Tetrahedron, 1958, Vol. 3, pp. 14–27. Pergamon Press Ltd., London

STEROIDS—XCII*

SYNTHESIS OF HALOGENATED STEROID HORMONES—II†

6α- AND 6β-FLUOROTESTOSTERONE AND 6α- AND 6β-FLUOROPROGESTERONE

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(*Received* 14 *November* 1957)

Abstract—Fission of 3β-acetoxy-5α,6α-epoxides in the cholestane, androstane and pregnane series with boron trifluoride etherate afforded the corresponding 3β-acetoxy-5α-hydroxy-6β-fluoro compounds.[1] By appropriate manipulation of these fluorohydrins 6α-fluorocholestenone and the biologically interesting 6α- and 6β-fluorotestosterone and 6α- and 6β-fluoroprogesterone were prepared.

INTEREST in fluoro steroids has been greatly stimulated during the last 3 years following the demonstration by Fried and Sabo[2] that 9α-fluorohydrocortisone has approximately eleven times the glucocorticoid activity of hydrocortisone and is highly effective in maintaining life in the adrenal insufficient rat,[3] dog,[4] and man.[4,5]

Extension of this finding to other series of compounds has fully confirmed the remarkable effect of the 9α-fluorine atom on biological activity. 9α-Fluorocorticosterone acetate[6] and 9α-fluorodehydrocorticosterone acetate[6] possess mineralocorticoid activity of the order of that observed with aldosterone. 9α-Fluoro-11β-hydroxy and 11-keto-progesterone have been shown[6] to have approximately the same glucocorticoid activity as cortisone acetate and 1-dehydro-9α-fluorohydrocortisone[7,8] and 6-dehydro-9α-fluorohydrocortisone[7] both have considerably enhanced glucocorticoid and salt retaining activities compared to the corresponding non-fluorinated compound. 2-Methyl-9α-fluorohydrocortisone acetate[9] exhibits thirty-eight times the activity of hydrocortisone in the glycogen deposition assay and is ninety times more potent than deoxycorticosterone acetate in the salt retention assay.[9]

It was pointed out recently[10] that the enhancement of adrenocorticoid activity by introduction of a 9α-substituent is paralleled by the electronegativity of the

* Paper XCI. A. Bowers, C. Casas Campillo and Carl Djerassi *Tetrahedron* **2**, 165 (1958).

† Part 1. H. J. Ringold, E. Batres, O. Mancera and G. Rosenkranz *J. Org. Chem.* **21**, 1432 (1956).

‡ This reference gives a detailed discussion of fission of 3β-acetoxy-5α,6α-epoxides with boron trifluoride. We are very grateful to Dr. H. B. Henbest, Kings College, London, for a copy of this manuscript prior to publication.

[1] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).‡

[2] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **76**, 1455 (1954).

[3] A. Borman, F. M. Singer and P. Numerof, *Proc. Soc. Exp. Biol. Med.* **86**, 570 (1954).

[4] G. W. Liddle, M. M. Pechet and F. C. Bartter, *Science* **120**, 496 (1954).

[5] A. Goldfien, G. W. Thorn, P. M. Beigleman and J. C. Laidlaw, *J. Clin. Endroclin.* **14**, 782 (1954).

[6] J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *J. Amer. Chem. Soc.* **77**, 1068 (1955).

[7] J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *J. Amer. Chem. Soc.* **77**, 4181 (1955).

[8] R. F. Hirshmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *J. Amer. Chem. Soc.* **77**, 3166 (1955).

[9] J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *J. Amer. Chem. Soc.* **77**, 6401 (1955).

[10] J. E. Herz, J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **78**, 2017 (1956).

9α-substituent, the effect being greatest with 9α-fluorine atom. These authors suggested that this effect may be due to an increase in the acidity constant of the 11β-hydroxyl group brought about by the inductive effect of the neighboring 9α-substituent. This hypothesis receives support by the reported activity of 12α-fluoro-11β-hydroxyprogesterone[8] and 12α-fluorocorticosterone[11] since both compounds show biological activity of the same order as their corresponding 9α-fluoro isomers.

Further interest was stimulated in fluoro steroids when it was shown[12] that 21-fluoroprogesterone is a potent progestational hormone being two to four times as active as progesterone and that introduction of a 21-fluorine atom into various cortical hormones enhances the glucocorticoid activity of the corresponding 21-deoxy compounds by approximately three to five times.[13]

In view of these remarkable biological findings it seemed desirable to investigate the synthesis of steroid hormone analogs with fluorine substituents in positions other than 9, 12 and 21.

It has been shown in these laboratories[14] and elsewhere[15] that introduction of a 6-methyl group favorably affects the biological activity of testosterone,[14] and progesterone[14] as well as glucocorticoids[15] and consequently the corresponding 6-fluoro compounds might be expected to be of biological interest.

A suitable system for the introduction of a fluorine atom at C-6 appeared to be the 5α,6α-epoxide since by analogy with the diaxial cleavage of a 9β,11β-epoxide or an 11β,12β-epoxide[11,12] one would expect to obtain the 6β-fluoro-5α-hydroxy compound from hydrogen fluoride fission. However under various experimental conditions[16] * we were not able to convert in reasonable yield a 3β-acetoxy 5α,6α-epoxide system to the corresponding fluorohydrin with anhydrous hydrogen fluoride and in view of our success with the boron trifluoride approach described below this reaction was not investigated further.

Treatment of a solution of cholesterol α-epoxide (Ia) (Fig. 1) or cholesterol acetate α-epoxide (Ib) in an ether–benzene mixture with an excess of boron trifluoride etherate[1] for 3 hr at room temperature afforded in good yield the corresponding 5α-hydroxy-6β-fluoro compound IIa or IIb. Acetylation of IIa readily gave IIb and lithium aluminum hydride hydrolysis of IIb afforded IIa in good yield.

Oxidation of the 6β-fluoro-diol (IIa) with 8 N chromic acid in acetone[17] smoothly afforded the C-3 ketone (III) which underwent acid catalyzed dehydration with hydrogen chloride in acetic acid to afford 6α-fluorocholestenone (IV). A discussion of the proof that this dehydration is attended by concomitant epimerization of the fluorine atom is deferred until the experimental evidence available from the transformations in the androstane series is described.

The following reaction sequences (I → IV) clearly demonstrated a feasible route to 6-fluoro-Δ^4-3-ketones in the biologically more interesting androstane and pregnane

* For detailed discussions of the factors involved in the fission of steroid epoxides with hydrogen fluoride see Hirschmann *et al.* and Fried and Sabo.

