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

Fluorinated Steroids. II.[1] The Reaction of Perchloryl Fluoride with Alkoxalylated Steroids. Synthesis of Certain 2α-Fluoro and 21,21-Difluoro Steroids

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The reaction of 2-alkoxalyl-Δ^4-3-ketones with perchloryl fluoride followed by dealkoxalylation affords 2α-fluoro-Δ^4-3-ketones. A 21-alkoxalyl-20-ketone gives either a 21-monofluoro or a 21,21-difluoro derivative depending on reaction conditions. The following new fluorinated steroids are reported: 2α-fluorohydrocortisone, 2α-fluoroprogesterone, 2α-fluorotestosterone, 2α-fluorodeoxycorticosterone, 2α,21-difluoroprogesterone, 21,21-difluoropregnenolone and 21,21-difluoroprogesterone.

The introduction of fluorine into various positions of certain steroid hormones has often resulted in enhancement of biological activity. Thus, incorporation of fluorine into the 6α-,[2] 9α-[3] and 12α-positions[4] of hydrocortisone has afforded highly active glucocorticoids. In other fields, 21-fluoroprogesterone has been reported[5] to be 2–4 times as active a progestational agent as progesterone,[6] and 9α-fluoro-11β,17β-dihydroxy-17α-methyl-4-androsten-3-one[7] is a potent androgen being approximately ten times as active as the non-fluorinated analog. Therefore, it is of general interest to synthesize and test other fluorinated steroid hormone derivatives. For such a program, the process reported from the Pennsalt laboratories by Inman and co-workers[8] whereby fluorine is introduced into the methylene group of β-dicarbonyl compounds *via* the reaction of sodio enolates with the new reagent perchloryl fluoride seemed particularly suitable.[9] Presumably, this method would allow the introduction of fluorine into any steroidal methylene or methyl group which can undergo acylation to give a β-dicarbonyl system. Adaptation of this method to the steroid nucleus therefore would require acylation of a methyl or methylene group adjacent to a carbonyl function, reaction with perchloryl fluoride and finally deacylation. In this paper we wish to describe the use of this procedure for the introduction of fluorine into the 2- and 21-positions of the steroid molecule.

For the preparation of the 2-fluoro derivatives of 4-pregnene-3,20-diones, it is first necessary to block the 20-carbonyl group so as to prevent acylation at C-21 or possible base-catalyzed rearrangements of the side chain. Thus, the conveniently available 20-ethylene ketal derivatives of hydrocortisone,[10] progesterone[11] and deoxycorticosterone[12] represented suitable starting materials for the incorporation of fluorine into these important hormones. Among the potential acyl groups which might be introduced at position C-2, the alkoxalyl was the most attractive. Alkoxalylation at C-2 has been shown to proceed, at least in certain instances, in good yields.[13] Furthermore, deacylation of brominated alkoxalyl steroids is usually a smooth reaction requiring relatively mild conditions.

For the synthesis of 2α-fluorohydrocortisone (IV), the 20-ethylene ketal of hydrocortisone (I)[10] was treated with methyl oxalate and sodium methoxide in benzene solution as described in a recent Australian patent.[14] This procedure gave two yellow, crystalline methoxalyl derivatives which were isomeric. The lower melting compound (m.p. 197–198°), obtained in about 22% yield, was brominated to give, after cleavage of the methoxalyl group with methanolic potassium acetate, a monobromide. Dehydrobromination with collidine and acid-catalyzed hydrolysis of the 20-ethylene ketal group afforded 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (prednisolone) in 28% over-all yield indicating that bromination had taken place at the 2-position and that therefore, in all probability, the lower melting product was the desired 2-methoxalylhydrocortisone 20-ethylene ketal (II). The structure of the higher melting methoxalyl derivative (m.p. 259–260°, 15% yield) has not been elucidated as yet. The isolation of only one methoxalyl derivative is described in the above-cited patent.[14] Although physical constants for this product are not given, its reported conversion to a 2-methyl derivative indicates that it is the lower melting isomer.

Perchloryl fluoride gas was bubbled into a cold methanolic solution containing the 2-methoxalyl

(1) A portion of the work described in this paper has been published in a preliminary form; *cf.* H. M. Kissman, A. M. Small and M. J. Weiss, THIS JOURNAL, **81**, 1262 (1959) (paper 1 of this series).

(2) (a) A. Bowers and H. J. Ringold, *ibid.*, **80**, 4423 (1958); (b) J. A. Hogg, *et al.*, *Chemistry & Industry*, 1002 (1958).

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

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

(5) P. Tannhauser, R. J. Pratt and E. V. Jensen, THIS JOURNAL, **78**, 2658 (1956).

(6) For the effect of a fluorine atom at C-6 on progestational activity see H. J. Ringold, E. Batres, A. Bowers, J. Edwards and J. Zderic, *ibid.*, **81**, 3485 (1959).

(7) M. E. Herr, J. A. Hogg and R. H. Levin, *ibid.*, **78**, 500 (1956).

(8) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling and F. L. Scott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, THIS JOURNAL, **80**, 6533 (1958). We would like to thank the Pennsalt Chemicals Corporation for a generous sample of perchloryl fluoride.

(9) In a recent paper, R. B. Gabbard and E. V. Jensen, [*J. Org. Chem.*, **23**, 1406 (1958)] reported the synthesis of 2α-fluorocholestanone by the reaction of perchloryl fluoride with cholestan-3-one pyrrolidyl enamine. The reaction of perchloryl fluoride with steroidal enol ethers has also been reported: S. Nakanishi, R. L. Morgan and E. V. Jensen, Abstracts of Papers, 136th Meeting of the A.C.S., Atlantic City, N. J., September, 1959, p. 55 P.

