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FLUORINATED STEROIDS

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When studying methods for introducing an oxygen substituent at position 11 of a steroid molecule, Fried and Sabo[1] in 1954 observed unexpectedly that 9α-fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione has a several times greater hormonal and anti-arthritic activity than has cortisol. This discovery formed the beginning of a new field of research — the synthesis of modified steroidal compounds — in steroid chemistry. The number of papers and patents which have appeared during the past decade on the chemistry and pharmacology of these compounds has already reached thousands. The introduction of additional alkyl groups, heteroatoms, and double bonds into a steroid molecule produces a considerable increase in the hormonal activity of natural steroids. Special interest attaches to fluorinated steroids among modified steroids, since the introduction of fluorine into a steroid molecule produces a great change in the physiological activity of the hormone.

I. METHODS OF INTRODUCING FLUORINE INTO A STEROID MOLECULE

The synthesis of 9α-fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione was first accomplished by Fried and Sabo[1], who opened the 9β,11β-oxide by means of hydrogen fluoride. Since then the cleavage of oxides has become one of the main methods for introducing fluorine into many positions in the steroid molecule. However, the exceptionally high physiological activity of fluorinated steroids has led investigators to seek new methods for the synthesis of fluorinated steroids. Thus methods have been worked out for introducing fluorine on the basis of the reaction of steroid olefins with an *N*-halogeno-amide and hydrogen fluoride[2] and with lead tetrafluoride[3], the reaction of steroid ketones with sulphur tetrafluoride[4], and of hydroxy-compounds with silver fluoride or hydrogen fluoride and other reagents; perchloryl fluoride has been studied and used for the synthesis of fluorinated steroids[5].

The above methods enable compounds to be prepared having isolated fluorine atoms, as well as *gem*- and *vic*-difluoro-derivatives. By combining several methods it is possible to introduce successively into the steroid molecule two, three, and four fluorine atoms, which produces a marked increase in the physiological activity of the steroids (see Section II).

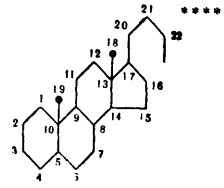
The scope of the various methods of synthesising fluorinated steroids is summarised in Table 1, from which it is seen that each method has its own specific field of application, seldom overlapping with those of other methods. Therefore the suitability of different processes for introducing fluorine at a given position in the steroid molecule can be compared only in a few cases. Thus the synthesis of 6-fluoro-steroids, for example, can be effected by three methods, based on the addition of fluorine-containing reagents to the 5–6 double bond. When the steroid contains one double bond, synthesis through the 5α,6α-oxides is mostly used. With polyunsaturated steroids the corresponding oxides are obtained unselectively and in very low yields, and it therefore becomes more convenient to apply the addition of mixed halogens. The addition of lead tetrafluoride has the advantage over both these methods that it enables fluoro-derivatives having the 6α configuration to be obtained directly.

1. Opening of Steroid Oxides by Fluorine-Containing Reagents

The introduction of a fluorine atom into a steroid molecule by opening an epoxide with hydrogen fluoride, which takes place by an S_N2 mechanism and leads to a *trans*-diaxial cleavage of the oxide ring, has become one of the principal methods for introducing a fluorine atom not only into position 9 but also into positions 2, 6, 12, 15, 17, and 20 in the steroid molecule, since the corresponding epoxides are quite accessible and the techniques are simple.

Fluorinating agents which have been used in these cases are, besides hydrogen fluoride, 48% hydrofluoric acid, potassium hydrogen fluoride, and the boron trifluoride–ether

TABLE 1. Preparative possibilities of various methods for the fluorination of steroids.



Method	Fluorine introduced at position																					
	2α	2β	3α	3β	4	5α	6α	6β	7α	7β	9α	10β	11α	11β	12α	15α	16α	16β	17α	17β	20α	20β	21	22
Cleavage of oxides		+***			+***	+		+			+	+			+	+			+			+		
Addition of mixed halogens to double bond								+						+				+						
Addition of PbF_4 to double bond						+*	+*		+															
Addition of $FClO_3$ to double bond					+					+														
Addition of HF to double bond						+		+		+	+													+
Addition of $C_6H_5IF_2$ to double bond							+		+			+												
Addition of $FClO_3$ to phenolic steroids			+	+			+							+		+			+	+				
Replacement of hydroxyls			+	+													+	+	+				+	
Replacement of toluene-p-sulphonate and methanesulphonate groups			+	+														+					+	
Replacement of other halogens by fluorine				+			+											+					+	
Replacement of hydrogen by fluorine ($FClO_3$)	+				+		+	+									+	+					+	
Replacement of >C=O by fluorine (SF_4)			+**	+**									+**	+**					+**	+**	+**	+**		

* Vicinal difluoride formed.

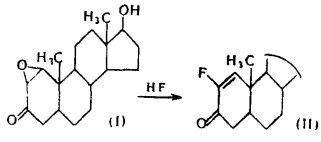
** Geminal difluoride formed.

*** Fluorine atom adjacent to double bond.

**** Here and subsequently the heavy black dots denote methyl groups.

complex. The effect of the solvent, the temperature, and the duration of the reaction, and also of neighbouring substituents, on the course of the reaction has been studied.

Relatively little work has been done on the action of fluorine-containing reagents on oxide groups in the A ring of a steroid molecule. Thus cleavage of the 1β,2β-oxide (I) with hydrogen fluoride is accompanied by dehydration and yields the 2-fluoride (II) containing a fluorine atom adjacent to a double bond[6]:

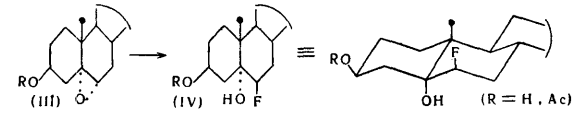


Fission of the 2α,3α-oxide under the same conditions gives the 2β-fluoro-3α-hydroxy-compound[7,8]. 4,5-Epoxides have been cleaved mainly with hydrochloric and hydrobromic acids, with the formation of 4-chloro- and 4-bromo-steroids[9,10].

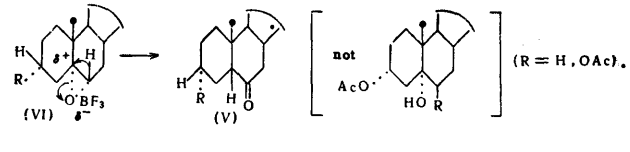
On the other hand, the cleavage of 5,6-epoxides has been subjected to quite detailed study on numerous examples and with various fluorinating reagents. The boron trifluoride–ether complex has been most widely used as such an agent, the reaction usually being conducted in benzene or in a mixture of benzene and ether at room temperature[11].

The opening of steroid 5α,6α-epoxides with the boron trifluoride–ether complex, first studied by Henbest and Wrigley[11,12], gives different products depending on the nature and the stereochemistry of the substituent attached to $C_{(3)}$. An epoxide which is unsubstituted at $C_{(3)}$ or else has a 3α-acetoxy-group (VI) gives as main product the corresponding $C_{(6)}$ ketone with rings A and B linked in the *cis*-configuration (V).

On the other hand, the 3β-hydroxy-epoxide — or its acetate (III) — undergoes cleavage by a quite different mechanism, the main product then being a fluorohydrin (IV).

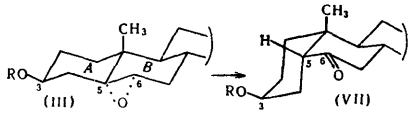


This course of the reaction was explained by considering the electronic and configurational factors. In unsubstituted epoxides (VI: R = H), boron trifluoride produces partial ionisation of the bond linking the epoxy-oxygen to the more alkylated $C_{(5)}$, promoting a simultaneous 1,2-hydride shift with the formation of a $C_{(6)}$ ketone (V).

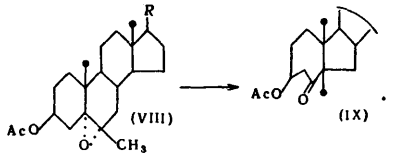


In the case of the 3β-alcohol (III) or its ester, however, two factors tend to prevent formation of the $C_{(6)}$ ketone. The first of these, the electronic factor, diminishes the partial ionisation of the bond linking the epoxy-oxygen to $C_{(5)}$ (this factor is necessary for formation of the $C_{(6)}$

ketone) owing to the increased inductive ($-I$) effect of the boron trifluoride–ether complex coordinated with the 3β--alcohol or ester. In this case the steric factor acts in the same direction, since formation of the $C_{(6)}$ ketone (VII) from (III) would have appreciably increased non-bonding 1,3-interactions in ring A, and the 3β-hydroxyl would have passed from the equatorial to the axial position.

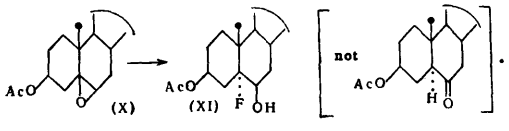


Thus in this case the second reaction, resulting in formation of the fluorohydrin (IV), should predominate. When position 6 is substituted (e.g. by a methyl group) the reaction of the 5α,6α-oxide (VIII) with boron trifluoride is anomalous, being accompanied by rearrangement to an *A*-homo--*B*-nor-compound (IX).[13]

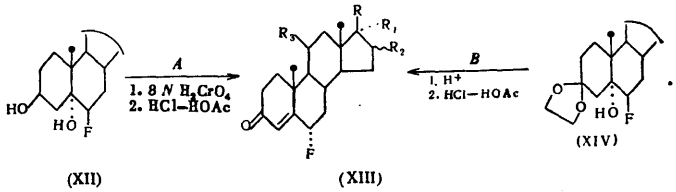


In the case of the 3α-acetate of the 5α,6α-epoxide (VI: R = OAc), the above electronic and conformational factors act in opposite directions, but the predominance of the latter results in a very high yield of $C_{(6)}$ ketones (V).