[11] D. Taub, R. D. Hoffsommer and M. L. Wendler, *J. Amer. Chem. Soc.* **78**, 2912 (1956).
[12] P. Tannhauser, R. J. Pratt and E. V. Jensen, *J. Amer. Chem. Soc.* **78**, 2658 (1956).
[13] J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *J. Amer. Chem. Soc.* **78**, 4812 (1956).
[14] H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.* **22**, 99 (1957).
[15] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Amer. Chem. Soc.* **78**, 6213 (1956).
[16] R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *J. Amer. Chem. Soc.* **78**, 4956 (1956); J. Fried and E. F. Sabo *Ibid.* **79**, 1130 (1957).
[17] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2548 (1953).

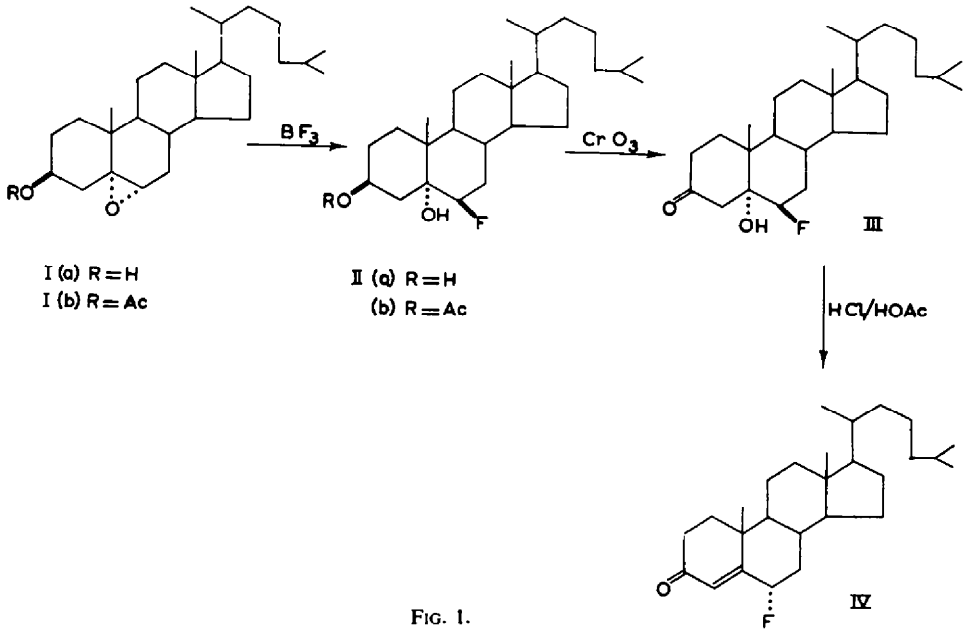

FIG. 1.

series. By application of this method for the introduction of a 6-fluorine atom and appropriate manipulation of the fluorohydrins we were able to synthesize 6α- and 6β-fluorotestosterone and 6α- and 6β-fluoroprogesterone.

Our starting material in the androstane series was the readily available Δ^5-androstene-3β,17β-diol-diacetate (V) (Fig. 2) which with permonophthalic acid afforded the α-epoxide (VI) in 70 per cent yield.*

Using the conditions developed in the cholesterol series the α-epoxide (VI) was cleaved with borontrifluoride etherate to the fluorohydrin (VII) in 80 per cent yield (allowing for recovered starting material). Lithium aluminum hydride hydrolysis of the acetyl groups of VII smoothly gave the 6β-fluoro-triol (X), which was oxidized in good yield to the corresponding 3,17-diketone (XIII). Dehydration of this β-hydroxyketone (XIII) with anhydrous hydrogen chloride in acetic acid smoothly afforded the 6α-fluoro-Δ^4-3,17 diketone (XVI) (see below for a discussion of the configuration of fluorine atom). Lithium aluminum hydride reduction of XVI gave a product having no maximal absorption in the ultraviolet and which probably was a mixture of two diols (XV), both containing a 17 β-hydroxyl group but being epimeric at C-3.[18]† The total reduction product however without purification was oxidized with manganese dioxide[19]‡ to afford 6α-fluorotestosterone (XIV), λ_{max} 236–238 mμ log ε, 4·17.

* An attempt was made to increase the yield of α-epoxide by carrying out the reaction at −60° and then allowing the reaction mixture to warm up to 0° during 16 hr. It was felt that at this low temperature the ratio of the sterically unfavorable β-epoxidation to α-epoxidation would be less than at 0°, which is the more usual temperature for reactions of this type. Although a quantitative study was not carried out, higher yields were obtained (70 per cent) at −80° than at 0°.

† Lithium aluminum hydride reductions of Δ^4-3-ketones are known to give a mixture of C-3 epimeric alcohols. See, for example, McKennis and Gaffney and Plattner *et al.*

‡ For the use of manganese dioxide as a specific oxidizing agent for allylic alcohols see Sondheimer *et al.*

[18] McKennis and Gaffney, *J. Biol. Chem.* 175, 217 (1949); P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* 32, 265 (1949).

[19] F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Amer. Chem. Soc.* 75, 5930 (1953).

