16α,21-Diacetoxy-17α-hydroxy-1,4,9(11)-pregnatriene-3,-20-dione (VII). A.—To a solution of 200 mg. of the 11β-ol VIIIb in 4 ml. of pyridine at −5° was added 3 ml. of thionyl chloride and the solution was kept at this temperature 2 hours. The resultant mixture was poured into ice-water and extracted with chloroform. After the chloroform was washed with saturated saline, it was dried and evaporated to give a semi-solid. This was allowed to stand 60 hours in a small amount of ethyl acetate to furnish crystals, m.p. 196–197°. A further quantity of VIIIb (200 mg.) in 10 ml. of pyridine was treated with 1 ml. of thionyl chloride as above for 5 hours. Extraction as above gave a glass which was combined with the above-mentioned solid and chromatographed on silica gel. Elution with chloroform yielded 75 mg. of VII, m.p. 195–198°. After recrystallization from ethyl acetate–petroleum ether (b.p. 90–100°) 59 mg., m.p. 200–201°, was obtained, $\lambda_{max}^{methanol}$ 238 mμ (ε 15,800); ν_{max} 3497, 1748, 1727, 1661, 1626, 1605 and 1227 cm.$^{-1}$; $[\alpha]^{25}D$ + 6° (*c* 1.122, methanol).

Anal. Calcd. for $C_{25}H_{30}O_7$ (442.49): C, 67.85; H, 6.83. Found: C, 67.54; H, 7.09.

B.—In a larger run 970 mg. of VIIIb dissolved in 20 ml. of pyridine and treated with 1.6 ml. of thionyl chloride for 2 hours at −5° as above gave without recourse to chromatography 532 mg. of VII, m.p. 199–201°.

16α,21-Diacetoxy-9α-bromo-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (VIIId).—A solution of the triene VII (200 mg.) in dioxane (10 ml.) and water was treated with N-bromoacetamide (80 mg.) and 10% perchloric acid (0.42 ml.). After standing for 20 minutes at 20°, 1 ml. of saturated sodium sulfite and excess water were added. The resultant amorphous solid was filtered off to give 60 mg. of VIIId, m.p. 147° dec., which could not be further purified; ν_{max} 3401, 1739, 1658, 1616 and 1232 cm.$^{-1}$.

16α,21-Diacetoxy-9β,11β-epoxy-17α-hydroxy-1,4-pregnadiene-3,20-dione (IX).—A solution of 620 mg. of the bromohydrin 16,21-diacetate VIIId and 200 mg. of potassium acetate in 150 ml. of absolute alcohol was refluxed for 18 hours. The reaction mixture was evaporated to dryness and the residue extracted with hot ethyl acetate. The extract was washed with saline, dried and evaporated. The semi-solid residue was treated with 5 ml. of pyridine and 2 ml. of acetic anhydride for 18 hours and the resultant solution was evaporated. The residue was chromatographed on a silica gel column and the desired product was eluted with chloroform to yield 303 mg. of a hard glass. Crystallization from acetone–petroleum ether furnished 223 mg., m.p. 211–215°. Recrystallization from the same solvent pair raised the melting point to 239.5–241°, $\lambda_{max}^{methanol}$ 247 mμ (ε 16,200); ν_{max} 3390, 1736, 1661, 1626, 1608 and 1239 cm.$^{-1}$ $[\alpha]^{25}D$ ± 0° (*c* 1.018, methanol).

Anal. Calcd. for $C_{28}H_{30}O_8$ (458.49): C, 65.49; H, 6.60. Found: C, 65.25; H, 6.73.

16α,21-Diacetoxy-9α-chloro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (VIIIe).—A solution of the 9β,11β-epoxy 16,21-diacetate IX (200 mg.) in chloroform (20 ml.) was treated with 10 ml. of chloroform saturated with hydrogen chloride at 0° for 4.5 hours. The chloroform was then evaporated at 0° and the resultant solid was crystallized from ethyl acetate–petroleum ether (b.p. 90–100°) to furnish 98 mg. of VIIIe, m.p. 229–231° dec. Recrystallization from the same solvent pair raised the melting point to 234–235° dec., $\lambda_{max}^{methanol}$ 239 mμ (ε 14,600); ν_{max} 3378, 1733, 1664, 1626, 1608(shoulder) and 1242 cm.$^{-1}$; $[\alpha]^{25}D$ + 82° (*c* 0.939, methanol).

Anal. Calcd. for $C_{25}H_{31}O_6Cl$ (494.96): C, 60.66; H, 6.31; Cl, 7.16. Found: C, 60.77; H, 6.60; Cl, 6.76.

9α-Chloro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione (VIIIf).—To a solution of the chlorohydrin 16,21-diacetate VIIIe (150 mg.) in methanol was added sodium methoxide (35 mg.) and the solution was allowed to stand at room temperature under nitrogen for 10 minutes. Acetic acid (0.1 ml.) was added and the solution evaporated to yield a solid. After the solid was slurried with water, it was crystallized from methanol–ethyl acetate to give 32 mg., m.p. 224° dec., λ_{max} 239 mμ (ε 15,800); ν_{max} 3340, 1714, 1662, 1618 and 1592(shoulder) cm.$^{-1}$; $[\alpha]^{25}D$ + 101° (*c* 0.561, methanol).

Anal. Calcd. for $C_{21}H_{27}O_6Cl$ (410.89): C, 61.38; H, 6.63; Cl, 8.63. Found: C, 61.40; H, 6.73; Cl, 8.36.

16α-21-Diacetoxy-9α-chloro-17α-hydroxy-1,4-pregnadiene-3,11,20-trione (Xb).—A solution of VIIIe (110 mg.) in 4 ml. of pyridine was treated with a solution of 130 mg. of chromium trioxide in 4 ml. of pyridine and allowed to stand at room temperature for 16 hours. The mixture was poured into ice-water, extracted with ethyl acetate, and the extract was washed with sodium bicarbonate, saline solution and dried. Evaporation gave a semi-solid. Chromatography on silica gel yielded the desired product in the chloroform elutions. Crystallization from ethyl acetate–petroleum ether yielded 31 mg. of Xb, m.p. 231–232°, $\lambda_{max}^{methanol}$ 237 mμ (ε 15,800), ν_{max} 3520, 1738, 1668, 1616, 1612(shoulder) and 1232 cm.$^{-1}$; $[\alpha]^{25}D$ + 172° (*c* 0.448, methanol).