(10) This compound was obtained by deacetylation of hydrocortisone acetate 20-ethylene ketal which in turn was prepared (S. Bernstein and R. Littell, unpublished work) from the bis-ethylene ketal of hydrocortisone acetate [W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954)] by acetic acid-catalyzed removal of the 3-ethylene ketal group [R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953)].

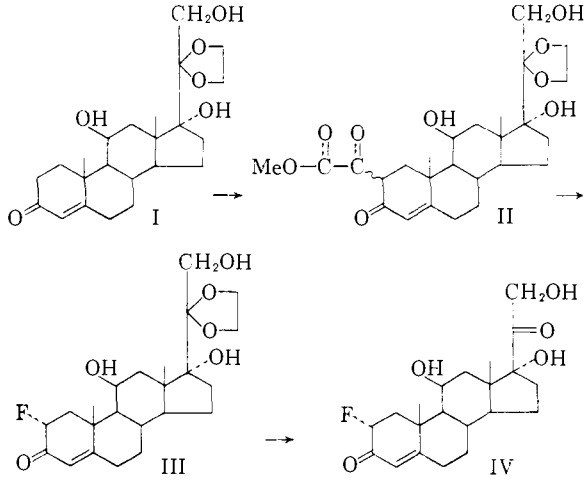
(11) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

(12) F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1959).

(13) G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959); earlier, pertinent references are cited in this paper.

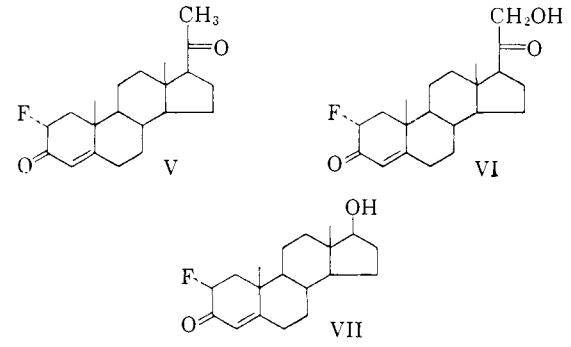
(14) Australian Patent 23,672, May 12, 1956, assigned to Merck and Co., Inc.

derivative II and an excess of sodium methoxide.[15] Loss of basicity and a negative enol test were taken as indications of completeness of reaction. Cleavage of the methoxalyl group was effected with potassium acetate in refluxing methanol to afford 2α-fluorohydrocortisone 20-ethylene ketal (III) in 43% yield. The ketal group was removed with sulfuric acid in methanol and there was obtained a 73% yield of crystalline 2α-fluorohydrocortisone (IV).



The α-configuration of the fluorine atom in compounds III and IV is assumed from spectral evidence, on the basis that a fluorine atom at C-2 would have effects on the infrared[16] and ultraviolet[17,18] absorption spectra similar to those exhibited by chlorine and bromine atoms at this position. Thus, when compared to the spectra of their respective parent compounds, the spectra of III and IV showed no shift of the ultraviolet absorption maxima and a hypsochromic shift of the 3-carbonyl bands in the infrared (*cf.* Table I).[20] On the basis of similar spectral evidence, the α-configuration also was assigned to all the other 2-fluoroketones reported in this paper. It may be noted that the change in molar rotation resulting from the introduction of a 2α-fluorine atom into the various steroids of this investigation is consistently positive (*cf.* Table I). That the α-epimer apparently is the more stable[22] is interesting since in comparison with bromo, chloro and methyl substituents, the probability of steric interaction of a 2α-fluorine with the angular methyl group at C_{10} is at a minimum and the probability of electrostatic repulsion between a 2α-fluorine and the 3-keto group is at a maximum.[23]

For the synthesis of 2α-fluoroprogesterone (V), the 20-ethylene ketal of progesterone[11] was prepared *via* Oppenauer oxidation of pregnenolone 20-ketal obtained by a modification of a literature method.[11] Ethoxalylation, reaction with perchloryl fluoride, cleavage of the ethoxalyl group and removal of the 20-ethylene ketal group were carried out without isolation of intermediates to give 2α-fluoroprogesterone (V) in 44% yield over-all from progesterone 20-ethylene ketal. A similar sequence gave 2α-fluorodeoxycorticosterone (VI) in 25% over-all yield from deoxycorticosterone acetate 20-ethylene ketal.[12] 2α-Fluorotestosterone (VII) was prepared from testosterone in 20% over-all yield *via* a crude, non-crystalline 2-methoxalyl derivative.



Since Inman and co-workers[8] had shown that the reaction of diethyl sodiomalonate with perchloryl fluoride afforded only the difluoro derivative, it seemed probable that perchloryl fluoride treatment of a 21-alkoxalylsteroid would give a 21,21-difluorosteroid, a hitherto unreported steroid class. Thus, the sodium salt of 21-ethoxalylpregnenolone (VIII)[24] was treated with perchloryl fluoride in methanol solution containing an additional equivalent of sodium methoxide. Contrary to the results expected on the basis of Inman's work,[8] a 67% yield of 21-monofluoropregnenolone (IX)[5] was isolated after cleavage of the alkoxalyl group. Oxidation of IV with aluminum isopropoxide gave the known 21-fluoroprogesterone (XI).[5] In order to obtain the desired 21,21-difluorosteroid XII, it was necessary to treat sodio ethoxalylpregnenolone repeatedly with excess sodium methoxide and perchloryl fluoride (see Experimental section). Even under these forcing conditions some 21-monofluoropregnenolone (IX) was obtained. Our best experiments afforded, after dealkoxalylation, a 56% yield of 21,21-difluoropregnenolone (X) and a 14% yield of the 21-monofluoro derivative IX.

