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16-Hydroxylated Steroids. XVI.[1] 16α-Hydroxy-6α-methylcorticoids. II[2,3]

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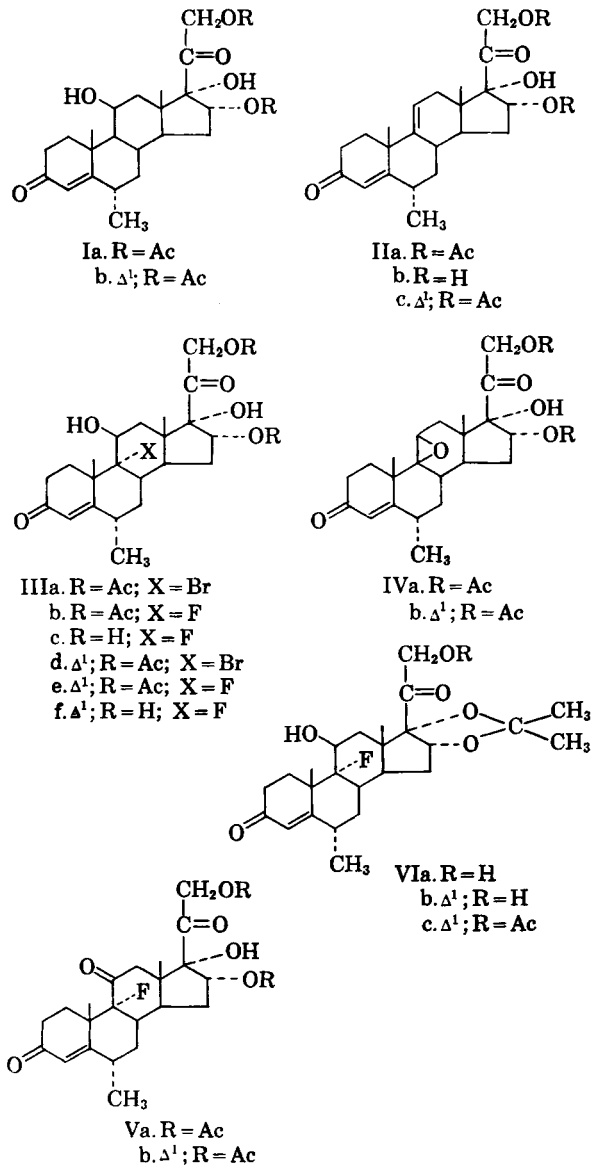
The synthesis of 6α-methyl-9α-fluoro-16α-hydroxyhydrocortisone (IIIc) and 6α-methyltriamcinolone (IIIf) is described.

In a continuation of the work described in Part I,[2] we now wish to report on the preparation of 9α-fluoro-16α-hydroxy-6α-methylcorticoids.

Treatment of 16α-hydroxy-6α-methylhydrocortisone 16,21-diacetate (Ia)[2] with thionyl chloride in pyridine at −5° for ten minutes[4] gave 16α,21-diacetoxy-17α-hydroxy-6α-methyl-4,9(11)-pregnadiene-3,20-dione (IIa).

The usual C ring elaboration[5] was then carried out. Addition of the elements of hypobromous acid to IIa gave the unstable, impure bromohydrin IIIa which was converted without purification into the 9β,11β-epoxide IVa by refluxing with potassium acetate in absolute ethanol. Cleavage of the latter compound IVa with hydrogen fluoride in tetrahydrofuran[6]–methylene chloride afforded 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (IIIb). The usual ester exchange conditions on IIIb gave 9α-fluoro-11β,16α,-17α,21-tetrahydroxy-6α-methyl-4-pregnene-3,20-dione (9α-fluoro-16α-hydroxy-6α-methylhydrocortisone) (IIIc), while oxidation of IIIb with chromium trioxide-pyridine yielded the 9α-fluoro-11-ketone 16,21-diacetate Va. Treatment of the tetrol IIIc with perchloric acid in acetone furnished 9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione(VIa).

An alternate approach to the synthesis of compound IIIc was also considered. Treatment of 21-acetoxy-3,20-bisethylenedioxy-5α,6α-epoxypregnane-11β,17α-diol (VIIa)[7,8] with thionyl chloride in pyridine[9] effected dehydration to yield 21-acetoxy-3,20-bisethylenedioxy-9(11),16-pregnadien-5α,6α-epoxide (VIII).[10] The epoxide VIII was reacted with methylmagnesium bromide to give after acetylation 21-acetoxy-3,20-bisethylenedioxy-6β-methyl-9(11),16-pregnadien-5α-ol (IX) as an in-



(1) Paper XV, S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.*, **82**, 3680 (1960).

(2) Part I, S. Bernstein and R. Littell, *J. Am. Chem. Soc.*, **82**, 1235 (1960).

(3) This work was presented in part at the First International Congress of Endocrinology, Copenhagen, Denmark, July 18–23, 1960.

(4) It was found that ten minutes was approximately the optimal time for the reaction during a study of the preparation of the 1,4,9(11)-pregnatriene IIc (*vide infra*).

(5) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953); **76**, 1455 (1954); **79**, 1130 (1957).