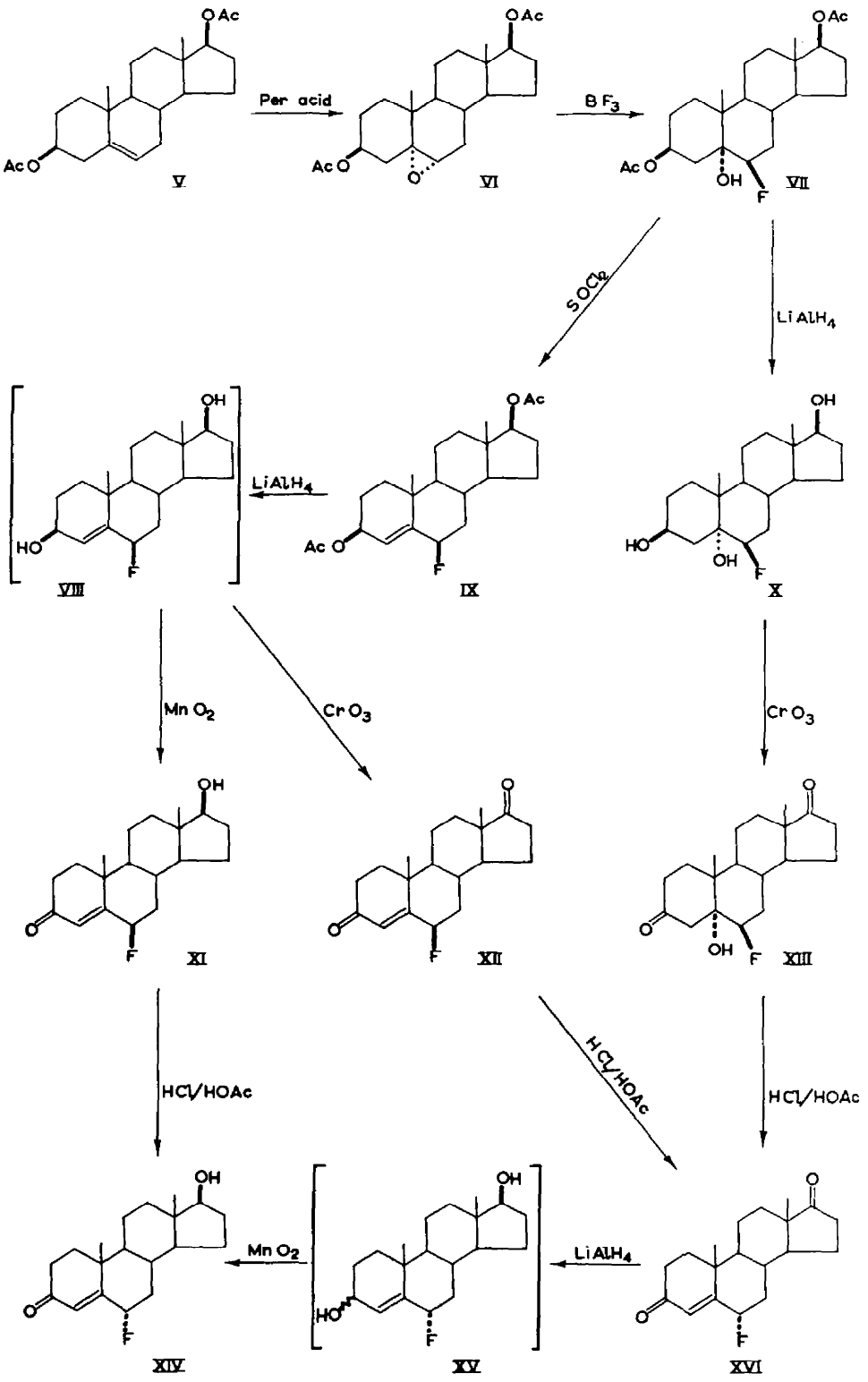
OAc
AcO
V
Per acid
VI
BF3
OH
F
VII
SOCl2
LiAlH4
HO
VIII
IX
X
Mn O2
CrO3
XI
XII
XIII
HCl/HOAc
XIV
XV
XVI

FIG. 2.

A route to the epimeric 6β-fluorotestosterone was then developed from the fluorohydrin (VII). Thionyl chloride dehydration of VII smoothly gave a compound which had lost the elements of water and which was formulated as the Δ^4-3β-acetate (IX) on the following grounds. The fluoro-diol (VIII) obtained by lithium aluminum hydride hydrolysis of IX, was smoothly converted to a 6-fluorotestosterone (XI) by manganese dioxide oxidation. Compound XI was different from 6α-fluorotestosterone (XIV) and also the fluoro-diketone (XII) from 8 N chromic acid oxidation of VIII was not identical with XVI.

Henbest and Wrigley[1] have unequivocably demonstrated the 5α-hydroxy-6β-fluoro stereochemistry for the fluorhydrin resulting from the boron trifluoride opening of a 3β-acetoxy-5α,6α-epoxide. Consequently (XI) must have the 6β-fluoro configuration, since the reaction sequence VII $\rightarrow$ IX $\rightarrow$ VIII $\rightarrow$ XI would not be expected to be accompanied by inversion at C_6 at any stage. Inversion at C_6 would necessitate abstraction of the 6α-hydrogen atom by either formation of the Δ^5-double bond during the thionyl chloride dehydration followed by rearrangement to the Δ^4-compound or by enolization of the Δ^4-3-ketone (XI) during the manganese dioxide oxidation. We consider both processes to be unlikely. However, the 6β-fluoro substituent is 1,3-diaxially situated with respect to the C-19 methyl group and the resulting non-bonded interactions will certainly make this a less stable arrangement than the corresponding 6α-epimer. Under enolizing conditions the axial 6β-fluoro-Δ^4-3-ketones would be expected to epimerize at C_6. This is in fact the case, and treatment of both XI and XII with hydrogen chloride in acetic acid smoothly gave the 6α-fluoro compounds XIV and XVI respectively.

Further confirmation of the structure assignments comes from an inspection of the molecular rotation differences between the two pairs of compounds XI and XIV, and XII and XVI differing only in the configuration of the fluorine at C_6. Barton and Miller[20] have previously commented on the difference in rotation between epimeric 6α- and 6β-bromo and 6α- and 6β-chloro cholestenones and it can be seen that the 6α-halo-Δ^4-3-ketones are always much more dextrorotatory than their 6β-epimers. This difference is enhanced even more in the 6-fluoroandrostane and pregnane series (Table 1).

A logical extension of this work was application of the same type of reaction sequence to pregnenolone acetate (XVII) (Fig. 3).

Using the low-temperature epoxidation technique, pregnenolone acetate α-epoxide (XVIII) was prepared in 70 per cent yield. Cleavage with boron trifluoride etherate gave the fluorohydrin (XIX), which underwent reduction and hydrolysis to the fluoro-triol (XXII) with lithium aluminum hydride. Oxidation of this triol (XXII) with 8 N chromic acid in acetone gave the 6β-fluoro-5α-hydroxy-3,20-diketone (XXV), which then underwent acid catalyzed dehydration to 6α-fluoroprogesterone (XXIV).

6β-Fluoroprogesterone (XXVI) was prepared by two alternative routes. The first and most direct route involved the alkaline dehydration of the 6β-fluoro-5α-hydroxy-3-ketone (XXV). When XXV was treated with a 0·25 per cent solution of potassium hydroxide in methanol it was possible to isolate 6β-fluoroprogesterone as the major product of the reaction. The 6β-stereochemistry of the fluorine atom

[20] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.* **72**, 1066 (1950).

