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UNIVERSITY OF DURHAM

A THESIS

entitled

SOME FLUORINE COMPOUNDS
OF PYRIDINE

submitted by

FREDERICK GERALD DRAKESMITH, B.Sc.

(University College)

A candidate for the degree of Doctor of Philosophy
1965.



TO
MARY

ACKNOWLEDGEMENTS

I should like to thank Professor W.K.R. Musgrave and Dr. R.D. Chambers for their continual help and encouragement in the supervision of this work.

I should also like to thank the Department of Scientific and Industrial Research for the Award of a Research Studentship, Dr. J. Hutchinson for many valuable discussions, Dr. J.W. Emsley and Dr. L. Phillips for nuclear magnetic resonance determinations and the many laboratory technicians for their considerable help and co-operation.

MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1962 and July 1965. 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 a publication with Professor W.K.R. Musgrave and Dr. R.D. Chambers in the Journal of the Chemical Society (J, in press)

SUMMARY

Some Fluorine compounds of Pyridine

Part I The Preparation of Highly Fluorinated Pyridines

The chlorination of pyridine with phosphorus pentachloride in a stainless steel autoclave at elevated temperatures has been developed to give good yields of pentachloropyridine, together with some tetrachloropyridines.

Halogen exchange between pentachloropyridine and anhydrous potassium fluoride in the absence of solvent produced chlorofluoropyridines, and, at a reaction temperature of 480°C , pentafluoropyridine.

Part II The introduction of Functional Groups into the Polyfluoropyridine nucleus

The Grignard reagents from 3-chlorotetrafluoropyridine and 3, 5-dichlorotrifluoropyridine have been prepared in diethyl ether solution but yields were low. Preparation of the Grignard reagent from 3-chlorotetrafluoropyridine in tetrahydrofuran at low temperature, followed by carbonation produced 2, 4, 5, 6-tetrafluoronicotinic acid. The use of Grignard reagents for the introduction of functional groups into the 3-position was severely limited by their tendency to polymerise via nucleophilic attack at the 4-position by the tetrafluoropyridyl anion formed from the Grignard reagent itself.

Chlorofluoropyridines and pentafluoropyridine have been catalytically reduced with hydrogen to hydrofluoropyridines. The hydrogen in these compounds is sufficiently acidic to undergo metallation by exchange reaction with alkyl lithiums and the resulting polyfluoropyridyl lithium derivatives have been shown to be useful intermediates in the synthesis of variously substituted polyfluoropyridyl compounds.

In this way, several polyfluoropyridine carboxylic acids have been prepared, their pKa values determined and relative acid strengths discussed.

Bis (2, 4, 5, 6-tetrafluoropyridyl) mercury has been prepared by decarboxylation of mercuric perfluoronicotinate, and the perfluoropyridyl mercurial shown to form a neutral coordination complex with 2, 2'-bipyridyl.

Preliminary investigations into the existence of trifluoropyridyne have indicated that this intermediate is formed by elimination of lithium fluoride from 3-lithio-tetrafluoropyridine, although this has not been categorically proven.

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PART I

THE PREPARATION OF HIGHLY FLUORINATED

PYRIDINES

Chapter I

HISTORICAL INTRODUCTION

INTRODUCTION

Investigations into the effects of replacing hydrogen by fluorine in compounds of pyridine have been promoted not only by the interest in the chemistry that such compounds might possess due to their heterocyclic aromatic nature, but also by the fact that the pyridine nucleus is often part of biologically active compounds.¹ The current hypothesis which attributes the antimetabolite activity of such compounds as sulphanilamide and pyridine-3-sulphonic acid to the structural similarity but functional dissimilarity of these compounds to essential metabolites suggests that various fluorine substituted pyridine derivatives such as nicotinic acid or nicotinamide may possess physiological activity. Of interest in this connection is the observation² that 3-fluorotyrosine and 3-fluorophenylalanine act as growth inhibitors for *Neurospora Crassa* 8815-3a. Many other examples of how the replacement of hydrogen by fluorine in biologically active compounds causes significant changes in the level of this activity have been reported.^{3,4,5}

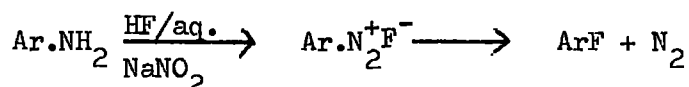
It will be obvious from a history of developments in the fluorine chemistry of pyridine that this has run parallel with the chemistry of the fluorobenzenes and in many cases it will be shown how a major advance in the latter has been reflected by a similar step with pyridine.

MONOFLUOROPYRIDINES.

The earliest attempts to prepare aromatic fluorides were based on the decomposition of diazonium salts in aqueous hydrofluoric acid. Thus in 1870, Schmitt and von Gehren⁶ synthesised p-fluorobenzoic acid by



diazotising the corresponding amine in 40% hydrofluoric acid.



In an analogous manner, Chichibabin and Rjazancev prepared 2-fluoro-5-nitropyridine and 2-fluoropyridine in 25% yield.^{7,8}

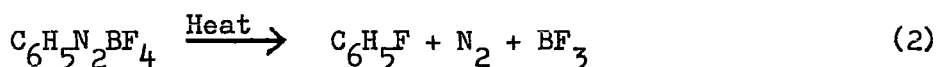
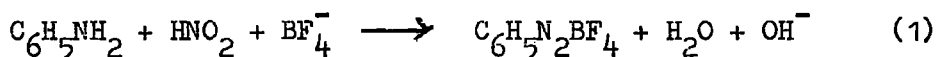
Several years later,⁹ Binz and Rath reported the preparation of 3-fluoropyridine in 22% yield using the same technique.

The obvious disadvantage of this method lies in the fact that decomposition of any diazonium salt in aqueous solution leads to the formation of hydroxy compounds with consequent reduction in the yield of the desired fluoro-derivative. More recently,¹⁰ anhydrous hydrogen fluoride has replaced the aqueous acid with considerable success in most aromatic systems, although when this method was applied to heterocyclic aromatic compounds,¹¹ Ferm and Vanderwerf reported, without giving definite figures, that only very poor yields of the corresponding fluoro derivatives were obtained. However, this work was repeated when Beaty diazotised 2-aminopyridine with sodium nitrite in anhydrous hydrogen fluoride and decomposed the diazonium salt "in situ" at 40°C to obtain a 20-22% yield of 2-fluoropyridine.¹²

A significant discovery was made in 1913 when Bart succeeded in isolating benzene diazonium fluoroborate,¹³ as well as p-chloro and p-nitrobenzene diazonium fluoroborate. He noted the great stability of these compounds and claimed them to be useful intermediates in the preparation of therapeutic agents and dyes, but did not prepare aromatic fluorides from them. It was not until 1927 when Balz and

Schiemann¹⁴ published their work on the controlled decomposition of diazonium fluoroborates that it was shown possible to obtain good yields of aromatic fluorides from these salts.

The method involves two steps: first the preparation and isolation of a dry diazonium fluoroborate, and second, the controlled decomposition of this salt by heat to yield an aromatic fluoride, nitrogen and boron trifluoride.

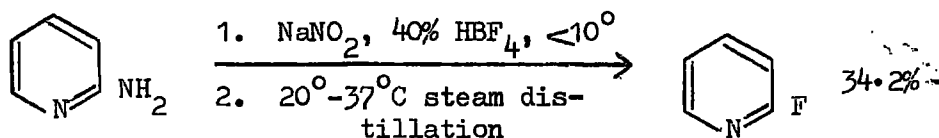


Since the original publication, Schiemann and others¹⁵ have applied the method to a large variety of amines and overall yields as high as 70% are not uncommon.

In 1947 Roe and Hawkins¹⁶ published their work on attempts to extend the scope of the Schiemann reaction by investigating its usefulness in the preparation of heterocyclic fluorine compounds. The first compounds they studied were the three aminopyridines. Preparation of 2- and 3-fluoropyridine from the corresponding amines in overall yields of 34 and 50%, respectively were achieved. However, in contrast to the diazonium fluoroborates of most aromatic compounds, which are quite stable, both 2- and 3-pyridine diazonium fluoroborate were reported to be quite unstable, thus necessitating modification of the usual Schiemann technique.

Attempts to isolate 2-pyridine diazonium fluoroborate were unsuccessful because the compound decomposed as fast as it was formed.

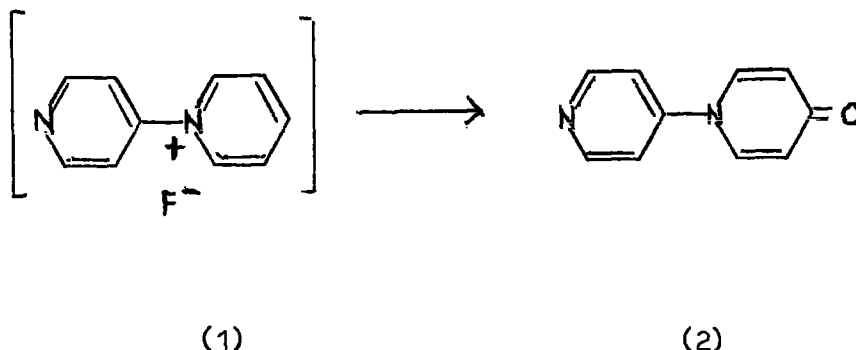
2-Fluoropyridine was obtained in 34% yield by diazotisation of 2-aminopyridine with sodium nitrite in 40% fluoroboric acid solution with the temperature maintained below 10°C. After warming the product was isolated by neutralisation of the reaction mixture with sodium carbonate



followed by steam distillation, and distillation. Decomposition of 2-fluoropyridine was indicated by the appearance of a yellow colour after several days, and the formation of a white precipitate on longer standing. The lability of 2-fluoropyridine was further demonstrated by Bradlow and Vanderwerf when they studied the acid hydrolysis of α -halogenated pyridine compounds.¹⁷

Isolation of 3-pyridine diazonium fluoroborate was accomplished by diazotising 3-aminopyridine with ethyl nitrite¹⁸ in ethanol-fluoroboric acid solution; addition of ether when diazotisation was complete caused precipitation of 3-pyridine diazonium fluoroborate. This substance is stable when moist with ether below about 10°C, but decomposes spontaneously when the last trace of ether is removed. It decomposes smoothly, however, when a suspension of it in high boiling petroleum ether is allowed to stand at 15-20°C. A 50% yield of 3-fluoropyridine was obtained by Roe and Hawkins in this manner. Efforts by these workers to isolate 4-fluoropyridine using similar techniques were unsuccessful. Solutions containing 4-pyridine diazonium fluoroborate started to decompose at about 15°C and pure 4-fluoropyridine was never

obtained as this appeared to be unstable. As Roe and Hawkins point out, the instability of 4-fluoropyridine is not surprising in view of the fact that 4-chloropyridine starts to decompose a few hours after its formation, and 4-bromopyridine is even less stable. They suggest that the 4-fluoropyridine is formed in the reaction but immediately reacts with itself to form N(4'-pyridyl)-4-fluoropyridinium (1) fluoride



which is readily hydrolysed to N(4'-pyridyl)-4-pyridone (2). A picrate of this ketone was obtained in several of the attempted preparations of 4-fluoropyridine. This is analogous to the reactions of 4-chloropyridine and 4-bromopyridine with themselves as reported by Wibaut and Broekman.¹⁹

In 1958 Wibaut and Holmes-Kamminga²⁰ reported the preparation of an impure sample of 4-fluoropyridine by diazotising 4-aminopyridine in hydrogen fluoride and working up the reaction while maintaining the reaction product at a low temperature.

Although most of the work carried out on the preparation of organic fluorides by the decomposition of diazonium salts has been done with fluoroborates, in a number of cases diazonium salts of other complex

acids have been used. Lange and Muller²¹ prepared 4,4'-difluorobiphenyl in low yield from the corresponding diazonium fluorophosphate, and Wiley²² has described the preparation of several diazonium fluorosilicates together with that of p-fluorobenzoic acid (12% crude yield from the diazonium salt), and the decomposition of benzene diazonium fluorosilicate by heat, but, in the last case, did not isolate any product and made no further attempt to use the diazonium fluorosilicate for purpose other than the preparation of dyes.

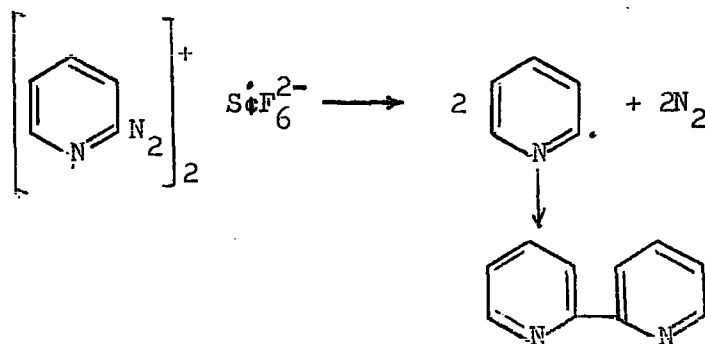
Hawkins and Roe²³ prepared the diazonium fluorosilicate of methyl 5-aminonicotinate by the reaction of ethyl nitrite with a suspension of the methyl 5-aminonicotinate fluorosilicate in glacial acetic acid. The dry diazonium salt was suspended in toluene and heated until decomposition was complete, giving methyl 5-fluoronicotinate in poor overall yield.

Cheek, Wiley and Roe,²⁴ applied this method of decomposing the dry, solid diazonium fluorosilicate to the preparation of several aromatic fluorides. In all cases except one their yields were lower than those from the fluoroborates, and attempts to prepare 2-fluoropyridine failed completely, it being impossible even to prepare the diazonium salt.

Later, Beaty and Musgrave²⁵ showed that 2- and 3-fluoropyridine could be prepared by decomposing the diazonium fluorosilicate either in suspension in organic liquids or in solution in inorganic acids. The best results for 2- and 3-fluoropyridine (40% yield) were obtained by diazotising the corresponding amines in aqueous fluorosilicic acid (30%) and decomposing the diazonium salts "in situ". The amount of 2-fluoro-

pyridine (42% yield) obtained in this way was appreciably greater than that obtained from the Schiemann method¹⁶ (34%), but when the same procedure was applied to 3-aminopyridine the reverse was true (i.e. 36% yield compared with 50% yield from the Schiemann method).

The inherent disadvantage of this method is due to the fact that in the diazonium fluorosilicate there are two diazonium groups in the molecule whereas in the diazonium fluoroborates there is only one, and if either a free radical mechanism or an intramolecular rearrangement¹⁵ is postulated for the decomposition of $[\text{RN}_2]_2\text{SiF}_6$, then the two groups R may be in closer arrangement than for the decomposition of RN_2BF_4 . If this were the case then one would expect more side reactions, such as polymerisation, to occur.

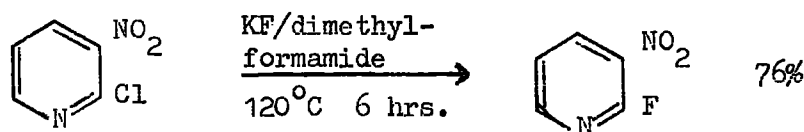


In fact, Beaty and Musgrave report the formation of a bipyridyl in one of the reactions.

In 1953, Gruber²⁶ compared three of the possible methods of preparing 2-fluoro-5-nitropyridine from 2-amino-5-nitropyridine. He obtained the fluoro derivative in 20-30% yield by the diazotisation of the amine in 60% hydrofluoric acid, but only trace amounts of the fluoro-pyridine by the decomposition of the diazonium fluoroborate and the decomposition of the diazonium fluorosilicate. Attempts to prepare either

2-fluoro-3-nitropyridine or 4-fluoro-3-nitropyridine by any of these methods failed.

Some 2-fluoronitropyridines were prepared in good yield by Finger and Starr when they accomplished halogen exchange in the α -position with 2-chloro-3-nitropyridine, 2-chloro-5-nitropyridine and 3-bromo-2-chloro-5-nitropyridine, using anhydrous potassium fluoride in dimethylformamide as solvent.



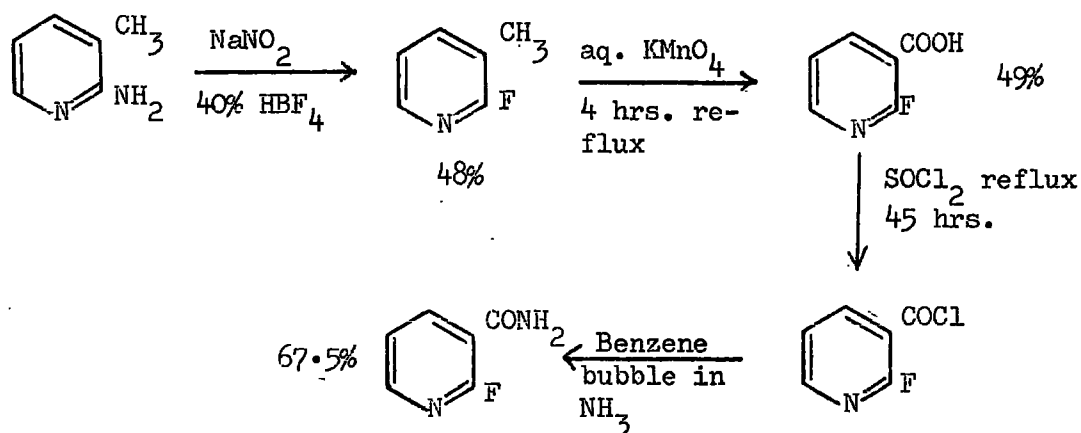
No fluoropyridine was isolated by the reaction of potassium fluoride with 2-bromopyridine, 2-bromopyridine-N-oxide, 2-chloropyridine or 2-chloropyridine hydrochloride in dimethylformamide.

However, using dimethylsulphone or tetramethylene sulphone²⁸ as solvent, 2-chloropyridine was heated with potassium fluoride at 200°-210° for 21 days to produce 2-fluoropyridine in approximately 50% yield. In a similar fashion, 3-chloro-2-fluoropyridine, 5-chloro-2-fluoropyridine and 3,5-dichloro-2-fluoropyridine were prepared.

In their investigations into the effect of substituting fluorine for hydrogen in nicotinic acid, isonicotinic acid and amides of these acids on the biological activity of these vitamin-B type compounds, Roe, Hawkins and co-workers prepared a large number of the possible mono-fluoro-isomers.

The general method of preparation started from the methylaminopyridine and involved the initial diazotisation of the amino-group in

aqueous fluoroboric acid and conversion to the fluoro-compound, followed by oxidation of the methyl group to the carboxylic acid. Chlorination with thionyl chloride and reaction with ammonia yield the amide.



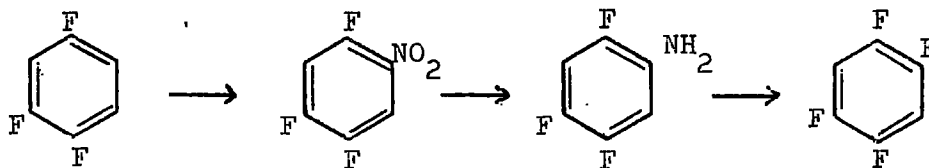
Using this technique, they prepared 2-fluoro nicotinic acid, 6-fluoro nicotinic acid,²⁹ 2-fluoroisonicotinic acid, 6-fluoropicolinic acid³⁰ and 5-fluoronicotinic acid.²³

Whereas Hawkins and Roe failed to prepare 5-fluoronicotinic acid by the Schiemann reaction from the 5-amino acid and ester because of the solubility of the diazonium fluoroborate, Beaty and Musgrave³¹ succeeded in the preparation from the amino acid by diazotising in aqueous fluoroboric acid and decomposing the diazonium fluoroborate "in situ". 2-Fluoronicotinic acid was prepared in a similar way.

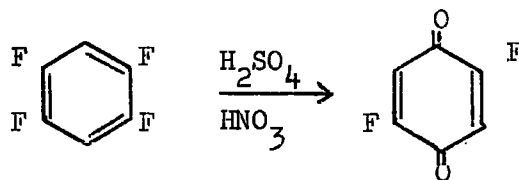
DIFLUOROPYRIDINES.

Finger³²⁻³⁵ showed that several fluorine atoms could be introduced into the benzene ring by applying the Schiemann technique in a stepwise manner. Thus fluorobenzene can be nitrated and then reduced to form the

amine, this on diazotisation and treatment with fluoroboric acid gives the monofluorophenyl diazonium fluoroborate; which gives the difluorobenzene on careful heating. This was repeated to give tri- and tetra-



fluorobenzenes. A large number of substituted fluorobenzenes have been isolated in this manner. When 1,2,4,5-tetrafluorobenzene was nitrated, oxidation occurred, and instead of the nitro compound being isolated, fluorine was eliminated, and a difluoroquinone was formed.



Thus pentafluoro- and perfluorobenzenes cannot be synthesised using the Schiemann technique.

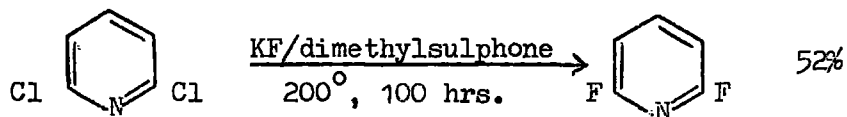
When Roe attempted to prepare a difluoropyridine from 2,6-diaminopyridine, by the simultaneous introduction of two fluorine atoms into the molecule, using the Schiemann method, no 2,6-difluoropyridine was isolated.³⁶

However, again using a stepwise approach, Finger and co-workers^{37,38} showed that two fluorine atoms could be introduced into the pyridine ring.

Starting with 2-amino-6-fluoropyridine and 3-amino-2-fluoropyridine, diazotisation in aqueous fluoroboric acid and warming produced 2,6-

difluoropyridine and 2,3-difluoropyridine, respectively. All attempts to prepare 2,5-difluoropyridine by diazotising 2-fluoro-5-aminopyridine failed. The amino-fluoropyridines were obtained, by, first preparing the fluoropyridine carboxylic acid by the Hawkins and Roe technique and then degrading the acid hydrazide using the Curtius method, or the acid amide using the Hofmann reaction.

Using anhydrous potassium fluoride in dimethyl sulphone,³⁹ 2,6-difluoropyridine has been prepared in 52% yield from the corresponding dichloro compound by halogen exchange.



When 2,3,5,6-tetrachloropyridine²⁸ was heated with anhydrous potassium fluoride in dimethyl sulphone, 3,5-dichloro-2,6-difluoropyridine was obtained in 33% yield after only twenty four hours, demonstrating the activating influence of the adjacent chlorine atoms.

Highly Fluorinated Pyridine Derivatives.

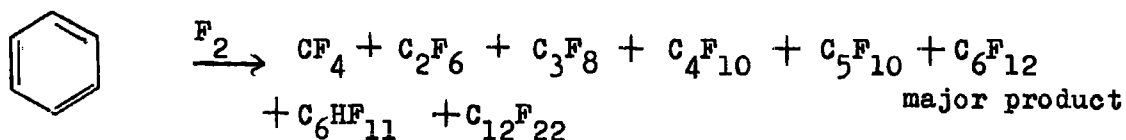
In the quest for highly fluorinated pyridine derivatives, the methods of fluorination used in the preparation of fluorocarbons from hydrocarbons have been applied to pyridine.

Elemental Fluorine.

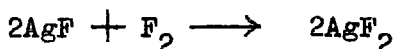
Thus, fluorine itself, usually in the presence of a "catalyst" has been used in the fluorination of hydrocarbons with considerable success by several workers.^{40, 41, 42}

This reaction inevitably destroys the aromatic system of the starting compound and gives rise to saturated fluorinated derivatives.

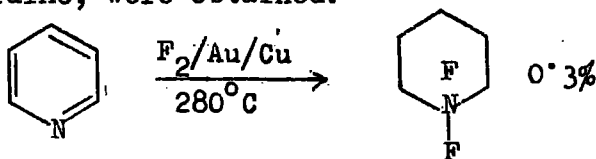
Bigelow⁴³ prepared a number of highly fluorinated products when benzene was reacted with elemental fluorine in a copper vessel. No unsaturated compounds were isolated and considerable break-down of the carbon skeleton occurred.



Similarly, Grosse, Cady et al.⁴⁴ using copper turnings coated with metallic silver as a catalyst, investigated the reaction of fluorine on several hydro-carbons including a number of aromatic compounds. In this way perfluorocyclohexane was prepared in 58% yield from benzene. It is likely in this system that the fluorocarbons are produced by the action of the fluorinating agent silver difluoride upon the hydrocarbon and that the supply of silver difluoride is maintained by the reaction:-

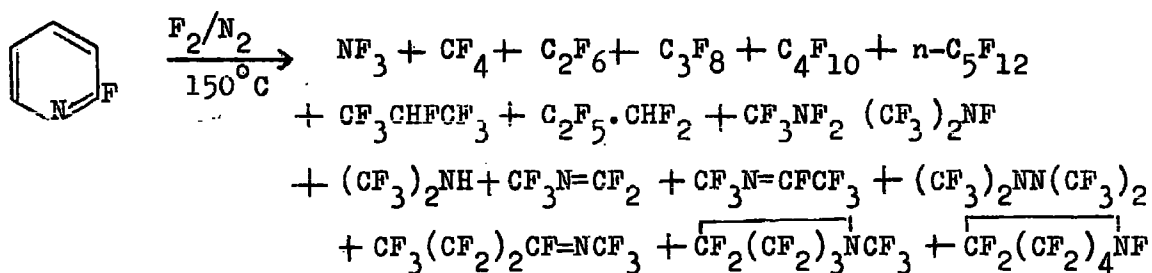


When similar techniques were explored using pyridine as starting material⁴⁵ only very poor yields of the expected product, perfluoropiperidine, were obtained.



Haszeldine conducted the reaction between pyridine vapour and

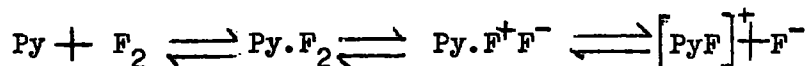
fluorine, both diluted with nitrogen, in a steel tube, packed with gold plated copper turnings, heated to 280°C. Breakdown of the pyridine nucleus occurred resulting in a yield of only 0.3% of undecafluoropiperidine. He reasoned that the yield was low due to the formation of a non-volatile hydrofluoride by the pyridine in the critical initial stages of the reaction and suggested that fluorination of heterocyclic compounds already containing fluorine would give much superior yields. This argument, however, is open to the criticism that the quaternary salts would in all probability be highly dissociated at the high temperature involved and their formation, therefore, considered unlikely. In fact, more recently, other workers⁴⁶ have performed the direct vapour-phase fluorination of 2-fluoropyridine, using a Bigelow "cool-flame" burner,⁴⁷ at 150° - 160° and reported extensive breakdown of the pyridine skeleton and the isolation of undecafluoropiperidine in less than 0.1% yield.



Of interest in this content of the reaction of pyridine with elemental fluorine is the report by Simons⁴⁸ that fluorine forms a molecular addition compound with pyridine at low temperature. This material decomposes at -40° to 0°C. A similar complex, which

is stable at room temperature, is formed by 2-fluoropyridine and fluorine, and is a potent fluorinating agent.

Further investigation into this reaction^{48a} has shown that when fluorine, diluted with nitrogen, is bubbled into a solution of pyridine in trichlorofluoromethane at -80°C , a well defined colourless solid is precipitated.



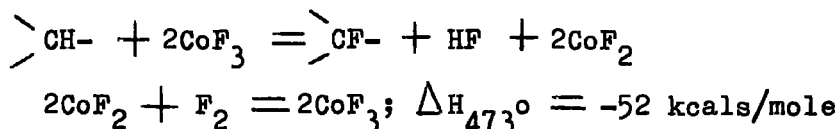
This has been shown to be an inner complex formed by reaction between one atom of pyridine and a molecule of fluorine. It is suggested that polarisation of the fluorine molecules in the presence of pyridine occurs. The electron sextet of the fluorine cation is then stabilized by the lone-pair of electrons of the pyridine nitrogen atom to produce the ionic complex formulated above.

THE METALLIC FLUORIDE PROCESS.

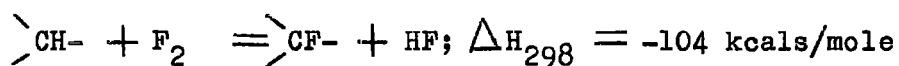
An important group of fluorinating agents is the high-valency metallic fluorides.⁴⁹ The most important member of this group of fluorinating agents is cobalt trifluoride. Silver difluoride,⁵⁰ manganese trifluoride, cerium tetrafluoride⁵¹ and lead tetrafluoride⁵² have also been used to some extent. On account of its easy and economical preparation cobalt trifluoride has become a favourite fluorinating reagent for the production of polyfluoro- and perfluoro-derivatives either from saturated, or unsaturated compounds. It is able to accomplish the addition of fluorine across double bonds and aromatic systems as well as the replacement of

hydrogen by fluorine.

The fluorinating action of cobalt trifluoride and the subsequent regeneration of the reagent may be expressed as follows:-



From the experimentally determined value of the heat of regeneration equation (52 kcal/mole),⁵³ it can be computed that, during the reaction of the organic compound with cobalt trifluoride, only approximately one half of the total reaction heat of the fluorination of the organic compound with elemental fluorine (102-104 kcal/mole) is liberated and hence less breakdown occurs.



The organic vapour, with or without nitrogen, is passed over the heated metal fluoride in a suitable reactor. Two types of reactor have been used, both of which will be briefly described.

In the first, or static method, the fluorinating agent is spread in a thin layer on the bottom of a long reactor tube. (Often a number of such tubes are connected in series of increasing temperature). No attempt is made to agitate the metallic fluoride, hence the term "static".

The other type of apparatus is a tubular reactor with a central rotating shaft with paddles which stir the reagent inside the reactor and improve the contact with the organic vapours. The reactor is usually made of nickel and is surrounded by several

heating segments which allow heating to different temperatures along its length. This type of reactor was originally used by Fowler et al.⁵³ and workers at Du Pont and Co.,⁵⁴ in the large scale fluorination of hydrocarbons, and was subsequently adopted by Barbour, Barlow and Tatlow,⁵⁵ who demonstrated that in the fluorination of a large number of hydrocarbons on a laboratory scale, smoother reactions occurred and higher yields of fluorinated products were obtained than with the static method.

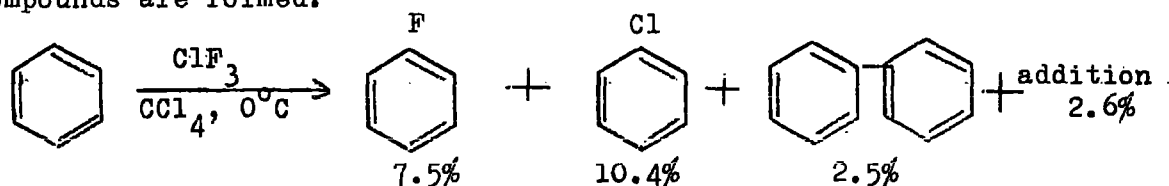
Thus, fluorination with cobalt trifluoride is a roundabout process which exposes the organic compounds to only half the thermal stress of direct fluorination. This usually brings easier handling and higher yields. Obviously, with this in mind, Haszeldine⁴⁵ attempted the fluorination with cobalt trifluoride of pyridine and its derivatives. He used the static method with a reactor 48" long and 2" in diameter. The fluorination of the organic compound was conducted at 350°C using nitrogen as a diluent. When all the pyridine had been added, the temperature of the vessel was raised to 450° and the apparatus shaken vigorously for two hours while a current of nitrogen swept out the fluorinated products. In this way he obtained perfluoropiperidine in 0.2% yield. Extensive decomposition and breakdown of the pyridine nucleus occurred.

Using a similar technique, 2:6 lutidine⁵⁶ was fluorinated to give a product reported to be perfluoro-2:6-dimethylpiperidine in about 5% yield. However in a later paper,⁵⁷ Haszeldine suggested

that in fact the product from the reaction of 2:6 lutidine with cobalt trifluoride gave an incompletely fluorinated compound.

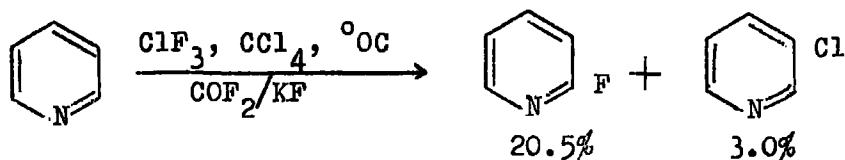
Halogen Fluorides.

Halogen fluorides, such as chlorine trifluoride bromine trifluoride and iodine pentafluoride, have been used as fluorinating agents,^{58,59} although their reactions with organic compounds are often vigorous and complicated, so limiting their application. Musgrave and Ellis^{60,61} have shown that chlorine trifluoride reacts with benzene in carbon tetrachloride solution; the main reaction being one of substitution although small amounts of addition compounds are formed.



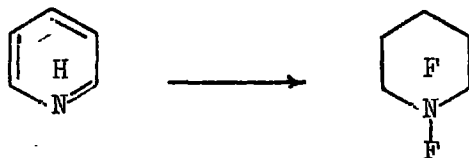
Beaty⁶² investigated the reaction of chlorine trifluoride on pyridine in carbon tetrachloride solution. He performed the reaction in a mild steel vessel at 0°C and diluted the fluorinating agent with nitrogen. Again, the main reaction was one of substitution, resulting in the formation, in poor yields, of 2-fluoropyridine and 3-chloropyridine. A number of catalysts, such as CoF_2 , AgF , SbF_3 were used, and were found to increase the yields considerably provided that the hydrogen fluoride produced during the reaction was adsorbed, as it was formed, by potassium fluoride. The ratio

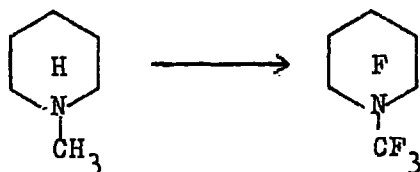
of fluoro- and chloro-pyridines were shown to depend to some extent on the catalyst employed



Electrochemical Fluorination.

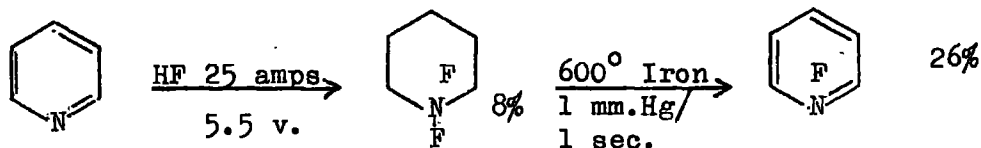
Very many organic substances dissolve readily in anhydrous hydrogen fluoride to give conducting solutions. When a direct current at low voltage (4-8 v.) is passed through such a solution, or through a suspension of an insoluble organic compound in hydrogen fluoride made conducting by the addition of an electrolyte, hydrogen is evolved at the cathode and the organic material is fluorinated. This process, known as the electrochemical method of fluorination, was first used to any extent by Simons and his associates. They showed that when pyridine, dissolved in anhydrous hydrogen fluoride, was electrolysed in such a way that the potential difference across the cell never reached that required to produce free fluorine, some 2-fluoropyridine was produced.⁶³ It was demonstrated later that the electrochemical fluorination of pyridine^{64,65} and its derivatives⁶⁶ led to fully fluorinated saturated compounds.





Two groups of workers in Britain used this method to prepare undecafluoropiperidine and found it was possible to defluorinate this compound to give the aromatic pentafluoropyridine. These results were reported almost simultaneously.^{67,68}

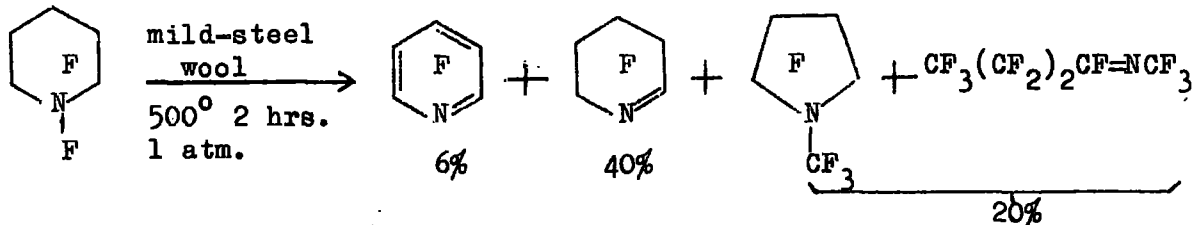
The workers at Manchester⁶⁹ prepared the undecafluoropiperidine by electrolysing a 3.35 mole % solution of pyridine in anhydrous hydrogen fluoride at 25 amps and 5.5 v. The product was obtained in 8% crude yield; final purification being effected by large-scale vapour phase chromatography. The yield from this stage was later⁷⁰ increased to 13% by using 2-fluoropyridine,¹³ prepared by the Balz-Schiemann reaction from 2-aminopyridine, as starting material. The replacement of an α -hydrogen atom by fluorine before electrolysis probably reduced the amount of fission of the C-N bonds during fluorination. The saturated compound was then defluorinated in a complex piece of apparatus by passing the vapour over a clean iron surface at 580° - 610° under reduced pressure (1 mm. Hg) with a contact time of about one second to give pentafluoropyridine in 26% yield. The Birmingham workers prepared pentafluoropyridine



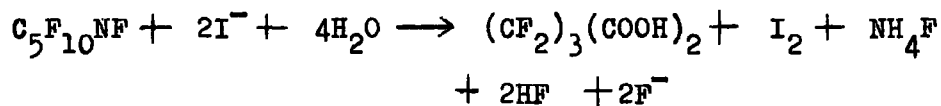
in 12% yield by defluorinating perfluoropiperidine with nickel at 560°C under atmospheric pressure.

This defluorination process at reduced pressure is interesting in that the defluorination of alicyclic fluorocarbons requires the use of long contact times (10-30 mins.) at atmospheric pressure.^{71,72} Thus, octafluorotoluene is produced in 25% yield by defluorination of perfluoro(methylcyclohexane) at 500°C at atmospheric pressure with a long contact time, whereas Haszeldine and co-workers have shown that perfluoro(methylcyclohexane) is recovered unchanged after contact with iron at 700°C for 1 sec. at 1 mm. Hg pressure. Clearly, it would seem in the aromatisation of undecafluoropiperidine to pentafluoropyridine the N-F bond appreciably facilitates defluorination.

Further evidence⁷⁰ for this theory was furnished when undecafluoropiperidine was heated with mild steel wool to 500°C for 2 hrs. at atmospheric pressure. The products were pentafluoropyridine (6%), perfluoro-2,3,4,5-tetrahydropyridine (40%), and a mixture (20% yield) consisting of perfluoro(1-methylpyrrolidine) and perfluoro-(N-butylidenemethylamine). No compounds containing^{only} carbon-carbon double bonds were isolated.

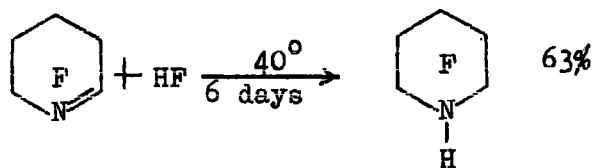


Undecafluoropiperidine is unaffected by aqueous sodium hydroxide or hydrochloric acid at 70°C, but it reacts with an excess of warm hydriodic acid or aqueous potassium iodide, to liberate iodine almost quantitatively and is converted into hexafluoroglutaric acid.



Perfluoropiperidine also reacts smoothly with ethanol at 100° to form diethyl hexafluoroglutarate as the main product together with acetaldehyde, diethyl ether and ethyl fluoride.

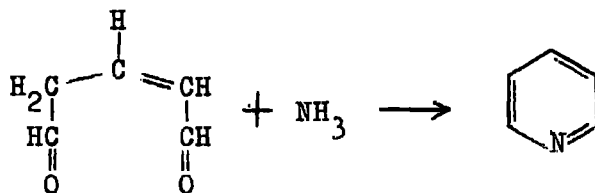
Perfluoro-2,3,4,5-tetrahydropyridine has been shown to⁷³ combine readily with hydrogen fluoride at 40°C to give 1H-decafluoropiperidine in 63% yield.



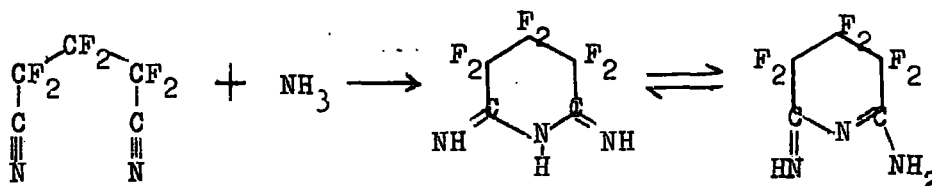
This 1H-decafluoropiperidine, which was the first secondary perfluorocycloalkylamine reported, has been nitrated to give decafluoro-1-nitropiperidine in 41% yield.

RING SYNTHESSES

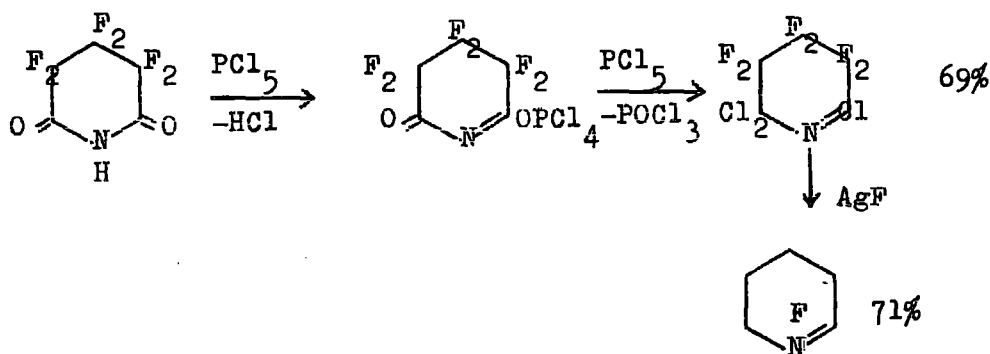
A well known synthesis of the pyridine ring system involves the reaction of pent-2-ene-1:5-dienes with ammonia. e.g. glutaconic dialdehyde and ammonia react as follows:-



During his investigations into the formation of stable polymers, Brown⁷⁴ found a similar reaction occurred when liquid ammonia reacted with perfluoroglutarodinitrile, forming the cyclic imidine.



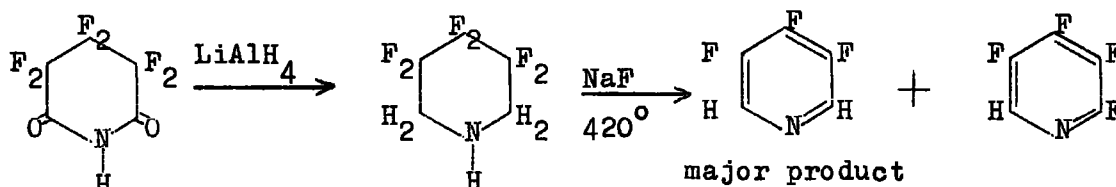
Hexafluoroglutarimide, prepared by cyclising the diamide of hexafluoroglutaric acid,⁷⁷ has been used in the preparation of perfluoro-1-piperidine. Chlorination of hexafluoroglutarimide with phosphorus pentachloride gave 2,2,6-trichloro-3,3,4,4,5,5-hexafluoro-1-piperidine. This was fluorinated into silver fluoride to produce perfluoro-1-piperidine in good yield.



