Part I investigation of synthetic routes to highly fluorinated benzo[b]furan compoumds Part II some fluoride-ion initiated reactions of fluoro-imines

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A THESIS

entitled

PART I. INVESTIGATION OF SYNTHETIC ROUTES TO HIGHLY FLUORINATED BENZO[b]FURAN COMPOUNDS

PART II. SOME FLUORIDE-ION INITIATED REACTIONS OF FLUORO-IMINES

submitted by

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Thanks are also due to the Science Research Council and Hartlepool Education Committee for the award of maintenance grants.

MEMORANDUM

The work described in this thesis was carried out in the University of Durham between March 1967 and September 1969. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

SUMMARY - (Part I)

By modifying synthetic routes described for the preparation of 4,5,6,7-tetrafluorobenzo[b]furan an attempt has been made to synthesise a benzo[b]furan derivative having fluorine atoms in the five-membered ring in addition to the four in the six-membered ring. The preparation of ethyl 2,3,4,5-tetrafluorophenoxy-fluoroacetate has been accomplished by treating the potassium salt of 2,3,4,5-tetrafluorophenol with ethyl-chlorofluoroacetate, with a view to cyclising the derived phenoxyfluoro-acetic acid by reaction with n-butyl lithium followed by carbonation. Ethyl 6-ethoxycarbonyl-2,3,4,5-tetrafluorophenoxy-fluoroacetate was synthesised by reaction of the potassium salt of ethyl 2,3,4,5-tetrafluoro salicylate with ethylchlorofluoroacetate and an attempt also made to cyclise this compound to a pentafluorobenzo[b]furan.

The synthesis of ω-hydroxy-2,3,4,5,6-pentafluoroacetophenone was undertaken, when ring closure might be expected to provide a more convenient route to 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one. Treatment of the ketone with SF_4 would then afford a more fully fluorinated benzo[b]furan.

The ring closure of 2,3,4,5,6-pentafluorophenylacetyl chloride by treatment with sodium hydride and with caesium fluoride was attempted but no displacement of ring fluorine occurred. The synthesis of 2,3,4,5,6-pentafluorophenyl pyruvic acid was undertaken, when, by a route analogous to that used by Tatlow et al [6] for the preparation of tetrafluoro-benzo[b]thiophen, the tetrafluorobenzo[b]furan could be more conveniently synthesised.

A further attempt to prepare the latter compound required 2,3,4,5,6-pentafluorophenylacetaldehyde which was synthesised by treating pentafluorophenylacetyl chloride with lithium tri-tertiary butoxyalumino hydride. Cyclisation of the aldehyde with sodium hydride would then afford the unsubstituted tetrafluorobenzo[b]furan.

SUMMARY - (Part II)

Fluorinated tertiary amines have been prepared by a process which can be considered the nucleophilic equivalent in fluorocarbon chemistry of the Friedel-Crafts synthesis in hydrocarbon chemistry. Perfluoro (methylene methylamine) was reacted with pentafluoropyridine in the presence of fluoride ion in an attempt to synthesise the 4-(N-dimethylamino) pyridine. Similar reactions were carried out using 1-chlorodecafluorobutylid-4-ene methylamine and perfluoro (N-isopropylidene aniline).

The isomeric 3- and 5-chloro-octafluoro-1-piperideines have been reacted with pentafluoropyridine, pentafluorobenzonitrile and the methyl- and ethyl-pentafluorobenzoates in the presence of fluoride ion. The structures of the resulting piperidine compounds and their derivatives were deduced from ^{19}F n.m.r. data. 2,3,5,6-Tetrafluoro-4(4'-bromononafluoro-piperidino) pyridine has been prepared by the fluoride-ion catalysed reaction of 4-bromo-octafluoro-1-piperideine with pentafluoropyridine.

The reactivity of perfluoro-4-piperidinopyridine and perfluoro-4-cyclo hexylpyridine toward methoxide ion was investigated in a competition reaction.

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CHAPTER VII. Experimental Work (Part II)

PART I

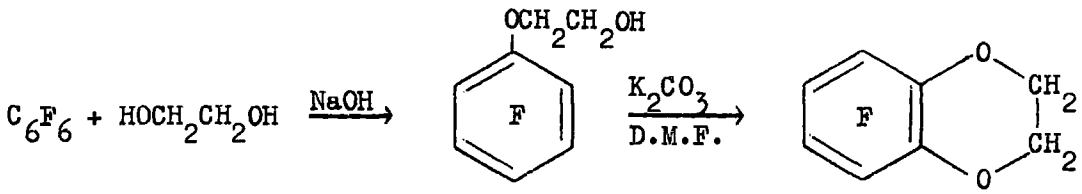
INVESTIGATION OF SYNTHETIC ROUTES TO HIGHLY FLUORINATED BENZO[b]FURAN COMPOUNDS

CHAPTER I

INTRODUCTION

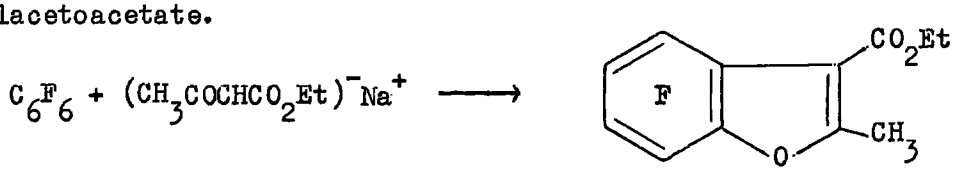
The Synthesis of Polyfluorinated Heterocycles by Nucleophilic Displacement of Fluoride Ion from Hexafluorobenzene and its Derivatives.

The synthesis of fluorinated fused ring heterocycles by intramolecular nucleophilic displacement of fluorine from the aromatic nucleus has been used previously and the majority of heterocyclic compounds obtained from polyfluorobenzene derivatives have been formed in this way. The first reported example of this type of reaction involved the treatment of hexafluorobenzene with a number of bidentate nucleophiles[1] such as ethyleneglycol and ethylenediamine, when the expected fused bicyclic compounds were isolated.

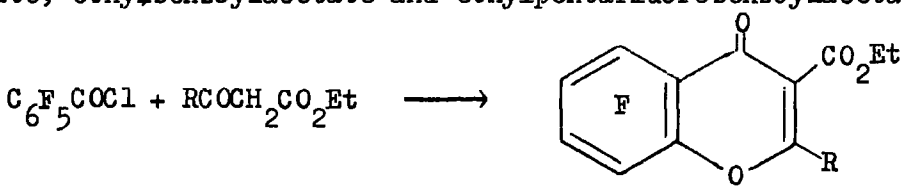


[In all rings containing an elemental symbol (e.g.F) all unmarked bonds are to that element (e.g.fluorine), and in those rings not containing a symbol all unmarked bonds are to hydrogen].

Other workers reported the preparation of this dioxin and also described the synthesis of a benzo[b]furan derivative[2] from C_6F_6 and the sodium salt of ethylacetoacetate.

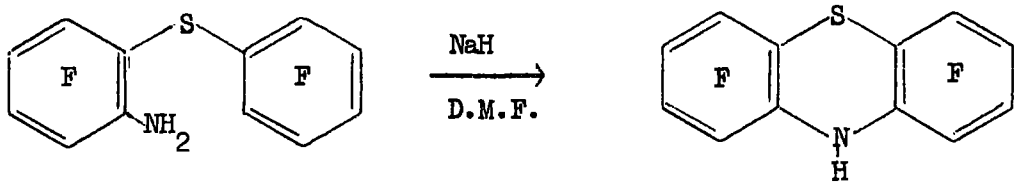


The synthesis of several γ-benzopyrone derivatives was reported by Vorozhtsov et al,[3] who treated pentafluorobenzoyl chloride with ethylacetoacetate, ethylbenzoylacetate and ethylpentafluorobenzoylacetate.

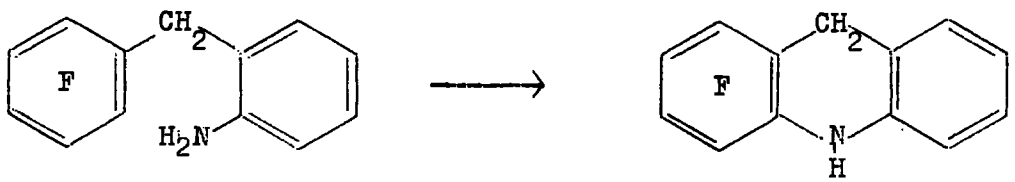


R = Me, C_6H_5, C_6F_5.

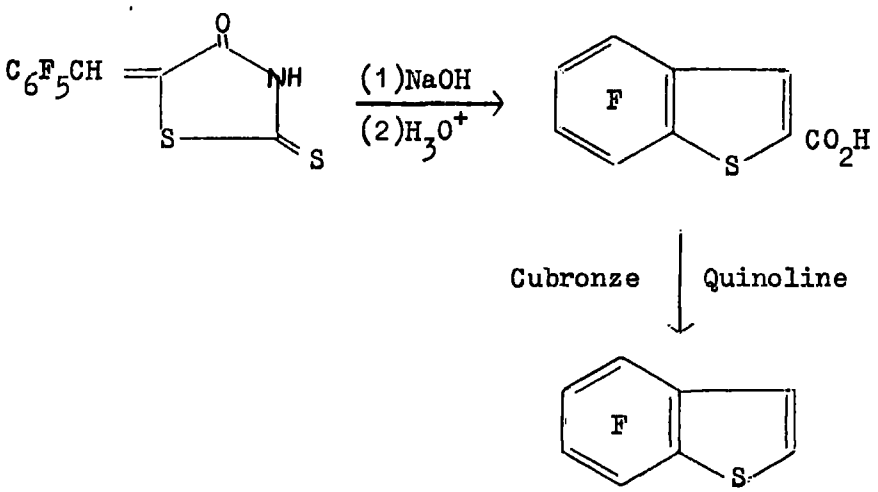
Octafluorophenothiazine has been prepared by a reaction involving displacement of the ring fluorine by a nitrogen nucleophile,[4]



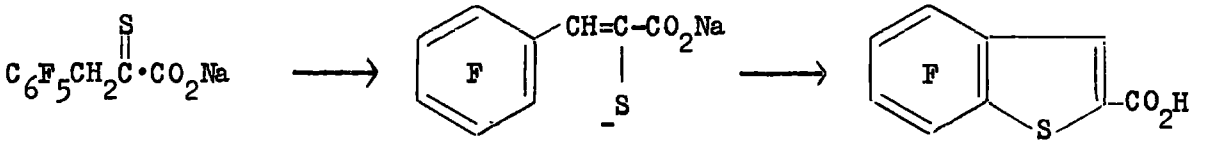
and a similar process was used for the synthesis of 1,2,3,4-tetrafluoro-acridan.[5]



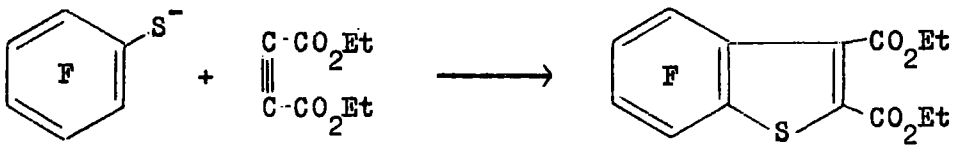
A ring closure step involving intramolecular displacement of fluorine by a hetero atom has been reported in the synthesis of 4,5,6,7-tetrafluoro-benzo[b]thiophen.[6] These workers heated the rhodanine complex of pentafluorobenzaldehyde with dilute sodium hydroxide, and on acidification obtained the benzo[b]thiophen-2-carboxylic acid.



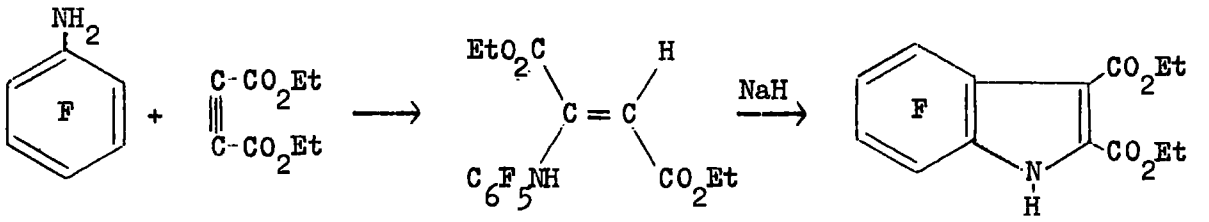
Breakdown of the complex to the thiopyruvic acid derivative, followed by enolisation, would lead to the thiolate which would then react as shown.



Tetrafluorobenzo[b]thiophen has been synthesised by other workers in a process which involved displacement of fluorine by a carbanion.[7]



A closely related reaction has been used for the preparation of fluorinated indoles.[8]

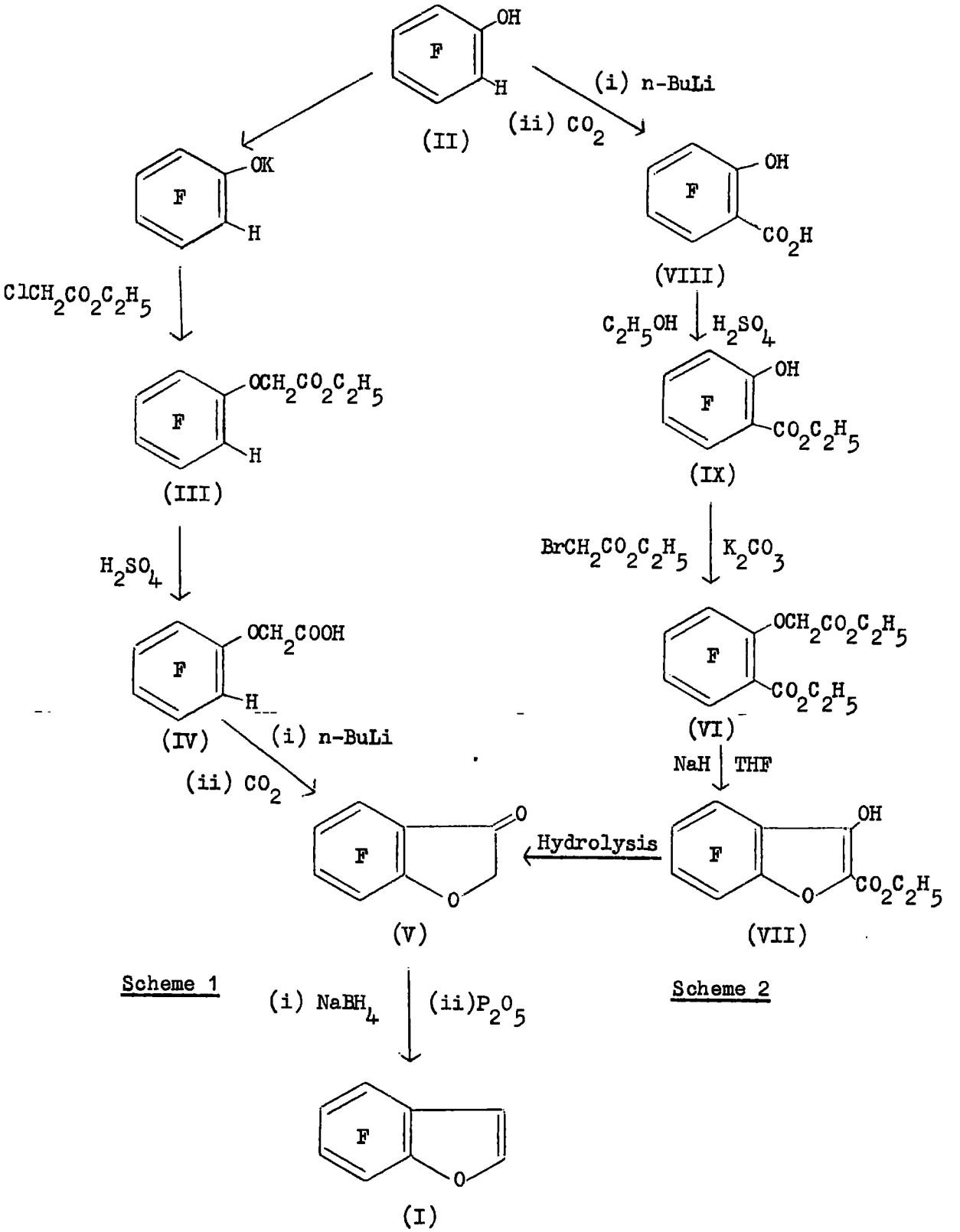


The synthesis of 4,5,6,7-tetrafluorobenzo[b]furan(I) has been accomplished recently[9] by two methods, both of which required 2,3,4,5-tetrafluorophenol(II)[9,10] as starting material. This compound was prepared in high yield by treatment of 1,2,3,4-tetrafluorobenzene with n-butyl

lithium, reacting the phenyl lithium derivative with trimethylborate and oxidising the resulting dimethyl ester of boronic acid with hydrogen peroxide.

In the first synthesis (Scheme 1) the phenol (II) was converted into ethyl 2,3,4,5-tetrafluorophenoxyacetate(III) which was hydrolysed to the corresponding acid (IV) and cyclised to 4,5,6,7-tetrafluoro-2H-benzo[b]furan-3-one(V) by reaction with n-butyl lithium followed by treatment with carbon dioxide. Reduction of (V) with sodium borohydride and dehydration of the product with phosphoric oxide, gave 4,5,6,7-tetrafluorobenzo[b]furan(I).

The second synthesis (Scheme 2), involved cyclisation of ethyl 6-ethoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate(VI) using sodium hydride to give the substituted benzo[b]furan(VII) which was hydrolysed and decarboxylated by aqueous alkali to the benzo[b]furan-3-one(V). The diester (VI) was synthesised from 2,3,4,5-tetrafluorophenol(II) by metalation followed by carbonation of the resulting lithium compound to give the salicylic acid (VIII). Esterification of this acid and treatment with ethyl bromoacetate afforded the diester (VI).


F
OH
H
(II)
(i) n-BuLi
(ii) CO_2
OK
$ClCH_2CO_2C_2H_5$
$OCH_2CO_2C_2H_5$
(III)
H_2SO_4
OCH_2COOH
(IV)
(i) n-BuLi
(ii) CO_2
O
(V)
Hydrolysis
CO_2H
(VIII)
C_2H_5OH
H_2SO_4
$CO_2C_2H_5$
(IX)
$BrCH_2CO_2C_2H_5$
K_2CO_3
(VI)
NaH
THF
(VII)
Scheme 1
(i) $NaBH_4$
(ii) P_2O_5
Scheme 2
(I)

CHAPTER II

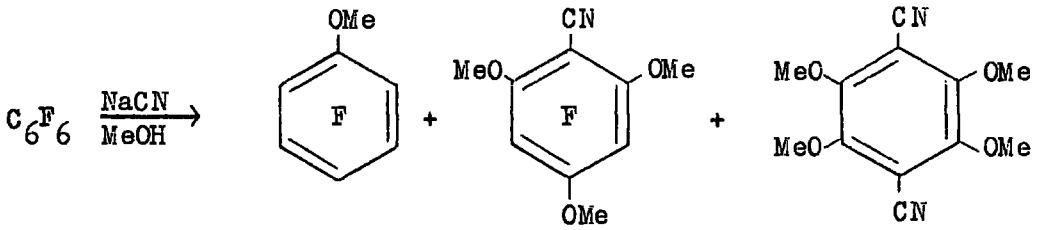
NUCLEOPHILIC SUBSTITUTION IN POLYFLUOROAROMATIC COMPOUNDS

Introduction

In contrast to the electrophilic substitution of hydrogen in hydrocarbons, the characteristic reaction of highly fluorinated aromatic compounds is the nucleophilic displacement of fluorine as fluoride ion.[39] The nucleophilic substitution of hexafluorobenzene and mono-substituted pentafluorobenzenes has been thoroughly investigated and a similar investigation, carried out initially on pentafluoropyridine, has been extended to other fluorinated heterocycles e.g. heptafluoroquinoline and -isoquinoline,[67] tetrafluoro-pyrazine,[69] -pyrimidine,[69,70] and -pyridazine.[69] In addition, the orientation of nucleophilic attack in polyfluorobenzo- and dibenzo-furans and -thiophens has been reported recently in the literature.[6,84,86,87,89,90]

Nucleophilic Substitution in Polyfluoroarenes.

The reactions of hexafluorobenzene with a wide variety of nucleophilic reagents such as MeO^-,[40,41] OH^-,[42,43] NH_3,[44,45] NH_2NH_2,[44] H^-,[39] SH^-,[46] result in the replacement of a single fluorine atom under moderate conditions, to give a good yield of the corresponding pentafluorophenyl compound. However, an exception to this behaviour, recently reported in the literature, is the reaction of hexafluorobenzene with sodium cyanide in methanol,[47,48] which afforded, among other products, a compound with all the fluorine atoms replaced.



(X)

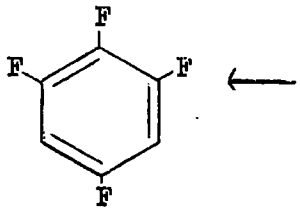
This reaction was rationalised by assuming initial attack by CN^- when the resulting pentafluorobenzonitrile reacted with methoxide ion at the positions ortho and para to the strongly activating CN group. Slow reaction of the CN^- with pentafluorobenzonitrile would then afford a small amount of the dicyano benzene from which all the fluorines would be displaced by methoxide ion to yield (X).

Further attack by nucleophiles on the monosubstituted products of hexafluorobenzene has been successfully investigated, mainly by research workers at Birmingham. In general, attack occurs predominantly (>90%) at the position para to the substituent (X), e.g. when X = H,[19,44,49]

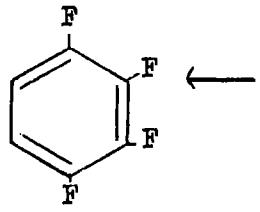
Me,[50] CF_3,[51,68] SMe,[52] SO_2Me,[52] NMe_2,[53] C_6F_5,[54,55,68] $N(CF_3)_2$,[56] OCF_3.[57] However, when the substituent is strongly electron donating e.g. X = O^-,[42,50] NH_2,[53], nucleophilic attack occurs mainly at the meta position. Comparable amounts of meta and para fluorine replacement occur for some substituents e.g. when X = OMe[50] and NHMe.[53] In the case of the halogens[19,68] (X = Cl,Br,I), ortho substitution occurred to a lesser extent than para substitution and decreased in the order Cl > Br > I.

In certain instances (X = NO_2,[58] NO,[59] CO_2^- [22]), the nucleophile appeared to govern the position of substitution, mainly para replacement occurring with sodium methoxide in methanol, but high (> 50%) ortho replacement with certain amines.

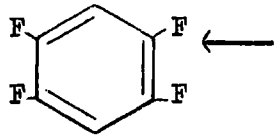
The three isomeric tetrafluorobenzenes (XI,XII,XIII) reacted with nucleophiles at the indicated positions,[60] 1,2,4,5-tetrafluorobenzene reacting significantly more slowly with methoxide than the other two compounds.



(XI)

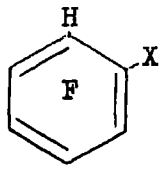


(XII)

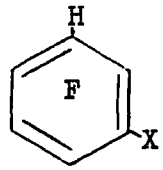


(XIII)

The reaction of the six tetrafluorohalogenobenzenes (XIV,XV) with



(XIV)

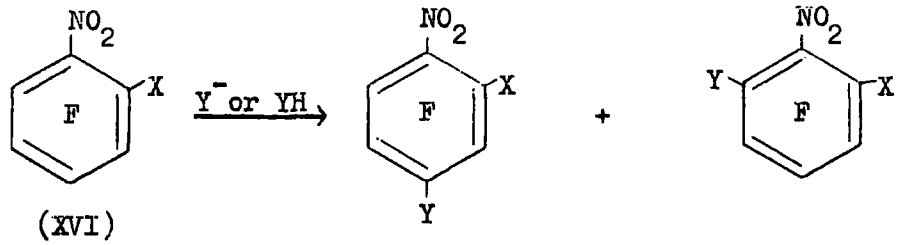


(XV)

(X = Cl, Br, I)

sodium methoxide and with dimethylamine has been investigated.[61] Replacement of the fluorine para to the hydrogen predominated when methoxide was used as the nucleophile, but the fluorine para to X was also replaced, the proportion increasing along the series Cl< Br <I. However, in the reaction between dimethylamine and the 1,2,3,5-tetrafluoro-4-halogenobenzene the fluorine para to X was replaced to a much greater extent than in the corresponding reaction with methoxide.

The nucleophilic replacement of fluorine in some 2-substituted tetrafluoronitrobenzenes (XVI) has been reported recently.[62]



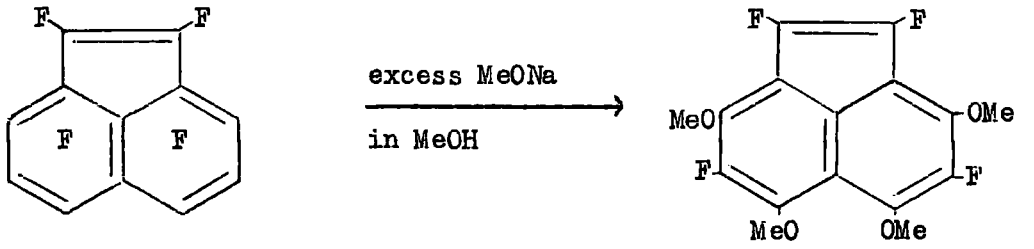
(XVI)

(X = NH_2,NHMe,NMe_2,OMe) (Y = NH_2,NHMe,NMe_2,OMe).

The 4- and 6- fluorines were displaced, the relative proportions, however, varied; the amount of 6-substitution decreased with the group ortho to the NO_2 group in the order NMe_2 > OMe > NHMe > F > NH_2, and the overall reactivities decreased in the reverse order.

The reaction of highly fluorinated polycyclic aromatic compounds with nucleophiles has also been studied, but much less extensively than those of the monocyclic compounds. Octafluoronaphthalene,[63] 1,2,3,4-tetrafluoronaphthalene,[64] and 1,2,3,4-tetrafluoroanthraquinone[65] all undergo nucleophilic replacement of the 2-fluorine. In the case of octafluoroacenaphthylene[66] (XVII)

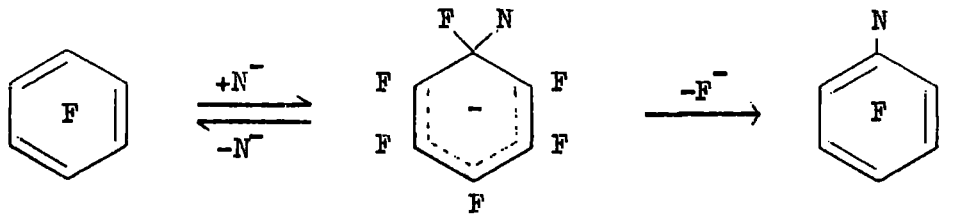
successive nucleophilic replacement of fluorine occurred at the 3,8,5 and 6 positions the tetrafluoro-tetramethoxyacenaphthylene (XVIII) being formed when four or more equivalents of sodium methoxide were employed.



(XVII) (XVIII)

The tetramethoxy compound was found to be inert to further attack by methoxide ion.

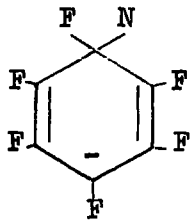
Burdon[18] has rationalised the observed orientation and reactivity in nucleophilic replacement reactions of aromatic polyhalo compounds by considering the relative stabilities of the Wheland-type intermediates for all possible positions of attack by the nucleophile. Thus, for hexafluorobenzene reacting with a nucleophile N^-, the Wheland-type intermediate (XIX)



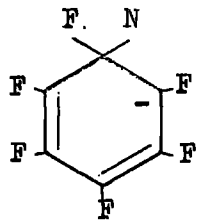
(XIX)

was used as an approximation to the transition state for the substitution reaction, and the para-quinonoid resonance hybrid (XX) was assumed to be the

main contributor to the intermediate, the ortho-quinonoid (XXI) having only secondary importance.

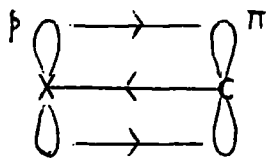


(XX)



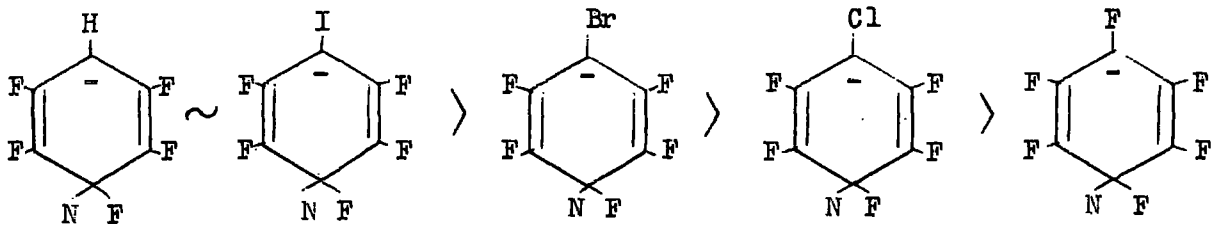
(XXI)

Thus, in the absence of solvent and steric effects, if a substituent X, in a C_6F_5X molecule, stabilizes the negative charge on the carbon to which it is attached, then nucleophilic attack would occur para to X, and to a lesser extent, ortho to X. On the other hand if the substituent X destabilizes the negative charge, more than fluorine, then nucleophilic attack would occur meta to X. In the event that the substituent has exactly the same influence as fluorine on the stability of the negative charge, ortho:meta:para replacement would occur in the statistical order 2:2:1 respectively. The halogens were assumed[45] to destabilize the negative charge in the order F > Cl > Br > I > H and this effect (I_π effect) was attributed to coulombic repulsion between the ring π-electrons on the C atom and the lone pair p-electrons on the halogen atom.[17] In a σ-bonded system the halogen tends to attract electrons, in an attempt to attain an inert gas configuration, but in a π-bonded system tends to repel π-electrons on the adjacent carbon atom.



I_π repulsive effects of oxygen and nitrogen were assumed to be in the order N > O > F.[18]

Thus, the order of stability of the <u>para</u>- quininoid hybrids, based on I_π repulsions, would be as follows:



This theory has been successfully applied to the nucleophilic substitution of fluorine in the vast majority of aromatic polyfluoro compounds, but, in certain cases mentioned previously, the observed orientations and reactivity were not in agreement with the theory. The C_6F_5X compounds, where X = NO_2,[58] NO,[59] CO_2^-,[22] when reacted with amines as nucleophiles, underwent <u>ortho</u> substitution to a great extent, but afforded mainly the <u>para</u> substituted derivatives when treated with methoxide. This has been attributed to the proximity of the nucleophile to the <u>ortho</u> position when hydrogen-bonded to the substituent. However, other factors must be involved[22] since it was shown that greater <u>ortho</u> replacement occurred when dimethylamine was used, instead of methylamine, in the reaction with pentafluorobenzoic acid, whilst the reverse effect was observed when pentafluoronitrobenzene and pentafluoronitrosobenzene were reacted with the amines.

Another factor that must be taken into consideration in certain instances is steric hindrance. This was used to explain the fact that dimethylamine displaced the fluorine para to iodine (92%) from 1,2,3,5-tetrafluoro-4-iodobenzene, whilst the less bulky methoxide anion replaced the fluorine para to hydrogen (i.e. ortho to iodine) to the extent of 60%.[61] The orientation of nucleophilic substitution in those C_6F_5X compounds where X = $N(Me)_2$,[53] $N(CF_3)_2$,[56] NHMe,[53] OMe[50] and OCF_3[57] has been explained in terms of steric repulsion between the bulky substituent X, and the two ortho ring fluorine atoms. The predicted position of substitution, based on the I_π effect (N > O > F), would be mainly meta; however, steric repulsion forces the plane of the p-orbitals of the hetero-atom out of the plane perpendicular to the ring thus lessening repulsion between the p-electrons of the hetero-atom and the π-electrons of the ring.[18] An approximate correlation can be made in these cases, of the amount of para substitution with the bulk of the substituent X.

Another related factor influencing the position of substitution is the solvent used in the reaction and several examples of this have been reported in the literature. When pentafluoronitrobenzene[22,64] was reacted with sodium methoxide 50% ortho replacement was achieved using 3·8% methanol in ether, and only 8% ortho in methanol alone. Treatment of hexafluorobenzene with excess hydrazine[55] in dioxan afforded equal amounts of the 1,3- and 1,4-disubstituted products, but when tetrahydrofuran was used as solvent, only the 1,4-isomer was formed. More recently pentafluoronitrobenzene[71] was reacted with methoxide in a variety of solvents of

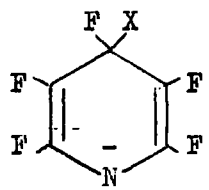
dielectric > 30 e.g. MeCN, $MeNO_2$, $HO(CH_2)_2OH$, to afford para substituted products, and when solvents of lower dielectric were employed e.g. dioxan, benzene, dichloroethane, the proportion of ortho isomer in the mixture predominated.

Nucleophilic substitution in Polyfluoro-heterocyclic Aromatic compounds.

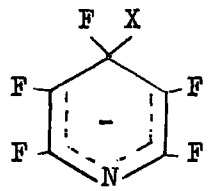
Most of the work on nucleophilic substitution has been concerned with the homocyclic compounds; however, investigations on the orientations of heterocyclic systems have been carried out but to a lesser extent and then mainly with the nitrogen-containing heterocycles. Of the nitrogen containing compounds, polyfluoro pyridines have been studied in greatest detail, the investigations largely carried out by workers at Durham[73] and Manchester.[74] Two points have emerged as a result of their work, in that nucleophilic displacement of fluorine from pentafluoropyridine occurred more readily than from hexafluorobenzene, and that substitution occurred preferentially in the 4-position. The milder reaction conditions required by C_5F_5N can be exemplified by the exothermic reaction with an ethanolic solution of aqueous ammonia at room temperature (quantitative after 2 hours at 80°), whereas the same reaction with hexafluorobenzene required a temperature of 167°.[44] Reaction between sodium methoxide in methanol and pentafluoropyridine occurred readily at 0° to afford the monomethoxy derivative, whereas at least 1 hour at the reflux temperature was necessary for the analogous preparation of pentafluoroanisole.[40]

That substitution occurs preferentially (≥ 90%) para to the ring nitrogen has been shown by a number of nucleophilic replacement reactions

with e.g. NH_3,[74,75] NH_2NH_2,[74,75] NaOMe,[74,75] Me_2NH,[74] $LiAlH_4$,[74] C_6F_5Li,[75] KOH,[76] NaOH.[74] Treatment of 4-methoxy-[74], or 4-bromotetrafluoropyridine,[77] with nucleophiles gave replacement of the 2-fluorine, and the use of excess sodium methoxide afforded the corresponding 2,6-dimethoxy compound. The order of displacement of the fluorine atoms, with methoxide ion, was shown to be 4, 2 and 6. An exception to this case was observed in the reaction of 2,3,5,6-tetrafluoro-4-nitropyridine with methoxide and with ammonia, when considerable replacement of the NO_2 group occurred as well as replacement of the 2- and 3-fluorines.[78] These results can be rationalised[78] by assuming the ring nitrogen to be the greatest single factor governing the position of substitution due to its ability to stabilize a negative charge placed on it, that is the hybrid (XXII) contributes most to the Wheland intermediate (XXIII).



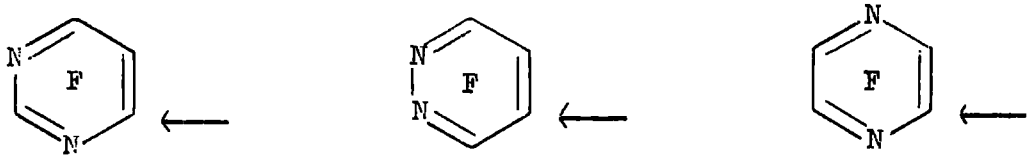
(XXII)



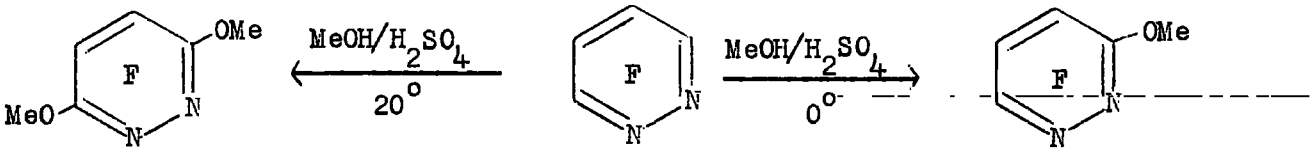
(XXIII)

A consideration of the other positions at which substitution could occur shows that the negative charge can only be localised on the nitrogen for displacement of the 2- or 6-fluorines.

The replacement reactions of the three tetrafluorodiazines also provide evidence for the influence of the ring nitrogen atom on the orientation of nucleophilic substitution. All three compounds were observed to be more reactive than pentafluoropyridine, displacement of fluorine occurring at the indicated positions.

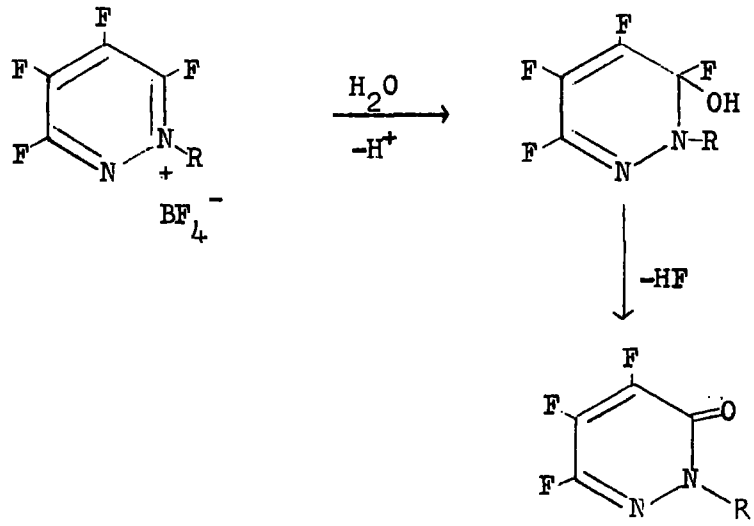


It was shown[77] however that perfluoropyrazine, in which there is no fluorine para to nitrogen, exhibits a reduced susceptibility to nucleophilic displacement of fluorine, compared with the pyrimidine and pyridazine, exemplified by the slow formation of 2-aminopyrazine on treating the pyrazine with ammonia at 20°. Under basic conditions perfluoropyridazine undergoes nucleophilic displacement at the 4- and 5-positions but in acidic media nucleophilic attack occurred at the 3- and 6-positions,[79] e.g. reaction of the pyridazine (XXIV) with $MeOH/H_2SO_4$ at 0° yielded the 6-methoxy compound (XXVI), and at 20° the 3,6-dimethoxy derivative (XXV).



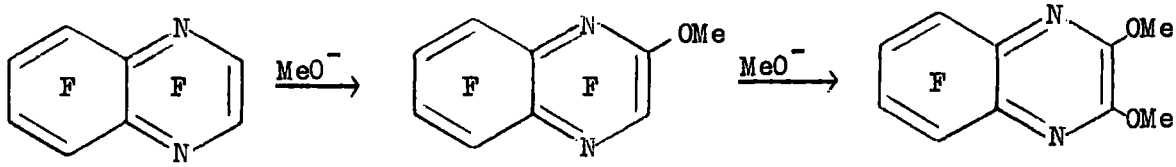
(XXV) (XXIV) (XXVI)

This reaction has been explained in terms of nucleophilic attack on a protonated polyfluoropyridazinium cation, and two N-alkyl-tetrafluoro-pyridazinium salts have been prepared. Treatment of these salts with water then yielded exclusively the 1-alkyl-3,4,5-trifluoropyridazin-6-ones, showing that nucleophilic attack occurred adjacent to the quaternary centre.



