Preparation and nucleophilic substitution of hexafluorophthalazine

Ian Stephen Reilly

U N I V E R S I T Y O F D U R H A M

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A T h e s i s

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PREPARATION AND NUCLEOPHILIC SUBSTITUTION OF HEXAFLUOROPHTHALAZINE

Submitted by

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

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M E M O R A N D U M

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

Part of this work has been the subject of the following publication :-

R.D. Chambers, J.A.H. MacBride, W.K.R. Musgrave, and I.S. Reilly,

Tetrahedron Letters, 1970, 57.

SUMMARY

Preparation and Nucleophilic Substitution of Hexafluorophthalazine

Conditions have been developed for the preparation of hexachlorophthalazine in good yield by direct chlorination of 1,4-dichlorophthalazine in the presence of aluminium trichloride.

The halogen exchange method for the preparation of polyfluoroaromatic compounds from their perchloro-analogues using potassium fluoride, has been applied to the relatively unstable phthalazine system and hexafluorophthalazine is thus obtained in good yield under carefully controlled conditions.

Hexafluorophthalazine is rapidly hydrolysed by atmospheric moisture and reacts readily with nucleophilic reagents. With sodium methoxide all the fluorine atoms can be progressively replaced and the mono-, di-, tri-, tetra-, and hexa-methoxy derivatives have been characterised and their structures deduced by ^{19}F n.m.r. spectroscopy. With ammonia the 1-amino derivative was obtained.

Hexafluorophthalazine is also susceptible to nucleophilic attack under acidic conditions and the 1-hydroxy derivative was obtained by reaction with water in sulphuric acid; 4-methoxy-pentafluorophthalazine and hexachlorophthalazine reacted in the same way.

Pentafluorohydroxyphthalazine was shown to exist in the lactam form by spectroscopic comparison with its N-methyl derivative, which was the sole product of methylation with diazomethane.

CONTENTS

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General Introduction

Since the preparation and characterisation of the first compounds of carbon and fluorine around 1930, an extensive new branch of organic chemistry, based on such derivatives, and known as fluorocarbon chemistry, has been developed. Research into fluorocarbons and their derivatives was given great impetus by the wartime Manhattan project for the development of atomic weapons. The use of the highly reactive uranium hexafluoride in a gaseous diffusion process for concentrating the fissionable ^{235}U isotope required inert coolants, lubricants and sealants, and intensive and successful research was applied to developing fluorocarbons for these applications. The interest in fluorocarbon chemistry aroused by the disclosure of these developments has been maintained. Fluorocarbon derivatives find important uses as chemically and thermally stable polymers, as refrigerants and as aerosol propellants. Academic interest has centred on the very different environment of carbon in fluorocarbons compared with hydrocarbons, and on the often closely analagous behaviour of the fluoride ion in fluorocarbon systems and the proton in hydrocarbon systems.

The fluoride ion–proton analogy is perhaps most clearly seen in the chemistry of fluoroaromatic and fluoroheterocyclic compounds which has been developed during the last fifteen years. Thus fluoroaromatic and fluoroheterocyclic compounds usually react with nucleophilic reagents in substitution reactions analogous to those of their hydrogen analogues with electrophilic reagents. An extensive study of such substitutions has undoubtedly added to our understanding of the chemistry of homo- and heteroaromatic systems. Industrial interest in aciclic and heterocyclic fluorine compounds has been in their possible use in polymers, dyestuffs, and in their biological activity.

This study of hexafluorophthalazine was undertaken as an extension of work carried out in Durham into perfluorinated heterocyclic compounds, particularly in view of the enhanced reactivity in nucleophilic substitution reactions shown by perfluorinated fused ring heterocyclic compounds such as quinoline, and by perfluoro-diazines such as pyridazine, compared with pentafluoro pyridine. It was hoped that such an investigation might deepen our understanding both of fluorinated aromatic systems, and of the phthalazine ring system.

I N T R O D U C T I O N

Chapter 1

The Preparation of Polyfluoroaromatic and Polyfluoroheterocyclic Compounds

Many approaches to the preparation of polyfluoroaromatic compounds have been reported, but three routes can be distinguished by their wide applicability:

(a) Conversion of cyclic hydrocarbons to alicyclic fluorocarbons, followed by defluorination or, in the case of partially fluorinated hydrocarbons, dehydrofluorination. The first stage in this route has been achieved by reaction with elemental fluorine, with a high valency metal fluoride, or by electrolysis in solution in hydrogen fluoride. Defluorination has usually been accomplished by passage of the vaporised fluorocarbon over hot, finely divided iron or nickel, and dehydrofluorination by refluxing the fluorocarbon with concentrated aqueous potassium hydroxide.

This route has been widely utilised in the preparation of perfluoroaromatic compounds, despite the complex mixture

of products frequently obtained in the first stage. When applied to the preparation of polyfluoroheterocyclic compounds, however, overall yields have usually proved to be low.

(b) From a diazonium salt. Diazonium salts containing fluoride, fluoroborate, fluorosilicate and similar anions have been decomposed to yield aryl fluorides. This method has been widely used to introduce single fluorine atoms into aromatic or heterocyclic compounds, and by a succession of such reactions, up to four fluorine atoms have been introduced. Complete fluorination of aromatic molecules by this route has not proved possible.

(c) From a perchloroaromatic compound. Perchloroaromatic compounds have been fluorinated to give chlorofluoroalicyclic compounds, which were dechlorinated to give perfluoroaromatic compounds. Alternatively, and more directly, halogen exchange has been effected by reaction of perchloroaromatic compounds with metal fluorides. This method has proved to be especially useful in preparing polyfluoroheterocyclic compounds.

1.1 Preparation of Polyfluoroaromatic Compounds from Hydrocarbons

a) Preparation of Saturated Fluorocarbons

(i) Using Elemental Fluorine. Both the experimental techniques and the theoretical aspects of direct fluorination of organic compounds have been reviewed by Tedder.[1]

The reaction between hydrocarbons and fluorine is generally accepted to proceed by a free radical chain mechanism analogous to that of photochlorination, and is extremely exothermic, as is shown by the approximate heats of reaction for aliphatic hydrocarbons:[2]

$$F_2 \rightleftharpoons 2F\cdot \qquad D_{(F-F)} = +36 \text{ kcal.}$$

$$F\cdot + RH \longrightarrow HF + R\cdot \qquad \Delta H \sim -34 \text{ kcal.}$$

$$R\cdot + F_2 \longrightarrow RF + F\cdot \qquad \Delta H \sim -68 \text{ kcal.}$$

and if the heat liberated is not rapidly dissipated, combustion and fragmentation occur.

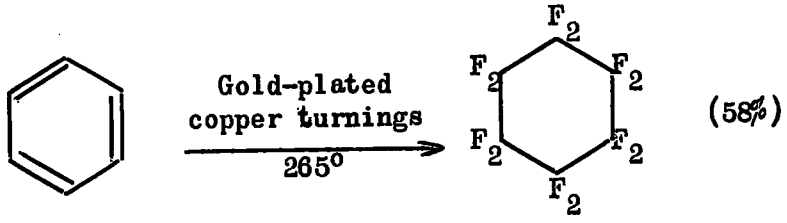
In an alternative mechanism, differing in its initiation step, Miller[3] considered that a fluorine molecule and a hydrocarbon molecule reacted to produce a fluorine atom and an alkyl radical:

$$RH + F_2 \longrightarrow R\cdot + F\cdot + HF \quad \Delta H \sim -4 \text{ kcal.}$$

The mechanism can be justified thermodynamically, and there is some qualitative experimental evidence to support it. [3,4].

Early attempts to moderate the fluorination reaction by the use of a relatively inert solvent such as carbon tetrachloride, have been described by Bigelow.[5] Results obtained by this method were discouraging, and attention was switched to the vapour phase reaction, first described by Fredenhagen and Cadenbach[6] and developed by Bigelow and co-workers[7] to produce dodecafluorocyclohexane in low yield by mixing benzene vapour with a fluorine-nitrogen mixture over a copper gauze packing.

Subsequent development by Cady and associates[8] gave good yields of dodecafluorocyclohexane:



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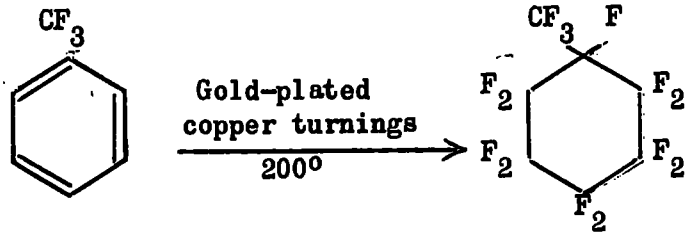
The highest yields were obtained with partly fluorinated compounds, e.g.:



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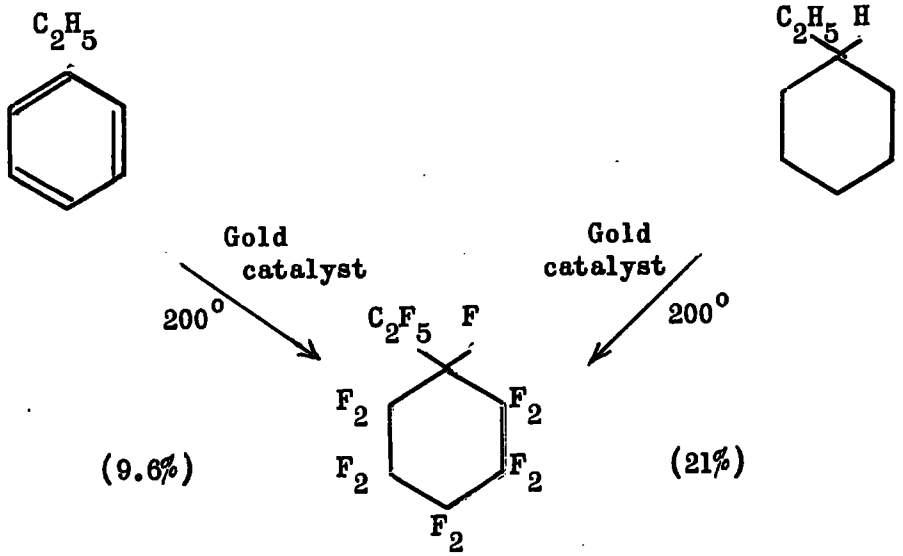
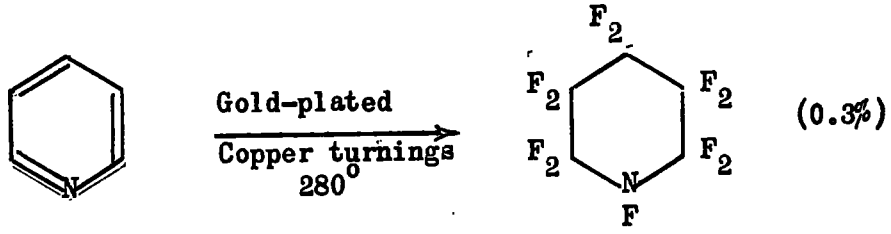
Aromatic hydrocarbons were reported to give higher yields than aliphatic hydrocarbons, a result which was contradicted by Haszeldine and Smith:[9]



Since the yields obtained by Haszeldine and Smith were markedly lower than those of Cady et al., it seems likely that the former

had failed to optimise the reaction conditions.

The "catalytic method" has been rather less successful in fluorination of heterocyclic compounds:[10]



The function of the metal packing has received considerable attention. Bigelow,[11] and Cady[8] considered that its effectiveness lay partly in its conversion into a fluoride which acted as a fluorinating agent. Subsequent work, particularly a comparative study of a number of different metal packings by Musgrave and Smith,[12] has suggested that the primary function of the metal is to disperse heat, and that fluorination by the metal fluoride is of secondary importance.

(ii) Using a High-Valency Metal Fluoride.

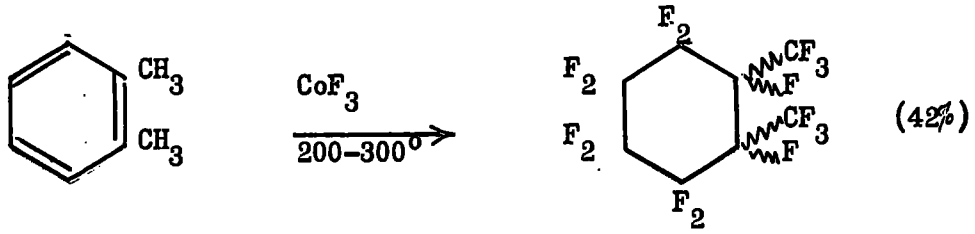
The use of a high-valency metal fluoride as a fluorinating agent for aromatic compounds was developed by Fowler and co-workers.[13]

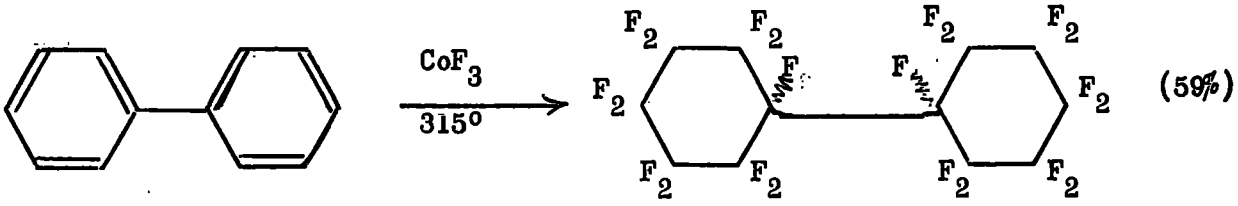
The reaction of hydrocarbons with cobalt trifluoride, the most widely used such reagent, proceeds thus:[2]

$$\rangle CH - + 2CoF_3 \rightarrow \rangle CF - + HF + 2CoF_2 \quad \Delta H \sim -58 \text{ kcal.}$$

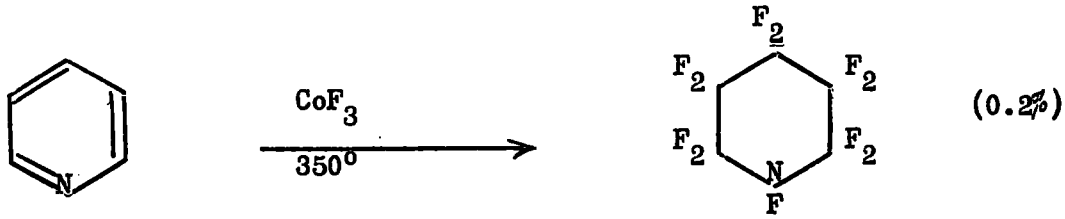
The fluorination is therefore less exothermic than the reactions of hydrocarbons with fluorine ($\Delta H \sim -102$ kcal. per mole of fluorine.), leading to a reduced tendency to carbon-carbon bond fission. Cobalt trifluoride is reduced during the reaction to cobalt difluoride, and in practical reactors, described in a review by Stacey and Tatlow,[14] the reagent was regenerated by passing fluorine through the reactor at about 200^{0}. A reaction scheme has been suggested by Stacey and Tatlow,[14] in which the reagent reacts with an aromatic ring by addition of fluorine to the 1,4-positions, followed, if possible, by elimination of hydrogen fluoride from the same positions. Fluorobenzene and p-difluorobenzene are therefore predicted to be intermediates in the fluorination of benzene, and these compounds have, in fact, been isolated in trace quantities from the products of this reaction. Fluorination of fluorobenzene and p-difluorobenzene, using potassium tetrafluoro cobaltate (III),[15] gives a similar product pattern to the fluorination of benzene by the same reagent, thus providing further evidence in favour of this reaction scheme.

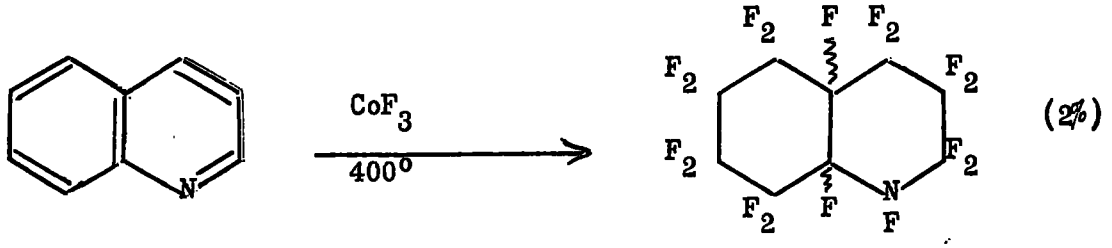
The method has generally proved superior to the "catalytic method", giving good yields from aromatic compounds:[13, 16].





The fluorination of heterocyclic compounds was less successful:[10, 17].





The isolation of perfluoro (n-propylcyclohexane), perfluoro (methylcyclohexane) and perfluorocyclohexane from the latter reaction provides strong evidence that cleavage of the heterocyclic ring may have been responsible for the poor yields in fluorination of such compounds.

