Pure and Appl. Chem., Vol. 49, pp. 1241-1249. Pergamon Press, 1977. Printed in Great Britain.

THE INVENTION OF REACTIONS USEFUL FOR THE SYNTHESIS OF SPECIFICALLY FLUORINATED NATURAL PRODUCTS

Derek H.R. Barton

Research Institute for Medicine and Chemistry, Cambridge, Mass., U.S.A.
and Department of Chemistry, Imperial College, London, SW7 2AY, U.K.

Abstract - Hypofluorites, especially CF_3OF and $CF_2(OF)_2$, are useful positive fluorine reagents. Addition to double bonds, aromatic substitution and N-fluorination are amongst the processes studied. In recent work the remarkable capacity of CF_3OF and F_2 to substitute electrophilically tertiary hydrogen to give (with retention) tertiary fluoro-compounds has been discovered. This reaction is very sensitive to electronegative substituents. It shows unprecedented regiospecificity and makes available readily 9α- and 14α- fluoro-steroids.

It can be argued that the major advances in Organic Chemistry have always come about through work on the Chemistry of Natural Products. Certainly the fundamental concepts of constitution, of configuration and of conformation were first generally used to explain and comprehend phenomena observed in natural product molecules. Even molecular orbital correlation theory, to which so many papers have been devoted in the last decade, was first recognised as important by R.B. Woodward as a by-product of his monumental work on the synthesis of Vitamin B_{12}.

Whilst the relevance of research in natural product chemistry for the continued advance of Organic Chemistry can still be sustained by logical argument, natural product chemistry itself continues to evolve.

The Chemistry of Natural Products drew its origins from the investigation of materia medica, mainly of plant origin, during the last century. It was selfevidently of importance to determine the chemical structures of biologically active natural products like morphine and quinine in order to attempt to understand their mode of action and, if possible, to effect an economic synthesis. In the course of this work other compounds were isolated which did not have biological activity. It seemed reasonable to determine the structures of these compounds also, at least as an academic challenge.

Structural analysis in the last century and in the first half of this century was extremely difficult, because it was based on patient chemical degradation the theoretical interpretation of which was always in doubt. It was a great intellectual challenge.

Nowadays the situation is entirely different, because powerful physical methods, especially X-ray crystallography, have rendered the determination of chemical structure a trivial matter. The only exception is structure determination of complex materials which will not crystallise under any circumstance.

The first major objective of Natural Product Chemistry, the determination of structure, has been referred to above. The second major objective remains, as it has always been, synthesis.

The revolutionary simplification of structure determination has no parallel in the synthesis of natural products. Although great progress has been made in devising new synthetic methods our accomplishments remain trivial in comparison with those of Nature. From Molecular Biology we know that Nature is capable of carrying out Syntheses which are thousands of steps in length with a yield and an optical specificity of 100% in each step. We are very far from any such feat. The best industrial syntheses may attain average yields of over 90% for a 30-40 step synthesis.

It is clear, therefore, that the synthesis of natural products remains an objective of great scientific value and of great social and economic significance.

Whilst the problem of how to secure a yield of 100% in any desired chemical reaction remains the fundament of chemical synthesis, it is intractable. Theory does not permit the calculation of absolute rate constants for any but the most simple reactions. Even if the absolute rate could be calculated, one would need to calculate the absolute rates of all possibly

competitive reactions. Clearly fundamental theory is not going to help very much in Organic Synthesis for a long time ahead.

If we can do nothing much yet about the absolute rate problem, we can try to invent useful new chemical reactions and also useful new reagents for carrying out known processes. We must, however,first define some terms. Reactions may be defined as desired bond changes, reagents as substances which produce desired bond changes. Useful implies that the reaction or reagent will be used, not necessarily in manufacturing industry but at least in the research laboratory, whether it be industrial or academic.

The word 'invent' is, of course, the most interesting one. Perhaps one can recognise three ways of inventing a reaction or a reagent: viz by conception, by misconception or by accident. It is certainly interesting to classify the known useful reactions under this heading. Most of them were, in fact, discovered by accident.

We will now proceed to examine some of our work on the synthesis of specifically fluorinated organic molecules from this philosophical point of view. All this work was carried out at the Research Institute for Medicine and Chemistry, in Cambridge, Massachusetts, a charitable organisation devoted to the synthesis of compounds of potential value in Medicine. The Director of the Institute is Dr. M.M. Pechet who is responsible for all studies of biological activity. Dr. R.H. Hesse is the co-supervisor of chemical research and he is the senior author on all our studies in organic fluorine chemistry.

