and the methylene dichloride layer of the filtrate was dried over sodium sulfate. This solution was concentrated to a residual solid which was heated for 1 hr. with 50 ml. of acetic anhydride and 100 ml. of pyridine. Cooling of the reaction mixture and dilution with 3 l. of cold water gave a solid which was recrystallized once from ethyl acetate. The **17β-acetoxy-5α-androstan-3-one** so obtained (62 g., 49% yield) melted at 156–159°. Its identity was confirmed by infrared spectral comparison with an authentic sample.

Acknowledgment.—Appreciation is extended to Mrs. G. A. Snyder for technical assistance, to Mr. Horace Warrington for gas chromatographic analyses, to Dr. B. F. Tullar and Mr. E. J. Johnson for checking and refining the procedure for preparation of the 2-ketone under optimum conditions, and to Dr. C. F. Koelsch for helpful discussions.

9α-Fluoro-11-deoxy Steroids[1]

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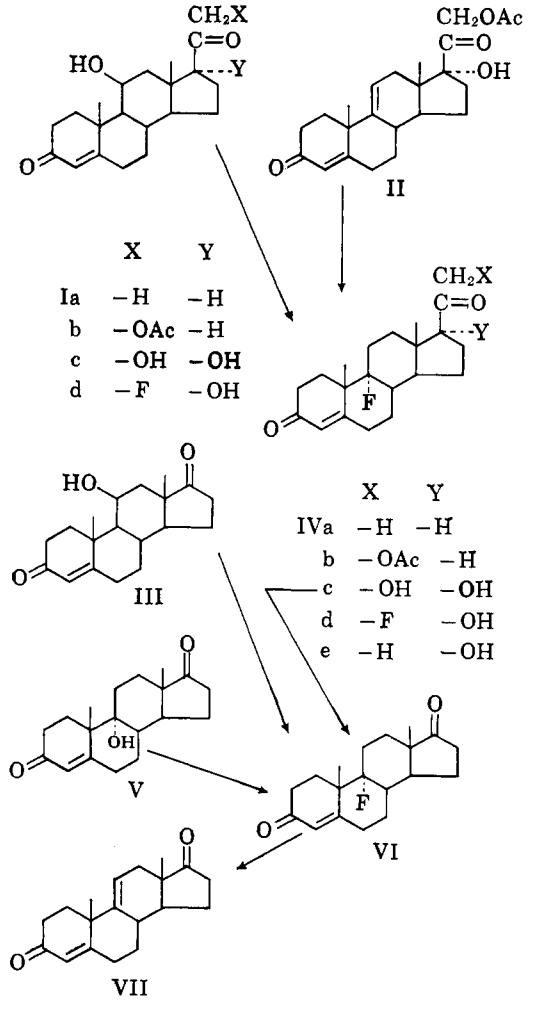
The treatment of a 9α- or 11β-hydroxy or a 9(11)-dehydro steroid with a 70% solution of hydrogen fluoride in pyridine resulted in the introduction of fluorine at 9α. Preliminary biological evaluation of representative compounds indicated activity similar to or greater than that of the 9α-hydrogen analog. 9α-Fluorodeoxycorticosterone acetate was twelve times as potent as deoxycorticosterone acetate as a salt retainer.

The great increase in the biological activity of the antiinflammatory corticoids resulting from the introduction of a 9α-fluoro group into these molecules has prompted the introduction of this group into many of the other steroid hormones. In all previous examples the 9α-fluoro group was accompanied by the introduction of an additional group (−OH,[2] halogen[3,4]) into ring C. In fact, it has been postulated[3,4] that the influence of the 9α-fluoro group on biological activity is mediated through its inductive effect on the adjacent oxygen function. Here, we report the synthesis of 9α-fluoro steroidal hormones devoid of other substituents in ring C. The increased biological activity of many of these compounds over that of the parent compounds clearly indicates that the influence of the 9α-fluoro group is not necessarily mediated through an adjacent oxygen function.

These new compounds resulted from a study of the reactions of a solution of pyridine in anhydrous hydrogen fluoride. When anhydrous hydrogen fluoride was bubbled into pyridine a clear straw-colored solution resulted which at least to outward appearances was stable at room temperature for months. The reagent began to fume strongly when the concentration of hydrogen fluoride was about 70% by weight, and it was this material which was used in the work to be described. Originally the interest in the hydrogen fluoride–pyridine solution resided in its possible use in the preparation of 9α-fluoro-11β-hydroxy steroids from 9β,11β-epoxides.[5] The results of these experiments were very discouraging. The reagent also was used in a study of the dehydration of 11β-hydroxy steroids and while the yields of 9(11)-dehydro steroids were poor, new fluorine-containing products were discovered.

When hydrocortisone acetate (Ic-acetate) was treated with hydrogen flouride-pyridine reagent, only the dehydration product II could be isolated by crystallization or chromatography. If, however, the mixture was treated with hypobromous acid followed by potassium acetate, thus converting the 9(11)-double bond to the 9β,11β-epoxide, it was possible by chromatography to separate from this mixture the least polar component, 9α-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate (IVc-acetate). This same fluoro compound was produced by the addition of hydrogen fluoride to 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate (II) but in even poorer yield. The protection



(1) For preliminary communications of this work, see C. G. Bergstrom and R. M. Dodson, *J. Am. Chem. Soc.*, **82**, 3479, 3480 (1960).

(2) J. Fried and A. Borman, "Vitamins and Hormones," Vol. XVI, Academic Press, Inc., New York, N. Y., 1958, p. 303.

(3) C. H. Robinson, L. Finckenor, E. P. Oliveto, and D. Gould, *J. Am. Chem. Soc.*, **81**, 2191 (1959).

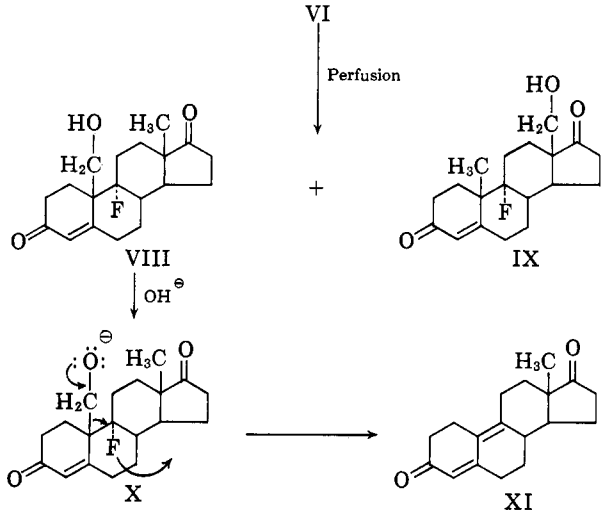
(4) (a) A. Bowers, *ibid.*, 4107 (1959); (b) C. G. Bergstrom and R. T. Nicholson, *J. Org. Chem.*, **25**, 1263 (1960).

(5) This problem was nicely solved by R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *J. Am. Chem. Soc.*, **78**, 4956 (1956).

of the 21-hydroxyl group by acetylation was unnecessary since free hydrocortisone (Ic) gave as good a yield of fluoro compound as the 21-acetate. The acetate group was removed from the fluoro compound by base-catalyzed hydrolysis without any noticeable elimination of hydrogen fluoride. Chromic acid oxidation of the 21-alcohol, IVc, resulted in the removal of the side chain and the production of 9α-fluoro-4-androstene-3,17-dione (VI) as evidenced by the loss of the hydroxyl bands in the infrared spectrum and the production of a band at 5.75 μ characteristic of a ketone group in a five-membered ring. The fluorine atom was not lost and so was not attached to the side chain. This same fluorinated androstenedione VI was produced by the action of hydrogen fluoride–pyridine reagent on 11β-hydroxyandrostenedione (III) and 9α-hydroxyandrostenedione (V).[6] 11α-Hydroxyprogesterone failed to give any fluorine-containing product. Attempts to eliminate the elements of hydrogen fluoride from VI with boiling pyridine or collidine were unsuccessful, the starting material being recovered in good yield. However, the use of hydrogen fluoride–pyridine reagent did lead to elimination, the product being 4,9(11)-androstadiene-3,17-dione (VII).

The reversible Markownikoff addition of hydrogen fluoride to the isolated 9(11)-double bond places the fluorine at C-9. The formation of the fluoro compound from the $\Delta^{9,11}$-steroid under equilibrating conditions should result in the retention of the stable *trans–anti–trans–anti–trans* steroid framework and so the configuration of the fluorine at C-9 should be α.[7] That the fluorine was indeed at C-9 was confirmed by the n.m.r. spectrum[8] of 9α-fluoroandrostenedione (VI) which showed no hydrogen on the carbon bearing the fluorine[9] (the region from 150 to 352 c.p.s. was free of resonance bands). The angular methyl resonance bands (56 and 80 c.p.s.) were within 2 c.p.s. of those expected from 9α-fluoro steroids. Additional evidence for the structural integrity of the ring system was supplied by the virtual identity of the optical rotatory dispersion curve of 9α-fluorotestosterone acetate (XIVa-acetate) with that of testosterone.