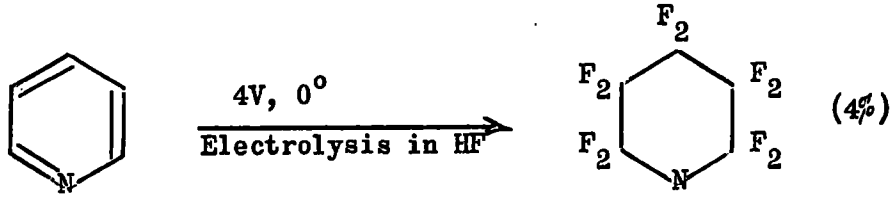
Whilst cobalt trifluoride has been most widely used as a fluorinating agent, many other fluorides have been employed. Silver difluoride is a vigorous fluorinating agent, but is rather less convenient in use than cobalt trifluoride.[14] Perhaps more useful, for synthetic purposes, are the milder fluorinating agents lead tetrafluoride,[18] cerium tetrafluoride,[19] and potassium tetrafluoro cobaltate (III).[15]

(iii) Electrochemical Fluorination

The electrochemical method of fluorination was developed by Simons and associates,[20] and has been reviewed by Burdon and Tatlow.[21] Many organic compounds were found to be soluble in anhydrous hydrogen fluoride to give conducting solutions which could be electrolysed, with evolution of hydrogen at the cathode and fluorination of the organic solute by an anodic process which is not fully understood. Where the organic substrate was insoluble

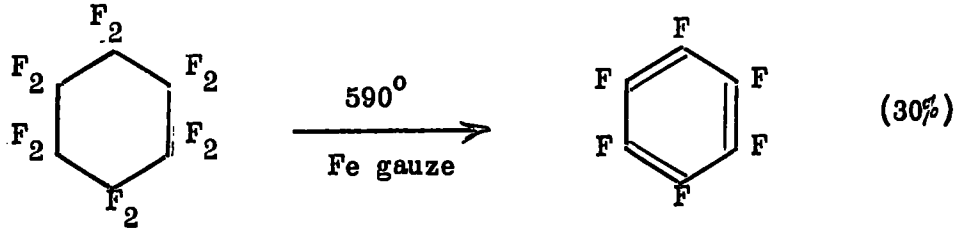
in anhydrous hydrogen fluoride, a suspension or emulsion was electrolysed, and non conducting solutions were made to conduct a current by the use of additives such as alkali metal fluorides.[20] Fluorine evolution at the anode, which would have led to extensive destruction of both the organic substrate and the anode, was prevented by using a potential of under 10 volts, an optimum figure being about 5 volts.[21]

The electrochemical process is considered inferior to the other methods of exhaustive fluorination of aromatic hydrocarbons,[21] but has proved superior to these methods in the preparation of undecafluoropiperidine from pyridine:[22,23].



b) Defluorination and Dehydrofluorination of Cyclic Fluorocarbons

Vapour phase defluorination by passage over finely divided iron or nickel at high temperatures has been widely used to aromatise cyclic fluorocarbons. Perfluorocyclohexanes, perfluorocyclohexenes and perfluorocyclohexadienes have been defluorinated in this way; the temperatures required decreased and the yields of hexafluorobenzone obtained increased in that order.[24]



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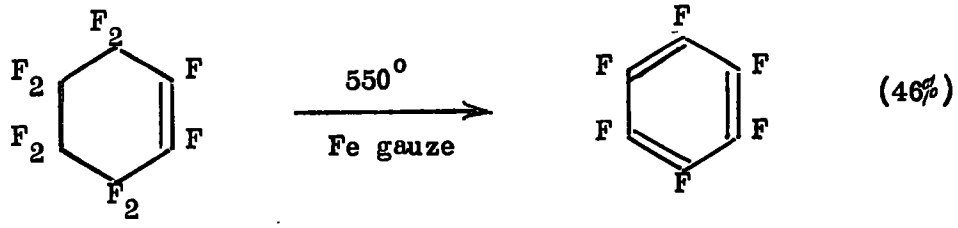

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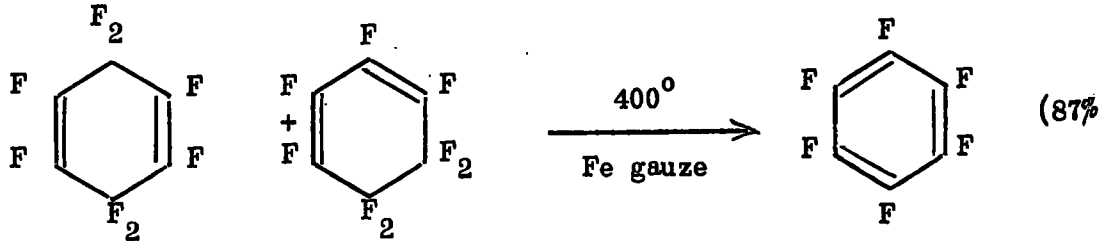

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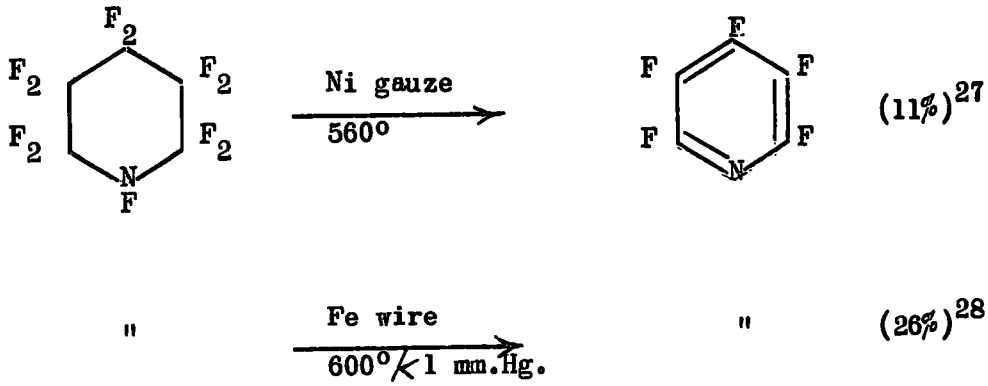
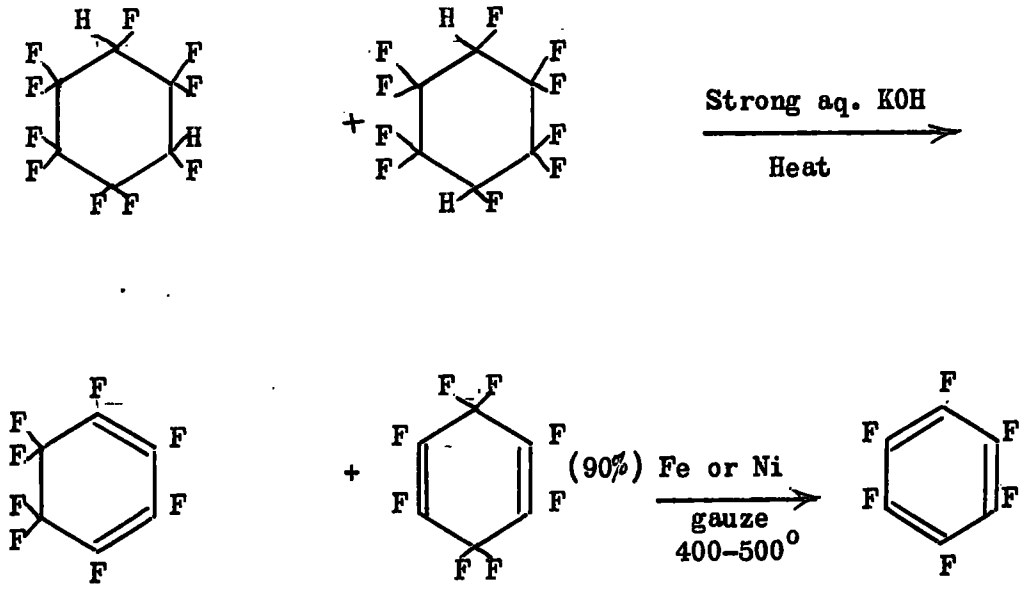
Defluorination of polycyclic fluorocarbons has given mixed results, perfluoronapthalene being obtained from perfluorodecalin in good yield,[25] whilst perfluorofluorene was not isolated from the products of defluorination of perfluoro (perhydrofluorene).[26]

Undecafluoropiperidine has been defluorinated by Tatlow and co-workers,[27] and Haszeldine and associates.[28] Haszeldine has stressed the desirability of defluorinating under reduced pressure to obtain good yields of pentafluoropyridine:[29]



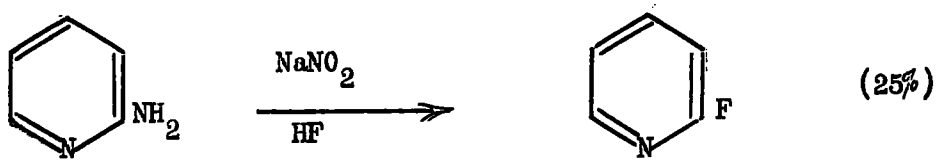
Partially fluorinated cycloalkanes may be dehydrofluorinated by heating with concentrated aqueous potassium hydroxide. This process forms a part of an important commercial synthesis of hexafluorobenzene based on defluorination of a mixture of octafluorocyclohexa-1, 3- and 1,4-dienes

obtained by dehydrofluorination of decafluorocyclohexanes, formed with other polyfluorocyclohexanes, when benzene was fluorinated with cobalt trifluoride at 150 - 200°:[2]



1.2 Fluorination via Aryldiazonium Salts

Schmidt and Von Gehren,[30] working in 1870, reported the first preparation of a fluoroaromatic compound by warming p-diazo benzoic acid with fuming hydro f luoric acid; they obtained p-fluorobenzoic acid in unreported yield. Subsequent development was slow, but included the preparation of 2-fluoropyridine by Tschitschibabin and Rjazancev:[31]



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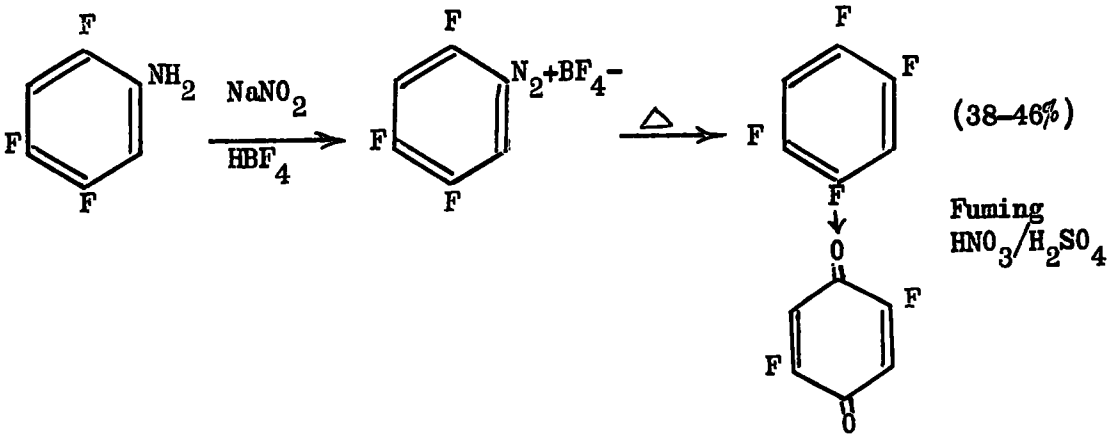
A most significant development was the discovery by Balz and Schiemann,[32] that the relatively stable aryl diazonium fluoroborates, precipitated by addition of fluoroboric acid or its alkali salts to a diazotised aromatic amine, could be thermally decomposed, yielding an aryl fluoride with liberation of nitrogen and borox trifluoride:

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

The application of what is commonly known as the "Schiemann reaction" to the preparation of a wide range of aryl fluorides, has been reviewed by Roe,[33] and more recently, by Suschitzky.[34] The scope of the reaction has been demonstrated by Finger and associates, [35] who were able to introduce up to four fluorine atoms into an aromatic ring, but subsequent nitration of 1, 2, 4, 5-tetrafluorobenzene led not to 1, 2, 4, 5 tetrafluoro-3-nitrobenzene, but to 2,5-difluorobenzoquinone:



The Schiemann reaction has also been applied to the synthesis of fluoroheterocyclic compounds, including 2- and 3-fluoropyridine,[36] 2,6-difluoropyridine,[37] monofluoroquinolines,[38] monofluoroisoquinolines,[39] and fluoropyrazine.[40] Roe and Hawkins were unable to isolate 4-fluoropyridine[36] or 4-fluoroquinoline.[38] Their explanation, in the case of 4-fluoropyridine, that this probably reacted with itself, has been supported by the finding of Wibaut and Broekman,[41] that 4-chloropyridine did slowly react with itself to give N-(4 pyridyl)-4' chloropyridinium chloride.

Whilst the Schiemann reaction has proved to be of great synthetic value, it has failed, or given poor yields, with certain classes of substrate. Yields of aryl diazonium fluoroborates have been affected by the high water solubility of some such salts, notably those containing hydroxyl or carboxyl substituents. The position and nature of substituents have also been found to affect the decomposition of the diazonium salt. In an isomeric series, the o-fluoro compound has usually been obtained in the smallest yield. Nitro-groups have a particularly adverse effect; thus o-fluoronitrobenzene has rarely been obtained in more than 10% yield,[34] and only a trace quantity of 1-fluoro-2, 4-dinitrobenzene was obtained by this method.[42] The

hetero-atom in nitrogen heterocyclic compounds exerts an influence similar to that of a nitro substituent, and yields of these compounds have usually been rather low. Side reactions occurring during either the diazotization or decomposition stages comprise a further serious limitation of the Balz-Schiemann method.[34]

These deficiencies of the Schiemann method have resulted in many attempts being made to find a superior general method, but usually results have been improved only in specific cases. Fern and Vanderwerf[43] decomposed aryl diazonium fluorides in anhydrous hydrogen fluoride, obtaining much improved yields of the three fluorobenzoic acids and of m-fluorophenol, but the improvement was not general, and the method inconvenient. Many alternative complex salts have been used to replace the fluoroborates. Roe and co-workers[44] concluded that the use of fluorosilicates instead of fluoroborates gave generally inferior yields of aromatic compounds, and Beatty and Musgrave[45] obtained similar results, except in special cases, with heterocyclic compounds. Rutherford, Redmond and Rigamonti[46] investigated the use of diazonium hexafluorophosphates, and found them to be preferable to fluoroborates in the preparation of fluorobenzoic acids and fluorophenols. The hexafluoroantimonates have been decomposed by Sellers and Suschitzky.[47] Their use was as practicable as that of

the corresponding fluoroborates, they were insoluble and light stable, and their decomposition points were lower than those of the corresponding fluoroborates and fluorosilicates. The method proved particularly useful in preparing o-fluoronitrobenzene in 40% yield, as opposed to the 10% usually obtained from the fluoroborate.[34]

1.3 Fluorination of Perchloroaromatic Compounds

a) The Fluorination - Dehalogenation Method

In 1947 McBee and co-workers[48] reported that when hexachlorobenzene was fluorinated with bromine trifluoride, the resulting mixture treated with antimony pentafluoride, and the product dehalogenated with zinc dust, a small amount (2%) of hexafluorobenzene was isolated. Fluorination of hexachlorobenzene, and the subsequent dehalogenation of the product has been developed by Musgrave and associates[49,50] to provide a useful route to hexafluorobenzene and chlorofluorobenzenes.

Chlorine trifluoride in large excess was employed to fluorinate hexachlorobenzene to give a mixture of chlorofluorocyclohexanes $C_6F_nFl_{12-n}$ (where n was mainly 5, 6 or 7) which could be dehalogenated over iron gauze:[49]

$$C_6F_7Cl_5 \xrightarrow[\text{Fe gauze}]{260^\circ} 21\%\ C_6F_6,\ 29\%\ C_6F_5Cl,\ 8\%\ C_6F_4Cl_2,\ 14\%\ C_6F_7Cl_3$$

The use of halogen fluorides as fluorinating agents has been reviewed by Musgrave.[51]

Liquid phase fluorination of hexachlorobenzene by fluorine was also reported:[50]

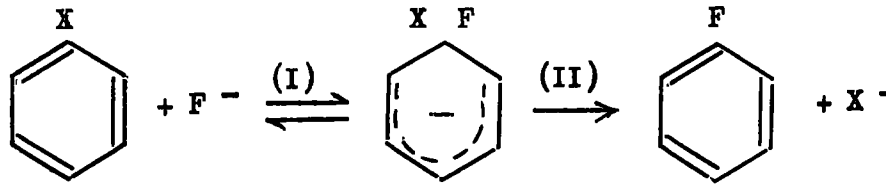
$$C_6Cl_6 + 3F_2 \xrightarrow[\text{Room temp.}]{CCl_2F\ CClF_2} \underset{>90\%}{[C_6Cl_6F_6]} \xrightarrow[330^\circ]{\text{Fe filings}} \begin{array}{ll} C_6F_6 & 22\% \\ C_6F_5Cl & 27\% \\ C_6F_4Cl_2 & 12.5\% \\ C_6F_3Cl_3 & 3\% \end{array}$$

b) <u>The Halogen Exchange Method</u>

Amongst the most useful methods which have been developed for the preparation of fluoroaromatic compounds is the halogen exchange method, in which fluoride ion displaces another halide ion from an aromatic compound. This substitution has been effected in the presence of a solvent, and in the absence of solvent.

(i) <u>Reactions in a Solvent</u>

The halogen exchange reaction is believed to proceed via. a charged transition state, which is considered to resemble the intermediate:[52]



In theory either the addition of fluoride ion to the substrate and the reverse process (I), or the decomposition of the intermediate (II) may be the rate determining step, but experimentally the first stage has normally been found to be rate determining.

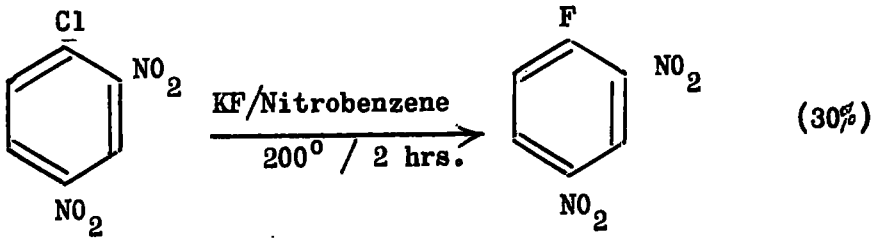
The choice of a suitable solvent is important; apart from the physical solution of the reactants, it must fully develop the nucleophilicity of the fluoride ion, and if possible, stabilize the transition state. Protic solvents are considered unsuitable for this purpose, since they strongly solvate, and therefore deactivate small anions. Dipolar aprotic solvents, e.g. dimethyl formamide, dimethyl sulphoxide and sulpholane solvate small anions much less strongly, and their powerful solvation of cations results in electrolytes being moderately soluble in such media.[53] In addition, polarizable charged transition states are more solvated, and hence more stabilized in dipolar aprotic solvents than in protic solvents. The characteristics and uses of dipolar aprotic solvents have been the subject of two reviews by Parker.[53,54.] Miller and Parker[55] have shown for some aromatic nucleophilic substitution reactions, that rate constants in dipolar aprotic solvents are up to 10^5 times greater than for reactions in protic solvents.

It is uncertain whether the reactive species in the fluorination of chloroaromatic compounds in dipolar aprotic solvents is fluoride ion or a metal fluoride ion-pair.[56] In either case, activity would be expected to increase with increasing cation size and Vorozhtsov and Yakobson[57] have verified experimentally that the order of activity of the alkali metal fluorides is:

$$LiF < NaF \ll KF < RbF < CsF.$$

Anhydrous potassium fluoride has been widely used because of its considerable activity in fluorination and low cost compared with the more active fluorinating agents, rubidium fluoride and caesium fluoride.

The fluorination of a chloroaromatic compound by this method was first described by Gottlieb:[58]



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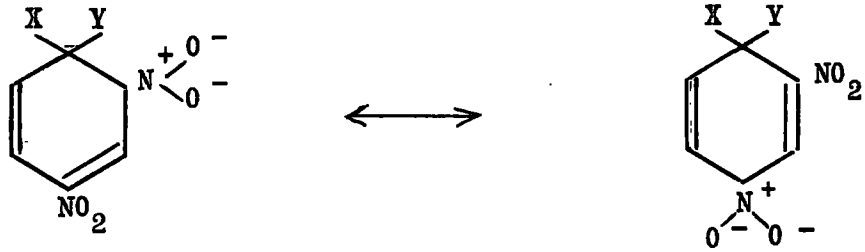
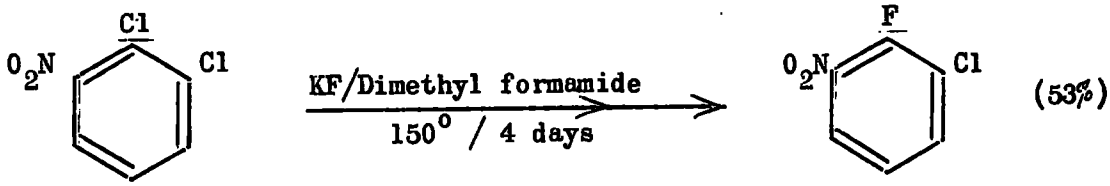
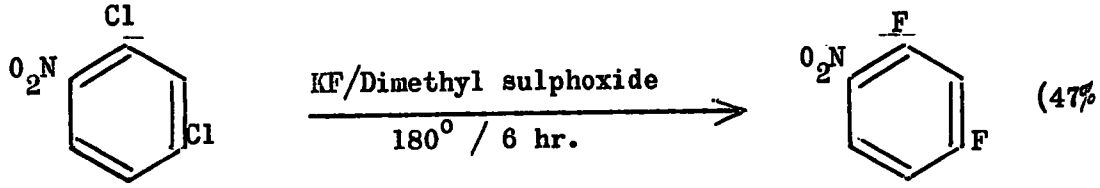
The effect of the ortho and para nitro-substituents is to strongly activate the molecule to nucleophilic attack, by delocalizing the negative charge in the transition state, which is considered to resemble the intermediate:[52]



By using more powerful dipolar aprotic solvents, Finger and co-workers were able to fluorinate mononitrochlorobenzenes:[59,60].

