and washed consecutively with water (twice), saturated sodium chloride solution, dried (Na_2SO_4), treated with Darco G-60, and evaporated to dryness under reduced pressure giving a partially crystalline material. The residue was taken up in methylene chloride (10 ml.) and adsorbed onto a column of 75 g. of Florisil made up with petroleum ether. The column was eluted during 25 fractions with a gradient of from 6 to 20% acetone–petroleum ether in 100-ml. fractions. Fractions 9–11 containing 206 mg. of crystalline solid were combined and the material recrystallized from acetone to give 45 mg. of 11β-hydroxypregnenolone, m.p. 228–237°. Recrystallization gave pure (XV), m.p. 243.5–249.5°. The infrared spectrum of this material was identical with that of an authentic sample of XV and a mixed melting point exhibited no depression.

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C-6 Hydroxylated Steroids. V.[1] 6β-Hydroxytriamcinolone and Related Compounds

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The synthesis of the 6β-hydroxy derivatives of 9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione (triamcinolone) and its corresponding 16α,17α-acetonide is described.

In continuation of our interest in C-6 hydroxylated steroids we wish here to report on the synthesis of 6β-hydroxytriamcinolone[2] and a number of related compounds which contain an oxygen function at C-16 and the fluorohydrin grouping at C-9,11.

A convenient starting material for the preparation of the titled compound was 9α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione (I) or its 16,21-diacetate II.[3] When the latter reacted with trimethyl orthoformate in the presence of sulfuric acid it was smoothly converted into its $\Delta^{3,5}$-enol ether which could be purified by chromatography on Florisil[4] affording an analytical sample of the enol ether.[5] Reaction of the enol ether III with monoperphthalic acid[6] gave a 35% yield of 16α,21-diacetoxy-9α-fluoro-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione (IV).[7] Aqueous potassium carbonate hydrolysis of IV gave 9α-fluoro-6β,11β,16α,17α,21 - pentahydroxypregn - 4 - ene - 3,20 - dione (V).

An alternate pathway for the preparation of a suitable 6-hydroxylated intermediate was based on 9α-fluoro-11β,21 - dihydroxy - 3 - methoxy - 16α,17α - methoxymethylenedioxypregna - 3,5 - dien - 20 - one (VI) and its 21-acetate VII.[8] Oxidation of an ethereal solution of VII[9] with monoperphthalic acid afforded 21-acetoxy-9α - fluoro - 6β,11β - dihydroxy - 16α,17α - methoxymethylenedioxypregn - 4 - ene - 3,20 - dione (VIII). Hydrolytic conditions required for removal of the ortho ester without isomerization of the 6β-hydroxy-Δ^4-3-one to the 3,6-dione[10] could be achieved by use of a hot aqueous acetic acid solution.[11] In this manner, the 21-monoacetate IX was prepared which was then hydrolyzed to the pentol V.

Introduction of the C-1,2-double bond was accomplished through the use of 2,3-dichloro-5,6-dicyanobenzoquinone.[12] To avoid the complications inherent in the use of the quinone reagent on the unprotected 6-hydroxyl function, the acetylation of IV afforded the triacetate X which could not be obtained crystalline. Subjecting this material to 1,2-dehydrogenation gave the $\Delta^{1,4}$-triacetate XI which also resisted crystallization. Aqueous potassium carbonate hydrolysis gave the desired 9α-fluoro-6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione (XII).[13] Whereas the reaction of XII with acetone in the presence of perchloric acid led to the formation of the 16α,17α-acetonide XIII,[2,14] an identical reaction on 9α-fluoro-6β,11β,16α,17α,21-pentahydroxypregn-4-ene-3,20-dione (V) yielded the 3,6-dione-16α,17α-acetonide XIV. In the latter, acetonide formation was accompanied by 6β-hydroxy-Δ^4-3-one rearrangement.

An alternate synthesis of the $\Delta^{1,4}$-acetonide XIII was accomplished from the starting material 21-acetoxy-9α-fluoro - 11β - hydroxy 16α,17α - isopropylidenedioxypregn-4-ene-3,20-dione (XV).[15] Oxidation of either the

(1) Paper IV, J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Org. Chem.*, **28**, 92 (1963).

(2) J. R. Florini, L. L. Smith, and D. A. Buyske, *J. Biol. Chem.*, **236**, 1038 (1961), have observed that triamcinolone is metabolized principally to 6β-hydroxytriamcinolone by the dog and, apparently, by man.

