Part I; the synthesis and reactions of polyhalogenated heterocyclic compounds containing nitrogen part II: polyhaloalkylation

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UNIVERSITY OF DURHAM

A THESIS

entitled

PART I: The Synthesis and Reactions of Polyhalogenated Heterocyclic Compounds Containing Nitrogen

PART II: Polyhaloalkylation

Submitted by

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A candidate for the degree of Doctor of Philosophy 1967.

ACKNOWLEDGEMENTS

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MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1964 and May 1967. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

Part of this work has provided material for four publications: J. Chem. Soc., (C), 1966, 2328 (with Dr. R.D. Chambers, Dr. M. Hole, Dr. B. Iddon and Professor W.K.R. Musgrave), J. Chem. Soc., (C), 1966, 2331 (with Dr. R.D. Chambers, Dr. M. Hole, Professor W.K.R. Musgrave and (in part) Dr. B. Iddon), J. Chem. Soc., (C), 1967, 53 (with Dr. R.D. Chambers, Dr. M. Hole and Professor W.K.R. Musgrave) and Chemical Communications, 1966, 384 (with Dr. R.D. Chambers and Professor W.K.R. Musgrave).

Summary

Part I: Synthesis and Chemistry of Polyhalogenoisoquinolines.

Heptachloroisoquinoline has been prepared by initial direct chlorination of isoquinoline and subsequent reaction of the product with phosphorus pentachloride at elevated temperatures. Reaction of the perchloro compound with potassium fluoride at elevated temperatures gave heptafluoroisoquinoline and chlorofluoroisoquinolines in good yield. The perhalogenoisoquinolines show no basic properties at all apart from their solubility in concentrated sulphuric acid.

Nucleophilic substitution in heptafluoroisoquinoline by various nucleophiles, e.g. sodium methoxide, ammonia, hydrazine, and lithium aluminium hydride etc. is described. Attack occurs first in almost all cases at the 1-position and then at the 6-position. Oxidation of heptafluoroisoquinoline and the methoxy-derivatives gives tri- and di-fluoropyridine dicarboxylic acids which aid the analysis of the ^{19}F n.m.r. spectra of the methoxy-derivatives and establish their structures. Some of the derivatives have been inter-related, structurally, by means of interconversion reactions.

Heptafluoroisoquinoline reacts with aqueous sodium hydroxide or with potassium hydroxide in t-butyl alcohol to give the 1-hydroxy derivative. 1-Hydroxyhexafluoroisoquinoline exists as a tautomer and reaction with diazomethane produces a mixture of O- and N-methyl

derivatives. The factors affecting tautomerism are outlined.

A plausible rationalisation of the orientation of nucleophilic attack on heptafluoroisoquinoline is given in terms of localisation energies as calculated by Hückel Molecular Orbital techniques. The drawbacks in this idea and a possible modification of this procedure to give a method which would be more general, is outlined.

Part II: Polyhaloalkylation.

Highly fluorinated aromatic compounds such as pentafluoropyridine, hexafluorobenzene, and their derivatives will react with carbanions produced from fluorinated olefins, such as hexafluoropropene and tetrafluoroethylene, and fluoride ion with the formation of polyfluoroalkylated derivatives.

The process is equivalent to the Friedel and Crafts reaction in hydrocarbon chemistry and, if it is carried out at pressures high enough to keep a reasonable concentration at the seat reaction, several fluoroalkyl groups can be introduced into the aromatic ring. Hexafluorobenzene is less reactive in the early stages of the polyalkylation than is pentafluoropyridine but when activating groups such as $-NO_2$, -COOMe, and particularly -CN are introduced into the hexafluorobenzene, reaction occurs much more readily.

Potassium fluoride or caesium fluoride can be used as sources of fluoride ion and sulpholane is a better solvent than dimethylformamide, diglyme, or triglyme.

CONTENTS

General Introduction.

Fluorine, like hydrogen, occupies a special place in chemistry, in that it gives rise to a whole system of organic compounds. First efforts were directed towards the synthesis and study of aliphatic fluorocarbons. The successful development of this field, along with the discovery of some fluorocarbons with very useful properties, led to the establishment of fluorine chemistry as a major field of organic chemistry. Aromatic fluorocarbon chemistry has been developed only recently, and has been limited to homocyclic systems because of the difficulties in extending early methods of synthesis from homocyclic systems to heterocyclic systems. The preparation of C_6F_6 from C_6Cl_6 by halogen exchange led the way to the successful preparation, on a reasonable scale, of pentafluoropyridine[1] by a halogen exchange reaction and indicated a possible general route to the preparation of polyfluorinated π-electron deficient nitrogen containing heterocyclic systems. Part of the present study was concerned with the application of this method, in the synthesis of heptafluoroisoquinoline and the subsequent development of the chemistry of this new fluorocarbon. Some of the points of interest in this project were the effect of the fluorine substituents on the basic properties of the ring nitrogen, and the influence of the latter on the nucleophilic substitution reactions on the fluorocarbon system, especially in comparison with homocyclic aromatic fluorocarbons, which have received considerable attention.[2a,2b,3]

With the rapid development of organic fluorine chemistry a large

number of synthetic problems have become apparent. Part of this work is designed to overcome one of the more important of these problems, which is the synthesis of perfluorinated homocyclic and heterocyclic aromatic systems, containing perfluorinated alkyl side chains. The synthesis of compounds of this type, by conventional methods, is usually extremely difficult, laborious, and the yields obtained very often quite poor. Derivatives of compounds of this type, such as sulphonic and carboxylic acids are of interest, in view of the possible commercial applications they may have.

PART I

The Synthesis and Reactions of Some Polyhalogenated Heterocyclic Compounds Containing Nitrogen

Chapter I

Historical Introduction

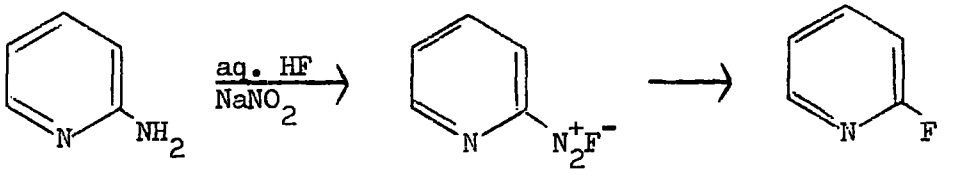
Historical Introduction.

Before the present work was undertaken, the nuclear substituted fluoroisoquinolines that had been prepared were limited to those containing one, or at the most two fluorine atoms. These have been prepared either by cyclisation methods, employing a suitably substituted fluorobenzene, or by direct replacement of a functional group in the isoquinoline nucleus to give fluoroisoquinolines substituted in either the benzene or heterocyclic ring.

Replacement of Functional Groups by Fluorine.

1) Replacement by the amino group.

As early as 1870, Schmitt and von Gehren[4] synthesised p-fluorobenzoic acid by diazotising the corresponding amine in aqueous hydrofluoric acid and decomposing the resultant diazonium fluoride 'in situ'. This method was soon applied to the preparation of nuclear substituted fluoroheterocyclic aromatic compounds when Tschitschabin[5] prepared 2-fluoropyridine.



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However, a considerable amount of 2-pyridone was produced and the use of an aqueous solution for decomposition of the diazonium salt is

an obvious disadvantage of this method.

An indirect method of converting aminated benzenes to the corresponding fluorides in good yields was discovered by Balz and Schiemann[6] when they found that diazonium fluoroborates could be decomposed to give the aromatic fluoride. The method involves the preparation and isolation of the dry diazonium fluoroborate, and its controlled thermal decomposition to yield the aromatic fluoride, nitrogen, and boron trifluoride.

$$ArNH_2 + HNO_2 + BF_4^- \longrightarrow ArN_2^+BF_4^- + H_2O + OH^-$$

$$ArN_2^+BF_4^- \xrightarrow{\text{heat}} ArF + N_2 + BF_3$$

Many of the heterocyclic diazonium fluoroborates are not stable enough to be isolated, although they do decompose to give the heterocyclic fluorine compounds; thus all three of the pyridine diazonium fluoroborates and 2- and 4-quinolinediazonium fluoroborates decompose at room temperature or below. In contrast, 3-, 5-, 6-, 7- and 8-quinolinediazonium fluoroborates are all relatively stable.

The first attempts to prepare fluorinated isoquinolines by the method of Balz and Schiemann, was by Roe and Teague,[7] who reported the syntheses of 1-, 3-, 4- and 5-fluoroisoquinoline. They claimed that the isolation of the isoquinolinediazonium fluoroborates was achieved only after considerable modification of the usual Schiemann techniques, and that the 3- and 4-isomers decomposed at room temperature or below.

The stability of the 1-isoquinolinediazonium fluoroborate was somewhat unexpected, in view of the marked instability of the roughly analogous 2-quinolinediazonium fluoroborate, as was the instability of the 4-isoquinolinediazonium fluoroborate, compared to the stability of the analogous 3-quinolinediazonium fluoroborate. 1- and 5-fluoroisoquinoline were obtained in 13% and 67% yields, respectively, by the dry thermal decomposition of the corresponding diazonium fluoroborates. 3-Fluoroisoquinoline was obtained in 49% yield by the decomposition of the fluoroborate in benzene at room temperature. 4-Fluoroisoquinoline was obtained in 36% yield by the decomposition of the fluoroborate in Xylene at room temperature. In all cases hydroxyisoquinolines were obtained as by products.

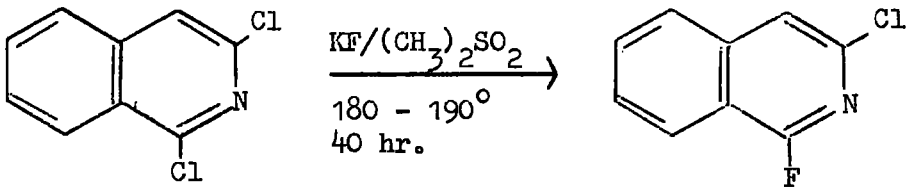
The preparation of all the monofluoroisoquinolines, except 1-fluoroisoquinoline, by means of a Schiemann reaction, has been described by Bellas and Suschitzky.[8] They were, in contrast to Roe and Teague, unable to obtain the 1-fluoro isomer by a Schiemann reaction. They used the same procedure as Roe and Teague[7] to prepare the 3- and 5-fluoroisoquinolines. A modification of this procedure was used to prepare 5-chloro-8-fluoroisoquinolinediazonium fluoroborate, 4-isoquinolinediazonium fluoroborate, 6-isoquinolinediazonium fluoroborate, and 7-isoquinolinediazonium fluoroborate. Thermal decomposition of these fluoroborates in boiling cumene gave 5-chloro-8-fluoroisoquinoline, 4-fluoroisoquinoline, 6-fluoroisoquinoline and 7-fluoroisoquinoline in

21%, 45%, 54% and 15% yields respectively. Attempts to prepare 8-fluoroisoquinoline by catalytic dehalogenation failed. 8-Fluoroisoquinoline, was however prepared in 89% yield by the dry thermal decomposition of 8-isoquinolinediazonium fluoroborate at 150°. Also prepared was 1-bromo-3-fluoroisoquinoline using a similar technique. These authors also reported the successful conversion of all the monofluoroisoquinolines, except the 1-fluoro isomer to the corresponding fluoroisoquinoline N-oxides with hydrogen peroxide in acetic acid.

The preparation of 8-fluoroisoquinoline, by a Schiemann reaction has also been reported by Belsten and Dyke.[9] They used a method similar to that of Bellas and Suschitzky, but reported a yield of only 28%.

2. Replacement of Chlorine.

The chlorine atom in 1-chloroisoquinoline was found to undergo halogen exchange when heated with anhydrous potassium fluoride in dimethylsulphone, giving 1-fluoroisoquinoline in 74% yield.[8] When this reaction was carried out on 1,3-dichloroisoquinoline, the more reactive 1-chlorine atom was replaced, giving 1-fluoro-3-chloroisoquinoline in 23% yield.



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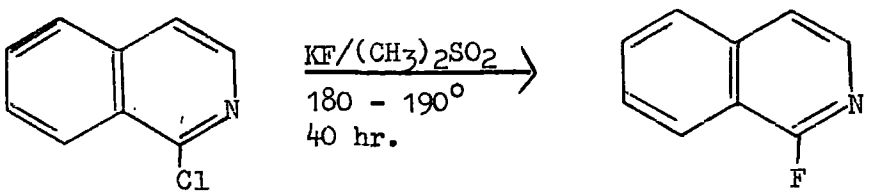
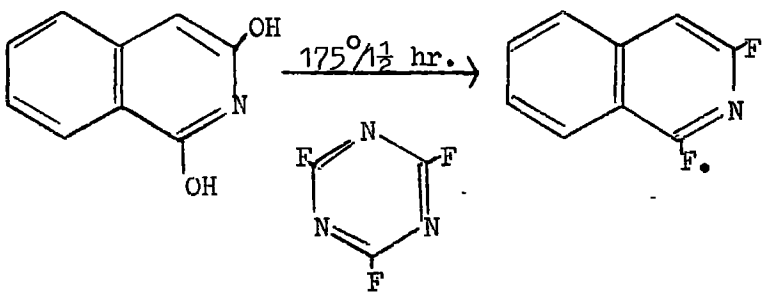


74%

3. Replacement of hydroxyl groups.

Hydroxyl groups in the 1- and 3-positions of the isoquinoline nucleus were found to undergo replacement by fluorine, when heated at 175° for 1½ hr. with 2,4,6-trifluoro-1,3,5-triazine in an autoclave.[10] This reaction is quite general for replacing hydroxyl groups α or γ to a heterocyclic-aza nitrogen.



Cyclisation Methods.

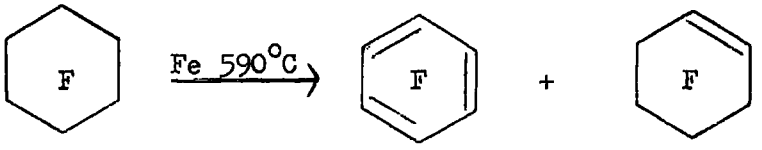
Although this method of synthesis has been used extensively for the synthesis of fluorine containing quinoline compounds,[11] very little has been done by way of its application to the synthesis of fluorine

containing isoquinoline compounds. The only published attempts at the direct synthesis of fluoroisoquinolines by a cyclisation method are by Roe and Teague,[7] who attempted the preparation of 6-fluoroisoquinoline by cyclisation of p-fluorobenzylideneaminoacetal, and Bellas and Suschitzsky,[8] who attempted to prepare 8-fluoroisoquinoline by means of a Pomeranz-Fritsch synthesis on o-fluorobenzylideneaminoacetal. Both these attempts however, failed.

The preparation of seven fluorinated 1-benzyl-3,4-dihydroisoquinolines and the corresponding tetrahydroisoquinolines, has been described by Belsten and Dyke.[9] They used the Bischler-Napieralski reaction on the corresponding amide. The tetrahydro compounds were obtained by reduction of the dihydroisoquinolines by sodium borohydride in methanol. The corresponding 2-methyl compounds were also prepared by the reduction of the 1-benzyl-3,4-dihydroisoquinolinium methiodides.

Conversion of Aromatic Compounds to Highly Fluorinated Aromatic Compounds by the Method of Halogen Exchange.

The most convenient method of preparing perfluorinated aromatic compounds is by defluorination of the corresponding alicyclic fluorocarbon.[12,13] Workers at Birmingham discovered that perfluorocyclohexadienes,[13,14] perfluorocyclohexenes,[12,13] and perfluorocyclohexanes,[12,13] were defluorinated to give good yields of perfluoroaromatic compounds when they passed in the vapour state over heated metals.



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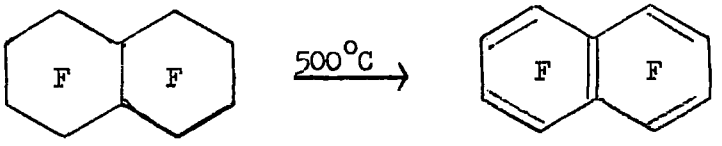

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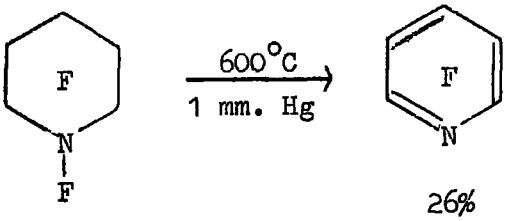

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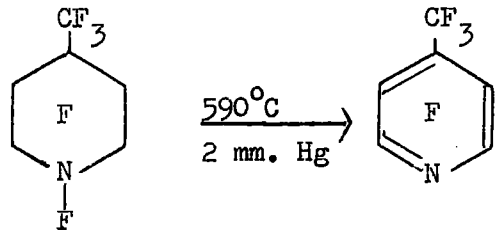

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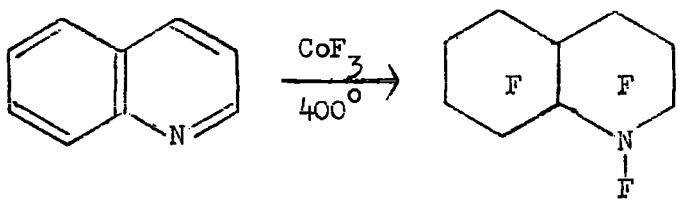
Obviously, this method is only of use if the necessary alicyclic fluorocarbon can be prepared easily. The methods by which aromatic compounds have been converted to the desired perfluoroalicyclic compound are those of exhaustive fluorination, with elemental fluorine and related methods, cobalt trifluoride and other high valency metal fluorides and electrochemical fluorination. Excellent review articles have been published on these methods and their applications.[17,18,19] However, attempts to utilise these methods for the exhaustive fluorination of aromatic nitrogen heterocyclic compounds brought only very poor and often inconsistent yields of the corresponding alicyclic compound, e.g.



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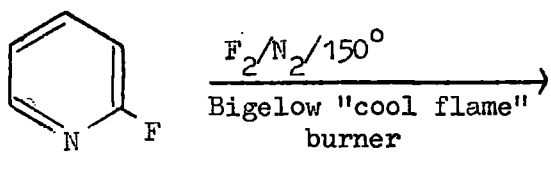

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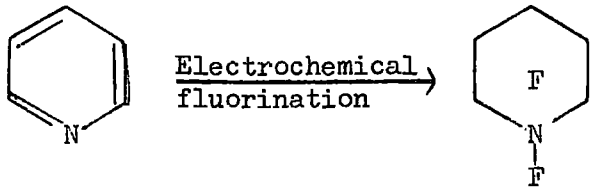

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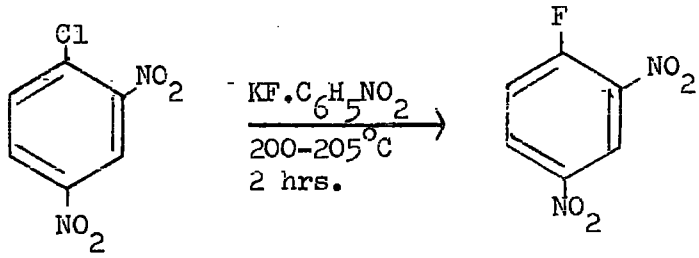
Very recently the method of halogen exchange,[23] which was first used by Gottlieb[24] in 1936 for the preparation of an aromatic fluoride from the corresponding aromatic chloride, has been developed as a means of producing perfluoroaromatics from perchloroaromatics,[25] including perfluoroaromatic nitrogen-heterocycles.[1,26]

The method of halogen exchange involves reaction under anhydrous conditions of an aromatic halide, usually the chloride, with a metal fluoride, often potassium fluoride, either in a suitable solvent heated to near its boiling point, or as an intimate mixture at elevated temperatures.

e.g.



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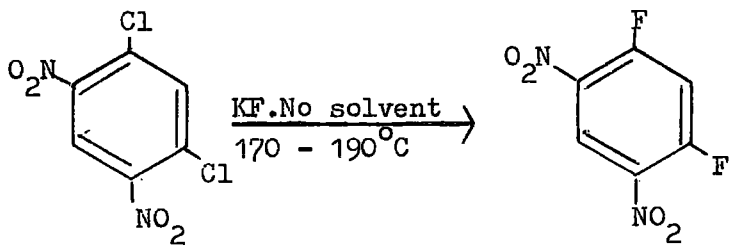

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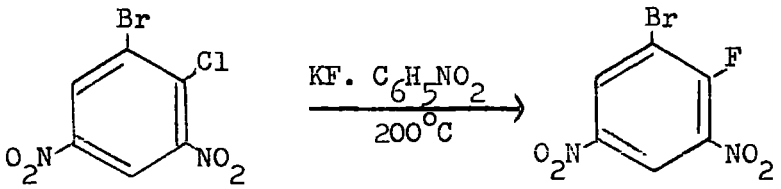
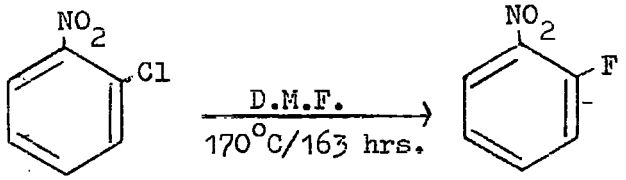
87%

When the reaction is carried out in the presence of a solvent the actual solvent used can greatly affect the extent of halogen replacement observed. Channing and Young[27] found that 3,5-dibromo-4-chloronitrobenzene did not undergo halogen exchange with potassium fluoride at 200°C in nitrobenzene, but 2,4-dinitro-6-bromo-chlorobenzene did.



It was therefore thought that activation by at least two nitro groups was necessary for halogen replacement. Finger[28,29] showed that the reaction could be extended to the less activated mono-nitro aromatic halides by employing the dipolar aprotic solvents dimethyl formamide (D.M.F.) and dimethyl sulphoxide (D.M.S.O.).



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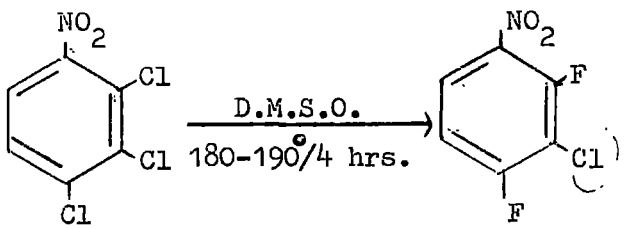
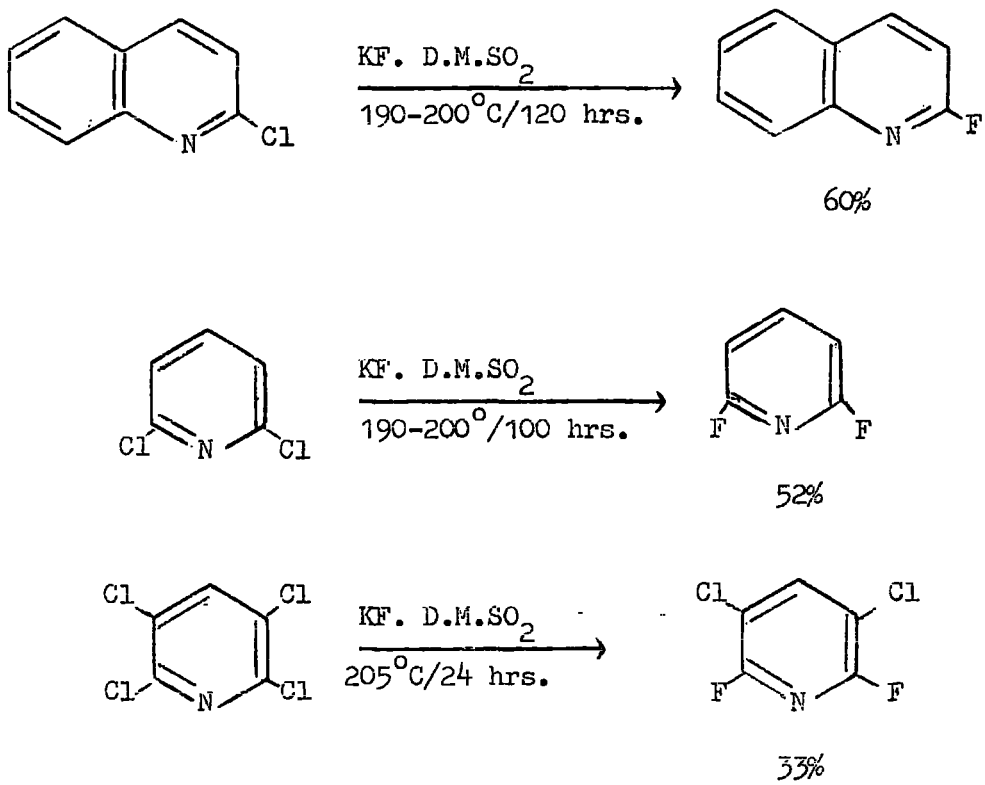
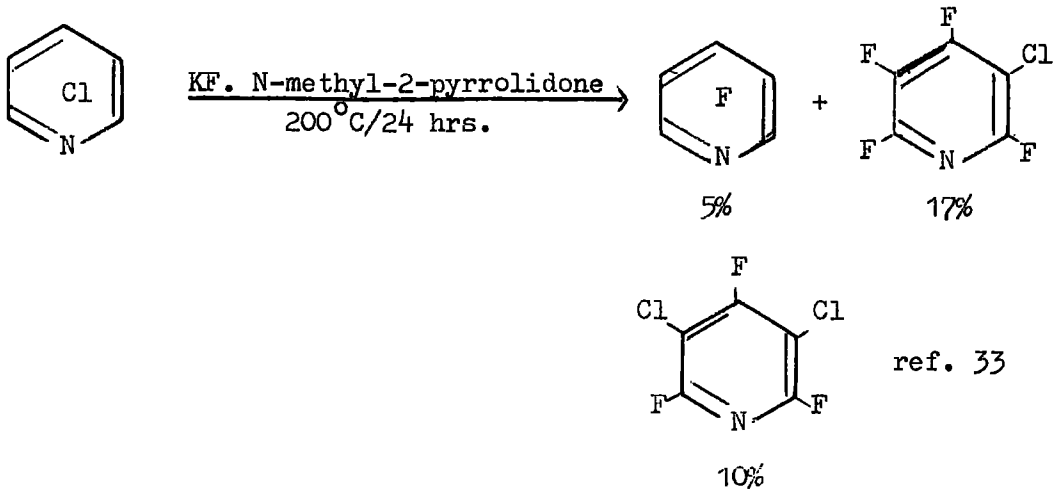
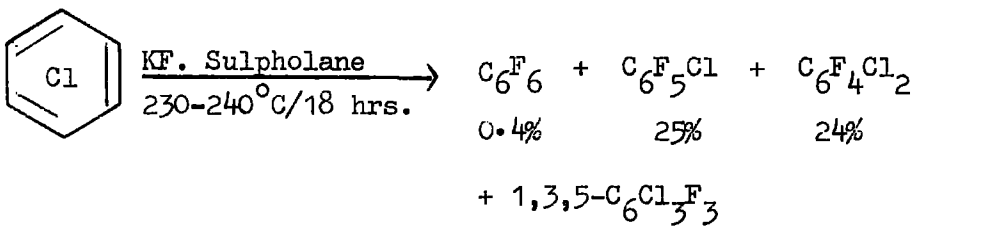


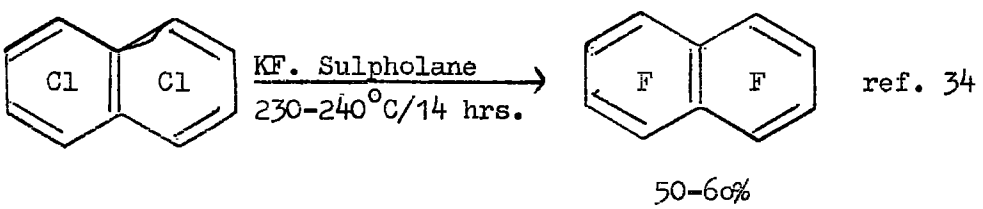
He further showed that the reaction did not occur in protic solvents (e.g. glycols) and the presence of moisture resulted in low yields. Dimethylsulphone (D.M.SO_2) was later found to be more effective as a reaction medium,[30] since it allowed a higher reaction temperature and with this solvent, the reaction was extended to halogenated aromatic nitrogen heterocyclic compounds.[31,32]



N-methyl-2-pyrrolidone and tetramethylene sulphone (sulpholane) are also very effective media for halogen exchange reactions, and have been used very recently to convert perhaloaromatic compounds to perfluoroaromatics.







The effectiveness of these dipolar aprotic solvents for halogen exchange has been studied by Parker[35,36] and co-workers.

Dipolar aprotic solvents are classed[36] as those with dielectric constants $>$ 15, which although they may contain hydrogen cannot donate

suitably labile hydrogen atoms to form strong hydrogen bonds with an appropriate species. Examples of such solvents include nitrobenzene, benzonitrile, nitromethane, acetone, dimethylformamide (D.M.F.), dimethylacetamide (D.M.A.C.), N-methyl-2-pyrrolidone, dimethylsulphoxide (D.M.SO), tetramethylenesulphone (sulpholane) and dimethylsulphone ($D.M.SO_2$). The more important properties of some of these are given in table A.

In this type of solvent, anions are poorly solvated, and much less so than cations,[35] solvation increasing with increasing size of the anion.[37] Solvation was found to increase down the series

$$I^- > SCN^- > Br^- > N_3^-, Cl^- \gg F^-$$

The low solvation appears to be due to a steric resistance to solvation of small anions by the bulky dipoles present in these solvents, with the result that the positive end of the dipole cannot fit closely round the small anion. Also in these solvents there is no significant contribution to solvation by hydrogen bonding, which if it occurred would be more important for the smaller anions. On the other hand when solvation is by the small unshielded proton of protic solvents (e.g. H_2O, MeOH, $HCONH_2$) steric resistance is negligible, so that small anions are highly solvated by the close fitting protic solvent dipoles. Furthermore, hydrogen bonding is important in protic solvents and these bonds are stronger the smaller the anion. Consequently, in protic solvents, small anions are more solvated than large anions and solvation

Table A

Solvent	M.p. °C	B.p. (76 cm.) °C	Di-electric Const.	Dipole Moment (Debyes)	Solubility in water
$C_6H_5NO_2$ [a]	5·7	210·8	34·5	4·27	slight decomp.
C_6H_5CN [b]	-12·9	191·1	25·2	4·05	Decomposes
CH_3CN [c]	-45	81·6	37·5	3·37	Very
Dimethyl Sulphoxide [c]	18·5	189	48·9	4·3	Soluble
Dimethyl Sulphone [a]	109	233·5		4·49	Soluble
Dimethylformamide [c]	-61	152·5	37·6	3·82	Very
Tetramethylene Sulphone	28·4 [d]	280(d) [e]	44 [d]	4·69 [f]	Soluble
N-Methyl-2-pyrrolidone [a]	-17	197-202			Very
Dimethylacetamide [c]	-20	165·5	37·8	3·79	Soluble

References to Table A.

a. Handbook of Chemistry and Physics, 46th Edition. The Chemical Rubber Co.

b. Technique of Organic Chemistry, Vol. VII, Ed. Weissberger, Proskauer, Riddick and Troops.

c. A.J. Parker, Advances in Organic Chemistry, Vol. 5, p.3, Interscience, 1965.

d. E.M. Arnett and C.F. Danty, J. Am. Chem. Soc., 1965, 86, 409.

e. R.D. Chambers, M. Hole and W.K.R. Musgrave, Unpublished Observation. Decomposition becomes appreciable above 240°C.

f. A.J. Parker, Quart. Rev., (London), 1962, 163.

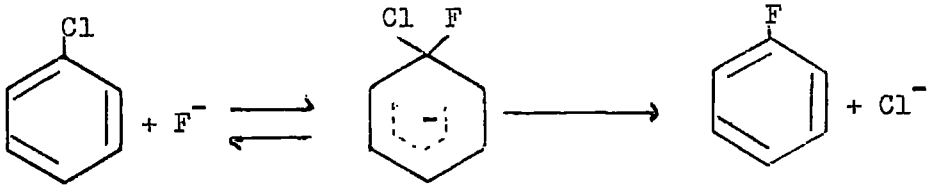
is found to increase through the series

$$SCN^- < I^- < Br^- < N_3^- < Cl^- < F^-$$

That phenyltrimethylammonium hydroxide has a base strength 10^6 times greater in sulpholane than in water,[38] and potassium fluoride in D.M.F. or D.M.SO. will abstract a proton from primary alkyl halides and cause dechlorination, or dehydrochlorination of highly chlorinated aliphatic compounds,[39] are a consequence of the low solvation of small anions in these solvents.

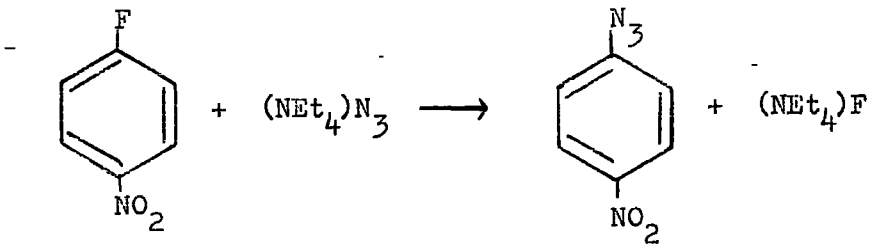
In contrast to the low solvation of anions in dipolar aprotic solvents, cations are highly solvated by these solvents. This is due to them having a region of high electron density; localised usually on a bare oxygen atom, which allows strong interaction with the cation. The type of dipole present is also important. Thus, although alkyl and aryl nitro compounds have high dielectric constants, cations are poorly solvated because the negative portion of the dipole is dispersed. It is this cation solvation that renders electrolytes soluble.

The reaction of an aromatic chloride with potassium fluoride to form the aromatic fluoride, most likely proceeds with the fluoride ion as the nucleophile, via a bimolecular mechanism,[40]



(A)

involving a definite intermediate, (A), the formation of which is the rate determining step. The intermediate (A), is a good approximation to the transition state. Thus compared with the attacking nucleophile, it is large with its negative charge well dispersed. As a result, hydrogen bonding between it and protic solvents will be less important than for small anions, and such transition states tend to be similarly solvated in dipolar aprotic and protic solvents.[41] The greater solvation of small anions in protic, than in dipolar aprotic solvents coupled with the similarity of solvation in the two kinds of solvents, of the transition state, results in the reaction proceeding faster in dipolar aprotic solvents than in protic solvents.[42] The lower solvation of the anion in dipolar aprotic solvents leads to a lower activation energy for the reaction with subsequent increase in rate. Miller and Parker[37] measured the rate of the bimolecular nucleophilic aromatic substitution reaction



in various dipolar aprotic solvents. They were compared with the rate in methanol (Table B) and show clearly the great increase in the rate of reaction caused by changing from a protic to a dipolar aprotic solvent.

Table B

Solvent	Ratio $\frac{k(solvent)}{k(MeOH)}$	Temp.
NH_2CHO	5·6	100°C
NHMeCHO	15·7	100°C
NMe_2CHO	$4·9 \times 10^3$	100°C
NMe_2CHO	$2·4 \times 10^4$	25·1°C
NMe_2COMe	$8·8 \times 10^4$	25·1°C
Me_2CO	$2·4 \times 10^4$	25·1°C

The marked increase in rate as the hydrogen atoms in formamide are replaced by methyl groups shows clearly that hydrogen bonding reduces the rate of the reaction.

The lower yields observed when water is present[28] can be partially attributed to hydrogen bonding by the protic impurity. However, the dipolar aprotic solvent will compete with the anion for the protic impurity, and Parker[42] has shown that small amounts of protic impurity do not cause a large reduction in the rate of bimolecular nucleophilic substitution reactions at saturated carbon. A similar effect on aromatic bimolecular nucleophilic substitution reactions will also presumably operate. Chemical reaction of the protic impurity with the substrate was the main reason for the low yields observed by Finger,[28] from halogen exchange reactions carried out in the presence of water.

As regards the relative efficiencies of dipolar aprotic solvents as media for the halogen exchange reaction, Parker[35] has suggested that general cation solvation may decrease in the series of solvents D.M.SO, D.M.A.C. > D.M.F. > $(CH_3)_2CO$, sulpholane > CH_3CN, CH_3NO_2 > PhCN, $PhNO_2$.

In the absence of any specific cation-solvent interaction, such as complex formation, this would be the expected order of their efficiency for promoting halogen exchange under the same conditions. Maynard[39] found the following order of effectiveness for the reaction between potassium fluoride and hexachloropropene.

Sulpholane > D.M.F. > N-methyl-2-pyrrolidone, $D.M.SO_2$ > D.M.A.C. $\gg$ $C_6H_5NO_2$.

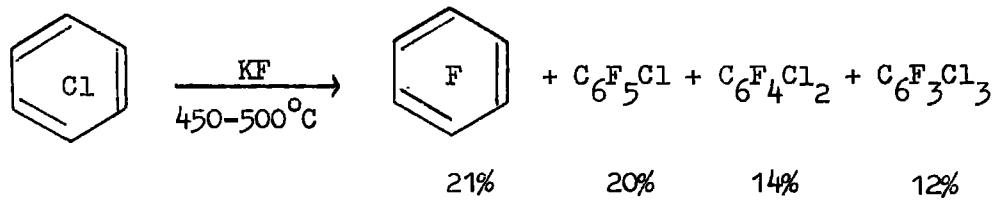
The order is somewhat approximate, as the reaction conditions were not standardised for each solvent, but it does show the low efficiency of nitrobenzene, the solvent used for the first aromatic halogen exchange reaction by Gottlieb.[24] Hexachlorobenzene has been reacted with potassium fluoride in a number of dipolar aprotic solvents to give products varying greatly in their fluorine content.[39,34,43] Some of these are tabulated below. The reaction conditions varied with each solvent so that no direct comparison of relative efficiencies can be made. The higher reflux temperature possible with sulpholane makes this perhaps the best solvent for the preparation of highly fluorinated aromatics by halogen exchange. It also has good thermal and chemical stability, an absence of side reactions which could form nucleophilic

Aprotic Solvent	Temp.	Time (hrs.)	Product (% yield)
C_6H_5CN	175	18	C_6Cl_6 recovered
$C_6H_5NO_2$	193	20	" "
D.M.F.	153	36	$C_6Cl_3F_3$(51), $C_6Cl_4F_2$(24)
D.M.SO.	180-190	5	C_6ClF_5(0·4), $C_6Cl_2F_4$(3), $C_6Cl_3F_3$(3)
N-methyl-2-pyrrolidone	195-200	3	C_6F_5Cl(trace), $C_6Cl_2F_4$(34) $C_6Cl_3F_3$(23)
Sulpholane	230-240	18	C_6F_6(0·4), C_6ClF_5(25), $C_6Cl_2F_4$(24), $C_6Cl_3F_3$(30)

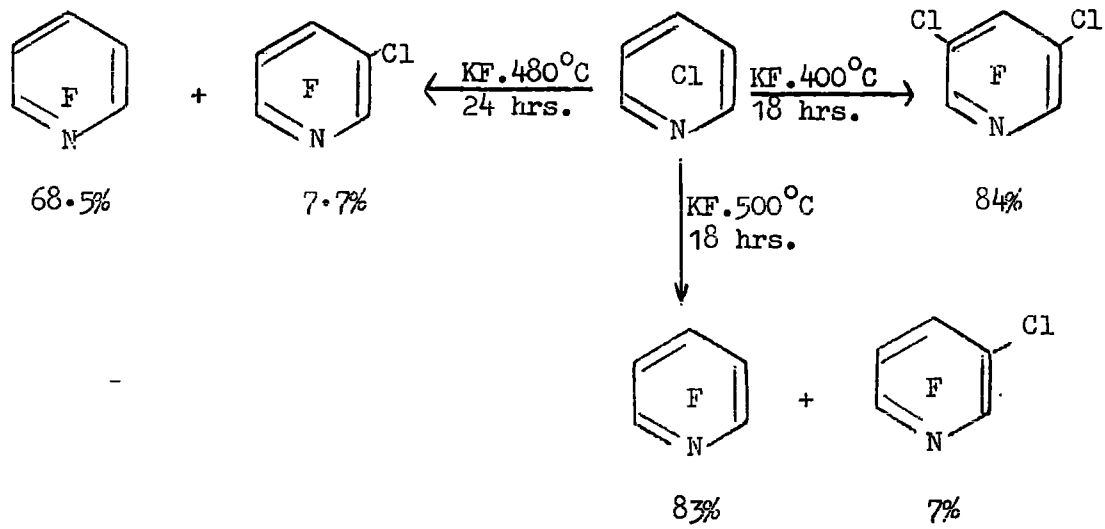
impurities and is miscible with water, allowing ready isolation of the product. The thermal instability of dimethyl sulphoxide and formation of sulphur containing by-products[31] reduces its usefulness. Dimethyl sulphone is rendered less convenient by the fact that it is a high-melting solid.

For the preparation of highly fluorinated aromatic compounds in good yield a higher temperature than is possible with the above solvents is normally required, and reaction in the absence of solvents at elevated temperatures made possible the preparation of perfluoro-aromatic compounds in good yield. Russian workers[25] converted

hexachlorobenzene to the perfluoro compound by heating with potassium fluoride at 450°-500°C.



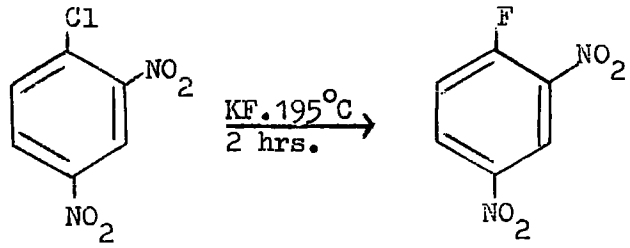
The reaction was extended to the preparation of pentafluoropyridine by workers at Durham[1] and later at Manchester.[33]



Subject to the starting material and product being stable at these elevated temperatures this method appeared the most promising for the preparation of highly fluorinated isoquinolines, although results cannot always be predicted in advance because heptachloroindole[44] was found

only to give decomposition products when heated with potassium fluoride at temperatures necessary to give complete replacement of chlorine by fluorine.

Although potassium fluoride is the most commonly used metal fluoride for the halogen exchange reaction with aromatic halides, several others have been used. Finger and Kruse[43] studied the reaction between 2,4-dinitrochlorobenzene and the alkali metal fluorides in D.M.F. They found that lithium and sodium fluorides showed no appreciable reaction under conditions for which potassium, rubidium and caesium fluorides were effective. The same compound was reacted in the absence of solvent, by a number of alkali and alkaline earth metals by Russian workers.[45]



51%

Under the same conditions, lithium fluoride and sodium fluoride were not reactive whilst rubidium and caesium fluorides were more reactive, giving yields of 88 and 98% respectively. Calcium and barium fluorides were found to be ineffective at 200°C for 5 hrs., as was zinc fluoride.

The observed order of the reactivity of the alkali metals,

$$LiF < NaF < KF < RbF < CsF$$

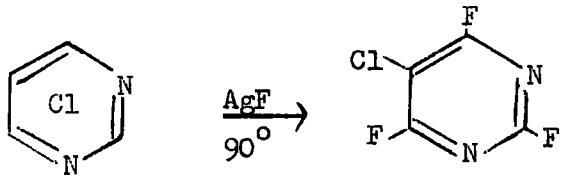
closely resembles their relative crystal lattice energies.

Compound	Lattice Energy (k.cal./g. formula wt.)*)
LiF	240
NaF	213·4
KF	189·7
RbF	181·6
CsF	173·7

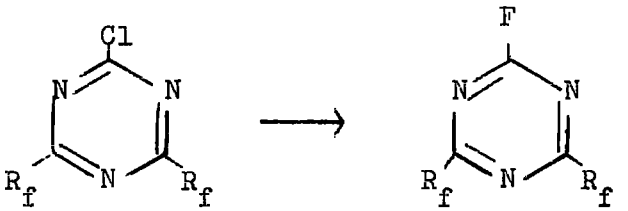
*Taken from the 'Handbook of Chemistry and Physics', 46th Edn., F.129, The Chemical Rubber Company.

Even in the absence of a solvent it is most likely that the reaction takes place in solution in the molten nitrochloro compound. From a consideration of the lattice energies, solubility will increase as the size of the cation increases (i.e. from Li to Cs). Also the larger cation results in a higher degree of dissociation of the metal fluoride, with the result that the concentration of fluoride ion in solution increases from lithium to caesium, accounting for the observed order of reactivity. It is possible that an ion-pair of the alkali fluoride is the reactive species. In this case, the increasing degree of polarisation of the ion-pair with increasing size of the cation and the increasing solubility of the metal fluoride from lithium to caesium accounts for the observed order of reactivity. Potassium fluoride is most widely used, because of its relative cheapness and availability.

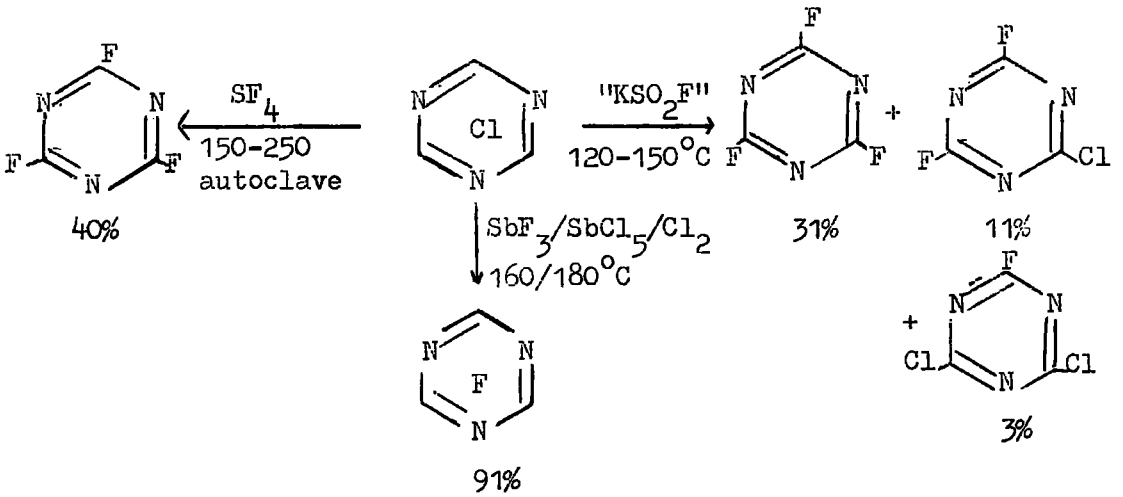
A number of other fluorides have been used to effect halogen exchange, notably with the "active" chlorine atoms of chloropyrimidines and chlorotriazines. Silver fluoride, AgF, was found to exchange the active chlorines in chloropyrimidines,[46]



and the exchange reaction of the triazine



was achieved using either silver monofluoride, silver difluoride, mercuric fluoride or antimony trifluoride dichloride (SbF_3Cl_2) but not lead difluoride.[47] Trichloro-1,3,5-triazine has been converted to the perfluoro analogue using sulphur tetrafluoride,[48] potassium fluoro sulphinate[49] or Swartz reagent.[50]



The Preparation of Bromo- and Chloro-Isoquinolines.

The successful conversion of hexachlorobenzene[25] and pentachloropyridine,[1] by means of the halogen exchange reaction, to the corresponding perfluoro-analogues, suggested that this approach might well provide a means of preparing heptafluoroisoquinoline. The success of this method of approach to the synthesis of this compound depends of course, upon an efficient method of preparing either of the hitherto unknown compounds, heptachloro- or heptabromo-isoquinoline.

A survey of the methods of preparing chloro- and bromo-isoquinolines reveals that, because of the desire to produce compounds of known orientation, cyclisation methods and replacement of functional groups at known positions have been used in preference to the direct introduction of the halogen. Generally, chloroisoquinolines are prepared from amino-isoquinolines by way of the Sandmeyer reaction; and from isocarbostyrils or isoquinoline-N-oxides by treatment with chlorides of phosphorus. Also, a number of chloroisoquinolines have been obtained as the products of a number of isoquinoline syntheses. Consequently, very little work has been done on the direct chlorination and bromination of the isoquinoline nucleus, and no attempts have been made at exhaustive halogenation.

The Direct Introduction of Chlorine and Bromine into the Isoquinoline Nucleus.

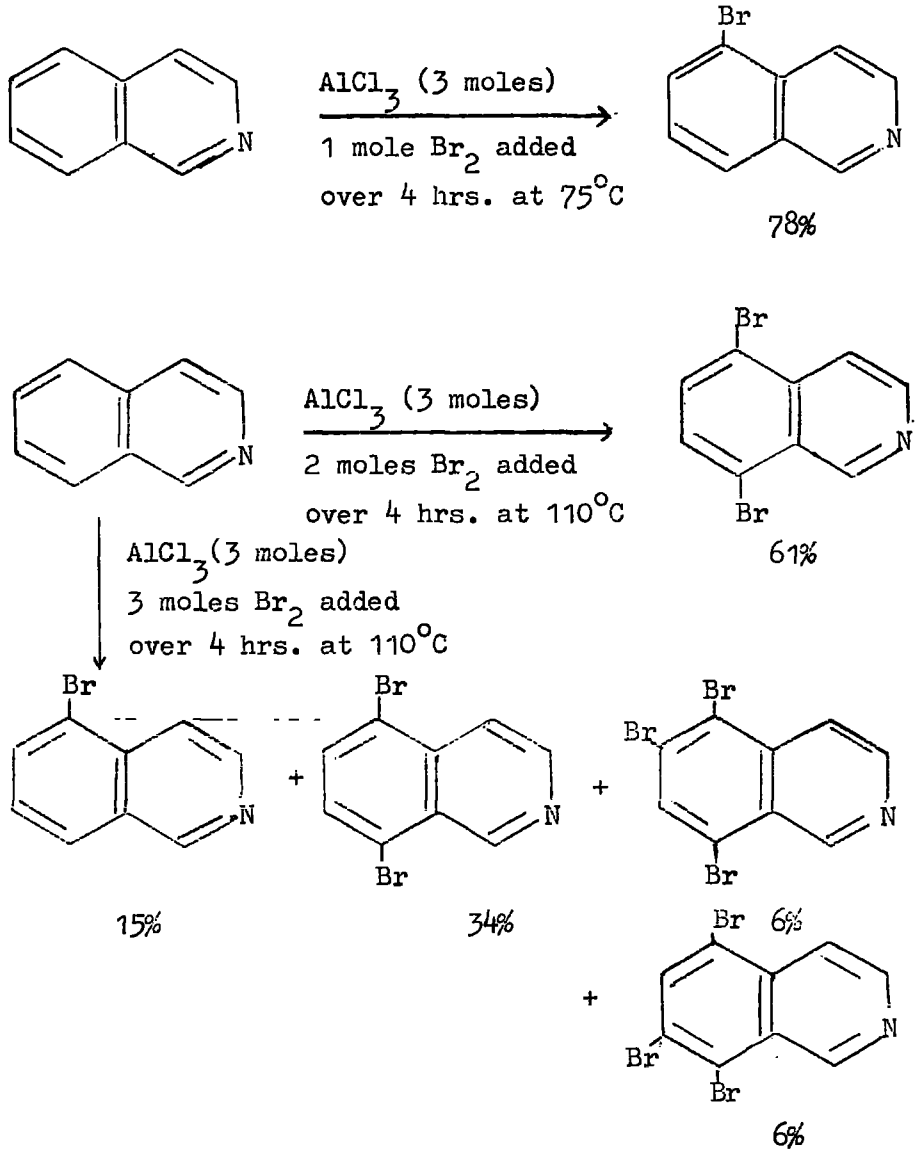
One of the few published attempts at the direct introduction of chlorine into isoquinoline, is the conversion of 7-acetamidoisoquinoline,

with chlorine in the presence of sodium acetate to 7-acetamido-8-chloro-isoquinoline.[51] This reaction however showed erratic behaviour. The bromination of isoquinoline in the gaseous phase has been extensively studied by Jansen and Wibaut.[52] They carried out the reaction at 480°C, introducing the isoquinoline and bromine with a stream of nitrogen into an empty glass reaction tube to prevent 'choking'. From this they reclaimed isoquinoline, 1-bromoisoquinoline, and traces of other unidentified products. At 300°C, no reaction took place. The tendency toward bromination in the position α to the ring nitrogen rather than β to the ring nitrogen suggests that bromine atoms are involved.