The direct jet fluorination of fluorinated aliphatic dinitriles was investigated by Bigelow et al.⁷⁶ when they showed that the dinitrile of glutaric acid reacted with fluorine to produce the cyclic products,

decafluorocyclopentane, monafluoro-1-piperidine and perfluoro-piperidine as well as many linear unsaturated and breakdown products.

Workers at Birmingham⁷⁸ have shown that hexafluoroglutarimide is reduced by lithium aluminium hydride to 3,3,4,4,5,5-hexafluoropiperidine, which, on treatment with sodium fluoride at 420° yields a mixture of polyfluoropyridines by pyrolytic dehydrofluorination.



The 3,4,5-trifluoropyridine was treated with hydrazine hydrate and the product, a difluorohydrazinopyridine, reacted with Fehlings solution to give an unknown difluoropyridine, presumably 3,5-difluoropyridine

THE CHLORINATION OF PYRIDINE.

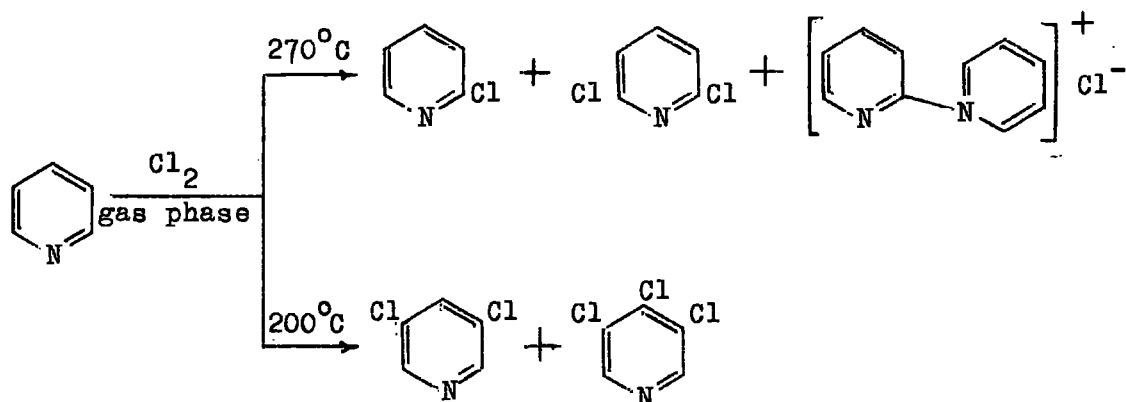
As none of the approaches hitherto reported provided a practical route to highly fluorinated pyridines in any significant yield, it was decided to approach the problem from a different direction. Thus, it seemed likely that, provided an efficient method of preparing pentachloropyridine could be achieved, it would be possible to convert this to highly substituted fluorine compounds by one or other of the techniques already used for analogous situations.

The introduction of chlorine into the pyridine nucleus has been studied in considerable detail by a large number of workers, and a review of the literature in this field revealed the most promising methods of obtaining highly chlorinated pyridines and the chlorinating agents available for this purpose.

The most obvious method of chlorination is that in which elemental chlorine is the chlorinating agent. Wibaut and co-workers¹ have studied the gas phase chlorination of pyridine intensively. The reaction was performed in a heated glass tube packed with granulated pumice, the pyridine being introduced as a vapour diluted with dry nitrogen.

The position of substitution by chlorine was found to vary with temperature, thus as observed in the bromination of pyridine,² there was a specific temperature effect on the type of substitution which

occurred, although in the chlorination, the temperature limits for both types of substitution were less divergent than those in the bromination.



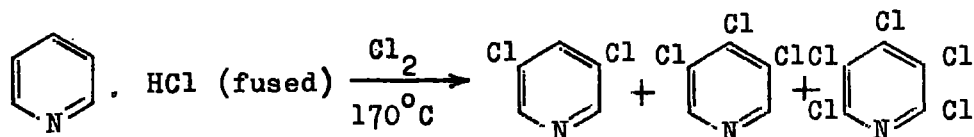
When the reaction was conducted at 270°C a good yield of 2-chloropyridine, together with a small quantity of 2,6-dichloropyridine was obtained. The presence of 1-(2-pyridyl)pyridinium chloride was indicated by the isolation of 2-aminopyridine from the reaction products upon hydrolysis.

Chlorination in the gas phase, it was reported, took place only very slowly at 200°C ; at this temperature 3,5-dichloropyridine was obtained together with 3,4,5-trichloropyridine.

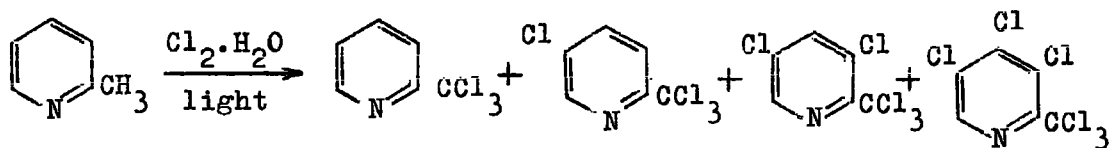
When the reaction temperature was increased to 400°C , extensive decomposition occurred and main product, in poor yield, was 2,6-dichloropyridine; suggesting that even with vigorous conditions this method was not likely to produce highly chlorinated pyridines efficiently.

The same workers explored the chlorination of fused pyridine

hydrochloride at 170°C when they showed the main product to be 3,5-dichloropyridine. Small unspecified amounts of 3,4,5-trichloropyridine and pentachloropyridine were also produced



Following the early investigations of Sell³ and Seyfferth,⁴ the chlorination of picolines has been studied by McBee et al.⁵ Substitution of the side chain took place first, but if sufficiently vigorous conditions were employed, chlorine was introduced into the nucleus.

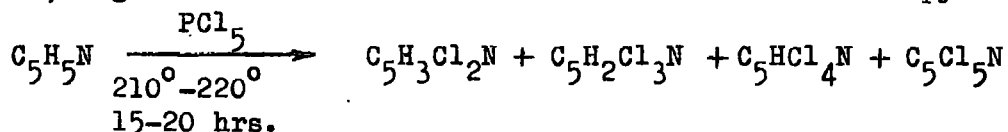


The structures of these products were determined by hydrolysis to the corresponding picolinic acids.

Recently this reaction has been patented,⁶ when photochlorination of 2 picoline at 50° - 150°C in the presence of a small proportion of water was reported to give a mixture of 2-trichloromethyl-dichloropyridines and 2-trichloromethyl-3,4,5-trichloropyridine, which was further chlorinated under anhydrous conditions at 110° - 160°C to 2,3,4,5-tetrachloro-6-trichloromethylpyridine. This route, although it might prove tedious to separate the various substituted products, could possibly be used as a starting point in the exploration

of the chemistry of the fluoropicolines, provided, of course, that a suitable method of replacing the chlorine by fluorine could be found.

As early as 1898, Sell and Dootson⁷ investigated the reaction of phosphorus pentachloride with pyridine. The reaction was conducted in sealed glass tubes at a temperature of 210° - 220°C for 15 to 20 hrs., the tubes being frequently opened to allow the escape of hydrogen chloride. Although no actual figures were quoted, the product obtained in greatest yield was reported to be pentachloropyridine, together with smaller amounts of less chlorinated pyridines.

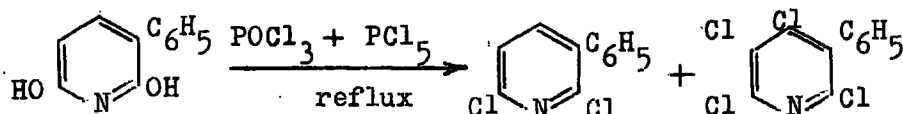


Obviously the reaction deserved further inspection, especially as no reports of its development since the early publication have appeared in the literature.

Even before their work on the chlorination of pyridine itself, the same workers had studied the chlorination of a derivative of pyridine, citrazinic acid⁸ (2,6-dihydroxyisonicotinic acid) with a mixture of phosphorus pentachloride and phosphorus oxychloride. When the reactants were refluxed together a mixture of products was obtained including pentachloropicoline, pentachloropyridine and chlorinated derivatives of isonicotinic acid. The significance of this reaction is more historical rather than its importance as a route to highly chlorinated pyridines, not only because of the complicated nature of

the products but also due to the relative inaccessibility of the starting material, citrazinic acid.

The same chlorinating agent ($\text{PCl}_5/\text{POCl}_3$) has been used in reaction with 3-phenyl-2,6-pyridinediol⁹ to produce a tetrachloro-substituted pyridine

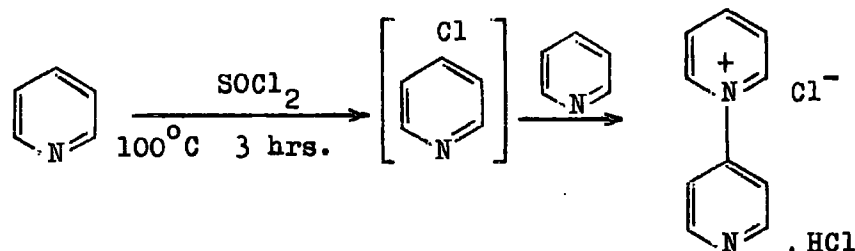


Such reactions are interesting as they may possibly provide a route to substituted fluoropyridines which are difficult to obtain otherwise.

The thermal decomposition of pyridine hydrochloride perchloride leads to nuclear chlorinated products. An aqueous solution of pyridine hydrochloride slowly absorbs chlorine to form a semi-solid perchloride. When this compound is heated rapidly to $160^\circ - 180^\circ\text{C}$, some chlorination occurs. In this way, McElvain and Goese reported obtaining 3-chloropyridine and 3,5-dichloropyridine, each in about 4% yield.

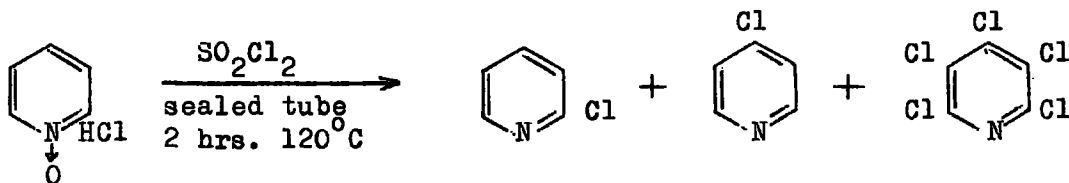
In a somewhat analogous manner, Sell and Dootson⁸ treated a solution of pyridine, saturated with hydrochloric acid, with chlorine for a period of one week, forming 3,5-dichloropyridine along with the main product 2,3,4,6-tetrachloropyridine. The very low degree of conversion to highly chlorinated pyridines precludes this method as an efficient route to the desired compounds.

Thionyl chloride has been used as a chlorinating agent with pyridine,¹¹ and, although no highly chlorinated compounds are produced, the reaction is interesting in that the main product is 1-(4-pyridyl)pyridinium chloride hydrochloride suggesting the intermediate formation of 4-chloropyridine



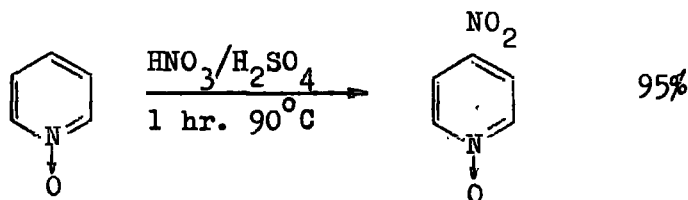
The use of pyridine 1-oxides as starting materials for the preparation of chlorine substituted pyridines has been investigated by several workers, although the direct reaction with chlorine has apparently not been reported.¹² Other chlorinating agents with pyridine 1-oxides often give rise to otherwise difficultly available chloropyridines.

Bobranski and co-workers¹³ reported that pyridine 1-oxide and sulphuryl chloride gave a 65% yield of a mixture comprising 57% 2-chloropyridine and 43% 4-chloropyridine, and a small amount of pentachloropyridine.



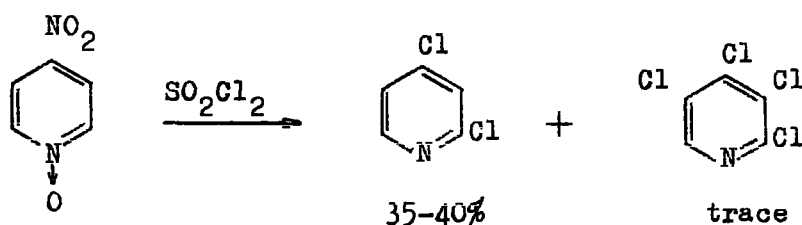
With phosphorus pentachloride, pyridine 1-oxide is said to lead to 4-chloropyridine,¹⁴ although later work in these laboratories¹⁵ has shown that more highly chlorinated pyridines can be obtained from this reaction.

Since 4-nitropyridine 1-oxide can be readily prepared by nitration of pyridine 1-oxide,¹⁶⁻¹⁸



it has been used as a starting material in the preparation of a number of halopyridines.

When heated with sulphuryl chloride, 4-nitropyridine 1-oxide loses the oxide function and the main product is 2,4-dichloropyridine together with some 2,3,4,5-tetrachloropyridine.^{19, 20}

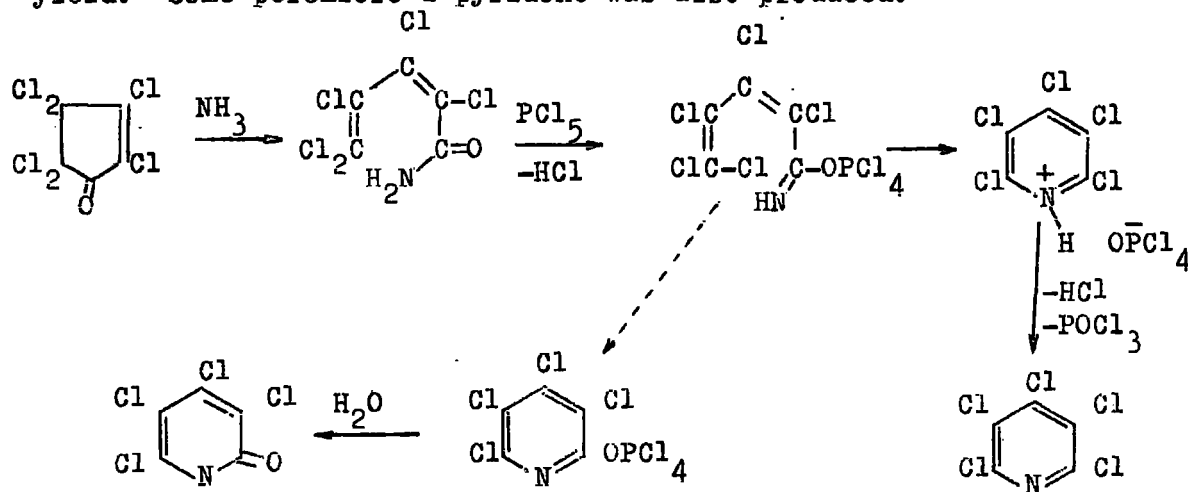


The obvious disadvantage of this method as a practical route to highly chlorinated pyridines is not only the poor yields obtained but also the fact that the starting material itself is not readily available but requires two reaction steps in its preparation from

pyridine.

Very recently, a new synthesis of pentachloropyridine has been reported²¹ in which the starting material was hexachloro-cyclopentenone. Reaction of the hexachloropent-1-ene-3-one with liquid ammonia in ether solution gave the amide of pentachloro-penta-2,4-dienoic acid.

Further chlorination of this in benzene solution followed by heating, to eliminate hydrogen chloride and phosphorus oxy-chloride, gave pentachloropyridine in approximately 58% overall yield. Some perchloro-2-pyridone was also produced.



This preparation of pentachloropyridine is very convenient and no doubt it will be used in these laboratories as route to the fluoropyridines in future studies.

THE CONVERSION OF PERCHLORO-AROMATIC COMPOUNDS TO PERFLUORO-AROMATIC
COMPOUNDS

Highly chlorinated compounds have been used in many cases as starting materials in the preparation of perfluoroaromatic compounds in both the carbocyclic and heterocyclic series, but notably in the conversion of hexachlorobenzene to chlorofluorobenzenes and perfluorobenzenes by several techniques. It was argued from this that, if it were possible to modify one of the methods of chlorination of pyridine to produce pentachloropyridine in good yield, then it should be possible to prepare perfluoropyridines by applying one of the fluorination techniques.

The methods of converting hexachlorobenzene to highly fluorinated benzenes can be divided into two main groups.

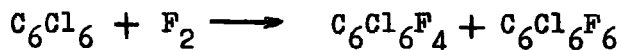
The first group includes those methods which involve the formation of halogenated cyclohexanes and cyclohexenes, by reaction with reagents such as fluorine, halogen fluorides and metal fluorides, followed by dehalogenation to give the desired fluoro-aromatic derivatives.

Reactions of the second group provide a more direct route to the fluorine containing compounds and involve the general principle of halogen exchange between the original chloro-compound and, usually, a metal fluoride.

GROUP I

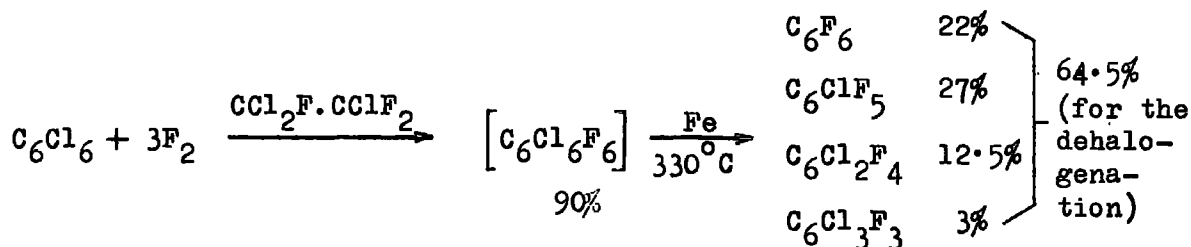
Hexachlorobenzene and Fluorine

Bigelow and Pearson¹ reported the isolation of hexachloro-tetrafluorocyclohexene and hexachlorohexafluorocyclohexane in small quantities by the reaction of hexachlorobenzene, as a suspension in carbon tetrachloride, with elemental fluorine. When the solid had disappeared into solution, the solvent was removed leaving an oil. This was further fluorinated at 0°C in a copper vessel.



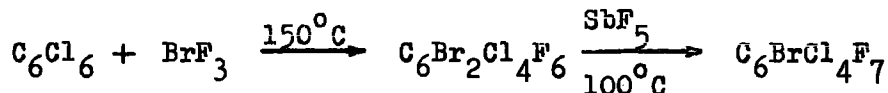
The amount of known product isolated was only a very small percentage of the fluorinated product. Later, Fukuhara and Bigelow² reacted hexachlorobenzene with fluorine in the vapour phase, using a copper gauze catalyst. The product was reduced with iron and glacial acetic acid, and on fractionation yielded twelve definite chemical entities. The properties of these were reported but no structures were assigned.

More recently,^{3,4} Musgrave and co-workers have reacted hexachlorobenzene as a slurry in 1,1,2-trichlorotrifluoroethane with elemental fluorine to give a mixture of saturated chlorofluorocyclohexanes. Dehalogenation of these gave a good yield of a mixture of hexafluorobenzene and chlorofluorobenzenes.



Hexachlorobenzene and Bromine Trifluoride.

Prior to the work in these laboratories described above, McBee, Lindgren and Ligett^{5,6,7} reacted hexachlorobenzene and bromine trifluoride in a stirred nickel tube heated to 150°C. The mixture of products from this reaction corresponded to the approximate molecular formula $\text{C}_6\text{Br}_2\text{Cl}_4\text{F}_6$. This was further fluorinated with antimony pentafluoride at 100°C, and a solid product formed of approximate molecular formula $\text{C}_6\text{BrCl}_4\text{F}_7$.



No attempt was made to realise its constitution and it was dehalogenated using zinc and ethanol,⁸ giving the aromatic compounds, C_6F_6 and C_6ClF_5 in small yield, and the cyclic unsaturated compounds C_6F_8 , C_6ClF_7 , $\text{C}_6\text{Cl}_2\text{F}_6$, $\text{C}_6\text{Cl}_3\text{F}_5$ and $\text{C}_6\text{Cl}_2\text{F}_8$, $\text{C}_6\text{Cl}_3\text{F}_7$. The total halocarbon product corresponded to a 53% yield based upon starting hexachlorobenzene. The physical properties of the products were reported, but there was no attempt to determine their configurations.

Hexachlorobenzene and Chlorine Trifluoride.

Workers in Durham⁹ have studied the reaction of hexachloro-

benzene with chlorine trifluoride in the liquid phase at 240°C. The principal products were a mixture of chlorofluorocyclohexenes, $C_6F_nCl_{10-n}$ (where n is mainly 4, 5 and 6). When a very large excess of chlorine trifluoride was used, saturation was achieved with difficulty to give chlorofluorocyclohexanes, $C_6F_nCl_{12-n}$ (where n is mainly 5, 6, 7).

Aromatisation of the cyclohexenes at 250° - 300° gave mainly chloropentafluorobenzene and dichlorotetrafluorobenzene, with some hexafluorobenzene and trichlorotrifluorobenzene. This was a very much more complex mixture of products than that obtained by the dehalogenation of chlorofluorocyclohexanes, since preferential elimination of chlorine from the saturated compounds took place. Preferential elimination of chlorine from the cyclohexenes did not readily occur as this would require migration of chlorine attached to a carbon on a double bond.

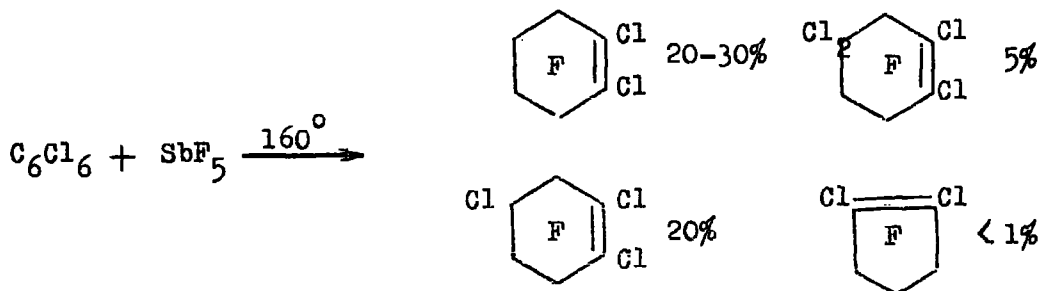
Hexachlorobenzene and Antimony Pentafluoride.

This reaction was first reported by McBee et al.,¹⁰ who heated hexachlorobenzene and antimony pentafluoride to 125°C and obtained 1,2-dichloro-octafluorocyclohexene in up to 60% yields. Later work¹¹ revealed that at 150°C the yield was increased to 87%.

Stilman¹² on heating hexachlorobenzene with antimony pentafluoride at 250°C, reported the isolation of a chlorofluorobenzene, $C_6Cl_2F_4$, together with the unsaturated cyclic $C_6Cl_2F_6$, prolonged

reaction gave the fully saturated cyclic C_6F_{12} , C_6ClF_{11} and $C_6Cl_2F_{10}$. This is the only report of an aromatic compound found in this reaction and although an analysis was quoted, no physical data were given.

More recent work on this reaction has been carried out by Leffler,¹³ who reacted hexachlorobenzene with antimony pentafluoride at $160^\circ C$. A careful control of the temperature was maintained, as an exothermic reaction occurred at $160^\circ C$ which resulted in loss of some of the product. The structure determinations were made by infra-red and N.M.R. spectroscopy and the products were shown to be 1,2-dichloro-octafluorocyclohexene, 1,2,4-trichloroheptafluorocyclohexene, 1,2,4,4-tetrachlorohexafluorocyclohexene and 1,2-dichlorohexafluorocyclopentene.



As previously described, compounds of this type, are not easily dehalogenated to simple mixtures of aromatic compounds because preferential elimination of chlorine cannot take place because of its presence as a substituent on a double bond.

Hexachlorobenzene and Metallic Fluorides.

The reaction between cobalt trifluoride and hexachlorobenzene, investigated in these laboratories,¹⁴ produced a large range of chlorofluorocyclohexanes. The hexachlorobenzene was vapourised and passed over cobaltic fluoride at 350°C in a cylindrical stirred reactor, to give good yields of the cyclohexanes of general formula $C_6Cl_nF_{12-n}$. (Where $n = 1-6$). The chlorofluorocyclohexanes were dehalogenated easily by passing over hot iron gauze at 430°C to give good yields of hexafluorobenzene.

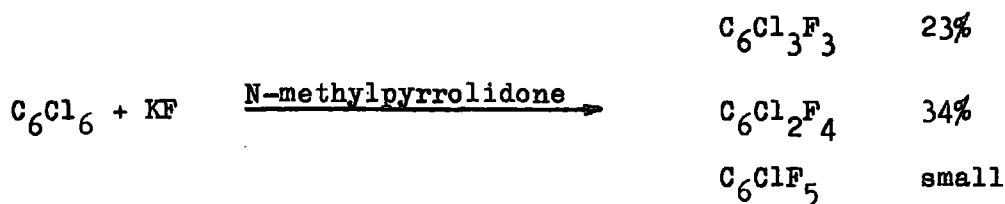
McBee and co-workers¹⁵ used a static reactor to fluorinate hexachlorobenzene with cerium tetrafluoride at 275°C. Cyclic $C_6Cl_3F_9$ was obtained in good yields; recycling the product produced the fully fluorinated cyclic C_6F_{12} .

Lindgren and McBee¹⁶ similarly fluorinated hexachlorobenzene with plumbic fluoride at 300°C to give cyclic $C_6Cl_3F_9$ in 8% yield.

GROUP II

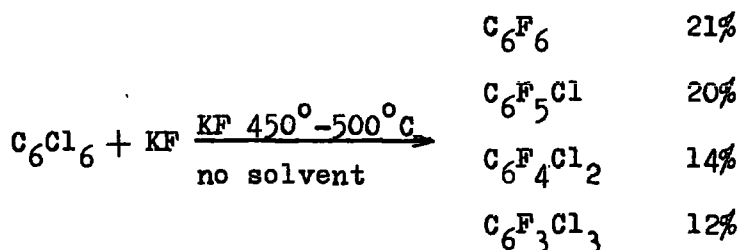
Halogen Exchange

Halogen Exchange was accomplished by Maynard¹⁷ when he reacted hexachlorobenzene with potassium fluoride at elevated temperature using N-methylpyrrolidone as solvent to give a



mixture of chlorofluorobenzenes.

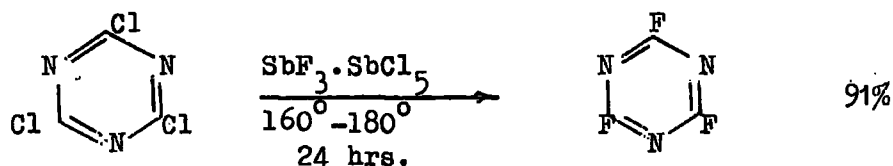
A number of Russian workers^{18, 19} have investigated this halogen exchange reaction between hexachlorobenzene and potassium fluoride, both with and without solvent. Vorozhtsov et al. heated hexachlorobenzene with anhydrous potassium fluoride in an autoclave at 450° - 500°C to produce good yields of mixtures of highly fluorinated aromatic compounds.



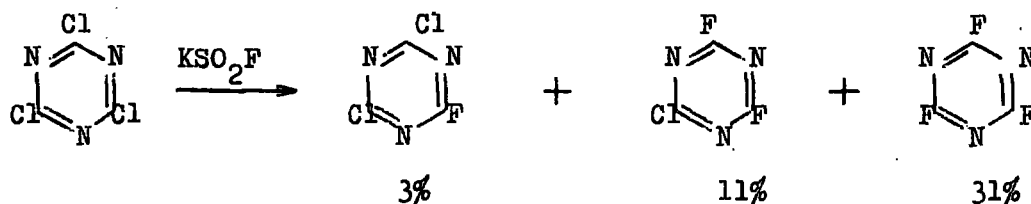
Many variations of this method have appeared in the patent literature as it will obviously lend itself to industrial application.

Chlorinated nitrogen containing aromatic heterocycles have been used as starting materials in the preparation of the corresponding fluoro-compounds.

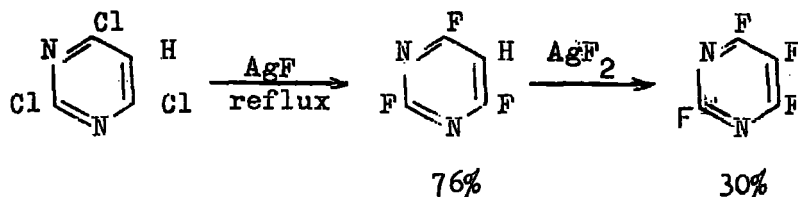
Thus, Kober and Grundmann²⁰ reported the preparation of sym. trifluorotriazine by the reaction of $\text{SbF}_3 \cdot \text{SbCl}_5$ with the "active" chlorine atoms in sym. trichlorotriazine.



The same starting material has been treated with potassium fluoro-sulphinate (KSO_2F)²¹ as fluorinating agent to produce a mixture of substituted products.

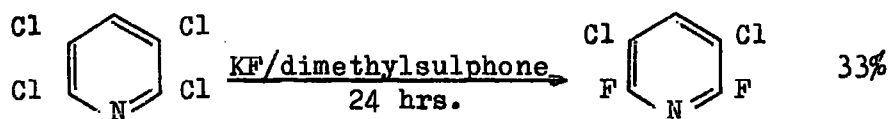
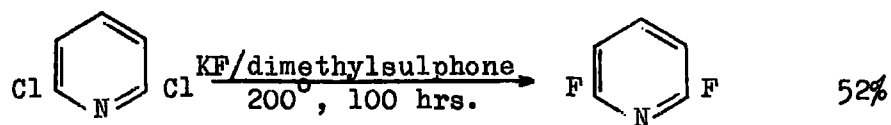


Perfluoro-aromatic heterocycles containing two nitrogen atoms per molecule have been prepared by the reaction of chloropyrimidines with silver fluorides.^{22,23}



The chlorine in the trichloropyrimidine was replaced by halogen exchange with silver fluoride, and the hydrogen in the trifluoropyrimidine replaced by reaction with silver difluoride.

As mentioned earlier, lightly fluorinated pyridines have been prepared by Finger and others by halogen exchange between a number of chloropyridines and potassium fluoride in the presence of solvent.^{24,25}



Chapter 2

DISCUSSION OF EXPERIMENTAL WORK

DISCUSSION OF EXPERIMENTAL WORK

As outlined in the historical introduction, none of the direct methods of fluorinating the pyridine system met with success; in most cases yields of highly fluorinated pyridines were very poor. Thus, in order to apply the indirect route to perfluoropyridines via the corresponding chloro-compounds, it was necessary to develop one of the existing methods for the preparation of pentachloropyridine.

CHOICE OF CHLORINATION METHOD

Since the indirect approach would necessitate more than one step in the preparation of highly fluorinated pyridines it would obviously be advantageous to keep the number of such steps to a minimum on account of both overall yield and economy.

Such considerations preclude the application of chlorination methods starting with compounds themselves several reactions distant from pyridine, e.g. the reaction by den Hertog of 4-nitropyridine-1-oxide with sulphuryl chloride;^{1,2} and the chlorination of citrazinic acid with a mixture of phosphorus pentachloride and phosphorus oxychloride.³

Ideally, the chlorination would involve the reaction of pyridine, which is readily available, and a simple chlorinating agent.

Unfortunately, the simplest chlorinating agent, elemental chlorine itself, does not react with pyridine to give good yields

of highly chlorinated pyridines.⁴ When the temperature of the reaction is raised, in order to introduce more chlorine into the pyridine ring, extensive breakdown occurs and tar is produced.

Other chlorinating agents, such as thionyl chloride,⁵ with pyridine tend to give lightly chlorinated pyridines. However the report by Sell and Dootson⁶ that the reaction between pyridine and phosphorus pentachloride gives, as well as lower chloro-compounds, an appreciable yield of pentachloropyridine has led us in these laboratories to develop this method as a practical and efficient route to highly chlorinated pyridines. Phosphorus pentachloride is both plentiful and cheap and lends itself to application on a relatively large scale.

THE REACTION OF PYRIDINE WITH PHOSPHORUS PENTACHLORIDE

Dry pyridine has been heated with phosphorus pentachloride in a large autoclave. Throughout the development process stainless steel autoclaves varying in size from 3 litres to 5 litres capacity have been used.

The results of early experiments have already been reported⁷ and it was shown that heating 200 gm. (2.5 moles) of pyridine with 2500 gm. (12 moles) of phosphorus pentachloride to 210° - 220°C for 72 hrs. produced mainly trichloro- and tetrachloropyridines, with pentachloropyridine formed in only 1.5% yield.

The effect of increasing the temperature to 280° - 285°C for 50 hrs. increased the yield of pentachloropyridine to 15%. The amount of tetrachloropyridines (18%) produced in this reaction was greater than that (13%) produced at the lower temperature. Of the three possible isomers of tetrachloropyridine, only those with hydrogen atoms in the 3- or the 4-position were formed. As pointed out in this paper, it was possible to convert the di-, tri- and tetrachloropyridines from several reactions, by further chlorination with phosphorus pentachloride, so that the overall yield of pentachloropyridine was good. Although this state of affairs provided a basis for obtaining suitable quantities of starting material for conversion to fluoropyridines it was realised that it would be more satisfactory if the yield of pentachloropyridine from a single stage chlorination of pyridine could be improved.

With this object in mind, we have been working as a team to obtain the results typified by the reactions shown in Table 1.

The early reactions were carried out in a 3 litre stainless steel autoclave, without an internal liner. This was heated electrically by means of heating elements around the outside of the vessel. The temperature was controlled by means of a variable transformer, which was set at a precalibrated value so that the temperature of the inside of the autoclave, measured by means of a thermometer in a central thermometer-well in the autoclave head, was

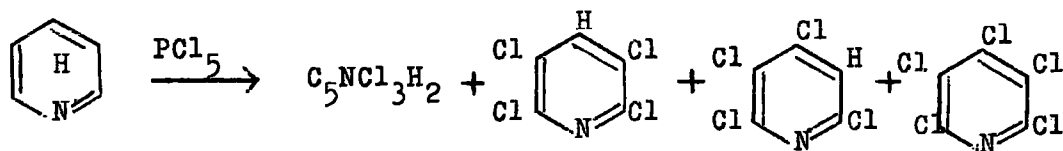
TABLE 1. Reaction of Pyridine with Phosphorus Pentachloride.

Expt.	Wt. PCl ₅ gm.	Wt. C ₅ NH ₅ gm.	"Catalyst"	Time hrs.	Temp. °C	Wt. Product gm.	mole % composition product					Liner
							C ₅ NCl ₂ H ₃	C ₅ NCl ₃ H ₂	C ₅ NCl ₄ H	C ₅ NCl ₅		
R. 1	3000	300	-	48	310	250	-	10	50	40	1	
R. 2	3000	300	-	48	300	120	-	50	45	5	2	
R. 3	3000	200	-	33	290	220	-	10	50	40	3	
R. 4	3000	250	CuCl ₂	11	350	150	-	10	50	40	3	
R. 5	3000	250	CrCl ₃	24	320	180	-	10	50	40	3	
R. 6	3000	430	-	24	320	130	30	35	30	5	4	
R. 7	4000	200	-	24	320	110	-	20	50	30	4	
R. 8	3000	250	-	24	293	140	15	35	35	15	4	
R. 9	3000	250	stainless steel turnings	24	293	130	15	35	35	15	4	
R. 10	3000	250	FeCl ₃	77	293	130	20	35	35	10	4	
R. 11	3000	250	-	73	295	130	10	40	35	15	4	
R. 12	3000	250	Mo	48	295	120	5	35	40	20	5	
R. 13	3000	250	-		280		Bursting disc blew at 300 ats.					6
R. 14*	1500	125	-	24	300	180	-	25	50	25	6	
R. 15	1500	125	-	24	300	225	-	10	45	45	6	
R. 16+	2175	100	-	24	300	234	-	-	30	70	6	
R. 17+	1640	125	-	24	360	160	-	decomposition			6	
R. 18	2500	100	-	24	300	250	-	-	10	90	6	
1	Stainless steel bomb - no liner					4	Second stainless steel liner - heavier than 3					3
2	Heavy mild steel liner					5	Third stainless steel liner, lighter than 4, heavier than 3					4
3	Thin stainless steel liner					6	Heavy nickel liner - in new bomb					

* Temperature raised very slowly.

+ Auxiliary heating element fitted.

attained slowly and maintained in thermal equilibrium. Typical of these reactions was R.I. in which 300 gm. of pyridine was heated to 310° for 48 hrs. with 3000 gm. of phosphorus pentachloride to produce 250 gm. of chlorinated pyridines. The proportions of tri-, tetra- and pentachloropyridines in this product were almost identical to those obtained by Hutchinson⁷ at a slightly lower temperature, i.e. the proportion of pentachloropyridine was 40 mole %, corresponding to a yield of 11%.



The products were separated from the reaction mixture by hydrolysis followed by steam distillation.

The organic steam distillate was dried by azeotropic distillation with benzene and fractionated through a 20" column packed with Dixon gauzes.

After many reactions such as that described above it was obvious that the inside of the autoclave was becoming seriously damaged and corroded by the vigorous conditions used. In an attempt to prevent this damage it was decided to fit an internal liner to the autoclave. Since mild steel was known to be more resistant to attack by halogens than was stainless steel, the liner was constructed of mild steel in the shape of a heavy cylindrical pot which fitted snugly inside the autoclave. The effect of this liner, demonstrated by R.2, was to

produce even worse yields of products than before. Starting with 300 gm. of pyridine, only 120 gm. of chlorinated products were produced, comprising of mainly tri- and tetrachloropyridines, less than 5 mole % being pentachloropyridine (corresponding to a yield of 1%).

At the time, this was considered to be due to the effect of minor constituents present in stainless steel but not in mild steel which were having a catalytic effect on the chlorination reaction. An alternative reason, involving the temperature factor, is now believed to be the cause of these low yields but this will be discussed later.

When the heavy mild steel liner was removed and replaced by a thin stainless steel liner, the results then obtained are typified by R.3 in which the conversion of pyridine to pentachloropyridine was improved over that from reactions without a liner (as R.1).

200 gm. of pyridine was heated with 3000 gm. of phosphorus pentachloride at 290°C for 33 hrs. to give a yield of 14% pentachloropyridine.

The influence of catalysts of the chlorination reaction.

The results above appeared to justify the belief that a component, of the stainless steel was "catalysing" the reaction, so a series of experiments were carried out in which a number of transition metal chlorides or the metals themselves were added to the reaction mixture in an attempt to improve the yields of pentachloropyridine.

Anhydrous cupric chloride and anhydrous chromium trichloride were added in 5 gm. amounts to the reaction mixtures. (R.4 and R.5 respectively). As can be seen from the results, this had little effect on the relative proportions of products as compared with the control experiment, R.3. No increase in the yield of pentachloropyridine was observed.

When a new, heavier, stainless steel liner was fitted to the autoclave due to the decomposition of that used in the experiments reported above, the yields of pentachloropyridine were again seen to fall, as exemplified by R.8 in which the yield of pentachloropyridine was 2.6%.

Using the same liner, the presence of stainless steel turnings, ferric chloride or molybdenum metal gave no significant increase in the yield of pentachloropyridine. (R.9, R.10, R.12).

The effect of altering the ratio of pyridine to phosphorus pentachloride

With the heating system previously described, throughout the series of reactions R.1 - R.12 the effect of altering the ratio of pyridine to chlorinating agent was investigated. It can be seen from the table, that, as a general rule, the greater the proportion of phosphorus pentachloride to pyridine used in the reaction the more highly chlorinated and the greater the yield of products were obtained.

The extreme conditions explored (R.6 and R.7) demonstrated that the yield of pentachloropyridine was greatest when a large excess of

phosphorus pentachloride was present. Thus, when 4000 gm. of PCl_5 was heated with 200 gm. of pyridine (mole ratio $\text{PCl}_5:\text{C}_5\text{NH}_5::7.5:1$) the conversion to pentachloride was doubled (5.2% yield) compared with a normal reaction (R.8), in which 3000 gm. PCl_5 was used with 250 gm. of pyridine (mole ratio $\text{PCl}_5:\text{C}_5\text{NH}_5::4.5:1$). In R.6, 3000 gm. phosphorus pentachloride were heated with 430 gm. of pyridine (mole ratio $\text{PCl}_5:\text{C}_5\text{NH}_5::2.65:1$) to give an extremely poor yield of pentachloropyridine (0.5%).

The influence of temperature on the chlorination reaction.

Sell and Dootson⁶ reported using a temperature of $210^\circ\text{--}220^\circ\text{C}$ in their chlorination reactions, to give an unspecified yield of pentachloropyridine. When workers in these laboratories⁷ heated the reactants in an autoclave, by the method previously described, to the same temperature a yield of only 1.5% of pentachloropyridine was obtained. Increasing the reaction temperature to $280^\circ - 285^\circ$ caused an increase in yield of pentachloropyridine to 15%. The effect of further elevation of the reaction temperature was investigated as shown in Table 1. Using the thermal equilibrium method of heating (R.1 - R.12), no significant improvement in yields was observed by raising the temperature even as high as 350°C (R.4).

However, when a new heating system was installed in which the heating elements were virtually in contact with the wall of the

autoclave and the electric power was controlled thermostatically by a thermocouple in the centre of the autoclave, such that full power was maintained, with the elements glowing red hot, until the centre of the reaction vessel attained the pre-set temperature (usually 300°C), a marked improvement in the yields of pentachloropyridine was obtained as demonstrated by R.13 - R.18.

In the first experiment using this new heating apparatus (R.13), together with a new 5 litre capacity autoclave, fitted with a heavy nickel liner, the quantities of reactants, normally used in previous reactions were placed in the autoclave. Before the centre of the reaction reached a temperature of 280°C , the safety bursting disc on the autoclave head blew at 300 atmospheres. As a result, all subsequent reactions were carried out on reduced quantities of reactants ~~so reducing the "dead-space" in the autoclave (i.e. the volume~~ occupied by virtually incompressible components) and the amount of hydrogen chloride gas, and therefore the pressure, produced.

Experiments using the same mole ratio of reactants as in the early studies, but using this new heating system, gave much superior results in terms of highly chlorinated products. (e.g. Compare R.11 with R.15).

The result of increasing the ratio of phosphorus pentachloride to pyridine over a number of reactions (R.15, R.16, R.18) had a beneficial effect, so that when 2500 gm. of phosphorus pentachloride

was heated with 100 gm. of pyridine (mole ratio approx. PCl_5 : C_5NH_5 :: 10:1) a 71% yield of pentachloropyridine was obtained.

