Synthesis of Certain C-2 and C-6 Substituted Derivatives of 9α-Fluoro-16α-hydroxyhydrocortisone 16,17-Acetonide

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By established procedures, the title compound was converted to the corresponding 2α-methyl, 2α-cyano, 6β-fluoro, 2α-fluoro and apparently the 2,2-difluoro derivatives. 2-Methyltriamcinolone, 2α-methyl-9α-fluoro-16α-hydroxyhydrocortisone and several 11-keto analogs also were prepared.

The availability in quantity in our laboratory of 9α-fluoro-16α-hydroxyhydrocortisone (I),[1] an intermediate in the manufacture of triamcinolone[2] prompted an investigation on our part into the possibility of transforming I into derivatives of greater biological interest. An appropriate intermediate for the modification of this molecule at C-2 appeared to be a 2-alkoxalyl derivative. Such a derivative[3] presumably could lead to the preparation, among other compounds, of 2α-methyl-9α-fluoro-16α-hydroxyhydrocortisone (X) and 2-methyltriamcinolone (XI).[4] These two compounds were of considerable biological interest in that they represented, at least to our knowledge at the time of this investigation, the only known[4] active 2-methyl corticoids which did not cause measurable salt retention. Since these compounds had only been prepared in very poor over-all yield by a multistep procedure from hydrocortisone 20-ethylene ketal,[4] a more convenient synthesis which would afford sufficient quantities of material for further biological evaluation was desired.

A blocked derivative of I suitable for a base-catalyzed alkoxalylation was the 16,17-acetonide 21-tetrahydropyranyl derivative II.[5] Ethoxalylation of II by the usual procedure furnished an amorphous

(1) 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.*, **81**, 1689 (1959).

(2) Aristocort®.

(3) The use of 2-alkoxalyl derivatives for the preparation of 2-alkyl-3-keto steryids is due to J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(4) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen and I. Ringler, *J. Am. Chem. Soc.*, **81**, 1696 (1959).

(5) L. J. Leeson and J. F. Weidenheimer, *J. Pharm. Sci.*, **50**, 86 (1961).

product containing substantial amounts of the 2-ethoxalyl derivative IV.[6] Intensive efforts *via* partition chromatography to purify this product or the corresponding 21-hydroxy derivative, prepared by mild treatment with acid, were unsuccessful. Treatment of the amorphous IV with methyl iodide in acetone in the presence of potassium carbonate followed by acetate-induced deethoxalylation and acid hydrolysis of the tetrahydropyranyl group gave the 2α-methyl acetonide V in 14-30% yield over-all from II. Hydrolytic removal of the acetonide group with formic acid[7] afforded 9α-fluoro-2α-methyl-16α-hydroxyhydrocortisone (X). 2-Methyltriamcinolone acetonide (VII) was conveniently obtained by 1,2-dehydrogenation of the 21-acetate of V with dichlorodicyanobenzoquinone.[8]

The 2α-methyl acetonide V was a highly active glucocorticoid (Table I) and in addition showed (rat assay)[9] profound diuretic properties. Since it is known that 2α-methyl-11-keto derivatives are essentially inactive as glucocorticoids,[10] it was of interest to prepare the 11-keto analog (VI) of V with the hope of separating the glucocorticoid from diuretic activity. Compound VI was prepared in the usual way from V by 21-acetylation, oxidation with pyridine-chromic oxide and deacetylation. Although this substance proved to be a relatively weak corticoid it was also without appreciable diuretic action.

In view of our interest in 2-fluoro steroids,[11] the sodium salt of the 2-ethoxalyl derivative IV was treated with perchloryl fluoride to give, after deethoxalylation, the 2α-fluoro acetonide VIII. A minor by-product of this preparation was by analysis a difluoro derivative of III. On the basis of the preparative method, we have assigned the 2,2-difluoro structure XII to this product,[12] which on comparison with the 2α-fluoro acetonide VIII, showed a hypsochromic shift[13] for

(6) Structure IV is assigned to this derivative on the basis of unpublished work by W. Fulmor and G. O. Morton of these laboratories.

(7) G. R. Allen, Jr., and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2840 (1960).

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

(9) This assay procedure involves oral administration of candidate compounds to normal rats and the determination of urine and urine electrolyte concentration [J. R. Cummings, J. D. Haynes, L. M. Lipchuck and M. A. Ronsberg, *J. Pharmacol. Exptl. Therap.*, **128**, 414 (1960)].

(10) W. E. Dulin, B. J. Bowman and R. O. Stafford, *Proc. Soc. Exptl. Biol. Med.*, **94**, 303 (1957).

(11) H. M. Kissman, A. M. Small and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960).

(12) 16,1-Difluoro-17-keto steroids have been obtained by an analogous procedure [C. H. Robinson, N. F. Bruce, E. P. Oliveto, S. Tolksdorf, M. Steinberg and P. L. Perlman, *J. Am Chem. Soc.*, **82**, 5256 (1960)].

(13) In contrast to this hypsochromic shift, it is interesting to note that significant bathochromic shifts have been reported for 2β-chloro and 2β-bromo-Δ^4-3-ketones, although the shift for the bromo derivative is greater than that for the chloro derivative.[14,15]

(14) B. Ellis and V. Petrow, *J. Chem. Soc.*, 1179 (1956).

(15) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 1334 (1958).