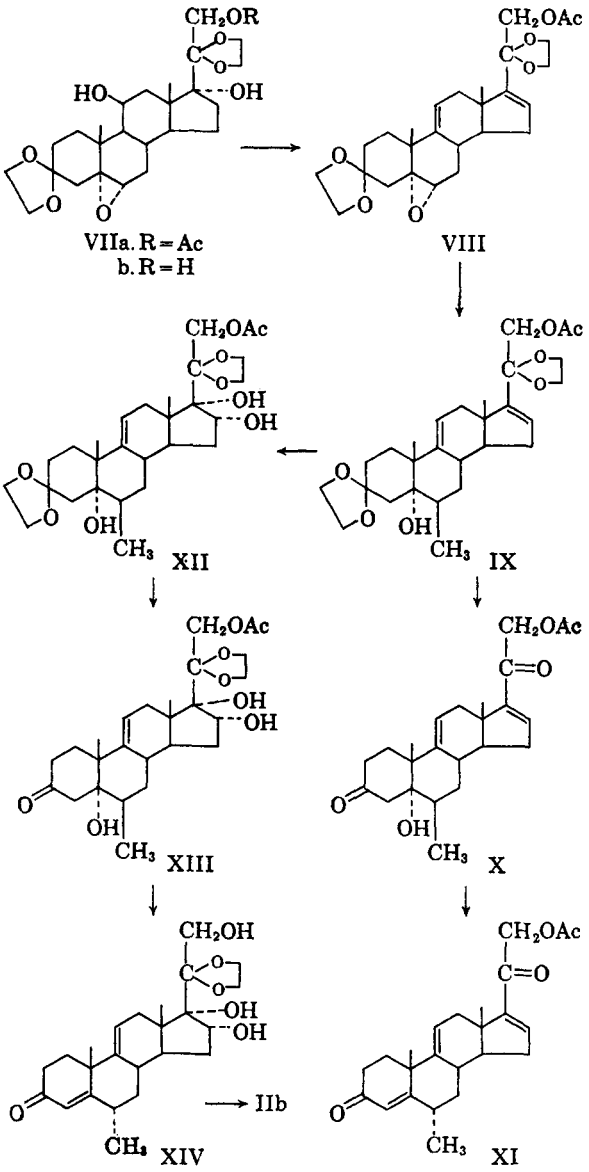
(6) R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *J. Am. Chem. Soc.*, **78**, 4956 (1956).

(7) S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.*, **77**, 2233 (1955).

(8) This compound was most conveniently prepared by mild acetylation of 3,20-bisethylenedioxy-5α,6α-epoxypregnane-11β,17α,21-triol (VIIb) first described by R. Littell and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 984 (1956).

(9) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **77**, 1028 (1955).

(10) It is interesting to note that the 5α,6α-epoxy function was not disturbed by the dehydration conditions, as it is well known that pyridine hydrochloride will cleave a 5,6-epoxide (P. N. Chakravorty and R. H. Levin, *J. Am. Chem. Soc.*, **64**, 2317(1942)). Very likely the lower temperature utilized in our procedure is the pertinent factor involved.



tractable oil. The protective ketal groups were then removed by refluxing 70% acetic acid[9] to form 21-acetoxy-5α-hydroxy-6β-methyl-9(11),16-pregnadiene-3,20-dione (X). The latter compound was dehydrated with hydrogen chloride to give 21-acetoxy-6α-methyl-4,9(11),16-pregnatriene-3,20-dione (XI).[11] Unfortunately, the intensity of the ultraviolet absorption spectrum of XI could not be brought to a satisfactorily high value, although the infrared spectrum appeared as expected. Osmylation[14] of the triene XI to form a 16α,17α-diol did not proceed well so that a somewhat different order of steps was attempted.

The bisethylene ketal alcohol IX was treated with osmic acid[14] in benzene and pyridine to form 21-acetoxy-3,20-bisethylenedioxy-6β-methyl-9(11)-pregnene-5α,16α,17α-triol (XII). Preferential removal of the C3 ketal group of XII with dilute acetic acid[2,15] afforded the 3-ketotriol 20-ketal XIII which was simultaneously saponified, dehydrated and epimerized with dilute alkali[2,12,16] to give 20-ethylenedioxy-16α,17α,21-trihydroxy-6α-methyl-4,9(11)-pregnadien-3-one (XIV). Removal of the C20 ketal group of XIV gave the 3,20-dione IIb which was acetylated to the 16α,21-diacetate IIa identical in all respects to the sample of IIa described in the previous synthesis, thus effecting a tie-in to the above described preparation of IIIc.

The synthesis of the Δ^1-analog of IIIc was accomplished by a procedure identical with the first pathway described above. Treatment of 16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (Ib)[2] with thionyl chloride in pyridine at $-5°$ furnished 16α,21-diacetoxy-17α-hydroxy-6α-methyl-1,4,9(11)-pregnatriene-3,20-dione (IIc). Addition of the elements of hypobromous acid to the triene IIc afforded 16α,21-diacetoxy-9α-bromo-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (IIId). The latter compound could not be obtained analytically pure and further recrystallization only caused decomposition. The bromohydrin IIId was cyclized in the previously described manner to the 9β,11β-epoxide IVb which was cleaved with hydrogen fluoride to 16α-21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (IIIe). This diacetate IIIe was readily saponified to 9α-fluoro-11β,16α,17α,21-tetrahydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (6α-methyltriamcinolone) (IIIf). Neither compound IIIe nor IIIf could be brought to completely satisfactory analysis. Some form of solvation seemed to be occurring in both instances.

The fluorohydrin diacetate IIIe was oxidized with chromium trioxide–pyridine to 9α-fluoro-16α-hydroxy-6α-methylprednisone 16,21-diacetate (Vb). The fluorohydrin tetrol IIIf was treated in the usual manner with acetone–perchloric acid to give 9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-6α-methyl-1,4-pregnadiene-3,20-dione (VIb), which was easily converted to the 21-acetate VIc.

