3,4-Dibenzyloxyphenylethyleneglycol (Va).—A solution of 18.0 g. (0.046 mole) of ethyl 3,4-dibenzyloxymandelate (IVa) and 200 ml. of tetrahydrofuran was added over 15 min. with stirring to a solution of 10.0 g. (0.26 mole) of lithium aluminum hydride and 400 ml. of tetrahydrofuran. The resulting mixture was stirred and refluxed for 2.5 hr., cooled, and decomposed with 14.2 ml. of water and 15 ml. of hydrochloric acid in 50 ml. of tetrahydrofuran. The suspension was refluxed for 15 min., filtered, and the cake extracted by refluxing with 100 ml. of tetrahydrofuran. The tetrahydrofuran was evaporated to give a solid, which was found to contain inorganic salts. Therefore, the material was taken up in a small amount of ethanol, acidified with a few drops of hydrochloric acid, diluted with water, and extracted with benzene. The benzene was dried over sodium sulfate and evaporated to an oil, which was covered with hexane and allowed to crystallize. There resulted 13.7 g. (85%) of Va, m.p. 63–69°. Recrystallization from benzene and hexane gave white needles, m.p. 77–79°.

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.27; H, 6.34. Infrared: 2.74 μ and 2.9 μ (OH).

3,4-Dihydroxyphenylethyleneglycol (VIa).—A mixture of 2.0 g. (0.0057 mole) of 3,4-dibenzyloxyphenylethyleneglycol (Va), 100 ml. of ethanol, 1.0 g. of 5% palladium on charcoal, and 2.8 kg./cm.^{2} of hydrogen was shaken for 3 hr. at room temperature. The catalyst was filtered, and the ethanol removed under reduced pressure. To the resulting oil was added 50 ml. of benzene and the mixture evaporated to dryness *in vacuo*. The oil was taken up in boiling ethyl acetate, charcoal treated, hexane added to the cloud point, and the mixture allowed to crystallize in the refrigerator. The pink crystalline solid was filtered, yielding 0.7 g. (72%) of VIa, m.p. 127–129°. Recrystallization from ethyl acetate and hexane with a charcoal treatment gave white needles, m.p. 128–129°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.62; H, 6.08. Ultraviolet: 204 mμ (28,900), 223 mμ (6330), and 282 mμ (3060).

Chromatography.—Thin layer [Merck silica gel G.; ethyl acetate–ethanol, 95:5; detected with 50% H_2SO_4 and heat] showed a single spot, R_f 0.78. Paper [descending; Whatman No. 1, 1-propanol–water, 70:30; detected with a dilute aqueous solution of $FeCl_3$ and $K_3Fe(CN)_6$] showed one spot, R_f 0.71.

4-Benzyloxy-3-methoxymandelonitrile Acetate (IIIb).—Following our procedure as previously described, from 24 g. (0.099 mole) of 4-benzyloxy-3-methoxybenzaldehyde[12] there was obtained 14.6 g. (47%) of 4-benzyloxy-3-methoxymandelonitrile acetate m.p. 70–71°. Recrystallization from ethanol gave a white crystalline product, m.p. 72–73°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.51; H, 5.40; N, 4.43. Infrared: 5.72 μ (C=O).

Ethyl 4-Benzyloxy-3-methoxymandelate (IVb).—The alcoholysis of 25 g. (0.08 mole) of IIIb, as reported above, yielded 17.2 g. (68%) of IVb, m.p. 120–123° (recrystallized from ethanol).

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.51; H, 6.56. Infrared: 2.80 μ (OH) and 5.80 μ (C=O).

4-Benzyloxy-3-methoxyphenylethyleneglycol (Vb).—Treatment of 14.0 g. (0.044 mole) of ethyl 4-benzyloxy-3-methoxymandelate (IVb) with lithium aluminum hydride as described previously gave 5.5 g. (47%) of Vb, m.p. 66–67° (from benzene then from a mixture of ethyl acetate and hexane).