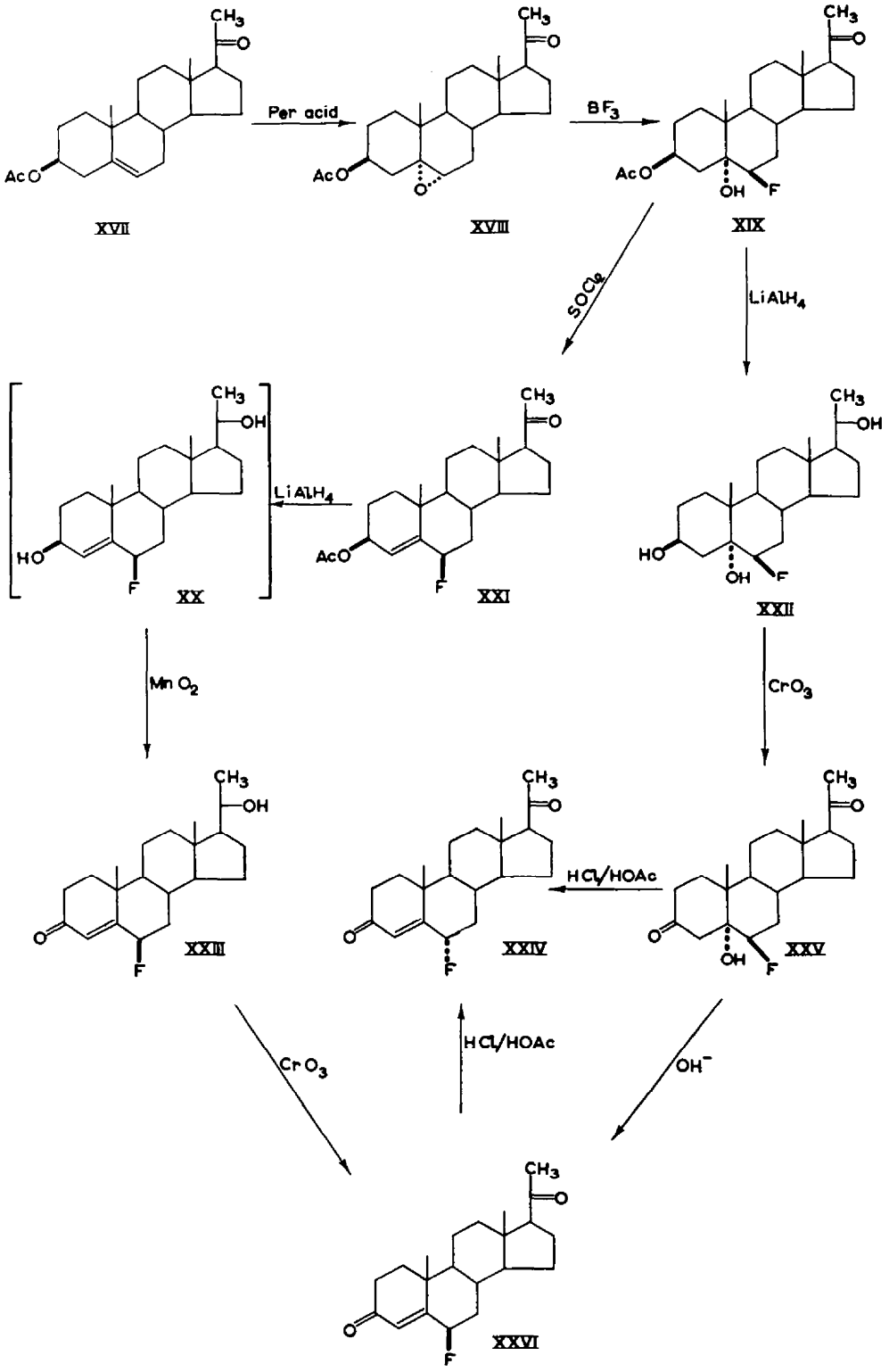
CH3
O
AcO
Per acid
O
BF3
OH
F
XVII
XVIII
XIX
SOCl2
LiAlH4
HO
XX
LiAlH4
XXI
XXII
MnO2
CrO3
XXIII
XXIV
HCl/HOAc
XXV
CrO3
HCl/HOAc
OH⁻
XXVI

FIG. 3.

TABLE 1. MOLECULAR ROTATION DATA OF EPIMERIC 6-HALO STEROIDS

Compound	$[M]_D^*$	$\Delta[M]_D$ (6α − 6β)
6α-bromocholestenone	+245†	+217
6β-bromocholestenone	+28†	
6α-chlorocholestenone	+247‡	+182
6β-chlorocholestenone	+65‡	
6α-fluoro-Δ⁴-androstene-3,17-dione (XVI)	+561§	+327
6β-fluoro-Δ⁴-androstene-3,17-dione (XII)	+234§	
6α-fluorotestosterone (XIV)	+312§	+312
6β-fluorotestosterone (XI)	0§	
6α-fluoroprogesterone (XXIV)	+660§	+322
6β-fluoroprogesterone (XXVI)	+338§	

* All rotations in chloroform. † Reference 22. ‡ D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.* 72, 370 (1950). § This paper.

was shown by the molecular rotation comparison with its 6α-epimer (XXIV) (Table 1) and its conversion to XXIV by treatment with hydrogen chloride in acetic acid.

An alternative route to 6β-fluoroprogesterone (XXVI) was similar to that developed for the synthesis of 6β-fluorotestosterone (XI), namely, dehydration of a 6β-fluoro-5α-hydroxy-3β-acetoxy system with thionyl chloride in pyridine to the 6β-fluoro-Δ⁴-3β-acetate followed by hydrolysis of the acetate and selective oxidation of the Δ⁴-3β alcohol. (Fig. 2. (VII) → (IX) → (VIII) → (XI).)

However, in contrast to the stereospecific dehydration observed in the testosterone series, treatment of (XIX) with thionyl chloride in pyridine for 5 min at 0° afforded a mixture of epimeric products. Elemental analysis of this mixture indicated that a molecule of water had been lost, but it was not possible to resolve it chromatographically. It was shown, however, to be a mixture of the expected product XXI and an unsaturated Δ⁵-compound. Hydrolysis (3β-acetate) and reduction (20-ketone) of this mixture with lithium aluminum hydride gave a mixture of glycols, the nature of which could be deduced from the following experiments:

(a) Oxidation with manganese dioxide[19] gave a product (λ_{max} 236 mμ, log ε 3·71) corresponding to 40 per cent of a 6β-fluoro-Δ⁴-3-ketone, which could only have arisen from a Δ⁴-3β alcohol.

(b) Oxidation with 8 N chromic acid in acetone under conditions where isomerization of a Δ^5-3-ketone to a Δ^4-3-ketone would not be expected to take place[21] gave a product (λ_{max} 236, log ε 3·80) corresponding to 50 per cent of a 6-fluoro-Δ^4-3-ketone. A trace of alkali raised the log ε to 4·10, indicating that 50 per cent of the reaction mixture was unconjugated Δ^5-3-ketone. These semiquantitative results are best explained by assuming that thionyl chloride dehydration gives an approximately 1 : 1 mixture of the Δ^4-3β acetate (IX) and a Δ^5-3β acetate.

However, it was found possible to utilize these results for a convenient preparation of 6β-fluoroprogesterone (XXVI). The total dehydration product (which contained approximately 40 per cent of XXI) was treated successively with lithium aluminum hydride and manganese dioxide to afford (XXIII), which was readily separated chromatographically from the more polar Δ^5-3β alcohol by-product. Oxidation of XXIII with 8 N chromic acid gave 6β-fluoroprogesterone (XXIV) in an overall yield of 25 per cent from XIX, the product being identical with that obtained by the alkaline dehydration of XXV.

