16-Fluorinated Corticoids. 16α-Fluoro- and 16β-Fluoroprednisolones[1]

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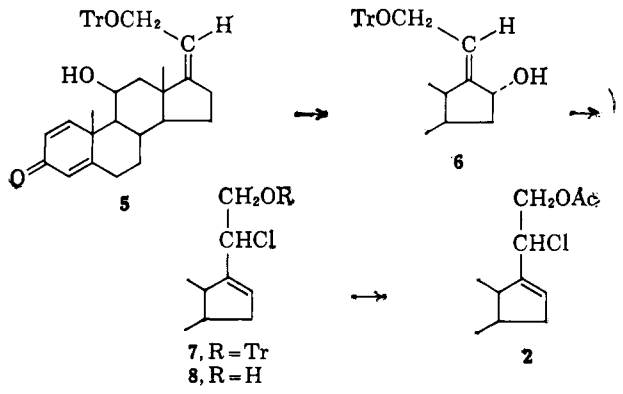
In the course of a program directed towards the development of new cortical hormones which might exhibit improved therapeutic ratios over existing drugs, the synthesis of 16-fluoro corticoids, particularly of the 16α-fluoro configuration, was desirable. This paper describes the conversion of 11β,16α,21-trihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one 21-acetate (1) to 16α-fluoro- and 16β-fluoroprednisolone acetates (20, 21) and related corticoids.

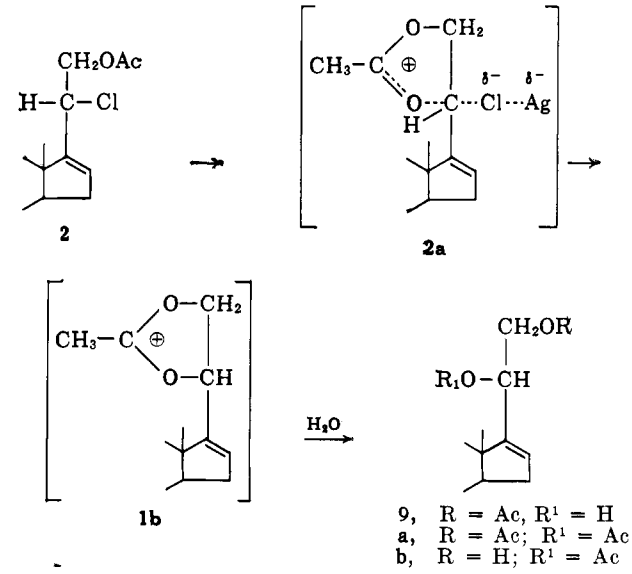
Treatment of 11β,16α,21-trihydroxy-1,4,17(20)-*cis*-pregnadien-3-one 21-acetate (1)[2] with thionyl chloride in the presence of tri-*n*-butylamine afforded a product which proved to be a mixture of chlorides as determined by paper chromatography. The major product, obtained in 69% yield, was assigned the Δ^{16}-20-chloro structure (2) on the following evidence. Treatment of 2 with osmium tetroxide yielded a diol (3) which on oxidation with chromic acid in acetone afforded the seco keto acid (4) in high yield. The structure of 4 was assigned on the basis of elemental analysis, spectral properties, and its solubility in sodium bicarbonate solution. Alternatively, the diol (3) was oxidized with lead tetraacetate to an oil whose infrared spectrum was in agreement with the keto aldehyde structure (3a). Further oxidation with chromic acid in acetone afforded 4. This sequence established the position of the double bond in 2 at C-16 and the position of the chlorine at C-20 or C-21. To eliminate the possibility that 21-substitution had taken place,[3] the same reactions, namely allylic oxidation and chlorination, were performed on the 21-trityl ether of 11β,21-dihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one (5), wherein the 21-position was blocked to cyclic acetoxonium ion formation. Treatment of the 16-hydroxy-21-trityl ether (6) with thionyl chloride in methylene chloride solution in the presence of tri-*n*-butyl amine yielded the expected Δ^{16}-20-chloro trityl ether (7) as well as a smaller amount of the detritylated derivate (8). Detritylation of 7 with anhydrous hydrogen chloride formed the diol 8 which was readily acylated to the 21-acetate (2) previously formed by chlorination of 1, thus eliminating the possibility



that the chlorine atom in 2 was at C-21. The structure of 2 was further substantiated by its n.m.r. spectrum.[4]

Treatment of the chloride (2) with silver fluoride in acetonitrile under anhydrous conditions afforded, in 8% yield, an unidentified fluorine-containing steroid and, in 81% yield, a more polar material which was halogen free and which proved to be the 20-alcohol (9). Manganese dioxide oxidation afforded the Δ^{16}-20-ketone (10) which was hydroxylated as previously reported[2] to the known 11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 21 acetate (11).[5]

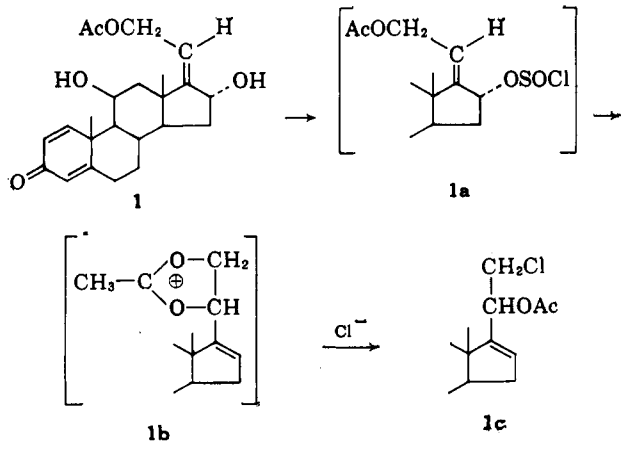
The formation of 9 probably proceeds through a cyclic acetoxonium ion (1b) formed by neighboring group participation[6] of the 21-acetoxy group during the sol-



(1) Previous paper in this series: 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. Org. Chem.*, **28**, 3474 (1963).

(3) One possible route to a 21-substituted derivative proceeds through a cyclic acetoxonium ion (**1b**) as shown below.



(4) Private communication from G. Slomp of these laboratories.

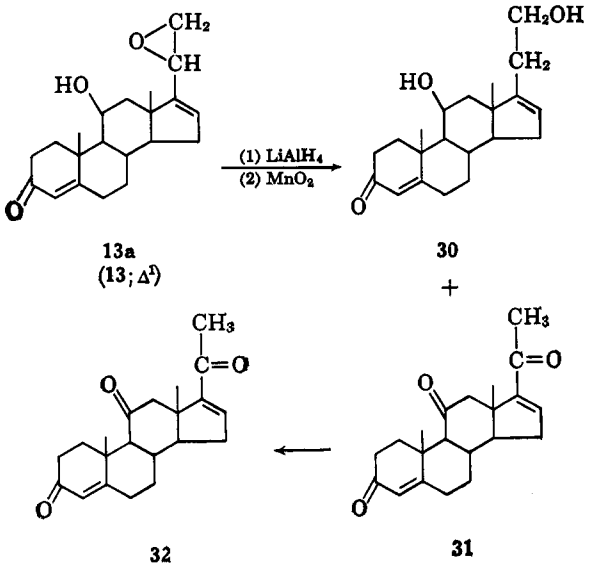
(5) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956).