There are, of course, three types of mechanism for the formation of a carbon-fluorine bond depending upon whether the fluorine is a radical (fluorine atom), anionic (negative fluorine) or cationic (positive fluorine). Fluorine atoms, whilst useful in preparation of perfluoro-compounds, do not, in general, show sufficient selectivity to be useful in synthesis. The classical, and most common, mechanism for the formation of the carbon-fluorine bond is by the combination of fluoride anion with positive or potentially positive carbon, for example in SN_1 or SN_2 type processes. Fluoride anion reagents include the obvious, such as AgF and HF or BF_3 and the sophisticated, such as $Et_2N\text{-}CF_2\text{-}CFClH$, SF_4 and $Et_2N\text{-}SF_3$. Until our own work began the only reagent containing positive fluorine was $ClO_3\text{-}F$, perchloryl fluoride. Of course, when we use the expression positive fluorine we mean fluorine which is polarised in such a way as to be positive. Since fluorine is the most electronegative of all elements, it can only be polarised in a positive sense by combination with a group containing electronegative elements of such a nature that the additive electronegativity of the group is greater than that of fluorine itself. The ClO_3 group is of this type.

Perchloryl fluoride has the disadvantage that the other product from the fluorination process is chloric acid. Using organic solvents gives potentially explosive mixtures which have, in fact, led to a number of unfortunate accidents.

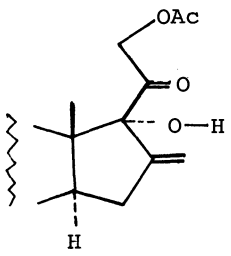
Organic molecules may have their biological properties profoundly changed when an atom of hydrogen is replaced by an atom of fluorine. This is because the C-H and C-F bonds have approximately the same steric bulk, but differ dramatically in their bond polarisation. A specific example of beneficial substitution in steroids is the introduction of 9α-fluorine.

For the last ten years we have been engaged in the development of reagents for electrophilic fluorination which would avoid the explosion hazards associated with ClO_3F and which, if possible, would be more powerfully electropositive and yet show selectivity. Our first efforts involved the reaction of hydrazone derivatives with halogen fluorides. However, in no case did we see positive fluorine behaviour; the reactions showed that it was the central halogen atom which was positive in character.

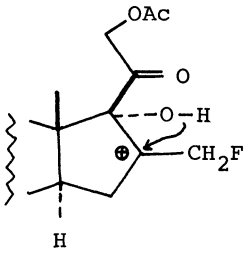
One day Bob Hesse and I were discussing our disappointing results. I remarked that there must be some other reagent with positive fluorine besides ClO_3F. Perhaps if we read through the catalogue of Peninsular Chem. Research (Gainesville, Florida) we might get some new ideas. When we got to the T's we found trifluoromethyl hypofluorite. I remembered this compound from Cady's pioneering paper in 1948 (1) and I at once said - that's it, that will be a positive fluorine reagent. I had not suggested it before because, I had no idea that it was commercially available. We express our appreciation to PCR for their seminal catalogue.

In fact, an analysis of the published work on trifluoromethyl hypofluorite showed that all the observed reactions were radical in character; positive fluorine behaviour had never been seen. However all the prior work had been carried out in the gas phase, where radical behaviour would have been encouraged.

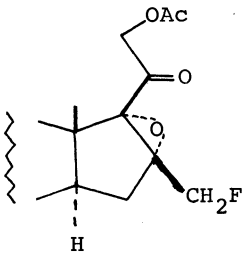
We found the hoped for electrophilic reactivity in a number of hypofluorites of which CF_3OF and $CF_2(OF)_2$ are the most useful. CF_3OF reacts in solution as $F^+ + {}^-OCF_3$ with the anion breaking down to $F^- + COF_2$. The reagent fluorinates smoothly enol esters, enol ethers and enamines to give α-fluoro-ketones (2). In the case of enol acetates the addition can afford adducts of $[CF_3OF]$ and of $[F_2]$ as well as the α-fluoro-ketone. However,the adducts give