When an auxiliary heating element was used in conjunction with the standard unit in order to increase the temperature at the centre of the autoclave to 360°C , extensive decomposition occurred yielding little useful product (R.17).

Conversion of lower chlorinated pyridines to pentachloropyridine was similarly improved using the new apparatus. A charge of 400 gm. of mixed trichloro- and tetrachloropyridines with 2500 gm. phosphorus pentachloride gave pentachloropyridine in almost quantitative yield after heating to 300°C for 24 hrs.

Very recently⁸ other workers, in Manchester, have reported obtaining good yields of pentachloropyridine by a similar reaction of pyridine with phosphorus pentachloride, although experiments were carried out on a very much smaller scale than in these laboratories, using a greater ratio of phosphorus pentachloride to pyridine.

FLUORINATION OF CHLOROPYRIDINES

Since highly chlorinated pyridines were now available in practical quantities the problem became one of converting these to the highly fluorinated derivatives.

It seemed preferable not to use a method involving the addition of fluorine to give saturated compounds, e.g. using reagents such as high valency metal fluorides or fluorine itself, followed by dehalo-

genation as this would involve a two stage process with the likelihood of low yields due to decomposition caused by fission of the carbon-nitrogen bonds.

Obviously a method in which halogen exchange between the chloropyridines and a source of fluoride ion would be more advantageous as this could be performed in a single step to give the desired fluoropyridines. Yields from this type of reaction are usually better than those obtained from a two stage "addition-dehalogenation" route.^{9, 10}

HALOGEN EXCHANGE

Hutchinson⁷ investigated the reaction of anhydrous potassium fluoride on an isomeric mixture of tetrachloropyridines in sulpholane at 210° - 220°C. A moderate yield of an approximately equimolar mixture of 3-chloro-2, 4, 6-trifluoropyridine and 3, 5-dichloro-2, 5 difluoropyridine was obtained. The reaction of potassium fluoride with isomeric tetrachloropyridines, in an autoclave, in the absence of solvent was also studied. Replacement of chlorine by fluorine was only slight at 340°C, but increased progressively with increase in reaction temperature to a maximum at 400°C when the products still contained chlorine. At this temperature the product consisted of a mono-chlorotrifluoropyridine (34%) and a mixture of dichlorodifluoropyridines (63%). Further increase in reaction temperature caused complete decomposition; this instability is probably attributable to the presence of hydrogen in the molecule as it was shown that pentachloropyridine

could be heated with potassium fluoride to considerably higher temperatures without decomposition.

Pentachloropyridine was fluorinated, by the same workers, when it was heated to 190° - 210° with potassium fluoride in sulpholane. A good yield of 3, 5-dichlorotrifluoropyridine was obtained together with a small amount of 3-chlorotetrafluoropyridine. Obviously a considerably higher temperature was required to cause complete replacement of chlorine and since this was incompatible with the use of a solvent, the reaction of potassium fluoride on pentachloropyridine in the absence of a solvent was investigated.

The results obtained by Hutchinson, using a small (120 ml.) autoclave as reaction vessel are shown in the following table:

TABLE II

C_5Cl_5N (gm)	KF (gm)	Temp ($^{\circ}C$)	Time (hr)	Product (gm)	Composition of product in mole%		
					(% yield in parentheses)		
					$C_5Cl_2F_3N$	C_5ClF_4N	C_5F_5N
15	40	480	24	7.8	-	10(7.7)	90(68.5)
20	60	480	19	13	5(5)	25(24)	70(66)
20	60	450	20	13	13(12)	44(40)	43(39)
20	60	440	17	14	60(53)	32(28)	8(15)
15	40	400	18	10	100(84)	-	-

Even with a reaction temperature as high as $400^{\circ}C$ no significant replacement of chlorine in the 3 or 5 position occurred. However, at

temperatures of 440°C and above, replacement did take place progressively so that at a reaction temperature of 480°C a good yield of pentafluoropyridine together with some 3-chlorotetrafluoropyridine was obtained.

This reaction has been developed so that greater amounts of pentachloropyridine can be fluorinated in a single reaction, a necessary step caused by the increased demand for the highly fluorinated pyridines which have been used as starting materials in multi-stage syntheses.

The reactants, anhydrous potassium fluoride and pentachloropyridine, were ^htreated electrically in an autoclave (750 ml) and the products distilled from the hot reaction vessel under reduced pressure. ~~Fractionation through a concentric tube column afforded~~ three main fractions,

1. Pentafluoropyridine, b.pt 84°C,
2. 3-Chlorotetrafluoropyridine, b.pt 119°C, and,
3. 3, 5-Dichlorotrifluoropyridine, b.pt 159° - 160°C.

Some typical results using the larger autoclave are shown in Table III below.

TABLE III

	C_5NCl_5 (gm)	KF (gm)	Temp (°C)	Time (hr)	Product (gm)	Composition of product in mole%		
						(% yield in parentheses)		
						$C_5Cl_2F_3N$	C_5ClF_4N	C_5F_5N
R.1	30	85	440	15	22	60(55)	30(30)	10(10)
R.2	50	160	440	17	29	50(36)	40(32)	10(8.5)
R.3	90	220	445	18	61	37(31.5)	33(30)	30(30)
R.4	100	300	440	19	65	32(26)	36(32)	32(31)
R.5	100	220	490	18	65	-	5(4.5)	95(92)

As can be seen from these results, the fluorination reaction gave products in good yield, usually ~ 90%, although difficulty was experienced in obtaining precisely consistent results. Thus, two consecutive reactions between identical quantities of reactants heated to apparently the same temperature for the same time, did not always produce the fluorinated pyridines in the same relative amounts. This presumably is due to the fact that over the period of heating, usually about 18 hrs overnight, different variations in mains voltage occurred causing the reaction temperature to vary for any given "variac" heater setting.

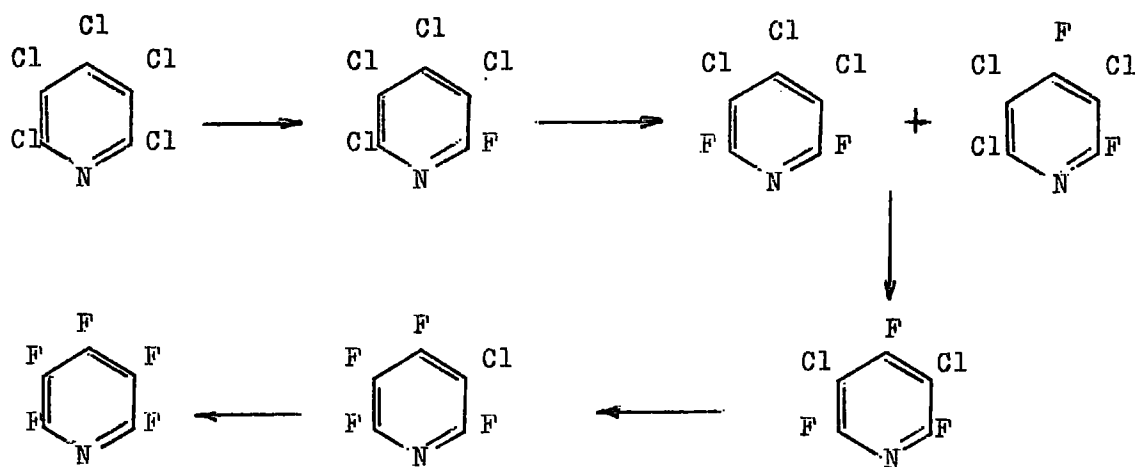
Another possible factor effecting the extent of reaction that occurs is the nature of the mixture of potassium fluoride and pentachloropyridine. Since the reaction is necessarily heterogeneous, the particle size of the potassium fluoride will play a significant role in governing the extent to which replacement of chlorine by

fluorine takes place. As the reaction proceeds, each particle will become coated with potassium chloride, thus, the smaller the particle size and the more intimate the mixture the further the reaction would be expected to go. During each experiment the reactants were thoroughly mixed but obviously it was impossible to reproduce exactly the same degree of mixing every time.

Workers at Manchester have recently reported⁸ results of their investigations on the reaction of pentachloropyridine with potassium fluoride which are very similar to those found in these laboratories.

In order to study this halogen exchange reaction further, and to learn the order of substitution of chlorine by fluorine in the different positions about the pyridine ring, an experiment was performed in which the temperature of the reaction was raised to 150° for a period of 2 hrs. The products were distilled under reduced pressure from the autoclave while still hot, in the normal manner, and shown by analysis and n.m.r. to consist of unreacted pentachloropyridine, 2-fluorotetrachloropyridine, a mixture of 2, 4-difluorotrichloro- and 2, 6-difluorotrichloropyridines (in mole ratio 2:3), and 3, 5 dichlorotrifluoropyridine.

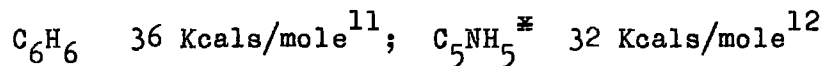
Thus the order of substitution for the complete reaction of pentachloropyridine with anhydrous potassium fluoride can be represented as follows:-



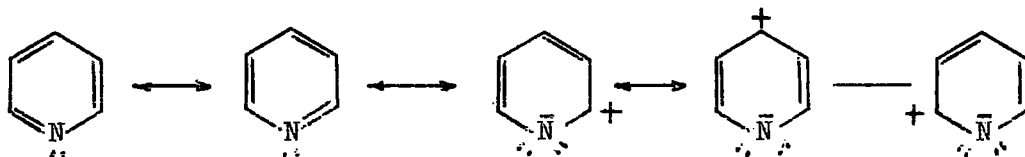
THEORETICAL CONSIDERATIONS

GENERAL ASPECTS

Pyridine resembles benzene in that it contains a conjugated system of six π -electrons, one being contributed by each atom in the ring. However, the electron affinity of nitrogen is greater than that of carbon; the π -electrons therefore tend to cluster round the nitrogen which thereby acquires a negative charge. The electronic structure of pyridine is therefore less symmetrical, and so its resonance energy smaller, than that of benzene.

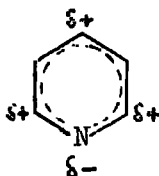


In terms of the resonance method, the electron density at various positions of the pyridine nucleus is derived from a summation of the contributing structures shown below.

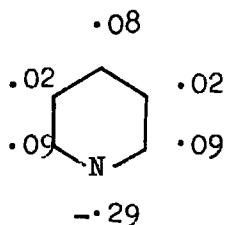


This approach predicts there will be a partial positive charge at the 2, 4 and 6 positions of pyridine and a net negative charge on the nitrogen

[#] This is the most recent evaluation and is calculated from heats of formation and hydrogenation, unlike earlier estimates which were calculated from heats of combustion alone and tended to give a range of values, some greater and some less than that of the resonance energy of benzene.



However, the magnitude of the charges cannot be estimated because these depend on the relative contributions of the charged structures, which are unknown. Alternatively, by considering the electronic structure of pyridine in terms of molecular orbitals it is possible to carry out calculation of the charge distributions in pyridine.



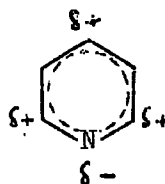
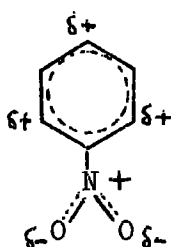
The magnitude of the charges varies somewhat with the parameters used for the calculations, but those cited above^{13a} give charges calculated from parameters chosen in such a way as to give reasonable agreement between calculated and observed dipole moments for a series of heterocyclic compounds. As can be seen, the charge at the α - and γ -positions is very similar. Slight variations in the parameters chosen can have the effect of indicating that the charge at the γ -position is greater than that at an α -position.^{13b} Pyridine has a dipole moment of 2.39D. (CCl₄, 25°C)²⁴.

CHEMICAL REACTIVITY

The chemical properties of the pyridine system may be broadly grouped into three categories:-

1. Properties roughly parallel to the benzene system usually modified by the presence of the ring nitrogen atom. These include the typical electrophilic substitution reactions such as sulphonation and halogenation, which are more difficult than with benzene, and radical reactions, which are rather similar.
2. Properties unusual for the benzene system; These include reactions in which the pyridine ring system interacts with a base or nucleophilic reagent, as in the amination with sodamide or the addition of organometallic compounds.
3. Properties associated with the unshared electron pair on the ring nitrogen. The formation of salts, quaternary compounds and N-oxides, which have no analogues among benzene derivatives, are included in this group.

It has been pointed out¹⁴ also that there are many analogies in reactivity between pyridine and nitrobenzene. This parallel behaviour results from the similarities in electron distribution. In both molecules π electrons are removed primarily from three positions on the ring by electronegative atoms. If the extent of electron withdrawal is about equal, then the reactions at the ring carbons of these molecules would be very similar.



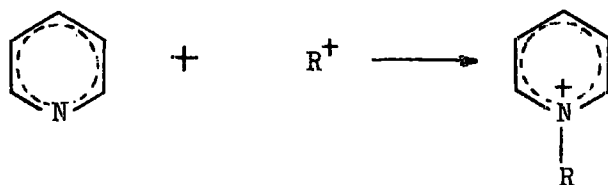
Aromatic Substitution

The replacement of a hydrogen atom by a substituent is a most characteristic reaction of aromatic systems. The questions as to the position which an entering group will take, if there are several choices, and the relative ease with which different aromatic nuclei will react with a given reagent have been extensively studied in the benzenoid aromatic systems.

Reagents are classified as electrophilic, nucleophilic, or radical depending on the nature of the species which actually attacks the aromatic nucleus. For benzene, electrophilic substitutions are most common, e.g. nitration and sulphonation, whereas for pyridine, nucleophilic reactions are relatively more important, e.g. amination by sodamide in Chichibabin reaction.

This general difference between pyridine and benzene is caused by the charge distribution in pyridine i.e. more energy is required to bring the positive reagent within bonding distance of the positively charged carbons of the nucleus. This situation is made even worse by the basic nature of the nitrogen atom. The formation of a pyridinium salt by interaction with R^+ means that a full positive charge is now distributed over the ring atoms, making

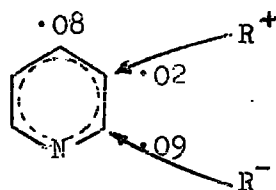
substitution even more difficult



Although the positive charge hinders electrophilic substitution, it must by the same mechanism, facilitate the approach of a negatively charged fragment in nucleophilic substitutions.

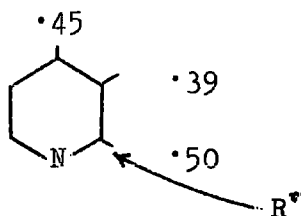
1. Static Approach

In the static approach the aromatic molecule in the ground state is examined and the relative charge at competing positions is estimated. The assumption is made that an electrophilic reagent will attack at the position of greatest electron density and a nucleophilic reagent at the position of lowest electron density. From the charge distribution previously cited, one would expect the different species to react as shown below:-



For free radical attack, the free valence is calculated,¹⁵ and it is assumed that a free radical will attack the position of maximum free valence. Free valence is defined as the difference between the maximum bond number of a carbon atom ($N_{\text{max}} = 3 + \sqrt{3}$) and the actual bond number, which is the sum of the bond orders for all

bonds the carbon atom in question makes with other atoms.¹⁶

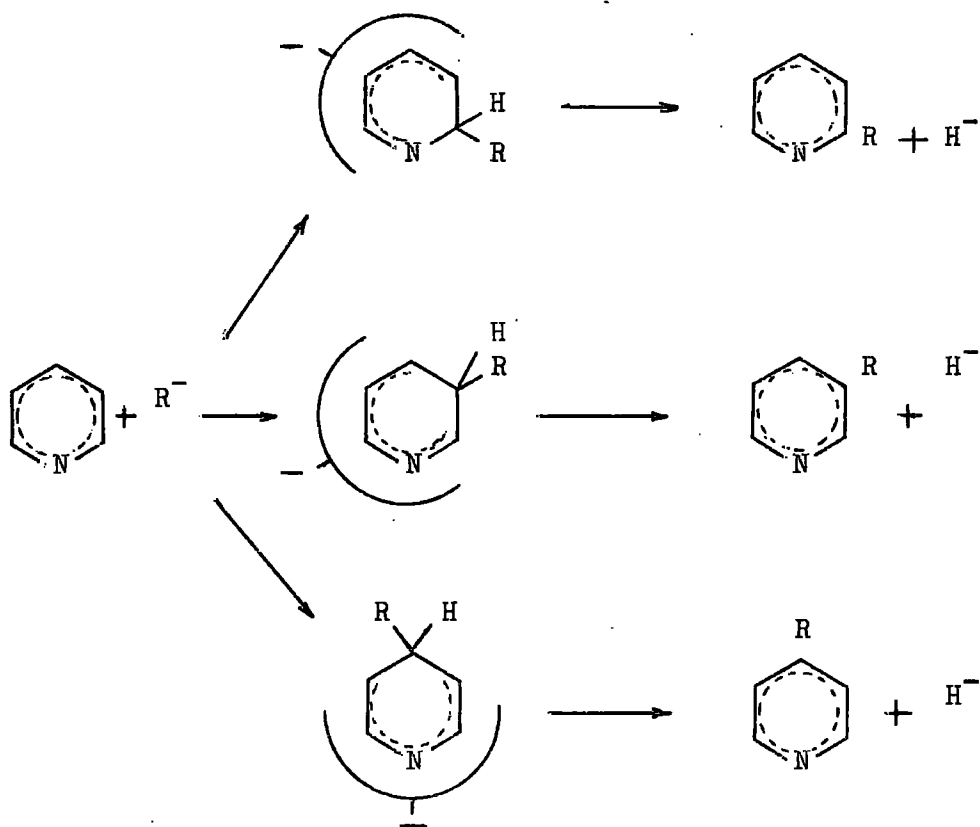


This procedure for predicting substitution frequently gives the correct answer, but in some instances it fails. The reason for these failures is that most substitutions are kinetically controlled processes in which the energy of activation is the important factor. Therefore the position which an entering substituent most frequently takes will be that one for which the energy requirement, in going from the initial state to the transition state, is the lowest. Thus in the ground state a certain position may have the greatest negative charge, but it does not necessarily follow that the partial bond formation with a positive fragment will require the least energy at this position.

2. Activation Energy Considerations

Although, usually, there is insufficient kinetic data to make definite predictions about a given aromatic substitution, it is often possible to decide which transition state is lowest in energy by considering the nature of the structure formed by reaction at each of the possible positions.

Thus for nucleophilic substitution in pyridine the three transition states would be:-

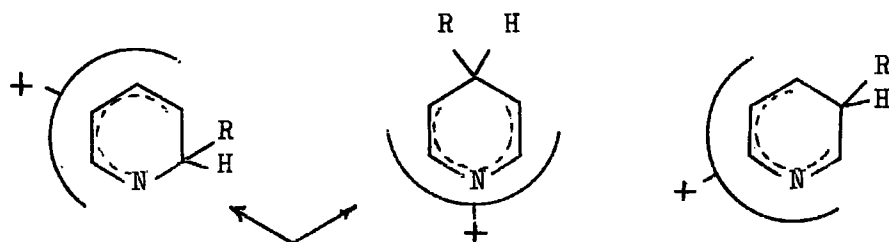


It can be shown by quantum mechanical arguments that in charged linear mesomeric systems of five atoms existing in transition states, the charge resides mainly on the 1, 3 and 5 atoms. Thus, due to the electron affinity of nitrogen, it will be obvious that the structures involving substitution in the α - and γ -positions will be of considerably less energy and therefore more stable than that formed in β -substitution.

Since nucleophilic substitution entails the placing of additional negative charge on the nitrogen atom, pyridine undergoes this type of reaction readily, with preferential attack occurring at the α - and γ -positions, since the nitrogen then occupies positions of

largest negative charge.

Conversely, in electrophilic substitution, because the formation of the transition state involves the removal of electrons from the nitrogen, this type of reaction occurs with difficulty and almost exclusively in the β -position, as would be predicted by examining the charge distribution in the transition states.



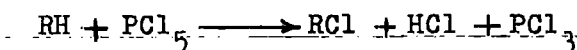
maximum +ve charge on nitrogen.

$\therefore$ least stable.

CHLORINATION OF PYRIDINE

Although no thorough investigation into the mechanism of the reaction between phosphorus pentachloride and pyridine has been carried out, it seems reasonable to suppose that the principle reaction involves initial attack by chlorine on the pyridine nucleus, since at the temperatures employed the phosphorus pentachloride will almost certainly be dissociated into phosphorus trichloride and chlorine.

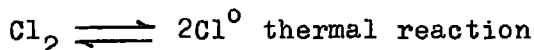
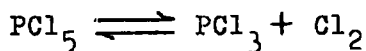
Other workers¹⁷ using the same reagent for the chlorination of aliphatic and alkylated aromatic hydrocarbons have shown this to be the case. They demonstrated that the chlorination proceeded smoothly in either a thermal or catalysed (benzoyl peroxide) reaction according to the equation:-

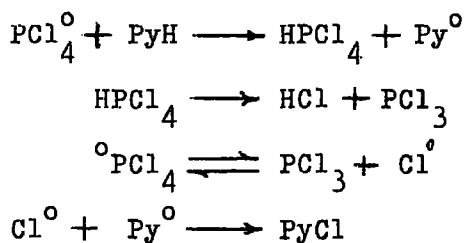


A detailed study of the mechanism was not made but it was suggested that thermal fission of chlorine molecules produced radicals which abstracted hydrogen from the substrate and by further reaction effected chlorination.

A similar type of reaction scheme is likely to prevail in the reaction of phosphorus pentachloride with pyridine.

i.e.





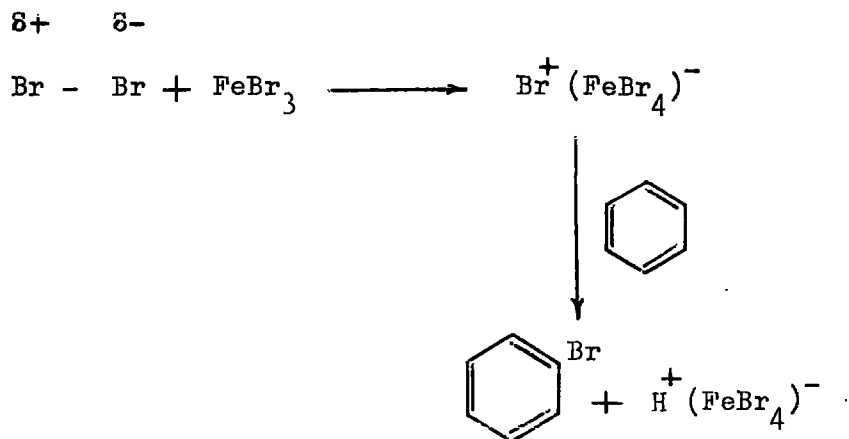
From the results of the elemental chlorination¹⁸ and bromination¹⁹ of pyridine by Wibaut and others, it has been shown that at least two different substitution mechanisms prevail at different temperatures.

In the bromination process, which demonstrates these two different mechanisms the more vividly, reaction between pyridine and elemental bromine at 300°C gives a mixture of 3-bromo- and 3, 5-dibromopyridine, whereas when the reaction temperature is raised to 500°C. 2-bromopyridine is produced.

Furthermore, reaction in the presence of iron bromide appears to encourage substitution in the β -position, since 3-bromopyridine with bromine in the presence of this "catalyst" at 300°C gives 3, 5-dibromopyridine. Under the same conditions, but with cuprous bromide as catalyst the product is 2, 5-dibromopyridine, i.e. the second substituent enters an α -position.

This effect of iron bromide on halogenation reactions is well known in the benzene series, where it has been demonstrated that the catalyst is capable of incorporating one atom of the bromine molecule into an anion, which can act as an acceptor for the hydrogen atom to be displaced from the benzene ring; the other atom is left as a

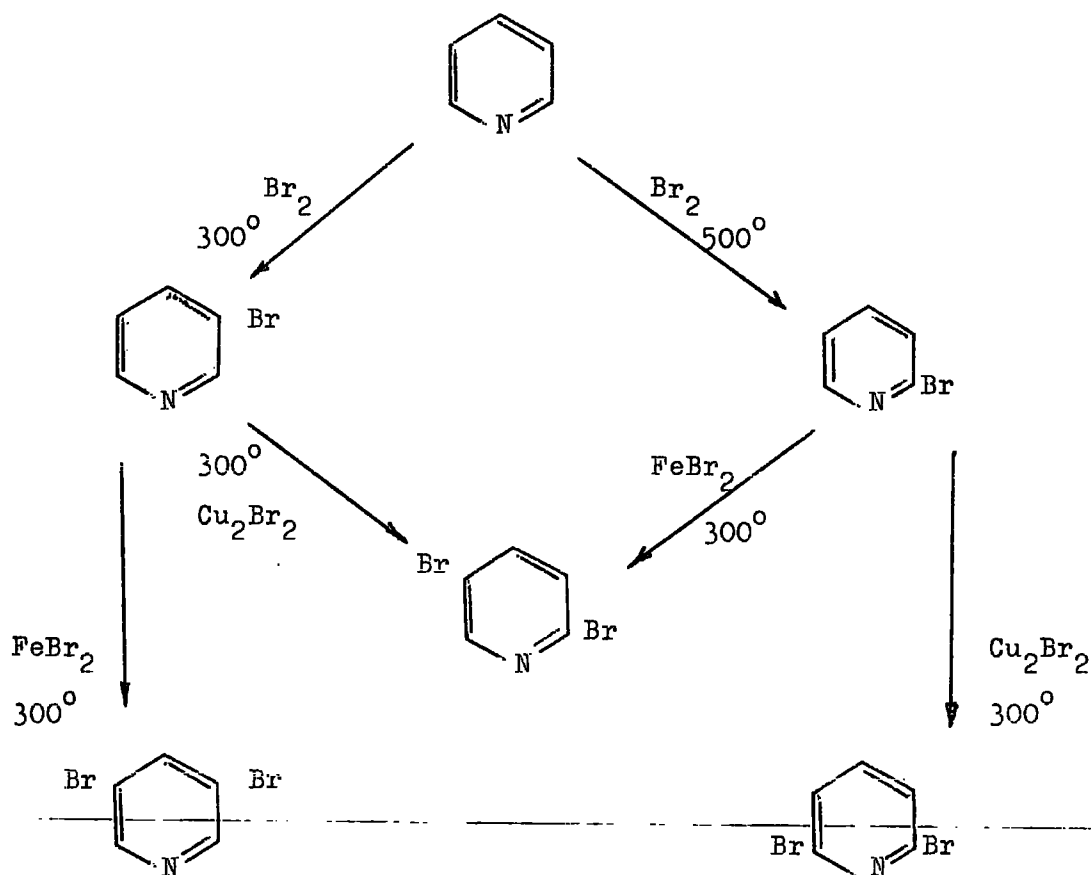
positively charged ion, which effects the electrophilic substitution.



Thus at the lower temperatures in which pyridine reacts with halogens to give β -substituted products it seems likely that the course followed is one of electrophilic attack, which is in accord with the theoretical predictions discussed earlier.

At temperatures above 300°C , free radicals will be formed preferentially by the homolytic fission of the halogen-halogen bond rather than heterolytic separation giving oppositely charged species.

With the mechanism being one of attack by free radicals, the position of substitution changes to mainly α -with some γ -replacement as is consistent with the free valence argument previously described.



A similar scheme is applicable to the direct chlorination of pyridine, as shown on page 25 , although the different positions of substitution occurring with variation in temperature are not nearly so dramatic.

From these considerations it is interesting to postulate on the relevant mechanism or mechanisms taking place in the autoclave reactions between phosphoruspentachloride and pyridine.

It is significant that good yields of highly chlorinated pyridines were obtained when the reaction temperature was high. In order to get the temperature at the centre of the reaction to 300°C it was necessary to heat the walls of the vessel to considerably higher temperatures than this, a situation which is conducive to radical formation from the chlorine produced by the dissociation of the phosphorus pentachloride.

Attack by a charged species on the pyridine may possibly occur, especially in the early stages of reaction as the autoclave is warming up, but this is doubtful in the light of the fact that the series of experiments carried out in which transition metals were added showed that no improvement in the yield of highly chlorinated products was obtained. The presence of iron halides has already been shown to have a beneficial effect on the electrophilic substitution by halogen in aromatic compounds.

It is important to note that, if one proton were replaced, a pyridinium salt would be formed which would hinder further attack by cationic species (page 60). Further, if an electrophilic mechanism was the most important, one would expect the hydrogens in the 3 and 5 positions to be first replaced. In fact, Hutchinson²¹ found that the two principal isomers of trichloropyridine formed were the 2, 4, 6-trichloro- and 2, 3, 6-trichloro- substituted compounds. Of the three possible isomers of tetrachloropyridine, only two were formed,⁷ one of which had a hydrogen in a β -position.

The other isomer was 2, 3, 5,6-tetrachloropyridine.

The presence of unsubstituted hydrogen in β -positions at these late stages in the reaction would suggest that an electrophilic substitution mechanism was not occurring to any significant extent in the phosphorus pentachloride chlorination reactions.

The possibility of a nucleophilic mechanism of halogen substitution exists, but the probability of this being important is slight, since the replacement of so unstable a species as a hydride ion by a stable chloride ion is unlikely. Also, one would have expected the presence of transition metals to have a noticeable effect on the yields the chlorination reactions had such a mechanism prevailed. No effect was detected.

The observation that best yields were obtained at high reaction temperatures seems to suggest that a free radical mechanism rather than an ionic mechanism was in operation.

Consistent with this theory, is the evidence that the α -hydrogens were among the first to be replaced, so that in the trichloro- and tetrachloropyridines no hydrogen remained in the 2 or 6 positions, as would be expected since these positions are of maximum free valence.

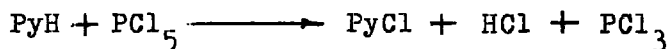
The experimental results on the yields from various reactions (Table I) would seem to substantiate a free radical mechanism. Thus, using the former method of heating, that of a variable transformer at a fixed setting, the rate of output of heat was

constant. When a thick, heavy liner, of large thermal capacity, was fitted to the autoclave the yields from such a system were low. This was presumably due to the fact that the inside wall temperature of the autoclave was lower than that attained without such a liner, with the result that less dissociation of phosphorous pentachloride to phosphorus trichloride and chlorine occurred and, more important, less thermal fission of halogen molecules to radicals took place. Obviously, the more radicals formed, the greater the amount of substitution obtained.

The yields from reactions in which other liners were used follow the expected trend. The thicker and weightier the liner the fewer the number of chlorine atoms introduced into the pyridine ring. With hindsight, it would now appear that the cause attributed to the early drop in yields (R.2), i.e. that of the removal of constituents present in stainless steel, was incorrect and the actual reason was due to a lowering of the temperature of the inside wall region of the autoclave where the critical reaction took place.

As explained previously, when the second method of heating was applied, the autoclave wall temperature must have been very close to that of the glowing heater elements, i.e. 500°C , with the result that considerably improved yields of chlorinated pyridines were obtained. Obviously, many more chlorine radicals will be produced at 500°C than at 300°C .

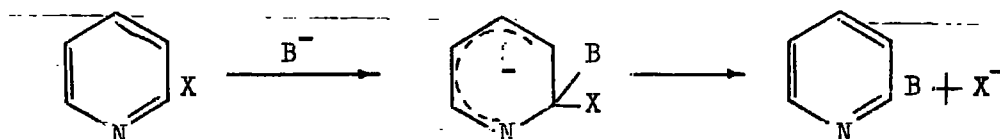
It is interesting to note that from the stoichiometry of the proposed chlorination reaction, i.e.



one would expect a 5:1 mole ratio of phosphorus pentachloride to pyridine to give complete chlorination and yields pentachloropyridine. However, as demonstrated (R.18), even a mole ratio of 10:1 does not give complete conversion to the fully chlorinated product. Presumably, the necessity of a large excess of phosphorus pentachloride is ~~required~~ to provide a sufficiently high concentration of chlorine radicals towards the end of the reaction, when most of the chlorinating agent has been converted to phosphorus trichloride, in order to effect the replacement of the remaining hydrogen in the lower chlorinated pyridines.

FLUORINATION OF PENTACHLOROPYRIDINE

From the theoretical arguments already outlined one would expect the pyridine system to undergo nucleophilic attack preferentially at the α - and γ -positions. Results obtained by Finger et al.²² and workers in these laboratories have shown that this is the case when substituting chlorine by fluorine in chlorinated pyridines using potassium fluoride as the fluorinating agent, a reaction which almost certainly goes by a nucleophilic mechanism involving halide ion exchange. If the pyridine nucleus has substituents which are capable of existing as stable anions, e.g. as Cl^- , it can be seen that the energy required to bring together the nucleophile and the pyridine to yield the intermediate



is not large and that the main difference between these reactions and the Chichibabin reaction ($\text{X} = \text{H}$) is in the stability of the anion which must be eliminated to form the product.

When pentachloropyridine was heated with potassium fluoride in the absence of a solvent to 150° for 2 hrs, the first chlorine atom to be replaced was in an α -position, forming 2-fluorotetrachloropyridine. The fact that the 2-position is replaced first

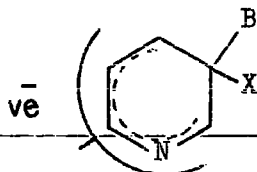
is interesting in that by so doing the perchloropyridine resembles the "perhydropyridine", in such reactions as that of Chichibabin, more closely than it does perfluoropyridine, which as will be illustrated later, undergoes initial nucleophilic replacement almost exclusively in the 4-position.

Other workers,²³ investigating the nucleophilic substitution reactions of pentachloropyridine with such reagents as ammonia and hydrazine have found that the substituent enters the 4-position. The difference in position of attack by these nucleophiles must, presumably be due to kinetic control of the substitution affected by the activation energies being lowest for the different positions of substitution between NH_3 , NH_2NH_2 and F^- . A more detailed study of the kinetics of these reactions must be made, however, before any categorical statements can be made.

Further reaction of 2-fluorotetrachloropyridine with potassium fluoride produces a mixture of 2, 6-difluorotrichloro- and 2, 4 difluorotrichloropyridine in the ratio 3:2, apparently the remaining α - and γ -chlorine atoms were of very much the same reactivity in the monofluorocompound.

Reaction with more fluoride ion produces the expected 3, 5 dichlorotrifluoropyridine. The temperature of the reaction must then be increased to $\sim 440^\circ\text{C}$ before replacement of the remaining chlorine atoms begins, demonstrating the reluctance of atoms in β -

positions to be replaced by a nucleophilic mechanism. Best yields of 3-chlorotetrafluoropyridine, i.e. when one of the β - chlorine atoms has been replaced, are obtained from reactions conducted at a temperature of $\sim 450^{\circ}\text{C}$. Complete replacement of chlorine by fluorine, to give pentafluoropyridine, occurs when the reaction temperature is raised to $\sim 490^{\circ}\text{C}$. Although substituents in β - positions are not easily displaced by nucleophiles, because the nitrogen atom cannot facilitate the process by acting as a major site for the negative charges, it should be pointed out that the unsaturated system over which the charge is distributed does have a nitrogen atom as a member and hence the transition state is



more stable than in the benzene series. Thus, 3-bromopyridine reacts with sodium methoxide at 150° while bromobenzene is unreactive below 250°C .

However, in the perfluoro series, it has been reported⁹ that temperatures of 500°C will replace all the chlorine atoms by fluorine in hexachlorobenzene when reacted with potassium fluoride, i.e. almost the same conditions required to convert pentachloropyridine to pentafluoropyridine.

When the tetrachloropyridines were heated with anhydrous

potassium fluoride⁷, the theoretical predictions as to the preferential positions of attack by the fluoride ion were again upheld. Thus, starting with a mixture of 2, 3, 4, 6-tetrachloro- and 2, 3, 5, 6-tetrachloropyridine the ultimate substitution products were 3-chloro- 2, 4, 6-trifluoropyridine and 3, 5-dichloro- 2, 6-defluoropyridine. Elevation of reaction temperature caused complete decomposition so that it was impossible to replace chlorine atoms in positions 3 or 5 in the tetrachloropyridines, and even chlorine atoms in positions 2, 4 and 6 were less easily replaced by fluorine than those in pentafluoropyridine. This is consistent with the result of Finger and co-workers²² who, working mainly with lightly chlorinated pyridines, showed that, while a chlorine atom in the 3-position activates chlorine atoms in both the positions 2 and 6, a chlorine atom in position 2 is rendered the more active.

Chapter 3

EXPERIMENTAL WORK

EXPERIMENTAL WORK

PREPARATION OF HIGHLY FLUORINATED PYRIDINES

Pyridine was converted to pentachloropyridine by reaction with phosphorus pentachloride. Fluorination of pentachloropyridine by halogen exchange with potassium fluoride gave highly fluorinated pyridines.

The products were separated by distillation and preparative scale vapour phase chromatography. Infra red (i.r.) spectra were recorded using Grubb-Parsons, type G.S. 2.A. or Spectromaster spectrometers. Nuclear magnetic resonance (n.m.r.) spectra were measured on an A.E.I. R.S.2. spectrometer at 60 Mc/sec. Fluorine analyses were carried out by Mr. T. Holmes, using the biphenyl-sodium method of decomposition.¹ Analytical-scale vapour phase chromatography (v.p.c.) was performed on Perkin Elmer or Griffin and George D.I. instruments and preparative scale vapour phase chromatography on an Aerograph "Autoprep" instrument.

CHLORINATION OF PYRIDINE

The pyridine used was technical grade, made by May and Baker Ltd. and was dried by refluxing over potassium hydroxide pellets for 3 - 4 hours followed by distillation from this drying agent under an atmosphere of dry nitrogen. Pyridine was stored under dry nitrogen until required for reaction. The phosphorus pentachloride was technical grade supplied by Albright and Wilson

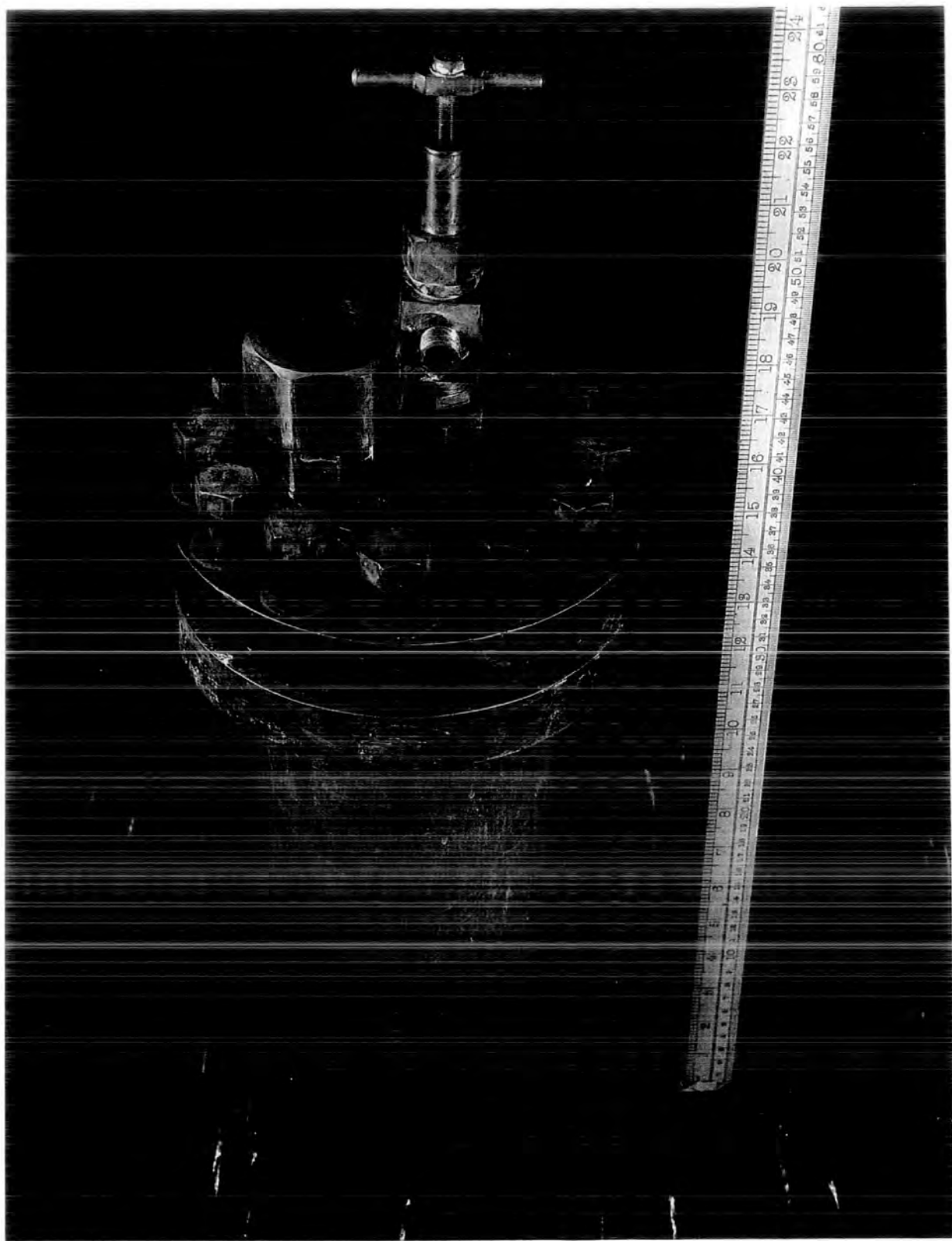


Fig. 1a.

Ltd.

The Autoclave

The autoclave (fig. 1a) was a high pressure reaction vessel of 5 litre capacity. It was of a seamless wall construction formed from a solid drawn tube of Firth Vickers' Stainless Steel (Quality F.D.P.) giving a wall thickness of $\frac{1}{2}$ inch. The base and flange were of heavy stainless steel and were welded to the cylindrical body of the vessel.

The head of the autoclave was constructed of heavy stainless steel and was fitted with a needle valve, thermocouple well, and a bursting disc assembly. The head was sealed to the flange on the top of the autoclave by a corrugated copper gasket and held in position by bolts of high tensile steel.

Inside the vessel was fitted a heavy nickel liner (14 B.S.W.G.) to prevent corrosion of the inner stainless steel wall.

Heating was effected by a 9' long Met. Vickers Pyrobar element (5/16" O.D.) of 2 K.Watt rating bent in the shape of a helix so that the body of the autoclave fitted snugly inside the heater coil.

Before a reaction the autoclave was thoroughly cleaned and dried by placing in the heater unit at 200°C for at least 2 hrs.