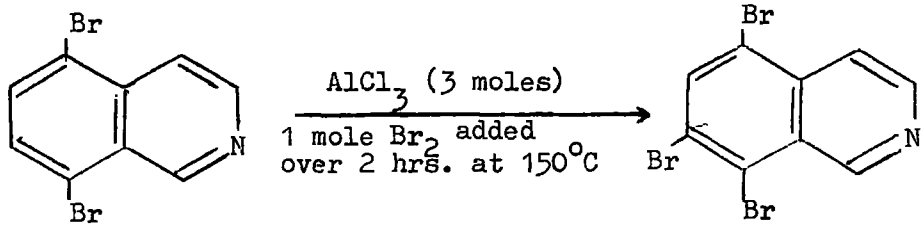
In contrast to the vigorous conditions required above, to achieve the substitution of but a single bromine atom, the bromine in isoquinoline perbromide[53,54] will substitute into the isoquinoline nucleus under very mild conditions. It was found that a tribromoisoquinoline[52] was formed on heating an alcoholic solution of isoquinoline perbromide. Edinger,[53] found that on heating the hydrobromide of isoquinoline perbromide to 190°C, 4-bromoisoquinoline was formed, its structure being demonstrated by oxidation using potassium permanganate.[55] No yields were quoted for these reactions.

4-Bromo-5-nitroisoquinoline,[56] 1-chloro-4-bromoisoquinoline,[57] and 4(?)-bromo-N-methylisocarbostyril[58] have been obtained from 5-nitro-isoquinoline, 1-chloroisoquinoline, and N-methylisocarbostyril, respectively, by bromination according to the method used for obtaining 4-bromoisoquinoline.

Gordon and Pearson[59] found that the complex formed between isoquinoline and aluminium trichloride, on treatment with chlorine or bromine at 80-150°C, resulted in good yields of halogenated isoquinolines. Substitution occurred only in the benzene ring and a trihaloisoquinoline was formed at a temperature of 150°C.



They found however, better yields of 5,7,8-tribromoisoquinoline were obtained by mono-bromination of 5,8-dibromoisoquinoline, i.e.

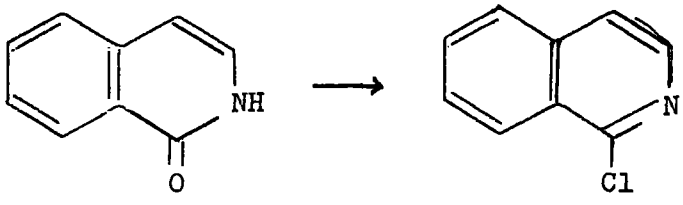


75%

Chlorination by this method was claimed to be similar to the bromination reaction, except that it was much less selective. The highly halogenated isoquinolines were readily isolated by simply decomposing the haloisoquinoline complex with ice, and filtering off the precipitated haloisoquinolines, thus providing a convenient preparation of 5,7,8-tribromo- or 5,7,8-trichloro-isoquinoline. This method was used in the present work as the first stage in a two stage synthesis of heptachloroisoquinoline, and is discussed in more detail later.

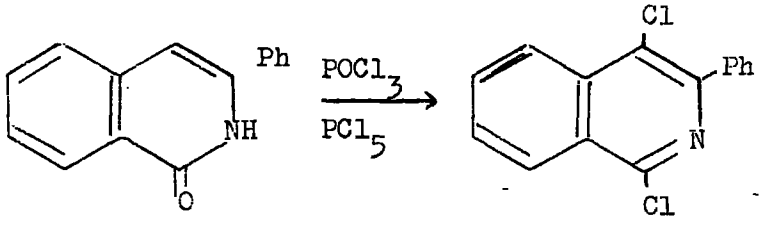
Replacement of Functional Groups and Cyclisation Methods.

a) Chlorination. The conversion of isocarbostyril to 1-chloroisoquinoline with phosphorus oxychloride (or other phosphorus chlorides) has been carried out. Substituted isocarbostyrils react in an analogous fashion.[60]



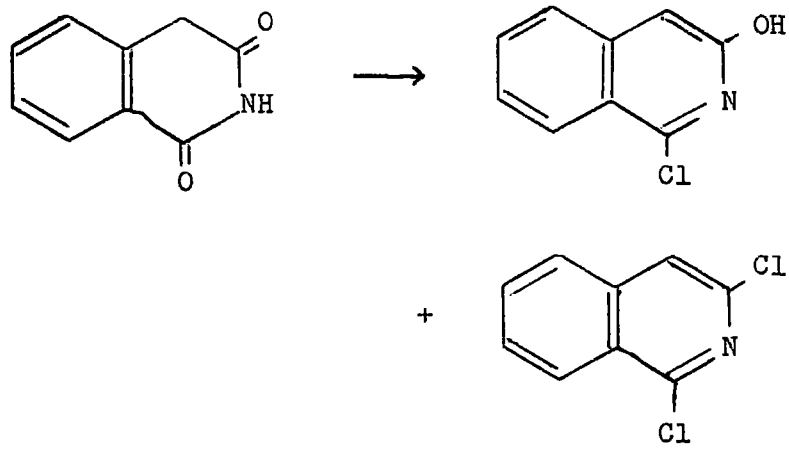
It is probable that the reaction involves the isocarbostyril in the form of a 1-hydroxyisoquinolinium derivative, and addition of chlorine to the reactive 1-position. An alkyl group attached to the nitrogen does not block the reaction; the conversion of N-alkylisocarbostyrils to 1-chloroisoquinolines occurs without much difficulty.[57] It is suggested that the N-alkylisocarbostyril gives rise to the quaternary 1-chloroisoquinolinium salt, which, under the conditions of the reaction, loses the alkyl group in the form of the chloride.

In this type of reaction, the insertion of chlorine not only at the 1-position, but also at the 4-position has been observed. Thus in the reaction of 3-phenylisocarbostyril with a mixture of phosphorus oxychloride and pentachloride, the main product is not 1-chloro-3-phenylisoquinoline but is, instead, 1,4-dichloro-3-phenylisoquinoline.[61]



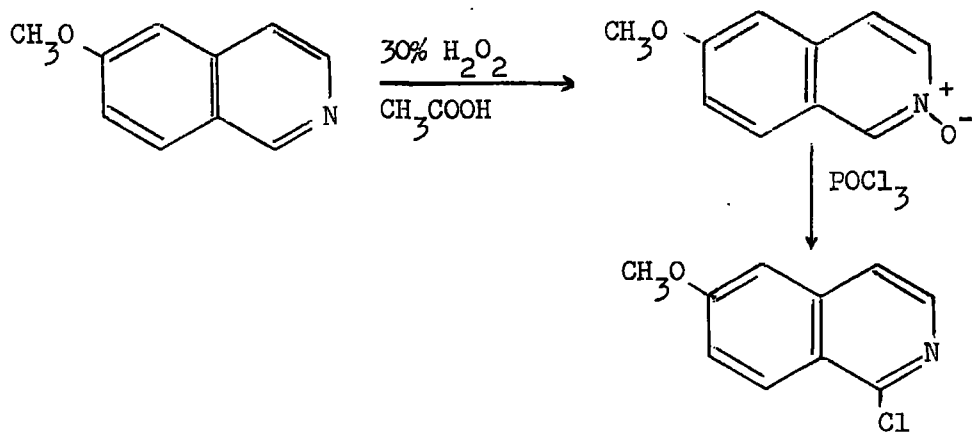
1,4-Dichloroisoquinoline has been found likewise in the product from N-methylisocarbostyril, but only in small amounts.[62]

Homophthalimide can be converted to 1-chloro-3-hydroxyisoquinoline and also to 1,3-dichloroisoquinoline[62] using similar reagents.



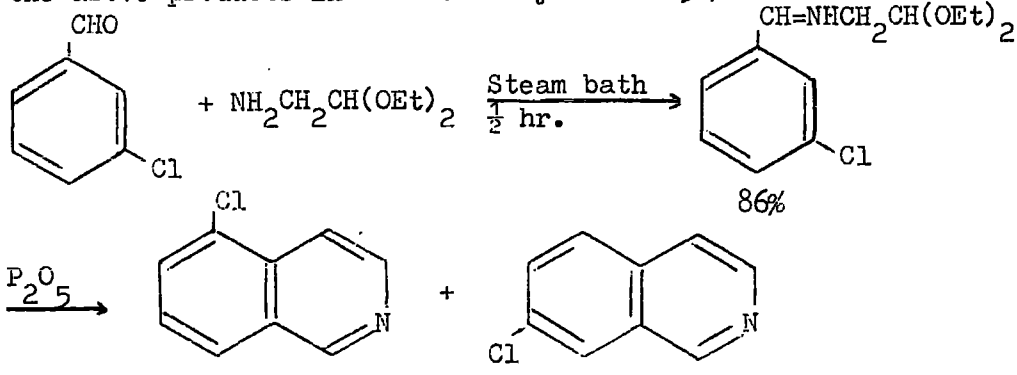
The conversion of 6-hydroxyisocarbostyril to 1,6-dichloroisoquinoline[63] involves the replacement of a Bz-hydroxyl group with chlorine. It should be noted that the conditions used to effect the transformation at the 6-position (as well as the 3-position) are more rigorous than those used for the 1-position.

The Meisenheimer procedure has been used effectively in the preparation of several 1-chloroisoquinolines.[64] The N-oxides were usually prepared by oxidation with hydrogen peroxide (30%) in glacial acetic acid. Treatment of the N-oxide with phosphorus oxychloride furnishes the corresponding 1-chloro-isoquinoline e.g.

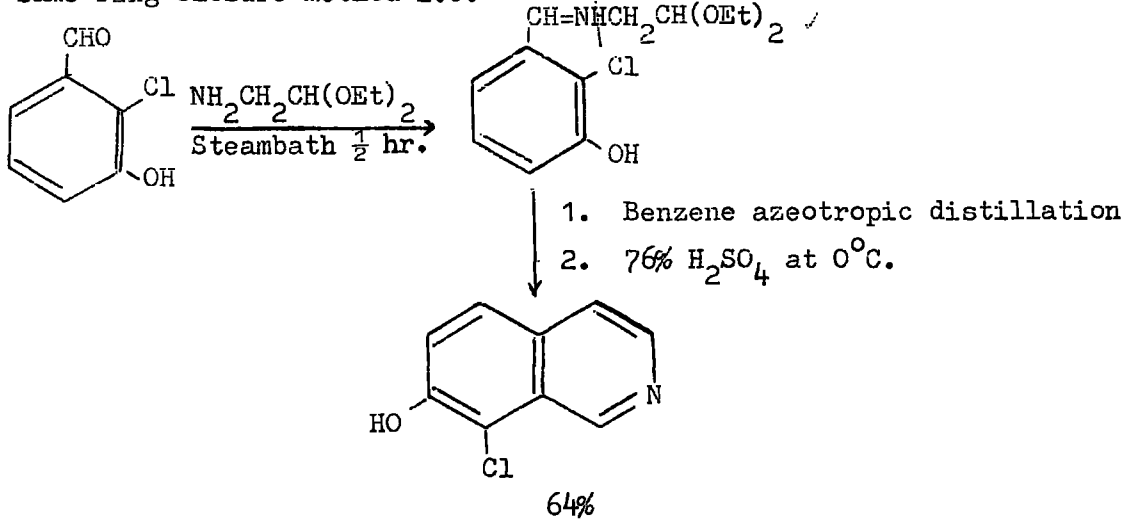


Diazotisation of 1-aminoisoquinoline in concentrated hydrochloric acid has been shown to give 1-chloro-isoquinoline;[65] and Sandmeyer reactions with 5-aminoisoquinoline and 7-aminoisoquinoline have been employed in the preparation of 5-chloro- and 7-chloro-isoquinoline, respectively.[64]

Ring syntheses have occasionally been used to prepare chlorinated isoquinolines and isoquinoline derivatives. 5- and 7-Chloro-isoquinolines have been prepared by Mauske and Kulka.[51] Using a suitably substituted chlorobenzaldehyde, they employed a Pomeranz-Fritsch synthesis to give the above products in an overall yield of 38%.



These workers also synthesised 7-hydroxy-8-chloroisoquinoline using the same ring closure method i.e.



b) Bromination.

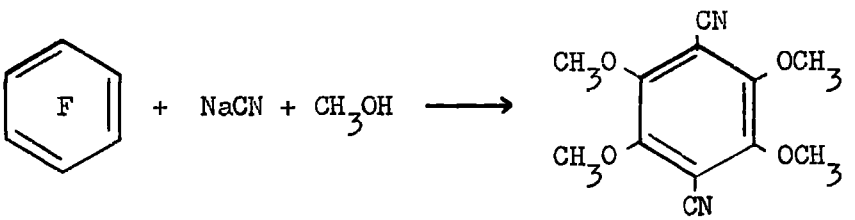
Isoquinoline-4-mercurichloride can be converted to 4-bromo-isoquinoline by treating the mercuri compound with bromine.[66] In contrast, the replacement of the sulphonic acid group in isoquinoline-5-sulphonic acid with bromine, by treatment with bromine water has not succeeded.[67] With phosphorus pentabromide at elevated temperatures, the sulphonic acid yielded a mono-bromo- as well as a dibromo-isoquinoline of undetermined structure. Diazotisation procedures have been employed effectively in the conversion of 5-amino- to 5-bromo-isoquinoline,[68] and in the conversion of 4-bromo-5-aminoisoquinoline to 4,5-dibromoisoquinoline.[53] 1-Bromoisoquinoline was formed in the reaction of isocarbostyril with phosphorus tribromide;[54] with phosphorus pentabromide a dibromide of unknown structure was obtained.[55]

Ring cyclisation methods, analogous to those used in the preparation of chloro-compounds, have been used to prepare monobrominated isoquinolines.

Nucleophilic Substitution in Polyfluoroaromatic and Heterocyclic Compounds.

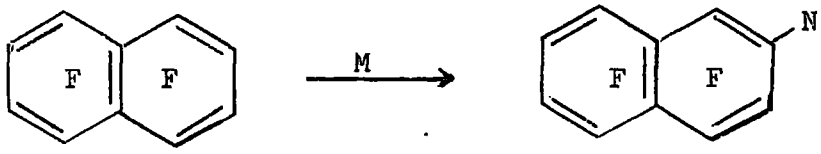
The most characteristic reaction of highly fluorinated aromatic compounds, is that involving the displacement of a fluoride ion by a nucleophile. The reactions of highly fluorinated homocyclic compounds, especially hexafluorobenzene and various substituted pentafluorobenzenes, with nucleophiles has been extensively studied. However, only relatively recently has it been possible for such an investigation to be carried out on a heterocyclic compound, and prior to the present work, the only available system for study was pentafluoropyridine.

The reaction of hexafluorobenzene with a wide variety of nucleophiles has been studied[69] principally by workers at the University of Birmingham. In the cases where the nucleophiles were OCH_3^-,[70] OH^-,[71,72] SH^-,[73] NH_3,[74] $NH_2NH_2H_2O$,[74] CH_3NH_2,[74] R^- [75,76] (where R = CH_3- or C_6H_5-), reaction under moderate conditions gave reasonably high yields of the C_6F_5X compound, where X = -OMe, -OH, -SH, $-NHNH_2$, $-NH_2$, CH_3NH-, and C_6F_5R (where R = CH_3- or C_6H_5-). A notable exception to the replacement of a single fluorine atom, was in the reaction with CN^-, in the presence of methanol,[77] where one of the compounds formed was that in which all the fluorine atoms were replaced.



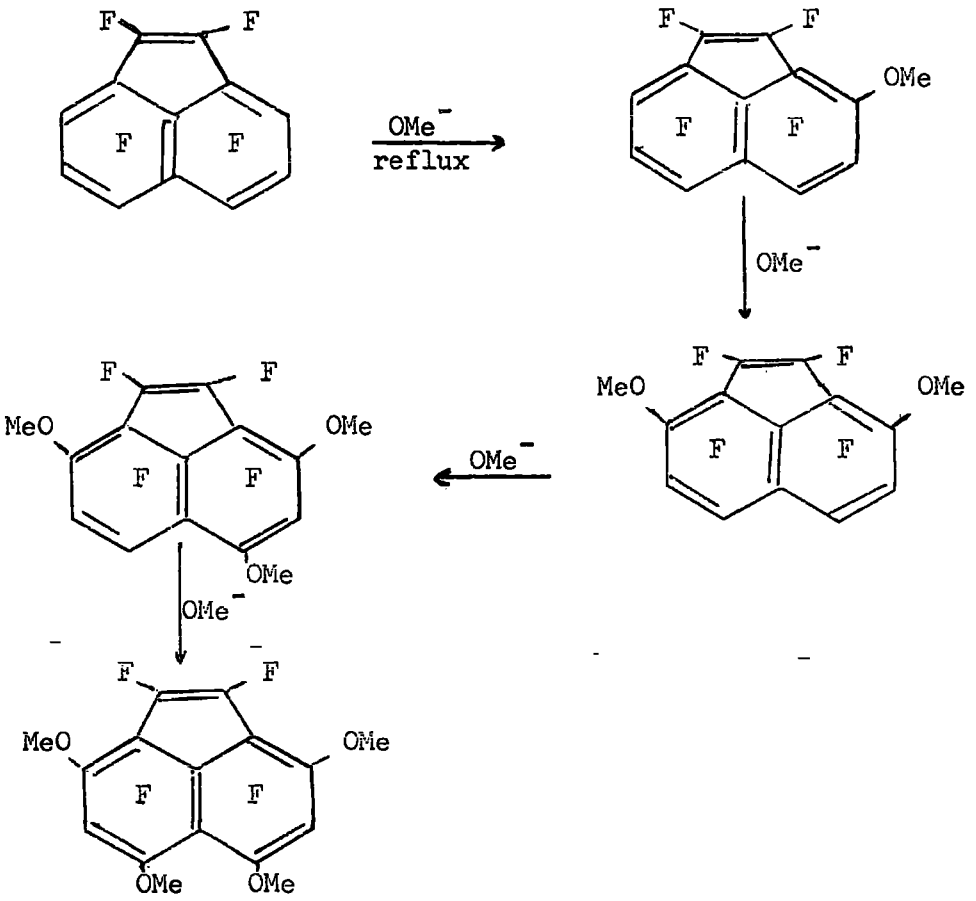
Further attack by nucleophiles on the C_6F_5X compounds can be accomplished, and is of considerable interest because different positional isomers can be formed. Nucleophilic replacement of fluorine in C_6F_5X compounds was found to occur at the position para[69] to the group X when, for example, X = H, CH_3, CF_3, SMe, SO_2Me, NMe_2, Cl, Br and I. However, when X = OMe, and NHMe, para and meta replacement of fluorine[78,79] occurred to a similar extent, while with X = NH_2 and O^-, predominantly meta replacement of fluorine occurred.[71,78,79] The nature of the nucleophile had relatively little effect on determining the orientation in these instances. In certain cases (X = NO_2, NO, CO_2^-), deviations from the above generalisation occurred,[80-82] and reaction took place mainly at the para position with sodium methoxide in methanol, but gave high ortho replacement (in some cases > 50%) with certain amines. It has also been shown that pentafluoronitrobenzene reacts with sodium methoxide in ether containing a little methanol to give high ortho replacement (> 50%).[83]

The reaction of highly fluorinated polycyclic aromatic compounds with nucleophiles has also been studied, but much less extensively than hexafluorobenzene. Octafluoronaphthalene reacts readily with nucleophiles,[84] fluorine displacement occurring in the β-position to give good yields of heptafluoronaphthalene derivatives.



M = $NH_2NH_2H_2O$, MeLi, $LiAlH_4$, NaOMe, KOH, giving N = $NHNH_2$, Me, H, OMe, and OH.

Octafluoroacenaphthylene is readily substituted by nucleophiles (NaOMe, NH_3, $NH_2NH_2.H_2O$ and $LiAlH_4$). With sodium methoxide in methanol, polysubstitution readily occurs i.e.

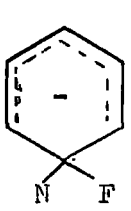


The tetramethoxytetrafluoroacenaphthylene was found to be inert towards further substitution by nucleophiles.

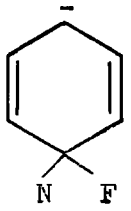
The first attempt to rationalise the results obtained from nucleophilic substitution reactions in C_6F_5X compounds, was a suggestion[69,86,87] that the five fluorines direct replacement para to X, and that X may enhance or oppose this directive effect. However, this explanation was found lacking as more information on the behaviour of C_6F_5X compounds towards nucleophilic substitution was obtained. For example, chloropentafluorobenzene[88] and pentafluoroanisole[80] gave more ortho-replacement than any other substrate (except for anomalous reactions of pentafluoronitrobenzene which involve specific nucleophile-substituent interactions). Also chloropentafluorobenzene reacted with methoxide ion faster than pentafluorobenzene did,[89] which implied that chlorine activates para attack more than hydrogen does. However, pentachlorobenzene reacted with nucleophiles at the position para to the hydrogen,[90] which implies the reverse. These early attempts provided no real explanation for the preferential attack of nucleophiles on octafluoronaphthalene at the β-position.[84]

The most successful attempt at a general rationalisation of orientation and reactivity in polyfluoroaromatic systems has been put forward in a paper by Burdon.[91] He suggested that all the results obtained on the orientation of nucleophilic substitution could be rationalised by a consideration of the relative stabilities of the transition states concerned, except in cases where steric, solvent and substituent-nucleophile effects were in operation. His ideas can be outlined as follows.

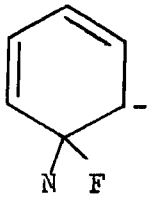
The transition state for the reactions of polyfluoroaromatic compounds with nucleophilic species can be discussed in terms of Wheland type intermediates (I), since these usually provide good guides to transition states.



I



II

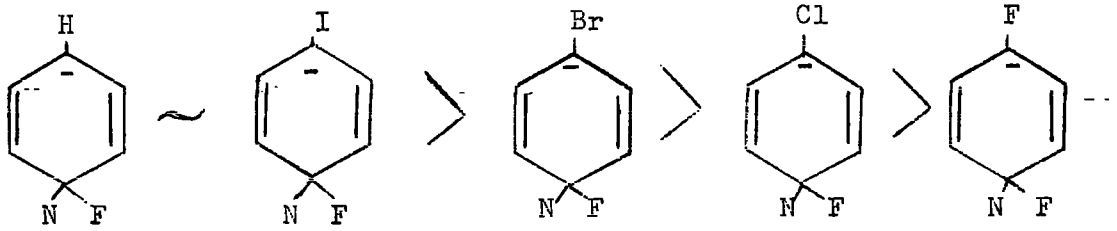


III

The resonance hybrid II can be assumed to be the main contributor to this intermediate, with the hybrid III of only secondary importance. This assumption receives considerable justification from the results of advanced molecular orbital calculations.[92] In considering substitution in C_6F_5X compounds, the problem resolves itself into a discussion of the influence of the substituent attached to the carbon bearing the negative charge, on the stability of the negative charge. If the substituent, X, stabilises the negative charge more than does fluorine then nucleophilic substitution will take place at the carbon para to it, and to a lesser extent, ortho; whereas if it destabilises the charge more than fluorine meta attack will occur.

Even though this approach is simple, a qualitative rationalisation is possible if substituents are considered to have a stabilising or destabilising effect on intermediates of type II and III.

The nitro and trifluoromethyl groups will stabilise negative charges on the carbon to which they are attached by inductive effects and in the case of the former by delocalisation as well. The halogens destabilise a negative charge on the carbon atom to which they are attached in the order F > Cl > Br > I ~ H. Although this is contrary to the normal electron attracting behaviour, it arises because the negative charge in question is in the π-electron system. This electron repulsion (I_π repulsion[93]), by halogens in the π-system, in the order F > Cl > Br > I has been postulated before,[93,94] in the interpretation of the U.V. spectra of the halobenzenes. It has been suggested that this effect is due either to coulombic repulsion between the p-electrons on the halogen and the π-electrons on the neighbouring atom,[93] or to unfavourable penetration of filled orbitals containing the same electrons.[94] Hence the order of stability of hybrids of type II is

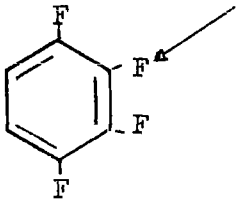


The I_π repulsion parameters of nitrogen and oxygen can not be derived from spectroscopic data and are taken as N > O > F.

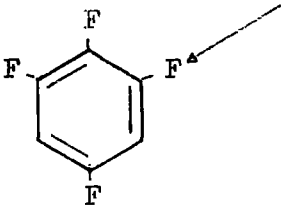
On this basis an explanation of the pentafluorochlorobenzene-pentachlorobenzene-chloropentafluorobenzene anomaly mentioned earlier

is immediately obvious. The first two compounds react para to the hydrogen and the latter para to the chlorine because the relative stabilities of negative charges on carbons bearing hydrogen, chlorine and fluorine are in the order H $>$ Cl $>$ F.

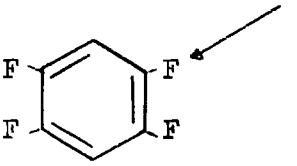
Further evidence in favour of this theory was found in consideration of the orientation of the three tetrafluorobenzenes shown below. They react at the positions indicated.[95]



IV



V



VI

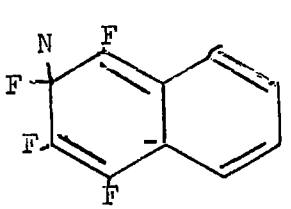
In IV and V, the positions attacked are those which lead to an intermediate of type II in which the negative charge is localised on a hydrogen bearing carbon atom. Moreover, in the case of VI, (where all positions are equivalent) the reaction with methoxide ion is about 10^3 times slower than IV or V. In this case, the intermediate of type II requires that a negative charge be localised on a fluorine bearing carbon. Since it can be assumed that the three tetrafluorobenzenes have comparable ground state stabilities, it was concluded that contributions to the transition state of type III are of only secondary importance. If they were equivalent to type II, then the tetrafluorobenzenes would react at comparable rates.

The more nearly the π-inductive effect of a substituent approaches that of fluorine, so does the isomer ratio approach the statistical para:ortho:meta = 1:2:2. This is illustrated by the increasing amount of ortho replacement obtained from the reaction of C_6F_5X compounds (X = halogen) with nucleophiles[96] as shown below. These results follow from a consideration of π-inductive effects of halogens in the order F > Cl > Br > I.

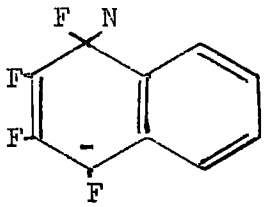
Compound	C_6F_5I	C_6F_5Br	C_6F_5Cl
% ortho replacement with OMe^-	5	12	17

These rationalisations are extremely valuable and account for most of the substitution reactions of polyfluorobenzene derivatives. Apparent anomalies can generally be convincingly explained by a consideration of solvent and steric effects, which have been neglected.

The theory is readily applied to substitution in 1,2,3,4-tetrafluoronaphthalene[97] and octafluoronaphthalene.[84] In both cases substitution takes place in the β-position VII.



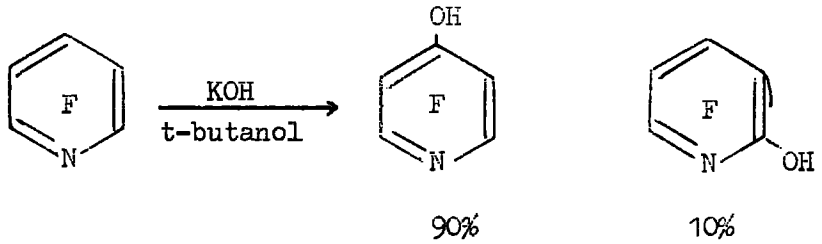
VII



VIII

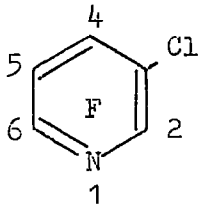
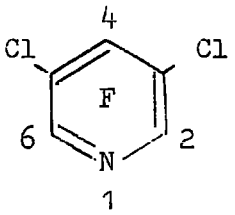
Only para-quinonoid structures need be considered as contributing to the transition state, and it can quickly be seen that α-substitution VIII would involve the negative charge being placed on a carbon bearing a fluorine atom.

Nucleophilic substitution in polyfluoroheterocyclic systems, in particular pentafluoropyridine has received much attention recently, and the results obtained will be briefly summarised. It was quickly established that nucleophiles replace the 4-fluorine atom first.[98,99] Only in the case of the reaction with potassium hydroxide were significant amounts of isomers formed.[100] In an aqueous medium only a single isomer, 4-hydroxytetrafluoropyridine was formed but in tertiary butanol a mixture of isomers was formed.

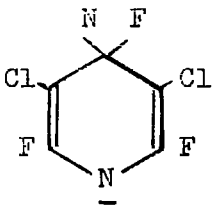


65% yield

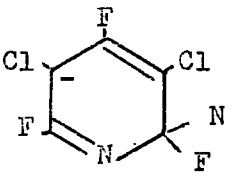
As a result of this, an investigation into the reaction of 3-chlorotetrafluoropyridine IX and 3,5-dichlorotrifluoropyridine X with potassium hydroxide was carried out. The results obtained were as follows.

Compound	Solvent	% yield	% Substitution at position 2	4	6
 IX	H_2O	65		90	10
	t.butanol	80	10	55	35
 X	H_2O	85	10	90	
	t.butanol	85	70	30	

It was suggested that the variations in the position of attack were due to steric considerations brought about by the solvation of the attacking hydroxyl ion by bulky butanol molecules.



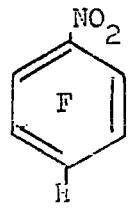
XI



XII

Another contributing factor may be that the transition state XI corresponding to 4-substitution in X is more heavily solvated than the corresponding transition state for 2-substitution XII, since in the latter the negative charge is shielded by the relatively large chlorine atom. Hence a strongly solvating medium would favour 4-substitution at the expense of 2-substitution. Similar arguments can be applied to substitution in the 3-chlorotetrafluoropyridine.

Further substitution in 4-substituted tetrafluoropyridines gives replacement of 2- and then the 6-fluorine atoms.[101] However an exception to this was the replacement reactions of 4-nitrotetrafluoropyridine.[102] With methoxide ion, 4-methoxytetrafluoropyridine was the major product (>70%) along with 2-methoxy- and smaller quantities of 3-methoxy-tetrafluoropyridine. This result contrasts with the reaction of 2,3,5,6-tetrafluoronitrobenzene XIII,



XIII

which gave exclusive replacement of fluorine ortho to the nitro-group, and no replacement of the nitro group. From these results it was concluded that the largest single factor in the substitution reactions of pentafluoropyridine and its derivatives was the affect of the ring

nitrogen. This fits in well with the theory of Burdon,[91] since the ring nitrogen can be taken as I_π attracting in a π-system.

Nucleophilic substitution in tetrafluoropyrimidine[103] XIV and tetrafluoropyridazine[104] XV has been reported. In each case a fluorine atom para to the nitrogen atom was replaced initially.

XIV

XV

Both compounds are much more reactive than pentafluoropyridine.

Chapter 2

Discussion of Experimental Work.

Section 1: The Synthesis of Heptachloro- and Heptafluoro-Isoquinoline.

Introduction. The most promising method for the preparation of heptafluoroisoquinoline appeared to be halogen exchange with potassium fluoride on heptachloroisoquinoline, and in order to apply this indirect method it was necessary to develop a convenient synthesis of heptachloroisoquinoline, which at the outset of this work had not been previously prepared. Since none of the known cyclisation reactions, or chlorination reactions of isoquinoline appeared likely to allow the direct synthesis of heptachloroisoquinoline, first efforts were directed towards the chlorination of isoquinoline. Since elemental chlorine and isoquinoline are both inexpensive and readily available then the ideal synthesis would be that involving the direct reaction between them. Pyridine has been reacted with phosphorus pentachloride at elevated temperatures in an autoclave,[1] to give pentachloropyridine and it was hoped that this method would achieve the desired conversion when applied to isoquinoline. The chlorination of pyridine-1-oxide with phosphorus pentachloride has been shown to be a suitable route to pentachloropyridine and it was thought that extension of this reaction to isoquinoline-2-oxide might be a suitable method of introducing a large amount of chlorine into the isoquinoline nucleus. The chlorination of benzothiazole[105] with chlorine in the presence of antimony trichloride has been shown to give pentachlorobenzothiazole, and this reaction therefore appeared to offer a reasonable degree of success on application to the

chlorination of isoquinoline. However, the above three reactions were found unsuitable for the exhaustive chlorination of isoquinoline and it was decided that a one step synthesis of heptachloroisoquinoline was unlikely by any of these three methods. Therefore, the direct chlorination of isoquinoline in the presence of aluminium trichloride,[59] a reaction known to give a high yield of trichloroisoquinoline, was developed, and it was found possible to convert the chloroisoquinolines obtained from this reaction to heptachloroisoquinoline using phosphorus pentachloride. It was important that not only should a method be developed to give heptachloroisoquinoline in good yield, but that the method should allow its complete separation from any lower chlorinated isoquinolines. Tetrachloropyridines[1] decompose when heated with potassium fluoride to the temperature necessary to effect complete replacement of chlorine by fluorine in pentachloropyridine, so one might expect partially chlorinated isoquinolines to behave in a similar manner. Even if such partially chlorinated isoquinolines underwent exchange without decomposition, the polyfluorinated isoquinolines produced would be expected to have boiling points similar to heptafluoroisoquinoline, rendering isolation of the pure heptafluoroisoquinoline difficult.

The Reaction of Pyridine-1-oxide and Isoquinoline-2-oxide with Phosphorus Pentachloride.

4-Chloro- and 2,4-dichloro-pyridine have been prepared by the reaction between pyridine-1-oxide and phosphorus pentachloride,[106]

and it has been recently shown[1] that lower chlorinated pyridines can be further chlorinated to give good overall yields of pentachloropyridine and (mixed) tetrachloropyridines. A consideration of these facts led to the suggestion that the reaction of isoquinoline-2-oxide with phosphorus pentachloride might lead to a possible synthesis of heptachloroisoquinoline. For initial investigations, pyridine was chosen as the substrate, since the availability of mono-, di-, tri-, tetra- and penta-chloropyridines, obtained from work on the chlorination of pyridine with phosphorus pentachloride,[1] would lead to ready identification of products by analytical scale v.p.c. analysis. Also it was known that all the chloropyridines were steam volatile and could be readily isolated by steam distillation. Since it was likely that isoquinoline-2-oxide would require similar conditions to pyridine-1-oxide, for its conversion to the fully chlorinated compound, the initial reactions with pyridine-1-oxide would indicate the conditions necessary for the chlorination of isoquinoline-2-oxide.

The procedure adopted for the reaction of pyridine-1-oxide with phosphorus pentachloride was to heat an intimate mixture of the two in a stainless steel autoclave and after the allotted reaction time the autoclave was cooled and the gases produced vented. The products formed were reclaimed by hydrolysis of the contents of the autoclave, with ice and water, followed by steam distillation and ether extraction of the steam distillate.

The results obtained from several reactions of pyridine-1-oxide are shown in Table I. These results showed that a large excess of phosphorus pentachloride was required, together with an optimum reaction temperature and reaction time, if high yields of pentachloropyridine were to be obtained. The use of lower temperatures and shorter reaction times afforded mixtures of partially chlorinated pyridines, whereas the use of smaller quantities of phosphorus pentachloride gave products which consisted of a mixture of tetra- and penta-chloropyridines in almost equal amounts.

At this point the reaction was extended to isoquinoline-2-oxide, and the experimental procedure adopted was essentially that used for the pyridine-1-oxide chlorination, except that product recovery was by filtration and not steam distillation. Employing the same reaction conditions that gave the optimum conversion of pyridine-1-oxide to pentachloropyridine, no product whatsoever was isolated from the reaction of isoquinoline-2-oxide with phosphorus pentachloride, and large quantities of tar and carbonised material were obtained. The reaction was repeated at lower temperatures but this did not afford much improvement for materials which were very dark coloured, and difficult to purify, were obtained from the reaction. At this stage the reaction was not investigated further, not only because of the poor results obtained in the chlorination process but also because the conversion of isoquinoline to isoquinoline-2-oxide was only of the order of 60%.[107]

Table I

Reaction of Pyridine-1-oxide with phosphorus pentachloride.

C_5H_5NO (g)	C_5H_5NO (moles)	PCl_5 (g.)	PCl_5 (moles)	Time (hr.)	Temp. (°C)	Product (g.)	Composition of product in mole % C_5HCl_4N	Composition of product in mole % C_5Cl_5N	Overall yield of C_5Cl_5N %
30	0·32	760	3·65	48	290	41	36	64	34·5
30	0·32	330	1·58	12	260	23*	32	7·5	2·0
28	0·30	700	3·35	14	300	54·1	45	55	42
30	0·32	1000	4·80	24	300	66·2	12	88	75·5

*This product also consisted of several chlorinated pyridines.

The Reaction of Isoquinoline with Phosphorus Pentachloride.

In the hope that a convenient one-step synthesis of heptachloroisoquinoline could be achieved the reaction between isoquinoline and phosphorus pentachloride was investigated.

The reaction of pyridine and phosphorus pentachloride, originally studied by Sell and Dootson in 1898,[108] was developed by Chambers, Hutchinson and Musgrave for the preparation of pentachloropyridine in good yields. Reaction at 210-220°C for 72 hrs. in an autoclave gave only 1·5% yield of pentachloropyridine but this was increased to 15% by reaction at 280-285°C for 50 hrs. Mixtures of lower chlorinated pyridines on further treatment with phosphorus pentachloride gave pentachloropyridine in good yield. The reactions were carried out using a mixture of 2·5 moles of pyridine and 12 moles of phosphorus pentachloride. Phosphorus pentachloride has been shown to react with aliphatic and aromatic hydrocarbons[109] according to the equation:

$$RH + PCl_5 \longrightarrow RCl + HCl + PCl_3$$

Presumably pyridine reacts in a similar manner i.e.

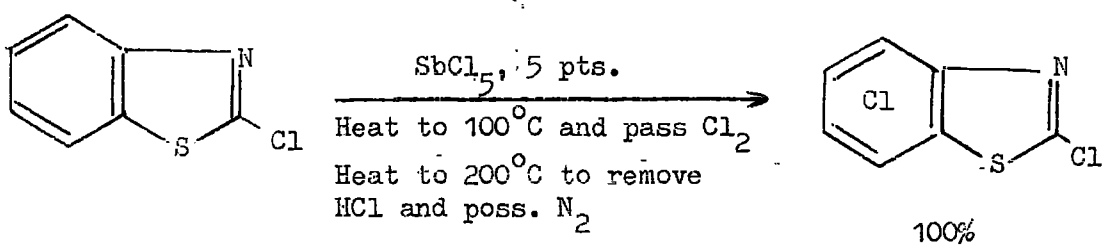
$$C_5H_5N + 5PCl_5 \longrightarrow C_5Cl_5N + 5PCl_3 + 5HCl$$

and thus the reactions were carried out using less than the theoretical amount of phosphorus pentachloride needed for complete conversion to pentachloropyridine. It was hoped that the reaction of isoquinoline with excess phosphorus pentachloride at 280-300°C in an autoclave would

lead to heptachloroisoquinoline being formed in good yield. The results of the reaction, again, as in the previous case, showed that appreciable decomposition was occurring resulting in very low yields of a product which was extremely difficult to purify. Furthermore, the large quantities of phosphorus pentachloride required made the reaction technically very inconvenient, and dangerous. The disadvantages of this approach were very obvious.

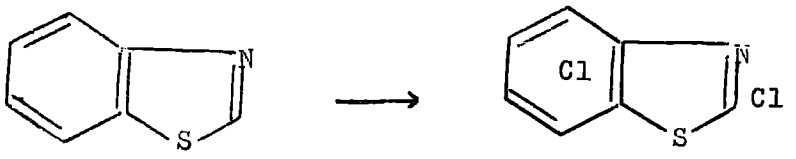
The Reaction of Isoquinoline with Chlorine in the presence of Antimony Trichloride.

This idea was extended from some information in the patent literature in which benzothiazole and some of its derivatives had been reacted with chlorine in the presence of antimony trichloride to give perchlorinated compounds.



100%

also



80%

The yields obtained from this reaction looked very impressive and yields as high as this in a one step synthesis of heptachloroisoquinoline would be ideal.

The reaction was carried out in a flange-head flask equipped with an efficient "Teflon" bladed stirrer. On adding the isoquinoline to the antimony trichloride an exothermic reaction took place and the cloudy solution which resulted turned clear on heating to 100°C. Chlorine gas was then passed through the reaction mixture which became very black, and in the end, so thick that it could no longer be stirred. Since at this stage sufficient chlorine had been passed to introduce 5 chlorine atoms the reaction was discontinued and heated to 200°C until the evolution of HCl ceased. On cooling, the mass set solid and had to be chipped out of the flask. On sublimation only product which had $=NH^+-$ stretch in the infra-red spectrum was obtained. On treatment with sodium hydroxide and steam distilling much isoquinoline along with lowly chlorinated isoquinolines was obtained (as shown by i.r., v.p.c. and elemental analysis). It was obvious at this stage that a one-step synthesis of heptachloroisoquinoline was not possible.

The Preparation of Heptachloroisoquinoline by the Two-Stage Synthesis.

The observation[110] that a mixture of dichloro- and trichloro-pyridines could be converted almost quantitatively to pentachloropyridine by heating with phosphorus pentachloride for 3-4 hrs. at about 300°C

led to the successful development of the two-stage synthesis of heptachloroisoquinoline in high yield. It was known[59] that 5,7,8-trichloroisoquinoline could be prepared in high yield and it was hoped that this could be readily converted to heptachloroisoquinoline by further chlorination with phosphorus pentachloride. This in fact has been realised. The initial chlorination has been developed to the stage where a hexachloroisoquinoline is obtained in excellent yield and the conversion of this to heptachloroisoquinoline in good yield, by reaction with phosphorus pentachloride, is a relatively simple matter.

The Direct Chlorination of Isoquinoline in the presence of Aluminium Trichloride.

Gordon and Pearson[59] found that the complex formed between isoquinoline and excess aluminium trichloride (a molar ratio of isoquinoline: aluminium trichloride of about 1:3 was used), on treatment with chlorine or bromine gave a halogenated isoquinoline, in which substitution in the Bz ring only had occurred, in high yield. Their method, termed the "Swamping Catalyst" method, has been developed to give hexachloroisoquinoline, and a mixture of penta- and hexa-chloroisoquinoline, in good yield as shown in Table II.

The complex formed is surprisingly mobile at temperatures greater than about 70° which permits it to be efficiently stirred as the gaseous chlorine is bubbled through. A large excess of chlorine was passed

TABLE II

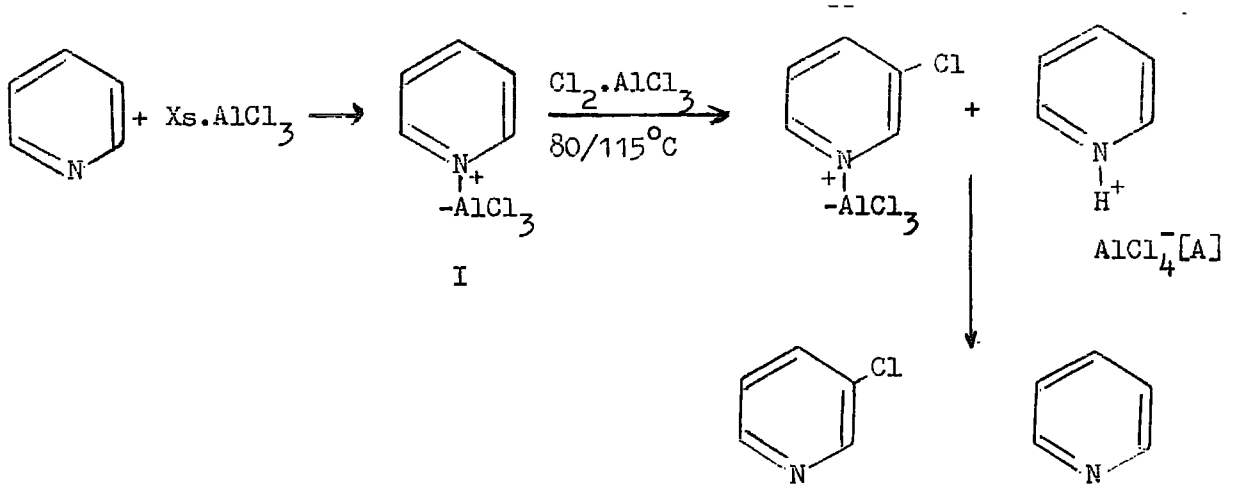
Experiment	C_9NH_7 g.	C_9NH_7 mole	$AlCl_3$ g.	Cl_2 g.	Cl_2 mole.	Temp. °C	Time hrs.	Product recrystallised from benzene gs.	Product recrystallised from benzene %	Insoluble material g.
R.1	100	0·77	310	496	6·99	140/150	36	180	69·7	20
R.2.	129	1·0	400	753	10·60	130/140	50	252	75·6	15
R.3.	158	1·22	500	1198	16·75	150/160	48	359	88·2	30
R.4.	280	2·17	750	2000	28·17	1451	72	800 (100%) not recrystallised		-

slowly through the complex in order to achieve a high conversion to the chlorinated isoquinolines and it was found that the excess required rose quite markedly as the scale of the experiment was increased.

Gordon and Pearson[59] prepared 5,7,8-trichloroisoquinoline by treating the aluminium trichloride complex of 5,8-dichloroisoquinoline with one equivalent of chlorine, and no mention was made in their paper of exhaustive chlorination of the complex. As can be seen, slow chlorination at ca. 140° surprisingly gave a compound which had a sharp melting point and whose analysis corresponded to C_9NHCl_6, in very good yield. Attempts to increase the reaction rate (which may be necessitated when very large scale reactions are done) by a steady increase in temperature, resulted in the increased formation of an insoluble glassy substance, presumably a polymer of some kind.

Theoretical Considerations.

The chlorination of pyridine by the "Swamping Catalyst" method has been shown to proceed in the following way.[111]

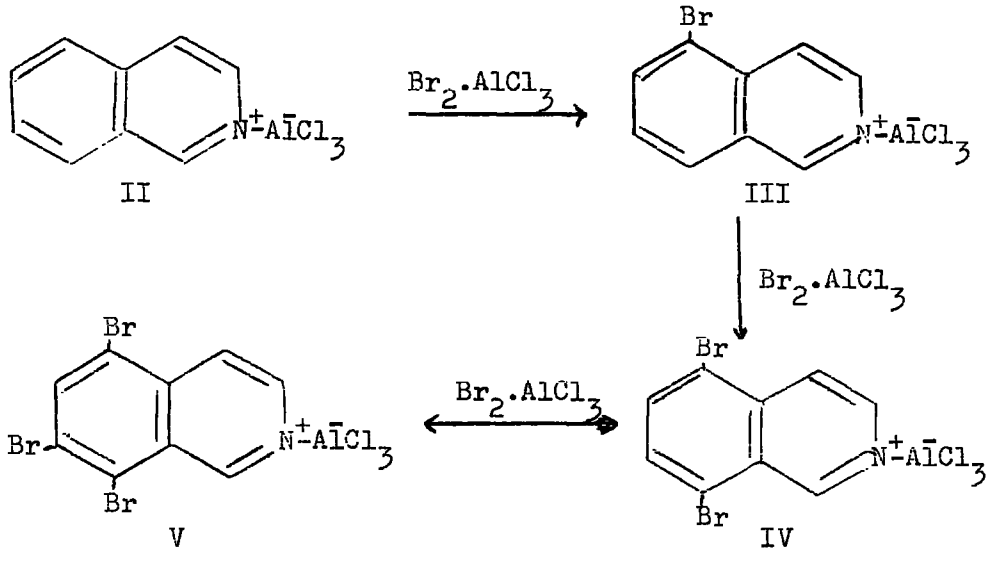


Half the pyridine was converted to 3-chloropyridine whilst the other half was deactivated by protonation to give A, which was shown in a separate experiment to be inert to chlorination under the conditions of the original reaction. It was also shown in the bromination of 4-methylpyridine that if only 1 mole of aluminium trichloride was used per mole of 4-methylpyridine, no bromination occurred, whilst if excess aluminium trichloride was used a 32% yield of 3-bromo-4-methylpyridine was obtained. That substitution occurs at the 3-position is in accord with an electrophilic mechanism and the fact that (I) is more reactive than A, suggests that pyridine-aluminium trichloride complex has a more covalent form in which the electrons on the nitrogen are not so firmly held as when the ring nitrogen is protonated. However both are deactivated towards electrophilic attack and it is surprising that halogenation occurs at all. The need for an excess of aluminium trichloride shows that its ability to increase the effectiveness of the attacking electrophilic species more than compensates for the above deactivation. The increased activity of the attacking species is due to the aluminium trichloride tending to remove one of the halogen atoms from its shared electrons i.e.

$$Cl_2 + AlCl_3 \longrightarrow Cl^+ + AlCl_4^-.$$

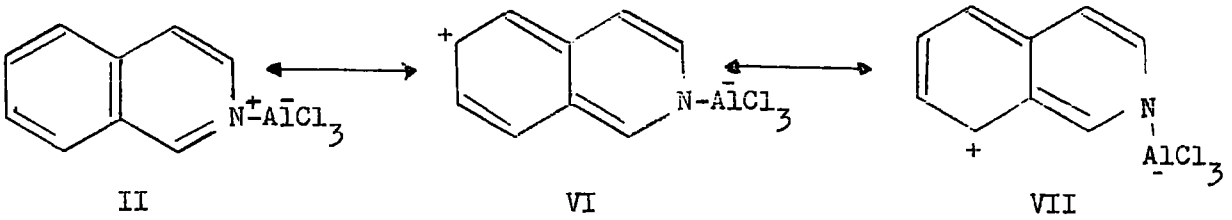
and the excess aluminium trichloride serves as a medium of high dielectric constant which assists the separation of any such charged species

produced. Ferric chloride, either alone or mixed with aluminium trichloride and boron trifluoride formed complexes with pyridine but no halogenation occurred on treatment with halogen as in the case of aluminium trichloride above. By controlled bromination of the isoquinoline-aluminium trichloride complex Gordon and Pearson[59] found the following order of substitution,



and a similar order no doubt holds for the chlorination. The observed order of substitution can be rationalised as follows. One considers substitution to occur only in the benzene ring because of the high degree of deactivation of the pyridine ring brought about by the quaternary nitrogen atom. The effect of the positively charged nitrogen

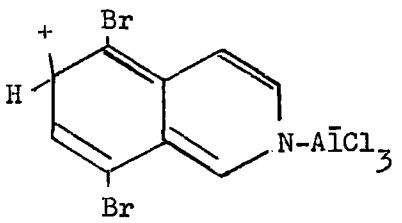
atom on the Bz ring can best be demonstrated as follows:-



II VI VII

It will be seen that the positions most affected are the 6 and 8, but the contribution by VI to the hybrid is greater than VII because of the overiding importance of the p-quinonoid form of the contributor VI. Hence the 6-position is the least reactive. The two positions least affected are the 5- and 7-positions, and since the 5-position has some of the characteristics of the α position in naphthalene, substitution occurs there first.