(R = Me, Et)

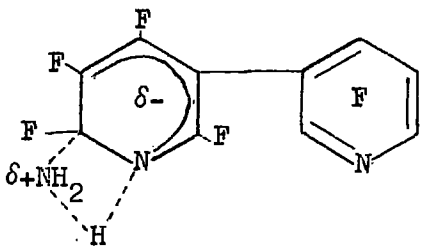
The orientation of nucleophilic substitution in hexafluoroquinoxaline has also been investigated.[80] Treatment of the quinoxaline with methoxide at -15° gave pentafluoro-2-methoxyquinoxaline, and when two moles of methoxide were employed the corresponding 2,3-dimethoxy derivative was isolated.



The carbocyclic ring was observed to be resistant to nucleophilic displacement of fluorine by methoxide in methanol under reflux.

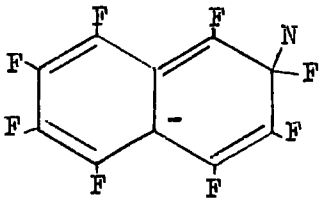
The influence of the heterocyclic ring nitrogen on orientation of substitutions can also be observed in the reaction of octafluoro-2,2'-dipyridyl[81] when treatment with methoxide ion gave exclusive replacement of the fluorine atoms <u>para</u> to the ring nitrogen. That orientation can be

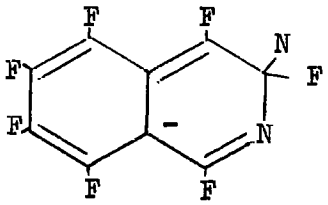
affected by steric and solvent factors however was shown by the nucleophilic reactions of octafluoro-3,3'-bipyridyl.[82] With methoxide in methanol the 4- and 6-fluorine atoms were replaced, but with MeLi in ether, and NH_3 in ether, substitution occurred exclusively at the 6-position. The explanation advanced for this involved a charged transition state in which the attacking nucleophile is held in the 6-position by fractional charges.



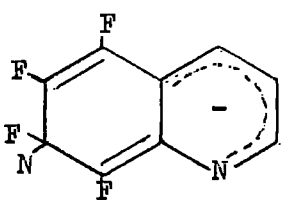
The simple qualitative theory, which afforded a satisfactory rationalisation of the orientation of nucleophilic substitution in most cases, suffered its first major failure when applied to heptafluoroquinoline and -isoquinoline.[67] Two monosubstituted products were obtained from the reaction of the quinoline with sodium methoxide, 2-methoxy- and 4-methoxy-hexafluoroquinoline in the ratio 3·4:1. According to the simple theory the para-quinonoid contribution to the transition states for each position of substitution indicated that the 2- or 4-positions were most likely to be the substitution points. There is no choice between these two possibilities however, on the basis of the simple qualitative theory, as the relative stabilizing effects of localising the charge on nitrogen, or delocalising the charge around the ring, are not known. Heptafluoroisoquinoline yielded exclusively the 1-substituted products with nucleophiles,

and further substitution gave the 1,6-dimethoxyisoquinoline. In this case 3-substitution might have been expected to predominate by analogy with octafluoronaphthalene[63] which is substituted in the 2-position.



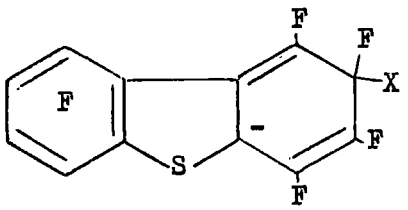


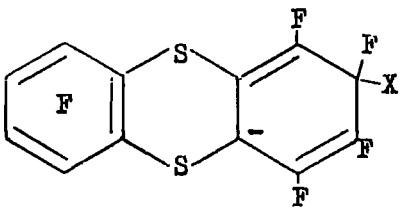
The rationalisation of the observed orientation of substitution in the monocyclic nitrogen heterocycles was based on two factors, the destabilising of a negative charge on a carbon bonded to fluorine (I_{π} effect), and the stabilising of a negative charge by localisation on nitrogen. In the case of pentafluoropyridine these two effects act in conjunction, but, when they oppose one another a satisfactory rationalisation cannot be obtained, which appears to be the case with fused ring heterocycles when substitution takes place in the heterocyclic ring. With 5,6,7,8-tetrafluoroquinoline[83] however, substitution occurs at the 7-position, a likely transition state being that where the negative charge can be localised on nitrogen.



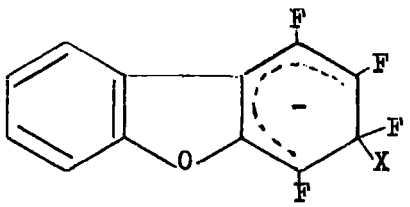
Octafluorothianthren and octafluorodibenzothiophen[84] both undergo nucleophilic displacement of the 2-fluorine by methoxide, further reaction then affords

the corresponding 2,8-dimethoxy derivatives. This orientation has been rationalised by assuming that a negative charge on a carbon attached to sulphur is stabilised by the sulphur d-orbitals.[85]

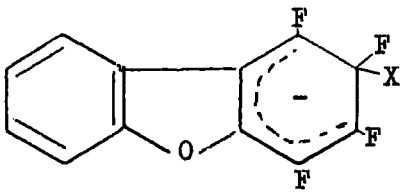




In the case of the dibenzofurans both the 1,2,3,4-tetrafluoro-[86] and the octafluoro-dibenzofuran[87] were substituted in the 3-position. The octafluoro-compound underwent further substitution with methoxide ion to yield the 3,7-dimethoxy compound. On consideration of the Wheland intermediates written for attack at the 2- and 3- positions it can be seen that (XXVII) would be preferred to (XXVIII) since the former has a greater degree of delocalisation and none of the destabilisation associated with an oxygen-substituted carbanion as in (XXVIII).

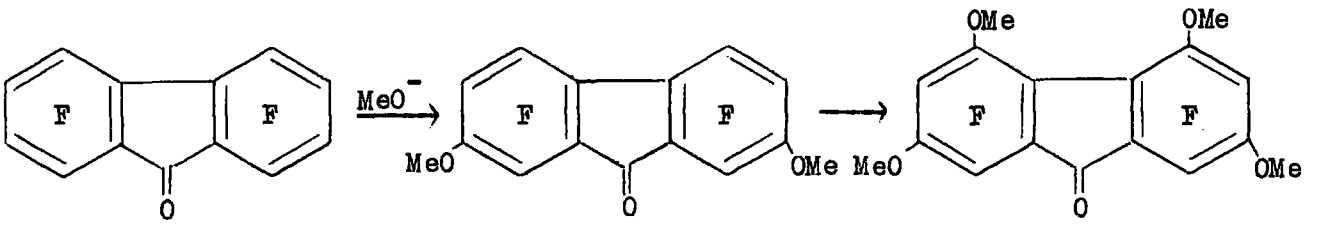


(XXVII)



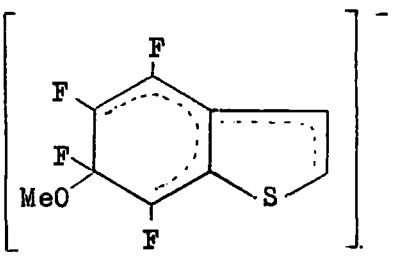
(XXVIII)

By comparison, substitution in octafluorofluoren-9-one[88] occurred <u>meta</u> to the carbonyl group e.g. methoxide in methanol displaced the 2- and 7-fluorine atoms, further substitution afforded the 2,4,5,7-tetramethoxy compound.



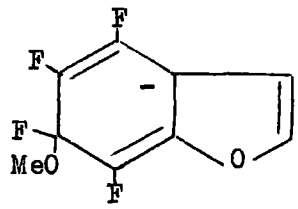
The initial displacement at the 2-position was not expected since it would appear that the greatest stabilisation would have resulted by an attack para to the carbonyl group. This result seems to be an exception to the generally accepted rule that a carbonyl group is best able to stabilise an adjacent carbanion when the geometry is planar.

Nucleophilic substitution in 4,5,6,7-tetrafluorobenzo[b]thiophen[6,89] occurs at the 6-fluorine, meta to sulphur. Just as in the substitution of octafluorodibenzothiophen where the negative charge in the intermediate was stabilised by the sulphur atom, so in tetrafluorobenzo[b]thiophen an intermediate can be written in which the charge is stabilised in a similar fashion. The corresponding 4,5,6,7-tetrafluorobenzo[b]furan[90] when treated



with methoxide in methanol in a sealed tube at 95° for 41 hours afforded three mono-methoxy isomers in the ratio 57:27:16, the 6-methoxy derivative predominating. This orientation was rationalised on the basis of a greater contribution to the Wheland-type intermediate by the para-quinonoid hybrid,

and that the I_{π} repulsion of oxygen is greater than that of fluorine. On these assumptions structure (XXIX) was thought to be the most stable, the negative charge being on a carbon common to both rings and not on a carbon bonded to fluorine.



(XXIX)

The other isomers were shown to be the 4- and 7-methoxy compounds in the ratio 27:16.

Tetrafluorofuran,[91] did not behave like a typical fluoroaromatic compound; nucleophilic substitution was unsuccessful, and polymerisation occurred even at room temperature in a few hours. However tetrafluorothiophen[92] did not polymerise at room temperature, or add bromine like the furan analogue, and on treatment with methoxide ion afforded the 2-methoxy derivative. This ether resinified over a period of 1 hour at room temperature.

CHAPTER III

DISCUSSION OF EXPERIMENTAL WORK (PART I)

Introduction

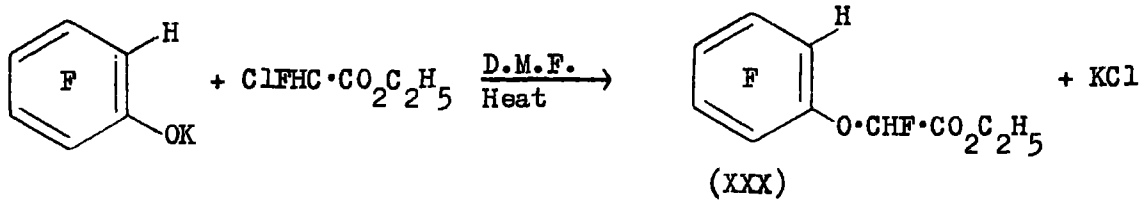
The available routes, described previously, for the preparation of 4,5,6,7-tetrafluorobenzo[b]furan(I) were modified in an attempt to synthesise a more fully fluorinated benzo[b]furan. Initially two approaches were employed, and the synthesis of the ethyl fluoroacetate esters analogous to compounds (III) and (VI) was undertaken. By the same reaction sequences depicted in schemes 1 and 2 a cyclisation was to be effected to afford products with a fluorine atom in the five-membered ring.

The second approach required a convenient route to a 4,5,6,7-tetrafluorobenzo[b]furan derivative, when fluorination of the five-membered ring would be attempted. Both these approaches were unsuccessful, the attempts to effect cyclisation did not result in intramolecular ring-fluorine displacement.

1.(i) Synthesis of Ethyl 2,3,4,5-Tetrafluorophenoxy-fluoroacetate (XXX)

The reactivity of the chlorine atom in ethyl chlorofluoroacetate towards nucleophilic replacement has been demonstrated[11] by its preferential replacement on treatment with the sodium salts of phenols. An attempt was made therefore to synthesise the esters analogous to (III) and (VI), having a fluorine atom in the phenoxyacetate function which on cyclisation would yield a five-membered ring containing fluorine. Conversion of this product to 2,4,5,6,7-pentafluorobenzo[b]furan would be relatively easy to carry out.

Treatment of the potassium salt of 2,3,4,5-tetrafluorophenol with ethyl chlorofluoroacetate gave the ester (XXX) in 59% yield.



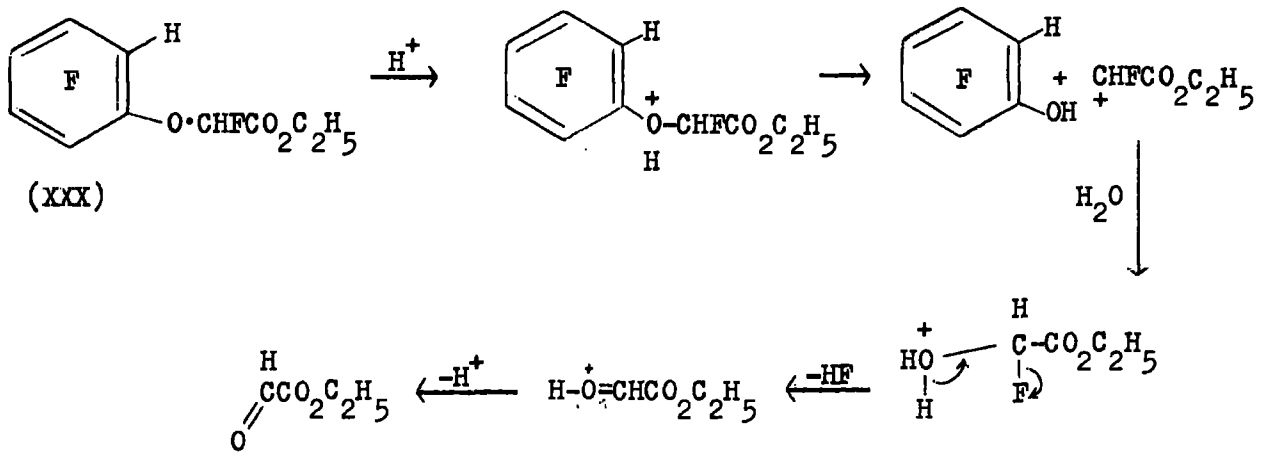
(XXX)

By analogy with Scheme 1 the next step was to hydrolyse (XXX) to the phenoxyfluoroacetic acid prior to ring closure. Several attempts were made to hydrolyse the ester (see Table 1 experimental work) but only starting material, and in some cases 2,3,4,5-tetrafluorophenol, were recovered.

Treatment of the potassium tetrafluorophenate with sodium chlorofluoroacetate under similar conditions used with ethyl chlorofluoroacetate, gave only a small amount of a tarry, unidentifiable material, and when chlorofluoroacetic acid was employed an intractable tar was again obtained.

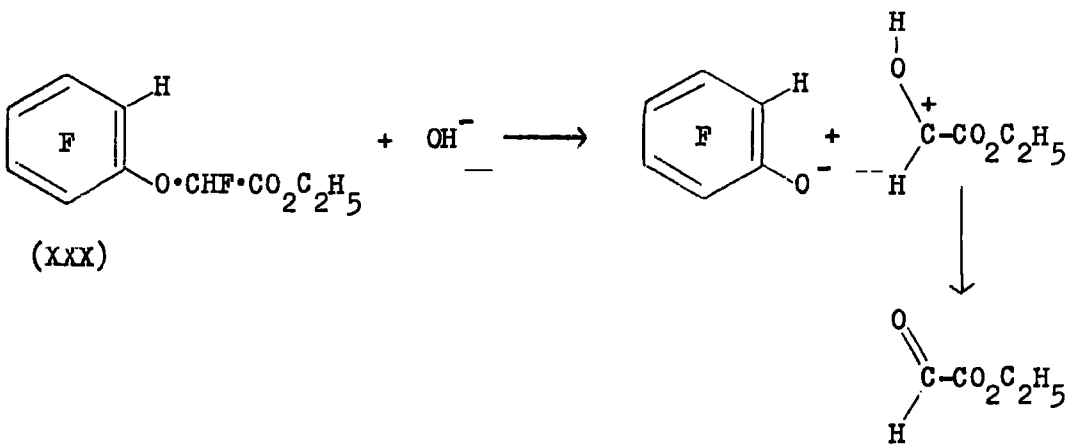
It appears that under the conditions used for hydrolysis the ether linkage undergoes cleavage. A possible mechanism for the reaction in the presence of mineral acid involves protonation of the ether oxygen followed by alkyl oxygen fission. Subsequent nucleophilic attack on the carbonium ion by a molecule of water, elimination of HF and loss of a proton would then afford

ethyl glyoxylate.



(XXX)

The reactivity of α-haloethers towards nucleophiles has been shown.[12,13,14,15,16] A possible mechanism for base catalyst cleavage would involve attack at the α-carbon requiring displacement of phenoxide or loss of fluoride.



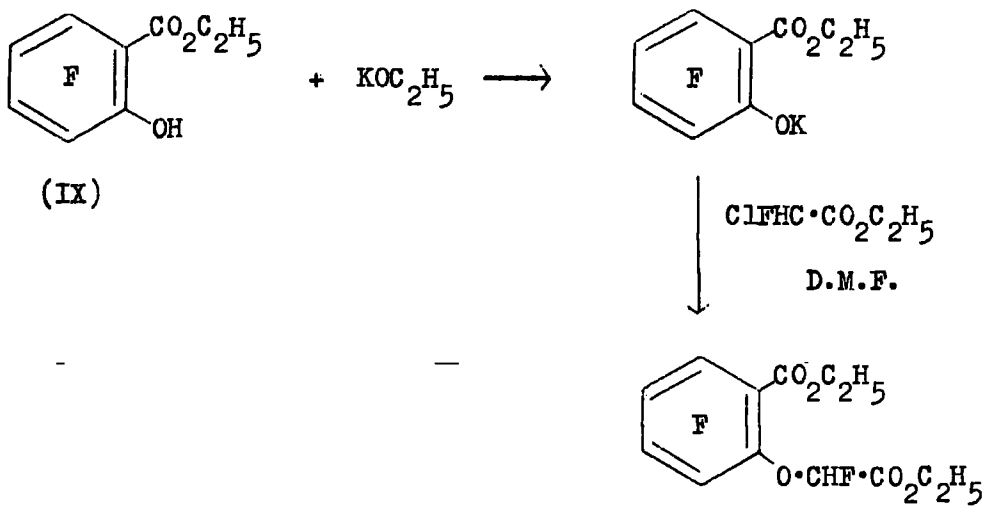
(XXX)

Following the failure of this reaction the synthesis of the diester (XXXI) was attempted with a view to following a reaction sequence analogous to Scheme 2. Treatment of (XXXI) with sodium hydride should then effect cyclisation to give a product with a fluorine in the five-membered ring.

1.(ii) Synthesis of Ethyl 6-ethoxycarbonyl-2,3,4,5-Tetrafluorophenoxyfluoroacetate(XXXI)

Several attempts were made to prepare this diester by treating the ethyl salicylate (IX) with ethyl chlorofluoroacetate using conditions analogous to those described in Scheme 2. However, only starting material was recovered.

When the ethyl salicylate was reacted with potassium ethoxide and the resulting salt boiled under reflux with ethyl chlorofluoroacetate in NN'-dimethylformamide, the expected diester (XXXI) was isolated in 55% yield.



(IX)

(XXXI)

Cyclisation of the diester was attempted several times using e.g. sodium hydride,[9] sodium ethoxide.

When a solution of the diester (XXXI) in tetrahydrofuran was added to a stirred suspension of sodium hydride no reaction occurred; the evolution of hydrogen, which was pronounced in the analogous reaction using ethyl-6-

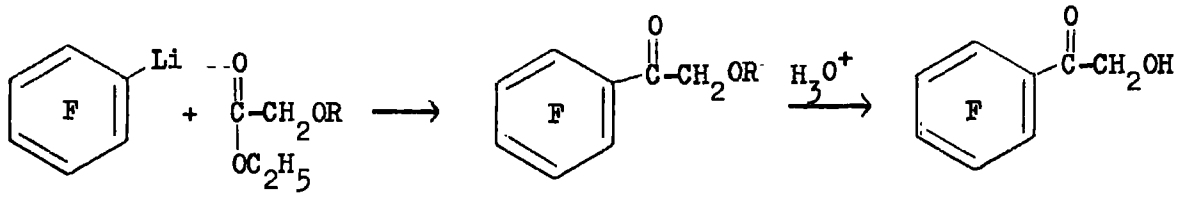
ethoxycarbonyl-4,5,6,7-tetrafluorophenoxyacetate, was not observed. Nevertheless, the mixture was heated under reflux as before, but after work-up, only the starting diester was isolated. On treatment of the diester (XXXI) with sodium ethoxide in refluxing ethanol, decomposition occurred and no identifiable product could be isolated from the reaction mixture.

Proton abstraction from the α-carbon to give the carbanion necessary for ring closure to occur is clearly energetically unfavourable in these reactions. This could be explained on the basis of the I_{π}[17] effect of the fluorine. The carbanion would be destabilised by the fluorine atom. This principle has been used to explain the orientation reactions of polyfluoro-aromatic compounds C_6F_5X to further nucleophilic replacement of fluorine.[17,18,19,20]

2. Synthesis of ω-Hydroxy-2,3,4,5,6-Pentafluoroacetophenone (XXXIII)

The next attempt at the synthesis of a more fully fluorinated benzo[b]furan envisaged the fluorination of 4,5,6,7-tetrafluorobenzo[b]furan-3-one(V) using sulphur tetrafluoride. The method available for the synthesis of (V) however was a six stage process having a low overall yield hence a search for a more convenient route was undertaken.

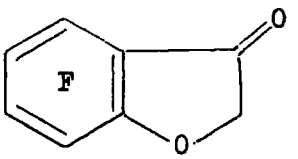
The new method required ω-hydroxy-2,3,4,5,6-pentafluoroacetophenone and the synthesis of this compound was attempted as shown by the reaction sequence. Pentafluorophenyl-lithium was reacted with ethyl glycollate, having the hydroxyl group suitable protected, the resulting keto ether (XXXII) was to be cleaved to afford the keto alcohol (XXXIII), and ring closure, effected by nucleophilic displacement of the ring fluorine atom ortho to the carbonyl function, would give the benzo[b]furan-3-one (V).



(XXXII)

(XXXIII)

NaH



(V)

The mixture of pentafluorophenyl-lithium and the lithium salt of ethyl glycollate was allowed several hours reaction time at -70° but on work-up only an unidentified polymeric material was obtained. A second attempt, in which inverse addition of reactants was employed, afforded the same polyphenylene compound, by self interaction of the C_6F_5Li.

The first successful attempt to prepare the keto alcohol (XXXIII) involved reacting pentafluorophenyl-lithium with the benzyl ether of ethyl glycollate prepared from the reaction between sodium benzylate and ethyl bromoacetate. A solution of the benzyl ether in diethyl ether was added to a stirred ethereal solution of pentafluorophenyl-lithium at -70°C and allowed several hours reaction time. Nucleophilic displacement of the ethoxy group afforded the benzylated ketone (XXXII; R = $C_6H_5CH_2$) in 20% yield.

Cleavage of this ether to afford the keto alcohol (XXXIII) was achieved by solution in concentrated sulphuric acid and dilution with water to give the keto alcohol in 20% yield.

Subsequent work showed that the keto alcohol could be prepared in higher yield by using the trityl ether of ethyl glycollate in place of the corresponding benzyl compound.

Treatment of pentafluorophenyl-lithium, under analogous conditions, with the trityl ether of ethyl glycollate prepared from trityl chloride and ethyl glycollate, afforded the pure tritylated ketone (XXXIII; R = $C(Ph)_3$) in 53% yield. Cleavage of this compound with concentrated sulphuric acid gave the pure keto alcohol in 51% yield.

Reaction of ω-Hydroxy-2,3,4,5,6-Pentafluoroacetophenone (XXXIII) with Sodium Hydride.

The experimental procedure employed was essentially the same in all these reactions in that a solution of the keto alcohol was added to a stirred suspension of prewashed sodium hydride under an atmosphere of dry nitrogen. Reaction times and temperatures are noted in Table 2, page 31.

Work-up involved removal of tetrahydrofuran (T.H.F.) by distillation, solution of the crude product in water, acidification and ether extraction. After removal of the ether the crude residue was analysed by thin layer chromatography (T.L.C.) and infra-red spectroscopy (see Table 2).

With the exception of the reaction carried out in monoglyme all products showed an absorption in the infra-red attributed to a carbonyl group, but in no case was the major product the required benzo[b]furan-3-one (V). The intractable nature of the products and the absence of a definite hydroxyl absorption in their infra-red spectra suggested that an intermolecular reaction may have occurred leading to polymeric material. Further attempts to cyclise the keto alcohol in basic reaction media were unsuccessful (see p.32 Table 3). The same work-up procedure was employed as in the previous sodium hydride reactions.

3. Attempted Cyclisation of 2,3,4,5,6-Pentafluorophenylacetyl Chloride (XXXIV)

This approach to a fluorinated benzo[b]furan derivative envisaged the ring closure of 2,3,4,5,6-pentafluorophenylacetylchloride (XXXIV), by treatment with sodium hydride.[9] It was expected that the enolate ion resulting from proton abstraction, would undergo an intramolecular nucleophilic displacement as depicted by the following reaction sequence.

Table 2.

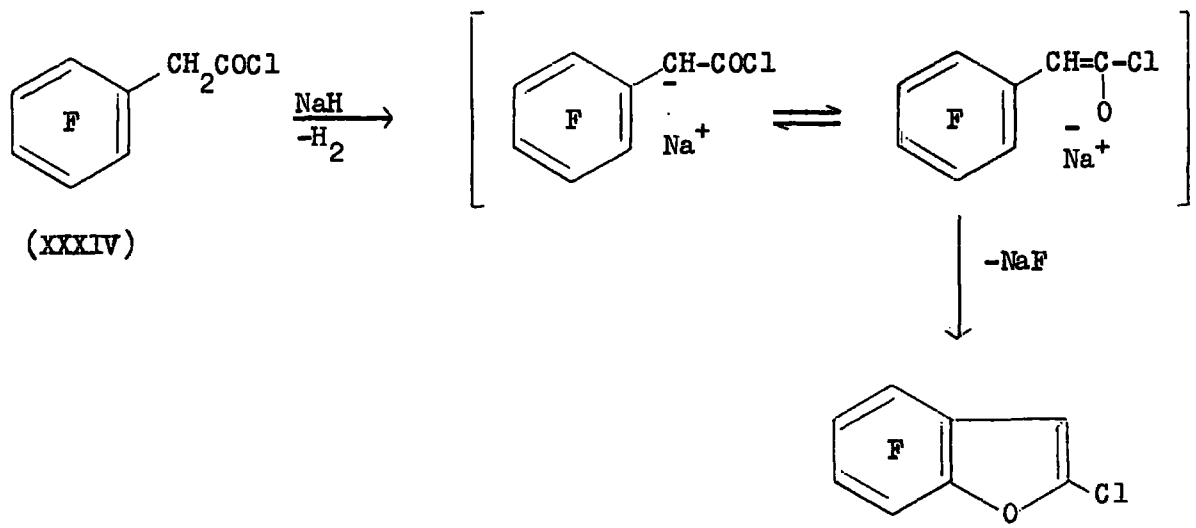
Reaction of the keto alcohol (XXXIII) with sodium hydride

Wt.of (XXXIII) (mole)	Wt. of 50% dispersion NaH in Oil.	Total vol. solvent	Initial temp.	Reaction time and temp.	Analysis T.L.C.	Analysis I.R.
0·001m	0·05g(0·001m/ 25 ml. T.H.F.	50 ml.T.H.F.	-75°	2 hr.reflux	Trace of furan-3-one	C=O present
0·01m	0·5g(0·01m)/ 50 ml. T.H.F.	150 ml.T.H.F.	20-25°	1 hr.reflux	Furan-3-one absent	Similar to furan-3-one
0·004m	0·25g(0·005m)/ 50 ml. T.H.F.	200 ml.T.H.F.	20-25°	3 hr.reflux	Furan-3-one absent	C=O present
0·004m	0·25g(0·005m)/ 100 ml.T.H.F.	200 ml.T.H.F.	-75°	3 hr.at -75°	Trace of furan-3-one	C=O present
0·0007m	0·1g(0·002m)/ 100 ml. Et_2O	250 ml. Et_2O	-75°	4 hr.at -75° ½ hr.reflux	Trace of furan-3-one	-OH and C=O present
0·002m	0·1g(0·002m)/ 100 ml.Et_2O	200 ml. Et_2O	-75°	3 hr.at -75° 2½ hr.reflux, 1 hr.at 100° in 50 ml.D.M.E	Furan-3-one absent	Similar to furan-3-one
0·001m	0·05g(0·001m)/ 100 ml.monoglyme	150 ml. monoglyme	-50°	1 hr.at -50° 1 hr.at 20°	Furan-3-one absent	Not furan-3-one

Table 3

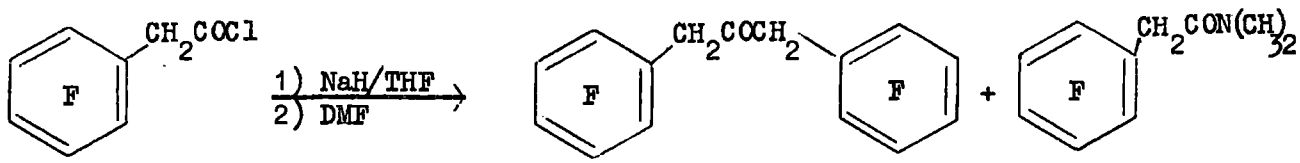
Attempted cyclisation of the keto alcohol (XXXIII)

Wt.of (XXXIII) (g.)	Reagent	Solvent	Reaction Time	Temp.	T.L.C.	I.R.
0·1	-	2 ml. pyridine	10 min.	Reflux	Starting material. Furan-3-one absent	Starting material
0·1 (0·45 mmole)	1 g.(7·25 mmole) dry K_2CO_3	10 ml. acetone	15 min.	Reflux	Furan-3-one absent	C=O absent
0·2 (0·9 mmole)	0·13 g. (0·95 mmole) dry K_2CO_3	10 ml. D.M.F.	30 min.	100°	No identifiable product	
0·1 (0·45 mmole)	0·024 g. (0·45 mmole) NaOMe	20 ml. CH_3OH	2¼ hr.	Reflux	Not furan-3-one or starting material	



(XXXIV)

A cyclisation and work-up procedure similar to that employed in the previous keto alcohol - sodium hydride reaction, was used. A solution of the acid chloride (XXXIV) was added to a stirred suspension of the sodium hydride under dry nitrogen. N,N'-Dimethylformamide (D.M.F.) was added and the T.H.F. distilled off. The mixture was then boiled under reflux and worked-up. Low yields of tarry material were obtained initially but on reducing the reflux time in D.M.F. a more tractable product was isolated, from which two compounds (XXXV) and (XXXVI) were separated, showing that intramolecular displacement of a ring fluorine atom had not occurred.



(XXXIV) (XXXV) (20%) (XXXVI) (51%)

The gas which was evolved before the mixtures were boiled under reflux was collected in a manometer and the volume found to be in accordance with that calculated for hydrogen from the sodium hydride used (see Table 4, p.35) Small samples of the gas were exposed to a lighted taper, as a qualitative test for hydrogen, and although no explosion occurred, in one case the gas burned quietly with a blue flame for a short time.

In the last experiment the manometer was connected to the apparatus throughout the reaction. 240 ml. of gas were collected before the THF was distilled off (in agreement with the calculated volume of hydrogen). This gas was transferred to a scrubber containing ammoniacal cuprous chloride[21] and scrubbed repeatedly in order to absorb any carbon monoxide present, but the volume was unaltered when the gas was transferred back into the manometer.

During the rest of the work-up procedure, removal of THF, boiling under reflux in DMF, and acidification, a further 115 ml. of gas were evolved and absorbed by the ammoniacal cuprous chloride solution. This volume was in close agreement with the volume of carbon monoxide calculated to be liberated during the formation of the ketone (XXXV).

After work-up, the aqueous phase was quantitatively analysed for chloride ion by Volhard's method when all the chloride due to the starting material was accounted for, showing that hydrogen chloride was not present in the evolved gas, the chloride being retained in the solution.

In this last reaction most of the THF was distilled off prior to the addition of DMF and none of the amide (XXXVI) was isolated from the reaction mixture, only the ketone (XXXV) was obtained. This would suggest that the intramolecular displacement of fluorine is not favoured under these reaction

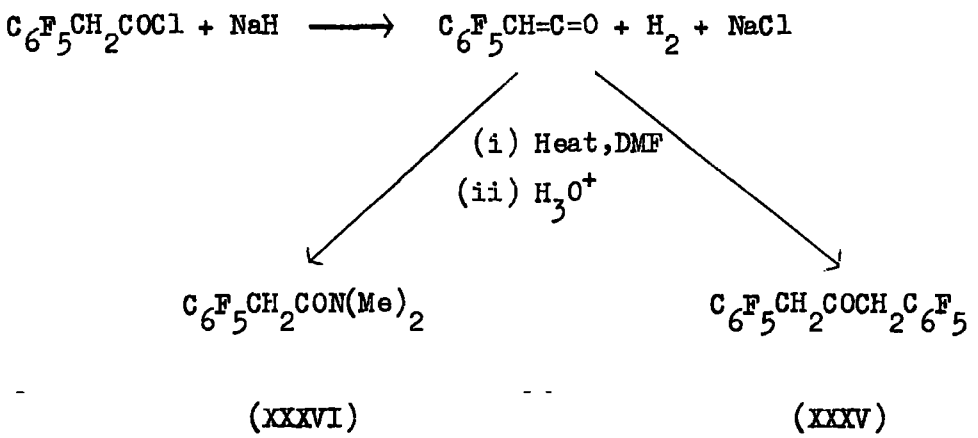
Table 4

Reaction of 2,3,4,5,6-Pentafluorophenylacetyl chloride (XXXIV) with sodium hydride

Wt.of acid chloride (XXXIV)	Wt. of NaH (50% dispersion in oil)	Temp. of addition	Reflux time	Volume gas evolved (ml.) before reflux	Compounds isolated
2·4g(0·01mole)/ 100 ml.THF	0·5g(0·01mole)/ 100 ml. THF	-65°	3 hr.in THF	210 (230)	$C_6F_5CH_2CO_2H$ (1·52g. 69%)
2·4g(0·01mole)/ 10 ml. THF	0·5g(0·01mole)/ 10 ml. THF	-65°	½ hr.in THF 2 hr.in DMF (50 ml.)	250 (230)	No isolatable product
2·4g(0·01mole)/ 15 ml. THF	0·6g(0·012mole)/ 10 ml. THF	Room temp.	2½ hr.in DMAC (30 ml.)	-	0·5g. crude product (three component mixture by VPC).
2·4g(0·01mole)/ 15 ml. THF	0·6g(0·012mole)/ 10 ml. THF	Room temp.	1 hr.in DMF (40 ml.)	300 (280)	0·6g. liquid 0·18g. viscous residue
4·9g(0·02mole)/ 60 ml. THF	1·0g(0·02mole)/ 15 ml. THF	Room temp.	Stirred overnight at room temp. 1 hr in DMF (80 ml.)	560 (560)	1·8g. liquid (XXXVI)(51%) 0·8g. solid (XXXV) (20%)
2·4g(0·01mole)/ 20 ml. THF	0·5g(0·01mole)/ 10 ml. THF	Room temp.	Stirred overnight at room temp. 1 hr.in DMF (40 ml.)	240 (230)	0·84g. solid (XXXV)(43%)

conditions, an intermolecular process being preferred, involving another molecule of starting material or of solvent (DMF).

The evolution of hydrogen on treating the acid chloride with sodium hydride shows that proton abstraction is preferred to aldehyde formation by hydride-ion attack on the carbonyl carbon and loss of Cl^-. A possible mechanism for the reaction would involve abstraction of a proton and loss of chloride ion to give a ketene intermediate which could then dimerise or react with a molecule of solvent (DMF).



4. Reaction of 2,3,4,5,6-Pentafluorophenylacetic Acid Derivatives with Nucleophiles.

In an attempt to determine the susceptibility of the nuclear fluorine atoms in the pentafluorophenylacetoxy compounds towards displacement by nucleophiles, several experiments were carried out with pentafluorophenylacetoxy derivatives and a number of nucleophiles. A knowledge of the positions of substitution would then enable the potentiality of an intramolecular nucleophilic displacement to be assessed.

Most of these reactions were carried out on the methyl ester (XXXVII; R = CH_3) prepared from the acid chloride in >80% yield. Initially the ester and nucleophile were boiled under reflux for various lengths of time but when it became apparent that no reaction was occurring the operations were carried out in Carius tubes or autoclaves.

Sodium hydroxide, sodium methoxide, hydrazine, ammonia and sodium thiophenoxide were all used and the results are summarised in Table 5. p.38.

With hydroxide and with methoxide only starting material was recovered from the reaction mixture. When the ester was treated with ammonia the acid amide (XXXVIII) was isolated and similarly when hydrazine was used as the nucleophile, the acid hydrazide (XXXIX) was obtained, which, on treatment with acetone afforded the corresponding hydrazone derivative (XL).

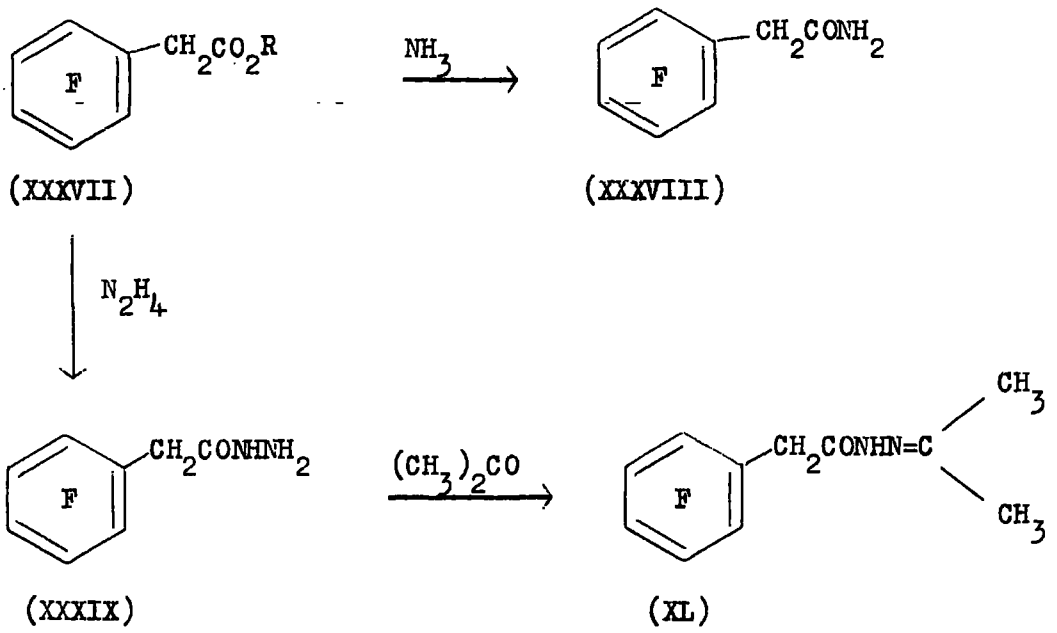


Table 5

Reaction of 2,3,4,5,6-Pentafluorophenylacetic Acid Derivatives with Nucleophiles

Starting material	Nucleophile and Solvent	Reaction time and temp.	Product
Acid chloride (XXXIV) 1·95 g. (8 mmoles)	40 ml. of 0·2N CH_3ONa (8 mmoles) (in CH_3OH)	15 hr. reflux	83% of methyl ester(XXXVII)
Methyl ester (XXXVII; R=CH_3). (5 mmole) 1·2 g.	90 ml. of 0·06N CH_3ONa (5·4 mmoles) (in CH_3OH)	64 hr.reflux	75% recovery of starting material
Ethyl ester (XXXVII; R=C_2H_5) (8·7 mmole) 2·2 g.	0·89 g.of $N_2H_4 \cdot H_2O$ (17·8 mmole) in 20 ml. of 1:1 $C_2H_5OH \cdot H_2O$	20 hr. reflux	82% acid hydrazide
Acid 1·4 g. (6·2 mmole)	0·5 g.of NaOH (12·5 mmole) in 10 ml.H_2O and 2 ml. C_2H_5OH	22 hr.reflux	90% recovery of starting material
Methyl ester 0·85 g. (3·5 mmole)	3·8 ml.of 1·07N CH_3ONa (4 mmole) (in CH_3OH)	42 hr.at 150° in bomb	Charred. 58% recovery of starting ester
Methyl ester 1·1 g. (4·6 mmole)	0·7 g.C_6H_5SNa (5·3 mmole) in 15 ml.of D.M.A.C.	2½ days at 150° in sealed tube	Charred. 36% recovery of impure starting ester. (0·39 g.)
Methyl ester 2·4 g. (10 mmole)	1·32 g. C_6H_5SNa (10 mmole) in 10 ml. D.M.A.C.	1 day at 150° in sealed tube	75% recovery of impure starting ester (1·77 g.)
Methyl ester 1·2 g. (5 mmole)	0·6 ml.of 0·88 ammonia (12 mmole)	2 days at 150° in bomb	Charred. 36% yield amide

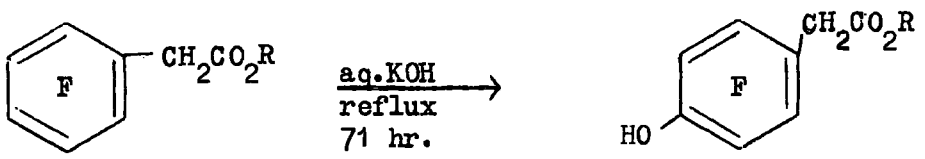
Those reactions involving sodium thiophenoxide afforded an impure product from which only the starting ester could be isolated.

