Acid induced reactions of polyfluoroaromatic compounds

Thorpe, John Graham

UNIVERSITY OF DURHAM

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ACID INDUCED REACTIONS OF POLYFLUOROAROMATIC COMPOUNDS

Submitted by

JOHN GRAHAM THORPE, B.Sc.

(UNIVERSITY COLLEGE)

A candidate for the degree of Doctor of Philosophy.

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A C K N O W L E D G E M E N T S

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MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1966 and May 1969. 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 been presented by Professor W.K.R. Musgrave at the Symposium on Fluoro-organic Compounds, held by the Fine Chemicals Group of the Society of Chemical Industry at Birmingham, March 1968, and also at the Fifth International Fluorine Symposium, in Moscow, July 1969.

SUMMARY

Acid Induced Reactions of Polyfluoroaromatic Compounds

This work is, in general, concerned with reactions of polyfluoro-N-heterocyclic aromatic compounds, which were previously regarded as exhibiting few basic properties, with acidic reagents. These reactions provide routes to compounds containing potentially functional groups by replacing fluorine with another halogen or hydrogen.

In reactions with hydrogen halides, heptafluoroquinoline reacts readily in sulpholan, giving 2-halohexafluoroquinolines and 2,4-dihalopentafluoroquinolines, whereas, the apparently less basic pentafluoropyridine and heptafluoroisoquinoline, react with difficulty, giving low yields of halo-derivatives. Under the forcing conditions required with pentafluoropyridine polysubstitution occurs, and appreciable quantities of 2,4,6-trihalodifluoropyridines are obtained. Appreciable amounts of water in the sulpholan inhibits these reactions and leads to hydroxy substituted compounds.

These observations may be interpreted in terms of halogen exchange or hydrolysis of the N-protonated heterocyclic compounds. Consequently, when more acidic reagents are used, both pentafluoropyridine and heptafluoroisoquinoline give more facile reactions.

Extension of the investigation to reactions of these polyfluoroheteroaromatic compounds with strong Lewis acids gives a good indication that co-ordination of the ring nitrogen occurs prior to substitution.

These studies have even led to the isolation of crystalline hexafluoroantimonates of some polyfluoroheteroaromatic compounds, and ^{19}F n.m.r. spectroscopic measurements on these salts are in accord with the reactive ring carbon atoms possessing appreciable carbonium ion characteristics.

The orientation of substitution in reactions of these acidic compounds has been determined by ^{19}F n.m.r. spectroscopy.

CONTENTS

General Introduction.

Hydrogen and fluorine both occupy a unique position amongst the elements in respect of their ability to produce extensive systems of organic compounds. Exhaustive replacement of hydrogen in a hydrocarbon by fluorine, producing a fluorocarbon system, can be achieved without serious distortion of the system due to steric effects. Thus $(CF_2\text{-}CF_2)_n$ is quite stable, as, of course, is $(CH_2\text{-}CH_2)_n$, but the corresponding chlorocarbon analogues $(CCl_2\text{-}CCl_2)_n$ where steric interactions between dichloromethylene groups are of some magnitude are unstable and indeed, unknown for large values of n since steric repulsions are sufficient to cause disintegration of the molecule in these cases. Replacement of a fluorine atom in a fluorocarbon by another atom or group leads to a vast number of possible derivatives and the chemistry of these compounds can be studied under conditions which are not dominated by steric effects although the latter may be involved to a minor extent in some cases. However the difference between hydrogen and fluorine creates, in the fluorocarbon derivatives, entirely different electronic environments for functional groups leading to novel properties and reactions which provide a good test for the present theories of chemical reactions.

The differences in chemical behaviour between hydrocarbon systems and fluorocarbon systems is generally such that the two fields of chemistry are complementary. In hydrocarbon chemistry reactions

frequently involve attack by an electrophilic species leading to an intermediate or transition state possessing carbonium ion characteristics, while in fluorocarbon chemistry, the initial step in a reaction is often attack by a nucleophile which leads to an intermediate or transition state having carbanionic character. From this unique opportunity to study two complementary systems of chemistry stems the great interest in fluorocarbon chemistry which has made organic fluorine chemistry such an important field of research in the past twenty years.

It should, however, be mentioned that the study of fluorocarbons is by no means limited to purely academic investigation. As is often the case in chemistry, research leads to not only new or modified theories but also to new materials. This has been the case with fluorocarbon chemistry. There has, therefore, been considerable interest from industry in fluorocarbon chemistry since replacement of hydrogen in a molecule by fluorine tends to promote greater stability within the molecule and often leads to novel physico-chemical properties. Fluorocarbon compounds are now used throughout industry as a basis for polymers and lubricants of high thermal stability. Demand from industry for materials of this type has furnished an invaluable stimulus to fluorocarbon chemistry.

The chemistry of aliphatic and homocyclic aromatic compounds has been extensively investigated but the chemistry of polyfluoroheteroaromatic compounds is of more recent development. The successful

application of the halogen exchange method of fluorination in the preparation of pentafluoropyridine has now been employed in the preparation of several other perfluoroazines and diazines and the chemistry of these compounds is, at present, being developed.

INTRODUCTION

CHAPTER 1

PERFLUOROHETEROAROMATIC COMPOUNDS CONTAINING NITROGEN

Introduction.

Perfluoroheteroaromatic nitrogen compounds have become available for study only within the last five years. Nevertheless, a considerable amount of chemistry has been carried out on these systems. It is the purpose of the first part of this chapter to describe the methods of introducing fluorine into aromatic compounds with particular reference to the preparation of polyfluoroheterocyclic compounds of nitrogen. The second part will deal with the general chemistry of polyfluoroazines, particular emphasis will be placed upon synthetic uses of these compounds and their derivatives.

A

Methods of introducing fluorine into aromatic systems

1. Replacement of functional groups by fluorine.

a) Replacement of the amino group by fluorine.

Amino groups in many aromatic and heteroaromatic compounds can be replaced by fluorine via the Balz-Schiemann reaction which requires the controlled thermal decomposition of a dry aryl diazonium tetrafluoroborate. Aryl diazonium tetrafluoroborates in general

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

are insoluble in water. Therefore they can readily be obtained from aqueous aryl diazonium salt solutions by addition of an excess of

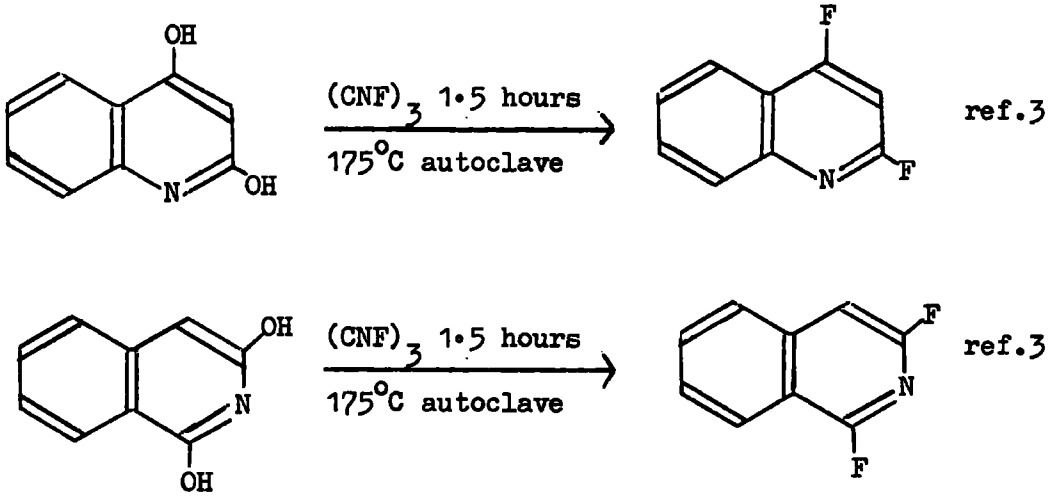
tetrafluoroborate anion. A convenient procedure is the addition of an alkali metal tetrafluoroborate to a solution of diazotised amine. Generally the diazonium tetrafluoroborates are of sufficient stability to permit drying and handling of the dry material without hazard.

A maximum of four fluorine atoms can be introduced into the benzene nucleus by successive nitration, reduction and Schiemann fluorination. Attempts to obtain penta- or hexafluorobenzene by this technique fail,[1] nitration of tetrafluorobenzene gives a difluoro-p-benzoquinone not a nitrotetrafluorobenzene. Because of the well known difficulties in nitration of heterocyclic compounds the procedure does not lend itself to the preparation of heteroaromatic compounds containing several fluorine atoms. Lowly fluorinated heteroaromatic compounds however can often be prepared by the Balz-Schiemann reaction. For instance Bellas and Suschitzky[2] have prepared all but one of the possible monofluoroisoquinolines via the Schiemann reaction. Although the Balz-Schiemann reaction can be used in the preparation of lowly fluorinated aromatic compounds its scope is limited. Difficulties in nitration, particularly in heterocyclic compounds, and the ease with which fluorine is lost from polyfluoro-diazonium ions prevent its use as a method of exhaustive fluorination.

b) Replacement of the hydroxyl group by fluorine.

Hydroxyl groups α or γ to the ring nitrogen of aromatic heterocyclic compounds can be replaced by fluorine on heating with

cyanuric fluoride in an autoclave.[3]



Compounds of this type will generally fluorinate readily under these conditions.

2. Direct fluorination techniques.

a. Fluorination of perchlorobenzene.

Hexafluorobenzene was first prepared by McBee[4,5] and co-workers by fluorination of hexachlorobenzene. Bromine trifluoride and antimony pentafluoride produce chlorobromofluorocyclohexanes which can be dehalogenated with zinc and ethanol giving moderate yields of hexafluorobenzene. A more direct route to hexafluorobenzene is the

$$C_6Cl_6 \xrightarrow{BrF_3} C_6Br_2Cl_4F_6 \xrightarrow{SbF_5} C_6BrCl_4F_7 \xrightarrow{Zn/EtOH} C_6F_6 \quad \text{ref.4}$$

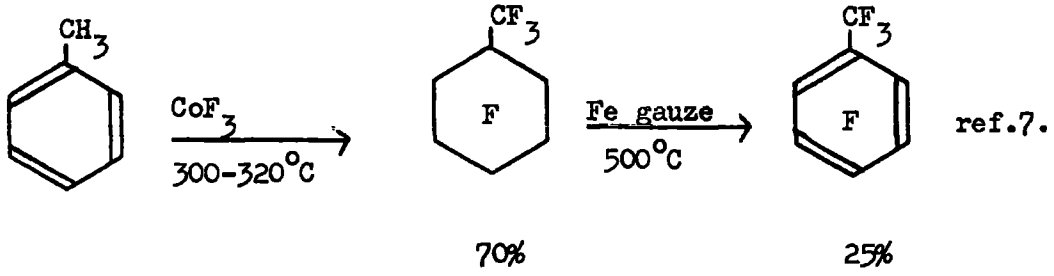
fluorination of perchlorobenzene with elemental fluorine,[6] subsequent dehalogenation of the chlorofluorocyclohexane over hot iron gives

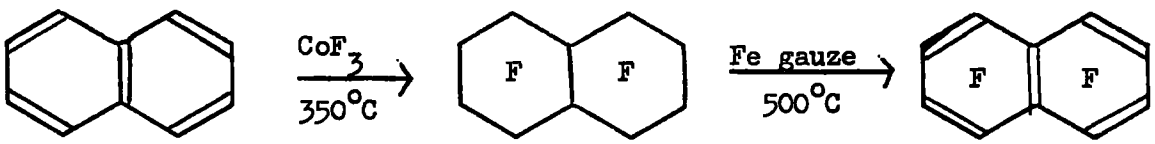
hexafluorobenzene.

$$C_6Cl_6 \xrightarrow{F_2/N_2} C_6Cl_6F_6 \xrightarrow[330^\circ]{Fe} C_6F_6 \quad 22\% \quad \text{ref. 6.}$$

b) Fluorination of the aromatic hydrocarbon.

Workers in Birmingham[7,8] have shown that a viable route to perfluoroaromatic systems is by fluorination of the parent aromatic hydrocarbon with cobalt trifluoride. This yields the corresponding perfluorocyclohexane which can be defluorinated and simultaneously aromatized by treatment with hot metals.



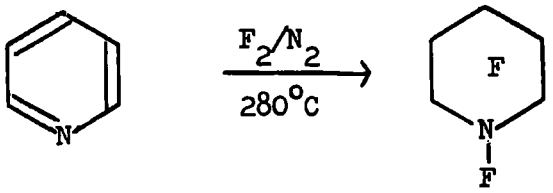


51% ref.7.

Excellent review articles on these methods have been published.[9,10,11,12]

Extension of this method to simple heterocyclic compounds has not provided a viable synthetic route to perfluoroheteroaromatic compounds. Fluorination of heterocyclic compounds by various methods leads to only very low yields of the corresponding saturated perfluoroheterocyclic

compound.[13,14,15]



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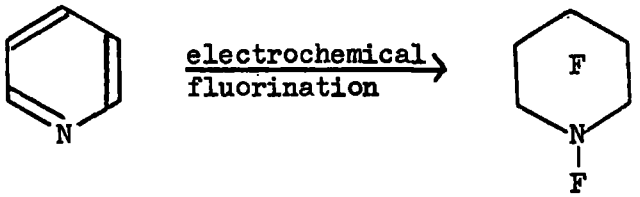

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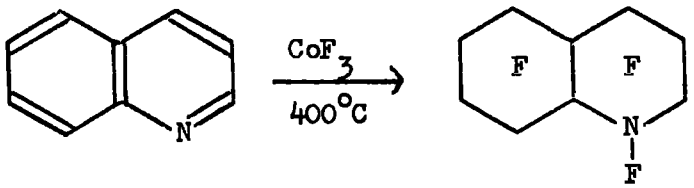
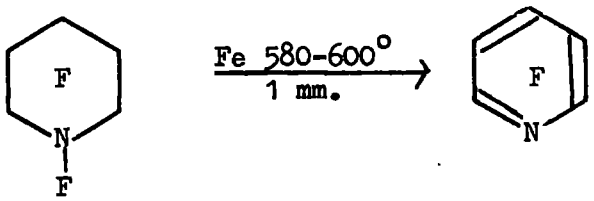


2% ref. 15

The low yields in these reactions appears to be due to extensive fission of the carbon-nitrogen bond on fluorination.[15] The defluorination step in the case of undecafluoropiperidine[16] can be effected only in much lower yield than that of perfluorocyclohexane.



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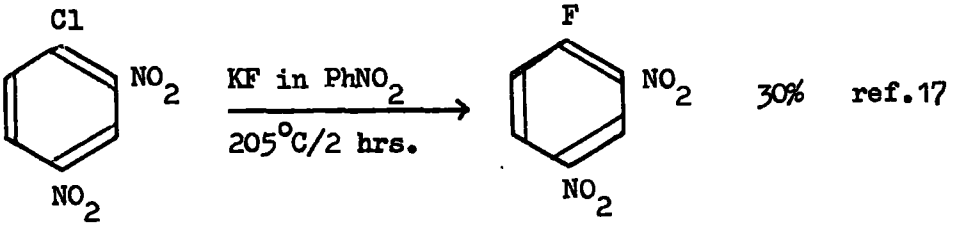
The extremely low overall yields obtained on fluorinating nitrogen heteroaromatic compounds by this method coupled with the relatively high cost of the starting material make the process uneconomic as a source of nitrogen containing heteroaromatic compounds. However, it is an excellent method for the preparation of perfluorinated benzene homologues, in these cases the parent hydrocarbons are more readily available and fluorination can be achieved in appreciably higher yields.

3. The halogen exchange method.

a) Lowly fluorinated aromatic compounds.

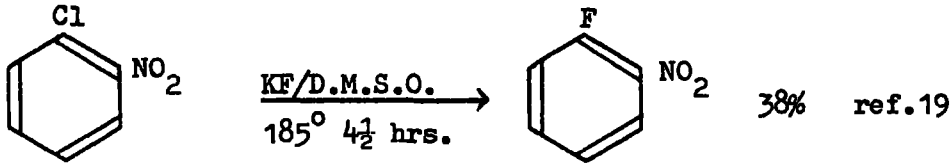
Preparation of a fluoroaromatic compound by halogen exchange between an alkali metal fluoride and a halobenzene was first demonstrated by Gottlieb.[17]



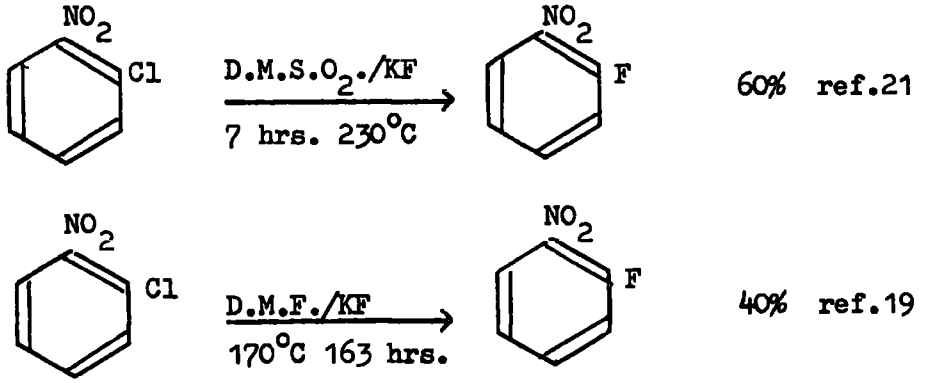
Using nitrobenzene as a solvent the exchange can only be effected on substrates activated by at least two nitro-groups.[18]

However, Finger[19] has shown that a careful choice of solvent permits exchange between potassium fluoride and less activated substrates. Thus, 2-chloronitrobenzene can be reacted with potassium fluoride in dimethyl sulphoxide (D.M.S.O.) or dimethyl formamide

(D.M.F.) giving the corresponding fluoronitrobenzene.



In general fluoroaromatic compounds can be prepared by heating an aryl chloride with anhydrous potassium fluoride in D.M.S.O. or D.M.F. for fourteen hours at 150°C.[20] Some less activated aryl chlorides react sluggishly with potassium fluoride in D.M.F. and, at temperatures required for reaction in D.M.S.O., appreciable quantities of sulphur containing by-products were produced due to solvent decomposition. These difficulties have been surmounted by employing dimethyl sulphone ($D.M.S.O_2.$) as the solvent.[21] Lack of nucleophilic decomposition products from this solvent, coupled with a higher working temperature and hence shorter reaction times make this solvent ideal for reactions involving relatively unreactive substrates.



Hydroxylic solvents[19] such as glycols do not permit exchange and

the presence of water in D.M.F. or D.M.S.O. can lead to reduced yields owing to side reactions of the substrate with water.

Dipolar aprotic solvents such as D.M.F., D.M.S.O. and tetramethylene sulphone (sulpholan) have been discussed extensively by Parker[22,23] who regards these as solvents with high dielectric constants (>15), which, although containing hydrogen atoms, are unable to hydrogen bond strongly with an appropriate species. Examples of such solvents are nitrobenzene, benzonitrile, nitromethane, acetone, dimethylacetamide (D.M.A.C.) and N-methyl-2-pyrrolidone as well as those mentioned previously.

It is suggested that in these solvents anions are less solvated than cations, (due to the inability of dipolar aprotic solvents to hydrogen bond to anions and the diffuse nature of the positive end of the solvent molecule dipole) and that solvation of anions increases with increasing ionic radius. Anion solvation is therefore believed to be increasing in the following order:

$$F^- \ll Cl^-, N_3^- < Br^- < SCN^- < I^-$$

It is maintained that the large solvent molecules cannot fit around small anions as well as around large anions. For halide ions in dipolar aprotic solvents the observed carbon nucleophilicity is:

$$F^- \gg Cl^-, Br^- > I^- > SCN^- \qquad \text{ref. 23}$$

and this has been explained in terms of anionic solvation, the least

solvated nucleophile being the most powerful nucleophile. However, more recent studies[24] suggest that, in D.M.S.O. fluoride ion is indeed more solvated than the other halide ions. Solvation enthalpies of some alkali metal halides in D.M.S.O. are in line with solvation increasing in the order:

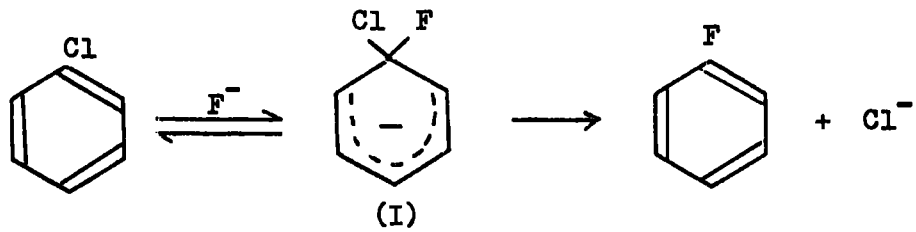
$$I^- < Br^- < Cl^- < F^-$$

Comparison of data[24] for halide ion solvation in D.M.S.O. and in D.M.S.O.-water mixture indicates that the overall level of solvation of halide ions in D.M.S.O. is lower than that in water. For a particular ion the difference in degree of solvation between D.M.S.O. and water is greatest for anions of small size. Because of extreme solvation of the smaller halide ions in protic media their true nucleophilicity is masked. Only in dipolar aprotic solvents does the true reactivity sequence become apparent. Kinetic data[24] from nucleophilic displacement reactions of halide ions with n-propyl tosylate is found to be in agreement with this argument. Clearly more work is required to ascertain the true reason for the enhanced reactivity of fluoride ion in dipolar aprotic solvents.

In contrast to anions, cations are very well solvated in dipolar aprotic solvents.[23] The negative end of the solvent molecule dipole is much less diffuse than the positive end, usually being located on an oxygen atom, thus encouraging solvent-cation interactions. Cation solvation must play an important role in the solubility of electrolytes

in these solvents. In aryl and alkyl nitro-compounds where the negative dipole region is smeared over the nitro-group electrolytes are found to be much less soluble.

An acceptable mechanism[25,26] for the reaction between an aryl halide and potassium fluoride involves rate determining addition of



(I)

fluoride ion to the substrate. The intermediate (I) is considered to be a good approximation to the transition state. Since (I) is large and the charge well delocalised it may be regarded as being solvated to the same degree by both protic and aprotic solvents. The lower solvation of the fluoride ion in dipolar aprotic solvents leads to a reduction of activation energy for the rate determining step and hence a rate increase relative to protic solvents.

Extreme solvation of anions in protic media appears to be due, in the main, to the formation of strong hydrogen bonds from solvent molecules to the negative ions in solution. Parker and Miller[27] have studied the reaction between p-nitro-fluorobenzene and tetraethyl ammonium azide in a series of related solvents, the rate of reaction in a particular solvent was expressed relative to the same reaction in methanol. (Table I).

TABLE I

SOLVENT	RATE $\frac{K_{(SOLVENT)}}{K_{(MeOH)}}$	TEMP.
$NH_2 \cdot CHO$	5·6	100°C
$NHMe \cdot CHO$	15·7	100°C
$N.Me_2 \cdot CHO$	$4·9 \times 10^3$	100°C
$NMe_2 \cdot CHO$	$2·4 \times 10^4$	25·1°C
$NMe_2 \cdot COMe$	$8·8 \times 10^4$	25·1°C
Me_2CO	$2·4 \times 10^4$	25·1°C

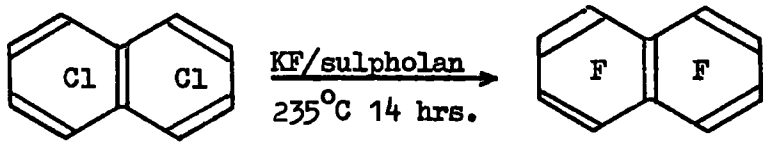
Methanol is a strong hydrogen-bonding solvent, sequential substitution of hydrogen atoms in formamide by methyl groups produces a series of solvents in which hydrogen bonding should become less important. Therefore, the observed trend in the value of $\frac{K_{(solvent)}}{K_{(MeOH)}}$ indicates that the hydrogen bonding property of a solvent is an important factor in determining the efficiency of the solvent to assist halogen exchange reactions.

The rate retarding effect of protic impurities on nucleophilic substitution reactions in dipolar aprotic solvents can be attributed[27] to a general hydrogen bonding of the protic species with the anion and consequent reduction in nucleophilicity of the anion.

b) Highly fluorinated aromatic compounds.

Halogen exchange reactions leading to highly fluorinated aromatic

compounds are possible. Fuller[28] has successfully obtained octafluoronaphthalene from octachloronaphthalene and potassium fluoride in sulpholan.



55% ref.28

Hexachlorobenzene can be reacted with potassium fluoride under various conditions but good yields of hexafluorobenzene cannot be realised. The reaction conditions and results of typical experiments can be seen in Table II.

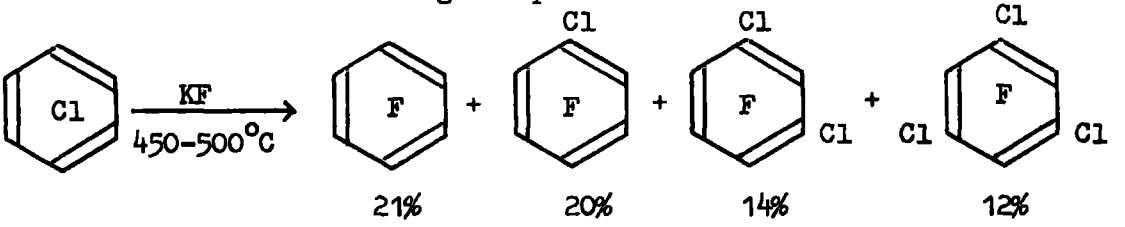
TABLE II (Ref.28)

Reactions between C_6Cl_6 (0·1 mole) and Potassium Fluoride (1·0 mole)

Aprotic Solvent	temp.(°C)	Time (hrs.)	Product (% molar yield)
Benzonitrile	175	18	C_6Cl_6 recovered
Nitrobenzene	193	20	C_6Cl_6 recovered
D.M.F.	153	36	$C_6Cl_3F_3$(51); $C_6Cl_4F_2$(24)
D.M.S.O.	180 - 190	5	C_6ClF_5(0·4); $C_6Cl_2F_4$(3); $C_6Cl_3F_3$(3)
N-methyl Pyrrolidone	195 - 200	3	C_6ClF_5(small); $C_6Cl_2F_4$(34); $C_6Cl_3F_3$(23)
Sulpholan	230 - 240	18	C_6F_6(0·4); C_6ClF_5(25); $C_6Cl_2F_4$(24); $C_6Cl_3F_3$(30)

Clearly sulpholan is the most effective medium and this can be attributed to some extent to a higher working temperature.[28] Complete replacement of all six chlorine atoms in hexachlorobenzene by fluorine using this technique would appear to need temperatures in excess of those possible with solvents.

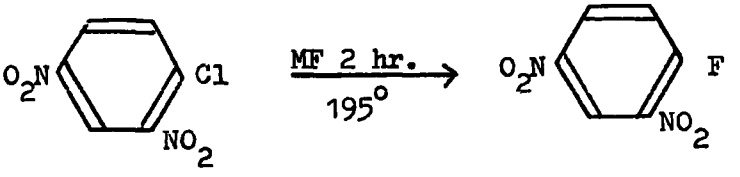
Hexafluorobenzene can be prepared by reaction of potassium fluoride with hexachlorobenzene at high temperatures in the absence of a solvent.[29]



ref. 29

An investigation of the reaction of 2,4-dinitro-1-chlorobenzene with alkali metal fluorides in the absence of solvent showed that lithium and sodium fluorides were inactive under conditions in which caesium, rubidium and potassium fluorides exchanged fluorine for chlorine.[30] (Table III)

TABLE III

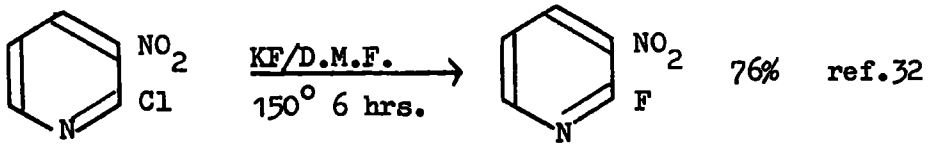


M	Yield (%)
Li	-
Na	-
K	51
Rb	88
Cs	98

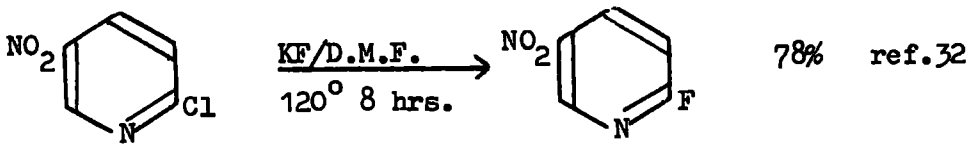
The reactivity order: CsF > RbF > KF >> NaF, LiF which has been observed in other exchange reactions,[19,30] is in the reverse order of lattice energy magnitude. In view of this Vorozhtsov and Yakobson[30] have suggested that reactions in the absence of solvent probably take place in the molten organic compound and the reaction involves either fluoride ion or alkali metal fluoride ion pairs. Thus the efficiency of the fluorinating agent will depend upon its solubility and hence the relationship between crystal lattice energy and reactivity.

c) Lowly fluorinated heterocyclic compounds.

Finger and Starr[32] have shown that halogen exchange can be utilised in the preparation of fluoroheterocyclic compounds.

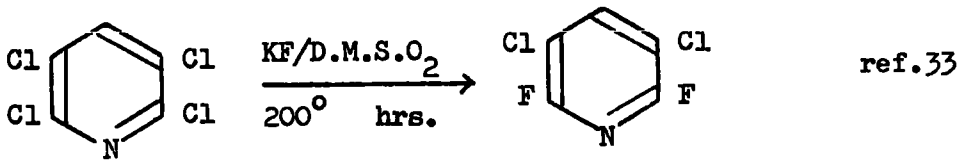


76% ref.32



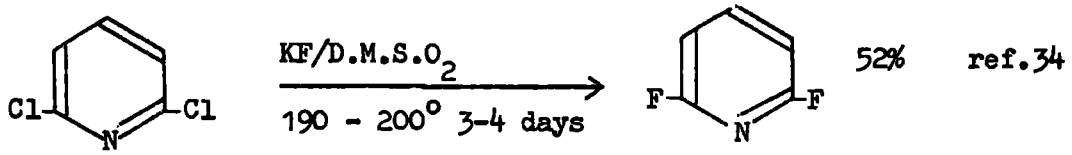
78% ref.32

Halogen α- to the pyridine nitrogen is more susceptible to replacement than that β- to nitrogen.[33]

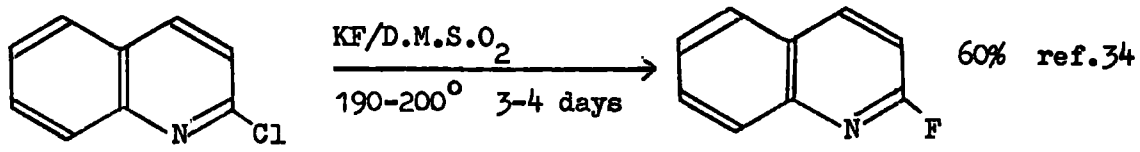


ref.33

Potassium fluoride in D.M.S.O$_2$ can be used to prepare 2,6-difluoropyridine and 2-fluoropyridine from their respective chloro-precursors.[34]



52% ref.34



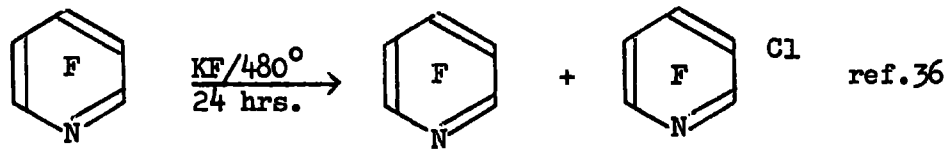
60% ref.34

Surprisingly 2-chloropyridine is reported as singularly unreactive, only 15% yield of 2-fluoropyridine was realised after almost twenty days reaction time with potassium fluoride in D.M.S.O$_2$ at 220°C.[34] On the other hand, Finger and co-workers[33] report yields of 2-fluoropyridine approaching 60% from similar reactions, while Boudakian[35] has prepared 2,6-difluoropyridine in 80% yield by halogen exchange using potassium fluoride in the absence of a solvent.

Because chlorinated heterocyclic compounds are relatively easy to obtain the method of halogen exchange offers a simple and efficient route to fluorinated heterocyclic compounds. The exchange is particularly facile at positions in the heterocyclic ring which are normally susceptible to nucleophilic attack.

d) Perfluoro-N-heteroaromatic compounds.

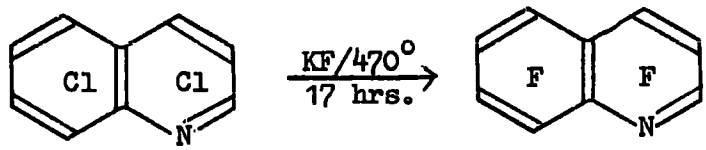
Preparation of pentafluoropyridine firstly by workers in Durham,[36] and shortly afterwards by others in Manchester,[37] by halogen exchange between pentachloropyridine and potassium fluoride in the absence of solvent has indicated a general route to nitrogen containing perfluoroheteroaromatic compounds.



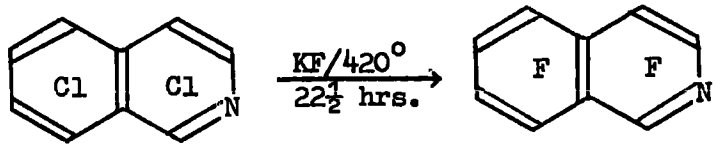
70% 10% ref.36

As is observed with hexachlorobenzene and potassium fluoride in the presence of a solvent (1,A,3,b) pentachloropyridine and potassium fluoride react to give only partially fluorinated compounds in sulpholan[36] or N-methyl-2-pyrrolidone.[37] Again this can be attributed to a lower reaction temperature, low temperature fluorinations in the absence of a solvent also give mixtures of chlorofluoropyridines.[36]

Heptafluoroquinoline and heptafluoroisoquinoline can be made by an analogous route.[38]



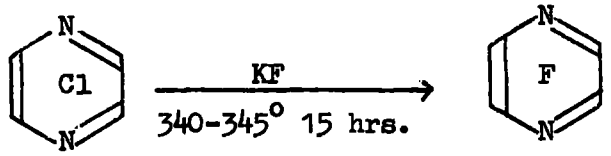
73% ref.38



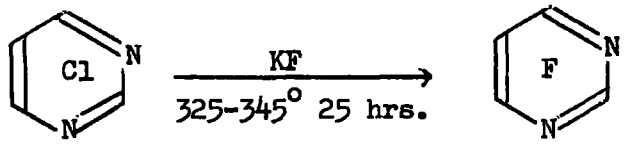
93% ref.38

It is worth noting that the bicyclic systems appear to exchange halogen under milder conditions than pyridine itself. Fuller[28] obtained a similar result in the exchange reactions of hexachlorobenzene and octachloronaphthalene; the latter giving a good yield of octafluoronaphthalene under conditions which did not afford hexafluorobenzene.

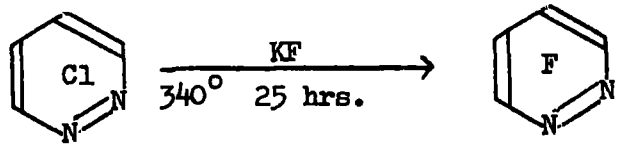
More recently the exchange reaction has been extended to members of the diazine series. The three isomeric perfluoromonocyclic diazines have been prepared[39,40,41] as well as one perfluorobenzodiazine, quinoxaline,[42] from their respective perchlorinated precursors.



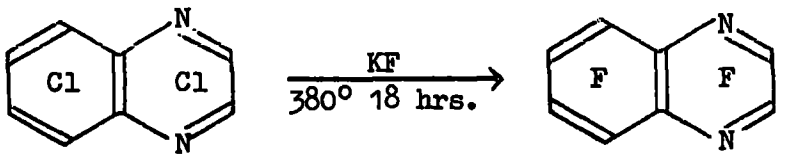
70% ref.39



15% ref.39



60% ref.40,41



50% ref.42

The perchlorodiazines undergo exchange with potassium fluoride under milder conditions than pentachloropyridine which presumably reflects the greater activating power of two aza-groups as compared with one in pyridine.

Halogen exchange between a perchloro-N-heteroaromatic compound and potassium fluoride in the absence of a solvent offers an excellent route to the preparation of perfluoro-N-heteroaromatic compounds subject to the perchloro and perfluoro heterocycles being stable under the reaction conditions. Perchlorination of the heterocyclic compounds can be achieved without undue difficulty and in good yields either by chlorination of the parent heterocyclic compound[36,37] or a suitable derivative[38,39,40,41,42] with phosphorus pentachloride under autogeneous pressure. Fluorination in the absence of a solvent is the preferred method since this allows a higher reaction temperature to be used if necessary, and also facilitates isolation of the products. Perfluoro-N-heteroaromatic compounds are invariably of sufficiently high volatility to permit their isolation from the hot reaction vessel by distillation under reduced pressure obviating the need for tedious and wasteful extraction procedures required when working using solvents.

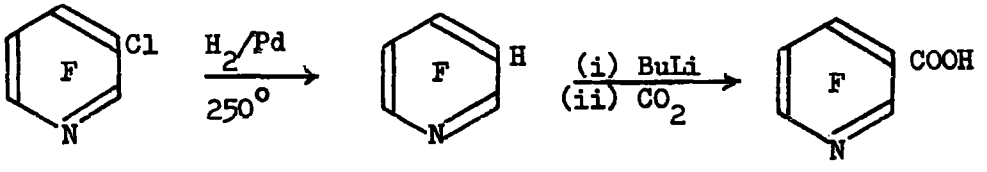
B

Some General Chemistry of Perfluoroheteroaromatic Compounds containing Nitrogen.

1. Pentafluoropyridine and its derivatives.

Pentafluoropyridine is a colourless almost odourless liquid (b.p. 84°C) and is an extremely weak base, for example, no hydrochloride or boron trifluoride co-ordination complex can be isolated.[43,44] A wide variety of nucleophilic substitution reactions leading to polyfluoropyridyl compounds can be carried out and these are summarized in Figure 1.

Both 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine can be obtained by low temperature halogen exchange between potassium fluoride and pentachloropyridine.[36] Nucleophilic displacement of fluorine readily occurs in these compounds[47] but of more importance is their use in synthesising 3-substituted and 3,5-disubstituted polyfluoropyridines, for example,[55,56]



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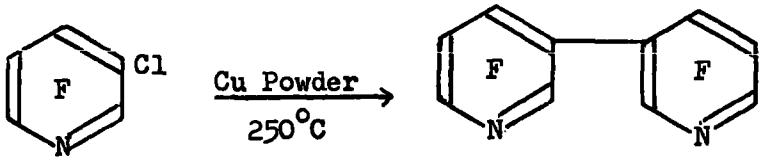
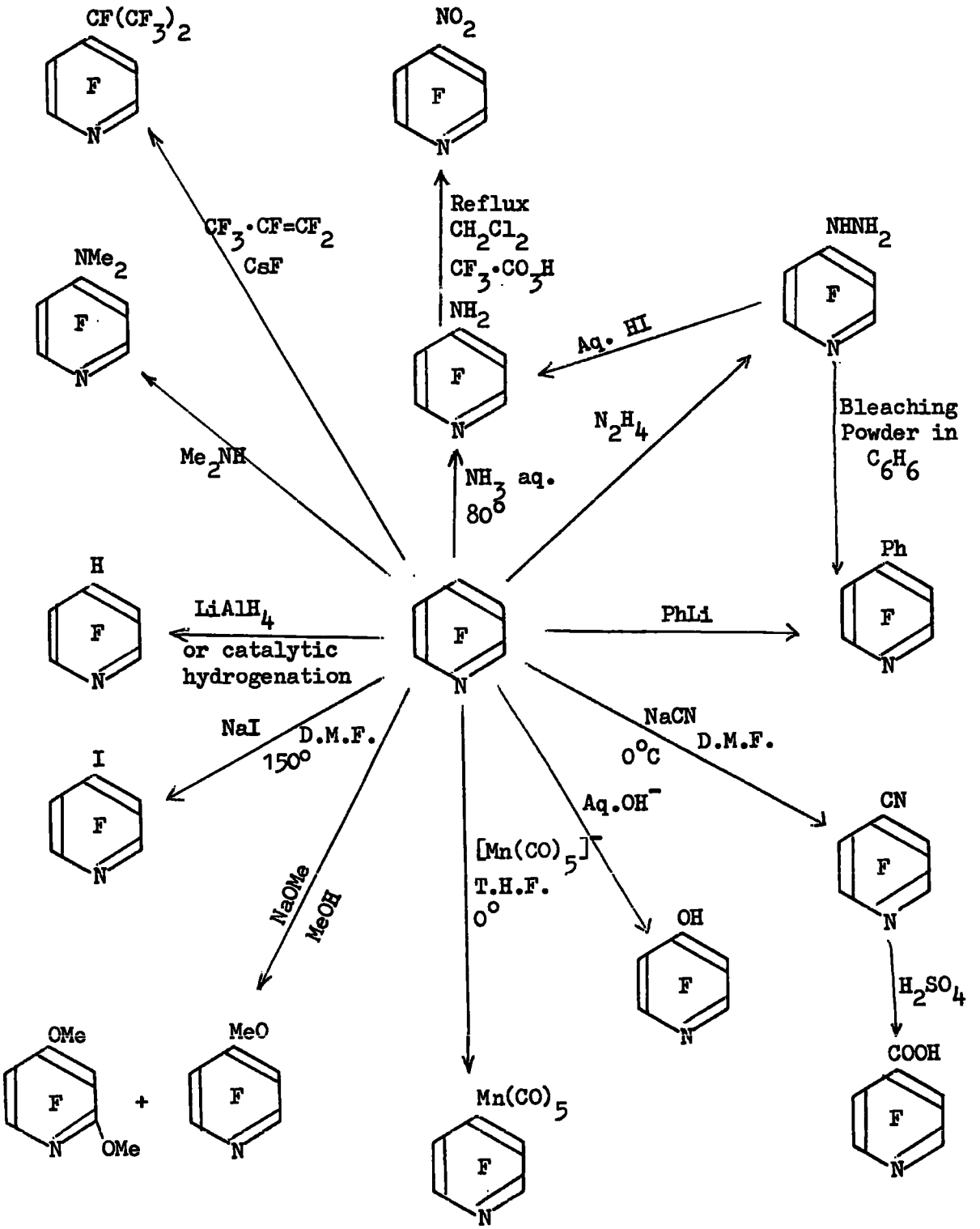


ref.56

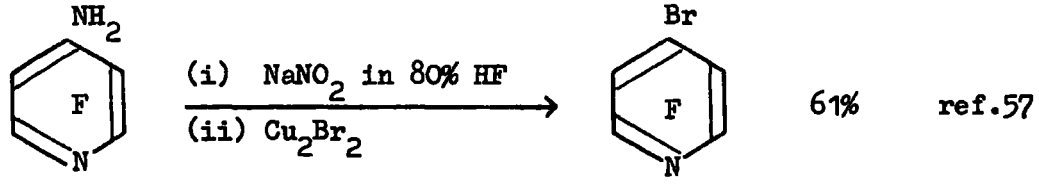
Fig. 1

Some nucleophilic substitution reactions of pentafluoropyridine



Refs. 44 to 55 inclusive.