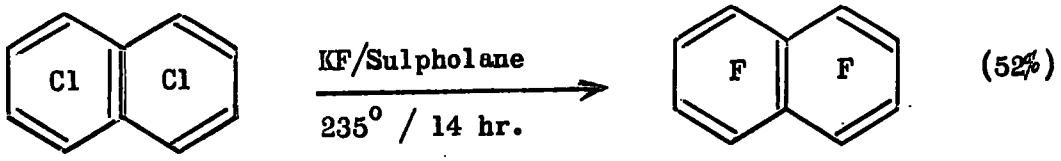




Since fluoronitrobenzenes are difficult to prepare in good yield by the Schiemann method,[34] this method has proved especially useful.

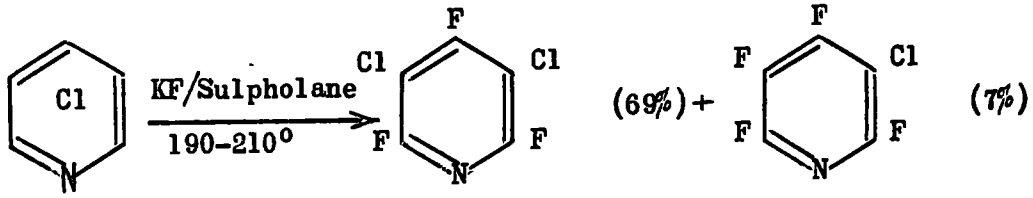
The scope of the halogen exchange method was further increased by the use of solvents which, while being of similar activity to those previously described, could be used at substantially higher temperatures. Thus Finger and associates[61] were able to prepare 2-fluoropyridine from 2-chloropyridine by heating with potassium fluoride in dimethyl sulphone or tetramethylene sulphone for 21 days. Fuller,[62] using sulpholane in the fluorination of hexachlorobenzene obtained small amounts of hexafluorobenzene, together with substantial yields of chlorofluorobenzenes, and was able to completely fluorinate perchloronapthalene:

$$C_6Cl_6 \xrightarrow[230\text{-}240^\circ/8\ hr.]{KF/Sulpholane} \begin{matrix} C_6F_6,\ 0.5;\ C_6ClF_5,25;\ C_6Cl_2F_4,24; \\ \text{and } C_6Cl_3F_3,\ 30\% \text{ molar yield.} \end{matrix}$$



Musgrave and co-workers [63] were unable to obtain pentafluoropyridine

from pentachloropyridine by using this solvent:



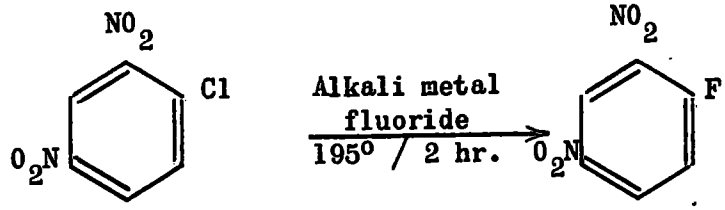
The halogen exchange method in a solvent therefore provides a useful route, complimentary to the Schiemann method, topartially fluorinated compounds with fluorine at positions which are most reactive in nucleophilic substitution. The method is not generally suited to the preparation of perfluoroaromatic and -heterocyclic compounds.

(ii) Reactions in the Absence of Solvents.

The scope of halogen exchange reactions in solvents is limited by either the boiling point (and the inconvenience of using pressure) or the decomposition temperature of the solvent, whichever is lower. By conducting the halogen exchange reaction in the absence of solvent, this limitation is removed, but some of the advantages of the solvent method are lost. This

method was first reported by Russian workers, and has been developed by workers in the University of Durham, and also at the University of Manchester Institute of Science and Technology.

Vorozhtsov and Yakobson,[57] comparing the activity of the alkali metal fluorides, as described in the previous section, reported reactions both in an autoclave in the absence of solvent and in dimethyl formamide. The order of activity in fluorination was the same in each case.



LiF,NaF - No reaction

KF,RbF,CsF - 51%, 88% and 98% yield resp.

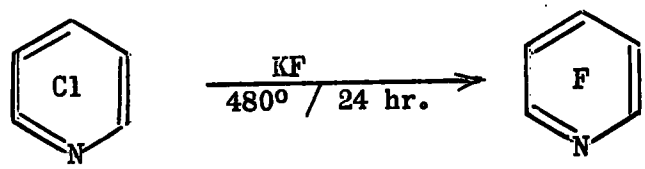
The decrease of the lattice energy, which must necessarily be overcome during the reaction, in the series of alkali metal fluorides from 242.8 kcal./mole in lithium fluoride to 176.0 kcal./mole in caesium fluoride,[54] may partly explain this order of activity.

In a later paper,[65] Vorozhtsov and Yakobson reported the preparation of hexafluorobenzene by the action of anhydrous potassium fluoride on hexachlorobenzene in the absence of solvent at 450 - 500°. The yield

of hexafluorobenzene was 21%, together with 46% of chloro-fluorobenzenes, which were separated and identified. This report clearly indicated the possibilities of this method and was soon followed by the preparation of a number of perfluoro-aromatic and perfluoroheterocyclic compounds from the corresponding perchloro-compounds.

Perchloroheterocyclic compounds may usually be fluorinated rather more readily than perchloroaromatic compounds, since the heterocyclic atom is able to stabilize the negative charge on the transition state, to a similar extent to the stabilization afforded by a nitro-group, as discussed in the previous section.

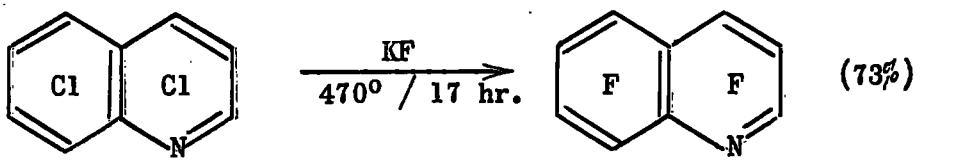
Chambers, Hutchinson and Musgrave,[63] and later Haszeldine and co-workers,[66] reported the preparation of pentafluoropyridine in high yield:

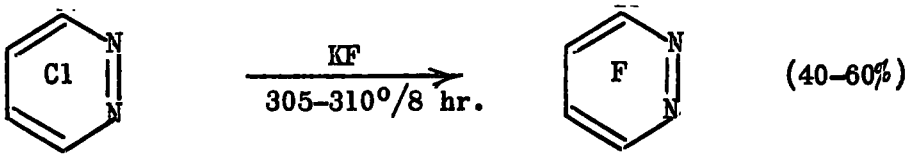


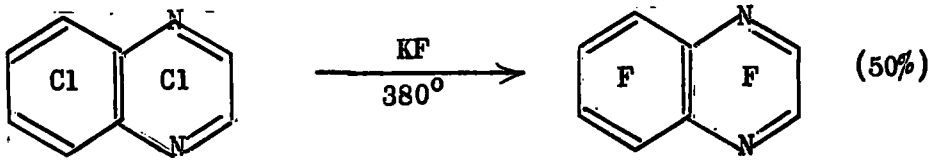
(68%)[63]

Preparations of heptafluoroquinoline and -isoquinoline,[67] tetrafluoropyrimidine,[68,69] tetrafluoropyrazine,[68] tetrafluoropyridazine,[70]

hexafluoroquinoxaline,[71] hexafluorocinnoline,[72] and hexafluoroquinazoline,[73] have subsequently been reported.



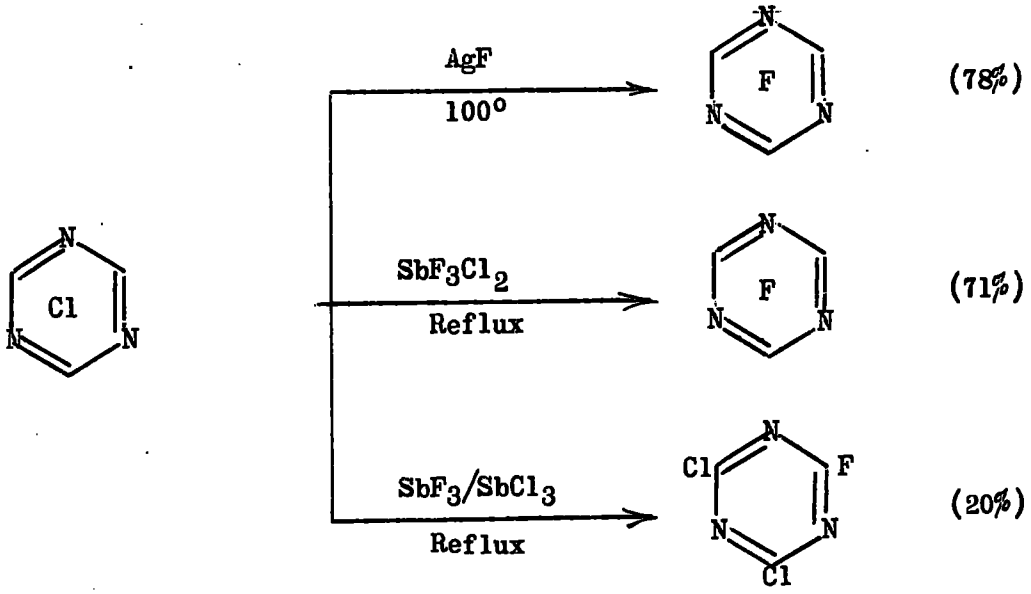




The conditions under which pentafluoropyridine was produced from pentachloropyridine caused complete decomposition of tetrachloropyridines, and Musgrave and co-workers[63] attributed this to the presence of hydrogen in the molecule. Boudakian has since made a study of the fluorination of partially chlorinated pyridines.[74,75]. Whilst complete degradation of 2-chloropyridine occurred with anhydrous potassium fluoride at 315°, the use of potassium hydrogen

fluoride under identical conditions resulted in a 74% yield of 2-fluoropyridine.[74] It was pointed out that the former was a liquid-solid phase reaction, whilst the latter reaction was homogeneous, both 2-chloropyridine and potassium hydrogen fluoride being liquids at 315°. Boudakian also prepared 2,6-difluoropyridine[75] in excellent yield by the solvent free process with anhydrous potassium fluoride, and remarked upon the inconsistent product pattern encountered in these fluorinations of partially chlorinated heterocyclic compounds.

The halogen-exchange reaction is not confined to the alkali metal fluorides. Schroeder and co-workers[76] reported the use of silver fluoride, and Bigelow and associates[77] used antimony chlorofluorides, for the fluorination of cyanuric chloride:



The development of the solvent free fluorination technique has provided a useful route to perfluoroaromatic compounds, but its value has been very much greater in the field of fluoroheterocyclic chemistry. It is the only technique which has been widely and successfully applied to the preparation of perfluoroheterocyclic compounds.

CHAPTER 2

Nucleophilic Substitution in Polyfluoroaromatic Compounds

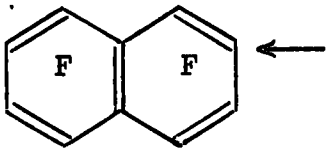
The most studied and most characteristic reaction of polyfluoroaromatic compounds is the displacement of a fluorine atom as fluoride ion by nucleophiles. Polyfluoroaromatic derivatives have been studied extensively, principally by workers in the University of Birmingham, and more recently, polyfluoroheterocyclic compounds have been investigated here, and at the University of Manchester Institute of Science and Technology.

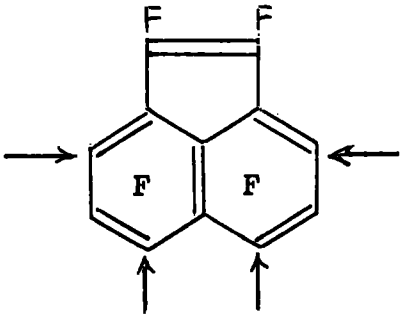
2.1 Substitution Reactions of Polyfluorocarbocyclic Compounds

Hexafluorobenzene reacts with a variety of nucleophiles e.g. $^{-}OCH_3$, [78] $^{78}OH^{-}$, [79] $^{79}NH_3$, [80] $^{80}NH_2CH_3$, [80] $^{80}NH_2NH_2$, [80] $^{80}SH^{-}$, [81] $^{81}CH_3^{-}$, [82] and $C_6H_5^{-}$, [83] giving monosubstitution products. Interest in these C_6F_5X derivatives has been chiefly in their ability to undergo further substitution, and in the orientation of the substituents in the products. In most cases (X = H, [84] CH_3, [84, 85] SMe, [84] CF_3, [84] and NMe_2 [86]) the fluorine <u>para</u> to X is replaced almost exclusively, but <u>meta</u> replacement

has been observed to predominate in a few cases ($X = NH_2$,[86] O^-,[85]). Two cases ($X = OMe$,[85] $NHMe$,[86]) where comparable amounts of *meta* and *para* replacement occur have been reported. Pentafluoronitrobenzene is substituted mainly in the *para* position when sodium methoxide in methanol is the attacking nucleophile, but with methylamine 65% *ortho* substitution was observed.[87] This has been ascribed to hydrogen bonding between the nitro group and the incoming nucleophile when this attacks the position *ortho* to the nitro group. When dimethylamine is the nucleophile the extent of *ortho* substitution is much reduced as a result, it is believed, of a steric effect. Similar increases in *ortho* substitution with amine nucleophiles to those observed in pentafluoronitrobenzene have been reported for pentafluoronitrosobenzene[88] and pentafluorobenzoic acid.[89] The interpretation of these results has been complicated by the subsequent finding of Tatlow and co-workers,[90] that *ortho* substitution of pentafluoronitrobenzene by sodium methoxide was dramatically increased by the change of solvent from methanol to diethyl ether containing a small proportion of methanol.

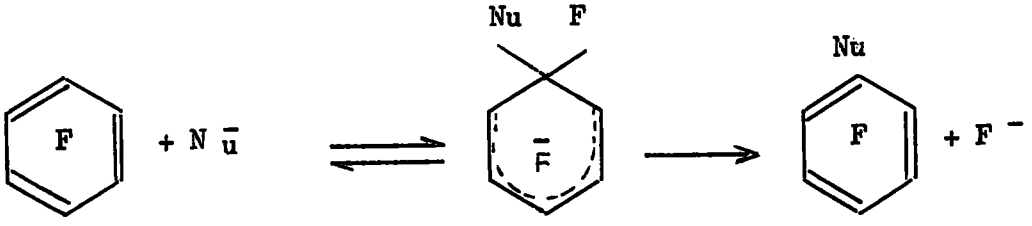
Octafluoronapthalene [91] is attacked by a number of nucleophilic reagents in the 2-position and perfluoroacenapthalene [92] reacts with sodium methoxide to give successive replacement in the 3-, 8-, 5-, and 6-positions.



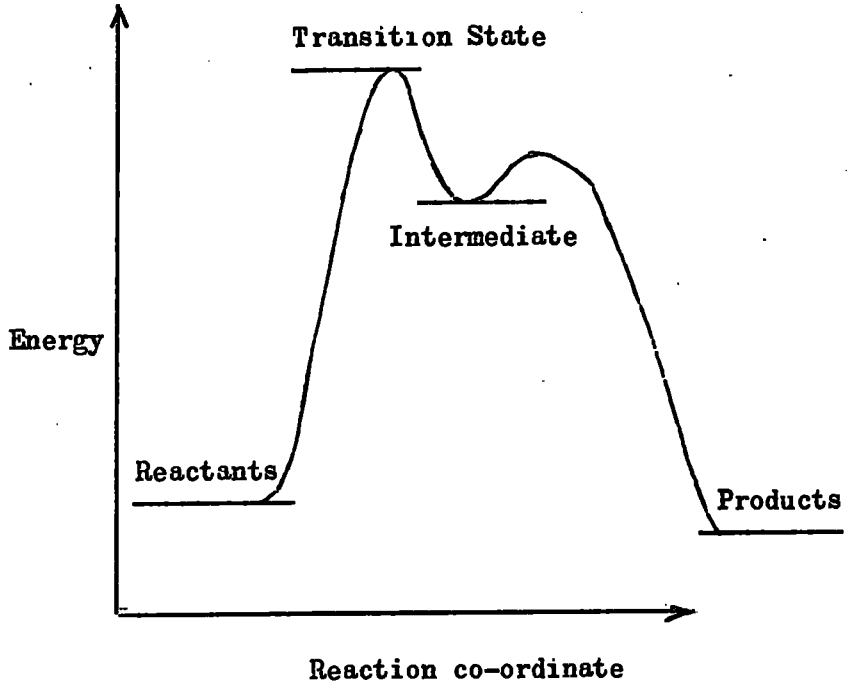


A rationalization of this series of reactions has been provided by Burdon, [93] and goes far towards explaining the orientation and reaction rate effects which have been observed.

The nucleophilic substitution of aromatic fluorocarbons is believed to proceed [56] <u>via</u> a charged transition state which is considered to resemble a Wheland-type intermediate:



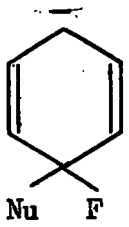
(I)

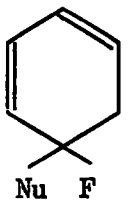


In those reactions which have been observed, the equilibrium leading to the formation of the intermediate has proved to be the rate-determining step.[56] Evidence for the formation of an intermediate of some stability in such reactions has been presented by Haszeldine and co-workers.[94]

Burdon[93] has suggested that the orientation of substituents can be rationalized by considering the relative stabilities of the transition states concerned, and reactivities of the fluoroaromatic compounds by considering the ground state stabilities as well. The resonance hybrid (II) is assumed to be the main contributor to the intermediate, with the hybrid (III) being of secondary importance. Molecular orbital

calculations [95] have provided evidence in support of this view.

