# Highly fluorinated diazines

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UNIVERSITY OF DURHAM

A Thesis

entitled

# Highly Fluorinated Diazines

Submitted by

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A candidate for the degree of Doctor of Philosophy

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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 the subject of the following publications:-

C.G. Allison, R.D. Chambers, J.A.H. MacBride and W.K.R. Musgrave, Chem. and Ind., 1968, 1402.

C.G. Allison, R.D. Chambers, J.A.H. MacBride and W.K.R. Musgrave, submitted to J. Chem. Soc. (C).

# SUMMARY

## Highly Fluorinated Diazines

The halogen exchange method for preparing polyfluoroaromatic compounds from perchloroaromatic compounds, using potassium fluoride, is extended to the 1,4-diazine system to produce tetrafluoropyrazine and its benzo-analogue, hexafluoroquinoxaline. Several chlorofluoropyrazines and quinoxalines obtained as by-products are also characterized.

Nucleophilic substitution of tetrafluoropyrazine, leading initially to a range of trifluoropyrazine-derivatives, is investigated, while further substitution of these trifluoropyrazines is of considerable theoretical interest. Unlike other polyfluoroheteroaromatic compounds, all positions are adjacent to the hetero-atoms and are therefore equivalent as far as the influence of the nitrogen atoms is concerned. Thus further substitution is largely controlled by the initial substituent which is similar to substitution in a series of pentafluorophenyl-derivatives. When the substituent attached to the trifluoropyrazine ring is an alkoxy group, ortho substitution is preferred, whereas substitution occurs para to chlorine and alkyl groups. Substitution in hexafluoroquinoxaline occurs initially at the 2- and 3-positions, and then, less readily, at the 6-position. Attack at the 6-position in the homocyclic ring is rationalized in terms of greater ease of localization of the negative charge in the intermediate onto a nitrogen atom.

Trifluorohydroxypyrazine, like its pyridine analogue, is shown to exist in the enol form, while tetrafluoro-2,3-dihydroxyquinoxaline appears to exist largely in the amide form.

Oxidation of several polyfluoroheteroaromatic hydrazino compounds is studied using cupric halides in the presence of halogen acids. These reactions may prove to be useful routes for the preparation of polyfluoroheteroaromatic halo-derivatives.

Attempts, by chemical methods, to determine the structures of the compound prepared were not successful and the structures are therefore assigned using nuclear magnetic resonance measurements. In most cases the structures can be assigned unambiguously using $^{19}F$ chemical shift data but, when known, the observed F-F coupling constants confirm these conclusions.

Measurement of the relative reactivity of tetrafluoropyrazine shows it to be about ten times less reactive than pentafluoropyridine, which is thought to be due to the absence of a nitrogen atom para to the point of substitution.

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## Introduction

## Experimental Work

## General Introduction.

Fluorine is unique amongst the elements in that extensive replacement of hydrogen, in organic compounds, can be achieved without gross distortion of the geometry of the system. The discovery of useful chemical and physical properties of some aliphatic fluorocarbons led to their large scale industrial use, and established fluorine chemistry as an important branch of organic chemistry. First efforts were directed towards the study of aliphatic fluorine compounds, and only in the last decade have polyfluoroaromatic compounds been prepared in quantity.

The marked differences that often exist, due to the entirely different electronic environment for functional groups, between polyfluoro-compounds and their hydrocarbon counterparts, have stimulated wide academic interest in fluorine chemistry, while the new routes to polyfluoroaromatic compounds have added substantially to the possibilities for further study. The successful adaptation of the halogen exchange method to the preparation of polyfluoronitrogen-heterocyclic compounds has added fresh impetus to the study of polyfluoroaromatics, particularly in the field of aromatic nucleophilic substitution. The influence of the nitrogen atom in polyfluoro-heterocyclic systems, in comparison with polyfluorohomocyclic systems, has led to a considerable increase in our knowledge of aromatic nucleophilic substitution.

The present work is concerned with the extension of these studies to the polyfluorodiazine series of aromatic compounds, particularly those in which the two nitrogen atoms are para to one another in the aromatic ring. Some of the points of interest in this work are the effect, on nucleophilic substitution, of substituents attached to the heterocyclic ring and a comparison of the effect, on substitution, of the heterocyclic nitrogen atoms in the 1- and 4-positions with the other alternative configurations, namely the 1,2- and 1,3-diazines.

Many compounds containing the pyrazine (1,4-diazine) nucleus are used extensively in the pharmaceutical industry; it is possible that suitable highly fluorinated pyrazine and quinoxaline derivatives could display physiological or biological activity, although the present study is not concerned with this aspect.

# INTRODUCTION

# CHAPTER 1

## The Preparation of Polyfluoroaromatic Compounds.

The purpose of this chapter is to outline the existing methods of obtaining polyfluoroaromatic compounds; while the homocyclic series are discussed, a greater emphasis has been placed upon the preparation of the nitrogen heterocyclic series as these are more relevant to the present work.

Although polyfluoroaromatic systems are of considerable interest, for the reasons outlined in the general introduction, it is only in the last decade that they have been prepared in quantity, the original methods of fluorination being suitable for only 'lightly' fluorinated compounds. The direct replacement of hydrogen in aromatic compounds by fluorine is extremely exothermic, severe decomposition usually occurring. The need to dissipate the heat of reaction rapidly, led to the use of metal 'catalysts' of high thermal conductivity and large surface area. No unsaturated compounds resulted, but a wide range of polyfluorocyclohexanes have been obtained using this method. The problem of heat dissipation to control the reaction of hydrocarbons with elemental fluorine was overcome by fluorinating indirectly using a high valency transition metal fluoride. The indirect fluorination of hydrocarbons in this way reduces the heat output to about half that of direct fluorination, thus limiting decomposition, but again only saturated fluorocarbons have been isolated. An electrochemical fluorination process involving the electrolysis of a solution of an organic compound in hydrogen fluoride has also been used and has shown itself to be useful for fluorinating the more polar compounds such as ethers and carboxylic acids. It is, however, only of limited use for fluorinating aromatic compounds, although pyridine has been successfully fluorinated using the procedure.

Nuclear halogenation, by substitution, in aromatic compounds in the liquid phase is an electrophilic process; the active halogenation species is the $X^+$ cation, displacing a proton to give halogen substituted aromatic compounds. The energy which would be required to produce a fluorine cation is too large to allow this type of mechanism to be of use, while nuclear substitution by the fluoride anion requires elimination of a hydride anion which is also unfavourable energetically. Displacement of an anion, such as chloride anion, by fluoride ion would, however, be energetically favourable. These observations led to the halogen exchange method of fluorination, using an alkali-metal fluoride to prepare polyfluoroaromatic compounds from perchloroaromatic compounds. The electron deficient nature of the nitrogen heterocyclic series allows them to undergo readily this type of reaction and a wide range of heterocyclic aromatic compounds have now been prepared by this method.

## 1.1. Preparation of Polyfluoroaromatic compounds from Hydrocarbons.

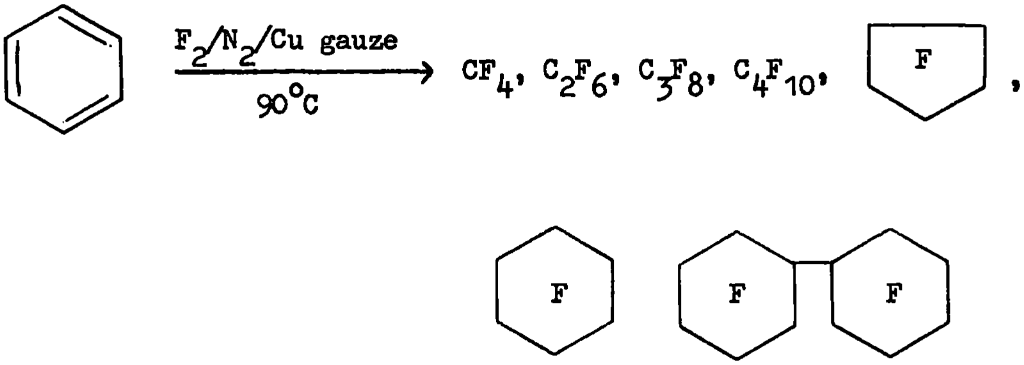
Two distinct stages are involved; initial fluorination to the saturated fluorocarbon, followed by defluorination to the aromatic compound.

### 1.1a. Conversion to Saturated Fluorocarbons (i) Using Elemental Fluorine.

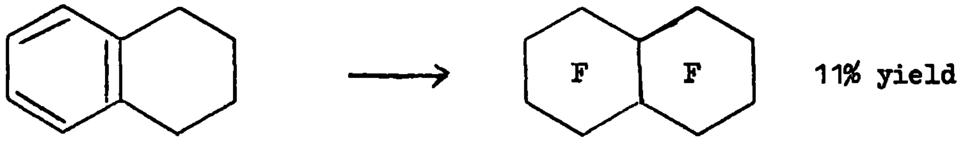
The reaction of fluorine with hydrocarbons is extremely exothermic:

$$-C-H \; + \; F_2 \longrightarrow -C-F \; + \; HF \qquad \Delta H \simeq -104 \text{ Kcal/mole}$$

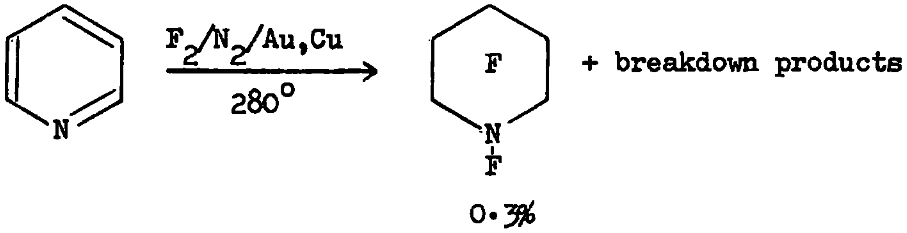
Furthermore, the introduction of fluorine into a molecule causes deactivation to further fluorination.[1] The problem of dissipating the heat of reaction before decomposition occurs led to the development of the so called 'Catalytic Method'.[1,2] Benzene was successfully fluorinated in a reactor packed with copper gauze.[3] The yield of



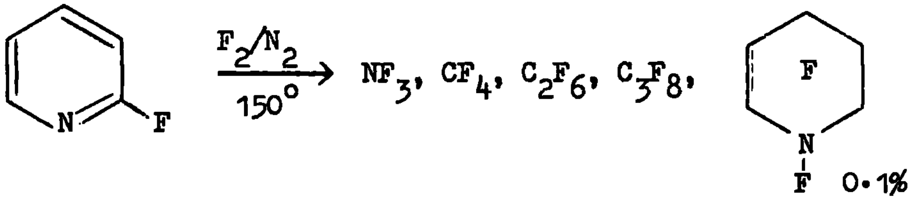
perfluorocyclohexane was low and no unsaturated compounds resulted. Cady[4] obtained a 58% yield of perfluorocyclohexane by using silver plated copper turnings as a catalyst. It was suggested that silver difluoride, formed *in situ*, was the fluorinating agent; the work of Musgrave and Smith[5] indicated, however, that the main function of the 'catalyst' was simply to dissipate the heat of reaction. Haszeldine and Smith[6] fluorinated benzene and several alicyclic hydrocarbons[7] using a gold plated copper catalyst. Haszeldine[8] attempted to extend



the method to nitrogen heterocyclics, by fluorinating pyridine, but extensive breakdown occurred, and undecafluoropiperidine was isolated in only 0·3% yield. The low yield was attributed to the initial



formation of non-volatile hydrofluorides, leading to breakdown, but even fluorination of the relatively non-basic 2-fluoropyridine[9] again gave mainly decomposition products, the yield of undecafluoropiperidine being only 0·1%.

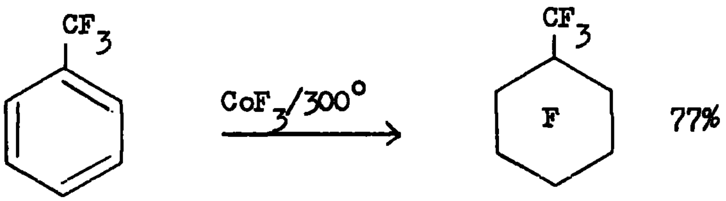


### 1.1a. (ii) Conversion to Saturated Fluorocarbons using a High Valency Metal Fluoride.

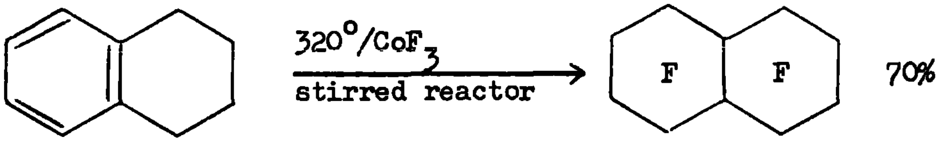
Fowler[10] found that a less vigorous fluorination occurred when a hydrocarbon vapour was passed over certain high valency metal fluorides and this led to the development of the 'High Valency Metal Fluoride Process'.[11] Cobalt trifluoride is the most widely used fluoride, although lead tetrafluoride,[12] manganese trifluoride,[10] and silver difluoride[10] have also been investigated. The fluorination may be expressed:

$$-\text{C}-\text{H} + 2\text{CoF}_3 \longrightarrow -\text{CF} + \text{HF} + 2\text{CoF}_2 \quad \Delta H \simeq -58 \text{ Kcal/mole}$$

This is about half the heat output of the 'Catalytic' Method thus giving less decomposition. Several aromatic compounds were fluorinated in this way.



Higher yields were obtained by workers at Birmingham[13] who kept the cobalt trifluoride agitated.

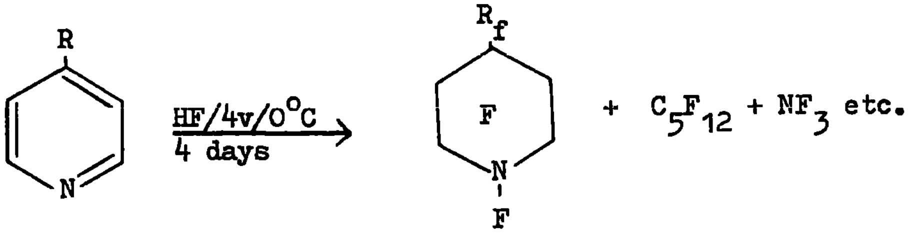


Attempts to fluorinate heterocyclic compounds were again unsuccessful; Haszeldine[8] showed that aromatic amines suffered extensive C-N bond fission while pyridine produced undecafluoropiperidine in only 0·2% yield, which was again attributed to the formation of non-volatile hydrofluorides. Quinoline[14] also suffered C-N bond fission, perfluoro-(decahydroquinoline) being produced in only 2% yield.

The previously described methods have both been used extensively to prepare polyfluorocycloalkanes but the presence of a nitrogen atom in the molecule, with its basic character, precludes their use in preparing heterocyclic compounds.

### 1.1a. iii) Conversion to Saturated Fluorocarbons by Electrochemical Fluorination.[15]

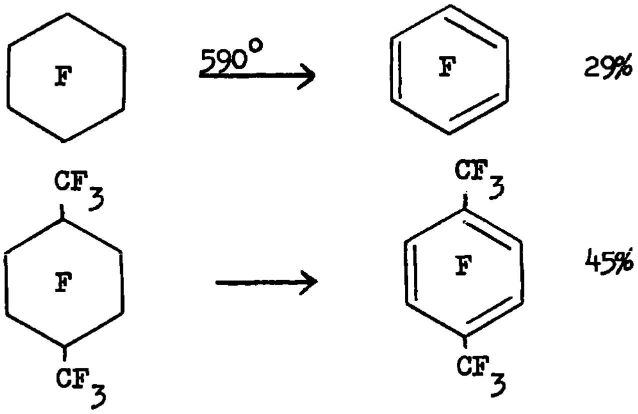
This process originally developed by Simons,[16] involves the electrolysis of a solution of an organic compound in hydrogen fluoride, or a suspension of a compound rendered conducting by the addition of potassium fluoride. The organic compound is fluorinated at the anode but the mechanism is not known. The great advantage of the process is that less replacement of functional groups occurs than with other methods. Simons[17] fluorinated several amines and substituted pyridines by this method.



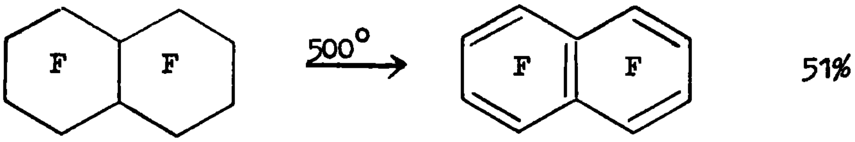
Later workers[18] reported a yield of 11% for the fluorination of pyridine to undecafluoropiperidine, while Haszeldine[19] was able to increase the conversion to 13% by fluorinating 2-fluoropyridine, the α-fluorine atom presumably reducing the extent of C-N bond fission. The method is most suited to more polar compounds such as ethers and carboxylic acids, hydrocarbons such as benzene being too insoluble in the electrolyte. Unfortunately cyclic amines seem to undergo C-N bond fission too readily, seriously reducing the yield of perfluoro derivatives.

### 1.1b. Conversion of Saturated Cyclic Fluorocarbons to Fluoroaromatic Compounds.

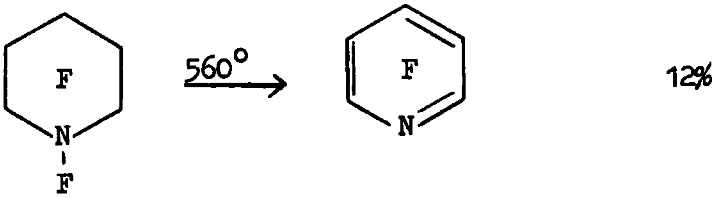
Workers at Birmingham observed that perfluorocyclohexadienes,[20,21] perfluorocyclohexenes,[22,20] and even perfluorocyclohexanes[22] were defluorinated to perfluorobenzenes if their vapours were passed over heated metal surfaces. The best results were obtained when the fluorocarbon vapour was passed at atmospheric pressure over nickel or iron using a contact time of 10-30 min.



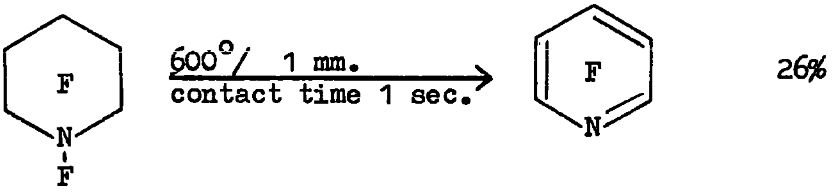
Perfluoropolycyclic compounds underwent similar defluorination.[22,23]



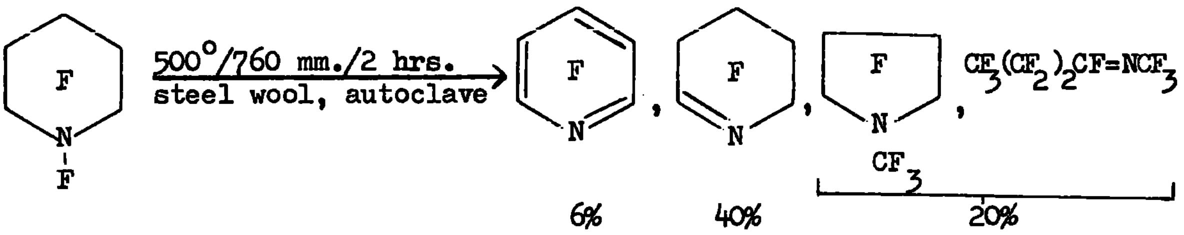
The method was extended to the preparation of pentafluoropyridine.[24]



Using modified conditions, workers in Manchester[25] defluorinated undecafluoropiperidine at reduced pressures with a short contact time to give a higher yield of pentafluoropyridine.



Under these conditions, perfluoro(methylcyclohexane) did not defluorinate, which suggested that the N-F bond makes defluorination easier. Defluorination of undecafluoropiperidine[19] on steel wool at atmospheric pressure produced a mixture of compounds, none of which contained solely carbon-carbon double bonds, perhaps further suggesting that the N-F bond facilitates defluorination.

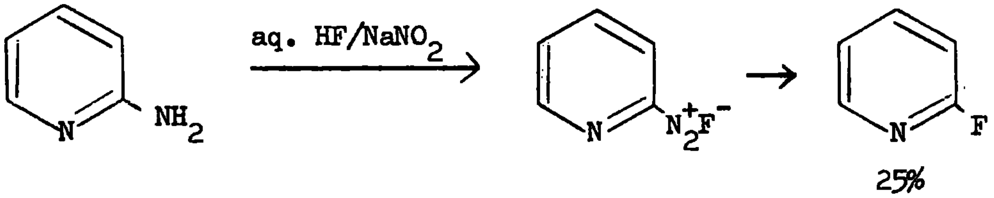


The isomeric perfluoro(methylpyridines)[26] have also been isolated in high yield from the defluorination of the corresponding perfluoro(methylpiperidine).

In general, therefore, the preparation of perfluoroaromatic compounds from 'hydrocarbons' is suitable for the homocyclic but not the heterocyclic series, since saturated perfluoro-heterocyclic compounds, which are the precursors to the heterocyclic series, are difficult to obtain.

## 1.2. Replacement of the $-NH_2$ group.

One of the earliest methods for preparing fluoroaromatic compounds was diazotization of an amine in aqueous hydrofluoric acid, followed by decomposition of the diazonium salt to the corresponding fluoro-compound. Schmitt and Van Gehren[27] synthesised p-fluorobenzoic acid from p-aminobenzoic acid in this way, decomposing the resulting diazonium fluoride *in situ*. Later Tschitschibabin[28] extended this method to the heterocyclic compounds by preparing 2-fluoropyridine.



The large amounts of hydroxy-compounds produced on decomposition of the diazonium salt in aqueous solution, led to the use of anhydrous hydrofluoric acid by Ferm and Van der Werf[29] who prepared many aromatic fluoro-compounds in high yields by diazotization at 0° of the corresponding amine in 100% hydrofluoric acid followed by decomposition of the diazonium fluoride in situ. Beaty and Musgrave[30] prepared 2-fluoroquinoline and 2-fluoropyridine using 100% hydrofluoric acid, but the yields were low (17% and 20% respectively).

An indirect route to fluoroaromatics from aminobenzenes was discovered by Balz and Schiemann[31] when they found that thermal decomposition of dry aromatic diazonium tetrafluoroborates gave the corresponding fluoro-compounds. The diazonium tetrafluoroborate can usually be isolated and dried before being pyrolysed.

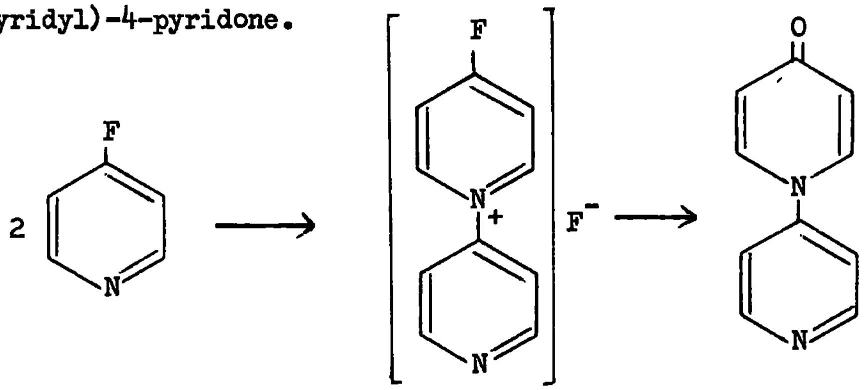
$$ArNH_2 + HNO_2 + BF_4^- \longrightarrow ArN_2BF_4 + H_2O + OH^-$$

$$ArN_2BF_4 \xrightarrow{\Delta} ArF + N_2 + BF_3$$

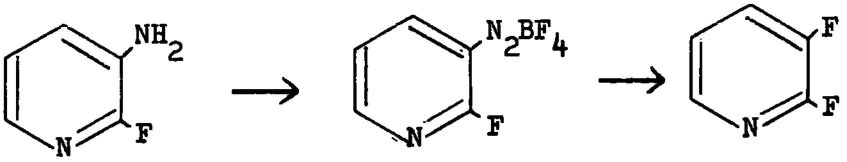
The method has been used to effect the stepwise replacement of four hydrogen atoms in benzene with fluorine giving 1,2,4,5- and 1,2,3,5-tetrafluorobenzene[32,33] by the sequence

$$ArH \longrightarrow ArNO_2 \longrightarrow ArNH_2 \longrightarrow ArN_2BF_4 \longrightarrow ArF$$

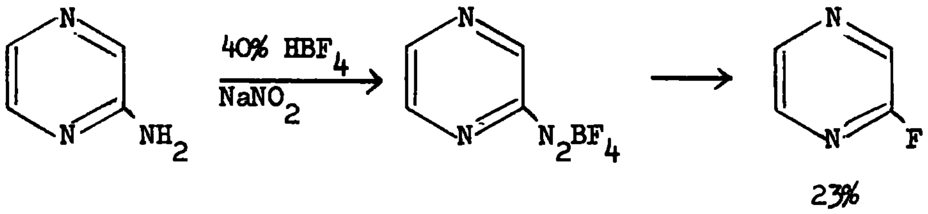
Attempts[32] to introduce more fluorine atoms in this way were not successful, since nitration of 1,2,4,5-tetrafluorobenzene gave only 2,5-difluoro-1,4-benzoquinone. Using this method Roe and Hawkins prepared 2-fluoro and 3-fluoropyridine[34] and several monofluoroquinolines.[35] Pyridine-2-diazonium tetrafluoroborate could not be isolated, but decomposed spontaneously to 2-fluoropyridine. When wet with ether pyridine-3-diazonium tetrafluoroborate could be isolated at 10° but decomposed violently on drying to give 3-fluoropyridine in 50% yield. Suschitzky,[36] however, was able to isolate the dry salt and showed that it is stable at room temperature. 4-Fluoropyridine could not be isolated, possibly due to self quaternization to give N-(4'-pyridyl)-4-fluoropyridinium fluoride, which would readily be hydrolysed to give N-(4'-pyridyl)-4-pyridone.

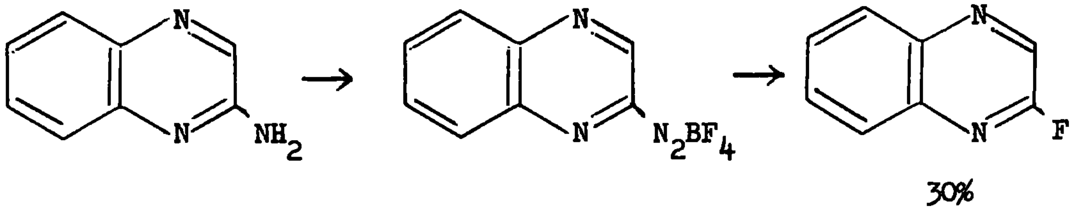


This is analogous to the self quaternization of 4-chloropyridine.[37] 2,3-Difluoro and 2,6-difluoropyridine[38] were later prepared by using a two stage synthesis.



Rutner and Spoerri[39] reported the first synthesis of 2-fluoropyrazine by diazotization of 2-amino pyrazine in 40% tetrafluoroboric acid, the diazonium salt slowly decomposing <u>in situ</u> to give 2-fluoropyrazine. They later prepared 2-fluoroquinoxaline[40] by the same procedure.





The instability of these diazonium tetrafluoroborates parallels that of the corresponding pyridine[34] and quinoline[35] diazonium salts.

Other complex fluoro-acids, besides fluoroboric acid, have been examined. The diazonium salts of hexafluoroantimonic acid are generally less soluble than the corresponding tetrafluoroborates, allowing easier separation and purification. On heating, pyridine-2-diazonium hexafluoroantimonate[41] gives 2-fluoropyridine in 50% yield. The arene diazonium salts of hexafluorophosphoric acid[42] and hexafluoro silicic acid[30,43] have also been investigated.

Overall, the method is most suitable for 'lightly' fluorinated aromatic compounds. The difficulty of nitration, particularly in the case of the heterocyclic compounds, restricts the number of fluorine atoms which can be introduced into the molecule.

## 1.3. From Perchloro-aromatic Compounds.

There are two important methods of converting perchloroaromatic compounds into perfluoroaromatic compounds; the first involves fluorination to the saturated halofluorocarbon followed by dehalogenation to the aromatic fluoro-compound, while the second, and more important, is the halogen exchange method using a metal fluoride to prepare the aromatic fluoro-compound in one step.

### 1.3a. The Fluorination-Dehalogenation Method.

The reaction of chlorocarbons with fluorinating agents is considerably less vigorous than the corresponding reaction of hydrocarbons, due principally to the fact that no hydrogen fluoride is produced. Bigelow[44] was able to prepare, in low yield, addition compounds of hexachlorobenzene by the action of elemental fluorine at 0°.

$$C_6Cl_6 \xrightarrow{F_2/CCl_4/0^{o}C} C_6Cl_6F_4 + C_6Cl_6F_6$$

As well as elemental fluorine,[45] many other fluorinating agents have been used to prepare chlorofluorocyclohexanes, including cobalt trifluoride,[46] antimony pentafluoride,[47] and halogen trifluorides.[46,48] Dehalogenation of the resulting halofluorocyclohexanes was achieved either by passing the vapour over iron gauze[46] at high temperatures, or by refluxing with zinc in ethanol,[47] bromine and chlorine being eliminated preferentially. McBee[47] reported the first synthesis of hexafluorobenzene using this procedure.

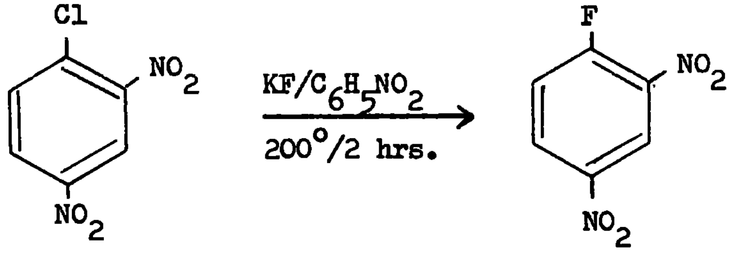
$$C_6Cl_6 + BrF_3 \longrightarrow C_6Br_2Cl_4F_6 \xrightarrow{SbF_5} C_6BrCl_4F_7$$

$$C_6BrCl_4F_7 \xrightarrow{Zn/EtOH} C_6F_6,\ C_6F_5Cl,\ C_6ClF_7,\ C_6Cl_2F_6,\ C_6Cl_3F_5,\ C_6Cl_2F_8,\ C_6Cl_3F_7$$

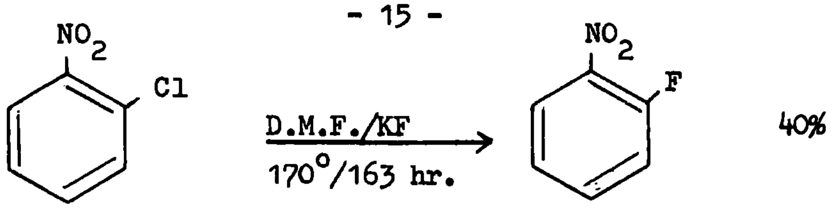
The main disadvantages of the method are the large amount of halogen consumed and the complexity of the products.

### 1.3b. Halogen Exchange using a Metal Fluoride.[49]

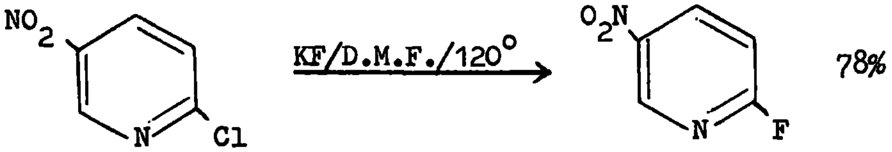
Perchloroaromatic compounds have allowed the use of readily available and cheap fluorinating agents such as potassium fluoride. The use of hydrocarbons with such fluorinating agents as the fluoride ion itself would require the elimination of a hydride ion, or similar species, from the molecule, but use of a chlorocarbon avoids this difficulty, as chloride ion is much more easily expelled. The method involves the reaction of an aromatic halide, usually chloride, with a metal fluoride. The reaction is conducted under anhydrous conditions at high temperatures, either in a solvent or as an intimate mixture. Gottlieb[50] prepared 2,4-dinitrofluorobenzene from 2,4-dinitrochlorobenzene by heating it with anhydrous potassium fluoride in nitrobenzene.

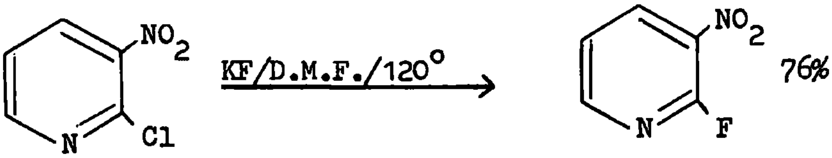


Finger and Kruse[51] investigated the role of the solvent and showed the superiority of dimethylformamide (D.M.F.) over nitrobenzene. This solvent allowed the less reactive mononitro aromatic halides to undergo halogen exchange.[52]

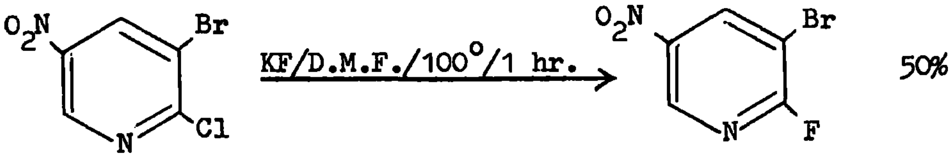


The method was extended to the heterocyclic series when Finger and Starr[53] prepared several fluoro-nitropyridines from the corresponding chloronitropyridines.

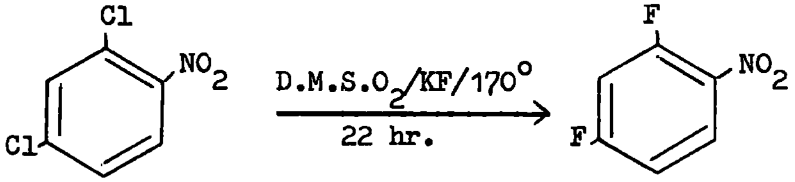




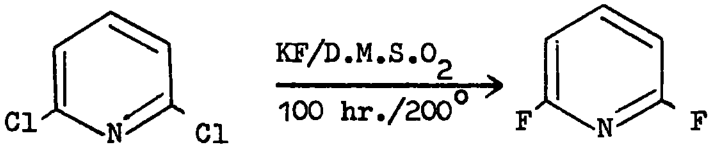
Halogen exchange was shown to occur more readily when a second halogen is placed adjacent to the one undergoing exchange. Thus 3-bromo-2-chloro-5-nitropyridine was converted to the fluoropyridine;



while under the same conditions 2-chloro-5-nitropyridine gave only a 23% conversion after one hour. The authors suggested that activation by a single ring nitrogen atom was insufficient to allow the simple 2-halopyridines to exchange. However, they later showed the greater efficacy of dimethyl sulphone (D.M.S.$O_2$)[54] which allowed higher temperatures to be used than were possible with D.M.S.O. and D.M.F. and did not give the sulphur-containing by-products derived from D.M.S.O.



Use of this solvent allowed the simple α-halogeno pyridines and quinolines to react.[55]



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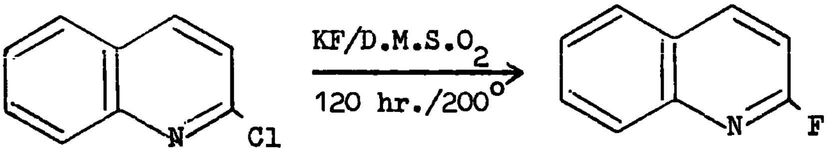
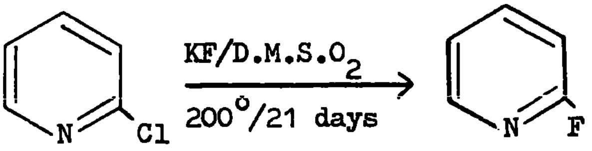


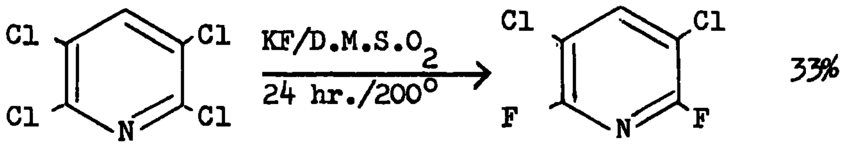
60%

The added activation produced by the second chlorine atom in 2,6-dichloropyridine was at first thought to be necessary for the exchange to occur,[55] but Finger and co-workers[56] were able to isolate 2-fluoropyridine after prolonged heating of 2-chloropyridine with potassium fluoride in D.M.S.$O_2$.

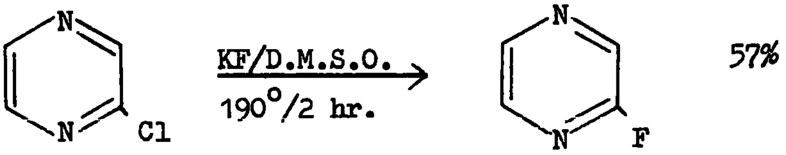


50%

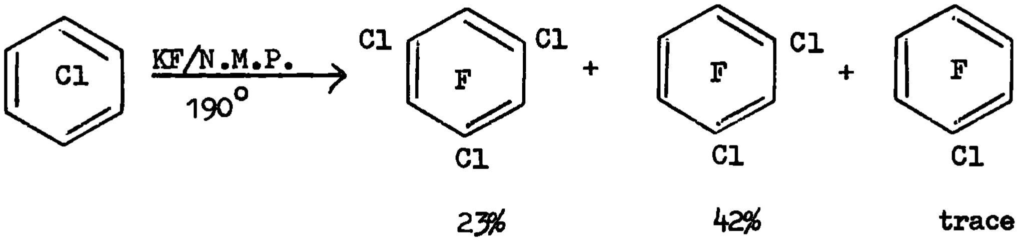
Under the same conditions 2,3,5,6-Tetrachloropyridine gave 3,5-dichloro-2,6-difluoropyridine after only 24 hrs.



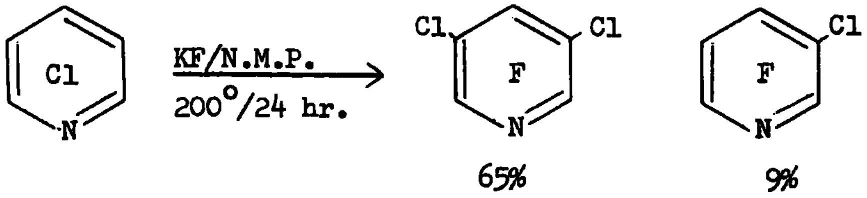
Similar results were obtained using tetramethylene sulphone (sulpholan). The easy conversion of 2-chloropyrazine to 2-fluoropyrazine illustrates the increased activation caused by a second ring nitrogen; fluoropyrazine was isolated in 57% yield on heating chloropyrazine with potassium fluoride in D.M.S.O. at 190° for only 2 hrs.[40]



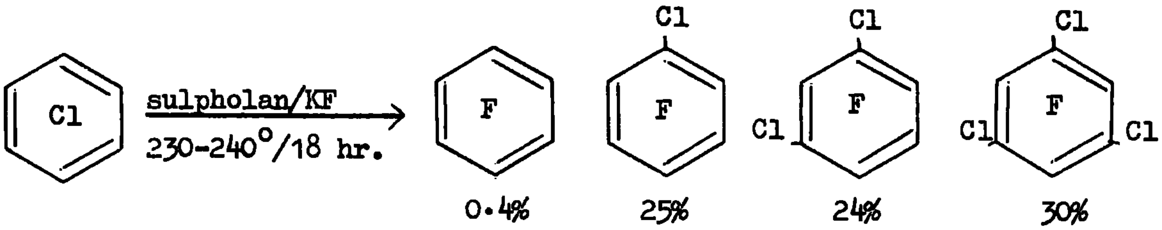
N-Methyl-2-pyrrolidone (N.M.P.) was found to be effective as a halogen exchange solvent by Maynard[57] who obtained a mixture of chlorofluorobenzenes from hexachlorobenzene.



