[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. CXXXVI.[1] Synthesis of a New Class of Potent Cortical Hormones. 6α-Fluoro- and 6α,9α-Difluoro-16α-methylprednisolone and Related Steroids[2]

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The multi-stage synthesis of 6α-fluoro-16α-methyl Reichstein's Substance S from 16α-methylpregnenolone is described. Adrenal incubation of the former led to 6α-fluoro-16α-methylhydrocortisone and thence by selenium dioxide oxidation to 6α-fluoro-16α methylprednisolone. The corresponding 6α,9α-difluoro-16α-methyl corticoids are also described and high anti-inflammatory activity is indicated for several of these steroids.

The two most important recent developments in the cortical hormone field have been the discovery of the potentiation of anti-inflammatory activity by the introduction of a 16α-methyl[3] or 6α-fluoro substituent[4] into the intact or modified hydrocortisone molecule. We should now like to record the experimental details[2,5] of a synthetic sequence which led to cortical hormones combining both structural features.

Our starting material was the well-known 16α-methylpregnenolone acetate (I)[6] which was epoxidized with monoperphthalic acid to the 5α,6α-epoxide II and then subjected to boron trifluoride-promoted ring opening.[7] Introduction of the 17α-hydroxy function into the fluorohydrin III was effected by Kritchevsky and Gallagher's procedure[8] by successive conversion to the enol acetate IV (not purified), treatment[9] with monoperphthalic acid and finally mild alkaline saponification. This last step was insufficient for hydrolysis of the 5α-acetoxy function, generated during the formation of the enol acetate (IV), but the resulting 6β-fluoro-16α-methyl-5α-pregnane-3β,5α,17α-triol-20-one 5-acetate (V) served equally well for the subsequent transformations. The complete dihydroxyacetone side chain was elaborated by the standard sequence[8,9] of bromination at C-21 (VI), followed by sodium iodide interchange and replacement of the halogen function with potassium acetate, yielding 6β-fluoro-16α-methyl-5α-pregnane-3β,5α,17α,-21-tetrol-20-one 5,21-diacetate (VII). Oxidation of the 3β-hydroxyl group of VII to the corresponding 3-ketone VIII was effected by means of chromium trioxide in acetone–sulfuric acid solution.[10] The 5α-acetoxy moiety, though surviving earlier exposure to alkali (see V), could now be eliminated readily by heating with ethanolic potassium acetate by virtue of β-activation on the part of the carbonyl group. 6β-Fluoro-16α-methyl Reichstein's substance S 21-acetate (IX), thus obtained, was transformed into the desired 6α-isomer Xa by inversion with hydrogen chloride–acetic acid. When these latter conditions were applied to the 3-keto-5α-acetoxy intermediate VIII, it was converted directly into 6α-fluoro-16α-methyl Reichstein's substance S 21-acetate (Xa) and thence by mild alkaline saponification to the free alcohol Xb.

The 11β-hydroxyl group was introduced into 6α-fluoro-16α-methyl Reichstein's substance S (Xb) in one step in 40–50% yield by incubation with bovine adrenal glands,[11] a remarkably simple operation which in our hands has worked successfully in a wide variety of substituted derivatives of substance S.[4a,4c,12,13] Purification of 6α-fluoro-16α-methylhydrocortisone (XIa) was best achieved through its 21-acetate XIb, which served as the key intermediate for the preparation of the other substituted corticoids. Introduction of a double bond in the 1–2 position to give 6α-fluoro-16α-methylprednisolone acetate (XII) was accomplished by the conventional selenium dioxide method[14] with the important modification that a base (pyridine) rather than an acid (*e.g.*, acetic acid) was added.

The original observation by Fried and collaborators[15] on the marked biological effect associated

(1) Paper CXXXV, J. S. Mills, THIS JOURNAL, **82**, 5515 (1959).

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(7) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957); A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958); J. Perez Ruelas, J. Iriarte, F. Kincl and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(8) T. H. Kritchevsky and T. F. Gallagher, THIS JOURNAL, **73**, 184 (1951).

(9) See G. Rosenkranz, J. Pataki, S. Kaufmann, J. Berlin and C. Djerassi, *ibid.*, **72**, 4081 (1950).

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

(11) For experimental details see A. Zaffaroni, U. S. Patent 2,671,-752; A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, THIS JOURNAL, **80**, 6110 (1958).

