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STEROIDS—CXX[1] SYNTHESIS OF HALOGENATED STEROID HORMONES

NEW ROUTES TO 6α-FLUOROTESTOSTERONE AND THE 6α- AND 6β-FLUORO ANALOGS OF PROGESTERONE. THE SYNTHESIS OF 6α- AND 6β-FLUORO REICHSTEIN'S COMPOUND "S" AND 6α- AND 6β-FLUORODESOXYCORTICOSTERONE ACETATE[2]

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Abstract—The conformational and electronic factors involved in the fission of steroid 5α,6α-epoxides with boron trifluoride-etherate are discussed with particular reference to C-3-keto-5α,6α-epoxides and their cycloethylene-dioxy derivatives.

These considerations led to the development of a new synthesis of 6-fluoro-Δ^4-3-ketones from the corresponding Δ^4-3-ketones via the boron trifluoride-etherate cleavage of their derived cycloethylene-ketal-5α,6α-epoxides.

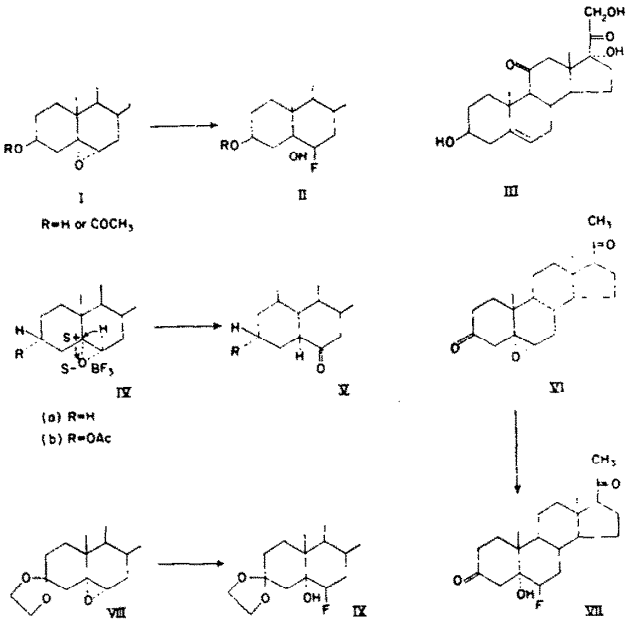
Application of this method led to the synthesis of 6α-fluorotestosterone and the 6α and 6β-fluoro analogs of progesterone desoxycorticosterone acetate and Reichstein's Compound "S" diacetate. The latter compound and its Δ^1-analog are valuable precursors for the 6-fluoro cortical hormones.

RECENTLY we described methods leading to the synthesis of the 6α- and 6β-fluoro analogs of testosterone and progesterone.[3] The introduction of the fluorine atom involved the rupture of a 3β-hydroxy-5α,6α-epoxide (or its derived acetate) with boron trifluoride etherate[3,4] to afford the corresponding 5α-hydroxy-6β-fluoro compound, (Fig. 1; I → II). In every case the precursor for the epoxide was the appropriate Δ^5-3β-alcohol. Although these compounds are readily accessible in most series, the synthesis of 6-fluorocortisone, for example, by application of this general method would necessitate as a precursor the Δ^5-3β-alcohol (III). However, such an intermediate is not readily available, and for this and other reasons it was desirable to develop alternate routes to 6-fluoro-Δ^4-3-ketones which could eventually be utilized for the synthesis of the C-6-fluoro-cortical hormones.

The fission of a steroid 5α,6α-epoxide with boron trifluoride has been shown to afford either the C-6 ketone (rings A/B *cis*) (Fig. 1; IV → V) or the diaxial 5α-hydroxy-6β-fluoro compound (I → II) depending upon the nature and stereochemistry of the substituent at C-3.[3,4] An epoxide unsubstituted at C-3 (IVa) or carrying a 3α-acetoxyl group (IVb) affords as the major product the corresponding C-6 ketone (V).[4] However, a 3β-hydroxy-epoxide (or its acetate ester) (I) undergoes fission by a completely different mechanism, and the major product is the fluorohydrin (II).[3,4]

Henbest and Wrigley[4] explained these results from a consideration of the electronic

[1] Part CXIX: J. A. Zderic, H. Carpio and C. Djerassi, *J. Org. Chem.* **24**, 909 (1959).
[2] Presented in part by A.B. at the Steroids and Natural Products Section of the Gordon Research Conference, August 1958.
[3] A. Bowers and H. J. Ringold, *Tetrahedron* **3**, 14 (1958).
[4] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).



I, II, IV, V, VIII, and IX represent partial steroid formulae

FIG. 1.

and the conformational factors involved. In the unsubstituted epoxide, boron trifluoride induces partial ionization of the bond from the epoxide oxygen to the more alkylated C-5 position, promoting a concerted 1,2-hydride shift with concomitant formation of the C-6 ketone (A/B-*cis*) (IV → V).

However, in the case of a 3β-alcohol or its ester two factors oppose the formation of the C-6 ketone. Firstly, the partial ionization of the epoxide oxygen-C-5 bond (necessary for C-6 ketone formation) is reduced by the magnified inductive effect (—I) of the boron-trifluoride co-ordinated C-3(β) alcohol or ester. Secondly, the formation of a C-6 ketone (rings A/B *cis*) would markedly increase the non-bonded interactions in ring A, for the 3β-hydroxyl group would then be axially orientated Thus, an alternative, secondary reaction leading to fluorohydrin formation predominates.

In the case of a 3α-acetate (axial)-5α,6α-epoxide (IVb) the electronic and conformational factors are in direct opposition, but the —I effect of the axial acetate group is not sufficient to overcome (a) the gain in energy resulting from the axial acetate group assuming an equatorial conformation upon C-6 ketone formation, and (b) the unfavorable 1,3-diaxial interaction (3α,5α-diol) which would result if fluorohydrin formation occurred. The net result is the formation of the C-6 ketone in very high yield.

In an attempt to assess the relative importance of the electronic factors, we studied the fission of a C-3-keto-5α,6α-epoxide with boron trifluoride. In this system the conformational factors outlined above which influenced the fission of both the 3α-acetoxy and the 3β-acetoxy epoxides are absent, and it is the balance between the boron trifluoride induced ionization of the C-5-epoxide oxygen and its inhibition by the —I effect of the ketone which determines the course and products of the

reaction. The inductive influence clearly predominated since treatment of 5α,6α-oxidopregnan-3,20-dione (VI)[5] with boron trifluoride-etherate afforded in 44 per cent yield the fluorohydrin (VII), identical with an authentic specimen.[3] This result indicated that fluorohydrin formation should be the major reaction for 5α,6α-epoxides which are substituted at C-3 by a group which (after co-ordination with boron trifluoride) will exert a reasonably strong —I effect, and in which there are no powerful conformational factors in opposition.

With this information available, we considered that a 3-cycloethylene-ketal-5α,6α-epoxide (VIII) should be a suitable substrate for conversion into a fluorohydrin. After coordination with two molecules of electron deficient boron trifluoride, it would be a reasonably strong —I group, and its symmetrical nature about C-3 would eliminate such conformational factors as an axial group becoming equatorial, and vice versa. This conclusion was verified experimentally. In four series investigated a reasonable yield of the fluorohydrin (IX) was obtained from the appropriate 3-cycloethylene-ketal-5α,6α-epoxide (VIII). The fluorohydrins were then converted into 6-fluoro-Δ^4-3-ketones by acid treatment as described in the sequel.

An alternate general method for the synthesis of 6-fluoro-Δ^4-3-ketones was thus available which did not require a Δ^5-3β-alcohol as a precursor. The ketal-epoxides can be prepared from the appropriate, readily available Δ^4-3-ketones by ketalization and epoxidation.