Reaction Procedure

In a typical experiment (Table I, R.15), the autoclave (5 litre capacity) charged with phosphorus pentachloride (1500 gm, 7.2 moles) and dry pyridine (125 gm, 1.59 moles) was heated electrically via an 8 amp variac which was controlled thermostatically by a thermocouple

placed in a well in the centre of the autoclave head. The heating elements around the wall of the autoclave operated at full power until the centre of the reaction attained a temperature of 300°C , when the electricity was switch off. The reaction was then maintained thermostatically at that temperature for 24 hrs. After allowing the autoclave to cool to room temperature, the hydrogen chloride generated during the reaction was released before the vessel was opened. The contents of the autoclave were hydrolysed by slow addition from a dropping funnel, to water in a 3-necked flask (3 litre) fitted with a reflux water condenser and a stirrer. Occasional cooling of the flask with an ice bath was necessary to prevent the hydrolysis reaction becoming too vigorous. During this stage of work up in a number of experiments, the inside of the hydrolysis apparatus became coated with an orange-red coloured solid and minor explosions occurred. These were probably due to reaction of small amounts of elemental phosphorus or phosphine formed during the chlorination. When hydrolysis was complete, the organic product was steam distilled and the while solid distillate removed by filtration. (Previous workers² reported that the steam distillate was extracted with methylenedichloride, but as the chloropyridines are only very slightly soluble in water and the volume of distillate to be extracted is considerable, usually 9 - 12 litres, this extraction process becomes both unnecessary and expensive). Removal of water from the mixture of chloropyridines was achieved by azeo-

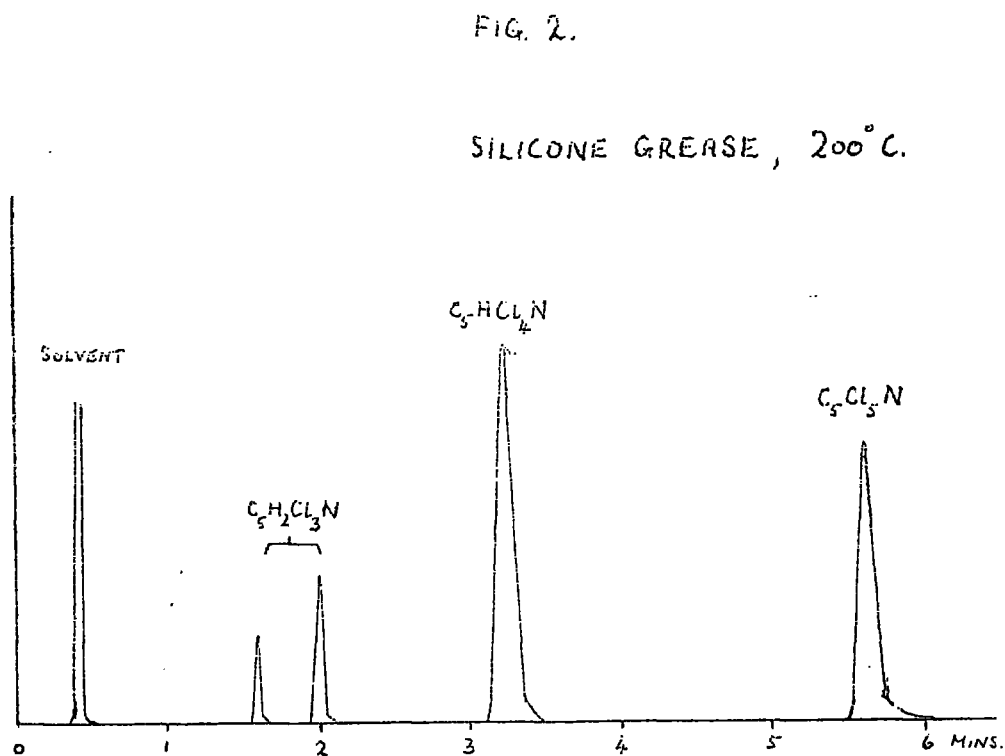
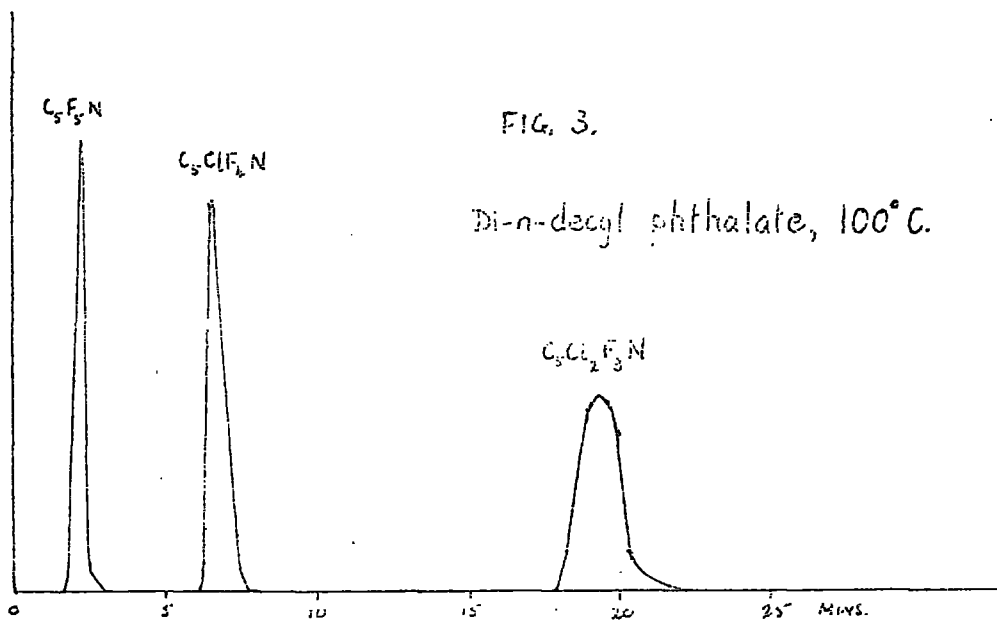
tropic distillation with benzene using a Dean-Stark distillation head. The dry chloropyridines (225 gm) were distilled through a 20 in. column packed with Dixon gauzes into three main fractions

- i) b.pt 220° - 248°C ,
- ii) b.pt 248° - 252°C and
- iii) b.pt 279° - 280°C .

Fraction i) was shown to contain mainly trichloropyridines with a small amount of tetrachloropyridines. Fraction ii) consisted of tetrachloropyridines (lit.,³ b.pt 248.5° - 252°C) and fraction iii) was pentachloropyridine, m.pt 124°C (lit.,³ b.pt 279° - 280°C , m.pt 125° - 126°) I.R. Spectrum No. 1 page 86.

The composition of the original product was estimated by analytical-scale v.p.c., using silicone grease as the stationary phase, to be $\text{C}_5\text{H}_2\text{Cl}_3\text{N}$, 10; $\text{C}_5\text{HCl}_4\text{N}$, 45; $\text{C}_5\text{Cl}_5\text{N}$, 45 mole-%. (fig. 2)

In later experiments, when conversion of pyridine to pentachloropyridine in a single reaction was achieved in high yield, it was found more satisfactory to omit the steam distillation stage of the work up procedure as this became very tedious due to the length of time required for complete distillation caused by the relative low steam volatility of pentachloropyridine. Also, constant unblocking of the apparatus was necessary due to the solidification of pentachloropyridine (mp 124°C) in the condensers. In such reactions, the contents of the chlorination autoclave were poured carefully into a large volume (3 litres) of iced water in a beaker.



The highly chlorinated pyridines fell to the bottom of the beaker and were removed by filtration. Drying and fractionation were then carried out as previously described.

FLUORINATION OF PENTACHLOROPYRIDINE

The dry pentachloropyridine was prepared as previously described. Potassium fluoride used was reagent grade, supplied by British Drug House Ltd., and was dried by heating in a nickel beaker over a bunsen burner for several hours followed by storage in an oven at 150° until required.

The Autoclave

The autoclave (Fig. 1B) was a high pressure reaction vessel of 750 ml. capacity. It was constructed of stainless steel by drilling out a solid piece of Firth Vickers' F.D.P. quality metal. The autoclave head was fitted with a needle valve and screwed into the body of the vessel to seal by a knife edge on the autoclave head against an aluminium gasket. Final tightening of the seal was effected by Allen screws in the head.

Before a fluorination reaction, the autoclave was tested, to ensure it was leak-proof, by charging with solid carbon dioxide and sealing. Immersion in a water-bath made obvious any leaks.

The autoclave was cleaned and dried in an oven at 150°C before a reaction.

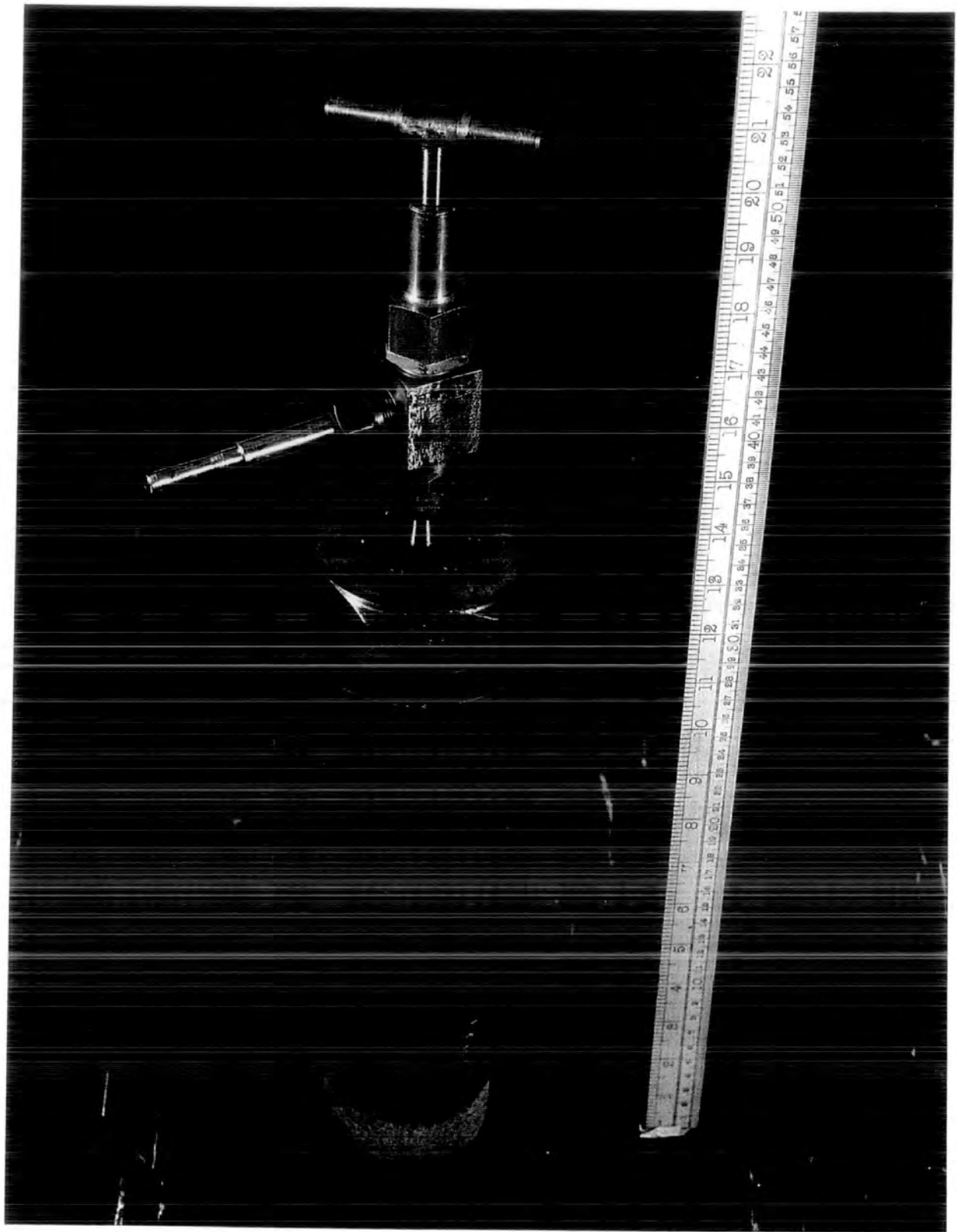


Fig. 1b.

Reaction Procedure

a) In a typical experiment (Table III. R.3), the autoclave (750 ml. capacity - fig 1B), charged with pentachloropyridine (90 gm, 0.36 moles) and anhydrous potassium fluoride (220 gm, 3.8 moles), was heated electrically to 445°C, via an 8 amp variable transformer set at a precalibrated value, and maintained in thermal equilibrium at that temperature for 18 hrs. While the reaction vessel was still hot the product (61 gm) was distilled under vacuum.

The composition of this product was estimated by analytical-scale v.p.c., using d-n-decyl phthalate as the stationary phase, to be C₅Cl₂F₃N, 37; C₅ClF₄N, 33; C₅F₅N, 30 mole-%. (fig. 3).

Distillation through a concentric tube column afforded three main fractions

- i) Pentafluoropyridine, b.pt 84°C (lit., b.pt 84°C⁴ - 83.5°C⁵).
I.R. Spectrum. No. 6, page 87, was identical to that of an authentic specimen.²
- ii) 3-Chlorotetrafluoropyridine, b.pt 119°C.
I.R. Spectrum. No. 5, page 87, was identical to that of an authentic specimen.²
- and iii) 3, 5-dichlorotrifluoropyridine, b.pt 159° - 160°C.
I.R. Spectrum. No. 4, page 87, was identical to that of an authentic specimen.²

In later experiments, when relatively large amounts of fluoropyridines were being handled, it was found that the through put of the concentric tube column was inconveniently low making the time for fractionation lengthy. Because of this, a new column was built, consisting of a 3' tube packed with glass helices, fitted with an automatic magnetic take-off head. This made the distillation considerably less tedious.

b) In a separate experiment, the autoclave charged with pentachloropyridine (30 gm., 0.12 mole) and anhydrous potassium fluoride (80 gm., 1.38 mole) was heated to 150°C for 2 hrs. While the reaction vessel was still hot the product (25 gm) was distilled under vacuum. Vapour phase chromatography, using silicone grease as the stationary phase, separated the product into four components, the retention times of the first and last components corresponding to 3, 5-dichlorotrifluoropyridine and pentachloropyridine, respectively. The unknown components were isolated by preparative-scale v.p.c., using silicone grease as stationary phase, and shown to be

- i) 2-Fluorotetrachloropyridine, m.pt 32° - 33°C (Found: C, 25.5; Cl, 61.0; F, 8.1. C_5Cl_4F requires C, 25.5; Cl, 60.5; F, 8.09%). I.R. Spectrum. No. 2, page 86.

One chemically shifted peak was observed in the fluorine - 19 n.m.r. spectrum at position 66.3 p.p.m. with respect to trichloromethane.^{fluoro}X
A

(CFCl_3) as internal reference.* This value for the chemical shift is in the region characteristic for a fluorine atom in the 2-position of the pyridine ring.

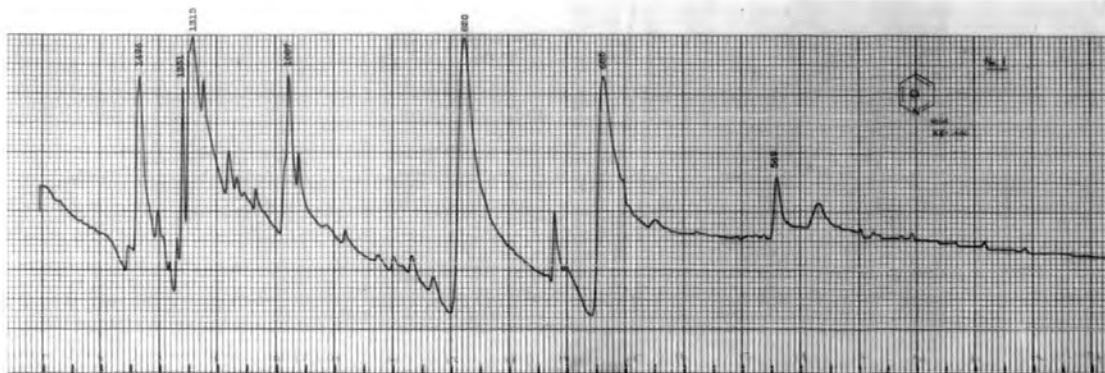
and ii) A mixture of isomeric difluorotrichloropyridines b.p. $196^\circ - 198^\circ\text{C}$, which were inseparable using silicone grease as stationary phase. (Found C, 27.5; Cl, 49.1; F, 18.0. $\text{C}_5\text{Cl}_3\text{F}_2\text{N}$ requires C, 27.5; Cl, 48.7; F, 17.4%).
I.R. Spectrum. No. 3, page 86.

The fluorine-19 spectrum of the mixture showed the isomers present were 2, 6-difluorotrichloropyridine, with an intense peak of chemical shift 67.6 p.p.m. relative to CFCl_3 as internal reference, and 2, 4-difluorotrichloropyridine with two groups of chemically shifted peaks of equal intensity at positions 66.8 p.p.m. (2-F) and 92.2 p.p.m. (4-F) relative to CFCl_3 as internal reference. The chemical shift assigned to the fluorine in the 4-position has a value characteristic of fluorine in that position of the pyridine ring. The relative intensities of the peaks due to fluorine atoms of these isomers showed their proportions to be 2, 6 difluorotrichloropyridine: 2, 4 difluorotrichloropyridine::3:2.

The composition of the original product of the fluorination reaction was estimated by analytical-scale v.p.c. to be $\text{C}_5\text{Cl}_5\text{N}$, 5; $\text{C}_5\text{Cl}_4\text{FN}$, 30; $\text{C}_5\text{Cl}_3\text{F}_2\text{N}$, 35; $\text{C}_5\text{Cl}_2\text{F}_3\text{N}$, 30 mole%.

* Shifts measured relative to CFCl_3 internal reference can be converted to C_6F_6 reference using the relationship:

$$\delta \text{ C}_6\text{F}_6 = 162.28 + \delta \text{ CFCl}_3$$





PART II

THE INTRODUCTION OF FUNCTIONAL GROUPS
INTO THE POLYFLUOROPYRIDINE NUCLEUS

Chapter 4

INTRODUCTION

INTRODUCTION

Two main routes are available for the synthesis of highly fluorinated aromatic compounds containing a functional group. Both these methods have been intensively applied in the case of the highly fluorinated benzenes and a study of the results obtained is interesting in view of the relationship between the benzene and pyridine systems.

The first route to substituted polyfluoro aromatic compounds is by the nucleophilic replacement of fluorine. A summary of the results obtained by the reaction of nucleophilic reagents with hexafluorobenzene is given below, and, as will be observed, many mono-substituted pentafluorobenzenes have been formed in this manner. The further attack by nucleophiles on these compounds is extremely interesting as various positional isomers may be produced.

The second route is via electrophilic substitution in hydrofluoro aromatic compounds, and using the reactivity of this new group in further reactions. The most widely investigated example of this is the electrophilic attack on pentafluorobenzene by iodine or bromine, to form iodo- or bromopentafluorobenzene.^{1, 2} These are readily formed into the Grignard reagents, from which a wide variety of mono-substituted pentafluorophenyl compounds have been formed.^{1,3-6} Recently,⁷ pentafluorophenyl Grignard reagents have been prepared directly by the exchange reaction between an alkyl magnesium halide and the "acidic" hydrogen of the fluoro aromatic nucleus. The

preparation of pentafluorophenyl lithium has been achieved by a similar technique which obviates the need to go via the reaction of a halopentafluorobenzene with lithium amalgam or n-butyl lithium.⁸ Pentafluorophenyl lithium has been shown to behave similarly to the Grignard reagent in many standard syntheses.

Reactions between Hexafluorobenzene and Nucleophilic Reagents

The nucleophilic attack on hexafluorobenzene has been thoroughly investigated, and a summary of these reactions shows that almost all occur under moderate conditions, to give good yields of the mono-substituted product.

<u>Nucleophile</u>	<u>Reaction Conditions</u>	<u>Product</u>	<u>Reference</u>
OCH_3^-	a) CH_3OH , CH_3ONa reflux.	$\text{C}_6\text{F}_5\text{OCH}_3$ 60%	9
		p- $\text{C}_6\text{F}_4(\text{OCH}_3)_2$ 3%	
	b) with pyridine	$\text{C}_6\text{F}_5\text{OCH}_3$	10
OC_2H_5^-	$\text{C}_2\text{H}_5\text{OH}$, $\text{C}_2\text{H}_5\text{ONa}$	$\text{C}_6\text{F}_5\text{OC}_2\text{H}_5$	11
OH^-	a) KOH , pyridine reflux.	$\text{C}_6\text{F}_5\text{OH}$ 20%	10
	b) KOH , t-butanol reflux.	$\text{C}_6\text{F}_5\text{OH}$ 71%	11
SH^-	H_2S , NaOH , ethylene glycol, pyridine	$\text{C}_6\text{F}_5\text{SH}$ 70%	12
NH_2^-	a) NaNH_2 , liq. NH_3	$\text{C}_6\text{F}_5\text{NH}_2$	13, 14
		$(\text{C}_6\text{F}_5)_2\text{NH}$ 3%	
NH_3	b) NH_3 , ethanol 167°C	$\text{C}_6\text{F}_5\text{NH}_2$ 70%	14

NH_2NH_2	$\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ ethanol, reflux.	$\text{C}_6\text{F}_5\text{NHNH}_2$ 73%	14, 15
NH_2CH_3	a) CH_3NH_2 , ethanol 115°C b) CH_3NH_2 , ethanol 170°C	$\text{C}_6\text{F}_5\text{NHCH}_3$ 69% p- $\text{C}_6\text{F}_4(\text{NHCH}_3)_2$ 60%	14 14
CH_3^-	a) CH_3Li , ether reflux. b) CH_3MgBr	$\text{C}_6\text{F}_5\text{CH}_3$ 69% p- $\text{C}_6\text{F}_4(\text{CH}_3)_2$ 10% $\text{C}_6\text{F}_5\text{CH}_3$ 3%	4, 16 10
R^-	a) n- $\text{C}_4\text{H}_9\text{Li}$ b) PhLi c) $\text{CH}_3\text{CH}=\text{CHLi}$ $2\text{CH}_3\text{CH}=\text{CHLi}$	$\text{C}_6\text{F}_5\text{C}_4\text{H}_9$ 56% $\text{C}_6\text{F}_4(\text{C}_4\text{H}_9)_2$ 20% $\text{C}_6\text{F}_5 \cdot \text{C}_6\text{H}_5$ $\text{C}_6\text{F}_5\text{CHCHCH}_3$ 70% p- $\text{C}_6\text{F}_4(\text{CH}=\text{CHCH}_3)_2$	16 17, 38 18 18
H^-	LiAlH_4	$\text{C}_6\text{F}_5\text{H}$	19
$\text{HN}^-\text{CH}_2\text{CH}_2\text{NH}_2^-$	$\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$, ethanol 110°	5,6,7,8-tetrafluoro- 1,2,3,4-tetrahydro quinoxaline	39

The pentafluorophenyl compounds prepared as above have been shown to exhibit the normal chemistry associated with these functional groups and in many cases derivatives have been formed to aid identification. Further reactions, on the functional groups of these compounds, which are of more synthetic importance are mentioned below.

<u>Reactant</u>	<u>Conditions</u>	<u>Product</u>	<u>Reference</u>
$C_6F_5OCH_3$	$AlCl_3, 120^\circ C$	C_6F_5OH 58%	10, 20
C_6F_5SH	Diazomethane	$C_6F_5SCH_3$ 45%	12
$C_6F_5NH_2$	CF_3CO_2H	$C_6F_5NO_2$ 85%	21
$C_6F_5NH_2$	HCO_2H	C_6F_5NO	22
$C_6F_5NH_2$	Diazotised in HF,		
	a) Cu_2X_2	C_6F_5X (X=Cl, Br, I)	17
	b) Copper bronze	$C_6F_5 \cdot C_6F_5$	
$C_6F_5NHNH_2$	Heat $180^\circ C$	C_6F_5H 39% $C_6F_5NH_2$ 44%	15
$C_6F_5NHNH_2$	Oxidation in Benzene	C_6F_5'	15
$C_6F_5CH=CHCH_3$	$KMnO_4$	C_6F_5COOH	18
$C_6F_5CF_3$	Fuming H_2SO_4	C_6F_5COOH	23, 24

Pentafluorophenyl Derivatives

Nucleophilic attack on mono-substituted pentafluorobenzenes has been closely studied especially by workers in Birmingham: The attack by another substituent is of considerable interest, as different positional isomers can be formed. Although nuclear magnetic resonance spectra can determine the orientation of these di-substituted compounds, it is necessary to compare them with tetra-fluorobenzene derivatives of known structure.

The compounds available for this work were the dihydrotetrafluorobenzenes, synthesised by the dehydrofluorination and defluorination of polyfluorocyclohexanes.^{25, 26, 27} The structures of the hydrofluorocompounds were confirmed by comparison with compounds prepared by Finger^{28, 29} and Wall³⁰ via different routes. Another compound which was used for comparison purposes was tetrafluoro-p-benzoquinone, prepared by the hydrolysis of octafluorocyclohexa-1, 4-diene with sulphuric acid. The reactions of pentafluorophenyl derivatives with nucleophilic reagents are summarized below.

<u>Reactant</u>	<u>Reagent</u>	<u>Product</u>	<u>Reference</u>
HC_6F_5	NH_2NH_2	p- $\text{HC}_6\text{F}_4\text{NHNH}_2$ 63% o-2%, m-O-3%	14, 32
	NH_3	p- $\text{HC}_6\text{F}_4\text{NH}_2$ 62%	14, 32
	NaOCH_3	$\text{HC}_6\text{F}_4\text{OCH}_3$ 47% 92% p-	33, 34
	NaSH	p- $\text{HC}_6\text{F}_4\text{SH}$ 85%	12
	KSPH	p- $\text{HC}_6\text{F}_4\text{SPH}$ 46%	12
	p- $\text{HC}_6\text{F}_4\text{SK}$	(p- HC_6F_4) ₂ S	17
	LiAlH_4	p- $\text{HC}_6\text{F}_4\text{H}$ 83% o-6%, m-1%	32
$\text{CH}_3\text{OC}_6\text{F}_5$	NH_2NH_2	$\text{C}_6\text{F}_5\text{ON}_2\text{H}_5$ 60%	20, 34
		p- $\text{CH}_3\text{OC}_6\text{F}_4\text{NHNH}_2$ 24%	
$\text{CH}_3\text{SC}_6\text{F}_5$	NH_3	p- $\text{CH}_3\text{SC}_6\text{F}_4\text{NH}_2$	17

$\text{CH}_3\text{SO}_2\text{C}_6\text{F}_5$	NH_3	$p\text{-CH}_3\text{SO}_2\text{C}_6\text{F}_4\text{NH}_2$	17
$\text{NH}_2\text{C}_6\text{F}_5$	NH_3	$m\text{-NH}_2\text{C}_6\text{F}_4\text{NH}_2$ 34%	14
	NH_2NH_2	$m\text{-NH}_2\text{C}_6\text{F}_4\text{NHNH}_2$ 24%	34
$\text{NH}_2\text{NHC}_6\text{F}_5$	NH_2NH_2	$m\text{-NH}_2\text{NHC}_6\text{F}_4\text{NHNH}_2$ 0.5%	34
$\text{CH}_3\text{NHC}_6\text{F}_5$	CH_3NH_2	$p\text{-CH}_3\text{NHC}_6\text{F}_4\text{NHCH}_3$ 24%	34
$\text{CH}_3\text{CONHC}_6\text{F}_5$	NaSH	$p\text{-CH}_3\text{CONHC}_6\text{F}_4\text{SH}$	17
$\frac{1}{2}\text{SO}_4^{--}\text{N}_2^*\text{C}_6\text{F}_5$	NaOH	$p\text{-NH}_2\text{C}_6\text{F}_4\text{OH}$	17
$\text{NO}_2\text{C}_6\text{F}_5$	NH_3	$\text{NO}_2\text{C}_6\text{F}_4\text{NH}_2$	21, 34
		$p\text{-31\%, o-69\%}$	
	NaOCH_3	$\text{NO}_2\text{C}_6\text{F}_4\text{OCH}_3$	37
		$p\text{-92\%, o-8\%}$	
	CH_3NH_2	$\text{NO}_2\text{C}_6\text{F}_4\text{NHCH}_3$	
		$p\text{-35\%, o-65\%}$	
	$(\text{CH}_3)_2\text{NH}$	$\text{NO}_2\text{C}_6\text{F}_4\text{N}(\text{CH}_3)_2$	
		$p\text{-81\%, o-19\%}$	
$\text{CH}_3\text{C}_6\text{F}_5$	CH_3Li	$p\text{-CH}_3\text{C}_6\text{F}_4\text{CH}_3$ 83%	3
$\text{CF}_3\text{C}_6\text{F}_5$	LiAlH_4	$p\text{-CF}_3\text{C}_6\text{F}_4\text{H}$ 50%	35
	CH_3Li	$p\text{-CF}_3\text{C}_6\text{F}_4\text{CH}_3$ 40%	35
	NH_2NH_2	$p\text{-CF}_3\text{C}_6\text{F}_4\text{NHNH}_2$ 36%	35
	NH_3	$p\text{-CF}_3\text{C}_6\text{F}_4\text{NH}_2$ 82%	35
	NaSH	$p\text{-CF}_3\text{C}_6\text{F}_4\text{SH}$ 52%	35
	NaOC_2H_5	$p\text{-CF}_3\text{C}_6\text{F}_4\text{OC}_2\text{H}_5$ 90%	35
$\text{C}_2\text{F}_5\text{C}_6\text{F}_5$	NH_2NH_2	$p\text{-C}_2\text{F}_5\text{C}_6\text{F}_4\text{NHNH}_2$	40
	NH_3	$p\text{-C}_2\text{F}_5\text{C}_6\text{F}_4\text{NH}_2$	40

	LiAlH_4	$\text{p-C}_2\text{F}_5\text{C}_6\text{F}_4\text{H}$	40
	NaOCH_3	$\text{p-C}_2\text{F}_5\text{C}_6\text{F}_4\text{OCH}_3$	40
	CH_3Li	$\text{p-C}_2\text{F}_5\text{C}_6\text{F}_4\text{CH}_3$	40
ClC_6F_5	NaOCH_3	$\text{p-ClC}_6\text{F}_4\text{OCH}_3$ 50%	36
		o-17%	
	NH_3	$\text{p-ClC}_6\text{F}_4\text{NH}_2$ 41%	36
		o-15%	
	NH_2NH_2	$\text{p-ClC}_6\text{F}_4\text{NHNH}_2$ 45%	36
		o-16%	
	LiAlH_4	$\text{C}_6\text{F}_5\text{H}$, $\text{p-ClC}_6\text{F}_4\text{H}$	36
		o- $\text{ClC}_6\text{F}_4\text{H}$	

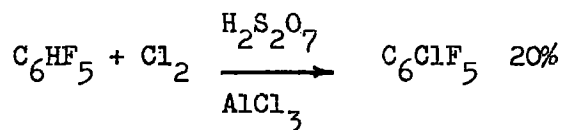
Further reactions on these functional groups, as described before, provide an even wider variety of disubstituted tetrafluorobenzenes with known structures. Some general observations have been made about the orientation of the product, from the nucleophilic attack on pentafluorobenzenes,^{21, 35} although no mechanisms are given. However, it seems extremely likely that a variety of factors will influence the result because of the large number of different reagents and conditions involved.

In most cases, the orientation of the products appears to depend little on the reagent used; and if the substituent has no powerful electronic effects, the five fluorine atoms direct the attack to the para position. Powerful electron donating substituents, such as $-\text{NH}_2$, deactivate the nucleus and direct attack into the meta position, whereas

powerful electron accepting substituents, such as $-\text{NO}_2$, render the ortho position more susceptible to nucleophilic attack, and activate the nucleus.

Reactions between Pentafluorobenzene and Electrophilic Reagents

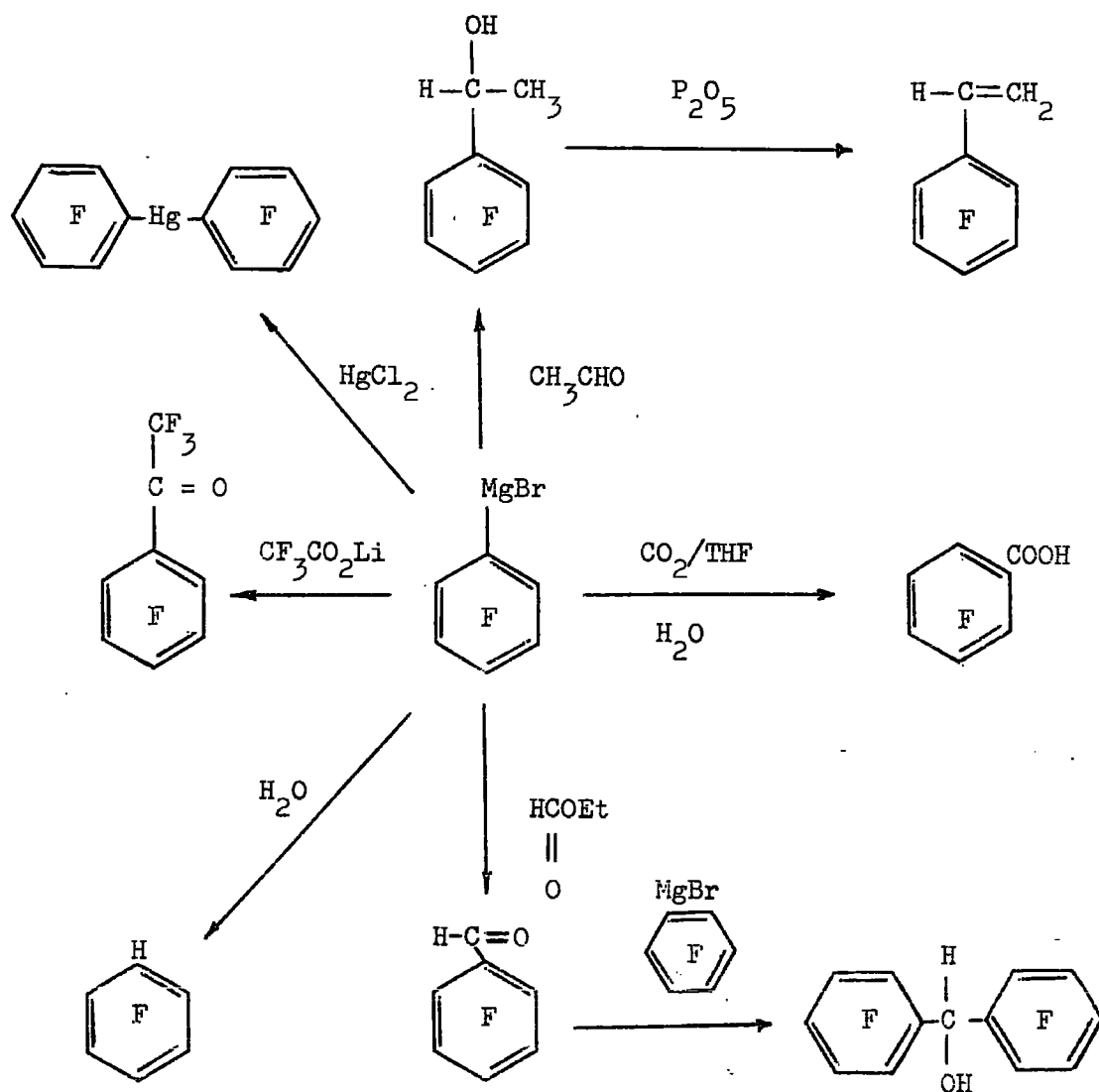
Standard electrophilic replacements such as those occurring in hydrocarbon aromatic chemistry have been tried on pentafluorobenzene, in an attempt to replace the hydrogen atom by a positive reagent. When the fluorobenzene was reacted with oleum, substitution occurred to give pentafluorobenzene sulphuric acid¹. Similarly, the corresponding halopentafluorobenzene was formed by reaction of pentafluorobenzene with bromine or iodine in sulphuric acid. Using the same technique, Mobbs⁴² obtained a 20% yield of chloropentafluorobenzene.



The chlorine was bubbled into a solution of pentafluorobenzene in fuming sulphuric acid, with aluminium trichloride present as a catalyst. The Grignard reagents and lithium derivatives formed from the halopentafluorobenzenes have been used to prepare a large number of compounds, (both organic and organo-metallic),^{1, 2, 8, 41} many of which would have been difficult to obtain by other routes.

Some typical syntheses carried out using pentafluorophenyl Grignard reagents are shown on the following page.

SYNTHESES FROM PENTAFLUOROPHENYL MAGNESIUM HALIDES



The Introduction of Functional groups into the Fluoro-pyridine nucleus

Bearing in mind that the route to highly fluorinated pyridines which was used provided exclusively halogenated compounds, i.e. primarily pentafluoropyridine, 3-chlorotetrafluoropyridine and 3, 5-dichlorotrifluoropyridine, it seemed obvious to apply the nucleophilic displacement method to introduce functional groups into the pyridine nucleus. Compared with the benzene case, where hydrogen containing fluorobenzenes were produced by the important route of dehydrofluorination and defluorination of polyfluorocyclohexanes, the analogous highly fluorinated pyridines containing hydrogen were not directly available, from the fluorination of pentachloropyridine, to investigate the possibilities of electrophilic substitution.

Nucleophilic Substitution in Pentafluoropyridine

The reaction of pentafluoropyridine with nucleophilic reagents has been studied by workers in Durham⁴³ and Manchester⁴⁴. The striking factor about these reactions is the greater ease of nucleophilic displacement of fluoride ion from pentafluoropyridine than from hexafluorobenzene. Thus, quantitative reaction of pentafluoropyridine with aqueous ammonia occurs at 80°C for 2 hrs, to give 4-aminotetrafluoropyridine, whereas a temperature of 167° is reported for the corresponding production of pentafluoroaniline from hexafluorobenzene.¹⁴ Also, reaction between pentafluoropyridine and methoxide ion is so vigorous that very mild conditions (0°C) must be used in order to obtain any

mono-ether, tetrafluoro-4-methoxypyridine. At ambient temperature, quantitative conversion to the diether, trifluoro-2, 4-dimethoxypyridine occurs during 15 minutes, whereas at least one hour at reflux is necessary for the analogous preparation of pentafluoroanisole.²⁰

If reflux conditions are used with pentafluoropyridine and excess sodium methoxide, trisubstitution occurs to give 3, 5-trifluoro-2, 4, 6-trimethoxypyridine. This trimethoxy derivative has also been prepared by a stepwise procedure, in distinct single stage reactions, which demonstrated that initial attack by methoxide ion occurred at the 4-position, followed by substitution in the 2- and then 6- position.

The other important point which this work brought out was the fact that with all the reagents studied, attack occurred almost exclusively at the 4-position first. The workers in Manchester reacted pentafluoropyridine with seven different nucleophilic reagents and in each case reported the isolation of the γ -substituted derivative as the product of the primary reaction.

The nucleophilic reactions on pentafluoropyridine described by both teams of workers are summarized below.

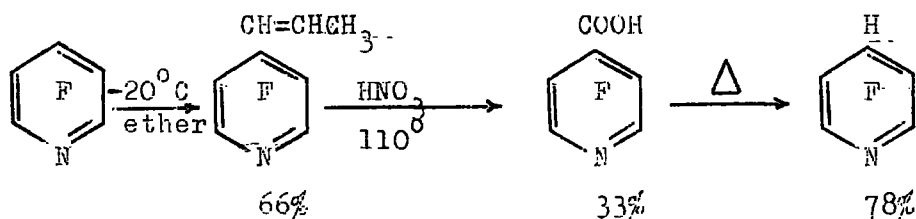
Reactions Between Pentafluoropyridine and Nucleophilic Reagents

<u>Nucleophile</u>	<u>Reaction Conditions</u>	<u>Product</u>		<u>Reference</u>
NH_3	a) NH_3 , 80° , 2 hrs.	$4\text{-NH}_2\text{C}_5\text{NF}_4$	70%	43
	b) NH_3 , ethanol 110° , 8 hrs.	$4\text{-NH}_2\text{C}_5\text{NF}_4$	81%	44
NH_2NH_2	a) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, dioxan reflux, 2 hrs.	$4\text{-NH}_2\text{NHC}_5\text{NF}_4$	70%	43
	b) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, ethanol 0°C , 2 hrs.	$4\text{-NH}_2\text{NHC}_5\text{NF}_4$	75%	44
OCH_3	a.i CH_3ONa , CH_3OH , 0°C	$4\text{-CH}_3\text{OC}_5\text{NF}_4$		43
	ii CH_3ONa , CH_3OH , 25°C	$2,4\text{-(CH}_3\text{O)}_2\text{C}_5\text{NF}_3$		43
	b.i CH_3ONa , CH_3OH reflux, 3 hrs.	$4\text{-CH}_3\text{O.C}_5\text{NF}_4$	57%	44
	ii CH_3ONa , CH_3OH reflux, 3 hrs.	$2,4,6\text{-(CH}_3\text{O)}_3\text{C}_5\text{NF}_2$	74%	44
C_6H_5^-	$\text{C}_6\text{H}_5\text{Li}$, ether, reflux	$4\text{-C}_6\text{H}_5\text{.C}_5\text{NF}_4$	26%	43
H^-	LiAlH_4 , ether, reflux	$4\text{-H.C}_5\text{NF}_4$	74%	44
$(\text{CH}_3)_2\text{NH}$	i $(\text{CH}_3)_2\text{NH}$, aq. ethanol, 0°C	$4\text{-(CH}_3)_2\text{N.C}_5\text{NF}_4$	51%	44
	ii $(\text{CH}_3)_2\text{NH}$, aq. ethanol 100° , 20 hrs.	$2,4\text{-[(CH}_3)_2\text{N}]_2\text{C}_5\text{NF}_3$	82%	44
$\text{CH}_3\text{CH=CH}$	i $\text{CH}_3\text{CH=CHLi}$, ether, -20° to room temp.	$4\text{-(CH}_3\text{CH=CH).C}_5\text{NF}_4$ cis:trans::6:1	66%	44
	ii $\text{CH}_3\text{CH=CHLi}$, ether, -20°	$2,4\text{-(CH}_3\text{CH=CH)}_2\text{C}_5\text{NF}_4$ 4-geometrical isomers 66:20:10:2	62%	44

<u>Nucleophile</u>	<u>Reaction Conditions</u>	<u>Product</u>	<u>Reference</u>
OH	a)i. KOH, water 85°, 20 hrs.	4-OH.C ₅ NF ₄	63% 51
	ii KOH, t-butanol reflux, 90 mins.	4-OH.C ₅ NF ₄ 2-OH.C ₅ NF ₄	90%) 10%) 65% 51
	b)i. NaOH, water, reflux, 2 hrs.	4-OH.C ₅ NF ₄	58% 44
	ii. 40% NaOH, water, 80°C, 12 hrs.	2,4-(OH) ₂ C ₅ NF ₃	20% 44
	iii. KOH, t-butanol, reflux, 2½ hrs.	4-OH.C ₅ NF ₄	64% 44

This method of introducing function groups in the fluoropyridine ring system is severely limited in application by the fact that the incoming group must be capable of existing as a nucleophilic agent, although, as in the chemistry of the substituted fluoro-benzenes, the functional group can often be converted by standard methods to other functions. This type of operation was demonstrated when tetrafluoro-4-propenylpyridine was oxidised by concentrated nitric acid at 110°C for 45 minutes to give tetrafluoro-isonicotinic acid in 33% yield.

When the tetrafluoro-isonicotinic acid was heated "in vacuo" to 250°C , decarboxylation occurred to give 2, 3, 5, 6-tetrafluoropyridine in 78% yield.

