Polyfluorobipyridyls

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entitled

POLYFLUOROBIPYRIDYLS

Submitted by

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TO AILEEN

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MEMORANDUM

The work described in this thesis was carried out in the University of Durham between September 1963 and July 1966. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

ABSTRACT

POLYFLUOROBIPYRIDYLS

The chlorination of pyridine and 2-methylpyridine, using phosphorus pentachloride has been developed to give good yields of pentachloropyridine. The reaction between pentachloropyridine and potassium fluoride gave high yields of pentafluoro-, 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoro-pyridines. Octachloro-2,2'-bipyridyl, obtained from the reaction between 2,2'-bipyridyl and phosphorus pentachloride has been reacted with potassium fluoride affording octafluoro-, 3-chloroheptafluoro-, 3,3'-dichlorohexafluoro-, and 3,3',5,5'-tetrachlorotetrafluoro-2,2'-bipyridyls. Octafluoro-3,3'-, and octafluoro-4,4'-bipyridyls have been synthesized from 3-chloro-, and 4-bromo-tetrafluoropyridines respectively, using the Ullmann technique. Octafluoro-4,4'-bipyridyl has also been prepared from the reaction between 2,3,5,6-tetrafluoropyridylmagnesium bromide and pentafluoropyridine. Under similar conditions, 3-chloroheptafluoro-, and 3,5-dichlorohexafluoro-4,4'-bipyridyls were obtained from the reaction between the Grignard reagent and 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoro-pyridines respectively.

The polyfluorobipyridyls have been reacted with several nucleophilic reagents and the orientations of the products determined from nuclear magnetic resonance spectrographic measurements.

The reaction between octafluoro-, 3-chloroheptafluoro-, and 3,3'-dichlorohexafluoro-2,2'-bipyridyls and sodium methoxide in methanol

afforded the mono- and di-ethers, the fluorine atom para to the ring nitrogen being replaced in each case.

The reaction between octafluoro-3,3'-bipyridyl and nucleophilic reagents led to replacement of the fluorine atoms ortho (6), and para (4) to the ring nitrogen. With the nucleophile, X = OCH_3, in methanol, substitution at the 4-position (> 95%) occurred when equi-molar amounts of octafluoro-3,3'-bipyridyl and sodium methoxide were used. When a 2:1 molar ratio of sodium methoxide to the bipyridyl was used, an equi-molar mixture of 4,4'-, and 4,6'-dimethoxyhexafluoro-3,3'-bipyridyls was obtained. When X = OC_2H_5, n-OC_3H_7, n-OC_4H_9, i-OC_3H_7 and t-OC_4H_9 replacement of both the 4- and 6-fluorine atoms took place, the amount of 4-substitution decreasing with a corresponding increase in 6-substitution, as the size of the nucleophilic reagent increased. When X = OCH_3, in t-C_4H_9OH, replacement of the 6-fluorine atom (> 80%) occurred and when X = NH_3 and CH_3Li, substitution at the 6-position (> 95%) took place. In the reaction between octafluoro-3,3'-bipyridyl and sodium i-propoxide, an increase in the extent of replacement of the 6-fluorine atom occurred when ether was added to the reaction medium. This solvent effect has also been demonstrated in nucleophilic substitution in 3,5-dichlorotrifluoropyridine. An attempt has been made to rationalize the orientations by consideration of steric and electrostatic interactions, and the solvation of the transition state.

Nucleophilic substitution in octafluoro-4,4-bipyridyl led to replacement of the fluorine atoms ortho to the ring nitrogen.

Nucleophilic substitution in 3-chloroheptafluoro-4,4'-bipyridyl takes place at the 6-position ($>95\%$).

CONTENTS

PART I

PREPARATION OF POLYFLUOROBIPYRIDYLS

CHAPTER 1. INTRODUCTION

PREPARATION OF FLUORINATED HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN WITH REFERENCE TO FLUOROCARBON SYNTHESIS.

A. REPLACEMENT OF HYDROGEN BY FLUORINE.

Decomposition of Diazonium Salts.

The indirect method for the preparation of aromatic fluoro-compounds containing a small number of fluorine atoms is by application of the Balz-Schiemann reaction.[1] Aniline was diazotized to form phenyl diazonium chloride, which on treatment with fluoroboric acid gave an insoluble precipitate of phenyl diazonium fluoroborate. The controlled decomposition of the diazonium fluoroborate by heat, led to the formation of fluorobenzene.

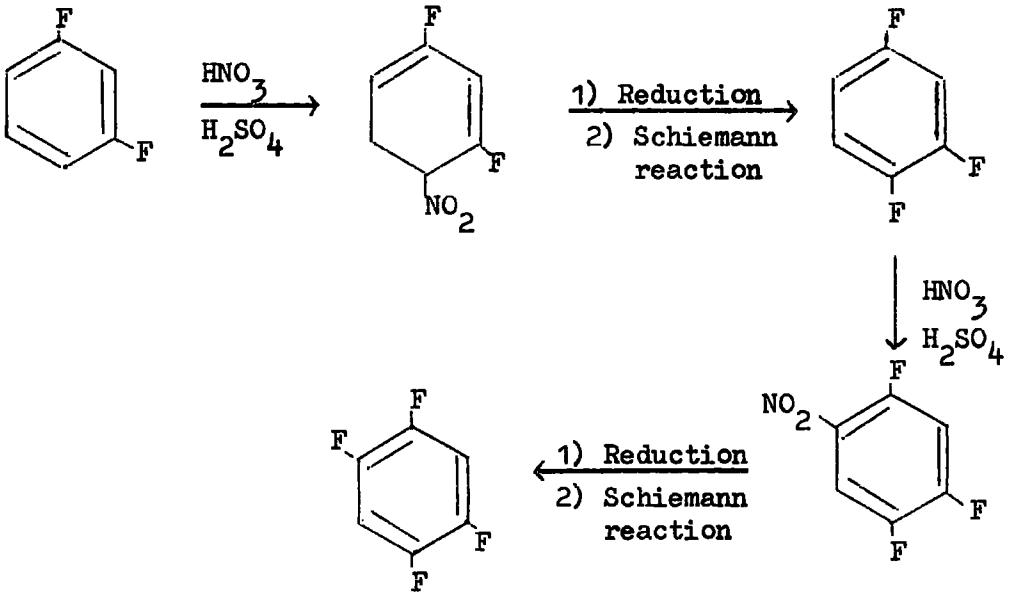
$$C_6H_5NH_2 + NaNO_2 + HCl \xrightarrow{0^\circ} C_6H_5\overset{+}{N}\equiv N.Cl^-$$

$$C_6H_5\overset{+}{N}\equiv N.Cl^- + HBF_4 \longrightarrow C_6H_5\overset{+}{N}\equiv N.BF_4^- \text{ (ppt.)}$$

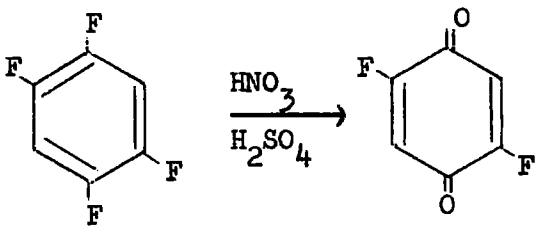
$$C_6H_5\overset{+}{N}\equiv N.BF_4^- \xrightarrow[\text{heat}]{} C_6H_5F + N_2 + BF_3.$$

This is now the standard method for the introduction of a small number of fluorine atoms into an aromatic system[2] and a large number of substituted fluorobenzenes have been isolated in this manner. However, the amount of fluorine that can be introduced into the benzene ring in this way is limited. Finger[3-6] showed that up to four fluorine atoms could be introduced into the benzene nucleus in a stepwise manner.

Thus fluorobenzene can be nitrated and then reduced to form the amine, which on diazotisation and treatment with fluoroboric acid yields the diazonium fluoroborate that gives the difluorobenzene on controlled decomposition. Finger repeated the process and obtained 1,2,4,5-tetrafluorobenzene.

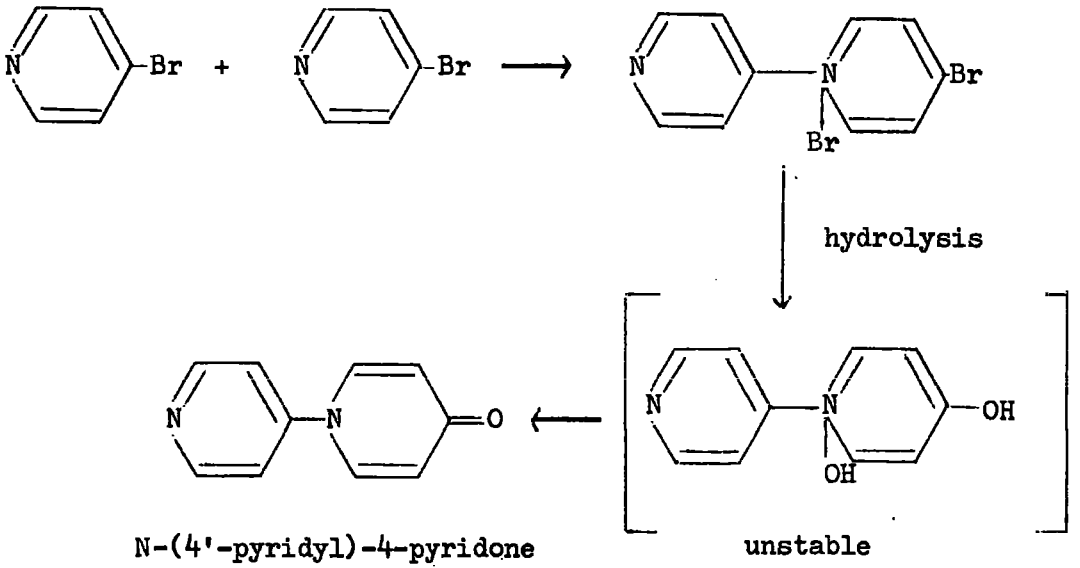


Nitration of 1,2,4,5-tetrafluorobenzene afforded a difluorobenzoquinone due to the expulsion of two para fluorine atoms, and not the tetrafluoronitrobenzene as expected.



Application of the Balz-Schiemann reaction to prepare fluoro derivatives of heterocyclic compounds has met with more difficulties and less success. Tschitschibabin and Rjazancev[7] prepared 2-fluoropyridine in 25% yield by diazotisation of the corresponding amine in concentrated hydrofluoric acid. Beaty[8] also prepared 2-fluoropyridine in 20-22% yield by diazotisation of 2-aminopyridine with sodium nitrite in anhydrous hydrofluoric acid and decomposition of the diazonium salt 'in situ' at 40°.

In 1947 Roe and Hawkins[9] 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. 2- and 3-Fluoropyridines were prepared in overall yields of 34 and 50% respectively. In contrast to the diazonium fluoroborates of most aromatic compounds which are quite stable, both 2- and 3-pyridine diazonium fluoroborates are unstable, and the decomposition is carried out in solution without isolation of the fluoroborates. Efforts to isolate 4-fluoropyridine using this modified Schiemann technique were unsuccessful, it being thought that N-(4-pyridyl)-4-pyridone had been formed in a manner similar to that reported by Wibaut and Broekman[10] for 4-chloro-, and 4-bromo-pyridines.



Wibaut and Holmes-Kamminga[11] however, reported that impure 4-fluoropyridine was obtained in poor yield by diazotisation of 4-amino-pyridine in hydrofluoric acid, the reaction product being isolated at the reaction temperature.

Preparation of fluoropyridines, utilizing the Schiemann reaction, has not been restricted to monofluoropyridines. Using a stepwise approach Finger and his co-workers[12] prepared 2,3- and 2,6-difluoro-pyridines from 2-fluoro-3-aminopyridine and 2-amino-6-fluoropyridine respectively. All attempts to isolate the 2,5-difluoropyridine under similar conditions failed, although in one instance some of the required fluoroborate was isolated but the product of the decomposition was lost in the work-up procedure. When Roe[13] attempted to prepare 2,6-difluoropyridine from 2,6-diaminopyridine by simultaneous introduction

of two fluorine atoms into the molecule using the Schiemann technique, none of the required difluoropyridine was isolated.

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. The stable diazonium salts of these other complex fluorine acids behave analogously to the borofluorides since on heating they yield fluoro aromatic compounds.

$$(ArN_2)_2^{++}.SiF_6^{--} \longrightarrow 2ArF + SiF_4 + 2N_2$$

$$ArN_2^{+}.PF_6^{-} \longrightarrow ArF + PF_5 + N_2$$

$$ArN_2^{+}.SbF_6^{-} \longrightarrow ArF + SbF_5 + N_2$$

The silicofluorides are formed in good yields but their subsequent decomposition into aryl fluorides is much less efficient. Beaty and Musgrave[14] prepared 2- and 3-fluoropyridines in 42% and 36% yields respectively, by diazotisation of the corresponding bases in fluorosilicic acid and decomposition of the diazonium salts "in situ". In some cases the yield of fluorinated product obtained via decomposition of the silicofluorides was higher than that obtained from the corresponding borofluorides, but in general, cases where this process gave better yields than the Schiemann reaction were exceptional.

The introduction of fluorine into the heterocyclic nucleus using

the Schiemann reaction has not been restricted to pyridine. All the monofluoroquinolines[15] (except 4-fluoroquinoline) have been isolated from the decomposition of the corresponding fluoroborates.

A recent comprehensive review by Suschitzky[16] on the Balz-Schiemann reaction has been published.

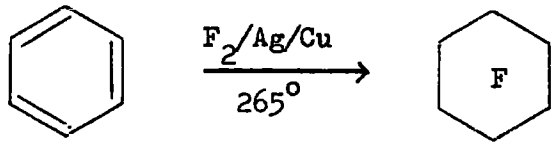
Fluorination Using Elemental Fluorine.

The first attempts to fluorinate organic compounds directly with undiluted elemental fluorine were completely unsuccessful. They were accompanied by explosions or at least charring, carbon being the only isolated product. The failure of the reaction was due to the exceedingly high heat of reaction which caused thermal decomposition of both the starting material and the reaction products. Several modifications, such as diluting the fluorine with an inert gas, usually nitrogen, or dissolving the organic compound in an inert solvent, or both, were used in an attempt to regulate the reaction.

It was not until the 1940's when Bigelow[17] published his work on the direct vapour phase fluorination, or as it is sometimes called, the catalytic method of fluorination, that a substantial step forward was taken in the attempt to prepare highly fluorinated organic compounds using elemental fluorine. Reaction of a hydrocarbon with fluorine proceeds via a free radical chain mechanism; progressive replacement of hydrogen and saturation of any multiple bonds or aromatic systems

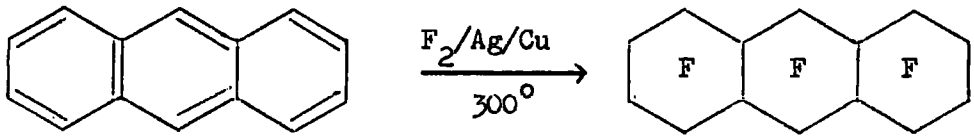
by fluorine occur. These reactions are highly exothermic, since heats of formation of C-F and H-F bonds are high (ca. 105 and 135 k.cal/mol. respectively) and the bond dissociation energy of fluorine is only 37 k.cal/mol., and unless the heat liberated is rapidly dispersed, combustion and extensive fragmentation of the carbon skeleton occurs. This 'catalytic' method of fluorination is carried out by passage of the organic vapour to be fluorinated, and fluorine, usually diluted with nitrogen, through a reactor filled with a divided metal packing, usually copper gauze or copper coated with another metal, at elevated temperatures. The catalyst probably serves two purposes;[18] first, to moderate the reaction by reducing local heating, and secondly to promote the reaction, the latter process supposedly to occur by the surface of the metal becoming coated with the metallic fluoride which acts as a fluorinating agent. Musgrave and Smith[19] used various catalysts including silver, gold, nickel, cobalt and steel wool, but found little variation in the overall yield of fluorinated material indicating that the principle function of the 'metal catalyst' was presumably to disperse the heat of reaction.

Cady, Grosse et al.[20] investigated the reaction between elemental fluorine and several hydrocarbons including benzene and anthracene using a silver coated copper catalyst:



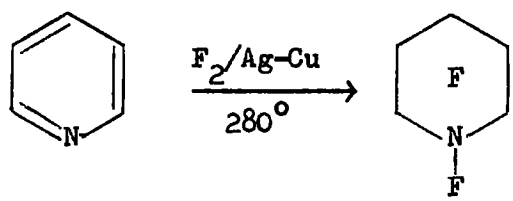
58%

perfluorocyclohexane



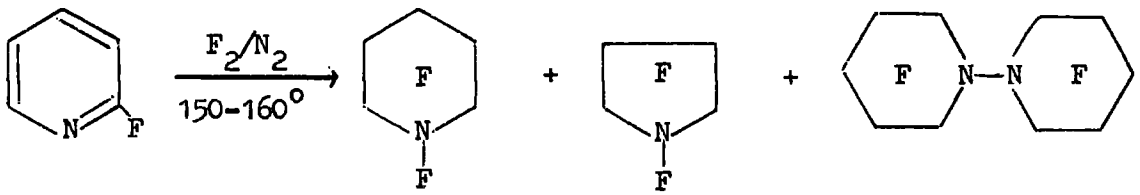
43%

Haszeldine and Smith[21] used a gold catalyst in the fluorination of many substituted benzenes and obtained high yields of the perfluoro derivatives. Haszeldine[22] then attempted to fluorinate several nitrogen-heterocyclic compounds under similar conditions using a gold catalyst. Fluorination of lutidine gave low yields of a compound that was identified as perfluoro-2,6-dimethylpiperidine. Haszeldine suggested that the low yield of the fluorinated product was due to the formation, and subsequent decomposition by fluorination, of the hydrofluorides of lutidine, and of compounds derived from lutidine by the interaction of one or more atoms of fluorine. When similar techniques were explored using pyridine as starting material[23] very poor yields of the expected product, perfluoropiperidine were obtained, extensive



0.3%

decomposition having taken place. The elimination of the nitrogen atom in pyridine during the reaction was shown to take place by the isolation of the straight chain hydrocarbon C_5F_{12} and nitrogen trifluoride. Haszeldine again reasoned that the low yield of product was due to the formation of a non-volatile hydrofluoride during the critical stages of the reaction and suggested that fluorination of heterocyclic compounds already containing fluorine would give superior yields. More recently Banks and Williamson[24] fluorinated 2-fluoropyridine using a Bigelow "cool-flame" burner[25] at 150-160°, but reported extensive breakdown of the pyridine skeleton and the isolation of perfluoropiperidine in less than 0·1% yield.



$$+CF_3\cdot(CF_2)_3\cdot CF{:}N\cdot CF_3 \;+\; (CF_3)_2\cdot N\cdot N\cdot(CF_3)_2$$

$$+CF_3\cdot N{:}CF\cdot CF_3 \;+\; CF_3\cdot N{:}CF_2 \;+\; (CF_3)_2\cdot NF$$

$$+(CF_3)_2\cdot NH \;+\; CF_3\cdot NF_2 \;+\; C_2F_5\cdot CHF_2 \;+\; CF_3\cdot CHF\cdot CF_3$$

$$+nC_5F_{12} \;+\; C_4F_{10} \;+\; C_3F_8 \;+\; C_2F_6 \;+\; CF_4 \;+\; NF_3$$

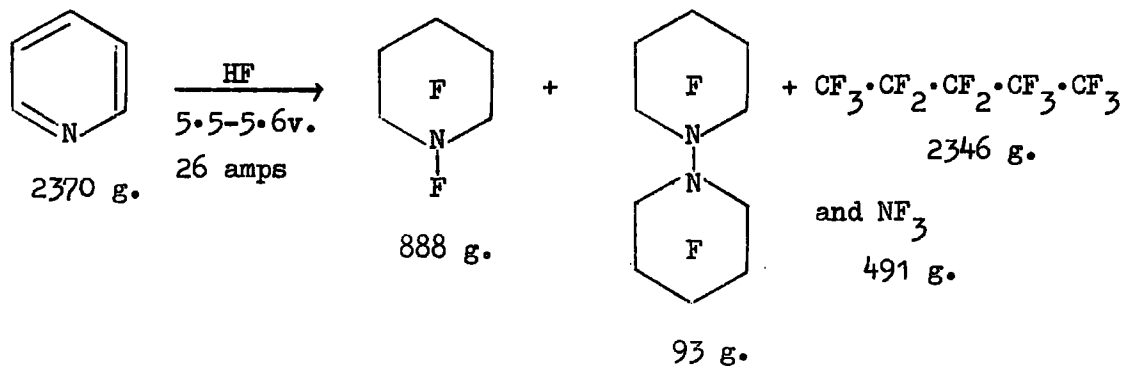
A recent review by Tedder[26] on the fluorination of organic compounds using elemental fluorine has been published.

Electrochemical Fluorination.[27]

Many organic substances dissolve readily in anhydrous hydrogen fluoride to give conducting solutions. When a direct electric current at low voltage (4-8v.) is passed through such a solution, or through a suspension of an insoluble organic compound made conducting by the addition of an electrolyte, so that free fluorine is not liberated, hydrogen is evolved at the cathode and the organic material is fluorinated by some unknown anodic process. This method of fluorinating organic compounds was discovered by Simons in 1941.[28] The electrochemical method for fluorinating organic compounds has many advantages; the apparatus is relatively simple to construct (iron or nickel cells equipped with a reflux condenser, nickel anodes and nickel or steel cathodes), the direct source of the fluorine introduced is the relatively cheap anhydrous hydrogen fluoride, rather than the more expensive elemental fluorine, and that during this method of fluorination many functional groups are retained unlike fluorination with elemental fluorine. The main disadvantage is that the compound to be fluorinated must have an appreciable solubility in the hydrogen fluoride. Many hydrocarbons like benzene (solubility of about 2% at 0^{o}) are not very soluble, and it appears that electrochemical fluorination is not very

efficient for carbocyclic systems.

More success was obtained when this process was applied to the fluorination of heterocyclic bases. Simons and his co-workers[28] electrolysed a solution of pyridine in anhydrous hydrogen fluoride at low voltage (5·5 - 5·6v.) and obtained along with the required product perfluoropiperidine, perfluorodipiperidyl and several decomposition products (perfluoropentane was the most abundant).



Using similar conditions Simons and his co-workers obtained the fully fluorinated derivatives of 1-methylpiperidine, 4-propylpyridine, 4-isopropylpyridine, morpholine and 1-methylmorpholine. Banks and Haszeldine[29] reported an 8% yield of perfluoropiperidine from the electrolysis of pyridine in hydrogen fluoride (25 amps, 5·5v.), confirming that the main product was perfluoropentane. Haszeldine[30] indicated that the low yield of perfluoropiperidine was due to the fission of the carbon-nitrogen bond and that this breakdown could be reduced

by replacement of an α-hydrogen atom by a fluorine atom before fluorination. Fluorination of 2-fluoropyridine (readily prepared by the Schiemann reaction from 2-aminopyridine) resulted in a 13% yield of perfluoropiperidine.

Fluorination Using High-Valency Metallic Fluorides.

Among the general methods by which fluoro-organic compounds may be synthesised are direct reactions of hydrocarbon-type organic derivatives with high valency metallic fluorides.[31] The most important member of this group of fluorinating agents is cobalt trifluoride. Silver difluoride, manganese trifluoride, cerium tetrafluoride and lead tetrafluoride have also been used to some extent.

In this process a deep-seated fluorination of the organic structure occurs; all substituents on the carbon skeleton can be replaced by fluorine and any unsaturation removed yielding highly fluorinated products and eventually fluorocarbons. The fluorinating action of cobalt trifluoride and the subsequent regeneration of the reagent may be expressed by the following equations:

$$>CH- + 2CoF_3 = >CF- + HF + 2CoF_2$$

$$2CoF_2 + F_2 = 2CoF_3; \quad \Delta H_{473}^{o} = -52 \text{ k.cal/mol.}$$

From the experimentally found value of the heat of reaction of

the regeneration equation (52 k.cal/mol.),[32] it can be computed that, during the reaction of the organic compound with cobalt trifluoride, approximately one half of the total heat of reaction of the fluorination of the organic compound with elemental fluorine (102 - 104 k.cal/mol.) is liberated.

$$\geq CH- + F_2 = \geq CF- + HF \qquad \Delta H_{298} = -104 \text{ k.cal/mol.}$$

Fluorination with cobalt trifluoride is thus a roundabout process which exposes the organic compound to only half the thermal stress of direct fluorination thus leading to less breakdown of the organic compound and hence higher yields of fluorinated product.

The inorganic fluorides exert their highest valency and in the course of the reaction the fluorides are reduced to a lower valency state, for example;

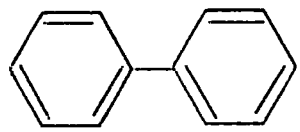
$$\geq C\text{-}H + 2MF_n \longrightarrow \geq C\text{-}F + HF + 2MF_{n-1}$$

$$\geq C{=}C\leq + 2MF_n \longrightarrow \geq CF\text{-}FC\leq + 2MF_{n-1}$$

Reactions between cobalt trifluoride (or other high valency metallic fluorides) and organic compounds can be carried out with the latter in either vapour or liquid phase. In the liquid phase process the reagent is added to a heated, stirred, sample of the material to be fluorinated, which may be dissolved or suspended in an inert diluent, usually a

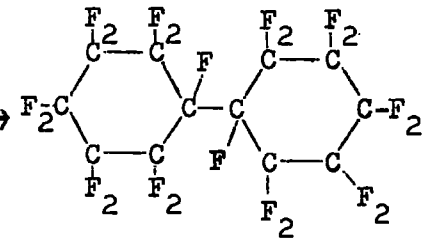
high-boiling fluorocarbon. In the vapour phase fluorinations a stream of the organic compound is swept over a bed of the fluoride in a heated tube. These two methods are quite distinct and the vapour phase process has been the more useful in the majority of cases.

Many aromatic compounds have been fluorinated using cobalt trifluoride. Benzene,[33] substituted benzenes,[34,35,36] naphthalene,[35] anthracene[37] and diphenyl[38] have all been converted into the saturated alicyclic fluorocarbons with corresponding carbon skeletons, for example:



diphenyl

$\xrightarrow[CoF_3]{310\text{-}320^\circ}$

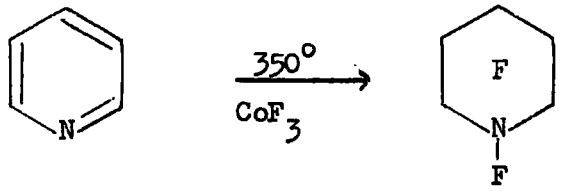


59%

perfluorodicyclohexyl

Although the cobalt trifluoride method of fluorination has been a large success in the preparation of fluorocarbons from aromatic hydrocarbons, particularly by the workers at Birmingham (yields generally in the region of 50-70%), the success was limited when this method was applied to the fluorination of heterocyclic compounds.

When pyridine, diluted with nitrogen, was passed over a bed of cobalt trifluoride maintained at 350°, perfluoropiperidine was obtained in 0.2% yield.[23]



The apparatus consisted of a preheater, maintained at 200° - 250°, through which a stream of nitrogen was passed to sweep the pyridine into a second furnace containing the cobalt trifluoride, the cobalt trifluoride having been prepared 'in situ' by passage of fluorine over the difluoride at 350°. In a previous note[22] Haszeldine reported that the fluorination of lutidine using a slight modification of the cobalt trifluoride process to prevent, as far as possible, the formation of the non-volatile hydrofluoride of lutidine, yielded perfluoro-(2,6-dimethylpiperidine) in approximately 5% yield. In a later communication the author[39] throws some doubt onto the structure of perfluoro-(2,6-dimethylpiperidine) indicating that it might have contained one hydrogen atom that had resisted fluorination but no further confirmation has been noted.

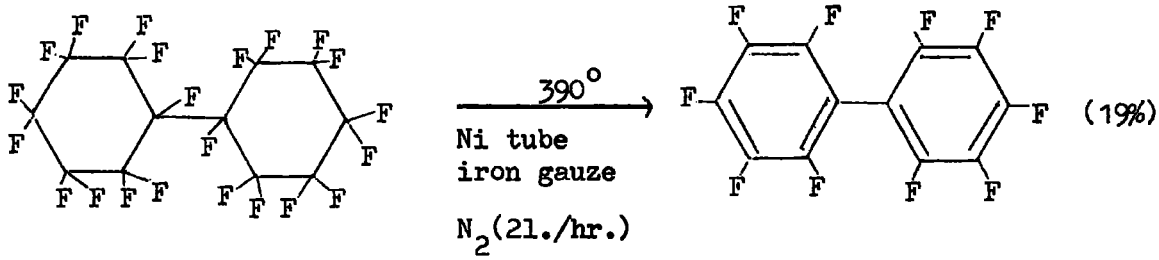
Haszeldine and Smith[40] fluorinated quinoline with cobalt trifluoride at 400° isolating heptadecafluorodecahydroquinoline in 2% yield.

Fluorination of 2-methyl indole[41] led, as with pyridine and quinoline, to extensive decomposition of the organic material, although it was reported that one fraction of the product contained organic material with the nitrogen ring system intact.

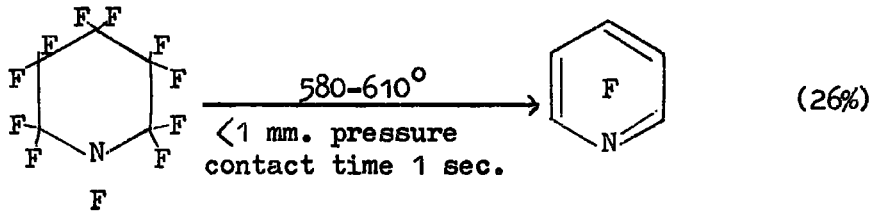
Silver difluoride has not been used extensively in the fluorination of heterocyclic compounds. One important result was the preparation of tetrafluoropyrimidine obtained by the action of silver difluoride on 2,4,6-trifluoropyrimidine in the presence of perfluorotributylamine as solvent.[42]

There are thus three methods available for converting hydrocarbons and heterocyclic compounds into their saturated fluorinated derivatives: direct vapour phase fluorination, electrolysis in anhydrous hydrogen fluoride and indirect fluorination with certain high valency metal fluorides.

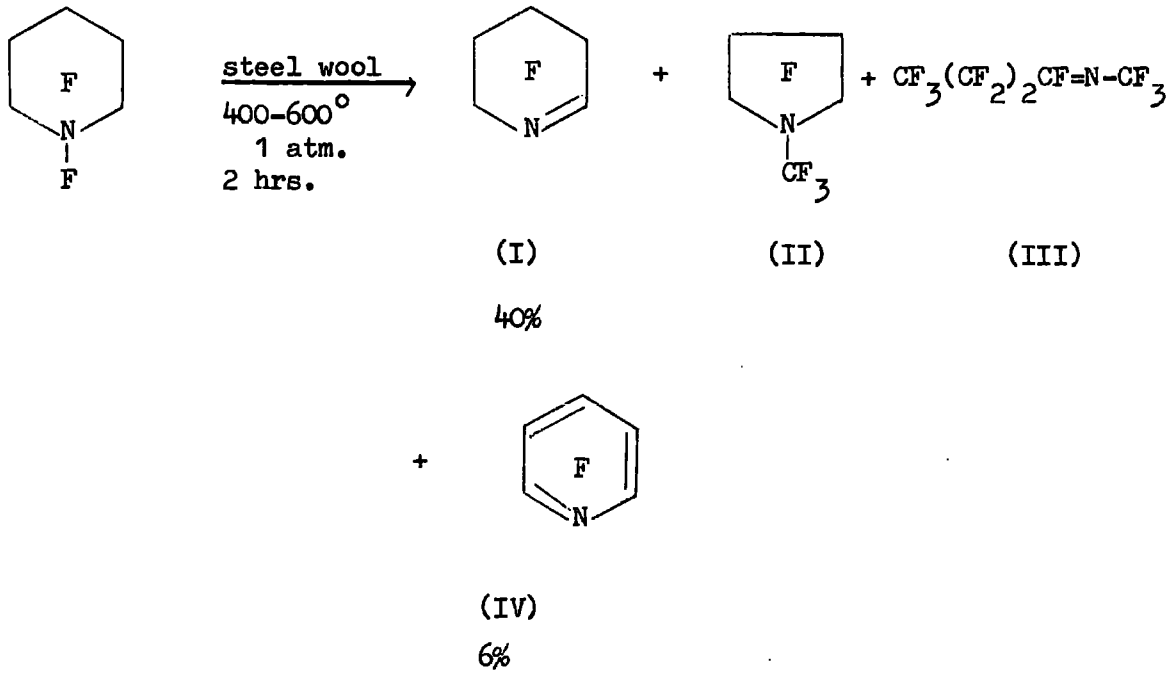
The discovery in the late 1950's by the workers of Birmingham that saturated fluorocarbons could be defluorinated with hot finely-divided nickel or iron, led to the first general preparative route to aromatic fluorocarbons.[43] This method of defluorination consists in passing the fluorocarbon in a stream of nitrogen through a metal tube packed with small pieces of iron gauze, heated to a temperature in the range of 400-600°. In this way Tatlow and his co-workers prepared perfluorotoluene from perfluoromethylcyclohexane, perfluoro-naphthalene from perfluorodecalin and perfluorobiphenyl from perfluorodicyclohexyl.



Two groups of workers adopted this defluorination procedure to defluorinate perfluoropiperidine, giving amongst other breakdown products pentafluoropyridine. Tatlow and his co-workers[44] obtained pentafluoropyridine in 12% yield by passing perfluoropiperidine, diluted with nitrogen, through nickel tubes at temperatures ranging from 400-600°. Haszeldine and co-workers[29] improved the yield of pentafluoropyridine using iron wire as the defluorinating agent and carrying out the defluorination at reduced pressure.



More recent work[30] has shown that the defluorination of undecafluoropiperidine with mild steel wool yields a mixture of perfluoro-2,3,4,5-tetrahydropyridine(I), perfluoro-(1-methylpyrrolidine) (II), a compound assumed to be perfluoro-(N-butylidine-methylamine) (III) and small amounts of pentafluoropyridine (IV).



Halogen Fluorides as Fluorinating Agents.

Halogen fluorides, such as chlorine trifluoride and bromine trifluoride have been used as fluorinating agents although their reactions with organic compounds are very complicated, thereby limiting their applicability. Musgrave and Ellis have investigated the reaction of chlorine trifluoride with benzene[45] and substituted benzenes[46] in carbon tetrachloride solution, in the presence of a variety of catalysts, and have shown that the main reaction is one of substitution, the products from benzene being fluorobenzene and chlorobenzene. Some halogenated addition compounds were produced in small quantities.

The reaction of pyridine with chlorine trifluoride was investigated by Beaty.[8] Chlorine trifluoride, diluted with nitrogen, was passed through a solution of pyridine in carbon tetrachloride at 0°. Low yields of 2-fluoropyridine (4-10%) and 3-chloropyridine were obtained. Several metallic fluorides were used as catalysts, and in the presence of potassium fluoride a difluorobipyridyl was isolated but the structure was not confirmed.

B. REPLACEMENT OF HALOGEN BY FLUORINE.

Chlorinated organic compounds have been used in many cases as starting materials in the preparation of fluoroaromatic compounds in both the carbocyclic and heterocyclic series. The methods for converting the chloro compounds into their fluoro derivatives can be roughly divided into three main groups.

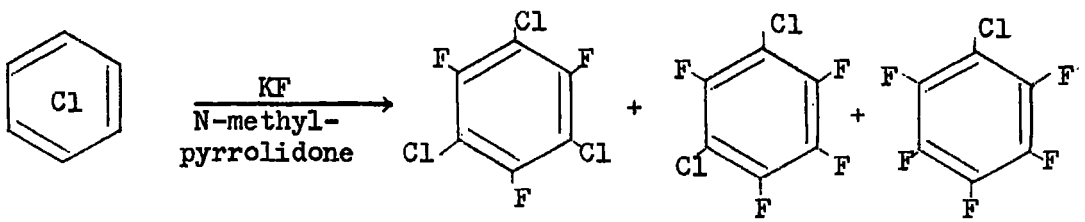
1. Halogen exchange using alkali metal fluorides.
2. Halogen exchange using metallic fluorides other than alkali metal fluorides.
3. Halogen exchange using non-metallic fluorides.

Replacement of Halogen Using Alkali Metal Fluorides.

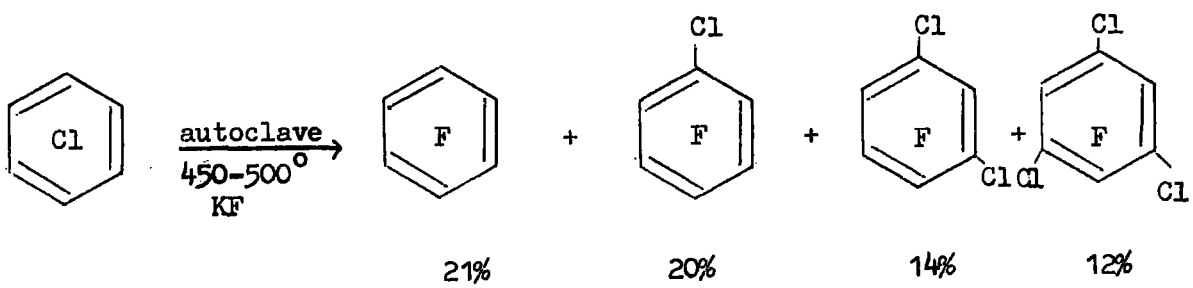
This type of exchange was first observed by Gottlieb,[47] who converted 1-chloro-2,4-dinitrobenzene into the 1-fluoro-compound in

30% yield, using potassium fluoride in nitrobenzene at 200°. Vorozhtsov and Yakobson[48] succeeded in converting 1,3-dichloro-4,6-dinitrobenzene and 1-fluoro-3-chloro-4,6-dinitrobenzene to the corresponding difluorides in 87 and 95% yields respectively, by heating with anhydrous potassium fluoride at 170-190°.

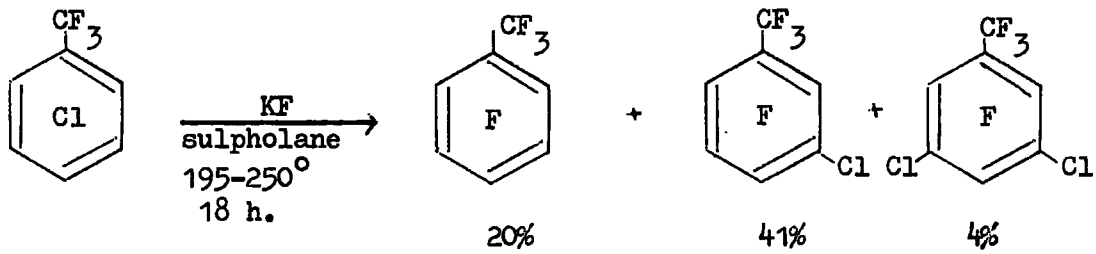
On the basis of these early results which yielded mono and disubstituted fluorobenzenes, Maynard[49] reacted hexachlorobenzene with potassium fluoride at elevated temperatures using N-methylpyrrolidone as solvent to give a mixture of chlorofluorobenzenes.

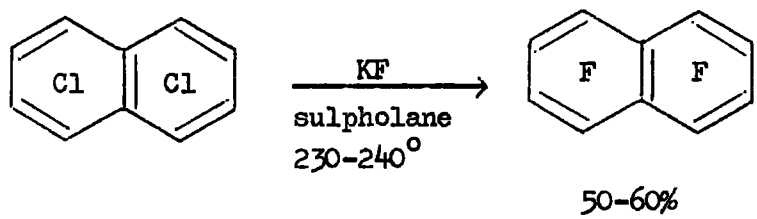


Vorozhtsov and his co-workers[50] reacted hexachlorobenzene with anhydrous potassium fluoride in the absence of solvent at temperatures ranging from 450-500° and obtained high yields of highly fluorinated benzenes.



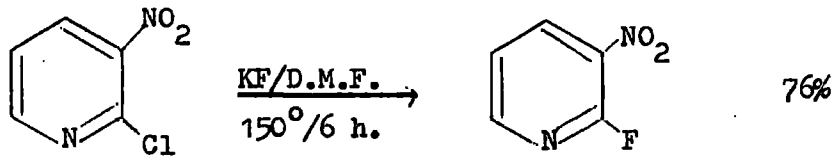
Hexachlorobenzene has recently been reported[51,52] to react with potassium fluoride in sulpholane at 230-240° for 18 h. to give mainly chloropentafluorobenzene (25%), dichlorotetrafluorobenzene (isomers) (24%) and trichlorotrifluorobenzene (30%) with traces of hexafluorobenzene. Hexafluorobenzene was readily obtained by reacting chloropentafluorobenzene with caesium fluoride in sulpholane at 160-190° for 18 h. Fuller[51] also prepared, under similar conditions, perfluoronaphthalene from perchloronaphthalene and perfluorotoluene from trifluoromethylpentachlorobenzene.

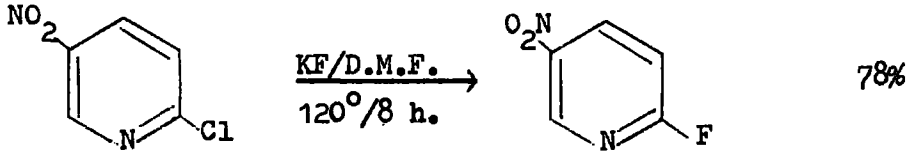




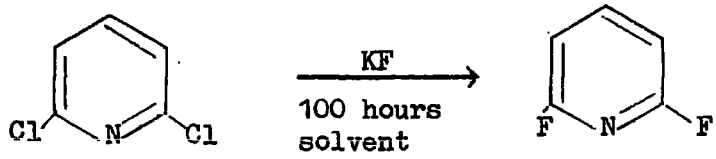
Chlorinated nitrogen containing aromatic heterocyclic compounds have been used as starting materials in the preparation of the corresponding fluoro-compounds.

Finger and Starr[53] found that potassium fluoride in dimethylformamide was effective for replacing suitably activated halogen atoms in the pyridine nucleus. The chlorine atom in both 2-chloro-3-nitropyridine and 2-chloro-5-nitropyridine is activated by the nitro group, and can easily be replaced by fluorine using potassium fluoride.

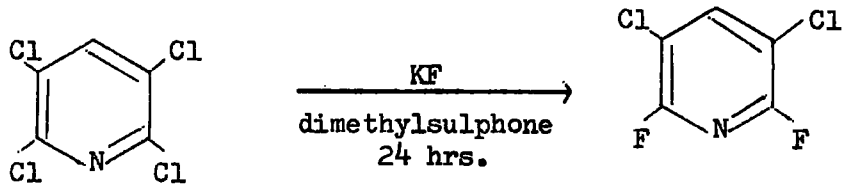




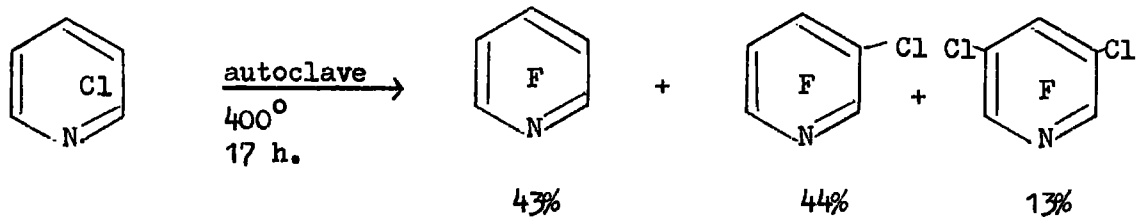
Reaction of 2,6-dichloropyridine with potassium fluoride in dimethyl sulphone at 200-210° yielded the difluoro derivative.[54,55]



Under similar conditions, 2,3,5,6-tetrachloropyridine gave 2,6-difluoro-3,5-dichloropyridine



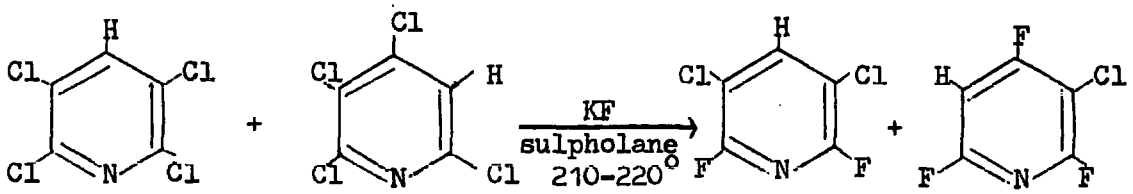
Finger was unable to replace the β-chlorine atoms in the pyridine nucleus using potassium fluoride in dimethylsulphone. However, Chambers, Hutchinson and Musgrave[56] succeeded in replacing all the chlorine atoms in pentachloropyridine using potassium fluoride in the absence of a solvent at elevated temperatures. Pentachloropyridine was reacted with anhydrous potassium fluoride in an autoclave for 17 h. at 480° and was converted into pentafluoropyridine in 70% overall yield. Lowering the reaction temperature to 400°, 3-chlorotetrafluoropyridine, 3,5-dichlorotrifluoropyridine and pentafluoropyridine were obtained.



3-Chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine were obtained, in the ratio 1:10, when pentachloropyridine was reacted with potassium fluoride in dry sulpholane at 190-210° for 36 hours.

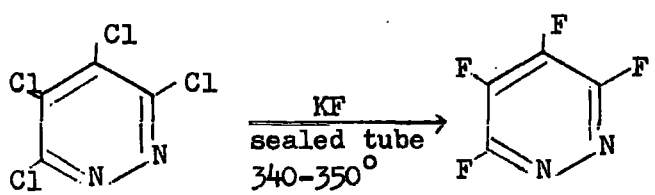
Treatment of isomeric tetrachloropyridines (a mixture of 3-hydro

and 4-hydro-tetrachloropyridines) with potassium fluoride in sulpholane at temperatures ranging from 210-220°, gave an equimolar mixture of 3-chloro-2,4,6-trifluoropyridine and 3,5-dichloro-2,6-difluoropyridine.



Haszeldine[57] and his co-workers also prepared pentafluoropyridine by treating pentachloropyridine with potassium fluoride under conditions similar to those reported by the Durham workers.

This method of preparing highly fluorinated pyridines has been adapted to the preparation of other highly fluorinated heterocyclic compounds. Perfluoroquinoline and perfluoroisoquinoline have recently been prepared[58] by reacting the corresponding perchloro compounds with potassium fluoride at elevated temperatures. Perfluoropyridazine[59] has been prepared in a similar way.



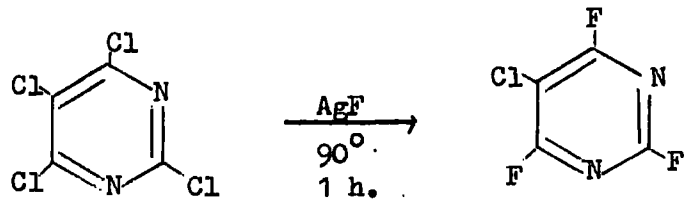
Replacement of Halogen by Fluorine Using Metallic Fluorides.

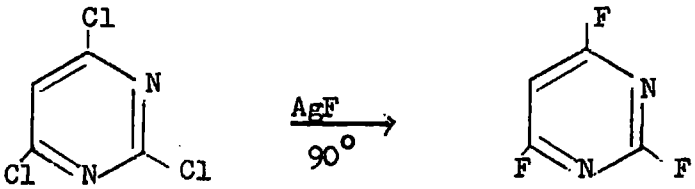
Hexachlorobenzene has been shown to react with cobalt trifluoride to produce a large number of chlorofluorocyclohexanes.[60] The hexachlorobenzene was vapourised and passed over a bed of cobalt trifluoride at 350° to give good yields of chlorofluorocyclohexanes of the general formula $C_6Cl_nF_{12-n}$ (where n = 1-6). The chlorofluorocyclohexanes were dehalogenated by passing them over a hot iron gauze at 430° to give good yields of hexafluorobenzene.

Hexachlorobenzene has also been fluorinated with cerium tetrafluoride[61] and lead tetrafluoride[62] at elevated temperatures, yielding nonafluorotrichlorocyclohexane as the main product.

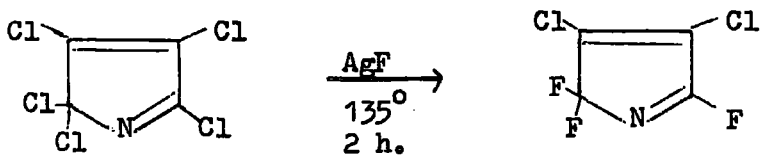
When highly chlorinated heterocyclic compounds are treated with metallic fluorides at lower temperatures no unsaturation is removed and the chlorine atoms are replaced by fluorine.

Grundmann and his co-workers[42] studied the reaction between tetrachloropyrimidine and silver fluoride. 2,4,6-Trifluoro-5-chloropyrimidine was obtained when tetrachloropyrimidine was heated with silver fluoride at 90° for 1 hour. Under similar conditions silver fluoride converted 2,4,6-trichloropyrimidine into 2,4,6-trifluoropyrimidine.

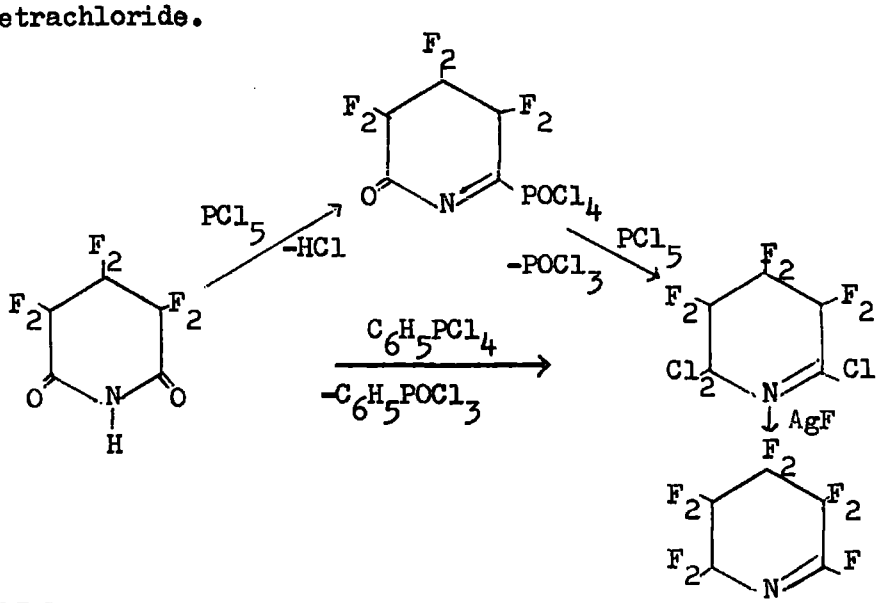


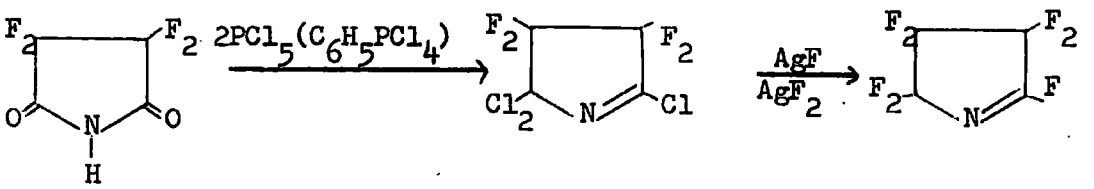


Silver fluoride has been used as the fluorinating agent in the preparation of 3,4-dichloro-2,2,5-trifluoropyrrolenine from pentachloropyrrolenine.[63]



Grundmann[63] synthesized perfluoro-1-piperideine and perfluoro-1-pyrroline by reacting 2,6,6-trichloro-3,3,4,4,5,5-hexafluoro-1-piperideine and 2,5,5-trichloro-3,3,4,4-tetrafluoro-1-pyrroline with silver fluoride respectively. The chloro compounds were readily prepared from hexafluoroglutarimide and tetrafluorosuccimide respectively by treatment with phosphorus pentachloride or phenylphosphorus tetrachloride.