Anal. Calcd. for $C_{25}H_{29}O_6Cl$ (492.94): C, 60.78; H, 5.92; Cl, 7.18. Found: C, 60.57; H, 6.29; Cl, 6.78.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL AND EXPERIMENTAL THERAPEUTICS RESEARCH SECTIONS, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. VII.[1] The Synthesis of the 16α-Hydroxy Derivatives of 2-Methyl Steroids[2]

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The 2α-methyl and Δ^1-2-methyl analogs of 16α-hydroxyhydrocortisone and 9α-fluoro-16α-hydroxyhydrocortisone have been synthesized.

In 1955, Hogg and co-workers[3] described a synthesis of 2α-methyl corticoids among which were 2α-methylhydrocortisone and 9α-fluoro-2α-methylhydrocortisone. Biological assays[3,4] revealed that these two compounds possessed greatly increased gluco- and mineralocorticoid activities when compared to the parent steroids, hydrocortisone and 9α-fluorohydrocortisone, respectively.

Previous work[1,5] from these laboratories has demonstrated that the introduction of a 16α-hydroxy group into a corticoid negated sodium retention activities without concomitant destruction of the glucocorticoid activity. In view of this important finding, it was decided to synthesize various corti-

(1) Paper VI, S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, THIS JOURNAL, **81**, 1689 (1959).

(2) For a preliminary announcement of part of this work see S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard and W. S. Allen, *ibid.*, **79**, 4555 (1957).

(3) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955).

(4) W. E. Dulin, B. J. Bowman and R. O. Stafford, *Proc. Soc. Exp. Biol. Med.*, **94**, 303 (1957).

(5) W. S. Allen and S. Bernstein, THIS JOURNAL, **78**, 1909 (1956).

coids in which both the 2-methyl and the 16-hydroxyl groupings were incorporated.

Hydrolysis of 21-acetoxy-3,20-bis-ethylenedioxy-5-pregnene-11β,16α,17α-triol (Ib)[6] with dilute acetic acid afforded 21-acetoxy-20-ethylenedioxy-11β,16α,17α-trihydroxy-4-pregnen-3-one (IIa).[7] Treatment of IIa with ethyl oxalate and sodium methoxide in *t*-butyl alcohol formed an amorphous yellow solid which had the characteristic properties of a sodium enolate.[8] Methylation of this enolate with methyl iodide in acetone containing potassium carbonate gave the crude 2-methyl-2-ethoxyoxalyl compound which underwent cleavage of the 1,3-diketone system with sodium methoxide in methanol to yield 20-ethylenedioxy-11β,16α,17α,21-tetrahydroxy-2α-methyl-4-pregnen-3-one (IIb)[9] as a glass. Hydrolysis of the 20-ketal group with dilute ethanolic sulfuric acid gave 11β,16α,17α,21-tetrahydroxy-2α-methyl-4-pregnene-3,20-dione (16α-hydroxy-2α-methylhydrocortisone) (IIIa) as solvated crystals after partition chromatography. A small amount of 11β,16α,17α,21-tetrahydroxy-4-pregnene-3,20-dione[6] was also isolated. Acetylation of IIIa gave the 16α,21-diacetate IIIb[10] which on saponification gave back the original tetrol, still as a solvate. Treatment of IIIa with 2,4-dinitrophenylhydrazine afforded only the C3 derivative IIIc. Oxidation of IIIb with chromium trioxide–pyridine reagent yielded 16α,21-diacetoxy-17α-hydroxy-2α-methyl-4-pregnene-3,11,20-trione (16α-hydroxy-2α-methylcortisone diacetate) (IVa).

A slightly different pathway was chosen to prepare the C-ring halohydrin analogs. Acetylation of 3,20-bis-ethylenedioxy-5-pregnene-11β,16α,17α,-21-tetrol (Ia)[5] gave the 16α,21-diacetate Ic which was highly solvated and could never be brought to a satisfactory analysis. Treatment with phosphorus oxychloride in pyridine[11] furnished 16α,21-diacetoxy-3,20-bis-ethylenedioxy-5,9(11)-pregnadien-17α-ol (V). Hydrolysis of V in dilute acetic acid afforded 16α,21-diacetoxy-20-ethylenedioxy-17α-hydroxy-4,9(11)-pregnadien-3-one (VIa).[7]

In a similar manner to that described above, condensation of the 16α,21-diacetate VIa with ethyl oxalate and sodium methoxide gave a sodium enolate as an amorphous solid which after treatment with methyl iodide and potassium carbonate followed by methanolic sodium methoxide furnished 20-ethylenedioxy-16α,17α,21-trihydroxy-2α-methyl-4,9(11)-pregnadien-3-one (VIb) as an impure solid. Acid hydrolysis of VIb followed by partition chromatography led to 16α,17α,21-trihydroxy-2α-methyl-4,9(11)-pregnadien-3,20-dione (VIIa) which was smoothly converted to its 16,21-diacetate VIIb.[12]

Well-established procedures for the introduction of the C-ring substituents[13] were then employed. Addition of N-bromoacetamide and 10% perchloric acid to a solution of the $\Delta^{4,9(11)}$-diene-3,20-dione XIIb gave the bromohydrin IIId which did not lend itself to purification but which, on treatment with potassium acetate in ethanol, yielded pure 16α,21-diacetoxy-9β,11β-epoxy-17α-hydroxy-2α-methyl-4-pregnene-3,20-dione (VIII). Hydrogen fluoride in chloroform opened the oxide to form the highly solvated 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIe). Saponification of the diacetate IIIe gave 9α-fluoro-11β,16α,17α,21-tetrahydroxy-2α-methyl-4-pregnene-3,20-dione (9α-fluoro-16α-hydroxy-2α-methylhydrocortisone) (IIIf). The diacetate IIIe was readily oxidized to afford 16α,21-diacetoxy-17α-hydroxy-9α-fluoro-2α-methyl-4-pregnene-3,11,20-trione (9α-fluoro-16α-hydroxy-2α-methylcortisone diacetate) (IVb).

In view of the well-known enhancement of activity in corticoids provided by the introduction of a Δ^1-double bond[1,6b,14] it was felt to be of interest to prepare the corresponding Δ^1-2-methyl analogs[15] of some of the compounds already discussed.

Treatment of 16α,21-diacetoxy-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIb) with selenium dioxide in *t*-butyl alcohol and glacial acetic acid according to procedures already described[16] gave after partition chromatography 16α,21-diacetoxy-11β,17α-dihydroxy-2-methyl-1,4-pregnadiene-3,20-dione (2-methylprednisolone diacetate) (IXa). Oxidation of IXa with chromium trioxide–pyridine reagent afforded the 3,11,20-trione (2-methylprednisone diacetate) (X).