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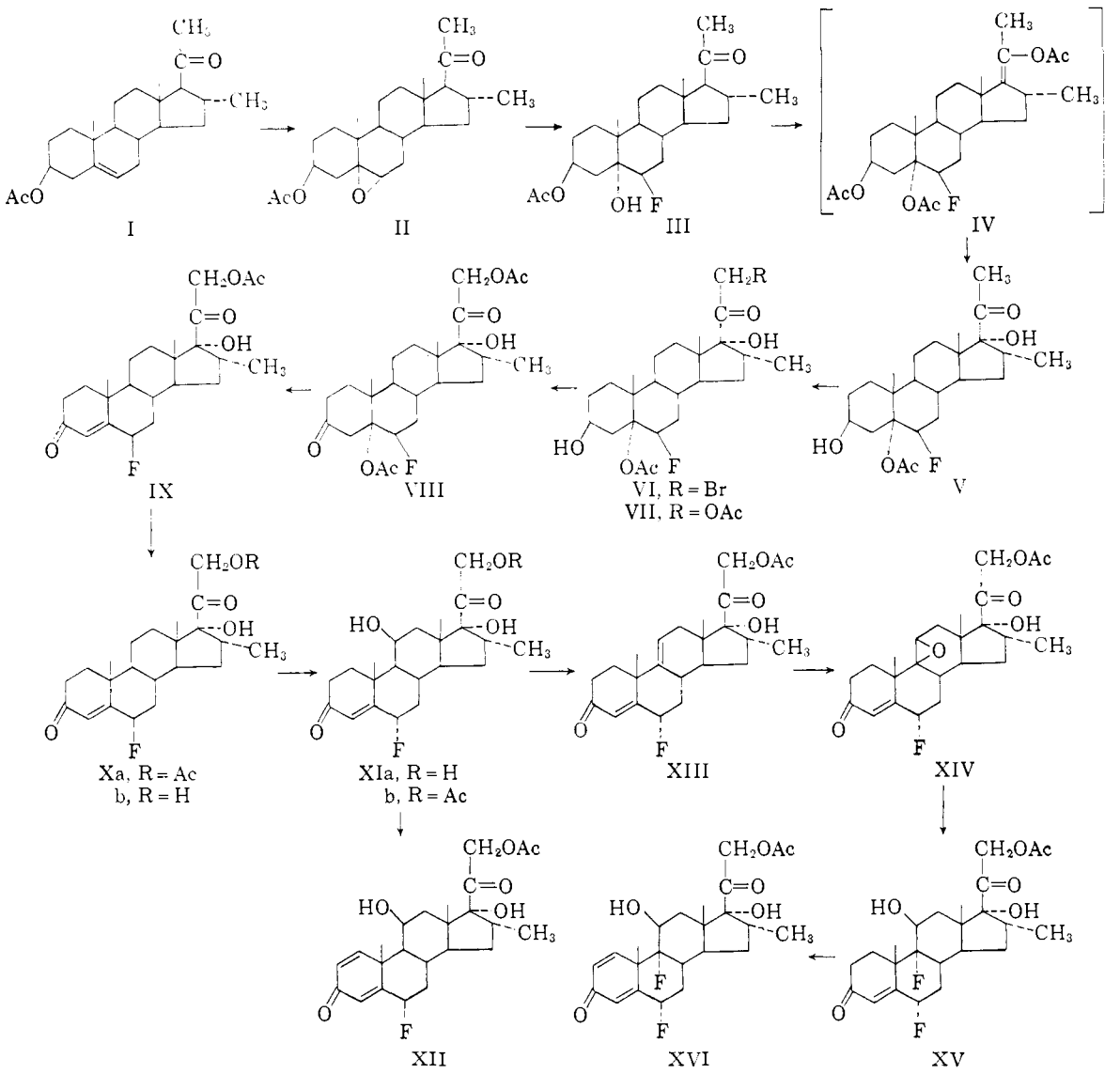
(15) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957), and earlier papers.



with the introduction of a 9α-fluorine atom prompted us to introduce the same substituent into 6α-fluoro-16α-methylhydrocortisone (XIa). For this purpose Fried's general method[15] was employed, which involved dehydration of 6α-fluoro-16α-methylhydrocortisone 21-acetate (XIb) with mesyl chloride in dimethylformamide–pyridine,[16] addition of hypobromous acid to the 9,11-double bond of XIII followed by potassium acetate treatment to afford the 9,11β-oxide XIV, and finally opening of the epoxide with hydrogen fluoride.[15,17] In order to complete the series of substituted cortical hormones required for biological examination, 6α,9α-difluoro-16α-methylhydrocortisone 21-acetate (XV) was transformed into 6α,9α-difluoro-16α-methylprednisolone 21-acetate (XVI) by oxidation with selenium dioxide.[14]

Biological Activity (Table I).—In the experimental animal, XII, XV and XVI exhibited extremely high anti-inflammatory potency without retention of sodium.[18] Table I lists the activity of these compounds compared to hydrocortisone as standard.