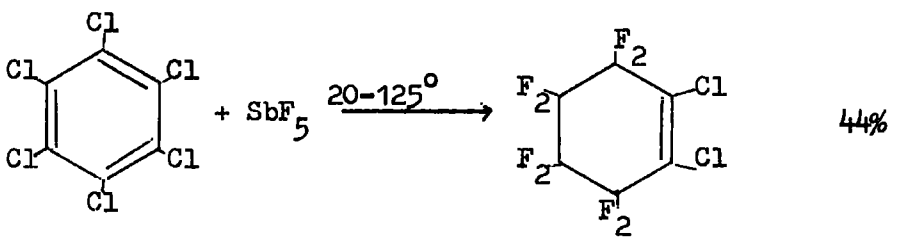




Silver difluoride has been used to fluorinate sym. trichlorotriazine, sym. trifluorotriazine being obtained in good yield.[64] Many derivatives of sym. trifluorotriazine have also been prepared. Grundmann and his co-workers[64] studied the reactions of various metallic fluorides, - silver fluoride, silver difluoride, mercuric difluoride and lead difluoride - on 2,4-bis(pentafluoroethyl)-6-chloro-s-triazine and showed that, except in the case of lead difluoride, good yields of the fully fluorinated product were obtained.

Antimony fluorides have been used as fluorinating agents in both the aromatic and heteroaromatic systems.

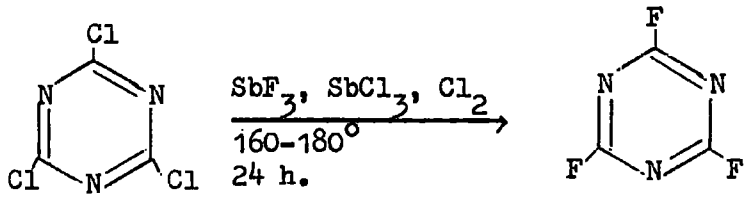
The reaction between hexachlorobenzene and antimony pentafluoride was first reported by McBee and his co-workers[65] in 1947. It was shown that antimony pentafluoride was able to add fluorine to double bonds as well as to replace chlorine by fluorine.

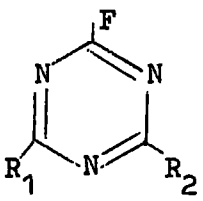


1,2-dichloroperfluorocycloalkene

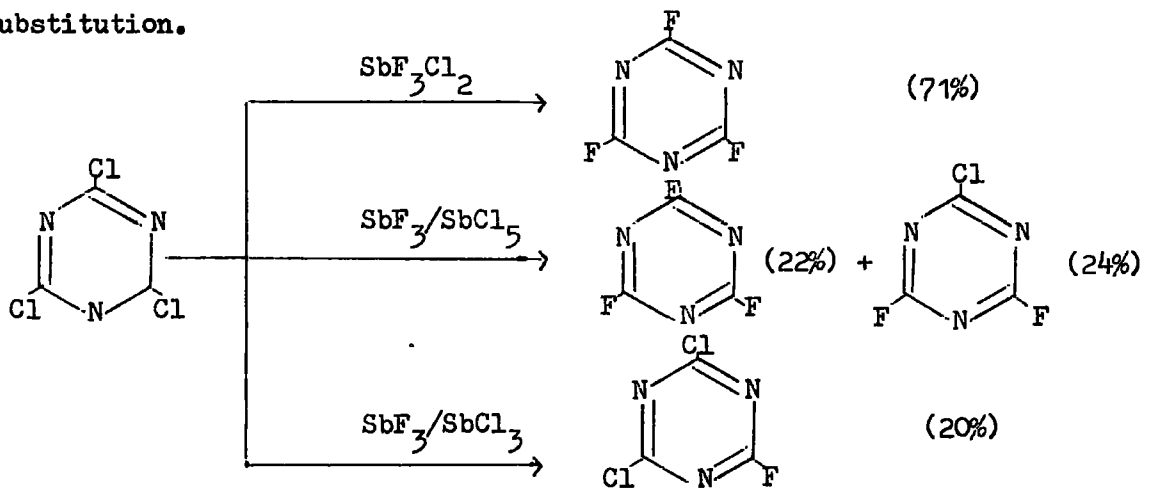
Later work[66] revealed that if the temperature was raised to 150° the yield of 1,2-dichloroperfluorocycloalkene was increased to 87%.

Kober and Grundmann[67] prepared sym. trifluorotriazine in 91% yield by reacting sym. trichlorotriazine with a mixture of antimony trifluoride, antimony trichloride and chlorine.

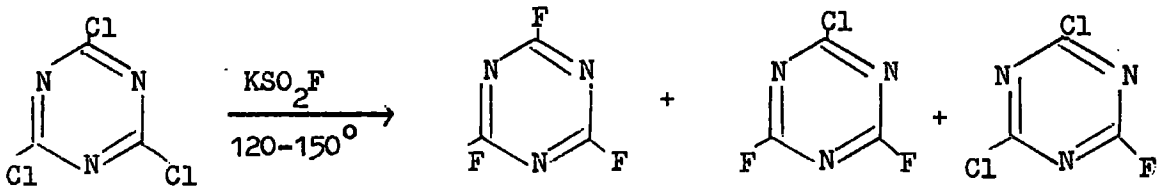


Triazines of the general formula  where R_1 and R_2 are either fluorine or the trifluoromethyl-group, have been prepared by exchange of chlorine for fluorine using antimony fluorides.

Bigelow and his co-workers[68] treated sym. trichlorotriazine with a variety of fluorinating agents obtaining various amounts of substitution.



Sym. trifluorotriazine, difluorochlorotriazine and fluorodichlorotriazine have also been obtained from the reaction of sym. trichlorotriazine with potassium fluorosulphinate.[69]



31% 11% 3%

Perchloro-N-phenylcarbazole has been fluorinated[70] with antimony pentafluoride and silver difluoride producing fluorochloro oils. No definite structures were given, but it was indicated that the nitrogen-carbon bonds were still intact.

Replacement of Halogen by Fluorine Using Non-Metallic Fluorides.

Hexachlorobenzene has been reacted with various non-metallic fluorides to give mixtures of chlorofluorocyclic products.

Bigelow and Pearson[71] reported the isolation of hexachlorotetrafluorocyclohexene and hexachlorohexafluorocyclohexane in small quantities by the reaction of hexachlorobenzene, as a suspension in carbon tetrachloride, with elemental fluorine.

$$C_6Cl_6 + F_2 \xrightarrow{F_2} C_6Cl_6F_4 + C_6Cl_6F_6$$

More recently workers at these laboratories[72] have reacted hexachlorobenzene, as a slurry in 1,1,2-trichlorotrifluoroethane, with

elemental fluorine to give a mixture of saturated chlorofluorocyclohexanes of the general formula $C_6Cl_xF_{(12-x)}$ where x = 5, 6, 7. Dehalogenation of these gave a good yield of a mixture of hexafluorobenzene and chlorofluorobenzenes.

$$C_6Cl_6 + 3F_2 \xrightarrow[N_2]{CCl_2F\cdot CClF_2} C_6Cl_xF_{(12-x)}\ (90\%) \xrightarrow[330^\circ]{Fe} \begin{matrix} C_6F_6 \\ C_6ClF_5 \\ C_6Cl_2F_4 \\ C_6Cl_3F_3 \end{matrix}$$

x = mainly 5,6 or 7

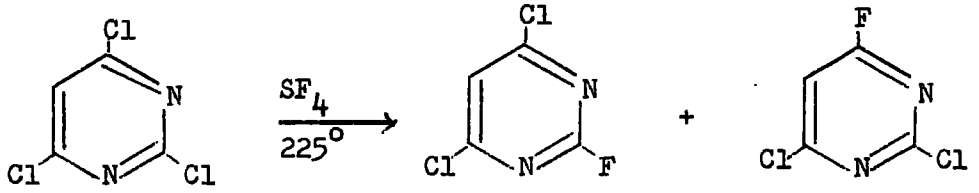
McBee, Lindgren and Ligett[73,74] reacted hexachlorobenzene with bromine trifluoride at 150° and obtained a mixture of products, the average composition corresponding to the molecular formula $C_6Br_2Cl_4F_6$.

Heyes[75] reacted hexachlorobenzene with various amounts of chlorine trifluoride at 240° to give good yields of perchlorofluorocyclohexenes, $C_6Cl_nF_{10-n}$ where n = 3-6, tetrachlorotetrafluorocyclohexadiene and unreacted hexachlorobenzene.

With a large excess of chlorine trifluoride, hexachlorobenzene reacted smoothly to yield chlorofluorocyclohexanes and -cyclohexenes of the general formula $C_6Cl_nF_{12-n}$ where n = 3-7 and $C_6Cl_nF_{10-n}$ where n = 3-6 respectively.

Tullock and his co-workers[76] fluorinated hexachlorobenzene with sulphur tetrafluoride at temperatures ranging from 200-400° and obtained cyclic $C_6Cl_2F_8$ and $C_6Cl_3F_9$.

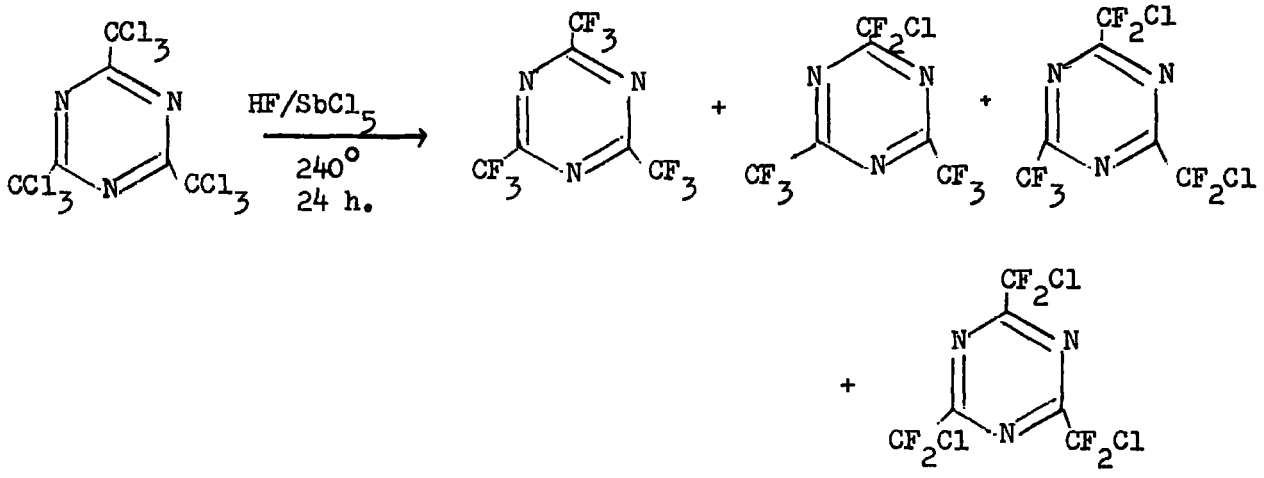
Sulphur tetrafluoride was used to replace chlorine atoms in 2,4,6-trichloropyrimidine. Tullock and his co-workers[76] partially fluorinated 2,4,6-trichloropyrimidine by treatment with sulphur tetrafluoride at 225°.



N-Bromoperfluoropiperidine has recently been prepared[77] by the reaction of bromine trifluoride on α,α,α'-trichlorohexafluoropiperidine at 50° with subsequent distillation of the reduced mass.

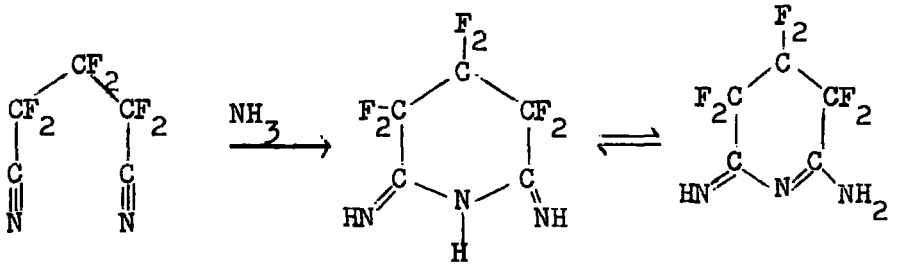
Hydrogen fluoride has been used to prepare fluoromethyl pyridines from chloromethylpyridines. McBee[78] prepared 2,6-bis(trifluoromethyl)-pyridine from 2,6-bis(trichloromethyl)pyridine by treating the chloro compound with hydrogen fluoride in a sealed autoclave for 30 h. at 300°.

McBee[79] prepared 2,4,6-tris(trifluoromethyl)-1,3,5-triazine by reacting the corresponding chloro compound with hydrogen fluoride in the presence of antimony pentachloride at 240° for 24 hours. Several lower fluorinated products were also obtained.

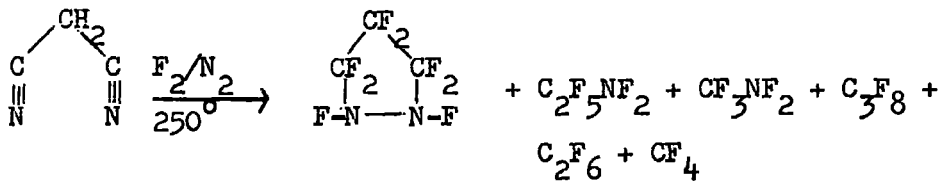


C. RING SYNTHESIS

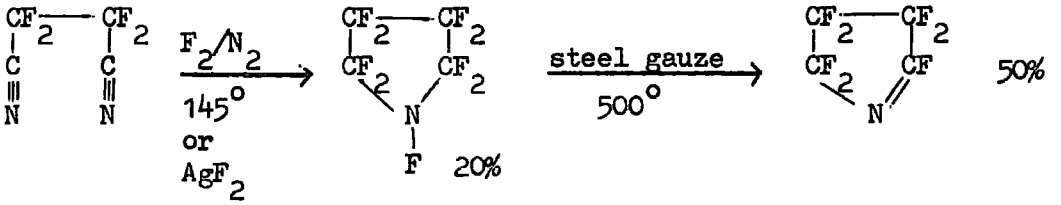
Many fluorinated heterocyclic compounds have been prepared via ring cyclization methods. Brown[80] prepared a cyclic imide by reacting perfluoroglutarodinitrile with excess liquid ammonia.



Perfluoropyrazolidine has been prepared[81] by the cyclization of malononitrile using elemental fluorine at elevated temperatures.

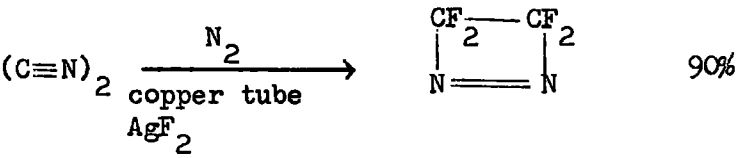


In a similar reaction, Bigelow[82] prepared perfluoroazacyclopentane(I) which was defluorinated to yield heptafluoro-1-pyrroline(II).

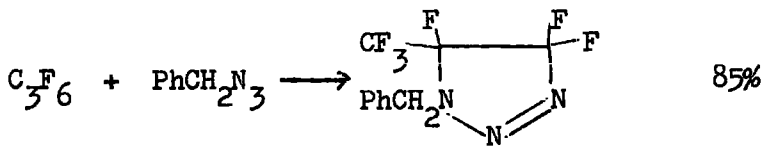


(I) (II)

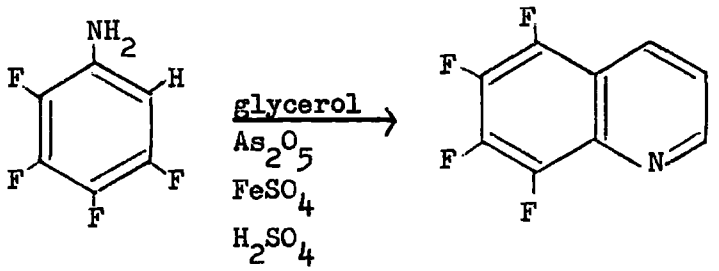
Tetrafluoro-3,4-dihydro-1,2-diazate has been prepared by Emeleus and Hurst[83] by the fluorination of cyanogen with silver difluoride.



Carpenter and co-workers[84] prepared a number of substituted triazolines. Benzyl azide reacted slowly with perfluoropropene and perfluorobutene-2 at 150° to give the triazolines, 1-benzyl-4,4,5-trifluoro-5-trifluoromethyl-1,2,3-triazoline and 1-benzyl-4,5-difluoro-4,5-bistrifluoromethyl-1,2,3-triazoline respectively.



The workers at Durham[85] have recently prepared 5,6,7,8-tetrafluoroquinoline by the Skraup reaction from 2,3,4,5-tetrafluoroaniline and glycerol.



CHAPTER 2

PREPARATION OF HIGHLY CHLORINATED NITROGEN-HETEROCYCLIC COMPOUNDS

PREPARATION OF HIGHLY CHLORINATED NITROGEN-HETEROCYCLIC COMPOUNDS.

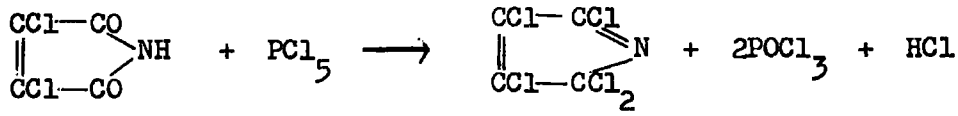
It has been shown that so far the only general practical route to highly fluorinated aromatic nitrogen-heterocyclic compounds is by the halogen-exchange reaction between highly-chlorinated heterocycles and metal fluorides.

The success of this method of preparing fluorinated heterocycles depends ultimately on the availability of the chlorinated heterocyclic compounds. Although the halogenation of nitrogen-heterocyclic compounds has been the subject of many workers, it has only recently become possible, except in one or two cases, to obtain the perchloro-heterocycles in substantial amounts.

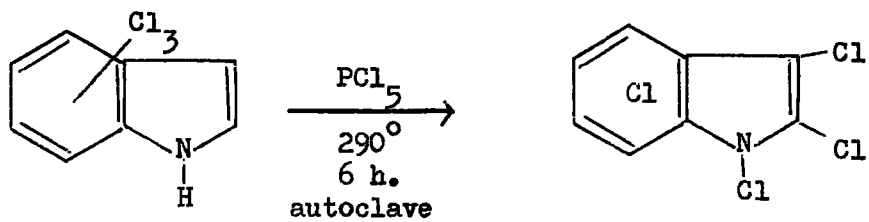
Chlorination of Compounds Containing a Five Membered Nitrogen Ring System.

Pyrrole, being very susceptible to electrophilic attack, undergoes chlorination under mild conditions with subsequent isolation of high yields of chloropyrroles. 2-Chloro-, 2,5-dichloro-, 2,3,5-trichloro-pyrrole have all been prepared by reacting pyrrole with sulphuryl chloride in ether at 0°.[86] Mazzara[87] reacted one mole of pyrrole, dissolved in ether, with four moles of sulphuryl chloride at 0° and obtained a 60% yield of 2,3,4,5-tetrachloropyrrole.

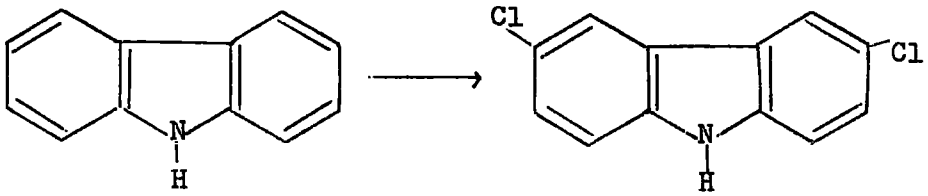
When dichloromaleic imide was heated with phosphorus pentachloride, 2,2',3,4,5-pentachloropyrrolenine was isolated in good yield.[88,63]



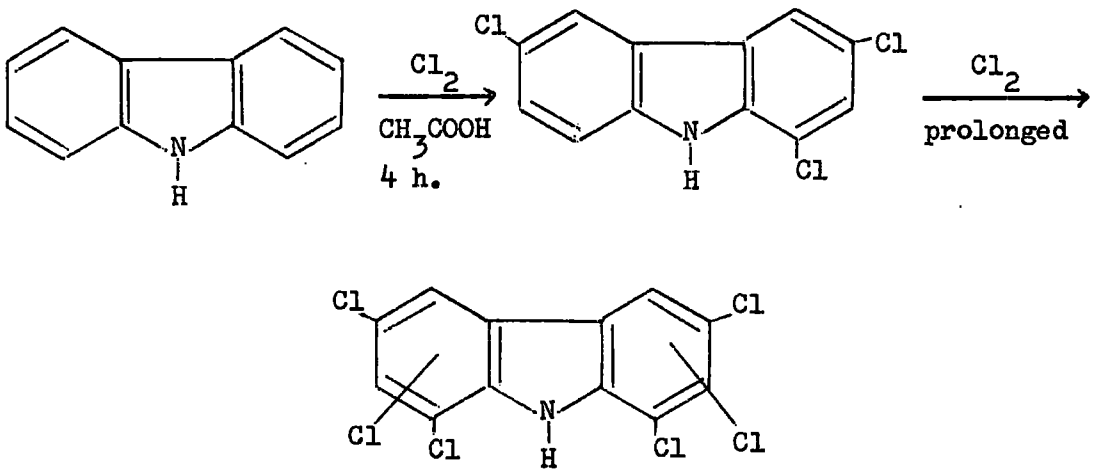
Highly chlorinated indoles have recently been prepared.[89] The reaction of N-acetylindoline-2-sodium sulphonate with chlorine at 5° produces a trichloroindole of unknown structure. Treatment of this trichloroindole, dissolved in carbon tetrachloride, with chlorine at room temperature resulted in a 65% yield of pentachloroindole, again the position of the chlorine atoms were not fixed. 1,x,x,x,x,x-Hexachloroindole was obtained in 75% yield when the reaction was carried out in the presence of a crystal of iodine. Heptachloroindole was obtained in 60% yield when the trichloroindole was heated with phosphorus pentachloride at 290° for approximately six hours.



Carbazole has been chlorinated by many of the well-known chlorinating agents. 3-Chlorocarbazole, and 3,6-dichlorocarbazole are obtaining in good yield when carbazole is reacted with sulphuryl chloride.[90]



1,3,6-trichlorocarbazole has been prepared[91] by passing chlorine through a solution of carbazole in glacial acetic acid for 4 hours. If the reaction time is prolonged 1,3,6,8,x,x,-hexachlorocarbazole is obtained.



When chlorine is passed through a solution of carbazole in carbon tetrachloride, 1,3,6,8-tetrachlorocarbazole is obtained in good yield.[92] Zalkindard and Konarenko[92] obtained 1,2,3,4,5,6,7,8-octachlorocarbazole in low yield, when chlorine was passed through a solution of 1,3,6,8-tetrachlorocarbazole, dissolved in carbon tetrachloride, to which a crystal of iodine had been added.

Weith[93] has also prepared octachlorocarbazole by reacting 1,3,6,8,x,x-hexachlorocarbazole with antimony pentachloride at 100°.

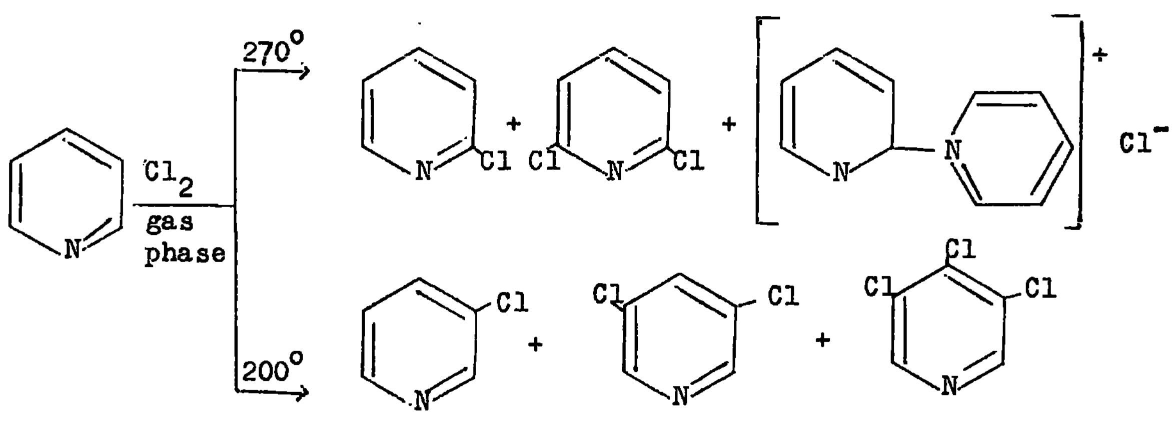
Chlorination of Compounds Containing a Six Membered Nitrogen Ring System.

Chlorination of Pyridine.

The introduction of chlorine into the pyridine nucleus has been studied in considerable detail by a large number of workers. A review of the literature has shown that although there are a considerable number of routes to lower chlorinated pyridines, it is only in recent publications that methods for preparing highly chlorinated pyridines in substantial amounts have been noted.

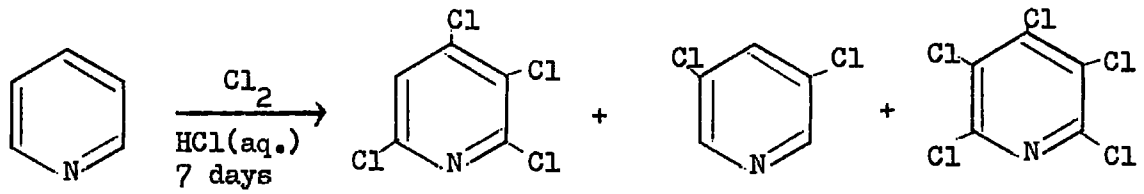
Preparation of lightly chlorinated pyridines.

The direct chlorination of pyridine using elemental chlorine has been extensively studied by Wibaut and his co-workers.[94,95] Pyridine mixed with chlorine and diluted with nitrogen was passed through a tube packed with pumice at elevated temperatures. Wibaut showed that the position of substitution varied with temperature. To effect 3- or 3,5-substitution the reaction is carried out at 200°. At 270° the main products were 2-chloro- and 2,6-dichloropyridines:

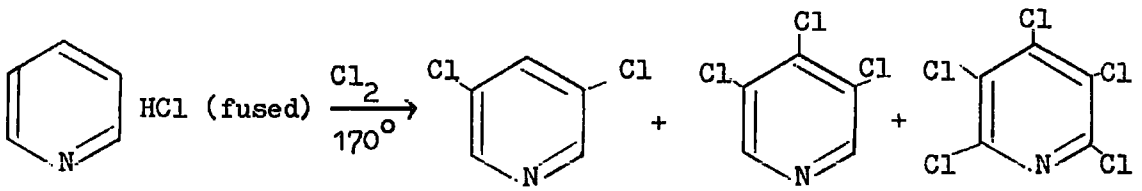


The presence of 1-(2-pyridyl)pyridinium chloride was indicated by the isolation of 2-aminopyridine from the reaction products upon hydrolysis. If the reaction temperature was raised to 400° much carbonization took place, with formation of 2,6-dichloropyridine as the main product. 2-Chloropyridine was also prepared when chlorine was reacted with pyridine in carbon tetrachloride at 400° [96] in the vapour state.

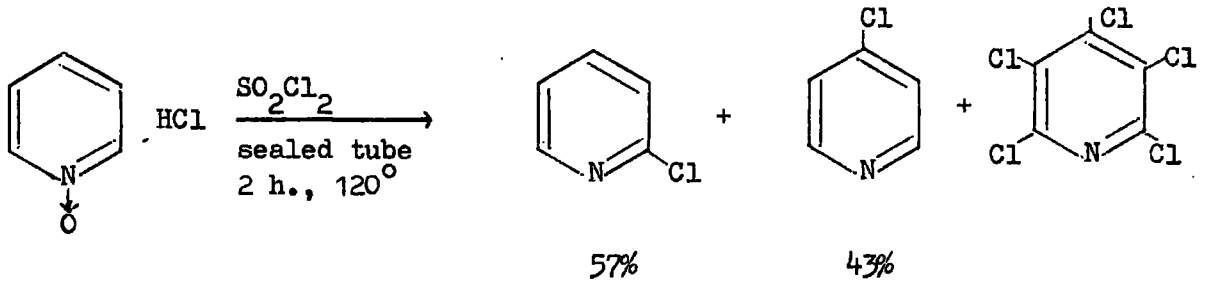
Sell and Dootson[97] obtained 2,3,4,6-tetrachloropyridine as the main product when they passed chlorine through a solution of pyridine saturated with hydrogen chloride for one week.



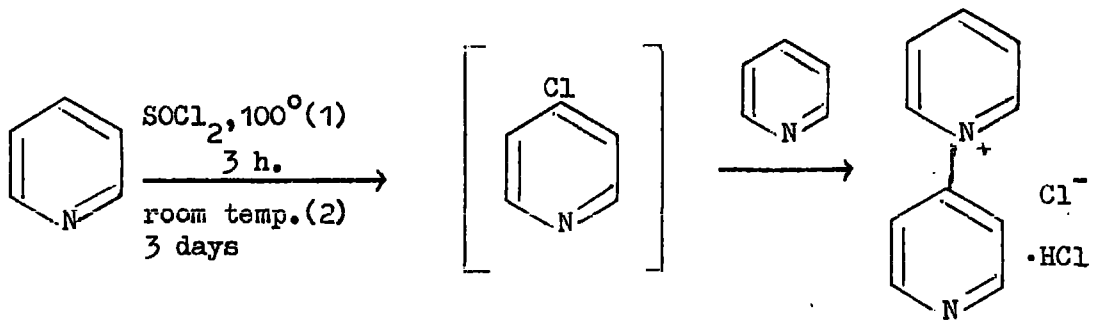
Wibaut and Nicoli[95] obtained similar results when they passed chlorine through fused pyridine hydrochloride at 170°.



Low yields of 2-chloro- and 4-chloropyridine were obtained when pyridine N-oxide was chlorinated with gaseous chlorine in chloroform.[98] Bobranski and co-workers[99] reported that pyridine 1-oxide and sulphuryl chloride gave a 65% yield of a mixture of 2-chloro- and 4-chloro-pyridines with a small amount of pentachloropyridine.

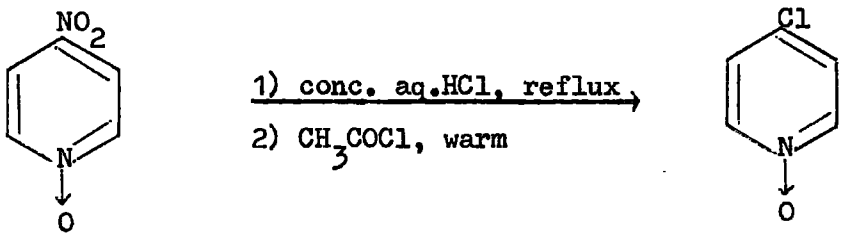


Thionyl chloride has also been used to chlorinate pyridine.[100] The formation of 1-(4-pyridyl)pyridinium chloride hydrochloride from the reaction between pyridine and thionyl chloride suggested the intermediate formation of 4-chloropyridine.

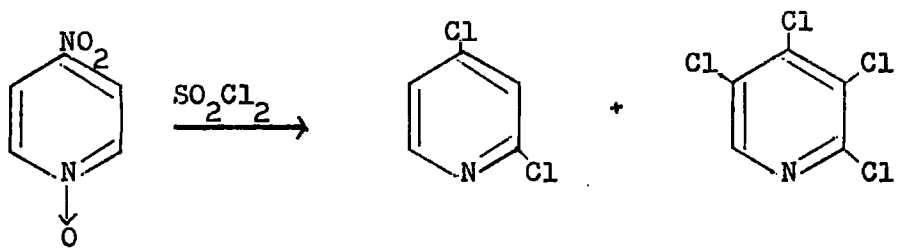


Chlorination of pyridine with aqueous $HCl/KClO_3$ mixture yielded a small quantity of chlorinated products but if the chlorination was carried out with dry HCl and $KClO_3$ a mixture of trichloropyridines were obtained.[101]

4-Nitropyridine N-oxide has been used as the starting material in the preparation of chloropyridines. 4-Nitropyridine N-oxide can readily be prepared by nitration of pyridine N-oxide.[102,103] When refluxed with aqueous hydrogen chloride, the nitro group is replaced to give an 80% yield of 4-chloropyridine N-oxide.[104] The yield is slightly increased if acetyl chloride is used to bring about the exchange.[105]

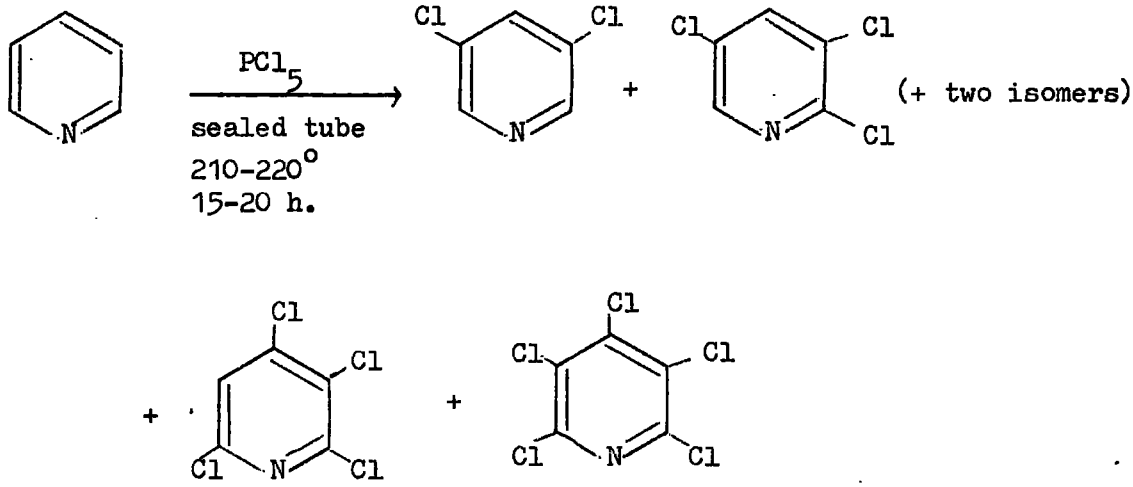


2,4-Dichloropyridine, with small amounts of 2,3,4,5-tetrachloropyridine were obtained when 4-nitropyridine N-oxide was heated with sulphuryl chloride.[106,107]



The reaction of 4-nitropyridine N-oxide with phosphorus oxychloride at 70° gave a mixture of 4-chloropyridine N-oxide and 2,4-dichloropyridine.[104]

Sell and Dootson[108] obtained a mixture of di-, tri-, tetra-, and pentachloropyridines when they chlorinated pyridine with phosphorus pentachloride in sealed tubes at 210-220°.

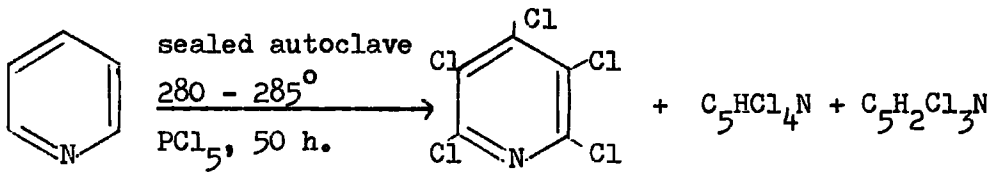


Sell and Dootson[109] had previously, after earlier attempts by Behrmann and Hofmann,[110] isolated pentachloropyridine by treating citrazinic acid with a mixture of phosphorus pentachloride and phosphorus oxychloride.

Highly Chlorinated Pyridines

The method used by Sell and Dootson[108] to obtain chlorinated pyridines was reinvestigated by Chambers, Hutchinson and Musgrave.[111,56]

Pyridine and excess phosphorus pentachloride where heated to 210-220° for 72 h. in a sealed autoclave to produce mainly trichloro and tetrachloropyridines, with pentachloropyridine formed in 1•5% yield. The yield of pentachloropyridine was increased to 15% when the reaction was carried out at 280-285°.



15% 18% 3•5%

Rechlorination of mixtures of di- and trichloropyridines led to good yields of pentachloropyridine and mixed tetrachloropyridines. Thus, by chlorinating pyridine with phosphorus pentachloride reasonable yields of pentachloropyridine can be obtained.

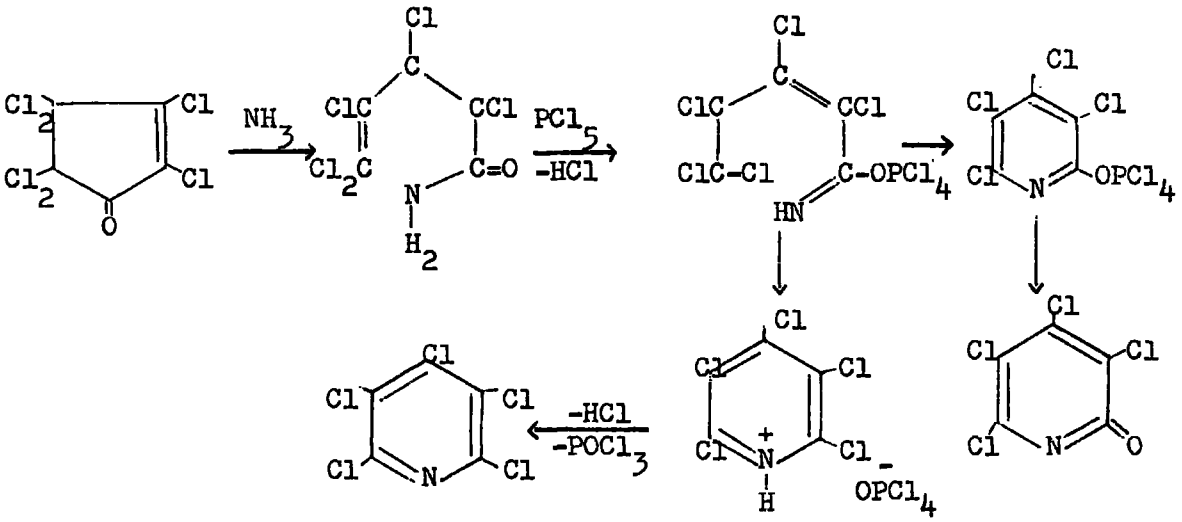
Another group of workers[57] have recently reported the reaction between pyridine and phosphorus pentachloride. Haszeldine and co-workers, using a large excess of phosphorus pentachloride obtained pentachloropyridine in 96% yield.

The flow method for producing chloropyridines used by Wibaut and Nicolai[94,95] has been investigated further in recent months.[112] The mixed vapours of pyridine, or 2-chloropyridine, and chlorine were passed through a steel tube containing coconut carbon at 300-450°

producing pentachloropyridine and lower chlorinated products in good overall yield.

In the last few years reports on several indirect methods leading to the preparation of pentachloropyridine have been published.

Pentachloropyridine has been synthesised from hexachlorocyclopentenone.[113] Reaction of the hexachlorocyclopent-1-ene-3-one with liquid ammonia in ether solution gave the amide of pentachloro-penta-2,4-dienoic acid. Further chlorination of the amide in benzene solution, followed by heating to eliminate hydrogen chloride and phosphorus oxychloride, produced pentachloropyridine in 58% overall yield. Perchloro-2-pyridone was produced as a by-product.



The gas-phase chlorination of carbamoyl chlorides has led to the preparation of highly chlorinated heterocyclic compounds.[114] Piperidine-N-carbonyl chloride was prechlorinated with chlorine using kieselguhr

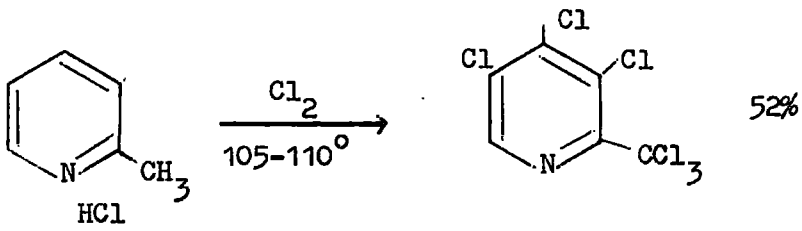
impregnated with copper II chloride as catalyst at 50-150°. The pre-chlorinated compound was then further chlorinated with chlorine at higher temperatures to give pentachloropyridine.

Highly chlorinated pyridines have also been prepared from methyl-pyridines. Chlorination of 3,5-dichloro-2-trichloromethylpyridine with chlorine for 23 hours at 190-210°, while irradiated with ultra-violet light, produced 2,3,5,6-tetrachloropyridine.[115] Using a similar procedure, pentachloropyridine and 2,3,4,5-tetrachloropyridine have been obtained from partially chlorinated pyridines.

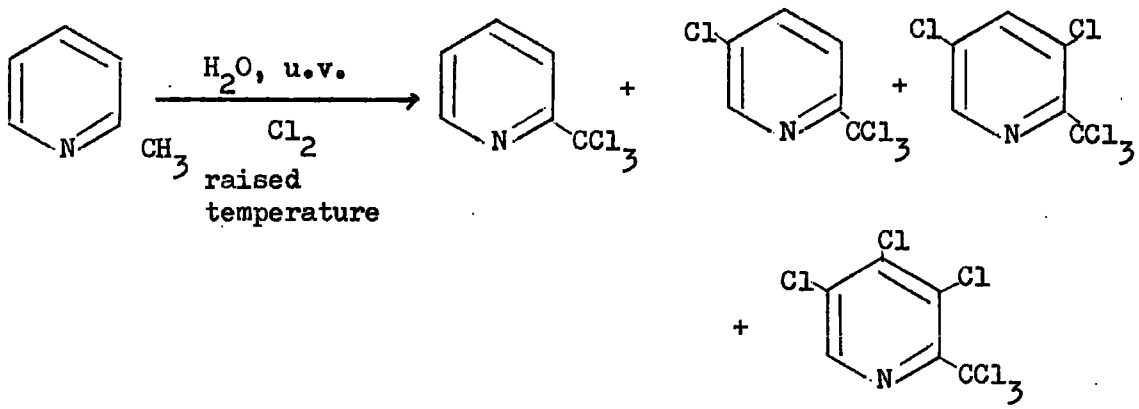
Pentachloropyridine was prepared when 2-methylpyridine was chlorinated with chlorine by passing the mixed vapours, diluted with nitrogen or carbon tetrachloride, over coconut carbon at elevated temperatures.[112] Holtschmidt and Zechler[116] obtained tetrachloro- and pentachloropyridines from the chlorination of N-methylpiperidine.

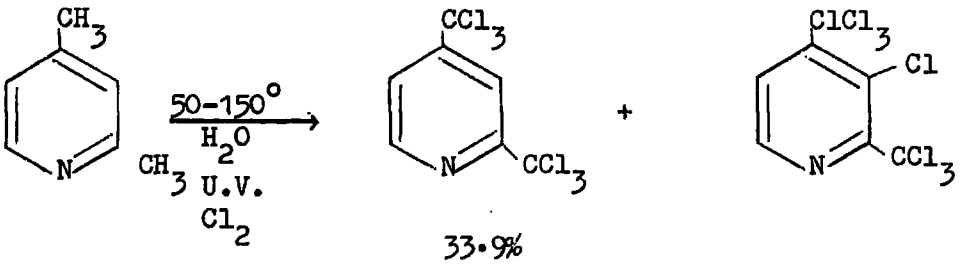
Chlorination of Methyl Pyridines.

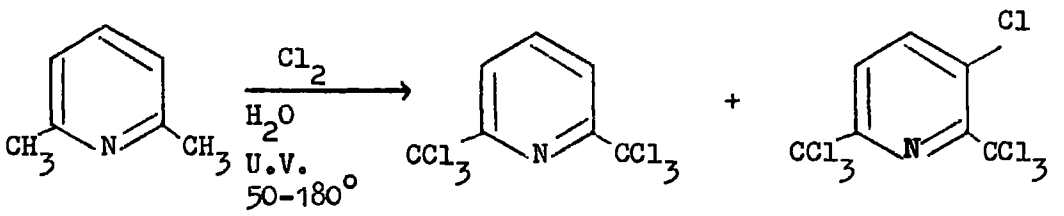
The earliest observations into the chlorination of the picolines were carried out by Sell.[117,118] 2-Methylpyridine hydrochloride was first prepared by saturating 2-methylpyridine with hydrogen chloride. The hydrochloride was then chlorinated at 105-100° by passing a stream of chlorine through the hydrochloride. A 52% yield of 3,4,5-trichloro-2-trichloromethylpyridine was obtained.

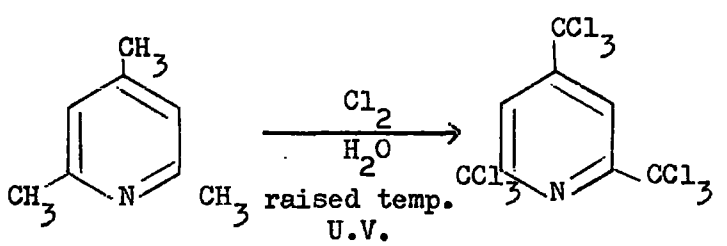


Following these earlier investigations by Sell, the chlorination of picolines has been further studied by McBee and co-workers.[78] McBee showed that substitution in the side-chain took place first, but if sufficiently vigorous conditions were employed, chlorine was introduced into the nucleus. McBee chlorinated mono-, di- and trimethyl pyridines using elemental chlorine at elevated temperature in the presence of water, acting as solvent to dissolve any hydrochlorides that were formed.

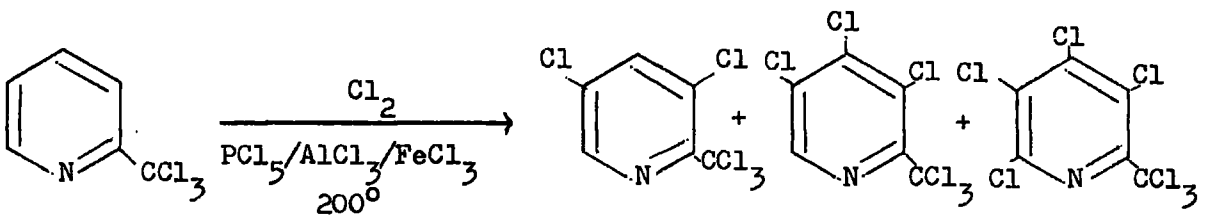


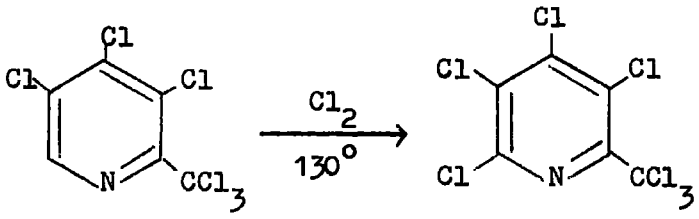






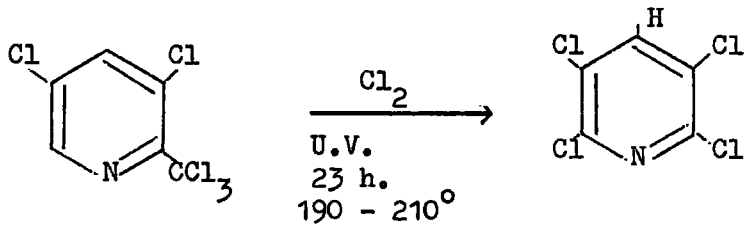
Several highly chlorinated 2-methylpyridines have been prepared by chlorinating partially chlorinated 2-methylpyridines.[119]





Perchloro-α-picoline has also been obtained by photochemical chlorination[120] of α-picoline.

If sufficiently vigorous conditions are employed chloropyridines are obtained from the chlorination of picolines, the chlorinated side chain being replaced by chlorine.[112,115]



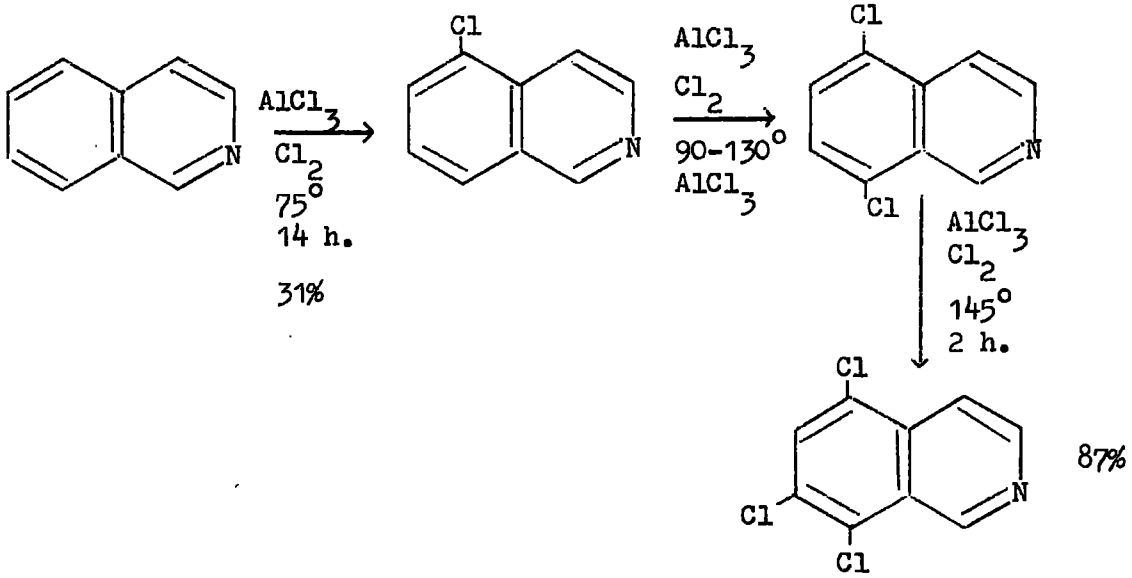
Chlorinated Bipyridyls.

A review of the literature has shown that only one chlorinated bipyridyl has been prepared.[121] 5,5'-dichloro-2,2'-bipyridyl was prepared in 8% yield by the Ullmann reaction from 2-bromo-5-chloro-pyridine.

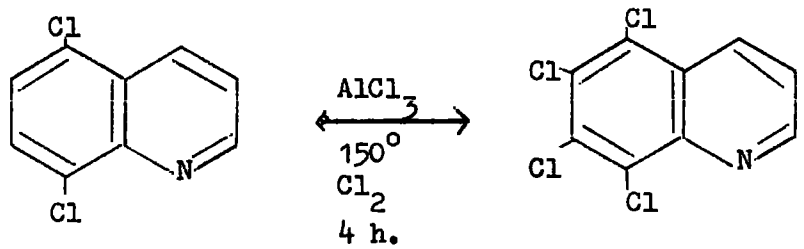
Chlorination of Quinolines.