Bioassays.[17] In Table I are given the biological activities of the 9α-fluoro-16α-hydroxy-6α-methyl steroids described above. Liver glycogen deposition

(11) The 6α-methyl configuration was assumed from previous references[12, 13] wherein this dehydration condition was described in similar systems.

(12) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, 78, 8213 (1956).

(13) M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957).

(14) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, 78, 1909 (1956).

(15) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, 18, 70 (1953); R. Antonucci, S. Bernstein, and R. H. Lenhard, *J. Am. Chem. Soc.*, 76, 2956 (1954); S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, *J. Am. Chem. Soc.*, 81, 1696 (1959).

(16) G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

(L.G.) and thymus involution were measured in the adrenalectomized immature male rat with hydrocortisone as the standard (F = 1) (weight basis). None of the compounds in the electrolyte assay displayed any sodium-retaining properties at the dose levels studied.

TABLE I

BIOLOGICAL ACTIVITIES

Compound	Glucocorticoid Activity (L.G. assay F = 1)	Thymus Involution Activity (F = 1)
9α-Fluoro-16α-hydroxy-6α-methylhydrocortisone		
Free steroid (IIIc)	3	4
16,17-Acetonide (VIa)	15	29
6α-Methyltriamcinolone		
Free steroid (IIIf)	5	6
16,21-Diacetate (IIIe)	7	7
16,17-Acetonide (VIb)	29	88
9α-Fluoro-16α-hydroxy-6α-methylprednisone		
16,21-Diacetate (Vb)	3	1

EXPERIMENTAL

All melting points are uncorrected. The ultraviolet spectra were determined in methanol unless indicated otherwise; the infrared spectra were determined in a potassium bromide disk. The petroleum ether used (unless otherwise noted) had a b.p. of 60–70° (Skellysolve B).

16α,21-Diacetoxy-17α-hydroxy-6α-methyl-4,9(11)-pregnadiene-3,20-dione (IIa). *A.* To a solution of 5.0 g. of 16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (Ia) in 100 ml. of pyridine cooled to −5° was added dropwise 7.4 ml. of thionyl chloride. The solution was kept at −5° for 10 min., then diluted with water, and extracted with chloroform. The combined extracts were washed with saturated aqueous sodium bicarbonate solution and with saline solution. The washed extracts were dried with magnesium sulfate and evaporated under reduced pressure. The residual gum was partitioned on a Celite[18] column using the system 8-parts petroleum ether (b.p. 90–100°), 2 parts-ethyl acetate, 3 parts-methanol, and 2 parts-water.[19] Hold-back volumes four, five, and six were evaporated under reduced pressure and the residue crystallized from acetone–petroleum ether (b.p. 90–100°) to yield 1.95 g. (40%) of white crystals, m.p. 200–203°. One recrystallization from the same solvent pair raised the melting point to 202.5–203°, λ_{max} 240 mμ (ε 16,600); ν_{max} 3400, 1740, 1665, 1600, 1230 cm.$^{-1}$ $[\alpha]_D^{25}$ +10° (chloroform).

Anal. Calcd. for $C_{26}H_{34}O_7$ (458.53): C, 68.10; H, 7.47. Found: C, 68.02; H, 7.74.

B. To a solution of 200 mg. of the triol IIb in 3 ml. of pyridine, was added 0.3 ml. of acetic anhydride and the reaction mixture was heated on the steam bath for 1 hr. Methanol was added and the solution was evaporated to give an oil which solidified on treatment with acetone. Two crystallizations from acetone-petroleum ether yielded 140 mg., m.p. 201.5–203.5°; mixed melting point determination with the diacetate prepared in *A* above gave no depression. The infrared spectra of the two samples were identical.

9α-Bromo-16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (IIIa). A solution of 1.91 g. of 16α,21-diacetoxy-17α-hydroxy-6α-methyl-4,9(11)-pregnadiene-3,20-dione (IIa) in 38 ml. of peroxide-free dioxane and 7.8 ml. of water was stirred in a 20° bath while 1.13 g. of *N*-bromoacetamide and 3.4 ml. of 10% perchloric acid were added. The solution was stirred for 15 min., then quenched with an excess of 10% sodium sulfite solution. The solution was diluted with 20 ml. of water and extracted with three 50-ml. portions of chloroform. The combined extracts were washed with saturated sodium bicarbonate solution and with saline solution. The organic solution was dried with magnesium sulfate and evaporated under reduced pressure at a bath temperature of 45–50°.

The residual glass was dissolved in a minimal amount (40 ml.) of acetone without heating and the solution brought to turbidity with petroleum ether (b.p. 90–100°) (140 ml.). The solution was aged at 5° for 18 hr. and produced 1.89 g. (81%) of white crystals, m.p. 149–150° dec. A 100-mg. sample was recrystallized from acetone–petroleum ether (b.p. 90–100°) to yield 50 mg. of white needles, m.p. 158–159° dec. (dried for 1 hr. under reduced pressure at room temperature); λ_{max} 242 mμ (ε 14,700); ν_{max} 3410, 1740, 1720, 1665, 1605, 1230 cm.$^{-1}$; $[\alpha]_D^{25}$ + 78° (chloroform).

Anal. Calcd. for $C_{26}H_{35}O_8Br$ (555.45): C, 56.22; H, 6.35; Br, 14.39. Found: C, 57.40; H, 7.11; Br, 13.61.