Preliminary clinical trials in Mexico and in the United States in rheumatoid arthritis patients indicated a high degree of potency for several of the above-described modified cortical hormones. Details of these clinical investigations will be published elsewhere.

Experimental[19]

16α-Methyl-5α,6α-oxido-5α-pregnan-3β-ol-20-one 3-Acetate (II).—16α-Methylpregnenolone 3-acetate (I)[6] (17 g.)

(16) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. Singer, *ibid.*, **77**, 4181 (1955).

(17) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(18) All assays were carried out in adrenalectomized rats by injection, the salt assays without sodium chloride load and the anti-inflammatory assays by cotton pellet implant. The anti-inflammatory assays were by the Endocrine Laboratories, Madison, Wisc. We wish to thank Drs. R. I. Dorfman and E. Rosemberg of The Worcester Foundation, Shrewsbury, Mass., for the salt assays.

(19) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. Infrared spectra were determined with a Perkin–Elmer model 21 spectrophotometer. We are grateful to Dr. L. Throop for determination of rotations and spectral data.

TABLE I

ANTI-INFLAMMATORY ACTIVITY OF 6α-FLUORO-16α-METHYL CORTICOIDS

Compound	Anti-inflammatory activity[18]
Hydrocortisone	1
6α-Fluoro-16α-methylprednisolone acetate (XII)	60
6α,9α-Difluoro-16α-methylhydrocortisone acetate (XV)	65
6α,9α-Difluoro-16α-methylprednisolone acetate (XVI)	300[a]

[a] Our preliminary activity of XVI (see ref. 2b) of 120 × hydrocortisone has been revised after further assay.

was dissolved in 500 ml. of dry chloroform and treated with a solution of 16 g. of monoperphthalic acid in 150 ml. of ether for 12 hours at room temperature. The precipitated phthalic acid was removed by filtration, and the reaction mixture washed with an excess of 5% sodium carbonate solution and water, dried over sodium sulfate and concentrated. The residue was dissolved in hexane–benzene (4:1) and adsorbed on 700 g. of neutral alumina. Elution with hexane–benzene (1:9) gave a crystalline mixture of α- and β-epoxides. Elution with pure benzene and benzene–ether (1:1) followed by crystallization of the fractions from acetone–hexane yielded 9.3 g. of the α-epoxide II, m.p. 159–161°. The analytical sample melted at 162–164°, $[\alpha]_D$ +8°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34; O, 16.47. Found: C, 73.86; H, 9.30; O, 17.04.

Rechromatography of the α- and β-epoxide mixture gave the pure β-epoxide after crystallization from acetone–hexane, m.p. 120–121°, $[\alpha]_D$ +40°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34; O, 16.47. Found: C, 74.07; H, 9.38; O, 16.59.

6β-Fluoro-16α-methyl-5α-pregnan-3β,5α-diol-20-one 3-Acetate (III).—The α-epoxide II (6.5 g.) from the preceding experiment was dissolved in 800 ml. of anhydrous benzene–ether (1:1) and 8 ml. of freshly distilled boron trifluoride etherate was added to the resulting solution. After standing for 24 hours, the reaction mixture was washed with an excess of 5% sodium bicarbonate solution and water, dried over sodium sulfate and the solvents removed. Crystallization of the product from acetone–hexane gave 4 g. of fluorohydrin III, m.p. 249–251°. Three additional crystallizations from acetone led to the analytical sample, m.p. 254–255°, $[\alpha]_D$ +34°.

Anal. Calcd. for $C_{24}H_{37}FO_4$: C, 70.55; H, 9.13; F, 4.65. Found: C, 70.86; H, 9.04; F, 4.35.

The mother liquors, dissolved in benzene, were chromatographed on 120 g. of neutral alumina. Elution with pure benzene and benzene–ether (1:1) and crystallization of the fractions gave 0.49 g. of the starting epoxide. Further elution with benzene–ether (3:1 and 1:1) followed by crystallization gave an additional 0.45 g. of fluorohydrin III, m.p. 245–248°.

