ADVANCES IN FLUORINE CHEMISTRY

VOLUME 4

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STRUCTURAL ASPECTS OF MONOFLUORO-STEROIDS

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INTRODUCTION

In recent years a wide range of steroids[1] containing fluorine have been synthesized. Interest has centred mainly around the fact that the hormonal activity of certain steroids, notably corticoids, is often enhanced by replacement by fluorine of a hydrogen atom, as in 9-fluorocortisone, or of a hydroxyl group, as in 21-deoxy-21-fluoro-cortisone. Although the biochemistry of steroids is now receiving considerable attention[2], it is not possible as yet to make precise correlations between the structure and activity of fluoro-analogues. It is now clear, however, that a wider range of structural modifications, with retention or enhancement of biological activity, is possible than was previously considered to be the case (see the review by Fried and Borman[3]). Methods of synthesis of fluorosteroids have been summarized recently by Chamberlain[3a].

In other fields, fluorinated analogues of biochemical intermediates and substrates (fluorosugars[4–7], fluorocarboxylic acids[8,9] and fluoroheterocyclics[10–12]), where fluorine replaces a hydroxyl group or a hydrogen atom, may undergo enzymic transformations. Where observed, these take the form of enzyme inhibition, either directly, e.g., sodium fluoromalate with malate dehydrogenase[13], or indirectly, as in the case of 'lethal synthesis' of fluorocitrate from fluoroacetate[14]. Elsewhere, incorporation of the fluoro-analogue

(e.g. 5-fluorouracil[15] or *p*-fluorophenylalanine[16]) may occur without apparent enzymic inhibition. With *Brucella abortus*, where erythritol is an obligatory growth factor, (±)-2-deoxy-2-fluoroerythritol exhibits anti-metabolite activity[17]. The further exploration of fluoro-analogues thus offers new means of studying hormonal action, enzymic pathways of metabolism and rational chemotherapeutic agents.

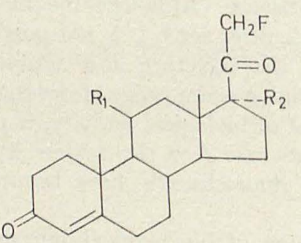
It is hoped that the wide variety of novel methods developed for the introduction of fluorine into steroids will assist and stimulate workers in other fields of organic fluorine chemistry. For the purpose of this review, the term 'monofluorosteroids' refers to the fact that only one fluorine atom is attached to one particular carbon atom (i.e. monofluorosubstitution), although the steroid molecule may contain more than one such fluorine atom (e.g. 9α,21-difluorohydrocortisone). Where possible, the fluoroderivatives have been classified as primary, secondary and tertiary and dealt with in that order.

DERIVATIVES CARRYING A FLUORINATED SIDE-CHAIN (PRIMARY FLUORODERIVATIVES)

(*a*) *21-Fluorosteroids*

So far these have been confined to cortisone or progesterone derivatives. A method of general applicability has been developed[18] which takes advantage of the fact that primary iodo-derivatives are readily replaced by fluoride anion, (*cf.* the fluorination of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[19]). In the reaction, the iodosteroid in moist acetonitrile is treated with 50 per cent aqueous silver fluoride at 30–40°. Silver iodide precipitates and the fluorosteroid remains in solution. In this way, 3β-acetoxy-21-iodopregn-5-en-20-one was converted to 3β-acetoxy-21-fluoropregn-5-en-20-one, which was deacetylated with methanolic HCl at room temperature. By an analogous reaction, 21-iodoprogesterone was converted to 21-fluoroprogesterone (I).

Using silver fluoride in methyl cyanide[20], 11β-hydroxy-21-iodo-6α-methylpregn-4-ene-3,20-dione was converted to the 21-fluoroanalogue

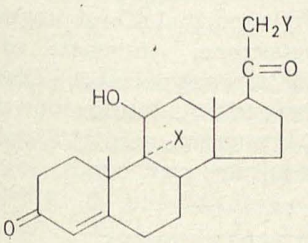


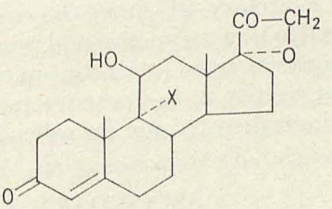
(I) R_1, H; R_2, H
(II) R_1, OH; R_2 H
(III) R_1,=O; R_2, OH
(IV) R_1, OH; R_2, OH

which was oxidized without defluorination to 21-fluoro-6α-methylpregn-4-ene-3,11,20-trione by means of chromic acid in acetic acid. Similarly, corticosterone 21-methanesulphonate was transformed, via the 21-iodosteroid, into 21-fluoro-11β-hydroxyprogesterone (II), cortisone 21-methanesulphonate into 21-fluoro-17α-hydroxypregn-4-ene-3,11,20-trione (III) and

hydrocortisone (cortisol) 21-methanesulphonate into 21-fluoro-11β-17α-dihydroxypregn-4-ene-3,20-dione (IV).

This method has since been improved by direct exchange of the methanesulphonate group by fluoride anion (thus eliminating the iodo step), resembling the Oldham and Rutherford reaction. Thus it has been found[21] that treatment of hydrocortisone 21-methanesulphonate with anhydrous potassium fluoride in dimethyl formamide (DMF) or dimethyl sulphoxide (DMS) at 110° for 18–24 h furnished the 21-fluoroanalogue (IV) and 17α,21-anhydro-11β-hydroxypregn-4-ene-3,20-dione as a side product (VIII). Extension of this reaction, in dimethyl sulphoxide, to the 21-methanesulphonates of 9α-fluorohydrocortisone[22] and 1-dehydro-9α-fluorohydrocortisone furnished the corresponding chloroform-insoluble 9α-21-difluorides (V) and (VI), and the side products (IX) and (X).





(V) X, F; Y, F

(VI) X, F; Y, F; double bond C_1—C_2

(VII) X, F; Y, Cl

(VIII) X, H

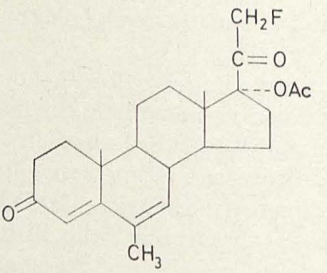
(IX) X, F

(X) X F; double bond C_1—C_2

Thus 9α-fluorohydrocortisone 21-methanesulphonate with potassium fluoride in dimethyl formamide at 100° led[22] to the 9α-21-difluoride, oxidation of which gave 9α-21-difluoro-17α-hydroxypregn-4-ene-3,11,20-trione. Successive replacement of the 21-hydroxyl group in corticosterone and 11-dehydrocorticosterone by chlorine, bromine and fluorine has been achieved[23], the latter involving exchange of bromine by means of silver fluoride. By similar means, 21-iodopregnenolone acetate was converted into the corresponding fluoro-analogue[24].

The introduction of fluorine into the 21-position was shown to enhance the glucocorticoid activity of the corresponding 21-deoxycorticoids by approximately 3–5 times. Replacement of the fluorine in (V) by the larger and less electronegative chlorine atom, to give 21-chloro-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione (VII) (prepared from the 9α-fluoro-21-methanesulphonate and lithium chloride in acetic acid), resulted in loss of glucocorticoid activity, even at 10 times the minimum effective dose of cortisone acetate.

Recently a new class of orally active progestational agents have been obtained by Sollman, Elton and Dodson[25] with the preparation of 17α-acetoxy-21-fluoro-6-methylpregn-4,6-diene-3,20-dione (XI).



(XI)

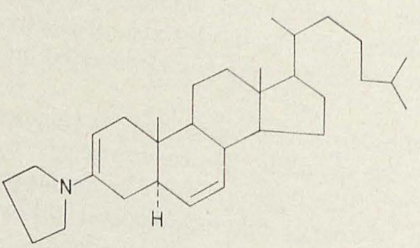
This was obtained by an exchange reaction between silver fluoride in acetonitrile and 17α-hydroxy-21-iodo-6-methylpregn-4,6-diene-3,20-dione. It was found that when (XI) was tested orally in the Clauberg assay[26,27], at a level producing a +2 degree of glandular arborization, it was 17 times as potent as subcutaneous progesterone, or 1,700 times that of oral progesterone.

17α-acetoxy-21-fluoro-6α-methylprogesterone, synthesized similarly, proved to be a very active oral progesterin, 20 times as potent as 17α-ethynyl-19-nortestosterone (norleutin) in the Clauberg test[25a]. Introduction of fluorine at position 21 in this series appeared to favour enhanced activity for oral administration but not for subcutaneously injected compounds.

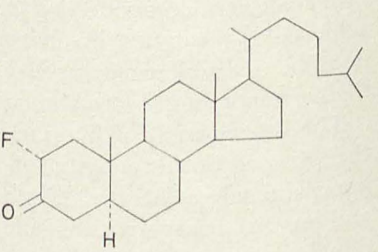
SECONDARY FLUORODERIVATIVES

(*a*) *2-Fluorosteroids*

The fluorination of active methylene groups by perchloryl fluoride has been demonstrated by Inman and co-workers[28,29] in their synthesis of difluoromalonic acid, and the reaction has been applied to 3-ketosteroids. Since both the hydrogen atoms in the active methylene group are replaced by fluorine (irrespective of proportions), 2-monofluorosteroids are made by the use of suitable blocking agents. Gabbard and Jensen[30] first utilized this reaction in the preparation of 2α-fluorocholestanone (XIII) from cholestanone pyrrolidylenamine (XII).