That the newly introduced double bond in IXa was actually in the Δ^1-(*endo*)-position was supported by the lack of *exo*-methylene absorption in

(6) W. S. Allen and S. Bernstein, This Journal, **78**, 3223 (1956).

(7) It has been established previously in these laboratories that reaction of a 3,20-bis-ethylene ketal 21-acetate with dilute acetic acid resulted in the selective hydrolysis of the C3-ethylene ketal group: see R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953), and R. Antonucci, S. Bernstein and R. H. Lenhard, This Journal, **76**, 2956 (1954).

(8) (a) L. Ruzicka and Pl. A. Plattner, *Helv. Chim. Acta*, **21**, 1717 (1938), first showed that this type of condensation occurred at the C2-position in a 3-keto-Δ^4-compound; (b) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, This Journal, **77**, 4438 (1955), have further confirmed this fact.

(9) This is essentially the method of ref. 3 to form a 2α-methyl-Δ^4-3-one. This procedure has also been used by H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(10) A comparison of the infrared absorption spectrum in bromoform of IIIb with that of 16α,21-diacetoxy-11β,17α-dihydroxy-4-pregnene-3,20-dione[6] indicated that the non-methylated compound possessed one additional band at 1417 cm.$^{-1}$ which is due to the perturbed C2 methylene group. The band was absent in the spectrum of VIb. We wish to thank Dr. Glynn Roberts of the Sloan-Kettering Institute for these spectra and the above interpretation.

(11) S. Bernstein, R. Littell and J. H. Williams, This Journal, **75**, 4830 (1953); S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

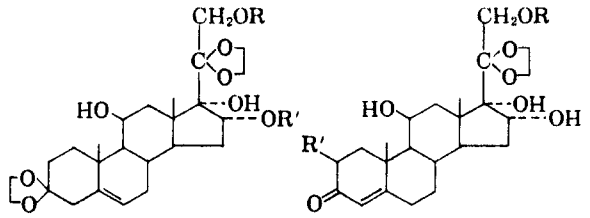
(12) As in ref. 10, Dr. Roberts has shown that the infrared spectrum in bromoform of 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione has a shoulder at 1415 cm.$^{-1}$ which is absent in the corresponding spectrum of VIIb.

(13) J. Fried and E. F. Sabo, This Journal, **75**, 2273 (1953); **76**, 1455 (1954); **79**, 1130 (1957).

(14) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955); H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955); R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, This Journal, **77**, 3166 (1955); A. Nobile, W. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik and E. B. Hershberg, *ibid.*, **77**, 4184 (1955); E. Vischer, Ch. Meystre and A. Wettstein, *Helv. Chim. Acta*, **38**, 1502 (1955).

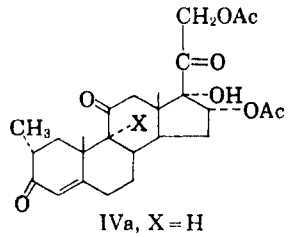
(15) Since completion of this work, the preparation of other Δ^1-2-methyl compounds has been revealed; (a) P. F. Beal, F. H. Lincoln and J. H. Hogg, Abstracts of Papers, New York Meeting of the American Chemical Society, Sept. 8–13, 1957, p. 12-O; (b) J. Iriarte and H. J. Ringold, *Tetrahedron*, **3**, 28 (1958).

(16) (a) C. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); (b) S. Szpilfogel, T. Posthumus, M. DeWinter and D. Van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).

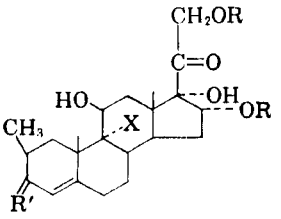


Ia, R = R′ = H
b, R = Ac, R′ = H
c, R = R′ = Ac

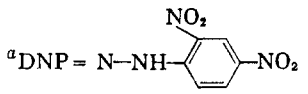
IIa, R = Ac, R′ = H
b, R = H, R′ = CH_3



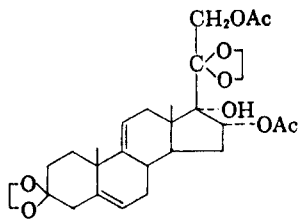
IVa, X = H
b, X = F



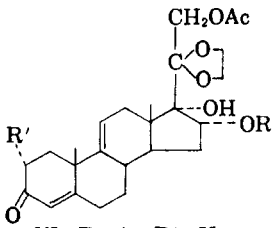
IIIa, X = R = H, R′ = O
b, X = H, R = Ac, R′ = O
c, X = R = H, R′ = DNP[a]
d, X = Br, R = Ac, R′ = O
e, X = F, R = Ac, R′ = O
f, X = F, R = H, R′ = O



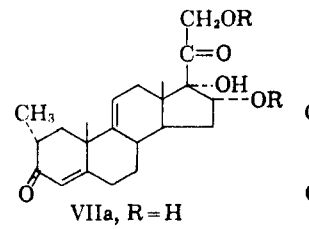
[a] DNP = N—NH— (2,4-dinitrophenyl)



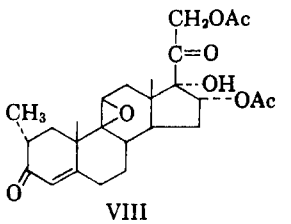
V



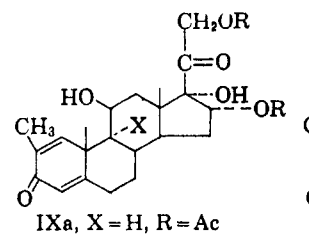
VIa, R = Ac, R′ = H
b, R = H, R′ = CH_3



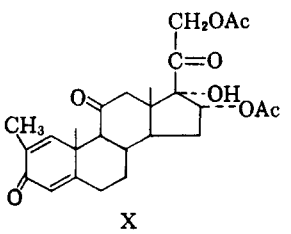
VIIa, R = H
b, R = Ac



VIII



IXa, X = H, R = Ac
b, X = F, R = H
c, X = F, R = Ac



X

the infrared spectrum and by a bathochromic shift of 7 mμ (predicted by known rules[17]) in the ultraviolet absorption band from that of the precursor IIIb. Furthermore, an *exo*-methylene compound would be expected to have two or more absorption bands as implied from the work of Beaton and coworkers.[18] The bathochromic shift, moreover, added corroborative evidence for the location of the methyl group at the C2-position in IIIa and IIIb rather than at the theoretically possible C6-position.