TABLE I[a]

THYMOLYTIC AND MINERALOCORTICOID EVALUATION

Compound	Thymus involution[b] (× hydrocortisone)	Mineralocorticoid[c]
2α-Methyl-9α-fluoro-16α-hydroxyhydrocortisone 16,17-acetonide (V)	56(47–67)	Excretor
2-Methyltriamcinolone 16,17-acetonide (VII)	17(14–21)[d]	No effect
2α-Methyl-9α-fluoro-16α-hydroxycortisone 16,17-acetonide (VI)	1.3(1.0–1.7)	Excretor[e]
2α,9α-Difluoro-16α-hydroxyhydrocortisone 16,17-acetonide (VIII)	4.7(3.6–6.1)	Excretor
2,2,9α-Trifluoro-16α-hydroxyhydrocortisone 16,17-acetonide (XII)	1.2	Excretor
2-Hydroxymethylene-9α-fluoro-16α-hydroxyhydrocortisone 16,17-acetonide (XIV)	2.7(2.1–3.4)	No effect
6β,9α-Difluoro-16α-hydroxyhydrocortisone 16,17-acetonide (XVII)	5.0(3.3–7.6)[f]	Excretor
9α-Fluoro-16α-hydroxyhydrocortisone 16,17-acetonide (III)	11(8–14)[d]	Excretor
2α-Methyl-9α-fluoro-16α-hydroxyhydrocortisone (X)	2.1(1.8–2.4)	Excretor[e]
2-Methyltriamcinolone (XI)	3–6[g]	No effect

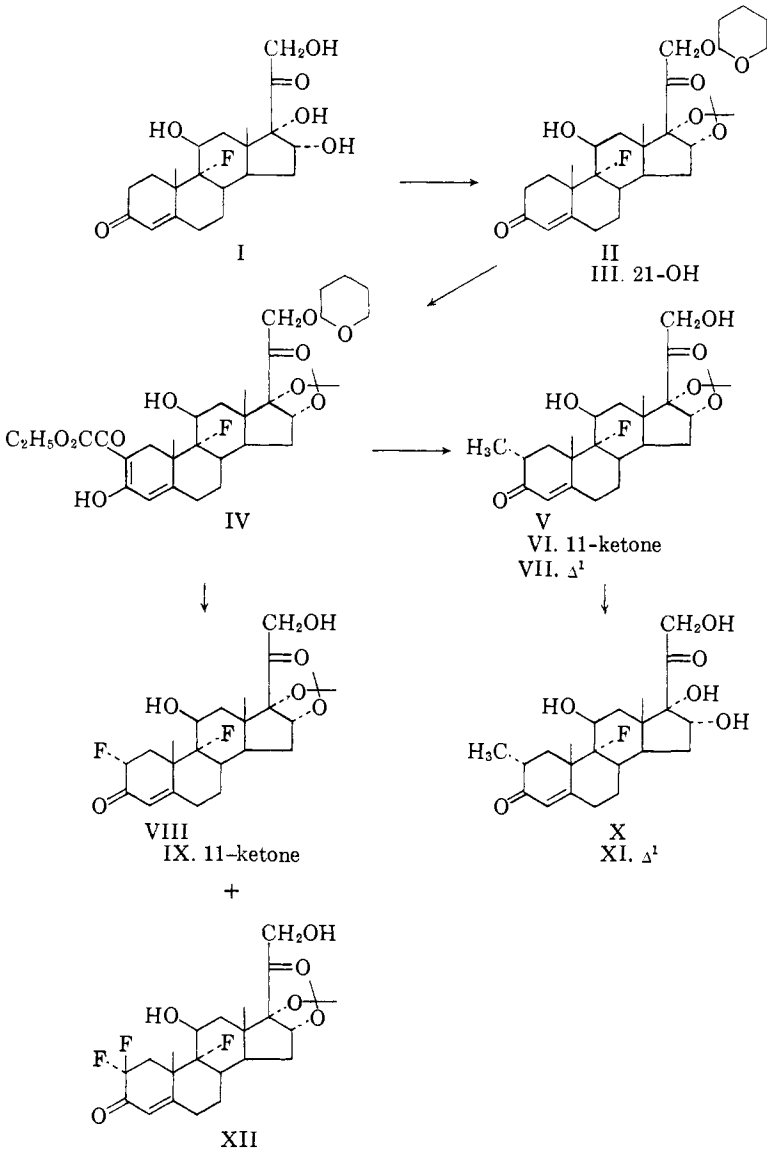
[a] We are indebted to Drs. S. Mauer, I. Ringler and G. Tonelli and their associates of the Experimental Therapeutics Section of these laboratories for the data reported in this table. [b] Unless otherwise noted, this assay (subcutaneous) was carried out by the procedure described by S. Bernstein, R. Littell, J. J. Brown and I. Ringler, *J. Am. Chem. Soc.*, **81**, 4573 (1959). Figures in parentheses represent 95% confidence limits. [c] The mineralocorticoid response was determined by the procedure of J. W. Perrine, L. Bortle, E. Heyder, R. Partridge, E. K. Ross and I. Ringler, *Endocrinology*, **64**, 437 (1959). [d] This assay (subcutaneous) was carried out by the procedure described by I. Ringler and R. Brownfield, *Endocrinology*, 66, 900 (1960). [e] Showed diuretic and kaliuretic activity but no natriuretic activity. [f] By analysis of variance, non-parallelism is indicated. [g] Liver glycogen assay, determined by the procedure given in the reference of footnote *c*.

the ultraviolet maximum ($\lambda_{max}^{CH_3OH}$ 238 mμ to 226 mμ) and an enhanced hypsochromic shift for the position of the 3-carbonyl band in the infrared (λ_{max}^{KBr} 5.90 μ to 5.83 μ).[16] The 11-keto analog (IX) of VIII was prepared from VIII by acetylation, chromic oxide-pyridine oxidation and deacetylation.