Adrenal perfusion[10] of 9α-fluoro-4-androstene-3,17-dione was carried out in an attempt to prepare the known 9α-fluoro-11β-hydroxy-4-androstene-3,17-dione. However, contrary to the usual course of adrenal hydroxylations the only products isolated were hydroxylated on the angular methyl groups. Thus 9α-fluoro-18-hydroxy-4-androstene-3,17-dione (IX) and 9α-fluoro-19-hydroxy-4-androstene-3,17-dione (VIII) were obtained. The structures of these compounds were inferred from the presence of the hydroxyl band in the infrared spectra and the disappearance of the appropriate methyl resonance bands in the n.m.r. spectra. In addition, treatment with aqueous sodium hydroxide resulted in the elimination of formaldehyde from both compounds (chromotropic acid test).[11] Finally, when the 19-hydroxy compound VIII was treated with 0.1 *N* ethanolic potassium hydroxide, the ultraviolet spectrum[12] immediately revealed a band at 302 mμ (ϵ 17,400) with a point of inflection at 238 mμ (ϵ 5850). After twenty-four hours these changed to 292 mμ (ϵ 4700), 246 (9250). Apparently base-catalyzed elimination of the 19-hydroxymethyl group occurred rapidly with concurrent elimination of the 9α-fluoro group to form 19-nor-4,10(9)-androstadiene-3,17-dione (XI) which slowly equilibrated to the δ, ϵ-unsaturated isomers.[13] The small bathochromic shift (2–3 mμ) associated with a 19-hydroxyl group[14] also was noticed in a comparison of the ultraviolet spectra of 9α-fluoro-19-hydroxy-4-androstene-3,17-dione (VIII) (λ_{max} 240 mμ) and 9α-fluoro-18-hydroxy-4-androstene-3,17-dione (IX) (λ_{max} 237 mμ).



It was assumed, at first, that the formation of the 9-fluoro steroid from the 11β-hydroxy steroid proceeded *via* an intermediate 9(11)-dehydro steroid. However, the much poorer yield of 9α-fluoro-17α,21-dihydroxyprogesterone 21-acetate (IVc-acetate) obtained from 9(11)-dehydro-17α,21-dihydroxyprogesterone 21-acetate (II) than from 11β,17α,21-trihydroxyprogesterone 21-acetate (Ic-acetate) under comparable conditions led us to investigate in greater detail the course of the reaction. Consequently, 11β-hydroxyandrostenedione (III) was treated with the hydrogen fluoride–pyridine reagent and a sample was withdrawn after 160 minutes and was analyzed by paper chromatography. This study showed that 9α-fluoroandrostenedione (VI) was formed more rapidly than 9(11)-dehydroandrostenedione (VII). A parallel experiment starting with 9(11)-dehydroandrostenedione showed that 9α-fluoroandrostenedione was produced too slowly from the 9(11)-dehydro steroid for it to be a necessary intermediate. This in-

(6) R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, **80**, 6148 (1958); **83**, 4631 (1961).

(7) Either ring B or C of 9β-fluoro-4-androstene-3,17-dione would, of necessity, possess a boat conformation and, therefore, would be far less stable than the normal steroid. For an analysis of the conformation of 9β-steroids, see A. Crawshaw, H. B. Henbest, E. R. H. Jones, and A. A. Wagland, *J. Chem. Soc.*, 3420 (1955).

(8) The n.m.r. spectra were run at 60 Mc.p.s. in deuterated chloroform using tetramethylsilane as an internal standard. We are indebted to Dr. LeRoy F. Johnson of Varian Associates, Palo Alto, Calif., for the determination and interpretation of this spectrum.

(9) The α-hydrogens of a primary alkyl fluoride are reported to absorb at 5.65 τ (261 c.p.s. from tetramethylsilane). L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 54. Also see ref. 17.

(10) R. W. Jeanloz, H. Levy, R. P. Jacobsen, O. Hechter, V. Schenker, and G. Pincus, *J. Biol. Chem.*, **203**, 453 (1953).

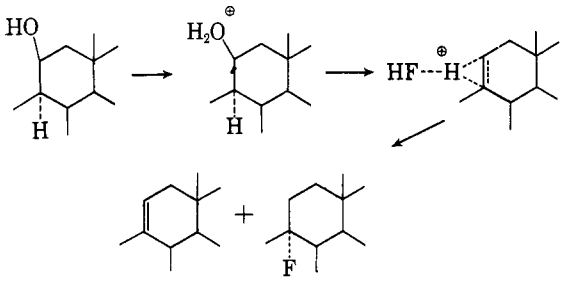
(11) K. H. Loke, G. F. Marrian, and E. J. D. Watson, *Biochem. J.*, **71**, 43(1959).

(12) A. S. Meyer, *Experientia*, **11**, 99 (1955).

(13) The $\Delta^{4,9(10)}$-3-one system was reported to absorb at 302–304 mμ (ϵ 18,000–21,000). See M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(14) F. W. Kahnt, R. Neher, and A. Wettstein, *Helv. Chim. Acta*, **38**, 1237 (1955).

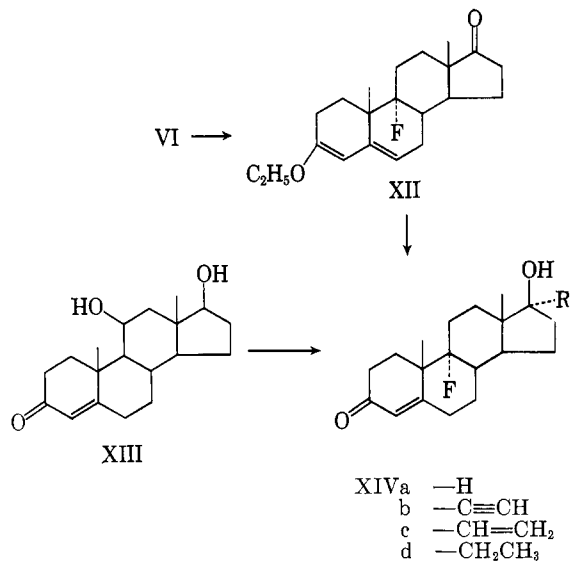
formation led us to the conclusion that much of the 9α-fluoro steroid was formed directly from the 11β-hydroxy compound. The reaction probably involves neighboring hydrogen participation as postulated by Cram and Tadanier[15] in studies on the rearrangement of the diastereomeric *p*-toluenesulfonate esters of 3-cyclohexyl-2-butanol. Protonation of the 11β-hydroxyl group followed by elimination of water should give a solvated bridged ion which can then form the 9α-fluoro compound and the 9(11)-dehydro compound. It is interesting to note that in the studies of Cram and Tadanier "to the extent that the rearrangement was stereospecific, solvent attacked tertiary carbon from the side originally occupied by the rearranged hydrogen atom." This would lead to a 9α-fluoro group in our reactions, a result in agreement with the evidence given previously.



It is possible that the formation of a 9α-fluoro-12β-hydroxy steroid by treatment of 11β,12β-epoxy-5α,22a-spirostan-3β-ol 3-acetate with hydrogen fluoride in chloroform as described by J. Fried and co-workers[16] also proceeded by a similar mechanism and not by addition of hydrogen fluoride to an intermediate $\Delta^{9(11)}$-12β-ol as originally postulated.

A variety of 11β-hydroxy steroids with variations in the side chain were converted to the 9α-fluoro analogs. 11β-Hydroxyprogesterone gave 9α-fluoroprogesterone[17] (IVa). 21-Fluoro-11β,17α-dihydroxyprogesterone gave 9α,21-difluoro-17α-hydroxyprogesterone (IVd). This compound, IVd, also was prepared from 9α-fluoro-17α,21-dihydroxyprogesterone by conversion of the 21-hydroxy group to the mesylate, then in turn to the iodide and the fluoride. Acetylation of IVd gave the 17-acetate. This latter route also led to the 21-deoxy steroid, IVe, by reduction of the 21-iodo intermediate. Corticosterone acetate (Ib) was converted to 9α-fluorodeoxycorticosterone acetate (IVb).