Similarly, selenium dioxide dehydrogenation of 16α,21 - diacetoxy - 9α - fluoro - 11β,17α - dihydroxy - 2α - methyl - 4 - pregnene - 3,20 - dione (IIIe) yielded the highly solvated $\Delta^{1,4}$-2-methyl diacetate (2-methyltriamcinolone diacetate) IXc. Saponification furnished 9α-fluoro-11β,16α,17α,21-tetrahydroxy - 2 - methyl - 1,4 - pregnadiene-3,20-dione (2-methyltriamcinolone) (IXb). In this instance also the introduction of the Δ^1-double bond resulted in a bathochromic shift of 8–9 mμ in the ultraviolet absorption band.

Bioassays.[19]—In Table I are given the biological activities of the 16α-hydroxy-2-methyl steroids described above. The glucocorticoid activity was measured by the liver glycogen deposition assay in the adrenalectomized rat, with hydrocortisone as the standard (F = 1). The mineralocorticoid assay was also in the adrenalectomized rat with deoxycorticosterone as the standard (DOC = 1).

TABLE I

THE BIOLOGICAL ACTIVITIES OF 16α-HYDROXY-2-METHYL STEROIDS

Compound	Glucocorticoid activity (L.G. assay, F = 1)	Mineralocorticoid activity (DOC = 1)
16α-Hydroxy-2α-methylhydrocortisone		
Free steroid (IIIa)	0.6	0.1
Diacetate (IIIb)	< .4[a]	< .1
16α-Hydroxy-2α-methylcortisone		
Diacetate (IVa)	< .4[a]	< .1
9α-Fluoro-16α-hydroxy-2α-methylhydrocortisone		
Free steroid (IIIf)	3 (2–5)[b]	< .1
Diacetate (IIIe)	2 (1–3)[b]	< .1
9α-Fluoro-16α-hydroxy-2α-methylcortisone		
Diacetate (IVb)	<0.4[a]	< .1
16α-Hydroxy-2-methylprednisolone		
Diacetate (IXa)	< .4[a]	< .1
16α-Hydroxy-2-methylprednisone		
Diacetate (X)	< .4[a]	< .1
2-Methyltriamicinolone		
Free steroid (IXc)	7 (5–10)[b]	< .1
Diacetate (IXb)	5 (4–7)[b]	< .1

[a] At a 250-μg. dose level. [b] 95% confidence limits.

Acknowledgment.—We wish to thank Louis M. Brancone and associates for the analytical data, William Fulmor and associates for the spectral data and optical rotational data, and Charles Pidacks and associates for the partition chromatographic separations.

Experimental

Melting Points.—All melting points are uncorrected.

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

(17) See L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," third edition, Reinhold Publishing Corp., New York, N. Y., 1949, pp. 190–192. The ultraviolet absorption spectra of the pertinent compounds of ref. 15 also are in agreement.

(18) J. M. Beaton, J. D. Johnston, L. C. McKean and F. S. Spring, *J. Chem. Soc.*, 3660 (1953).

(19) The assays were done by L. Bortle, E. Heyder, J. Perrine and E. Ross of the Experimental Therapeutics Section of these laboratories.

Absorption Spectra.—The ultraviolet absorption spectra were determined in absolute alcohol unless otherwise noted. The infrared absorption spectra were determined in a potassium bromide disk.

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

21-Acetoxy-20-ethylenedioxy-11β,16α,17α-trihydroxy-4-pregnen-3-one (IIa).—A solution of 21-acetoxy-3,20-bis-ethylenedioxy-5-pregnene-11β,16α,17α-triol (Ib, 500 mg.) in glacial acetic acid (10 ml.) was heated on a steam-bath for 20 minutes. The mixture was then poured into ice-water and extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution, followed by three washes with saturated saline solution. The extract was dried and evaporated to give crystals, m.p. 254–256°. A portion was crystallized from acetone–petroleum ether, m.p. 262–263°; λ_{max} 241–242 mμ (ε 14,400); ν_{max} 3520, 1742, 1678, 1626, 1238 and 1048 cm.$^{-1}$; $[\alpha]^{24}D$ + 85° (*c* 1.145).

Anal. Calcd. for $C_{25}H_{36}O_8$ (464.54): C, 64.63; H, 7.81. Found: C, 64.77; H, 8.03.

20-Ethylenedioxy-11β,16α,17α,21-tetrahydroxy-2α-methyl-4-pregnen-3-one (IIb).—To 8.0 g. of 21-acetoxy-20-ethylenedioxy-11β,16α,17α-trihydroxy-4-pregnen-3-one (IIa) suspended in 100 ml. of *t*-butyl alcohol was added 3.2 g. of commercial (95%) sodium methylate. To this mixture under nitrogen was added 5 ml. of diethyl oxalate and the mixture was stirred under nitrogen for 6 hours. (Complete solution occurred and the product precipitated within 10 minutes.) Addition of ether followed by filtration gave 13 g. of a yellow powder, soluble in water but insoluble in dilute acid.

A mixture of the crude sodium enolate, 13 g. of potassium carbonate, 300 ml. of acetone and 50 ml. of methyl iodide was refluxed 20 hours, filtered while hot and the filtrate concentrated to a small volume.

A large amount of water was added to the filtrate which was then extracted with ethyl acetate. The extract was washed with a saline solution, dried and treated with activated carbon to give after evaporation 7.8 g. of a pale yellow glass which could not be induced to crystallize.

To this methylated glass in 250 ml. of absolute methanol was added 1.0 g. of (95%) sodium methylate and the mixture was allowed to stand at room temperature for 4 hours. After the addition of a few drops of acetic acid and 20 ml. of water, the methanol was removed under reduced pressure at a temperature not exceeding 35°. The ethyl acetate extract of the mixture was washed to neutral with a saline solution and treated with magnesium sulfate and activated carbon. Evaporation gave 5.7 g. of yellow glass IIb which could not be induced to crystallize.

11β,16α,17α,21-Tetrahydroxy-2α-methyl-4-pregnene-3,20-dione (IIIa). A.—A mixture of 5.7 g. of 20-ethylenedioxy-11β,16α,17α,21-tetrahydroxy-4-pregnen-3-one (IIb), 200 ml. of methanol and 12 ml. of 8% (v./v.) sulfuric acid was refluxed for 1 hour, concentrated under reduced pressure, extracted with ethyl acetate and the extract was washed with sodium bicarbonate, saline and water. Treatment of the extract with magnesium sulfate and activated carbon, filtration and evaporation gave 4.1 g. of yellow glass.

