml.), then was added; the mixture was stirred for 3 hours and then for a further 0.5 hour after the addition of chloroform (500 ml.). The organic layer was separated from the filtered reaction mixture and combined with the chloroform extracts (3 × 250 ml.) of the aqueous layer, the chloroform having been used previously in washing the filter cake. The combined chloroform was washed with water (500 ml.), dried, and removal of solvent gave a greenish-yellow solid which was washed with a little methanol and dried. The solid (11 g.), m.p. 209–215°, was pure enough for the next stage. A specimen of the diol crystallized as prisms, m.p. 211–215°, from chloroform–methanol. The same specimen had m.p. 215–220° after drying at 140° *in*

(30) Experiment carried out by Mr. F. J. McEvoy.

(31) Experiment carried out by Mr. R. E. Schaub and Dr. M. J. Weiss.

vacuo overnight, $[\alpha]^{25}D$ + 76° (*c* 1.077), λ_{max} 240 mμ (ε 17,100); ν_{max} 3344, 1706, 1647 and 1608 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 72.93; H, 7.91.

16α-Acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XIb).—The diol (XIa, 1 g.), acetic anhydride (5 ml.) and pyridine (5 ml.) were allowed to stand for 16 hours at room temperature. The solution was diluted with water and the solid which separated was filtered off, washed with water, and dried. Crystallization from benzene–petroleum ether gave 16α-acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,-20-dione as long needles (900 mg.), m.p. 183–188°, $[\alpha]^{25}D$ +35.7° (*c* 1.066), λ_{max} 238 mμ (ε 17,200); ν_{max} 3448, 1742, 1709, 1661, 1616 and 1244 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.79; H, 8.21.

16α-Acetoxy-9α-bromo-11β,17α-dihydroxy-4-pregnene-3,20-dione (XIIa).—16α-Acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XIb, 500 mg.) was dissolved in peroxide-free dioxane (10 ml.), water (2 ml.) was added, and the solution was cooled to 15°. N-Bromosuccinimide (280 mg.) then was added, followed by perchloric acid (1 ml., 10%) to the resulting solution. The reaction mixture was kept at room temperature for 15 minutes, a few drops of aqueous sodium sulfite solution was added until the yellow color disappeared, then the mixture was poured into water (150 ml.), and the solid which separated was filtered off, washed with water, ethanol, ether, and dried. The bromohydrin (385 mg.) thus obtained had m.p. 180° dec. The pure product was obtained as needles, m.p. 185° dec., from aqueous methanol; $[\alpha]^{25}D$ +96.5° (*c* 0.997), λ_{max} 242 mμ (ε 16,100); ν_{max} 3436, 1742, 1715, 1672, and 1247 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}BrO_6$ (483.40): C, 57.14; H, 6.46; Br, 16.53. Found: C, 57.35; H, 6.44; Br, 16.35.

16α-Acetoxy-9α-chloro-11β,17α-dihydroxy-4-pregnene-3,20-dione (XIIb).—To a solution of 16α-acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XIb, 500 mg.) in peroxide-free dioxane (10 ml.) and water (2 ml.), was added 1,3-dichloro-5,5-dimethylhydantoin (280 mg.) followed by perchloric acid (1 ml., 10%). After being kept at room temperature for 15 minutes, the solution was treated with sodium sulfite as before and then was diluted with water (150 ml.). The solid which was filtered off was washed with water, air-dried, and crystallized from acetone–petroleum ether to give the chlorohyrin as prisms (200 mg.), m.p. 222–224° dec. The analysis sample had m.p. 234–235° dec., $[\alpha]^{25}D$ +75.3° (*c* 1.05, pyridine), λ_{max} 240 mμ (ε 18,000) ν_{max} 3448, 1742, 1689, 1664, 1629 and 1244 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}ClO_6$ (438.94): C, 62.93; H, 7.12; Cl, 8.08. Found: C, 62.98; H, 7.18; Cl, 8.59.