Little work on the direct chlorination of quinoline and isoquinoline has been reported in the literature. Gordon and Pearson[122] chlorinated

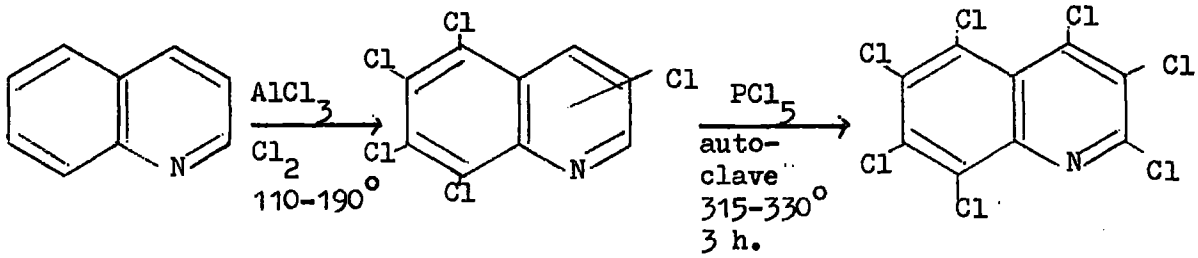
the aluminium chloride complexes of isoquinoline and quinoline to give in good yield, halogen derivatives substituted in the benzenoid ring. 5-Chloro-, 5,8-dichloro-, and 5,7,8-trichloroquinolines were obtained when chlorine was passed through the aluminium chloride complexes of quinoline and isoquinoline



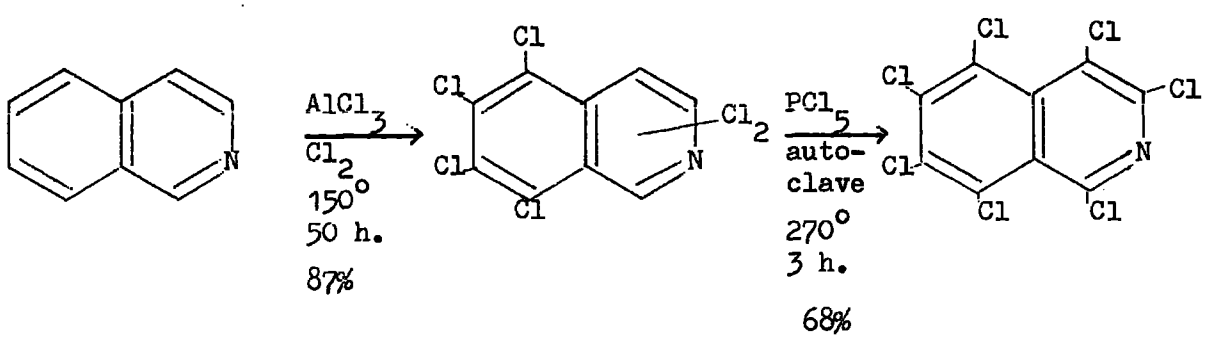
Complete chlorination of the benzenoid ring was achieved in the case of quinoline giving 5,6,7,8-tetrachloroquinoline.



Workers at Durham[58] have developed Gordon and Pearson's method, and by prolonging the reaction time managed to substitute chlorine into the heterocyclic ring. Thus, the complex formed between quinoline and aluminium chloride was chlorinated at 110-190° over 48 hours. The product was decomposed with ice to yield a mixture of tetra- and pentachloroquinoline. Further chlorination of this mixture with phosphorus pentachloride at 315-330° yielded heptachloroquinoline in 78% yield.



Similarly the chlorination of the aluminium chloride complex of isoquinoline was developed to yield hexachloroisoquinoline which on further chlorination with phosphorus pentachloride, gave a good yield of heptachloroisoquinoline.



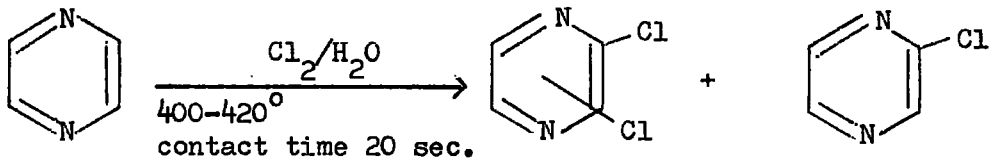
Heptachloroquinoline has also been prepared by the chlorination of 1,2,3,4-tetrahydroquinoline N-carbonyl chloride at elevated temperatures.[114]

Chlorinated Diazines.

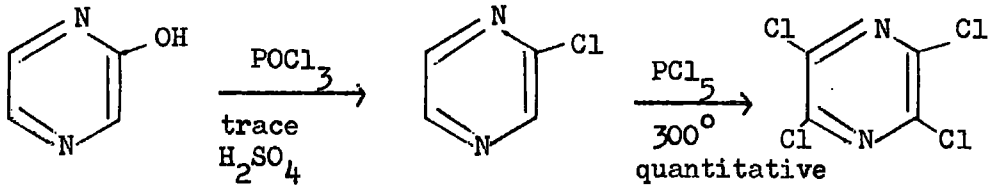
The three isomeric perchlorodiazines have all been prepared.

Pyrazine.

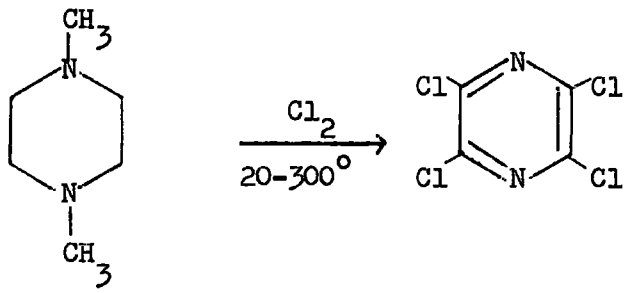
Lightly chlorinated pyrazines have been obtained by the reaction of chlorine with the heterocycle at elevated temperatures[123-127] utilizing an extension of the flow method used by Wibaut and Nicoli[95] to obtain lightly chlorinated pyridines. Thus chlorine and pyrazine, preheated to 200° and mixed with water vapour, were passed through a metal tube maintained at 400-420° to give mostly dichloropyrazines with some 2-chloropyrazine.



2-Chloropyrazine, prepared by replacing the hydroxy group in 2-hydroxypyrazine with chlorine using phosphorus oxychloride, has been further chlorinated with phosphorus pentachloride to give tetrachloropyrazine in good yield.[128]



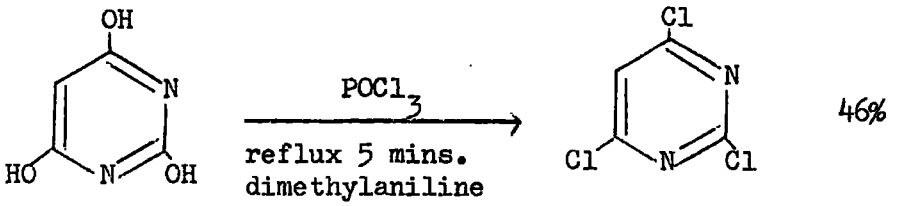
Holtschmidt and Zechar[116] obtained tetrachloropyrazine from the chlorination of N,N'-dimethylpiperazine or N,N'-bis(hydroxyethyl)-piperazine



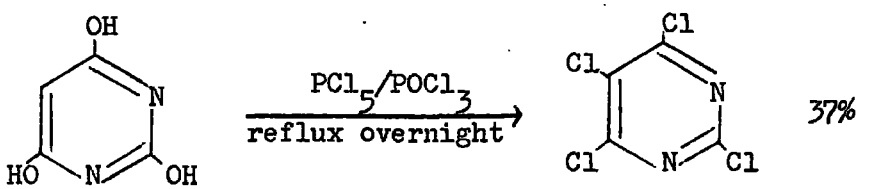
Pyrimidine.

Chlorinated pyrimidines have been readily prepared from the chlorination of barbituric acid and hence no attempt has been made to prepare highly chlorinated pyrimidines from the direct chlorination of pyrimidine.

The reaction between barbituric acid and phosphorus oxychloride, carried out in sealed tubes at elevated temperatures, was developed to give 2,4,6-trichloropyrimidine.[129] Baddiley and Topham[130] improved the yield of 2,4,6-trichloropyrimidine by carrying the reaction out in the presence of dimethylaniline.



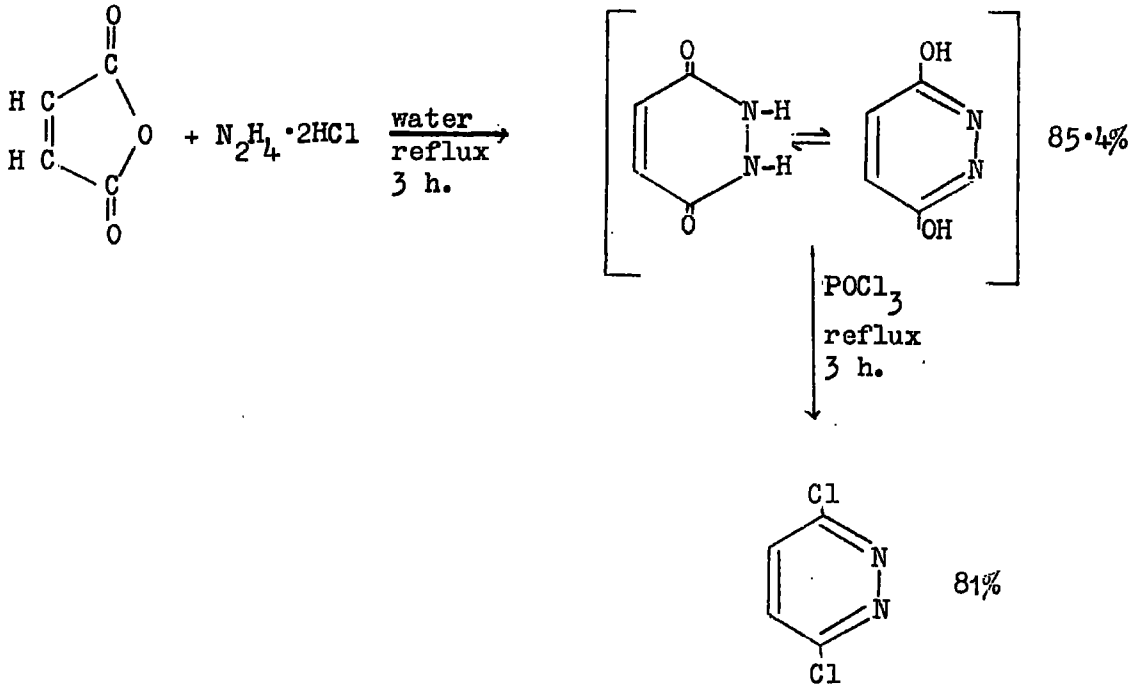
Two groups of workers[131,132] prepared tetrachloropyrimidine from barbituric acid. Childress and McKee[132] obtained a 37% yield of tetrachloropyrimidine on refluxing barbituric acid with a mixture of phosphorus pentachloride and phosphorus oxychloride.



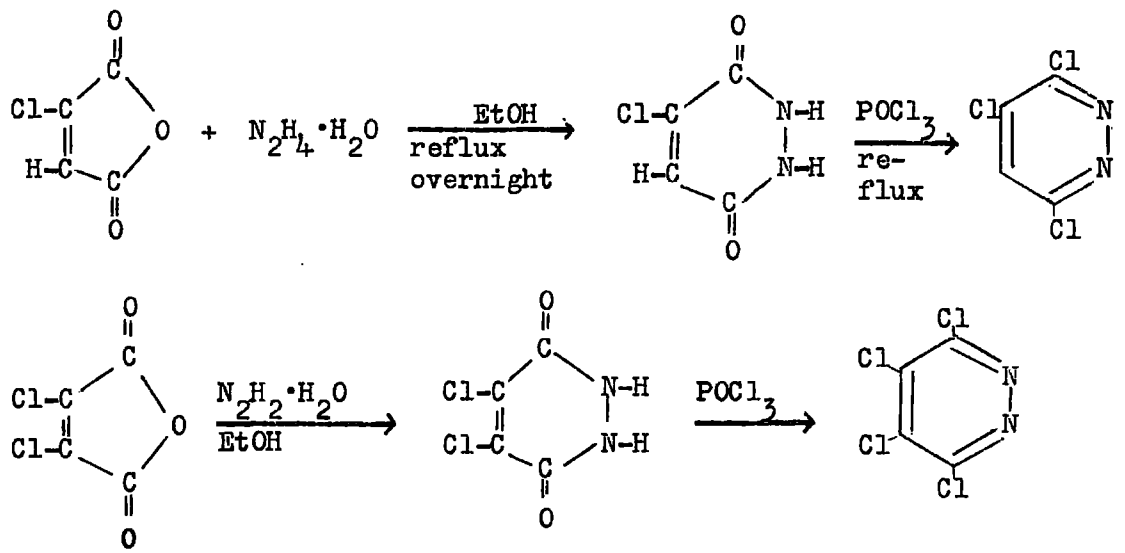
Pyridazine

Pyridazine has not been chlorinated directly, but several chloropyridazines have been prepared by exchange of hydroxyl groups for chlorine in substituted pyridazines.

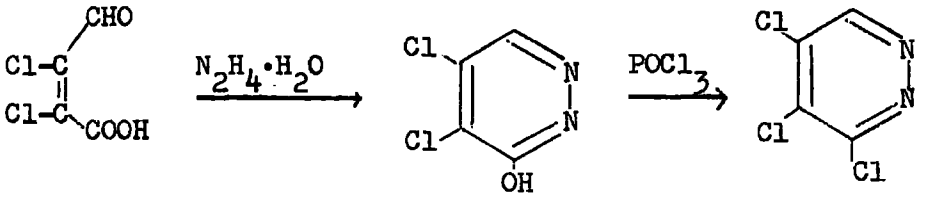
Gabriel[133] obtained 3-chloropyridazine from the reaction of phosphorus oxychloride with 3-hydroxypyridazine. Mizzoni and Spoerri[134] prepared 3,6-pyridazine-diol from maleic anhydride and hydrazine hydrochloride and replaced the hydroxy groups using phosphorus oxychloride.



By similar routes 3,4,6-trichloropyridazine[135,136] and 3,4,5,6-tetrachloropyridazine[136] have been prepared from monochloromaleic anhydride and dichloromaleic anhydride respectively.

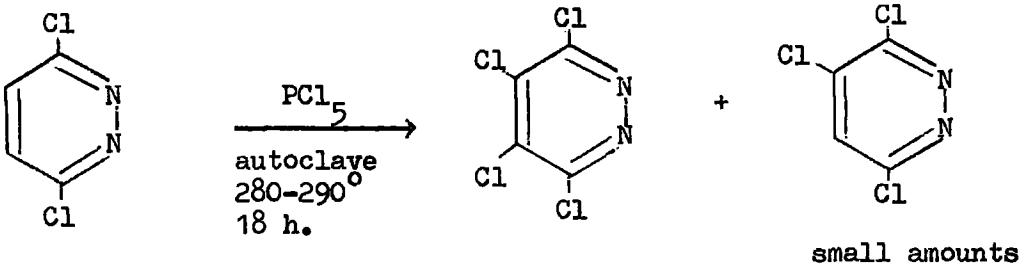


3,4,5-Trichloropyridazine has also been prepared.[137]



Recent workers[138] threw some doubt on the purity of the chloropyridazines obtained by these methods and outlined several processes by which the chloropyridazines could be purified.

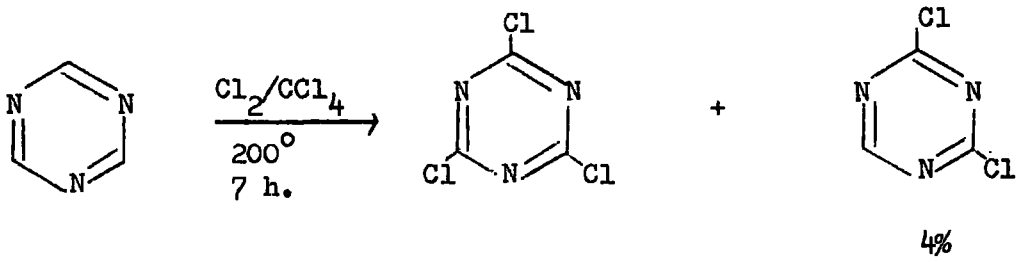
Chambers, MacBride and Musgrave[59] prepared tetrachloropyridazine in 56% yield from the chlorination of 3,6-dichloropyridazine[134] using phosphorus pentachloride



small amounts

Chlorinated Triazines.

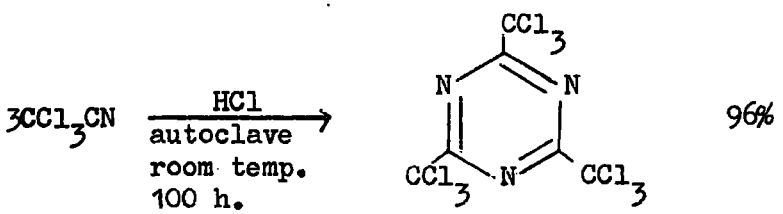
The chlorination of 1,3,5-triazine has been developed to give the perchloroheterocycle, 2,4,6-trichloro-1,3,5-triazine.[139] A mixture of s-triazine and carbon tetrachloride-chlorine solution was heated in a sealed tube at 200° to give a 25% yield of perchloro-s-triazine with small amounts of dichloro-s-triazine.



4%

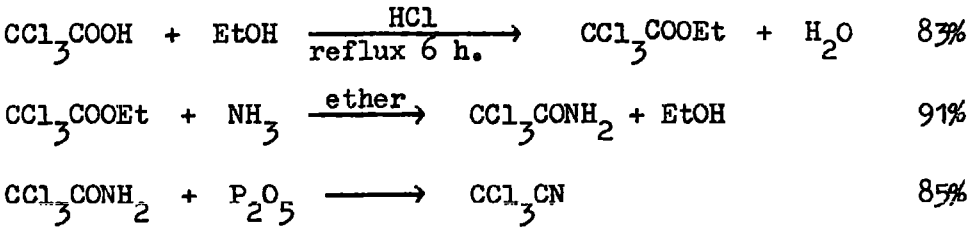
Holtschmidt and Zecher[116] obtained trichloro-s-triazine from the ultraviolet chlorination at elevated temperatures of hexamethylenetetramine.

Several polychloromethyl-s-triazines have been prepared. McBee[79] obtained 2,4,6-tris(trichloromethyl)-1,3,5-triazine from the polymerisation of trichloroacetonitrile in the presence of anhydrous hydrogen chloride.



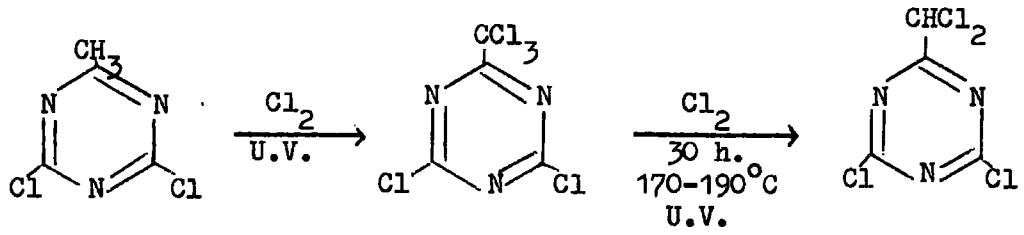
96%

The trichloroacetonitrile was obtained by the following sequence of reactions.



Kober and Grundmann[67] prepared 2,4-dichloro-6-trichloromethyl-s-triazine from the vapour phase chlorination of either 2,4-dichloro-6-

methyl-s-triazine or 2,4-dichloro-6-dichloromethyl-s-triazine.



CHAPTER 3

DISCUSSION OF EXPERIMENTAL. PART 1.

DISCUSSION OF EXPERIMENTAL. PART 1.

The three isomeric octafluoro-2,2'-; -3,3'-; and -4,4'-bipyridyls have been prepared together with several chlorofluorobipyridyls. The route to these polyfluorobipyridyls is represented schematically in DIAGRAM 1.

The synthesis of octafluoro-3,3'-(V), octafluoro-4,4'-(VI), 3-chloroheptafluoro-4,4'-(VII), and 3,5-dichlorohexafluoro-4,4'-(VIII)-bipyridyl depends ultimately on:-

(1) the availability of pentachloropyridine(I), and

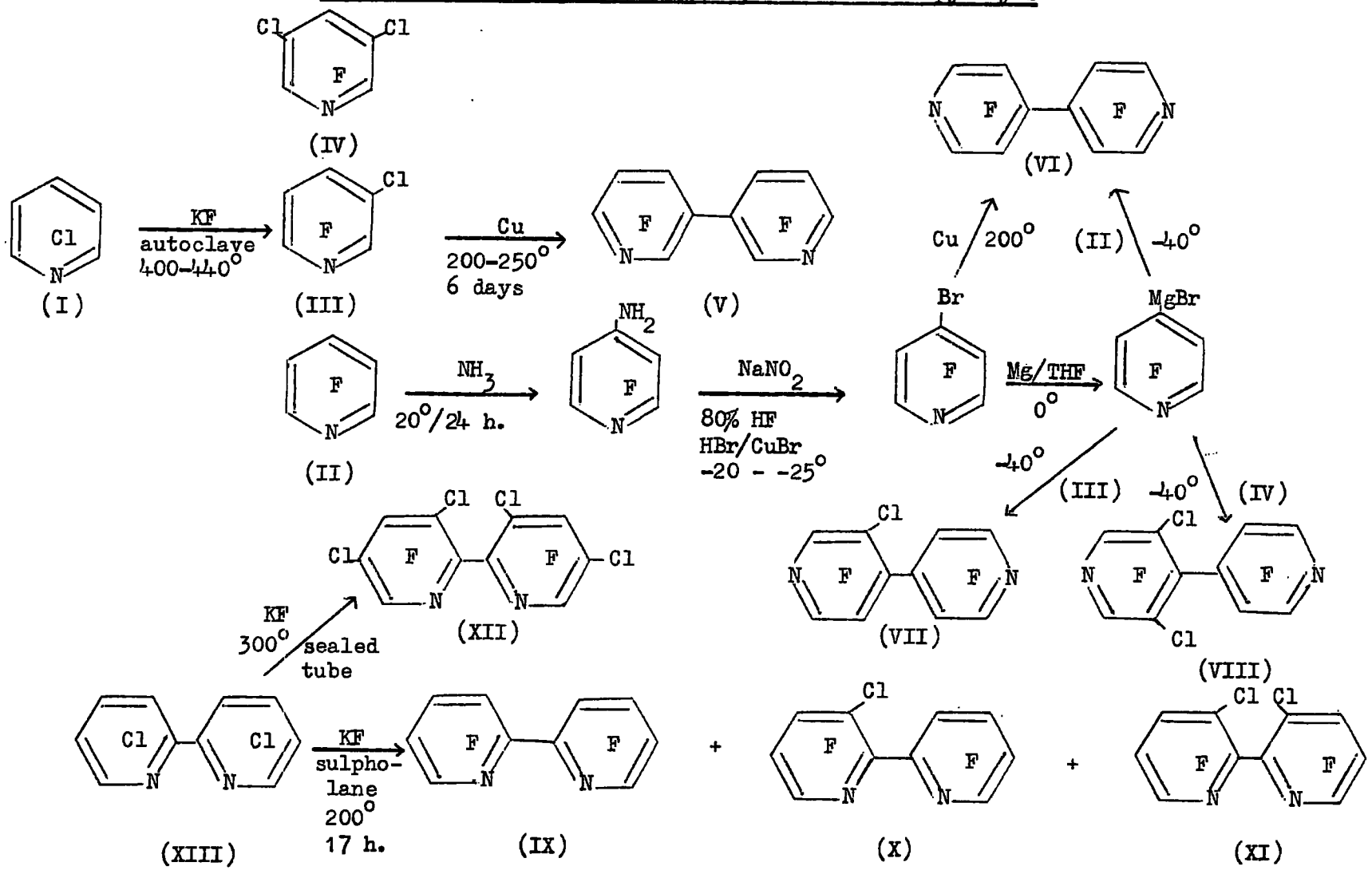
(2) the halogen-exchange reaction between chlorine and fluorine in pentachloropyridine to give pentafluoropyridine(II), 3-chlorotetrafluoropyridine(III), and 3,5-dichlorotrifluoropyridine(IV).

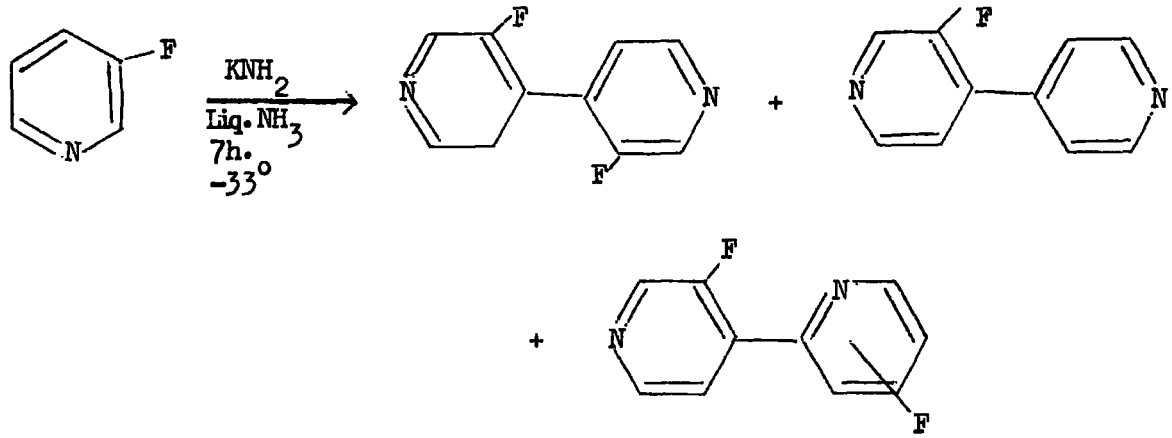
The synthesis of octafluoro-2,2'-(IX), 3-chloroheptafluoro-2,2'-(X), 3,3'-dichlorohexafluoro-2,2'-(XI), and 3,3',5,5'-tetrachlorotetrafluoro-2,2'-(XII) bipyridyls has been accomplished by the halogen-exchange reaction between chlorine and fluorine in octachloro-2,2'-bipyridyl(XIII) using potassium fluoride.

The only previously prepared fluorinated bipyridyls were the mono- and difluoro-bipyridyls obtained from the reaction of potassium amide on 3-fluoropyridine in liquid ammonia.[140]

DIAGRAM 1

Preparation of Octafluoro- and Perfluorochlorobipyridyls

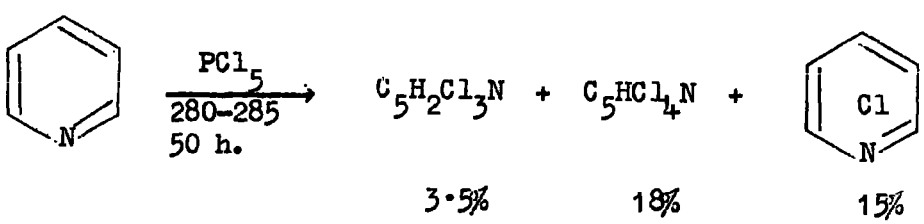




Chlorination of Pyridine.

Although several routes to highly chlorinated pyridines have recently been reported in the literature,[112-116] at the time this research programme was initiated none had been reported that gave pentachloropyridine in substantial yields.

Pentachloropyridine was first prepared by Sell and Dootson[108] by reacting pyridine with phosphorus pentachloride in sealed tubes at 210-220°. Chambers, Hutchinson and Musgrave[56] developed this reaction obtaining mixtures of tri-, tetra-, and pentachloropyridines, the yield of pentachloropyridine being approximately 15%.



The lower chlorinated pyridines could then be rechlorinated with phosphorus pentachloride to give mainly tetra- and pentachloropyridine. Thus, although this route was tedious, pentachloropyridine could be obtained in approximately 50% overall yield.

As the demand for pentafluoropyridine and the chlorofluoropyridines increased it soon became apparent that a better route to pentachloropyridine had to be found. The main disadvantage of the two stage reaction used by the Durham workers[56] was the time spent in preparing the pentachloropyridine, usually up to a period of fourteen days being required to complete the two stage synthesis.

On the basis of the results obtained by Sell and Dootson and the workers at these laboratories a detailed study of the reaction between pyridine and phosphorus pentachloride was carried out eventually leading to preparation of pentachloropyridine in 70-80% yield in a one step process. The results are recorded in TABLE 1.

Procedure.

The autoclave, charged with the reactants, was heated for the required time and then allowed to cool. The hydrogen chloride, formed during the reaction, was allowed to escape before the autoclave was opened. The contents of the autoclave were hydrolysed with ice and water. The chloropyridines, obtained by steam distillation, were extracted into methylene dichloride and the solvent removed by distillation. (In latter reactions, when the product consisted mainly

TABLE 1.

Chlorination of Pyridine with Phosphorus Pentachloride

Reaction	Wt. of PCl_5 (gms.)	Wt. of C_5H_5N (gms.)	"Catalyst"	Time hr.	Temp. °C	Wt. of Chlorinated pyridines (gms.)	Mole % Composition of Product $C_5H_3Cl_2N$	$C_5H_2Cl_3N$	C_5HCl_4N	C_5Cl_5N	Liner
1	2,500	250	-	50	294	204	trace	35	55	10	1
2	3,000	250	-	24	290	140	15	35	35	15	2
3	3,000	250	-	74	295	130	10	30	45	15	2
4	3,000	430	-	24	290	130	20	30	45	5	3
5	3,000	250	$FeCl_3$	17·5	290	130	20	35	35	10	3
6	3,000	250	Stainless steel turnings	24	290	140	10	40	35	15	3
7	3,000	250	Mo	48	295	120	5	30	50	15	3
8	3,000	250	$CuCl_2$	15	355	150	-	10	50	40	4
9	3,000	200	-	33	290	220	-	10	50	40	4
10	1,640	125	-	24	350	160 (some decomposition)	-	35	45	20	5
11	2,175	100	-	24	300	234	-	-	30	70	5
12	2,190	100	-	24	300	225	-	-	10	90	5
13	2,500	100	-	24	300	250	-	-	5	95	5

1. 1st stainless steel liner
2. 2nd stainless steel liner - slightly thicker than 1st.
3. 3rd stainless steel liner - slightly thicker than 2nd
4. 4th stainless steel liner - thiner than 1st, 2nd, or 3rd
5. 1st nickel liner

REACTIONS: 1-9 carried out in 3 litre autoclave
9-13 carried out in 5 litre autoclave

of tetra- and pentachloropyridine, the chloropyridines were filtered off, dispensing with the use of the organic solvent). The chloropyridines were dried by azeotropic distillation with benzene and then distilled through a 20 in. column packed with Dixon gauze into two fractions:-

(i) di-, tri- and tetrachloropyridines, which were then re-chlorinated with phosphorus pentachloride.

(ii) pentachloropyridine, which was used without further purification to prepare the fluoropyridines.

Reaction 1 is typical of the earlier reactions carried out by Hutchinson[56] except that the autoclave had been fitted with a stainless steel liner to prevent, as far as possible, corrosion of the inner faces of the autoclave by the phosphorus chlorides and hydrogen chloride. The autoclave 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 attained slowly and then maintained at the preset value. As with the reactions carried out by Hutchinson, the main products of the reaction were the isomeric tetrachloropyridines.

When a thicker liner was fitted to the autoclave (reactions 2,3) a considerable drop in the overall yield of chlorinated pyridines was obtained although the percentage of pentachloropyridine in the product showed a slight increase. At this time it was reported[141] that when a similar reaction was carried out in which the autoclave had been fitted with a mild steel liner (introduced because of the rapidity with which the stainless steel liners were being corroded) a considerable drop in the yield of chloropyridines was noticed, pentachloropyridine being present in only trace amounts. This justifiably led to the belief that a component (or components) present in the stainless steel in trace amounts was 'catalysing' the reaction. Several reactions were carried out in which a transition metal or metal chloride was added to the reactants in an attempt to improve the overall yield of pentachloropyridine. These reactions are typified by reactions 5,6,7 and 8 in which ferric chloride, finely divided stainless steel turnings, molybdenum and copper(II) chloride were added in catalytic amounts. There was no noticeable change in the yield or composition of the chloropyridines obtained. It was originally thought that the inclusion of copper(II)chloride had had a beneficial effect on the reaction but a control reaction under the same conditions (reaction 9), without the 'catalyst' being present, produced the same result.

To reduce the number of reactions that were necessary to prepare a substantial amount of pentachloropyridine a 5-litre autoclave, fitted

with a nickel liner, was constructed. This autoclave was heated electrically but the temperature of the reaction was controlled in a different way to that previously described. In this heating system 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°). With this system of heating the equilibrium temperature was reached very rapidly (approx. 2 h.).

Typical of the reactions carried out in the large autoclave were Reactions 11, 12 and 13. A considerable improvement in the yield of chloropyridines was obtained and in the case of Reaction 13 a 75% yield of pentachloropyridine and 5% yield of the tetrachloropyridines were obtained.

Conclusions.

Effect of Time.

The majority of the chlorination reactions were carried out over a period of 24 h. Little variation could be found in the composition of chloropyridines by prolonging the reaction time.

Effect of catalyst.

None.

Effect of Temperature.

The results in the table (reactions 1-9) show that to replace all the hydrogen atoms in pyridine with chlorine a temperature greater than 300° is required. The reactions carried out in the larger autoclave with the new system of heating gave virtually complete replacement of the hydrogen atoms even though the maximum temperature recorded at the centre of the autoclave was 300° (Reactions 11-13). However with the new system of heating it is probably true to say, that as the outer walls of autoclave are virtually in contact with red-hot elements, they must be at a considerably higher temperature than 300°. It is probable that, as the autoclave is heating up to the preset temperature the walls of the autoclave are at a temperature in the region of 350-500° and this is the temperature at which reaction is taking place.

A comparison of the results (Reactions 1-9) from this reaction of pyridine with phosphorus pentachloride will show that the thinner the liner the better the overall yield of chlorinated pyridines with a corresponding increase in the percentage of pentachloropyridine. At the time these reactions were performed this effect was not directly connected with the temperature of the reaction, but in the light of the latter results, it could be concluded that as the thickness of the liner was increased the thermal capacity of the autoclave increased, causing a lowering of the temperature of the inside wall of the autoclave.

Mechanism of the Chlorination of Pyridine

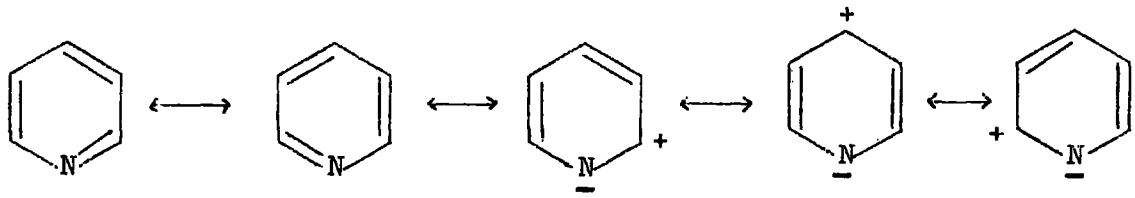
From the results of the elemental chlorination of pyridine by Wibaut and co-workers,[95] it has been shown that at least two different substitution mechanisms prevail at different temperatures. On chlorinating pyridine in the gas phase at 270° a good yield of 2-chloropyridine was obtained together with a small quantity of 2,6-dichloropyridine. If the reaction is carried out at 400° the main product is 2,6-dichloropyridine. Chlorination in the gas phase takes place very slowly at about 200°; at this temperature 3-chloro-, and 3,5-dichloropyridines are obtained with smaller amounts of 3,4,5-trichloropyridine.

Thus, at the lower temperatures at which pyridine reacts with halogens to give β-substituted products it seems likely that the course followed is one of electrophilic attack. At temperatures above 270°, free radicals will be formed due to the homolytic fission of the chlorine-chlorine bond, and the position of substitution by free radical attack is mainly at the α positions. These positions of substitution, whether electrophilic or free radical, are in agreement with theoretical considerations involving substitution reactions in pyridine.

Pyridine contains a conjugated system of six π-electrons, one being contributed by each atom in the ring. The electron affinity of nitrogen is greater than that of carbon and as a result the π-electrons tend to be drawn towards the nitrogen which thereby acquires a negative charge.

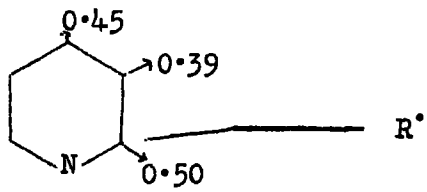
In terms of the resonance approach, the electron density at various

positions of the pyridine nucleus is derived from the summation of the contributing structures shown below.



Thus, the resonance method predicts from the summation of all the contributing structures that there will be a partial positive charge at the 2,4, and 6 positions in pyridine. The assumption is made that an electrophilic reagent will attack at the position of greatest electron density, and hence,electrophilic substitution takes place in the 3, and 5 positions.

For free radical attack, the free valence (the free valence is defined as the difference between the maximum bond number of a carbon atom ($N_{max} = 3+\sqrt{3}$) 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) is calculated and it is assumed that a free radical will attack at the position of maximum free valence.[142]



Thus free radical attack will take place in the 2 and 6 positions.

Although no investigation into the mechanism of the reaction between phosphorus pentachloride and pyridine has been carried out, Wyman and co-workers[143] chlorinated various alkylated aromatic hydrocarbons using phosphorus pentachloride showing that the chlorination proceeded in either a thermal or catalysed (benzoyl peroxide) reaction:

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

A detailed study of the mechanism was not made, but it was suggested that dissociation of phosphorus pentachloride into phosphorus trichloride and chlorine, followed by thermal fission of the chlorine-chlorine bond to give chlorine radicals which then abstracted hydrogen from the hydrocarbon was a possible reaction mechanism.

Drakesmith[146] has postulated a similar type of reaction scheme which could apply in the chlorination in pyridine using phosphorus pentachloride.*

$$C_5H_5N + PCl_5 \longrightarrow C_5H_4ClN + PCl_3 + HCl$$

$$PCl_5 \rightleftharpoons PCl_3 + Cl_2$$

$$Cl_2 \rightleftharpoons 2Cl^{\bullet} \quad \text{(thermal)}$$

$$R\text{-}H + Cl^{\bullet} \longrightarrow R^{\bullet} + HCl$$

*One mole-equivalent of PCl_5 is required to replace each hydrogen atom in pyridine.

$$R^{\cdot} + PCl_5 \longrightarrow RCl + PCl_4^{\cdot}$$

$$PCl_4^{\cdot} + R\text{-}H \longrightarrow HPCl_4 + R^{\cdot}$$

$$HPCl_4 \longrightarrow HCl + PCl_3 \qquad R = C_5H_4N$$

$$PCl_4^{\cdot} \rightleftharpoons PCl_3 + Cl^{\cdot}$$

In the first instance, it would seem reasonable to suppose that as the autoclave was warming up there would be some electrophilic attack in the pyridine ring at positions β to the nitrogen in view of the fact that Wibaut and co-workers[95] have shown that at 200° electrophilic substitution with chlorine does take place.

However Chambers, Hutchinson and Musgrave[56] have shown that of the three possible isomers of tetrachloropyridine, only those with hydrogen atoms in either the 3- or the 4-position are formed. In view of the theoretical considerations already mentioned, the fact that 3-hydrotetrachloropyridine was obtained probably rules out the possibility of electrophilic attack, and hence the reaction between phosphorus pentachloride and pyridine is essentially a free radical reaction.

Chlorination of 2-methylpyridine.

It was initially considered that a possible route to a 2-substituted tetrafluoropyridine could be achieved by the chlorination of 2-methylpyridine giving perchloro(2-methylpyridine) which on reaction with potassium fluoride and hydrofluoric acid would give the corresponding

perfluoro(methylpyridine). Although perchloro-(2-methylpyridine) has been prepared by the photochemical chlorination of 2-methylpyridine,[119] in view of the success recorded in the chlorination of pyridine using phosphorus pentachloride, it was decided to react 2-methylpyridine under similar conditions as those used to prepare pentachloropyridine.

However, the reaction of phosphorus pentachloride with 2-methylpyridine did not give the expected perchloro-(2-methylpyridine) but, as can be seen in TABLE 2, good yields of pentachloropyridine were obtained.

It soon became apparent that this route to pentachloropyridine had certain advantages over the chlorination of pyridine. It was the first time that pentachloropyridine had been obtained without being contaminated with lower chlorinated pyridines (Reactions 1 and 2), and hence it was unnecessary to fractionally distil the product which had, in the previous preparations, been necessary and time consuming. The reaction time (8 h.) was only a third of the time required to chlorinate pyridine enabling the production of pentachloropyridine to be speeded up considerably, and also having the beneficial effect of reducing the corrosion to the autoclave.

Mechanism of chlorination of 2-methylpyridine.

The reaction probably proceeds via a free radical process similar to the one postulated for the chlorination of pyridine. McBee and co-workers[118] photochemically chlorinated 2-methylpyridine, 2,4-dimethylpyridine and 2,6-dimethylpyridine and obtained the respective

TABLE 2

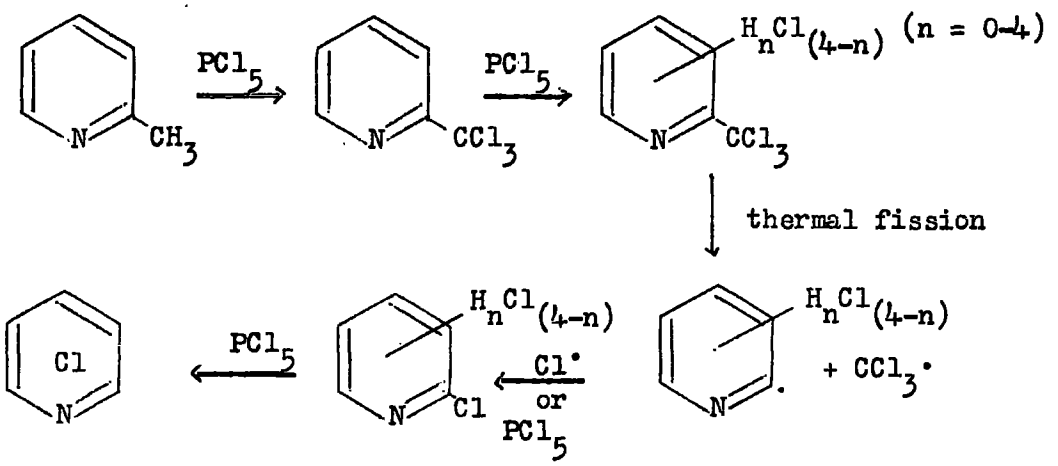
Chlorination of 2-Methylpyridine with Phosphorus Pentachloride

Reaction	Wt. of PCl_5 (gms.)	Wt. of C_6H_7N (gms.)	Time (hours)	Temp. °C	Wt. of Chlorinated pyridines	Mole % Composition of Product	
						C_5HCl_4N	C_5Cl_5N
1	1,350	30	8·5	300	72 (85%)	-	100
2	2,000	40	6·5	300	82 (72%)	-	100
✱ 3	2,500	80	8·0	300	175	10	90
✱ 4	2,000	40	8·0	300	100	5	95 *
✱ 5	1,460 (7 mole)	93 (1 mole)	8·0	300	163	40	60
✱ 6	1,668 (8 mole)	93 (1 mole)	8·0	300	166	20	80

* A trace, < 1% of $C_5NCl_3H_2$ was obtained.

✱ Carried out by Mr. B. Whitley under the supervision of the author.

heterocycles with the methyl side chains fully chlorinated. In view of these results it is probable that in the reaction of 2-methylpyridine with phosphorus pentachloride, free radical attack takes place primarily in the side chain to give 2-trichloromethylpyridine. McBee[78] also obtained from the photochemical chlorination of 2-methylpyridine appreciable amounts of 3,5-dichloro-trichloromethylpyridine which has been further chlorinated at 190-210° under ultraviolet light to give 2,3,5,6-tetrachloropyridine.[115] Thus it is probable that in the chlorination of 2-methylpyridine with phosphorus pentachloride some chlorine is substituted in the pyridine nucleus before fission of the carbon-carbon bond joining the methyl group to the ring takes place.



$$CCl_3\cdot + Cl\cdot \longrightarrow CCl_4$$

$$\text{or } CCl_3\cdot + PCl_5 \longrightarrow CCl_4 + PCl_4\cdot$$

Chlorination of 2,2'-Bipyridyl.

A convenient route to octafluoro-2,2'-bipyridyl would of course have been via the Ullmann reaction on a 2-halogenotetrafluoropyridine, but although several routes to such a compound have been visualized, a 2-halogenotetrafluoropyridine has not yet been prepared.

It was decided that provided the octachloro-2,2'-bipyridyl could be prepared, the halogen-exchange reaction, used to replace chlorine for fluorine in the preparation of pentafluoropyridine, would be a convenient way of preparing octafluoro-2,2'-bipyridyl.

The reaction between 2,2'-bipyridyl and phosphorus pentachloride was carried out in the 5-litre autoclave with conditions similar to those used in the chlorination of pyridine and α-picoline. The chlorinated material was recovered using the sublimation procedure as outlined in the preparation of pentachloropyridine from 2-methylpyridine. Fractional sublimation, followed by recrystallization from benzene, yielded the octachloro-2,2'-bipyridyl. The results of the chlorination reactions are shown in TABLE 3.

In the chlorination of 2,2'-bipyridyl an equilibrium had to be reached in which chlorination of the ring system took place but thermal fission of the carbon-carbon bond joining the two rings was kept to a minimum. In reaction 1 an auxiliary heating element was used in conjunction with the main heating element with the result that a considerable amount of fission of C-C bond took place yielding pentachloro-

TABLE 3

Chlorination of 2,2'-Bipyridyl with Phosphorus Pentachloride.

Reaction	Wt. of PCl_5 (gms.)	Wt. of $C_{10}H_8N_2$ (gms.)	Time hours	Temp. °C	Wt. of chlorinated Product (gms.)	Mole-% Composition of Product		
						C_5Cl_5N	$C_{10}H_nCl_{(8-n)}N_2$ (n = 1-7)	$C_{10}Cl_8N_2$
1	500	20	12	300*	18.0	35	25	40
2	2,000	40	12	300	101	3	2	95
3	2,500	50	12	300	123	5	5	90

* Auxil i ary heating elements used.

pyridine. In reactions 2 and 3, the auxiliary heating system was disconnected and although a temperature of 300° was still recorded at the centre of the autoclave, good yields of octachloro-2,2'-bipyridyl were obtained. (Although the reaction temperature recorded was 300° in each of the three reactions, it is presumed that in reaction 1, when the auxiliary heating elements were used, that a higher temperature at the walls of the autoclave would have been recorded than in reactions 2 and 3).

Mechanism of the chlorination of 2,2'-bipyridyl.

It is already known that bromination of pyridine in the vapour phase at 500° gives 2-bromo and 2,6-dibromopyridine, which, similarly to the chlorination of pyridine at 270°, is thought to proceed via free radical attack. Burstall[144] found that application of this bromination process to 2,2'-bipyridyl gave mainly 6-bromo-, and 6,6'-dibromo-2,2'-bipyridyl which is in agreement with the theoretical considerations regarding free radical replacement. It is presumed that 2,2'-bipyridyl is chlorinated via a free radical mechanism analogous to that described for the chlorination of pyridine.

Fluorination of Pentachloropyridine.

Workers at these laboratories[56] have already shown that the halogen-exchange reaction between chlorine and fluorine using potassium fluoride is a good route for preparing pentafluoro-, and perfluorochloropyridines

from pentachloropyridine. Fluorination of pentachloropyridine with potassium fluoride in sulpholane at 190-210° gave good yields of 3,5-dichlorotrifluoropyridine with small amounts of 3-chlorotetrafluoropyridine. As a higher temperature is required for the replacement of the β-chlorines in pentachloropyridine the solvent was dispensed with and the reaction between pentachloropyridine and potassium fluoride was investigated in the absence of solvent. The results obtained from this reaction by the Durham workers have been published[56] and are shown in TABLE 4.

The fluorination reactions were carried out in a 120 ml. autoclave, heated electrically in a furnace. From the results it can be seen that by varying the temperature from between 400 to 480° good yields of pentafluoropyridine, 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine were obtained.

The reaction between pentachloropyridine and potassium fluoride was further investigated using a 150 ml. autoclave heated in a similar fashion to the one described above. The results of this investigation are shown in TABLE 5, and it can be seen that from a comparison of these results with those obtained by the previous workers (TABLE 4) similar yields and composition of products were obtained.

Procedure.

The autoclave, charged with the reactants, was heated for the

TABLE 4

Reactions of Pentachloropyridine with Potassium Fluoride

Reactions Carried out in 120 ml. Autoclave.[56]

C_5Cl_5N (g.)	KF (g.)	Temp. (°C)	Time (hr.)	Product (g.)	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)		

TABLE 5

Reactions of Potassium Fluoride on Pentachloropyridine.

Reactions Carried out in 150 ml. Autoclave.

Wt. of KF gms.	Wt. of C_5Cl_5N gms.	Time h.	Temp. °C	Yield gms.	Mole-% Composition of Products (% yield in parentheses)		
					$C_5Cl_2F_3N$	C_5ClF_4N	C_5F_5N
80	30	15•25	350	21•0	85(74)	15(14)	trace
80	30	13•0	390	21•0	70(61)	25(23)	5(5)
80	30	18•0	390	21•5	50(45)	45(41)	5(6)
80	30	17•25	390	21•0	50(44)	35(33)	15(16)
80	30	14•0	400	18•5	10(8)	60(50)	30(27)
80	30	16•25	400	19•0	5(4)	60(52)	35(33)
80	30	17•0	400	19•0	trace	50(43)	50(47)
80	30	16•25	400	18•5	-	60(50)	40(37)
80	30	17•0	400	15•5	-	5(4)	95(73)
80	30	17•5	420	18•5	-	20(17)	80(73)
80	30	26•0	445	16•0	-	trace	100(79)
80	30	18•0	470	14•5	-	-	100(72)

prescribed period at the temperatures denoted. While the autoclave was still hot the product was distilled out from the autoclave. The products from several reactions were combined and fractionated through a concentric-tube column into three main fractions:

(1) pentafluoropyridine.

(2) 3-chlorotetrafluoropyridine.

(3) 3,5-dichlorotrifluoropyridine.

A comparison of TABLES 4 and 5 will show that the halogen-exchange reactions depicted in TABLE 5 were carried out at lower temperatures than those recorded in TABLE 4 which gave the same approximate percentage composition of products. This is possibly due to the different autoclaves used in the reactions, although it is important to note that fluctuations in the mains voltage (especially overnight) cause considerable variations in the reaction temperatures. The mains voltage fluctuation is probably the reason why identical reaction conditions gave varying amounts of replacement.