It was also possible to effect the C-2 formylation of II by treatment with methyl formate and sodium hydride.[17] The resulting 2-hydrox-

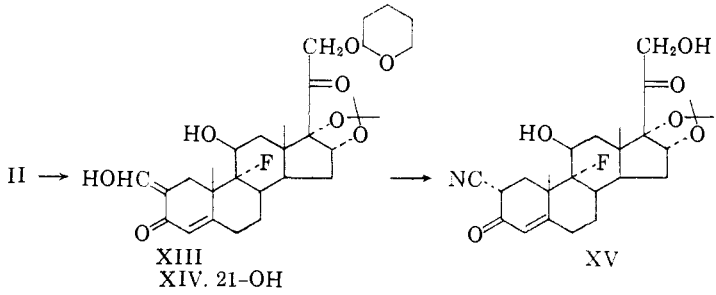
(16) Allinger and co-workers [N. L. Allinger, H. M. Blatter, M. A. Da Rooge and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961)] have reported a shift of about 20 cm.$^{-1}$ for axial 2-fluorocyclohexanones.

(17) F. L. Weisenborn, D. C. Remy and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954).



ymethylene derivative XIII and its free 21-ol XIV were of interest as potentially useful intermediates and *per se* since they represent, to our knowledge, the first examples of 2-hydroxymethylene derivatives of fully elaborated glucocorticoids.[18] We have previously demon-

strated[21] the facile conversion of hydroxymethylene steroids to the corresponding cyano derivatives by treatment with O,N-bis-trifluoroacetylhydroxylamine.[22] Application of this procedure to the hydroxymethylene derivative XIII furnished the 2α-cyano acetonide XV.[23]



The reported[24] sodium-retaining property of the very potent corticoid 6α,9α-difluoroprednisolone suggested the synthesis in this laboratory[25] of 6α-fluorotriamcinolone[26] in the hope that 16α-hydroxylation would negate the sodium-retaining property of the former compound. In fact, 6α-fluorotriamcinolone is not a sodium retainer and has high corticoid activity.[25] The report by Nakanishi, Morita and Jensen[27] that fluorine can be introduced into the 6-position of a Δ^4-3-keto steroid *via* reaction of the derived enol ether with perchloryl fluoride prompted us to investigate the possible utilization of this procedure for the preparation of 6α-fluorotriamcinolone by a sequence starting with the acetonide III, the 3-ethyl enol ether 21-acetate (XVI) of which had already been reported.[28]

(18) The 21-tetrahydropyranyl derivative II and of course compound III[19] itself are active glucocorticoids. 2-Hydroxymethylene derivatives in the testosterone series have important anabolic activity.[20]

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

(20) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

(21) H. M. Kissman, A. S. Hoffman and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961); full paper in press (*J. Org. Chem.*). The initial communication contains a preliminary report on the preparation of compounds XIII and XV.

(22) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959).

(23) The assignment of epimeric configuration of the 2-cyano group is based on stability, spectroscopic and polarimetric considerations discussed in ref. 21.

(24) J. A. Hogg, Sixth Nat. Medicinal Chem. Symposium A.C.S., Madison, Wisc., June 23–25, 1958.

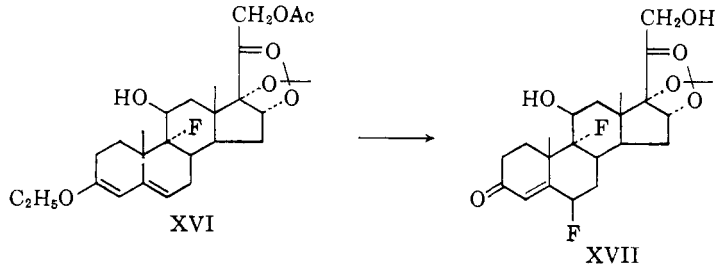
(25) Private communication from Drs. C. E. Holmlund, N. E. Rigler and co-workers.

(26) J. S. Mills, A. Bowers, C. Djerassi and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 3399 (1960).

(27) S. Nakanishi, K. E. Morita and E. V. Jensen, *J. Am. Chem. Soc.*, **81**, 5259 (1959).

(28) H. J. Ringold, O. Mancera, C. Djerassi, A. Bowers, E. Batres, H. Martínez, E. Necoechea, J. Edwards, M. Velasco, C. C. Campillo and R. I. Dorfman, *J. Am. Chem. Soc.*, **80**, 6464 (1958); J. P. Dusza of these laboratories, private communication.

Treatment of this enol ether with perchloryl fluoride followed by deacetylation afforded a relatively low yield of what was apparently the expected 6β-fluoro derivative XVII. An intensive effort to improve this yield by a study of certain experimental variables, such as solvent, time and temperature, failed to give material improvement. Preliminary attempts to effect an acid-catalyzed epimerization of the 6β-fluorine in XVII failed.



XVI XVII

Biological Evaluation.—Increased activity resulted from 2α-methyl substitution and a decrease in activity resulted from the substitution of 2α-cyano, 2α-fluoro, 6β-fluoro and 2-hydroxymethylene groups into the 9α-fluoro-16α-hydroxyhydrocortisone 16,17-acetonide molecule (III). Activity was also decreased by the apparent substitution of a 2β-fluorine atom into 2α,9α-difluoro-16α-hydroxyhydrocortisone 16,17-acetonide (VIII). The thymolytic and mineralocorticoid activity of most of the compounds prepared in this investigation are given in Table I.