In order to obtain the 17α-substituted 9α-fluorotestosterones, 9α-fluoroandrostenedione (VI) was converted to its 3-enol ether XII which was ethynylated. Hydrolysis gave 9α-fluoroethynyltestosterone (XIVb) which was hydrogenated in stages, first to 9α-fluorovinyltestosterone (XIVc) and then to 9α-fluoroethyltestosterone (XIVd). Overhydrogenation gave rise to a 9α-fluorodihydrotestosterone derivative whose rotatory dispersion curve showed a negative Cotton effect. By analogy with the curve shown by 17α-hydroxy-5β-androstan-3-one,[18] the configuration of C-5 must be β and the compound must be 9α-fluoro-17β-hydroxy - 17α - ethyl - 5β - androstan - 3 - one. Additional testosterone derivatives were prepared by the conversion of 11β-hydroxytestosterone (XIII) and its acetate to 9α-fluorotestosterone (XIVa) and its acetate. The propionate also was prepared from 9α-fluorotestosterone.



Biological Evaluation.[19]—Preliminary screening assays indicate that the 9α-fluoro compounds are qualitatively similar to the hydrogen analogs with the fluoro compound generally being the more potent. 9α-Fluoro-17α,21-dihydroxyprogesterone 21-acetate (IVc-acetate) had 5–10% of the activity of cortisone acetate in the neoglycogenetic assay.[20] Progesterones were evaluated in the Clauberg assay[21] using subcutaneous progesterone as the standard. The results are summarized in Table I. The testosterone derivatives were compared to testosterone propionate in the androgenic and myotrophic[22] assays and the results are tabulated in Table II. 9α-Fluorodeoxycorticosterone

TABLE I

Compound	Progesterone substitution 9α	17α	21	Progestational activity Subcutaneous	Oral
Progesterone	H	H	H	1	
IVa	F	H	H	5	0.5
17-Acetoxyprogesterone	H	OAc	H	10	.5
IVe-Acetate[a]	F	OAc	H	5	
21-Fluoro-17-acetoxyprogesterone	H	OAc	F	10	2.5
IVd-Acetate	F	OAc	F	10	5

[a] This sample may have been impure. *Anal.* Calcd. for $C_{23}H_{31}FO_4$: C, 70.74; H, 8.00. Found: C, 70.16; H, 7.65.

TABLE II

Compound	4-Androsten-3-one substitution 9α	17	Activity Androgenic	Myotrophic
Testosterone propionate	H	-OCOEt	1	1
VI	F	=O	0.04	0.05
XIVa-Acetate	F	-OAc	.3–1.0	.5
XIVa-Propionate	F	-OCOEt	.5	.5

(15) D. J. Cram and J. Tadanier, *J. Am. Chem. Soc.*, **81**, 2737 (1959).

(16) J. Fried, J. E. Herz, E. F. Sabo, and M. H. Morrisson, *Chem. Ind.* (London), 1232 (1956).

(17) 9α-Fluoroprogesterone also has been prepared by D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(18) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co. Inc., New York, N.Y., 1960, p. 49.

(19) We are indebted to the staff members of the Division of Biological Research, G. D. Searle and Co., for this data.

(20) M. L. Pabst, R. Sheppard, and M. H. Kuizenga, *Endocrinology*, **41**, 55 (1947).

(21) M. K. McPhail, *J. Physiol.*, **83**, 145 (1934).

(22) F. J. Saunders and V. A. Drill, *Proc. Soc. Exptl. Biol. Med.*, **94**, 646 (1957).

(23) C. M. Kagawa and R. S. Jacobs, Jr., *ibid.*, **104**, 60 (1960).

acetate (IVb) showed outstanding activity as a salt retainer,[23] being twelve times as potent as deoxycorterosterone acetate.

Experimental[24]

Hydrogen Fluoride–Pyridine Reagent.—A weighed amount of pyridine in a polyethylene bottle was treated with anhydrous hydrogen fluoride until the composition of the solution was about 30% pyridine–70% hydrogen fluoride. The temperature was maintained at 50° or less by external cooling. The solution appears to be stable but since this may not be true, and the age of the reagent varied, both the original per cent by weight of hydrogen fluoride and the age in days are given in parenthesis in each experiment.

Fluoride Test.—This test is a modification of the method of Bennett, *et al.*[25] Ten drops of a saturated solution of chromium trioxide in concentrated sulfuric acid is placed in a 13 × 34 mm. tube. About 1 mg. of test compound is added and a 13 × 100 mm. test tube with a drop of water suspended from the bottom is placed tightly over the first tube. The sulfuric acid solution is heated until white fumes appear and then for 30 sec. After cooling the drop is transferred to a test tube. A second drop is used to rinse the upper tube. Five drops of water are added to the test tube followed by 1 drop of 6 *M* formic acid, 1 drop of 3 *M* sodium hydroxide, 2 drops of 0.12% sodium alizarine sulfonate in ethanol, and 2 drops of 0.0005 *M* thorium nitrate tetrahydrate. A yellow solution indicates the presence of fluoride while a pink color indicates its absence. The test worked on all of the compounds tried with the exception of a trifluoroacetate.

9α-Fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-Acetate (Ic-Acetate → IVc-Acetate).—To 100 ml. of a cold solution of hydrogen fluoride–pyridine (69%, 1 day) was added 10.25 g. of 11β,17α-21-trihydroxy-4-pregnene-3,20-dione 21-acetate. The reaction mixture was kept in an ice bath for 4 hr. during which time its color became red with a hint of green fluorescence. The reaction mixture was partitioned between 2.5 l. of ethyl acetate and 1 l. of water. The organic phase was separated and was washed with two 1-l. portions of water, 0.5 l. of saturated aqueous sodium bicarbonate solution, and two 0.5-l. portions of water. After being dried over anhydrous sodium sulfate the solution was distilled at reduced pressure and gave a crystalline mixture which contains the desired fluoro compound (IVc-acetate) and 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate.[26] Since this mixture cannot be separated satisfactorily by silica gel chromatography or by crystallization, the following scheme was used.

The mixture was dissolved in 250 ml. of purified dioxane[27] and 5.0 g. of N-bromoacetamide and 50 ml. of 1 *N* perchloric acid were added. After 21 min. 0.25 l. of 2% sodium sulfite solution was added and this mixture was poured into a separatory funnel containing 2 l. of ethyl acetate and 1 l. of water. The organic phase was separated and was washed with two 1-l. portions of water. The ethyl acetate solution was dried with anhydrous sodium sulfate and the solvent was removed by distillation at reduced pressure. A yellow mass of partially crystalline gum was obtained. This residue was refluxed for 1 hr. in 0.5 l. of ethanol containing 25 g. of potassium acetate. Much of the alcohol was distilled and the residue was partitioned between 2 l. of benzene and 1 l. of water. A significant amount of insoluble solid was separated with the aqueous layer. The benzene layer was washed with two 1-l. portions of water. All three aqueous washes were combined and the mixture was extracted with 1 l. of ethyl acetate. The insoluble material dissolved. The ethyl acetate solution was separated and was washed with two 1-l. portions of water. The combined benzene and ethyl acetate solutions were dried over anhydrous calcium sulfate[28]; then the solvent was removed by distillation at reduced pressure. The resulting gummy residue was chromatographed on 1 kg. of silica gel. Elution of the column with increasingly more polar mixtures of ethyl acetate in benzene gave no significant quantity of material until 20% ethyl acetate was reached. Here 2.1 g. of crude solid was obtained which was crystallized from acetone–hexane to yield 1.0 g. of 9α-fluoro-17α-21-dihydroxy-4-pregnene-3,20-dione 21-acetate,[29] m.p. 259–264°. The analytical sample was obtained by additional crystallizations from acetone and had the following properties, m.p. 264–267° dec.; λ_{max} 238 mμ (ε 18,200); λ_{max}^{KBr} 2.96, 5.73, 5.82, 6.09, 6.21 (shoulder), 8.05, 11.26, 11.47 μ; $[\alpha]D$ +123° (*c* 0.79); n.m.r., 44 (18-CH_3), 77.5 (19-CH_3), 130 (CH_3-C=O), 297 (—$COCH_2$—O—), 349 (4-H) c.p.s.

Anal. Calcd. for $C_{23}H_{31}FO_5$: C, 67.96; H, 7.69; F, 4.7. Found: C, 67.73; H, 7.59; F, 4.5, 4.3.[30]

Further development of the column with 25% ethyl acetate in benzene gave 2.5 g. of material which on repeated crystallization yielded 0.22 g. of 17α,21-dihydroxy-4-pregnene-3,11,20-trione 21-acetate, m.p. 248–251°. Identity with cortisone acetate was established by a comparison of infrared spectra. Elution of the column with 30% ethyl acetate in benzene gave after crystallization, 0.21 g., m.p. 219–222°, of 11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate, identified by infrared spectra and mixture melting point.