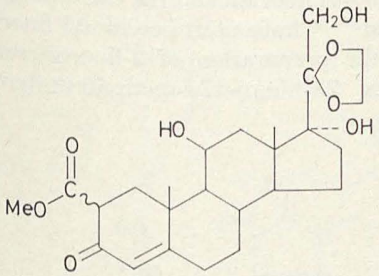
(XII)



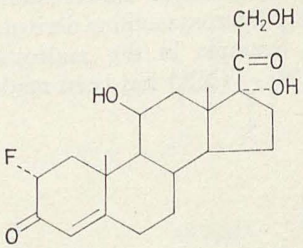
(XIII)

Kissman, Small and Weiss[31] subsequently modified the reaction[32] by introducing the methoxalyl group at the 2-position of the steroid. Thus 2α-fluorohydrocortisone (XV) was made via the sodium salt of 20-ethylenedioxy-2-methoxalyl-11β, 17α,21-trihydroxypregn-4-ene-3, 20 dione

(XIV) and perchloryl fluoride in methanolic sodium methoxide at −10°, followed by base catalysed cleavage of the 2-methoxalyl group and acid hydrolysis of the resulting ketal.



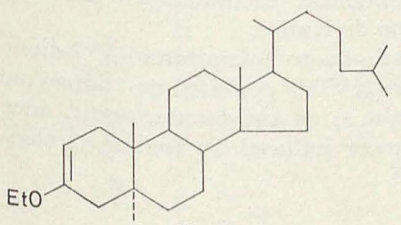
(XIV)



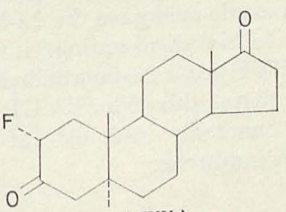
(XV)

The configuration of the fluorine atom was assumed from spectral data. Thus the 2-fluorosteroid exhibited similar effects on the infra-red (shift of the carbonyl maximum) and ultra-violet (no shift of the carbonyl maximum) absorption spectra to those exhibited by chlorine and bromine at this position[33,34]. 2α-Fluorohydrocortisone had no pronounced glucocorticoid activity.

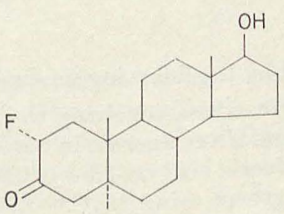
Jensen and co-workers[35] found that treatment of 1-ethoxycyclohexene in pyridine with perchloryl fluoride at 0° followed by dilution and acidification gave 2-fluorocyclohexanone. Application of this reaction to enolic ethers in the steroid series provided another route to 2-fluoroderivatives. Thus 2α-fluorocholestanone (XIII) was obtained from 3-ethoxy-5α-cholestan-2-ene (XVI). Treatment of the respective 3-ethoxy-2-ene compounds with perchloryl fluoride and subsequent hydrolysis yielded 2α-fluoro-5α-androstane-3,17-dione (XVII) and 2α-fluorodihydrotestosterone acetate which on acid hydrolysis gave the alcohol (XVIII).



(XVI)

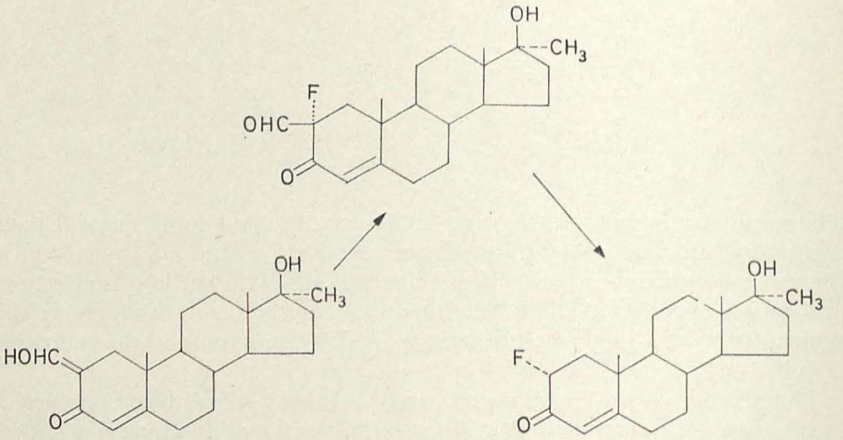


(XVII)



(XVIII)

The fluorine atom was shown to be at C–2 by conversion of 2α-fluorocholestanone (XIII) to 5α-cholestan-1-en-3-one, identified as the 2,4-dinitrophenylhydrazone. The α-orientation of the fluorine was established by optical rotatory dispersion[36] and nuclear magnetic resonance. The same compounds are also obtained from perchloryl fluoride and the corresponding steroid enamines. Edwards and Ringold[37–38] have used perchloryl fluoride and 2-hydroxymethine derivatives for the preparation of 2-fluorosteroids. For example in the androstane series, 2α-fluoro-17α-methyltestosterone (XIX) → (XX) has been made.



(XIX) (XX)

2α-Fluorodihydrotestosterone prepared by this route is identical with that prepared previously[35].

Treatment of 2α,3α-epoxy-5α-androstan-17-one with hydrogen fluoride in tetrahydrofurane-chloroform and subsequent chromic acid oxidation gave 2β-fluoro-5α-androstane-3,17-dione[39]. This epimerizes in acidic conditions, at room temperature to the 2α-fluoride. Bromination of the latter in acetic acid gave the 2α-fluoro-2β-bromo derivative.

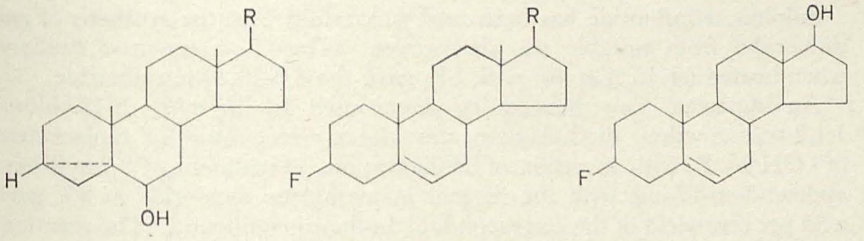
In biological testing[40] it was found that 2α-fluoro-5α-androstan-3,17-dione (XVII) and 2α-fluorodihydrotestosterone (XVIII) possessed no androgenic activity, although (XVIII) showed promise as an anti-tumour agent, since it markedly inhibited rat mammary cancer induced by feeding methylcholanthrene.

(*b*) *3-Fluorosteroids*

These have been obtained by the following methods:

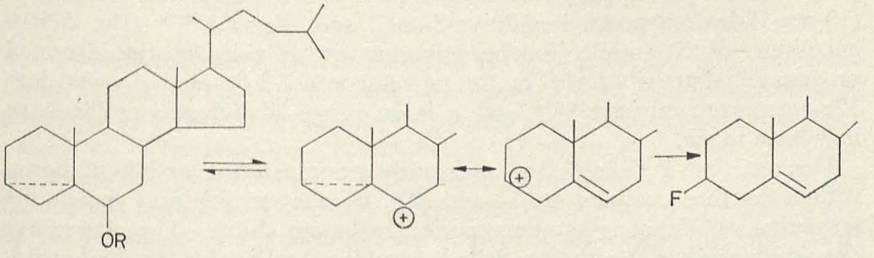
(*i*) Secondary exchange reactions, involving the use of suitably substituted 3-iodosteroids and silver fluoride in acetonitrile[41].
(*ii*) The action of hydrofluoric acid on 3,5-cycloderivatives of steroids[44]
(*iii*) Replacement of oxo groups using SF_4[42].
(*iv*) Replacement of OH by F[44a].

Thus when 3β-iodoandrost-5-en-17-one was treated with a suspension of anhydrous silver fluoride in a mixture of dry xylene and acetonitrile at room temperature, silver iodide formed almost immediately. 3β-fluoroandrost-5-en-17-one (XXII, R, =O) was obtained from the supernatant.



(XXI) (XXII) (XXIII)

Borohydride reduction of (XXII R,=O) gave the 3β-fluoroandrost-5-en-17β-ol (XXIII). In a similar fashion 3β-hydroxypregn-5-en-20-one and cholesterol were converted, via their toluene-sulphonic esters, to the corresponding 3β-iododerivatives and the iodine exchanged for fluorine. Catalytic hydrogenation of the 3β-fluoroandrost-5-en-17-one gave the androstane derivative and borohydride reduction the 17β-ol. The cholesteryl fluoride prepared by this method was found to be identical with the product, obtained in small yield, from the action of anhydrous hydrogen fluoride in acetic acid on 6β-methoxy-3α,5-cyclo-5α-cholestane (XXIV, R, CH_3). By analogy with other hydrogen halides where this reaction produces 3β-halogenosteroids[43], the fluorosteroids were assigned the β-configuration. Furthermore, the 3β-fluoroandrost-5-en-17-one (XXII R, =O) was recovered unchanged after boiling with collidine or methanolic potassium acetate, which further supports an equatorial β-configuration for the F atom. These exchange reactions occur, therefore, without inversion.