Anal. Calcd. for $C_{16}H_{18}O_4$: C 70.05; H, 6.61; O, 23.33. Found: C, 69.73; H, 6.87; O, 23.22. Infrared: 2.74 μ and 2.89 μ (OH).

Bis-(4-hydroxy-3-methoxyphenylethyleneglycol) Piperazine Salt (VIb).—A mixture of 0.90 g. (0.0033 mole) of Vb, 0.4 g. of 5% palladium on charcoal, 200 ml. of ethanol, and 2.8 kg./cm.^{2} of hydrogen was shaken for 3 hr. at room temperature. The catalyst was removed and the ethanol evaporated *in vacuo*. To the resulting oil was added benzene and the mixture evaporated to dryness. All attempts to crystallize the oil met with failure. Therefore, the oil was dissolved in 3 ml. of ethanol, diluted with 100 ml. of benzene, and the gray solution filtered. To the clear filtrate was added 3 ml. (0.0016 mole) of a dry solution of piperazine in benzene (5 g./100 ml.), and the product crystallized by addition of 150 ml. of hexane. The white crystalline solid was filtered giving 0.7 g. (84%) of VIb, m.p. 115–116°. The product was recrystallized from benzene, m.p. 116–118°.

Anal. Calcd. for $C_{22}H_{34}N_2O_8$: C, 58.13; H, 7.54; N, 6.17. Found: C, 58.04; H, 7.30; N, 6.03. Ultraviolet: 204 mμ (34,800), 229 mμ (10,000), and 281 mμ (3850).

Chromatography.—Thin layer [Merck silica gel G.; ethyl acetate–ethanol, 95:5; detected with 50% H_2SO_4 and heat] had a single spot R_f 0.64. On the same plate were run a sample of sublimed free glycol oil, a sample of the complex which had been acidified with acetic acid, and piperazine. Each of the glycol samples indicated single spots R_f 0.64, while piperazine itself was not detected. Paper [descending; Whatman No.4, 1-propanol–water, 70:30; detected with dilute aqueous $FeCl_3$ and $K_3Fe(CN)_6$] showed one spot, R_f 0.80. Attempts to detect piperazine from the complex failed. Also run on paper were the sublimed material and the acidified complex both showing spots, R_f 0.80. A concentrated spot of piperazine on paper detected with phenolphthalein had R_f 0.48.

(12) K. W. Merz and J. Fink, *Arch. Pharm.*, **289**, 354 (1956).

The Synthesis of 15β-Fluoro Corticoids

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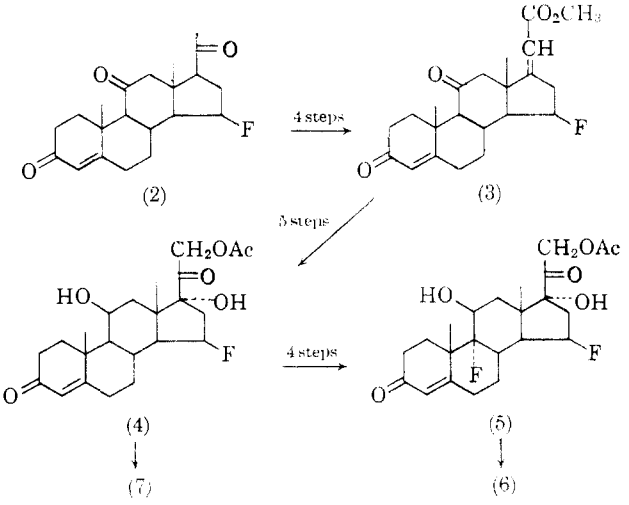
The availability of 15β-fluoropregn-4-ene-3,11,20-trione[1] (2) from the reaction of 15α-hydroxypregn-4-ene-3,11,20-trione (1) with N-(2-chloro-1,1,2-trifluoroethyl)diethylamine has made possible the synthesis of a series of 15β-fluorocortical steroids. The conversion of (2) to 15β-fluorohydrocortisone acetate (4) was achieved utilizing procedures described previously.[2] The intermediate methyl 3,11-dioxo-15β-fluoropregna-4,17(20)-[*cis*]-dien-21-oate (3) obtained from (2) by bisethoxa-