(6) S. Winstein, H. V. Hess, and R. E. Buckles, *ibid.*, **64**, 2796 (1942); S. Winstein and R. E. Buckles, *ibid.*, **64**, 2780, 2787 (1942); **65**, 613 (1943).

volysis of the 20-halogen atom. Attack of water on **1b** might be expected to yield both the 20-hydroxy-21-acetate (**9**) and the 20-acetoxy-21-hydroxy compound[7] (**9b**), and indeed this was found to be the case, with the major product being **9**. Treatment of **9** with acetic anhydride and pyridine afforded the 20-acetate (**9a**) in high yield. A large positive shift in molecular rotation on acetylation indicated that the 20-hydroxyl group in **9** had the β-configuration.[8a,b] This fact coupled with the well documented backside attack made by a neighboring acetate group during anchimerically assisted reactions suggested that the chlorine in **2** was present in the α-configuration.

Expoxidation of **9** with peracetic acid gave the expected oxide (**12**); however, no fluorine containing entities could be isolated from the reaction of **12** with hydrogen fluoride. This is not surprising since Shapiro and coworkers[9] have shown that hydrogen fluoride causes certain steroidal 16α,17α-oxides to undergo Wagner–Meerwein rearrangement.

Treatment of **2** with dilute alkali in aqueous methanol afforded a good yield of the 20β,21-oxide (**13**). Structure assignment was made on the basis of analogous work in the 3-keto-Δ^4-series wherein the oxide **13a** was treated with lithium aluminum hydride followed by manganese dioxide oxidation of the total reaction mixture. Chromatography led to the isolation of the Δ^{16}-20-ketone (**31**) and the Δ^{16}-21-alcohol (**30**). The former was oxidized with chromic acid to the known 4,16-pregnadiene-3,11,20-trione (**32**).[10] The β-configuration for **13** follows from the fact that it was formed by displacement of the 20α-chloro group.

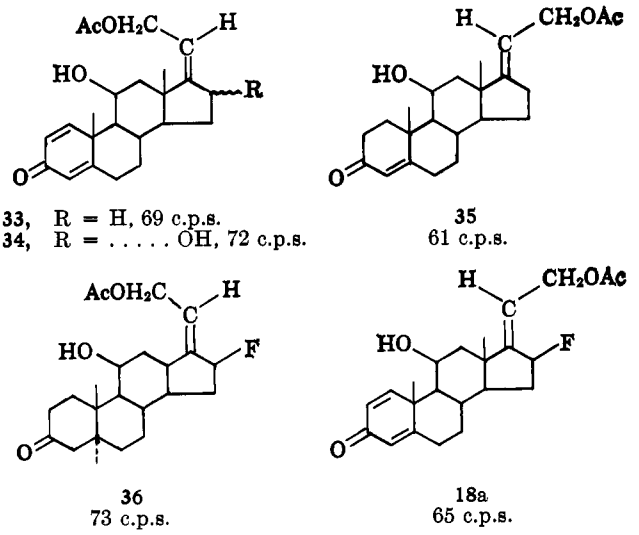


Opening of the oxide (**13**) with hydrogen fluoride followed by acetylation led to a mixture of fluorides, the main components of which were the 20-fluoro derivative (**15**) and the 16α-fluoro derivative (**18a**), the latter being contaminated with a small amount of the 16β-epimer (**18b**). Structure assignment for **15** was made on the basis of conversion to the seco acid (**16**) by ozonization followed by chromic acid oxidation. The keto acid structure was assigned to **16** on the basis of its elemental analysis, infrared spectrum, and its solubility in sodium bicarbonate solution. In contrast to the behavior of **15**, 16α-fluoro-11β,21-dihydroxy-1,4-17(20)-*trans*-pregnatrien-3-one 21-acetate (**18a**) on ozonization afforded the 16-fluoro-17-ketone (**22**) having a carbonyl frequency at 1758 cm.$^{-1}$ in its infrared spectrum. Additional structural evidence pertaining to **15** was obtained by alkaline hydrolysis to the 21-alcohol (**14**) which proved to be inert to manganese dioxide under conditions which are ordinarily used for the oxidation of allylic alcohols. The 16α-fluoro derivative (**18a**), on the other hand, was hydrolyzed to an α,β-unsaturated aldehyde (**19**) on treatment with manganese dioxide in ethyl acetate. The ozonization and the hydrolysis–oxidation data unequivocally established the structure of **18a**. In contrast to the almost quantitative conversion of the 20-chloro derivatives (**2** and **2a**) to the 20,21-oxides (**13** and **13a**), the corresponding 20-fluoro analog (**15**) yielded very little oxide under similar conditions.

The n.m.r. spectra of **15** and **18** were in accord with the assigned structures. Slomp[4] has examined the n.m.r. spectra of a series of steroid $\Delta^{17,20}$-olefins and has shown that *trans*s tereochemistry about the 17,20 bond produces a greater shielding effect (smaller chemical shifts from tetramethylsilane) on the C-18 protons than the corresponding *cis* isomers by approximately 6–12 c.p.s. (at 60 Mc.). In Chart I, a comparison of the C-18 proton frequencies of **18a** with **36** and **33** with **35** makes it evident that the stereochemistry about the 17,20 double bond in **18a** is *trans*.

CHART I

C-18 PROTON FREQUENCIES IN *cis* AND *trans* STEROID $\Delta^{17,20}$-OLEFINS (AT 60 MC.), DOWNFIELD FROM TMS



Treatment of **18** with osmium tetroxide and N-methylmorpholine oxide–hydrogen peroxide complex[11] converted the small amount of 16β-fluoro epimer to

(7) This compound was isolated by W. P. Schneider of these laboratories.

(8) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 615; (b) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1165 (1949).

(9) E. L. Shapiro, M. Steinberg, D. Gould, M. J. Gentles, H. L. Herzog, M. Gilmore, W. Charney, E. B. Hershberg, and L. Mandell, *ibid.*, **81**, 6483 (1959).

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

(11) W. P. Schneider and A. R. Hanze, U. S. Patent 2,769,823 (November 6, 1956).