16α,21-Diacetoxy-9β,11β-epoxy-17α-hydroxy-6α-methyl-4-pregnene-3,20-dione (IVα). To a solution of 1.80 g. of 9α-bromo-16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (IIIa) in 100 ml. of absolute ethanol was added 1.8 g. of anhydrous potassium acetate. The solution was refluxed for 18 hr. and then evaporated under reduced pressure. The residual solid was dissolved in a mixture of ethyl acetate and water. The organic layer was separated, washed with saline solution, dried with magnesium sulfate, and evaporated under reduced pressure. The residual gum was dissolved in 18 ml. of pyridine and 6 ml. of acetic anhydride added. The solution was allowed to stand at room temperature for 18 hr., then evaporated several times with methanol under reduced pressure. The residual gum was crystallized from 20 ml. of methanol to yield 900 mg. of yellow needles, m.p. 124–125°. One recrystallization from methanol gave 750 mg. of white crystals, m.p. 201–202°. Further recrystallization did not change the m.p.; λ_{max} 242 mμ (ε 15,200); ν_{max} 3500, 1750, 1675, 1620, 1235 cm.$^{-1}$; $[\alpha]_D^{25}$ −26° (chloroform).

Anal. Calcd. for $C_{26}H_{34}O_8$ (474.53): C, 65.80; H, 7.22. Found: C, 66.03; H, 7.61.

16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (IIIb). A solution of 500 mg. of 16α,21-diacetoxy-9β,11β-epoxy-17α-hydroxy-6α-methyl-4-pregnene-3,20-dione (IVa) in 10 ml. of methylene chloride at −60° was added to a solution of 2.0 ml. of hydrogen fluoride, 4.3 ml. of tetrahydrofuran, and 1.5 ml. of methylene chloride at −60°. The solution was allowed to stand at −5° for 4 hr. and then poured slowly into a mixture of 75 ml. of saturated aqueous sodium bicarbonate and 25 ml. of methylene chloride. The organic layer was separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and with water, dried with magnesium sulfate and evaporated. The residue was crystallized from acetone-petroleum ether (b.p. 90–100°) to yield 340 mg. of white crystals, m.p. 154–155°. One recrystallization from the same solvent pair gave 244 mg. of white needles, m.p. 233–234°. Further recrystallization did not raise the

(17) The assays were done by I. Ringler, S. Mauer, E. Heyder, and J. Perrine of the Experimental Therapeutics Section of these laboratories. The procedures employed were essentially those described by S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 1696 (1959).

(18) Celite is Johns-Manville's registered trade-mark for diatomaceous silica products.

(19) This chromatographic technique was fully described by S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 1696 (1959).

melting point; λ_{max} 238 mμ (ε 17,400); ν_{max} 3500, 1745, 1670, 1620, 1240 cm.$^{-1}$; $[\alpha]_D^{25}$ + 58° (chloroform).

Anal. Calcd. for $C_{26}H_{35}O_5F$ (494.54): C, 63.14; H, 7.13; F, 3.84. Found: C, 63.37; H, 7.50; F, 3.68.

9α-Fluoro-11β,16α,17α,21-tetrahydroxy-6α-methyl-4-pregnene-3,20-dione (IIIc). A solution of 200 mg. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (IIIb) in 23 ml. of methanol in a nitrogen atmosphere was treated with 0.6 ml. of 10% potassium carbonate at 25° for 20 min. Acetic acid (0.23 ml.) was added and the volume of the solution was reduced to about 5 ml. by concentration under reduced pressure at a bath temperature of 40°. To the remaining solution was added slowly with stirring 40 ml. of ice water and the resultant white crystals were collected and washed with water to yield 128 mg. (75%), m.p. 218–220°. Recrystallization from acetone–petroleum ether (b.p. 90–100°) raised the melting point to 229–230°. λ_{max} 240 mμ (ε 16,800); ν_{max} 3400, 1710, 1665, 1615 cm.$^{-1}$; $[\alpha]_D^{25}$ + 86° (methanol).

Anal. Calcd. for $C_{22}H_{31}O_6F$ (410.47): C, 64.38; H, 7.61; F, 4.63. Found: C, 64.72; H, 7.96; F, 4.51.

16α,21-Diacetoxy-9α-fluoro-17α-hydroxy-6α-methyl-4-pregnene-3,11,20-trione (Va). A solution of 80 mg. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methyl-4-pregnene-3,20-dione (IIIb) in 2.0 ml. of pyridine was added to a slurry prepared by adding 0.8 ml. of pyridine to 60 mg. of chromic anhydride. The mixture was shaken vigorously and then allowed to stand at room temperature for 18 hr. The mixture was diluted with 20 ml. of water and filtered. The residual brown solid was extracted several times with hot ethyl acetate and the combined extracts washed with saline, dried with magnesium sulfate, and evaporated under reduced pressure. The residual glass was crystallized from acetone–petroleum ether (b.p. 90–100°) to yield 40 mg. of white needles, m.p. 244–246°. Recrystallization from the same solvent pair raised the m.p. to 246–247°; λ_{max} 235 mμ (ε 16,500); ν_{max} 3410, 1740, 1670, 1610, 1235 cm.$^{-1}$; $[\alpha]_D^{25}$ + 80° (chloroform).

Anal. Calcd. for $C_{26}H_{33}O_6F$ (492.52); C, 63.40; H, 6.75; F, 3.86. Found: C, 63.65; H, 6.97; F, 3.86.