(II) 

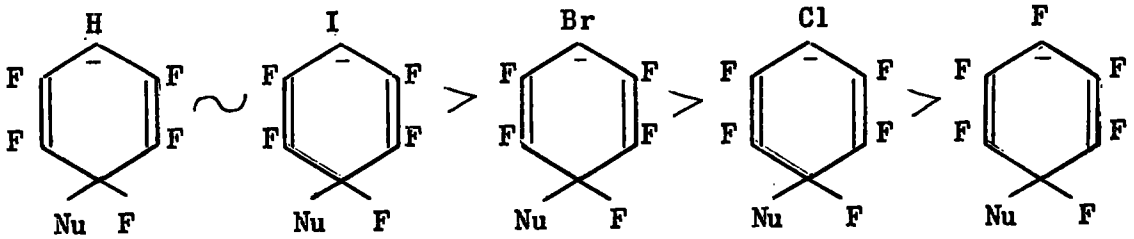
(III) 

The effect of substituents on the stability of the transition state (which is believed to resemble the intermediate) is supposed to depend upon the influence of the substituent attached to carbon bearing a negative charge on the stability of that charge. If the substituent stabilizes the negative charge, attack is predicted to occur mainly at the para position, with some ortho substitution. If, on the other hand, the substituent destabilizes the negative charge to greater extent than does fluorine, meta substitution is predicted to predominate. A substituent equivalent to fluorine in its destabilizing effect would lead to substitution in the statistical ortho:meta:para ratio of 2:2:1, since isomer distribution depends only on the relative energies of the transition states.

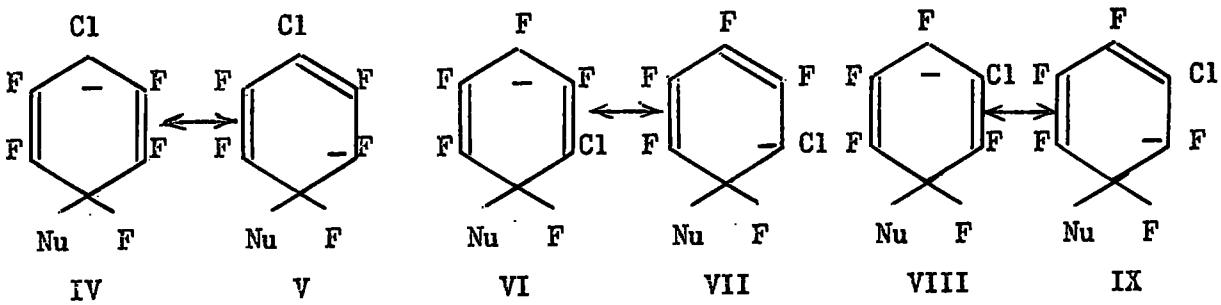
Stabilization of negative charge on carbon occurs when the substituent is a nitro or trifluoromethyl group as a result of inductive effects, and also, in the former case, by delocalization. Halogens destabilize

a negative charge on the carbon to which they are attached in the order F > Cl > Br > I ~ H. This is quite contrary to the normal electron-attracting behaviour of the halogens, and is attributed [93] to I II electron repulsion, a concept previously used to explain the ultra-violet spectra of halobenzenes. [96] This effect, decreasing in the series F → I is due, it has been suggested, to Coulombic repulsion between the p-electrons on the halogen and the ring π - electrons on the neighbouring carbon atom, [96] or to unfavourable penetration of filled orbitals containing these electrons. [97] The magnitude of the I II effect for nitrogen and oxygen substituents has not been determined, but is assumed [93] to be in the order N > O > F.

These concepts may be applied, for example, to the nucleophilic substitution of pentafluorobenzene and halopentafluorobenzenes, in which the order of stability of type II hybrids is considered to be:



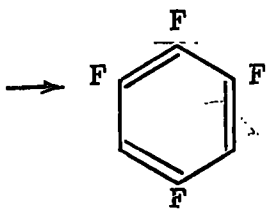
In the reaction of chloropentafluorobenzene with nucleophiles, the negative charge is located on chlorine-bearing carbon in the hybrids (IV) and (VII). Since (IV) is the more important <u>para</u>-quinonoid form, and (VII) the lesser <u>ortho</u>-quinonoid form,



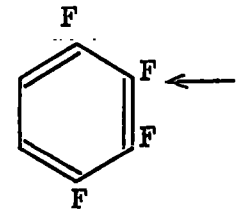
the intermediate to which hybrids (IV) and (V), leading to <u>para</u> substitution, contribute is favoured over that with hybrids (VI) and (VII), leading to <u>ortho</u> substitution. The intermediate with hybrids (VIII) and (IX), leading to <u>meta</u> substitution, is destabilized with respect to both of these intermediates, since in neither hybrid is the negative charge located on chlorine-bearing carbon. The substitution of chloropentafluorobenzene by sodium methoxide in methanol has been observed to give mostly the <u>para</u> substituted product, with about 17% <u>ortho</u> and negligible <u>meta</u> substitution.[98] The extent of ortho substitution decreases further in the series bromopentafluorobenzene (12%), iodopentafluorobenzene (5%) and pentafluorobenzene (3%). This is believed to be due to the transition

state for bromopentafluorobenzene being of lower energy than that for chloropentafluorobenzene, and to a greater difference in stability between bromo analogues of canonicals (IV) and (V), and (VI) and (VIII) than in the case of chloropentafluorobenzene. This difference is accentuated in iodopentafluorobenzene and pentafluorobenzene, although steric influences could be important, particularly in the case of iodopentafluorobenzene.

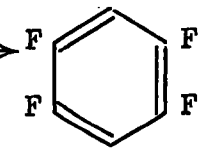
The same concepts explain the substitution of the tetrafluorobenzenes, which react with nucleophiles at the positions shown:[99]



X



XI

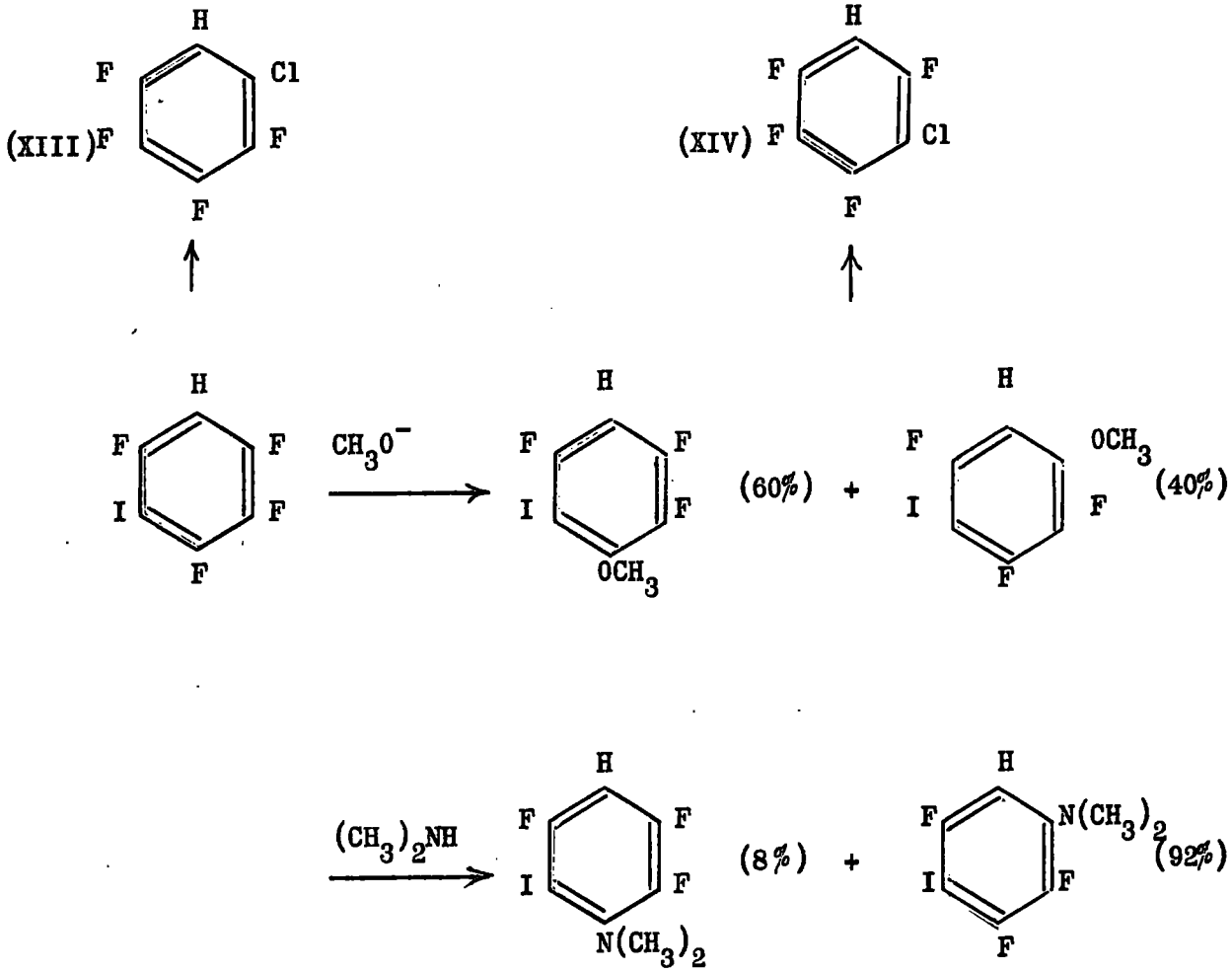


XII

The positions attacked in (X) and (XI) are those for which intermediates of type II, having the negative charge localized on a hydrogen-bearing carbon, are postulated. There is no orientation problem with tetrafluorobenzene (XII) but this compound reacts 10^3 times more slowly with sodium methoxide than the other tetrafluorobenzenes.[100] Since in this case the type II hybrid requires the negative charge to be located on a

fluorine-bearing carbon, and the three tetrafluorobenzenes will have comparable ground state energies, Burdon [93] concluded that these results confirmed the hypothesis that fluorine destabilizes a negative charge in an adjacent Π-system, and also that contributions to the transition state of type III intermediates were of only secondary importance.

The 1, 2, 3, 4-tetrafluoro-5-halogenobenzenes react with sodium methoxide or dimethylamine [100] mainly to replace the fluorine *para* to hydrogen (XIII), but some replacement of fluorine *para* to the halogen does occur, and increases in the series Cl→I, whilst remaining less than replacement *para* to hydrogen. Similar results were observed in the substitution of 1, 2, 3, 5-tetrafluoro-4-halogenobenzenes (XIV) with sodium methoxide, but with dimethylamine replacement of fluorine *para* to the halogen predominated when the halogen was Br or I. These results have been interpreted in terms of the relative I Π repulsions of the halogens as previously discussed, and in the case of substitution of 1, 2, 3, 5-tetrafluoro-4-bromo-and-iodo-benzenes with dimethylamine, steric hindrance is postulated to explain the unexpectedly high proportion of *para* substitution.



Octafluoronapthalene [91] and -acenapthalene [92] react with nucleophiles at the positions indicated on page 31. Attack at the 2-position of the napthalene localizes the negative charge in a type II hybrid on a bridgehead carbon atom, whereas attack at the 1-position would localize the charge in this hybrid type on to a fluorine bearing carbon. In the acenapthalene, the 3, 4, and 5 positions each have bridgehead carbon in the para position, but the 3- and 5-positions have only one ortho fluorine-

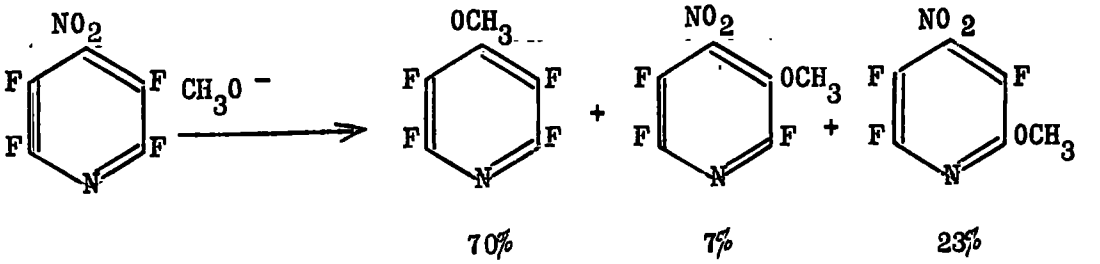
bearing carbon and the 4-position has two; the 1-position cannot be considered in these terms, but has been found to be relatively inactive in nucleophilic substitution.

2.2 Nucleophilic Substitution in Polyfluoroheterocyclic Compounds

Preparations of polyfluoroheterocyclic compounds have only been reported fairly recently, and these compounds have not therefore been examined in such depth as the derivatives of hexafluorobenzene. Most reported studies have concerned nitrogen-heterocyclic compounds.

Pentafluoropyridine was reported by Musgrave and co-workers,[101] and later by Haszeldine [102] to undergo nucleophilic substitution in the 4-position with a wide range of nucleophilic reagents. A particularly significant point was that pentafluoropyridine was substituted much more readily than hexafluorobenzene; thus pentafluoropyridine reacted with aqueous ammonia at 80° to give 4-amino tetrafluoropyridine, [101] whilst hexafluorobenzene reacted with the same reagent to give pentafluoroaniline at a convenient rate only above 160°. [80]

Several investigations of the nucleophilic substitution reactions of 4-substituted tetrafluoropyridines have been reported. When the substituent is OCH_3 [101,102] or Br, [103] further replacement occurs at the 2-position, then at the 6-position, and with excess sodium methoxide, 3,5-difluoro-2,4,6-trimethoxy pyridine [102] and 4-bromo-3,5-difluoro-2, 6-dimethoxypyridine [103] have been obtained. The reaction of 4-nitro-tetrafluoropyridine with sodium methoxide in methanol, however, gives a mixture of products: [104]

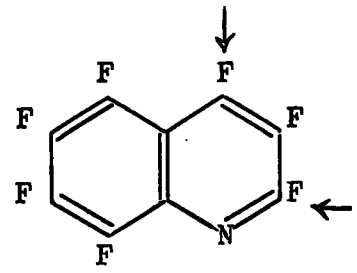


These results were quite unexpected: some replacement of fluorine ortho to the nitro group had been anticipated because of the powerful ortho activation of that substituent, but replacement of the nitro group was not expected because only replacement of fluorine occurs in the reaction of pentafluoronitrobenzene with nucleophilic reagents. [87] Furthermore, in 2, 3, 5, 6 - tetrafluoronitro-

benzene, a compound more akin to 4-nitrotetrafluoropyridine in having no fluorine atom para to the nitro group, the nitro group was not displaced by methoxide ion.[104]

The product distribution in the substitution of 4-nitrotetrafluoropyridine by sodium methoxide has been rationalized, by assuming that the ring nitrogen is the greatest factor in determining the orientation of substitution.[104] Furthermore, localization of negative charge in the transition state on nitrogen inevitably means a relatively lower electron density on the carbon atoms compared with the transition state for substitution of a polyfluorobenzene, and the effect of I II destabilization in the heterocyclic system is therefore diminished.[105]

Other perfluoroheterocyclic compounds have been reported to give mono substituted derivatives even more readily than pentafluoropyridine by attack at the positions shown:



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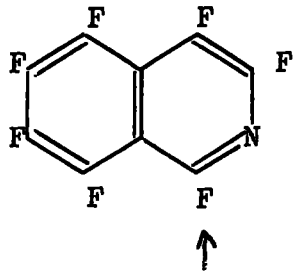

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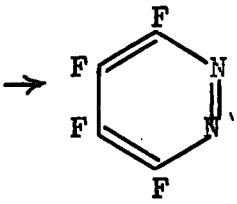

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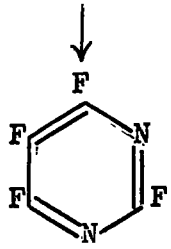

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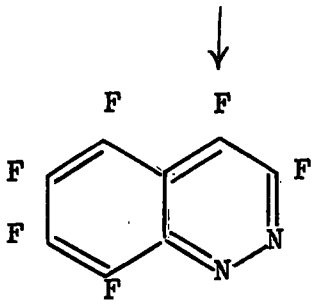
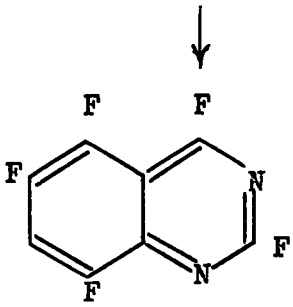
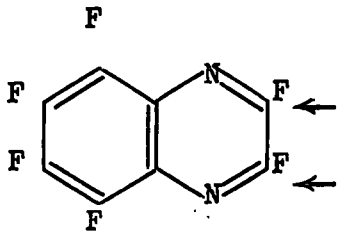
(107)



(72)



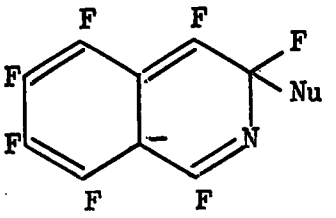
(73)



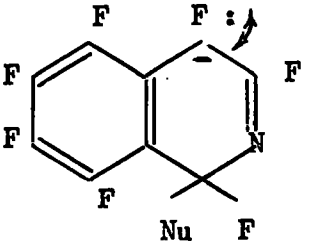
(71)

It may be predicted, by assuming control by the I II affect of fluorine, that the 4-positions of tetrafluoropyridazine and tetrafiuoropyrinidine will be the most reactive, and that positions 2 and 4 of heptafluoroquinoline will be of similar reactivity. This approach would appear to predict, however, that the 3-position in heptafluoro-

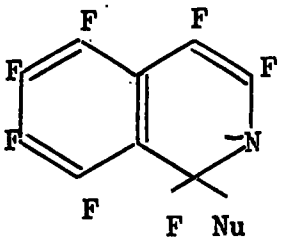
isoquinoline would be the first to be attacked, through a transition state represented by (XV), by analogy with the observed 2-substitution of octafluoronapthalene.[91] That 1-substitution occurs in spite of the apparently opposed I II effect, has been taken to indicate control by ring-nitrogen[105] as postulated to explain the substitution of 4-nitro-tetrafluoropyridine by methoxide ion.[104] Since 1-substitution through (XVII) occurs, rather than 3-substitution through (XVIII), the transition state represented by (XVII) is believed to have a lower localization energy, probably because it maintains the aromaticity of the carbocyclic ring.