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

(16) (a) M. Fieser, M. A. Romero and L. F. Fieser, THIS JOURNAL, **77**, 3305 (1955); (b) E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

(17) B. Ellis and V. Petrow, *ibid.*, 1179 (1956).

(18) Comparison of the spectra of an unequivocal axial α-fluoroketone with those of the parent desfluoro compound showed a bathochromic shift in the ultraviolet absorption maximum and no shift in the position of the carbonyl band in the infrared.[19]

(19) A. S. Kende, *Tetrahedron Letters*, in press. We would like to thank Dr. Kende for making available to us this information prior to publication.

(20) In a recent paper, Djerassi and co-workers[21] reported that 2α-fluorocholastan-3-one,[9] which showed a similar hypsochromic shift of the 3-one band in the infrared,[9] has a rotatory dispersion curve akin to those of other equatorial α-haloketones.

(21) C. Djerassi, I. Fornaguera and O. Mancera, THIS JOURNAL, **81**, 2383 (1959).

(22) Presumably, base-catalyzed cleavage of the alkoxalyl group proceeds *via* an intermediate carbanion which allows ample opportunity for conformational equilibration of the fluoroketone; *cf.* Allen and Weiss.[12]

(23) See E. J. Corey [THIS JOURNAL, **76**, 175 (1954)] for a discussion of the factors determining the relative stability of epimeric α-bromoketones in the steroid field. It is even more surprising that the stable epimer of 2-fluorocyclohexanone also has the equatorial conformation; *cf.* A. S. Kende.[19]

(24) H. Ruschig, *Chem. Ber.*, **88**, 878 (1955).

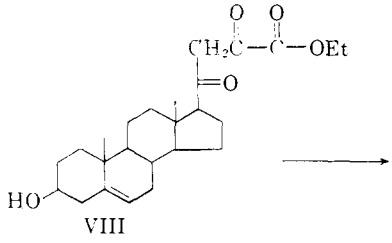
TABLE I

CHANGES IN POSITION OF INFRARED CARBONYL ABSORPTION BANDS AND OF MOLAR ROTATION VALUES RESULTING FROM INTRODUCTION OF FLUORINE

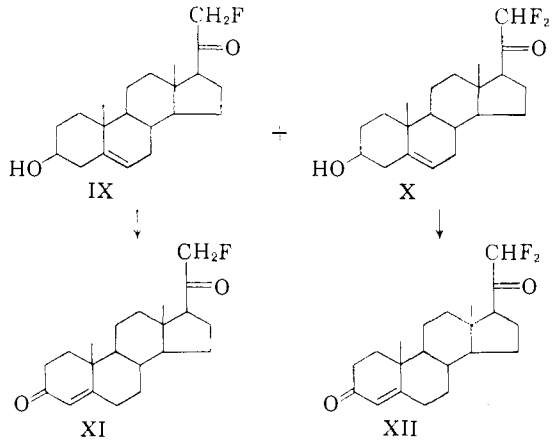
	Fluorinated compounds Infrared bands, μ			Non-fluorinated parent compounds Infrared bands, μ			Differences Δμ		
	3-C=O	20-C=O	M_D[a]	3-C=O	20-C=O	M_D[a]	3-C=O	20-C=O	ΔM_D
2α-Fluorohydrocortisone 20-ethylene ketal (III)	5.87		+560	5.99		+418	−0.12		+142
2α-Fluorohydrocortisone (IV)	5.90		+723[b]	6.02		+590[c]	− .12		+133
2α-Fluoroprogesterone (V)	5.92		+685	6.01		+639[d]	− .09		+ 46
2α-Fluorodeoxycorticosterone (VI)	5.90		+815	5.99		+587[e]	− .09		+228
2α-Fluorotestosterone (VII)	5.90		+401	6.00		+337[f]	− .10		+ 64
21-Fluoropregnenolone (IX)		5.85			5.95			−0.10	
21,21-Difluoropregnenolone (X)		5.76			5.95			− .19	
21-Fluoropregesterone (XI)		5.79			5.88			− .09	
21,21-Difluoroprogesterone (XII)		5.76			5.88			− .12	
2α,21-Difluoropregsterone (XIV)	5.92	5.80	+765	6.01	5.88	+639[d]	− .09	− .08	+126

[a] In chloroform at 23–26° unless stated otherwise. [b] In MeOH. [c] In MeOH [N. L. Wendler, *et al.*, THIS JOURNAL, **74**, 3630 (1952)]. [d] A. Lardon, *Helv. Chim. Acta*, **32**, 1517 (1949). [e] In EtOH [Ch. Meystre and K. Miescher, *ibid.*, **34**, 2286 (1951)]. [f] S. A. Julia, Pl. A. Plattner and H. Heusser, *ibid.*, **35**, 665 (1952).

Oppenauer oxidation of X yielded 21,21-difluoroprogesterone (XII).