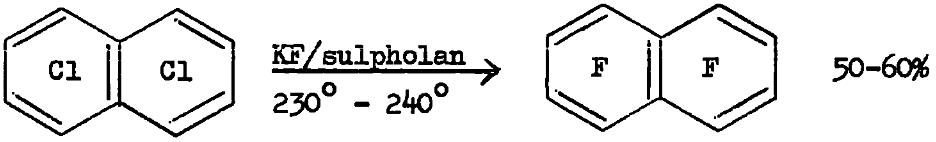
This solvent was later used by Haszeldine[58] who prepared chlorofluoropyridines from pentachloropyridine by the action of potassium fluoride at 200°.



Fuller[59] used sulpholan to prepare chlorofluorobenzenes from hexachlorobenzene and potassium fluoride.



The same solvent was used to prepare octafluoronaphthalene from octachloronaphthalene.



3.b(i). <u>The Role of the Solvent in Halogen Exchange Reactions:</u> The effectiveness of these dipolar aprotic solvents in halogen exchange reactions has been studied by Parker.[60,61] Dipolar aprotic solvents are defined[61] as those which have dielectric constants greater than 15, and which, although they may contain hydrogen, cannot form strong hydrogen bonds with appropriate species. Some solvents in this category are nitrobenzene, acetone, dimethyl formamide (D.M.F.), dimethyl acetamide (D.M.A.C.), N-methyl-2-pyrrolidone (N.M.P.), dimethyl sulphoxide (D.M.S.O.), tetramethylene sulphone (sulpholan), and dimethyl sulphone (D.M.S.$O_2$).

In this type of solvent, anions are poorly solvated, much less so than cations.[60] Anion solvation increases with size so that solvation decreases down the series:

$$\text{picrate}^- > I^- > SCN^- > Br^- > N_3^- > Cl^- \gg F^-$$

The lower degrees of solvation appear to be due to steric resistance by bulky dipoles, the positive ends of which cannot fit closely around a small anion. Stabilization of a solvate by mutual polarization of anion and solvent molecule would also be more important for large anions.

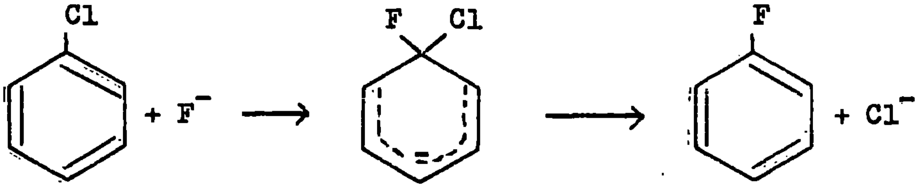
Alternatively when solvation is by protic solvents (e.g. water or methanol), small anions are strongly solvated by protons. The contribution due to hydrogen bonding in these solvents is higher for small anions. Solvation in protic solvents decreases down the series.

$$F^- \gg Cl^- > Br^- > N_3^- > I^- > SCN^- > \text{picrate}^-$$

That picric acid is a stronger acid than hydrogen bromide in D.M.F. and weaker than hydrogen bromide in water is in agreement with the relative order of solvation of the anion in the two solvents.[60] The ability of potassium fluoride in D.M.F. or D.M.S.O. to cause dehydrochlorination of highly chlorinated aliphatic compounds,[57] as well as its tendency to act as a nucleophile, is a consequence of the low solvation of the small anion in these solvents giving rise to high base strength.

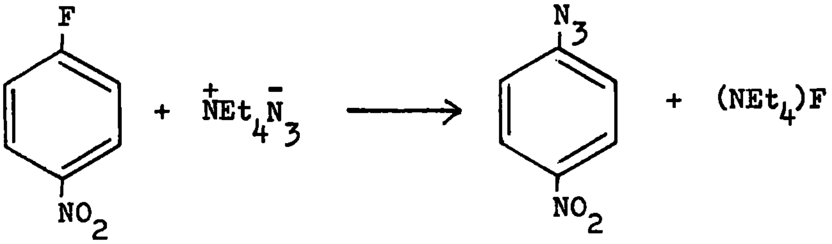
In contrast to the low solvation of anions, cations are strongly solvated by dipolar aprotic solvents, as these solvents have a region of high electron density, usually located on an exposed oxygen atom, which allows strong interaction with the cation. Although nitrobenzene has a high dielectric constant, cations are poorly solvated because the negative portion of the dipole is dispersed over two oxygen atoms, showing that the type of dipole is also important. It is mainly this cation solvation which renders electrolytes soluble in dipolar aprotic solvents.[62]

The conversion of chloro-aromatic to fluoro-aromatic compounds with alkali metal fluorides seems most likely to proceed with fluoride ion acting as a nucleophile through a bimolecular aromatic nucleophilic substitution mechanism, $S_NAr_2$.[63] This is thought to occur via a definite intermediate, (I), the formation of which is the rate determining step.



(I)

The intermediate (I) is taken as a good approximation to the transition state and compared with the attacking nucleophile is large with a well dispersed negative charge. As previously stated most anions, in this case a nucleophile, are much less solvated in dipolar aprotic than in protic solvents, but polarizable charged transition states tend to be similarly solvated in both types of solvent.[64] The result is that these halogen exchange reactions are much faster in dipolar aprotic than in protic solvents.[65] Miller and Parker[66] observed a marked increase in rate for the reaction of azide ion with 4-fluoronitrobenzene on changing from a protic to a dipolar aprotic solvent.



The capacity of the amide solvents to form hydrogen bonds diminishes as successive hydrogen atoms are replaced by methyl groups accounting for the increasing rate of reaction.

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

This concept of anion solvation fits in well with the earlier observations of Finger,[51] who showed that hydroxylic solvents, such as glycols, are unsuitable, and that moisture must be excluded. However, Parker[66] has shown that a dipolar aprotic solvent will compete with the anion for the protic impurity, so that traces of these impurities do not cause a drastic reduction in rate. Finger[51] had suggested that the low yields obtained in the conversion of nitrochlorobenzenes to the nitrofluorobenzenes were due to chemical reaction of the impurity with the substrate, resulting in formation of nitrophenols.

Recently[67] it has been shown from measurement of enthalpy of solvation, for a series of alkali halides (e.g. LiCl, LiBr, LiI) that the degree of solvation is in the same sequence in both water and D.M.S.O. The important factor is that the loss of solvation on changing the solvent from water to D.M.S.O. is greater for chloride and least for iodide ion, and the suggestion is that differences of solvation in a series of halide ions are much less in D.M.S.O. than in water. Thus the solvated chloride ion is still a better nucleophile than the less solvated iodide ion in D.M.S.O., while in water the extremely strong chloride hydration diminishes the reactivity of the ion to less than that of the weakly solvated iodide ion. Although alkali fluorides were not investigated the same argument probably applies.

The relative efficiency of the various dipolar aprotic solvents in halogen exchange reactions seems not to be solely dependent on their relative cation solvation capacities, as the maximum working temperature of some of them limits their effectiveness. The higher reflux temperatures possible with sulpholan makes this perhaps the best solvent, while its thermal-stability is also good compared to D.M.S.O. for example, which at high temperatures, gives sulphur containing by-products.

3.b(ii). Role of the Cation on Halogen Exchange Reactions: The nature of the cation also affects the relative efficiency of various metal fluorides, and Finger and Kruse[51] showed that in the reaction of 2,4-dinitrochlorobenzene and alkali metal fluorides in D.M.F., lithium and sodium fluorides gave no appreciable reaction, while potassium, rubidium and caesium fluorides were effective under the same conditions. Russian workers[68] gave the order of reactivity of the alkali metal fluorides for the same reaction in D.M.F., and in the absence of a solvent as

$$\mathrm{LiF} \sim \mathrm{NaF} < \mathrm{KF} < \mathrm{RbF} < \mathrm{CsF}$$

The alkaline earth metal fluorides were found to be ineffective. This order is the inverse of their relative crystal lattice energies.

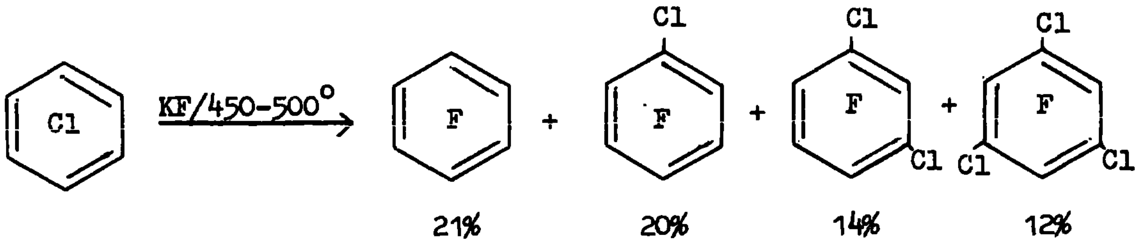
| Compound | Lattice Energy (kcal./g. formula wt.)* |
|---|---|
| LiF | 240 |
| NaF | 213·4 |
| KF | 189·7 |
| RbF | 181·6 |
| CsF | 173·7 |

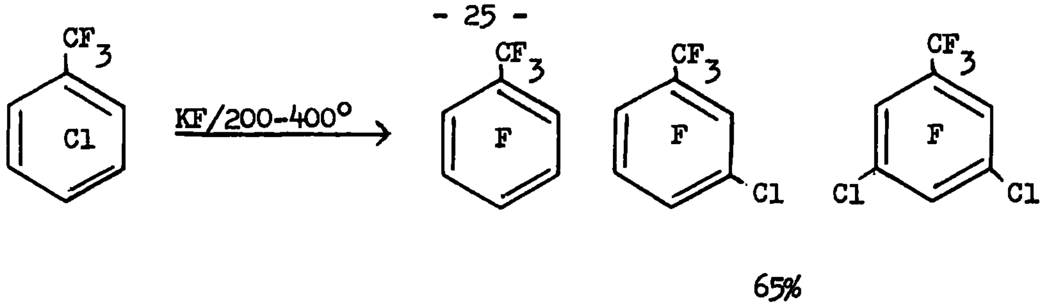
*Taken from Handbook of Chemistry and Physics, 46th Edn., F.129, The Chemical Rubber Company.

In the fluorination of chloro-compounds, either fluoride ion or a metal-fluoride ion pair may be the reacting species. In either case, the solubility of the metal fluoride will increase as cation size increases (from Li to Cs), while the larger cations will give rise to a higher degree of dissociation resulting in a higher concentration of free fluoride ion. Alternatively, if an ion pair is the reactive species, rates will depend on the degree of its polarization which also increases with increasing cation size. In practice, although caesium fluoride is the most reactive fluoride, potassium fluoride is most widely used because of its cheapness and ease of handling.

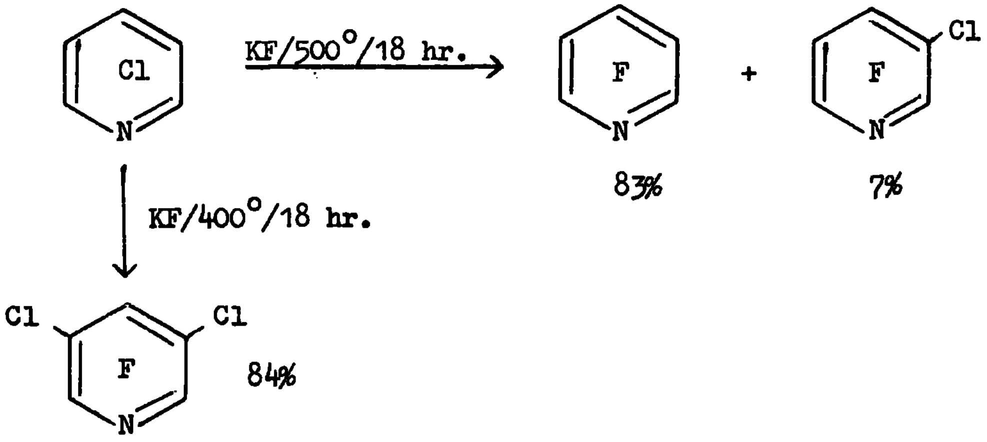
3.b(iii). Reactions in the Absence of a Solvent.

Even with such high boiling solvents as sulpholan, the temperatures attainable are frequently too low for complete fluorination of perchloroaromatic compounds in high yield. As stated earlier, Russian[68] workers fluorinated 2,4-dinitrochlorobenzene using potassium fluoride in the absence of a solvent, and later, other workers[69,70] obtained hexafluorobenzene in high yield by heating a mixture of hexachlorobenzene and potassium fluoride at 450-500° in the absence of a solvent. A similar reaction produced octafluorotoluene and chlorofluorotoluenes from pentachlorobenzotrifluoride.[71]

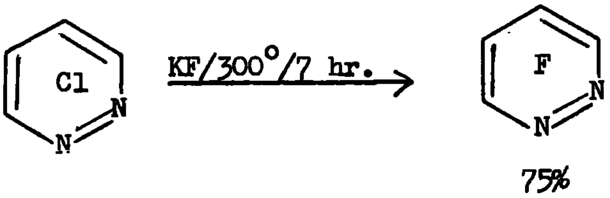


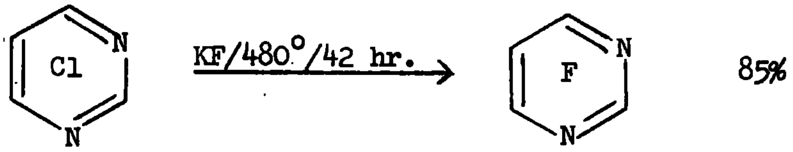


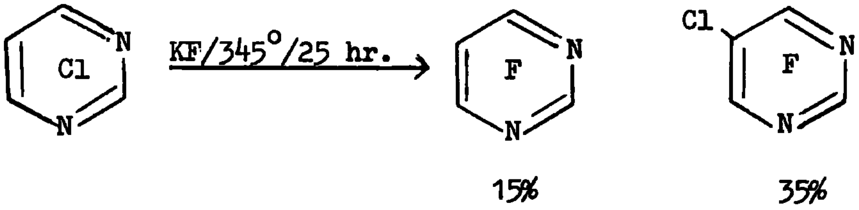
Workers at Durham[72] and later at Manchester[58] were able to prepare pentafluoropyridine from pentachloropyridine using potassium fluoride in the absence of a solvent.

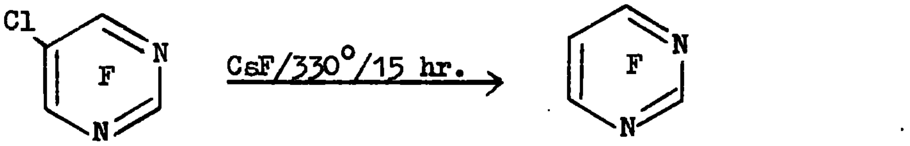


The method was later extended to the fluorination of the more reactive tetrachloropyridazine[73] and pyrimidine,[74,75] caesium fluoride was found to be effective for replacement of the less reactive 5-chlorine in the latter compound.

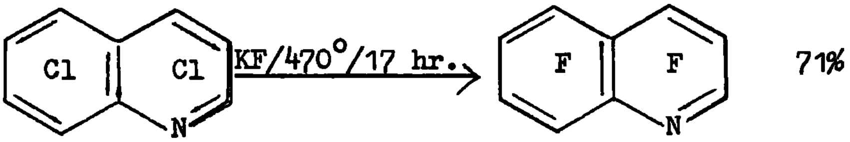


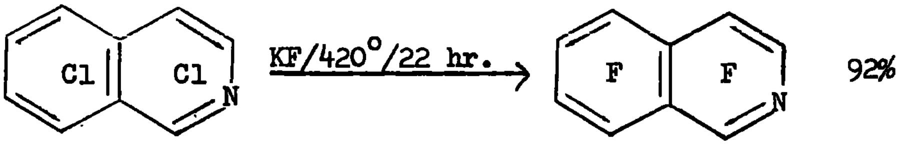




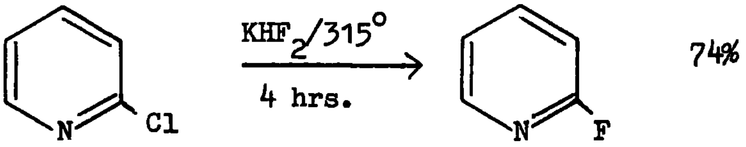


Application to the fused ring heterocyclic series has also been investigated in Durham, resulting in the preparation of heptafluoroquinoline and isoquinoline[76] in high yield from the corresponding perchloro-compounds.

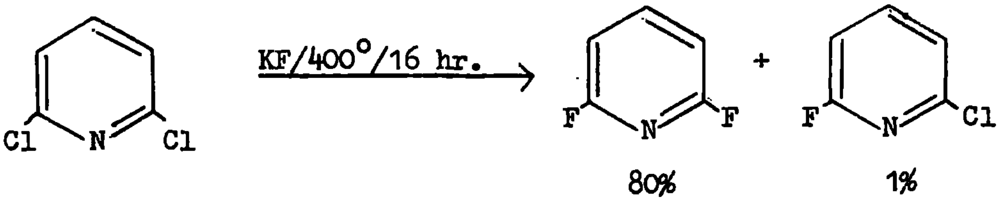




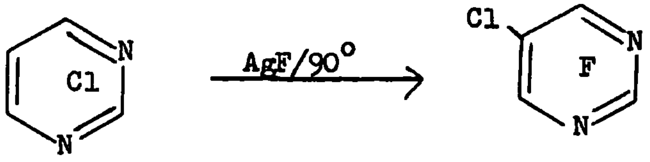
Attempts to prepare partially fluorinated heterocyclic compounds by heating mixtures of potassium fluoride and tetrachloropyridines, in the absence of a solvent, led to extensive decomposition at the temperatures required for complete exchange, which was attributed to the presence of hydrogen in the molecule.[72] Recently, however, Boudakian[77] was able to obtain 2-fluoropyridine in high yield by heating 2-chloropyridine with potassium bifluoride.



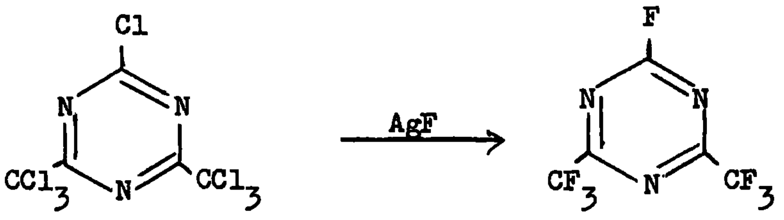
Use of potassium fluoride with 2-chloropyridine resulted in decomposition, but 2,6-dichloropyridine[78] exchanged readily with this reagent in the absence of a solvent to give the corresponding difluoropyridine.



Numerous other metal fluorides have been used to effect halogen exchange, most of them, however, have been of greatest use in preparing aliphatic fluorocarbons, but some have been used successfully to exchange the "active" chlorine atoms of chloropyrimidines and triazines. Silver fluoride has been used extensively on a laboratory scale to replace active halogens.



Ref. 79



Ref. 80

Since metal fluorides, notably potassium fluoride, are readily available sources of fluorine, and a wide range of perchloro-aromatic compounds are becoming increasingly available, this method of producing polyfluoroaromatic compounds is probably the most versatile. In particular its application to the polyfluoroheterocyclic field, has contributed significantly to chemical knowledge.

# CHAPTER 2

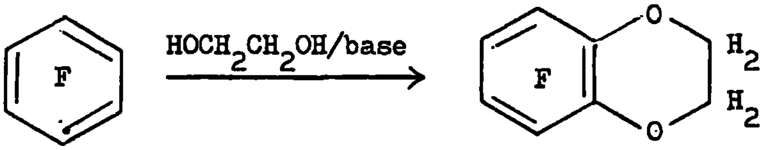
## Nucleophilic Substitution in Polyfluoroaromatic and Heterocyclic Compounds.

The most characteristic reaction of polyfluoroaromatic compounds involves displacement of fluoride ion by a nucleophile, which is analogous to the displacement of a proton by an electrophile in aromatic hydrocarbon chemistry. These reactions of polyfluorohomocyclic compounds have been studied principally at the University of Birmingham. More recently, the investigation of the reactions of polyfluoronitrogen-heterocyclic compounds has been made possible by the development of convenient synthetic routes. The polyfluoroheterocyclic compounds have been studied principally in these laboratories and in the University of Manchester.

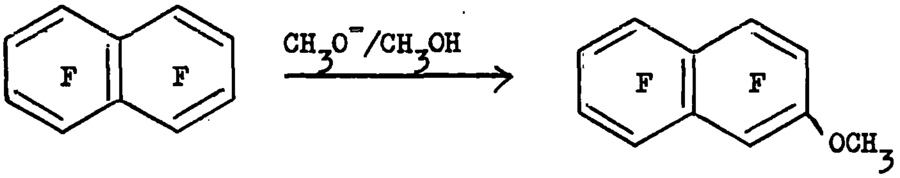
### 2.1. Nucleophilic Substitution in Polyfluoroaromatic Compounds.

Hexafluorobenzene has been reacted with a great variety of nucleophilic species such as $^{-}OCH_3$,[81] $^{-}OH$,[81,82] $NH_3$,[83] $NH_2CH_3$,[83] $NH_2NH_2$,[83] $^{-}SH$,[84] $^{-}CH_3$,[85] and $^{-}C_6H_5$[86] resulting in replacement of a single fluorine atom under fairly moderate conditions to give the corresponding pentafluorophenyl compound in good yield.

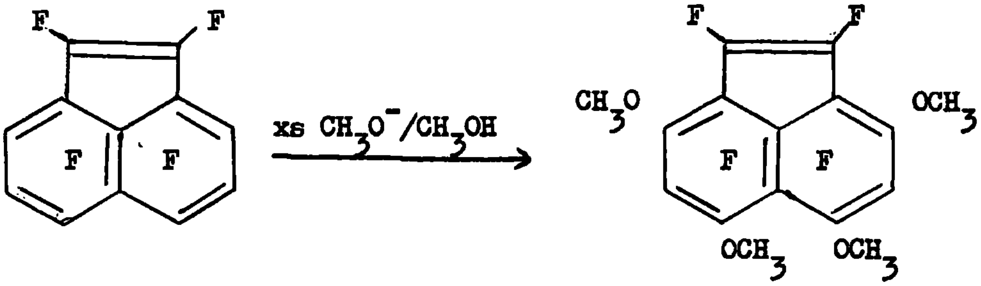
The further reaction of a series of pentafluorophenyl compounds ($C_6F_5X$) with nucleophiles is of great interest and has received considerable attention because of the different positional isomers formed. Substitution para to the first substituent occurs in most cases.[87] For example, when X = H, $CH_3$, $CF_3$, $SCH_3$, $SO_2CH_3$, $N(CH_3)_2$ the proportion of para substitution is greater than 90%. However when X = $^-O$[88] and $-NH_2$,[89] meta replacement predominates and when X = $OCH_3$[88] and $NHCH_3$,[89] comparable amounts of meta and para replacement occurred. In all the cases cited, the effect of the nucleophile on determining the position of substitution is small. However in a few cases (X = $NO_2$,[90] NO,[91] and $^-O_2C$[92]), when the nucleophilic reagent is $NaOCH_3$ in methanol, substitution para to X occurred but, particularly with certain amines, high ortho replacement ( 50%) was observed. This was rationalized in terms of specific hydrogen bonding between nucleophile and substituent. The effect of solvent on orientation of substitution has also been noted,[93,94] thus in 3·8% methanol in ether $NaOCH_3$ gives over 50% ortho replacement on reaction with pentafluoronitrobenzene. Ortho disubstitution of hexafluorobenzene has also been achieved using difunctional nucleophiles.[95]



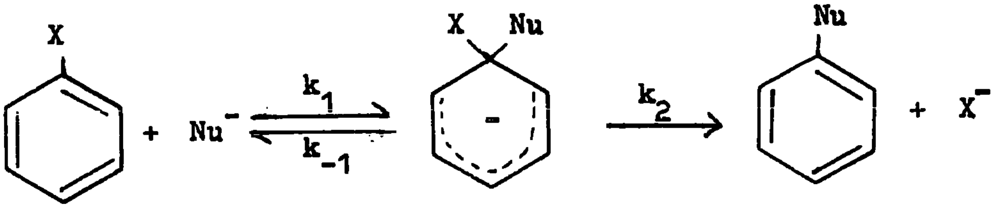
Perfluoropolycyclic aromatic compounds have also been studied; octafluoronaphthalene[96] reacts with nucleophiles to give high yields of 2-substituted heptafluoronaphthalene derivatives.



Octafluoroacenaphthalene[97] is also readily substituted, stepwise replacement occurring at the 3,8,5, and 6 positions.



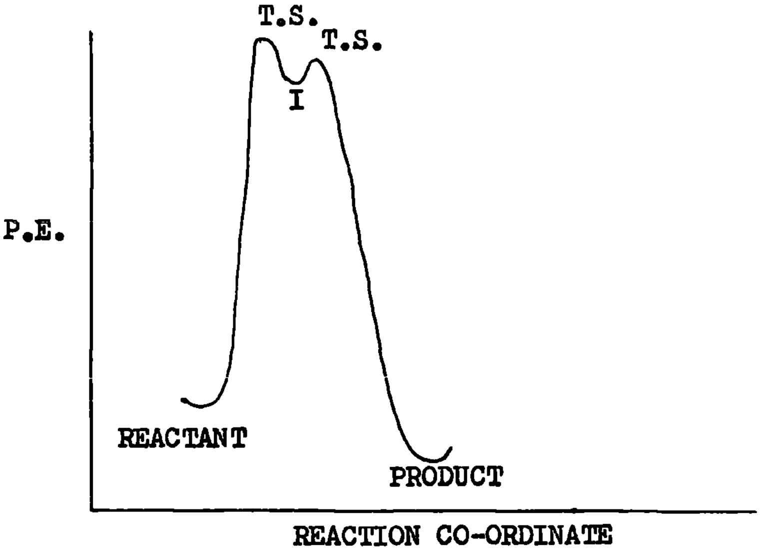
Burdon[98] has put forward a most successful rationalization of orientation of substitution and reactivity in polyfluoroaromatic compounds. Nucleophilic substitution is thought to occur by a bimolecular two stage process. The rate determining step is the formation of a definite charged intermediate by the addition of the nucleophile to the substrate.



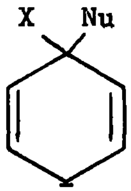
I

$k_2 \gg k_{-1}$

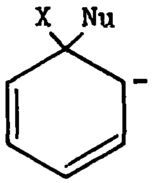
The potential energy diagram would appear thus:



The intermediate I will be similar to the transition state leading to it, and therefore any estimation of the relative energies of intermediates similar to I will provide information about the relative energies of their transition states. In the intermediate, the charge is thought to be mainly located on the atom para to the point of substitution. This can be represented by Wheland-type intermediates in which a canonical of type II would provide a greater contribution than type III to the true structure.



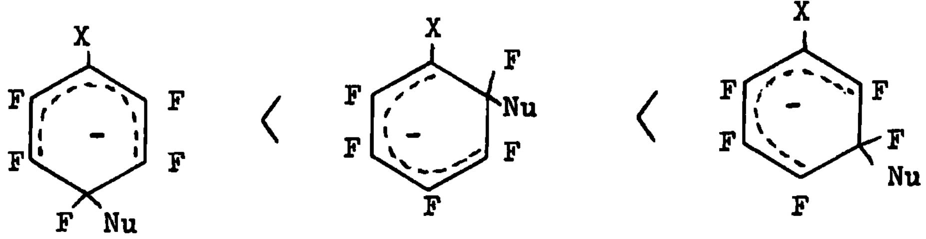
II



III

This assumption seems to be given considerable support from the result of advanced molecular orbital calculations.

In a series of pentafluorophenyl compounds the problem becomes one of determining the relative energies of the intermediates of type II, with a small contribution from the type III canonical, for substitution at the various different positions round the ring. If a substituent X is able to stabilize (by lowering the potential energy) a carbanion, to which it is attached, more effectively than fluorine, then substitution will occur mainly para to X with a small proportion ortho to X. The energies of the intermediates, and therefore the transition states, would be in the order:

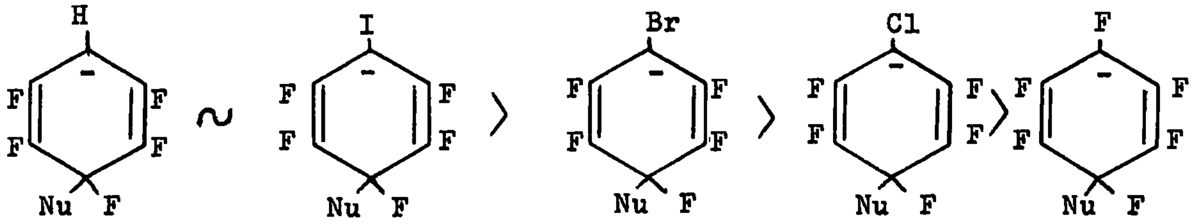


If the substituent X stabilizes the carbanion less effectively than fluorine, then substitution will occur meta to X; and if to the same degree as fluorine, then the substitution will be in the statistical ratio ortho:meta:para, 2:2:1.

The halogens were assumed to destabilize a negative charge on a carbon atom to which they are attached, in the order:

$$F > Cl > Br > I \sim H$$

This order was attributed to the Iπ effect.[98] Hence the order of stability of the intermediates is:

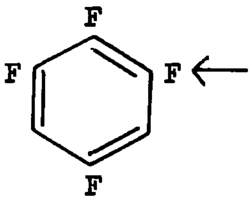


This series would account for the increasing proportion of ortho replacement in the series of halopentafluorophenyl compounds.

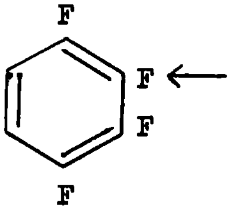
| Cpd. | $C_6F_5H$ | $C_6F_5I$ | $C_6F_5Br$ | $C_6F_5Cl$ | $C_6F_5F$ |
|---|---|---|---|---|---|
| % ortho | 3% | 5% | 12% | 17% | (40%) |

i.e. the proportion of the ortho isomer approaches the statistical one.[100]

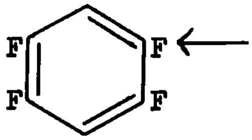
The orientation of substitution of the three isomeric tetrafluorobenzenes[100] reinforces the importance of the Iπ effect in aromatic compounds. The position of substitution in each case is indicated by an arrow.



IV



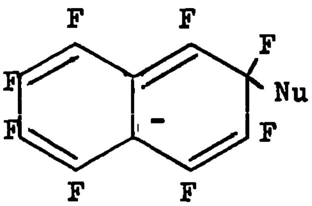
V



VI

In the case of IV and V, the positions attacked are those which lead to intermediates in which the negative charge is mainly localized on a hydrogen-bearing carbon. However, in the case of VI, no alternative orientation is possible, but the compound reacts $10^3$ times slower than the other isomers as the intermediate requires localization of the negative charge on a carbon atom attached to fluorine.

The position of attack on octafluoronaphthalene has been rationalized in terms of the Iπ destabilizing effect of fluorine, substitution occuring at the position where localization of the negative charge on a ring junction carbon via a type II canonical is possible.



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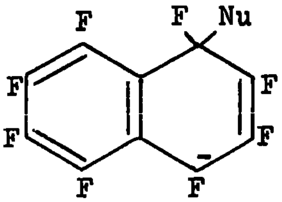
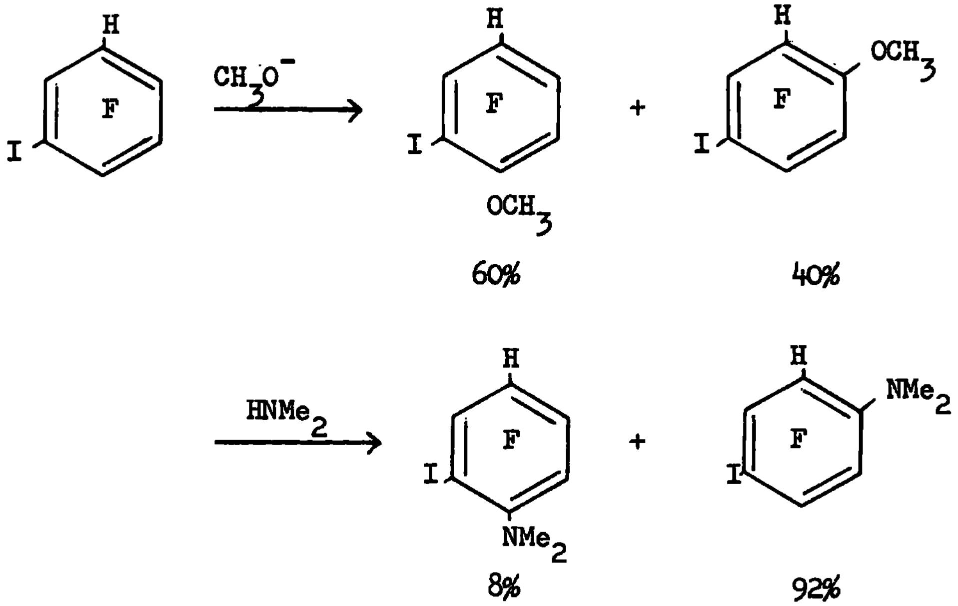


This simple approach has been modified in some cases to account for possible steric factors:



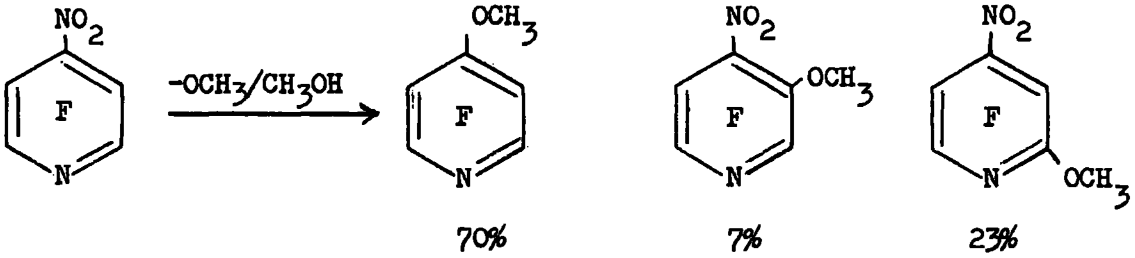
This, at first sight surprising, result has been rationalized[102] in terms of steric interaction between the dimethylamino group and the bulky iodine atom. On the basis of Iπ repulsions, (N > O > F), when X = $N(CH_3)_2$,[89] $NHCH_3$,[89] and $OCH_3$,[88] meta substitution would be expected to occur, but there is evidence to suggest that the p-orbitals on X are somewhat twisted out of alignment with the aromatic π orbitals by steric interaction between X and the ortho fluorine atoms, thus reducing the effective Iπ repulsion[98] which accounts for the observed para replacement.

## 2.2. Nucleophilic Substitution in Polyfluoroheterocyclic Compounds.

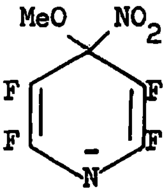
Until recently the non-availability of polyfluoroheterocyclic compounds had precluded their use in investigating nucleophilic substitution in polyfluoroaromatics. However, the development in 1964 of the halogen exchange method to prepare pentafluoropyridine made the extension of investigations to the nitrogen heterocyclic compounds possible. Many perfluoronitrogen-heterocyclic compounds have now been recorded and their reactions with nucleophiles investigated.

Pentafluoropyridine, the first perfluoroheterocyclic compound to be made, reacts with nucleophiles to give 4-substituted tetrafluoropyridines[103,104] under conditions which are much milder than those required for the corresponding reaction of hexafluorobenzene.

Further nucleophilic substitution of the 4-substituted tetrafluoropyridines has been investigated; for example when the substituent X is $-OCH_3$[103] or -Br[105], replacement of the 2-fluorine occurs. However, when 4-nitrotetrafluoropyridine was treated with methoxide ion, a mixture of products consisting mainly of 4-methoxytetrafluoropyridine resulted.[106]



This result shows that the ring nitrogen is the major factor controlling orientation in these reactions, with the Iπ effect of secondary importance. The position of substitution is dominated by the large stabilizing influence of the ring nitrogen atom rather than by the absence of fluorine para to the point of substitution. On the basis of Iπ effect alone, 2,3,5,6-tetrafluoronitrobenzene should be similar to 4-nitrotetrafluoropyridine,[106] but while the latter undergoes substitution mainly with loss of a nitro-group, the former substitutes ortho to the nitro-group with loss of fluoride ion.



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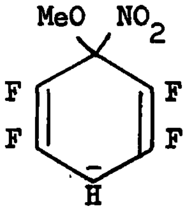
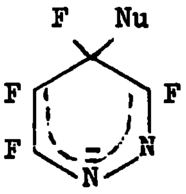


The increased reactivity of pentafluoropyridine over pentafluorobenzene, which is not much more reactive than hexafluorobenzene, again exemplifies the fact that a ring nitrogen is much more stabilizing than the mere absence of a fluorine atom would be.

The perfluorodiazines, tetrafluoropyrimidine[75] and tetrafluoropyridazine[107] readily undergo substitution reactions with nucleophiles. Again, the position of substitution is para to a nitrogen atom, but added stability is conferred on the transition state by the presence of a second nitrogen atom, leading to greater reactivity than pentafluoropyridine. The very high reactivity of the 4-position



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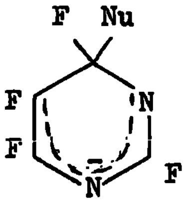

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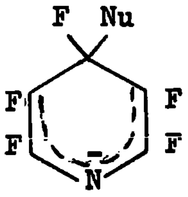
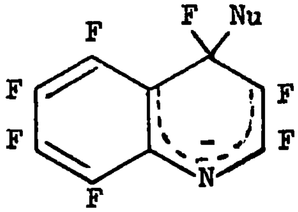


compared to the 2-position in tetrafluoropyrimidine illustrates the much greater importance of localization of the negative charge onto a nitrogen atom para rather than ortho to the position of substitution.

Heptafluoroquinoline[108] reacts readily with nucleophiles; methoxide ion in methanol gives a mixture of 2-methoxy- and 4-methoxyhexafluoroquinoline in the ratio 3•4:1. The orientation of substitution has been rationalized in terms of localization of the negative charge onto the ring nitrogen but annelation of a benzene ring onto the pyridine system distorts the relative energies of the transition states for substitution at the 2- and 4-positions. A possible factor is that the presence of the ring nitrogen atom may distort somewhat the relative importance of the canonicals of type II and III.



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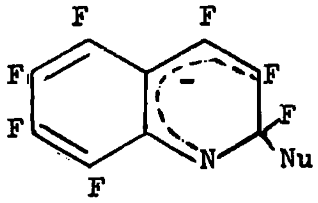
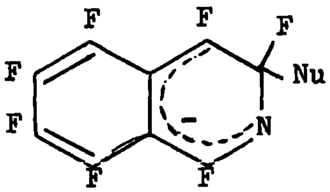


On the basis of substitution in octafluoronaphthalene and heptafluoroquinoline, heptafluoroisoquinoline[108] would be expected to substitute at the 3-position. However, substitution has been observed



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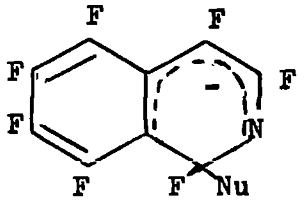
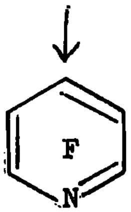
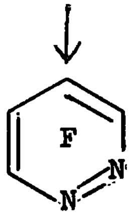
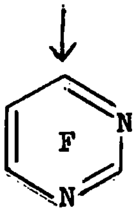
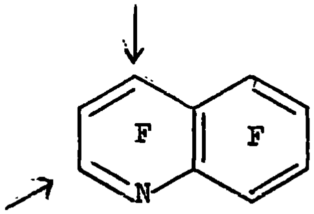


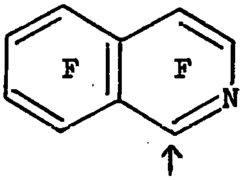
to occur preferentially at the 1-position in apparent violation of the Iπ effect. This has been rationalized as possibly indicating that the negative charge in the intermediate resides primarily on the nitrogen atom, as this distorts the aromaticity of the homocyclic ring least of all. It has been pointed out[107] that in all the cases studied so far the positions of nucleophilic substitution in perfluoro-heterocyclic compounds also corresponds to the positions where single halogen atoms are most susceptible to nucleophilic displacement from derivatives of the corresponding hydrocarbons. This shows that the orientation of substitution in perfluoro-heterocycles is governed primarily by the ring nitrogen(s) rather than the fluorine atoms. The position of substitution for some perfluoro-heterocycles is indicated below.