SCHEME I

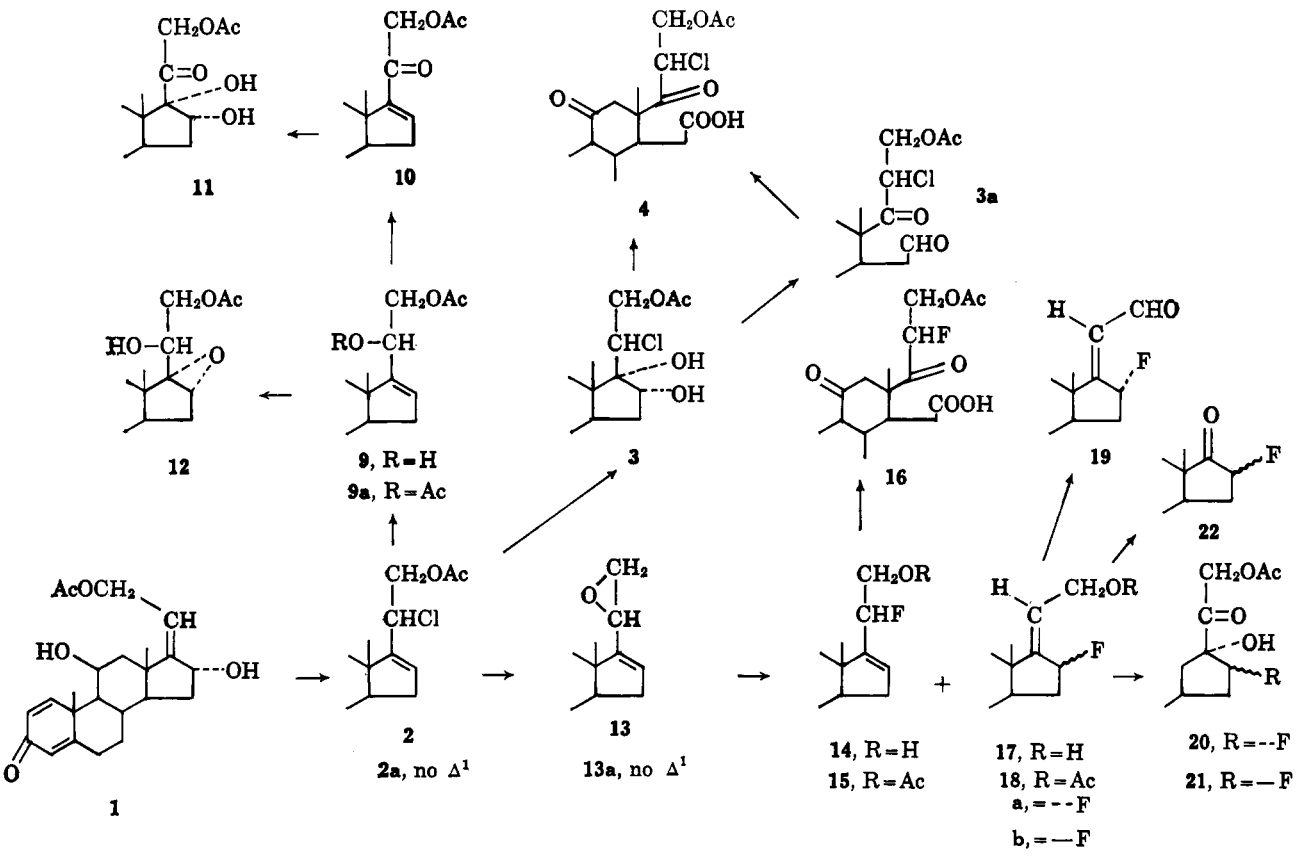


TABLE I

EFFECT OF 16-FLUORINATION ON BIOLOGICAL ACTIVITY

Compound (21-acetates)	Anti-inflammatory[a] (x hydrocortisone)	Liver glycogen deposition[b] (x hydrocortisone)
Prednisolone[c]	3	4
16α-Fluoro	16	8
9α-Fluoroprednisolone[b]	14	50
16α-Fluoro	77	60
16β-Fluoro	1	3

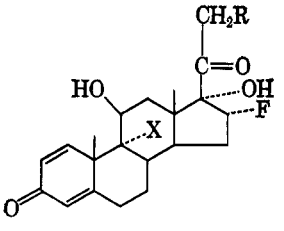
[a] A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957). [b] R. Stafford, L. Barnes,. B. Bowman, and M. Meinzinger, *Proc. Soc. Exptl. Biol. Med.*, **89**, 371 (1955). [c] W. E. Dulin, L. E. Barnes, E. M. Glenn, S. C. Lyster, and E. J. Collins, *Metab., Clin. Exptl.*, **7**, 398 (1958).

16β-fluoroprednisolone 21-acetate (**21**), identical with a sample prepared by another synthetic route.[12] The major constituent of **18** afforded on oxidative hydroxylation[11] a 16-fluoroprednisolone 21-acetate which, *ipso facto*, was concluded to have the 16α-configuration. Hydrolysis to the 21-alcohol and conversion to the 21-methanesulfonate, followed by treatment with sodium iodide and reduction with sodium iodide in glacial acetic acid, yielded 21-desoxy-16α-fluoroprednisolone (**24**).

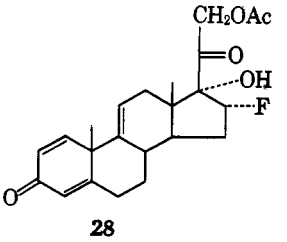
Dehydration of 16α-fluoroprednisolone 21-acetate (**20**) and introduction of the 9α-fluoro substituent by standard methods[13] formed 9α,16α-difluoroprednisolone 21-acetate (**25**) from which the free alcohol (**26**) was readily obtained. Preliminary biological data are tabulated in Table I.

In summary, a series of 16-fluoro corticoids has been prepared (Scheme I). In this report the 16α-fluoro group has been shown to have significant potentiating effects on the biological activity of prednisolone and 9α-fluoroprednisolone. The synthesis and biological properties of 6α-methyl and 6α-fluoro analogs has been reported in a previous communication.[1]

CHART II



20, R = OAc, X = H
23, R = OH, X = H
24, R = H, X = H
25, R = OAc, X = F
26, R = OH, X = F
27, R = OAc, X = Br



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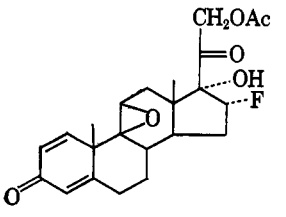

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Experimental[14]

20α-Chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-Acetate (2).—A solution of 965 mg. (2.5 mmoles) of 11β,16α,21-trihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one 21-acetate (**1**)[2] and

(12) D. E. Ayer and W. P. Schneider, *J. Am. Chem. Soc.*, **82**, 1249 (1960).
(13) J. Fried and E. Sabo, *ibid.*, **76**, 1455 (1954).

556 mg. (3 mmoles) of tri-*n*-butyl amine in 100 ml. of methylene chloride was cooled in an ice–salt bath to 0°. While maintaining this temperature 393 mg. (3.3 mmoles) of thionyl chloride dissolved in 25 ml. of methylene chloride was added over a period of 5 min. After stirring for 1 hr. at 0° the reaction mixture was washed with three 20-ml. portions of dilute hydrochloric acid and four 50-ml. portions of water, and was filtered through anhydrous sodium sulfate. The filtrate was evaporated to a volume of about 25 ml. and subjected to chromatography. A column of Florisil[15] (80 g.) in Skellysolve B[16] was prepared and the methylene chloride solution poured onto it. The column was eluted with acetone–Skellysolve B mixtures, the acetone concentration gradually being increased. A crystalline fraction was obtained at an eluting concentration of 9 to 12% acetone. After two recrystallizations from acetone–Skellysolve B, the product melted at 160–161° and weighed 700 mg., 69% yield; $[\alpha]_D$ +65° (chloroform); λ_{max}^{EtOH} 242 mμ (ε 15,550).