Modification of the usual Sandmeyer reaction leads to 4-chloro-, and 4-bromotetrafluoropyridine from the readily available 4-aminotetrafluoropyridine. Some chemistry of 4-bromotetrafluoropyridine is



illustrated by Figure 2.

4-Iodotetrafluoropyridine can be made directly from sodium iodide and pentafluoropyridine and its reactions parallel those of 4-bromotetrafluoropyridine.[48]

Alkyl and alkenyl substituted pyridines[36,46,48] are easily available, an outline of the chemistry of these compounds is provided by Figure 3.

Perfluoroalkyl pyridines have recently been prepared utilising a nucleophilic equivalent of the Friedel-Crafts reaction.[50,51] Rearrangement of a perfluoroalkylpyridine under the influence of fluoride ion has been observed.[51]

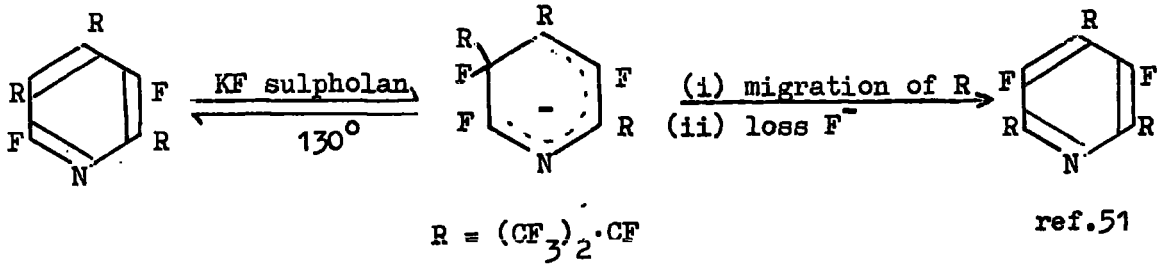
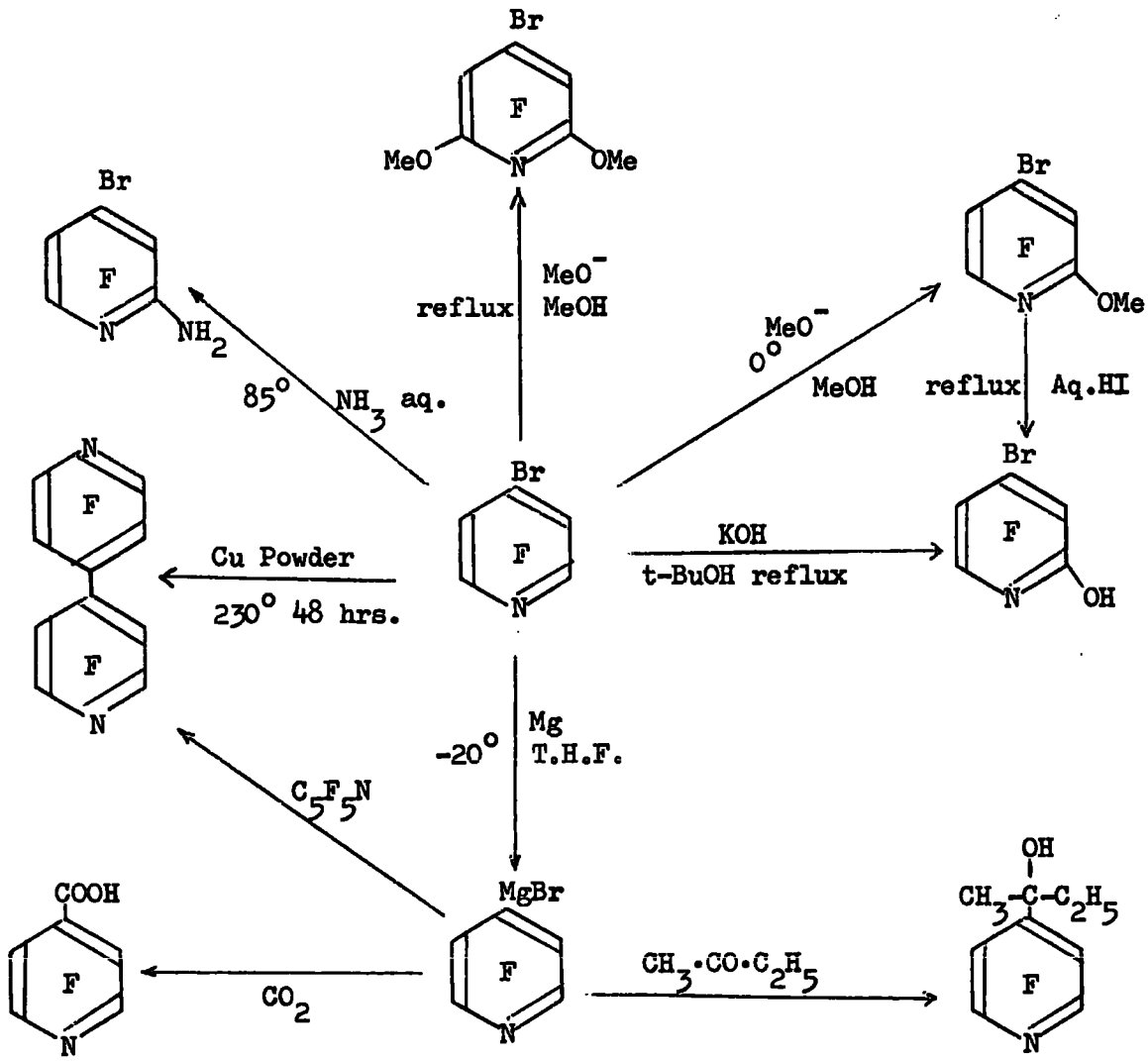


Fig. 2.

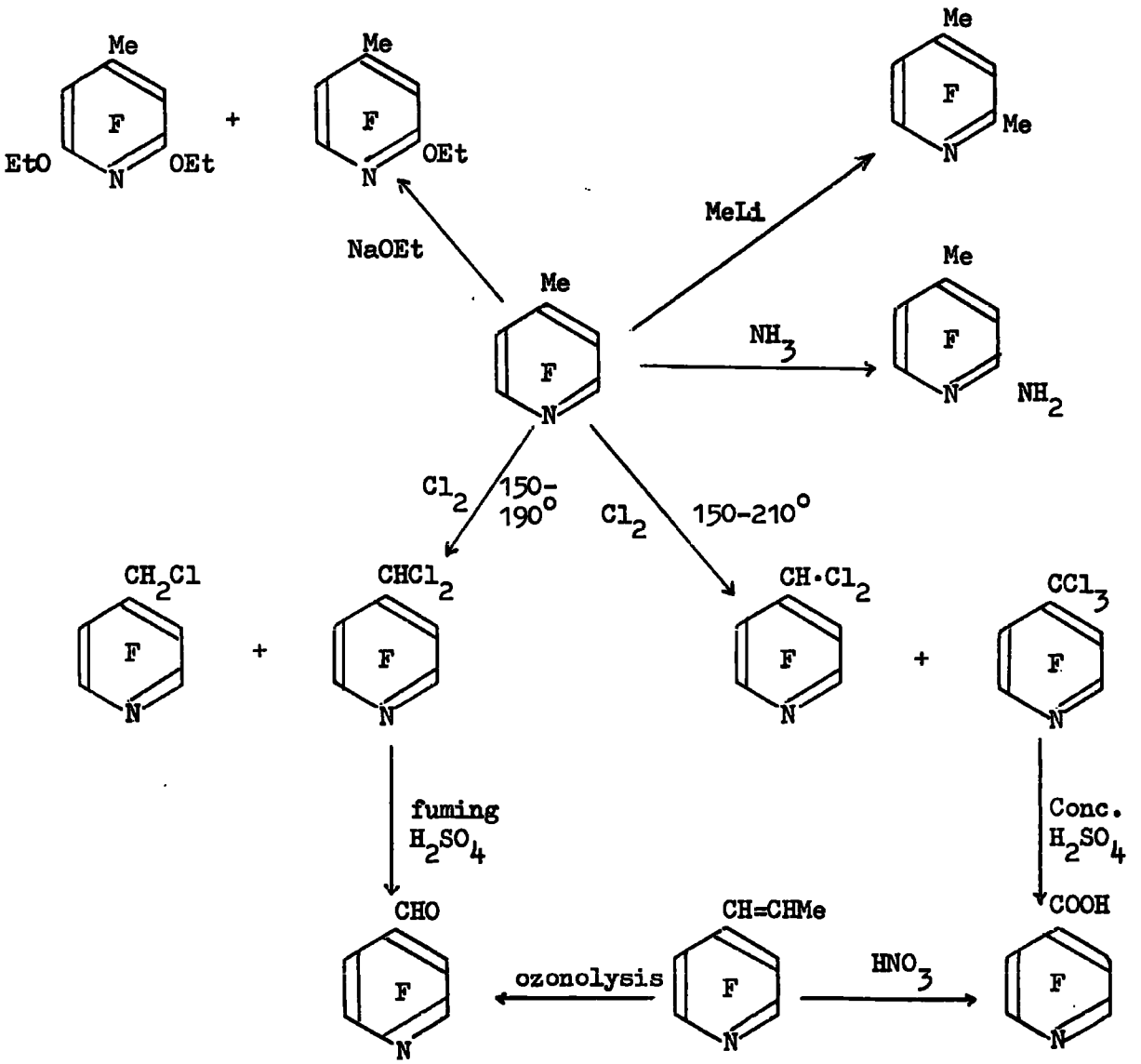
Reactions of 4-bromotetrafluoropyridine and some of its derivatives.



Ref. 57.

Fig. 3

Some reactions of alkyl tetrafluoropyridines



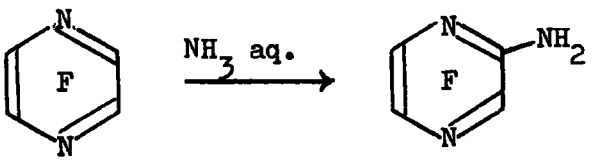
Refs. 36, 46, 48.

2. Heptafluoroquinoline and heptafluoroisoquinoline.

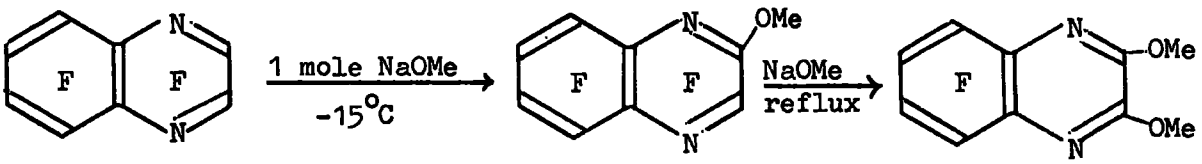
Heptafluoroquinoline and heptafluoroisoquinoline are both white solids (m.p. 95°, b.p. 205°, and m.p. 45·5°, b.p. 212° respectively) and, like pentafluoropyridine, do not have any obvious basic properties.[38] Both compounds have similar chemical properties[58] and their chemistry is summarised in Figures 4 and 5.

3. Perfluorodiazines.

Tetrafluoro-1,2-diazine and tetrafluoro-1,3-diazine have been shown to be extremely reactive towards nucleophiles;[40,52,60] some examples of their reactions may be seen in Figures 6 and 7. Detailed chemistry of tetrafluoro-1,4-diazine[39] and hexafluorobenzo-1,4-diazine[42] has not yet been reported apart from reactions shown below.



Ref.39

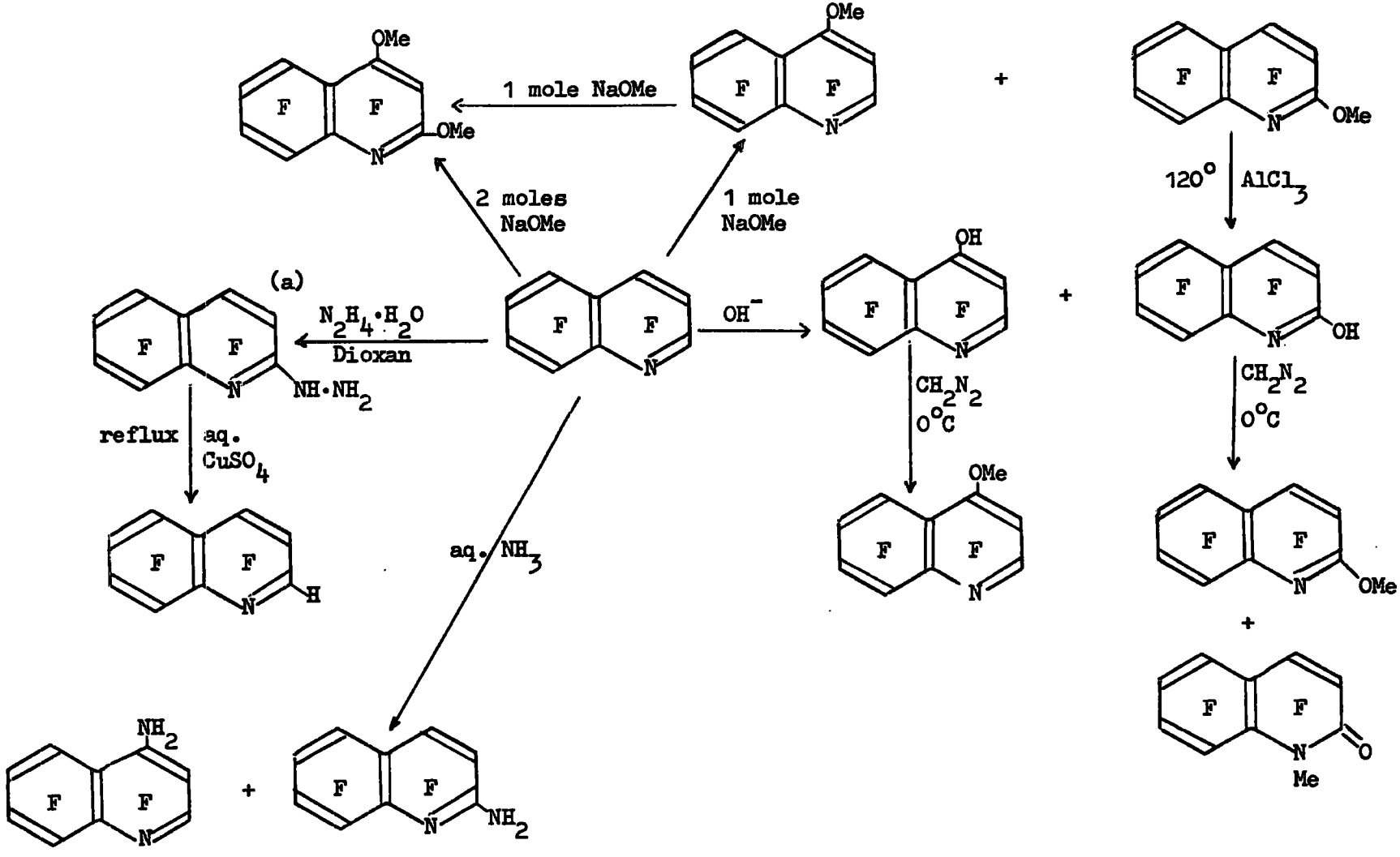


Ref.42

Fluorine in the carbocyclic ring of hexafluorobenzo-1,4-diazine is extremely resistant to nucleophilic displacement.[42]

Fig. 4

Some reactions of heptafluoroquinoline and its derivatives

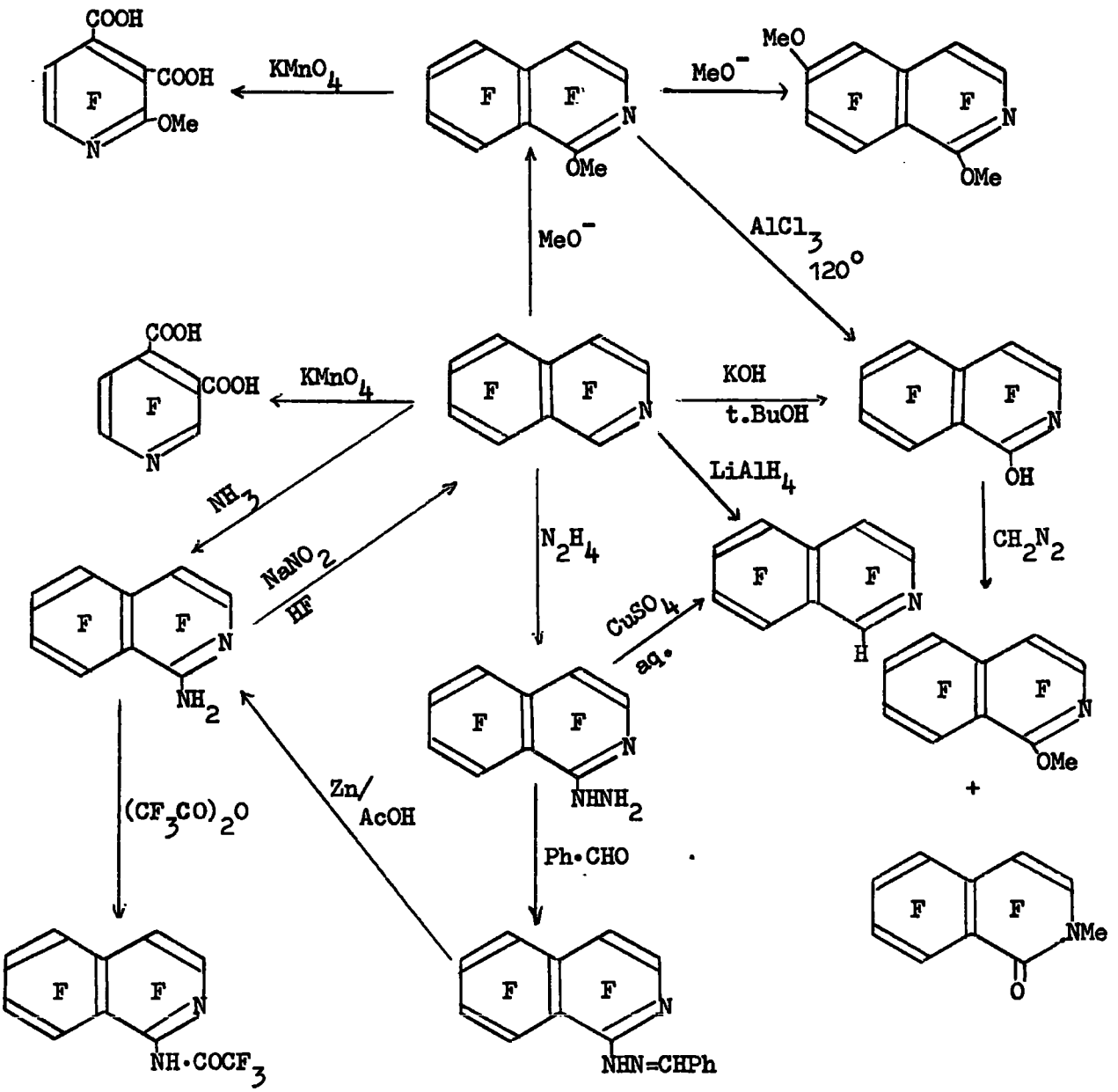


(a) Although this reaction is formulated as giving only hexafluoro-2-hydrazinoquinoline the presence of a small amount of the 4-isomer has been detected.[58]

Refs. 38, 58, 59.

Fig. 5

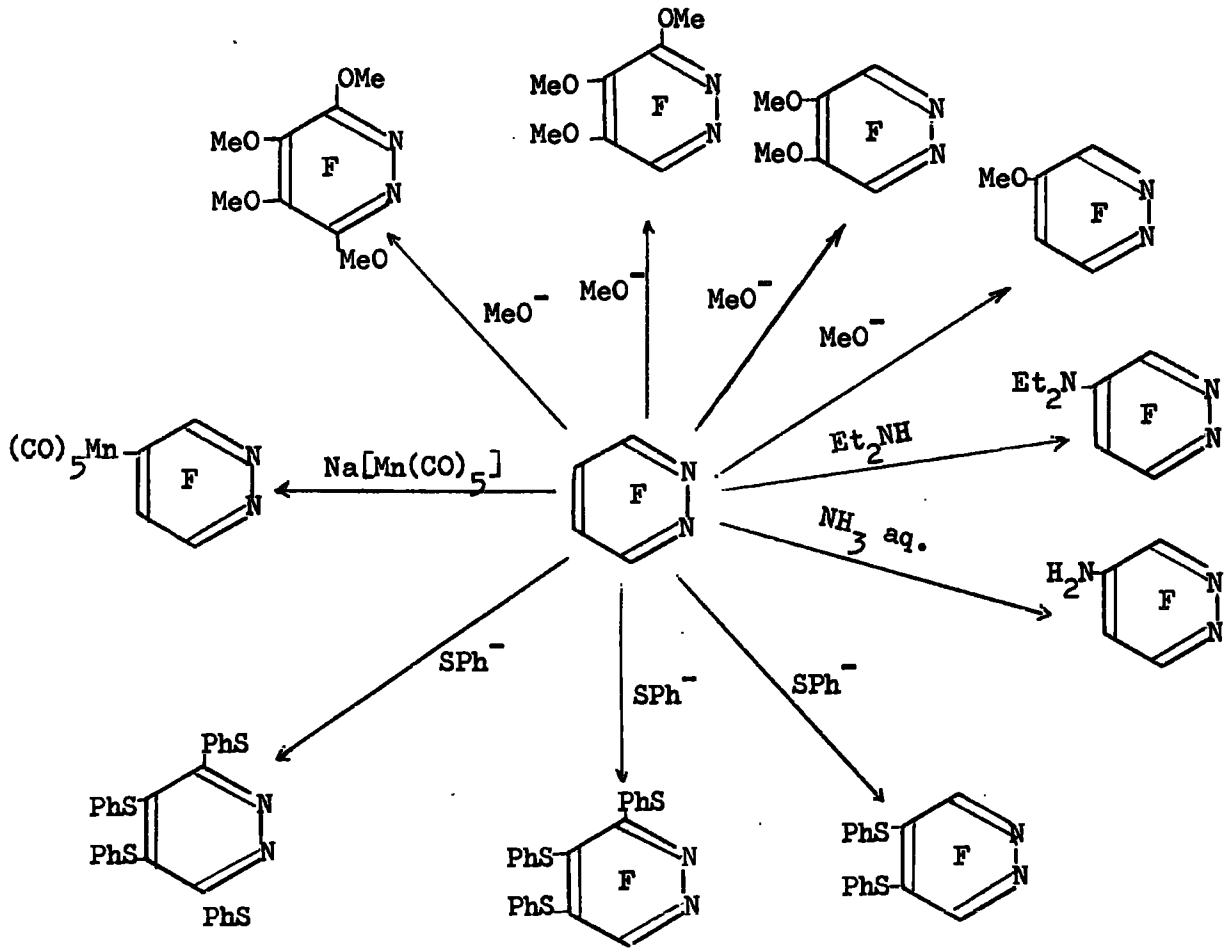
Some reactions of heptafluoroisoquinoline and its derivatives



Refs. 38, 58, 59.

Fig. 6

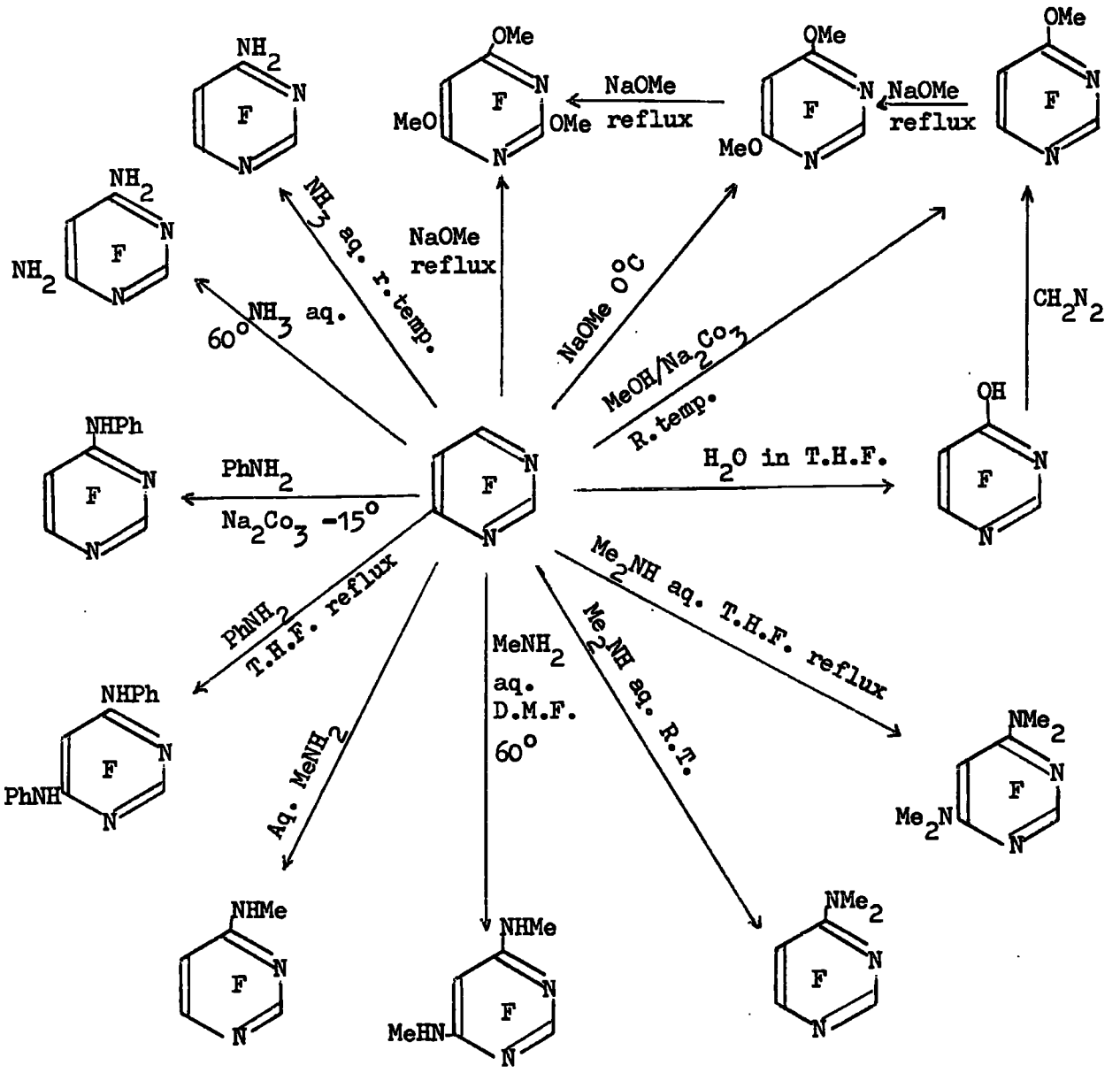
Nucleophilic Substitution in tetrafluoro-1,2-diazine



Refs. 40, 52.

Fig. 7

Nucleophilic displacement of fluorine from tetrafluoro-1,3-diazine



Ref. 60

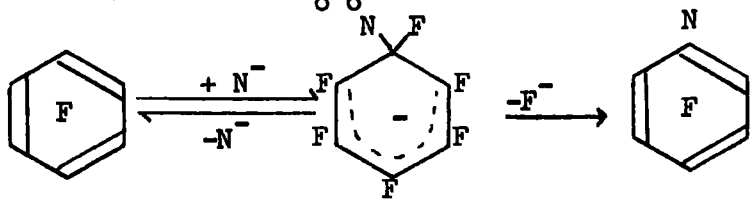
4. Nucleophilic substitution in polyfluoroaromatic compounds.

Displacement of fluoride ion from polyfluoroaromatic compounds by a nucleophile has been studied extensively and some of the factors controlling the substitution process successfully elucidated. The subject may be conveniently divided into two parts, substitution in carbocyclic systems and substitution in N-heteroaromatic compounds. Substitution in carbocyclic systems will be briefly dealt with followed by a more detailed discussion of substitution in N-heteroaromatic compounds.

a. Polyfluorohomocyclic compounds.

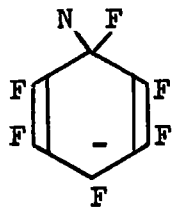
Hexafluorobenzene will react with many nucleophilic species such as $^{-}OCH_3$,[61] ^{-}OH,[62] ^{-}SH,[63] NH_3,[64] $N_2H_4 \cdot H_2O$,[64] CH_3NH_2,[64] $^{-}CH_3$[65] and $^{-}C_6H_5$[66] to give, under moderate conditions, good yields of the corresponding pentafluorophenyl derivatives. More interest is attached to nucleophilic substitution in C_6F_5X compounds since different positional isomers may be formed. In general when X = H, Me, SMe, CF_3, NMe_2, SO_2Me, and halogen, para substitution predominates;[67] when X = NH_2 or O^{-}, meta substitution occurs[68] and when X = NHMe or OMe, equal para and meta substitution occurs.[69] In some cases, when X = NO_2, NO, CO_2^{-}, the orientation may be determined by substrate-nucleophile interactions[70,71] or solvent effects.[72,73]

Burdon[74] has successfully rationalised substitution in these systems (except where solvent effects or nucleophile-substrate interactions occur) by assuming that the reaction involves addition of the nucleophile to the substrate proceeding through a definite intermediate, thus with C_6F_6;

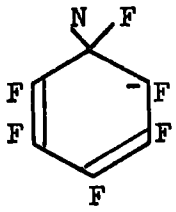


(II)

Some recent kinetic evidence[75] is in favour of this assumption. The Wheland intermediate (II) was used as an approximation to the transition state and it was assumed that in the transition state the electron density was localised largely at the position para to the site of attack and to a much lesser extent at the ortho position. This may be pictorially represented by (III) and (IV).



(III)



(IV)

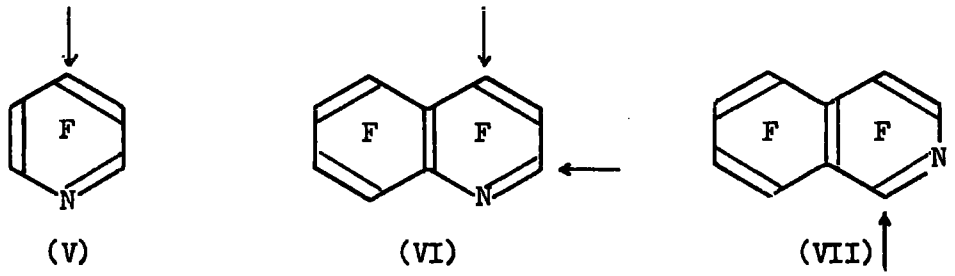
Substitution in C_6F_5X compounds resolves into a consideration of the effect of substituent X on the localisation of charge at the carbon atom to which X is attached. Halogens, because of π-inductive effects, are assumed to be unfavourable to the localisation of charge

on carbon atoms to which they are attached when, as in this case, it leads to a planar carbanionic species.[74] Streitwieser and Mares[76] have recently demonstrated the unfavourable effect of fluorine attached to a planar carbanionic centre. Halogen π-repulsions are believed to be in the order F > Cl > Br > I > H, and for oxygen and nitrogen, N > O > F.[74] If X, by π-repulsive effects does not destabilise the negative charge localised on the same carbon to which X is attached as much as fluorine then substitution will occur predominantly para to X. Some ortho substitution will also occur since contributions to the transition state of the type represented by (IV) cannot be completely ignored and will increase as the group X approaches fluorine in magnitude of π-repulsion.[74] Conversely if X has a π-repulsive effect exceeding that of fluorine (as with NH_2 and O^-) then meta substitution should predominate; para as well as meta substitution which is observed when X = NMe_2 or OMe[68] can be attributed to steric effects which reduce the π-repulsive effects of X by twisting the group out of the plane of the ring.

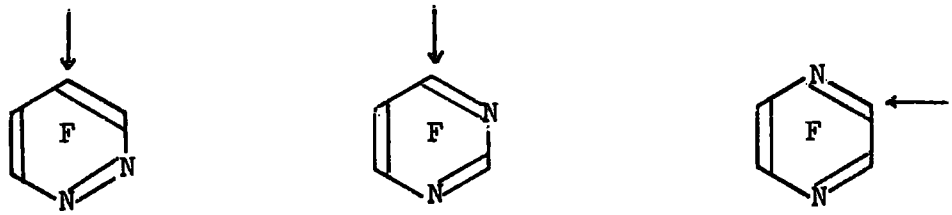
Application of these principles can give a rationale of orientation, including isomer distribution in pentafluorophenyl derivatives,[74,77] halotetrafluorobenzenes,[78] tetrafluorobenzenes[79] as well as in octafluoronaphthalene[80] and acenaphthalene.[81]

b. Polyfluoroheterocyclic nitrogen compounds.

Each of the perfluoroheterocyclic compounds shown below (V - X) give monosubstituted derivatives at the arrowed positions (Ch.I,B, 1, 2 and 3).



(V) (VI) (VII)



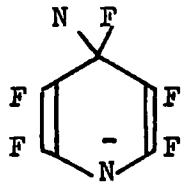
(VIII) (IX) (X)

In some cases the normal orientation can be changed by altering the steric requirements of the nucleophile. For example, pentafluoropyridine reacts with hydroxyl ion in water as expected, but in t-butanol 10% of the 2-hydroxy compound is obtained. Both 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine are, as expected, even more susceptible to this change of orientation with solvent.[47] A dramatic result due to effects of this nature can be found in the reactions of methoxide ion with octafluoro-3,3'-bipyridyl; in methanol, 4-substitution occurs ($>95\%$) whereas in t-butanol only 20% of the 4-methoxy derivative is produced, reaction occurring to

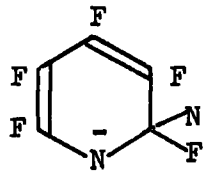
an extent of 80% at the 6-position.[56]

In the absence of steric and solvent effects a rationale of the orientation of nucleophilic substitution in perfluoroheterocyclic compounds is possible along lines suggested by Chambers and Musgrave.[41] They have noted that monosubstitution occurs in these compounds at positions where a single halogen[2,82,83] or methyl sulphonyl group[84,85] appears to be displaced most readily in the non-fluorinated systems and maintain that this suggests that ring nitrogen atom(s) control the orientation in perfluoroheterocyclic compounds.

In polyfluorohomocyclic compounds the orientation may be successfully rationalised in terms of π-repulsion on a localised negative charge attached to the same carbon atom as fluorine, or a substituent, in the transition state (Ch.I, B.4a). Although the Iπ effect should be considered in substitution of heterocylic compounds it appears to be adumbrated by the stabilising effect of ring nitrogen on localised negative charge in the transition state. Thus assuming a similar mechanism for substitution in the heterocyclic compounds as for homocyclic compounds, localisation of electron density on nitrogen will be preferred in transition states for the former series of compounds. This may be achieved most efficiently when substitution occurs para or ortho to ring nitrogen and, in the case of pentafluoropyridine may be represented by (XI)and(XII) respectively.



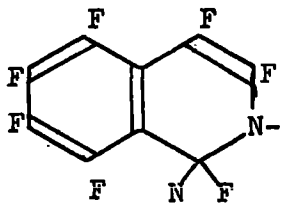
(XI)



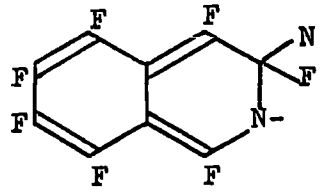
(XII)

Because a high electron density occurs on nitrogen in the transition state the electron density at ring carbon will be correspondingly reduced relative to substitution in a polyfluorobenzene, hence the Iπ effect will be of less importance.[41]

Arguments based on Iπ effects have been used to attempt rationalisation of substitution in perfluoroheterocyclic compounds and can successfully predict the sites of attack in some systems, (V, VI, VIII, IX).[60] However, such an argument is clearly invalidated by its inability to predict the site of attack in heptafluoroisoquinoline (VII).[41] By analogy with octafluoronaphthalene such an argument would give C-3 as the site of attack, not the observed C-1. Substitution at position-1 would be predicted by assuming control by ring nitrogen and electron density can be localised in the transition state as shown in (XIII).



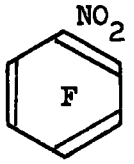
(XIII)



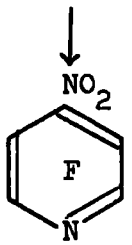
(XIV)

Substitution at C-1 rather than C-3, through (XIV) is indicative of a lower localisation energy for (XIII) possibly because it maintains the aromaticity of the carbocyclic ring.[58,41]

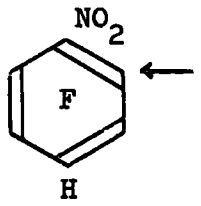
Substitution in some polyfluoronitro compounds shows clearly that orientation control by nitrogen is operative in heterocyclic compounds. Positions of substitution in the relevant nitro compounds (XV)-(XVII) are arrowed.[86,41]



(XV)

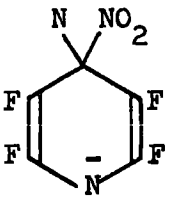


(XVI)

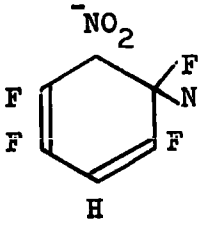


(XVII)

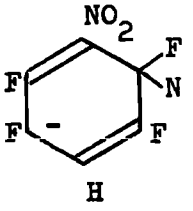
If the reactions of (XV) and (XVI) were controlled by Iπ interactions then (XVII) should react by displacement of the nitro group. This difference in behaviour of (XVI and XVII) can be attributed to extreme stabilisation of a transition state in which the negative charge is localised onto a ring nitrogen (XVIII), or a nitro group, (XIX) rather than to avoidance of transition states destablished by fluorine Iπ effects as in (XX).[41]



(XVIII)



(XIX)



(XX)

The observed reactivity order of perfluoroaromatic compounds, hexafluorobenzene < pentafluoropyridine < heptafluoroquinoline and isoquinoline < tetrafluoropyridazine and pyrimidine < tetrafluoropyrazine is completely in line with this argument and is reflected in the reactivity of the relevant methyl sulphonyl derivatives of the non-fluorinated systems towards attack by methoxide ion[84,85] or amines.[87]

It is clear therefore, that nucleophilic substitution in polyfluorobenzene derivatives is governed by the Iπ effect of fluorine in the absence of any substrate-nucleophile interactions or solvent effects. The same is not true of substitution in polyfluoronitrogen heterocyclic compounds, where, in the absence of external factors, the greatest single factor controlling the substitution is the effect of the ring nitrogen in stabilising the transition state.

CHAPTER II

Acid Induced Nucleophilic Heteroaromatic Substitution

Introduction.

Aza groups in N-heteroaromatic compounds are often of sufficient basicity to enable protonation to readily occur, the cation produced in such a reaction will be more susceptible to nucleophilic attack than the free base. Activation by this process can be regarded as due to the greater electron withdrawing power of $-\overset{+}{N}H=$ compared with $-N=$. Related to this of course are such derivatives as N-alkyl salts and N-oxides which are also extremely susceptible to nucleophilic attack.

Quaternization of the ring nitrogen, although activating to nucleophilic attack, deactivates the system to electrophilic attack.[88] Appreciation of the factors involved can lead to more facile electrophilic substitution reactions which are often carried out under acidic conditions.[89,90]

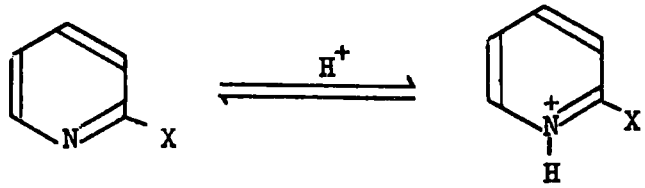
Part A of this chapter will discuss the possible mechanism and major factors controlling acid catalysed nucleophilic heteroaromatic substitution whereas part B will cover activation by groups, other than the proton, attached to ring nitrogen.

A

Acid Catalysis in Nucleophilic Heteroaromatic Substitution

1. Mechanistic Aspects.

Acid induced nucleophilic substitution in N-heteroaromatic compounds involves three basic stages as shown, but these need not occur in



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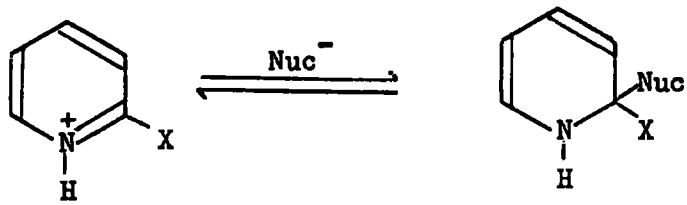
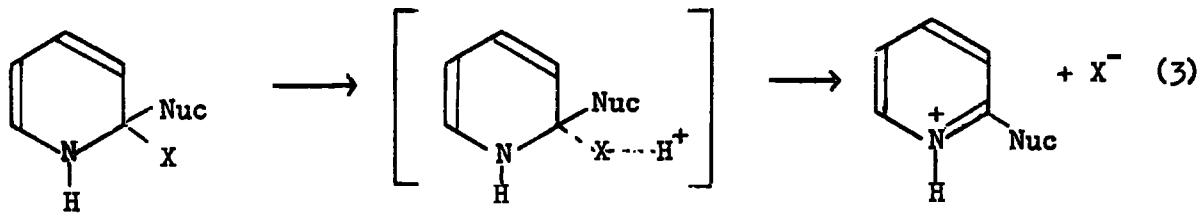


(2)

(XXI)



(3)

(XXII)

practice as distinct separated steps.

N-protonation can occur via a simple acid-base equilibrium (1), before any nucleophilic attack takes place but could also occur synchronously with addition of the nucleophile to the substrate.

Assuming that nucleophilic attack on the heterocyclic cation occurs, (2), this is likely to be analogous to rate determining addition of a nucleophile during a normal aromatic nucleophilic substitution reaction and leads to the intermediate (XXI). Loss of X^- from (XXI) gives the reaction product (3).

In (2) if addition of the nucleophile is rate determining then the polarity of the C-X bond will be important. Thus, when X = halogen, addition of the nucleophile is likely to be fastest for X = fluorine and should decrease with increasing electronegativity of the halogen.

