of 3 *M* methylmagnesium bromide. The resulting mixture then was treated with 8.25 mmoles of the appropriate acid chloride in 20 ml. of ether and stirred at room temperature for 60 hr. Cold concentrated sodium bicarbonate solution was then added. The ether layer was separated, washed well with sodium bicarbonate solution and with water, dried over magnesium sulfate, and concentrated to dryness to yield the crude ester.

O. 17β-Ethers (35 and 36).—To a stirred mixture of 1.0 g. of sodium borohydride in 100 ml. of ether cooled in an ice bath was added a solution of 5.55 mmoles of the appropriate ester of 1-chloro-4,17α-dimethylestra-1,3,5(10)-trien-17β-ol (**31** and **32**) in 50 ml. of ether and 50 ml. of tetrahydrofuran. Freshly distilled boron trifluoride etherate (20 ml.) was then added and the resulting mixture was cooled to 0°. To this cold solution was then slowly added 50 ml. of distilled diglyme, and the mixture was stirred and allowed to warm to room temperature over a 2-hr. period. It was then heated to distil 50 ml. of ether and refluxed for 1 hr. The solution was cooled, diluted with 200 ml. of ether, and treated with 5 ml. of 12 *N* HCl. The ether layer was separated, washed with water, dried over magnesium sulfate, and evaporated to an oil. The oil was dissolved in 100 ml. of petroleum ether (b.p. 35–60°) and chromatographed on 15 g. of alumina. Elution with petroleum ether gave the pure 17β-ether.

P. 1-Chloro-4-methyl-17α-vinylestra-1,3,5(10)-trien-17β-ol (41).—A solution of 2.00 g. of 1-chloro-4-methyl-17α-ethinylestra-1,3,5(10)-trien-17β-ol (**39**) in 120 ml. of pyridine was treated with 0.20 g. of 5% palladium on calcium carbonate and hydrogenated at atmospheric pressure until 1.0 equiv. of hydrogen had been absorbed. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure, giving the crude vinyl compound.

Q. 1-Chloro-4-methyl-17α-(3-hydroxypropyl)estra-1,3,5(10)-trien-17β-ol (46).—A solution of diborane in tetrahydrofuran was prepared by adding 14.2 g. of boron trifluoride etherate in 40 ml. of tetrahydrofuran to a stirred mixture of 3.1 g. of powdered sodium borohydride in 60 ml. of tetrahydrofuran cooled in an ice bath. The mixture was allowed to stand overnight at room temperature.

A solution of 1.35 g. of 1-chloro-4-methyl-17α-allylestra-1,3,5(10)-trien-17β-ol (**44**) in 50 ml. of tetrahydrofuran was treated with 15 ml. of the above diborane solution. After 2 hr. at room temperature, the solution was cooled to 0° and treated with 16 ml. of 30% hydrogen peroxide and 16 ml. of 10% aqueous sodium hydroxide solution. This mixture was stirred for 0.5 hr. and then refluxed for 1.5 hr. The solvent was removed under reduced pressure and the residue was poured into water. The aqueous suspension was extracted with ether. The ether solution was dried over magnesium sulfate and concentrated to dryness, yielding the crude oil.

R. 1-Chloro-4-methylestra-1,3,5(10)-trien-17β-ol-17α-propionic Acid, Lactone (47).—A solution of 1.27 g. of 1-chloro-4-methyl-17α-(3-hydroxypropyl)estra-1,3,5(10)-trien-17β-ol (**46**) in 120 ml. of acetic acid and 40 ml. of propionic acid was cooled to 0°, covered with an atmosphere of nitrogen, and treated with 1.90 ml. of a solution of chromium trioxide (prepared by dissolving 26.72 g. of chromium trioxide in 23 ml. of 36 *N* sulfuric acid and diluting to 100 ml. with water) over a period of 30 min. The reaction was stirred for an additional 15 min., poured into water, and filtered. The precipitate was dissolved in benzene and chromatographed on 20 g. of Florisil. Elution with 4:1 benzene–ether afforded the pure lactone.