16α,17α-Dihydroxy-17β-methyl-4,9(11)-D-homoandrostadiene-3,17a-dione (XIV). A.—A solution of 16α,17α-dihydroxy-4,9(11)-pregnadiene-3,20-dione (XIa, 250 mg.) chloroform was passed through a column (1.5 × 10 cm.) of alkaline alumina. The column was eluted with more chloroform and evaporation of solvent followed by crystallization of the residue from aqueous methanol gave the D-homo compound as needles (200 mg.), m.p. 210–214°, depressed to 195–197° on mixing with starting material. Further crystallization gave m.p. 218–220°, $[\alpha]^{25}D$ +93° (*c* 1.026), λ_{max} 239 mμ (ε 17,700); ν_{max} 3571, 3484, 1706, 1672, 1623 and 1000 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.04; H, 8.37.

The acetate, 16α-acetoxy-17α-hydroxy-17β-methyl-4,9-(11)-D-homoandrostadiene-3,17a-dione, prepared by treating the compound XIV with acetic anhydride–pyridine overnight, crystallized from benzene–petroleum ether as prisms, m.p. 225–226°, $[\alpha]^{25}D$ +24.6° (*c* 1.018), λ_{max} 237 mμ (ε 18,300); ν_{max} 3497, 1751, 1706, 1664, 1621, 1245, and 994 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.61; H, 7.99.

The isopropylidene derivative, 16α,17α-isopropylidenedioxy-17β-methyl-4,9(11)-D-homoandrostadiene-3,20-dione, prepared by the method described for XV below, crystallized as needles, m. p. 242–245°, from aqueous methanol, $[\alpha]^{26}D$ +51.5° (*c* 2.012), λ_{max} 238 mμ (ε 17,100); ν_{max} 1718, 1675, 1618, 1110 and 992 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_4$ (384.50): C, 74.97; H, 8.39. Found: C, 74.90; H, 8.50.

B.—16α-Acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XIb, 500 mg.) and anhydrous potassium acetate (250 mg.) were heated under reflux in ethanol (25 cc.) for 11 hours. The reaction mixture was evaporated to dryness, and water (25 cc.) was added to the residue which then was extracted in chloroform (3 × 20 cc.). The combined chloroform extracts were dried and evaporation of solvent gave a solid which crystallized from aqueous methanol as needles (350 mg.), m.p. 202–204°, undepressed on mixing with the product from A but depressed with the diol XIa. Recrystallization raised the m.p. to 205–210°, $[\alpha]^{25}D$ +90.5° (*c* 0.994). Infrared analysis showed the compound to be identical to that obtained in A.

16α,17α-Isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione (XV).—To a solution of 16α,17α-dihydroxy-4,9(11)-pregnadiene-3,20-dione (XIa, 1 g.) in acetone (25 ml.) was added concentrated hydrochloric acid (3 drops, d. 1.19) and the solution was boiled gently for 2 minutes. After the reaction mixture had been kept at room temperature for 18 hours, the product was separated by the addition of water (75 ml.) and by ether extraction (3 × 50 ml.), the combined extracts being washed with aqueous sodium hydrogen carbonate solution (50 ml.), water (50 ml.) and then dried. The solid obtained by removal of solvent was crystallized from petroleum ether to give the isopropylidene compound as needles (885 mg.), m.p. 200–210°, $[\alpha]^{25}D$ +107° (*c* 2.060), λ_{max} 239 mμ (ε 17,700); ν_{max} 1715, 1681, 1647 (inflection), 1621 and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_4$ (384.50): C, 74.97; H, 8.39. Found: C, 74.95; H, 8.70.

16α,17α-Dihydroxy-4,9(11)-pregnadiene-3,20-dione (XIa) from the Isopropylidene Derivative XV.—16α,17α-Isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione (XV, 200 mg.) was heated under reflux in a mixture of methanol (7.5 ml.), water (2 ml.) and hydrochloric acid (0.5 ml., d. 1.19) for 5 hours. The reaction mixture was diluted with water (25 ml.) and extracted with chloroform (3 × 20 ml.). The combined chloroform extracts were washed with water (20 ml.) and dried. The residue obtained by removal of solvent was collected with the aid of a little benzene to give crude 16α,17α-dihydroxy-4,9(11)-pregnadiene-3,20-dione (50 mg.), m.p. 192–197°. The melting point was raised to 205–209° when the compound was crystallized (needles) from aqueous methanol. The melting point was depressed on mixing with starting material and also with the D-homo compound. The infrared spectrum showed the compound to be identical to XIa prepared above.