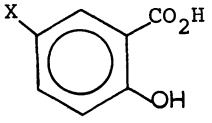
(I)



(II)

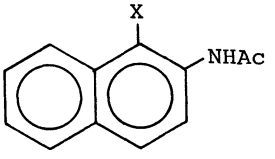


(III)



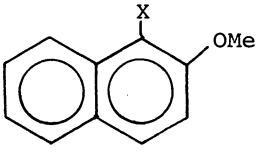
(IV) X=H

(V) X=F



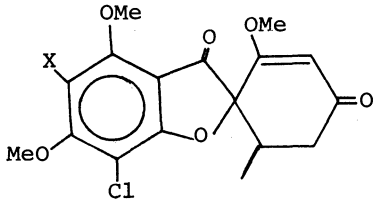
(VI) X=H

(VII) X=F

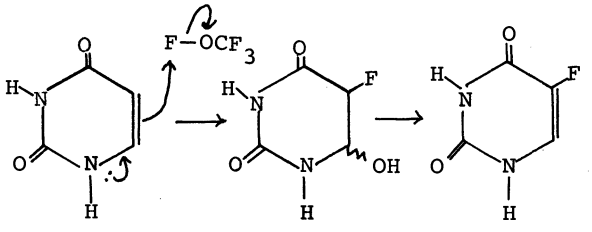


)VIII) X=H

(IX) X=F

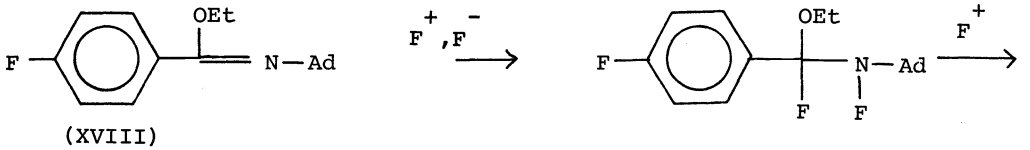


(X) X=H (XI) X=F

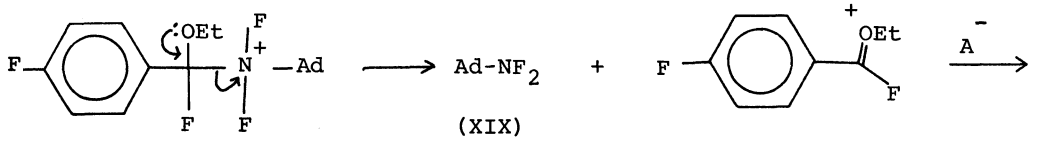


(XII) (XIII) (XIV)

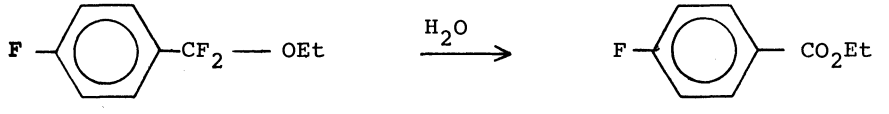
(XV) (XVI) (XVII)



(XVIII)



(XIX)



(XXI) (XX)

smoothly the α-fluoro-ketone on mild base hydrolysis. From the nature of these adducts the reactions observed could be ionic or radical in character. However, CF_3OF can be used in solvents like ether, toluene, acetone and tetrahydrofuran which certainly would not permit radical reactions. Moreover, the reactions are not inhibited by oxygen which is an effective inhibitor for fluorine atom reactions.

The reaction of CF_3OF with an appropriate 9(11)-enol benzoate has been developed into a new procedure for the synthesis of the medicinally important 9α-fluoro-corticoids (2,3,4).

$CF_2(OF)_2$ is a more desirable reagent (4) than CF_3OF in that it is equivalent to $2F^+ + 2F^- + CO_2$. Thus two out of four fluorines have the desired positive character and the reagent can give only difluoride adducts. In contrast, CF_3OF has only one positive fluorine in four fluorines. The use of $CF_2(OF)_2$ for fluorination has been reported (4) and a comparison made with other hypofluorite fluorinating agents.

The addition of CF_3OF to the ordinary ethylenic linkage would be an interesting reaction. Unfortunately, the yields of adduct are low and rearrangements predominate. We consider that this is due to the high energy level of an ordinary α-fluoro-carbonium ion giving an extra incentive for carbonium ion rearrangement (5).