6β-Fluoro-16α-methyl-5α-pregnan-3β,5α,17α-triol-20-one 5-Acetate (V).—6β-Fluoro-16α-methyl-5α-pregnan-3β,5α-diol-20-one 3-acetate (III) (76 g.) was suspended in a mixture of 1400 ml. of acetic anhydride and 380 ml. of freshly distilled acetyl chloride. The steroid dissolved on warming and the resulting solution was heated under reflux for 98 hours. Two 100-ml. portions of acetyl chloride were added after 48 and 72 hours. The mixture was concentrated to a thick sirup under reduced pressure and dissolved in 2 l. of ether. This solution was washed with cold 5% potassium hydroxide solution to remove the remaining acetic anhydride and finally with water to neutrality. After concentration of the ether the residual oil (containing the enol acetate IV) was dissolved in 2.7 l. of benzene and 200 ml. of solvent was distilled from this mixture to remove moisture. Then a solution of 60 g. of monoperphthalic acid in 500 ml. of ether was introduced after cooling the benzene and the epoxidation was permitted to proceed overnight. The reaction mixture was processed in the manner described previously and the product in 650 ml. of methanol was treated for one hour at room temperature with a solution of 45 g. of potassium hydroxide in 130 ml. of water and 520 ml. of methanol. Then 45 ml. of acetic acid was added followed by dilution with 2.5 l. of saturated sodium chloride solution and the precipitated steroids were extracted with methylene chloride. The combined organic extracts were washed once with saturated salt solution, dried and concentrated to give 70 g. of yellow oil. This material was dissolved in 1 l. of benzene and chromatographed on 2.6 kg. of neutral alumina. The column was developed with benzene and ether. Elution with 5 l. of ether–methylene chloride (4:1) gave a series of crystalline fractions, melting range 160–165° (fraction A). Elution with 2 l. of ether–methylene chloride (1.5:1) furnished crystals melting between 170–180° (fraction B). Elution with 4 l. of ether–methylene chloride (1:1.5), 4 l. of ether–methylene chloride (1:4) and finally with pure methylene chloride gave crystalline fractions melting between 195–205° (fraction C). Crystallization of this last portion (C) from ether–hexane gave 10.9 g. of 6β-fluoro-16α-methyl-5α-pregnan-3β,5α,17α-triol-20-one 5-acetate, m.p. 211–214°. Crystallization of fraction B from ether–hexane gave 1.4 g., m.p. 212–214°. This material was undepressed in melting point when mixed with a sample from fraction C. The analytical sample prepared from ether–hexane showed m.p. 214–216°, $[\alpha]_D$ −35°.

Anal. Calcd. for $C_{24}H_{37}FO_5$: C, 67.89; H, 8.78. Found: C, 67.78; H, 8.55.

Crystallization of fraction A from acetone–hexane yielded 30 g. of 6β-fluoro-16α-methyl-5α-pregnan-3β,5α-diol-20-one 5-acetate, m.p. 164–166°. Three additional crystallizations raised the m.p. to 169–171°, $[\alpha]_D$ +27°.

Anal. Calcd. for $C_{24}H_{37}FO_4$: C, 70.55; H, 9.13. Found: C, 70.60; H, 9.04.

6β-Fluoro-21-bromo-16α-methyl-5α-pregnan-3β,5α,17α-triol-20-one 5-Acetate (VI).—To 17 g. of 6β-fluoro-16α-methyl-5α-pregnan-3β,5α,17α-triol-20-one 5-acetate (V) dissolved in 250 ml. of dioxane was added dropwise a solution of 6.8 g. of bromine in 70 ml. of dioxane during 15 minutes. The bromine was rapidly consumed and after 10 minutes the reaction was diluted with 2 l. of cold water. The precipitate was filtered, washed well with water and dissolved in 500 ml. of ether. This solution was dried over calcium chloride and concentrated to dryness at 30° under reduced pressure. Crystallization of the product from ethyl acetate–hexane gave 12.3 g. of the 21-bromide VI, m.p. 207–209° dec. Concentration of the mother liquors furnished a second crop of 3.7 g., m.p. 206–208° dec. A small sample melted constantly at 212–214° dec. after four more crystallizations from ethyl acetate–hexane, $[\alpha]_D$ +9°.