As the availability of pentachloropyridine increased and the demand for highly fluorinated pyridines grew, it became advantageous to fluorinate pentachloropyridine on a larger scale. A 750 ml. stainless steel autoclave was constructed of similar design and similar heating arrangements as the smaller autoclaves. The results obtained using this larger autoclave have been tabulated in TABLE 6.

TABLE 6

Reaction of Potassium Fluoride on Pentachloropyridine.

Reactions Carried out in 750 ml. Autoclave.

Wt. of KF gms.	Wt. of C_5Cl_5N gms.	Time h.	Temp. °C	Yield gms.	Mole-% Composition of Products (% yield in parentheses)		
					$C_5Cl_2F_3N$	C_5ClF_4N	C_5F_5N
200	80	16·5	380	58·5	80(72·8)	20(19·8)	-
200	80	16·5	400	54·0	65(54·6)	25(22·9)	10(10)
320	120	17·0	410	76·5	60(47·6)	35(30·3)	5(4·8)
200	60	16·0	420	43·0	50(44·6)	30(29·1)	20(21·3)
110	42	18·0	400-410	27·5	30(24·5)	35(31)	35(34·1)
160	60	21·5	410	40·0	20(16·6)	40(36·1)	40(39·7)
80	30	18·0	440	15·0	-	10(6·8)	90(67)
200	80	15·0	445	48	-	5(4·1)	95(86)
180	60	18·0	460	37·0	-	10(8·4)	90(82·6)

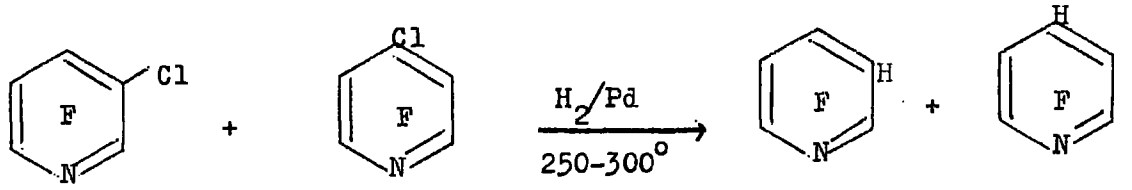
Again, by varying the temperature of the reaction between 380° and 460° good yields of highly fluorinated pyridines were obtained. The products were obtained as above and fractionated through a 3' tube packed with glass helices, fitted with an automatic take-off head into three main fractions:

(1) pentafluoropyridine,

(2) a mixture of 3-chlorotetrafluoro- and 4-chlorotetrafluoropyridines (mole ratio approximately 4:1 respectively),

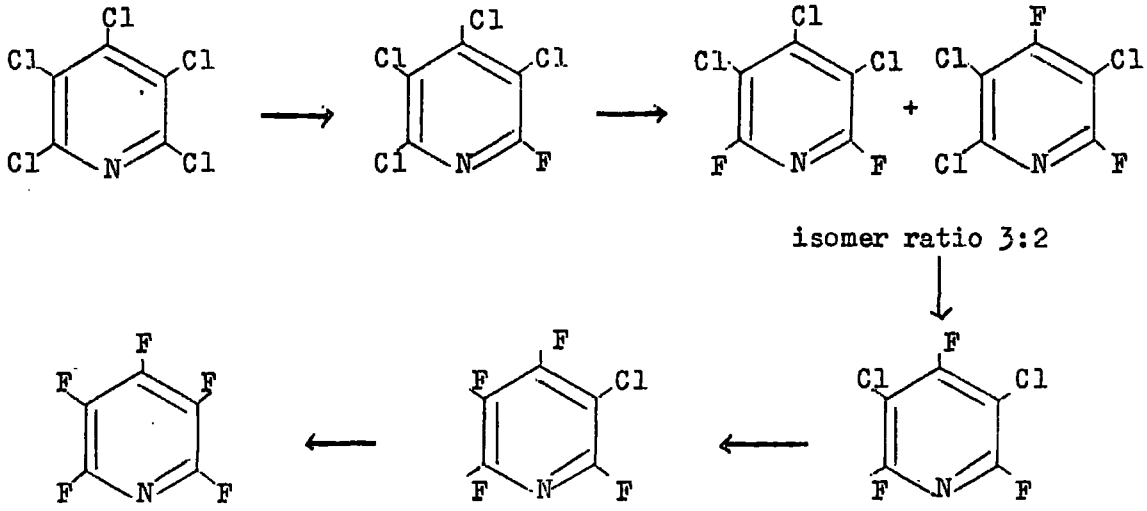
(3) 3,5-dichlorotrifluoropyridine.

The main difference between halogen-exchange reactions carried out in the small autoclave to the reactions carried out in the larger autoclave is that in the former only one isomer of monochlorotetrafluoropyridine (3-chlorotetrafluoropyridine) was produced, whilst in the latter a mixture of isomers of monochlorotetrafluoropyridine was obtained. The isomers were identified as 3- and 4-chlorotetrafluoropyridine by fluorine-19 nuclear magnetic resonance spectra and by reducing the mixed chlorotetrafluoropyridines, using hydrogen and palladium catalyst[145] to 4-hydro- and 3-hydrotetrafluoropyridines. The monohydrotetrafluoropyridines were identified from their infrared spectra.



(isomer ratio 4:1).

Drakesmith[146] has shown that the path taken by the pentachloropyridinepotassium fluoride reaction is as follows.



This result, coupled with the earlier observations by Chambers, Hutchinson and Musgrave[56] who showed that the β-chlorine atoms in pentachloropyridine were the last to be replaced, it would be highly unlikely that in the reaction in the large autoclave the β-chlorine atoms had been replaced preferentially to the γ-chlorine atom. In the reaction between pentachloropyridine and potassium fluoride, potassium chloride is formed as a by-product and under certain conditions it has been shown that the fluorine atom can be replaced by chlorine.[147] The reaction between potassium chloride and pentafluoropyridine at 520° in an autoclave produced an equimolar mixture of 3- and 4-chlorotetrafluoropyridines, although when the

reaction was carried out at 460° no reaction took place. As the fluorination of pentachloropyridine was carried out at a considerably lower temperature than 520°, there must have been some localized heating in the large autoclave to produce this unexpected result.

Although the formation of 4-chlorotetrafluoropyridine in the halogen-exchange reaction can be explained by the nucleophilic attack of chloride ion on pentafluoropyridine it is difficult to rationalize the presence of 3-chlorotetrafluoropyridine from the reaction of pentafluoropyridine and potassium chloride. It is now a well established fact that nucleophilic substitution in pentafluoropyridine takes place primarily in the γ-position.[148,149] In no case has β-substitution been recorded in pentafluoropyridine, and hence the formation of 3-chlorotetrafluoropyridine is not by simple nucleophilic attack on pentafluoropyridine. It is possible that at the considerably high temperature employed to bring about the substitution some thermal rearrangement has taken place similar to those reported in the high temperature defluorination of perfluoro(dimethylcyclohexanes).[150]

Fluorination of Octachloro-2,2'-bipyridyl.

The halogen-exchange reaction between chlorine and fluorine using alkali metal fluorides has been shown to be a good method for preparing pentafluoro-, 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoropyridines.[56] This halogen-exchange reaction has been adapted

to the preparation of highly fluorinated 2,2'-bipyridyls from octachloro-2,2'-bipyridyl, the results of which are summarised in TABLES 7 and 8.

Fluorination in the absence of solvent (TABLE 7)

Under similar conditions to those used for the preparation of pentafluoropyridine and the perfluorochloropyridines from pentachloropyridine (TABLES 4, 5 and 6) only decomposition products were obtained when octachloro-2,2'-bipyridyl was fluorinated with potassium fluoride (Reactions 1 and 2). It has already been suggested that at high temperatures fission of the carbon-carbon bond joining the two rings takes place. Comparison of reactions 6 and 7 indicates that the fission of the C-C bond probably takes place more readily in highly fluorinated 2,2'-bipyridyls than in the partially fluorinated 2,2'-bipyridyls (based on the fact that caesium fluoride is a stronger fluorinating agent than potassium fluoride and under similar conditions more replacement would have taken place with caesium fluoride).

Fluorination in the presence of a polar solvent (sulpholane) TABLE 8

Fluorination of octachloro-2,2'-bipyridyl with potassium fluoride in sulpholane at 200^{o} yielded a mixture of octafluoro-2,2'-bipyridyl, 3-chloroheptafluoro-2,2'-bipyridyl and 3,3'-dichlorohexafluoro-2,2'-bipyridyl.

TABLE 7

Reactions of Octachloro-2,2'-Bipyridyl with Alkali-Metal Fluoride in the Absence of a Solvent.

Reaction	Wt. of Alkali-Metal Fluoride (g.)	Wt. of $C_{10}ClFN_2$ (g.)	Temp. (°C)	Time (hr.)	Product (g.)	Composition of product in mole-% (% yield in parentheses)			
						$C_{10}Cl_4F_4N_2$	$C_{10}Cl_2F_6N_2$	$C_{10}ClF_7N_2$	$C_{10}F_8N_2$
1	50(KF)	4	460	17	-	Decomposition			
2	50(KF)	4	400	17	-	Decomposition			
3	10(CsF)	2	350	21·5	-	Decomposition			
4	9(KF)	0·94	355	15	trace				
5	15(KF)	2	340-346	16·25	0·2	10(1·2)	40(5·2)	trace	trace
6	15(KF)	3	296-316	16·25	2·1	90(74·7)	trace	trace	
7	10(CsF)	2	296-316	16·25	gas	Decomposition			

The product from Reaction 5 contained another product (50%) which was thought to be 3,3',5,-trichloro-pentafluoro-2,2'-bipyridyl.

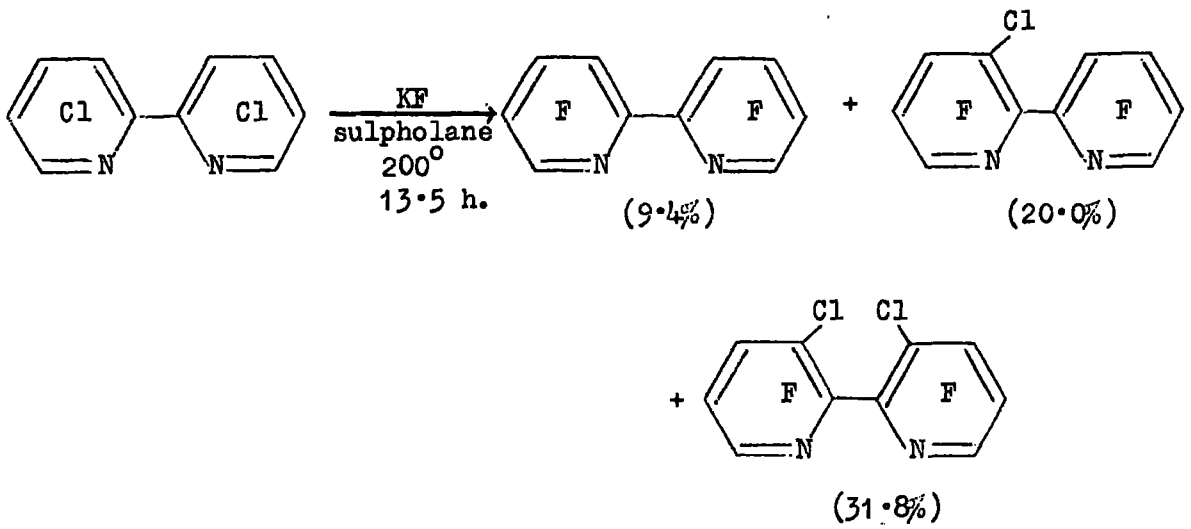
The product from Reaction 6 contained 10% of this trichloropentafluoro-2,2'-bipyridyl.

TABLE 8

Reactions of Octachloro-2,2'-Bipyridyl with Potassium Fluoride in Sulpholane

Reaction	Wt. of Alkali Metal Fluoride (g.)	Wt. of $C_{10}Cl_8N_2$ (g.)	Temp. (^oC)	Time (hr.)	Product (g.)	Composition of product in mole % (% yield in parentheses) $C_{10}Cl_2F_6N_2$	$C_{10}ClF_7N_2$	$C_{10}F_8N_2$
1	15 (KF)	5	140 200-210	6 16	0.8	40(8.3)	20(4.4)	35(8.1)
2	20 (KF)	5	200	22.5	2.15	85(47.5)	5.8(3.9)	2.3(1.4)
3	100 (KF)	20	200	15.75	8.9	63.4(36.6)	26.7(16.2)	9.9(6.3)
4	375 (KF)	75	200	13.5	34.6	53.1(31.8)	32.7(20.6)	14.2(9.4)

The product from Reactions 1 and 2 contained small amounts of trichloropentafluoro-2,2'-bipyridyl.



Mechanism and Orientation of Products of the Fluorination of Pentachloropyridine and Octachloro-2,2'-Bipyridyl.

From the theoretical considerations already mentioned it would be expected that nucleophilic attack would take place first at the α and γ positions in the pyridine nucleus. Similar considerations show that the α and γ positions in 2,2'-bipyridyl would be the most susceptible to nucleophilic attack.

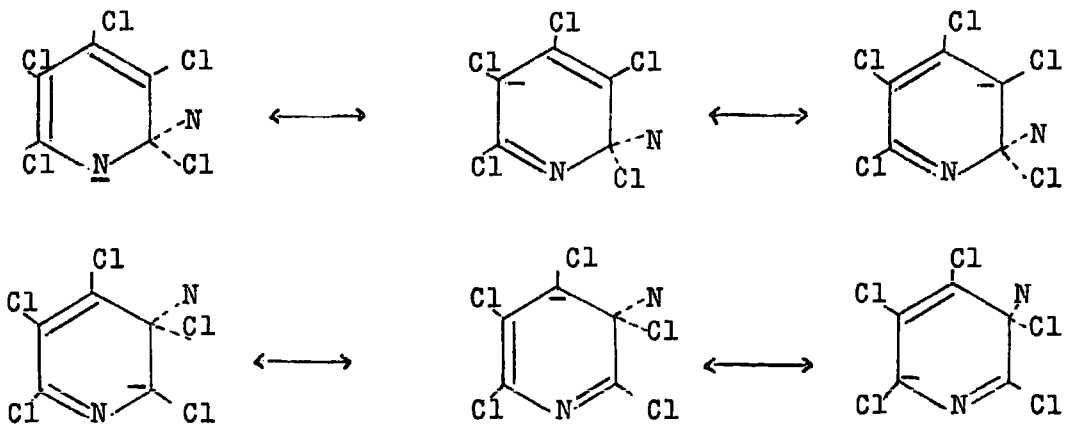
The halogen-exchange reaction between potassium fluoride and the perchloroheterocycles almost certainly goes via a nucleophilic mechanism.

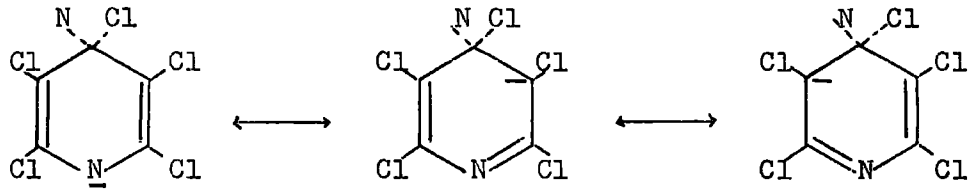
The orientation of the products from the reaction of aromatic polyhalo compounds with nucleophiles can be discussed by considering the transition state stabilities in terms of Wheland-type intermediates.

The para quinonoid resonance hybrid will be considered to stabilize the transition state to a greater extent than the ortho quinonoid resonance structure. This assumption is based on the results of advanced molecular orbital calculations which show that in the transition state the charge density distribution is delocalized to a greater extent at the para position.[151] Other workers,[152] on the basis of their experimental results, have also argued that the para-quinonoid structure is more important that the ortho quinonoid structure in nucleophilic aromatic substitution.

The transition states for the three positions of nucleophilic substitution in pentachloropyridine may be expressed in terms of the following Wheland-type intermediates:-

N = nucleophile



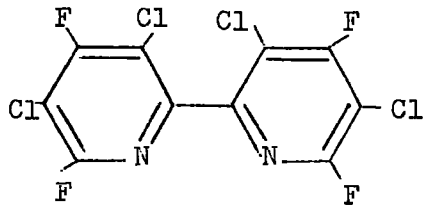


As the ring-nitrogen is able to accommodate the negative charge to a greater extent than a carbon bearing a chlorine atom, it is clear from the Wheland intermediates that nucleophilic substitution will be facilitated in the α- and γ-positions compared with the β-position (in nucleophilic substitution at the β-position the negative charge cannot be delocalized onto the ring nitrogen). Thus, to a first approximation it is clear that nucleophilic attack will take place at the α- and γ-positions in pentachloropyridine. In view of the fact that a para quinonoid resonance form stabilizes the transition state to a greater extent than the ortho quinonoid form, it would be expected that nucleophilic attack in pentachloropyridine would take place initially at the γ-position followed by attack at the α-position.

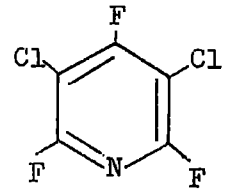
Drakesmith,[146] however, has shown that nucleophilic attack takes place at the α-positions followed by attack at the γ-position. This could possibly be rationalized by the fact that the γ-position in pentachloropyridine is flanked by two ortho chlorine atoms and considerable steric hindrance is present. The α-position has only one chlorine atom flanking the position and is hence sterically more favourable.

The orientation of the products, and the relative ease of halide ion exchange in octachloro-2,2'-bipyridyl as compared with pentachloropyridine, can be rationalized by consideration of the Wheland type intermediates of the fluorochloropyridines and the fluorochloro-2,2-bipyridyls.

As initially stated fluorination of pentachloropyridine with potassium fluoride at 200° for 36 h. gives 3,5-dichlorotrifluoropyridine and 3-chlorotetrafluoropyridine in the ratio 10:1. Fluorination of octachloro-2,2'-bipyridyl at 200° for 13·5 h. gives 3,3'-dichlorohexafluoro-, 3-chloroheptafluoro-, and octafluoro-2,2'-bipyridyl in the ratio 4:2·8:1. It had previously been found that 3,3',5,5'-tetrachlorotetrafluoro-2,2'-bipyridyl is formed when octachloro-2,2'-bipyridyl is reacted with potassium fluoride at 300° in the absence of solvent. This latter result is in agreement with the fact that α- and γ-chlorine atoms are replaced first, as in pentachloropyridine. From these experimental results it has been shown that the β-chlorine atoms in 3,3'5,5'-tetrachlorotetrafluoro-2,2'-bipyridyl(I) (it is considered that this tetrachlorotetrafluoro-2,2'-bipyridyl is formed when the reaction is carried out in solvent as is the case when carried out in the absence of solvent) are more easily replaced than the β-chlorine atoms in 3,5-dichlorotrifluoropyridine(II).

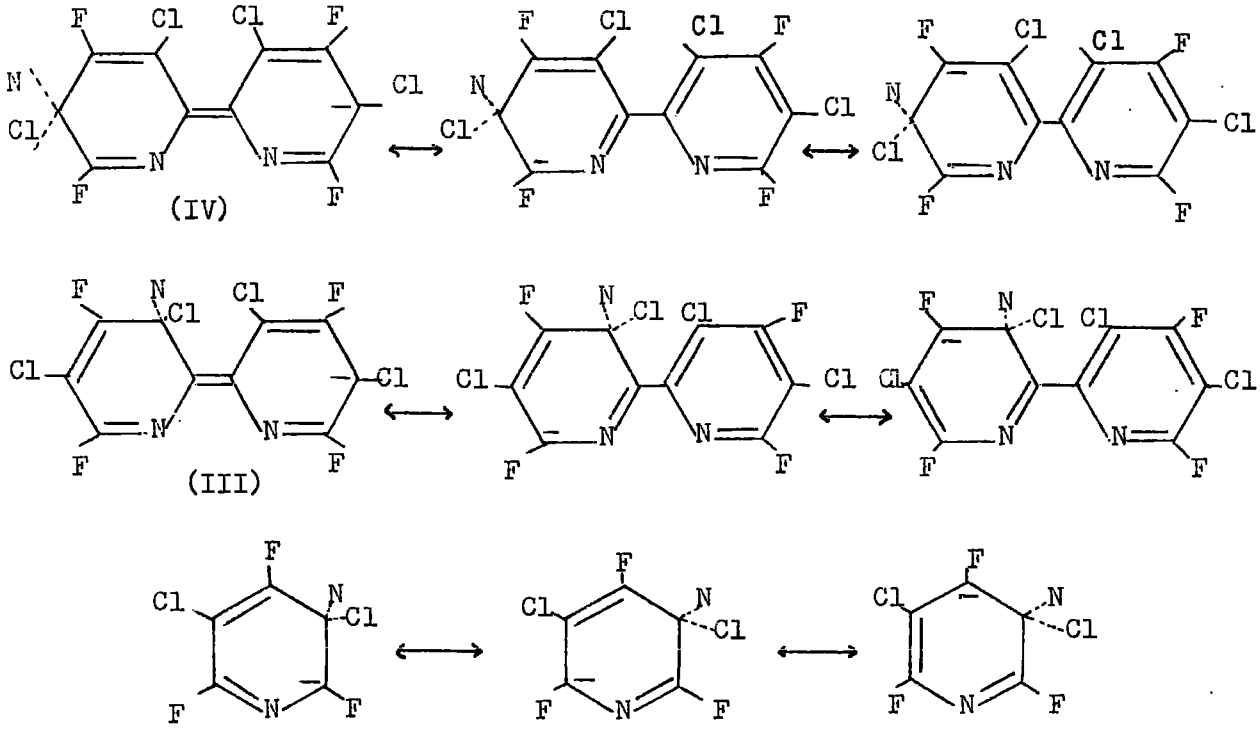


(I)



(II)

By consideration of the Wheland intermediates shown below it can be seen that replacement of the β-chlorines in the perchlorofluorobipyridyl is more favourable than in 3,5-dichlorotrifluoropyridine.



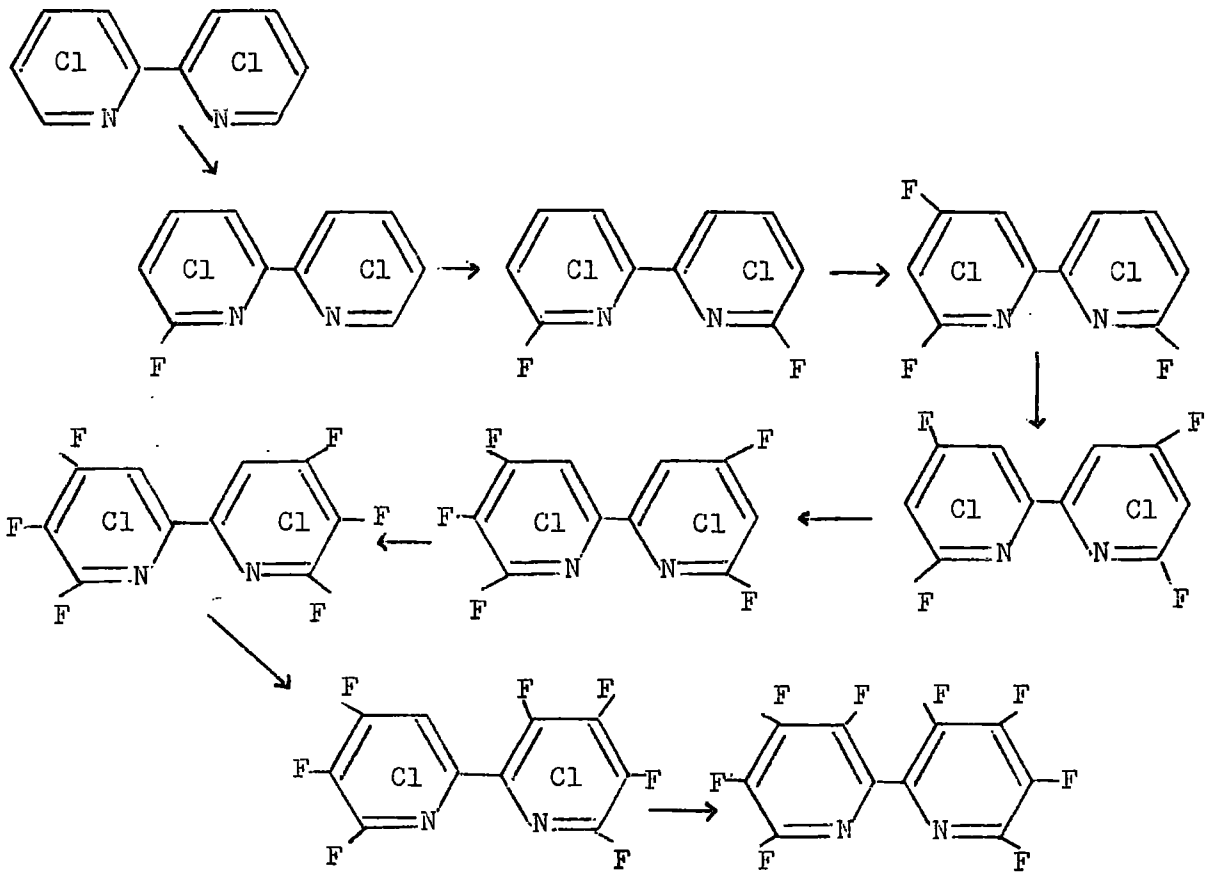
(IV)

(III)

From the Wheland-type intermediates it is possible in the case of tetrafluorotetrachloro-2,2'-bipyridyl for the transition state to be stabilized by delocalization of the charge into the other ring whether attack takes place in the 3- (III) or 5- (IV) position. The transition state in 3,5-dichlorotrifluoropyridine cannot be stabilized in any such way but only by delocalization of the negative charge onto carbon atoms bearing fluorine atoms, which by consideration of the I_{π} effect,[153,154] do not stabilize a negative charge as well as a carbon bearing a chlorine atom.

Consideration of Wheland-type intermediates III and IV will show, by analogy with pentachloropyridine, that position 5 is more favourable to nucleophilic substitution than position 3 by virtue of the fact that in nucleophilic attack at position 5 (IV) the negative charge can be delocalized via a para quinonoid form throughout the molecule, whereas in structure III the delocalization of charge is only partially by a para-quinonoid form. This fact is illustrated by the isolation of 3,3'-dichlorohexafluoro-2,2'-bipyridyl uncontaminated by either 3,5-, 3,5'-, or 5,5'-dichlorohexafluoro-2,2'-bipyridyl.

Thus, by analogy with pentachloropyridine the order of replacement of chlorine by fluorine in octachloro-2,2'-bipyridyl is as follows.



The Ullmann Synthesis of Polypyridyls.

A general method for the preparation of a biaryl consists in the coupling of two moles of aromatic halide in the presence of a metallic agent with the elimination of metal halide.[155,156]

$$RX + R'X + M \longrightarrow R\text{-}R' + MX_2$$

Work by F. Ullmann[157] showed that copper was effective in this coupling reaction so that biaryl or polyaryl formation with the elimination of copper halide has become known as the Ullmann reaction.

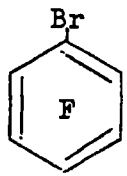
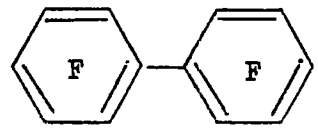
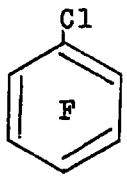
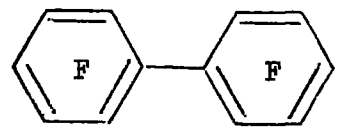
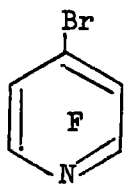
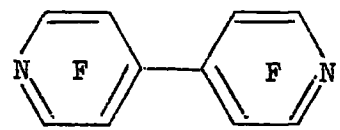
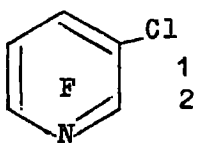
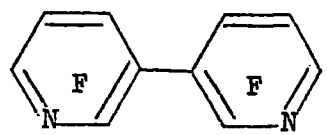
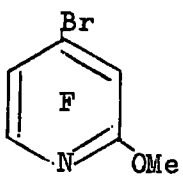
The Ullmann reaction has been effectively used in the preparation of perfluorobiaryls, the results of which are shown in TABLE 9.

The success of any Ullmann reaction is dependent upon the nature of the aromatic halide. Chlorine, bromine or iodine (an aromatic fluorine atom has never been reported to be active in Ullmann reactions) may be eliminated of which the order of reactivity is I > Br > Cl. This order of reactivity is in agreement with the results obtained in TABLE 9. Perfluorobiphenyl[158] and octafluoro-4,4'-bipyridyl[159] were obtained from pentafluorobromobenzene and 4-bromotetrafluoropyridine respectively under less severe conditions than those required to obtain perfluorobiphenyl[160] and octafluoro-3,3'-bipyridyl from the respective monochlorofluoro derivatives. Fluorine could not be eliminated from pentafluoropyridine to form a bipyridyl.

Substituents in the aromatic nucleus can affect the overall success of the Ullmann reaction. Certain electronegative groups in the ortho and para position to the halogen atom, activate the latter through operation of their inductive and mesomeric effects leaving the carbon atom to which the halogen is attached with a residual positive charge. On the basis of this assumption it would be expected that an electron-donating group substituted into the nucleus would have the reverse effect, tending to deactivate the halogen atom. The results obtained in the

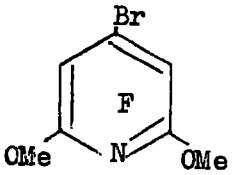
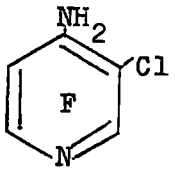
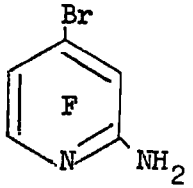
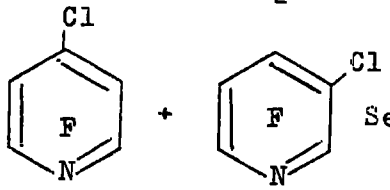
TABLE 9

Ullmann Synthesis of Polyfluorinated Biaryls

Reactant	Conditions	Temp. °C	Time (Hr.)	Product		Reference
	sealed tube	200	42		(85%)	158
	sealed tube	230	280		(70%)	160
	1) dimethylformamide 2) sealed tube	reflux 230	5 48		(1) (40%) (2) (50%)	159
	1) dimethylformamide 2) sealed tube	reflux 250	12 140		(1) (0%) (2) (70%)	
	sealed tube	200	48	Decomposition		

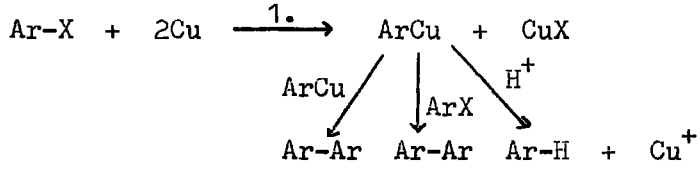
/Cont.

TABLE 9 (Cont.)

Reactant	Conditions	Temp. °C	Time (hr.)	Product	Reference
	dimethylformamide	reflux	4	no reaction	
	sealed tube	140 240	108 72	no reaction	
	sealed tube	210	120	deccmposition	
	dimethylformamide	reflux	2	2-amino-3,5,6-trifluoro-pyridine (46%)	159
	Sealed tube	250°	48	octafluorobipyridyls (44%)	

pyridine series are in agreement with this assumption. 4-Bromo-2-methoxytrifluoropyridine and 4-bromo-2,6-dimethoxydifluoropyridine do not undergo condensation under conditions that effected coupling in 4-bromotetrafluoropyridine. This result is in direct opposition to the results obtained by Forrest[161] who showed that a methoxy group present in the aromatic nucleus, irrespective of orientation, increases the activity of the halogen.

The mechanism of the Ullmann reaction is not yet fully understood but recent evidence for the existence of a copper intermediate in the Ullmann reaction has been discovered.[162]



Since the formation of the intermediate step 1 would involve the donation of electrons from the copper to the aryl compound, electron withdrawing groups present in the ring system stabilize the transition state. Conversely electron-donating groups would tend to destabilize the transition state. This explanation is in agreement with the results obtained. The reaction of phenyl copper with protons to give benzene is an expected and known reaction[163] and explains the formation of 2-amino-3,5,6-trifluoropyridine from 2-amino-4-bromotrifluoropyridine when the Ullmann reaction was carried out in dimethylformamide.[154]

The Ullmann reaction between copper powder and 3-chlorotetrafluoropyridine was investigated more fully, the results of some of the reactions are shown in TABLE 10. When the reaction was carried out in dimethylformamide no bipyridyl was formed. Several products were obtained, the structures of which could not be elucidated, although the presence of carbon-hydrogen bonding in the products was indicated from their infrared spectra. When the reaction between copper powder and 3-chlorotetrafluoropyridine was carried out in the absence of solvent octafluoro-3,3'-bipyridyl was obtained in yields of up to 70%.

The Ullmann reaction has been used to prepare many polyfluorinated polyphenyls from the respective bromofluorobenzenes, the results of which are shown in TABLE 11. Under more forcing conditions, the reaction between copper, 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoropyridine resulted in the preparation of perfluoro-3,3',3''-terpyridyl and perfluoro-3,3',3'',3'''-quaterpyridyl. Analysis of the reaction product by analytical-scale vapour phase chromatography indicated the existence of several other products which have been tentatively identified as the intermediate chlorofluoropolypyridyls.

3-Chloroheptafluoro-2,2'-bipyridyl afforded perfluoro-2,2',3,3'',-2'',2'''-quaterpyridyl but under similar conditions 3-chloroheptafluoro-4,4'-bipyridyl remained unchanged. In an attempt to prepare perfluoro-2,2',3,3'-bipyridylene from the reaction between copper powder and 3,3'-dichlorohexafluoro-2,2'-bipyridyl, 3,3'-dichlorohexafluoro-2,2'-

TABLE 10.

Reaction of Copper Powder with 3-Chlorotetrafluoropyridine

Cu (g.)	C_5ClF_4N (g.)	Conditions	Temp. (°C)	Time (h.)	Yield of perfluoro-3,3-bipyridyl (g.) (% yield in parentheses)
1·88	1·0	dimethyl-formamide	150-160	20	No identifiable product
3·0	2·0	dimethyl-formamide	150-160	60	No identifiable product
0·9	1·5	sealed tube	240	168	0·3 (24·7)
5	7·6	sealed tube	250-260	135	4·2 (68·3)
10	12	sealed tube	250	140	6·5 (67)
8	3·8	sealed tube	210-230	94·5	1·9 (61·9)
15·5	10·5	sealed tube	210-230	123	5·0 (58·9)
13·0	10	sealed tube	210-230	153	5·8 (71·7)

TABLE 11

Ullmann Synthesis of Polyfluorinated Polyaryls

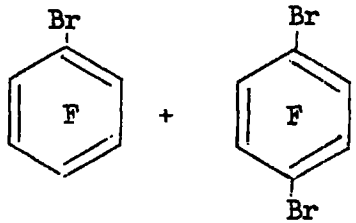
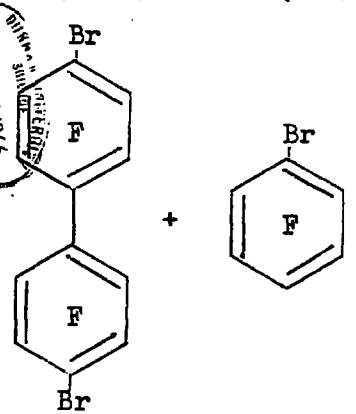
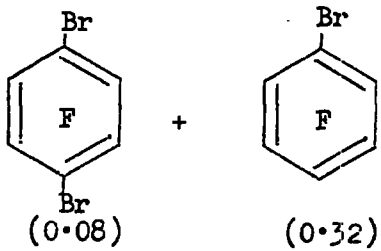
Reactants (molar amounts in parentheses)	Conditions	Temp. (°C)	Time (h.)	Product(s) (% yield in parentheses)	Reference
 (0·81) (0·13)	dimethylformamide	reflux	7	decafluorobiphenyl + perfluoro-p-terphenyl (28%)	164
 (0·01) (0·04)	dimethylformamide	reflux	2·5	decafluorobiphenyl + perfluoro-p-quaterphenyl (15%)	164
 (0·08) (0·32)	dimethylformamide	reflux	4 hr.	decafluorobiphenyl + perfluoro-p-terphenyl + perfluoro-p-quinquephenyl (1%)	164

TABLE 11 (Cont.)

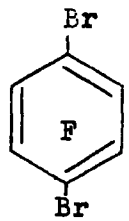
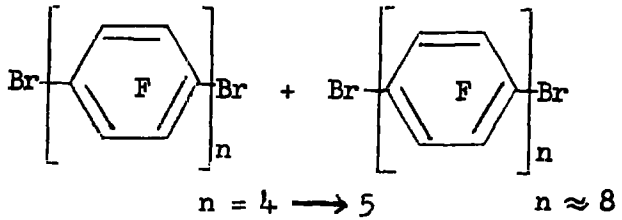
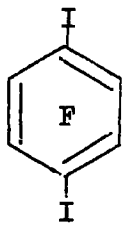
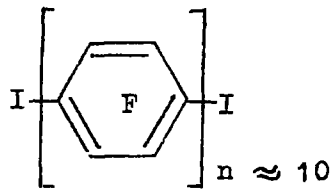
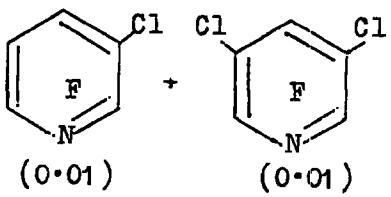
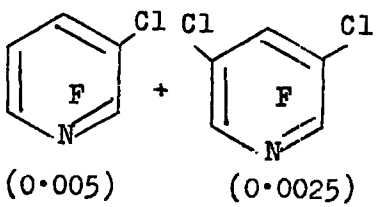
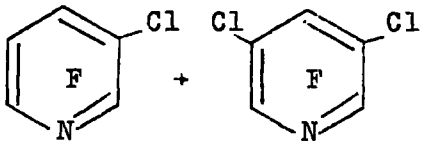
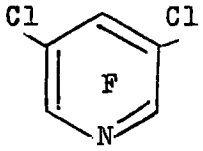
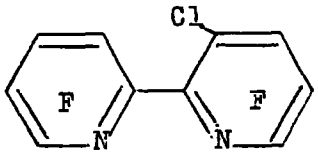
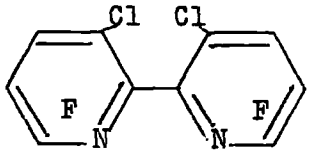
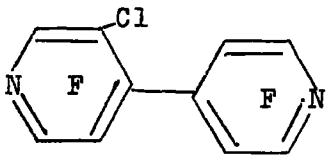
Reactants	Conditions	Temp. (°C)	Time (h.)	Product(s) (% yield in parentheses)	Reference
	sealed tube	200	80	 $n = 4 \longrightarrow 5$; $n \approx 8$	165
	sealed tube	200–250	80	 $n \approx 10$	165
 (0·01) (0·01)	sealed tube	250	160	polypyridyls $+C_5F_3N+_n$ $n > 4$	
 (0·005) (0·0025)	sealed tube	250–260	96	perfluoro-3,3'-bipyridyl (40%), perfluoro-3,3',3"-terpyridyl (10%), perfluoro-3,3',3",3'''-quaterpyridyl (2%)	

TABLE 11 (Cont.)

Reactants (molar amounts in parentheses)	Conditions	Temp. (°C)	Time (h.)	Product(s) (% yield in parentheses)	Reference
 (0·008) (0·0027)	sealed tube	250-260	96	perfluoro-3,3'-bipyridyl (58%), perfluoro-3,3',3"-terpyridyl (5%)	
	sealed tube	230	104	$Cl-(C_5F_3N)_n-Cl$ $n > 5$	
	sealed tube	190-210	86	perfluoro-2,2',3,3",2",2'''-quaterpyridyl	
	sealed tube	1) 190-210 2) 230-240	119·5 116·5	recovered starting material decomposition	
	sealed tube	230	92	recovered starting material	

bipyridyl was recovered unchanged at 190-210° and if the reaction temperature was raised to 230-240° total decomposition resulted.

Reactions of other polyfluorochloropyridines and polyfluorochlorobipyridyls with copper obviously provide a route to a considerable number of polyfluoro- and polyfluorochloropolypyridyls.

The reaction between equimolar amounts of 4-chloro-, and 3-chlorotetrafluoropyridine and copper at elevated temperatures was investigated. A white crystalline product was obtained which showed up as one component on vapour phase chromatography, the retention time of which was the same as octafluoro-3,3'-bipyridyl. From its infrared and fluorine-19 nuclear magnetic resonance spectra the product was identified as a mixture of octafluorobipyridyls, octafluoro-4,4'-bipyridyl being the main component of the mixture.

The reaction between 4-bromo-2-nitrotrifluoropyridine and copper powder afforded only traces of what was thought to be the dinitrobipyridyl.

Synthesis of Polyfluorinated Polyaryls via the Grignard Intermediate.

Pentafluorophenylmagnesium bromide has been found to be a valuable intermediate in the synthesis of polyfluorinated polyphenylenes.[164] Pentafluorophenylmagnesium bromide, prepared from pentafluorobromobenzene and magnesium turnings,[164,166,158] has been found to decompose in

refluxing tetrahydrofuran to give fluorinated polyphenylenes, containing bromine, of relatively high molecular weight. When the decomposition was carried out in the presence of decafluorobiphenyl at room temperature,[164] perfluoro-p-terphenyl, -quaterphenyl and -quinquephenyl were isolated.

The formation of these para-linked polyphenylenes strongly supports the suggestion that the build-up of the polymers from the decomposition of C_6F_5MgBr, both alone and in the presence of decafluorobiphenyl, involves repeated nucleophilic attack on a pentafluorophenyl group. The production of these para-linked compounds is consistent with the results obtained by the Birmingham workers that in the majority of cases the second substituent enters a position para to the first substituent.

Brooke and Musgrave[167] have shown that the reaction of pentafluorophenylmagnesium bromide with pentafluoronitrobenzene in tetrahydrofuran, at -10 to 4°, gave a mixture of products identified as (i) pentafluoronitrobenzene (16%); (ii) decafluorobiphenyl (1%); (iii) nonafluoro-2-nitrobiphenyl (6%); (iv) nonafluoro-4-nitrobiphenyl and (v) 2,4-bispentafluorophenyl-3,5,6-trifluoronitrobenzene (13%), by simple nucleophilic replacement of fluorine. The presence of decafluorobiphenyl has been attributed to the nucleophilic displacement of bromine in pentafluorobromobenzene by pentafluorophenylmagnesium bromide.

4-Bromotetrafluoropyridine readily forms a Grignard reagent at low temperature with magnesium in tetrahydrofuran and has been shown to react

at -35 to -40° with pentafluoropyridine to give octafluoro-4,4'-bipyridyl.[159] This synthesis of octafluoro-4,4'-bipyridyl was extended to prepare 3-chloroheptafluoro-, and 3,5-dichlorohexafluoro-4,4'-bipyridyl by adding 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoropyridine respectively to 2,3,5,6-tetrafluoropyridylmagnesium bromide at -40°. Under similar conditions the Grignard reagent did not react with 3-hydrotetrafluoro- or 3,5-dihydrotrifluoropyridine.

Chambers, Hutchinson and Musgrave[159] showed that although pentafluorophenylmagnesium bromide reacted with pentafluoropyridine to give 4-(pentafluorophenyl)tetrafluoropyridine, pentafluorophenylmagnesium bromide did not react with hexafluorobenzene under the same conditions. This is consistent with present observations (which will be discussed more fully later) that pentafluoropyridine is more susceptible to nucleophilic attack than hexafluorobenzene.

2-Methoxyheptafluoro-4,4'-bipyridyl was prepared by reacting 2-methoxy-3,5,6-trifluoropyridylmagnesium bromide with pentafluoropyridine at -40°. Under similar conditions, the reaction between pentafluoropyridine and 2,6-dimethoxy-3,5-difluoropyridylmagnesium bromide did not afford the expected 2,6-dimethoxyhexafluoro-4,4'-bipyridyl, but 2,6-dimethoxy-3,5-difluoropyridine was obtained upon hydrolysis.

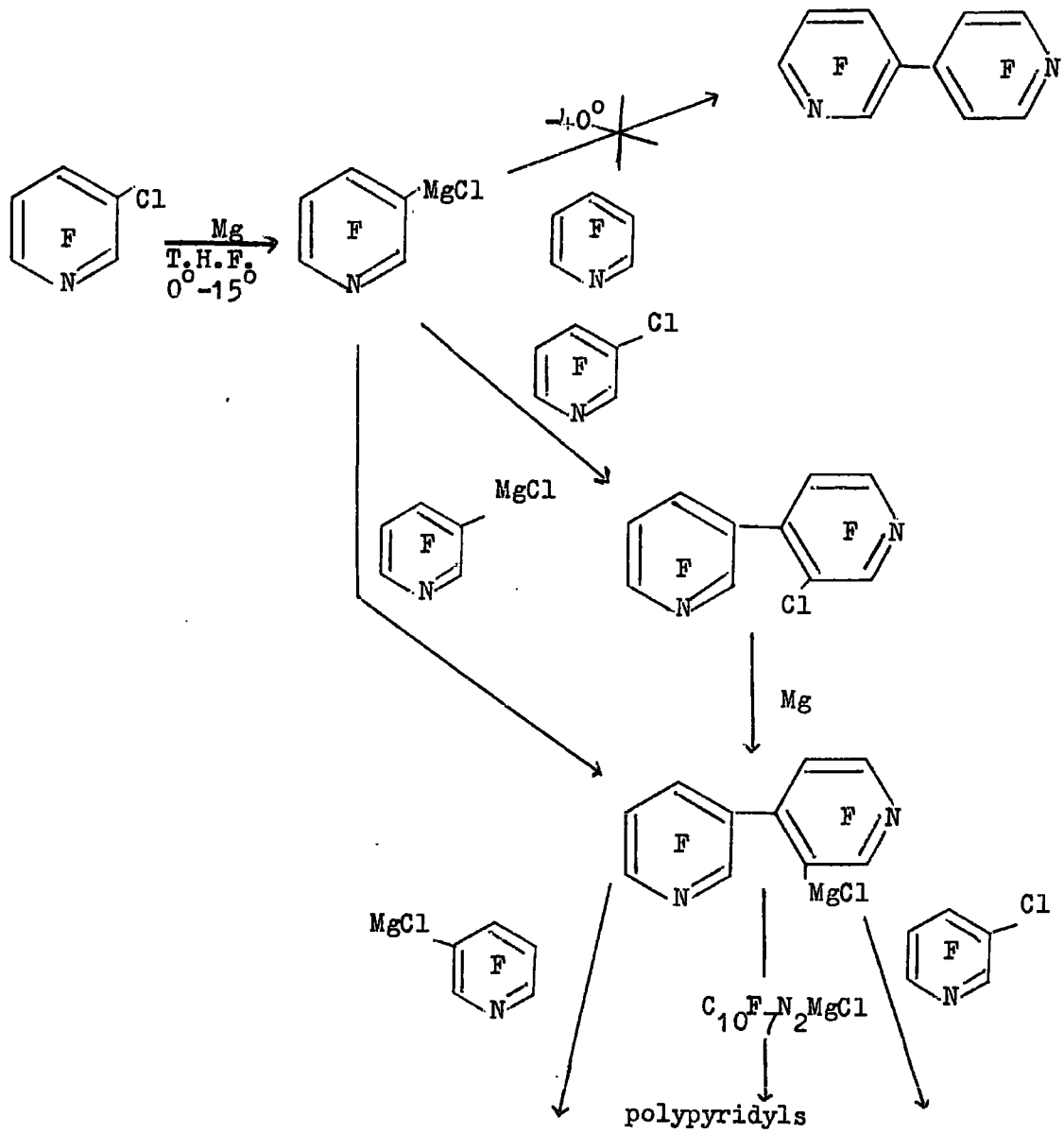
In a recent publication[160] the preparation of a Grignard reagent from chloropentafluorobenzene in diethyl ether using magnesium activated by 1,2-dibromoethane has been described. When the Grignard reagent was

prepared in tetrahydrofuran, polymeric material similar to that which was obtained when reacting bromopentafluorobenzene with magnesium in boiling tetrahydrofuran, was produced in good yield.

Similar results were obtained when the Grignard reagent from 3-chlorotetrafluoropyridine was prepared in tetrahydrofuran; polymeric material, tentatively identified as consisting of polyfluoropyridyl units, being obtained.[146]

In an attempt to prepare octafluoro-3,4'-bipyridyl by adding pentafluoropyridine to a stirred solution of 2,4,5,6-tetrafluoropyridylmagnesium chloride in tetrahydrofuran only a dark brown solid which did not sublime ($150^{o}/0{\cdot}1$ mm.) was isolated. The solid product was shown by infrared spectra to be similar to that obtained by Drakesmith[146] from the decomposition of 2,4,5,6-tetrafluoropyridyl-magnesium chloride.

The formation of polymeric material is probably due to the nucleophilic attack of the Grignard reagent at the 4-position in any unreacted 3-chlorotetrafluoropyridine and also at the 4-position in 2,4,5,6-tetrafluoropyridylmagnesium chloride. Thus, a chain mechanism can be set up leading eventually to high-molecular weight polypyridyls.


Cl
F
N
Mg
T.H.F.
0°-15°
MgCl
-40°
F
N
F
N
Cl
MgCl
F
N
F
N
Cl
Mg
F
N
F
N
MgCl
MgCl
F
N
Cl
F
N
$C_{10}F_7N_2MgCl$
polypyridyls

Introduction of Halogen into the Pyridine Nucleus via the Diazonium Reaction

The versatility of the diazonium reactions is well known in aromatic chemistry as they provide a route to a variety of compounds not available by other methods.

Wall, Pummer and co-workers[168] have prepared pentafluoroiodo- and pentafluorobromobenzene by diazotisation of pentafluoroaniline in anhydrous hydrogen fluoride followed by addition of potassium iodide and cuprous bromide/potassium bromide mixture respectively. Brooke and co-workers[169] diazotised pentafluoroaniline in 80% hydrofluoric acid and prepared chloro-, bromo-, and iodo-pentafluorobenzene by treatment with the usual reagents.

4-Aminotetrafluoropyridine,[170] readily obtained by the reaction between aqueous ammonia and pentafluoropyridine, has been shown to be a useful intermediate in the synthesis of other 4-substituted tetrafluoropyridines. Diazotisation of negatively substituted aromatic amines usually requires special considerations but diazotisation of 4-aminotetrafluoropyridine was further complicated by the possible loss of fluoride ion from the diazonium salt, a difficulty that has been encountered by other workers using fluorinated aromatic amines.

Workers at Durham[159] have found that 80% hydrofluoric acid is suitable for the preparation of 4-bromotetrafluoropyridine from the addition of aqueous hydrogen bromide/cuprous bromide mixture to 2,3,5,6-tetrafluoropyridinediazonium fluoride at -20 to -25°. Under similar

reaction conditions 4-iodo- and 4-chlorotetrafluoropyridine have been prepared by addition of potassium iodide and aqueous hydrochloric acid/ cuprous chloride respectively to 2,3,5,6-tetrafluoropyridine diazonium fluoride at -20 - -30°.