lylation, tribromination, Favorskii rearrangement, and zinc reduction was converted to the 3-cycloethylene ketal, reduced with lithium aluminum hydride, acetylated, subjected to mild acid hydrolysis, and allowed to react with N-methylmorpholine oxide–hydrogen peroxide complex in the presence of catalytic amounts of osmium tetroxide[3] to yield (4). The intermediate compounds were not rigorously purified. By

(1) D. E. Ayer, *Tetrahedron Letters*, **No. 23**, 1065 (1962).

(2) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955). For recent examples of this sequence see P. A. Diassi, J. Fried, R. M. Palmere, and E. F. Sabo, *ibid.*, **83**, 4249 (1961), and references therein.

(3) W. P. Schneider and A. R. Hanze, U. S. Pat. 2,769,823 (Nov. 6, 1956).

application of the well known sequence[4] for introducing a 9-fluoro substituent, 9α,15β-difluorohydrocortisone acetate (5) was obtained from (4). Dehydrogenation of (4) and (5) with selenium dioxide[5] gave 15β-fluoroprednisolone acetate (7) and 9α,15β-difluoroprednisolone acetate (6), respectively. Preliminary biological data are presented in Table I.[6]

TABLE I

Compoun	Antiinflammatory (XF)[a]	Sodium retention (XDCA)[b]
4	1.8 (1)	
7	10 (3)	
5	12 (8)	0.14 (5)
6	22 (16)	0.04 (4.6)

[a] F = Hydrocortisone; see ref. 7. [b] DCA = Desoxycorticosterone acetate; see ref. 8. Data in parentheses are for the corresponding compounds unsubstituted at C_{15}.

Experimental[9]

15β-Fluoropregn-4-ene-3,11,20-trione (2).—A solution of 10 g. (29 mmoles) of 15α-hydroxypregn-4-ene-3,11,20-trione (1)[10] in 300 ml. of methylene chloride was cooled to 5° with exclusion of moisture and 9 ml. (10.7 g., 56.4 mmoles) of N-(2-chloro-1,1,2-trifluoroethyl)diethylamine[11] was added. The resultant solution was allowed to stand 4.5 hr. at 5° and then poured into 150 ml. of ice water. The organic layer was separated, washed with sodium bicarbonate solution, and dried. Evaporation of the solvent left an oil which was heated several hours at 100° under a stream of nitrogen to remove N,N-diethylchlorofluoroacetamide. The residue was dissolved in methylene chloride and chromatographed on Florisil[12] (500 g.). Elution with 4 l. of 12.5% acetone–87.5% Skellysolve B[13] gave 1.98 g. of 4,14-pregnadiene-3,11,20-trione, m.p. 191–193°, identical with an authentic sample.[14] Continued elution with the same solvent mixture gave intermediate fractions containing olefin, the chlorofluoroacetate of (1) and product. Elution with 15–30% acetone in Skellysolve B and crystallization from acetone–Skellysolve B gave 4.2 g. of (2), m.p. 157–159°. Recrystallization from the same solvent mixture gave an analytical sample, m.p. 159–161°, λ_{max} 237 mμ (ε 15,100); $[\alpha]_D$ +259° ($CHCl_3$); n.m.r. 49,50 c.p.s. (C_{18}); 87 c.p.s. (C_{19}).

Anal. Calcd. for $C_{21}H_{27}FO_3$: C, 72.80, H, 7.86; F, 5.48. Found: C, 72.56; H, 7.79, F, 5.42.