(3) 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); **81**, 1689 (1959).

(4) A registered trademark of the Floridin Corporation for a synthetic magnesium silicate.

(5) Passage through the adsorbent not only removed unchanged Δ^4-3-one but also solvating molecules which tend to hydrolyze the enol ether. However, the purified enol ether is also rather easily hydrolyzed on exposure to atmospheric moisture.

(6) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Org. Chem.*, **27**, 4046 (1962).

(7) Chromatographically pure enol ether was not essential in this preparation. An ethereal solution of the crude material could be oxidized in equally good yields.

(8) J. P. Dusza and S. Bernstein, *J. Org. Chem.*, **27**, 4677 (1962).

(9) As in the oxidation of III with monoperphthalic acid, a crude preparation of VII may be used with equal success. The acetates, although necessitating an additional hydrolysis step, have a more favorable solubility factor than the free alcohols and are apparently subject to fewer side reactions.

(10) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951).

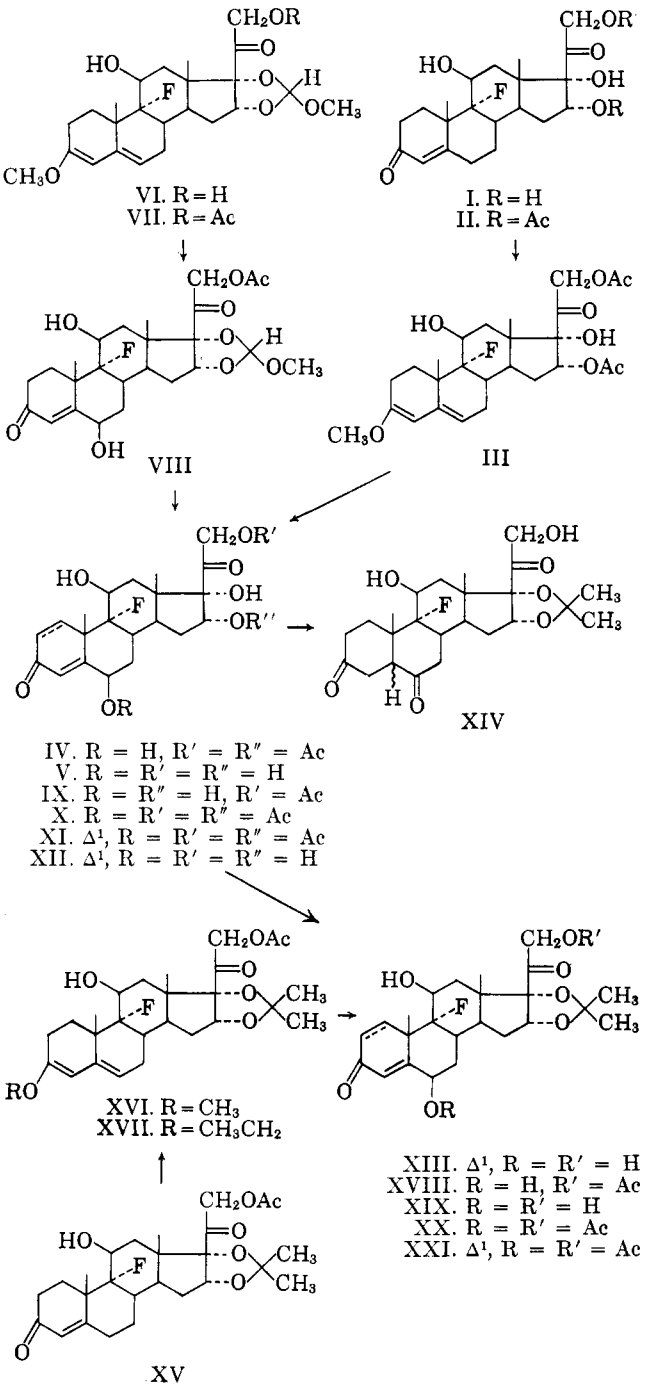
(11) It has been observed that the hydrolysis of 16α,17α-ortho esters using brief mineral acid treatment leads to the formation of 16α-esters; ref. 8.

(12) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(13) Poor yields are encountered with aqueous potassium carbonate hydrolyses (methanol) due to the solubility of the polyhydroxylated compounds in the reaction mixture. These compounds are also quite insoluble in the normal organic solvents employed in product isolation.