Anal. Calcd. for $C_{24}H_{36}BrFO_5$: C, 57.25; H, 7.21; F, 3.77. Found: C, 57.15; H, 7.27; F, 3.85.

6β-Fluoro-16α-methyl-5α-pregnan-3β,5α,17α,21-tetrol-20-one 5,21-Diacetate (VII).—The 21-bromo compound VI (16 g.) from the previous experiment in 2.6 l. of acetone was heated under reflux for 1 hour with 10.8 g. of sodium iodide. After the introduction of 120 g. of anhydrous potassium acetate the heating was continued for 20 hours. The potassium acetate was removed by filtration and the greater part of the acetone distilled off. One liter of water was added and the product isolated by extraction with methylene chloride and distillation. The resulting oil in benzene deposited 13.2 g. of the 21-acetoxy compound as a crystalline benzene solvate, m.p. 135–140° and 180–190°. Five additional crystallizations from benzene gave the analytical sample exhibiting only one melting point 198–200°, $[\alpha]_D$ +6°.

Anal. Calcd. for $C_{26}H_{39}FO_7$: C, 64.71; H, 8.13; F, 3.94. Found: C, 64.37; H, 7.92; F, 3.62.

6β-Fluoro-16α-methyl-5α-pregnan-5α,17α,21-triol-3,20-dione 5,21-Diacetate (VIII).—A solution of 13.2 g. of 6β-fluoro-16α-methyl-5α-pregnan-3β,5α,17α,21-tetrol-20-one 5,21-diacetate (VII) in 225 ml. of acetone was cooled in ice-water and treated dropwise with 9 ml. of 8 *N* chromium trioxide reagent.[10] After 5 minutes the reaction was poured into 2.5 l. of water, the precipitate filtered, washed well with water and dried on the steam-bath to give 10.7 g. of product, m.p. 223–225°. Several crystallizations from acetone–hexane raised the melting point to 228–230°, $[\alpha]_D$ +5°.

Anal. Calcd. for $C_{26}H_{37}FO_7$: C, 64.98; H, 7.76; F, 3.95. Found: C, 64.93; H, 7.82; F, 3.76.

6β-Fluoro-16α-methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-Acetate (IX).—A solution of 0.24 g. of 6β-fluoro-16α-methyl-5α-pregnan-5α,17α,21-triol-3,20-dione 5,21-di-

acetate and 0.24 g. of anhydrous sodium acetate was heated under reflux for 3 hours. After concentration of the ethanol, water was added and the product extracted with methylene chloride. Evaporation of the dried organic extracts and crystallization of the residue from acetone–hexane gave 0.2 g. of crystals, m.p. 175–178°. The analytical sample exhibited a melting point of 178–180°, $[\alpha]D$ +19°, λ_{max}^{EtOH} 234 mμ, log ε 4.04.

Anal. Calcd. for $C_{24}H_{33}FO_5$: C, 68.54; H, 7.90; F, 4.51. Found: C, 68.72; H, 7.90; F, 3.97.

6α-Fluoro-16α-methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-Acetate (Xa). From (VIII).—6β-Fluoro-16α-methyl-5α-pregnan-5α,17α,21-triol-3,20-dione 5,21-diacetate (VIII) (11 g.) was dissolved in 500 ml. of acetic acid and a slow current of hydrogen chloride gas passed through the solution for 30 minutes. The reaction mixture was cooled during the hydrogen chloride treatment and then left at room temperature for 5.5 hours. After dilution with 4 l. of water the product was extracted with methylene chloride. The organic extracts were washed with water, 5% sodium carbonate solution and again with water to neutrality. After concentration of the sodium sulfate-dried extracts, the resulting product was crystallized from ethyl acetate–hexane to give 7.6 g. of 6α-fluoro-16α-methyl-Δ⁴-pregnene-17α, 21-diol-3,20-dione 21-acetate, m.p. 189–191°. The analytical specimen prepared from the same solvent pair melted at 196–198°, $[\alpha]D$ + 76°, λ_{max}^{EtOH} 237 mμ, log ε 4.21; λ_{max}^{KBr} 5.75, 5.80, 5.95 and 6.10 μ.

Anal. Calcd. for $C_{24}H_{33}FO_5$: C, 68.54; H, 7.91. Found: C, 68.24; H, 8.07.