15α-Hydroxypregn-4-ene-3,11,20-trione 15-Chlorofluoroacetate.—Fractional crystallizations of intermediate fractions from the above chromatogram from aqueous methanol and acetone–Skellysolve B gave an analytical sample of the chlorofluoroacetate, m.p. 182–183°; λ_{max} 237 mμ (ε 15,590), ν_{max} 1765, 1750, 1705, 1665, 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}ClFO_5$: C, 62.94; H, 6.43; Cl, 8.08; F, 4.33. Found: C, 62.90; H, 6.48; Cl, 8.12; F, 4.42.

Thin layer chromatography on silica gel (cyclohexane:ethyl acetate, 1:1) showed this sample to be a mixture of two closely related compounds, probably diastereoisomers.

Methyl 3,11-Dioxo-15β-fluoropregna-4,17(20)-[*cis*]-dien-21-oate.—Ethyl oxalate (3.8 ml., 4.08 g., 28 mmoles) was added to a stirred, warm (60°) nitrogen-purged solution of 2.42 g. (7.0 mmoles) of (2) in 50 ml. of *t*-butyl alcohol followed by 3.9 g. (17.5 mmoles) of methanolic sodium methoxide. A heavy yellow precipitate appeared immediately. Stirring was continued for 45 min., then a cold solution of 1.0 ml. (17.5 mmoles) of acetic acid and 0.85 g. of sodium acetate in 25 ml. of methanol was added yielding a neutral solution still containing yellow insoluble material. The mixture was cooled to 0° and a solution of 1.075 ml. (3.36 g., 21 mmoles) of bromine in 10 ml. of cold (−30°) methanol was added dropwise over 5 min. The solids partly dissolved. A methanolic solution of sodium methoxide (8.55 g., 38.5 mmoles) was added over 2.5 min. keeping the temperature below 15°. The pale brown reaction mixture was warmed to 25° and stirred for 1 hr., acetic acid (3 ml.) and 2.4 g. of zinc dust were added and the mixture was stirred for an additional 30 min. The reaction mixture was filtered through Celite, evaporated to a small volume, dissolved in methylene chloride, and washed with water, sodium bicarbonate solution, and water. Evaporation of the extract yielded a yellow oil that was chromatographed on 250 g. of Florisil. Elution with about 2 l. of 12.5%-acetone–87.5% Skellysolve B gave 0.157 g. of partly crystalline material. Further elution with 4 l. of the same solvent mixture gave 1.52 g. of crude (3). Two crystallizations from acetone–Skellysolve B yielded 0.58 g. of pure (3), m.p. 220–222°, λ_{max} 231 mμ (ε 32,200); n.m.r. 76,77 c.p.s. (C_{18}); 87.5 c.p.s. (C_{19}).

Anal. Calcd. for $C_{22}H_{27}FO_4$: C, 70.56; H, 7.27; F, 5.07. Found: C, 70.15, H, 7.38; F, 5.09.

15β-Fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione 21-Acetate (4).—A mixture of 2.59 g. of (3), 150 mg. of *p*-toluenesulfonic acid monohydrate, and 5 ml. of ethylene glycol in 120 ml. of benzene was heated under reflux with stirring and azeotropic separation of water for 7 hr. The mixture was cooled to 40°, 0.4 ml. of pyridine added, and, after cooling to 25°, the benzene layer was separated, washed twice with water, and dried. Evaporation of solvent *in vacuo* left 3 g. of the **3-cycloethyleneketal** of (3). A sample recrystallized from ethyl acetate–Skellysolve B had m.p. 203–205°.

A mixture of about 1 g. of lithium aluminum hydride and 75 ml. of ether was stirred at 25° for 2 hr.; a solution of 3 g. of the crude 3-cycloethyleneketal in 30 ml. of benzene was added and the resultant white suspension stirred for 1 hr. at 25°. Excess hydride was decomposed with ethyl acetate (2.5 ml.) and water (5 ml.). The mixture was filtered and the filter cake washed with ethyl acetate. Evaporation of solvent *in vacuo* gave about 3 g. of crude 11β,21-dihydroxypregna-4,17(20)-[*cis*]-dien-3-one 3-cycloethyleneketal.