Acknowledgment.—We wish to thank Drs. S. Mauer, I. Ringler, G. Tonelli and J. Cummings and their associates of the Experimental Therapeutics Section for biological assay data, Mr. W. Fulmor and staff for spectroscopic and polarimetric data, Mr. C. Pidacks and staff for the partition chromatographic work and Mr. L. Brancone and staff for microanalytical data.

Experimental

General.—**Melting points** were taken on a Kofler micro hot-stage and are corrected. **Ultraviolet spectra** were determined in methanol on a Cary recording spectrophotometer. Aliquots were diluted 1:10 with 0.1 *N* aqueous hydrochloric acid for the acid spectra and 1:10 with 0.1 *N* aqueous sodium hydroxide for the base spectra. **Infrared spectra** were determined in potassium bromide disks on a Perkin Elmer spectrophotometer (Model 21). **Polarimetric data** were obtained in chloroform solution at 25° unless stated otherwise. Solutions were dried over magnesium sulfate and **evaporations** were carried out *in vacuo*. Ethanolic solutions of ferric chloride and blue tetrazolium (BT) were used for the

enol and α-ketol tests respectively. The **sodium hydride-oil** dispersion (50%) was obtained from Metal Hydrides Inc., Beverly, Mass. The material used in the **partition chromatography** columns was *Celite 545*,[29] *diatomaceous earth*, which had been washed with 6 *N* hydrochloric acid, then with distilled water until the washings were neutral, and finally with methanol. The material was dried to give a fluffy powder. **Hold back volume** (h.b.v.) is the volume of solvent required to fill the packed chromatographic column. Solvents were mixed volume by volume. The effluent stream from the column was monitored at a given wave length by passing it through a flowcell in a Beckman DU spectrophotometer which was attached to a recorder. **Nitrogen analyses** on cyano steroids were carried out by the Kjeldahl method, since the Dumas method gave erroneous and unrepeatable results. **Water analyses** were carried out, when possible, by the Karl Fischer method.

9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-2α-methyl-4-pregnene-3,20-dione (V). A.—Solvent (20 ml.) was distilled from a mixture of 45 ml. of benzene and 45 ml. of ethanol, and 0.776 g. of sodium was added to the remaining solution. Refluxing was continued until solution was complete and the mixture was then evaporated. To the residue was added 90 ml. of benzene, 9.15 ml. of diethyl oxalate and 5.9 g. of 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-(tetrahydropyran-2-yloxy)-4-pregnene-3,20-dione (II).[5] The mixture was stirred at room temperature for 22 hr., diluted with 100 ml. of ether and was extracted thoroughly with several portions of cold 1% aqueous potassium hydroxide solution. Each extract was washed with a small amount of 50% benzene–ether and the washings were returned each time to the original reaction mixture. The alkaline extracts were added as soon as possible to a cold aqueous 30% sodium dihydrogen phosphate solution and this mixture (pH 5–6) was in turn extracted several times with chloroform. The combined chloroform extracts were washed with water, dried and evaporated to leave 5.9 g. of crude ethoxalyl derivative IV (strong + enol test) as a dark orange gum which was redissolved in 120 ml. of acetone and 12 ml. of methyl iodide and was stirred overnight with 10 g. of finely powdered potassium carbonate. Another 10 ml. of methyl iodide was added and stirring was continued for 48 hr. The light yellow mixture, which still gave a positive enol test, was filtered, evaporated and distributed between ethyl acetate and water. The organic phase was washed several times with 1% potassium hydroxide solution and then with water till neutral. The dried solution was evaporated and the residue was dissolved in 100 ml. of methanol and heated to reflux with 4 g. of potassium acetate for 2 hr. The filtered solution was evaporated and the residue distributed between water and ethyl acetate. The organic phase was washed again with 1% potassium hydroxide solution and then with water. The dried solution was evaporated, and the residue dissolved in 80 ml. of methanol containing 1 ml. of 8% aqueous sulfuric acid. After 1 hr., the solution was diluted with 50 ml. of methanol and was neutralized by stirring with Duolite A4 anion exchange resin (HO^- form).[30] The filtered solution was evaporated and the residue (3.9 g.) was dissolved in 30 ml. of the lower phase and 30 ml. of the upper phase of the system, heptane–ethyl acetate–methanol–water (7:4:3:2), and the solution was mixed thoroughly with 60 g. of Celite. The mixture was added to the top of a column which had been pre-

(29) Celite® is a trademark for diatomaceous silica products.

(30) Duolite® A4, a weakly basic anion exchange resin from Chemical Process Company, Redwood City, California.

pared in approx. 2 cm. increments from 650 g. of Celite, intimately mixed with 325 ml. of the lower phase. Elution of the column (6.5 × 64 cm.), which had a h.b.v. of 1230 ml., with the upper phase, and monitoring at 240 mμ produced a major peak in the 2nd h.b.v. Evaporation and crystallization from ethyl acetate afforded 740 mg. (14.6%) of white solid, m.p. 221–228°. The analytical sample was prepared by two recrystallizations from ethyl acetate and showed m.p. 243–246°; $[\alpha]_D$ + 147° (*c*, 0.57); $\lambda_{max.}$ 238 mμ (ε 15,040); 5.78 (m), 5.97 μ (s).

Anal. Calcd. for $C_{25}H_{35}FO_6$: C, 66.64; H, 7.83; F, 4.21. Found: C, 66.78; H, 8.10; F, 4.51.

From a smaller peak, which preceded the main peak on the column, there was obtained by crystallization from ether–methylene chloride 200 mg. of solid, m.p. 219–223°; $[\alpha]_D$ −142° (*c*, 0.63); λ_{max} 330 mμ (ε 21,600); 5.6-5.7 (broad, s) 5.82 (m), 6.17 μ (m).