A small scale experiment was undertaken in an attempt to substitute methoxide into the phenyl rings of the ketone (XXXV). The ketone was heated in a Carius tube with a methanolic solution of sodium methoxide over a period of 72 hours. A 50% recovery of unchanged starting material was achieved from the somewhat charred reaction mixture.

Reaction of 2,3,4,5,6-Pentafluorophenylacetic acid (XXXVII; R = H) with potassium hydroxide

In a recent paper[22], Tatlow et al, reported the effect of solvent on orientation of nucleophilic substitution in pentafluorobenzoic acid. By analogy with their findings further experiments were carried out in an attempt to prepare the ortho-hydroxytetrafluorophenylacetic acid. With the knowledge of a solvent media promoting substitution by an O^- nucleophile ortho to the acid function, an intramolecular nucleophilic displacement, involving the enolate anion derived by proton abstraction from the acid chloride, could be attempted.

Vigorous treatment of the acid (XXXVII; R = H) with aqueous potassium hydroxide, afforded the 4-hydroxy derivative[23] (XLI) in 66% yield.



(XXXVII) (XLI)

A mixture of the acid and potassium hydroxide was then dissolved in a methanol-ether solution and boiled under reflux for 68 hr. It had been shown that the proportion of ortho substitution, in the reaction between pentafluoronitrobenzene and methoxide ion,[22] was increased with increase in ether content of the solvent. On work up however only the starting acid was recovered, in 85% yield.

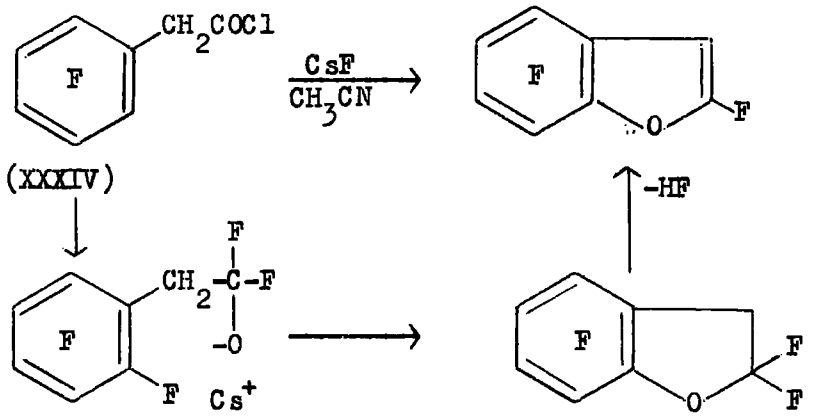
The experiment was repeated using the methyl ester (XXXVII; R = CH_3) and potassium hydroxide, in a methanol-ether mixture as before, but after boiling under reflux for 94 hr. the only compound isolated on work up was pentafluorophenyl acetic acid, in 90% yield.

As the synthesis of the 4-hydroxy acid (XLI) required the reflux temperature of an aqueous solution, the next attempt at the preparation of the corresponding 2-hydroxy acid, was carried out using a higher boiling solvent, t-butanol. A mixture of the acid and potassium hydroxide was dissolved in a solution of t-butanol and ether, and boiled under reflux for 53 hr. Only the starting acid was isolated from the reaction mixture, in 82% yield.

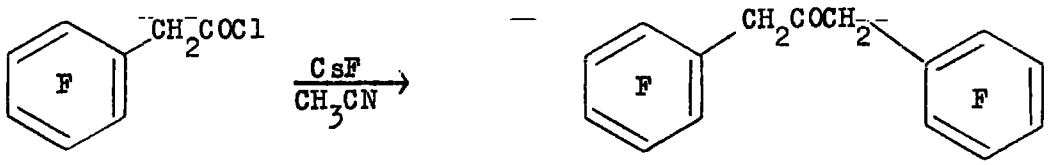
5. Reactions of 2,3,4,5,6-Pentafluorophenylacetyl Derivatives with Fluorides.

Another possible route, leading to a more highly fluorinated benzo[b]furan, was undertaken on the basis of fluoride ion reactions carried out with activated carbonyl compounds.[24,25,26]

The nucleophilic displacement, depicted in the reaction sequence below, would be preceded by the formation of the required fluoro-oxyanion. Elimination of hydrogen halide would then afford the pentahalobenzo[b]furan.



2,3,4,5,6-Pentafluorophenylacetyl chloride and caesium fluoride, in 1:2 molar ratio respectively, were stirred in acetonitrile at 90° for one week. The reaction afforded a 10% yield of the ketone (XXXV) and a 33% yield of pentafluorophenylacetic acid, no other product was isolated.



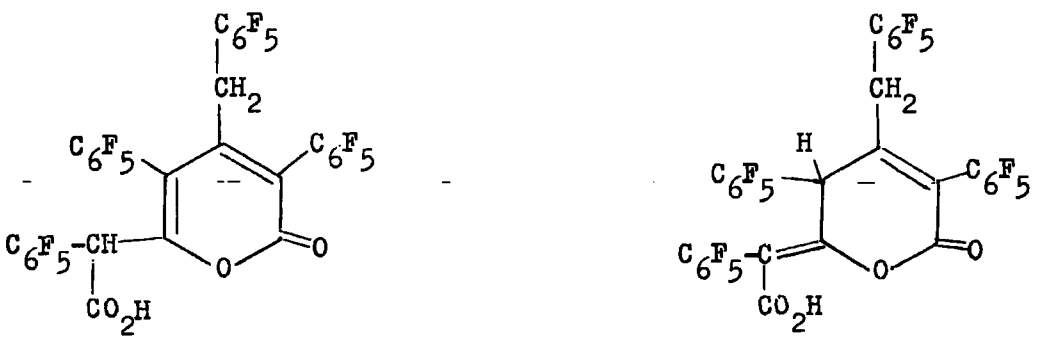
(XXXIV) (XXXV)

On the assumption that the carbonyl group in the acid chloride was insufficiently active to form the required adduct with caesium fluoride, the synthesis of the acid fluoride was attempted with a view to repeating the reaction.

A five molar excess of potassium fluoride was placed in a sealed

tube with the acid chloride (XXXIV) and heated at 200° for 57 hours. The contents charred completely. When this reaction was repeated at 150° for 22 hours the only product isolated was the ketone (XXXV) in 12% yield. After 22 hours at 75° no reaction occurred at all, unchanged acid chloride was recovered in >90% yield. The reaction was repeated at 100° for 16 hours when three compounds were isolated from the mixture; the acid fluoride (XLII), the acid, and a white solid which had the same infrared spectrum as the crystalline compound deposited over a period of several hours from a sample of the acid fluoride stored in a stoppered flask at room temperature.

On the basis of the available evidence the following are speculative structures which may be written for the compound.

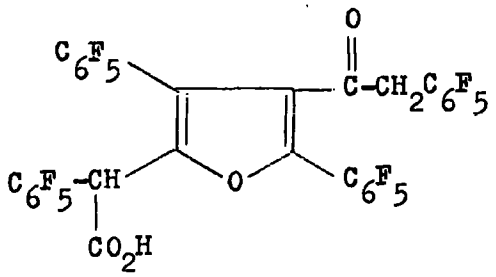


(XLIII)

As the signals in the ^{1}H n.m.r. spectrum do not appear to be of an aromatic or olefinic nature, the intense absorption in the ultraviolet spectrum would arise from conjugation with substituted double bonds. The

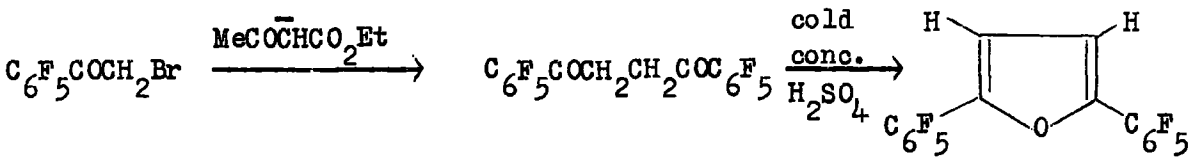
two carbonyl absorptions in the infrared spectrum at 1750 cm^{-1} and 1800 cm^{-1} could then be assigned to the carboxylic acid and lactone carbonyls respectively, depicted in the structures shown.

If the inability of the compound to form a 2,4-dinitrophenyl hydrazone derivative is due to steric reasons then other structures are possible, e.g. a furan derivative.



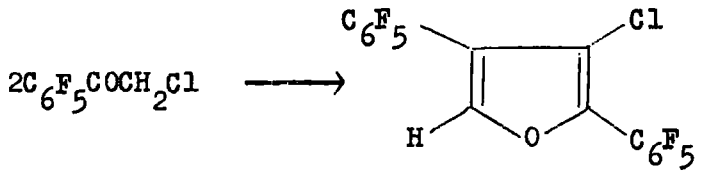
(XLIV)

2,5-Bis(pentafluorophenyl)furan[27] (XLV) has been synthesised by treating $(C_6F_5COCH_2)_2$ with cold concentrated sulphuric acid,



(XLV)

and in a more recent publication 2,4-bis(pentafluorophenyl)-3-chloro-furan[28] (XLVI) was prepared by the self condensation of 2 chloro-2',3',4',5',6'-pentafluoroacetophenone.

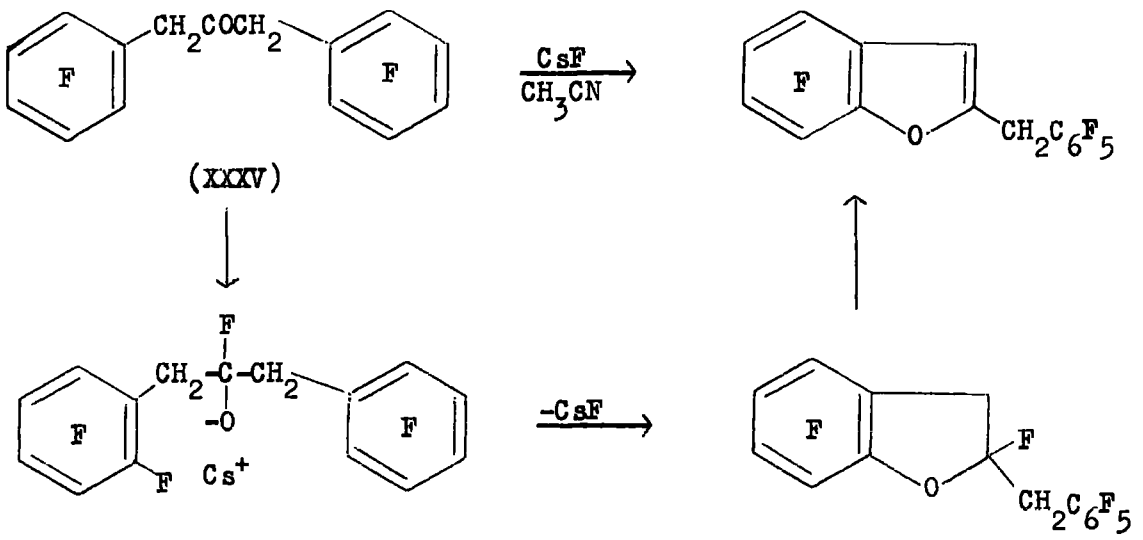


(XLVI)

U.v. absorption maxima were reported for this compound as occurring at 214 mμ (log ε 4·23) and 261 mμ (log ε 4·14), and the 2,4-bis(pentafluorophenyl)furan (XLV) showed an absorption at 310 mμ (log ε 4·48). The u.v. spectrum of the suspected furan product (XLIV) derived from the acid fluoride (XLII) showed bands at 246, 268 and 307 mμ. $C_6F_5CH_2CO_2H$ (XXXII; R = H) and $C_6F_5CH_2COCH_2C_6F_5$ (XXXV) both showed bands at about 260 mμ (see experimental) which can be assigned to the individual C_6F_5 rings as in the spectrum of decafluorobiphenyl[29] where two absorptions were observed at 230 and 267 mμ.

Reaction of α:α'-(Di-2,3,4,5,6-Pentafluorophenyl)acetone (XXXV) with CsF.

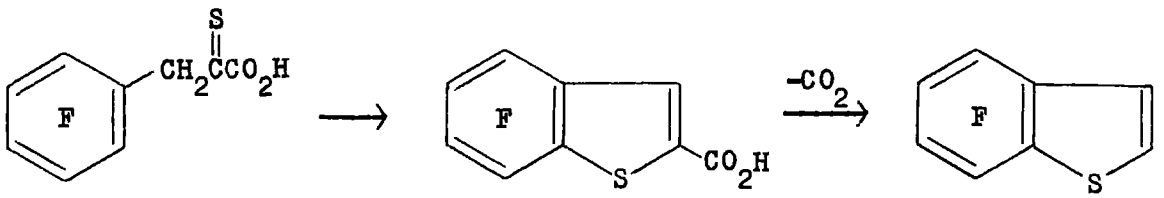
By analogy with the previous caesium fluoride reaction the ketone (XXXV) was stirred with caesium fluoride in acetonitrile under the same conditions. Upon formation of the oxyanion an intramolecular nucleophilic displacement would afford the substituted tetrafluorobenzo[b]furan shown in the following reaction sequence.



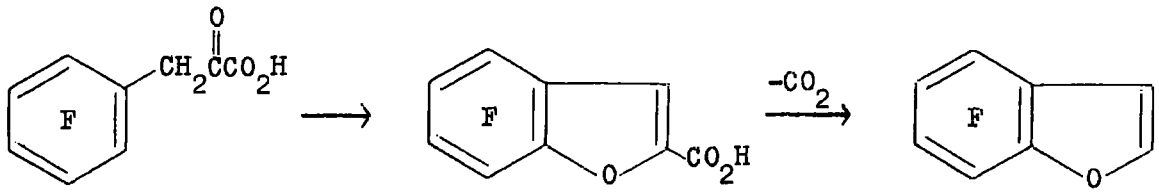
The only compound isolated from the reaction mixture was the starting ketone (XXXV) in 60% yield, inferring that the carbonyl group is not sufficiently active to form the required oxyanion.

6. Attempted Synthesis of 2,3,4,5,6-Pentafluorophenylpyruvic Acid (XLVII)

– In a recent publication Tatlow et al[6] described the synthesis of tetrafluorobenzo[b]thiophen from a thiopyruvic acid precursor.

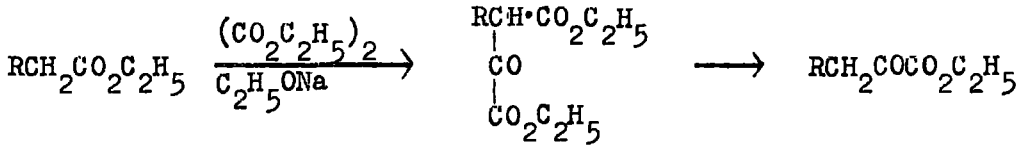


As an extension of this method, the preparation of the phenylpyruvic acid (XLVII) was attempted when, by an analogous reaction sequence, the synthesis of the corresponding benzo[b]furan (I) could be undertaken.



(XLVII) I

The synthesis of the phenylpyruvic acid (XLVII) was approached in two ways. A general method for the preparation of α-keto acids, described by Adickes and Andresen,[30] involves the condensation of a fatty acid ester with ethyl oxalate in the presence of sodium ethoxide.



A mixture of the methyl ester of pentafluorophenylacetic acid, methyl oxalate and sodium methoxide in diethyl ether, was boiled under reflux for $2\frac{1}{2}$ days. The mixture was cooled, acidified and ether extracted. On removing the ether by distillation, an 80% recovery of the starting ester was achieved, no other product being isolated. The reaction was repeated using pyridine in place of ether and heating on a boiling water bath for 4 days. On work-up a 80% recovery of the starting ester was again attained, but none of the required α-oxalo ester was isolated.

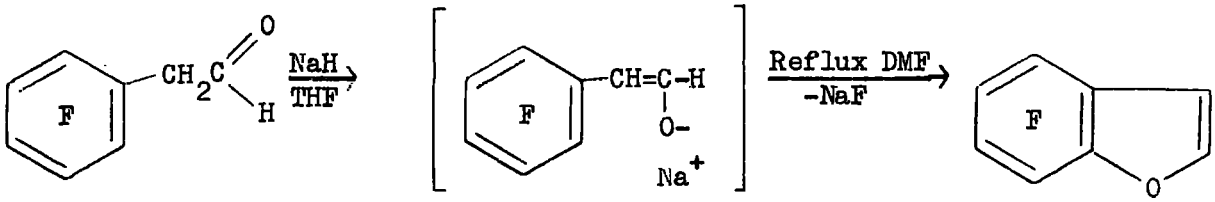
The second method employed for the preparation of the pyruvic acid required the pentafluorophenylacetyl cyanide as precursor. The synthesis of this compound was based on the general method utilised for preparing aryl cyanides from aryl halides. Friedman and Shechter describe an

effective method[31] which incorporates an efficient decomposition of the cyanide cuprous halide complex, an aspect of the work-up which had presented some difficulty to earlier workers.

A solution of the acid chloride (XXXIV) in N,N'-dimethylacetamide was stirred with cuprous cyanide for 2 hours in an oil bath at 130° when the mixture became very dark. After destroying the complex, and extracting the resulting solution with ether, the only identifiable product isolated was the pentafluorophenylacetic acid. Pronounced charring was observed when the crude product was distilled under reduced pressure, which is not characteristic of the phenylacetic acid. The possibility exists therefore that during work-up the acyl cyanide had been hydrolysed to the keto acid which was then decarboxylated on heating.

7. Reaction of 2,3,4,5,6-Pentafluorophenylacetyl chloride (XXXIV) with lithium tri-tertiarybutoxyalumino hydride.

As an extension of the method used to prepare 2-methyl-4,5,6,7-tetrafluorobenzo[b]furan[23] by treatment of the pentafluorophenylpropan-2-one with sodium hydride, the synthesis of the pentafluorophenyl acetaldehyde (XLVIII) was undertaken when a similar cyclisation would yield the unsubstituted tetrafluorobenzo[b]furan (I) according to the following reaction sequence.



(XLVIII) I

The alumino hydride reagent was prepared according to the method of Brown et al[32] by the addition of three moles of dry t-butanol[33] to a solution containing one mole of lithium aluminium hydride in dry ether. When the reaction between the t-butanol and lithium aluminium hydride was complete, two techniques were employed for the utilisation of the reagent. The ether was decanted and the wet residue taken up in dry diglyme and stored in a stoppered flask. Alternatively the crude product was sublimed and the white lithium tri-tertiarybutoxyalumino hydride dissolved in dry diglyme and stored in the same way. Aliquots of both solutions were hydrolysed with water and the evolved hydrogen collected in a manometer in order to determine the concentration of the reagent. On the basis of this determination, equimolar quantities of the reagent prepared by the former method, and the acid chloride, were reacted at -75^{o}. A four component mixture was obtained from the crude reaction product, which, on distillation under reduced pressure afforded the somewhat impure aldehyde (XLVIII). Pentafluorophenyl acetic acid was isolated from the residue remaining in the distillation apparatus, in 66% yield which suggested incomplete reaction of the acid chloride and the hydride reagent. On repeating this experiment a longer reaction time was allowed, but pentafluorophenyl acetic acid was again isolated, in 49% yield, as well as the aldehyde. In an attempt to ensure complete reaction of the acid chloride, the experiment was repeated using an excess of the hydride reagent. An examination of the crude product by TLC showed that it contained four components. On work up, 2,3,4,5,6-pentafluorophenyl ethanol, and an unidentified white solid, were isolated.

In a further attempt to increase the yield of aldehyde, the hydride reagent was purified by sublimation and then dissolved in diglyme. The concentration was determined by hydrolysing an aliquot of the solution with water and measuring the volume of hydrogen evolved in a manometer. Equimolar quantities of the acid chloride and reagent, in diglyme, were stirred under nitrogen at -75° and worked up as before. Distillation of the crude product afforded the aldehyde, which, on examination by TLC showed only a trace of three other components. On sublimation of the residue after distillation, pentafluorophenyl acetic acid was isolated in 24% yield which suggested incomplete reaction of the acid chloride. The yield of aldehyde, calculated from the amount of acid chloride consumed by the hydride reagent, was 44%.

Attempted cyclisation of 2,3,4,5,6-Pentafluorophenylacetaldehyde (XLVIII)

A solution of the aldehyde in dry THF was added to a stirred suspension of sodium hydride in THF at -75°. After stirring at this temperature for one hour after the addition was complete, the mixture was then allowed to warm to room temperature. As the temperature reached 0° effervescence was observed, and stirring was continued until this ceased. The solution was then boiled under reflux for 2 hr. and an aliquot removed and worked up, when the only compound isolated was unreacted aldehyde, identified by its infrared spectrum. DMF was then added to the mixture, the THF distilled off, and the remaining solution boiled under reflux for 1½ hr. On working up the tarry residue only the starting aldehyde was isolated in 58% yield. The reaction was repeated and the reflux time in DMF increased to 3 hrs.

However the crude reaction product was very tarry and on work up only a very small amount of product was obtained. Analysis of this crude product by TLC showed the presence of a minor amount of unreacted aldehyde, the major component having a shorter retention time.

The infrared spectrum of the product, separated by transferring under reduced pressure, showed no carbonyl absorption and was similar to the spectrum of an authentic sample of tetrafluorobenzo[b]furan. Substituting DMAC for DMF in the reaction afforded a cleaner product, the infrared spectrum of which was similar to that of the benzo[b]furan, but still contained a little unreacted aldehyde. A sample was purified and an examination of its mass spectrum showed that it was not the benzo[b]furan but a higher molecular weight compound, on comparison with the mass spectrum of an authentic sample of the benzo[b]furan.

CHAPTER IV

EXPERIMENTAL WORK (PART I)

Experimental

Dried Solvents.

Diglyme. Dried initially over potassium hydroxide. Boiled under reflux with calcium hydride for 2 days and distilled. Stored over calcium hydride.

Diethyl ether. Dried over sodium wire until effervescence ceased.

Tetrahydrofuran (T.H.F.). Distilled from $LiAlH_4$ in an atmosphere of dry nitrogen.

N,N'-Dimethylformamide (D.M.F.). Distilled from P_2O_5 under reduced pressure.

Monoglyme. Distilled from $LiAlH_4$ in an atmosphere of dry nitrogen.

Acetonitrile. Distilled from P_2O_5 and boiled under reflux for 3 days with calcium hydride. Stored over calcium hydride.

N,N'-Dimethylacetamide (D.M.A.C.). Distilled from P_2O_5 and then dried over calcium hydride.

Methyl alcohol. Dried using the magnesium and iodine method according to Vogel, Practical Organic Chemistry, page 169.

Sulpholan. Distilled several times under reduced pressure until distillate readily solidified. Stored over molecular sieve under nitrogen.

1,1,2-Trifluoro-2-chloroethylene.[34]

Zinc powder (500 gm.) in methylated spirits (750 ml.) was placed in a 5 litre three-necked flask fitted with a double surface condenser incorporating a carbon tetrachloride - liquid air cold finger. 1,1,2-Trifluoro-1,2,2-trichloroethane (500 gm.) was added from a dropping funnel to

the stirred boiling mixture when the heat of reaction maintains reflux. The resulting olefin was condensed in a liquid air trap. After the addition was completed the flask and contents were heated for a further 1·5 hr. The reaction afforded the 1,1,2-trifluoro-2-chloroethylene (236 gm.), (75% yield).

1,1,2-Trifluoro-2-chloroethyl ether was prepared according to the method of Englund.[35] A solution of sodium (2·5 gm.) in ethanol (292 ml.) was placed in the first scrubber fitted with a sintered glass bubbler. The olefin (275 gm.) was passed into the solution from a cylinder, the flow being regulated by a second scrubber containing ethanol (50 ml.) which acted as a flow meter in addition to absorbing any unreacted olefin. When the reaction was complete the combined ethanol solutions were washed with water and the product separated and dried with calcium chloride (50 gm.) to afford the ether m.p. 87-89° (360 gm., 93%).

Ethyl chlorofluoroacetate was synthesised by the method given by Englund.[36] The ether (360 gm.) from the previous preparation was placed in a three-necked flask fitted with a stirrer, thermometer and a separating funnel, provision was made to allow the escape of any hydrofluoric acid produced in the reaction. The flask and contents were cooled in ice to 5-10° and concentrated sulphuric acid (242 ml.) added dropwise with stirring. On completion of the addition stirring was continued for a further 2 hr. when the reaction mixture was poured on to ice (1 Kg) and water (500 ml.). The lower organic layer was separated and washed with saturated aqueous sodium

bicarbonate followed by water, and then dried ($MgSO_4$) to afford the crude ester (253 gm., 82%). On distillation the pure ester was collected, b.p. 127-130° (222 gm., 71·5%).

2,3,4,5-Tetrafluorophenol (II).[9,10] A solution of n-butyl-lithium in hexane (500 ml., 2·75M)[37] was added to a stirred solution of 1,2,3,4-tetrafluorobenzene (220 gm.) in dried tetrahydrofuran (1 l.) such that the internal temperature remained between -70° and -75°. The mixture was stirred for 5 hr. at -70° after the addition and then a solution of trimethylborate (154 gm.) in dry tetrahydrofuran (220 ml.) was added over 2 hr. with stirring, maintaining the internal temperature below -70°. Stirring was continued for a further hour when hydrogen peroxide (370 ml., 100 vol.) was added carefully keeping the temperature below -70°. After completion of the addition the reaction mixture was allowed to attain room temperature and kept overnight. A solution of sodium metabisulphite (500 gm.) in water (400 ml.) was then added to the stirred reaction mixture maintaining the temperature below 0°. Sodium hydroxide (250 gm.) in water (600 ml.) was added to the mixture and the organic solvents distilled off at atmospheric pressure. The mixture was cooled and acidified with concentrated hydrochloric acid, the crude phenol separated and the aqueous phase extracted with methylene chloride. The organic extract was dried ($MgSO_4$), filtered and distilled at atmospheric pressure up a 2 ft. fractionating column to give 2,3,4,5-tetrafluorophenol (168 gm.) b.p. 148-150° (70%).

Ethyl 2,3,4,5-Tetrafluorophenoxyfluoroacetate (XXX).

This synthesis required the anhydrous potassium salt of the phenol which was prepared by treating the phenol with concentrated potassium hydroxide solution, recrystallising the resulting hydrated salt from a small amount of water and distilling the azeotrope produced between benzene and the water of crystallisation of the salt in a Dean-Stark apparatus.

A mixture of the anhydrous potassium phenate (26 gm.), ethyl chlorofluoroacetate (20 gm.) and dry N,N'-dimethylformamide (130 ml.) was heated under reflux for 5 min. The mixture was cooled, poured into water (500 ml.) and extracted with ether. After drying the ether extract ($MgSO_4$) and evaporating the solvent, the residue was distilled under reduced pressure to afford ethyl 2,3,4,5-tetrafluorophenoxyfluoroacetate (20·2 gm., 59%) b.p. 55-56°/0·05 mm. (Found: C, 44·0; H, 2·52. M (mass spectroscopy) 270. $C_{10}H_7F_5O_3$ requires C, 44·4; H, 2·61%. M 270).

Attempted hydrolysis of Ethyl 2,3,4,5-Tetrafluorophenoxyfluoroacetate (XXX)

Amount of ester (gm.)	Hydrolysing agent	Temperature	Time	Recovered
2·7	100 ml. 0·1N NaOH	Reflux	0·5 hr.	ester and phenol
2·7	50 ml. 2N Na_2CO_3	Reflux	2 hr.	ester
2·7	25 ml. 0·4N $Ba(OH)_2$	Room temp.	3 hr.	phenol
2·7	100 ml. 0·1N HCl	Reflux	1·75 hr.	ester
2·7	50 ml. 4N HCl	Reflux	5 hr.	phenol and ester
2·7	5 ml. 36N H_2SO_4	Room temp.	0·5 hr.	ester
8·96	150 ml. 18N H_2SO_4	Reflux	2 hr.	phenol

Attempted synthesis of 2,3,4,5-Tetrafluorophenoxyfluoroacetic acid.

Chlorofluoroacetic acid was prepared according to the method of Tarrant et al.[36] by alkaline hydrolysis of ethyl chlorofluoroacetate.

A mixture of anhydrous potassium 2,3,4,5-tetrafluorophenate (5 gm.) and chlorofluoroacetic acid (2·9 gm.) in N,N'-dimethylformamide (25 ml.) was heated under reflux for 10 min., cooled and poured into water (200 ml.). The aqueous phase was extracted with ether, the extract dried ($MgSO_4$) and after removal of solvent, distilled under reduced pressure. No identifiable product was obtained.

Ethyl 6-ethoxycarbonyl-2,3,4,5-Tetrafluorophenoxyfluoroacetate (XXXI)

Ethyl 2,3,4,5-tetrafluoro-6-hydroxybenzoate was treated with a solution of potassium (3 gm.) in ethanol (26 ml.) and the resulting potassium salt crystallised from water and then dehydrated using a Dean and Stark apparatus and benzene.

The anhydrous potassium salt (13·8 gm.) and ethyl chlorofluoroacetate (7·5 gm.) were placed in a flask with dry N,N'-dimethylformamide (50 ml.) and boiled under reflux for 1 hr. The mixture was cooled, poured into water (500 ml.), ether extracted and the dried extract distilled to remove ether. Further distillation, under vacuum afforded 10·4 gm. of a liquid boiling 94-106° at 0·1 mm. On redistillation the pure diester was obtained (9·4 gm., 55%) b.p. 110-111°/0·1 mm. (Found: C, 45·3; H, 3·11. M(mass spectroscopy 342. $C_{13}H_{11}F_5O_5$ requires C, 45·6; H, 3·27%. M 342).

(i) Reaction of Ethyl 6-ethoxycarbonyl-4,5,6,7-Tetrafluorophenoxyfluoroacetate (XXXI) with Sodium Hydride.

A solution of the diester (9·4 gm.) in dry tetrahydrofuran (30 ml.) was added dropwise to a stirred suspension of sodium hydride (1·2 gm. of a 60% suspension in oil) in dry tetrahydrofuran (20 ml.). No hydrogen was evolved. The mixture was boiled under reflux for 7 hr., cooled and unreacted sodium hydride filtered off. After removal of solvent the residue was distilled under vacuum but only the starting diester was recovered (6·9 gm.) b.p. 110-111°/0·1 mm., identified by comparing its infrared spectrum with that of an authentic sample.

(ii) Reaction of the Diester (XXXI) with Sodium Ethoxide.

A solution of the diester (6·9 gm.) in ethanol (20 ml.) was boiled under reflux with a solution of sodium (0·46 gm.) in ethanol (10 ml.) for 14 hr. The mixture was cooled and ethanol distilled off when the residue was distilled affording unchanged diester (3·3 gm.) b.p. 110-111°/0·1 mm. identified by comparing its infrared spectrum with that of an authentic sample, and a dark red intractable residue.

Reaction of 2,3,4,5,6-Pentafluorophenyl-lithium with the Lithium salt of Ethyl Glycollate.

A solution of pentafluorobromobenzene (25 g.) in dry THF (160 ml.) was placed in a three-necked round-bottomed flask fitted with a stirrer, condenser, thermometer and a dropping funnel and cooled, under nitrogen, to -75°, when n-butyl lithium (50 ml., 2·0M) in dry THF (100 ml.) was added over ½ hr. On completion of the addition the mixture was stirred for a further 3 hr. maintaining the temperature between -65 and -70°, and a solution of ethyl glycollate (5·2 g.) in dry THF (160 ml.) added from the

dropping funnel over several minutes. This mixture was stirred for 4 hr., keeping the temperature at -55°, and then allowed to attain room temperature to ensure complete reaction. Hydrochloric acid (100 ml. 5M) was added to the stirred solution, cooled to -60°, and the temperature allowed to reach 25°. Filtration of the hydrolysed reaction mixture afforded a white polymer (18 g.) which was ether insoluble. The filtrate was extracted with ether, the extract dried ($MgSO_4$), filtered and distilled to yield a small amount of intractable tar from which no identifiable product was isolated.

On repeating this reaction with inverse addition of the ethyl glycollate and pentafluorobromobenzene a polyphenylene compound was isolated with the same infrared spectrum as that of the white solid obtained from the first experiment.

ω-Benzyloxy-2,3,4,5,6-Pentafluoroacetophenone (XXXII; R = $C_6H_5CH_2$).

A solution of pentafluorobromobenzene (24·7 g.) in a 1:1 mixture of dry ether and hexane (75 ml.) was cooled to -70°, under nitrogen, in a three-necked flask fitted with a condenser, stirrer, thermometer and dropping funnel. n-Butyl lithium (47 ml. 2·2M) in 1:1 ether-hexane (50 ml.) was then added from the dropping funnel over 2½ hr., the temperature being maintained at -70° throughout. On completion of the addition the mixture was stirred for a further 2½ hr. when a solution of the benzyl ether of ethyl glycollate (19·4 g.) in 1:1 ether-hexane (50 ml.), prepared from the reaction of sodium benzylate and ethyl

bromoacetate, was added over 3/4 hr. At the end of this time the mixture was stirred for a further 1 hr. at -70°, and then allowed to reach room temperature before cooling to -60° prior to hydrolysis with hydrochloric acid (150 ml. 1M). The solution was allowed to attain room temperature over 6 hr., before phase separation and ether extraction of the aqueous layer. The combined organic extract was dried ($MgSO_4$), filtered, and distilled to afford a crude solid (7 g.) which was crystallised from petroleum ether (b.p. 60-80°) to yield ω-benzyloxy-2,3,4,5,6-pentafluoroacetophenone (XXXII; R = $C_6H_5CH_2$) (6·3 g., 20%) m.p. 79-80·5°. (Found: C, 57·1; H, 2·9 $C_{15}H_9F_5O_2$ requires C, 57·0; H, 2·9%). An accurate mass measurement was made of the molecular ion at 316 (observed: 316·0521. $C_{15}H_9F_5O_2$ calculated, 316·0523). The infrared spectrum shows a strong absorption at 1725 cm^{-1} attributed to the C=O group.

ω-Triphenylmethoxy-2,3,4,5,6-Pentafluoroacetophenone (XXXII; R = $(C_6H_5)_3C$).

The synthesis of this compound required the trityl ether of ethyl glycollate as starting material and this was prepared by stirring trityl chloride (58 g.) and ethyl glycollate (25 g.) in dry pyridine (80 ml.) at 100° for 2 hr. The reaction mixture was cooled, poured into water, the crude product filtered and washed free of pyridine with water and crystallised from petroleum ether (b.p. 60-80°) to afford the trityl ether (43 g. 60%) m.p. 92-92·5°. (Found: C, 79·8; H, 6·1 M(mass spectroscopy) 346 $C_{23}H_{22}O_3$ requires C, 79·73; H, 6·4% M 346). The infrared spectrum shows strong absorption at 1755 cm^{-1} attributed to the C=O group.

A solution of pentafluorobromobenzene (7 g.) in dry ether (100 ml.) was cooled to -70° under nitrogen in a three-necked flask fitted with a condenser, stirrer, thermometer and dropping funnel. n-Butyl lithium (17 ml. of 2M) in dry ether (50 ml.) was added from the dropping funnel over ½ hr. the temperature being maintained below -70° throughout. The solution was stirred for 2 hr. after the addition was complete, when the trityl ether of ethyl glycollate (9 g.) in dry ether (100 ml.) was added from the funnel over ¼ hr. This solution was stirred for 3 hr. maintaining the temperature at -50 to -55°. Stirring was continued while the mixture was allowed to attain room temperature, to complete reaction, and then cooled to -60° prior to the addition of water (100 ml.). The hydrolysed product was then allowed to reach room temperature and the phases separated. The aqueous phase was extracted with ether and the combined organic extract dried ($MgSO_4$), filtered and distilled affording a crude yellow solid (11·6 g., 88%). Crystallisation of the solid from petroleum ether (b.p. 40-60°) afforded ω-triphenylmethoxy-2,3,4,5,6-pentafluoroacetophenone (XXXII; R = $(C_6H_5)_3C$) (7·05 g., 53%) m.p. 130-131°. (Found: C, 69·5; H, 3·6. $C_{27}H_{17}F_5O_2$ requires C, 69·23; H, 3·66%). The infrared spectrum showed an absorption at 1710 cm^{-1} attributed to the C=O group.

ω -Hydroxy-2,3,4,5,6-Pentafluoroacetophenone (XXXIII)

The triphenylmethoxy compound (XXXII; R = $(C_6H_5)_3C$) (0·8 g.) was dissolved in concentrated sulphuric acid (10 ml.) and the solution diluted with water (50 ml.), cooling in ice. The precipitated triphenyl carbinol

was removed by filtration and washed with warm water. The filtrate and washings were combined and extracted with ether; the extract dried ($MgSO_4$), filtered, and distilled to afford a crude solid which, on crystallising from petroleum ether (b.p. 40-60°) yielded ω-hydroxy-2,3,4,5,6-pentafluoroacetophenone (XXXIII) (0·2 g. 52%) m.p. 63-64°. (Found: C, 42·3; H, 1·2 M(mass spectroscopy) 226. $C_8H_3F_5O_2$ requires C, 42·48; H, 1·3% M 226). The infrared spectrum shows a sharp absorption at 3450 cm^{-1} attributed to the -OH group, and a strong absorption at 1710 cm^{-1} assigned to the C=O group.

Cleavage of the benzyloxy ether (XXXII; R = $C_6H_5CH_2$) was achieved in a similar manner. The ether (2·5 g.) was dissolved in concentrated sulphuric acid (10 ml.) and diluted with water (200 ml.) cooling in ice. The aqueous phase was separated from a gummy intractable solid which was washed with water. The aqueous phase was combined with the washings and the whole extracted with ether. After the extract was dried ($MgSO_4$) and filtered, the solvent was removed by distillation to give a crude solid which on crystallising from petroleum ether (b.p. 40-60°) afforded the keto alcohol (XXXIII) (0·37 g. 20%) identified by comparison of its infrared spectrum with that of an authentic sample.

Reaction of ω-Hydroxy-2,3,4,5,6-Pentafluoroacetophenone (XXXIII) with Sodium Hydride.