The crude reduction product was dissolved in 4 ml. of pyridine and 8 ml. of acetic anhydride and allowed to stand for 18 hr. at 25°. Decomposition of excess anhydride with 150 g. of ice and water gave a somewhat gummy crystalline product which was collected and washed with water. The wet crude 21-acetate was dissolved in 100 ml. of acetone, 10 ml. of 5% sulfuric acid added, and the solution allowed to stand 20 hr. at 25°. Following addition of 40 ml. of 4% sodium bicarbonate solution, the mixture was evaporated to a small volume, extracted with methylene chloride, and the extract washed with sodium bicarbonate solution and water. Evaporation of solvent gave a white foam that was chromatographed on 250 g. of Florisil. Elution with 1.25 l. of 12.5% acetone–87.5% Skellysolve B gave 63 mg. of oils that were discarded. Further elution with 4 l. of the same solvent mixture gave 1.93 g. of partly crystalline material, m.p. 120–135°. This crude sample of **11β,21-dihydroxy-15β-fluoropregna-4,17(20)-[cis]-dien-3-one 21-acetate** was used directly in the next step without further purification.

A solution of the crude product in 106 ml. of *t*-butyl alcohol containing 0.6 ml. of pyridine, 12 mg. of osmium tetroxide, and about 12 mequiv. of N-methylmorpholine oxide hydrogen peroxide complex was allowed to stand at 25° under an atmosphere of nitrogen for 21 hr. A solution of 250 mg. of sodium hydrosulfite in 50 ml. of water was added, the mixture stirred for 30 min.,

(4) (a) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954); (b) R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(5) Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(6) We are grateful to W. E. Dulin, E. M. Glenn, and associates of our Biological Research Division for these assays.

(7) A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957).

(8) R. O. Stafford, L. E. Barnes, B. J. Bowman, and M. M. Meinzinger, *Proc. Soc. Exptl. Biol. Med.*, **89**, 371 (1955).

(9) Melting points were determined on a Fisher–Johns block; the infrared spectra were taken as Nujol mulls and ultraviolet spectra in 95% ethanol. The n.m.r. (60 Mc.) data were obtained in deuteriochloroform and are reported in c.p.s. downfield from internal tetramethylsilane standard. We wish to thank J. L. Johnson, W. A. Struck, and associates for elemental and spectral analyses and rotations and G. Slomp and F. A. MacKellar for n.m.r. data.

(10) A. Schubert, R. Siebert, and G. Langbein, German Pat. 1,067,020 (Oct. 15, 1959). We wish to thank D. R. Colingsworth, G. S. Fonken, and co-workers for supplies of (1) used in the course of this work.

(11) The procedure of R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, Jr., *J. Am. Chem. Soc.*, **72**, 3646 (1950), was modified to moderate the exothermic reaction. Trifluorochloroethylene was condensed at −40° in a pressure tube and diluted with an equal volume of methylene chloride prior to addition of diethylamine. The tube was sealed and allowed to stand for 48 hr. at 25°.

(12) Activated magnesium silicate, Floridin Co., Tallahassee, Florida.

(13) Petroleum ether fraction, b.p. 60–68°.

(14) P. F. Beal and R. W. Jackson, U.S. Pat. 3,021,327 (Feb. 13, 1962).

evaporated to a small volume, and extracted with ethyl acetate. The extract was washed with water, sodium bicarbonate solution, water, dried over magnesium sulfate, and evaporated to 2.05 g. of a foam that was chromatographed on Florisil (200 g.). Elution with 5.2 l. of 12.5% acetone–87.5% Skellysolve B gave 0.39 g. of oils. Further elution with 2 l. each of 15% acetone–85% Skellylsolve and 20% acetone–80% Skellyslolve B gave 0.90 g. of a gelatinous precipitate. Crystallization of the latter from methanol-water (1:2) gave 0.63 g. of (4), m.p. 206–208° dec. The analytical sample had m.p. 210–211° dec. from methanol-water; λ_{max} 241 mμ (ε 16,100).