Anal. Calcd. for $C_{23}H_{29}ClO_4$: C, 68.22; H, 7.22; Cl, 8.76. Found: C, 68.17; H, 7.32; Cl, 8.88.

20α-Chloro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadien-3-one 21-Acetate (3).—A solution of 1.2 g. of 20-chloride (2) and 764 mg. of osmium tetroxide in 25 ml. of benzene was stirred at 25° for 18 hr. To the reaction mixture was added 20 ml. of benzene, 55 ml. of water, 36 ml. of methanol, 5.6 g. of sodium sulfite, and 5.6 g. of potassium bicarbonate. After stirring for 5 hr., the inorganic salts were removed by filtration. The steroid was recovered by extraction with methylene chloride and purified by chromatography over Florisil. The fraction of 819 mg., eluted with Skellysolve B-15% and 20% acetone, was recrystallized from ethyl acetate–Skellysolve B yielding 700 mg. of **3**, m.p. 218–221°. The analytical sample, $[\alpha]_D$ +2° (chloroform), was prepared by further recrystallization and melted at 221–223°.

Anal. Calcd. for $C_{23}H_{31}ClO_6$: C, 62.93; H, 7.12. Found: C, 62.99; H, 7.64.

20-Chloro-21-hydroxy-3,11,17-trioxo-16,17-seco-1,4-pregnadien-16-oic Acid 21-Acetate (4). **A.**—Diol **3**, 100 mg., dissolved in 10 ml. of acetone was treated with an excess of chromic acid reagent.[17] The crude product, 50 mg., isolated by evaporation of the solvent and dilution with water, was recrystallized from ethyl acetate, and melted at 238–241° dec.; λ_{max}^{EtOH} 238 mμ (ε 15,000).

Anal. Calcd. for $C_{23}H_{27}ClO_7$: C, 61.26; H, 6.04; Cl, 7.86. Found: C, 61.13; H, 6.32; Cl, 7.80.

B. 20-Chloro-11β,21-dihydroxy-3,17-dioxo-16,17-seco-1,4-pregnadien-16-al 21-Acetate (3a).—A solution of 450 mg. of **3** in 25 ml. of acetic acid containing 550 mg. of lead tetraacetate was stirred at 26° for 16 hr. The acetic acid was removed under reduced pressure, and ice–water was added to the residue. The product obtained by extraction was an oil whose infrared spectrum was in accord with structure **3a**. This oil was oxidized with chromic acid in acetone[17] to yield 90 mg. of crystals, m.p. 238–240°, identical by infrared data with **4** prepared by method A.

11β,21-Dihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one 21-Trityl Ether (5).[18]—A mixture of 10.0 g. of 11β,21-dihydroxy-1,4,17-(20)-*cis*-pregnatrien-3-one and 10.4 g. of trityl chloride in 90 ml. of pyridine was stored at room temperature for 16 hr. followed by warming on a steam bath for 2 hr. Ice was added to the cooled mixture, and the resulting oil was extracted with methylene chloride. Following the usual work-up there was obtained, upon recrystallization from 2-propanol, 14.8 g. of crystalline **5**, m.p. 204–214°. Several recrystallizations from acetone afforded material melting at 215–221°.

Anal. Calcd. for $C_{40}H_{42}O_3$: C, 84.17; H, 7.42. Found: C, 84.00; H, 7.40.

11β,16α,21-Trihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one 21-Trityl Ether (6).—A solution of 4.0 g. of trityl ether (**5**) and 1.2 g. of selenium dioxide in 60 ml. of dioxane and 12 ml. of water was heated under reflux for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure. The residue was partitioned between methylene chloride and water. The organic layer, after chromatography over 200 g. of Florisil, yielded a fraction of 2.8 g., eluted with Skellysolve B–20% acetone. A solvate, melting slowly at about 123° with gassing, was obtained upon recrystallization from 2-propanol (2.36 g., 38.2%).

Anal. Calcd. for $C_{40}H_{42}O_4 \cdot C_3H_8O$: C, 79.84; H, 7.79. Found: C, 79.59; H, 7.38 (dried at 26°).

Several recrystallizations from ethyl acetate raised the melting point to 221–223°, but a satisfactory analysis for the nonsolvated product could not be obtained.

20α-Chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-Trityl Ether (7).—Over a period of 20 min. there was added 0.16 ml. of thionyl chloride to a solution of 1.18 g. of **6** (dried to constant weight at 120°) in 40 ml. of methylene chloride and 1.0 ml. of collidine. The temperature of the reaction was maintained at 6°. The reaction mixture was washed with dilute acid and water and dried. Chromatography over 80 g. of Florisil yielded a crystalline fraction of 794 mg. eluted with Skellysolve B–12% acetone. Recrystallization from ethyl acetate gave 550 mg. (45%) of a solvate, m.p. 120–130° dec. Two recrystallizations from ethyl acetate afforded an analytical sample, m.p. 193–195°.

Anal. Calcd. for $C_{40}H_{41}ClO_3$: C, 79.38; H, 6.83; Cl, 5.86. Found: C, 79.80; H, 7.11; Cl, 5.74.

When compound **7** was recrystallized from isopropyl alcohol–Skellysolve B, a solvate, m.p. 151–157° with gassing, was obtained.

Anal. Found: C, 79.09; H, 7.13; Cl, 6.08 (dried at 80°).

A more polar fraction, eluted from the Florisil with Skellysolve B–20% acetone was identified as **8** by mixture melting point and infrared absorption spectrum.

20α-Chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one (8).—Anhydrous hydrogen chloride was bubbled for 1 min. through a solution of 470 mg. of **7** in 30 ml. of methylene chloride cooled to −8°. The solution was maintained at −8° for 1 hr. and then washed with sodium bicarbonate solution. Chromatography over Florisil using Skellysolve B–acetone mixture afforded a fraction of 166 mg. (83%) of triphenylcarbinol and 183 mg. (65%) of diol **8**. The latter after recrystallization from ethyl acetate melted at 167–171° dec. The yield was 125 mg. (44.5%). The analytical sample, m.p. 169–170° dec., was recrystallized from ethyl acetate.

Anal. Calcd. for $C_{21}H_{27}ClO_3$: C, 69.50; H, 7.50; Cl, 9.77. Found: C, 69.26; H, 7.39; Cl, 9.34.

Acylation of 80 mg. of **8** with acetic anhydride–pyridine yielded 40 mg. (44.8%) of 20α-chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**2**), m.p. 159–161°, identical with a known sample.