For (3) the C-X bond strength will be of importance since this step involves fission of the C-X bond. So far as the halogens are concerned iodine should be the best leaving group and leaving group ability should decrease through bromine and chlorine becoming least for fluorine. However, the possibility of assistance at this point by protons, as typified by (XXII), cannot be ignored and there is evidence (Ch.II, A.2,c) that such a process may be of great importance for fluorine. Interactions between X and protons will clearly be at a maximum for fluorine and the possibility of such interactions between a fluorine substituent and protons before addition of the nucleophile in step (2) cannot be discounted. This may, in the case of fluorine, lead to some bond breaking in the rate limiting step, and at least enhances the polarity of the C-F bond which facilitates attack by the nucleophile. Such a process may be looked on as a merging of steps (2) and (3).

2. Heterocycle base strength.

a. Variations in base strength with the parent systems.

Pyridine is a relatively weak base because the geometry of the aza group forces the lone pair to occupy a plane trigonal orbital i.e. one

having a large proportion of S-character. This means that the electrons of the lone pair are concentrated more around the nitrogen nucleus than if they occupied a tetrahedral orbital as they do in trimethylamine.

Annelation of benzene rings onto the pyridine ring may produce either a slight increase in base strength as in isoquinoline or a slight decrease as in quinoline (see Table IV). A possible rationalization is that the electron attracting effect of the annelated benzene ring is less from the β position than the α-position.[92]

Table IV

Base strengths of some six membered N-heteroaromatic compounds

Base	pKa in water
Pyridine	5·17[a]
Isoquinoline	5·40[a]
Quinoline	4·87[a]
Pyrazine	0·65[c]
Pyrimidine	1·3[b]
Pyridazine	2·33[b]
Cinnoline	2·42[b]
Phthalazine	3·47[b]
Quinoxaline	0·56[b]

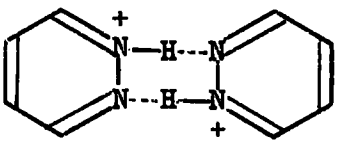
[a] at 25°C

[b] at 20°C

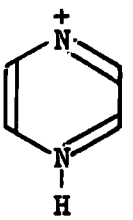
[c] at 27°C.

Reference 92

Insertion of a second -N= into a pyridine ring lowers the base strength because of the electron withdrawing effect of the second ring nitrogen. Base weakening by the second ring nitrogen is not purely inductive since this would give the order of diazine base strength as pyridazine < pyrimidine < pyrazine.[92] In fact the opposite order is observed (Table IV). So far as pyrimidine is concerned, the base weakening can be attributed to inductive effect. The strength of pyridazine as a base may be due to stabilization of the cation as a dimer with two hydrogen bonds, whereas the weakness of pyrazine as a



base may be due to reluctance of the unprotonated nitrogen in the cation to accept some of the positive charge.[92]

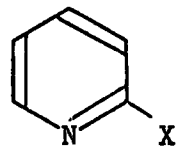
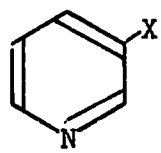


b. Effect of halogen.

Halogen substituents have a profound effect upon the base strength of a heterocycle. Brown and McDaniel[93] have measured the base strengths of 2- and 3-halopyridines and the results are given in Table V.

Table V

Base strengths of some halopyridines

Pyridine	
	pKa (25°C in water)
X = H	5·17
F	-0·44
Cl	0·72
Br	0·9
I	1·82
	
X = H	5·17
F	2·97
Cl	2·84
Br	2·84
I	3·25

Ref. 93.

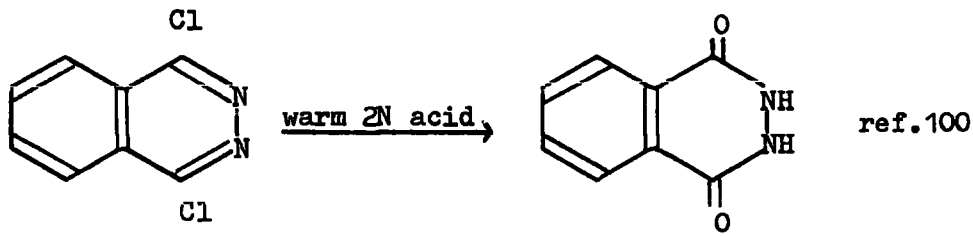
Base weakening by halogen is apparently due to its powerful inductive effect, degree of base weakening for a given substituted pyridine decreasing as the atomic number of the halogen increases, and for a particular halogen, decreasing as the distance of the substituent from the aza-centre increases. Analogous observations have been made for the haloquinolines by Knight[94,95,96] and his co-workers.

c. Reactivity and base strength.

Displacement of halogen by water in 2-halo-5-nitropyridines has been shown to be acid catalysed.[97] However, 4-chloro-5-nitropyridine should be a stronger base than the isomeric 2-chloro-5-nitropyridine and hence more susceptible to acid catalysis. Chapman and Rees[98] have reacted both compounds with aniline and shown that the 4-chloro isomer is more susceptible to acid catalysis than the 2-chloro-derivative.

Illuminati[99] and co-workers have also shown the same trend in the quinoline series. Thus 4-chloroquinoline more readily undergoes acid catalysis than 2-chloroquinoline.

Conditions for the acid hydrolysis[100] of some chloroazines set out below illustrate qualitatively the greater base weakening effect of two halogens ortho to the aza centre.



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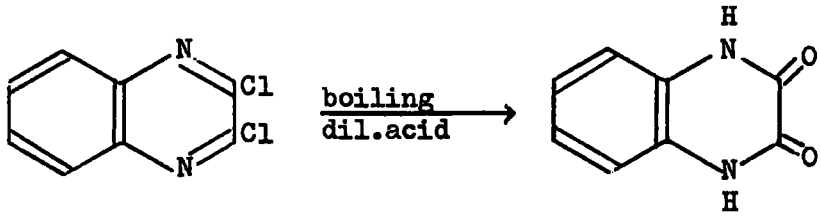
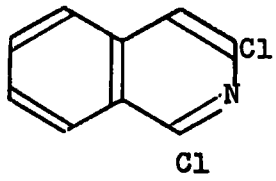


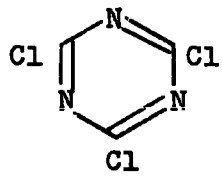


Stable under acid hydrolysis conditions.

Phthalazine and quinoxaline are both weaker bases than isoquinoline (Table IV). In 1,3-dichloroisoquinoline the two α-chlorine atoms have reduced the basicity of the system so much that hydrolysis does not occur, the other two dichloroazines have only one α chlorine per aza group and consequently hydrolyse under moderate conditions.

It is worth noting that the ease of hydrolysis of the two dichlorodiazines also appears to relate to their base strengths. Phthalazine is a considerably stronger base than quinoxaline and consequently dichlorophthalazine undergoes acid hydrolysis under milder conditions than dichloroquinoxaline.

Cyanuric chloride (XXI), because each aza group has two α-chlorines, should be insensitive to acid catalysis; this has been observed for the



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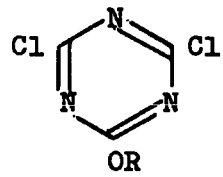

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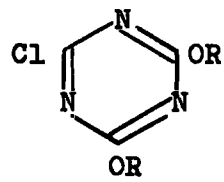


(XXIII)

displacement of the first chlorine with alcohols[101] and water.[102] Mesomeric electron release from alkoxy or hydroxy substituents in (XXII) and (XXIII) when R = alkyl or hydrogen produces a series of stronger bases and these compounds are observed to be increasingly sensitive to acid catalysis.[101,102]

Fluorine inductive effect is greater than that of the other halogens. Consequently it would be expected that α-fluoroheterocyclic compounds would be such weak bases that acid hydrolysis would not occur or take place under more vigorous conditions than those required for the corresponding chloro-, bromo-, and iodo-derivatives. Table VI shows that generally the opposite is true.

Table VI

Acid hydrolysis of α-halo heterocyclic compounds

Compounds hydrolysed in acid	Compounds not hydrolysed in acid
2-fluoropyridine[a]	2-chloropyridine[a]
2-fluoro-3-methylpyridine[a]	2-bromopyridine[a]
2-fluoro-5-methylpyridine[a]	2-bromo-3-methylpyridine[a]
2-fluoroquinoline[b]	2-bromo-5-methylpyridine[a]
1-fluoroisoquinoline[b]	2-chloroquinoline[b]
	1-chloroisoquinoline[b]

[a] 24 hours reflux with 6N HCl.[103]

[b] dilute acid room temperature.[94,104]

Reactivity of fluorine in these compounds towards acid hydrolysis has been attributed to assistance by hydroxonium ion in removing the incipient fluoride ion rather than N-protonation followed by nucleophilic attack by water.[103,104,105] Similar explanations have been proposed to explain acid catalysis in the hydrolysis of benzyl fluoride[106] and benzotrifluoride.[107]

Rutner and Spoerri[108] however, note that 2-fluoropyrazine is less susceptible to acid hydrolysis than 2-fluoropyridine. They suggest therefore, that since pyrazine is a weaker base than pyridine then the same order of basicity should hold for the monofluoro derivatives. On this basis 2-fluoropyridine may be regarded as being N-protonated in 6N hydrochloric acid whereas 2-fluoropyrazine is not and the latter is therefore less susceptible to acid hydrolysis.

It may be, therefore, that α-fluoroheterocyclics may undergo N-protonation in acid media to some extent and that hydroxonium ions assist the removal of fluoride ion, thus greatly enhancing the reactivity of fluoro derivatives relative to the other halo analogues.

3. Base strength of the nucleophile.

In an acid catalysed nucleophilic heteroaromatic substitution the base strength of the nucleophile must be considered since both the substrate and nucleophile will compete for protons.

Displacement of chlorine from some chloropyrimidines by aromatic amines was observed to be acid catalysed by Banks.[109] Morley and

Simpson[110] showed that the reactions of 4-chloronitroquinazolines with amines were not catalysed if the amine was a much stronger base than the substrate. In these cases the nucleophile was preferentially protonated and produced the non nucleophilic ammonium ion. Reactions of some amines with 2-amino-4-chloro-6-methyl pyrimidine catalysed by different acids of varying strength illustrate the point,[111] (Table VII).

Table VII

Reactions of 2-amino-4-chloro-6-methylpyrimidine with amines under catalysis by various acids

Amine K_b	Product (%)				
	Acid K_a	HCl 1·0	$CH_3 \cdot COOH$ 2×10^{-5}	$C_6H_5 \cdot OH$ 10^{-10}	H_2O 10^{-14}
Aniline 5×10^{-10}		100	-	-	100
Morpholine 2×10^{-6}		20	76	81	72
Piperidine 1×10^{-3}		5	11	51	48

Aniline, the weakest base, gives high yields in either strong or weak acids since it is not appreciably protonated in either medium. Morpholine, the intermediate base gives highest yields in weak acids, the stronger the acid the more the morpholine is protonated and the yield of product is reduced accordingly.

Piperidine, the strongest base, gives very low yields in strong acids and only moderate yields in weak acids.[111]

Greater susceptibility towards acid catalysis with morpholine and haloheterocyclic compounds as compared with similar reactions of piperidine with the same substrates has been observed on other occasions.[82,112]

4. Solvent effects.

a. Base strength of the solvent.

Both substrate and solvent may also compete for protons, particularly in solvolysis reactions, and, in these cases, the basicity of the solvent may determine whether or not acid catalysis occurs.

Acid catalysis in the reactions of dichloromethoxy-1,3,5-triazine with methanol has previously been mentioned (Ch.II, A1), however, the hydrolysis of analogous compounds in water-acetone media do not appear to be acid catalysed.[113] This may be due to the greater basic strength of water compared with alcohols.

Illuminati[114] and co-workers have noted that piperidinolysis of 4-chloroquinoline with dilute solutions of piperidine in a variety of solvents is autocatalytic, (Ch.II, A5). Autocatalysis is absent in neat piperidine which reflects the ability of the solvent to compete more effectively for protons than the substrate.

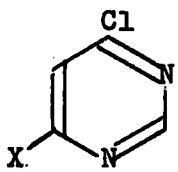
It has been suggested[115] that for a particular substrate susceptibility to acid catalysis due to increasing solvent basicity, should decrease in the order alcohols > water > piperidine in solvolytic reactions in these media.

b. Activation by hydrogen bonds to azine nitrogen.

Hydroxylic solvents can hydrogen bond strongly with the aza-group of a heterocyclic compound[116] and this produces an effect qualitatively similar to that of protonation.

Recently, Illuminati[114] and co-workers have examined the reactions of 2-chloro- and 4-chloroquinoline with piperidine in various solvents. Rate enhancement with methanol as solvent relative to ethyl acetate as solvent was observed. This rate enhancement was more marked with the stronger base 4-chloroquinoline and can be attributed to hydrogen bonding between the methanol and aza-group. Such an effect would be expected to be more important for the strongest base.[114]

Bulky groups, such as t-butyl, ortho to the ring nitrogen may sterically interfere with hydrogen bond formation. Reactions of some 4-chloropyrimidines (XXIV) and (XXV) in which the alkyl group may be



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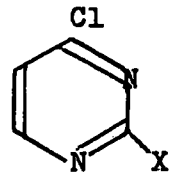


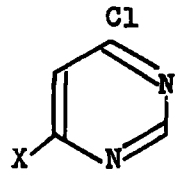
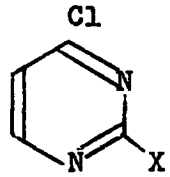
(XXV)

X = Methyl, t-Butyl

varied from methyl to t-butyl can be used to illustrate this effect.[117] In compounds of the type (XXIV) only one aza group is ortho to an alkyl substituent, whereas in the (XXV) type, both aza centres are ortho to the alkyl group, any effect due to inhibition of solvation should be more marked for (XXV).[117]

Reactivity ratios $^{KMe}/KtBu$ in reactions of these substrates with piperidine in ethanol and toluene can be seen in Table VIII.

Table VIII ref.117

Pyrimidine (X = Me or t.Bu)	Toluene[a] $^{KMe}/KtBu$	Ethanol[a] $^{KMe}/KtBu$
	1·62	2·57
	2·36	17·34

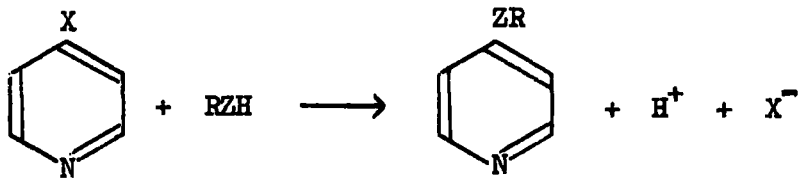
[a] at 30°C

The reactivity ratio $^{KMe}/Kt\text{-}Bu$ increases in passing either from the less polar to more polar solvent or from 6-alkyl to 2-alkyl substituted pyrimidines. In the former case the increase in reactivity can be ascribed to the stronger hydrogen bonding of ethanol with the aza centre, whereas the increase in the second case is due to inhibition of hydrogen bonding by the bulky t-butyl groups leading to greater relative reactivity of the methyl derivative.[117] This effect is particularly marked in strong hydrogen bonding solvents such as ethanol, where $^{KMe}/Kt\text{-}Bu$ for the 6-alkyl compounds is almost ten times greater than that for the 2-alkyl pyrimidines.

Steric hindrance to specific solvation by peri-t-butyl groups in 8-t-butyl-4-chloroquinoline has also been noted.[118] Rate depression relative to the corresponding methyl compound in reactions with methoxide and piperidine is extremely pronounced in methanolic solution.[118]

5. Autocatalysis.

Autocatalysis may arise when the nucleophilic atom of the reagent is bound to hydrogen which is eventually eliminated during the reaction, for example

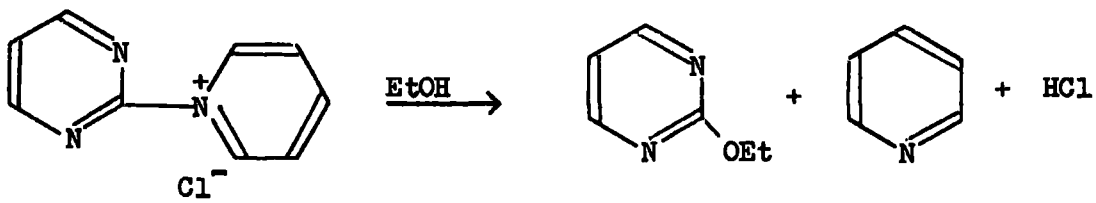


If the group X is a sufficiently weak base the proton is effectively transferred to any basic reagent present, often the substrate. Since the stoichiometry of the reaction produces the acid then autocatalysis occurs in the absence of any initial acid. Autocatalytic reactions are easily recognised kinetically by virtue of the fact that their rate constants increase as reaction proceeds.

Whether or not autocatalysis occurs depends to a great extent on interplay between the basicities of substrate, nucleophile and solvent since any protons produced by the reaction will be distributed amongst these components.

In ethanol solution, with a two and four fold excess of amine, reactions of chloropyrimidines and their methyl derivatives with aniline are strongly autocatalytic.[112] With the stronger bases morpholine and piperidine autocatalysis does not occur.

Reaction of 2-chloropyrimidine with pyridine in ethanol is observed to be autocatalytic.[112] This is surprising since pyridine does not have a hydrogen atom attached to nitrogen which may be eliminated as a proton. Intervention of acid catalysis in this reaction is attributed to solvolysis of the product 2-pyrimidyl-pyridinium chloride.[112]



Reactions between piperidine and 4-chloroquinoline in dilute solution are autocatalytic whereas regular kinetics are observed with the less basic substrate, 2-chloroquinoline, under similar conditions.[82,114]

With a less basic nucleophile, such as morpholine, 2-chloroquinoline will give autocatalytic reactions.[82]

Substituents which alter the basicity of the aza nitrogen in a given substrate can clearly control the importance of autocatalysis.[114] In the 4-chloroquinoline series, electron withdrawing substituents

(2-CF_3, 2-COOEt) prevent autocatalysis at low piperidine concentrations. However electron releasing groups such as 2-CH_3, 2-OR or 2-NH_2 enhance autocatalysis, 2-amino-4-chloroquinoline gives autocatalytic reactions with neat piperidine (in agreement with the powerful electron releasing ability of the NH_2 group).[114] Derivatives of 2-chloroquinoline do not generally undergo autocatalytic reactions, however, strongly electron releasing groups in the 4-position promote autocatalysis in this series.[114]

Solubility of acidic products in the reaction medium may also determine whether or not autocatalysis occurs. In reactions of a number of 2- and 4-chloroquinolines with p-thiocresol in toluene solution the quinolinium chlorides produced are only of limited solubility and eventually separate as a solid mass.[119] A detailed study has revealed that the extent of autocatalysis depends on the basicity of the starting quinoline and on the steady state concentration of the acidic reaction product.[119] For example, 2-chloroquinoline is of low basicity and the quinolinium chloride produced only of low solubility in toluene. Autocatalysis occurs only for the first few percent of reaction after which regular kinetics are observed. However, a higher substrate basicity coupled with a higher product solubility (4-chloro-7-p-tolylthioquinoline), can lead to kinetic complexity due to autocatalysis throughout the whole reaction.[119]

Autocatalysis depends primarily on the reaction itself producing acid and the substrate competing for the proton more efficiently than either the nucleophile or solvent. If the acidic product is insoluble in the reaction medium then autocatalysis may be inhibited.

B

Reactions involving Quaternization of the Aza Group

1. Quaternary salts and N-oxides.

a. Preparation.

Pyridine, its homologues and their derivatives will react with alkyl, acyl, sulphonyl and similarly activated halides, in what are probably S_N2 type replacements to give quaternary salts.

Electron releasing substituents in the heterocyclic system facilitate reaction whereas electron withdrawing substituents retard the reaction.[120] Bulky substituents, such as t-butyl, in the α-positions may prevent reaction completely due to steric effects.[121,122] Quaternization reactions have been reviewed recently by Duffin.[123]

Heterocyclic compounds of nitrogen will often react readily with suitable oxidising agents to give the corresponding N-oxide. Peroxycarboxylic acids are most commonly used as oxidising agents.

Substituent effects on the substrate towards its reactivity with oxidising agents are similar to those for quaternization reactions. For example, 2,6-dibromopyridine resists oxidation with perbenzoic acid or peracetic acid but can be oxidised with peroxytrifluoroacetic acid, a more powerful oxidising agent.[124]

Methods of preparation and properties of aromatic amine oxides have recently been the subject of an excellent book by Ochiai.[125]

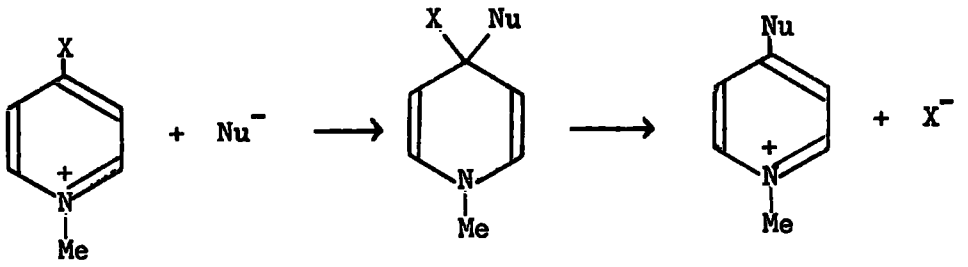
b. Nucleophilic substitution.

Quaternization or N-oxidation of heterocyclic compounds increases the system's susceptibility to nucleophilic attack, this may be attributed to effectively increasing the electronegativity of the ring nitrogen.[126] The order of reactivity in the pyridine series is found to be quaternary salt $>$ N-oxide $>$ pyridine.[127,128] This order is readily understood bearing in mind that the N-oxide group also activates the ring to electrophilic attack by mesomeric electron release from the negative oxygen. This offsets the activating influence of the positively polarised nitrogen towards nucleophilic substitution.[127] Presumably a similar reactivity series will hold for other simple heterocyclic systems.

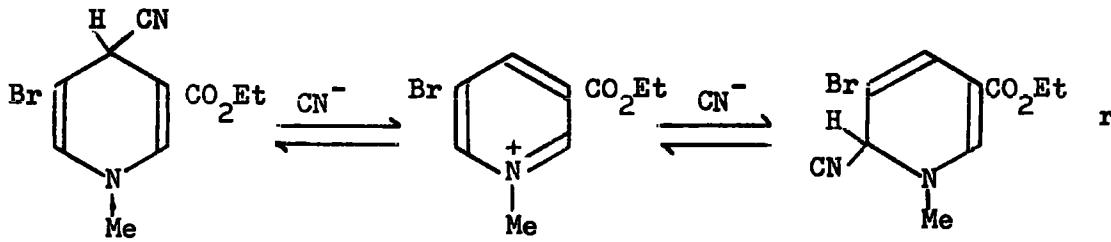
Positional reactivity is found to be 4 $>$ 2 $>$ 3 for pyridine and its N-oxide and 2 $>$ 4 $>$ 3 for N-methyl pyridinium compounds.[127] This change over of reactivity at the 2- and 4-positions is attributed to a high entropy of activation for the 2-substituted pyridinium compound since the activation energies for all positions is found to be in the order 4 $<$ 2 $<$ 3 for all types of pyridine substrate.[127,129]

Much interest has been attached in recent years to the reactions of pyridinium ions with nucleophiles. Reaction of substituted pyridinium ions with nucleophiles usually occurs with the formation of the corresponding 1,2-, 1,4-, or 1,6-dihydropyridine. If the

initial substituent is a good leaving group, such as a halogen, it will be displaced as shown:[130]

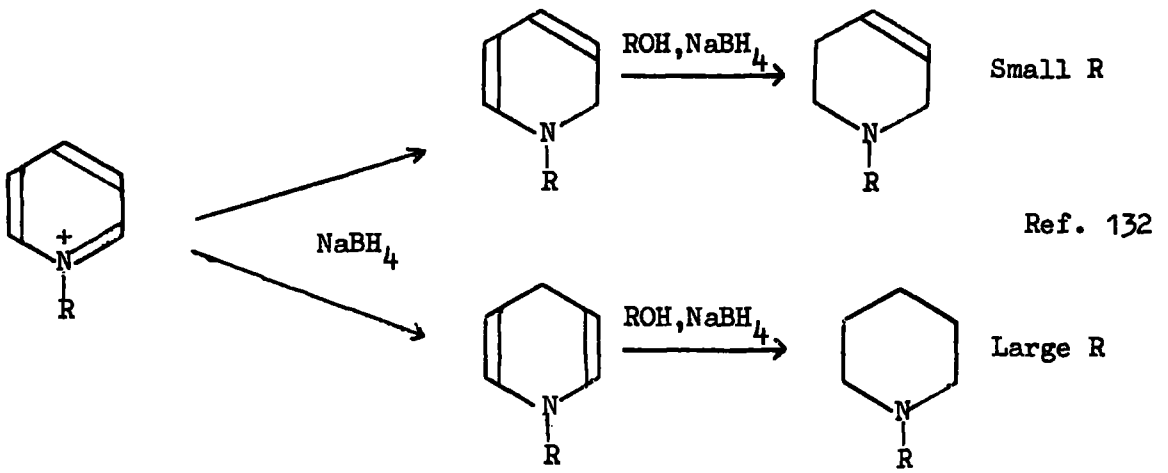


If the group X is not a good leaving group the corresponding dihydropyridine may be isolated.[131] It has been shown that addition of a nucleophile to N-methylpyridinium halides (not substituted in the 2-, 4-, or 6-positions) occurs initially at the position adjacent to the positive nitrogen unless the nitrogen is bonded to a bulky group when addition at position-4 occurs. If the addition step is reversible, as it is when the nucleophile is cyanide ion, then the initially formed 1,2-dihydropyridine, the product of kinetic control, is converted slowly in solution to an equilibrium mixture composed largely of the 1,4-dihydropyridine, the thermodynamically controlled product.[131,132]



ref.131

When irreversible additions to the pyridinium ion occur the products are controlled by the size of the quaternizing group R.[132] Borohydride reductions of pyridinium ions are suitably irreversible



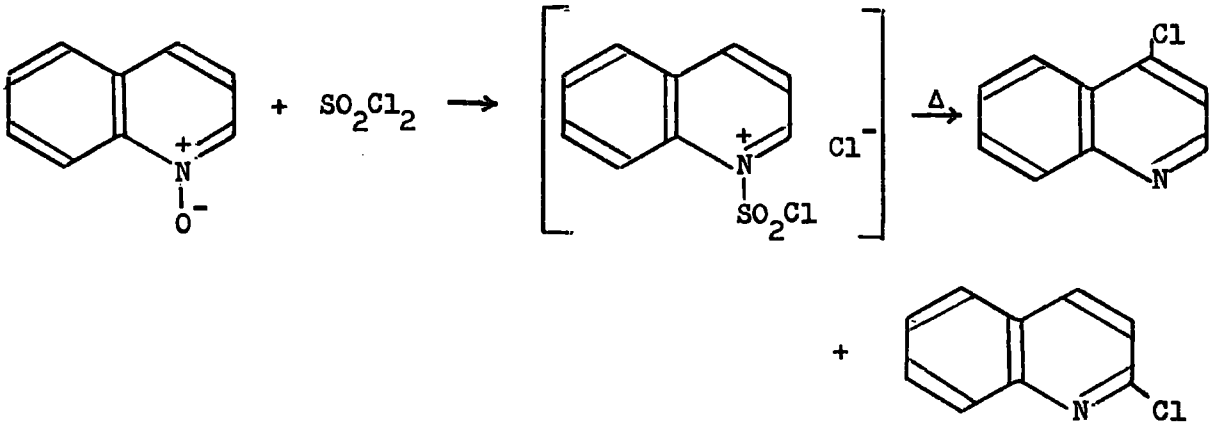
nucleophilic additions, and the amount of piperidine produced is found to increase with the bulk of the group R.[133] This indicates considerable steric hindrance by R to the approach and attack of hydride ion at the α-positions.[133]

Nucleophilic attack in quinolinium ions is not so well understood as in pyridinium ions. Powerful nucleophiles tend to attack at position-2 giving 1,2-dihydroquinolines whereas weak nucleophiles attack at the 4-position leading to 1,4-dihydroquinolines.[134,135] However, the 2- and 4-positions in quinoline are much closer in reactivity than they are in pyridine and presumably the same trend is found in the respective cationic species. Because of the similarity in reactivity between 2- and 4-positions in quinoline systems the N-substituent may have an effect upon the orientation of nucleophilic attack.[135] Thus N-cyanoquinolinium ions react with a wide variety of nucleophiles to give 1,2-dihydroquinolines and these reactions appear to be irreversible.[134,135,136] N-methylquinolinium ions have a marked tendency

to react at the 4-position and this suggests that some orientation control by the N-substituent is operative.[135]

Nucleophilic attack in isoquinolinium salts occurs, as expected, at the 1-position.[137]

As mentioned previously the reactivity of N-oxides is intermediate between that of N-alkylpyridinium salts and pyridines. Quite often the reactivity of N-oxides may be enhanced by co-ordination of the oxygen atom and a suitable electron acceptor.[138] For example the reaction of sulphuryl chloride with quinoline-N-oxide takes place as shown below.[139]

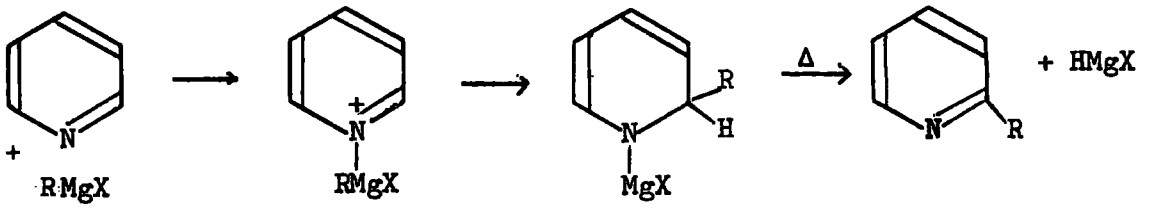


2. Co-ordination of the ring nitrogen with metals.

Because of the donor properties of ring nitrogen in heteroaromatic compounds co-ordination of the aza group to metals would be expected to occur during reactions of organometallic reagents with heterocyclic substrates.

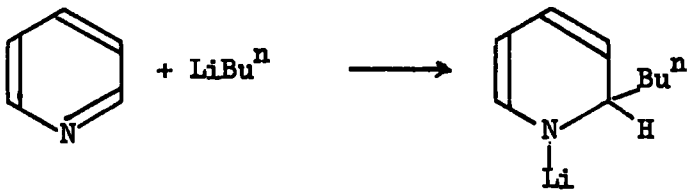
Reaction of S-butyl magnesium bromide with pyridine in ether gives, after removal of ether and heating to 150°C to eliminate HMgX, a low

yield (6%) of 2-S-butylpyridine.[140]



$R = CH_3 \cdot CH \cdot C_2H_5$

Reaction of S-butyl-lithium with pyridine in petroleum ether takes place readily at 100°C and gives good yields (60%) of the butylpyridine.[140] More effective reaction with lithium alkyls than with Grignard reagents may be due, in part, to more facile co-ordination between the ring nitrogen and lithium. Giam and Stout[141] have recently isolated and characterized a series of adducts produced from reactions of alkyl lithiums with pyridines.



ref.141

Analogous adducts have been suggested as intermediates in the Chichibabin[142] reaction and in the reaction of phenyl calcium iodide with pyridine.[143]

In general organometallic reagents substitute the pyridine nucleus at the α-positions (unless they are blocked by other groups), however, the reaction of benzyl magnesium bromide is somewhat unusual in that the major product is 4-benzylpyridine.

DISCUSSION OF EXPERIMENTAL

CHAPTER III

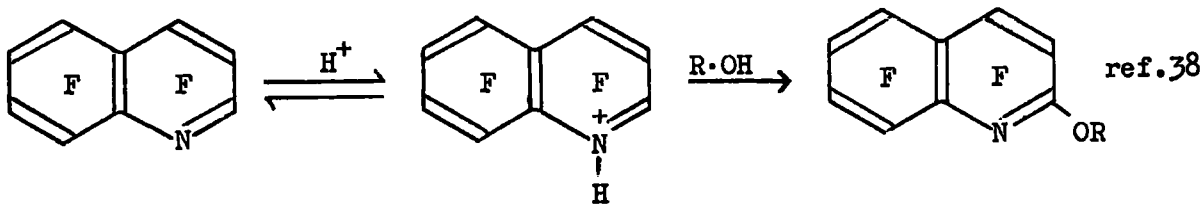
Reactions of Protonic Acids with Polyfluoro-N-heteroaromatic Compounds

Introduction.

While early work with perfluoro-N-heteroaromatic compounds did not reveal obvious basic properties it was later noted that they will dissolve freely in concentrated sulphuric acid.[38] Since the corresponding homocyclic compounds are not soluble this suggests that N-protonation of the heterocyclic compounds occurs in sulphuric acid and, indeed, u.v. spectral data supports this conclusion.[38]

Slow dilution of such solutions of heptafluoroquinoline with water or methanol lead to high yields of 2-hydroxy or 2-methoxyhexafluoroquinoline.[38] Although under these conditions heptafluoroisoquinoline and pentafluoropyridine were recovered unchanged, surprisingly, rapid dilution of heptafluoroquinoline solutions also precipitated unchanged starting material.[38]

Reaction of heptafluoroquinoline with water or methanol in concentrated sulphuric acid was interpreted in terms of nucleophilic attack on the protonated quinoline.



R = H or Me

It was appropriate therefore, to investigate the scope of reactions of perfluoro-N-heteroaromatic compounds with acidic reagents because reactions of this type could provide routes to compounds which otherwise are difficult to prepare, e.g. 2-substituted tetrafluoropyridines.

A

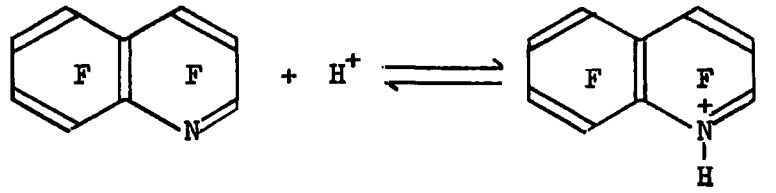
Reactions of Hydrogen Halides with Perfluoro-N-heteroaromatic Compounds

Reactions of hydrogen halides with perfluoro-N-heteroaromatic compounds were studied first of all in an attempt to prepare halo-derivatives which are of use in generating reactive intermediates such as lithio derivatives or Grignard reagents.

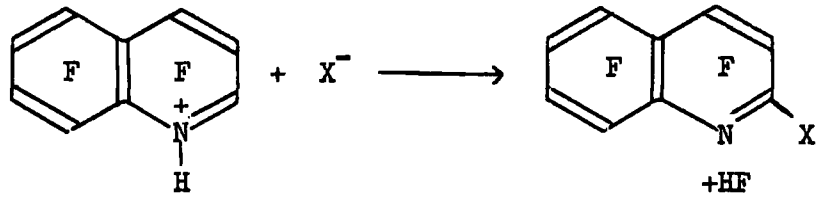
1. Choice of solvent.

Earlier work in this department had shown that aqueous solutions of hydrogen chloride or hydrogen bromide reacted with heptafluoro-quinoline producing large amounts of hydroxy-derivatives rather than replacing fluorine by another halogen. Clearly, a solvent which did not produce side reactions leading to unwanted products was required but consideration of the proposed reactions shows that other properties of the solvent will also be important. Basically, the intended reaction can be summarized in the following steps using heptafluoro-quinoline as an example:

$$HX \rightleftharpoons H^+ + X^- \qquad (4)$$



(5)

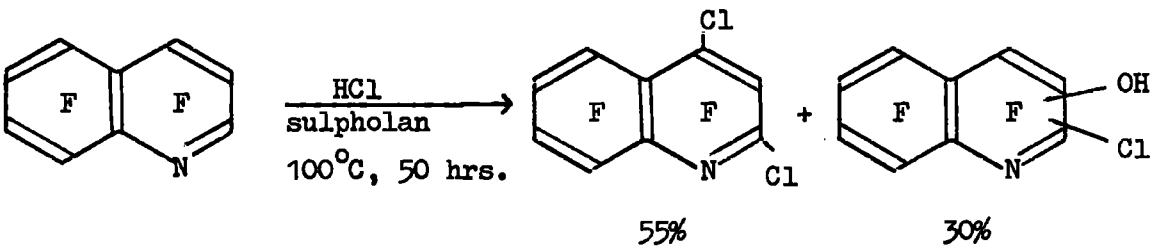


(6)

Dissociation of H-X, (4), will be favoured by solvents of high dielectric constant and because the substrates are very weak bases the solvent may compete for the available protons and hinder (5). Thus solvent basicity is also a factor to be considered. Solvents in which halide ions are good nucleophiles will facilitate the final stage (6) of the reaction.

Dipolar aprotic solvents are known to be valuable solvents for reactions involving nucleophilic displacement by halide ions (Ch.I, A, 3a) and, furthermore, have relatively high dielectric constants. Arnett and Douty[146] have investigated sulpholan, a dipolar aprotic solvent, as a medium for acid-base reactions and have shown that solutions of sulphuric acid in sulpholan are highly acidic. Furthermore, sulpholan does not appear to be protonated by concentrated sulphuric acid indicating that it is a very weakly basic solvent and will favour stage (5) of the reaction.

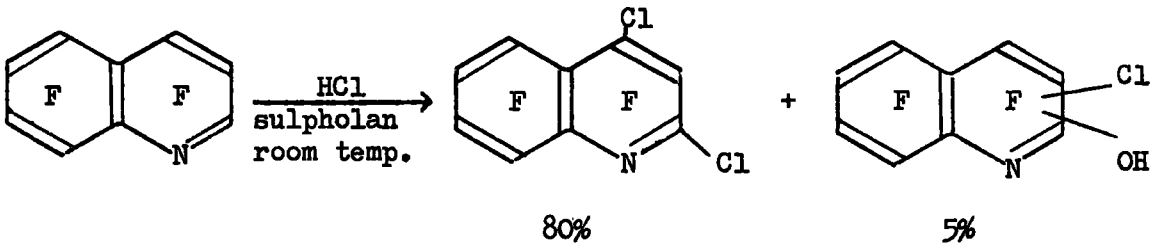
Some exploratory reactions were carried out between hydrogen chloride and heptafluoroquinoline in sulpholan which had been purified by fractional distillation under high vacuum. Fractions which solidified at room temperature were considered to be pure sulpholan.[147] In this solvent reaction occurred between excess hydrogen chloride and heptafluoroquinoline only on heating at 100°C for 50 hours, two products were isolated 2,4-dichloropentafluoroquinoline (55% yield) and a hydroxychloropentafluoroquinoline (30% yield).



Initially, it was thought that the hydroxy compound had been produced during the work-up procedure when the sulpholan solution was diluted with water but dilution of a solution of 2,4-dichloropentafluoroquinoline in sulpholan saturated with hydrogen chloride did not produce any hydroxylated compounds.

Obviously then, the hydroxy compound was being produced during the reaction by water impurity in the solvent. (See Ch.III, A, 2,e). Further drying of the distilled solvent using a molecular sieve (Type IVA) produced a more effective solvent. Reaction between hydrogen chloride and heptafluoroquinoline occurred at room temperature but

removal of the last traces of water is difficult[146] and small amounts (ca. 5%) of hydroxy compounds were still obtained.



80% 5%

Appreciable quantities of water in the sulpholan appear to deactivate the system by either competing with the weakly basic substrate for protons or by increasing the solvation of the halide ions.

A preliminary investigation of the effect of various solvents on the reactions of heptafluoroquinoline was carried out by reacting equimolar solutions of heptafluoroquinoline with hydrogen chloride. Direct analysis of the products using a Griffin and George D6 Gas Density Balance Chromatograph was possible with all the solvents used except sulpholan. In the latter case the reaction mixture was poured into water and the products extracted into ether before analysis.

Table IX

Reactions of Heptafluoroquinoline with Hydrogen Chloride in various Solvents at Room Temperature

Solvent	Dielectric Constant	Time (hrs.)	Products (% Composition)* $2\text{-ClC}_9\text{NF}_6$	$2,4\text{-Cl}_2\text{C}_9\text{NF}_6$
Sulpholan	44	24	65	30
Acetone	20·7	24	20	70
Ether	4·3	24	50	1
Hexane	1·9	24	0	0
		48	5	0

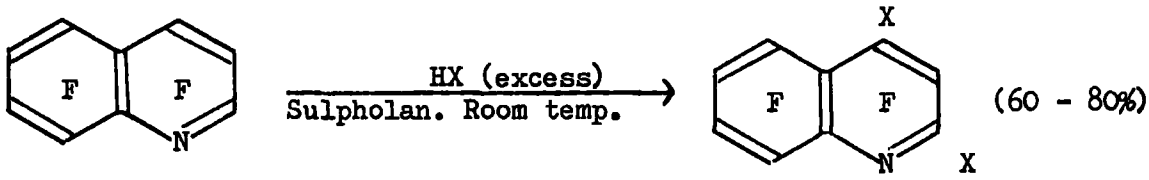
* Remaining percentage is heptafluoroquinoline.

The results (Table IX) show that reaction occurs most readily in the solvents of highest dielectric constants, namely, sulpholan and acetone, both dipolar aprotic solvents. In hexane, the solvent with the lowest dielectric constant investigated, there is virtually no reaction after 48 hours. A separate experiment showed that hydrogen chloride and heptafluoroquinoline do not react in the absence of a solvent even after heating at 100°C for 50 hours.

2. Heptafluoroquinoline.

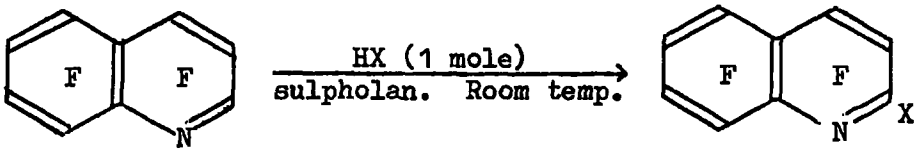
a. Reactions with hydrogen chloride and hydrogen bromide.

Heptafluoroquinoline reacted readily with hydrogen chloride and hydrogen bromide in dry sulpholan at room temperature. When the molar ratio of hydrogen chloride or hydrogen bromide was $\geqslant 2$ the corresponding 2,4-dihalopentafluoroquinoline was obtained in high yield.



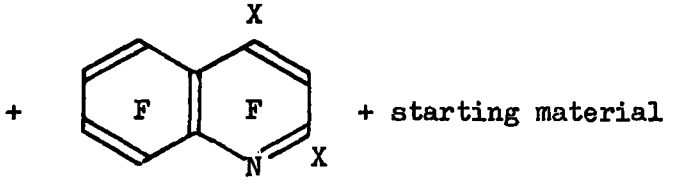
X = Cl, Br

It did not prove possible to prepare monohalohexafluoroquinolines as sole reaction products using equivalent quantities of heptafluoroquinoline and hydrogen halides. Under these conditions mixtures of monohalo-, dihalo-fluoroquinolines and unreacted starting material were isolated.