(14) C. Holmlund, L. I. Feldman, R. H. Evans, Jr., N. E. Rigler, B. Nielsen, and N. Barbacci, (unpublished work), have also prepared 6β-hydroxytriamcinolone 16α,17α-acetonide (XIII) and the corresponding Δ^4-compound XIX by a microbiological route.

(15) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo. *J. Am. Chem. Soc.*, **80**, 2338 (1958).



Flow Sheet

$\Delta^{3,5}$-methyl enol ether XVI or the $\Delta^{3,5}$-ethyl enol ether XVII[16] gave in essentially identical yields 21-acetoxy-9α-fluoro-6β,11β-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (XVIII). Alkaline hydrolysis of this material gave XIX which, as described above could not be prepared by direct acetonide formation from the pentol V. Introduction of the C-1,2-double bond was accomplished in the manner previously used in this paper. The Δ^4-acetonide diacetate XX[17] was dehydrogenated with the quinone reagent to yield the $\Delta^{1,4}$-acetonide diacetate XXI, which like compounds X, XI, and XX was not obtained in crystalline form. Hydrolysis of XXI gave 6β-hydroxytriamcinolone acetonide (XIII) identical to that obtained from 9α-fluoro-6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione (XII).

Experimental

Melting points are uncorrected. The ultraviolet spectra were determined in methanol and the rotations in the solvents specified. The infrared absorption spectra were determined in potassium bromide disks. The authors are indebted to William Fulmor and associates for the infrared, ultraviolet absorption and optical rotation data. We wish also to thank Louis M. Brancone and associates for analyses. Petroleum ether refers to the fraction, b.p. 60–70°.

16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-3-methoxypregna-3,5-dien-20-one (III.)—A solution of 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione (II, 2.0 g.) in methylene chloride (20 ml.), dioxane (10 ml.), trimethyl orthoformate (2.0 ml.), and absolute methanol (0.1 ml.) was cooled to 0–5° and stirred briskly. Concentrated sulfuric acid (4 drops) was added and after 7 min. the reaction was terminated by the addition of pyridine (1.0 ml.). The entire reaction mixture was reduced in volume at aspirator pressure and subsequently poured into water and extracted with ether. The organic layer was thoroughly washed with a saturated saline solution and dried over sodium sulfate.

Evaporation of the solution gave a residue which was dissolved in methylene chloride and chromatographed on Florisil[4] (75 g.). The desired enol ether was eluted primarily in the 1% acetone–methylene chloride (4 × 100 ml.) and 2% acetone–methylene chloride (4 × 100 ml.) fractions and totalled 0.90 g. Crystallization of a portion of this material from absolute ether–petroleum ether gave long needles of the enol ether III, m.p. 202–206° (m.p. 197–198° after drying *in vacuo*); $[\alpha]^{25}D$ −62° (1% pyridine in chloroform); λ_{max} 238 mμ (ϵ 22,100); ν_{max} 3530, 1750–1730, 1728, 1655, 1640, 1235, and 860 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{35}O_8F$ (494.54): C, 63.11; H, 7.48; F, 3.94. Found: C, 63.15; H, 7.14; F, 3.85.

16α,21-Diacetoxy-9α-fluoro-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione (IV).—A. 16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-3-methoxypregna-3,5-dien-20-one (III, 0.25 g.) was dissolved in ether (15 ml.) and to this solution was added an ethereal monoperphthalic acid solution (3.0 ml., 0.064 g./ml.). Within 10 min. crystallization of the product was noted. After standing overnight, the ether was decanted and the solid washed repeatedly with small portions of ether and then petroleum ether to give IV (0.092 g.). Crystallization from acetone–petroleum ether gave fine prisms, m.p. 272–273°.

B. The 16α,21-diacetate II (10.0 g.) was converted to its enol ether in the manner cited previously. The ether solution of the crude material (125 ml.) was oxidized by monoperphthalic acid (40 ml., 0.055 g./ml.) to give IV (4.5 g.). Crystallization from ethyl acetate afforded an analytical sample, m.p. 274–276°; $[\alpha]^{30}D$ +66° (pyridine); λ_{max} 232 mμ (ϵ 16,400); ν_{max} 3470, 1728, 1682, and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}O_9F$ (496.51): C, 60.47; H, 6.70; F, 3.85. Found: C, 60.51; H, 6.83; F, 3.82.