5β,6β-Epoxides with no 3-substituent yield the $C_{(6)}$ ketone, whereas the 3β-acetoxy-compound (X) gives 5α--fluoro-6β-hydroxy-derivatives (XI).



Bowers et al.[14], in an attempt to assess the role of electronic factors, studied the cleavage of 3-keto-5α,6α--epoxides with boron trifluoride. The above conformational factors, which play an important part in the fission of 3α- and 3β-acetoxy-epoxides, are absent from this system, and therefore the composition of the reaction products is determined by competition between the increase in ionisation of the epoxy-oxygen under the influence of the boron trifluoride and its decrease due to the $-I$ effect of the keto-group. The latter obviously predominates, since treatment of 5α,6α-epoxypregnane-3,20-dione with the boron trifluoride–ether complex gives a 44% yield of the corresponding fluorohydrin.



Route *A*

(XIII)

(*a*) R = OH; $R_1 = R_2 = R_3 = H$
(*b*) R = $COCH_3$; $R_1 = R_2 = R_3 = H$
(*c*) R = $COCH_3$; R_1 = OAc; $R_2 = R_3 = H$
(*d*) R = $COCH_3$; R_1 = Br; $R_2 = R_3 = H$
(*e*) R = $COCH_2OH$; $R_1 = R_3$ = OH; R_2 = ...CH_3
(*f*) R = $COCH_3$; R_1 = OH; R_2 = Cl; $R_3 = H$
(*g*) R = OH; R_1 = CH=CH_2; $R_2 = R_3 = H$

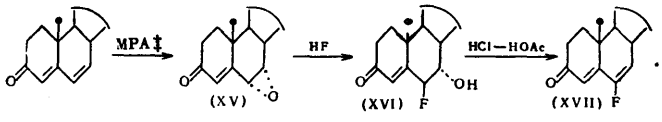
Route *B*

(*a*) R = OH; $R_1 = R_2 = R_3 = H$
(*b*) R = $COCH_3$; $R_1 = R_2 = R_3 = H$
(*c*) R = $COCH_2OH$; $R_1 = R_3$ = OH; R_2 = ...CH_3
(*d*) R = $COCH_2OH$; R_1 = OAc; $R_2 = R_3 = H$
(*e*) R = $COCH_2OH$; $R_1 = R_3 = R_2 = H$
(*f*) R = $COCH_2OH$; R_1 = OAc; R_2 = H; R_3 = =O

It was concluded from this that 3,3-ethylenedioxy--5α,6α-epoxides are suitable compounds for conversion into fluorohydrins, as was confirmed experimentally[14]. Thus the precursors of 6β-fluoro-5α-hydroxy-compounds may be either 5α,6α-epoxy-3β-hydroxy-steroids and their acetates[11] or 5α,6α-epoxy-3,3-ethylenedioxy-steroids[14]. The last stage in the synthesis was the transition from 6β-fluoro-5α-hydroxy-derivatives (XII) and (XIX) to the physiologically active 6α-fluoro-4-en-3-ones (XIII), which was accomplished in two ways, *A* and *B*.[5-17] It was established that, when the 6β-fluoro-5α-hydroxy-3-ones undergo isomerisation under the influence of hydrogen chloride in acetic acid, 6β-fluoro-analogues of 4-en-3-ones are formed, and these on further treatment are converted into 6α-fluoro-4-en-3-ones. The scheme *A* has been used to synthesise the 6α-fluoro-analogues of testosterone (XIII*a*), progesterone (XIII*b*),[15] 17α-acetoxyprogesterone† (XIII*c*),[18] 17α-bromoprogesterone (XIII*d*),[19,20] 16α-methylcortisol (XIII*e*),[21,22] 16β-chloro-17α-hydroxyprogesterone (XIII*f*),[23] 17α-vinyltestosterone (XIII*g*),[24] and other derivatives[25-27]. Route *B* has provided syntheses of 6α-fluoro-analogues of testosterone (XIII*a*), progesterone (XIII*b*), cortexone 17--acetate (XIII*h*), cortexone (XIII*i*), cortisone (XIII*j*),[14,17,28] and 16α-methylcortisol (XIII*e*);[29] here, owing to the well--known instability of 17α-hydroxy-20-ones to some types of Lewis acids, in the presence of which they undergo *D*-homo-rearrangement, the 17α-hydroxy-group of the precursors was protected by acetylation (R_1 = OAc).

A modification of the above method is the synthesis of 6α-fluorinated analogues of steroid hormones with the use of potassium hydrogen fluoride[30], hydrogen fluoride[31-39], or 48% hydrofluoric acid[40] to open the 5α,6α-oxides. In the last case 17α-alkyl-6α-fluorotestosterones[40], 6α--fluorocortisone[41], 6α-fluoro-16α-methylcortisol[42], and other 6α-fluorinated analogues[43-49] have been obtained.

6-Fluoro-steroids can also be prepared from 6,7-epoxides (XV) and hydrogen fluoride. Dehydration of the resulting 6β-fluoro-7α-hydroxy-derivative (XVI) yields a steroid 6-fluoro-4,6-dien-3-one (XVII).[50-55]

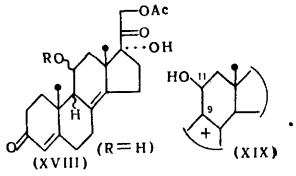


† The Russian text has been largely followed in the use of trivial names (Ed. of Translation).

‡ Monoperphthalic acid.

This procedure has been used to obtain 6-dehydro-6--fluoro-derivatives of 17α-ethynyltestosterone, progesterone, 17α-acetoxyprogesterone, cortexone, prednisone, etc.[50]

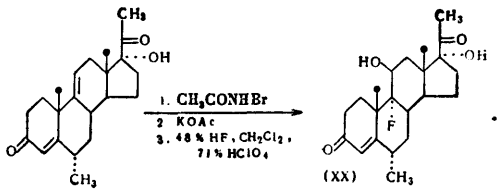
After Fried and Sabo's discovery of 9α-fluorocortisol[1,56], the cleavage of 9β,11β-epoxides of steroid hormones with hydrogen fluoride became the main method for introducing a fluorine atom into position 9 of a steroid molecule. Hirschmann et al.[57], and later Fried and Sabo[58], having carefully studied the reaction conditions, the kinetics, and the role of solvents, showed that, when the reaction is conducted in absolute chloroform, formation of 9α-fluoro--derivatives (obtained in 50% yield) is accompanied by that of a product (XVIII) containing no fluorine, the quantity of this compound depending on the reaction conditions. When the reaction is conducted in liquid hydrogen fluoride at -70°, (XVIII) becomes the main product.



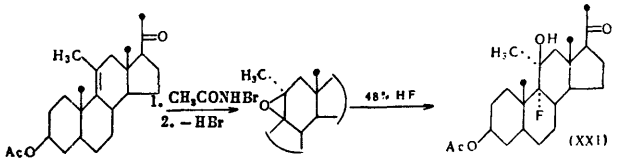
Formation of (XVIII) is probably due to inadequate concentration of the fluoride ion, resulting from the feeble dissociation of HF into H^+ and F^- ions. Addition of a Lewis base (such as tetrahydrofuran) to the reaction medium raised the concentration of F^- and diminished the quantity of (XVIII) with an increased yield of the fluorohydrin. Since, however, interaction of hydrogen fluoride with bases (in particular with tetrahydrofuran) lowers the acidity of the reaction medium, it is very important to select their optimum ratio. A kinetic study showed that, with a molar ratio of hydrogen fluoride to tetrahydrofuran of ~1.65 or above, the epoxide reacts at a sufficient rate at -30°. With a ratio of 1.94 the yield of the fluorohydrin reaches ~65%. The order in which the reagents are added is also important in this reaction: it is best to add a solution of the oxide in chloroform to a mixture of tetrahydrofuran and hydrogen fluoride cooled below -30°, which raises the yields to 75%. This reaction is kinetically of the first order with respect to the epoxide[57].

Fried and Sabo's method has been used to synthesise 9α-fluorinated derivatives of the pregnane[59-63] and androstane series[64-66]. Since 9α-fluorocortisol has found only limited application in medical practice owing to its broad spectrum of action[67], the same method has been used to prepare 9α-fluoro-analogues of corticosteroids containing also 2-alkyl,[68-72] 4-chloro,[73,74] 6-methyl,[75-79] 16-alkyl,[80-86] and 16-hydroxy-groups[75,76,87-94]. These substituents produce a considerable narrowing of the spectrum of biological action, at the same time intensifying the various types of activity (see Section II). For this purpose syntheses were made of compounds containing more than one fluorine atom, e.g. in the positions 6,9, 6,9,21, etc. A 9α-fluorine atom was introduced by Fried and Sabo's method into compounds already containing fluorine in position 6 or 21. In this way 6α,9α-difluoropregnanes[17,40,95-110] and 9α,21-difluoropregnanes[77,79,110,111] have been obtained.