The Reaction of 11β,17α,21-Trihydroxy-4-pregnene-3,20-dione with Hydrogen Fluoride–Pyridine (Ic → IVc-Acetate).—A solution of 2.00 g. of the free alcohol (Ic) in 20 ml. of hydrogen fluoride–pyridine reagent (72%, 4 days) was kept at ice bath temperature for 4 hr. The red-brown reaction mixture was partitioned between 0.25 l. of ethyl acetate and 0.1 l. of water. The organic phase was washed with two 0.1-l. portions of water, two 0.1-l. portions of saturated aqueous sodium bicarbonate solution, and two 0.1-l. portions of water. After being dried with anhydrous sodium sulfate the solvent was distilled at reduced pressure. The residue was crystallized from acetone–hexane and twice from acetone to give 121 mg. of 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione, m.p. 245–250° dec.[31] The structure was established by mixture melting point and a comparison of infrared spectra.

The mother liquor residue was acetylated in 10 ml. of pyridine with 5 ml. of acetic anhydride overnight at room temperature and the acetylated material was treated with N-bromoacetamide and perchloric acid and then by potassium acetate as described above. The product so obtained was chromatographed on 200 g. of silica gel. Elution with 20% ethyl acetate in benzene gave 294 mg. of crystals which after two crystallizations from acetone gave 130 mg. of 9α-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate, m.p. 264–267° dec. Admixture with material prepared directly from the 21-acetate of Ic did not depress the melting point; the infrared spectra were identical.

9α-Fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-Acetate from 17α,21-Dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-Acetate (II → IVc-Acetate).—A solution of 2.00 g. of the diene II in 20 ml. of hydrogen fluoride–pyridine reagent (74%, 0 days) was kept at −2° for 4 hr. The reaction mixture was red with green fluorescence. It was worked up by essentially the method described for the preparation of IVc-acetate from Ic-acetate. The crude product was chromatographed on 200 g. of silica gel. Elution with 20% ethyl acetate in benzene gave two weight peaks which were poorly separated. The first peak gave 142 mg. of crystals which on repeated crystallization gave about 20 mg. of 9α-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate, m.p. 258–262° dec. Admixture with a sample prepared from the 11β-hydroxy compound, Ic-acetate, did not depress the melting point and the infrared spectra were identical. The second weight peak gave 484 mg. of crystals, m.p. 202–214°. Repeated crystal-

(24) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Rotations were determined in chloroform at 25 ± 2° at the indicated concentration (*c* g./100 ml.). Ultraviolet spectra were determined in methanol. Microanalyses, rotations, and spectral data were supplied by the Analytical Department, G. D. Searle and Co. N.m.r. spectra were run at 60 Mc. in deuterated chloroform with internal tetramethylsilane as the zero of reference.

(25) E. L. Bennett, C. W. Gould, Jr., E. H. Swift, and C. Niemann, *Anal. Chem.*, **19**, 1035 (1947).

(26) Repeated crystallization of similar material from another run gave 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate, m.p. 240–243°; λ_{max} 239 mμ (ε 15,800); $[\alpha]D$ +115° (*c* 0.96).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.36; H, 8.10.

This material was identical (infrared spectra and m.m.p.) with the diene prepared by the methanesulfonyl chloride-pyridine dimethylformamide dehydration of 11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate. It was first reported by J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957), who found m.p. 236–237°; $[\alpha]D$ +120° (*c* 1.0).

(27) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., Heath and Co., Boston, Mass., 1941, p. 368.

(28) W. A. Hammond Drierite Co., Xenia, Ohio.

(29) Very careful chromatography and numerous crystallizations of the fractions immediately preceding the 9-fluoro compound gave a compound, m.p. 186–192° dec., which gave a satisfactory analysis for $C_{21}H_{28}BrFO_3$.

(30) Huffman Microanalytical Laboratories, 3830 High Court, P. O. Box 125, Wheatridge, Colo.

(31) We are indebted to Mr. Ivar Laos of these laboratories for a sample of this material. Fried and Sabo, see ref. 26, report m.p. 247–250° dec.

lization failed to yield any pure product. A parallel run starting with 2.00 g. of 11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate gave 179 mg. of the fluoro compound, m.p. 258–265° dec.

9α-Fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione (IVc-Acetate → IVc).—A solution of 174 mg. of IVc-acetate in 35 ml. of methanol was treated with 4.20 ml. of 0.101 *N* sodium hydroxide for 30 min. at room temperature under nitrogen. Two drops of acetic acid were added and the reaction mixture was concentrated at reduced pressure until crystals began to form. Additional water was added and 122 mg. of crystals, m.p. 219–225° dec., were isolated. Two crystallizations from acetone gave 55 mg. of 9α-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione as plates, m.p. 235–238°; λ_{max} 238 mμ (ε 17,100); $[\alpha]_D$ +105° (*c* 0.71); λ_{max}^{KBr} 2.94, 5.82, 5.97, 6.15, 11.36 μ.

Anal. Calcd. for $C_{21}H_{29}FO_4$: C, 69.22; H, 8.02. Found: C, 69.37; H, 7.78.

9α-Fluoro-17α-hydroxy-4-pregnene-3,20-dione (IVc → IVe).—Crude 9α-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione was prepared from 30 g. of 11β,17α,21-trihydroxy-4-pregnene-3,20-dione and 300 ml. of hydrogen fluoride–pyridine reagent (73%, 1 day) as described before. The 27 g. of crude product in 190 ml. of pyridine was treated with 10.5 ml. of methanesulfonyl chloride at 0°. After 2 hr. 1 l. of water was slowly added. A gummy solid formed which was collected on a filter and was triturated with toluene to give a crystalline product. Evaporation of the toluene solution gave a residue which was combined with the solid. This crude 21-mesylate was refluxed in 0.70 l. of acetone with 27 g. of sodium iodide for 1 hr. The reaction mixture was cooled, filtered, and the filtrate was concentrated nearly to dryness. The crude 21-iodide–sodium iodide mixture was dissolved in 540 ml. of acetic acid. The solution was divided in two equal parts. After 1.5 hr. one part was poured into 2.5 l. of ethyl acetate and 1 l. of dilute sodium thiosulfate solution. The organic phase was washed with two 1-l. portions of water, four 0.40-l. portions of saturated aqueous sodium bicarbonate solution, and two 1-l. portions of water. After being dried over anhydrous sodium sulfate the solvent was distilled at reduced pressure, leaving 11.1 g. of residue. This residue was dissolved in 550 ml. of purified dioxane followed by 6.58 g. of N-bromoacetamide and 55 ml. of 1 *N* perchloric acid. After 10 min. at room temperature 176 ml. of 2% aqueous sodium sulfite solution was added. The addition of water and chilling produced 7.97 g. of a granular solid. This was heated at reflux under nitrogen for 2 hr. in 172 ml. of ethanol containing 7.96 g. of potassium acetate. The addition of water and chilling caused the separation of 4.74 g. of brown-yellow solid. Chromatography on 450 g. of silica gel gave a series of fractions on elution with 15% ethyl acetate in benzene, from which 1.96 g. of crystals were obtained. Three crystallizations from acetone gave 1.42 g. of pure 9α-fluoro-17α-hydroxy-4-pregnene-3,20-dione, m.p. 278° dec.; λ_{max} 238 mμ (ε 17,800); $[\alpha]_D$ +73.2° (*c* 1.02); λ_{max}^{KBr} 2.86, 5.88, 5.98, 6.18, 11.35 μ. The fluoride test was positive.

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39. Found: C, 72.54; H, 8.32.

9α,21-Difluoro-17α-hydroxy-4-pregnene-3,20-dione 17-Acetate. (A) Id → IVd-Acetate.—A solution of 3.00 g. of 21-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione[32] in 80 ml. of hydrogen fluoride–pyridine reagent (76%, 253 days) was kept at −2° for 17 hr. This brownish solution was poured into 0.5 l. of cold water and the resulting solid was collected on a filter and, after drying, weighed 2.06 g., m.p. 210–213°. Four crystallizations from acetone gave 0.16 g. of 9α,21-difluoro-17α-hydroxy-4-pregnene-3,20-dione, m.p. 254–256° dec.; λ_{max} 238 mμ (ε 17,400); λ_{max}^{KBr} 2.91, 5.78, 6.01, 6.19, 11.33 μ.

Anal. Calcd. for $C_{21}H_{28}F_2O_3$: C, 68.83; H, 7.70. Found: C, 69.65; H, 8.01.

Further efforts to obtain a sample which would analyze better were not successful.