(XXIV) (XXV) (XXVI)

The action of hydrogen halides on 3α,5-cyclo-5α-cholestan-6β-ol (XXIV, R, H) is considered to afford immediately the mesomeric cation (XXV). By suitable control of the equilibria, the cholesteryl halides may be obtained in high yields[43]. Shoppee and Summers[44] applied this reaction to the preparation of cholesteryl fluoride (XXVI). 6β-Hydroxy-3α-5-cyclo-5α-pregna-20-one (XXI, R, $COCH_3$) and 6β-hydroxy-3α,5-cyclo-5α-androstan-17-one

(XXI, R, =O) which on treatment with hydrofluoric acid in benzene gave the fluoroderivatives, 3β-fluoropregn-5-en-20-one (XXII, R, $COCH_3$) and 3β-fluoroandrost-5-en-17-one (XXII, R, =O) respectively. Reduction of (XXII, R, =O) with lithium aluminium hydride afforded 3β-fluoroandrost-5-en-17α-ol (XXIII).

Sulphur tetrafluoride has been used successfully[42] in the synthesis of *gem* difluorides from suitable oxo derivatives. Thus 5α-pregnane-3,20-dione when heated for 15 h at 40° with SF_4 gave the 3,3-20,20-tetrafluoride.

An important new fluorinating agent used by Ayer[44a], *N*-(2-chloro-1,1,2-trifluoroethyl) diethylamine, provides a direct route for replacement of –OH by F, with inversion of configuration. Treatment of 3β-hydroxyandrost-5-en-17-one with the reagent in methylene dichloride at 25° gave a 95 per cent yield of the corresponding 3α-fluoro-compound. The reaction, probably proceeding via an homoallylic cation, has been applied to hydroxyls in other positions.

(*c*) *4-Fluorosteroids*

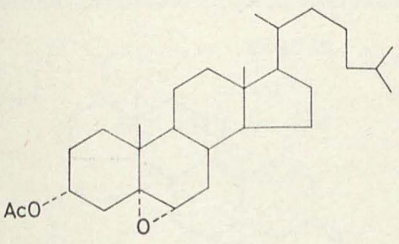
Perchloryl fluoride has proved of particular value for the introduction of fluorine into conjugated oxosteroids[45,46]. When pyrrolidylenamines of 3-oxo-Δ^4 steroids were treated with $FClO_3$ in ether at 0° for 5–10 min, a mixture of the 4,4-difluoro-3-oxo-Δ^5 compound and the corresponding 4-monofluoride resulted in 25–50 per cent yield. 4,4-Difluoropregn-5-ene-3,20-dione obtained in this way had 20 per cent of the progestational activity of progesterone. Diminution of hormonal activity was also noted in other 4-fluorinated compounds as for instance in 4-fluoro-17β-hydroxyandrost-4-en-3-one propionate which had 8 per cent of the androgenic activity of testosterone propionate in castrated mice.

(*d*) *6-Fluorosteroids*

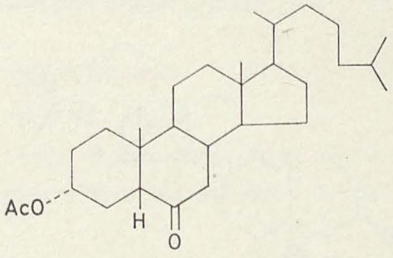
Much of the work with 6-fluorosteroids has been stimulated by the possibility of obtaining active progestational hormones (with possible application as oral contraceptives) which are cheaper and more effective than 'Norlutin'[47] (19-nor-17-hydroxypregn-4-en-20-yn-3-one) and 'Enovid'[49,50] (the 5(10)-ene isomer of 'Norlutin'). Further stimulus was provided by the increased progestational activity found by the introduction of a 6α-methyl group into 17α-acetoxyprogesterone[51–53] and a wide range of 6-fluorosteroids have now been made.

Henbest and Wrigley[54] had previously examined the action of boron trifluoride-ether complex on α- and β-5, 6-epoxysteroids and shown the formation of 6-ketones by stereospecific hydrogen shifts. The alternative reaction leading to the fluorohydrin, is considered to involve the dual attack of the Lewis acid and an external fluoride nucleophile resulting in a diaxial product. The mode of attack of the fluoride nucleophile and the nature of the initial reaction product [postulated as $\rangle CF{\cdot}C(OBF_2)\langle$] have not yet been determined. In order to investigate the effects of nearby groups, Henbest and Wrigley examined the action of BF_3 on 3-substituted 5,6-epoxyderivatives and found that the products were either 6-ketones or axial fluorohydrins, the predominance of one or the other depending on certain stereochemical factors. Thus, 3α-acetoxy-5α,6α-epoxycholestane (XXVII) gave a higher

yield of the 6-ketone (XXVIII) (3α-acetoxy-5β-cholestane) than the corresponding 6-fluorocompound.

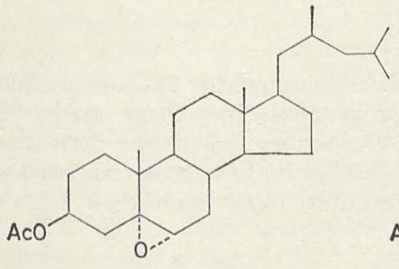


(XXVII)

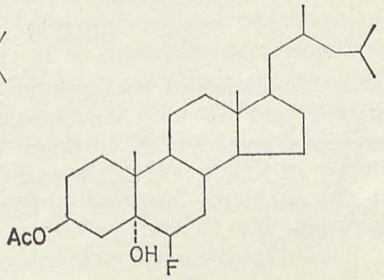


(XXVIII)

It was suggested that the ionization of the C_5—O bond would be inhibited by the electron attracting acetyl group at C_3 and that the increased compression of the 3α- and 5α-axial substituents would discourage the formation of the diaxial fluorohydrin. Their view received support when the 3β-acetoxy-5α,6α-epoxysteroid (XXIX) gave very little ketone, the fluorohydrin (XXX) being the major product.



(XXIX)

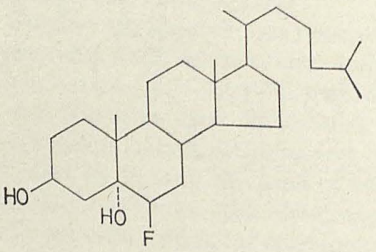


(XXX)

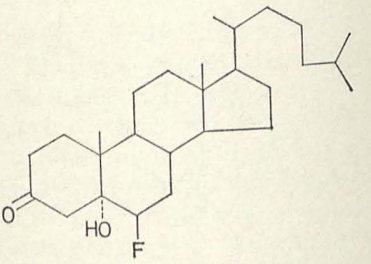
The formation of the ketone is inhibited for both electronic and conformational reasons. The reaction was also studied with 5β,6β-epoxysteroids and the introduction of the acetoxy substituent at C_3 found to alter profoundly the course of the reaction. Thus whereas 5β,6β-epoxycholestane afforded cholestan-6-one, 3β-acetoxy-5β,6β-epoxycholestane gave 3β-acetoxy-5α-fluorocholestan-6β-ol. Formation of either the fluorohydrin or the ketone can derive assistance by a conformational change of the acetate group (axial to equatorial) and so the difficulty in ionizing the O—C–5 bond, necessary for the production of the ketone, is decisive in this case. The rate of reaction of the substituted epoxide was also slower than that of the unsubstituted compound, agreeing with the general suggestion that the slower reaction leading to the formation of the fluorohydrin becomes of importance only when the more rapid ionization and hydrogen shift is inhibited.

Bowers and Ringold[55–57] have applied this reaction widely in the cholestane, progesterone and testosterone series for the synthesis of 6α- and β-fluoro-derivatives. Thus 6β-fluorocholestan-5α,3β-diol (XXXI) on

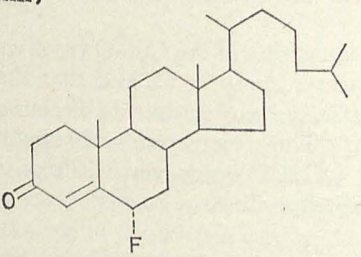
oxidation with chromic acid afforded the 3-ketone (XXXII). This underwent dehydration with HCl/acetic acid to yield, with concomitant epimerization of the fluorine atom, 6α-fluorocholestenone (XXXIII). By a



(XXXI)



(XXXII)



(XXXIII)

similar manipulation of the appropriate fluorohydrins 6β- and 6α-fluorotestosterone and 6β- and 6α-fluoroprogesterone have been made. The progestational potency of the 6α-fluoro-17α-acetoxyprogesterone derivatives[56] (XXXIV), (XXXV), (XXXVI) and (XXXVII) have been compared with 19-nor-17α-ethynyltestosterone[47] ('Norlutin') using multi-dose Clauberg assays (Table 1).