60%

X = Cl or Br



20% 20%

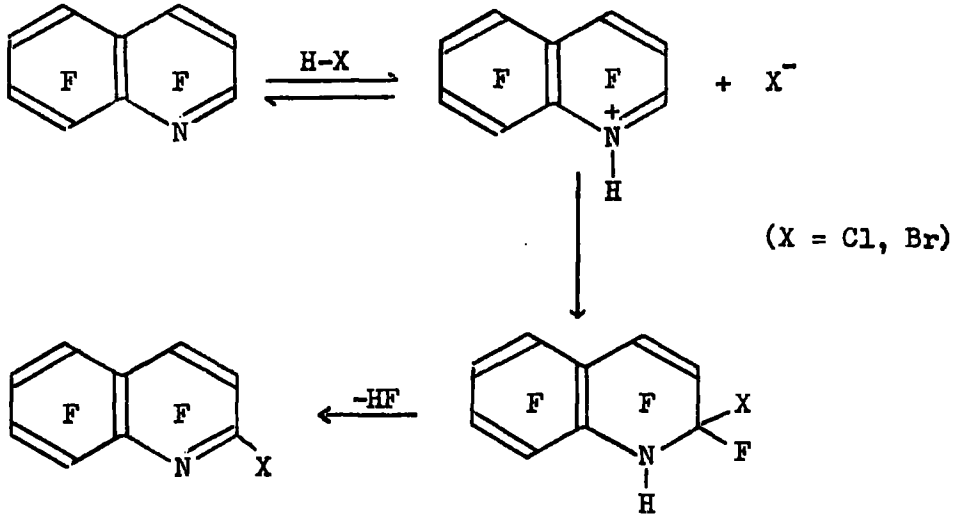
Mixtures of this type are not readily separated since all the components are of similar solubility and volatility and their retention times on preparative v.p.c. (at 200°C) are of such a length as to make this method of separation impracticable.

However, earlier ^{19}F n.m.r. work on polyfluoro-N-heteroaromatic compounds shows that the resonances of fluorine nuclei ortho to ring nitrogen appear at very low fields[36,58] and that the next signal to high field is due to fluorine para to the ring nitrogen. In the spectra of polyfluoroquinolines the 4-fluorine atom, if present in the molecule, is further characterised by a very large coupling (45-50 c.p.s.), which arises from peri-coupling between 4- and 5-fluorine atoms.[58]

Examination of the ^{19}F n.m.r. spectra of the mixtures obtained from reactions of equimolar quantities of hydrogen chloride or hydrogen bromide with heptafluoroquinoline with respect to the major component did not reveal a very low field peak which could be ascribed to a 2-fluorine resonance (See Chapter V). Furthermore, the lowest

field peak showed a doublet of doublets (J = 45 - 50 c.p.s. and 15 - 16 c.p.s.) characteristic of a 4-fluorine resonance. This showed clearly that monosubstitution had occurred at the 2-position and no evidence was obtained to suggest that any monosubstitution had occurred at position-4.

A probable mechanism for these reactions involves N-protonation of heptafluoroquinoline followed by nucleophilic attack of a halide ion on the perfluoroheterocyclic cation.



Specific monosubstitution at position-2 indicates that the mechanism is different from that of heptafluoroquinoline with neutral nucleophiles where monosubstitution occurs at 2- and 4-positions. Furthermore, 2,4-dichloroquinoline and 2,4,7-trichloroquinoline react with acidic reagents solely at the 2-position[148] but at the 2- and 4-positions with neutral nucleophiles.

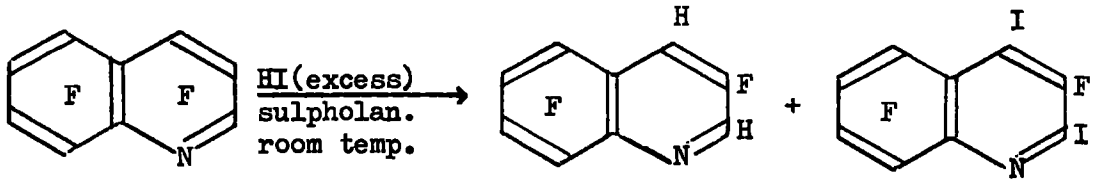
Replacement of the 2-fluorine in heptafluoroquinoline by another halogen should lead to an increase in base strength (Ch.II.A,2,b). Thus 2-halohexafluoroquinolines will be more readily protonated than heptafluoroquinoline and, because of this, reaction of equivalent amounts of heptafluoroquinoline and hydrogen halide always leads to mixtures of mono-halo and dihalo derivatives containing unreacted starting material.

Neither potassium chloride nor potassium bromide will react with heptafluoroquinoline in sulpholan at room temperature and no reaction was detected between potassium bromide and heptafluoroquinoline even after heating for nine days at 170°C. It would appear therefore, that the presence of acid is essential in these reactions.

b. Reactions with hydrogen iodide.

Reactions of hydrogen iodide with heptafluoroquinoline were found to be more complex than the corresponding reactions with hydrogen chloride or hydrogen bromide.

Reaction of heptafluoroquinoline with a four-fold excess of hydrogen iodide in sulpholan gave two products which were readily separable by fractional sublimation. A very volatile compound was first isolated and identified as 3,5,6,7,8-pentafluoroquinoline (51·2% yield) followed by a much less volatile compound which was identified as 2,4-di-iodopentafluoroquinoline (28·2%), the expected product.



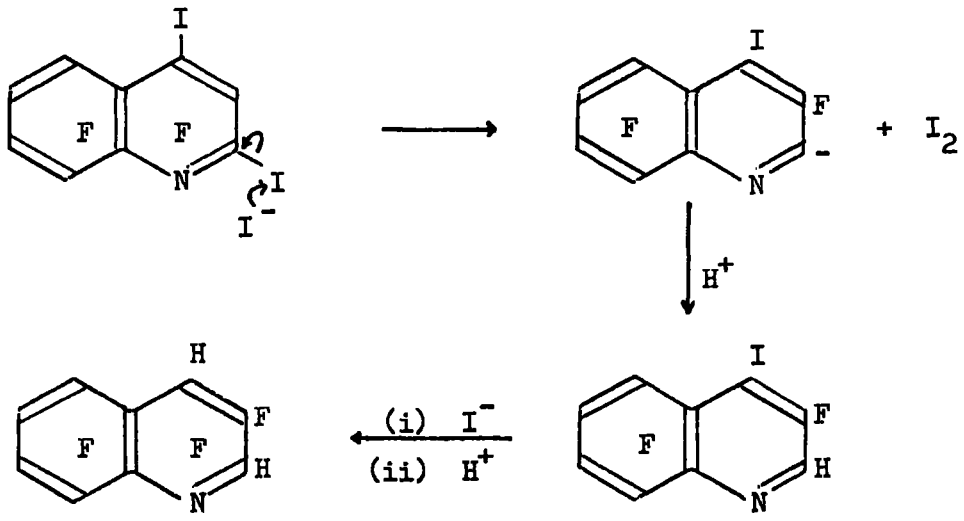
(51·2%) (28·2%)

Surprisingly, hydrogen iodide was found to react with heptafluoroquinoline in aqueous solution giving the same two products 3,5,6,7,8-pentafluoroquinoline and 2,4-di-iodopentafluoroquinoline in 40% and 30% yield respectively.

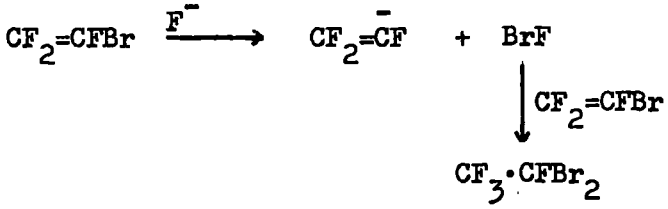
This contrasts markedly with reactions of heptafluoroquinoline with aqueous hydrogen chloride or hydrogen bromide which produce only hydroxy compounds.[145] No doubt the greater reactivity of aqueous hydrogen iodide towards heptafluoroquinoline reflects the greater nucleophilic activity of iodide ion in aqueous solutions compared with the other halide ions.[149]

The formation of 2,4-di-iodopentafluoroquinoline can be regarded as an analogous reaction to those with hydrogen chloride or hydrogen bromide giving 2,4-dihalopentafluoroquinolines (Ch.III.A,2,a).

However, the occurrence of 3,5,6,7,8-pentafluoroquinoline in the reaction product was not anticipated and this probably arises via a mechanism involving abstraction of positively polarised iodine, from 2,4-di-iodopentafluoroquinoline, by an iodide ion. The resulting carbanion can easily pick up a proton from the highly acidic reaction medium.



Abstraction of halogens by halide ions is not uncommon, for instance bromotrifluoroethylene in the presence of fluoride ion, gives 1,1-dibromotrifluoroethane via a reaction involving abstraction of bromine by fluoride ion.[150]



Abstraction of iodine by iodide ion from 4-iodotetrafluoropyridine followed by protonation of the tetrafluoropyridylcarbanion also explains the formation of 2,3,5,6-tetrafluoropyridine during the preparation of 4-iodotetrafluoropyridine.[48]

After reaction of hydrogen iodide with heptafluoroquinoline the reaction mixture always contained much free iodine which is consistent with the abstraction mechanism.

c. Attempted reactions with hydrogen cyanide.

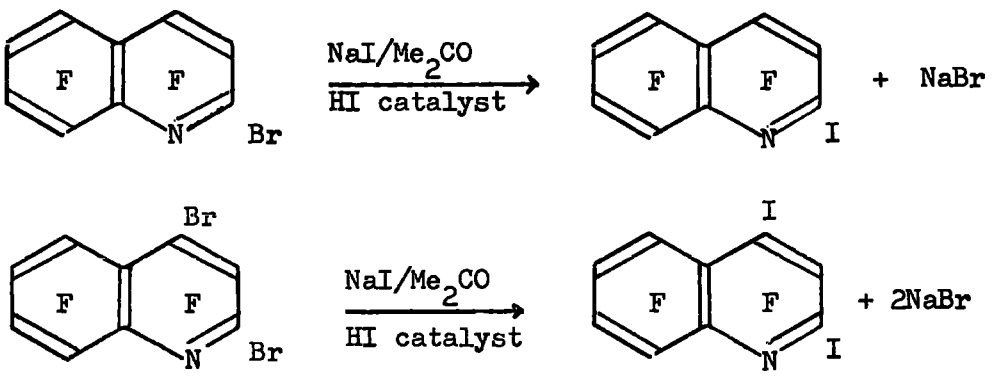
In view of the success of reactions with hydrogen halides attempts were made to introduce nitrile groups into heptafluoroquinoline by direct reaction with hydrogen cyanide.

No reaction occurred at room temperature or on heating at 110°C for 50 hours between hydrogen cyanide and heptafluoroquinoline in sulpholan.

Presumably hydrogen cyanide is such a weak acid that protonation of heptafluoroquinoline does not occur and consequently reaction is not possible.

d. Replacement of bromine in bromofluoroquinolines.

Both 2-bromohexafluoroquinoline and 2,4-dibromopentafluoroquinoline reacted readily with sodium iodide in acetone solution in the presence of a catalytic amount of hydrogen iodide giving the corresponding iodo compound.



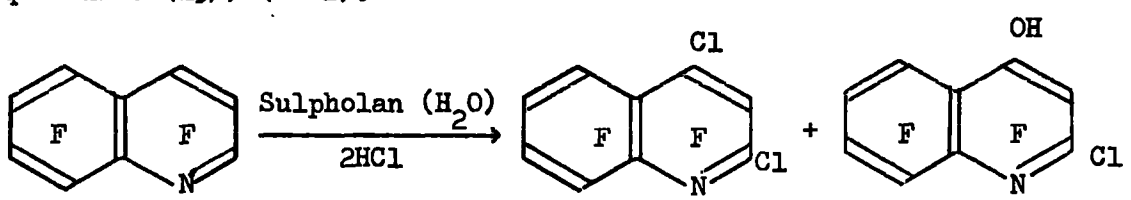
These reactions are clearly acid catalysed since no reaction occurred in the absence of a small amount of hydrogen iodide.

Heptafluoroquinoline did not react with sodium iodide under analogous conditions presumably because it is a much weaker base than the bromo derivatives and competes unfavourably with the solvent for the acid catalyst.

Reactions of this type have been used to prepare iodo heterocyclic compounds from the corresponding chloro- or bromo-precursor.[151,152,153]

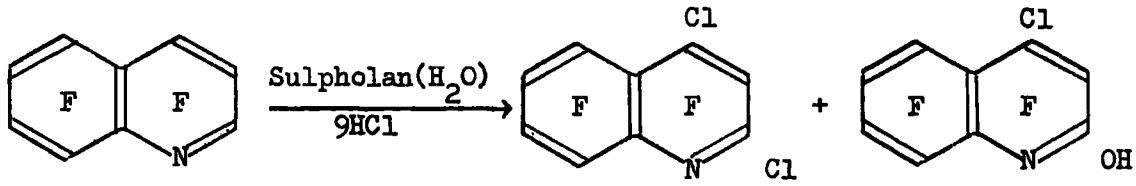
e. Preparation of, and tautomerism in, halohydroxypolyfluoroquinolines.

During initial reactions of heptafluoroquinoline with hydrogen chloride in sulpholan purified only by distillation, appreciable quantities of hydroxy derivatives were obtained. Indeed, two isomeric compounds were obtained depending on the ratio of hydrogen chloride to heptafluoroquinoline. With a heptafluoroquinoline-hydrogen chloride molar ratio of 1:2, reaction gave 2,4-dichloropentafluoroquinoline (57%), and a compound subsequently identified as 2-chloro-4-hydroxypentafluoroquinoline (23%) (XXVI).



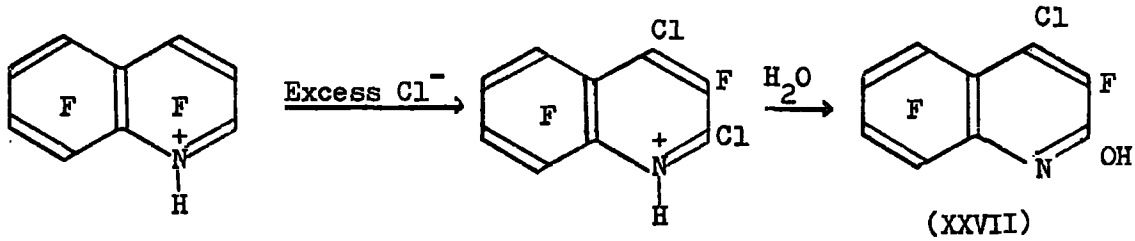
(XXVI)

On the other hand, a large excess of hydrogen chloride gave the same dichloropentafluoroquinoline (49%), and the isomeric 2-hydroxy-4-chloropentafluoroquinoline (29%).



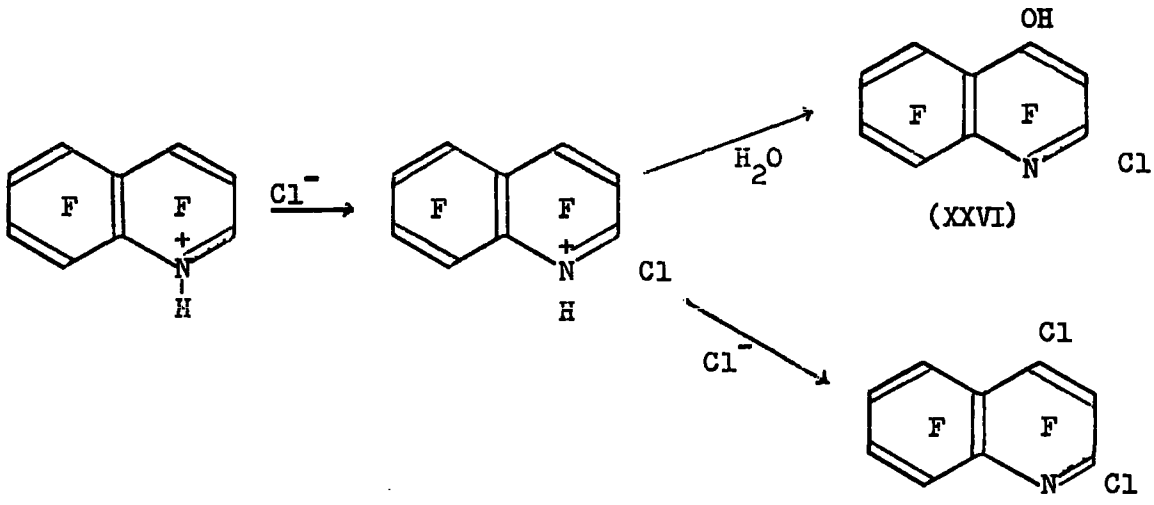
(XXVII)

Therefore, it appears that a large excess of hydrogen chloride rapidly produces 2,4-dichloropentafluoroquinoline and the conjugate acid of this dichloro derivative reacts further with water impurity in the sulpholan specifically replacing the 2-chlorine.



(XXVII)

However with a small excess of hydrogen chloride 2-chlorohexafluoroquinoline is produced initially and, because the concentration of chloride ion is much less in this case, competition for the substitution of the 4-fluorine takes place between water and chloride ion.



(XXVI)

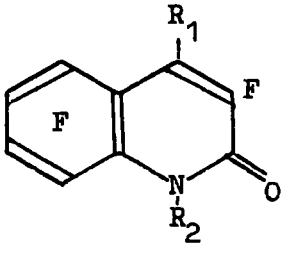
If the 4-fluorine is replaced by OH then the isomeric hydroxychloropentafluoroquinoline (XXVI) is produced.

This hypothesis was confirmed by reacting both 2-chlorohexafluoro- and 2,4-dichloropentafluoroquinoline with hydrogen chloride and water in sulpholan when the expected hydroxy compounds were obtained. These reactions indicate that fluorine is replaced in preference to chlorine even when the fluorine is in the less reactive 4-position.

Tentative assignment of the position of the hydroxy groups in the two isomeric chlorohydroxypentafluoroquinolines was possible from their i.r. spectra. The spectrum of (XXVII) showed a strong carbonyl absorption (1,670 $cm.^{-1}$) in common with those of other 2-hydroxypolyfluoroquinolines[59] (Table X), the carbonyl absorption is due to the

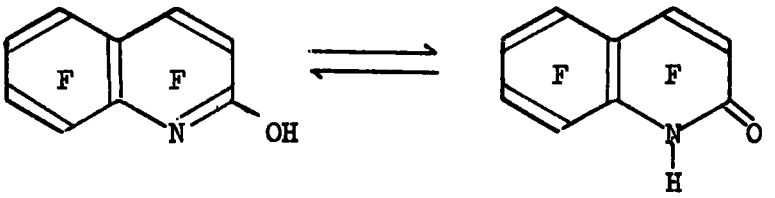
Table X

Carbonyl absorptions of 2-hydroxypolyfluoroquinolines and related compounds.



R_2	R_1	$\nu_{C=O}$ ($cm.^{-1}$)
H	F	1,704
H	OMe	1,661
Me	F	1,686
Me	OMe	1,678

fact that the 2-hydroxypolyfluoroquinolines are tautomeric systems i.e.



(XXVIII) (XXIX)

Polyfluoro-4-hydroxyquinolines show no evidence of tautomerisation within the limits of detection. For example their i.r. spectra do not show a strong carbonyl absorption and, on methylation with diazomethane, they give only an o-methyl derivative.[59] Methylation of the 2-hydroxypolyfluoroquinolines using the same reagent gives two isomeric methylated products due to reaction with(XXVIII)and(XXIX).

The product of hydrolysis of 2,4-dichloropentafluoroquinoline was methylated with diazomethane and v.p.c. showed a mixture of two products in the ratio of 3:1 with the most volatile component in excess.

A specimen of the least volatile component was obtained pure by fractional sublimation and recrystallisation and was identified as N-methyl-4-chloropentafluoro-2-quinolone, its i.r. spectrum showed a characteristic carbonyl absorption at 1,670 $cm.^{-1}$

The other isomer could not be purified by recrystallisation or by preparative scale v.p.c. but ^{1}H and ^{19}F n.m.r. spectral data were consistent with those expected for 2-methoxy-4-chloropentafluoroquinoline. The products of methylation confirm that (XXVI) is tautomeric and the n.m.r. of the o-methyl derivative confirms that the compound has the hydroxy group in the 2-position.

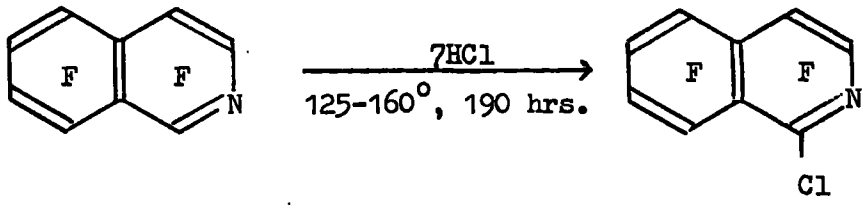
Methylation of (XXVII) gave only a single product which was identified as 4-methoxy-2-chloropentafluoroquinoline. Similarly 4-hydroxy-2-bromopentafluoroquinoline gave only the corresponding methoxy compound on methylation. These results are in agreement with other observations on polyfluorohydroxyquinolines.[59]

3. Heptafluoroisoquinoline.

a. Reactions with hydrogen chloride.

Heptafluoroisoquinoline was found to be much less reactive than heptafluoroquinoline towards hydrogen chloride. Conditions required for reaction were such that extensive decomposition occurred.

After heating heptafluoroisoquinoline with a two molar ratio of hydrogen chloride in sulpholan for 100 hours at 125°C only a 10% yield of 1-chlorohexafluoroisoquinoline was obtained and starting material (52%) was recovered. With a 7 molar excess of hydrogen



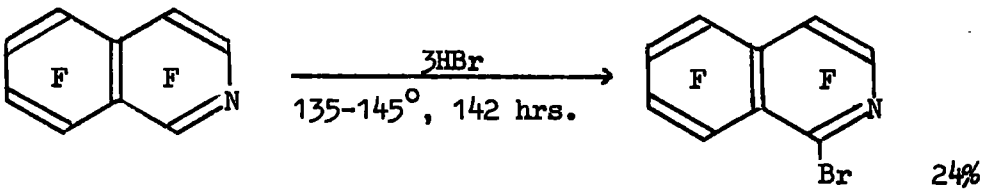
42%

chloride the yield of 1-chlorohexafluoroisoquinoline was increased to 42% but no unreacted starting material could be detected.

b. Reactions with hydrogen bromide.

Reactions of heptafluoroisoquinoline with hydrogen bromide were similar to those with hydrogen chloride except that decomposition

occurred apparently even more readily. The best conversion to 1-bromohexafluoroisoquinoline was 24%, obtained on heating a 3:1 molar ratio of hydrogen bromide and heptafluoroisoquinoline at 135-145° for 142 hours.



24%

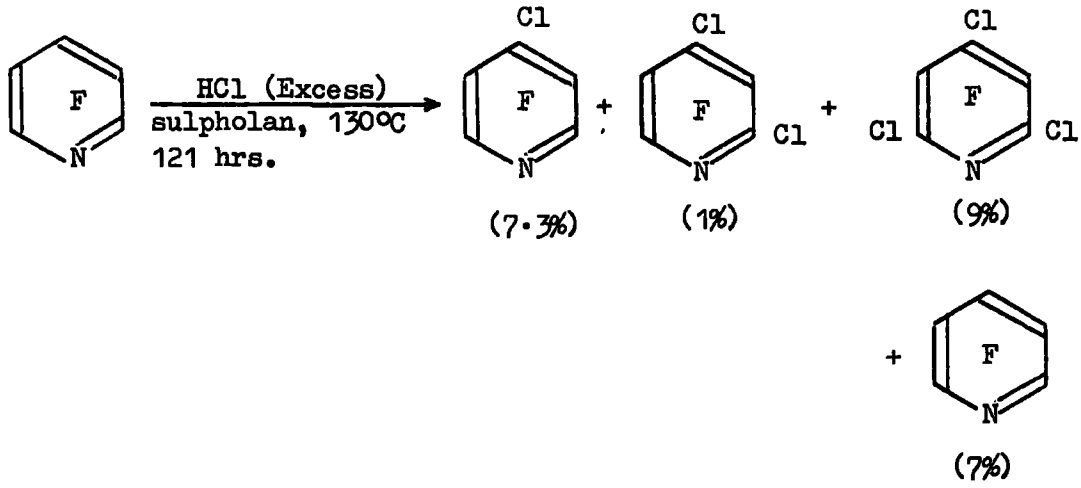
Small amounts of hydroxy derivatives were obtained from reactions of hydrogen chloride or hydrogen bromide with heptafluoroisoquinoline but not, unfortunately, in sufficient yield to permit full characterization. However, their mass spectra indicated a molecular formula C_9NF_5OHX (X = Cl or Br) and both compounds showed a strong carbonyl absorption in their i.r. spectra (1,724 $cm.^{-1}$, X = Cl; 1,715 $cm.^{-1}$, X = Br) and they are, therefore, probably 1-hydroxyhalo-pentafluoroisoquinolines.

The reactivity of heptafluoroisoquinoline towards nucleophiles in neutral solution is almost equal to that of heptafluoroquinoline and both are approximately 2·5 times more reactive than pentafluoro-pyridine.[58] If reactions of hydrogen halides involve direct nucleophilic substitution by halide ion, rather than an acid catalysed path, then both heptafluoroquinoline and heptafluoroisoquinoline would be expected to be equally reactive. The difference in reactivity observed can most obviously be attributed to differences in base strength of the two compounds.

4. Pentafluoropyridine.

a. With hydrogen chloride.

Pentafluoropyridine was also found to be much less reactive then heptafluoroquinoline with hydrogen chloride. Reaction of two molar proportions of hydrogen chloride with one of pentafluoropyridine gave only starting material (60% recovery) after heating at 130°C for 121 hours. However, a 9:1 molar excess of hydrogen chloride reacted with pentafluoropyridine under similar conditions to give a product containing three different chlorofluoropyridines and starting material. Analytical scale v.p.c. and ^{19}F n.m.r. spectroscopy showed the product to comprise 4-chlorotetrafluoropyridine[154] (7·3%), a trace (~1%) of what was assumed to be 2,4-dichlorotrifluoropyridine and 2,4,6-trichlorodifluoropyridine (9%), as well as starting material (7%).

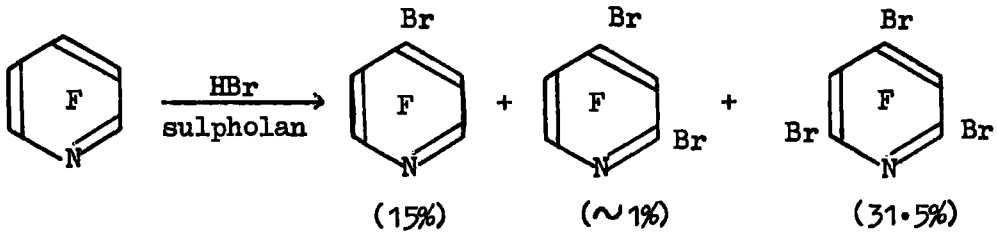


b. With hydrogen bromide.

Hydrogen bromide also reacted sluggishly with pentafluoropyridine

but slightly higher yields of bromo derivatives were obtained.

A three fold excess of hydrogen bromide with pentafluoropyridine under conditions analogous to those described for hydrogen chloride gave a similar series of bromofluoropyridines and no starting material



was recovered.

Pentafluoropyridine appears to be even less reactive than heptafluoroisoquinoline towards hydrogen halides. Again this is consistent with the probable order of base strengths of these compounds, the factor which would, of course, be critical for reactions involving N-protonation. Unfortunately, the orientation of substitution in pentafluoropyridine is the same as that observed for nucleophilic attack on the neutral molecule and so acid induced reactions are of less value with this system.

B

Reactions of Polyfluoro-N-heteroaromatic Compounds with 'Super Acids'.

Introduction.

It was noted in Part A of this Chapter that both pentafluoropyridine and heptafluoroisoquinoline were much less reactive than heptafluoroquinoline towards hydrogen halides and this is probably due to differences in basicity between these systems. It was therefore decided to use more acidic reagents which should produce more facile reactions with the less basic substrates.

Mixtures of hydrogen halides with boron or aluminium halides produce very acidic media, for example HBF_4 (from HF and BF_3) is a factor of 10^5 stronger than concentrated sulphuric acid.[155]

Reagents of this type have been used to add hydrogen halides to fluoro-olefins via an electrophilic mechanism.[156,157,158] The first step of such a reaction of course, is essentially protonation of the weakly basic olefin.

$$CF_3 \cdot CF=CF_2 \xrightarrow{HBr,\ AlBr_3} CF_3 \cdot CFH \cdot CF_2Br \qquad 70\% \qquad \text{Ref.157}$$

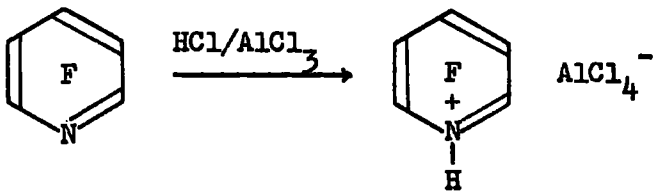
It was therefore decided to investigate the reactions of perfluoro-N-heteroaromatic compounds with reagents of this type.

1. Pentafluoropyridine.

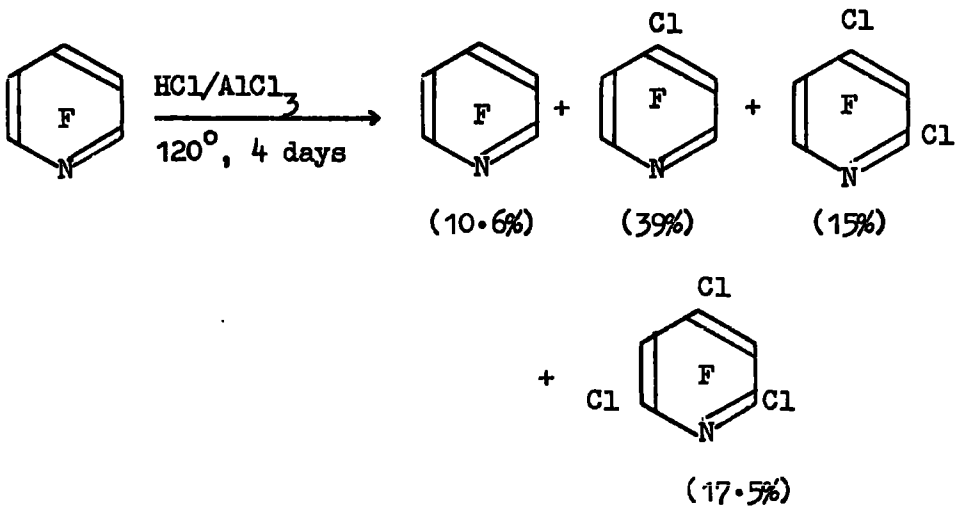
a. Reaction with hydrogen chloride and aluminium chloride.

Molar equivalents of hydrogen chloride, aluminium chloride and

pentafluoropyridine were sealed into an evacuated tube. On standing, the aluminium chloride appeared to dissolve in pentafluoropyridine giving a viscous oil, and, on shaking, so that hydrogen chloride was mixed well with the oil, the contents of the tube turned to an off white solid. Presumably this was pentafluoropyridinium tetrachloroaluminate.

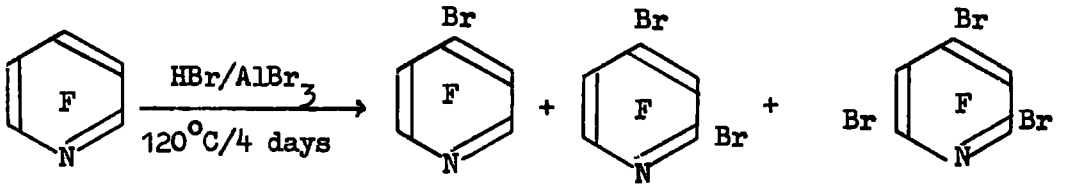


The tube was heated for four days at 120°C and, after hydrolysis and extraction, gave pentafluoropyridine (10·6% recovery), 4-chlorotetrafluoropyridine (39%), 2,4-dichlorotrifluoropyridine (15%), and 2,4,6-trichlorodifluoropyridine (17·5%).



b. Reaction with hydrogen bromide and aluminium bromide.

Pentafluoropyridinium tetrabromoaluminate was prepared and treated in an analogous fashion to the tetrachloroaluminate, the reaction product was the expected mixture of bromofluoropyridines but unreacted pentafluoropyridine was not detected.



(33%) (9·2%) (17%)

Reaction carried out at 150°C for 40 hours gave only 4-bromotetrafluoropyridine and 2,4,6-tribromodifluoropyridine in 44% and 31% yield respectively.

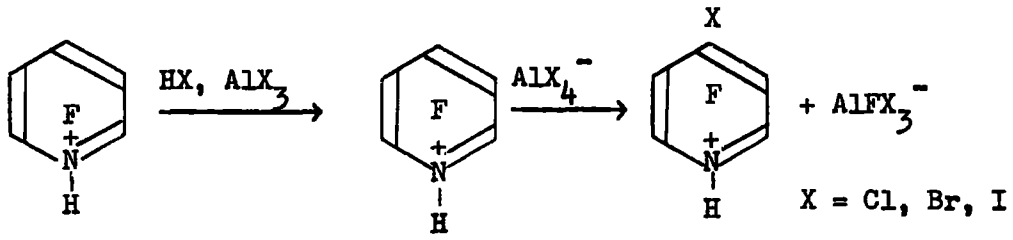
c. Reaction with hydrogen iodide and aluminium iodide.

Reaction of equimolar quantities of hydrogen iodide, aluminium iodide and pentafluoropyridine at 120°C for 24 hours gave 4-iodotetrafluoropyridine (46%). Traces of unreacted starting material and similar quantities of two other components, with slightly longer retention times, could be detected on v.p.c. analysis of the crude product but they were present in such small amounts that isolation and characterisation was not possible. It is likely that the unknown compounds were lowly fluorinated pyridines arising from iodide abstraction side reactions.

Comparison of the extent of halogenation using these 'super' acid reagents with that of simple hydrogen halides shows that the former gives much more facile reaction. Replacement of fluorine by chlorine or bromine using a 'super' acid gave a 60-70% yield of halogenated materials whereas the reactions of hydrogen halides gave only 20-35% yields of halogenated compounds under more forcing conditions. Enhanced reactivity with 'super' acids can most obviously be attributed to more extensive protonation by these strongly acidic materials.

It is worth noting that the yields of 2,4-dihalotrifluoropyridines are always low in reactions of hydrogen halides or 'super' acid media and this may be related to the expected order of base strength. Replacement of a fluorine ortho to ring nitrogen will produce a greater base strengthening than replacement of fluorine atoms further removed from ring nitrogen (Ch.III. A.2,a). Thus, 2,4-dihalotrifluoropyridines will be considerably stronger bases than either pentafluoropyridine or 4-halotetrafluoropyridines and will compete more readily for protons resulting in its rapid reaction to 2,4,6-trihalodifluoropyridines.

Reaction can therefore be interpreted in terms of halogen exchange between pentafluoropyridinium ions and tetrahaloaluminate ions.

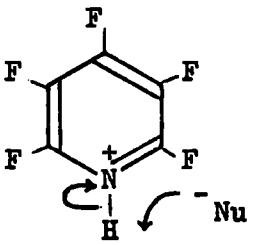


A similar exchange reaction involving the perfluorotrityl carbonium ion and $[AlX_3OH]^-$ has recently been reported.[160] The high bond energy of Al-F bonds ensures that fluorine is retained by aluminium in reactions of this type and also offsets the energy required to break the aromatic C-F bond.[161,162]

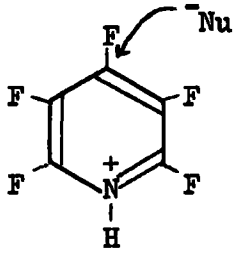
Substitution in pentafluoropyridine using these acidic reagents occurs at position-4, then sequentially at the 2- and 6-positions. Kinetic data for substitution in isomeric N-methylchloropyridinium ions indicates that the 4-position has the lowest activation energy although entropy effects cause the rate of reaction to be greatest for the 2-chloro isomer. It is likely that in pentafluoropyridinium ions the activation energy for substitution at the 4-position is lower than that at any other position and that entropy effects are not important enough to cause greater reactivity at position-2 rather than position-4.

Furthermore, pyridinium ions produced by protonation of pyridine differ from N-methyl pyridinium ions in that the former are not irreversibly quaternised, whereas the latter are, and this may be important so far as the rate of attack at the 2- or 4-positions

is concerned.[163] Coulombic attraction between the nucleophile and the proton may, prior to attack at the 2-position, result in deprotonation rather than substitution (XXXI).



(XXXI)



(XXXII)

However, approach of the nucleophile for attack at the 4-position is not likely to cause deprotonation (XXXII). Such an effect would lead to faster reaction at position-4 as compared with position-2 and is likely to be of some importance for very weak bases such as pentafluoropyridine which readily undergo deprotonation.

d. Attempted reactions with hydrogen halides and boron halides.

Because extensive polysubstitution of pentafluoropyridine occurred using mixtures of hydrogen halides and aluminium halides this limited the use of the reaction in the preparation of halotetrafluoropyridines.

The possibility of obtaining a higher yield of 4-bromotetrafluoropyridine and less polybromo compounds using a mixture of boron fluoride and hydrogen bromide (hypothetically HBF_3Br) in which there is only one bromine atom compared with four in hydrogen bromide-aluminium bromide mixture was investigated.

Reaction of equimolar quantities of boron fluoride, hydrogen bromide and pentafluoropyridine at 120°C for three days gave only starting material, furthermore, reaction did not occur between boron chloride and hydrogen chloride under similar conditions.

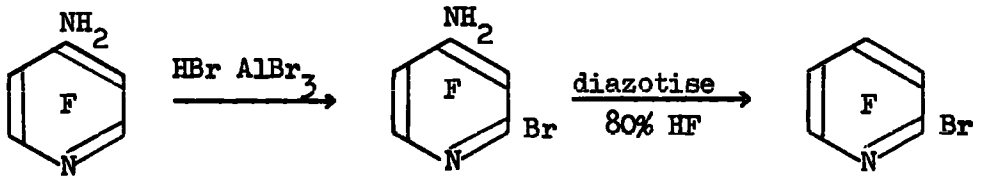
Lack of reaction in these systems is probably due to the fact that the reaction

$$C_5F_5N + HX + BX_3 \longrightarrow C_5F_5\overset{+}{N}H \quad BX_4^-$$

does not occur (the contents of the Carius tubes after filling remained liquid) although the corresponding pyridinium tetrahaloborates $C_5H_5\overset{+}{N}H \quad BCl_4^-$ are known.[164]

2. Reaction of 4-aminotetrafluoropyridine with hydrogen bromide and aluminium bromide

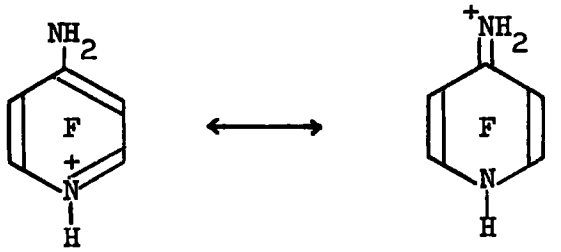
A possible route to 2-bromotetrafluoropyridine appeared to be bromination of 4-aminotetrafluoropyridine using hydrogen bromide and aluminium bromide, followed by replacement of the amino group in 2-bromo-4-aminotrifluoropyridine by diazotisation in 80% hydrogen fluoride.



However, this scheme was not possible since 4-aminotetrafluoropyridine did not give brominated compounds on heating for three days at 140°C or 160°C with hydrogen bromide and aluminium bromide, starting

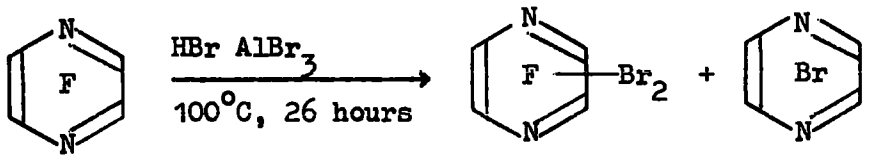
material only was recovered.

Considering the effect of substituents on the base strengths of pyridines (Ch.II.A,2b) 4-aminotetrafluoropyridine should be a stronger base than pentafluoropyridine. However, activation to nucleophilic substitution by protonation may be offset, in 4-amino-tetrafluoropyridine, by localisation of the charge onto the exocyclic amino group nitrogen. It is interesting to note that in non-



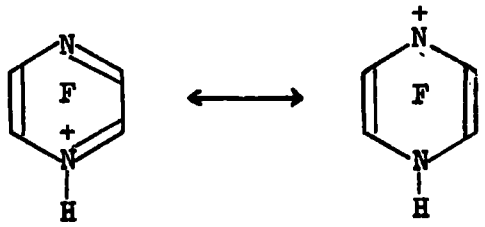
fluorinated heterocyclic compounds if an amino group is α or γ to the aza group then acid catalysed nucleophilic substitution does not occur.[110]

Tetrafluoro-1,4-diazine reacted readily with hydrogen bromide and aluminium bromide although this compound is most likely a weaker base than pentafluoropyridine (Ch.II. A,2a).



If charge localisation onto the unprotonated ring nitrogen occurs to any extent in this compound it is unlikely that any appreciable

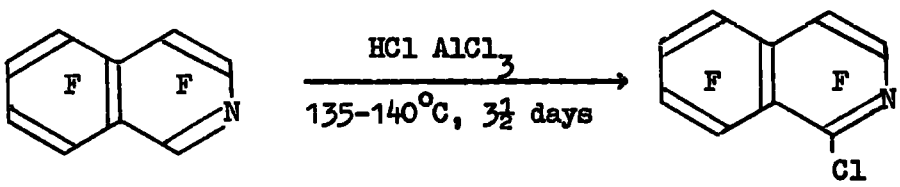
decrease in activation will ensue, since the nitrogen, in this case, is not an exocyclic substituent as in 4-aminotetrafluoropyridine.



