4-Keto-7β-chlorocholestane (XII).—A sample of 0.1017 g. of the *i*-ketone X was dissolved in 30 ml. of hot glacial acetic acid and concd. hydrochloric acid was added to turbidity. Sufficient ether was added to clear the turbidity and the solution was cooled to give a crystalline product. Upon recrystallization from acetone–water, 0.0778 g. of the chloro ketone as matted needles, m.p. 109–111°, $[\alpha]D + 88°$, was produced.

Anal. Calcd. for $C_{27}H_{45}OCl$: C, 77.00; H, 10.77. Found: C, 77.34; H, 10.88.

Twenty ml. of an ethanolic solution of 0.060 g. of XII was treated with two pellets of potassium hydroxide and heated for 0.5 hour. After standing at room temperature overnight, the solution was diluted with water to precipitate 0.050 g. of directly pure *i*-ketone X.

4ξ-Hydroxy-5,7-cyclocholestane (XI).—To 0.26 g. of the *i*-ketone X contained in 50 ml. of dry ether was added 1.0 g. of lithium aluminum hydride. The mixture was refluxed for 1 hour and then the excess hydride was destroyed with wet methanol. The resulting suspension was filtered free of solids and evaporated to a pale yellow oil. This oil was chromatographed on a 1 inch × 7 inch alumina column. Petroleum ether elution produced a small amount of yellow oil. Benzene eluted an oil which, upon trituration with methanol, produced book-like plates, m.p. 89–90°. Recrystallization of the combined benzene eluates from acetone–water or methanol–water gave slow crystallization of 0.10 g. of the *i*-alcohol XI as chunky prisms, m.p. 91–92°, $[\alpha]D + 5.8°$.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.85; H, 11.92. Found: C, 84.20; H, 12.00.

Hydrogenation of XI by the procedure of Shoppee[10] produced an oil. No solid products could be obtained from this oil.

By addition of benzene–ether (4:1) to the column there was eluted an oil which, upon methanol–water trituration, produced clumps of needle crystals of XIV. The study of this substance is reported adequately in the Discussion portion of this paper. It should be pointed out that the hygroscopicity of XIV prevented accurate weighing, and thus the $[\alpha]D + 89°$ should be considered a minimum rotation.

Rearrangement of *i*-Pseudocholesterol.—(a) To 10 ml. of an acetic acid solution of 0.03 g. of the *i*-steroid XI was added one drop of concd. sulfuric acid. The resulting solution was heated at 70° for 1 hour and then evaporated to an oily solid. This mixture was washed with water to remove the acid and the solid remaining was recrystallized from acetone–water to give 0.02 g. of diamond-shaped crystals, m.p. 95–98°. When mix-melted with authentic pseudocholesteryl acetate (m.p. 96–97°),[1a] the m.p. of the authentic material was not depressed. X-Ray powder diagrams and infrared spectra of this compound and authentic pseudocholesteryl acetate were superimposable.

(b) In another experiment the solution of XI, after acid treatment, was made basic with ethanolic potassium hydroxide, filtered to remove inorganic salts, and refluxed for one hour. Addition of water produced needle-like crystals, m.p. 119–123°. This was demonstrated to be authentic pseudocholesterol by melting point, X-ray and infrared comparison with authentic material.

CRAWFORDSVILLE, IND.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. XV.[1] Synthetic Corticoids Related to 9α-Fluoro-16α-hydroxy-hydrocortisone and -prednisolone (Triamcinolone)

BY SEYMOUR BERNSTEIN AND ROBERT H. LENHARD

RECEIVED DECEMBER 4, 1959

A number of synthetic variants of 9α-fluoro-16α-hydroxy-hydrocortisone (Ia) and -prednisolone (triamcinolone) (IIa) have been prepared. These include 9α-fluoro-11β,16α,17α,21-tetrahydroxy-4,6-pregnadiene-3,20-dione (IVa) and 6-dehydrotriamcinolone (VIIa).

In this paper we wish to describe the preparation of certain compounds related to 9α-fluoro-16α-hydroxyhydrocortisone (Ia) and triamcinolone (9α-fluoro-16α-hydroxyprednisolone) (IIa).[2]

Bromination of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (Ib)[2a] in cold acetic acid–ether[3] with one equivalent of bromine gave the 6-bromo compound III (not characterized) which was dehydrobrominated in refluxing *s*-collidine to afford the 4,6-diene diacetate IVb. Saponification with potassium hydroxide in methanol gave 9α-fluoro-11β,16α,17α,21-tetrahydroxy-4,6-pregnadiene-3,20-dione (IVa), isomeric with triamcinolone (IIa). Chromic anhydride–pyridine oxidation of the 4,6-diene diacetate IVb yielded the 11-ketone V. The free tetrol IVa in acetone containing a trace of perchloric acid readily formed an acetonide VI.