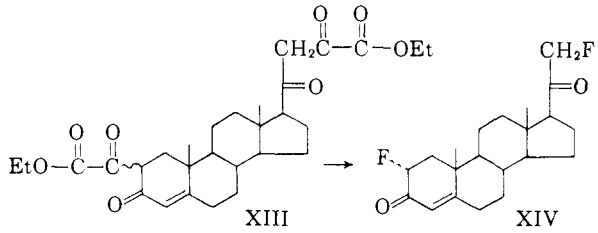
VIII



IX X

XI XII

It was also possible to effect concurrent reaction of perchloryl fluoride with two ethoxalyl groups situated at different sites on the steroid molecule. Thus, reaction of perchloryl fluoride with 2,21-bisethoxalylprogesterone (XIII)[25] followed by deethoxalylation afforded 2α,21-difluoroprogesterone (XIV) in 41% yield over-all from progesterone. The assigned structure is supported by the observed hypsochromic shift of the 3- and the 20-carbonyl bands[26] (*cf.* Table I). With respect to the effect of C-21 fluorine on the 20-carbonyl band, it is interesting to note that the 21,21-difluoro-20-keto derivatives show an enhanced shift.[27]



XIII XIV

Biological Data.—In contrast to the activity of the various fluorohydrocortisone derivatives mentioned at the beginning of this paper, the activity of 2α-fluorohydrocortisone (IV) is undistinguished, being approximately one-third that of hydrocortisone as measured by the liver-glycogen, thymus-involution and asbestos-granuloma inhibition tests in adrenalectomized rats.[28] This relatively low activity of IV stands in contrast to the high activity of 6α-fluorohydrocortisone[2] and is interesting when one considers the high activity of both the 2α-methyl-[29] and 6α-methylhydrocortisone[30] derivatives.

The other compounds reported in this paper are in the process of biological evaluation.

Acknowledgment.—We would like to thank Dr. G. R. Allen, Jr., and Mr. W. S. Allen for advice and helpful discussions. We are grateful to Mr. W. Fulmor and staff for spectrophotometric and polarimetric data, to Mr. L. Brancone and staff for microanalyses, to Mr. C. Pidacks and staff for chromatographic separations and to Dr. H. G. Arlt, Jr., and staff of the Chemical Preparations Laboratory for the large scale preparation of certain intermediates.

Experimental

General.[15]—Melting points were taken on a Kofler micro hot-stage and are corrected. Ultraviolet spectra were determined in methanol unless stated otherwise, using a Cary

(25) J. A. Hogg and co-workers, U. S. Patent 2,862,010; THIS JOURNAL, **77**, 4438 (1955).

(26) Similar Δμ values have been reported by R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *ibid.*, **74**, 2828 (1952).

(27) A similar effect has been observed on comparison of 21-bromo with 21,21-dibromo-20-keto derivatives; G. R. Allen, Jr., and M. J. Weiss, unpublished results.

(28) We wish to thank L. Bortle, E. Heyder, A. Montforte, E. Ross and I. Ringler of the Experimental Therapeutics Research Section of these laboratories for these results.

(29) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955).

(30) G. B. Spero, *et al.*, *ibid.*, **78**, 6213 (1956).

recording spectrophotometer and infrared spectra (KBr disks) on a Perkin–Elmer spectrophotometer (model 21). Polarimetric data were obtained in chloroform solution unless stated otherwise. Solutions were dried over magnesium sulfate and evaporations were carried out *in vacuo*. An ethanolic solution of ferric chloride was used for the enol test.

Hydrocortisone 20-Ethylene Ketal (20-Ethylenedioxy-11β,17α,21-trihydroxy-4-pregnen-3-one, I).—A solution of 5.38 g. (12 mmoles) of hydrocortisone acetate 20-ethylene ketal (21-acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-4-pregnen-3-one)[10] in 400 cc. of dry methanol was stirred under nitrogen with 12 cc. of a 1 *N* methanolic sodium methoxide solution for 30 minutes at room temperature. Acetic acid (0.72 cc.) was added and the solvent was removed by evaporation. The residue was triturated with several portions of hot acetone and the mixture was filtered. The combined acetone extracts and filtrate were evaporated to a small volume. The solid which crystallized was collected, washed with a small amount of acetone and dried *in vacuo;* 4.59 g. (94%), m.p. 208–210°. The analytical sample was recrystallized several times from acetone; m.p. 212–215°, $[\alpha]^{29}D$ +103° (*c* 1.44), λ_{max} 241 mμ (ε 17,100).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.79; H, 8.43.

2-Methoxalylhydrocortisone 20-Ethylene Ketal (20-Ethylenedioxy-11β,17α,21-trihydroxy-2-methoxalyl-4-pregnen-3-one, II).[14]—Sodium methoxide was prepared from 0.46 g. of sodium in 120 cc. of benzene and 8 cc. of methanol. The stirred mixture was distilled until the distillation temperature reached 80°. The suspension was allowed to come to room temperature, and 4 g. of anhydrous dimethyl oxalate and 2 g. (4.92 mmoles) of hydrocortisone 20-ethylene ketal (I) was added. The mixture was stirred for 16 hours. Chloroform (320 cc.) was then added to the dark brown suspension and the mixture was washed three times with 20-cc. portions of cold 30% aqueous sodium dihydrogen phosphate solution and with water. The organic phase was dried and evaporated. The residue was treated with a small amount of hot ethyl acetate and the orange solid which crystallized on cooling was collected, washed with a little ethyl acetate and dried to afford 0.36 g. (15%) of the higher melting methoxalyl derivative (positive enol test), m.p. 253–255°. This product (obtained in another experiment) was recrystallized twice from ethyl acetate–chloroform; m.p. 259–260°, $[\alpha]^{25}D$ +93° (*c* 0.61 in pyridine); λ_{max} 244 mμ, 348 mμ (ε 9,900 and 5,170 in methyl Cellosolve–methanol) 250 and 353 mμ (ε 12,800 and 9,350 in methyl Cellosolve–methanol brought to *p*H 14 with aqueous sodium methoxide).

Anal. Calcd. for $C_{26}H_{36}O_9 \cdot 1/2H_2O$: C, 62.27; H, 7.24. Found: C, 61.97; H, 6.92.