In contrast steroidal allylic alcohols and allylic esters undergo smooth addition reactions to give CF_3OF and F_2 adducts (5,6). This difference is possibly explained by hyperconjugative stabilisation of the α-fluoro-carbonium by the allylic substitution. In any case the reaction gives cis-addition in the Markownikoff manner. The latter phenomenon is normal for electrophilic addition. The occurrence of cis-addition is also acceptable when one realises that the common electrophiles form intermediate bridged cations which necessarily afford trans-addition. An α-fluorocarbonium is not bridged and, therefore, the alternative cis-addition is observed. There is some evidence that cis-addition is normal for non-bridged ions.

The alternative explanation for cis-addition would be concerted addition. This is contra-indicated (5,6) by the carbonium ion rearrangements that can complicate these reactions and especially by the steroid of partial structure (I) which affords via the α-fluorocarbonium ion (II) a very high yield of the fluoro-epoxide (III). Clearly the cation is captured by an intramolecularly delivered nucleophile, the hydroxyl group, rather than by an external nucleophile (CF_3O^- or F^-).

As might be expected CF_3OF is a good reagent for the fluorination of aromatic rings which are electron rich (7,8). For example salicylic acid (IV) gives 5-fluorosalicylic acid (V), acetyl-β-naphthylamide (VI) gives the 1-fluoro-derivative (VII), β-naphthol methyl ether (VIII) affords the 1-fluoro-derivative (IX) and griseofulvin (X) gives the 5-fluoro-derivative (XI) (9).

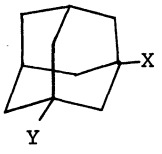
CF_3OF is an excellent reagent for the preparation of 5-fluoro-uracil (10) and for the fluorination of uracil derived nucleotides (11) and for pyrimidines (12). Thus uracil (XII) gives, in the presence of water, firstly the adduct (XIII) and then, on heating, the useful 5-fluorouracil (XIV). This synthesis avoids the toxic hazards of working with the dangerous fluoroacetic acid.

We have also worked on the synthesis of N-fluoro-compounds (13), substances which were little known in the literature. A primary methylamide (XV) gives firstly the monofluoro-amide (XVI) and then, via the fluoro-ammonium ion (XVII), a mixture of R-COF, $R\text{-}CO_2CF_3$ and $MeNF_2$. In contrast monosubstituted sulphonamides gave only mono-N-fluorosulphonamides which were stable to further treatment with CF_3OF.

Clearly N-fluorination would be made more facile if the nitrogen could be made more basic. We studied, therefore, the fluorination of imino-ethers. The imino-ether (XVIII) (Ad = adamantyl), on treatment with CF_3OF in the presence of water, gave a 70% yield of N,N-difluoroadamantylamine (XIX) as well as the ester (XX). Working under anhydrous conditions the difluoro-ether (XXI) could be isolated, which, on treatment with water, gave the ester (XX). The mechanism of the N-fluorination process is as indicated.

By this approach we were able to prepare the biologically interesting N,N-difluoro-tyramine and the (+)- and (-)- forms of N,N-difluoroamphetamine (13).

The most convenient procedure (14) for the preparation of N,N-difluoroamines was, however, as follows. The amine was converted to its p-carboxybenzylidene derivative which, as the sodium salt, was then treated with CF_3OF in methanol. As the nitrogen was fluorinated methanol was added to the double bond to give very smoothly by spontaneous cleavage the N,N-difluoroamine and the dimethylacetal of p-carboxybenzaldehyde. The latter was readily removed by washing with mild base to leave pure N,N-difluoroamine.



(XXII) X = $NHCOCF_3$, Y = H

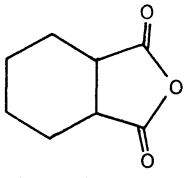
(XXIII) X = $NHCOCF_3$, Y = F

(XXIV) X = H, Y = H

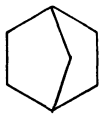
(XXV) X = H, Y = F

(XXVIII) X = $OCOCF_3$, Y = H

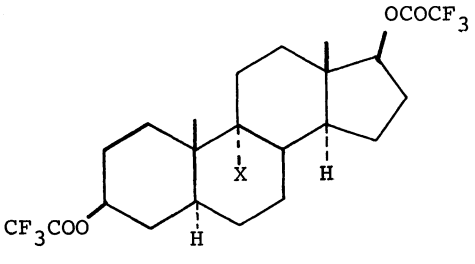
(XXIX) X = $OCOCF_3$, Y = F



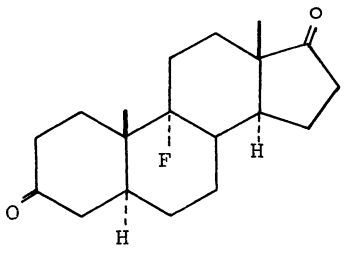
(XXVI)