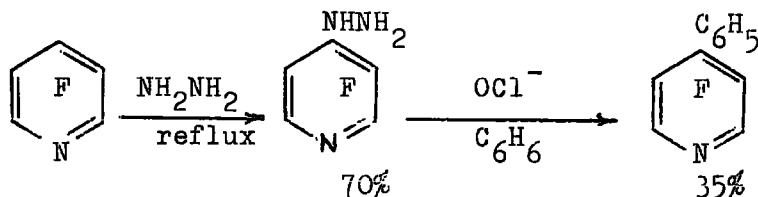


The same compound, 2, 3, 5, 6-tetrafluoropyridine, has been prepared by the reaction of tetrafluoro-4-hydrazinopyridine with copper sulphate. The reaction occurred spontaneously in aqueous solution at 20°C , with the liberation of 80% of the theoretical volume of nitrogen, to give the hydrofluoropyridine in 54% yield.

If the hydrazine derivative is treated with a suspension of bleaching power in benzene, again nitrogen is evolved, and the product isolated is 2, 3, 5, 6-tetrafluoro-4-phenylpyridine in



35% yield. Formation of this product presumably involved attack on benzene by tetrafluoropyridyl radicals generated by oxidation of the hydrazine derivative by hypochlorite ions, as in the analogous formation of pentafluorophenyl radicals by oxidation of pentafluorophenylhydrazine.¹⁵



It is interesting to note that tetrafluoro-4-phenylpyridine prepared in this way differed slightly from the sample prepared by reaction of pentafluoropyridine and phenyl lithium in its infrared spectrum, as well as that fact that the product of the direct nucleophilic reaction melted at a lower temperature and over a range of 5°C. This evidence would seem to suggest that the phenyl lithium, being a strongly nucleophilic reagent, attacks other positions to a small extent, as well as the 4-position, giving rise to an unseparated mixture of isomers.

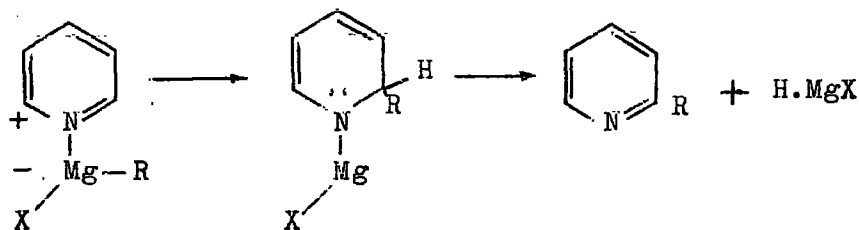
A much more serious limitation on the nucleophilic method introducing function groups into the fluoropyridine system is the lack of variety of positions of substitution achieved. From the results reported it can be seen that the vast majority of

substituents enter the 4-position, and in a very limited number of cases, such as the reaction of pentafluoropyridine with potassium hydroxide in t-butanol, or, perhaps, with phenyl lithium, are 2-substituted products obtained. In none of the reactions studied has a 3-substituted derivative been formed; demonstrating that this method does not provide a synthetic route to such compounds.

The observation that pentafluoropyridine is more susceptible to nucleophilic attack than hexafluorobenzene is not altogether unexpected since, as previously discussed (page 64), pyridine is considerably less reactive than benzene towards electrophilic substitution and even nucleophilic displacement of a hydrogen atom in the 2-position in pyridine can be achieved by the Chichibabin⁴⁵ reaction or reaction with an organo-metallic reagent.⁴⁶ An increased susceptibility towards nucleophilic attack is consistent with the introduction of fluorine into the pyridine ring as the halogen will have the effect of reducing the electron density on the ring carbon atom to which it is attached. It is noteworthy that in pyridine the nitrogen atom has a comparatively much greater electron affinity than any of the other atoms in the molecule, with the resultant effect on the electron distribution (page 57), whereas in pentafluoropyridine the nitrogen atom has to compete with the five fluorine atoms, with their high electron affinity, for its share of the electrons and so the electron density of the

system, compared with the hydrogen compound, is not nearly so distorted. This is apparent in the dipole moment of the per-fluorocompound which is 0.53 D.,⁴⁹ compared with 2.39 D. for pyridine. (Both in CCl_4 , 25°C).

On the basis of reactions such as that of Chichibabin, nucleophilic substitution in pentafluoropyridine may have been expected to be orientated towards the 2-position. However, the mechanisms of the Chichibabin⁴⁷ and organo-metallic reactions are uncertain, and are by no means simple nucleophilic displacements, probably involving co-ordination of the lone pair of the pyridine nitrogen with the metal atom of the attacking species and so rendering the 2-position most susceptible to attack.



The fact that substitution does occur predominantly in the 4-position would seem to suggest that pentafluoropyridine resembles pentafluorobenzene⁵⁰ rather than pyridine in that the orientation appears to be governed by the presence of the five fluorine atoms. More recent work, however, especially on the nucleophilic reactions of tetrafluoro-4-nitropyridine⁶¹ indicates that the greater single factor in determining the orientation of substitution in poly-fluoropyridines is the presence of the ring nitrogen by its striking

activation of the 4-position.

This was demonstrated in the reactions of tetrafluoro-4-nitropyridine with ammonia and sodium methoxide.

In both of these reactions substantial replacement of the nitrogroup occurred, and in the case of methoxide attack, the nitro group was preferentially displaced to fluorine, giving tetrafluoro-4-methoxy pyridine as the major product.

A study of the reaction of sodium methoxide with 2, 3, 5, 6-tetrafluoro-nitrobenzene, which resembles tetrafluoro-4-nitropyridine more closely than does pentafluoronitrobenzene as the former benzene has no fluorine para to the nitrogroup, showed that no replacement of the nitrogroup occurred, only replacement of fluorine, and the sole product was 2, 3, 6-trifluoro-5-methoxy-4-nitrobenzene. Thus, it was argued, since the nitrogroup and fluorine are comparable in their efficiency as leaving groups in nucleophilic substitution⁵⁹, and, because the nitrogroup is displaced by nucleophilic reagents from tetrafluoro-4-nitropyridine but not from pentafluoronitrobenzene^{21, 37, 57, 58} or, more significantly, from 2, 3, 5, 6-tetrafluoronitrobenzene, it would seem that the ring nitrogen is the most important factor in governing the orientation of nucleophilic attack.

This proposed activation of the 4-position by the ring nitrogen is consistent with the results of Chapman and co-workers⁶⁰ who found that displacement of chloride ion by ethoxide occurred at

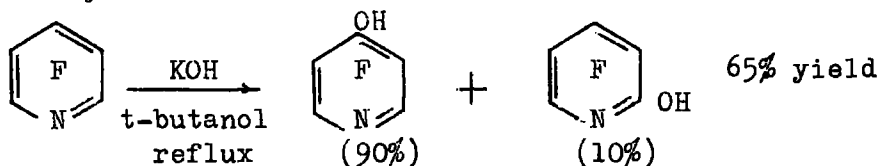
a much faster rate from 4-chloropyridine than from 2-chloropyridine.

Further, it must be noted, that in highly fluorinated pyridines, apart from the activation of position 4 by the ring nitrogen, this position is unique in that it does not have a para fluorine atom which could afford stabilization in the event of nucleophilic attack by way of mesomeric electron release, and so, relative to the other positions, which do have para fluorine substituents, the 4-position is doubly activated.

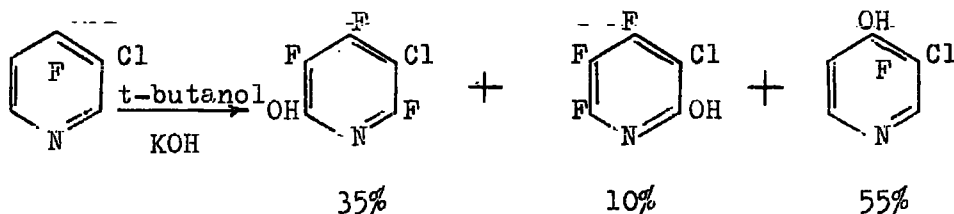
Nucleophilic Substitution in Perhalogenopyridines

Following their investigations into the reaction of pentafluoropyridine with a number of nucleophilic reagents, workers in these laboratories⁵¹ have studied the substitution occurring in 3-chlorotetrafluoropyridine and 3, 5-dichlorotrifluoropyridine with nucleophiles, especially in relation to that occurring in pentafluoropyridine.

When pentafluoropyridine was treated with potassium hydroxide in aqueous solution a single product was isolated, tetrafluoro-4-hydroxypyridine. However, when t-butanol was used as solvent a mixture of isomers, with the substituent in the 4- and 2-position, respectively was obtained.



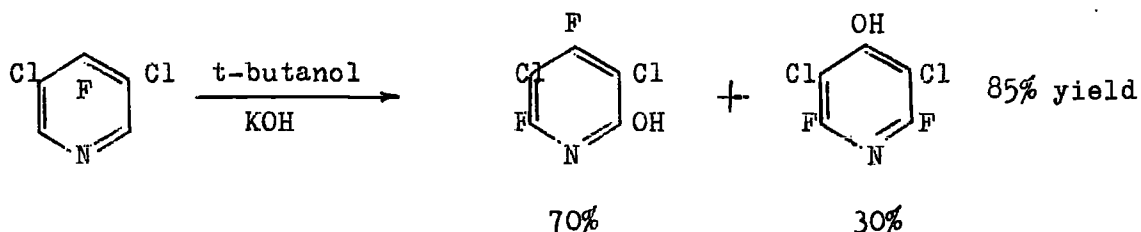
When 3-chlorotetrafluoropyridine was heated with an aqueous solution of potassium hydroxide, again a mixture of two isomers was produced. These were 4-hydroxy-3-chlorotrifluoropyridine and 6-hydroxy-3-chlorotrifluoropyridine in the ration 9:1. More surprising still, in the light of the large number of examples of nucleophilic displacement in polyfluoropyridines, which have resulted in at least 90% preference for the 4-position, is the reaction between 3-chlorotetrafluoropyridine and potassium hydroxide when t-butanol is used as solvent. Here, the product was a mixture of three isomers, the 4-hydroxy-, 6-hydroxy-, and 2-hydroxy-compounds in the ratio 5.5:3.5:1 respectively.



The considerable amount of attack at the 6-position, which is not reflected in other reactions suggests that steric factors are influencing the orientation of attack, as this position is the most favourable from the view of a large approaching nucleophilic fragment.

This is confirmed by the observation that potassium hydroxide in t-butanol gave with 3, 5-dichlorotrifluoropyridine a mixture

containing a predominance of the 2-hydroxy-derivative, i.e. 3, 5-dichloro-2-hydroxydifluoropyridine (70%) and 3, 5-dichloro-4-hydroxydifluoropyridine (30%), whereas the composition of the product obtained by using aqueous potassium hydroxide was 90% 4-hydroxy- and 10% 2-hydroxy- 3, 5-dichlorodifluoropyridine.

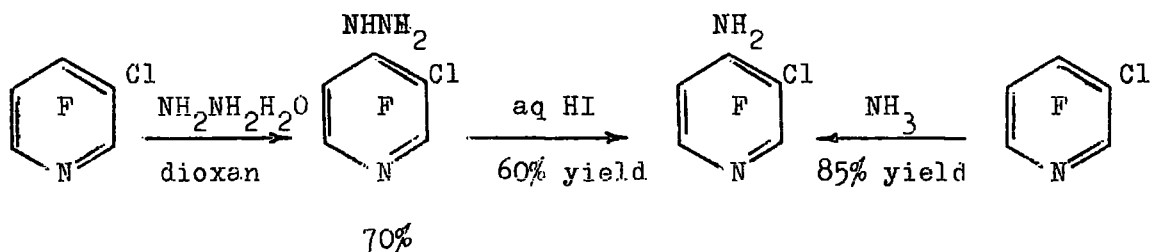


The exact mechanism of attack in these reactions is not fully understood but it seems likely that the variations in positions of attack described above are due to steric considerations brought about by the solvation of the attacking hydroxyl ion by bulky butanol molecules. Obviously, these factors will not be as pronounced when water is the solvent, the attacking fragment being so much smaller.

The possibility that these reactions in butanol as solvent involve initial attack by t-butoxide ion is unlikely, since it has been shown that a t-butoxy substituent is not cleaved to give a hydroxy-derivative by the conditions used in these reactions.⁵²

Reactions between 3-chlorotetrafluoropyridine and 3, 5-dichloro-

trifluoropyridine with nitrogen bases such as ammonia and hydrazine demonstrated that the 4-position was still the most reactive site in each case. Thus, 3-chlorotetrafluoropyridine reacts with hydrazine hydrate in dioxan to give exclusively 3-chlorotrifluoro-4-hydrazinopyridine in 70% yield. This was converted to 3-chlorotrifluoro-4-aminopyridine by reaction with aqueous hydroiodic acid. The same amino-compound was formed by direct reaction between aqueous ammonia and 3-chlorotetrafluoropyridine.



Similar reactions were carried out with 3, 5-dichlorotrifluoropyridine.

In a number of competition experiments with ammonia it was shown that the susceptibility towards nucleophilic substitution increases in the series pentafluoropyridine < 3-chlorotetrafluoropyridine < 3, 5-dichlorotrifluoropyridine in the ratio 1:3.7:12.6, respectively. This trend is consistent with the known greater resultant (of inductive and mesomeric effects) electron withdrawing capacity of chlorine over fluorine in an aromatic system.

"The increase of covalency involved in mesomeric effect is partial double bond formation, and, because of the overlap principle, double bonds are more easily formed when the atoms concerned, in particular the p-orbitals of their valency shells, are about the same size. Therefore one can understand that the halogens stand in the following order with respect to their capacity to increase covalency by the mesomeric effect:-



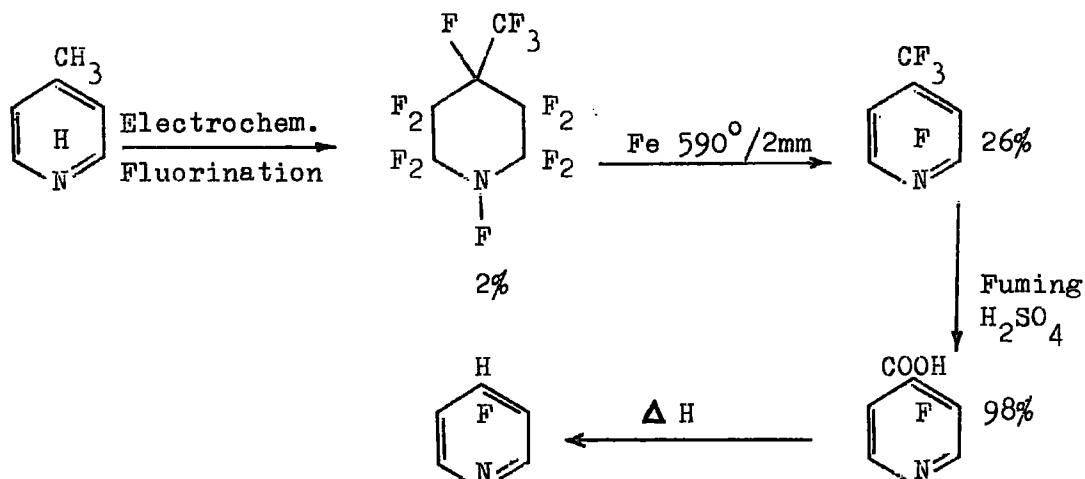
Preparation of Fluoropyridines with functional groups by

Fluorination of Hydrogen Compounds

A completely different method of approaching the problem of obtaining fluoropyridines containing functional groups has been explored by workers in Manchester.⁵⁴ This involves starting with a pyridine already possessing a functional group in the ring and carrying out an electrochemical fluorination followed by defluorination as in the preparation of pentafluoropyridine itself,^{55, 56} to give the aromatic fluoropyridine retaining the fluorinated substituent.

In this way, perfluoro- (2-, 3- and 4- methylpyridines) have been prepared. This method, of course, suffers from the great disadvantage that the yields from the first stage of the process, the electrochemical fluorination, are very low; so low as to — — — preclude it as a practical route to substituted compounds.

It does have the advantage, however, of being able to produce fluoropyridines with substituents in positions other than that of position 4.



It has been demonstrated that perfluoro-(4-methylpyridine) can be converted into fluoropyridines with other functional groups in the 4-position, but no report has been made of the application of the other perfluoropicolines to the preparation of fluoropyridines with substituents in positions other than position-4.

The conversion of perfluoro-(4-methylpyridine) to perfluoro-isonicotinic acid by hydrolysis with sulphuric acid, and the subsequent decarboxylation to 2, 3, 5, 6 tetrafluoropyridine has proved chemically the structures of the compounds obtained by the direct reaction of pentafluoropyridine⁴⁴ with propenyl lithium and lithium aluminium hydride, respectively.

Chapter 5

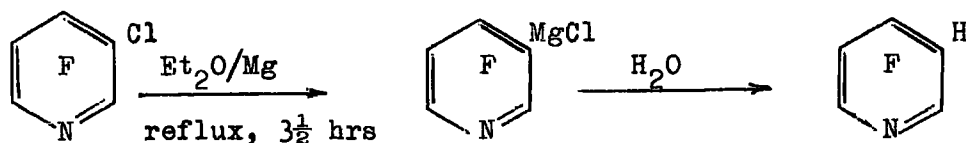
DISCUSSION OF EXPERIMENTAL WORK

Preparation of Grignard Reagents of Polyfluoropyridines

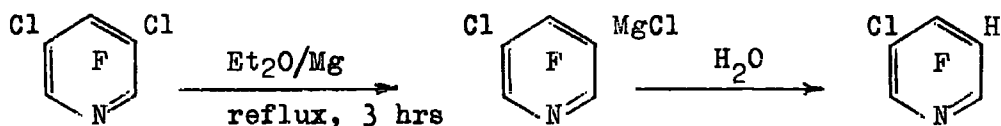
Investigations into the nucleophilic reactions of perfluoro- and polyfluoro pyridines demonstrated that this method of introducing functional groups was completely unsatisfactory for synthesising compounds with the substituent in a β -position.

The ready availability of 3-chlorotetrafluoro- and 3, 5-dichlorotrifluoropyridine makes them natural starting materials in a study of β -substituted compounds since the chlorine atoms act as reactive centres in the molecule in the preparation of Grignard reagents.

3-Chlorotetrafluoropyridine was refluxed with dry magnesium, previously activated by grinding with a crystal of iodine, in diethyl ether for $3\frac{1}{2}$ hours, with occasional addition of dibromoethane to maintain an active surface on the magnesium. After hydrolysis of the mixture, analytical-scale v.p.c. showed that Grignard formation had occurred, although reaction was incomplete since approximately equimolar quantities of 3-chlorotetrafluoropyridine and 2, 4, 5, 6-tetrafluoropyridine were obtained.



Using the same solvent, an attempt was made to prepare a Grignard derivative of 3, 5-dichlorotrifluoropyridine. The magnesium was dried and activated with ethylene dibromide and the reaction mixture refluxed for 3 hours. After hydrolysis and work up as before, incomplete reaction was again observed. The product was shown to contain 60% unreacted starting material and 40% 3-chloro -2, 4, 6-trifluoropyridine, demonstrating the formation of a mono-Grignard reagent.



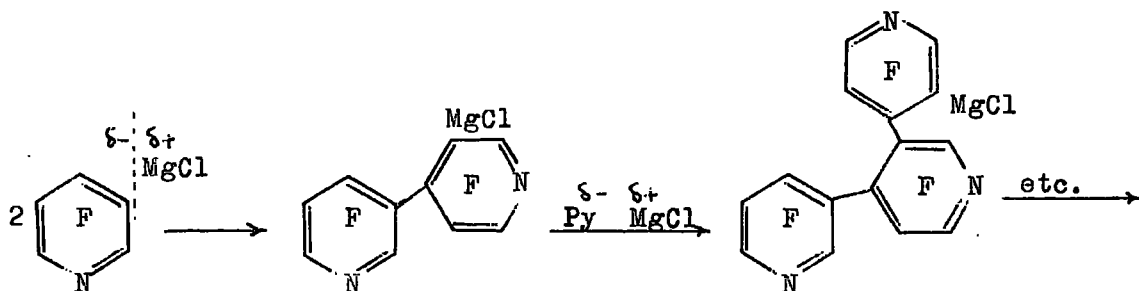
Because, in both these experiments, incomplete reaction was achieved, it was decided to use a higher boiling ether as solvent in the hope that the increased reflux temperature would push the reaction through to completion.

3-Chlorotetrafluoropyridine was refluxed with activated magnesium in di-n-butyl ether for 18 hours. After hydrolysis analytical-scale v.p.c. showed that no 2, 4, 5, 6-tetrafluoropyridine had been produced and the starting material was recovered unreacted. Failure to form any Grignard reagent at all in this solvent is presumably due to the fact that this much larger ether molecule is unable, due to steric hinderance, to stablize the fluoropyridyl magnesium chloride.

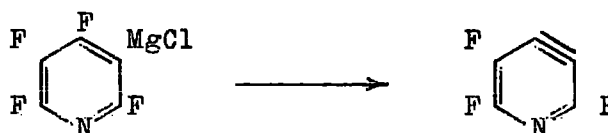
Tetrahydrofuran has been used with success on many occasions in the formation of Grignard reagents and the possibilities of its application in the synthesis of perfluoropyridyl magnesium halides were explored.

When 3-chlorotetrafluoropyridine was added to activated magnesium in dry tetrahydrofuran at room temperature a spontaneous reaction occurred causing the solvent to reflux. The reaction was maintained at a temperature of 60°C for a further hour, cooled and hydrolysed. Vapour phase chromatography showed that all the starting material had been consumed to produce a small quantity of 2, 4, 5, 6-tetrafluoropyridine. Removal of the volatile components from the reaction product gave a brown polymeric residue. This was shown by infra red spectroscopy to contain polyfluoropyridyl units as well as carbon-hydrogen functions.

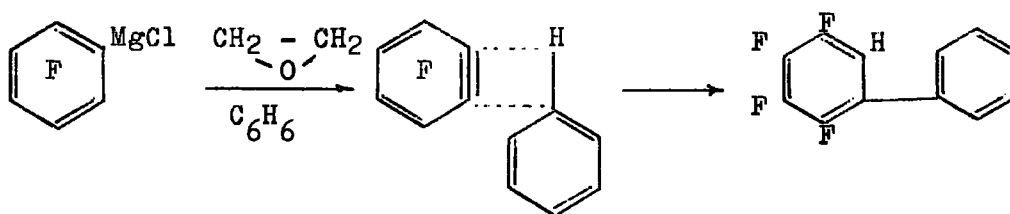
The formation of polymeric material in the reactive system using T.H.F. as solvent is probably due to two types of decomposition of the Grignard taking place. The first is one in which the 4-fluorine of known susceptibility to nucleophilic substitution, in a molecule of 3-chlorotetrafluoropyridine, or in a "molecule" of Grignard reagent is attacked by the carbonionic part of more pyridyl magnesium halide. A series of such reactions will obviously produce polymeric material.



The second mechanism of decomposition is via a pyridyne intermediate. Since it has been shown that a fluorine atom in the 4-position is easily removed as a fluoride ion, it seems quite likely that this process might occur intra-molecularly with the formation of a trifluoropyridyne.



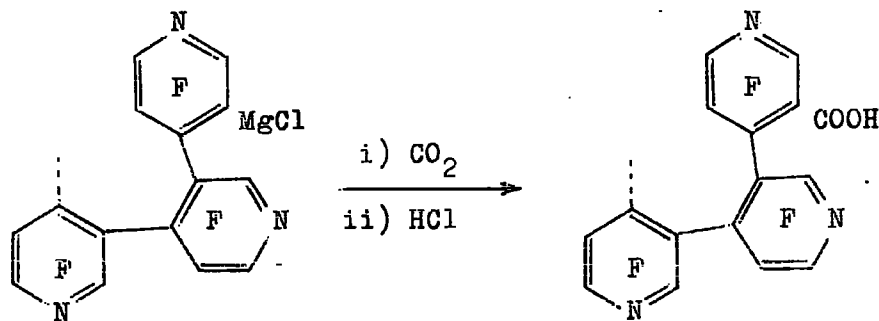
This of course will be extremely reactive and probably react with an adjacent solvent molecule. A similar mechanism has been postulated for the decomposition of pentafluorophenyl magnesium chloride in benzene to give 2, 3, 4, 5-tetrafluorobiphenyl.¹



Thus, when tetrahydrofuran was used as a solvent Grignard formation apparently took place and the problem then became one of moderating the conditions of the reaction so that the Grignard reagent existed for a length of time sufficient for a controlled reaction with a desired reactant.

Several experiments were performed in which the Grignard reagent of 3-chlorotetrafluoropyridine in T.H.F. was reacted with carbon dioxide.

None of these reactions produced material other than polymeric fluoropyridine carboxylic acids when the temperature was above 0°C. The acid polymers will be formed by carbonation of the remaining Grignard functions in the polymer described previously.



In an attempt to reduce the amount of polymerisation, 2, 4, 5, 6-tetrafluoropyridyl magnesium chloride was prepared in T.H.F. while the temperature was maintained between -10°C and 0°C. After 15 minutes carbon dioxide was bubbled into the reaction mixture at -10°C. Following acidification and ether extraction, the product was shown to contain 2, 4, 5, 6-tetrafluoronicotinic acid in 28%

yield, the major product still being polymeric perfluoropyridine carboxylic acids.

The yield of perfluoronicotinic acid by this route may possibly be increased by preparing the Grignard reagent in T.H.F. through which a stream of carbon dioxide is passing, in the hope that carbonation will occur immediately the reagent is formed. This technique has been applied to other systems² in which unstable Grignard reagents are used.

In a separate experiment, tetrafluoropyridyl magnesium chloride was prepared in T.H.F. at -15°C , and allowed to warm to room temperature in the presence of N-methylformanilide. No 3-alde-hydo-tetrafluoropyridine was produced; the only product was a brown polymeric solid.

Experiments conducted at temperatures lower than -20°C showed that Grignard formation, even with activated magnesium, was very slow under such conditions.

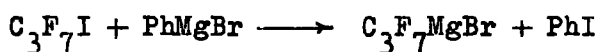
The overriding disadvantage of these Grignard reagents as intermediates in the synthesis of new β -substituted compounds is their tendency to form polymers. The problem is associated with the fact that at the temperature required to form the reagent, the adjacent labile fluorine atom tends to react with another species

in the system. This situation does not arise to the same extent in the preparation of Grignard reagents from bromo- or iodo-compounds because normally initial Grignard formation occurs more readily than in the corresponding chloro-compound. This is demonstrated in the preparation of pentafluorophenyl magnesium halides from iodo-, bromo- and chloro- pentafluorobenzene. The iodo- and bromo- compounds react readily with magnesium in diethyl ether,³ but continuous activation with ethylene dibromide is necessary before reaction with chloro-pentafluorobenzene⁴ is complete.

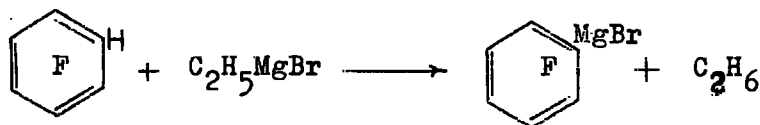
A further example is the relative ease of formation of the Grignard reagent from 4-bromotetrafluoropyridine,⁵ the stability of which is greater than that from 3-chloro-tetrafluoropyridine by virtue of the fact that the adjacent β -fluorine atoms are not nearly so labile as that in the 4-position.

Preparation of Grignard Reagents by Exchange Reactions

Apart from the direct preparation of fluorine containing Grignard reagents described above, a relatively new method involving an exchange process had also been reported. Thus, McBee et al.⁶, prepared heptafluoropropyl magnesium bromide by reaction between phenyl magnesium bromide and perfluoropropyl iodide.



Also, Tamborski and co-workers⁷ have shown that hydrogen in certain polyfluorobenzenes is sufficiently acidic to participate in an exchange reaction of the type:-



Since Rochow⁸ indicates that for the replacement of hydrogen as in the latter type of reaction a pka value of 21 or less is required, it would appear that the value for pentafluorobenzene is 21 or less. In view of this, it seemed likely that the values for the hydrofluoropyridines prepared by the catalytic reduction process (see later) would probably be such as to allow an analogous exchange reaction to take place.

A few experiments were performed to see if this was the case.

When 2, 4, 5, 6-tetrafluoropyridine was mixed with excess methyl magnesium iodide in diethyl ether at room temperature 87% of the theoretical volume of methane was evolved. However, when carbon dioxide was bubbled into the mixture and the reaction worked up as previously described, no detectable quantity of 2, 4, 5, 6-tetrafluoronicotinic acid was recovered. This was not altogether surprising as it had been reported³ that carbonation of pentafluorophenyl magnesium halides in diethyl ether gives very poor yields of pentafluorobenzoic acid. Later work⁹ showed that the yields were considerably improved when tetrahydrofuran was used as solvent. With this in view, the experiment was repeated under the same conditions except that the hydrofluoropyridine was dissolved in T.H.F. and cooled to -70°C . The alkyl Grignard reagent, in diethyl ether, was added at -70°C and the mixture allowed to warm slowly to 0°C . Carbon dioxide was passed into the reaction at 0°C and, after acidification and ether extraction, 2, 4, 5, 6-tetrafluoronicotinic acid was recovered in 2% yield. Apparently, the presence of diethyl ether in the system was sufficient to stabilise the fluoropyridyl Grignard reagent against reaction with carbon dioxide. Because considerably more success was being achieved using polyfluoropyridyl lithium derivatives at this time, the exchange reactions of Grignard reagents was pursued no further.

Catalytic Reduction of Perfluoro and Chlorofluoro-pyridines

Highly fluorinated pyridines containing hydrogen and chlorine can be prepared by the reaction of anhydrous potassium fluoride on tetra chloropyridines¹⁰ but, attempts to replace all of the chlorine by fluorine caused decomposition so that the tetra-fluoropyridines were not directly available via this route. The symmetrical 2, 4, 6-trifluoropyridine can however be prepared by the halogen exchange reaction on the corresponding trichloropyridine.¹¹

As this was the state of affairs when work was begun, it seemed reasonable to explore the possibilities of reducing the highly fluorinated pyridines, which were available by the fluorination of pentachloropyridine, with the intention of producing pyridines containing only fluorine and hydrogen as substituents. It was thought that if this could be accomplished, the hydrogen in the molecule would probably act as a reactive centre and prove these compounds to be valuable intermediates in the synthesis of new derivatives. This has, in fact, been shown to be the case.

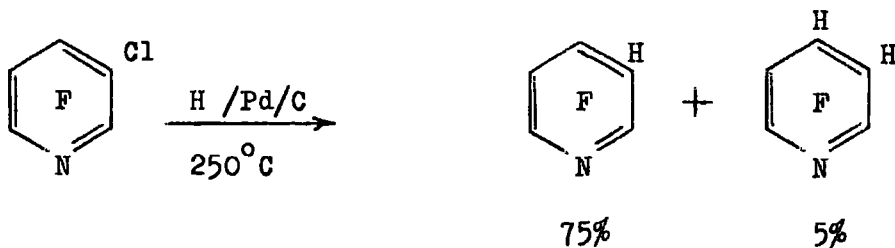
The method used for the reduction of the perfluoro- and chlorofluoropyridines involved the passage of the vapour of the pyridine derivative on a stream of dry hydrogen over a heated catalyst consisting of palladium on activated charcoal. This method had previously been applied to the replacement of aromatic chlorine by hydrogen.¹²

The catalyst, 10% palladium and 90% activated charcoal, was prepared by dissolving a palladium salt or palladium hydroxide in dilute hydrochloric acid and adding hot activated charcoal. The palladium was deposited on the surface of the carbon and most of the water was removed by evaporation. Final drying of the catalyst was effected by warming under vacuum followed by heating to 300°C in a current of dry nitrogen. The catalyst was maintained at 200° - 300°C between reduction experiments to prevent the absorption of moisture.

The reduction apparatus (Fig. 4, page 172) consisted of a flow meter through which the dry hydrogen passed before entering a flash distillation unit, from where the vapour of the compound to be reduced was carried on the current of hydrogen into a silica tube packed with the catalyst and heated by an electric furnace. The emergent product was condensed in a trap cooled in liquid air and the excess hydrogen allowed to escape through a window.

Chlorine in 3-chlorotetrafluoropyridine was replaced by hydrogen in preference to fluorine. Thus when 3-chlorotetrafluoropyridine was passed, in a stream of dry hydrogen (50 ml/min), over the catalyst at 250°C, the principal product was 2, 4, 5, 6-tetrafluoropyridine (~75% yield). However, this was accompanied by a small amount (~5%) of 2, 5, 6-trifluoropyridine resulting from

the replacement of the 4-fluorine in the starting material.



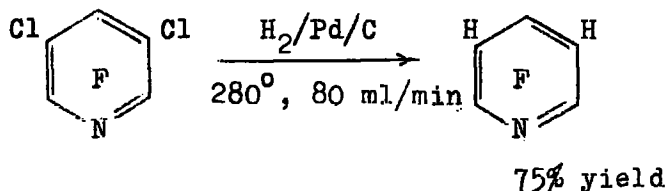
The reaction temperature and hydrogen flow rate quoted above were those found to give the optimum yield of 2, 4, 5, 6-tetrafluoropyridine. A higher catalyst temperature caused a greater proportion of 2, 5, 6-trifluoropyridine to be formed. When a lower flow rate and/or temperature was employed unreacted 3-chlorotetrafluoropyridine was recovered together with the products at the end of the reaction. Similarly, by trial and error it was found that when using apparatus of these dimensions (see EXPERIMENTAL SECTION) the most efficient rate of addition of 3-chlorotetrafluoropyridine was of the order 0.1 gm/min. If the rate of addition was greater than this, incomplete reaction occurred and starting material was recovered. Slower addition made the time of a reaction unnecessarily long. Presumably, if a larger apparatus, containing more catalyst, were employed the through-put would be greater.

With experiments on the scale reported, at least 1 gm. of 3-chlorotetrafluoropyridine was required before useful products were obtained.

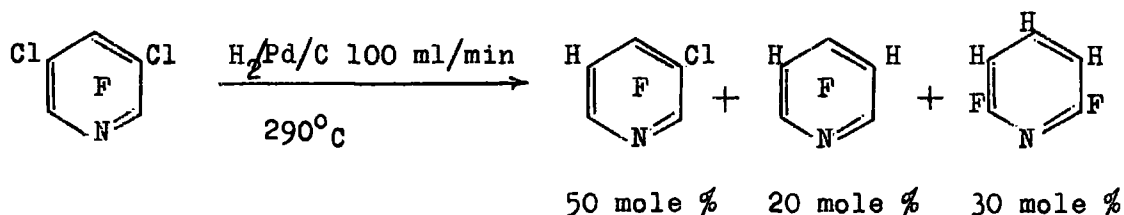
After all the starting material had been flash-distilled the apparatus was swept with hydrogen for a further two hours in order

that all of the product absorbed by the catalyst would be carried into the liquid air trap.

When 3, 5-dichlorotrifluoropyridine was passed through the reductor, again preferential replacement of chlorine over fluorine by hydrogen was shown to occur. Using the same experimental technique as that employed in the reduction of the monochloro-compound, but carrying the dichlorotrifluoropyridine vapour on a current of hydrogen flowing at 80 ml/min, over the catalyst at a temperature of 280°C , a single compound was produced. This was shown to be 2, 4, 6-trifluoropyridine (75% yield), i.e. both chlorine atoms had been replaced without substitution of a fluorine atom.



Under different reaction conditions, with a catalyst temperature of 290°C and a hydrogen flow rate of 100 ml/min, three products were isolated. These were 3-chloro-2, 4, 6-trifluoropyridine, 2, 4, 6-trifluoropyridine and 2, 6-difluoropyridine, demonstrating the stepwise replacement of first one chlorine, then the second chlorine followed by replacement of the 4-fluorine.

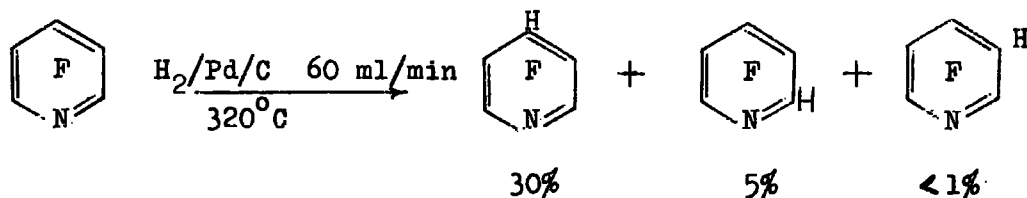


The higher temperature in this second case enabled the replacement of fluorine to occur but because of the high flow rate the compounds were swept through the apparatus before complete substitution could take place. Presumably by using a lower flow rate and/or higher temperatures a greater proportion of the dihydro- and trihydro-pyridines would be produced.

When conditions intermediate between those which produced only 2, 4, 6-trifluoropyridine, and those which produced 2, 6-difluoropyridine were used, the relative proportions of the three products described above varied as expected.

Following the observation that replacement of fluorine was possible using this technique it was decided to investigate the catalytic reduction of pentafluoropyridine. Pentafluoropyridine was passed through the reductor, with a catalyst temperature of 320°C . Considerable decomposition occurred and the product trap was shown to contain principally unreacted pentafluoropyridine together with 2, 3, 5, 6-tetrafluoropyridine (30% yield), 3, 4, 5, 6-tetrafluoropyridine (5% yield) and 2, 4, 5, 6-tetrafluoropyridine

(<1% yield).



With reaction temperatures less than 320°C, lower yields of hydrofluorocompounds were obtained as illustrated by the experiment conducted with the catalyst temperature at 250°C when conversion of pentafluoropyridine produced 2, 3, 5, 6-tetrafluoropyridine and 3, 4, 5, 6-tetrafluoropyridine in only 15% and 3% yield respectively.

In experiments where catalyst temperatures higher than 320°C were employed, excessive decomposition tended to occur and the yields of hydrofluoropyridines were very low. The extent of breakdown of the perfluorocompound was so great that the catalyst soon became poisoned and inefficient. The hydrogen fluoride produced in the decomposition eventually destroyed the silica furnace tube necessitating its replacement together with the catalyst.

Thus, the best yields of monohydrofluoropyridines from pentafluoropyridine were obtained by carrying out the reduction at 320°C, and recycling the product until a good conversion was obtained.

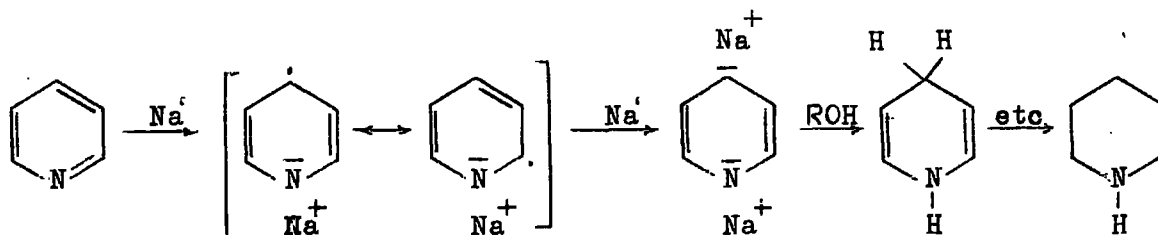
Obviously, the larger the number of such recycling operations, the greater the amount of decomposition which occurred, but this procedure was necessary in order to reduce the proportion of unreacted pentafluoropyridine relative to 3, 4, 5, 6-tetrafluoro-

pyridine so that a vapour phase chromatographic separation of these two compounds, which had very similar retention times, could be effected.

The results of the catalytic reduction of these fluorinated pyridines are interesting for a number of reasons.

In none of the experiments performed was a compound isolated in which addition of hydrogen had occurred to destroy the aromatic character of the system, i.e. only substitution took place. This is quite different from the case of pyridine which is very easily reduced by a number of techniques including both chemical and catalytic methods.

Typical of the chemical methods of reduction is the reaction of pyridine with sodium in ethanol,¹³ the mechanism of which is believed to involve the initial addition of sodium to the ring. Proton abstraction from the solvent then produces hydropyridines although normally the reaction proceeds all the way to the piperidine derivative.



Most catalysts which have been used for the addition of hydrogen to multiple linkages have also been used for reduction of pyridines to piperidines e.g. H_2 /Raney nickel at $120^\circ C$. Reduction with noble metal catalysts proceeds smoothly even at $20^\circ C$ when the bases are in the form of hydrochlorides; the free bases tend to poison the catalyst presumably because they are strongly absorbed on the active surface. Using a 5% rodium carbon¹⁴ catalyst at $55^\circ - 60^\circ C$ reductions have been performed in the absence of acid.

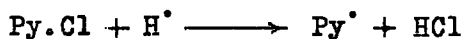
Apart from this aspect of the difference in the susceptibility to hydrogenation between pyridine and its fluorinated analogues, it is interesting to compare the products obtained from the hydrogenation, which is a free radical reaction, and nucleophilic reactions of pentafluoro- and chlorofluoropyridines.

As previously discussed in some detail (page 107), 3-chloro-tetrafluoropyridine and 3, 5-dichlorotrifluoropyridine are highly susceptible to nucleophilic attack but in none of the reactions reported¹⁵ was chlorine replaced, i.e. all the nucleophilic reagents preferentially replaced a fluorine atom in an α - or γ -position. However, when these same chlorofluoro-compounds were reacted with hydrogen in the presence of the catalyst preferential replacement of chlorine occurred and only when all the available chlorine had been removed was fluorine substituted.

The difference in the results of the two types of substitution is apparently caused by the different factors which govern the mode of attack of nucleophiles and free radicals.

In the one case, nucleophilic reagents will primarily attack those carbon atoms of lowest electron density, which in the poly-fluoropyridine system, are in the 2, 4, 6-positions, the 3-position normally being most susceptible, although, as explained (page 108) steric considerations often have some bearing on the result.

In the catalytic reduction process, on the other hand, free radical substitution will occur at the weakest bond. Thus in the chlorofluoropyridines, the chlorine-carbon bonds are weaker than the fluorine-carbon bonds and so the attacking atom substitutes chlorine preferentially.



When no chlorine is present in the molecule, as with penta-fluoropyridine, the hydrogen atoms will preferentially replace the fluorine atom whose bond with the ring carbon is weakest. The experimental evidence would seem to suggest that the weakest bond is the one formed by the fluorine in the 4-position. This is not surprising as this position is unique in not having a para fluorine atom which could increase the electron density in the carbon-fluorine bond region by mesomeric electron release. Further, as had been demonstrated in other situation, the ring nitrogen

maintains its overriding influence on the electronic arrangements within the polyfluoropyridines and so it is not unlikely that its electronegativity will cause electrons to be withdrawn from the carbon-fluorine bond region with subsequent further weakening of that linkage. This argument is borne out by the observation that the second most susceptible fluorine to replacement in pentafluoropyridine is that in position-2, i.e. adjacent to the electronegative nitrogen atom. The fluorine in position-3 is substituted only to a very slight degree producing 2, 4, 5, 6-tetrafluoropyridine.

The overall picture of free radical attack by hydrogen atoms in pentafluoropyridine shows that although replacement is preferred at definite positions, $\gamma > \alpha > \beta$, specificity of substitution is not nearly so marked as in nucleophilic substitution in the same compound.