A three-necked flask was fitted with a low-temperature thermometer, a dropping funnel and a reflux condenser. A stream of dry nitrogen was introduced into the system via a two-way adaptor into which the dropping

funnel was fitted, and an exit was provided at the top of the condenser leading to a sulphuric acid bubbler. The whole apparatus was flamed out, while being purged with nitrogen, before the reaction was commenced.

A calculated amount of the 50% oil dispersion of sodium hydride was thoroughly washed with dried solvent and quickly slurried into the flask. When temperatures down to -70° were required the flask and contents were cooled in an acetone-solid carbon dioxide bath, and stirring was supplied by an external magnetic stirrer.

A solution of the keto-alcohol in dry solvent was then added from the dropping funnel to the stirred, cooled suspension of sodium hydride over $\frac{1}{2}$ hour, and the evolution of hydrogen was observed. Maintaining the nitrogen flow the flask and contents were allowed to attain room temperature, except when a longer period at -75° was required (p.31 Table 2) and then boiled under reflux. At this point the T.H.F. was distilled off. In one case 50 ml. of D.M.F. were added and the mixture stirred at 100° for a further hour.

The work-up procedure at this stage was the same in all cases. The reaction mixture was cooled, dissolved in water (250 ml.) and extracted with ether. On evaporation of the dried ether extract no residue was observed, and the aqueous phase was acidified (dilute hydrochloric acid) and re-extracted with ether. The residual gum, after distillation of the dried ethereal extract, was then analysed by thin layer chromatography (T.L.C.) and infrared spectroscopy. All attempts to purify the crude product e.g. crystallisation, sublimation, were unsuccessful.

Dilute ether solutions of the crude reaction product, starting keto

alcohol, and authentic tetrafluorobenzo[b]furan-3-one, were placed on the fluorescent layer and the plate placed in a chromatography tank containing 30% chloroform in carbon tetrachloride (200 ml.). On irradiation of the eluted plate with ultra-violet light it was possible to detect the presence of starting material or benzo[b]furan-3-one in the product. In all cases the crude product showed only a trace of the furan-3-one, the major component having a much shorter retention time.

Attempted Cyclisation of ω-Hydroxy-2,3,4,5,6-Pentafluoroacetophenone (XXXIII).

The keto alcohol solutions were heated for various lengths of time (p.32 Table 3), the solvent removed by distillation (after filtering and washing the potassium carbonate residue) and the residues crystallised from petroleum ether (b.p. 60-80°).

The reaction with sodium methoxide in dry methanol required a different work-up procedure. After cooling, the reaction mixture was poured into water (250 ml.), acidified with dilute hydrochloric acid (4N, 50 ml.), and extracted with ether. The ether extract was dried ($MgSO_4$) and the ether removed by distillation to yield a small amount of a gum. Distillation of the gum under reduced pressure afforded a colourless liquid (b.p. 80-85°/ 0·001 mm.) which gradually solidified on standing.

An examination of the infra-red spectrum of this product suggested that the keto alcohol and furan-3-one were not present. A positive identification of this compound was not possible, however, as there was insufficient material for further analysis.

Reaction of 2,3,4,5,6-Pentafluorophenylacetyl Chloride (XXXIV) with Sodium Hydride.

The experimental procedure employed was based on that used in the previous reactions between the keto alcohol (XXXIII) and sodium hydride.

A weight of sodium hydride (50% dispersion in oil) to yield after washing with T.H.F., an amount equimolar with, or slightly in excess of, the quantity of acid chloride (XXXIV) used, was slurried into a pre-dried three-necked flask purged with dry nitrogen. The nitrogen flow was stopped and the system connected to the manometer. A solution of the acid chloride in T.H.F. was added from the dropping funnel to the stirred suspension of sodium hydride, and cooling supplied, where necessary, by means of an acetone-solid carbon dioxide bath. In the first experiment the reaction mixture was boiled under reflux in T.H.F. for 3 hr., after the addition of the acid chloride was completed, and the volume of evolved gas was measured. The solvent was removed by distillation, the crude residue dissolved in water (300 ml.), the resulting solution acidified with nitric acid (25 ml., 4N) and then extracted with ether. The ether extract was dried ($MgSO_4$), filtered and distilled to yield a crude solid which, on crystallising from petroleum ether (b.p. 60-80°), afforded 2,3,4,5,6-pentafluorophenylacetic acid (1·52 gm., 69%) m.p. 105-106° (lit.[38] 109°). The infra-red spectrum of this compound was found to be identical with that of an authentic sample of the pentafluorophenylacetic acid.

Treatment of the aqueous phase, from the ether extraction, with silver nitrate solution gave a white precipitate soluble in ammonium hydroxide, inferring the presence of chloride ion.

The volume of gas evolved before the mixture was boiled under reflux, was almost in agreement with that volume of hydrogen calculated (these latter figures in parentheses) to be evolved from the sodium hydride (see Table 4). On repeating this reaction the mixture was boiled under reflux for $\frac{1}{2}$ hr. in T.H.F., dry D.M.F. added (50 ml.), the T.H.F. removed by distillation and the resulting mixture boiled under reflux for a further 2 hr. The volume of gas evolved before boiling under reflux was slightly in excess of the calculated volume. On work-up no identifiable compound was isolated from the tarry intractable mass.

The reaction was repeated but the addition of the acid chloride was carried out at room temperature, this process being only very slightly exothermic. On completion of the addition N,N'-dimethylacetamide (D.M.A.C., 30 ml.) was added, the T.H.F. distilled off and the reaction mixture boiled under reflux for $2\frac{1}{2}$ hr. On cooling, the mixture was dissolved in water (300 ml.), acidified with dilute nitric acid (25 ml., 4N) and extracted with ether. Distillation of the dried ether extract yielded a tarry residue which on distillation under reduced pressure afforded a semi-solid (0·49 g.). Examination of this product by gas-liquid chromatography showed that it consisted of three components. However a separation could not be effected by further distillation or crystallisation. This experiment was carried out again, the acid chloride being added at room temperature. After the addition was complete, D.M.F. was added (40 ml.), the T.H.F. removed by distillation and the resulting mixture boiled under reflux for 1 hr. On work-up two impure compounds were isolated from the crude product. A

liquid (0·61 g.) was transferred under reduced pressure from the crude product, leaving a dark viscous solid (0·18 g.). Analysis of these two components by T.L.C. showed that the liquid contained a minor impurity with the same retention time as the major component of the viscous solid. Further purification of the viscous compound, which contained two other minor components, did not afford a tractable crystalline solid.

The reaction was repeated on twice the scale when distillation of the crude residue, left after removal of the ether, afforded N,N'-dimethyl-2,3,4,5,6-pentafluorophenylacetamide (XXXVI) (1·8 g., 51%), b.p. 126-128°/30 mm. (Found: C, 47·2; H, 3·05 M(mass spectroscopy) 253. $C_{10}H_8F_5NO$ requires C, 47·4; H, 3·18% M 253). The ^1H n.m.r. spectrum of the liquid showed three sets of magnetically different protons in the ratio 3:3:2 at τ 8·8 and τ 8·7, attributed to the CH_3 groups, and τ 6·3 due to the CH_2 group. The ^{19}F n.m.r. spectrum showed three magnetically different fluorine atoms in the ratio 2:1:2 centred at 143, 157 and 164 p.p.m. upfield from $CFCl_3$ as internal reference, assigned to the o-, p- and m-fluorine atoms respectively.

The crude solid remaining after distillation of the liquid(XXXVI), was crystallised from petroleum ether (b.p. 60-80°) to yield α:α'-(di-2,3,4,5,6-pentafluorophenyl)acetone (XXXV) (0·8 g., 20%), m.p. 99-100° (Found: C, 44·2; H, 1·6. M(mass spectroscopy) 390 $C_{10}H_4F_{10}O$ requires C, 44·0; H, 1·4% M 390). The ^1H n.m.r. spectrum in acetone showed a single absorbance at τ 5·65 attributed to the CH_2 protons. The ^{19}F n.m.r. spectrum showed three magnetically different fluorine atoms in the ratio 2:1:2 centred at 142,

157 and 164 p.p.m. upfield from $CFCl_3$ as internal reference, assigned to the o-, p- and m-fluorine atoms respectively. Treatment of the ketone (XXXV) with 2,4-dinitrophenylhydrazine and crystallisation of the resulting precipitate from methylated spirit afforded the 2,4-dinitrophenylhydrazone, m.p. 152-152·5° (Found: C, 44·2; H, 1·4 M(mass spectroscopy) 570 $C_{21}H_8F_{10}N_4O_4$ requires C, 44·0; H, 1·6%, M 570).

This reaction was repeated and the gas evolved collected in the manometer while the mixture was stirring overnight. The volume collected at this stage was 240 ml., the calculated volume being 230 ml. The gas was transferred to an ammoniacal cuprous chloride[21] scrubber and scrubbed several times. On transferring the gas back to the manometer no absorption had taken place.

The T.H.F. was distilled to low volume (~1-2 ml.) and the apparatus allowed to cool before the manometer reading was taken. 50 ml. of gas had been liberated at this point which was absorbed by the ammoniacal cuprous chloride. Dry D.M.F. was added (40 ml.) from the dropping funnel and the increase in volume of 40 ml. observed in the manometer. The apparatus was then flushed with dry nitrogen (200 ml.) and the gas collected in the manometer. On scrubbing the contents of the manometer with ammoniacal cuprous chloride solution, 40 ml. were absorbed. The mixture was boiled under reflux for 1 hr. after which time no increase in volume was observed in the manometer on cooling to room temperature. Water was added (100 ml.) to the cooled reaction mixture when the displaced gas was not absorbed by the scrubber. Dilute nitric acid (50 ml., 4N) was then added and the

system flushed with dry nitrogen. The contents of the manometer were scrubbed again when 25 ml. of gas were absorbed.

The usual work-up procedure was then commenced when the crude reaction mixture afforded only the ketone (XXXV) (0·84 g., 43%) on crystallisation from petroleum ether (b.p. 60-80°). This compound was identified by comparison of its infrared spectrum with that of an authentic sample.

The aqueous phase from the extraction was quantitatively analysed for chloride by titration with standard $AgNO_3$ and KCNS and found to contain 0·37 g. (before control) of chloride, i.e. accounting for all the chloride in the starting acid chloride.

Of the gas liberated 115 ml. were absorbed by the ammoniacal cuprous chloride. Assuming that CO was evolved 112 ml. would be evolved from 2·45 g. of acid chloride which is in close agreement with the total volume which was absorbed.

2,3,4,5,6-Pentafluorophenylacetamide (XXXVIII) was prepared according to the method of Tatlow et al,[38] m.p. 181-182° (lit. 187°).

Ethyl-2,3,4,5,6-Pentafluorophenylacetate (XXXVII; R = C_2H_5)

A solution of the acid chloride (XXXIV) (4·9 g.) in absolute ethyl alcohol (1·84 g.) containing concentrated sulphuric acid (0·5 ml.) was boiled under reflux in dry ether (25 ml.) for 0·75 hr. The solution was cooled, poured into water (250 ml.) and extracted with ether. The ether extract was washed several times with sodium bicarbonate solution (3 x 25 ml. 5%), dried ($MgSO_4$), filtered, and the ether removed by distillation.

Fractionation of the residue yielded the ethyl ester (4·3 g., 85%), b.p. 104-105°/20 mm. (Lit.[38] 95-96°/14 mm.). (Found: C, 47·2; H, 2·76 M(mass spectroscopy) 254. $C_{10}H_7F_5O_2$ requires C, 47·2; H, 2·78% M 254). The ^{19}F n.m.r. spectrum showed three magnetically different fluorine atoms in the ratio 2:1:2 centred at 141, 155 and 161 p.p.m. upfield from $CFCl_3$, as internal reference, attributed to the o-, p- and m- fluorine atoms respectively.

Methyl-2,3,4,5,6-Pentafluorophenylacetate (XXXVII; R = CH_3).

A mixture of the acid chloride (1·95g.) and sodium methoxide in methyl alcohol (40 ml. 0·2N CH_3ONa) was boiled under reflux for 13 hr. The product was cooled, poured into water (600 ml.) and ether extracted. The extract was washed with sodium bicarbonate solution (3 x 25 ml., 5%), dried ($MgSO_4$), filtered, and solvent removed by distillation. The crude residue was distilled under reduced pressure to afford the methyl ester (1·8g., 83%) b.p. 94-95·5/14 mm. (Found: C, 45·1; H, 2·3 M(mass spectroscopy) 240 $C_9H_5F_5O_2$ requires C, 45·02; H, 2·1% M 240). The ^{19}F n.m.r. spectrum shows three magnetically different fluorine atoms in the ratio 2:1:2 at 141, 155 and 161·5 p.p.m. upfield from $CFCl_3$, attributed to the o-, p- and m-fluorine atoms respectively.

Reaction of the Methyl Ester (XXXVII) with Sodium Methoxide.

A mixture of the methyl ester (XXXVII; R = CH_3) and sodium methoxide solution (90 ml., 0·06N) was boiled under reflux for 64 hr. The reaction mixture was cooled, poured into water (600 ml.), extracted with ether and

the extract dried ($MgSO_4$). The solvent was removed by distillation to afford impure starting material (0·8g., 75%). This compound was identified by comparison of its infrared spectrum with that of an authentic sample of methyl ester (XXXVII; R = CH_3).

Reaction of the ethyl ester (XXXVII; R = C_2H_5) with hydrazine.

A mixture of the ethyl ester (XXXVII) (2·2 g.), ethyl alcohol (10 ml.), water (10 ml.) and hydrazine hydrate (0·98 g.) was boiled under reflux for 20 hr. The mixture was cooled, poured into water (600 ml.) and extracted. The extract was dried ($MgSO_4$), filtered, and the solvent removed by distillation to afford a crude pale yellow solid. Continuous ether extraction of the aqueous phase provided more of this solid, total amount (1·7 g.) which crystallised from ethylacetate - petroleum ether (b.p. 60-80°) to afford 2,3,4,5,6-pentafluorophenylacetohydrazide (XXXIX) (1·7 g. 82%) m.p.168-169°. (Found: N, 11·36, M(mass spectroscopy) 240, $C_8H_5F_5N_2O$ requires N, 11·66% M 240). The infrared spectrum shows two absorptions, at 3300 cm^{-1} and 3175 cm^{-1}, attributed to the NH stretches, and a strong absorption at 1640 cm^{-1} attributed to the C=O group.

Treatment of this compound with hot acetone afforded the corresponding pentafluorophenylacetohydrazone (XL), crystallised from ethyl acetate - petroleum ether (b.p. 60-80°) m.p. 157-158°. (Found: C, 46·9; H, 3·0 M(mass spectroscopy) 280. $C_{11}H_9F_5N_2O$ requires C, 47·1; H, 3·2% M 280. Accurate mass measurements were carried out on the parent and the first decomposition fragment at mass 265 (Observed: 280·0639, $C_{11}H_9F_5N_2O$

Calculated 280·0634; Observed: 265·0401, $C_{10}H_6F_5N_2O$ Calculated 265·0400). This fragmentation corresponds to loss of CH_3 from the parent. The ^1H n.m.r. spectrum in deutero-chloroform showed four absorbances in the ratio 1:2:3:3, a broad singlet at τ 0·55, attributed to the N-H proton; a singlet at τ 5·95 attributed to the CH_2, and two at τ 8·0 and τ 8·2 assigned to the two methyl groups. The ^{19}F n.m.r. spectrum showed three magnetically different fluorine atoms in the ratio 2:1:2 centred at 144, 158 and 165 p.p.m. upfield from $CFCl_3$ as internal reference, assigned to the o-, p- and m-fluorine atoms respectively. The infrared spectrum showed absorptions at 3175 cm^{-1} attributed to the NH stretch, and a strong absorption at 1670 cm^{-1} assigned to the C=O group.

Reaction of the Pentafluorophenylacetic acid (XXXVII; R = H) with Sodium Hydroxide.

A mixture of the acid (XXXVII; R = H) (1·4 g.), sodium hydroxide (0·5 g.), water (10 ml.) and ethyl alcohol (2 ml.) was boiled under reflux for 20 hr. The mixture was cooled and poured into water (500 ml.), acidified and extracted with ether. The extract was dried ($MgSO_4$), filtered and distilled to remove ether. Crystallisation of the crude solid from petrol ether (b.p. 60-80°) afforded the starting acid (XXXVII; R = H) (1·25 g., 90%) identified by comparison of its infrared spectrum with that of an authentic sample of the acid.

Reaction of the Methyl Ester (XXXVII; R = CH_3) with Sodium Methoxide.

The methyl ester (0·85 g.) and sodium methoxide solution (3·8 ml. of 1·07N CH_3ONa) were placed in a bomb and heated for 42 hr. at 150°. The

contents of the bomb were extracted with ether, the extract dried ($MgSO_4$), filtered, and distilled to afford impure starting ester (0·49 g.). identified by T.L.C. and comparison of the infrared spectrum with an authentic sample of the methyl ester (XXXVII; R = CH_3).

(i) Reaction of the Methyl Ester (XXXVII; R = CH_3) with Sodium Thiophenoxide.

A solution of the methyl ester (1·1 g.) and sodium thiophenoxide (0·7 g.) in DMAC (15 ml.) was heated in a Carius tube at 150° for $2\frac{1}{2}$ days. The tube was cooled and the contents poured into water (500 ml.) and extracted with ether. The extract was dried ($MgSO_4$), filtered and distilled to afford impure starting ester (0·37 g., 36%) identified by comparison of its infrared spectrum with an authentic sample, and its retention time by T.L.C. The experiment was repeated (p.38 Table 5) and a higher recovery of starting material achieved but in both cases distillation of the impure ester did not effect a complete separation. Two fractions were obtained, (0·67 g., 36%) b.p. 29-30°/0·01 mm. and a second fraction (1·10 g.) b.p. 118-125°/0·1 mm. An examination of both fractions by T.L.C. showed that the former appeared to be one component and the latter to contain the same number of components as the crude product. The first fraction, which solidified on standing, melting just above room temperature, was submitted for elemental analysis. (Found: C, 44·94; H, 1·96 $C_9H_5F_5O_2$ calculated for C, 45·02; H, 2·1%). The infrared spectrum of this compound was virtually identical to that of an authentic sample of the methyl ester (XXXVII; R = CH_3). T.L.C. on the

impure ester and the distillates showed the same number of components each time.

(ii) Reaction of the Methyl Ester (XXXVII; R = CH_3) with Ammonium Hydroxide

A mixture of the methyl ester (1·2 g.) and ammonium hydroxide (SG 0·88, 0·6 ml.) was heated in a 100 ml. bomb for 2 days at 150°. The charred contents were extracted with ether and water (200 ml.), the organic extract dried ($MgSO_4$), filtered, and distilled to yield a crude solid (1 g.). Crystallisation of the solid from ethyl acetate - petroleum ether (b.p. 60-80°) afforded the amide (XXXVIII) (0·4 g., 36%) m.p. 176-178° (pure sample 181-182°) identified by comparison of its infrared spectrum with that of an authentic sample.

(i) Reaction of the Pentafluorophenylacetic acid (XXXVII; R = H) with Potassium Hydroxide.

A mixture of the acid (XXXVII; R = H) (4·0 g.), potassium hydroxide (4·0 g.), water (20 ml.) and methyl alcohol (2 ml.), was boiled under reflux for 71 hr. The mixture was cooled, poured into water (300 ml.) acidified and extracted with ether. The extract was dried ($MgSO_4$), filtered, and distilled yielding a residue which, on crystallising from petroleum ether (b.p. 80-100°), afforded the 4-hydroxy-2,3,5,6-pentafluorophenylacetic acid (XLI; R = H) (2·57 g., 66%) m.p. 160-161° (lit.[22] 161-163°). (Found: C, 42·96; H, 1·86. M(mass spectroscopy) 224 $C_8H_4F_4O_3$ calculated for C, 42·88; H, 1·80% M 224). The ^1H n.m.r. spectrum in acetone showed two absorptions, one at τ 1·4, attributed to the

hydroxylic protons, and another at τ 6·35 assigned to the CH_2 protons. The ^{19}F n.m.r. spectrum in acetone showed two magnetically different fluorine atoms, of equal intensity, centred at 2·25 p.p.m. and 19·75 p.p.m. downfield from C_6F_6 as internal reference. The infrared spectrum was the same as that of an authentic sample of the 4-hydroxy acid.

The mother liquor from the crystallisation of the hydroxy acid was evaporated and the residue sublimed, 90°/0·5 mm, to afford pentafluorophenylacetic acid (XXXVII; R = H) (0·52 g., 13%) identified by comparing its infrared spectrum with that of an authentic sample.

(ii) Reaction of 2,3,4,5,6-Pentafluorophenylacetic acid (XXXVII; R = H) with Potassium Hydroxide in Methanol-Ether.

A mixture of the acid (1·6 g.) and a four molar excess of potassium hydroxide (1·6 g.), was dissolved in dry methanol (8 ml.) and ether (50 ml.) and boiled under reflux, with stirring, for 68 hr. The mixture was cooled, poured into water (300 ml.), acidified with hydrochloric acid, and ether extracted. The extract was dried ($MgSO_4$), filtered and distilled to afford a crude residue which crystallised from petroleum ether (b.p. 60-80°), identified as the starting acid (1·35 g., 85%) by comparison of its infrared spectrum with an authentic sample.

Reaction of Methyl-2,3,4,5,6-Pentafluorophenylacetate (XXXVII; R = CH_3) with Potassium Hydroxide in Methanol-Ether.

A mixture of the ester (2·77 g.) and a three molar excess of potassium hydroxide, was dissolved in dry methanol (10 ml.) and ether (80 ml.) and boiled under reflux for 94 hr. The reaction mixture was cooled, poured

into water (300 ml.), acidified with hydrochloric acid, and ether extracted. The extract was dried ($MgSO_4$), filtered and distilled to afford the crude pentafluorophenylacetic acid (2·4 g., 90%) identified by comparison of its infrared spectrum with that of an authentic sample of the acid.

Reaction of 2,3,4,5,6-Pentafluorophenylacetic acid with Potassium Hydroxide in t-Butanol-Ether.

A mixture of the acid (0·5 g.) and a four molar excess of potassium hydroxide (0·5 g.) was dissolved in dry t-butanol (20 ml.) and ether (40 ml.). The solution was boiled under reflux, with stirring, for 53 hr., cooled, poured into water (300 ml.), acidified and ether extracted. The extract was dried ($MgSO_4$), filtered and the ether removed by distillation yielding unchanged starting material (0·41 g., 82%), identified by its infrared spectrum which was identical to that of the starting material.

(i) Reaction of α:α'-(di-2,3,4,5,6-Pentafluorophenyl)acetone (XXXV) with Sodium Methoxide.

A mixture of the ketone (0·27 g.) and sodium methoxide solution (1·4 ml. 0·5N CH_3ONa) was placed in a Carius tube and heated at 100° for 3 days. The tube and contents were cooled and the crude reaction mixture poured into water (250 ml.) and ether extracted. The extract was dried ($MgSO_4$), filtered and distilled to yield a small amount of solid. Crystallisation of the solid from petroleum ether (b.p. 60-80°) afforded the starting ketone (0·1 g., 37%) identified by comparison of its infrared spectrum with that of the starting material.

(ii) Reaction of α:α'-(di-2,3,4,5,6-Pentafluorophenyl)acetone (XXXV) with Caesium Fluoride.

A solution of the ketone (XXXV) (0·5 g.) in acetonitrile (10 ml.) was stirred magnetically with caesium fluoride (0·2 g.) in a round-bottomed flask fitted with a condenser and drying tube ($CaCl_2$) heated in an oil bath at 90° for 1 week. The contents of the flask were cooled, poured into water and ether extracted. The extract was dried ($MgSO_4$), filtered, and distilled giving a crude solid. Crystallisation of the solid from petroleum ether (b.p. 60-80°) yielded the starting ketone (0·3 g., 60%), identified by comparison of its infrared spectrum with that of an authentic sample of the ketone.

(i) Reaction of 2,3,4,5,6-Pentafluorophenylacetyl chloride (XXXIV) with Caesium Fluoride.

A mixture of the acid chloride (XXXIV) (2·6 g.), dried, powdered caesium fluoride (3·26 g.) and acetonitrile (10 ml.) was placed in a dry 50 ml. two-necked round-bottomed flask, fitted with a condenser and drying tube ($CaCl_2$), and stirred magnetically in an oil bath at 90° for 1 week.

The liquid was removed under high vacuum and the remaining solid sublimed (80°/0·01 mm). Crystallisation of this compound from petroleum ether (b.p. 60-80°) afforded pentafluorophenylacetic acid (XXXVII; R = H) (0·8 g., 33%). The charred residue from the sublimation was boiled under reflux with petroleum ether (b.p. 60-80°), filtered and cooled affording a white solid, α:α'-(di-2,3,4,5,6-pentafluorophenyl)acetone (XXXV) (0·1 g., 10%). Both compounds were identified by comparison of their infrared spectra with authentic samples. The infrared spectrum of the liquid transferred

under vacuum was identical to that of an authentic sample of acetonitrile.

(ii) Reaction of 2,3,4,5,6-Pentafluorophenylacetyl chloride (XXXIV) with Potassium Fluoride.

Freshly dried and ground potassium fluoride (3 g.) was placed in a Carius tube and gently heated under high vacuum for 15 min. The tube was then cooled, the acid chloride (2·4 g.) added, and the tube sealed under high vacuum while cooling in liquid air. The tube and contents were heated at 200° for 57 hr. The charred reaction mixture was extracted with ether. Distillation of the dried ($MgSO_4$) and filtered extract afforded no residue so the reaction was repeated at 150° for 22 hr. Distillation of the tarry liquid remaining after removal of the ether, afforded a viscous liquid which solidified inside the condenser. Crystallisation of the solid from petrol ether (b.p. 60-80°) gave α:α'-(di-2,3,4,5,6-pentafluorophenyl)acetone (0·24 g., 12%) identified by comparison of the infrared spectrum with that of an authentic sample.

A third experiment was carried out, using the same quantities of reagents, but heating at 75° for 22 hrs. The contents of the tube were not charred and the liquid was transferred under high vacuum into a pre-dried flask. Distillation of this liquid under reduced pressure afforded the acid chloride (XXXIV) (2·2 g., 90%) identified by comparison of its infrared spectrum with that of an authentic sample.

On repeating this reaction the tube and its contents were heated at 100° for 16 hr. after which time the reaction mixture had darkened appreciably but still contained some liquid. The tube was cooled and

the volatile material transferred into a pre-dried flask under reduced pressure (0·001 mm) affording 2,3,4,5,6-pentafluorophenylacetyl fluoride (XLII) (0·87 g., 38%) (Found: F, 50·6, M(mass spectroscopy) 228. $C_8H_2F_6O$ requires F, 50·0% M 228. The infrared spectrum shows a strong absorption at 1850 cm^{-1} attributed to the C=O group compared with the absorption at 1800 cm^{-1} observed in the infrared spectrum of the acid chloride. A shift of the carbonyl absorption to higher wave number would be expected on replacing the chlorine with a fluorine atom.

The residue left after the acid fluoride was transferred, was heated gently under reduced pressure (0·001 mm) when a white solid sublimed inside the transfer apparatus. Crystallisation from ethyl acetate-petroleum ether (b.p. 60-80°) afforded a white crystalline solid (0·4 g.) m.p. 200-202°. (Found: C, 46·45; H, 0·7, M(mass spectroscopy) 832 $C_{32}H_4F_{20}O_4$ requires C, 46·16; H, 0·48%, M 832). The infrared spectrum of this solid was identical with that of the compound deposited over a period of several hours from a sample of the acid fluoride stored in a stoppered flask. Two absorptions were observed at 1800 cm^{-1} and 1755 cm^{-1} attributed to carbonyl groups. Treatment of this compound with 2,4-dinitrophenylhydrazine however, did not afford a hydrazone derivative.

A solution of the compound (0·00175 g.) in chloroform (10 ml.) showed three absorptions in the ultraviolet spectrum, λ_{max} 246, 268, 307 mμ [ϵ_{max} 5·5 x 10^3, 3·3 x 10^3, 6·7 x 10^3] indicating extended conjugation compared with pentafluorophenyl acetic acid λ_{max} ($CHCl_3$) 260 mμ (ϵ_{max} 0·63 x 10^3), and the pentafluorophenyl acetone (XV) λ_{max} ($CHCl_3$) 262 mμ (ϵ_{max} 1·11 x 10^3).

The ^{1}H n.m.r. spectrum in deuterochloroform showed a singlet at -1·8 τ, assigned to an acidic proton, and an unsymmetrical doublet centred at 6·15τ, in the ratio 1:1:2. The ^{19}F n.m.r. spectrum in deuterochloroform, showed two superimposed sets of multiplets attributed to C_6F_5 nuclei; a multiplet at 144 p.p.m., two triplets, in the approximate ratio 1:3, centred at 155 and 157 p.p.m. respectively, and a multiplet at 164 p.p.m., all upfield from $CFCl_3$ as reference. On summation of the two triplets, the three absorbances centred at 144, 156 and 164 p.p.m. were shown to be in the ratio 2:1:2 and were assigned to the o-, p-, and m- fluorine atoms respectively.

The residue, after removal of the acid fluoride (XLII) and the unidentified compound, was sublimed at 90°/0·5 mm. to afford a white solid which was crystallised from petroleum ether (b.p. 60-80°) yielding pentafluorophenylacetic acid (0·5 g., 22%) identified from a comparison of its infrared spectrum with that of an authentic sample.

Reaction of Methyl-2,3,4,5,6-Pentafluorophenylacetate (XXXVII; R = CH_3) with Methyl Oxalate and Sodium Methoxide.

(i) A solution of the methyl ester (1·2 g.), methyl oxalate (0·7 g.) and sodium methoxide (10 ml. 0·5N CH_3ONa) in dry ether (50 ml.), was boiled under reflux for $2\frac{1}{2}$ days according to the method used by Adickes and Andresen[14] for the synthesis of α-keto acids.

The mixture was cooled in ice and acidified with sulphuric acid (15 ml., 50%). This solution was then extracted with ether, the extract washed with potassium carbonate solution (2 x 25 ml. 10%) dried ($MgSO_4$),

filtered and then distilled to afford somewhat impure starting ester (XXXVII; R = CH_3) (0·97 g., 81%) identified by comparison of its infrared spectrum with that of an authentic sample.

(ii) The same quantities of reagents were taken and heated on a boiling water bath in dry pyridine (15 ml.), in place of ether, for 4 days. The reaction mixture was cooled, diluted with water (250 ml.), acidified with dilute sulphuric acid (25 ml., 50%) and extracted with ether. The ether extract was washed with potassium carbonate solution (2 x 25 ml., 10%), dried ($MgSO_4$), filtered, and distilled. The residual liquid, free of solvent, was transferred under vacuum, to afford the starting ester (XXXVII; R = CH_3) (1·0 g., 83%), identified by comparing its infrared spectrum with that of an authentic sample.

Reaction of 2,3,4,5,6-Pentafluorophenylacetyl chloride (XXXIV) with Cuprous Cyanide.[31]

A solution of the acid chloride (XXXIV) (2·45 g.) in anhydrous D.M.A.C. (5 ml.) was placed in a dry flask, fitted with a condenser and drying tube ($CaCl_2$), containing dried cuprous cyanide (1·0 g.). The contents of the flask were stirred magnetically for 3 hr. in an oil bath at 130° when the mixture darkened rapidly. The reaction product was cooled and a mixture of ferric chloride (1 g.), concentrated hydrochloric acid (1 ml.) and water (6 ml.) added and the whole stirred for ½ hr. at 100°. At the end of this time the contents of the flask were cooled and poured into water (250 ml.) extracted with ether, the extract washed with water (4 x 50 ml.) and then dried ($MgSO_4$), before filtering. The ether was

removed by distillation to yield a tarry liquid which was sublimed at 80°/0·01 mm. affording crude pentafluorophenylacetic acid (XXXVII; R = H) crystallised from petroleum ether (b.p. 60-80°) (0·7 g., 30%). The acid was identified by comparing its infrared spectrum with that of an authentic sample of pentafluorophenylacetic acid.

Preparation of Lithium tri-(tertiarybutoxy)aluminohydride.

(i) This compound was made using the method described by Brown et al.[32] Lithium aluminium hydride (4·7 g.) was placed in a dropping funnel containing dry ether (300 ml.). The suspension was agitated for ¼ hr. and allowed to settle when the ether insoluble portion was discarded, and the clear supernatant solution run into a three-necked flask previously flamed out under nitrogen and fitted with a stirrer, dropping funnel, condenser and thermometer.

Maintaining the flow of dry nitrogen a solution of anhydrous t-butanol (38 g.) in ether (200 ml.) was added slowly from the dropping funnel and stirred for 1 hr. on completion of the addition. The ethereal layer was decanted from the white solid and the latter dissolved in dry diglyme (100 ml.) and stored in a stoppered flask. On hydrolysis of an aliquot (1 ml.) the volume of hydrogen collected was 40 ml., the solution containing 0·45g/ml. of the hydride reagent (calculated as $Li(t\text{-}C_4H_9O)_3AlH$).

(ii) The second technique employed, involved isolation of the solid reagent.

Lithium aluminium hydride (3·1 g.) was added to dry ether (500 ml.) in a dropping funnel, as before, and agitated. The insoluble portion was discarded and an aliquot of the supernatant liquid hydrolysed and the

hydrogen collected in a manometer. From 5 ml. of the solution 55 ml. of H_2 were evolved i.e. 2·3 g. $LiAlH_4$ per 500 ml. A solution of anhydrous t-butanol (16 ml., 12·6 g.) in dry ether (250 ml.) was added slowly to the lithium aluminium hydride solution as in the previous experiment, and on completion of the addition stirring was continued for 1 hr. The ether was then decanted and the wet residue transferred to a bowl sublimator, dried under reduced pressure, and then sublimed at 260°/0·1 mm. The white sublimate (4·1 g.) was then dissolved in dry diglyme (20 ml.) and stored in a tightly stoppered flask. Hydrolysis of an aliquot (1 ml.) gave 10 ml. of hydrogen which would be evolved by 0·226 g. of the lithium tri-(ter-butoxy)-aluminohydride reagent.

In both cases it appeared that the reagent was not pure, but contaminated with lithium aluminium hydride, although this was greatly reduced by using the second technique.

Reaction of 2,3,4,5,6-Pentafluorophenylacetyl chloride (XXXIV) with Lithium tri-tertiarybutoxyaluminohydride.

A solution of the acid chloride (2·45 g.) in dry diglyme (15 ml.) was placed in a dry three-necked flask fitted with a condenser, thermometer, dropping funnel and magnetic stirrer. The flask and contents were cooled to -75° while purging with dry nitrogen. A solution of the hydride reagent (prepared by method (i)) (5·5 ml., 2·5 g. $Li(t\text{-}BuO)_3AlH$) in dry diglyme (15 ml.), was added slowly from the dropping funnel over 1 hr. keeping the temperature between -75 and -70°. The flask and contents were then allowed to reach room temperature, stirring continued throughout, when the crude

product was poured on to an ice-water mixture and ether extracted. The ether extract was washed with water (3 x 50 ml.) to remove diglyme, dried ($MgSO_4$), filtered and distilled yielding a viscous residual liquid. Distillation of the crude product under reduced pressure gave two fractions (0·2 g.) b.p. 61-81°/12 mm and (0·4 g.) b.p. 81-130°/12 mm having similar absorptions in the infrared spectrum, notably a strong absorption at 1730 cm^{-1} attributed to the C=O group. Examination of the fractions by T.L.C. and V.P.C. showed the presence of four components, the second fraction containing one major and three minor components. The mass spectrum of the second fraction showed an intense peak at mass 210, $C_8H_3F_5O$ requires 210. Treatment of a portion of the second fraction with 2,4-dinitrophenylhydrazine afforded a yellow precipitate which crystallised from methylated spirit to afford the pentafluorophenylacetaldehyde 2,4-dinitrophenylhydrazone m.p. 151-152° (Found: C, 43·4; H, 1·83. M(mass spectroscopy 390. $C_{14}H_7F_5N_4O_4$ requires C, 43·1; H, 1·81% M 390).

The solid remaining in the distillation apparatus was crystallised from petroleum ether (b.p. 60-80°) yielding pentafluorophenyl acetic acid (1·5 g. 66%) identified by comparison of its infrared spectrum with that of an authentic sample of the acid.

The reaction was repeated using the same quantities of reagents but allowing 3 hr. reaction time at -75°. The mixture was allowed to reach room temperature over 1 hr. and then stirred for 22 hr. before the usual work up procedure. Distillation of the crude product afforded three fractions (0·09 g.) b.p. 92-96°/10 mm., (0·19 g.) b.p. 96-97°/10 mm.,

and (0·16 g.) b.p. 97-125°/10 mm. having virtually the same infrared spectrum showing an intense absorption at 1730 cm^{-1}. An examination of all three fractions by T.L.C. and V.P.C. showed that the aldehyde was the major component and there were three other minor constituents present.

On crystallising the residue, left after distillation, from petroleum ether (b.p. 60-80°) pentafluorophenylacetic acid (1·1 g. 49%) was recovered, identified by its infrared spectrum on comparison with that of an authentic sample.

The acid chloride (2·45 g.) was treated with the same solution of lithium tri-tertiarybutoxyalumino hydride reagent (20 ml., 9 g. as $Li(t\text{-}BuO)_3AlH$) in an attempt to ensure complete reaction of the acid chloride. The mixture was stirred at -75° for 1 hr. as previously, allowed to reach room temperature, poured on to crushed ice, acidified and ether extracted. The extract was washed with water (3 x 50 ml.) and worked up as previously.

The crude product was examined by T.L.C. and was shown to contain four components, two major and two minor constituents. Distillation of thecrude product afforded three fractions, 2,3,4,5,6-pentafluorophenyl-ethanol (0·62 g. 29%) b.p. 46-48°/0·01 mm. identified by comparison of its infrared spectrum with that of an authentic sample; and (0·52 g.) b.p. 158-160°/0·001 mm. and (0·50 g.) b.p. 160-170°/0·001 mm. The last two fractions solidified on standing but the solid material, which crystallised from petroleum ether (b.p. 60-80°) (0·6 g.) m.p. 128-129°, is unidentified at the present time.

No identifiable product could be isolated from the charred residue remaining in the distillation flask.

The reaction was carried out using the reagent prepared by method (ii). A solution of the acid chloride (4·89 g.) in dry diglyme (30 ml.) was treated with an equimolar quantity of the hydride reagent (23 ml. 5·2 g.) in dry diglyme (20 ml.) at -75°. On completion of the addition stirring was continued for a further 1 hr. The mixture was allowed to reach room temperature and stirred for a further 2½ hr. The crude product was poured on to crushed ice and worked up as before. Distillation of the crude residue left after removal of the ether, afforded two fractions, (0·14 g.) b.p. 90-95°/10 mm., and (1·24 g.) 95-98°/10 mm. Examination of both fractions by V.P.C. and T.L.C. showed they contained one major component and only traces of three other constituents. The infrared spectrum of these fractions was virtually identical to that obtained in the previous experiments for the pentafluorophenylacetaldehyde, (XLVIII). --

The residue in the distillation apparatus was sublimed (80°/0·01 mm) yielding pentafluorophenylacetic acid (1·1 g. 24%) identified by its infrared spectrum. On the basis of acid chloride consumed by the hydride reagent, the slightly impure pentafluorophenylacetaldehyde (1·38 g.) was isolated in 44% yield.

Attempted cyclisation of 2,3,4,5,6-Pentafluorophenylacetaldehyde (XLVIII).