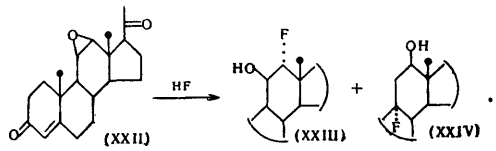
A somewhat modified method, involving the use of 48% hydrofluoric acid to cleave the 9β,11β-oxides, has been used to synthesise[112] 9α-fluoro-11β,17α-dihydroxy-6α--methylprogesterone (XX) and its 1-ene analogue:



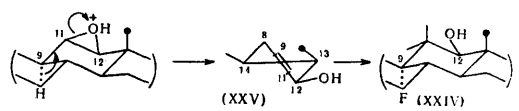
Introduction of a 9α-fluorine atom has been effected under the same conditions in the presence of an 11-methyl group[113,114]:



9α-Fluoro-analogues can be obtained also (together with 12-fluoro-derivatives) from 11β,12β-epoxides and hydrogen fluoride under the conditions employed by Fried and Sabo for the cleavage of 9β,11β-oxides. Thus in 1956 a paper appeared[115] on the synthesis of 12α-fluoro--11β-hydroxy- and -11-keto-progesterones. 11-Dehydroprogesterone gave with *N*-bromoacetamide a 45% yield of a bromohydrin, which formed in quantitative yield the 11β,12β-epoxide (XXII), from which the 11,12-fluorohydrin (XXIII) was obtained by the action of hydrogen fluoride in chloroform. In addition to a 70% yield of (XXIII), the hydrofluorination gives a 15% yield of the 9α-fluoro-12β-ol (XXIV). Application of the same reaction to an 11β,12β-epoxide in which ring A is saturated, and rings A and B are linked in the *cis* configuration, gives (XXIV) as the main product, whereas the 12α-fluoro-11β-hydroxy-derivative of type (XXIII) is formed only in small amounts[116]. This occurs also in the cleavage of 11β,12β-oxides of the spirostan series[117-119]:

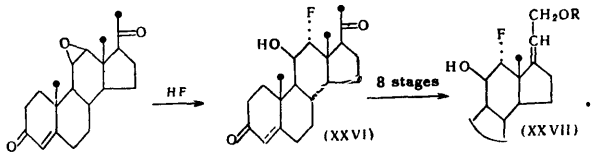


Formation of 9α-fluoro-12β-hydroxy-compounds of type (XXIV) from 11β,12β-oxides can be regarded as a simultaneous reaction involving the intermediate formation of the 9(11)-en-12β-ol (XXV) as an intermediate stage, followed by addition of HF to the resulting 9–11 double bond:

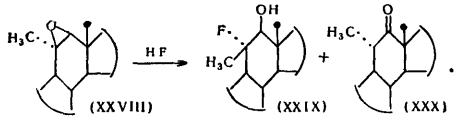


11β,12β-Epoxides have been used as starting materials for the synthesis of 12α-fluoro-analogues of androstane[120-123], progesterone[115,124,125], corticosterone[126-128], cortisone and prednisolone[129], 16α-hydroxyprednisolone[130],

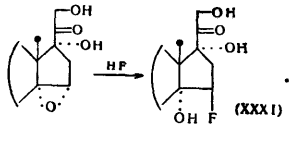
and other pregnanes[131-134]. For the synthesis of 12α--fluorocortisol, Fried et al.[135] tried to use 12α-fluoroprogesterone (XXVI) as intermediate, with subsequent introduction of the 17α- and 21-hydroxy-groups:



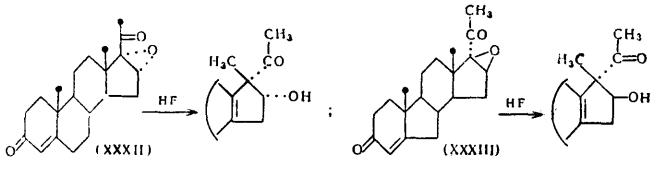
But it was found that, owing to steric and electronic factors, a 12α-fluorine atom prevents osmium tetroxide from approaching the 17–20 double bond, and the latter could not be oxidised in the compound (XXVII). This apparently explains the difficulty of cyclising the fluorohydrin (XXVI) to the oxide[135]. In order to avoid the effect of a 12α-fluoro--substituent, 11β,12β-epoxycortisone acetate was first synthesised, and smoothly converted in the usual way into the 12β-fluoro-analogue of cortisol. It is interesting that with 11α-methylated 11β,12β-epoxides (XXVIII) hydrogen fluoride reacts in two ways: under the influence of the electron-donor 11-methyl group, the oxide opens up with the formation of the 11α-fluoro-12β-hydroxy-11β-methyl derivative (XXIX), and this is accompanied by the acid--catalysed isomerisation of the epoxide to the 11α-methyl--12-one (XXX), the 12α-fluoro-derivative not being detected[136]:



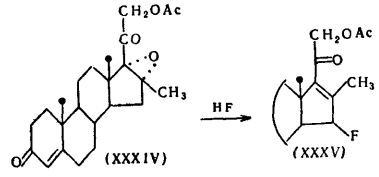
The 14α,15α-epoxide, in contrast to other steroid oxides, was extraordinarily stable towards such reagents as boiling acetic acid, trichloroacetic acid, etc.[137] Nevertheless, hydrogen fluoride[138,139] gives the normal *trans*-diaxial cleavage of the epoxide to form the corresponding 15β-fluoro-14α-hydroxy-derivative (XXXI):



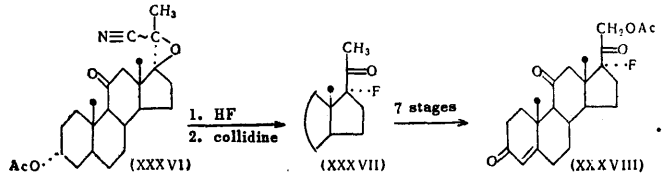
Attempts to cleave the 16α,17α-epoxide and obtain 16-fluoro-compounds, by using hydrogen fluoride under the conditions described for the cleavage of 5α,6α- and 9β,11β-oxides, were unsuccessful[140-144]. It was shown[145] that, when hydrogen fluoride acts on 16,17-epoxides, in particular 16α,17α- and 16β,17β-epoxyprogesterones (XXXII) and (XXXIII), the latter undergo the Wagner–Meerwein rearrangement, no fluorine-containing products being detected:



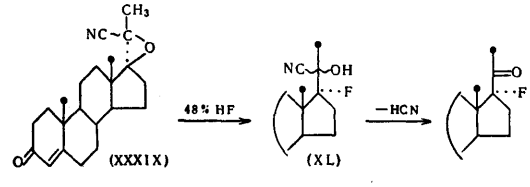
Fission of a 16α,17α-epoxide containing a 16β-methyl group (XXXIV) yielded the 15β-fluoro-16-methyl-16-ene (XXXV):[146]



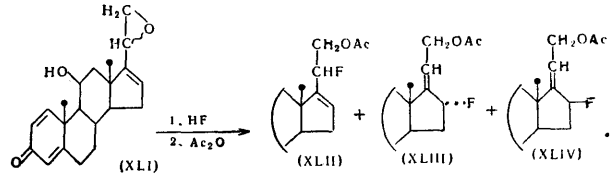
Attempts to introduce fluorine into position 17 by the cleavage of 16,17-epoxypregnanes with hydrogen fluoride were likewise unsuccessful. A similar reaction with 20ξ-cyano--17,20-epoxy-17α-pregnanes (XXXVI) was investigated for the introduction of fluorine at position 17.[147-149] In this case the 17,20-oxide ring is opened under the influence of hydrogen fluoride with the formation of a 17α-fluoro-20--hydroxy-derivative; subsequent elimination of hydrocyanic acid yields the 17α-fluoro-20-ketone (XXXVII). This route has been used for the synthesis of 11-dehydro--17α-fluorocorticosterone acetate (XXXVIII):[147]



It is interesting that in the case of progesterone derivatives the cyano-epoxide (XXXIX) does not react with anhydrous hydrogen fluoride, giving the fluorohydrin (XL) only with 48% hydrofluoric acid[148]:

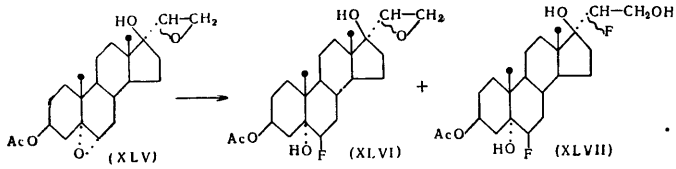


20ξ,21-Oxides have been least studied in relation to the action of fluorine-containing reagents. Until recently only the reaction of the 20ξ,21-epoxy-16-ene derivative (XLI) with hydrogen fluoride in the presence of acetic acid had been investigated[142,150]. The course of the reaction was ambiguous, the 16α (XLIII), 16β (XLIV), and 20ξ (XLII) fluorides being formed:



In the reaction of 5α,6α: 20ξ,21-dioxides, which are epimeric at $C_{(20)}$, with fluorine-containing reagents, it has been shown[24,151] that with one isomer (XLV) both oxide rings are cleaved with the formation of the 6β-fluoride (XLVI) and the 6β,20ξ-difluoride (XLVII). The entry of

fluorine at position 20 in the difluoride (XLVII) was established by nuclear magnetic resonance (with ^{19}F).



(XLV) (XLVI) (XLVII)

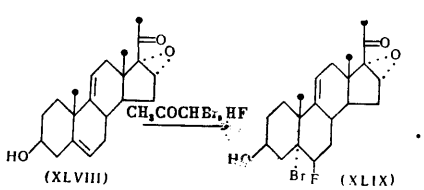
2. Preparation of Fluorinated Steroids From Olefinic Steroids

Direct addition of fluorine to carbon–carbon multiple bonds has not yet found application because of the extremely vigorous and uncontrollable reaction of fluorine both with C=C and with C–H bonds, even at low temperatures and with the halogen diluted with nitrogen.