This paper describes the application of this method for the synthesis of 6α-fluorotestosterone and the 6α- and 6β-fluoro analogs of progesterone, Reichstein's Compound "S" and desoxycorticosterone acetate.

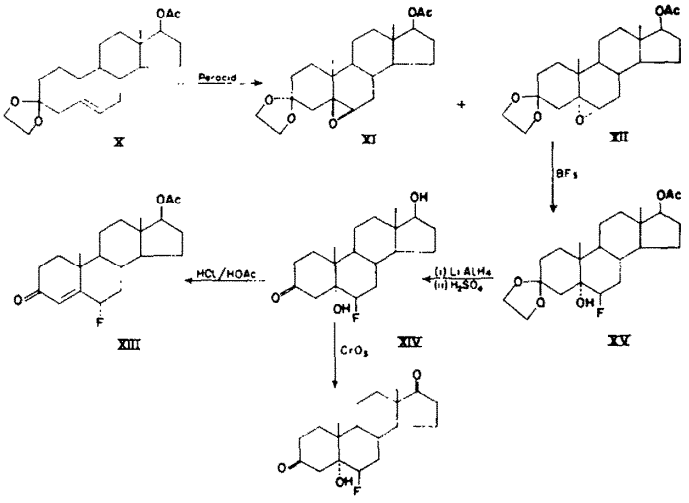


FIG. 2.

Epoxidation of testosterone acetate ketal (X)[6] (Fig. 2) with permonophthalic acid afforded a mixture of the 5β,6β-epoxide (XI) and the 5α,6α-epoxide (XII) which could be separated by chromatography over alumina. The structure proof and configurations assigned to these two epoxides followed from their mode of preparation

[5] B. Ellis and V. Petrow, *J. Chem. Soc.* 4417 (1956).
[6] R. Antonucci, S. Bernstein, R. Littel, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1341 (1952).

elemental analysis, their relative polarities towards alumina and a comparison of their molecular rotations. It is known that the epoxidation of Δ^5-3β-alcohols and their esters always leads to a mixture of epoxides with the α-epoxide being predominant. Examples taken from three different series, namely the α and β-epoxides derived

TABLE 1. MOLECULAR ROTATION DIFFERENCES BETWEEN 3-CYCLOETHYLENE-KETAL-5α,6α AND 5β,6β-EPOXIDES

Compound		M_D	$\Delta M_D(\alpha - \beta)$
Testosterone acetate-3-ketal	α-Epoxide[a]	−243	−208
	β-Epoxide[a]	−35	
Progesterone-3,20-bisketal	α-Epoxide[a,b]	−209	−209
	β-Epoxide[a]	±0	
Compound S diacetate-3-mono-ketal	α-Epoxide[a]	−383	−383
	β-Epoxide[a]	±0	
Desoxicorticosterone acetate-3-mono-ketal	α-Epoxide[a]	+86	−145
	β-Epoxide[a]	+251	
21-Desoxycortisone-3,20-bisketal	α-Epoxide[c]	−177	−159
	β-Epoxide[c]	−18	
17α-Hydroxyprogesterone-3,20-bisketal	α-Epoxide[d]	−252	−196
	β-Epoxide[d]	−56	
11α-Acetoxyprogesterone-3,20-bisketal	α-Epoxide[e]	−256	−174
	β-Epoxide[e]	−82	

[a] This paper. [b] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957). [c] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 3091 (1958). [d] J. A. Edwards and H. J. Ringold, forthcoming publication. [e] 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).

from cholesterol,[7] Δ^5-androstene-17-one[8] and Δ^5-pregnene3β,21-diol-20-one diacetate,[9] show that the α-epoxide is always more polar towards alumina and has a more levorotatory specific rotation than the epimeric β-epoxide. Sufficient evidence is now available to demonstrate that these characteristic differences also apply to C-3-cycloethylene-ketal-5,6-epoxides. In Table 1 the molecular rotations of a series of epimeric 3-ketal-5,6-epoxides are collected. In every case the α-epoxide is considerably more levorotatory than the β-epimer. In addition the β-epoxides were

[7] P. A. Plattner, T. Petrzilka and W. Lang, *Helv. Chim. Acta* **27**, 513 (1944).
[8] L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta* **27**, 503 (1944).
[9] L. Ruzicka, P. A. Plattner, H. Heusser and V. Ernst, *Helv. Chim. Acta* **29**, 248 (1946).

isolated from the mixture by chromatography over alumina, and in every case the β-epoxide was the less polar of the two compounds. It is possible to conclude therefore, that in any mixture of epimeric 5,6-epoxides, one can confidently define the stereochemistry of each epimer by rotation measurements and the behaviour of the mixture on chromatography over alumina.

Fission of the α-epoxide of testosterone acetate 3-cycloethylene ketal (XII) with boron trifluoride-etherate in an ether-benzene solution smoothly afforded the corresponding 6β-fluoro-5α-hydroxy-fluorohydrin (XV). Hydrolysis of the 17β-acetate group of XV with lithium aluminum hydride and mild acid hydrolysis of the ketal group led to 6β-fluoro-androstan-5α,17β-diol-3-one (XIV). Oxidation of XIV with 8 N chromic acid in acetone solution readily gave the 3,17-diketone (XVI) which was identical in every respect with an authentic specimen.[3] Treatment of XIV with anhydrous hydrogen chloride in acetic acid for 5 hr led to dehydration of the tertiary hydroxyl group at C-5, inversion of the fluorine atom from 6β to 6α[3] and acetylation of the 17β-hydroxyl group to afford in good yield 6α-fluorotestosterone acetate (XIII), identical with an authentic sample prepared by the acetylation of 6α-fluorotestosterone.[3]

Similarly 6α-fluoroprogesterone was prepared by this general method. Progesterone-bisketal[10] (XVII; Fig. 3) underwent epoxidation to give the expected mixture of α and β-epoxides.

However, in addition to the two epoxides XVIII and XIX a by-product was isolated which displayed a strong carbonyl band at 1700 cm^{-1} in the infrared which could be attributed to an unconjugated keto group at either or C-3 or C-20. Taken in conjunction with the elemental analysis this evidence indicated that the compound

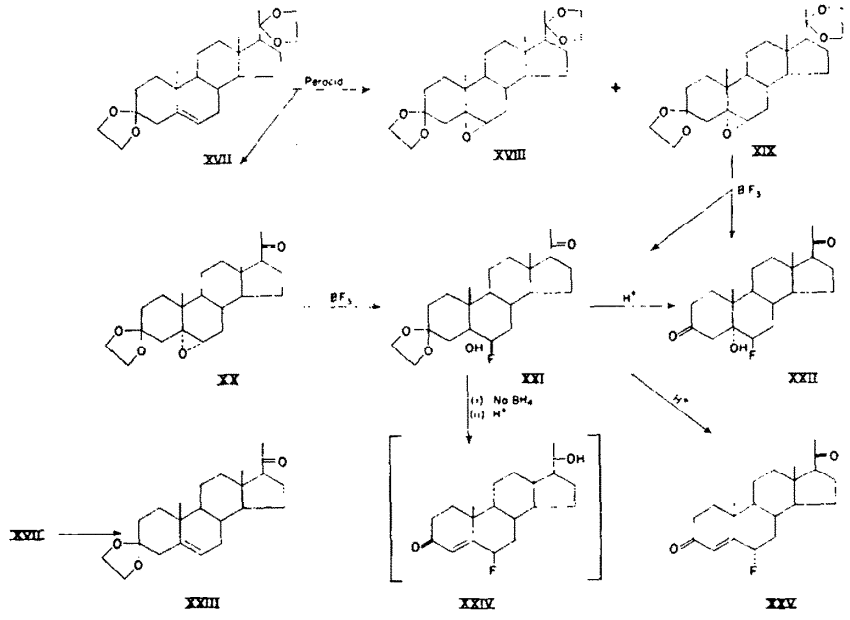


FIG. 3.