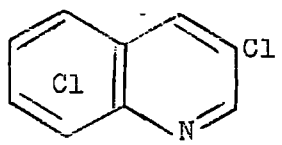
Bromination of the complex of 5-bromoisoquinoline III, gives the 5,8-dibromo-compound IV, because in the position of attack in III is governed to some extent by the 8-position possessing some of the characteristics of the α position in naphthalene, and also by resonance contributions. On further attack on IV, the following canonical form is an important enough contributor to the hybrid to favour 7-substitution.



The formation of 5,6,7,8-tetrabromo or 5,6,7,8-tetrachloro-isoquinoline is feasible, but to obtain a hexachloro-compound means that substitution would have to occur twice in the pyridine ring. To visualize this taking place by an electrophilic mechanism is difficult. One could justify the formation of a pentachloroisoquinoline by saying that in the pyridine ring the position meta to the nitrogen is little affected by the positive charge - hence substitution may occur there. i.e.

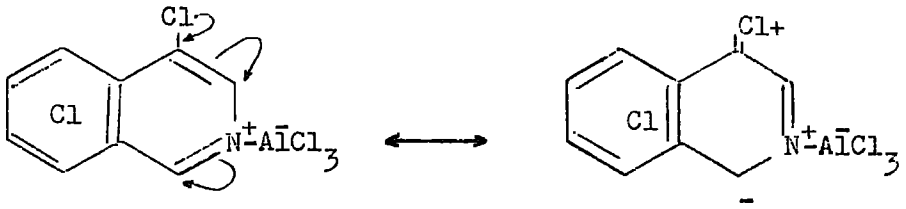
IX

In fact quinoline also chlorinates by the same procedure to give a pentachloroquinoline[112] of presumed structure VIII



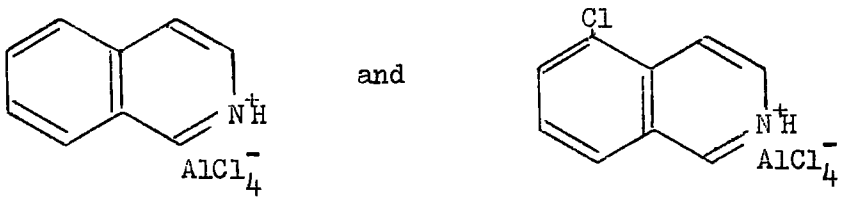
VIII

The only way in which a hexachloroisoquinoline could be formed, is by activation of the 1-position (more than the 3-position) by the 'mesomeric' effect of the 4-chlorine atom in IX, i.e. contributions by



Although not convincing, there appears to be some slight justification for this in view of the fact that no such activation of the 2- or 4-position in the presumed 3,5,6,7,8-pentachloroquinoline VIII is possible, and in fact no further substitution occurs.

The orientation observed in the halogenation has been discussed in terms of the aluminium trichloride complex II, although the hydrochloric acid formed most probably reacts to some extent to form initially the protonated species.



However the factors affecting orientation will be the same for II and the protonated species. The increase in reactivity over the pyridine complex may be due to the greater possible delocalisation of the positive charge developed in the transition state, for the bicyclic system.

Chlorination of Hexachloroisoquinoline with Phosphorus Pentachloride.

The conversion of hexachloroisoquinoline to heptachloroisoquinoline in good yield was found to be possible by heating it with phosphorus pentachloride in an autoclave, if the reaction conditions were carefully controlled. The dependence of the yield on reaction conditions is shown in Table III. The autoclave was heated by means of a heating coil which fitted closely around the lower half of the autoclave and the temperature was measured by means of a thermocouple placed into a well, in the centre of the autoclave and which terminated on a level with the top of the heating coil. The lower end of the autoclave was therefore heated to a much higher temperature than that actually recorded, and in the first reaction, R.I., it is likely that the decomposition occurred because the hexachloroisoquinoline was placed in the bottom of the autoclave. This decomposition was greatly reduced, and in fact almost eliminated, by placing phosphorus pentachloride in the bottom of the autoclave and the hexachloroisoquinoline above, and on a level with the bottom of the thermocouple well. Thus the phosphorus pentachloride, as well as acting as a chlorinating agent, served as a "thermal shield" between the hexachloroisoquinoline and the hot walls thus reducing decomposition. By so placing the phosphorus pentachloride, which was used in a large excess, the conditions were most favourable for the production of a high concentration of chlorine radicals, so ensuring complete conversion to the fully chlorinated compound. It was found that at a temperature of

Table III

Reaction No.	PCl_5	Hexachloro I.Q.	Max. temp. attained	Time taken to reach max. temp.	Yield of heptachloro I.Q. after recrystallisation from acetone gms.	%	% C	% Cl	m.pt.
R1	85 gms. (0·41 moles)	34 gms. (0·1 moles)	300°C	5 hrs. 35 mins.	Decomposition				
R2	900 gms. (4·3 moles)	65 gms. (0·193 moles)	255°C	4 hrs.	54	75	29·2	66·8	126/127°C
R3	900 gms. (4·3 moles)	65 gms. (0·193 moles)	245°C	4 hrs. 20 mins.	69	mixture of hexa/hepta-chloro			112°-118°C
R4	900 gms. (4·3 moles)	60 gms. (0·179 moles)	270°C	4 hrs. 30 mins.	44	70	29·1	-	126/127°C
R5	900 gms. (4·3 moles)	70 gms. (0·21 moles)	275°C	4 hrs. 40 mins.	53	69	29·1		126/127°C
R6	850 gms. (4·06 moles)	120 gms. (0·357 moles)	270°C	3 hrs.*	90	68	29·0	66·7	126·5°-128°C

*Autoclave head washer leaked.

245°C the conversion of hexachloro- to heptachloro-isoquinoline was very slow and even after ca. 5 hrs. the reaction was incomplete. The ideal conditions are possibly those in R.2. Using the optimum conditions the solid remaining, after the hydrochloric acid had been vented, the phosphorus trichloride poured off, and the autoclave contents added to ice-water, was simply filtered off and a single recrystallisation from acetone gave pure heptachloroisoquinoline.

It can be seen that this route to heptachloroisoquinoline is very convenient, using very inexpensive starting materials and possibly the most important asset is that the overall yield is ca. 65-70%.

The Fluorination of Heptachloroisoquinoline.

Of the methods available for the conversion of aromatic perchloro-compounds to the corresponding perfluoro compounds, the method of halogen exchange appeared the most promising for the preparation of heptafluoroisoquinoline from heptachloroisoquinoline. In comparison with the single step halogen exchange reaction the other method, involving the addition of fluorine to give the alicyclic compound followed by dehalogenation, suffers from the fact that being a two-step reaction it is more laborious and there is the likelihood of lower yields on this account, but more important the facile cleavage of the C-N bond on fluorination with such reagents as fluorine, high valency metal fluorides, or halogen fluorides would be expected to occur resulting in extensive decomposition.

Halogen exchange reactions between potassium fluoride and hexachlorobenzene[25,34] or pentachloropyridine[1,33] were found to require a temperature greater than was possible in a solvent in order to effect total replacement of chlorine by fluorine in good yield. The reaction between heptachloroisoquinoline and potassium fluoride was therefore studied in the absence of a solvent in an autoclave. The isolation of any fluorinated isoquinolines formed is also simplified by the absence of a solvent, the product being simply distilled from the hot autoclave under reduced pressure.

The reaction between an intimate mixture of finely ground anhydrous potassium fluoride and heptachloroisoquinoline was studied over a range of conditions and the results are contained in Table IV. Since the desired product was heptafluoroisoquinoline, which was expected to have a boiling point similar to isoquinoline itself, only the material which distilled from the hot autoclave under reduced pressure (0·2 - 0·4 mm.) was investigated. Under these conditions it was found that heptafluoroisoquinoline distilled readily. The distillate invariably contained varying amounts of material which boiled much lower than heptafluoroisoquinoline. This decomposition product was not investigated. Analytical scale v.p.c. of the reaction R.3. showed that both the pentafluorodichloroisoquinoline and hexafluoro-monochloroisoquinoline were apparently single isomers.

Table IV. Reaction of heptachloroisoquinoline with potassium fluoride in the absence of solvent.

	C_9NCl_7		KF				Product	Composition of Product $i\text{-}C_9NF_6Cl$		$i\text{-}C_9NF_7$		
	g.	mole	g.	mole	Temp.	Time	g.	mole %	yield	mole %	yield	Comments
R.1.	15	·0405	55	·948	440°C	15 hrs.	7·1	10	6·8%	90	61·7%	
R.2.*	15	·0405	55	·948	490°C	15 hrs.	5·2	5		70		Contained products lower boiling than $i\text{-}C_9NF_7$ (decomposition) (25%)
R.3	25	·0675	70	1·27	365°C	19 hrs.	17·0	40		10		Contained 50% of a compound of longer retention time than $i\text{-}C_9NF_6Cl$ - shown to be $C_9NF_5Cl_2$
R.4.	25	·0675	70	1·27	420°C	19 hrs.	13·5	10	7·8%	90	71%	
R.5.*	25	·0675	70	1·27	440°C	19 hrs.	10·5	10		70		Contained 20% compounds, lower boiling than $i\text{-}C_9NF_7$ (decomposition)
R.6.	28	·0756	70	1·27	420°C	22½ hrs.	18·5	4	3·4%	96	92·5%	

Composition of products estimated by analytical g.l.c.

*Could not work out yields from chromatogram, because molecular weights of decomposition products are not known.

Heptafluoroisoquinoline, m.p. 45·5°, b.p. 211/212° (756 mm.) was obtained by the fractional distillation of the combined products of several reactions. The ^{19}F n.m.r. spectrum of heptafluoroisoquinoline showed seven distinct groups of peaks centred at 61·02, 96·52, 138·96, 144·56, 145·23, 152·45 and 154·65 p.p.m. to high field of $CFCl_3$. By analogy with pentafluoropyridine,[1] the low field peaks, which exhibit quadrupolar broadening, were assigned to the 1- and 3-fluorines. Since the electron density at the 1-position is lowest (from Hückel Molecular Orbital calculations) it is concluded, even though the ^{19}F chemical shift in aromatic systems is influenced by factors other than the π-electron density, that probably the 1-fluorine is the resonance at 61·02 p.p.m.

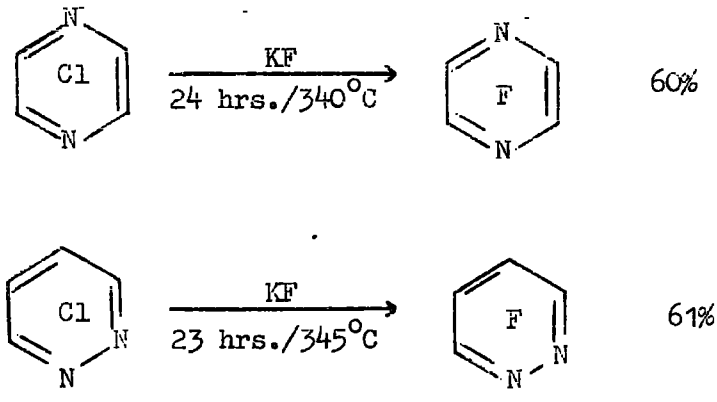
The ^{19}F spectrum of the pentafluorodichloroisoquinoline showed ten groups of peaks, thus demonstrating it was not in fact a single isomer but a mixture of two isomers. The ^{19}F n.m.r. spectrum of the monochlorohexafluoroisoquinoline showed six groups of chemically shifted peaks centred at 61·06, 78·20, 138·73, 142·80, 144·78 and 154·48 p.p.m. to high field of $CFCl_3$. The two peaks at 61·06 and 78·20 p.p.m. can be assigned to the 1- and 3-fluorines by the fact that they are at much lower field than the rest. The effect of introducing chlorine into a pentafluoropyridine nucleus in place of fluorine, is to displace the fluorine resonances ortho and para to the chlorine atom to lower field. In the ^{19}F n.m.r. spectrum of

3-chlorotetrafluoropyridine for instance, the 2- and 4-fluorine resonances are displaced by 15·5 p.p.m. and 19·7 p.p.m. respectively to low field, relative to their positions in pentafluoropyridine,[1,113] whereas the resonance of the 6-fluorine is only displaced by 1 to 2 p.p.m. to low field. In the ^{19}F n.m.r. spectrum of monochlorohexafluoroisoquinoline the resonance at 78·2 p.p.m. is displaced 18·32 p.p.m. to low field to the peak at 96·52 p.p.m. in heptafluoroisoquinoline, whereas the resonance at 61·06 p.p.m. is almost the same as the peak at 61·02 in heptafluoroisoquinoline. From a consideration of these figures it is evident that the monochlorohexafluoroisoquinoline is in fact 4-chlorohexafluoroisoquinoline.

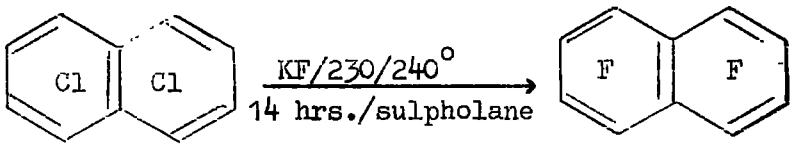
Reaction Conditions and Extent of Fluorination. The complete exchange of chlorine by fluorine occurred very readily and easily at temperatures greater than 400°C. Below this both 4-chlorohexafluoroisoquinoline and the pentafluorodichloroisoquinoline mentioned above are produced in appreciable quantities. 420°C appeared to be the ideal temperature at which to carry out the reaction, because of the small extent of decomposition and the high yield of heptafluoroisoquinoline obtained. Shorter reaction times lead to an increase in the amount of 4-chlorohexafluoroisoquinoline formed which can be seen from a comparison of R.4. and R.6. An increase in the reaction temperature above 440°C brought about the ready formation of low boiling decomposition products. This was particularly noticeable at 490°C (R.2.) where

25% of the product was decomposition product. The optimum conditions are considered to be those in R.6., giving a 92·5% yield of heptafluoroisoquinoline. If 4-chlorohexafluoroisoquinoline is required then the conditions in R.3. with an increased reaction time should be used.

The reaction of potassium fluoride and pentachloropyridine in the absence of solvent has been studied in some detail and it was found that at 480°C for 19 hrs. the fully fluorinated compound was produced in 66% yield,[1] hence showing the slightly greater overall reactivity of heptachloroisoquinoline towards replacement of chlorine by fluorine. The chlorines in the β positions were found to be the most resistant to replacement, only 2,4,6-trifluoro-3,5-dichloropyridine being formed at 400°C for 18 hrs.[1] The greater reactivity of a chlorine α or γ to a ring nitrogen atom is shown by the complete replacement of chlorine when tetrachloro-1,2- or tetrachloro-1,4-diazines[104] is heated to about 340° with potassium fluoride in the absence of solvent.



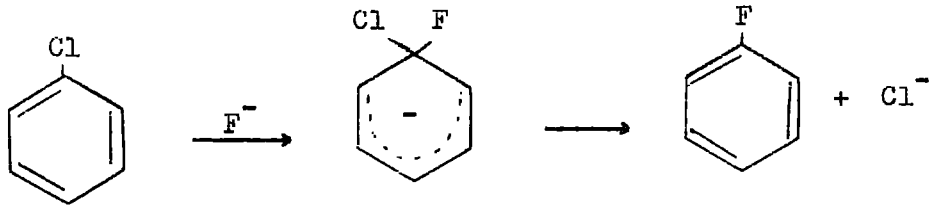
It was thought initially that to obtain heptafluoroisoquinoline from heptachloroisoquinoline in good yield, a higher temperature than was possible using a solvent would be required. However the recently reported[34] preparation of octafluoronaphthalene in high yield using potassium fluoride in a solvent,



58%

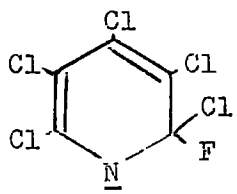
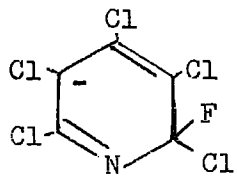
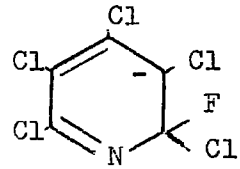
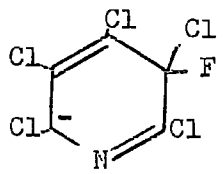
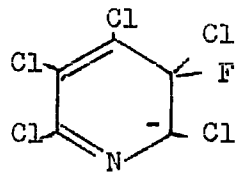
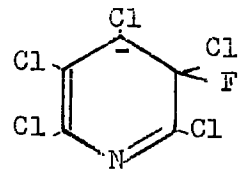
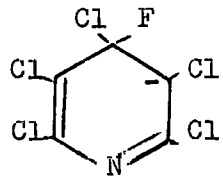
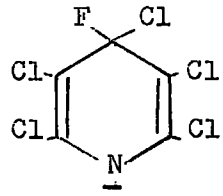
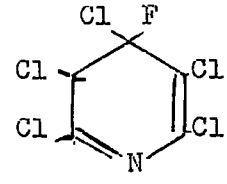
and the fact that hexachlorobenzene gives hexafluorobenzene in only 0·4% yield under similar conditions, shows the much greater susceptibility of the bicyclic system to halogen exchange and suggests it might have been possible to fully fluorinate heptachloroisoquinoline by reaction in a solvent.

The halogen exchange reaction is most likely to be a bimolecular nucleophilic substitution reaction involving replacement of a chloride ion by a fluoride ion, i.e.,



(A)

proceeding via a definite intermediate A. This Wheland-type intermediate is considered to be a good approximation to the transition state and will be assumed to be so for the following discussion. We can now attempt to discuss the course taken by the fluorination reaction in terms of the stability of the transition states for substitution at the various positions in heptachloroisoquinoline, using some of the ideas put forward by Burdon[91] in his rationalisation of nucleophilic substitution in polyfluorobenzenes. As regards nitrogen containing heterocycles, the ring nitrogen, by virtue of its high electron affinity, will stabilise a negative charge placed upon it. If one considers substitution by fluoride ion in pentachloropyridine, then the transition states at α, β and γ positions are as follows.

These show that for attack at the α- and γ-position, but not β-, the negative charge can be placed onto the nitrogen. Because of the importance of the p-quinonoid form, order of replacement is therefore expected to be γ > α > β. The order found is α > γ > β.[114] Steric requirements are important for polychloro-compounds and possibly the observed order for pentachloropyridine is a result of greater steric hindrance at the γ-position compared with the α-position. The low susceptibility towards nucleophilic attack of the β-position reflects the great stabilisation resulting from it being possible to localise the negative charge in the transition state onto the nitrogen and the great ease, compared with pentachloropyridine, with which tetrachloro-1, 2- and -1,4-diazine undergo total exchange with potassium fluoride can be attributed to such stabilisation.

As mentioned previously the reaction of heptachloroisoquinoline and potassium fluoride was directed towards the preparation of the fully fluorinated compound and consequently the lower fluorinated compounds were not investigated to any extent.

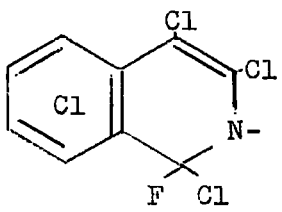
In the subsequent discussion of the orientation of nucleophilic substitution of chlorine by fluorine in heptachloroisoquinoline,

a) those resonance hybrids in which the negative charge can be localised on to the nitrogen will be assumed to contribute significantly to the transition state whether the hybrid has a para-quinonoid form or not.

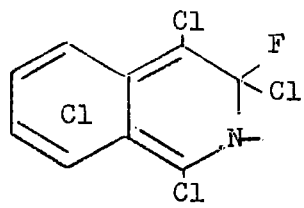
b) Such resonance hybrids will be more stabilised than those in which the negative charge is localised onto a carbon bearing a halogen or a bridgehead carbon atom.

c) Where localisation of the negative charge onto the ring nitrogen is not possible those resonance hybrids having a para-quinonoid form and which involve rearrangement of the π-electrons of one ring only will be assumed to contribute most to the transition state for attack at any such position.

For attack at the 1- and 3-positions (α to the ring nitrogen atom) I and II will be the main contributors to the transition state.



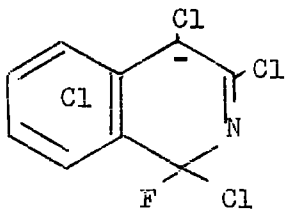
I



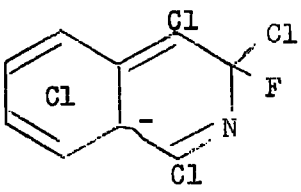
II

It will be noticed that in II both rings are in an o-quinonoid form whereas in I the Bz ring is unaffected i.e. II will be of higher energy than I. However, in I, another contributor is III, a para-quinonoid form in which the negative charge is localised on a carbon bearing a halogen atom, whereas in IV, the corresponding p-quinonoid form for 3-substitution, the negative charge is localised onto

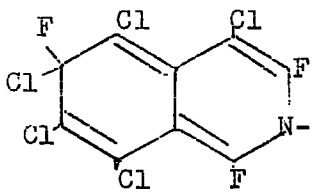
a bridgehead carbon which is a reasonably favourable state (cf. transition states for α- and β-substitution in octafluoronaphthalene). Hence III will be of higher energy than IV. To decide which of these factors is the most important is difficult, but it would appear that the most favourable site for nucleophilic substitution is the 1-position, since in 1,3-dichloroisoquinoline[8] the 1-chlorine is replaced by fluorine much more readily than is the 3-chlorine. Also (see later) nucleophilic substitution in heptafluoroisoquinoline occurs at the 1-position. Hence it seems likely that the 1-chlorine will be replaced before the 3-chlorine.



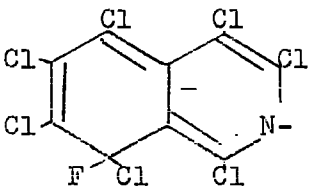
III



IV



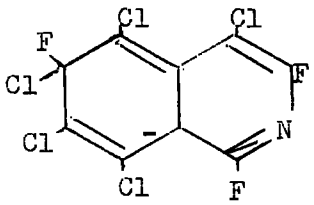
V



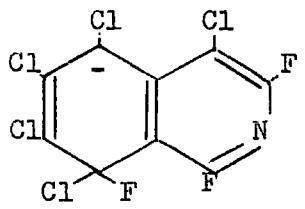
VI

For substitution in the Bz ring the positions from which one can place the negative charge on to the nitrogen atom, are the 6- and 8-positions, and the two most important contributors are V and VI. In the

case of V both rings are in a p-quinonoid form, whereas in VI, the Bz ring has an ortho-quinonoid form. Also of importance are VII and VIII



VII

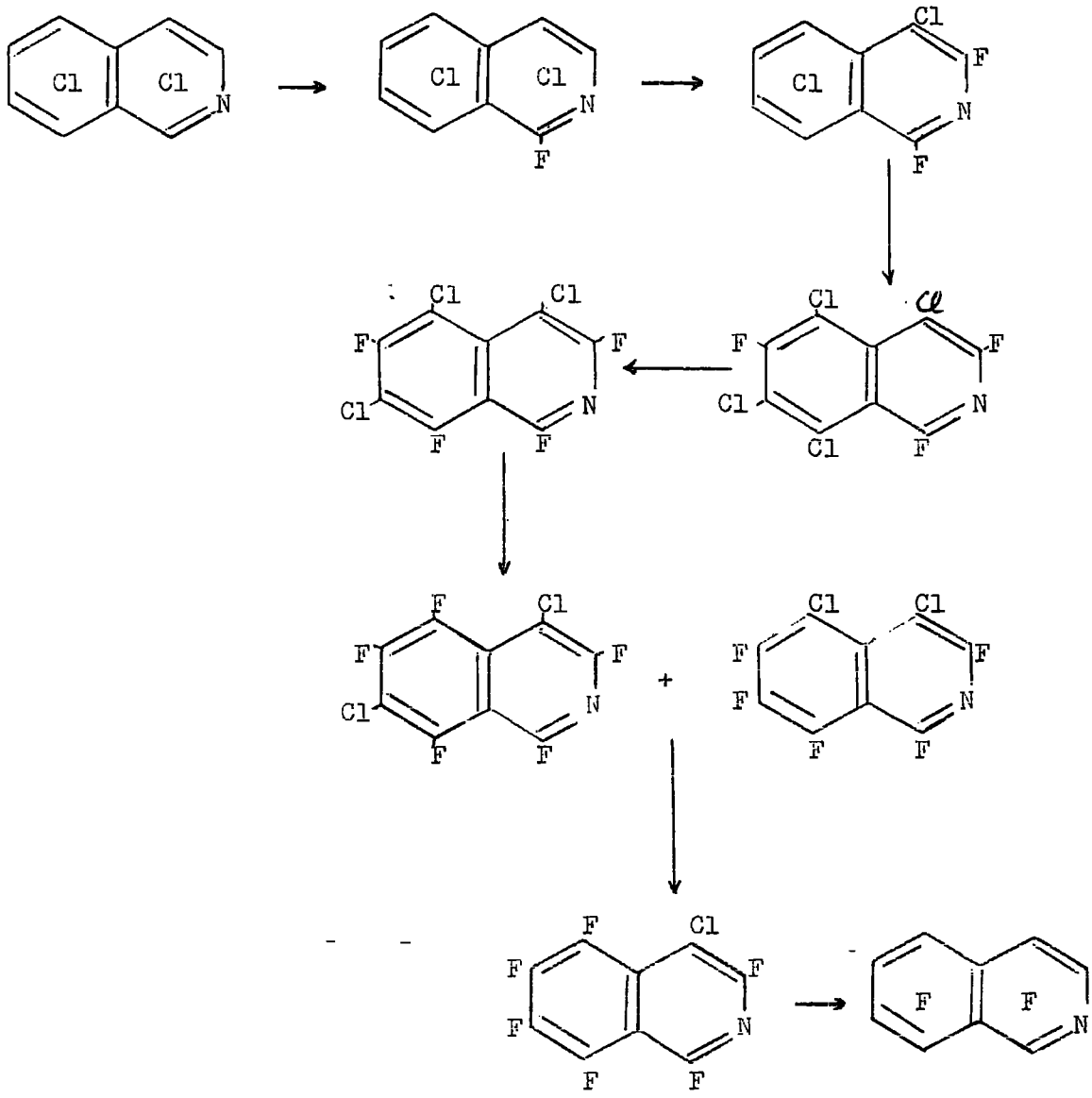


VIII

Clearly VIII is of higher energy than VII and hence substitution should occur at the 6-position before the 8-position.

In the case of substitution in the next available positions, the 4-, 5- and 7-, the negative charge cannot be localised onto the nitrogen atom, therefore one might expect these positions to be of similar reactivity. However, the fact that 4-chlorohexafluoroisoquinoline and no other monochlorohexafluoroisoquinoline is formed indicated that the least reactive position is the 4-position; and also the fact that two dichloropentafluoroisoquinolines are formed, shows that the positions 5- and 7- are of approximately equal reactivity.

The speculative reaction scheme proposed is therefore:



Section II. The Chemistry of Heptafluoroisoquinoline and some of its Derivatives.

Introduction: The work in this section was designed to be an extension of the study of aromatic nucleophilic substitution. There is a considerable amount of information in the literature concerned with nucleophilic substitution in benzenes and heteroaromatics,[133] but some facts are still not well understood. Polyfluoroaromatic compounds are appropriate compounds for the study of nucleophilic substitution reactions for several reasons. Because of the electronic properties of fluorine, the presence of several fluorine atoms in an aromatic system usually renders it extremely susceptible to attack by nucleophilic species. The choice of fluorine over chlorine, bromine and other groups which are strongly activating with respect of nucleophilic substitution, arises mainly from steric considerations. Any contribution to the course of nucleophilic substitutions by 'steric effects', should be less in the case of fluorine, because of its relatively small size. The fact that products arising from substitution reactions can be examined by their ^{19}F n.m.r. spectra is of great assistance in problems of the orientation of nucleophiles.

Nucleophilic substitution in polyfluorinated aromatic compounds has been extensively studied by workers at Birmingham[69] and from this work certain dominating factors influencing the orientation of nucleophiles in such systems became apparent. An examination of the

chemistry of pentafluoropyridine[1] was designed to assess the perturbing influence of a heteroaromatic aza group on the course of nucleophilic substitution in six membered polyfluorinated aromatic ring systems and also afforded an interesting comparison with pentafluoronitrobenzene. A study of the behaviour of heptafluoroisoquinoline is a logical extension to this work. This compound gives information relating to the effect of 3,4-annellation of a perfluorinated carbocyclic ring on the position and ease of substitution in pentafluoropyridine. More information thus becomes available for the formulation of any general theory of aromatic nucleophilic substitution, the factors influencing the reactivity of the substrate, and the orientation of the nucleophiles in such substrates.

The Reactions of Heptafluoroisoquinoline involving the Ring Nitrogen.

The replacement of hydrogen by highly electronegative fluorine in the isoquinoline nucleus would be expected to cause a reduction in base strength. This reduction has been shown[115] to be greater for substitution of fluorine in the pyridine ring than in the benzene ring. Heptafluoroisoquinoline, like pentafluoropyridine did not form a hydrochloride when gaseous hydrogen chloride was bubbled through a solution of heptafluoroisoquinoline in ether under anhydrous conditions, and did not give a precipitate when boron trichloride was condensed into a solution of it in carbon tetrachloride. The much reduced

availability of the nitrogen lone pair in heptafluoroisoquinoline is demonstrated by the insolubility of heptafluoroisoquinoline in dilute mineral acids. However, heptafluoroisoquinoline will dissolve in sulphuric acid (S.G. 1·84) and indications are that this is a consequence of protonation of the ring nitrogen rather than interaction of the proton with the π-electron system.

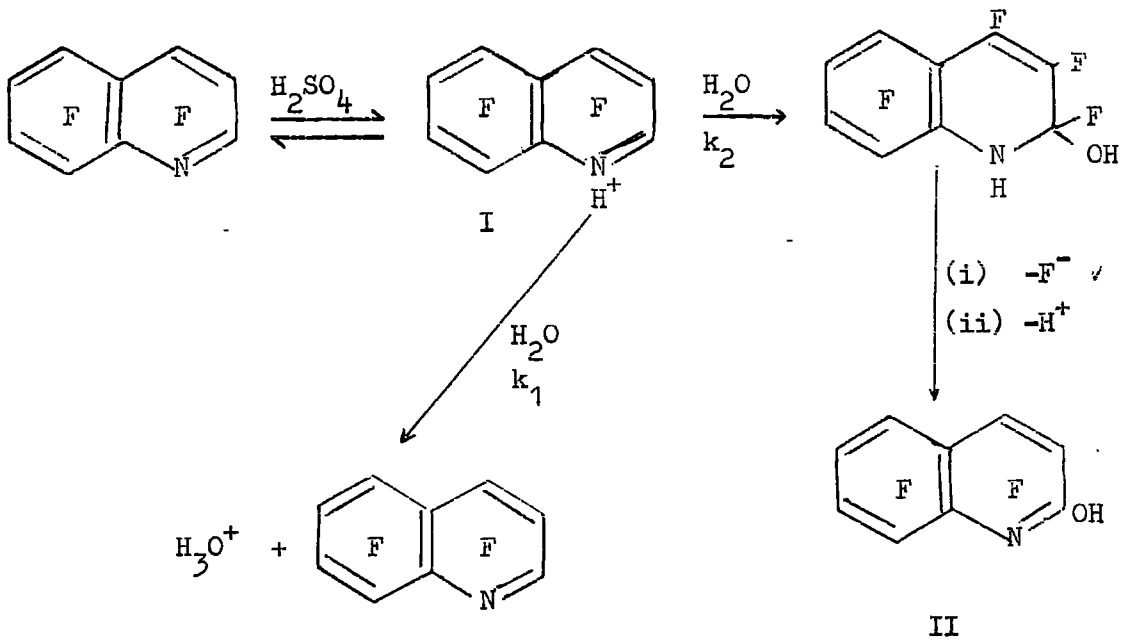
A very strong indication of N-protonation can be obtained from the ^{19}F n.m.r. spectrum in sulphuric acid. This (10% molar solution) shows that the fluorine resonances have been shifted relative to their positions in heptafluoroisoquinoline, but the most noticeably shifted are the α-fluorine resonances, assuming no crossing over has taken place on protonation.

^{19}F shifts (rel. to $CFCl_3$) p.p.m.

Heptafluoroisoquinoline	Protonated Heptafluoroisoquinoline
61·0	79·76
96·5	118·89
138·9	133·27
144·5	135·49
145·2	142·29
152·4	145·71
154·6	148·69

The insolubility of polyfluorinated aromatics in general (e.g. hexafluorobenzene, octafluoronaphthalene) is a good indication that the solubility of heptafluoroisoquinoline is not due to interaction between its π-electrons and a proton; otherwise if this were not the case, then there is no reason why perfluorinated aromatic compounds should not also be soluble. The solubility of heptafluoroquinoline has been attributed to N-protonation by U.V. spectral analysis.[116]

Nucleophilic substitution in isoquinolinium[117] salts is well known[118] e.g. the formation of nuclear hydroxy-derivatives by the reaction of base on methylisoquinolinium iodide. The hydroxylation of heptafluoroquinoline in concentrated sulphuric acid was assumed to be a similar process[116] i.e.



In excess water k_1 is much faster than k_2, therefore the unreacted quinoline is recovered. However on gradual dilution a stage is reached where the equilibrium condition permits some quinolinium salt and unprotonated water to be present allowing the substitution (k_2) to occur.

Perfluoroisoquinoline dissolves in concentrated sulphuric acid, quite slowly, but this is presumably due to some surface effect, and it is possible to make a 10% molar solution. When the solution is diluted rapidly with water only heptafluoroisoquinoline is recovered, as is the case with perfluoroquinoline.[116] When the experiment was repeated using slow addition of water, under the conditions where perfluoroquinoline gives 2-hydroxyhexafluoroquinoline,[116] again only perfluoroisoquinoline was recovered. Using the same molar proportions of concentrated sulphuric acid to perfluoroisoquinoline as was the case for the quinoline reaction, only half as much water as in the quinoline case could be added before the perfluoroisoquinoline was reprecipitated and so it appears that, even at equilibrium conditions, the substitution k_2 is very much slower than the deprotonation reaction k_1. Pentafluoropyridine behaves in an analogous manner to heptafluoroisoquinoline and a possible explanation for the behaviour exhibited by heptafluoroisoquinoline and pentafluoropyridine in this context, is that the availability of the nitrogen lone pair in both cases will be considerably less than that in heptafluoroquinoline. Because of the large σ-inductive

effects of the fluorines in the positions α- to the nitrogen the overall effect will be largest in pentafluoropyridine and heptafluoroisoquinoline where there are two α-fluorines, compared with perfluoroquinoline where there is only one.

Attempts to force the reaction to proceed by heating were unsuccessful. Water was added, just short of that necessary to cause reprecipitation of the heptafluoroisoquinoline, to the solution in concentrated sulphuric acid, and the whole was transferred to a Carius tube and heated to 140/150°C. In this case excessive decomposition occurred. On dilution of a solution in concentrated sulphuric acid, heptachloroisoquinoline behaved in a similar fashion to the fluorocompound.

It is evident from what has been said that heptafluoroisoquinoline is a very weak base indeed. Its conjugate acid will be very strong and that is the reason why the deprotonation is much more rapid than substitution.

The reaction of Heptafluoroisoquinoline with Nucleophiles.

The fluorine atoms in heptafluoroisoquinoline were found to be extremely susceptible to displacement on nucleophilic attack with sodium methoxide, ammonia, hydrazine hydrate, lithium aluminium hydride and butyl lithium. The reactions with aqueous sodium hydroxide and potassium hydroxide in tertiary butanol, will be discussed under a

separate section, even though they are examples of nucleophilic reactions.

a) The Reaction with Sodium Methoxide in Methanol.

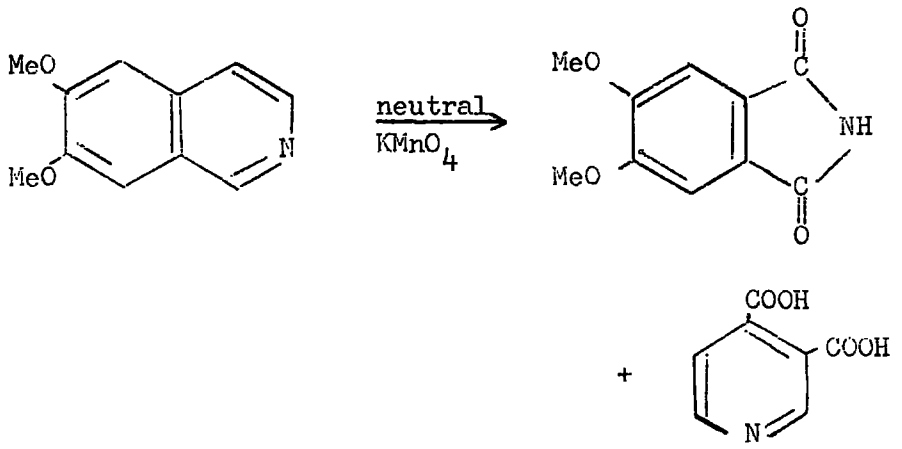
The reaction of heptafluoroisoquinoline with one molecular equivalent of sodium methoxide in methanol occurred very readily at $0^{\circ}C$ to give very high yields of a monomethylether. The same reaction occurred at $-30^{\circ}C$. On refluxing heptafluoroisoquinoline with two molecular equivalents of sodium methoxide in methanol, a high yield of a dimethoxy-derivative was obtained. No other compounds were found present on examination of the crude reaction products by v.p.c. and both the mono- and di-substituted compounds appeared as single peaks on a silicone elastomer column. The absence of any isomers was shown also by their ^{19}F n.m.r. spectra.

It was thought at the outset of this investigation that the assignment of the orientation of nucleophiles could be based purely on examination of their ^{19}F n.m.r. spectra. However the ^{19}F n.m.r. spectrum of isoquinoline itself is very complex, apparently first order, and analysis is complicated by the fact that in this seven-spin system all spins are interacting with each other. This makes unambiguous assignments very difficult.

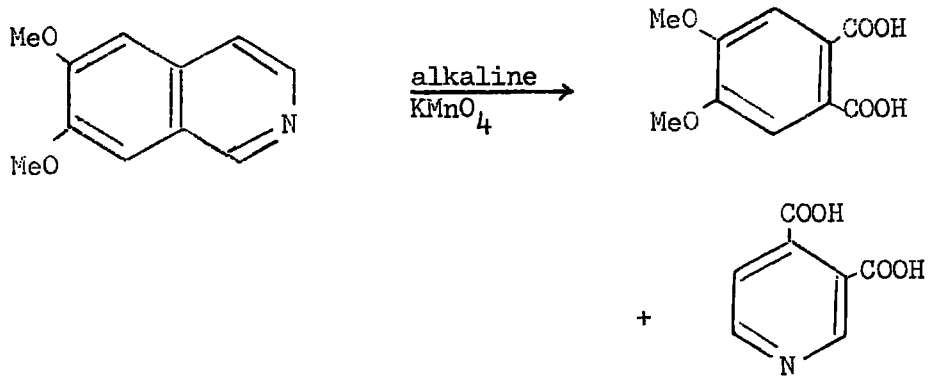
The answer to the problem of orientation therefore lay in degradation of the compounds, if possible, to compounds of known structure, or to products whose ^{19}F n.m.r. spectra could easily be

interpreted. The most common method of degradation i.e. by oxidation, was chosen.

The products of oxidation of the isoquinoline hydrocarbon system depends to a large extent upon the reagent used and the nature and position of substituents.[119] Isoquinoline with alkaline permanganate yields both phthalic and cinchomeronic acids.[120] Analogous results are obtained from 6,7-dimethoxyisoquinoline; in neutral solution the benzenoid product appears as the phthalimide rather than as the phthalic acid.[121]



Oxidation of 6,7-dimethoxyisoquinoline with alkaline potassium permanganate gives 4,5-dimethoxyphthalic acid.[122]



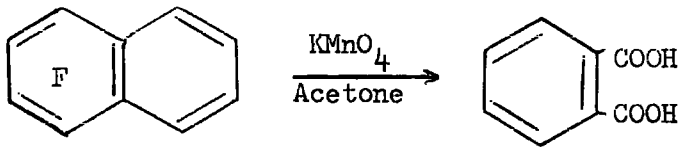
Both phthalic and cinchomeronic acids are obtained in the reaction of isoquinoline with ozone.[123]

Isoquinolines bearing electron attracting groups such as nitro,[124] iodo,[125] or carboxyl[126] in the 5-position are converted to the corresponding 3-substituted phthalic acids. 4-Bromoisoquinoline furnishes 4-bromocinchomeronic acid,[127] but 4(?)-iodoisoquinoline[128] as well as 3-phenyl-4-chloroisoquinoline,[129] gives only phthalic acid. 6-Methyl cinchomeric acid has been obtained from 3-methylisoquinoline.

Oxidation of the benzene ring in isoquinoline leading to cinchomeronic acid can be carried out with permanganate,[120] ozone,[123] or at elevated temperatures with nitric acid using phosphoric acid as solvent.[131] In the presence of selenium compounds hot concentrated sulphuric acid has been used effectively.[132]

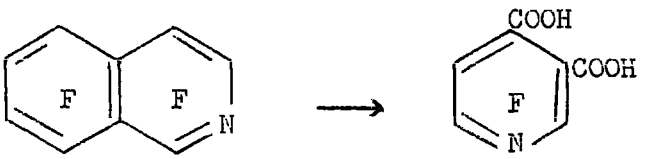
Fluoro-olefins are frequently subject to oxidation for their characterisation and for the synthesis of carboxylic acids. The oxidizing agent most frequently used is aqueous potassium permanganate.[135-138] Since many perhalogeno-olefins are, however, considerably more resistant to this reagent than are hydrocarbon olefins, the procedure is rather drastic and time consuming. Thus, although the yields are satisfactory the method is often inconvenient for small scale work.

A much more convenient method of oxidising small quantities of halogeno-olefins has been the use of potassium permanganate in dry acetone.[134] The oxidations were found to proceed rapidly giving good yields of the acids. This is a well known reagent for the oxidation of hydrocarbon olefins, and it has been used successfully in the facile oxidation of the fluorinated aromatic ring of tetrafluoronaphthalene.[139]

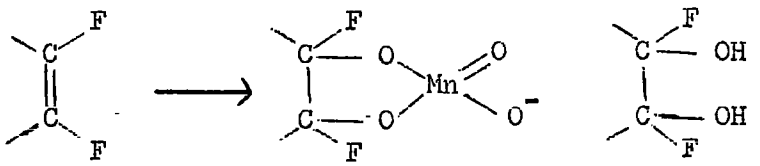


In the present work the reagent was initially used on heptafluoroisoquinoline to obtain some indication of the conditions that were required for the oxidation of the methoxy-compound. An extremely rapid and exothermic reaction took place when a solution of heptafluoroisoquinoline was added to potassium permanganate in acetone. The purple colour of the permanganate was discharged almost instantly and a heavy precipitate of manganese dioxide was formed. The reaction was over in a matter of seconds, but the mixture was kept for 1½ hours. The work up procedure was designed to isolate the free acid. Water was added and the acetone removed under vacuum. The manganese dioxide was removed by passing sulphur dioxide through the acidified solution and the free acid isolated by a continuous ether extraction procedure.

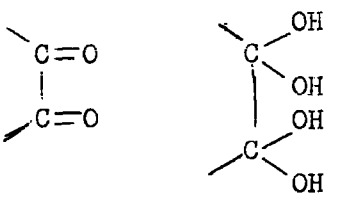
Purification was usually very difficult, requiring several recrystallisations from dry benzene. Sublimation could be used if the pressure and temperatures were carefully controlled, for there was a strong tendency to form the anhydride of the dicarboxylic acid. The product isolated from this reaction was the pyridine-3,4-dicarboxylic acid, with no tetrafluorophthalic acid being formed.



It is suggested[134] that in the case of fluoro-olefins, since one mole of potassium permanganate is required for every double bond to be oxidised, that the oxidation takes place via a cyclic manganese complex (e.g. III)



III IV



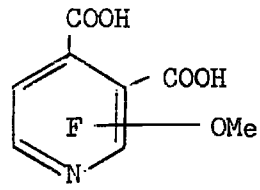
V VI

analogous to that postulated[140] to explain the oxidation of hydrocarbon olefins by dilute aqueous alkaline permanganate. Addition of the permanganate ion across the double bond in perhalogeno-olefins would be expected to occur fairly readily because of the known ease of attack by nucleophilic species. On addition of water the cyclic complex would be hydrolysed leaving incipiently, a fluorodiol (IV). This in a polar solvent would immediately lose hydrogen fluoride to give a α-diketone (V) which might well be hydrated immediately to the dihydrate e.g. VI. Either V or VI could presumably be readily oxidised by the residual oxidising power of the oxymanganese ion (resulting from the original hydrolysis of the complex) to give the final acidic material.

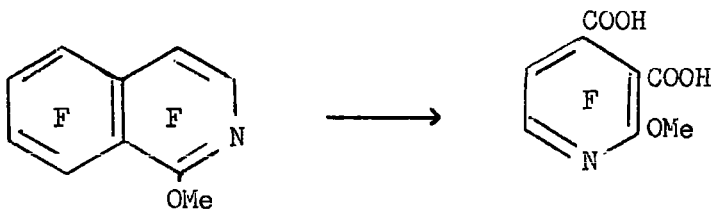
In the case of heptafluoroisoquinoline, the position most susceptible to nucleophilic attack is the 1-position (see later). Therefore, if the reaction proceeded initially by nucleophilic attack of the permanganate ion, one might expect the initial ring cleavage to occur across the 1,2-bond i.e. in the pyridine ring; since this does not occur it is highly likely that the mechanism in this case is not quite as straight forward as that proposed above.

With the successful oxidation of heptafluoroisoquinoline, the acetone-permanganate oxidising system was tried on the monomethoxy-hexafluoroisoquinoline. The first observation of interest that was made, was that the methoxy-compound was very resistant to oxidation. When

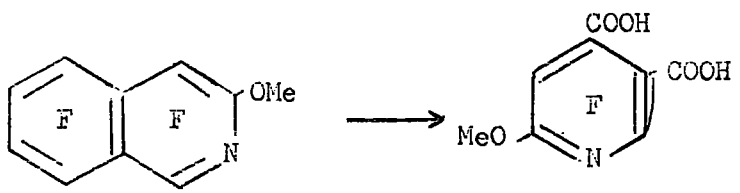
the reaction was carried out at room temperature, no reaction took place (as indicated by the absence of any decolourisation of the permanganate). Under reflux, using 1·05 moles of potassium permanganate for every double bond required to be oxidised, a reaction did take place, but from this, mainly starting material was recovered. Before appreciable quantities of products could be obtained from the reaction, the amount of permanganate had to be stepped up to ca. 1·2 mole for every double bond to be oxidised and even in this case a considerable amount of starting-material was recovered. The ideal method of carrying out the oxidation of the methoxy compound, was to add initially 1 mole for every double bond to be oxidised and reflux for $2\frac{3}{4}$ hrs. Then a further 0·5 mole for every double bond to be oxidised was added and the reaction mixture refluxed for a further $1\frac{1}{4}$ hrs, when only a very small quantity of starting material was recovered. The product was isolated as above and again was extremely difficult to purify. Analysis of the product showed that it was a difluoromethoxypyridine dicarboxylic acid.



An examination of the ^{19}F n.m.r. spectrum showed that it had two fluorine resonances (both doublets, J = 24·8 c.p.s.) which corresponded to shifts for α- and β-fluorines in a fluoropyridine nucleus.[141] This acid could have arisen from both the 1- and 3-substituted isoquinolines i.e.



VII VIII



IX X

It was not possible to distinguish between VIII and X on the basis of the F-F coupling constant, because ortho and para F-F coupling constants in pentafluoropyridine derivatives are quite similar.[142] Therefore VIII and X had necessarily to be distinguished on the basis of their ^{19}F chemical shifts.

There is a large difference in the chemical shifts for the 2,6-, 3,5-, and 4-fluorine atoms in a polyfluoropyridine and the introduction

of substituent groups has an effect which can be predicted on the basis of observations on similar compounds to a degree which distinguishes the orientation of many groups.[141] The observed shifts for a number of compounds are shown in Table I, and for example we see that the effect of introducing a carboxyl group into pentafluoropyridine in the 4-position shifts the 2,6- and 3,5-fluorine atom resonances by +1·6 and -21·7 p.p.m., respectively relative to the shifts in pentafluoropyridine.