Anal. Calcd. for $C_{25}H_{35}FO_7$: C, 64.50; H, 7.15, F, 4.08. Found: C, 64.89, 64.67; H, 7.03, 6.97; F, 4.02.

From a peak, which succeeded the main peak on the column, there was isolated by crystallization from ether 392 mg. of solid with m.p. 235°. This compound, obtained in another experiment and recrystallized several times from methylene chloride–ether had m.p. 248–257°; $[\alpha]_D$ + 57.6° (*c*, 0.99); λ_{max} 255 mμ (ε 21,700); 295 mμ (ε 19,820); 5.74 (s), 5.80 (s), 5.97 (s), 6.13 (s), 6.22 μ (m); + BT test; −$FeCl_3$ test.

Anal. Calcd. for $C_{29}H_{39}FO_9$ (methylated 2-ethoxalyl-9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione derivative): C, 63.24; H, 7.14; F, 3.45; O, 26.15. Found: C, 63.21, H, 7.46; F, 3.57; O, 25.49.

B. In a large-scale experiment 42 g. of II was acylated with 66.8 ml. of diethyl oxalate, 13.7 g. of sodium hydride (50% solid oil dispersion) and 2200 ml. of benzene under nitrogen for 18 hr. Work-up, methylation, removal of the alkoxalyl group and liberation of the 21-hydroxy group was carried out as described above. The crude product (29 g.) was chromatographed from 250 ml. of methylene chloride on 400 g. of Florisil[31] synthetic magnesium silicate. Elution with 1500 ml. of methylene chloride afforded a yellow oil which was discarded. Further elution with 2500 ml. of methylene chloride and then with 3500 ml. of 10% ether–methylene chloride followed by evaporation and crystallization from methylene chloride–ether afforded 5 g. (13.8%) of good quality V, m.p. 245–248°.

C. In one instance a preparation from 10.5 g. of II by procedure A afforded 2.77 g. (30%) of V, m.p. 235–240°.

21-Acetoxy-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-2α-methyl-4-pregnene-3,20-dione.—The acetonide V (345 mg., 0.765 mmole) was acetylated in pyridine with acetic anhydride in the usual manner to give, after crystallization from acetone–hexane, 266 mg. (71%) of product, m.p. 207–209°. The analytical sample was prepared by recrystallization from acetone-hexane and then from ether, m.p. 215–217°; $[\alpha]_D$ +142.8° (*c*, 1.98); λ_{max} 237 mμ (ε 17,220).

Anal. Calcd. for $C_{27}H_{37}FO_7 \cdot 0.5\ H_2O$: C, 64.44; H, 7.63; F, 3.79; for $C_{27}H_{37}FO_7$: C, 65.84; H, 6.96; F, 3.86. Found: C, 64.95; H, 7.74; F, 3.73.

9α-Fluoro-21-hydroxy-16α,17α-isopropylidenedioxy-2α-methyl-4-pregnene-3,11,20-trione (VI).—To a chilled solution of 492 mg. (1 mmole) of V 21-acetate in 5 ml. of pyridine was added a suspension prepared from 400 mg. of chromic oxide and 3 ml. of chilled pyridine. The mixture was stirred in the cold for 1 hr. and at room temperature overnight. Methanol (20 ml.) was added and the

(31) Florisil is the trademark of the Floridin Co. for a magnesia-silica gel adsorbent.

brown mixture was evaporated. The residue was mixed with 80 ml. of ethyl acetate and was filtered through Celite. The material on the filter was washed well with ethyl acetate and the combined filtrates were washed with 1 *N* sulfuric acid, water, bicarbonate solution, water and saturated saline solution. The dried organic phase was evaporated and the residue was taken up in 40 ml. of methanol and was stirred with 1 ml. of 1 *N* methanolic sodium methoxide at room temperature for 25 min. The mixture was neutralized with a few drops of acetic acid and was evaporated. The residue was distributed in water–chloroform and the organic phase was washed with water, dried and evaporated to afford a residue which was crystallized from ether, 284 mg. (63%); m.p. 220–225°. Recrystallization from ether–hexane gave material with m.p. 225–227°; $[\alpha]_D$ +161° (*c*, 2.02); λ_{max} 243 mμ (ϵ 16,140); 5.79 (s), 5.94 μ (broad, s).

Anal. Calcd. for $C_{25}H_{33}FO_6$: C, 66.94; H, 7.42; F, 4.23. Found: C, 66.64; H, 7.72; F, 4.21.

21-Acetoxy-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-2-methyl-1,4-pregnadiene-3,20-dione (VII 21-acetate).—A solution of 246 mg. (0.5 mmole) of V 21-acetate and 171 mg. (0.75 mmole) of 2,3-dichloro-5,6-dicyanobenzoquinone[32] in 22 ml. of dry dioxane was allowed to reflux with stirring for 3 days. The cooled solution was filtered, evaporated and the residue was dissolved in 60 ml. of benzene. The solution was washed with water, cold 1% aqueous potassium hydroxide, water and was dried and evaporated. The residue was crystallized from ether–hexane to afford 160 mg. (65%) of product with m.p. 229–235°. Recrystallization from a large volume of ether with activated charcoal gave a sample with m.p. 238–239°; $[\alpha]_D$ + 81.7° (*c*, 1.04); λ_{max} 243 mμ (ϵ 17,300) with trace absorption at 300 mμ[33]; 5.67 (s), 5.77 (s), 5.97 (s), 6.10–6.20 μ (s). The material was shown to be substantially free from Δ^4-3-one by polarography.[34]

Anal. Calcd. for $C_{27}H_{35}FO_7$: C, 66.11; H, 7.19; F, 3.87. Found: C, 66.43; H, 7.50; F, 4.22.