Attempted Sulphonation of Hydrofluoropyridines

The development of the catalytic reduction of pentafluoro- and chlorofluoropyridines to give highly fluorinated pyridines containing hydrogen provided starting materials to investigate the possibilities of electrophilic substitution in these new compounds.

In a few tentative experiments the reactions of oleum (20% sulphur trioxide) with tetrafluoro- and trifluoropyridines were investigated, but little success was achieved.

2, 4, 5, 6-Tetrafluoropyridine was stirred with oleum for 48 hours at room temperature. After pouring onto crushed ice and extracting with ether, starting material was recovered and no electrophilic substitution of the hydrogen atom to give 2, 4, 5, 6-tetrafluoropyridine sulphonic acid had occurred.

In a similar experiment, 2, 4, 6-trifluoropyridine was stirred with oleum for 6 days. Again, apparently no reaction took place and no sulphonic acid was isolated. When the same di-hydrofluoropyridine was heated with oleum to 200°C for 24 hours complete decomposition occurred and no useful products were recovered.

The conditions of the first two experiments were very similar to those employed in the electrophilic sulphonation of pentafluorobenzene³ when the desired pentafluorobenzene sulphonic acid was produced in good yield.

This result, that the hydrofluoropyridines are much less susceptible to electrophilic substitution than pentafluorobenzene is not surprising since pyridine itself is considerably more resistant to electrophilic attack than is benzene. Benzene is sulphonated by conc. sulphuric acid at 150°C whereas a temperature of 350°C is required to produce pyridine 3-sulphonic acid. Further, it has been shown by n.m.r. measurements¹⁶ that the nitrogen atom in pentafluoropyridine is highly protonated in conc. sulphuric acid, thus it seems reasonable to suppose that the hydrofluoropyridines will likewise be protonated in the same medium. This pyridinium ion, as previously illustrated (page 60), will be even less susceptible to electrophilic attack, because of the additional positive charge in the ring, than the unprotonated molecule.

These conclusions demonstrate that even in highly fluorinated pyridines the overriding feature governing the reaction is the ability of the ring nitrogen to participate electronically in the system in the same way as in unsubstituted pyridine.

Perhaps sulphonation may be achieved using a temperature intermediate between that of the room and 200°C , at which decomposition, probably initiated by attack of an anionic species in the oleum on the 4-position, occurs.

Preparation of Lithium derivatives of Polyfluoropyridines

Pyridyl-lithium derivatives have been prepared from halogenopyridines by halogen metal exchange with n-butyl lithium¹⁷, and by direct metallation with lithium¹⁸ in the same way as phenyllithium^{19, 20, 21} compounds have been formed.

All these organo-lithium derivatives have been shown to be useful intermediates in the synthesis of new compounds and generally react in a similar fashion to the corresponding Grignard reagents.

Because the Grignard reagents prepared from 3-chlorotetrafluoropyridine and 3, 5-dichlorotrifluoropyridine were not altogether satisfactory as synthetic intermediates owing to their tendency to decompose, it was decided to explore the possibilities of preparing the corresponding lithium derivatives from the hydrofluoropyridines prepared by the catalytic reduction technique.

It was hoped to bring about the exchange reaction:-



This would, it was anticipated, go through to completion as it was essentially an acid base reaction in which the hydrogen of butane was considerably less acidic than that attached to the pyridine ring. During the course of this work Tamborski and coworkers reported a similar series of reactions with hydrofluorobenzenes.⁷

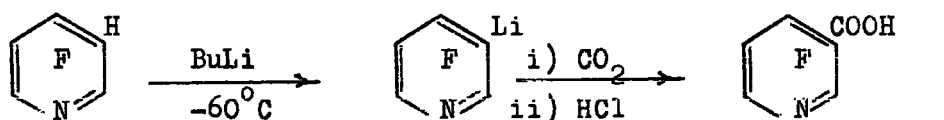
Initial experiments showed that 2, 4, 5, 6-tetrafluoropyridine reacted violently when added quickly to butyl lithium in hexane even when cooled to -65°C . The rapid addition of the reactants obviously caused localised heating and the reaction ran out of control producing only a brown polymeric solid, presumably formed in the same way as that formed during the decomposition of the Grignard reagents, although in this case there is also the added complication of nucleophilic substitution of fluorine atoms by butyl ions.²²

In the next experiment the same reactants were mixed slowly at a temperature of -75°C in a Zerwittenoff flask and then allowed to warm to 0°C , when a violent reaction occurred. Carbon dioxide was then passed into the mixture and after acidification and work up the product was shown to be polymeric polyfluoropyridine carboxylic acids, very similar to those obtained by carbonation of the decomposing Grignard reagents.

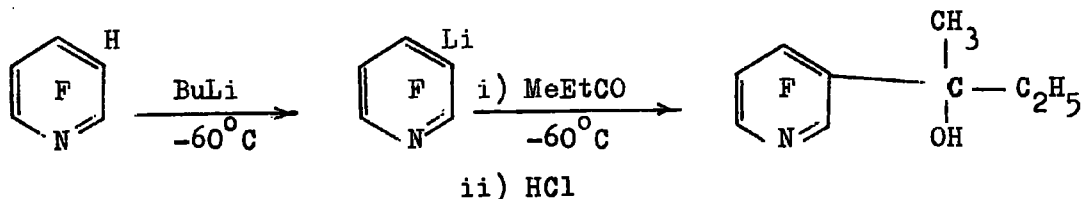
These exploratory experiments indicated that in order to achieve a controlled exchange reaction, and to obtain a useful derivative from the polyfluoropyridyl lithium compound the reactants must be added slowly and maintained at a low temperature.

Acting upon these conclusions, all subsequent reactions were conducted in the apparatus shown in Fig. 5 (page 135). This enabled the slow addition of the reactants with rapid stirring by a teflon covered magnet. Also, the end of the dropping funnel was arranged so that the solution would run down the cooled wall of the

flask before coming into contact with the other reactant, tending to minimise the effect of localised heating. Using this apparatus, butyl lithium in hexane was added to a stirred solution of 2, 4, 5, 6-tetrafluoropyridine at -60°C . After 15 minutes a dense white precipitate, presumably the lithio-derivative had formed and while the temperature was maintained at -60°C , dry carbon dioxide was passed into the reaction for 30 minutes. The mixture was allowed to warm to room temperature with CO_2 passing and then dilute hydrochloric acid was added. After ether extraction, the product was shown to be 2, 4, 5, 6-tetrafluoronicotinic acid in 62% yield.



This method of preparing 2, 4, 5, 6-tetrafluoropyridyl lithium was repeated and the lithium compound further characterised by its reaction with methyl ethyl ketone to give methyl ethyl (2, 4, 5, 6-tetrafluoropyridyl) carbinol in 48% yield.



Obviously, this lithium derivative reacts in the normal manner expected for such compounds and therefore affords a valuable route to all the analogous compounds prepared via pentafluorophenyl lithium and Grignard reagents (page 46). Only lack of time prevented the application of this method to the preparation of a whole series of β -substituted polyfluoropyridines.

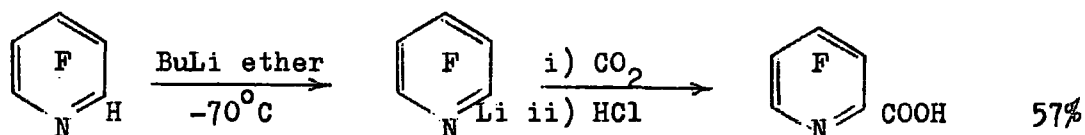
Preparation of Polyfluoropyridine Carboxylic Acids

Having established that the hydrogen atom in 2, 4, 5, 6-tetrafluoropyridine underwent an exchange process with butyl lithium to give the expected tetrafluoropyridyl lithium, which would undergo the characteristic reactions of such a compound and since several other hydrofluoropyridines were available, it was interesting to see if the hydrogen atoms in these compounds would also allow metallation to occur and so afford a generally applicable route to α -, β - and γ -substituted fluoropyridines.

Because of the convenience of preparing and isolating the carboxylic acid derivative, the variously substituted lithium polyfluoropyridyls were reacted with carbon dioxide to characterise the organo-metallic compound.

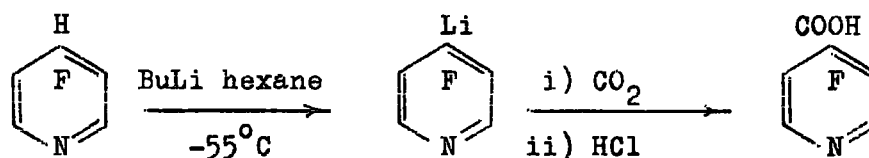
When 3-lithio-tetrafluoropyridine in hexane was reacted with carbon dioxide it had been shown that tetrafluoronicotinic acid was produced in 62% yield. However, later work indicated that this could be improved considerably by using diethyl ether as solvent when the carboxylic acid was produced in 99% crude yield.

Following this observation, 2, 3, 4, 5-tetrafluoropyridine in diethyl ether was mixed with butyl lithium in a mixed solvent of hexane and diethyl ether at -70°C . Carbonation at this temperature produced 3, 4, 5, 6-tetrafluoropicolinic acid, demonstrating that the 2-lithio derivative had been formed.



It seems reasonable to suppose that if 2-lithio-tetrafluoropyridine reacts with carbon dioxide then it will undergo other normal reactions and lead to a whole series of 2-substituted tetrafluoropyridines. The obvious disadvantage of this is the fact that 2, 3, 4, 5-tetrafluoropyridine is, as yet, not readily available, and is produced only in small yield by the catalytic reduction of pentafluoropyridine.

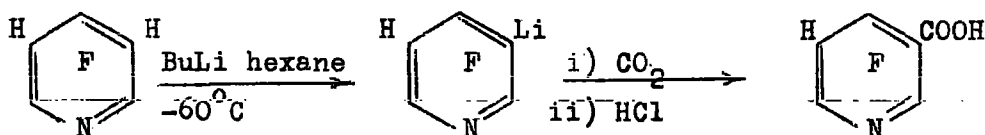
Tetrafluoroisonicotinic acid was prepared in 50% yield by carbonation of a mixture of 2, 3, 5, 6-tetrafluoropyridine and butyl lithium in hexane at -55°C .



It is interesting to observe that this reaction occurs, although it is not nearly so significant as the previous examples since polyfluoropyridines with substituents in the 4-position are readily prepared by methods involving nucleophilic substitution in pentafluoropyridine.

As described in the section on the catalytic reduction of chlorofluoropyridines, two isomers of dihydrotrifluoropyridine were available and it was decided to investigate whether or not it would be possible to prepare di-lithio fluoropyridines and subsequent derivatives from these.

2, 4, 6-Trifluoropyridine was dissolved in hexane and cooled to -60°C . Butyl Lithium in hexane was added and after 15 minutes at -60°C a dense white precipitate had formed. Carbonation of this followed by work up in the usual manner, produced 2, 4, 6-tri-fluoronicotinic acid in 65% yield, with no di-acid being isolated.

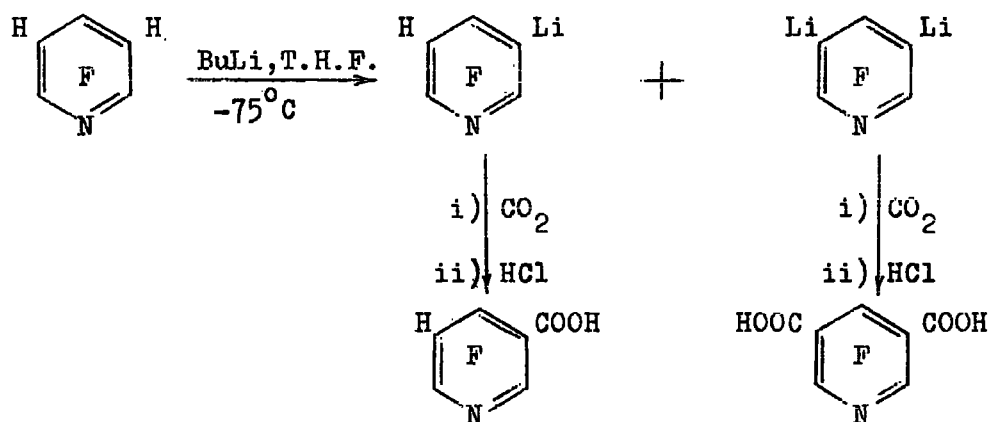


In separate experiments, even when large volumes of hexane were used as solvent, no di-carboxylic acid was produced. Presumably this was because the mono lithio-derivative was so insoluble in hexane that precipitation occurred thus preventing the replacement of the second hydrogen atom by lithium.

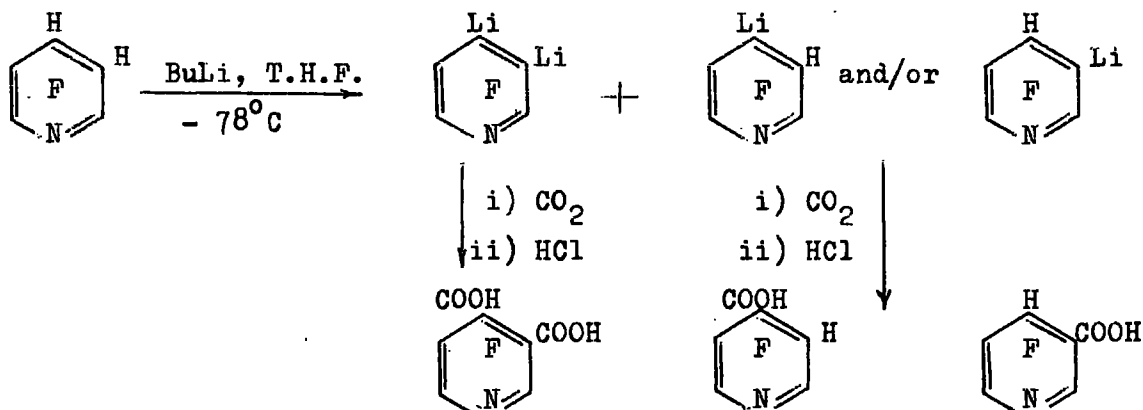
In order to achieve bi-metallation in the same molecule it appeared to be necessary to use a solvent in which the mono-lithium compound is soluble and so allow a homogeneous exchange reaction.

A number of experiments were carried out in which tetrahydrofuran was used as solvent, but it was discovered that when reaction

temperatures higher than -75°C were employed only poor yields of 2, 4, 6-trifluoronicotinic acid were obtained and no dicarboxylic acid was isolated. The main product was involatile polymeric pyridine carboxylic acids similar to those produced by the carbonation of decomposing poly-fluoropyridyl Grignard reagents. However, when the exchange reaction between 2, 4, 6-tetrafluoropyridine and butyl lithium was conducted in this same solvent at -75°C , a dense pale orange precipitate was formed after 15 minutes. Carbon dioxide, diluted with an equal volume of nitrogen, was then passed into the mixture which was worked up in the usual fashion to give a mixture of 2, 4, 6-trifluoronicotinic and 2, 4, 6-trifluoropyridine-3, 5-dicarboxylic acid, demonstrating that in this system the 3, 5-dilithio trifluoropyridine had been formed.



The other dihydrotrifluoropyridine which was readily available was the isomer 2, 5, 6-trifluoropyridine. This compound raised the problem of whether the two adjacent hydrogen atoms would be sufficiently acidic to participate in an exchange metallation reaction. Tamborski⁷ had shown that for Grignard exchange to occur in the hydrofluorobenzenes it was essential for the hydrogen atom to have two ortho fluorine atoms, i.e. 1, 2, 4, 5-tetrafluorobenzene would undergo exchange, whereas 1, 2, 3, 4-tetrafluorobenzene would not undergo exchange metallation with Grignard reagents. It was found that bi-metallation did occur when 2, 5, 6-trifluoropyridine was mixed with butyl lithium in T.H.F. at -78°C . 3, 4-Dilithio-trifluoropyridine was characterised by its reaction with carbon dioxide to produce the expected 2, 5, 6-trifluoropyridine-3, 4-dicarboxylic acid. Some mono carboxylic acid, too small a quantity to permit characterisation, was also produced in the reaction demonstrating that bi-metallation had not gone through to completion.



The results of the experiments just described indicate that with the variety of hydrofluoropyridines investigated metallation is generally applicable and the resultant lithium derivatives will be useful in the synthesis of many substituted polyfluoropyridines.

Strengths of Polyfluoropyridine Carboxylic Acids

The dissociation constants of the polyfluoropyridine carboxylic acids synthesised in the previous section were determined by potentiometric titration in aqueous solution against standard sodium hydroxide solution.

The pKa value was calculated from the pH value at half equivalence point according to the Henderson equation.

The dissociation of an acid can be represented as:-



where $K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]}$ (Ka - dissociation const.)

and the Henderson equation states

$$\text{pH} = \text{pKa} + \log \frac{[\text{Salt}]}{[\text{acid}]} .$$

Therefore at half equivalence where, $[\text{Salt}] = [\text{acid}]$

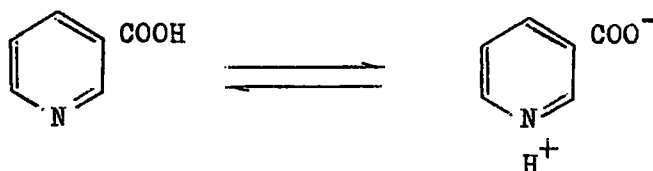
$$\underline{\text{pKa} = \text{pH}}$$

The values of pKa for the acids which have been prepared are recorded in Table IV, together with the values for benzoic, pentafluorobenzoic, and pyridine carboxylic acids. The latter are those for the dissociation according to eqtn.²⁵ II and not eqtn.²⁴ I (see below) .

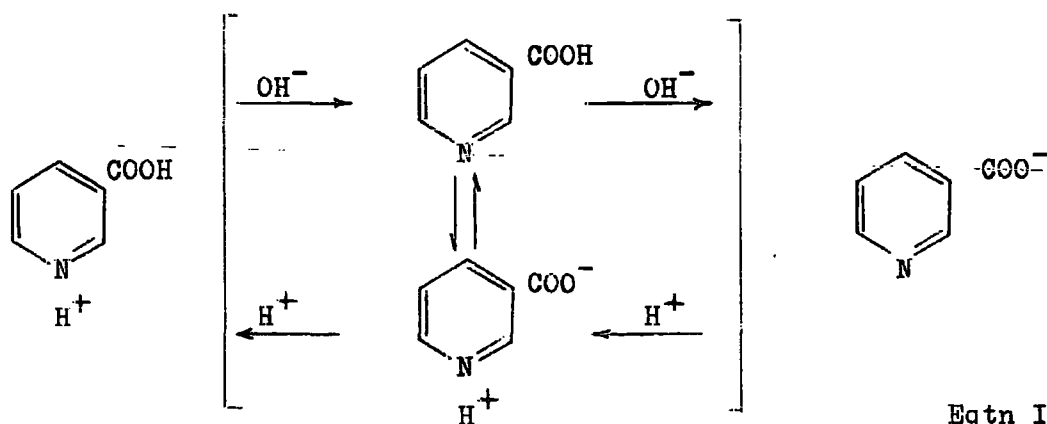
It is first necessary to consider the effect of dissolving a pyridine carboxylic acid in water, since the equilibria set up are not nearly so simple as those with acids which do not have an internal base, the nitrogen atom, which can react with a proton.

This problem has been discussed in the literature²³ where

the existence of the acids in the zwitter ion form is explained.



The dissociation constants (K_1 and K_2) have been measured^{23, 24} for the loss of one and two protons from the protonated undissociated acid.



It is clear however that these constants apply to the equilibrium mixture of the acid and its zwitter ion.

In order to evaluate the equilibrium constant for the ionisation of the pyridine acids, so that comparison with acids not containing an internal base can be made, it is necessary to determine the constant for the equilibrium.

TABLE IV STRENGTHS OF POLYFLUOROPYRIDINE CARBOXYLIC ACIDS

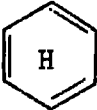
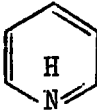
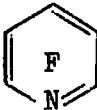
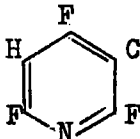
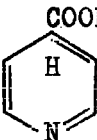
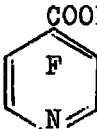
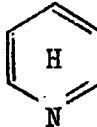
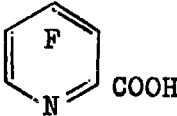
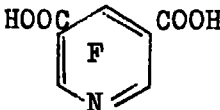
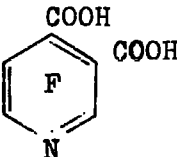
<u>ACID</u>	<u>pKa</u> [†]	<u>EQ. WT.</u>	
		<u>FOUND</u>	<u>THEORY</u>
 <chem>c1ccccc1C(=O)O</chem>	4.21 ²⁴		
 <chem>Fc1ccccc1C(=O)O</chem>	3.38 ^x	208	212
 <chem>c1ccncc1C(=O)O</chem>	3.75 ²⁵		
 <chem>Fc1ccncc1C(=O)O</chem>	3.45	191	195
 <chem>Fc1cc(F)c(C(=O)O)cn1</chem>	3.55	175	177
 <chem>c1ccncc1C(=O)O</chem>	3.44 ²⁵		
 <chem>Fc1ccncc1C(=O)O</chem>	3.21	192	195
 <chem>c1cc(C(=O)O)ccn1</chem>	4.12 ²⁵		

TABLE IV
(contd)

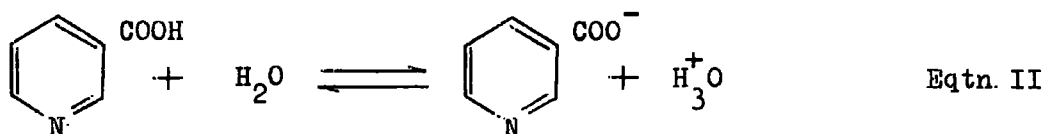
STRENGTHS OF POLYFLUOROPYRIDINE CARBOXYLIC ACIDS

EQ. WT

<u>ACID</u>	<u>pKa</u>	<u>FOUND</u>	<u>THEORY</u>
	3.96	192	195
	3.33	111.8	110.5
	3.30	114	110.5

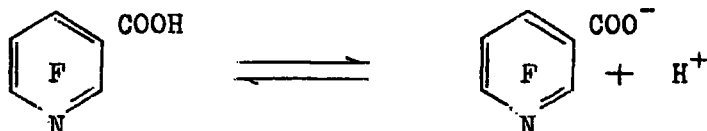
† These values are for the dissociation of a proton from a carboxyl group attached to a ring which does not contain a protonated nitrogen atom.

* This disagrees with the value of 0.8 given by Tatlow and coworkers, but Professor Tatlow has informed us that the published value is incorrect.



Green and Tong²⁵ have assumed that the equilibrium constant for the loss of a proton from the nitrogen atom of the acids is the same as for the corresponding methyl esters and in this way they were able to calculate the desired equilibrium constant and pKa value for the acid dissociation according to equation II.

The most significant feature of the results obtained is that whereas nicotinic and isonicotinic acids, when considering the dissociation as represented in equation II, are considerably stronger than benzoic acid, as would be expected since a proton should be lost more readily from an acid function attached to a positively charged ring, the corresponding tetrafluoro-nicotinic and isonicotinic acids are of similar strength to that of pentafluorobenzoic acid. This difference between the two series must be due to the considerably reduced basic character of the nitrogen atom in polyfluoropyridine systems. Because of this reduction in the basicity of the nitrogen and the subsequent reduction in degree of protonation occurring, the pKa results obtained by the direct measurement technique employed will give values which are very nearly those of the desired equilibria, e.g. tetrafluoronicotinic acid will dissociate as follows:-



This argument is borne out by the results of n.m.r. measurements by Emsley and Phillips¹⁶ who have shown that in acid solution of comparable strength to the polyfluoropyridine carboxylic acids, a negligible degree of protonation of the nitrogen in perfluoropyridine occurs. However, it must be noted that a very small amount of self protonation is observed in the n.m.r. spectra of the polyfluoropyridine acids.

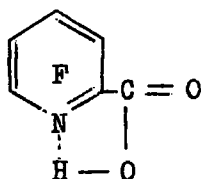
It can be seen that the presence of several fluorine atoms is the most important factor affecting the strength of the polyfluoropyridine carboxylic acids since the differences in strength between the various acids is generally quite small. Because of these small differences and because the experimental accuracy is not easy to calculate, it is only possible to discuss trends in the pKa values of the various acids measured.

Of the mono-carboxylic acids measured tetrafluoroisonicotinic acid was the strongest. This is probably due to one or both of the following factors. (a) the 4-position is unique in that it does not have a para fluorine atom which could have an acid weakening effect due to mesomeric electron release, or, (b) the carbon atom in the 4-position is rendered the most positive by the influence of the ring nitrogen atom. (This has been demonstrated by the results of nucleophilic substitution on polyfluoropyridines).

The strength of tetrafluoronicotinic acid is slightly less than that of its 4-substituted isomer; this could well be due to the reasons cited above, i.e. the 3-carboxylic acid group does have a para fluorine substituent and the position is not able to conjugate mesomerically with the ring nitrogen with the resultant relative reduction in the positive charge on that carbon atom.

2, 4, 6-Trifluoronicotinic acid is weaker than the fully fluorinated nicotinic acid, demonstrating the effect of the withdrawal of electrons from the ring by fluorine atoms with subsequent increase in acid strength.

It might have been expected that tetrafluoropicolinic acid would be of greater strength than tetrafluoronicotinic acid because of the proximity of the point of attachment on the ring of the functional group to the electronegative nitrogen atom. However, this was found not to be the case, in fact tetrafluoropicolinic acid was the weakest of all the acids measured. This would suggest that the adjacent nitrogen played some role other than one of reducing the electron density on the carbon in position 2. It is interesting that the same effect is observed in the hydrogen series of pyridine acids and would seem to indicate that some kind of intramolecular bonding occurred of the type:-



which would cause the proton in this position to be less readily removed, relative to those in the nicotinic and isonicotinic acids which cannot form analogous structures.

The other important feature which would have an effect on the acid strength of tetrafluoropicolinic acid is that the carboxyl group in this position has only one fluorine atom as neighbour, whereas the carboxyl group in both tetrafluoro-nicotinic and tetrafluoroisonicotinic acids has two other fluorine atoms.

When the values of pKa for the dicarboxylic acids were determined only one dissociation was obvious from the titration curve indicating that the second dissociation constant was considerably less than the first.

The value obtained for 2, 4, 6-trifluoropyridine-3, 5-dicarboxylic acid showed that this was a stronger acid than tetrafluoronicotinic acid suggesting that the resultant electron withdrawal effect of the carboxyl group in the 5-position was greater than that of a fluorine in the same position. Unfortunately, due to impurity, the sample of 2, 5, 6-trifluoropyridine-3, 4-dicarboxylic acid did not give a pKa value of sufficient accuracy to say any more than that this acid was of a strength comparable with that of tetrafluoroisonicotinic acid and 2, 4, 6-trifluoro-3, 5-dicarboxylic acid.

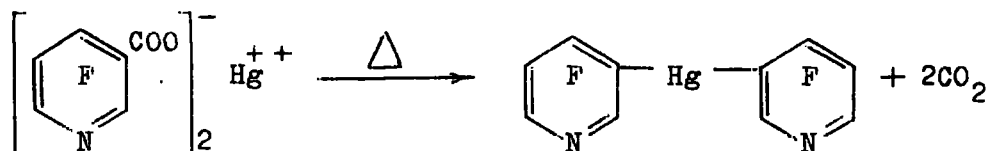
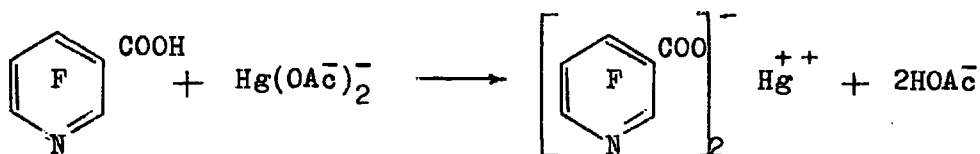
Preparation of Polyfluoropyridine Mercury Compounds

In view of the current interest in perfluoroalkyl and perfluoroaryl^{26, 27} compounds of metals and metalliods it was decided to consider the possibilities of preparing compounds which would involve bonding between perfluoropyridyl functions and metals.

Recently, a useful route to pentafluorophenyl mercurials has been reported.²⁸ This involved the decarboxylation of mercury salts of fluorophenyl carboxylic acids, and, since several carboxylic acid derivatives of polyfluoropyridines were readily available by carbonation of the corresponding polyfluoropyridyl lithium compounds, the application of this method to the preparation of perfluoropyridyl mercurials was studied.

Mercuric (2, 4, 5, 6-tetrafluoronicotinate) was prepared by adding an aqueous solution of 2, 4, 5, 6-tetrafluoronicotinic acid to an aqueous solution of the corresponding amount of mercuric acetate. The insoluble mercuric perfluoronicotinate precipitated, was filtered and dried. This salt, obtained in 81% yield, was involatile and melted with decomposition at 225°C.

Decarboxylation proceeded smoothly when it was heated under reduced pressure to a temperature just above its melting point.



A white solid, formed during the decarboxylation, sublimed and was shown to be bis (2, 4, 5, 6-tetrafluoropyridyl) mercury, which melted at 200°C without apparent decomposition. The thermal stability of this compound would therefore seem to be comparable with that of bis pentafluorophenyl mercury which remains unchanged even after 5 hours at 250°C.²⁹ This observation on the thermal stability of the perfluoropyridyl mercurial is consistent with reports by other workers,^{30, 31} that the introduction of electron-withdrawing substituents tends to enhance the thermal stability of aryl-mercurials.

Further demonstration of the extent of electron-withdrawal by the tetrafluoropyridyl group, is the observation that bis (2, 4, 5, 6-tetrafluoropyridyl) mercury is capable of forming a stable coordination compound with 2, 2'-bipyridyl. This was prepared simply by mixing a benzene/hexane solution of the mercurial with a solution of 2, 2'-bipyridyl in benzene. The adduct crystallised preferentially

to give a white solid melting at $142^{\circ} - 3^{\circ}\text{C}$.

The formation of this co-ordination compound is remarkable in that, together with the bispentafluorophenyl- and cyanide derivatives, these are the only reported compounds in which mercury involved in a linkage with carbon has sufficient electron-accepting capacity to enable neutral co-ordination complexes to be isolated. It is interesting to note that methylpentafluorophenyl- , pentafluorophenylphenyl- , dimethyl- and diphenyl- mercury do not form complexes with bipyridyl.

By the decarboxylation of mercuric salts of other polyfluoropyridine carboxylic acids it seems likely that isomers of the mercurial described above will be prepared.

Investigations into the cleavage reactions, by reagents such as hydrogen chloride, bromine and other mercurials, of these bis polyfluoropyridyl mercurials may provide some interesting reactions.

Another route to perfluoropyridyl mercurials was tentatively investigated. This involved the reaction of a per-fluoropyridyl lithium derivative with mercuric bromide.

2, 4, 5, 6-Tetrafluoropyridyl lithium, prepared by low temperature metallation of 2, 4, 5, 6-tetrafluoropyridine with butyl lithium in hexane, was allowed to react with a slurry of mercuric bromide in hexane while warming from -60°C to room

temperature. The white solid volatile product was shown by infra red spectroscopy to contain polyfluoropyridyl units as well as carbon-hydrogen functions. Elemental analysis and melting point demonstrated that no single pure product was obtained even after sublimation and recrystallisation. However, the separation of the products, which probably consisted of a mixture of unreacted mercuric bromide together with mixed alkyl- and fluoropyridyl-mercurials, could probably be effected if the experiment were carried out on a larger scale.

Although this initial experiment was unsuccessful in that no pure compound was isolated, it seems likely that if the reaction could be developed to produce polyfluoropyridyl mercurials then it may also be used in the preparation of other polyfluoropyridyl metal and metalloid compounds, considering the way in which pentafluorophenyl- Grignard reagents and lithium derivatives have been applied to the synthesis of many pentafluorophenyl-metal and metalloid compounds.^{29, 32, 33}

Stability of Polyfluoropyridyl-metal Compounds

It has been shown that the stability of halogenophenyl-lithium and Grignard reagents depends on the orientation of the halogen in the ring. Thus, while meta- and para-halogenophenyl lithium compounds are relatively stable, ortho-halogeno systems show a marked instability in the order: $\text{o-Br} > \text{o-Cl} > \text{o-F}$. The instability of such compounds has been attributed to ready elimination of lithium halide to form a benzyne^{19c, 19d} system, the transience of which has been established in a number of ways, usually involving coupling reactions of the Diels-Alder type with furan^{19d}, cyclopentadiene²⁰, anthracene, etc.

Highly fluorinated phenyl lithium and Grignard reagents however are comparatively stable, presumably due to the electron withdrawal of five fluorine atoms stabilising the carbanion, as is shown by the observation that pentafluorophenyl magnesium bromide²¹ and 2-bromotetrafluorophenyl magnesium bromide are largely unaffected by refluxing diethyl ether, whereas o-fluoro³⁴ and o-bromo-phenyl³⁵ magnesium halides are relatively unstable.

The relative stability of pentafluorophenyl lithium²¹ was further demonstrated by its fairly slow reaction at 15°C in ethereal solution with mercury to give bis-pentafluoro-phenylmercury.

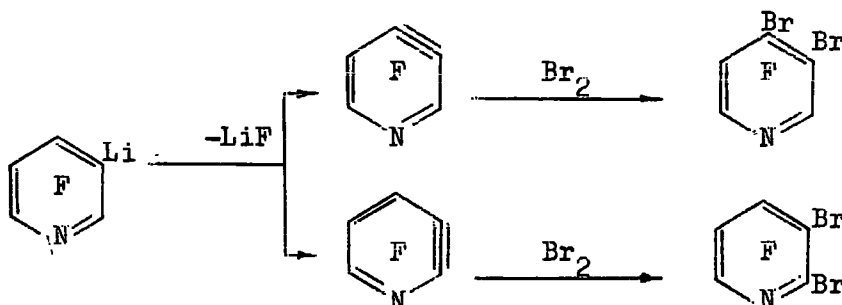
With these considerations in mind, it might be expected that tetrafluoropyridyl lithium and Grignard reagents would show a similar stability to their perfluorophenyl analogues owing to the presence of

four fluorine atoms and a nitrogen atom which could bring about the stabilisation of the carbanion. In fact, it has been shown that 2, 3, 5, 6-tetrafluoropyridyl magnesium bromide⁵ and 4-lithio tetrafluoropyridine¹¹ are of comparable stability to the corresponding pentafluorophenyl compounds, but 2, 4, 5, 6-tetrafluoropyridyl lithium and Grignard reagents are much less stable. The instability of these latter compounds must be due to the presence of a fluorine atom in the 4-position, adjacent to the metallic function. A fluorine atom in this position has already been shown to be very easily removed as fluoride ion and presumably elimination of magnesium chlorofluoride or lithium fluoride in this way would impart a reactivity to 3-metallic perfluoropyridines comparable with that of the ortho-halogenophenyl lithium and Grignard reagents discussed above.

As previously described, it is essential that 2, 4, 5, 6-tetrafluoropyridyl lithium is prepared at low temperatures, otherwise decomposition occurs and no useful products are obtained. When methyl lithium and 2, 4, 5, 6-tetrafluoropyridine were mixed in an ether/tetrahydrofuran solvent at -70°C the desired tetrafluoropyridyl lithium was formed. The mixture was allowed to warm slowly and at approximately -40°C decomposition began to occur. When the reaction reached room temperature and was worked up the product was found to be polyperfluoropyridylenes. This yellow polymer was

involatile and did not melt below 300°C . The average molecular weight was measured by vapour pressure osmometry and calculated to be 1230, corresponding to a polymer consisting of 9 to 10 $-(\text{C}_5\text{F}_3\text{N})-$ units per molecule.

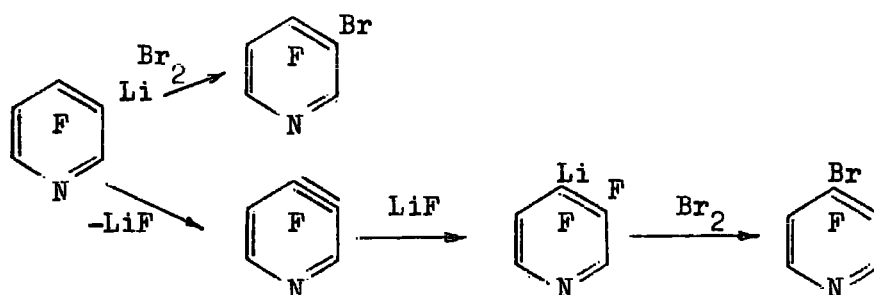
In order to establish the existence of a pyridyne formed by the elimination of lithium fluoride from 2, 4, 5, 6-tetrafluoropyridyl lithium it was decided to investigate the reaction of the decomposing lithium compound with bromine in the hope that ortho dibromotrifluoropyridine might be produced according to the reaction scheme:-



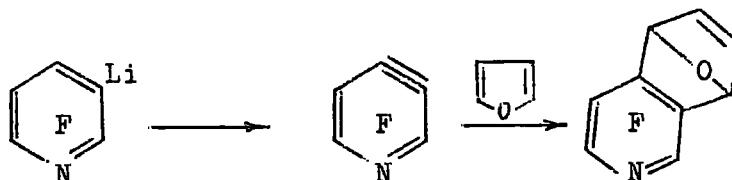
Analytical scale v.p.c. of the reaction products showed that a small quantity of two compounds of relatively long retention time had been formed but all attempts to obtain pure samples of these compounds failed as they appeared to decompose spontaneously. The infra red spectrum of the impure compounds showed that they contained polyfluoropyridine functions.

The major product (22% yield) from the reaction was 3-bromo-tetrafluoropyridine; this too was unstable and decomposed on

standing. Significantly, however, a small amount of 4-bromo-tetrafluoropyridine was also detected in the reaction mixture. As the starting material, 2, 4, 5, 6-tetrafluoropyridine, was pure the 4-bromo compound could only have been formed by reaction with 4-lithio-tetrafluoropyridine produced by the elimination of lithium fluoride and its readdition, the other wayabout, to the pyridyne.



Workers in Birmingham had characterised tetrafluoro-benzynes by its reaction with furan to give 5, 8-epoxy-1, 2, 3, 4-tetrafluoro-5, 8-dihydronaphthalene. In an analogous manner it was hoped to prepare a trifluoroisoquinoline derivative by the reaction of trifluoropyrid-3-yne with furan.

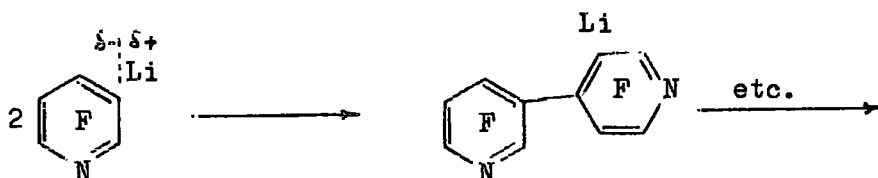


Unfortunately, when 3-lithio tetrafluoropyridine was allowed to warm in furan solution, the sole product was a polyfluoropyridine polymer, suggesting that the organo-metallic compound reacted preferentially with itself.

Thus, it can be seen that in a system containing 2, 4, 5, 6-tetrafluoropyridyl lithium three types of reaction can occur.

These are:

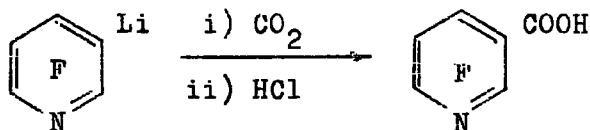
1. Intermolecular elimination of fluoride ion, involving nucleophilic attack by the carbanion of polyfluoro-pyridyl lithium with more pyridyl lithium on the γ -position, so giving polymeric material.



2. Intramolecular elimination of fluoride ion giving a trifluoropyridyne, which will then react with its environment, be it the leaving lithium fluoride, another component of the mixture, or solvent.

and 3. The standard reaction of perfluoropyridyl lithium as a synthetic intermediate.

e.g.



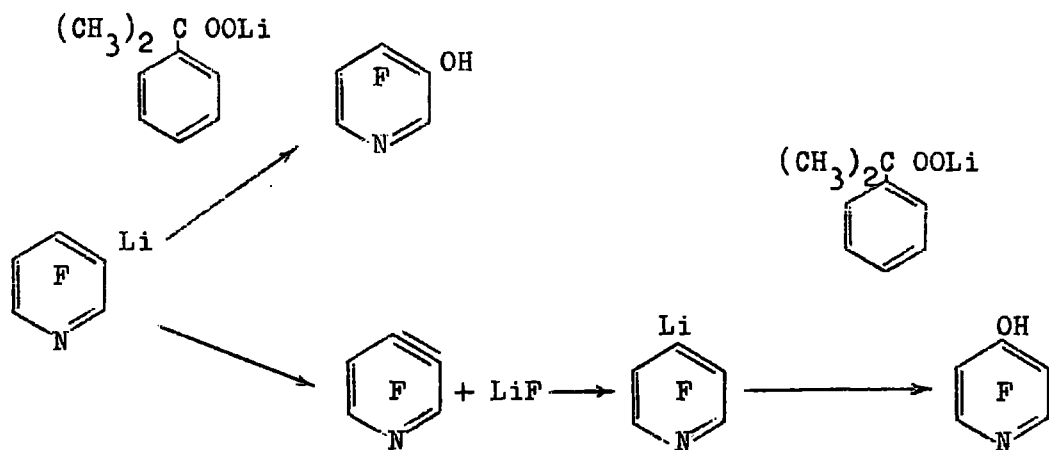
The course which any given reaction will take depends on whether the desired controlled reaction can occur before decomposition of the pyridyl lithium begins by reaction with itself.

These three types of reaction were demonstrated in a single experiment when the preparation of 3-hydroxy-tetrafluoropyridine³⁶

was performed, using a method developed in these laboratories for the synthesis of pentafluorophenol.³⁷

2, 4, 5, 6-Tetrafluoropyridyl lithium was mixed with lithium cumene peroxide, prepared by the addition of butyl lithium to cumene hydroperoxide, in diethyl ether at -78°C and allowed to warm relatively quickly to room temperature. The products were found to be polymeric perfluoropyridines, formed by the intermolecular reaction of the lithium compound, and a mixture of 3-hydroxy- and 4-hydroxy-tetrafluoropyridines.

The 3-hydroxy-compound was formed in the standard reaction of the 3-lithio pyridyl with an organic peroxide³⁸, but the 4-hydroxy derivative must have arrived by way of an intramolecular elimination, giving a pyridyne, followed by readdition of lithium fluoride and the reaction of this product with lithium cumene peroxide.



The same experiment was repeated but instead of allowing the temperature to rise quickly to that of the room, the mixture was maintained at -50°C for 30 minutes. The only product from this reaction was 3-hydroxytetrafluoropyridine, i.e. no polymer and no 4-hydroxytetrafluoropyridine had been formed, demonstrating that the standard reaction occurred before intermolecular decomposition or pyridyne formation could take place.