S. 1-Chloro-4-methyl-19-norpregna-1,3,5(10)-trien-21-ol-20-one (52).—A solution of 1.50 g. of 1-chloro-4-methyl-19-norpregna-1,3,5(10)-trien-21-ol-20-one 21-acetate (**53**) in 430 ml. of methanol was treated with a solution of 1.60 g. of potassium bicarbonate in 32 ml. of water and refluxed for 1 hr. under an atmosphere of nitrogen. The solution was then concentrated under reduced pressure to about 150 ml. and poured into water. The precipitated crude 21-alcohol was filtered and recrystallized.

T. 1-Chloro-4-methyl-17a-oxa-D-homoestra-1,3,5(10)-trien-17-one (59).—A solution of 1.00 g. of 1-chloro-4-methylestra-1,3,5(10)-trien-17-one (**11**) and 0.05 g. of *p*-toluenesulfonic acid monohydrate in 10 ml. of acetic acid and 3 ml. of 40% peracetic acid was allowed to stand at 4° for 7 days. The solution was poured into water and filtered to give the crude lactone.

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6α-Fluoro- and 6α-Methyl-16α-fluoroprednisolones[1]

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The preparation of 6α-fluoro- and 6α-methyl-16α-fluoroprednisolones is described.

Recently we described the synthesis of 16α-fluoroprednisolone acetate and showed that the 16α-fluoro group strongly enhanced the antiinflammatory property of prednisolone acetate.[2] The 16α-fluoro substituent has now been introduced into suitable 6α-fluoro[3] and 6α-methyl[4] intermediates and the corresponding 6α-fluoro- and 6α-methyl-16α-fluoroprednisolones have been prepared and evaluated biologically.

The method of synthesis for the 6-substituted 16α-fluorocorticoids was essentially that previously described.[2] The processes are outlined in Chart I.

Preliminary endocrine data for the 16α-fluorocorticoids are summarized in Table I.

Experimental[5]

6α-Fluoro-11β,16α,21-trihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-Acetate (2).—A mixture of 40 g. of 11β,21-dihydroxy-6α-fluoro-4,17(20)-*cis*-pregnadien-3-one 21-acetate (1),[6] 18.5 g. of selenium dioxide, 150 ml. of water, and 960 ml. of dioxane was heated under reflux for 1 hr. The dioxane was distilled *in vacuo*. The residue was partitioned between methylene chloride and water. After drying, the organic phase was percolated through 4 kg. of Florisil (synthetic magnesia–silica gel). The fraction eluted with 20:80 acetone–Skellysolve B (saturated hydrocarbon fraction, b.p. 60–71°) weighed 49 g. This product when recrystallized from ethyl acetate weighed 22 g. (52.8% yield) and

(1) A preliminary account of a portion of this work appeared earlier, B. J. Magerlein, F. H. Lincoln, R. D. Birkenmeyer, and F. Kagan, *Chem. Ind.* (London), 2050 (1961).

(2) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Am. Chem. Soc.*, **82**, 1252 (1960); B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, in press.

(3) J. A. Hogg, *et al.*, *Chem. Ind.* (London), 1002 (1958).

(4) G. B. Spero, *et al.*, *J. Am. Chem. Soc.*, **78**, 6213 (1956).

(5) Melting points were taken in capillary tubes and are corrected. Rotations were observed at 26°.

(6) B. J. Magerlein, J. E. Pike, R. W. Jackson, G. E. VandenBerg, and F. Kagan, *J. Org. Chem.*, **29**, 2982 (1964).