3. Heptafluoroisoquinoline.

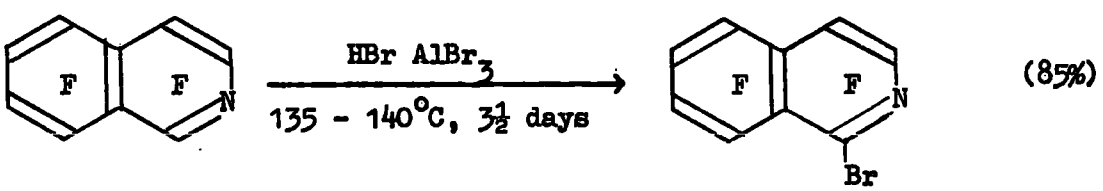
a. Reaction with hydrogen chloride and aluminium chloride.

As expected, in view of the results obtained with pentafluoropyridine, heptafluoroisoquinoline gave an excellent yield of 1-chlorohexafluoroisoquinoline on reaction with hydrogen chloride and aluminium chloride.



b. Reaction with hydrogen bromide and aluminium bromide.

Similarly, these reagents gave a good yield of 1-bromohexafluoroisoquinoline under conditions analogous to those used for the preparation of the chloro derivative.

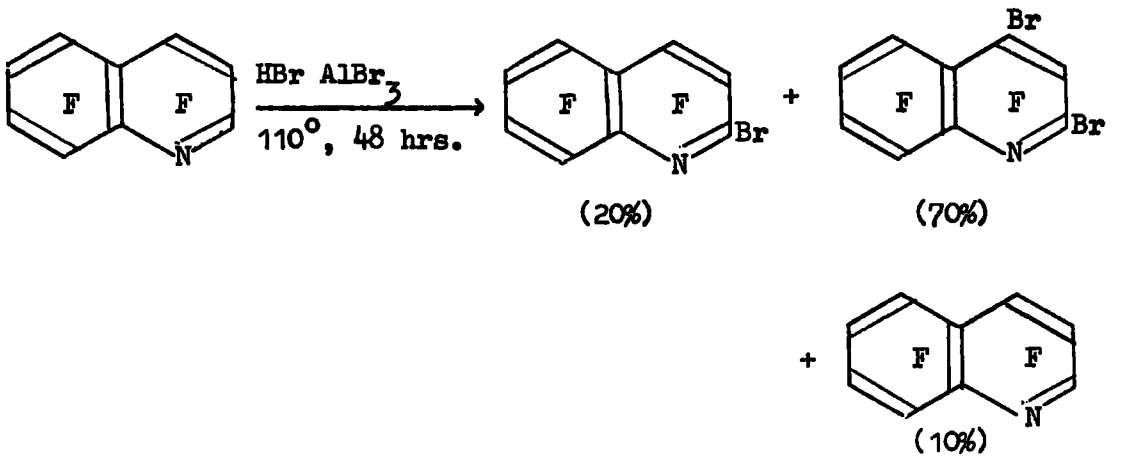


The increase in reactivity of heptafluoroisoquinoline and pentafluoropyridine can best be explained in terms of a much more strongly acidic reagent. Although, in the case of pentafluoropyridine extensive polysubstitution occurs this method offers an excellent route to 1-chloro- and 1-bromohexafluoroisoquinolines.

4. Heptafluoroquinoline.

Reaction with hydrogen bromide and aluminium bromide.

Although there was little doubt that heptafluoroquinoline would react with these reagents, a reaction was carried out under intentionally mild conditions, so that the monosubstituted compound could be detected.



Formation of 2-bromohexafluoroquinoline as the sole monosubstituted product gives a clear indication that, as in reactions with hydrogen halides alone, N-protonation is involved.

5. Attempted extensions to benzenoid systems.

It was interesting to find that pentafluoroaniline would react with hydrogen bromide and aluminium bromide giving brominated materials, but the reaction was complex. Various isomers of bromofluoroanilines were produced which could not be separated, as well as substantial amounts of black, involatile and ether insoluble material, which, judging by its featureless infra-red spectrum, was probably polymeric material.

Decafluorobenzophenone is apparently protonated in sulphuric or fluorosulphonic acid.[165] It seemed likely that this compound would

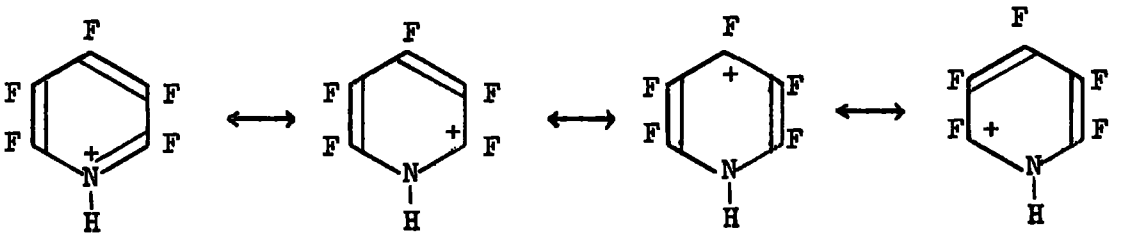
react with hydrogen bromide and aluminium bromide, furthermore, if the product was 2,2'-dibromo-octafluorobenzophenone this would be an invaluable material for the preparation of octafluorofluoren-9-one.[165] However, from reaction of decafluorobenzophenone with hydrogen bromide and aluminium bromide at 160°C for two days only starting material (75%) was recovered.

Clearly, reactions involving protonation of exocyclic groups do not give satisfactory results so far as the preparation of synthetically useful compounds is concerned.

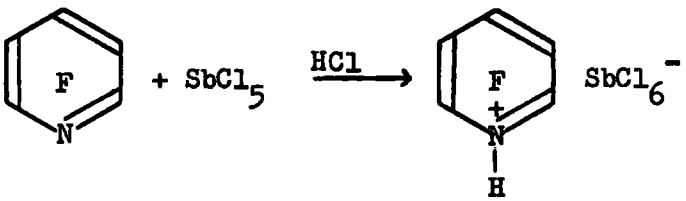
6. The preparation and isolation of stable polyfluoroheterocyclic hexafluoroantimonate salts.

Because polyfluoroheterocyclic compounds were very reactive

towards hydrogen halide - aluminium halide mixtures, which are regarded as 'super' acid systems, it was of interest to determine whether or not crystalline salts could be isolated using acids of this type. One may regard these compounds as having appreciable carbonium ion character since the positive charge produced on nitrogen can be transmitted to the ring carbon atoms and, of course, fluorine attached to ring carbon will facilitate such an effect.



One of the simplest procedures for preparing salts appeared to be saturation of an equimolar solution of antimony pentachloride and fluoroheterocyclic compound with hydrogen chloride to produce a hexachloroantimonate. This was attempted, using methylene chloride



as a solvent, and on addition of hydrogen chloride gas, a white crystalline precipitate was thrown down, however isolation of the material was not possible. Shortly after formation it darkened and finally gave a black tarry material. This could probably arise from halogen exchange reactions between $SbCl_6^-$ ion and the heterocyclic compound. Such complications do not arise when the anion is SbF_6^-,

and indeed, as shown by Olah, SbF_6^- can stabilise weakly basic protonated species.

Reaction of perfluoroheterocyclic compounds with hydrogen fluoride and antimony pentafluoride in liquid sulphur dioxide gave quantitative yields of the corresponding hexafluoroantimonates. The crystals produced on removal of the solvent were removed from the apparatus in, and stored in, a dry box.

Analysis of the salts for fluorine by the technique used in Durham was not possible, since antimony interfered, but correct carbon analyses were obtained. Furthermore i.r. spectroscopy on these compounds always showed a broad intense band at 666 $cm.^{-1}$, typical of hexafluoroantimonates.[166]

^{19}F N.m.r. spectra of the salts and their free bases were recorded at $-10^{\circ}C$ in liquid sulphur dioxide solvent. For the free bases $CFCl_3$ was used as internal reference but trifluoroacetic acid was used as internal reference for the salts. This was because $CFCl_3$ probably reacts with $HSbF_5$ (from dissociation of the salts) and leads to reference complications. However, $CF_3 \cdot COOH$ is known to be stable towards $HSbF_5$.[167] All shifts were related to $CFCl_3$ by measuring the shift of $CF_3 \cdot COOH$ from $CFCl_3$ in liquid sulphur dioxide.

The spectral data was interesting from the point of comparison with non-fluorinated heterocyclic ions and in comparison with fluorobenzenonium ions.

TABLE XI

^{19}F n.m.r. Data for Pentafluoropyridine, 3,5-Dichlorotrifluoropyridine and their Conjugate Acids

Pentafluoropyridine	89·5(2,6) complex	135·0(4) T.T. J = 13·8, 18·0 c.p.s.	163·5(3,5) complex
Conjugate acid	97·8(2,6) complex	107·1(4) T.T. J = 21·6, 27·3 c.p.s.	156·4(3,5) complex
δ	+8·3	-28·9	-7·1
3,5-Dichlorotrifluoropyridine	71·1(2,6) D.$J_{2,4}$ = 14·0 c.p.s.		96·8(4) T.$J_{2,4}$ = 14·0 c.p.s.
Conjugate acid	79·1(2,6) D.$J_{2,4}$ = 25·3 c.p.s.		96·8(4) T.$J_{2,4}$ = 25·3 c.p.s.
δ	+8·0		-28·7

T. = Triplet

D. = Doublet

Assignments in parentheses

Shifts relative to $CFCl_3$ (p.p.m.)

For pentafluoropyridine, (Table XI), and its conjugate acid, three signals are observed with relative intensities 2:1:2, and clearly, in both cases, the signal of lowest intensity can be assigned to the 4-position. Indeed, this signal showed the expected triplet of triplets splitting and, for the free base, the coupling constants are J = 13·8 and J = 18·0 c.p.s., whereas, for the ion J = 21·6 and

27·3 c.p.s. The remaining resonances show more complex splitting patterns, particularly in the spectrum of the ion, and were therefore assigned from chemical shift, the lowest field resonance being assigned to the 2,6-fluorines.

The spectrum of the 3,5-dichlorotrifluoropyridinium ion, (Table XI), was simpler, and could be fully analysed. Two signals were observed, the least intense (triplet, $J_{2,4}$ = 25·3), again due to the 4-fluorine, the remaining resonance (doublet J = 25·3 c.p.s.) must be due to 2- and 6-fluorines. As can be seen in the Table the internal shift values, (δ), between protonated and unprotonated species correlate well with each other supporting the assignments made on chemical shift basis for pentafluoropyridinium ions.

Spectral data for heptafluoroquinolinium, heptafluoroisoquinolinium and tetrafluoro-1,4-diazinium hexafluoroantimonates were also recorded, and can be found in Table XII.

Spectra of heptafluoroquinoline and isoquinoline and their conjugate acids are very complex. Full analyses and assignment of resonances is not possible but certain peaks can be assigned from the low field position of fluorine ortho to nitrogen, (1- and 3-fluorine resonances in isoquinoline, and 2-fluorine resonance in heptafluoroquinoline), or using the large peri couplings (4 and 5-fluorines in heptafluoroquinoline, and 1 and 8-fluorines in the isoquinoline). It is interesting to note that the peri coupling, $J_{4.5}$ in heptafluoro-

Table XII

^{19}F n.m.r. Data for Conjugate Acids of some Perfluoroheterocyclic Compounds

Heptafluoroquinoline								
Free Base	75·0(2)	126·5(4)		148·5(5)	151·0	154·2	157·5	163·7
Conjugate Acid	78·1(2)	95·2(4)	138·1	140·0(5)	147·7	150·7	159·4	
δ	+3	-31·3		-8·5				
Heptafluoroisoquinoline								
Free Base	63·5(1)	99·3(3)	141·6	147·3	148·0	155·3	157·5	
Conjugate Acid	69·1(1)	113·9(3)	133·2	134·8(8)	142·7	147·1	150·3	
δ	+5·6	+14·6						
Tetrafluoro-1,4-diazine								
Free Base	95·9							
Conjugate Acid	90·9							
δ	-5·9							

Shifts (in p.p.m.) rel. to $CFCl_3$, assignments in parentheses.

quinoline is ca. 42 c.p.s. and is increased to 55 c.p.s. on protonation, whereas $J_{1.8}$ in heptafluoroisoquinoline remains constant at 65 c.p.s. on protonation.

Tetrafluoro-1,4-diazinium hexafluoroantimonate shows only one signal, presumably because rapid exchange of the proton between the two nitrogen atoms occurs.

Examination of the internal shifts of nuclei (δ), shows clearly that on protonation, the fluorines ortho to ring nitrogen are shifted upfield, whereas meta and para fluorines are shifted downfield. The shift of the latter being of the order of 30 p.p.m.

This is clearly due to N-protonation since solutions of these compounds in concentrated sulphuric or fluorosulphonic acid show the same trend in their n.m.r. spectra (Table XIII) and u.v. evidence is consistent with N-protonation in these solvents.[38]

The proton n.m.r. of the pyridinium ion has been studied,[168,169,170] and although all proton signals are downfield from the signals in the neutral base, the shift of protons ortho to nitrogen is extremely small. This has been attributed either to paramagnetic effects of the lone pair on nitrogen,[169] or possibly to an increase in electron density at the carbon atoms bonded to nitrogen.[170]

In the light of this evidence it appears as though any correlation of ortho fluorine shifts with charge density on ring carbon is not possible, since these positions are likely to be

Table XIII

^{19}F Chemical Shifts of some Perfluoro-N-Heteroaromatic Compounds in Acids

Pentafluoropyridine							
H_2SO_4	91·0(2,6)		123·4(4)	158·1(3,5)			
δ	+1·5		-11·6	+5·4			
FSO_3H	90·6(2,6)		120·3(4)	157·2(3,5)			
δ	+1·1		-14·7	-6·3			
Heptafluoroquinoline							
H_2SO_4	86·1(2)	92·1(4)	134·1	136·3(5)	144·9	146·5	156·2
δ	+8·10	-34·4		-2·2			
FSO_3H	85·3(2)	91·5(4)	134·1	136·0(5)	143·8	146·2	156·0
δ	+10·3	-35		-2·5			
Heptafluoroisoquinoline							
H_2SO_4	69·8(1)	118·9(3)	133·3	135·5	142·3	145·7	148·7
δ	+5·3	+19·6					

Shifts in p.p.m. rel. to $CFCl_3$, assignments in parentheses.

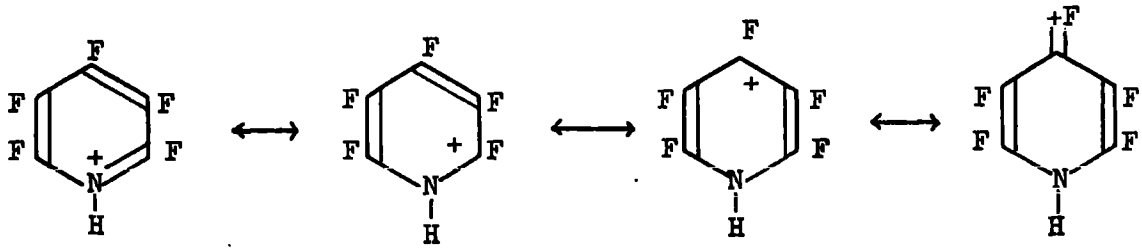
δ values computed from shift values of free base in liquid SO_2.

affected by other factors.

However, meta and para fluorine shifts would appear to reflect the carbonium ion character of carbon atoms at these positions in the ring.

Olah[171] has prepared and measured n.m.r. spectra of some fluorobenzenonium ions and noted that the fluorines ortho and para to the site of protonation are shifted downfield by ca. 100 p.p.m., and those meta by 10 p.p.m. Furthermore, large increases in F-F coupling constants are observed e.g. in the 2,4-difluorobenzenonium ion, the F-F coupling is 80 cycles/sec., whereas in fluorobenzenes, meta F-F couplings are of the order 2-4 cycles/sec.

It is concluded that the observed downfield n.m.r. shifts of meta and para fluorines in the conjugate acids of perfluoro-heterocyclic compounds, and the observed increase in coupling constants, is indicative of considerable carbonium ion character of carbon atoms at these positions. The large downfield shift of fluorine para to the site of protonation shows the localisation of charge on the para position, and this correlates with the high reactivity of that position.



7. Other attempted quaternisation reactions.

a. Attempted N-oxidation of heptafluoroquinoline.

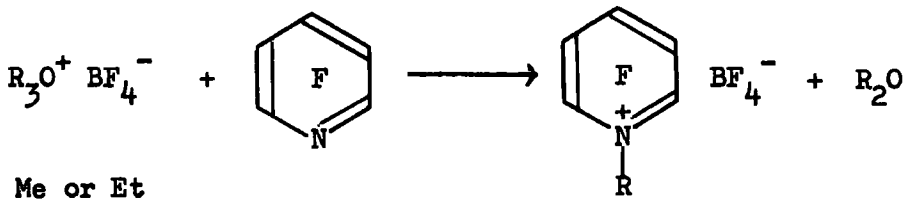
Heptafluoroquinoline was refluxed with a solution of peroxytrifluoroacetic acid in methylene chloride for two hours which produced a bright yellow solution. The reaction mixture was allowed to stand overnight at room temperature and, after extraction, gave a very small amount of bright yellow gum whose i.r. spectrum was featureless, and starting material (80%) was recovered.

A similar reaction, using a large excess of peroxytrifluoroacetic acid in excess trifluoroacetic acid as solvent, gave, after 5 hours reflux, only a similar yellow gum and starting material was not recovered.

Pentachloropyridine may be converted to its N-oxide with peroxytrifluoroacetic acid, but prolonged reaction times (> 5 hours), result in deoxygenation and regeneration of starting material.[172] Heptafluoroquinoline, in the light of these results, is apparently destructively oxidised by peroxytrifluoroacetic acid rather than N-oxidation occurring to any appreciable extent.

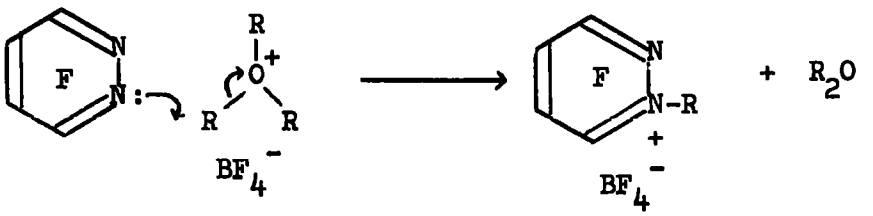
b. N-alkylation of pentafluoropyridine and heptafluoroquinoline.

Meerwein's reagents, triethyl and trimethyl oxonium tetrafluoroborates, are known to be excellent reagents for N-alkylation of weakly basic heterocyclic compounds.[123] Both trimethyl and triethyl oxonium tetrafluoroborate were prepared,[173] and reactions of these alkyloxonium salts with pentafluoropyridine and heptafluoroquinoline were attempted.



R = Me or Et

After refluxing in methylene chloride for several hours neither heterocyclic compound gave N-alkyl derivatives. Examination of the crude reaction mixture, (in the case of pentafluoropyridine), by ^{19}F n.m.r. did not show any peaks which could be attributed to a quaternised species. Furthermore, after addition of wet ether to the crude heptafluoroquinoline reaction mixtures, starting material was recovered quantitatively, rather than the expected N-alkylhexafluoro-2-quinolone from reaction of water with an N-alkyl salt. It is interesting to note that tetrafluoro-1,2-diazine can be quaternised using trialkyloxoniumfluoroborates[174] which no doubt indicates that tetrafluoro-1,2-diazine is a better nucleophile, and therefore, most likely a stronger base, than pentafluoropyridine or heptafluoroquinoline.



R = Me or Et

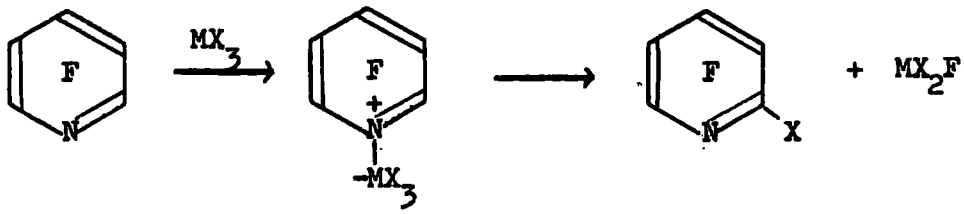
CHAPTER IV

Reactions of Perfluoroheteroaromatic Compounds with Lewis Acids

Introduction.

Reactions of protonic acids with perfluoroquinoline and pentafluoropyridine give good yields of polysubstituted compounds but since polysubstitution occurs readily with these reagents, these reactions do not offer a viable route to monosubstituted compounds.

It appeared possible that N-co-ordination of these heterocyclic compounds with strong Lewis acids could be achieved and, therefore, the investigation was extended to reactions of boron and aluminium halides with perfluoroheteroaromatic compounds. Co-ordination of the ring nitrogen in this fashion should produce an effect qualitatively the same as N-protonation and, furthermore, potentially nucleophilic halogen is produced adjacent to the α-positions which should facilitate substitution at these positions.



M = Al or B.
X = Cl, Br or I

Part A of this chapter will discuss reactions of boron halides with perfluoroheteroaromatic compounds and Part B will deal with corresponding

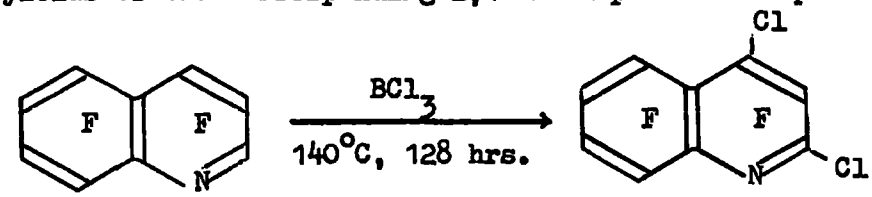
reactions of aluminium halides.

A

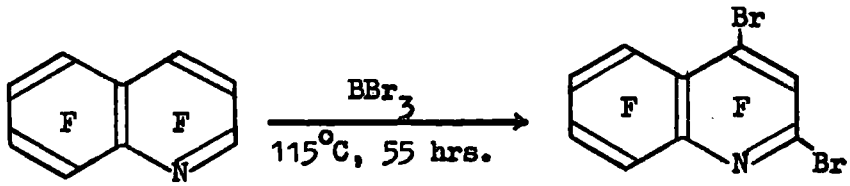
Reactions of Perfluoro-heteroaromatic Compounds with Boron Halides.

1. Heptafluoroquinoline.

Equimolar quantities of boron trichloride and heptafluoroquinoline at 160°C for 72 hours gave a mixture of 2-chlorohexafluoroquinoline (~10%), 2,4-dichloropentafluoroquinoline (~90%) and a small amount (< 1%) of unreacted starting material. However, an excess of boron trichloride or boron tribromide with heptafluoroquinoline gave very high yields of the corresponding 2,4-dihalopentafluoroquinolines.



(91%)



(87%)

Under similar conditions, where both boron trichloride and boron tribromide gave smooth reaction with heptafluoroquinoline, boron tri-iodide gave an intractable tar. At 75°C, no reaction occurred between boron tri-iodide and heptafluoroquinoline, apparently the boron halide was decomposing even at this temperature since iodine was observed subliming from the reaction mixture.

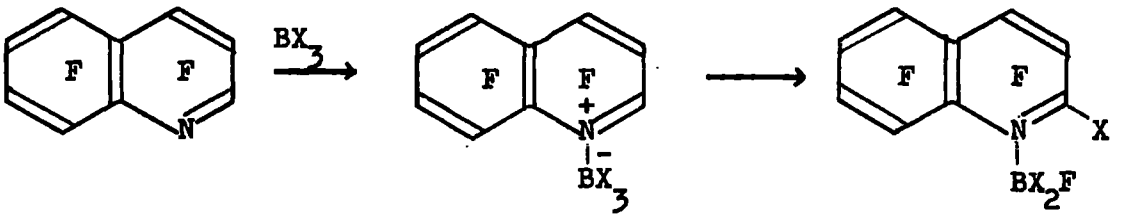
2. Pentafluoropyridine and Heptafluoroisoquinoline.

Pentafluoropyridine did not react with boron trichloride after 85 hours at 75°C. Even after heating for 209 hours at 160°C with a large excess (5 molar) of boron trichloride there was still no appreciable reaction, although v.p.c. analysis did show a trace (~0·5%) of a compound with a retention time similar to that of a monochlorotetrafluoropyridine.

Heptafluoroisoquinoline did not react with boron tribromide, a stronger Lewis acid than boron trichloride,[175] after heating for 284 hours at 150°C, starting material (85%) was recovered.

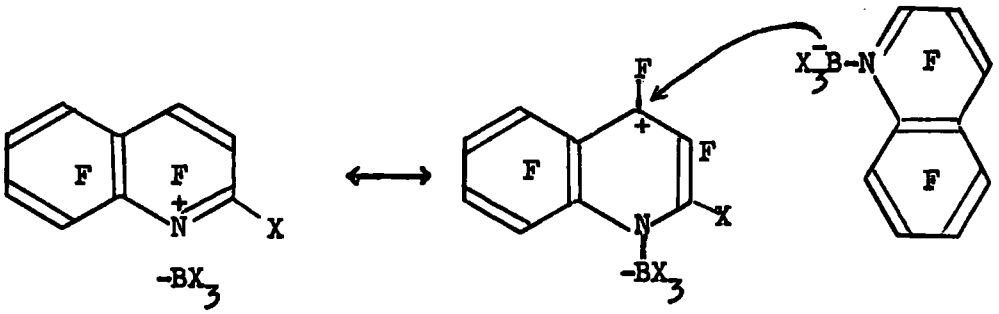
Again the difference in reactivity of pentafluoropyridine and heptafluoroisoquinoline, compared with heptafluoroquinoline, can most obviously be attributed to differences in base strength.

The orientation of substitution in heptafluoroquinoline in reactions with boron trichloride and boron tribromide is the same as that observed with other acidic reagents. Substitution at position-2 may arise by an intramolecular halogen exchange within the adduct (XXIII), but such a process cannot give replacement of the 4-fluorine, leading

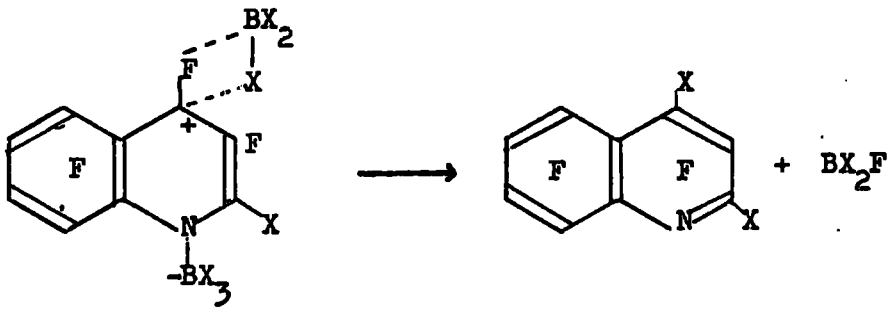


(XXIII)

to the 2,4-disubstituted compound. It is probable that this occurs via an intermolecular process as shown below:

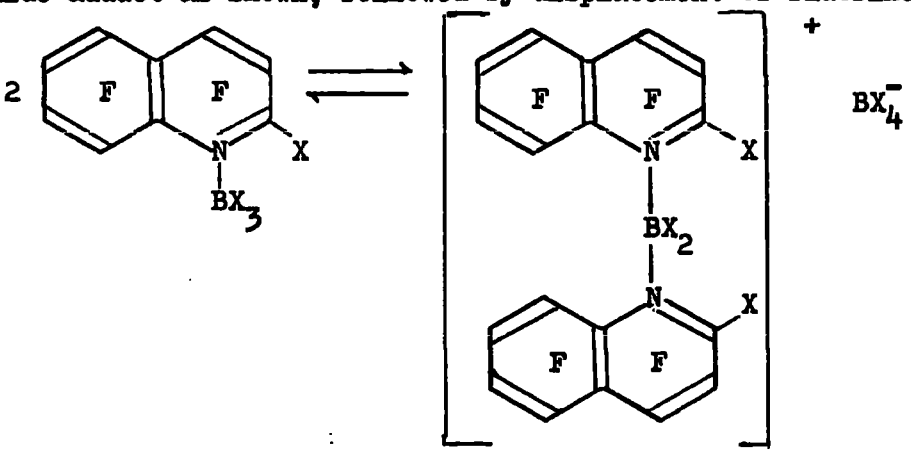


or in a similar fashion to the halogen exchange reaction in boron halide mixtures, i.e.



Indeed, initial reaction at the 2-position could equally well occur via such mechanisms.

A less probable mechanism involves dissociation of the boron halide adduct as shown, followed by displacement of fluorine



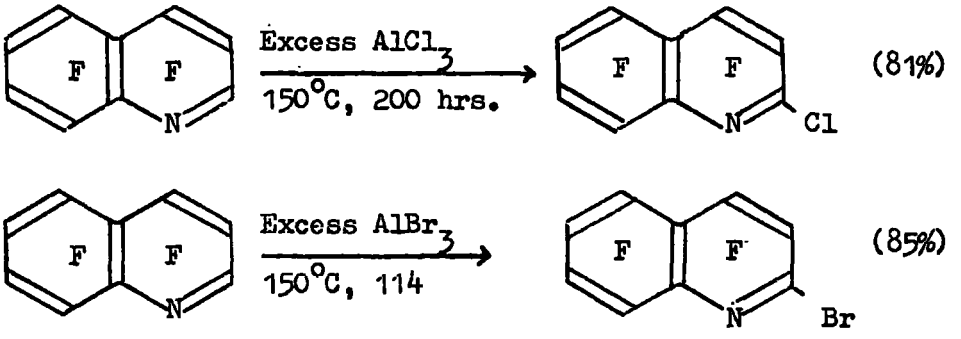
by BX_4^-. Dissociation of this type in pyridine-boron trichloride melts has been detected.[176]

B

Reactions of Perfluoroheteroaromatic Compounds with Aluminium Halides.

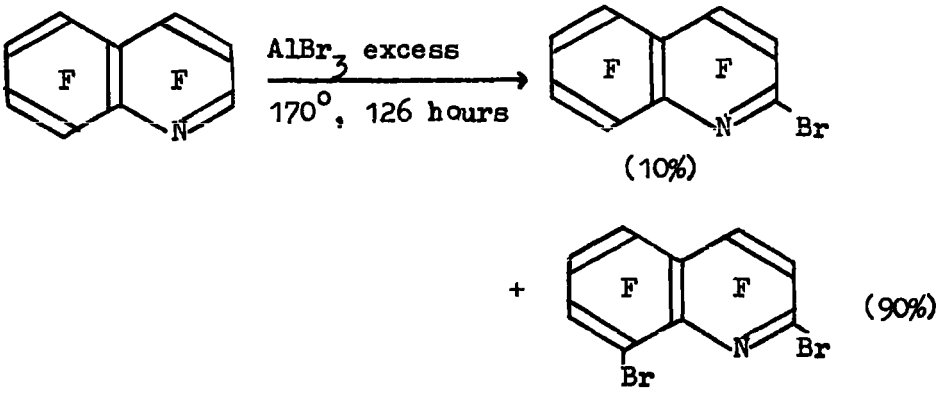
1. Heptafluoroquinoline.

Both aluminium chloride and aluminium bromide reacted with heptafluoroquinoline, on heating at 150°C, to give excellent yields of the corresponding 2-halohexafluoroquinolines.

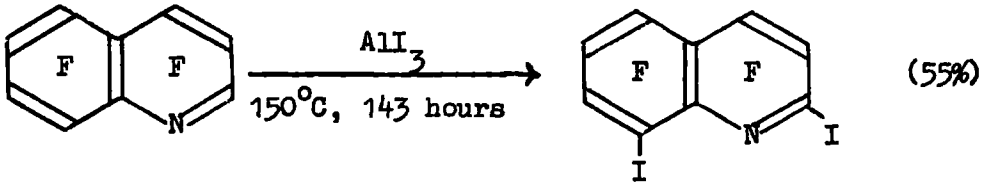


At temperatures below 150°C only traces of the haloderivatives could be detected and starting material was recovered.

On heating heptafluoroquinoline with excess aluminium bromide, at 170°C, a mixture of 2-bromohexafluoroquinoline (10%) and a dibromopentafluoroquinoline (90%) was obtained. The latter compound was isolated pure, and identified by ^{19}F n.m.r. spectroscopy as 2,8-dibromopentafluoroquinoline.



Aluminium iodide gave only 2,8-di-iodopentafluoroquinoline under conditions where aluminium bromide gives only 2-bromohexafluoroquinoline.



(55%)

The rather low yield from this reaction appears to be due to extensive decomposition of the product at 150°C; appreciable quantities of involatile tarry material were noticed during the work up procedure.

2. Pentafluoropyridine and Heptafluoroisoquinoline.

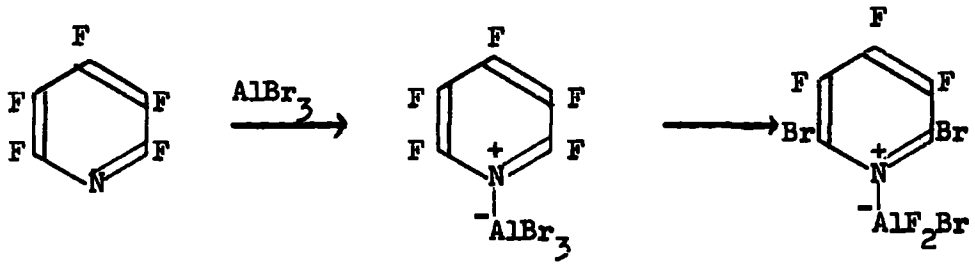
Pentafluoropyridine was much less reactive than heptafluoroquinoline towards aluminium bromide. After heating at 165°C for 10 days only trace amounts of bromofluoropyridines were produced and extensive decomposition occurred. A small quantity of a mixture of two bromofluoropyridines together with starting material was isolated. Mass spectrometry showed that the mixture contained a bromotetrafluoropyridine and a dibromotrifluoropyridine. Only the latter could be isolated as a pure specimen and was identified as 2,6-dibromotrifluoropyridine by ^{19}F n.m.r. spectroscopy although there was insufficient for complete characterization. Therefore, although 2-bromotetrafluoropyridine is the most likely monobromo derivative

contained in the product, this reaction does not present a useful route to this compound.

Under conditions where aluminium bromide gave trace amounts of bromo derivatives with pentafluoropyridine, heptafluoroisoquinoline was completely decomposed.

Reactions of aluminium halides with pentafluoropyridine and heptafluoroquinoline give a good indication that reaction occurs on the heterocycle-Lewis acid adduct. In the case of pentafluoropyridine the 2- and 6-fluorines are replaced by bromine on reaction with aluminium bromide and the 2- and 8-fluorines are replaced in heptafluoroquinoline on treatment with aluminium bromide or aluminium iodide. This contrasts with substitution in these substrates using either hydrogen halides alone, or as a mixture with aluminium halides, when the 4-fluorine is replaced in pentafluoropyridine and the 2- and 4-fluorines in heptafluoroquinoline.

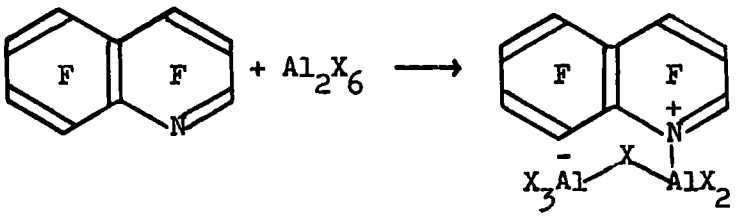
Replacement of the 2- and 6-fluorines in pentafluoropyridine can occur by halogen exchange in the adduct (XXIV).



(XXIV)

It was surprizing that disubstitution in heptafluoroquinoline occurred at the 8-position during reactions with aluminium halides, whereas, boron halides gave the 2,4-disubstituted derivative.

It may be that this is due to the dimeric nature of aluminium halides and the very weak donor properties of heptafluoroquinoline giving rise to an adduct of the type (XXV), which would facilitate

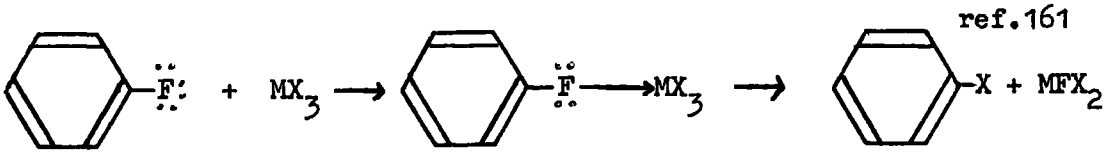


(XXV)

substitution at the 8-position.

An adduct such as (XXV) would be analogous to the heptachlorodialuminate anion $Al_2Cl_7^-$. Formation of this type of compound with boron halides of course, is not possible.

An exchange mechanism as described by Olah,[161] involving complex formation between the Lewis acid and non bonding electrons on fluorine, does not appear to apply in the reactions described here.



During the course of this work Russian[177] workers have published results on the exchange of fluorine between hexafluorobenzene and aluminium halides. They have found that, at temperatures of 300°C, mixtures of starting material, C_6X_6, C_6F_5X and all possible isomers of $C_6F_4X_2$, $C_6F_3X_3$, and $C_6F_2X_4$ are obtained, which is consistent with the mechanism described above. Hexafluorobenzene did not react to any appreciable extent with boron trichloride on heating for 7 days at 150°C, only trace amounts of C_6Cl_6, C_6Cl_5F, $C_6F_4Cl_2$ and starting material (70% recovery) were isolated. It would appear that reactions of perfluoroheterocyclic compounds do not involve this type of mechanism. If such a mechanism were operating one would expect all the heterocyclic compounds to be of similar reactivity which is clearly not so. They do appear to be generally more reactive than hexafluorobenzene towards Lewis acids and this suggests that the mechanism involves N-co-ordination of the heterocyclic compound by the Lewis acid. This is supported by the appearance of strong orange-brown colourations on mixing aluminium halides, and, for example, heptafluoroquinoline since quinoline-aluminium halide adducts are known to be highly coloured.[178]

CHAPTER V

Assignment of Orientation in Halopolyfluoroheteroaromatic Compounds

Because chemical methods of proving orientation of substitution in polyfluoro-N-heteroaromatic compounds are not often successful, particularly with polyfluoroquinolines,[145] the only suitable method of general applicability is that of ^{19}F n.m.r. spectroscopy.

A

Nuclear Magnetic Resonance Spectra of Halopolyfluoroheteroaromatic Compounds

^{19}F n.m.r. spectra were recorded using a Perkin-Elmer R.10 spectrometer operating at 56·45 Mc/sec. and samples were examined as solutions in carbon tetrachloride with hexafluorobenzene as internal reference. Chemical shifts are given relative to trichlorofluoromethane (i.e. $\delta_{CFCl_3} = 162{\cdot}3 + \delta_{C_6F_6}$).

^{1}H n.m.r. spectra were recorded on the Perkin-Elmer R.10 spectrometer operating at 60 Mc/sec. Samples were examined as solutions in carbon tetrachloride using tetramethylsilane (T.M.S.) as internal reference.

Both ^{19}F and ^{1}H n.m.r. data can be found in Appendix 1.

The resolution available for ^{19}F n.m.r. work coupled with the complex nature of the spectra, did not permit complete analysis in the case of polyfluoroquinolines and isoquinolines. Consequently the assignment of

orientation in these derivatives has been made principally on chemical shifts of positions in the heterocyclic ring, and the presence or absence of large peri coupling constants in the spectra.

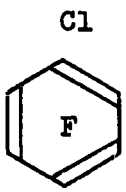
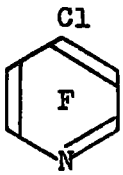
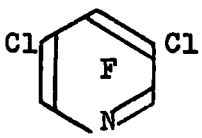
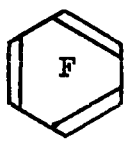
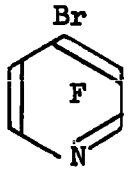
Before any assignment of orientation on the basis of chemical shifts can be made it is necessary to assess the effect of substituents on fluorine chemical shifts. The most common substituent encountered in this work was a halogen, other than fluorine, and Table XIV shows the effect of a halogen on fluorine ortho, meta or para to the halogen. Where the terms ortho, meta and para lead to ambiguity the number in [ ] refers to the fluorine shifted. Negative shifts refer to shifts to lower field, whereas positive shifts refer to ones to higher field.

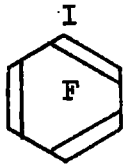
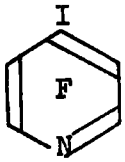
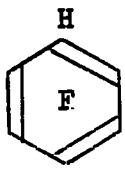
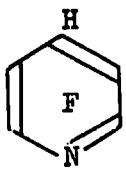
It is clear from Table XIV that, for pentafluorophenyl derivatives and polyfluoropyridyl derivatives, the effect of halogen is greatest on fluorine ortho to it, and produces downfield shifts of the order 20 p.p.m., 30 p.p.m. and 40 p.p.m. respectively for chlorine, bromine, and iodine. Halogen substituent effects for meta and para fluorines in a polyfluoropyridine system do not show a consistent trend as in pentafluorophenyl compounds. However, these effects are small ($\pm$ 1-5 p.p.m.) compared with the corresponding ortho effects and do not prevent reliable structural assignments being made.

A number of polyfluoroquinoline and isoquinoline derivatives have been studied[58] and it appears that substituent effects obtained for

Table XIV

The effect of halogen substituents on ^{19}F n.m.r. chemical shifts in polyfluoroaromatic compounds

Halogen substituent	Compound	ortho	meta	para	ref. compound	Ref.
Cl		-23 -22·1	-1 -1·5	-7 -6·6	C_6F_6	179 180
		-20	+1	-	C_5F_5N	154
	(A) 	[2]-16 [4]-20	+2	-2	C_5F_5N	47
		[2]-16	-	+2	(A)	47
Br		-30 -30	-2·0 -2·0	-8 -10·0	C_6F_6	179 180
		-27·7	+0·9	-	C_5F_5N	

Halogen substituent	Compound	ortho	meta	para	ref. compound	Ref.
I		-43 -43.4	-3.0 -2.9	-10.0 -10.0	C_6F_6	179 180
		-40.6	+0.2	-	C_5F_5N	48
H		-24	0	-9	C_6F_6	179
		-21	+5	-	C_5F_5N	55

polyfluoropyridyl derivatives are applicable to the quinoline systems.

B

Halopolyfluoropyridines

The relevant data obtained for the halopolyfluoropyridines is given in Table XV.

1. 2,4-Dihalotrifluoropyridines.

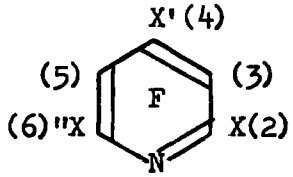
The lowest field signal is assigned to the 6-fluorine because it falls in the same shift region as the 2- and 6-resonances in pentafluoropyridine, and in the 4-halotetrafluoropyridines. The highest field peak can be assigned to the 5-fluorine resonance, which again occurs in the same region as the 3- and 5-resonances of the corresponding 4-halotetrafluoropyridines.