9α-Fluoro-6β,16α,17α,21-pentahydroxypregn-4-ene-3,20-dione (V).—A. from IV and B. from IX.—A. A suspension of 16α,21-diacetoxy-9α-fluoro-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione (IV, 0.70 g.) in methanol (50 ml.) was agitated by a stream of nitrogen for 5 min. and then an aqueous potassium carbonate solution (10%, 6.0 ml.) was added.[18] The flow of nitrogen was continued for an additional 45 min. and then the reaction mixture was neutralized with acetic acid and poured into water. The clear solution was thoroughly extracted with ethyl acetate, and the extract was washed with a saturated sodium bicarbonate solution and dried. Evaporation yielded a crystalline residue which was recrystallized from acetone–petroleum ether to give the pentol V (0.17 g.), m.p. 240–245°. Another crystallization

(16) H. J. Ringold, O. Mancera, C. Djerassi, A. Bowers, E. Batres, H. Martinez, E. Necoechea, J. Edwards, M. Velasco, and R. I. Dorfman, *J. Am. Chem. Soc.*, **80**, 6464 (1958).

(17) Attempted epimerization (hydrogen chloride–chloroform–trace ethanol) of the diacetate XX and the triacetate X led to recovery of starting material with no evidence of the 6α-acetoxy epimer being formed.

(18) An alternate procedure which we now employ for the hydrolysis of acetylated polyhydroxylated steroids utilizes anhydrous sodium methoxide in absolute methanol. Neutralization of the reaction mixture with glacial acetic acid followed by evaporation gives the steroid plus inorganic salts. Extraction with acetone separates the inorganic salts. The compounds are crystallized by gradual displacement of the acetone with hexane.

raised the m.p. to 268–271°; $[\alpha]^{25}D$ +32° (pyridine); λ_{max} 232 mμ (ε 16,300); ν_{max} 3450, 1720, 1685 (shoulder) and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}O_7F$ (412.44): C, 61.15; H, 7.09; F, 4.61. Found: C, 61.19; H, 7.53; F, 4.57.

B. To a suspension of 21-acetoxy-6β,11β,16α,17α-tetrahydroxypregn-4-ene-3,20-dione (IX, 0.17 g.) in methanol (25 ml.), agitated by a stream of nitrogen, was added a 10% aqueous potassium carbonate solution (1.0 ml.). The reaction was continued for 45 min. and then most of the solvent was removed at reduced pressure. The reaction mixed was then poured into water and filtered to give a solid which was crystallized from ethyl acetate-heptane affording V (40 mg.), m.p. 261–263°. The ethyl acetate extract of the dilute reaction mixture provided additional V (100 mg.). This material was identical to that obtained from the hydrolysis of the 16,21-diacetate IV.

21-Acetoxy-9α-fluoro-6β,11β-dihydroxy-16α,17α-methoxymethylenedioxypregn-4-ene-3,20-dione (VIII).—An ether solution (150 ml.) of 21-acetoxy-9α-fluoro-11β-hydroxy-3-methoxy-16α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (VII, 5.5 g.) was treated with ethereal monoperphthalic acid (50 ml. −0.48 N). After standing overnight at room temperature, the precipitated material (1.83 g.) was collected, m.p. 180–200°. Crystallization from ethyl acetate–heptane afforded VIII (0.81 g.), m.p. 239–244°; $[\alpha]^{25}D$ +97° (pyridine); λ_{max} 231 mμ (ε 15,000); ν_{max} 3500, 1740, 1692–1670, and 1236 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}O_9F$ (496.51): C, 60.47; H, 6.70; F, 3.83. Found: C, 60.83; H, 7.09; F, 4.05.

21-Acetoxy-9α-fluoro-6β,11β,16α,17α-tetrahydroxypregn-4-ene-3,20-dione (IX).—A solution of 21-acetoxy-9α-fluoro-6β,11β-dihydroxy-16α,17α-methoxymethylenedioxypregn-4-ene-3,20-dione (VIII, 0.5 g.) in water (10 ml.) and acetic acid (6 ml.) was heated on a steam bath for 30 min. After being cooled the solution was poured into water, neutralized with solid sodium bicarbonate and extracted with ethyl acetate. Evaporation of the dried extract gave a crystalline residue which was crystallized several times from acetone–petroleum ether to give the 21-monoacetate IX (0.17 g.), m.p. 231–236°; $[\alpha]^{25}D$ +52° (pyridine); λ_{max} 232 mμ (ε 15,300); ν_{max} 3500, 1740, 1687 (shoulder), 1670, and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_8F$ (454.48): C, 60.78; H, 6.88; F, 4.19. Found: C, 60.47; H, 6.86; F, 4.39.