Controlled addition of fluorine to olefins can be achieved only by replacing the gaseous halogen by various fluorine-containing reagents, among which have been used lead tetrafluoride, fluorine perchlorate, hydrogen fluoride, iodobenzene difluoride, trifluoroiodomethane, and difluorocarbene, as well as *N*-halogeno-amides together with hydrogen fluoride.

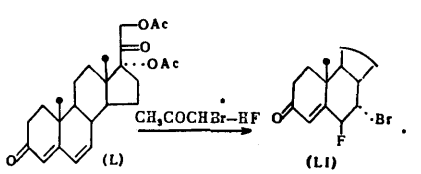
Addition of mixed halides. Fluorine can be introduced into a steroid molecule together with another halogen by the reaction of steroid olefins with *N*-halogeno-amides and hydrogen fluoride.

The halogeno-amides usually employed are *N*-bromo- and *N*-chloro-acetamide and *N*-chloro- and *N*-iodo-succinimide. The reaction is conducted at -80° in the presence of a proton-acceptor, must often pyridine or tetrahydrofuran, to increase the degree of ionisation of the hydrogen fluoride, which is present in large excess. This method of preparation enables fluorine to be introduced into positions 6, 11, and 16 of the steroid molecule, and is preferable to the cleavage of oxides, especially with polyunsaturated steroids, since the oxides of such compounds are obtained in very low yields. The present method is highly selective: in the case of 16α,17α-epoxy-3β-hydroxy-pregna-5,9(11)-dien-20-one (XLVIII), for example, reaction occurs primarily at the 5–6 double bond[152] with formation of the 5α-bromo-6β-fluoro-derivatives (XLIX):



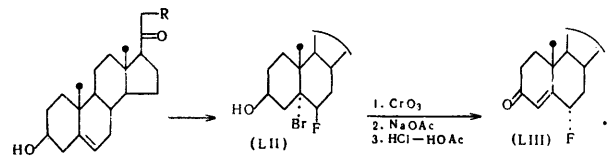
(XLVIII) (XLIX)

In the case of the 4,6-diene (L), however, the 7α-bromo-6β-fluoro-derivative (LI) is formed[152,153]:



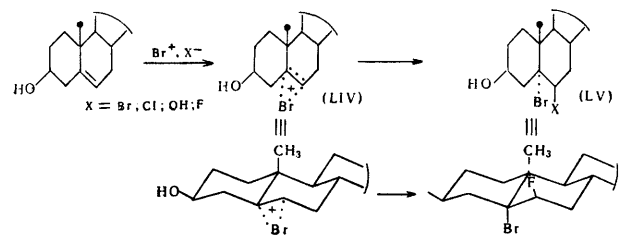
(L) (LI)

When the steroid molecule contains both 4–5 and 9–11 double bonds, the same pair of reagents add on at the latter bond[152,153]. This method of fluorination provides one of the best approaches to the biologically important 6α-fluorinated steroid hormones[152,154–156]. Conversion of 6β-fluorinated (LII) to 6α-fluorinated (LIII) compounds is accomplished by successive oxidation of the 3-hydroxy-group, dehydrohalogenation, and isomerisation in acetic acid:



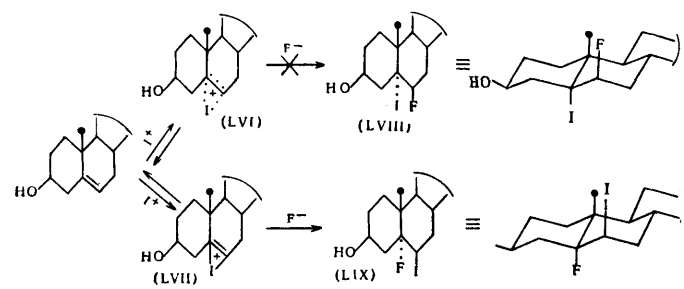
(LII) (LIII)

The halogenation of steroids with mixed halides, which is conducted in a polar medium, takes place by a mechanism of ionic addition. In the first stage an intermediate α-bromonium cation (LIV) is formed. Approach of the bromine ion from the α region of the molecule is controlled by stereochemical factors[157]. Then the cation (LIV), on nucleophilic attack by the fluoride ion, forms the *trans*-diaxial cleavage product (LV).[158,159] Thus *trans*-diaxial addition of two halogens occurs in each case:



(LIV) (LV)

Reaction of steroids with *N*-iodosuccinimide and hydrogen fluoride shows an anomalous order of addition of the halogens, with the formation of a 5α-fluoro-6β-iodo-derivative (LIX)[157] instead of the 6β-fluoro-5α-iodo-compound (LVIII). This course of the reaction is explained by the existence of two possibilities — formation of an α- or a β-iodonium cation (LVI) or (LVII) — in the first stage of the reaction:

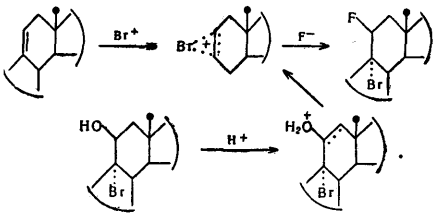


(LVI) (LVIII) (LVII) (LIX)

Two products (LVIII) and (LIX) can be formed on further attack by the fluoride anion. If formation of an iodonium ion is regarded as a reversible process, in which an equilibrium is present between the olefin and the two possible ions (LVI) and (LVII), the former (LVI) is kinetically preferred, as indicated above for the bromonium ion, in view of the preferred approach to the 5–6 double bond from the α-region

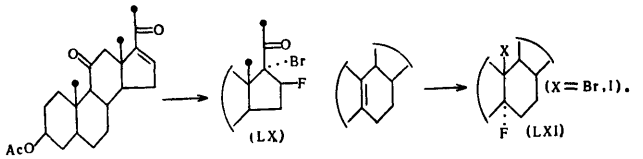
of the molecule. However, reaction of (LVI) with the fluoride anion yields the thermodynamically less stable (LVIII) of the two possible products (LVIII) and (LIX). From an examination of the non-bonding interaction of the iodine atom in these products, and also in view of the greater stability of secondary compared with tertiary iodides, it follows that (LIX) is more stable than (LVIII). Thus reaction involving the kinetically less preferred ion (LVII), but resulting in the thermodynamically more stable final product (LIX), is the dominant mode of addition of I^+F^-.

A particularly detailed study has been made of the addition of mixed halogens to the 9–11 double bond, which enables 9α-bromo(chloro, iodo)-11β-fluoro-derivatives to be obtained[153,160–167]. It was found that these products can be prepared from 9α-bromo-11-hydroxy-compounds by reaction with hydrogen fluoride in pyridine[160]. In both cases the reaction involves the 9,11-bromonium ion as intermediate stage, which is converted into the final product on nucleophilic attack by the fluoride ion:

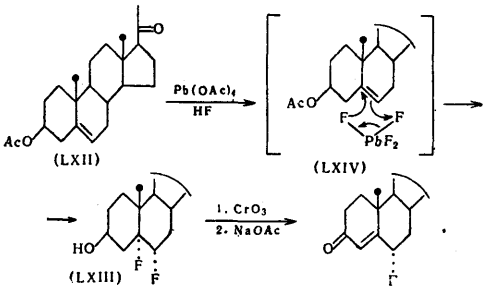


It is interesting that 9α,11β-difluoro-derivatives could not be obtained from 9α-fluoro-11β-hydroxy-steroids. It is probable that fluorine is too electronegative to form an onium ion[153,160].

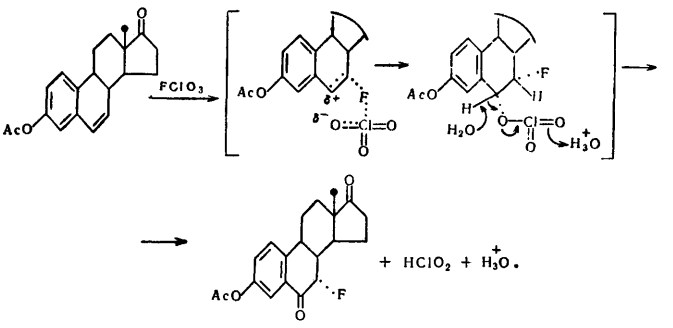
Addition of BrF to the 16–17 double bond enables 17α--bromo-16β-fluoro-derivatives (LX) to be obtained[152,153], while reaction of hydrogen fluoride and *N*-bromoacetamide or *N*-iodosuccinimide with 5–10 olefinic steroids yields 10β-bromo(or iodo)-5α-fluoro-derivatives of the type (LXI).[168]



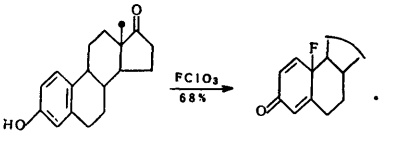
Addition of lead tetrafluoride to double bonds. Only one example of this reaction — with acetoxypregnenone (LXII) — is known at the present time. Lead tetrafluoride attacks this steroid at the instant of formation from lead tetraacetate and anhydrous hydrogen fluoride, the reaction being conducted in dichloromethane at -75°. The reaction product — the vicinal 5α,6α-difluoride (LXIII) — is formed in 27% yield based on the acetate (LXII) introduced into the reaction. The *cis*-addition of fluorine can be explained by the occurrence of reaction via a cyclic transition state (LXIV), in an analogous manner to the *cis* hydroxylation of steroids by osmium tetroxide. Oxidation of the 3β-hydroxyl with chromic acid and elimination of the 5α-fluorine by means of sodium acetate yield 6α-fluoroprogesterone; thus this reaction can serve also for the synthesis of 6α-fluorinated steroids[2,3,169]:



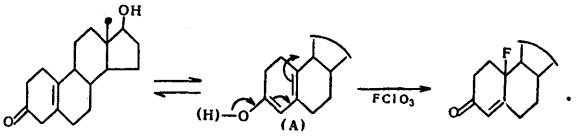
Addition of $FClO_3$. The action of perchloryl fluoride on steroids containing a double bond conjugated with an aromatic ring involves oxofluorination of the double bond, a reaction in which an oxo-group and a 7α--fluorine atom are simultaneously introduced into the steroid molecule. The suggested reaction mechanism is illustrated by the scheme[170]:



Reaction of steroids containing an aromatic ring A with perchloryl fluoride yields 10β-fluoro-19-norsteroids[171–174], the reaction being conducted in dimethylformamide at room temperature.