Table I

^{19}F chemical shifts relative to $CFCl_3$*

(positions of F nuclei in parenthesis)

Pentafluoropyridine	87·6(2,6); 162·0(3,5); 134·1(4)
Tetrafluoronicotinic acid	65·8(2); 80·9(6); 112·4(4); 167·0(5)
Tetrafluoroisonicotinic acid	89·2(2,6); 140·3(3,5)
Trifluoropyridine-3,4-dicarboxylic acid	65·5(2); 79·1(6); 144·4(5)
Difluoromethoxypyridine-3,4-dicarboxylic acid	82·9(6); 154·8(5)

*Solutions examined using acetone as solvent.

A carboxyl group in the 3-position shifts the resonances of the 2-, and 4-fluorine atoms by -21·8 and -21·7 p.p.m., the 5-fluorine atom by +5·0 p.p.m., and the 6-fluorine atom by -6·7 p.p.m. Using these effects, the calculated shifts arising from the introduction of two carboxyl groups in the 3- and 4-positions are 67, 145 and 82 p.p.m., based

on the shifts observed for pentafluoropyridine, and these values agree with those observed as shown in Table I.

In order to determine the effect of putting a methoxyl group in the 2-position on the ^{19}F chemical shifts, a large number of substituted 2-methoxyfluoropyridines were examined (see Table II). It can be observed that in general the effect of a methoxyl group in the ortho-fluorines is very small, 0 to +2 p.p.m., the meta effect is in the region +2 to +7 p.p.m., and the para effect is large, +6 to +12 p.p.m. Using averages of these effects with the observed shifts for trifluoro-pyridine-3,4-dicarboxylic acid then the calculated shifts for the 5- and 6-fluorine atoms in VIII are 153 and 83 p.p.m., and the 2-, and 5-fluorine atoms in X are 69 and 145 p.p.m. There is clearly a distinction between these values, and since the former agree with the observed values (Table I), the mono-ether must be VIII. Therefore, the isoquinoline which gave rise to this must have been the 1-substituted compound and the position of substitution of the first nucleophile is the 1-position in the case of attack by methoxide ion.

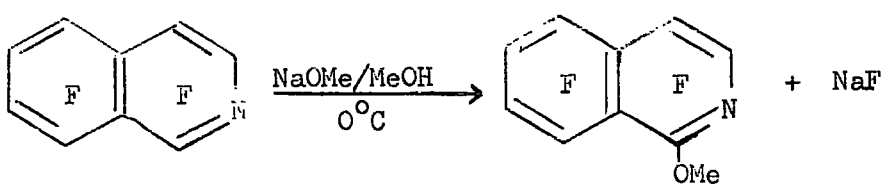


Table II

^{19}F shifts of some substituted 2-methoxyfluoropyridines relative to $CFCl_3$

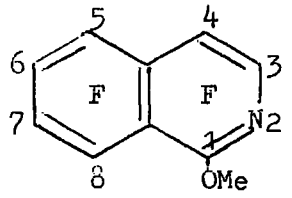
(fluorine positions in brackets)

Measured at 60 Mc/sec. in acetone.

Reference Number	Compound	^{19}F Chemical shifts (fluorine positions in brackets) p.p.m. relative to $CFCl_3$	Reference Compound	Positional effects of the 2-methoxy-group ortho	meta	para
A	pentafluoropyridine	87·10(2,6); 160·53(3,5); 132·7(4)	-	-	-	-
B	2-methoxytetrafluoropyridine	161·03(3); 140·23(4); 171·23(5); 90·70(6)	A	+0·5	+3·6 through nitrogen	+10·7
C	4-aminotetrafluoropyridine	94·03(2,6); 163·93(3,5)	-	-	-	-
D	2-methoxy-4-aminotrifluoro-pyridine	164·63(3); 170·99(5); 96·43(6)	C	+0·7	+2·4	+6·5
E	4-nitrotetrafluoropyridine	84·73(2,6); 145·63(3,5)	-	-	-	-
F	2-methoxy-4-nitrotetrafluoro-pyridine	147·23(3); 158·03(5); 86·73(6)	E	+1·6	+2·0	+12·4
G	4-bromotetrafluoropyridine	88·83(2,6); 134·23(3,5)	-	-	-	-
H	2-methoxy-4-bromotrifluoro-pyridine	134·43(3); 144·53(5); 91·53(6)	G	+0·2	+2·7	+10·3

Establishing the orientation of the dimethoxypentafluoroisoquinoline, formed by the reaction of heptafluoroisoquinoline with two equivalents of sodium methoxide, proved to be quite difficult. The first clue as to its orientation was obtained on oxidising the dimethoxy-compound with permanganate in acetone, when the only product that was identified was VIII the same compound as that which was isolated from the oxidation of the 1-methoxyhexafluoroisoquinoline. This result showed that the second methoxide nucleophile enters the benzene ring of heptafluoroisoquinoline. The problem of determining exactly where was only possible using detailed ^{19}F n.m.r. spectral analysis.

Since the orientation of the 1-methoxyhexafluoroisoquinoline was now known, some important information (e.g. coupling constant values etc.), which would be of value in the analysis of the spectrum of the dimethoxy-compound, was initially deduceable from its ^{19}F n.m.r. spectrum. The ^{19}F n.m.r. spectrum of 1-methoxyhexafluoroisoquinoline consists of six groups of peaks centred at 164·75, 156·59, 148·73, 146·73, 136·25 and 97·69 p.p.m., relative to $CFCl_3$. The peak at 97·69 is assigned to the fluorine in position 3 because a) the 3-carbon atom has very low electron density (see later) giving rise to a strong deshielding effect, and b) of the broadened character of the component bands arising from close proximity to a ^{14}N quadrupolar nucleus. The peak was essentially a broad doublet having a J value ($J_{3,4}$) of ca. 17 c.p.s.



The peak at 164·75 p.p.m. was assigned to the 4-fluorine for two reasons. In the first place the 4-fluorine is attached to the carbon atom which has the highest π-electron density in the system and therefore would be expected to be the least deshielded. In the second place, an examination of a large number of polyfluoropyridine derivatives which had methoxyl groups in the 2-position (see Table 2), showed that a fluorine atom para to the methoxyl group was shifted upfield by the order of 8-12 p.p.m., whereas the ortho and meta fluorines were hardly affected. In heptafluoroisoquinoline, the two highest field peaks occur at 152·45 p.p.m., and 152·65 p.p.m.; therefore the peak at 164·75 p.p.m. in the 1-methoxy compound has been shifted upfield by the correct magnitude from either of the above for a p-methoxyl effect (7·7 p.p.m. and 9·9 p.p.m. respectively). This peak consisted of a doublet of doublets of triplets of doublets, and from the spectrum the following coupling constants were evaluated.

$J_{4\cdot5}$ = 49·7 c.p.s.

$J_{4\cdot3}$ = 17·7 c.p.s. (see 3F spectrum)

$J_{4\cdot6}$ = $J_{4\cdot7}$ $\sim$ 4·0 c.p.s.

$J_{4\cdot8}$ = 1·5 c.p.s.

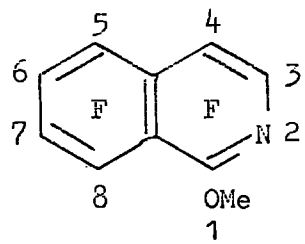
$J_{4.5}$ was assigned on the basis that in heptafluoroisoquinoline a large coupling is also observed, $J_{1.8}$ (ca. 65 c.p.s.), which is absent in all 1-substituted derivatives, and also the 1-fluorine in the 4-chlorohexafluoroisoquinoline shows a very large coupling (ca. 70 c.p.s.). These facts can only therefore be interpreted in terms of very strong peri fluorine-fluorine couplings. Hence the large value in the above peak must be also assigned to peri F-F interaction.

The 5-fluorine was assigned because of the large coupling with the 4-fluorine of $J_{4.5}$ = 49·7 c.p.s. Two other major coupling constants of 17·3 c.p.s. and 15·8 c.p.s. were assigned to $J_{5.6}$ and $J_{5.8}$ respectively. $J_{5.7}$ and $J_{5.3}$ were assigned the values 4·7 c.p.s. and 0·7 c.p.s. respectively. The peak at 148·73 p.p.m., can be shown to arise from the 7-fluorine by an examination of its structure. The peak consisted of a complex multiplet which was analysed as a series of overlapping triplets. The following coupling constants were obtained, $J_{7.6}$ = 19·0 c.p.s., $J_{7.8}$ = 17·8 c.p.s., $J_{7.4} = J_{7.5}$ = 3·7 c.p.s. and $J_{7.3}$ = 7·9 c.p.s. The triplet states arose from the almost equivalent coupling of the 7-fluorine with the 4- and 5-fluorines. The 3·7 c.p.s. coupling indicated that this was the 7-fluorine since the other two fluorines in the benzene ring (6 and 8) have a much larger coupling constant.

The 6- and 8-fluorines are very similar in fine structure (peaks at 156·59 and 136·23 p.p.m.) and it was very difficult to distinguish

between them by an examination of the coupling constants. However on both peaks there is a medium range coupling constant of ca. 8 c.p.s. which was assigned to $J_{6.8}$, and this distinguishes the 6- and 8-fluorines from the 7-fluorine. Note that on the 7-fluorine a coupling of 7·9 c.p.s. was observed, but this was not present on the 5-fluorine (which can be unambiguously assigned) so this coupling was assumed to be $J_{7.3}$. The peak at 156·59 p.p.m. (6F) has two couplings of 17·3 c.p.s. and 19 c.p.s. and the assignment of these can be based on an examination of the coupling constants observed on the 5-fluorine, followed by comparison with those on the peak at 136·23 p.p.m. (8F).

The above assignment of the 6- and 8-fluorines will also be shown to be correct by an examination of the chemical shifts in 1,6-dimethoxypentafluoroisoquinoline. However any ambiguity which may exist between the 6- and 8-fluorines does not in any way affect the final assignment of the methoxyl positions in 1,6-dimethoxypentafluoroisoquinoline. The data obtained can be summarised as follows.



$J_{i.j.c.p.s.}$	3	4	5	6	7	8
3	X	17·7	0·7	0	7·9	4·7
4	17·7	X	49·7	3·7	3·7	1·5
5	-	49·7	X	17·3	4·0	15·8
6	-	3·7	17·3	X	19·0	8·0
7	-	3·7	4·0	19·0	X	17·8
8	-	1·5	15·8	6·4	17·8	X

19_F shifts rel. to $CFCl_3$ (soln. in acetone). (Assignments in parentheses)

97·6(3); 136·2(8); 146·9(5); 148·7(7); 156·5(6); 164·7(4)

Consideration will now be given to the orientation of the second methoxyl group in the dimethoxypentafluoroisoquinoline. This spectrum shows five groups of chemically shifted peaks centred at 165·22 p.p.m., 150·88 p.p.m., 139·67 p.p.m., 138·85 p.p.m. and 100 p.p.m., relative to $CFCl_3$.

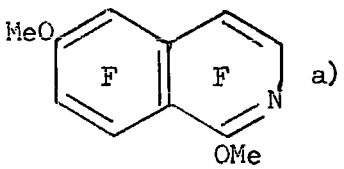
The highest field peak was assigned to the 4-fluorine because of the reasons stated in the analysis of the 1-methoxyhexafluoroisoquinoline. From the other peaks present the 5-fluorine was easily assigned because of the presence of a large coupling constant of the order of 50 c.p.s., which was also present on the 4-fluorine. The 3-fluorine was also easily recognised by the fact that it occurred at very low field. Thus we have

139·67 p.p.m. - 5F

165·22 p.p.m. - 4F

102·0 p.p.m. - 3F

The problem was to determine which of the 6-, 7-, or 8-fluorines had been replaced by the methoxyl group, i.e. whether the dimethoxy compound was

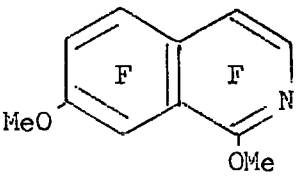


a)

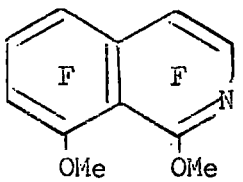
or

XI

or



XII



b)

These three possibilities were distinguished from each other in a number of ways, which will be outlined.

If one considers the absorption due to the 5-fluorine, which occurs at 139·67 p.p.m., in the case of a XIa the major couplings will be $J_{5.4}$, which should be of the order of 50 c.p.s. (the large coupling which was shown to be present on the 4-fluorine at 165·22 p.p.m.), and $J_{5.8}$ which should be of the order of 15-16 c.p.s. (from analogy with the 1-methoxyhexafluoroisoquinoline). Therefore we should expect a doublet

of doublets. Further splitting would occur due to $J_{5.7}$, $J_{5.3}$, and also due to coupling with the protons of methoxyl group.

For XIb we would also expect the 5-fluorine to be a doublet of doublets, arising from $J_{5.4}$ = ca. 50 c.p.s., $J_{5.6}$ = ca. 16 c.p.s. with further smaller splittings due to $J_{5.7}$, $J_{5.3}$ and coupling with the methoxyl protons. However if the 7-fluorine, as in XII, had been replaced then we would still have three major coupling constants, $J_{5.4}$, $J_{5.6}$ and $J_{5.8}$. This would give a series of doublets, which would make the peak look similar to a doublet of triplets if $J_{5.8}$ differed slightly from $J_{5.6}$ or, an actual doublet of triplets if $J_{5.8} = J_{5.6}$.

When the peak at 139·67 p.p.m., due to the 5-fluorine (i.e. the one with a large 50 c.p.s. coupling on it) was examined, it was essentially a doublet of doublets with other fine structure present. It can therefore be seen that the 7-fluorine cannot have been replaced, and that the dimethoxy compound must be either XIa or XIb. The values for the coupling constants are $J_{5.4}$ = 50·7 c.p.s., $J_{5.8}$ = 14·3 c.p.s. (see later for proof of 6-fluorine having been replaced) and a small coupling of 2 c.p.s. This 2 c.p.s. coupling was responsible for splitting each of the components of the doublet of doublets into a sextet. This must arise from an equivalent 2 c.p.s. coupling of the 5-fluorine to the 3-fluorine, the 7-fluorine and to the three protons of the methoxyl group in the benzene ring. (See later for p.m.r.

measurements). This would require the formation of a sextet of relative line intensities 1:5:10:10:5:1, which is approximately that obtained for each of the lines in the 5-fluorine spectrum.

Differentiating between the two possibilities i.e. 1,8-dimethoxy- and 1,6-dimethoxy-hexafluoroisoquinoline was attempted in two ways. In the first instance the proton magnetic resonance (p.m.r.) spectra were examined. Chemical shifts were not measured but the coupling constants were evaluated.

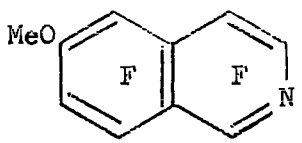
It has been shown by workers in the field of polyfluorinated aromatic compounds that methoxyl protons couple only to fluorine atoms adjacent to the methoxyl group.[143] If this is true then for compound XIa we would expect the proton resonance spectrum to consist of a doublet of doublets and a singlet (possibly a double) arising from 6-methoxyl to 5-fluorine and 7-fluorine coupling, and the 1-methoxyl which may or may not couple with the 8-fluorine. However for XIb we would only expect a doublet for 8-methoxyl to 7-fluorine coupling and a singlet for the 1-methoxyl peak. The following results were obtained.

1-Methoxyhexafluoroisoquinoline. In this case a single peak was obtained but it was quite broad. The fact that no coupling with the 8-fluorine occurs is not really too surprising since no doublet was obtained from polyfluoropyridines substituted in the 2-position with methoxyl groups due to coupling with the 3-fluorine atom.[99] Also the methoxy group

4-methoxyhexafluoroquinoline only gives a doublet since there is no coupling with the 5-fluorine atom.[144]

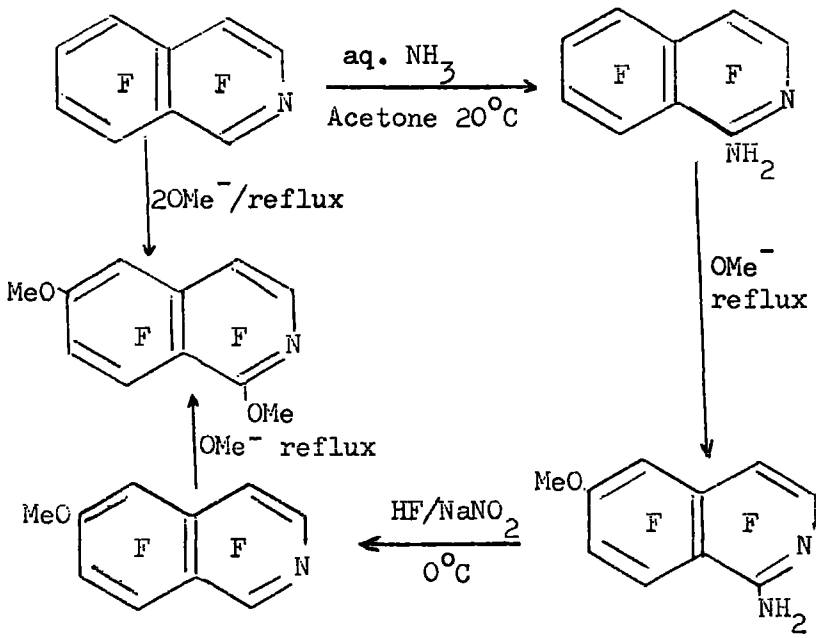
Dimethoxypentafluoroisoquinoline. The proton spectrum shows a broad single peak (cf. the 1-methoxyhexafluoroisoquinoline) and also a doublet of doublets which must arise from couplings with two ortho fluorine atoms. The coupling constants were J = 1·3 c.p.s. and J = 2·8 c.p.s. (cf. β-methoxyheptafluoronaphthalene where J = 0·9 and 1·9 c.p.s.). It is thus evident that the compound produced from the reaction of heptafluoroisoquinoline with two equivalents of methoxide ion is 1,6-dimethoxypentafluoroisoquinoline, XIa.

The second method for demonstrating the orientation of the second methoxyl group was to synthesise the compound XIII, and examine its ^{19}F n.m.r. spectrum, particularly the peak due to the 1-fluorine. If this peak has a large (~ 65 c.p.s.) coupling on it, then the 8-fluorine is still present.



XIII

The compound was synthesised as follows:



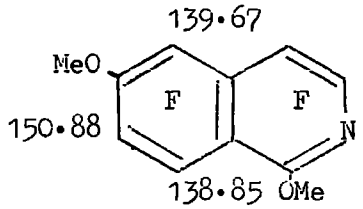
The reaction of heptafluoroisoquinoline has been shown to give 1-aminohexafluoroisoquinoline and removal of this amino group by diazotisation is quite easily carried out (see later). The reaction of 1-aminohexafluoroisoquinoline with one equivalent of methoxide ion was carried out under reflux to give a good yield of a monomethoxy-1-aminopentafluoroisoquinoline. The amino group was replaced by fluorine on diazotisation in anhydrous hydrogen fluoride to give a monomethoxyhexafluoroisoquinoline. This compound was shown to be the required compound XIII by reaction with a further equivalent of methoxide ion, when the 1-fluorine was readily replaced, to give the

same dimethoxy-compound XIa as was obtained by the direct reaction of heptafluoroisoquinoline with two equivalents of sodium methoxide.

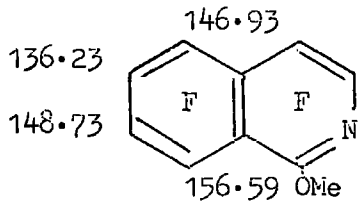
An examination of both the ^{19}F and ^{1}H n.m.r. spectra of XIII showed conclusively that the 8-fluorine was still present, and that it must therefore be the 6-fluorine that had been replaced. In the ^{19}F n.m.r. spectra, the 1-fluorine was shown to be present because of its very low field position (see later). An examination of the fine structure of this peak showed that it had on it a coupling constant at ca. 65 c.p.s., i.e. the 8-fluorine was still therefore present. The ^{1}H spectrum showed a doublet of doublets. This also indicated that the 8-fluorine had not been replaced, because if it had been replaced only a doublet would have been obtained. It can be seen therefore that the above evidence conclusively shows that the dimethoxy-compound is 1,6-dimethoxypentafluoroisoquinoline.

As regards the actual assignment of the 7- and 8-fluorines in 1,6-dimethoxypentafluoroisoquinoline, the 7-fluorine must be the peak at 150·88 p.p.m. because it is now basically a doublet (6-fluorine coupling removed), and the peak at 138·85 must be the 8-fluorine (now a triplet arising from the equivalence of F_8-F_7 and F_8-F_5 coupling). This enables one to assign the two peaks at 136·23 p.p.m., and 156·59 p.p.m., in the 1-methoxyhexafluoroisoquinoline to the 8-fluorine and the 6-fluorine purely on the basis of ^{19}F chemical shifts and the effect of the 6-methoxyl group on fluorines ortho and meta to it. The chemical

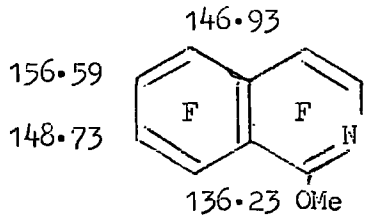
shifts of the benzene ring fluorine atoms in the 1,6-dimethoxypentafluoro-isoquinoline are:



The possible benzene ring fluorine chemical shifts in 1-methoxy-hexafluoroisoquinoline are:



possibility a)



possibility b) in which the F_6 and F_8 in a) are reversed.

If the assignments that the 6- and 8-fluorines were as in a), is correct then the effect of introducing a methoxyl group into position 6 on the neighbouring fluorines is

5-fluorine has shifted -7·2 p.p.m., ortho-effect

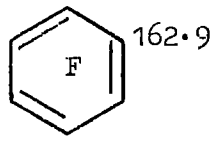
7-fluorine " " +2·1 p.p.m.,

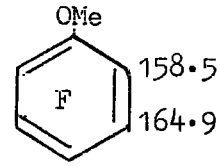
8-fluorine " " +18/+19 p.p.m., meta-effect

If the assignment that the 6- and 8-fluorines are as in b) is correct then the effect would be,

5-fluorine has shifted	-7·2 p.p.m.	ortho-effect
7-fluorine " "	+2·1 p.p.m.	
8-fluorine " "	+2·0 p.p.m.	meta-effect

If these effects are compared against the ortho- and meta-effects in pentafluoroanisole,[145]





where the ortho effect is -4·4 p.p.m., and the meta effect is +2 p.p.m., then the assignment b) must be correct, since a meta effect of 18/19 p.p.m., (as in a)) is highly unrealistic.

The coupling constants and chemical shift assignments for 1,6-dimethoxypentafluoroisoquinoline are shown below in tabular form.

J_{ij}	3	4	5	7	8
3	X	16·3	2·0*	4·0*	4·3
4	-	X	50·7	3·8	1·5
5	-	50·7	X	2·0*	14·3
7	-	3·8	2·0*	X	14·3
8	-	1·5	14·3	14·3	X

No data could be obtained from the peaks due to 3F since it was very broad

* - assignment tentative.

Chemical Shift data (fluorine assignments in parentheses) - relative to $CFCl_3$ (p.p.m.).

100·0(3); 138·85(8); 139·7(5); 150·9(7); 165·2(4)

The Reaction of Heptafluoroisoquinoline with Nitrogen Containing Nucleophiles.

a) Hydrazine Hydrate. Refluxing with a two molar equivalent of hydrazine hydrate, as for pentafluoropyridine,[146] resulted in almost complete decomposition of the isoquinoline and no pure products were isolated. However, reaction occurred readily at 20° and 1-hydrazino-hexafluoroisoquinoline was isolated in good yield. The reaction was also carried out using ethanol as the solvent at 0°, when almost identical results to those using dioxan were obtained. The hydrazino compound was extremely difficult to purify giving on sublimation a white solid which when exposed to sunlight turned a pale yellow colour.

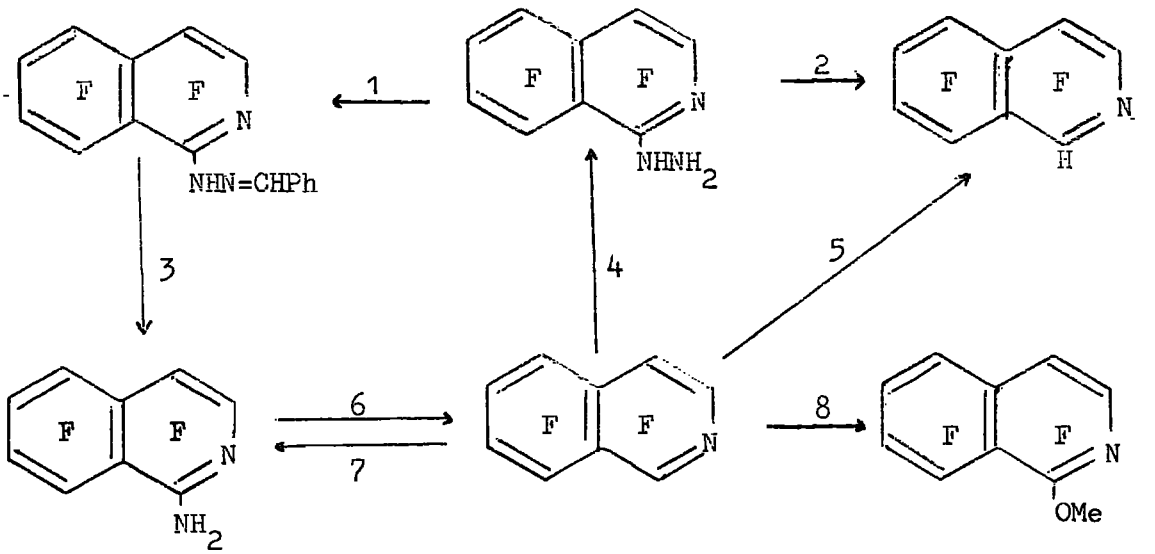
b) Ammonia. Excess aqueous ammonia in acetone reacted exothermically at 20°C to give a high yield of 1-aminohexafluoroisoquinoline. The reaction with ammonia was repeated, this time under completely anhydrous conditions. The solvent used was ether, and when ammonia gas was bubbled through a solution of heptafluoroisoquinoline in anhydrous ether, the product obtained was identical to that obtained in the above case, with no indications of the formation of any other isomers. Attempted

oxidation of 1-aminohexafluoroisoquinoline by refluxing with trifluoroperoxyacetic acid in methylene dichloride, a procedure used to oxidise 4-aminotetrafluoropyridine to the corresponding nitro compound,[101] resulted in decomposition. Carrying out the reaction at room temperature also resulted in very extensive decomposition and again no nitro compound was formed.

The Reaction of Heptafluoroisoquinoline with Lithium Aluminium Hydride.

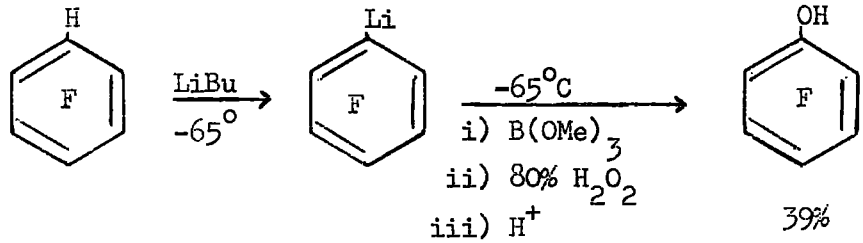
The reaction of one equivalent of lithium aluminium hydride with an ethereal solution of heptafluoroisoquinoline at 0°C resulted in the formation of 1-hydrohexafluoroisoquinoline, along with unreacted starting material.

The orientation of the groups in the above three products were partly related by interconversion reactions, as shown in Figure I.

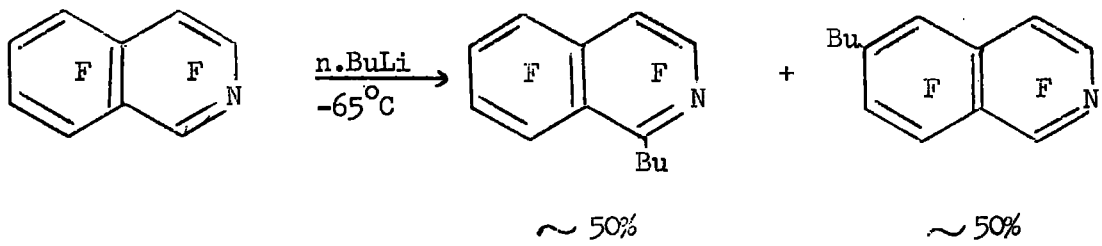


Reagents: 1, PhCHO; 2, aqueous $CuSO_4$; 3, Zn-$MeCO_2H$; 4, dioxan $NH_2 \cdot NH_2 \cdot H_2O$; 5, $LiAlH_4$-Et_2O; 6, anhydrous HF-$NaNO_2$; 7, aqueous NH_3 or NH_3-Et_2O; 8, NaOMe

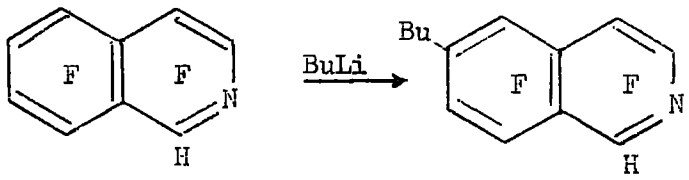
The basic idea behind these interconversion reactions, was to attempt to relate all products obtained from the nucleophilic reactions of heptafluoroisoquinoline, back to the 1-methoxyhexafluoroisoquinoline and show that they were in fact all 1-substituted. It was hoped to relate the 1-hydro compound to the 1-methoxy compound via the 1-hydroxy compound, using a reaction which has been developed by Furniss and Quasem[147] for the preparation of fluorophenols from the corresponding hydrogen compounds, i.e.



When this reaction was attempted using 1-hydrohexafluoroisoquinoline, a very complex product was obtained which most certainly did not contain any 1-hydroxy compound. The reason for this became apparent when heptafluoroisoquinoline itself was treated with n-butyl-lithium in both hexane and diethyl ether. Substitution was occurring, in both cases, at both positions 1- and 6-, in almost equal amount.

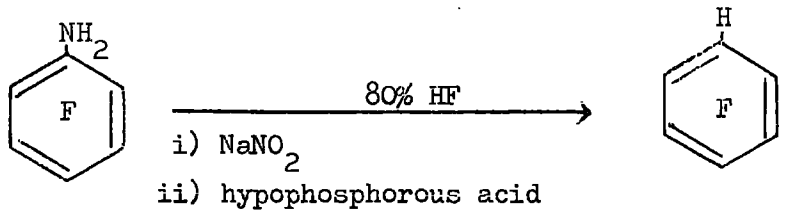


Thus in the case of the 1-hydrohexafluoroisoquinoline the mole of butyl-lithium that was added to make the lithio-isoquinoline, was reacting by replacing a fluorine atom in the 6-position, rather than exchanging the acidic proton on the 1-position.



It was therefore not possible to carry out the final stage in the proposed interconversion reactions.

The hydrazino-compound could only be related to the amino-compound by indirect conversion via the benzaldehyde condensation product. Even in this case, reduction of this condensation product by zinc dust and acetic acid gave the amino-compound in only 15% yield. Attempted direct conversion, using aqueous hydriodic acid as the reducing agent resulted in complete decomposition of the 1-hydrazino compound. Attempted conversion of the 1-amino-compound to the 1-hydro compound via the diazonium salt and subsequent treatment with hypophosphorus acid was unsuccessful. The diazotisation was carried out in both 80% aqueous and anhydrous hydrofluoric acid, a solvent in which polyfluoroaromatic amines have successfully been diazotised[148] and converted to the hydrogen-compound i.e.

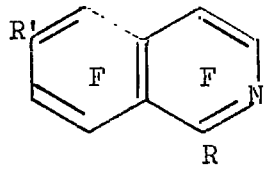


The diazotisation of 1-aminohexafluoroisoquinoline, in either anhydrous or 80% hydrofluoric acid resulted in the formation of heptafluoroisoquinoline, or mixtures of the latter with unreacted 1-aminohexafluoroisoquinoline depending upon reaction times. Clearly in hydrogen fluoride the diazotisation process is relatively slow compared with the rate at which the diazonium group is displaced by fluoride ion. Addition of hypophosphorous acid did not affect the course of the reaction because no hydro-derivative could be isolated. Diazotisation in 50% hydrogen bromide gave a compound which has not yet been characterised.

While it is not possible to relate the 1-methoxyhexafluoroisoquinoline with the other monosubstitution products, the ^{19}F n.m.r. spectra clearly indicate that, in all these reactions, nucleophilic attack occurs at the 1-position. The chemical shift data for heptafluoroisoquinoline, and substitution products is shown below; the two low field peaks in heptafluoroisoquinoline, as has been stated earlier, must arise from the 1- and 3-fluorine atoms, being ortho to nitrogen, since this low field shift is observed in the pyridine and

pyridazine[104] series. The very low field peak that was observed in the spectrum of heptafluoroisoquinoline, does not appear in the case of the 1-methoxy derivative and thus must arise from the 1-fluorine atom, while the peak at 96·5 c.p.s. must be due to the 3-fluorine atom. The 1-fluorine atom is further characterised by an abnormally large coupling constant of 60-65 c.p.s. and this arises from coupling with the 8-fluorine atom, which also distinguishes the latter. Since the very low field peak is absent in the other monosubstitution products, this indicates that 1-substitution is general and this conclusion is further confirmed by the absence of any very large 60-65 c.p.s. couplings in the spectra of these compounds. The spectra of the monosubstituted derivatives were not analysed in any great detail.

Chemical shifts for polyfluoroisoquinolines* rel. to $CFCl_3$



R	R'							
F	F	61·0	96·5	138·9	144·5	145·2	152·4	154·6
H	F	-	97·2	145·6	146·4	148·1	150·9	154·6
NH_2	F	-	94·4	140·0	146·6	147·3	150·4	159·9
OMe	F	-	97·6	136·2	146·9	148·7	156·5	164·7
F	OMe	62·7	98·9	141·5†	142·5†	147·4	155·9	
OMe	OMe	-	100·0	138·8	139·7	150·9	165·2	
nBu	F	-	98·2	-	137·2	145·2	149·2	155·2[x]
F	nBu	62·4	98·0	122·7	136·9	144·2	154·5	

*Solutions in acetone.

† Peak centre in doubt because of two overlapping peaks.

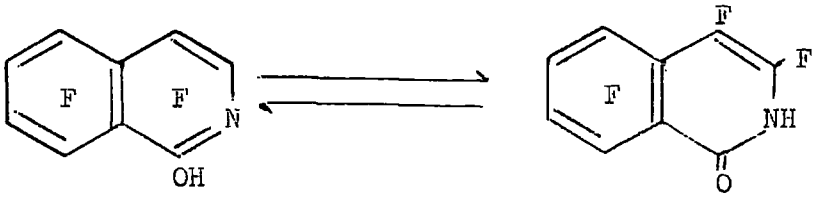
[x]Contains two peaks superimposed.

The Synthesis of, and Tautomerism in 1-Hydroxyhexafluoroisoquinoline.

Heptafluoroisoquinoline reacted very readily with both aqueous sodium hydroxide and potassium hydroxide in tertiary butanol as solvent, to give good yields of 1-hydroxyhexafluoroisoquinoline. In the former case refluxing was required to cause formation of the hydroxy-compound, while in the case of potassium hydroxide in tertiary butanol as solvent, a water-bath temperature of 70/80° was sufficient to give good yields of the hydroxy-compound.

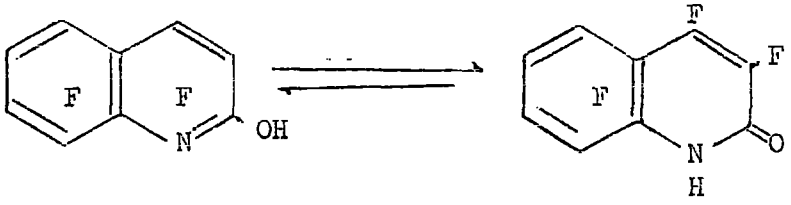
The first feature of interest of the hydroxy-compound was that it could not be recrystallised to give a constant melting point (benzene solvent). An examination of its ^{19}F n.m.r. spectrum (solution in acetone - the only solvent in which it was sufficiently soluble to give a strong signal) showed that the spectrum was normal for a 1-substituted hexafluoroisoquinoline, and its ultra-violet spectrum (solution in ethanol) also showed the spectrum to be similar, for example, to that of 1-methoxyhexafluoroisoquinoline.

However, the infra-red spectrum (solid state-KBr disc) showed a band at $\sim$ 1720 cms.$^{-1}$, which was not found to be present in any other 1-substituted isoquinoline. This band is at far too high a frequency to be aromatic C=C, even though fluorine does shift vibrations of this kind to a higher frequency. The position of this band is however, consistent with the presence of the keto-tautomer of the hydroxy form i.e.



I II

Similar results have been obtained from 2-hydroxyhexafluoroquinoline,[150] the infra-red spectrum of which showed a conjugated carbonyl absorption at 1704 cms.$^{-1}$ In 2-hydroxyquinoline[149] the conjugated carbonyl absorption occurs at 1648 cms.$^{-1}$ which represents a change on going to the perfluoro-analogue of 56 cms.$^{-1}$ The conjugated carbonyl absorption in 1-isoquinolone occurs at 1653 cms.$^{-1}$,[149] and so it can be seen that there is a similar frequency shift with the perfluoro-analogue in this case. In the case of the isoquinoline compound, II, the absorption due to the conjugated carbonyl group is less intense than that of the corresponding quinoline compound IV,



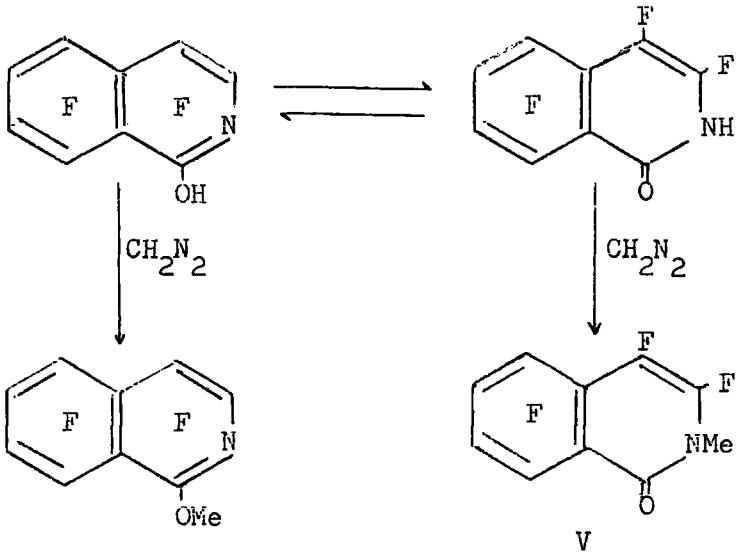
III IV

indicating that the amount of keto-tautomer present in the equilibrium mixture is possibly less in the case of 1-hydroxyhexafluoroisoquinoline than in 2-hydroxyhexafluoroquinoline. It is interesting to note that

1-hydroxyhexafluoroisoquinoline showed a very complex broad band in the region of 3300 - 2500 cms.$^{-1}$, indicating extensive hydrogen bonding to be occurring in the solid state and rendering identification of any discrete -NH or -OH absorption impossible.

The 1-hydroxyhexafluoroisoquinoline was methylated by adding an ethereal solution of diazomethane to an ethereal solution of the hydroxy compound at room temperature. The method of methylation has been used to methylate a number of aromatic polyfluorohydroxy compounds,[151,152] and in all cases the only product obtained was the O-methyl compound. The product from this reaction was examined by v.p.c., and it was found that two products were present. The major component (80%) was shown to be 1-methoxyhexafluoroisoquinoline, while the other compound of longer retention time (20%) was shown by analysis and a molecular weight determination, to be isomeric with it.

The infra-red spectrum of this compound was found to have a reasonably strong absorption at $\sim$1720 cms.$^{-1}$ The position of this absorption is comparable with the high frequency absorption in the spectrum of the 1-hydroxyhexafluoroisoquinoline, and is due to the presence of a conjugated carbonyl group. Indications were that this compound was in fact hexafluoro-N-methylisoquinol-1-one (V).



V

The relative proportions of the O-methyl and N-methyl compounds obtained on methylation of the tautomeric mixture (I and II) need bear no relation to the equilibrium proportions of I and II since they are unlikely to react at the same rate. An example[155] of this is 2-hydroxypyridine which exists principally as the pyrid-2-one but on reaction with diazomethane gives mainly 2-methoxypyridine.

Further evidence for this structure was obtained on examination of its ^{19}F n.m.r. spectrum, which was found to be markedly different from those of 1-methoxyhexafluoroisoquinoline and 1,6-dimethoxypentafluoroisoquinoline. It can be seen from the table below that two of the peaks in V (due to the 3- and 4-fluorine atoms) have been shifted to high-field by a factor of $\sim$ 20 p.p.m., compared to their positions in the O-methyl compounds.

^{19}F Chemical Shifts* of Polyfluoroisoquinolines (p.p.m.)

1-methoxyhexafluoroisoquinoline	1,6-dimethoxypentafluoroisoquinoline	V
97·6	100·0	†119·1
136·2	138·8	137·1
146·9	139·6	146·6
148·7	-	147·8
156·5	150·8	157·5
164·7	165·2	†181·2

*Solutions in acetone. Shifts rel. to $CFCl_3$ as external reference.

† Peaks shifted upfield.

Quite apart from the large chemical shift effect on the 3- and 4-fluorine resonances, the $J_{3,4}$ value was found to have collapsed from 17-19 c.p.s. in the methoxy-compounds to < 3 c.p.s. in V, which is quite a remarkable overall effect.

An examination of the ultra-violet spectra of 1-methoxyhexafluoro-, 1,6-dimethoxypentafluoro-isoquinolines and V showed some similarity in the spectra of the former two compounds, with a completely anomalous spectrum for V (see table below).

U.V. Spectra [λ_{max} mμ (ε_{max})] in cyclohexane solution.

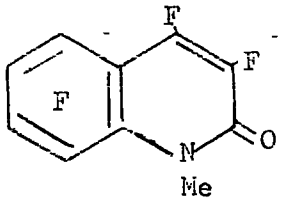
Heptafluoroisoquinoline	1-methoxy-	1,6-dimethoxy-	V
213·0(41,880)	214·3(25,922)	235·3(35,293)	206·4(19,190)
260·0(5,660)	268·6 infl	280·0(4,659)	225·6(15,426)
271·5(6,650)	277·3(7,310)	292·3(4,324)	247·1 infl
282·0sh(5,660)	289·0(7,361)	337·6(4,659)	251·3(6,508)
323·0sh(5,660)	330·9(5,028)	351·7 infl	283·7(7,824)
332·0(5,940)			292·8(8,222)
			345·2(4,968)

infl = inflexion

sh = shoulder

A carbonyl group in conjugation with an ethylenic double bond gives rise[153] to a strong π-π* absorption in the region 215-250 mμ ($\varepsilon_{max} > 10,000$) and a weak n-π* absorption near the region 300-350 mμ ($\varepsilon_{max} < 100$). The spectra were recorded at a resolution where the detection of the weak n-π* absorption was not possible. Accordingly most information was obtained from the 200-250 mμ region. In the 1-methoxyhexafluoroisoquinoline the band at 214·3 is probably due to the highly fluorinated isoquinoline nucleus as it is comparable to the most intense band in heptafluoroisoquinoline itself. In the U.V. spectrum of hexafluoro-N-methylisoquinol-1-one there are two strong bands in this region, one at 206·4 mμ and one at 225·6 mμ and so one of these is due to the isoquinoline nucleus and the other due to the conjugated carbonyl group. It is not clear which is which but probably the absorption at 225·6 mμ is due to the conjugated carbonyl absorption.

In the case of the hexafluoro-N-methylquinol-2-one (VI),



VI

the U.V. spectrum is different in that the bands due to the quinoline nucleus and the conjugated carbonyl group are not separated, but give rise to a broad intense band.[112]

An interesting feature of VI is its ^{19}F n.m.r. spectrum, which also shows marked differences from the corresponding isoquinoline compound V. As was stated earlier, in V the 3- and 4-fluorine atom signals were shifted upfield by ~20 p.p.m., and the coupling between them almost disappeared. In VI both the 3- and 4-fluorine chemical shifts and coupling constants remain unaffected. The reason for this is not immediately obvious.

1-Hydroxyhexafluoroisoquinoline was also prepared from 1-methoxyhexafluoroisoquinoline by demethylation using aluminium trichloride. It had been found previously[100] that 4-methoxytetrafluoropyridine was readily demethylated using aqueous hydriodic acid, but that aluminium trichloride gave a complex mixture of products of unknown identity, in contrast to the ready demethylation of pentafluoroanisole by this reagent.[154] On heating the polyfluoromethoxyisoquinoline with anhydrous aluminium trichloride at 120° for 3 hrs., a good yield of the 1-hydroxy compound was obtained. The i.r. spectrum was identical to that of the product obtained by reaction of hydroxide ion with heptafluoroisoquinoline.

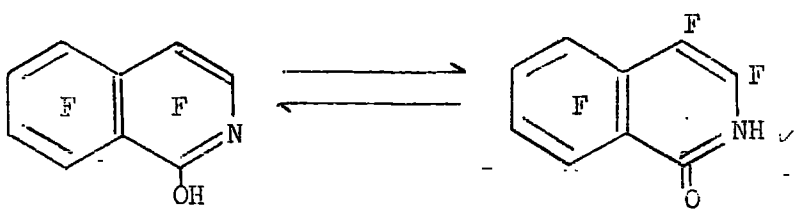
Methylation of the product with ethereal diazomethane, in the manner described previously, produced, as in the methylation of the product obtained from the reaction of hydroxide ion with heptafluoroisoquinoline, a mixture of 1-methoxyhexafluoroisoquinoline (80%) and hexafluoro-N-methyl-1-isoquinolone (20%).

Thus the formation of hexafluoro-N-methyl-1-isoquinolone by methylation of 1-hydroxyhexafluoroisoquinoline, together with the infrared spectrum of the latter show that 1-hydroxyhexafluoroisoquinoline is in equilibrium with its tautomer, II.

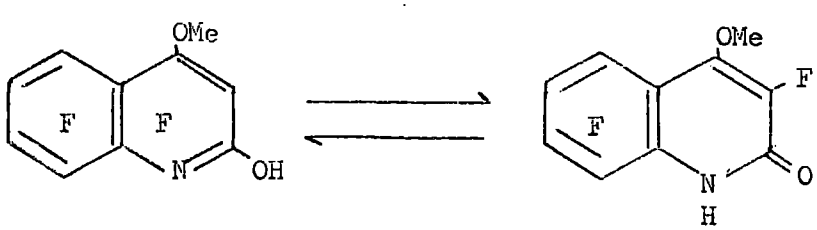
Factors affecting Tautomerism in Polyfluorohydroxy-N-hetero Aromatic Compounds.

In pyridine, quinoline and isoquinoline a hydroxyl group α or γ to the ring nitrogen gives rise to a tautomeric system in which the keto form predominates.[156] In contrast, the evidence available so far indicates that only the polyfluoro-1-hydroxyisoquinoline and polyfluoro-2-hydroxyquinoline systems lead to tautomeric mixtures in which the keto forms are present in significant amounts. An important difference between the above hydroxy-N-heteroaromatic compounds and their polyfluoro derivatives is that the lone pair on the nitrogen is more readily available in the former compounds. The absence of tautomerism in 4-hydroxytetrafluoropyridine,[100] and 4-methoxy-2-hydroxytrifluoropyridine,[157] in contrast to the corresponding hydro-analogues, can be attributed to the reduced electron availability on the ring nitrogen. The work on hexafluoro-1-hydroxyisoquinoline and the polyfluorohydroxyquinolines[150] indicates that this is only one of several possible factors involved. The fact that a polyfluoro-2-hydroxyquinoline gives rise to a tautomeric mixture in which the concentration of the keto form is much greater than for a polyfluoro-4-hydroxyquinoline,[150] indicates two further possible factors.

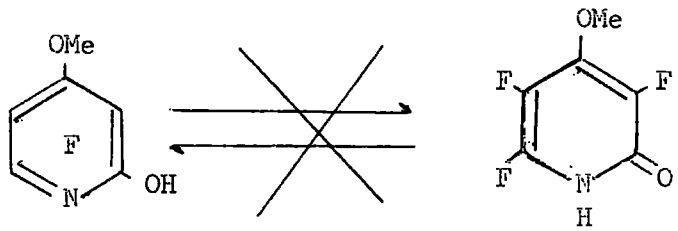
Firstly, the position of the fluorine relative to the ring nitrogen could be important since this will affect the availability of the nitrogen lone pair and, secondly, the relative position of the hydroxyl group could be important if the mechanism of proton transfer were intramolecular. The latter factor is unimportant in the hydro-analogues since both 2- and 4-hydroxyquinolines exist predominantly in the keto form, and suggests that the important factor in these systems is the availability of the nitrogen lone pair. The fact that hexafluoro-1-hydroxyisoquinoline and 4-methoxy-2-hydroxypentafluoro-isoquinoline give rise to a tautomeric system whereas 4-methoxy-trifluoropyridine does not, suggests that the degree of conjugation possible in the keto form is another factor affecting the extent of tautomerism.



I II



VII VIII



IX X

I and IX are very similar in that the nitrogen is flanked by fluorine and hydroxyl and in neither compound does the nitrogen have a para-fluorine atom, whilst the hydroxyl does. In forming II from I and X from IX the loss of aromatic resonance stabilisation is less in the former case and could possibly be the controlling factor in determining the extent of tautomerism. The fusion of a perfluorobenzene ring at the 5,6-positions of IX to give VII leads to a tautomeric system and although the environment of the nitrogen in VII and IX is changed by this fusion the greater degree of conjugation possible in VIII than in X is probably the important factor leading to tautomerism in VII but not in IX. The existence of 2-hydroxypyridines and -quinolines in predominantly the keto form shows that this latter factor is not important in systems where the nitrogen lone pair is readily available.

Summarising, it would appear that in hydroxy-N-heteroaromatic compounds the ready availability of the nitrogen lone pair is the controlling factor in determining the formation of a tautomeric system, but that in the polyfluorohydroxy-N-heteroaromatic compounds, where the availability of the nitrogen lone pair is reduced, the factors discussed above play an important role.

An Attempted Rationalisation of the Reactivity and Orientation in Heptafluoroisoquinoline.

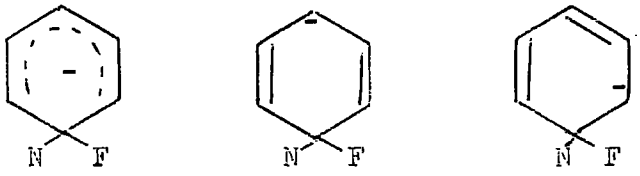
It is not possible to rationalise the reactions of heptafluoroisoquinoline with nucleophiles solely in terms of the theory put forward by Burdon[91] with the object of rationalising nucleophilic substitution in polyfluoroaromatic systems. A more rigorous approach has been attempted and is explained below. This does not give a complete explanation of the experimental facts, but it does indicate the lines along which the problem can be solved.