The above glass was subjected to partition chromatography on a diatomaceous silica product with the following solvent system: ethyl acetate (3 parts), petroleum ether (b.p. 90–100°) (2 parts), methanol (3 parts), water (2 parts). Paper strip chromatography indicated that the desired product was collected from 2.5 to 5 hold-back volumes. These were combined and evaporated to give 1.4 g. of a glass.

One crystallization from acetone–petroleum ether gave 700 mg., m.p. 193–196°. A 200-mg. portion was recrystallized twice from acetone–petroleum ether to give 23 mg. of IIIa, m.p. 201–203°, λ_{max} 240–241 mμ (ε 16,600).

Anal. Calcd. for $C_{22}H_{32}O_6$ (392.48): C, 67.32; H, 8.22. Found: C, 65.59; H, 8.39.

The column was washed with methanol and gave 1.17 g. of an oil. Two recrystallizations from acetone gave 70 mg. of crystals which were identical with 11β,16α,17α,21-tetrahydroxy-4-pregnene-3,20-dione by admixture melting point and infrared spectral analysis.

B.—To 167 mg. of 16α,21-diacetoxy-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIb) in 15 ml. of absolute methanol was added 40 mg. of commercial (95%) sodium methylate in 5 ml. of methanol and the mixture was flushed with a stream of nitrogen at room temperature for 10 minutes. After addition of 2 drops of glacial acetic acid and removal of solvent to one-third of its original volume, water was added and 54 mg., m.p. 195–198°, was filtered. Two crystallizations from acetone–petroleum ether gave 21 mg. of IIIa, m.p. 200–202°; ν_{max} 3400, 1702, 1656, 1620 and 1056 cm.$^{-1}$; $[\alpha]^{25}D$ + 145° (*c* 0.145).

Anal. Calcd. for $C_{22}H_{32}O_6$ (392.48); C, 67.32; H, 8.22. Found: C, 65.79; H, 8.38.

C-3-(2,4-Dinitrophenylhydrazone) IIIc, m.p. 263–264° dec.; γ_{max} 3413, 3300, 3106, 1706, 1618 and 1587 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{36}O_9N_4$ (572.60): C, 58.76; H, 6.34; N, 9.79. Found: C, 58.44; H, 6.27; N, 9.49.

16α,21-Diacetoxy-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIb).—A mixture of 11β,16α,17α,21-tetrahydroxy-2α-methyl-4-pregnene-3,20-dione (IIIa, 130 mg.), 3 ml. of pyridine and 0.5 ml. of acetic anhydride was heated at about 110° for 1 hour. Methanol was added and the solvents removed under reduced pressure to a small volume. Water was added and the mixture was extracted with ethyl acetate. The extract was washed with cold dilute sulfuric acid, dilute sodium bicarbonate, and finally with water to neutrality, treated with magnesium sulfate and activated carbon, filtered and evaporated. The resulting oil was caused to crystallize by the addition of acetone and petroleum ether to give 70 mg., m.p. 252–254°. Two crystallizations from the same solvent pair gave 25 mg., m.p. 253–254°; λ_{max} 240–241 mμ (ε 17,500); ν_{max} 3450, 1743, 1654, 1620 and 1053 cm.$^{-1}$; $[\alpha]^{25}D$ + 91.8° (*c* 1.09).

Anal. Calcd. for $C_{26}H_{36}O_8$ (476.55): C, 65.53; H, 7.61. Found: C, 65.43; H, 7.75.

16α,21-Diacetoxy-17α-hydroxy-2α-methyl-4-pregnene-3,-11,20-trione (IVa).—To a previously prepared and cooled mixture of 180 mg. of chromium trioxide in 3 ml. of pyridine was added a cooled solution of 240 mg. of 16α,21-diacetoxy-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIb) in pyridine and the solution was allowed to stand at 20° for 18 hours. Methanol was added and the solvents removed at about 30°. The residue was extracted with ethyl acetate which was washed with cold dilute sulfuric acid, cold dilute sodium bicarbonate and then with water. The extract was treated with magnesium sulfate and activated carbon, filtered and evaporated to give a white powder. Three crystallizations from acetone–petroleum ether gave 77 mg., m.p. 240.5–241.5°; λ_{max} 237 mμ (ε 15,200); ν_{max} 3500, 1733, 1701, 1664, 1618, 1263, 1238, 1224 and 1052 cm.$^{-1}$; $[\alpha]^{25}D$ + 129° (*c* 1.015).

Anal. Calcd. for $C_{26}H_{34}O_8$ (474.55): C, 65.80; H, 7.22. Found: C, 65.49; H, 7.30.

3,20-Bis-ethylenedioxy-16α,21-diacetoxy-5-pregnene-11β,17α-diol (Ic).—To a solution of 3.5 g. of Ia in 30 ml. of pyridine was added 4.0 ml. of acetic anhydride. The mixture was allowed to stand for 17 hours at room temperature and then poured into water. The resulting solid was collected and washed with water to give 4.0 g., m.p. 130–135°. One crystallization from acetone–petroleum ether gave 3.8 g., m.p. 129–135°; ν_{max} 3470, 1736, 1239 and 1095 cm.$^{-1}$; $[\alpha]^{25}D$ − 61.5° (*c* 2.132).

Anal. Calcd. for $C_{29}H_{42}O_{10}$ (550.63): C: 63.25: H, 7.69. Found: C, 62.49; H, 7.81.

3,20-Bis-ethylenedioxy-16α,21-diacetoxy-5,9(11)-pregnadien-17α-ol (V).—To a solution of 1.0 g. of Ic in 10.0 ml. of pyridine cooled to −5° was added 1.0 ml. of phosphorus oxychloride and the mixture was allowed to stand at room temperature for 24 hours. The solution was poured into ice-water and the resulting solid collected and washed well with water to give 0.84 g., m.p. 205–211°. Four crystallizations from acetone–methanol gave 0.31 g., m.p. 221–224°; ν_{max} 3560, 1737, 1238 and 1093 cm.$^{-1}$; $[\alpha]^{25}D$ −48° (*c* 1.050).

Anal. Calcd. for $C_{29}H_{40}O_9$ (532.61): C, 65.39; H, 7.57. Found: C, 65.52; H, 7.67.

20-Ethylenedioxy-16α,21-diacetoxy-3-oxo-4,9(11)-pregnadien-17α-ol (VIa).—A solution of 0.53 g. of V in 45 ml. of 66% (v./v.) acetic acid was heated on the steam-bath for 30 minutes, water was added and the mixture was cooled and filtered to give 0.23 g., m.p. 182–185°. Three crystallizations from acetone-petroleum ether gave 0.16 g., m.p. 184.5–186°; λ_{max} 239–240 mμ (ε 16,700); ν_{max} 3510, 1742, 1671, 1619, 1230 and 1090 cm.$^{-1}$; $[\alpha]^{26}D$, 0° (*c* 1.075).