[10] [a] R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1369 (1952); [b] W. S. Allen, S. Bernstein and R. Littel, *J. Amer. Chem. Soc.* **76**, 6116 (1954).

was a monoketal-5,6-epoxide. Presumably the acid medium of the epoxidation reaction was sufficient to partially hydrolyze one of the ketal groups. This compound could have one of four possible structures, being either a 5α,6α epoxide or a 5β,6β-epoxide with a free carbonyl group at C-3 or C-20. As will be shown in the sequel its structure was shown to be 5α,6α-oxidopregnan-3,20-dione-3-cycloethylene-ketal (XX).

Treatment of XX with boron trifluoride-etherate in benzene–ether solution led in 51 per cent yield to the fluorohydrin (XXI) which was smoothly hydrolyzed with *p*-toluenesulphonic acid and acetone to afford 6β-fluoro-5α-hydroxypregnan-3,20-dione (XXII) identical in every respect with an authentic sample.[3] Under more vigorous acid conditions, namely hydrogen-chloride in acetic acid, XXI directly afforded 6α-fluoroprogesterone (XXV).[3] These two experiments clearly demonstrated the α-configuration for the epoxide in the original monoketal-epoxide (XX)[11] but did not discriminate between the two alternate possibilities for the position of the keto group (i.e. at C-3 or C-20). To establish this point the derived fluorohydrin (XXI) was reduced with sodium borohydride and the crude product, which did not exhibit any carbonyl absorption in the infrared, was treated with anhydrous hydrogen chloride in acetic acid for 4 hr at room temperature. The resulting product (XXIV) had maximum absorption in the ultraviolet at 234–236 mμ, ε 9,970 and bands in the infrared at 1670 and 1615 cm^{-1}. This spectral data can only be interpreted on the basis of the assigned formulas for XX, XXI and XXIV.

The boron trifluoride-etherate fission of the bisketal-5α,6α-epoxide (XIX) was then studied and rather surprisingly none of the corresponding 5α-hydroxy-6β-fluoro-3,20-bisketal could be isolated. Instead we obtained two products; the major one, being formed in 46 per cent yield was the monoketal fluorohydrin (XXI) identical in every respect with the compound obtained from the boron trifluoride cleavage of the monoketal-epoxide (XX). The minor product, isolated in 9 per cent yield was the diketo-fluorohydrin (XXII). The transformation of XXII into 6β-fluoroprogesterone has been described previously.[3]

The facile selective hydrolysis of the C-20 ketal group by boron trifluoride etherate suggested a new and more convenient route for the preparation of the C-3 monoketal of progesterone (XXIII) than those described previously.[12] The bisketal of progesterone (XVII) can be obtained in high yield from progesterone[13] and when it was treated with boron trifluoride etherate in an ether–benzene solution the C-3 monoketal (XXIII), identical with an authentic sample,[12] was obtained in 82 per cent yield together with a 6 per cent yield of progesterone.

In Fig. 4 the approaches used to prepare the 6α and 6β-fluoro analogs of desoxycorticosterone acetate and Compound "S" are outlined. The starting materials were desoxycorticosterone acetate (XXVIa) and Compound "S" 17,21-diacetate (XXVIb) respectively. In each case the 3-monoketals XXVII (a and b) were prepared by the dioxolane method,[14] whence permonophthalic acid oxidation, chromatographic separation of the epimeric α- and β-epoxides (XXXI) and (XXVIII) and fission of the

[11] 3β-Acetoxy-5β,6β-epoxides are known to afford 5α-fluoro-6β-hydroxy fluorohydrins upon treatment with boron trifluoride etherate.[4]

[12] F. Sondheimer, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 192 (1955).

[13] In Ref. 10b the authors report a 79 per cent yield, but even higher yields (85–90%) have been obtained for this reaction; private communication from Dr. J. A. Zderic.

[14] H. Dauben, B. Loken and H. J. Ringold, *J. Amer. Chem. Soc.* **76**, 1359 (1954).

α-epoxides (XXXIa and b) with boron trifluoride-etherate followed the usual procedure. Treatment of the derived ketal-fluorohydrin (XXXa) in the desoxycorticosterone acetate series with hydrogen chloride in acetic acid for 4 hr smoothly led to 6α-fluorodesoxycorticosterone acetate (XXXIV). In the Compound "S" diacetate series mild hydrolysis of XXXb with *p*-toluenesulphonic acid hydrate and acetone afforded the 3-keto-fluorohydrin (XXIX). This compound gave 6α-fluoro-Compound "S" diacetate (XXXVa) after treatment for 4 hr with hydrogen chloride in acetic acid.

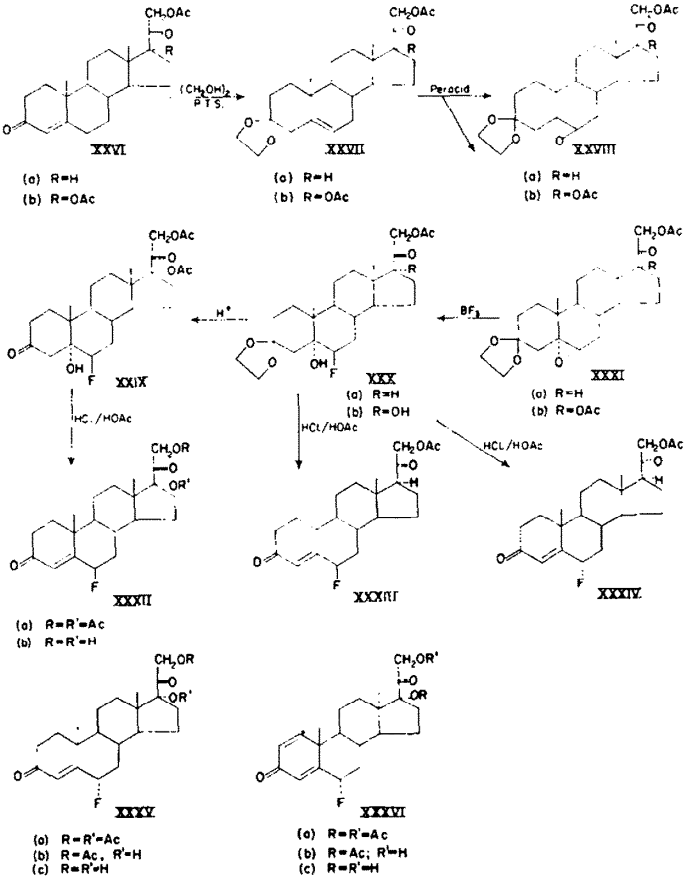


FIG. 4.

Attempts were then made to prepare 6β-fluoro-Compound "S" 17,21-diacetate (XXXIIa) by dehydration of the 3-ketofluorohydrin (XXIX) without concomitant inversion of the fluorine atom. Mild alkaline dehydration had been used successfully for the synthesis of 6β-fluoroprogesterone[3] but the instability of the dihydroxyacetone side-chain precluded its use in this series in other than low yield. However, replacement of acetic acid by anhydrous and alcohol free chloroform in the hydrogen chloride catalyzed dehydration was successful and 6β-fluoro-Compound "S" diacetate (XXXIIa) was obtained as the major product of the reaction. Unfortunately, this

[15] The lack of reproducibility in the epimerization of the 6β- to the 6α-fluoro compounds with "alcohol free" chloroform is reminiscent of the related epimerizations of 6β- to 6α-hydroxy-Δ^4-3-ketones, cf. P. T. Herzig and M. Ehrenstein, *J. Org. Chem.* **16**, 1050 (1951).

reaction was capricious and sometimes the only product isolated was the epimeric 6α-fluoro compound (XXXVa).[15] A reproducible method of preparation was developed when a careful study was made of the acetic acid-hydrogen chloride reaction. It was observed that after 25 min reaction time the product had maximum absorption at 232–234 mμ, $\varepsilon = 10{,}000$. Accordingly, if the reaction was stopped after this period 6β-fluoro-Compound "S" diacetate (XXXIIa) could be isolated in 60 per cent yield. Further treatment of XXXIIa with hydrogen-chloride in acetic acid readily converted it into the epimeric 6α-fluoro-Δ^4-3-ketone (XXXVa). Application of this method to XXXa led to 6β-fluorodesoxycorticosterone acetate (XXXIII).