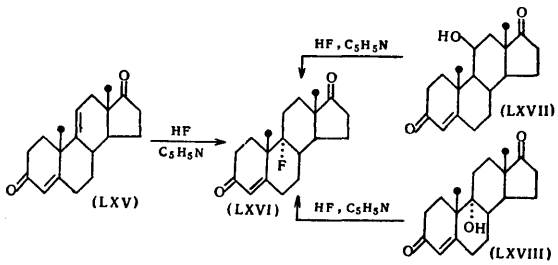


Compounds of the same type are formed from 3-oxo--5(10)-ene steroids[173], the enol (A) or the corresponding enolate ion probably being formed as an intermediate stage:

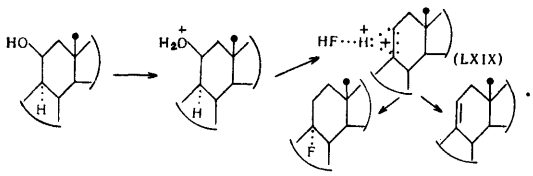


Addition of hydrogen fluoride (HF). The reaction of solutions of anhydrous hydrogen fluoride in pyridine with unsaturated steroids or the corresponding

hydroxy-compounds involves addition of HF to the double bond. An example of this reaction is provided by formation of the 9α-fluoroandrostenedione (LXVI) from the compound containing a 9–11 double bond (LXV), the 9α-hydroxy--derivative (LXVIII), and the 11β-hydroxy-derivative (LXVII). The 9α-configuration assumed for the fluorine atom is based on nuclear magnetic resonance spectra[175].

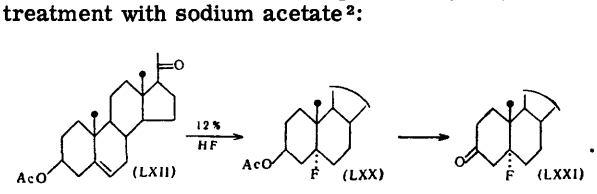


This reaction permits a 9α-fluorine atom to be introduced into derivatives of androstane and pregnane[176–179] without the simultaneous introduction of a hydroxy-group, as occurs in the cleavage of α-oxides. The most reasonable hypothesis is that hydrogen fluoride adds on, in accordance with the Markovnikov rule, to a double bond which is already present or is formed in the reaction. Actually, however, the matter is more complicated. Thus the yield of the 9α-fluoride (LXVI) is far higher from the 11β-ol (LXVII) than from the 9,11-dehydro-derivative (LXV); furthermore, paper chromatography of the reaction products shows that the fluoride (LXVI) is formed more rapidly from the 11β-ol (LXVII) than from the olefin (LXV). This suggests that 9α-fluoro-steroids may be formed directly from 11β-hydroxy-compounds. A probable mechanism of such a change involves protonation of the 11β-hydroxyl followed by elimination of the elements of water with formation of a solvated cation (LXIX), which can then be converted both into 9α-fluoro- and into 9,11-dehydro-compounds[175]:



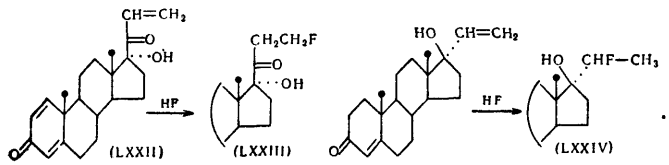
It is quite possible that the formation of 9α-fluoro-12β--hydroxy-steroids by the opening of 11β,12β-epoxides with hydrogen fluoride also occurs according to this scheme, and not by addition of hydrogen fluoride to an intermediate 9(11)-en-12β-ol, as has been assumed previously[117].

Addition of hydrogen fluoride to a 5–6 double bond is accomplished by a somewhat different method. Acetoxy-pregnenone (LXII) reacts with hydrogen fluoride only in the presence of a proton-acceptor (tetrahydrofuran), forming a 5α-fluoro-derivative (LXX); hydrolysis and oxidation of the latter under mild conditions give 5α-fluoropregnane-3,20-dione (LXXI), which splits off hydrogen fluoride on treatment with sodium acetate[2]:

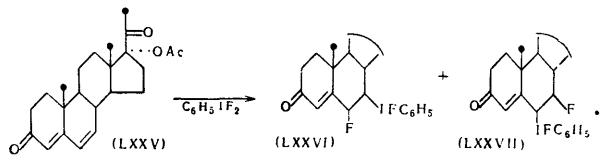


With the non-acetylated hydroxypregnenone under the same conditions, the action of hydrogen fluoride results in replacement of the 3β-hydroxy-group by the fluorine atom instead of addition to the 5–6 double bond.

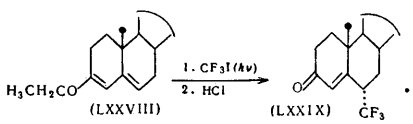
An example is also known of the addition of hydrogen fluoride to the 21–22 double bond§ in the compound (LXXII) with formation of the 22-fluoro-derivative (LXXIII),[180] and also to the 20–21 double bond of 17α-vinyltestoesterone to form the 20-fluoro-compound (LXXIV).[181] In these cases the reaction is also conducted in tetrahydrofuran with antimony trifluoride as catalyst.



Addition of iodobenzene difluoride $C_6H_5IF_2$. This reagent is formed *in situ* in chloroform solution from iodobenzene, hydrogen fluoride, and potassium hydrogen fluoride. Its reaction with the 4,6-diene (LXXV) gives a mixture of the compounds (LXXVI) and (LXXVII), containing fluorine in positions 6β and 7β, the adduced structures being assigned to them on the basis of nuclear magnetic resonance spectra[182].



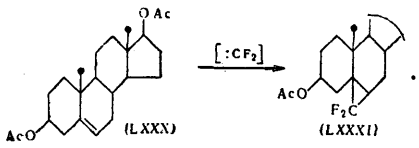
Addition of trifluoroiodomethane. Under the influence of ultraviolet radiation this reagent adds on to the 5–6 double bond of 3-enolic ethers of steroid 4-en--3-ones of the androstane and pregnane series (LXXVIII). Subsequent hydrolysis of the reaction products with hydrochloric acid yields 6α-trifluoromethylated steroids (LXXIX):[183–185]



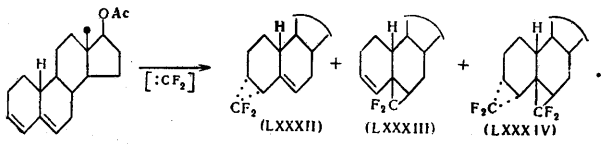
Addition of difluorocarbene. A peculiar method of introducing fluorine into unsaturated steroids is their reaction with difluorocarbene CF_2, which is formed when sodium chlorodifluoroacetate $CF_2ClCOONa$ is heated in high-boiling organic solvents[186]. Thus addition of difluorocarbene to the 5–6 bond of (LXXX) yields the 5β,6β--difluoromethano-derivative (LXXXI). The β configuration was assigned to the cyclopropane ring in (LXXXI) on the basis of steric hindrance to approach of the reagent from the α region, and is supported by the infrared and nuclear magnetic resonance spectra. It is interesting

§ Numbering as in formula in Table 1.

that the more bulky dichlorocarbene does not in general react with the 5–6 double bond in 10β-methylated steroids.



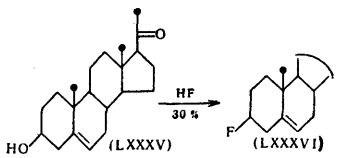
Addition of difluorocarbene to a 2–3 double bond gives two products, in which the three-membered ring has the 2α,3α and 2β,3β configuration respectively. Reaction with 3,5-dienes is more complicated, a mixture of the three products (LXXXII)–(LXXXIV) being formed.



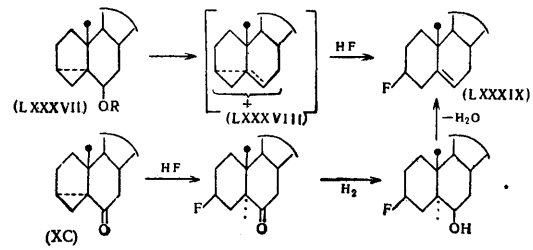
3. Replacement of Other Groups and Other Halogen Atoms by Fluorine

The last group of methods for synthesising fluorinated steroids comprises reactions in which other groups and also other halogens are replaced by fluorine. These include primarily the hydroxy-group and its toluene-*p*-sulphonyl or methanesulphonyl derivatives, which are replaced by fluorine on reaction with hydrofluoric acid or its salts. The substitution of fluorine for other halogens — bromine, chlorine, iodine — occurs in a similar manner. The present Section includes the reactions of perchloryl fluoride with compounds containing active hydrogen, and reactions of sulphur tetrafluoride with steroid ketones.