The ethyl acetate filtrate from which the above-described higher melting solid had been separated was evaporated under reduced pressure and the residue was dissolved in 40 cc. of chloroform. The solution was extracted several times with ice-cold portions of 1% aqueous potassium hydroxide. Each portion of extract was added quickly to a mixture of 30% aqueous sodium dihydrogen phosphate solution and methylene chloride. The methylene chloride layer was separated quickly and was washed with water. The combined methylene chloride solutions, so obtained, were dried, filtered and evaporated. The residue was triturated with ether containing a little ethyl acetate and the solid was collected, washed with ether and dried; 0.52 g. (22%), m.p. 178–180° (positive enol test). Compound II so obtained in a pilot experiment was recrystallized from ether–methylene chloride; m.p. 197–198°, $[\alpha]^{25}D$ +47° (*c* 0.63 in pyridine) and +64.5° (*c* 1.24 in chloroform); λ_{max} 244 mμ, 325 mμ (ε 11,580 and 5,420 in methanol); 252 mμ, 353 mμ (ε 13,540 and 11,580 in methanol brought to *p*H 14 with aqueous sodium hydroxide).

Anal. Calcd. for $C_{26}H_{36}O_9 \cdot 1/4H_2O$: C, 62.83; H, 7.40. Found: C, 62.88; H, 7.32.

2α-Bromohydrocortisone 20-Ethylene Ketal (2α-Bromo-20-ethylenedioxy-11β,17α,21-trihydroxy-4-pregnen-3-one).—The lower melting methoxalyl derivative II (0.2 g., 0.4 mmole) was added to a solution of 0.08 g. of potassium acetate in 5 cc. of methanol. To the stirred, cold solution was added dropwise a solution of bromine in carbon tetrachloride (0.61 g. of bromine/cc.) until the solution, which was originally dark yellow, became colorless and gave a negative enol test. This required 1.06 cc. of bromine solution (*i.e.*, 0.41 mmole of bromine). The solution was mixed with 0.41 cc. of 1 *N* methanolic sodium methoxide. The mixture was kept under reflux for 10 minutes and was then evaporated. The residue was partitioned between water and ethyl acetate–ether (1:1), and the organic phase was washed with a little water, dried and evaporated. The residue was crystallized from methylene chloride–ether; 0.141 mg. (71%), m.p. 153–159°. For analysis the compound was recrystallized from the same solvent mixture; m.p. 155–157°. The infrared spectrum showed a carbonyl band at 5.94 μ. In the ultraviolet the compounds showed λ_{max} 244 mμ (ε 13,100).

Anal. Calcd. for $C_{23}H_{33}O_6Br$: C, 56.90; H, 6.85; Br, 16.48. Found: C, 56.62; H, 6.99; Br, 16.08.

Prednisolone (11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione).—A solution of 0.5 g. (1.03 mmoles) of the bromohydrocortisone 20-ethylene ketal, obtained as described above from the lower melting ethoxalyl derivative II, in 10 cc. of freshly distilled collidine was allowed to reflux for 1 hour. The dark solution was filtered and the filtrate was diluted with 30 cc. of methylene chloride. The chilled mixture was treated with 5% aqueous sulfuric acid and the organic phase was separated, washed with water, dried and evaporated. The residual gum (0.36 g.) was dissolved in 30 cc. of methanol and there was added 1 cc. of 8% aqueous sulfuric acid. The mixture was allowed to reflux for 1 hour and then was cooled and neutralized by stirring with Duolite A-4 anion exchange resin (OH form).[31] The mixture was filtered and the resin was washed thoroughly with methanol. The combined filtrate and washings were evaporated and the residue was crystallized from acetone with activated charcoal; 140 mg. (40%), m.p. 235–240° undepressed by addition of prednisolone. Identity was confirmed by comparison of infrared spectra.

2α-Fluorohydrocortisone 20-Ethylene Ketal (2α-Fluoro-20-ethylenedioxy-11β,17α,21-trihydroxy-4-pregnen-3-one, III).—To a cooled solution (−10°) of 0.535 g. (1.08 mmoles) of 2-methoxalylhydrocortisone 20-ethylene ketal (II) in 25 cc. of absolute methanol was added 1.08 cc. of a 1 *N* methanolic sodium methoxide solution. Into the stirred mixture was bubbled a vigorous stream of perchloryl fluoride gas[15] until the mixture was netural and no longer gave a positive enol test (2–4 minutes). The solution was allowed to come to room temperature and was evaporated. The residue was partitioned between water and chloroform, and the aqueous phase was separated and washed with a small amount of chloroform. The combined chloroform layers were washed with a little water, dried and evaporated. The residue was redissolved in 10 cc. of methanol containing 0.19 g. of potassium acetate and the solution was allowed to reflux for 1 hour. It was then evaporated to dryness and the residue was partitioned between water and chloroform. The chloroform layer was dried and evaporated. The residue was crystallized from ether to afford 0.2 g. (43%) of a white crystalline solid with m.p. 215–219°. A sample recrystallized from ethyl acetate showed m.p. 224–226°, $[\alpha]^{25}D$ +132° (*c* 0.63); λ_{max} 242 mμ (ε 14,000).

Anal. Calcd. for $C_{23}H_{33}FO_6$: C, 65.07; H, 7.84; F, 4.48. Found: C, 64.87; H, 8.45; F, 4.43.