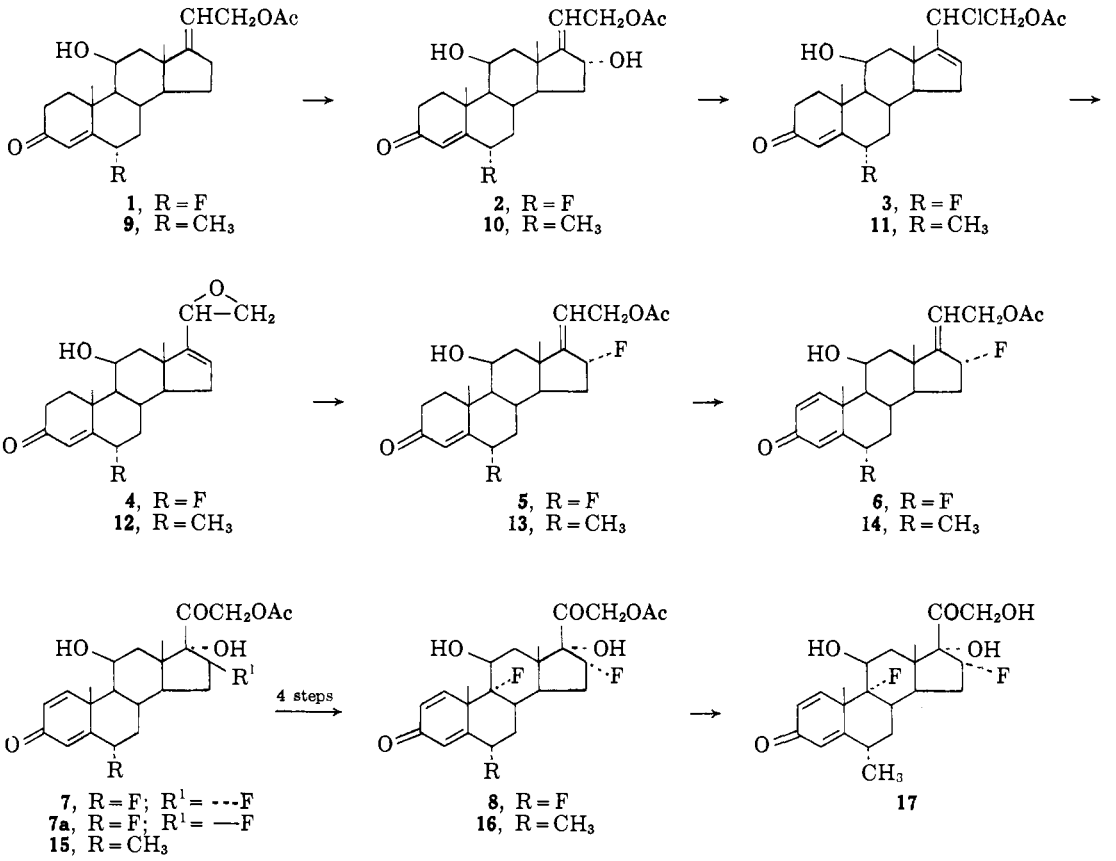

TABLE I

Compd.	Anti-inflammatory[a] (× hydrocortisone)	Glucocorticoid[b] (× hydrocortisone)
6α-Fluoroprednisolone[3]		81
6α,16α-Difluoroprednisolone 21-acetate (**7**)	100	116
6α-Methyl-16α-fluoroprednisolone 21-acetate (**15**)	20	25
6α,9α,16α-Trifluoroprednisolone 21-acetate (**8**)	480	425
6α-Methyl-9,16-difluoroprednisolone 21-acetate (**16**)	190	250
6α-Methyl-9,16-difluoroprednisolone (**17**)	141	

[a] A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957). [b] R. O. Stafford, L. E. Barns, B. J. Bowman, and M. M. Meinzinger, *Proc. Soc. Exptl. Biol. Med.*, **89**, 371 (1955).

melted at 177–180°. The analytical sample, $[\alpha]_D$ +105° ($CHCl_3$), prepared by two recrystallizations from the same solvent, melted at 185–187°.

Anal. Calcd. for $C_{23}H_{31}FO_5$: C, 67.96; H, 7.69; F, 4.67. Found: C, 68.04; H, 8.04; F, 4.70.