4-Aminotetrafluoropyridine was obtained when 2,4-diaminotrifluoropyridine was diazotised in anhydrous hydrofluoric acid and the resulting 2-diazonium-3,5,6-trifluoro-4-aminopyridine fluoride allowed to decompose in solution. The ease of replacement of α-amino groups by fluorine in polyfluoroheterocyclic compounds has also demonstrated in the case of 1-aminohexafluoroisoquinoline.[171] When an attempt to replace the amine group of 4-aminotetrafluoropyridine was made a red solid was obtained which could have been a fluorinated azoaminopyridine.

A route to mixed chlorobromofluoropyridines was shown to be available as 2,6-difluoro-3,5-dichloro-4-bromopyridine was obtained from the diazonium salt of 2,6-difluoro-3,5-dichloro-4-aminopyridine.

The results of these reactions are shown in TABLE 12.

Nucleophilic Substitution in Polyfluoropyridines.

Several substituted fluoropyridines, used as starting materials in the preparation of polyfluorobipyridyls, have been prepared from the reaction of nucleophilic reagents with polyfluoropyridines. Nucleophilic substitution in polyfluoroaromatic and polyfluoroheteroaromatic compounds is dealt with in Chapter 5.

TABLE 12

Replacement of Diazonium Ion by Fluorine, Chlorine, Bromine and Iodine.

Amine	Reaction Conditions	Product (% yield in parentheses)	reference
Pentafluoroaniline	anhydrous HF, -20 - -10° $NaNO_2$, KI	pentafluoroiodobenzene (56%)	168
"	anhydrous HF, -20 - -10° $NaNO_2$, KBr/CuBr	pentafluorobromobenzene (35%)	168
"	80% HF, $NaNO_2$, HCl/CuCl, 100°	pentafluorochlorobenzene (46%)	169
"	80% HF, $NaNO_2$ HBr/CuBr	pentafluorobromobenzene (63%)	109
"	80% HF, $NaNO_2$ KI	pentafluoroiodobenzene (42%)	169
4-Aminotetrafluoropyridine	conc. H_2SO_4, $NaNO_2$ HBr/CuBr	No reaction	159
"	80% HF, $NaNO_2$ -20 - -25° CuBr/HBr	4-bromotetrafluoropyridine (61%)	159
"	80% HF, $NaNO_2$ -20 - -30° CuCl/HCl	4-chlorotetrafluoropyridine (52%)	
"	80% HF, $NaNO_2$ -20 - -30° KCl/H_2O	4-iodotetrafluoropyridine (15%)	
"	80% HF, $NaNO_2$ -30 - 20°	(azoaminopyridine)	
2,4-diaminotrifluoropyridine	anhydrous HF, $NaNO_2$, -30 - 20°	4-aminotetrafluoropyridine (21%)	
3,5-dichloro-4-amino-difluoropyridine	80% HF, $NaNO_2$ -30° CuBr/HBr	3,5-dichloro-4-bromo-difluoro pyridine (64%)	

C H A P T E R 4

EXPERIMENTAL. PART 1

PREPARATION OF OCTAFLUORO- AND POLYFLUOROCHLORO-BIPYRIDYLS

Infrared (i.r.) spectra were recorded using a Grubb-Parsons, type G.S.2.A. or Spectromaster spectrometers. Refractive index were measured on a Bellingham and Stanley Abbe type refractometer. Chemical analyses were carried out by Mr. T.F. Holmes, and in the case of fluorine analyses using the biphenyl-sodium method of decomposition.[172]

Qualitative analytical-scale vapour phase chromatography (v.p.c.) was performed on Perkin Elmer and Griffin and George type instruments. Quantitative analytical-scale vapour phase chromatography was performed on the Griffin Gas Density Balance type instrument. Preparative-scale vapour phase chromatography was performed on an Aerograph "Autoprep" instrument unless otherwise stated.

The orientations of compounds were determined from nuclear magnetic resonance spectra (n.m.r.) and are reported in Chapter 8.

CHLORINATION REACTIONS.

The chlorination reactions were carried out in a high pressure reaction vessel of 1·5, 3, or 5 litre capacity. The autoclaves were constructed from stainless steel giving a wall thickness of approximately $\frac{1}{2}$ inch. The heads of the autoclaves were constructed of heavy stainless steel and fitted with a needle valve, thermocouple well, and in the case of the 5-litre autoclave a bursting disc assembly. The head of the autoclave was sealed to the flange on the body by a copper gasket and held in position by steel bolts. The body of the autoclave was fitted with a heavy metal liner to prevent as far as possible corrosion of the inner stainless steel wall.

The autoclaves were heated by a 2 kilowatt element arranged in the shape of a spiral so that the body of the autoclave fitted inside.

Chlorination of Pyridine.

The pyridine was dried by refluxing over potassium hydroxide pellets for several hours followed by distillation from potassium hydroxide under an atmosphere of dry nitrogen.

In a typical experiment, an autoclave (3 litre) charged with dry pyridine (250 g., 3·16 mole) and phosphorus pentachloride (2,500 g., 12 mole) was heated to 294° over a period of 6 hr. and then at that temperature for 44 h. After allowing the autoclave to cool to room temperature the hydrogen chloride generated during the reaction was released before the vessel was opened and then the product was hydrolysed

CHLORINATION AUTOCLAVES

LEFT: 1·5 Litre RIGHT: 5 litre

by slowly adding it to a mixture of ice and water. When the hydrolysis was complete, the organic product was steam distilled and the distillate extracted with methylene dichloride. The solvent was removed by distillation to yield a mixture of chloropyridines. (204 g.). The water was then removed by azeotropic distillation with benzene. The chloropyridines were distilled through a 20 in. column packed with Dixon gauze into two fractions;

(i) b.p. 140-278° which was shown to be a mixture of tri- and tetrachloropyridines with a little pentachloropyridine by analytical-scale v.p.c. by comparison of retention times (silicone elastomer on celite at 200°) with authentic samples of polychloropyridines.

(ii) b.p. 278-280°. This fraction was redistilled to give pentachloropyridine b.p. 279-280°, m.p. 123-124° (from benzene) (lit.[56] b.p. 279-280°, m.p. 124°).

The composition of the original product was estimated by analytical-scale v.p.c. to be $C_5H_2Cl_3N$, 30; C_5HCl_4N, 50; C_5Cl_5N, 20 mole-%.

In a typical reaction an autoclave (5 litre) charged with pyridine (100 g., 1·26 mole) and phosphorus pentachloride (2,500 g., 12 mole) was heated rapidly to 300° (2 h.) and then heated at this temperature for 22 h. After allowing the autoclave to cool to room temperature, the hydrogen chloride generated during the reaction was released before the vessel was opened and then the product was hydrolysed by slowly adding it to ice. When this was complete, the organic product

was steam distilled to give a mixture of chloropyridines (250 g.). The white solid material was filtered off and the remaining water was removed by azeotropic distillation with benzene. The chloropyridines were distilled through a 20 in. column packed with Dixon gauze into two fractions;

(i) b.p. 240-258° shown by analytical-scale v.p.c. and infrared spectra to be essentially tetrachloropyridines (lit.[56] b.p. 248-252°).

(ii) 279-280° (225 g., 70%), which was redistilled to give pentachloropyridine b.p. 280°, m.p. 123-124°.

The composition of the original product was estimated by analytical-scale v.p.c. to be C_5HCl_4N, 5; C_5Cl_5N, 95 mole-%.

Reaction of Phosphorus Pentachloride with Tri- and Tetrachloropyridines.

In a typical experiment an autoclave (3-litre) charged with a mixture of tri- and tetrachloropyridines (582 g.) (obtained from previous experiments) and phosphorus pentachloride (2,000 g., 9·6 mole) was heated at 296° for 8 h. The reaction was worked up as in previous experiment to yield after distillation, pentachloropyridine (365 g.) m.p. 124°, and a mixture of tetra- and pentachloropyridine (150 g.).

Chlorination of 2-Methylpyridine.

In a typical experiment an autoclave (5 litre) charged with 2-methylpyridine (30 g., 0·32 mole) and phosphorus pentachloride (1350 g.,

6·5 mole) was heated rapidly to 300° (2 h.) and then heated at this temperature for a further 6·5 h. The autoclave was allowed to cool and vented to remove the hydrogen chloride formed during the reaction. The contents of the autoclave were then hydrolysed by slowly adding to ice and the solid material filtered off. The water was removed under vacuum (P_2O_5) and the solid sublimed under reduced pressure (0·2 mm., 180°) to give a white solid (72 g.). Distillation through a short still head gave pentachloropyridine (72 g., 89%) m.p. 120-124°. Analytical-scale v.p.c. indicated that there were no lower-chlorinated pyridines present.

Chlorination of 2,2'-Bipyridyl.

In a typical experiment, an autoclave (5 litre) charged with 2,2'-bipyridyl (40 g., 0·26 mole) and phosphorus pentachloride (2,000 g., 9·6 mole) was heated rapidly to 300° (2 h.) and then heated at this temperature for a further 10 h. The autoclave was allowed to cool and vented to release hydrogen chloride formed during the reaction before the vessel was opened. The product was then hydrolysed by slowly adding it to ice. When this was complete the chlorinated product was filtered off and dried (P_2O_5), after which the product was sublimed under reduced pressure to give a white solid (101 g.). Fractional sublimation (0·2 mm. Hg raised temperature) afforded three main fractions.

(i) Pentachloropyridine (2·0 g.) m.p. 120-123° (from benzene), identified by its infrared spectrum.

(ii) A white solid (0·5 g.) m.p. 175-178° which was thought to be a mixture of hexa- and heptachloro-2,2'-bipyridyls.

(iii) Octachloro-2,2'-bipyridyl (97 g., 87%) m.p. 184-187° (from benzene).

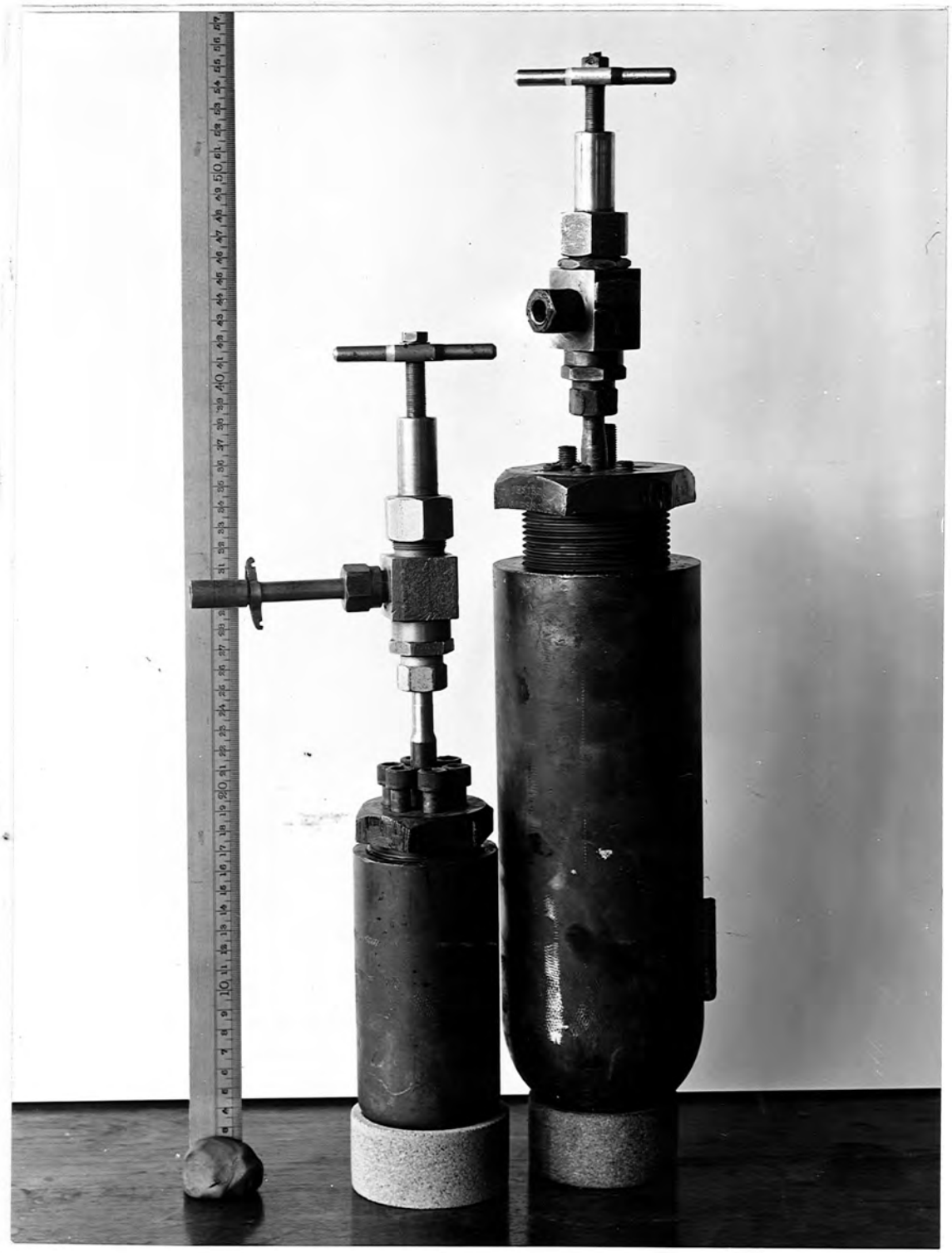
(Found: C, 27·9; Cl, 65·6. $C_{10}Cl_8N_2$ requires C, 27·8; Cl, 65·7%).

Replacement of Chlorine by Fluorine in Pentachloropyridine.

The potassium fluoride used was reagent grade and was dried before use by heating for 2-3 days in a nickel beaker.

The autoclave was a high pressure reaction vessel constructed out of stainless steel of 120 or 150 ml. capacity. The autoclave head, fitted with a needle valve, was screwed into the body of the vessel and sealed with a copper or aluminium gasket. The temperature was recorded using an external thermocouple fixed to the side of the autoclave.

In a typical experiment an autoclave (150 ml.) charged with pentachloropyridine (30 g., 0·12 mole) and anhydrous potassium fluoride (80 g., 1·38 mole) was evacuated before being heated to 410° for 17·25 h. While the reaction vessel was still hot the product (21 g.) was distilled out under vacuum. Distillation through a 24 in. concentric tube column of the combined products from several reactions gave three fractions:



FLUORINATION AUTOCLAVES

LEFT: 150 ml. RIGHT: 750 ml.

(i) Pentafluoropyridine b.p. 84° (lit.[56,29] b.p. 84°, 83·30) identified from its infrared spectrum.

(ii) 3-Chlorotetrafluoropyridine, b.p. 118-119° (lit.[56] b.p. 119°) the infrared spectrum of which was identical with that of an authentic sample.

(iii) 3,5-Dichlorotrifluoropyridine b.p. 158-159° (lit.[56] 159-160°) the infrared spectrum of which was identical with that of an authentic sample.

Replacement of Chlorine by Fluorine in Octachloro-2,2'-bipyridyl.

a) Using potassium fluoride in the absence of solvent.

Octachloro-2,2'-bipyridyl (3 g., 0·007 mole) and anhydrous potassium fluoride (15 g., 0·26 mole) were sealed under vacuum in a Carius tube and heated to 296-316° for 16·25 h. The tube was allowed to cool and the contents added to water. The aqueous mixture was extracted with ether and the combined extracts dried ($MgSO_4$). The ether was removed by distillation to give a clear liquid which when distilled under reduced pressure afforded a thick oil (2·1 g.) that was shown by analytical v.p.c. (silicone oil on celite at 200°) to be a mixture of two components in the ratio 9:1. Fractional distillation under reduced pressure gave 3,3',5,5'-tetrachloro-4,4',6,6'-tetrafluoro-2,2'-bipyridyl (the main component of the mixture), (b.p. 305-308°), (Found: C, 32·8; F, 20·7; Cl, 38·5. $C_{10}F_4Cl_4N_2$ requires: C, 32·8; F, 20·8; Cl, 38·8%).

The other component in the reaction was thought to be 3,3',5-

trichloropentafluoro-2,2'-bipyridyl but was not isolated.

b) Using potassium fluoride in sulpholane.

Octachloro-2,2'-bipyridyl (20 g., 0·046 mole), potassium fluoride (100 g., 1·7 mole) and dry sulpholane (310 g.) were vigorously stirred at 200° for 15·75 h. The contents of the reaction flask were cooled to room temperature and water was added. The aqueous mixture was extracted with ether, and the combined extracts washed well with water. The extracts were dried ($MgSO_4$) and the solvent removed by distillation to give a black oil (10·4 g.). Distillation under reduced pressure, (64-70°/0·9 mm.), afforded a clear oil (8·9 g.), the composition of which was shown by analytical scale v.p.c. (silicone oil on celite at 170°) to be a mixture of three components in the ratio 10:27:63. The three components were separated using preparative scale v.p.c. (silicone elastomer on celite at 160°) to give: a) octafluoro-2,2'-bipyridyl (6·3%) (Found: C, 39·8; F, 50·2. $C_{10}F_8N_2$ requires, C, 40·0; F, 50·67%) as a low melting solid b.p. 223° - 224°.

b) 3-chloroheptafluoro-2,2'-bipyridyl (16·2%) (Found: C, 38·0; F, 41·7; Cl, 11·8. $C_{10}F_7ClN_2$ requires C, 37·9; F, 42·0; Cl, 11·2%) b.p. 233-234°.

c) 3,3'-dichlorohexafluoro-2,2'-bipyridyl (36·6%), (Found: C, 36·3; F, 33·5; Cl, 20·7. $C_{10}F_6Cl_2N_2$ requires: C, 36·04; F, 34·2; Cl, 21·3%) m.p. 45-48°.

Preparation of 4-Bromotetrafluoropyridine[159] from 4-Aminotetrafluoropyridine.[170]

In a typical reaction, to a stirred solution of the amine (28·0 g.) 0·17 mole) in aqueous hydrofluoric acid (200 ml., 80% w/w) in a polythene beaker fitted with a polythene lid and metal stirrer, was added sodium nitrite (28·0 g.) at -25° to -30° over 25 minutes. The solution was stirred for a further 15 min. with the temperature maintained at -25°. A solution of cuprous bromide in hydrobromic acid (made by dissolving the cuprous bromide produced from hydrated copper(II)sulphate (160 g.), potassium bromide (120 g.) and hydrated sodium sulphite (60 g.) in hydrogen bromide (20 ml. 54% w/w)) was added dropwise over 45 minutes to the diazonium salt, the temperature being kept constant at -30°. After a further 2 h., during which time the reaction vessel had warmed to room temperature, the mixture was diluted with water (2 l.) and extracted with ether. The ether extracts were washed well with water and then dried ($MgSO_4$). The solvent was then distilled off to yield a brown liquid (33 g.), which when distilled (from P_2O_5) gave 4-bromotetrafluoropyridine (30 g., 77%) b.p. 132-134° (lit. 134-135°).

Preparation of 4-Chlorotetrafluoropyridine from 4-Aminotetrafluoropyridine.

To a stirred solution of the amine (6 g., 0·036 mole) in aqueous hydrofluoric acid (50 g., 80% w/w) was added sodium nitrite (6 g.) at -25° over 30 minutes. With the temperature maintained at -25° to -30° a solution of copper(I)chloride in hydrochloric acid (made by dissolving the copper(I)chloride produced from hydrated copper(II)chloride (30 g.) and

sodium thiosulphite (22·8 g.) in hydrochloric acid (60 ml., 36·5% w/w.)) was added dropwise over 30 minutes. After a further 2 h., during which time the solution had warmed to room temperature, the mixture was diluted with water (750 ml.) and extracted with ether. The ether extracts were washed well with water and then dried ($MgSO_4$). The solvent was then removed by distillation to yield a pale brown liquid (4·1 g.), which when distilled (from P_2O_5) afforded 4-chlorotetrafluoropyridine (3·5 g., 52·2%) (Found: C, 32·8; F, 40·6; Cl, 19·1. C_5ClF_4N requires C, 32·4; F, 41·0; Cl, 19·1%), b.p. 122-123°; n_D^{20} 1·4315.

Preparation of 4-Iodotetrafluoropyridine from 4-Aminotetrafluoropyridine.

To a stirred solution of the amine (6 g., 0·036 mole) dissolved in aqueous hydrofluoric acid (50 g., 80% w/w.) was added sodium nitrite (6 g.) at -30° over 30 minutes. With the temperature maintained at -30° an aqueous solution of potassium iodide (12 g.) was added slowly over 30 minutes. The solution was then allowed to warm slowly to room temperature before being diluted with water (1 l.). The aqueous solution was extracted with methylene dichloride and the combined extracts well washed with water. The extracts were dried ($MgSO_4$) and removed by distillation to give a red solid (2·0 g.). Sublimation under reduced pressure afforded a white solid, 4-iodotetrafluoropyridine (1·5 g., 15%) (Found: C, 21·5; F, 27·2; I, 44·8. C_5IF_4N requires C, 21·66; F, 27·4; I, 45·8%) m.p. 48·5° - 49·5° (resublimation).

Attempted replacement of Amino group by Fluorine in 4-Aminotetrafluoropyridine.

To a stirred solution of the amine (3·32 g., 0·02 mole) in aqueous hydrofluoric acid (44 g., 80% w/w.) was added sodium nitrite (1·4 g.) at -30° over 30 minutes. The mixture was stirred at -30° for a further 15 min. and then allowed to warm slowly to room temperature (2·5 h.). The mixture was diluted with water (500 ml.) and the aqueous mixture then extracted with methylene dichloride, which after washing well with water and drying ($MgSO_4$) was removed by distillation to afford a red solid. No pentafluoropyridine was detected. The red solid did not sublime (130°, 0·1 mm.) and was thought to be a fluorinated azoaminopyridine.

Replacement of the Amino group by Fluorine in 2,4-diaminotrifluoropyridine.

To a stirred solution of the amine (3·26 g., 0·02 mole) dissolved in anhydrous hydrofluoric acid (54 ml., 100%) was added sodium nitrite (1·4 g., 0·02 mole) at -30° over 25 minutes. The solution was stirred for a further 15 minutes at -30° and then allowed to warm slowly to 0° (1·5 h.). The hydrofluoric acid was allowed to evaporate off leaving an orange coloured liquid. Water was added and the aqueous solution extracted with methylene dichloride, which after washing well with water, drying ($MgSO_4$), was removed by distillation to give a red solid (0·9 g.). Sublimation under reduced pressure afforded a pale yellow solid which after recrystallization for petroleum-ether (40-60° fraction) gave

4-aminotetrafluoropyridine (0·7 g., 21·2%) m.p. 85-86° (lit.[170] 85-86°). The compound had an infrared spectrum identical with that of an authentic sample.

Preparation of 2,6-difluoro-3,5-dichloro-4-bromopyridine from 2,6-difluoro-3,5-dichloro-4-aminopyridine.

To a stirred solution of the amine (10 g., 0·05 mole) in aqueous hydrofluoric acid (80 ml., 80% w/w.) was added sodium nitrite (10 g.) at -25° to -35° over 30 minutes. The solution was stirred for a further 30 minutes. A solution of copper(I)bromide in hydrobromic acid (made by dissolving the copper(I)bromide produced from hydrated copper(II) sulphate (20 g.), potassium bromide (40 g.) and hydrated sodium sulphite (20 g.) in hydrogen bromide (12 ml., 54% w/w.)) was added dropwise to the diazonium salt, the temperature being maintained at -30°. The solution was stirred for a further 30 min. and then allowed to warm slowly to room temperature. The mixture was diluted with water and the aqueous mixture extracted with methylene dichloride, which after washing well with water, drying ($MgSO_4$), was removed by distillation to give a dark brown solid (9·4 g.). Sublimation under reduced pressure gave 2,6-difluoro-3,5-dichloro-4-bromopyridine (8·5 g., 64·4%), (Found: C, 23·0; F, 14·15. $C_5BrCl_2F_2N$ requires C, 22·81; F, 14·4%), m.p. 42-44° (from petroleum-ether, 40-60° fraction.)

Reaction between 3-Chlorotetrafluoropyridine and Copper.

a) 3-Chlorotetrafluoropyridine (7·6 g., 0·041 mole) was sealed under vacuum in a Carius tube with copper powder (5 g., 0·08 mole) and heated to 250-260° for 120 h. The tube was cooled, opened and the contents extracted with ether. The ether extracts were dried ($MgSO_4$), and the solvent removed by distillation to give a light brown oil. Sublimation under reduced pressure (50°, 0·1 mm.) afforded white crystals of octafluoro-3,3'-bipyridyl (4·2 g., 68%), (Found: C, 40·0; F, 51·1. $C_{10}F_8N_2$ requires C, 40·0; F, 50·67%), m.p. 38·0 - 38·5° (from petroleum-ether, 40-60° fraction).

b) 3-Chlorotetrafluoropyridine (1·85 g., 0·01 mol), NN-dimethylformamide (27·8 g.) and copper powder (2 g.) were stirred and heated under reflux for 48 h. After this time the mixture was allowed to cool and poured into water. The aqueous mixture was extracted into methylene dichloride, which after being washed well with water, dried ($MgSO_4$), was removed by distillation to give a red solid. Sublimation under reduced pressure afforded a white solid (0·2 g.), m.p. 80·5 - 81° (from methanol), (Found: C, 48·2; F, 31·4%). No further investigation of the structure was attempted.

Reaction of 3-Chlorotetrafluoropyridine and 3,5-Dichlorotrifluoropyridine with Copper powder.

3-Chlorotetrafluoropyridine (0·93 g., 0·005 mole), 3,5-dichlorotrifluoropyridine (0·5 g., 0·0025 mole) and copper powder (1·45 g.)

were sealed under vacuum in a Carius tube and heated at 250-260° for 96 h. The tube was cooled, opened, and the contents were transferred to a sublimation apparatus. Sublimation under reduced pressure afforded a tacky solid (0·45 g.) which was shown by analytical v.p.c. (silicone elastomer as stationary phase, 200°) to consist mainly of three components with several other components present in trace amounts. The three main components in the %-age ratio 72 : 23: 2·5 were separated by preparative v.p.c. (silicone elastomer on celite at 260°) to give

i) octafluoro-3,3'-bipyridyl, m.p. 39°, which had an infrared spectrum identical with that of an authentic sample.

ii) perfluoro-3,3',3''-terpyridyl (a soft glassy material) b.p. 301-302° (slight decomposition), (Found: C, 41·5; F, 48·5. $C_{15}F_{11}N_3$ requires C, 41·76; F, 48·5).

iii) perfluoro-3,3',3'',3'''-quaterpyridyl, m.p. 111-113° (from ether), (Found: C, 42·4; $C_{20}F_{14}N_4$ requires C, 42·7%).

There was insufficient sample for a fluorine analysis.

Reaction of 3,5-Dichlorotrifluoropyridine with Copper powder.

3,5-Dichlorotrifluoropyridine (1·0 g., 0·005 mole) was sealed under vacuum in a Carius tube with copper powder (2 g.) and then heated at 230° for 104 h. The tube was cooled and the contents were transferred to a sublimation apparatus. Sublimation under reduced pressure (200°, 0·1 mm.) did not afford any material. The contents of the flask were then extracted with ether but again no solid material was obtained. Extraction of the product with tetrahydrofuran afforded a

black solid which had an infrared spectrum similar to that obtained from a mixture of polyfluoropolypyridyls.[146] As the solid would not sublime below 220° at reduced pressure, it is probable that there are more than five pyridine rings joined together.

Reaction of 3-, and 4-Chlorotetrafluoropyridine with Copper.

3-Chlorotetrafluoropyridine (1 g., 0·0054 mole) and 4-chlorotetrafluoropyridine (1 g., 0·0054 mole) were sealed under vacuum in a Carius tube with copper (2·0 g.) and heated to 250° for 48 h. The tube was allowed to cool to room temperature, opened, and the contents transferred to a sublimation apparatus. Sublimation under reduced pressure afforded a white solid (0·7 g.) which was shown by analytical scale v.p.c. to consist of one component, the retention time of which was identical with that of perfluoro-3,3-bipyridyl. As the compound melted over a range (25-60°) it was probably a mixture of perfluoro-3,3'-, 3,4'-, and 4,4'-bipyridyls. The infrared spectrum was similar to that expected from a mixture of octafluorobipyridyls.

Reaction of 3-Chloroheptafluoro-2,2'-bipyridyl with Copper powder.

3-Chloroheptafluoro-2,2'-bipyridyl (0·3 g., 0·00095 mole) was sealed under vacuum in a Carius tube with copper powder (3 g.) and then heated to 190° - 210° for 96 h. The tube was cooled and the contents were transferred to a sublimation apparatus. Sublimation under reduced pressure afforded, after recrystallization from petroleum-ether (40-60° fraction), perfluoro-2,2',3,3",2",2'''-quaterpyridyl (0·1 g., 37·5%) (Found: C, 42·7; F, 46·3. $C_{20}F_{14}N_4$ requires, C, 42·7;

F, 47·3%), m.p. 128-130°.

Reaction of 4-Bromotetrafluoropyridine with Copper powder.

a) In a typical reaction, 4-bromotetrafluoropyridine (6 g., 0·026 mole) and copper powder (6 g.) were sealed under vacuum in a Carius tube and then heated to 200° for 48 h. The tube was allowed to cool to room temperature and the contents were transferred to a sublimation apparatus. Sublimation under reduced pressure gave octafluoro-4,4'-bipyridyl (1·6 g., 41%), m.p. 81-82° (from petroleum-ether (40-60° fraction)) (lit.[159] 81-82°), the infrared spectrum of which was identical with that of an authentic sample.

b) In a typical reaction, 4-bromotetrafluoropyridine (4 g., 0·017 mole), copper powder (2 g., 0·032 mole) and dry NN-dimethylformamide were refluxed for 3 h. The contents of the flask were allowed to cool and then added to water. The white precipitate that was formed was extracted into methylene dichloride and the combined extracts washed well with water. The extracts were dried ($MgSO_4$), and the solvent removed by distillation giving a brown oil. Sublimation under reduced pressure, followed by recrystallization from petroleum-ether (40-60° fraction), afforded octafluoro-4,4'-bipyridyl (1·5 g., 57·5%), m.p. 80-81°.

Reaction of 2-Nitro-4-bromotrifluoropyridine with Copper powder.

Copper powder (1 g.), 2-nitro-4-bromo-trifluoropyridine (0·5 g., 0·002 mole) and NN-dimethylformamide were stirred and heated to 150° for 2 h. The mixture was allowed to cool and then poured into water. The aqueous mixture was extracted with methylene dichloride, the combined extracts washed well with water, dried ($MgSO_4$), and the solvent removed by distillation to give a brown oil (0·4 g.). Distillation and sublimation of the brown oil afforded 2-nitro-4-bromotrifluoropyridine (0·3 g.) and a pale yellow solid (0·05 g.) which was thought to be 2,2'-dinitrohexafluoro-4,4'-bipyridyl; m.p. 117-118·5°.

Preparation and Reactions of 2,3,5,6-Tetrafluoropyridylmagnesium Bromide.

A three-necked flask fitted with stirrer, dropping funnel, and condenser, containing magnesium turnings (1·5 g.) and dry tetrahydrofuran (25 ml.), was purged with dry nitrogen and cooled to -20° to -15°. A solution of 4-bromotetrafluoropyridine (6·9 g., 0·03 mole) in dry tetrahydrofuran (4 ml.) was added and after several minutes the reaction commenced. The mixture was allowed to warm to -10° to 0° and maintained at this temperature for 1 h. before further reactants were added.

(a) Reaction with pentafluoropyridine.[159] To the Grignard reagent was added pentafluoropyridine (5·07 g., 0·03 mole) at -40°. After a few minutes the solution became dark blue and remained this colour while the mixture was stirred for 1 h. at -40°. With the temperature

maintained at -40° the mixture was then hydrolysed with dilute sulphuric acid and the mixture extracted with ether. The combined ether extracts were dried ($MgSO_4$) and the ether distilled off to give a dark brown crystalline material. Sublimation under reduced pressure afforded octafluoro-4,4'-bipyridyl (2·9 g., 32·2%) identified from its infrared spectrum, m.p. 80-82° (lit.[159] 81-82°) (from light petroleum-ether (40-60°)).

(b) Reaction with 3-chlorotetrafluoropyridine. To the Grignard reagent from 4-bromotetrafluoropyridine (2·3 g., 0·01 mole) and magnesium turnings (1·0 g.) was added 3-chlorotetrafluoropyridine (1·85 g., 0·01 mole) at -35° to -40°. Again after a few minutes the reaction mixture became dark blue and remained this colour whilst the reaction mixture was maintained at -40° over a period of 1 h. The mixture was then hydrolysed with dilute sulphuric acid and the aqueous mixture extracted with ether. The ether extracts were washed well with water and then dried ($MgSO_4$). The ether was removed by distillation to give a brown crystalline material. Sublimation under reduced pressure (45°, 0·1 mm.) afforded 3-chloroheptafluoro-4,4'-bipyridyl, (1·7 g., 54%) m.p. 54·5° - 55·5° (from petroleum-ether, (40-60°)). (Found: C, 38·3; Cl, 11·2: Calc. for $C_{10}ClF_7N_2$: C, 37·9; Cl, 11·2%).

(c) Reaction with 3,5-dichlorotrifluoropyridine. To the Grignard reagent, prepared from 4-bromotetrafluoropyridine (2·3 g., 0·01 mole) and magnesium turnings (1·0 g.), was added 3,5-dichlorotrifluoropyridine

(2·02 g., 0·01 mole) at -40°. After a few minutes the reaction mixture turned to a deep blue colour and remained this colour whilst the reaction mixture was stirred for a further 1 h., the temperature being maintained at -35° to -40°. The mixture was then hydrolysed with dilute sulphuric acid and the aqueous mixture extracted with ether. The ether extracts were washed well with water and then dried ($MgSO_4$). The ether was removed by distillation to give a dark brown crystalline material. Sublimation under reduced pressure (55°, 0·1 mm.) gave 3,5-dichloro-hexafluoro-4,4'-bipyridyl (0·9 g., 27·3%), m.p. 67·5 - 68·0° (from petroleum-ether, 40-60° fraction). (Found: C, 36·4; F, 33·6; Cl, 20·8. Calc. for $C_{10}Cl_2F_6N_2$: C, 36·04; F, 34·2; Cl, 21·3%).

(d) Reaction with 3-hydrotetrafluoropyridine. To the Grignard reagent prepared from 4-bromotetrafluoropyridine (2·3 g., 0·01 mol) and magnesium turnings (1·7 g.) was added 3-hydrotetrafluoropyridine[145] (1·5 g., 0·01 mm.) at -40°. No colour change was observed as the mixture was stirred for 1 h. at -30° to -40°. The mixture was hydrolysed with dilute sulphuric acid and the aqueous mixture extracted with ether. The combined ether extracts were washed well with water and dried ($MgSO_4$). The ether was distilled off to leave a dark brown oil which afforded a clear liquid on distillation under reduced pressure. No sublimable product was obtained. The liquid was shown by analytical v.p.c. to consist mainly of two peaks of nearly equal retention time. The retention times were consistent with those from samples of 3-, and 4-

hydrotetrafluoropyridines. No further investigation was carried out.

e) Reaction with 3,5-dihydrotrifluoropyridine. To the Grignard reagent, prepared from 4-bromotetrafluoropyridine (1·15 g., 0·005 mole) and magnesium turnings (0·5 g.) was added 3,5-dihydrotrifluoropyridine[145] (0·67 g., 0·005 mole) at -40°. The solution was stirred at -40° for a further 1 h., again no colour change was observed. The mixture was hydrolysed with dilute sulphuric acid and the aqueous mixture extracted with ether. The ether extracts were dried ($MgSO_4$) and the ether removed by distillation to give a black oil. Distillation under reduced pressure gave a clear liquid which analytical-scale v.p.c. showed to consist mainly of two components. One component had a retention time similar to 3,5-dihydrotrifluoropyridine and the other a retention time similar to 4-hydrotetrafluoropyridine. No further investigation of these compounds was carried out. No bipyridyl was isolated.

Preparation of 2-Methoxy-3,5,6-trifluoropyridylmagnesium Bromide and Reaction with Pentafluoropyridine. A three necked flask fitted with stirrer, condenser and dropping funnel, containing magnesium turnings (0·4 g.) and dry tetrahydrofuran (8 ml.), was purged with dry nitrogen and cooled to -10°. A solution of 2-methoxy-3,5,6-trifluoro-4-bromopyridine[159] (0·54 g., 0·0022 mole) in tetrahydrofuran (3 ml.) was added and after 15 minutes the reaction commenced. The mixture was stirred at between 0° and 15° for a further 30 minutes. The mixture was cooled to 0° and pentafluoropyridine (0·37 g., 0·0022 mole) added

dropwise over 10 minutes. The mixture was stirred at between 0° and -10° for a further hour and then hydrolysed with dilute sulphuric acid. The aqueous mixture was extracted with ether and the ether extracts washed well with water. The solvent was removed by distillation affording a black crystalline material. Sublimation under reduced pressure gave 2-methoxyheptafluoro-4,4'-bipyridyl (0·05 g., 7%) m.p. 97-99° (from petroleum-ether, 40-60° fraction) and was characterised from its infrared spectrum by comparison with that of a previously prepared sample.

Preparation of 2,6-dimethoxy-3,5-difluoropyridylmagnesium Bromide and the attempted reaction with Pentafluoropyridine. A three necked flask fitted with stirrer, dropping funnel and condenser, containing magnesium turnings (1 g.) and dry tetrahydrofuran (15 ml.), was purged with dry nitrogen and cooled to 0°. A solution of 2,6-dimethoxy-3,5-difluoro-4-bromopyridine[159] (1·27 g., 0·005 mole) in dry tetrahydrofuran (2 ml.) was added over 10 minutes. After addition of dibromoethane (1 ml.) and constant stirring and slight warming the reaction commenced. After 0·5 h. the reaction vessel was cooled to 0° and pentafluoropyridine (0·85 g., 0·005 mole) added. The mixture was stirred for a further 1 h. and then hydrolysed by the addition of dilute sulphuric acid. The aqueous mixture was extracted with ether and the ether extracts washed well with water. The solvent was dried ($MgSO_4$) and then removed by distillation to give a dark-brown solid. Sublimation under reduced pressure afforded 2,6-dimethoxy-3,5-difluoropyridine (0·5 g., 58%)

m.p. 86·5 - 87·0° (lit.[159] m.p. 87°) identified from its infrared spectrum.

Preparation of 2,4,5,6-Tetrafluoropyridylmagnesium Chloride and attempted reaction with pentafluoropyridine. A three-necked flask fitted with stirrer, dropping funnel and condenser, containing magnesium turnings (1·8 g.) and dry tetrahydrofuran (25 ml.) was purged with dried nitrogen. The magnesium was activated by the entrainment method with dibromoethane. A solution of 3-chlorotetrafluoropyridine (1·85 g., 0·01 mole), dibromoethane (2 ml.), and dry tetrahydrofuran (2 ml.) was added dropwise over 15 minutes. The reaction did not start and required addition of several more drops of dibromoethane and heating before the reaction commenced. The mixture was cooled to -30° and pentafluoropyridine (1·7 g., 0·01 mole) added. The mixture was stirred for a further 1 h. and then hydrolysed with dilute sulphuric acid. The mixture was extracted with ether and the ether extracts dried ($MgSO_4$). The solvent was removed by distillation to yield a black tar. Prolonged pumping under high vacuum gave a dark brown solid which did not sublime under reduced pressure and raised temperature.

The solid had an infrared spectrum similar to that of polyfluoropyridyls.[146]

Reaction of Pentafluoropyridine with aqueous Ammonia.[170]

(i) Pentafluoropyridine (20 g., 0·118 mole) and ammonia (30 ml., s.g. 0·88) were sealed in a Carius tube and left for 24 h. at room

temperature. After this time the organic layer had solidified. The contents of the tube were added to water and the aqueous mixture extracted with methylene dichloride. The combined extracts were dried ($MgSO_4$) and the solvent removed by distillation to give a white solid (18 g.). Sublimation under reduced pressure (90°/0·1 mm.) afforded 4-aminotetrafluoropyridine (18 g., 92%) m.p. 84-85° (lit.[170] 85-86°) identified from its infrared spectrum.

(ii) Pentafluoropyridine (13 g., 0·077 mole) and ammonia (20 ml. s.g. 0·88) were sealed in a Carius tube and heated to 130° for 17 h. On cooling the organic layer solidified and the contents of the tube were then added to water. The aqueous mixture was extracted with methylene dichloride, the combined extracts dried ($MgSO_4$), and the solvent removed by distillation to give a brown solid (9·7 g.). Sublimation under reduced pressure afforded 2,4-diaminotrifluoropyridine (9·2 g., 74%) m.p. 112-113° (lit.[173] 111-112°) identified from its infrared spectrum.

Reaction of 4-Bromotetrafluoropyridine with Ammonia.[159]

4-Bromotetrafluoropyridine (6·0 g., 0·026 mole) and ammonia (10 g., s.g. 0·88) were sealed in a Carius tube and heated at 80-100° for 6 h. On cooling the organic layer solidified, which together with the remaining contents of the tube was added to cold water. The aqueous mixture was extracted with methylene dichloride, the combined extracts dried ($MgSO_4$), and the solvent distilled off to give a dark

brown solid (4·3 g.). Sublimation under reduced pressure afforded a pale pink solid, 2-amino-4-bromotrifluoropyridine (3·7 g., 63%) m.p. 116-118° (lit.[159] 116-117°), identified from its infrared spectrum.

Oxidation of 2-Amino-4-bromotrifluoropyridine.

A mixture of methylene dichloride (60 ml.), trifluoroacetic anhydride (15 ml.), and ca. 80% hydrogen peroxide (6·0 ml.) was stirred and heated under reflux for 20 min.[159] A solution of 2-amino-4-bromotrifluoropyridine (5·14 g., 0·0023 mole) in methylene dichloride (50 ml.) was then added to the refluxing solution and the mixture immediately became bright green. The colour changed to pale yellow after 45 min. Hydrogen peroxide (3 ml.) was added after a further 15 min., and then again after 3 h., together with trifluoroacetic anhydride (3 ml.) and methylene dichloride (3 ml.). The mixture was stirred and refluxed for a further 16 h. and then allowed to cool. Water was then added carefully and the methylene dichloride layer separated off. The organic layer was then washed well with water, dried ($MgSO_4$), and the solvent distilled off through a 12" Vigreux column to leave a pale brown oil. Distillation under reduced pressure (90-94°/1·5 - 2 mm.) of the residual liquid (from P_2O_5) afforded a yellow liquid, 2-nitro-4-bromo-trifluoropyridine (3·2 g., 55%) b.p. 214-216°, n_D^{20} 1·5311. (Found: C, 23·8; F, 21·9; Br, 31·3. $C_5O_2F_3BrN_2$ requires: C, 23·4; F, 22·2; Br, 31·1%).

Reaction of 4-Bromotetrafluoropyridine with Sodium Methoxide.[159]

(i) To a stirred solution of 4-bromotetrafluoropyridine (2·3 g., 0·01 mole) in dry methanol (25 ml.) was added slowly, at 0°, a solution made from sodium (0·27 g., 0·012 mole) and dry methanol (20 ml.). The reaction was allowed to warm to room temperature and then stirred for 1 h. Water was then added and the aqueous mixture extracted with methylene dichloride. Removal of the solvent from the dried ($MgSO_4$) extracts afforded a pale yellow liquid (1·9 g.). Distillation under reduced pressure afforded 4-bromo-2,3,5-trifluoromethoxypyridine (1·5 g., 62%) b.p. 189-191° (lit.[159] 193-194°), identified from its infrared spectrum.

(ii) To a stirred solution of 4-bromotetrafluoropyridine (4·6 g., 0·02 mole) in dry methanol (40 ml.) was added dropwise, at room temperature, a solution made from sodium (1·12 g., 0·05 mole) dissolved in dry methanol (35 ml.). The reaction mixture was refluxed for 45 min. and then treated as above. Sublimation of the product (3·9 g.) under reduced pressure followed by recrystallization from petroleum-ether (40-60° fraction) afforded 4-bromo-3,5-difluorodimethoxypyridine (2·7, 53%) m.p. 121° (lit.[159] 120·5 - 121·5°), identified by its infrared spectrum.

Reaction of 3,5-dichlorotrifluoropyridine with Ammonia.

3,5-Dichlorotrifluoropyridine (8·1 g., 0·04 mole) and ammonia (20 ml. s.g. 0·88) were stirred at 20° until the organic layer solidified (ca. 2 h.). Water was added to the mixture and the aqueous

mixture extracted with methylene dichloride. Distillation of the dry ($MgSO_4$) extracts afforded a white solid (7·2 g.). Sublimation under reduced pressure afforded 4-amino-3,5-dichlorodifluoropyridine (7·0 g., 88%) m.p. 114°, (lit. 112-113°), identified by its infrared spectrum.

Reaction of 4-Chlorotetrafluoropyridine with Ammonia

4-Chlorotetrafluoropyridine (0·5 g., 0·0027 mole), ammonia (2·0 g., s.g. 0·88) and acetone (5 ml.) were sealed in a Carius tube and heated for 6 h. at 80°. The tube was then cooled, opened, and the contents added to water. The aqueous mixture was extracted with methylene dichloride, the combined extracts dried ($MgSO_4$), and the solvent distilled off to give a brown solid (0·35 g.). Sublimation under reduced pressure followed by recrystallization from petroleum-ether (40-60° fraction) afforded white crystals of 4-chloro-2,3,5-trifluoroaminopyridine (0·3 g., 60%) m.p. 117-117·5° (Found: C, 33·1; H, 0·93. $C_5H_2F_3ClN_2$ requires C, 32·9; H, 1·1%). A correct halogen analysis could not be obtained.

Catalytic Reduction of 3-Chlorotetrafluoropyridine.[145]

3-Chlorotetrafluoropyridine (15·0 g., 0·08 mole) was dropped, over 2·5 h., into a flash-distillation flask heated to 200°, through which a stream of dry hydrogen (50-60 ml./min.) was passing. The chlorofluoropyridine was immediately vapourised and carried in the hydrogen stream over a palladised-carbon catalyst maintained at 250°. The product was collected in a cold-trap (liquid air) and dried by

vacuum distillation from P_2O_5. The product (7·2 g.) was shown by analytical-scale v.p.c. to consist of one main compound which was separated from the minor impurities by preparative-scale v.p.c. (tritolyl phosphate as stationary phase at 120°) and identified from its infrared spectrum as 3-hydrotetrafluoropyridine (4·6 g., 38%).

Catalytic Reduction of 3,5-Dichlorotrifluoropyridine.[145]

Using the same procedure as above, 3,5-dichlorotrifluoropyridine (8·0 g., 0·04 mole) was flasked distilled at 240° and passed, in a stream of dry hydrogen over the catalyst at 280°. The product was isolated as above, purified by preparative-scale v.p.c., and identified by its infrared spectrum as 3,5-dihydrotrifluoropyridine (2·7 g., 52%).

Reaction between Pentafluoropyridine and Potassium chloride.

Pentafluoropyridine (8·5 g., 0·05 mole) and potassium chloride (120 g.) were heated in a sealed autoclave (150 ml.) at 520° for 17 h. The autoclave was vented whilst still hot and the products collected in cold trap (liq. air). Analytical-scale v.p.c. showed that the product (4·7 g.) consisted of two major components in the ratio 2:3. The first component had a retention time equal to that of pentafluoropyridine and the second component had a retention time equal to that of monochlorotetrafluoropyridine. The second component was isolated by preparative-scale v.p.c. (silicone elastomer on celite at 100°) and identified as an

equi-molar mixture of 3- and 4-chlorotetrafluoropyridines, b.p. 118°. (Found: C, 32·3. C_5F_4ClN requires C, 32·3%). The orientation of the chlorotetrafluoropyridines were determined from nuclear magnetic resonance spectra.

PART II.

NUCLEOPHILIC SUBSTITUTION IN POLYFLUOROBIPYRIDYLS

CHAPTER 5

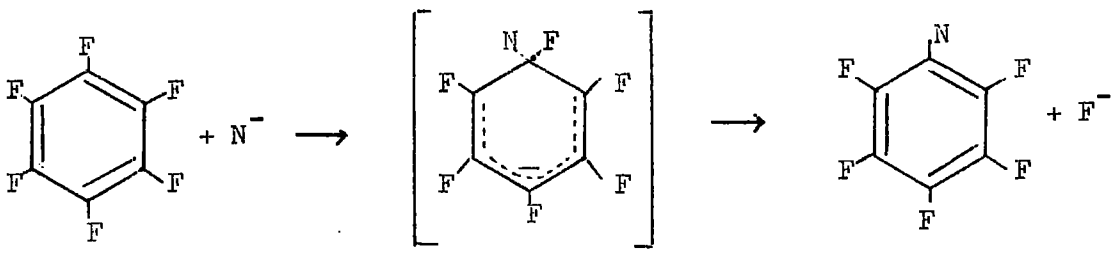
INTRODUCTION

Nucleophilic Substitution in Aromatic and Heteroaromatic Polyfluoro-Compounds.

The introduction of functional groups into the polyfluoro-aromatic nucleus via nucleophilic substitution reactions has been extensively investigated mainly by the workers at Birmingham and at The National Bureau of Standards. Nucleophilic substitution in polyfluoropyridines has been investigated by the workers here at Durham and to a minor extent by the workers at Manchester.

Nucleophilic substitution reactions which involve the elimination of fluoride ion probably occur by way of a reactive intermediate complex analogous to that proposed by Bunnett and Zahler[174] for aromatic bimolecular nucleophilic substitution.

Nucleophilic substitution in Hexafluorobenzene.[175,176]



Hexafluorobenzene has been reacted with a number of nucleophilic reagents and a whole series of pentafluorophenyl derivatives have been obtained; the conditions under which these reactions take place are shown in TABLE 13.

TABLE 13

Nucleophilic Substitution in Hexafluorobenzene

Nucleophile	Reaction Conditions	Product	Reference
CH_3O^-	CH_3OH, CH_3ONa, reflux	$C_6F_5OCH_3$ $p\text{-}OCH_3C_6F_4OCH_3$	178,179
	CH_3OH, CH_3ONa, pyridine, reflux	$C_6F_5OCH_3$	177
$C_2H_5O^-$	C_2H_5OH, C_2H_5OK, reflux	$C_6F_5OC_2H_5$	180
$C_6H_5CH_2O^-$	$C_6H_5CH_2OH$, $C_6H_5CH_2ONa$, reflux	$C_6F_5OCH_2C_6H_5$	168
OH^-	KOH, pyridine, ethanol, reflux	C_6F_5OH $C_6F_4(OH)_2$	177
	KOH, pyridine, reflux	C_6F_5OH	177
	t-butanol, KOH, reflux	C_6F_5OH	180
	KOH aq.	C_6F_5OH	168
	NaOH aq., heat	No reaction	180
$C_6H_5O^-$	D.M.F., 120°, C_6H_5OK	$C_6F_5\text{-}O\text{-}C_6H_5$	168
$C_6F_5O^-$	D.M.F., reflux C_6F_5OK	$C_6F_5\text{-}O\text{-}C_6F_5$	
SH^-	NaSH, pyridine, reflux	C_6F_5SH	181
$C_6H_5S^-$	PhSK, pyridine, reflux	$p\text{-}C_6H_5S\text{-}C_6F_4\text{-}SC_6H_5$	182

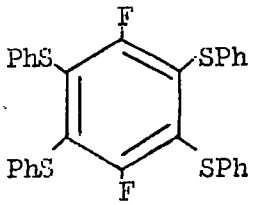


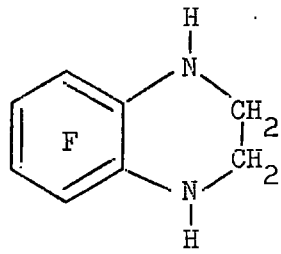
TABLE 13 (Cont.)