From (IX).—Treatment of 14 g. of 6β-fluoro-16α-methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (IX) in 700 ml. of acetic acid with hydrogen chloride under the conditions exactly as described above gave 11.2 g. of the 6α-fluoro isomer Xa, m.p. 194–196°.

6α-Fluoro-16α-methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione (Xb).—A suspension of 7.3 g. of 6α-fluoro-16α-methyl-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (Xa) in 100 ml. of methanol was cooled in an ice-bath to 5°. The air in the reaction flask was displaced by nitrogen and then a cooled solution of 0.95 g. of potassium hydroxide in 10 ml. of methanol–water (4:1) was introduced into the stirred mixture. After 20 minutes the steroid completely dissolved and the product precipitated shortly thereafter. After 1 hour the mixture was poured into 1 l. of cold saturated sodium chloride solution containing 1 ml. of glacial acetic acid. The precipitated steroid was filtered, washed with water and dried to give 6.2 g. of product, m.p. 169–172°. The analytical sample from acetone–hexane melted at 178–180°, $[\alpha]D$ +93°, λ_{max}^{EtOH} 236 mμ, log ε 4.17.

Anal. Calcd. for $C_{22}H_{31}FO_4$: C, 69.83; H, 8.25. Found: C, 70.21; H, 8.19.

6α-Fluoro-16α-methylhydrocortisone 21-Acetate (XIb).—The following solutions were prepared: 425 ml. of aqueous potassium hydrogen phosphate (1.74%) and 75 ml. of aqueous sodium dihydrogen phosphate (1.38%) were diluted to 5 l. (A); 1 l. of aqueous sodium chloride (4.5%) was mixed with 40 ml. of aqueous potassium chloride (5.75%) and 10 ml. of aqueous magnesium sulfate (19.1%) (B); 20.9 g. of fumaric acid and 14.4 g. of sodium hydroxide were made up to 1.2 l. (C). Crude 6α-fluoro-16α-methyl-Δ⁴-pregnen-17α,-21-diol-3,20-dione (Xb) (6 g.) in 30 ml. of propylene glycol was added to 9 kg. of minced, defatted, fresh beef adrenals suspended in 9 l. of buffer solution prepared by mixing 950 ml. of solution A, 8.64 l. of solution B and 2.4 l. of solution C. The mixture was incubated at 30° for 3 hours with continuous agitation in open erlenmeyer flasks and then 35 l. of acetone was added. The suspension was stirred well for 1 hour, filtered and the residue washed with 5 l. of hot acetone. The filtrate, after concentration *in vacuo* to approximately 8 l. at 35°, was extracted with two 4-l. portions of hexane. The aqueous phase was then extracted exhaustively with methylene chloride and the organic extracts after drying over sodium sulfate were concentrated under reduced pressure. The product, a dark brown oil, was dissolved in methylene chloride and adsorbed on a column of 200 g. of silica gel (Davidson Corporation, grade 922, 200 mesh). Elution with methylene chloride and methylene chloride–acetone (9:1) gave a series of oils. Further elution with methylene chloride–acetone (5:1 and 4:1) yielded a series of crystalline fractions which were combined and recrystallized from acetone–hexane to provide 3.1 g. of 6α-fluoro-16α-methylhydrocortisone (XIa), m.p. 200–205°. This material was left overnight in 60 ml. of acetic anhydride–pyridine (1:2). Isolation of the product with methylene chloride gave 2.6 g. of the 21-acetate XIb, m.p. 245–248°, which crystallized out during the concentration of the solvent. Two additional crystallizations from ethyl acetate–hexane did not raise the melting point, $[\alpha]D$ +115°, λ_{max}^{EtOH} 237, log ε 4.22; λ_{max}^{KBr} 5.72, 5.80, 6.05 and 6.15 μ.

Anal. Calcd. for $C_{24}H_{33}FO_6$: C, 66.03; H, 7.62; F, 4.35. Found: C, 66.50; H, 7.93; F, 4.01.