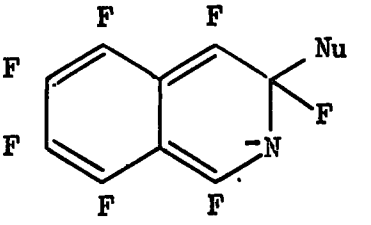
(XV)



(XVI)

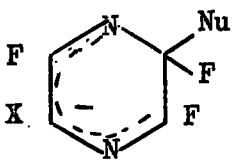


(XVII)

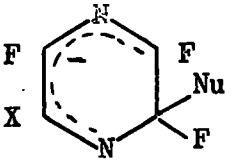


(XVIII)

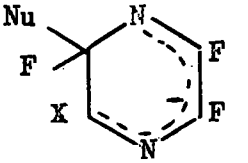
Despite the absence of fluorine para to ring-nitrogen, tetrafluoropyrazine reacts readily with nucleophilic reagents to give monosubstituted derivatives.[108] Disubstitution has also been reported;[107] alkoxy-substituents direct the second substituent to the ortho position, and other groups investigated to the para position. Each of the three positions of entry available to the second substituent is ortho to one of the ring nitrogen atoms and meta to the other, so that the dominant factor in determining orientation of substitution is not the ring-nitrogen atoms, but the nature of the first substituent. The transition states leading to substitution in the trifluoropyrazines can be represented by (XXI) to (XXIV):



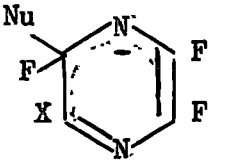
(XXI)



(XXII)



(XXIII)



(XXIV)

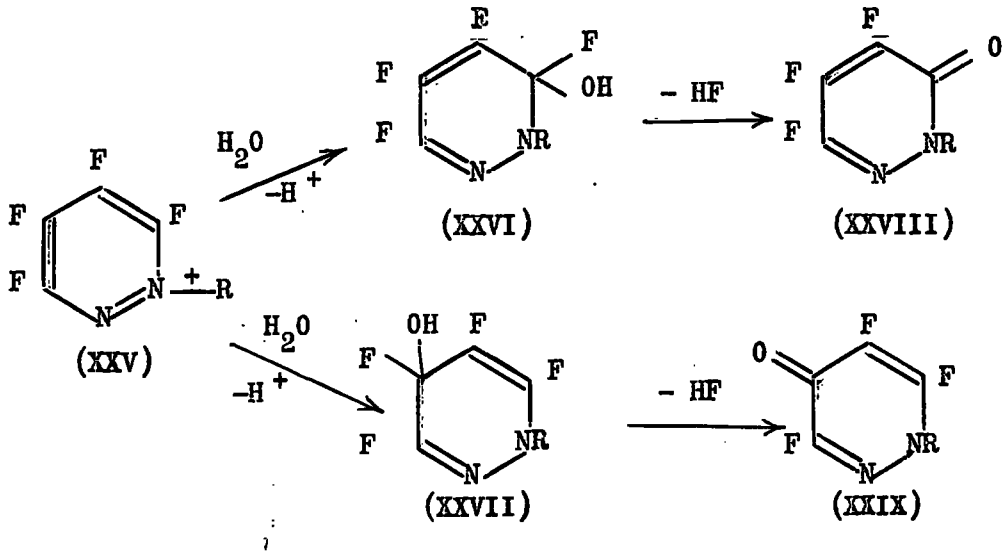
When X is alkyl, (XXI) is preferred because it is more favourable for the higher charge to be on a carbon atom bound to X than on one bound to fluorine. When the substituent X is alkoxy, however, I II repulsion from oxygen can be comparable to, or greater than, that of fluorine and

(XXI) is no longer preferred. Andreades [108] has suggested that while a fluorine atom destabilizes a negative charge on an attached carbon atom by I $\overline{\text{II}}$ repulsion, it stabilizes a negative charge on an adjacent position. This may explain why (XXIII) is preferred to (XXII), since fluorine would be expected to be more effective than alkoxy in stabilizing the system (XXIV) with the highest charge on the adjacent nitrogen atom.

The substitution reactions of the recently reported hexafluorocinnoline, [72] - quinazoline, [73] and - quinoxaline [71] are in accord with the preceding arguments. Thus hexafluorocinnoline and hexafluoroquinazoline are substituted first in the position para to one of the ring nitrogen atoms, and hexafluoroquinoxaline, with no para fluorine, is substituted ortho to ring nitrogen.

The nucleophilic substitution reactions so far described have been conducted under basic conditions, but substitution under acidic conditions has been reported. [67, 109] Tetrafluoropyridazine undergoes substitution at the 4- and 5- positions under basic conditions, [105] but under acidic conditions attack occurs at the 3- and 6- positions, adjacent to the ring nitrogen atoms. [109] Substitution under acidic conditions is

believed to proceed by protonation of tetrafluoropyridazine to give a tetrafluoropyridazinium cation (XXV) which would then be subject to nucleophilic attack to give either, or both, of the uncharged intermediates represented by (XXVI) and (XXVII), followed by the elimination of hydrogen fluoride to give the pyridazin ones (XXVIII) and (XXIX).



The relative energies of the transition states leading to these intermediates are believed to govern the orientation of substitution. If the transition states resemble the intermediates, the conjugated diene nature of (XXVI) probably lowers its energy compared with the unconjugated diene (XXVII). Nucleophilic substitution would also be expected to be facilitated at the 6-position adjacent to the positive

nitrogen atom, because this is the most electron deficient position and (XXVIII) is the observed product. This mechanism, involving initial protonation, is supported by the observation that quaternary salts of tetrafluoropyridazine (XXV, R = Me or Et) are hydrolysed to the corresponding pyridazinones (XXVIII, R = Me or Et), and by n.m.r. studies of tetrafluoropyridazine in solution in conc. sulphuric acid.

The significant difference in behaviour under nucleophilic substitution between polyfluoroheterocyclic compounds and polyfluorobenzenes is interpreted as being due to the ability of the hetero-atom to so affect the system as to outweigh repulsion effects. The great facility with which polyfluoroheterocyclic compounds undergo nucleophilic substitution, and many of the observed orientational effects can best be explained by considering the influence of the hetero-atom to be predominant, with I TI repulsion effects being of secondary importance.

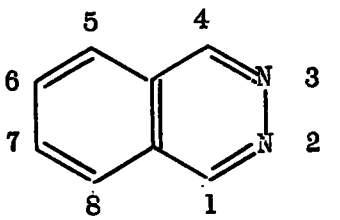
CHAPTER 3

Some Aspects of the Chemistry of Phthalazines

The chemistry of phthalazines has been discussed in reviews by Vaughan,[110] Simpson,[111] and more recently by Elderfield.[112] Two aspects of phthalazine chemistry, namely the nucleophilic substitution reactions and tautomeric behaviour of phthalazine derivatives, have particular relevance to the present study and are discussed below.

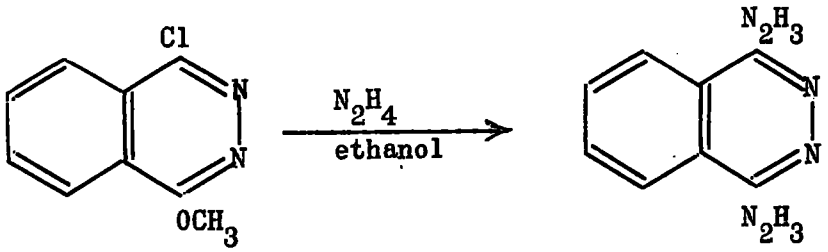
3.1 Nucleophilic Substitution of Phthalazine Derivatives

Phthalazine is benzo [d] pyridazine and the numbering system used in "Chemical Abstracts" and throughout this work is shown below:

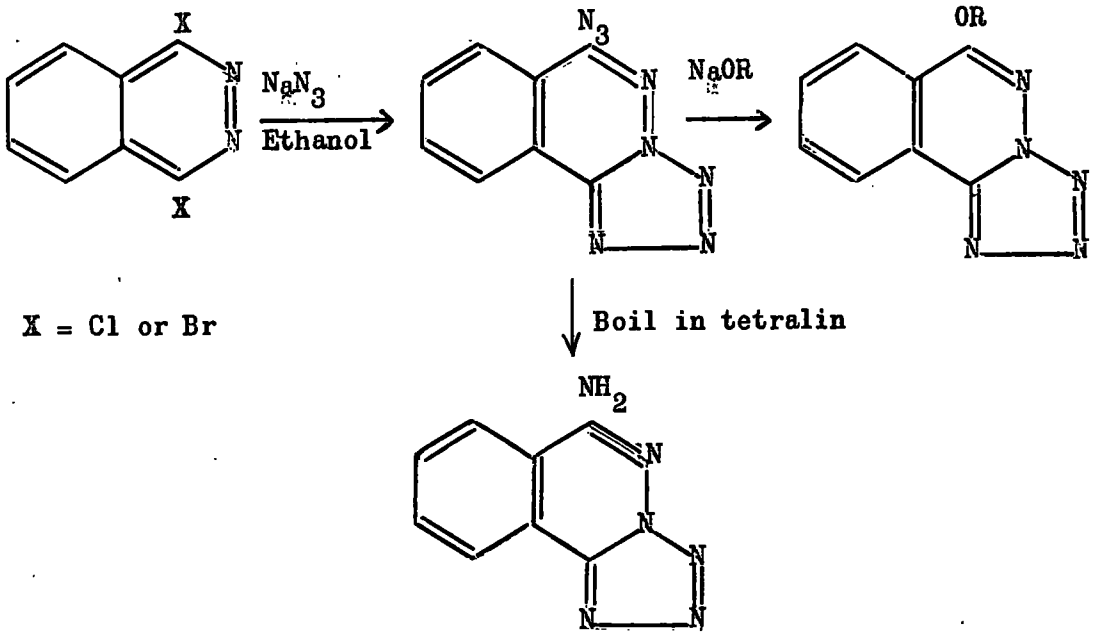


Halogen substituents in the 1 and 4 positions of phthalazine are readily susceptible to nucleophilic displacement reactions with amines[113-115] and with sodium alkoxides[116-121] to yield the corresponding amino- and alkoxy-phthalazines. Hydrazine replaces both the chloro- and

methoxy-groups of 1-chloro-4-methoxyphthalazine to give 1,4-dihydrazinophthalazine.[122]



Stolle and Stoch [123] reported the preparation of an interesting series of compounds from the reaction of 1,4-dichloro- or 1,4-dibromo-phthalazine and sodium azide:



Kinetic studies have been reported by Chapman and Russell-Hill [124] for the reaction of sodium etnoxide with a series of chloro-heterocyclic compounds:

Compound	Rate Constant at 20°C. (l. mole $^{-1}$ sec.$^{-1}$)
2-chloropyridine	2.2×10^{-9}
4-chloropyridine	8.7×10^{-8}
2-chloroquinoline	6.3×10^{-7}
4-chloroquinoline	6.5×10^{-7}

/...

/... | Compound | Rate Constant at 20°C. (l.mole $^{-1}$ sec. $^{-1}$)

1-chloroisoquinoline	6.9×10^{-7}
4-chlorocinnoline	4.77×10^{-3}
2-chloroquinoxaline	8.28×10^{-3}
1-chlorophthalazine	1.86×10^{-3}

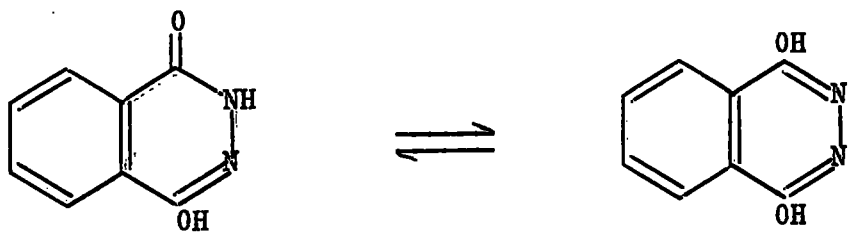
These results clearly indicate that 1-chlorophthalazine, together with 2-chloroquinoxaline and 4-chlorocinnoline, are far more reactive towards sodium ethoxide than chloro-pyridines, -quinolines and -isoquinolines.

Further evidence of the high reactivity of 1-substituted phthalazines in nucleophilic substitution reactions has been described by Barlin and Brown [125, 126] who examined the reactions of 1-methylsulphonyl-, 1 methylsulphinyl-, and 1-methylthio-phthalazine with sodium methoxide, in comparison with other heterocyclic compounds containing the same substituents. Their results indicate an approximate order of increasing reactivity: 2- and 4- substituted pyridines $<$ 2- and 4-substituted quinolines $\sim$ 3-substituted isoquinoline $<$ 2-substituted pyrazine $\sim$ 3-substituted pyridazine $<$ 4-substituted pyridazine $<$ 2-substituted quinoxaline $\sim$ 4-substituted cinnoline $\cup$ 1-substituted phthalazine. The differences are substantial; thus the rate constants for the reactions of 4-methylsulphinyl-pyridine and 1-methylsulphinyl-phthalazine with sodium methoxide are respectively 2.41×10^{-2} at 110° and 261×10^{-2}

1. mole $^{-1}$ sec $^{-1}$ at 30°C.

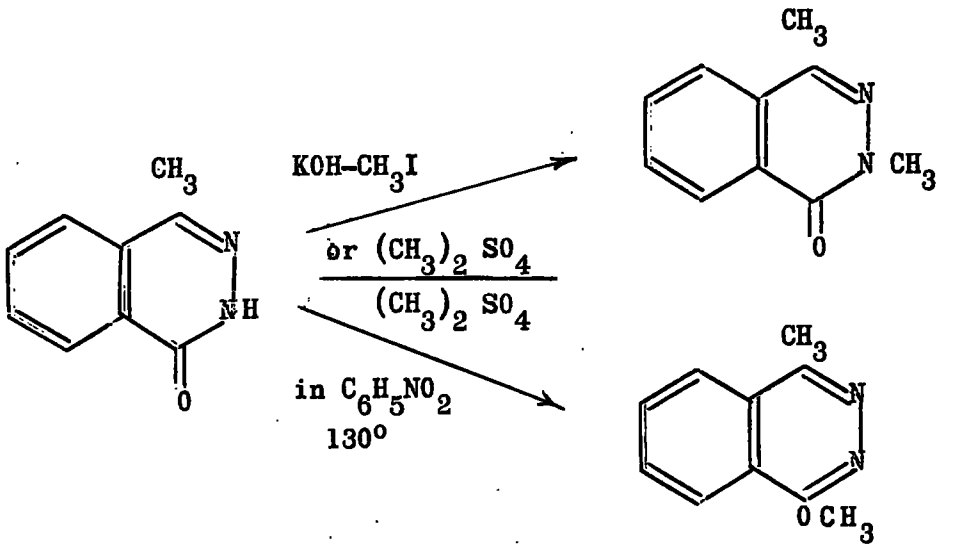
3.2 Tautomerism in 2H-Phalazin-1-one and 2H, 3H-Phthalazin-1,4-dione

2H-Phthalazin-1-one (I) is tautomeric with 1-hydroxy-phthalazine (II) and evidence has been reported in favour of each of these possible structures:



(I) (II)

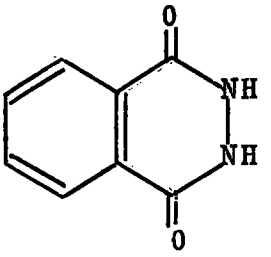
Chemical evidence from alkylation and acetylation of 2H-phthalazinones is inconclusive since either N - or O - alkylated and acetylated derivatives may be formed under appropriate conditions.[111, 112] Only N-alkyl derivatives have been detected on alkylation of 2H-phthalazin-1-one,[111] but 4-methyl-phthalazin-1-one may form either N - or O - methyl derivatives:[127]



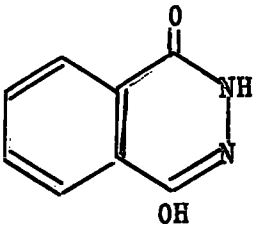
Alkylation and acetylation experiments cannot indicate the position of tautomeric equilibrium, since a minor amount of one tautomer (at equilibrium) which reacts much faster than the major tautomer, may lead to the major product.

More recently Mason [128] and Sheinker and Pomerantsov [129] have reported infrared spectroscopic evidence favouring the existence of 2H-phthalazin-1-one as the lactam form (I). Thus N-H stretching frequencies of 3292 cm^{-1} and 3240 cm^{-1} and a strong C = O stretching vibration at 1658 cm^{-1} were observed in the solid state. This evidence may be considered to be of greater value than the results of alkylation experiments.

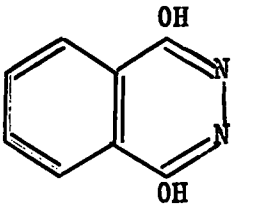
The structure of 2H, 3H-phthalazin-1, 4-dione or phthalhydrazide has received some attention, with the three tautomeric forms (III), (IV), and (V) being a priori possibilities:



(III)

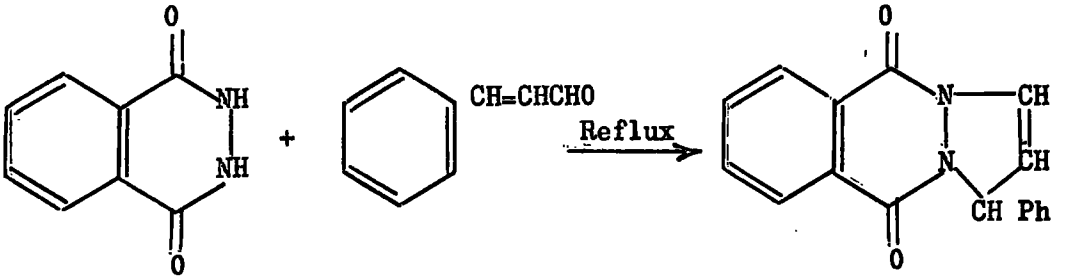


(IV)



(V)

Radulescu and Georgescu [130] considered that the compound was best represented by formula (III) whilst Rowe and Peters [127] considered that there was no justification for the dione form (III) and that, 1,4-dihydroxyphthalazine (V) existed in acid or neutral solution and 1-hydroxyphthalazin-4-one (IV) in alkaline solution. Drew and Hatt [131] subsequently asserted the predominance of the dione formula (III) emphasising the result of the reaction with cinnamaldehyde:



Little significance can be attached to these conclusions because the results of alkylation and acetylation experiments may be so affected by reaction rate factors, as previously described.

Spectroscopic evidence has been reported independently by Sheinker and co-workers, [132] and by Elvidge and Redman [133] which clearly supports the structure (IV). Thus the ultraviolet spectrum of 2H, 3H-phthalazin-1, 4-dione resembled that of its O, N-dimethyl derivative, and was dissimilar to those of the N, N^1 and OO^1 dimethyl-derivatives [133]. Further evidence that the structure was at least partially of a lactam form was provided by the infrared spectrum which had a strong C = O stretching band at 1655 cm^{-1} and a N-H stretching frequency of 3130 cm^{-1} in the solid state.

DISCUSSION OF EXPERIMENTAL WORK

CHAPTER 4

Preparation of Hexafluorophthalazine

The preparation of fluorophthalazines had not been reported prior to this work, and it was necessary to consider how hexafluorophthalazine might be prepared from readily accessible starting materials. Previous syntheses of perfluoroheterocyclic compounds, described in Chapter 1, have demonstrated the wide applicability of the halogen exchange method of fluorination of a perchloroheterocyclic compound, and this method was therefore envisaged as a potential final stage in the synthesis of hexafluorophthalazine. Hexachlorophthalazine, which is an essential intermediate in such a route, has not been described and two approaches to its preparation were considered as *a priori* possibilities:

(a) High temperature chlorination of phthalazine, a known polychlorophthalazine or 2H, 3H phthalazin-1, 4-dione. 1,4,5-Trichlorophthalazine [134] and 1,4,6,7-tetrachlorophthalazine [135] have been reported, but were apparently much less accessible than 1,4-dichlorophthalazine. [136] Phthalazine is also less readily

obtained than 1,4-dichlorophthalazine, but 2H, 3H phthalazin-1,4-dione is perhaps the most easily prepared phthalazine derivative.[111]

(b) Replacement of the enolic hydroxyl groups in the 1- and 4- positions of the reported [137] 5, 6, 7, 8-tetrachloro-2H, 3H-phthalazin-1,4-dione. Since Drew and Pearson [138] suggested that the compound obtained by condensation of tetrachlorophthalic acid or its anhydride with hydrazine hydrate, and described by early workers as 5, 6, 7, 8-tetrachloro-2H, 3H-phthalazin-1, 4-dione was in fact N-amino-3,4,5,6-tetrachlorophthalimide, grave doubts existed as to the viability of such a route.