Selenium dioxide dehydrogenation[4] of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4,6-pregnadiene-3,20-dione (IVb) in *t*-butyl alcohol and acetic acid gave the expected 1,4,6-triene diacetate VIId together with an approximately equal amount of a by-product assigned the structure 11β,16α,21-triacetoxy-9α-fluoro-17α-hydroxy-1,4,6-pregnatriene-3,20-dione (VIIb).[5]

Saponification of the 1,4,6-triene diacetate VIId gave 6-dehydro-triamcinolone (9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4,6-pregnatriene-3,20-dione, VIIa). Oxidation of VIIa afforded 16α,21-diacetoxy-9α-fluoro-17α-hydroxy-1,4,6-pregnatri-

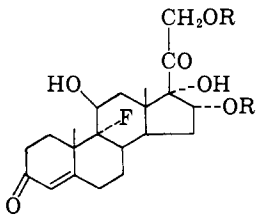
(1) Paper XIV, S. Bernstein and R. Littell, THIS JOURNAL, **82**, 1235 (1960).

(2) For previously described modifications or related compounds, see: (a) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **78**, 5693 (1956); **81**, 1689 (1959); (b) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard and W. S. Allen, *ibid.*, **79**, 4555 (1957); (c) S. Bernstein, *Recent Progress in Hormone Research*, **14**, 1 (1958); (d) J. Fried, A. Borman, W. B. Kessler, P. Grabowich and E. F. Sabo, THIS JOURNAL, **80**, 2338 (1958); (e) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen and I. Ringler, *ibid.*, **81**, 1696 (1959); (f) S. Bernstein and R. Littell, *J. Org. Chem.*, **24**, 429 (1959); (g) S. Bernstein, J. J. Brown, L. I. Feldman and N. E. Rigler, THIS JOURNAL, **81**, 4956 (1959); (h) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **81**, 4968 (1959); and (i) S. Bernstein, M. Heller and S. M. Stolar, *ibid.*, **81**, 1256 (1959).

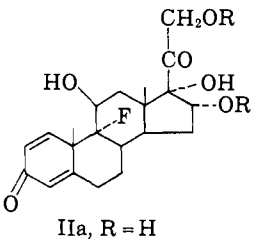
(3) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, *ibid.*, **72**, 4534 (1950).

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

(5) Acetylation in a selenium dioxide–acetic acid dehydrogenation is not without precedent; M. E. Urion, *Compt. rend.*, **199**, 363 (1934), found that under these conditions 1-methylcyclohexene was converted into 1-methylcyclohexene-6-ol acetate in 40% yield.



Ia, R = H
b, R = Ac



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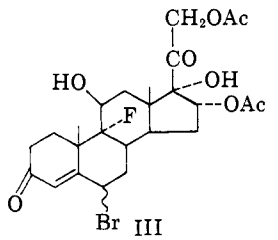
b, R = Ac



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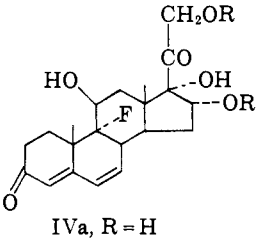
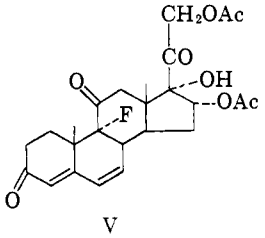


IVa, R = H
b, R = Ac



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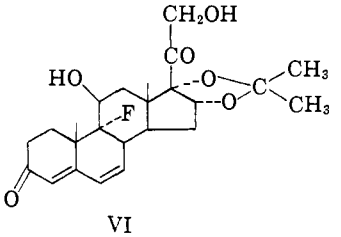

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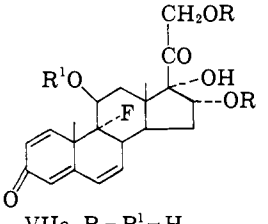
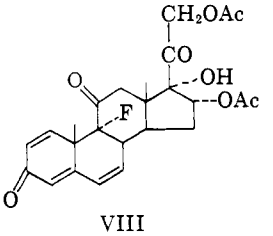
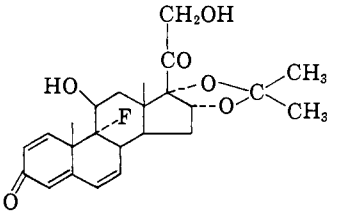


VIIa, R = R¹ = H
b, R = R¹ = Ac
c, R = H; R¹ = Ac
d, R = Ac; R¹ = H



VIII



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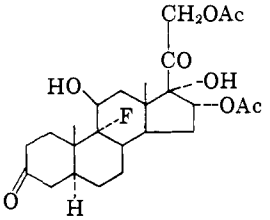
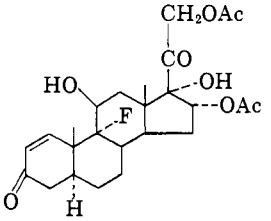