11β,20β,21-Trihydroxy-1,4,16-pregnatrien-3-one 21-Acetate (9).—Five grams (123 mmoles) of 20α-chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**2**), 5.0 g. (39 mmoles) of dry silver fluoride, and 500 ml. of freshly distilled acetonitrile were stirred and heated at reflux for 1 hr. The reaction mixture was cooled and filtered, and the filtrate evaporated. The solid residue, 4.7 g., was purified by chromatography over Florisil (400 g.) to afford 400 mg. (8.4%) of crystalline product, obtained at an eluting concentration of 12% acetone in Skellysolve B. Recrystallization from ethyl acetate–Skellysolve B gave an unidentified analytical sample melting at 182–183°; $[\alpha]_D$ +95° (chloroform); λ_{max}^{EtOH} 243 mμ (ε 15,700).

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.11; H, 7.52; F, 4.89. Found: C, 71.00; H, 7.53; F, 4.60.

A second and major product, 3.8 g. (81%), of 11β,20β,21-trihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**9**), was obtained by elution from the Florisil column at a concentration of 15 to 18% acetone in Skellysolve B. Recrystallization from ethyl acetate–Skellysolve B gave an analytical sample melting at 194–196°; $[\alpha]_D$ +92° (chloroform); M_D 355.6; λ_{max}^{EtOH} 243 mμ (ε 15,600).

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 71.48; H, 7.82. Found: C, 71.29; H, 7.73.

11β,21-Dihydroxy-1,4,16-pregnatrien-3,20-dione 21-Acetate (10).—In a 200-ml. one-necked flask were placed 1.3 g. (3.36 mmoles) of 11β,20β,21-trihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**9**), 140 ml. of ethyl acetate, and 5.0 g. of activated manganese dioxide. The flask was stoppered and shaken at 25° for 17 hr. After filtering, the filtrate was concentrated and chilled, and the white precipitate collected, 925 mg. (72%), m.p. 200–208°.

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

(15) A synthetic magnesia–silica gel manufactured by the Floridin Co., Warren, Pa.

(16) A saturated hydrocarbon fraction, b.p. 60–71°, available from Skelly Oil Co., Kansas City, Mo.

(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(18) The authors are indebted to A. R. Hanze of these laboratories for the preparation of this compound.

An analytical sample melted at 208–209°; $[\alpha]_D$ +146° (chloroform); λ_{max}^{EtOH} 242 mμ (ε 23,750).

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 72.08; H, 7.30.

11β,20β,21-Trihydroxy-1,4,16-pregnatrien-3-one 20,21-diacetate (9a).—A solution composed of 1.0 g. (2.6 mmoles) of 11β,20β,21-trihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**9**), 5 ml. of acetic anhydride, and 5 ml. of pyridine was stirred under nitrogen at about 25° for 22 hr. and poured into 100 ml. of ice–water. Extraction of the water mixture with methylene chloride and chromatography of the extract over 100 g. of Florisil gave, after elution with 10% acetone–90% Skellysolve B, a 76% yield of product. Recrystallization from ethyl acetate yielded material melting at 114–116° which showed one spot on paper-gram analysis (FBF system[19]); $[\alpha]_D$ +125° (chloroform); M_D 535.6; λ_{max}^{EtOH} 243 mμ (ε 14,900).

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.09; H, 7.36.

11β,20β,21-Trihydroxy-16α,17-oxido-1,4-pregnadien-3-one 21-Acetate (12).—One gram of 11β,20β,21-trihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**9**) and 16.5 ml. of perbenzoic acid in 240 ml. of benzene were allowed to stand at room temperature for 2 hr. The benzene solution was then washed with 1% sodium hydroxide solution and water. The crystalline product, m.p. 196–199°, 600 mg., was obtained by concentrating the benzene solution after drying over anhydrous sodium sulfate. The analytical sample, m.p. 203–204°, $[\alpha]_D$ +65° (chloroform), λ_{max}^{EtOH} 243 mμ (ε 14,850), was recrystallized from ethyl acetate.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.96; H, 7.66.

11β-Hydroxy-20β,21-oxido-1,4,16-pregnatrien-3-one (13).—In a 125-ml. erlenmeyer flask were placed 965 mg. (2.66 mmoles) of 20α-chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**2**) and 50 ml. of methanol. After the solids had dissolved, the solution was cooled in an ice bath, and 54 ml. of 0.1 *N* sodium hydroxide solution was added with vigorous stirring over a 2-min. period. After standing in the ice bath an additional 5 min., the reaction mixture was filtered and the white crystalline solid was collected. After drying, the product weight 0.58 g. (66.5%) yield). Recrystallization from acetone–Skellysolve B afforded 11β-hydroxy-20β,21-oxido-1,4,16-pregnatrien-3-one (**13**), m.p. 195–204°. An analytical sample prepared by further recrystallizations from acetone–Skellysolve B melted at 195–204°; $[\alpha]_D$ +100° (chloroform); λ_{max}^{EtOH} 243 mμ (ε 14,750).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.84; H, 8.23.

In other experiments quantitative yields of crude oxide precipitated from the reaction mixture during the course of the experiments. Paper chromatography (carbitol–methylcyclohexane)[20] indicated that these materials contained two components, which were concluded to be the α- and β-forms of the oxide.

20α-Chloro-11β,21-dihydroxy-4,16-pregnadien-3-one 21-acetate (2a).—A solution of 2.0 g. of 11β,16α,21-trihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-acetate,[2] 1.4 ml. of tri-*n*-butylamine, and 0.44 ml. of thionyl chloride in 45 ml. of methylene chloride and 130 ml. of ether was stirred at 0° for 1 hr. The reaction was worked up in the usual manner and chromatographed over Florisil. Recrystallization of the crystalline fraction gave 0.9 g. (42.0%) of chloride, m.p. 156–158°. The analytical sample, m.p. 159–160°, $[\alpha]_D$ +172° (chloroform), was prepared by recrystallization from the same solvent.

Anal. Calcd. for $C_{23}H_{31}ClO_4$: C, 67.88; H, 7.68; Cl, 8.71. Found: C, 67.89; H, 8.06; Cl, 8.49.

11β-Hydroxy-20β,21-oxido-4,16-pregnadien-3-one (13a).—A solution of 1.0 g. of **2a** in 50 ml. of methanol was treated with 26.0 ml. of 0.1 *N* sodium hydroxide. After 2 hr. at 26° titration of the excess alkali with standard acid showed that 1 mole of alkali was consumed. Most of the alcohol was removed by distillation. Dilution of the residue with water precipitated 690 mg. (84.5%) of **13a**, m.p. 145–150°. Several recrystallizations from ethyl acetate gave an analytical sample; m.p. 154–155°; λ_{max}^{EtOH} 242 mμ (ε 16,300); $[\alpha]_D$ +212° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.04; H, 8.93.