(XXIV) Double bond at $C_4—C_5$

(XXXV) Double bonds at $C_4—C_5$; $C_1—C_2$

(XXXVI) Double bonds at $C_4—C_5$; $C_6—C_7$

(XXXVII) Double bonds at $C_4—C_5$; $C_1—C_2$; $C_6—C_7$

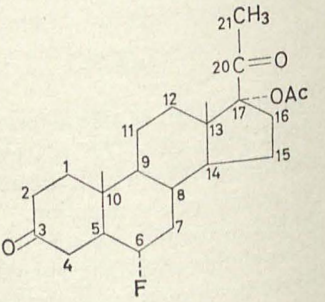
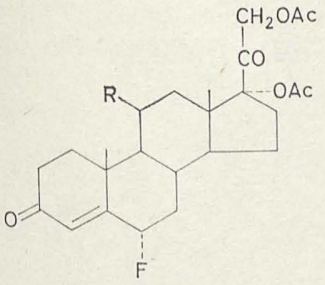


TABLE 1[56]

Compound	*Oral progestational activity*
19-Nor-17α-ethynyltestosterone	1
17α-acetoxy-6α-fluoroprogesterone	1
17α-acetoxy-1-dehydro-6α-fluoroprogesterone	6
16α-acetoxy-6-dehydro-6α-fluoroprogesterone	15
17α-acetoxy-1, 6-bishydro-6α-fluoroprogesterone	8

6α-Fluorocorticoids have also been made by this method[55]. 17α-Acetoxy-5α, 6α-epoxy-3β-hydroxypregn-20-one was the starting point for the synthesis of 6α-fluorocortisol acetate (XXXVIII), 6α-fluorocortisone (XXXIX), 6α-fluoroprednisolone (XL) and 6α-fluoroprednisone (XLI).



(XXXVIII) R,OH

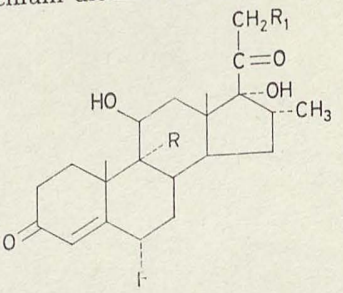
(XXXIX) R,=O

(XL) R,OH; double bond C_1-C_2

(XLI) R,=O; double bond C_1-C_2

The fluorocortisones and fluoroprednisones were shown to have 10 and 20 times the anti-inflammatory and thymolytic activity of cortisol acetate, respectively.

Potentiation of anti-inflammatory activity by the introduction of the 6α-fluoro- or 16α-methyl[58] substituent into the intact or modified hydrocortisone molecule prompted Edwards, Ringold and Djerassi[59] to synthesize corticoid hormones combining both structural features. Thus, starting from the accessible 3α-acetoxy-5α,6α-epoxy-16α-methylpregnan-20-one and BF_3, 6α-fluoro-16α-methylcortisol (XLII) was obtained which served as a key intermediate in the preparation of 6α-fluoro-16α-methylprednisolone acetate (XLIII) and 6α,9α-difluoro-16α-methylcortisol acetate (XLIV). The latter compound was obtained from (XLII) by Fried's general method, involving dehydration of (XLIII), addition of hypobromous acid to the 9,11-double bond followed by potassium acetate treatment to afford the 9,11-epoxide, and final opening of the epoxide with hydrogen fluoride to give (XLIV). In order to complete the series, (XLIV) was converted into the prednisolone analogue (XLV) by selenium dioxide oxidation.



(XLII) R,H;R_1,OH

(XLIII) R, H;R_1,OAc; double bond C_1-C_2

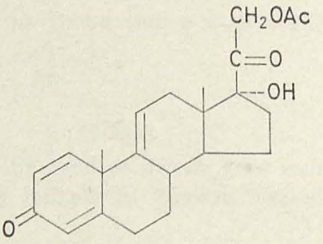
(XLIV) R,F;R_1,OAc

(XLV) R,F;R_1,OAc; double bond C_1-C_2

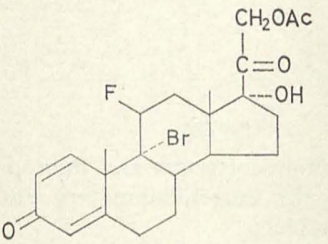
TABLE 2[59]

	Anti-inflammatory activity
Cortisol	1
6α-Fluoro-16α-methylprednisolone acetate	60
6α,9α-Difluoro-16α-methylcortisol acetate	65
6α,9α-Difluoro-16α-methylprednisolone acetate	300

Recently, a useful method[60] for the introduction of fluorine into steroids has been developed by the use of hydrogen fluoride and *N*-bromoacetamide, giving *trans* ionic addition of bromine and fluorine to unsaturated substances. Thus, 21-acetoxy-17α-hydroxypregn-1,4,9(11)-triene-3,20-dione (XLVI) gave a product which was formulated as 21-acetoxy-9α-bromo-11β-fluoro-17α-hydroxypregn-1,4-diene-3,20-dione (XLVII). Hydrolysis with methanolic perchloric acid gave the corresponding 21-alcohol.

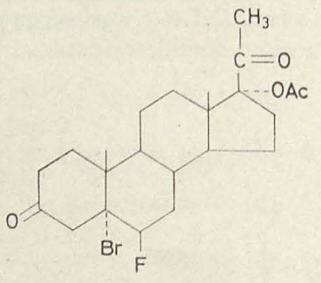


(XLVI)

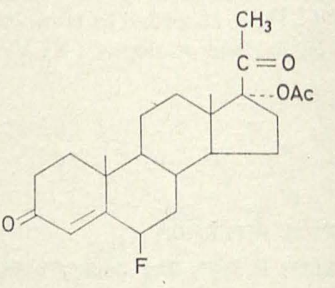


(XLVII)

Bowers[61] has applied this reaction to a wide range of unsaturated steroids and considers this the best route to the biologically important 6-fluorosteroids. Thus addition of the elements of BrF to 17α-acetoxy-3β-hydroxypregn-5-en-20-one afforded 17α-acetoxy-5α-bromo-6β-fluoro-3β-hydroxypregn-20-one. Oxidation with chromic acid in acetone gave the corresponding C-3 ketone (XLVIII), which was converted into 17α-acetoxy-6β-fluoroprogesterone (XLIX) by sodium in methanol.



(XLVIII)



(XLIX)

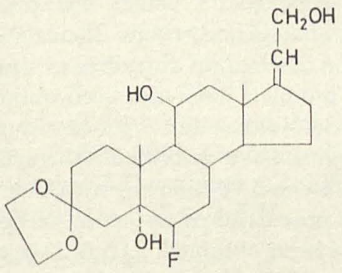
Similarly, 3β-hydroxypregn-5-en-20-one and 17α, 21-diacetoxy-3β-hydroxypregn-5-en-20-one gave the 6β and hence the 6α-fluoroanalogues of progesterone and compounds 'S'-diacetate (6α- or 6β-fluoro-17α, 21-diacetoxypregn-4-ene-3,20-dione). A much higher degree of selectivity was obtained with the BrF reaction, especially in the case of polyunsaturated steroids, where the formation of epoxides and the addition of HF or BF_3, is usually precluded. For example, 16α, 17α-epoxy-3β-hydroxypregn-5

9(11)-dien-20-one gave 5α-bromo-16α,17α-epoxy-6β-fluoro-3β-hydroxy-pregn-9(11)-en-20-one and thence 16α,17α-epoxy-6β-fluoropregn-4, 9 (11)-diene-3, 20-dione.

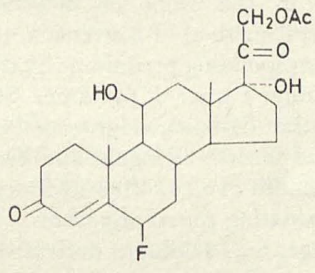
Treatment of pregnenolone with *N*-iodosuccinimide and hydrogen fluoride under analogous conditions, led to a fluoro-iodo derivative, which proved unexpectedly to be the 5α-fluoro-6β-iodo adduct[62]. A possible explanation may lie in the non-bonded interactions which are less in this product than in the 5α-iodo-6β-fluoride. Though some difficulty has been encountered in selectively displacing the one halide whilst preserving the C—F bond, the method has led to the synthesis[63] of 5α-hydroxy-6β-fluorides.

It is of interest that in the carbohydrate series, *N*-bromosuccinimide and hydrogen fluoride react with triacetyl glycals giving *cis* epimeric products having the structure of 2-bromo-2-deoxy-hexosyl fluorides[64].