Anal. Calcd. for $C_{27}H_{36}O_8$ (488.56): C, 66.37; H, 7.43. Found: C, 66.63; H, 7.65.

20-Ethylenedioxy-16α,17α,21-trihydroxy-2α-methyl-4,9-(11)-pregnadien-3-one (VIb).—To a suspension of 4.89 g. (10 millimoles) of VIa in 65 ml. of *t*-butyl alcohol was added 1.74 g. of sodium methoxide (31.5 millimoles) and the mixture allowed to stir under nitrogen for 10 minutes. A solution of 3.4 ml. (25 millimoles) of ethyl oxalate in 20 ml. of *t*-butyl alcohol was added dropwise and stirring under nitrogen was continued for 5 hours. Ether (approximately 100 ml.) was added and the reaction mixture was filtered and washed well with ether to give 8.5 g. of yellow solid. This product was water soluble, precipitated with dilute acid and gave a positive color test with ferric chloride solution. No attempt was made to further purify this compound.

In another run, the sodium methoxide was dissolved in 15 ml. of methanol and added to the suspension of VIa in *t*-butyl alcohol. This procedure gives a cleaner reaction as the methoxide tends to lump if not dissolved before addition.

To a suspension of 8.5 g. of the crude sodium enolate in 250 ml. of acetone (dried over potassium carbonate) was added 8.0 g. of anhydrous potassium carbonate and 60 ml. of methyl iodide and the reaction mixture was refluxed for 20 hours. After filtration of the inorganic salts, the yellow solution was evaporated. The residue was dissolved in ethyl acetate, washed several times with water and evaporated to give 4.11 g. of a yellow oil which gave no color with ferric chloride solutions.

To a solution of 4.1 g. of the above oil in 200 ml. of methanol was added 0.56 g. of sodium methoxide and the solution was allowed to stand at room temperature under nitrogen for 4 hours. Water was added (100 ml.) followed by a dropwise addition of acetic acid to make the solution neutral and then most of the methanol was removed at a bath temperature of 40–45°. The mixture was cooled, filtered and washed with water to give 2.5 g., m.p. 185–205°, λ_{max} 239–240 mμ (ε 7,700). This solid was dissolved in chloroform, washed several times with 2% sodium hydroxide (to remove most of the color) and then with water until the washings were neutral. The extract was dried over sodium sulfate and evaporated to give 2.3 g. of semi-solid.

16α,17α,21-Trihydroxy-2α-methyl-4,9(11)-pregnadiene-3,20-dione (VIIa).—To a solution of 2.3 g. of VIb in 200 ml. of methanol was added 25 ml. of 8% (v./v.) sulfuric acid and the mixture was refluxed for 45 minutes. Water was added, most of the methanol was removed under reduced pressure and the residue was extracted with ethyl acetate. The extract was washed with sodium bicarbonate solution and then with water until the washings were neutral, dried over sodium sulfate and evaporated to give 1.6 g. of yellow oil. This oil was then submitted to partition chromatography on a diatomaceous silica product column (400 g.) in the following manner. The solvent was 2 parts of ethyl acetate, 3 parts of petroleum ether (b.p. 90–100°), 3 parts of methanol and 2 parts of water with the upper phase of this mixture as the mobile phase and the lower phase as the stationary phase. The oil was dissolved in 15 ml. of stationary phase, slurried with 30 g. of a diatomaceous silica product and packed on top of a diatomaceous silica product column which was previously prepared with 200 ml. of stationary phase. Chromatography was then initiated with the mobile phase, and 128 fractions of 20 ml. volume each were collected. Fractions 71–119 showed a strong color with Blue Tetrazolium and were combined and evaporated to give 0.75 g. of crude solid. Five crystallizations from acetone–petroleum ether gave 0.13 g., m.p. 203–207°, λ_{max} 237–238 mμ (ε 17,400); ν_{max} 3370, 1711, 1672 and 1620 cm.$^{-1}$; $[\alpha]^{26}D$ + 103° (*c* 1.088).

Anal. Calcd. for $C_{22}H_{30}O_5$ (374.46): C, 70.56; H, 8.08. Found: C, 70.75; H, 8.29.

In another run of the same size, 0.68 g. of VIIa of sufficient purity for further reaction was isolated by chromatography.

16α-21-Diacetoxy-17α-hydroxy-2α-methyl-4,9(11)-pregnadiene-3,20-dione (VIIb).—To a solution of 0.62 g. of crude VIIa in 8.0 ml. of pyridine was added 2.0 ml. of acetic anhydride, and the mixture was allowed to stand at room temperature overnight. The solution was poured into water, cooled, filtered and the solid residue was washed well with water. The solid was dissolved in ethyl acetate, dried over magnesium sulfate and evaporated to give 0.35 g. Three crystallizations from acetone–petroleum ether gave 0.17 g., m.p. 221.5–224°; λ_{max} 238–239 mμ (ε 16,900); ν_{max} 3510, 1742, 1737, 1671, 1622 and 1237 cm.$^{-1}$; $[\alpha]^{26}D$ + 104° (*c* 0.04).

Anal. Calcd. for $C_{26}H_{34}O_7$ (458.53): C, 68.10; H, 7.47. Found: C, 68.10; H, 7.53.

In another run, 0.68 g. of VIIa gave 0.50 g. of VIIb, m.p. 219–223°.

16α,21-Diacetoxy-11β,17α-dihydroxy-9α-bromo-2α-methyl-4-pregnene-3,20-dione (IIId).—To a solution of 0.10 g. of VIIb in 5.0 ml. of dioxane (peroxide-free) and 1.0 ml. of water cooled to 15° was added 0.042 g. of N-bromoacetamide and 0.21 ml. of 10% perchloric acid. The reaction mixture was allowed to stand at 20° for 20 minutes and then 0.5 ml. of saturated sodium sulfite was added followed by water until solid was formed. The mixture was cooled, more water was added and the solid was collected and washed with water to give 0.095 g., m.p. 131–134° dec. This solid gave a positive Beilstein test for halogen. All attempts to purify it led only to further decomposition.