Proof of Structure of 11β-Hydroxy-20,21-oxido-4,16-pregnadien-3-one (13a).—One gram of 11β-hydroxy-20,21-oxido-4,16-pregnadien-3-one (**13a**) in 50 ml. of benzene was added to a stirred suspension of 1 g. of lithium aluminum hydride in 100 ml. of ether. The reaction mixture was heated under reflux for 1 hr. and then hydrolyzed by the addition of water. The organic layer was decanted from the precipitated salts and the solvent distilled under reduced pressure. The oily residue was dissolved in 150 ml. of ethyl acetate and shaken with 5 g. of manganese dioxide for 18 hr. The reaction mixture was filtered and evaporated, and the residue was chromatographed over 80 g. of Florisil. The crystalline fraction of 339 mg. eluted by Skellysolve B–12% acetone was recrystallized from ethyl acetate–Skellysolve B to yield 150 mg. of **31**, m.p. 167–171°. The analytical sample, λ_{max}^{EtOH} 241 mμ (ε 25,200), melted at 171–173°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.26; H, 8.96.

A more polar fraction, eluted by Skellysolve B–20% acetone, weighed 384 mg. One recrystallization afforded 200 mg. of **30**, m.p. 147–150°. The analytical sample, λ_{max}^{EtOH} 242 mμ (ε 25,200), melted at 151–153°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 76.32; H, 9.15. Found: C, 76.32; H, 9.27.

4,16-Pregnadiene-3,11,20-trione (32).—A slight excess of chromic acid solution was added to 95 mg. of **31** dissolved in 3 ml. of acetone. The excess oxidizing agent was destroyed with a few drops of methanol. The solvent was evaporated and the product extracted with methylene chloride. The fraction (20 mg.) eluted from a Florisil column with Skellysolve B–20% acetone was crystallized from a few drops of ethyl acetate. It melted at 200–203° and did not depress the melting point of an authentic sample. The infrared spectrum of this material was identical with that of a known sample of **32**.

20ξ-Fluoro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-Acetate (15) and 16α- and 16β-Fluoro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one 21-Acetate (18a and 18b).—In a 1-gal. polyethylene bottle were placed 500 ml. of methylene chloride and 108 g. (1.5 moles) of tetrahydrofuran. The bottle was flushed with nitrogen, cooled in a Dry Ice–acetone bath to about −60°, and 60 g. (3.0 moles) of anhydrous hydrogen fluoride condensed into the bottle. A solution of 19.4 g. (0.06 mole) of 11β-hydroxy-20,21-oxido-1,4,16-pregnatrien-3-one (**13**), dissolved in 2 l. of methylene chloride and cooled to about −60°, was poured into the methylene chloride–tetrahydrofuran–hydrogen fluoride solution, mixed well by swirling, and the polyethylene bottle was placed in an ice bath and kept at about 0° for about 4 hr. The reaction mixture was then cooled to about −50° and poured into a stirred solution of 414 g. (3.0 moles) of potassium carbonate dissolved in 2 l. of water. After stirring for about 15 min. the methylene chloride phase was separated and the aqueous phase extracted with three 200-ml. portions of methylene chloride. The methylene chloride extracts were combined, washed once with 200 ml. of water, filtered, and evaporated. The residual white solid weighed 22 g. This white solid was placed in a 500-ml. erlenmeyer flask together with 140 ml. of acetic anhydride and 140 ml. of pyridine. After standing at about 25° for about 18 hr. the reaction mixture was poured into about 2 l. of ice–water, stirred for about 15 min., and then extracted three times with 200-ml. portions of methylene chloride. The combined methylene chloride extracts were washed with two 200-ml. portions of water. The methylene chloride phase was filtered and evaporated to dryness, yielding 22 g. of white solid which was purified by chromatography over Florisil. A column of Florisil (2 kg.) in Skellysolve B was prepared. About 100 ml. of methylene chloride solution containing 33.5 g. of the fluoroacetates prepared as described earlier was poured onto the column which was then developed and eluted with acetone–Skellysolve B, (8:92, by volume). Four-liter fractions were collected and evaporated, and their composition determined by paper chromatography (Bush B-3a system).[21] Fractions 1–7 contained small amounts of oils and were discarded. Fractions 8–13 contained one material (by paper chromatography) and were combined. Recrystallization of these fractions from ethyl acetate gave an analytical sample of 20ξ-fluoro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**15**), m.p. 173–178°; $[\alpha]_D$ +80° (chloroform).

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.11; H, 7.52; F, 4.89. Found: C, 71.28; H, 7.55; F, 4.59.

Fractions 14–33 were shown to contain two major materials (by paper chromatography), one of which was **15**. Combina-

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tion of these fractions and repeated chromatography in the manner described before yielded the second component, 16-fluoro-11β,21-dihydroxy-1,4-,17(20)-*trans*-pregnatrien-3-one 21-acetate (**18**). Recrystallization from ethyl acetate gave material melting at 184–186°; [α]D +61° (chloroform).

Another sample prepared in a similar manner melted at 178–179°; [α]D +61° (chloroform); λ_{max}^{EtOH} 242 mμ (ε 15,300).

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.11; H, 7.52; F, 4.89. Found: C, 71.25; H, 7.52; F, 4.84.

The 16-fluoro 21-acetate obtained by this procedure is predominantly the 16α isomer contaminated with a small amount of the 16β-epimer. The 16β-compound (**18b**) was not isolated. Pure 16α-fluoro 21-acetate (**18a**), m.p. 190–191°, [α]D +63° (chloroform), was obtained by treatment of the mixed 16α- and 16β-epimers (**18a** and **18b**) with osmium tetroxide-N-methylmorpholine oxide peroxide complex as shown in the preparation of **20** and **21**.

20ξ-Fluoro-21-hydroxy-3,11,17-triketo-16,17-seco-1,4-pregnadien-16-oic Acid 21-Acetate (**16**).—A 10% molar excess of ozone was absorbed by a solution of 1.0 g. of **15** in 70 ml. of methylene chloride maintained at 0°. The solvent was distilled under reduced pressure and the residue dissolved in 60 ml. of methanol containing 10 ml. of N-hydrochloric acid. The solution was heated under reflux for 16 min., concentrated almost to dryness, and the steroid extracted with methylene chloride An acidic fraction was recovered by extraction with potassium bicarbonate solution. This fraction of 168 mg. was oxidized in acetone solution with chromic acid reagent[17] to yield 90 mg. of a crystalline product, m.p. 203–208°. Several recrystallizations from ethyl acetate provided the analytical sample, m.p. 221–224°.

Anal. Calcd. for $C_{23}H_{27}FO_7$: C, 63.58; H, 6.27; F, 4.37. Found: C, 63.14; H, 6.37; F, 4.44.

16-Fluoro-11β-hydroxy-1,4-androstadiene-3,7-dione (**22**).—A solution of 1.3 g. (3.35 mmoles) of 16α-fluoro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one 21-acetate (**18a**) in 200 ml. of methylene chloride was cooled to −70 to −75°. A total of 2.85 mmoles of ozone was absorbed when bubbled through the solution. The residue obtained after removing the solvent under vacuum was dissolved in 20 ml. of N-hydrochloric acid and 90 ml. of methanol. The solvent was again removed under reduced pressure after a 15-min. reflux period. The residue was dissolved in methylene chloride and washed with water and then saturated salt solution. Chromatography over Florisil yielded a material which when recrystallized three times from ethyl acetate afforded 60 mg. of white crystals, m.p. 197–198°.