Hogg and his co-workers[65] have also reported the synthesis of several 6-fluorosteroids in the progesterone and androstane series by the addition of 48 per cent hydrofluoric acid to epoxysteroids. Thus the addition of 48 per cent HF to the 3-ethylene ketal of methyl 5α,6α-epoxy-3,11-dioxo-pregn-17(20)-en-21-oate, reketalization with ethane-diol and reduction with lithium aluminium hydride gave 3-ethylene ketal of 6β-fluoro-5α,11β, 21-trihydroxypregn-17-en-3-one (L).



(L)



(LI)

The 21-acetate of (L), after treatment with hydrogen peroxide and catalytic amounts of osmium tetroxide, hydrolysis of the Acetal group, and dehydration of the 5α-hydroxyl group, gave 21-acetoxy-6-fluorocortisol (LI). This was isomerized to the more stable 6α-fluorocompound with hydrogen chloride in chloroform containing ethanol[66]. Microbial dehydrogenation of (LI) gave the corresponding prednisolone derivative. These compounds were transformed into their 9α-,6α-di-fluoroanalogues by the method of Fried and Sabo[104,105]. 9α,6α-Difluoroprednisolone was reported to have 427 times the activity of cortisol.

Cleavage of 5α, 6α epoxides with BF_3 in ether-benzene mixtures has been employed in the synthesis of 6β-fluoro-5α-hydroxy derivatives[67,67a]. When 5α,6α-epoxy-3β,11α-dihydroxy-16α-methylpregnan-20-one was treated with the reagents at room temperature for 3 h, 6β-fluoro-3β,5α,11α-trihydroxy-16α-methylpregnan-20-one resulted.

Similarly, 6α,7α-epoxycortisone 21-acetate reacted[68] with hydrogen fluoride in tetrahydrofuran-chloroform to give the 6β-fluoro-7α-ol, which, on treatment with hydrogen bromide in acetic acid, gave 6-fluoro-7-dehydrocortisone 21-acetate.

In the 6β position, fluorine exhibits considerable stability, and does not readily undergo elimination. The fluorine in 3β-acetoxy-6β-fluoro-5α-methylcholestan-5-ol withstands the action of acetic anhydride and potassium hydrogen sulphate at 65–75°, 3β-acetoxy-6β-fluoro-5α-methyl-19-nor-5β-cholest-9-ene resulting[69]. In other circumstances, as in 11β-acetoxy-6β-fluoro-17α-hydroxy-16α-methylpregn-4-ene-3,20-dione, acid conditions lead to rearrangement of the fluorine atom into the 6α position[67–67a]. Ozonolysis of 6β-fluoro-11,18-oxido-20,21-dipropionyloxypregnan-3-one resulted in cleavage of the anhydro ring with oxidation to the corresponding fluoropregnan-18-oic acid and, hence by dehydration to the 11,18 lactone[70]. Ruthenium tetroxide[71] in carbon tetrachloride reacted with 6α-fluoro-11,18-oxido derivatives giving analogous 18-acids.

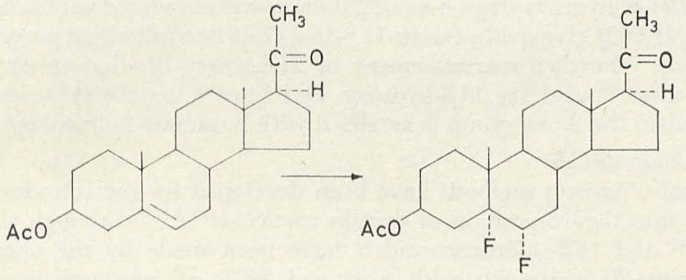
Perchloryl fluoride provides a valuable means[72] of obtaining 6β-fluoro derivatives; 3,17α,21-triacetoxypregna-3,5,9(11)-trien-20-one, when treated with the gas in potassium acetate and ethanol gave 17α,21-diacetoxy-6β-fluoropregna-4,9(11)-diene 3,20-dione.

Further evidence of the stability of 6α-fluorosteroids towards oxidation is found in the work of Bowers and colleagues[73] which has provided a general method of conversion of the 6α-halogenocortisone 21-acetate into the corresponding prednisone by the action of selenium dioxide in *tert*-butanol containing a trace of pyridine. Similar products have also been obtained[74] from the 6α-halogenopregna-1,4-diene-3,20-diones as well as from the reduced form[75]. Ringold and his colleagues have described[76] the synthesis of 6α-fluoro-11α,17α,21-trihydroxypregn-4-ene-3,20-dione by means of C–11 hydroxylating micro-organisms. By the now classical approach of epoxide cleavage, 6α,9α-difluoro derivatives have been obtained. Thus 21-acetoxy-6α-fluoro-17α-hydroxypregna-4,9(11)-diene-3,20-dione with *N*-bromoacetamide gave the 6α-fluoro-9α-bromide which, in turn, reacted with potassium acetate in ethanol to give the 9β-11β-epoxide. This with hydrogen fluoride in chloroform led to the 6α,9α-difluoride[74]. Under analogous conditions 5α,6α-epoxy-17,17-ethylenedioxy-5α-androstan-3β-ol, was converted[77] to the 6β-fluoro-3β,5-dihydroxy-5α-androstan-17-one. With 5α,6α-epoxides of the pregnane series, treatment with BF_3 led to the 6β-fluoro-5α-hydroxy products[78]. Thus 3β,17α,20,21-tetra-acetoxy-5α,6α-epoxypregnan-11-one reacted with the BF_3-ether complex giving, after 3 h at room temperature, 6β-fluoro-5α-hydroxy-3β,17α,20,21-tetra-acetoxypregnan-11-one. Treatment of 6β-fluoro-3β,17α,21-trihydroxy-pregna-3,11,20-trione with potassium hydroxide gave 6β-fluorocortisone, while epimerization with hydrogen chloride/AcOH gave 6α-fluorocortisone. Enolization of this type of derivative proceeds with ease at C–3, where conjugation is possible, as in the formation of 6α,9α-difluoro-3-ethoxy-11β,16α,17α,21-tetrahydroxy-pregna-3,5-dien-20-one from the corresponding pregn-4-ene-3,20-dione by the action of triethylorthoformate and toluene-*p*-sulphonic acid[79].

Selective oxidation of polyhydroxy-fluorosteroids has been reported by Beal, Hogg and Jackson[80], using *Septomyxa affinis* (ATCC 6737); 6α-fluoro-11β,17α,21-tri-hydroxy-2α-methylpregn-4-ene-3,20-dione, its epimer and dihydroxy analogues were successfully converted into the 1,4-pregnadienes.

Halogen exchange reactions have had little success as a means of introducing fluorine into secondary positions. In contrast, the 6α-fluoromethyl derivative of 3β,20β-diacetoxy-5α-pregnane was obtained when the 6α-iodomethyl compound was treated with silver fluoride in acetonitrile[81]. Similar treatment of 11β,17α-dihydroxy-6α-fluoro-21-iodo-2α-methylpregn-4-ene-3,20-dione gave the 6α,21-difluoride[80].

An important reaction for the synthesis of *cis*-difluorides, devised by Bowers and co-workers[82], has employed lead tetrafluoride (hydrogen fluoride and lead tetracetate in methylene dichloride) in reactions with an unsaturated steroid, e.g. (LI.a), giving the 5α,6α-difluoride (LI.b):

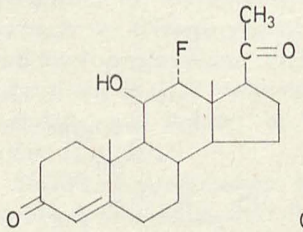


(LIa) (LIb)

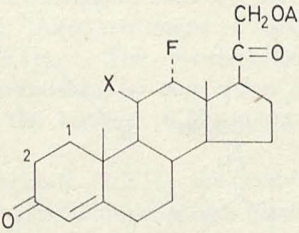
The mechanism of this reaction is probably complex in that with simple alkenes, *gem* difluorides are obtained[83] and with unsaturated monosaccharides, e.g. di-O-acetyl-D-arabinal, 1,1-difluorides are formed, with accompanying ring contraction (1:5 to 2:5)[84].

(*e*) *12-Fluorosteroids*

These have been prepared[85] by the action of hydrogen fluoride (in chloroform containing 5 per cent ethanol at 0°) on suitable epoxysteroids. Thus 11β, 12β-epoxyprogesterone gave 12α-fluoro-11β-hydroxyprogesterone (LII) which after oxidation with chromic acid furnished the 11-ketone. A similar reaction was carried out in the corticosterone series[86].



(LII)



(LIII) X, OH

(LIV) X,= O

(LV) X, OH double bond C_1—C_2

21-Acetoxy-11β,12β-epoxypregn-4-ene-3,20-dione and HF yielded 12-fluorocorticosterone acetate (LIII) which on oxidation (sodium dichromate in acetic acid) gave 11-dehydro-12α-fluorocorticosterone acetate (LIV).

Microbial dehydrogenation of (LIII) at position 1, 2 using *Bacillus sphaericus*[87], gave 1-dehydro-12α-fluorocorticosterone, isolated after acetylation as the 21-acetate (LV). The 12α-fluorocorticosterones exhibited the same enhanced glucocorticoid activity (relative to cortisone acetate) as did the corresponding 9α-fluoroisomers (vide, 9-fluorosteroids).