EXPERIMENTAL

Melting points were determined in capillary tubes in sulfuric acid, and are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Mr. E. Avila for these measurements and for the infrared spectra which were obtained with a Perkin Elmer model-21 spectrophotometer with a sodium chloride prism. Neutral alumina refers to alumina which has been suspended in boiling ethyl acetate for 6 hr, filtered and dried at 100°. We are indebted to Miss L. Cuellar and Mr. E. Denot for skilled technical assistance The elemental analyses were carried out by J. F. Alicino, Metuchen, N. Jersey, and A. Bernhardt, Mulheim/Ruhr, Germany.

6β-Fluorocholestane-3β,5α-diol (IIa). (a) Boron trifluoride etherate (5 cm^3) was added to a solution of cholesterol-α-epoxide (Ia) (5·0 g) in anhydrous ether–benzene (1 : 1; 500 cm^3). After keeping at room temperature for 3 hr the solution was washed with 5% sodium bicarbonate solution, water, and then dried (Na_2SO_4) and evaporated. A solution of the residue in benzene (250 cm^3) was absorbed onto neutral alumina (300 g). Elution with benzene–ether (80 : 20; 700 cm^3) afforded cholesterol-α-epoxide (1·75 g) m.p. 138–142° undepressed on admixture with starting material. Further elution with ether (1·5 l.) gave 6β-fluorocholestane-3β,5α-diol (IIa) (2·21 g) m.p. 189–202°, raised by several crystallizations from acetone–hexane to 219–221°, $[\alpha]_D$ +36°,

Anal. Calcd. for $C_{27}H_{47}O_2F$: C, 76·7; H, 11·2; F, 4·50. Found: C, 76·5; H, 11·2; F, 4·3.

(b) A solution of 6β-fluorocholestane-3β,5α-diol 3-monoacetate (IIb) (1·5 g) in tetrahydrofuran (150 cm^3) was added over a 10 min period to a suspension of lithium aluminum hydride (1·5 g) in tetrahydrofuran (200 cm^3). After stirring for a further 10 min at room temperature the excess of reagent was decomposed with ethyl acetate. Hydrochloric acid (2 N, 200 cm^3) was then added and the product extracted with ether. The combined ether extracts were washed with water, 5% sodium bicarbonate solution and finally water. Evaporation of the dried ether solution gave 6β-fluorocholestane-3β,5α-diol (IIa) (1·4 g.) m.p. 188–197°, raised by crystallization

[21] C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

from acetone-hexane to 220–221°, $[\alpha]_D$ +31°, undepressed on admixture with a sample prepared as in (a).

6β-Fluorocholestane-3β,5α-diol 3-monoacetate (IIb). (a) Boron trifluoride etherate (1·0 cm³) was added to a solution of cholesterol acetate α-epoxide (1·0 g) in anhydrous ether–benzene (1:1; 100 cm³). After keeping at room temperature for 3 hr the solution was washed with 5% sodium bicarbonate solution, water, and then dried (Na_2SO_4) and evaporated. A solution of the product in benzene–hexane (1 : 1; 50 cm³) was adsorbed onto neutral alumina (50 g). Elution with benzene (400 cm³) gave 6β-fluorocholestane-3β,5α-diol 3-monoacetate (IIb) (470 mg) m.p. 202–207°, raised by three crystallizations from acetone–hexane to 214–216°, $[\alpha]_D$ −20°.

Anal. Calcd. for $C_{29}H_{49}O_3F$: C, 75·0; H, 10·6. Found: C, 75·1; H, 10·9.

(b) Acetylation of 6β-fluorocholestane-3β,5α-diol (IIa) (acetic anhydride-pyridine at room temperature for 16 hr) readily afforded the 3-monoacetate (IIb), m.p. 212–214°, $[\alpha]_D$ −22°, identical with a sample prepared by method (a).

6β-Fluorocholestane-5α-ol-3-one (III). A solution of 6β-fluorocholestane-3β, 5α-diol (IIa) (1·24 g) in acetone (100 cm³) at 0° was treated with an excess of 8 N chromic acid in aqueous sulfuric acid.[17] After 3 min at 0° addition of water and filtration gave 6β-fluorocholestane-5α-ol-3-one (III), m.p. 223–227°, raised by several crystallizations from acetone–hexane to 230–231°, $[\alpha]_D$ +66°. Compound III exhibited no maximal absorption in the ultraviolet.

Anal. Calcd. for $C_{27}H_{45}O_2F$: C, 77·1; H, 10·8; F, 4·5; Found: C, 76·9; H, 10·7; F, 4·5.

6α-Fluoro-Δ⁴-cholestene-3-one (IV). A solution of 6β-fluorocholestane-5α-ol-3-one (III) (300 mg) in acetic acid (50 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 2 hr and then kept at room temperature for an additional 2 hr. Water was added and the product isolated with ether. The combined ether extracts were washed with water, 5% sodium carbonate solution and water and then dried (Na_2SO_4) and evaporated to afford 6α-fluoro-Δ⁴-cholestene-3-one (IV) (280 mg) m.p. 114–118, raised by three crystallizations from hexane to 116–118°, $[\alpha]_D$ +103°, λ_{max} 236–238 mμ, log ε 4·18.

Anal. Calcd. for $C_{27}H_{43}OF$:C, 80·5; H, 10·8; F, 4·7. Found: C, 80·2; H, 10·8; F, 4·5.

5α,6α-Oxidoandrostane-3β,17β-diol diacetate (VI). To a solution of Δ⁵-androstene-3β,17β-diol diacetate (V) (35 g) in chloroform (300 cm³) at −60 to −70° (acetone–CO_2 bath) was added dropwise over 30 min with stirring a solution of per monophthalic acid (30 g) in ether (800 cm³). The mixture was kept at −80° for a further 2 hr and then at 0–5° for 16 hr. Chloroform (300 cm³) was added and the organic phase washed with 5% sodium carbonate solution and water, dried (Na_2SO_4) and evaporated to afford a product which crystallized after the addition of methanol, yielding 5α,6α-oxidoandrostane-3β,17β-diol-diacetate (VI) (26·1 g), m.p. 155–160°, raised by recrystallization from methanol to 166–168° $[\alpha]_D$ −66°, reported,[22] m.p. 165–166°, $[\alpha]_D$ −69°.