9α-Bromo-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIa). A.—N-Bromosuccinimide (143 mg.) was dissolved in a solution of 16α,17α-dihydroxy-4,9(11)-pregnadiene-3,20-dione (XIa, 250 mg.) in peroxide-free dioxane (5 ml.) and water (1 ml.) and to this solution was added perchloric acid (0.5 ml., 10%). The reaction mixture was kept at room temperature for 15 minutes, excess hypobromous acid was destroyed by addition of a few drops of sodium sulfite solution, and the solid obtained by pouring the solution into water (25 ml.) and filtering was washed with a little methanol and then ether. This product (XIIc, 220 mg.), m.p. 185° dec., was dissolved in acetone (50 ml.), concentrated hydrochloric acid (4 drops, d. 1.19) was added, and after being heated under reflux for 2 minutes, the solution was kept at room temperature for 18 hours. The isopropylidene compound XVIa was isolated as before and crystallized from benzene–petroleum ether as needles (120 mg.), m.p. 185° dec., $[\alpha]^{25}D$ +150° (*c* 1.013), λ_{max} 242 mμ (ε 16,850); ν_{max} 3401, 1712, 1672, 1639 (inflection) and 1049 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}BrO_5$ (481.42): C, 59.87; H, 6.91; Br, 16.60. Found: C, 59.55; H, 7.12; Br, 16.66.

B.—16α,17α-Isopropylidenedioxy-4,9(11)-pregnadiene-3,20-dione (XV, 200 mg.), dissolved in peroxide-free dioxane (5 ml.) and water (1 ml.), was treated with N-bromosuccinimide (102 mg.) and perchloric acid (0.36 ml., 10%) as before. The bromohydrin crystallized as needles (115 mg.), m.p. 185° dec., from benzene–petroleum ether and infrared analysis proved its identity to preparation A.

9β,11β-Epoxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVII).—9α-Bromo-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIa, 250 mg.), anhydrous potassium acetate (125 mg.) and ethanol (25 ml.)

were heated under reflux on the steam-bath for 18 hours. The solvent was evaporated, water (25 ml.) added, and the solid was extracted in chloroform (3 × 20 ml.). The combined chloroform extracts were dried and the solid obtained by removal of solvent was crystallized from benzene–petroleum ether to give the epoxide XVII as needles (100 mg.), m.p. 244–246°. Several crystallizations from methanol gave m.p. 250–252°, $[\alpha]^{25}D$ +224° (*c* 0.979), λ_{max} 242 mμ (ε 15,600); ν_{max} 1712, 1664, 1623 and 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_5$ (400.50): C, 71.97; H, 8.05. Found: C, 72.13; H, 8.21.

9α-Fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIb).—Anhydrous hydrofluoric acid (5 ml.) was added slowly, with shaking, to tetrahydrofuran (10.3 ml.) and methylene chloride (3.64 ml.) was cooled to −60° and to the mixture was added a solution of 9β,11β-epoxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVII, 300 mg.) in methylene chloride (1.5 ml.) cooled to −60°. The mixture was kept at −60° for 15 minutes and then at 0° for 3 hours. The reaction mixture was poured into iced sodium hydrogen carbonate solution and the mixture was extracted with chloroform. The extract was dried and evaporation of solvent gave a gummy solid (300 mg.) which was dissolved in benzene and chromatographed on silica gel (12 g.); 25% ether in benzene eluted starting material (19 mg., needles from methanol, m.p. 242–245°) and then the fluorohydrin which crystallized as needles (92 mg.), m.p. 243–247° dec., from benzene–petroleum ether. The analysis sample had m.p. 250.5–251.5° dec., $[\alpha]^{25}D$ +143° (*c* 1.428), λ_{max} 238 mμ (ε 17,100); ν_{max} 3778, 1718, 1664, 1637(inflection) and 1058 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}FO_5$ (420.50): C, 68.55; H, 7.91; F, 4.52. Found: C, 68.36; H, 7.88; F, 4.64.