Nucleophile	Reaction Conditions	Product	Reference
$p\text{-}HC_6F_4S^-$	$p\text{-}HC_6F_4SK$, pyridine, reflux	$p\text{-}HC_6F_4S\text{-}C_6F_4\text{-}SC_6F_4H$	182
$o\text{-}NH_2C_6H_4S^-$	$o\text{-}NH_2C_6H_4SNa$, pyridine, reflux	$p\text{-}NH_2C_6H_4S\text{-}C_6F_4\text{-}SC_6F_4NH_2$	182
NH_2^-	$NaNH_2$, NH_3 liq.	$C_6F_5NH_2$	183
$C_6H_5NH^-$	NaH, $C_6H_5NH_2$, dioxan, reflux	$C_6F_5NHC_6H_5$	184
$C_6F_5NH^-$	$C_6F_5NH_2$, Na, liq. NH_3, ether	$C_6F_5NHC_6F_5$	184
$(C_6H_5)_2N^-$	NaH, $(C_6H_5)_2NH$, dioxan, copper powder	$C_6F_5\text{-}N(C_6H_5)_2$ $p(C_6H_5)_2N\text{-}C_6F_4\text{-}N(C_6H_5)_2$	184
$(C_6F_5)_2N^-$	$(C_6F_5)_2NH$, p-Tolyl-sodium, heptane, dioxan	$C_6F_5\text{-}N(C_6F_5)_2$	184
NH_3	aq. ethanolic NH_3, 167°/18 h.	$C_6F_5NH_2$	185
	aq. NH_3, 235°/2 h.	$C_6F_5NH_2$	168
		$C_6F_4(NH_2)_2$	168
CH_3NH_2	CH_3NH_2, C_2H_5OH, H_2O 270°/12 h.	$p\text{-}CH_3NH\text{-}C_6F_4\text{-}NHCH_3$	185
	CH_3NH_2, C_2H_5OH, H_2O, 115°/24 h.	$C_6F_5NHCH_3$	185
	aqueous CH_3NH_2 220°/3 h.	$C_6F_5NHCH_3$	168
		$p\text{-}CH_3NH\text{-}C_6F_4\text{-}NHCH_3$	168

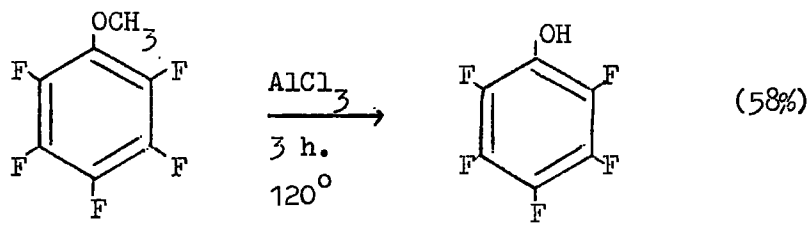
TABLE 13 (Cont.)

Nucleophile	Reaction Conditions	Product	Reference
$(CH_3)_2NH$	aq.$(CH_3)_2NH$, 235°/2 h.	$C_6F_5N(CH_3)_2$	168
		$C_6F_4[N(CH_3)_2]_2$	166
$H_2N.NH_2$	$H_2N.NH_2.H_2O.$, H_2O, C_2H_5OH reflux	$C_6F_5NHNH_2$	185
CH_3^-	CH_3Li, ether, pentane reflux	$C_6F_5CH_3$	168
	CH_3MgBr, ether	$C_6F_5CH_3$	177
$CH_3CH_2CH_2CH_2^-$	$CH_3CH_2CH_2CH_2Li$, ether -10°	C_6F_5-$CH_2CH_2CH_2CH_3$	168
$CH_3.CH=CH^-$	$CH_3CH=CHLi$, ether reflux 1 h.	C_6F_5-$CH=CHCH_3$	168
$CH_2=CH^-$	$CH_2=CHLi$, ether, reflux	C_6F_5-$CH=CH_2$	168
$C_6H_5^-$	C_6H_5Li, ether, 24 h./20°	C_6F_5-C_6H_5	168
	C_6H_5Li, ether	C_6F_5-C_6H_5	186
	reflux 3 h.	p-C_6H_5-C_6F_4-C_6H_5	
H^-	$LiAlH_4$, ether, reflux, 8 h.	C_6F_5H	168
	LiH, ether, reflux or 200°/24 h.	No reaction	168
$HOCH_2CH_2O^-$	NaOH, ethylene glycol, reflux	$C_6F_5OCH_2CH_2OH$	187
$HOCH_2CH_2NH_2$	$NH_2CH_2CH_2OH$, C_2H_5OH, H_2O, 110°/22 h.	$C_6F_5NHCH_2CH_2OH$	187

TABLE 13 (Cont.)

Nucleophile	Reaction Conditions	Product	Reference
$NH_2CH_2CH_2NH_2$	$NH_2CH_2CH_2NH_2$, C_2H_5OH, H_2O, $110^{\circ}/43$ h.		187
$HOCH_2CH_2S^-$	$HOCH_2CH_2SH$, K_2CO_3, dioxan, reflux	p-$HOCH_2CH_2S$-C_6F_4-SCH_2CH_2OH	187

In general, nucleophilic substitution reactions proceed readily and high yields (in the region of 70%) of the pentafluorophenyl derivatives are obtained. The functional groups introduced in this way can be further treated to give other pentafluorophenyl derivatives using the standard reactions of organic chemistry. For example, pentafluoroanisole can be demethylated with HI,[177] HBr[178] or $AlCl_3$[178] yielding pentafluorophenol, and as already shown, pentafluoroaniline can be diazotised in hydrofluoric acid with sodium nitrite.[169,177]



(58%)

Nucleophilic Substitution in Pentafluorophenyl Compounds.[175]

$$C_6F_5X + N^- \longrightarrow N\text{-}C_6F_4\text{-}X + F^-$$

Many nucleophilic replacement reactions of pentafluorophenyl derivatives are known and are listed in TABLE 14. Nucleophilic substitution in pentafluorophenyl derivatives takes place under conditions similar to those under which hexafluorobenzene is substituted, with the following general proviso: "The more electron-withdrawing the substituent X is over fluorine, the more readily the substitution will proceed relative to hexafluorobenzene, and conversely, the more

TABLE 14

Reaction of Pentafluorophenyl Derivatives with Nucleophilic Reagents

$$C_6F_5X + N^- \longrightarrow N\text{-}C_6F_4\text{-}X + F^- \quad (N = \text{nucleophile})$$

Pentafluorophenyl derivative C_6F_5X X	Nucleophilic Reagents N	Orientation of Products (>90% unless stated) ortho	meta	para	Reference
CF_3	$LiAlH_4$, CH_3Li, KSC_6H_5, NH_2NH_2, NaSH, NH_3, C_2H_5ONa			para	188
	KOH (t.butanol)			(polyphenols)	
CF_2CF_3	$LiAlH_4$, CH_3Li, NH_2NH_2, NH_3, CH_3ONa			para	189
	KOH (t-butanol)			$(C_8F_8O)_n$	
CH_3	CH_3ONa, NH_2NH_2, NH_3,			para	190
	CH_3Li			para	166
C_6H_5	NH_2NH_2, NH_3, NaSH			para	186
H	NaSH, KSC_6H_5, σ-$NH_2C_6H_4SNa$, KSC_6F_4H, CH_3ONa, NH_3			para	175, 182, 185, 181
	$LiAlH_4$	7	1	92	191
	$NH_2.NH_2$	3	0.5	96.5	191
NO	CH_3ONa			>90	
	$(CH_3)_2NH$			>90	192
	CH_3NH_2	(40)		(60)	

TABLE 14 (Cont.)

Pentafluorophenyl derivative C_6F_5X X	Nucleophilic Reagents N	Orientation of Products (>90% unless stated) ortho	meta	para	Reference
COOH	$NaOCH_3$			90	
	$NaSCH_3$			90	
	NH_3	decarboxylation			193
	CH_3NH_2	37		63	
	$(CH_3)_2NH$	45		55	
NO_2	NH_3	69		31	194
	CH_3NH_2	65		35	
	$(CH_3)_2NH$	19		81	195
	CH_3ONa	8		92	
OCH_3	CH_3ONa	16	32	52	190, 168
	CH_3Li	10	34	56	190
Cl	$LiAlH_4$, NH_3, CH_3ONa, $NH_2.NH_2$	25	5	70	196
Br	KOH	(20)		(80)	168
	CH_3ONa, NH_3			para	168
I	CH_3ONa, KOH, NH_3			para	168
OH	KOH (t.-butanol)		>90		190
NH_2	NH_3	0	87	13	
	CH_3NH_2	0	88	12	
	$(CH_3)_2NH$	0	90	10	197 (185)
	CH_3ONa	5	79	16	
$NHCH_3$	NH_3	0	40	60	
	CH_3NH_2		60	40	197 (185)
	$(CH_3)_2NH$		52	48	
	CH_3ONa	5	93	52	

TABLE 14 (Cont.)

Pentafluorophenyl derivative C_6F_5X X	Nucleophilic Reagents N	Orientation of Products (>90% unless stated) ortho	meta	para	Reference
$N(CH_3)_2$	NH_3	0	7	93	197
	CH_3NH_2		6	94	
	$(CH_3)_2NH$	3	5	92	
	CH_3ONa	1	2	97	

electron-donating X is over fluorine, then replacement is only accomplished if more forcing conditions are used."

The introduction of a further substituent into the pentafluorophenyl nucleus has given rise to some interesting orientational problems. Varying amounts of ortho, meta, and para substitution have been recorded, the orientations depending on the group already present in the fluoroaromatic ring. When X = CH_3, CF_3, C_2F_5, C_6H_5, Br, I and H nucleophilic substitution takes place mainly at the para position relative to X. When X = CH_3O and Cl substantial amounts of ortho, meta, and para replacement take place, although the para isomer still predominates. When X = OH and NH_2 nucleophilic substitution takes place at the meta position, although nucleophilic substitution in pentafluoroaniline gives some of the para isomer. When X = NO_2, COOH and NO varying amounts of ortho and para substitution are obtained depending upon the nucleophilic reagent used.

Initially it was suggested that the five fluorine atoms in the benzene ring determined the position of replacement which was para to X, and that X itself may either enhance or oppose this effect.[194] This suggestion is based on the observation that electrophilic substitution in fluorobenzene takes place para to the fluorine atom and hence by analogy this position should be the least susceptible to nucleophilic attack. Thus for pentafluorobenzene the combined effect of the five fluorine atoms should leave the fluorine atom para to the hydrogen atom

most susceptible to nucleophilic attack. Substituents in place of hydrogen can be considered as having a modifying influence on this directing effect of the five fluorine atoms. Groups only weakly electron attracting or repelling would be expected only to influence the relative rate of replacement of the fluorine atom para to them. Groups strongly electron-repelling, however, should increase by a conjugative mechanism, the electron density at the ortho and para positions more than at the meta position, the amount of meta replacement, as compared with pentafluorobenzene, should therefore increase, while the overall rate of reaction decreases. Strongly electron-attracting substituents should decrease the electron density at the ortho and para positions and increase the rate of reaction of substitution at these positions.

Although this argument gives a general picture for the orientation of nucleophilic replacement in pentafluorophenyl derivatives of hexafluorobenzene, Burdon[154] has pointed out that it is unsatisfactory in a number of cases.

Pummer and Wall[168] have suggested that the reactivity of the nucleophilic reagent plays an important role in determining the orientation of the products. From the results in TABLE 14 it is obvious that the nucleophilic reagent used has some bearing on the orientation of the products and so also has the solvent (this will be discussed more fully later) in which the reaction is carried out.

Burdon[154] has rationalized the orientations of the products obtained when pentafluorophenyl derivatives are reacted with nucleophilic reagents by considering the relative stabilities of the Wheland-type intermediates involved.

The high ortho replacement in pentafluoronitrobenzene, pentafluorobenzoic acid, and pentafluoronitrosobenzene with amines has been attributed to hydrogen bonding,[185,197] the amount of ortho substitution deminishing when sodium methoxide was reacted with the pentafluorophenyl-derivative.

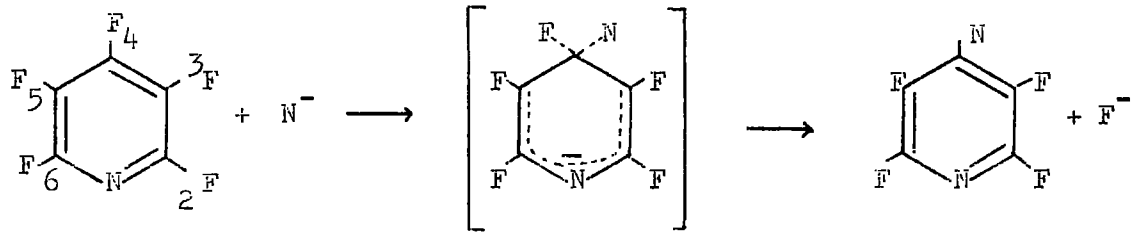
The variation in the position of substitution in pentafluoro-aniline, -N-methylaniline, and -NN-dimethylaniline has been attributed to steric inhibition of resonance.[197] With pentafluoro-NN-dimethylaniline, the ortho fluorine - N-methyl interactions have been postulated to bend or twist the NN-dimethyl group out of the plane of the ring and hence the effect of the nitrogen lone-pair on the ring is reduced. The NN-dimethyl group therefore behaves largely as an inert substituent analogous to pentafluorobenzene and as can be seen leads to preferential para replacement. Similarly with N-methylpentafluorobenzene, the same effect will operate but not to the same extent and as seen in TABLE 14 approximately equal ortho-para substitution is observed. With pentafluoroaniline no ortho fluorine interactions take place and the lone pair can interact with π-electron system of the ring, deactivating the ortho and para positions towards nucleophilic attack.

Nucleophilic Substitution in Tetrafluorobenzene Derivatives.

$$X\text{-}C_6F_4\text{-}Y + N^- \longrightarrow X,Y,C_6F_3N + F^-$$

Disubstituted tetrafluorobenzenes have been reacted with various nucleophilic reagents, the results of which are shown in TABLE 15. The orientations of the products can be determined by the summation of the effects due to each substituent X, Y in the ring, and comparing them with the observations outlined in determining the orientations in substituted pentafluorophenyl derivatives.

Nucleophilic Substitution in Pentafluoropyridine.



Nucleophilic attack in pentafluoropyridine takes place in the majority of cases at the 4-position, followed by substitution at the 2- and 6-positions. The reactions between nucleophilic reagents and pentafluoropyridine are listed in TABLE 16. Only two cases of preferential replacement of the 2-fluorine atom have been reported in the literature. Phenyl-lithium reacts readily with pentafluoropyridine to give mainly 4-phenyltetrafluoropyridine ($> 95\%$) and another isomer ($< 5\%$), this isomer presumably being 2-phenyltetrafluoropyridine. The more interesting

TABLE 15

Nucleophilic Substitution in Polyfluorobenzenes Containing two Functional Groups.

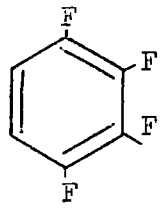
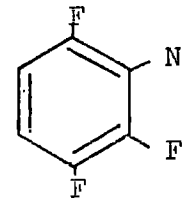
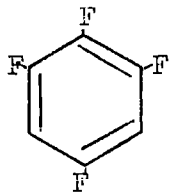
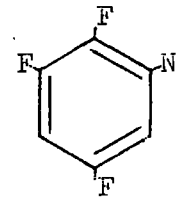
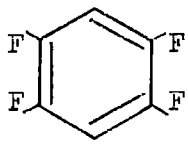
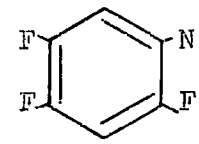
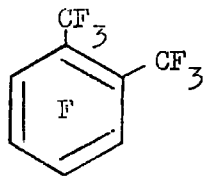
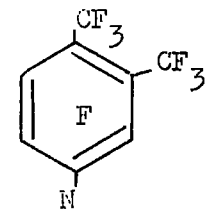
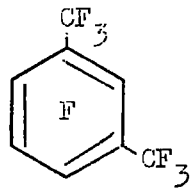
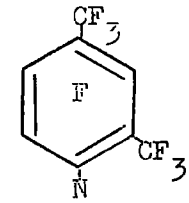
Starting Material	Nucleophilic Reagent(N)	Orientation of Product	Ref.
	CH_3ONa, NH_2NH_2, $LiAlH_4$		198
	CH_3ONa, NH_2NH_2 $LiAlH_4$		198
	CH_3ONa		198
	$NaSH, NH_2NH_2, NH_3$		199
	NH_2NH_2, NaSH, CH_3Li, CH_3ONa		200

TABLE 15 (Cont.)

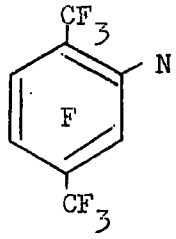
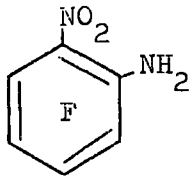
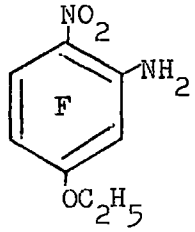
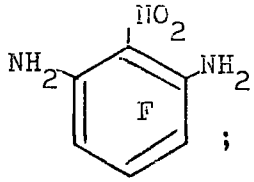
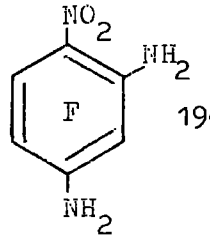
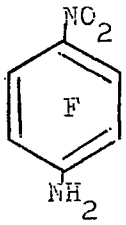
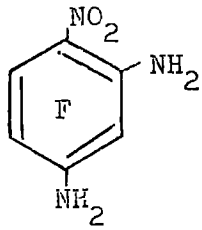
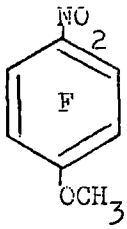
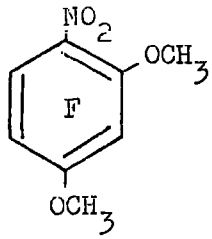
Starting Material	Nucleophilic Reagent (N)	Orientation of Product	Ref.
	CH_3Li, C_6H_5Li, CH_3ONa, NH_3, NH_2NH_2, KSC_6H_5, $NaSH$, $LiAlH_4$		199
	C_2H_5ONa		194
	NH_3	 ; 	194
	NH_3		194
	CH_3ONa		195

TABLE 16

Reaction between Pentafluoropyridine and Nucleophilic Reagents

Nucleophile	Reaction Conditions	Product	Reference
CH_3O^-	CH_3OH, CH_3ONa, 0°, 15 min.	4-$OCH_3.C_5F_4N$	148
	CH_3OH, CH_3ONa 20°, 15 min.	2,4$(OCH_3)_2.C_5F_3N$	148
	CH_3OH, CH_3ONa reflux, 3 h.	4-$OCH_3.C_5F_4N$ (57%)	149
	CH_3OH, CH_3ONa reflux, 6 h.	2,4,6-$(OCH_3)_3.C_5F_2N$ (74%)	149
OH^-	aq.KOH, 85°, 20 h.	4-$OH.C_5F_4N$ (63%)	148
	KOH, t-butanol, reflux, 90 min.	4-$OH.C_5F_4N$(90%) (65%) 2-$OH.C_5F_4N$(10%)	148
	aq.NaOH, reflux, 2 h.	4-$OH.C_5F_4N$ (58%)	149
	40% NaOH, 80°, 12 h.	2,4-$(OH)_2.C_5F_3N$ (20%)	149
	KOH, t-butanol, reflux, 2·5 h.	4-$OH.C_5F_4N$ (64%)	149
NH_3	NH_3 aq., 80°, 2 h.	4-$NH_2.C_5F_4N$ (70%)	148
	NH_3 aq., 130°	2,4-$(NH_2)_2.C_5F_3N$	201
	ethanol, NH_3 aq., 110°, 8 h.	4-$NH_2.C_5F_4N$ (81%)	149
$(CH_3)_2NH$	$(CH_3)_2NH$, ethanol, 0°	4-$(CH_3)_2N.C_5F_4N$(51%)	149
	$(CH_3)_2NH$, ethanol 100°, 20 h.	2,4-$((CH_3)_2N)_2.C_5F_3N$ (82%)	149

Nucleophile	Reaction Conditions	Product	Reference
$NH_2.NH_2$	$NH_2.NH_2.H_2O$, dioxan, refluxed, 2 h.	4-$NH_2NH.C_5F_4N$ (70%)	148
	$NH_2.NH_2.H_2O$, ethanol, 0^o, 2 h.	4-$NH_2NH.C_5F_4N$ (75%)	149
$C_6H_5^-$	C_6H_5Li, ether, reflux, 1 h.	4-$C_6H_5.C_5F_4N$ (> 95%) (26%) x-$C_6H_5.C_5F_4N$ (< 5%)	148
$CH_3.CH=CH^-$	$CH_3.CH=CHLi$, ether -20^o to 20^o (equi-mole)	4-$CH_3CH=CH.C_5F_4N$ (66%)	149
	$CH_3.CH=CHLi$, ether -20^o to 20^o (mole ratio 1:2)	2,4-$(CH_3CH=CH)_2.C_5F_3N$ (62%)	149
H^-	$LiAlH_4$, ether, initially at 0^o, then reflux 4 h.	4-$H.C_5F_4N$ (74%)	149

case of 2-substitution is the reaction of potassium hydroxide with pentafluoropyridine. When potassium hydroxide is reacted with pentafluoropyridine in aqueous solution only 4-hydroxytetrafluoropyridine is obtained. When the reaction is carried out in t-butanol 2-, and 4-hydroxytetrafluoropyridines (in the ratio 1:9) are obtained. The difference between reactions carried out in aqueous solution and t-butanol has been attributed to the active part played by the t-butoxide ion in the reaction.

Nucleophilic Substitution in Perhalogenofluoropyridines.

The preparation of pentafluoropyridine involves the halogen exchange reaction between chlorine and fluorine in pentachloropyridine and as a consequence substantial amounts of 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine are obtained as by-products.[56] These chlorofluoropyridines have been reacted with various nucleophilic reagents, the results of which are shown in TABLE 17. 3-Chlorotetrafluoropyridine reacts with ammonia, hydrazine and lithium aluminium hydride to give the 4-substituted chlorofluoropyridine. With potassium hydroxide a different ratio of isomers is obtained depending on whether the reaction is carried out in aqueous solution or in t-butanol. With aqueous potassium hydroxide a mixture of 4- and 6-substituted hydroxy compounds is obtained (ratio 9:1), whereas when the reaction is carried out in t-butanol 4-, 6-, and 2-hydroxychlorofluoropyridines (in ratio 55:35:10)

TABLE 17

Reaction between Halogenofluoropyridines and Nucleophilic Reagents.

Nucleophile	Reaction Conditions	Products	Ref.
3-Chlorotetrafluoropyridine			
OH^-	KOH, t-butanol, reflux, 90 min.	4-OH.C_5F_3ClN (55%) 6-OH.C_5F_3ClN (35%) (79%) 2-OH.C_5F_3ClN (10%)	202
	KOH aq. 85°, 20 h.	4-OH.C_5F_3ClN (90%) 6-OH.C_5F_3ClN (10%) (63%)	202
NH_3	NH_3 aq., 80°, 1 h.	4-NH_2.C_5F_3ClN (85%)	202
$NH_2.NH_2$	$NH_2NH_2.H_2O$, 20°, dioxan, 15 min.	4-NH_2NH.C_5F_3ClN (70%)	202
H^-	$LiAlH_4$, ether reflux, 30 min.	4-H.C_5F_3ClN	57
4-Chlorotetrafluoropyridine			
NH_3	NH_4OH, 80°, 6 h. acetone	2-NH_2.C_5F_3ClN (60%)	
4-Bromotetrafluoropyridine			
NH_3	NH_3 aq., 85°, 2 h.	2-NH_2.C_5F_3BrN (86%)	159
OH^-	t-butanol, KOH, reflux, 2 h.	2-OH.C_5F_3BrN (92%)	159
CH_3O^-	CH_3OH, CH_3ONa, 0-20°, 30 min.	2-OCH_3.C_5F_3BrN (90%)	159
	CH_3OH, CH_3ONa reflux, 30 min.	2,6-$(OCH_3)_2$.C_5F_2BrN	159

TABLE 17(Cont.)

Nucleophile	Reaction Conditions	Products	Ref.
3,5-Dichlorotrifluoropyridine			
OH^-	KOH, t-butanol, reflux, 90 min.	2-OH.$C_5F_2Cl_2N$(70%) (85%) 4-OH.$C_5F_2Cl_2N$(30%)	202
	KOH, water, 85°, 20 h.	4-OH.$C_5F_2Cl_2N$(90%) (10%) 2-OH.$C_5F_2Cl_2N$(10%)	202
CH_3O^-	CH_3OH,CH_3ONa, 10°, 20 min.	4-OCH_3.$C_5F_2Cl_2N$(80%) 2,4-$(OCH_3)_2$.C_5FCl_2N (20%)	202
$NH_2.NH_2$	$NH_2.NH_2.H_2O$, dioxan 10-20°, 20 min.	4-NH_2NH.$C_5F_2Cl_2N$(90%)	202
NH_3	NH_3 aq., 80°, 15 min.	4-NH_2.$C_5F_2Cl_2N$(89%)	202

are obtained. The same trend is observed in 3,5-dichlorotrifluoropyridine which reacts with sodium methoxide in methanol, ammonia in aqueous solution and hydrazine in dioxan to give only replacement of the 4-fluorine. However, with aqueous potassium hydroxide a mixture of isomers, 4-hydroxy-3,5-dichloro-, and 2-hydroxy-3,5-dichlorodifluoropyridines (in the ratio 9:1) is obtained, but when the reaction is carried out in t.-butanol the ratio of 4-hydroxy-, to 2-hydroxy-3,5-dichlorodifluoropyridine is 3:7.

Again the variation of the ratio of isomers has been explained by the participation of t.-butoxide ion in the reaction.

Nucleophilic substitution in 4-chloro-, and 4-bromotetrafluoropyridine takes place at the 2-position.

Order of Reactivity between Pentafluoro-, 3-Chlorotetrafluoro-, and 3,5-Dichlorotrifluoro-pyridines.[202]

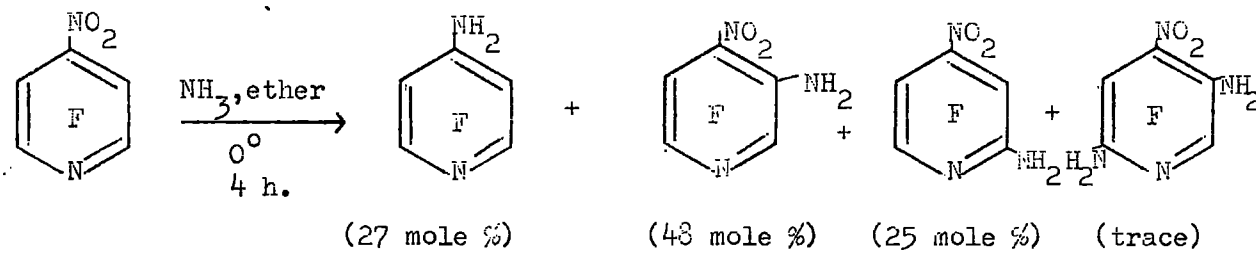
The order of reactivity; determined by competition experiments with ammonia, towards nucleophilic substitution increases in the series $C_5F_5N < 3\text{-}ClC_5F_4N < Cl_2C_5F_3N$ in the ratio 1:3·7:12·6 respectively. This trend is consistent with the known greater resultant (of inductive and mesomeric effects) electron withdrawing capacity of chlorine over fluorine in aromatic systems.

Nucleophilic Substitution in 4-Substituted Tetrafluoropyridines.

As already indicated 4-halogenotetrafluoropyridines react with nucleophilic reagents with displacement of the fluorine atom from the

2-position. This trend is followed with 4-amino-, and 4-methoxy-tetrafluoropyridines. 4-Aminotetrafluoropyridine reacts with ammonia at 130-135° to give 2,4-diaminotrifluoropyridine. Similarly Haszeldine[149] has reacted 4-methoxytetrafluoropyridine with sodium methoxide obtaining 2,4-dimethoxytrifluoropyridine.

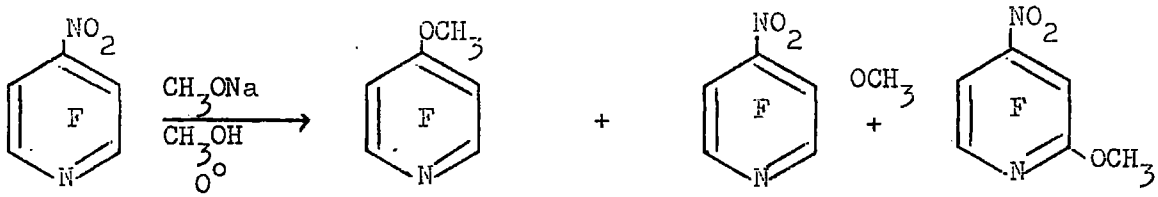
Nucleophilic substitution in 4-nitrotetrafluoropyridine has been investigated by the workers at Durham,[201] and as in the case of pentafluoronitrobenzene, the electron withdrawing effect of the nitro group has rendered the ring system more susceptible to nucleophilic attack. 4-Nitrotetrafluoropyridine reacts with ammonia at 0° to give the products shown.



Unlike pentafluoronitrobenzene, 4-nitrotetrafluoropyridine reacts with ammonia with displacement of the nitro group leading to 4-amino-tetrafluoropyridine. This is the first reported nucleophilic substitution reaction in which a nitro group has been replaced in preference to fluorine. The high percentage yield of 3-amino-4-nitrotrifluoropyridine has been attributed to hydrogen bonding between ammonia and the

nitro group, which is consistent with the results obtained by the Birmingham workers[194,195] from the reaction of ammonia with pentafluoronitrobenzene.

Reaction of 4-nitrotetrafluoropyridine with sodium methoxide has been investigated and again replacement of the nitro group by the attacking nucleophile is observed.



(70 mole %) (7 mole %) (23 mole %)

Rationalization of Orientation and Reactivity of Nucleophilic Replacement Reactions in Pentafluoropyridine.

Analogies have been drawn between pentafluoropyridine and pentafluorobenzene to rationalize the replacement of the fluorine atom at the 4-position by nucleophilic reagents. Nucleophilic substitution in pentafluorobenzene takes place para to the hydrogen, the position of substitution being said to be governed by the overall effect of the five fluorine atoms. Similarly in pentafluoropyridine the nucleophile enters the position para to the nitrogen and by comparison with pentafluorobenzene, the orientation was said to be governed by the five fluorine atoms.

The nitro-group in tetrafluoro-4-nitropyridine has been shown to be displaced by nucleophilic reagents, but not in pentafluoronitrobenzene or 2,3,5,6-tetrafluoronitrobenzene. As the nitro-group and fluorine are comparable in their efficiency as leaving groups in nucleophilic aromatic substitution,[174] it has been concluded that the ring nitrogen is the greatest single factor in determining the orientation of nucleophilic attack in pentafluoropyridine.

Pentafluoropyridine has been shown to undergo nucleophilic displacement of fluoride ion more readily than hexafluorobenzene. Quantitative reaction of pentafluoropyridine with aqueous ammonia occurs at 80° over 2 h. (by the author at 20° over 24 h.), whereas a temperature of 167° is reported for the corresponding production of pentafluoroaniline from hexafluorobenzene. The same ease of replacement of fluorine in pentafluoropyridine over hexafluorobenzene is again noted in the reactions with sodium methoxide. Sodium methoxide reacts rapidly with pentafluoropyridine at 0° affording the mono-ether and at 20° quantitative conversion to the diether is obtained. For the analogous preparation of pentafluoroanisole from hexafluorobenzene, the substrate has to be refluxed for 1 h. with sodium methoxide to give the mono ether. It has also been shown that pentafluorophenylmagnesium bromide reacts with pentafluoropyridine to give 4-(pentafluorophenyl)tetrafluoropyridine whereas pentafluorophenylmagnesium bromide will not react with hexafluorobenzene under the same conditions.[159]

This increased reactivity of pentafluoropyridine over hexafluorobenzene is consistent with the electron-withdrawing effect of the ring-nitrogen in pyridine, deactivating the ring system towards electrophilic attack, and by analogy, activating the system towards nucleophilic attack.

CHAPTER 6

DISCUSSION OF EXPERIMENTAL, PART II.

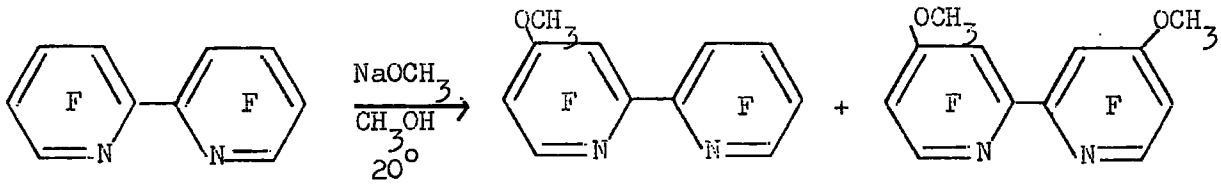
Nucleophilic Substitution in Polyfluorobipyridyls.

Several polyfluorobipyridyls have been reacted with various nucleophilic reagents and the orientation of the products determined from nuclear magnetic resonance spectra (CHAPTER 8).

The introduction of substituent groups into the bipyridyls can be regarded, in general, as being similar to nucleophilic substitution in pentafluoropyridine and its derivatives.

Nucleophilic Substitution in Polyfluoro-2,2'-bipyridyls.

Octafluoro-2,2'-bipyridyl(I) reacts at room temperature with one equivalent of sodium methoxide to give the mono-(II) and di-ether(III) in the ratio 4:1 respectively.

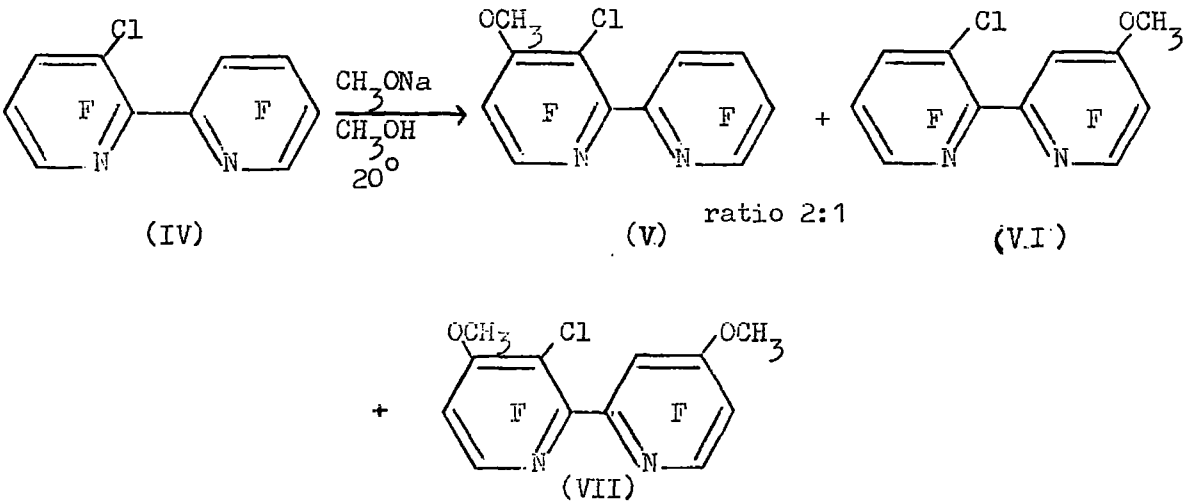


(I) (II) (III)

The position of substitution has been shown to be para to the nitrogen in each ring system, consistent with results obtained for nucleophilic attack in pentafluoropyridine.[148,149]

Reaction of sodium methoxide with 3-chloroheptafluoro-2,2'-bipyridyl(IV) at room temperature produced two isomers of the mono-ether, 3-chloro-4-methoxyhexafluoro-2,2'-bipyridyl(V) and 3-chloro-4'-methoxyhexafluoro-2,2'-bipyridyl(VI), in the ratio 2:1, along with the

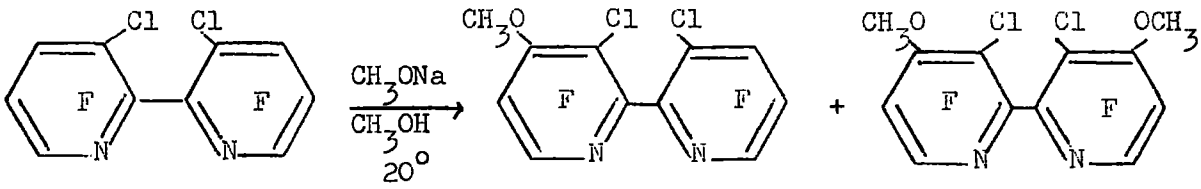
di-ether, 3-chloro-4,4'-dimethoxypentafluoro-2,2'-bipyridyl(VII)



Again the orientation of the products is that expected from considerations in the polyfluoropyridine series. The isolation of two isomers of the mono ether is interesting in view of the work carried out on 3-chlorotetrafluoropyridine.[202] 3-Chlorotetrafluoropyridine reacts with sodium methoxide to give predominately (>95%) 3-chloro-4-methoxytrifluoropyridine.[141] With potassium hydroxide, in aqueous solution or t-butanol, a mixture of isomers is obtained, the cause being attributed to steric hindrance. 3-Chlorotetrafluoropyridine also afforded a mixture of isomers when it was reacted with sodium iso-propoxide in iso-propanol. In 3-chloroheptafluoro-2,2'-bipyridyl there are two positions in the molecule that will be of similar reactivity towards nucleophilic reagents i.e. the 4- and the 4'-positions. The 4-position should be the more reactive of the two due

to the known greater resultant (of inductive and mesomeric effects) electron withdrawing capacity of chlorine over fluorine in an aromatic system. However, as indicated the 4-position in 3-chlorotetrafluoropyridine is slightly sterically hindered towards nucleophilic attack and presumably the same state of affairs exists in 3-chloroheptafluoro-2,2'-bipyridyl. Thus, the increased reactivity of the 4-position due to the ortho chlorine atom is reduced on steric grounds and hence some substitution will also take place at the next reactive site.

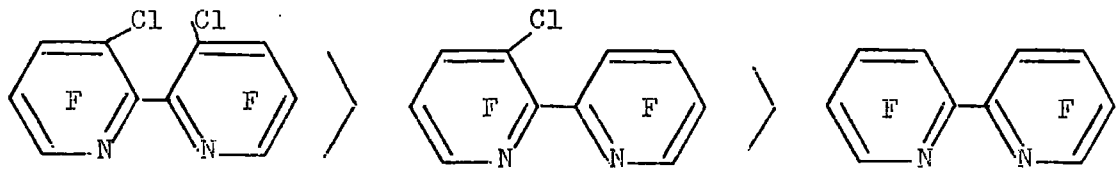
The reaction of sodium methoxide with 3,3'-dichlorohexafluoro-2,2'-bipyridyl(VIII) yields the mono- and di-ethers, 3,3'-dichloro-4-methoxypentafluoro-2,2'-bipyridyl(IV) and 3,3'-dichloro-4,4'-dimethoxytetrafluoro-2,2'-bipyridyl(X), the orientations of the products being those expected from comparison with nucleophilic substitution in 3-chlorotetrafluoropyridine.



(VIII) (IX) (X)

Although no competition reactions have been carried out between the three polyfluoro-2,2'-bipyridyls (I, IV, VIII), from the results of

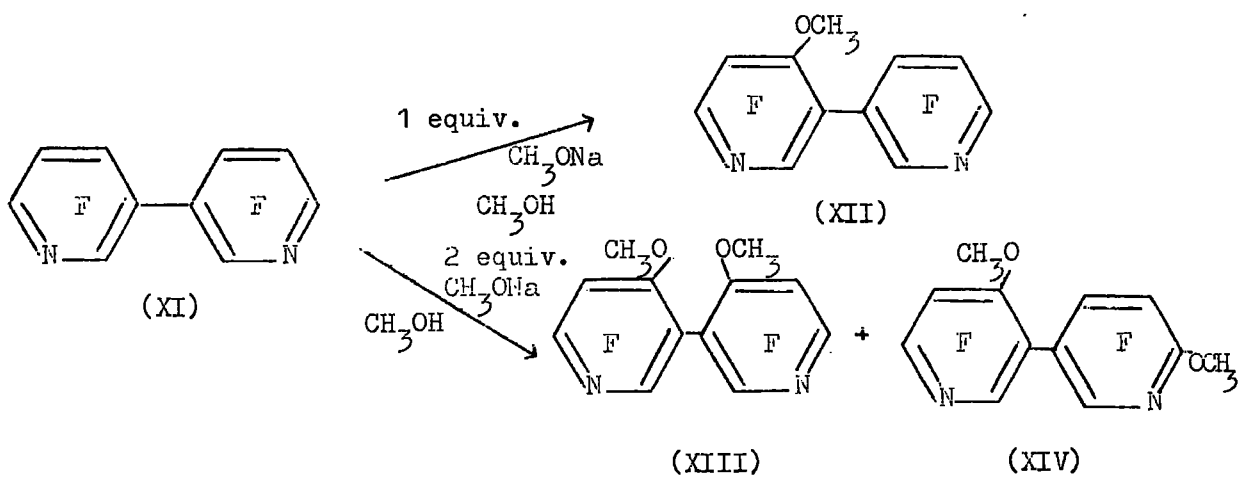
the sodium methoxide reactions, the probable order of reactivity towards nucleophilic reagents is:-



(VIII) (IV) (I)

Nucleophilic Substitution in Octafluoro-3,3'-bipyridyl (TABLE 18)

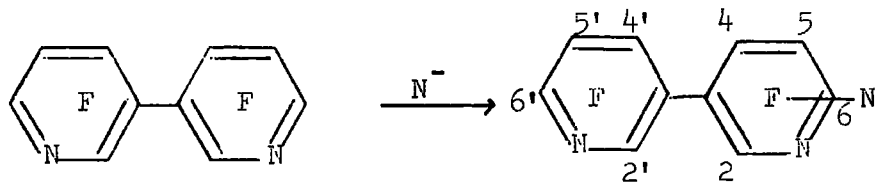
Octafluoro-3,3'-bipyridyl (XI) has been reacted with several nucleophilic reagents and some interesting orientational results have been obtained. Reaction with (1) an equi-molar amount, (2) a 2:1 molar ratio of sodium methoxide to the bipyridyl, in methanol, afforded in the first case 4-methoxyheptafluoro- (XII), and in the second case an equi-molar mixture of 4,4'-dimethoxy- (XIII), and 4,6'-dimethoxy-hexafluoro- (XIV) -3,3'-bipyridyls.

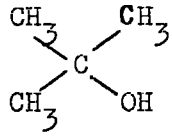
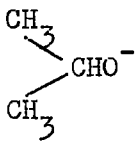
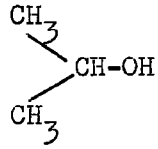
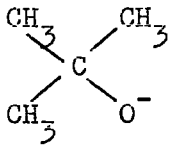
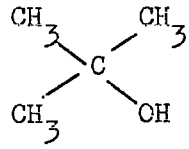


(XI) (XII) (XIII) (XIV)

TABLE 18

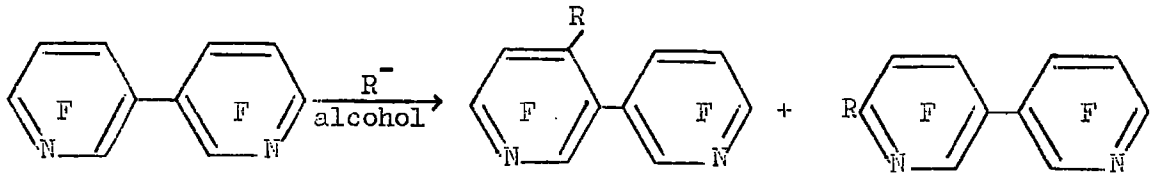
Nucleophilic Substitution in Octafluoro-3,3'-Bipyridyl.



Nucleophile	Solvent	Orientation of Products (Estimated from Gas Chromatography and nuclear magnetic resonance spectra measurements)		
		4-position	6-position	x-position
CH_3O^-	CH_3OH	> 95%	0%	
CH_3O^-		20%	80%	
$C_2H_5O^-$	C_2H_5OH	85%	15%	
$CH_3CH_2CH_2O^-$	$CH_3CH_2CH_2OH$	80%	20%	
$CH_3CH_2CH_2CH_2O^-$	$CH_3CH_2CH_2CH_2OH$	72%	28%*	
		40%	60%	
		37%	63%*	
CH_3Li	$(C_2H_5)_2O$		> 95%	
NH_3	$(C_2H_5)_2O$		> 95%	< 5%
NH_2NH_2	Dioxan		(polymer)	

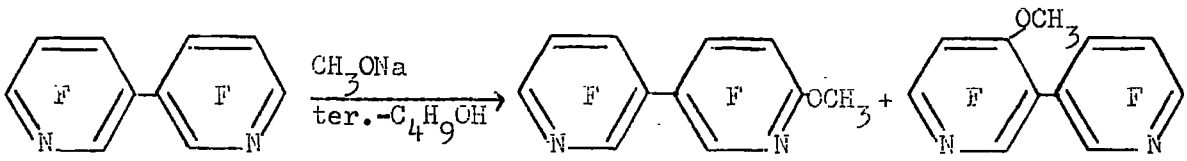
*Compounds not isolated, but ratio of isomers determined from gas chromatographic evidence.

As the size of the nucleophilic reagent is increased and the alcohol is varied, nucleophilic replacement of the 4-fluorine atom in octafluoro-3,3'-bipyridyl decreases with a corresponding increase in replacement of the fluorine atom at position 6 (TABLE 18)

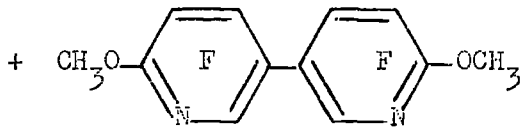


(R = C_2H_5O, n-C_3H_7O, n-C_4H_9O, iso-C_3H_7O and t-C_4H_9O)

When the reaction between octafluoro-3,3'-bipyridyl and sodium methoxide was carried out in tertiary butanol, the main products of the reaction were 6-methoxyheptafluoro- (XV) and suspected 6,6'-dimethoxy-hexafluoro- (XVI) 3,3'-bipyridyls. Analytical-scale v.p.c. of the reaction product indicated the presence of another isomer of mono-methoxyheptafluoro-3,3'-bipyridyl (< 20% of the mixture of mono-substituted derivatives), but due to the poor resolution of the n.m.r. spectra the orientation could not be completely determined. However in view of the previous results obtained, it is probable that this minor isomer is 4-methoxyheptafluoro-3,3'-bipyridyl (XII).

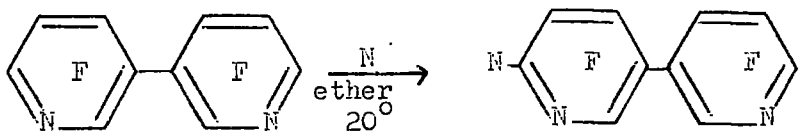


(XV) (XII)



(XVI)

Reaction of octafluoro-3,3'-bipyridyl with ammonia and methyl lithium in ether afforded the 6-substituted-heptafluoro-3,3'-bipyridyl (>95%).

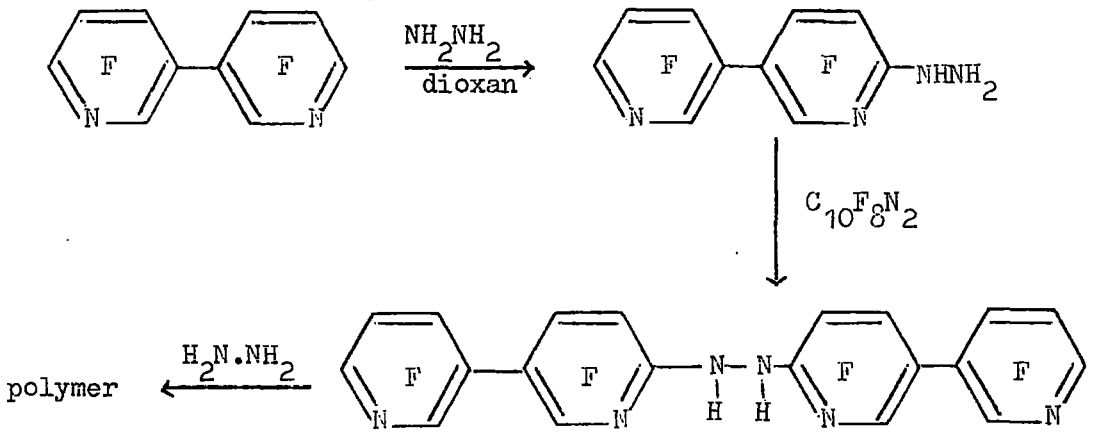


(N = NH_3 (XVII), CH_3Li (XVIII))

In the reaction between the bipyridyl and methyl lithium a further product was isolated but the composition or structure could not be elucidated.

Reaction of the bipyridyl with hydrazine hydrate afforded a deep red coloured solid that would not sublime (220°/0·01 mm.). A possible

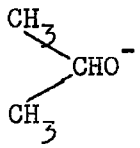
explanation is that initial attack of hydrazine takes place giving the monohydrazinoheptafluoro-3,3'-bipyridyl which then attacks (acting as a nucleophilic reagent) a molecule of octafluoro-3,3'-bipyridyl. In this way it is possible to form long-chain polymers by subsequent nucleophilic attack by hydrazine on the 1,2-di-(6,6'-heptafluoro-3,3'-bipyridyl)hydrazine, at the 6-position in the unsubstituted ring.



A solvent effect in the reaction between octafluoro-3,3'-bipyridyl and sodium iso-propoxide has been investigated, the results of which are shown in TABLE 19. In ether containing very little iso-propanol it was found that a larger percentage of 6-substitution occurred than when the reaction was carried out in iso-propanol. The same effect was also found with 3,5-dichlorotrifluoropyridine, more 2-substitution

TABLE 19

Nucleophilic Substitution in Octafluoro-3,3'-bipyridyl in a Mixture of Solvents.

Nucleophile	Ratio of Ether/Alcohol (v/v)			Orientation of Products (determined from Gas Chromatography Evidence)	
	Ether	:	Appropriate Alcohol	4-position	6-position
CH_3O^-	0	:	1	>95%	-
CH_3O^-	10	:	1	>95%	-
	0	:	1	40%	60%
"	4	:	1	20%	80%
"	19	:	1	16%	84%
"	70	:	1	16%	84%

taking place when ether was added to the reaction solution. (TABLE 20). No variation in isomers was found by including ether in the reaction medium when octafluoro-3,3'-bipyridyl was reacted with sodium methoxide.

Rationalization of Orientation in the Nucleophilic Replacement Reactions of Octafluoro-3,3'-bipyridyl.