Reactivity towards Nucleophilic Attack.

Pentafluoropyridine is markedly more reactive towards nucleophilic attack than hexafluorobenzene[98] and competition reactions between heptafluoroisoquinoline and pentafluoropyridine show that the isoquinoline system is of the order of 2·3 times more reactive towards methoxide ion at 0°. The greater reactivity of the heterocyclic system is ascribed to the greater stabilisation of the transition state resulting from the possibility of delocalising the negative charge onto the ring nitrogen. The greater reactivity of the isoquinoline system compared with pentafluoropyridine can be attributed to the greater possible delocalisation of the negative charge in the transition state for the bicyclic system.

The Orientation of Nucleophilic Attack in the Perfluorinated Isoquinoline System.

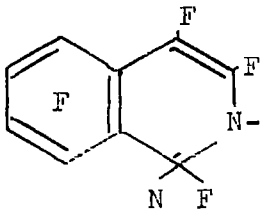
Burdon has rationalised, in a qualitative manner, the orientation of nucleophilic attack in polyfluoroaromatic systems by a consideration of transition and ground state stabilities.[91] The transition states for the reactions of aromatic polyfluoro-compounds were discussed in terms of Wheland-type intermediates (I), as these provide good guides to the transition states in question.



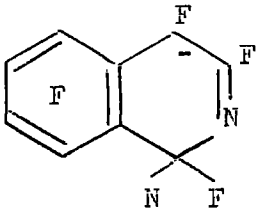
I II III

The resonance hybrid II was assumed to be the main contributor, with hybrid III of minor importance, since it has been argued by other authors[92] that p-quinonoid structures are more important than ortho-quinonoid structures in nucleophilic aromatic substitutions.

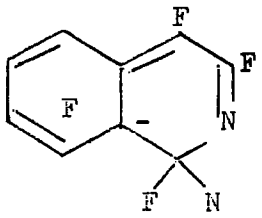
Heptafluoroisoquinoline has been shown to be attacked by nucleophiles, in nearly all cases, at the 1-position. This can be shown to be in direct opposition to the ideas put forward by Burdon. The transition state leading to substitution at this position can be represented by the resonance hybrids IV, IVa and IVb.



IV



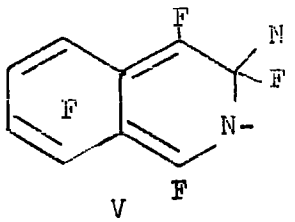
IVa



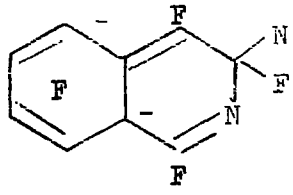
IVb

If, as assumed in the arguments put forward by Burdon, the p-quinonoid form IVa is the most important contributor to the transition state, then the negative charge will be localised on a carbon to which a fluorine is attached. Since fluorine is Iπ repelling,[93] then this contributor would be expected to have a strong destabilising effect on the transition state.

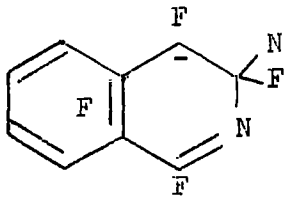
In the case of substitution at the 3-psotion, the p-quinonoid hybrid of the transition state, Va, has the negative charge delocalised onto a bridgehead carbon atom which will stabilise the transition state with respect to IVa, since it has no Iπ repelling substituents attached to it.



V

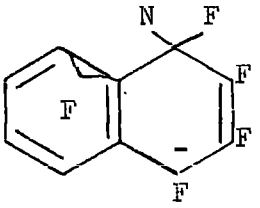


Va

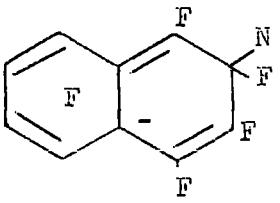


Vb

So, on the basis of the ideas put forward by Burdon, then one would anticipate 3-substitution to occur before 1-substitution. This situation is comparable to the transition states for nucleophilic substitution at the α- and β-positions in octafluoronaphthalene. Considering only the p-quinonoid forms VI and VII,



VI



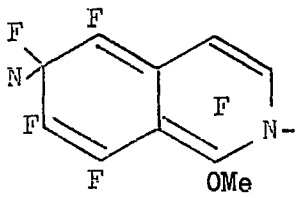
VII

it can be seen that in the transition state leading to α-substitution (VI), the negative charge is placed on a carbon bearing fluorine atom, while in the transition state for β-substitution (VII), the negative charge is placed on a bridgehead carbon atom. In this case, in accord with the relative stabilities of the two transition states, β-substitution occurs.[69]

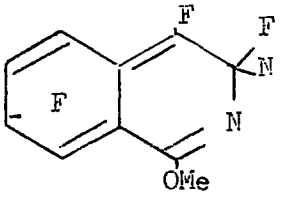
Since substitution occurs at the 1-position of heptafluoroisoquinoline, it is evident that IV, i.e. an orthoquinonoid hybrid, must make a significant contribution to the transition state, since in this case there is favourable placing of the negative charge on the ring nitrogen atom, which is Iπ attracting.[165] The importance of such o-quinonoid hybrids in systems of this nature is also evidenced by the

large amount of 2-substitution that occurs in the reactions of perfluoroquinoline with nucleophiles.[160,161]

The attack at the 6-position in 1-methoxyhexafluoroisoquinoline can be rationalised using the ideas put forward by Burdon.[91] If the p-quinonoid hybrid for the transition state resulting from nucleophilic attack at the 6-position (VIII) is considered it can be seen that the negative charge is localised on the ring nitrogen atom, thereby stabilising the transition state.



VIII



IX

3-Substitution may have been expected since this position is α- to the ring nitrogen and would be expected to be activated towards nucleophilic attack. However, in this case the p-quinonoid hybrid of the transition state for attack at the 3-position (IX) has the negative charge localised on a carbon bearing a fluorine atom.

The basic ideas behind Burdon's approach,[91] although sound in their application to substitution in polyfluorobenzenes prove inadequate for substitution in polyfluoro-isoquinolines and -quinolines where the relative importance of the ortho- and para-quinonoid

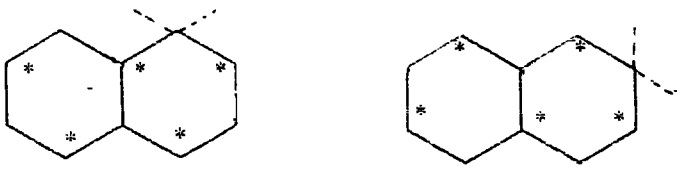
hybrids of the transition state is not clear cut, as has been illustrated above.

In discussing the orientation of compounds resulting from nucleophilic substitution of fluorine in highly fluorinated aromatic systems the factor which determines the nature of the product or products is the rate at which each fluorine atom is replaced. Assuming that the entropy of activation for reaction at each position in heptafluoroisoquinoline is similar, the critical factors governing the orientation of substitution will be the relative magnitudes of the activation energies. The latter reflects the difference in energy between the ground state of the molecule and the transition state. Differences in energy between transition states reflect differences in the energies of the π-electron systems. The problem resolves into an analysis of the distribution of electrons in the π-electron system and factors influencing the energy of the electrons therein.

In 1942 Wheland[162] proposed the use of a reactivity index which has since become known as a 'localisation energy'.[163] In the activated complex for nucleophilic substitution, the reactants are linked by an incipient σ-bond involving two electrons from the attacking species. Thus the formation of the activated complex may be regarded as a process of partial localisation of a positive charge at the points of the molecule at which substitution is going to take

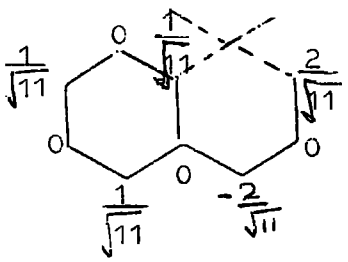
place. If it is assumed that this localisation process proceeds to completion it is a simple matter to compute the energy change, or localisation energy, of all the sets of positions which could possibly react with the attacking reagent. The most reactive site will be that with the smallest localisation energy. During this localisation procedure all σ-bond changes are treated as being effectively constant.

In a substitution reaction involving an alternant aromatic hydrocarbon with 2n conjugated atoms, the residual conjugated system in the transition state is an odd-membered alternant hydrocarbon with 2n-1 atoms. This implies that these 2n-1 atoms can be dividied into two sets of n and n-1 members in such a way that no two members of the same set are directly linked by a chemical bond. The atoms of the more numerous set are usually distinguished by asterisks as shown for α- and β-substitution in naphthalene, i.e.

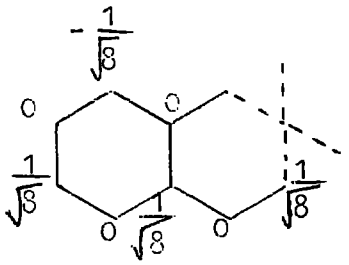


Such an odd-membered alternant conjugated system possesses one zero-energy molecular orbital (taking the coulomb integral, α, as an arbitrary energy zero). The coefficients (c_{oi}) determining the contribution of each atomic π-orbital to this zero-energy molecular

orbital can be very easily determined from the following rules: (1) the value of c_{oi} is zero for all unstarred atoms; (2) for any groups of starred atoms directly linked to a given unstarred atom, the sum of the c_{oi} values is zero; (3) the normalisation condition $\Sigma_i c_{oi} = 1$. The way in which these three conditions determine the c_{oi} values has been clearly set out by Dewar,[164] and the c_{oi} values for α- and β-substitution in naphthalene, X and XI respectively are shown.



X



XI

These values are significant because they can be used to obtain an approximate value of the localisation energy (ΔE) for substitution in an alternant aromatic hydrocarbon. The appropriate equation for calculation of the localisation energy is:-[186]

$$-\Delta E = 2\beta\ (c_{op} + c_{oq})$$

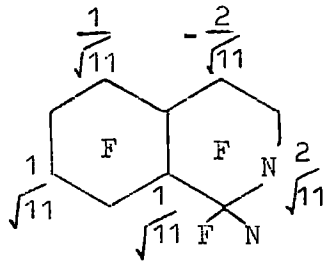
where c_{op} and c_{oq} are the coefficients of the zero energy orbital at the two carbon atoms on either side of the point of substitution. These values of ΔE differ from those obtained by more exact calculations, but usually lie in the right order, e.g., the values of ΔE from the

above equation for α- and β-substitution in naphthalene are -1·81β and -2·12β; the corresponding results obtained by more exact calculations are -2·30β and -2·48β.[187]

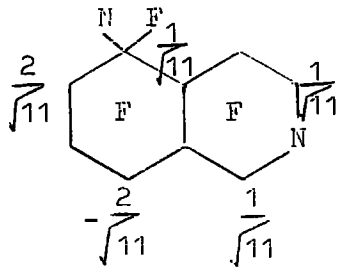
In applying this approximate method to nucleophilic substitution in heptafluoroisoquinoline, a carbon atom in the naphthalene system is replaced by a heteroaromatic nitrogen atom. This will effectively reduce the energy of the transition state by a degree dependent on the value of the π-inductive parameter of the nitrogen atom and by the fraction of the negative charge that lies on the nitrogen atom (obtained from the square of the Non-Bonding Molecular Orbital coefficients at this point). Extensive perturbations have to be allowed for in the case of the fluorine atoms. These, because they are Iπ repelling,[93] will raise the energy of the transition state by an extent dependent upon the value of the Iπ parameter of fluorine, and the values of the N.B.M.O. coefficients at the carbon atoms to which the fluorines are attached.

The Iπ parameter of a substituent is the amount by which the potential energy of an electron at the position of substitution is changed by this substituent. Taking the Iπ parameters of fluorine and a heterocyclic aza-nitrogen as -0·419β and +0·894β respectively,[165] the approximate localisation energies for substitution at the various positions in heptafluoroisoquinoline are as given below.

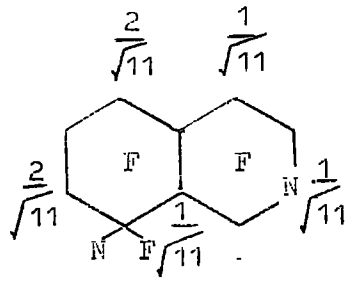
Transition State (N = nucleophile) $-\Delta E/\beta$



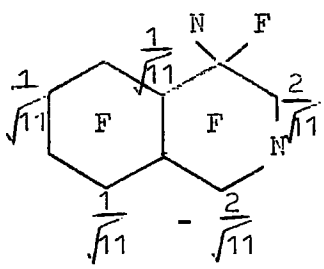
$$2\left(\frac{2}{\sqrt{11}} + \frac{1}{\sqrt{11}}\right) - 0.894 \times \frac{4}{11} + 0.419 \times \frac{6}{11} = \underline{1.713}$$



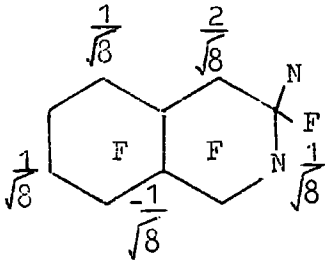
$$2\left(\frac{2}{\sqrt{11}} + \frac{1}{\sqrt{11}}\right) + {}^{10}/_{11} \times 0.419 = \underline{2.191}$$



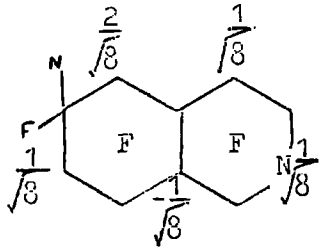
$$2\left(\frac{2}{\sqrt{11}} + \frac{1}{\sqrt{11}}\right) - {}^{1}/_{11} \times 0.894 + {}^{9}/_{11} \times 0.419 = \underline{2.072}$$



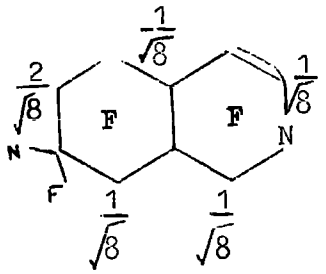
$$2\left(\frac{2}{\sqrt{11}} + \frac{1}{\sqrt{11}}\right) - {}^{10}/_{11} \times 0.419 = \underline{2.191}$$



$$2\left(\frac{2}{\sqrt{8}} + \frac{1}{\sqrt{8}}\right) - \frac{1}{8} \times 0.894 + \frac{6}{8} \times 0.419 = \underline{2.324}$$



$$2\left(\frac{2}{\sqrt{8}} + \frac{1}{\sqrt{8}}\right) - \frac{1}{8} \times 0.894 + \frac{6}{8} \times 0.419 = \underline{2.324}$$

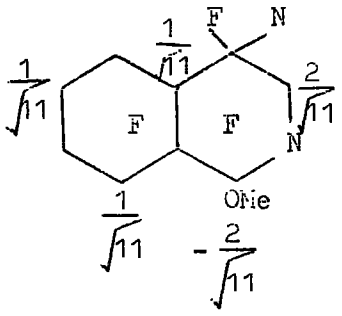
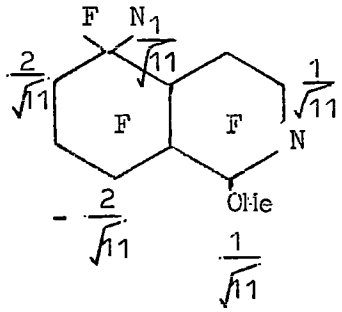
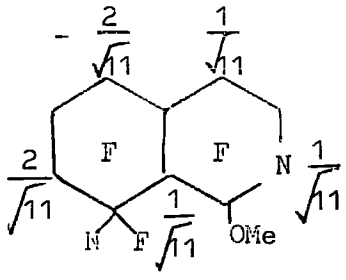


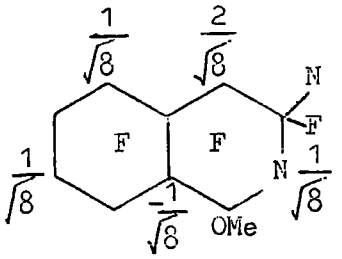
$$2\left(\frac{2}{\sqrt{8}} + \frac{1}{\sqrt{8}}\right) + \frac{7}{8} \times 0.419 = \underline{2.439}$$

From these figures it can be seen that the order of localisation energy values is $1 < 8 < 5 = 4 < 3 = 6 < 7$, so that all other effects being equal, substitution should occur much more readily at the 1-position which is in agreement with experiment.

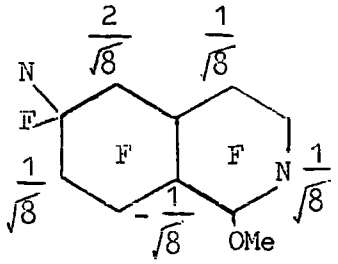
To determine the position of nucleophilic attack in 1-methoxy-hexafluoroisoquinoline the transition states for substitution at the various positions in 1-methoxyhexafluoroisoquinoline have to be

examined as above. Taking the Iπ parameter for the methoxyl group to be twice the value of that for fluorine[165] then the localisation energies for substitution at the various positions in 1-methoxyhexafluoroisoquinoline are given below.

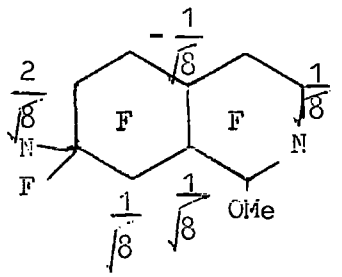
Transition State (N = nucleophile)	$-\Delta E/\beta$
	$2\left(\frac{2}{\sqrt{11}} + \frac{1}{\sqrt{11}}\right) + \frac{14}{11} \times 0.419$ $= \underline{2.342}$
	$2\left(\frac{2}{\sqrt{11}} + \frac{1}{\sqrt{11}}\right) + 1 \times 0.419$ $= \underline{2.229}$
	$2\left(\frac{2}{\sqrt{11}} + \frac{1}{\sqrt{11}}\right) - \frac{1}{11}$ $\times 0.894 + \frac{9}{11} \times 0.419$ $= \underline{2.072}$



$$2\left(\frac{2}{\sqrt{8}} + \frac{1}{\sqrt{8}}\right) - \frac{1}{8} \times 0.894 + \frac{6}{8} \times 0.419 = \underline{2.324}$$



$$2\left(\frac{2}{\sqrt{8}} + \frac{1}{\sqrt{8}}\right) - \frac{1}{8} \times 0.894 + \frac{6}{8} \times 0.419 = \underline{2.324}$$



$$2\left(\frac{2}{\sqrt{8}} + \frac{1}{\sqrt{8}}\right) + 1 \times 0.419 = \underline{2.541}$$

It can be seen that the order of localisation energies is $8 < 5 < 3 = 6 < 4 < 7$, so that all other effects being equal, then nucleophilic substitution should occur at the 8-position. It is known that substitution in 1-methoxyhexafluoroisoquinoline occurs at the 6-position in nearly all instances.

The most likely reason for the failure of this approach in

predicting the position of attack of the second nucleophile is that, at the best, the method only claims to be approximate, and that a very large number of perturbations are present, in the form of the ring nitrogen atom and the fluorine atoms, the exact effect of which are not known in such a system. Even so, it is an improvement over the approach offered by Burdon for dealing with polyfluorinated isoquinolines. It can also be applied with quite reasonable success to other systems for which the transition states for nucleophilic substitution are odd alternant anions.

More accurate calculations of the π-electron energy of the various transition states for nucleophilic substitution in heptafluoroisoquinoline have been carried out using a Hückel Molecular Orbital method. The exact details of how the calculations were carried out are given in appendix I.

The results from the two series of calculations carried out so far are shown in tables I and II. The parameters used for the calculations of the results in table I were as follows:-

Coulomb Integrals. $\alpha_C = 0$; $\alpha_N = \alpha_C + 0{\cdot}5\beta$; $\alpha_F = \alpha_C + 3{\cdot}0\beta$; α for a carbon atom which is bonded directly to fluorine = $\alpha_C - 0{\cdot}4\beta$.

Resonance Integrals. $\beta_{C-C} = 1{\cdot}0$; $\beta_{C-F} = 0{\cdot}9$; $\beta_{CN} = 0{\cdot}8$.

The parameters used to calculate the results in table II were as those above, except that the Coulomb integral for a carbon atom

bonded directly to fluorine (except those adjacent to the nitrogen atom which remained as above) was changed to $\alpha_c - 0{\cdot}6\beta$, and β_{CN} was changed to 1·0. The reason for these changes was to try to allow for the σ-inductive effects of the ring nitrogen.

Table I

State	E_π in units of β
Heptafluoroisoquinoline groundstate	54·4121
Transition state for 1-substitution	46·4802
" " " 3- "	46·1548
" " " 4- "	45·8139
" " " 5- "	45·7996
" " " 6- "	45·8851
" " " 7- "	45·6851
" " " 8- "	45·9991

Table II

Transition State	E_π in units of β
1-substitution	45·649223
3- "	45·341441
6- "	45·405551
8- "	45·515188

It can be seen from an examination of table II (results using the best parameters) that the order of the π-electron energies of the transition states is $1 < 8 < 6 < 3$. Calculations using these parameters, were not carried out on the 4-, 5-, and 7-transition state because, as is evident from table I the π-electron energies of these transition states are much higher and hence of no importance in nucleophilic substitution. Therefore, the orientation of nucleophilic attack should approximate to this order. Since nucleophilic substitution occurs first at the 1-position and secondly at the 6-position, the H.M.O. method fails in its prediction of the orientation of the second nucleophile.

The reason for this discrepancy is probably due to the use of incorrect π-inductive repulsion terms for fluorine. The value used was that derived from monofluorobenzene, which is unlikely to be suitable for direct use in heptafluoroisoquinoline. Also, the value of the π-inductive effect will be dependent upon the π-electron density at the carbon atom to which the fluorine is attached. Better results would be obtained using an ω -technique, and putting ω equal to the π-inductive parameter for fluorine that was derived from monofluorobenzene, i.e.

$$\alpha'' = \alpha' + 0{\cdot}4\ (1 - q')\beta$$

where

α'' = coulomb integral to be used in second iteration,

α' = coulomb integral used in first iteration,

q' = π-electron density obtained from the first iteration.

Several iterations would probably give the π-electron energies for the transition states, in the correct order. At the moment it has not been possible to obtain a computer programme to do these calculations. However it is felt that this approach will be the one to give a satisfactory general explanation of the orientation of nucleophilic substitution in such systems.

Chapter 3

Experimental Work

Experimental Work

Preparation of Highly Halogenated Isoquinolines.

Isoquinoline was exhaustively chlorinated first in the form of the N-oxide with phosphorus pentachloride, secondly with chlorine gas in the presence of antimony trichloride as a catalyst, thirdly with phosphorus pentachloride and finally successful conversion to heptachloroisoquinoline, in high yield, was achieved by a two-stage process involving the chlorination of an isoquinoline-aluminium trichloride complex with elemental chlorine and then further chlorination of the hexachloroisoquinoline so formed with phosphorus pentachloride. Fluorination of heptachloroisoquinoline by halogen exchange with potassium fluoride has been developed to give heptafluoroisoquinoline in high yield. The reactions of these highly halogenated isoquinolines have been studied.

Infra-spectra were recorded using Grubb-Parsons, type G.S.2A or Spectromaster, spectrometers. U.V. spectra were recorded using an Optica C.F.4 or Unicam S.P.800 spectrophotometer. Molecular weights were determined mass spectrometrically using an A.E.I. M.S.9 mass spectrometer. Analytical-scale v.p.c. was performed on a Perkin-Elmer 'Fractometer' model 451 and preparative scale v.p.c. on an Aerograph "Autoprep" A-700 instrument. ^{19}F N.M.R. spectra were recorded on an A.E.I. R.S.2 spectrometer, operating at 60 Mc/sec., except the 1-methoxy- and 1,6-dimethoxy-derivatives of heptafluoroiso-

quinoline which were recorded on a Varian HA100 spectrometer operating at 94·2 Mc/sec. ^{1}H spectra were recorded on a Perkin-Elmer R10 spectrometer operating at 60 Mc/sec.

The Autoclaves.

Two autoclaves were used, one of 120 ml. capacity and a larger one of $1\frac{1}{2}$ litre capacity.

The body of the smaller high pressure reaction vessel (fig. 1a) was constructed by drilling out a solid piece of stainless steel. The autoclave head was fitted with a needle valve and screwed into the body of the vessel to seal by a knife edge on the autoclave head against an aluminium gasket. Final tightening of the seal was affected by Allen screws in the head. The autoclave was heated by a 2 k.w. heated and the applied voltage controlled by means of a precalibrated variable transformer.

The larger autoclave (fig. 1b) was also constructed of stainless steel with the base and flange welded to the cylindrical body of the vessel. The stainless steel autoclave head was fitted with a needle valve and thermocouple well and was sealed to the flange on the top of the autoclave by a corrugated copper gasket and held in position by steel bolts. Inside the vessel was fitted a nickel liner to prevent corrosion of the inner stainless steel wall. The autoclave was heated by a 9' long, 2 k.w. heating element coiled so that the body of the

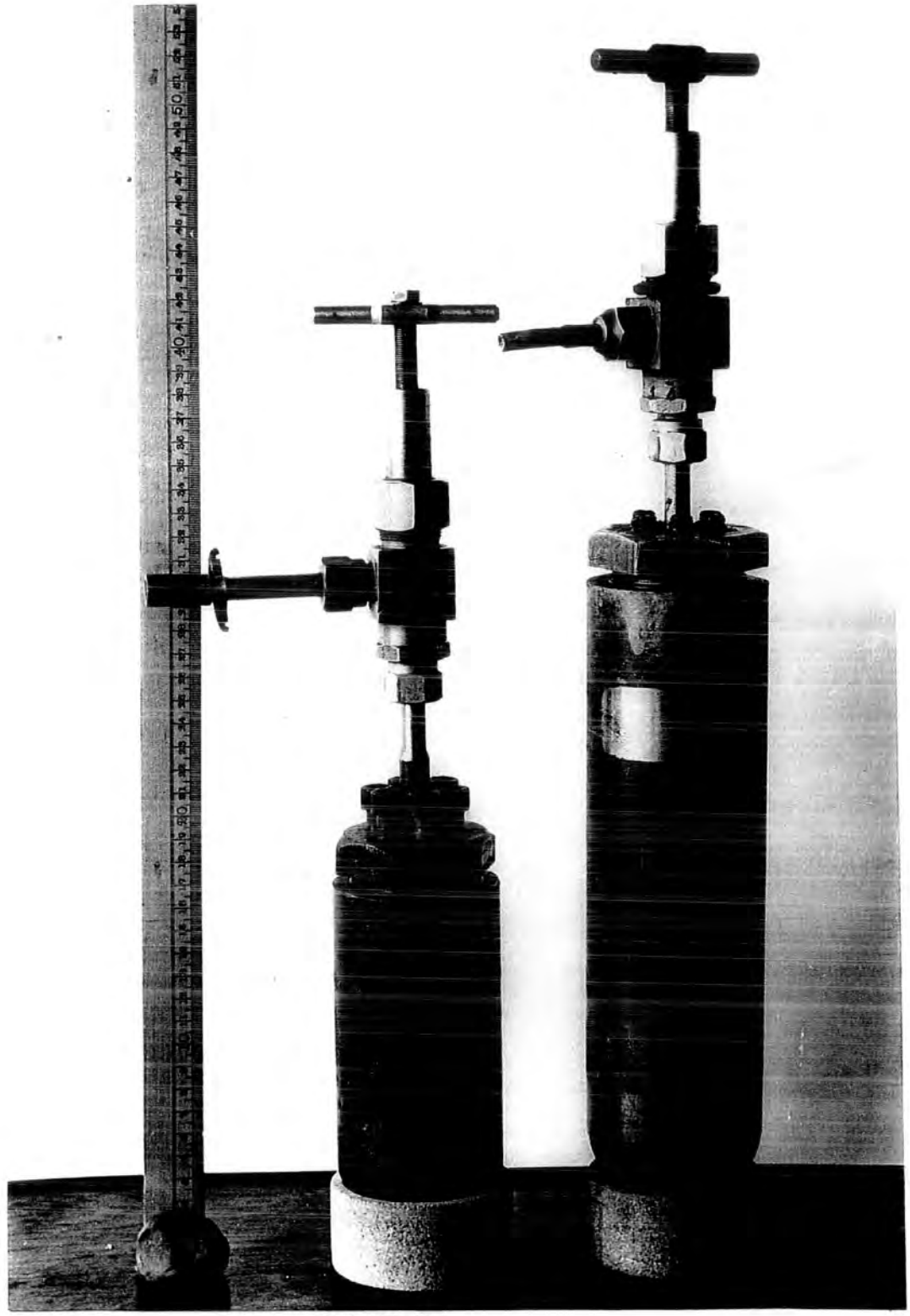


FIGURE 1a

autoclave fitted snuggly inside. The temperature was controlled by means of a precalibrated variable transformer. The voltage was set so that it took about 5 hrs. to reach the required temperature.

Before a reaction both autoclaves were tested to ensure they were leak proof by charging with solid carbon dioxide and sealing. Immersion in a water bath made obvious any leaks. They were then cleaned and dried at 150-200^{o}C for 2 - 3 hrs. before use.

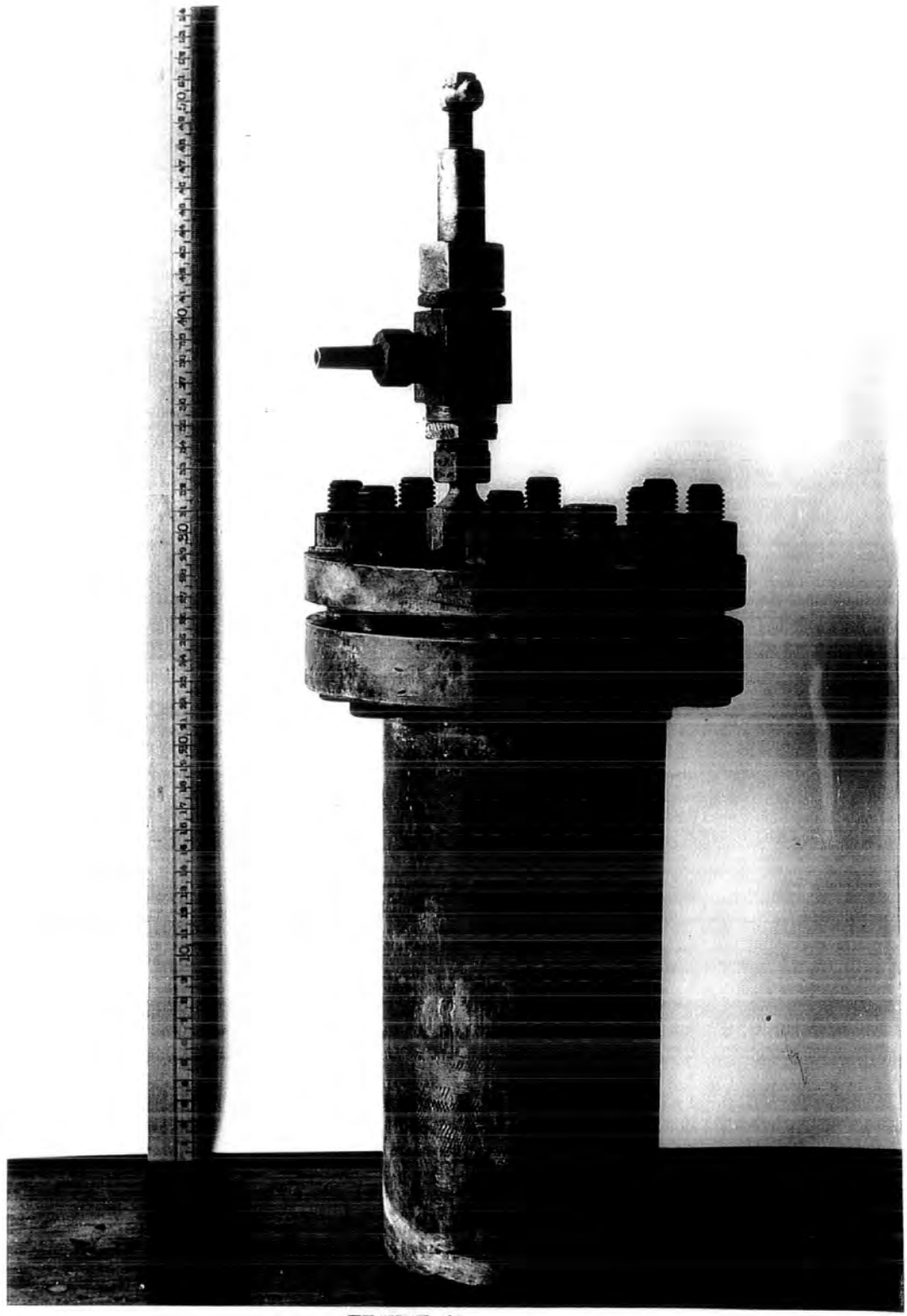


FIGURE 1b

Preparation of Pyridine-1-oxide. This compound was prepared by the method of Ochiai.[107] Yield 88% (from 200 g. of commercial pyridine. Lit.[107] 98% from 40 g. of pyridine). B.p. 112-114°/2 mm. (Lit.[107] 138-140/15 mm.).

Chlorination of pyridine-1-oxide. In a typical experiment dry pyridine-1-oxide (30 g., 0·320 mole) and dry phosphorus pentachloride (1000 g., 4·80 moles) were placed in an autoclave (2 l.) which was flushed with dry nitrogen and evacuated under reduced pressure (1-2 mm.). After heating the autoclave at 300° for 24 hrs. it was cooled to room temperature and the hydrogen chloride generated during the reaction was released before the vessel was opened. The contents of the vessel were poured onto ice and the products were obtained by steam distillation. The mixed products were filtered off, and dried to constant weight over phosphorus pentoxide in a vacuum desiccator.

The mole-% composition of the product was estimated by analytical-scale g.l.c.

The Preparation of Isoquinoline-2-oxide. This compound was prepared as by the method of Robison and Robison.[158] Yield 70% (Lit. 63%) m.p. 104-105° (Lit. 105-106°).

The Chlorination of Isoquinoline-2-oxide. Phosphorus pentachloride (800 g., 3·8 mole) and isoquinoline-2-oxide (43 g., 0·33 mole) were reacted for 24 hrs. at a temperature of 300° (similar conditions for the pyridine-1-oxide-phosphorus pentachloride). The work-up procedure used as for the corresponding pyridine-1-oxide reaction yielded only insoluble black tars.

The Chlorination of Isoquinoline with Chlorine in the presence of Antimony Trichloride. Isoquinoline (100 g., 0·775 mole) was added slowly to antimony trichloride (5 g., 21.9 m.mole) in a flange-necked flask, efficient stirring being maintained all the time. The solution obtained was heated to 120°, chlorine gas passed and after 275 g., (3·87 mole) of chlorine the reaction mixture was very black and stirring difficult. The mass was therefore heated to 200° and the flask swept with nitrogen to remove all hydrochloric acid. On cooling the mass set solid and had to be chipped out of the flask. Vacuum sublimation gave a white solid, m.p. 155-160 whose i.r. spectrum showed $=\overset{+}{N}H-$ and C-Cl bonds. This solid on treatment with dil. caustic soda and steam distillation gave a yellow oil most of which was isoquinoline.

The Preparation of Hexachloroisoquinoline. The apparatus and procedure have been described previously;[59] the complex formed between isoquinoline (158 g., 1·23 mole) and aluminium trichloride was chlorinated using a large excess of chlorine (1198 g., 16·87 mole) at 150° over a period of 50 hr. The black viscous solid formed on cooling was decomposed with ice, the precipitate collected, dissolved in boiling benzene and the hot solution filtered to remove the insoluble material. The solution was dried by azeotropic distillation of the benzene and on concentrating the solution and cooling hexachloroisoquinoline was obtained (359 g., 87%) (Found: C, 32·2; Cl, 62·4. C_9HCl_6N requires C, 32·1; Cl, 63·3%), m.p. 174-174·5° (i.r. spectrum No. 1).

Preparation of Heptachloroisoquinoline by Chlorination of Hexachloroisoquinoline with Phosphorus Pentachloride. In a typical experiment an autoclave (1½ l.) charged with hexachloroisoquinoline (120 g., 0·357 mole) and phosphorus pentachloride (850 g., 4·08 mole) was heated from 20 to 270° over a period of 5 hr. and then allowed to cool. When cold the hydrogen chloride was vented and the remaining product was added slowly to ice and water. A precipitate was collected and recrystallised from acetone to give heptachloroisoquinoline (90 g., 68%) (Found: C, 29·1; Cl, 66·8. C_9Cl_7N requires C, 29·2; Cl, 67·0%) m.p. 128° (i.r. spectrum No. 2).

Fluorination of Heptachloroisoquinoline with Anhydrous Potassium Fluoride. An autoclave (120 ml.) charged with an intimate mixture of heptachloroisoquinoline (28 g., 75·6 m.mole) and anhydrous potassium fluoride (70 g., 1·19 mole) was evacuated before being heated to 420° for 22½ hr. The product (14·5 g.) was distilled from the hot autoclave under reduced pressure and shown by v.p.c. to consist of a mixture of heptafluoroisoquinoline (92·5% yield) and a compound which was shown by its ^{19}F n.m.r. spectrum to be 4-chlorohexafluoroisoquinoline. The combined product of several reactions was distilled through a concentric tube column giving heptafluoroisoquinoline (Found: F, 52·0%; M, 255. C_9F_7N requires F, 52·1%; M, 255), m.p. 45·5°, b.p. 212°/759 mm. (i.r. spectrum No. 3), and 4-chloroheptafluoroisoquinoline m.p. 41-42°, b.p. 250° (Found: C, 39·6; Cl, 13·4; F, 41·7. C_9ClF_6N requires C, 39·8; Cl, 13·05; F, 42·0%). (i.r. spectrum No.4).

Reaction between Heptafluoroisoquinoline and Gaseous Hydrogen Chloride.

Gaseous dry hydrogen chloride (large excess) was bubbled through a solution of heptafluoroisoquinoline (0·64 g., 2·52 m.mole) in sodium dried ether (25 ml.) for 2 hrs. at room temperature. The solution remained clear at all times and distillation of the solvent left heptafluoroisoquinoline (0·6 g.) identified by its i.r. spectrum.

The Reaction between Boron Trichloride and Heptafluoroisoquinoline.

Boron trichloride (0·91 g., 7·78 m.mole) was condensed under vacuum into a cooled (liquid air) 100 ml. B24 single necked flask containing heptafluoroisoquinoline (0·96 g., 3·76 m.mole) dissolved in dry carbon tetrachloride (10 ml.). The flask was connected to the vacuum system by a B24/B10 double cone with a tap at its centre. With the tap closed the flask was allowed to warm to 0-10°C (ice bath) and maintained at this temperature for 1½ hr. The solution remained clear and colourless during this period. The solvent and boron trichloride were pumped off at room temperature and reduced pressure (0·01 mm.) to leave heptafluoroisoquinoline.

The Reaction of a Solution of Heptafluoroisoquinoline in concentrated Sulphuric Acid with Water.

a) Heptafluoroisoquinoline (1·0 g., 3.92 m.mole) was dissolved in c.sulphuric acid (S.G. 1·84) (36 g.). With the solution being stirred by a high speed stirrer, water was added dropwise from a burette. After 7 ml. of water had been added a white solid began to deposit.

Water was added until 17 ml. had in all been added. The resulting solution was added to a large excess of water, and extracted with methylene chloride, washed, dried ($MgSO_4$) and the solvent removed by distillation to leave heptafluoroisoquinoline, identified by its i.r. spectrum.

b) Heptafluoroisoquinoline (1·0 g., 3.92 m.mole) was dissolved in c. sulphuric acid (S.G. 1·84) (36 g.) and water (4 ml.) added to this solution which was then placed into a Carius tube. The tube was heated to 140/150° for a period of 12 hr. after which time the tube was cooled, opened and the contents added to water. Extraction with methylene chloride followed by washing with dil. sodium hydroxide and removal of the solvent gave a trace of heptafluoroisoquinoline, but nothing could be isolated from the aqueous layer except dark decomposed material.

<u>The Reaction of Heptafluoroisoquinoline with Sodium Methoxide in Methanol.</u>

a) Sodium (0·069 g., 3·0 m.mole) was added to dry methanol (7 ml.) and the resulting solution was added slowly with stirring to heptafluoroisoquinoline (0·765 g., 3·0 m.mole) in dry methanol (7 ml.) at 0°. The mixture was stirred for a further 15 min. after which time it was poured into ice. The white solid which precipitated was extracted with methylene chloride, the combined extracts dried ($MgSO_4$)

and the solvent removed to yield a white solid (0·610 g.) which was shown by analytical scale v.p.c. (silicone elastomer on Celite at 200°) to consist essentially of hexafluoro-1-methoxyisoquinoline together with trace amounts of unreacted starting material and a disubstituted compound. The hexafluoro-1-methoxyisoquinoline was purified by preparative scale v.p.c. (silicone elastomer on Celite at 230°) and recrystallisation from methanol gave white crystals, m.p. 86-87° (Found: C, 44·9; H, 1·5; F, 42·3. $C_{10}H_3F_6NO$ requires C, 44·95; H, 1·1; F, 42·7%) (i.r. No. 5).

b) Sodium (0·138 g., 6·0 m.mole) was added to dry methanol (10 ml.) and the resulting solution was added, with stirring to heptafluoroisoquinoline (0·765 g., 3·0 m.mole) in dry methanol (7 ml.) at 20°. The mixture was refluxed for 2 hrs. after which time it was poured into ice. The solid precipitated was extracted into methylene chloride, the combined extracts dried ($MgSO_4$), and distillation of the solvent afforded a white solid. Recrystallisation from methanol gave 0·63 g. (75%) of pentafluoro-1,6-dimethoxyisoquinoline, m.p. 99-100° (Found: C, 47·3; H, 2·15; F, 34·4. $C_{11}H_6F_5NO_2$ requires C, 47·3; H, 2·15; F, 34·0%) (i.r. No. 6).

Reaction of Heptafluoroisoquinoline with Aqueous Ammonia. Aqueous ammonia (0·80 ml., d 0·88) was added to a stirred solution of heptafluoroisoquinoline (0·765 g., 3·0 m.mole) in acetone (5 ml.) at

20°C, and the mixture was stirred for a further 30 minutes after which time it was poured into cold (0°) water. The product which precipitated was extracted with methylene dichloride, the combined extracts dried ($MgSO_4$), and distillation of the solvent afforded 0·61 g. (81%) of a pale yellow solid, which on recrystallisation from light petroleum (b.p. 80-100°) followed by sublimation under reduced pressure, gave 1-aminohexafluoroisoquinoline, m.p. 160-161° (Found: C, 42·8; H, 1·1; F, 45·0. $C_9H_2F_6N_2$ requires C, 42·9; H, 0·8; F, 45·2%) (i.r. No. 7).

Reaction of Heptafluoroisoquinoline with Ammonia in Ether. Ammonia was passed through a solution of heptafluoroisoquinoline (1·009 g., 3·913 m.mole) in dry ether (10 ml.) for 1 hr. at room temperature. Water was then added, the ethereal layer separated, dried ($MgSO_4$), and the ether evaporated to leave a white solid. Recrystallisation from light petroleum (b.p. 80-100°) gave 1-aminohexafluoroisoquinoline (0·69 g., 70%) as white needles, m.p. 160-161° and infrared spectrum identical to the authentic sample.

The Reaction of 1-Aminohexafluoroisoquinoline with Trifluoroacetic Anhydride. 1-Aminohexaflucroisoquinoline (0·2 g., 0·793 m.mole) was added to trifluoroacetic anhydride (5 ml.) containing 1 drop of c.hydrochloric acid. The reaction mixture was heated under reflux for

10 min. and cooled. The trifluoroacetic acid and trifluoroacetic anhydride were removed under vacuum to leave an oil. This was washed (twice) with water and triturated with light petroleum (b.p. 40-60°) and the solid which formed was filtered and dried over phosphorus pentoxide in vacuo. Recrystallisation from light petroleum (b.p. 40-60°) gave 1-trifluoroacetylamino-3,4,5,6,7,8-hexafluoroisoquinoline as a white solid, m.p. 82-83° (Found: C, 38·3; H, 0·46. CHF_9N_2O requires C, 37·95; H, 0·3%) (i.r. No. 8).

The Reaction of Heptafluoroisoquinoline with Hydrazine Hydrate.

Hydrazine hydrate (0·600 g., 12·08 m.mole) was added to a stirred solution of heptafluoroisoquinoline (1·540 g., 6·04 m.mole) in dioxan (7 ml.) and the mixture was stirred for a further 60 min. after which it was poured into cold (0°) water. The product which precipitated was extracted with methylene dichloride, the combined extracts dried ($MgSO_4$) and distillation of the solvent afforded a product (1·20 g.) which was purified by sublimation under reduced pressure followed by recrystallisation from chloroform to give 1-hydrazinohexafluoroisoquinoline which decomposed on heating completely at 190°. (Found: C, 39·9; H, 1·0; F, 42·5*. $C_9H_3F_6N_3$ requires C, 40·5; H, 1·1; F, 42·7%) (i.r. No. 9).

*The fluorine analysis was carried out by combustion of the compound in an oxygen filled flask followed by the spectrophotometric determination with cerium (III) alizarin complexone.[159]

The Reaction of Heptafluoroisoquinoline with Lithium Aluminium Chloride. To a cooled (0^{o}) solution of heptafluoroisoquinoline (3·9 g., 15·26 m.mole) in ether (100 ml.) was added an ethereal solution of lithium aluminium hydride (12 ml. of a solution containing 0·0159 g. of ml., 4·39 m.mole), over a period of $\frac{3}{4}$ hr. The reaction mixture was stirred for a further 1 hr. at 0^{o}, and then at room temperature for 1 hr., and finally heated under reflux for $1\frac{1}{2}$ hr. The reaction mixture was cooled and 2N-sulphuric acid (5 ml.) added cautiously, followed by water (50 ml.). The ethereal layer was separated, dried, and the ether distilled to yield a brown liquid which was shown by v.p.c./silicone elastomer on Celite at 150^{o}), to contain heptafluoroisoquinoline and a major product in the ratio 20:80. Also present was a small amount of ether and another product ca. 2% of the total. The major product was separated by preparative v.p.c. to give as a colourless liquid 1H-hexafluoroisoquinoline (Found: C, 45·9; H, 0·65; F, 47·9. C_9HF_6N requires C, 45·6; H, 0·42; F, 48·1%), b.p. 68^{o} at 1 mm., n_D^{20} 1·5043 (i.r. No. 10).

The Preparation of 2,5,6-Trifluoropyridine-3,4-dicarboxylic Acid from Heptafluoroisoquinoline. Heptafluoroisoquinoline (3·06 g., 0·012 mole) in acetone (50 mls.) which had dried ($MgSO_4$), was added slowly at room temperature to a well stirred solution of potassium permanganate (3·98 g., 0·0252 mole) in acetone (100 ml.). After 2 min. a vigorous exothermic reaction took place and the reaction mixture turned a dark brown in colour. Stirring was continued for a further 90 min., water

(100 ml.) added and the acetone was removed under reduced pressure. The solution was acidified with 2N-sulphuric acid and a stream of sulphur dioxide was then passed until the solution was completely decolourised. The solution was filtered, and the filtrate continuously extracted with ether for 24 hr. The ethereal solution was dried ($MgSO_4$) and distilled to leave a sticky solid (1·45 g.). This solid was triturated with carbon tetrachloride, and the suspension filtered to leave a pale yellow solid (1·38 g., 52%). Further purification of the solid was effected by sublimation at very low pressures (120°) and by recrystallisation from benzene to give 2,5,6-trifluoropyridine-3,4-dicarboxylic acid as a white solid, m.p. 163-166° (Found: C, 38·3; H, 1·24; F*, 26·0. $C_7H_2F_3NO_4$ requires C, 38·0; H, 0·9; F, 25·8%). (i.r. No. 11).

*The fluorine analysis was carried out by combustion of the compound in an oxygen filled flask followed by spectrophotometric determination with Cerium (III) alizarin complexone.[159]

The Preparation of 5,6-Difluoro-2-methoxypyridine-3,4-dicarboxylic Acid from 1-Methoxyhexafluoroisoquinoline. 1-Methoxyhexafluoroisoquinoline (3·215 g., 12·04 m.mole) dissolved in dry acetone (50 ml.) was added to a well stirred solution of potassium permanganate (4·300 g., 0·02722 mole) in acetone (150 ml.) at room temperature. The reaction mixture was heated under reflux for $2\frac{3}{4}$ hr. when further solid potassium permanganate (1·28 g., 8·1 m.mole) was added. The reaction mixture

was heated under reflux for a further $1\frac{1}{4}$ hr., when water (100 ml.) was added and the acetone distilled off. The remaining aqueous mixture was acidified with 2N-sulphuric acid, decolourised with sulphur dioxide and filtered to remove unreacted 1-methoxyhexafluoroisoquinoline (0·18 g.). The filtrate was continuously extracted with ether for 30 hr., the ethereal solution dried ($MgSO_4$) and the solvent distilled to leave a pale yellow solid (1·38 g., 49·3%). Purification was effected by recrystallisation from benzene to leave 5,6-difluoro-2-methoxypyridine-3,4-dicarboxylic acid as a white solid m.p. 154-156° (Found: C, 40·9; H, 2·34; F*, 16·3. $C_8H_5F_2NO_5$ requires C, 41·2; H, 2·14; F, 16·3%). Equiv., Found: 117, 115; required, 116·3 (i.r. No. 12).

*See ref. 159.

The Reaction between Aqueous Copper Sulphate and 1-Hydrazinohexafluoroisoquinoline. To a suspension of 1-hydrazinohexafluoroisoquinoline (1·089 g., 4·044 m.mole) in water (20 ml.) was added copper sulphate (3·93 g., 15·75 m.mole) in water (90 ml.) over a period of 1 hr., with stirring, at room temperature. The reaction mixture was heated under reflux for a further 1 hr. and then steam distilled. The distillate was extracted with ether and the combined extracts dried ($MgSO_4$) and the ether distilled to leave a brown liquid which was shown by v.p.c. to contain a little ether plus a product which had a retention time identical with that of 1H-hexafluoroisoquinoline. The product was

separated from the ether by v.p.c. and its infrared spectrum was identical to that of 1H-hexafluoroisoquinoline.

The Reaction of 1-Hydrazinohexafluoroisoquinoline with Benzaldehyde.