Chapter 6

EXPERIMENTAL WORK

Preparation of Solvents for Metallation Reactions

Because of the susceptibility to hydrolysis of Grignard reagents and organo-lithium compounds, it was essential that all solvents used in reactions involving such compounds were dry. The methods of drying employed are described below:-

Hexane

Hexane fraction boiling 68° - 70°C was distilled from phosphorus pentoxide and stored over freshly prepared sodium wire.

Tetrahydrofuran

Tetrahydrofuran was refluxed with sodium for 3 hours, and stored under dry nitrogen in a distillation apparatus containing lithium aluminium hydride. The solvent was freshly distilled under nitrogen as required.

Diethyl Ether

Diethyl ether was dried by extruding freshly prepared sodium wire directly into the solvent until effervescence due to hydrogen evolution ceased. The solvent was allowed to stand over sodium for several days before use.

Di-n-butyl ether

Di-n-butyl ether was dried in a manner similar to that employed with diethyl ether.

Preparation of Grignard Reagents of Polyhalogenopyridines

3-Chlorotetrafluoropyridine and Magnesium in Diethyl Ether

Magnesium (1.0 gm., 0.041 moles), activated by grinding with a crystal of iodine, was placed in a two necked flask with dry diethyl ether (10 mls) under an atmosphere of dry nitrogen. 3-Chlorotetrafluoropyridine (1 gm., 5.4 m.moles), mixed with 1, 2-dibromoethane, (0.5 gm.) was added to the flask which was then warmed slightly. Reaction occurred causing the ether to reflux. Dibromoethane (0.5 gm) was added dropwise over a period of $3\frac{1}{2}$ hrs while the reaction was maintained at reflux temperature by a water bath. The dark solution was allowed to cool to room temperature and was hydrolysed with water (15 mls.). The etherial layer was separated, dried (MgSO_4), and fractionated to remove almost all the ether. Analytical-scale v.p.c. (di-n-decyl phthalate as stationary phase, 100°C) showed the residue (0.8 gm) to contain approximately equal molar quantities of unreacted 3-chlorotetrafluoropyridine and a product of identical retention time to 2, 4, 5, 6-tetrafluoropyridine.

3-Chlorotetrafluoropyridine and Magnesium in di-n-butyl ether

Magnesium (1gm, 0.041 moles), in dry di-n-butyl ether (10 mls), was refluxed with ethylene dibromide (1.0 ml) for 10 mins. 3-Chlorotetrafluoropyridine (1.0 gm., 5.4 m.moles) was added slowly and the reaction mixture warmed to reflux temperature when more ethylene

dibromide (1.5 mls) was added intermittently over 1hr. The mixture was maintained at reflux over night causing a slight darkening in the colour of the solution. After allowing to cool to room temperature, water (10 ml) was added and the etherial layer separated and dried (MgSO_4). Analytical-scale v.p.c. (di-n-decyl phthalate as stationary phase, 100°C) showed that no 2, 4, 5, 6-tetrafluoropyridine had been produced. The starting material, 3-chlorotetrafluoropyridine was recovered unreacted.

3-Chlorotetrafluoropyridine and Magnesium in Tetrahydrofuran

Magnesium (0.5 gm., 0.021 moles), activated by grinding up with a crystal of iodine, placed in a flask containing dry tetrahydrofuran (10 ml.). 3-Chlorotetrafluoropyridine (1 gm., 5.4 m.moles) added to the flask, followed by two drops of ethylene dibromide. A spontaneous reaction ensued causing the solvent to reflux. The temperature of the mixture was maintained at 60°C for 1 hr, during which time a very dark colour formed. After allowing to cool to room temperature, water (10 ml) was added, causing effervescence, and the upper organic layer separated. Analytical-scale v.p.c. (di-n-decyl phthalate as stationary phase, 100°C) showed that all the 3-chlorotetrafluoropyridine had been consumed to produce a small quantity of a compound of retention time coincident with 2, 4, 5, 6-tetrafluoropyridine. Removal of the volatile components of the organic layer gave a brown polymeric residue (0.8 gm), shown by infra

red spectroscopy to contain fluoropyridine components.

3, 5-Dichlorotrifluoropyridine and Magnesium in di-ethyl ether

Magnesium (1 gm., 0.042 moles), in dry di-ethyl ether (10 ml), was refluxed with ethylene dibromide (0.5 gm) for 10 mins. 3, 5-dichlorotrifluoropyridine (1 gm., 4.95 m.moles) was added to the flask which was then warmed to reflux temperature. Ethylene dibromide (1 gm.) was added intermittently over 3 hrs while the reaction was maintained at reflux. After allowing to cool to room temperature, water (10 ml.) was added and the organic layer separated, dried (MgSO_4), and most of the ether removed by fractionation. The residue (0.6 gm) was shown by analytical-scale v.p.c. (di-n-decyl phthalate, 160°C) to contain two principal components, one, present in 60%, was of identical retention time to that of the starting material, 3, 5-dichlorotrifluoropyridine, and the other (in 40%) was of retention time coincident with that of an authentic sample of 2, 4, 6-trifluoro-3-chloropyridine. Isolation of this product by preparative scale v.p.c. (di-n-decyl phthalate, 160°C) showed it to have an identical i.r. spectrum to that of an authentic sample of 2, 4, 6-trifluoro-3-chloropyridine. (I.R. Spectrum N.11 page 2c7).

3-Chlorotetrafluoropyridine and Magnesium in T.H.F. followed by

Carbonation

To Magnesium (1 gm., 0.042 moles), in dry tetrahydrofuran (10 ml) was added 3-chlorotetrafluoropyridine (2 gm., 10.8 m.moles) at room

temperature. Ethylene dibromide (0.2 gm) was added to initiate the reaction which, was then maintained between 0°C and room temperature for 2 hrs. Dry carbondioxide was then passed into the reaction mixture at 0°C for 1 hr, after which water (10 ml) was added followed by dilute hydrochloric acid (10 mls). The organic layer was separated and pumped to remove the solvent leaving a brown solid polymeric residue. The aqueous layer was extracted with ether, the extracts combined and the solvent removed under vacuum leaving a brown solid residue. The total solid residue (1.7 gm) was shown by infra red spectroscopy to contain aromatic fluoro-pyridyl, carboxyl and hydroxyl functions by their characteristic absorption bands. The brown solid was soluble in 5N sodium hydroxide solution and was precipitated when this solution was made acid. All attempts to recrystallise the product failed, and it was shown to be involatile by heating under vacuum without sublimation.

3-Chlorotetrafluoropyridine and Magnesium in T.H.F. followed by

Carbonation

Magnesium (2 gm., 0.084 moles) was activated by reaction with methyl iodide (0.5 gm) in tetrahydrofuran at room temperature. This magnesium was then washed with ether and T.H.F. and transferred to a separate flask containing tetrahydrofuran (20 ml) which was cooled to 20°C. 3-Chlorotetrafluoropyridine (0.5 gm., 2.7 m.moles)

followed by ethylene dibromide (0.2 gm), was added and a spontaneous reaction occurred. The reaction temperature was maintained between -10°C and 0°C for 15 mins. during which time a very dark colour was formed. Dry carbon dioxide was passed into the reaction at -10°C and the temperature allowed to rise to that of the room with carbon dioxide passing. Water (20 ml) was added and the reaction mixture filtered. The filtrate was acidified (20 ml. dilHCl) and extracted with ether (2 x 20 ml). The extracts were combined, dried (MgSO_4), and the solvent removed by distillation leaving a brown solid residue (0.35 gm). When this residue was heated under vacuum a white solid (0.15 gm) sublimed at 55°C . The i.r. spectrum of the sublimate was identical to that of an authentic sample of tetrafluoronicotinic acid (I.R. Spectrum No. 14. page 208). Yield, 28%. The involatile residue (0.2 gm) had an infra red spectrum very similar to the polymeric pyridine carboxylic acids from previous reactions.

3-Chlorotetrafluoropyridine and Magnesium in T.H.F. with N-methyl-
formanilide

Magnesium (2 gm., 0.084 moles), in tetrahydrofuran (20 ml), was activated by reaction with ethylene dibromide (0.5 gm) at 0°C . The reaction mixture was cooled to -15°C and 3-chlorotetrafluoropyridine (1 gm., 5.4 m.moles) mixed with ethylene dibromide (1 gm) in T.H.F. (2 ml) added slowly causing the development of a dark

colouration. After 10 mins, a further amount (0.5 gm) of ethylene dibromide was added, followed by N-methylformanilide (1 gm) in tetrahydrofuran (2 ml) while the temperature was maintained at -15°C . After allowing to warm to room temperature and stirring for 2 hrs, water (15 mls) and dilute hydrochloric acid (15 mls) were added and the contents of the reaction flask steam distilled. The steam distillate was extracted with ether, dried (MgSO_4), and most of the solvent removed by distillation. Vapour phase chromatographic analysis showed no detectable quantities of useful product.

The brown solid residue (0.7 gm) in the steam distillation flask gave an infra red spectrum very similar to the polymeric fluoropyridyl material obtained from previous Grignard reactions.

Exchange Reactions

2, 4, 5, 6-Tetrafluoropyridine and Methyl magnesium iodide

2, 4, 5, 6-Tetrafluoropyridine (0.5 gm., 3.3 m.moles) was placed in one limb of a Zerewittenoff flask connected to a gas burette. Excess methyl magnesium iodide in diethyl ether (5 ml) was placed in the other limb of the apparatus, and the contents of both limbs mixed at room temperature. Methane (68 ml., 87% theoretical quantity) was evolved and then carbon dioxide was passed into the reaction mixture for 1 hr. Dilute hydrochloric acid (10 ml) was added, the aqueous and organic layers separated,

and the aqueous layer extracted with ether. The organic solutions were combined, dried (MgSO_4), and the solvent removed by distillation leaving no solid residue of tetrafluoronicotinic acid.

2, 4, 5, 6-Tetrafluoropyridine and Ethyl magnesium bromide

2, 4, 5, 6-Tetrafluoropyridine (0.5 gm., 3.3 m.moles) was dissolved in dry tetrahydrofuran and cooled to -70°C . Ethyl magnesium bromide (3.3 m.moles) in diethyl ether was added with stirring at -70°C , and then the mixture allowed to warm slowly to 0°C , during which time 20 ml of gas had been evolved. Carbon dioxide was passed into the mixture at 0°C for 15 mins, the solution acidified with dil. HCl (10 ml), and extracted with ether. The ethereal extracts were combined, dried (MgSO_4), and the solvent removed to yield a tacky white solid (0.01 gm). This was shown by i.r. spectroscopy to be mainly 2, 4, 5, 6-tetrafluoronicotinic acid (crude yield 2%).

Catalytic Reduction of Perfluoro and Chlorofluoro-pyridines

Preparation of the Catalyst

Palladium hydroxide (3.3 gm., 2.5 gm Pd.) was dissolved in dilute hydrochloric acid (150 ml.) and the solution heated to boiling. Active carbon (25 gm., 8-14 mesh), heated to 100°C in an oven, was poured into the hot solution which was then stirred and evaporated to a small volume (20 ml.). Concentrated hydrochloric acid (5 ml.) was added and heating continued until most of the water was removed. The palladised carbon was warmed under vacuum for 5 hrs. and then packed in the reductor furnace where it was heated at 300°C for 24 hrs. in a current of dry nitrogen to remove the final traces of water.

The Reductor

The catalytic reduction apparatus (Fig. 4 page 172) comprised of a flask-distillation unit through which a metered current of dry hydrogen passed before entering the electrically heated furnace, consisting of a silica tube 1" in diameter x 12" long. The central 6" of this tube was packed with palladised carbon (10% Pd, 90% C) catalyst, prepared as described above, and held in position by glass wool plugs. A thermocouple (chromel-alumel) ran along the central axis of the tube to give a direct reading of the temperature at the the centre of the furnace. The product emerging from the catalyst

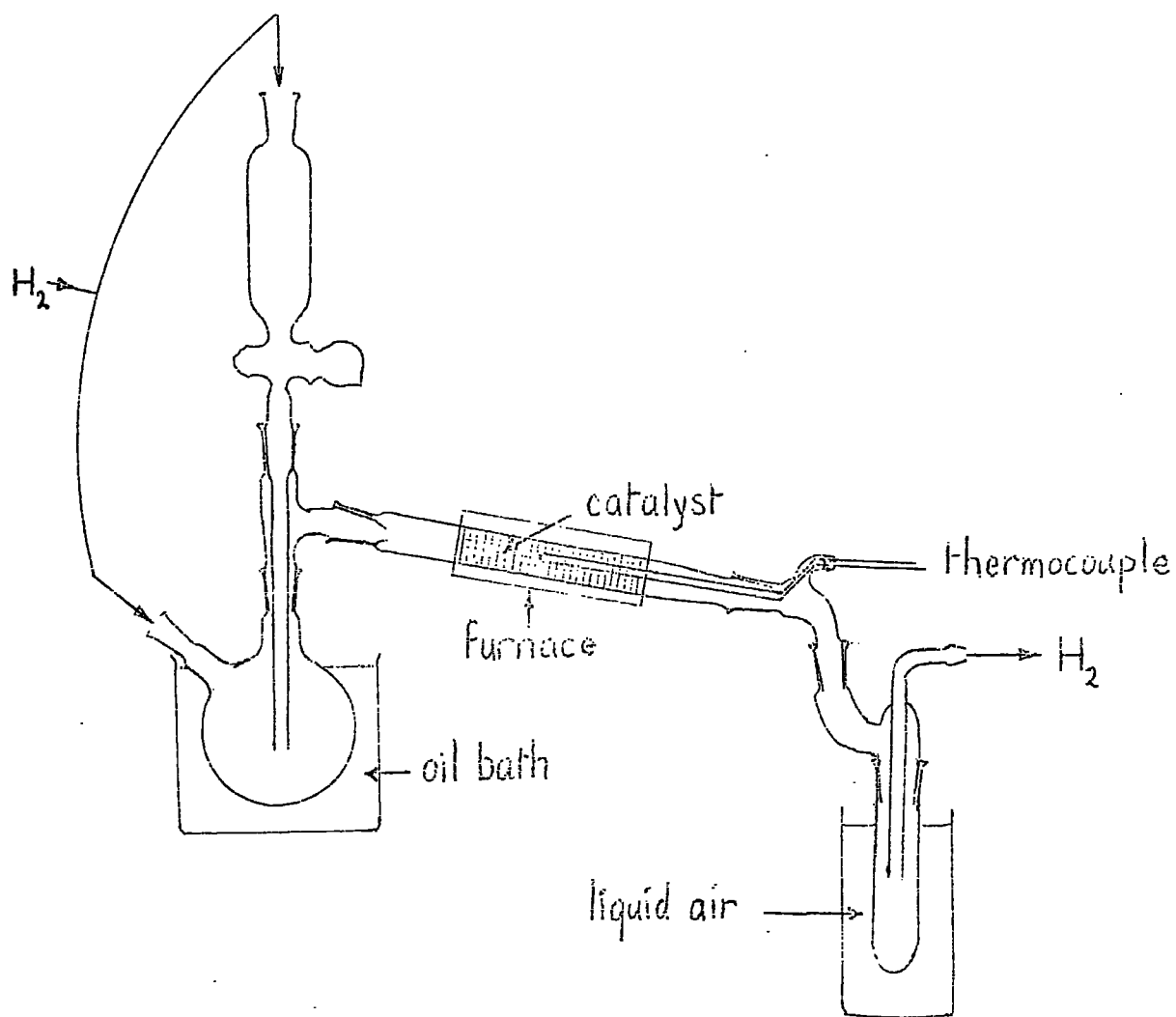


Fig. 4

was condensed by a trap cooled by liquid air, the excess hydrogen being let out of a window.

Between reactions the apparatus was stoppered and the furnace maintained at 200° - 300°C to prevent moisture being absorbed by the catalyst.

Reduction of 3-chlorotetrafluoropyridine

3-Chlorotetrafluoropyridine (4 gm., 21.6 m.moles) was dropped at a rate of 0.1 gm/min into the flash-distillation flask heated to 200°C , through which a stream of dry hydrogen (50 ml/min.) was passing. The chlorotetrafluoropyridine vaporised immediately and was carried in the gas stream over the palladised carbon catalyst heated to 250°C . Product emerging from the catalyst was condensed in a trap cooled by liquid air and then dried by distillation under vacuum from phosphorus pentoxide. This material (2.5 gm) was then separated by vapour phase chromatography, using tritolyl phosphate as stationary phase, and shown to contain approximately 80% of 2, 4, 5, 6-tetrafluoropyridine, b.pt 89° - 90° (Found: C, 40.1; F, 49.9. $\text{C}_5\text{NF}_4\text{N}$ requires C, 39.7; F, 50.3%) I.R. Spectrum No. 7 page 206

The fluorine 19 n.m.r. spectrum confirmed that migration of fluorine to the 3-position had not occurred during the process. The spectrum showed four chemically shifted groups of peaks, of equal intensity, two of which were broad and at low field (indicating the proximity to the ^{14}N nucleus):

$\delta = 67.6$ p.p.m. (2-F, shifted to lower field due to adjacent hydrogen);
83.3 p.p.m. (6-F); 113.1 p.p.m. (5-F); 99.2 p.p.m. (4-F).

These chemical shifts were measured relative to CFCl_3 as internal reference.

Also present in the product (5%) was 2, 5, 6-trifluoropyridine
b.pt $115^\circ - 116^\circ\text{C}$ (Found: C, 45.2; F, 42.6. $\text{C}_5\text{H}_2\text{F}_3\text{N}$ requires C,
45.1; F, 42.9%) I.R. Spectrum No. 8. page 206.

The fluorine - 19 n.m.r. spectrum showed three chemically shifted
peaks of equal intensity, two of which were broad and to low field,
indicating the proximity to the ^{14}N nucleus;

$\delta = 74.4$ p.p.m. (2-F); 88.69 p.p.m. (6-F); and 147.4 p.p.m. (5-F),
relative to CFCl_3 as internal reference.

Experiments in which a higher flow of hydrogen and/or a greater
rate of addition of 3-chlorotetrafluoropyridine were used tended to
result in small amounts of starting material being recovered unreacted
together with the product, from the liquid air cooled trap.

An increase in the temperature of the catalyst caused a greater
proportion of 2, 5, 6-trifluoropyridine to be formed.

Reduction of 3, 5-dichlorotrifluoropyridine

a) Using the same technique as that employed in the previous
experiment, 3, 5-dichlorotrifluoropyridine (5 gm., 25 m.moles) was
flash-distilled at 240° and passed, in a stream of dry hydrogen

(80 ml/min), over the catalyst at 280°C.

The product was 2, 4, 6-trifluoropyridine, b.pt 94° - 95°C (75% yield). (Found: C, 44.7; F, 43.3. $C_5H_2F_3N$ requires C, 45.1; F, 42.9%). I.R. Spectrum No. 9. page 206.

The fluorine -19 n.m.r. spectrum confirmed that no migration of fluorine had taken place. The spectrum was approximately the AXX' part off an APP'XX' system and contained two chemically shifted groups of peaks of intensity 2:1 and the peak due to the 2- and 6-fluorine atoms was broadened due to the ^{14}N nucleus. The peak due to the 4-fluorine was a triplet of triplets, showing the coupling that would be expected from an ortho proton and a meta fluorine atom.

$\delta = 65.05$ p.p.m. (2- and 6-F); 93.15 p.p.m. (4-F)

$J = 19.7 \pm 0.2$ c/s = $J_{F.F. \text{ meta}}$; $J = 7.6 \pm 0.2$ c/s = $J_{F.H. \text{ ortho}}$.

Also, the proton spectrum showed a pair of triplets and demonstrated the same ortho H-F coupling constant as indicated above;

$\delta = 6.61$ p.p.m.; $J = 1.2 \pm 0.1$ c/s = $J_{H.F. \text{ para}} = J_{H.H. \text{ meta}}$;

$J = 7.5 \pm 0.1$ c/s = $J_{H.F. \text{ ortho}}$.

The ^{19}F and 1H chemical shifts were recorded with reference to $CFCl_3$ and Me_4Si respectively, as internal standard.

b) Using the same technique as that employed in the previous experiment, 3, 5-dichlorotrifluoropyridine (15 gm. 75 m.moles) was flash-distilled at 240°C and passed, in a stream of dry hydrogen (100 ml/min), over the catalyst at 290°C.

The product (10 gm) was shown by analytical scale v.p.c. (di-n-decyl phthalate as stationary phase, 100°C) to contain three components, the one present in least amount having a retention time coincident with 2, 4, 6-trifluoropyridine. The unknown components were isolated by preparative scale v.p.c. using di-n-decyl phthalate as stationary phase at 120°C and shown to be:-

i) 3-chloro-2, 4, 6-trifluoropyridine, b.pt $128^{\circ} - 129^{\circ}\text{C}$ (Lit¹., b.pt $128^{\circ} - 129^{\circ}\text{C}$). (Found: C, 36.1; H, 0.61; F, 34.0; Cl, 21.1. $\text{C}_5\text{HClF}_3\text{N}$ requires C, 35.8; H, 0.60; F, 34.0; Cl, 21.2%).

I.R. Spectrum No. 11. page 207.

The fluorine -19 n.m.r. spectrum showed each fluorine to have hydrogen or chlorine neighbours but no fluorine neighbour. The structure of this compound is determined from the magnitude of the chemical shifts. The effect of introducing chlorine and hydrogen into a pyridine nucleus in place of fluorine atoms is to displace the neighbouring fluorine resonances to low fields by predictable amounts.² In this case the 2- and 6-fluorine chemical shifts become 67.6 p.p.m. and 65.0 p.p.m. and the 4-fluorine becomes 93.0 p.p.m. with respect to CFCl_3 as internal reference.

and ii) 2, 6-difluoropyridine, b.pt. 124°C (lit.,³ b.pt $122^{\circ} - 124.5^{\circ}\text{C}$ (Found: C, 51.6; H, 2.28; F, 32.7. Calculated for $\text{C}_5\text{H}_3\text{F}_2\text{N}$ C, 52.1; H, 2.61; F, 33.0%). I.R. Spectrum No 10. page 207.

The fluorine -19 spectrum showed a single broad peak of chemical shift 66.5 p.p.m. with respect to CFCl_3 , corresponding to fluorine in the α -position. The composition of the original product was estimated by analytical scale v.p.c. to be $\text{C}_5\text{HClF}_3\text{N}$, 50; $\text{C}_5\text{H}_2\text{F}_3\text{N}$, 20; $\text{C}_5\text{H}_3\text{F}_2\text{N}$ 30 mole - %

Reduction of Pentafluoropyridine

Pentafluoropyridine (5 gm) was flash-distilled at 180°C during 2 hrs in a stream of dry hydrogen (60 ml/min) over the catalyst at 320°C . The product (2.6 gm) was condensed out, dried by distillation under vacuum from P_2O_5 , and shown by analytical-scale v.p.c. (di-n-decyl phthalate as stationary phase 100°C) to contain four components, the largest of which was unreacted starting material. The other components were isolated by preparative scale v.p.c. (di-n-decyl phthalate, 100°C) and shown to be:

i) 2, 3, 5, 6-tetrafluoropyridine (30% yield), b.pt $98-99^\circ\text{C}$.

(Found: C, 39.9; mol. wt. 152. $\text{C}_5\text{HF}_4\text{N}$ requires C, 39.7%; mol. wt. 151).

The infra red spectrum (No. 12 page 207) of this compound was identical to that of a sample obtained by the reaction of lithium aluminium hydride on pentafluoropyridine.⁴ The fluorine-19 n.m.r. spectrum was typical of that of the PP'XX' part of an APP'XX' system. This can only occur if the system has a two fold axis of symmetry,

i.e. the substituent is in the 4-position.

Two chemically shifted groups of peaks were obtained.

$\delta = 92.28$ p.p.m. (2-, 6-F), broadened by the ^{14}N nucleus, and 140.97 p.p.m. (3-, 5-F) with respect to CFCl_3 as internal reference.

ii) 3, 4, 5, 6-tetrafluoropyridine (5% yield), b.pt $87^\circ - 88^\circ\text{C}$.

(Found: C, 39.5; F, 50.2. $\text{C}_5\text{HF}_4\text{N}$ requires C, 39.7; F, 50.3%).

Infra Red Spectrum No. 13, page 208.

The fluorine-19 n.m.r. spectrum showed four chemically shifted groups of peaks of equal intensity only one of which was broad and at low field.

$\delta = 83.9$ p.p.m. (broad, 6-F), 140.5 p.p.m. (4-F), 157.9 p.p.m. (5-F), and 148.8 p.p.m. (3-F shifted to lower field due to adjacent hydrogen).

The proton spectrum showed only one complex chemically shifted group of peaks.

iii) The other component (<1% yield) was probably 2, 4, 5, 6-tetrafluoropyridine, as this product had a retention time identical to that of an authentic sample of 2, 4, 5, 6-tetrafluoropyridine.

Since the v.p.c. retention times of pentafluoropyridine and 3, 4, 5, 6-tetrafluoropyridine were very similar, it was advantageous to have as large a proportion as possible of this hydro-

fluoro compound to facilitate the chromatographic separation of these components, i.e. a very small amount of 3, 4, 5, 6-tetrafluoropyridine would not be resolved from the "tail" of a large peak due to pentafluoropyridine.

Because of the conversion of pentafluoropyridine to hydrogen containing compounds from a single passage over the catalyst was low, it was found necessary to recycle the product ~~th~~^hrough the reductor until the proportion of 3, 4, 5, 6-tetrafluoropyridine relative to pentafluoropyridine was such that a v.p.c. separation could be effected. Usually, two or three recycling operations were sufficient, but obviously the larger the number of such procedures the greater the amount of decomposition which occurred.

When reaction temperatures lower than 320°C were used, the amount of replacement of fluorine by hydrogen was less. Thus, when pentafluoropyridine was passed over the catalyst at 250°C on a current of hydrogen, (60 ml/min), the yield of products was 2, 3, 5, 6-tetrafluoropyridine, 15%, and 3, 4, 5, 6-tetrafluoropyridine, $\sim 3\%$.

In experiments where catalyst temperatures higher than 320°C were used, excessive decomposition occurred giving very poor yields of hydrofluorocompounds.

Considerably more decomposition took place when pentafluoropyridine was passed through the reductor than when either of the chlorine containing compounds were reduced. The extent of breakdown,

with the subsequent formation of hydrogen fluoride, was such that after the passage of approximately 50 gms of pentafluoropyridine the catalyst became poisoned and inefficient, necessitating its replacement together with the silica tube which was corroded to wafer thickness.

Attempted Sulphonation of Hydrofluoropyridines

2, 4, 5, 6-Tetrafluoropyridine and Oleum

2, 4, 5, 6-Tetrafluoropyridine (1 gm) and oleum (20% SO_3 , 10 gm) were stirred for 48 hours at room temperature and then poured carefully on to crushed ice (200 gm). This was ether extracted continuously for 24 hours, the ether extract dried, and the solvent removed by distillation. The residue was shown by analytical-scale v.p.c. to contain unreacted 2, 4, 5, 6-tetrafluoropyridine. Addition of water and barium carbonate to the residue did not yield barium tetrafluoropyridine sulphonate.

2, 4, 6-Trifluoropyridine and Oleum

2, 4, 6-Trifluoropyridine (0.3 gm) and oleum (20% SO_3 , 9 gm) were stirred for 6 days at room temperature and then poured on to crushed ice (100 gm). This was ether extracted continuously for 24 hours, the ether extract dried, and the solvent removed by distillation. The residue was shown by analytical scale v.p.c. to contain unreacted 2, 4, 6-trifluoropyridine. Addition of water and barium carbonate to the residue did not yield a barium fluoropyridine sulphonate.

2, 4, 6-Trifluoropyridine and Oleum

2, 4, 6-Trifluoropyridine (0.5 gm) and oleum (20% SO_3 , 4 gm) were heated in a carius tube to 200°C for 24 hrs. Only decomposition products were obtained when the tube was opened.

Preparation of Polyfluoro- and Perfluoro-pyridine Lithium Derivatives

2, 4, 5, 6-Tetrafluoropyridine and Butyl Lithium in Hexane

2, 4, 5, 6-Tetrafluoropyridine (0.5 gm., 3.3 m.moles), and butyl lithium (10.0 m.moles) in hexane (4 mls) were placed in the separate limbs of a Zeriwittenoff flask, filled with dry nitrogen and connected to a gas burette. The limbs were cooled to -65°C and the reactants quickly mixed by pouring from one limb to the other. A violent reaction occurred, with the liberation of a large volume of gas and the formation of a brown solid polymeric material. I.R. Spectroscopy suggested that this polymer was made up of fluoropyridyl units, similar to the polymers obtained by the decomposition of fluoropyridine Grignard reagents.

2, 4, 5, 6-Tetrafluoropyridine and Butyl Lithium, followed by

Carbonation

2, 4, 5, 6-Tetrafluoropyridine (0.4 gm, 2.6 m.moles) in dry hexane (5 ml), and butyl lithium (5.0 m.moles) in dry hexane (5 ml) were placed in the separate limbs of a Zeriwittenoff flask, filled with dry nitrogen and connected to a gas burette. The limbs were cooled to -75°C , and the butyl lithium solution added slowly to the solution of 2, 4, 5, 6-tetrafluoropyridine. The mixture was allowed to warm slowly to 0°C when a violent reaction occurred.

Immediately, dry carbon dioxide was passed into the dark reaction mixture for 1 hr. Dilute hydrochloric acid (10 ml) was added, and the brown solid, which was insoluble in both the aqueous and organic layer, was filtered and dried under vacuum, I.R. Spectroscopy showed this polymeric material (0.4 gm) to contain, carboxyl, hydroxyl and fluoropyridyl functions by the presence of their characteristic absorption bands. This material was very similar to the polymeric pyridine carboxylic acids produced by carbonation of fluoropyridyl Grignard reagents.

The hexane layer was shown to contain no tetrafluoronicotinic acid.

2, 4, 5, 6-Tetrafluoropyridine and Butyl Lithium, followed by

Carbonation

Butyl lithium (3.3 m.moles) in dry hexane (1 ml) was added to a stirred solution of 2, 4, 5, 6-tetrafluoropyridine (0.5 gm, 3.3 m.moles) in dry hexane (5 ml) at -60°C and under an atmosphere of dry nitrogen in the apparatus shown in Fig. 5. After 15 minutes a dense white precipitate, presumably the lithio-derivative, had formed and while the temperature was maintained at -60°C , dry carbon dioxide was passed into the reaction mixture for 30 minutes. Then the mixture was allowed to warm up to room temperature while the introduction of CO_2 continued. Water (5 ml) was added and, on stirring, the white precipitate dissolved, then, on the addition of

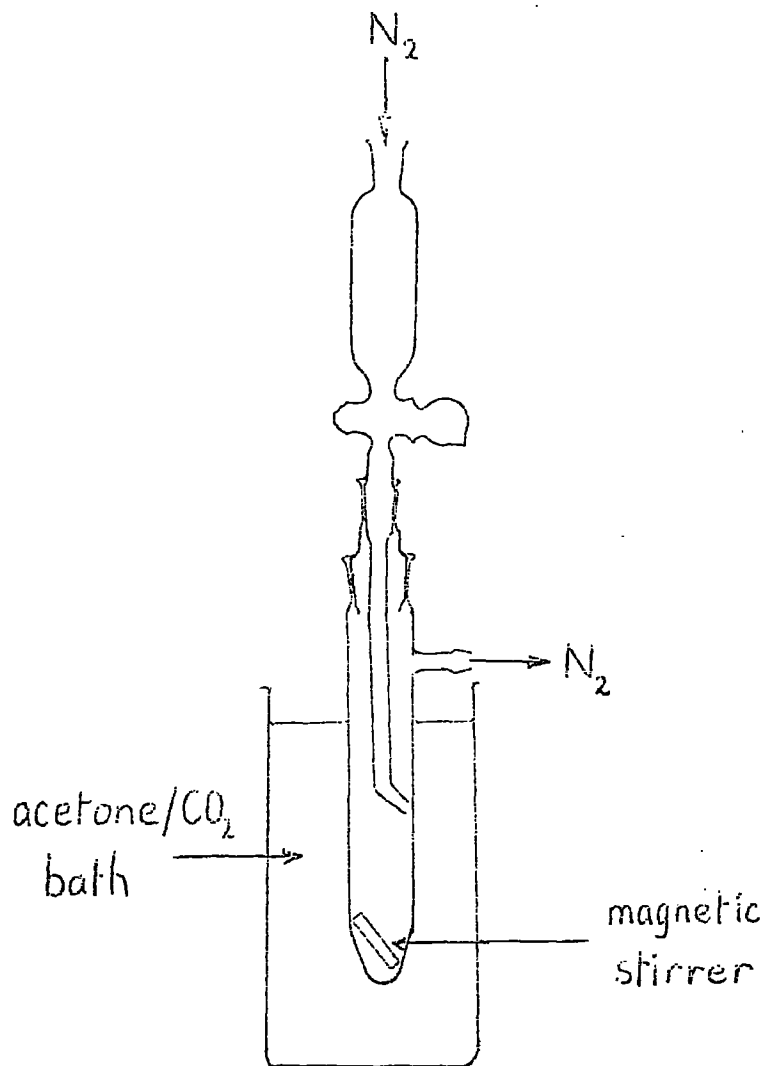


Fig. 5

dilute hydrochloric acid (5 ml), a further white precipitate was formed which quickly redissolved. The mixture was extracted with ether, the organic ethereal layer separated and dried (MgSO_4) and then solvent was removed by distillation leaving 2, 4, 5, 6-tetrafluoronicotinic acid (0.4 gm, 62% yield) which, after vacuum sublimation ($55^\circ\text{C} / 10^{-5}$ mm) and recrystallisation (hexane) gave a m.pt $121^\circ - 122^\circ\text{C}$. (Found: C, 37.1; F, 38.6; eq. wt. 191. $\text{C}_6\text{HF}_4\text{NO}_2$ requires C, 36.9; F, 38.9%; eq.wt. 195). pKa 3.45. I.R. Spectrum No. 14, page 208.

2, 4, 5, 6-Tetrafluoropyridine and Methyl lithium

Methyl lithium (3.3 m.moles) and dry diethyl ether (6.6 ml) was added to a stirred solution of 2, 4, 5, 6-tetrafluoropyridine (0.5 gm, 3.3 m.moles) in dry tetrahydrofuran (5.5 ml) at -70°C , and under an atmosphere of dry nitrogen. The reaction temperature was allowed to mix slowly to that of the room, during which time 41.0 ml. of gas (CH_4) were evolved.

Water (10 ml) was added, the organic layer separated, dried (MgSO_4) and the solvent removed by distillation leaving a yellow solid residue (0.2 gm). This solid was soluble in T.H.F. but insoluble in diethyl ether. I.R. Spectroscopy (I.R. Spectrum No. 20, page 210) suggested that the compound was made up of fluoropyridyl units.

The average molecular weight of these polyperfluoropyridylenes

was determined by vapour pressure osmometry to be 1230. Considering that $[\text{C}_5\text{NF}_3] = 131$, it would seem that the average polymer molecule was made up of approximately 9 - 10 peryfluoropyridyl units.

When this experiment was repeated, but carbon dioxide bubbled into the reaction mixture after the temperature had risen from -70° to 0°C , the same product was obtained. Thus, no reactive lithium remained in the molecule at 0°C as this would have been carbonated and the characteristic carboxyl absorption bands would have been observed in the i.r. spectrum of the product.

Preparation of Polyfluoropyridine Carboxylic Acids

2, 4, 5, 6-Tetrafluoronicotinic acid

2, 4, 5, 6-Tetrafluoropyridine (1 gm, 6.6 m.moles) in dry diethyl ether (8 ml) added slowly to a stirred solution of butyl lithium (6.6 m.moles) in a mixed solvent, (hexane (2ml)/Ether (10 ml)) at -70°C and under an atmosphere of dry nitrogen. The temperature was allowed to rise to -60°C , when a brown colouration developed, during 15 minutes then dry carbon dioxide was passed into the reaction while the temperature was at -60°C . A dense white precipitate formed and the temperature was allowed to rise to that of the room while the introduction of CO_2 continued. Water (10 ml) was added and, on stirring, the precipitate dissolved. The mixture was transferred to a separating funnel and dil. HCl (10 ml), followed by conc. HCl (5 ml), was added. This was then extracted with ether, the extracts dried (MgSO_4), and the solvent removed by distillation to leave white crystals of crude 2, 4, 5, 6-tetrafluoronicotinic acid (1.15 gm., 99% crude yield). Vacuum sublimation and recrystallisation from hexane afforded the pure compound m.pt $121^{\circ} - 122^{\circ}\text{C}$.

2, 3, 5, 6-Tetrafluoroisonicotinic acid

Butyl lithium (3.3 m.moles) in dry hexane (1 ml) was added with stirring to a solution of 2, 3, 5, 6-tetrafluoropyridine (0.5 gm,

3.3 m.moles) in hexane (18 ml) at -55°C , as described above. After 20 minutes a precipitate had formed and then the temperature was lowered to -60°C before carbon dioxide was passed into the reaction. The introduction of CO_2 was continued as the temperature was allowed to rise to that of the room. Water (5 ml) was added, followed by dilute hydrochloric acid (5 ml). Then the mixture was extracted with ether, the ethereal solution dried (MgSO_4) and when solvent was removed by distillation 2, 3, 5, 6-tetrafluoroisonicotinic acid (0.32 gm, 50%) was obtained which, after vacuum sublimation (55°C) and recrystallisation from hexane gave m.pt $102^{\circ} - 103^{\circ}\text{C}$. (Found: eq.wt. 192. Calculated for $\text{C}_6\text{HF}_4\text{O}_2\text{N}$ eq.wt. 195); the I.R. Spectrum (No. 15 page 208) and m.pt. were identical with those of an authentic specimen of the acid.⁵ p.k.a 3.21.

3, 4, 5, 6-Tetrafluoropicolinic acid

Butyl lithium (3.0 m.moles) in a mixed solvent, (hexane (1 ml)/ ether (5 ml)), was added slowly to a stirred solution of 2, 3, 4, 5-tetrafluoropyridine (0.3 gm, 1.8 m.moles) in dry diethyl ether (10 ml) at -78°C and under an atmosphere of dry nitrogen. The temperature was allowed to rise to -70°C when a very deep purple colouration developed. After maintaining the reaction at -70°C for a further 15 minutes, dry carbon dioxide was introduced. The mixture became very dark in colour but as the temperature was allowed to rise to that of the room, with CO_2 passing, the colour lightened to give a

clear pale purple solution. Water (5 ml) was added, followed by dilute hydrochloric acid (10 ml), and the mixture was transferred to a separating funnel, where the organic layer was separated. The remaining aqueous layer was made strongly acid, with hydrochloric acid, and ether extracted. The organic solutions were combined, dried (MgSO_4), and the solvent removed by distillation leaving a viscous liquid residue. This smelled strongly of valeric acid, presumably produced by the carbonation of excess butyl lithium in the reaction. The viscous residue was heated under vacuum causing 3, 4, 5, 6-tetrafluoropicolinic acid (0.2 gm, 57% crude yield) to sublime at 50°C . After recrystallisation from hexane this gave a white solid m.pt $109^\circ - 110^\circ\text{C}$.

(Found: C, 36.9; F, 38.7; eq.wt. 192. $\text{C}_6\text{HF}_4\text{O}_2\text{N}$ requires C, 36.9; F, 38.98%; eq.wt. 195). p.k.a 3.96

I.R. Spectrum No. 16 page 209.

2, 4, 6-Trifluoronicotinic acid

Butyl lithium (6.4 m.moles) in dry hexane (2 ml) was added to a stirred solution of 2, 4, 6-trifluoropyridine (0.425 gm, 3.2 m.moles) in dry hexane (6 ml) at -60°C and under an atmosphere of dry nitrogen. The reaction mixture was maintained at -60°C for 30 minutes, during which time a dense white precipitate formed, and then carbonated as previously described. After warming to room temperature, water (5 ml), followed by dilute hydrochloric acid (20 ml) was added and then the

organic layer was separated. The aqueous layer was further extracted with ether, the organic layers combined, dried (MgSO_4), and the solvent distilled leaving a crystalline residue of 2, 4, 6-trifluoronicotinic acid (0.4 gm, 65% yield) which, after sublimation under vacuum and recrystallisation from hexane, gave m.pt $125^\circ - 126^\circ\text{C}$.

(Found: C, 40.3; F, 32.2; eq.wt. 175. $\text{C}_6\text{H}_2\text{F}_3\text{NO}_2$ requires C, 40.6; F, 32.3%; eq.wt. 177) p.k.a 3.55.

I.R. Spectrum No. 7 page 209.

2, 4, 6-Trifluoropyridine -3, 5-dicarboxylic acid

2, 4, 6-Trifluoropyridine (0.85 gm, 6.4 m.moles) in dry tetrahydrofuran (3 ml) was added slowly to a stirred solution of butyllithium (19.2 m.moles) in hexane (6 ml) and tetrahydrofuran (10 ml) at -75°C and under an atmosphere of dry nitrogen. After 5 minutes a dense pale orange precipitate formed and the temperature was maintained at -75°C for a further 15 minutes and then dry carbon dioxide, diluted with an equal volume of nitrogen, was passed into the mixture. Initially a dark crimson colour was formed which turned dark brown and the reaction mixture solidified to a stiff paste. Continued passage of CO_2 caused the dark colouration to disappear and as the temperature was allowed to rise to that of the room, the reaction mixture became fluid. Water (5 ml) was added, followed by dilute hydrochloric acid (50 ml) and the organic layer was removed.

The aqueous layer was extracted with ether (2 x 25 ml) and the combined organic layers was dried (MgSO_4) and the solvent removed by distillation leaving a solid (0.6 gm). When this solid was heated to 50°C under high vacuum a white solid sublimed (0.25 gm) and both the m.pt and infra red spectrum of this compound were identical with those of an authentic specimen of 2, 4, 6-trifluoronicotinic acid. The remaining solid was heated to 140°C also under high vacuum when it was observed to sublime slowly, and gave 2, 4, 6-trifluoropyridine -3, 5-dicarboxylic acid, m.pt 218°C (decomp). (Found: C, 38.2; F, 25.5; eq.wt. 111.8. $\text{C}_7\text{H}_2\text{F}_3\text{NO}_4$ requires C, 38.1; F, 25.7%; eq.wt. 110.5). p.k_a 3.33. I.R. Spectrum No. 18 page 209.

When this exchange reaction in tetrahydrofuran was carried out at temperatures higher than -75°C , poor yields of 2, 4, 6-trifluoronicotinic acid were obtained and no dicarboxylic acid was isolated. The main product was involatile polymeric pyridine carboxylic acids similar to those obtained from the carbonation of decomposing fluoropyridyl Grignard reagents and fluoropyridyl lithium derivatives.