TABLE 2. MOLECULAR ROTATION AND U.V. LIGHT ABSORPTION DIFFERENCES BETWEEN EPIMERIC 6α AND 6β-FLURO-Δ^4-3-KETONES

Compound	M_D	$\Delta M_D(6\alpha - 6\beta)$	λ_{max}	ε_{max}
6α-Fluorotestosterone[3]	−312	+312	237 mμ	14,450
6β-Fluorotestosterone[3]	±0		234 mμ	12,300
6α-Fluoro-Δ^4-androstene-3,17-dione[3]	+561	+327	235 mμ	15,490
6β-Fluoro-Δ^4-androstene-3,17-dione[3]	+234		234 mμ	12,590
6α-Fluoroprogesterone[3]	+660	+322	236 mμ	15,490
6β-Fluoroprogesterone[3]	+338		235 mμ	13,180
6α-Fluoro-Compound S 17,21-diacetate[a]	+232	+293	236 mμ	15,490
6β-Fluoro-Compound S 17,21-diacetate[a]	−61		233 mμ	11,220
6α-Fluoro-Compound S[a]	+491	+406	236 mμ	16,220
6β-Fluoro-Compound S[a]	+85°		234 mμ	12,300
6α-Fluorodesoxy-corticosterone acetate[a]	+624	+285	236 mμ	15,490
6β-Fluorodesoxy-corticosterone acetate[a]	+339		234 mμ	10,230

[a] This paper.

From a study of several pairs of 6α and 6β-fluoro-Δ^4-3-ketones two characteristic differences between the C-6 epimers have emerged. The rotatory dispersion curve of a 6α-fluoro-Δ^4-3-ketone is very similar to that of the non-fluorinated parent compound,[16] whereas the 6β-fluoro-compound exhibits striking differences. At the sodium-D-line the molecular rotation difference [ΔM_D (6α-6β)] ranges from +293 to +406 (see Table 2). Secondly, although the difference in the position of maximum absorption of the two series in the ultraviolet is quite small (usually 1–3 mμ) an appreciable difference in the intensities has been observed (see Table 2). The 6α-fluoro-Δ^4-3-ketones exhibit maximum ε values from 14,450 to 16,220, whereas the

[16] C. Djerassi, J. Osiecki, R. Riniker and B. Rinker, *J. Amer. Chem. Soc.* **80**, 1216 (1958).

6β-fluoro-Δ^4-3-ketones have a much less intense maximum absorption, ranging from 10,230 to 13,180 (see Table 2).

In accordance with these characteristics 6α-fluoro-Compound "S" diacetate (XXXVa) had a rotatory dispersion curve virtually identical to that of Compound "S" diacetate and exhibited maximum ultraviolet absorption at 236 mμ, $\varepsilon = 15{,}490$, whereas 6β-fluoro-Compound "S" diacetate (XXXIIa) had a strikingly different rotatory dispersion curve and exhibited maximum absorption at 234 mμ, $\varepsilon = 11{,}220$. The 6α and 6β-fluoro analogs of desoxycorticosterone acetate (XXXIV) and (XXXIII) also had light absorption properties and rotatory dispersion curves in full accord with their assigned structures.

Mild alkaline hydrolysis of 6α-fluoro-Compound "S" diacetate (XXXVa) afforded 6α-fluoro-Compound "S" (XXXVc) characterized as the C-21-mono acetate (XXXVb). Similarly XXXIIa readily gave 6β-fluoro compound "S" (XXXIIb).

Selenium dioxide oxidation[17] of 6α-fluoro-Compound "S" diacetate (XXXVa) in tertiary butanol smoothly yielded the corresponding Δ^1-analogue (XXXVIa) which upon mild hydrolysis gave Δ^1-6α-fluoro-Compounds S (XXXVIc), characterized as the C-21 mono acetate (XXXVIb).

The syntheses of these C-6 fluoro analogs of Compound "S" and their Δ^1-derivatives made available substrates which by biochemical methods have been directly converted into 6α-fluoro-hydrocortisone and 6α-fluoroprednisolone and hence indirectly into the cortisone and prednisone analogs. These studies will form the basis of a future publication.

EXPERIMENTAL

Melting points are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. The rotatory dispersion measurements were obtained with a Rudolph Spectropolarimeter in dioxane solution using a xenon arc lamp (250–350 mμ) and a zirconium arc lamp (350–700 mμ). We are grateful to Dr. L. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin Elmer Model 21 spectrophotometer with a sodium chloride prism. The alumina used for chromatography had been suspended in boiling ethyl acetate solution for 6 hr, filtered and dried for 36 hr at 100°. The elemental analyses were carried out by Mr. J. F. Alicino Metuchen, N. Jersey and Dr. A. Bernhadt, Mulheim, Ruhr, Germany.

Boron trifluoride cleavage of 5α,6α-*oxidopregnan*-3,20-*dione* (VI)

Boron trifluoride etherate (0·5 cc) was added to a solution of 5α,6α-oxidopregnane-20-one[5] (500 mg) in benzene-ether (1 : 1; 50 cc). After keeping at room temp for 3 hr the solution was washed with 5% sodium carbonate solution and water and finally dried over sodium sulphate. Removal of the solvent afforded a product which was adsorbed from benzene (300 cc) onto alumina (30 g). Elution with benzene–ether (90 : 10; 600 cc) afforded 6β-fluoropregnan-5α-ol-3,20-dione (VII) (220 mg) m.p. 265–270°, raised by crystallization from aqueous pyridine to 276–279°, undepressed on admixture with an authentic sample.[a] The infrared spectra of the two compounds were identical.

Peracid oxidation of testosterone acetate (X)

Permonophthalic acid (3·5 g) in ether (100 cc) was added to a solution of testosterone acetate cycloethylene-ketal (X) (4·0 g) in chloroform (100 cc) at 0° over 10 min. After keeping at 0° for 16 hr the solution was washed with cold sodium carbonate solution (5%) until it was free of acid and then washed with water and finally dried over sodium sulphate. Removal of the solvent afforded a product which was adsorbed from benzene–hexane (50 : 50; 100 cc) onto neutral alumina (200 g). Elution with benzene–hexane (50 : 50; 400 cc) and benzene (400 cc) afforded after one crystallization from benzene–hexane 5β,6β-*oxidoandrostan*-17β-*ol*-3-*one*-3-*cycloethylene*-*ketal* 17-*acetate* (XI)

[17a] H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.* **21**, 239 (1956). [b] Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta* **39**, 734 (1956). [c] S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. Van Dorp, *Rec. Trav. Chim.* **75**, 475 (1956).

(950 mg) m.p. 141–143°, raised by crystallizations from benzene–hexane to 146–148°, $[\alpha]_D$ −9°. (Found: C, 71·02; H, 9·04; O, 20·10. $C_{23}H_{34}O_5$ requires: C, 70·74; H, 8·78; O, 20·48%).

Further elution with benzene–ether (90 : 10; 1·6 l.) gave after one crystallization from benzene–hexane 5α,6α-*oxidoandrostan*-17β-*ol*-3-*one*-3-*cycloethylene-ketal* 17-*acetate* (XII) (1·5 g), m.p. 182–184°, raised by several crystallizations to 184–185°, $[\alpha]_D$ −88°. (Found: C, 70·52; H, 8·71; O, 20·41. $C_{23}H_{34}O_5$ requires: C, 70·74; H, 8·78; O, 20·48%).