A suspension of 0.155 g. of difluoro compound, IVd, in a mixture of 8 ml. of acetic acid and 0.8 ml. of acetic anhydride containing 0.062 g. of *p*-toluenesulfonic acid monohydrate was stirred overnight in an itrogen atmosphere. As the steroid failed to dissolve, equal additional amounts of solvents and catalyst were added and the reaction was continued for an additional day. The resulting solution was poured into water and this suspension was extracted with ethyl acetate. The ethyl acetate solution was washed with water and saturated aqueous sodium bicarbonate solution. After being dried over anhydrous sodium sulfate, the solvent was distilled at reduced pressure. The resulting gum was dissolved in 10 ml. of methanol containing 0.1 ml. of concentrated hydrochloric acid and this solution was kept under nitrogen at room temperature for 3 hr. The addition of water and cooling induced the separation of 0.127 g. of crystals, m.p. 139–162°. The crystals were chromatographed on 15 g. of silica gel. Elution with a 7% solution of ethyl acetate in benzene gave 0.025 g. of solid which on crystallization from acetone–hexane gave 0.018 g. of 9α,21-difluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate, m.p. 232–233.5°; λ_{max} 236 mμ (ε 17,200); λ_{max}^{KBr} 5.73, 5.94, 6.14, 8.04, 11.29 μ.

Anal. Calcd. for $C_{23}H_{30}F_2O_4$: C, 67.63; H, 7.40. Found: C, 67.49; H, 7.47.

(B) IVc → IVd-Acetate.—A solution of 0.247 g. of IVc in 2.5 ml. of benzenesulfonyl chloride containing 0.25 ml. of collidine was kept overnight at room temperature. The reaction mixture was chromatographed on 20 g. of silica gel. Elution with 5% ethyl acetate in benzene removed the benzenesulfonyl chloride and elution with 50% ethyl acetate in benzene removed the steroid as a mixture of 21-chloride and 21-benzenesulfonate. This mixture was refluxed for 1 hr. in 50 ml. of acetone containing 1 g. of sodium iodide. The acetone was removed by distillation at reduced pressure and the residue was partitioned between 0.25 l. of benzene and 0.1 l. of water. The benzene layer was washed with dilute sodium thiosulfate and with water. After being dried with anhydrous sodium sulfate the solvent was distilled at reduced pressure leaving crude 9α-fluoro-17α-hydroxy-21-iodo-4-pregnene-3,20-dione. The iodide was dissolved in 25 ml. of acetonitrile and the solution was refluxed for 17 hr. in a Soxhlet extractor whose thimble contained 1 g. of silver fluoride.[33] The reaction mixture was partitioned between 0.25 l. of ethyl acetate and 0.10 l. of water. The ethyl acetate solution was further washed with water and after drying with anhydrous sodium sulfate the solution was concentrated at reduced pressure leaving 0.222 g. of crude 9α,21-difluoro-17α-hydroxy-4-pregnene-3,20-dione. This was acetylated by essentially the method used in A but for only half as long. Chromatography on silica gel gave in the early 10% ethyl acetate in benzene fractions, 9 mg. of crystals, m.p. 195–209°. Repeated crystallization from acetone gave 3 mg. of 9α,21-difluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate identical with the material prepared in A (m.m.p. and infrared spectra). The later 10% ethyl acetate in benzene fractions gave 9 mg. of 9α,21-difluoro-17α-hydroxy-4-pregnene-3,20-dione. Identity with the material prepared in A was established by mixture melting point and infrared spectra.

9α-Fluoro-4-pregnene-3,20-dione (Ia → IVa).—A solution of 1.00 g. of 11β-hydroxy-4-pregnene-3,20-dione in 10 ml. of hydrogen fluoride–pyridine reagent (80%, 35 days) was kept in an ice bath for 4 hr. A reddish brown color developed. The reaction mixture was partitioned between 0.20 l. of ethyl acetate and 50 ml. of water. The organic phase was washed with three 50-ml. portions of water, 50 ml. of saturated aqueous sodium bicarbonate solution, and two 50-ml. portions of water. The solution was dried with anhydrous sodium sulfate and the solvent was removed by distillation at reduced pressure. Three crystallizations from acetone–hexane gave 42 mg. of pure 9α-fluoro-4-pregnene-3,20-dione, m.p. 196–200°; λ_{max} 237.5 mμ (ε 17,400); $[\alpha]_D$ +161° (*c*, 0.54); λ_{max}^{KBr} 5.85, 5.98, 6.17, 11.37 μ. The fluoride test was positive.

Anal. Calcd. for $C_{21}H_{29}FO_2$: C, 75.87; H, 8.79. Found: C, 76.11; H, 8.87.

9α-Fluoro-21-hydroxy-4-pregnene-3,20-dione 21-Acetate (Ib → IVb).—A solution of 4.83 g. of 11β,21-dihydroxy-4-pregnene-3,20-dione 21-acetate in 48 ml. of hydrogen fluoride–pyridine reagent (70%, 1 day) was kept at room temperature for 2 hr. The reaction mixture was poured into ice–water and the product was collected on a filter and after drying weighed 4.17 g. This mixture was treated with N-bromoacetamide and perchloric acid followed by potassium acetate as described earlier (Ic-acetate → IVc-acetate).[34] The crude product was chromatographed on 200 g. of silica gel. Elution with 10% ethyl acetate in benzene gave

(32) P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956).

(33) Harshaw Chemical Co., 1945 E. 97th St., Cleveland 6, Ohio.

(34) The product of a similar run was crystallized from acetone–hexane and acetone to give 21-hydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate, m.p. 161.5–162.5°; λ_{max} 238 mμ (ε 17,200); $[\alpha]_D$ +164° (*c* 0.57).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.46; H, 8.38. J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953), report m.p. 160–160.5°; $[\alpha]_D$ +150° (*c* 0.80).

0.638 g. of crystals which were crystallized from acetone–hexane to 0.347 g., m.p. 191.5–194.5°. The material was identical with 9α - fluoro - 21 - hydroxy - 4 - pregnene - 3,20 - dione 21 - acetate similarly prepared earlier, as shown by mixture melting point and infrared spectra. The analytical sample had the following properties: m.p. 188–190°; λ_{max} 238 mμ (ε 17,900); $[\alpha]_D$ +169.5° (*c* 0.613); λ_{max}^{KBr} 5.72, 5.81, 5.96, 6.18, 8.04, 11.28 μ.

Anal. Calcd. for $C_{23}H_{31}FO_4$: C, 70.74; H, 8.00. Found: C, 70.49; H, 7.83.[35]

Elution of the column with 1% ethyl acetate in benzene gave 1.554 g. of material which on repeated crystallization from acetone–hexane gave 0.292 g. of 9β,11β-epoxy-21-hydroxy-4-pregnene-3,20-dione 21-acetate,[36] m.p. 142–143°; λ_{max} 243.5 mμ (ε 14,500); $[\alpha]_D$ +61.5° (*c* 1.0).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.55; H, 8.14.

9α-Fluoro-4-androstene-3,17-dione from 9α-Fluoro-1 α,21-dihydroxy-4-pregnene-3,20-dione (IVc → VI).—A solution of 0.40 g. of chromium trioxide in 3.3 ml. of water was added to 50 ml. of acetic acid followed by 0.66 g. of 9α-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione. An additional 16 ml. of acetic acid was used to rinse out the sample vial and this was added to the reaction mixture. After having stood at room temperature overnight, the now blue-black solution was poured into a mixture of 2 l. of benzene and 1 l. of water. The benzene layer was separated and was washed with two 1-l. portions of water, 0.5 l. of saturated aqueous sodium bicarbonate solution, and two 1-l. portions of water. After being dried with anhydrous sodium sulfate the solvent was removed by distillation at reduced pressure. A crystalline residue weighing 0.51 g., m.p. 185–195°, was obtained. Chromatography on 45 g. of silica gel gave 260 mg. of crystals on elution with 15% ethyl acetate in benzene. Crystallization from acetone–hexane gave 129 mg. of 9α-fluoro-4-androstene-3,17-dione as prisms, m.p. 227–228°; λ_{max} 237 mμ (ε 17,800); $[\alpha]_D$ +158° (*c* 0.62); λ_{max}^{KBr} 5.73, 6.00, 6.17, 11.31 μ; n.m.r., 56 (18-CH_3), 80 (19-CH_3), 352 (4-H) c.p.s.

Anal. Calcd. for $C_{19}H_{25}FO_2$: C, 74.95; H, 8.28; F, 6.24. Found: C, 74.98; H, 8.26; F, 6.03.

9α-Fluoro-4-androstene-3,17-dione from 11β-Hydroxy-4-androstene-3,17-dione (III → VI).—A solution of 1.12 g. of 11β-hydroxy-4-androstene-3,17-dione in 11 ml. of hydrogen fluoride–pyridine reagent (69%, 0 days) was kept at +2° for 3 days. The dark red reaction mixture was partitioned between 0.1 l. of ethyl acetate and 0.05 l. of water. The ethyl acetate solution was washed with two 0.05-l. portions each of water, saturated aqueous sodium bicarbonate solution, and water. After being dried with anhydrous sodium sulfate, the solution was evaporated at reduced pressure. A crystalline residue weighing 1.006 g. was obtained of which 0.929 g. was chromatographed on 100 g. of silica gel. Elution with 8% ethyl acetate in benzene gave 218 mg. of crystals. Two crystallizations from acetone–hexane gave 125 mg. of 4,9(11)-androstadiene-3,17-dione, m.p. 208–209°, identical with an authentic sample[37] (mixture melting point and infrared spectra).