6α-Fluoro-16α-methylprednisolone 21-Acetate (XII).—A mixture of 1 g. of 6α-fluoro-16α-methylhydrocortisone 21-acetate (XIb) and 0.53 g. of selenium dioxide in 45 ml. of *t*-butyl alcohol containing 0.14 ml. of pyridine was heated under reflux for 60 hours with stirring in a nitrogen atmosphere. The *t*-butyl alcohol was removed *in vacuo* and the residue dissolved in ethyl acetate and treated with charcoal. The clear solution was washed 4 times with water, dried over sodium sulfate and the solvent distilled. The yellow residue (crystalline) was dissolved in methylene chloride and chromatographed on a column prepared by mixing 40 g. of silica gel with an equal volume of Celite. Elution with methylene chloride–acetone (9:1 and 4:1) followed by crystallization of the fractions from acetone–hexane afforded 0.51 g. of product melting at 180°, partially solidifying and melting completely at 220–224°. Three additional crystallizations gave the analytical sample, m.p. 180° and 230–233°, $[\alpha]D$ +85°, λ_{max}^{EtOH} 243, log ε 4.16; λ_{max}^{KBr} 5.80–5.85, 6.03, 6.16 and 6.22(sh.) μ.

Anal. Calcd. for $C_{24}H_{31}FO_6 \cdot C_3H_6O$: C, 65.83; H, 7.57; F, 3.86. Found: C, 65.70; H, 7.17; F, 3.48.

6α-Fluoro-16α-methyl-Δ⁴(⁹,¹¹)-pregnadiene-17α,21-diol-3,20-dione 21-Acetate (XIII).—A solution of 1.55 g. of 6α-fluoro-16α-methylhydrocortisone 21-acetate in 40 ml. of dimethylformamide, 1.86 ml. of mesyl chloride and 2.9 ml. of pyridine was heated on the steam-bath for 3 hours. After cooling, the reaction mixture was diluted with water and the product extracted with methylene chloride. The organic extracts were washed with dilute hydrochloric acid, and dilute sodium carbonate solutions and finally with water to neutrality. Concentration of the dried organic extracts led to 1.3 g. of brown crystals which were chromatographed on a column prepared by mixing 60 g. of silica gel with an equal volume of Celite. The column was developed with methylene chloride and the product eluted with methylene chloride–acetone (9:1). Crystallization of the fractions from acetone gave 0.8 g. of the Δ⁹⁽¹¹⁾-olefin XIII, m.p. 184–187°. An additional 0.22 g. of product, m.p. 181–184°, was obtained on rechromatography of the mother liquors. The analytical sample melted at 188–190°, $[\alpha]D$ +74°, λ_{max}^{EtOH} 235 mμ, log ε 4.17; λ_{max}^{KBr} 5.80, 6.00 and 6.15 μ.

Anal. Calcd. for $C_{24}H_{31}FO_5$: C, 68.87; H, 7.46; F, 4.51. Found: C, 69.28; H, 7.24; F, 3.99.

6α-Fluoro-16α-methyl-9β,11β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-Acetate (XIV).—One gram of 6α-fluoro-16α-methyl-Δ⁴,⁹⁽¹¹⁾-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIII) was suspended in a mixture of 10 ml. of dioxane and 1.3 ml. of 0.5 *N* perchloric acid. N-Bromoacetamide (0.43 g.) was then added in small portions during 40 minutes. The steroid completely dissolved after 20 minutes and a total reaction time of 2 hours was permitted. Water containing a slight excess of sodium sulfite was added to the reaction and the product extracted with ether. The combined organic extracts were dried over calcium chloride and concentrated *in vacuo* at 30°. The resulting oily bromohydrin was dissolved in 37 ml. of acetone and refluxed for 17 hours with 1.5 g. of potassium acetate. The greater part of the acetone was distilled off, water added and the product after isolation with ether was adsorbed on a column of 40 g. of silica gel mixed with an equal volume of Celite. The 9β,-11β-epoxide (0.8 g.) was eluted with methylene chloride–acetone (19:1 and 10:1). Recrystallization of this material from acetone–hexane gave 0.53 g., m.p. 189–191°. Paper chromatography indicated that the product was contaminated with the Δ⁹⁽¹¹⁾-olefin. Consequently the epoxide was not characterized further but employed directly for the next reaction.

6α,9α-Difluoro-16α-methyl-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (XV).—To a solution of 1.46 g. of hydrogen fluoride and 2.6 g. of tetrahydrofuran maintained at −70° in a polyethylene flask was added 0.52 g. of 9β,11β-epoxide dissolved in 20 ml. of methylene chloride. After 15

minutes the flask was transferred to an ice–salt-bath and kept at −10° for 6.25 hours. The reaction mixture was carefully poured into an excess of cold 5% sodium bicarbonate solution and the methylene chloride layer separated. The aqueous phase was extracted three times with methylene chloride and the combined organic extracts were then washed with water, dried over sodium sulfate and concentrated to dryness. The crystalline residue was treated overnight with 5 ml. of pyridine and 2.5 ml. of acetic anhydride. The product isolated with methylene chloride in the usual way crystallized on concentration of the dried extracts. Filtration gave 0.24 g. of 6α,9α-difluoro compound, m.p. 240–243° and raised to 255–260° after four crystallizations from acetone–hexane, $[\alpha]_D$ +113°, λ_{max}^{EtOH} 234 mμ, log ε 4.22; λ_{max}^{KBr} 5.75, 6.05 and 6.15(sh.) μ.