6β-Fluoroandrostan-5α,17β-*diol*-3-*cycloethylene-ketal* 17-*acetate* (XV)

Boron trifluoride-etherate (0·25 cc) was added to a solution of the 5α,6α-epoxide (XII) (250 mg) in benzene–ether (1 : 1; 30 cc) and kept at 20° for 4 hr. After washing the solution with water (4 × 20 cc) and drying (Na_2SO_4), removal of the solvent gave a product which was adsorbed from benzene (20 cc) onto alumina (15 g). Elution with benzene (100 cc) afforded 6β-*fluoroandrostan*-5α,17β-*diol*-3-*cycloethylene-ketal* 17-*acetate* (XV) (130 mg) m.p. 157–160°, raised by crystallizations from benzene–hexane to 162–164°. (Found: C, 66·19; H, 8·55; F, 4·16. $C_{23}H_{35}O_5F$. $\frac{1}{2}CH_3OH$ requires: C, 66·11; H, 8·75; F, 4·45%).

6β-Fluoroandrostan-5α,17β-*diol*-3-*one* (XIV)

The monoketal-17-acetate (XV) (400 mg) in dry ether (30 cc) was added over 5 min with stirring to a suspension of lithium aluminum hydride (300 mg) in ether (30 cc) at room temp. After stirring at room temp for a further 30 min the excess of reagent was destroyed with ethyl acetate. Isolation of the product using the saturated sodium sulphate technique[18] afforded a product which without further purification was dissolved in methanol (15 cc) containing 1 cc of aqueous sulphuric acid (8%v/v) and heated under reflux for 35 min. Addition of water and filtration afforded a crude product (230 mg) m.p. 180–185° λ_{max}^{EtOH} 232–234 mμ, ε 3,160. One crystallization from acetone–hexane afforded 6β-*fluoroandrostan*-5α,17β-*diol*-3-*one* (XIV) m.p. 207–210°, λ_{max}^{EtOH} 232–234 mμ, ε 347. The analytical sample had m.p. 220–222°, $[\alpha]_D$ +15° and did not exhibit selective absorption in the ultraviolet; λ_{max}^{KBr} 1690 and 3325 cm^{-1}. (Found: C, 70·66; H, 9·00; F, 4·86. $C_{19}H_{29}O_3F$ requires: C, 70·34; H, 9·00; F, 5·85%).

6α-*Fluorotestosterone acetate* (XIII)

(a) 6β-Fluoroandrostan-5α,17β-diol-3-one (XIV) (150 mg) in acetic acid (10 cc) at 15–20° was treated with a steady stream of dry hydrogen chloride for 30 min and then kept at room temp for a further 5 hr. Addition of water and filtration afforded 6α-*fluorotestosterone acetate* (XIII) (100 mg) m.p. 160–169°, raised by crystallizations from benzene–hexane to 176–178°, $[\alpha]_D$ +98°. λ_{max}^{EtOH} 236 mμ, ε 15,500; λ_{max}^{KBr} 1740, 1680 and 1620 cm^{-1}. (Found: C, 72·31; H, 8·68; F, 5·84. $C_{21}H_{29}O_3F$ requires: C, 72·38; H, 8·38; F, 5·45%).

(b) Acetic anhydride (0·5 cc) was added to a solution of 6α-fluorotestosterone[3] (100 mg) in pyridine (3 cc). After keeping at 20° for 17 hr addition of water and filtration afforded the 17-acetate (XIII) (85 mg) m.p. 170–176°, raised by crystallizations from acetone–hexane to 175–177°, undepressed on admixture with the product prepared as in method (a). The infrared spectra were identical.

6β-Fluoroandrostan-5α-*ol*-3,17-*dione* (XVI)

A solution of 6β-fluoroandrostane-5α,17β-diol-3-one (XIV) (100 mg) in acetone (10 cc) was oxidized with 8 N-chromic acid in the usual way.[19] After precipitation with water filtration afforded 6β-fluoroandrostane-5α-ol-3,17-dione (XVI) (80 mg) m.p. 210–215°, raised by crystallizations from acetone–hexane to 233–235°, undepressed on admixture with an authentic sample,[8] $[\alpha]_D$ +90°. The infrared spectra of the two compounds were identical.

Peracid oxidation of progesterone 3,20-*bisketal* (XVII)

Permonophthalic acid[20] (29 g) in ether (400 cc) was added over 15 min to a solution of progesterone-bisketal[19] (XVII) (30 g) (m.p. 190–192° and having no carbonyl band in the infrared) in chloroform

[18] C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, *J. Amer. Chem. Soc.* **76**, 2969 (1954).
[19a] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* **39**, (1946); [b] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *Ibid*, 2548 (1953).
[20] Prepared according to the method of E. A. Royals and L. L. Harrel, Jr., *J. Amer. Chem. Soc.* **77**, 3405 (1955).

(750 cc) at 0°. After keeping at 0–5° for 16 hr the solution was washed with 5% sodium carbonate solution (3 × 200 cc), water (4 × 100 cc) and dried over sodium sulphate. Removal of the solvent afforded a product which was adsorbed from benzene–hexane (50 : 50; 500 cc) onto neutral alumina (1·5 K). Elution with benzene (2 l.) afforded *5β,6β-oxidopregnan*-3,20-*biscycloethylene-ketal* (XVIII) (8·5 g) m.p. 151–156°, raised by crystallizations from hexane to 161–163°, $[\alpha]_D \pm 0°$. (Found: C, 71·42; H, 8·98; O, 19·51. $C_{25}H_{36}O_5$ requires: C, 71·74; H, 9·15; O, 19·11%).

Further elution with benzene (3 l.) and benzene–ether (90 : 10; 2·5 l.) afforded 5α,6α-oxidopregnan-3,20-biscycloethylene-ketal (XIX) 13·5 g) m.p. 154–168°, raised by three crystallizations from ethyl acetate–hexane to 178–181°, $[\alpha]_D$ −48°, (7·3 g). Further crystallizations raised the m.p. to 183–185°, $[\alpha]_D$ −50°. Lit.[21] records m.p. 186–187°, $[\alpha]_D$ −51°.

The mother liquors from the crystallizations of the bisketal-α-epoxide were combined and the product was rechromatographed over alumina (300 g). Elution with benzene (2·2 l.) afforded 5α,6α-oxidopregnan-20-one-3-cycloethylene ketal (XX) (3·3 g) m.p. 152–175°, raised by three crystallizations from ethyl acetate to 190–193° (1·24 g). The analytical sample had m.p. 197–199°, $[\alpha]_D$ +11°. λ_{max}^{KBr} 1695 and 1097 cm^{-1}. (Found: C, 73·68; H, 8·94; O, 17·34. $C_{23}H_{34}O_4$ requires: C, 73·76; H, 9·15; O, 17·09%).

6β-Fluoropregnan-5α-ol-20-one-3-cycloethylene-ketal (XXI)

Boron trifluoride-etherate (1·0 cc) was added to a solution of the 3-monoketal-α-epoxide (XX) (0·95 g) in benzene–ether (50 : 50; 100 cc). After 16 hr at room temp the solution was washed with water (4 × 50 cc), dried over sodium sulphate and evaporated to afford a residue which was adsorbed from benzene–hexane (50 : 50; 100 cc) onto alumina (100 g). Elution with benzene–hexane (50 : 50; 400 cc) afforded *6β-fluoro-pregnan-5α-ol-20-one-3-cycloethylene-ketal* (XXI) (500 mg) m.p. 132–140°, raised by several crystallizations from benzene–hexane to 145–147°, $[\alpha]_D$ +38°; λ_{max}^{KBr} 3550 and 1710 cm^{-1}. (Found: C, 69·68; H, 8·93; F, 4·57. $C_{23}H_{35}O_4F$ requires: C, 70·01; H, 8·94; F, 4·82%).