The small shift of the 5- and 6-fluorines on replacement of the 2-fluorine by another halogen in 4-halotetrafluoropyridines is to be expected since meta and para substituent effects for halogens are small.

Resonances occurring at 119·8 p.p.m. and 107·3 p.p.m. are therefore ascribed to the 3-fluorine in 2,4-dichloro and 2,4-dibromotrifluoropyridine respectively. Assuming that chlorine and bromine shift ortho fluorines by -20 and -28 p.p.m. respectively, then using the shift data for 4-halotetrafluoropyridines, one computes that the 3-fluorine resonance in 2,4-dichloro- and 2,4-dibromotrifluoropyridine should occur at 122·0 and 106·3 p.p.m. respectively, which agree well with the observed values.

Table XV

^{19}F n.m.r. data for halopolyfluoropyridines.[a]



		Shift from $CFCl_3$		
A	X = X' = Cl	84·8(6)	119·8(3)	143·0(5)
	X" = F	D.D. $J_{3,6}$ = 28, $J_{5,6}$ = 23	D. $J_{3,6}$ = 28	D. $J_{5,6}$ = 24
B	X = X' = Br	85·3(6)	107·3(3)	130·9(5)
	X" = F	D.D. $J_{3,6}$ = 27, $J_{5,6}$ = 23	D. $J_{3,6}$ = 27	D. $J_{5,6}$ = 23
	X = X" = Br	130·2(3,5)[b]	139·4(4)	
	X' = F	T. $J_{3,4}$ = 18·4	D. $J_{3,4}$ = 18·6	
	X = X' = X" = Cl	117·6(3,5)		
	X = X' = X" = Br	104·4(3,5)		

Effect on ^{19}F shifts				
Group	ortho	meta	para	ref. compound
Cl(2)	-22·2	-3·8	+1	4-ClC_5F_4N
Br(2)	-27	-3·2	-3·4	4-BrC_5F_4N
Br(2,6)	-31·8	+5·3	-	C_5F_5N
Cl(6)	-25·4	-	-2·2	A
Br(6)	-26·5	-	-2·9	B

[a] Solutions in CCl_4

[b] Intensity twice that of other peak

Coupling constants J in c.p.s.

Assignments in parentheses

D = Doublet

T = Triplet

Examination of the coupling constants also supports these assignments. The 6-resonance is a doublet of doublets, J = 28, 23 c.p.s. and the two remaining signals are doublets J = 28(3) and J = 24(5). Hence $J_{3,6}$ = 28 c.p.s. and $J_{5,6}$ = 23·5 c.p.s., in the ranges observed for other polyfluoropyridine derivatives,[181,182] and $J_{3,5}$ must be zero or near zero[182] to account for the absence of any observable coupling between the 3- and 5-fluorine nuclei.

2. 2,6-Dibromotrifluoropyridine.

This spectrum shows two resonances at 130·2 and 139·4 p.p.m. with the former being twice the intensity of the latter. Since no signal is observed in the region 80-90 p.p.m. the 2,6-fluorines are assumed absent. Because of its intensity, and also since it occurs in the same region as the 4-fluorine in pentafluoropyridine, the resonance at 139·4 p.p.m. is assigned to the 4-fluorine. This is confirmed by its appearance as a triplet, $J_{3,4}$ = 18·6 c.p.s.

The remaining resonance, a doublet $J_{3,4}$ = 18·4 c.p.s., is assigned to the 3,5-resonance and is shifted to lowfield by 31·8 p.p.m. due to the ortho bromine atoms, relative to its position in pentafluoropyridine.

3. 2,4,6-Trihalodifluoropyridines.

Only a sharp singlet resonance is observed, and can, in view of the fact that the compounds are produced along with 2,4-dihalopyridines,

only arise from the symmetrical 2,4,6-trihalo compounds.

Although 3,4,5-trihalodifluoropyridines would also show a single resonance, it would be expected to be a broadened signal (due to ring nitrogen), and also to occur below 90 p.p.m.

C

Halopolyfluoroquinolines

1. 2-Halohexafluoroquinolines.

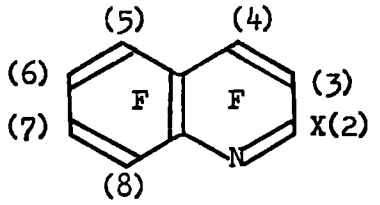
The absence of any resonance in the region of 77 p.p.m., or below (Table XVI), indicates that the 2-fluorine has been replaced.[58] Two resonances showing large (45-47 c.p.s.) couplings are discernible, and, by analogy with other spectral data on polyfluoroquinolines,[58,145] can be assigned to the 4- and 5-fluorines which undergo peri-coupling of this magnitude.

The 4-fluorine resonance can be distinguished from the 5-fluorine resonance by its lower field position, and by the coupling it shows with the 3-fluorine ($J_{3,4} \sim 17$ c.p.s.). Because halogens are known to shift ortho fluorines to low field, the remaining low field resonance (below 147 p.p.m.) may be assigned to the 3-fluorine, and its appearance as a doublet ($J_{3,4}$ = 15-17 c.p.s.) confirms this assignment.

In the spectrum of heptafluoroquinoline only the 2-, 4- and 5-fluorine resonances may be assigned with certainty,[145] but the resonance of the 3-fluorine clearly must be one of the remaining signals, all of which occur above 146 p.p.m. Examination of the spectra of the 2-halo-

Table XVI

^{19}F n.m.r. data for 2-halohexafluoroquinolines.[a]



X	Shifts relative to $CFCl_3$ (p.p.m.)						
F	77·2(2) T(broad) J 21-25	126·0(4) D.D.D. $J_{4,5}$ = 49 J = 25 and 17	145·7(5) D. $J_{4,5}$ = 49	148·3	150·7	154·4	160·6
Cl	-	128·0(4) D.D. $J_{4,5}$ = 47, $J_{3,4}$ = 16	142·3(3) D. $J_{3,4}$ 15	146·0(5) D.T.D. $J_{4,5}$ = 47 J = 17 and 7	147·2	150·0	153·1
Br	-	128·7(4) D.D. $J_{4,5}$ = 45, $J_{3,4}$ = 16	135·5(3) D. $J_{3,4}$ 15	145·8(5) D.T.D. $J_{4,5}$ = 45 J = 17 and 7	147·2	150·2	153·1
I	-	125·7(3) D. $J_{3,4}$ 17	130·6(4) D.D. $J_{4,5}$ = 45 $J_{3,4}$ = 17	146·0(5) D.T.D. $J_{4,5}$ = 45 J = 17 and 7	147·1	150·2	153·1

[a] As solutions in CCl_4

Assignments in parentheses Coupling constants J in c.p.s.

derivatives shows three signals in this region, which clearly must be due to the 6-, 7- and 8-fluorine resonances. Furthermore, the shift values resemble closely three of the four high field signals in the heptafluoroquinoline spectrum, viz., 148·3, 150·7 and 154·4 p.p.m. This suggests that, in the heptafluoroquinoline spectrum, the peak at 160·6 p.p.m. is due to the 3-fluorine. Furthermore, the 3,5-fluorines in pentafluoropyridine, which are in a similar environment, have a similar shift value, i.e. 162·0 p.p.m.[36] On this basis, substituent shift effects due to halogen in the 2-position in polyfluoroquinoline systems may be determined for the 3-, 4-, and 5-positions.

Halogen	Position (3)	(4)	(5)
Cl	-18·3	+2	+0·3
Br	-24·1	+2·7	+0·1
I	-34·9	+4·6	+0·3

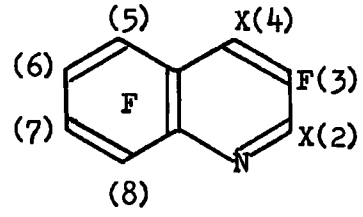
Reference compound heptafluoroquinoline.

As can be seen, large downfield shifts of the ortho (3) fluorine are again observed of similar magnitude to those in the pyridine systems.

2. 2,4-Dihalopentafluoroquinolines.

Table XVII

^{19}F chemical shifts for 2,4-dihalopentafluoroquinolines



X	Shift rel. to $CFCl_3$ (p.p.m.)						
F	77·2(2)	126·0(4)	145·7(5)	148·3	150·7	154·4	160·6(3)
Cl		116·8(3)	144·7	146·6	152·2†		
Br		100·7(3)	143·9	146·1	151·9†		
I		73·9(3)	143·0	146·4	152·5†		

Solutions in CCl_4; assignments in parentheses.

† Intensity twice that of other peaks.

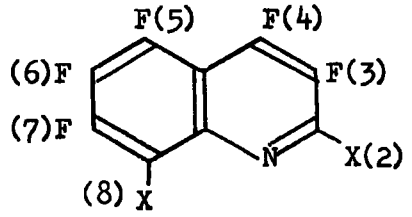
The absence of any very low field peaks shows the 2-fluorine to have been replaced. Since no large coupling, which can be ascribed to peri interaction between the 4- and 5-fluorines, can be detected then either the 4- or 5-fluorine has been substituted. The position of the 3-fluorine assuming the compounds are 2,4-disubstituted, may be

calculated from the shift effect of halogen on ortho fluorine in 4-halotetrafluoropyridines (Table XIV) and the known shifts of the 3-fluorine in 2-halohexafluoroquinolines (Table XVI). This gives 122·3, 107·8, and 85·1 as the expected shifts for the 3-fluorine in 2,4-dichloro, 2,4-dibromo, and 2,4-di-iodopentafluoroquinolines respectively. Thus the lowest field resonances observed in these spectra may be assigned to the 3-fluorine. As expected, it appears as a singlet since it has no ortho fluorines and coupling between other halogens and fluorine does not occur.

3. 2,8-Dihalopentafluoroquinolines.

Table XVIII

^{19}F n.m.r. shifts for 2,8-dihalopentafluoroquinolines



X					
Br	115·8(7)	128·4(4)	136·3(3)	140·8(5)	153·6(6)
		$J_{4,5}$ = 51		$J_{4,5}$ = 51	J ~ 20
I	101·6(7)	126·8(3)	129·6(4)	139·4(5)	153·4(6)
			$J_{4,5}$ = 50	$J_{4,5}$ = 49	J ~ 20

J in c.p.s.
Shifts relative to $CFCl_3$ (p.p.m.)
Assignments in parentheses.

Both the 4-, and 5-fluorine atoms are present since large peri-coupling ($J_{4,5}$ = 49-51) is easily detected but the absence of a very low field peak shows the 2-fluorine to be replaced. The 4-fluorine is further distinguished by comparison of its shift with that in the relevant 2-halohexafluoroquinolines, as is the 3-fluorine. As shown previously, the carbocyclic fluorines give resonance generally in the region 145-155 p.p.m., and are not appreciably affected by substituents in the heteroaromatic ring. Assuming that substituent shift effects in pentafluorophenyl compounds (Table XIV) hold for the carbocyclic ring in polyfluoroquinolines (i.e. ortho fluorines are shifted by -30 and -40 p.p.m. for Br and I respectively), then fluorine in the carbocyclic ring in these compounds should fall in the region 115-130 and 100-115 p.p.m. respectively. Only one carbocyclic resonance occurs in the requisite range for each compound. Since the 5-fluorine is known to be present this can only occur if the 8-fluorine is substituted.

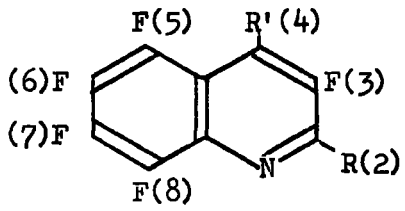
The low field carbocyclic fluorine must, therefore, be due to the 7-fluorine and the remaining resonance at $\sim$153 p.p.m. must be the 6-fluorine. The appearance of the latter as a triplet (J$\sim$20 c.p.s.), due to ortho F-F coupling with the 5- and 7-fluorines, confirms this assignment.

4. Halomethoxypolyfluoroquinolines and related compounds.

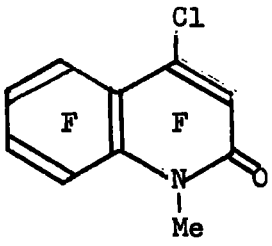
The requisite spectral information from ^{19}F and ^{1}H n.m.r. spectroscopy can be found in Tables XIX and XX.

Table XIX

^{19}F n.m.r. shifts for halomethoxypolyfluoroquinolines and related compounds



R	R'					
H	H	125·3(3)	149·2	150·9	155·5†	
Cl	OMe	140·9(3)	144·5	149·7	153·5	156·6
Br	OMe	133·8(3)	144·5	148·9	153·7	156·3
OMe	Cl*	133·9(3)	146·1	150·0	153·4	158·9



120·3(3) 140·8 148·5 151·2 161·7

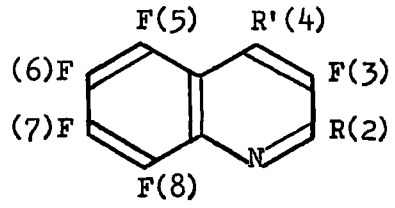
Shifts relative to $CFCl_3$ (p.p.m.); (solutions in CCl_4)

Assignments in parentheses.

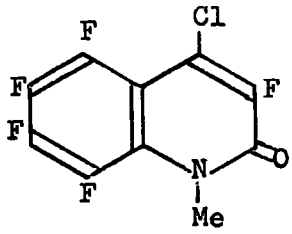
* As mixture with pentafluoro-4-chloro-N-methyl-2-quinolone.

† Intensity twice that of other signals.

Table XX



R	R'			
H	H	1·13(2)	D.	$J_{2,4}$ = 2·5 c.p.s., $J_{2,3}$ = 0
		1·98(4)	D.D.D.	$J_{2,4}$ = 2·5, $J_{4,3}$ = 8·1, $J_{4,5}$ = 1·7 c.p.s.
Cl	OMe	5·62	D.	$J_{3F-4-OMe}$ = 5·7, $J_{4OMe-5F}$ = 0 c.p.s.
Br	OMe	5·66	D.	$J_{3F-4-OMe}$ = 5·0, $J_{4OMe-5F}$ = 0 c.p.s.
OMe	Cl*	5·83	S.	$J_{2-OMe-3F}$ = 0



A 6·20 D. $J_{1-OMe-8F}$ = 10·0 c.p.s.

Solutions in CCl_4 with $SiMe_4$ as internal reference

* means as a mixture with A.

For 3,5,6,7,8-pentafluoroquinoline its orientation follows from its formation via 2,4-di-iodopentafluoroquinoline. The known effect[179,183] of hydrogen on ortho fluorine chemical shifts allows assignment of the 3-fluorine, and the range of shifts attributed to the 5,6,7 and 8-fluorines is very similar to that for fluorines in 5,6,7,8-tetrafluoroquinoline.[184] Its ^1H n.m.r. spectrum shows the expected features except for the non-coupling of the 2-hydrogen with the 3-fluorine. However, a similar phenomenon occurs in 2,4,6-trifluoropyridine where the hydrogen atoms do not couple with the 2-fluorine.[183]

The spectra of 2-chloro-4-methoxypentafluoroquinoline and 2-bromo-4-methoxypentafluoroquinoline, obtained from methylation of the corresponding halohydroxypentafluoroquinolines, are in accord with other 4-methoxypolyfluoroquinolines and support the fact that coupling does not occur between the 5-fluorine and 4-methoxyl group.[145]

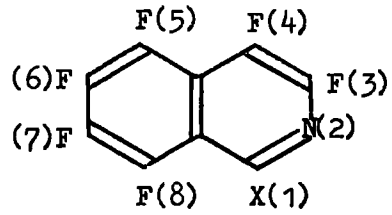
Methylation of 2-hydroxy-4-chloropentafluoroquinoline gave two products and, as stated previously (Ch.III, A,2,e.), only one compound was obtained pure. However, the n.m.r. data obtained was sufficient to permit characterization. The compound which was obtained pure was readily identified as pentafluoro-4-chloro-N-methyl-2-quinolone since its ^1H n.m.r. spectrum showed a doublet at τ 6·2 ($J_{1\text{-Me-}8F}$ = 10·0 c.p.s.), as observed for other polyfluoro-N-methyl-2-quinolones.[145] Similarly, the isomeric 2-methoxy-4-chloropentafluoroquinoline could be

identified by virtue of the singlet peak in its ^{1}H n.m.r. at τ 5·83, because, as with other methoxyl groups adjacent to ring nitrogen in polyfluoro-N-heteroaromatic compounds, coupling between methoxyl protons and the ortho fluorine does not occur.[44,182] In both cases the ^{19}F n.m.r. spectra were as expected, taking into account the effect of halogen substituents on fluorine shifts, in comparison with similar derivatives of polyfluoroquinolines.

D. 1-Halohexafluoroisoquinolines.

^{19}F chemical shift data is given in Table XXI.

Table XXI



X							
F	61·0(1)	96·5(3)	138·9	144·5	145·2	152·4	154·6
Cl		94·0(3)	136·9	144·7	146·2	152·1†	
Br		93·9(3)	136·4	145·2	146·0	151·6†	

Solutions in CCl_4.
Shifts relative to $CFCl_3$ (p.p.m.)

†Intensity twice that of other peaks.

Both the 1- and 3-fluorines in heptafluoroisoquinoline are readily distinguished by their low field positions, the 1-fluorine occurring at lowest field, and the large peri coupling between the 1- and 8-fluorines (J = 60-65 c.p.s.).[58] The absence of a very low field peak in the spectra of the monohalo derivatives and the presence of only two peaks with large couplings, arising from peri-coupling of the 5 and 4-fluorine atoms, (the latter being obscured by overlapping to give a broad band with width at half peak height $\sim$ 100 c.p.s.) shows that the 1-fluorine atom has been replaced.

EXPERIMENTAL

Reagents.

Perfluoroheterocyclic compounds were prepared as described in the literature.[36,38]

Hydrogen halides were prepared using the standard procedures described by Vogel,[185] and hydrogen cyanide was supplied by I.C.I.

Boron halides and antimony pentafluoride were reagent grade materials supplied by B.D.H. and Peninsular Chem. Research Inc. respectively, and were used without further purification.

Both aluminium chloride and aluminium bromide were reagent grade chemicals supplied by B.D.H., and aluminium iodide was prepared via Nespital's method as described in Gmelin's Handbuch.[186] Aluminium halides were sublimed prior to use.

All operations involving air sensitive materials were carried out either under an atmosphere of dry nitrogen or in a dry box.

Sulpholan, unless otherwise stated, was purified by distillation, only the middle fractions, which were solid at room temperature, were retained and dried further by storage over molecular sieve (Type IVA) at 40°C.

Instrumentation.

Infrared spectra were recorded using either a Grubb-Parsons G.S.2A or 'Spectromaster' Spectrometers. Liquid samples were in the form of thin films between potassium bromide discs, or, in the case of

solids, pressed into thin discs with potassium bromide. Air sensitive solids were made into mulls with Nujol.

Proton and fluorine nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R10 Spectrometer operating at 60 Mc/s. and 56·45 Mc/s. respectively.

Mass spectra were recorded using an A.E.I. M.S.9. spectrometer and all molecular weights were determined using this machine.

Analytical scale vapour phase chromatography was carried out using either a Griffin and George, D.6. Gas Density Balance or Perkin-Elmer "Fractometer" models 451 and 452. Analysis was performed on columns packed with di-n-decylphthalate on Celite (Column 'A') and silicone elastomer on Celite (Column 'D')

CHAPTER VI

Experimental for Chapter III

A

Reactions of Polyfluoroheteroaromatic Compounds with Hydrogen Halides and Related Reactions

1. An investigation of the effect of various solvents on the reaction of hydrogen chloride with heptafluoroquinoline.

(a) In organic solvents.

A solution of heptafluoroquinoline (1·5 g., 5·2 m.mole) in either sulpholan, ether, acetone or hexane (15 ml.) was reacted with excess hydrogen chloride by continually passing the gas through the solution. After a standard reaction time the composition of the resulting mixture for each solvent was determined using a Griffin and George D6 Gas Density Balance Chromatograph and the results are given in Table IX (p. 65).

b) In the absence of a solvent.

Heptafluoroquinoline (2·0 g., 7·8 m.mole) and hydrogen chloride (0·29 g., 8·0 m.mole) were heated for 50 hours at 100°C in the absence of any solvent. The tube was vented and the solid was sublimed (25° at 0·05 mm.) to give heptafluoroquinoline (1·75 g., 88% recovery identified by comparison of its i.r. spectrum with that of an authentic sample).

2. Reactions of heptafluoroquinoline with hydrogen halides.

a. With hydrogen chloride in sulpholan purified only by distillation.

(i) using two moles of hydrogen chloride.

A mixture of heptafluoroquinoline (5·0 g., 19·6 m.mole), hydrogen chloride (1·46 g., 40·0 m.mole) and sulpholan (40 ml.) was heated in a Carius tube for 50 hours at 100°C.

After cooling, the tube was vented and the brown solution poured into water. The products were extracted into ether and the ether extract washed thoroughly with water (to remove sulpholan), separated and dried ($MgSO_4$). Removal of the solvent gave a pale brown solid. Sublimation (40-45° at 0·05 mm.) and recrystallisation (benzene) gave 2,4-dichloropentafluoroquinoline (3·2 g., 57%) m.p. 76·5 - 77·5° (Found: C, 37·7; Cl, 22·3; F, 32·3%; M = 287. $C_9Cl_2F_5N$ requires C, 37·5; Cl, 24·6; F, 33·0%; M, 287). I.R. Spectrum No.4.

Sublimation of the residue (100° at 0·05 mm.) gave 2-chloro-4-hydroxypentafluoroquinoline (1·2 g., 23%) m.p. 164-165° after recrystallisation from methylene chloride - petroleum ether (b.p. 60-80°) (Found: C, 39·7; H, 0·3; Cl, 13·5; F, 35·7%; M, 269. C_9HClF_5NO requires C, 40·1; H, 0·4; Cl, 13·2; F, 35·2%; M, 269). I.R. Spectrum No.10.

(ii) Using ten moles of hydrogen chloride.

Heptafluoroquinoline (2·0 g., 7·8 m.mole) and hydrogen chloride

(2·9 g., 79·5 m.mole) were reacted in sulpholan (25 ml.) as described above. The crude reaction producted, isolated as described previously, was fractionally sublimed to give two compounds. Sublimation (40°C at 0·05 mm.) gave 2,4-dichloropentafluoroquinoline (1·1 g., 49%, identified by comparison of its i.r. spectrum with that of an authentic sample). The residue sublimed (100° - 110° at 0·05 mm.) to give 2-hydroxy-4-chloropentafluoroquinoline (0·6 g., 29%) m.p. 200-204° (decomp.) (Found: C, 40·2; H, 0·33, Cl, 13·7; F, 35·5%; M, 269. C_9HClF_5NO requires C, 40·1; H, 0·4; Cl, 13·2; F, 35·2%; M, 269). I.R. Spectrum No.8.

b. With hydrogen chloride in dry sulpholan.

(i) Using one mole of hydrogen chloride.

Heptafluoroquinoline (5·0 g., 19·6 m.mole), hydrogen chloride (0·73 g., 20·0 m.mole) and sulpholan (20 ml.) were reacted at room temperature for 10 days in a sealed tube.

The tube was vented and a slight excess of triethylamine added (to remove acid) and the tube contents poured into water. The alkaline aqueous mixture was extracted with ether, the extracts washed with water, dried ($MgSO_4$) and the solvent distilled. The solid remaining was sublimed (40°C at 0·05 mm.) to give a white solid (4·5 g.) which was shown by analytical scale v.p.c. (Col. 'O', 200°C) and ^{19}F n.m.r. spectroscopy to comprise starting material (20%), 2-chlorohexafluoroquinoline (60%) and 2,4-dichloropentafluoroquinoline (20%).

Acidification of the aqueous alkaline layer gave a pale brown solid (0·7 g.) whose i.r. spectrum showed it to be a mixture of 2-hydroxyhexafluoroquinoline ($\nu_{C=O}$, 1704 cm.$^{-1}$)[145] and 2-chloro-4-hydroxypentafluoroquinoline. Mass spectroscopy confirmed this giving M, 253 (C_9HF_6NO) and M, 269 (C_9HClF_5NO).

(ii) Using excess hydrogen chloride.

Hydrogen chloride was bubbled continuously through a stirred solution of heptafluoroquinoline (1·0 g., 3·9 m.mole) in sulpholan (15 ml.) at room temperature for 50 hours. The solution was allowed to stand for a further 30 hours and the product was extracted as described in the previous experiment to give 2,4-dichloropentafluoroquinoline (0·9 g., 80%, identified by comparison of its i.r. spectrum with that of an authentic specimen).

No hydroxyl containing material was precipitated on acidification of the basic aqueous layer.

c. With hydrogen bromide in dry sulpholan.

(i) Using one mole of hydrogen bromide.

Heptafluoroquinoline (5·0 g., 19·6 m.mole) was reacted for 10 days at room temperature with hydrogen bromide (1·6 g., 19·8 m.mole) in sulpholan (20 ml.) in a sealed tube. Extraction as described previously gave, after sublimation (65° at 0·005 mm.), a pale yellow solid (3·9 g.) which was shown by v.p.c. (Col. 'O', 200°) and

^{19}F n.m.r. spectroscopy to comprise starting material (20%), 2-bromohexafluoroquinoline (60%) and 2,4-dibromopentafluoroquinoline (20%). Acidification of the aqueous layer gave 2-hydroxyhexafluoroquinoline[145] (0·25 g., 5% identified by its i.r. spectrum and mass spectroscopy).

(ii) Using two moles of hydrogen bromide.

A mixture of heptafluoroquinoline (5·0 g., 19·6 m.mole), hydrogen bromide (3·3 g., 40·9 m.mole) and sulpholan (20 ml.) were stood at room temperature for ten days. Extraction using triethylamine as previously described gave, after sublimation (60° at 0·001 mm.) and recrystallization (pet. ether 40-60°), 2,4-dibromopentafluoroquinoline (4·5 g., 61%), m.p. 85-86° (Found: C, 28·9; Br, 42·6; F, 24·7%; M, 375. $C_9Br_2F_5N$ requires C, 28·7; Br, 42·4; F, 25·2%; M, 375). I.R. Spectrum No.5).

Acidification of the aqueous layer gave 2-bromo-4-hydroxypentafluoroquinoline (0·7 g., 8·5%), m.p. 176-177° (decomp.) (Found: C, 34·7; H, 1·3; Br, 25·42; F, 30·4%; M, 313. C_9HBrF_5NO requires C, 34·4; H, 0·32; Br, 25·48; F, 30·26%; M, 313). I.R. Spectrum No.12.

d. With hydrogen iodide.

(i) In dry sulpholan.

Heptafluoroquinoline (5·0 g., 19·6 m.mole), hydrogen iodide (10·24 g., 80·0 m.mole) and sulpholan (30 ml.) were reacted for 10 days at room temperature in a sealed tube. The extraction technique was as described

previously except that the ether extracts were initially washed with aqueous sodium metabisulphite solution to remove free iodine. The ether extract gave, after washing with water, drying ($MgSO_4$), and removal of the solvent, a pale yellow solid. Sublimation (room temperature at 0·001 mm.) gave 3,5,6,7,8-pentafluoroquinoline (2·2 g., 51·2%) as a white solid, m.p. 49·5 - 50·5° (Found: C, 49·2; H, 0·9; F, 42·5%; M, 219. $C_9F_5H_2N$ requires C, 49·3; H, 0·9; F, 43·3%; M, 219). I.R. Spectrum No.7. The residue sublimed (80°C at 0·001 mm.) to give 2,4-di-iodopentafluoroquinoline (2·6 g., 28·2%), m.p. 118-119° (Found: C, 22·8; F, 19·6; I, 53·8%; M, 471. $C_9F_5I_2N$ requires C, 22·9; F, 20·1; I, 53·9%; M, 471). I.R. Spectrum No.6.

(ii) In aqueous solution.

A mixture of heptafluoroquinoline (5·0 g., 19·6 m.mole), iodine free hydriodic acid (50 ml., 56% $^w/_w$) and hydrogen iodide (5·1 g., 40·0 m.mole) was shaken in a sealed tube for 36 hours at room temperature and then heated to 85° over 4 hours. After cooling, sodium metabisulphite was added to remove free iodine and the products extracted into ether. Distillation of the dried ether extract gave a solid. Sublimation (50° at 0·001 mm.) gave 3,5,6,7,8-pentafluoroquinoline (1·7 g., 39% identified by comparison of its i.r. spectrum). The residue sublimed (90° at 0·001 mm.) to give 2,4-di-iodopentafluoroquinoline (2·7 g., 28·7% identified by its i.r. spectrum.

e. Attempted reactions with hydrogen cyanide.

(i) At room temperature in dry sulpholan.

Heptafluoroquinoline (2·0 g., 7·8 m.mole) and hydrogen cyanide (0·43 g., 16·0 m.mole) in sulpholan (20 ml.) were maintained at room temperature for three weeks. The tube was cooled in liquid air, vented and hydrogen cyanide removed by pumping through a cold trap. The contents of the tube were then poured into water, and extracted into ether. Distillation of the dried ($MgSO_4$) ether extract gave a white solid which sublimed completely (room temperature at 0·001 mm.) to white crystals of heptafluoroquinoline (1·9 g., 96% recovery, identified by its i.r. spectrum and v.p.c. (Col. 'O' 200°C) analysis).

(ii) At 110°C in dry sulpholan.

Heptafluoroquinoline (5·0 g., 19·6 m.mole) and hydrogen cyanide (1·08 g., 40 m.mole) were heated in sulpholan in a sealed tube for 50 hours at 110°C. Extraction as previously described gave only heptafluoroquinoline (4·9 g., 98% recovery, identified by i.r. spectroscopy).

f. Attempted reactions with potassium halides.

(i) With potassium chloride at room temperature.

Heptafluoroquinoline (2·0 g., 7·9 m.mole) and potassium chloride (0·59 g., 8·0 m.mole) were sealed into a Carius tube containing sulpholan (30 ml.). After 13 days the contents of the tube were poured into water

and the aqueous mixture extracted with ether. Distillation of the dried ($MgSO_4$) extract gave a white solid which sublimed readily (room temperature at 0·001 mm.). V.p.c. analysis (Col. '0' 200°C) and i.r. spectroscopy showed this to be heptafluoroquinoline (1·9 g., 95% recovery).

(ii) With potassium bromide at room temperature.

Heptafluoroquinoline (2·0 g., 7·9 m.mole) and potassium bromide (0·95 g., 8·0 m.mole) were reacted as previously described for potassium chloride. Only heptafluoroquinoline (1·7 g., 86%) was recovered.

The same quantities of potassium bromide and heptafluoroquinoline after heating at 170°C for nine days gave only starting material (1·5 g., 75% recovery).

g. Acid induced displacements of bromine in bromofluoroquinolines by iodide ion.

(i) Preparation of 2,4-di-iodopentafluoroquinoline.

2,4-Dibromopentafluoroquinoline (0·95 g., 2·5 m.mole) dissolved in dry acetone (5·0 ml.) was added dropwise, under dry nitrogen, to a solution of anhydrous sodium iodide (0·75 g., 5·0 m.mole) in acetone (5·0 ml.), containing a few drops of a solution of anhydrous hydrogen iodide in acetone. An immediate yellow precipitate formed and the reaction mixture was refluxed overnight. Ether was added to precipitate

inorganic salts, which were filtered off; the ether layer was washed with sodium metabisulphite (to remove free iodine), water, and dried ($MgSO_4$). Removal of the solvent and sublimation (70° at 0·001 mm.) gave a solid which analytical v.p.c. (Col. '0' 200°) and mass spectrometry showed to be a mixture of 2,4-di-iodopentafluoroquinoline, an iodobromopentafluoroquinoline, and starting material. The mixture was retreated in exactly the same way and the sublimed product after recrystallization (diethyl ether and pet. ether 40-60° mixture) gave pure 2,4-di-iodopentafluoroquinoline (0·75 g., 68%). Identified by its i.r. spectrum.

No reaction occurred between these reagents in the absence of hydrogen iodide.

(ii) Preparation of 2-iodohexafluoroquinoline.

A solution of 2-bromohexafluoroquinoline (1·0 g., 3·17 m.mole) in acetone (25 ml.) was added dropwise to a refluxing solution of sodium iodide (0·476 g., 3·17 m.mole) in acetone to which a few drops of an acetone solution of hydrogen iodide had been added. An immediate precipitate was produced. The mixture was refluxed for two hours and worked up as described previously. T.l.c. analysis (silica eluted with pentane) showed a small amount of starting material remained. A pure specimen of the product was obtained after elution down a short chromatography Column (silica eluted with pentane benzene mixture 9:1) to give 2-iodohexafluoroquinoline (0·6 g., 53%),

m.p. 83-84° (Found: C, 29·5; F, 31·2; I, 34·9, M, 363. C_9F_6IN requires C, 29·75; F, 31·41; I, 34·98; M, 363). I.R. Spectrum No.3. No reaction occurred in the absence of added acid nor did heptafluoroquinoline react under conditions where 2-bromohexafluoroquinoline and 2,4-dibromopentafluoroquinoline reacted.

h. Hydrolysis reactions of chloropolyfluoroquinolines.

(i) Hydrolysis of 2,4-dichloropentafluoroquinoline.

2,4-Dichloropentafluoroquinoline (2·88 g., 10·0 m.mole), water (0·18 g., 10·0 m.mole), and hydrogen chloride (0·365 g., 10·0 m.mole) were heated together in sulpholan in a sealed tube at 100°C for 168 hours. The contents of the tube were poured into aqueous base, after stirring well, the mixture was extracted with ether. The ether extract was found not to contain any unreacted dichloropentafluoroquinoline. Acidification of the basic solution with concentrated hydrochloric acid produced a white precipitate which was extracted into a large volume of ether. Distillation of the dried ($MgSO_4$) extract and sublimation (100-110°C at 0·005 mm.) gave a white solid (1·9 g., 57·6%) identified as 2-hydroxy-4-chloropentafluoroquinoline by its i.r. spectrum.

(ii) Hydrolysis of 2-chlorohexafluoroquinoline.

A mixture of 2-chlorohexafluoroquinoline (1·35 g., 5·0 m.mole),

hydrogen chloride (0·183 g., 5·0 m.mole) and water (0·09 g., 5·0 m.mole) were reacted in sulpholan (5·0 ml.) as described previously for 2,4-dichloropentafluoroquinoline. The products were separated using the acid-base technique previously described. A component insoluble in base (0·49 g.) was identified as impure starting material (29·6% recovery) by its i.r. spectrum. The material soluble in base gave, after sublimation (100° at 0·005 mm.) a white solid identified as 2-chloro-4-hydroxypentafluoroquinoline (0·65 g., 49·3% yield) by its i.r. spectrum.

i. Methylation of halohydroxypolyfluoroquinolines.

(i) 2-Hydroxy-4-chloropentafluoroquinoline.

2-Hydroxy-4-chloropentafluoroquinoline (1·5 g., 4·43 m.mole) was reacted with an excess of ethereal diazomethane[187] at 0°C. V.p.c. analysis (Col. '0', 200°C) of the crude product showed two components (relative peak areas 3:1, the material with shortest retention time was present in excess). Fractional sublimation (room temperature and 80°C at 0·001 mm.) gave a pure specimen (0·4 g., 33%) of the least volatile component 1-methyl-4-chloropentafluoro-2-quinolone, m.p. 100-101°C (Found: C, 42·5; H, 1·3; F, 33·9; Cl, 13·0%; M, 283. $C_{10}H_3F_5NOCl$ requires C, 42·4; H, 0·82; F, 33·57; Cl, 12·09%; M, 282). I.R. Spectrum No.9.

The other component could not be isolated as a pure compound but had the expected ^{19}F and ^{1}H n.m.r. spectral properties for the isomeric

2-methoxy-4-chloropentafluoroquinoline.

(ii) 2-Chloro-4-hydroxypentafluoroquinoline.

2-Chloro-4-hydroxypentafluoroquinoline (0·55 g., 2·05 m.mole) was reacted with ethereal diazomethane as above. V.p.c. analysis (Col. 'O', 200°) showed a single component which, after sublimation (80°C at 0·005 mm.), gave pure 2-chloro-4-methoxypentafluoroquinoline (0·5 g., 86·4%), m.p. 61-62° (Found: C, 42·3; H, 0·73; Cl, 13·2; F, 34·0%; M, 283. $C_{10}H_3ClF_5NO$ requires C, 42·4; H, 0·82; Cl, 12·09; F, 33·57%; M, 283). I.R. Spectrum No.11.

(iii) 2-Bromo-4-hydroxypentafluoroquinoline.

2-Bromo-4-hydroxypentafluoroquinoline (0·6 g., 1·92 m.mole) was reacted with ethereal diazomethane as previously and gave, after recrystallization (hexane), 2-bromo-4-methoxypentafluoroquinoline (0·4 g., 65%) M.p. 76-77° (Found: C, 36·0; H, 0·7; Br, 24·1; F, 31·2%; M, 327. $C_{10}H_3BrF_5NO$ requires C, 35·8; H, 0·9; Br, 24·4; F, 29·0%; M, 327. I.R. Spectrum No.13.

3. Reactions of heptafluoroisoquinoline with hydrogen halides.

a. With hydrogen chloride.

(i) Using 7 moles of hydrogen chloride.

Heptafluoroisoquinoline (2·0 g., 7·8 m.mole), hydrogen chloride (2·0 g., 54·6 m.mole) and sulpholan (15 ml.) were heated, in a sealed

tube, for 160 hours at 125-130° and then for a further 30 hours at 155-160°. The black mixture was poured into water and extracted with ether. After filtering, to remove a small amount of carbonaceous material, the dried extract was distilled to leave a viscous brown oil. Sublimation (25° at 0·01 mm.) gave a white solid (0·95 g.) which analytical v.p.c. (Col. '0' 200°) and mass spectrometry showed to comprise starting material and a chlorohexafluoroisoquinoline (~1% and 99% respectively estimated from the chromatogram, corresponding to 42% conversion of starting material to the chloro-derivative). Recrystallization (ether) gave a small amount of the pure chlorohexafluoroisoquinoline (0·3 g.), m.p. 35-36° insufficient for full elemental analysis but whose mass, ^{19}F n.m.r. and i.r. spectra were identical with those of 1-chlorohexafluoroisoquinoline (see the reaction of HCl and $AlCl_3$ with heptafluoroisoquinoline, (see Ch.VI, B.3.a.).

The residue sublimed (85° at 0·01 mm.) to a pale yellow solid (0·2 g.) which was soluble in aqueous base, its mass spectrum was consistent with the molecular formula C_9HClF_5NO (Found: M, 269) and its i.r. spectrum (No.18) had an intense peak at 1,724 $cm.^{-1}$ indicative of a carbonyl group. Although there was insufficient for analysis the compound is probably chloropentafluoro-1-hydroxyisoquinoline.

(ii) Using 2-moles of hydrogen chloride.

A mixture of heptafluoroisoquinoline (2·0 g., 7·8 m.mole), hydrogen

chloride (0·58 g., 16·0 m.mole) and sulpholan (15 ml.) heated at 125° for 100 hours and extracted as above gave a white solid (1·2 g.) comprising 1-chlorohexafluoroisoquinoline and starting material (15% and 85% respectively estimated from the chromatogram, representing a 10% conversion and 50% recovery of starting material).

b. With hydrogen bromide.

(i) Using 3 moles of hydrogen bromide.

Heptafluoroisoquinoline (2·0 g., 7·8 m.mole) and hydrogen bromide (1·9 g., 23·4 m.mole) were reacted in sulpholan (20 ml.) at 135-145° for 142 hours. Extraction as above gave a viscous brown oil which, after vacuum transfer (80-100° at 0·01 mm.), gave a colourless liquid (0·6 g.). Analytical v.p.c., ^{19}F n.m.r. spectroscopy and mass spectrometry showed this to comprise starting material (~2%), and 1-bromohexafluoroisoquinoline[a] (98%) estimated from the chromatogram, representing 24% conversion of starting material to the bromo-derivative.

Sublimation (125-140° at 0·1 mm.) of the residue from the vacuum transfer gave a brown solid (0·05 g.) whose mass spectrum gave M = 313, consistent with C_9HBrF_5NO, and since its i.r. spectrum (No.19) had its most intense absorption at 1,715 $cm.^{-1}$ this suggests the compound is bromopentafluoro-1-hydroxyisoquinoline. Left unsublimed was a black solid (0·5 g.).

[a] See this chapter B,3.b.

(ii) Using 1 mole of hydrogen bromide.

Heptafluoroisoquinoline (2·0 g., 7·8 m.mole) and hydrogen bromide (0·62 g., 7·8 m.mole) were reacted as above to give starting material (25% recovery), 1-bromohexafluoroisoquinoline (8% yield based on reacted starting material), bromopentafluoro-1-hydroxyisoquinoline (0·02 g.), and a black involatile solid (0·1 g.).

4. Reactions of pentafluoropyridine with hydrogen halides.

a. With hydrogen chloride.

(i) Using 9 moles of hydrogen chloride.

Pentafluoropyridine (10·0 g., 60 m.mole) and hydrogen chloride (19·0 g., 520 m.mole) were heated in a sealed tube containing sulpholan (20 ml.) as solvent for 17 hours at 50-80° followed by 135 hours at 110-130°. The black semi solid was poured into water, extracted with ether and filtered to remove the black, insoluble material (1·3 g.). Concentration of the dried ($MgSO_4$) layer by distillation through a Vigreux column gave a clear yellow liquid (5·6 g.). Analytical scale v.p.c. (Col. 'A', 50° and 100°) and ^{19}F n.m.r. showed this to be a mixture (percentage yield/recovery in parentheses) of starting material (7%), 4-chlorotetrafluoropyridine[154] (7·3%), 2,4-dichlorotrifluoropyridine[a] (~1%) and 2,4,6-trichlorodifluoropyridine[a] (9%).

[a] This chapter B,1.a.

(ii) Using 2 moles of hydrogen chloride.

Pentafluoropyridine (10·0 g., 60 m.mole) and hydrogen chloride (4·4 g., 120 m.mole) were heated, in sulpholan (20 ml.), in a Carius tube for 14 hours at 100°C followed by 121 hours at 130°C. Extraction as described previously gave starting material (6·0 g., 60% recovery). Although examination of the crude product on v.p.c. (Col. 'A', 150°) showed a trace (~0·5%) of a compound with a retention time identical with that of 4-chlorotetrafluoropyridine there was insufficient for isolation.

b. With hydrogen bromide.

A mixture of pentafluoropyridine (10·0 g., 60·0 m.mole), hydrogen bromide (12·9 g., 180 m.mole) and sulpholan (15 ml.) was heated in a sealed tube for 20 hours at 100°C followed by 148 hours at 130°-160°. Extraction of the black mixture as described above and subsequent analysis on v.p.c. (Col. 'A', 150° and Col. 'O', 150°) showed 4-bromotetrafluoropyridine,[57] and two other possible bromofluoropyridines. The most volatile unknown compound had a retention time identical with 2,4-dibromotrifluoropyridine[a] but was not present in sufficient quantity to permit isolation. Concentration of the extract by distillation caused crystallization of the least volatile compound which was filtered, washed with ether and sublimed (70°C at 0·005 mm.) to give

[a] This chapter B,1.b.