Further elution of the column with 8% ethyl acetate in benzene gave 114 mg. of crystals. Two crystallizations from acetone–hexane gave 53 mg. of 9α-fluoro-4-androstene-3,17-dione, m.p. 227–228°, identical with the sample prepared above (m.m.p. and infrared spectra). Development of the column with 15–20% ethyl acetate in benzene gave 369 mg. of solid which was crystallized three times from acetone–hexane to give 70 mg. of 11β-hydroxy-4-androstene-3,17-dione, m.p. 203.5–204°, identical (mixture melting point and infrared spectra) with an authentic sample.

9α-Fluoro-4-androstene-3,17-dione from 9α-Hydroxy-4-androstene-3,17-dione (V → VI).—A solution of 2.0 g. of 9α-hydroxy-4-androstene-3,17-dione in 18.5 g. of hydrogen fluoride–pyridine reagent (74%, 0 days) was kept at +2° for 6.5 hr. The pale yellow reaction mixture was partitioned between 0.5 l. of ethyl acetate and 0.25 l. of water. The organic phase was washed with two 0.25-l. portions of water, 0.25 l. of saturated aqueous sodium bicarbonate solution, and 0.25 l. of water. The solution was dried with anhydrous sodium sulfate and the solvent was removed by distillation at reduced pressure. The crude product was crystallized three times from acetone–hexane and each time the melting point of the product was 207–208°. This material gave a positive fluoride test and admixture with 9α-fluoro-4-androstene 3,17-dione did not lower the melting point nor did admixture with 4,9(11)-androstadiene-3,17-dione. A mixture of the 9-fluoro compound and the diene had a melting point between that of the pure compounds.

All of the fractions were combined and this mixture was chromatographed on 200 g. of silica gel. Elution with 8% ethyl acetate in benzene gave a series of fractions weighing, after crystallization, 0.805 g. and melting at 207–208° to 209–211°. The infrared spectra were identical with that of 4,9(11)-androstadiene-3,17-dione. A second crop, weighing 0.172 g., m.p. 206.5–208.5°, also was obtained by crystallization of the mother liquor residue from acetone–hexane. Further elution with 8% ethyl acetate gave 0.129 g. of mixed crystals. Using the same solvent system there was obtained a series of fractions melting at 226.5–227.5° to 230–231°, 0.203 g., identical with 9α-fluoro-4-androstene-3,17-dione (mixture melting point and infrared spectra). Elution with 64% ethyl acetate in benzene gave 23 mg. of crystals which on crystallization from acetone–hexane gave 8 mg. of 9α-hydroxy-4-androstene-3,17-dione, m.p. 221–223°. Admixture with an authentic sample, m.p. 224–225.5°, did not depress the melting point; the infrared spectra were identical.

The Dehydrohalogenation of 9α-Fluoro-4-androstene-3,17-dione (VI → VII).—A solution of 102 mg. of 9α-fluoro-4-androstene-3,17-dione in 2.0 ml. of hydrogen fluoride–pyridine reagent (69%, 0 days) was kept at +2° for 2 days. The reaction mixture was partitioned between 10 ml. of water and 20 ml. of ethyl acetate. The organic phase was washed with two 10-ml. portions of water, 10 ml. of saturated aqueous sodium bicarbonate solution, and two 10-ml. portions of water. After being dried with anhydrous sodium sulfate the solvent was distilled at reduced pressure and the crystalline residue was chromatographed on 18 g. of silica gel. Elution with 10% ethyl acetate in benzene gave 18 mg. of crystals, which were crystallized twice from acetone–hexane, giving 13 mg. of 4,9(11)-androstadiene-3,17-dione, m.p. 209–210.5°. Identity was established by mixture melting point and infrared spectra. Further elution gave 17 mg. of mixed crystals and finally 51 mg. of crystals which after two crystallizations from acetone–hexane gave 35 mg. of 9α-fluoro-4-androstene-3,17-dione, m.p. 228–230°, identical (mixture melting point and infrared spectra) with an authentic sample.

Attempted dehydrohalogenation of 45 mg. of 9α-fluoro-4-androstene-3,17-dione using refluxing pyridine for 2 hr. gave a recovery of 36 mg. of the 9-fluoro compound VI, m.p. 223.5–227°. Similarly 36 mg. of VI refluxed in Swiss collidine[38] for 48 hr. gave a 23-mg. recovery of starting material and no olefin, even after careful chromatography.

9α-Fluoro-17β-hydroxy-4-androsten-3-one 17-Acetate (XIII → XIVa-Acetate).—A solution of 1.13 g. of 11β,17β-dihydroxy-4-androsten-3-one 17-acetate in 11 ml. of hydrogen fluoride–pyridine reagent (80%, 11 days) was kept in an ice bath for 4 hr. The red-brown reaction mixture was partitioned between 0.25 l. of ethyl acetate and 0.1 l. of water. The organic phase was separated and was washed with two 0.1-l. portions of water, 0.1 l. of saturated aqueous sodium bicarbonate solution, and two 0.1-l. portions of water. After being dried over anhydrous sodium sulfate, the solution was concentrated at reduced pressure. Five crystallizations from acetone–hexane gave 51 mg. of 9α-fluoro-17β-hydroxy-4-androsten-3-one 17-acetate, m.p. 197.5–198.5°; λ_{max} 237.5 mμ (ε 16,800); $[\alpha]_D$ +71° (*c*, 0.79); λ_{max}^{KBr} 5.76, 5.96, 6.14, 7.95, 11.31 μ. The fluoride test was positive. The rotatory dispersion curve[39] is virtually identical with that of testosterone.

Rotatory dispersion in dioxane (*c* 0.05, 28°): $[\alpha]_{100}$ +56°, $[\alpha]_{589}$ +72°, $[\alpha]_{425}$ +120°, $[\alpha]_{370}$ −176°, $[\alpha]_{365}$ −152°, $[\alpha]_{355}$ −248°, $[\alpha]_{342.5}$ +256° (shoulder), $[\alpha]_{327.5}$ +1068° (shoulder,) $[\alpha]_{315}$ +1622° (shoulder), $[\alpha]_{305}$ +1840° (shoulder), $[\alpha]_{265}$ +3360°, $[\alpha]_{260}$ +5040°.

(35) Micro-Tech Laboratories, 5044 Warren, Skokie, Ill.

(36) This compound was reported by J. Fried, J. F. Herz, E. F. Sabo, A. Borman, F. M. Singer, and P. Numerof, *J. Am. Chem. Soc.*, **77**, 1068 (1955). Its properties were m.p. 137–138°; λ_{max} 243 mμ (ε 15,100); $[\alpha]_D$ +61° (*c* 0.66).

(37) This sample was prepared from 11α-hydroxy-4-androstene-3,17-dione *via* the mesylate. It had the following properties: m.p. 208–209°; λ_{max} 238.5 mμ, (ε 17,500); λ_{max}^{KBr} 5.76, 6.03, 6.23, 11.45 μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.28; H, 8.49.

This compound was reported to have m.p. 202.5–204.5° by S. Bernstein, R. H. Lenhard, and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

(38) Swiss Tar Industries, Ltd.

(39) We are indebted to Professor Carl Djerassi, Stanford University, for this determination. See *J. Am. Chem. Soc.*, **78**, 6362, 6377 (1956).

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39. Found: C, 72.52; H, 8.34.

9α-Fluoro-17β-hydroxy-4-androsten-3-one (XIII → XIVa).—A solution of 2.00 g. of 11β,17β-dihydroxy-4-androsten-3-one in 20 ml. of hydrogen fluoride–pyridine reagent (72%, 4 days) was kept at ice bath temperature for 4 hr. The yellow-brown reaction mixture was partitioned between 0.25 l. of ethyl acetate and 0.1 l. of water. After being washed with two 0.1-l. portions of water, two of saturated sodium bicarbonate solution, and two more of water, the solution was dried with anhydrous sodium sulfate. The solvent was removed by distillation at reduced pressure. The residue was crystallized from acetone–hexane and twice from acetone to give 170 mg. of starting material XIII, m.p. 242–244°, identity being established by mixture melting point and a comparison of infrared spectra.

The mother liquor residue was chromatographed on 200 g. of silica gel. Elution of the column with 15% ethyl acetate in benzene gave, after crystallization from acetone–hexane and from acetone, 102 mg. of 17β-hydroxy-4,9(11)-androstadien-3-one,[40] m.p. 160–162°; λ_{max} 239 mμ (ε 17,000); [α]D +98° (*c* 0.87); λ_{max}^{KBr} 2.95, 6.02, 6.21 μ.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.77; H, 9.07.