X



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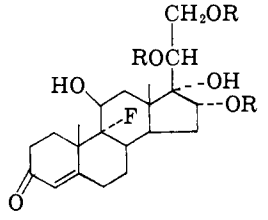
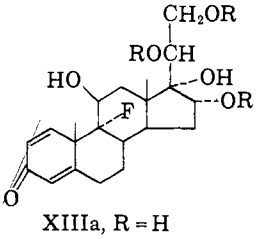
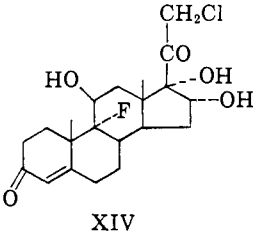


XIIa, R = H
b, R = Ac



XIIIa, R = H
b, R = Ac



XIV

ene-3,11,20-trione (VIII). The acetonide IX was prepared from VIIa in the usual manner.

The 1,4,6-triene triacetate VIIb structure was based on the following. Its infrared spectrum showed hydroxyl absorption at 3485 cm.$^{-1}$. Moreover, an attempt to oxidize VIIb with chromic anhydride–pyridine led only to the recovery of unreacted starting material thereby confirming the absence of a non-esterified hydroxyl group at C-11. In addition, saponification of VIIb with an excess of aqueous potassium carbonate in methanol[6] gave a product which retained the ester bands in the infrared spectrum (ν_{max} 1749 and 1228 cm.$^{-1}$). The ultraviolet absorption spectrum of VIIb showed that the 3-keto-$\Delta^{1,4,6}$-triene moiety was still intact, λ_{max} 220–221 mμ (ε 11,400), λ_{max} 247 mμ (ε 9,000), and λ_{max} 295–297 mμ (ε 12,000).[7] In order to establish unequivocally the structure of the by-product VIIb, it was synthesized. 16α,21-Diacetoxy - 9α - fluoro - 11β,17α - dihydroxy - 1,4,6 - pregnatriene-3,20-dione (VIId) was acetylated under vigorous conditions (acetic anhydride–pyridine, 80–85° for 24 hr.). The residue after saponification with aqueous potassium carbonate in methanol was reacetylated under mild conditions (room temperature) to afford 11β,16α,21-triacetoxy-9α-fluoro-17α - hydroxy - 1,4,6 - pregnatriene - 3,20 - dione (VIIb). The latter compound was contaminated with approximately 25% of starting material VIId and was purified by partition chromatography. The 11,16,21-triacetate prepared in this manner was identical with the by-product VIIb as confirmed by infrared absorption data, admixture melting point determination and paper strip chromatography.

Catalytic hydrogenation of 16α,21-diacetoxy-9α - fluoro - 11β,17α - dihydroxy - 4 - pregnene - 3,-

(6) E. P. Oliveto, C. Gerold, L. Weber, H. Jorgensen, R. Rausser and E. Hershberg, THIS JOURNAL, **75**, 5486 (1953).

(7) Pertinent references on this chromophore are: L. Dorfman, *Chem. Revs.*, **53**, 70 (1953); E. J. Agnello and G. D. Laubach, THIS JOURNAL, **79**, 1257 (1957); and D. Gould, E. L. Shapiro, H. L. Herzog, M. J. Gentles, E. B. Hershberg, W. Charney, M. Gilmore, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **79**, 502 (1957).

20-dione (Ib) in ethanol with 10% palladium-on-carbon afforded presumably the 5α(allo)-compound X, which in turn was dehydrogenated with selenium dioxide in *t*-butyl alcohol and acetic acid.[4] The latter reaction mixture consisted of approximately equal parts of starting material X, Δ^1-analog XI and Δ^4-analog Ib. The desired 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-1-allopregnene-3,20-dione (XI) was isolated by partition chromatography.

Reduction of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (Ib) with sodium borohydride in methanol at 0°, followed by acetylation, gave 16α,20β,21-triacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnen-3-one (XIIb). The *provisional* assignment of the 20β-configuration was based on the work of Norymberski and Woods.[8] Saponification of XIIb gave the solvated free alcohol, 9α-fluoro-11β,16α,17α,20β,21-pentahydroxy-4-pregnen-3-one (XIIa). Similarly, triamcinolone 16,21-diacetate (IIb) has been reduced to 16α,20β,21-triacetoxy-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadien-3-one (XIIIb), and saponification gave 9α-fluoro-11β,16α,17α,20β,21-pentahydroxy-1,4-pregnadien-3-one (XIIIa).[9]

Treatment of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-4-pregnene-3,20-dione (Ia) in pyridine with one equivalent of methanesulfonyl chloride[10] at room temperature for 20 hr. gave in low yield 21-chloro-9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIV).