2,4,6-tribromodifluoropyridine (5·3 g.), m.p. 105·5 - 106·5° (Found: C, 17·0; Br, 69·6; F, 10·1%; M, 349. $C_5Br_3F_2N$ requires C, 17·1; Br, 68·1; F, 10·8%; M, 349). I.R. Spectrum No.24. Fractionation of the ethereal filtrate gave 4-bromotetrafluoropyridine[57] (2·0 g., 15% yield), b.p. 132-134° (lit. 134-135°).[57] The residue from the distillation sublimed (70° at 0·005 mm.) to give a further quantity of 2,4,6-tribromodifluoropyridine (1·2 g.), the combined weights (6·5 g.) of this compound represent a yield of 31·5%.

B

Reactions of Polyfluoro-N-Heteroaromatic Compounds with 'Super Acids'

1. Reactions of pentafluoropyridine.

a. With hydrogen chloride and aluminium chloride.

Pentafluoropyridine (10·9 g., 64·4 m.mole), aluminium chloride (8·6 g., 64·4 m.mole) and hydrogen chloride (2·35 g., 64·4 m.mole) were heated for 4 days at 120°C in a sealed tube. The black complex was dissolved up in dry ether and hydrolysed by cautious addition of ice. The organic layer was separated, washed and dried ($MgSO_4$). Analytical scale v.p.c. (Col. 'A', 50° and 150°) showed starting material and three other components. Distillation of the ether extract gave two fractions, the first (boiling range 34-38°) was solvent ether, and the second (boiling range 90° - 128°C), contained starting material and two chlorofluoropyridines. Separation of the latter by preparative g.l.c. (Col. 'O', 150°) to give starting material (1·15 g., 10·6% recovery) 4-chlorotetrafluoropyridine[154] (4·15 g., 39%) identified by comparison of its i.r. spectrum with that of an authentic specimen, and 2,4-dichlorotrifluoropyridine (1·8 g., 15%). B.p. 161°C. (Found: C, 30·0; Cl, 35·6; F, 29·2%; M, 201. $C_5Cl_2F_3N$ requires C, 29·73; Cl, 35·15; F, 28·21%; M, 201). I.R. spectrum No.20. The residue from distillation sublimed readily, (room temperature at 0·01 mm.), to give 2,4,6-trichlorodifluoropyridine, (2·2 g., 17·5%), m.p. 38-39°. (Found: C, 27·3; Cl, 49·0; F, 17·0%; M, 217. $C_5Cl_3F_2N$ requires

C, 27·46; Cl, 48·7; F, 17·39%; M, 217). I.R. Spectrum No.23.

b. With hydrogen bromide and aluminium bromide.

A mixture of pentafluoropyridine (5·0 g., 28·9 m.mole), aluminium bromide (8·2 g., 31·0 m.mole), and hydrogen bromide (1·8 g., 23·0 m.mole) were reacted together at 115-120° for 4 days. The reaction was extracted as previously to give a solution (ether), containing three bromofluoropyridines (v.p.c.) and no starting material. Ether was removed by distillation and higher boiling liquids were separated from the solid, which crystallized after concentration, by pumping under high vacuum and collecting in a liquid air cooled trap. The solid sublimed (room temperature (0·001 mm.) to give 2,4,6-tribromodifluoropyridine (1·75 g., 16·6%). M.p. 103-104°, (after recrystallization from ethanol). (Found: C, 17·0; Br, 69·6; F, 10·1%; M, 349. $C_5Br_3F_2N$ requires C, 17·05; Br, 68·2; F, 10·8%; M, 349. I.R. Spectrum No.24. Liquids from the vacuum transfer process were separated by preparative g.l.c. (Col. 'O', 140°) to give 4-bromotetrafluoropyridine[57] (2·3 g., 33·3%) identified by comparison of its infrared spectrum with that of an authentic sample, and 2,4-dibromotrifluoropyridine (0·8 g., 9·2%), b.p. 172°. (Found: C, 20·6; Br, 56·0; F, 19·6%; M, 289. $C_5Br_2F_3N$ requires C, 20·58; Br, 54·98; F, 19·59%; M, 289). I.R. Spectrum No.25.

A similar reaction using a mixture of pentafluoropyridine (16·9 g., 100 m.mole), aluminium bromide (26·7 g., 100 m.mole) and hydrogen bromide (8·1 g., 100 m.mole) gave, after heating at 150° for 40 hours, only 4-bromotetrafluoropyridine (10·0 g., 43·5%) and 2,4,6-tribromodifluoropyridine (11·05 g., 31·4%). No 2,4-dibromotrifluoropyridine was obtained under these conditions.

c. With hydrogen iodide and aluminium iodide.

Pentafluoropyridine (5·0 g., 28·9 m.mole) was reacted with aluminium iodide (12·6 g., 31·0 m.mole) and hydrogen iodide (3·84 g., 30·0 m.mole) in a sealed tube at 120°C for 24 hours.

The contents of the tube were extracted as previously described and tarry, ether insoluble material was rejected. Ether extracts were washed with a solution of $Na_2S_2O_5$ (to remove free iodine) and then with water. Concentration of the dried ($MgSO_4$) extract by distillation and v.p.c. analysis (Col. 'A', 100°C) showed trace amounts of pentafluoropyridine and similar quantities of two other components of slightly higher retention times. Further v.p.c. analysis (Col. 'O', 150°C) showed the major component, which was obtained pure by preparative g.l.c. (Col. 'O', 150°), and found to be 4-iodotetrafluoropyridine,[48] (3·7 g., 46·2%), m.p. 51-52° (lit.[48] 47-48°). Identified by comparison of its i.r. and ^{19}F n.m.r. spectra. Unreacted pentafluoropyridine and the other unknown compounds were not present in sufficient quantities to permit isolation and characterization.

d. Attempted reactions using hydrogen halides and boron halides.

(i) With hydrogen bromide and boron trifluoride.

Pentafluoropyridine (10·0 g., 59·2 m.mole), boron trifluoride (3·93 g., 59·2 m.mole) and hydrogen bromide (8·3 g., 59·2 m.mole) were heated in a sealed tube, at 120°C for 3 days. After venting, the low boiling materials were removed by vacuum transfer at room temperature, and the remaining liquid transferred under vacuum (40°C at 0·001 mm.). Distillation of the latter gave pentafluoropyridine (8·1 g., 81% recovery), b.p. 82° (lit.[36] 84°), and no bromofluoropyridines were found.

(ii) With hydrogen chloride and boron trichloride.

A mixture of pentafluoropyridine (5·0 g., 29·6 m.mole), hydrogen chloride (1·15 g., 29·6 m.mole) and boron trichloride (3·12 g., 29·6 m.mole) were heated in a sealed tube for 76 hours at 155°C. After working up, as described previously, only pentafluoropyridine (4·3 g., 86% recovery) was isolated.

2. Attempted reactions of 4-aminotetrafluoropyridine and tetrafluoro-1,4-diazine with hydrogen bromide and aluminium bromide.

a. 4-Aminotetrafluoropyridine.

A Carius tube containing 4-aminotetrafluoropyridine[44] (8·3 g., 50·0 m.mole), aluminium bromide (13·35 g., 50·0 m.mole) and hydrogen bromide (4·05 g., 50·0 m.mole) was heated for 3 days at 140°C. After extraction, the brown ether solution was distilled to leave a brown solid which sublimed (30° at 0·001 mm.) to give white crystals of

4-aminotetrafluoropyridine (7·5 g., 90% recovery).

A negligible amount of brown material (0·01 g.) remained unsublimed.

A further reaction using the same quantities of reagents as above gave only starting material (85% recovery) after heating at 160°C for 3 days.

b. Tetrafluoro-1,4-diazine.

Tetrafluoro-1,4-diazine[188] (7·4 g., 49·0 m.mole), aluminium bromide (12·0 g., 45·0 m.mole) and hydrogen bromide (3·97 g., 49·0 m.mole) were reacted in a sealed tube for 26 hours at 100°C. Products were extracted as described for similar reactions using pentafluoropyridine as substrate. V.p.c. analysis (Col. 'O', 220°C and Col. 'A', 100°C) of the crude ethereal product showed two unknown compounds and unreacted starting material. Starting material was recovered by co-distillation with ether followed by low temperature (-80°) vacuum transfer of the ether giving starting material, (0·9 g., 12% recovery). Fractional sublimation of the solids remaining gave (room temperature at 0·001 mm.) a dibromodifluoro-1,4-diazine, (1·6 g., 13·7%), m.p. 51-52° (Found: C, 17·6; Br, 59·0; F, 14·05%; M, 272. $C_4Br_2F_2N_2$ requires C, 17·52; Br, 58·38; F, 13·85%; M, 272). I.R. Spectrum No.21. The residue sublimed (90° at 0·001 mm.) to give tetrabromo-1,4-diazine, (5·0 g., 28·8%), m.p. 148-149° (Found: C, 12·3; Br, 81·1%; M, 392. $C_4Br_4N_2$ requires C, 12·12; Br, 80·81%; M, 392). I.R. Spectrum No. 26.

3. Reactions of heptafluoroisoquinoline.

a. With hydrogen chloride and aluminium chloride.

Heptafluoroisoquinoline (2·55 g., 10·0 m.mole), aluminium chloride (1·06 g., 10·0 m.mole) and hydrogen chloride (0·37 g., 10·0 m.mole), were reacted together for 89 hours at 135-140°C. The black solid remaining was hydrolysed with water and extracted into ether, the extracts were washed well with water, separated, and dried ($MgSO_4$). Distillation of the extract to remove ether, gave a viscous oil which crystallised after cooling just below room temperature. Sublimation (35°C at 0·001 mm.) gave white needles of 1-chlorohexafluoroisoquinoline (2·6 g., 96%), m.p. 34·5 - 35° (Found: C, 39·6; Cl, 14·0; F, 42·6%; M, 271. C_9ClF_6N requires C, 39·8; Cl, 13·1; F, 42·1%; M, 271). I.R. Spectrum No.16.

b. With hydrogen bromide and aluminium bromide.

A mixture of heptafluoroisoquinoline (2·55 g., 10·0 m.mole), aluminium bromide (2·67 g., 10·0 m.mole) and hydrogen bromide (0·81 g., 10·0 m.mole) were reacted as above. Extraction as previously described gave a yellow oil which, after freezing, melted at room temperature. Sublimation (60°C at 0·001 mm.) gave a solid (3·2 g.) which melted on removal from the cold finger. Resublimation of this semi-solid gave a white solid identified as 1-bromohexafluoroisoquinoline (3·0 g., 85%), m.p. 30-31° (Found: C, 34·3; Br, 25·2; F, 37·5%; M, 315. C_9BrF_6N requires C, 34·18; Br, 25·3; F, 36·08%; M, 315). I.R. Spectrum No.17.

4. Reaction of heptafluoroquinoline with hydrogen bromide and aluminium bromide.

Heptafluoroquinoline, (2·55 g., 10·0 m.mole), aluminium bromide (5·34 g., 20 m.mole) and hydrogen bromide (1·62 g., 20·0 m.mole) were heated in a sealed tube at 110°C for 49 hours. The tube contents were extracted as described in similar experiments and sublimation (60°C/ 0·001 mm.) of the crude product gave a white solid (3·2 g.), which was shown to comprise starting material (~10%), 2-bromohexafluoroquinoline[a] (~20%), and 2,4-dibromopentafluoroquinoline (~70%) by ^{19}F n.m.r. spectroscopy and v.p.c. analysis (Col. 'O', 200°C).

5. Reactions using other substrates.

a. Attempted reaction of decafluorobenzophenone with hydrogen bromide and aluminium bromide.

A mixture of decafluorobenzophenone (3·62 g., 10·0 m.mole), aluminium bromide (2·67 g., 10·0 m.mole) and hydrogen bromide (0·81 g., 10 m.mole) were heated at 160°C for 43 hours in a sealed tube. The reaction product was extracted as in other reactions of this type. Sublimation (100°C at 0·001 mm.) of the solid remaining after distillation of the solvent from the extract, gave starting material (2·7 g., 75% recovery) identified by analytical scale v.p.c. (Col. 'O', 220°) and its i.r. spectrum.

[a] Chapter VII, B,1.b.(i).

b. Reaction of pentafluoroaniline with hydrogen bromide and aluminium bromide

A mixture of pentafluoroaniline (18·3 g., 100 m.mole), aluminium bromide (26·7 g., 100 m.mole) and hydrogen bromide (8·1 g., 100 m.mole) was heated in a sealed tube for three days at 150°C. The black complex was dissolved in dry ether and cautiously hydrolysed by addition of ice; after washing the ether extract with water, separating and drying ($MgSO_4$), the ether was removed by distillation at atmospheric pressure. Distillation of the black oil remaining gave three fractions. The first (b.p. 70-75°C/2 mm., 6·4 gm.) a light brown solid, contained starting material, isomeric monobromo anilines (M, 243) and dibromo anilines (M, 303) by v.p.c. analysis (Col. 'O', 200°C) and mass spectrometry. The second fraction (2·0 g., b.p. 75-84°/2 mm.) was a similar mixture but contained more dibromo compounds while the third fraction (7·0 g., b.p. 90-100°/2 mm.) was a brown solid containing dibromotrifluoro and tribromodifluoroanilines along with small amounts of monobromotetrafluoro compounds.

After distillation there remained a black residue (4·5 g.) whose i.r. spectrum was featureless and the material was not further investigated.

6. Preparation of heterocyclic cation salts.

a. Attempted preparation of pentafluoropyridinium hexachloroantimonate.

Into a dry, nitrogen flushed double Schlenk tube were introduced

(into one limb), pentafluoropyridine (1·69 g., 10·0 m.mole), antimony pentachloride (2·99 g., 10·0 m.mole) and methylene chloride (~20 ml.). The mixture was stirred well, while the nitrogen in the apparatus was replaced with hydrogen chloride, producing an immediate white precipitate. During filtration the white material darkened, and finally produced a dark brown tar which was not investigated.

b. Preparation of pentafluoropyridinium hexafluoroantimonate.

Pentafluoropyridine (10·09 g., 59·7 m.mole), and hexafluoroantimonic acid (14·15 g., 59·7 m.mole) (prepared by adding an equimolar quantity of anhydrous hydrogen fluoride to antimony pentafluoride) were syringed into a dry double Schlenk tube containing liquid sulphur dioxide at -70°C. The mixture was well stirred and allowed to warm up when the sulphur dioxide boiled off, leaving light brown crystals of pentafluoropyridinium hexafluoroantimonate (23·7 g., 97·9%), m.p.98-102 (decomp.) after recrystallization from sulphur dioxide (Found: C, 14·4%; $C_5HF_{11}NSb$ requires C, 14·7%). I.R. Spectrum No.27. The crystals were removed from the apparatus in, and stored in, a dry box.

c. Preparation of 3,5-dichlorotrifluoropyridinium hexafluoroantimonate.

3,5-Dichlorotrifluoropyridine (8·49 g., 42·0 m.mole) was reacted with hexafluoroantimonic acid (9·58 g., 42·0 m.mole) in liquid sulphur dioxide as in the previous experiment to give, after removal of solvent, 3,5-dichlorotrifluoropyridinium hexafluoroantimonate

(14·0 g., 80%), m.p. 95-98 (decomp.) after recrystallization from sulphur dioxide (Found: C, 13·4%; $C_5HCl_2F_9NSb$ requires C, 13·7). I.R. Spectrum No.28.

d. Preparation of heptafluoroquinolinium hexafluoroantimonate.

Heptafluoroquinoline (14·75 g., 57·8 m.molé) and hexafluoroantimonic acid (13·7 g., 57·8 m.mole) were reacted in liquid sulphur dioxide as previously described. The apparatus was transferred to a dry box, after the solvent had boiled off, and the solid removed. This was found to be heptafluoroquinolinium hexafluoroantimonate (27·51 g., 96·5%), m.p. 102-104° decomp. after recrystallization from sulphur dioxide (Found: C, 22·2%; $C_9HF_{13}NSb$ requires C, 21·98%). I.R. Spectrum No.29.

e. Preparation of heptafluoroisoquinolinium hexafluoroantimonate.

Heptafluoroisoquinoline (4·96 g., 19·4 m.mole) and hexafluoroantimonic acid (4·6 g., 19·4 m.mole) were reacted at -70°C in liquid sulphur dioxide. After removal of the solvent, there remained a white solid which was removed in, and stored in, a dry box. This was identified as heptafluoroisoquinolinium hexafluoroantimonate (9·4 g., 97·9%), m.p. 120-124° (decomp.) after recrystallization from sulphur dioxide (Found: C, 22·3%; $C_9HF_{13}NSb$ requires C, 21·98%) I.R. Spectrum No.29.

f. Preparation of tetrafluoro-1,4-diazinium hexafluoroantimonate.

Tetrafluoro-1,4-diazine (3·22 g., 21·2 m.mole) was reacted with hexafluoroantimonic acid (4·9 g., 21·2 m.mole). On removal of solvent tetrafluoro-1,4-diazinium hexafluoroantimonate (5·0 g., 62%), m.p. 101-103° (decomp.) after recrystallization from sulphur dioxide,(Found: C, 11·9%; $C_4HF_{10}N_2Sb$ requires C, 12·1%). I.R. Spectrum No.31.

7. Attempted quaternization reaction.

a. Attempted N-oxidation of heptafluoroquinoline.

(i) Peroxytrifluoroacetic acid was prepared by addition of high test peroxide (5·0 ml.) to trifluoroacetic anhydride (20 ml.) at -20°C contained in a three necked flask (250 ml.) fitted with a dropping funnel, reflux condenser and magnetic stirrer. The mixture was stirred well and allowed to warm up to room temperature. A solution of heptafluoroquinoline (1·03 g., 3·9 m.mole) in trifluoroacetic anhydride (10 ml.) was added dropwise over 30 minutes and the mixture then refluxed for five hours. Methylene chloride (100 ml.) was added to the bright yellow reaction mixture and the solution washed well with water. The organic layer was separated, dried ($MgSO_4$) and the solvent evaporated to leave a yellow gum whose i.r. spectrum was featureless. The material was also too involatile to obtain a mass spectrum.

The aqueous washings (which were bright yellow) were made alkaline with sodium carbonate and re-extracted with methylene chloride to give a further small quantity of tacky yellow which was not investigated further.

(ii) Heptafluoroquinoline (5·0 g., 19·6 m.mole) in methylene chloride (10 ml.) was added dropwise to a solution of peroxytrifluoroacetic acid in methylene chloride (30 ml.) prepared by adding trifluoroacetic anhydride (7·5 ml.) to high test peroxide (1·25 ml.) in methylene chloride at 0°. The mixture was refluxed for two hours and became bright yellow, it was then allowed to stand overnight at room temperature. Removal of the solvent gave an oily semi-solid which was washed with water and the solid which precipitated was filtered off. This was dried over phosphorus pentoxide and was found to sublime (room temperature at 0·001 mm.) to a white solid (4·02 g.) identified as heptafluoroquinoline (80% recovery) from its i.r. spectrum.

b. <u>Attempted reaction of pentafluoropyridine with triethyloxonium tetrafluoroborate.</u>

Triethyloxonium tetrafluoroborate[173] (9·7 g., 51·05 m.mole) and pentafluoropyridine (8·9 g., 52·0 m.mole) were mixed in methylene chloride (5 ml.) under dry nitrogen. After $1\frac{1}{2}$ hours at room temperature a small specimen was withdrawn for a ^{19}F n.m.r. spectrum. Only resonances due to pentafluoropyridine were observed. The mixture was refluxed for $2\frac{1}{2}$ hours and re-examination by ^{19}F n.m.r. spectroscopy showed that only pentafluoropyridine was still present.

c. Attempted reaction of heptafluoroquinoline with triethyloxonium tetrafluoroborate.

A mixture of triethyloxonium tetrafluoroborate (4·55 g., 23·9 m.mole) and heptafluoroquinoline (6·15 g., 23·9 m.mole) was refluxed under dry nitrogen for two hours in methylene chloride (10 ml.). The mixture was cooled, wet ether (10 ml. satd. soln. of water in ether) was added and the mixture stirred overnight. Water was then added and more methylene chloride, the organic layer was washed with water, separated and dried ($MgSO_4$). Removal of the solvent left a tacky, pale brown solid which sublimed readily (room temperature at 0·001 mm.), to give heptafluoroquinoline (6·0 g., 98% recovery) identified by its i.r. spectrum.

d. Attempted reaction of trimethyloxonium tetrafluoroborate with heptafluoroquinoline.

Trimethyloxonium tetrafluoroborate[173] (5·15 g., 34·79 m.mole) and heptafluoroquinoline (13·25 g., 34·7 m.mole) were refluxed under dry nitrogen for 12½ hours in methylene chloride (20 ml.). After cooling, a saturated solution of water in ether (10 ml.) was added and stirring continued for 14 hours. The mixture was extracted as before and starting material (13·1 g., 98% recovery) was isolated by sublimation (room temperature at 0·001 mm.).

CHAPTER VII

Experimental for Chapter IV

A

Reactions of Perfluoroheteroaromatic Compounds with Boron Halides.

1. Reactions of heptafluoroquinoline.

a. With boron trichloride.

(i) A mixture of heptafluoroquinoline (1·0 g., 3·92 m.mole) and boron trichloride (0·47 g., 4·0 m.mole) were heated in a sealed tube for 72 hours at 160°C. After venting the boron halides were removed by pumping and the solid remaining was dissolved out in ether. Removal of the solvent followed by sublimation (30° at 0·001 mm.), gave a white solid (1·05 gm.), whose i.r. spectrum was identical with that of 2,4-dichloropentafluoroquinoline. However, v.p.c. analysis (Col. 'O', 200°) showed the product to contain 2-chlorohexafluoroquinoline[a] (10%) (mixed injection) and starting material (~1%) as well as 2,4-dichloropentafluoroquinoline.

(ii) Heptafluoroquinoline (2·0 g., 7·8 m.mole) and boron trichloride (7·64 g., 65·0 m.mole) were heated together in a sealed tube at 140°C for 128 hours. The product was isolated as described in the previous experiment and found to be 2,4-dichloropentafluoroquinoline (2·1 g., 91%), identified by comparison of its i.r. spectrum with that of an authentic specimen.

b. With boron tribromide.

Heptafluoroquinoline (1·0 g., 3·9 m.mole) and boron tribromide (5·24 g., 20·9 m.mole) were heated in a sealed tube for 55 hours at

[a] This Chapter B,1.a.

115°C. After venting the contents of the tube were poured into a flask and boron halides destroyed by passing a current of damp nitrogen through the flask overnight. The remaining solid was taken up in ether, washed with water, separated and dried ($MgSO_4$). Removal of the solvent gave a pale yellow solid which sublimed (50° at 0·001 mm.) to a white solid (1·3 g.) identified as 2,4-dibromopentafluoroquinoline (87·5%), by comparison of its i.r. spectrum and mixed injection on analytical v.p.c. (Col. '0', 200°), with an authentic sample.

c. With boron tri-iodide.

(i) Heptafluoroquinoline (1·5 g., 5·9 m.mole) and boron iodide (4·5 g., 11·5 m.mole), contained in a dry, nitrogen flushed, two necked flask (50 ml.) fitted with a short air condenser and magnetic stirrer, were heated to 95°C when they melted. The temperature was reduced to 75° (mixture remained molten) and maintained at this temperature for 50 hours. During this time the contents of the flask became highly discoloured and free iodine was observed subliming to the cooler parts of the apparatus. The mixture was cooled and dissolved in dry pentane, cautious addition of ether produced an initial precipitate (presumed to be $BI_3 \cdot OEt_2$) which dissolved on addition of more ether. Water was cautiously added, followed by an aqueous solution of $Na_2S_2O_5$ to remove free iodine. The organic layer was separated, washed with water, and dried ($MgSO_4$). Removal of the solvent and sublimation (room temperature at 0·001 mm.) gave a pale yellow solid identified by

v.p.c. (Col. 'O', 200°), and i.r. spectroscopy, as starting material (1·3 g., 87% recovery).

(ii) A mixture of heptafluoroquinoline (1·7 g., 6·7 m.mole) and boron tri-iodide (3·3 g., 8·42 m.mole) was heated in a sealed tube at 150°C for 4 days. The contents of the tube were extracted as in the previous reaction, sublimation of the crude product yielded a yellow solid (0·1 g., which sublimed at 100°C at 0·001 mm.) whose i.r. spectrum was featureless. The residual material was a black tar which was not investigated further.

2. Reactions of pentafluoropyridine and heptafluoroisoquinoline.

a. Reactions of pentafluoropyridine with boron trichloride.

(i) Pentafluoropyridine (5·0 g., 28·9 m.mole) was heated in a sealed tube with boron trichloride (3·4 g., 28·9 m.mole) for 20 hours at 55-60° followed by a further 65 hours at 75°C. At the end of this time the tube contained a pale brown clear solution. After venting and removal of volatile materials the contents were taken up in ether, the ether solution was washed with water, separated and dried ($MgSO_4$). The extract was concentrated by distillation through a Vigreux column and v.p.c. analysis (Col. 'A', 100° and 60°) showed only pentafluoropyridine.

(ii) Pentafluoropyridine (5·0 g., 28·9 m.mole) and boron trichloride (28·47 g., 112·7 m.mole) were heated for 209 hours at 160° in a Carius

tube. At the end of this time the tube contained a pale yellow liquid plus some black solid. The products were extracted into ether as previously described, v.p.c. analysis (Col. 'A', 100° and 60°) of the concentrated extract showed pentafluoropyridine (>95%) plus a slight trace (~0·5%) of a component with a retention time identical with that of 4-chlorotetrafluoropyridine.

b. Attempted reaction of heptafluoroisoquinoline with boron tribromide.

Heptafluoroisoquinoline (2·1 g., 8·2 m.mole) and boron tribromide (5·76 g., 23·0 m.mole) were heated together in a sealed tube for 284 hours at 150°C. After cooling, the contents were poured into a flask and boron bromide destroyed by passing a stream of damp nitrogen through the flask overnight. Ether extraction of the solid remaining in the usual way gave, after removal of ether, a brownish-violet liquid which slowly solidified. Sublimation (50°C at 0·001 mm.) gave a white solid which was identified as unchanged starting material (1·8 g., 85% recovery) by v.p.c. analysis (Col. 'O', 200°C) and i.r. spectroscopy.

3. Reaction of boron trichloride with hexafluorobenzene.

A mixture of hexafluorobenzene (6·0 g., 32·3 m.mole) and boron trichloride (3·79 g., 32·3 m.mole) was heated for one week at 150°C in a sealed tube. The tube was vented and boron halides removed from the products by vacuum transference, the remaining liquid was distilled and unchanged starting material (4·0 gm., 66% recovery) was collected.

The black residue after distillation was subjected to sublimation (60° at 0·001 mm.) to give a white solid (0·05 g.) whose mass spectrum contained parent ions at $^{m}/e$ 282 (C_6Cl_6), 276 (C_6Cl_5F), 250 ($C_6Cl_4F_2$). The black residue after sublimation was not further investigated.

B

Reactions of Perfluoroheteroaromatic Compounds with Aluminium Halides

1. Reactions of heptafluoroquinoline.

a) With aluminium chloride.

A mixture of heptafluoroquinoline (4·0 g., 15·6 m.mole) and aluminium chloride (12·0 g., 89·8 m.mole) was heated in a sealed tube for 200 hours. The tube was vented and the contents washed out with dry ether. Water was cautiously added to hydrolyse excess aluminium halide and the organic layer separated and dried ($MgSO_4$). Removal of the solvent followed by sublimation (room temperature at 0·001 mm.) of the residue gave 2-chlorohexafluoroquinoline (3·5 g., 81·3%), m.p. 78-79°. (Found: C, 40·1; Cl, 13·8; F, 42·8%; M, 271. C_9ClF_6N requires C, 39·8; Cl, 13·1; F, 42·1%; M, 271). I.R. Spectrum No. 1.

b. With aluminium bromide.

(i) at 150°

A mixture of heptafluoroquinoline (5·0 g., 19·6 m.mole) and

aluminium bromide (19·5 g., 73·0 m.mole) was heated in a Carius tube at 150° for 114 hours. The products were extracted as described above and, after removal of solvent and sublimation (40° at 0·001 mm.), gave 2-bromohexafluoroquinoline (6·3 g., 85·3%), m.p. 71-72° (Found: C, 33·99; Br, 25·2; F, 35·8%; M, 315. C_9BrF_6N requires C, 34·18; Br, 25·31; F, 36·08%; M, 315). I.R. Spectrum No.2.

(ii) At 170°.

Heptafluoroquinoline (2·55 g., 10·0 m.mole) and aluminium bromide (6·3 g., 23·6 m.mole) were reacted at 170° for 150 hours as described above. Extraction of the products was carried out in the usual way and analysis of the sublimate (sublimation at 60° and 0·001 mm. gave 2·4 g. of crude product) by analytical v.p.c. (Col. 'O', 200°) showed 2-bromohexafluoroquinoline (10%), and a possible dibromopentafluoroquinoline whose retention time was not identical with that of 2,4-dibromopentafluoroquinoline. Recrystallization from chloroform gave pure 2,8-dibromopentafluoroquinoline (1·8 g., 48%), m.p. 112-113° (Found: C, 28·4; Br, 42·3; F, 24·7%; M, 375. $C_9Br_2F_5N$ requires C, 28·65; Br, 42·44; F, 25·2%; M, 375). I.R. Spectrum No.14.

c. With aluminium iodide.

Heptafluoroquinoline (2·55 g., 10·0 m.mole) was heated with aluminium iodide at 150°C for 7 days. The reaction mixture was

extracted with dry ether and then cautiously hydrolysed, material which was insoluble in ether or water was filtered off (2·9 g.) and not investigated further. The organic layer was separated, washed with $Na_2S_2O_5$ solution and water, and finally dried ($MgSO_4$). Removal of the solvent left a brown solid which sublimed (85° at 0·001 mm.) to a tan solid (2·6 g.),which t.l.c. analysis (Silica eluted with pentane-benzene 9:1) showed to be a single compound. Resublimation (80° at 0·001 mm.) gave 2,8-di-iodopentafluoroquinoline (2·6 g., 55%), m.p. 95-96° as a pale yellow solid (Found: C, 23·3; F, 19·8; I, 53·0%; M, 471. $C_9F_5I_2N$ requires C, 22·93; F, 20·1; I, 53·93%; M, 471). I.R. Spectrum No.15.

2. Reactions of pentafluoropyridine and heptafluoroisoquinoline.

a. Reaction of pentafluoropyridine with aluminium bromide.

Pentafluoropyridine (6·5 g., 38·5 m.mole) and aluminium bromide (10·9 g., 40·8 m.mole) were heated in a sealed tube for ten days at 160-165°. The contents were then dissolved out with ether and the extract was washed with water, material which was insoluble in ether or water was rejected and not investigated further. After drying ($MgSO_4$) the extract, ether was removed by distillation and the remaining liquid fractionally distilled. The first fraction (0·8 g. boiling range 75-85°) was unchanged starting material. The second fraction (0·65 g., boiling range 85° - 165°) contained three components in

approximate ratios 1:1:2, these were identified as starting material, probably 2-bromotetrafluoropyridine[189] (Col. 'A', 150°) and 2,6-dibromotrifluoropyridine by v.p.c. mass spectrometry and ^{19}F n.m.r. The third fraction (0·4 g., boiling range 110° - 120°C at 10 mm.) was apparently a mixture of 2-bromotetrafluoropyridine and 2,6-dibromotrifluoropyridine in ratio 5:95 by v.p.c. (Col. 'A', 150°), ^{19}F n.m.r. and mass spectroscopy. Vacuum transference (room temperature at 0·05 mm.) gave pure 2,6-dibromotrifluoropyridine (0·2 g.). Unfortunately there was insufficient for full analysis (Found: C, 20·0%; M, 289. $C_5Br_2F_3N$ requires C, 20·6%; M, 289). I.R. Spectrum No.22.

b. Reaction of heptafluoroisoquinoline with aluminium bromide.

Heptafluoroisoquinoline (1·5 g., 5·9 m.mole) and aluminium bromide (5·0 g., 18·3 m.mole) were heated together in a sealed tube for 210 hours at 156°. The contents of the tube were highly discoloured and were extracted with ether, insoluble material was ignored. The extracts were washed well with water, dried ($MgSO_4$) and distilled to leave a brown solid. Sublimation (95° at 0·001 mm.) gave a yellow solid (0·6 g.) which was deliquescent and whose i.r. spectrum was featureless. The residue from the sublimation was not investigated further.

APPENDIX 1

Nuclear Magnetic Resonance Data

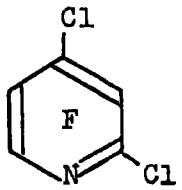
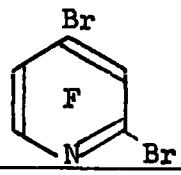
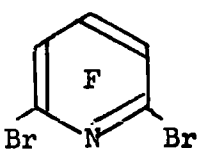
Spectra were recorded on a Perkin-Elmer R.10 nuclear magnetic resonance spectrometer, as described in Chapter VA. Coupling constants, J c.p.s., are recorded where possible, and assigned to specific F-F interactions by first order analysis, except where the complex nature of the spectra, or limited resolution prevented this.

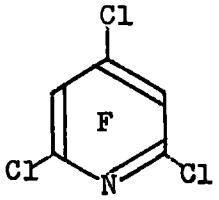
Shifts are in p.p.m. relative to $CFCl_3$ (^{19}F) or T.M.S. (^{1}H); † denotes a peak twice the intensity of other peaks.

S. = singlet

D. = doublet

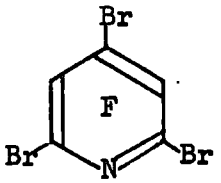
T. = triplet

	Peak appearance		
	^{19}F n.m.r.		
	84.8 (6)	D.D.	$J_{3,6} = 28$, $J_{5,6} = 23$
	119.8 (3)	D.	$J_{3,6} = 28$
	143.0 (5)	D.	$J_{5,6} = 24$
	^{19}F n.m.r.		
	85.3 (6)	D.D.	$J_{3,6} = 27$, $J_{5,6} = 23$
	107.3 (3)	D.	$J_{3,6} = 27$
	130.9 (5)	D.	$J_{5,6} = 23$
	^{19}F n.m.r.		
	†130.2 (3,5)	D.	$J_{3,4} = 18.4$
	139.4(4)	T.	$J_{3,4} = 18.6$



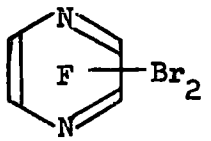
^{19}F n.m.r.

117·6 (2,5) S.



^{19}F n.m.r.

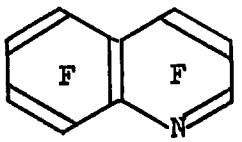
104·4 (3,5) S.



^{19}F n.m.r.

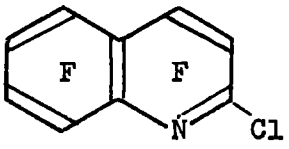
74·9 S.

orientation unknown because of symmetry



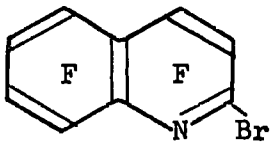
^{19}F n.m.r.

77·2(2)	T(Broad)	J 21-25
126·0 (4)	D.D.D.	$J_{4,5}$ = 49, J = 25 and 17
145·7 (5)	D.	$J_{4,5}$ = 49, showing poorly resolved smaller splitting
148·3	T.	J = 18
150·7	T.	J = 18
154·4	T.	J = 18
160·6 (3)	no splitting apparent	



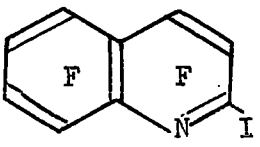
^{19}F n.m.r.

128·0(4)	D.D.	$J_{4,5}$ = 47, $J_{3,4}$ = 16
142·3(3)	D.	$J_{3,4}$ = 15 (poorly resolved)
146·0(5)	D.T.D.	$J_{4,5}$ = 47, J = 17 and 7
147·2	T	J = 17
150·0	T.D.	J = 17 and 8
153·1	T.	J = 17



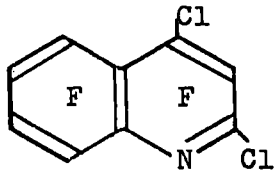
^{19}F n.m.r.

128·7(4)	D.D.	$J_{4,5}$ = 45, $J_{3,4}$ = 16
135·5(3)	D.	$J_{3,4}$ 15
145·8(5)	D.T.D.	$J_{4,5}$ = 45, J = 17 and 7
147·2	T.	J = 17
150·2	T.D.	(poorly resolved) J = 17 and 8
153·1	T.	J = 17



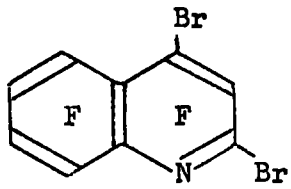
^{19}F n.m.r.

125·7(3)	D.	$J_{3,4}$ = 17 (poorly resolved)
130·6(4)	D.D.	$J_{4,5}$ = 45, $J_{3,4}$ = 17
146·0(5)	D.T.D.	$J_{4,5}$ = 45, J = 17 and 6
147·1	T.	J = 18
151·6	T.D.	J = 20 and 8
153·0	T.	J = 18



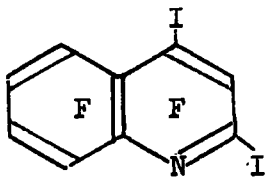
^{19}F n.m.r.

116·8(3)	S. (showing very complex small splittings).	
144·7	T.D.	J = 17 and 6
146·6	T.D.	J = 21 and 9
†152·2	Two coalesced signals, one probably T.D. J = 20,8, the other probably T.J = 16.	



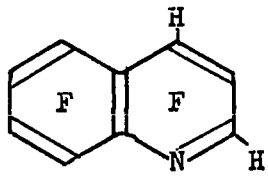
^{19}F n.m.r.

100·7(3)	S. (showing small complex splittings	J 6 and 2
143·9	T.D.	J = 17, and 10
146·1	T.D.	J = 17, and 5
†151·9	Two coalesced signals, probably T.D. J = 20,8 and T.J = 18	



^{19}F n.m.r.

73·9(3)	Complex peak, essentially a singlet	
143·0	T.D.	J = 17 and 6, showing further unresolved splitting
146·4	T.	J 20 (poorly resolved)
†152·5	Complex multiplet due to overlapping peaks.	

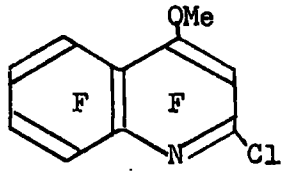


^{19}F n.m.r.

125·3(3)	S. showing complex unresolved small splitting	
149·2	T.D.	J = 17 and 6 but showing further fine splitting
150·9	T.D.	J = 17, 6
†155·5	Two coalesced signals perhaps T.D. J = 19 and 9 and T.J = 19.	

^{1}H n.m.r.

1·13(2)	D.	$J_{2,4}$ = 2·5, $J_{2,3}$ = 0
1·98(4)	D.D.D.	$J_{2,4}$ = 2·5, $J_{4,3}$ = 8·1

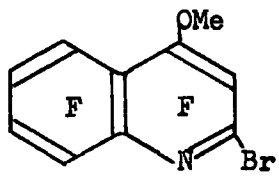


^{19}F n.m.r.

140·9(3)	S.	
144·5	T.D.	J = 17 and 6
149·7	T.	J = 18 showing further unresolved small splitting
153·5	T.D.	J = 18, and 8
156·6	T.	J = 18

^{1}H n.m.r.

5·62	D.	$J_{4\text{-OMe-}3F}$ = 5·62

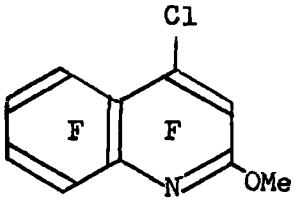


^{19}F n.m.r.

133·8(3)	D.	
144·5	T.D.	J = 17 and 6
148·9	T.	J = 17 showing more unresolved splitting
153·7	T.D.	J = 20 and 9 (poorly resolved)
156·3	T.	J = 20

^{1}H n.m.r.

5·66	D.	$J_{4\text{-OMe-}3F}$ = 5·0



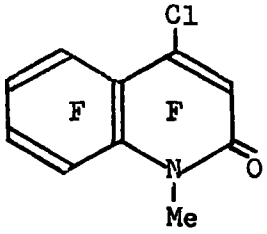
as mixture with pentafluoro-4-chloro-N-methyl-2-quinolone

^{19}F n.m.r.

133·9(3)	S.	
146·1		
150·0		
153·4		
158·9		

^{1}H n.m.r.

5·83	S.	$J_{2\text{-Ome-}3F} = 0$

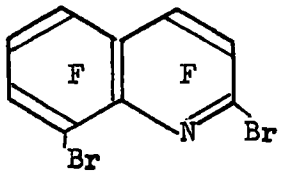


^{19}F n.m.r.

120·3(3)	T.D.	J = 9 and 5
140·8	very complex multiplet	
148·5	very complex multiplet	
151·2	T.D.	J = 20 and 9 but showing further unresolved small couplings
161·7	T.	J = 21

^{1}H n.m.r.

6·20	D.	$J_{1\text{-Me-}8F} = 10{\cdot}0$ c.p.s.



^{19}F n.m.r.

115·8(7)	D.T.	J = 22 and 8 showing further complex small coupling
128·4(4)	D.D.T.	$J_{4,5}$ = 51 and J = 15 and 5
136·3(3)	D.T.	J = 17 and 7 showing more unresolved small splittings
140·8(5)	D.D.T.	$J_{4,5}$ = 51, $J_{5,6}$ = 16 and J = 6
153·6(6)	T.	J = 20 showing poorly $_{5,7}$ $_{6,7}$ resolved complex smaller splittings

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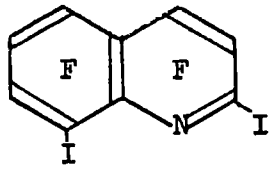

^{19}F n.m.r.

101·6 (7)	D.T.	J = 23 and 8 showing further small splittings
126·8 (3)	D.T.	J = 17 and 8
129·6(4)	D.D.T.	$J_{4,5}$ = 51, J = 17 and 5
139·4(5)	D.D.T.	$J_{4,5}$ = 49, $J_{5,6}$ = 17 and J = 8
153·4(6)	T.	$J_{5,6}$ = 20 showing more $_{6,7}$ complex fine coupling

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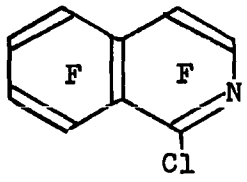
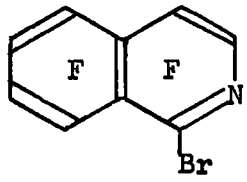


^{19}F n.m.r.