Anal. Calcd. for $C_{23}H_{31}FO_6 \cdot 0.25H_2O$: C, 64.69; H, 7.44; F, 4.45. Found: C, 64.54; H, 7.68; F, 4.41.

9α,15β-Difluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione 21-Acetate (5).—N-Bromoacetamide (0.38 g.) was added to a solution of 0.7 g. (1.65 mmoles) of (4) in 15 ml. of pyridine. The mixture was stirred under an atmosphere of nitrogen for 20 min. at 25°, cooled to 10° in an ice bath, and sulfur dioxide was introduced over the surface for 15 min.[15] The temperature rose rapidly to 20°, then dropped gradually to 10°. The reaction mixture was diluted to 250 ml. with ice water yielding a white precipitate of the 9(11)-dehydro compound, amounting to 0.53 g. after filtration and drying *in vacuo*. The crude 9(11)-olefin (0.53 g.) was dissolved in a mixture of 10 ml. of methylene chloride and 18 ml. of *t*-butyl alcohol; perchloric acid (70%) (0.16 ml.) in 1.25 ml. of water and 0.25 g. of N-bromoacetamide in 2.5 ml. of *t*-butyl alcohol were added. The mixture was stirred for 15 min. at 25–30° and 0.25 g. of sodium sulfite in 2.5 ml. of water was added. Concentration of the solution *in vacuo* and dilution with 100 ml. of ice water gave after filtration and drying 0.55 g. of the bromohydrin which was dissolved in acetone (15 ml.) and heated under reflux with 0.6 g. of potassium acetate for 24 hr. The mixture was evaporated to dryness, the residue partitioned between water and methylene chloride, and the organic extract washed with water and dried over magnesium sulfate. Evaporation of solvent gave 0.486 g. of a yellow foam which was chromatographed on 50 g. of Florisil. Elution with 1 l. of 12.5% acetone-Skellysolve B removed trace of material, further elution with 2.2 l. of the same solvent mixture gave 0.359 g. of crystalline **17α,21-dihydroxy-15β-fluoro-9β,11-epoxypregn-4-ene-3,20-dione 21-acetate**, m.p. 205–207°.

A solution of 0.35 g. of the epoxide in 3.5 ml. of methylene chloride was cooled to −70° and added to a mixture of anhydrous hydrogen fluoride (3.0 g.) and tetrahydrofuran (5.3 ml.) at −20°. The mixture was allowed to stand 16 hr. at −20° and 4 hr. at +5°, then poured into a stirred ice-cold suspension of 21.6 g. of sodium bicarbonate in 160 ml. of water. Extraction with ethyl acetate yielded 0.386 g. of a yellow foam. Two crystallizations from acetone–Skellysolve B gave 110 mg. of (5), m.p. 213–214° dec., λ_{max} 238 mμ (ε 16,000).

Anal. Calcd. for $C_{23}H_{30}F_2O_6$: C, 62.71; H, 6.87; F, 8.63. Found: C, 63.02; H, 6.85, F, 8.12.

9α,15β-Difluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-Acetate (6).—About 300 mg. of crude (5) in 40 ml. of *t*-butyl alcohol containing 0.4 ml. of acetic acid was heated under reflux with 150 mg. of selenium dioxide for 44 hr. An additional 150 mg. of selenium dioxide was added and heating was continued for 19 hr. The mixture was evaporated to dryness, taken up in 150 ml. of ethyl acetate, and washed with cold aqueous sodium bicarbonate, aqueous ammonium polysulfide, dilute ammonium hydroxide, water, dilute hydrochloric acid, and water. Evaporation of the solvent gave 0.326 g. of an orange foam that was chromatographed on 100 g. of Florisil in methylene chloride. Elution with 1.5 l. of 7.5% acetone–92.5% methylene chloride and 750 ml. of 12.5% acetone–87.5% methylene chloride gave 200 mg. of partly crystalline product. Three crystallizations from acetone–Skellysolve B gave 60 mg. of pure (6), m.p. 232–233° dec.; λ_{max} 238 mμ (ε 16,000).