20ξ-Chloro-11β,21-dihydroxy-6α-fluoro-4,16-pregnadien-3-one 21-Acetate (3).—To a solution of 30 g. of **2** in 860 ml. of methylene chloride and 18.2 ml. of tri-*n*-butylamine cooled to 0–10°, there was added 5.1 ml. of thionyl chloride over a period of 5 min. The mixture was stirred at 0–10° for 30 min. and then washed twice with dilute HCl and once with water. The reaction mixture was chromatographed over 2 kg. of Florisil. The fraction eluted with Skellysolve B–acetone (85:15) weighed 18.5 g. (58.9% yield) and melted at 148–151°. The crude product from other runs melted as high as 158–160°.

Anal. Calcd. for $C_{23}H_{30}ClFO_4$: C, 65.07; H, 7.12; Cl, 8.35; F, 4.48. Found: C, 65.08; H, 7.09; Cl, 8.55; F, 4.71.

6α-Fluoro-11β-hydroxy-20ξ,21-oxido-4,16-pregnadien-3-one (4).—A solution of 9.5 g. of crude chloride **3** in 270 ml. of methanol was cooled to 0° and 45 ml. of *N* NaOH was added at such a rate as to keep the temperature below 10°. After stirring for 20 min. at 4–6°, the reaction mixture was seeded with oxide **4** and gradually diluted with 250 ml. of water. The product, collected by filtration, after drying weighed 6.4 g. (82% yield) and melted at 139–145°. Recrystallization of a portion of this material from ethyl acetate–Skellysolve B afforded the analytical sample, m.p. 152–154°, $[\alpha]_D$ +189° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{27}FO_3$: C, 72.80; H, 7.86; F, 5.48. Found: C, 72.88; H, 7.78; F, 5.34.

6α,16-Difluoro-11β,21-dihydroxy-4,17(20)-pregnadien-3-one 21-Acetate (5).—A mixture of 13.7 g. of anhydrous HF, 24.2 ml. of tetrahydrofuran, and 6.7 ml. of methylene chloride was cooled to −70° and a similarly cooled solution of 6.4 g. of oxide **4** in 95 ml. of methylene chloride was added thereto. The resulting mixture was stirred at about −70° for 2 hr. and then cautiously poured into a solution of 55 g. of K_2CO_3 in 330 ml. of water. The methylene chloride layer was separated. After extracting the aqueous layer twice with methylene chloride the organic extracts were combined and evaporated. The residue was acylated with 9.5 ml. of acetic anhydride in 9.5 ml. of pyridine in the usual manner. The crude product was chromatographed over 500 g. of Florisil. The fraction eluted with Skellysolve B–acetone (88:12) weighed 3.95 g. (52.6%). This partially crystalline product was not purified further but used directly in the next step. A portion recrystallized from acetone melted at 130–135°.

6α,16-Difluoro-11β,21-dihydroxy-1,4,17(20)-pregnatrien-3-one 21-Acetate(6).—A mixture of 3.8 g. of **5**, 1.8 g. of selenium dioxide, 0.6 ml. of pyridine, and 110 ml. of *t*-butyl alcohol was heated under reflux for 18 hr. The reaction mixture was clarified by filtration and concentrated under vacuum. The residue was partitioned between methylene chloride–water. The organic layer was percolated through 225 g. of Florisil. The fraction eluted with Skellysolve B–acetone (88:12) weighed 3.27 g. (86.2% yield). This oily product showed several spots on paper chromatography. Unreacted **6** recovered from the succeeding step by chromatography was crystallized from ethyl acetate. It melted at 137–149°, $[\alpha]_D$ +59° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{28}F_2O_4$: C, 67.96; H, 6.94; F, 9.34. Found: C, 66.58; H, 7.38; F, 9.12.

This product appeared to be a mixture of isomeric 16- and 20-fluorinated steroids.