It has been shown that octafluoro-3,3'-bipyridyl reacts with nucleophilic reagents (N) to replace the fluorine atoms ortho (4) and para (6) to the carbon-carbon bond joining the two rings. When $N=OCH_3$ (in CH_3OH) the 4-fluorine atom is the one that in replaced ($> 95\%$). When N = OC_2H_5, n-OC_3H_7, n-OC_4H_9, i-OC_3H_7 and t-OC_4H_9 varying amounts of replacement of the fluorine atoms at the 4- and 6-positions is obtained, the percentage of 4-substitution decreasing with a corresponding increase in 6-substitution as the size of the alkoxide group increases from OC_2H_5.....t-OC_4H_9. When N = i-OC_3H_7, a larger percentage of 6-substitution has been found to take place when ether has been added to the reaction mixture. When N = OCH_3 (in t-C_4H_9OH), the 6-fluorine ($> 80\%$) is replaced and when N = NH_3, CH_3Li (in ether) the 6-fluorine ($> 95\%$) is replaced.

Octafluoro-3,3'-bipyridyl is one of the few known fluorine-containing compounds that has two positions (in one ring) which are of equal susceptibility towards nucleophilic attack. Because of this, effects, that do not affect the position of nucleophilic attack (to any large extent) in pentafluoropyridine, have been shown to be important in

TABLE 20

Nucleophilic Substitution in 3,5-Dichlorotrifluoropyridine in a mixture of solvents

Nucleophile	Ratio of Ether/Iso-propanol (v/v)			Orientation of Products (determined from Gas Chromatography Evidence)	
	Ether	:	Alcohol	4-position	2-position
$(CH_3)_2CHO^-$	0	:	1	77%	23%
	10·5	:	1	60%	40%
	35	:	1	60%	40%

determining the orientation of products in octafluoro-3,3'-bipyridyl. An attempt has been made to rationalize the orientation of products obtained from octafluoro-3,3'-bipyridyl by consideration of (1) steric interactions, (2) solvation of the transition state and (3) electrostatic interactions.

Rationalization of Orientation based on Steric Considerations.

The 4-position in octafluoro-3,3'-bipyridyl has been shown to be sterically hindered by the ortho fluorines present in the other ring. From n.m.r. spectra measurements,[203] the position of minimum energy in decafluorobiphenyl has been shown to be when the rings are at an angle of 50° to one another, the distortion of the rings being attributed to the steric interactions between the ortho fluorines. By analogy, this interaction between the ortho fluorines would be expected in octafluoro-3,3'-bipyridyl, the probable position of minimum energy being when these two rings are at an angle of $\approx 50^{\circ}$ to each other.

Experimental evidence also indicates that there is considerable steric hindrance between the 4- and 4'-positions. One mole-equivalent of $NaOCH_3$ in methanol reacts with the bipyridyl to give 4-methoxy-heptafluoro-3,3'-bipyridyl ($> 95\%$), and with a 2:1 molar ratio of $NaOCH_3$ to the bipyridyl an equi-molar mixture of 4,4'-, and 4,6'-dimethoxyhexafluoro-3,3'-bipyridyls is obtained. Neglecting steric interactions, it would have been expected that only 4,4'-dimethoxyhexa-

fluoro-3,3'-bipyridyl would have been obtained. The result implies that the OCH_3 group in the 4-position is sterically hindering the 4'-position to a large extent, and substitution is also taking place at the next most reactive position in the molecule (the 6'-position).

As the size of the nucleophile is increased($C_2H_5O^-$ ..... $t\text{-}C_4H_9O^-$), substitution at the 4-position decreases with a corresponding increase in 6-substitution. Initially it was thought that the ratio of isomers obtained (4- and 6-substitution) was directly proportional to the size of the nucleophile, but spectroscopic evidence[204] indicates that replacement of CH_3 by C_2H_5, $n\text{-}C_3H_7$ or $n\text{-}C_4H_9$ does not greatly increase the steric interaction as the chains of the longer n-alkyl groups can orientate themselves so that they do not greatly increase the steric hindrance. Branched chain alkyl groups do increase the steric interactions with respect to the straight chain alkyl groups.[205]

Reaction of octafluoro-3,3'-bipyridyl with $NaOCH_3$ (in $t\text{-}C_4H_9OH$) gives 6-methoxy- ($> 80\%$) and (4-methoxy- ($< 20\%$)) heptafluoro-3,3'-bipyridyls. Based on steric grounds, this result implies that the nucleophile is solvated by the alcohol thereby increasing its effective size. If this 'solvation of the nucleophile' by the alcohol is a true picture of the reaction conditions, then for all the reactions between octafluoro-3,3'-bipyridyl and sodium alkoxides, the effective size of the nucleophile will be increased. Thus, as the size of the alkoxide

group increases its effective size will also be increased as it will be solvated by a larger solvent molecule. This solvation effect will probably be more important with branched chained alcohols.

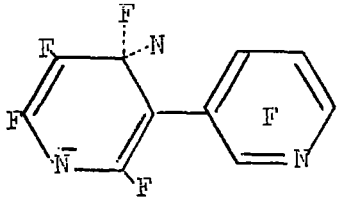
Thus, nucleophilic substitution in octafluoro-3,3'-bipyridyl, based purely on steric interactions, probably depends on, (1) the size of the nucleophilic reagent and (2) the effective size of the nucleophile after solvation.

Rationalization of Orientation based on the Solvation of the Transition State.

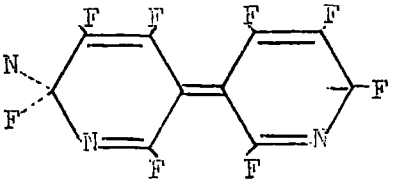
The reaction of nucleophilic reagents with polyfluoroaromatic- and polyfluoroheteroaromatic compounds has led to replacement of fluorine with isolation of isomeric products. This ratio of isomers has been shown to vary when ether is added to the reaction medium. Pentafluoronitrobenzene reacts with $NaOCH_3$ (in CH_3OH) to replace (> 90%) the fluorine atom para to the nitro-group. However, in ether containing very little methanol, sodium methoxide replaces both the ortho and para fluorine atoms in approximately equal amounts.[206] The same effect has been observed in nucleophilic substitution in 4-nitrotetrafluoropyridine.[201] 4-Nitrotetrafluoropyridine reacts with sodium methoxide in methanol to replace, besides the nitro-group, the 2- and 3-fluorine atoms in the ratio 3:1 respectively. When the reaction is carried out in an ether/methanol (9:1 v/v) mixture, the replacement at the 2- and 3-positions is in the ratio 3:2 respectively.

This variation of isomer ratios, due to ether, has also been recorded in nucleophilic substitution reactions with octafluoro-3,3'-bipyridyl and 3,5-dichlorotrifluoropyridine. (TABLES, 19,20). Sodium iso-propoxide in iso-propanol reacts with the bipyridyl to replace the 4- and 6-fluorines in the ratio 2:3 respectively. In ether containing a little iso-propanol, sodium iso-propoxide replaces the 4- and 6-fluorines in the ratio 1:4. Sodium iso-propoxide in iso-propanol reacts with 3,5-dichlorotrifluoropyridine to replace the fluorine atoms in the 4- and 2-positions in the ratio 3:1. In ether containing very little iso-propanol, sodium iso-propoxide replaces the 4- and 2-fluorines in the ratio 3:2. Reaction of octafluoro-3,3'-bipyridyl with ammonia and methyl lithium in ether gives predominantly (>95%) 6-substitution. Hence, in octafluoro-3,3'-bipyridyl, it appears that ether is directing the nucleophile into the 6-position.

Provided that the two most important transition states are A and B (the para quinonoid forms of the Wheland-type intermediates) for nucleophilic attack at the 4- and 6-positions in octafluoro-3,3'-bipyridyl, then the ratio of isomers obtained from the nucleophilic replacement of fluorine in the bipyridyl can be rationalized by postulating the solvation of the transition state.



(A)



(B)

The charge dispersion in A is less than in B and A will therefore be solvated to a greater extent by more polar solvents (i.e. those with a high dielectric constant) than by non-polar solvents. This increased solvation of A over B means that the transition state A will be more stabilized than B and hence will be more favoured in nucleophilic substitution. The dielectric constants of the solvents used in the nucleophilic substitution reactions have been measured and are listed in TABLE 21.[207]

TABLE 21

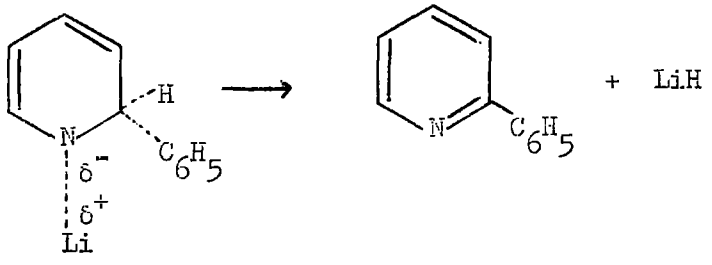
SOLVENT	DIELECTRIC CONSTANT
CH_3OH	32·6
C_2H_5OH	24·3
$n\text{-}C_3H_7OH$	20·1
$n\text{-}C_4H_9OH$	17·1
$i\text{-}C_3H_7OH$	18·3
$t\text{-}C_4H_9OH$	10·9
$(C_2H_5)_2O$	4·3

Comparison of the isomer ratios obtained for the mono-ether (TABLE 18) with the dielectric constants of the solvents shows that as the dielectric constant of the solvent decreases (i.e. the solvent becomes less polar and is unable to stabilize transition state A as readily) the amount of substitution in the 6-position increases. The effect of adding ether to the reaction medium causing more 6-

substitution could then be explained on the basis that the dielectric constant of the solvent medium will be lowered giving less stabilization of the transition state A and causing the equilibrium to be moved towards 6-substitution.

Rationalization of Orientation based on Electrostatic Interactions.

Pyridine reacts with phenyl lithium to give 2-phenylpyridine, it being postulated that the reaction proceeds via an intermediate of the type C.



(C)

It is possible with octafluoro-3,3'-bipyridyl for the same intermediate complex to be present in the reaction between the bipyridyl and methyl lithium. This attraction between the positive lithium and negatively charged ring nitrogen would have the effect of attracting the nucleophilic reagent towards the 6-position, and it is therefore not surprising that with methyl lithium a proponderance of 6-substitution is obtained. Similarly, hydrogen bonding between the ring nitrogen and ammonia could explain the isolation of 6-aminohepta-fluoro-3,3'-bipyridyl.

CONCLUSIONS.

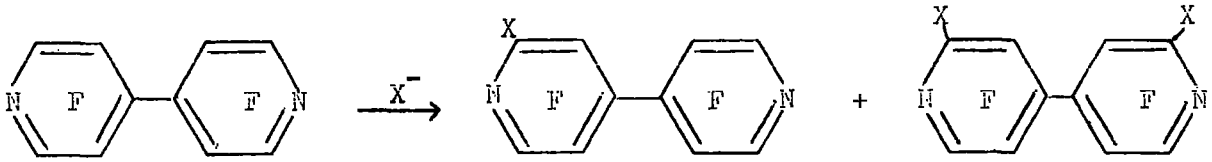
Nucleophilic attack in octafluoro-3,3'-bipyridyl cannot be readily rationalized by any one of the three considerations discussed. A combination of all three effects is necessary before an adequate explanation is obtained. Steric interactions could possibly explain the isomer ratios obtained with sodium alkoxides, and this, coupled with electrostatic interactions, explains the variation of substitution at the 4- and 6-positions. However, a combination of both these effects does not explain the effect of diluting the alcohol with ether giving more 6-substitution. Conversely, the combination of steric interactions and solvation of the transition state does not completely rationalize all the results. It would have been expected that when the reaction between the bipyridyl and sodium iso-propoxide in ether containing very little iso-propanol was carried out, it would have eventually terminated (if sufficient ether was added) with total 6-substitution occurring. From TABLE 19 it is seen that at least 16% of the 4-isomer is obtained, even when large amount of ether is used. A combination of electrostatic interactions and solvation of the transition state cannot completely explain all orientations, as the reaction between the bipyridyl and sodium iso-propoxide in iso-propanol gives more replacement of the 6-fluorine atom than the reaction of sodium n-propoxide in n-propanol, although from the polarity of the solvents the reverse would be implied.

Thus, it is possible that all three effects are necessary to explain completely the orientation of nucleophilic replacement reactions in octafluoro-3,3'-bipyridyl.

It is clear that before any definite reaction mechanism can be postulated, more controlled experiments will have to be performed. Reactions are envisaged between 3,5-dichlorotrifluoropyridine and various nucleophilic reagents in different solvents.

Nucleophilic Substitution in Polyfluoro-4,4'-bipyridyls.

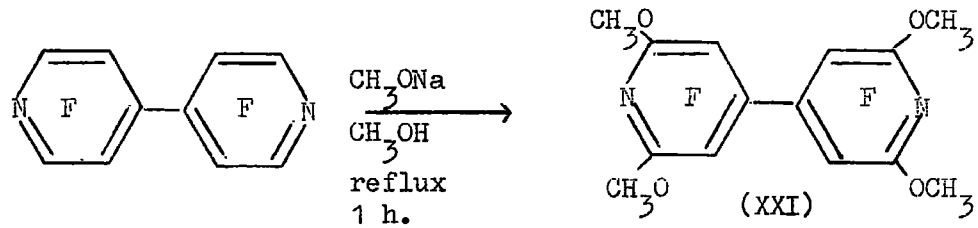
Octafluoro-4,4'-bipyridyl has been reacted with sodium methoxide (in methanol) and ammonia to give a mixture of the mono- (XIX) and di-substituted-4,4'-bipyridyls (XX).



(XIX) (XX)

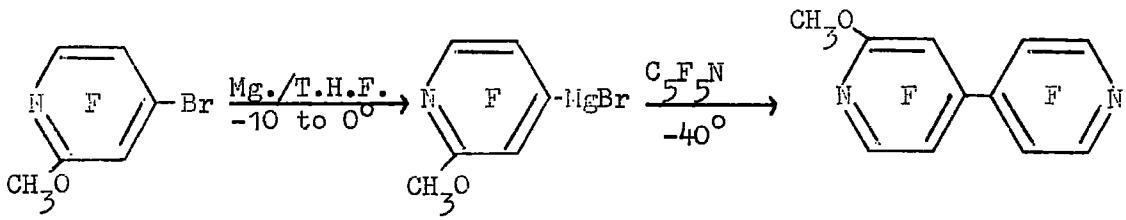
(X = OCH_3, NH_3)

Octafluoro-4,4'-bipyridyl was reacted with excess sodium methoxide but only four fluorine atoms could be replaced: 2,2',6,6'-tetramethoxytetrafluoro-4,4'-bipyridyl (XXI) being isolated in good yield.



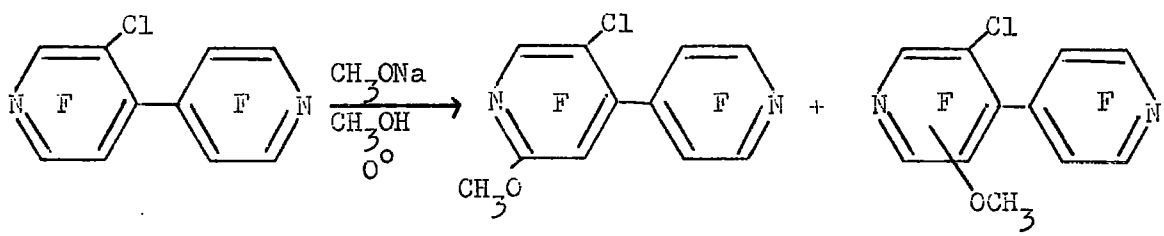
(XXI)

2-Methoxyheptafluoro-4,4'-bipyridyl ((XIX), when X = OCH_3) has also been prepared by adding pentafluoropyridine to 2-methoxytrifluoropyridylmagnesium bromide (XXII) at low temperature.



(XXII)

3-Chloroheptafluoro-4,4'-bipyridyl (XXIII) reacted readily at 0° with a solution of sodium methoxide in methanol, giving 3-chloro-6-methoxyhexafluoro-4,4'-bipyridyl (XXIV) (> 95%) and a trace (< 5%) of an isomer, the structure of which has not yet been elucidated.



(XXIII) (XXIV) (XXV)

Rationalization of Orientation in Substituted-polyfluoro-4,4'-bipyridyls.

The replacement of the fluorine atom ortho to the nitrogen in polyfluoro-4,4'-bipyridyls is consistent with the results expected by comparison with nucleophilic attack in 4-X-tetrafluoropyridine (X = OCH_3, NH_2, Br and Cl), with which octafluoro-4,4'-bipyridyl can be directly related by considering it to be 4-(tetrafluoropyridyl)-tetrafluoropyridine. The known activating effect, towards nucleophilic replacement, of the chlorine atom is again indicated by the isolation of 3-chloro-6-methoxyhexafluoro-4,4'-bipyridyl (> 95%) from the reaction of 3-chloroheptafluoro-4,4'-bipyridyl with sodium methoxide.

CHAPTER 7

EXPERIMENTAL PART II

Purification of Solvents.

The alcohols, methanol, ethanol, propanol and isopropanol.

The commercial grade alcohol was refluxed with sodium pellets for 10 minutes and then distilled from the reaction flask under a current of dry nitrogen. The alcohol (50-100 ml.) was added slowly to dry magnesium turnings (5-10 g.) containing a crystal of iodine and heated gently for 10 minutes until the iodine had disappeared. Alcohol (1000 ml.) was added and refluxed for 3 h. The alcohol was distilled under a current of dry nitrogen and stored under dry nitrogen until used.

The alcohols, n-butanol and tertiary butanol.

The same procedure outlined above was used except that powdered aluminium was used instead of magnesium turnings.

Diethyl-ether.

The ether was refluxed with sodium pellets for 2 h. and then distilled from the reaction flask. The ether was stored under sodium until required.

The Reaction of Polyfluorobipyridyls and Polyfluoropyridines with Sodium Alkoxides in Alcohol.

General Procedure.

A three necked flask fitted with a dropping funnel, gas inlet tap, reflux condenser, and a magnetic stirrer was flushed with dry nitrogen for 30 minutes prior to use. During the reaction a stream of dry nitrogen was passed through the apparatus.

To a stirred solution of the polyfluoroheterocyclic compound dissolved in dry alcohol, was added dropwise over a period of 5-30 min., at temperatures varying from -20 to 20°, a solution of sodium alkoxide (prepared by adding the required amount of sodium to alcohol) in dry alcohol. The solution was stirred for a further 20 to 60 min. and then poured into cold water. The white precipitate which resulted was extracted into organic solvent (ether or methylene dichloride), washed well with water, dried ($MgSO_4$), and the solvent removed by distillation. The composition of the reaction product was investigated using analytical-scale gas chromatography and the products purified by preparative-scale g.l.c., unless otherwise stated.

The percentage yields of the products purified by preparative-scale g.l.c., were obtained by estimation of peak areas from analytical-scale g.l.c. and based on the actual amount of reactant used. This was necessary as a true value for the yields of the products could not be obtained after purification, as the recovery from the preparative-scale g.l.c. apparatus was very low. In general, the conversion of the

starting material into the mono- and di-substituted products was in the region of 70-90%.

In the reactions between octafluoro-3,3'-bipyridyl and sodium alkoxides, compounds believed to be disubstituted derivatives of the bipyridyls were detected on gas chromatography apparatus but were not isolated.

Reaction between Octafluoro-2,2'-bipyridyl and Sodium Methoxide.

To a stirred solution of the bipyridyl (0·835 g., 0·0028 mole) dissolved in methanol (15 ml.) was added dropwise over 5 min., at 20°, a solution of sodium (0·068 g., 0·003 mole) in methanol (20 ml.). The reaction solution was stirred for a further 30 min., then treated as described. The reaction products (0·81 g.) were separated by preparative-scale v.p.c. and identified as: (i) unreacted octafluoro-2,2'-bipyridyl, (ii) 4-methoxyheptafluoro-2,2'-bipyridyl (75%), (Found: C, 42·2; H, 0·94; F, 42·0. $C_{11}H_3OF_7N_2$ requires: C, 42·3; H, 0·96; F, 42·6%), m.p. 39-40·5°, (iii) 4,4'-dimethoxyhexafluoro-2,2'-bipyridyl (16%), (Found: C, 43·9; H, 1·76. $C_{12}H_6O_2F_6N_2$ requires: C, 44·4; H, 1·85%. There was insufficient compound available for a fluorine analysis), m.p. 50-51°.

Reaction between 3-Chloroheptafluoro-2,2'-bipyridyl and Sodium Methoxide.

To a stirred solution of the bipyridyl (0·826 g., 0·0026 mole) dissolved in methanol (20 ml.) was added dropwise over 10 min., at 20°, a solution of sodium (0·06 g., 0·0026 mole) in methanol (20 ml.).

The solution was stirred for a further 30 min., then treated as described. The reaction products (0·73 g.) were separated by preparative-scale v.p.c. and identified as: (i) unreacted 3-chloro-heptafluoro-2,2'-bipyridyl, (ii) a 2:1 molar ratio of 3-chloro-4-methoxyhexafluoro-2,2'-bipyridyl and 3-chloro-4'-methoxyhexafluoro-2,2'-bipyridyl (67%), (Found: C, 40·3; H, 0·95; F, 35·5; Cl, 11·0. $C_{11}H_3OF_6ClN_2$ requires: C, 40·2; H, 0·91; F, 34·7; Cl, 10·8%), b.p. (of mixture) 273-276°, (iii) 3-chloro-4,4'-dimethoxypentafluoro-2,2'-bipyridyl (14%), (Found: C, 41·8; H, 1·71. $C_{12}H_6O_2F_5ClN_2$ requires: C, 42·3; H, 1·76%. There was insufficient compound available for a fluorine analysis), m.p. 72-74°.

Reaction between 3,3'-Dichlorohexafluoro-2,2'-bipyridyl and Sodium Methoxide.

To a stirred solution of the bipyridyl (1·12 g., 0·0034 mole) dissolved in methanol (15 ml.) was added dropwise over 15 min., at 20°, a solution of sodium (0·078 g., 0·0034 mole) in methanol (20 ml.). The solution was stirred for a further 30 min., then treated as described. The reaction products (1·05 g.) were separated by preparative g.l.c. and identified as (i) unreacted 3,3'-dichloro-hexafluoro-2,2'-bipyridyl, (ii) 3,3'-dichloro-4-methoxypentafluoro-2,2'-bipyridyl (68%), (Found: C, 38·1; H, 0·92; F, 27·1; Cl, 20·8. $C_{11}H_3OF_5Cl_2N_2$ requires: C, 38·26; H, 0·87; F, 27·5; Cl, 20·6%), b.p. 299-301°, (iii) 3,3'-dichloro-4,4'-dimethoxytetrafluoro-2,2'-bipyridyl (16%),

(Found: C, 40·1; H, 1·70; F, 20·1; Cl, 19·8. $C_{12}H_6O_2F_4Cl_2N_2$ requires: C, 40·3; H, 1·68; F, 21·3; Cl, 19·9%), m.p. 135·5°.

Reaction between Octafluoro-3,3'-bipyridyl and Sodium Methoxide.

a) In methanol. To a stirred solution of the bipyridyl (2·13 g., 0·0071 mole) dissolved in methanol (30 ml.) was added dropwise over 20 min., at 0°, a solution of sodium (0·165 g., 0·0072 mole) in methanol (50 ml.). The solution was stirred for a further 45 min. as it warmed slowly to room temperature, then treated as described. The reaction product (2·0 g.) was purified by preparative-scale g.l.c. and identified as 4-methoxyheptafluoro-3,3'-bipyridyl (88%), (Found: C, 42·4; H, 0·94; F, 42·7. $C_{11}H_3OF_7N_2$ requires: C, 42·3; H, 0·96; F, 42·6%), b.p. 256°. Only a trace (< 1%) of unreacted starting material was detected by gas chromatography.

To a stirred solution of the bipyridyl (0·064 g., 0·00213 mole) dissolved in methanol (50 ml.) was added dropwise over 15 min., at 20°, a solution of sodium (0·0985 g., 0·0043 mole) in methanol (30 ml.). The solution was stirred for a further 20 min., then treated as described. The reaction products (0·6 g.) were separated by preparative-scale g.l.c. and identified as: (i) 4-methoxyheptafluoro-3,3'-bipyridyl (9%), identified from its infrared spectrum, (ii) an equi-molar mixture of 4,4'-dimethoxyhexafluoro-3,3'-bipyridyl and 4,6'-dimethoxyhexafluoro-3,3'-bipyridyl (74%), (Found: C, 44·3; H, 2·20; F, 35·0. $C_{12}H_6O_2F_6N_2$ requires: C, 44·4; H, 1·9; F, 35·2%), b.p. (of mixture)

267-269°.

Evidence of isomers of trimethoxypentafluoro-3,3'-bipyridyl was indicated from gas chromatography, but only present in small amounts, < 5%.

b) In t-butanol. To a stirred solution of the bipyridyl (1·13 g., 0·0038 mole) in t-butanol (40 ml.) was added dropwise over 15 min., at 20°, a solution of sodium alkoxide (obtained from dissolving sodium (0·096 g., 0·0042 mole) in methanol (10 ml.) and distilling off the methanol under a current of dry nitrogen) in t-butanol (45 ml.). The solution was stirred for a further 60 min., then treated as described. The reaction products 0·95 g. were separated by preparative-scale g.l.c. and identified as: (i) unreacted octafluoro-3,3'-bipyridyl, (ii) a mixture of 6-methoxyheptafluoro-3,3'-bipyridyl and presumed 4-methoxyheptafluoro-3,3'-bipyridyl (in %-age ratio > 80 : < 20 respectively) (43%), (Found: C, 42·5; H, 1·34. $C_{11}H_3OF_7N_2$ requires: C, 42·3; H, 0·96%), b.p. (of mixture) 240-242°, (iii) 6,6'-dimethoxy-hexafluoro-3,3'-bipyridyl (30%), (Found: C, 42·2; H, 2·90. $C_{12}H_6O_2F_6N_2$ requires: C, 44·4; H, 1·85%) b.p. 279-280°. No other isomer of the dimethoxy derivative was indicated either from n.m.r. spectra or gas chromatography, but it is probable that the 6,6'-dimethoxy derivative is slightly contaminated by other isomers.

Reaction between Octafluoro-3,3'-bipyridyl and Sodium Ethoxide.

To a stirred solution of the bipyridyl (1·14 g., 0·0038 mole)

dissolved in ethanol (20 ml.) was added dropwise over 10 min., at 20°, a solution of sodium (0·095 g., 0·0041 mole) in ethanol (20 ml.). The solution was stirred for a further 20 min., then treated as described. The reaction products (0·92 g.) were separated by preparative-scale g.l.c. and identified as: (i) unreacted octafluoro-3,3'-bipyridyl, (ii) a mixture of 4-ethoxyheptafluoro-3,3'-bipyridyl and 6-ethoxyhepta-fluoro-3,3'-bipyridyl (in %-age ratio 85:15) (62%), (Found: C, 44·0; H, 1·72; F, 40·3. $C_{12}H_5OF_7N_2$ requires: C, 44·2; H, 1·53; F, 40·8%) b.p. (of mixture) 260-262°. Compounds which were thought to be di-substituted -3,3'-bipyridyl were detected by gas chromatography but not isolated.

Reaction between Octafluoro-3,3'-bipyridyl and Sodium n-Propoxide.

To a stirred solution of the bipyridyl (1·1 g., 0·0037 mole) dissolved in n-propanol (15 ml.) was added dropwise over 10 min., at 0°, a solution of sodium (0·083 g., 0·0036 mole) in n-propanol (15 ml.). The solution was stirred for a further 60 min. as it warmed slowly to room temperature, then treated as described. The reaction products (0·9 g.) were separated by preparative-scale g.l.c. and identified as: (i) unreacted octafluoro-3,3'-bipyridyl, (ii) a mixture of isomers in ratio 4:1, 4-n-propoxyheptafluoro-3,3'-bipyridyl and 6-n-propoxyhepta-fluoro-3,3'-bipyridyl (63%) (Found: C, 45·8; H, 1·79; F, 38·9. $C_{13}H_7OF_7N_2$ requires: C, 45·9; H, 2·06; F, 39·1%) b.p. 260-265°.

Compounds which were thought to be isomeric di-n-propoxy-3,3'-

bipyridyls were detected by gas chromatography but not isolated.

Reaction between Octafluoro-3,3'-bipyridyl and Sodium iso-propoxide.

To a stirred solution of the bipyridyl (1·5 g., 0·005 mole) dissolved in iso-propanol (15 ml.) was added dropwise over 10 min., at 0°, a solution of sodium (0·114 g., 0·005 mole) in iso-propanol (15 ml.). The solution was stirred for a further 30 min. as it warmed slowly to room temperature, then treated as described. The reaction products (1·4 g.) were separated by preparative-scale g.l.c. and identified as: (i) unreacted octafluoro-3,3'-bipyridyl, (ii) a mixture of isomers in the ratio 2:3, 4-iso-propoxyheptafluoro-3,3'-bipyridyl and 6-iso-propoxy-heptafluoro-3,3'-bipyridyl (82%), (Found: C, 46·0; H, 2·22; F, 39·3. $C_{13}H_7OF_7N_2$ requires: C, 45·9; H, 2·06; F, 39·1%), b.p. (of mixture) 259-260°.

Traces (< 2%), of compounds thought to be isomeric di-iso-propoxyhexafluoro-3,3'-bipyridyls were detected on gas chromatography but were not isolated.

Reaction between Octafluoro-3,3'-bipyridyl and a) sodium 1-butoxide and b) sodium-t-butoxide.

The reaction between octafluoro-3,3'-bipyridyl and the alkoxides were carried out under the usual conditions using equi-molar amounts of the bipyridyl and sodium alkoxide. The two sodium butoxides were dissolved in their respective alcohols and added to the bipyridyl in the same alcohol. The products of the reaction were not isolated but only

investigated on gas chromatography. The products of the reaction were tentatively identified as isomers of monosubstituted-3,3'-bipyridyls by comparison with previous reactions.

Reaction between Octafluoro-4,4'-bipyridyl and Sodium Methoxide.

To a stirred solution of the bipyridyl (1·2 g., 0·004 mole) dissolved in methanol (30 ml.) was added dropwise over 10 min., at -10 to -15°, a solution of sodium (0·092 g., 0·004 mole) in methanol (15 ml.). The reaction solution was stirred for a further 20 min. as it warmed slowly to room temperature, then treated as described. The reaction products (1·1 g.) were separated by preparative-scale g.l.c. and identified as: (i) unreacted octafluoro-4,4'-bipyridyl, (ii) 2-methoxyheptafluoro-4,4'-bipyridyl (70%), (Found: C, 42·1; H, 1·11; F, 42·9. $C_{11}H_3OF_7N_2$ requires: C, 42·3; H, 0·96; F, 42·6%), m.p. 101-101·5° (from pet. ether, 40-60° fraction), (iii) a white solid m.p. 127° (15%).

To a stirred solution of the bipyridyl (0·75 g., 0·0025 mole) dissolved in methanol (15 ml.) was added dropwise over 10 min., at 20°, a solution of sodium (0·12 g., 0·0052 mole) in methanol (20 ml.). The solution was stirred for a further 30 min., then treated as described. The reaction products (0·7 g.) were separated by preparative-scale g.l.c. and identified as: (i) 2-methoxyheptafluoro-4,4'-bipyridyl (10%), identified from its infrared spectrum, (ii) 2,2'-dimethoxy-hexafluoro-4,4'-bipyridyl (75%), (Found: C, 44·4; H, 1·93; F, 35·0.

$C_{12}H_6O_2F_6N_2$ requires: C, 44·4; H, 1·85; F, 35·2%), m.p. 128-129° (from pet. ether, 40-60° fraction). The compound isolated in the previous reaction, (fraction iii), was shown to be identical to 2,2'-dimethoxyhexafluoro-4,4'-bipyridyl by comparison of infrared spectra.

To a stirred solution of the bipyridyl (1·0 g., 0·0033 mole) dissolved in methanol (15 ml.) was added at 20° a solution of sodium (0·5 g., 0·022 mole) in methanol (30 ml.). The solution was refluxed for 60 mins., then treated as described. The reaction product (1·05 g.) was purified by sublimation affording 2,2',6,6'-tetramethoxytetrafluoro-4,4'-bipyridyl (0·95 g., 82%), (Found: C, 48·1; H, 3·38; F, 22·1. $C_{14}H_{12}O_4F_4N_2$ requires: C, 48·3; H, 3·45; F, 21·8%), m.p. 230-233° (resublimed).

Reaction between 3-chloroheptafluoro-4,4'-bipyridyl and Sodium Methoxide.

To a stirred solution of the bipyridyl (0·64 g., 0·002 mole) dissolved in methanol (15 ml.) was added dropwise over 10 min., at -20°, a solution of sodium (0·05 g., 0·0022 g.) in methanol (15 ml.). The solution was stirred for a further 60 min. as it warmed slowly to room temperature, then treated as described. The reaction products (0·6 g.) were separated by preparative-scale g.l.c. and identified as: (i) unreacted 3-chloroheptafluoro-4,4'-bipyridyl, (ii) 3-chloro-6-methoxyhexafluoro-4,4'-bipyridyl (77%), (Found: C, 40·2; H, 1·00; Cl, 10·3. $C_{11}H_3OF_6ClN_2$ requires: C, 40·2; H, 0·91; Cl, 10·8%), m.p. 97-101°. Because of the large range over which the compound melted, there is

probably present a small amount of another isomer (< 5%), the structure of which has not been elucidated.

Reaction between Pentafluoropyridine and Sodium iso-propoxide.

To a stirred solution of pentafluoropyridine (0·904 g., 0·054 mole) in iso-propanol (20 ml.) was added dropwise over 5 min., at 20°, a solution of sodium (0·123 g., 0·054 mole) in iso-propanol. The reaction was stirred for a further 20 min., then treated as described. Distillation of the product afforded 4-iso-propoxytetrafluoropyridine (0·7 g., 62·5%), (Found: C, 46·1; H, 3·49; F, 36·0. $C_8H_7OF_4N$ requires: C, 45·9; H, 3·35; F, 36·4%), b.p. 179·5°.

Reaction between 3-Chlorotetrafluoropyridine and Sodium iso-propoxide.

To a stirred solution of 3-chlorotetrafluoropyridine (0·976 g., 0·0053 mole) in iso-propanol (20 ml.) was added dropwise over 10 min., at 20°, a solution of sodium (0·121 g., 0·0053 mole) in iso-propanol (20 ml.). The solution was stirred for a further 20 min., then treated as described. Distillation of the product afforded a mixture of isomers (in %-age ratio 80:16:4) of mono-iso-propoxy-3-chlorotrifluoropyridine (0·72 g., 60·5%). The main isomer was identified as 4-iso-propoxy-3-chlorotrifluoropyridine and it is probable that the other isomers are 6-iso-propoxy-3-chlorotrifluoropyridine and 2-iso-propoxy-3-chlorotrifluoropyridine respectively. (Found: C, 42·8; H, 3·26; F, 25·4; Cl, 15·8. $C_8H_7OF_3ClN$ requires: C, 42·6; H, 3·12; F, 25·3; Cl, 15·7%), b.p. (of mixture) 205-208°.

Reaction between 3,5-Dichlorotrifluoropyridine and Sodium Iso-propoxide.

To a stirred solution of 3,5-dichlorotrifluoropyridine (1·06 g., 0·0053 mole) in iso-propanol (15 ml.) was added dropwise over 15 min., at 20°, a solution of sodium (0·116 g., 0·005 g.) in iso-propanol (45 ml.). The solution was stirred for a further 15 mins., then treated as described. Distillation of the product under reduced pressure afforded a mixture of isomers, in the ratio 77:23, and were identified as, 3,5-dichloro-4-iso-propoxydifluoropyridine and 2-iso-propoxy-3,5-dichlorodifluoropyridine respectively (0·64 g., 50%), (Found: C, 40·2; H, 3·06; F, 15·7; Cl, 29·2. $C_8H_7OF_2Cl_2N$ requires: C, 39·7; H, 2·89; F, 15·7; Cl, 29·3%), b.p. (of mixture) 230-232°.

Reaction of Octafluoro-3,3'-bipyridyl and 3,5-dichlorotrifluoropyridine with Sodium Isopropoxide in Iso-propanol/Ether mixtures.

General Procedure.

The apparatus was the same as described for the reaction of sodium alkoxides with polyfluoro-bipyridyls.

To a stirred solution of the polyfluoro-heterocyclic compound in a solution of iso-propanol and ether, was added dropwise over 10 min., at 20°, a solution of sodium in iso-propanol/ether mixture, the ratio of which was the same as that in which the heterocycle was dissolved in. The solution was stirred for a further 30 min., then poured into water. The ether layer was separated off, washed well with water, dried ($MgSO_4$), and the ether removed by distillation. The composition of the product

was investigated using analytical-scale gas chromatography and the products identified by comparison of retention times with known samples of the products. The results and reaction conditions are shown in TABLE 22.

Reaction between Octafluoro-3,3'-bipyridyl and Ammonia.

i) To a stirred solution of octafluoro-3,3'-bipyridyl (0·6 g., 0·003 mole) in dry ether (15 ml.) was added ammonia (0·7 g., 0·88 s.g.) in ether (15 ml.) at 20°. The solution was stirred vigorously for a further 30 min. and then poured into water. The ether layer was separated off, dried ($MgSO_4$), and the ether removed by distillation to give a light brown solid (after prolonged pumping) (0·45 g.), which sublimed 'in vacuo' as a tacky gum. Analytical-scale g.l.c. (silicone elastomer on celite at 180°) showed that the gum consisted of two components in the ratio 1:3 (from peak areas), the minor component (i.e. the one with the shortest retention time) having a retention time identical to that of octafluoro-3,3'-bipyridyl. The major component was purified by preparative-scale g.l.c. (silicone elastomer on celite at 200°) and identified as 6-aminoheptafluoro-3,3'-bipyridyl (0·17 g., 28%), (Found: C, 40·6; H, 0·87; F, 44·4. $C_{10}H_2F_7N_3$ requires: C, 40·4; H, 0·67; F, 44·8%), m.p. 79-86°.

Due to the large range over which the compound melted, it is probable that another isomer is present (< 5%). This isomer could not be detected from nuclear magnetic resonance spectra.

TABLE 22

Poly-fluoroheterocycle	Sodium	Ratio Ether/ Iso-propanol (w/w)	Composition of Product (from chromatographic evidence)	
Octafluoro-3,3'-bipyridyl (0·5 g., 0·0017 mole) dissolved in iso-C_3H_7OH (5 ml.) and ether (20 ml.)	0·057 g., (0·0025 mole) in ether (20 ml.) and iso-C_3H_7OH (5 ml.)	4 : 1	4-OC_3H_7 iso-$C_{10}F_7N_2$ 6-OC_3H_7 iso-$C_{10}F_7N_2$	(20%) (80%)
(0·4 g., 0·0013 mole) dissolved in iso-C_3H_7OH (5 ml.) and ether (95 ml.)	0·048 g., (0·0021 mole) in ether (95 ml.) and iso-C_3H_7OH (5 ml.)	19 : 1	4-OC_3H_7 iso-$C_{10}F_7N_2$ 6-OC_3H_7 iso-$C_{10}F_7N_2$	(16%) (84%)
(0·35 g., 0·0012 mole) dissolved in iso C_3H_7OH (5 ml.) and ether (350 ml.)	0·042 g., (0·0018 mole) in ether (350 ml.) and iso-C_3H_7OH (5 ml.)	70 : 1	4-OC_3H_7 iso-$C_{10}F_7N_2$ 6-OC_3H_7 iso-$C_{10}F_7N_2$	(16%) (84%)
3,5-Dichlorotrifluoropyridine (1·206 g., 0·006 mole) dissolved in ether (160 ml.) and iso-C_3H_7OH (60 ml.)	0·1370 g., (0·006 mole) in iso-C_3H_7OH (20 ml.) and ether (50 ml.)	10·5: 1	4-OC_3H_7 iso-$C_5F_2Cl_2N$ 2-OC_3H_7 iso-$C_5F_2Cl_2N$	(60%) (40%)
(1·00 g., 0·005 mole) dissolved in ether (500 ml.) and iso-C_3H_7OH (40 ml.)	0·1160 g., (0·005 mole) in iso-C_3H_7OH (20 ml.) and ether (250 ml.)	35 : 1	4-OC_3H_7 iso-$C_5F_2Cl_2N$ 2-OC_3H_7 iso-$C_5F_2Cl_2N$	(60%) (40%)

ii) When the reaction between octafluoro-3,3'-bipyridyl and ammonia was carried out in methanol, 4-methoxyheptafluoro-3,3'-bipyridyl was isolated in good yield and identified from its infrared spectrum.

Oxidation[159] of 6-Aminoheptafluoro-3,3'-bipyridyl.

To a refluxing solution of trifluoroacetic anhydride (1·25 ml.), 80% hydrogen peroxide (0·5 ml.), and methylene dichloride (5 ml.) was added dropwise a solution of 6-aminoheptafluoro-3,3'-bipyridyl (95% pure; 0·5 g., 0·0017 mole) in methylene dichloride (15 ml.). The solution was refluxed for 1 h., during which time the solution had turned bright green, and then a further 0·25 ml. of hydrogen peroxide was added. After a further 2 h. hydrogen peroxide (0·25 ml.), trifluoroacetic anhydride (0·25 ml.) and methylene dichloride (5 ml.) were added. The reaction mixture was refluxed and stirred for a further 16 h. during which time the bright green colour initially obtained had turned yellow. The solution was allowed to cool and water was carefully added. The methylene dichloride layer was separated off, washed well with 2N. H_2SO_4, dried ($MgSO_4$), and the methylene dichloride then removed by distillation yielding a pale yellow solid (0·5 g.), the composition of which was shown by analytical-scale g.l.c. to consist of unreacted starting material and a component of longer retention time. The major component (i.e. the one with the longer retention time) was purified by preparative-scale g.l.c. (silicone elastomer on celite at 230°) and identified as 6-nitroheptafluoro-3,3'-bipyridyl (a pale yellow

solid) (0·1 g., 18%), (Found: C, 36·4; F, 41·1. $C_{10}O_2F_7N_3$ requires: C, 36·7; F, 40·7%), m.p. 70-71° (from petroleum-ether, 40-60° fraction).

Reaction between Octafluoro-3,3'-bipyridyl and Hydrazine Hydrate.

To a stirred solution of the bipyridyl (1·0 g., 0·003 mole) in dioxan (10 ml.) was added dropwise over 20 min., at 20°, a solution of hydrazine hydrate (0·5 g., 0·01 mole) in dioxan (15 ml.). After the addition of three drops of the hydrazine solution to the bipyridyl the reaction mixture turned a deep red colour. After the addition of the hydrazine solution was complete, water was added to the reaction solution. The aqueous mixture was extracted with ether, the combined extracts washed well with water, dried ($MgSO_4$), and the solvent removed by distillation to give a dark red solid that did not sublime 'in vacuo' (220°/0·01 mm.). No further investigation of this solid was carried out.

Reaction between Octafluoro-3,3'-bipyridyl and Methyl Lithium.

To a stirred solution of the bipyridyl (1·0 g., 0·0033 mole) in dry ether (20 ml.) was added dropwise over 30 min., at 20°, a solution of methyl lithium (0·0033 mole) in dry ether (20 ml.). On addition of the methyl lithium to the bipyridyl, a red coloured solution was obtained which rapidly dispersed to give a yellow-green solution. The solution was stirred for a further 60 min. and then poured into water. The ether layer was separated off, washed well with water, dried ($MgSO_4$), and

the ether distilled off to give a pale yellow solid (0·8 g.), the composition of which was shown by analytical-scale g.l.c. to consist of three components in the approximate ratio 2:1:1 (from peak areas). The three components were separated by preparative-scale g.l.c. (silicone elastomer on celite at 220°) and identified as: (i) unreacted octafluoro-3,3'-bipyridyl (largest component in mixture), (ii) 6-methylheptafluoro-3,3'-bipyridyl (the component with the intermediate retention time), (Found: C, 44·5; H, 1·06; F, 44·9. $C_{11}H_3F_7N_2$ requires: C, 44·6; H, 1·01; F, 44·9%), m.p. 43-45°, (iii) a white solid (Found: C, 42·1; H, 0·90; F, 47·2%), m.p. 42-43°. The structure of this compound could not be resolved.

Reaction between Octafluoro-4,4'-bipyridyl and Ammonia.

(i) Octafluoro-4,4'-bipyridyl (0·7 g., 0·0023 mole), ammonia (1·0 ml., 0·88 s.g.), and acetone (5 ml.) were sealed in a Carius tube and heated for 2·5 h. at 80°. The tube was then cooled, opened, and the contents added to water. The aqueous mixture was extracted with methylene dichloride and the combined extracts dried ($MgSO_4$). The solvent was distilled off leaving a yellow solid (0·5 g.) which after fractional sublimation 'in vacuo' and recrystallization from ether afforded 2-aminoheptafluoro-4,4'-bipyridyl (0·23 g., 33%), (Found: C, 40·4; H, 0·75; F, 44·7. $C_{10}H_2F_7N_3$ requires: C, 40·4; H, 0·67; F, 44·8%), m.p. 124-125° (slight decomposition).

(ii) Octafluoro-4,4'-bipyridyl (2·0 g., 0·0067 mole) and ammonia (10 ml., 0·88 s.g.) were sealed in a Carius tube and heated at 160° for 31 h. The tube was shaken throughout the time of the reaction. The tube was then allowed to cool, opened, and the contents added to water. The aqueous mixture was extracted with ether and the combined extracts dried ($MgSO_4$). The ether was removed by distillation giving a dark brown solid (1·2 g.). Sublimation 'in vacuo', followed by recrystallization from ether afforded 2,2'-diaminohexafluoro-4,4'-bipyridyl (0·7 g., 36%), (Found: C, 41·3; H, 1·4; F, 38·5. $C_{10}H_4F_6N_4$ requires: C, 40·8; H, 1·36; F, 38·8%), m.p. 243-246° (decomposition).

PART III

CHAPTER 8

ELUCIDATION OF ORIENTATION IN SUBSTITUTED POLY-FLUOROBIPYRIDYLS (AND SUBSTITUTED FLUOROPYRIDINES) FROM NUCLEAR MAGNETIC RESONANCE SPECTRA MEASUREMENTS.

Elucidation of Orientation in Substituted Polyfluorobipyridyls (and substituted fluoropyridines) from Nuclear Magnetic Resonance Spectra Measurements.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on an A.E.I. R.S.2. spectrometer at 60 Mc./sec. Samples were examined as neat liquids or as solids dissolved in inert solvents, with hexafluorobenzene or trichlorofluoromethane as internal reference. Chemical shifts measured relative to $CFCl_3$ were related to C_6F_6 by incorporating the relationship that the Fluorine-19 chemical shift due to C_6F_6 is 162·28 p.p.m upfield from $CFCl_3$.

The effect of the solvent on the chemical shifts is neglected as the determination of the orientations is made purely on an emperical basis to the nearest 2-3 p.p.m.

The structures of the various substituted polyfluorobipyridyls were deduced from their n.m.r. spectra by incorporating the known effects of substituent groups on the Fluorine-19 chemical shifts in pentafluoropyridine and related compounds. As already mentioned an octafluorobipyridyl can be considered as a monosubstituted-tetrafluoropyridine and to a first approximation the effect of a substituent on the Fluorine-19 chemical shifts in pentafluoropyridine will be of the same order as the effect the same substituent group would have on the Fluorine-19 chemical shifts in octafluorobipyridyl. Thus, if a group X in 4-X-tetrafluoropyridine shifts the chemical shift of the ortho fluorine by γ p.p.m. relative to the chemical shift of the same fluorine

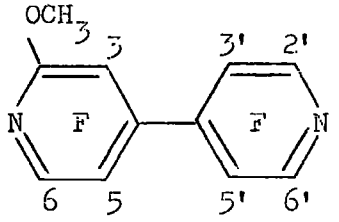
in pentafluoropyridine, then in 4-X-heptafluorobipyridyl the same effect on the chemical shift of the ortho fluorine relative to octafluorobipyridyl can be expected.

From the Fluorine-19 chemical shift data listed in TABLE 23, it is possible to calculate the chemical shifts for any substituted polyfluorobipyridyl. When two substituents are present in one ring then the combined effects of both substituents are incorporated to calculate the expected chemical shifts. In monosubstituted heptafluorobipyridyls it has been assumed that the substituent has little or no effect on the chemical shifts due to the fluorine atoms in the other ring. When more than one orientation is possible the chemical shifts have been calculated for all possible orientations and the correct structure assigned on the assumption that the calculated chemical shifts for any orientation must closely agree with the measured values of the chemical shifts.

Although the Ullmann synthesis of biaryls has been used in many instances as a method of confirming orientations in substituted biaryls, the structures of the octafluorobipyridyls can be further confirmed from n.m.r. data. In monosubstituted-tetrafluoropyridines it has been found, without exception, that the chemical shifts due to the fluorine atoms ortho to the ring nitrogen are found to low field, the chemical shifts due to the fluorine atoms meta to the ring nitrogen are found to high field, and the chemical shift due to

the fluorine atom para to the ring nitrogen is found to middle field. Thus, by considering octafluorobipyridyl to be a mono-(tetrafluoropyridyl)-tetrafluoropyridine, the chemical shifts due to the fluorine atoms can be readily assigned. Further confirmation of the structure of an octafluorobipyridyl is obtained by comparison of the Fluorine-19 chemical shifts obtained from the bipyridyl with those obtained from decafluorobiphenyl.

EXAMPLE. Elucidation of the Structure of 2-Methoxyheptafluoro-4,4'-bipyridyl.



(ref. XI, TABLE 24)

Confirmation of Orientation of Octafluoro-4,4'-bipyridyl (ref. X, TABLE 24)

From the symmetry of the compound, two chemically shifted peaks of equal intensity would be expected. In polyfluoropyridines, the chemical shifts due to the fluorine atoms ortho to the nitrogen are always found to low-field (-70 ± 20 p.p.m.), and the chemical shifts due to the fluorine atoms meta to the nitrogen are always found to high field (-5 ± 20 p.p.m.), relative to C_6F_6 as indicated in TABLE 23. Considering octafluoro-4,4'-bipyridyl to be a 4-substituted-

tetrafluoropyridine, two chemically shifted peaks, one to low field and one to high field would be expected. The n.m.r. spectrum of octafluoro-4,4'-bipyridyl consists of two chemically shifted peaks, -72·3 and -23·7 p.p.m. downfield of C_6F_6, and because of the very large difference in the values of the chemical shifts and their close comparison with the values obtained for the α and β fluorines in polyfluoropyridines, they can be assigned to the 2,6 and 3,5 fluorines respectively in octafluoro-4,4'-bipyridyl.

Further confirmation of the sturcture of octafluoro-4,4'-bipyridyl is obtained by comparison with decafluorobiphenyl. (This comparison is more important in determining the values of the chemical-shifts in octafluoro-3,3'-, and 2,2'-bipyridyls.) Decafluorobiphenyl can be considered as a mono-substituted pentafluorophenyl derivative. To a first approximation the effect of the C_6F_5 group in decafluorobiphenyl on the chemical shifts of the ortho and meta fluorines will be of the same order as the effect of a C_5F_4N group in octafluoro-4,4'-bipyridyl on the respective fluorine atoms. From TABLE 23, it can be seen that a C_6F_5 group shifts the chemical shifts due to the ortho and meta fluorines in decafluorobiphenyl downfield by -24 and -1·5 p.p.m. respectively (ref. K), relative to hexafluorobenzene. Thus, in octafluoro-4,4'-bipyridyl the ortho and meta fluorine chemical shifts will be equivalent to the chemical shifts due to the 3 and 2 fluorines in pentafluoropyridine moved downfield by -24 and -1·5 p.p.m. respectively.