Next, still eluting with 15% ethyl acetate, came a series of fractions from which 340 mg. of crystals were obtained. A 51-mg. sample was taken from a 63-mg. center fraction, m.p. 206–207°, and this sample was acetylated overnight in 1.0 ml. of pyridine containing 0.5 ml. of acetic anhydride. The acetate was precipitated with water and was crystallized from acetone–hexane to give 44 mg. of 9α-fluoro-17β-hydroxy-4-androsten-3-one 17-acetate, m.p. 196–197.5°. Admixture with the fluoro compound obtained from using the 17-acetate (XIII-acetate) as starting material did not depress the melting point and the infrared spectra were identical. The remainder of the unacetylated material was crystallized from acetone–hexane and then from acetone to give 158 mg. of 9α-fluoro-17β-hydroxy-4-androsten-3-one as prisms, m.p. 204–206.5°; λ_{max} 238 mμ (ε 17,600); [α]D +88° (*c* 1.03); λ_{max}^{KBr} 2.95, 6.03, 6.18, 11.35 μ.

Anal. Calcd. for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88. Found: C, 74.81; H, 9.20.

Further development of the column with 50% ethyl acetate in benzene gave 621 mg. of starting material.

9α-Fluoro-17β-hydroxy-4-androsten-3-one 17-Propionate.—A solution of 181 mg. of 9α-fluoro-17β-hydroxy-4-androsten-3-one in 2 ml. of pyridine was treated with 2 ml. of propionic anhydride, and the mixture was kept at room temperature overnight. Ice and water were added and a crystalline precipitate, weighing 211 mg., m.p. 160–162.5°, was obtained. Crystallization from acetone–hexane gave 179 mg. of 9α-fluoro-17β-hydroxy-4-androsten-3-one 17-propionate, m.p. 163–165°; λ_{max} 238 mμ (ε 17,300); [α]D +62° (*c* 0.50); λ_{max}^{KBr} 5.78, 6.00, 6.18, 8.05, 11.31 μ.

Anal. Calcd. for $C_{22}H_{31}FO_3$: C, 72.89; H, 8.62. Found: C, 73.13; H, 8.54.

The Perfusion of 9α-Fluoro-4-androstene-3,17-dione through Surviving Bovine Adrenal Glands (VI → VIII + IX).[41]—A solution of 343 mg. of VI in 10 ml. of propylene glycol was poured into 4 l. of vigorously stirred bovine blood containing 20 mg. of Terramycin. This medium was perfused cyclically six times through four blood-washed bovine adrenal glands with a total wet tissue weight of 76 g. At the end of this 2.5 hr. run, 600 ml. of saline solution was perfused through the glands as a wash and was combined with the perfusate. This mixture was extracted with 16 l. of isopropyl acetate. Evaporation of the solvent left a residue of 1.554 g., which was chromatographed on 50 g. of silica gel. Elution with benzene gave 415 mg. of material that was crystallized from methanol to give 112 mg. of plate-like crystals, m.p. 75–147°. Two additional crystallizations from methanol–pentane gave 39 mg. of cholesterol, m.p. 147–149°. The melting point was not depressed on admixture with authentic cholesterol and the infrared spectra were identical. Elution with 5% ethyl acetate in benzene gave 106 mg. of material which after three crystallizations from acetone–hexane gave 24 mg. of 9α-fluoro-4-androstene-3,17-dione, m.p. 228–229°. Identity was established by mixture melting point and infrared spectra.

Elution with 30% ethyl acetate in benzene gave a series of crystalline fractions weighing 177 mg. which could not be satisfactorily purified by crystallization and so were rechromatographed on 6 g. of silica gel. Elution with 25% ethyl acetate in benzene gave 64 mg. of material. Three crystallizations from acetone gave 13 mg. of 9α-fluoro-19-hydroxy-4-androstene-3,17-dione (VIII), m.p. 238.5° dec.; λ_{max}^{EtOH} 240 mμ (ε 15,300); λ_{max}^{KBr} 3.01, 5.74, 6.03, 6.27, 11.43 μ. The ultraviolet spectrum of VIII in 0.1 *N* ethanolic potassium hydroxide showed a maximum at 302 mμ (ε 17,400) and a point of inflection at 238 mμ (ε 5850) after 2 min. After 24 hr. these changed to λ_{max} 292 mμ (ε 4770) and λ_{max} 246 mμ (ε 9250), respectively. The distillate obtained on treatment of VIII with aqueous sodium hydroxide gave a positive reaction with chromotropic acid. The fluorine test was positive. The n.m.r. spectrum showed absorption at 55 (18-CH_3), an AB type multiplet (J_{AB} = 20 c.p.s., δ_{AB} = 17 c.p.s.) centered around 237 (19-$HOCH_2$–) and a band at 360 (4-H) c.p.s.

Anal. Calcd. for $C_{19}H_{25}FO_3$: C, 71.22; H, 7.87. Found: C, 71.19; H, 7.74.

Further elution of the column with 25% ethyl acetate in benzene gave 66 mg. of material which after crystallization from acetone–hexane and twice from acetone gave 11 mg. of 9α-fluoro-18-hydroxy-4-androstene-3,17-dione (IX), m.p. 236–239° slight dec.; λ_{max} 237 mμ (ε 15,100); [α]D +135° (*c* 0.534); λ_{max}^{KBr} 2.96, 5.78, 6.00, 6.20, 11.39 μ. The ultraviolet spectrum of IX in 0.1 *N* ethanolic potassium hydroxide showed only a slight decrease in extinction coefficient after 24 hr. The distillate obtained on treatment of IX with aqueous sodium hydroxide gave a positive reaction with chromotropic acid. The fluorine test was positive. The n.m.r. spectrum showed absorption at 79 (19-CH_3), 221 (18-$HOCH_2$–) and 350 (4-H) c.p.s.

Anal. Calcd. for $C_{19}H_{25}FO_3$: C, 71.22; H, 7.87. Found: C, 71.09; H, 7.73.

9α-Fluoro-3-ethoxy-3,5-androstadien-17-one (VI → XII).—In a nitrogen filled flask were placed 585 mg. of 9α-fluoro-4-androstene-3,17-dione, 28 ml. of purified dioxane, 5.8 ml. of ethyl orthoformate (both distilled the day before and peroxide free), 58 mg. of *p*-toluenesulfonic acid, and 0.58 ml. of anhydrous ethanol. The mixture was stirred at room temperature for 7 hr. and then was poured into 0.25 l. of saturated aqueous sodium bicarbonate solution. The resulting suspension was extracted with 0.25 l. of benzene and the benzene solution was washed with two 0.25-l. portions of water. After being dried with anhydrous sodium sulfate the solution was concentrated at reduced pressure. The sirupy residue was treated with 25 ml. of pentane containing a drop of pyridine. Pale yellow prisms weighing 429 mg., m.p. 139–144°, were obtained and were crystallized twice from benzene–pentane to give a constant melting product weighing 249 mg., m.p. 153–162°. The crystals and mother liquors were dissolved in 500 ml. of benzene and this solution was poured through 50 g. of Merck chromatography grade aluminum oxide. The column was developed with benzene. Crystallization of the eluted products from benzene–pentane gave 397 mg. of needles, m.p. 154–157°. Two more crystallizations from the same solvent pair gave 173 mg. as a mixture of rods, m.p. 146–162° and needles, m.p. 138–144°. The crystals and mother liquor were again combined and the residue was crystallized from benzene–pentane giving 433 mg. of 9α-fluoro-3-ethoxy-3,5-androstadien-17-one as rods, m.p. 153–161°; λ_{max} 240 mμ (ε 21,400).

Anal. Calcd. for $C_{21}H_{29}FO_2$: C, 75.87; H, 8.79. Found: C, 76.04; H, 8.97.

Hydrolysis of the enol ether (20 mg.) with dilute hydrochloric acid in acetone as described later gave 12 mg. of 9α-fluoro-4-androstene-3,17-dione, m.p. 228.5–229.5°, identical with an authentic sample as shown by mixture melting point and infrared spectra.

9α-Fluoro-17β-hydroxy-17α-ethynyl-4-androsten-3-one (XII → XIVb).—A suspension of potassium hydroxide was prepared by heating 5.34 g. of pellets to 139–146° in a well stirred mixture of 30 ml. of diethylene glycol dimethyl ether and 2 ml. of diethylene glycol monomethyl ether for 30 min. Acetylene was passed over the surface of 10 ml. of the stirred dispersion for 2 hr. and then 94 mg. of 9α-fluoro-3-ethoxy-3,5-androstadien-17-one in 2.5 ml. of diethylene glycol dimethyl ether was added.[42] The reaction was carried out in an ice bath with constant stirring, and acetylene addition. Three hours after the addition of the steroid the reac-

(40) This was first prepared by F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.* **77**, 488(1955), who report m.p. 153–154°; [α]D +89°.