9α-Fluoro-6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione (XII).—A solution of 16α,21-diacetoxy-9α-fluoro-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione (IV, 2.7 g.) in acetic anhydride (15 ml.) and dry pyridine (15 ml.) was allowed to stand overnight at room temperature. The reaction mixture was poured into water and thoroughly extracted with ether. The extract was washed *repeatedly* with a cold 1% aqueous hydrochloric acid solution and then with a saturated saline solution. After being dried, the ether was evaporated to give an oily residue of X (2.75 g.). This material was dissolved in dry dioxane (45 ml.) and 2,3-dichloro-5,6-dicyanobenzoquinone (1.74 g.) was added. The reaction mixture on being heated became homogeneous and was refluxed for 20 hr. On cooling, the precipitated hydroquinone was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in ethyl acetate and washed in turn with water, cold 1% aqueous sodium hydroxide, and a saturated saline solution. After drying the solvents were removed to give the crude noncrystalline $\Delta^{1,4}$-diene triacetate XI (1.1 g.).

To a solution of this material in methanol (40 ml.), agitated by a stream of nitrogen, was added a solution of 10% aqueous potassium carbonate (10 ml.). After 45 min., the reaction mixture was neutralized with acetic acid and poured into water. The aqueous solution was extracted with ethyl acetate (10 × 50 ml.). The ethyl acetate extract was washed with saturated saline and dried. Evaporation of the solvent produced a residue which was crystallized from acetone–petroleum ether and afforded XII (0.22 g.), m.p. 247–250°. After two more crystallizations from the same solvent pair there was obtained 0.127 g. of needles; m.p. 266–268°; $[\alpha]^{25}D$ +5° (pyridine); λ_{max} 240 mμ (ε 16,000); ν_{max} 3420, 1723, 1665, 1625, and 1060 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}O_7F$ (410.43): C, 61.44; H, 6.64; F, 4.63. Found: C, 61.57; H, 7.20; F, 4.47.

9α-Fluoro-6β,11β,21-trihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione (XIII). **A. From XII. B. From XVIII.**—A. Perchloric acid (72%, 2 drops) was added to a suspension of 9α-fluoro-6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione (XII, 50 mg.) in acetone (10 ml.). The reaction mixture was stirred for 3 hr. at which time the solution was complete. The solution was neutralized with aqueous sodium bicarbonate and then most of the acetone removed at reduced pressure. After pouring the reaction mixture into water, the suspension was filtered and dried. Crystallization from acetone–petroleum ether afforded the desired acetonide XIII (35 mg.), m.p. 268–269°. A sample crystallized from ethyl acetate–heptane had m.p. 277–282°; $[\alpha]^{25}D$ +72° (pyridine); λ_{max} 240 mμ (ε 16,000); ν_{max} 3430, 1715, 1670, and 1635 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}O_7F$(450.49): C, 63.98; H, 6.94; F, 4.22. Found: C, 64.01; H, 7.10; F, 4.12.

B. A solution of 21-acetoxy-9α-fluoro-6β,11β-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (XVIII, 0.9 g.) in pyridine (10 ml.) and acetic anhydride (5 ml.) was allowed to stand overnight at room temperature and then was poured into water. The ethyl acetate extract of this solution was washed well with 2% aqueous hydrochloric acid solution and then repeatedly with a saturated saline solution. Evaporation of the dried extract left a glass XX (1.0 g.) which could be converted to a white amorphous powder.

A solution of the glass in dioxane (15 ml.) was refluxed with 2,3-dichloro-5,6-dicyanobenzoquinone (0.64 g.) for 24 hr. On cooling the hydroquinone (0.35 g.) precipitated and was separated. The filtrate was evaporated and the residue taken up in ethyl acetate. The extract was washed successively with water, cold 2% sodium hydroxide and saturated saline. The dried extract upon evaporation gave the crude $\Delta^{1,4}$-acetonide diacetate XXI (0.875 g.). The infrared of this material demonstrated the presence of the $\Delta^{1,4}$-3-one system.