A solution of the aldehyde (0·5 g.) in dry T.H.F. (50 ml.) was added over 1½ hr. to a stirred suspension of sodium hydride (0·114 g., 50% dispersion in oil) in dry T.H.F. (25 ml.) under an atmosphere of nitrogen,

in a three-necked flask fitted with a stirrer, condenser and thermometer, cooled to -75°. On completion of the addition the contents of the flask were stirred for a further 2 hr. and then allowed to reach room temperature. As the temperature of the mixture reached 0° a pronounced effervescence was observed. The solution was then boiled under reflux for 2 hr. and an aliquot of the deep red solution was acidified and ether extracted. The extract was dried ($MgSO_4$), filtered and the ether evaporated when the infrared spectrum of the residual liquid was shown to be identical with that of the starting aldehyde. Dry D.M.F. (10 ml.) was then added to the reaction mixture, the T.H.F. removed by distillation, and the resulting solution boiled under reflux for $1\frac{1}{2}$ hr. The solution was cooled, poured into water (250 ml.), and extracted with ether when evaporation of the dried extract did not yield a residue. The aqueous solution was then acidified and re-extracted with ether, the extract dried ($MgSO_4$), filtered and distilled. Purification of the somewhat tarry residue was attempted by heating the product under reduced pressure when a clear liquid was collected (0·29 g. 58%) identified as the starting phenylacetaldehyde by comparison of its infrared spectrum with that of the starting material.

The reaction was repeated but the mixture boiled under reflux for 3 hr. in D.M.F. After work up the tarry residue was examined by T.L.C. and shown to contain two components, the minor constituent having the same retention time as the starting aldehyde.

In an attempt to obtain a more tractable product D.M.A.C. was used in place of D.M.F. A solution of the aldehyde (0·63 g.) in dry T.H.F. (50 ml.)

was added to sodium hydride (0·14 g.) in dry T.H.F. (25 ml.) under the conditions used in the previous experiment. Dry D.M.A.C. (10 ml.) was added, the T.H.F. removed by distillation, and the resulting solution boiled under reflux for $3\frac{1}{2}$ hr. before work up. An examination of the crude reaction product by T.L.C. showed the presence of two components. The crude product was heated gently under reduced pressure (0·001 mm.) and the liquid (0·2 g.) which transferred just above room temperature was collected. Further heating afforded a second fraction (0·21 g.). An examination of both fractions by T.L.C. showed that the lower boiling portion was one component whereas the high boiling liquid contained in addition a trace of another compound having a shorter retention time. Both fractions showed virtually identical absorptions in the infrared spectrun, and on comparison with the spectrum of an authentic sample of tetrafluorobenzo[b]furan some similarities were observable. The mass spectrum of the purified product was compared with that of an authentic sample of tetrafluorobenzo[b]furan when the absence of the molecular ion at mass 190 showed that no benzo[b]furan was present in the product. Ions were observed at mass 201 and 355 inferring a higher molecular weight product but this compound is as yet unidentified.

PART II

SOME FLUORIDE-ION INITIATED REACTIONS OF FLUOROIMINES

CHAPTER V

INTRODUCTION

Introduction

The predominant feature in the chemistry of fluoro-olefins[93] and -aromatic compounds[39,74,75] is their susceptibility to nucleophilic attack. It has been shown[94] that fluoro-olefins react with fluoride ion in aprotic solvents, and that the carbanions so generated react with halogens,[95] acid fluorides,[96] tetrafluoroethylene,[97] fluoroketones,[98] and carbon dioxide.[99]

As a result of these reactions an analogy can be drawn between the fluoride ion in fluorocarbon chemistry and the proton in hydrocarbon chemistry. On this basis the reactions of polyfluoro carbanions, generated from fluoro-olefins with fluoride ion, with polyfluoroaryl systems have been successfully investigated.[100,101]

1. Reactions of Fluoro-olefins with Halide Ions.

The work of Miller et al[94,102,103,107,108] on the reactions of halide ions with fluoro-olefins provided the basis for this type of work.

$$CF_2{=}CCl{-}CClF_2 \xrightarrow[\text{acetone}]{NaI} CF_2{=}CClCF_2I$$

$$CF_2{=}CF{-}CF_2Cl \xrightarrow{F^-} CF_3CF{=}CF_2$$

$$CF_2{=}CF{-}CF_3 \underset{}{\overset{F^-}{\rightleftharpoons}} CF_3\overset{-}{C}FCF_3 \xrightarrow[(\text{solvent})]{H^+} CF_3CHFCF_3$$

$$CF_2{=}CFCF{=}CF_2 \xrightarrow[150^\circ]{CsF} CF_3C{\equiv}CCF_3$$

Also, Graham and co-workers[97,98,99] have recently reported similar reactions involving fluorocarbanions produced by the action of fluoride ion on fluoro-olefins, and in an analogous manner, fluoro-oxyanions by treating fluoro ketones with fluoride ion.

$$CF_2{=}CF_2 \xrightarrow[\text{diglyme}]{CsF} \text{polymeric material} - C_{14}F_{28}$$

e.g. $$CF_2{=}CF_2 \xrightarrow[(ii)CO_2\ (iii)H_3O^+]{(i)CsF} CF_3CF_2CO_2H$$

$$(CF_3)_2C{=}O \xrightarrow[(ii)CF_2{=}CF_2]{(i)CsF\text{-diglyme}} CF_3CF_2C(CF_3)_2OH$$

A variety of solvents and sources of fluoride ion have been investigated. Inorganic fluorides tend to be insoluble in inert aprotic solvents,[110] but in protogenic solvents the transfer of hydrogen ion to fluorocarbanions

occurs and the solvent anions produced may then attack the olefin yielding unwanted by-products.

The choice of reaction conditions suitable for studying the behaviour of fluoride ion with fluoro-olefins presents some difficulty and the inherent disadvantages of some systems were reported by early workers. Two solvent-initiator systems were reported by Miller,[94,102] potassium fluoride in formamide, and tetraethylammonium fluoride in chloroform, methylene chloride or acetone. Although formamide dissolves relatively large amounts of potassium fluoride, it is a poor solvent for fluoro-olefins. It easily loses a proton to a fluoro carbanion to give a reactive solvent anion, and at elevated temperatures some fluoro-olefins react with the solvent alone, e.g. 3,3-dichloro-1,1,3-trifluoropropene[94] is completely converted into water soluble products and a dark coloured reaction mixture, when heated with formamide at 105° for 90 hrs. Tetraethylammonium fluoride also has disadvantages in that it is very hygroscopic, thermally unstable, difficult to prepare pure, and its solutions in chlorinated solvents decompose at room temperature.[94] However the use of these reagents made it possible to realise a number of reactions of fluoro-olefins with fluoride ion.

The search for more suitable solvents led to the successful use of glycols,[104,105] dimethyl sulphone,[106] acetonitrile,[95,96] N-methyl-2-pyrrolidone,[106] sulpholan,[101,109] and diglyme,[97,98,101] triglyme,[97,99,101] and tetraglyme.[97,101]

Two different reaction types, a substitution and an addition process have been established by Miller et al,[94] for the reaction of halide ions

with fluoro-olefins,

(i) Substitution with rearrangement (SN_2'),

$$\text{e.g. } F^- + CF_2 = CF - CF_2(Cl) \rightleftharpoons CF_3 - CF = CF_2 + Cl^-$$

(ii) Addition,

$$\text{e.g. } F^- + CF_2 = CF - CF_3 \rightleftharpoons CF_3 - \overline{C}F - CF_3$$

$$\downarrow H^+ \text{ (from solvent).}$$

$$CF_3 - CHF - CF_3.$$

Substitution with rearrangement.

A series of publications[94,107] has established that the SN_2' process governs the reactions of fluoroallyl halides. It was deduced that fluoride ion attacked the terminal CF_2 group, followed by allylic shift of the double bond and elimination of chloride ion. That the α-carbon was not attacked was shown when $CF_2=CF-CF_2Cl$ or $\overline{CF_2}=\overline{CCl}-\overline{CF_2Cl}^-$ were treated with iodide ion, because under equivalent reaction conditions $C_6H_5CClF_2$, $CClF=CF\cdot CClF_2$ and $CCl_2=CCl-CClF_2$ were all unreactive.[107]

In the SN_2' process the relative order of reactivity of halide ion with fluoro-olefins is $F^- > Cl^- >> I^-$.[19]

$$\text{e.g. } X^- + CF_2 = CH\cdot CCl_2F \longrightarrow X - CF_2CH = CClF + Cl^-$$

(where X = Cl, F or I).

In SN_2 reactions the relative nucleophilicities of halide ions in bond formation to carbon is $I^- > Cl^- > F^-$, which suggests that in the

reaction between fluoro-olefins and halide ions the polarizability of large halide ions is offset by steric hindrance and that the strength of the new bond is of prime importance. An apparent exception is replacement of allylic chlorine by iodine in $CF_2=CX-CF_2Cl$ (X = F, or Cl) yielding $CF_2=CX\cdot CF_2I$,[107] which arises as a result of the low solubility of sodium chloride in anhydrous acetone.

It has been shown that, when substitution of allylic or vinylic halogen by fluorine is possible, it occurs in preference to the addition of HF by a carbanion intermediate, and that a terminal CF_2 group is more susceptible to attack by F^- than a terminal CFCl.

These facts were illustrated by the reaction of $CFCl=CF-CClF_2$ with potassium fluoride in formamide,[94] which required relatively vigorous conditions, compared with $CF_2=CH-CFCl_2$ (which reacted quickly at room temperature) and CF_3CHFCF_3 was obtained in 52% yield.

The former reaction has been interpreted as two SN_2' replacements of Cl^- by F^- and then addition of HF.

$$F^- + CClF = CF - CF_2 - Cl \xrightarrow[60^\circ/3 \text{ days}]{KF/\text{formamide}} CClF_2 - CF = CF_2 + Cl^-$$

$$F^- + CF_2 = CF - CF_2 - Cl \longrightarrow CF_3 - CF = CF_2 + Cl^-$$

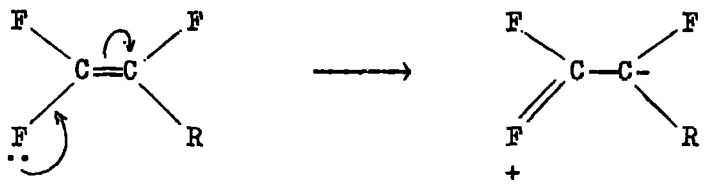
$$F^- + CF_2 = CF - CF_3 \longrightarrow [CF_3-\bar{C}F-CF_3] \xrightarrow{H^+} CF_3CHFCF_3$$

52%

$$\text{cf. } F^- + CF_2=CH-CFCl_2 \xrightarrow[\text{room temp. overnight}]{Et_4NF/CHCl_3} CF_3CH=CClF$$

74%

It has been suggested that the terminal CF_2 is the most reactive site toward nucleophiles because mesomeric electron release by the non-bonding electron pair of the fluorine is more efficient than with other vinylic halogens, as fluorine and carbon are more nearly equal in size and therefore p-π interaction is facilitated.[93]

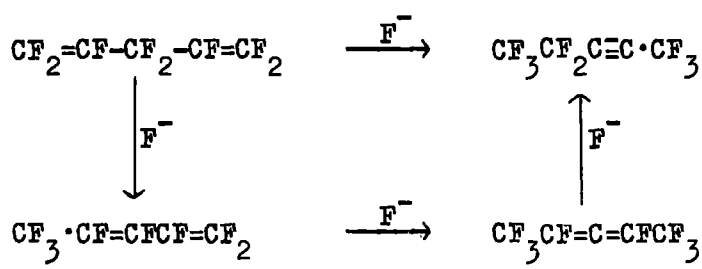


e.g. R = Cl, Br, I, CF_3, H.

Fluoride ion catalysed rearrangements.

This type of reaction involves SN_2' displacement of fluorine by fluoride ion. As a terminal olefin is more susceptible to attack than an internal olefin the tendency is for a terminal to be rearranged to an internal olefin. Under more vigorous reaction conditions attack then occurs at internal unsaturation and subsequent double bond shift affords the most thermodynamically stable product i.e. the most highly substituted olefin. Treatment of perfluoro-1-heptene with tetraethylammonium fluoride in chloroform for five minutes at room temperature yielded a mixture of olefins containing only 12% of the original olefin.[94] When a higher concentration of fluoride ion was used over a 24 hr. contact time, less than 2% of the original olefin remained. Analysis of the reaction mixtures showed that rearrangement had occurred with very little addition of fluoride ion.

Other examples of fluoride-ion catalysed rearrangements are described in the literature. Perfluorodienes rearrange to perfluoro-acetylenes[103] when treated with anhydrous caesium fluoride at 150° for ½ hr. This process has been regarded as a series of SN_2' displacements of fluoride ion.



The isomerisation of β-substituted perfluoro-olefins[118] is also catalysed by fluoride ion.

$$C_6H_5C(C_2F_5) = CF_2 \xrightarrow[\text{diglyme}]{F^-,\ 100^\circ} C_6H_5C(CF_3) = CF\cdot CF_3$$

(cis & trans isomers)

Perfluorodimethyl ketene (XLIX) undergoes a rearrangement under the influence of fluoride ion,[111] to yield the isomeric perfluoromethacryloyl fluoride (L).

$$(CF_3)_2C{=}C{=}O \underset{}{\overset{F^-}{\rightleftharpoons}} [(CF_3)_2\bar{C}{-}\overset{O}{\overset{\|}{C}}{-}F] \overset{F^-}{\rightleftharpoons} CF_2{=}\overset{CF_3}{\overset{|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}F$$

(XLIX) (L)

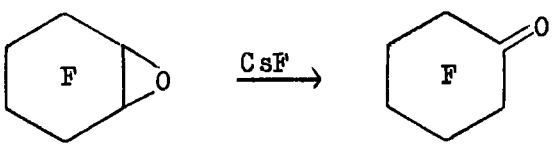
$$[(CF_3)_2\bar{C}{-}\overset{O}{\overset{\|}{C}}{-}F] \xrightarrow{H^+} (CF_3)_2CH\overset{O}{\overset{\|}{C}}F$$

This reaction occurs in a flow system over a bed of sodium fluoride at 300° and a pressure of 1 atmosphere.

The rearrangement of perfluoroepoxides is catalysed by heavier metal fluorides, affording acid fluorides[112] in the case of terminal epoxides, and ketones in the case of symmetrically substituted epoxides.

e.g. $CF_3CF\text{-}CF_2$ (epoxide) $\xrightarrow{CsF}$ CF_3CF_2COF

$$CF_3CF\text{-}CF_2 + CF_3\text{-}\overset{CF_3}{\overset{|}{C}}F\cdot COF \xrightarrow{CsF} (CF_3)_2CF\cdot CF_2O\overset{CF_3}{\overset{|}{C}}F\cdot COF$$



The rearrangement of unsaturated fluorine-containing nitrogen compounds catalysed by fluoride ion has been reported.

$$CF_3CF_2CF_2N{=}CF_2 \xrightarrow{F^-} CF_3CF_2CF{=}N{-}CF_3$$

e.g. $$CF_2{=}N{-}CF_2{-}N{=}CF_2 \xrightarrow{F^-} CF_3N{=}C{=}N{\cdot}CF_3$$

$$CF_2{=}N{-}CF_2CF_2{-}N{=}CF_2 \xrightarrow{F^-} CF_3N{=}CF{-}CF{=}N{=}CF_3$$

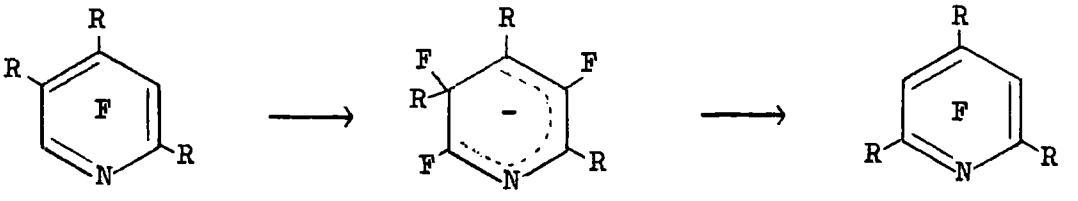
While these isomerisations were fairly rapid, perfluoro-(2-aza-hex-1-ene) isomerises only in the presence of a strong source of fluoride ion e.g. CsF, and perfluoro-(2-aza-3-methyl-but-1-ene) does not isomerise at all.[113]

Difluorocyanamide[114,117] rearranges rapidly, and almost quantitatively, to difluorodiazirine (LI) in the presence of CsF.

$$F_2NCN \xrightarrow[24^\circ]{CsF} F_2C\begin{smallmatrix}N\\ \|\\ N\end{smallmatrix}$$

(LI)

More recently the rearrangement of a polyfluoro-alkylated aromatic system has been observed.[115] It has been shown that in the presence of potassium fluoride perfluoro 2,4,5-tri(isopropyl)pyridine (LII) is rearranged to the perfluoro 2,4,6-tri-isopropylpyridine (LIII).

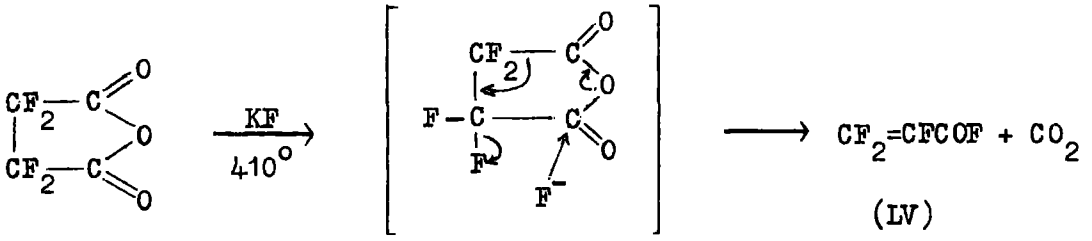


(LII) (LIII)

(R = $CF(CF_3)_2$)

When the reaction was carried out in the presence of an excess of perfluoro quinoline, which is known to be easily polyfluoro-alkylated, some cross over products were observed which indicated that an intermolecular process occurred.

In a recent publication[127] the pyrolysis of tetrafluorosuccinic anhydride (LIV) was reported, and the yield of product, trifluoro-acryloyl fluoride (LV), shown to improve markedly when the pyrolysis was carried out over anhydrous potassium fluoride at 410°. Lower yields were realised when platinum or silica were used, but a 95% yield of acryloyl fluoride was obtained on pyrolysis over KF.



(LIV) (LV)

From these results it has been suggested that the mechanism involves catalytic intermolecular attack by fluoride ion since the same product was obtained when Pt and SiO_2 were used in the pyrolysis stage, the F^- being present in the solid by product, a residue containing sodium fluoride and a large proportion of carbon.

Direct vinyl substitution.

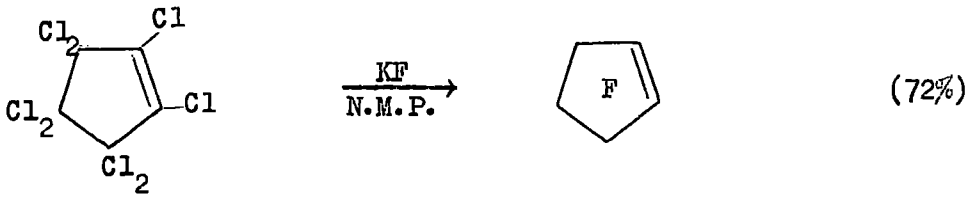
Substitution of vinylic chlorine in $CClF{=}CF{-}CClF_2$, by fluoride ion is considered to occur via two SN_2' processes. Although direct vinyl

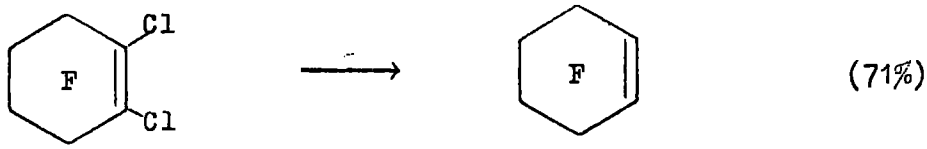
substitution by fluoride ion has not been established, it has been proposed as the first step in the reaction of $CClF{=}CCl{-}CF_3$ with potassium fluoride in formamide at 60° to give $CF_3CHClCF_3$.[94]

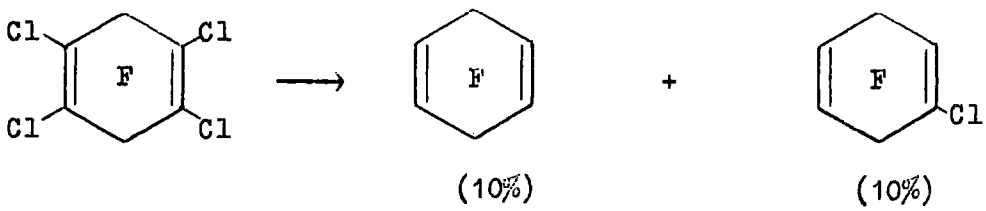
$$CClF{=}CCl{-}CF_3 \xrightarrow{F^-} CF_2{=}CCl{-}CF_3$$

$$CF_2{=}CClCF_3 \xrightarrow{F^-} [CF_3{-}\bar{C}Cl{-}CF_3] \xrightarrow{H^+} CF_3CHClCF_3 \qquad 52\%$$

The reactions of polychlorofluoro-olefins with potassium fluoride in N-methyl-2-pyrrolidone (N.M.P.) probably involve direct substitution of vinylic chlorine by fluoride ion. The reaction required a temperature > 190° and gave good yields of the perfluoro-olefins.[106]







Addition Reactions. Hydrogen fluoride.

In the previous reactions it was shown that when substitution of allylic or vinylic halogen by fluoride ion could occur it did so in preference to an addition process. When the addition of fluoride ion does take place then the resultant carbanion can abstract a proton from the solvent, as can be seen from the table of results.[94]

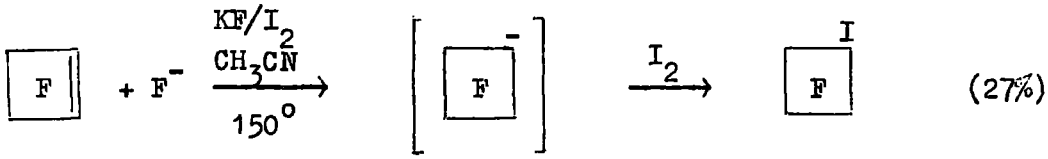
Olefin	Temp. °C	Reaction Time (a) hr.	Product	Yield %
$CF_2=CFCl$	55	3	CF_3CHClF	72%
$CF_2=CFCF_3$	25	5	CF_3CHFCF_3	60
$CF_2=CFCF_3$	65	b	CF_3CHFCF_3	21 [c]
$CF_2=CCl\cdot CF_3$	25	6	$CF_3CHClCF_3$	61
$CF_3CF=CFCF_3$	81	24	$CF_3CHFCF_2CF_3$	ca.35

[(a) - in a rocker shaker, (b) - bubbled very slowly through the KF-formamide solution, (c) - Recovered 50% of $CF_2=CFCF_3$].

As these reactions occurred in mildly basic media with a high concentration of fluoride ion, the only consistent mechanism involves the initial addition of fluoride ion.

$$F^- + F_2C{=}\overset{\curvearrowright}{C}{-} \quad \rightleftharpoons \quad [F_3C{-}\overset{-}{C}{-}] \xrightarrow{H^+} CF_3{-}\overset{H}{\overset{|}{C}}{-}$$

The carbanion generated by fluoride ion attack on a fluoro-olefin will also react with iodine[95] in acetonitrile solution affording fluoroalkyl iodides.

e.g.  (27%)

Alternatively the carbanion can react with other molecules of the olefin and polymerise.[119]

$$CF_3CF{=}CF_2 + KHF_2 \xrightarrow[25\text{-}30^\circ]{DMF} \begin{cases} CF_3CF{=}CFCF(CF_3)_2 & 98\% \\ CF_3CF_2CF{=}C(CF_3)_2 & 2\% \end{cases}$$

$$\text{and} \quad \begin{cases} (CF_3)_2CFC(CF_3){=}CFCF(CF_3)_2 & 44\% \\ (CF_3)_2C{=}C(CF_3)CF_2CF(CF_3)_2 & 51\% \end{cases}$$

An analogous process takes place with fluoro-aza-olefins:[120,121,130]

e.g. $CF_3N{=}CF_2 \xrightarrow{F^-} (CF_3)_2NCF{=}NCF_3$

$(CF_3)_2N.N{=}CF_2 \xrightarrow{F^-} ((CF_3)_2N.\bar{N}{=}CF_2) \longrightarrow (CF_3)_2NN{=}CFN\begin{matrix} CF_3 \\ \diagdown \\ \diagup \\ N(CF_3)_2 \end{matrix}$

$F_5SN{=}CF_2 \xrightarrow[225^\circ]{F^-} F_5SN{=}CFN(CF_3)SF_5$ [122]

Acid fluorides

The metal fluoride catalysed addition of COF_2 at the ethylenic bond in perfluoro-olefins has been shown[96] to yield the corresponding perfluoroacyl fluorides as illustrated in the following table, using caesium fluoride in acetonitrile with an excess of COF_2.

Olefin	Product	Temp.	Conversion %
$CF_3CF=CF_2$	$(CF_3)_2CFCOF$	50-100°	80
$CF_3CF=CFCF_3$	$CF_3CF_2CF(CF_3)COF$	150	62
$CF_3OCF=CF_2$	$CF_3OCF_2CF_2COF$	50-125	62
$\overline{CF_2CF_2CF=CF}$	$\overline{CF_2CF_2CF_2CFCOF}$	125-150	54
$CF_2=CF_2$	CF_3CF_2COF	100-150	13
$CF_3N=CF_2$	$(CF_3)_2NCOF$	50-150	56

The scope of this reaction has been demonstrated by treating hexafluoropropene with a variety of acylfluorides.[96]

Acylfluoride	Product	Conversion %
COF_2	$(CF_3)_2CFCOCF(CF_3)_2$	39
CF_3COF	$CF_3COCF(CF_3)_2$	75
nC_3F_7COF	$CF_3CF_2CF_2COCF(CF_3)_2$	60
$FCOCOF$	$(CF_3)_2CFCOCOCF(CF_3)_2$	28
$FCO(CF_2)_3COF$	$(CF_3)_2CFCO(CF_2)_3COCF(CF_3)_2$	75

As the acylfluorides have a displaceable fluorine they can react further with olefins to give ketones as shown in the table. It is assumed that these reactions proceed by the initial formation of a carbanion which then reacts with the acid fluoride e.g. $F^- + CF_2=CFCF_3 \longrightarrow (CF_3)_2\bar{C}F \xrightarrow{RCOF} (CF_3)_2CFCOR + F^-$ (where R = F or fluorocarbon group).

The reaction of hexafluoropropene with pentafluorobenzoylfluoride, and tetrafluoroisonicotinylfluoride in the presence of catalytic amounts

of potassium fluoride in acetonitrile solution, has been reported recently;[123] perfluoro(isopropylphenylketone) and perfluoro(isopropyl-4-pyridylketone) were obtained respectively.

Another product isolated from the reaction between pentafluorobenzoyl fluoride and hexafluoropropene was perfluoro(isopropyl-4-isopropylphenyl-ketone) (LVI) as a result of attack by perfluoroisopropyl anion on the perfluoro(isopropylphenylketone), (LVII).

$$C_6F_5COF \xrightarrow{(CF_3)_2\bar{C}F} C_6F_5COCF(CF_3)_2 \xrightarrow{(CF_3)_2\bar{C}F} (CF_3)_2C(F)C_6F_3COCF(CF_3)_2 + F^-$$

(LVII) (LVI)

That the ketone is formed before nucleophilic attack on the aromatic ring by the heptafluoro-isopropyl carbanion occurs, is substantiated by the fact that no perfluoro-(4-isopropylbenzoylfluoride) was isolated. Also, under the same reaction conditions, pentafluorobenzoylchloride did not react with perfluoroisopropyl anion. This suggests that the $COCF(CF_3)_2$ group is more powerfully electron attracting than the COCl and COF groups, as it activates the <u>para</u> fluorine atom to nucleophilic attack.

2. <u>Perfluoro-oxyanions</u>.

The preparation of perfluorinated alkoxides of the heavier alkali metals has been reported.[124] Treatment of potassium, rubidium and caesium fluorides with COF_2 afforded the corresponding trifluoromethoxides which are stable, crystalline, ionic solids. The general nature of the reaction was demonstrated by the synthesis of the analogous ethoxides, n-propoxides, iso-propoxides and n-butoxides from the appropriate acyl fluorides.

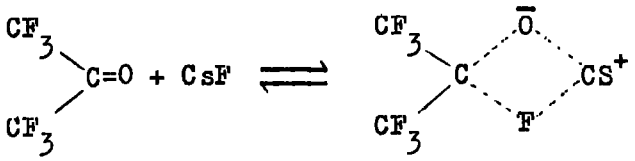
1) $MF + COF_2 \rightleftharpoons MOCF_3$

2) $MF + RfCOF \rightleftharpoons MOCF_2Rf$

3) $MF + (CF_3)_2CO \rightleftharpoons MOCF(CF_3)_2$

(where M = Rb or Cs, Rf = CF_3, C_2F_5 or C_3F_7)

It has been shown[97,98] that when tetrafluoroethylene was treated with a metal fluoride in an aprotic solvent, the addition of certain perfluoroketones results in a condensation affording the corresponding tertiary perfluoroalcohols. Generally the ketone is added to the metal fluoride-solvent slurry, when a soluble complex is formed.



Subsequent addition of tetrafluoroethylene produces the perfluoro-t-pentylalcohol. The formation of the ether anion $CF_3CF(CF_3)OCF_2CF_2^-$ was not detected indicating that the anion derived from the caesium fluoride complex is too weak a nucleophile to attack the tetrafluoroethylene. Hence $CF_3CF_2^-$ is strongly favoured as the active nucleophile. It was noted that in the presence of an excess of caesium fluoride the rate of formation of the alcohol was greatly increased, but the polymerisation of tetrafluoroethylene was observed.

Perfluorocarboxylic acids have been synthesised[99] by the direct addition of a metal fluoride-perfluoro-olefin complex, to carbon dioxide.

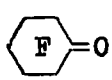
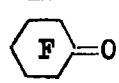
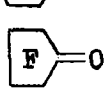
Acidification and distillation afforded the expected carboxylic acid. The condensation reaction proved to be reversible, the stability of the carboxylic acid metal salt decreasing with increasing complexity of the olefin. At 100° the condensation of tetrafluoroethylene and carbon dioxide was shown to be essentially quantitative. However, the thermal reversal of direction of the reaction,

$$Rf^- + CO_2 \rightleftharpoons RfCOO^-$$

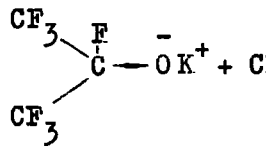
made it necessary to lower the reaction temperature from 100° for $CF_2=CF_2$ to 70° for $CF_3CF=CF_2$ and to 25° for $(CF_3)_2C=CF_2$.

Adducts of hexafluoroacetone[25,124,125] have been prepared from several metal fluorides, CsF, AgF and KF, and with tetraethyl ammonium fluoride, in acetonitrile and other polar organic solvents; adduct formation was not observed with NaF, LiF, ZnF_2, MgF_2, CuF_2 or BeF_2, attributed to the large lattice energy of these salts, and the stability of the adduct decreases with increasing lattice energy of the metal fluoride.[125]

The scope of the adduct formation was studied using several carbonyl compounds and the results are summarised below.

Carbonyl Compound	Metal fluoride	Temp. Change. °C.	Adduct formation
CF_3COCF_2Cl	KF	15	YES
$(CF_2Cl)_2CO$	KF	7	YES
$CF_2ClCOCFCl_2$	KF	0	NO
$CF_2ClCOCFCl_2$	CsF	6	YES
	KF	2	NO
	CsF	15	YES
	CsF	5	YES

The formation of an adduct was signalled by a rise in temperature on mixing the reactants, and confirmed by the isolation of a derivative from the reaction mixture. It was then shown that if the adduct was treated with an olefin, in the presence of a halogen, the corresponding ether (LVIII) was produced by attack of the fluorinated alkoxide anion on a halonium ion, or olefin-halogen complex.

e.g.  $+ CF_2{=}CH_2 \xrightarrow[CH_3CN]{\text{halogen}} (CF_3)_2CFOCF_2CH_2X$

(LVIII)

I_2, Cl_2, Br_2 and ICl were used (X = I with ICl)

Non-fluorinated olefins can be utilised in this synthesis, but when cyclic ketones and acid fluorides are used they must be perhalogenated.

The preparation of trifluoromethyl hypochlorite, reported recently,[126] involves a fluoride ion catalysed process. It was found that in the presence of CsF at -20°, COF_2 and ClF react to afford CF_3OCl. Similarly with hexafluoroacetone the corresponding isopropyl hypochlorite (LIX) was isolated.

$$(CF_3)_2CO + ClF \xrightarrow[-20^{\circ}]{CsF} (CF_3)_2\overset{F}{C}OCl$$

(LIX)

and $O{=}SF_4 + ClF \xrightarrow[-20^{\circ}]{CsF} SF_5OCl$

In the presence of fluorine and a metal fluoride e.g. KF, RbF or CsF, the fluoro-oxyperfluoroalkyl compounds can be synthesised.[132]

X = Rf or F, Y = Rf or F, M = K, Rb, Cs.

e.g.

$COF_2 + F_2 \xrightarrow{MF}$	CF_3OF	97%
$CF_3COF + F_2 \longrightarrow$	C_2F_5OF	96%
$C_2F_5COF + F_2 \longrightarrow$	C_3F_2OF	97%
$(CF_3)_2CO + F_2 \longrightarrow$	$(CF_3)_2CFOF$	98%

$$NF_2CF_2COF + F_2 \xrightarrow[-78^\circ]{CsF} NF_2CF_2CF_2OF$$

$$CF_3CF(NF_2)COF + F_2 \longrightarrow CF_3CF(NF_2)CF_2OF$$

By a similar process bis(fluoroxy)difluoromethane (LX) has been prepared recently[139,140] in a pressure vessel at room temperature for up to 1 day.

$$CO_2 + F_2 \xrightarrow[25^\circ]{CsF} CO_2F_4$$

(LX)

3. Perfluoroanions containing sulphur or nitrogen

The generation of fluorocarbanions and fluoro-oxyanions, catalysed by fluoride ion, has been discussed in the previous sections. Displacement reactions on fluoro-sulphur and -nitrogen containing compounds have also been reported in the literature.

The treatment of inorganic and organic compounds containing C-N multiple bonds with SF_4 afforded organoiminosulphur compounds.[128]

e.g. $C_6H_5-N=C=O + SF_4 \longrightarrow \left[C_6H_5N(-C(=O)F)-SF_2F \right] \longrightarrow C_6H_5-N=SF_2 + COF_2$

$R-C\equiv N + SF_4 \longrightarrow \left[R-C(F)=N-SF_2F \right] \longrightarrow RCF_2N=SF_2$

$KSCN + 3SF_4 \longrightarrow 2CF_3N=SF_2 + 3S + 2KF$

When a mixture of hexafluoropropene and an iminosulphur difluoride was treated with powdered CsF at 80°-90° the perfluorocarbanion generated, complexed with the sulphur atom, and fluoride ion was eliminated.[129]

$$CF_3N=SF_2 + CF_3CF=CF_2 \xrightarrow[83^\circ,\ 5\ hrs.]{CsF} CF_3N=SF-CF(CF_3)_2$$

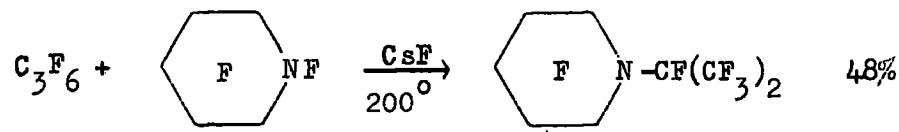
Similarly, $C_2F_5N=SF_2$ and $C_3F_7N=SF_2$ afforded the corresponding perfluoroethyl and -propyl imino sulphur difluorides.

The reaction between NF_3, CF_3CN and $CF_3CF=CF_2$ at 520°[120] with sodium fluoride afforded a mixture consisting mainly of iso-C_3 to C_6 fluorocarbons and fluorocarbon imines. However when NaF was replaced by CsF the reaction proceeded at a reduced temperature, 320°, and different products were isolated, approximately equal amounts of $(CF_3)_2CFNF_2$, $(CF_3)_2C=NF$, and $(CF_3)_2CFCF(CF_3)_2$ were obtained.

The reaction was assumed to proceed by a radical mechanism, and the formation of $(CF_3)_2CFCF(CF_3)_2$ indicated that such a mechanism was responsible in part, but such an effect involving a change in the nature

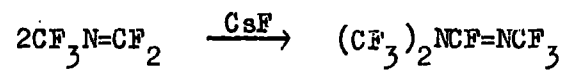
of the surface, but not the area, corresponds better to an ionic mechanism. When the reaction was carried out at 520° with CsF, only destructive fluorination was observed.

The same workers[130] have reported other reactions catalysed by fluoride ion. Hexafluoropropene will react with undecafluoro piperidine, in the absence of solvent, in the presence of CsF, to yield perfluoro isopropyl-N-piperidine (LXI).



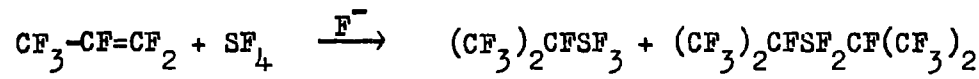
(LXI)

The dimerisation of $CF_3N{=}CF_2$ appeared to proceed via a negative ion process. At 25°C a 98% conversion of the azapropene to its dimer (LXII) was achieved using CsF and when passed over CsF with NF_3, only a high yield of the dimer was obtained at temperatures up to 450-500°.



(LXII)

Hexafluoropropene reacted easily with sulphur tetrafluoride in the presence of CsF.[137]



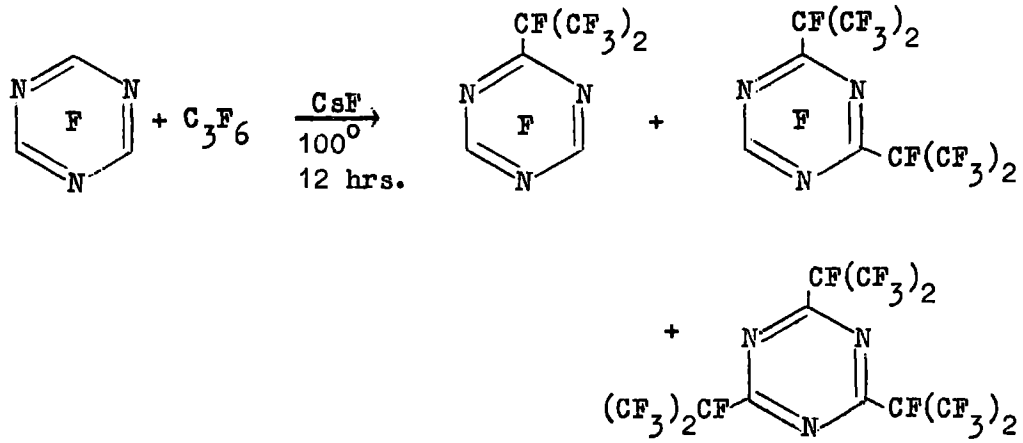
A similar reaction occurred, in the absence of solvent, with thionyl fluoride.[136,137]

$$CF_3\text{-}CF{=}CF_2 + SOF_2 \xrightarrow{F^-} (CF_3)_2CFSOF + (CF_3)_2CFSOCF(CF_3)_2$$

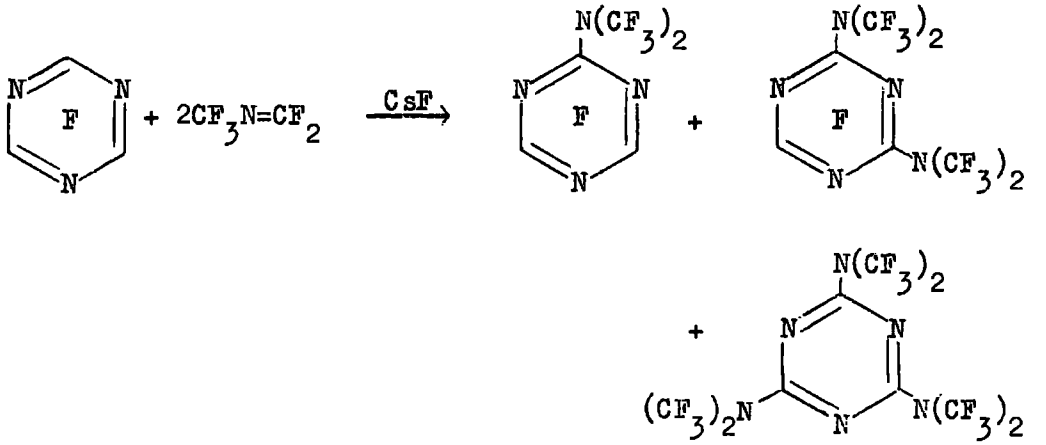
4. Perfluoroalkylation of aromatic compounds.