Anal. Calcd. for $C_{23}H_{28}F_2O_6$: C, 63.00; H, 6.44; F, 8.67. Found: C, 63.26; H, 6.24; F, 8.62.

11β,17α,21-Trihydroxy-15β-fluoropregna-1,4-diene-3,20-dione 21-Acetate (7).—A solution of 0.42 g. of (4) in *t*-butyl alcohol (50 ml.) containing 0.5 ml. of acetic acid was dehydrogenated with a total of 0.41 g. of selenium oxide as in the previous example. Chromatography on Florisil (100 g.) using linear gradient elution (2 l. each of 1:9 acetone–Skellysolve B and 4:6 acetone–Skellysolve B) gave 0.358 g. of (7). Crystallization from acetone–Skellysolve B and aqueous acetone gave an analytical sample, m.p. 235–238°; λ_{max} 243 mμ (ε 15,200).

Anal. Calcd. for $C_{23}H_{29}FO_6$: F, 4.52. Found: F, 4.51.

(15) **H. A.** Drake, R. B. Howard, and A. E. Fonken, U.S. Pat. 3,005,834 Oct. 24, **1961**).

Steroid Dimethylhydrazones

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Interest in the relative anabolic-androgenic activities[1] of some of the previously unknown steroid dimethylhydrazones prepared in our Laboratories has suggested the desirability of reporting the methods of preparation and physical characterization data for these materials. The properties of the steroid dimethylhydrazones are given in Table I. All were prepared by reaction of the sterol in excess dimethylhydrazine with a trace of acetic acid as a catalyst. The sterols are readily soluble in dimethylhydrazine and the product precipitates on standing or is precipitated by addition of water. In the absence of acetic acid to catalyze the reaction, the steroid is often recovered unchanged. A typical preparation is described in the following paragraph.

Pregnenolone Dimethylhydrazone.—Pregnenolone (1 g.) was heated with 5 ml. of dimethylhydrazine containing 2 drops of acetic acid until a clear solution was obtained. The solution was kept 12 hr. at room temperature. On dilution with 30 ml. of water, a white precipitate was formed. This was collected, washed with water, and recrystallized from methanol. Data characterizing the product are given in Table I.

The biological activity of these compounds is of interest in providing further examples of the observation that the oxygen atom of the three position in steroids is not essential to activity[2] and of the biological activity of the dimethylhydrazones.[3] These hydrazones may be regarded as acyclic derivatives of the steroidal pyrazoles[2,4] some of which have shown enhanced anabolic activity[4] or antiinflammatory activity.[2] In standard assay procedures in rats,[1] the dimethylhydrazones of the five testosterone derivatives (Table I) have shown a considerably reduced anabolic-androgenic activity as compared to the corresponding carbonyl compounds. The 19-nor derivative, however, retains the differentiation between anabolic and androgenic activities observed with other 19-nor types.

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(1) G. R. McKinney and H. G. Payne, *Proc. Soc. Expil. Biol. Med.*, **108**, 273 (1961).

(2) R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, M. Tishler, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 120 (1963).

(3) R. H. Wiley and R. L. Clevenger, *J. Med. Pharm. Chem.*, **5**, 1367 (1962), and references cited therein.

(4) R. O. Clinton, R. L. Clarke, F. W. Stonner, A. J. Manson, K. F. Jennings, and D. K. Phillips, *J. Org. Chem.*, **27**, 2800 (1962).