Biological Assays.[11]—In the liver glycogen deposition assay (hydrocortisone = 1), 9α-fluoro-11β,16α,17α,21-tetrahydroxy-4,6-pregnadiene-3,20-dione (IVa) exhibited an activity approximately equal to the standard, whereas 6-dehydrotriamcinolone (VIIa) was 2.3 (1.4–3.7) times more active. The figures in parentheses represent 95% confidence limits.

Acknowledgment.—The elemental analyses were done by Mr. Louis M. Brancone and associates. Infrared and ultraviolet absorption spectra and optical rotations were done by Mr. William Fulmor and associates. Appreciation is extended to Mr. Charles Pidacks and his associates for advice and help in developing the partition chromatography systems.

Experimental

Melting Points.—All melting points are uncorrected.

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

Absorption Spectra.—The ultraviolet absorption spectra were determined in methanol (unless otherwise noted). The infrared absorption spectra are for pressed potassiumbromide.

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

16α,21-Diacetoxy-6ξ-bromo-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (III).—A stirred suspension of 4.6 g. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione[3] (Ib) in 75 ml. of glacial acetic acid and 375 ml. of ether was treated at 0° with 0.5 ml. of 0.2 *N* hydrogen bromide–acetic acid solution followed by the dropwise addition of 25 ml. of 0.39 *M* bromine–acetic acid solution. During the addition, over a 20-minute period, decolorization was almost instantaneous and complete solution was attained. Stirring was continued for 1 hr. and then the reaction mixture was concentrated under reduced pressure to remove the ether. It then was poured into ice-water and the resultant white solid was collected by filtration and washed with water to afford 4.28 g. of III (positive Beilstein test for bromine), m.p. 136–141.5° dec. The product was dried and used as such in the subsequent dehydrobromination reaction.

16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-4,6-pregnadiene-3,20-dione (IVb).—A solution of 4.28 g. of 16α,21-diacetoxy-6ξ-bromo-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (III) in 60 ml. of *s*-collidine was refluxed for 45 minutes. The collidine hydrobromide precipitate was removed by filtration and washed with ethyl acetate. The filtrate, after being washed successively with 2% sulfuric acid (v./v.), saturated sodium bicarbonate and saline solution, was dried and evaporated to yield 2.74 g. of crude product, $\lambda_{max}^{abs.\ alc.}$ 281 mμ (ε 17,100). The residue was triturated with warm ether, cooled and filtered to afford 1.89 g., m.p. 234–239°. The latter fraction was submitted to partition chromatography on Celite[12] using a solvent system consisting of 2 parts (by volume) of ethyl acetate, 3 parts of petroleum ether (b.p. 90–100°), 3 parts of methanol and 2 parts of water. The cut containing the product was evaporated, and the residue was crystallized from acetone–petroleum ether to give 1.34 g. of pure IVb, m.p. 247–249.5°, $\lambda_{max}^{abs.\ alc.}$ 280–281 mμ (ε 22,500). Two additional crystallizations from the same solvent pair did not alter the melting point nor the ultraviolet extinction coefficient; ν_{max} 3480, 1750, 1710, 1666, 1626, 1591 and 1238 cm.$^{-1}$; $[\alpha]^{25}D$ + 43°.

Anal. Calcd. for $C_{25}H_{31}FO_5$ (478.50): C, 62.75; H, 6.53; F, 3.97. Found: C, 63.02; H, 6.74; F, 4.07.

9α-Fluoro-11β,16α,17α,21-tetrahydroxy-4,6-pregnadiene-3,20-dione (IVa).—A solution of 200 mg. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4,6-pregnadiene-3,20-dione (IVb) in 25 ml. of methanol was cooled to 0°, flushed with nitrogen and treated with a solution of 70 mg. of potassium hydroxide in 2 ml. of methanol. After standing at room temperature for 1 hr., the solution was acidified with glacial acetic acid and evaporated. The residue was triturated with saturated ammonium chloride solution, cooled, filtered and washed with water to yield 125 mg. of crude tetrol, m.p. 222–250° (solvated). Four recrystallizations from acetone–petroleum ether gave 79 mg. of IVa, m.p. 234–241° with dec. (solvated); $[\alpha]^{25}D$ +53° (pyridine); $\lambda_{max}^{abs.\ alc.}$ 280–281 mμ (ε 22,500), ν_{max} 3435, 1720, 1669, 1632 and 1598 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}FO_6$ (394.43): C, 63.94; H, 6.90; F, 4.82. Found: C, 64.15; H, 7.15; F, 5.13.