6α,16α-Difluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (7).—A solution of 3.27 g. of crude fluoride **6**

in 130 ml. of *t*-butyl alcohol, 3.9 ml. of pyridine, 10 ml. of N-methylmorpholine oxide peroxide (2 *N*), and 65 mg. of osmium tetroxide was stirred at ambient temperature for 18 hr. Twenty milliliters of 2% sodium hydrosulfite solution was added. The solvent was distilled under vacuum. The residue was extracted with methylene chloride and the extracts were washed with dilute acid. Chromatography over Florisil (200 g.) afforded 837 mg. of recovered **6**, 298 mg. of a mixture of **7a**, and an unidentified polar material. One fraction of 107 mg. contained **6** and **7**. In one experiment the **7a** fraction was crystallized from ethyl acetate–Skellysolve B to yield material melting at 140–160°. Recrystallization from ethyl acetate gave a few crystals, m.p. 172–178°, whose solution infrared curve indicated the 16β-fluoro corticoid (**7a**). Total yield of **7a** was 21 mg.

Anal. Calcd. for $C_{23}H_{28}F_2O_6$: F, 8.67. Found: F, 8.73.

In the manner described above, the recovered **6** was recycled four times. The amount of **7a** decreased permitting easier isolation of **7**. The crude fractions of **7** totaling 648 mg., were combined and rechromatographed yielding a fraction of 549 mg. of **6**. Based on this chromatographic fraction the over-all yield for this step was about 2.5%. A portion of the chromatographic fraction was recrystallized from methanol–ether to yield **7**, m.p. 204–206°.

Anal. Calcd. for $C_{23}H_{28}F_2O_6$: C, 63.00; H, 6.44; F, 8.67. Found: C, 63.59; H, 6.58; F, 8.25.

6α,9α,16α-Trifluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (8).—A portion of 267 mg. of **7** was dissolved in 3 ml. of dry pyridine and 131 mg. of N-bromoacetamide was added. The reaction mixture was stirred at 26° for 20 min., and an excess of SO_2 was passed over the top of the solution. The mixture was poured into cold dilute acid and the product was recovered by extraction with methylene chloride. Chromatography over Florisil yield a partially crystalline fraction of 230 mg. whose papergram analysis on the FBF system[7] showed no **7** but a less polar spot at R_f 0.82. This product was used without further purification. To a solution of the 230 mg. of crude compound from above in 4 ml. of methylene chloride and 8 ml. of *t*-butyl alcohol there was added a solution of 0.72 ml. of 70% perchloric acid in 4.5 ml. of water followed by 100 mg. of *N*-bromoacetamide dissolved in 3 ml. of *t*-butyl alcohol. After stirring at ambient temperature for 15 min., a solution of 120 mg. of sodium sulfite in 5 ml. of water was added. Water was added and the crude bromide was recovered by filtration. It weighed 250 mg. and had R_f 0.13 on the FBF system. The crude bromide was dissolved in 15 ml. of acetone, 300 mg. of anhydrous potassium acetate was added, and the mixture was heated under reflux for 18 hr. The solvent was distilled *in vacuo*. The residue was triturated with methylene chloride and the extract was passed over 20 g. of Florisil. An oxide fraction (based on a papergram mobility, R_f 0.69) of 102 mg. was obtained. This was dissolved in 3 ml. of methylene chloride cooled to −70° and added to a similarly cooled solution of 750 mg. of HF and 1.3 ml. of tetrahydrofuran. After 18 hr. at 4°, the reaction mixture was poured into 100 ml. of water containing 2.5 g. of K_2CO_3. The steroid, recovered by extraction, was purified by chromatography over 10 g. of Florisil. A crystalline fraction of 52 mg. was recrystallized from ether acetate–Skellysolve B to give 35 mg. of **8**, m.p. 270–277° dec. A second crop was obtained from the mother liquors which when recrystallized melted at 266–270° dec. It weighed 4 mg. The total yield was 39 mg. (8% based on **7**).

Anal. Calcd. for $C_{23}H_{27}F_3O_6$: F, 12.49. Found: F, 12.90.