A solution of XXI in methanol (15 ml.) was agitated by a slow stream of nitrogen and to this was added a 10% aqueous potassium carbonate solution (6.0 ml.). After 45 min. the reaction mixture was neutralized with glacial acetic acid and most of the methanol removed at reduced pressure. Ethyl acetate (400 ml.) was added to the solution and the resultant organic layer was washed with a saturated sodium bicarbonate solution followed by a saturated saline solution. The residue obtained on evaporation of the dried extract was crystallized from ethyl acetate-heptane to give an initial precipitate which was impure. The mother liquor from the recrystallization, on standing overnight, precipitated XIII (60 mg.). After two crystallizations from ethyl acetate–heptane the desired acetonide XIII (32 mg.) was obtained, m.p. 277–282°. This material was identical to the sample prepared from direct acetonide formation on XII.

9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-5ζ-pregnane-3,6,20-trione (XIV).—A suspension of 9α-fluoro-6β,11β,16α,17α,21-pentahydroxypregn-4-ene-3,20-dione (V, 50 mg.) in acetone (10 ml.) was stirred briskly for 5 hr. after the addition of 72% perchloric acid (1 drop). The reaction mixture was neutralized by the addition of a sodium bicarbonate solution and then most of the acetone was removed at reduced pressure. Filtration provided a solid which after several crystallizations from acetone–petroleum ether melted at 262–265°. The infrared spectrum showed no α,β-unsaturated ketone absorption; ν_{max} 3500, 3430, and 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}O_7F$ (452.50): C, 63.70; H, 7.36; F, 4.19. Found: C, 63.73; H, 7.67; F, 4.13.

21-Acetoxy-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-3-methoxypregna-3,5-dien-20-one (XVI).—A suspension of 21-acetoxy-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (XV, 2.0 g.) in dioxane (15 ml.), trimethyl orthoformate (1.5 ml.) and absolute methanol (0.3 ml.) was treated with a solution of concentrated sulfuric acid (0.05 ml.) in dioxane (1.0 ml.). Solution occurred in about 5–7 min. and a deep red color developed over the course of an additional 20 min. The reaction was stopped by the addition of pyridine (1.1 ml.) which discharged the red color of the reaction mixture. This mixture was then poured into water to give an oily precipitate which crystallized and was filtered to give 2.1 g. of the crude enol ether XVI. A portion of this material was crystallized from methanol to give prisms, m.p. 189–191°; $[\alpha]^{25}D$ −21° (1% pyridine in chloroform); λ_{max} 239 mμ (ε 20,900); ν_{max} 3520, 1755, 1730, 1660, and 1635 cm.$^{-1}$.[19]

21-Acetoxy-9α-fluoro-6β,11β-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (XVIII).—A solution of 21-acetoxy-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-3-methoxypregna-3,5-dien-20-one (XVI, 1.1 g.) in absolute ether

(19) This material was solvated and on being heated *in vacuo* in a drying apparatus, a considerable amount of hydrolysis to the Δ^4-3-one was observed which precluded the obtaining of satisfactory elemental analyses.

(25 ml.) was treated with an ethereal monoperphthalic acid solution (0.62 *N*, 5.0 ml.). On standing at room temperature, there precipitated the crystalline 6β-hydroxy compound XVIII (0.28 g.), m.p. 272–276°. One crystallization from ethyl acetate–heptane afforded 0.145 g., m.p. 286–288°; $[\alpha]^{25}D$ +89° (chloroform); λ_{max} 232 mμ (ε 16,500); ν_{max} 3430, 1760, 1728, 1680 (shoulder), 1665, 1618, and 1060 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{35}O_6F$ (494.54): C, 63.14; H, 7.14; F, 3.84. Found: C, 63.16; H, 7.37; F, 3.51.

When the ethyl enol ether XVII[16] (1.0 g.) was oxidized as above, XVIII (0.27 g.) was also obtained, m.p. 277–280°.