9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-6α-methyl-4-pregnene-3,20-dione (VIa). To a suspension of 76 mg. of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-6α-methyl-4-pregnene-3,20-dione (IIIc) in 4 ml. of acetone was added 8λ of 72% perchloric acid. Solution was complete after 10 min. stirring. The reaction was allowed to stand at room temperature for 2 hr. and then treated with 2 ml. of water and 0.15 ml. of saturated aqueous sodium bicarbonate solution. Evaporation of the acetone and addition of 10 ml. of saturated saline solution produced a white solid which was collected and washed with water to yield 66.5 mg. of white crystals, m.p. 219–221°. One recrystallization from acetone-petroleum ether (b.p. 90–100°) raised the melting point to 223–227° at which point it remained constant during several further recrystallizations; λ_{max} 238 mμ (ε 16,100); ν_{max} 3450, 1725, 1675, 1620 cm.$^{-1}$; $[\alpha]_D^{25}$ + 125° (chloroform).

Anal. Calcd. for $C_{25}H_{35}O_6F$ (450.53): C, 66.64; H, 7.83; F, 4.22. Found: C, 66.84; H, 8.07; F, 4.08.

21-Acetoxy-3,20-bisethylenedioxy-9(11),16-pregnadien-5α,6α-oxide (VIII). To a solution of 0.40 g. of 21-acetoxy-3,20-bisethylenedioxy-5α,6α-epoxypregnane-11β,17α-diol (VIIa) in 25 ml. of pyridine, cooled to −5°, was added 0.5 ml. of thionyl chloride dropwise and the reaction mixture was kept at −5° for 24 hr. The solution was then poured into water and extracted several times with ethyl acetate. The combined extracts were washed with water until neutral, dried over magnesium sulfate, and evaporated to give an oil which solidified on treatment with acetone. Three crystallizations from acetone-petroleum ether gave 170 mg., m.p. 127–129°; ν_{max} 1748, 1240, 1050 cm.$^{-1}$; $[\alpha]_D^{25}$ −29° (chloroform).

Anal. Calcd. for $C_{27}H_{36}O_7$ (472.56): C, 68.62; H, 7.68. Found: C, 69.04; H, 8.02.

21-Acetoxy-3,20-bisethylenedioxy-6β-methyl-9(11),16-pregnadien-5α-ol (IX). To a solution of 35 ml. of 3*M* ethereal methylmagnesium bromide in 40 ml. of tetrahydrofuran, in a nitrogen atmosphere, was added a solution of 1.0 g. of the 5α,6α-epoxide VIII in 60 ml. of tetrahydrofuran. The reaction mixture was refluxed for 18 hr., cooled to room temperature, and saturated ammonium chloride solution (20 ml.) was added cautiously. The mixture was filtered and the filter cake was washed thoroughly with hot tetrahydrofuran. The combined filtrates were evaporated; the residue was dissolved in ethyl acetate and washed several times with water, dried over magnesium sulfate, and evaporated to give 1.12 g. of oil which was treated with acetic anhydride in pyridine overnight at room temperature. Evaporation of the acetylation mixture gave an oil which was dissolved in 1:1 benzene–petroleum ether and chromatographed on 25 g. of silica gel. Elution with 4:1 benzene-ether gave 0.38 g. of oil which could not be made to crystallize. The infrared spectrum of this oil was consistent with the proposed product.

21-Acetoxy-5α-hydroxy-6β-methyl-9(11),16-pregnadiene-3,20-dione (X). A solution of 0.38 g. of 21-acetoxy-3,20-bis-ethylenedioxy-6β-methyl-9(11),16-pregnadien-5α-ol (IX) in 25 ml. of 70% acetic acid was heated on the steam bath for 40 min. Addition of water gave a solid which was cooled, filtered, and washed with water to yield 0.19 g., m.p. 182–185°. Two crystallizations from acetone-petroleum ether gave 0.10 g., m.p. 185–187°; $\lambda_{max}^{abs.\ alc.}$ 240 mμ (ε 7700); ν_{max} 3420, 1743, 1712, 1688, 1588 cm.$^{-1}$; $[\alpha]_D^{25}$ + 83° (chloroform); positive blue tetrazolium color test.

Anal. Calcd. for $C_{24}H_{32}O_5$ (400.50): C, 71.97; H, 8.05. Found: C, 71.83; H, 8.23.

21-Acetoxy-6α-methyl-4,9(11),16-pregnatriene-3,20-dione (XI). Dry hydrogen chloride gas was passed through a solution of 200 mg. of X in 90 ml. of methylene chloride a 0° for 3 hr. The solution was then washed with sodium bicarbonate and water until neutral, dried and evaporated to give an oil which solidified on treatment with acetone. Three crystallizations from acetone–petroleum ether and one from ether gave 50 mg., m.p. 136–160°; $\lambda_{max}^{abs.\ alc.}$ 238 mμ (ε 15,200).