16α,21-Diacetoxy-17α-hydroxy-9β,11β-epoxy-2α-methyl-4-pregnene-3,20-dione (VIII).—To a solution of 0.19 g. of IIId in 60 ml. of absolute ethanol was added 0.055 g. of potassium acetate (dried at 110°) and the mixture was refluxed for 17 hours and then evaporated to dryness. The residue was dissolved in ethyl acetate and water, the ethyl acetate was washed several times with water, dried over sodium sulfate and evaporated to give 0.14 g. of oil. This oil was dissolved in 4.0 ml. of pyridine and treated with 1.0 ml. of acetic anhydride overnight at room temperature. The solution was poured into water, cooled and the resulting solid collected and washed with water to give 0.042 g., m.p. 202–208°. The aqueous mother liquor was extracted with ethyl acetate, washed with water, dried over sodium sulfate and evaporated to give an oil, which when treated with methanol gave 0.056 g., m.p. 218–221°. Three crystallizations from methanol gave 0.035 g., m.p. 222–223.5°; λ_{max} 242–243 mμ (ε 14,100); ν_{max} 3380, 1754, 1740, 1657, 1630 (shoulder) and 1240 cm.$^{-1}$; $[\alpha]^{25}D$ −34° (*c* 1.098).

Anal. Calcd. for $C_{26}H_{34}O_8$ (474.83): C, 65.80; H, 7.22. Found: C, 65.57; H, 7.49.

16α,21-Diacetoxy-11β,17α-dihydroxy-9α-fluoro-2α-methyl-4-pregnene-3,20-dione (IIIe).—To a solution of 0.10 g. of VIII in 25 ml. of chloroform (alcohol-free), previously cooled to −5° was added 1 ml. of anhydrous hydrogen fluoride. The reaction mixture was placed on a mechanical shaker, allowed to shake for 2 hours at −5°, poured into ice-water and neutralized with sodium bicarbonate. The mixture was extracted several times with chloroform and the combined extracts were washed to neutral with water, dried over sodium sulfate and evaporated. The residue was dissolved in 5 ml. of pyridine, acetic anhydride (1.0 ml.) was added and the solution allowed to stand at room temperature for 16 hours. It was then poured into water and extracted several times with ethyl acetate. The combined extracts were washed to neutral with water, dried over sodium sulfate and evaporated to give an oil. The oil was submitted to partition chromatography on a diatomaceous silica product using a solvent system consisting of 3 parts of ethyl acetate, 2 parts of petroleum ether, (b.p. 90–100°), 3 parts of methanol and 2 parts of water. The upper phase of this solvent mixture was used as the mobile phase and the lower phase was used as the stationary phase. The eluate from the column was passed through a Beckman spectrophotometer fitted with an automatic recorder set to read at 240 mμ. The recorder indicated four distinct peaks, each one kept separate. Only the last peak (at approximately 2 hold-back volumes) was investigated. This peak was evaporated to give 13.0 mg. of oil. This oil crystallized from acetone–petroleum ether to give 5.5 mg., m.p. 140–200°. One crystallization from acetone–petroleum ether gave 3.0 mg., m.p. 140–200°, positive ketol test with blue tetrazolium, one spot on paper chromatogram.

Anal. Calcd. for $C_{26}H_{35}O_6F$ (494.54): F, 3.83. Found: F, 4.47.

In another run, 100 mg. of VIII gave 10.5 mg. of IIIe, m.p. 130–215°. In another run, 137 mg. of VIII gave 27.5 mg. of IIIe, m.p. 135–214°. These two were combined and recrystallized from acetone–petroleum ether to give 30 mg., m.p. 130–215°, one spot on paper strip; λ_{max} 237–238 mμ (ε 16,300); ν_{max} 3420, 1740, 1732, 1725, 1660, 1627 (shoulder) and 1235 cm.$^{-1}$.

Anal. Found: F, 4.29.

11β,16α,17α,21-Tetrahydroxy-9α-fluoro-2α-methyl-4-pregnene-3,20-dione (IIIf).—To a solution of 54 mg. of IIIe in 5 ml. of methanol previously cooled to 0° and covered with nitrogen was added a solution of 19 mg. of potassium hydroxide dissolved in 2 ml. of methanol. After standing one hour at room temperature, the solution was neutralized with acetic acid and evaporated to give a solid. The solid was washed with water to give 26 mg. of crystals, m.p. 222–225°. Crystallization from acetone–petroleum ether yielded 23.8 mg. of IIIf, m.p. 228.5–231°; λ_{max} 237–238 mμ (ε 15,300); ν_{max} 3380, 1712, 1660 and 1633 cm.$^{-1}$; $[\alpha]^{25}_{D}$ + 105° (*c* 0.354, pyridine).

Anal. Calcd. for $C_{22}H_{31}O_6F$ (410.47): C, 64.37; H, 7.61; F, 4.63. Found: C, 64.61; H, 7.78; F, 5.68, 5.80.

9α-Fluoro-16α,21-diacetoxy-17α-hydroxy-2α-methyl-4-pregnene-3,11,20-trione (IVb).—To a mixture of 180 mg. of chromic anhydride in 2 ml. of pyridine was added a solution of 200 mg. of 9α-fluoro-16α,21-diacetoxy-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIe) in 10 ml. of pyridine at 0°. The mixture was stirred and allowed to stand at room temperature for 18 hours. Water (25 ml.) was added followed by 6 ml. of saturated aqueous sodium sulfite solution and the mixture was shaken for 1 hour. The resulting solid was filtered off, washed with water, dissolved in acetone, dried over magnesium sulfate and crystallized from acetone–petroleum ether to give 100 mg., m.p. 197–199.5°. Recrystallization from acetone–petroleum ether gave 85 mg., m.p. 197.5–199.5°; λ_{max} 235 mμ (ε 15,000); ν_{max} 3450, 1750, 1730, 1668, 1635, 1240 cm.$^{-1}$; $[\alpha]^{25}_{D}$ + 94.7° (*c* 1.045).

Anal. Calcd. for $C_{26}H_{33}O_8F$ (492.52): C, 63.40; H, 6.75; F, 3.86. Found: C, 63.27; H, 6.72; F, 3.65.

16α,21-Diacetoxy-11β,17α-dihydroxy-2-methyl-1,4-pregnadiene-3,20-dione (IXa).—To 110 mg. of 16α,21-diacetoxy-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIb) in 10 to 15 ml. of *t*-butyl alcohol and 0.5 ml. of glacial acetic acid was added 50 mg. of sublimed selenium dioxide and the mixture refluxed for 24 hours. Paper strip chromatographic analysis showed approximately 20% conversion. To the reaction was added 75 mg. of selenium dioxide and the mixture was refluxed an additional 24 hours. Paper strip analysis showed approximately 50% conversion.