In the previous sections perfluoro-olefins were seen to react with acid fluorides in the presence of fluoride ion, yielding perfluoro ketones. Compounds containing fluorine atoms whose reactivity is comparable to that of an acid fluoride, in structures otherwise inert toward fluoride ion, should undergo similar reactions. Some reactions within this definition have recently been reported.[131,136]

The halotriazines are, in some respects, similar to acid halides and the fluorotriazines will undergo F^- catalysed reactions with polyfluoro compounds containing C-C or C-N unsaturation, for example cyanuric fluoride with C_3F_6 heated to 100° without solvent for 12 hrs. with CsF gave a mixture of mono-, bis- and tris(heptafluoroisopropyl)-triazines, in over 95% yield.



Under the same conditions, but using perfluoroazapropene in place of perfluoropropene, a similar reaction occurred,[131] affording the mono-, bis- and tris-(perfluorodimethylamino)-substituted triazines in the ratio 1:2:1.



However when a less reactive substrate was employed i.e. C_6F_5Br, C_6F_6, neither C_3F_6 nor $CF_3N{=}CF_2$ reacted, even when a solvent was used, and the temperature was raised to 175°.

Benzene and halogenated benzenes have been polyfluoroalkylated[133] by reaction with tetrafluoroethylene and an alkali metal fluoride at 280-370°. Mono- and poly-substitution occur, $C_2F_4H^-$, CF_3^- and $C_2F_5^-$ groups are introduced into the aromatic ring.

Similar reactions have been carried out using pentafluoropyridine,[100,101,115] a more reactive substrate than hexafluorobenzene.[74,75] Treatment of pentafluoropyridine with C_3F_6 and KF in sulpholan in a Carius tube at 120° afforded perfluoro-(4-isopropylpyridine) (LXIII), the major product, and a trace of the 2,4-disubstituted pyridine (LXIV).

$$C_5F_5N + CF_3CF{=}CF \xrightarrow[130^\circ,\ 12\ hr.]{KF,\ sulpholan} \underset{(LXIII)}{4\text{-}[(CF_3)_2CF]C_5F_4N} \quad 94\%$$
$$+\ 2,4\text{-}[(CF_3)_2CF]_2C_5F_3N \quad (trace)$$
$$(LXIV)$$

The conditions were varied in order to establish the relative effectiveness of sulpholan, diglyme, triglyme, and dimethylformamide as solvents and KF and CsF as initiators. Two series of reactions were carried out, one with KF in different solvents at 130°, and the other with KF or CsF at 20°. The results are shown in the following table.

Reaction of Pentafluoropyridine (3·0 g.) and C_3F_6 (5·0 g.)

Initiator-solvent	Temp.	Total yield (g)	Mono-substituted product (g)	Perfluoro pyridine recovered (g)	Conversion of perfluoro-pyridine %	Yield % (based on perfluoro pyridine (consumed)	Olefin dimers etc. (g)
KF/diglyme	130°	5·0	1·3	2·0	33	69	1·7
KF/triglyme	130	6·3	2·7	1·5	50	95	2·1
KF/DMF	130	6·0	2·4	1·38	54	79	2·18
KF/sulpholan	130	8·0	4·8	0·32	89	95	2·88
KF/diglyme	20	4·5	0·23	2·73	9	45	1·5
KF/sulpholan	20	6·5	3·38	1·1	63	94	2·52
CsF/diglyme	20	6·0	1·9	1·8	40	84	2·3
CsF(8g)/diglyme	20	6·5	2·0	1·74	42	84	2·26
CsF/sulpholan	20	7·3	4·7	0·37	88	95	2·9
CsF(8g)/sulpholan	20	8·5	5·61	0·07	98	100	2·82

All reactions in Carius tubes (100 ml.) with solvent 15 ml.). All reactions at 20° were shaken. Except where stated quantity of fluoride was 3·0 g.

As can be seen from the results sulpholan is the most useful solvent for this system; however this may not apply to others particularly where different fluoro-olefins are employed. Tetraglyme appears to be more effective than sulpholan in reactions with octafluorotoluene. Caesium fluoride is more effective than potassium fluoride as an initiator, in agreement with the results of the study of fluorination reactions with alkali metal fluorides,[134] in which the effectiveness of the fluoride decreases with increase in lattice energy.[125,135]

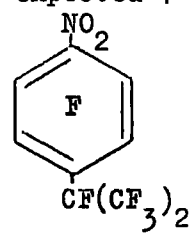
These polyfluoroalkylation reactions occur, at least partly, in solution which highlights the importance of the effect of the gegenions on the nucleophilic strength of the fluoride ion;[110] the smaller gegenions apparently have a greater influence, which could be interpreted in terms of their solvation. These reactions in which KF was used without a solvent were unsuccessful, whereas those in which CsF was used proceeded as expected but with less efficiency in the absence of a solvent.

When the reactions were carried out at higher pressures 150° 30 ats. in an attempt to increase the concentration of olefin at the reaction site, 4-, 2, 4-bis-, and a mixture of 2,4,5- and 2,4,6-(heptafluoroisopropyl)isomers were obtained.[101,115,116] However when tetrafluoroethylene was used in place of hexafluoropropene a mixture of mono- to penta-kis-pentafluoroethyl derivatives was realised. The greater reactivity of the primary anion $CF_3CF_2^-$, compared with the secondary anion $CF_3\bar{C}FCF_3$, was illustrated by the reaction of the $CF_3CF_2^-$ at the 3- and 5- positions of pentafluoropyridine which

were not substituted by the $(CF_3)_2\bar{C}F$. This is in agreement with Andreades' findings[138] that a secondary carbanion $(CF_3)_2\bar{C}F$, is more stable than a primary anion $CF_6\bar{C}F_2$, and hence the latter would be expected to be a more effective nucleophile. Also greater steric requirements would inhibit polysubstitution by the former.

To study the scope of the reaction several polyfluorobenzenes with various substituents were investigated. The expected 4-substituted products were obtained using octafluorotoluene and methylpentafluorobenzoate. With pentafluoronitrobenzene however, displacement of the NO_2 group led to m- and p- disubstituted products in addition to the expected 4-isopropyl derivative.

$$C_6F_5NO_2 + CF_3CF{=}CF_2 \xrightarrow[12\ hr.\ 120^\circ]{KF,\ sulpholan}$$



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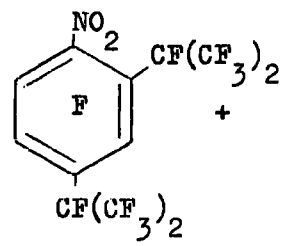

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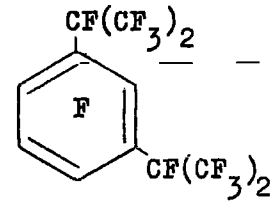

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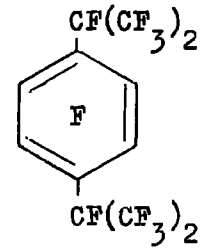
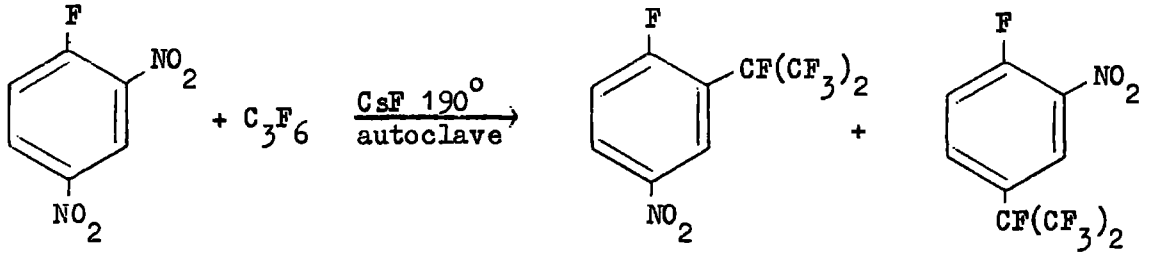


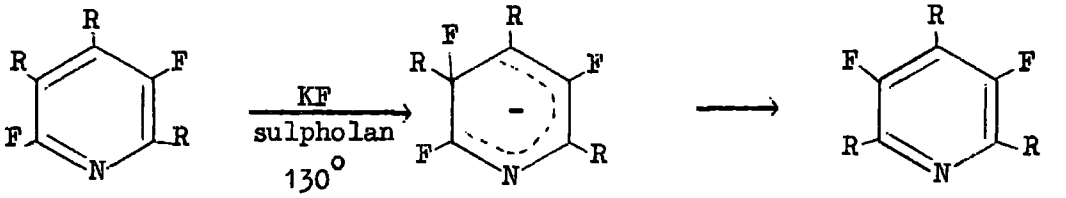
No reaction occurred with hexafluorobenzene,[131] bromopentafluorobenzene or 1,3,5-trichlorotrifluorobenzene. The reaction with benzonitrile however could only be controlled at 20°C when the 4-heptafluoroisopropyl derivative

was obtained. With 2,4-dinitrofluorobenzene, the NO_2 group was displaced as with pentafluoronitrobenzene.



The low yield of these derivatives is attributed to abstraction of ring protons by F^- in aprotic solvent, and the tendency for the olefin to give high molecular weight material in the presence of alkali metal fluorides.[119]

Further investigation of these polyfluoroalkylation reactions[115] has shown that under the influence of fluoride ion the polyfluoroalkyl groups migrate within the aromatic system.



$$R = CF(CF_3)_2$$

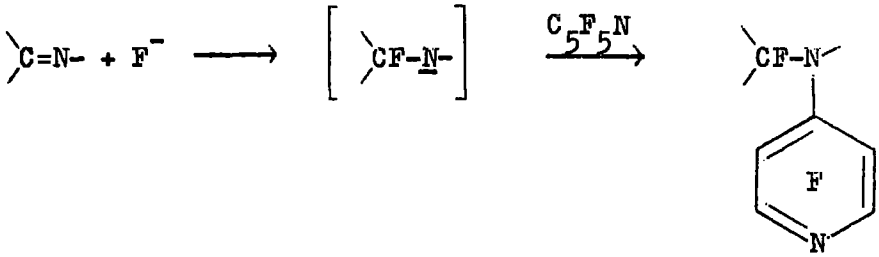
The 2,4,5-trisubstituted isomer, obtained in greater yield after a short reaction time, and the 2,4,6-trisubstituted isomer, are the products of kinetic and thermodynamic control respectively.

CHAPTER VI

DISCUSSION OF EXPERIMENTAL WORK (PART II)

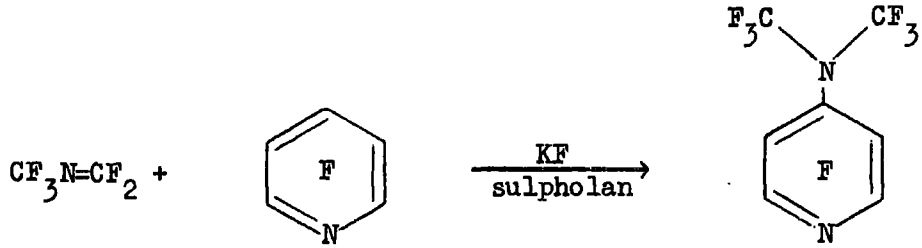
Introduction

The reactions of carbanions generated by the action of fluoride ion on fluoro-olefins are well established and have been discussed in the previous section. Perfluoro-oxyanions, generated in a similar manner, have been shown to undergo analogous nucleophilic reactions, but little work has been carried out with the corresponding fluoroaza-anions. The aim of this work was to synthesise fluorinated tertiary amines by nucleophilic attack of the anion produced by addition of fluoride ion to a C=N linkage, on suitable substrates.

e.g. 

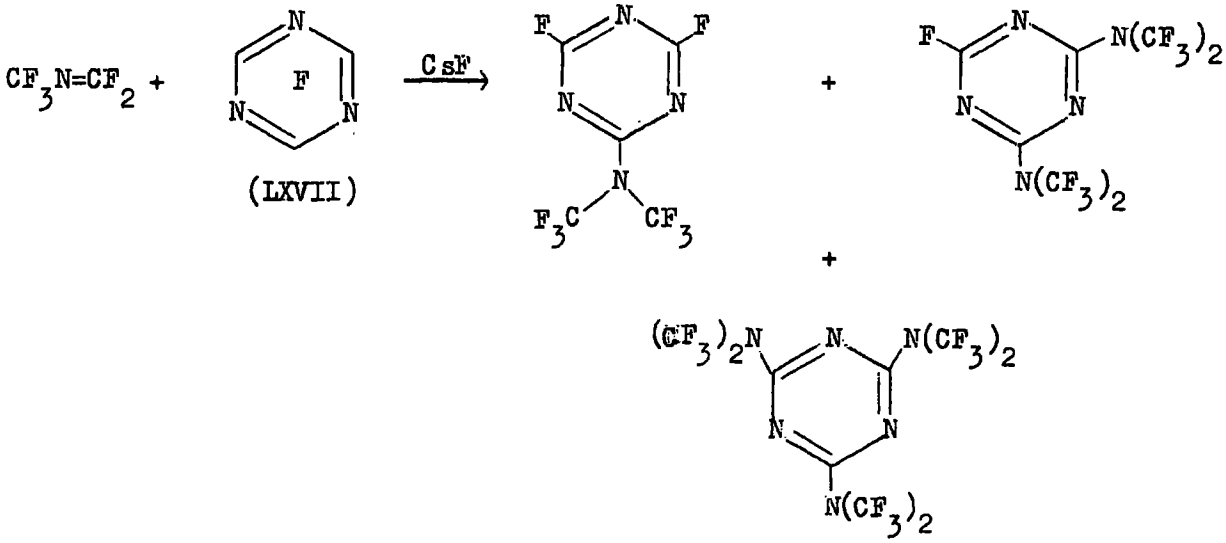
1. Reactions of the Exo- and Non-cyclic Fluoroimines with Fluoride Ion.

The preparation of perfluoro-(4-isopropyl pyridines), reported recently,[101] led to a study[145] of the conformational isomerism of these systems by ^{19}F n.m.r. spectroscopy. Large energy differences were shown to exist between the various conformations, and, as an extension of this work, the synthesis of perfluoro(methylenemethylamine) (LXV) was undertaken in order to prepare the corresponding perfluoro-4-(N-dimethylamino pyridine) (LXVI) and to investigate the ^{19}F n.m.r. spectrum.



(LXV) (LXVI)

The feasibility of this route had been demonstrated previously by Dressler and Young[131] who reacted perfluoro(methylenemethylamine) with a fluorotriazine (LXVII) in the presence of fluoride ion, and isolated mono-, di-, and tri-substituted products.



(LXVII)

The reaction of Pentafluoropyridine with Perfluoro(methylenemethylamine)(LXV)

Perfluoro(methylenemethylamine) was prepared according to the method of Haszeldine[143,144] by pyrolysis of the oxazetidine resulting from the reaction between trifluoronitrosomethane and chlorotrifluoroethylene.

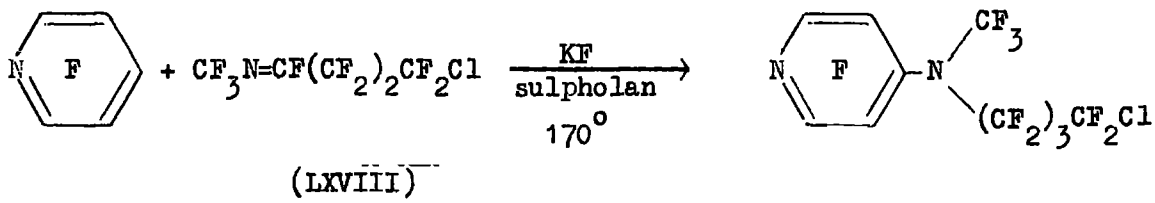
$$CF_3I + NO \xrightarrow[Hg]{U.V.} CF_3NO \xrightarrow[\text{Carius Tube}\ 70^\circ\ 24\ hrs.]{CF_2=CFCl} CF_3N(-O-CF_2-CFCl) \xrightarrow{Pyrolyse} CF_3N=CF_2 + (COFCl)$$

A mixture of CF_3NO and chlorotrifluoroethylene left at room temperature in a Carius tube for 1 week afforded a viscous liquid which, on pyrolysis, gave a mixture of $CF_3N=CF_2$ and $CF_3N=CFCl$. Several reactions were carried out using potassium fluoride, sulpholan, pentafluoropyridine and the perfluoro-(methylenemethylamine) in Carius tubes but in all cases only unreacted pentafluoropyridine was isolated from the reaction mixture. The failure of these reactions was attributed to the ease with which some of the aza-olefins and particularly perfluoro(methylenemethylamine) dimerize in the presence of fluoride ion.[121,122,130] In an attempt to induce the olefin to react with the substrate in preference to dimerization, the pentafluoropyridine, potassium fluoride, sulpholan mixture was heated to the reaction temperature and the perfluoro(methylenemethylamine) allowed to expand into the reaction mixture. It appeared that even under these conditions the pentafluoropyridine was not reactive enough to compete with the dimerization process only unreacted pentafluoropyridine was isolated. While the triazine (LXVII),[131] comparable

in reactivity with an acid halide, reacted with the olefin, the same authors showed that less activated systems like C_6F_6, C_6F_5Br did not afford the expected substituted products.

The reaction of Pentafluoropyridine with 1-Chloro-Decafluorobutylid-4-ene methylamine (LXVIII)

A further attempt to prepare a 4-(N-dialkylamino)pyridine involved the synthesis of 1-chloro-decafluorobutylid-4-ene methylamine. This compound was prepared by the fluorination of 3-chlorotetrafluoropyridine with CoF_3.[141] Treatment of this olefin (LXVIII) with fluoride ion would generate the corresponding nitrogen-containing anion which would then react in the expected fashion with pentafluoropyridine.



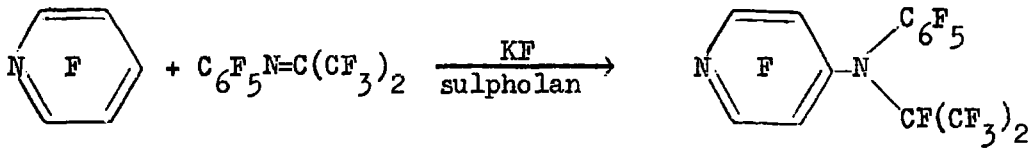
(LXVIII)

The only identifiable product isolated from this reaction however, was pentafluoropyridine which suggested that this olefin, like perfluoro(methylene-methylamine), may dimerize in the presence of fluoride ion rather than react with the pentafluoropyridine.

The reaction of Pentafluoropyridine with Perfluoro(N-isopropylideneaniline) (LXIX).

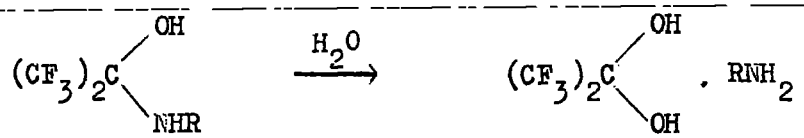
As an extension of this investigation the synthesis of perfluoro-(N-isopropylideneaniline) (LXIX) was undertaken with a view to preparing the

perfluoro-4-(N-isopropylanilinopyridine) (LXX) as shown.



(LXIX) (LXX)

Pentafluoroaniline and hexafluoroacetone were heated together in a Carius tube at 100° for 22 hours when the aminoalcohol adduct (LXXI; R = C_6F_5) was isolated. The inability of the aminoalcohols derived from hexafluoroacetone and hydrocarbon amines to undergo spontaneous dehydration has been reported recently[146] and this also appeared to be the case with the perfluoro(acetone-aniline) adduct. The same authors showed that the adducts (LXXI) were sensitive to traces of water, affording stable amine salts.



(LXXI)

Treatment of the aminoalcohols with dehydrating agents e.g. acetic anhydride, benzoyl chloride, did not yield the desired imines. When a sample of the perfluoro(acetone-aniline) adduct was allowed to stand for 24 hours, crystals of pentafluoroaniline were deposited, and, after a period of 1 week, analysis

of the small amount of supernatant liquid confirmed the absence of nitrogen. In spite of the strong donor properties of hydrated hexafluoroacetone[147,148] the weak basic nature of pentafluoroaniline does not appear to favour salt formation. A method originated by Middleton and Krespan,[149] had been used successfully to synthesise a number of fluoroimines from fluoroketones and hydrocarbon amines, employing cold, excess pyridine to promote the formation of fluoroalcohol salt, and phosphorus oxychloride in the dehydration step.

$$(CF_3)_2CO + RNH_2 \longrightarrow (CF_3)_2\overset{OH}{\overset{|}{C}}NHR \xrightarrow[POCl_3]{Py} CF_3\text{-}\overset{}{\underset{\underset{R}{|}}{\overset{||}{C}}}\text{-}CF_3$$

(R = H, Me, Et)

By using this procedure the perfluoro(N-isopropylideneaniline) (LXIX) was prepared. A solution of hexafluoroacetone and pentafluoroaniline in pyridine at low temperature, was treated with $POCl_3$ and then heated at 90° for 30 minutes. On work up the expected perfluoro(N-isopropylideneaniline) (LXIX) was isolated, and a 79% yield of the aminoalcohol adduct (LXXI; R = C_6F_5) obtained.

$$(CF_3)_2CO + C_6F_5NH_2 \xrightarrow[POCl_3]{Py} C_6F_5N{=}C(CF_3)_2$$

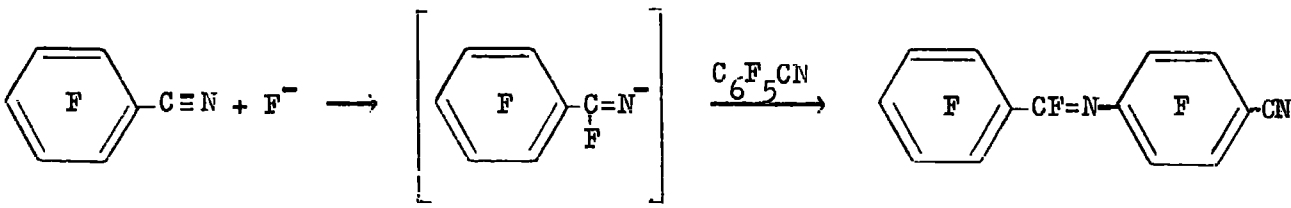
(LXIX)

On heating a mixture of the isopropylidene aniline and pentafluoropyridine with potassium fluoride in sulpholan however, only unreacted starting materials were obtained.

Reaction of Pentafluorobenzonitrile with Fluoride ion.

On the basis that the addition of fluoride ion to a carbon-nitrogen multiple bond in a perfluoro compound would generate the expected anion, the reaction of pentafluorobenzonitrile with potassium fluoride was investigated. Nucleophilic attack by the anion could then lead to polymeric products.

e.g.



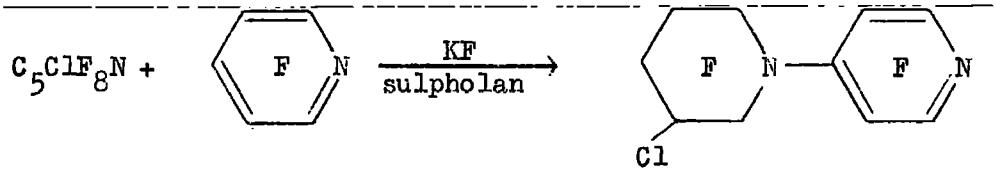
An equimolar mixture of the nitrile and potassium fluoride in sulpholan was heated in a Carius tube for 13 hours at 200° but on work up only unreacted benzonitrile was recovered. On repeating the reaction with a two-molar excess of potassium fluoride and heating at 150° only unreacted benzo-nitrile was obtained.

2. Reactions of the Cyclic fluoroimines with Fluoride ion.

The fluorination of 3-chloro-tetrafluoropyridine with CoF_3 by a method developed in these laboratories[141] provided a mixture of the 3- and 5-chloro-octafluoro-1-piperideines. (LXXII). The fluorination of 4-bromotetrafluoro-pyridine by a similar method afforded the corresponding 4-bromo-octafluoro-1-piperideine (LXXIII). On reacting these cyclic fluoroimines with substrates in the presence of fluoride ion the expected tertiary amines were obtained.

2,3,5,6-Tetrafluoro-4-(3'-chlorononafluoropiperidino)pyridine (LXXIV).

This compound was prepared by heating an equimolar mixture of pentafluoro-pyridine and the monochloropiperideines (LXXII) with potassium fluoride in sulpholan. Addition of fluoride ion to the sp^2 carbon of the C=N bond in both isomeric piperideines would yield the same anionic species. Nucleophilic attack by this anion would then be expected to occur at the 4-position in pentafluoro-pyridine, the most reactive site for nucleophilic substitution.[74,75]



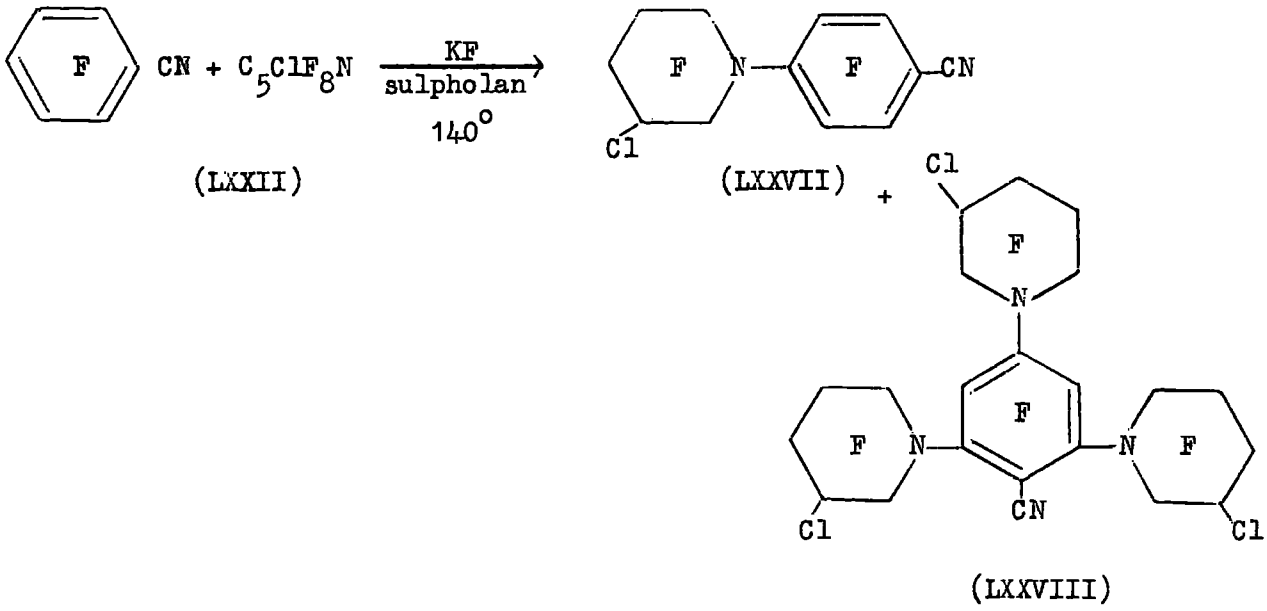
(LXXII) (LXXIV)

In addition to the expected product (LXXIV) another compound was isolated from the reaction mixture and identified as perfluoro(4-piperidino pyridine) (LXXV) arising from the replacement of the chlorine atom during the course of the reaction. No poly-substituted products were isolated from the reaction mixture.

The orientation of nucleophilic attack in pentafluoropyridine has been established as occurring predominantly at the 4-position, subsequent substitution then taking place at the 2- and 6-positions. On reacting the 3'-chloropiperidinopyridine (LXXIV) with potassium methoxide a dimethoxy derivative was isolated which was identified as the expected 2,6-dimethoxy compound (LXXVI) from the ^{19}F n.m.r. spectrum.

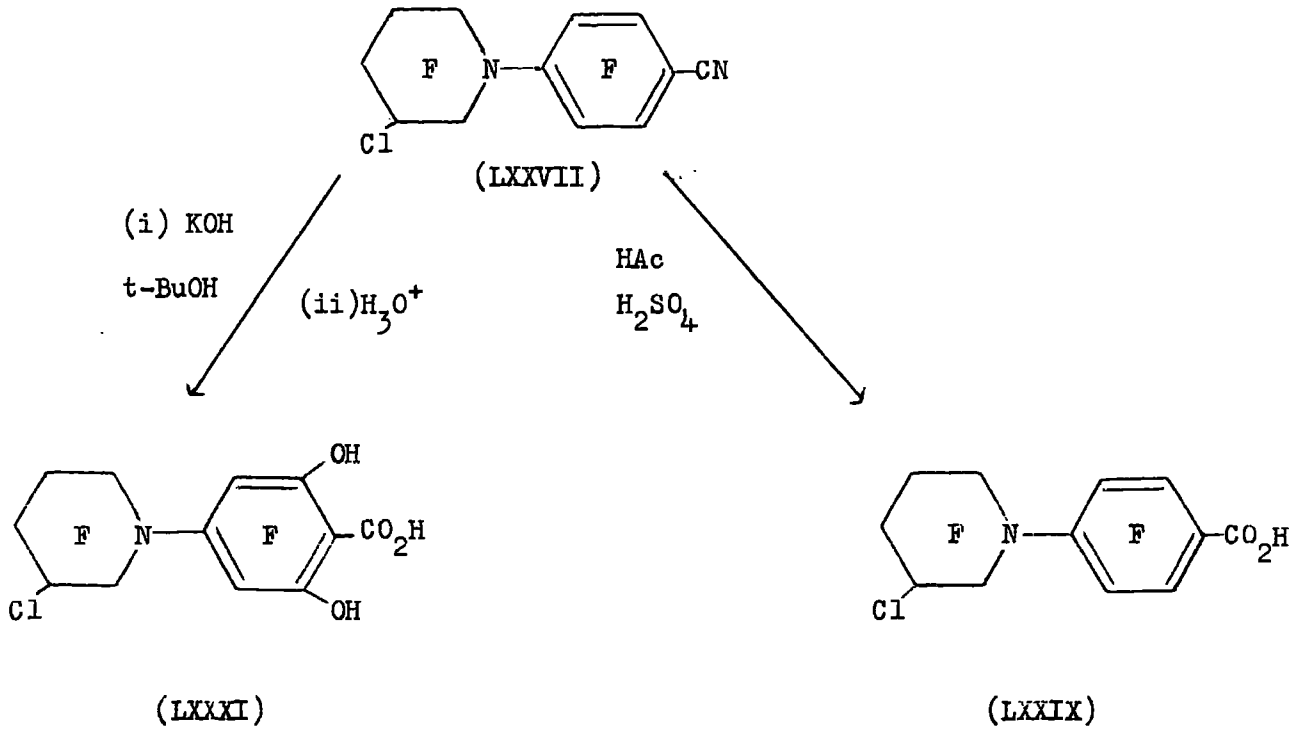
2,3,5,6-Tetrafluoro-4-(3'-chlorononafluoropiperidino)benzonitrile (LXXVII)

A method similar to that used in the previous reaction was employed in the preparation of this compound. An equimolar mixture of the pentafluorobenzonitrile and the monochloropiperideines (LXXII) was heated in a Carius tube with potassium fluoride and sulpholan. On work up the expected 4-piperidinobenzonitrile (LXXVII) was isolated, but unlike the analogous reaction with pentafluoropyridine a small amount of the trisubstituted benzonitrile (LXXVIII) was also obtained. No disubstituted product was isolated. The ^{19}F n.m.r. spectrum of the 4-piperidinobenzonitrile (LXXVII) was very similar to that of the corresponding pyridine analogue showing a signal at 79 p.p.m. assigned to the 2,6-fluorines, which was absent in the spectrum of the trisubstituted product. These results are consistent with the expected orientation of attack on the benzonitrile, occurring initially at the 4-position and then at the 2,6-positions.



(LXXII) (LXXVII) (LXXVIII)

On boiling a mixture of the monosubstituted nitrile (LXXVII), glacial acetic acid and concentrated sulphuric acid under reflux for 6 hours, hydrolysis occurred to afford the corresponding piperidinobenzoic acid (LXXIX) whereas similar treatment of the trisubstituted compound afforded the amide (LXXX). The bulky piperidino groups in the 2- and 6- positions might be expected to hinder hydrolysis. Alkaline hydrolysis of the monosubstituted nitrile (LXXVII) was effected by boiling a solution of the compound under reflux in t-butanol with KOH, when nucleophilic substitution also occurred.

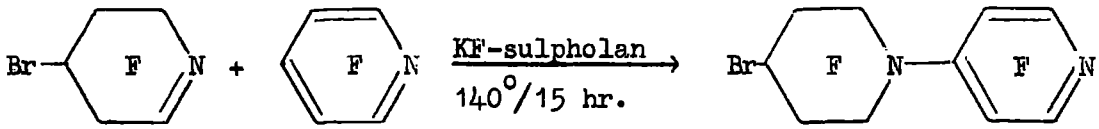


An examination of the ^{19}F n.m.r. spectrum of the dihydroxy acid (LXXXI) showed the absence of the signals assigned to the 2,6-fluorines present in the spectrum of the piperidinobenzoic acid (LXXIX). The ^{1}H n.m.r. of the dihydroxy acid showed two signals in the ratio 1:2 at -3τ and $2{\cdot}5\tau$ attributed to the carboxylic and phenolic protons respectively.

2,3,5,6-Tetrafluoro-4-(4'-bromononafluoropiperidino)pyridine (LXXXII).

Using a procedure similar to that employed in the previous experiments with the chloropiperideines, an equimolar mixture of 4-bromo-octafluoro-1-piperideine[141] (LXXIII) and pentafluoropyridine was heated in a Carius tube with potassium fluoride and sulpholan at 140° for 15 hrs. On work-up the

expected 4-bromopiperidinopyridine (LXXXII) was obtained, together with some unreacted starting materials.



(LXXIII) (LXXXII)

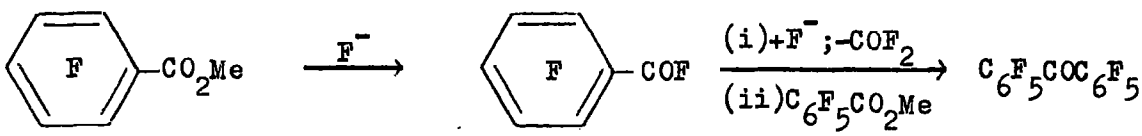
The ^{19}F n.m.r. spectrum of the product (LXXXII) showed a signal at 79 p.p.m. downfield from C_6F_6 attributed to the 2,6-fluorines of the pyridine ring.

Reactions of the mono-chloropiperideines (LXXII) with other C_6F_5X compounds

These reactions were initially investigated using Carius tubes according to the procedure used previously. A mixture of pentafluorobromobenzene and the chloropiperideines (LXXII) was heated in a Carius tube with potassium fluoride and sulpholan at 170° for 18 hours but on work-up only unreacted starting material was recovered. The reaction was repeated using the 'flow' method employed with perfluoro(methylenemethylamine) described previously, (page 115), and again on work-up only starting materials were isolated. The Carius tube reaction was repeated using pentafluorobenzene in place of pentafluorobromobenzene and this was also unsuccessful. In a further attempt ethyl pentafluorobenzoate, a more reactive substrate, was employed. The methyl ester had been reacted with perfluoropropene[101] in the presence of fluoride ion, and shown to give the expected 4-isopropyl derivative. However several experiments were performed in Carius tubes and by the 'flow' method

but the only identifiable compound isolated was unreacted ethyl pentafluorobenzoate. Under more vigorous conditions intractable tarry liquids were obtained from which only small amounts of unreacted starting ester were isolated.

In another experiment equimolar amounts of methyl pentafluorobenzoate and the chloropiperideines (LXXII) were heated in a Carius tube with potassium fluoride and sulpholan at 170° for 16 hours. On work-up unreacted ester and starting piperideine were recovered, and in addition a white solid was sublimed from the crude residue remaining after distillation. This solid was identified as decafluorobenzophenone by comparing its infrared spectrum with that of an authentic sample. The ^{19}F n.m.r. spectrum showed the pattern expected for a C_6F_5X compound. It appears that under these conditions nucleophilic attack on the aromatic ring is not favoured, reaction occurring at the site of the functional group. A possible mechanism for this reaction would involve nucleophilic displacement of the methoxy group by fluoride ion followed by loss of COF_2 and nucleophilic attack of the resulting carbanion on the electron deficient carbonyl carbon of another molecule of ester.

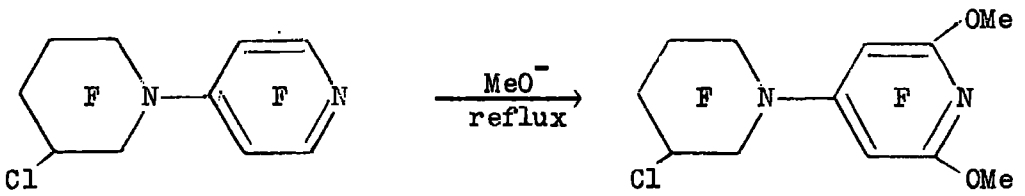


The reactivity of acid halides toward anions in the presence of fluoride ion has been demonstrated previously[96,123] but the resulting ketones were formed by a nucleophilic displacement on the acyl carbon by the fluoride

ion generated carbanion. In some cases further attack then occurred in the aromatic ring due to the activating influence of the $-COR_f$ group. However in the methyl benzoate reaction no other identifiable product was isolated.

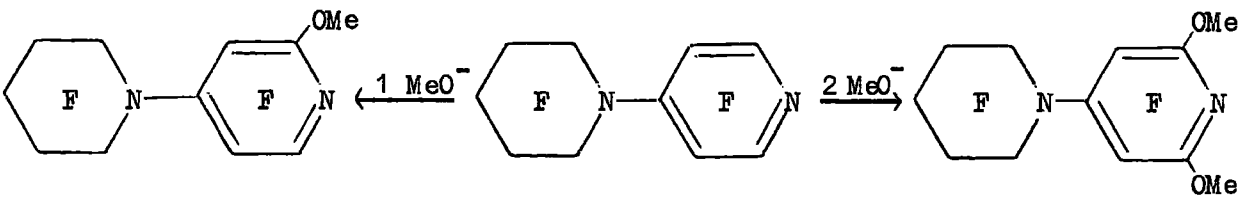
3. Nucleophilic substitution reactions of the Piperidinopyridines.

Treatment of the 3'-chloropiperidinopyridine (LXXIV) with excess methoxide afforded the 2,6-dimethoxy derivative (LXXVI) the expected positions of substitution being confirmed from the ^{19}F n.m.r. spectrum.