6α-Methyl-11β,16α,21-trihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-Acetate (10).—A mixture of 167 g. (0.43 mole) of 6α-methyl-11β,21-dihydroxy-4,17(20)-pregnadien-3-one 21-acetate[7] (**9**), 46.7 g. of selenium dioxide, 2500 ml. of dioxane, and 584 ml. of water was heated under reflux with stirring for 1 hr. After cooling to room temperature 80 g. of Magnesol[8] was added, the mixture was stirred for 15 min. and then filtered. The filtrate was diluted with water and extracted with methylene chloride. The dried extract was evaporated to a viscous oil which was purified by chromatography on 4 g. of Florisil. The product was eluted with 15 and 25% acetone in Skellysolve B and recrystallized from acetone–Skellysolve B to give a total of 99.8 g. (57.5%) of **10** melting in the range of 174–181°. An analytical sample was obtained as prisms after two recrystallizations from acetone, m.p. 176–180°.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.22; H, 9.05.

20ξ-Chloro-11β,21-dihydroxy-6α-methyl-4,16-pregnadien-3-one 21-Acetate (11).—In the manner described above 50.0 g. of **10** was chlorinated to yield 32.7 g. (62%) of **11**, m.p. 160–164°. Recrystallization from acetone–Skellysolve B gave plates, m.p. 161–163°, $[\alpha]_D$ +106° ($CHCl_3$), λ_{max}^{alc} 241.5 mμ (ε 15,650).

Anal. Calcd. for $C_{24}H_{33}ClO_4$: C, 68.47; H, 7.90; Cl, 8.42. Found: C, 68.71; H, 7.82; Cl, 8.66.

20ξ-21-Epoxy-11β-hydroxy-6α-methyl-4,16-pregnadien-3-one (12).—Treatment of 68.4 g. of **11** with alkali afforded 51.5 g. (94%) of **12**, m.p. 137–144°. A sample was recrystallized for analysis from acetone–Skellysolve B to give fluffy needles, m.p. 142–144°, $[\alpha]_D$ +176° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.06; H, 9.24.

16ξ-Fluoro-11β,21-dihydroxy-6α-methyl-4,17(20)-pregnadien-3-one 21-Acetate (13).—When treated with HF, 42.5 g. of **12** gave 17.3 g. (34%) of a mixture of crude fluoride. A portion was purified by repeated crystallization from acetone–Skellysolve B to give plates of **13**, m.p. 137–138°, $[\alpha]_D$ +88° ($CHCl_3$), λ_{max}^{alc} 241.5 mμ (ε 15,400).

Anal. Calcd. for $C_{24}H_{33}FO_4$: C, 71.08; H, 8.45; F, 4.69. Found: C, 71.49; H, 8.66; F, 4.67.

16ξ-Fluoro-11β,21-dihydroxy-6α-methyl-1,4,17(20)-pregnatrien-3-one 21-Acetate (14).—A quantity of 16.7 g. of crude **13** was treated with 8.0 g. of dry selenium dioxide as previously described. After chromatography over Florisil, 8.2 g. (49%) of **7** was obtained substantially free of **6** by papergram. This material was still gummy, however, and it was not until after recovery from the following osmium tetraoxide oxidation that **7** was obtained crystalline. After recrystallization from acetone–Skellysolve B, shiny plates were obtained, which melted at 162–163°, $[\alpha]_D$ +50° ($CHCl_3$), λ_{max}^{alc} 242 mμ (ε 15,250).

Anal. Calcd. for $C_{24}H_{31}FO_4$: C, 71.61; H, 7.76; F, 4.72. Found: C, 71.78; H, 8.01; F, 4.73.