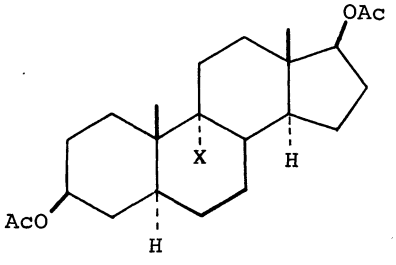
(XXVII)



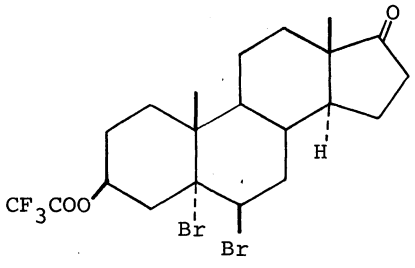
(XXX) X = H (XXXI) X = F



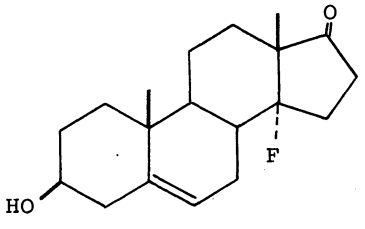
(XXXII)



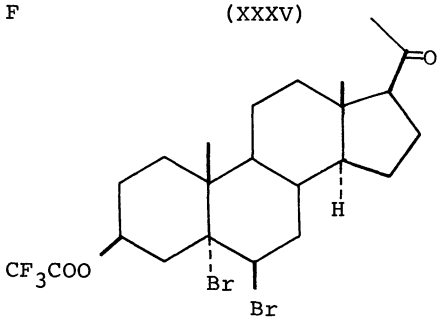
(XXXIII) X = H (XXXIV) X = F



(XXXV)



(XXXVI)



(XXXVII)

TABLE I[a] Effect of Radical Inhibitors on Fluorination Reaction

Solvent and/or additive	% composition of product (XXII)	(XXIII)	secondary and polyfluoro	Approx ratio (XXII)/other products
CH_2Cl_2	70	15	15	1
$CHCl_3$	66	31.5	2.5	13[b]
$CFCl_3$	30	46	24	2
$CFCl_3$ + 0.1 equiv of metadinitrobenzene	25	62	13	5
$CFCl_3$ + 0.1 equiv of nitrobenzene	25.5	69	5.5	12.5[b]
$CFCl_3$ + 0.1 equiv of $MeNO_2$	33.5	38.5	28	1.5
$CFCl_3$ + 0.1 equiv of 1,4-benzoquinone	22.5	71	6.5	11[b]
$CFCl_3$ + O_2 (slow stream)	20	73	7	11[b]
$CFCl_3$ + C_6Cl_6	34	28.5	37.5	0.6

[a]Adamantane (250 mg) in 30 ml of solvent at -25° was exposed to CF_3OF (2 mmol) and allowed to react under anaerobic conditions (unless otherwise stated) for 30 min. The product composition was determined by VPC.

[b]Fully inhibited reactions.

TABLE II[a] Fluorination of Adamantyl Derivatives

Substrate	Reagent	Product and % yield		Mp, °C
(XXII)	CF_3OF	(XXIII)	65	68.5-69.5°
(XXII)	F_2	(XXIII)	83	
(XXIV)	CF_3OF	(XXV)	75	
(XXIV)	F_2	(XXV)	84	
(XXVIII)	CF_3OF	(XXIX)	45	28-32°

[a]The CF_3OF reactions were in the presence of 0.1 equiv of nitrobenzene or m-dinitrobenzene as inhibiter. No inhibiter was needed for F_2 reactions.

N,N-Difluoroamines are quite stable substances at physiological pH and stable thermally.