16α,21-Diacetoxy-9α-fluoro-17α-hydroxy-4,6-pregnadiene-3,11,20-trione (V).—A cold solution of 200 mg. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4,6-pregnadiene-3,20-dione (IVb) in 5 ml. of pyridine was added to a slurry of 150 mg. of chromic anhydride in 2 ml. of cold pyridine. After standing at 26° for 17.5 hr., the reaction mixture was shaken for 1 hr. with a solution of 0.45 g. of sodium sulfite in 5 ml. of water, and then poured into water. The solution was extracted several times with ethyl acetate, and the extract was washed with saturated saline solution, dried and evaporated. Crystallization of the residue from acetone–petroleum ether yielded 82 mg. of product, m.p. 206.5–214.5°. Recrystallization from the same solvents afforded 77 mg., m.p. 210–216° (solvated). One additional crystallization did not alter the melting point. Paper strip chromatography seemed to indicate that the compound was partially deacetylated; therefore all fractions were combined and evaporated. The residue, in 2 ml. of pyridine, was treated with 1 ml. of acetic anhydride and allowed to stand

(8) J. Norymberski and G. Woods, *J. Chem. Soc.*, 3426 (1955).

(9) The sodium borohydride reduction of triamcinolone 16,21-diacetate (IIb) was performed by L. L. Smith, J. J. Garbarini, J. J. Goodman, M. Marx and H. Mendelsohn, THIS JOURNAL, **82**, 1437 (1960).

(10) W. Leanza, J. Conbere, E. Rogers and K. Pfister, 3rd., *ibid.*, **76**, 1691 (1954).

(11) The biological assays were performed by I. Ringler, L. Bortle, E. Heyder, A. Monteforte, J. Perrine and E. Ross of the Experimental Therapeutics Research Section of these laboratories. For a description of the assay procedure see S. Bernstein, R. Littell, J. J. Brown and I. Ringler, *ibid.* **81**, 4573 (1959).

(12) The adsorbent was specially treated Celite "545" which had been washed with 6 *N* hydrochloric acid, water, and finally with 3A alcohol, and then dried at 100°. Celite is the trademark of Johns-Manville Co. for diatomaceous silica products. For a complete description of this technique see R. Littell and S. Bernstein, *ibid.* **78**, 984 (1956).

at room temperature overnight. Methanol was added and after evaporation of solvents the residue was crystallized three times from acetone–petroleum ether to afford 53 mg. of V, m.p. 210–216° (solvated),[13] $[\alpha]^{25}D$ + 111°; $\lambda_{max}^{abs.\ alc.}$ 277–278 mμ (ε 19,300); ν_{max} 3480, 1741, 1668, 1633, 1599 and 1238 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{29}FO_8$ (476.48): C, 63.01; H, 6.13; F, 3.99. Found: C, 63.30; H, 6.47; F, 3.70.

9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4,6-pregnadiene-3,20-dione (VI).—A suspension of 200 mg. of 9α-fluoro-11β,16α,17α,-21-tetrahydroxy-4,6-pregnadiene-3,20-dione (IIIa) in 10 ml. of acetone was treated with 0.02 ml. of 70–72% perchloric acid. After stirring at room temperature for 2 hr. (complete solution after a few minutes), 5 ml. of water and 0.4 ml. of saturated sodium bicarbonate solution were added. Evaporation of the acetone produced a crystalline solid. Saturated saline solution was added and, after cooling, the mixture was filtered and washed with water to afford 204 mg. of product, m.p. 227–250° with effervescence at 160° and resolidification at *ca.* 200°. Recrystallization from acetone–petroleum ether gave 190 mg. of pure VI, m.p. 238–250° with effervescence at 120° and resolidification at *ca.* 180°. One additional crystallization from acetone–petroleum ether did not alter the melting point; λ_{max} 282 mμ (ε 23,000); ν_{max} 3420, 1720, 1659, 1623, 1591 and 857 (acetonide)[14] cm.$^{-1}$; $[\alpha]^{25}D$ + 100°.

Anal. Calcd. for $C_{24}H_{31}FO_6$ (434.49): C, 66.34; H, 7.19; F, 4.37. Found: C, 66.59; H, 7.27; F, 4.65.