16α-Fluoro-6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (15).—To a stirred solution of 9.5 g. of crude **14** in 170 ml. of *t*-butyl alcohol was added 10 ml. of pyridine, 27.6 ml. of N-methylmorpholine oxide hydrogen peroxide solution (titration 42.9 ml. of 0.1 *N* sodium thiosulfate/ml.), and 190 mg. of osmium tetroxide. After 18 hr., a solution of 1.5 g. of sodium hydrosulfite in 100 ml. of water was added, the dark solution was concentrated at reduced pressure and extracted with methylene chloride. Chromatography on 500 g. of Florisil yielded 4.06 g. (42%) of recovered starting material (eluted 10:90 acetone–Skellysolve B), 1.388 g. of mixed material containing the desired product (eluted 10 and 15% acetone–Skellysolve B mixtures), and 1.3 g. of still more polar material. The 1.388-g. portion was rechromatographed in the same manner on 100 g. of Florisil to give an additional 219 mg. (2.3%) of **14**, 116 mg. of mixed **14** and **15**, 153 mg. of crude **15** containing some **15** and some of the corresponding 16β-fluoro isomer, and 263 mg. of more polar material. The fractions were determined by paper chromatography using the benzene–formamide system. The desired product spot (R_f about 0.55) was determined by its positive Tollens test. The 153 mg. of crude **15** was crystallized by trituration with anhydrous ether, m.p. 214–217° (yield 90 mg.). After recycling the recovered starting material three times in the above manner, a total of 0.52 g. (5.3%) of crystalline **15** was obtained. A small sample was crystallized from ether as hard prisms, m.p. 218–220°, λ_{max}^{alc} 242 mμ (ε 14,800).

Anal. Calcd. for $C_{24}H_{31}FO_5$: C, 66.34; H, 7.19; F, 4.37. Found: C, 65.99; H, 7.20; F, 4.59.

9α,16α-Difluoro-6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (16).—To a stirred solution of 0.45 g. of **15** in 6 ml. of pyridine was added 0.20 g. of N-bromoacetamide. The solution was stirred for 18 min. after which it was cooled to 10° and saturated with sulfur dioxide. Water (100 ml.) was added and the near white precipitate was collected on a filter, washed with water, and air-dried. The yield was 0.43 g. The material was purified by chromatography on 25 g. of Florisil. The product (406 mg., 94%) was eluted with 10 and 12% acetone in Skellysolve B (R_f 0.90, benzene–formamide papergram system). To a stirred solution of 406 mg. of the above product in 25 ml. of *t*-butyl alcohol and 7 ml. of methylene chloride, was added a mixture of 1.3 ml. of 70% perchloric acid, 8 ml. of water, and a solution of 174 mg. of N-bromoacetamide in 5 ml. of *t*-butyl alcohol. After 15 min. a solution of 0.25 g. of sodium sulfite in 12 ml. of water was added and

(7) J. M. Reineke, *Anal. Chem.*, **28**, 1853 (1956).

(8) From Waverly Chemical, Inc., Mamaroneck, N. Y.

the mixture was concentrated at reduced pressure, diluted with 100 ml. of water and filtered. The white crystalline product weighed 0.44 g. (88%) after air drying (R_f 0.39, benzene–formamide papergram system).

A mixture of 0.44 g. of crude bromohydrin, 0.6 g. of potassium acetate, and 20 ml. of acetone was stirred and heated under reflux for 30 hr. It was then evaporated to dryness at reduced pressure, and the residue was extracted with methylene chloride. The extract was concentrated and poured onto a chromatographic column containing 25 g. of Florisil. The product was eluted with 10 and 12.5% acetone in Skellysolve B to yield 329 mg. (92.4%) of oxide (R_f 0.87, benzene–formamide papergram system).

To 9.5 g. of HF cooled in a solid Dry Ice–alcohol bath was added 17 ml. of cold tetrahydrofuran and a cold solution of 329 mg. of oxide dissolved in 17 ml. of methylene chloride. The mixture was swirled and then kept at 5° for 19 hr. The amber-colored solution was poured cautiously into a stirred mixture of 45 g. of Na_2CO_3 and 1 l. of water and ice. The organic phase was separated and the aqueous phase repeatedly was extracted with methylene chloride. The combined extract was dried and evaporated to a partly crystalline residue which was purified by chromatography on 25 g. of Florisil. The product was eluted with 15 and 20% acetone–Skellysolve B mixtures as crystalline plates, yield 332 mg. Recrystallization from acetone–Skellysolve B gave two crops: (a) 0.19 g. of shiny plates, m.p. 259–262° dec., λ_{max}^{alc} 239 mμ (ε 15,450); and (b) 0.06 g., m.p. 252–256° dec., total yield 72.5%.

Both crops gave but one spot on a benzene–formamide papergram (R_f 0.25).