6β-Fluoroandrostane-3β,5α,17β-triol 3,17-diacetate (VII). To a solution of 5α,6α-oxidoandrostane 3β,17β-diacetate (VI) (28·7 g) in a mixture of anhydrous benzene–ether (1 : 1; 2860 cm³) boron trifluoride etherate (40 cm³) was added at room temperature. After 3 hr the solution was washed with 5% sodium carbonate

[22] L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta* **27**, 503 (1944).

solution, water, dried (Na_2SO_4) and evaporated to approximately 1 l., when the solution was adsorbed onto neutral alumina (1·5 kg). Elution with benzene (2·2 l.) afforded VI (14·3 g), m.p. 152–156°, identical with starting material. Further elution with benzene–ether (50 : 50; 1500 cm³) gave 6β-fluoroandrostane-3β,5α,17β-triol 3,17-diacetate (VII) (9·8 g), m.p. 195–210°, raised by several crystallizations from acetone–hexane to m.p. 212–214°, $[\alpha]_D$ −24°.

Anal. Calcd. for $C_{23}H_{35}O_5F$: C, 67·3; H, 8·6; F, 4·6. Found: C, 67·0; H, 8·6; F, 4·4.

6β-Fluoroandrostane-3β,5α,17β-triol (X). A solution of 6β-fluoroandrostane-3β, 5α,17β-triol 3,17-diacetate (VII) (5·0 g) in tetrahydrofuran (200 cm³) was added with stirring to a suspension of lithium aluminum hydride (4·0 g) in tetrahydrofuran (150 cm³) at 0° during 15 min. After stirring for a further 15 min at 0–10° the excess of reagent was destroyed with acetone. Hydrochloric acid (2 N, 200 cm³) was added and the product extracted with ether. The combined ether extracts were washed with 2 N hydrochloric acid, water, and dried (Na_2SO_4) and evaporated to afford 6β-fluoroandrostane-3β,5α,17β-triol (X) (4·28 g), m.p. 185–190°, raised by several crystallizations from acetone to 204–207°, $[\alpha]_D \pm 0°$.

Anal. Calcd. for $C_{19}H_{31}O_3 \cdot \frac{1}{2}(CH_3)_2CO$: C, 69·3; H, 9·6. Found: C, 69·3; H, 9·7.

6β-Fluoroandrostane-5α-ol-3,17-dione (XIII). To a solution of 6β-fluoroandrostane-3β,5α,17β-triol (X) (2·55 g) in acetone (200 cm³) at 0–5° was added dropwise an excess of 8 N chromic acid[17] in aqueous sulfuric acid. After 3 min water was added and the product extracted with ether. The combined ether extracts were washed several times with water, dried (Na_2SO_4) and evaporated to afford 6β-fluoroandrostane-5α-ol-3,17-dione (XIII) (2·05 g), m.p. 217–220°, raised by three crystallizations from acetone–hexane to 231–232° $[\alpha]_D$ +100°. XIII exhibited no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{19}H_{27}O_3F$:C, 70·8; H, 8·4. Found: C, 71·2; H, 8·5.

6α-Fluoro-Δ⁴-androstene-3,17-dione (XVI). (a) A solution of 6β-fluoroandrostane-5α-ol-3,17-dione (XIII) (180 mg) in acetic acid (20 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 1 hr. After a further 1 hr at room temperature, water was added and the product isolated with ether. The combined ether extracts were washed with saturated salt solution, 5% sodium carbonate solution, water, dried (Na_2SO_4) and evaporated. The oily product was adsorbed from benzene–hexane (1 : 1; 30 cm³) onto neutral alumina (10 g). Elution with benzene–hexane (1 : 1; 150 cm³) afforded 6α-fluoro-Δ⁴-androstene-3,17-dione (XVI) (63 mg), m.p. 212–228°, raised by crystallization from acetone–hexane to 229–231°, $[\alpha]_D$ +185°; λ_{max} 234–236, log ε 4·19.

Anal. Calcd. for $C_{19}H_{25}O_2F \cdot \frac{1}{2}(CH_3)_2CO$: C, 73·9; H, 8·4; F, 5·7. Found: C, 74·3; H, 8·5; F, 5·7.

(b) This was performed by isomerization of compound XII. 6β-Fluoro-Δ⁴-androstene-3,17-dione (XII) (100 mg) in glacial acetic acid (15 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 1 hr and then kept at room temperature for 1 hr. Isolation of the product as in (a) afforded 6α-fluoro-Δ⁴-androstene-3,17-dione (XVI) (50 mg) m.p. 216–218°, raised by crystallization from acetone-hexane to 230–232°, undepressed on admixture with a sample prepared as in (a); $[\alpha]_D$ +190°; λ_{max} 236 mμ, log ε 4·19.

6α-Fluorotestosterone (XIV). (a) A solution of 6α-fluoro-Δ⁴-androstene-3, 17-dione (XVI) (490 mg) in ether–tetrahydrofuran (1 : 1; 60 cm³) was added to a suspension of lithium aluminum hydride (400 mg) in ether (30 cm³) over a 10 min period. After stirring for a further 15 min at room temperature the excess of reagent was destroyed with ethyl acetate. Hydrochloric acid (2 N, 50 cm³) was then added and the product isolated with ether. The combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated to afford a mixture of alcohols (XV) epimeric at C-3. The total product was dissolved in chloroform (45 cm³) and stirred for 22 hr with manganese dioxide[23*](4· 4 g). Filtration and evaporation of the solvent gave a product (λ_{max} 238 mμ, log ε 3·93), which was adsorbed from benzene onto neutral alumina (30 g). Elution with benzene–ether (80 : 20; 400 cm³) afforded 6α-fluorotestosterone (XIV) m.p. 150–157°, raised by several crystallizations from benzene–hexane to 164–166°, $[\alpha]_D$ +111°, λ_{max} 236–238 mμ, log ε 4·16, $\lambda_{max}^{CHCl_3}$ 3450 cm⁻¹, 1675 cm⁻¹.

Anal. Calcd. for $C_{19}H_{27}O_2F\frac{1}{2}H_2O$: C, 72·3; H, 8·9; F, 6·0. Found: C, 72·5; 72·2; H, 8·9; 8·9. F, 5·7.

(b) Isomerization of 6β-fluorotestosterone was performed as follows: 6β-Fluorotestosterone (XI) (100 mg) in acetic acid (15 cm³) at 15–18° was treated with a steady stream of dry hydrogen chloride for 1 hr and then kept for an additional hour at room temperature. Isolation of the product in the manner described for the conversion of XII to XVI afforded 6α-fluorotestosterone (XIV) (42 mg) m.p. 156–163°, raised by crystallization from benzene–hexane to 163–166°, $[\alpha]_D$ +105°, undepressed on admixture with a sample prepared as in (a).