1-Hydrazinohexafluoroisoquinoline (1·60 g., 5·992 m.mole) was dissolved in methanol and a little concentrated sulphuric acid. A slight excess of benzaldehyde was added and the reaction mixture stirred at room temperature. After 15 min. a pale yellow solid was precipitated and stirring was continued for a further 1 hr. The solid was then filtered and recrystallised several times benzene-light petroleum to give benzaldehyde-3,4,5,6,7,8-hexafluoroisoquinolylhydrazone (1·25 g., 59%), m.p. 213-213·5° (Found: C, 53·7; H, 2·26. $C_{16}H_7F_6N_3$ requires C, 54·1; H, 1·97%). (i.r. No. 13).

The Reduction of Benzaldehyde-3,4,5,6,7,8-hexafluoroisoquinolylhydrazone.

Benzaldehyde-3,4,5,6,7,8-hexafluoroisoquinolylhydrazone (0·50 g., 1·4 m.mole) was added to a suspension of zinc dust (0·419 g.) in glacial acetic acid (30 ml.). The reaction mixture was heated under reflux for 1 hr. when a further quantity of zinc dust (0·29 g.) was added and heating continued for a further $2\frac{1}{2}$ hr. Water was added and the reaction mixture steam distilled. The distillate was extracted with ether, and the extracts dried ($MgSO_4$) and the ether distilled to leave a white solid. This solid was recrystallised from light petroleum (b.p. 80-100°) to yield 1-aminohexafluoroisoquinoline

(0·050 g., 14·3%), m.p. and mixed m.p. 160-161°. The infrared spectrum was identical with that of authentic 1-aminohexafluoroisoquinoline prepared as described earlier.

The Diazotisation of 1-Aminohexafluoroisoquinoline in Anhydrous Hydrogen Fluoride. 1-Aminohexafluoroisoquinoline (0·85 g., 3·373 m.mole) was dissolved in anhydrous hydrogen fluoride (25 ml.) in a polyethylene beaker equipped with a magnetic stirrer covered with polytetrafluoroethylene, and cooled to -15°. Sodium nitrite (0·7 g., 10·1 m.mole) was added slowly over a period of 20 min. and the reaction mixture kept at -10 to -15° for a further 3¼ hr., with stirring. Hypophosphorous acid (75 ml., 50% v/v) was added, the reaction mixture allowed to warm to room temperature, and then heated on a water bath at 80° for 2½ hr. Water was then added, and the mixture extracted with ether. The combined extracts were dried ($MgSO_4$) and the ether distilled to give 0·3 g. of a solid which was sublimed under reduced pressure (20°, 0·11 mm.) to yield heptafluoroisoquinoline, m.p. 45° and with an infrared spectrum and retention time on v.p.c. identical with authentic heptafluoroisoquinoline.

Diazotisation in 80% hydrofluoric acid followed by addition of hypophosphorous acid yielded, depending on the reaction time, heptafluoroisoquinoline or a mixture of heptafluoroisoquinoline and 1-aminohexafluoroisoquinoline. Diazotisation in 50% hydrobromic acid followed by addition of hypophosphorous acid, yielded an impure high

melting white solid, m.p. 205-210°. The infrared spectrum showed the presence of C=O absorption plus a complex spectrum in the range 2·5-3·5 microns but this material could not be characterised.

Preparation of 1-Aminopentafluoro-6-methoxyisoquinoline. Sodium (0·125 g., 5·32 m.mole) in methanol (20 ml.) was added to 1-amino-hexafluoroisoquinoline (1·35 g., 5·35 m.mole) dissolved in methanol (40 ml.) and the mixture was heated under reflux for 12 hr., and then water added. A white solid was precipitated which was extracted with methylene dichloride, the combined extracts dried ($MgSO_4$) and the methylene dichloride distilled to leave a white solid (1·15 g.). This was recrystallised several times from methanol to give 1-aminopenta-fluoro-6-methoxyisoquinoline as white needles, m.p. 162·5 - 163·5° (Found: C, 45·3; H, 2·16. $C_{10}H_5F_5N_2O$ requires C, 45·5; H, 1·9%). M (mass spectrometry), 264; required 264 (i.r. No. 14).

Preparation of 6-Methoxyhexafluoroisoquinoline. 1-Aminopentafluoro-6-methoxyisoquinoline (2·1 g., 7·95 m.mole) was dissolved in hydrogen fluoride (50 ml.) at -30° in a polyethylene beaker. Stirring was attained by means of a nickel stirrer. Solid sodium nitrite (2·1 g., 35·6 m.mole) was added over a period of 20 min. The mixture was left to stir overnight, during which time the temperature rose slowly and the hydrogen fluoride evaporated to leave a yellow mass in the bottom of the beaker. Water was added and the mixture was extracted with

ether and the ether layer separated, was with water and aqueous sodium bicarbonate, dried ($MgSO_4$) and distilled to leave a very low-melting solid. This was sublimed (20°, 0·1 mm.) twice to give 6-methoxy-hexafluoroisoquinoline as a white solid (0·55 g.), m.p. 32-33·5° (Found: C, 45·3; H, 1·3. $C_{10}H_3F_6NO$ requires C, 44·9; H, 1·5%). M (mass spectrometry), 267; required 267. (i.r. No.15).

Some other, presumably polymeric, material was also isolated which was insoluble in water, acids, alkali and organic solvents.

The Reaction of n-Butyl-lithium with Heptafluoroisoquinoline in Diethyl Ether. To a cooled (-70°) well stirred solution of heptafluoro-isoquinoline (4·0 g., 15·68 m.moles) in diethyl ether (100 ml.) was added a solution of n-butyl-lithium (16·5 m.moles) in a mixture of diethyl ether/hexane solvent (10 ml: 7·3 ml.) over a period of 30 minutes. This produced a deep turquoise colouration. The temperature was maintained at -65/-70° for a further ¾ hr. After which time the temperature was allowed to rise to room temperature (producing a colour change to red). Dilute sulphuric acid (10 ml.) was then added slowly followed by water (20 ml.). The ethereal layer was separated, washed with water (twice), dried ($MgSO_4$) and distilled to leave a liquid which was shown by g.l.c. (silicone elastomer on Celite) to consist of a little ether, unreacted heptafluoroisoquinoline and two products with very close retention times.

These two products were separated by preparative v.p.c. (silicone elastomer on Celite) to give 1-n-butylhexafluoroisoquinoline (lowest retention time on v.p.c.) as a thick almost colourless liquid, b.p. 270° (micro) with slight decomposition (Found: C, 53·0; H, 3·15. $C_{13}H_9F_6N$ requires C, 53·2; H, 3·07%. M.W. (mass spectrometry) 293; required 293 (i.r. No. 16), and 6-n-butylhexafluoroisoquinoline (longer retention time) as a colourless liquid, b.p. 278-280° (micro) with decomposition (Found: C, 53·5; H, 3·24. $C_{13}H_9F_6N$ requires C, 53·2; H, 3·07%. M.W. (mass spectrometry) 293; required 293). (i.r. No. 17).

Competition of Heptafluoroisoquinoline with Pentafluoropyridine for Methoxide Ion. A solution of sodium (0·129 g., 5·6 m.mole) in dry methanol (10 ml.) was added during 5 min. to a well stirred solution of pentafluoropyridine (0·86 g., 5·09 m.mole) and heptafluoroisoquinoline (1·298 g., 3·09 m.mole) in methanol (20 ml.) at 0°. The solution was stirred for 40 min. and water (100 ml.) added. The aqueous solution was extracted with methylene dichloride, the combined extracts dried, and distilled. The crude product was examined by v.p.c. (Griffin and George Gas Density Balance detector; silicone elastomer column at 142°, which had been precalibrated with the expected products) and the peak areas of the 4-methoxytetrafluoropyridine and the 1-methoxyhexafluoroisoquinoline were obtained by means of a planimeter. From these areas it was deduced that the ratio of reactivity of pentafluoropyridine to heptafluoroisoquinoline was 1:2·3.

Reaction of Heptafluoroisoquinoline with aqueous Sodium Hydroxide. A mixture of heptafluoroisoquinoline (3·90 g., 15·26 m.moles) sodium hydroxide (1·2 g., 30·0 m.moles) and water (100 ml.) was heated under reflux for 2 hr. (oil bath temperature 135°). The orange coloured reaction mixture was cooled, acidified with dilute hydrochloric acid, extracted with methylene dichloride and the combined extracts dried ($MgSO_4$). Distillation of the methylene dichloride afforded a white solid (1·92 g.) which was recrystallised from benzene several times to yield 1-hydroxyhexafluoroisoquinoline as a white crystalline solid, m.p. 178-182°. No improvement in m.p. was afforded by further recrystallisation (Found: C, 42·7; H, 0·28; F, 45·3. C_9HF_6O requires C, 42·7; H, 0·4; F, 45%). (i.r. No. 18).

Reaction of Heptafluoroisoquinoline with Potassium Hydroxide in Tertiary Butanol. A mixture of heptafluoroisoquinoline (1·28 g., 5·01 m.moles), potassium hydroxide (0·58 g., 10·33 m.moles), and t-butyl alcohol (30 ml.) was heated on a water-bath at 75° with stirring for 1½ hr. The reaction mixture was cooled and water (70 ml.) added, and the t-butyl alcohol distilled off through a vigreux column. The cooled aqueous solution was acidified with dilute hydrochloric acid, extracted with methylene dichloride, and the combined extracts dried ($MgSO_4$). Distillation of the methylene dichloride afforded a solid which was recrystallised from benzene to yield a white crystalline solid (0·93 g.), m.p. 176-182°, identical to that obtained in the reaction between heptafluoroisoquinoline and aqueous sodium hydroxide.

Methylation of 1-Hydroxyhexafluoroisoquinoline with Diazomethane.

1-Hydroxyhexafluoroisoquinoline, prepared by the reaction of heptafluoroisoquinoline with aqueous sodium hydroxide, was dissolved in ether and a slight excess of an ethereal solution of diazomethane added at room temperature with stirring. Nitrogen was immediately evolved and stirring was continued for a further 1 hr., when the ether was distilled to leave a white solid (1·73 g.). When this product was examined by v.p.c. (silicone elastomer on Celite at 200°), two products were shown to be present. The major product (80%) had a retention time identical with that of authentic 1-methoxyhexafluoroisoquinoline. The other product (20%) had a longer retention time than authentic 1-methoxyhexafluoroisoquinoline, but shorter than 1,6-dimethoxypentafluoroisoquinoline. The two compounds were separated by preparative scale v.p.c. to give 1-methoxyhexafluoroisoquinoline, m.p. 86-87° mixed m.p. 86-87°, and gave an infrared spectrum identical with that of authentic 1-methoxyhexafluoroisoquinoline. The other compound, m.p. 135-135·5° from light petroleum (b.p. 40-60°) (Found: C, 44·80; H, 1·32; F, 43·0. M.W. 267. $C_{10}H_3F_6NO$ requires C, 44·95; H, 1·12; F, 42·7%. M.W. 267) appears to be, from spectral evidence, N-methylhexafluoro-1-isoquinolone. (i.r. No. 19).

Demethylation of 1-Methoxyhexafluoroisoquinoline with Aluminium Trichloride. 1-Methoxyhexafluoroisoquinoline (1·5 g., 5·61 m.mole) and aluminium trichloride (3·0 g., 22·55 m.mole) were heated together at 120°

for a period of 3 hr. The reaction mixture was cooled and ice added. The resultant solution was extracted with methylene dichloride, and the latter extracts shaken with dilute sodium hydroxide. The methylene dichloride solution was dried ($MgSO_4$) and distilled to give a white solid (0·2 g.) which was shown to be 1-methoxyhexafluoroisoquinoline (infrared spectrum). The aqueous layer was acidified and the white solid which was precipitated was extracted into methylene dichloride, dried ($MgSO_4$), and the solvent distilled to leave a white solid (0·8 g.). This solid was recrystallised to give 1-hydroxyhexafluoroisoquinoline (m.p. and i.r. spectrum identical with an authentic specimen).

Methylation of this compound with diazomethane as previously described gave 1-methoxyhexafluoroisoquinoline and N-methylhexafluoro-1-isoquinolone in the ratio 80:20 (shown by v.p.c.).

Reaction of 4-Chlorohexafluoroisoquinoline with Sodium Methoxide.

To a cold (0°) solution of 4-chlorohexafluoroisoquinoline (1·35 g., 4·97 m.mole) in anhydrous methanol (25 ml.) was added dropwise a solution of sodium (0·115 g., 5·0 m.mole) in methanol over a period of 10 minutes, with continual stirring.

The reaction mixture was allowed to stir for a further 5 minutes at 0° and then for 10 minutes at room temperature after which time 100 ml. of water was added and a white solid deposited. This was

extracted into methylene dichloride and the combined extracts dried ($MgSO_4$) and distilled to yield 1·0 g. of a white solid. Examination of the crude material by v.p.c. showed principally 1 component, a single isomer. (Silicone elastomer and apiezon-L as stationary states).

Purification of the solid was affected by reduced pressure sublimation and by recrystallisation from 40/60 petroleum ether to give 4-chloro-1-methoxypentafluoroisoquinoline as white crystals, m.p. 72-73°C. (Found: C, 42·00; H, 1·03; F, 33·3; Cl, 12·4. $C_{10}H_3ClF_5NO$ requires C, 42·3; H, 1·06; F, 33·6; Cl, 12·5%).

PART II

Polyhaloalkylation

Chapter 4

Introduction

Introduction.

In dealing with reactions of unsaturated hydrocarbon compounds, the reagents taking part are often electrophilic in nature. The chemistry of fluoro-olefins[166] and polyfluoroaromatics[69,102] involves nucleophilic reagents and carbanions. Fluoro-olefins are known to react with fluoride ion in aprotic solvents[166,167] and there is, to some extent, an analogy between the role of fluoride-ion in fluorocarbon chemistry and the proton in hydrocarbon chemistry. This suggests the possibility of the nucleophilic equivalent of Friedel Crafts reaction using a fluoro-olefin and a polyfluoroaromatic compound, in the presence of fluoride ion.

The Reaction of Fluoro-olefins with Fluoride Ion and Related Reactions.

This field of work has received its foundation and present stimulus from the work of Miller and his colleagues, who have systematically studied the reaction of halide ions with fluoro-olefins. A suitable source of fluoride ion is itself a problem and merits mention. Stable inorganic fluorides tend to be insoluble in inert aprotic organic solvents while in protogenic solvents hydrogen ion transfer to fluorocarbanions limits the usefulness of such systems. Hydrogen ion transfer takes place with the formation of solvent anions, which in turn may attack the olefin to yield undesired by-products.

The use of two fluoride-ion reagents was reported by Miller.[167]

These consisted of potassium fluoride in formamide solution[168] and tetraethylammonium fluoride in such solvents as chloroform, methylene chloride or acetone. Both these type of reagents have serious limitations.

Formamide has the valuable property of dissolving relatively large amounts of potassium fluoride but, however, is a poor solvent for fluoro-olefins. It readily yields a proton to a fluorocarbanion with the resultant formation of a reactive solvent anion. Another difficulty is that fluoro-olefins sometimes show appreciable reactivity towards the solvent alone when heated at elevated temperatures, e.g. 3,3-dichloro-1,1,3-trifluoropropene was completely converted into dark water soluble products when heated with formamide for ninety hours at 105°C.[167]

Tetraethylammonium fluoride is appreciably soluble in chlorinated solvents such as chloroform. As with potassium fluoride in formamide, this reagent has certain disadvantages. It is extremely hygroscopic, thermally unstable and difficult to prepare pure. Solutions of this in chlorinated solvents have been shown to undergo partial decomposition even at room temperature.[167] However the use of solutions of tetraethylammonium fluoride in methylene chloride or chloroform has made possible the examination of some reactions of fluoro-olefins with relatively high concentrations of fluoride ion in homogeneous solution.

As a consequence of the disadvantage stated above, the successful use of glycols,[169,170] dimethylsulphone,[171] acetonitrile,[172] and N-methyl-2-pyrrolidone and a number of other solvents[171] for reactions using inorganic fluorides has been reported.

Miller and his colleagues[167] have established two different reaction types for the reaction of halide ions with fluoro-olefins.

(1) Substitution with rearrangement (SN_2'),

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

(2) Addition,

$$F^- + CF_2{=}CF{-}CF_3 \rightleftharpoons CF_3{-}\bar{C}F{-}CF_3$$
$$\downarrow H^+ \text{ (solvent)}$$
$$CF_3{\cdot}CHF{\cdot}CF_3$$

Substitution with Rearrangement (SN_2'). The SN_2' process governs the reactions of fluoroallyl halides; this has been established in a series of publications.[167,173-175] That attack by fluoride ion on the terminal difluoromethylene occurs and not on the α-carbon atom in the reactions of $CF_2{=}CF{\cdot}CF_2Cl$ or $CF_2{=}CCl{-}CF_2Cl$ with iodide ion may be deduced from the observation that under identical conditions $C_6H_5CClF_2$, $CClF{=}CF{\cdot}CClF_2$ and $CCl_2{=}CCl{\cdot}CClF_2$ are all unreactive.[174] The relative order of reactivity of halide ions with fluoro-olefins in the SN_2' process has been shown to be $F^- > Cl^- \gg I^-$,[167,175] e.g. this is the observed order

of reactivity for the series

$$X^- + CF_2{=}CH{\cdot}CCl_2F \longrightarrow XCF_2{\cdot}CH{=}CClF + Cl^-$$

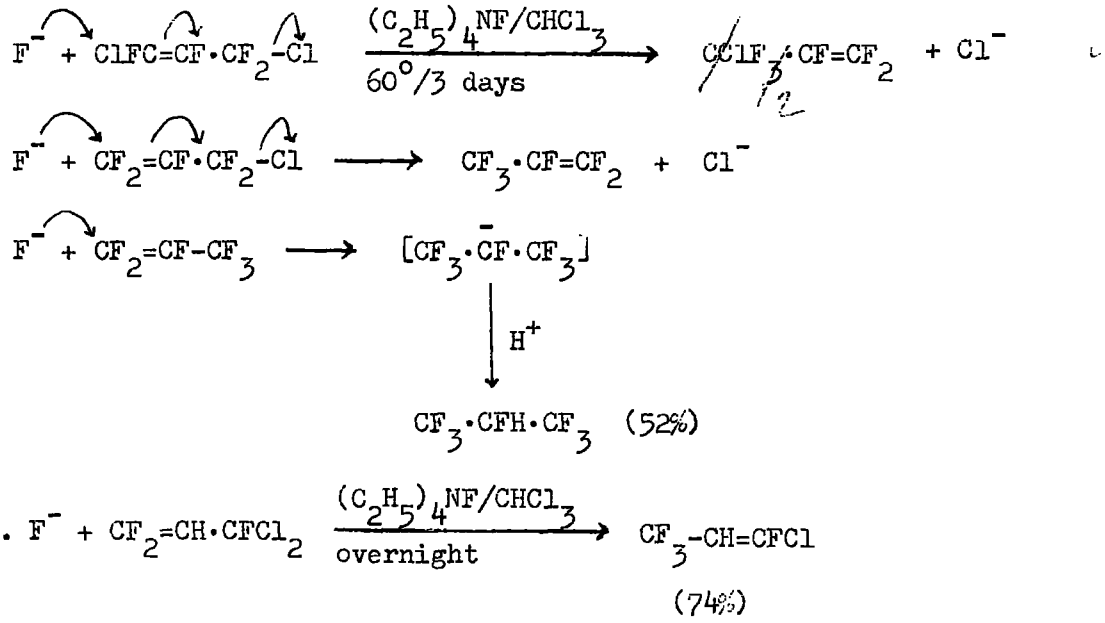
(X = Cl, F, or I)

This order is the reverse of that which has been assigned to the relative nucleophilicities of halide ions in bond formation to carbon in SN_2 reactions and suggests that in attack of halide ions on fluoroolefins, polarizability of large halide ions is offset by steric hindrance and that it is the strength of the new bond which is of prime importance. The apparent anomaly of replacement of allylic chlorine by iodine in $CF_2{=}CX{\cdot}CClF_2$ (X = F, or Cl) giving $CF_2{=}CX{\cdot}CF_2I$[173,174,176] is a result of the low solubility of sodium chloride in anhydrous acetone.[173]

$$NaI + CF_2{=}CF{\cdot}CF_2Cl \xrightarrow[\text{room temp.}\ 10\ \text{days}]{\text{Acetone}} CF_2{=}CF{\cdot}CF_2I + NaCl\downarrow\ (60\%)$$

When substitution of allylic or vinylic fluorine is possible this reaction occurs in preference to addition of hydrogen fluoride by a carbanion intermediate. Also a terminal difluoromethylene group is more susceptible to attack by fluoride ion than a terminal CFCl=. All of these facts have been illustrated by the reaction of $CFCl{=}CF{\cdot}CClF_2$ with potassium fluoride in formamide.[167] Relatively vigorous conditions were required as compared with $CF_2{=}CH{\cdot}CFCl_2$ (which reacted quickly at room temperature) and $CF_3{\cdot}CHFCF_3$ was obtained in 52% yield. The former

reaction has been interpreted as proceeding via two SN_2' replacements of chlorine by fluoride ion, and then addition of hydrogen fluoride.



Fluoride ion Catalysed Rearrangements.

Reactions of this type involve SN_2' displacement of fluorine by fluoride ion. A terminal olefin is much more susceptible to attack than an internal olefin and so there is a great tendency for a terminal- to be rearranged to an internal-olefin. Treatment of perfluoro-1-heptene with tetraethylammonium fluoride in chloroform solution for 5 min. at room temperature gave a mixture of olefins containing only 12% of the original starting olefin.[167] When a higher concentration of fluoride ion was used and a longer contact time allowed, then only 2% starting olefin remained. The following series of reactions was proposed to have taken place.

$$CF_3\cdot CF_2\cdot CF_2\cdot CF_2\cdot CF_2\cdot CF{=}CF_2 \xrightleftharpoons{F^-}$$

$$CF_3\cdot CF_2\cdot CF_2\cdot CF_2\cdot CF{=}CF\cdot CF_3 \xrightleftharpoons{F^-}$$

$$CF_3\cdot CF_2\cdot CF_2\cdot CF{=}CF\cdot CF_2\text{-}CF_3.$$

Similar conversion of perfluoro-1-heptene to -2-heptene occurs when the former is passed, with an inert carrier-gas, over a mixed alkali-alkaline earth metal fluoride catalyst at 200-300°.[177] Perfluorodienes are rearranged to acetylenes by caesium fluoride.[178,179] Perfluorobutadiene and caesium fluoride, heated together in a sealed ampoule at 100°C without a solvent, gave perfluoro-2-butyne (88% yield); and $CF_2{=}CF\cdot CF_2\cdot CF{=}CF_2$ gave $CF_3\cdot C{\equiv}C\cdot CF_2\cdot CF_3$ either by reaction in the vapour (95% yield) or liquid (68% yield) phase with caesium fluoride.[178] This interesting rearrangement is regarded as a series of SN_2' displacements by fluoride ion.

$$\begin{array}{ccc} CF_2{=}CF\cdot CF_2\cdot CF{=}CF_2 & \xrightarrow{F^-} & CF_3\cdot CF_2C{\equiv}C\cdot CF_3 \\ \downarrow F^- & & \uparrow F^- \\ CF_3\cdot CF{=}CF\cdot CF{=}CF_2 & \xrightarrow{F^-} & CF_3\cdot CF{=}C{=}CF\cdot CF_3 \end{array}$$

Rearrangement of a terminal olefin, containing more than three carbon atoms has been achieved using aluminium tribromide or trichloride;[180] the reaction involves migration of fluorine but the mechanism is obscure e.g.,

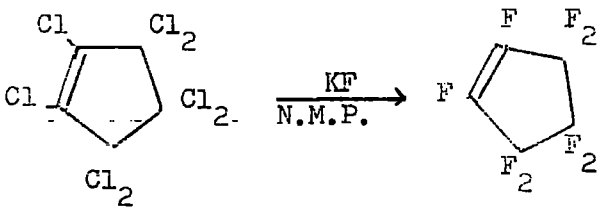
$$CF_2{=}CCl\cdot CF_2\cdot CCl{=}CF_2 \xrightarrow{AlCl_3} CF_2{=}CCl\cdot CF{=}CCl\cdot CF_3$$

Direct Vinyl Substitution. Although substitution of vinyl chlorine in $CClF{=}CF{\cdot}CClF_2$ by fluoride ion has been mentioned already, this process is considered to occur via two SN_2' sequences. Direct vinyl substitution by fluoride has not been established but has been suggested as being the first step in the reaction of $CClF{=}CCl{\cdot}CF_3$ with potassium fluoride-formamide at 60°, yielding $CF_3{\cdot}CHCl{\cdot}CF_3$.[167]

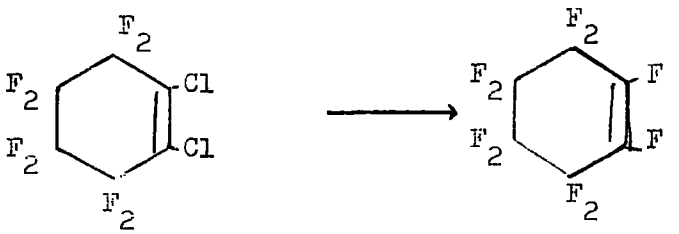
$$CClF{=}CCl{\cdot}CF_3 + F^- \longrightarrow CF_2{=}CCl{\cdot}CF_3$$

$$CF_2{=}CCl{\cdot}CF_3 + F^- \longrightarrow [CF_3{\cdot}\bar{C}Cl{\cdot}CF_3] \xrightarrow{H^+} CF_3{\cdot}CHCl{\cdot}CF_3 \quad (55\%)$$

Reactions of potassium fluoride in N-methyl-2-pyrrolidone (N.M.P.) with polychlorofluoro-olefins[171] probably involve direct substitution of vinylic chloride by fluoride ion. The reactions require a temperature of 190° and above and proceed most readily with cyclic perchlorofluorocyclic olefins which give high yields of perfluoro-olefins.



(72%)



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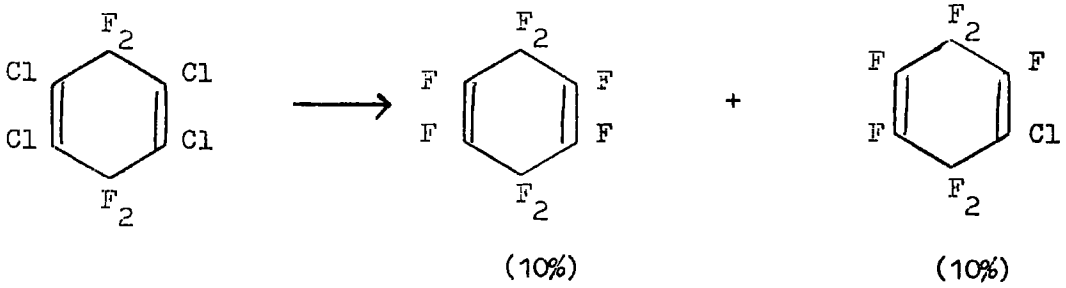


Addition Reactions.

Hydrogen Fluoride. In the olefin-fluoride ion reactions described above where substitution of vinyl or allylic halogen by fluorine or addition to form a carbanion could result from attack on a given unsaturated carbon, substitution was observed to take place first. The resulting more highly fluorinated olefins which contained a terminal CF_2= grouping were then rapidly converted into their hydrogen fluoride adducts while olefins with an internal -CF=CF- grouping reacted more slowly. When olefins which did not contain replaceable vinyl or allylic halogen other than fluorine and which would not undergo rearrangement by an SN_2' mechanism were allowed to react with potassium fluoride in formamide the results summarised in table I were obtained.[167] Dark coloured reaction mixtures were formed due to reactions with the solvent.

As was expected, olefins with a terminal CF_2= group readily added hydrogen fluoride while hexafluoro-2-butene which has an internal -CF=CF- group reacted much more slowly.

It is important to note that these hydrogen fluoride addition reactions took place in mildly basic media with a high concentration of fluoride ion present. The only consistent mechanism involves the

Table I

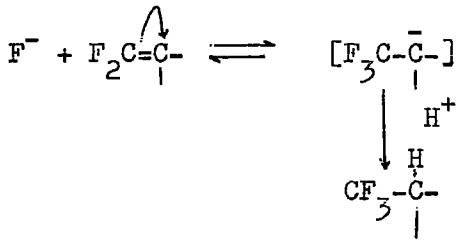
Olefin	Temp. °C	Reaction time hr.[a]	Product	Yield %
$CF_2=CFCl$	55	30	CF_3CHClF	72
$CF_2=CF\cdot CF_3$	25	5	CF_3CHFCF_3	60
$CF_2=CF\cdot CF_3$	65	b	CF_3CFHCF_3	21[c]
$CF_2=CCl\cdot CF_3$	25	6	$CF_3\cdot CHCl\cdot CF_3$	61
$CF_3\cdot CF=CF\cdot CF_3$	81	24	$CF_3CHF\cdot CF_2CF_3$	ca.35

a) - in a rocker shaker.

b) - bubbled very slowly through the KF-formamide mixture.

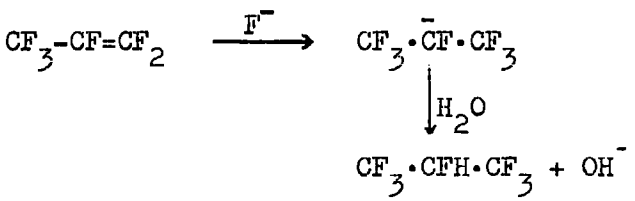
c) Recovered 50% of the starting olefin.

initial addition of fluoride ion.



This reaction unfortunately yields a solvent anion, along with the hydrogen fluoride addition product, which can then react with the fluoro-olefin in competition with fluoride ion. This secondary reaction limits the yield of hydrogen fluoride adduct.

This reaction mechanism was further substantiated by isolation of the hydrogen fluoride adduct CF_3CHFCF_3 from the reaction of hexafluoropropene with an aqueous dioxan solution of potassium fluoride.[167]



Fluorocarbanion formation was also shown by hydrogen abstraction when fluoro-olefins were allowed to react with tetraethylammonium fluoride in homogeneous chloroform solution.[167] 2-Chloropentafluoropropene reacted very rapidly. After 10 minutes at 15° none of the starting olefin could be recovered and the only product characterised was the hydrogen fluoride adduct $CF_3 \cdot CHCl \cdot CF_3$, obtained in 55% yield. Collapse of the cation and carbanion may have occurred to some extent to form neutral products but is considered more probable that protons

were largely furnished by water present in the reaction mixture.

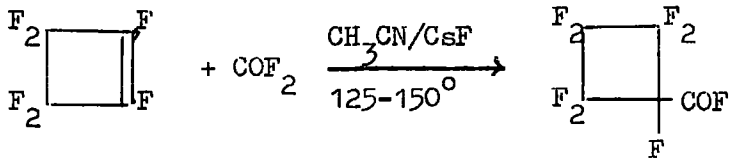
The conversion of hexafluoropropene to unsaturated dimers and trimers, using potassium hydrogen fluoride in dimethyl formamide, has been reported,[181] and this is presumed to occur via an anionic process initiated by fluoride ion.[166]

$$CF_3\cdot CF=CF_2 + KHF_2 \xrightarrow[25\text{-}30^\circ]{HCON(CH_3)_2} \left.\begin{array}{ll} CF_3\cdot CF=CF\cdot CF(CF_3)_2 & (98\%) \\ CF_3\cdot CF_2\cdot CF=C(CF_3)_2 & (2\%) \end{array}\right\} + \left.\begin{array}{ll} (CF_3)_2\cdot CF\cdot C(CF_3)=CF\cdot CF(CF_3)_2 & (44\%) \\ (CF_3)_2C=C(CF_3)\cdot CF_2\cdot CF(CF_3)_2 & (51\%) \end{array}\right\}$$

Addition of Acid Fluorides. Workers of the Du Pont company have recently developed a method for the addition of acid fluorides to fluoro-olefins.[182,183] The additions of carbonyl fluoride to $CF_3\cdot CF=CF_2$ (80% conversion), $CF_3\cdot CF=CF\cdot CF_3$ (62%), $CH_3O\cdot CF=CF_2$ (62%) and $CF_2=CF_2$ were achieved using excess carbonyl fluoride in acetonitrile in the presence of catalytic amounts of caesium fluoride, potassium hydrogen fluoride or tetraethylammonium fluoride

$$CF_3\cdot CF=CF_2 + COF_2 \xrightarrow[50/100^\circ]{CH_3CN/KF} (CF_3)_2CF\cdot COF$$

$$2CF_3\cdot CF=CF_2 + COF_2 \xrightarrow[75\text{-}100^\circ]{CsF/CH_3CN} [(CF_3)_2CF]_2CO \text{ (39\% conversion)}$$



(54% conversion)

Fluoroacyl fluorides reacted with hexafluoropropene in an analogous manner, giving polyfluoroisopropyl ketones; and diketones were obtained from oxalyl fluoride and perfluoroglutaryl fluoride.

$$CF_3COF + CF_2{=}CF{\cdot}CF_3 \xrightarrow[100\text{-}125^\circ]{KHF_2/CH_3CN} CF_3{\cdot}CO{\cdot}CF(CF_3)_2 \quad (75\%\ \text{conversion})$$

$$FCO(CF_2)_3COF + CF_2{=}CF{\cdot}CF_3 \xrightarrow[100\text{-}125^\circ]{KHF_2/CH_3CN} (CF_3)_2CF{\cdot}CO(CF_2)_3{\cdot}CO{\cdot}CF(CF_3)_2$$

(75% conversion)

$$FCO{\cdot}COF + CF_2{=}CF{\cdot}CF_3 \xrightarrow[75\text{-}100^\circ]{CH_3CN/KHF_2} (CF_3)_2CF{\cdot}CO{\cdot}CO{\cdot}CF(CF_3)_2$$

(28% conversion)

It is assumed that these additions proceed by the initial generation of carbanions and subsequent reaction with the acid fluorides, e.g.

$$F^- + CF_2{=}CF{\cdot}CF_3 \longrightarrow (CF_3)_2CF^-$$

$$(CF_3)_2CF^- + O{=}CFR \longrightarrow (CF_3)_2CF{\cdot}CO{\cdot}R + F^-$$

R = F or fluorocarbon group)

The polymerisation of tetrafluoroethylene has been brought about by anionic catalysis using fluoride ion. Caesium fluoride as an active-carbon support did catalyse the reaction of tetrafluoroethylene

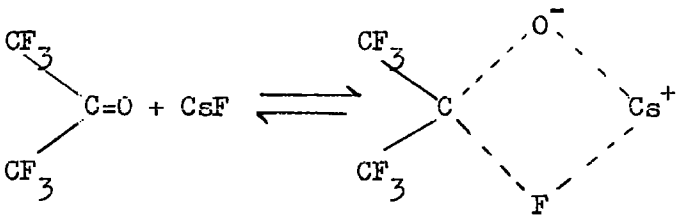
with itself, but the products were so tightly bound to the catalyst that temperatures in excess of 100° were required to remove them.[184] The product was an extensive mixture of saturated compounds, olefins and diolefins. Some of the compounds formed contained an uneven number of carbon atoms, indicating rupture of the carbon to carbon bond. A milder reaction was obtained with a catalyst system comprising caesium fluoride suspended in an activating solvent such as di-, tri-, or tetra-ethylene glycol dimethyl ether (di-, tri-, and tetra-glyme).

The condensation of tetrafluoroethylene with itself in the presence of solvent activated caesium fluoride was presumed[184] to follow a cycle comprising the following steps: (1) formation of the perfluoro carbanion $CF_3CF_2^-$ by addition of fluoride ion to tetrafluoroethylene; (2) addition of the perfluoro carbanion to a molecule of tetrafluoroethylene; (3) elimination of a fluoride ion to yield an olefin; and (4) addition of another perfluoro carbanion etc.

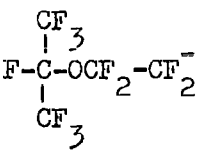
An interesting aspect of this reaction was that the velocity was roughly proportional to the amount of caesium fluoride added, although caesium fluoride is only slightly soluble in the solvent employed. This suggests that the surface of the caesium fluoride crystal must be involved in the initial polarisation of the tetrafluoroethylene forming the carbanion, and that the caesium atom of the ion-pair $CF_3 \cdot CF_2^- Cs^+$ may retain its position in the lattice of the caesium fluoride crystal.

It has also been recently found that tetrafluoroethylene in the presence of a suitable metal fluoride - polar solvent combination,

will condense with certain ketones to yield the corresponding perfluorinated tertiary alcohols.[185] In the actual experiment the ketone is added to the metal fluoride - solvent slurry followed by the tetrafluoroethylene. For example, hexafluoroacetone was added to a slurry of caesium fluoride in diglyme. The ketone and caesium fluoride formed a soluble complex.



Subsequent addition of tetrafluoroethylene produced the perfluoro-t-pentyl alcohol. No evidence of formation of the ether anion



was found, indicating that the anion related to the ketone-caesium fluoride complex is too weak as a nucleophile to attack tetrafluoroethylene. Thus the assumption that the reaction producing the alcohol involves attack by the anion $CF_3CF_2^-$ (from tetrafluoroethylene and caesium fluoride) upon the equilibrium concentration of the ketone is strongly favoured.

An interesting observation in this work was that when the caesium

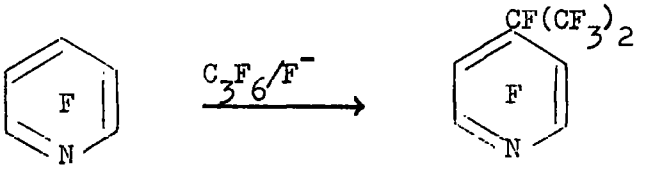
fluoride was completely complexed by the ketone (i.e. completely dissolved), the addition of tetrafluoroethylene produced no by-product of a liquid perfluoro-olefin polymer. However, when excess caesium fluoride was present, the rate of formation of the alcohol was greatly increased, but there was also some polymerisation of the tetrafluoroethylene.[184]

The condensation of perfluoro-α-olefins with carbon dioxide to yield perfluorocarboxylic acids has been initiated with fluoride ion in a suitable solvent.[188] The reaction comprised the direct addition of a metal fluoride complex of a perfluoro-olefin to carbon dioxide followed by separation of the free acid by acidification and distillation. The condensation proved to be reversible, the stability of the carboxylic acid metal salt decreasing with increasing complexity of the olefin. The condensation of tetrafluoroethylene with carbon dioxide at 100° was quantitative and the free acid was stable to distillation at its normal boiling point. In the case of hexafluoropropene, however, it was necessary to drop the temperature to 70° to avoid thermal decarboxylation, an effect accentuated by the tendency of hexafluoropropene to form dimers and trimers irreversibly.

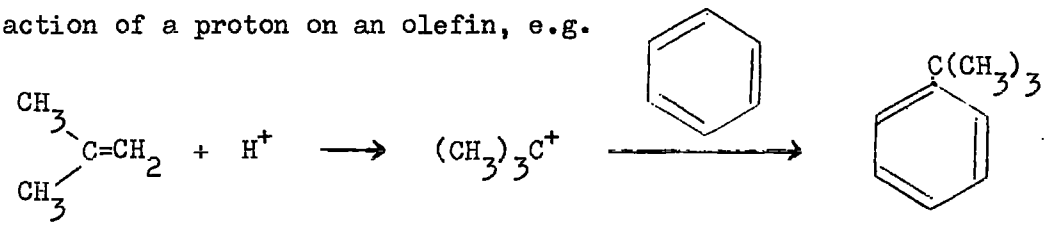
Chapter 5

Discussion of Experimental

Highly fluorinated aromatic compounds such as pentafluoropyridine, hexafluorobenzene, and their derivatives will react with carbanions produced from fluoride ions and fluoro-olefins, such as hexafluoropropene and tetrafluoroethylene. Polyfluoroalkylated derivatives are formed.



The process is equivalent to the Friedel and Crafts reaction in hydrocarbon chemistry, in which the intermediate is produced by the action of a proton on an olefin, e.g.

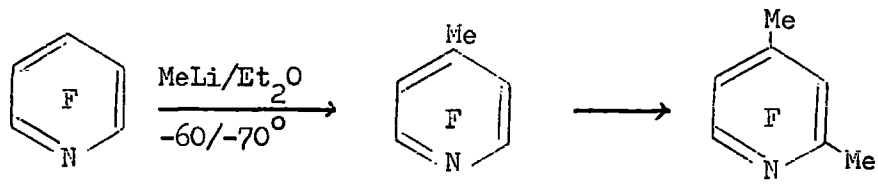


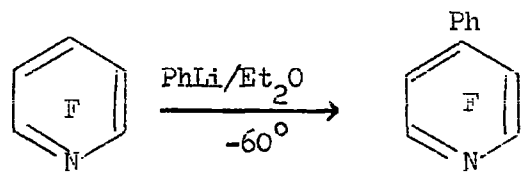
If it is carried out at pressures high enough to keep a reasonable concentration of olefin at the seat of the reaction, several fluoroalkyl groups can be introduced into the aromatic ring. Hexafluorobenzene is less reactive than pentafluoropyridine, but when activating groups such as nitro-, nitrile and trifluoromethyl are introduced into the hexafluorobenzene, reaction occurs much more readily.

Potassium fluoride or caesium fluoride can be used as sources of fluoride ion and sulpholane is a better solvent than dimethylformamide, diglyme, or triglyme.

Polyhaloalkylation of Pentafluoropyridine.

Pentafluoropyridine was chosen as the substrate for the first investigations in this work, because of its high reactivity towards nucleophilic species.[98] For example, pentafluoropyridine has been shown to react very readily with lithium alkyls in ether,[193] substitution occurring at the 4-position and then at the 2-, and 6-positions, e.g.





ref. 98

a) With Hexafluoropropene as the Olefin.

Hexafluoropropene, as has been demonstrated by the work of Miller and his co-workers,[167] very readily adds a fluoride ion to the terminal difluoromethylene group giving a very reactive carbanion.

The facile addition of fluoride ion to a terminal difluoromethylene group in a fluoro-olefin is general and is a consequence of repulsion of the π-electrons by the p-electrons on the fluorine atoms, thus making the terminal carbon atom slightly electron deficient. This, coupled with the electron attracting characteristics of the trifluoromethyl group in hexafluoropropene, produces a very strong polarisation of the π-bond, as shown below, and makes addition of fluoride ion to give a secondary carbanion very easy i.e.

$$CF_3 \leftarrow CF{=}C\begin{matrix}\swarrow F \\ \nwarrow F\end{matrix} \xrightarrow{F^-} CF_3\text{-}\overset{-}{C}F\text{-}CF_3$$

Thus the advantages of using hexafluoropropene as the olefin in conjunction with pentafluoropyridine as the substrate are, that if the reaction is at all feasible, then these reactants were the most likely to produce results and give some indication of the possibilities of extending the scope of the reaction.

When hexafluoropropene and pentafluoropyridine were heated together in a Carius tube at 120° for 14 hr., using anhydrous potassium fluoride as a source of fluoride ion, no reaction took place and the starting materials were recovered almost quantitatively. However, when the reaction was repeated under identical conditions using anhydrous caesium fluoride as the source of fluoride ion, a 99% yield of perfluoro(4-isopropylpyridine) was obtained. The large difference in efficiency of the initiator can be considered to be due

to the large difference in lattice energy between caesium fluoride and potassium fluoride (see Table 1). The difference between these two compounds as sources of fluoride ion has been pointed out in work done on reactions involving the nucleophilic displacement of chloride ion by fluoride ion, in an aromatic nucleus.[194,195] The reaction was also attempted with lithium fluoride but, as was anticipated, did not produce any products.

Since potassium fluoride would not initiate the reaction alone, the investigations were extended to the use of solvent systems, along with both potassium fluoride and caesium fluoride. Ideally the reaction would involve potassium fluoride as the source of fluoride ion, because of its very low cost compared with caesium fluoride.

The choice of solvents for the investigation was based on past work and results obtained from those solvents in reactions of a similar nature. The use of dimethylformamide as a solvent for carrying out fluoride initiated reactions of fluoro-olefins has been demonstrated in particular by Miller and his co-workers.[167] The relative advantages and disadvantages of this solvent have been discussed in the introduction to this section.

The use of sulpholane as a solvent medium for performing reactions involving the use of fluoride ion has recently become widespread, in particular in reactions involving the displacement of chlorine and bromine atoms attached to an aromatic nucleus.[34]

The most important factors which make sulpholane such a useful solvent in reactions of this nature are its high thermal stability, the low susceptibility towards proton abstraction by a carbanion and the very low solvation of anions by the solvent. For example, the basicity of tetraethylammonium hydroxide in sulpholane is greater by a factor of 10^4, than in water.

Recently some work by Graham[184,185,188] has demonstrated the suitability of di-, tri-, and tetra-glyme as solvents for the reactions involving carbanions derived from olefins by the addition of fluoride ion from caesium fluoride with electrophilic centres e.g. CO_2 and compounds containing a carbonyl function.

These solvents, with the exception of tetraglyme, were used under controlled reaction conditions in the reaction between hexafluoropropene and pentafluoropyridine in the presence of both potassium fluoride and caesium fluoride as sources of fluoride ion. The conditions used, and the results obtained are shown in Table 1.

An examination of these results shows that for the reaction,

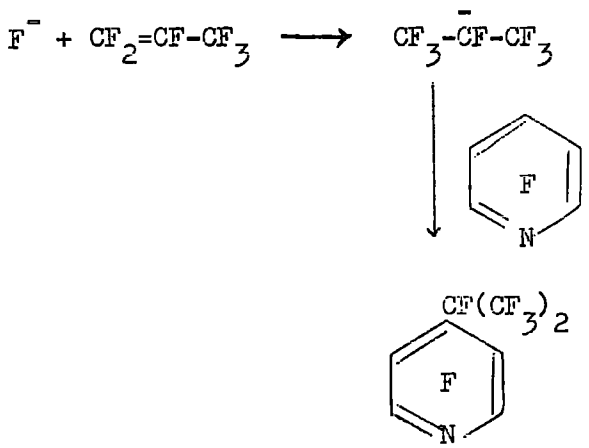


Table 1

Reaction Between C_5F_5N (3·0 g., 17·75 m.moles) & C_3F_6 (5·0 g., 33·3 m.moles)

Initiator/ Solvent	Temp.	Total Yield (g)	$C_3F_7 \cdot C_5F_4N$ (g)	C_5F_5N unreacted	% C_5F_5N to react	% yield based on C_5F_5N to react	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/D.M.F.	130°	6·0	2·4	1·38	54	79	2·18
KF/Sulpholane	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/sulpholane	20°	6·5	3·38	1·1	63	94	2·52
CsF/diglyme	20°	6·0	1·9	1·8	40	84	2·3
(8·0 g.)CsF/diglyme	20°	6·5	2·0	1·74	42	84	2·26
CsF/sulpholane	20°	7·3	4·7	0·37	88	95	2·9
(8·0 g.)CsF/ sulpholane	20°	8·5	5·61	0·07	98	100	2·82

All reactions in 100 ml. Carius tubes using 15 ml. of solvent.

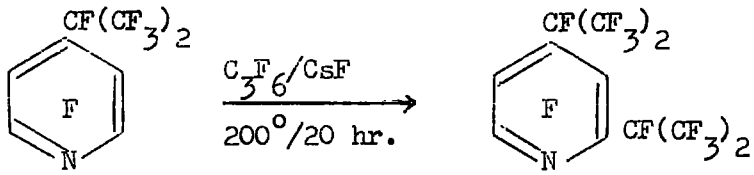
All reactions at 20° were shaken.

Except where stated, 3·0 g. of initiator used.

sulpholane is superior to the other solvents used, both in the yields of perfluoro-(4-isopropylpyridine) obtained and in the percentage conversion obtained. The results are most striking when the reactions are carried out at ambient temperatures. Caesium fluoride was also used as a source of fluoride ion with two of these solvents and was found to be considerably better than potassium fluoride, which is to be expected from lattice energy considerations. It was more effective at lower temperatures and the table shows a comparison with potassium fluoride in which they were shaken with the solvents at an initial temperature of 20°. In the more vigorous of these reactions the temperature rose to about 60° because of the heat given out during the reaction.

In all of these reactions, under the conditions described, no more than trace amounts of disubstituted products were detected and there was little indication that the reactivity of the ring system increased as substitution took place. However, there are several factors to take into consideration in evaluating this. The amount of olefin that was initially present in the reaction mixture, was only about twice the theoretical amount of olefin needed for mono-substitution to occur completely. The concentration of this must have been quite low once monosubstitution had occurred. The concentration of the remaining olefin is reduced even further by the strong tendency of hexafluoropropene towards dimerisation. It is also quite possible that there is an effect due to the decrease in solubility

of the product in the solvent with increase in molecular size, making reaction very difficult. This suggested itself, on the basis of a reaction carried out in which perfluoro-(4-isopropylpyridine) was reacted with hexafluoropropene (approximately four times the theoretical amount required to produce perfluoro-(2,4-di-isopropylpyridine)), in sulpholane as solvent and using caesium fluoride as a source of fluoride ion. The starting material is not soluble to any large extent in sulpholane. Extreme conditions had to be used to bring about any appreciable degree of reaction and a temperature of 200° for 20 hr. only produced a 50% conversion of perfluoro-(4-isopropylpyridine) to perfluoro-(2,4-di-isopropylpyridine) in only 54% yield.



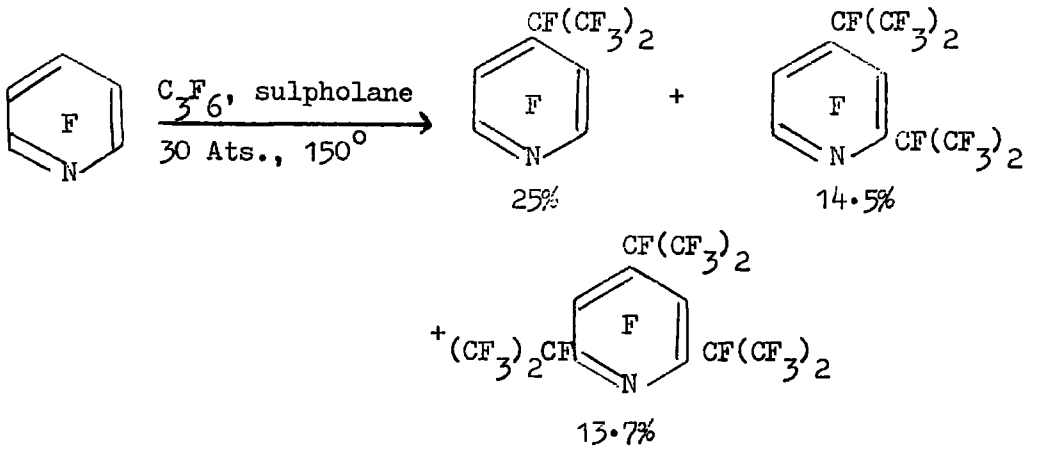
54%

However, some doubt may be cast upon this by the fact that the same reaction does not occur to any extent in diglyme as solvent, even though perfluoro-(4-isopropylpyridine) is completely soluble in diglyme. Another factor which had a small extent on the reaction was the surface area of the catalyst (see table 1). This effect has been suggested by other authors[184] to be evidence that the surface of the caesium fluoride crystal is involved in the initial polarisation of the fluoro-

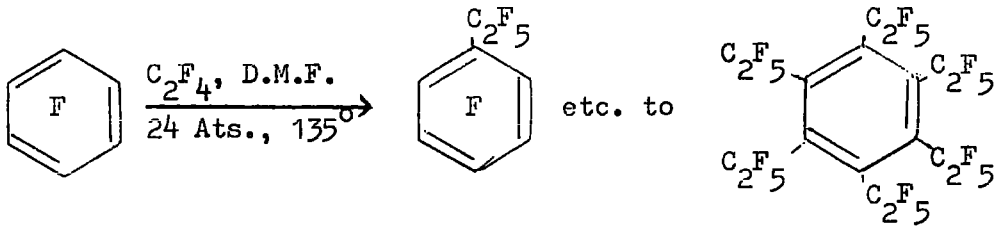
olefin forming the fluorocarbanion and that the caesium atom of the ion pair $Cs^+ CF_3CF_2^-$ may retain its position in the lattice of the caesium fluoride crystal.