The mother liquors were combined with the solid and evaporated and the total residue was partitioned on a Celite[18] column using the system 7 parts petroleum ether (b.p. 90–100°), 2 parts ethyl acetate, 3 parts methanol, and 2 parts water. Hold-back volume one was evaporated to give a solid which was recrystallized from methanol-water to yield 50 mg., m.p. 145–149°; $\lambda_{max}^{abs.\ alc.}$ 238 mμ (ε 18,600); ν_{max} 1751, 1683, 1618, 1599 cm.$^{-1}$

21-Acetoxy-3,20-bisethylenedioxy-6β-methyl-9(11)-pregnene-5α,16α,17α-triol (XII). To a solution of 1.0 g. of the diene bisketal IX in 75 ml. of benzene and 0.7 ml. of pyridine was added a solution of 1.0 g. of osmium tetroxide in 17 ml. of benzene. The reaction mixture was stirred for 45 min. at which time there was added 45 ml. of methanol and 90 ml. of an aqueous solution containing 7.5 g. of potassium bicarbonate and 7.5 g. of sodium sulfite. This mixture was stirred vigorously for 3 hr., chloroform (150 ml.) was added, and the stirring continued for an additional 0.5 hr. The suspension was filtered and the cake was washed thoroughly with chloroform. The aqueous phase was drawn off and extracted several times with chloroform. The combined extracts were washed until neutral with water, dried, and evaporated to give 1.4 g. of brown oil which was chromatographed on 50 g. of Florisil.[20] Elution with petroleum ether–16% acetone gave 0.88 g. of oil which solidified on treatment with acetone. Four crystallizations from acetone–petroleum ether yielded 0.16 g., m.p. 216–217°; ν_{max} 3490, 1740 cm.$^{-1}$; $[\alpha]_D^{25}$ −32.5° (chloroform).

Anal. Calcd. for $C_{28}H_{42}O_9$ (522.62): C, 64.35; H, 8.10. Found: C, 64.17; H, 8.31.

In another run, 9.0 g. of starting material gave 5.5 g. of product, m.p. 214–216°, without chromatography.

(20) Florisil is the Floridin Company's registered trademark for a synthetic magnesium silicate.

21-Acetoxy-20-ethylenedioxy-5α,16α,17α-trihydroxy-6β-methyl-9(11)-pregnen-3-one (XIII). A solution of 1.0 g. of the bisketal XII in 50 ml. of acetic acid was heated on the steam bath for 40 min. Water was added, followed by sodium bicarbonate until the solution was just slightly acid. The mixture was then extracted with ethyl acetate; the combined extracts were washed with water until neutral, dried, and evaporated to yield a solid. Four crystallizations from acetone–petroleum ether afforded 0.42 g.; m.p. 218–220°; ν_{max} 3430, 1731, 1711 cm.$^{-1}$; $[\alpha]_D^{25}$ −16° (chloroform).

Anal. Calcd. for $C_{26}H_{38}O_8$ (478.56): C, 65.25; H, 8.00. Found: C, 65.21; H, 8.25.

In a later run, 3.4 g. of product, m.p. 216–219°, was obtained from 4.5 g. of starting material upon addition of water to the reaction mixture.

20-Ethylenedioxy-16α,17α,21-trihydroxy-6α-methyl-4,9(11)-pregnadiene-3-one (XIV). To a solution of 0.50 g. of XIII in 20 ml. of methanol, previously flushed with nitrogen, was added 2 ml. of 2.5% methanolic potassium hydroxide. The reaction mixture was refluxed for 1 hr., cooled, and neutralized with acetic acid. Addition of water yielded 0.41 g., m.p. 247–250°. Two crystallizations from acetone–petroleum ether did not change the melting point; λ_{max} 241 mμ (ε 17,100); ν_{max} 3400, 1669, 1611 cm.$^{-1}$; $[\alpha]_D^{25}$ + 25° (chloroform).

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 69.04; H, 8.50.

16α,17α,21-Trihydroxy-6α-methyl-4,9(11)-pregnadiene-3,20-dione (IIb). To a suspension of 2.45 g. of the 20-ketal XIV in 150 ml. of methanol, was added 25 ml. of 8% (v./v.) aqueous sulfuric acid. The mixture was refluxed for 1 hr. (complete solution occurred in 10 min.) and evaporated under reduced pressure until solid formed. Water was added; the mixture was cooled and filtered to give 1.75 g. of solid. Two crystallizations from acetone-petroleum ether gave 0.76 g.; m.p. 210–215°; λ_{max} 240 mμ (15,300); ν_{max} 3330, 1719, 1660, 1603 cm.$^{-1}$; $[\alpha]_D^{25}$ + 45° (chloroform).

Anal. Calcd. for $C_{22}H_{30}O_5$ (374.46): C, 70.56; H, 8.08. Found: C, 70.74; H, 8.35.

16α,21-Diacetoxy-17α-hydroxy-6α-methyl-1,4,9(11)-pregnatriene-3,20-dione (IIc). To a solution of 112 mg. of 16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,-20-dione (Ib) in 5.0 cc. of pyridine cooled to −5° was added 0.25 cc. of thionyl chloride. The solution was kept at −5° for 1 hr., then diluted with water, and extracted several times with chloroform. The combined extracts were washed with saturated aqueous sodium bicarbonate solution and with saline solution. The washed extracts were dried with magnesium sulfate and evaporated under reduced pressure. The residual white glass was partitioned on a Celite[18] column using the system 6 parts petroleum ether (b.p. 90–100°), 3 parts ethyl acetate, 3 parts methanol, and 2 parts water. The first half of hold-back volume two was evaporated under reduced pressure and the residue crystallized from acetone-water to yield 41 mg. of amorphous white solid. Recrystallization from acetone-water gave 29 mg. of white needles, m.p. 129–131°. One recrystallization from acetone–petroleum ether raised the melting to 214–217°. Three more recrystallizations gave 17.7 mg. of white plates, m.p. 224–225°; λ_{max} 239 mμ (ε 16,500); ν_{max} 3450, 1760, 1670, 1630, 1240 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{32}O_7$ (456.52): C, 68.40; H, 7.07. Found: C, 68.17; H, 7.43.