After filtration of the inorganic residue through a diatomaceous silica product, the solvents were evaporated under reduced pressure, the residue dissolved in ethyl acetate, washed twice with 1 *N* sodium hydroxide, then with saturated saline to neutral. After treatment with magnesium sulfate and activated carbon, the extract was filtered through a diatomaceous silica product and evaporated.

The 106 mg. of oil so obtained was subjected to partition chromatography on a diatomaceous silica product (72 g.) with a solvent system of ethyl acetate (2 parts), petroleum ether (4 parts), methanol (3 parts) and water (2 parts). The hold-back volume was 100 ml. The eluate was followed by a continuous recording ultraviolet spectrometer at 245 mμ. The first main peak which appeared at the fourth hold-back volume was unreacted starting material and was not examined further. The second major peak at five to six holdback volumes was evaporated to a white solid and crystallized from acetone–petroleum ether to give 25 mg. of white crystals, m.p. 239–241°. Three additional crystallizations from the same solvent pair gave 14 mg. of crystals with a constant melting point of 241.5–242.5°; $\lambda^{methanol}_{max}$ 247 mμ (ε 15,900); ν_{max} 3450, 1748, 1670, 1630, 1602, 1272 and 1238 cm.$^{-1}$; $[\alpha]^{25}_{D}$ + 7° (*c* 0.552).

Anal. Calcd. for $C_{28}H_{34}O_8$ (474.53): C, 65.80; H, 7.22. Found: C, 65.84; H, 7.45.

16α,21-Diacetoxy-17α-hydroxy-2-methyl-1,4-pregnadiene-3,11,20-trione (X).—To 78 mg. of chromic anhydride in 1 ml. pyridine at 0° was added 103 mg. of 16α,21-diacetoxy-11β,-17α-dihydroxy-2-methyl-1,4-pregnadiene-3,20-dione (IXa) in 4 ml. of pyridine at 0°. The mixture was stirred and allowed to stand at room temperature for 18 hours. Methanol was then added and the solvents were removed at a temperature no greater than 40°. The mixture was extracted with ethyl acetate and the extract was washed once with cold dilute hydrochloric acid, once with saturated sodium bicarbonate and twice with saturated saline. The organic extract was treated with anhydrous magnesium sulfate and activated carbon, filtered through a diatomaceous silica product and evaporated to a tan glass. Paper strip chromatographic analysis showed a homogeneous spot slightly more mobile than the chromatogram of its precursor.

The crude glass was slurried with acetone–petroleum ether to deposit a tan, low melting residue. Concentration of the mother liquor gave 39 mg. of white crystals, m.p. 180–182°. Two further crystallizations from ether gave 20 mg. of pure product, m.p. 182–183°; $\lambda^{methanol}_{max}$ 243 mμ (ε 13,800); ν_{max} 3490, 1748, 1710, 1670, 1636, 1268 and 1235 cm.$^{-1}$; $[\alpha]^{24}_{D}$ + 85.5° (*c* 0.807).

Anal. Calcd. for $C_{26}H_{32}O_8$ (472.52): C, 66.08; H, 6.83. Found: C, 66.34; H, 7.13.

9α-Fluoro-16α,21-diacetoxy-11β,17α-dihydroxy-2-methyl-1,4-pregnadiene-3,20-dione (IXc).—To a solution of 500 mg. of 9α-fluoro-16α,21-diacetoxy-11β,17α-dihydroxy-2α-methyl-4-pregnene-3,20-dione (IIIe) in 75 ml. of *t*-butyl alcohol and 2.5 ml. of acetic acid was added 250 mg. of selenium dioxide. The mixture was placed under nitrogen and refluxed for 24 hours. Paper strip analysis showed that the reaction was about 20% complete. An additional 250 mg. of selenium dioxide was added and the reaction mixture refluxed for another 24 hours at which time paper strip analysis showed about 50% conversion. Selenium dioxide was added (250 mg.) and the reaction permitted to reflux for another 24 hours. Paper strip analysis now showed about 70% conversion. An additional 250 mg. of selenium dioxide was added, the reaction mixture refluxed for 24 hours, cooled to room temperature and the solid filtered off. The filtrate was evaporated. The residue obtained was dissolved in ethyl acetate, washed three times with 1 *N* sodium hydroxide and then with water until neutral. Treatment of the extract with magnesium sulfate and activated carbon, filtration through a diatomaceous silica product, and evaporation gave an oil which was acetylated in pyridine with acetic anhydride overnight. This was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated to give 500 mg. of oil.

The above oil was partitioned on a diatomaceous silica product column (60 g.) using the solvent system 4:2:3:2 petroleum–ether (b.p. 90–100°), ethyl acetate, methanol, water. Hold-back volumes five and part of six, were evaporated to give an oil which was crystallized from acetone–petroleum ether to give 160 mg. of solid, m.p. 154–203°, one spot on paper strip, positive ketol test, λ_{max} 245 mμ (ε 16,400); ν_{max} 3480, 1750, 1738, 1730, 1670, 1630, 1235 cm^{-1}.

Further crystallization did not change the melting point, indicating that the compound forms a solvate.

9α-Fluoro-11β,16α,17α,21-tetrahydroxy-2-methyl-1,4-pregnadiene-3,20-dione (IXb).—To a solution of 70 mg. of 9α-fluoro-16α-21-diacetoxy-11β,17α-dihydroxy-2-methyl-1,4-pregnadiene-3,20-dione (IXc) in 8 ml. of methanol, previously cooled to 0° and placed under nitrogen, was added 25 mg. of potassium hydroxide in 3 ml. of methanol. The reaction was allowed to stand at room temperature for 1 hour and was then neutralized with acetic acid and evaporated *in vacuo* at 40–50°. The solid residue was slurried with water, filtered and washed with water, dissolved in acetone, dried over magnesium sulfate and crystallized from acetone–petroleum ether to give 40 mg. of IXb, m.p. 232–240°. Two crystallizations from acetone–petroleum ether gave 15 mg., m.p. 239–242°.

Anal. Calcd. for $C_{22}H_{29}O_6F$ (408.45): C, 64.69; H, 7.15; F, 4.65. Found: C, 64.36; H, 7.31; F, 4.39.

In another run, 150 mg. of IXc gave 47 mg., m.p. 240–242°; λ_{max} 245 mμ (ε 15,500); ν_{max} 3420, 1718, 1670, 1628 cm.$^{-1}$; $[\alpha]^{25}_{D}$ + 43.7° (*c* 1.097, pyridine).

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