The factor of major importance in determining the extent of the reaction was shown to be the concentration of the fluoro-olefin at the site of the reaction by carrying out the reaction at considerably higher pressures. Since fluoro-olefins are not very soluble in the solvents that were under consideration, then a very high initial reaction pressure increases the solubility of the olefin and hence the concentration at the site of the reaction which will either be a $Cs^+ F^-$ ion pair in solution, or on the surface of the solid caesium fluoride if the suggestion that the polarisation of the olefin occurs at the surface of the crystal lattice by the fluoride ion is correct.[184]

By carrying out the reaction at 150° and an initial pressure of 30 ats. it was possible to prepare not only perfluoro-(4-isopropylpyridine) but perfluoro-(2,4-di-isopropylpyridine) and perfluoro-(2,4,6-tri-isopropylpyridine) in reasonably good yields.

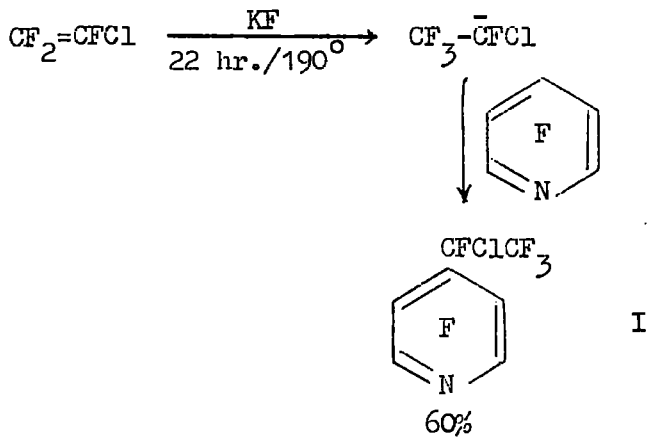


These results fit in well with those since published by Imperial Chemical Industries[189] in the patent literature, who have been able to prepare a mixture of perfluoro- (mono-, di-, tri-, tetra-, penta-, and hexa-ethyl benzenes) from hexafluorobenzene, tetrafluoroethylene and potassium fluoride at 135° for 6 hrs. at 34 ats. pressure.



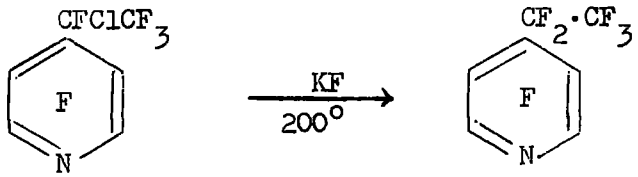
b) <u>With Chlorotrifluoroethylene as the Olefin.</u>

Reaction of chlorotrifluoroethylene with pentafluoropyridine in sulpholane, and using potassium fluoride as the source of fluoride ion, did not occur under the conditions that brought about reaction with hexafluoropropene. However, when more severe conditions were employed reaction did occur after heating at 190° for 22 hr. to give a 60% yield of 1-chloro-1-tetrafluoropyridyl tetrafluoroethane(I) as well as 40% unreacted starting material.



I

As well as this product, the v.p.c. trace showed the presence of a trace quantity of a lower boiling component which is thought to be due to benzylic replacement of chlorine by fluorine i.e.

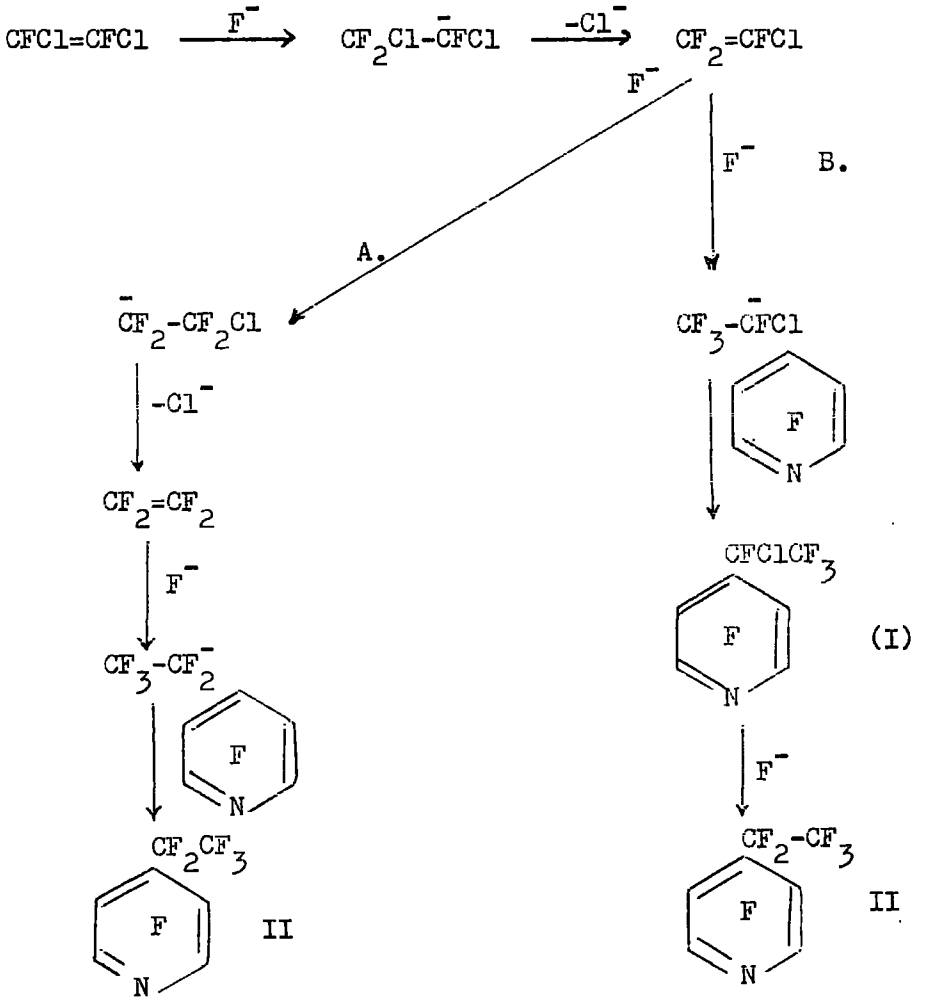


It was significant that the proportion of this component was increased, but was still insufficient to separate by preparative scale v.p.c., when the source of fluoride ion used was caesium fluoride. Further evidence for the occurrence of benzylic replacement of chlorine by fluorine has been obtained from reactions involving 1,2-dichloro-1,2-difluoroethylene with pentafluoropyridine and will be discussed later. Under the same conditions as above, the yield of product was lower due to the increased amount of decomposition that occurred.

The reasons for the difference in reactivity of hexafluoropropene and chlorotrifluoroethylene in this reaction are not immediately apparent. These two olefins should be approximately equally susceptible to attack by a fluoride ion at their respective difluoromethylene groups, and the stability of the carbanions obtained would be expected to be similar. It is possible that the difference could arise by virtue of differing concentrations at the reaction site, arising from a difference in solubility of the olefins in sulpholane.

c) With 1,2-dichloro-1,2-difluoro-ethylene as the Olefin.

As in the case of chlorotrifluoroethylene, the fluoride ion initiated reaction of 1,2-dichloro-1,2-difluoroethylene with pentafluoropyridine occurred, but only under the extreme forcing conditions of heating for 18 hr. at 200°. The difficult nature of the reaction presumably arises out of the initial difficulty in polarising the olefin prior to fluoride ion addition. The principle product arising from the reaction of a carbanion intermediate with pentafluoropyridine was 2,3,5,6-tetrafluoropyridylperfluoroethane(II). A proposed mechanism for its formation is outlined as follows.



The reaction sequence B is considered to be the correct one rather than A because trace quantities of 1-chloro-1-tetrafluoropyridylethane (I) was shown to be present by v.p.c. In a separate experiment under conditions similar to those of this experiment, tetrafluoroethylene did not react with pentafluoropyridine and therefore mechanism A would appear to be unreasonable. Also, in this mechanism, the step involving,

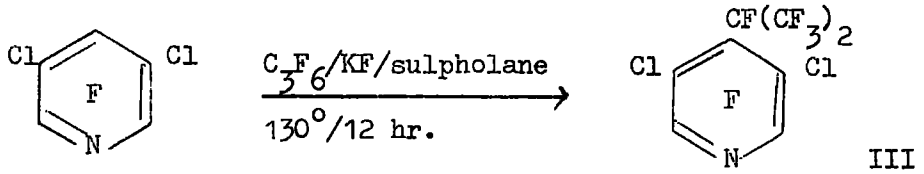
$$CF_2{=}CFCl + F^- \longrightarrow \overset{-}{C}F_2\text{-}CF_2Cl \xrightarrow{-Cl^-} CF_2{=}CF_2$$

involves attack by fluoride ion at the wrong carbon atom.

Polyhaloalkylation of Pentafluoropyridine derivatives.

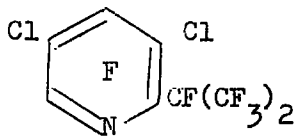
Hexafluoropropene was found to react readily with chlorofluoropyridines in the presence of anhydrous potassium fluoride as the source of fluoride ion and in sulpholane as the solvent.

a) 3,5-dichlorotrifluoropyridine. The reaction with hexafluoropropene was carried out at 130° over a period of 12 hr. The major products recovered from this reaction were those in which 2- and 4-substitution had occurred in approximately equal amounts (IV and III). These isomers were inseparable and were characterised by their ^{19}F n.m.r. spectra.



III

+



IV

Also obtained from this reaction was a separable mixture of compounds of lower boiling point. This mixture did not analyse correctly for a mixture of compounds of a given molecular formula. Chemical analysis indicated that replacement of chlorine by fluorine had occurred. Replacement of the chlorine atoms in III and IV would be expected to occur much more readily than in the starting material due to activation by the adjacent perfluoroisopropyl groups.

b) 3-Chlorotetrafluoropyridine. The reaction with hexafluoropropene occurred very readily under the conditions that had been used for pentafluoropyridine. Analysis of the reaction products by v.p.c. showed that as well as in reacted starting material (15%) there were two products of higher boiling point than the starting material. The compound with the lowest boiling point of these two, was shown to be a monoperfluoroisopropyl-3-chlorotrifluoropyridine but its structure could not be assigned. The fraction of higher boiling point was shown

by analysis to be disubstituted, and its ^{19}F n.m.r. spectrum showed the presence of two components, but the respective structure could not be assigned. A fraction of lower boiling point than the starting material was obtained and again was shown to be an inseparable mixture of compounds arising from chlorine displacement from the nucleus by fluorine.

Polyhaloalkylation of Hexafluorobenzene and its Derivatives.

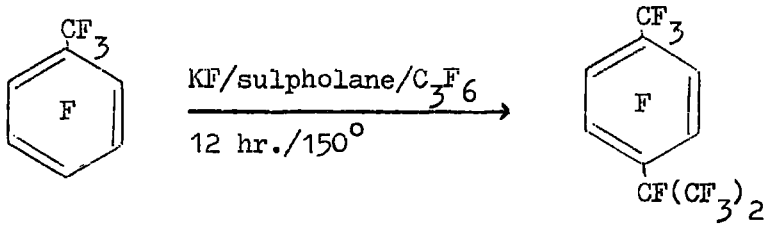
Most of the investigations with hexafluorobenzene and its derivatives were carried out using hexafluoropropene as the olefin.

a) Hexafluorobenzene. Numerous attempts were made to induce reaction between hexafluorobenzene and hexafluoropropene using both potassium and caesium fluorides in sulpholane and at the low pressures that were used throughout most of this work. The temperatures used ranged from 130° to nearly 300° and reaction times of 12 to 24 hr. No alkylated products were obtained, and at the higher temperatures the hexafluorobenzene usually decomposed. Since this work was carried out two publications have confirmed this result.

Dressler and Young[196] found that at the low pressures which they used, no reaction occurred between hexafluoropropene and hexafluorobenzene using acetonitrile as the solvent. However, as mentioned earlier, I.C.I. claimed that the reaction between hexafluorobenzene and tetrafluoroethylene occurred under high pressures.[189]

The reaction was repeated using bromopentafluorobenzene, hoping that the bromine atom would activate the system, but under the extreme conditions used (220°, 12 hr.) no alkylated product was obtained; there was however a small yield of hexafluorobenzene. The results of Dressler and Young[195] also confirm this.

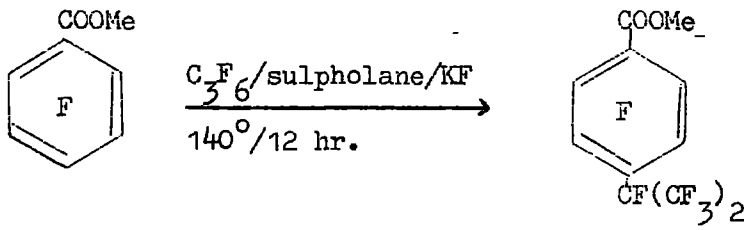
b) Octafluorotoluene. It was initially thought that the reaction of octafluorotoluene with hexafluoropropene would occur reasonably easily, by virtue of the powerful inductive effect of the trifluoromethyl activating the para carbon atom towards nucleophilic attack by the intermediate carbanion. When the reaction was attempted at room temperature by shaking for 12 hr. in sulpholane as solvent and caesium fluoride as the initiator, very little reaction occurred. The reaction was repeated using potassium fluoride as the source of fluoride ion in sulpholane as the solvent and heating for 12 hr. at 150°. This produced an almost equal proportion of unreacted starting material and perfluoro-(4-isopropyltoluene) V, the latter in 52% yield based on the perfluorotoluene that had reacted.



V 52%

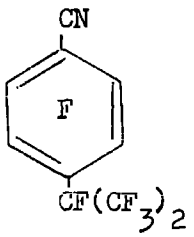
In order to improve the overall conversion of perfluorotoluene to perfluoro-(4-isopropyltoluene)V the amount of olefin was almost doubled, the amount of potassium fluoride increased and both the temperature and reaction time increased. This produced a ratic of 2:4 of unreacted starting material to V, but an overall lower yield of 42%. It was thought that some of the difficulties in this reaction were due to the insolubility of octafluorotoluene in sulpholane. However, when the sulpholane was replaced by triglyme, a solvent in which octafluorotoluene is completely soluble, only c.a. 5% reaction took place. The reasons for behaviour of this nature are not entirely obvious.

c) Methylpentafluorobenzoate. The reaction of methylpentafluorobenzoate with hexafluoropropene in sulpholane, using potassium fluoride as the source of fluoride ion was successful, although the best conversion that could be obtained was 50%.



d) Pentafluorobenzonitrile. This compound, as was expected reacted very readily with hexafluoropropene in sulpholane, using potassium fluoride as the source of fluoride ion. Initial reactions were

carried out using a slight excess of olefin over the theoretical amount required to replace a single fluorine atom. After heating at 125° for 15 hr., a very complicated mixture of products was obtained. Separation by v.p.c. was practically impossible although after passing several times through di-n-decylphthalate and silicon elastomer columns a trace quantity of a compound whose n.m.r. mass spectrum, and i.r. spectrum indicated that in fact it was 4-perfluoroisopropyl-2,3,5,6-tetrafluorobenzonitrile VI.



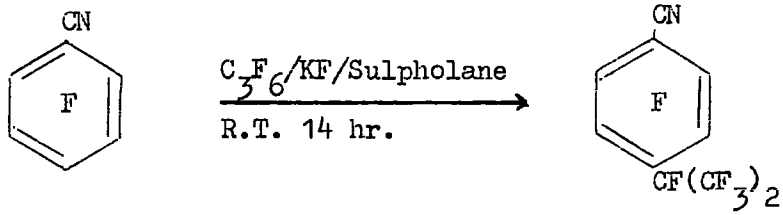
VI

Also separated from the reaction mixture, by fractional crystallisation, was a white solid which appeared from its reasonably sharp melting point of 128-130° to be a single compound. Its i.r. spectrum contained no -C≡N absorption and its mass spectrum gave a parent peak at a very high mass number (642); however its exact structure remains unknown, but most probably arose via polyalkylation.

When the initial amount of olefin was increased to below the level required to replace a single fluorine in the starting material, exactly the same complex mixture of products was obtained, except that more starting material remained. Attempts to carry out the reaction at

atmospheric pressure, by passing a slow stream of the olefin through the nitrile dissolved in sulpholane, were unsuccessful.

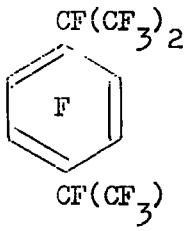
The most controllable conditions found were those which involved simply shaking the reaction mixture on a vibroshaker at room temperature, using a ratio of olefin to nitrile of c.a. 1:1. In reactions carried out in this way, the polyalkylation was kept down to a minimum and when carried out on a sufficiently large scale, the product was separable from starting material by distillation.



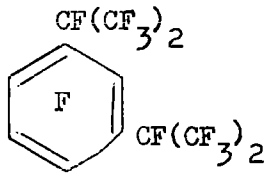
The ease with which this reaction occurs is obviously due to the presence of the very strong electron attracting nitrile group. The nitrile group in the presence of perfluoroisopropyl groups, would be very susceptible to replacement by fluoride ion and hence the formation of products which had no nitrile groups present.

e) Pentafluoronitrobenzene. In accordance with the known chemistry of pentafluoronitrobenzene[69] its reaction with the heptafluoroisopropyl carbanion, derived from the addition of fluoride ion to hexafluoropropene, was very easy. The solvent used was sulpholane and the source of fluoride ion was potassium fluoride.

After 12 hr. reaction time at 120°, the expected products 1-nitro-4-heptafluoroisopropyltetrafluorobenzene, IX, and 1-nitro-2,4-heptafluoroisopropyltetrafluorobenzene, X, were obtained, both in approximately 30% yield. However, also obtained was a mixture of two inseparable components, containing no nitro-groups. The only structures that could be consistent with the mode of formation and the ^{19}F n.m.r. spectrum (appendix 2) are VII and VIII.

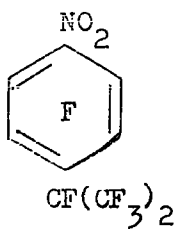


VII

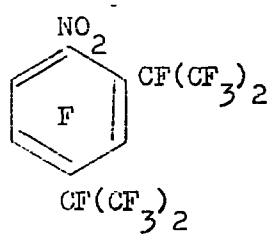


VIII

These presumably arise via displacement of the nitro group. VII would be formed from displacement of the nitro-group from IX and subsequent attack of a heptafluoroisopropyl carbanion, and VIII would be formed from fluoride ion displacement of the nitro-group from X.

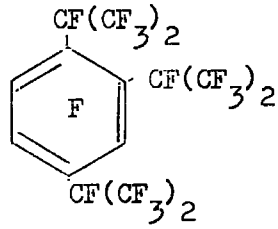


IX



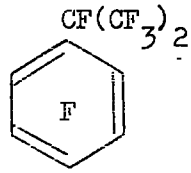
X

Trace quantities of a third compound, slightly higher boiling than the mixture of VII and VIII, which appeared to be a single compound from v.p.c. analysis, was presumably XI, which would arise from attack of a heptafluoroisopropyl carbanion on both VII and VIII. The structure of XI could not be confirmed, because of the small quantities present and the difficulty in separating it from VII or VIII.



XI

Some support for this scheme is given from the formation of perfluoroisopropylbenzene XII in 64% yield, when the reaction is carried out at 150°. In this case, the amount of IX and X formed is considerably decreased.



XII

f) Methylpentafluorobenzenesulphonate. First indications from this compound are that reaction does not occur below 150°. However, at this temperature and above only an insoluble dark coloured polymer was obtained.

Through lack of time, the investigations by the author ceased at this point. However the scope of the reaction can be seen to be very wide and the usefulness of the reaction as a synthetic tool is immediately obvious.

Chapter 6

Experimental Work

Experimental Work.

Infrared (i.r.) spectra were recorded using Grubb-Parsons, type G.S.2A., or Spectromaster spectrometers. ^{19}F Nuclear magnetic resonance (n.m.r.) spectra were recorded on A.E.I. R.S.2. or Perkin-Elmer N10 spectrometers operating at 60 Mc/s. or a Varian H.A.100 spectrometer operating at 94·2 Mc/s. Mass spectra were recorded using an A.E.I. M.S.9. spectrometer. Analytical scale vapour phase chromatography (v.p.c.) was carried out using a Perkin-Elmer 'Fractometer' model 451 and preparative scale vapour phase chromatography (v.p.c.), unless otherwise stated was carried out using an Aerograph 'Autoprep' instrument.

Purification of Reagents used.

The potassium and caesium fluorides used were reagent grade, supplied by British Drug House Ltd., and were dried by heating in a nickel beaker over a bunsen burner for several hours followed by storage in an oven at 150° until required. The sulpholane was dried and purified by repeated distillation under vacuum, collecting the middle fraction in each case, until the distillate readily solidified. Dimethylformamide (D.M.F.) was purified by repeated distillation. Acetonitrile was dried by distillation from phosphorus pentoxide. Diglyme and triglyme were dried by distillation from magnesium sulphate under vacuum.

The fluoro-olefins used were as commercially supplied except for chlorotrifluoroethylene, which was prepared by dehalogenation of Isceon 113, using zinc dust and ethanol.[190]

The Reaction of Pentafluoropyridine with Hexafluoropropene in the presence of Anhydrous Potassium Fluoride. Pentafluoropyridine (3·0 g., 17·75 m.moles) anhydrous potassium fluoride (3·0 g., 55·9 m.moles) were placed into a Carius tube, hexafluoropropene (5·0 g., 33·3 m.moles) condensed into it and the tube evacuated and sealed. It was heated at a temperature of 120° for a period of 14 hr., cooled and opened into a vacuum system. Only pentafluoropyridine was recovered in approximately a quantitative amount. Hexafluoropropene (4·3 g.) was also recovered. The experiment was repeated with agitation, but made no difference to the course of the reaction.

The Reaction of Pentafluoropyridine with Hexafluoropropene in the presence of Potassium Fluoride and Sulpholane. Pentafluoropyridine (3·0 g., 17·75 m.moles) anhydrous potassium fluoride (3·0 g., 55·9 m.moles), sulpholane (15 ml.) were placed into a Carius tube into which was then condensed hexafluoropropene (5·0 g., 33·3 m.moles). The tube was evacuated, sealed and heated for 12 hr. at a temperature of 130°. The tube was cooled and opened into a vacuum system and the volatile components collected. Fractionation gave hexafluoropropene (0·5 g.) and products (8·0 g.) which were shown by analytical scale v.p.c. (silicone elastomer on Celite) to consist of one major product and appreciable quantities of low boiling materials which were presumed to arise by olefin dimerisation reactions. The major product

was separated by preparative scale v.p.c. and was shown to be perfluoro-(4-isopropylpyridine) b.p. 128/129° (Found: C, 29·9; F, 65·0; M, 319 (mass spectrometry). C_8NF_{11} requires C, 30·1; F, 65·5%; M, 319). (i.r. spectrum No. 20). The amount present (estimated by v.p.c.) was 4·8 g., and the yield, based on the amount of pentafluoropyridine that had reacted (2·68 g.) was 94%. Also isolated but present in only trace amount was perfluoro-(2,4-di-isopropylpyridine), b.p. 158/160° (micro). (Found: C, 27·8; M, 469. $C_{11}NF_{17}$ requires C, 28·1%; M, 469) (i.r. spectrum No. 21). In both cases, the respective structures were shown by ^{19}F n.m.r. spectroscopy (see appendix 2).

The Reaction of Hexafluoropropene with Pentafluoropyridine using various Solvent-Initiator Systems. The general reaction scheme is as follows. Pentafluoropyridine (3·0 g., 17·75 m.moles), anhydrous potassium or caesium fluoride (see Table 1 in Chap. 5 for quantities), solvent (15 ml., see Table 1 in Chap. 5) were placed into a Carius tube of approx. 100 ml. capacity and hexafluoropropene (5·0 g., 30·0 m.moles) was condensed into the tube. The tube was then evacuated and sealed. For reactions at room temperature, the tube was shaken vigorously on a vibroshaker for 12 hr. The products were obtained by cooling the tubes and opening them into a vacuum system. The amounts of products, starting materials etc. were estimated from the v.p.c. trace (see Table 1, Chap. 5).

The Reaction of Pentafluoropyridine with Hexafluoropropene in the presence of Anhydrous Caesium Fluoride as Initiator. Pentafluoropyridine (3·0 g., 17·75 m.moles), anhydrous caesium fluoride (3·0 g., 19·7 m.moles) were placed into a Carius tube and hexafluoropropene (5·0 g., 33·3 m.moles) was condensed into it. The tube was evacuated, sealed and heated at a temperature of 130° for 12 hrs. The tube was cooled, opened into a vacuum system and the volatile components collected (8·1 g.). Examination by v.p.c. showed that perfluoro-(4-isopropylpyridine), 4·4 g., (99% yield based on the pentafluoropyridine that had reacted), pentafluoropyridine, 0·69 g., and low boiling components 2·95 g., were present.

The Reaction of Perfluoro-(4-isopropylpyridine) with Sodium Methoxide. To a stirred solution of perfluoro-(4-isopropylpyridine), (2·512 g., 7·847 m.mole) dissolved in methanol (20 ml.), was added a solution of sodium (0·168 g.) in methanol (20 ccs.) over a period of 15 minutes at room temperature. The reaction mixture was stirred for a further 30 minutes, heated under reflux for 1 hr., then poured into water and the aqueous mixture extracted with methylene chloride. The combined extracts were dried ($MgSO_4$), and the solvent distilled to leave a pale yellow coloured oil. Distillation of this oil gave 2-methoxy-4-perfluoroisopropyl-3,5,6-trifluoropyridine, (2·1 g., 80%), b.p. 170°/760 mm. (Found: C, 32·9; H, 0·96. $C_9NF_{10}H_3O$ requires

C, 32·6; H, 0·90%) (i.r. spectrum No. 22). Its structure was shown by its ^{19}F n.m.r. spectrum - see appendix 2).

The Reaction of Perfluoro-(4-isopropylpyridine) with Hexafluoropropene using Caesium Fluoride and Sulpholane as Initiator - Solvent System.

Perfluoro-(4-isopropylpyridine) (3·0 g., 9·40 m.moles) anhydrous caesium fluoride (3·0 g., 19·70 m.moles), sulpholane (15 ml.) were placed into a Carius tube (100 ml.) into which was then condensed hexafluoropropene (6·0 g., 40·0 m.moles). The tube was evacuated, sealed, and heated at a temperature of 200° for 20 hr. After cooling the tube was opened into a vacuum system, and the volatile components (6·3 g.) collected by vacuum transfer. Examination of the product by analytical scale v.p.c. showed the presence of perfluoro-(4-isopropyl-pyridine), perfluoro-(2,4-di-isopropylpyridine), and a low boiling fraction, consisting of olefin dimers in the ratio 19:23:57. This represents a yield of 2,4-di-isopropyl derivative of 54% based on perfluoro-(4-isopropylpyridine) that had reacted.

The Reaction of Octafluorotoluene with Hexafluoropropene using Potassium Fluoride and Sulpholane as Initiator - Solvent System.

a) Octafluorotoluene (4·6 g., 19·4 m.moles), anhydrous potassium fluoride (3·0 g., 50·8 m.moles), sulpholane (15 ml.) were placed in to a Carius tube (100 ml.) and hexafluoropropene (4·5 g., 30·0 m.moles)

was condensed into the tube which was evacuated and sealed. The tube was heated at 150° for a period of 12 hrs., allowed to cool and opened into a vacuum system. The transferred material (7 g.) was examined by v.p.c. (silicone elastomer on Celite) and shown to consist of a low boiling fraction, octafluorotoluene and product in the ratio 4:5:6. The product was separated by preparative scale v.p.c. and shown to be perfluoro-(4-isopropyltoluene) b.p. 148/150° (Found: C, 31·0; F, 68·4. $C_{10}F_{14}$ requires C, 31·0; F, 68·9%) (i.r. spectrum No.23). The yield was 52·6% based on the octafluorotoluene that had reacted. The structure was shown by ^{19}F n.m.r. spectroscopy (see appendix 2).

b) Octafluorotoluene (4·6 g., 19·4 m.moles) anhydrous potassium fluoride (5·0 g., 84·7 m.moles) sulpholane (20 ml.) were placed into a Carius tube (100 ml.) and hexafluoropropene (8·0 g., 53·3 m.moles) was condensed into the tube, which was then evacuated, sealed and heated at a temperature of 175° for a period of 20 hr. The tube was cooled, opened into a vacuum system and the transferred material (6·3 g.) examined by v.p.c. This showed the presence of a low boiling material, octafluorotoluene and perfluoro-(4-isopropyltoluene) in the ratio 5:2:4. This represent a yield of 42% based on the octafluorotoluene that had reacted.

c) Octafluorotoluene (4·6 g., 19·4 m.moles) anhydrous caesium fluoride (8·0 g., 52·6 m.moles) sulpholane (15 ml.) were placed into a Carius tube (100 ml.) into which was condensed hexafluoropropene

(4·5 g., 30·0 m.moles). The tube was evacuated, sealed and shaken on a vibroshaker for a period of 12 hr. at room temperature. After this time the tube was opened into a vacuum system, and the transferred material (5·1 g.) by v.p.c. This showed that very little reaction had taken place.

d) Octafluorotoluene (4·6 g., 19·4 m.moles) anhydrous potassium fluoride (3·0 g., 50·8 m.moles), triglyme (15 ml.) were placed into a Carius tube and hexafluoropropene (4·5 g., 30·0 m.moles) was condensed into the tube, which was then evacuated and sealed. The tube was then heated at a temperature of 170° for a period of 18 hr., allowed to cool and opened into a vacuum system. The transferred material was examined by v.p.c. which showed that only about 5% reaction had occurred.

<u>The Reaction of Methylpentafluorobenzoate with Hexafluoropropene using Potassium Fluoride and Sulpholane as Initiator-Solvent System.</u>

Methylpentafluorobenzoate (3·9 g., 17·25 m.moles) anhydrous potassium fluoride (3·0 g., 50·8 m.moles), sulpholane (15 ml.) were placed into a Carius tube (100 ml.) and hexafluoropropene (5·0 g., 33·3 m.moles) was condensed into the tube. The tube was evacuated, sealed and heated at a temperature of 140° for 12 hr. After this time the tube was cooled, opened and the contents washed out with water. The aqueous mixture was extracted with ether and the combined extracts washed well with water, dried ($MgSO_4$) and the solvent removed by distillation.

The residue (5·5 g.) was examined by v.p.c. (silicone elastomer on Celite) and shown to consist of low boiling olefin dimers, methyl-pentafluorobenzoate and product in the ratio 4:8:6. The product was separated by preparative scale v.p.c. and shown to be 4-perfluoroisopropyl-2,3,5,6-tetrafluoromethylbenzoate, b.p. 42°/1·0 m. (Found: C, 35·4; H, 0·84; F, 55·6. $C_{11}H_3F_{11}O_2$ requires C, 35·1; H, 0·80; F, 55·6%) (i.r. spectrum No. 24). Its structure was shown by ^{19}F n.m.r. spectroscopy.

The Reaction of Bromopentafluorobenzene with Hexafluoropropene using Potassium Fluoride - Sulpholane as the Initiator - Solvent System.

Bromopentafluorobenzene (3·0 g., 12·2 m.moles), anhydrous potassium fluoride (3·0 g., 50·8 m.moles) sulpholane (15 ml.) were placed into a Carius tube and hexafluoropropene (5·5 g., 36·7 m.moles) was condensed into the tube, which was evacuated, sealed and heated at 140° for 12 hr. After this time the tube was cooled and opened into a vacuum system. Bromopentafluorobenzene was recovered almost quantitatively. The reaction was repeated at 220° but only traces of hexafluorobenzene were recovered along with unreacted bromopentafluorobenzene.

The Reaction of Pentafluorobenzonitrile with Hexafluoropropene.

a) Pentafluorobenzonitrile (4·0 g., 20·7 m.moles), anhydrous potassium fluoride (3·0 g., 50·8 m.moles), sulpholane (15 ml.) were placed into

a Carius tube (100 ml.) and hexafluoropropene (7·0 g., 46·6 m.moles) was condensed into it. The tube was evacuated, sealed and heated for 15 hr. at a temperature of 125°. After this time the tube was cooled, opened and the contents washed out with water. The resulting aqueous mixture was extracted with ether, the combined extracts washed with water, dried ($MgSO_4$) and the solvent removed to leave a pale yellow liquid. This was examined by v.p.c. (di-n-decyl-phthalate) on Celite), and shown to consist of several compounds (including pentafluorobenzonitrile), all having very close retention times (no resolution attainable on a Silicone elastomer column). On standing, the solution deposited a white solid which was filtered and shown to be a single compound (the one with the lowest retention time). This compound m.p. 128-130° (from 60-80° petroleum) contained no -C N absorption in its infrared spectrum and the mass spectrum indicated a high molecular weight (642); however its exact structure remains unknown. Other fractions of crystals were obtained on standing the solution, but these were shown to be mixtures of several components. From the residual solution, a small amount of a compound, shown by infrared, n.m.r., and mass spectrometry to be 4-perfluoro-isopropyl-2,3,5,6-tetrafluorobenzonitrile. A correct elemental analysis was not possible because of the presence of a trace amount of an impurity, which could not be removed.

b) Pentafluorobenzonitrile (6·5 g., 33·6 m.moles), anhydrous potassium fluoride (3·0 g., 50·8 m.moles), sulpholane (15 ml.) were placed into a Carius tube and hexafluoropropene (4·5 g., 30·0 m.moles) was condensed into the tube which was then evacuated, sealed and heated to 90° for a period of 12 hr. The products were obtained as above. Examination by v.p.c. showed that a similar mixture to the above had been obtained, but with more starting material present.

c) Pentafluorobenzonitrile (20·0 g., 103·6 m.moles), sulpholane (30 ml.), and potassium fluoride (4·0 g., 67·8 m.moles) were placed into a flask equipped with a stirrer, condenser and gas inlet system. The flask was heated to 90/100° and a slow stream of hexafluoropropene (10 g., 66·6 m.moles) passed through over a period of 1 hr. The flask was cooled and the reaction mixture worked up as described above. Examination by v.p.c. showed that no reaction had taken place.

d) Pentafluorobenzonitrile (6·5 g., 33·6 m.moles), anhydrous potassium fluoride (3·0 g., 55·9 m.moles), sulpholane (15 ml.) were placed into a Carius tube and hexafluoropropene (4·5 g., 30·0 m.moles) was condensed into the tube. The tube was evacuated, sealed and shaken on a vibroshaker for 14 hrs. at room temperature. After this time the tube was opened and the reaction mixture worked up as above. This gave a mixture (7·3 g.) consisting of a low boiling fraction, pentafluorobenzonitrile, and two products, in the ratios 3:6:3:1 respectively. Separation, by preparative scale v.p.c. gave

4-perfluoroisopropyl-2,3,5,6-tetrafluorobenzonitrile, b.p. 191-192° (Found: C, 34·5. $C_{10}F_{11}N$ requires 35%) (i.r. spectrum No. 25) in 30% yield (based on the amount of pentafluorobenzonitrile that had reacted). The other fraction (higher boiling) was presumed to be higher alkylated products, but was not present in sufficient quantity to permit any reasonable amount to be separated by the above method.

The Reaction of Pentafluoronitrobenzene with Hexafluoropropene.

a) Pentafluoronitrobenzene (4·2 g., 20·48 m.moles) anhydrous potassium fluoride (4·0 g., 74·57 m.moles) and sulpholane (15 ml.) were placed into a Carius tube (100 ml.) and hexafluoropropene (4·5 g., 30·0 m.moles) was condensed into the tube. The tube was evacuated, sealed and heated for 12 hr. at 120°. After this time the tube was cooled and opened into a vacuum system. The volatile components were shown to consist of a blue gas (which turned brown readily on exposure to the air), which was not identified but is evidently some oxide of nitrogen, and a trace of hexafluoropropene (as shown by infrared spectroscopy). The sulpholane solution remaining in the tube was added to water and extracted with ether. The combined extracts were repeatedly washed with water, dried ($MgSO_4$) and the solvent removed by distillation. Examination of the residue by v.p.c. (silicone elastomer on Celite at 100°) showed three major products, two with boiling points higher than the starting material and one with a lower boiling point. These products were separated by preparative scale

v.p.c. to give a) 1-nitro-4-perfluoroisopropyltetrafluorobenzene as a yellow liquid, b.p. 189-190° (Found: C, 29·2; M, 363. $C_9NF_{11}O_2$ requires C, 29·7%; M, 363) (i.r. spectrum No. 26) in approximately 30% yield. b) Perfluoro-(1-nitro-2,4-di-isopropylbenzene) as a crystalline solid (from methanol/water), m.p. 76-77° (Found: C, 28·3; M, 513. $C_{12}NF_{17}O_2$ requires C, 28·0%; M, 513). (i.r. spectrum No. 27) in approximately 30% yield. c) The third component was shown by ^{19}F n.m.r. spectroscopy to be a 50/50 mixture of perfluoro-(1,3-di-isopropylbenzene) and perfluoro-(1,4-di-isopropylbenzene) (see appendix 2). The yield of each of these was between 15 and 20%. They could not be separated because of the identical retention times.

b) Pentafluoronitrobenzene (21 g., 98·60 m.moles), anhydrous potassium fluoride (20 g., 344·8 m.moles), sulpholane (70 ml.), were placed into a rocking autoclave and hexafluoropropene (24·0 g., 160·0 m.moles) was condensed into it. The autoclave was heated at 150° for a period of 13 hr., cooled and the contents worked up as above. This gave a mixture (28 g.) in the ratio of 4:9:4 respectively of a) pentafluoronitrobenzene, b) perfluoroisopropylbenzene, b.p. 128° (Found C, 31·8. C_9F_{12} requires C, 32·1%) in 64% yield (i.r. spectrum No. 28), c) the 1,3- and 1,4-dialkylated products obtained in the reaction above, in 24% yield. Separation of these components was achieved by preparative scale v.p.c.

The Reaction of Chlorotrifluoroethylene with Pentafluoropyridine.

a) Pentafluoropyridine (5·3 g., 31·3 m.moles) anhydrous potassium fluoride (3·0 g., 55·9 m.moles) and sulpholane (15 ml.) were placed into a Carius tube (100 ml.), and chlorotrifluoroethylene (6·0 g., 51·72 m.moles) condensed into the tube which was evacuated and sealed. The tube was heated at 190° for 22 hr., allowed to cool and opened into a vacuum system. By vacuum transfer, and fractionation, ca. 1 g. of chlorotrifluoroethylene and 2 g. pentafluoropyridine was obtained. The sulpholane solution remaining in the tube was washed out with water, extracted with ether, the combined extracts washed well with water, dried ($MgSO_4$) and distilled to leave a dark brown liquid. This was vacuum distilled to give a light brown distillate (3·1 g.), leaving lots of tar behind. The distillate was examined by v.p.c. (silicone elastomer on Celite) and shown to consist of a major and two minor products. The former was separated by preparative scale v.p.c. and shown by ^{19}F n.m.r. spectroscopy and elemental analysis to be 1-chloro-1-tetrafluoropyridyltetrafluoroethane, b.p. 140° (Found: C, 29·8; F, 53·5; Cl, 11·9. C_7NClF_8 requires C, 30·1; F, 53·2; Cl, 12·5%) in 60% yield based upon the amount of pentafluoropyridine that had reacted (i.r. spectrum No. 29).

b) When the above reaction was repeated using a weight for weight replacement of potassium fluoride by caesium fluoride, the major product was 1-chloro-1-tetrafluoropyridylethane in 40%. The

by-products producted in the above reaction were now present in slightly higher proportion and one of these products is probably produced by replacement of chlorine by fluorine to give 4-pentafluoroethyltetrafluoropyridine.

The Reaction of 1,2-difluoro-1,2-dichloroethylene with Pentafluoropyridine.

Pentafluoropyridine (3·7 g., 21·9 m.moles), anhydrous potassium fluoride (5·0 g., 84·7 m.moles) sulpholane (15 ml.) were placed into a Carius tube (100 ml.) and 1,2-dichloro-1,2-difluoroethylene (6·5 g., 48·9 m.moles) was condensed into the tube, which was then evacuated, sealed and heated at 200° for 18 hr. The tube was cooled, opened into a vacuum system and the transferred material (5·8 g.) examined by v.p.c. and shown to consist of a volatile gas, pentafluoropyridine and a product of longer retention time in the ratio of 4:2:1 respectively. This product was separated by v.p.c. and shown to be 2,3,5,6-tetrafluoropyridylperfluoroethane, b.p. 115° (micro) (Found: C, 31·1%; M, 269. C_7NF_9 requires C, 31·2%; M, 269) (i.r. spectrum No. 30). Its structure was shown by ^{19}F n.m.r. spectroscopy (see appendix 2).

The Reaction of 3,5-Dichlorotrifluoropyridine with Hexafluoropropene.

3,5-Dichlorotrifluoropyridine (4·0 g., 19·8 m.moles) anhydrous potassium fluoride (5·0 g., 84·7 m.moles) sulpholane (20 ml.) were placed into a Carius tube (100 ml.) and hexafluoropropene (7·0 g.,

46·7 m.moles) was condensed into the tube, which was then evacuated, sealed, and heated at 130° for 12 hr. After this time the tube was cooled, opened and the contents washed out with water. The aqueous mixture was extracted with ether, the combined extracts washed with water, dried ($MgSO_4$), and distilled to leave a pale yellow liquid (7·3 g.). Examination by v.p.c. (silicone elastomer on Celite) showed the presence of a) a low boiling fraction containing ether and olefin dimers (30%), b) unreacted starting material (30%), c) an inseparable mixture of two compounds (30%), of longer retention time than the starting material, which was separated from the rest of the reaction product by preparative scale v.p.c., and was shown by elemental analysis, mass spectrometry and ^{19}F n.m.r. spectroscopy to consist of 3,5-dichloro-2-perfluoroisopropyl-4,6-difluoropyridine, and 3,5-dichloro-4-isopropyl-2,6-difluoropyridine in approximately equal amounts (Found: C, 27·0; M, 351. $C_8NCl_2F_9$ requires C, 27·3%; M, 351). An inseparable mixture (10%) of compounds of lower retention time than the starting material was present, which was separated from the rest of the reaction mixture by preparative scale v.p.c. This fraction did not analyse correctly for a mixture of compounds of a given molecular formula, but the ^{19}F n.m.r. spectrum showed there was at least three compounds present, and analysis indicated that replacement of chlorine by fluorine had occurred.

The Reaction of 3-Chlorotetrafluoropyridine with Hexafluoropropene. 3-Chlorotetrafluoropyridine (4·0 g., 21·5 m.moles) anhydrous potassium fluoride (3·0 g., 50·8 m.moles), sulpholane (15 ml.) were placed into a Carius tube (100 ml.) and hexafluoropropene (6·0 g., 40·0 m.moles) was condensed into the tube which was then evacuated and sealed. The tube was heated at 120° for a period of 14 hr., cooled, opened and the contents washed out with water. The aqueous mixture was extracted with ether, the combined extracts washed well with water, dried ($MgSO_4$) and the solvent removed by distillation. Examination of the residual liquid (6·7 g.) by v.p.c. (silicone elastomer on Celite) showed the presence of a) a low boiling fraction consisting of olefin dimers (37%), b) unreacted starting material (15%), c) a mixture of lower retention time than the starting material (11%), d) and e) two compounds of longer retention time than the starting material (15% and 22% respectively). Separation of the compounds was achieved by preparative scale v.p.c. Compound d) was shown to be a monoperfluoroisopropyl-3-chlorotrifluoropyridine (Found: C, 28·8; M, 335. C_8NClF_{10} requires C, 28·6%; M, 335), in 24% yield based on the 3-chlorotetrafluoropyridine that had reacted. The structure was not assignable on the basis of the ^{19}F n.m.r. spectrum, but appears to be a single isomer, e) appeared to be disubstituted but the ^{19}F n.m.r. spectrum showed at least two compounds were present. The fraction c) was again an inseparable mixture of compounds probably

resulting from displacement of chlorine in the nucleus by fluorine.

The Reaction of Pentafluoropyridine with Hexafluoropropene at High Pressure. Pentafluoropyridine (4·0 g., 23·66 m.moles), anhydrous potassium fluoride (3·0 g., 50·8 m.moles), sulpholane (15 ml.) were placed into a 50 ml. rocking autoclave and hexafluoropropene (16 g., 100·0 m.moles) was condensed into it. The autoclave was evacuated, closed, and heated at 150° for 17 hr. The initial pressure at this temperature was ca. 500 p.s.i., and the final pressure about 50 p.s.i. The autoclave was cooled and opened and the contents washed out with water. The aqueous mixture was extracted with ether and the combined extracts were washed with water, dried ($MgSO_4$) and the solvent distilled. The liquid residue (7·3 g.) was examined by v.p.c. and shown to consist of solvent, perfluoro-(4-isopropylpyridine), perfluoro-(2,4-di-isopropylpyridine) and perfluoro-(2,4,6-tri-isopropylpyridine), b.p. 190-192° in the ratio 26:26:22:26, corresponding to 25%, 14·5% and 13·7% yields respectively. The latter compound was identified by analysis and mass spectrometry (Found C, 27·14; M, 619. $C_{14}NF_{24}$ requires C, 27·3%; M, 619).

The Reaction of Hexafluoropropene with Perfluoro-(4-isopropyl-pyridine) using Caesium Fluoride and Acetonitrile as Initiator - Solvent System. Perfluoro-(4-isopropylpyridine), (3·0 g., 9·4 m.moles) anhydrous caesium fluoride (3·0 g., 19·8 m.moles), acetonitrile (15 ml.)

were placed into a Carius tube into which was then condensed hexafluoropropene (8·0 g., 50·0 m.moles). The tube was evacuated, sealed and heated for 18 hr. at 180°. After this time the tube was cooled and opened into a vacuum system. Examination of the products (7 g.) by v.p.c. showed the presence of a low boiling fraction (4·60 g.), unreacted perfluoro-(4-isopropylpyridine) (1·54 g.), and perfluoro-(2,4-di-isopropylpyridine (0·84 g.).

The Preparation of the Methyl Ester of Pentafluorobenzene Sulphonic Acid. Sulphuric acid (40 ml. $^{N}/_{1}$) was added to the barium pentafluorobenzoate (12·61 g., 19·98 m.moles) with stirring and after 15 min. the solution was filtered. To the filtrate was added an excess of solid silver carbonate (prepared from 10 g., silver nitrate and excess potassium carbonate) and the suspension obtained stirred for 30 min. After this time the solution was filtered and evaporated to dryness under reduced pressure, to give silver pentafluorobenzenesulphonate as white plates. To this was then added methyl iodide (20 ml.) and an exothermic reaction took place depositing silver iodide. The reaction mixture was filtered and washed with a small quantity of methyl iodide, and the methyl iodide removed from the solution by distillation. This left a yellow solid which was purified by recrystallisation from petroleum ether (b.p. 40-60°) and by sublimation under reduced pressure to give methylpentafluorobenzene sulphonate, m.p. 62-64° (lit.[191] 64°).

Appendix 1

Hückel Molecular Orbital Calculations on Perfluoroisoquinoline.