On a larger scale, anhydrous hydrofluoric acid (7 ml.) was added to tetrahydrofuran (15 ml.) and methylene chloride (5 ml.) cooled to −60°. A solution of the epoxide (XVII, 2 g.) in methylene chloride (25 ml.) was cooled to −60° and added, a further 5 ml. of methylene chloride being used to complete the addition. The reaction mixture was treated as before to give a gummy solid (2 g.) which was dissolved in benzene and chromatographed on silica gel (100 g.). The fluorohydrin was obtained by eluting with 25% ether in benzene and was crystallized as needles (1.3 g.), m.p. 253–255° dec., from benzene–petroleum ether.

9α-Bromo-16α,17α-epoxy-11β-hydroxy-4-pregnene-3,20-dione (XVIIIa).—Water (2 ml.) was added to a solution of 16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (X, 500 mg.) in peroxide-free dioxane (10 ml.), then N-bromosuccinimide (300 mg.), and subsequently perchloric acid (1 ml. 10%). The reaction mixture was treated as before and the solid, obtained by pouring the mixture into water and filtering, was dried by dissolving it in methylene chloride and adding anhydrous sodium sulfate. Evaporation of solvent followed by crystallization of the residue from benzene-petroleum ether gave the bromohydrin as needles (283 mg.), m.p. 152° dec. The pure compound had m.p. 155° dec., $[\alpha]^{25}D$ +164° (*c* 0.979), λ_{max} 242 mμ (ε 16,700); ν_{max} 3448, 1709, 1664 and inflection at 1631 cm.$^{-1}$ [lit.[9] m.p. 152.5–153° dec., $[\alpha]D$ +166° (*c* 0.5), λ_{max} 243 mμ (ε 15,000)].

Anal. Calcd. for $C_{21}H_{27}BrO_4$ (423.35): C, 59.57; H, 6.43; Br, 18.88. Found: C, 59.38; H, 6.60; Br, 19.06.

On a larger scale, the epoxide (X, 10 g.) gave crystalline bromohydrin (XVIIIa, 9.4 g.), m.p. 152° dec.

9β,11β;16α,17α-Bis-epoxy-4-pregnene-3,20-dione (XIX).—9α-Bromo-16α,17α-epoxy-11β-hydroxy-4-pregnene-3,20-dione (XVIIIa, 280 mg.), anhydrous potassium acetate (140 mg.) and ethanol (28 ml.) were heated under reflux on the steam-bath for 17 hours. Solvent was removed and the residue was collected with the aid of water, washed with water, and crystallized from benzene to give 9β,11β;16α,17α-bis-epoxyprogesterone as plates (110 mg.), m.p. 240–243°. Recrystallization gave m.p. 244–245°, $[\alpha]^{25}D$ +59.5° (*c* 1.025), λ_{max} 242 mμ (ε 15,700); ν_{max} 1712, 1675 and 1626 cm.$^{-1}$ [lit.[9] m.p. 228–235°, $[\alpha]D$ +49° (*c* 0.4), λ_{max} 244 mμ (ε 13,000)]. Improved yields were obtained in larger runs.

Anal. Calcd. for $C_{21}H_{26}O_4$ (342.42); C, 73.66; H, 7.66. Found: C, 73.48; H, 7.71.