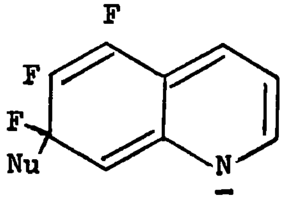




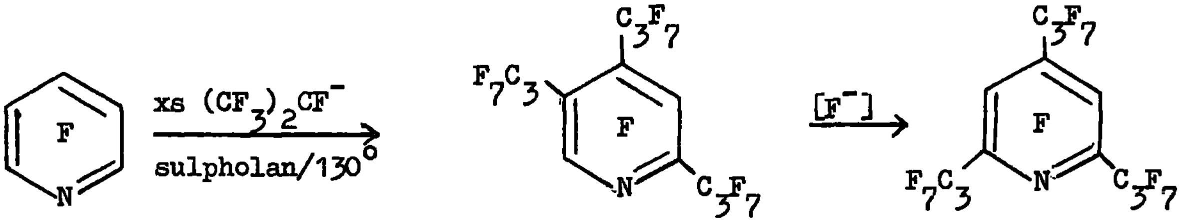


The only other highly fluorinated nitrogen heterocyclic system which has been studied is 5,6,7,8-tetrafluoroquinoline.[109] The pattern of nucleophilic substitution is rather similar to 1,2-disubstituted tetrafluorobenzene derivatives. The observed substitution at the

7 position has been rationalized as this being the only position where it is possible to effectively delocalize the negative charge in the intermediate onto the nitrogen atom.



An interesting example of nucleophilic substitution, in which the powerful directive influence of the hetero nitrogen atom is overruled by substituent directive effects, has been shown recently. Substitution of pentafluoropyridine by perfluoroisopropyl anions,[110] produced by the addition of fluoride ion to hexafluoroisopropene, has been shown to follow the usual sequence of 4-substitution followed by the 2-substitution but then the powerful combined ortho-para directive influence of the two perfluoroisopropyl groups causes the third nucleophile to enter the ring at the 5-position.



Under the influence of fluoride ion the 2,4,5-trisubstituted fluoropyridine rearranges to the thermodynamically more stable perfluoro-(2,4,6-trisisopropylpyridine).

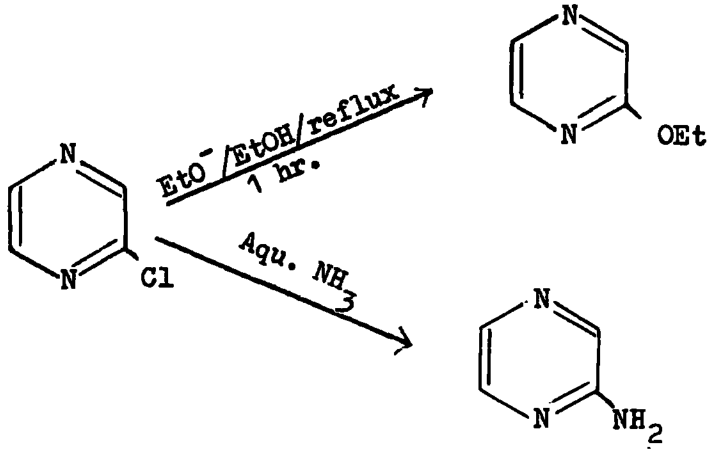
# CHAPTER III

## Nucleophilic Substitution in Pyrazine and Quinoxaline Derivatives.

It is relevant at this stage to discuss briefly some of the salient features of the chemistry of pyrazines and quinoxalines, with particular reference to nucleophilic substitution, and their relation to other nitrogen heteroaromatic compounds.

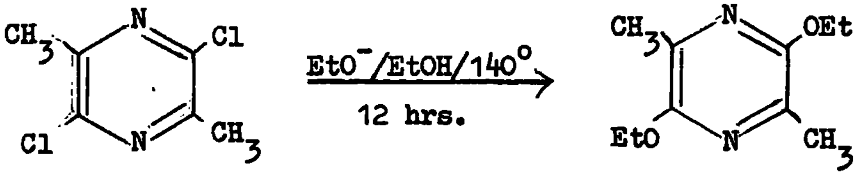
### 3.1. Nucleophilic Substitution of Pyrazine Derivatives.

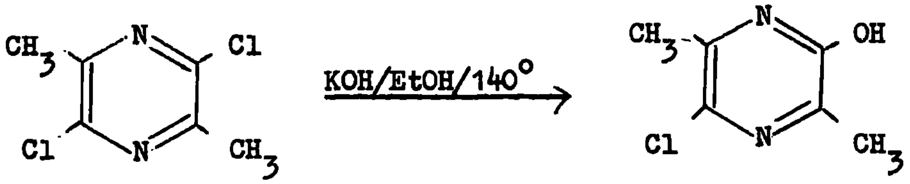
Relatively little work has been reported on the chemistry of the 1,4-diazines compared to the other aza- and diaza-aromatic compounds. However, the best documented reactions are probably those of nucleophilic replacement of halogen and other good leaving groups by nucleophiles. Erickson and Spoerri[112] prepared chloropyrazine and reacted it with several nucleophilic reagents.



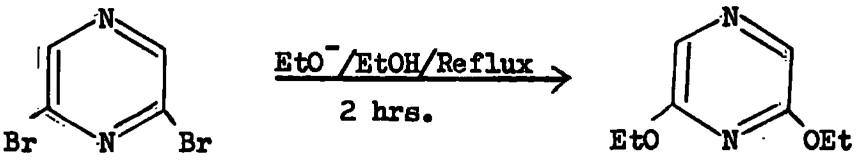
The increased reactivity of the halopyrazine compared to the similar 2-chloropyridine was illustrated by their reaction with 28% aqueous ammonia; this reagent with chloropyrazine gave the amino derivative in

80% yield after heating at 200° for 20 hr. while 2 chloropyridine required heating to 250° for a similar time. Later workers[113] prepared several alkylated dichloropyrazines and showed them to be reactive towards nucleophiles. Even though substitution of a single chlorine atom in dichloropyrazine occurs easily, disubstitution of para-dichloropyrazines required forcing conditions. This was attributed to deactivation of the second halogen by the para methoxy or hydroxy group.

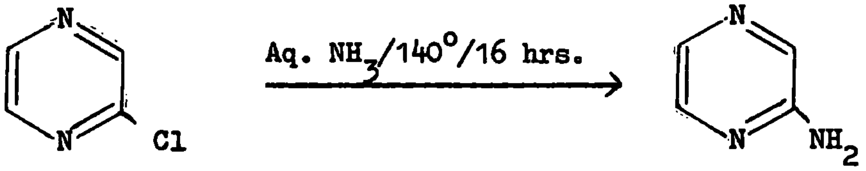


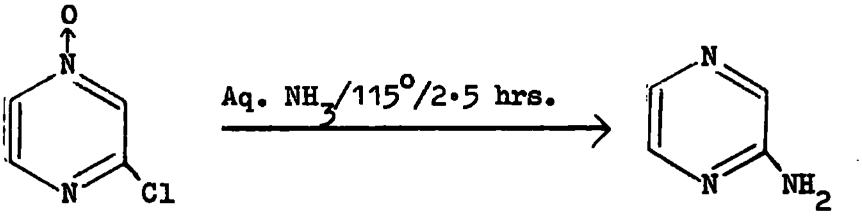


Karnas and Spoerri[114] studied nucleophilic substitution of many isomeric dihalopyrazines and concluded that a methoxy group deactivated a halogen atom in the order para > ortho > meta. Thus for three isomeric dihalopyrazines, the expected ease of disubstitution should be meta- ortho- para-dihalopyrazine. 2,6-Dibromopyrazine[115] had previously been shown to undergo substitution readily with nucleophiles to give a disubstituted product.



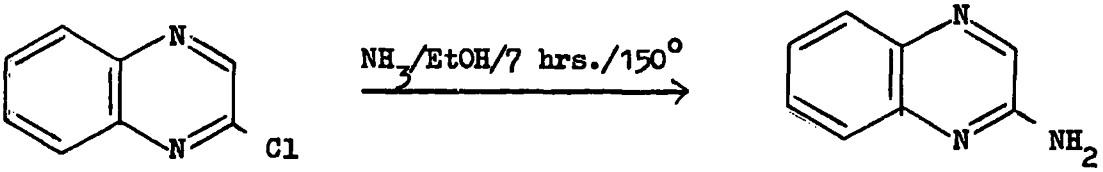
Enhancement of reactivity to nucleophilic substitution by halopyrazine N-oxides, even when the N — O function is meta to the replaceable halogen, was demonstrated by Klein[116,117] et. al. who were able to prepare several pyrazine derivatives under mild conditions.



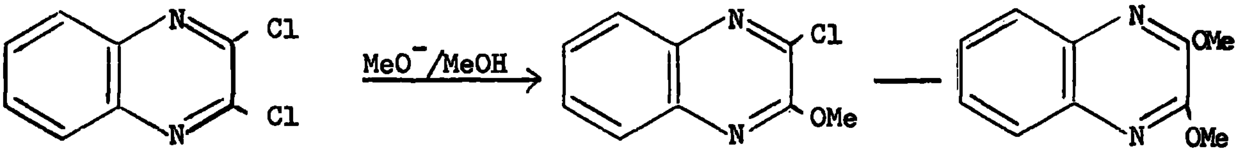


## 3.2. Nucleophilic Substitution of Quinoxaline Derivatives.

2-Chloro- and 2,3-dichloroquinoxalines are also reactive toward nucleophiles; Newbold and Spring[118] were able to synthesise several quinoxaline derivatives by the action of nucleophilic reagents on 2-chloroquinoxaline.

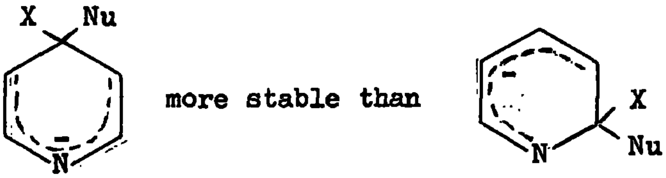


In the case of 2,3-dichloroquinoxaline, the substitution can be terminated after one chlorine has been replaced or allowed to continue to completion.[119]

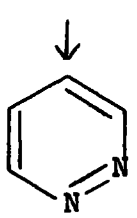


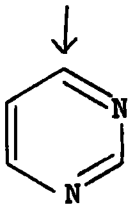
## 3.3. Relative Reactivity of Positional Isomers of a Substituted Azine.

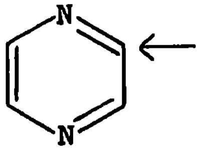
Nucleophilic attack on pyridine derivatives occurs more readily at the 4-position than at the 2-position; this high reactivity of the 4-position is a consequence of the charge in the intermediate being localized mainly para to the point of substitution and thus onto an electronegative nitrogen atom.



Chapman[120] suggested that activation by a para aza group is of the same order as the activation caused by a para nitro-group, but that an ortho aza-group is less activating than an ortho nitro-group. The greater reactivity of positions para to an aza group is illustrated by the diazines, nucleophilic attack occurring most readily at the positions indicated.





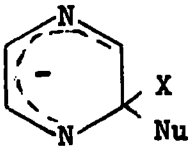


In pyrazine derivatives, however, all positions are identical, but the lower reactivity of pyrazines compared to the other diazines is a consequence of the fact that the charge in the intermediate cannot be localized onto a para nitrogen atom.

On ring annelation, however, the situation becomes more complex. The reactivity of the 2-position increases relative to the 4-position, thus Barlin and Brown[121] showed that in pyridines at 110° the ratio of reactivity of the 4-methylsulphonyl compound to the 2-isomer is about 20, while in the corresponding quinolines at 60° it is only about 2·6, and indeed in the case of heptafluoroquinoline,[108] the order of reactivity has reversed, the 2-position being favoured more than the 4-position. Again, as with pyrazine, there is only one position for nucleophilic attack in the heterocyclic ring of quinoxaline.

## 3.4. Relative Reactivity of the Azine Systems.

Brower[122] and co-workers compared the reactivity of 2-chloropyrazine with 2-chloropyridine and showed the former to be more reactive to nucleophiles. This increased reactivity was attributed to increased stabilization of the transition state by the second nitrogen atom.



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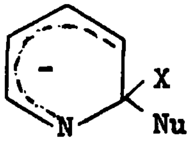
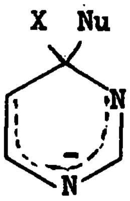
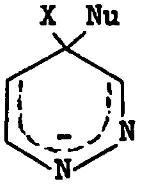
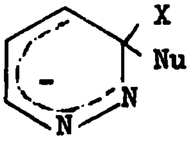
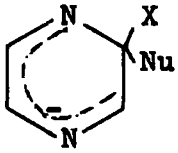


Chan and Miller[123] determined the relative reactivity of a series of chlorine substituted azabenzenes and showed that 2-chloropyrazine was even more reactive than 4-chloropyridine, thus showing that the stabilizing effect of the second nitrogen atom in the transition state more than compensates for the fact that the charge cannot be localized onto a para nitrogen atom. The relative reactivity of the isomeric chlorodiazabenzenes illustrates the greater reactivity of a system where substitution can occur para to a ring nitrogen. The order of reactivity reflects the order of the relative energies of the intermediates leading to substitution. On ring annelation the reactivity increases compared to the monocyclic systems; this was attributed by Chapman[120] to increased possibilities for delocalization of the charge on the intermediate into the homocyclic ring. Thus Rutner and Spoerri[40] estimated that the rate of substitution by 0·01N sodium hydroxide increased 240 times on changing from 2-fluoropyrazine

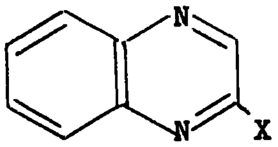








to 2-fluoroquinoxaline. Also the increased reactivity of the 2-position relative to the 4-position on ring annelation is parallelled by the relative reactivity of the isomeric diazanaphthalenes. Barlin and Brown[123] showed that 2-methylsulphonylquinoxaline is almost twice as reactive as the 4-substituted cinnoline derivative.



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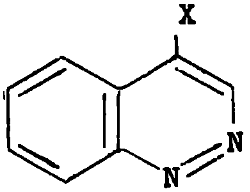


The reactivity of quinazoline derivatives is so high that quantitative estimates of reactivity have not proved possible so far.

# DISCUSSION OF EXPERIMENTAL

# CHAPTER 4

## The Preparation of Polyfluoro-Pyrazines and Quinoxalines

Until workers at Durham prepared tetrafluoropyrazine,[74] using the halogen exchange method, the only known fluorinated pyrazine derivatives were 2-fluoropyrazine,[40] prepared either from chloropyrazine or aminopyrazine, and tetrakis(trifluoromethyl)pyrazine,[124] prepared by the action of sulphur tetrafluoride on pyrazine-tetracarboxylic acid. Also, apart from a reference inferring the existence of 2,3-difluoroquinoxaline,[125] 2-fluoroquinoxaline[40] was the only known fluorinated benzo-analogue of pyrazine. The halogen exchange method of fluorination should be particularly suitable to the preparation of tetrafluoropyrazine, as all positions are activated by a nitrogen atom; tetrachloropyrazine would therefore be expected to undergo halogen exchange much more readily than pentachloropyridine which has unactivated halogen atoms β to the heterocyclic nitrogen atom. Tetrachloropyrazine[126] had been mentioned briefly in 1948, in the patent literature, and hexachloroquinoxaline was unknown when this work was commenced. The tetrachloropyrazine reported had been prepared by the vapour phase chlorination of pyrazine, with elemental chlorine.

✓

Pyrazine itself is not commercially available, but several derivatives were investigated with a view to chlorination to give tetrachloropyrazine. Workers at Durham[74] had previously obtained tetrachloropyrazine by the chlorination of 2-chloropyrazine, hydroxypyrazine, or 2,5-diketopiperazine, but these compounds are only prepared with difficulty, and in low yield. First efforts were, therefore, directed towards developing a convenient synthesis of tetrachloropyrazine.

A route starting with commercial piperazine hexahydrate, although useful on a small scale, was not adaptable to large scale chlorinations. However, a convenient synthetic route was found, starting with the readily accessible pyrazine-2,3-dicarboxylic acid, which is suitable for large scale chlorination reactions.

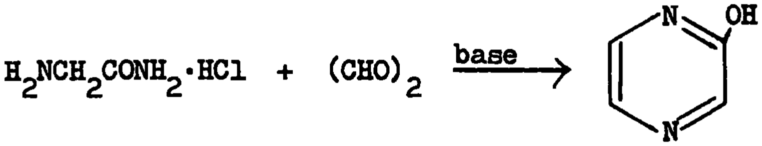
Attempts to extend the 'swamping catalyst' method, used to prepare tetrachloroquinoline,[76] failed, but chlorination of the known 2,3-dichloroquinoxaline, in an autoclave, produced hexachloroquinoxaline in high yield.

## 4.1. Preparation of Tetrachloropyrazine.

### a) From 2-Hydroxypyrazine or 2-Chloropyrazine.

Hydroxypyrazine was prepared by the procedure of Karmas and Spoerri,[127] in which glycine amide hydrochloride is condensed with glyoxal under basic conditions. Glycine amide hydrochloride was prepared by the ammonolysis of α-chloroacetamide with excess aqueous ammonia. However, purification of this product was difficult, while if impure amide was used for the condensation stage the yields were low.

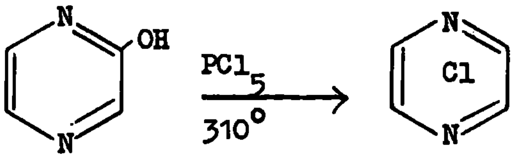
$$ClCH_2CONH_2 \xrightarrow{NH_3,\ 0^{\circ}} H_2NCH_2CONH_2 \cdot HCl$$



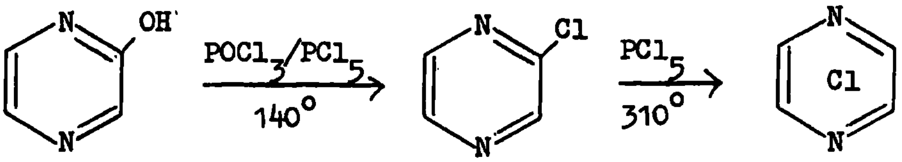
30%

Condensation to the aromatic compound was carried out in aqueous methanol, at -40°, in the presence of base. However, isolation of the product in high yield was difficult as the reaction mixture readily gave polymeric tars above 30°. Isolation of the hydroxypyrazine was finally accomplished by continuous extraction with chloroform. As the yields were low, around 30%, the reaction was not considered suitable for large scale work.

Chloropyrazine was readily prepared by treating hydroxypyrazine with a mixture of phosphorus oxychloride and phosphorus pentachloride, while further chlorination of the mono-chloro compound using phosphorus pentachloride at 310° in glass Carius tubes, gave tetrachloropyrazine in 70% yield. Alternatively, hydroxypyrazine was chlorinated directly with phosphorus pentachloride at 310° in Carius tubes to give tetrachloropyrazine in 70% yield.



70%

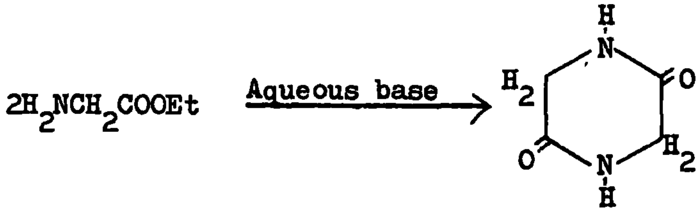


Attempts to scale up the chlorination by using a 240 ml. nickel autoclave gave only decomposition products. This fact, in conjunction with the difficulty of preparing useful quantities of the pyrazine-derivative, limited the use of the route.

### b) From 2,5-Diketopiperazine.

2,5-Diketopiperazine[128] was prepared using the method of Viscontini,[129] in which glycine ethyl ester condenses with itself under basic conditions to give the cyclic amide. Glycine ethyl ester was isolated from the reaction of commercial glycine ethyl ester hydrochloride with ammonia in chloroform.

$$EtOOCCH_2NH_2{\cdot}HCl \xrightarrow{NH_3} H_2NCH_2COOEt + NH_4Cl$$



The yield of the self condensation stage was low, probably due to the formation of long chain polymers rather than the cyclic product. Even in very dilute solution the ester produced mainly insoluble polymers. Chlorination of 2,5-diketopiperazine by phosphorus pentachloride at 300° in Carius tubes gave tetrachloropyrazine in 60% yield. However, as with hydroxypyrazine, only decomposition products were obtained when attempts were made to scale up the reaction by using a nickel-lined autoclave. As useful quantities of tetrachloropyrazine could not be produced by this route it was not further investigated.

### c) From Piperazine.

Commercial piperazine hexahydrate was dried by azeotropic distillation of benzene and precipitated as the dihydrochloride salt by passing dry hydrogen chloride into the hot solution. Samples of the dry salt, or free piperazine, were heated in glass Carius tubes, with excess phosphorus pentachloride to determine the optimum conditions for chlorination. After work-up, the product was characterized. The results of these experiments are set out in Table 4.I.

Table 4.I.

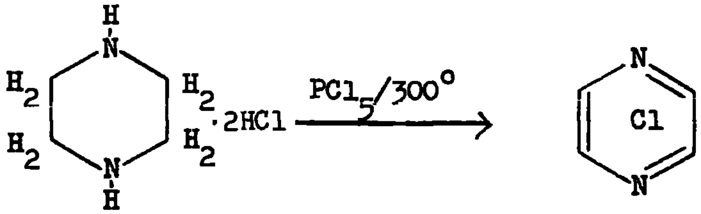
| Weight of $C_4H_{10}N_2\cdot 2HCl$ (mmole) | Weight of $PCl_5$(mmole) | Time (hr.) | Temp. (°) | Weight of $C_4Cl_4N_2$ | Yield % |
|---|---|---|---|---|---|
| 1·6 g. (10·0) | 16 g. (78·5) | 12 | 250 | 0·20 g. | 9 |
| 1·6 g. (10·0) | 16 ( " ) | 12 | 275 | 0·88 g. | 40 |
| 1·6 g. (10·0) | 16 ( " ) | 12 | 290 | 1·13 g. | 52 |
| 1·6 g. (10·0) | 16 ( " ) | 12 | 300 | 1·34 g. | 61 |
| 1·6 g. (10·0) | 16 ( " ) | 12 | 320 | 1·70 g. | 70 |
| 1·6 g. (10·0) | 16 ( " ) | 12 | 340 | 0·79 g. | 36 |
| 1·6 g. (10·0) | 16 ( " ) | 12 | 360 | 0·61 g. | 28 |
| 1·0[a] g. (11·6) | 16 ( " ) | 12 | 320 | 0·47 g. | 19 |

[a] free piperazine.

In all cases tetrachloropyrazine was the sole product, the yields increasing to a maximum around 320°. Chlorination of the dihydrochloride salt gave higher yields than did piperazine itself, probably due to charring of the piperazine during the exothermic reaction which occurs between the free base and hydrogen chloride contaminating the phosphorus pentachloride.

The mechanism of the reaction is possibly free radical, as phosphorus pentachloride has been shown to react with aliphatic hydrocarbons following a free radical mechanism.[131]

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



As no other products have been isolated, the step by which the saturated compound aromatizes can only be surmised. Piperazine is known to be easily aromatized at high temperatures,[132] while a partially chlorinated piperazine molecule could, perhaps, eliminate hydrogen chloride, eventually leading to the aromatic compound.

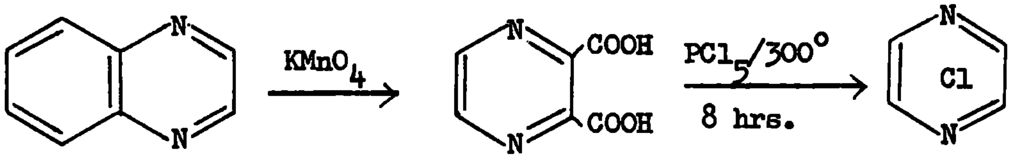
The scale of the reaction is limited in glass apparatus by the large amount of hydrogen chloride produced per mole of heterocycle. It was hoped, therefore, that the chlorination could be carried out on a larger scale, using an autoclave, without a drastic reduction in yield. Because of the decomposition caused by using a metal autoclave when chlorinating 2,5-diketopiperazine and hydroxypyrazine, comparative results were obtained by running identical chlorination reactions in Carius tubes containing samples of stainless steel or nickel as these are the usual metals used as autoclave linings.

Both the metals investigated substantially reduce the yield; nickel, however, is least corroded by the reactants and caused the least reduction in yield. The yield of tetrachloropyrazine was, however, only 30%, at best, when a nickel lined autoclave was used, compared to about 70% in glass apparatus. The large increase in the scale of the chlorination made the process suitable for preparing tetrachloropyrazine, despite the low efficiency, but this method was used only until the process starting with pyrazine dicarboxylic acid was developed.

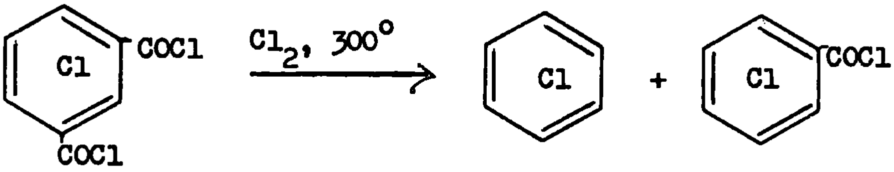
### d) From Pyrazine-2,3-Dicarboxylic Acid.

In contrast to the scarcity of simple routes to pyrazines, its benzo-analogue, quinoxaline, is readily prepared.[133] Oxidation of quinoxaline with neutral potassium permanganate gives pyrazine-2,3-dicarboxylic acid[134] in high yield. The dicarboxylic acid can be easily decarboxylated[135] to give pyrazine, but it was hoped that decarboxylation and chlorination could be carried out simultaneously to produce chloropyrazines. In any event, as pyridine can be successfully chlorinated,[72] it was hoped that pyrazine would also undergo a similar reaction.

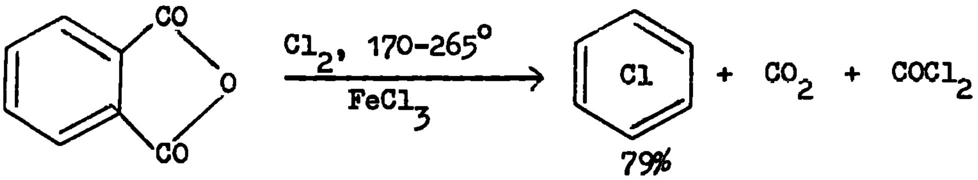
When pyrazine-dicarboxylic acid was treated with excess phosphorus pentachloride in glass Carius tubes, over a wide range of temperatures, only decomposition occurred. However, when the same reaction was carried out in a nickel lined autoclave, heated at 300°, tetrachloropyrazine was isolated in 75% yield.



Kirpal and Kunze[136] noted that tetrachlorophthalyl chloride gave hexachlorobenzene and pentachlorobenzoylchloride on heating with chlorine at 300°, while other workers[137] have prepared hexachlorobenzene by heating phthalic anhydride with chlorine in the presence of a catalytic amount of ferric chloride.



Ref.136

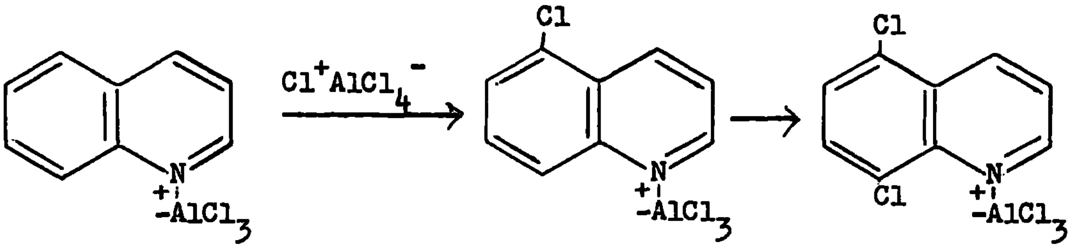


Ref.137

Use of a ferric chloride catalyst suggests that an electrophilic mechanism could be involved, while the fact that chlorination of pyrazine dicarboxylic acid readily occurs only in a metal autoclave may be significant. Surprisingly, however, repeating the chlorination reaction in glass Carius tubes with the addition of ferric chloride or nickel chloride, still produced no tetrachloropyrazine. It seems likely that the reaction is at least partially free radical, but it is difficult to explain the marked effect of glass and nickel on the reaction yield. The amount of gaseous products produced on chlorination is considerably less than that produced on chlorination of piperazine, thus allowing a much greater amount of tetrachloropyrazine to be obtained from each reaction.

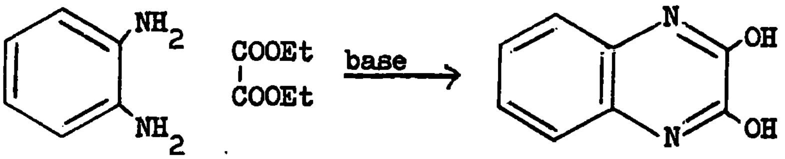
## 4.2. Preparation of Hexachloroquinoxaline.

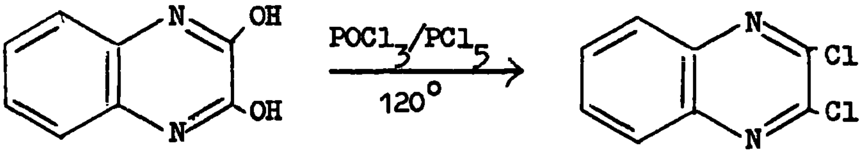
The successful conversion of quinoline to tetrachloroquinoline[76] by passing chlorine into a quinoline-aluminium chloride complex suggested a possible route to polychloroquinoxalines from quinoxaline. Addition of one molar proportion of quinoxaline to three of aluminium chloride produced a complex melting at 130°. Unfortunately, the action of excess chlorine for three days at 180° on this complex produced an intractable tar. Vacuum sublimation of a sample of this tar gave a small amount of colourless solid whose mass spectrum suggested a mixture of mono-, di-, tri-, and tetra-chloroquinoxalines. A repeat experiment at 160° for five days gave the same result. Gordon and Pearson[138] have shown that these chlorinations follow an electrophilic mechanism, an $X^+$ species attacking the complexed quinoline.



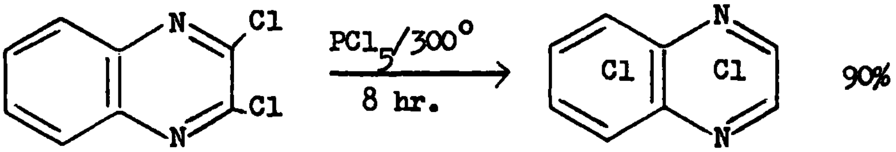
Quinoxaline should be more resistant to electrophilic attack than quinoline, while the formation of a positive charge on the heterocyclic nitrogen atom would further deactivate the molecule. It is also possible that two aluminium chloride molecules complex with quinoxaline, deactivating the system still more. Thus at the temperatures required to achieve substitution, decomposition occurs readily.

2,3-Dichloroquinoxaline[119] can be prepared from 2,3-dihydroxyquinoxaline, which in turn is produced, in high yield, by the condensation of ortho-phenylene diamine with diethyl oxalate.

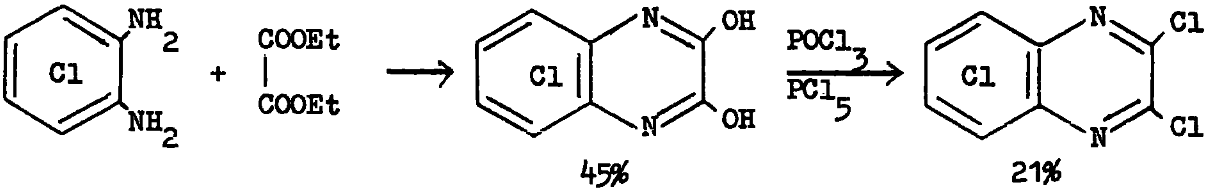




Further chlorination of this dichloroquinoxaline with excess phosphorus pentachloride in a nickel lined autoclave produced hexachloroquinoxaline in high yield.



The mechanism is not known as no other products were isolated, although the mode of preparation suggests a free radical mechanism. After hexachloroquinoxaline had been obtained by this route, an alternative synthesis, starting with tetrachloro-ortho-phenylene diamine was published.[130] However, this compound is not readily prepared and the yields are low.



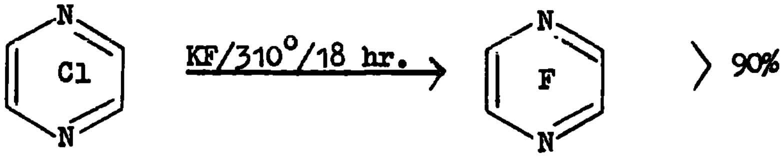
## 4.3. Conversion of Perchlorodiazines to Polyfluorodiazines.

Fluorination using halogen exchange is particularly suited to the preparation of fluorinated 1,4-diazines, as the maximum possible number of ring positions are activated by the nitrogen atoms. Thus tetrachloropyrazine should undergo complete fluorination at temperatures lower than those required to fully fluorinate pentachloropyridine on tetrachloropyrimidine as both these compounds contain halogen atoms β to nitrogen atoms. The mechanism of halogen exchange in heterocyclic compounds has been discussed in 1.3b, while the activating influence of a heterocyclic nitrogen atom with reference to nucleophilic substitution has been discussed in 2.2.

## 4.3a. Fluorination of Tetrachloropyrazine.

Because of the high reactivity of tetrachloropyrazine compared to pentachloropyridine, lower temperatures can be used to effect complete exchange. A series of reactions were carried out, in Carius tubes, in which tetrachloropyrazine was fluorinated with excess potassium fluoride. The results are set out in Table 4.II.

The optimum conditions for complete fluorination are 310° for 18 hr. At lower temperatures or shorter times, mixtures of chlorofluoropyrazines were obtained which could be analysed and separated by G.L.C. After separation, the components of the mixtures were identified by their mass spectra and $^{19}F$ N.M.R. spectra.



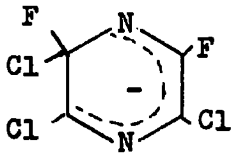
It is of interest to determine the path taken by the reaction. Initially all positions are equivalent, only one isomer of trichlorofluoropyrazine being possible, while similarly, chlorotrifluoropyrazine is unambiguous. However, there are three possibilities for the second position of substitution, leading to dichloro-2,3-, -2,5-, or -2,6-difluoropyrazine, only one of which is isolated in practice.

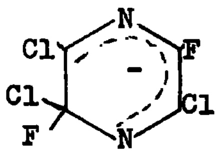
The mass spectrum of the dichlorodifluoropyrazine obtained shows a fragment at m 78 with a single chlorine isotope pattern. This can

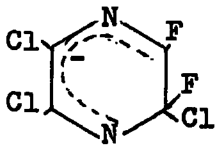
Table 4.II.

| Weight of $C_4Cl_4N_2$ (mmole) | Weight of KF (mole) | Temp. | Time in hrs. | $C_4F_4N_2$ (yield %) | $C_4ClF_3N_2$ (yield %) | $C_4Cl_2F_2N_2$ (yield %) | $C_4Cl_3CN_2$ (yield %) |
|---|---|---|---|---|---|---|---|
| 10 g. (46 mmole) | 100 g. (1·7) | 250° | 10 | 0·7 g.(10%) | 0·9 g. (12%) | 2·1 g. (25%) | 4·8 g.(52%) |
| 15 g. (69 mmole) | 150 g. (2·55) | 250° | 22 | 1·2 g.(11%) | 4·1 g. (35%) | 4·9 g. (39%) | 1·8 g.(13%) |
| 5 g. (23 mmole) | 50 g. (0·85) | 280° | 9 | 0·8 g.(23%) | 1·8 g. (48%) | 1·1 g. (26%) | - ( - ) |
| 12 g. (55 mmole) | 120 g. (2·1) | 300° | 18 | 7·7 g.(93%) | - ( - ) | - ( - ) | - ( - ) |
| 15 g. (69 mmole) | 150 g. (2·55) | 310° | 18 | 10·2 g.(97%) | - ( - ) | - ( - ) | - ( - ) |
| 5 g. (23 mmole) | 50 g. (0·85) | 340° | 12 | 1·7 g.(49%) | - ( - ) | - ( - ) | - ( - ) |
| 9·7 g. (45 mmole) | 100 g. (1·7) | 360° | 15 | 2·3 g.(35%) | - ( - ) | - ( - ) | - ( - ) |

only be $(FCCCl)^+$, which, excluding gross rearrangement, cannot have arisen from 2,3-dichlorodifluoropyrazine. Also the $^{19}F$ n.m.r. spectrum of the dichlorodifluoropyrazine shows a single resonance at -85·1 p.p.m. downfield from hexafluorobenzene. While a partial analysis of the $^{19}F$ n.m.r. spectrum of chlorotrifluoropyrazine leads to the conclusion that such a resonance is incompatible with the dichlorodifluoropyrazine having two adjacent fluorine atoms, assuming that the substituent for chlorine are additive. On the basis of Iπ repulsion of fluorine, the energy of the intermediate leading to meta-substitution would be lowest.





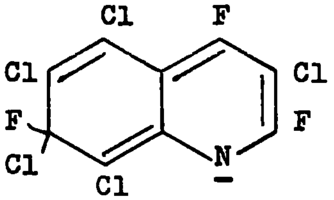


However, it has not been possible to distinguish between the two remaining possibilities, namely 2,5-dichloro- and 2,3-dichlorodifluoropyrazine.

### 4.2b. Fluorination of Hexachloroquinoxaline.

On the basis of the conditions required to fully fluorinate heptachloroquinoline,[76] temperatures in the range 340-380° were used to fluorinate hexachloroquinoxaline with potassium fluoride in a steel autoclave. The optimum conditions required to give hexafluoroquinoxaline were found to be 360° for 18 hrs. Above this temperature, yields were reduced, while below 360° a greater proportion of a second product was obtained. Increasing the time of the reaction reduced the total yield, while any decrease in time resulted in an increased proportion of the minor product. The fluorinated material was obtained by vacuum-distillation from the hot autoclave and the products separated by fractional distillation at atmospheric pressure. The yield of perfluoroquinoxaline was 50% while the minor product, whose mass spectrum showed it to be a chloropentafluoroquinoxaline, was isolated in 5% yield, no other compounds were isolated. A comparison of the $^{19}$F n.m.r. spectrum of the two products suggested that the minor one was 5-chloropentafluoroquinoxaline. It is worth noting that the substituent shift due to the single chlorine atom corresponds closely with the value quoted by Lawrenson[140] for fluorobenzene derivatives.

With reference to the fluorination pathway, the 2- and 3-positions would be the most reactive, by analogy with 2,3-dichloroquinoxaline, followed by the 6- and 7-positions, by analogy with heptachloroquinoline.[139] The reactivity of these two positions is thought to arise from the fact that the negative charge in the particular intermediate can be readily delocalized onto a nitrogen atom.[139]



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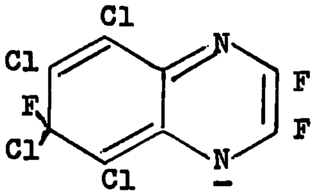
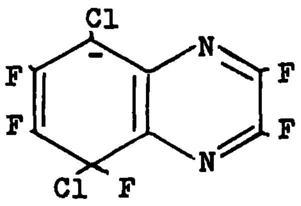
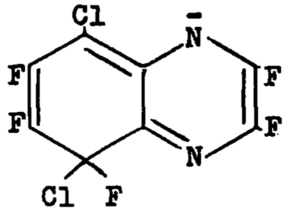


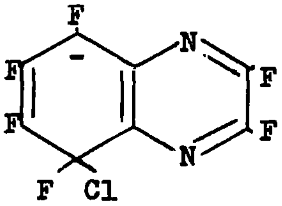
On the other hand, delocalization of the negative charge onto a nitrogen for substitution at the 5- or 8-positions in quinoxaline will not be so favourable.