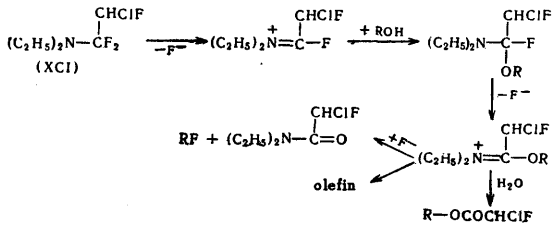
Replacement of hydroxyls by fluorine. This replacement occurs when certain steroid alcohols are treated with anhydrous hydrogen fluoride in tetrahydrofuran medium. Thus the hydroxypregnenone (LXXXV)[2] and its 16-dehydro-derivative[186–188] form 3β-fluoro-compounds (LXXXVI). The hydroxyl of 2-hydroxymethylated steroids is exchanged for fluorine under the same conditions[189].



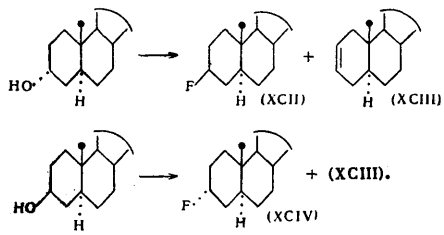
Analogous products are formed when 3,5-cyclosteroids of the androstane and pregnane series of the type (LXXXVII), where R = H or CH_3, react with hydrogen fluoride in benzene[190–192]. Reaction occurs via the homoallylic cation (LXXXVIII) and gives a 40–50% yield of the 3β-fluorinated derivatives (LXXXIX). Cleavage of the 3,5-ring occurs also when the 6-ketone (XC) is treated under the same conditions[190].



Replacement of hydroxyl by fluorine can be accomplished also by the action of *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine (XCI), which is formed when chlorotrifluoroethylene is passed through cooled diethylamine[193]. Products in which the hydroxyl has been split off and in which it has been esterified to form a chlorofluoroacetate are formed as side-products of this reaction and therefore the yields of the desired products do not usually exceed 20–50%. The reaction occurs according to the scheme[194,195] (in which R represents the residue of a steroid alcohol)



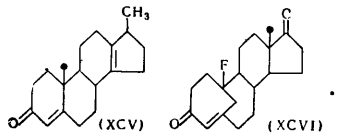
3α-Hydroxy-5α-androstan-17-one on treatment with the reagent (XCI) gives the 3β-fluoro-derivative (XCII), whereas its 3β-epimer yields the 3α-fluoro-derivative (XCIV), the reaction thus involving complete inversion of the configuration. In both cases the olefin — 5α-androst-2-en-17-one (XCIII) — is formed as a byproduct[194].



11α-Hydroxyprogesterone under these conditions forms a mixture of the 9α- and 11β-fluoro-derivatives, together with a small amount of the 9–11-olefinic derivative. The latter is the main product when the reagent (XCI) acts on 11β-hydroxyprogesterone[194]. Complete inversion of the configuration occurs when this reagent is used to substitute fluorine for a hydroxyl in the positions 6β,[194] 15β,[194,196,197] 17α,[198] and 17β.[194,195,198] Substitution of fluorine for hydroxy-groups in 2-, 16β-, and 19-hydroxymethylated steroids has also been reported[194,198–200].

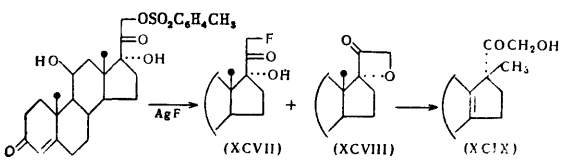
The reactions of steroids with the reagent (XCI) can be complicated by various rearrangements. For example, testosterone yields, besides the normal reaction product, the Wagner–Meerwein rearrangement product (XCV), and

19-hydroxyandrostenediol gives the compound (XCVI), containing the bicyclo[4,4,1]undecane system[198].

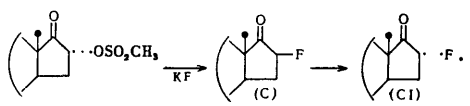


Replacement of toluene-*p*-sulphonate and methanesulphonate groups by fluorine. Since the direct replacement of hydroxyls by fluorine by the action of hydrofluoric acid may result in various rearrangements, and cannot be applied to polyols, methods have been worked out for accomplishing this substitution under milder conditions. One such method consists in converting the hydroxy-group into a toluene-*p*-sulphonate or a methanesulphonate, reaction of which with salts of hydrochloric acid enables the corresponding fluoro-derivatives to be obtained. The use of toluene-*p*-sulphonates is preferable, since they are formed more readily and give higher yields of the fluoro-derivatives (up to 75–90%)[201,202]. The reaction is conducted with potassium fluoride or silver fluoride in diethylene glycol, dimethylformamide, dimethyl sulphoxide, or acetonitrile[203–213].

The main field of application of this reaction comprises the conversion of 21-hydroxy-steroids into the corresponding 21-fluoro-compounds (XCVII). As a result of the considerable basic strength of the fluoride ion, the oxide (XCVIII) is often formed as a byproduct, and under the influence of acids rearranges to the compound (XCIX)[207,214,215].

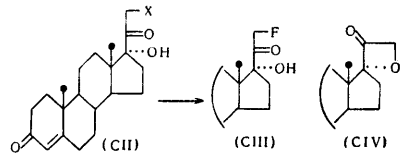


The action of potassium fluoride on methanesulphonates of 16α-hydroxy-17-keto-steroids gives 16β-fluoro-compounds (C), which in the course of the reaction rearrange to the 16α-fluoro-derivatives (CI).[216,217]

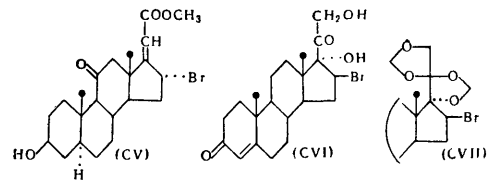


This reaction is employed also to substitute fluorine for hydroxy-groups in 6α- and 16α-hydroxymethyl-steroids[218–221]. Tetrabutylammonium fluoride $(C_4H_9)_4NF$ in acetone solution can be used instead of salts of hydrofluoric acid as source of fluoride ions in this reaction; under these conditions, structural rearrangements accompanying nucleophilic substitutions are diminished. The reaction involves a complete inversion of configuration: 3β-toluene-*p*-sulphonates give 3α-fluoro-derivatives, whereas their 3α-epimers yield the 3β-fluoro-compounds; testosterone toluene-*p*-sulphonate forms the 17α-fluoro-derivative[222].

Replacement of other halogens by fluorine. This reaction is analogous to the replacement of alkane- and arene-sulphonates by fluorine. It occurs when potassium and silver fluorides act on halogenated steroids dissolved in acetonitrile or various alcohols. Ease of replacement by fluorine diminishes in the sequence iodine > bromine > chlorine. Thus when X = I, the main product of the action of salts of hydrofluoric acid on the compound (CII) is the fluoro-derivative (CIII) slightly contaminated with the 17,21-oxide (CIV); but when X = Cl, this oxide becomes the main product of the reaction[223,224]



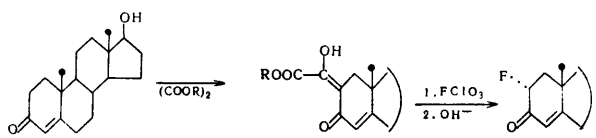
Interest attaches to the replacement of halogens in position 16 by fluorine. Whereas 16α-iodooestrone[225] and the 16α-bromo-steroid (CV)[226] form 16β-fluoro-derivatives, the reaction thus entailing an inversion of configuration, with 16β-bromocortexone (CVI) or its bismethylenedioxy-derivative (CVII) the configuration is preserved during the reaction, and 16β-fluoro-derivatives are produced[227–230]. The reasons for this difference in the stereochemical course of the reaction have not yet been elucidated.



Replacement of halogens by fluorine has been used also to prepare 3β-fluorinated[231], 6α-fluorinated[232], 6α-fluoromethylated[233], and 16β-fluoromethylated[234] steroids. Being one of the principal methods for introducing fluorine into position 21 (because of activation of the 21-halogen by the adjacent $C_{(20)}$ carbonyl group[235–245]), this route serves also for the preparation of polyfluorinated steroids[246–250].

Replacement of hydrogen by fluorine. In contrast to bromination or chlorination, the direct fluorination of steroid ketones in the α-position is impossible. Indirect routes are therefore necessary for this purpose, by the action of fluorine-containing reagents, e.g. perchloryl fluoride $FClO_3$, on those derivatives of keto-steroids in which the activity of the α-hydrogen has been substantially increased.

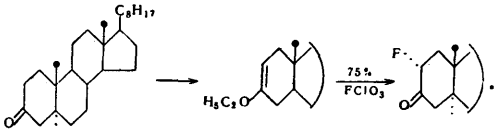
The first scheme for introducing fluorine into keto-steroids comprises three stages — preparation of an alkoxalyl or hydroxymethylene derivative of the steroid, followed by treatment with sodium ethoxide and perchloryl fluoride, and finally alkaline hydrolysis of the product to remove the alkoxalyl group — an example being the synthesis of 2α-fluorotestosterone[251]:



A fluorine atom can be introduced into steroids by this method not only at the 2α position[5,170,251–262] but also at

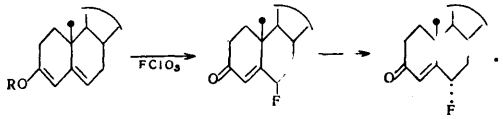
the 16α, 16β,[263-268] and 21 [251,256,268] positions. In the two latter cases not only monofluoro-derivatives (16α or 21) can be obtained but also difluoro-compounds[270-272].