16α,17α-Epoxy-9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione (XVIIIb).—Anhydrous hydrofluoric acid (7 ml.) was added cautiously, with shaking, to a mixture of tetrahydrofuran (15 ml.) and methylene chloride (5 ml.) was cooled to −60°. A cooled (−60°) solution of 9β,11β;16α,17α-bis-epoxy-4-pregnene-3,20-dione (XIX, 2 g.) in methylene chloride (25 ml. + 5 ml. for transfer) was added and the mixture was kept at −60° for 15 minutes and then at 0° for 3 hours. The red solution was poured into iced sodium hydrogen carbonate solution and the mixture was extracted with chloroform. The extract was washed with water, dried, and the yellow solid obtained after removal of solvent was crystallized from methanol to give 9α-fluoro-16α,17α-epoxy-11β-hydroxy-4-pregnene-3,20-dione as prisms (1.36 g.), m.p. 269–272° dec. The mother liquor afforded a further amount (166 mg.), m.p. 266–269° dec. The analysis sample had m.p. 273–274° dec., $[\alpha]^{25}D$ +178° (*c* 1.036), λ_{max} 238 mμ (ε 18,600); ν_{max} 3425, 1695, 1672 and 1626 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}FO_4$ (362.43): C, 69.59; H, 7.51; F, 5.24. Found: C, 69.88; H, 7.83; F, 5.5.

9α-Fluoro-11β-hydroxy-4,16-pregnadiene-3,20-dione (XX). Chromous chloride in acetic acid (11.6 ml., 0.6*N*) was added to a solution of 16α,17α-epoxy-9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione (XVIIIb, 1 g.) in acetic acid (40 ml.), the operation being conducted in an atmosphere of carbon dioxide. After 5 minutes at room temperature, the solution was diluted with water (200 ml.) and the solid which separated was extracted in chloroform (3 × 150 ml.). The combined chloroform extracts were washed with water (150 ml.), sodium hydrogen carbonate solution (3 × 150 ml., 10%), water (150 ml.), and dried. The colorless residue obtained by evaporation of solvent was heated under reflux for 1 hour in a mixture of chloroform (5 ml.), acetone (15 ml.) and hydrochloric acid (0.2 ml., 10%). The reaction mixture was poured into water (25 ml.) and the product extracted in chloroform (3 × 30 ml.). Removal of the dried solvent and then crystallization from ethyl acetate-petroleum ether gave 9α-fluoro-11β-hydroxy-4,16-pregnadiene as needles (440 mg.), m.p. 228–230°. Recrystallization gave m.p. 229–231°, $[\alpha]^{25}D$ +204° (*c* 1.05), λ_{max} 238 mμ (ε 26,800); ν_{max} 3390, 1681, 1656, 1634 (inflection) and 1585 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}FO_3$ (346.43): C, 72.80; H, 7.86; F, 5.48. Found: C, 72.56; H, 7.98; F, 5.35.

9α-Fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIId). **A.**—A solution of osmium tetroxide (5 g.) in benzene (100 ml.) was added dropwise, with stirring, to a solution of 9α-fluoro-11β-hydroxy-4,16-pregnadiene-3,20-dione (XX, 6.5 g.) in benzene (318 ml.) and pyridine (5 ml.). When addition was complete, stirring was continued for 1 hour and then for a further 3 hours after the addition of methanol (250 ml.) followed by a solution of sodium sulfite (27 g.) and potassium hydrogen carbonate (27 g.) in water (375 ml.). The red-brown solid from the filtered reaction mixture was extracted exhaustively with hot ethyl acetate (total volume *ca.* 3 liters). The extract was washed with water (500 ml.) and the solid obtained by evaporation of solvent was collected with the aid of methanol, washed with methanol, and dried. 9α-Fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (5.5 g.) thus obtained had m.p. 228–235°. The analysis specimen, obtained as needles from methanol, had the same melting point and $[\alpha]^{25}D$ +89.4° (*c* 0.963, pyridine), λ_{max} 238 mμ (ε 17,800); ν_{max} 3509, 3436, 3311, 1712, 1667 and 1626 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}FO_5$ (380.44); C, 66.29; H, 7.68; F, 4.99. Found: C, 66.47; H, 8.11; F, 4.98.

The acetate, 16α-acetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (XIIe), prepared by acetic anhydride–pyridine overnight, crystallized from acetone–petroleum ether as needles, m.p. 254–257°, $[\alpha]^{25}D$ +69° (*c* 1.016), λ_{max} 238 mμ (ε 19,600); ν_{max} 3448, 1748, 1695, 1667, 1629 and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}FO_6$ (422.48): C, 65.38; H, 7.40; F, 4.50. Found: C, 65.24; H, 7.45; F, 4.61.