The reduction and acid treatment of 6β-fluoropregnan-5α-ol-20-one-3-cycloethylene ketal (XXI)

Sodium borohydride (100 mg) in water (0·25 cc) and dioxane (2 cc) was added to a solution of the fluorohydrin-monoketal (XXI) (100 mg) in dioxane (5 cc). After 2 hr at room temp addition of water and isolation with ethyl acetate afforded a product which did not exhibit any carbonyl absorption in the infrared. The total product in acetic acid (2·0 cc) was treated with a dry stream of hydrogen chloride for 15 min and then kept at room temp for a further 3 hr. Addition of water and isolation with ether afforded a product λ_{max}^{EtOH} 234–236 mμ, ε 9970; λ_{max}^{KBr} 1670 and 1615 cm^{-1}.

6β-Fluoropregnan-5α-ol-3,20-dione (XXII)

6β-Fluoropregnan-5α-ol-20-one-3-cycloethylene-ketal (XXI) (50 mg) in acetone (5cc) containing *p*-toluenesulphonic acid hydrate (5·0 mg) was kept at 20° for 16 hr. Evaporation of the acetone and crystallization of the residue from aqueous pyridine afforded 6β-fluoropregnan-5α-ol-3,20-dione (XXII) (20 mg), m.p. 278–282°, undepressed on admixture with an authentic sample.[3] The infrared spectra of the two compounds were identical.

6α-Fluoroprogesterone (XXV)

6β-Fluoropregnan-5α-ol-20-one-3-cycloethylene-ketal (XXI) (250 mg) in acetic acid (15 cc) at 15–20° was treated with a steady stream of dry hydrogen chloride for 30 min and then kept at 20° for 4½ hr. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene–hexane (50 : 50; 20 cc) onto alumina (10 g). Elution with benzene–hexane (50 : 50; 350 cc) afforded 6α-fluoroprogesterone (XXV) (170 mg) m.p. 90–115°, raised by crystallizations from acetone–hexane to 146–147°, (90 mg); m.p. was undepressed on admixture with an authentic sample.[3] The infrared spectra of the two samples were identical.

Boron trifluoride-etherate fission of progesterone-α-epoxide-3,20-biscycloethylene ketal (XIX)

Boron trifluoride-etherate (1·25 cc) was added to a solution of the 5α,6α-epoxide (XIX) (1·0 g) in benzene–ether (1 : 1; 100 cc) and kept at room temp for 2½ hr. After washing the solution with

[21] G. Cooley, B. E. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).

5% sodium carbonate solution (2 × 50 cc) and water (3 × 100 cc) and drying (Na_2SO_4) the solution was diluted with benzene (150 cc), concentrated to 100 cc and then adsorbed onto alumina (50 g). Elution with benzene (400 cc) afforded 6β-fluoropregnan-5α-ol-20-one-3-cycloethylene-ketal (XXI) (460 mg) m.p. 128–133°, raised by several crystallizations from benzene–hexane and methanol–water to 144–146° undepressed on admixture with the sample prepared as described above. The infrared spectra of the two samples were identical.

Further elution with benzene–ether (90 : 10; 250 cc) afforded after one crystallization from ethyl acetate–pyridine 6β-fluoropregnan-5α-ol-3,20-dione (XXII) (90 mg) m.p. 278–279 undepressed on admixture with an authentic specimen;[3] $[\alpha]_D$ +76° (pyridine). The infrared spectra were identical.

Boron trifluoride-etherate treatment of progesterone-biscycloethylene-ketal (XVII)

Boron trifluoride-etherate (0·5 cc) was added to a solution of progesterone biscycloethylene-ketal[10] (XVII) (500 mg) (m.p. 177–179°; $[\alpha]_D$ −29°; no carbonyl bond in the infrared) in dry benzene–ether (1 : 1; 50 cc). After 2 hr at room temp the solution was washed with 5% sodium bicarbonate solution (25 cc) and water (3 × 50 cc) and then dried (Na_2SO_4) and the solvent removed under vacuo. The product in benzene–hexane (1 : 1; 50 cc) was adsorbed onto alumina (30 g). Elution with benzene–hexane (350 cc) afforded Δ⁵-pregnen-20-one-3-cycloethylene-ketal (XXIII) (360 mg) m.p. 175–177°, raised by one crystallization from benzene–hexane to 178–180°, undepressed on admixture with an authentic sample,[12] $[\alpha]_D$ +47°; +45° (pyridine). It exhibited no selective absorption in the ultraviolet λ_{max}^{KBr} 1710 cm^{-1} Lit[12] reports m.p. 180–181°, $[\alpha]_D$ +53° (pyridine).

Further elution with benzene (200 cc) afforded progesterone (65 mg) m.p. 114–117°, λ_{max}^{EtOH} 240–242 mμ, ε 16,200. After one crystallization from methanol–water it had m.p. 120–121°, undepressed on admixture with an authentic sample of progesterone.

Peracid oxidation of desoxycorticosterone acetate 3-monocyclo-ethylene-ketal (XXVIIa)

A solution of permonophthalic acid (53 g) in ether (800 cc) was added over 30 min to a solution of desoxycorticosterone acetate 3-monocycloethylene ketal[10a] (XXVII) (30 g) in chloroform (500 cc) at 0°. After keeping at 0° for 20 hr a further 500 cc of chloroform was added and the organic phase was washed acid free with sodium carbonate solution (5%). The solution was then washed with water (4 × 200 cc), dried (Na_2SO_4) and evaporated to afford a product which was dissolved in benzene (1 l.) and adsorbed onto neutral alumina (1 kg). Elution with benzene (5 l.) afforded after one crystallization from benzene–hexane 5β,6β-*oxido-pregnan*-21-*ol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXVIIIa) (3·7 g) m.p. 195–197°, raised by crystallizations from benzene–hexane to 199–200°, $[\alpha]_D$ +58°. (Found: C, 69·52; H, 8·41; O, 22·08. $C_{25}H_{36}O_6$ requires: C, 69·42; H, 8·39; O, 22·19%).

Further elution with benzene–ether (90 : 10, 10 l.) afforded 5α,6α-*oxidopregnan*-21-*ol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXXIa) (15·1 g) m.p. 238–245°, raised by several crysallizations from methanol–chloroform to 243–245°, $[\alpha]_D$ +20°. (Found: C, 69·71; H, 8·36; O, 21·81. $C_{25}H_{36}O_6$ requires: C, 69·42; H, 8·39; O, 22·19%).

6β-*Fluoropregnane*-5α,21-*diol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXXa)

Boron trifluoride-etherate (4·0 cc) was added to a stirred suspension of the 5α,6α-epoxide (XXXIa) (2·0 g) in benzene–ether (1 : 1; 200 cc) at room temp. The epoxide gradually dissolved and after 6 hr the solution was washed with sodium carbonate solution (5%) and then with water. After drying (Na_2SO_4) the solvent was removed under vacuo to afford a product which was adsorbed from benzene (250 cc) onto alumina (100 g). Elution with benzene (750 cc) and benzene–ether (90 : 10; 300 cc) gave 6β-*fluoropregnan*-5α,21-*diol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXXa) (930 mg) m.p. 215–218°, raised by crystallizations from benzene–hexane to 220–221°, $[\alpha]_D$ +40°. (Found: C, 66·30; H, 8·36; F, 3·95. $C_{25}H_{37}O_6F$ requires: C, 66·34; H, 8·24; F, 4·20%).