16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-1,4,6-pregnatriene-3,20-dione (VIId).—A solution of 500 mg. of 16α,-21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4,6-pregnadiene-3,20-dione (IVb) and 250 mg. of selenium dioxide (resublimed) in 50 ml. of *t*-butyl alcohol and 1 ml. of glacial acetic acid was refluxed for 23 hr. An additional 500 mg. of selenium dioxide was added and refluxing was continued for 4 additional hours. The selenium was removed by filtration through Celite and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate and washed several times with cold 1 *N* sodium hydroxide solution and then by saline solution. The dried solution was evaporated and the residue (0.35 g. of yellow glass) was dissolved in 2 ml. of pyridine and 1 ml. of acetic anhydride and allowed to stand at room temperature overnight. Methanol was added and the solvents were evaporated. The residue was chromatographed on Celite[12] using a solvent system consisting of 3 parts (by volume) of petroleum ether (b.p. 90–100°), 2 parts of ethyl acetate, 3 parts of methanol and 2 parts of water. An automatic fraction cutter set to take 25-ml. fractions was utilized and the products were located by means of Blue Tetrazolium reagent. Fractions 113 through 145 were combined and evaporated. The residue was crystallized from acetone–petroleum ether to give 61 mg. of the desired triene VId, m.p. 224–230°. Recrystallization from acetone–petroleum ether afforded 57 mg. of pure VIId, m.p. 227–230°; $\lambda_{max}^{abs.\ alc.}$ 221–222, 248 and 296–298 mμ (ε 11,700, 10,100 and 10,700, respectively). An additional crystallization from the same solvents did not alter the melting point; ν_{max} 3440, 1740, 1659, 1600 and 1234 cm.$^{-1}$; $[\alpha]^{25}D$ −7°.

Anal. Calcd. for $C_{25}H_{29}FO_8$ (476.48): C, 63.01; H, 6.13; F, 3.99. Found: C, 63.29; H, 6.37; F, 3.69.

Fractions 70 through 95 were combined and evaporated. The residue was crystallized from acetone–petroleum ether–ether to give 115 mg. of the crude by-product assigned the structure 11β,16α,21-triacetoxy-9α-fluoro-17α-hydroxy-1,4,-6-pregnatriene-3,20-dione (VIIb), m.p. 222–234°. Recrystallization from acetone–petroleum ether afforded 86 mg., m.p. 234–243°; $\lambda_{max}^{abs.\ alc.}$ 220–221, 247 and 295–297 mμ (ε 11,400, 9,000 and 12,000, respectively). Four recrystallizations of the latter from ethyl acetate–petroleum ether (b.p. 90–100°) gave 54 mg. of pure VIb, m.p. 244.5–245.5°; $[\alpha]^{25}D$ +24°; $\lambda_{max}^{abs.\ alc.}$ 221,247–251 and 296–297 mμ (ε 11,000, 8,100 and 11,700, respectively); ν_{max} 3485, 1752, 1664, 1612, 1598 and 1235 cm.$^{-1}$.

(13) The behavior of V on paper strip chromatography was the same as before re-acetylation. Its expected mobility was obtained only by spotting very lightly; otherwise, streaking from the origin occurred.

(14) A prominent band occurs in the 857–860 cm.$^{-1}$ region in potassium bromide for a large number of 16α,17α-acetonides. This observation also has been observed independently by L. L. Smith and co-workers, ref. 9.

Anal. Calcd. for $C_{27}H_{31}FO_9$ (518.52): C, 62.54; H, 6.03; F, 3.66. Found: C, 62.47; H, 6.03; F, 3.79.

Attempted oxidation of VIb with chromic anhydride–pyridine led only to the recovery of unchanged starting material as indicated by melting point and infrared absorption spectrum.

Saponification of VIIb with an excess of aqueous potassium carbonate in methanol (room temperature, 20 min.) gave a product which retained the ester band in the infrared absorption spectrum (ν_{max} 3400, 1749, 1724, 1665, 1609 and 1228 cm.$^{-1}$).

Acetylation of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-1,4,6-pregnatriene-3,20-dione (VIId) in pyridine–acetic anhydride (80–85°, 24 hours), followed by saponification of the residue (same conditions as with VIIb above) and finally reacetylation under mild conditions (room temperature, 2.5 days) gave the 11β,16α,21-triacetate VIIb. The residue consisted of approximately 25% of VIId and 75% of VIIb as indicated by paper strip chromatography. The product VIIb was isolated by partition chromatography on Celite[12] and was shown to be identical to the by-product obtained in the selenium dioxide oxidation of IVb above by infrared absorption spectrum and admixture melting point.

9α-Fluoro-11β,16α,17α,21-tetrahydroxy-1,4,6-pregnatriene-3,20-dione (VIIa).—A solution of 500 mg. of 16α,21-diacetoxy-9α-fluoro-17α-hydroxy-1,4,6-pregnatriene (VIId) in 50 ml. of methanol was treated with 1.55 ml. of a 10% aqueous potassium carbonate solution at room temperature. Nitrogen was bubbled through the solution for 10 minutes before the addition of the carbonate solution and continued for 20 minutes after the addition. The reaction mixture was then neutralized with glacial acetic acid, concentrated to a small volume, diluted with saturated saline solution and cooled. The crystalline product was filtered and washed with water to afford 315 mg. of the crude tetrol, m.p. 224–235°. One recrystallization from acetone–petroleum ether and one from acetone gave 150 mg. of VIIa, m.p. 244–251°; $[\alpha]^{25}D$ + 12° (pyridine); λ_{max} 218–221, 246–248 and 295–298 mμ (ε 12,800, 9,800 and 11,300, respectively); ν_{max} 3335, 1718, 1664, 1609 and 1597 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{25}FO_6$ (392.41): C, 64.27; H, 6.42; F, 4.84. Found: C, 64.22; H, 6.63; F, 4.97.