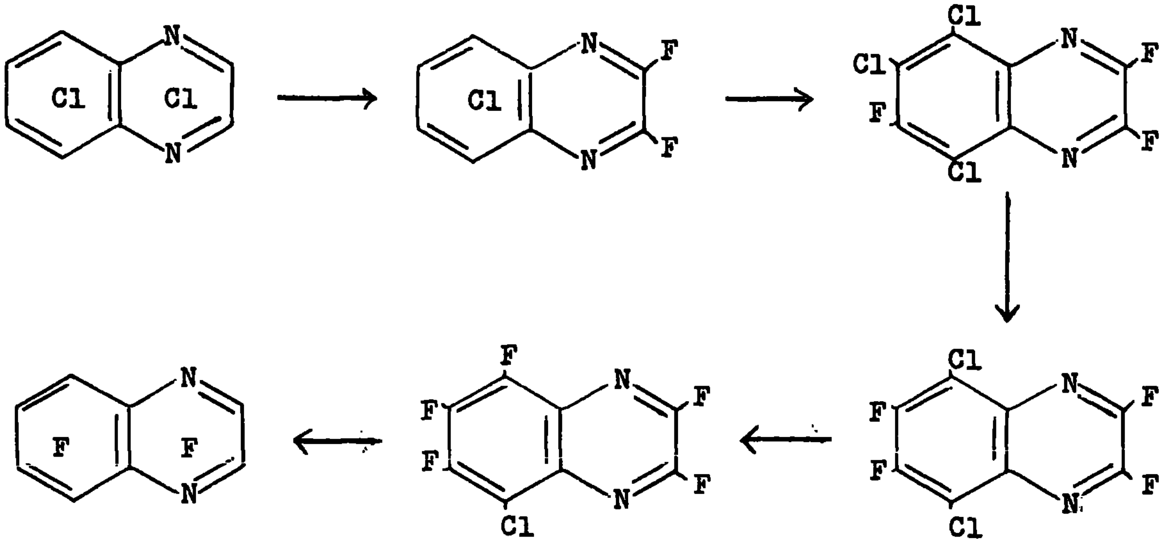
or



This could account for the small amount of 5-chloropentafluoroquinoxaline obtained, as further reaction of this compound with fluoride ion involves a transition state in which the negative charge is mainly located on a carbon atom attached to fluorine.

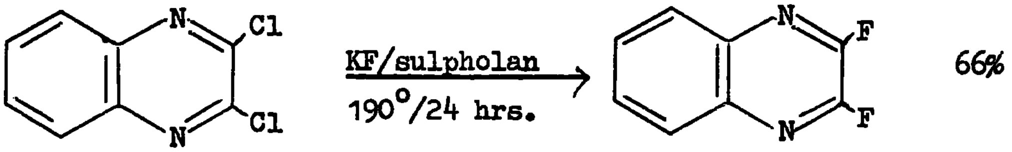


Thus the order of substitution is most probably (2,3), (6,7) followed by the 5- or 8-positions.



## 4.3c. Fluorination of 2,3-Dichloroquinoxaline.

As 2,3-dichloroquinoxaline was available an attempt was made to prepare the 2,3-difluoro-analogue by the halogen exchange reaction. It was hoped that oxidation of this compound would lead to fluorinated pyrazine carboxylic acids. It had previously been reported that 2,3 difluoroquinoxaline[125] was extremely susceptible to nucleophilic attack as attempts to isolate the compound by steam distillation from the halogen-exchange reaction mixture produced only dihydroxyquinoxaline. However, 2,3-difluoroquinoxaline was produced in 60% yield by heating a solution of the dichloro compound in sulpholan at 190° with potassium fluoride for 24 hrs. The product was isolated by adding the mixture to water, and extracting with ether rather than by steam distillation as before. The ease of reaction compared to the halogen exchange reaction to prepare 2-fluoroquinoline[55] illustrates the activating influence of the second nitrogen atom.



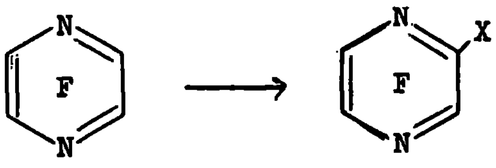
# CHAPTER V

## Nucleophilic Substitution of Polyfluoropyrazines and Polyfluoroquinoxalines.

Nucleophilic displacement of a fluoride ion by a nucleophile, the characteristic reaction of polyfluoroaromatic compounds, is discussed in this chapter. The first two sections are devoted to substitution in fluorinated pyrazine and quinoxaline derivatives, under basic conditions, while the third section discusses substitution in acidic media. The methods used to assign the structures of these compounds are discussed in Chapter VIII.

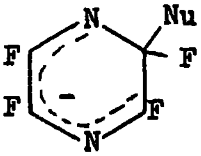
### 5.1. Nucleophilic Substitution in Polyfluoropyrazines. (i) Substitution in Tetrafluoropyrazine.

Nucleophilic substitution on pentafluoropyridine has been shown to occur preferentially, for the reasons outlined in 2.2., at the 4-position,[103] followed by substitution at the positions ortho to the ring nitrogen atom. On the other hand, substitution in tetrafluoropyrazine can only occur ortho to a ring nitrogen, as all positions are equivalent.

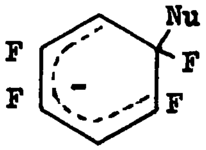


X = OMe, OEt, OtBu, OH, $NH_2$, $NHNH_2$, $CH_3$ and nBu.

Despite the fact that, during substitution, stabilization of the transition state cannot be achieved by localization of the negative charge onto a para nitrogen atom, the influence of the nitrogen atoms is still considerable. Tetrafluoropyrazine reacts rapidly with methoxide ion at low temperatures, while 1,2,4,5-tetrafluorobenzene,[101] which has the same arrangement of fluorine atoms, reacts with methoxide ion only after prolonged heating at 125°. The intermediates can, therefore, be put in the order:-



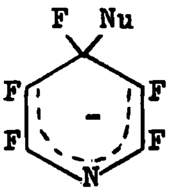
much more stable than



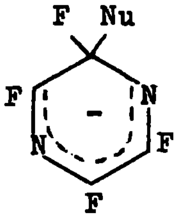
Tetrafluoropyrazine reacted with one molecular proportion of sodium methoxide, in methanol at -20°, to give a high yield of the monomethoxy-derivative. At higher temperatures, with one molecular proportion of methoxide ion, a mixture of the disubstituted product, the monomethoxy compound, and starting material were recovered. The high residual reactivity of the monosubstituted pyrazine contrasts with the reactivity of tetrafluoro-4-methoxypyridine. Whereas in the pyridine case the remaining positions are less reactive than the first, in the pyrazine there must be a site remaining which is of similar reactivity to tetrafluoropyrazine itself. Other alkoxide ions, in the parent alcohol, also gave the monosubstituted derivatives in high yield following treatment of tetrafluoropyrazine, in the same solvent, at low temperatures. The monoethoxy- and tertiary butoxy-, as well as the monomethoxy-derivatives, were prepared in this way. On heating tetrafluoropyrazine with excess potassium hydroxide in t-butanol to reflux for 8 hrs., the monohydroxy-derivative was obtained. Attempts, however, to obtain the disubstituted compound by this route were not successful, as, even at 120°, in a sealed tube, only the monohydroxy-derivative was produced in low yield. Nitrogen bases gave the mono-substituted derivatives; thus aqueous ammonia in dioxan or ethanol reacted readily with tetrafluoropyrazine at room temperature to give the amino-derivative, and hydrazine hydrate in the same solvent at room temperature gave the monohydrazino compound. In this second case, however, the yield was low, as the product is unstable towards atmospheric oxidation, yielding unidentified black solids.

Reaction with methyl lithium in ether at -30° gave a high yield of the monomethyl derivative while normal butyl-lithium produced the mono-butyl compound.

Because iodo-compounds are useful for further syntheses, attempts were made to prepare a monoiodo-derivative by nucleophilic substitution of tetrafluoropyrazine with iodide ion in D.M.F., but no iodine-containing products were obtained. This suggested that tetrafluoropyrazine is of lower reactivity than pentafluoropyridine which gave the 4-iodo-derivative in high yield on heating to 150° with sodium iodide in D.M.F.[141] It seems, therefore, that the intermediates leading to substitution are in the order:



more stable than

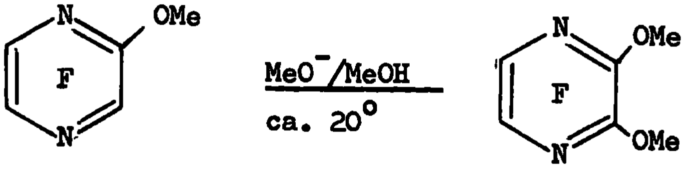


No identifiable products were produced when tetrafluoropyrazine was treated with a slight excess of lithium aluminium hydride in ether. It may be that the introduction of one hydrogen into the molecule increases the reactivity of the system compared to tetrafluoropyrazine which causes it to react with any other nucleophiles present leading to complex mixtures of products.

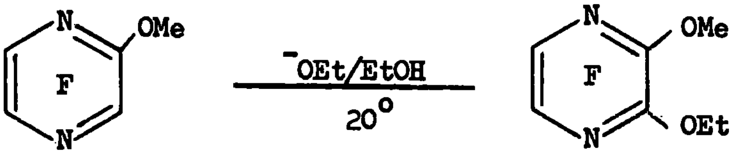
## ii. Substitution in Trifluoropyrazines.

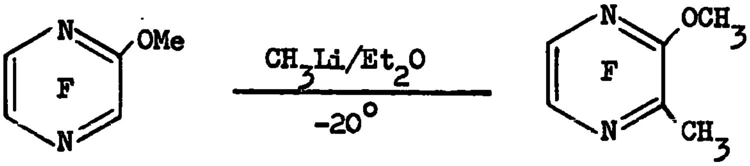
Further substitution of a series of trifluoropyrazines, $(C_4F_3N_2)X$, is of interest as the directive influences of the two nitrogen atoms cancel out. In a trifluoropyrazine, all the positions for substitution are adjacent to nitrogen, leaving only the substituent (X) to control the second position of substitution. This is analogous to a series of pentafluorophenyl-derivatives, where all positions are equivalent, until the influence of the substituent is taken into account.

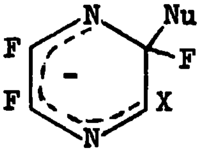
Further reaction of a trifluoroalkoxypyrazine (i.e. X = OR), with nucleophiles, leads to substitution at the position ortho to the alkoxy group. Thus, the reaction of the monomethoxy-derivative with a further molar equivalent of methoxide ion, or tetrafluoropyrazine with two molar equivalents of methoxide ion, produced 2,3-difluoro-5,6-dimethoxypyrazine in high yield.



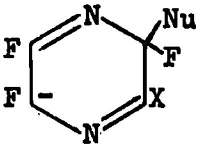
Similarly, the monomethoxy-derivative produced the ortho disubstituted-derivative on reaction with one molar equivalent of sodium ethoxide or methyl lithium.



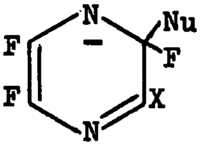




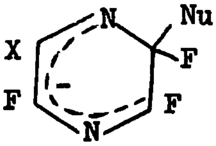
I



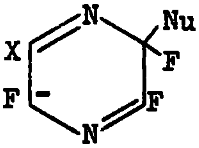
IA



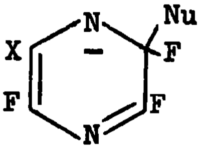
IB



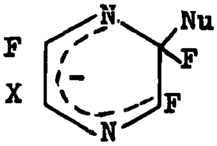
II



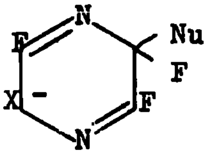
IIA



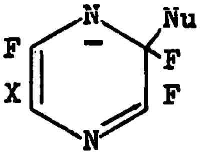
IIB



III



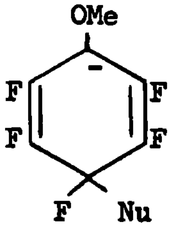
IIIA

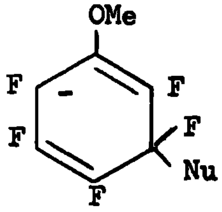


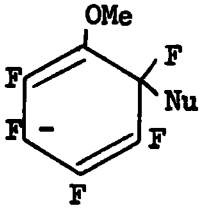
IIIB

The three alternative intermediates leading to substitution of a trifluoropyrazine are shown (I to III); these are also represented as Wheland-type intermediates showing the ortho and para quinonoid structures (IA and B to IIIA and B). Amongst the intermediates in which the charge is localized ortho to the point of substitution, only those in which the charge is localized on a nitrogen atom are shown, as these are considered to be of prime importance.

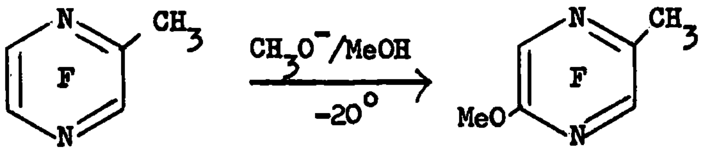
When X is an alkoxy group, e.g. $OCH_3$, the para quinonoid type intermediate, (IIIA) in which X is para to the point of substitution, will be more strongly destabilized than those in which a fluorine is located para to the point of substitution (IA and IIA). This is due to the methoxyl group having a larger $I\pi$ destabilizing effect than fluorine.[98] In the case of pyrazine, this $I\pi$ effect will probably be more effective than is the case with pentafluoroanisole, since trifluoromethoxypyrazine lacks one ortho fluorine, allowing greater freedom of rotation for the methoxyl group. This results in maximum interaction between the p-orbitals of the oxygen and the π-system. Of the two lower energy para-quinonoid intermediates (IA and IIA), IA, leading to ortho substitution, would be expected to be of lowest energy, as this intermediate will be stabilized somewhat by the fluorine atom ortho to the negative charge. Any stabilization of this type would be less when the methoxyl group is located ortho to the negative charge, as in IIA. A similar argument can be used to explain the relatively high ortho-replacement in substitution of pentafluoroanisole.[88]



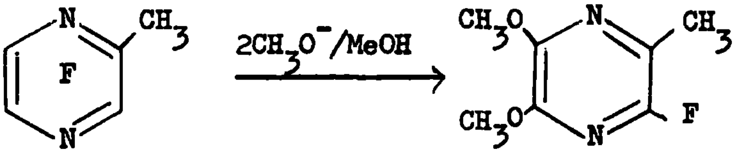




Here, the full I$\pi$ destabilizing influence of the oxygen atom is probably reduced somewhat by steric interactions between the methoxyl group and the ortho fluorine atoms, allowing para substitution to predominate. However, the energy of the intermediate leading to ortho substitution may be of slightly lower energy, relative to the meta intermediate, than would initially be supposed, as the negative charge is stabilized by two ortho fluorine atoms. Further reaction of alkyltrifluoropyrazines with nucleophiles leads to substitution para to the alkyl group. Thus, the reaction of the monomethyl-derivative with sodium methoxide produced 2,5-difluoro-3-methoxy-6-methylpyrazine.



This derivative is isomeric with the product obtained from the reaction of the monomethoxy-derivative with methyl lithium. A coupling of 50 c/s in the $^{19}$F n.m.r. spectrum of the monomethoxy-derivative was attributed to the para fluorines, while the spectrum of this new derivative showed a coupling of 49 c/s, indicating that the fluorine atoms were para. The ortho-disubstituted isomer showed a coupling of 22 c/s which is slightly higher than the ortho coupling constant observed in the spectrum of the monomethoxy-derivative (16 c/s). Reaction of the monomethyl-derivative with two moles of sodium methoxide, at room temperature, produced a trisubstituted derivative. As will be shown later in 8.3., this compound was assigned the structure I. The position of substitution by the third



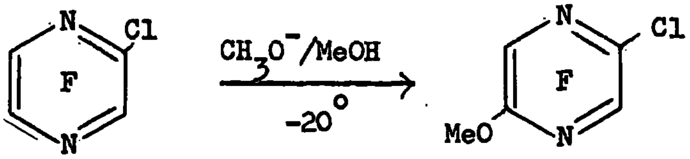
I

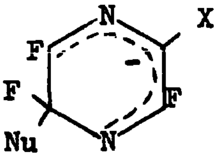
nucleophile, ortho to the methoxyl group, again shows the orientating influence of this substituent.

Analysis, by g.l.c., of the crude reaction mixture from the reaction of tetrafluoropyrazine with excess methyl lithium, showed a small proportion of two other products, in the ratio of approximately 5:1, both of which had longer retention times than the monomethyl-derivative. Separation of the reaction mixture was achieved using preparative scale g.l.c. Only the major impurity could be obtained in sufficient quantity for even partial characterization, as the minor impurity was present in only trace amounts. The mass spectra of both these new products indicated dimethyl-derivatives, while the n.m.r. spectrum of the major isomer was consistent with a para-dimethyl derivative. This would be expected by analogy with the reaction of the methyl derivative with methoxide ion. The minor impurity could perhaps be the ortho-dimethyl compound.

The dibutyl-derivative, prepared by the action of excess normal-butyl-lithium on tetrafluoropyrazine, would be expected to be the para isomer. Further substitution of the monobutyl compound should occur at the same site as with methyl derivatives, for the same reasons, as shown below.

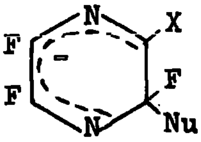
Reaction of chlorotrifluoropyrazine with one mol of sodium methoxide gave a product whose $^{19}F$ n.m.r. spectrum was most consistent with a pyrazine, having two para fluorine atoms. This indicated that substitution had occurred solely at the position para to the chlorine atom. A consideration of the Wheland-intermediates for substitution of a trifluoropyrazine-derivative $(C_4F_3N_2)X$ would suggest that the intermediate leading to para substitution (i.e. IIIA) would be of lowest energy when the group X offers a lower Iπ destabilizing effect than fluorine. This would certainly be so when X = $CH_3$ or Cl as these groups offer a lower Iπ effect than fluorine.[98] Substitution by thiophenoxide ion





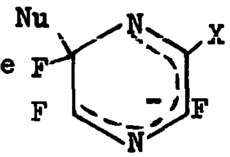
(III)

more stable than



(I)

more stable than



X = $CH_3$ or Cl

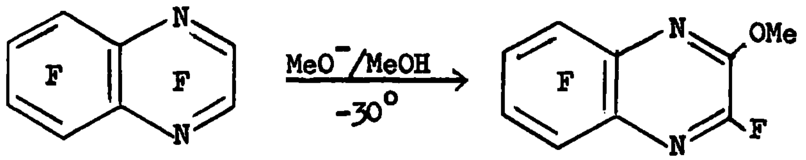
(II)

results in immediate disubstitution, even with excess tetrafluoropyrazine at low temperatures. The fact that no monosubstituted product could be isolated suggests that the addition of a sulphur nucleophile to the ring activates the system to further substitution. A similar effect has been noted in the case of substitution on tetrafluoropyridazine[107] and also by Haszeldine.[99] The geometry of this disubstituted derivative could not be determined as the compound proved to be too insoluble to obtain a $^{19}F$ n.m.r. spectrum which may have helped in the assignment of the structure by extrapolation from the spectra of known sulphur substituted fluoroheterocyclic compounds.

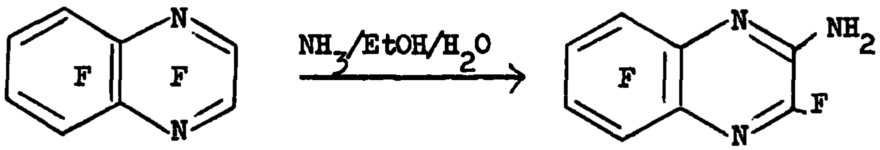
## 5.2. Nucleophilic Substitution of Polyfluoroquinoxalines.

Haloquinoxalines are extremely reactive towards nucleophiles compared to halopyrazines, as explained in 3.2. This has been rationalized in terms of increased delocalization of the charge on the intermediate into the homocyclic ring. Rutner and Spoerri[40] showed that 2-fluoroquinoxaline is 240 times more reactive than fluoropyrazine; therefore, on this basis, polyfluoroquinoxalines would be expected to undergo rapid substitution with nucleophiles.

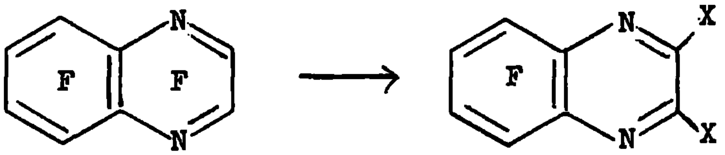
Reaction of one mole of sodium methoxide at $-30^{\circ}$ with hexafluoroquinoxaline gave the 2-substituted derivative. At higher temperatures, one mole of methoxide ion produces mixtures of mono- and 2,3-disubstituted compounds plus starting material.



Addition of hexafluoroquinoxaline at room temperature to excess aqueous ammonia in ethanol or dioxane resulted in evolution of heat, and produced the 2-amino derivative in high yield.



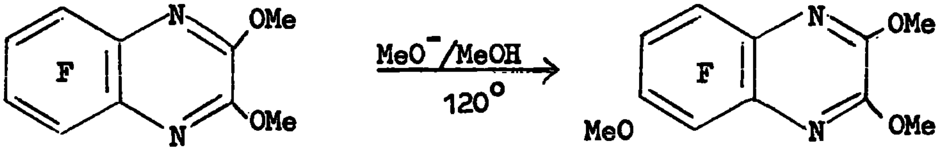
Reaction with potassium hydroxide in tertiary butanol produced the 2,3-dihydroxy-derivative, while reaction with hydrazine hydrate in dioxan or ethanol gave the 2,3-dihydrazino-derivative. Two moles of sodium methoxide in methanol gave the 2,3-dimethoxy compound mentioned above.



$X = OCH_3$, OH or $NHNH_2$

The ease of preparation of these disubstituted derivatives illustrates the high reactivity of the quinoxaline system, compared to the pyrazine system. Under the conditions which produced monosubstituted derivatives from tetrafluoropyrazine, hexafluoroquinoxaline readily yielded disubstituted compounds, e.g. tetrafluoropyrazine yields the monohydroxy compound with potassium hydroxide in t-butanol at 80°, while under the same conditions, hexafluoroquinoxaline produces the disubstituted compound.

Further substitution of the disubstituted compounds proved difficult, the reactivity of these derivatives resembling that of fluorobenzene derivatives. Prolonged refluxing of a mixture of the dimethoxy-derivative with sodium methoxide in methanol produced no new products. However, reaction did occur when tetrafluoro-2,3-dimethoxyquinoxaline was heated with sodium methoxide in methanol at 120°. A trimethoxy-derivative was produced, whose $^{19}F$ n.m.r. suggested it was the 2,3,6-trisubstituted compound.



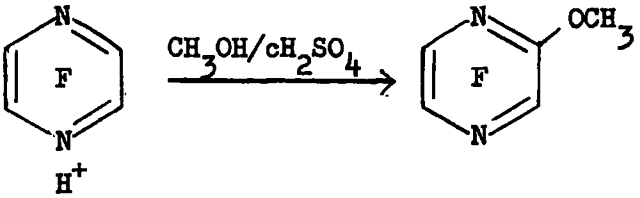
This orientation would agree with the suggested order of nucleophilic replacement of the chlorine atoms in hexachloroquinoxaline, in which the 6- and 7-positions were considered to be more reactive than the 5 or 8 positions, as localization of the charge in the intermediate onto a nitrogen atom is easier for substitution at these positions, than at the 5 or 8 positions.

The position of any further substitution would presumably depend on the nature of the initial carbocyclic ring substituent, as with substitution in pentafluorophenyl derivatives.

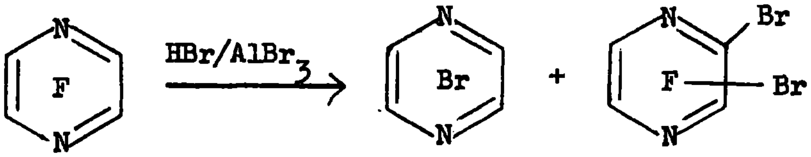
## 5.3. Nucleophilic Substitution of Polyfluoro-pyrazines and Quinoxalines in Acidic Media.

It has been shown that the slow addition of water to a solution of heptafluoroquinoline in concentrated sulphuric acid produces hexafluoro-2-hydroxyquinoline as the sole product, while addition of methanol to a similar solution gave the 2-methoxy-derivative.[76] The predominance of 2-substitution to the exclusion of 4-substitution in such reactions was thought to be due to nucleophilic attack occurring on the protonated species rather than on the free base.[76] Pentafluoropyridine, however, did not show the same reactions, and it was therefore decided to investigate the method further by using the polyfluoro-1,4-diazine system.

Tetrafluoropyrazine was found to dissolve only slowly in concentrated sulphuric acid to give a clear solution, while dropwise addition of methanol to this solution produced the monomethoxy-derivative in 60% yield. On the other hand, dropwise addition of water to such a solution produced only starting material. This difference in reactivity could possibly be due to the extremely low basicity of tetrafluoropyrazine which allows deprotonation to occur faster than nucleophilic attack when water is added to the solution, while on the otherhand, when methanol is added, substitution must occur faster than deprotonation.



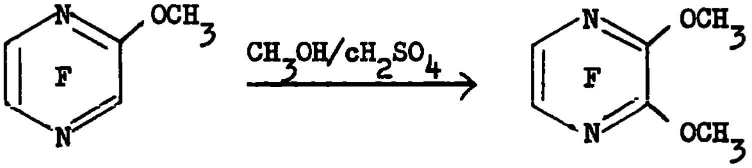
Reaction of tetrafluoropyrazine with an excess of an equimolar mixture of aluminium tribromide and hydrogen bromide at 100° produced a mixture of tetrabromopyrazine and a dibromodifluoropyrazine.



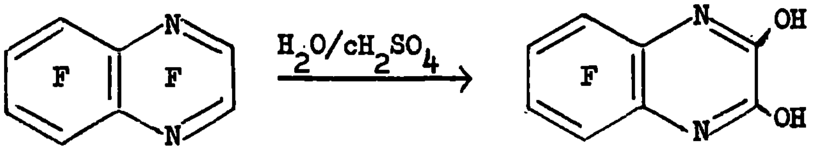
40%   10%

This reagent presumably protonates the fluorinated heterocycle[142] to give a complex acid salt. The resulting complex anion then substitutes the aromatic ring, probably eventually producing ionic aluminium fluoride and hydrogen fluoride.[142] The substitution of one fluorine atom seems to result in activation of the system to further substitution, thus producing a disubstituted compound, while similarly any trisubstituted derivative formed probably substitutes rapidly to produce tetrabromopyrazine. The predominance of tetrabromopyrazine over the dibromo derivative was observed even with an excess of tetrafluoropyrazine and suggests that the rate of substitution increases as fluorine is replaced. This could result from an increase in base strength, following replacement of successive fluorine atoms, leading to a higher degree of protonation and thus an increase in reaction rate. The orientation of the dibromo-derivative has not been established, although the existence of a fragment corresponding to $(FCCBr)^+$ in its mass spectrum suggests that the two bromine atoms are either para or meta but not ortho.

It was hoped that further substitution with methanol of the monomethoxy-derivative in concentrated sulphuric acid would produce a different isomer from that produced under basic conditions, since if protonation occurs solely at the 1-position in the monomethoxy-derivative, then meta substitution would possibly be expected. However, addition of methanol to a solution of the monomethoxy compound in concentrated sulphuric acid produced only the ortho disubstituted isomer, which suggests that protonation occurs on either nitrogen atom, and thus the factors which control substitution in basic media still apply in this case. Surprisingly, slow addition of either water or methanol to a sulphuric acid solution of the monomethyl-derivative resulted in only starting material being recovered. The reason for this is not obvious.



Hexafluoroquinoxaline dissolves readily in concentrated sulphuric acid to give a pink solution, while slow addition of water to the solution produced the 2,3-dihydroxy-derivative in quantitative yield. If a deficiency of water was added, and then the mixture was poured rapidly into a large volume of water, starting material and the disubstituted product were recovered, which suggests that any monosubstituted



product produced reacts further before more hexafluoroquinoxaline is substituted. This is probably due to an increase of base strength following the initial substitution. Addition of methanol to a sulphuric acid solution of hexafluoroquinoxaline, followed by rapid addition of the mixture to a large volume of water prior to extraction of the product, resulted in the isolation of the dihydroxy-derivative as the sole product. Even when a large excess of methanol was added to the sulphuric acid solution, followed by addition of the mixture to water, only the dihydroxy compound was isolated. The dimethoxy compound dissolves readily in concentrated sulphuric acid, while slow addition of water to the resulting solution again produced the dihydroxy derivative in quantitative yield. It seems likely therefore, that the dimethoxy derivative is initially formed on slow addition of methanol to a sulphuric acid solution of hexafluoroquinoxaline, but that the resulting increase in base strength leads to a greater degree of protonation even in relatively dilute acid and that hydrolysis occurs readily.

## CHAPTER VI

### Tautomerism in Polyfluorohydroxy-Pyrazines and Quinoxalines

Pyridines, quinolines, pyrazines and quinoxalines etc., with a hydroxyl-group α or γ to a nitrogen atom, are known to be tautomeric,[143] while of the corresponding polyfluoro-derivatives, only 2-hydroxyquinoline,[144] 1-hydroxyisoquinoline,[144] and 3-hydroxypyridazine[145] have been shown to exist in the amide form. A list of some of the tautomeric and non-tautomeric polyfluorohydroxyheterocyclic compounds is given below.

#### Tautomeric Polyfluorohydroxyheterocycles

| | | |
|---|---|---|
| Trifluoro-3-hydroxypyridazine | Ref. | 145 |
| Hexafluoro-2-hydroxyquinoline | " | 144 |
| Pentafluoro-2-hydroxy-4-methoxyquinoline | " | 144 |
| Hexafluoro-1-hydroxyisoquinoline | " | 144 |

#### Non-tautomeric Polyfluorohydroxyheterocycles

| | | |
|---|---|---|
| Tetrafluoro-4-hydroxypyridine | Ref. | 146 |
| Trifluoro-2-hydroxy-4-methoxypyridine | " | 147 |
| Hexafluoro-4-hydroxyquinoline | " | 144 |
| Pentafluoro-2-methoxy-4-hydroxyquinoline | " | 144 |

A combination of several factors are possibly involved in controlling the degree of tautomerism in polyfluorohydroxyheterocyclic compounds. Some of the more important are: (a) the total number of fluorine atoms in the molecule, (b) the position of the fluorine atoms relative to the nitrogen atom or the hydroxyl group, (c) the relative positions of the nitrogen atom and the hydroxyl group, (d) the amount of conjugation in the particular tautomeric forms, and (e) the $\pi$-electron densities at the oxygen and nitrogen atoms in the tautomers. Factors (a) and (b), would affect the acidity of the hydroxyl group and the basicity of the nitrogen atom, and would seem to control the tautomerism in tetrafluoro-4-hydroxypyridine which exists solely in the enol form, probably due to the very low base strength of the nitrogen atom. If the mechanism of proton transfer is intramolecular then (c) would be important, while the probable importance of factors (d) and (e) is illustrated by the fact that trifluoro-2-hydroxy-4-methoxypyridine[147] does not exist in the amide form, unlike hexafluoro-1-hydroxyisoquinoline. In both cases, the ring nitrogen is flanked by a hydroxyl group and a fluorine atom, and while both hydroxyl-groups have a para fluorine atom, neither nitrogen atom has a para fluorine. Thus the differences in tautomerism are likely to be due to factors such as conjugation. It is of interest, therefore, to determine whether the hydroxy-derivatives of tetrafluoropyrazine and hexafluoroquinoxaline, which have been prepared, are tautomeric.

## 6.1. Tautomerism in Trifluoro-2-hydroxypyrazine.

Examination of the infrared spectrum of trifluorohydroxypyrazine shows a broad absorption with a maximum at 3,390 cm.$^{-1}$, but no band which can be attributed to a carbonyl group. Also the $^{19}F$

## Table 6I

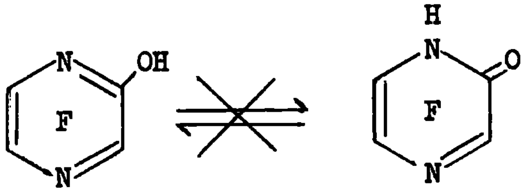
## Ultraviolet Spectra of some N-Methyl and O-methyl Derivatives of Fluorinated Pyrazines and Quinoxalines

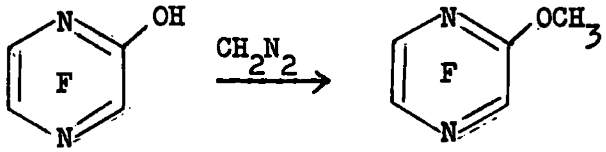
| Compound | $\lambda_{max}$ (mμ)$^{a)}$ ε log in parentheses | | | | | | | | Solvent |
|---|---|---|---|---|---|---|---|---|---|
| Trifluoro-2-hydroxypyrazine | 207<br>(3·59) | 225sh<br>(2·82) | | | 293<br>(3·83) | | | | Cyclohexane |
| Trifluoro-2-methoxypyrazine | 211<br>(3·54) | | | | 295<br>(3·61) | | | | Cyclohexane |
| Tetrafluoro-2,3-dihydroxy-quinoxaline | | | 244<br>(4·60) | | 295<br>(3·65) | 308<br>(3·85) | 315<br>(3·72) | 321<br>(3·82) | Ethanol |
| Tetrafluoro-2,3-dimethoxy-quinoxaline | | 227<br>(4·01) | | 255<br>(3·90) | | 303<br>(3·94) | 316sh<br>(3·83) | | Ethanol |
| Tetrafluoro-1,4-dimethyl-quinoxaline-2,3-dione | | 230<br>(4·18) | 245sh<br>(4·15) | 255sh<br>(4·07) | | 307<br>(3·90) | 315sh<br>(3·84) | | Ethanol |

a) All spectra recorded on a UNICAM SP.800 ULTRAVIOLET SPECTROMETER.

n.m.r. spectrum is very similar to the monomethoxy-derivative. A comparison of the ultraviolet spectra of the hydroxy- and methoxy-derivatives shows distinct similarities (see Table 6.I.). If the hydroxy-derivative was tautomeric, the presence of a conjugated carbonyl-group would be expected to cause their ultraviolet spectra to differ substantially, while on the other hand, the spectrum of a non-tautomeric hydroxy-derivative and a methoxy-derivative would be very similar. Accordingly, the hydroxy-derivative, in ether solution, was treated at room temperature with an excess of ethereal diazomethane. The same procedure has been successfully used to methylate other polyfluorohydroxy-compounds.[144,145] After complete reaction, the solution was concentrated and the reaction mixture analysed by g.l.c. Using a variety of conditions, only one product could be detected which had an identical retention time to that of the monomethoxy-derivative. After isolation, the product was shown to be identical with the known O-methyl derivative. It is important to point out that the relative proportions of the O- and N-methyl derivatives does not indicate the position of tautomeric equilibrium, as methylation of the two isomers is unlikely to occur at the same rate, which may be slow compared to the rate of equilibrium. However, in the cases where, within the limits of detection, the derivatives exist solely in the enol form, only the O-methyl products have been detected.

The complete absence of an N-methyl compound, in conjunction with the spectral evidence, indicates that trifluoro-2-hydroxypyrazine exists, to the limits of detection, in the enol form.



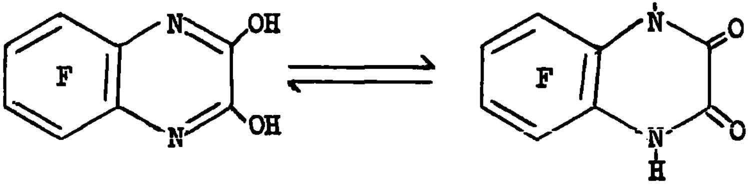


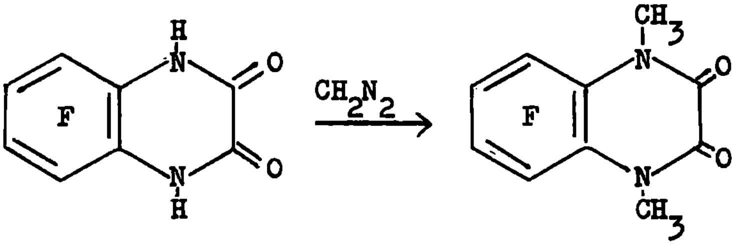
Attempts to obtain 2,3-difluoro-5,6-dihydroxypyrazine were unsuccessful. Further reaction of the monohydroxy-derivative with potassium hydroxide in t-butanol produced no identifiable product, while attempted demethylation of the 2,3-dimethoxy-derivative using both aqueous hydroiodic acid or aluminium trichloride gave only intractable products.

## 6.2. Tautomerism in Tetrafluoro-2,3-dihydroxyquinoxaline.

The infrared spectrum of the 2,3-dihydroxy-derivative shows a broad multiplet band at 3049 cm.$^{-1}$ and a strong band at 1,724 cm.$^{-1}$ which is absent in the 2,3-dimethoxy-derivative, which suggests a conjugated carbonyl compound. This hydroxy-derivative is too insoluble to obtain an $^{19}$F n.m.r. spectrum, but the u.v. spectrum is substantially different in appearance from that of the 2,3-dimethoxy-derivative. A suspension of the dihydroxy-compound in ether was treated with excess ethereal diazomethane, which caused the suspension to dissolve. Analysis of the reaction mixture by g.l.c. showed only one product which had a much higher retention time than the 2,3-dimethoxy compound. After isolation, elemental analysis showed this compound to be isomeric with the dimethoxy-derivative but, under the conditions which caused the O-methyl-derivative to readily sublime, the new compound was involatile. Comparison of the ultraviolet spectra of this new derivative and the isomeric dimethoxy compound shows marked differences (see Table 61). However, the ultraviolet spectrum of this new derivative is very similar to the original dihydroxy-derivative. The infrared spectrum shows a strong absorption at 1,695 $cm.^{-1}$, indicating a carbonyl group. This new dimethylated-derivative must be either the N,N'-dimethyl compound or the mixed N,O-dimethyl-derivative. The mass spectrum, however, after comparison with the dimethoxy compound, points to an N,N'-dimethyl-derivative, as no breakdown pattern attributable to an O-methyl group is observable.

The spectral evidence, in addition to the observed N-methyl products, shows that this dihydroxy-derivative exists in the amide form.





## 6.3. Factors Affecting Tautomerism in Trifluorohydroxypyrazine and Tetrafluoro-2,3-dihydroxyquinoxaline

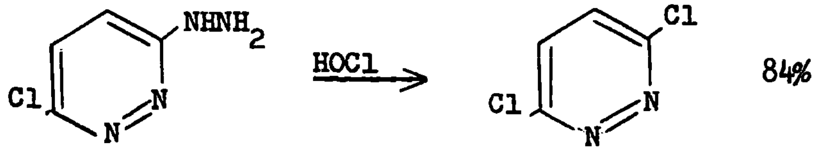
The factors controlling the tautomerism of polyfluorohydroxypyridines are also likely to control the tautomerism of polyfluorohydroxypyrazines. The base strength of hydroxypyrazine is very low (pKa -0·1),[148] and consequently the base strength of the polyfluoro-analogue must be extremely low. On the other hand, the isomeric trifluoro-3-hydroxypyridazine is tautomeric. This isomeric compound, however, must have a much higher base strength than the pyrazine isomer, as it has two adjacent nitrogen atoms and consequently the basicity of the nitrogen atoms would seem to control the tautomerism of trifluorohydroxypyrazine.