Anal. Calcd. for $C_{24}H_{30}F_2O_6$: C, 63.70; H, 6.68; F, 8.40. Found: C, 63.40; H, 6.78; F, 8.63.

16α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (17).—A solution of 160 mg. of acetate **16**, 75 mg. of $KHCO_3$, 15 ml. of methanol, and 1 ml. of water was stirred for 5 hr. under nitrogen at ambient temperature. After the addition of 0.2 ml. of acetic acid and 10 ml. of water, the mixture was concentrated to a small volume. The product (130 mg.) was recovered by filtration. Recrystallization from acetone–Skellysolve B afforded 69 mg. of **17**, m.p. 245–247° dec., and 21 mg., m.p. 240–244° dec.

Anal. Calcd. for $C_{22}H_{28}F_2O_5$ (material melting at 245–247°): F, 9.26. Found: F, 8.90.

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The Synthesis of 16α-Chloro Corticoids[1]

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The synthesis and biological activity of a group of 16α-chloro corticoids is reported. 16α-Chloro-6α,9α-difluoroprednisolone 21-acetate is 1100 times as potent as hydrocortisone in the granuloma pouch antiinflammatory assay in rats.

In previous papers in this series[1] the synthesis and biological properties of a series of 16α-fluoro corticoids was reported. This paper records the preparation of a group of 16α-chloro-substituted prednisolone analogs and a preliminary account of their biological activity.

Although the synthesis of 16β-chlorocortisone acetate was reported in 1956, this compound showed no appreciable activity in glycogen deposition, granuloma inhibition, adrenal atrophy, thymus involution, or mineralocorticoid assays.[2] The preparation of 16α-chloro steroids bearing a fully elaborated corticoid side chain at C-17 has not been described.

Treatment of 11β-hydroxy-20β,21-oxido-1,4,16-pregnatrien-3-one (**1**) with hydrogen chloride in methylene chloride provided a mixture of 20- and 16-chloro derivatives (**2** and **3**). Purification by chromatography afforded a material identical with the 20α-chloro compound (**2**) obtained by treating 11β,16α,21-trihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one 21-acetate (**13**) with thionyl chloride.[1a,b] The 16-chloro fraction, mainly **4a**, was assigned *trans*-17(20) stereochemistry by analogy with the 16-fluoro analog prepared in a like manner.[1a,b] Oxidation of crude **4a** with osmium tetroxide in the presence of N-methylmorpholine oxide–hydrogen peroxide complex[3] yielded 16α-chloroprednisolone 21-acetate (**5a**). Structure assignment was made on the basis of analytical and spectroscopic data, molecular rotation, and by analogy with 16α-fluoroprednisolone 21-acetate prepared in a similar manner.[1a,b]

Dehydration of 16α-chloroprednisolone acetate (**5a**) with N-bromoacetamide and sulfur dioxide in pyridine[4] and introduction of the 9α-fluoro substituent according to the procedure of Fried and Sabo[5] afforded 16α-chloro-9α-fluoroprednisolone 21-acetate (**9a**).

The syntheses of 6α-fluoro and 6α-methyl-16α-chloro corticoids were essentially the same as described for the 6-unsubstituted compounds with the exception that the sequences **10b** and **c** → **11b** and **c** → **12b** and **c**, were in the 3-keto-Δ^4-series in contrast to the sequence **1** → **4a** which was in the $\Delta^{1,4}$-series. Dehydrogenation of **12b** and **12c** with selenium dioxide merged the two routes at **3**.

The molecular rotation data presented in Table I for 16-halo pregnane derivatives provides the following information.

(1) The contribution to molecular rotation of a 16α-halo substituent in pregnane derivatives is consistently negative.

(2) 16β-Halo substituents generally make negative contributions to molecular rotation in pregnane derivatives; however, 16β-bromo-17α,21-dihydroxy-4-preg-

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(2) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

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

(4) H. A. Drake, R. B. Howard, and A. E. Fonken, U. S. Patent 3,005,834 (1961).

(5) J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954).