6α-*Fluoro*-Δ⁴-*pregnen*-21-*ol*-3,20-*dione* 21-*acetate* (6α-*fluorodesoxycorticosterone acetate*) (XXXIV)

Dry hydrogen chloride was passed briskly through a solution of 6β-fluoropregnan-5α,21-diol-20-one-21-acetate 3-cycloethylene-ketal (XXXa) (500 mg) in glacial acetic acid (20 cc) at 15–20° for 30 min. The solution was then kept at room temp for 4 hr. Addition of water and filtration afforded a product (360 mg) m.p. 145–156°. One crystallization from acetone–hexane yielded 6α-fluorodesoxycorticosterone acetate (XXXIV) (230 mg) m.p. 166–168°, raised by several crystallizations from

acetone–hexane to 169–171°, $[\alpha]_D$ +161°. λ_{max}^{EtOH} 236 mμ, ε 15,500. λ_{max}^{KBr} 1735, 1715, 1670 and 1625 cm^{-1}. (Found: C, 71·05; H, 7·91; F, 4·62. $C_{23}H_{31}O_4F$ requires: C, 70·73; H, 8·00; F, 4·86%).

6β-Fluoro-Δ⁴-pregnene-21-ol-3,20-dione 21-acetate (6β-fluorodesoxycorticosterone acetate (XXXIII)

Dry hydrogen chloride was passed briskly through a solution of the ketal-fluorohydrin (XXXa) (500 mg) in glacial acetic acid (25 cc) for 20 min. Addition of ice water and filtration gave a product (400 mg) m.p. 127–129° which was adsorbed from methylene dichloride (50 cc) onto a silica-celite column (50 : 50; 40 g). Elution with methylene–dichloride-benzene (50 : 50; 700 cc) afforded 6β-fluorodesoxycorticosterone acetate (200 mg) m.p. 128–132°. One crystallization from acetone-hexane gave a pure product (156 mg) m.p. 150–152°. The analytical sample had m.p. 152–154°, $[\alpha]_D$ +87°. λ_{max}^{EtOH} 234 mμ, ε 10,000 λ_{max}^{KBr} 1735, 1715, 1670 and 1625 cm^{-1}. (Found: C, 70·48; H, 8·00; F, 5·43. $C_{23}H_{31}O_4F$ requires: C, 70·73; H, 8·00; F, 4·86%).

Δ⁴-Pregnen-17α,21-diol-20-one 17,21-diacetate-3-cycloethylene-ketal (Compound "S" diacetate 3-monoketal) (XXVIIb)

A solution of Compound "S" diacetate[22] (XXVIa) (15 g) in dioxalane (300 cc) (ethylendioxy ketal of methyl ethyl ketone)[14] containing *p*-toluene-sulphonic acid (300 mg) was distilled at such a rate that 200 cc of distillate was obtained in 2½ hr. A further 200 cc of dioxalane was then added and the distillation continued for an additional 2½ hr at the same rate. The reaction mixture was then cooled, filtered and washed with a little cold methanol to afford a crude product (11·1 g) m.p. 114–117°, λ_{max}^{EtOH} 242 mμ ε 4,300. After one crystallization from methanol containing a few drops of pyridine the *monoketal* (XXVIIb) had m.p. 160–163°, λ_{max}^{EtOH} 240–242 mμ, ; 520; (6·3 g). This product was used for subsequent work. The analytical sample had m.p. 165–167°, $[\alpha]_D$ −25° and did not exhibit selective absorption in the ultraviolet. (Found: C, 68·58; H, 8·26; O, 23·02. $C_{27}H_{38}O_7$ requires: C, 68·33; H, 8·07; O, 23·60%).

Peracid oxidation of Compound "S" diacetate 3-monoketal (XXVIIb)

Permonophthalic acid (4 g) in ether (100 cc) was added over 10 min to a solution of the monoketal (XXVIIb) (3 g) in chloroform (100 cc) at −15°. After keeping at 0° for 16 hr the solution was washed with sodium bicarbonate solution (5%) until it was free of acid and then to neutrality with water. The dried solution (Na_2SO_4) was evaporated to afford a product which was adsorbed from benzene onto alumina (200 g). Elution with benzene–ether (80 : 20; 400 cc) afforded *5β,6β-oxidopregnan-17α,21-diol-20-one 17,21-diacetate 3-cycloethylene-ketal* (XXVIIIb) (630 mg) m.p. 167–169°, raised by crystallizations from ethyl acetate to 170–171°, $[\alpha]_D$ ±0°. (Found: C, 64·47; H, 7·82; O, 27·26. $C_{27}H_{38}O_8$ CH_3COOEt requires: C, 64·34; H, 8·01; O, 27·65%).

Further elution with benzene-ether (70 : 30; 600 cc) afforded after one crystallization from ethyl acetate-hexane *5α,6α-oxido-pregnan-17α,21-diol-20-one 17,21-diacetate 3-cycloethylene-ketal* (XXXIb) (780 mg) m.p. 180–182°, raised by several crystallizations from ethyl acetate to 186–188°, $[\alpha]_D$ −78°. (Found: C, 66·10; H, 7·72; O, 25·62. $C_{27}H_{38}O_8$ requires: C, 66·10; H, 7·81; O, 26·09%).

6β-Fluoropregnan-5α,17α,21-triol-20-one 17,21-diacetate 3-cycloethylene-ketal (XXXb)

Boron trifluoride-etherate (0·5 cc) was added to a solution of the α-epoxide ketal (XXXIb) (500 mg) in ether–benzene (1 : 1; 60 cc) and kept at room temp for 3½ hr. The product, isolated in the usual way, was adsorbed from benzene (50 cc) onto alumina 30 g). Elution with benzene afforded after one crystallization from benzene–hexane *6β-fluoropregnan-5α,17α,21-triol-20-one 17,21-diacetate 3-cycloethylene-ketal* (XXXb) (250 mg) m.p. 215–219°, raised by several crystallizations from benzene–hexane to 218–219°, $[\alpha]_D$ −31°. (Found: C, 63·90; H, 7·87; F, 3·87. $C_{27}H_{39}O_8F$ requires: C, 63·51; H, 7·70; F, 3·72%).

6β-Fluoropregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX)

A solution of the monoketal-fluorohydrin (XXXb) (100 mg) in acetone (10 cc) containing *p*-toluenesulphonic acid (5 mg) was kept at room temp for 8 hr. Evaporation of the solvent and

[22] Prepared according to the method of H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 820 (1956).

crystallization of the product from chloroform–methanol afforded *6β-fluoro-pregnan*-5α,17α,21-*triol*-3,20-*dione* 17,21-*diacetate* (XXIX) (53 mg) m.p. 215–219°, raised by further crystallizations to 225–227°, $[\alpha]_D \pm 0°$. (Found: C, 63·49; H, 7·73; F, 3·94. $C_{35}H_{35}O_7F$ requires: C, 63·60; H, 7·85; F, 3·74%).

6α-Fluoro-Δ⁴-pregnen-17α,21-*diol*-3,20-*dione* 17,21-*diacetate* (*6α-fluoro-Compound "S" diacetate*) (XXXVa)

Dry hydrogen chloride was bubbled for 1 hr through a solution of 6β-fluoropregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX (1·5 g) in glacial acetic acid (100 cc) at 10–15° (just above the freezing point of the solution). The flask was then stoppered and kept at room temp for a further 3 hr. Addition of water and filtration afforded *6α-fluoro-Compound "S" diacetate* (XXXVa) (1.17 g) m.p. 225–227°, raised by crystallizations from acetone–hexane to 241–143°, $[\alpha]_D +53°$; λ_{max} 236 mμ, ε 15,490. $\lambda_{max}^{CHCl_3}$ 1730, 1680 and 1620 cm⁻¹; XXXVa gave a positive test with triphenyltetrazolium chloride.[23]

Rotatory dispersion curve: (C, 0·061 in dioxane) $[\alpha]_{700} +14·8°$, $[\alpha]_{589} +51·1°$, $[\alpha]_{450} +87·5°$, $[\alpha]_{370} -48°$, $[\alpha]_{355} -64·4°$, $[\alpha]_{310} +1850°$, $[\alpha]_{295} +1605°$.