During the course of this work we had occasion to attempt the N-fluorination of trifluoroacetyladamantylamine (XXII). However, instead of N-fluorination we observed smooth C-fluorination to give the 3-fluoro-derivative (XXIII) in good yield. This reaction was surprising to us, but it was confirmed when adamantane itself (XXIV) was cleanly fluorinated with CF_3OF to the tertiary fluoroadamantane (XXV). In contrast treatment of hexahydrophthalic anhydride (XXVI) and of norbornane (XXVII) gave a mixture of compounds containing secondary fluorine. At first we considered that this unexpected tertiary fluorination must be due to a radical reaction. The addition of inhibitors to the fluorination of trifluoroacetylamide (XXII) (see Table I) gave very striking effects. If we take the ratio of monofluorinated product (XXIII) to all other products we see that the presence of radical inhibitors ($CHCl_3$, $PhNO_2$, benzoquinone and oxygen) gives a limiting high ratio and affords a good yield of monofluoro-product. Under the inhibited conditions the substrates (XXVI) and (XXVII) were not attacked at all. Clearly we are dealing with two different mechanisms of fluorination. One of these is radical in nature, the other is non-radical.

The nature of this mechanism was further illuminated by the results summarised in Table II. A comparison of the rates and yields from the inhibited CF_3OF fluorination of (XXIV), (XXII) and (XXVIII) showed the order (XXIV) > (XXII) > (XXVIII). This is the same as the electronegativity order of the groups H, $-NHCOCF_3$ and $-OCOCF_3$. In addition there is a marked preference for monosubstitution and an exclusive regioselectivity for tertiary hydrogen substitution.

Obviously we are dealing with an electrophilic substitution process which could involve hydride abstraction to HF, CF_3O^- and carbonium ion. However, we see no sign of the expected product from such a reaction which would be the compound $AdOCF_3$. We much prefer, therefore, the electrophilic pentacovalent substitution process proposed by Olah (15). This is the first time that this mechanism has been demonstrated for fluorination.

From the point of view of practical synthesis we were pleased to discover (Table II) that the same process can be seen using elemental fluorine (with or without inhibitor). Indeed the yields with fluorine itself were better than with CF_3OF.

With these preliminaries completed we were in a position to apply these new fluorination reactions to steroid chemistry. By the introduction of strongly electronegative functions we hoped to direct fluorination to selected tertiary positions.

Treatment of the bis-trifluoroacetate (XXX) with CF_3OF in the presence of inhibitor gave the 9α-fluoro-derivative (34%) (XXXI) which was characterised by conversion to the known 9α-fluoroandostan-3,17-dione (XXXII). Better yields were obtained with fluorine itself. Treatment of the diacetate (XXXIII) with fluorine gave the 9α-fluoro-derivative (XXXIV) in 70% yield (allowing for recovered starting material). This provides a very convenient synthesis of 9α-fluoro-compounds.

The trifluoro-acetate dibromide (XXXV) gave, with CF_3OF followed by debromination and alkaline hydrolysis, the 14α-fluoro-derivative (XXXVI) (47%). Similarly the pregnenolone derivative (XXXVII) afforded 14α-fluoro-compound (XXXVIII) (38%). Both 14α-fluoro-ketones were quite stable to base, but readily lost HF when treated with HF or BF_3 under mild conditions, to furnish the known 14(15)-olefins (XXXIX) and (XL) respectively. This shows that the fluorine, which from n.m.r. evidence is tertiary, must be at C_{14}.

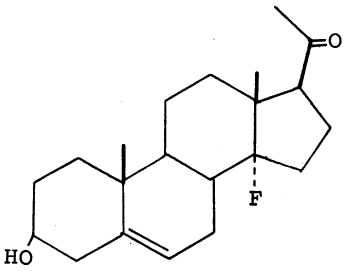
14(15)-Unsaturated olefins like (XL) are of potential importance for the synthesis of steroid cardenolides. The compound (XL) can be readily prepared using fluorine. Thus treatment of the acetate dichloride (XLI) with fluorine, Zn dust, alkali and then BF_3 gave the pregnadienolone (XL) in 45% overall yield. The dibromide (XXXVII) could not be used for this purpose, because fluorine liberates bromine from 1,2-dibromides.

With the 14α-fluoro-compounds in hand it was possible to synthesise the two hormone analogues (XLII) and (XLIII). 14α-Fluoro-compounds have never been prepared before and their biology is, therefore of interest.