9α-Fluoro-11β-21-dihydroxy-16α,17α-isopropylidenedioxy-2-methyl-1,4-pregnadiene-3,20-dione (VII).—Deacetylation of 100 mg. of VII 21-acetate in 8 ml. of methanol and 0.2 ml. of 10% aqueous potassium carbonate under nitrogen for 1 hr. in the usual manner afforded after crystallization from ether–methylene chloride, 60 mg. of product; m.p. 280–283° dec.; $[\alpha]_D$ + 90° (*c*, 0.223); λ_{max} 245 mμ (ϵ 15,280) with trace absorption at 300 mμ[33]; 5.81 (s), 5.97 (s), 6.13–6.20 μ (s).

Anal. Calcd. for $C_{25}H_{33}FO_6$: C, 66.94; H, 7.42; F, 4.23. Found: C, 66.84; H, 7.84; F, 4.16.

9α-Fluoro-11β,16α,17α,21-tetrahydroxy-2α-methyl-4-pregnene-3,20-dione (X).[4]—The acetonide V (250 mg., 0.556 mmole) was mixed with 9.75 ml. of water and was heated to boiling with stirring under nitrogen. Formic acid (5.25 ml.) was added and refluxing was continued for 3.25 hr. (all in solution after approx. 1 hr.). The cooled mixture was added to 50 ml. of ice water and the acid was partially neutralized with 4 g. of potassium hydroxide in 10 ml. of water. Ethyl acetate (60 ml.) was added and the mixture was washed carefully with saturated aqueous sodium bicarbonate solution and then with water (back-extracted with ethyl acetate). The dried organic phase was evaporated and the residue crystallized

(32) E. A. Braude, A. G. Brook and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).

(33) It has been found that the conversion of Δ^4-3-keto steroids to $\Delta^{1,4}$-3-ketones with 2,3-dichloro-5,6-dicyanobenzoquinone also affords small amounts of $\Delta^{4,6}$- and $\Delta^{1,4,6}$-3-ones as by-products.

(34) P. Kabasakalian and J. McGlotten, *J. Am. Chem. Soc.*, **78**, 5032 (1956).

from acetone–hexane to afford 170 mg., m.p. 210–216°. Recrystallization from that solvent pair gave 130 mg. (57%) of product with m.p. 214–217° (lit.[4] m.p. 228.5–231°) and an infrared spectrum which was identical with one obtained from authentic material.[4]

Anal. Calcd. for $C_{22}H_{31}FO_6 \cdot 0.5\ H_2O$: C, 62.99; H, 7.69; F, 4.53; H_2O, 2.15. Found: C, 62.45; H, 7.41; F, 4.58; H_2O, 2.32.

2α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (VIII).—Crude ethoxalyl derivative (6.8 g.) prepared from 5.90 g. (11.3 mmoles) of II, as described above for the preparation of V, was dissolved in 50 ml. of methanol, the solution was cooled to −10° and 20 ml. of 1 *N* methanolic sodium methoxide solution was added. Perchloryl fluoride[35] gas was bubbled through the cooled solution to neutrality (approx. 3 min.). The solution was evaporated partially *in vacuo* and another 10 ml. portion of the methoxide solution was added with cooling.[36] The solution was again treated with perchloryl fluoride at −10° and was then evaporated, mixed with chloroform, washed with water, 1% aqueous sodium hydroxide and water. The dried organic phase was evaporated and the residue was dissolved in 60 ml. of methanol, refluxed with 4 g. of potassium acetate for 75 min. and evaporated. The residue was distributed in water–chloroform and the organic phase washed with water and evaporated. The residue was redissolved in 50 ml. of methanol containing 1 ml. of 5% sulfuric acid and was allowed to stand for 90 min. The solution was neutralized by stirring with Duolite A4 anion exchange resin (HO^- form) and the resin was removed by filtration. The filtrate was evaporated and there was obtained 4.1 g. of a yellow glass which gave only a weak enol test and a strong BT test.

The gum was dissolved in 30 ml. of the upper and 30 ml. of the lower phase of the system heptane–ethyl acetate–methanol–water (4:3:3:2) and 30 g. of Celite was added. The moist mixture was added to a column, prepared from 620 g. of Celite which had been well mixed with 310 ml. of the lower phase. The column (6.5 × 65 cm., 1160 ml. h.b.v.) was eluted with the upper phase and the effluent stream was monitored at 240 mμ. Evaporation of the fractions containing the major peak (4–5th h.b.v.) and crystallization with ether afforded 1.34 g. (26%) of product with m.p. 227–229°. The analytical sample obtained from a similar experiment after two recrystallizations from methylene chloride–ether had m.p. 238–240°; $[\alpha]_D$ + 149° (*c*, 1.12); λ_{max} 238 mμ (ε 16,200); 5.80 (shoulder), 5.90 μ (s).

Anal. Calcd. for $C_{24}H_{32}F_2O_6 \cdot {}^1/_3H_2O$: C, 62.59; H, 7.15; F, 8.25; H_2O, 1.30. Found: C, 62.35; H, 7.33; F, 8.08; H_2O, 0.58.

2,2,9α-Trifluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XII).—Material which preceded (2nd h.b.v.) VIII on the partition column, described above, was collected (601 mg.) and rechromatographed on Celite from the system heptane–ethyl acetate–methanol–water (6:3:3:2). The main peak (3rd h.b.v.) afforded 354 mg. of solid. After three recrystallizations from ether the material (150 mg.) had m.p. 250–257° dec.; $[\alpha]_D$ + 73.5° (*c*, 0.86); λ_{max} 226 mμ (ε 13,900); 5.83 μ (s) (no other band in the carbonyl region).