Anal. Calcd. for $C_{19}H_{23}FO_3$: C, 71.67; H, 7.28; F, 5.97. Found: F, 5.98.

Another sample, had m.p. 193–195°, [α]D +135° (chloroform).

Anal. Found: C, 71.36; H, 7.41.

20ξ-Fluoro-11β,21-dihydroxy-1,4,16-pregntrien-3-one (**14**).—A solution composed of 1.55 g. of 20ξ-fluoro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**15**), 80 ml. of methanol, and 80 ml. of 0.1 *N* sodium hydroxide was stirred at 25° for 1 hr. (In the case of the corresponding 20-chloro analog, a copious precipitate formed in 5 min., whereas this reaction mixture remained clear; *cf.* preparation of **13**.) The methanol was evaporated under reduced pressure and the aqueous residue extracted with methylene chloride. The methylene chloride extract was filtered and evaporated, and the solid white residue purified by chromatography over Florisil. A small amount of crystalline material was obtained at an elution concentration of 15% acetone–85% Skellysolve B. This material (12%) proved to be the oxide (**13**). No attempt was made to purify the mixed fractions by further chromatography. The desired fluorohydrin (16%) was eluted with 20% acetone–80% Skellysolve B and recrystallized three times to a melting point of 132–142°; [α]D +78° (chloroform); λ_{max}^{EtOH} 243 mμ (ε 14,850).

Anal. Calcd. for $C_{21}H_{27}FO_3$: C, 72.80; H, 7.86; F, 5.48. Found: C, 72.89; H, 8.17; F, 5.37.

Acylation of **14** with acetic anhydride–pyridine afforded the acetate (**15**) identical with the starting material. The alcohol (**14**) failed to react with manganese dioxide, only starting material being detected by infrared analysis.

16α-Fluoro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one (**17**).—A solution composed of 520 mg. of 16α-fluoro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one 21-acetate (**18**), 27 ml. of methanol, and 27 ml. of 0.1 *N* sodium hydroxide was stirred at 25° for 1 hr. The methanol was evaporated under vacuum and the aqueous residue extracted with methylene chloride. The methylene chloride extract was filtered and evaporated, and the solid white residue purified by chromatography over Florisil. The crystalline material eluted with 20% acetone–80% Skellysolve B, 246 mg. (53%), was recrystallized three times from ethyl acetate to a melting point of 110–125° (ethyl acetate solvate); [α]D +57° (chloroform); λ_{max}^{EtOH} 243 mμ (ε 13,550). The analytical sample was dried under high vacuum at 100° overnight before analysis.

Anal. Calcd. for $C_{21}H_{27}FO_3$: C, 72.80; H, 7.86; F, 5.48. Found: C, 72.96; H, 7.93; F, 5.20.

Treatment of **17** with acetic anhydride–pyridine regenerated the acetate (**18**) in good yield.

16α-Fluoro-11β-hydroxy-3-oxo-1,4,17(20)-*trans*-pregnatrien-21-al (**19**).—A mixture composed of 480 mg. of 16α-fluoro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one (**17**), 3.5 g. of activated manganese dioxide,[22] and 80 ml. of ethyl acetate was stirred at 25° for 18 hr. Filtration, followed by evaporation of the solvent yielded a white solid which was recrystallized three times from acetone to a melting point of 223–224°; [α]D +107° (chloroform); λ_{max}^{EtOH} 237 mμ (ε 29,400).

Anal. Calcd. for $C_{21}H_{25}FO_3$: C, 73.23; H, 7.32; F, 5.52. Found: C, 72.90; H, 7.45; F, 5.39.

16α- and 16β-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadien-3,20-one 21-Acetate (**20 and 21**).—To a solution of 200 ml. of *t*-butyl alcohol, 5 ml. of pyridine, 86 mg. of osmium tetroxide, and 4.3 g. (11 mmoles) of a mixture of 16α- and 16β-fluoro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one 21-acetate (**18a** and **18b**) was added 5 ml. of a 2 *N* solution of N-methylmorpholine oxide-peroxide.[11] After stirring at about 25° for 16 hr., 10 ml. of a freshly prepared 1% solution of sodium hydrosulfite was added, stirred for 5 min., and the reaction mixture filtered through a mat of filter aid. The *t*-butyl alcohol was evaporated from the filtrate under vacuum, the residue taken up in methylene chloride and washed with dilute hydrochloric acid and water. The methylene chloride phase was dried and evaporated under reduced pressure to give a tan solid weighing 4.1 g. A column of 300 g. of Florisil was prepared, and the crude product in 100 ml. of methylene chloride was poured over it. The column was developed by eluting with 10–15% acetone in Skellysolve B with 600-ml. fractions being collected and the composition of each fraction being determined by papergram analysis (FBF system[19]). Judicious selection of fractions and several additional chromatograms resulted in the recovery of 2.2 g. of starting material, 278 mg. (12%) of the 16α isomer (**20**), and 105 mg. (4.9%) of the 16β isomer (**21**). Recrystallization of the 16α isomer (**20**) from ethyl acetate afforded a material with a melting point of 219–220°; λ_{max}^{EtOH} 243 mμ (ε 16,100); [α]D +83° (chloroform).

Anal. Calcd. for $C_{23}H_{29}FO_6$: C, 65.70; H, 6.95; F, 4.52. Found: C, 65.23; H, 7.01; F, 4.52.

Recrystallization of the 16β isomer from ethyl acetate gave material whose melting point (174–177°), infrared spectrum, and mobility on paper chromatography were identical with material prepared by another route and identified as 16β-fluoroprednisolone acetate[11] (**21**).

Subsequent recycles of the recovered starting material resulted in an increased yield of the 16α isomer (**20**), 22% being obtained from the third recycle. No 16β isomer was observed in the recycle.

The purified 16α-fluoro starting material (**18a**), recovered after several recycles as described, was recrystallized from ethyl acetate to a melting point of 190–191°; λ_{max}^{EtOH} 242 mμ (ε 15,300); [α]D +63° (chloroform).

Anal. Calcd. for $C_{23}H_{29}FO_4$: C, 71.11; H, 7.52; F, 4.89. Found: C, 71.21; H, 7.84; F, 4.77.

16α-Fluoro-17α,21-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione 21-Acetate (**28**).—16α-Fluoroprednisolone acetate (**20**) (3.03 g. of a chromatographic fraction—one spot on papergram) was dissolved in 42 ml. of pyridine, and 1.68 g. of *N*-bromoacetamide was added. The reaction mixture was stirred for 20 min., and then an excess of sulfur dioxide was passed over the solution while cooling in an ice–water bath. The crude product was precipitated by addition of the reaction mixture to 300 ml. of water containing 56 ml. of concentrated hydrochloric acid. This material (2.70 g.) was dissolved in methylene chloride and percolated through 190 g. of Florisil. The fractions eluted with Skellysolve B containing 12–20% acetone were shown by paper chromatography to be free from **20** and were combined to give 2.65 g.