4.1 Preparation of 2H, 3H-Phthalazin-1, 4-dione

Mihailescu and Florescu [139] reported the preparation of 2H, 3H-phthalazin-1, 4-dione by condensation of phthalic anhydride and hydrazine sulphate in glacial acetic acid containing sodium acetate. This method was adapted by adding hydrazine hydrate, rather than the sulphate, and no sodium acetate was found to be required. The method reported by Radulescu and Georgescu, [130] in which phthalic anhydride in refluxing ethanol was treated with hydrazine hydrate, and the

product precipitated by addition of conc. hydrochloric acid, was found to give poor yields of a product contaminated by hydrazine hydrochloride, which could only be removed with difficulty.

4.2 Preparation of 1,4-dichlorophthalazine

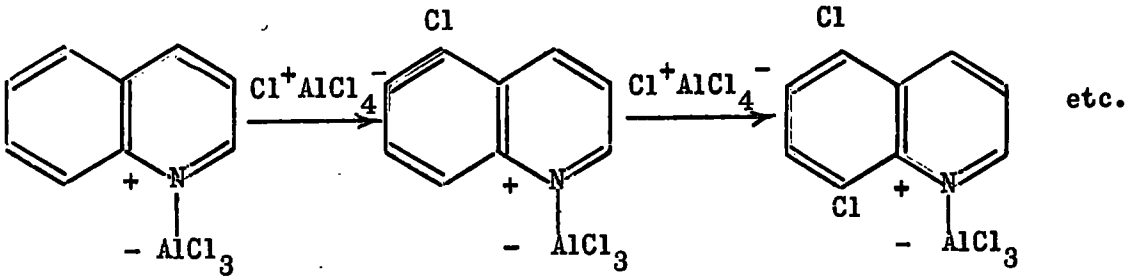
Hirsch and Orphanos [136] surveyed the methods available for the preparation of 1,4-dichlorophthalazine, and found that they gave yields which were usually poor and difficult to reproduce. They reported a method in which 2H, 3H-phthalazin-1,4-dione was heated with phosphorus pentachloride at 140-160° for 4 hours in a sealed and stirred pressure vessel. The product was treated with ice, neutralized with ammonia solution, and extracted with dichloromethane. This method was adopted here with minor modifications, after similar difficulties to those described by Hirsch and Orphanos had been encountered with other reported methods. Stirred autoclaves were not available, and the absence of stirring may account for the reduced yield (75%) compared with 96% reported by Hirsch and Orphanos. Neutralization by ammonia solution after the product had been treated with ice was found to improve neither the quality nor the quantity of the product, and this step was therefore omitted.

4.3 Preparation of Hexachlorophthalazine

Perchloroheterocyclic compounds have been prepared by the reaction of heterocyclic compounds with phosphorus pentachloride at high temperatures in sealed vessels. Thus pentachloropyridine [63] was obtained by the action of phosphorus pentachloride on pyridine in a sealed autoclave at 280° and perchloropyrazine [107], perchloropyridazine, [105] perchloropyrimidine, [69] perchloroquinoxaline [71] and perchloroquinazoline [73] have also been obtained from partially chlorinated derivatives under similar conditions. Wyman and co-workers [140] believed that an ionic mechanism, involving addition-elimination of the PCl_4^+ ion, was usually responsible for nuclear chlorination of aromatic compounds by phosphorus pentachloride, and postulated a free radical mechanism for side chain chlorination.

A series of experiments in which 2H, 3H-phthalazin-1,4-dione or 1,4-dichlorophthalazine, and excess of phosphorus pentachloride were heated in a nickel-lined autoclave to various temperatures between 260 and 320°, all resulted in extensive decomposition.

Gordon and Pearson [141] described the chlorination of quinoline with chlorine in the presence of aluminium trichloride to give 5,8-dichloro- and 5, 6, 7, 8-tetrachloroquinoline and also a similar preparation of 5-chloro-, 5,8-dichloro-, and 5, 7, 8-trichloro isoquinoline. The method was subsequently developed by Musgrave and Chambers and their co-workers [67] to prepare pentachloroquinoline and hexachloro-isoquinoline. The following mechanism has been advanced by Gordon and Pearson for chlorination of the complexed heterocyclic compound:



This method has been applied to the chlorination of 1,4-dichloro-phthalazine and under appropriate conditions, resulted in exhaustive chlorination to give hexachlorophthalazine in good yield. The extent of reaction could be determined at any stage by sampling the reaction mixture, treating this sample with water, and examining it by t.l.c. At 200 - 210° chlorination was complete after approximately $2\frac{1}{2}$ days. Hexachlorophthalazine was isolated by hydrolysis of the $AlCl_3$-complex with water and was moderately resistant to hydrolysis by atmospheric moisture, but it was readily hydrolysed if, for example, inadequately

dried solvents were used for its recrystallisation.

4.4 Attempted Preparation of 5, 6, 7, 8-Tetrachloro-2H,3H-phthalazin-1,4-dione.

The preparation of 5, 6, 7, 8-tetrachloro-2H, 3H-phthalazin-1, 4-dione was reported by Phelps [137] who heated tetrachlorophthalic acid with hydrazine hydrate at 140 - 150°. Drew and Pearson [138] repeated this preparation and reported that the product was N-amino-3,4,5,6-tetrachlorophthalimide. Their investigations of the reactions of a range of substituted phthalic anhydrides and acids with hydrazine hydrate suggested that an N-amino phthalimide was an intermediate in the reaction, and might, or might not, rearrange to give a phthalazin-1,4-dione, depending on the relative stabilities of the 5- and 6-membered ring systems. They considered that the tetrachlorophthalazin-1,4-dione was, for steric reasons, less stable than the N-amino-tetrachlorophthalimide.

As 5, 6, 7, 8-tetrachloro-2H, 3H-phthalazin-1,4-dione was potentially an excellent intermediate in a synthesis of hexachlorophthalazine, these conclusions warranted further investigation. In particular, it was

considered that under acid-catalysed conditions, the isomerization of the N-amino-tetrachlorophthalimide to the tetrachlorophthalazin-1, 4-dione might be encouraged. Accordingly, tetrachlorophthalic anhydride in conc. sulphuric acid was treated with hydrazine sulphate at 200° for 11 h. The product was identified as N-amino-3, 4, 5, 6-tetrachlorophthalimide by comparison of its i.r. spectrum and melting point with those of an authentic sample. The same product was obtained from this condensation under various conditions.

4.5 Preparation of Hexafluorophthalazine

The halogen exchange method has been extensively discussed in Chapter 1. Fluorinations of hexachlorophthalazine were carried out in a 240 ml. nickel-lined autoclave, sealed with copper washers. The results of a number of fluorination reactions are tabulated below:

Molar ratio, KF: $C_8F_6N_2$	Temperature	Reaction Time	Product
37:1	360°	10½ h.	Decomposition. No pure product isolated.
36:1	320°	4½ h.	Decomposition. No pure product isolated.
23:1	300°	16 h.	~20% hexafluoro-phthalazine

/...

Molar ratio, KF: $C_8F_6N_2$	Temperature	Reaction Time	Product
/.....			
39:1	290°	12 h.	60% hexafluorophthalazine.
31:1	280°	12 h.	70% hexafluorophthalazine and (mostly) chlorofluorophthalazines.

The conditions of fluorination were therefore especially critical. The product was isolated by sublimation from the hot autoclave and g.l.c. analysis of the product of reaction at 290° showed it to be pure hexafluorophthalazine.

Hexafluorophthalazine was a white solid, m.p. 91-93°, and was sensitive to atmospheric moisture, being rapidly hydrolysed to give 4, 5, 6, 7, 8-pentafluoro-2H-phthalazin-1-one. The reaction is autocatalytic, since the hydrofluoric acid produced catalyses further hydrolysis. The n.m.r. spectrum of hexafluorophthalazine showed complex bands at 81.5, 140.7, and 145.6 p.p.m. upfield from external trichlorofluoromethane. The signal at 81.5 p.p.m. was a doublet (J = 57 c.p.s.) and was assigned to the 1- and 4- fluorine atoms, since such a chemical shift is typical of fluorine atoms on carbon adjacent to heterocyclic nitrogen.[63,106]

Furthermore, the coupling constant of 57 c.p.s. is close to the peri coupling observed in octafluoronapthalene [142] and in similar heterocyclic compounds. [106] The absorption at 140.7 p.p.m. also showed a coupling of 57 c.p.s. and was therefore assigned to the 5- and 8-fluorines. By elimination, the signal at 145.6 p.p.m. was assigned to fluorine at the 6- and 7-positions.

CHAPTER 5

Nucleophilic Substitution Reactions of Hexafluorophthalazine under Basic Conditions

Hexafluorophthalazine is extremely reactive towards nucleophilic reagents and under basic conditions, with methanolic sodium methoxide, all six fluorine atoms can be successively replaced. Hexafluorophthalazine also reacts readily with aqueous ammonia to give a mono-substituted derivative. The orientation of the substituents in the derivatives prepared has been determined by spectroscopic methods, ^{19}F n.m.r. spectra proving particularly useful.

5.1 Reaction of Hexafluorophthalazine with One Molecular Proportion of Methanolic Sodium Methoxide

Hexafluorophthalazine reacted readily at -15° with 1 mol. of methanolic sodium methoxide to give a mono-methoxy derivative in 70% yield. The product was slightly sensitive to moisture, undergoing gradual hydrolysis. The ^{19}F n.m.r. spectrum showed that the expected replacement of fluorine in the heterocyclic ring had occurred to give a 1-methoxy derivative. The spectrum (assignments in parenthesis) consisted of five complex signals of equal intensity at + 86.4 (4F), + 136.5 (8F), + 140.7 (5F), + 148.6 and + 149.2 (6 and 7 F's) p.p.m. The assignments

were made by comparison of the chemical shifts with those of hexafluorophthalazine, and on the basis of a coupling of 56 c.p.s., typical of the magnitude observed [142] for peri coupling, in the signals at + 86.4 and + 140.7 p.p.m. The substitution of hexafluorophthalazine in the 1-position was as expected: whilst there is no position in hexafluorophthalazine para to ring nitrogen, localization of negative charge in the transition state for 1-substitution on to an ortho nitrogen atom should reduce the energy of this transition state, relative to transition states for substitution in the carbocyclic ring.

5.2 Reaction of Hexafluorophthalazine with Two Molecular Proportions of Methanolic Sodium Methoxide

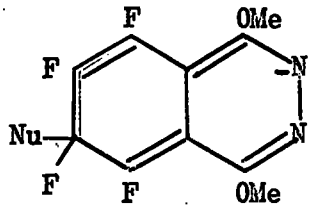
Hexafluorophthalazine gave a 1,4-dimethoxy-derivative by reaction with two mols. of methanolic sodium methoxide at -15°. The ^{19}F n.m.r. spectrum (assignments in parenthesis) consisted of two complex doublet bands of equal intensity at + 137.4 (5,8 F's) and + 149.5 (6,7 F's) p.p.m. The absence of any signal near + 85 p.p.m., and of any peri coupling indicated that the 1- and 4- fluorine atoms, ortho to ring nitrogen, had been replaced.

5.3 Reaction of Hexafluorophthalazine with Three Molecular Proportions of Methanolic Sodium Methoxide

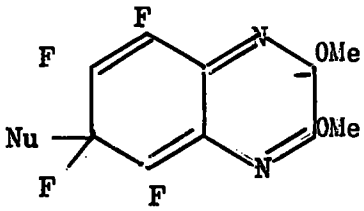
Reaction of hexafluorophthalazine with three mols. of methanolic sodium methoxide at 0° gave 5, 7, 8-trifluoro-1,4,6-trimethoxyphthalazine in 65% yield. Three ^{19}F n.m.r. signals were observed (assignments in parenthesis) at + 131.4 (5F), + 140.1 (8F), and + 144.6 (7F) p.p.m. Lawrenson [143] reported the ^{19}F n.m.r. spectra of a number of compounds of the type C_6F_5X and the effect of substituents on the chemical shifts of the fluorine atoms. A methoxy substituent caused approximate changes in the chemical shifts of ortho, meta, and para fluorines of -4.5, + 2.0 and + 1.7 p.p.m. respectively. Comparison of the observed chemical shifts of the di- and trimethoxy-derivatives of hexafluorophthalazine shows shift changes of -6.0 (5F-ortho to the methoxy group), + 2.7 (8F-meta) and -4.9 (7F-ortho) p.p.m., and the assignments are therefore consistent with the substituent effects reported by Lawrenson.

The ease of formation of a trisubstituted derivative of hexafluorophthalazine contrasts with the formation of a trimethoxy-derivative of hexafluoroquinoxaline, which was only accomplished by reaction of 5, 6, 7, 8-tetrafluoro-2, 3-dimethoxyquinoxaline and methanolic sodium methoxide (1 mol.) in a sealed tube at 120° for 18 hr. [144] The high

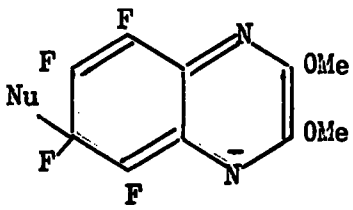
reactivity of the 6-position in fluorophthalazines compared with fluoroquinoxalines can be rationalised by considering the hybrids which contribute to the intermediate through which nucleophilic substitution is considered to proceed, and which is also believed to resemble the transition state:



(I)



(II)



(III)

The <u>para</u>-quinonoid type hybrid (I) localizes negative charge in the transition state upon ring nitrogen, whilst in a similar hybrid (II) for the substitution of the quinoxaline derivative, the charge is localized on carbon bearing the highly destabilizing methoxy-group. In the quinoxaline derivative, the negative charge may only be localized on ring nitrogen via an <u>ortho</u>-quinonoid type hybrid (III), and this type of hybrid is considered to be a much less important contributor to the intermediate than the <u>para</u>-quinonoid type.[93] The transition state for 6-substitution of tetrafluoro-1, 4-dimethoxyphthalazine can therefore be expected to have a lower energy than that for 6-substitution of

tetrafluoro-2, 3-dimethoxyquinoxaline. This argument would predict that the most reactive sites in the carbocyclic rings of hexafluorocinnoline and hexafluoroquinoxaline would be the 6-and 7-positions respectively. Substitution in the carbocyclic ring of hexafluorocinnoline has not been reported, but 5, 6, 8-trifluoro-2,4,7-trimethoxyquinazoline has been shown to be the product of reaction between excess methanolic sodium methoxide and hexafluoroquinazoline at 30°. [107]

5.4 Reaction of Hexafluorophthalazine with Four Molecular Proportions of Methanolic Sodium Methoxide

Methanolic sodium methoxide (4 mols.) reacted at 45° with hexafluorophthalazine to give a 75% yield of a compound analysing as the tetramethoxy-derivative. The ^{19}F n.m.r. spectrum showed a single line at + 132.3 p.p.m., clearly indicating that symmetrical substitution had occurred. Since it must be formed *via* the trimethoxy-derivative, the tetramethoxy-derivative must therefore be 5,8-difluoro-1,4,6,7-tetramethoxy-phthalazine. The ^{19}F n.m.r. shift confirms this structure since if substitution had occurred in the 5- and 8- positions, the substituent shift relative to the 1,4-dimethoxy derivative would be -17.2 p.p.m., quite at variance with the values reported by Lawrenson[143] and discussed in Section 5.3. If substitution has occurred at the

6- and 7- positions, as it believed to be the case, the substituent shift is -5.1 p.p.m., and this value is consistent with the findings of Lawrenson.

5.5 Reaction of Hexafluorophthalazine with Excess of Methanolic Sodium Methoxide

Hexafluorophthalazine was treated with excess of methanolic sodium methoxide in a sealed tube, heated to 85° for 13 hr. The product, isolated by ether extraction and recrystallisation from petroleum ether (b.p. 60-80°) was hexamethoxyphthalazine, a colourless crystalline solid, melting at 104-106°. This result further emphasises the great reactivity of fluorine atoms in the carbocyclic ring of the phthalazine system in comparison with other bicyclic nitrogen heterocyclic systems, for which complete replacement of fluorine by methoxide ion has not so far been reported.

5.6 Reaction of Hexafluorophthalazine with Aqueous Ammonia

Treatment of hexafluorophthalazine with excess of aqueous ammonia at 0°, and isolation of the product by precipitation from water and recrystallisation from acetonitrile gave 1-amino-4,5,6,7,8 -pentafluoro-

phthalazine. The ^{19}F n.m.r. spectrum showed absorption (with assignments in parenthesis) at + 92.9 (4F), + 139.1 (8F), + 142.1 (5 F), + 149.1 and + 149.7 (6- and 7- F's) p.p.m. The signals at + 92.9 and + 142.1 p.p.m. showed peri-coupling of 55 c.p.s. The presence of only one resonance in the region of + 85 p.p.m., typical of fluorine ortho to ring nitrogen, clearly indicated that substitution had occurred in one of the two such positions in hexafluorophthalazine.

CHAPTER 6

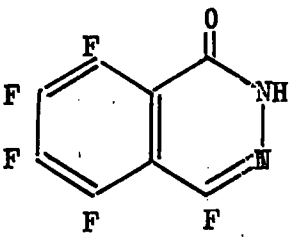
Acid Catalysed Nucleophilic Substitution Reactions of Halophthalazines and Tautomeris m in the Products of these Reactions.

Acid catalysed nucleophilic substitution reactions of polyfluoropyridazines have been reported, [109] and are believed to involve nucleophilic attack on protonated polyfluoropyridazinium cations, as discussed in Chapter 2. Polyhalophthalazines undergo nucleophilic substitution under similar conditions, and the tautomeris m of the derivatives so formed has been examined by reference to their infra red and ultraviolet spectra, and in the case of the hydroxy derivative of hexafluorophthalazine, by reference to the spectra of its methylated derivative.

6.1 Hydrolysis of Hexafluorophthalazine under Acidic Conditions

Musgrave and co-workers [67] reported that gradual addition of water to a solution of heptafluoroquinoline in conc. sulphuric acid resulted in precipitation of the 2-hydroxy-derivative. This method was adopted to prepare the hydroxy derivative of hexafluorophthalazine, and gave an 85% yield after recrystallisation from ethanol, of 4, 5, 6, 7, 8-

pentafluoro-2H-phthalazin-1-one. This derivative was identical to that obtained by the action of atmospheric moisture on hexafluorophthalazine. The infrared spectrum, with a strong C=O stretching band at 1656 cm^{-1} and bands at 3206, 3115 and 3095 cm^{-1}, which were considered to be more likely to be due to N-H than to O-H stretching, suggested that the pentafluoro-2H-phthalazin-1-one existed as the lactam tautomer:



Further evidence of this was obtained by comparison of its ultraviolet spectrum with that of the N-methyl derivative (Section 6.4.); the two were very similar and neither resembled the spectrum of 4,5,6,7,8-pentafluoro-1-methoxy-phthalazine.