B.—9α-Fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIb, 80 mg.) was heated under reflux in methanol (3.75 ml.), water (1 ml.) and hydrochloric acid (0.25 ml., d. 1.19) for 2 hours. The reaction mixture was diluted with water (50 ml.) and the solid which separated was extracted in ethyl acetate (3 × 25 ml.). The dried extract was evaporated, the residue was washed with chloroform, and crystallization from ethyl acetate–petroleum ether gave crude 9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (20 mg.), m.p. 215–220° raised to 220–224° on further crystallization. Infrared analysis proved

the compound to be identical to that obtained in preparation A.

9α-Fluoro 11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (Ib).—Fifty flasks, each containing a beef extract, yeast extract, peptone and cerelose medium (100 ml.), were inoculated with 1% of an 8-hour growth of *Nocardia corallina* (ATCC 999). The flasks were placed on a reciprocating shaker and incubated at 28° for 17 hours when a solution of 9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIId, 20 mg.) in methanol (2 ml.) was added to each flask. The fermentation was continued for 11 hours and the flasks then were harvested and their contents pooled. The beer was extracted with ethyl acetate (3 × 4 l.) and the combined extracts were washed with water and dried. The dried solvent was concentrated to a volume of 1 liter, treated with charcoal, and concentrated further until crystals (750 mg.) separated. This material was chromatographed on Celite using a partition system of cyclohexane (4 vols.), dioxane (5 vols.) and water (1 vol.) and the product (528 mg. after washing with a little ether) crystallized from acetone as small prisms, m.p. 286–287° dec., $[\alpha]^{25}D$ +62° (*c* 0.502, methanol), +41.5° (*c* 1.062, pyridine), λ_{max} 238 mμ (ε 15,100); ν_{max} 3509, 3401, 1709, 1667, 1618 and 1603 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}FO_5$ (378.43): C, 66.65; H, 7.19; F, 5,02. Found: C, 66.86; H, 7.40; F, 4.81.

The acetate, 16α-acetoxy 9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (Ic), was prepared by treating the triol Ib with acetic anhydride–pyridine overnight and it crystallized from ethyl acetate–petroleum ether as needles, m.p. 242–244°, $[\alpha]^{25}D$ +27.3° (*c* 0.768, methanol), λ_{max} 239 mμ (ε 16,200); ν_{max} 3509, 3413, 1736, 1695, 1672, 1629 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}FO_6$ (420.46): C, 65.70; H, 6.95; F, 4.52. Found: C, 65.69; H, 7.17; F, 4.86.

The isopropylidene derivative, 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (XXI), prepared as for **XV** above, was obtained as needles, m.p. 307° dec., from ethyl acetate-petroleum ether; $[\alpha]^{25}D$ +102° (*c* 0.975), λ_{max} 238 mμ (ε 15,500); ν_{max} 3333, 1712, 1667, 1626, 1176, and 1059 cm.$^{-1}$ [lit.[10] m.p. 308–310° dec., $[\alpha]^{25}D$ +102° (*c* 1.0), λ_{max} 238 mμ (ε 15,500); ν_{max} 3344, 1709, 1661, 1621, 1603, 1379, 1374, 1171 and 1057 cm.$^{-1}$].

Anal. Calcd. for $C_{24}H_{31}FO_5$ (418.49): C, 68.88; H, 7.47; F, 4.54. Found: C, 69.01; H, 7.77; F, 4.54.

9α-Fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (XXI) and 9α-Fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4,6-pregnadiene-3,20-dione (XXII).—Ethyl oxalate (4.65 g.) was added to a solution of sodium methoxide (1.15 g.) in methanol (7.8 ml.) and the mixture was added to a solution of 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVIb, 7.8 g.) in *t*-butyl alcohol (62.4 ml.). The reaction mixture was kept at room temperature for 24 hours and was then diluted with a large volume of petroleum ether. The yellow sodium salt which separated was filtered off, washed with ether, and dried. Starting material (3.4 g.), m.p. 240–244°, was obtained from the filtrate. A solution of this salt in water was acidified (congo red) with dilute hydrochloric acid (10%) and the precipitated light-yellow solid was collected, washed with water, and dried. The weight of dried product was 4 g.