Anal. Calcd. for $C_{24}H_{31}F_3O_6$: C, 61.01; H, 6.63; F, 12.07. Found: C, 61.72; H, 7.02; F, 12.04.

(35) Perchloryl fluoride was obtained from Pennsalt Chemicals Corp.

(36) V. Papesh [*Chem. Eng. News*, **37**, (No. 28), 60 (1959)] has reported an explosion resulting from the addition of sodium ethoxide to a vessel containing the mixed vapors of methanol and perchloryl fluoride.

In a subsequent experiment, the 2α-fluoro derivative VIII was isolated in 47% yield without partition chromatography by seeding a concentrated methanol solution of crude material.

21-Acetoxy-2α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (VIII 21-acetate).—The 2α-fluoro derivative VIII (454 mg., 1 mmole) was acetylated with pyridine and acetic anhydride in the usual manner to afford 408 mg. (82%) of product with m.p. 253–265°. Recrystallization from methylene chloride–ether gave a sample with m.p. 269–279°; $[\alpha]_D$ + 146° (*c*, 2.06); λ_{max} 239 mμ (ε 15,000); 5.69 (s), 5.76 (s), 5.88 μ (s).

Anal. Calcd. for $C_{26}H_{34}F_2O_7$: C, 62.89; H, 6.86; F, 7.67. Found: C, 62.77; H, 7.10; F, 7.49.

2α,9α-Difluoro-21-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,11,20-trione (IX).—The 21-acetate of VIII (1.059 g., 2.4 mmoles) in 11 ml. of cold pyridine was treated with 850 mg. of chromic anhydride in 7 ml. of cold pyridine for 16 hr. at room temperature. The mixture was evaporated and the residue triturated with ethyl acetate. The suspension was filtered through Celite and the filtrate was washed with 1 *N* sulfuric acid and then with water till neutral. The dried solution was evaporated and the residue was taken up in 100 ml. of methanol. Nitrogen was bubbled through the solution, 2.5 ml. of 1 *N* methanolic sodium methoxide was added and the mixture was kept at room temperature for 1 hr. Neutralization with a few drops of acetic acid and evaporation gave a residue which was dissolved in chloroform–water. The organic phase was washed with a little water and was dried and evaporated. The residue was crystallized from ether–hexane to afford 717 mg. (74%) of product with m.p. 220–230°. Recrystallization from methylene chloride–ether afforded a sample with m.p. 210–215°; $[\alpha]_D$ + 164° (*c*, 0.993); λ_{max} 234 mμ (ε 15,600); 5.80 (s), 5.86 (s), 5.92 μ (shoulder, s).

Anal. Calcd. for $C_{24}H_{30}F_2O_6$: C, 63.70; H, 6.68; F, 8.42. Found: C, 63.77; H, 7.00; F, 8.35.

9α-Fluoro-11β-hydroxy-2-hydroxymethylene-16α,17α-isopropylidenedioxy-21-(tetrahydropyran-2-yloxy)-4-pregnene-3,20-dione (XIII).—A mixture of 2.6 g. (5 mmole) of 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-(tetrahydropyran-2-yloxy)-4-pregnene-3,20-dione II,[5] 2 ml. of ethyl formate, 1 g. of sodium hydride–oil dispersion and 100 ml. of dry benzene was stirred under nitrogen. The reaction was started with the addition of a few drops of absolute ethanol and stirring was continued for 23 hr. Ether (100 ml.) was added to the mixture which was then extracted with several portions of water. The organic phase was dried and evaporated to afford 0.97 g. of starting material. The dark yellow water extracts were neutralized through the addition of 30% aqueous sodium dihydrogen phosphate solution. The mixture was extracted with several portions of chloroform and the combined extracts were dried and evaporated to afford 1.13 g. (66% yield corrected for recovered starting material) of yellow glass. This material could be crystallized partially from ether to afford 460 ml. (26.8%, corrected for recovered starting material) of bright yellow solid with m.p. 120–128°. For analysis, the material was recrystallized from ether, m.p. 125–128°; $[\alpha]_D$ + 68.5° (*c*, 1.02); λ_{max} 5.78 (s), 6.07 (broad, s), 6.32 μ (m); 246 mμ (ε 13,900) and 305 mμ (ε 2,470) in acid, 248 mμ (ε 12,500) and 307 mμ (ε 4,180) in methanol, 242 mμ (ε 14,400) and 358 mμ (ε 9,600) in base.

Anal. Calcd. for $C_{30}H_{41}FO_8$: C, 65.70; H, 7.54; F, 3.46. Found: C, 65.64; H, 7.83; F, 3.44.

9α-Fluoro-11β,21-dihydroxy-2-hydroxymethylene-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XIV).—To a suspension of XIII (300 mg., 0.55 mmole) in 12 ml. of water was added 18 ml. of glacial acetic acid. The mixture was stirred at room temperature for 30 min. and the solvent was removed *in vacuo* (at less than 30°). The residue was partitioned between methylene chloride and water, and the organic phase was washed with water, saline solution, dried, decolorized and evaporated. The residue was crystallized from ether to yield 159 mg. (62%) of pale yellow crystals, m.p. 220–227°. For analysis, the product was recrystallized 3 times from methylene chloride–ether, m.p. 224–232°; $[\alpha]_D$ + 90° (*c*, 0.89); λ_{max} 2.87 (m); 5.80 (m), 6.02 (broad, s), 6.30 μ (m); 247 mμ (ε 14,400) and 305 mμ (ε 2,780) in acid, 250 mμ (ε 12,800) and 308 mμ (ε 5,350) in methanol, 242 mμ (ε 15,300) and 357 mμ (ε, 10,900) in base.