The ^{19}F n.m.r. spectrum of the phthalazinone consisted of five multiplet bands (with assignments in parenthesis) of equal intensity at + 93.7 (4F), + 138.9 (8F), + 140.8 (5F), + 147.4 and + 149.0 (6 and 7 F's) p.p.m.

The absence, relative to hexafluorophthalazine, of one resonance in the region of + 85 p.p.m. indicated that substitution had occurred in the 1-position, ortho to ring nitrogen. The signals at + 93.7 and + 140.8 p.p.m. both had peri coupling constants of 58.5 c.p.s. and were therefore assigned to the fluorine atoms in the 4- and 5-positions respectively. Other assignments were made by comparison of the observed chemical shifts with those of hexafluorophthalazine.

6.2 Hydrolysis of 4,5,6,7,8-Pentafluoro-1-methoxyphthalazine under Acidic Conditions

Water was slowly added, as described in Section 6.1., to a solution of 4,5,6,7,8-pentafluoro-1-methoxyphthalazine in conc. sulphuric acid, and the precipitate twice recrystallised from ethanol to give 5,6,7,8-tetrafluoro-4-methoxy-2H-phthalazin-1-one in 50% yield. The infrared spectrum included a strong C=O stretching band at 1653 cm^{-1} and bands at 3153 and 3011 cm^{-1}, believed to be due to N-H stretching. This suggested that the tetrafluoro-4-methoxy-2H-phthalazin-1-one existed as the lactam tautomer. Neither the O- nor the N-methyl derivative could be obtained by reaction of the tetrafluoro-4-methoxy-2H-phthalazin-1-one with diazomethane, however, and comparison of the ultraviolet spectrum with those of the 1,4-dimethoxy-tetrafluorophthalazine and

pentafluoro-2H-phthalazin-1-one showed no strong similarity to either.

The ^{19}F n.m.r. spectrum consisted of two pairs of bands, each due to two non-equivalent fluorine atoms, at + 137.7 and + 138.9 p.p.m. and at + 148.7 and + 151.2 p.p.m. The former pair was assigned to fluorine at the 5- and 8-positions, no distinction between the two being possible, and the latter pair to fluorine at the 6- and 7- positions, and once again, distinction between the two was impossible.

6.3 Hydrolysis of Hexachlorophthalazine under Acidic Conditions

Hexachlorophthalazine was hydrolysed under acidic conditions, as previously, and gave 4,5,6,7,8-pentachloro-2-phthalazin-1-one in 75% yield. The infrared spectrum of the pantachloro-2 H-phthalazin-1-one included a strong C = 0 band at 1667 cm^{-1} and bands, probably due to N-H stretching, at 3174 and 3065 cm^{-1}. The ultraviolet spectrum strongly resembled that of the pentafluoro-2H-phthalazin-1-one. Both infrared and ultraviolet spectra therefore suggest that the pentachloro-2H-phthalazin-1-one exists predominantly in the lactam form.

6.4 Reaction of 4,5,6,7,8-Pentafluoro-2H-phthalazin-1-one with Ethereal Diazomethane

Treatment of 4,5,6,7,8-pentafluoro-2H-phthalazin-1-one with excess of ethereal diazomethane at 35° and evaporation of the ether gave a white crystalline solid whose ^{19}F n.m.r. spectrum was recorded before purification. Recrystallisation from acetone/hexane gave the 2-methyl derivative. The infrared and ultraviolet spectra of this derivative did not resemble those of 4,5,6,7,8-pentafluoro-1-methoxyphthalazine, but as stated in Section 6.1., the ultraviolet spectrum was similar to that of the pentafluoro-2H-phthalazin-1-one. The ^{19}F n.m.r. spectrum, identical with that of the crude material, consisted of signals of equal intensity (assignments in parenthesis) at + 91.8 (4F), + 138.3 (8F) + 140.7 (5F), + 147.1 and + 148.1 (6 and 7 F's) p.p.m. The peri coupling constant of the 4- and 5- fluorine atoms was 59 c.p.s. No resonance signals were observed corresponding with those of pentafluoro-1-methoxyphthalazine in the crude reaction product. Whilst methylation of the pentafluoro-2H-phthalazin-1-one resulted in detection only of the N-methyl derivative, this cannot be considered to prove that the pentafluoro-2H-phthalazin-1-one exists only as the lactam tautomer, for reasons outlined in Chapter 3. The spectroscopic data obtained for

the pentafluoro-2H-phthalazin-1-one, however, clearly indicates the predominance of the lactam form.

6.5 Reaction of 5,6,7,8-Tetrafluoro-4-methoxy-2H-phthalazin-1-one with Ethereal Diazomethane

Methylation of 5,6,7,8-tetrafluoro-4-methoxy-2H-phthalazin-1-one with excess of ethereal diazomethane at 35° gave only unreacted starting material. Failure of methylation in this case may be due to reduced acidity of the NH protons; similar methylation of fluoropyridazinones [109, 145] became increasingly difficult with substitution of fluorine by methoxy groups.

EXPERIMENTAL WORK

CHAPTER 7

Experimental Work

Infra-red spectra were measured on either a Grubb-Parsons Spectromaster or G.S.2A spectrophotometer, and ultra violet spectra on a Unicam SP800. Molecular weights were determined by mass spectrometry using an A.E.I. M.S.9 instrument. Thin-layer chromatography was on Kieselgel-G (baked at 100° for 40 mins.) using benzene as eluent and iodine vapour for detection. Ether solutions were dried over magnesium sulphate.

7.1

Preparation of Phthalazin-1, 4-dione

This compound was prepared using the method of Mihailescu and Florescu.[139]

Phthalic anhydride (44.8g.) in glacial acetic acid (150 ml.) was treated dropwise with hydrazine hydrate (20 ml.) during 2 hr. with stirring at 110°. The precipitate which formed on cooling was separated, washed successively with water, ethanol, and acetone, and dried (in vacuo) to give colourless plates of phthalazin-1, 4-dione (44.4g., 90%) m.p. 338-339.5° (lit., 342-344°).

7.2

Preparation of 1, 4-Dichlorophthalazine

This compound was prepared using the following modification of the method of Hirsch and Orphanos.[136]

Phthalazin-1, 4-dione (263 g.) and phosphorus pentachloride (1 Kg.) were closed in vacuo in a stainless steel autoclave (1½ l. capacity) and heated to 140° for 3½ hr.

The autoclave was cooled, vented, and its contents added to ice. The precipitate was separated, extracted with dichloromethane, and the extract was washed with water, dried (in vacuo), and evaporated to give 1,4-dichlorophthalazine (252 g., 75%) as long pale yellow needles, m.p. 159.5-162° (lit.,[136] 164°).

7.3

Reaction of Phthalazin-1, 4-dione with Phosphorus pentachloride at high temperatures

In a typical reaction, phthalazin-1, 4-dione (9.8 g.) and phosphorus pentachloride (74.3 g.) were closed in vacuo in a nickel lined autoclave (240 ml. capacity) and heated to 260° for 18 hr. The

autoclave was cooled, vented, and its contents added to ice. From the black amorphous precipitate (8.2 g.) a white solid (260 mg.) was obtained by sublimation at 100° / 0.005 m.m. but this was shown, by t.l.c., to contain at least seven components.

7.4

Preparation of N-amino tetrachlorophthalimide

This compound was prepared using the procedure of Drew and Hatt.[131]

7.5

Reaction of Tetrachlorophthalic anhydride with Hydrazine sulphate in Conc. sulphuric acid

Tetrachlorophthalic anhydride (2.94 g.) in conc. sulphuric acid (80 ml.) was treated with hydrazine sulphate (1.40 g.) during 11 hr. with stirring at 200°. The mixture was added carefully to ice, the precipitate was washed with acetone, and identified as N-amino tetrachlorophthalimide (1.80 g., 60%) by comparison of its i.r. spectrum and m.p. with those of an authentic sample.

7.6

Preparation of Hexachlorophthalazine

A mixture of finely ground anhydrous aluminium chloride (302 g.) and 1,4-dichlorophthalazine (150 g.) was slowly heated to 200-210° in a dry nitrogen-flushed flange flask, fitted with a gas-inlet tube, a liquid sealed glass stirrer, and an air condenser connected to an outlet gas bubbler containing conc. sulphuric acid. The molten complex thus formed was maintained at this temperature, under a stream of dry chlorine (754 g.). Samples were removed at intervals, treated with water, and examined by t.l.c; the appearance of a spot of R_f *ca.* 0.5, and the subsequent disappearance of other spots of lower R_f indicated the completion of the reaction (63 hr.). The dark brown solid formed on cooling was treated with ice, and the precipitate was dried (in vacuo) and extracted with dichloromethane. The solvent was evaporated and the residue was recrystallised from dry tetrahydrofuran to give hexachlorophthalazine (141 g., 55%), as pale yellow plates, m.p. 193-195°. Further recrystallisation from the same solvent gave an almost colourless sample, m.p. 194.5-195.5°. (Found: C, 28.3: Cl, 63.1%; M, 334. $C_8Cl_6N_2$ requires C, 28.5; Cl, 63.2%, M, 334), I.R. Spectrum No. 1, λ_{max} (cyclohexane) 253.5, 306, 315, 337 infl., and 349 infl. nm. (Log ϵ 4.73, 3.90, 3.92, 3.70, and 3.51).

Preparation of hexafluorophthalazine

Hexachlorophthalazine (33.5 g.) and freshly dried potassium fluoride (109 g.) were closed in vacuo in a nickel-lined autoclave (240 ml. capacity) and heated to 290° for 12 hr. The contents of the hot autoclave were pumped out into a trap at room temperature, and the product (14.3 g., 60%) was shown by g.l.c. (silicone elastomer, 225°) to be pure hexafluorophthalazine, m.p. 91-93° (Found: C, 40.2; F, 48.3%; M, 238. $C_8F_6N_2$ requires C, 40.3; F, 47.9%: M, 238), I.R. Spectrum No. 3, λmax (ethanol) 260, 287, 300 and 313nm. (Log ε 3.64, 3.46, 3.60 and 3.66), λ max (cyclohexane) 249 infl., 259, 267 infl., 288 infl., 299.5, and 313 nm.

Further experiments, using the same procedure, but varying the temperature of fluorination, were carried out. At 300° for 16 hr. the product was extensively decomposed, and the yield of hexafluorophthalazine was reduced to less than 20%. At 280° for 12 hr. the product (70%) was shown by g.l.c. (silicone elastomer, 225°) and mass spectrometry to contain a large proportion of chlorofluorophthalazines.

Hexafluorophthalazine was rapidly hydrolysed by atmospheric moisture, and the hydrolysed material was recrystallised from ethanol to give 4, 5, 6, 7, 8-pentafluoro-2H-phthalazin-1-one, m.p. 244-246° (Found:

C, 40.8; H, 0.4; N, 12.1; F, 40.6%; M, 236. $C_8HF_5N_2O$ requires C, 40.7; H, 0.4; N, 11.9; F, 40.3%; M, 236), I.R. Spectrum No. 10, λmax (ethanol) 225, 257, 297 and 303 nm. (Log ε 3.98, 3.79, 3.67 and 3.66).

7.7

Reactions of Hexafluorophthalazine with Sodium Methoxide

(a) Preparation of 4, 5, 6, 7, 8-Pentafluoro-1-methoxyphthalazine

Hexafluorophthalazine (7.19 g.) in methanol (40 ml.) was treated dropwise with methanolic sodium methoxide (28.9 ml., 1.0 mol; 1.1M) during 1.5 hr. with stirring at -15°. The mixture was allowed to reach room temperature during 2 hr., evaporated to ca. 10 ml., and extracted with ether. The extract was washed with water, dried and evaporated. The residue was recrystallised from petroleum ether (b.p. 40-60°) to give the mono methoxy-derivative (5.23 g., 70%), m.p. 67.5-69.5°. (Found; C, 43.2; H, 1.3; N, 11.1; F, 38.4%; M, 250 $C_9H_3F_5N_2O$ requires C, 43.2; H, 1.2; N, 11.2; F, 38.0%; M, 250), I.R. Spectrum No. 4, λmax (ethanol) 270, 288.5 infl., 302.5, and 316 nm. (log ε 3.84, 3.74, 3.73, and 3.69).

(b) Preparation of 5, 6, 7, 8-Tetrafluoro-1, 4-dimethoxyphthalazine

Hexafluorophthalazine (4.34 g.) in methanol (60 ml.) was treated dropwise, at -15°, with methanolic sodium methoxide (2.0 mol.) as in the previous experiment and the product, similarly isolated, was twice recrystallised from a mixture of acetone and hexane to give colourless plates of the dimethoxy-derivative (1.04 g., 20%), m.p. 155.5-157° (Found: C, 45.8; H, 2.3; N, 10.9; F, 28.5%; M, 262. $C_{10}H_6F_4N_2O_2$ requires C, 45.8; H, 2.3; N, 10.5; F, 29.0%; M, 262), I.R. Spectrum No. 5, λmax (ethanol) 283, 294.5, 309.5 and 320.5 nm. (log ε 3.73, 3.71, 3.74, and 3.65).

(c) Preparation of 5, 7, 8-Trifluoro-1, 4, 6-trimethoxyphthalazine

Hexafluorophthalazine (4.0 g.) in methanol (30 ml.) was similarly treated, at 0°, with methanolic sodium methoxide (3.0 mol.), and the product, isolated as before, was twice recrystallised from ethanol to give the trimethoxy-derivative (2.9 g., 65%) m.p. 142-143° (Found: C, 48.0; H, 3.2; N, 10.3; F, 20.6%; M, 274. $C_{11}H_9F_3N_2O_3$ requires C, 48.2; H, 3.3; N, 10.2; F, 20.8%; M, 274), I.R. Spectrum No. 6, λ max (ethanol) 280, 296.5, 310.5, and 323 nm. (Log ε 3.69, 3.67, 3.74, and 3.70).

(d) Preparation of 5, 8-Difluoro-1, 4, 6, 7-tetramethoxyphthalazine

Similarly hexafluorophthalazine (3.54 g.) in methanol (60 ml.) was treated, at 45°, with methanolic sodium methoxide (4.0 mol.) and the product, similarly isolated, was recrystallised from ethanol to give colourless needles of the tetramethoxy-derivative (3.1 g., 75%) m.p. 137-139° (Found: C,50.3; H, 4.4; F, 13.4; N, 9.4%; M, 286. $C_{12}H_{12}F_2N_2O_4$ requires C, 50.3; H, 4.2; F, 13.4; N, 9.8%; M, 286), I.R. Spectrum No. 7, λ max (ethanol) 225, 273, 296, 312 and 325 nm. (Log ε 4.53, 3.75, 3.67, 3.73, and 3.72).

(e) Preparation of Hexamethoxyphthalazine

Hexafluorophthalazine (700 mg.) and sodium methoxide (2.3g; 14 mol.) in methanol (30 ml.) were sealed in a Carius tube and treated to 85° for 13 hr. The tube was cooled, its contents evaporated to ca. 3 ml., and extracted with ether. The extract was washed with water, dried and evaporated; the residue was recrystallised from petroleum ether (b.p. 60-80°) to give hexamethoxyphthalazine (80 mg., 10%), m.p. 104-106° (Found: C, 54.0; H, 5.3%; M, 310. $C_{14}H_{18}N_2O_6$ requires C, 54.2;

H, 5.8%; M, 310) I.R. Spectrum No. 8, λmax (ethanol) 231, 286, 297, 314, and 327 nm. (Log ε 4.59, 3.79, 3.78, 3.78 and 3.76).

7.8

Preparation of 1-Amino-4, 5, 6, 7, 8-Pentafluorophthalazine

Hexafluorophthalazine (4.94 g.) in acetone (12 ml.) was treated with aqueous ammonia (d, 0.880; 3 ml.) during 30 mins. with stirring at 0°. The mixture was poured into water, the precipitate was dried in vacuo and recrystallised from acetonitrile to give yellow needles of the amino-derivative (720 mg., 15%), m.p. 159-165° decomp. (Found C, 40.8; H, 0.9; N, 17.6; F, 40.9%; M, 235. $C_8H_2F_5N_3$ requires C, 40.9; H, 0.9; N, 17.9; F, 40.5%; M, 235), I.R. Spectrum No. 9, λmax (ethanol) 227, 237 infl., 243 infl., and 305 nm. (log ε 4.11, 4.08, 4.08 and 3.89).

7.9

Preparation of 4, 5, 6, 7, 8-Pentafluoro-2H-phthalazin-1-one

Hexafluorophthalazine (4.16 g.) in conc. sulphuric acid (40 ml.) was treated dropwise with water (200 ml.) during 2 hr. with vigorous

stirring and cooling in ice, the addition being regulated to keep the temperature below 25°. The precipitate was dried *in vacuo* and recrystallised from ethanol to give colourless plates of the phthalazinone (3.39 g., 85%), identical (m.p. and i.r.) with material obtained by the atmospheric hydrolysis of hexafluorophthalazine.

7.10

Preparation of 5, 6, 7, 8-Tetrafluoro-4-methoxy-2H-phthalazin-1-one

4, 5, 6, 7, 8 -Pentafluoro-1-methoxy phthalazine (1.18 g.) in conc. sulphuric acid (50 ml.) was treated dropwise with water (200 ml.) as in the previous experiment, and the product, similarly isolated, was twice recrystallised from ethanol to give colourless needles of 5, 6, 7, 8-tetrafluoro-4-methoxy-2H-phthalazin-1-one (600 mg., 50%) m.p. 239-241° (Found: C, 43.5; H, 1.6; N, 11.4: F, 31.1%; M, 248. $C_9H_4F_4N_2O_2$ requires C, 43.6; H, 1.6; N, 11.3; F, 31.2%; M, 248), I.R. Spectrum No. 11, λ max (ethanol) 227, 265 and 305 nm. ($\log \varepsilon$ 3.99, 3.65, and 3.74).

7.11

Preparation of 4, 5, 6, 7, 8-Pentafluoro-2-methyl phthalazin-1-one

4, 5, 6, 7, 8-pentafluoro-2H-phthalazin-1-one (1.03 g.) in ether (40 ml.) was treated with excess ethereal diazomethane, at 35°, the ether was evaporated, and the ^{19}F n.m.r. spectrum of the residue was recorded. Recrystallisation from a mixture of acetone and hexane gave colourless plates of 4, 5, 6, 7, 8-pentafluoro-2-methylphthalazin-1-one (390 mg., 35%), m.p. 150-152° (Found: C, 43.2; H, 1.2; N, 11.2%; M, 250), I.R. Spectrum No. 12, λ_{max} (ethanol) 225.5, 259, 302 infl., and 313 nm. (log ε 4.01, 3.68, 3.76, and 3.79). The ^{19}F n.m.r. spectrum (No. 9) was identical with that of the crude material.