(LXXIV) (LXXVI)

When a similar reaction was carried out with the perfluoropiperidinopyridine (LXXV) and a two molar quantity of methoxide, in addition to disubstitution (LXXXIII) there was some evidence from the mass spectrum of the crude product that a third molecule of methoxide had entered the ring. When an equimolar mixture of the perfluoropiperidinopyridine (LXXV) and methoxide was boiled under reflux the expected mono-methoxy derivative (LXXXIV) was isolated.



(LXXXIV) (LXXV) (LXXXIII)

By analogy with the (N-dialkylamino)benzenes,[53,56] steric repulsion between the 3,5-pyridine fluorines and the fluorines adjacent (α) to the piperidine nitrogen would force the plane of the lone pair on the latter

atom out of the plane perpendicular to the aromatic ring. Under these conditions delocalisation of the piperidine nitrogen lone pair into the π-system would not be favoured and hence little de-activation of the 2,6-positions would be expected. In a competition reaction between the piperidinopyridine (LXXV) and perfluoro-4-cyclohexylpyridine[150] for methoxide ion, it was shown that the cyclohexylpyridine reacted three times as rapidly as the piperidinopyridine. Known quantities of the cyclohexyl- and piperidinopyridines were boiled under reflux with a 0·1 molar quantity of methoxide, being allowed to compete for the nucleophile over a period of 22 hours. The reaction product was extracted with ether, distilled to low volume and diluted to 10 ml. with methanol, in a volumetric flask. An examination of this solution and a calibration mixture containing accurately known amounts of both starting materials and their mono-methoxy derivatives, by g.l.c. (Gas Density Balance), enabled a quantitative measure to be made of the relative reactivity of the substrates. The relationship between chromatographic peak areas and weight of component was calculated by simple proportions using nitrobenzene as an arbitrary response standard. The ratio of methoxy-cyclohexylpyridine to methoxy-piperidinopyridine was approximately 75:25.

4. ^{19}F n.m.r. spectra of the Piperidino substituted compounds

That these spectra were not first order was apparent on integration when certain anomalies were observed in the relative intensities of the signals, however on inspection certain structurally significant factors emerged. The more poorly resolved signals at higher field could not be accurately assigned but an investigation of spectra taken at elevated temperatures led to a partial assignation.

On the basis of evidence in the literature[151-158] and molecular models the equatorially substituted chair form of these compounds would be expected to predominate, and by analogy with the ^{19}F n.m.r. spectra obtained for the perfluoro-4-alkylpiperidines,[153,154,155,157] (Tables 7-11) the resonances were assigned as shown in Table 6 (page 130).

In principle, axial and equatorial protons in cyclohexane resonate at different fields and so the n.m.r. spectrum might be expected to consist of two lines, probably further split by spin-spin coupling. That only one line is seen, at room temperature, implies the two (most stable) chair forms are in such rapid equilibrium that a time averaged n.m.r. spectrum is obtained. When cyclohexane is cooled ($-90 \rightarrow -100^{9}$) the rate of chair interconversion is reduced and two sets of signals are observed[130] corresponding to the equatorial and axial fluorines. A similar situation has been observed in the case of piperidine where the chair form is preferred, in the absence of H-bonding, and it appeared that N-substituents take up an equatorial position. However, due to inversion about the N atom, a time averaged n.m.r.

6

Constants for the Piperidino Compounds

	Internal Chemical Shifts					
	Equatorial 3',5' and 3,5.(d.d.) 3,5	3',(5')	Axial and equatorial 4'(d.d.)	Reference Compound	2,6	3,5
	33 (89)	28 (113)	23 (80·6)	C_6F_5CN	48·7	29·6
	31	27	24	C_6F_5CN	-	27·6
	33 (80·5)	29 (137)	23 (88·5)	C_5F_5N	7·1	35·3
	35·5	30	25	C_5F_5N	-	37·8
	24·5		12	$C_6F_5CO_2H$	0·2	22·9
	24·0		6	$C_6F_5CO_2H$	-	22·4
	37·0 (96·5)	26·5 (137)	23 (129)	C_5F_5N	6·6	39·3

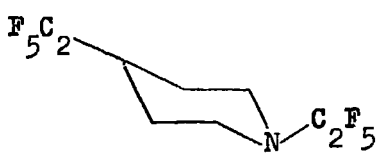
(d.d.- distorted doublet).

All n.m.r. spectra were measured on a Perkin Elmer R10 spectrometer. Chemical shifts expressed in p.p.m. downfield from C_6F_6 as reference, and coupling constants (c.p.s.) are shown in parentheses below each doublet.

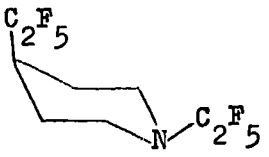
Compounds (LXXVII) and (LXXIV) measured as neat liquids, (LXXVI), (LXXXI) and (LXXXII) in Me_2CO solution, (LXXVIII) in $CHCl_3$ solution and (LXXIX) in CCl_4 solution.

spectrum is seen and in perfluoro-piperidine the temperature independence of the N-F absorption indicated that even at -74° there was rapid inversion at the nitrogen.

The n.m.r. spectrum of perfluoropiperidine[164] at -74° shows thirteen bands, twelve signals due to the magnetically different axial and equatorial fluorines in α β and γ positions relative to the ring nitrogen and one for the N-F. It is also known that in the substituted fluoro-cyclohexanes[151,152,156] the conversion of one conformation into another goes considerably more slowly than in the hydrogen-containing analogues, because of the size of the substituents, thus enabling the difference in chemical shifts of the axial and equatorial fluorines to be observed at room temperature. Often only one conformation is met, the equatorially substituted compound in the chair form. This is thought to be the more stable because strong repulsion is observed between axial substituents at the 2-, 4- and 6-positions and on this basis it was assumed that of the structures shown for perfluoro 1,4-diethylpiperidine,[153] (a) would be energetically the more favourable.



(a)

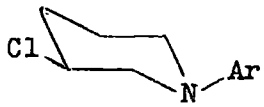


(b)

By analogy, the piperidino compounds were assumed to have similar

conformations in which the substituents were equatorially situated.

(Ar = C_5F_4N)



(Ar = C_5F_4N, C_6F_4CN, $C_6F_4CO_2H$ etc.)

All unmarked bonds to fluorine.

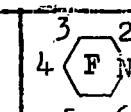
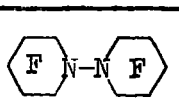
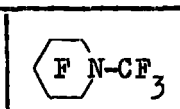
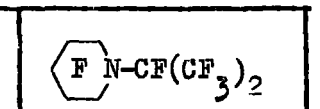
In all the spectra examined large coupling constants were observed of the order 200-280 cps for the distorted doublets which are too high to be assigned to the aromatic fluorines and so were attributed to axial and equatorial coupling in the piperidine ring. The largest coupling constants for perfluoro-pyridine, benzonitrile and benzoic acid derivatives are usually of the order 20-30 cps.[47,50,74,159,160,162]

The chemical shifts and J values assigned to the piperidine fluorines (Table 6) p.130-131, are of the same order as those given in the literature for fluorinated piperidines, (see Tables 7-11).

The most significant difference between the ^{19}F n.m.r. spectrum of the 4'-bromopiperidino-pyridine (LXXXII) and that of the 3'-chloropiperidino derivatives was in the number of signals attributed to the piperidine fluorines. In the case of the former compound three doublets were observed centred at 91·0, 64·5 and 54·0 p.p.m. downfield from C_6F_6 whereas the 3'-chloropiperidino derivatives showed six doublets in this area of the spectrum.

TABLE 7

^{19}F Chemical Shifts of some Perfluoro Piperidine Compounds[153,157]

Compound					
Position of fluorines (p.p.m. from C_6F_6)	2,6	50·96	64·56	66·86	64·26
	3,5	29·16	28·36	28·46	23·86
	4	26·95	27·46	25·86	42·46

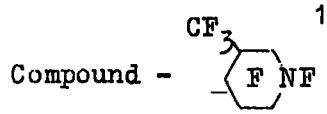
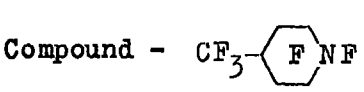
Compound -  [163]

TABLE 8

Position of fluorine	Chemical Shift (p.p.m.)	Coupling Constant (c.p.s.)
2a, 2e	60·3	-
6a	55·7	184
6e	49·5	191
4a,5a	41·2	175
4e	30·1	299
5e	23·7	299
3F	-21·7	-

(a - axial, e - equatorial
Shift downfield from C_6F_6)

TABLE 9

Compound -  [164]

Position of fluorine	Chemical shift (p.p.m.)	Coupling constant (c.p.s)
2a, 6a	57·6	199
2e, 6e	51·0	183
3a, 5a	44·8	285
3e, 5e	31·5	287
4F	-26·3	-

(a - axial, e - equatorial)

(- denotes shift upfield from C_6F_6)

TABLE 10 [163]

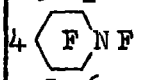
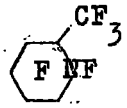
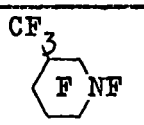
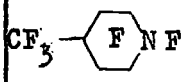
Compound	Axial/Equatorial chemical shift	Ring Position	$J_{ax/eq}$ (c.p.s.)
	6·5	2,6	185
	19·2	3,5	282
	17·6	4	285
	?	3,5	?
	13·6	2,6	156
	8·8	6	199
	11·2	3	293
	18·4	4,5	289
	~ 0	2	?
	6·2	6	198
	11·1	4	289
	17·6	5	284
	6·6	2,6	196
	13·3	3,5	286

TABLE 11

Perfluoro-N-fluoro piperidines [163]

Position of fluorines	Range of geminal coupling constants ($J_{ax/eq}$)	Mean
2,6	185-199	195
3,5	282-293	287
4	285-289	288

It has been shown that the deshielding of the piperidine fluorines increases with their proximity to the nitrogen atom[153] and hence those fluorine atoms α to the nitrogen will absorb at lowest field followed by the β-fluorines, the γ-fluorine absorbing at highest field. The presence of bulky substituents in the ring considerably reduces the already low rate of inversion of the two conformers[153] and this makes possible the separate recording of axial and equatorial fluorines. Also, Homer and Thomas[152] have deduced that in any perfluoromethylene group the equatorial fluorine will be more shielded than the axial and hence the latter would be expected to absorb at lower field. Thus in the case of the relatively symmetrical 4'-bromopiperidine (LXXXII) the lowest field doublet can be assigned to the 2',6'-axial fluorines, the next higher field doublet to the 2',6'-equatorial fluorines and the next doublet to the 3',5'-axial fluorines. In the case of the unsymmetrical 3'-chloro-piperidino derivatives the 3'-chlorine would deshield the vicinal fluorines, and hence a difference in chemical shifts would be expected for each of the piperidine fluorines. In a recent publication[163] the effect of a CF_3 substituent in a fluorinated piperidine was reported to deshield the vicinal equatorial fluorines by ~10 p.p.m. and the corresponding axial fluorines by ~4 p.p.m. The apparent electron withdrawing power of various groups have been reported by Tiers[161] as $I > Br > Cl > F >> CF_2I > CF_2Br > CF_2Cl > CF_3$ in systems like XCF_2Y, and on this basis a greater deshielding by Cl and Br than CF_3 would be expected resulting in a shift to lower field of the piperidine fluorines. Therefore the first six doublets observed in the spectra of the 3'-chloro-piperidino

derivatives can be assigned, from low field to high field, to the 2'-axial, 6'-axial, 2'-equatorial, 6'-equatorial, 3'-axial and 5'-axial fluorines.

The signal at 79 p.p.m. downfield from C_6F_6 in the spectra of the pyridine compounds (LXXIV) and (LXXXII) and benzonitrile derivative (LXXVII) was assigned to the 2,6-fluorines and the resonance in the region 33 to 37 p.p.m. from C_6F_6 assigned to the 3,5-fluorines. The shift to weaker field observed for these signals on comparison with the values given in Tables 12 and 13 can be attributed to the electron withdrawing effect of the piperidine substituent which might be expected to deshield the 3,5- more than the 2,6-fluorines. The remaining signals in the spectrum of the 4'-bromopiperidino compound (LXXXII) were a poorly resolved doublet at 26·5 p.p.m. and another doublet, with fine structure, at 23 p.p.m. downfield from C_6F_6. These were assigned to the 3',5'-equatorial and 4'-axial and equatorial fluorines respectively. Similarly the absorbances at 28-29 p.p.m. and 23 p.p.m. from C_6F_6 in the 3'-chloropiperidino compounds (LXXVII) and (LXXIV) were attributed to the 5'- and 4'-fluorines respectively. However in the case of the 3'-chloropiperidino compounds the coupling constants of the doublet centred at about 50 p.p.m. are characteristic of germinal axial and equatorial fluorines and hence could be attributed to the 5'- and not the 3'- axial fluorine. In this case the signal assigned to the 5'-fluorine at 27-30 p.p.m. from C_6F_6 would be attributed to the 3'-fluorine when a smaller vicinal coupling might be expected. However different coupling constants in this instance could be attributed to strain in the

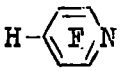
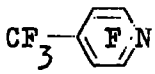
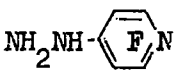
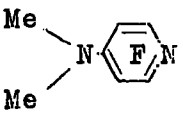
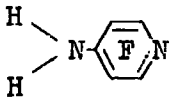
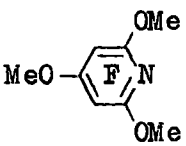
ring resulting in stronger vicinal coupling.

The signals in the spectrum of the tri-substituted nitrile (LXXVIII) were assigned in a similar fashion, the absence of a signal at 79 p.p.m. attributed to substitution in the 2,6-positions. At higher field the poorly resolved nature of the spectrum did not allow accurate measurement and this also proved to be the case with the di-methoxy pyridine (LXXVI). The two benzoic acid derivatives (LXXIX) and (LXXXI), showed similar ^{19}F n.m.r. absorptions, all the signals assigned to the piperidine fluorines being shifted to higher field (Table 6) the less electron-attracting nature of the phenyl ring having a smaller deshielding effect. As might be expected the aromatic fluorines in these two compounds would absorb at higher field than those in the corresponding pyridine and benzonitrile derivatives (see Tables 13 and 14, pages 140,141).[159] On this basis the signal at 23 p.p.m. in the spectrum of the acid (LXXIX) was assigned to the 2,6-fluorines and the poorly resolved signal at 24-24·5 p.p.m. from C_6F_6 in (LXXIX) and (LXXXI) attributed to the 3,5-fluorines. By analogy with the other spectra and from an integration of this portion of the spectrum it appeared that there was another resonance in this region superimposed on the 3,5-fluorine signal and this was attributed to the other fluorine in the β-position.

The effect of the piperidino substituent on the chemical shifts of the aromatic fluorines appeared to be predominantly deshielding. The 2,6- and 3,5-fluorines in the 4-substituted compounds (LXXVII), (LXXIV), (LXXIX) and (LXXXII) (see Table 6) are all shifted to low field to a slightly

TABLE 12

^{19}F Chemical Shifts of substituted Pyridines (p.p.m. downfield C_6F_6) 74,82,159

Compound	2,6	3,5
	68·05	19·56
	71·8	18·06
	64·7	-2·4
	65·24	3·0
	60·86	-6·34
	-	-6·84

(- denotes higher field than C_6F_6)

TABLE 13

22,44,68,159

^{19}F Chemical Shifts of 1,4-Disubstituted Tetrafluorobenzenes (p.p.m.C_6F_6)

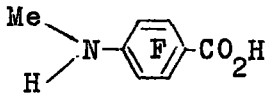
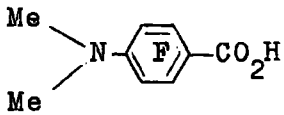
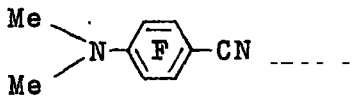
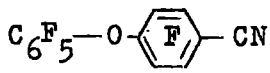
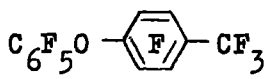
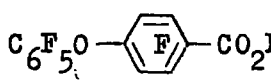
Compound	2,6	3,5
	19·6	0·96
	25·56	19·36
	17·46	-2·34
	18·06	8·16
	31·3	15·7
	30·46	8·66
	32·5	10·8
	21·36	5·16
	22·6	5·36

TABLE 14

Internal ^{19}F Chemical Shifts[159] in X-  and  -X

Group X	Pyridine 3,5	Pyridine 2,6	Benzene 2,6	Benzene 3,5
$-CO_2H$	-0·8	-2·55	-0·4	-1·9
-H	0·0	0·0	0·0	0·0
-OMe	20·1	0·39	19·7	1·7
-F	21·9	-3·84	25·4	1·2
$-NHNH_2$	22·0	3·39	17·8	0·1
-OH	22·0	1·39	24·9	2·0

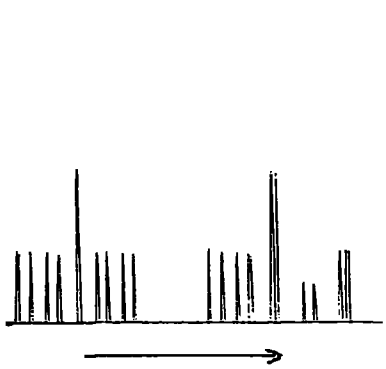
(- denotes higher field)

greater extent than that produced by a CF_3 group (see Tables 12-14).[159]

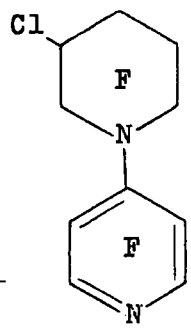
In the trisubstituted compounds (LXXVIII), (LXXVI) and (LXXXI) the shifts to lower field of the 3,5-fluorines are slightly less than those observed in the former parent compounds. While errors in measurement may have been incurred in the poorly resolved parts of the spectra these differences are significant and must be due to a slight shielding of the 3,5-fluorines.[82,159]

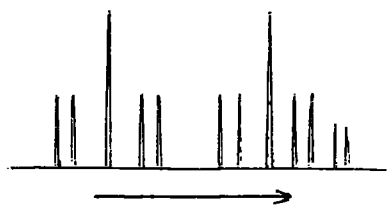
While the geminal coupling constants do not appear to have been greatly affected by substituents on the piperidine ring[163] the internal chemical shifts do show a dependence. In the 3'-chloropiperidino compounds (see Table 15, p.144) there is a progressive shift to stronger field with decrease in the electron attractive nature of the N-substituent. The spectrum of the 4'-bromopiperidinopyridine (LXXXII) shows a greater deshielding of the 3',5'-axial fluorines (see Table 6) probably due to their proximity to the 4'-Br atom.

The spectra obtained for the piperidino pyridines approximated to the following simplified figures



High field





High field

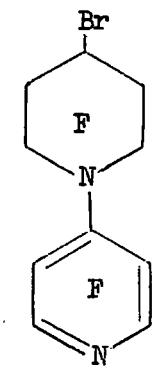
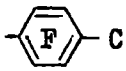
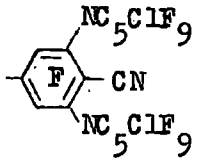
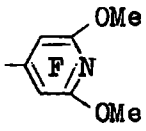
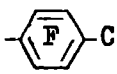
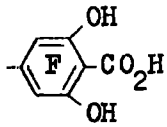


TABLE 15

Internal Chemical Shifts of Piperidine Fluorines (p.p.m.)

N-Substituent	Ring Substituemt	2',6' ax.	2',6' eq.	(3'),5' ax.	3'(5') eq.	4' ax./eq.
	3'-Cl	0,0	0,0	0,0	0	0
	"	0,0	0,0	0, -3	1	0
	"	0•5, 0•5	3, 3	3, 0	2	-1
	"	3, 2•5	3•5, 3	2, -5	-1	-2
	"	5, 5	1, 5	8, 4	4•5	11
	"	6, 5	1, 5	9, 4	5	17

(- denotes shift to lower field)

An examination of the spectra of the piperidinopyridine and benzonitrile compounds (LXXIV) and (LXXVII) over a temperature range up to 1200 revealed a change in intensity of the unsymmetrical doublet centred at 33 p.p.m. downfield from C_6F_6. The relative areas of the lower field and higher field limbs changed from approximately 2:1 at room temperature to 1:2 at 120°. On raising the temperature to 50° the intensity of the high field limb decreased and at 75° the signal appeared as an unresolvable multiplet until at 100° the signal was resolved into an unsymmetrical doublet of intensity ~1:2 centred at 33 p.p.m. downfield of C_6F_6. The inversion of intensities of this doublet was attributed to a change in conformation of the 3,5-fluorines of the aromatic ring with those α to the N in the piperidine ring.

In the piperidino-pyridine and -benzonitrile compounds examined the splitting of the 3,5-fluorine signal could not be measured in some cases due to poorly resolved spectra but values of 89 and 80·5 c.p.s. were obtained for compounds (LXXVII) and (LXXIV) respectively. This value is comparable with that observed for coupling between the 3,5-pyridine fluorines and the iso- propyl fluorines in 4-iso-propyl pyridine.[145]

CHAPTER VII

EXPERIMENTAL WORK (PART II)

Perfluoro(N-iso-propylidene aniline) (LXIX)

(i) A mixture of pentafluoroaniline (2 g.) and hexafluoroacetone (2 g.) was sealed under vacuum in a 100 cc Carius tube and heated at 100° for 22 hours. The tube was cooled, opened, and the contents allowed to reach room temperature and transferred under vacuum (25°/0·001 mm) to remove unreacted aniline, affording the unstable (amino alcohol adduct (LXXI; R=C_6F_5) (0·7 g., b.p. 120-125°) (Found: F, 60·0; N, 3·56. $C_9H_2F_{11}NO$ requires F, 59·9; N, 3·88%). The ^1H n.m.r. spectrum showed a broad signal at 5·7 attributed to the protons on nitrogen and oxygen. The ^{19}F spectrum showed two singlets at 89 and 84 p.p.m. assigned to the CF_3 groups, a multiplet at 12·7, triplet at 3·6 and a sextet at 1·8 p.p.m. downfield from C_6F_6 in the ratio 2:1:2 attributed to the o-, p- and m-fluorines of the C_6F_5 respectively. Over a period of 24 hours white crystals were deposited from the liquid and shown to be pentafluoroaniline by comparison of its infrared spectrum with that of an authentic sample. A similar sample was allowed to stand over a period of 1 week when analysis of the supernatant liquid confirmed the absence of nitrogen.

(ii) Hexafluoroacetone (8·5 g.) was condensed into an evacuated dry three-necked flask cooled in carbon dioxide-acetone and then let down to atmospheric pressure under dry nitrogen. A solution of pentafluoroaniline (8 g.) in dry pyridine (10 ml.) was added, and the flask fitted with a low temperature thermometer, reflux condenser, carbon dioxide 'cold finger' and a dropping funnel. The mixture was stirred magnetically for 1 hour at -78°

and then allowed to reach room temperature when phosphorus oxychloride (20 ml.) was added over 15 minutes. The flask and contents were then heated in an oil bath to 90°. As the temperature rose to 40° a precipitate formed becoming progressively thicker but eventually melting into immiscible oily drops. The mixture was stirred for ½ hour at 90° and then distilled to yield a pale yellow liquid (25°/0·001 mm.). Crystallisation of the residue from petroleum ether (b.p. 60-80°) gave the white perfluoro-(N-iso-propylidene aniline) (2 g., 14%) m.p. 192-193° (Found: F, 63·1 M (mass spectroscopy) 331 $C_9F_{11}N$ requires F, 63·1% M 331). The ^{19}F n.m.r. spectrum in ether showed an unsymmetrical doublet centred at 88·0 p.p.m., attributed to the CF_3 groups, a doublet at 24·25 p.p.m., a distorted triplet at 14·2 p.p.m. and a sextet at 2·7 p.p.m. in the ratio 2:1:2 attributed to the C_6F_5 group, all downfield from C_6F_6.

The pale yellow distillate was hydrolysed with ice-water yielding an oil. The aqueous phase was ether extracted and the extract combined with the oil and washed several times with 10% potassium carbonate followed by water. The ethereal extract was dried ($MgSO_4$), filtered and distilled to afford a crude liquid (12 g. 79%), the infrared spectrum of which was identical with that of the amino alcohol adduct (LXXI; R = C_6F_5) isolated from the previous reaction (i).

Reaction of Perfluoro(N-iso-propylidene aniline) with Pentafluoropyridine.

A mixture of the iso- propylidene aniline (0·71 g.), pentafluoropyridine (0·25 g.), sulpholan (5 ml.) and anhydrous potassium fluoride (1 g.) was

placed in a 70 cc. Carius tube and sealed under vacuum. The tube and contents were heated at 130° for 18 hours. On cooling the tube was opened into a vacuum system when the somewhat charred contents were distilled and the volatile material condensed in a liquid air trap. Examination of the crude distillate by g.l.c. showed the presence of two components, pentafluoropyridine and one other compound of longer retention time. Fractionation of the crude product afforded impure pentafluoropyridine (0·17 g.) and iso-propylidene aniline (0·26 g.).

Reaction of Pentafluorobenzonitrile with Potassium Fluoride.

(i) A mixture of pentafluorobenzonitrile (1·93 g.), anhydrous potassium fluoride (0·58 g.) and dry sulpholan (10 ml.) were sealed, under vacuum, in an 80 cc. Carius tube and heated at 200° for 13 hours. The tube was cooled, opened, and the charred contents poured into water (250 ml.) and ether extracted. The extract was washed with water, dried ($MgSO_4$), filtered and distilled. Distillation of the residue under reduced pressure afforded unreacted pentafluorobenzonitrile (1·3 g.), identified by comparison of its infrared spectrum with that of an authentic sample.

(ii) This reaction was repeated using a three-molar quantity of potassium fluoride (1·74 g.) in sulpholan (15 ml.) with pentafluorobenzonitrile (1·93 g.). The tube was heated at 150° for 14 hours. On work-up only unreacted pentafluorobenzonitrile was recovered.

Trifluoronitrosomethane.

This compound was prepared according to the method of Haszeldine et al.[143]

A mixture of trifluoroiodomethane (11 g.), nitric oxide (4 g.) and mercury (100 cc.) was irradiated with a water-cooled u.v. lamp in a 10 l. flask for 6 hours. The crude product (5 g.) was fractionated, scrubbed with sodium hydroxide solution (30%) and fractionated again to afford the blue gaseous trifluoronitrosomethane (3·5 g. 63%) (Found: M99 (mass spectroscopy) CF_3NO requires M99).

Reaction of Trifluoronitrosomethane with Chlorotrifluoroethylene.

(i) This reaction was carried out according to the method reported by Haszeldine.[144] A mixture of the nitroso compound (0·3 g.) and the fluoro-olefin (1 g.) was sealed in a foil-covered 70 cc. Carius tube and allowed to stand for 1 week at room temperature when the blue colour had disappeared. Pyrolysis of the contents of the tube at 550°/5 mm. afforded the gaseous aza olefin (0·3 g.) which was fractionated and shown by infrared and mass spectroscopy to be a mixture of the perfluoro- and mono-chloro-tetrafluoro-aza olefins, the latter predominating. (Found: M (mass spectroscopy) 149. Calc. for C_2ClF_4N 149). The infrared spectrum showed a characteristic absorption at 1730 cm^{-1} [144] attributed to the N=CFCl stretch, and a weaker absorption at 1800 cm^{-1} attributed to the $N=CF_2$ stretch.

(ii) A mixture of CF_3NO (0·6 g.) and CF_2CFCl (0·7 g.) was heated in a sealed 70 cc. Carius tube at 70° for 24 hours.[144] Pyrolysis of the contents at 450°/0·01 mm. (recycled once) afforded the expected perfluoro(methylene-methylamine) (0·6 g.). (Found: M (mass spectroscopy) 133. Calc. for C_2F_5N M 133). The infrared spectrum showed a characteristic absorption at

1800 cm^{-1} [144] assigned to the $N{=}CF_2$ stretch.

Reaction of Perfluoro(methylenemethylamine) with Pentafluoropyridine.

(i) A mixture of pentafluoropyridine (0·5 g.), potassium fluoride (3 g.), sulpholan (5 ml.) and the perfluoro(methylenemethylamine) (0·5 g.) was heated in a sealed evacuated 120 cc. Carius tube at 150° for 14 hours. The tube was cooled and opened into a vacuum system and the contents distilled to afford pentafluoropyridine (0·4 g.) identified by comparing its infrared spectrum with that of an authentic sample. The residue from the distillation was dissolved in water (250 ml.) and extracted with ether. The ether extract was then washed with water, dried ($MgSO_4$), filtered, and distilled to afford a small amount of intractable gum from which no identifiable product could be isolated. The reaction was repeated at 170° for 15 hours affording unreacted pentafluoropyridine (0·3 g.) and a small amount of intractable residue.

(ii) Pentafluoropyridine (0·8 g.), potassium fluoride (3 g.) and sulpholan (15 ml.) were placed in a dry three-necked flask fitted with a reflux condenser, thermometer, gas lead and liquid air condenser. The mixture was stirred under dry nitrogen and heated to 120°, when the azapropene (0·6 g.) was passed through the stirred mixture, unreacted olefin was condensed in a liquid air trap and recycled. The contents of the flask were then distilled under vacuum, condensing the distillate in a liquid air trap, to afford only pentafluoropyridine, by g.l.c. (0·4 g.) identified by comparing its infrared spectrum with that of an authentic sample. After removal of the pentafluoropyridine, the residue was dissolved in water (250 ml.) and ether extracted.

The extract was washed with water, dried ($MgSO_4$), filtered and distilled affording a small amount of tar. Sublimation of this residue at 80°/0·01 mm. gave a semi-solid from which no identifiable product could be isolated.

The reaction was repeated at 140° on the same scale and only unreacted pentafluoropyridine (0·5 g.) was recovered. A further reaction was carried out using pentafluoropyridine (0·8 g.), potassium fluoride (4 g.) and sulpholan (25 ml.) under the same conditions used previously. When the temperature reached 180° the olefin (0·6 g.) was expanded into the mixture in the flask via the gas lead. Using the same work-up procedure employed previously, only pentafluoropyridine was isolated. The residue left after distillation under vacuum, was dissolved in water and extracted as before. Purification of this residue could not be effected by sublimation, crystallisation or chromatography on alumina.

Fluorination of 3-Chloro-2,4,5,6-tetrafluoropyridine.

This reaction was carried out according to a method[141] developed in these laboratories. 3-Chloro-2,3,5,6-tetrafluoropyridine (80 g.) was passed over stirred cobalt trifluoride at 95-98°, in a stream of dry nitrogen (80 ml./min.) at a rate of 10 ml/hour, and the product condensed by liquid air. A partial separation of the crude product was effected by preparative scale g.l.c. affording unreacted 3-chlorotetrafluoropyridine (40 g.) and an inseparable mixture of the isomeric 3-, and 5-chloro-octafluoro-1-piperideines (30 g.).

By raising the fluorination temperature to 120° decafluoro(1-chlorobutylid-4-ene-methylamine) was isolated.

2,3,5,6-Tetrafluoro-4-(3'-chloro-nonafluoropiperidino)pyridine (LXXIV).

The monochloropiperideine mixture (LXXII) (2·6 g.), pentafluoropyridine (1·7 g.), potassium fluoride (3 g.) and sulpholan (5 ml.) were sealed under vacuum in a 120 cc. Carius tube and heated at 170° for 16 hours. The tube was cooled, opened into a vacuum system and the contents distilled to give pentafluoropyridine (0·41 g.) b.p.→70°/10 mm., and the expected 4-(3'-chloropiperidino)pyridine (1·5 g. 46%) b.p. 76-78°/10 mm. (Found: C, 28·25; Cl, 9·28; F, 57·8. M (mass spectroscopy) 430. $C_{10}ClF_{13}N_2$ requires C, 27·90; Cl, 8·2; F, 57·4% M.430). On further heating a white crystalline solid sublimed in the condenser. The contents of the condenser and distillation flask were placed in water (250 ml.) and extracted with ether, the extract water-washed, dried ($MgSO_4$), filtered, and distilled to afford perfluoro(4-piperidino pyridine) (LXXV) crystallised from petroleum ether (b.p. 60-80°) (0·63 g. m.p. 54-55°) identified by comparison of its infrared spectrum with that of an authentic sample.[141]

Reaction of 2,3,5,6-Tetrafluoro-4-(3'-chloro-nonafluoropiperidino)pyridine(LXXIV) with Methoxide.

A mixture of the 3'-chloropiperidinopyridine (0·5 g.), methanol (1 ml.), potassium hydroxide (1 g.) and t-butanol (20 ml.) was heated under reflux for 12 hours. The mixture was diluted with water (250 ml.) and extracted with ether. The extract was dried ($MgSO_4$), filtered, and distilled giving an oily residue, purified by transfer under vacuum (180°/0·01 mm.) to yield the expected 2,6-dimethoxy derivative (LXXVI) (0·3 g. 57%) b.p. 262-265° (d) (Found: C, 31·84; H, 1·44; Cl, 6·64; F, 47·2, M (mass spectroscopy) 454

$C_{12}H_6ClF_{11}N_2O_2$ requires C, 31·7; H, 1·32; Cl, 7·79; F, 46·0% M.454). The ^{19}F n.m.r. spectrum in acetone showed the absence of the signal at 79 p.p.m. from C_6F_6, attributed to the 2,6-fluorines of the pyridine ring.

Reaction of Perfluoro(4-piperidino pyridine) with Methoxide.

(i) A mixture of the piperidinopyridine (LXXV) (0·54 g.) and sodium methoxide in methanol (18·5 ml. 0·071 N) was placed in a two-necked flask fitted with a reflux condenser and $CaCl_2$ guard tube, and a dropping funnel, and heated under reflux for 9 hours. Analytical scale g.l.c. showed that the starting piperidinopyridine (LXXV) was absent and that only one compound was present. The solvent was removed under vacuum at room temperature, and the residue (0·5 g.) purified by transferring under vacuum to afford the 2-methoxy substituted compound (LXXXIV) (0·44 g. 79%) b.p. 212°. (Found: C, 31·3; H, 0·64. $C_{11}H_3F_{13}N_2O$ requires C, 31·0; H, 0·71%).

(ii) A solution of the perfluoro-piperidinopyridine (0·41 g.) in methanol (25 ml.) was placed in a two-necked flask fitted with a condenser, a $CaCl_2$ guard tube, and a dropping funnel, and heated until near boiling when a solution of sodium (0·046 g.) in methanol (10 ml.) was added from the funnel. The mixture was boiled under reflux for 17 hours and worked up as in the previous experiment. The residue was purified by vacuum transfer to give the di-methoxy derivative (LXXXIII) (0·24 g., 55%) b.p. 255° (d.) (Found: C, 32·8; H, 0·97; M (mass spectroscopy) 438. $C_{12}H_6F_{12}N_2O_2$ requires C, 32·9; H, 1·38% M.438). After removal of the dimethoxy compound, an examination of the impure residue by mass spectroscopy was consistent with the presence of a tri-methoxy derivative.

Reaction of Pentafluoropyridine with 4-Bromo-octafluoro-1-piperideine (LXXIII).

A mixture of pentafluoropyridine (1·2 g.), potassium fluoride (3 g.), sulpholan (10 ml.) and the 4-bromo-piperideine[141] (2 g.) was sealed under vacuum in a 100 cc. Carius tube and heated at 140° for 15 hours. The charred reaction product was distilled under reduced pressure, according to the previously employed work-up procedure, when a white solid sublimed in the condenser (0·001 mm/60°). Crystallisation of this solid, and the contents of the distillation flask, from petrol ether (b.p. 60-80°) afforded the 4-(4'-bromopiperidino)pyridine (LXXXII) (1·39 g. 41%) m.p. 48-50°. (Found: C, 25·5; M (mass spectroscopy) 475. $C_{10}BrF_{13}N_2$ requires C, 25·3% M 475). During the distillation the volatile material was condensed in a liquid air trap and was shown by analytical scale g.l.c. to be unreacted 4-bromo-1-piperideine (0·7 g. 35%) with a trace of pentafluoropyridine.

2,3,5,6-Tetrafluoro-4-(3'-chlorononafluoropiperidino)Benzonitrile.

Pentafluorobenzonitrile (1·9 g.), potassium fluoride (3 g.), sulpholan (10 ml.) and the monochloropiperideine mixture (LXXII) (2·6 g.), were sealed in a 100 cc. Carius tube and heated for 15 hours at 140°. The same work-up procedure as used previously was employed. Distillation of the crude residue afforded unreacted pentafluorobenzonitrile (0·68 g. 36%) b.p. 52-111°/10 mm. identified by comparing its infrared spectrum with that of an authentic sample. Further distillation gave the expected 4-(3'-chloropiperidino)benzonitrile (LXXVII) (1·84 g. 63%) b.p. 110-112°/0·01 mm. (Found: C, 32·0; Cl, 9·7; F, 54·5 M (mass spectroscopy) 454. $C_{12}ClF_{13}N_2$ requires C, 31·7; Cl, 7·8; F, 54·3% M 454). On more vigorous heating a viscous yellow liquid distilled

(>112°/0·01 mm.) which gradually solidified. Crystallisation of this crude solid from petroleum ether (b.p. 60-80°) afforded the trisubstituted benzonitrile) (LXXVIII) (0·1 g. 1·6%) m.p. 173-174° (Found: C, 28·25 M (mass spectroscopy) 976 $C_{22}Cl_3F_{29}N_4$ requires C, 28·46% M 976). An examination of the mass spectrum showed that the intensities of the P, P+2, P+4 and P+6 peaks were in the ratio expected for a molecule containing three chlorine atoms i.e. 1:1:0·32:0·035.[142] The ^{19}F n.m.r. spectrum in $CHCl_3$ showed the absence of the signal at 79 p.p.m. downfield of C_6F_6, attributed to the 2,6-fluorines.

Hydrolysis of the (Piperidino)benzonitriles.

(i) A mixture of the mono-piperidino-benzonitrile (LXXVII) (0·6 g.), potassium hydroxide (1 g.) and t-butanol (10 ml.) was boiled under reflux for 61 hours. On cooling, the crude reaction product was poured into water (250 ml.), acidified with dilute hydrochloric acid, and extracted with ether. The extract was water-washed, dried ($MgSO_4$), filtered and distilled, when sublimation of the residue (100°/0·001 mm.) afforded a white solid which crystallised from petroleum ether (b.p. 60-80°) yielding the 2,6-dihydroxy (piperidino)benzoic acid (LXXXI) (0·3 g. 48%) m.p. 145-146° (Found: C, 30·4; H, 0·56 M (mass spectroscopy) 469. $C_{12}H_3ClF_{11}NO_4$ requires C, 30·68; H, 0·64% M 469). The ^1H n.m.r. spectrum in acetone showed two signals at -3·0 τ and 2·5 τ in the ratio 1:2 attributed to the carboxylic and phenolic protons respectively. The ^{19}F n.m.r. spectrum showed the absence of the signal attributed to the 2,6-fluorines at 23 p.p.m. downfield of C_6F_6, in the parent acid (LXXIX).

(ii) A solution of the mono-piperidino-benzonitrile (LXXVII) (0·5 g.) in glacial acetic acid (5 ml.) and concentrated sulphuric acid (2 ml.) was boiled under reflux for 6 hours. On cooling, the mixture was poured into water (250 ml.) and ether extracted. The extract was washed with water, dried ($MgSO_4$), filtered and the solvent removed by distillation to afford a residue which was crystallised from petroleum ether (b.p. 60-80°) to give the 4-(piperidino)benzoic acid (LXXIX) (0·25 g. 48%) m.p. 135-136° (Found: C, 30·8; H, 0·48 M (mass spectroscopy) 473 $C_{12}HClF_{13}NO_2$ requires C, 30·43; H, 0·21% M 473). The ^1H n.m.r. spectrum of the acid in CCl_4 showed a signal at -3·0 τ assigned to the carboxylic proton.