2, 5, 6-Trifluoropyridine-3, 4-dicarboxylic acid

2, 5, 6-Trifluoropyridine (0.30 gm, 2.26 m.moles) was dissolved in tetrahydrofuran (10 ml), the solution cooled to -78°C and then n-butyl lithium (6 m.moles) dissolved in a mixed solvent (hexane

(2 ml)/T.H.F. (6 ml)) was added slowly with stirring at -78°C . The reaction temperature was allowed to rise to -70°C over 15 minutes when dry carbon dioxide was passed into the mixture. The passage of carbon dioxide was continued while the temperature of the mixture was allowed to rise to that of the room. Dilute hydrochloric acid (5 ml) was added, and the mixture transferred to a separating funnel and then conc. HCl (10 ml) was added. After ether extraction, the extracts were combined, dried (MgSO_4), filtered, and the solvent removed by distillation leaving a viscous brown liquid residue. This was heated "in vacuo" to 50°C when a white solid (0.08 gm) sublimed. This was probably 2, 5, 6-trifluoropyridine-3-carboxylic acid and/or 2, 5, 6-trifluoropyridine-4-carboxylic acid. Further heating of the residue to 140°C "in vacuo" caused a tacky solid (0.2 gm, 42% crude yield) to sublime. This was recrystallised with difficulty from benzene to give a compound of m.pt $160^{\circ} - 5^{\circ}\text{C}$.

(Found: eq.wt. 114. $\text{C}_7\text{H}_2\text{F}_3\text{NO}_4$ requires eq.wt. 110.5)

This gave a mixed m.pt with an authentic sample of 2, 5, 6-trifluoropyridine-3, 4-dicarboxylic acid (prepared by the oxidative degradation of perfluorosisquinoline⁶) of $160^{\circ} - 5^{\circ}\text{C}$, causing no depression in the melting point of the authentic specimen.

The infra red spectrum of this compound prepared in this experiment was identical to that of an authentic sample of 2, 5, 6-trifluoropyridine-3, 4-dicarboxylic acid. pKa 3.30.

I.R. Spectrum No. 19 page 210.

Determination of p.k.a values of Polyfluoropyridine Carboxylic acids

Equivalent weights and p.k.a values of the carboxylic acids in aqueous solution were determined by potentiometric titration against standard sodium hydroxide solution, using an E.I.L. pH meter and calomel and glass electrodes. p.k.a was given by the pH value at half equivalence point according to the Henderson equation.

A typical determination is described below.

The determination of p.k.a and equivalent weight of 2, 4, 6-Trifluoro-nicotinic acid

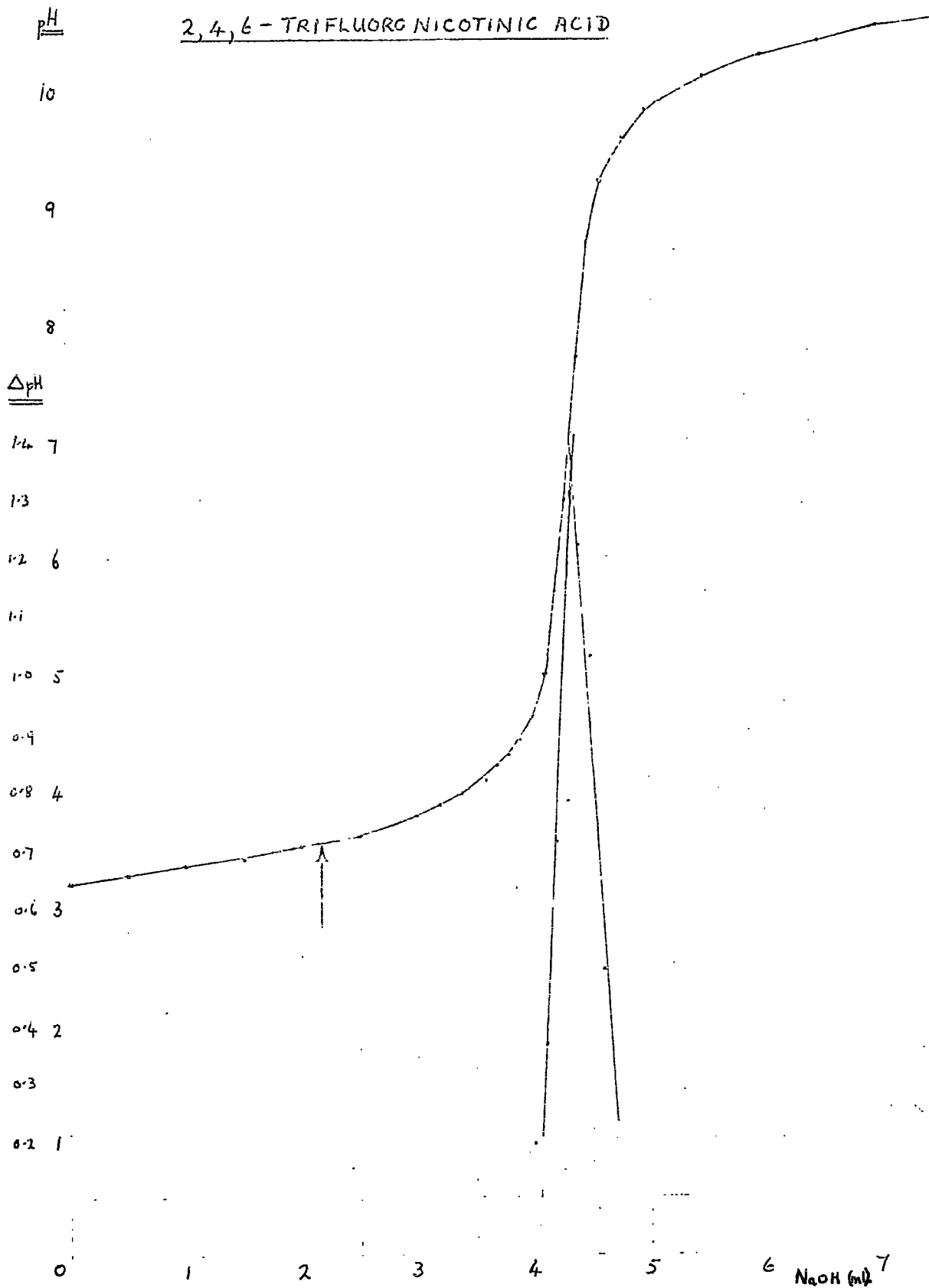
A known weight of 2, 4, 6-trifluoronicotinic acid was dissolved in distilled water (100 ml) and this solution titrated against standard sodium hydroxide solution. A graph of pH vs volume of NaOH soln added was drawn, and the end point determined by the maximum value of Δ pH.

Wt. of 2, 4, 6-trifluoronicotinic acid = 0.0160 gm.

Sodium hydroxide solution = 0.02100 N.

DETERMINATION OF pK_a AND EQ. WT. OF

2,4,6-TRIFLUORONICOTINIC ACID



NaOH (ml)	pH	Δ pH	NaOH (ml)	pH	Δ pH
0	3.22		4.2	5.70	0.71
0.5	3.29		4.3	6.48	0.78
1.0	3.36		4.4	7.70	1.22
1.5	3.42		4.5	8.73	1.03
2.0	3.51		4.6	9.22	0.49
2.5	3.61		4.8	9.60	
3.0	3.79		5.0	9.84	
3.2	3.89		5.5	10.12	
3.4	3.99		6.0	10.30	
3.6	4.09		6.5	10.41	
3.7	4.21		7.0	10.52	
3.8	4.30		7.5	10.60	
3.9	4.44		8.0	10.67	
4.0	4.63	0.19	8.5	10.72	
4.1	4.99	0.34	9.0	10.79	

From the graph:- End pt. = 4.35 ml NaOH soln.

$$\therefore \text{Eq.Wt.} = \frac{0.0160 \times 1000}{4.35 \times 0.02100}$$

$$\text{Eq.Wt.} = 175 \text{ (Theoretical eq.wt.} = 177).$$

$$\underline{\text{pka} = \text{pH}_{2.18} = 3.55}$$

Methyl Ethyl (2, 4, 5, 6-Tetrafluoropyridyl) - Carbinol

Butyl lithium (6.6 m.moles) in hexane (2 ml) was added to a stirred solution of 2, 4, 5, 6-tetrafluoropyridine (1 gm. 6.6 m.moles) in dry hexane (5 ml) at -60°C and under an atmosphere of dry nitrogen. After 15 minutes a dense white precipitate had formed and methyl ethyl ketone (0.475 gm, 6.6 m.moles) was added dropwise while maintaining the temperature at -60°C . The mixture was allowed to warm slowly to room temperature, dilute hydrochloric acid (5 ml) was added, and the organic layer was separated and dried (MgSO_4). The products were separated by preparative-scale v.p.c. (silicone grease as stationary phase, 200°C). The main product was methyl ethyl (2, 4, 5, 6-tetrafluoro-pyridyl)-carbinol b.pt. $75^{\circ} - 76^{\circ}\text{C}/13\text{ mm Hg}$; (0.7 gm. 48% yield) $n_{20}^D 1.4457$. (Found: C, 48.1; F, 34.3; H, 3.87. $\text{C}_9\text{H}_9\text{F}_4\text{NO}$ requires C, 48.3; F, 34.1; H, 4.0%).

I.R. Spectrum No. 22 page 211.

Reaction of 2, 4, 5, 6-Tetrafluoropyridyl Lithium with mercuric
bromide

2, 4, 5, 6-Tetrafluoropyridyl lithium was made as previously described, by adding butyl lithium (3.3 m.moles) in hexane (1 ml) to 2, 4, 5, 6-tetrafluoropyridine (0.5 gm, 3.3 m.moles) in hexane (10 ml) at -60°C and under an atmosphere of dry nitrogen. After 15 minutes a slurry of mercuric bromide (0.61 gm, 1.7 m.moles) in dry hexane

(10 ml) was added while maintaining the temperature at -60°C .

The reaction temperature was allowed to rise to that of the room and dilute hydrochloric acid (10 ml) was added. On stirring, part of the precipitate dissolved and the remainder was filtered (0.4 gm). The aqueous layer was extracted with hexane, the hexane solutions combined, dried (MgSO_4), and the solvent removed by distillation leaving a white crystalline solid (0.1 gm).

Both this residue and the solid obtained by filtration were sublimed ($100^{\circ}\text{C}/0.1$ mm Hg) and recrystallised from hexane but analysis and melting points demonstrated that no single pure substance was obtained by these operations. I.R. Spectroscopy showed the presence of carbon-hydrogen bonds and fluoropyridyl units in the product, which was probably a mixture of unreacted mercuric bromide and mixed alkyl and fluoropyridyl mercurials. Separation of these to yield the desired bis (2, 4, 5, 6-tetrafluoropyridyl) mercury could probably be accomplished if the experiment were performed on a larger scale.

Reaction of 2, 4, 5, 6-tetrafluoronicotinic acid and Mercuric Acetate

To a solution of 2, 4, 5, 6-tetrafluoronicotinic acid (0.5 gm, 2.56 m.moles) in water (50 ml) was added a solution of mercuric acetate (0.4 gm, 1.26 m.moles) in water (10 ml) with stirring. After 15 minutes a dense white precipitate had formed and the solution was filtered. The white solid filtrate was dried under reduced pressure

to give mercuric (2, 4, 5, 6-tetrafluoronicotinate). (0.60 gm, 81% yield) m.pt 225°C (decomp.)

(Found: C, 24.6; $\text{C}_{12}\text{F}_8\text{N}_2\text{O}_4\text{Hg}$ requires C, 24.5%)

I.R. Spectrum No. 23 page 212.

Decarboxylation of Mercuric (2, 4, 5, 6-Tetrafluoronicotinate).

Mercuric (2, 4, 5, 6-tetrafluoronicotinate) (0.45 gm, 0.76 m. moles) was heated to 230°C under reduced pressure in a sublimation apparatus when it decarboxylated smoothly and caused a white solid to sublime (0.3 gm).

This sublimate was recrystallised from carbon tetrachloride and shown to be bis (2, 4, 5, 6-tetrafluoropyridyl) mercury, m.pt $200^{\circ} - 201^{\circ}\text{C}$. (sealed tube). (79% crude yield).

(Found: C, 24.2; mol.wt. 507, vapour pressure osmometer.

$\text{C}_{10}\text{F}_8\text{N}_2\text{Hg}$ requires C, 24.0%; mol.wt. 500.6).

I.R. Spectrum No. 24 page 212.

Bis (2, 4, 5, 6-tetrafluoropyridyl) (bipyridyl) mercury

Bis (2, 4, 5, 6-tetrafluoropyridyl) mercury, (0.018 gm, 0.0036 m.moles), prepared as described above, in 1:1 v/v benzene-hexane (10 ml) was added to 2, 2'-bipyridyl (0.010 gm, 0.0072 m.moles) in benzene (1 ml). The volume of the mixture was reduced to (5 ml) by boiling and allowed to cool when white crystals began to appear. After some time, the supernatant liquid was decanted and the crystals

washed with cold benzene to remove any excess bipyridyl. The solvent was removed from the crystals under vacuum leaving pure bis (2, 4, 5, 6-tetrafluoropyridyl)(bipyridyl) mercury m.pt $142^{\circ} - 3^{\circ}$, (0.015 gm, 75% yield). Recrystallised from benzene/hexane to give m.pt 142°C .

(Found: C, 36.6; H, 1.63. $\text{C}_{20}\text{H}_8\text{F}_8\text{N}_4\text{Hg}$ requires C, 36.6; H, 1.22%).

I.R. Spectrum No. 25 page 212.

2, 4, 5, 6-Tetrafluoropyridyl Lithium and Bromine

Butyl lithium (9.0 m.moles) in hexane (3 ml) was added to a stirred solution of 2, 4, 5, 6-tetrafluoropyridine (1.2 gm, 8.0 m.moles) in hexane (25 ml) at -60°C and under an atmosphere of dry nitrogen. The temperature was maintained at -60°C for 45 minutes, then allowed to rise to -45°C when excess bromine was added. The reaction was allowed to warm to room temperature and was poured on to crushed ice. The mixture was stirred with sodium metabisulphite solution to remove the excess bromine and the organic layer was separated. The aqueous layer was extracted with ether and the organic solutions combined and dried (MgSO_4). Analytical scale v.p.c. showed the presence of butyl bromide (30 mole %), an unknown major product (40 mole %), a product (2 mole %) of identical retention time to an authentic sample of 4-bromotetrafluoropyridine, and two minor components (10 mole %) of considerably longer retention time. The major product was separated by preparative scale v.p.c. (silicone elastomer, 100°C) and shown to be 3-bromotetrafluoropyridine, b.pt $\sim 130^{\circ}\text{C}$ (decomp.) (0.4 gm 22% yield).

(Found: C, 25.8; Br, 34.4. $\text{C}_5\text{F}_4\text{BrN}$ requires C, 26.1; Br, 34.8%)

I.R. Spectrum No. 21 page 210.

This compound decomposed rapidly on standing giving a very dark blue-green colour. All attempts to isolate the compounds of long retention time failed as these too appeared to decompose, although



an i.r. spectrum of an impure sample showed that they contained the perfluoropyridyl function.

2, 4, 5, 6-Tetrafluoropyridyl Lithium with Lithium cumene peroxide

The Lithium salt of cumene hydroperoxide was prepared by adding butyl lithium (6.95 m.moles) in mixed solvent (hexane (3 ml)/ether(10 ml)) To a solution of cumene hydroperoxide (1.34 gm, 6.6 m.moles) in diethyl ether (2 ml) at -78°C and allowing to stand for 30 minutes.

2, 4, 5, 6-Tetrafluoropyridyl lithium was prepared by adding butyl lithium (6.5 m.moles) in mixed solvent (hexane(2.7 ml)/diethyl ether (10 ml)) to a stirred solution of 2, 4, 5, 6-tetrafluoropyridine (1 gm, 6.6 m.moles) in diethyl ether (10 ml) cooled to -78°C .

After allowing both reactions to stand for at least 30 minutes, lithium cumene peroxide was added slowly with stirring to the solution of tetrafluoropyridyl lithium at -78°C under an atmosphere of dry nitrogen. This mixture was allowed to warm to room temperature and dilute hydrochloric acid (10 ml) was added. The reaction mixture was then transferred to a separating funnel where conc. hydrochloric acid (10 ml) was added. The contents of the separating funnel were extracted with ether and an insoluble yellow solid (0.3 gm) was filtered. The i.r. spectrum of this solid showed it to be similar to the polyperfluoropyridylenes formed by

decomposition of 3-lithio-tetrafluoropyridine. The etherial extracts were combined and shaken with aqueous sodium bicarbonate (10%). The aqueous layer was separated, acidified with hydrochloric acid, and extracted with methylene dichloride. The combined organic extracts were dried (MgSO_4), filtered, and most of the solvent removed by distillation leaving a viscous brown liquid (0.5 gm) with a phenolic smell, which solidified at 0°C . Vacuum sublimation ($70^\circ\text{C}/2\text{ mm}$) gave a white solid (0.3 gm) which melted to a colourless viscous liquid on warming to room temperature. Analytical scale v.p.c. showed this to contain two components, the minor one (10 mole %) having a retention time identical to that of an authentic sample of 4-hydroxy-tetrafluoropyridine.

The major product (27% yield) was probably 3-hydroxy-tetrafluoropyridine although at this time of writing an elemental analysis has not yet been obtained.

I.R. Spectroscopy suggested that the mixture was of fluoropyridyl hydroxy compounds, one component being 4-hydroxy-tetrafluoropyridine.

The fluorine-19 n.m.r. spectrum confirmed the presence of 4-hydroxytetrafluoropyridine as a minor component by its characteristic chemically shifted peaks,

$\delta = 162.6\text{ p.p.m.}$ (3-, 5-F) and 90.5 p.p.m. (2-, 6-F), with respect to CCl_3F .

The main component showed four chemically shifted groups of

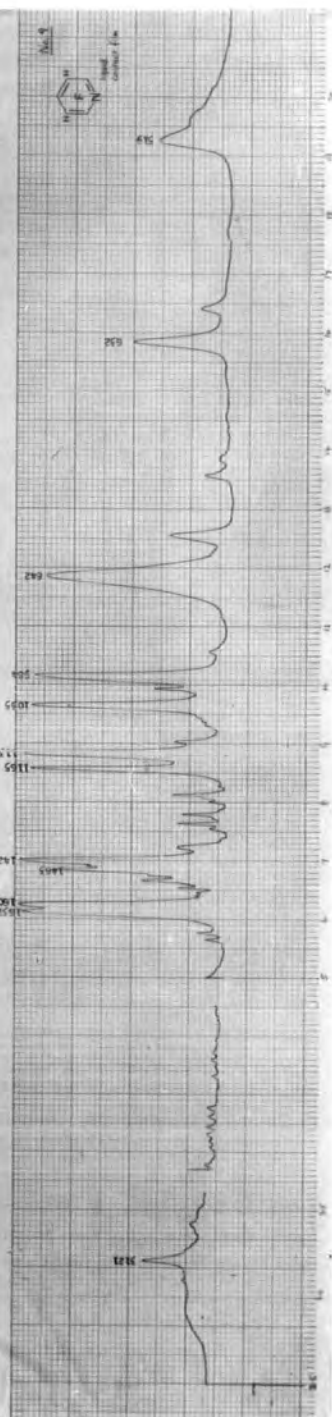
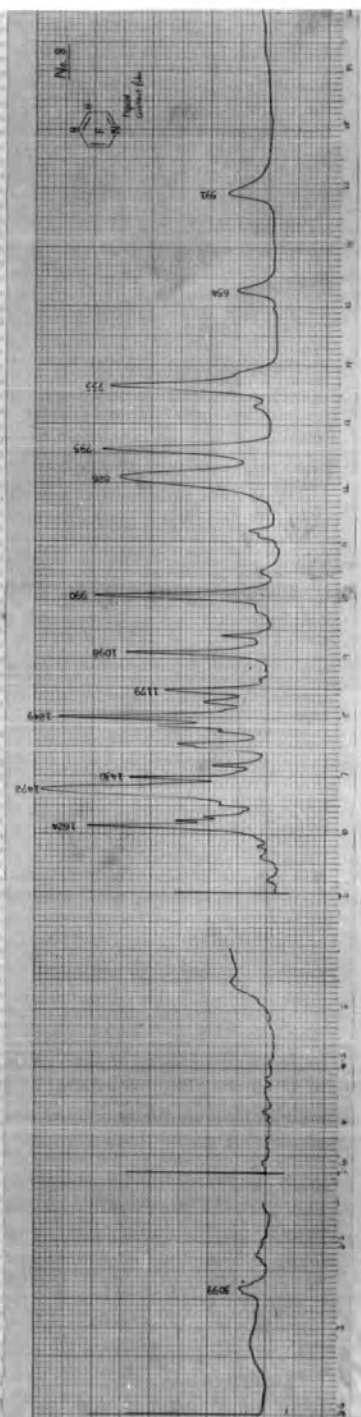
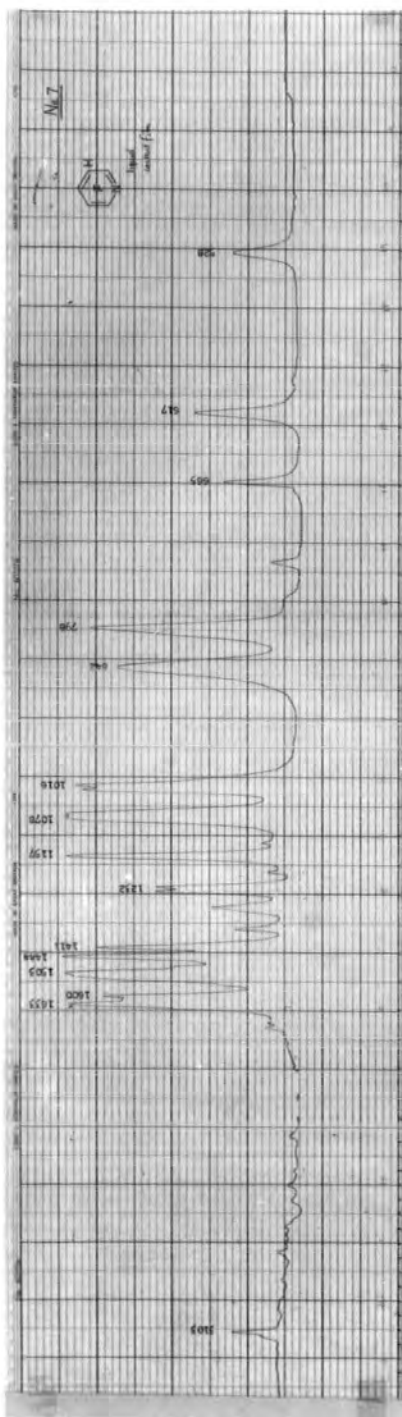
peaks of equal intensity,

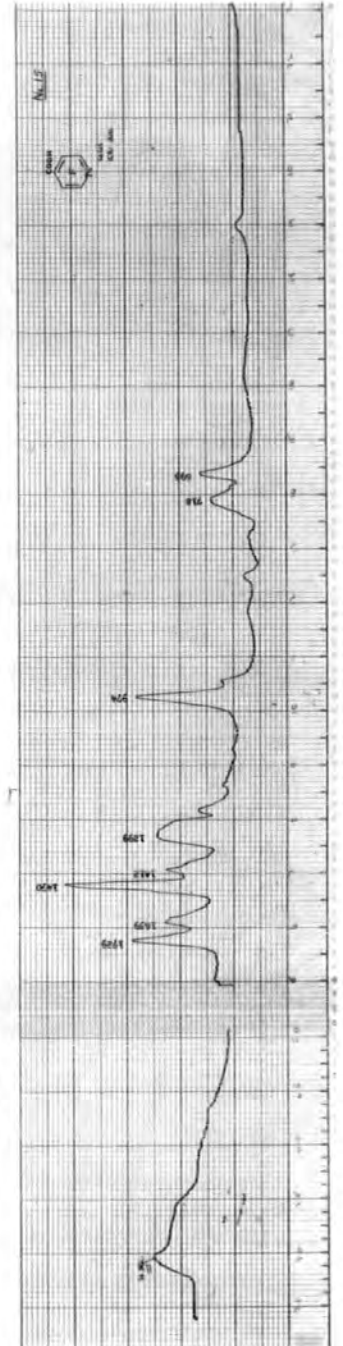
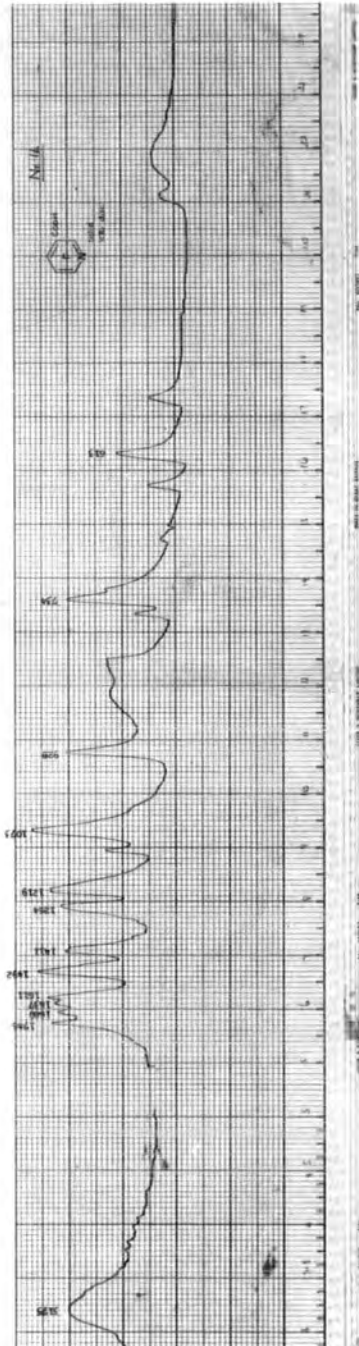
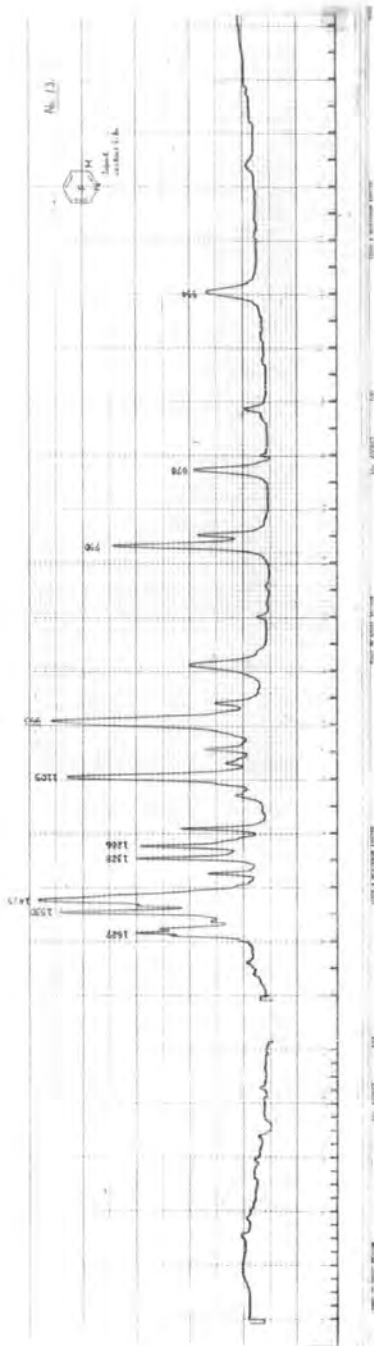
δ = 87.6 p.p.m. (6-F), 96.1 p.p.m. (2-F), 133.2 p.p.m. (4-F), and 165.2 p.p.m. (5-F) with respect of CClF_3 . These values are consistent with those expected for a 3-substituted tetrafluoropyridine.

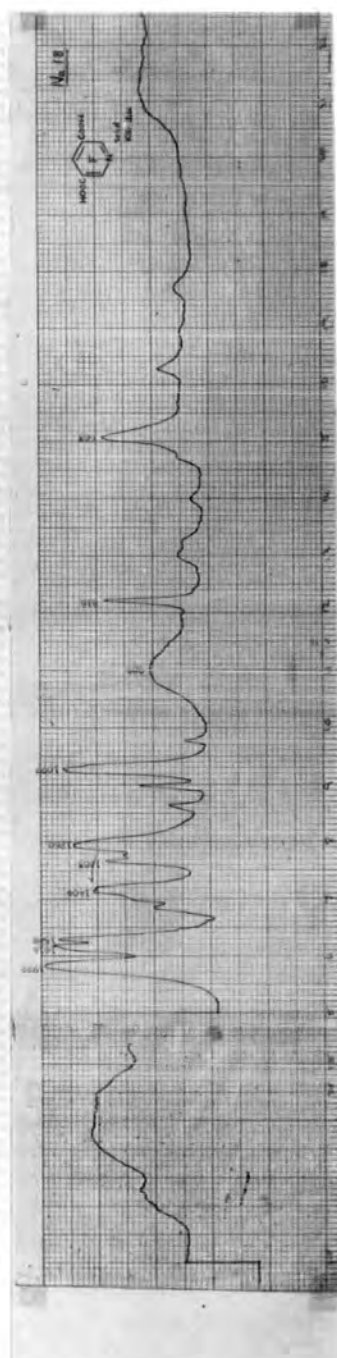
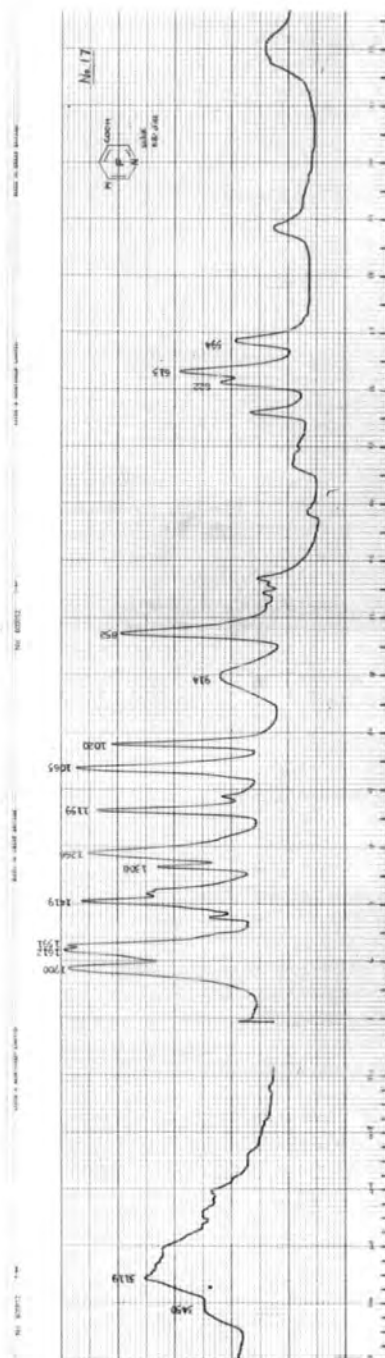
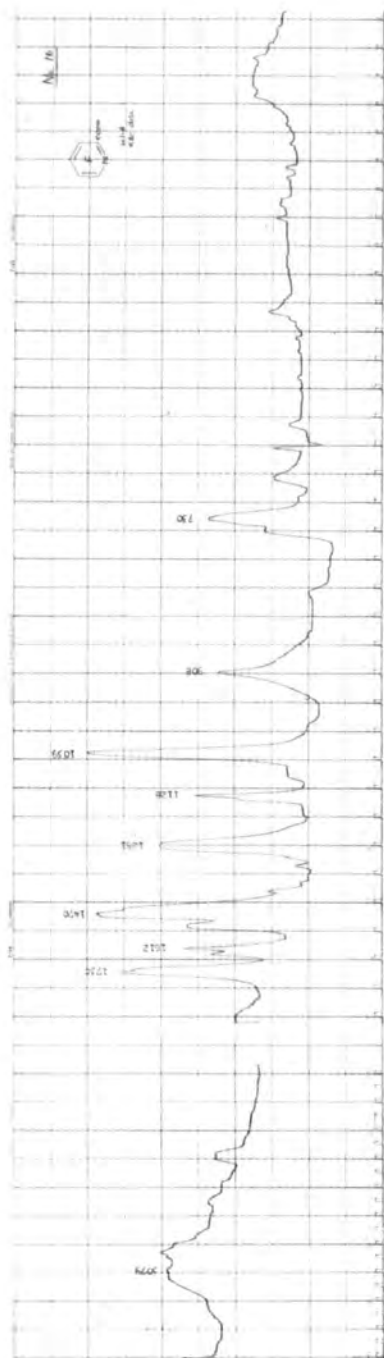
This experiment was repeated except that instead of allowing the mixture of tetrafluoropyridyl lithium and lithium cumene peroxide to warm directly to room temperature, the mixture was maintained at -50°C for 30 minutes. The product from this reaction was only 3-hydroxy-tetrafluoropyridine, i.e. no polymer and no 4-hydroxy-tetrafluoropyridine were produced.

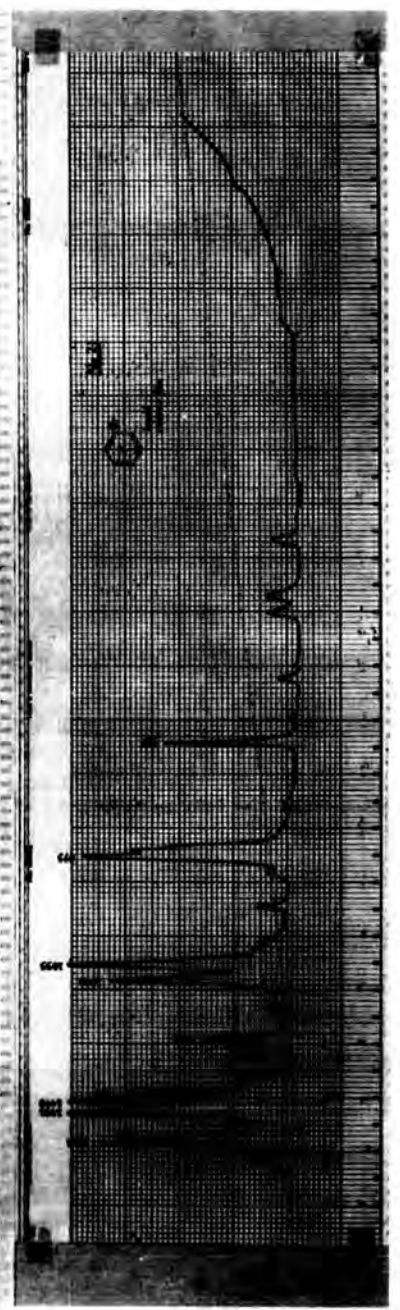
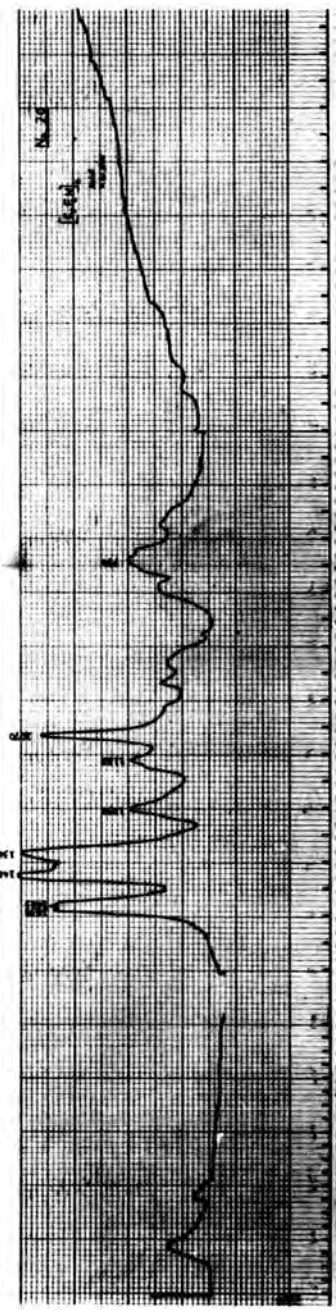
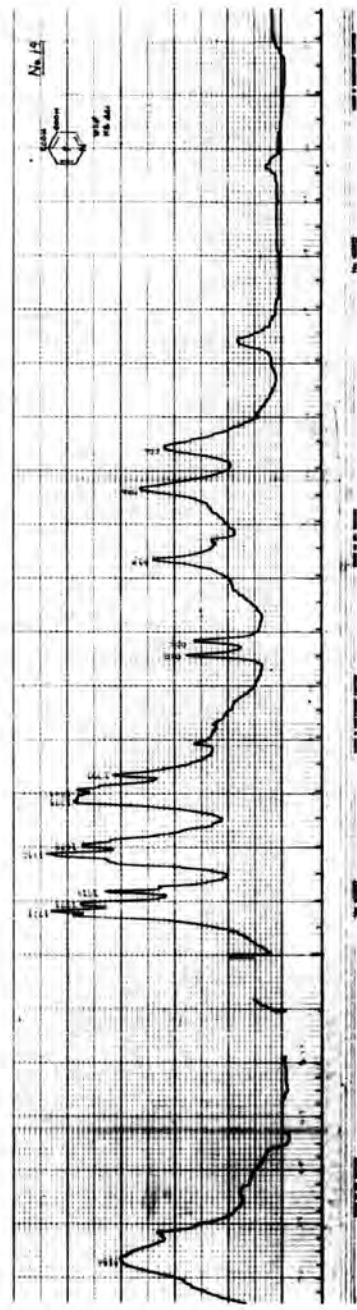
2, 4, 5, 6-Tetrafluoropyridyl Lithium with Furan

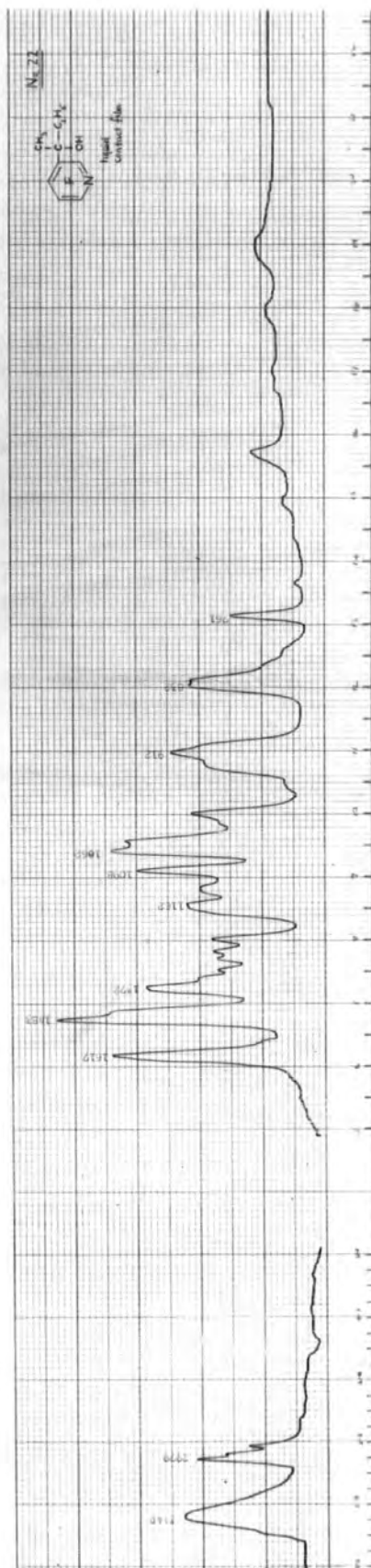
Butyl lithium (6.6 m.moles) in mixed solvent (hexane (2.8 ml)/Furan (5 ml)) was added slowly to a stirred solution of 2, 4, 5, 6-tetrafluoropyridine (1 gm, 6.6 m.moles) in dry furan (10 ml) at -75°C under an atmosphere of dry nitrogen. The reaction temperature was maintained at -75°C for 20 minutes and then allowed to warm slowly to 10°C when a vigorous reaction occurred causing the mixture to turn very dark in colour. After stirring for 1 hour at room temperature, water (10 ml) was added and the mixture extracted with ether. The etherial extracts were combined, dried (MgSO_4), filtered, and the solvent removed by distillation to give an involatile yellow-brown solid (0.8 gm). Infra red spectroscopy showed this to be similar to the product obtained from the decomposition of tetrafluoropyridyl lithium in previous experiments.

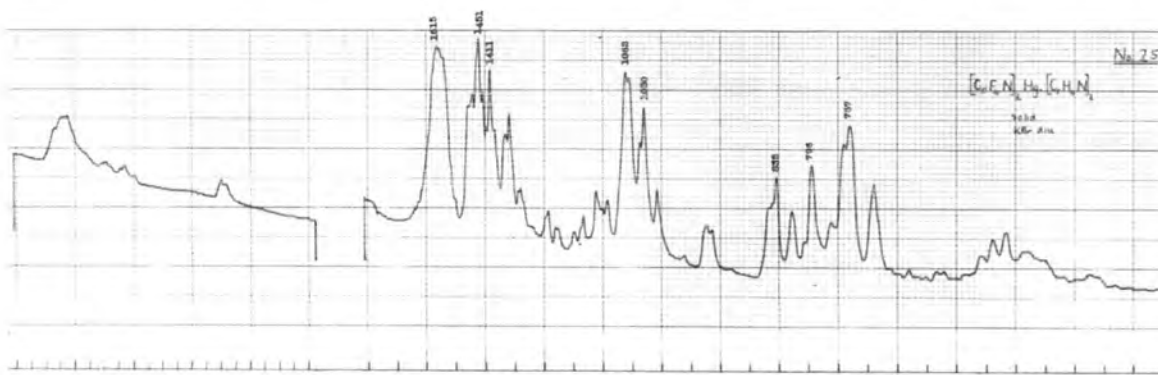
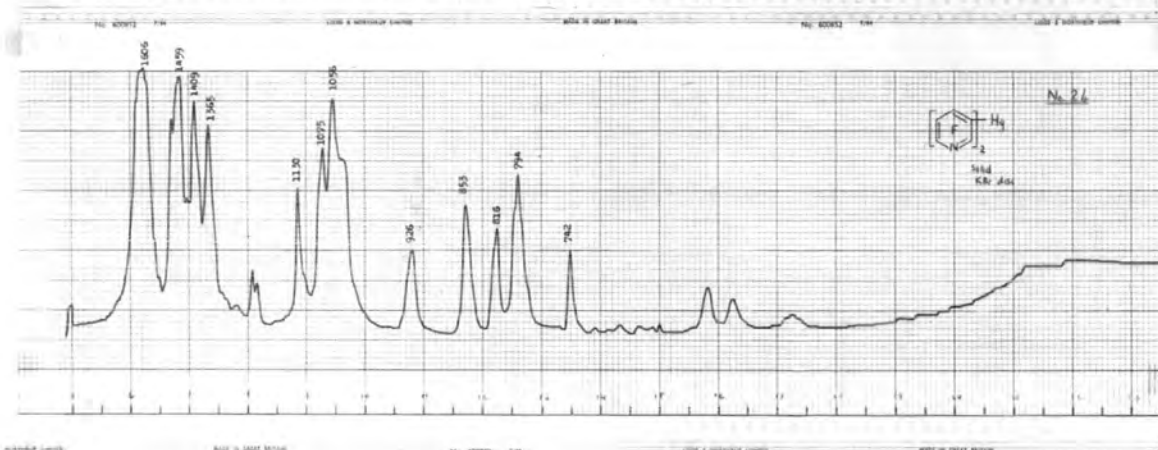












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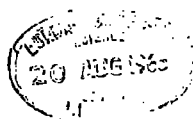
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