7.12

Reaction of 5, 6, 7, 8 -Tetrafluoro-4-methoxy-2H-phthalazin-1-one with ethereal diazomethane

5, 6, 7, 8 -Tetrafluoro-4-methoxy-2H-phthalazin-1-one (350 mg) in ether (40 ml.) was treated with excess ethereal diazomethane as in the previous experiment, the ether was evaporated, and the ^{19}F n.m.r. spectrum of the residue was examined and found to be identical with that of the starting material.

7.13

Preparation of 4, 5, 6, 7, 8 -Pentachloro-2H-phthalazin-1-one

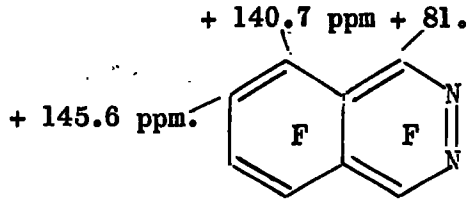
Hexachlorophthalazine (10.1 g) in conc. sulphuric acid (125 ml.) was treated dropwise with water (500 ml.) during 2 hr. with stirring at 0°. The precipitate was dried in vacuo and twice recrystallised from ethanol to give colourless plates of 4, 5, 6, 7, 8 -pentachloro-2H-phthalazin-1-one (7.27 g., 75%), m.p. 230-231.5° (Found: C, 29.9; H, 0.55; Cl, 56.0%; M, 316. $C_8H Cl_5N_2O$ requires C, 30.1; H, 0.3; Cl, 55.7%; M, 316), I.R. Spectrum No. 2, λ max (ethanol) 237, 270, 282, 321 and 337 nm. (Log ε 4.52, 3.85, 3.86, 3.81 and 3.74).

A P P E N D I X I

^{19}F Nuclear Magnetic Resonance Spectra of Fluorophthalazines

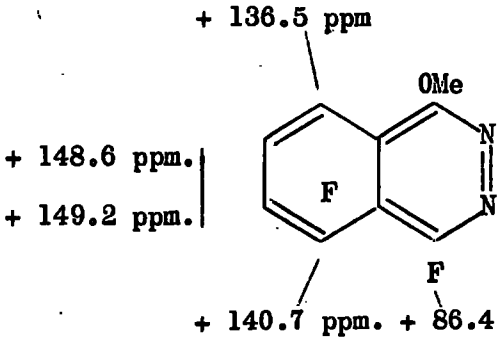
^{19}F n.m.r. spectra were measured on a Varian A56/60D spectrometer operating at 56.46 MHZ, using trichloromethane as internal standard (upfield shifts are quoted as positive). Coupling constants are given where tnese could be determined; in other cases either the splitting was too complex to analyse (i.e. by assuming first order splitting), or else the solubility of the compound was too low for any fine structure to be observed. Spectra were measured in acetone solution except where otherwise stated.

1. Hexafluorophthalazine



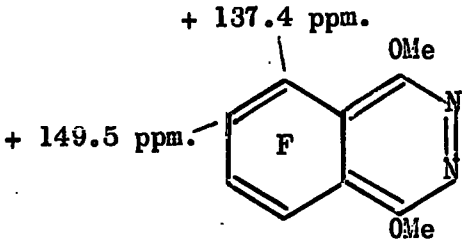
$J_{4,5} = J_{1,8} = 57$ c.p.s.

2. 4, 5, 6, 7, 8 - Pentafluoro-1-methoxy-phthalazine.

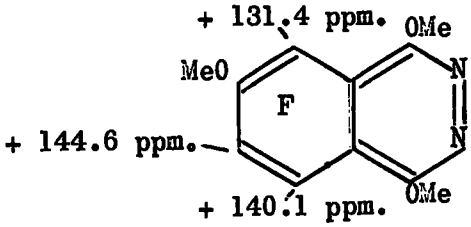


$J_{4,5} = 56$ c.p.s.

3. 5, 6, 7, 8-Tetrafluoro-1, 4-dimethoxy-phthalazine



4. 5, 7, 8 - Trifluoro-1,4, 6-trimethoxy-phthalazine

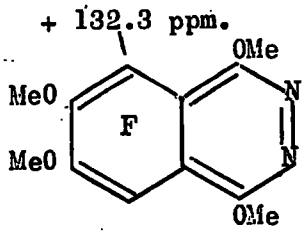


$J_{5,7} = \pm 10.5$ c.p.s.

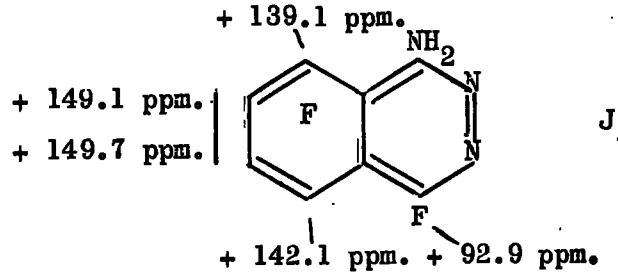
$J_{5,8} = \pm 16.5$ c.p.s.

$J_{7,8} = \pm 18.5$ c.p.s.

5. 5, 8-Difluoro-1, 4, 6, 7-tetramethoxy-phthalazine



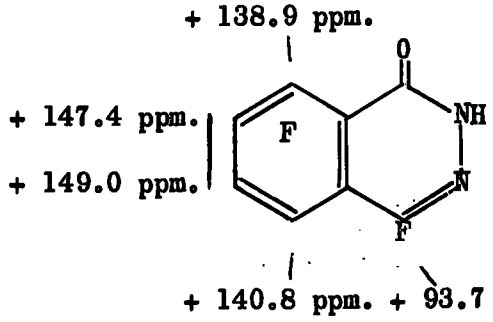
6. 4, 5, 6, 7, 8 - Pentafluoro-1-amino-phthalazine



$J_{4,5} = 55$ c.p.s.

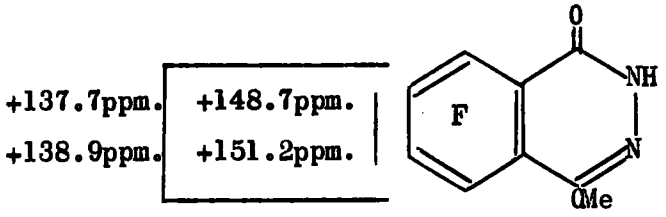
7. 4, 5, 6, 7, 8 - Pentafluoro-2H-phthalazin-1-one.

(In N-methyl pyrrolidone)

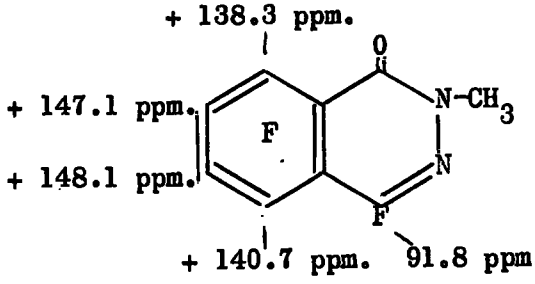


8. 5, 6, 7, 8 - Tetrafluoro-4-methoxy-2H-phthalazin-1-one

(In N-methyl pyrrolidone)



9. 4, 5, 6, 7, 8 - Pentafluoro-2-methyl phthalazin-1-one

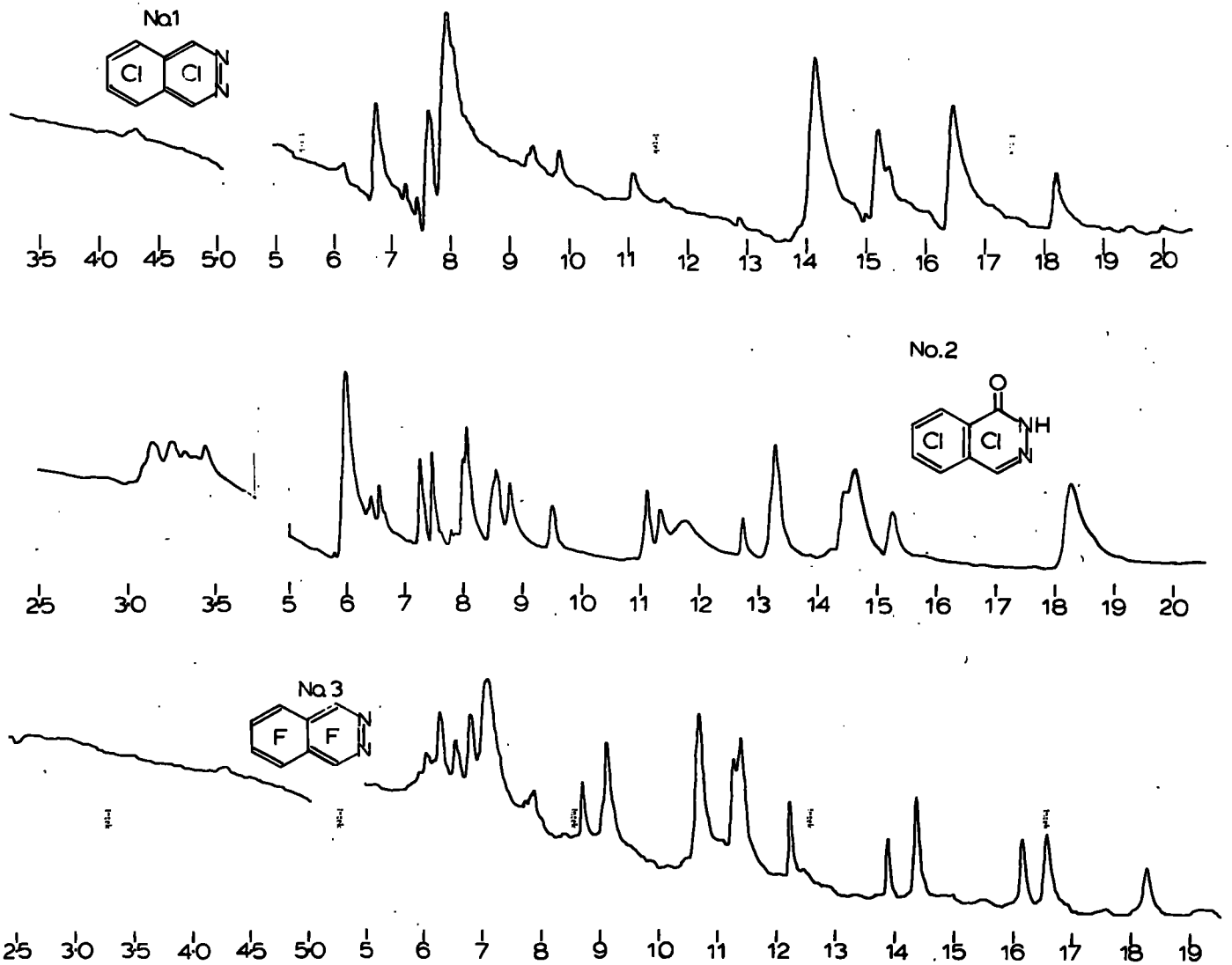


$J_{4,5}$ = 59 c.p.s.

A P P E N D I X I I

Index to Infra-Red Spectra

Spectra were measured as intimate mixtures with anhydrous potassium bromide, pressed into a disc, on either a Grubb-Parsons Spectromaster or G.S.2A spectrophotometor.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N
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No.2
O
NH
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N
2·5 3·0 3·5 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
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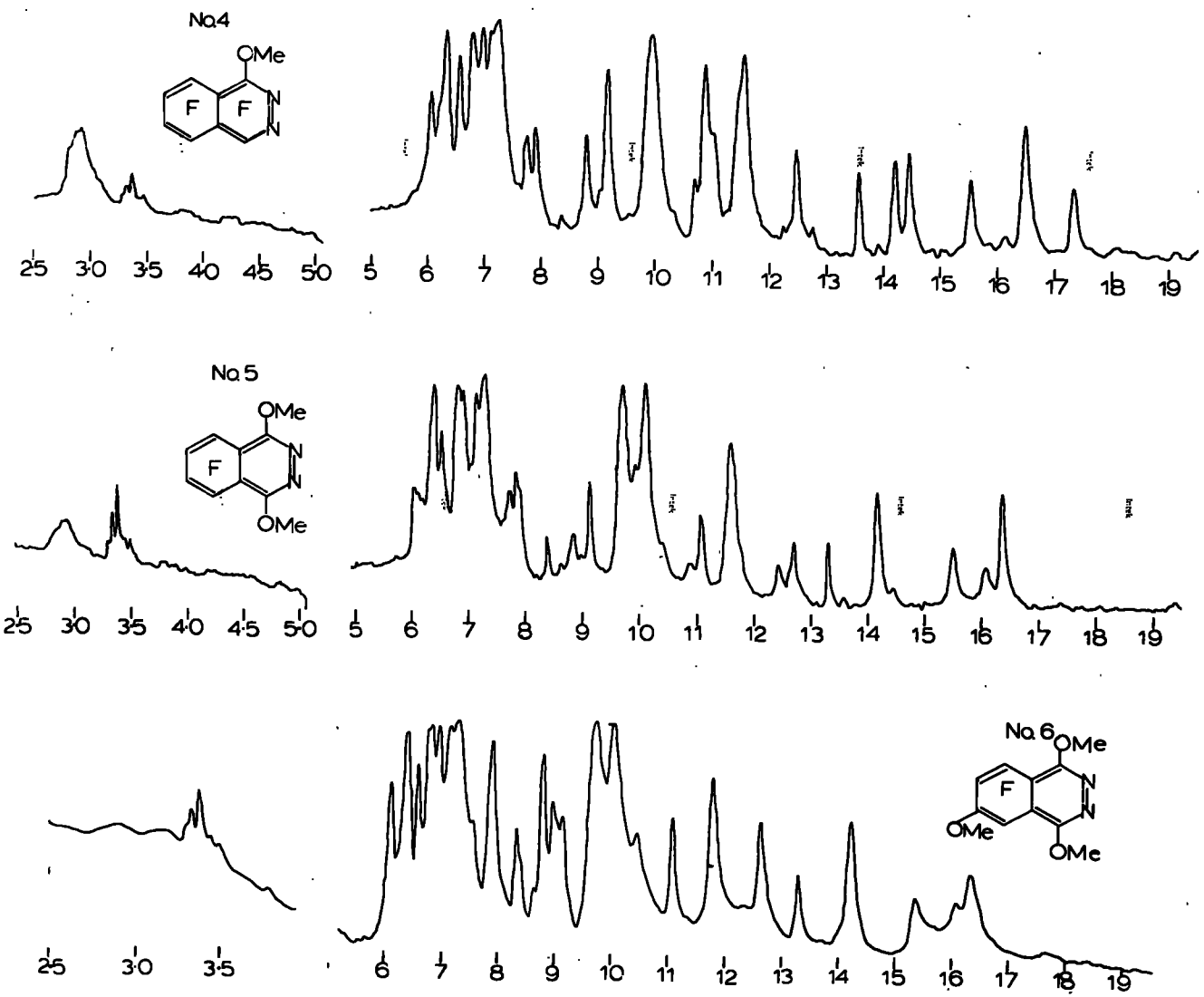
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F
F
N
N
2·5 3·0 3·5 4·0 4·5 5·0 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
No.5
OMe
F
N
N
OMe
2·5 3·0 3·5 4·0 4·5 5·0 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
No.6
OMe
F
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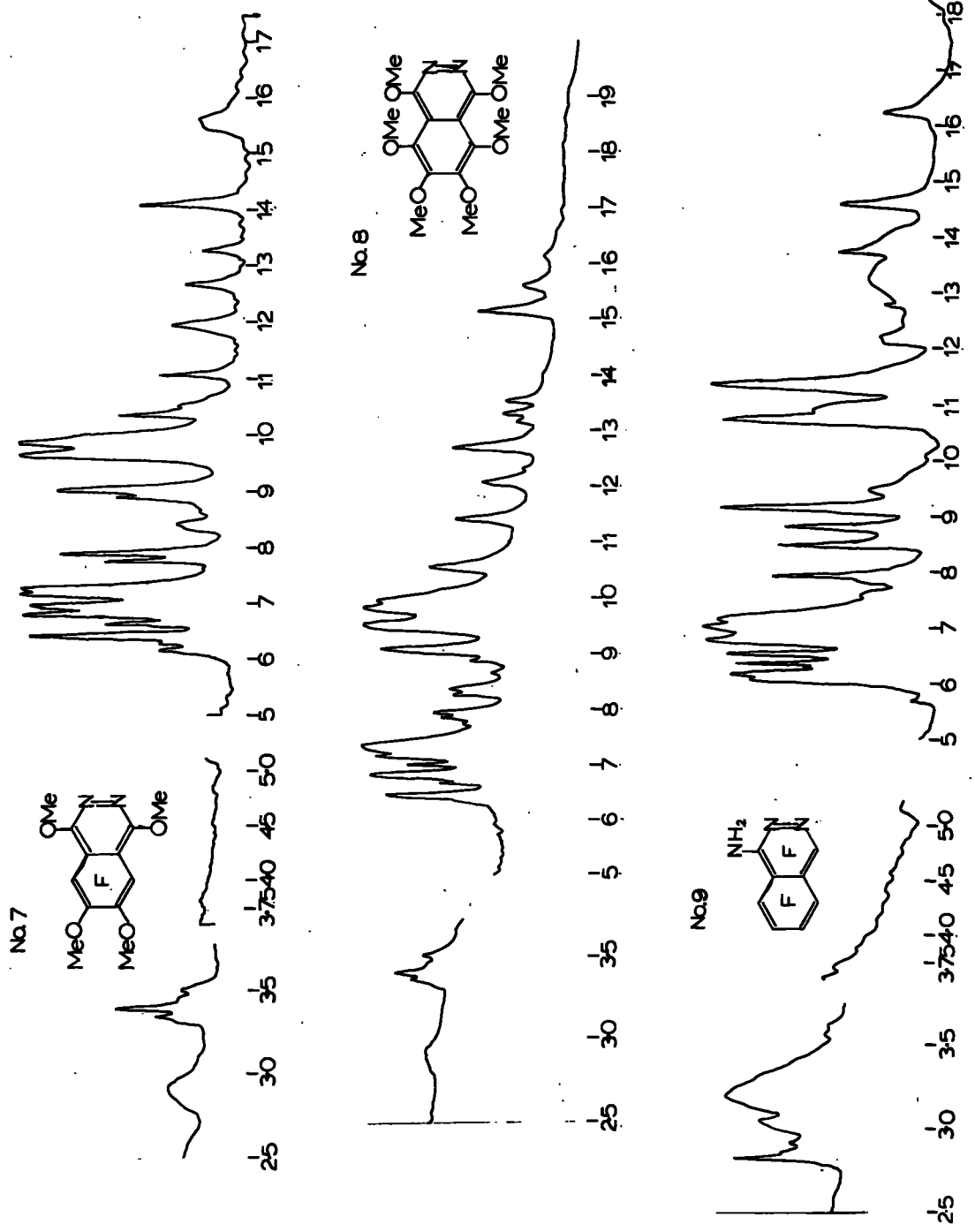
OMe
2·5 3·0 3·5 6 7 8 9 10 11 12 13 14 15 16 17 18 19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NH2
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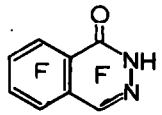
F

No.10



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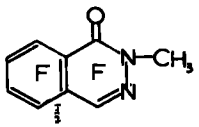

R E F E R E N C E S

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