16α,21-Diacetoxy-9α-fluoro-17α-hydroxy-1,4,6-pregnatriene-3,11,20-trione (VIII).—A cold solution of 200 mg. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-1,4,6-pregnatriene-3,20-dione (VIId) in 5 ml. of pyridine was added to a slurry of 150 mg. of chromic anhydride in 2 ml. of cold pyridine. After standing at 24° for 18 hr., the reaction mixture was poured into ice-water and the precipitate was filtered and washed with water. The crude product was dissolved in ethyl acetate and filtered through Celite to remove the inorganic residue. The filtrate was washed with saturated saline and water, dried and evaporated. The residue was crystallized from acetone–petroleum ether to give 131 mg. of VIII, m.p. 231–234°. Two recrystallizations from acetone–petroleum ether afforded 103 mg. of pure trione, m.p. 235–236°, $[\alpha]^{25}D$ + 97°; λ_{max} 216–218, 248–252 and 291–293 mμ (ε 11,900, 9,500 and 11,800, respectively); ν_{max} 3450, 1738, 1663, 1612, 1596(infl.) and 1233 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{27}FO_8$ (474.47): C, 63.28; H, 5.74; F, 4.00. Found: C, 63.08; H, 6.05; F, 3.96.

9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4,6-pregnatriene-3,20-dione (IX).—A suspension of 180 mg. of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4,6-pregnatriene-3,20-dione (VIIa) in 10 ml. of acetone was treated with 0.02 ml. of 70–72% perchloric acid. The reaction time and work up was the same as in the preparation of VI above except that the addition of saturated saline solution to the evaporated reaction mixture produced a soft solid which was extracted with ethyl acetate. The washed and dried extract was evaporated, and the residue was crystallized from acetone–petroleum ether to afford 150 mg. of product, m.p. 212–215° with effervescence and previous softening. Two recrystallizations from acetone–petroleum ether gave 108 mg. of IX, m.p. 213–216°; $[\alpha]^{25}D$ + 68°; λ_{max} 218, 246–250 and 294–296 mμ (ε 11,200, 9,500 and 11,100, respectively); ν_{max} 3450, 1715, 1660, 1639(infl.), 1603 and 858[14] cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{29}FO_6$ (432.47): C, 66.65; H, 6.76; F, 4.39. Found: C, 66.60; H, 7.06; F, 4.40.

16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-5α-pregnane-3,20-dione (X).—A solution of 2.0 g. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (Ib) in 175 ml. of absolute ethanol was hydrogenated at atmospheric pressure and room temperature over 0.2 g. of a 10% palladium–carbon catalyst. After 3 hours when hydrogen uptake had ceased, the catalyst was removed by filtration. The filtrate was evaporated and the residue was dissolved in acetone, treated with animal charcoal, filtered through Celite and evaporated. Crystallization of the residue (λ_{max} none) from ethyl acetate–petroleum ether (90–100°) gave 1.72 g. of product, m.p. 217–220.5°. Two recrystallizations from the same solvent pair afforded 1.26 g. of X, m.p. 222–225°; $[\alpha]^{25}D$ + 9°; ν_{max} 3470, 1740, 1718, 1245 and 1234 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{35}FO_8$ (482.53): C, 62.22; H, 7.31; F, 3.94. Found: C, 62.26; H, 7.64; F, 3.93.

16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-1-allopregnene-3,20-dione (XI).—A solution of 200 mg. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-allopregnane-3,20-dione (X) and 67 mg. of selenium dioxide (resublimed) in 15 ml. of *t*-butyl alcohol and 1.5 ml. of glacial acetic acid was refluxed for 5.5 hours. The course and extent of the reaction was followed by paper strip chromatography. The Δ^4-compound Ib was formed at the same rate as the desired Δ^1-analog XI. After 5.5 hours the starting material, Δ^4-compound and Δ^1-compound were approximately of equal strength. The reaction was stopped at this time due to the appearance of a compound having the same mobility on paper as the $\Delta^{1,4}$-diene. The reaction mixture was worked up as in the preparation of VIId above and the residue from the ethyl acetate extract was chromatographed on Celite[12] using a solvent system consisting of 6 parts (by volume) of petroleum ether (b.p. 90–100°), 2 parts of ethyl acetate, 3 parts of methanol and 2 parts of water. An automatic fraction cutter set to take 20-ml. fractions was utilized. Fractions 31 through 44 contained unreacted starting material X as indicated by paper strip chromatography. Fractions 96 through 116 were evaporated and crystallized from acetone–petroleum ether to give 34 mg. of Ib, m.p. 236.5–239.5° (infrared spectrum identical with that of a known specimen). Fractions 48 through 66 were evaporated and crystallized from acetone–petroleum ether to afford 40 mg. of pure XI, m.p. 222–225°; $\lambda_{max}^{abs.\ alc.}$ 221–222 mμ (ε 10,300). Recrystallization from the same solvent pair did not alter the melting point nor the extinction coefficient; ν_{max} 3510, 1745, 1682, 1654(infl.) and 1240 cm.$^{-1}$; $[\alpha]^{25}D$ + 48°.