In a subsequent experiment, 7.8 g. of Ib in 155 cc. of pyridine was treated with 11.5 cc. of thionyl chloride for 10 min. to give 4.74 g. (63%) of triene IIc, m.p. 222–226°.

9α-Bromo-16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (IIId). A solution of 20.3 g. of 16α,21-diacetoxy-17α-hydroxy-6α-methyl-1,4,9(11)-pregnatriene-3,20-dione (IIc) in 406 cc. of peroxide-free dioxane and 83 cc. of water was stirred in a 20° bath while 12.2 g. of *N*-bromoacetamide and 36.2 cc. of 10% perchloric acid were added. The solution was stirred for 15 min. and then quenched with excess 10% sodium sulfite solution. The solution was diluted with 200 cc. of water and extracted with three 500-cc. portions of chloroform. The combined extracts were washed with saturated sodium bicarbonate solution and with saline solution. The organic solution was dried with magnesium sulfate and evaporated under reduced pressure at a bath temperature of 45–50°.

The white solid residue was dissolved in a minimal amount (1700 cc.) of acetone without heating and the solution brought to turbidity with petroleum ether (5050 cc.). The solution was aged at 5° for 18 hr. and produced 18.8 g. (77%) of white crystals, m.p. 176–178° dec. This material was dried for 90 min. under reduced pressure at room temperature; λ_{max} 242 mμ (ε 13,000); ν_{max} 3410, 1745, 1725, 1662, 1620, 1235 cm.$^{-1}$; $[\alpha]_D^{25}$ + 45° (chloroform).

Anal. Calcd. for $C_{26}H_{33}O_8Br$ (553.44): C, 56.42; H, 6.01; Br, 14.44. Found: C, 57.00; H, 6.84; Br, 13.71.

16α,21-Diacetoxy-9β,11β-epoxy-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (IVb). To a solution of 330 mg. of 9α-bromo-16α,21-diacetoxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (IIId) in 13.5 cc. of peroxide-free dioxane was added a solution of 350 mg. of anhydrous potassium acetate in 7.5 cc. of absolute ethanol. The solution was refluxed for 75 min. The solution was cooled, diluted with water, and extracted several times with chloroform. The combined extracts were dried with magnesium sulfate and evaporated under reduced pressure. The residual gum was dissolved in 5 cc. of pyridine and treated with 0.5 cc. of acetic anhydride for 18 hr. at room temperature. The reaction mixture was diluted with water and stirred for 30 min., then extracted several times with chloroform. The combined extracts were washed with saturated sodium bicarbonate solution, dried with magnesium sulfate, and evaporated under reduced pressure to give 266 mg. of gum. The gum was partitioned on a Celite[18] column using the system 8 parts petroleum ether (b.p. 90–100°), 3 parts ethyl acetate, 3 parts methanol, and 2 parts water. The end part of hold-back volume two and the first half of three were evaporated to give a white solid which was crystallized from acetone-petroleum ether yielding 109 mg. of white needles, m.p. 188–189°. Two recrystallizations from the same solvent pair gave; 74 mg.; m.p. 189–190°; λ_{max} 248 mμ (ε 16,700); ν_{max} 3400, 1750, 1660, 1620, 1232 cm.$^{-1}$; $[\alpha]_D^{25}$ −15° (chloroform).

Anal. Calcd. for $C_{26}H_{32}O_8$ (472.52): C, 66.08; H, 6.83. Found: C, 65.78; H, 6.98.

A larger preparation (18.8 g. of bromohydrin IIId) was refluxed for 20 hr. in absolute ethanol with anhydrous potassium acetate and gave 8.78 g. (55%) of epoxide IVb, m.p. 185–189°.

16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (IIIe). To a solution of 410 mg. of 9β,11-epoxide IVb in 90 cc. of methylene chloride at −60° was added a solution of 6 cc. of hydrogen fluoride in 12 cc. of tetrahydrofuran at −60°. The solution was allowed to stand at −5° for 19 hr. and then poured slowly into a mixture of 300 cc. of saturated aqueous sodium bicarbonate and 300 cc. of methylene chloride. The organic layer was separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and with water, dried with magnesium sulfate, and evaporated. The residue, crystallized from acetone-petroleum ether, yielded 124 mg. of white plates, m.p. 243–244°.

A sample of this material was recrystallized twice from acetone–petroleum ether without changing the melting point; λ_{max} 240 mμ (ε 14,800); ν_{max} 3420, 1750, 1735, 1660, 1615, 1235 cm.$^{-1}$; $[\alpha]_D^{25}$ + 4° (chloroform).

Anal. Calcd. for $C_{26}H_{33}O_8F$ (492.52): C, 63.40; H, 6.75; F, 3.86. Found: C, 63.43; H, 7.52; F, 3.70.

Chromatography of the mother liquors on silica gel yielded 128 mg. of recovered 9β,11-epoxide IVb.

In a larger run (4.88 g. of 9β,11-epoxide IVb) the reaction time was reduced to 3.5 hr. and the ratio of tetrahydrofuran (17 cc.) to hydrogen fluoride (13.8 cc.) was reduced. The

yield of fluorohydrin IIIe was increased to 55%, and 28% of 9β,11-epoxide IVb was recovered.