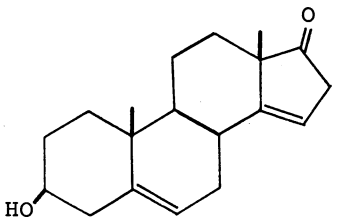
The configuration of the 14-fluorine atom is assigned as α- on the basis of both ^{19}F and ^{1}H n.m.r. and by molecular rotation arguments. If the fluorine had been 14β- then compounds like (XLIII) would have readily inverted the configuration of their side-chain.

That the fluorine is 14α- is a second good argument that the mechanism of fluorination is of the Olah-type and does not involve a free carbonium ion. The latter would have afforded the 14β-fluoro-compounds with the more stable cis-C/D ring fusion.

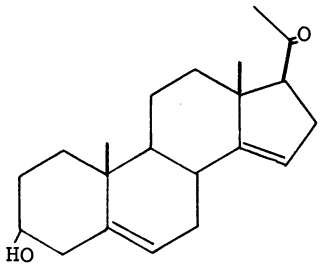
We have also studied the fluorination with F_2 of cholestanol trifluoroacetate (XLIV) and of cholesterol trifluoroacetate dichloride (XLV). The cholestanol derivative gave 17α--fluoro-cholestanol trifluoroacetate (XLVI) (25%) whilst the cholesterol derivative afforded



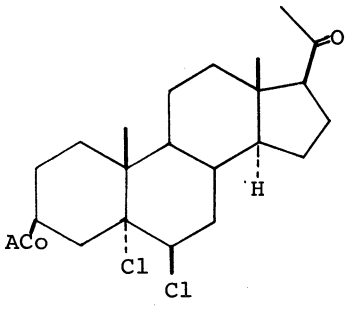
(XXXVIII)



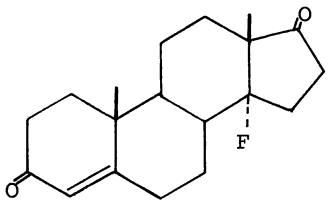
(XXXIX)



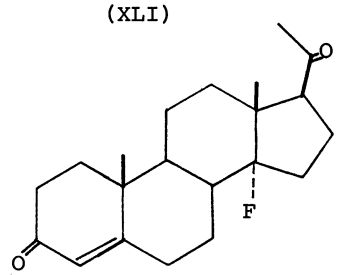
(XL)



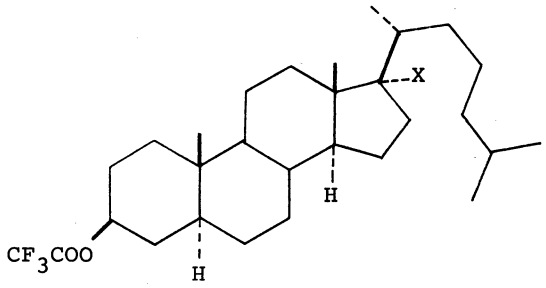
(XLI)



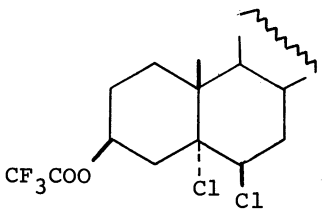
(XLII)



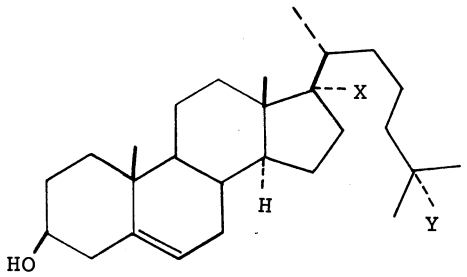
(XLII)



(XLIV) X=H (XLVI) X=F



(XLV)



(XLVII) X=F, Y=H

(XLVIII) X=Y=F

(after reduction with zinc and alkaline hydrolysis) a mixture of 17α-fluorocholesterol (XLVII) (40%) and 17α,25-difluorocholesterol (XLVIII) (20%). The assignment of the fluorine to C_{17} in (XLVI) and in (XLVII) is based on ^{19}F n.m.r. measurements (tertiary fluorine, not at C_9 or C_{14}) and on chemical degradation. The assignment of the second fluorine in (XLVIII) to the C_{25} position is by exclusion since it is tertiary and cannot be at C_9, C_{14} or C_{20}. The second fluorine at C_{25} is introduced by further fluorination of the C_{17} monofluoro--compound.