In the second scheme for the fluorination of keto--steroids, solutions of derivatives of the enolic form of these steroids in organic solvents are treated with perchloryl fluoride. Thus 2α-fluorocholestan-3-one is formed from cholestanone via 3-ethoxycholest-2-ene:[269]

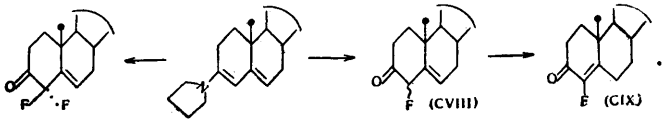


Enamines of 3-keto-5α-steroids[273] react similarly, as also acetates of the enolic form of 17-keto-steroids[274]. In the latter case the yield of 16α-fluoro-17-keto-steroids can be considerably increased by replacing the acetates by the acetamide derivatives of the enolic form[274-277].

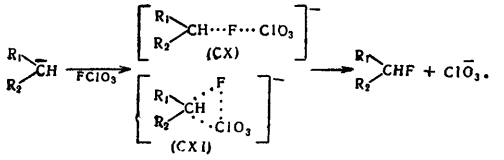
The reactions of perchloryl fluoride with derivatives of the steroid 4-en-3-ones are rather more complicated, the composition of the reaction products depending on the conditions and the type of enolic derivatives. Thus acetates[48,277] and ethyl ethers[269,278-280] of the enolic form of these steroid derivatives yield 6β-fluoro-compounds, which can be isomerised under the reaction conditions to the 6α-fluoro-derivatives:



In contrast to this, the fluorination of pyrrolidine enamines of steroid 4-en-3-ones yields 4-fluorinated products. When the reaction is conducted in methanol[281-285], 4ξ--fluoro-5-ene derivatives (CVIII) are obtained, which in the presence of acids isomerise to 4-fluoro-4-enes (CIX); when the reaction was conducted in ether[284,286], only 4,4--difluoro-5-ene derivatives were isolated.



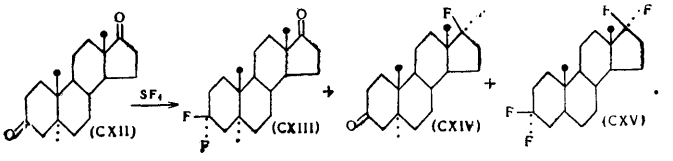
Since perchloryl fluoride has no dipole moment[287], it is difficult to predict *a priori* the type of ionisation and the mechanism of fluorination with this compound. It is possible that perchloryl fluoride will dissociate in different ways depending on the conditions[288,289]. It is assumed in most cases that the fluorine is electrophilic in character in this reaction, i.e. that fluorination consists in attack by an F^+ ion on a carbanion or a carbon atom of a double bond having a greater electron density. This view is supported by the formation of axial α-halogeno--ketones both on fluorination with perchloryl fluoride and in the reaction of ketones with Br^+.[48,172,269] It is probable that in this case fluorination is a single-stage process, involving transition states of the type (CX) or (CXI):[290,291]



Conversion of carbonyl group into a *gem*--difluoro-derivative. Treatment of steroid aldehydes or ketones with sulphur tetrafluoride (SF_4) enables two fluorine atoms to be introduced simultaneously into the steroid molecule. This reaction is conducted at room temperature with hydrogen fluoride, boron trifluoride, or other fluorides (AsF_3, TiF_4, PF_5), as catalyst[292]. Although hydrogen fluoride is a less active catalyst than boron trifluoride its use is to be preferred, since fewer byproducts of the reaction are then formed[293]. Hydrogen fluoride can be generated directly during the reaction by adding to the mixture a quantity of ethanol, which forms hydrogen fluoride on reaction with sulphur tetrafluoride[4].

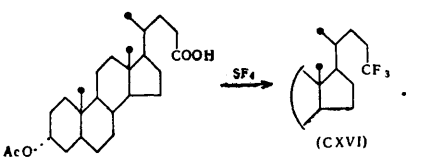
Comparatively mild reaction conditions ensure that esters, acetals, and bismethylenedioxy-derivatives shall be stable, and permit considerable expansion of the field of application of the reaction among such multifunctional compounds as steroids. Reaction with sulphur tetrafluoride has been used to introduce two fluorine atoms into positions 3, 11, 17, and 20 of the steroid molecule[4,293-297], and also to obtain 2- and 6-difluoromethylated steroids from the corresponding hydroxymethylene derivatives[293,298-300].

Compounds containing more than one carbonyl group in the molecule can react either at one or at all the reaction centres. Thus 5α-androstane-3,17-dione (CXII) forms a mixture of di- and tetra-fluorinated derivatives (CXIII)--(CXV), with fluorination at $C_{(3)}$ predominating in the ratio 3:1.[4]



The reactivity of carbonyl groups in different positions in the steroid molecule towards sulphur tetrafluoride was found to decrease in the sequence 3-one $\simeq$ 6-formyl > 17--one > 20-one > conjugated 3-one > 11-one.[293]

Steroid acids on reaction with sulphur tetrafluoride form trifluoromethylated derivatives. Thus acetoxy--lithocholic acid yields the 24-trifluoro-derivative (CXVI):[293]

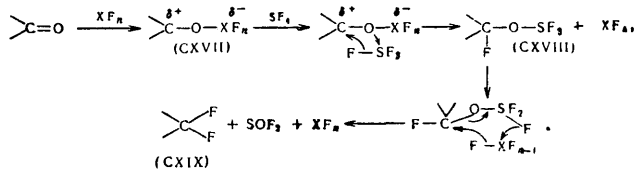


The reaction probably involves the intermediate formation of the acid fluoride, the hydrogen fluoride which is thus

evolved catalysing the further changes, so that in this case separate addition of a catalyst is not necessary[293]:

$$R{-}CO_2H + SF_4 \rightarrow R{-}COF + HF + SOF_2,$$
$$R{-}COF + SF_4 \rightarrow R{-}CF_3 + SOF_2.$$

Several schemes have been suggested for the mechanism of the reaction of ketones with sulphur tetrafluoride, the most probable of them being[293,294]



According to this scheme, the ability of XF_n to catalyse the reaction is associated with its ability to polarise the carbonyl group as a Lewis acid. The first stage in the reaction consists in formation of the complex (CXVII) between the carbonyl group and the catalyst. Attack by a sulphur tetrafluoride molecule on this complex yields the adduct (CXVIII), cleavage of which by means of the catalyst forms the difluoride (CXIX).

II. PHYSIOLOGICAL ACTIVITY OF FLUORINATED STEROIDS

The introduction of fluorine atoms into steroid compounds results in fundamental and varied changes in their physiological activity. The changes of greatest interest and practical importance are found in the corticosteroid series. The introduction of fluorine affects primarily the hormonal activity of these compounds — their control of the metabolism of carbohydrates (glucocorticoid activity) and salts (mineralcorticoid activity). The discovery of the anti-arthritic, antiallergic, and anti-inflammatory properties of modified corticosteroids extended the therapeutic effects of these compounds beyond the range of natural hormonal activity, and enabled their clinical application to be greatly expanded. At the present time fluorinated steroids are employed for the treatment of various types of arthritis, Addison's disease, dermatoses, etc. Since fairly detailed reviews are available in this field[67,301,302], only a brief account with the most recent results need be given here.

Introduction of fluorine at the 2α position in ring A of a steroid molecule lowers all forms of hormonal activity[253]; nevertheless, anti-tumour activity has been observed in 2α-fluorotestosterone[254]. The only compound containing a 3β-fluorine atom which has been studied is 17α-acetoxy-3β-fluoropregn-5-en-20-one, and this on oral application has three times the gestagenic activity of 17α-acetoxyprogesterone[192]. Replacement of the 4-hydrogen atom by fluorine lowers the androgenic, gestagenic, and corticoid activities[284,303].

Compounds containing a 6α-fluorine atom have, in comparison with the corresponding unsubstituted compounds, far greater glucocorticoid, anti-inflammatory, and thymolytic activities and at the same time diminished mineralcorticoid activity[17,28,40,304]. Increased anti-arthritic activity in 6α-fluorocorticoid steroids has also been reported, although the increase is not quite so large as with the 9α-fluoro-analogues[305]. The gestagenic and anabolic activities of the 6α-fluoro-derivatives of progesterone and testosterone are also considerably enhanced[18,40,306]. On the other hand, the 6β-fluoro-epimers have a lower gestagenic activity than the unsubstituted compounds[306]. 6α-Fluoromethylated steroids, like the 6β-fluoro-compounds, possess increased glucocorticoid and diminished mineralcorticoid activities[218].