(iii) A solution of the trisubstituted benzonitrile (LXXVIII) (0·5 g.) in glacial acetic acid (5 ml.) and concentrated sulphuric acid (2 ml.) was boiled under reflux for 8 hours. The mixture was cooled, diluted with water (250 ml.) and ether extracted. The extract was washed with water, dried ($MgSO_4$), filtered and the solvent removed by distillation to give a crude solid. Sublimation of this residue (120°/0·01 mm.) yielded a white solid which crystallised from petroleum ether (b.p. 60-80°) affording the trisubstituted amide (LXXX) (0·2 g. 39%) m.p. 191-192° (Found: Cl, 11·7; F, 54·3 M (mass spectroscopy) 994 $C_{22}H_2Cl_3F_{29}N_4O$ requires Cl, 10·7; F, 55·3% M 994). An examination of the mass spectrum showed the expected isotope pattern for three chlorine atoms in the molecular ion, as in the parent trisubstituted benzonitrile. The infrared spectrum showed a doublet, at 3280 cm^{-1}, attributed to the NH_2 group.

Reaction of Pentafluoropyridine with Decafluoro-(1-chlorobutylid-4-ene methylamine) (LXVIII).

A mixture of the butylidene methylamine[141] (LXVIII) (1·9 g.) pentafluoropyridine (1·1 g.), potassium fluoride (3 g.) and sulpholan (10 ml.) was sealed under vacuum in a 100 cc. Carius tube and heated at 170° for 23 hours. The tube was cooled, opened into a vacuum system and the contents distilled to afford pentafluoropyridine (0·9 g. 81%). Examination of the residue (0·1 g.) by g.l.c. showed it to consist of two major components, one of which was pentafluoropyridine, and a third minor component. Further separation could not be effected and no other identifiable product was isolated.

Reactions of Pentafluorobenzenes with the Monochloropiperideines (LXXII).

(i) Pentafluorobenzene (1·7 g.), the monochloropiperideine mixture (LXXII) (2·7 g.), potassium fluoride (3 g.) and sulpholan (10 ml.), were sealed under vacuum in a 100 cc. Carius tube and heated at 170° for 18 hours. The usual work-up procedure was employed, and an examination of the crude product (4 g.) by g.l.c. showed only a mixture of unreacted starting materials.

(ii) Pentafluorobromobenzene (2·5 g.), the monochloropiperideine mixture (2·6 g.), potassium fluoride (3 g.) and sulpholan (15 ml.) were sealed in a 120 cc. Carius tube under vacuum and heated at 170° for 18 hours. The same work-up procedure was employed and distillation of the residue under reduced pressure afforded unreacted starting materials (4·5 g.), identified by g.l.c. retention time, and a higher boiling fraction (0·4 g.) 60-80°/0·01 mm.,

consisting of unreacted pentafluorobromobenzene and an unidentified compound of longer retention time in the approximate ratio 3:2 respectively. This latter fraction could not be separated by further distillation.

(iii) A further reaction was carried out with pentafluorobromobenzene. A mixture of potassium fluoride (3 g.), pentafluorobromobenzene (1·6 g.) and sulpholan (20 ml.) was stirred under nitrogen in a three-necked flask fitted with a dropping funnel, thermometer, reflux condenser and liquid air condenser leading to a liquid air trap with a $CaCl_2$ guard tube. The mixture was heated to 140°, the monochloropiperideine mixture (1·5 g.) added, and the mixture stirred for 5 min. None of the starting piperideine was found in the liquid air trap, indicating complete reaction, so the mixture was allowed to cool. The flask was half-filled with glass wool and the contents distilled under reduced pressure, the volatile materials being condensed in a liquid air trap. Examination of the contents (1·9 g.) of the liquid air trap by g.l.c. showed only unreacted pentafluoropyridine and monochloropiperideines in the approximate ratio 5:1. The involatile material left in the distillation flask was dissolved in water (250 ml.) and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), filtered and the solvent removed by distillation, to give a small amount of intractable tar.

Reaction of Perfluoro(4-piperidinopyridine) and Perfluoro(4-cyclohexyl-pyridine), with Sodium Methoxide.

A solution of the piperidinopyridine (0·410 g.) and the cyclohexyl-pyridine (0·428 g.) in dry methanol (25 ml.) was placed in a predried two-necked flask fitted with a dropping funnel and a reflux condenser with a $CaCl_2$ guard tube. The mixture was heated to near boiling and a solution

of sodium methoxide in methanol (25 ml. 0·005N) was added from the dropping funnel when the mixture was boiled under reflux for 22 hours. Most of the methanol was removed by distillation, the residue dissolved in water and extracted with ether. The ether extract was dried ($MgSO_4$), filtered and distilled to low volume (~2-3 ml.), nitrobenzene (0·6039 g.) added and the whole diluted to 10 ml. in a volumetric flask, with methanol. A calibration solution was prepared containing the cyclohexylpyridine (0·2990 g.) and the corresponding mono-methoxy derivative (0·0435 g.), the piperidinopyridine (LXXV) (0·3038 g.) and its mono-methoxy derivative, and nitrobenzene (0·5987 g.). This mixture was then diluted to 10 ml. with methanol in a volumetric flask. On examining both solutions by g.l.c. (Gas Density Balance) the amounts of each of the mono-methoxy derivatives produced in the competition reaction were found. Only mono substitution occurred to yield 2-methoxy-4-cyclohexylpyridine (0·03996 g. 76%) and the 2-methoxy-4-(piperidino)pyridine (0·0134 g. 26·6%).

Reactions of Pentafluorobenzoate esters with the monochloro piperideine mixture. (LXXII)

(i) Ethyl pentafluorobenzoate (2·5 g.), potassium fluoride (3 g.), sulpholan (8 ml.) and the monochloropiperideine mixture (2·4 g.) were sealed under vacuum in a 120 cc. Carius tube and heated at 165° for 27 hours. After the usual work-up procedure, distillation afforded unreacted ethyl pentafluorobenzoate (2·42 g.) and an impure fraction (b.p. 54-123°/1 mm.) (0·41 g.) Examination of this latter liquid by T.L.C. showed the presence of three components one of which was identified, by comparison of retention times, as unreacted ethylpentafluorobenzoate. Further separation could not be effected

by distillation.

(ii) The reaction was repeated using an excess of the ethylbenzoate (4·8 g.) with potassium fluoride (3 g.), sulpholan (10 ml.) and the monochloropiperideine isomers (4 g.). This mixture was heated in a 120 cc. Carius tube for 20 hours at 180° and then worked up as in the previous experiment. The residue was fractionated under reduced pressure to give a mixture (1·85 g.) of ester and piperideine, ethyl pentafluorobenzoate (1·92 g.) and a yellow viscous liquid (1·1 g.) (138-140°/0·001 mm.). This latter product was eluted through a column of activated alumina when a partial separation was effected yielding sulpholan (0·3 g.) and a yellow oil from which no identifiable product could be isolated.

(iii) A third experiment was carried out using the 'flow' method employed previously. Ethyl pentafluorobenzoate (0·74 g.), potassium fluoride (4 gm.) and sulpholan (15 ml.) were stirred under nitrogen in a three-necked flask fitted with a reflux condenser, liquid air condenser, dropping funnel and thermometer. The mixture was heated to 180° when the monochloropiperideine isomers (0·9 g.) were added. On work-up however, only unreacted starting materials (0·58 g.) could be isolated from the charred reaction product, which on examination by g.l.c. was shown to be mainly ethyl pentafluorobenzoate with a trace of the piperideine starting material.

(iv) Methyl pentafluorobenzoate (2·3 g.), potassium fluoride (3 g.), sulpholan (10 ml.) and the monochloropiperideines (2·6 g.) were sealed under vacuum in a 100 cc. Carius tube and heated at 170° for 16 hours. Distillation of the somewhat charred reaction product gave unreacted starting materials

(1·08 g.) identified by g.l.c. retention time. Further heating yielded a white solid which crystallised in the condenser. The contents of the liquid air trap (1 g.) were examined by g.l.c. and shown to be unreacted piperideines and a little methyl pentafluorobenzoate. The residue from the distillation was sublimed ($80^{\circ}/0{\cdot}005$ mm.) to give a white solid having the same infrared spectrum as the material in the condenser. These products were combined and crystallised from petroleum ether (b.p. 60-80°) affording decafluorobenzophenone (0·5 g.) identified by comparing its infrared and mass spectra with that of an authentic sample. The ^{19}F n.m.r. spectrum in CCl_4 showed signals at 7·0, 20·5 and 25·5 p.p.m. downfield from C_6F_6, in the ratio 2:1:2, attributed to the m-, p- and o-fluorines of C_6F_5 nucleii respectively.

INFRARED SPECTRA

The spectra of all liquids were measured as contact films using potassium bromide cells except for the mono- and dimethoxy-4-(piperidino)-pyridines spectra nos. 23 and 24, which were measured using sodium chloride cells. The spectra of all solids were measured as potassium bromide discs except for 2,6-dihydroxy-4-(piperidino)benzoic acid spectrum no.20 and 2,3,4,5,6-pentafluorophenylacetohydrazide spectrum no.9, which were measured as nujol mulls in sodium chloride cells.

Spectrum	Compound
1	Ethyl 2,3,4,5-Tetrafluorophenoxyfluoroacetate.
2	Ethyl 6-Ethoxycarbonyl-2,3,4,5-Tetrafluorophenoxyfluoroacetate.
3.	ω-Benzyloxy-2,3,4,5,6-Pentafluoroacetophenone.
4.	Ethyl-(Triphenylmethoxy)acetate.
5.	ω-Triphenylmethoxy-2,3,4,5,6-Pentafluoroacetophenone.
6.	ω-Hydroxy-2,3,4,5,6-Pentafluoroacetophenone.
7.	N,N'-Dimethyl-2,3,4,5,6-Pentafluorophenylacetamide.
8.	α,α'-Bis(2,3,4,5,6-Pentafluorophenyl)acetone.
9.	2,3,4,5,6-Pentafluorophenylacetohydrazide.
10.	Iso-propylidene-2,3,4,5,6-Pentafluorophenylacetohydrazone.
11.	2,3,4,5,6-Pentafluorophenylacetylfluoride.
12.	Product derived from pentafluorophenylacetylfluoride, MW 832, speculative structures XLIII, XLIV.
13.	2,3,4,5,6-Pentafluorophenylacetaldehyde (slightly impure).
14.	Perfluoro(N-isopropylidene aniline).

15. Hexafluorodimethyl-2,3,4,5,6-Pentafluoroanilino carbinol.

16. 2,3,5,6-Tetrafluoro-4-(3'-chlorononafluoropiperidino)pyridine.

17. 2,6-Dimethoxy-3,5-difluoro-4-(3'-chlorononafluoropiperidino)pyridine.

18. 2,3,5,6-Tetrafluoro-4-(3'-chlorononafluoropiperidino)benzonitrile.

19. 3,5-Difluoro-2,4,6-tris(3'-chlorononafluoropiperidino)benzonitrile.

20. 2,6-Dihydroxy-3,5-difluoro-4-(3'-chlorononafluoropiperidino) benzoic acid.

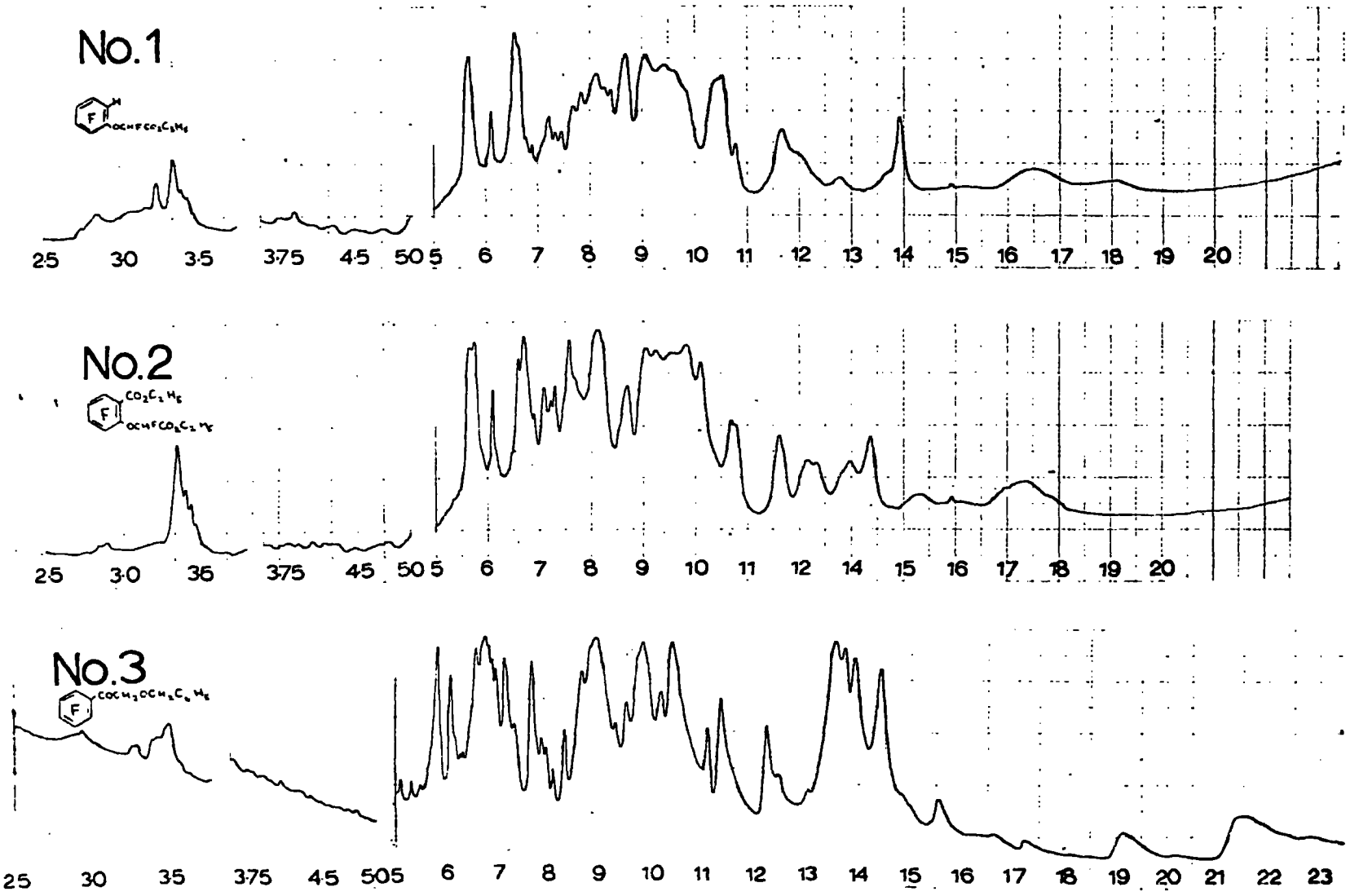
21. 2,3,5,6-Tetrafluoro-4-(3'-chlorononafluoropiperidino)benzoic acid.

22. 3,5-Difluoro-2,4,6-tris(3'-chlorononafluoropiperidino)benzamide.

23. 2-Methoxy-3,5,6-trifluoro-4-(decafluoropiperidino)pyridine.

24. 2,6-Dimethoxy-3,5-difluoro-4-(decafluoropiperidino)pyridine.

25. 2,3,5,6-Tetrafluoro-4-(4'-bromononafluoropiperidino)pyridine.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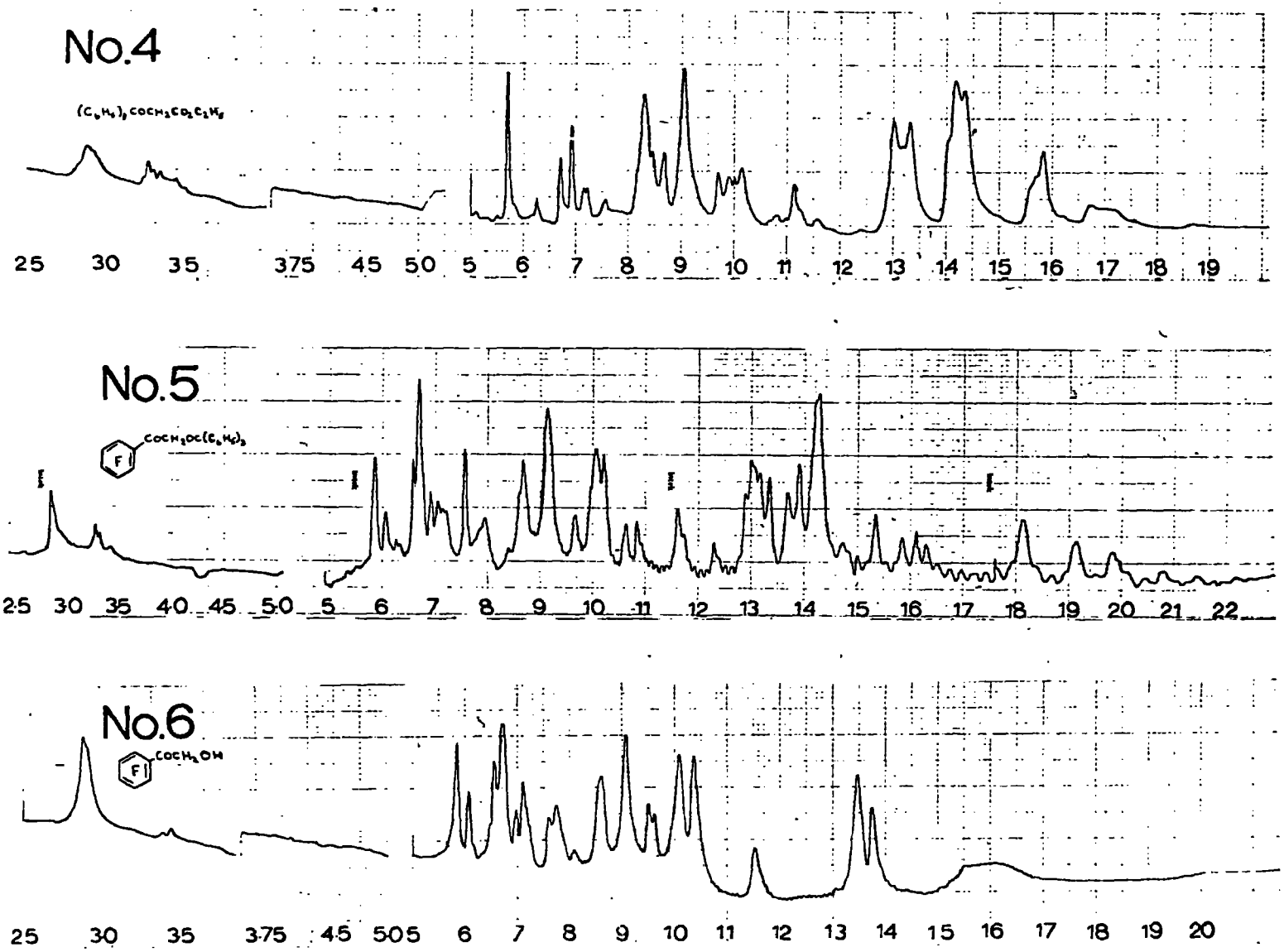
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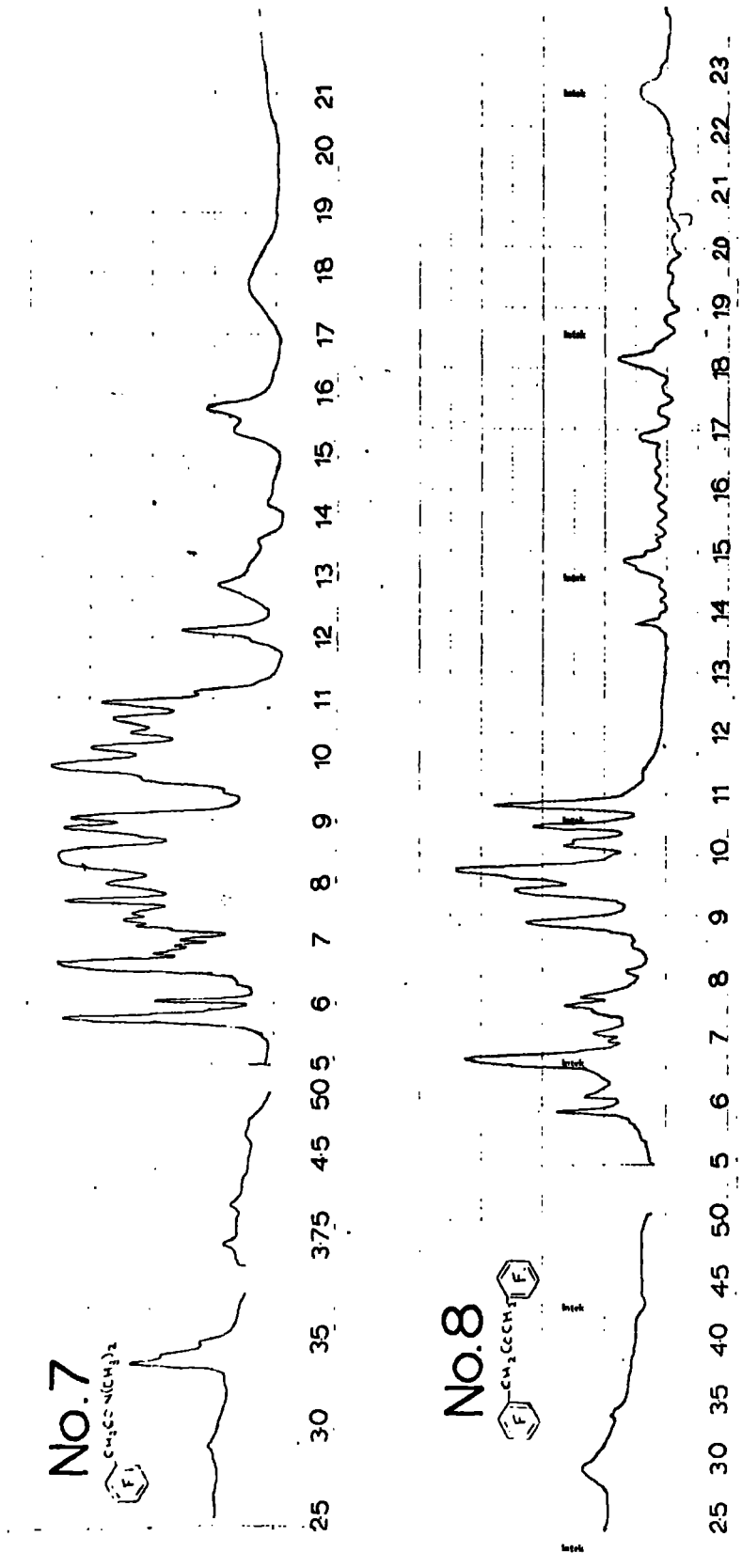
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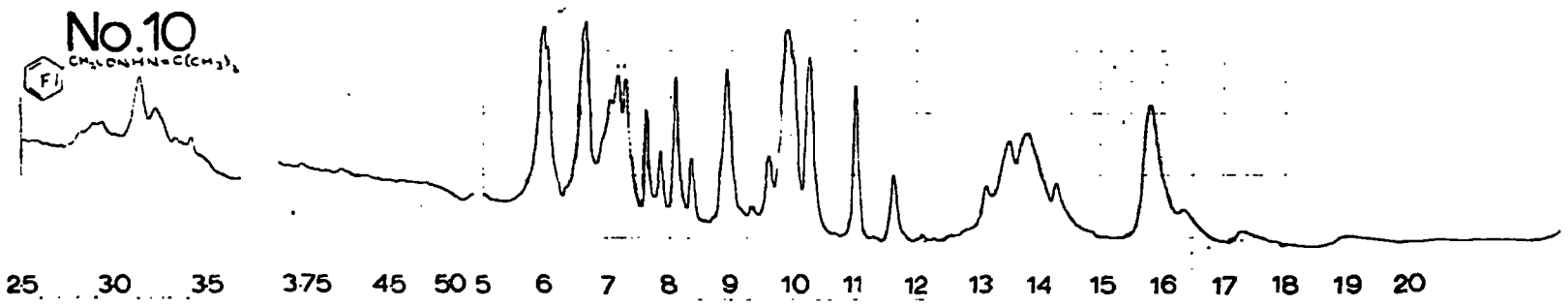
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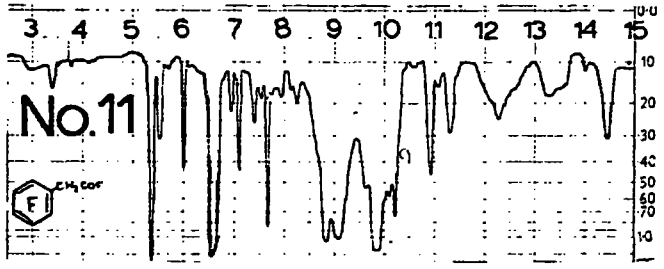
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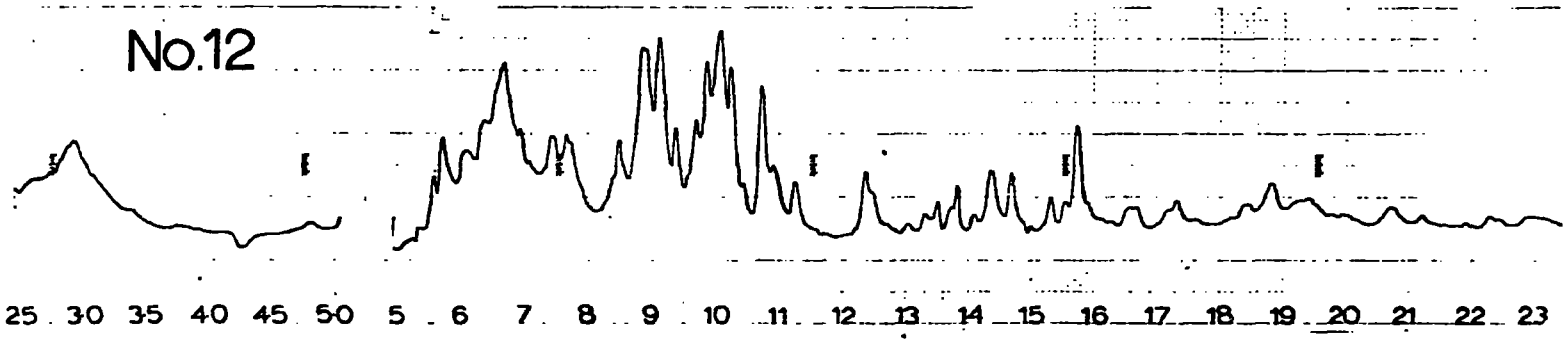
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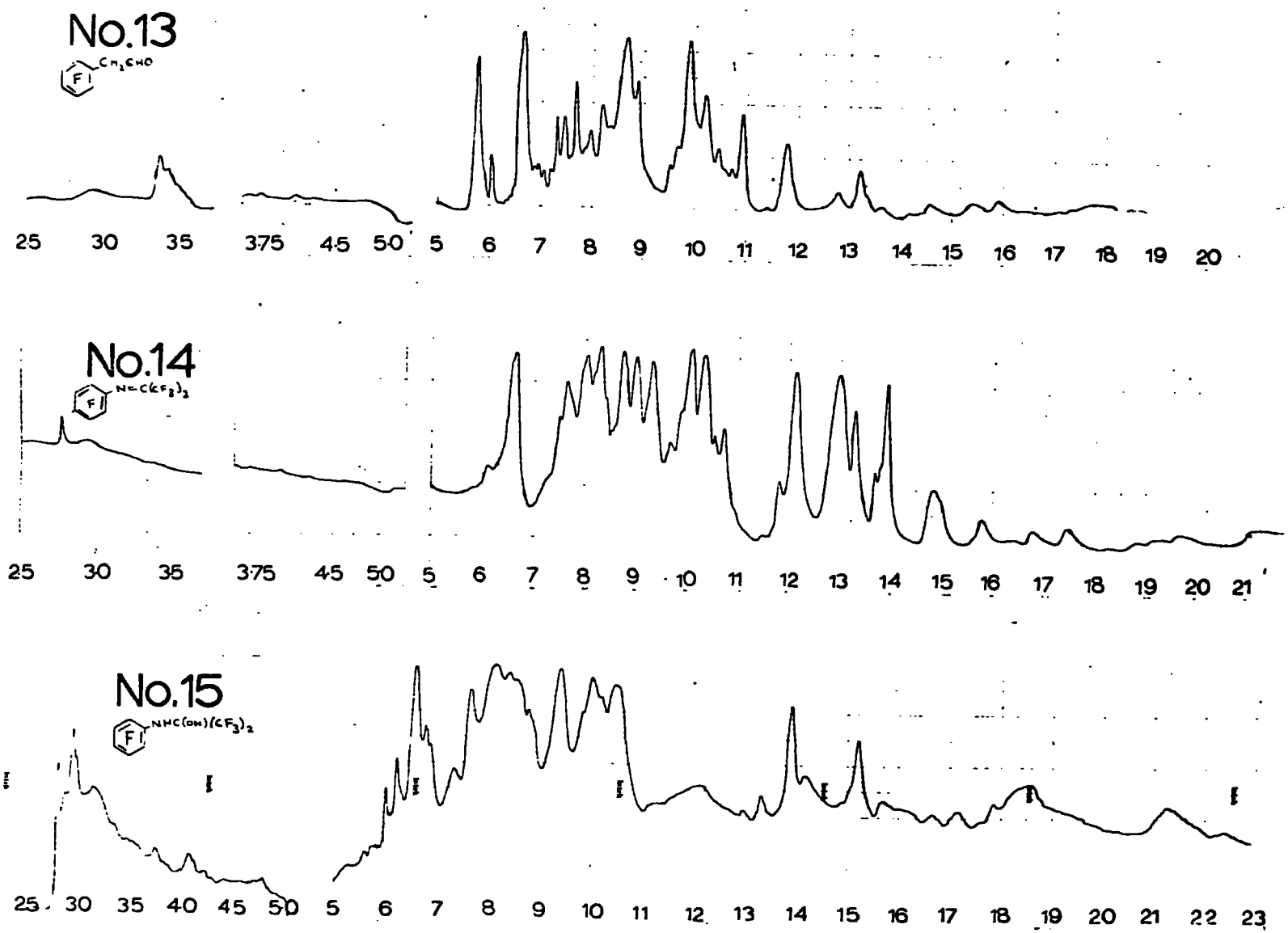
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No.14
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No.15
NHC(OH)(CF3)2
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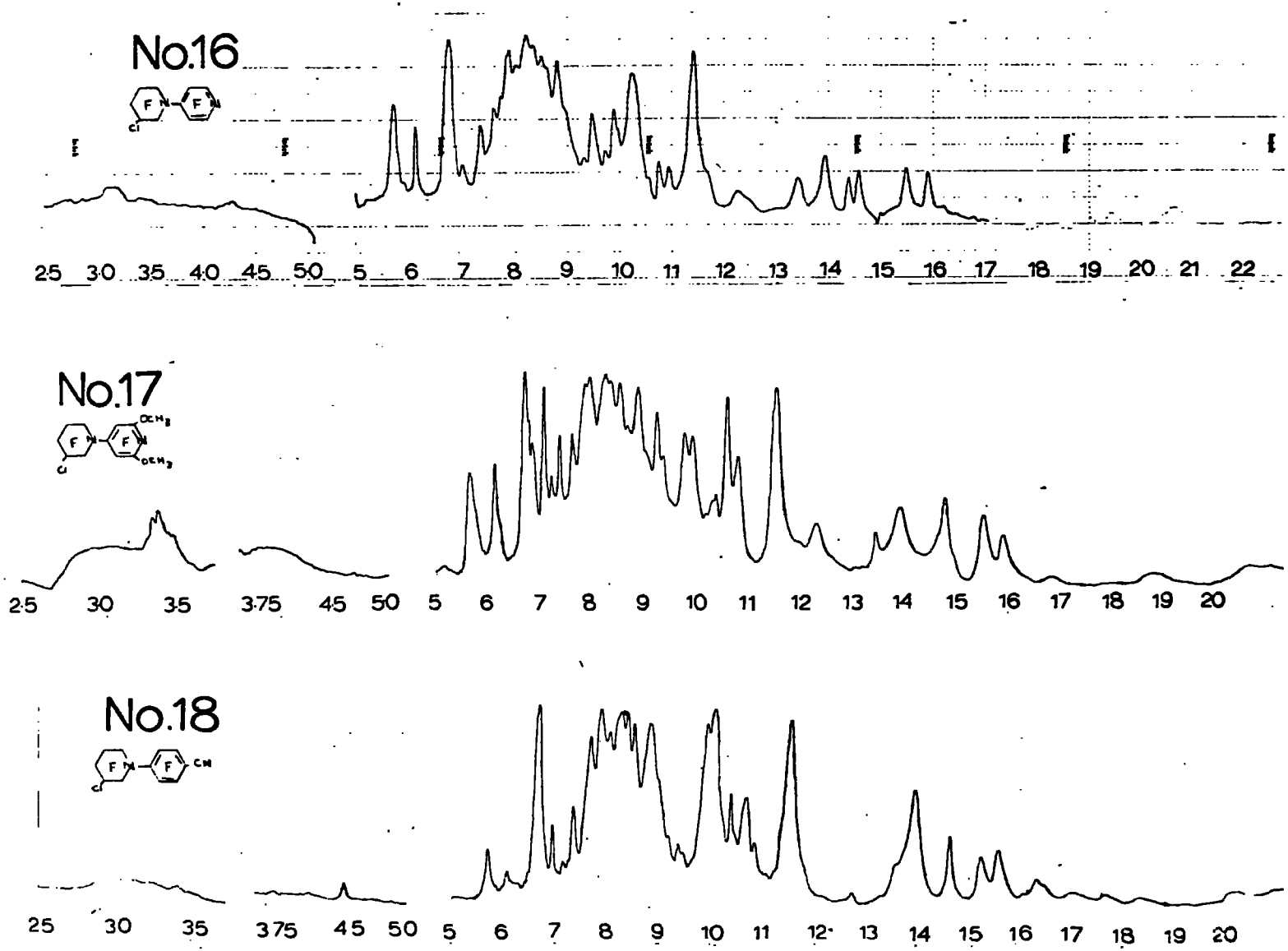
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No.17
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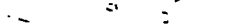
No.19



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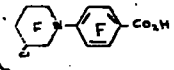

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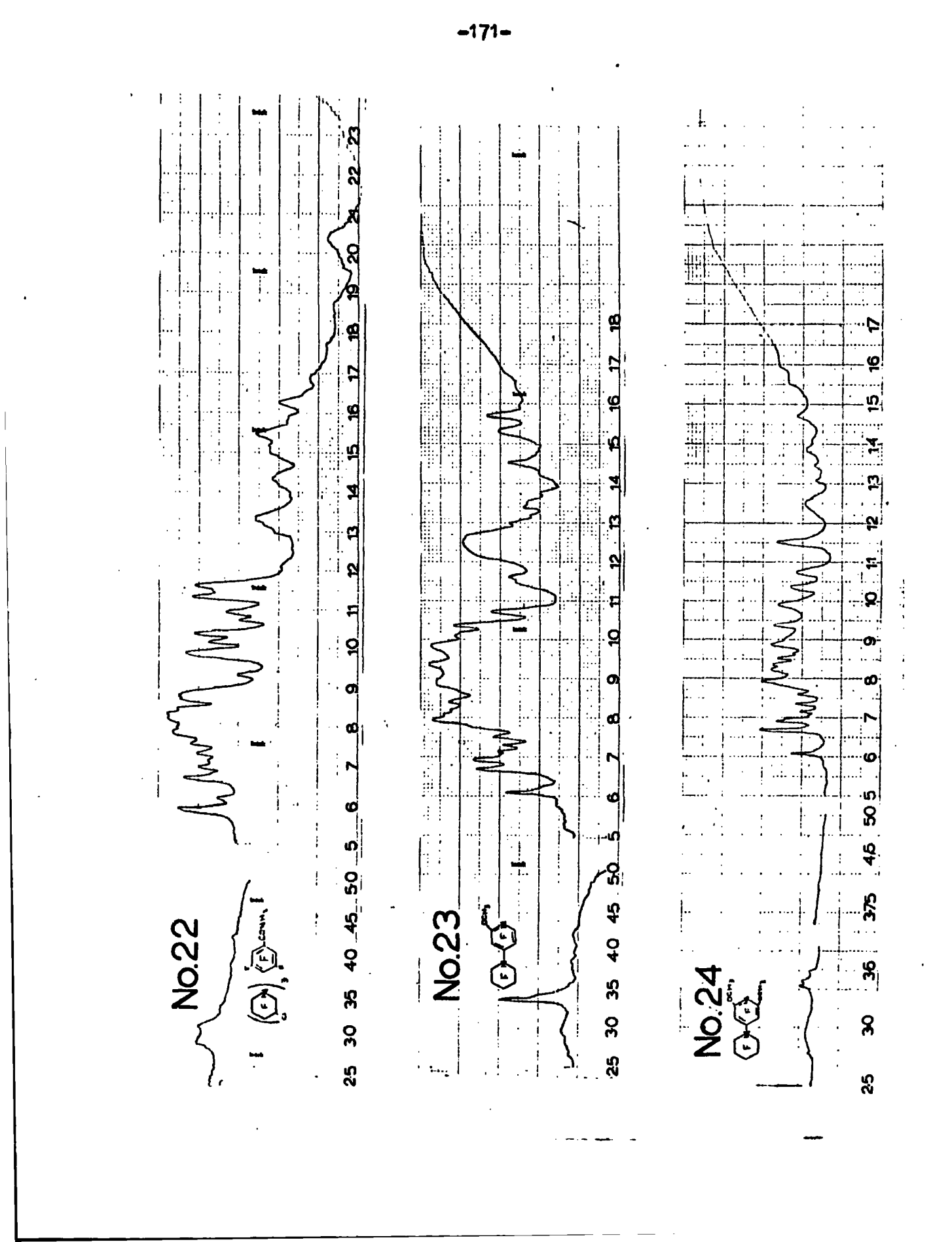
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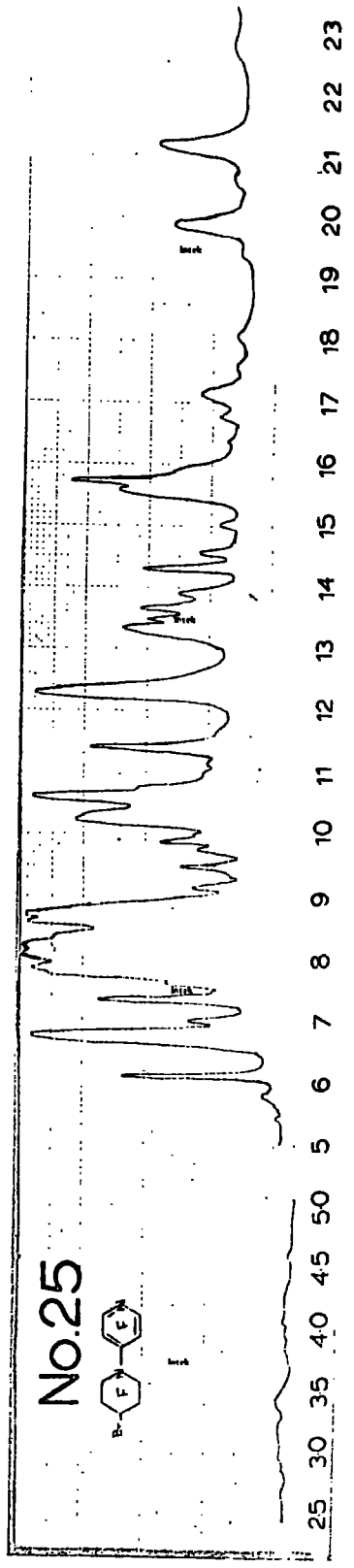
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