Anal. Calcd. for $C_{25}H_{33}FO_7$: C, 64.64; H, 7.16; F, 4.09. Found: C, 64.91; H, 7.38; F, 3.82.

2α-Cyano-9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XV).—A solution of 274 mg. (0.5 mmole) of the 2-hydroxymethylene derivative XIII and 225 mg. (1 mmole) of *O,N*-bis-(trifluoroacetyl) hydroxylamine[22] in 0.4 ml. of pyridine and 10 ml. of benzene was allowed to reflux with stirring for 2 hr. The cooled solution was washed with water and the organic phase was dried and evaporated. The gummy residue (300 mg.) could not be crystallized and was therefore dissolved in 20 ml. of methanol containing 1 ml. of 8% aqueous sulfuric acid and the solution was stirred at room temperature for 1 hr. The mixture was neutralized by stirring with Duolite A4 anion exchange resin (HO^- form) and the filtrate and washings were evaporated. The residue was crystallized from methanol with activated charcoal to give 124 mg. (54%) of product with m.p. 285–290° dec. A sample was recrystallized from acetone–hexane, m.p. 293–296° dec.; $[\alpha]_D$ + 132° (*c*, 0.58 in acetone); λ_{max} 2.98 (m), 4.44 (w), 5.82 (s), 5.91 (s), 6.13 μ (m); 244 mμ (ε 17,750) in acid, 238 mμ (ε 17,300) in methanol, 333 mμ (ε 5,990) in base.

Anal. Calcd. for $C_{25}H_{32}FNO_6$: C, 65.06; H, 6.94; N, 3.03; F, 4.12. Found: C, 65.48; H, 7.33; N, 3.12; F, 4.43.

The base-soluble (+ $FeCl_3$ test) gum from the mother liquors of the 2-hydroxymethylene derivative XIII preparation (above), when taken through this reaction sequence, afforded a 27% yield of crystalline 2α-cyano compound (XV).

6β,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (XVII).—Perchloryl fluoride was bubbled through a chilled solution (0–3°) of 2.13 g. (4 mmoles) of enol ether XVI[23] in 25 ml. of pyridine for 15 min. The internal temperature rose to 17° for a few min. and then fell back to 3°. Excess perchloryl fluoride was removed by bubbling nitrogen through the mixture, which was then poured into 200 ml. of cold 2 *N* hydrochloric acid. After 20 min., the mixture was filtered and the precipitate was washed with water, dissolved in methylene chloride, washed with water to neutrality, dried and evaporated. The residual gum (1.18 g.) was dissolved in 20 ml. of methanol and treated with 2.5 ml. of 10% aqueous potassium carbonate solution under nitrogen at room temperature for 1 hr. The mixture was neutralized with a few drops of acetic acid, added to water and the resulting suspension was extracted with several portions of chloroform. The extracts were washed with a little water, dried and evaporated to leave 1.1 g. of gum. This was dissolved in 26 ml. of the lower and 26 ml. of the upper phase of the solvent system heptane–ethyl acetate–methanol–water (4:2:3:2), and 50 g. of Celite was added. The moist mixture

was packed on top of a column prepared from 500 g. of Celite and 250 ml. of the lower phase and the column (5.5 × 60 cm.) was developed with the upper phase (800 cc. h.b.v.). The effluent stream was monitored at 240 mμ, and the large peak eluted in the 2nd and 3rd h.b.v. was collected by evaporation of relevant fractions. The material so obtained (386 mg.) was still impure and was recolumned in the same manner on 300 g. of Celite from the system cyclohexane–dioxane–methanol–water (10:8:2:2).[37] The column (3.8 × 66 cm.; 410 ml. h.b.v.) was developed with the upper phase of the solvent system and there was isolated from a major peak in the 4th h.b.v. 246 mg. of solid which after several recrystallizations from ether–methylene chloride afforded 126 mg. (6.7%) of product; m.p. 211–213°; $[\alpha]_D$ + 62.4° (*c*, 1.01), MD + 281.7, ΔMD (product-parent) − 345; λ_{max} 230 mμ (ε 13,860); 5.85 (s), 5.94 (s), 5.99 μ (shoulder). The corresponding 6α-epimer[25] has $[\alpha]_D^{CH_3OH}$ + 120°, MD + 545; compound III has $[\alpha]_D^{CH_3OH}$ + 129°, MD + 563; ΔMD (6α epimer-III) − 18.

Anal. Calcd. for $C_{24}H_{32}F_2O_6$: C, 63.41; H, 7.10; F, 8.36. Found: C, 63.62; H, 7.29; F, 8.65.

(37) In subsequent experiments it was found that this solvent system could be used directly on crude material to give the desired product in a single chromatogram.

Synthesis of Certain 16α-Substituted Derivatives of 9α-Fluoro-11-dehydrocorticosterone, Progesterone and Deoxycorticosterone

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The various 16-substituted derivatives were prepared by 1,4-addition to the appropriate 16-dehydro-20-keto steroids of certain mercaptans, thioacetic acid, hydrogen chloride, nitromethane, methanol, and certain primary and secondary amines.

The introduction of new groups into the 16-position of steroids having glucocorticoid activity has often resulted in compounds with significantly enhanced biological utility. In fact, substitution at C-16 has been one of the most fruitful approaches to corticoid analog research in recent years. Among the groups which have been introduced at this position and which have exerted a favorable biological