The therapeutic effects produced by the introduction of a 9α-fluorine atom have been studied the most widely. It has been reported that the glucocorticoid activities of the 9α-fluoro-analogues of cortisol and corticosterone exceed those of the unsubstituted compounds by factors of 8 and 3.5 respectively[80,115]. The mineralcorticoid, thymolytic, anti-inflammatory, and anti-arthritic activities are correspondingly increased too[76,80,304,305,307-309]. 9α-Fluoroprogesterone has a greater gestagenic activity than has unsubstituted progesterone[63,175]; nevertheless, the 9α-fluoro-11β-hydroxy-analogue has a lower progestative activity than the unsubstituted compound[310-312]. Analogous effects are found in the androstane series. The introduction of 9α-fluorine into testosterone propionate increases the androgenic and anabolic activities of the steroid roughly fivefold[175], whereas 9α-fluoroandrostan-11β-ols have an appreciably diminished androgenic activity[66]. Enhanced aldosterone-blocking activity is also noted when 9α-fluorine is introduced into 17-spirolactones of the androstane series[313]. 9α-Fluoro-11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione is an effective anti-tumour agent, arresting the growth of mouse adenocarcinoma and rat fibroadenoma[314].

An 11β-fluorine atom is introduced only together with another halogen — bromine, chlorine, or iodine — in the 9α position. In comparison with the corresponding unsubstituted compounds, such dihalogenated derivatives of progesterone have lower gestagenic activity[160,162], those of testosterone lower anabolic and androgenic activities[166], and those of cortexolone lower glucocorticoid activity[315].

12α-Fluorinated analogues of corticosterone and 11β-hydroxyprogesterone have enhanced glucocorticoid activity, which is approximately equivalent to that of the corresponding 9α-fluoro-derivatives[311,312]. Nevertheless, 12α-fluorocortisone possesses neither glucocorticoid nor mineralcorticoid activity[135]. There are also data indicating enhanced gestagenic and anti-oestrogenic activity in 12α-fluoro-11β-hydroxyprogesterone compared with progesterone itself[311,312].

Introduction of a fluorine atom into the 16α position increases the glucocorticoid and anti-inflammatory activity and sharply diminishes the mineralcorticoid activity[142,150]. Analogous effects are produced by introducing a 16α-fluoromethyl group into a steroid[219]. Yet 16β-fluorinated steroids have diminished glucocorticoid and anti-inflammatory activity in comparison with the unsubsituted compounds[142,316]. The 17α-fluoro-analogue of progesterone is a rather less active gestagen than is progesterone[148].

Compounds containing a fluorine atom in position 21 have glucocorticoid and mineralcorticoid activity intermediate between those of the relatively inactive 21-deoxy-compounds and the highly active 21-hydroxy-analogues[214,301]. 21-Fluoroprogesterone is a more active gestagen than is progesterone by a factor of 2–4.[223,224]

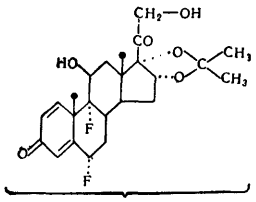
Data on the effect of fluorine atoms on the main forms of physiological activity of steroids are summarised in Table 2.

TABLE 2. Physiological activity of fluorinated steroids (+ = enhancement of activity; - = diminution in activity).

Position of F	Activity compared with unsubstituted compound				Position of F	Activity compared with unsubstituted compound			
	gestagenic	glucocorticoid	mineralcorticoid	anti-inflammatory		gestagenic	glucocorticoid	mineralcorticoid	anti-inflammatory
2α	−	−	−		12α	+	+	−	
3β	+				16α		+	−	+
4	−	−	−		16β		−		
6α	+	+	−	+	17α	−			
6β	−				21	+	+	+	+
9α	+	+	+	+					

The clinical application of corticosteroids is impeded by the fact that many of them show mineralcorticoid activity, which on prolonged treatment produces oedema and a rise in blood pressure[317]. In order to obtain compounds suitable for practical application, therefore, it was necessary to suppress the mineralcorticoid activity, which in this case was a secondary effect. This was achieved by introducing appropriate substituents into the molecule, in particular fluorine atoms in positions 6α and 16α. The same effect can be obtained by introducing into the molecule a 1–2 ethylenic bond[60,62,305,312], methyl groups in positions 2α,[304,305,312] 6α,[301,304,305] and 16α and 16β,[80,83,96,304,305,318-320] or a 16α-hydroxy-group[87,301,305]. There occurs not only a sharp drop in mineralcorticoid activity but also a substantial increase in glucocorticoid and anti-inflammatory activity.

Results obtained for the modification of the cortisol molecule (Table 3) show that, when the molecule contains more than one modifying substituent, their effects on the activity are additive. This has enabled compounds to be prepared which have an extremely high level of physiological activity, exceeding that of natural corticosteroids several hundredfold. It must also be noted that 16α,17α-acetals of 16α-hydroxycorticosteroids, which are not included in Table 3, have 3–4 times the anti-inflammatory activity of the unsubstituted compounds[95,321,322].



Dexamethasone (9α-fluoro-11β,17α,21-trihydroxy-16α--methylpregna-1,4-diene-3,20-dione) and triamcinolone (16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxypregna-1,4--diene-3,20-dione) have been used in medical practice as antiarthritic and anti-inflammatory remedies[305]. Synalar (6α,9α-difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione) is used in the treatment of psoriasis and skin diseases[326].

The problem of the particular mechanism by which the introduction of fluorine affects physiological activity has not yet been solved. Fried[115,311] suggested that this effect was associated with the inductive (-*I*) effect of the fluorine atom on the neighbouring oxygen-containing group in position 11. This hypothesis was based on the parallelism observed between the effect of various 9α-substituents on the activity of a steroid hormone and their inductive effects assessed from the strengths of the corresponding substituted acetic acids (Table 4).

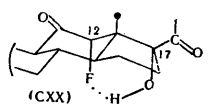
TABLE 3. Physiological activity of analogues of cortisol.

Substituents in cortisol molecule				Physiological activity			Refs.
1–2	6α	9α	16α	glucocorticoid (cortisol = 1)	anti-inflammatory (cortisol = 1)	mineralcorticoid (cortexone = 1)	
	F			10			17
		F		8	10	2.7	80, 301
	F	F		50	100		17,96
Δ	F			81	8		17, 40, 305
Δ		F		43	20	4	62, 80
Δ			F	8	16		142, 150
	F		CH_3	40	5		96, 97
		F	CH_3	12	14		80
Δ	F		CH_3	160	50		97, 305
Δ		F	CH_3	17	40		80, 326
Δ	CH_3	F		120	24	0.1	301
Δ	CH_3		F	25	20		278
Δ		F	OH	13	5		87, 95
Δ	F	F		427	200		17, 40, 96
Δ	F		F	116	100		278
Δ		F	F	60	75		150, 301
	F	F	CH_3		50		96
	F	F	OH		15		95
Δ	F	F	CH_3	730	165		96, 97,305
Δ	CH_3	F	F	250	190		278
Δ	F	F	F	425	480		278

TABLE 4. Glucocorticoid activity of 9α-substituted cortisols and acid dissociation constants of the substituted acetic acids[312].

Substituent	Glucocorticoid activity	Acid dissociation constant $10^5 K_a$
Fluorine	10.7	217.00
Chlorine	4.7	155.00
Bromine	0.3	138.00
Iodine	0.1	75.00
Hydroxyl	0.2	16.00
Methoxyl	<0.2	33.00
Hydrogen	1.00	1.82

This hypothesis was regarded as supported also by the presence in 12α-fluoro-steroids (12α-fluorocorticosterone[115] and 12α-fluoro-11β-hydroxyprogesterone[311]) of enhanced glucocorticoid activity of the same order as in the 9α-fluoro-analogues, which are symmetrically substituted about $C_{(11)}$. The difficulty presented by the absence of glucocorticoid or mineralcorticoid activity in 12α-fluorocortisone[135] could be bypassed on the assumption that in this case such absence resulted from the formation of a hydrogen bond between the axial 12α-fluoro- and 17α--hydroxy-groups (CXX).



(CXX)

However, recently discovered facts have considerably diminished the value of this hypothesis. The acetate of 9α-fluorocortexone, *containing no oxygen in position 11*, shows twelve times the mineralcorticoid activity of cortexone acetate[177]. This indicates that the increase in hormonal activity accompanying introduction of 9α-fluorine is not due to an inductive effect on a neighbouring oxygen function. It is evidently more probable that modified hormones are less rapidly metabolised by the organism, and

thus remain for a longer period in an active state in the latter[323]. In particular, the presence of fluorine atoms may prevent one of the normal metabolic processes, hydroxylation. It is interesting in this connection that the most active fluorinated steroids have the fluorine atoms in the positions 6, 9, 16, and 21, i.e. in those positions in which enzymic hydroxylation of steroid hormones occurs in the animal organism[324].

The enhanced activity of fluorinated steroids has been explained also by a diminution in their bonding by blood plasma[325]. Real progress in explaining the phenomena observed in this field can be made only when a deeper understanding has been obtained of the molecular mechanism of the action of steroids, about which almost nothing is known at the present time[324].

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THE PHOSPHORYLATION OF CELLULOSE

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I. INTRODUCTION

Although a large number of monographs and reviews have been published on the chemical modification of cellulose, questions associated with the phosphorylation of this important polysaccharide are treated superficially and incidentally in them, or even omitted altogether, as has been done in the latest treatise on the chemistry of cellulose [1].

The task of the present paper is to fill the gap: it represents the first attempt to collect together all the information on methods of preparation as well as the properties and practical application of phosphorus-containing derivatives of cellulose. The paper summarises investigations on the phosphorylation of cellulose, made mainly during the past thirty years, recent progress being reported in the greatest detail. A special place is given to describing the achievements made in the practical application of phosphorus-containing cellulosic materials.

The large amount of experimental work on the preparation of phosphorus-containing cellulose derivatives can be divided into two groups, according as phosphorylation is effected with derivatives of acids containing quinquevalent or tervalent phosphorus. The first group is in turn divided into two subgroups, the first of which comprises