Rotatory dispersion curve of Reichstein's Compound "S" 17,21-diacetate: (C, 0·071 in dioxane) $[\alpha]_{700} +21°$, $[\alpha]_{589} +42°$, $[\alpha]_{450} +119°$, $[\alpha]_{365} -71·6$, $[\alpha]_{355} -55°$, $[\alpha]_{305} +2320°$, $[\alpha]_{290} +1805°$. (Found: C, 66·97; H, 7·70; F, 4·48. $C_{25}H_{33}O_6F$ requires: C, 66·93; H, 7·41: F, 4·24%).

6α-Fluoro-Δ⁴-pregnen-17α,21-*diol*-3,20-*dione* (*6α-fluoro-Compound "S"*) (XXXVc)

A suspension of 6α-fluoro-Compound "S" 17,21-diacetate (XXXVa) (800 mg) in methanol (8 cc) containing potassium hydroxide (80 mg) was stirred under nitrogen at 0° for 1¼ hr. After 45 min a complete solution was obtained. Acidification with acetic acid, addition of ice–salt water and filtration afforded *6α-fluoro-Compound "S"* (XXXVc) (510 mg) m.p. 188–192, raised by several crystallizations from acetone–hexane and benzene to 203–205°, $[\alpha]_D +135°$, λ_{max}^{EtOH} 236 mμ, ε 16,220 $\lambda_{max}^{CHCl_3}$ 3450, 1710, 1678 and 1625 cm⁻¹. (Found: C, 69·34; H, 8·34; F, 5·53. $C_{21}H_{29}O_4F$ requires: C, 69·20; H, 8·02; F, 5·21%).

The C-21 *mono acetate* (XXXVb) prepared in the usual way had m.p. 229–231° $[\alpha]_D +130°$ λ_{max}^{EtOH} 236 mμ, ε 16,100 λ_{max}^{KBr} 3470, 1745, 1720, 1660, 1620 cm⁻¹. (Found: C, 68·15; H, 7·84; F, 4·67 $C_{23}H_{31}O_5F$ requires: C, 67·99; H, 7·69; F, 4·67%).

6α-Fluoro-Δ¹,⁴-pregnadien-17α,21-*diol*-3,20-*dione* 17,21-*diacetate* (XXXVIa)

6α-Fluoro-Compound "S" diacetate (XXXVa) (2·0 g) in anhydrous tertiary butanol (100 cc) was heated under reflux with stirring under nitrogen with selenium dioxide (1·0 g) for 24 hr. Ethyl acetate (100 cc) was then added and the solution filtered through celite to remove the precipitated selenium. Evaporation of the solvent afforded a product which was slurried with water (200 cc) filtered, dried and crystallized from acetone–hexane to afford *6α-fluoro-Δ¹,⁴-pregnadien*-17α,21-*diol*-3,20-*dione* 17,21-*diacetate* (XXXVIa) (1·11 g) m.p. 246–248; raised by crystallizations from acetone–hexane to 251–253° $[\alpha]_D \pm 0$. λ_{max} 242 mμ, ε 16,950. (Found: C, 67·03; H, 7·09; F, 4·69. $C_{25}H_{31}O_6F$ requires: C, 67·23; H, 7·00; F, 4·26%).

6α-Fluoro-Δ¹,⁴-pregnadien-17α,21-*diol*-3,20-*dione* (XXXVIc)

A suspension of 6α-fluoro-Δ¹,⁴-pregnadiene-17α,21-diol-3,20-dione 17,21-diacetate (XXXVIa) (1·0 g) in methanol (10 cc) containing potassium hydroxide (100 mg) was stirred under nitrogen at 0° for 1 hr. After 35 min a complete solution was obtained. Acidification with acetic acid, addition of ice–salt water and filtration afforded 6α-fluoro-Δ¹,⁴-pregnadien-17α,21-diol-3,20-dione (XXXVIc) (740 mg) m.p. 209–214°, raised by several crystallizations from ethyl acetate–hexane to 210–212°, $[\alpha]_D +66°$; λ_{max}^{EtOH} 240–242 mμ, ε 16,600. (Found: C, 69·40; H, 7·74; F, 5·06. $C_{21}H_{27}O_4F$ requires: C, 69·60; H, 7·51; F, 5·24%).

The C-21-*mono acetate* (XXXVIb) prepared in the usual way (pyridine–acetic anhydride) had m.p. 224–224°, $[\alpha]_D +104°$; λ_{max} 240 mμ, ε 16,000. (Found: C, 68·76; H, 7·55; F, 4·83. $C_{23}H_{29}O_5F$ requires: C, 68·31; H, 7·23; F, 4·70%).

[23] R. B. Burton, A. Zaffaroni and H. E. Keutmann, *J. Biol. Chem.* **188**, 763 (1951).

6β-Fluoro-Δ⁴-pregnen-17α,21-diol-3,20-dione 17,21-diacetate (6β-fluoro-Compound "S" diacetate) (XXXIIa)

(a) Dry hydrogen chloride was bubbled for 3 hr through a suspension of 6β-fluoro-pregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX) (500 mg) in anhydrous and alcohol free chloroform[24] (50 cc) at 0–5°. The flask was then stoppered and kept for 16 hr at room temp with occasional shaking. During this period the steroid gradually dissolved in the solution. Addition of water and isolation with chloroform afforded 6β-fluoro-Compound "S" diacetate (XXXIIa) (409 mg), λ_{max} 234–236 mμ, ε 9,750, m.p. 175–183° raised by several crystallizations from acetone–hexane to 187–189°, $[\alpha]_D$ −14°, λ_{max} 234 mμ, ε 11,220.

Rotatory dispersion curves: (C, 0·072 in dioxane) $[\alpha]_{700}$ −48·6° $[\alpha]_{589}$ −41°, $[\alpha]_{370}$ −352°, $[\alpha]_{365}$ −377°, $[\alpha]_{310}$ +1340° $[\alpha]_{300}$ +1215°. (Found: C, 66·53; H, 7·36; F, 4·42. $C_{25}H_{33}O_6F$ requires: C, 66·93; H, 7·41; F, 4·24%).

This experiment was not reproducible,[15] from 5 experiments the 6β-fluoro-compound (XXXIIa) was isolated twice and in the other three experiments only the 6α-fluoro compound (XXXVa) could be isolated.

(b) Dry hydrogen chloride was bubbled for 15 min through a solution of 6β-fluoropregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX) (1·0 g) in glacial acetic acid (100 cc) at 15°. The stoppered flask was then kept at room temp for 10 min when addition of water and filtration afforded 6β-fluoro-Compound "S" diacetate (XXXIIa) (750 mg) m.p. 170–175°, raised by chromatography over neutral alumina to 185–187°, (510 mg). This product was identical with the compound prepared by method (a).

6β-Fluoro-Δ⁴-pregnene-17α,21-diol-3,20-dilne (6β-fluoro-Compound "S") (XXXIIb)

A suspension of 6β-fluoro-Compound "S" 17,21-diacetate (XXXIIa) (1·2 g) in methanol (12 cc) containing potassium hydroxide (120 mg) was stirred under nitrogen at 0° for 1½ hr. After 1 hr a complete solution was obtained. Acidification with acetic acid, addition of ice–salt water and filtration afforded 6β-fluoro-Compound "S" (XXXIIb) (800 mg) m.p. 215–218°, raised by crystallizations from acetone–hexane to 222–224°, $[\alpha]_D$ −25°. (Found: C, 69·18; H, 8·22; F, 4·95. $C_{21}H_{29}O_4F$ requires: C, 69·20; H, 8·02; F, 5·21%).

[24] Obtained by washing commercial chloroform several times with concentrated sulphuric acid and then water and finally distilling from calcium chloride.