2α-Fluorohydrocortisone (2α-Fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione, IV).—To a solution of 0.622 g. (1.46 mmoles) of III in 50 cc. of methanol was added 2 cc. of an 8% aqueous sulfuric acid solution and the mixture was allowed to reflux for 1 hour. Solvent was removed under reduced pressure with occasional addition of water so as to keep the volume at approximately 40–50 cc. The cooled mixture was extracted thoroughly with chloroform and the combined extracts were washed with water, dried and evaporated. The residue was crystallized from methylene chloride–ether to afford 0.407 g. (73%), m.p. 220–226° (sintering above 215°). Recrystallization from the same solvent mixture gave material with m.p. 216–220°, $[\alpha]^{25}D$ +190° (*c* 0.76 in methanol), λ_{max} 241 mμ (ε 14,800).

Anal. Calcd. for $C_{21}H_{29}FO_5$: C, 66.30; H, 7.68; F, 5.00. Found: C, 66.02; H, 7.82; F, 5.00.

Pregnenolone 20-Ethylene Ketal (20-Ethylenedioxy-3β-hydroxy-5-pregnene).[11]—Pregnenolone was ketalized by distillation with ethylene glycol according to the method of

(31) Duolite A-4 is the trademark of the Chemical Process Co., Redwood City, Calif., for an anion exchange resin.

Allen, Bernstein and Littell.[32] Ethylene glycol (1000 cc.) was heated at 10–15 mm. pressure in a three-necked flask containing an efficient stirrer until 25 cc. had distilled out. Pregnenolone (50 g., 0.158 mole) was added and distillation *in vacuo* was continued until another 100 cc. of distillate had been collected. There was then added 2.5 g. of *p*-toluenesulfonic acid and heating under reduced pressure was continued with vigorous stirring until 500 cc. of distillate had been collected. During this period, the starting material dissolved and the product precipitated. The reaction mixture was cooled and the catalyst was neutralized with solid sodium bicarbonate. The solid was removed by filtration, washed thoroughly with water and dried *in vacuo* to afford 55 g. (97%), m.p. 140–145°. This product was sufficiently pure for conversion to progesterone 20-ethylene ketal.[11] A small amount was recrystallized successively from ethanol, methylene chloride–ether and, finally, ethanol; m.p. 154–162° (lit.[11] m.p. 163–166°). Identity was established by comparison of infrared curves with an authentic sample.[33]

2α-Fluoroprogesterone (2α-Fluoro-4-pregnene-3,20-dione, V).—Sodium methoxide in benzene was prepared by dissolving 0.114 g. of sodium in 45 cc. of benzene and 3.7 cc. of methanol. Solvent was removed by distillation until the distillation temperature reached 80°. To the cooled solution was added 1.5 cc. of redistilled diethyl oxalate and 1.63 g. (4.55 mmoles) of progesterone 20-ethylene ketal[11] in 20 cc. of benzene. The reaction mixture was stirred at room temperature with exclusion of moisture for 21 hours. Ether (200 cc.) was then added to the deeply colored suspension and the mixture was extracted with several portions of ice-cold 1% aqueous potassium hydroxide solution. The extracts were individually washed with ether and were then poured into enough 30% sodium dihydrogen phosphate solution to give a solution having *p*H 4–5. This mixture was in turn extracted quickly with several portions of chloroform until the extracts gave a negative enol test. The combined chloroform extracts were washed with water, dried and evaporated to leave 1.92 g. of yellow amorphous solid. This was redissolved in 50 cc. of methanol and to the cooled (−20°) solution was added 8.4 cc. of 1 *N* methanolic sodium methoxide solution. The stirred, cooled mixture was saturated quickly with perchloryl fluoride gas (3 minutes) and was evaporated. The residue was partitioned between chloroform and water. The chloroform phase was washed with a little water, dried and evaporated. The residue was dissolved in 50 cc. of methanol and to the solution was added 2 g. of anhydrous potassium acetate. The mixture was allowed to reflux for 75 minutes and was then evaporated. The residue was once more partitioned between chloroform and water, and the organic phase was washed with water, dried, and evaporated to afford a residue which crystallized when triturated with methanol; 1.3 g., m.p. 168–176°, λ_{max} 5.91 μ (carbonyl region). Without further purification, this material (presumably 2α-fluoroprogesterone 20-ethylene ketal) was redissolved in 50 cc. of methanol containing 2 cc. of 8% aqueous sulfuric acid and the solution was allowed to reflux for 80 minutes. It was cooled to room temperature and was neutralized by stirring with Duolite A-4 anion exchange resin (OH form). The mixture was filtered and the resin was washed well with methanol. The filtrate and washings were evaporated and the residue was crystallized by trituration with methanol to afford 0.66 g. (44% over-all from progesterone ketal), m.p. 188–192°. Several recrystallizations from methylene chloride–ether gave a sample with m.p. 198–200°, $[\alpha]^{25}D$ + 206° (*c* 1.29), λ_{max} 241 mμ (ε 15,600).

Anal. Calcd. for $C_{21}H_{29}FO_2$: C, 75.86; H, 8.79; F, 5.71. Found: C, 75.56; H, 8.98; F, 5.66.