The degree of conjugation in the tautomers has been suggested to be important in the case of hexafluoro-1-hydroxyisoquinoline and hexafluoro-2-hydroxyquinoline; however, the degree of conjugation in the amide form of tetrafluoro-2,3-dihydroxyquinoxaline is less than in the enol form, yet the compound is tautomeric. The tautomerism is more probably controlled by the basicity of the nitrogen atoms. Neither nitrogen is adjacent to a fluorine, and in fact, the base strength may not be much lower than the non-fluorinated analogue. Thus, the relatively high base strength probably controls the tautomerism.

# CHAPTER VII

## Oxidation of Polyfluoroheterocyclic Hydrazino-Derivatives

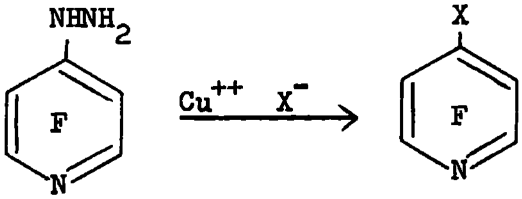
Substituted hydrazines are readily oxidized; monosubstituted hydrazines usually undergo a four electron exchange to give a diazonium group. The reaction has been used to prepare halopyridazines from the corresponding hydrazino-derivatives using hypohalites as the oxidizing agent.[149]



Tatlow and co-workers[83] oxidized pentafluorophenylhydrazine to pentafluorobenzene, using Fehling's solution or aqueous copper sulphate, while Haszeldine and co-workers[150] used halogens as the oxidizing agent and prepared the corresponding halopentafluorobenzene. Haszeldine[141] later prepared 4-iodotetrafluoropyridine by oxidation of the hydrazino-derivative with silver oxide in the presence of excess methyl iodide. Workers at Durham[103] oxidized tetrafluoro-4-hydrazinopyridine with aqueous copper sulphate to give the corresponding hydro-derivative. Recently, it has been shown that 2-hydrazinoquinoline can be converted into the 2-chloro-derivative using ferric chloride in dilute hydrochloric acid.[151] It was therefore decided to investigate this reaction with a view to preparing halofluoroaromatic compounds, as the hydrazino-derivatives of many polyfluoroheterocyclic compounds are readily obtained.

## 7.1. Oxidation of Tetrafluoro-4-hydrazinopyridine.

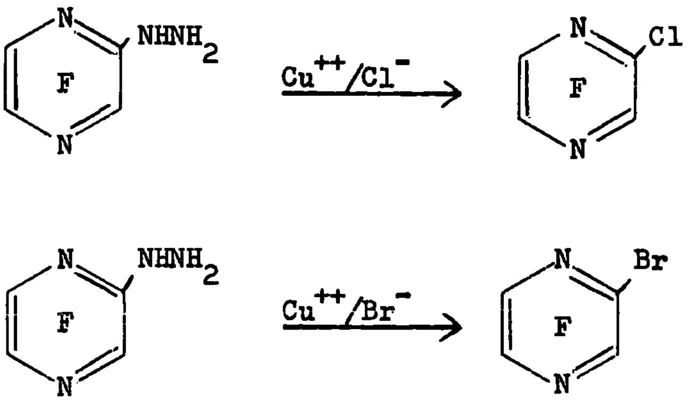
Tetrafluoro-4-hydrazinopyridine was used as a representative hydrazine derivative as it is readily prepared in high yield by the action of hydrazine hydrate on pentafluoropyridine.[103] The addition of this hydrazine compound to a solution of ferric chloride in 2N-hydrochloric acid at room temperature caused immediate evolution of nitrogen, and steam distillation of the reaction mixture gave 4-chlorotetrafluoropyridine in 35% yield. It was hoped that the use of some other oxidizing metal halide would give a higher yield of the halo-derivative, and in fact oxidation of the hydrazino-derivative with cupric bromide in 2N-hydrobromic acid gave the 4-bromo-derivative in 76% yield, after steam distillation. Oxidation using cupric chloride in hydrochloric acid gave the 4-chloro-compound in 75% yield.



An attempt to prepare the iodo-derivative using an aqueous suspension of iodine and calcium carbonate[151] gave no identifiable products.

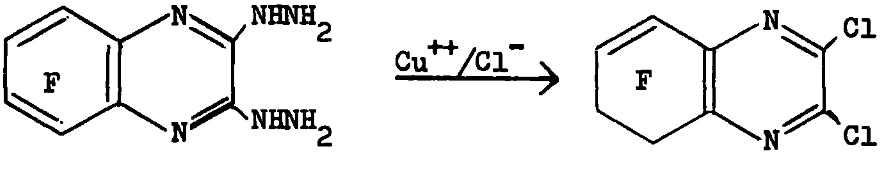
## 7.2. Oxidation of Trifluoro-2-hydrazinopyrazine.

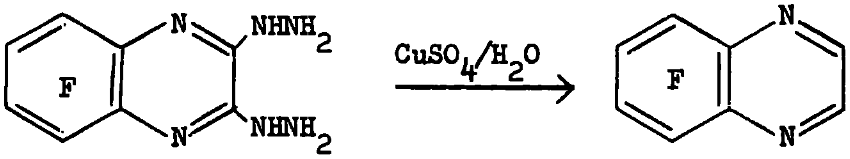
Extension of the reaction to the pyrazine series is not so useful, as trifluoro-2-hydrazinopyrazine is unstable towards oxidation by atmospheric oxygen and thus is difficult to prepare in high yield. However, oxidation of this derivative with cupric bromide in hydrobromic acid produced bromotrifluoropyrazine in 77% yield, after steam distillation of the reaction mixture. Oxidation with cupric chloride in hydrochloric acid gave chlorotrifluoropyrazine in high yield, which had been obtained previously by the mild fluorination of tetrachloropyrazine with potassium fluoride.



## 7.3. Oxidation of 5,6,7,8-Tetrafluoro-2,3-dihydrazinoquinoxaline.

The dihydrazino-derivative, obtained from the reaction of hexafluoroquinoxaline with hydrazine hydrate, gave 5,6,7,8-tetrafluoroquinoxaline in high yield on oxidation with aqueous copper sulphate. Oxidation with cupric chloride in hydrochloric acid gave 2,3-dichloro-5,6,7,8-tetrafluoroquinoxaline in 60% yield, after steam distillation. The products from these two reactions were taken as evidence for the orientation of the dihydrazinoquinoxaline-derivative as it had proved to be too insoluble to show an $^{19}F$ n.m.r. spectrum.





## 7.4. Mechanism of the Oxidation.

The mechanism is thought to involve the initial formation of a diazonium group by oxidation of the hydrazine entity, followed by elimination of nitrogen.

$$RNH\overset{+}{N}H_3Cl^- \xrightarrow{Cu^{++}} RN_2^+ \quad Cl^-$$

$$RN_2^+Cl^- \longrightarrow RCl + N_2$$

The decomposition of hydrocarbon diazonium compounds [152] usually follow first order kinetics in which the rate determining step is the elimination of nitrogen to give a carbonium ion, which then reacts rapidly with nucleophiles, such as water or halide ion, to give the final product.

$$RN_2^+ \xrightarrow{slow} R^+ + N_2$$

$$R^+ + X^- \xrightarrow{fast} RX$$

$$R^+ + H_2O \xrightarrow{fast} ROH + H^+$$

In the heterocyclic fluorocarbon case, the formation of a carbonium ion seems unlikely, especially as all the compounds investigated contain electronegative ring-nitrogen atom(s). However, there is some evidence[153] that even in the case of hydrocarbon diazonium compounds, a bimolecular nucleophilic substitution occurs concurrently, particularly when electron withdrawing groups are attached to the aromatic ring. Such a process, with the halide ion acting as the nucleophile, would seem more probable in this case. However, hydroxyl-derivatives would be expected to occur as impurities and these have not been isolated.

The higher yields obtained with cupric halides, compared to the ferric halides, suggest that a Sandmeyer-Type of reaction[154] could be involved. The initial reduction of the cupric halide by the primary hydrazine would ensure a good supply of cuprous halide, which could then react in the normal Sandmeyer-reaction. Formation 'in situ' of cuprous halide which further reacts with diazonium compounds has been observed by Brackman and Smit,[155] who were able to produce aryl halides, in one step, by the reaction of aromatic amines with cupric-halide nitrosyl complexes.

$$CuCl_2NO + C_6H_5NH_2 \longrightarrow C_6H_5N_2^+\ Cl^- + CuCl + H_2O$$

$$C_6H_5N_2^+\ Cl^- \xrightarrow{CuCl} C_6H_5Cl + N_2$$

The fact that the reaction does work in the absence of cuprous ions may indicate that some other mechanism apart from the Sandmeyer reaction is involved.

Haszeldine[150] suggested that a pentafluorobenzene diazonium salt reacts with unchanged primary hydrazine to give a tetrazen which decomposes to pentafluoroaniline and pentafluorophenylazide

$$C_6F_5N_2^+ + C_6F_5NHNH_2 \longrightarrow C_6F_5{\cdot}N{:}N{\cdot}NHNHC_6F_5 \longrightarrow C_6F_5N_3 + C_6F_5NH_2$$

A small amount of 4-aminotetrafluoropyridine was isolated from the reaction mixture after the oxidation of tetrafluoro-4-hydrazinopyridine, but no azides have been detected.

The reaction is of great potential, as it allows the preparation of highly fluorinated aryl-diazonium compounds without using 80% hydrofluoric acid with its attendant difficulties. It is also the only route, so far, leading to trifluoropyrazine-diazonium compounds, as amino-trifluoropyrazine could not be diazotized even in 80% hydrofluoric acid.

# CHAPTER VIII

## Assignment of Structure in Polyfluoro-pyrazines and Quinoxalines

Several attempts, by chemical methods, were made to determine the structures of the prepared fluorinated pyrazines and quinoxalines. This approach was not successful, however, and most of the structures were determined using spectroscopic evidence (mainly $^{19}F$ n.m.r. and $^{1}H$ n.m.r.).

### 8.1. The $^{19}F$ n.m.r. Spectra of Polyfluoropyrazines.

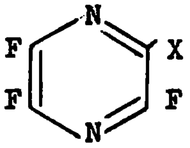
A complete table of the $^{19}F$ n.m.r. spectra of the compounds prepared is given in Appendix I, the only data given in this section is that relevant to the compounds under discussion.

In $^{19}F$ n.m.r. spectra, the effect of a single substituent on the chemical shift of the fluorine atoms ortho, meta and para to it, must be known before any assignment of structure, based on chemical shifts, can be made. Accordingly, the $^{19}F$ n.m.r. spectra of most of the monosubstituted derivatives prepared were recorded and interpreted. In the case of the monosubstituted-derivatives, the structures were known from the mode of preparation. The effect of a substituent on the remaining fluorine atoms, relative to tetrafluoropyrazine is shown in table 8.I.

It is worth noting that the resonances in the spectra of fluoropyrazines are very sharp, in spite of the fact that all the fluorine atoms are adjacent to nitrogen. This contrasts markedly with

## Table 8.I.

The Observed $^{19}F$ n.m.r. spectra of a series of Trifluoropyrazines



| X | Solvent | Shifts relative to Tetrafluoropyrazine | | | Coupling Constants ($J_{FF}$) $H_z$ | | |
|---|---|---|---|---|---|---|---|
| | | ortho | meta | para | ortho | meta | para |
| -F | $(Et_2O)$ | 0 | 0 | 0 | 0 | 0 | 0 |
| $-NH_2$ | $(Et_2O)$ | +1 | +6·1 | +19·1 | 16·2 | 10·8 | 49·8 |
| -Cl | $(Et_2O)$ | -13·3 | -2·2[a] | -2·2[a] | [b] | [b] | [b] |
| -Br | $(Et_2O)$ | -16·7 | -6·7[a] | -6·7[a] | [b] | [b] | [b] |
| $-NHNH_2$ | $(Et_2O)$ | -0·5 | +7·4 | +21·6 | 15·0 | 13·2 | 50·1 |
| -OH | $(Et_2O)$ | -0·2 | +4·7 | +12·1 | 16·5 | 12·0 | 51·0 |
| $-OBu^t$ | $(Et_2O)$ | -2·6 | +4·4 | +12·6 | 16·1 | 12·0 | 50·1 |
| -OEt | $(Et_2O)$ | -1·4 | +5·1 | +13·0 | 13·8 | 12·0 | 50·7 |
| $-OCH_2CH_2OH$ | $(CH_3)_2CO$ | -1·8 | +5·1 | +12·0 | 14·8 | 11·7 | 50·6 |
| $-OCH_3$ | $(Et_2O)$ | -1·7 | +4·9 | +12·4 | 15·1 | 12·3 | 51·2 |
| $-CH_3$ | $(Et_2O)$ | -10·9 | -0·2 | -1·5 | 19·7 | 7·9 | 43·9 |

[a] Approximate average values due to coincidence of resonances.

[b] Values not determined.

the resonance corresponding to the 3 and 6 fluorines in tetrafluoropyridazine, which is appreciably broadened by the adjacent nitrogen atoms.

Using the substituent shift values, shown in Table 8.I, the alternative $^{19}F$ n.m.r. spectra of the possible disubstituted derivatives were calculated as shown in Table 8.II. In the cases where the two substituents were identical, the three possible isomers are all symmetrical, which results in only a single fluorine resonance being observed, with no coupling. However, as can be seen in these cases, the observed and calculated chemical shifts are in good agreement. Thus, on the basis of the methoxy-substituent shift from Table 8.I., the dimethoxy derivative was assigned the ortho disubstituted structure as were all the other dialkoxy-derivatives.

Similarly, the disubstituted derivative produced by the addition of methyl-lithium to the monomethoxy-derivative was assigned the ortho structure on the basis of the observed chemical shifts. The observed F-F coupling constant is closest to the value of the ortho coupling constant observed in the monomethoxy compound. The n.m.r. spectrum of the remaining methoxy methyl-derivative, produced by further substitution of the methyl-derivative with methanolic sodium methoxide, indicated a para disubstituted compound. The observed chemical shifts are closest to the shifts calculated for the para isomer, while the F-F

## Table 8.II.

## $^{19}F$ n.m.r. Spectra of Difluoropyrazines

| Substituents | | Calculated shift(s) rel. to $C_6F_6$ using data from Table 8.I. | | | Expected[a] $J_{FF}$ (c.p.s.) | | |
|---|---|---|---|---|---|---|---|
| X | Y | ortho Y | meta Y | para Y | ortho Y | meta Y | para Y |
| $-OCH_3$ | $-OC_2H_5$ | -50·9;<br>-50·5 | -57·1;<br>-55·4 | -64·9;<br>-50·5 | 16 | 12 | 50 |
| $-OCH_3$ | $-OCH_3$ | -51·1 | -57·7 | -65·2 | - | - | - |
| $-OCH_2CH_2OH$ | $-OCH_2CH_2OH$ | -51·3 | -58·2 | -65·1 | - | - | - |
| $-CH_3$ | $-OCH_3$ | -56·2;<br>-65·0 | -71·6;<br>-66·9 | -74·4;<br>-70·3 | 16 | 10 | 45 |
| $-CH_3$ | $-CH_3$ | -70·1 | -80·8 | -79·5 | - | - | - |
| -Cl | -Cl | -64·0[b] | -83·9[b] | -83·9[b] | - | - | - |
| -Cl | $-OCH_3$ | -58·2;<br>-65·7[b] | -72·3;<br>-59·3[b] | -66·8;<br>-72·3[b] | 15 | 12 | 50 |
| -Br | -Br | -73·8[b] | -87·8[b] | -87·8[b] | - | - | - |

| | | Observed shift(s) rel. to $C_6F_6$ (solvent) | | Observed $J_{FF}$ (c./s.) |
|---|---|---|---|---|
| $OCH_3$ | $OC_2H_5$ | -51·5; -51·7 | ($Et_2O$) | 16 |
| $OCH_3$ | $OCH_3$ | -51·2 | ($Et_2O$) | - |
| $OC_2H_4OH$ | $OCH_2CH_2OH$ | -51·8 | ($Me_2CO$) | - |
| $CH_3$ | $OCH_3$ | -75·6; -72·8 | ($Et_2O$) | 49·3 |
| $OCH_3$ | $CH_3$ | -65·7; -58·2 | ($Et_2O$) | 22·5 |
| $CH_3$ | $CH_3$ | -79·4 | ($Et_2O$) | - |
| $nC_4H_9$ | $nC_4H_9$ | -78·1 | ($Et_2O$) | - |
| Br | Br | -88·0 | ($Et_2O$) | - |
| Cl | Cl | -85·1 | ($Et_2O$) | - |
| Cl | $OCH_3$ | -71·7; -77·4 | ($Et_2O$) | 47 c./s. |

[a] Coupling constant expected on the basis of observed coupling in the corresponding monosubstituted derivatives.

[b] Approximate values based on an average meta and para substituent shift.

coupling constant is of the correct order for para fluorine atoms. The $^{19}F$ n.m.r. spectra of the monohalo-derivatives have not been interpreted as they are not first order. However, the resonance due to the fluorine atom adjacent to the halogen is remote from the remainder of the spectrum, and therefore an ortho halogen substituent shift could be calculated, while an average of the meta and para substituted shifts could be estimated. By using these values to calculate the spectra of the dihalo-compounds, it was shown that the dichloro compound, produced by low temperature fluorination of tetrachloropyrazine, and the dibromo compound, obtained by heating tetrafluoropyrazine with hydrogen bromide and aluminium tribromide, could not have fluorine atoms ortho to a halogen and must therefore be the meta or para isomers. As an average meta and para substituent shift was used, it was not possible to distinguish between the remaining two possibilities.

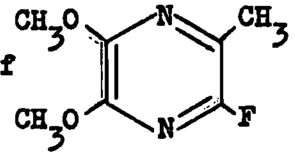
The compound produced by substitution of chlorotrifluoropyrazine with methanolic sodium methoxide shows an n.m.r. spectrum whose chemical shifts are closest to the values calculated for the para disubstituted compound, while the observed F-F coupling constant (47 c./s.) again indicates para fluorine atoms.

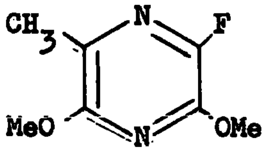
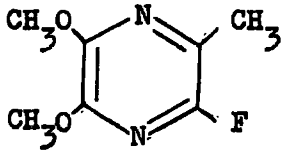
The observed chemical shift of the dimethyl-derivative did not sufficiently differentiate between the meta and para isomers, as can be seen from 8.II. However, as will be discussed later in 8.3. this compound was shown to have the para dimethyl structure.

The additivity of chemical shifts becomes less reliable when dealing with trisubstituted derivatives, as the calculated value of the chemical shift must by then have accumulated the sum of the errors derived from the three individual shifts. However, if the calculation is based on a disubstituted precursor whose spectrum is known, rather than on tetrafluoropyrazine, the error should be less. Thus, as shown in Table 8.III., the calculated chemical shift for the trisubstituted fluorodimethoxymethylpyrazine, prepared by the addition of two molar equivalents of methoxide to the monomethyl-derivative, shows a much smaller error when the calculation is based on the spectrum of the known para-disubstituted precursor.

Table 8.III

The $^{19}F$ n.m.r. Spectra of Fluorodimethoxymethylpyrazines

Observed chemical shift of  66·1 p.p.m.

| Isomer | | Shift based on p-$C_4F_4N_2$ | Shift based on di-substituted precursor |
|---|---|---|---|
|  | (I) | -57·9 | -57·9 |
|  | (II) | -62·0 | -63·2 |

The reasons for assigning structure II to the compound are given in 8.3. below.

## 8.2. The $^{19}$F n.m.r. Spectra of Polyfluoroquinoxalines.

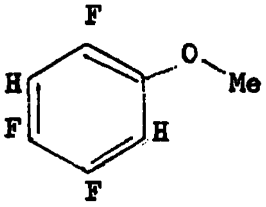
The solubility of many of the fluoroquinoxalines prepared proved too low to allow $^{19}$F n.m.r. spectra to be measured. However, the spectra of the methoxy-derivatives could be recorded. The dimethoxy-derivative was readily assigned to the 2,3-disubstituted structure as, compared to the spectrum of hexafluoroquinoxaline, the spectrum of this derivative lacked any very low field resonances. If substitution had occurred in the carbocyclic ring, the resonances due to the fluorine atoms adjacent to nitrogen would have been apparent at low field. On the other hand, the spectrum of the monomethoxy-derivative exhibits a single resonance at low field, shifted slightly relative to hexafluoroquinoxaline, and signals attributable to four fluorine atoms close to the resonance of hexafluorobenzene, thus indicating that substitution had occurred in the hetero-ring. It is worth pointing out that the substituent shift of the single methoxyl group, in the hetero-ring, is the same at the ortho position as in the corresponding trifluoromethoxypyrazine (-1·7 p.p.m.). The trimethoxy-derivative showed resonances at -14·8, -7·8 and -7·2 p.p.m. One methoxyl group must be in the carbocyclic ring, and therefore this compound could be regarded as a substituted fluorobenzene. Lawrenson[140] observed that the methoxyl group in pentafluoroanisole produced a small upfield shift at the meta and para positions and a downfield shift at the ortho positions. A similar trend in sign can be observed for fluoropyrazines in 8.I. The spectrum of this trisubstituted compound, compared to the 2,3-dimethoxy-derivative precursor, shows that two resonances have been shifted downfield, while the third has remained largely unchanged. This has been taken as indicating that the third methoxyl group is flanked by two fluorine atoms and therefore substitution must have occurred at the 6- (7-) position para to a ring junction. Such substitution would be expected from a consideration of the relative energies of the various transition states for substitution, as explained in 5.2.

The spectrum of the chloropentafluoroquinoxaline, obtained as a minor product from the fluorination of hexachloroquinoxaline, showed resonances at -85·4 and -83·3 p.p.m., which were attributed to the hetero-ring fluorines, and three other resonances (-35·8, -17·0 and -10·1 p.p.m.). This confirmed that the single chlorine atom was in the carbocyclic ring. Lawrenson[140] has shown that a chlorine substituent in pentafluorophenyl-derivatives results in a large downfield shift of the resonances of ortho fluorine atoms, and a small downfield shift at the meta and para positions. Similarly regarding the chloropentafluoroquinoxaline as a substituted chlorofluorobenzene, if the chlorine was located at the 6 or 7 positions, then two resonances would be shifted downfield relative to hexafluoroquinoxaline, while if it was situated at the 5 (or 8) position, only one resonance would be substantially shifted downfield. Therefore on the basis of this large downfield shift, the single chlorine was assigned to the 5(8) position. The resulting ortho chlorine substituent shift is quite close to the value quoted by Lawrenson[140] for chloropentafluorobenzene (-25·5 and -22·0 respectively).

The amino- and dihydrazino-derivatives proved to be too insoluble to obtain n.m.r. spectra. Substitution at the 2- or 2 and 3-positions was assumed by analogy with the other products of nucleophilic substitution. Some proof was obtained for this assumption in the case of the dihydrazino compound, as the hydrazine groups could be oxidized to give either the corresponding dihydro- or dichloro-derivatives (see 7.3). The $^{19}F$ n.m.r. of both these new compounds showed no resonances at lowfield, attributable to fluorine atoms adjacent to nitrogen. Thus the hydrazino substituents in the original dihydrazino compound must have been at the 2- and 3-positions.

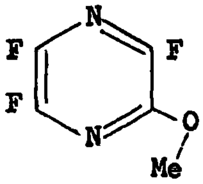
## 8.3. $^{1}H$ n.m.r. of Some Methoxy- and Methyl-Derivatives of Fluoropyrazines.

The $^{1}H$ n.m.r. spectrum of trifluoro-2-methyl pyrazine shows a triplet (coupling constant 2 c./s.) in which the relative peak intensities are 1:2:1. Such a spectrum could only be produced if the methyl protons were coupling equally with two fluorine atoms. The monomethoxyderivative, on the other hand, shows no coupling. Burdon[101] has shown that the methoxyl protons couple with the ortho fluorine atoms in pentafluoroanisole, but that if one of the ortho fluorine atoms is replaced by hydrogen, no coupling is observed. This was thought to be due to the coupling occurring mainly through space,[156] and that perhaps when a substituent, smaller than fluorine, is placed ortho to the methoxyl group, the configuration shown in III is preferred. Thus the possibility for coupling with the remaining ortho fluorine atom is considerably reduced.



III

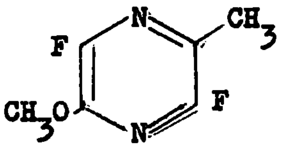
It seems likely that in the case of trifluoromethoxypyrazine a similar configuration is preferred, although in this instance the =CH group has been replaced by an =N group. Thus, the derivative probably exists preferentially as shown in IV.



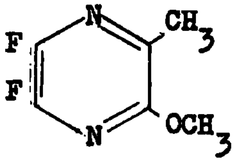
IV

The monomethyl-derivative, however, does not have such rotational modes, and therefore probably couples with the ortho fluorine atom, and also one other fluorine.

Massey[157] suggested that the coupling observed in the proton spectrum of pentafluorotoluene was due to the ortho and para fluorine atoms ($J_{para}$ = 1·5 c./s.: $J_{ortho}$ 2·5 c./s.) rather than the meta fluorine. The $^1H$ n.m.r. spectrum of V showed a singlet which was attributed to the methoxyl protons, and a doublet (J = 2·1 c./s.) due to the methyl protons. This shows that removal of the fluorine atom para to the methyl group eliminates one coupling, confirming that a para fluorine couples with a methyl group in methyl derivatives.



V



VI

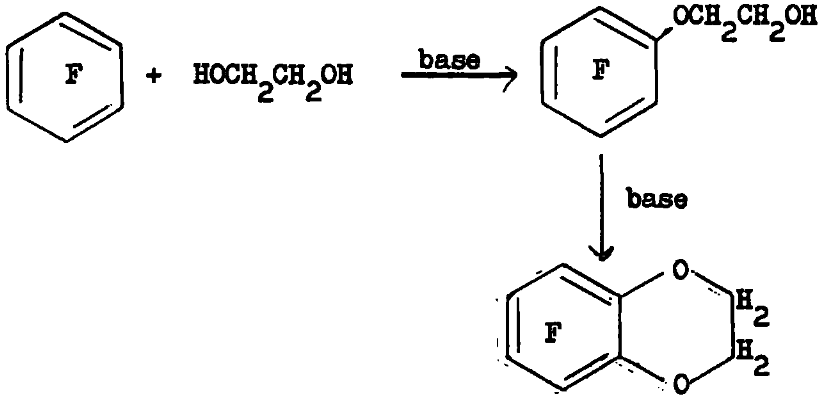
Similarly, the spectrum of VI showed a singlet due to the methoxyl protons, and a doublet (J = 1·9 c.p.s.) which must have been due to the methyl protons coupling with the para fluorine atom, thus confirming that an ortho fluorine atom couples with the methyl protons in the monomethyl-derivative. The spectrum of the dimethyl derivative shows a doublet (J = 2·0 c./s.) which indicates that it cannot be the meta-dimethyl isomer whose n.m.r. spectrum would show a triplet. As was shown in 8.1. the $^{19}$F n.m.r. indicated either a meta or para dimethyl compound, and so elimination of the meta isomer leaves only the para dimethyl derivative.

The $^{1}$H n.m.r. spectrum of the methyldimethoxy-derivative (II) shows a doublet (J = 2·0 c./s.) attributed to the methyl protons as well as two singlets due to the methoxyl protons. Thus, this compound must have a fluorine atom either ortho or para to the methyl group. However, the mode of preparation from the monomethyl-derivative has been shown to involve para substitution leading to the para disubstituted compound, which presumably can then further react with methoxide ion. Therefore, the compound cannot contain a fluorine atom para to the methyl group and must be structure II shown in Table 8.III.

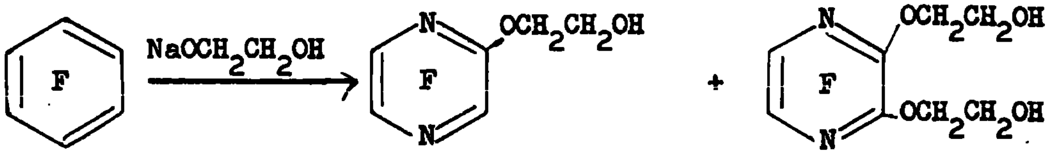
## 8.4. Attempted Chemical Methods.

Several attempts were made to confirm, chemically, the orientation of 2,3-difluoro-5,6-dimethoxypyrazine by demethylation, which would yield the corresponding dihydroxy-derivative. Any one of the standard procedures could then have been used to show that this derivative had adjacent hydroxy groups. However, attempts at demethylation with 50% aqueous hydroiodic acid produced no identifiable products. This is in contrast to the ready demethylation of tetrafluoro-4-methoxypyridine[146] and pentafluoro-2,4-dimethoxyquinoline[144] with this reagent. Similarly, demethylation using aluminium trichloride also failed to give any characterizable product. The approach was therefore not continued.

An attempt was also made to prepare a disubstituted alkoxy-derivative of known orientation. Workers at Birmingham[95] prepared a cyclic ortho-disubstituted derivative of hexafluorobenzene, by using difunctional nucleophiles, such as ethylene glycol, as shown:

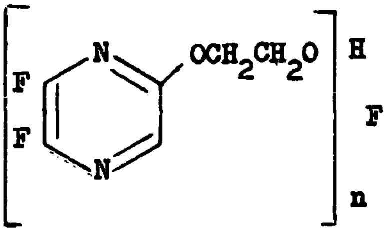


It was hoped, therefore, that a similar fluoropyrazine derivative could be prepared, which would allow a comparison of the $^{19}F$ n.m.r. chemical shift of the dimethoxy-derivative with that of this known ortho-disubstituted compound. The monosubstituted derivative was prepared by the reaction of tetrafluoropyrazine with ethylene glycol monosodium salt. The monosodium salt was prepared by adding sodium hydride to excess dry ethylene glycol, followed by standardization of the solution by titration with dilute acid.

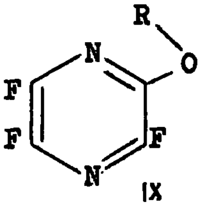


(VIII)

A small amount of the disubstituted product (VIII) was also characterized, whose $^{19}F$ n.m.r. showed a singlet at -51 p.p.m., characteristic of the disubstituted alkoxy-derivatives. Under the conditions used by the Workers at Birmingham[95] (anhydrous potassium carbonate and refluxing D.M.F.), a product was obtained which was shown by its mass spectrum to have a molecular weight exceeding 1000. A solution of this polymer in D.M.S.O. showed a singlet at -51 p.p.m., which suggested that polymerization through substitution at the ortho position, rather than cyclization, had occurred. The polymer could therefore be represented:



Because of this unexpected polymerisation, alternative conditions were tried. However, reaction of an extremely dilute solution of the monosubstituted derivative with one equivalent of base (potassium t-butoxide was used as it was thought less likely to substitute the pyrazine nucleus than other basic reagents) still gave only the same polymeric product. Obviously, the nucleophilic substitution at the ortho position occurs readily, but the intermolecular reaction is more favoured than the intramolecular. One of the factors which may be involved has been discussed in 8.1. On the basis of $^{1}H$ n.m.r. spectra, it was suggested that the preferred configuration of trifluoroalkoxypyrazines is the one in which the C-O bond is angled towards the nitrogen atom, away from the adjacent fluorine. If this is so, then the monosubstituted derivative under discussion would exist predominantly as shown in (IX).



IX

R = $CH_2CH_2OH$

Thus the intermolecular reaction would differ little, sterically, from substitution in the monomethoxy-derivative, while the intramolecular reaction would not be favoured.

As heptafluoroisoquinoline and derivatives can be oxidized by potassium permanganate to the corresponding pyridine-dicarboxylic acids,[108] it was hoped that oxidation of suitable polyfluoroquinoxalines would lead to pyrazine derivatives, of known configuration, which could be related to pyrazines of unknown structure. However, slow addition of an acetone solution of potassium permanganate (1 mole of permanganate per double bond to be oxidized) to either hexafluoroquinoxaline or 2,3-difluoroquinoxaline in acetone produced no identifiable products. Oxidation did occur, as manganese dioxide was precipitated, but possibly indiscriminate oxidation of either ring took place, resulting in a mixture of products. Similar results[158] were obtained when heptafluoroquinoline was oxidized with potassium permanganate in acetone.

# CHAPTER IX

## Reactivity, towards Nucleophilic Substitution, of Tetrafluoropyrazine Relative to Pentafluoropyridine

As nucleophilic substitution is considered to occur via a carbanionic intermediate, a measure of the relative rates of substitution of a series of polyfluoroazines should yield information about the relative stabilities of the transition states involved. As very little work has been done on the quantitative determination of relative rates of substitution, it was thought that a preliminary study of the least reactive of the perfluorodiazines, tetrafluoropyrazine, would provide information which could lead to a more detailed investigation of any features which seemed interesting.

### 9.1. General Theory of the Method.

Workers at Birmingham[159,160] measured the kinetics of substitution in a series of $C_6F_5X$ compounds with $CH_3O^-$, while Tamborski,[161] measured the relative rates of substitution in a series of $C_6F_5X$ compounds with $C_6F_5O^-$. In both these works, the reactions occur at a useful rate at slightly elevated temperatures; however, the perfluorodiazines and -azines react very rapidly with nucleophiles even at room temperature. The measurement of true rates was thought, therefore, not to warrant the development of a suitable experimental procedure. Efforts were directed towards obtaining rate data, relative to pentafluoropyridine.

If two reactants A and B compete for a deficiency of a third species, X;

$$A + X \xrightarrow{K_A} \text{products}$$

$$B + X \xrightarrow{K_B} \text{products}$$

then the ratio of the rate constants, $({}^{K_A}/_{K_B})$, is given by the expression[162]

$$^{K_A}/_{K_B} = \frac{\log_{10}[A]/[A^o]}{\log_{10}[B]/[B^o]}$$

where $[A^o]$ and $[A]$ are the initial and final concentrations of A, and $[B^o]$ and $[B]$ the initial and final concentrations of B. If the volume remains effectively constant throughout the reaction, then the concentrations can be taken as the amounts (i.e. number of moles). Then, if the final amounts can be determined, and knowing the initial amounts, $^{K_A}/_{K_B}$ can be calculated.

This procedure has been previously used to determine the relative reactivity of olefins to free radicals,[162] and by Tamborski[161] to determine relative reactivities of a series of pentafluorophenyl-derivatives. Workers at Durham[163] also used this procedure to determine the relative reactivity of a series of $(C_6F_5)_2X$ and $(C_6F_4)_2X$ compounds. In all these cases, the final amounts of reactants were measured by analysis of the reaction mixtures using g.l.c. In this case, however, the reactants are not separable using the g.l.c. equipment available, and an alternative method of analysis was therefore adopted. The amount (number of moles) of each reactant in the mixture can be determined from the $^{19}F$ n.m.r. spectrum. The number of moles of a compound is directly proportional to the peak area (i.e. integration step height) of a resonance divided by the number of fluorine atoms corresponding to that resonance in the spectrum of the compound. Thus

$$M_Y \propto {}^{S_Y}/_{N_Y}$$

where $M_Y$, $S_Y$ and $N_Y$ are respectively the number of moles of the compound (Y), step height of the chosen resonance in the spectrum, and the number of fluorine atoms corresponding to that particular resonance. Therefore, if a known amount of a standard (R) is introduced into the reaction product mixture, then;

$${}^{M_Y}/_{M_R} = \frac{S_Y}{S_R} \cdot \frac{N_R}{N_Y}$$

$M_Y$ can be calculated as $N_R$ and $N_Y$ are known and $S_Y$ and $S_R$ can be measured. In this way the final amount of both reactants can be determined, and thus ${}^{K_A}/_{K_B}$ calculated.

## 9.2. Experimental Procedure.

An advantage of this type of analysis is that no work-up of the reaction mixture is required; the $^{19}F$ n.m.r. can be measured on an aliquot taken from the final reaction mixture, after addition of the standard.

The initial procedure was to weigh out 400-600 mg. of the two reactants (p-$C_4F_4N_2$ and $C_5F_5N$), in roughly equimolar amounts, since this minimizes the errors, and to transfer them quantitatively to the reaction vessel. This mixture was made up to about 5 ml. with dry methanol and cooled to -23° (carbon tetrachloride/Drikold bath) with stirring under dry nitrogen. After the mixture had been left to stir for a period, to ensure thorough mixing and temperature equilibration, a known weight of solid sodium methoxide was added with stirring under dry nitrogen. The amount of methoxide added was such that there was a deficiency of between 30% and 70%. It follows from the relative rates expression that if reactant analysis is used, rather than product analysis, the higher the conversion then the more reliable is the rate constant ratio so determined.[162] After complete reaction, a known weight of standard, in this case hexafluorobenzene, was introduced quantitatively, and after thorough mixing, an aliquot was removed and the $^{19}F$ n.m.r. spectrum recorded.

Integration of the spectrum was achieved by accumulating about five spectra using a 'Digico C.A.T.', followed by integration of the accumulated spectrum. Use of such an instrument allows weak signals to be multiplied accurately, as it employs a direct multiplication system. In later experiments the amounts of reactants were weighted slightly in favour of the less reactive pyrazine, in order to obtain a better balanced spectrum. A resonance remote from any others can be chosen, thus resulting in a more accurate integration.

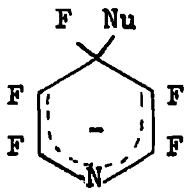
In order to check the method, a blank run was analysed omitting the methoxide. Integration of the spectrum gave a mole ratio of 0·93, while the ratio calculated from the initial weights of the two components was 0·97, indicating a difference of about 3%. Care must be taken to limit the amount of hexafluorobenzene standard, as it is possible to overload the C.A.T. on any particular resonance, and thus distort the integration.

## 9.3. Results and Discussion

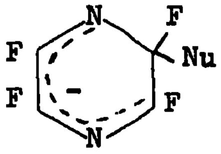
About ten values for the ratio of reactivity of tetrafluoropyrazine to pentafluoropyridine were obtained, all of which were in fair agreement:

$$\frac{K_{p-C_4F_4N_2}}{K_{C_5F_5N}} = 0\cdot12$$

The initial value (0·47) must be divided by four, for statistical reasons, resulting from the fact that tetrafluoropyrazine has four equivalent sites for substitution, compared to one for pentafluoropyridine. This ratio would put the energies of transition states in the order:



more stable than



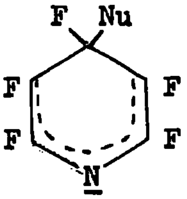
I

II

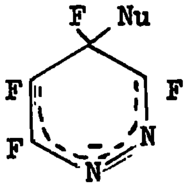
Such a result clearly shows the stabilization gained by localization of the charge on the intermediate onto a para nitrogen atom and shows that a second ring-nitrogen atom, at the meta position, does not compensate greatly for this loss of stabilization. It would be expected, therefore, that tetrafluoropyrazine is slightly more reactive than the 2-position would be in pentafluoropyridine, as the charge para to the point of substitution may be stabilized somewhat by the adjacent second nitrogen atom. In the case of the monohalo=derivatives, 2-chloropyrazine is more reactive than 4-chloropyridine, but in the perfluoro-analogues, the Iπ repulsion of fluorine may increase the energy of the transition state in the pyrazine case, until it is higher than the transition state leading to 4-substitution in pentafluoropyridine.

A consideration of the intermediates (I) and (II) shows that (I) is destabilized by two ortho fluorine atoms and stabilized by the para nitrogen and two metafluorine atoms, while (II) is stabilized by one meta fluorine and one ortho nitrogen atom and destabilized by one ortho and one para fluorine atom.

Two preliminary experiments with tetrafluoropyridazine suggested that it is of the order of 20 times more reactive than pentafluoropyridine, which is in the expected direction. Further stabilization of a transition state by the inductive effect of the second nitrogen atom adjacent to the negative charge has been postulated[164] for the hydrocarbon analogues.



less stable than



Hexafluoroquinoxaline proved to be too insoluble in suitable solvents to obtain useful $^{19}$F n.m.r. spectra, and therefore relative data could not be obtained using this procedure.

# EXPERIMENTAL WORK

# CHAPTER X

## Experimental for Chapter IV

The chloroacetamide, glycine ethyl ester hydrochloride, piperazine hexahydrate, and ortho phenylenediamine were supplied by Koch-Light Laboratories Ltd. and glyoxal (glyoxal monohydrate powder) and diethyl oxalic ester by B.D.H. Chemicals Ltd.