It is of interest now to analyse the synthetic work outlined above on fluorinated natural products in terms of conception, misconception and accident. The idea that hypofluorites would show electrophilic fluorine behaviour in organic solvents was clearly a conception. Granted this, then the synthesis of α-fluoro-ketones, the addition of the reagent to double bonds and the synthesis of fluorinated aromatics all follow logically. The preparation of N-fluoro-compounds would follow in the same way from a consideration of electronegativities. The most original invention is the highly selective electrophilic mechanism for the preparation of tert.-fluoro-compounds and of 9α-,14α- and 17α-monofluorinated steroids. As explained above this was discovered by accident, but at least we did undertand the implications of the accident. The fact that fluorine itself will also behave as a very selective positive fluorinating species is also unexpected and of undoubted practical significance.

Acknowledgements- The earlier work on the use of hypofluorites was ably carried out by those cited in the references given. The work on the synthesis of tert.fluoro-derivatives (16) was begun by Dr. H.T. Toh and continued by Dr.R.E. Markwell and Dr. S. Rozen. It is to them, and to my other colleagues, that much credit must be given.

REFERENCES

1. K.G. Kellogg and G.H. Cady, J. Amer. Chem. Soc., 1948, 70, 3986.
2. D.H.R. Barton, L.S. Godinho, R.H. Hesse and M.M. Pechet, J. Chem. Soc. Chem. Comm., 1968, 804.
3. D.H.R. Barton, R.H. Hesse, G. Tarzia and M.M. Pechet, J.Chem.Soc.Chem.Comm., 1969, 1497.
4. D.H.R. Barton, R.H. Hesse, M.M. Pechet, G. Tarzia, H.T. Toh and N.D. Westcott, J. Chem. Soc. Chem. Comm., 1972, 122.
5. D.H.R. Barton, L.J. Danks, A.K. Ganguly, R.H. Hesse, G. Tarzia and M.M. Pechet, J. Chem. Soc. Chem. Comm., 1969, 227.
6. D.H.R. Barton, L.J. Danks, A.K. Ganguly, R.H. Hesse, G. Tarzia and M.M. Pechet, J. Chem. Soc. Perk. I, 1976, 101.
7. D.H.R. Barton, A.K. Ganguly, R.H. Hesse, S.N. Loo and M.M. Pechet, J. Chem. Soc. Chem. Comm., 1968, 806.
8. J. Airey, D.H.R. Barton, A.K. Ganguly, R.H. Hesse and M.M. Pechet, Anal. de Quim., 1974, 70, 871.
9. D.H.R. Barton, R.H. Hesse, L. Ogunkoya, N.D. Westcott and M.M. Pechet, J. Chem. Soc. Perk I, 1972, 2889.
10. D.H.R. Barton, R.H. Hesse, H.T. Toh and M.M. Pechet, J. Org. Chem., 1972, 37, 329.
11. M.J. Robins and S.R. Naik, J. Amer. Chem. Soc., 1971, 93, 5277; J. Chem. Soc. Chem. Comm., 1972, 18.
12. D.H.R. Barton,W.A. Bubb, R.H. Hesse and M.M. Pechet, J. Chem. Soc. Perk. I, 1974, 2095.
13. D.H.R. Barton, R.H. Hesse, M.M. Pechet and H.T. Toh, J. Chem. Soc. Perk. I, 1974, 732.
14. D.H.R. Barton, R.H. Hesse, T.R. Klose and M.M. Pechet, J. Chem. Soc. Chem. Comm., 1975, 97.
15. G.A. Olah, Y. Halpern, J. Shen and Y.K. Mo, J. Amer. Chem. Soc., 1971, 93, 1251; G.A. Olah and J.A. Olah, ibid., 1971, 93, 1256; G.A. Olah and H.C. Lin, ibid., 1971, 93, 1259.
16. D.H.R. Barton, R.H. Hesse, R.E. Markwell, M.M. Pechet and H.T. Toh, J. Amer. Chem. Soc., 1976, 98, 3034; D.H.R. Barton, R.H. Hesse, R.E. Markwell, M.M. Pechet and S. Rozen, ibid., 1976, 98, 3036.