(41) We are indebted to Dr. James Carlo and The Worcester Foundation for Experimental Biology, Shrewsbury, Mass., for this perfusion.

(42) We are indebted to Mr. E. A. Brown for these directions. See N. W. Atwater, R. H. Bible, Jr., E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted, and P. B. Sollman, *J. Org. Chem.*, **26**, 3077 (1961).

tion mixture was poured into water. The precipitate was collected on a filter and after drying weighed 78 mg., m.p. 117–134°. This crude enol ether was dissolved in 4 ml. of acetone and 4 ml. of dilute hydrochloric acid (1 ml., concentrated, diluted to 20 ml. with water) was added. Crystals separated but dilution to about 14 ml. with acetone–hydrochloric acid of the same concentration caused them to dissolve. After 10 min. the product was precipitated with water. The crude dry product weighed 63 mg., m.p. 269–273° dec. The product was difficulty soluble in all the solvents used, but it was successfully crystallized from ethanol followed by two crystallizations from acetone. The purified 9α-fluoro-17β-hydroxy-17α-ethynyl-4-androsten-3-one (19 mg.) showed variable melting points of 285°, 300°, and 289.5° dec. in three trials. The ultraviolet spectrum showed λ_{max} 237.5 mμ (ε 16,600); λ_{max}^{KBr} 2.91, 3.06, 6.01, 6.15, 11.28 μ. A satisfactory analysis was not obtained. The fluorine test was positive.

Anal. Calcd. for $C_{21}H_{27}FO_2$: C, 76.33; H, 8.24. Found: C, 75.57; H, 8.06.

9α-Fluoro-17β-hydroxy-17α-vinyl-4-androsten-3-one (XIVb → XIVc).—A solution of 153 mg. of 9α-fluoro-17β-ethynyl-17α-hydroxy-4-androsten-3-one in 20 ml. of pyridine containing 100 mg. of 5% palladium on calcium carbonate was treated with hydrogen at room temperature and atmospheric pressure until about 1 mole of hydrogen (10.6 ml.) had been added per mole of steroid. The catalyst was removed by filtration, and the solvent was distilled at reduced pressure. The residue could not be purified by crystallization. Chromatography on 15 g. of silica gel gave a series of crystalline fractions on elution with 10% ethyl acetate in benzene. A center cut was taken and three crystallizations from acetone–hexane gave 44 mg. of 9α-fluoro-17β-hydroxy-17α-vinyl-4-androsten-3-one, m.p. 193.5–196.5°; λ_{max} 237.5 mμ (ε 16,100); $[\alpha]_D$ +56.5° (*c* 1.00 dioxane); λ_{max}^{KBr} 2.86, 5.98, 6.16, 11.37 μ. The fluorine test was positive.

Anal. Calcd. for $C_{21}H_{29}FO_2$: C, 75.87; H, 8.79. Found: C, 76.05; H, 8.74.[35]

9α-Fluoro-17β-hydroxy-17α-ethyl-4-androsten-3-one (XIVc → XIVd).—A solution of 93 mg. of 9α-fluoro-17β-hydroxy-17α-vinyl-4-androsten-3-one in 10 ml. of dioxane containing 30 mg. of 5% palladium on carbon was treated with hydrogen at room temperature and atmospheric pressure (7.05 ml.) until about 1 mole per mole of steroid had been absorbed. After filtration and distillation of the solvent at reduced pressure the residue was chromatographed on 10 g. of silica gel. Elution of the column with 10% ethyl acetate in benzene gave 34 mg. of material. Two crystallizations from acetone–hexane gave 25 mg. of 9α-fluoro-17β-hydroxy-17α-ethyl-5β-androstan-3-one, m.p. 143–144°; $\lambda_{max}^{CHCl_3}$ 2.67, 2.73, 5.84, 11.25 μ. RD in dioxane (*c* 0.122, 28°); $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −13°, $[\alpha]_{312}$ −516° $[\alpha]_{307}$ −478°, $[\alpha]_{305}$ −492°, $[\alpha]_{291}$ +349°, $[\alpha]_{287}$ −136°, $[\alpha]_{284}$ −7°, $[\alpha]_{283}$ −66°, $[\alpha]_{281}$ +46°, $[\alpha]_{279}$ −2°, $[\alpha]_{275}$ +175°. The fluorine test was positive and there was no absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{33}FO_2$: C, 74.96; H, 9.89. Found: C, 74.85; H, 9.81.

Further elution with 10% ethyl acetate in benzene gave 49 mg. of material which was crystallized twice from acetone–hexane to give 33 mg. of 9α-fluoro-17β-hydroxy-17α-ethyl-4-androsten-3-one, m.p. 198–199°; λ_{max} 237.5 mμ (ε 17,400); $[\alpha]_D$ +51° (*c* 0.54); $\lambda_{max}^{CHCl_3}$ 2.68, 2.73, 5.98, 6.17, 11.25, 11.43 μ.

Anal. Calcd. for $C_{21}H_{31}FO_2$: C, 75.41; H, 9.34; F, 5.68. Found: C, 75.74; H, 9.40; F, 6.37.

The Reaction of 11α-Hydroxy-4-pregnene-3,20-dione with Hydrogen Fluoride–Pyridine Reagent.—A solution of 1.00 g. of 11α-hydroxy-4-pregnene-3,20-dione in 10 ml. of hydrogen fluoride–pyridine reagent (75%, 3 days) was kept at room temperature for 25 hr. The reaction mixture was partitioned between 0.1 l. of water and 0.25 l. of ethyl acetate. The organic phase was washed with ten 0.1-l. portions of water and was dried over anhydrous sodium sulfate. The solution was concentrated to dryness and the residue was crystallized from acetone–hexane. A 0.40-g. yield of starting material (identified by mixture melting point and infrared spectra) was obtained. The mother liquor residue gave a negative test for fluorine.

Semiquantitative Study.—A solution of 103 mg. of 11β-hydroxyandrostenedione in 9.99 ml. of hydrogen fluoride–pyridine reagent (72%, 0 days) was kept in an ice bath and a 1.91-ml. sample was taken after 160 min., at a time when the reaction should not have proceeded very far. The sample was added to a mixture of 25 ml. of ethyl acetate and 10 ml. of water. The layers were mixed and were separated. The organic phase was washed with two 10-ml. portions of water. It was dried over 10 g. of anhydrous sodium sulfate, filtered, and concentrated to dryness under nitrogen. The residue was analyzed in duplicate as follows. An aliquot was spotted on Whatman no. 1 filter paper along with a mixture of known amounts of 9α-fluoroandrostenedione and 4,9(11)-androstadienedione to serve as a control. The paper was developed using a hexane–propylene glycol system and then the spots were outlined under ultraviolet light. The spots were cut out and weighed. Two blank spots were also taken to determine the background absorption. The cutouts were cut into small pieces and 10.00 ml. of methanol was added: the mixture was swirled every 15 min. for 2 hr.; then the ultraviolet spectrum of the solution was determined. A parallel experiment, using 100 mg. of 4,9(11)-androstadienedione was conducted at the same time. From the ultraviolet absorption of the solution so obtained, the per cent conversion of the initial substrate to 9α-fluoroandrostenedione and 4,9(11)-androstadienedione were calculated. The results of these analyses are listed in Table II.

TABLE III

Substrate	% Recovery or yield 9F-Steroid	% Recovery or yield $\Delta^{9(11)}$-Steroid
11β-Hydroxyandrostenedione[a]	1.54–1.85[b]	0.89–0.83[b]
4,9(11)-Androstadienedione	9.1–10.1[b]	98–114[c]
Control	117–79[d]	104–64[d]
	148–137[c]	124–101[c]

[a] An unidentified material approximately equal in concentration to that of the $\Delta^{9(11)}$-steroid was obtained from the reaction of 11β-hydroxyandrostenedione with the hydrogen fluoride–pyridine reagent. This was not observed in the parallel reaction with 4,9(11)-androstadienedione. With this paper-chromatographic system, 4,9(11)-androstadienedione ran more rapidly than the 9α-fluoroandrostenedione. The unidentified material was observed just following the spot for the 9-fluoro steroid. [b] Per cent yield. [c] Per cent recovery from 4,9(11)-androstadienedione run. [d] Per cent recovery from 11β-hydroxyandrostenedione run.

While it is apparent that the results so obtained are very far from accurate, it is also apparent that, at least initially the 9α-fluoro steroid is formed at a faster rate than the $\Delta^{9(11)}$-steroid. The $\Delta^{9(11)}$-steroid is not formed and converted rapidly enough to account for the formation of most of the 9α-fluoroandrostenedione.