These calculations were carried out on an Elliot 803 digital computer. The secular determinant was set up by standard methods.[192] Expansion of the secular determinant and the solution of the corresponding polynomial equation was achieved by the use of the library programme 803 M106 (issue 2) which can be found in the 803 Programme Library Vol.3 supplied by Elliot Bros. (London) Ltd. This programme is designed to give the eigenvalues and eigenvectors of a symmetric real matrix. The details with regard to data preparation, data entry, operating and output form are given. The programme itself is supplied in 5-hole Elliot Algol and therefore all the calculations were carried out using this mode. A programme has been written by Dr. D.T. Clark of this department which uses the output tape from M106 with the eigenvalues in ascending order from bonding first to antibonding last, to calculate electron densities, bond orders, π-electron energies etc. The programme is written in 5-hole Elliot Algol and is given below.

```
THIS PROGRAM CALCULATES HUCKEL DELOCALIZATION ENERGIES
CHARGE DENSITIES AND BOND ORDERS'
BEGIN
REAL Z,DE,SUM'
INTEGER C,P,I,J,Q,N,M,K,X,Y'
SWITCH SS := S1'
S1: READ  M,K,X,Y,Z'
```

```
N:=M*(M+3)'
BEGIN
REAL ARRAY EIG(1:N)'
FOR P:=1 STEP 1 UNTIL N DO BEGIN  READ READER(2), EIG(P) END'
I:= M-1
I:= I*(M+3)'
DE:=0'
Q:=0'
PRINT ££L?ENERGY LEVELS ARE IN UNITS OF BETA ?'
FOR J:=0 STEP (M+3) UNTIL I DO BEGIN
EIG(J+2):=EIG(J+2)*10**(SIGN(EIG(J+3)))'
Q:= Q+1
IF EIG(J+2) GR 0.0001 THEN BEGIN PRINT ££L?BONDING ORBITAL ?,
££L? ENERGY?,SAMELINE,£££S16?NUMBER?,££L??,EIG(J+2),£££S8??,Q,
££L?ORBITAL COEFICIENTS?'
FOR C:=0 STEP 1 UNTIL (M-1) DO BEGIN
PRINT£££L??,EIG(J+4+C)'
END'
END
ELSE BEGIN
IF EIG(J+2) LESS -0.0001 THEN BEGIN
PRINT ££L?ANTIBONDING ORBITAL?,
££L?ENERGY?,SAMELINE,£££S16?NUMBER?,££L??,EIG(J+2),£££S8??,Q,
££L?ORBITAL COEFICIENTS?
FOR C:=0 STEP 1 UNTIL (M-1) DO BEGIN
PRINT£££L??,EIG(J+4+C)'
END'
END
ELSE BEGIN
PRINT ££L?NON BONDING ORBITAL?,
££L?ENERGY?,SAMELINE,£££S16?NUMBER?,££L??,EIG(J+2),£££S8??,Q,
££L?ORBITAL COEFICIENTS?'
FOR C:=0 STEP 1 UNTIL (M-1) DO BEGIN
PRINT£££L??,EIG(J+4+C)'
END'
END'
END'
END'
I:= K-1'
I:= I*(M+3)'
FOR J:=0 STEP (M+3) UNTIL I DO BEGIN DE := DE + EIG(J+2)'
END'
DE:= 2*DE -2*X -2*Z*Y'
PRINT£££L?DELOCALIZATION ENERGY IN UNITS OF BETA?,££L??,DE'
FOR Q:=0 STEP 1 UNTIL M-1 DO BEGIN FOR C:=0 STEP 1 UNTIL
```

```
(M-Q-1) DO BEGIN SUM:=0'
P:=Q+1'
I:=C+1+Q'
BEGIN FOR J:=0 STEP 1 UNTIL K-1 DO BEGIN
SUM :=SUM +EIG(Q+4+J*(M+3))*EIG(Q+4+J*(M+3)+C)'
END'
END'
SUM:=2*SUM'
IF C=0 THEN BEGIN
PRINT££L?ELECTRON DENSITY ?,SAMELINE,££S8?NUMBER?,
££L??,SUM,SAMELINE,££S8??,P'
END
ELSE BEGIN
PRINT££L?BOND ORDER?,SAMELINE,££S20?NUMBER?,
££L??,SUM,SAMELINE,££S8??,P,££S2??,I'
END'
END'
END'
END'
GOTO S1'
END'
```

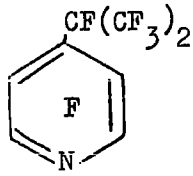
After entering this programme, the output data from M106 is placed in reader 2 and then the number of orbitals M, the number of occupied orbitals N, the number of double bonds in classical structure X, the number of heteroatoms Y, the difference in units of β between the coulomb integral for the heteroatom and carbon, Z, placed in reader 1 and entered by changing the sign of the F_2 function on the operating keyboard. If X, Y and Z are set equal to zero the total π-electron energy will be calculated, which is of use when localisation energies are being calculated. If they are set equal to their respective values then the delocalisation energy is calculated.

Appendix 2

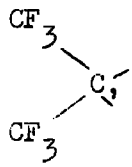
^{19}F n.m.r. Spectra of some Products from Polyhaloalkylation Reactions.

Chemical shift data is relative to hexafluorobenzene as internal reference unless otherwise stated.

Perfluoro-(4-isopropylpyridine).



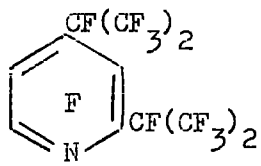
2F and 6F, δ = -76 p.p.m., a broad unresolved multiplet. 3F and 5F, δ = -28 p.p.m., a broad unresolved multiplet, 90/100 c.p.s. wide at half peak height (due to extensive coupling with the perfluoroisopropyl group.



CF_3, δ = -89 p.p.m., $J_{CF_3 \cdot CF}$ = 5 c.p.s., $J_{CF_3 \cdot 3F,5F}$ = 10 c.p.s.

CF-, δ = +16 p.p.m., $J_{CF \cdot 3F,5F}$ = 40 c.p.s.

Perfluoro-(2,4-di-isopropylpyridine).



6F, δ = -80 p.p.m., broad unresolved multiplet.

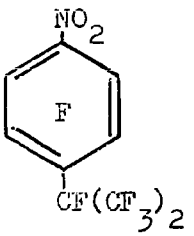
3F and 5F, because of their very broad nature could not be measured accurately. $CF_3>C<CF_3$, Complex band for both groups, centred at -89 p.p.m.

$>CF-$, in position 2, δ = +19·5 p.p.m., $J_{CF.CF_3}$ = 6·5 c.p.s., $J_{CF.3F}$ = 60 c.p.s.

$>CF-$, in position 4, δ = +14·1 p.p.m., $J_{CF.3F,5F}$ = 55 c.p.s.

2-Methoxy-4-heptafluoroisopropyl-3,5,6-trifluoropyridine. This structure was shown by a change of the ^{19}F n.m.r. spectrum from AA'XX' type to one containing only three peaks.

1-Nitro-4-heptafluoroisopropyl-2,3,5,6-tetrafluorobenzene.



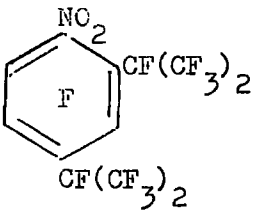
Two aromatic ring fluorine resonances were found at -18·3 p.p.m. and -31 p.p.m.

$CF_3>C<CF_3$, δ = -89 p.p.m., J = 5·2 c.p.s. (doublet) coupling with

$>CF-$, $J_{CF_3.2F,6F}$ = 13 c.p.s.

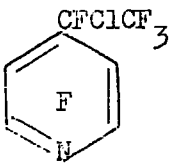
$>CF-$, δ = +14·7 c.p.s.

1-Nitro-2,4-heptafluoroisopropyltrifluorobenzene.



The only peaks measured were the $(CF_3)_2C<$ groups. These occurred at -90 p.p.m., (2-$CF(CF_3)_2$ group) as a doublet of doublets, and at -88 p.p.m., (4-$CF(CF_3)_2$ as a triplet of doublets.

1-Chloro-1-tetrafluoropyridyltetrafluoroethane.



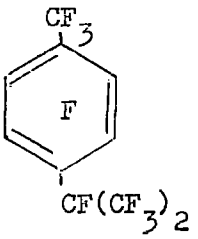
CF_3-, δ = -81 p.p.m., $J_{CF_3 \cdot 3F,5F,CF}$ = 7 c.p.s. (1:3:3:1 quartet).

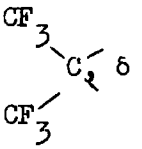
3F and 5F, δ = -28·7 p.p.m.

2F and 6F, δ = -75·6 p.p.m.

-CFCl-, δ = -40 p.p.m., $J_{CF \cdot 3F,5F}$ = 45 c.p.s.

Perfluoro-(4-isopropyltoluene).





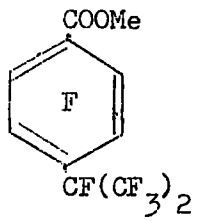
δ = -90 p.p.m.

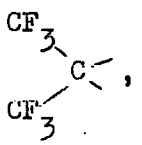
, δ = +14·7 p.p.m.

CF_3-, δ = -107 p.p.m.

Two other unresolved peaks (due to ring fluorines) at -26·5 and -32·4 p.p.m.

4-Heptafluoroisopropyl-2,3,5,6-tetrafluoromethylbenzoate.



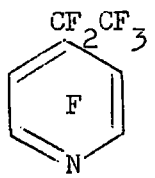


, δ = -82·8 p.p.m.

, δ = +14·5 p.p.m.

Ring fluorines at -39 p.p.m. and -41 p.p.m.

Perfluoro-(4-ethylpyridine).



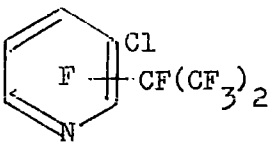
CF_3-, δ = -79 p.p.m.

$-CF_2-$, δ = -25 p.p.m.

3F and 5F, δ = -51 p.p.m.

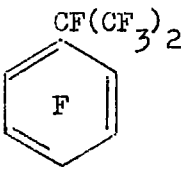
2F and 6F, δ = -76·3 p.p.m.

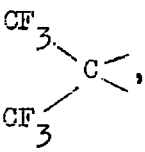
Monoheptafluoroisopropyl-3-chlorotrifluoropyridine.



The peaks in this spectrum were not assignable, and were centred at +12·3 p.p.m., -29·6 p.p.m., -77·4 p.p.m., -89·8 p.p.m., and -96 p.p.m.

Perfluoroisopropylbenzene. (Shifts relative to $CFCCl_3$ as internal reference).





, δ = +82 p.p.m.

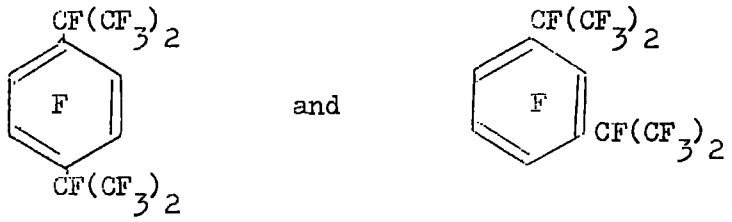
CF-, δ = +188 p.p.m.

4F, δ = 157 p.p.m.

2F and 6F, δ = +144 p.p.m.

3F and 5F, δ = +170 p.p.m.

Mixture of Perfluoro-(1,4-di-isopropylbenzene) and Perfluoro-(1,3-di-isopropylbenzene). (Shifts relative to $CFCl_3$ as internal reference).



CF_3
C<, - a complex peak, due to the groups of both molecules was
CF_3

centred at δ = +90 p.p.m.

>CF-, a complex peak, due to the group in both molecules, was centred at δ = +194 p.p.m. Unassignable ring fluorine atoms were found at δ = +135 p.p.m., 145 p.p.m., 175 p.p.m., and 194 p.p.m.

Infra-red Spectra

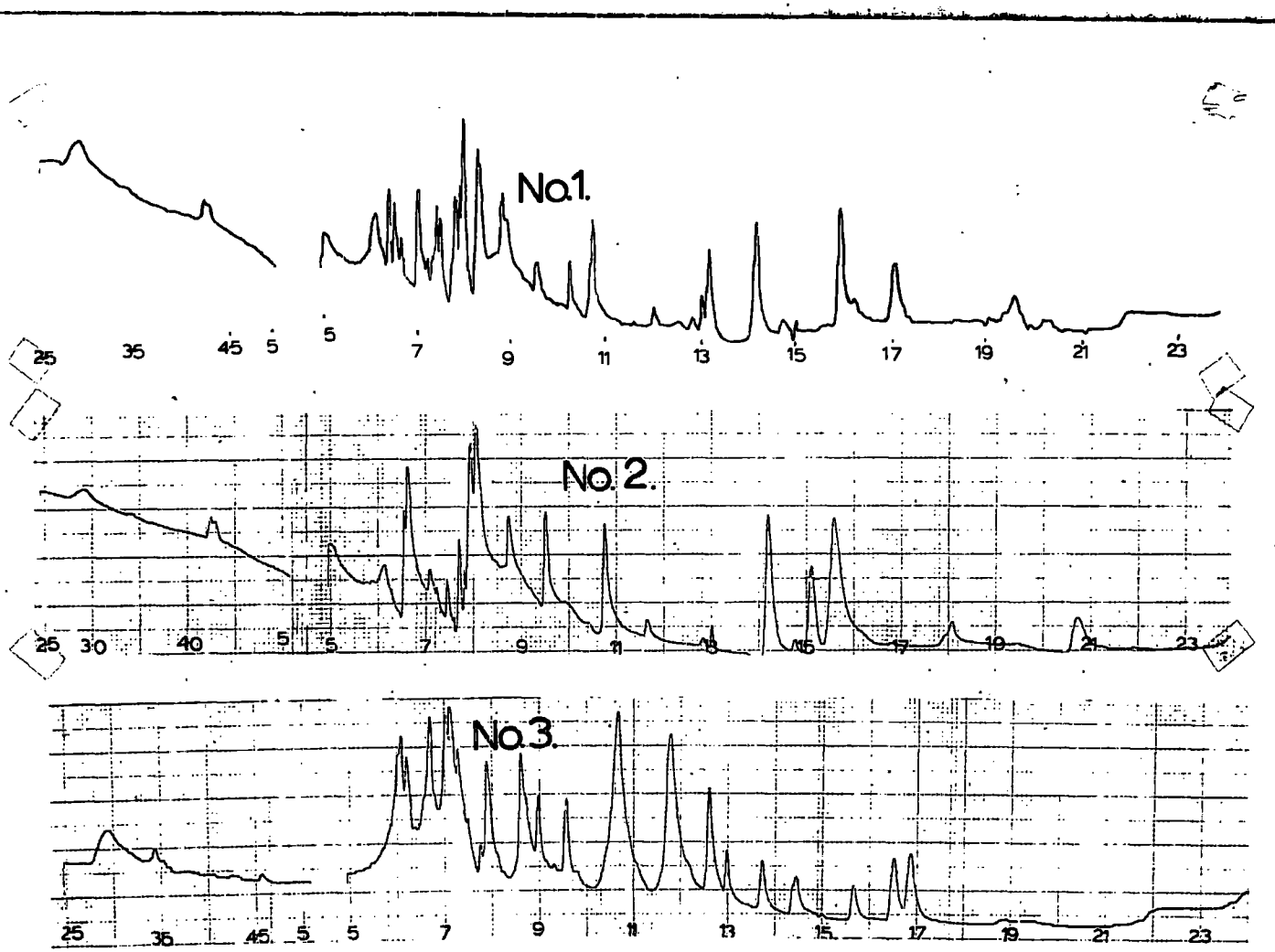
Compound	Number
Hexachloroisoquinoline (s)	1
Heptachloroisoquinoline (s)	2
Heptafluoroisoquinoline (s)	3
4-Chlorohexafluoroisoquinoline (s)	4
1-Methoxyhexafluoroisoquinoline (s)	5
1,6-Dimethoxyhexafluoroisoquinoline (s)	6
1-Aminohexafluoroisoquinoline (s)	7
1-Trifluoroacetylaminohexafluoroisoquinoline (s)	8
1-Hydrazinohexafluoroisoquinoline (s)	9
1-Hydrohexafluoroisoquinoline (l)	10
Trifluoropyridine-3,4-dicarboxylic acid (s)	11
5,6-Difluoro-2-methoxypyridine-3,4-dicarboxylic acid (s)	12
Benzaldehyde-3,4,5,6,7,8-hexafluoroisoquinolylhydrazone(s)	13
1-Amino-6-methoxypentafluoroisoquinoline (s)	14
6-Methoxyhexafluoroisoquinoline (s)	15
1-Butylhexafluoroisoquinoline (l)	16
6-Butylhexafluoroisoquinoline (l)	17
1-Hydroxyhexafluoroisoquinoline (s)	18
N-Methylhexafluoro-1-isoquinolone (s)	19
Perfluoro-(4-isopropylpyridine) (l)	20
Perfluoro-(2,4-di-isopropylpyridine) (l)	21
Perfluoro-(4-isopropyltoluene) (l)	23
4-Perfluoroisopropyl-2,3,5,6-tetrafluoromethylbenzoate(l)	24

Compound	Number
Perfluoro-(4-isopropylbenzonitrile)(l)	25
4-Perfluoroisopropyl-2,3,5,6-tetrafluoronitrobenzene(l)	26
2,4-Perfluoroisopropyl-3,5,6-trifluoronitrobenzene(s)	27
Perfluoro-(isopropylbenzene)(l)	28
1-Chloro-1-tetrafluoropyridylperfluoroethane (l)	29
Perfluoro-(4-ethylpyridine) (l)	30

Key

(s) - Spectrum recorded as a pressed KBr disc.

(l) - Spectrum recorded as a liquid film on a KBr cell.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No.2.
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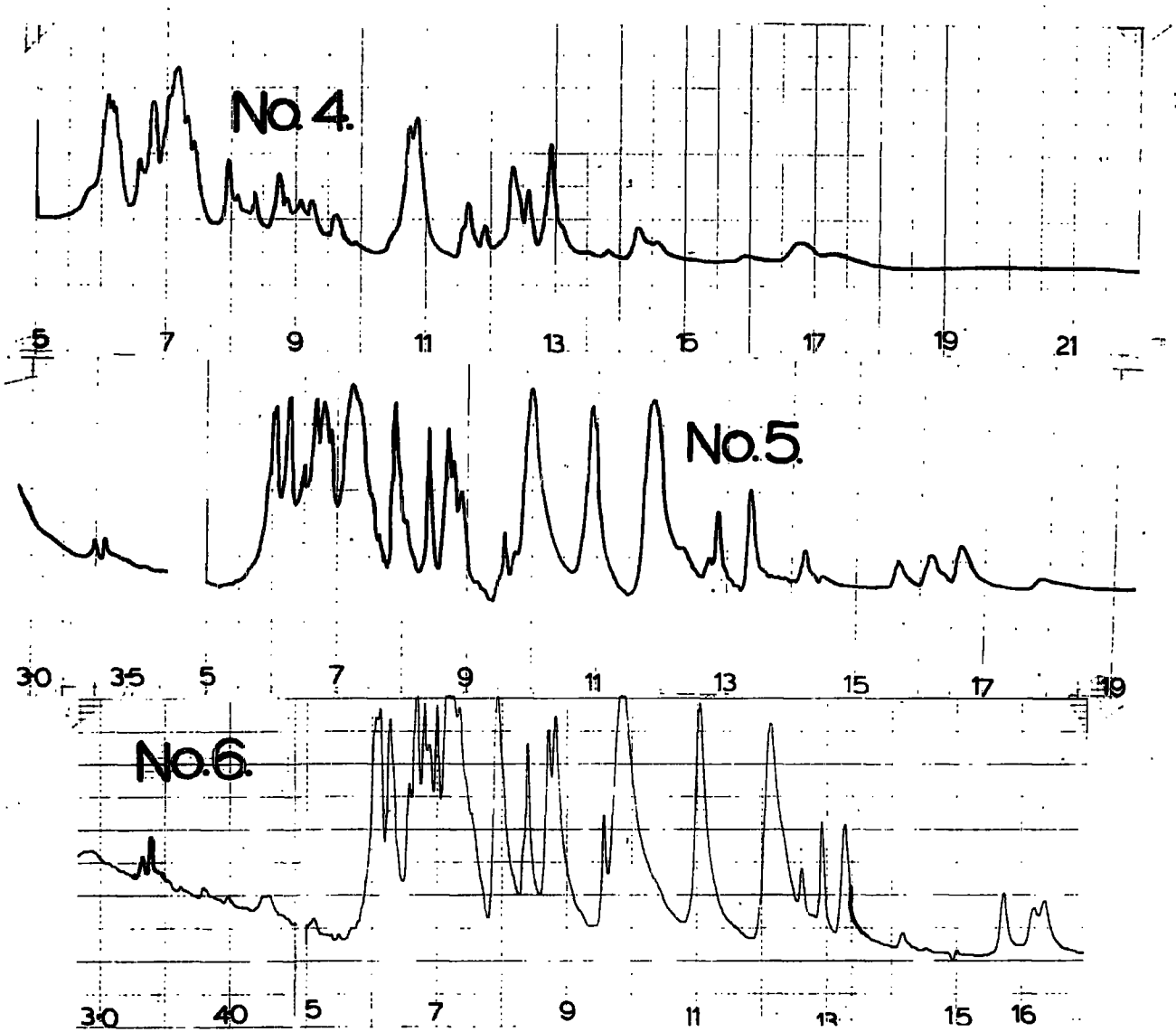
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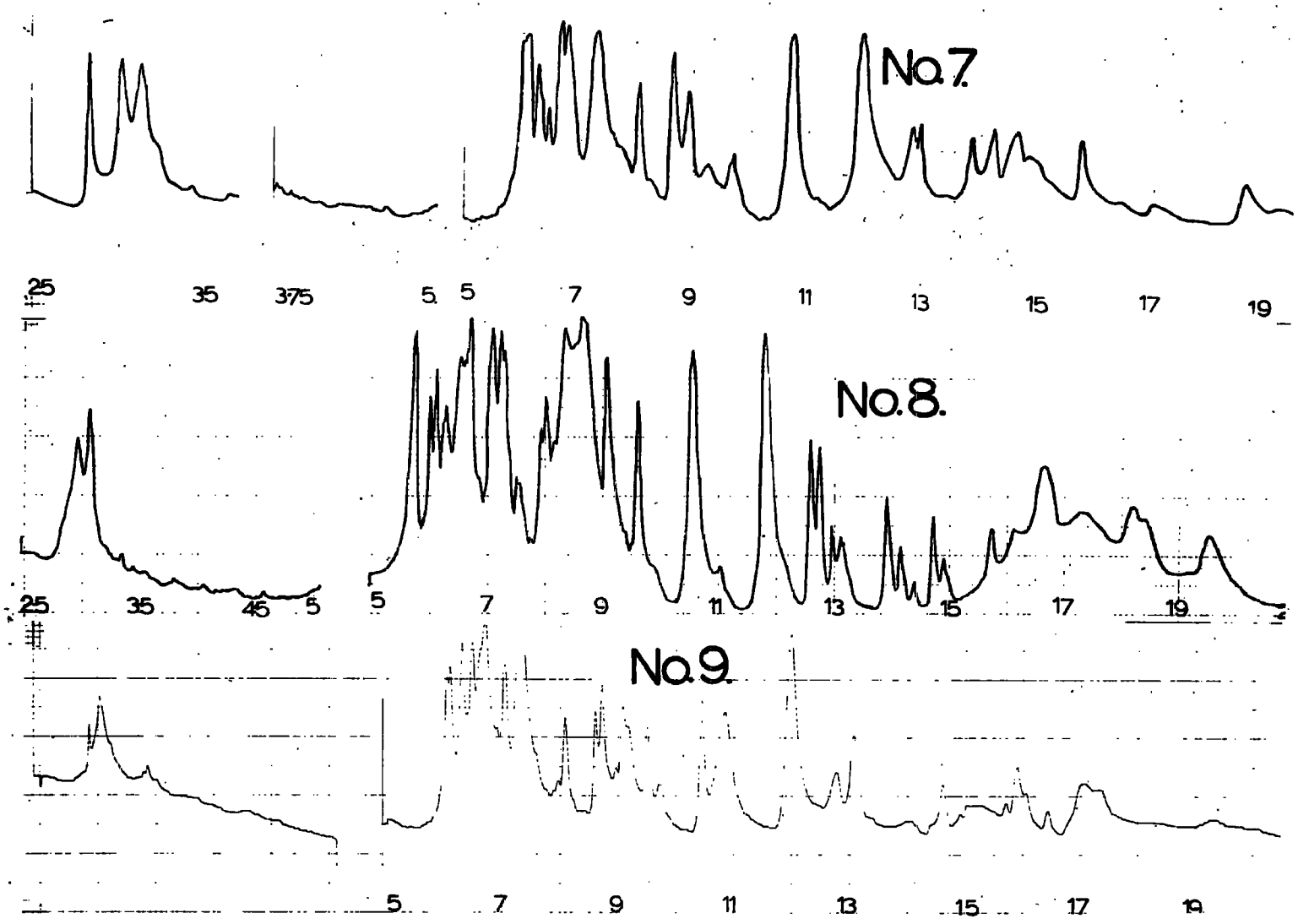
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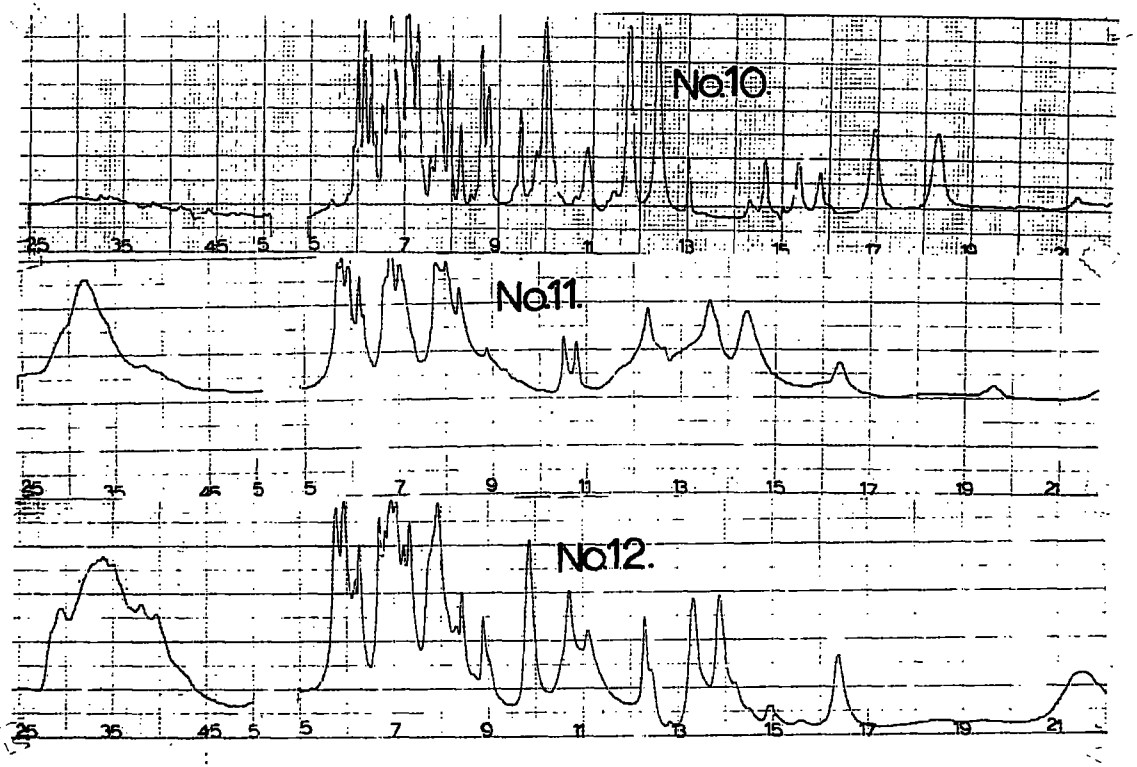
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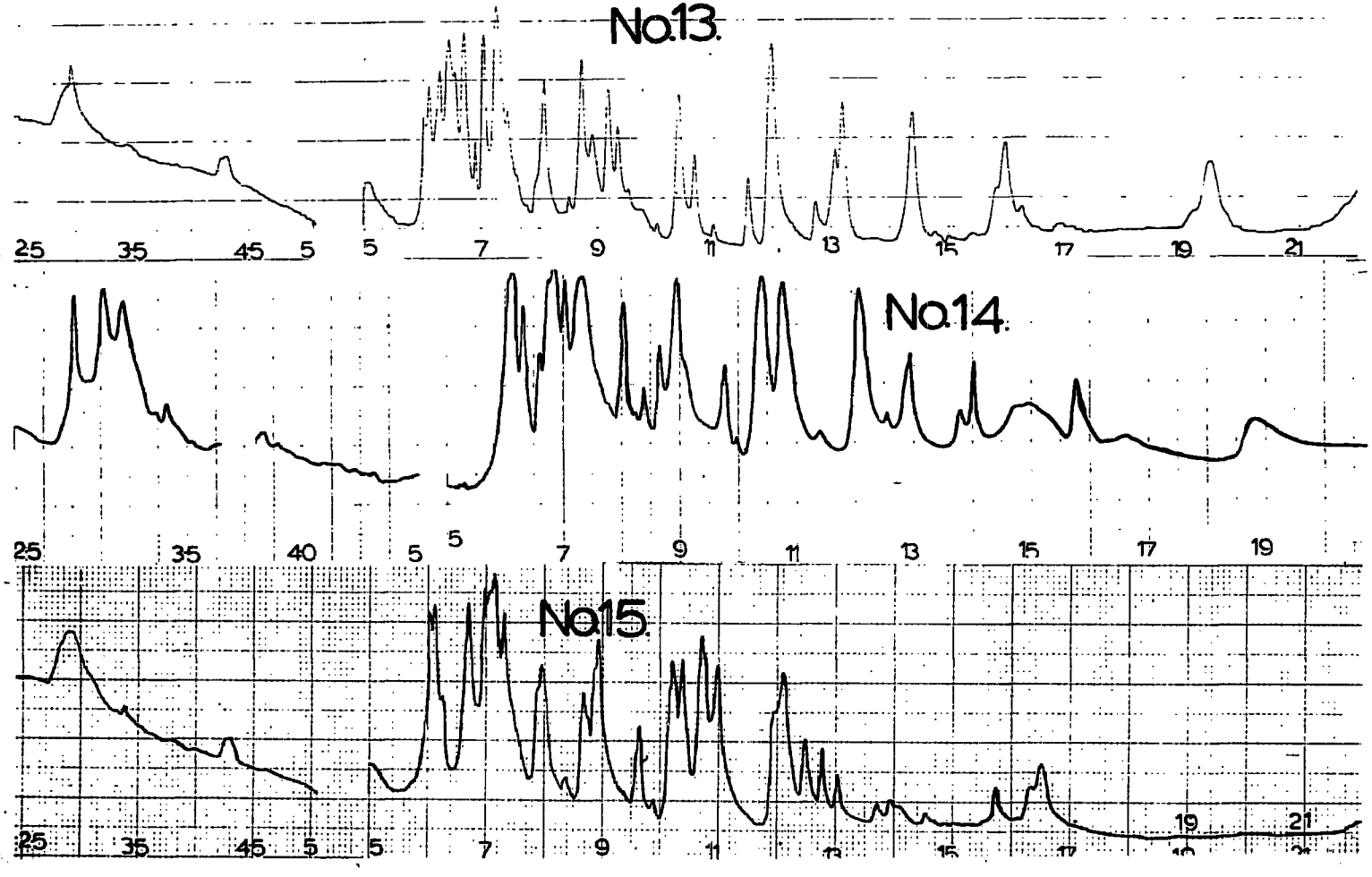
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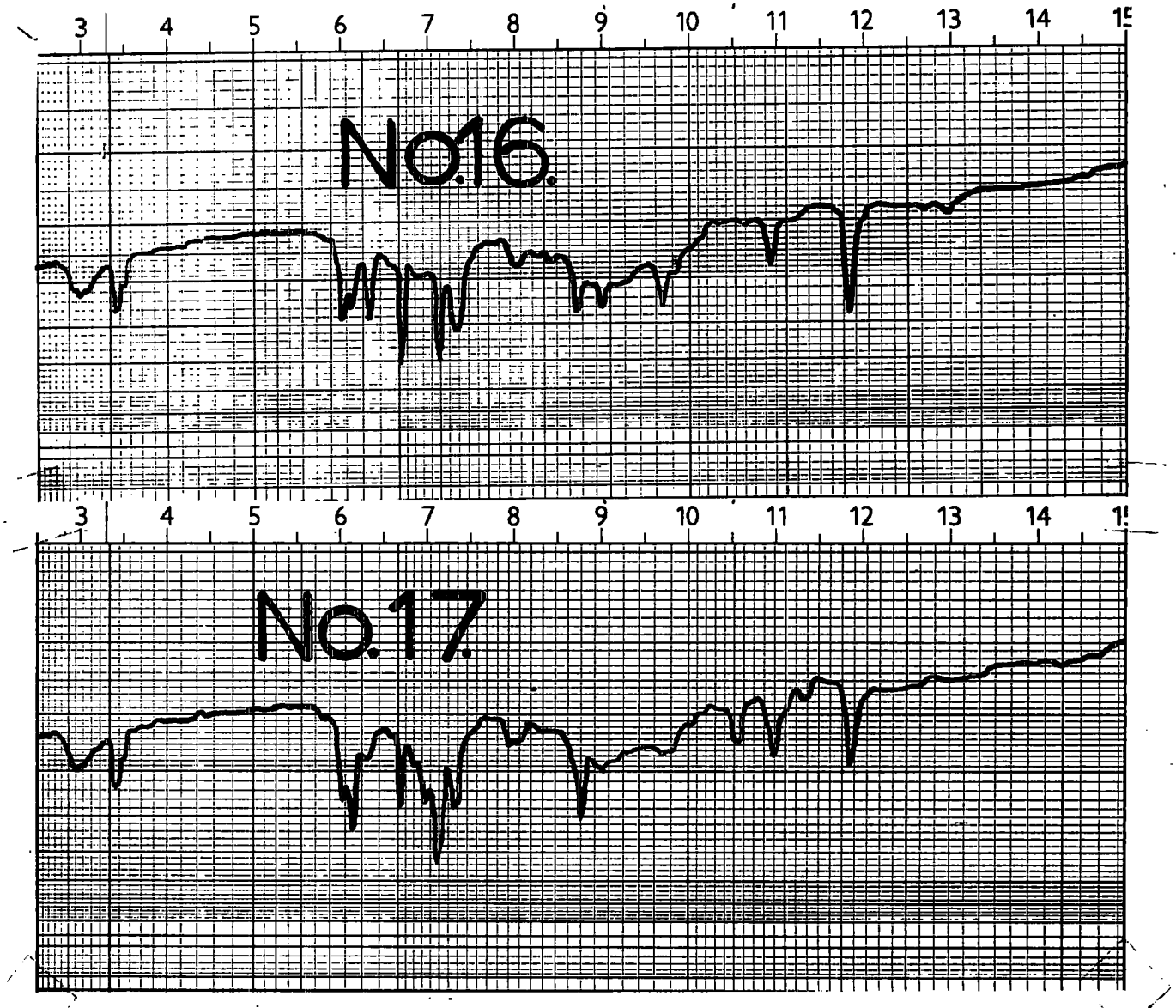
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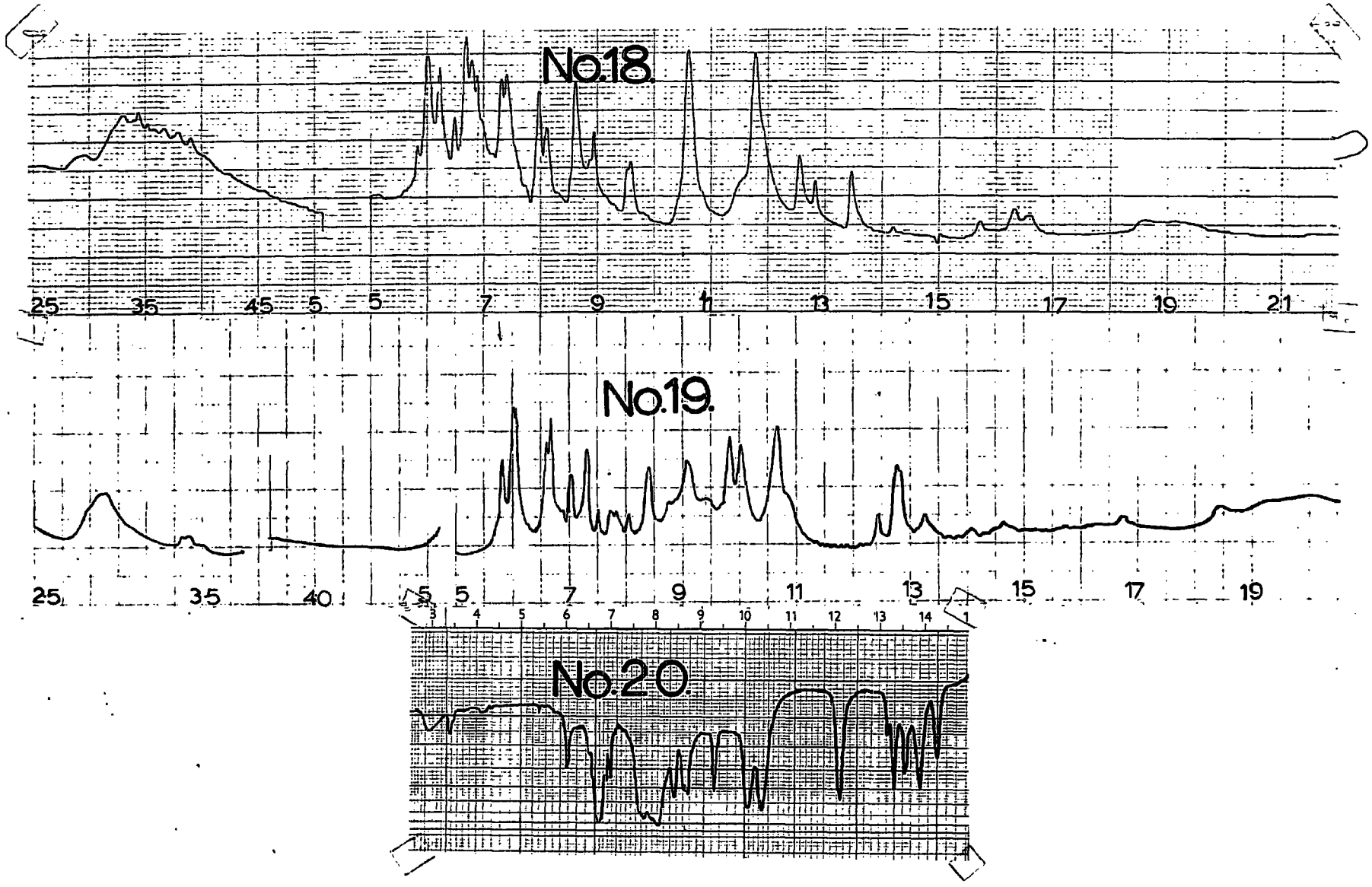
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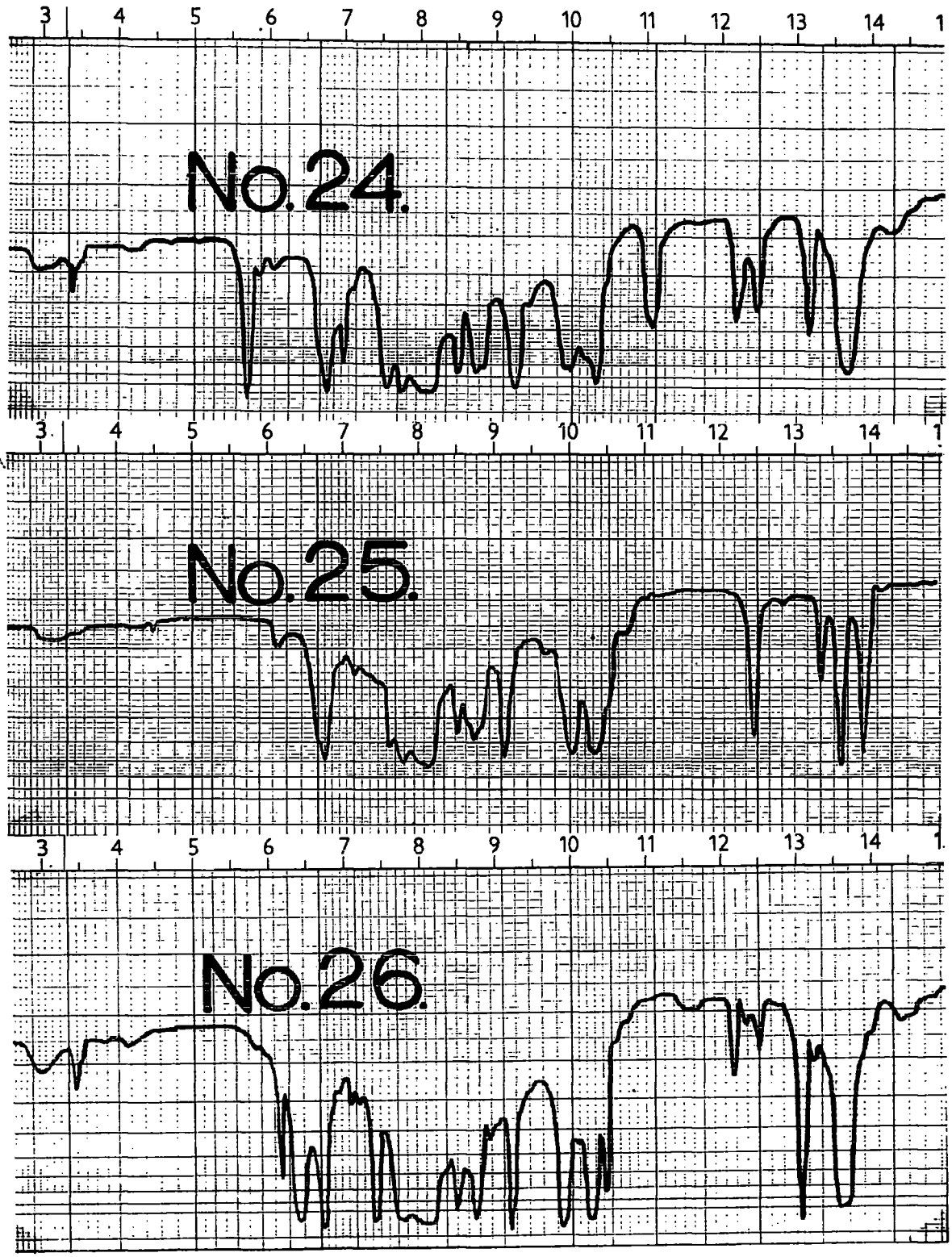
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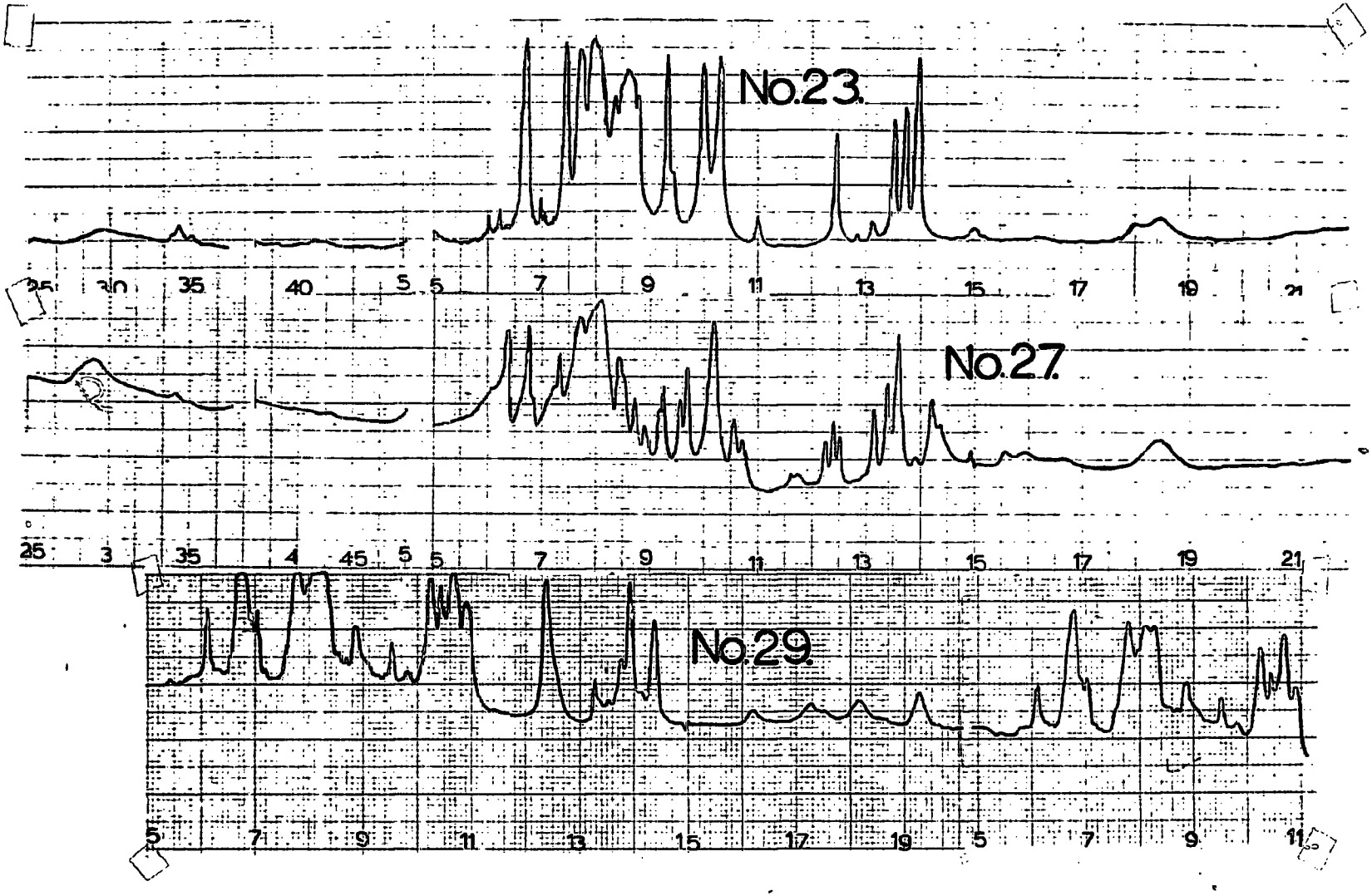
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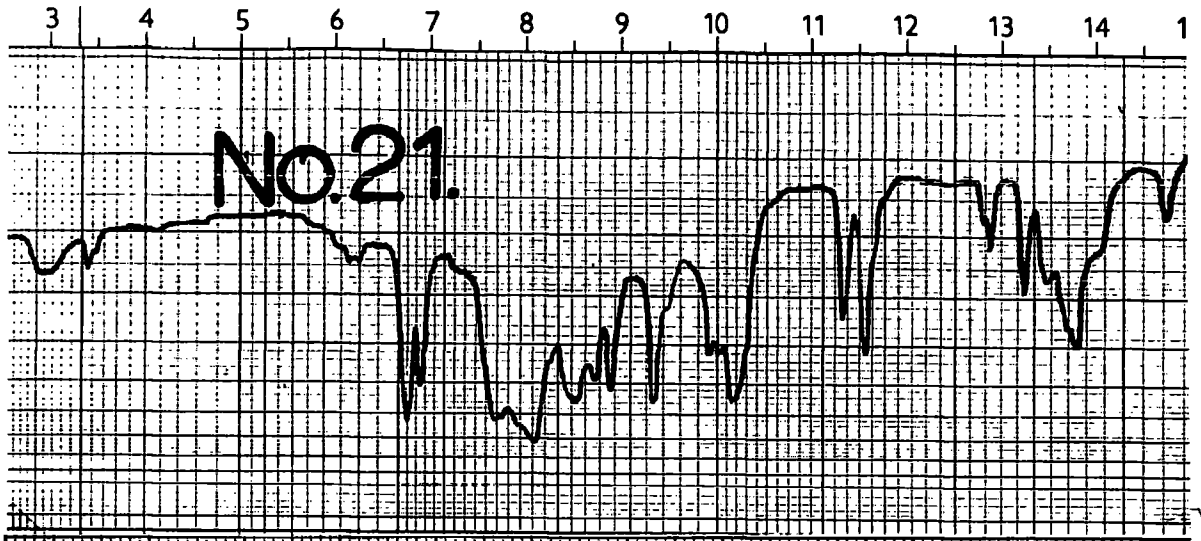
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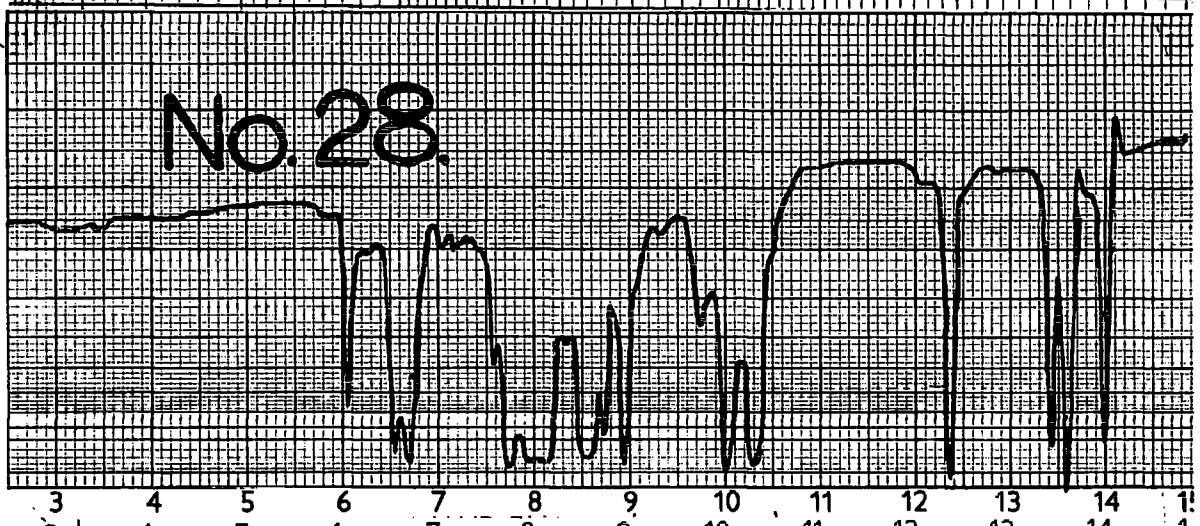
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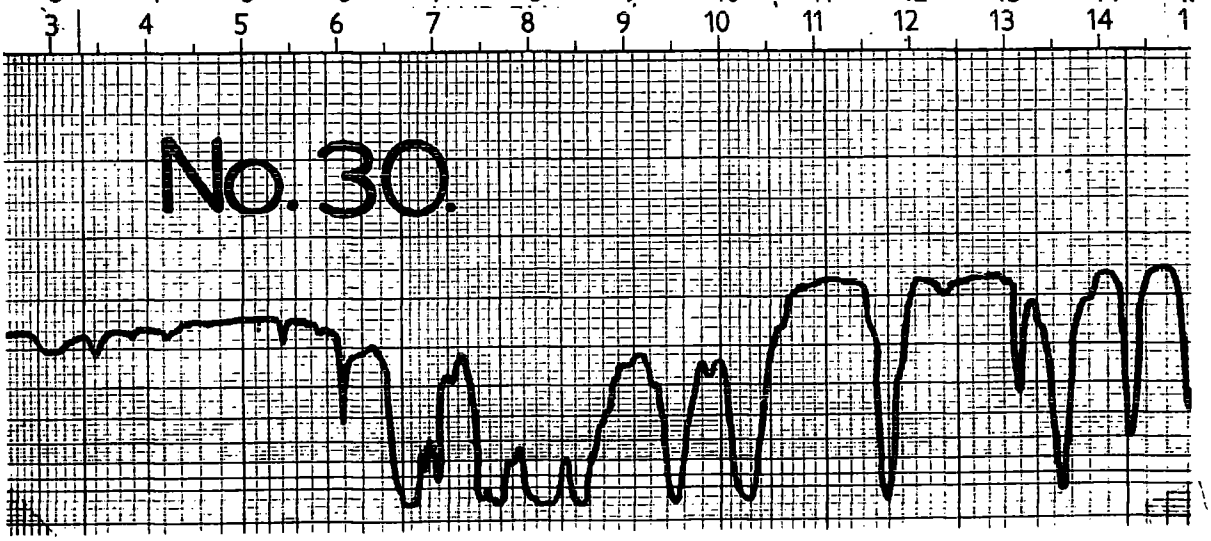
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