6β-Fluoro-Δ⁴-androstene-3β,17β-diol diacetate (IX). Thionyl chloride (0·2 cm³) was added to a solution of 6β-fluoroandrostane-3β,5α,17β-triol 3,17-diacetate (VII) (500 mg) in pyridine (10 cm³) at 0°, and the mixture kept at that temperature for 5 min. Water was added and the product isolated with ether. The combined ether extracts were washed with 2 N hydrochloric acid, water, dried (Na_2SO_4) and evaporated to afford a product which was adsorbed from benzene–hexane (50 : 50; 50 cm³) onto neutral alumina (25 g). Elution with benzene–hexane (50 : 50; 300 cm³) afforded 6β-fluoro-Δ⁴-androstene-3β,17β-diol diacetate (450 mg), m.p. 130–135°, raised by several crystallizations from hexane to 136–138°. $[\alpha]_D$ −42°.

Anal. Calcd. for $C_{23}H_{33}O_4F$: C, 70·4; H, 8·5; F, 4·8. Found: C, 70·9; H, 8·5; F, 4·6.

6β-Fluorotestosterone (XI). A solution of 6β-fluoro-Δ⁴-androstene-3β,17β-diol-diacetate (IX) (2·0 g) in ether (200 cm³) was added to a suspension of lithium aluminum hydride (1·0 g) in ether (100 cm³) at 0–5° over 10 min and then stirred for a further 10 min, when the excess of reagent was destroyed with acetone. Saturated sodium sulfate solution (5·0 cm³) and sufficient anhydrous sodium sulfate to give a clear supernatant ether solution was then added. The solution was filtered and the solid residue was extracted several times with chloroform. The combined extracts were evaporated under reduced pressure at 30° and the residue (1·8 g) had no carbonyl absorption in the infrared. A portion of this crude diol (1·6 g) in chloroform (100 cm³) was stirred with manganese dioxide (16 g) for 16 hr at room temperature. Filtration and evaporation of the filtrate afforded a product (λ_{max} 236 mμ, log ε 4·03) which

* The manganese dioxide was prepared according to the directions of O. Mancera *et al.*

[23] O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 2189 (1953).

was adsorbed from benzene (100 cm³) onto neutral alumina (100 g). Elution with benzene–ether (80 : 20; 50 cm³) afforded 6β-fluorotestosterone (XI) (1·08 g), m.p. 160–164°, raised by several crystallizations from benzene–hexane to 169–171°, $[\alpha]_D$ ±0°, λ_{max} 234 mμ, log ε 4·09, $\lambda_{max}^{CHCl_3}$ 3550, 1680 and 1625 cm⁻¹.

Anal. Calcd. for $C_{19}H_{23}O_2F$: C, 74·5; H, 8·9; Found: C, 74·1; H, 8·9.

6β-Fluoro-Δ⁴-androstene-3,20-dione (XII). A solution of 6β-fluoro-Δ⁴-androstene-3β,17β-diol diacetate (IX) (2·0 g) was hydrolyzed with lithium aluminum hydride as described in the previous experiment. The crude diol in acetone (50 cm³) was oxidized with 8 N chromic acid in the usual way. Isolation with ether afforded a product (1·5 g) m.p. 101–115°, which was adsorbed from benzene–hexane (1 : 1; 100 cm³) onto alumina (80 g). Elution with benzene (900 cm³) afforded 6β-fluoro-Δ⁴-androstene-3,17-dione (XII) (1·1 g) m.p. 130–137°, raised by crystallization from acetone–hexane to 136–138°, $[\alpha]_D$ +78°, λ_{max} 234, log ε 4·10, $\lambda_{max}^{CHCl_3}$ 1730 cm⁻¹ and 1675 cm⁻¹.

Anal. Calcd. for $C_{19}H_{25}O_2F$: C, 75·0; H, 8·3; F, 6·2. Found: C, 75·3; H, 8·3; F, 5·5.

5α,6α-Oxidopregnane-3β-ol-20-one 3-acetate (XVIII). A solution of per monophtalic acid[24] (15 g) in ether (500 cm³) was added during 20 min to a solution of pregnenolone acetate (XVII) in chloroform (800 cm³) at −60° to −70° (acetone–CO_2 bath). After keeping at −60° for a further 2 hr the mixture was kept at 0–5° for 16 hr. Chloroform (200 cm³) was added and the organic phase was washed with 5% sodium carbonate solution and water, dried (Na_2SO_4) and evaporated. The residue crystallized from methanol to afford 5α, 6α-oxido-pregnane-3β-ol-20-one acetate (XVIII) (13·5 g) m.p. 158–160°, raised by crystallization from methanol to 166–168°, $[\alpha]_D$ +11°. Ehrenstein and Decker[25] report m.p. 163–165° but give no $[\alpha]_D$ measurement. Urushibora *et al.*[26] report m.p. 165–166°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73·8; H, 9·1. Found: C, 73·8; H, 9·0.

6β-Fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX). Boron trifluoride etherate (8·7 cm³) was added to a solution of 5α,6α-oxidopregnane-3β-ol-20-one 3-acetate (8·7 g) in anhydrous ether–benzene (1 : 1; 700 cm³). After keeping at room temperature for 6 hr the solution was washed with 5% sodium bicarbonate solution, water, and then dried (Na_2SO_4) and evaporated. A solution of the product in benzene–hexane (1 : 1; 200 cm³) was adsorbed onto alumina (400 g). Elution with benzene (1·0 l.) afforded 5α,6α-oxidopregnane-3β-ol-20-one-3-acetate (2·4 g) identical with starting material. Further elution with benzene–ether (80 : 20; 1·7 l.) afforded 6β-fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX) (3·6 g), m.p. 218–220°, raised by several crystallizations to 223–224°, $[\alpha]_D$ +42°.

Anal. Calcd. for $C_{23}H_{35}O_4F$: C, 70·5; H, 8·9; F, 4·6. Found: C, 70·8; H, 8·9; F, 4·8.

6β-Fluoropregnane-3β,5α,20β-triol (XXII). A solution of 6β-fluoropregnane-3β, 5α-diol-20-one 3-monoacetate (XIX) (3·1 g) in dry ether (850 cm³) was added with stirring during 20 min to a suspension of lithium aluminum hydride (3·0 g) in ether (750 cm³) at 10°. After stirring at room temperature for a further 15 min the excess of reagent was destroyed with ethyl acetate. Saturated sodium sulfate solution

[24] *Organic Synthesis* (Coll. Vol. 3) p. 619. Wiley, New York (1955).
[25] M. Ehrenstein and M. T. Decker, *J. Org. Chem.* **5**, 544 (1940).
[26] Y. Urushibora, M. Chuman and S. Wada, *Bull. Chem. Soc. Japan* **24**, 83 (1951).