N.M.R. spectra were recorded using a Perkin-Elmer R.10 Spectrometer. Mass spectra were recorded on an A.E.I. M.S.9. mass spectrometer, and ultraviolet spectra on a Unicam SP800 spectrometer. Analytical v.p.c. work was done on a Perkin Elmer 'Fractometer'.

The 240 ml. autoclave consisted of 4•5 cm. internal diameter nickel tube total length 15•0 cm. enclosed in a stainless steel jacket. The autoclave was closed by two nickel end plates sealing onto copper washers. The end plates were reinforced with stainless steel caps to which were attached the Allen screws for sealing. One nickel end plate was fitted with a needle valve vent which passed loosely through the steel reinforcing cap. The 480 ml. autoclave was of identical construction but was of twice the length.

The 3 l. autoclave consisted of a steel cylinder with a base and an external flange on the open end. The inside was fitted with a nickel liner. The head consisted of a stainless steel disc which was seated onto the flange on the body with a corrugated copper gasket and sealed by tightening steel bolts. A needle-valve vent and a thermocouple well were fitted into the head. The 1·5 l. autoclave was of identical construction.

## 10.1. Preparation of 2,5-Diketopiperazine.

This compound was prepared using the method of Viscontini.[129]

Glycine ethyl ester hydrochloride (36 g.) suspended in dry chloroform (200 ml.) was treated with dry ammonia for 2 hrs. The resulting ammonium chloride was filtered, and the solution evaporated at 35°/0·5 mm. to give an oily residue. The oil was added to water (200 ml.) and, after standing for 2 days at room temperature, the mixture was filtered and the product recrystallized from ethanol to give 2,5-diketopiperazine (8 g., 27%), m.p. 146°. (Found: C, 42·0; H, 5·28%; Calc. for $C_4H_6N_2O_2$: C, 42·1; H, 5·26%).

## 10.2. Preparation of Hydroxypyrazine and Chloropyrazine.

These two compounds were prepared by the procedure of Karmas and Spoerri.[127]

## 10.3. Preparation of Pyrazine-2,3-dicarboxylic Acid.

This compound was prepared using the procedure of Jones and McLaughlin.[134]

## 10.4. Preparation of Tetrachloropyrazine (i) from 2,5-Diketopiperazine.

Diketopiperazine (0·68 g., 5·9 m.mole) and phosphorus pentachloride (7·5 g., 36 m.mole) were sealed in an evacuated Carius tube (80 ml.

capacity) and heated to 300° for 12 hr. After cooling the tube was frozen, opened, the contents added to ice (20 g.), and the mixture extracted with ether (2 x 20 ml.). The ether extracts were dried ($MgSO_4$) and evaporated to dryness to give crude tetrachloropyrazine. Recrystallization from ethanol gave tetrachloropyrazine (0·3 g., 46%), m.p. 98° - 99° (lit.,[126] 97-99°) (Found: C, 22·1; Cl, 65·0. Calc. for $C_4Cl_4N_2$: C, 22·0; Cl, 65·1%), I.R. spectrum No. 1, $\lambda_{max}$ (cyclohexane) 231, 272, 305, 309 and 315 mμ (log $\epsilon$ 3·77, 2·97, 3·67, 3·70, and 3·63).

(ii) from Hydroxypyrazine or Chloropyrazine. Hydroxypyrazine (1·06 g.) and phosphorus pentachloride (13·0 g.) or chloropyrazine (2·6 g.) and phosphorus pentachloride (25·0 g.) were heated in Carius tubes (80 ml. capacity) and the product isolated as described above to give tetrachloropyrazine (1·3 g., 58%) and (4·0 g., 80%) respectively.

(iii) from Piperazine Dihydrochloride. Piperazine dihydrochloride (0·88 g.) and phosphorus pentachloride (15 g.) were sealed in an evacuated Carius tube (capacity 120 ml.) and heated at 320° for 12 hrs. The products were isolated as described above in 10·4(i) to give tetrachloropyrazine (0·94 g., 78%). Alternatively, piperazine dihydrochloride (36·5 g., 0·23 mole) and phosphorus pentachloride (360 g., 1·84 mole) were closed in vacuo in a nickel-lined autoclave

(3·0 l. capacity) and heated to 320° for 18 hrs. The autoclave was cooled, vented, and its contents added to ice. The mixture was extracted with ether, the extracts washed with water, dried ($MgSO_4$) and evaporated. The residue was distilled <u>in vacuo</u> to give tetrachloropyrazine (16·6 g.), b.p. 100°/0·1 mm., recrystallization from light petroleum (b.p. 80–100°) gave colourless plates (14·0 g., 25%), m.p. 99–100·5°.

(iv) <u>from Pyrazine-2,3-dicarboxylic Acid.</u> Pyrazine dicarboxylic acid (72 g., 0·43 mole) and phosphorus pentachloride (600 g., 2·9 mole) were closed <u>in vacuo</u> in a nickel-lined autoclave (capacity 1·5 l.) and heated to 300° for 8 hr. The product was isolated as described above, in 10.4(iii) for the large scale chlorination of piperazine dihydrochloride to give tetrachloropyrazine (73 g., 80%), m.p. 99–100°.

## 10.5. <u>Preparation of Tetrafluoropyrazine.</u>

Tetrachloropyrazine (65 g., 0·30 mole) and freshly dried potassium fluoride (300 g., 5·2 mole) were closed <u>in vacuo</u> in a nickel-lined autoclave (480 ml. capacity) and heated to 310–320° for 15 hr. The contents of the autoclave were pumped out into a cold trap and the condensate (42 g., 95%) was shown by g.l.c. (ether solution on dinonyl phthalate at 100°) to be pure <u>tetrafluoropyrazine</u>, m.p. 53–54° [Found: C, 31·0; F, 49·5%; <u>m</u> (mass spectrum), 152. $C_4F_4N_2$ requires:

C, 31·6; F, 50·0%; m, 152], I.R. Spectrum No.2, $\lambda_{max}$ (cyclohexane) 280 mμ.

## 10.6. Preparation of Chlorofluoropyrazines.

(i) Tetrachloropyrazine (5·0 g., 23·0 m.mole) and freshly dried potassium fluoride (50 g., 0·85 mole) were sealed in vacuo in a Carius tube and heated to 280° for 9 hr. After cooling, the contents of the tube were pumped out into a cold trap and the mixture of products separated by g.l.c. (ether solution on di-nonylphthalate at 150°C) to give tetrafluoropyrazine (0·8 g., 20%), chlorotrifluoropyrazine (1·8 g., 48%), m.p. 61-63° (Found: C, 28·5; Cl, 21·1; F, 34·0%; m, 168. $C_4ClF_3N_2$ requires C, 28·6; Cl, 21·1; F, 33·9%; m, 168), I.R. Spectrum No.3, $\lambda_{max}$ (cyclohexane) 288 mμ (log ε 2·74), and dichlorodifluoropyrazine (1·1 g., 25%), m.p. 69-72° (Found: C, 25·8; Cl, 38·3; F, 21·1%; m, 184. $C_4Cl_2F_2N_2$ requires C, 26·0; Cl, 38·4; F, 20·5%; m, 184), I.R. Spectrum No.4, $\lambda_{max}$ (cyclohexane) 218, 248 and 294 mμ (log ε 2·78, 1·98, 2·87).

(ii) Similarly, tetrachloropyrazine (10·0 g., 46·0 m.mole) and potassium fluoride (100 g., 1·7 mole) heated to 250° for 10 hr. gave tetrafluoropyrazine (0·7 g., 10%), chlorotrifluoropyrazine (0·9 g., 12%), dichlorodifluoropyrazine (2·1 g., 25%), and trichlorofluoropyrazine (4·8 g., 52%), m.p. 76-77° (Found: C, 24·0; Cl, 52·1; F, 9·8%; m, 200. $C_4Cl_3FN_2$ requires C, 23·8; Cl, 52·9; F, 9·44%; m, 200), I.R.

Spectrum No.5, $\lambda_{max}$ (cyclohexane) 298 mµ (log $\varepsilon$ 2·97).

## 10·7. Preparation of 2,3-Dihydroxy- and 2,3-Dichloroquinoxaline.

These compounds were prepared by the procedure of Stephens, Pfister and Wolf.[119]

## 10.8. Preparation of Hexachloroquinoxaline.

2,3-Dichloroquinoxaline (100 g., 0·5 mole) and phosphorus pentachloride (600 g., 2·9 mole) were closed *in vacuo* in a nickel lined autoclave (1·5 l. capacity) and heated to 300° for 17 hr. The autoclave was cooled, vented, and its contents added to ice. The mixture was extracted with ether, the extract was washed, dried ($MgSO_4$) and evaporated. The residue was recrystallized from benzene to give *hexachloroquinoxaline* (152 g., 90%), m.p. 200-201° (Found: C, 27·9; Cl, 63·8%; m, 334. $C_8Cl_6N_2$ requires C, 28·5; Cl, 63·2%; m, 334), I.R. Spectrum No. 6, $\lambda_{max}$ (ethanol) 267, 323, 337 and 351 mµ.

## 10,9. Preparation of Hexafluoroquinoxaline and 5-Chloropentafluoroquinoxaline.

Hexachloroquinoxaline (60 g., 0·14 mole) and freshly dried potassium fluoride (400 g., 6·9 mole) were closed *in vacuo* in a stainless steel autoclave (700 ml. capacity) and heated to 380° for 19 hrs. The contents of the autoclave were pumped out into a cold trap and the condensate fractionally distilled through a concentric tube column to give *hexafluoroquinoxaline* (20·2 g., 47%), m.p. 142-143°, b.p. 196-198°/760 mm. (Found: C, 40·2; F, 48·5%; m, 238. $C_8F_6N_2$ requires C, 40·6; F, 47·9%; m, 238), I.R. Spectrum No.7, $\lambda_{max}$ (cyclohexane) 239, 305·5, 312·5 and 318 mμ (log ε 4·47, 3·61, 3·61 and 3·57), and 5-chloropentafluoroquinoxaline (1·9 g., 4%), m.p. 119-120° (Found: C, 38·0; Cl, 12·9; F, 37·4%; m, 254. $C_8ClF_5N_2$ requires C, 37·7; Cl, 13·2; F, 37·3%; m, 254), I.R. Spectrum No.8, $\lambda_{max}$ (cyclohexane) 242, 308, 314·5 and 320 mμ (log ε 4·43, 3·70, 3·71 and 3·67).

## 10.10. Preparation of 2,3-Difluoroquinoxaline.

2,3-Dichloroquinoxaline (20 g., 0·1 mole) and freshly dried potassium fluoride (36·5 g., 0·63 mole) in dry sulpholan (150 ml.) were heated to 190° with stirring for 24 hr. The mixture was cooled, added to water (500 ml.) and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$) and evaporated to dryness. The solid residue was twice sublimed at 20°/·01 mm. to give 2,3-difluoroquinoxaline (9·8 g., 59%), m.p. 94-95° (Found: C, 57·5; H, 2·42; F, 22·7%; m, 166. $C_8H_4F_2N_2$ requires C, 57·8; H, 2·41; F, 22·9%; m, 166), I.R. Spectrum No.9, $\lambda_{max}$ (cyclohexane) 239sh, 242, 246, 307, 313, 320, 327 and 335 (log ε 4·39, 4·50, 4·45, 3·78, 3·83, 3·91, 3·87 and 3·98).

# CHAPTER XI

## Experimental for Chapters V and VI

### 11.1. Preparation of Trifluoro-2-methoxypyrazine.

Tetrafluoropyrazine (5·0 g.) in methanol (20 ml.) was treated dropwise with methanolic sodium methoxide (20 ml., 1·63M; 1 mol.) during 30 min. with stirring at -20°. The mixture was stirred for a further 30 min. at -20°, allowed to reach room temperature during 30 min., poured into water and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The oily residue was distilled to give the monomethoxy-derivative (3·3 g., 60%), b.p. 142°/760 mm. (Found: C, 36·3; H, 1·79; F, 34·6%; m, 164. $C_5H_3F_3N_2O$ requires C, 36·6; H, 1·85; F, 34·8%; m, 164), I.R. Spectrum No.10, $\lambda_{max}$ 207, 225sh and 293 mμ (log $\varepsilon$ 3·59, 2·82 and 3·83).

### 11.2. Preparation of 2-Ethoxytrifluoropyrazine.

Tetrafluoropyrazine (2·93 g.) in ethanol (20 ml.) was treated dropwise, at -10°, with ethanolic sodium ethoxide (20 ml., 0·95M; 0·99 mol.) as in the previous experiment. The product was similarly isolated to give the ethoxy-derivative (1·93 g., 55%), b.p. 148-152°/760 mm. (Found: C, 40·2; H, 2·90; F, 32·1%; m, 178. $C_6H_5F_3N_2O$ requires C, 40·5; H, 2·81; F, 32·0%; m, 178), I.R. Spectrum No.11, $\lambda_{max}$ (cyclohexane) 216 and 296 mμ.

### 11.3. Preparation of 2-t-Butoxytrifluoropyrazine.

Tetrafluoropyrazine (5·0 g.) in dry ether (10 ml.) was treated dropwise, at -20°, with butanolic sodium <u>t</u>-butoxide (20 ml., 2·0M; 1·2 mol.) as described above and the product similarly isolated to give the <u>mono-t-butyl-derivative</u> (5·1 g., 75%), b.p. 42°/0·05 mm. (Found: C, 46·8; H, 4·17; F, 27·8%; <u>m</u>, 206. $C_8H_9F_3N_2O$ requires C, 46·6; H, 4·37; F, 27·2%; <u>m</u>, 206), I.R. Spectrum No.12, $\lambda_{max}$ (cyclohexane) 308 mμ (log ε 3·74).

## 11.4. <u>Preparation of 2-Aminotrifluoropyrazine.</u>

Tetrafluoropyrazine (3·9 g.) was stirred with aqueous ammonia (d. 0·880; 20 ml.) for 8 hr. at room temperature. The mixture was extracted with ether, the extract washed with water, dried ($MgSO_4$) and evaporated. The residue was sublimed at 25°/0·01 mm. to give the <u>monoamino derivative</u> (2·2 g., 58%), m.p. 70-71° (Found: C, 32·3; H, 1·54; F, 37·7%; <u>m</u>, 149. $C_4H_2F_3N_3$ requires C, 32·2; H, 1·34; F, 38·25%; <u>m</u>, 149), I.R. Spectrum No.13, $\lambda_{max}$ (ethanol) 222 and 317 mμ (log ε 3·82 and 3·56).

## 11.5. <u>Preparation of Trifluoro-2-hydroxypyrazine.</u>

Tetrafluoropyrazine (2·0 g.), potassium hydroxide (2·0 g.) and dry t-butanol (40 ml.) were heated under reflux for 15 hr. The solvent was evaporated to ca. 20 ml. and water (20 ml.) was added. The remaining t-butanol was then evaporated, the mixture acidified with hydrochloric acid (15 ml., 36%), and extracted with ether. The extract was dried ($MgSO_4$), evaporated, and the residue sublimed at 25°/0·01 mm. to give the <u>hydroxy derivative</u> (1·07 g., 60%), m.p. 79-81°

(Found: C, 31·7; H, 0·67; F, 37·8%; <u>m</u>, 150. $C_4HF_3N_2O$ requires C, 32·0; H, 0·67; F, 38·0%; <u>m</u>, 150), I.R. Spectrum No.14 $\lambda_{max}$ (cyclohexane) 225sh and 294 mµ (log $\varepsilon$ 2·82 and 3·83).

### 11.6. <u>Preparation of Trifluoro-2-hydrazinopyrazine</u>.

Tetrafluoropyrazine (5·0 g.) in ethanol (20 ml.) was treated dropwise with a solution of hydrazine hydrate (2·0 g., 1·2 mol.) in ethanol (20 ml.) during 5 min. The mixture was stirred for a further 5 min., added to water (100 ml.) and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated. The residue was sublimed at 20°/0·01 mm. to give the <u>monohydrazino-derivative</u> (2·1 g., 40%), m.p. 48-50° (Found: C, 29·8; H, 1·70; F, 34·9%; <u>m</u>, 164. $C_4H_3F_3N_4$ requires: C, 29·3; H, 1·82; F, 34·8%; <u>m</u>, 164), I.R. Spectrum No.15, $\lambda_{max}$ (ethanol) 310 mµ.

### 11.7. <u>Preparation of Trifluoro-2-methylpyrazine.</u>

i) Tetrafluoropyrazine (5·0 g.) in ether (10 ml.) was treated dropwise with ethereal methyl-lithium (68 ml., 0·5M; 1·03 mol.) during 30 min. with stirring at -70° under an atmosphere of dry nitrogen. The mixture was stirred for a further 30 min. at -70°, allowed to reach room temperature during 1 hr., and diluted with water. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The oily residue was distilled to give the <u>monomethyl-derivative</u> (3·5 g., 70%), b.p. 115°/760 mm. (Found: C, 40·5; H, 2·7; F, 38·4%;

m, 148. $C_5H_3F_3N_2$ requires C, 40·5; H, 2·72; F, 38·5%; m, 148), I.R. Spectrum No.16, $\lambda_{max}$ (cyclohexane) 247 and 280 mμ (log ε 2·95 and 3·85).

ii) In a similar experiment in which tetrafluoropyrazine (5·0 g.) was treated as described with ethereal methyl lithium (120 ml., 0·6M; 2·2 mol), separation of the reaction mixture by g.l.c. (ether solution on di-nonylphthalate at 150°) gave the monomethyl-derivative (3·0 g., 61%), the 3,6-dimethyl-derivative (0·3 g., 3%), b.p. 131-134° (m, 144). I.R. Spectrum 17, and a trace amount of a third product whose mass spectrum indicated a second difluorodimethylpyrazine.

## 11.8. Preparation of n-Butylfluoropyrazines.

Tetrafluoropyrazine (5·0 g.) in dry ether (20 ml.) was treated dropwise with n-butyl-lithium in hexane (13 ml., 2·6M; 1·02 mol.) during 40 min. with stirring at -70°. The mixture was stirred for a further 30 min. at -70°, allowed to reach room temperature during 1 hr., and diluted with water. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The oily residue was fractionally distilled to give the tri-n-butyl-derivative (3·3 g., 40%), b.p. 70°/760 mm. (Found: C, 72·0; H, 10·15; F, 7·1%; M, 266. $C_{16}H_{27}FN_2$ requires C, 72·2; H, 10·15; F, 7·1%; m, 266), I.R. Spectrum No.18, $\lambda_{max}$ (cyclohexane) 279 mμ (log ε 3·16), the mono-n-butyl-derivative (1·85 g., 30%) b.p. 170°/760 mm. (Found: C, 50·3; H, 4·74; F, 30·1%;

*m*, 190. $C_8H_9F_3N_2$ requires C, 50·5; H, 4·74; F, 30·0%; *m*, 190), I.R. Spectrum No.19, $\lambda_{max}$ (cyclohexane) 281 mμ (log $\varepsilon$ 3·87). The less volatile residue was distilled *in vacuo* to give the *2,5-di-n-butyl-derivative* (0·9 g., 10%), b.p. 49-50°/·025 mm. (Found: C, 52·8; H, 7·9; F, 16·6%; *m*, 228. $C_{12}H_{18}F_2N_2$ requires C, 52·6; H, 7·89; F, 16·7%; *m*, 228), I.R. Spectrum No.20, $\lambda_{max}$ (cyclohexane) 285 mμ (log $\varepsilon$ 4·02).

## 11.9. Preparation of 2,3-Difluoro-5,6-dimethoxypyrazine.

Tetrafluoropyrazine (4·99 g.) in methanol was treated dropwise with methanolic sodium methoxide (30 ml., 2·32M; 2·1 mol.) during 30 min. with stirring at ca. 20°. The mixture was stirred for a further 30 min., at the same temperature, poured into water and extracted with ether. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was sublimed at 20°/0·01 mm. to give the *dimethoxy-derivative* (5·15 g., 90%), m.p. 79-81° (Found: C, 41·2; H, 3·49; F, 21·5%; *m*, 176. $C_6H_6F_2N_2O_2$ requires C, 40·9; H, 3·41; F, 21·6%; *m*, 176), I.R. Spectrum No.21, $\lambda_{max}$ 217 and 305 mμ (log $\varepsilon$ 3·94 and 3·87).

## 11.10. Preparation of 2-Ethoxy-5,6-difluoro-3-methoxypyrazine.

Trifluoro-2-methoxypyrazine (0·63 g.) in methanol (5·0 ml.) was treated as in 11.9 with ethanolic sodium ethoxide (2·5 ml., 1·54M; 1·0 mol.). The product was similarly isolated and sublimed at

$20^{\circ}$/0·01 mm. to give 2-ethoxy-5,6-difluoro-3-methoxypyrazine (0·54 g., 75%), m.p. 26-$28^{\circ}$ (Found: C, 44·6; H, 4·24; F, 19·9%; m, 190. $C_7H_8F_2N_2O_2$ requires C, 44·2; H, 4·21; F, 20·0%; m, 190). I.R. Spectrum No.22, $\lambda_{max}$ (cyclohexane) 219 and 308 mμ (log $\varepsilon$ 3·99 and 3·90).

## 11.11. Preparation of 2,3-Difluoro-5-methoxy-6-methylpyrazine.

Trifluoro-2-methoxypyrazine (1·5 g.) in ether (5 ml.) was treated dropwise with ethereal methyl lithium (25 ml., 0·4M; 1·1 mol.) during 30 min. with stirring at $-40^{\circ}$ under an atmosphere of dry nitrogen. The mixture was stirred for a further 30 min., at $-40^{\circ}$, allowed to reach room temperature during 30 min., and diluted with water (20 ml.). The ether layer was washed with water, dried ($MgSO_4$), and evaporated. The oily residue was distilled in vacuo to give 2,3-difluoro-5-methoxy-6-methylpyrazine (1·1 g., 90%), b.p. $48^{\circ}$/0·5 mm. (Found: C, 45·2; H, 3·76; F, 23·9%; m, 160. $C_6H_6F_2N_2O$ requires C, 45·0; H, 3·75; F, 23·8%; m, 160), I.R. Spectrum No.23, $\lambda_{max}$ (cyclohexane) 246·5 and 297 mμ (log $\varepsilon$ 2·79 and 4·46).

## 11.12. Preparation of 2,5-Difluoro-3-methoxy-6-methylpyrazine.

Trifluoro-2-methylpyrazine (1·0 g.) in methanol (10 ml.) was treated dropwise, at $-40^{\circ}$, with methanolic sodium methoxide (7·8 ml., 0·92M; 1·05 mol.) during 30 min. with stirring. The mixture was stirred at $-40^{\circ}$ for a further 30 min., allowed to reach room temperature during 1 hr., poured into water and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and evaporated. The oily residue was distilled in vacuo to give 2,5-difluoro-3-methoxy-6-methylpyrazine (0·9 g., 85%), b.p. 55°/0·5 mm. (Found: C, 44·8; H, 3·78; F, 23·35%; m, 160), I.R. Spectrum No. 24, $\lambda_{max}$ (cyclohexane) 242·5 and 293·5 mμ (log ε 2·81 and 3·89).

## 11.13. Preparation of 2-Fluoro-5,6-dimethoxy-3-methylpyrazine.

Trifluoro-2-methylpyrazine (0·8 g.) in dry methanol (5 ml.) was treated as described in 11.12. with methanolic sodium methoxide (6 ml., 2·0M; 2·2 mol.). The product was similarly isolated and sublimed at 25°/0·01 mm. to give 2-fluoro-5,6-dimethoxy-3-methylpyrazine (0·5 g., 55%) m.p. 77-79° (Found: C, 48·9; H, 5·20; F, 11·2%; m, 172. $C_7H_9FN_2O_2$ requires C, 48·8; H, 5·23; F, 11·1%; m, 172), I.R. Spectrum No.25, $\lambda_{max}$ (cyclohexane) 221 and 303 mμ (log ε 3·94 and 3·93).

## 11.14. Difluoro-bisphenylthiopyrazine.

Tetrafluoropyrazine (2·0 g.) in N-methyl-2-pyrrolidone (10 ml.) was treated with sodium thiophenate (3·5 g., 2·0 mol.) in the same solvent (10 ml.) during 10 min. with stirring at ca. 25°. The mixture was poured into water and the resulting precipitate was separated and recrystallized from ethyl acetate to give a bisphenylthio-derivative (2·85 g., 70%), m.p. 182-184° (Found: C, 57·8; H, 3·0; F, 11·6%; m, 332. $C_{16}H_{10}F_2N_2S_2$ requires C, 57·8; H, 3·0; F, 11·45%; m, 332), I.R. Spectrum No.26, $\lambda_{max}$ (ethanol) 244 and 301 mμ.

## 11.15. 2-Chloro-3,6-difluoro-5-methoxypyrazine.

2-Chlorotrifluoropyrazine (0·5 g.) in methanol (10 ml.) was treated dropwise, at -15°, with methanolic sodium methoxide (3·2 ml., 0·93M; 1·0 mol.) during 30 min. with stirring. The mixture was stirred for a further 30 min. at -15°, allowed to reach room temperature over 30 min., poured into water and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and evaporated. The oily residue was distilled to give 2-chloro-3,6-difluoro-5-methoxypyrazine (0·5 g., 90%), b.p. 156-157°/760 mm. (Found: C, 33·4; H, 1·68; Cl, 19·8; Cl, 19·8; F, 21·1%; m, 180. $C_5H_3ClF_2N_2O$ requires C, 33·3; H, 1·7; Cl, 19·7; F, 21·1%; m, 180), I.R. Spectrum No.27, $\lambda_{max}$ (cyclohexane) 220 and 299 mμ.

## 11.16. Preparation of Pentafluoro-2-methoxyquinoxaline.

Hexafluoroquinoxaline (1·0 g.) in methanol (20 ml.) was treated dropwise, at -20°, with methanolic sodium methoxide (7·3 ml., 1·0M; 1·0 mol.) during 30 min. with stirring. The mixture was stirred for a further 10 min. at -20°, allowed to reach room temperature during 15 min. and poured into water. The mixture was extracted with ether, the ether extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was sublimed at 20°/0·001 mm. to give the monomethoxy-derivative (·81 g., 80%), m.p. 70-72. (Found: C, 43·5; H, 1·1; F, 38·6%; m, 250. $C_9H_3F_5N_2O$ requires C, 43·2; H, 1·2; F, 38·0%; m, 250), I.R. Spectrum No.28, $\lambda_{max}$ (cyclohexane) 243·5 and 312 mμ (log $\varepsilon$ 4·48 and 3·70).

## 11.17. Preparation of Tetrafluoro-2,3-dimethoxyquinoxaline.

Hexafluoroquinoxaline (1·0 g.) in methanol (15 ml.) was treated with methanolic sodium methoxide (14·6 ml., 1·0M; 2·0 mol.), at 18°, as described in the previous experiment. The product, similarly isolated, was sublimed at 60°/0·001 mm. to give the dimethoxy-derivative as colourless needles (·86 g., 85%), m.p. 146-148°. (Found: C, 45·6; H, 2·0; F, 28·6%; m, 262. $C_{10}H_6F_4N_2O_2$ requires C, 45·8; H, 2·3; F, 29·0%; m, 262), I.R. Spectrum No.29, $\lambda_{max}$ (cyclohexane) 222·5, 246, 284·5, 291, 296, 303, 309, 316 and 323 mμ (log $\varepsilon$ 4·14, 4·42, 3·47, 3·54, 3·68, 3·73, 3·90, 3·76 and 3·91.

## 11.18. Preparation of Trifluoro-2,3,6-trimethoxyquinoxaline.

2,3-Dimethoxyquinoxaline (1·0 g.) and methanolic sodium methoxide (2·5 m/ml., 1·63M; 1·07 mol.) were sealed in a Carius tube and heated to 120° for 18 hr. The tube was cooled, opened, the contents added to water and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was sublimed at 60°/·001 mm. to give trifluoro-2,3,6-trimethoxyquinoxaline (0·9 g., 68%) m.p. 132-134° (Found: C, 42·7; H, 3·0; F, 21·0%; m, 274. $C_{11}H_9F_3N_2O_3$ requires C, 42·6; H, 2·90; F, 20·8%; m, 274), I.R. Spectrum No.30, $\lambda_{max}$ (cyclohexane) 245 and 311 mμ (log $\varepsilon$ 4·34 and 3·60).

## 11.19. Preparation of Tetrafluoro-2,3-dihydroxyquinoxaline.

Hexafluoroquinoxaline (1 g.), potassium hydroxide (2·0 g.) and dry t-butanol (40 ml.) were heated under reflux for 15 hr. The solvent was evaporated to ca. 20 ml. and water added. The remaining t-butanol was then evaporated, the mixture acidified with hydrochloric acid (15 ml., 36%), and the precipitate filtered. The residue was recrystallized from ethyl acetate to give the 2,3-dihydroxy-derivative (0·55 g., 56%) m.p. > 300° decomp. (Found: C, 41·0; H, 0·79; F, 32·7%; m, 234. $C_8H_2F_4N_2O_2$ requires C, 41·0; H, 0·85; F, 32·5%; m, 234). I.R. Spectrum No.31, $\lambda_{max}$ (ethanol) 227, 235, 303 and 316 mμ (log ε 4·01, 3·90, 3·94 and 3·83).

## 11.20. Preparation of 2-Aminopentafluoroquinoxaline.

Hexafluoroquinoxaline (1·0 g.) in ethanol (10 ml.) was treated dropwise, at room temperature, with aqueous ammonia (15 ml., d. 0·880) in ethanol (15 ml.) during 10 min. with stirring. The mixture was stirred at room temperature for a further 15 min., added to water and the resulting precipitate filtered. The filtrate was dried in air and recrystallized from D.M.S.O. to give the 2-amino-derivative (0·76 g., 77%) m.p. > 320 (Found: C, 41·1; H, 0·72; F, 41·0%; m, 235. $C_8H_2F_5N_3$ requires C, 40·9; H, 0·85; F, 40·4%; m, 235). I.R. Spectrum No.32.

## 11.21. Preparation of Tetrafluoro-2,3-dihydrazinoquinoxaline.

Hexafluoroquinoxaline (1·0 g.) in ethanol (10 ml.) was treated dropwise, at room temperature, with hydrazine hydrate (1 g.) in ethanol (10 ml.) during 5 min. with stirring. The mixture was stirred for a further 30 min. at room temperature, added to water and the resulting precipitate filtered. The filtrate was dried in air and recrystallized from hot ethyl acetate to give the 2,3-dihydrazino-derivative (1·05 g., 95%), m.p. 280 decomp. (Found: C, 36·1; H, 2·17; F, 29·4%; m, 262. $C_8H_6F_4N_6$ requires C, 36·6; H, 2·29; F, 29·0%; m, 262). I.R. Spectrum No.33.

## 11.22. Substitution of Tetrafluoropyrazine by Methanol in Concentrated Sulphuric Acid.

Tetrafluoropyrazine (2 g.) in concentrated sulphuric acid (30 ml.) was treated dropwise, at room temperature, with methanol (100 ml.) during 2 hr. with stirring. The mixture was poured into excess water, extracted with ether, and the ether extract washed with water, dried ($MgSO_4$) and evaporated. The residue was distilled to give trifluoro-2-methoxypyrazine (1·29 g., 60%), b.p. 142°/760 mm. Spectral and elemental analysis showed that the compound was identical to the monomethoxy-derivative prepared by the action of methanolic sodium methoxide on tetrafluoropyrazine at reduced temperatures.

## 11.23. Preparation of Dibromodifluoropyrazine and Tetrabromopyrazine.

Tetrafluoropyrazine (8·6 g.), freshly sublimed aluminium tribromide

(15·4 g.), and hydrogen bromide (4·74 g.) were sealed in an evacuated Carius tube (capacity 100 ml.) and heated to 100° for 48 hr. The tube was cooled, frozen in liquid air, opened and its contents added to ice. The mixture was extracted with ether, and the extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was sublimed at 20°/0·01 mm. to give a *dibromodifluoropyrazine* (1·7 g., 11%) m.p. 51-52° (Found: C, 17·5; Br, 61·0; F, 14·6%; *m*, 274. $C_4Br_2F_2N_2$ requires C, 17·5; Br, 58·4; F, 13·8%; *m*, 274), I.R. Spectrum No.34, $\lambda_{max}$ (cyclohexane) 218, 240 and 290 mµ (log $\varepsilon$ 2·61, 1·90 and 2·94).

The less volatile residue was further sublimed at 100°/0·01 mm. and recrystallized from light petroleum (b.p. 80-100°) to give *tetrabromopyrazine* (9·2 g., 41%) m.p. 148-149° (Found: C, 12·1; Br, 81·1%; *m*, 396. $C_4Br_4N_2$ requires C, 12·1; Br, 80·8%; *m*, 396), I.R. Spectrum No.35, $\lambda_{max}$ (cyclohexane) 246, 283, 312·5, and 323 mµ (log $\varepsilon$ 5·09, 4·49, 5·05 and 4·96).

### 11·24. Substitution of Trifluoromethoxypyrazine by Methanol in Concentrated Sulphuric Acid.

Trifluoromethoxypyrazine (2 g.) in concentrated sulphuric acid (30 ml., d. 1·8 ) was treated dropwise, at room temperature, with methanol (100 ml.) during 2 hrs. with stirring. The mixture was poured into water, extracted with ether and the ether extract washed with water, dried ($MgSO_4$) and evaporated. The residue was sublimed at 20°/0·01 mm. to give a dimethoxy-derivative, m.p. 79-80°. Spectral and elemental analysis showed this compound to be identical with that prepared by the addition of excess methanolic sodium methoxide to tetrafluoropyrazine at room temperature.

## 11.25. Methylation of Trifluoro-2-hydroxypyrazine.

Trifluoro-2-hydroxypyrazine (0·50 g.) in ether (10 ml.) was treated with ethereal diazomethane with stirring at ca. 20° until there was no further effervescence and the pale yellow colour persisted. The mixture was stirred for a further 1 hr. at ca. 20° and the ether evaporated. The liquid residue was shown by g.l.c. (di-n-decyl-phthalate at 150°) to be a single compound which was vacuum transferred to give the pure monomethoxy-derivative (0·41 g., 71%), b.p. 141-142°. Comparison, by g.l.c., of this product with an authentic sample of trifluoromethoxypyrazine indicated that they had identical retention times while the $^{19}F$ n.m.r. spectrum revealed that the compound was identical with the authentic sample.

## 11.26. Methylation of Tetrafluoro-2,3-dihydroxyquinoxaline.

Tetrafluoro-2,3-dihydroxyquinoxaline (1·0 g.) suspended in ether (150 ml.) was treated with ethereal diazomethane with stirring at 0° until there was no further effervescence and the pale yellow colour persisted. The resulting clear solution was stirred for a further 3 hr. at ca. 20° and concentrated. The solution was shown by g.l.c. (silicone elastomer at 230°) to contain a single product whose retention time differed from that of the known 2,3-dimethoxy-derivative. The solution was evaporated and the residue sublimed at 40°/·01 mm. to give tetrafluoro-1,4-dimethylquinoxaline-2,3-dione (0·95 g., 85%), m.p. 134-136° (Found: C, 45·7; H, 2·26; F, 29·4%; m, 262. $C_{10}H_6F_4N_2O_2$ requires C, 45·8; H, 2·29; F, 29·0%; m, 262), I.R. Spectrum No.36, $\lambda_{max}$ (ethanol) 230, 245sh, 307 and 315sh mμ (log $\varepsilon$ 4·18, 4·15, 3·90 and 3·84).

# CHAPTER XII

## Experimental for Chapter VII

### 12.1. Preparation of 4-Chlorotetrafluoropyridine.

(i) Tetrafluoro-4-hydrazinopyridine (5 g.) was added to a solution of ferric chloride (25 g.) in hydrochloric acid (100 ml., 36%) during 30 min. with stirring at room temperature. The mixture was stirred for a further 30 min. at room temperature and distilled until about 40 ml. of distillate had been collected. The distillate was extracted with ether, the ether extract dried ($MgSO_4$), and evaporated. The residue was distilled to give 4-chlorotetrafluoropyridine (1·7 g., 33%) b.p. 120-122° (Found: C, 32·0; Cl, 19·2; F, 40·8%; Calc. for $C_5ClF_4N$: C, 32·3; Cl, 19·1; F, 41·0%).

(ii) Tetrafluoro-4-hydrazinopyridine (3·0 g.) was added to a solution of cupric chloride (20 g.) in hydrochloric acid (80 ml., 36%). The product was isolated similarly to above to give 4-chlorotetrafluoropyridine (2·4 g., 77%) b.p. 120-123°.

### 12.2. Preparation of 4-Bromotetrafluoropyridine.

(i) Tetrafluoro-4-hydrazinopyridine (3·0 g.) was added to a solution of ferric bromide (20 g.) in hydrobromic acid (80 ml., 50%). The product was isolated as described in 12(i) to give 4-bromotetrafluoropyridine (1·33 g., 35%), b.p. 133-135° (Found: C, 26·3; Br, 34·6; F, 33·4%; Calc. for $C_5BrF_4N$: C, 26·1; Br, 34·8; F, 33·0%).

(ii) Tetrafluoro-4-hydrazinopyridine (3·0 g.) was added slowly to a solution of cupric bromide (20 g.) in hydrobromic acid (80 ml., 50%). The product was isolated as described above in 12(i) to give 4-bromotetrafluoropyridine (2·9 g., 76%) b.p. 132-135°.

## 12.3. Preparation of 2-Chlorotrifluoropyrazine.

Trifluoro-2-hydrazinopyrazine (1·2 g.) was added to a solution of cupric chloride (10 g.) in hydrochloric acid (40 ml., 36%). The mixture was distilled until ca. 20 ml. of distillate had been collected. The distillate was extracted with ether, the ether extract dried ($MgSO_4$) and evaporated. The residue was sublimed at 20°/·01 mm. to give chlorotrifluoropyrazine (0·95 g., 77%), m.p. 61-63°. Analysis showed it to be identical with a sample obtained from the low temperature fluorination of tetrachloropyrazine with potassium fluoride.

## 12.4. Preparation of 2-Bromotrifluoropyrazine.

Trifluoro-2-hydrazinopyrazine (1·6 g.) was added to a solution of cupric bromide (10 g.) in hydrobromic acid (40 ml., 50%). The product was isolated as described above in 12 to give 2-bromotrifluoropyrazine (1·6 g., 77%), m.p. 37-39° (Found: C, 25·7; Br, 34·8; F, 41·7%; m, 230. $C_4BrF_3N_2$ requires C, 26·1; Br, 34·8; F, 41·6%; m, 230), I.R. Spectrum No.37, $\lambda_{max}$ (cyclohexane) 243 and 289 mμ (log ε 3·09 and 3·95).

## 12.5. Preparation of 2,3-Dichlorotetrafluoroquinoxaline.

Tetrafluoro-2,3-dihydrazinoquinoxaline (1·0 g.) was added to a mixture of cupric bromide (10 g.) in hydrobromic acid (40 ml., 50%) and the mixture distilled until ca. 20 ml. of distillate had been collected. The distillate was extracted with ether and the ether extract dried and evaporated. The residue was sublimed at 20°/·01 mm. to give <u>2,3-dichlorotetrafluoroquinoxaline</u> (0·85 g., 82%), m.p. 80-82° (Found: C, 35·9; Cl, 23·6; F, 28·0%; <u>m</u>, 270. $C_8Cl_2F_4N_2$ requires C, 35·6; Cl, 23·9; F, 28·2%; <u>m</u>, 270), I.R. Spectrum No.38, $\lambda_{max}$ 222, 250, 256, 311, 317, 324, 331 and 338 (log $\varepsilon$ 4·05, 4·63, 4·63, 3·65, 3·73, 3·81, 3·78 and 3·82).

## 12.6. Preparation of 5,6,7,8-Tetrafluoroquinoxaline

Tetrafluoro-2,3-dihydrazinoquinoxaline (2·0 g.) was added to a solution of copper sulphate ($CuSO_4 \cdot 5H_2O$, 10 g.) in water (40 ml.) and the mixture distilled until ca. 20 ml. of distillate had been collected. The distillate was extracted with ether and the ether extract dried and evaporated. The residue was sublimed at 20°/·01 mm. to give <u>5,6,7,8-tetrafluoroquinoxaline</u> (1·01 g., 66%), m.p. 90-91° (Found: C, 47·8; H, 0·91; F, 37·8%; <u>m</u>, 202. $C_8H_2F_4N_2$ requires C, 47·5; H, 0·990; F, 37·6%; <u>m</u>, 202), I.R. Spectrum No.39, $\lambda_{max}$ 237, 306 and 314 mμ (log $\varepsilon$ 4·59, 3·53 and 3·55).