9α-Fluoro-6β,11β,21-trihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (XIX).—Aqueous 10% potassium carbonate (1.0 ml.) was added to a suspension of 21-acetoxy-9α-fluoro-6β,11β-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (XVIII, 0.1 g.) in methanol (10 ml.) agitated by a nitrogen stream. Solution was complete in 30 min. and after an additional 15 min., the reaction mixture was neutralized with acetic acid and poured into water. The aqueous solution was extracted with ethyl acetate, and the dried extract on evaporation provided crude XIX. Crystallization from ethyl acetate–heptane yielded prisms (13 mg.), m.p. 238–241°; $[\alpha]^{25}D$ +90° (pyridine); λ_{max} 232 mμ (ε 13,600); ν_{max} 3430, 1723, 1675, (shoulder), and 1667 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}O_7F$ (452.50): C, 63.70; H, 7.36; F, 4.19. Found: C, 63.83; H, 7.57; F, 3.91.

Nuclear Magnetic Resonance Spectra of Heterocyclic Compounds. II. Abnormal Products from the Ketalization of Cortisone[1]

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It was demonstrated that compounds having 1,2-bisethylene dioxide and *trans*-naphthodioxide moieties at C-17 are formed as ketalization by-products of steroids with a dihydroxyacetone side chain. The compounds were identified by the use of n.m.r. spectroscopy.

Protection of ketones with ethylene ketals[2] is frequently used in the synthetic elaboration of steroids.[3] Unfortunately, on many occasions and especially in the case of steroids with a dihydroxyacetone moiety the utility of the method is limited severely because the ketals are obtained in low yields, and because large amounts of unknown by-products are formed.[4]

The isolation of unidentified by-products from ketalization of dihydrocortisone,[4] cortisone, and 11-epicortisol[5] has recently been reported by two laboratories. The only product identified[5] (**12a**) was assigned its structure in analogy to **12b**, obtained by Tsuda, *et al.*,[6] as a by-product of ketalization of 17α,21-dihydroxy-4-pregnene-3,20-dione (Reichstein's substance S). To account for their observations the Japanese workers have suggested a mechanism analogous to the Mattox rearrangement.[7] Bernstein, *et al.*,[5] isolated from the mother liquors of ketalization of 11-epicortisol an 11α-hydroxy compound, $C_{27}H_{40}O_7$. They oxidized it to the 11-keto analog, $C_{27}H_{38}O_7$, m.p. 173–174°, to which we assign structure **8a** (see Fig. 2). On treatment of cortisone with anhydrous ethylene glycol containing hydrogen chloride, the Lederle group obtained another compound identified by us as **9a** (see Fig. 2).

Structures like **2**, **8**, and **10** were considered for the by-products of ketalization of corticosteroids.[4,5] Structures **8** and **10** were suggested solely on the basis of their resistance toward acid hydrolysis,[4] analogous to sugar anhydrides, sapogenins, and oxetones. Isolation[6] of **12b** and later of **12a** indicated the possible existence of compounds similar to **2**. Inspection of models revealed that the pentacyclic–heptacyclic structures **11** are also feasible. (See Flow Sheet, Fig. 2.)

It has been reported that α-dicarbonyls on treatment with ethylene glycol in the presence of acids yield *trans*-naphthodioxanes[8] and 1,2-bisdioxolanes.[9] Recent reports on the course of the Porter–Silber[10a] reaction, and on the acid-catalyzed rearrangement of the dihydroxyacetone moiety[10b] support the view that α-dicarbonyls might be formed during ketalization of steroids with such moieties, as suggested by Tsuda, *et al.*[6] Should this be the case, the unknown by-products could have 1,2-bisethylene dioxide or naphthodioxide moieties attached at C-17. Thus, in order to elucidate structures of the unknown by-products, two problems had to be solved: namely, (a) establishing the nature and points of attachment of the blocking groups in the side chain, and (b) providing conclusive proof for existence of an unchanged steroid carbon skeleton in the products. In view of the failure encountered by us (see later) and others,[4,5] in the attempted acid-catalyzed hydrolysis of the blocking groups, a chemical degradation approach was not considered promising.

In the previous paper of this series[11] we compared the n.m.r. spectra of substituted dioxolanes and dioxanes and observed the dependence of the chemical shift of the peaks for the single hydrogen on a carbon bearing two oxygens on the size of the ring. In the 2-substituted dioxolanes and 1,2-bisdioxolanes this peak appears at lower field (*ca.* τ 5.0–5.2) than does the corresponding peak for the 1,4;5,8-naphthodioxane derivative (*ca.* τ 5.3–5.5). The nature of the signals arising from the —O—CH_2—CH_2—O— moiety also appears to

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