(10 cm³) was then added and sufficient anhydrous sodium sulfate to give a clear supernatant ether solution, which was filtered and the solid residue was extracted several times with chloroform. The combined extracts were evaporated to afford crude 6β-fluoropregnane-3β,5α,20β-triol (XXII) (2·6 g), m.p. 218–220°, raised by crystallization from acetone–hexane to 228–230°, $[\alpha]_D \pm 0°$ (dioxan).

Anal. Calcd. $C_{21}H_{35}O_3F$: C, 71·1; H, 9·4; F, 5·3. Found: C, 71·4; H, 9·7; F, 5·1.

6β-Fluoropregnane-5α-ol-3,20-dione (XXV). A solution of 6β-fluoropregnane-3β, 5α,20β-triol (XXII) (3 g) in acetone (200 cm³) at 0–5° was treated with an excess of 8 N chromic acid in the usual way. Addition of water and filtration afforded 6β-fluoropregnane-5α-ol-3,20-dione (XXV) (2·4 g), m.p. 245–247°, raised by one crystallization from aqueous pyridine to 279–281°, $[\alpha]_D +78°$ (pyridine).

Anal. Calcd. for $C_{21}H_{31}O_3F$: C, 71·9; H, 8·9; F, 5·4. Found: C, 71·8; H, 9·1; F, 4·9.

6α-Fluoroprogesterone (XXIV). A suspension of 6β-fluoropregnane-5α-ol-3, 20-dione (XXV) (800 mg) in acetic acid (80 cm³) at 15° was treated with a steady stream of dry hydrogen chloride for 2 hr and then kept at room temperature for 16 hr. Water was added and the product isolated with ether. After washing the combined ether extracts with 5% sodium carbonate solution, water, and drying over sodium sulfate, evaporation afforded a product which was adsorbed from benzene–hexane (50 : 50; 100 cm³) onto alumina (40 g). Elution with benzene–ether (90 : 10; 400 cm³) gave 6α-fluoroprogesterone (XXIV) (260 mg), m.p. 123–133°, raised by crystallization from acetone–hexane to 146–148°, $[\alpha]_D +191°$, λ_{max} 236, log ε 4.19.

Anal. Calcd. for $C_{21}H_{29}O_2F$: C, 75·9; H, 8·8; F, 5·7. Found: C, 75·8; H, 9·0; F, 5·8.

Dehydration of 6β-fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX). Thionyl chloride (0·1 cm³) was added to a solution of XIX (250 mg) in pyridine (5 cm³ at 0°). After 5 min at 0°, water was added and the product isolated with ether. The combined ether extracts were washed with 2 N hydrochloric acid, water, dried (Na_2SO_4) and evaporated to afford a product (200 mg), m.p. 90–94°, raised by crystallization from hexane to 94–97°, $[\alpha]_D +33°$.

Anal. Calcd. for $C_{23}H_{33}O_3F$: C, 73·5; H, 8·8. Found: C, 73·7; H, 8·8.

Hydrolysis (3β-acetate) and reduction (20 ketone) of the dehydration product. The total dehydration product (from the previous experiment) in ether (10 cm³) was added dropwise over 5 min to a stirred suspension of lithium aluminum hydride (200 mg) in ether (10 cm³) at 15°. After stirring for a further 15 min the excess of reagent was destroyed with acetone and the product isolated by the sodium sulfate method (as described above), to afford a non-crystalline product having no carbonyl absorption in the infrared.

Oxidation of the product from the previous experiment. (a) With manganese dioxide. The crude product (50 mg) in chloroform (5 cm³) was stirred with manganese dioxide (500 mg) for 24 hr. Filtration and evaporation of the solvent gave a product λ_{max} 236 mμ, log ε 3·71.

(b) With 8 N chromic acid in sulfuric acid. Crude product (100 mg) in acetone (10 cm³) at 0° was treated with an excess of 8 N chromic acid under nitrogen at 0°. After 3 min water was added and filtration afforded a product (92 mg) m.p. 156–160°, λ_{max} 236 mμ, log ε 3·80, raised by one drop of dilute alkali to 4·10.

6β-Fluoroprogesterone (XXVI). (a) 6β-Fluoropregnane-3β,5α-diol-20-one 3-monoacetate (XIX) (2·2 g) was treated with thionyl chloride in pyridine as described above. The total dehydration product in ether (100 cm³) was then added dropwise over 10 min to a stirred suspension of lithium aluminum hydride (2·0 g) in ether (100 cm³) at 15°. After stirring for a further 15 min at room temperature the excess of reagent was destroyed with acetone and the product isolated by the sodium sulfate method to afford a non-crystalline product having no carbonyl absorption in the infrared. The total product in chloroform (100 cm³) was stirred for 16 hr with manganese dioxide (20 g). Filtration afforded a product λ_{max} 236 mμ, log ε 3·78, indicating that approximately 47 per cent of XXIII was present in this mixture. A solution of the total oxidation product in benzene (100 cm³) was adsorbed onto alumina (100 g). Elution with benzene–ether gave a product (850 mg) m.p. 150–155°, λ_{max} 236 mμ, log ε 4·07. Without further purification a solution of this product in acetone (50 cm³) at 0–5° was treated with an excess of 8 N chromic acid in the usual way. Addition of water and filtration gave 6β-fluoroprogesterone (XXVI) (640 mg), m.p. 156–159°, raised by several crystallizations from benzene–hexane to 159–161° $[\alpha]_D$ +104°. λ_{max} 234–236 mμ, log ε 4·12.

Anal. Calcd. for $C_{21}H_{29}O_2F$: C, 75·9; H, 8·8; F, 5·7. Found: C, 75·7; H, 8·8; F, 5·6.

(b) 6β-Fluoropregnane-5α-ol-3,20-dione (XXV) (1·5 g) was suspended in methanol (100 cm³) containing potassium hydroxide (0·25 g) and heated under reflux under nitrogen for 60 min, when a clear solution resulted. After acidification with acetic acid and concentration of the solution to 15 cm³, water was added. Filtration of the precipitate gave a product (1·1 g), m.p. 125–130°, $[\alpha]_D$ +133°. Chromatography over alumina and crystallization from benzene–hexane afforded 6β-fluoroprogesterone (XXVI) (300 mg), m.p. 156–158°, $[\alpha]_D$ +110°, undepressed on admixture with a sample prepared in method (a) and markedly depressed (119–124°) on admixture with 6α-fluoroprogesterone (XXIV).

Isomerization of 6β-fluoroprogesterone (XXVI). 6β-Fluoroprogesterone (100 mg) in acetic acid (15 cm³) at 15° was treated with a steady stream of dry hydrogen chloride for 90 min. After keeping at room temperature for an additional 90 min, water was added. Isolation with ether afforded 6α-fluoroprogesterone (XXIV), m.p. 138–142°, $[\alpha]_D$ +188°, raised by crystallization from hexane–ether to 143–145°, undepressed on admixture with an authentic sample.