# CHAPTER XIII

## Experimental for Chapter VIII

### 13.1. Preparation of 2-(2'-hydroxyethoxy)trifluoropyrazine and 2,3-Bis-(2'-hydroxyethoxy)difluoropyrazine.

Tetrafluoropyrazine (8·0 g.) in ether (20 ml.) was treated dropwise, during 30 min. at $-15^{\circ}$, with a solution of glycol monosodium salt (25 ml., 2·46M; 1·2 mol.), prepared by adding sodium hydride to excess dry ethylene glycol. The mixture was stirred for a further 30 min. at $-15^{\circ}$, allowed to reach room temperature during 30 min., poured into water and extracted with ether. The organic layer was washed with water, dried, and evaporated. The oily residue was distilled to give 2-(2'-hydroxyethoxy)trifluoropyrazine (4·3 g., 42%), b.p. $165-167^{\circ}/$ 760 mm. (Found: C, 37·0; H, 2·57; F, 29·4%; m, 194. $C_6H_5F_3N_2O_2$ requires C, 37·1; H, 2·58; F, 29·4%; m, 194), I.R. Spectrum No.40, $\lambda_{max}$ (cyclohexane) 296 mμ (log ε 3·75).

The solid residue from the distillation was twice sublimed at $100^{\circ}/0{\cdot}001$ mm. to give 2,3-bis(2'-hydroxyethoxy)difluoropyrazine (1·1 g., 9%), m.p. $80-81^{\circ}$ (Found: C, 40·8; H, 4·24; F, 16·0%; m, 236. $C_8H_{10}F_2N_2O_4$ requires C, 40·7; H, 4·23; F, 16·1%; m, 236), I.R. Spectrum No.41, $\lambda_{max}$ (ethanol) 225 and 295 mμ.

### 13.2. Attempted Cyclisation of 2-(2'-hydroxyethoxy)trifluoropyrazine.

(i) 2-(2'-Hydroxyethoxy)trifluoropyrazine (1·0 g.) in D.M.F. (50 ml.) and potassium carbonate (1·0 g.) were sealed in an evacuated Carius tube and heated to 120° during 5 hr. The tube was cooled, opened, its contents added to water, and the precipitate filtered. The filtrate was dried in air and recrystallized from D.M.S.O. to give a polymer (0·60 g.), m.p. 204-206° (Found: C, 41·0; H, 2·4; F, 22·0%; m, > 1,000. $(C_6H_4F_2N_2O_2)_n$ requires C, 41·4; H, 2·30; F, 21·8%), I.R. Spectrum No.42.

(ii) 2-(2'-Hydroxyethoxy)trifluoropyrazine (0·9 g.) in t-butanol (80 ml.) was treated dropwise, at room temperature, with potassium t-butoxide in butanol (4 ml., 1·2M; 1·03 mol.) with stirring during 3 hr. The mixture was stirred at room temperature for a further 1 hr., added to water and the precipitate filtered. The filtrate was dried in air and recrystallized from D.M.S.O. to give a polymer (0·52 g.) m.p. 202-204°. Elemental analysis and mass spectrum indicated that the polymer was similar to the one prepared above in 13.2(i).

### 13.3. Attempted Demethylation of 2,3-difluoro-5,6-dimethoxypyrazine.

(i) 2,3-Difluoro-5,6-dimethoxypyrazine (2·0 g., 11·4 m.mole) and aqueous hydroiodic acid (15 ml., 54% w/w) were heated to reflux during 4 hrs. The solution was cooled, decolourized with sodium metabisulphite, acidified with hydrochloric acid (15 ml., 36%) and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to give a brown solid (0·2 g.), m.p. 180-210° (decomp.) (Found: C, 41·8; H, 1·4;

F, 35·3%; $C_4H_2F_2N_2O_2$ requires C, 32·4; H, 1·35; F, 25·7%).

(ii) 2,3-Difluoro-5,6-dimethoxypyrazine (2·0 g., 11·4 m.mole) and freshly sublimed aluminium trichloride (3·5 g., 30 m.mole) were heated in a Carius tube at 130° during 4 hrs. The tube was cooled and the contents added to ice. The mixture was acidified with hydrochloric acid (15 ml., 36%) and extracted with ether. The ether extract was dried ($MgSO_4$), evaporated and the residue was sublimed at 100°/·01 mm. to give a light brown solid (0·8 g.), m.p. 210-230° (Found: C, 38·4; H, 1·8; F, 21·4%; $C_4H_2F_2N_2O_2$ requires C, 32·4; H, 1·35; F, 25·7%).

## 13.4. Attempted Oxidation of Hexafluoroquinoxaline.

Hexafluoroquinoxaline (0·95 g., 4·0 m.mole) in acetone (10 ml.) was treated dropwise, at room temperature, with potassium permanganate (1·3 g., 8·0 m.mole) in acetone (1·5 ml.) during 30 min. with stirring. The mixture was stirred for a further 2 hrs. at room temperature and added to water. The aqueous mixture was acidified with hydrochloric acid (10 ml., 36%), extracted with chloroform, and the chloroform extract dried ($MgSO_4$) and evaporated to give a brown solid (0·14 g.). This residue was sublimed at 80°/·01 mm. to give a white solid, m.p. 149-156° (decomp.) (Found: C, 58·1; H, 1·9; F, 28·2%; $C_6H_2F_2N_2O_4$ requires C, 35·3; H, 0·98; F, 18·6%).

## 13.5. Attempted Oxidation of 2,3-Difluoroquinoxaline.

2,3-Difluoroquinoxaline (1·0 g., 6·0 m.mole) in acetone (10 ml.) was treated with potassium permanganate (2·0 g., 12·1 m.mole) as described above in 13.4. The product was similarly isolated to give a white solid (0·1 g.), m.p. 112-120° (decomp.) (Found: C, 41·8; H, 2·14; F, 10·1%; $C_6H_2F_2N_2O_2$ requires C, 35·3; H, 0·98; F, 18·6%).

# CHAPTER XIV

## Relative Reactivity

### 14.1. General Method.

The reaction vessel used consisted of a 5 ml. round-bottomed flask fitted with two B10 necks and a magnetic stirrer. One neck was attached to a dry nitrogen inlet while the remaining neck was used as a dry nitrogen outlet after the sodium methoxide had been added. Tetrafluoropyrazine (0·4888 g., 3·216 m.mole) and pentafluoropyridine (0·4329 g., 2·562 m.mole) were transferred quantitatively to the reaction vessel, which was well purged with dry nitrogen, and dissolved in dry methanol (5 ml.). The mixture was stirred for 30 min. at -23° ($CCl_4$/Drikold slush bath), sodium methoxide (0·973 g., 1·806 m.moles) was added and the mixture stirred at -23° for a further 2 hrs. At the end of this time the mixture was allowed to come to room temperature during 30 min., hexafluorobenzene (0·1406 g., 0·799 m.mole) was quantitatively added, and the mixture stirred during 5 min. An aliquot was removed from the mixture and its $^{19}F$ n.m.r. spectrum, with integrations, obtained using a Digico C.A.T.

Using the formula given (see 9.2.), the number of moles of the two reactants present at the end of the reaction could be determined from these integration step heights.

$$\frac{M_Y}{M_R} = \frac{S_Y}{S_R} \cdot \frac{N_R}{N_Y}$$

in the present example

$S_R$ = 8·90 units, $N_R$ = 6 (for hexafluorobenzene)

S = 18·90 units, N = 4 (for tetrafluoropyrazine)

and S = 5·30 units, N = 2 for pentafluoropyridine (measuring the 3(5)-F resonance)

Which gives

final amount of tetrafluoropyrazine = 2·545 m.mole

final amount of pentafluoropyridine = 1·427 m.mole

Using

$$\frac{K_A}{K_B} = \frac{\log_{10}[A]/[A^o]}{\log_{10}[B]/[B^o]} \qquad \text{(see 9.1.)}$$

$$\frac{K_{p\text{-}C_4F_4N_2}}{K_{C_5F_5N}} = 0{\cdot}4002$$

Dividing by statistical factor of 4 due to tetrafluoropyrazine having four sites for attack compared to one for pentafluoropyridine, then

$$\frac{K_{p\text{-}C_4F_4N_2}}{K_{C_5F_5N}} = 0{\cdot}10$$

similarly other identical experiments gave:

$$\frac{K_{p\text{-}C_4F_4N_2}}{K_{C_5F_5N}} = \begin{array}{l} 0{\cdot}13,\ 0{\cdot}12,\ 0{\cdot}11,\ 0{\cdot}12,\ 0{\cdot}12 \\ 0{\cdot}13,\ 0{\cdot}13,\ 0{\cdot}12,\ 0{\cdot}11 \end{array}$$

i.e.

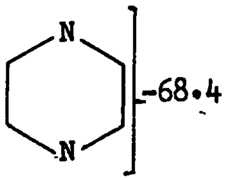
$$\frac{K_{p\text{-}C_4F_4N_2}}{K_{C_5F_5N}} = 0{\cdot}12 \pm {\cdot}01$$

# Appendix I

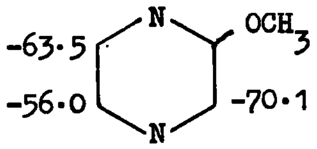
## $^{19}$F N.M.R. DATA

Shifts are quoted from $C_6F_6$, which was used as an internal reference. Spectra were recorded on a Perkin-Elmer R10 Spectrometer. Coupling constants are given where these could be determined, in the other cases either the splitting was too complex to analyse (i.e. by assuming first order splitting), or else the solubility of the compound was too low to observe any fine structure.

1. Tetrafluoropyrazine $(C_2H_5)_2O$

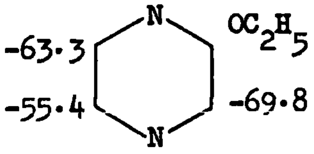


2. Trifluoro-2-methoxypyrazine $(C_2H_5)_2O$



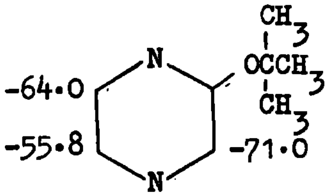
$J_{36}$ = 51•2, $J_{56}$ = 15•1, $J_{35}$ = 12•3 c./s.

3. 2-Ethoxytrifluoropyrazine $(C_2H_5)O$



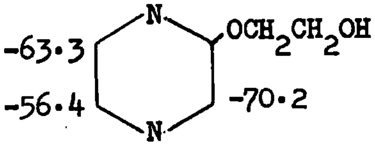
$J_{36}$ = 50•7, $J_{56}$ = 13•8, $J_{35}$ = 12•0 c./s.

4. 2-t-Butoxytrifluoropyrazine $(C_2H_5)O$



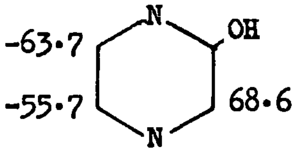
$J_{36}$ = 50·1, $J_{56}$ = 16·1, $J_{35}$ = 12·0 c./s.

5. 2-(2'-Hydroxyethoxy)trifluoropyrazine $(C_2H_5)_2O$



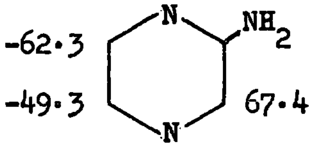
$J_{36}$ = 50·6, $J_{56}$ = 14·8, $J_{35}$ = 11·7 c./s.

6. Trifluoro-2-hydroxypyrazine $(C_2H_5)_2O$



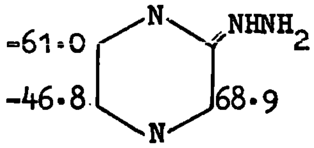
$J_{36}$ = 51·0, $J_{56}$ = 16·5, $J_{35}$ = 12·0 c./s.

7. 2-Aminotrifluoropyrazine $(C_2H_5)_2O$



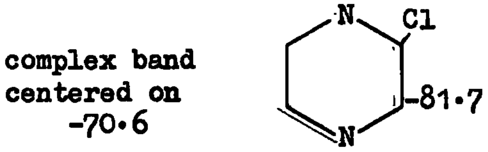
$J_{36}$ = 49·8, $J_{56}$ = 16·2, $J_{35}$ = 10·8 c./s.

8. Trifluoro-2-hydrazinopyrazine $(C_2H_5)_2O$

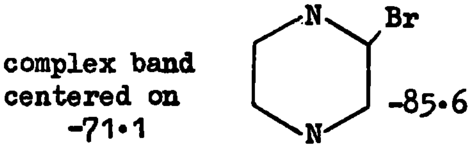


$J_{36}$ = 50·1, $J_{56}$ = 15·0, $J_{36}$ = 13·2 c./s.

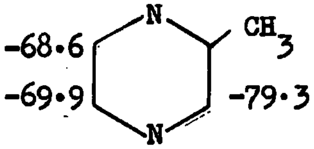
9. <u>2-Chlorotrifluoropyrazine</u> $(C_2H_5)_2O$



10. <u>2-Bromotrifluoropyrazine</u> $(C_2H_5)_2O$

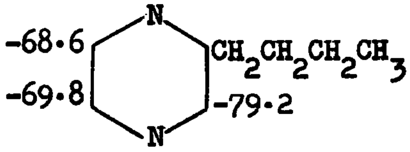


11. <u>Trifluoro-2-methylpyrazine</u> $(C_2H_5)_2O$



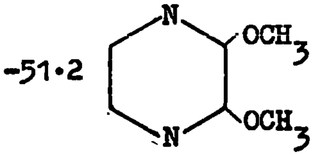
$J_{36}$ = 43·9, $J_{56}$ = 19·7, $J_{35}$ = 7·9 c./s.

12. <u>2-n-Butyltrifluoropyrazine</u> $(C_2H_5)_2O$

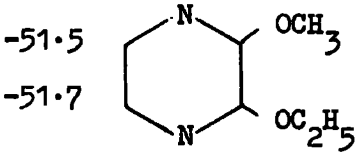


$J_{36}$ = 43·9, $J_{56}$ = 20·7, $J_{35}$ = 6·9 c/s.

13. <u>2,3-Difluoro-5,6-dimethoxypyrazine</u> $(C_2H_5)_2O$

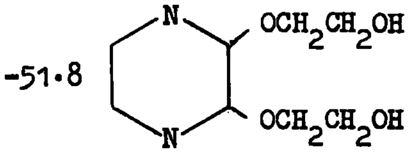


14. 2-Ethoxy-5,6-difluoro-3-methoxypyrazine $(C_2H_5)_2O$

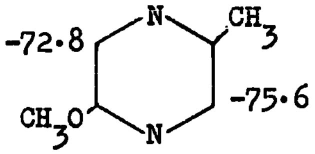


$J_{56}$ = 16 c./s.

15. 2,3-Bis(2'-hydroxy-ethoxy)-5,6-difluoropyrazine $(CH_3)_2CO$

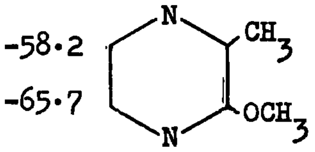


16. 2,5-Difluoro-3-methoxy-6-methylpyrazine $(C_2H_5)_2O$



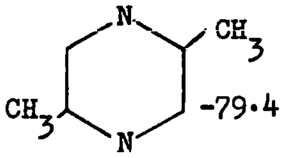
$J_{36}$ = 49·3 c./s.

17. 2,3-Difluoro-5-methoxy-6-methylpyrazine $(C_2H_5)_2O$

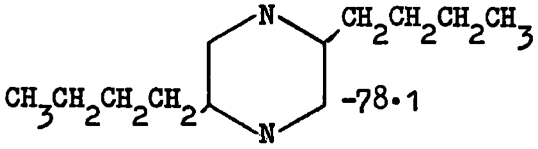


$J_{56}$ = 22·5 c./s.

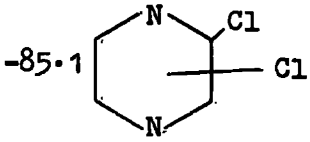
18. 2,5-Difluoro-3,6-dimethylpyrazine



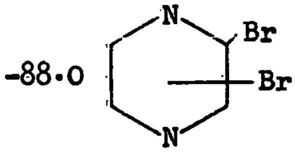
19. 2,5-Di-n-butyl-3,6-difluoropyrazine $(C_2H_5)_2O$



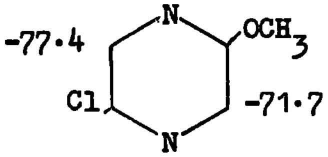
20. Dichlorodifluoropyrazine $(C_2H_5)_2O$



21. Dibromodifluoropyrazine $(C_2H_5)_2O$

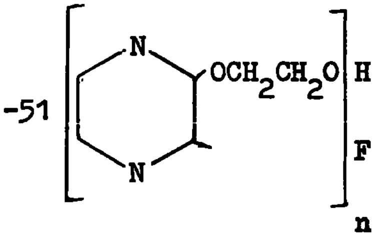


22. 2-Chloro-3,6-difluoro-5-methoxypyrazine $(C_2H_5)_2O$

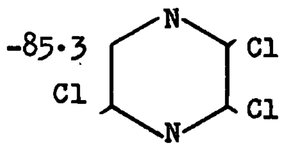


$J_{36}$ = 47 c./s.

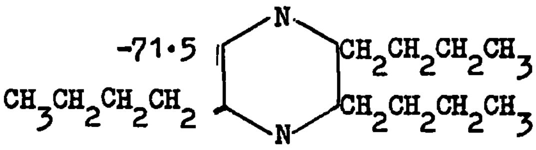
23. Polymer (D.M.S.O.).



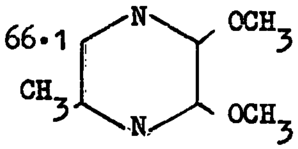
24. Trichlorofluoropyrazine $(C_2H_5)_2O$



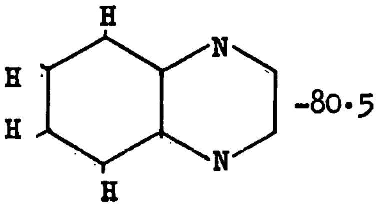
25. Tri-n-butylfluoropyrazine $(C_2H_5)_2O$



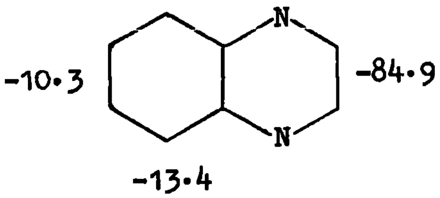
26. 2-Fluoro-5,6-dimethoxy-3-methylpyrazine $(C_2H_5)_2O$



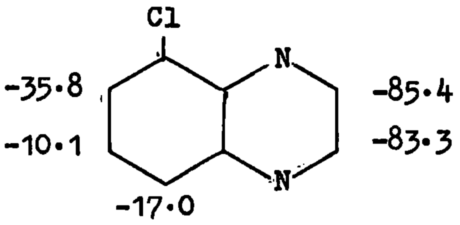
27. 2,3-Difluoroquinoxaline $(CH_3)_2CO$



28. Hexafluoroquinoxaline $(CH_3)CO$

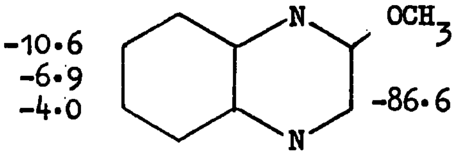


29. 5-Chloropentafluoroquinoxaline $(CH_3)_2CO$

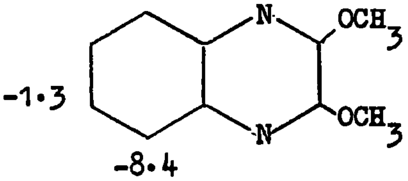


$J_{23}$ = 30 c./s.

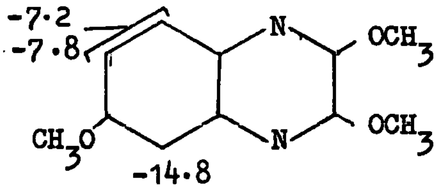
30. Pentafluoro-2-methoxyquinoxaline $(CH_3)_2CO$



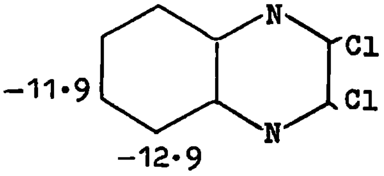
31. Tetrafluoro-2,3-dimethoxyquinoxaline $(CH_3)_2CO$



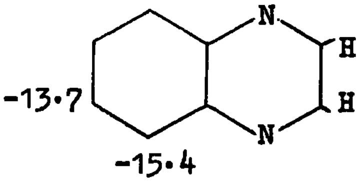
32. Trifluoro-2,3,6-trimethoxyquinoxaline $(CH_3)_2CO$



### 33. 2,3-Dichlorotetrafluoroquinoxaline



### 34. 5,6,7,8-Tetrafluoroquinoxaline $(CH_3)_2CO$



# Appendix II

## INFRARED SPECTRA

| | | |
|---|---|---|
| 1. | Tetrachloropyrazine | (d) |
| 2. | Tetrafluoropyrazine | (g) |
| 3. | 2-Chlorotrifluoropyrazine | (g) |
| 4. | Dichlorodifluoropyrazine | (g) |
| 5. | Trichlorofluoropyrazine | (d) |
| 6. | Hexachloroquinoxaline | (d) |
| 7. | Hexafluoroquinoxaline | (d) |
| 8. | 5-Chloropentafluoroquinoxaline | (d) |
| 9. | 2,3-Difluoroquinoxaline | (d) |
| 10. | Trifluoro-2-methoxypyrazine | (cf) |
| 11. | 2-Ethoxytrifluoropyrazine | (cf) |
| 12. | 2-t-Butoxytrifluoropyrazine | (cf) |
| 13. | 2-Aminotrifluoropyrazine | (d) |
| 14. | Trifluoro-2-hydroxypyrazine | (d) |
| 15. | Trifluoro-2-hydrazinopyrazine | (d) |
| 16. | Trifluoro-2-methylpyrazine | (cf) |
| 17. | 2,5-Difluoro-3,6-dimethylpyrazine | (cf) |
| 18. | Tri-n-butylfluoropyrazine | (cf) |
| 19. | 2-n-Butyltrifluoropyrazine | (cf) |
| 20. | 2,5-Di-n-butyl-3,6-difluoropyrazine | (cf) |
| 21. | 2,3-Difluoro-5,6-dimethoxypyrazine | (d) |

| | | |
|---|---|---|
| 22. | 2-Ethoxy-5,6-difluoro-3-methoxypyrazine | (d) |
| 23. | 2,3-Difluoro-5-methoxy-6-methylpyrazine | (cf) |
| 24. | 2,5-Difluoro-3-methoxy-6-methylpyrazine | (cf) |
| 25. | 2-Fluoro-5,6-dimethoxy-3-methylpyrazine | (d) |
| 26. | Difluorobisphenylthiopyrazine | (d) |
| 27. | 2-Chloro-3,6-difluoro-5-methoxypyrazine | (cf) |
| 28. | Pentafluoro-2-methoxyquinoxaline | (d) |
| 29. | Tetrafluoro-2,3-dimethoxyquinoxaline | (d) |
| 30. | Trifluoro-2,3,6-trimethoxyquinoxaline | (d) |
| 31. | Tetrafluoro-2,3-dihydroxyquinoxaline | (d) |
| 32. | 2-Aminopentafluoroquinoxaline | (d) |
| 33. | Tetrafluoro-2,3-dihydrazinoquinoxaline | (d) |
| 34. | Dibromodifluoropyrazine | (d) |
| 35. | Tetrabromopyrazine | (d) |
| 36. | Tetrafluoro-1,4-dimethylquinoxaline-2,3-dione | (d) |
| 37. | 2-Bromotrifluoropyrazine | (g) |
| 38. | 2,3-Dichlorotetrafluoropyrazine | (d) |
| 39. | 5,6,7,8-Tetrafluoropyrazine | (d) |
| 40. | 2-(2'-Hydroxyethoxy)trifluoropyrazine | (cf) |
| 41. | 2,3-Bis(2'-hydroxyethoxy)-5,6-difluoropyrazine | (d) |
| 42. | Poly(2-ethylenedioxy-5,6-difluoropyrazine) | (d) |

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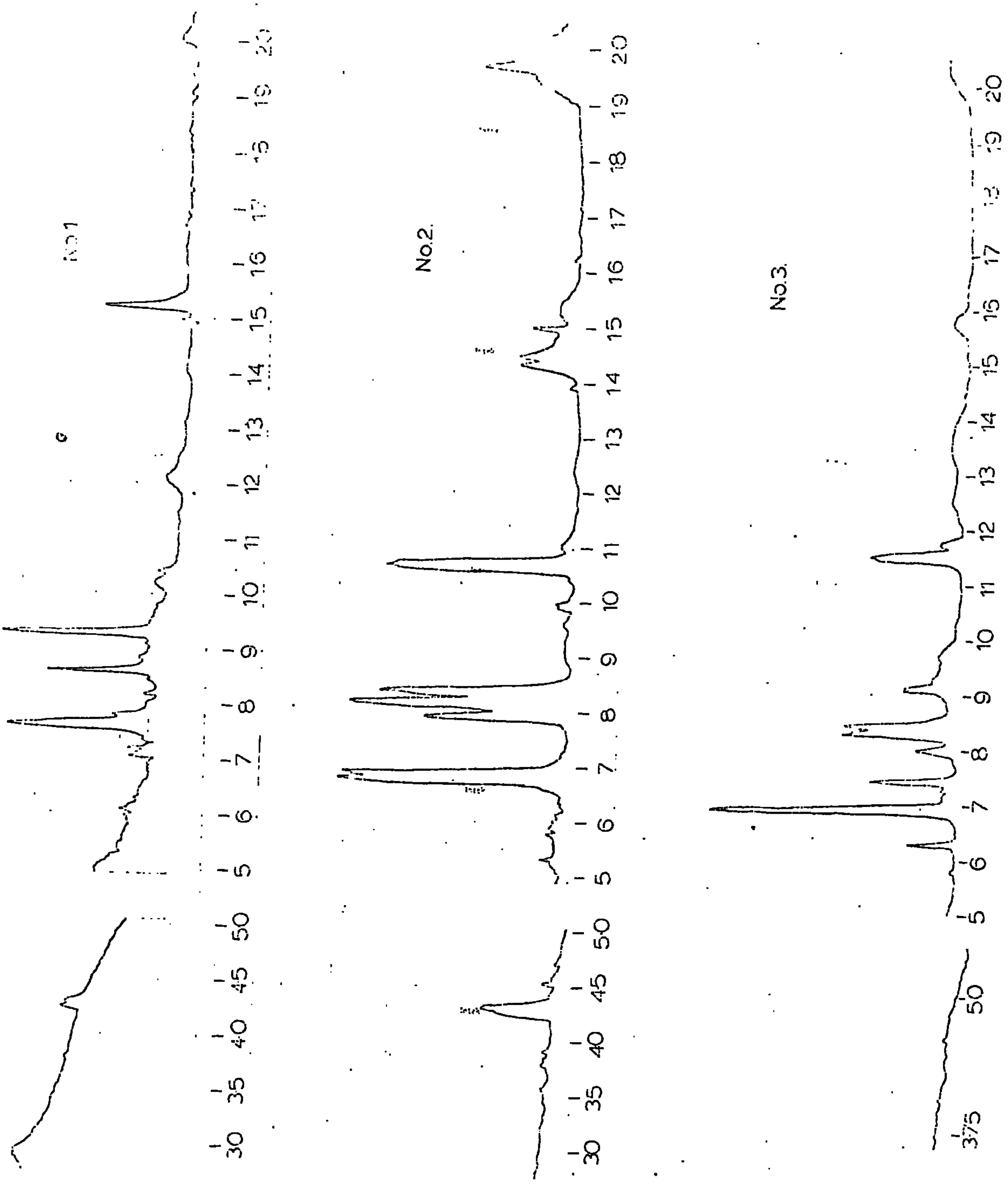
|---|---|
| (d) | KBr disc |
| (cf) | liquid contact film sample |
| (g) | gas sample |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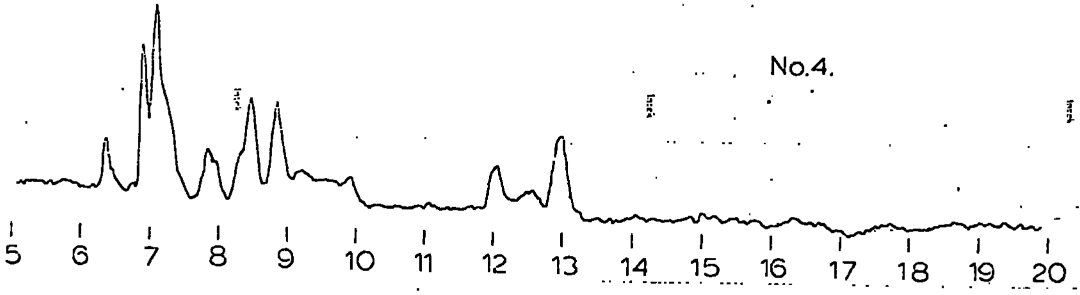
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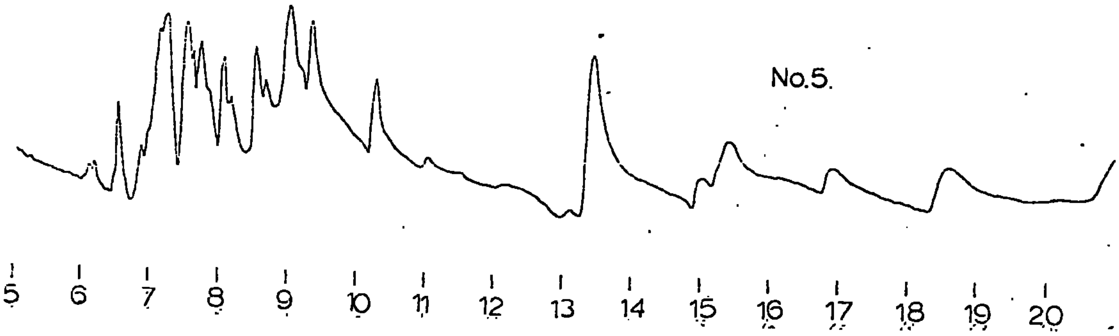
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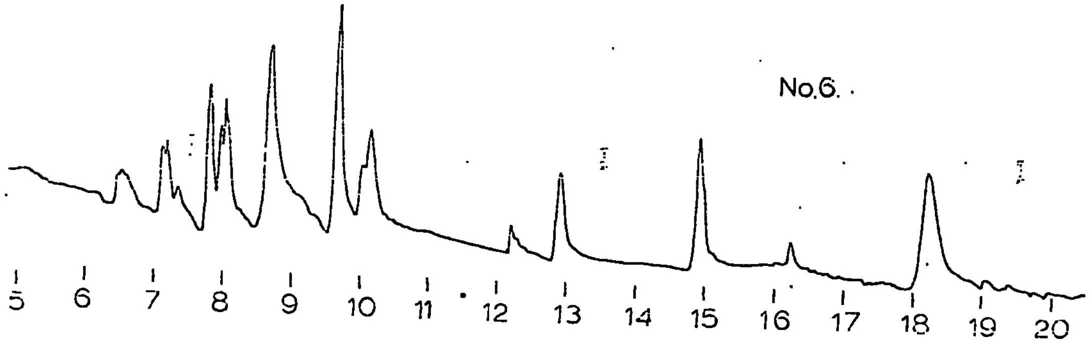
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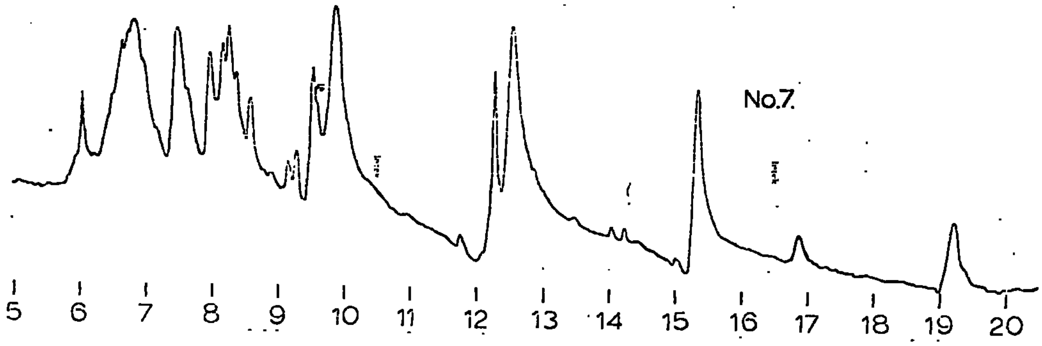
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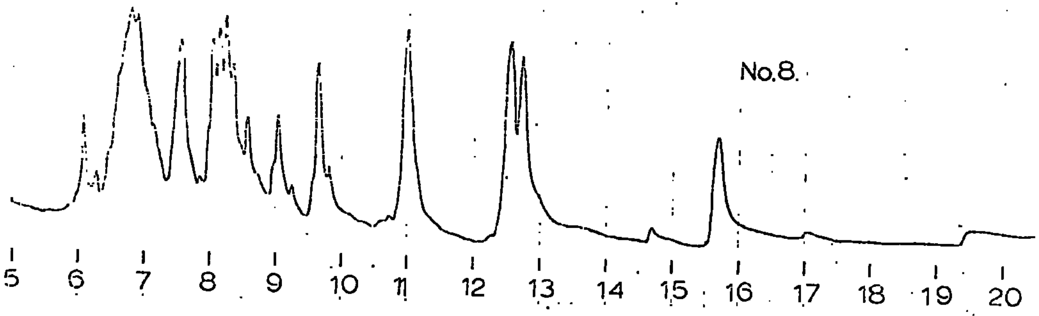
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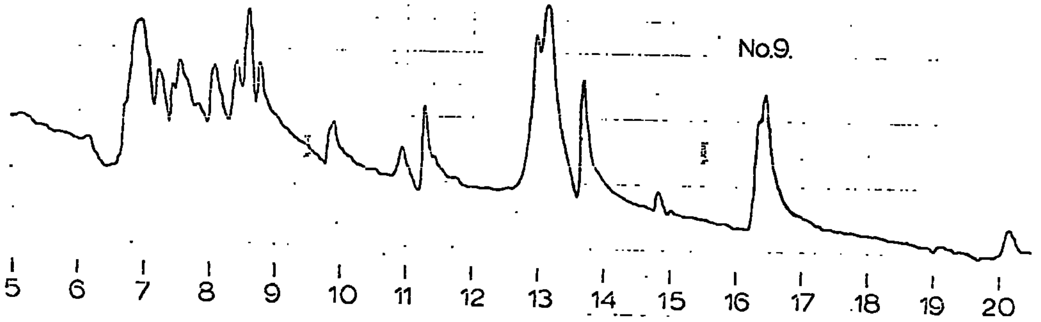
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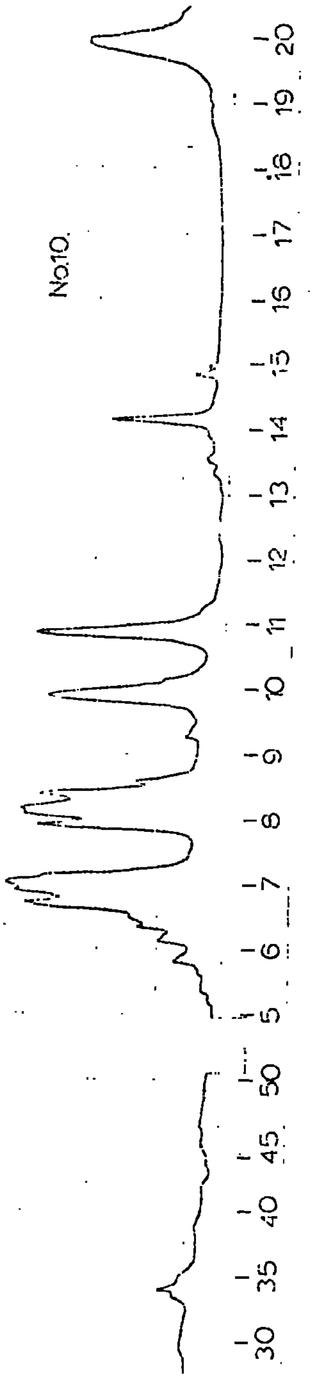

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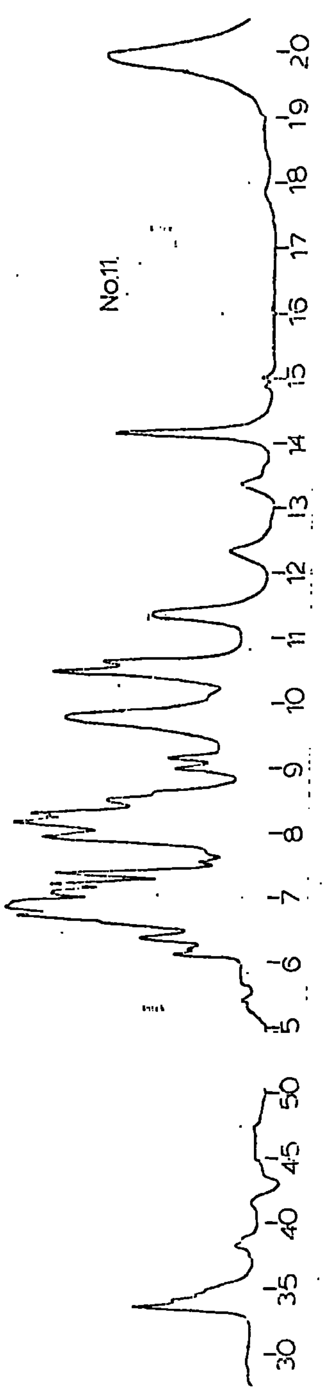

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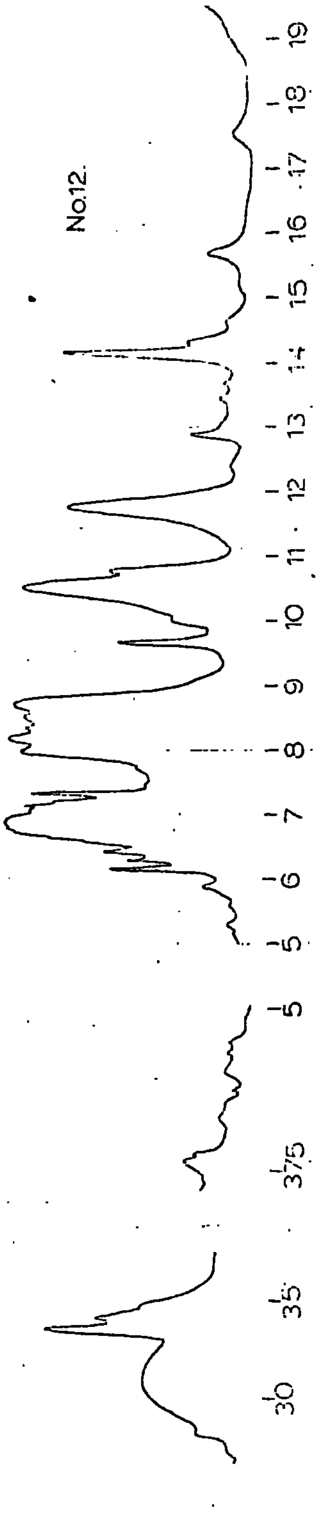