2α-Fluorodeoxycorticosterone (2α-Fluoro-21-hydroxy-4-pregnen-3,20-dione, VI).—To a suspension of sodium ethoxide (prepared from 0.1 g. of sodium) in 30 cc. of anhydrous benzene was added 0.833 g. (2 mmoles) of deoxycorticosterone acetate 20-ethylene ketal[12] and 2 cc. of diethyl oxalate. The mixture was stirred at room temperature for 16 hours and was then diluted with ether. The mixture was extracted with water and three times with 20-cc. portions of cold 1% aqueous potassium hydroxide solution. Each portion of extract was washed with a little ether and was added to a mixture of 30% sodium dihydrogen phosphate solution and chloroform. The layers were separated and the aqueous phase was extracted with additional portions of chloroform until these extracts no longer gave a positive enol test. The combined chloroform extracts were washed with water, dried and freed from solvents *in vacuo* to leave 0.89 g. of an orange gum. This was dissolved in 20 cc. of methanol, and to the cooled solution (−20°) was added 5 cc. of 1 *N* sodium methoxide solution. The mixture was saturated quickly with a vigorous stream of perchloryl fluoride and was then evaporated. The residue was dissolved in methylene chloride and the solution was washed with 2% aqueous sodium hydroxide and with water. The organic phase was dried over magnesium sulfate, evaporated and the residue was dissolved in methanol (20 cc.) containing 0.5 g. of potassium acetate. The mixture was kept under reflux for 70 minutes and was then evaporated. The residue was partitioned between water and methylene chloride and the organic phase was dried and evaporated. The residue crystallized when triturated with ether. It was collected (0.48 g.) and dissolved in 20 cc. of methanol containing 1 cc. of 8% aqueous sulfuric acid. The mixture was refluxed for 1 hour and was then neutralized with Duolite A-4 anion exchange resin as described above. Evaporation of the filtrate afforded a residue which crystallized from ether; 0.177 g. (25% yield over-all from deoxycorticosterone acetate 20-ethylene ketal), m.p. 128–132°. A sample of material prepared in a similar manner and recrystallized from ether had m.p. 138–141°, $[\alpha]^{25}D$ +234° (*c* 1.37), λ_{max} 242 mμ (ε 15,300).

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.37; H, 8.39; F, 5.45. Found: C, 72.62; H, 8.60; F, 5.53.

2α-Fluorotestosterone (2α-Fluoro-17β-hydroxy-4-androsten-3-one, VII).—To a suspension of sodium methoxide (prepared from 0.55 g. of sodium) in 60 cc. of benzene was added 3.45 g. (12 mmoles) of testosterone and 6.0 g. of anhydrous dimethyl oxalate. The mixture was stirred for 18 hours at room temperature with exclusion of moisture and was then worked up as described under the preparation of VI. The crude 2-methoxalyltestosterone (1.8 g.) was obtained as a yellow glass. It was dissolved in 50 cc. of methanol containing 4.8 cc. of a 1 *N* methanolic sodium methoxide solution and the cooled solution (−20°) was treated with a vigorous stream of perchloryl fluoride for a few minutes. Since the reaction mixture was neutral at this time but still gave a positive enol test, it was evaporated partially to remove excess perchloryl fluoride and 1 cc. of the sodium methoxide solution was added.[15] The mixture was cooled to −20° and was once more saturated with perchloryl fluoride until it gave a negative enol test. The mixture was evaporated and the residue was partitioned between chloroform and water. The chloroform phase was washed with a little water and was dried, filtered and evaporated. The residue was treated with 1 g. of potassium acetate in 40 cc. of refluxing methanol for 1 hour and the reaction mixture was worked up as described above (preparation of VI). Crystallization of the crude product from methylene chloride–ether afforded 0.72 g. (20% yield over-all from testosterone), m.p. 149–151°. A sample recrystallized from the same solvent mixture showed m.p. 150–151°, $[\alpha]^{25}D$ + 131° (*c* 0.46), λ_{max} 240 mμ (ε 15,112).

Anal. Calcd. for $C_{19}H_{27}FO_2 \cdot 1/2H_2O$: C, 72.33; H, 8.94; F, 6.02. Found: C, 72.59; H, 9.01; F, 6.08.

21-Fluoropregnenolone (21-Fluoro-3β-hydroxy-5-pregnen-20-one, IX).[5]—The sodium salt of 21-ethoxalylpregnenolone[24] (1.8 g., 41.1 mmoles) was mixed with 50 cc. of methanol containing 4.1 cc. of a 1 *N* methanolic sodium methoxide solution and the mixture was cooled to −20°. Perchloryl fluoride was added until the solution was neutral (3–5 minutes) and the mixture was evaporated to a volume of 30 cc. There was added 2 g. of potassium acetate, and the mixture was allowed to reflux for 85 minutes. Solvent was removed by evaporation and the residue was partitioned between chloroform and water. The organic phase was washed with a little water, dried and evaporated. The residue crystallized from ether, 0.92 g. (67%), m.p. 180–183°. Recrystallization from methylene chloride–ether gave a sample with m.p. 184–185°, $[\alpha]^{26}D$ +36.9° (*c* 1.03) (lit.[5] m.p. 178.5–179.5°, $[\alpha]^{25}D$ +25°).

Anal. Calcd. for $C_{21}H_{31}FO_2$: C, 75.40; H, 9.35; F, 5.68. Found: C, 75.04; H, 9.50; F, 6.08.

(32) W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954).

(33) We would like to thank Mr. S. M. Stolar of these laboratories for this information.

21-Fluoroprogesterone (21-Fluoro-4-pregnene-3,20-dione, XI).[5]—A solution of 0.415 g. (1.24 mmoles) of 21-fluoropregnenolone (IX)[5] in 25 cc. of toluene and 3.8 cc. of cyclohexanone was distilled until 5 cc. of distillate had been collected. There was then added 2 cc. of toluene containing 0.5 g. of aluminum isopropoxide and the mixture was distilled very slowly under partial reflux until another 5 cc. of distillate had been collected (75 minutes). The solution was mixed with 50 cc. of water and was evaporated. To the residue was added ether and 35 cc. of 5% aqueous hydrochloric acid. The ether layer was separated and the aqueous phase was extracted thoroughly with ether. The combined organic extracts were washed with water, dried and evaporated. The residue was crystallized from pentane to afford 0.23 g. (56%), m.p. 136–140°. Two recrystallizations from ether gave a sample with m.p. 143–145°, $[\alpha]^{26}D$ +206° (*c* 1.00) [lit.[5] m.p. 141.5–142.2°; $[\alpha]^{25}D$ +208°, λ_{max} 240 mμ (ε 17,050).