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(92.0%) of crystalline $\Delta^{9,11}$ compound (**28**) showing a single spot on paper chromatography.

9α-Bromo-16α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (27).—A solution of 8.3 ml. of 70–72% perchloric acid in 53 ml. of water was added to 2.65 g. of **28** dissolved in 48 ml. of methylene chloride and 160 ml. of *t*-butyl alcohol. To this mixture was added 1.19 g. of N-bromoacetamide in 32 ml. of *t*-butyl alcohol. After stirring the reaction mixture for 15 min., an excess of dilute sodium sulfite solution was added. Most of the *t*-butyl alcohol was distilled under vacumn, and 200 ml. of water was added. The bromide (**27**) recovered by filtration weighed 2.98 g. (90.5%). Paper chromatography showed only one spot moving slower than the starting unsaturated compound.

16α-Fluoro-17α,21-dihydroxy-9β,11β-oxido-1,4-pregnadiene-3,-20-dione 21-Acetate (29).—A mixture of 2.98 g. of bromide (**27**) and 3.6 g. of potassium acetate in 160 ml. of acetone was heated under reflux for 17 hr. The solvent was distilled under vacuum and the residue triturated four times with methylene chloride. The methylene chloride solution was passed over 200 g. of Florisil. The fractions eluted with Skellysolve B–15% and 20% acetone were combined to yield 2.13 g. (84.0% yield) of oxide. A fraction of 367 mg. which contained both oxide and bromohydrin was recycled to yield 135 mg. (5.4% yield) of additional oxide.

9α,16α-Difluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (25).—A solution of 2.26 g. of oxide (**29**) dissolved in 88 ml. of methylene chloride was cooled to −20° and added to a similarly chilled solution of 18.1 g. of hydrogen fluoride dissolved in 31 ml. of freshly distilled tetrahydrofuran. After thorough mixing the solution was maintained at 4° for 15 hr. The reaction mixture was added to 2.3 l. of water containing 57 g. of potassium bicarbonate. The product was removed by extraction with methylene chloride. Chromatography over Florisil (eluted with Skellysolve B–20% acetone) afforded 2.02 g. (85.3% yield) of crystalline difluoride (**25**). Paper chromatography[19] showed only one spot. The analytical sample, prepared from ethyl acetate–Skellysolve B, melted at 265–268° dec.

Anal. Calcd. for $C_{23}H_{28}F_2O_6$: C, 63.00; H, 6.44; F, 8.67. Found: C, 62.61; H, 6.59; F, 8.60.

9α,16α-Difluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (26).—A mixture of 1.31 g. of 9α,16α-difluoroprednisolone acetate (**25**), 1.3 g. of potassium bicarbonate, 13 ml. of water, and 130 ml. of methanol was stirred at 26° under nitrogen for 5 hr. The solution was neutralized with acetic acid and concentrated to dryness. The residue was triturated with water and filtered to yield 1.04 g. (89%) of crude product. Recrystallization from acetone afforded 700 mg. (59.4%) of **26**, m.p. 275–278° dec., and a second crop of 160 mg. (13.5%), m.p. 275–278° dec.

The analytical sample prepared from ethyl acetate–acetone melted at 278–280°.

Anal. Calcd. for $C_{21}H_{26}F_2O_5$: C, 63.62; H, 6.61. Found: C, 63.62; H, 6.60.

16α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (23).—Saponification of 880 mg. of **20** in the manner described for the preparation of **26** afforded 725 mg. (91.8%) of crude product. Recrystallization from acetone–ethyl acetate gave 450 mg. (57.0% yield) of **23**; m.p. 243–247° dec.; $[\alpha]_D$ +81° (acetone).

Anal. Calcd. for $C_{21}H_{27}FO_5$: C, 66.65; H, 7.19; F, 5.02. Found: C, 66.68; H, 7.55; F, 5.18.

16α-Fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (24).—16α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (**23**) (640 mg., made up in part of mother liquors) was dissolved in 6 ml. of pyridine, cooled to 0°, and 0.8 ml. of mesyl chloride added. After 15 hr. at 4° the dark solution was poured into 150 ml. of dilute hydrochloric acid. The yield of crude mesylate was 530 mg. This solid was dissolved in 30 ml. of acetone, 500 mg. of sodium iodide added, and the mixture heated under reflux for 15 min. The solvent was distilled under reduced pressure and the residue was taken up in 8 ml. of acetic acid. After 50 min. at 26° a solution of 0.6 g. of sodium thiosulfate in 8 ml. of water was added followed by 70 ml. of water. The steroid was recovered by extraction with methylene chloride. The extract was passed over 40 g. of Florisil. The fractions eluted with Skellysolve B–20% and 30% acetone were combined and recrystallized from acetone–ethyl acetate yielding 210 mg. of **24**, m.p. 256–260° dec. One recrystallization from acetone raised the melting point to 266–270° dec. (140 mg.).

Anal. Calcd. for $C_{21}H_{27}FO_4$: C, 69.59; H, 7.51. Found: C, 69.38; H, 7.54.

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Purine Nucleosides. V. Preparation and Reactions of Some 9β-D-Ribofuranosyl-3,5′-purine Cyclonucleosides[1,2]

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The 3,5′-cyclonucleosides of guanosine and xanthosine have been prepared. It has been established that cyclization occurred at position 3 since acid hydrolysis gave a 3-substituted purine as judged by ultraviolet absorption data. The synthesis of 2′,3′-*O*-isopropylidene-3,5′-inosine cyclonucleoside has been accomplished. Acid hydrolysis of 2′,3′-*O*-isopropylidene-3,5′-adenosine cyclonucleoside *p*-tolylsulfonate resulted in cleavage of the glycosidic linkage at position 9 to give 3,5′-(5′-deoxy-D-ribofuranosyl)adenine (XIII).

The first reported isolation and characterization of a purine cyclonucleoside was that of Clark, Todd, and Zussman[3] who prepared 2′,3′-*O*-isopropylidene-3,5′-adenosine cyclonucleoside *p*-tolylsulfonate (I) from 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)adenosine. An X-ray analysis confirmed the structure of I and provided proof of the β configuration of adenosine. Baker and Joseph[4] have reported a similar cyclization at position 3 with the compound 6-dimethylamino-9-(3′-amino-3′-deoxy-5′-mesyl-β-D-ribofuranosyl)purine 2′,3′-carbonate. The ease of formation of a 3,5′-purine cyclonucleoside has been related to the basicity of the heterocyclic system.[3,5] Khorana and co-workers[6] have reported that 2′,3′-*O*-isopropylideneguanosine 5′-*O*-[di(*p*-nitrophenyl)phosphate] was converted to a cyclonucleoside in refluxing acetonitrile. Baker and co-workers[5] treated 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)guanosine with sodium iodide in acetonylacetone to obtain a 2′,3′-*O*-isopropylideneguanosine cyclonucleoside as the iodide

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