94·0(3)	D.	J = 16 (broad)
136·9	D.D.D.	J = 25, 18, 6 c.p.s. showing further fine splitting
144·7	D.T.	$J_{4,5}$ = 56 and J = 17 showing unresolved complex splitting

^{19}F n.m.r.

146·2	T.	J = 17 with poorly resolved fine splitting
†152·1		Complex multiplet due to two overlapping peaks



^{19}F n.m.r.

93·9(3)	D.	J = 17 (broad)
136·4	T.	Poorly resolved J 20
145·2	D.T.	$J_{4,5}$ = 57 and J = 18 showing further complex couplings
146·0		Poorly resolved complex peak
†151·6		Complex multiplet due to overlapping signals

APPENDIX II

Infra-red Spectra

Index of Infra-red Spectra

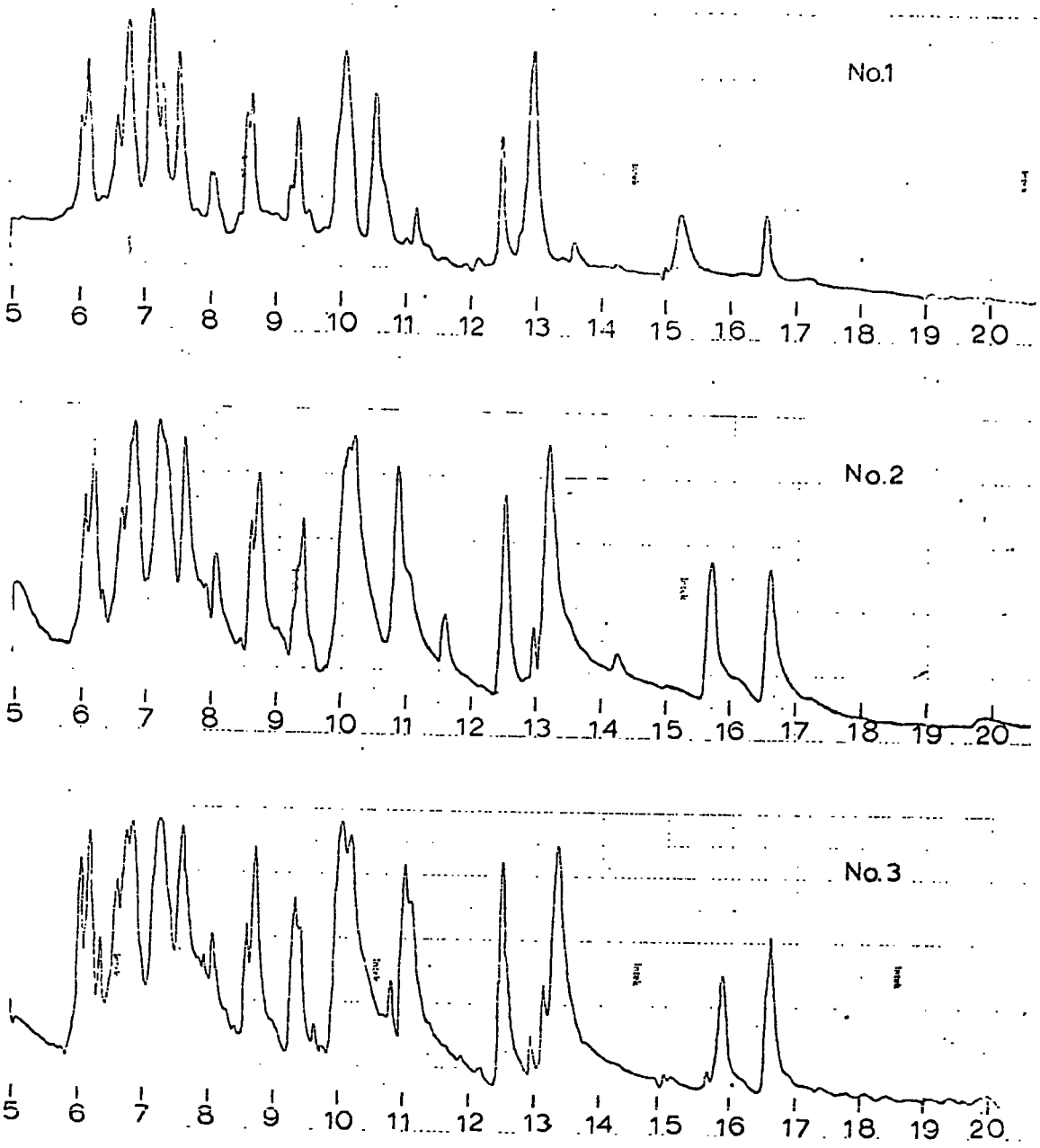
Spectrum No.	Compound	State
1	2-Chlorohexafluoroquinoline	(d)
2	2-Bromohexafluoroquinoline	(d)
3	2-Iodohexafluoroquinoline	(d)
4	2,4-Dichloropentafluoroquinoline	(d)
5	2,4-Dibromopentafluoroquinoline	(d)
6	2,4-Di-iodopentafluoroquinoline	(d)
7	3,5,6,7,8-Pentafluoroquinoline	(d)
8	2-Hydroxy-4-chloropentafluoroquinoline	(d)
9	N-Methyl-4-chloropentafluoro-2-quinolone	(d)
10	2-Chloro-4-hydroxypentafluoroquinoline	(d)
11	2-Chloro-4-methoxypentafluoroquinoline	(d)
12	2-Bromo-4-hydroxypentafluoroquinoline	(d)
13	2-Bromo-4-methoxypentafluoroquinoline	(d)
14	2,8-Dibromopentafluoroquinoline	(d)
15	2,8-Di-iodopentafluoroquinoline	(d)
16	1-Chlorohexafluoroisoquinoline	(l)
17	1-Bromohexafluoroisoquinoline	(l)
18	1-Hydroxychloropentafluoroisoquinoline	(d)
19	1-Hydroxybromopentafluoroisoquinoline	(d)
20	2,4-Dichlorotrifluoropyridine	(l)

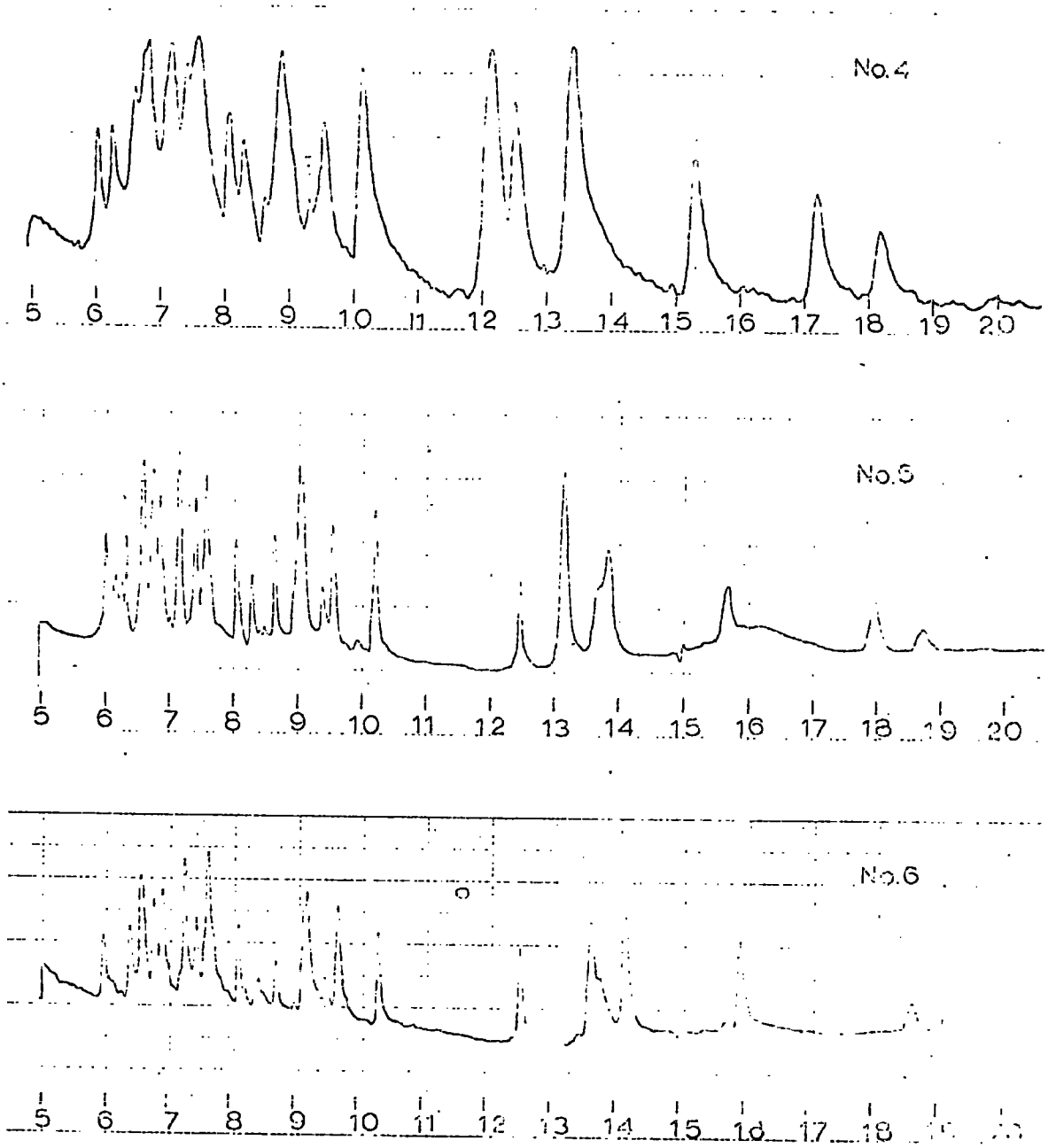
Spectrum No.	Compound	State
21	Dibromodifluoropyrazine	(l)
22	2,6-Dibromotrifluoropyridine	(l)
23	2,4,6-Trichlorodifluoropyridine	(d)
24	2,4,6-Tribromodifluoropyridine	(d)
25	2,4-Dibromotrifluoropyridine	(l)
26	Tetrabromopyrazine	(d)
27	Pentafluoropyridinium Hexafluoro-antimonate	(m)
28	3,5-Dichlorotrifluoropyridinium Hexafluoroantimonate	(m)
29	Heptafluoroquinolinium Hexafluoro-antimonate	(m)
30	Heptafluoroisoquinolinium Hexafluoro-antimonate	(m)
31	Tetrafluoropyrazinium Hexafluoro-antimonate	(m)

(d) Potassium bromide disc

(l) Liquid contact film

(m) Nujol mull


No.1
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
No.2
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
No.3
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20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No.5
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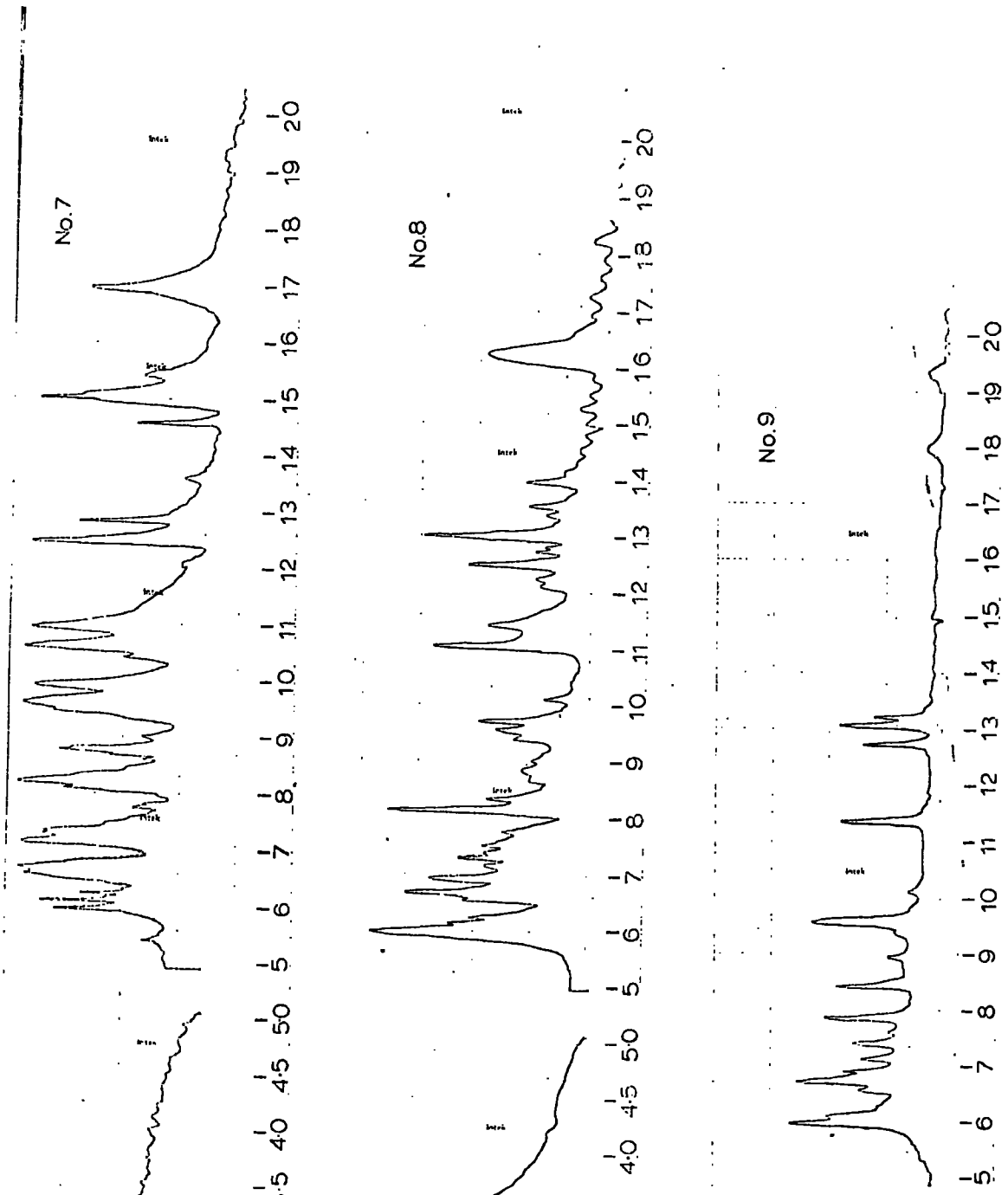
No.6
5 6 7 8 9 10 11 12 13 14 15 16 17 18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No.8
No.9
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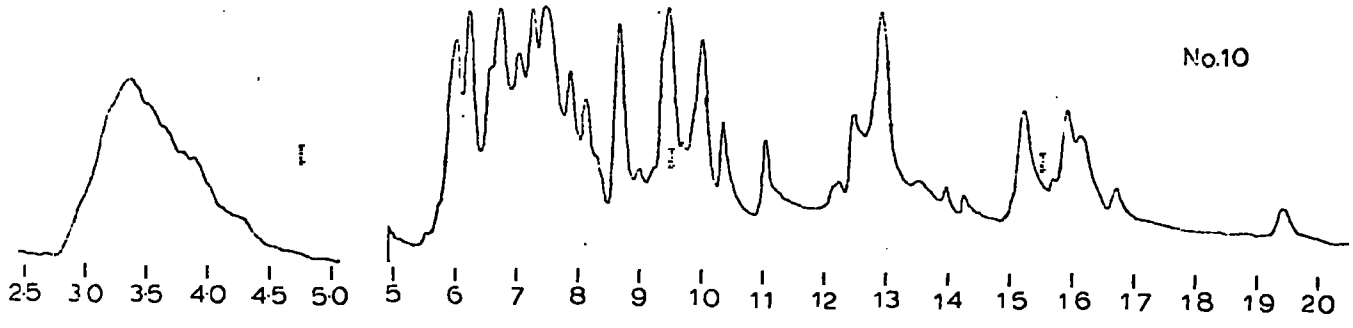
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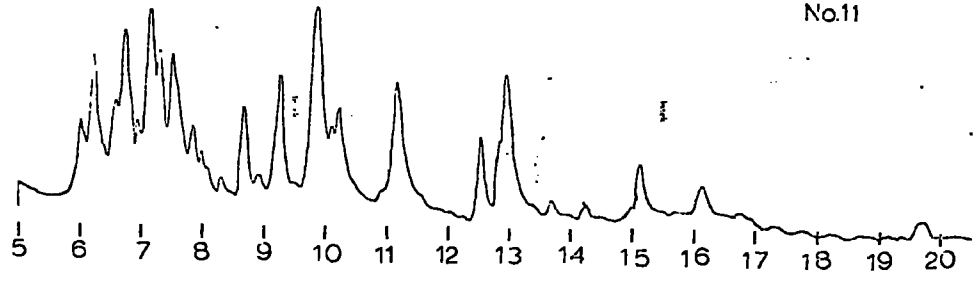
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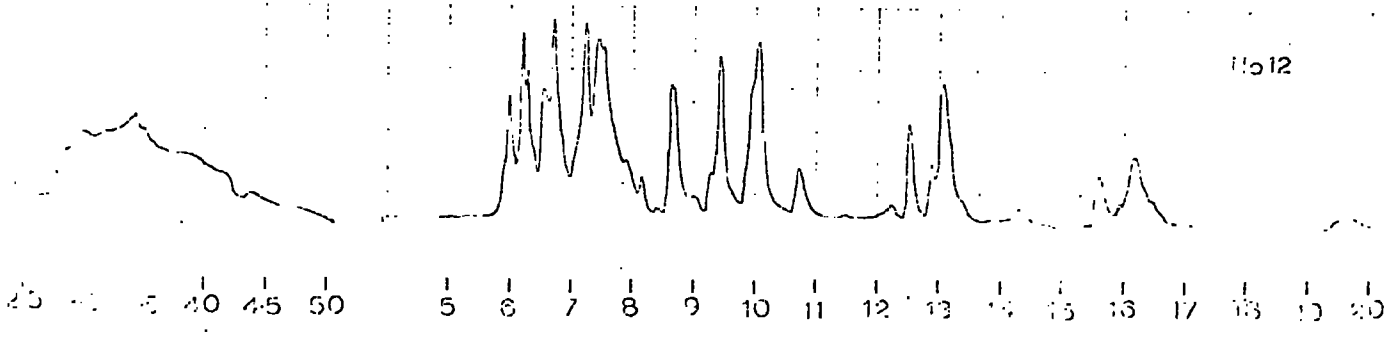
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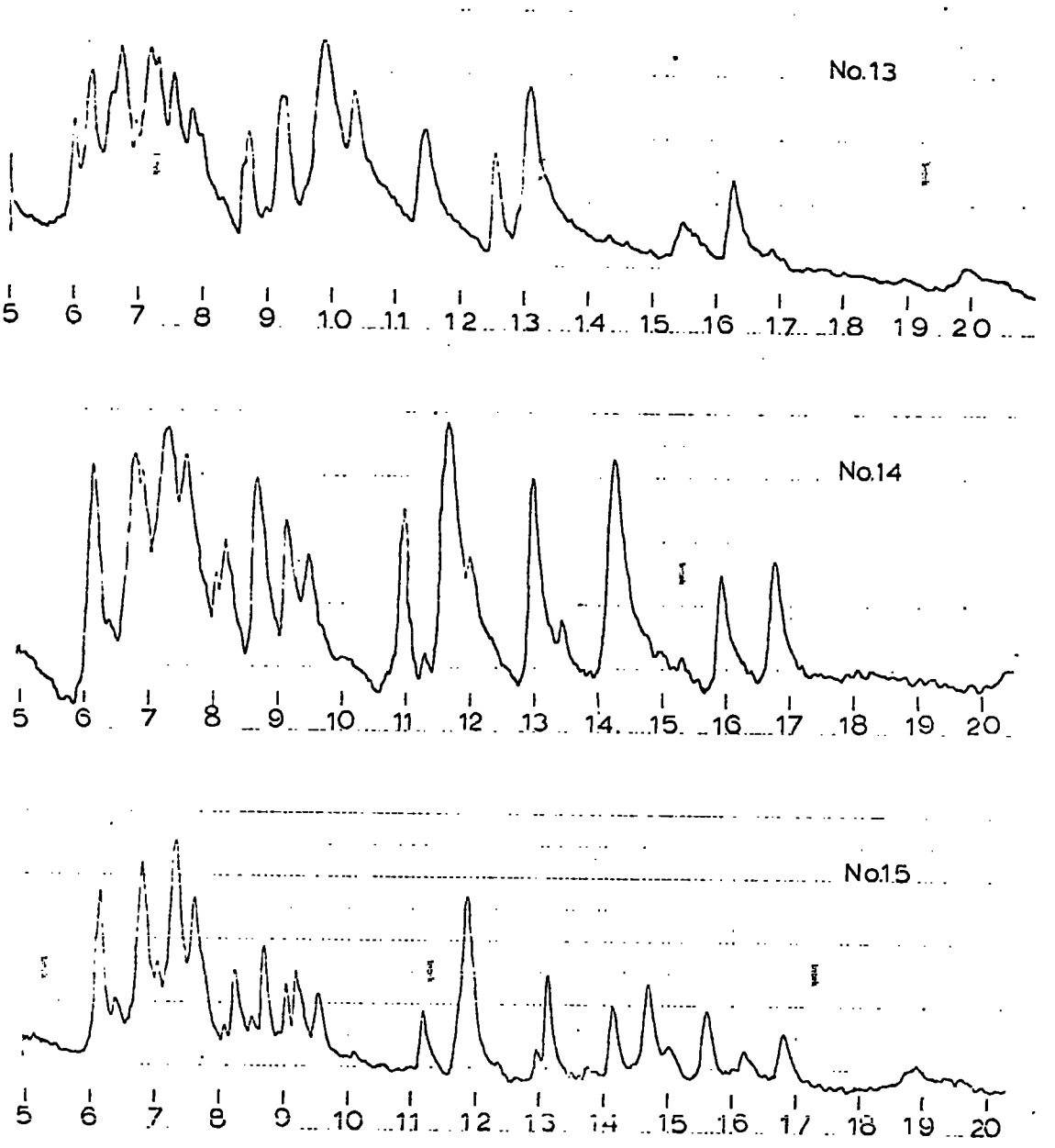
No.13
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No.14
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
No.15
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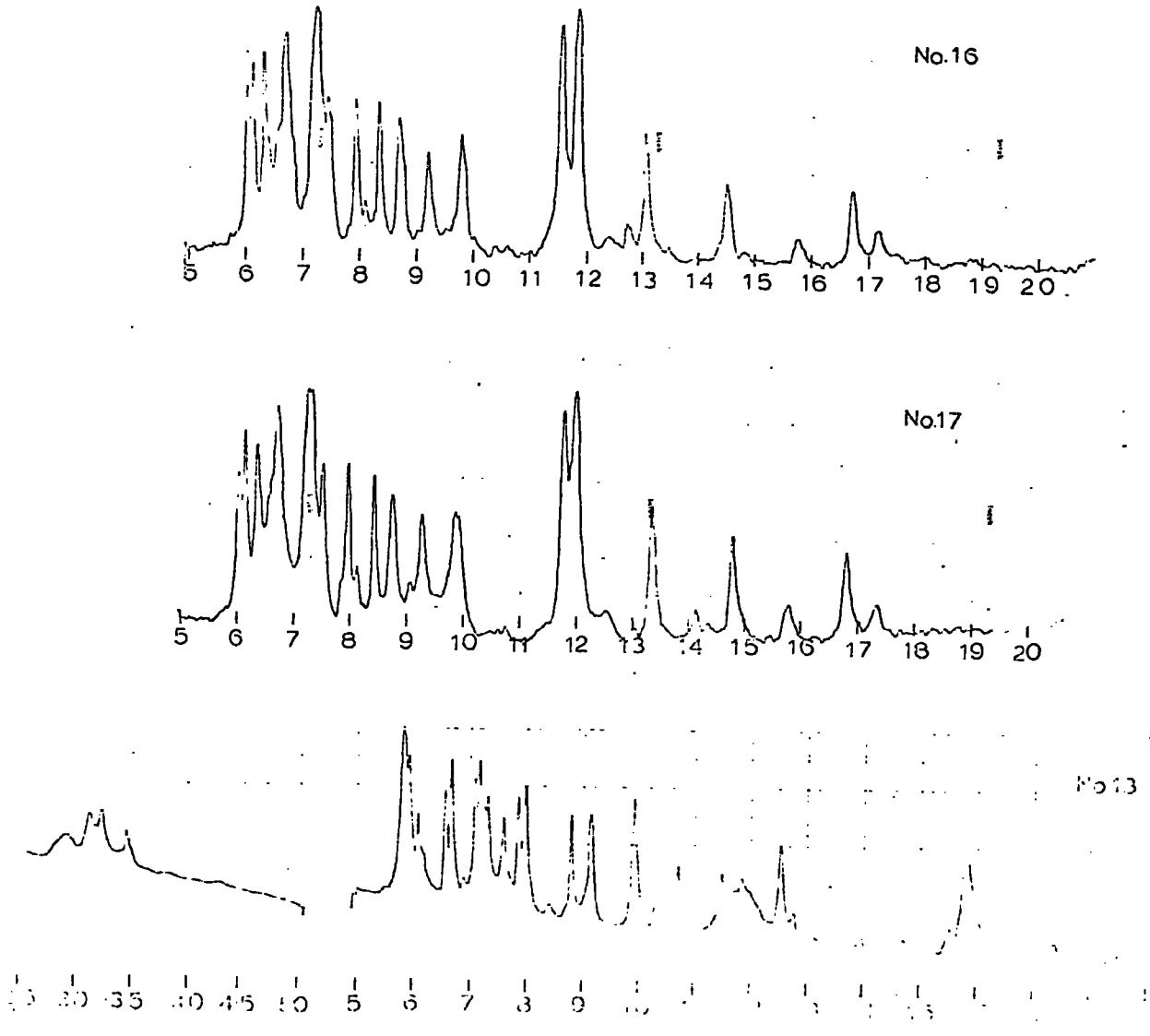
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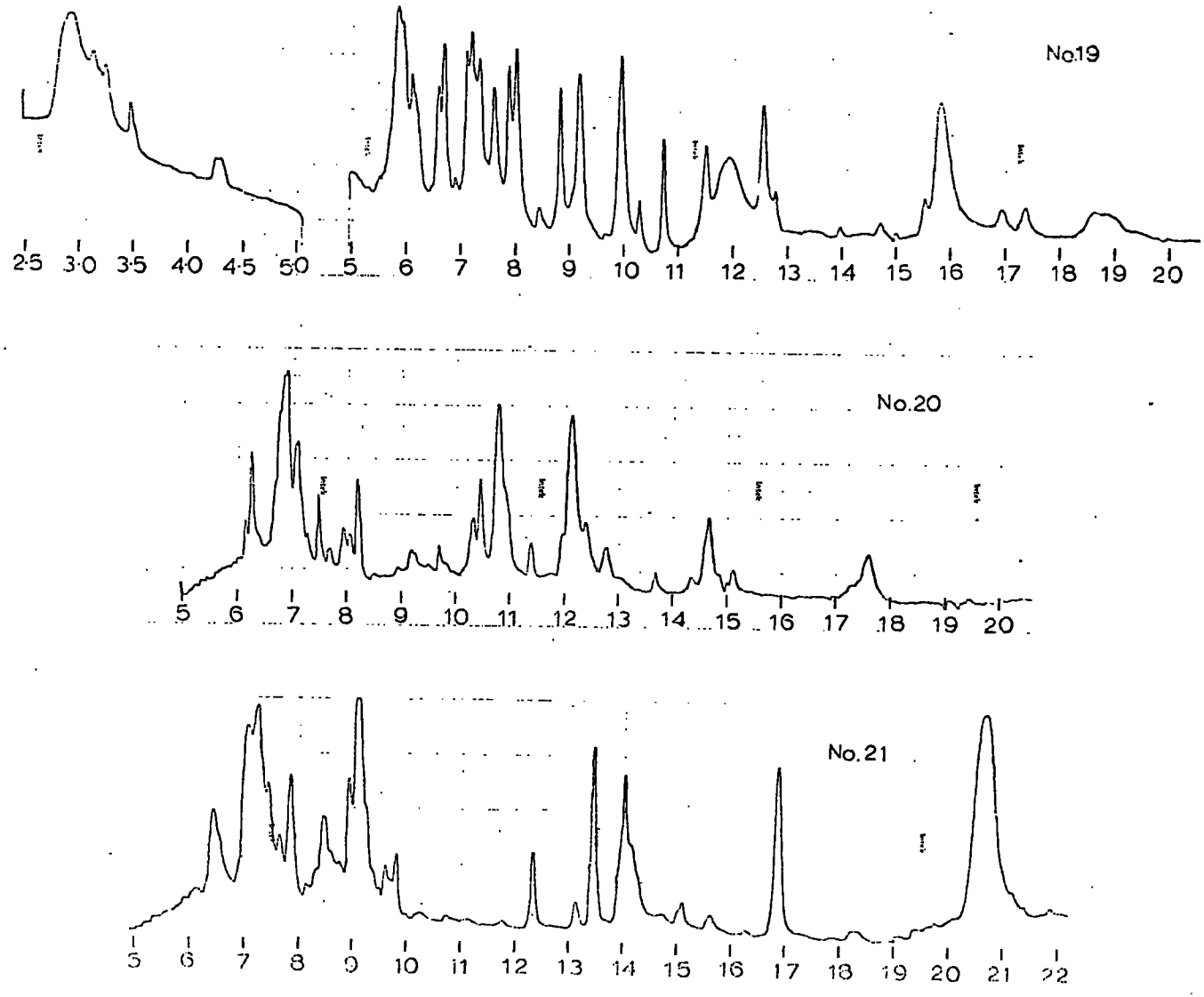
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No.20
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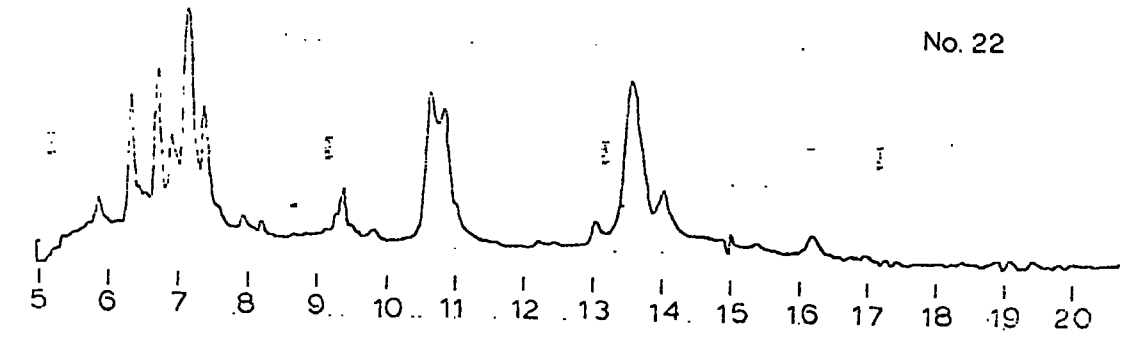
No.21
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22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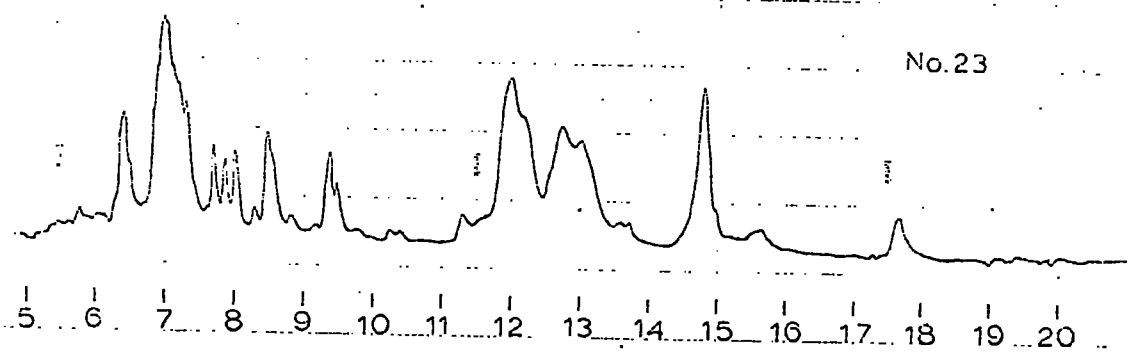
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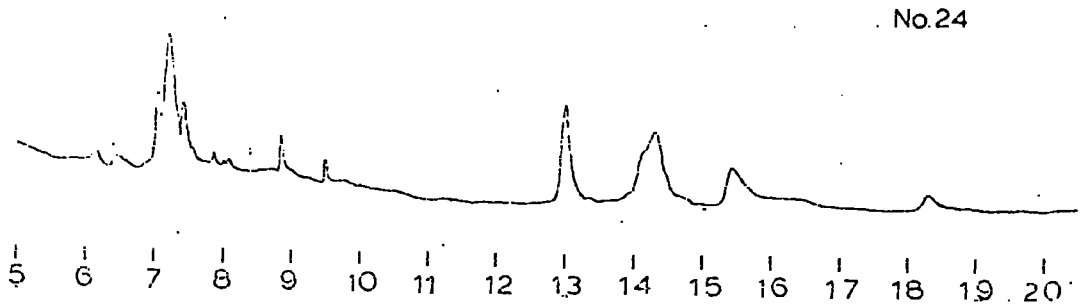
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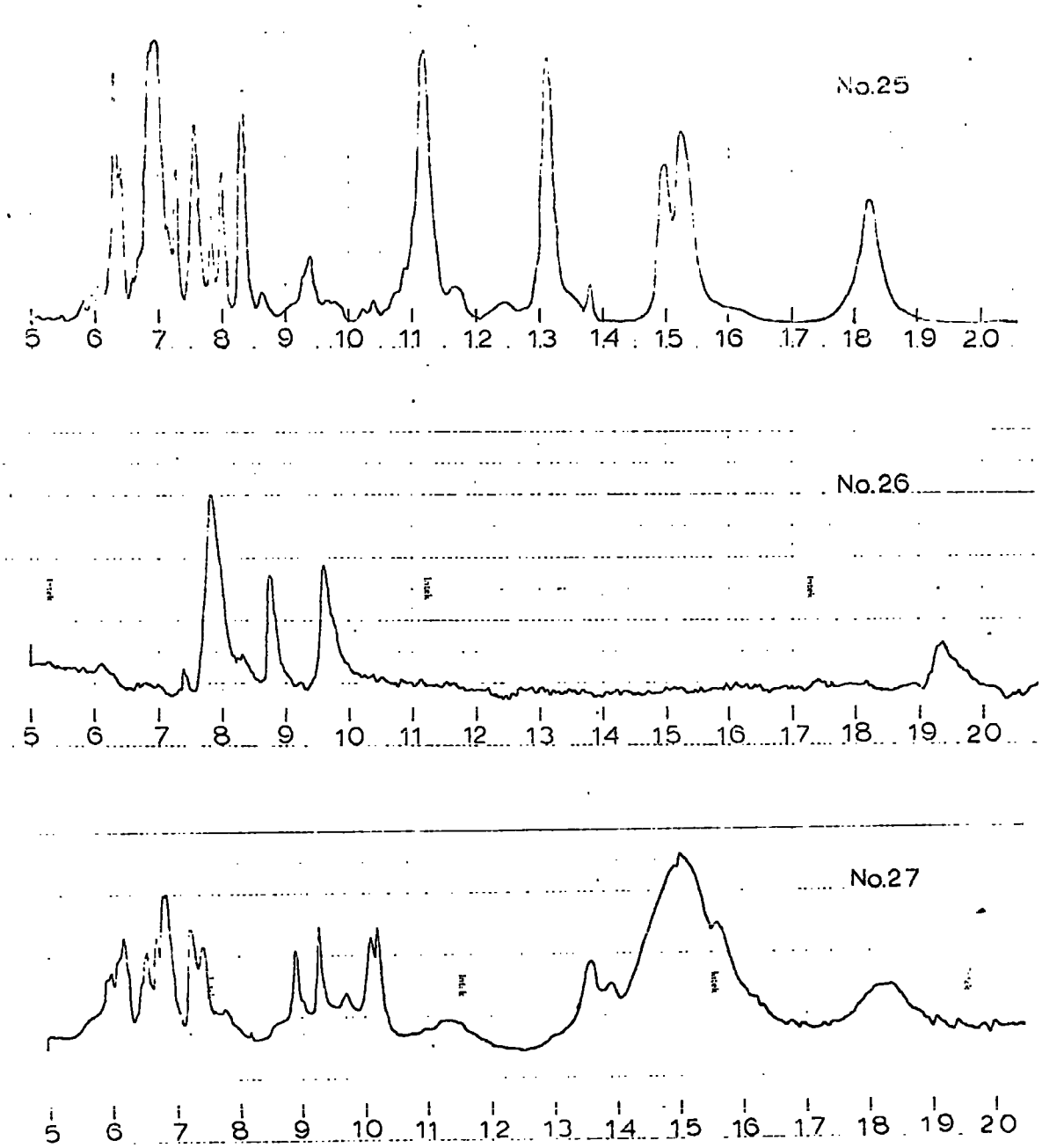
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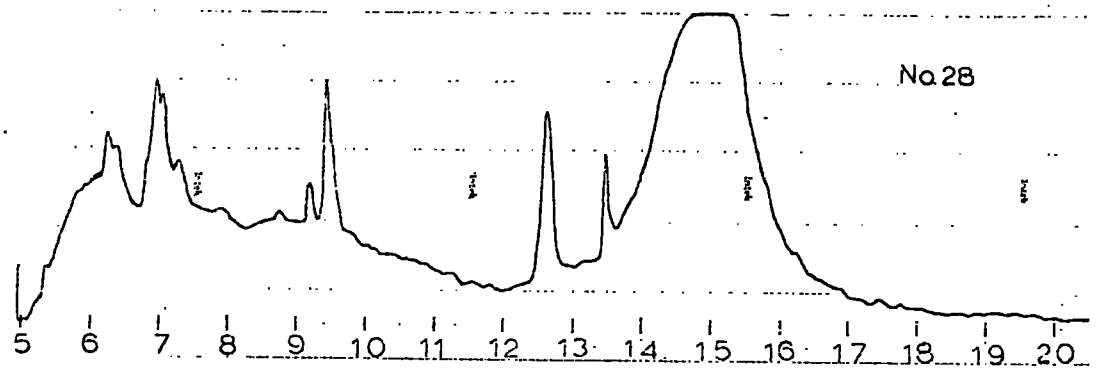
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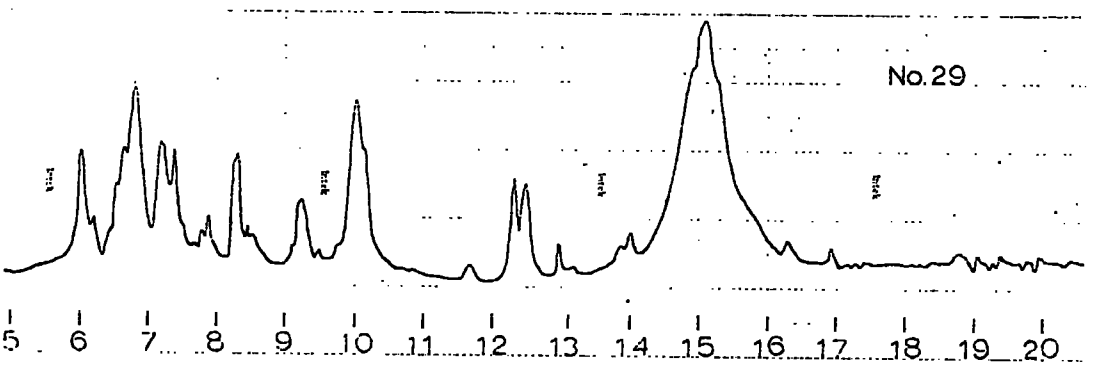
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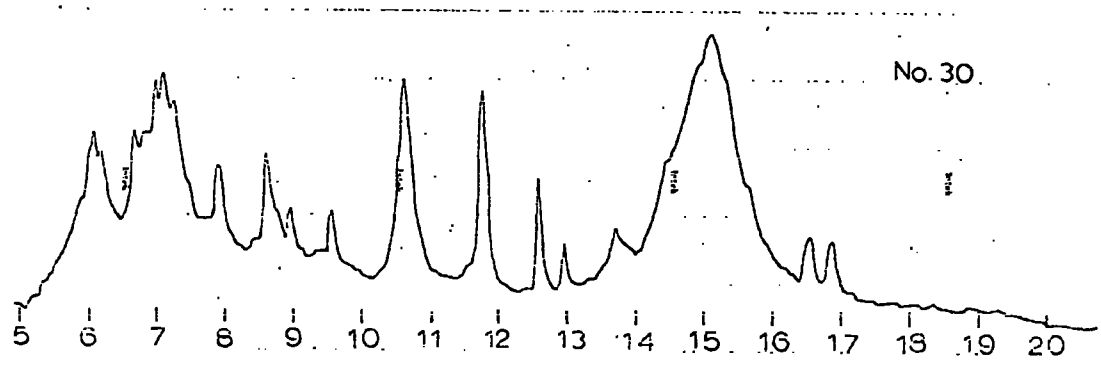
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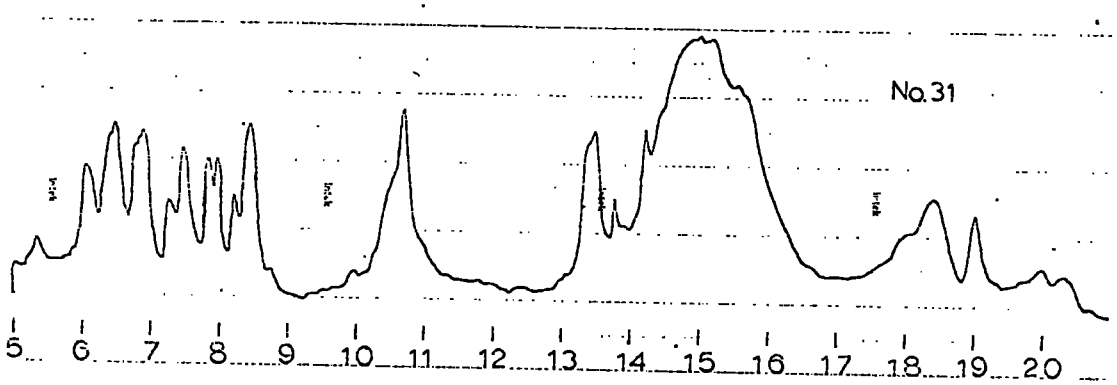
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