9α-Fluoro-11β,16α,17α,21-tetrahydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (IIIf). A solution of 4.10 g. of diacetate IIIe in 465 cc. of methanol in a nitrogen atmosphere was treated with 12.0 cc. of 10% potassium carbonate at 25° for 20 min. Acetic acid (4.56 cc.) was added and volume of solution was reduced to about 100 cc. by concentration under reduced pressure at a bath temperature of 40°. To the remaining solution was added slowly with stirring 800 cc. of ice water and the resultant white crystals were filtered and washed with water to yield 2.95 g. (87%), m.p. 229–231°. One recrystallization from acetone–petroleum ether raised the melting point to 252–253° (further recrystallizations gave inconsistent melting points); λ_{max} 239 mμ (ε 15,100); ν_{max} 3380, 1710, 1660, 1618 cm.$^{-1}$; $[\alpha]_D^{25}$ + 57° (methanol).

Anal. Calcd. for $C_{22}H_{29}O_6F \cdot 1/2H_2O$ (417.46): C, 63.29; H, 7.24; F, 4.55; O, 24.91; H_2O, 2.16. Found: C, 63.36; H, 7.35; F, 4.55; O, 24.18; H_2O, 1.15.

16α,21-Diacetoxy-9α-fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11,20-trione (Vb). A solution of 250 mg. of fluorohydrin IIIe in 6 cc. of pyridine was added to a slurry prepared by adding 2.5 cc. of pyridine to 188 mg. of chromic anhydride. The mixture was shaken vigorously and allowed to stand at room temperature for 18 hr. The mixture was diluted with 50 cc. of water and filtered. The residual brown solid was extracted several times with hot ethyl acetate and the combined extracts evaporated to a white solid under reduced pressure. Crystallization of the solid from acetone–petroleum ether yielded 170 mg. (68%) of white needles, m.p. 247–249°. Two recrystallizations from acetone-petroleum ether raised the melting point to 249–250°; λ_{max} 235 mμ (ε 14,800); ν_{max} 3325, 1730, 1665, 1620, 1610 (shoulder), 1230 cm.$^{-1}$; $[\alpha]_D^{25}$ + 59° (chloroform).

Anal. Calcd. for $C_{26}H_{31}O_8F$ (490.51): C, 63.66; H, 6.37; F, 3.87. Found: C, 63.95; H, 6.53; F, 4.10.

9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-6α-methyl-1,4-pregnadiene-3,20-dione (VIb). To a suspension of 1.36 g. of tetrol IIIf in 68 cc. of acetone was added 0.138 cc. of 72% perchloric acid. Solution became complete after 10 min. of stirring. The reaction was allowed to stand at room temperature for 2 hr. and then treated with 35 cc. of water and 2.72 cc. of saturated aqueous sodium bicarbonate solution. Evaporation of the acetone gave a white solid which was filtered and washed with water to yield 1.41 g. (95%) of white crystals, m.p. 259–262°. A sample of this material was recrystallized four times from acetone-petroleum ether to give pure VIb, m.p. 258–260° dec., λ_{max} 240 mμ (ε 15,400); ν_{max} 3400, 1715, 1665, 1625, 1610 (shoulder) cm.$^{-1}$; $[\alpha]_D^{25}$ + 98.5° (chloroform).

Anal. Calcd. for $C_{25}H_{33}O_6F$ (448.51): C, 66.94; H, 7.42; F, 4.24. Found: C, 67.18; H, 7.56; F, 4.59.

21-Acetoxy-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-6α-methyl-1,4-pregnadiene-3,20-dione (VIc). To a suspension of 160 mg. of acetonide VIb in 7 cc. of pyridine was added 0.5 cc. of acetic anhydride. The mixture was heated on the steam-bath for 1 hr., solution being complete after several minutes. The solution was diluted with methanol and evaporated under reduced pressure. The residue was evaporated several times with toluene and the white solid residue crystallized from acetone–petroleum ether to yield 110 mg. of white needles, m.p. 307–308° dec. A second crop from the mother liquor was obtained 35 mg., m.p. 301–302° dec.

The first crop material was recrystallized twice from acetone–petroleum ether without changing the melting point; λ_{max} 238 mμ (ε 15,800); ν_{max} 3300, 1750, 1725, 1660, 1610, 1230 cm.$^{-1}$; $[\alpha]_D^{25}$ + 83° (chloroform).

Anal. Calcd. for $C_{27}H_{35}O_7F$ (490.55): C, 66.10; H, 7.19; F, 3.87. Found: C, 66.15; H, 7.31; F, 4.05.

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[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA]

Investigations on Steroids. XXXII. Preparation of 14β,19-Dihydroxycortexone[1]

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By ozonolysis, strophanthidol (I) was converted into 3β,5,14,19,21-pentahydroxy-5β,14β-pregnan-20-one (IV), which in turn, by way of 5,14,19,21-tetrahydroxy-5β,14β-pregnane-3,20-dione (VIII), was transformed into 14β,19-dihydroxycortexone (IX) and its 19,21-diacetate (X). Data concerning the molecular rotation of X have been discussed. The rotatory dispersion curves of some pertinent compounds are recorded.

The syntheses of 19-hydroxy and 19-oxo analogs of a number of steroid hormones have been described by this laboratory.[2-7] During the course of these investigations it became desirable to prepare 14β,19-dihydroxycortexone[8] (IX) for the purpose of subjecting it to microbiological hydroxylation. The work on the synthesis and characterization of IX was concluded in May 1958. As the hydroxyla-

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