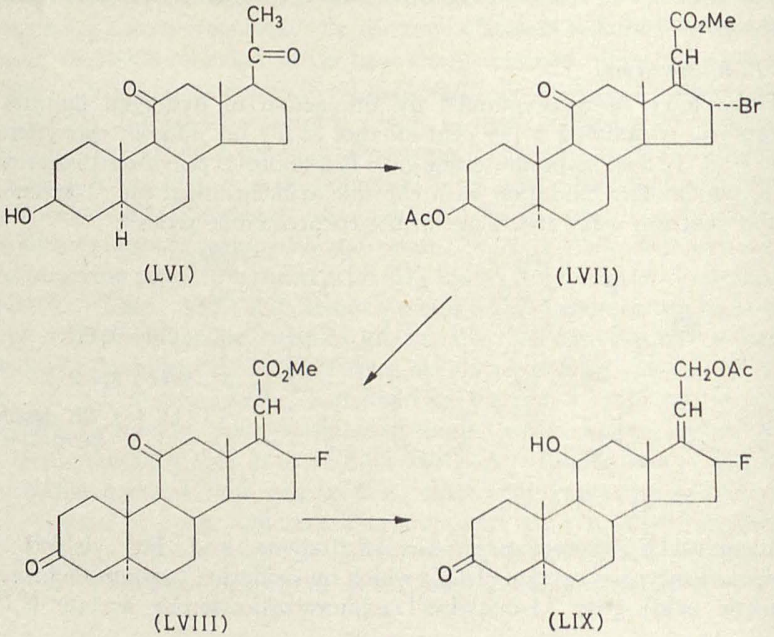
Fluorine has also been introduced into cortisone analogues by the action of HF in chloroform-tetrahydrofuran at −30° on 11,12 or 9,11-epoxides[88]. 11β,12β-Epoxyprogesterone[89] reacted with HF in chloroform-ethanol at 0° to give 12α-fluoro-11β-hydroxyprogesterone.

A di-halogeno compound was obtained[90] when *N*-bromoacetamide and HF reacted with 21-acetoxy-17α-hydroxypregna-1,4,9(11)-triene-3,20-dione; viz. 9α-bromo-11β-fluoro-17β-hydroxyandrost-1,4-diene-3-one.

Compounds with powerful anti-inflammatory activities were obtained[91] by microbial hydroxylation of fluorohydroxypregnenes. Thus, 12α-fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione was fermented with *Actimomyces* (ATCC 11,009) giving 12α-fluoro-11β-16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione. Further rearrangement of 21-acetoxy-12α-fluoropregn-4-ene-3,11,20-trione[92] and its 11β-hydroxy derivative[93] to the Δ^5 compounds occurs when the 3-oxo group is ketalized with butanone-2-dioxolane.

(*f*) *16-Fluorosteroids*

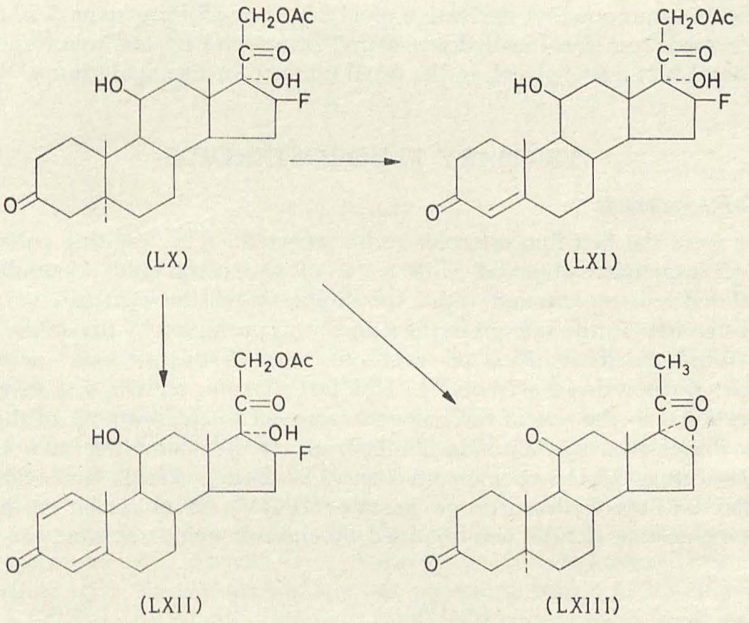
Recently, indirect methods have been developed for the introduction of fluorine into the 16-position of certain corticoids[94,48]. Although the 16β-bromo-[95] and 16β-chlorocorticoids[96] have been made by the opening of 16,17-epoxy-20-oxosteroids with HBr and HCl, all attempts to prepare the 16β-fluorosteroids by this route have been unsuccessful[96]. In a preliminary communication, Ayer and Schneider[94] describe the synthesis of 16β-fluorohydrocortisone acetate from 3β-hydroxy-5α-pregnane-11,20-dione (LVI).



(LVI) (LVII)

(LVIII) (LIX)

This was converted through the 21-ethoxyoxalyl derivative, Faworski rearrangement, acetylation and the action of *N*-bromosuccinimide to methyl 3α-acetoxy-16α-bromo-11-oxo-5α-pregn-17(20)-oate (LVII). Refluxing the latter with silver fluoride in acetonitrile gave good yields of the 16β-fluoroanalogue which on solvolysis and oxidation with chromic acid gave the 3-ketone (LVIII). Ketalization of (LVIII) with ethane-diol, followed by $LiAlH_4$ reduction, acetylation of the resulting alcohol and ketal hydrolysis gave 21-acetoxy-16β-fluoro-11β-hydroxy-5α-pregn-17 (20)-en-3-one (LIX). Oxidation of this with *N*-methylmorphiline oxidoperoxide[97] and catalytic amounts of osmium tetroxide gave 21-acetoxy-11β,17α-dihydroxy-16β-fluoro-5α-pregnane-3,20-dione (LX).



(LX) was converted (bromination, treatment with NaI in acetone and reduction) to 16β-fluorohydrocortisone acetate (LXI), which was purified through the Girard reagent. Also, treatment of (LX) with SeO_2 afforded-16β-fluoroprednisolone (LXII). The β-orientation of the 16-fluoro substituent in (LX) was established by conversion of the 21-alcohol (via mesylate and iodide) to the known 16,17α-epoxy-5α-pregnane-3,11,20-trione (LXIII).

16β-Fluoroprednisolone acetate (LXII) was converted by the method of Fried and Sabo into 9α,16β-difluoroprednisolone. In the bioassays, the latter compound was shown to be three times as active as hydrocortisone by glycogen deposition[99]. In contrast to 9α-fluoroprednisolone acetate there was no sodium retention. 16α-Fluoroprednisolone and 9α,16α-difluoro-prednisolone have also been reported[100]. Preliminary anti-inflammatory

assays show that the former steroid is 16 times and the latter 75 times more active than hydrocortisone.

19α,16β-Difluorohydrocortisone 21-acetate has been synthesized[101] by microbial hydroxylation with *Pestolatia* of 16α,17α-epoxydeoxycorticosterone acetate in the 11 position. Mesylation and ester elimination led to 16α,17α-epoxy-21-hydroxypregna-4,9(11)-diene-3,20-dione from which the 16β-fluoro was obtained by epoxide fission by HF.

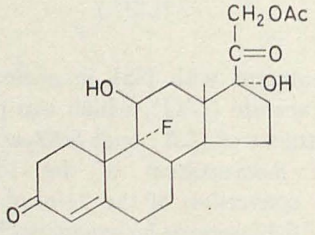
Berg and his colleagues[102] have also obtained 16β-fluorocortisol by hydroxylation of 16β-fluorocortexolone using *Curvularia lunata* (NRRL-2380). Treatment of the 9α-bromo analogue with acetone, triethylamine and acetic acid followed by anhydrous HF resulted in the formation of 9α,16β-difluorocortisol 21-acetate. This was converted by selenium dioxide and acid into 9α,16β-difluoroprednisolone.

The 16α-fluoromethyl derivative of 11β-hydroxy-5β-pregnane-3,20-dione was formed from the 16α-hydroxymethyl compound by tosylation and KF exchange in ethylene glycol, in the usual manner for terminal groups[103].

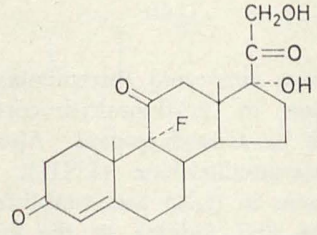
TERTIARY FLUOROSTEROIDS

(*a*) *9-Fluorosteroids*

These were the first fluorosteroids to be reported. The resulting enhanced biological activity observed with some of the compounds undoubtedly stimulated subsequent and rapid developments in the synthesis of other fluorosteroids. Initial interest in the subject was prompted by the observation that 9-halogenoderivatives of cortisone and hydrocortisone possessed marked glucocorticoid acitivity[104]. The fact that this activity was inversely proportional to the size of the halogen atom led to the synthesis of the 9α-fluoro-derivatives. By the action of anhydrous HF, in alcohol-free chloroform, on 21-acetoxy-9β,11β-epoxypregn-4-ene-3,20-dione, Fried and Sabo[105] isolated 9α-fluorohydrocortisone acetate (LXIV), from which 9α-fluorocortisone acetate (LXV) was obtained by chromic acid oxidation.