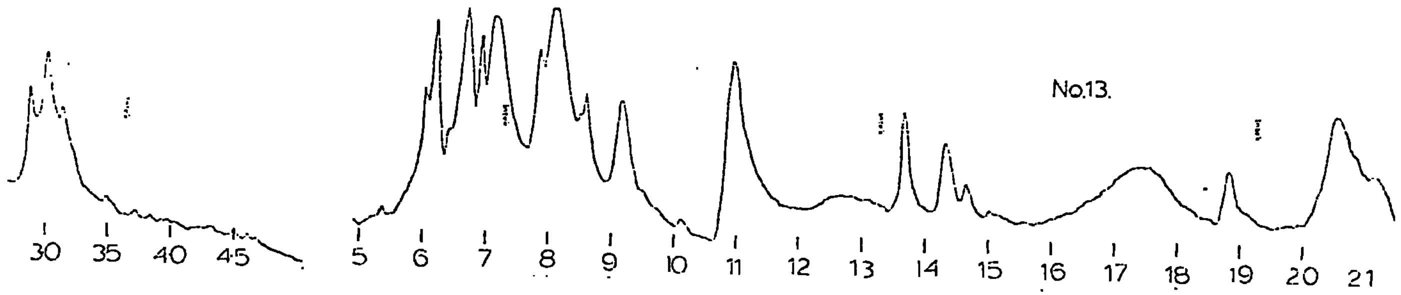
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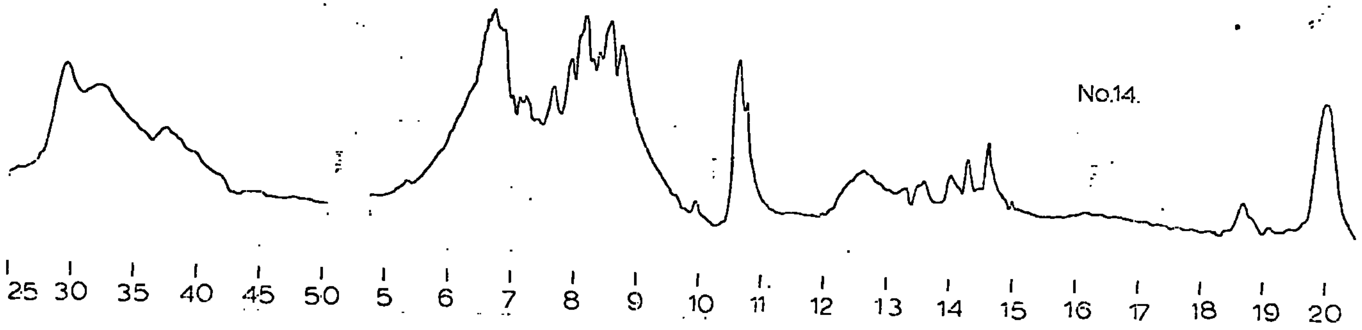
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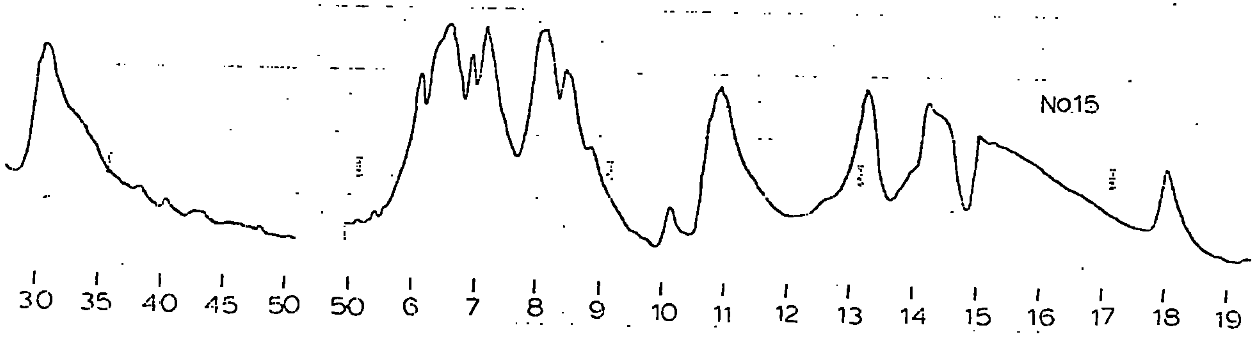
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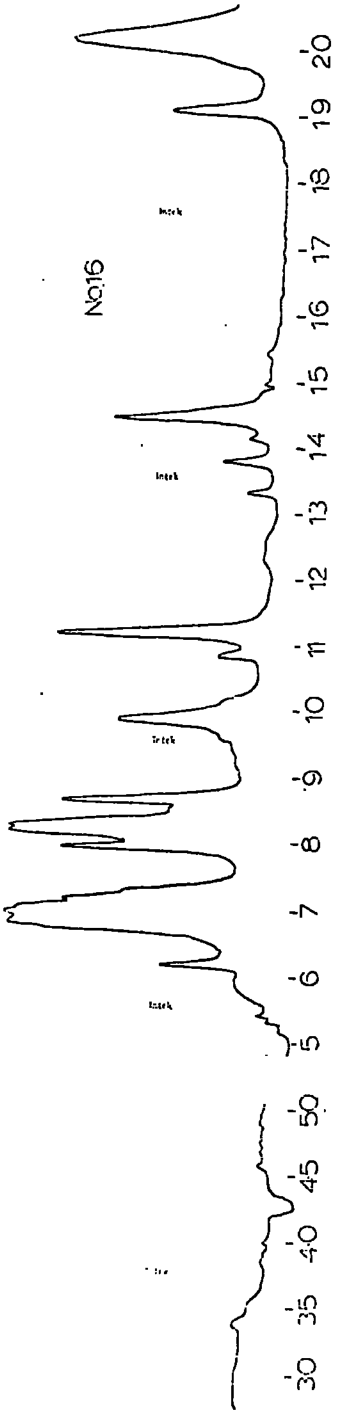
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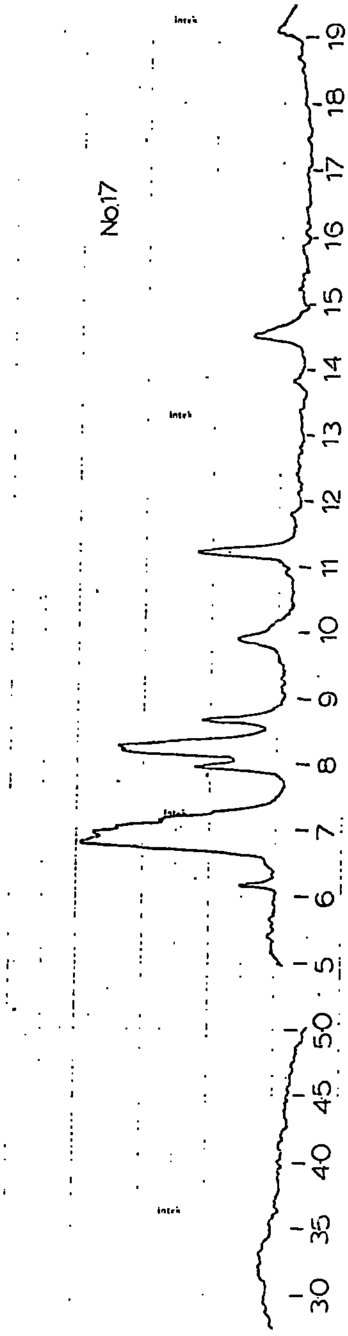
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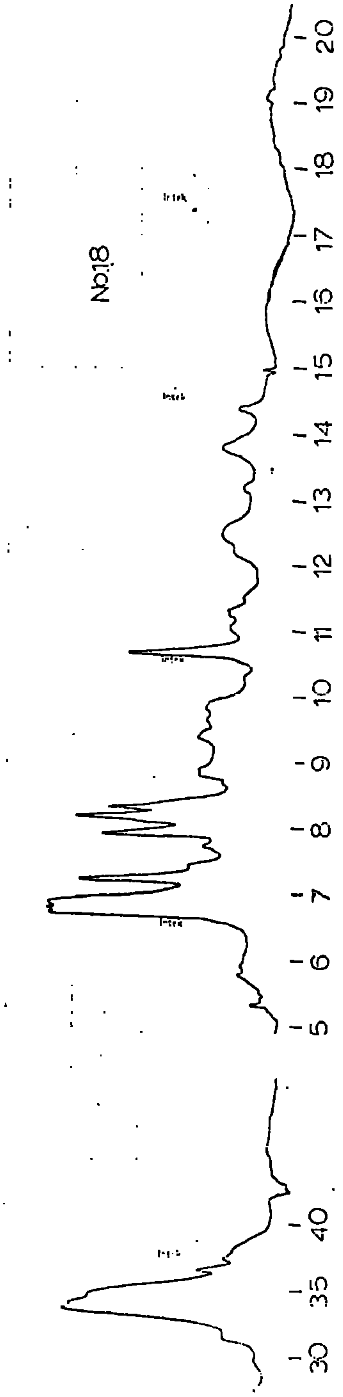
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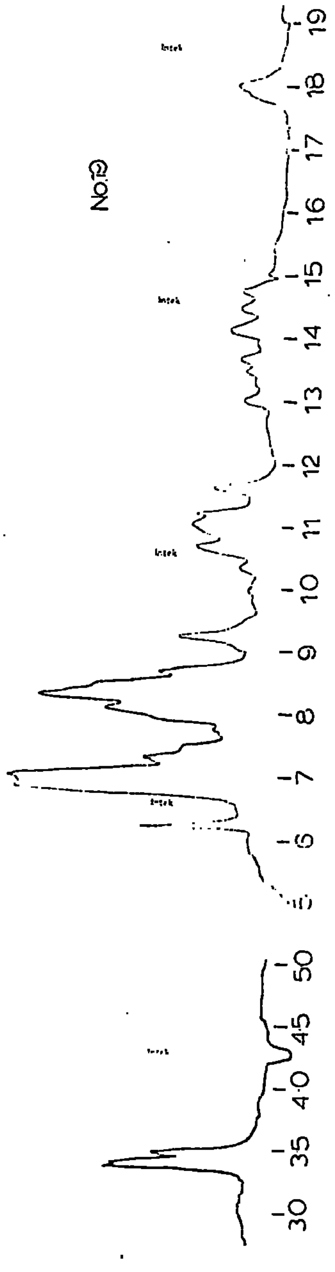
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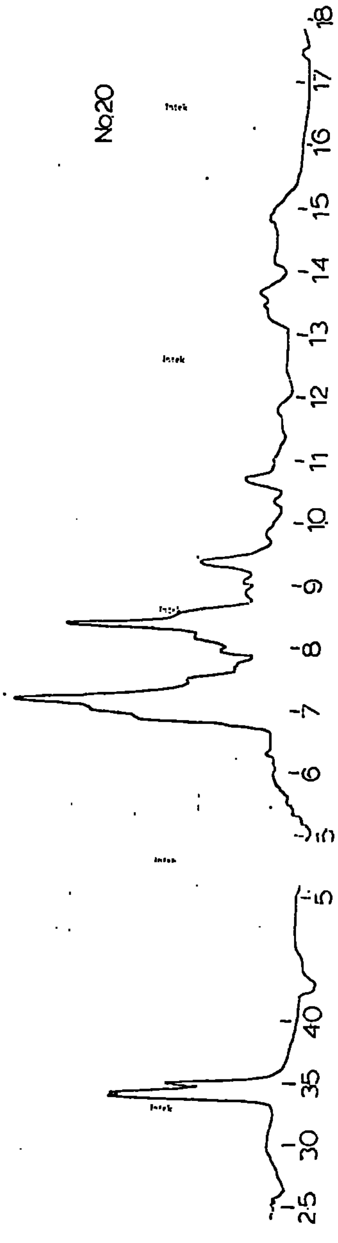
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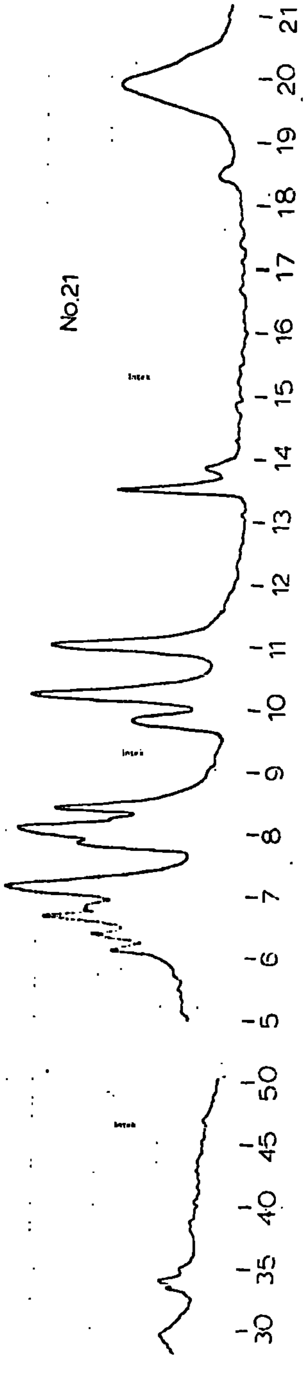
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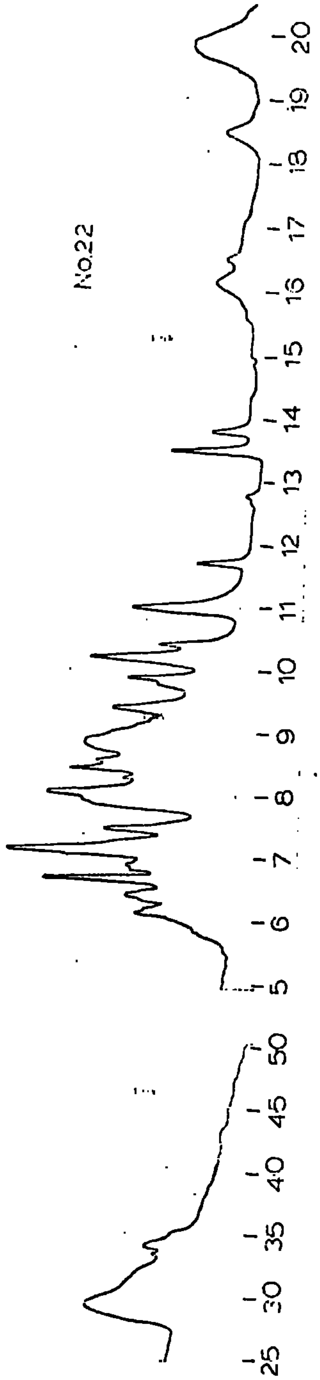

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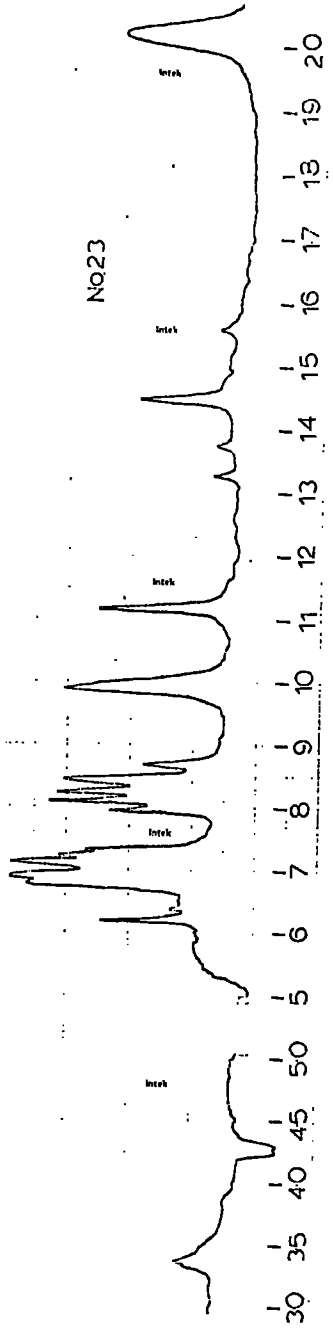

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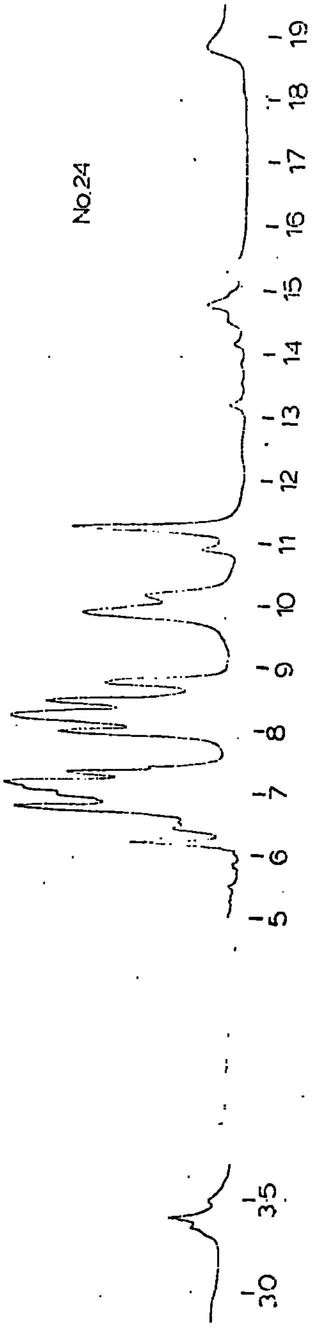

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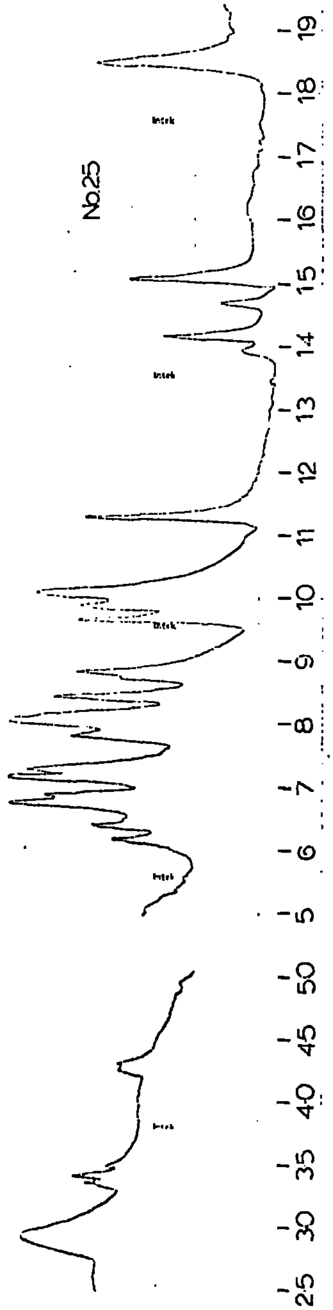

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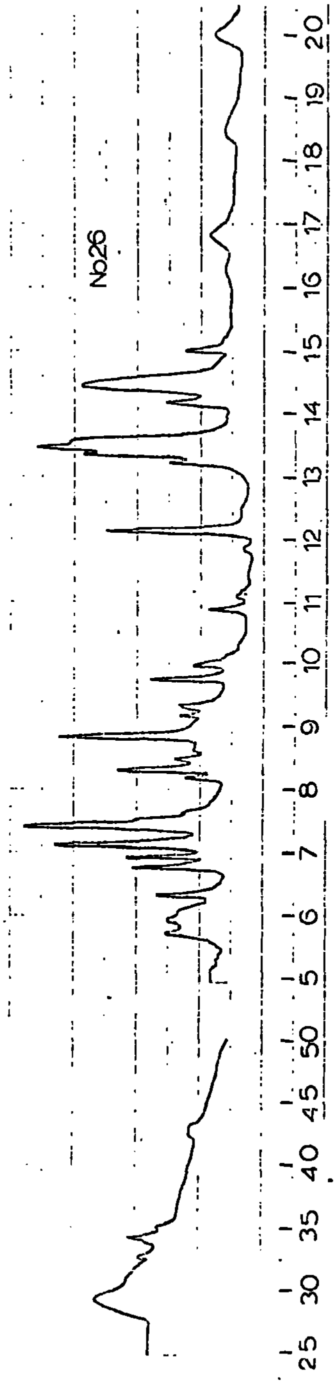

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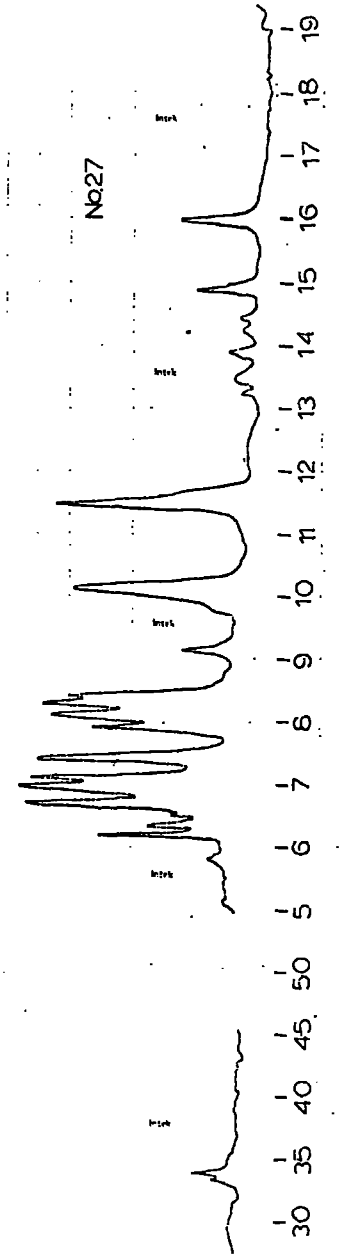

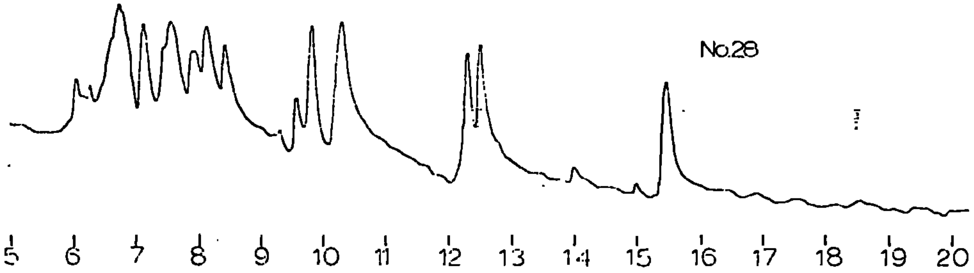
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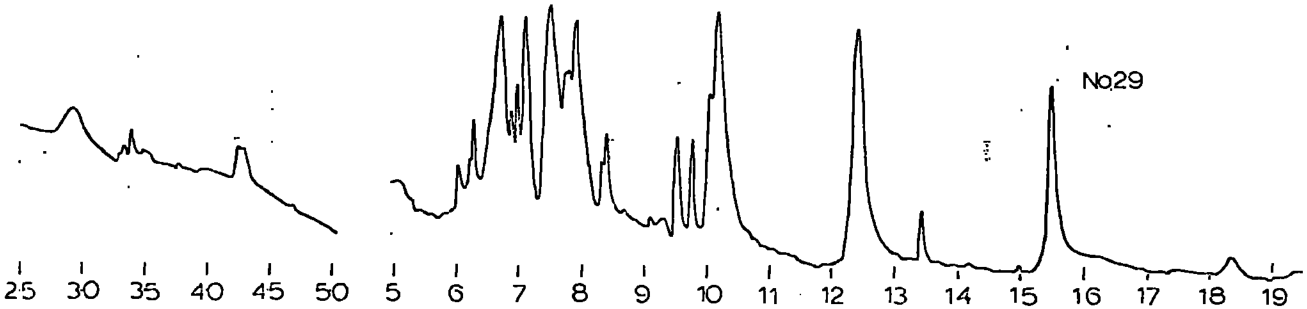
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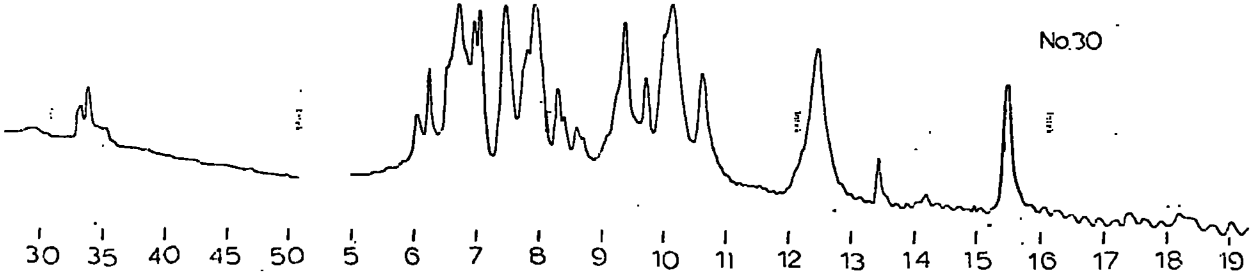
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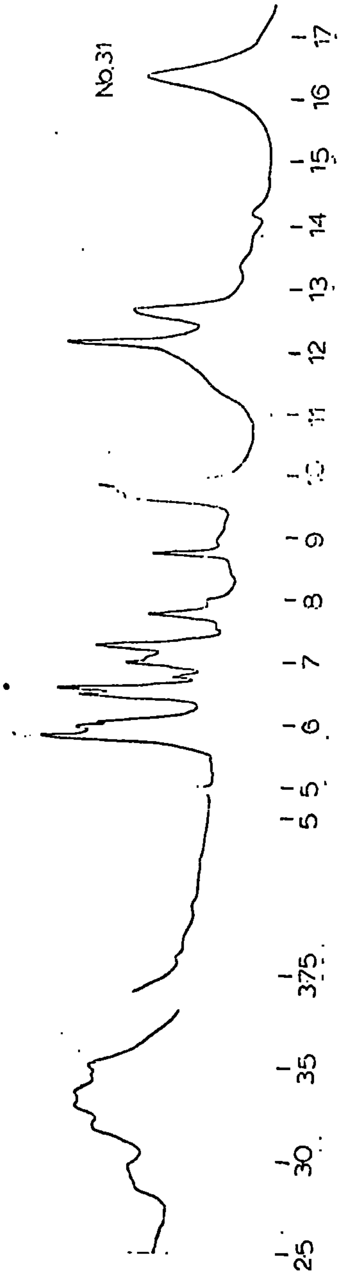
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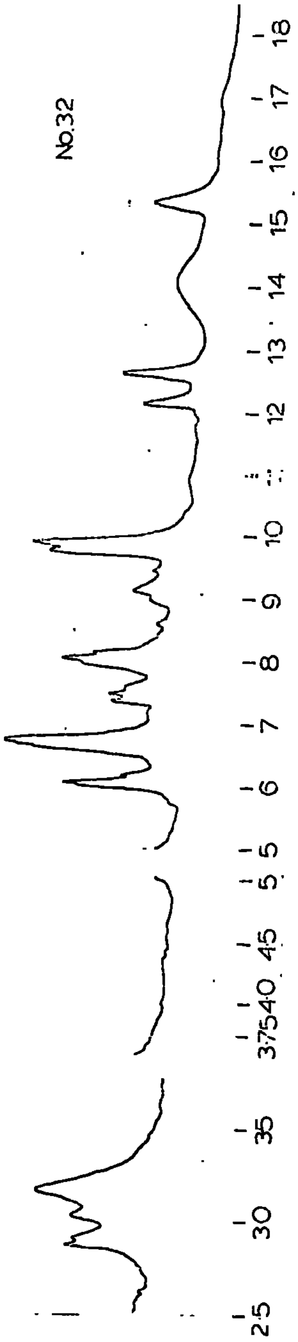
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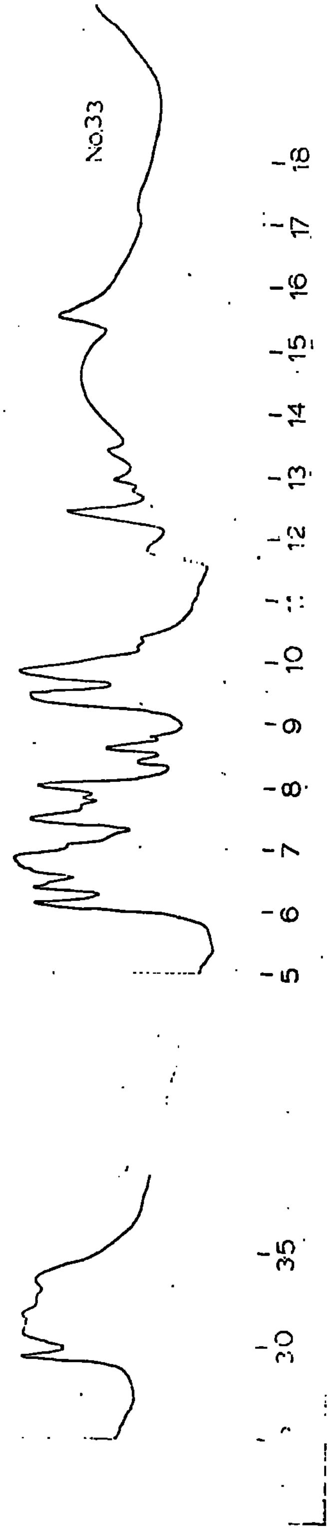
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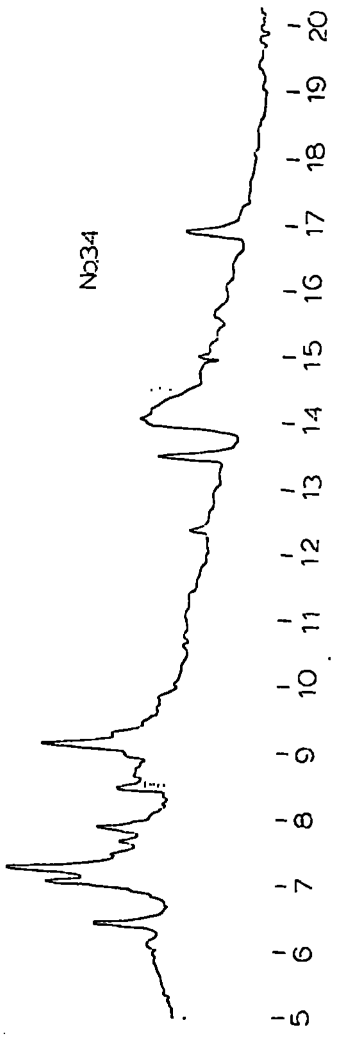

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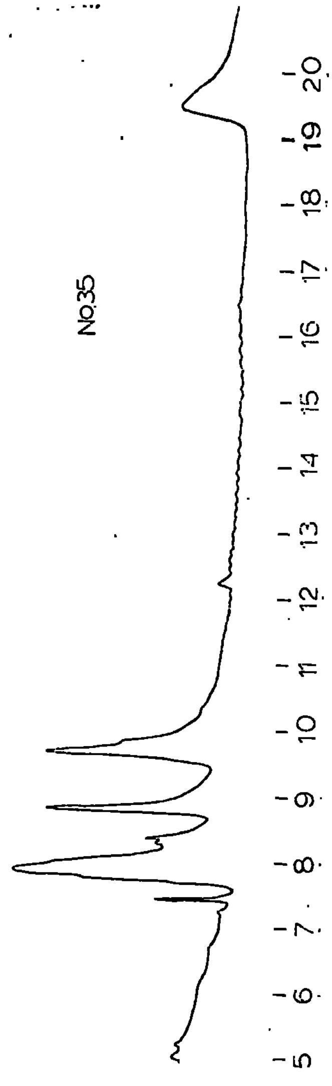

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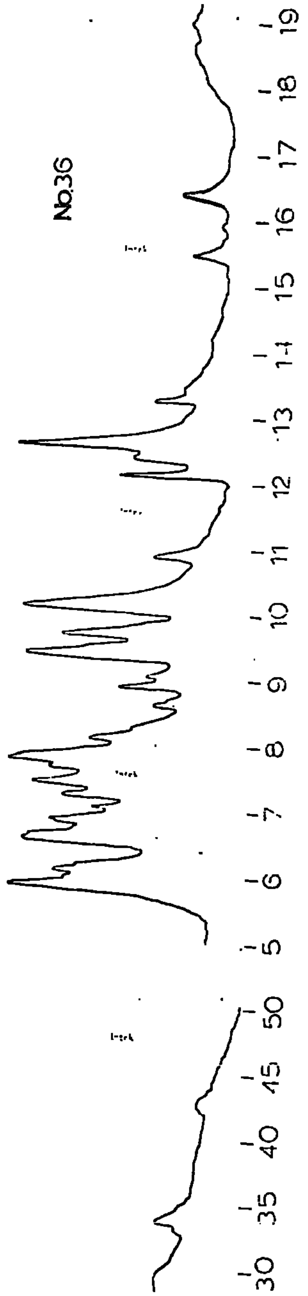

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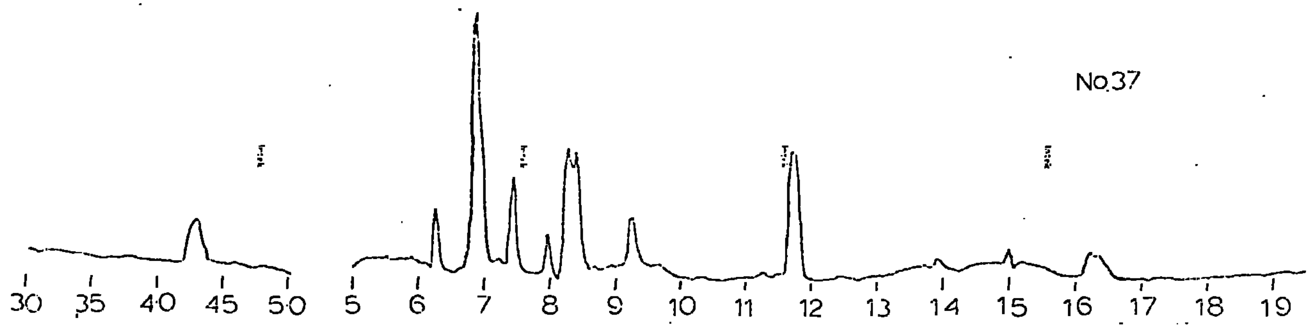
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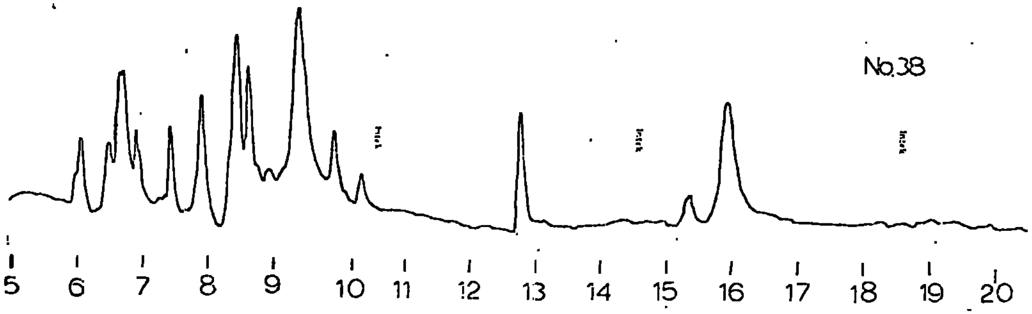
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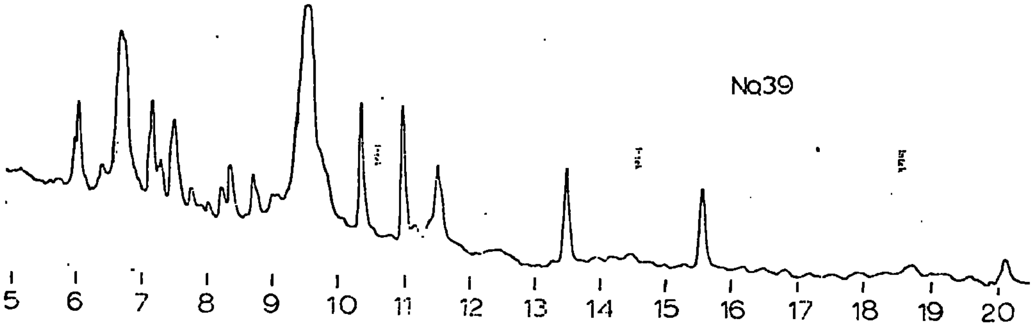
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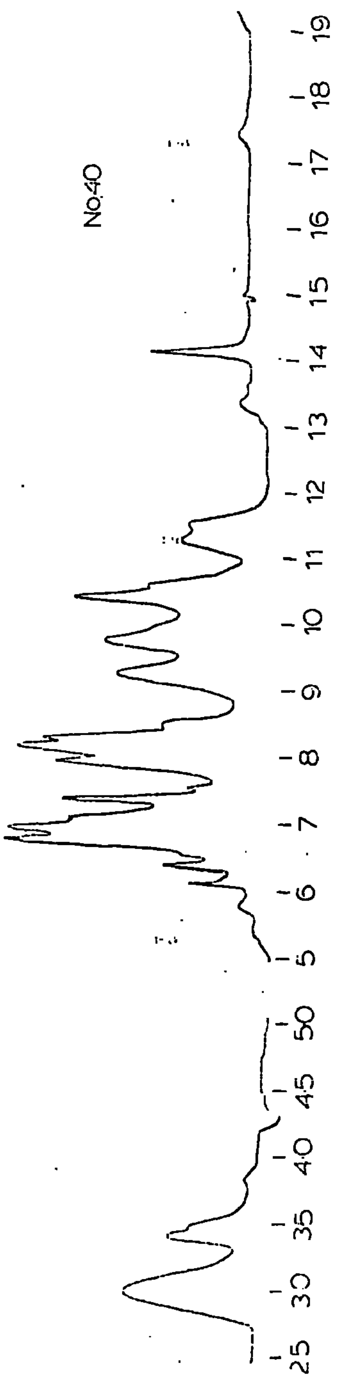
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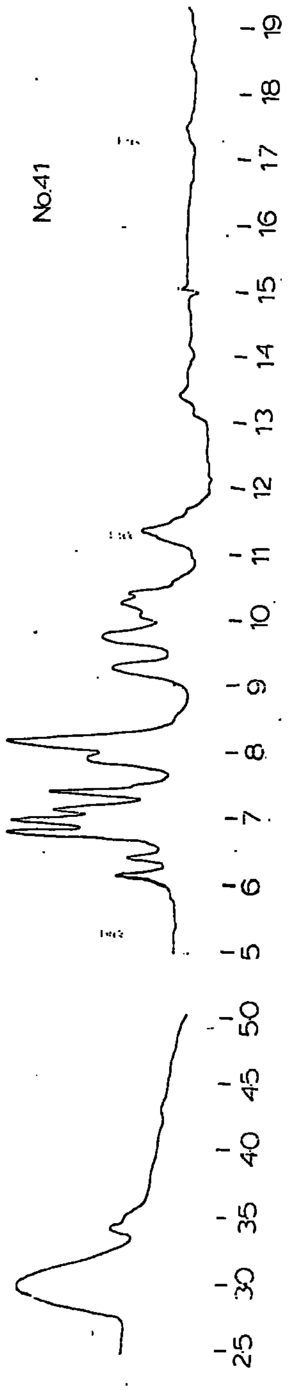
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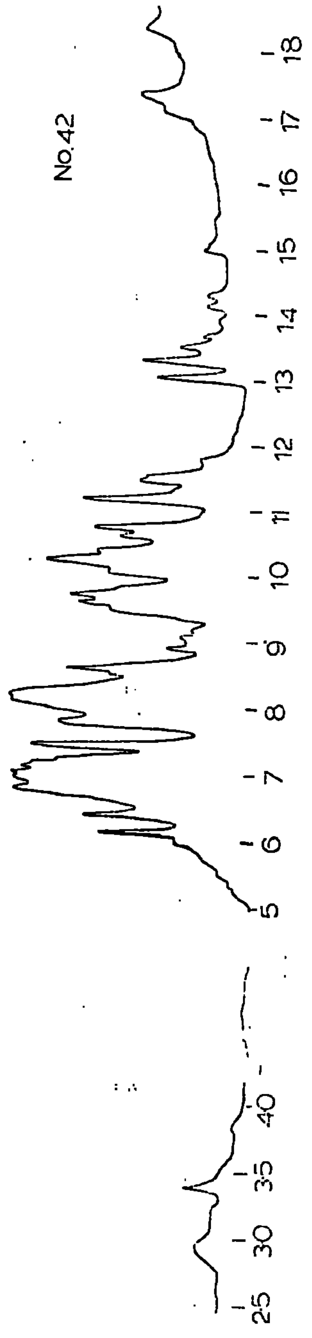
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