Anal. Calcd. for $C_{21}H_{29}FO_2$: C, 75.84; H, 8.79; F, 5.72. Found: C, 76.14; H, 8.90; F, 5.79.

21,21-Difluoropregnenolone (21,21-Difluoro-3β-hydroxy-5-pregnene-20-one, X).—Perchloryl fluoride gas was bubbled rapidly into a cooled (−5°), stirred suspension (5.4 g., 12.3 mmoles) of the sodium salt of 21-ethoxalylpregnenolone[24] in 180 cc. of methanol and 24.6 cc. of 1 *N* methanolic sodium methoxide. When the solution was neutral (4 minutes), part of the solvent was removed *in vacuo* and another 24 cc. portion of the methoxide[15] solution was added. The mixture was again cooled to −5° and perchloryl fluoride was bubbled in for a few minutes. Partial evaporation and treatment with additional methoxide and perchloryl fluoride were repeated once more and the mixture was then evaporated. The residue was partitioned between chloroform and water and the contents of the (dried) chloroform phase were dissolved in 125 cc. of methanol containing 5 g. of potassium acetate. The mixture was kept under reflux for 90 minutes and was evaporated. The residue was again dissolved in chloroform and water and the organic phase was dried and evaporated. This left 4.09 g. of solid residue which was purified by partition chromatography on Celite[34] from the system heptane–methanol. Celite (500 g.) was mixed with 250 cc. of the lower phase of the solvent system and the mixture was packed in small increments into a glass column. The reaction product was dissolved in 25 cc. of the lower phase plus 25 cc. of the upper phase, and the solution was mixed with 50 g. of Celite. This mixture was also packed on top of the column (5.5 × 68 cm.). Elution was carried out with the upper phase and solids were detected by evaporation of equal effluent fractions. A plot of weights *vs.* fraction number showed that two major peaks had been eluted. Fractions belonging to the same peak were pooled, evaporated, and the residues crystallized from acetone–hexane. In this manner, there was obtained from the first peak 2.43 g. (56% yield) of X with m.p. 120–130°, and from the second peak 0.59g. (14%) of solid with m.p. 171–178°. The latter material was identified, after recrystallization, as 21-fluoropregnenolone[5] (IX) by mixed m.p. and comparison of infrared spectra. Recrystallization from acetone–hexane of the lower melting substance X obtained in a similar experiment gave a sample with m.p. 135–136°, $[\alpha]^{25}D$ + 50.2° (*c* 2.12).

Anal. Calcd. for $C_{21}H_{30}F_2O_2$: C, 71.55; H, 8.58; F, 10.78. Found: C, 71.61; H, 8.60; F, 11.08.

21,21-Difluoroprogesterone (21,21-Difluoro-4-pregnene-3,20-dione, XII).—A solution of 0.415 g. of the difluoropregnenolone X in 25 cc. of toluene and 3.8 cc. of cyclohexanone was oxidized with 0.5 g. of aluminum isopropoxide as described under the preparation of XI. The crude reaction product was crystallized from pentane to afford 0.273 g. (66%) with m.p. 137–140°. Recrystallization from acetone–hexane gave material with m.p. 140–141°, $[\alpha]^{25}D$ +195° (*c* 1.16), λ_{max} 241 mμ (ε 15,800).

Anal. Calcd. for $C_{21}H_{28}F_2O_2$: C, 71.98; H, 8.05; F, 10.85. Found: C, 72.39; H, 8.56; F, 10.90.

2α,21-Difluoroprogesterone(2α,21-Difluoro-4-pregnene-3,20-dione, XIV)—To a suspension of sodium methoxide (prepared from 0.505 g. (22 mmoles) of sodium) in 30 cc. of anhydrous benzene was added 5 g. of diethyl oxalate and 3.14 g. (10 mmoles) of progesterone. The mixture was stirred at room temperature for 24 hours. Ether (100 cc.) was added and the yellow precipitate was collected, washed well with ether and dried *in vacuo* (5.87 g.). The material was dissolved in 60 cc. of methanol containing 20 cc. of a 1 *N* methanolic sodium methoxide solution. The mixture was cooled to −20° and perchloryl fluoride gas was passed in rapidly until most of the color had disappeared. The solution, which still gave a positive enol test, was evaporated partially and 3 g. of potassium acetate was added. After refluxing for 90 minutes, the reaction mixture was evaporated to dryness and the residue was dissolved in a mixture of chloroform and water. The organic phase was washed with a little water, dried and evaporated to afford a residue which crystallized from ether; 1.63 g., m.p. 150–164°. Recrystallization from methylene chloride–ether gave 1.45 g. (41%) with m.p. 175–178°. For analysis, a sample was recrystallized once from methanol and once from ethanol (with activated charcoal); m.p. 179–180°, $[\alpha]^{25}D$ +218° (*c* 0.84), λ_{max} 242 mμ (ε 15,100).

Anal. Calcd. for $C_{21}H_{28}F_2O_2$: C, 71.98; H, 8.05; F, 10.85. Found: C, 71.63; H, 8.17; F, 10.63.

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(34) Celite is the Johns-Manville Corporation trademark for diatomaceous earth. The material used for partition chromatography was Celite 545 which had been washed with 6 *N* hydrochloric acid, with distilled water until neutral and finally with methanol. The material was dried at 50°.