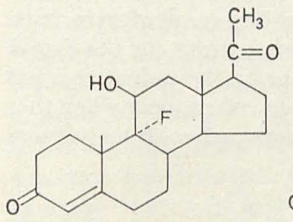
(LXIV)



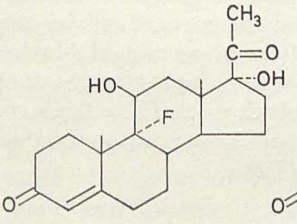
(LXV)

This method of making (LXIV) has since been improved[106,106a] by allowing the 9β,11β-epoxysteroid to react with hydrogen fluoride in the presence of a suitable Lewis base (e.g., tetrahydrofuran). The kinetics of this reaction have also been studied by this method and were shown to be first order[106].

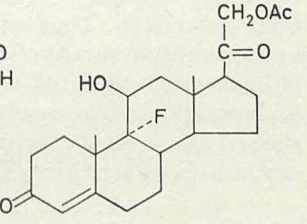
In this series, the most active member, 9α-fluorohydrocortisone acetate, was found to possess approximately 10 times the activity of cortisone acetate in the rat liver glycogen assay[107]. In addition to being potent glucocorticoids, these compounds are effective in controlling electrolyte balance and in maintaining life in the rat[108], dog[109,110] and man[109,111]. Fried and colleagues[112], therefore, investigated the influence of variations in the side-chain on the adrenocorticoid activity of such fluorinated derivatives. For this purpose, they prepared the 9α-fluorinated derivatives of 11β-hydroxyprogesterone (LXIV), 11β,17α-dihydroxyprogesterone (LXVII) and corticosterone acetate (LXVIII).



(LXVI)



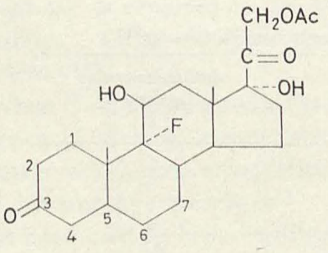
(LXVII)



(LXVIII)

The synthesis depended, as previously, on the addition of hydrogen fluoride to the 9β,11β-epoxysteroids. Oxidation with chromic acid furnished the corresponding 11-ketones. 9α-Fluoro-11β-hydroxyprogesterone (LXVI) and the 11-oxo-progesterone, although lacking the 17 and 20-hydroxyl groups approximately equalled cortisone acetate in glucocorticoid activity. The most powerful mineralocorticoids of the series were 9α-fluorocorticosterone acetate (LXVIII) and 9α-fluorodehydrocorticosterone acetate, which possessed activities similar to aldosterone[113].

The introduction of a double bond into the 1:2 position of cortisone and hydrocortisone leads to a three to fourfold increase in both glucocorticoid[114] and antirheumatic activity[116]. Subsequent investigations[117–118] were concerned with the activities of steroids possessing both a 1, 2-double bond and a 9α-fluorine atom. Starting from 9α-fluorohydrocortisone acetate (LXIV), catalytic hydrogenation gave a product which was formulated as the *allo*dihydro-9α-fluorohydrocortisone acetate (LXIX). This was treated



(LXIX) H at C_5 formulated as α

(LXX) Double bond at C_1-C_2
H at C_5 as α

(LXXI) Double bonds at C_1-C_2 and C_4-C_5

(LXXII) Double bonds at C_4-C_5 and C_6-C_7

with bromine (1 mole) and the resulting bromoketone dehydrohalogenated via the semicarbazone. Removal of the semicarbazone with pyruvic acid gave the ketone (LXX). Bromination of (LXIX) (2 mole) followed by

dehydrohalogenation with collidine afforded the dienone (LXXI) and the isomeric dienone (LXXII). 1-Dehydro-9α-fluorohydrocortisone acetate (LXXI) possessed about 25 times the activity of hydrocortisone acetate. The 2-methyl-9α-fluorohydrocortisone acetate, made by the action of hydrofluoric acid on 21-acetoxy-9β,11β-epoxy-17α-hydroxy-2-methylpregn-4-ene-3,20-dione, has also been shown to possess considerable adrenocorticoid activity[110]. This enhancement of adrenocorticoid activity, resulting from the substitution of a fluorine atom (and other halogens) at the 9α-position of 11β-hydroxy and 11-ketosteroids in the pregnane series has been interpreted by Herz, Fried and Sabo[120]. They have suggested a correlation between the electronegativity of the substituent at the 9α-position and adrenocorticoid activity. Thus enhancement of activity may be a result of an increase in the acidity constant of the important 11β-hydroxyl group (or the degree of polarization of the 11-keto group), brought about by the inductive effect of the neighbouring 9α-substituent. Their thesis received support when they showed that both the 9α and 12α-substituted halogenocorticoids had similar glucocorticoid activities (Table 3).

TABLE 3[120]

Glucocorticoid Activities of 9α- and 12α-halogeno-11β-hydroxyprogesterone (Cortisone acetate=1)

	Position 12α	*Position* 9α
Bromo-11β-hydroxyprogesterone	0·25–0·35	0·1–0·2
Chloro-11β-hydroxyprogesterone	0·50–0·60	0·35
Fluoro-11β-hydroxyprogesterone	0·60–0·90	0·85

Bergstrom and colleagues[121] have recently reported the synthesis and activity of 17α-acetoxy-9α-fluoro-11β-hydroxyprogesterone. When tested orally in the Clauberg assay, this compound was 2,500 times as potent as progesterone.

Extensions of the foregoing methods have led to other, differently substituted, hormonally-active fluorosteroids. When 16α,17α-epoxy-21-acetoxy-3β-hydroxypregn-5-en-20-one was submitted to the tried reaction sequence and followed by adrenal incubation, 6α-fluoro-16α-hydroxyhydrocortisone resulted. This compound, as well as 6, 9α-difluoro-16α-hydroxy-prednisolone and its acetonide possessed high levels of anti-inflammatory activity without sodium ion retention[122] (Table 4).

TABLE 4

Biological Activity of 6α-fluoro-16α-hydroxycorticoids[122]

Hydrocortisone	*Anti-inflammatory activity* 1
9α-Fluoro-16α-hydroxyprednisolone	5
6α-Fluoro-16α-hydroxyhydrocortisone	5
6α-Fluoro-16α-hydroxyhydrocortisone 16, 17-acetonide 21-acetate	4
6α-Fluoro-16α-hydroxyprednisolone	20
6α, 9α-Difluoro-16α-hydroxyhydrocortisone	15
6α, 9α-Difluoro-16α-hydroxyhydroprednisolone	35
6α, 9α-Difluoro-16α-hydroxyprednisolone 16, 17-acetonide	100

Derivatives of 9α-fluorohydrocortisone have been extensively studied[123,124]. Fermentative hydroxylation of 9α-fluorohydrocortisone by *Streptomyces rimosus* gave[125] the 6β-hydroxy derivative whereas, 11β,21-dihydroxy-9α-fluoro-16α,17α-isopropyldioxypregn-4-ene-3,20-dione with *Trichoderma glaucum* was acetylated in the 21 position[126].

Hydroxylation in the 14α position has been accomplished[127] in 9α-fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione by means of *Pleospora gacumanni* in 70 per cent beer wort, and the 16α-hydroxy derivative of 9-fluorohydrocortisone has been obtained by the action of *S. roseochromogeus*[128].

Synthetic variants of 9α-fluoro-16α-hydroxyhydrocortisone and 9α-fluoro-16α-hydroxyprednisolone (triamcinolone)[129] include 9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-4,6-diene-3,20-dione and 6-dehydrotriamcinolone. In the liver glycogen deposition test, the former product had an activity equal to that of hydrocortisone, while the latter was 2·3 times more active[129]. Acylation of 9α-fluorocortisone 21-acetate by means of toluene *p*-sulphonic acid in acetic acid-acetic anhydride led to the 17α,21-diacetate-3-*enol*-acetate while 9α-fluorohydrocortisone, treated similarly, gave the 11β,17α,21-triacetate-3-*enol*-acetate, both being potent long acting anti-inflammatory agents[130].

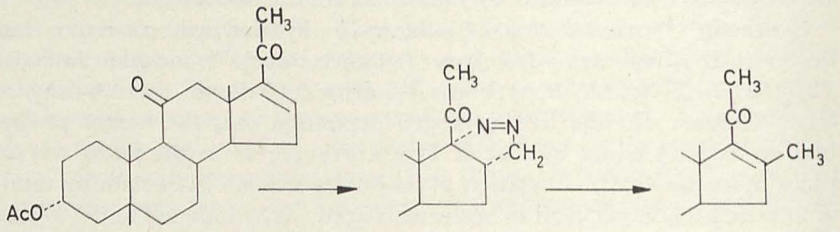
Unsaturated analogues of 9α-fluorocortisone, e.g. 1-dehydro-9α-fluoro-6α-methylhydrocortisone[131], also show high anti-inflammatory activity. Dehydration of 9α-fluoroprednisolone 21-acetate has been accomplished without loss of halogen and with the production of the pregna-1,4,16-triene[132]. Other unsaturated derivatives investigated include 9α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene and the corresponding pregna-1,4-diene and pregna-1,4,6-triene[133,134] and 9α-fluoro-11β,17α-dihydroxy-6-methylpregna-1,4-diene-3,20-dione (Oxylone)[135], which possess both glucocorticoid and anti-inflammatory activities.