The above product (620 mg.) and anhydrous potassium acetate (233 mg.) were dissolved in methanol (7.5 ml.) and the dark-green solution was cooled in an ice-bath. A solution of bromine (190 mg.) in methanol (2 ml.) was added dropwise (1 drop per second) to the stirred solution. When the addition was complete, methanolic sodium methoxide (1.5 ml., 1 *N*) and phenol (10 mg.) were added to the almost colorless solution and the mixture was heated under reflux on the steam-bath for 10 minutes. The cooled reaction mixture was poured into water and the product was filtered off, washed with water, and dried. The crude bromo compound weighed 540 mg.

The crude bromo product (3.5 g.) and *s*-collidine (70 ml.) were heated under reflux for 5 hours. The cooled reaction mixture was diluted with ether, filtered, and the filtrate was washed with dilute hydrochloric acid (3 *N*), water, and dried. The brown solid (2.085 g.), obtained by removal of solvent, was dissolved in benzene and chromatographed on neutral alumina (63 g.). The materials eluted with 75% ether in benzene, ether and 5% acetone in ether, were combined and crystallized from ethyl acetate–petroleum ether to give 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4,6-pregnadiene-3,20-dione as needles (790 mg.), m.p. 288–294° dec., $[\alpha]^{25}D$ +112° (*c* 0.981) λ_{max} 281 mμ (ε 23,800); ν_{max} 3448, 1712, 1658, 1621, 1587, 1081, 1055 and 1037 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}FO_5$ (418.49): C, 68.88; H, 7.47; F, 4.54. Found: C, 69.05; H, 7.68; F, 4.72.

The material eluted with 10% acetone in ether was crystallized from ethyl acetate to give 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione as plates (330 mg.), m.p. 308° dec., $[\alpha]^{25}D$ +103° (*c* 1.018, pyridine), λ_{max} 238 mμ (ε 15,400).

The compound XXI was identical to that prepared from 9α-fluoro-11β,16α-17α-trihydroxy-1,4-pregnadiene-3,20-dione (Ib).

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Studies in the Synthesis of Triamcinolone. The Ethoxalylation of 4,9(11),16-Pregnatriene-3,20-dione and 11α-Hydroxy-4,16-pregnadiene-3,20-dione

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Preferential 21-mono-ethoxalylation of the subject compounds (I and IX) was essentially unsuccessful. However, I and IX could be converted into 2,21-bis-ethoxalyl derivatives (IV and X, respectively). Bromine treatment of IV gave the corresponding dibromide V which, upon acetolysis followed by dehydrobromination, afforded 21-acetoxy-1,4,9(11),16-pregnatetraene-3,20-dione (VII). Bromine treatment of X gave dibromide XI which, on acetolysis followed by dehalogenation, produced 21-acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (XIII). Compounds VII and XIII previously have been converted into triamcinolone.

The important adrenocorticoid activity of 9α-fluoro-11β,16α,17α-21-tetrahydroxy-1,4-pregnadiene-3,20-dione[1] (Aristocort[2] triamcinolone) made it of interest to investigate the development of other syntheses for this valuable therapeutic agent.[3] An attractive starting material for this purpose

(1) S. Bernstein and co-workers, THIS JOURNAL, **78**, 5693 (1956); **81**, 4956 (1959).

(2) Aristocort is the Lederle Laboratories Division, American Cyanamid Co., trademark for triamcinolone.

(3) Other investigations concerning the development of new syntheses for triamcinolone are described in an accompanying paper.[4b] The general utility of 16α,17α-epoxy steroids for the synthesis of triamcinolone will be discussed in a forthcoming publication.[4a]

(4) (a) W. S. Allen, S. Bernstein, L. I. Feldman and M. J. Weiss, paper in preparation; (b) G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959).