Anal. Calcd. for $C_{25}H_{33}FO_8$ (480.51): C, 62.49; H, 6.92; F, 3.95. Found: C, 62.34; H, 7.43; F, 4.19.

16α,20β,21-Triacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnen-3-one (XIIb).—A solution of 200 mg. of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (Ib) in 40 ml. of methanol was cooled to 0° and treated with 24 mg. of sodium borohydride. After standing at 0° for 1 hour, the solution was acidified with 0.1 ml. of glacial acetic acid, and the methanol was evaporated. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate solution and saline, dried and evaporated. The colorless glass was dissolved in 5 ml. of pyridine and 1 ml. of acetic anhydride. The mixture was kept at room temperature for 16 hours, methanol was added and the solvents were evaporated to afford a white solid (negative Blue Tetrazolium test). The product was crystallized from acetone–petroleum ether to give 112 mg., m.p. 280–283°. Two additional crystallizations from the same solvent pair gave 82 mg. of pure XIIb, m.p. 281–283°, $[\alpha]^{25}D$ + 40°, $\lambda_{max}^{abs.\ alc.}$ 238–239 mμ (ε 16,700); ν_{max} 3495, 1740, 1664, 1625 and 1243 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{37}FO_9$ (524.57): C, 61.82; H, 7.11; F, 3.62. Found: C, 61.67; H, 7.09; F, 3.33.

9α-Fluoro-11β,16α,17α,20β,21-pentahydroxy-4-pregnen-3-one (XIIa).—A solution of 250 mg. of 16α,20β,21-triacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnen-3-one (XIIb) in 50 ml. of methanol was treated with sodium methoxide (33 mg. of sodium in 7 ml. of methanol). Dry nitrogen was bubbled through the reaction mixture, and, after 10 minutes at room temperature, the reaction was stopped by the addition of 0.14 ml. of glacial acetic acid. The solution then was evaporated to a white solid. The residue was partially dissolved in acetone and the insoluble sodium acetate was removed by filtration. Concentration of the filtrate with simultaneous addition of petroleum ether afforded 125 mg. of product, m.p. 168–175° with effervescence. Two recrystallizations from acetone–petroleum ether gave 92 mg. of XIIa, m.p. 177.5–180° with effervescence (solvated); $[\alpha]^{25}D$ + 45° (acetone); $\lambda_{max}^{abs.\ alc.}$ 239mμ (ε 15,600); ν_{max} 3395, 1657 and 1633(infl.) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}FO_6$ (398.46): C, 63.30; H, 7.84; F, 4.77. Found: C, 60.12, 59.80; H, 8.53, 8.38; F, 4.51.

21-Chloro-9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (XIV).—A solution of 2.56 g. of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-4-pregnene-3,20-dione (Ia) in 15 ml. of cold dry pyridine was treated with 0.50 ml. (1 equivalent) of methanesulfonyl chloride and allowed to stand at room temperature for 20 hours. The reaction mixture was poured into ice-water and the resultant somewhat pasty solid was filtered and washed with water. The moist solid was dissolved in a large amount of ethyl acetate and washed once with saturated sodium bicarbonate (the extract turned yellow, and bicarbonate was drained immediately) followed by several water washes. The dried extract was evaporated to a white solid which was crystallized from acetone and a very small amount of petroleum ether to afford 0.48 g. of XIV, m.p. 229–235° dec. (positive Beilstein test for halogen). One recrystallization from acetone did not appreciably alter the melting point, m.p. 230–235.5° dec., $[\alpha]^{25}D$ + 109° (pyridine); λ_{max} 238 mμ (ε 17,000); ν_{max} 3450, 3185, 1732 and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}ClFO_5$ (414.89): C, 60.79; H, 6.80; Cl, 8.55; F, 4.58. Found: C, 61.10; H, 6.90; Cl, 8.18; F, 4.46.

An ethyl acetate extract of the aqueous phase afforded 0.58 g. of a material, m.p. 206–212° dec., which was not further investigated.

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