Enhanced glucocorticoid activity has been found in some alkylated fluorosteroids. 16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-2α-methylpregn-4-ene-3,20-dione has an activity approximately equal to that of hydrocortisone[136]. Treatment of 17α-acetoxy-9α-bromo-11β-hydroxy-2α-methylpregn-4-ene-3,20-dione with potassium acetate in acetone gave the 9β,11β-epoxide which was converted[137] into the 9α-fluoro-11β-hydroxy derivative by the action of HF in methylene dichloride at −78°. This compound is reported to be useful in treating severe functional uterine bleeding. Other 2-alkylprogesterones are reported by Nathan and Schneider[138].

When 9α-fluoro-2α-methylhydrocortisone was injected into rats, in the absence of dietary sodium chloride, over a period of eight months, all animals developed myocarditis, nephrosclerosis and periarteris nodosa and became hypersensitive[139]. The influence of the 6α-methyl group has been examined in 11β,17α-dihydroxy-9α-fluoro-6α-methylpregn-4-ene-3,20-dione[140], (obtained by the action of HF on the corresponding 9β,11β-epoxide) and 16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methylpregn-4-ene-3,20-dione[141]. 5α-Pregnane derivatives, some having methyl

groups in the 11α-position, have been synthesized by the CIBA group; 21-acetoxy-9β,11β-epoxy-17α-hydroxy-11α-methyl-5α-pregnane-3,20-dione, treated with 48 per cent aqueous HF in the presence of methylene dichloride gave the 9α-fluoro-11β,17,21-triol[142].

A novel method[143] of introducing a methyl group into the 16β-position has been developed. The action of diazomethane on the conjugated Δ^{16}-ketone (LXXIII), giving an intermediary pyrazoline (LXXIV), gave on decomposition in alkaline solution the Δ^{16}-16β-methyl derivative (LXXV).



(LXXIII) (LXXIV) (LXXV)

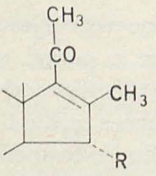
A series of 16β-methyl steroids, some fluorinated, have the activity reported in Table 5.

TABLE 5

Biological Activity of 16β-Methylcorticoids[143]

16β-methyl derivative of:	*Liver glycogen assay*	*Systemic granuloma*
Cortisone	0·4	2
Hydrocortisone	0·6	4
Prednisone	1·0	26
Prednisolone	1·5	23
9α-Fluorohydrocortisone	8·5	23
9α-Fluoroprednisolone	11·0	70

Adjacent substitution of (LXXV) by halogen at the 15-position (achieved by the action of hydrogen halide on the 16α,17α-epoxide of LXXIII) gave products which produced a hypsochromic shift in the absorption maximum of the Δ^{16}-20-keto chromophores, the effect increasing with the electronegativity of the halogen:



	λ_{max} (mμ)
R,H	249
Br	249
Cl	244
F	240

This was considered to be in accordance with the structure of the 15α (quasiequatorial) halogenated compounds.

Other active compounds related to this type, e.g. 21-acetoxy-11β,17α-dihydroxy-9α-fluoro-16α-methylpregna-1,4-diene-3,20-dione have been obtained by the Upjohn Group[144] and by Mannhardt and co-workers[145]. The synthesis of 6α-fluoro-16α-methyl Reichstein S substance has been accomplished[59] from 16α-methylpregnolone by a sequence involving adrenal incubation.

6α-Fluoro-16α-methylprednisolone is reported to have high anti-inflammatory activity[59], the parent 16α-fluoroprednisolone acetate has 16 times the activity and the 9α-fluoro derivative about 75 times the activity of hydrocortisone[100]. The 6α,16α-dimethyl-9α-fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione has also been reported[100a]. The 9α-fluoro-11β-hydroxy-*A*-norprogesterone has been synthesized[146] by cleavage of the 9β,11β-epoxide with HF in chloroform-tetrahydrofuran at 4° for 5 h.

A number of 9α-fluoro analogues of the androstane series are known. The route to the synthesis[147] of 9α-fluoroandrost-4-ene-3,11-dione involved the formation of the 9β,11β-epoxide from 17α-hydroxycorticosterone 21-acetate and its cleavage with HF. The fluoroproduct and the 9α-fluorodeoxycorticosterone had 12 times the sodium retaining potency of deoxycorticosterone acetate[147].

Microbial oxidation[148] of 9α-fluoro-11β-hydroxyprogesterone by *Cylindrocarpem radicola* (ATCC-11,011) gave 9α-fluoroandrost-4-ene-3,11,20-trione. Treatment of 9β,11β-epoxyandrosta-1,4-diene-3,17-dione with HF gave 9α-fluoro-11β-hydroxyandrosta-1,4-diene-3,17-dione[149]. Other related compounds which have been studied include 11β,17β-dihydroxy-9α-fluoro-17α-methylandrosta-1,4-dien-3-one[150] and 9α-fluorotestosterone acetate[151].

A number of authors have sought to improve the solubility of the corticoid analogues by formation of ionic derivatives such as 9α-fluoro-16α-methylprednisolone 21-sulphate[152] and 9α-fluoro-17α-hydroxy-2α-methylpregn-4-ene-3,11,20-trione 21-phosphate[153]. The 21-mercapto derivatives of 9α-fluorosteroids are also known[154] as well as the 16α-carboxymethylthio derivatives of 9α-fluoroprednisolone[155].

(*b*) *17-Fluorosteroids*

The indication that 17α-chloroprogesterone, its 6α-fluoro-17α-bromo derivative and related compounds were all orally active progesterins without androgenic effects[156] led to the exploration of 17-fluorosteroids[156a]. Deghenghi and Gaudry[157] found that 17α-bromoprogesterone treated with potassium cyanide, followed by potassium acetate, gave 20-cyano-17α,20-epoxypregn-4-ene-3,20-dione[156a]. This was converted by the action of hydrofluoric acid at room temperature (in 1 h) to 17α-fluoropregn-4-ene-3,20-dione 20-cyanohydrin, which in turn gave 17α-fluoroprogesterone. The fluorine could be removed when the latter was heated with a mixture of lithium bromide and lithium carbonate in dimethyl formamide (in an atmosphere of nitrogen) to give the 16-dehydroprogesterone. In another method, 3α-acetoxy-17α-bromopregnane-11,20-dione has been converted into the 21-acetoxy-17α-fluoropregn-4-ene-3,11,20-trione. Replacement of

the 17α-hydroxy group by a halogen atom results in diminished adrenocorticoid activities, as measured by the eosinophil test in mice. Large negative optical rotatory dispersion effects due to the 17α side chains, as in the pregnane-20-ones substituted at C–16, have also been reported by Struck and Hautman[159].

Other Fluorosteroids

Fluorine has been successfully introduced into the 11β-position of the steroid nucleus, by treatment of 9(11)-dehydroprogesterone with *N*-bromoacetamide and HF, giving 9α-bromo-11β-fluoroprogesterone[160]. This compound was 0·7 times as active as progesterone itself in the McPhails assay[40]. Comparison of the biological activity of various 11-halogeno derivatives is made in Table 6.

TABLE 6

Progestational Activity of Dihaloprogesterones[160]

9α,11β-Dichloroprogesterone	5·5*
9α-bromo-11β-chloroprogesterone	1·0
9α-bromo-11β-fluoroprogesterone	0·7
9α,11β-Dichloropregna-1,4-diene-3,20-dione	3·0
1-Dehydro-9α-chloro-11β-fluoropregna-1,4-diene-3, 20-dione	2·0

(*Progesterone 1)

Other investigations have led to the synthesis of 20-fluorosteroids; Magerlein, Birkenmeyer and Kagan[100] found that 21-acetoxy-11β,16α-dihydroxypregna-1,4,17(20)-trien-3-one reacted with thionyl chloride and tributylamine to give 21-acetoxy-20-chloro-11β-hydroxypregna-1,4,16-trien-3-one which, on titration with 0·1 *N*-sodium hydroxide, gave the corresponding 20,21-epoxide. Cleavage of the epoxide occurred readily with HF giving, after acetylation, a mixture of 21-acetoxy-20-fluoro-11β-hydroxypregna-1,4,16-trien-3-one and the 16α-fluoro-1,4,17(20)-triene. Attempts to exchange the 20-chloro atom using AgF resulted mainly in the 20-hydroxy compound but with some of the mixed 20- and 16α-fluorides as resulted from the epoxide experiment.

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