Anal. Calcd. for $C_{24}H_{32}F_2O_6$: C, 63.42; H, 7.10; F, 8.36. Found: C, 63.15; H, 6.96; F, 8.01.

6α,9α-Difluoro-16α-methyl-Δ^{1,4}-pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (XVI).—A mixture of 0.163 g. of 6α,9α-difluoro-16α-methyl-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate and 0.081 g. of selenium dioxide in 21 ml. of *t*-butyl alcohol containing 0.02 ml. of pyidine was boiled with stirring in a nitrogen atmosphere for 62 hours. Ethyl acetate (100 ml.) was then added and the solution treated with charcoal, filtered and concentrated to dryness *in vacuo*. The residue was dissolved in methylene chloride and washed three times with water. The dried organic extracts were concentrated to a small volume and the solution adsorbed on a column containing 8.4 g. of silica gel (mixed with an equal volume of Celite). Elution with mixtures of methylene chloride–acetone (12:1 and 9:1) gave 0.125 g. of product. Three recrystallizations from acetone–hexane gave the analytical sample, m.p. 260–264°, $[\alpha]_D$ +91°, λ_{max}^{EtOH} 237 mμ, log ε 4.16; λ_{max}^{KBr} 5.73, 5.80, 6.03 and 6.23 μ.

Anal. Calcd. for $C_{24}H_{30}F_2O_6 \cdot C_3H_6O$: C, 63.51; H, 7.10. Found: C, 63.90; H, 7.40.

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

21-Halo-17-acyloxyprogesterones

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The preparation and progestational activity of a series of 21-halo-17α-acyloxyprogesterones and 21-halo-17α-acetoxy-6α-methylprogesterones are described. 21-Fluoro-17α-acetoxy-6α-methylprogesterone (XX) is 20 times as potent orally in the Clauberg assay as 17α-ethynyl-19-nortestosterone (Norlutin).

The successful modification of the natural steroid hormone, hydrocortisone,[1] to produce compounds of increased clinical utility has aroused the hope that similar possibilities may exist for progesterone. In this paper we shall describe the synthesis and pharmacology of 21-halo-17-acyloxyprogesterones and the corresponding 6α-methylprogesterones. The enhancement of progestational activity upon fluorination of progesterone at C-21 was first reported by Tannhauser, Pratt and Jensen[2] and was independently discovered in this Laboratory. The striking effect resulting from the introduction of the 17-acetoxy group into progesterone was reported by Junkmann.[3] The combination of these two changes on progesterone, also combined with the demonstrated utility of 6-methylation,[4] produced a series of highly active progestational agents. 21-Fluoro-17α-acetoxy-6α-methylprogesterone (XX) is the most active oral progestin of the series and is 20 times as potent in the Clauberg assay as 17α-ethynyl-19-nortestosterone (Norlutin).[5]

17α,21-Dihydroxyprogesterone (I) (Reichstein's Compound S) was converted to the corresponding 21-chloro derivative II[6] with benzenesulfonyl chloride and collidine. This, in turn, was converted to the desired 21-bromide III and 21-iodide V by the use of lithium bromide and sodium iodide, respectively. The desired 21-fluoro-17α-hydroxyprogesterone (VI) was obtained from the 21-iodide V by reaction with silver fluoride in acetonitrile. From this reaction 17,21-epoxy-4-pregnene-3,20-dione (VII)[7] was also obtained. When 21-chloro-17α-hydroxyprogesterone (II) was treated with potassium fluoride in ethanol, this epoxide, VII, became the major product. The acylation of the fluoride VI, chloride II and bromide III was accomplished by the use of the desired anhydride and *p*-toluenesulfonic acid.[8] When an attempt was made to acetylate 21-iodo-17α-hydroxyprogesterone (V) by this method the iodine was lost and 17α-acetoxyprogesterone was obtained.

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