Pentafluoropyridine (ref. A, TABLE 23) has three non-equivalent fluorines, and the chemical shifts due to the 3 and 2 fluorines are -0·3 and -74·7 p.p.m. respectively. Hence, the chemical shifts due to the 3 and 2 fluorines is octafluoro-4,4'-bipyridyl will have the calculated values of:

i) -0·3 + -24 = -24·3 p.p.m. (3 fluorine)

ii) -74·7 + -1·5 = -76·2 p.p.m. (2 fluorine)

relative to hexafluorobenzene.

The measured values of the chemical shifts are -23·7 and -72·3 p.p.m. and have been assigned to the 3 and 2 fluorine atoms respectively as these measured values agree closely to the calculated values.

Confirmation of Orientation of 2-Methoxyheptafluoro-4,4'-bipyridyl.

From an examination of the structural formula, the Fluorine-19 n.m.r. spectrum of 2-methoxyheptafluoro-4,4'-bipyridyl would be expected to consist of five different chemically shifted peaks of different intensity. The chemical shifts due to the fluorine atoms at positions 2' and 6', will have the same values as both fluorine atoms are magnetically equivalent. Similarly the chemical shifts due to the fluorine atoms at 3' and 5' will be the same. The chemical shifts due to the fluorine atoms at positions 3, 5 and 6 are non-equivalent, and will be only half the intensity of the chemical shifts due to the pairs of fluorine atoms in the other ring. It is assumed that the effect of a substituent group in one ring does not effect

the values of the chemical shifts due to the fluorine atoms in the other ring. Thus, the values of the chemical shifts due to the fluorine atoms at positions 2', 6' and 3', 5' will be equivalent to the values for the same fluorine atoms in octafluoro-4,4'-bipyridyl, i.e. -72·3 and -23·7 p.p.m. respectively. From TABLE 23, a methoxy group shifts the value of the chemical shift due to an ortho fluorine upfield by +2 p.p.m., a meta fluorine (across nitrogen) upfield by +3 p.p.m., and a para fluorine upfield by +9 p.p.m. (ref. D). By application of these shifts in 2-methoxyheptafluoro-4,4'-bipyridyl, the chemical shifts due to the 3, 5 and 6 fluorine atoms can be calculated;

i) -23·7 + +2 = -21·7 p.p.m. (3 fluorine)

ii) -23·7 + +9 = -14·7 p.p.m. (5 fluorine)

iii) -72·3 + +3 = -69·3 p.p.m. (6 fluorine)

relative to C_6F_6.

The measured values of the chemical shifts due to the fluorine atoms in 2-methoxyheptafluoro-4,4'-bipyridyl are: -74·2 (intensity 2); -71·2 (intensity 1); -24·7 (intensity 1); -23·7 (intensity 2); and -13·0 (intensity 1) p.p.m. relative to C_6F_6. The peaks of double intensity can unambiguously be assigned to the fluorine atoms 2',6' (-74·2 p.p.m.) and 3',5' (-23·7 p.p.m.) as they are in agreement with the calculated values and also by comparison with pentafluoropyridine. Comparison of the calculated values of the chemical shifts due to the fluorine atoms at positions 3,5 and 6 and the measured shifts allow only one possible assignment i.e., -71·2 (6 fluorine);

-24.7 (3 fluorine) and -13.0 (5 fluorine). Thus the n.m.r. spectrum of the compound is in agreement with the substituent entering the position ortho to the nitrogen i.e. 2-methoxyheptafluoro-4,4'-bipyridyl.

This method of approach has been used to elucidate the structures of the compounds listed in TABLES 24 and 25.

TABLE 23

Fluorine-19 Chemical Shifts in Derivatives of Pentafluoropyridine

(position of the fluorine atom in parentheses)

	Compound	Chemical shift from hexafluorobenzene (p.p.m.) (+ve shifts are measured to higher field)	Effect on fluorine-19 shifts				
			Group (position in parentheses)	ortho	meta	para	Ref. Compound
A	Pentafluoropyridine	-74·7(2,6); -0·3(3,5); -28·1(4)					
B	4-Aminotetrafluoro-pyridine	-67·0(2,6); -1·2(3,5)	$NH_2(4)$	-1	+8	-	A
C	4-Methoxytetrafluoro-pyridine	-70·0(2,6); -1·2(3,5)	$OCH_3(4)$	-1	+5	-	A
D	6-Methoxytetrafluoro-pyridine	-71·5(2); 1·7(5); 9·0(3); -22·0(4)	$OCH_3(6)$	+2	(+6) (+3)	+9	A
E	4-methyltetrafluoro-pyridine	-69·8(2,6); -18·3(3,5)	$CH_3(4)$	-18	+5	-	A
F	4-Isopropoxytetrafluoro-pyridine	-71·3(2,6); -4·5(3,5)	C_3H_7Oiso(4)	-4	+3	-	A
G	3-Chlorotetrafluoropyr-idine	-90·2(2); -48·0(4); 1·6(5); -76·6(6)	Cl(3)	(-16) (-20)	+2	-2	A
H	3,5-Dichlorotri-fluoropyridine	-92·4(2,6); -68·1(4)	Cl(3,5)	(-20) (-16)	-	-2	G
I	4-Chlorotetrafluoro-pyridine	-73·7(2,6); -20·1(3,5)	Cl(4)	-20	+1	-	A
J	2,4-Diaminotrifluoro-pyridine	-65·8(6); 1·9(3) 13·0(5)	$NH_2(2)$	+3	+1	+12	B
K	Decafluorobiphenyl	-24·03(0); -1·52(m); -12·01(p)	C_6F_5	-24	-1·5	-12	C_6F_6

TABLE 24

Fluorine-19 Chemical Shifts in Derivatives of Octafluorobipyridyls. (position of the fluorine atom in parentheses)

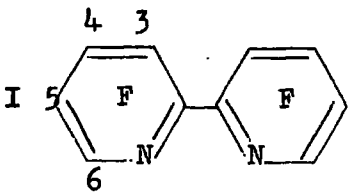
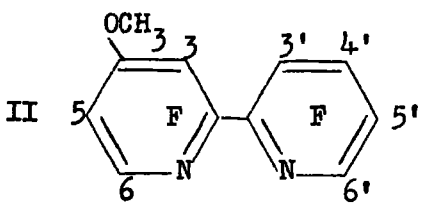
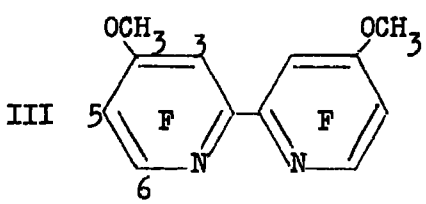
Compound (intensity ratio of peaks in parentheses in order of increasing value of the chemical shift from low to high field)	Chemical shift from hexafluorobenzene (p.p.m.) (+ve shifts are measured to higher field)			Reference Compound(s) (incorporating Table 20)
	Measured		Calculated	
I  (1:1:1:1)	-20·9	(3)	-24	K; A
	-25·4	(4)	-30	
	- 9·1	(5)	-12	
	-81·2	(6)	-76	
II  (1:1:2:1:1:1)	-23·8	(3)	-23	I; C
	- 7·4	(5)	-10	
	-76·6	(6)	-76	
	-20·3	(3')	-21	
	-23·8	(4')	-25	
	- 9·7	(5')	-9	
	-79·7	(6')	-81	
III  (1:1:1)	-23·2	(3)	-24	II
	- 8·4	(5)	-7	
	-76·1	(6)	-77	

TABLE 24 (Cont.)

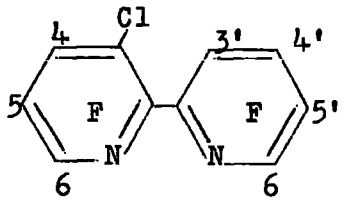
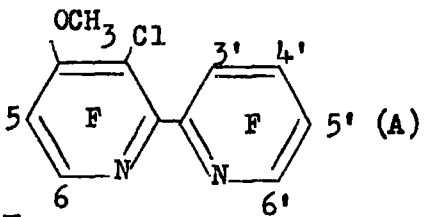
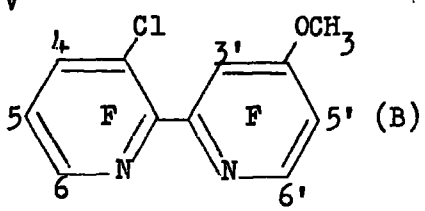
Compound		Chemical shift from hexafluorobenzene (p.p.m.)			Reference Compound(s)
		Measured		Calculated	
IV 		-46·1	(4)	-44	
		-6·0	(5)	-7	
		-80·9	(6)	-83	
		-21·8	(3')	-21	G; I
		-24·9	(4')	-25	
(2:1:1:1:1:1)		- 8·6	(5')	-9	
		-80·8	(6')	-81	
V 	(A)	- 4·3	(5)	-7	
		-75·6	(6)	-76	
		-19·4	(3')	-21	
	(A)	-22·8	(4')	-25	I; IV; C
		- 5·3	(5')	-9	
		-78·4	(6')	-81	
	(B)				
isomers in ratio 2:1(A to B)		-44·0	(4)	-46	
(3:2:1:1:3:2:1:4:1)		- 3·3	(5)	-6	
		-78·4	(6)	-81	
	(B)	-22·6	(3')	-22	IV; I; C
		-7·1	(5')	-10	
		-74·8	(6')	-76	

TABLE 24 (cont.)

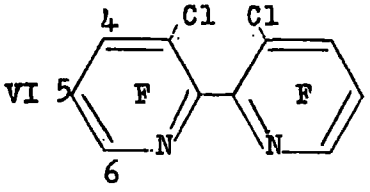
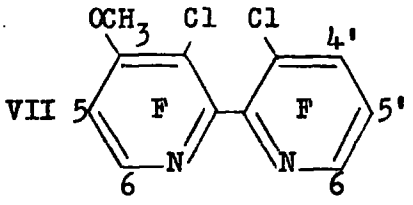
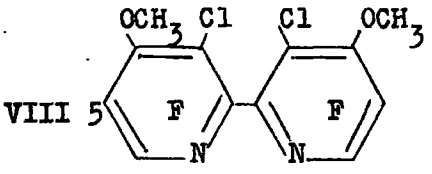
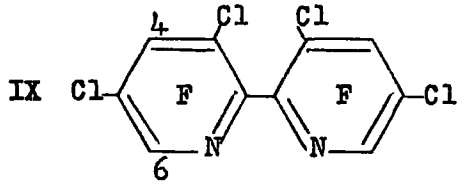
Compound	Chemical shift from hexafluorobenzene (p.p.m.) Measured		Calculated	Reference Compound(s)
VI  (1:1:1)	-45·8	(4)	-46	
	- 5·6	(5)	-6	IV
	-81·4	(6)	-81	
VII  (1:1:1:1:1:1)	-6·1	(5)	-7	
	-77·1	(6)	-76	
	-44·8	(4')	-46	VI; C
	-4·4	(5')	-6	
	-80·3	(6')	-81	
VIII  (1:1)	- 5·2	(5)	-6	VII
	-76·8	(6)	-77	
IX  (1:1)	-66·7	(4)	-65	I; H
	-95·6	(6)	-98	

TABLE 24 (cont.)

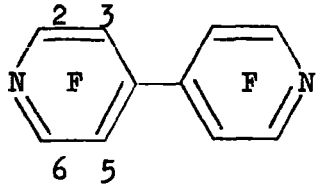
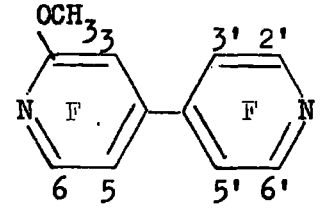
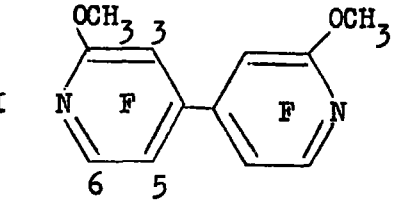
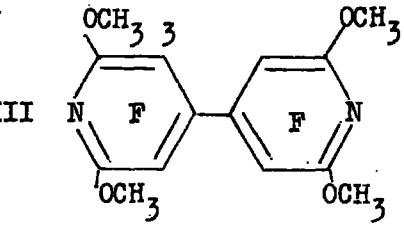
Compound	Chemical shift from hexafluorobenzene (p.p.m.) Measured		Calculated	Reference Compound(s)
X  (1:1)	-72·3	(2,6)	-76	K; A
	-23·7	(3,5)	-24	
XI  (2:1:1:2:1)	-24·7	(3)	-22	X; C; D
	-13·0	(5)	-15	
	-71·2	(6)	-69	
	-74·2	(2', 6')	-72	
	-23·7	(3', 5')	-24	
XII  (1:1:1)	-24·1	(3)	-25	XI
	-13·0	(5)	-13	
	-70·2	(6)	-71	
XIII  (1)	-6·8	(3)	-15	XII; D

TABLE 24 (cont.)

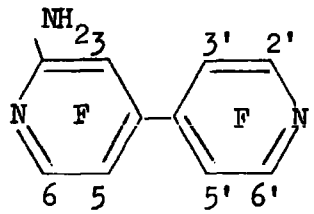
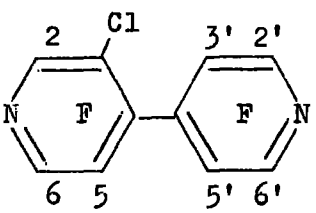
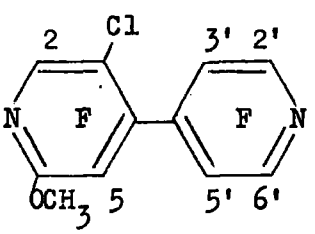
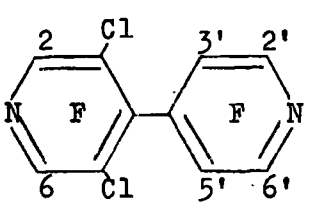
Compound	Chemical shift from hexafluorobenzene (p.p.m.) Measured		Calculated	Reference Compound(s)
XIV  (2:1:2:1:1)	-21·9	(3)	-25	X; B; J; A
	- 5·9	(5)	-14	
	-71·3	(6)	-65	
	-23·7	(3',5')	-24	
	-73·4	(2',6')	-72	
XV  (1:1:2:1:2)	-91·9	(2)	-92	X; I; G
	-24·2	(5)	-23	
	-77·1	(6)	-74	
	-23·8	(3',5')	-24	
	-74·9	(2',6')	-72	
XVI  (1:2:1:2)	-89·0	(2)	-89	XV; C; D
	-24·9	(5)	-25	
	-24·0	(3',5')	-24	
	-74·2	(2',6')	-75	
XVII  (1:1:1)	-94·5	(2,6)	-94	X; XV; G
	-23·5	(3',5')	-24	
	-78·4	(2',6')	-72	

TABLE 24 (cont.)

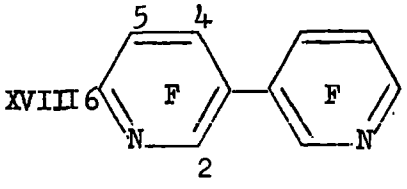
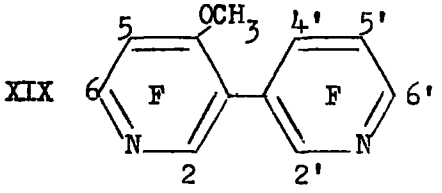
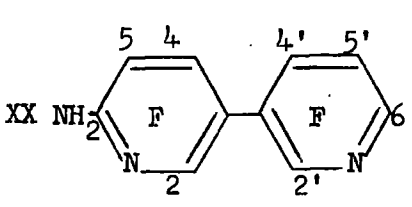
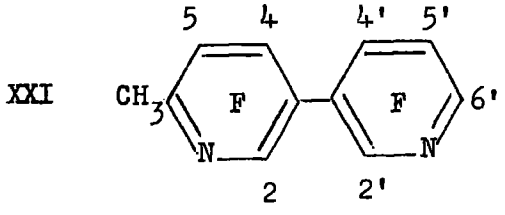
Compound	Chemical shift from hexafluorobenzene (p.p.m.) Measured		Calculated	Reference Compound(s)
XVIII  (1:1:1:1)	-94·4	(2)	-99	K; A
	-52·2	(4)	-52	
	-1·7	(5)	-2	
	-86·6	(6)	-87	
XIX  (1:1:1:1:1:1:1)	-88·6	(2)	-89	XVIII; C
	-2·4	(5)	-3	
	-82·0	(6)	-81	
	-92·3	(2')	-94	
	-49·5	(4')	-52	
	-3·4	(5')	-2	
	-82·9	(6')	-87	
XX  (1:1:1:1:1:1:1)	-86·3	(2)	-86	XVIII; B
	-40·4	(4)	-44	
	- 2·4	(5)	-3	
	-94·3	(2')	-94	
	-49·5	(4')	-52	
	+2·4	(5')	-2	
	-82·0	(6')	-87	
XXI  (2:1:1:1:1:1)	-95·6	(2)	-89	XVIII, E
	-43·4	(4)	-47	
	-11·2	(5)	-20	
	-95·6	(2')	-94	
	-50·7	(4')	-52	
	+ 3·12	(5')	-2	
	-81·3	(6')	-87	

TABLE 24 (Cont.)

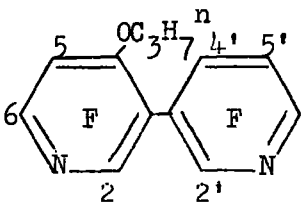
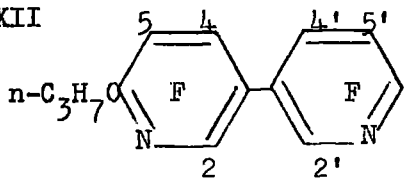
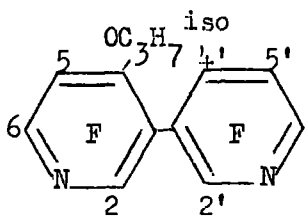
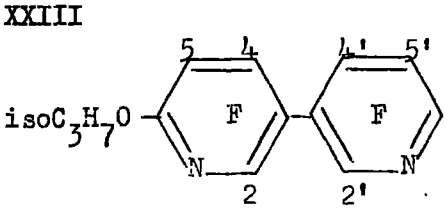
Compound		Chemical shift from hexafluorobenzene (p.p.m.) Measured		Calculated	Reference Compound(s)
	6'(A)	-90·8	(2)	-91	
		+ 4·3	(5)	-6	
		-78·2	(6)	-84	
XXII 	(A)	-95·0	(2')	-94	XVIII; F
		-50·8	(4')	-52	
	6'(B)	+ 0·8	(5')	-2	
		-80·0	(6')	-87	
isomers in ratio 4:1 (A to B) (5:1:4:5:4:5:1:5:4:1)		-92·8	(2)	-91	
	(B)	-42·5	(4)	-49	
		- 5·3	(5)	-6	
		-95·0	(2')	-94	XVIII; F
		-50·8	(4')	-52	
		+ 0·8	(5')	-2	
		-80·0	(6')	-87	
		-89·3	(2)	-91	
	6'(A)	+ 2·6	(5)	-6	
		-76·6	(6)	-84	
	(A)	-93·1	(2')	-94	XVIII; F
XXIII 		-48·8	(4')	-52	
		+ 5·7	(5')	-2	
	6'(B)	-78·7	(6')	-87	
		-91·0	(2)	-91	
isomers in ratio 2:3 (A to B) (5:3:2:3:2:5:3:2:5:3)		-40·5	(4)	-49	
		+ 6·23	(5)	-6	XVIII; F
	(B)	-93·1	(2')	-94	
		-48·8	(4')	-52	
		+ 5·7	(5')	-2	
		-78·7	(6')	-87	

TABLE 24 (Cont.)

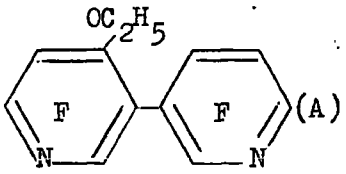
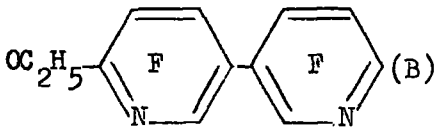
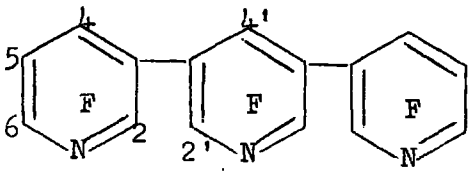
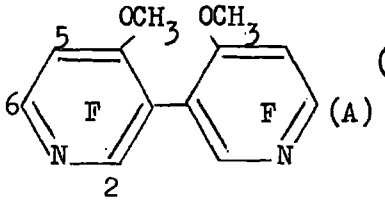
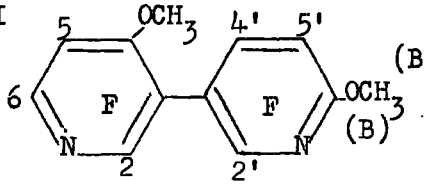
Compound	Chemical shift from hexafluorobenzene (p.p.m.) Measured		Calculated	Reference Compound(s)
 (A)				
XXIV				
 (B)				
isomers in ratio (17:3) (A to B)				
10 peaks of different intensity.				
Characteristic of spectrum obtained from XXII and XXIII.				
Due to low intensity of spectrum; the chemical shifts were not able to be measured accurately.				
XXV 	-94·0	(2)	-94	
	-44·0	(4)	-52	
	+ 3·0	(5)	-2	XVIII, K
	-82·5	(6)	-86	
	-66·3	(4')	-76	
(2:2:2:1:2:2)	-100·9	(2')	-106	
 (A)	- 89·5	(2)	-89	
	(A)- 76·2	(6)	-82	XIX
	+ 2·1	(5)	-3·4	
XXVI  (B)	- 89·5	(2)	-89	
	(B)-76·2	(6)	-82	XIX; XVIII; D
	+ 2·1	(5)	-3·4	
	-91·5	(2')	-91	
	-42·3	(4')	-46	
mixture of isomers ratio 1:1 (A to B) (1:3:3:1:3:1)	+ 9·4	(5')	+0·3	

TABLE 24 (Cont.)

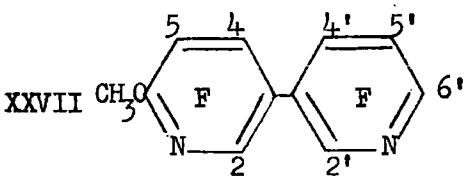
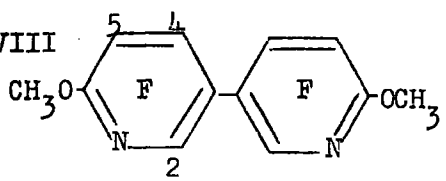
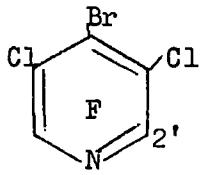
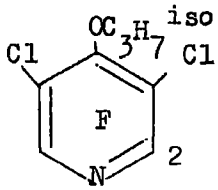
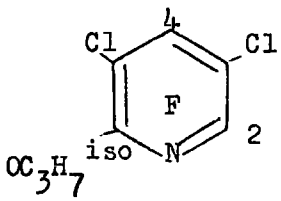
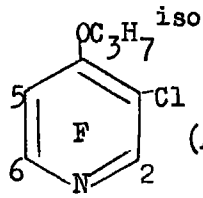
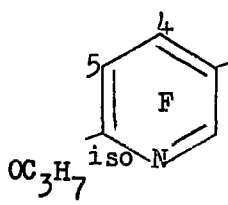
Compound	Chemical shift from hexafluorobenzene (p.p.m.)			Reference Compound(s)
	Measured		Calculated	
XXVII  (1:1:1:1:1:1:1)	-93·1	(2)	-91	D; XVII
	-43·0	(4)	-46	
	+ 5·2	(5)	0	
	-94·5	(2')	-94	
	-50·7	(4')	-52	
	+ 3·2	(5')	-2	
	-80·5	(6')	-87	
XXVIII  (1:1:1)	-91·7	(2)	-93	XXVII
	-42·8	(4)	-43	
	- 6·8	(5)	+5	

TABLE 25

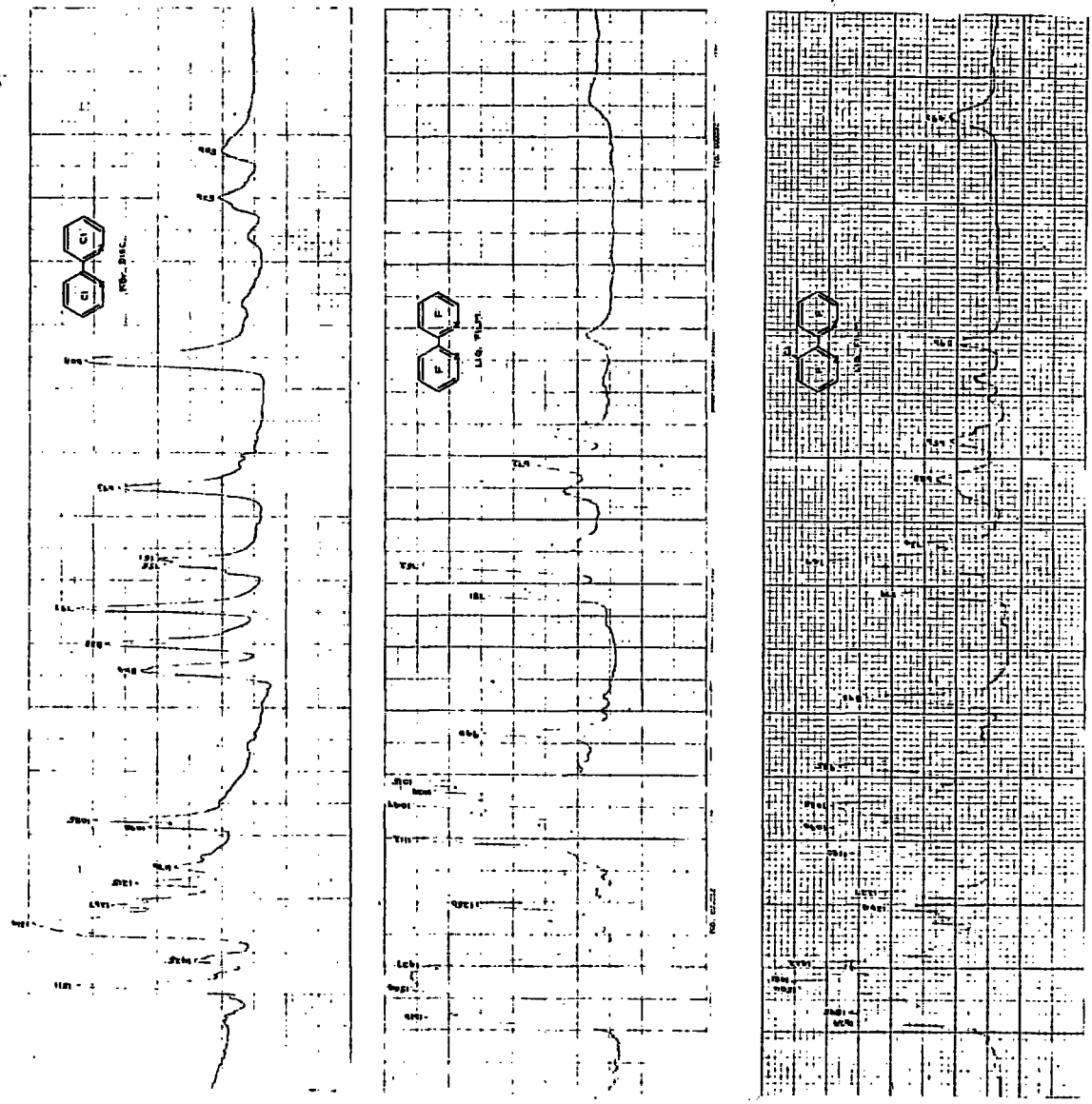
Fluorine-19 Chemical Shifts in Derivatives of Polyfluoropyridines

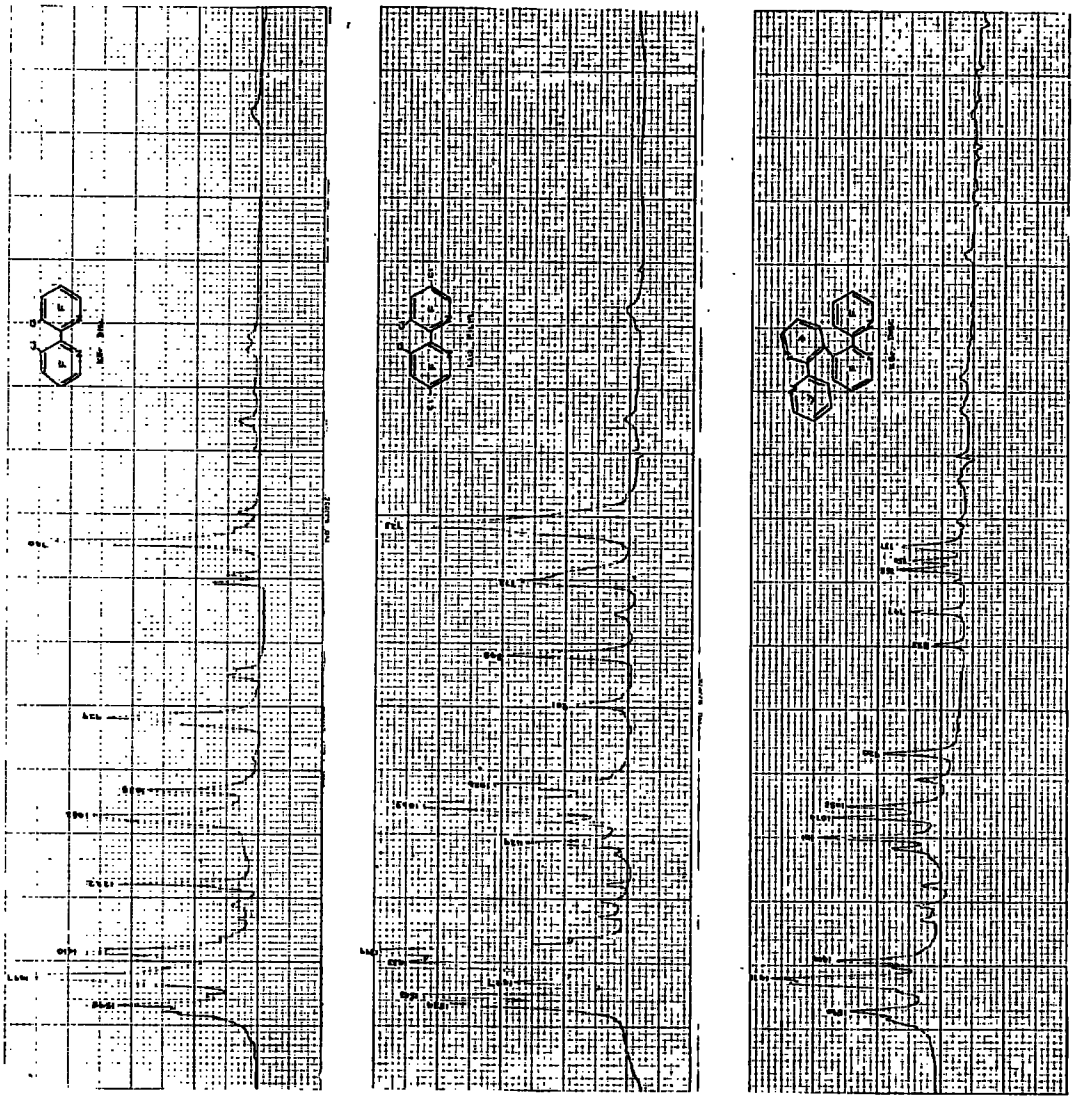
(position of the fluorine atom in parentheses)

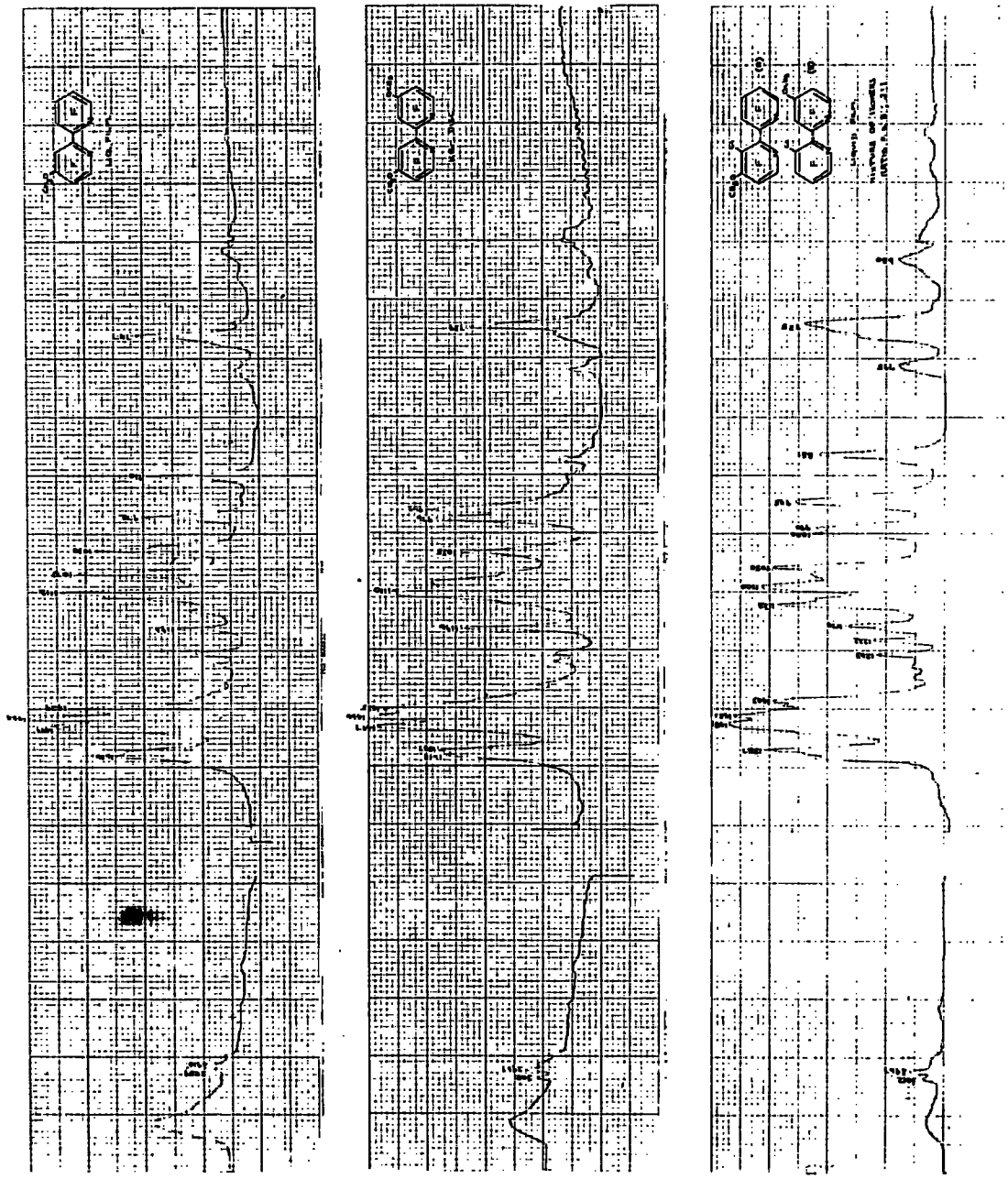
Compound (intensity ratio of peaks in parentheses)	Chemical shift from hexafluorobenzene (+ve shifts are measured to higher field	Reference Compound
	-95·1(2)	H
 (A)	-91·1(2)	H; F
 (B)	-90·3(2); -63·59(4)	H; F
isomers in ratio 87:13 (A to B) (6·5 : 1)		
 (A)	-88·2(2); -3·0(5); -73·3(6)	G; F
 (B)	-88·2(2); -41·0(4); +1·8(5)	G; F
isomers in approx. ratio 5:1 (A to B) (6:5:1:5:1)		

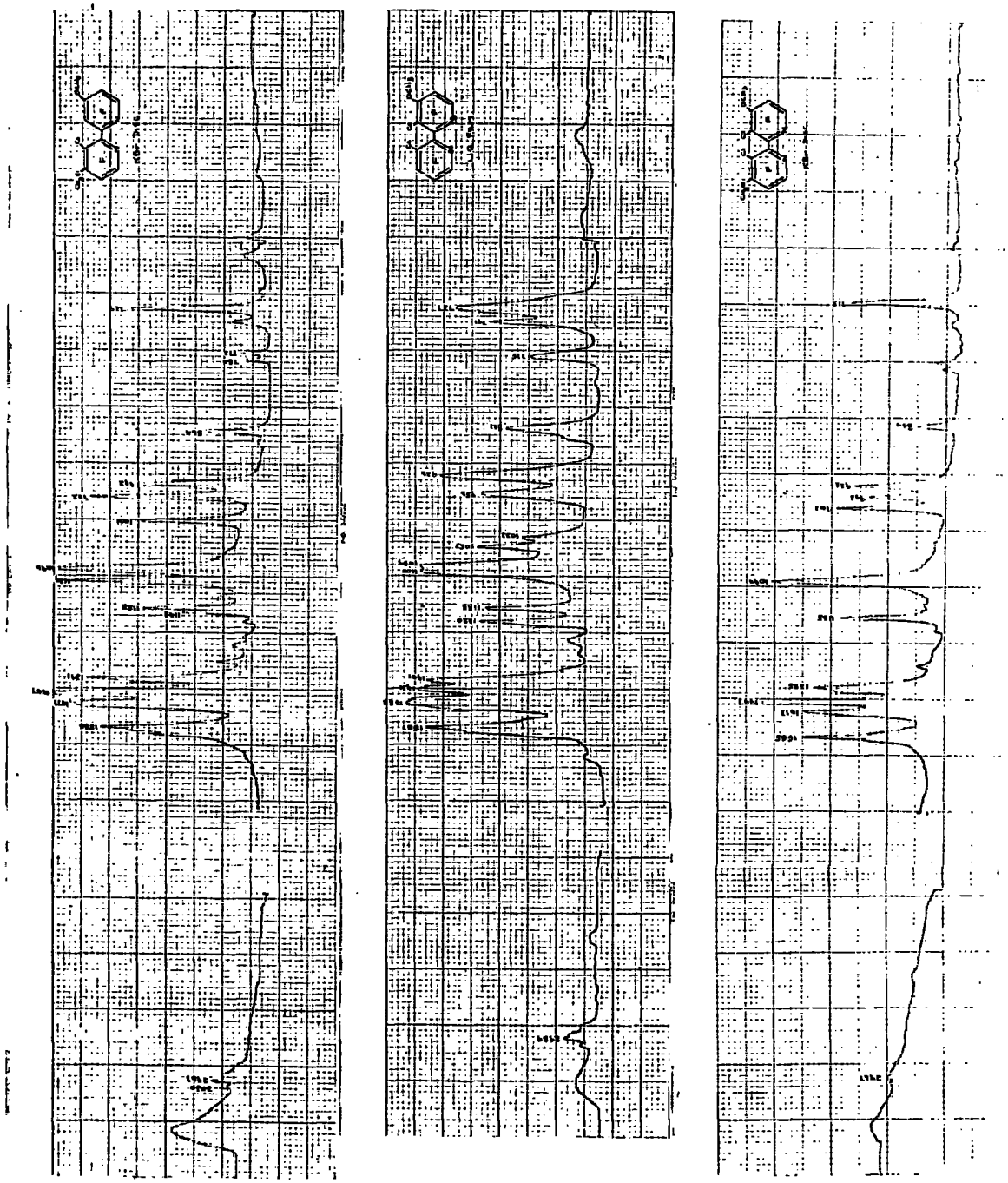
CHAPTER 9

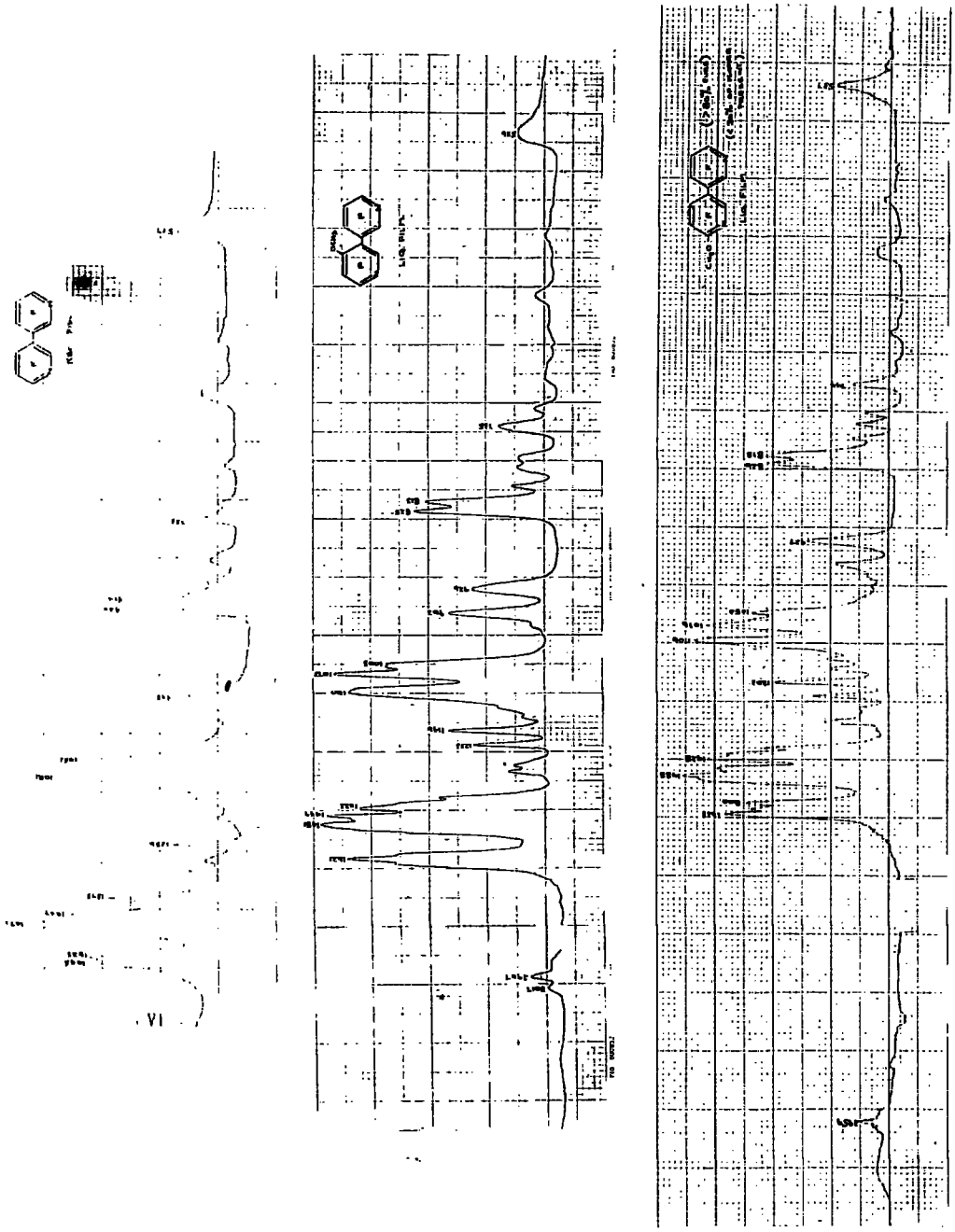
INFRARED SPECTRA

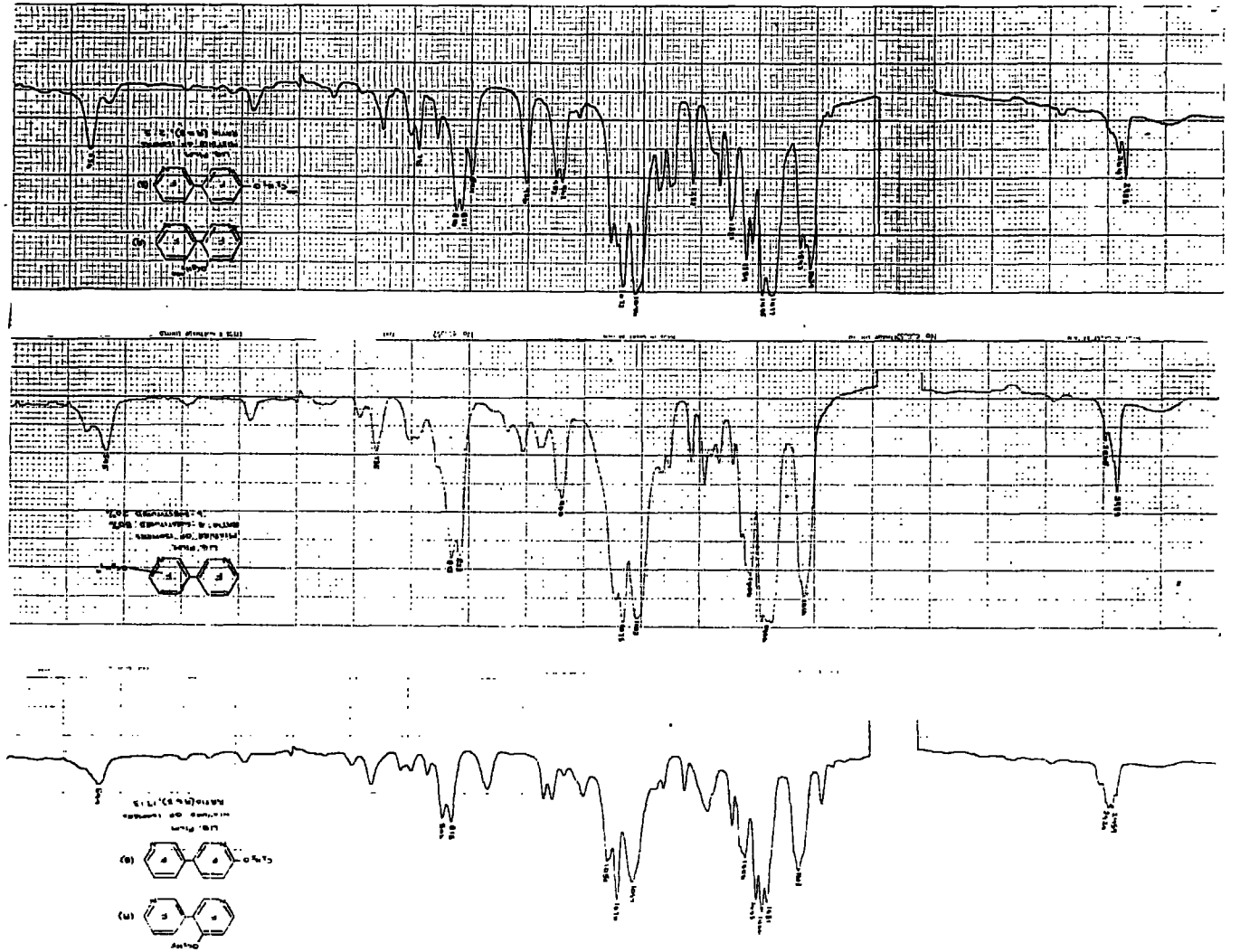


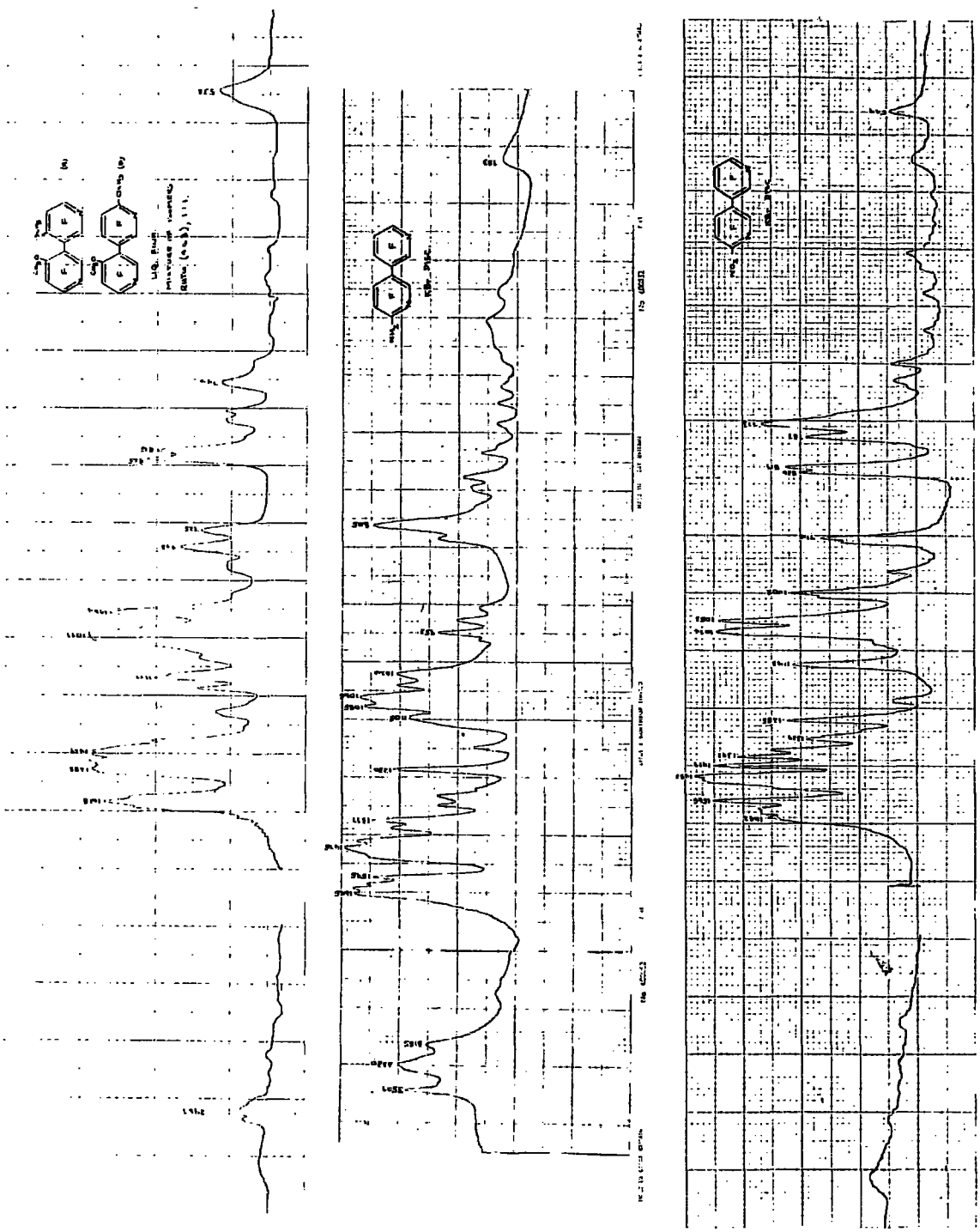


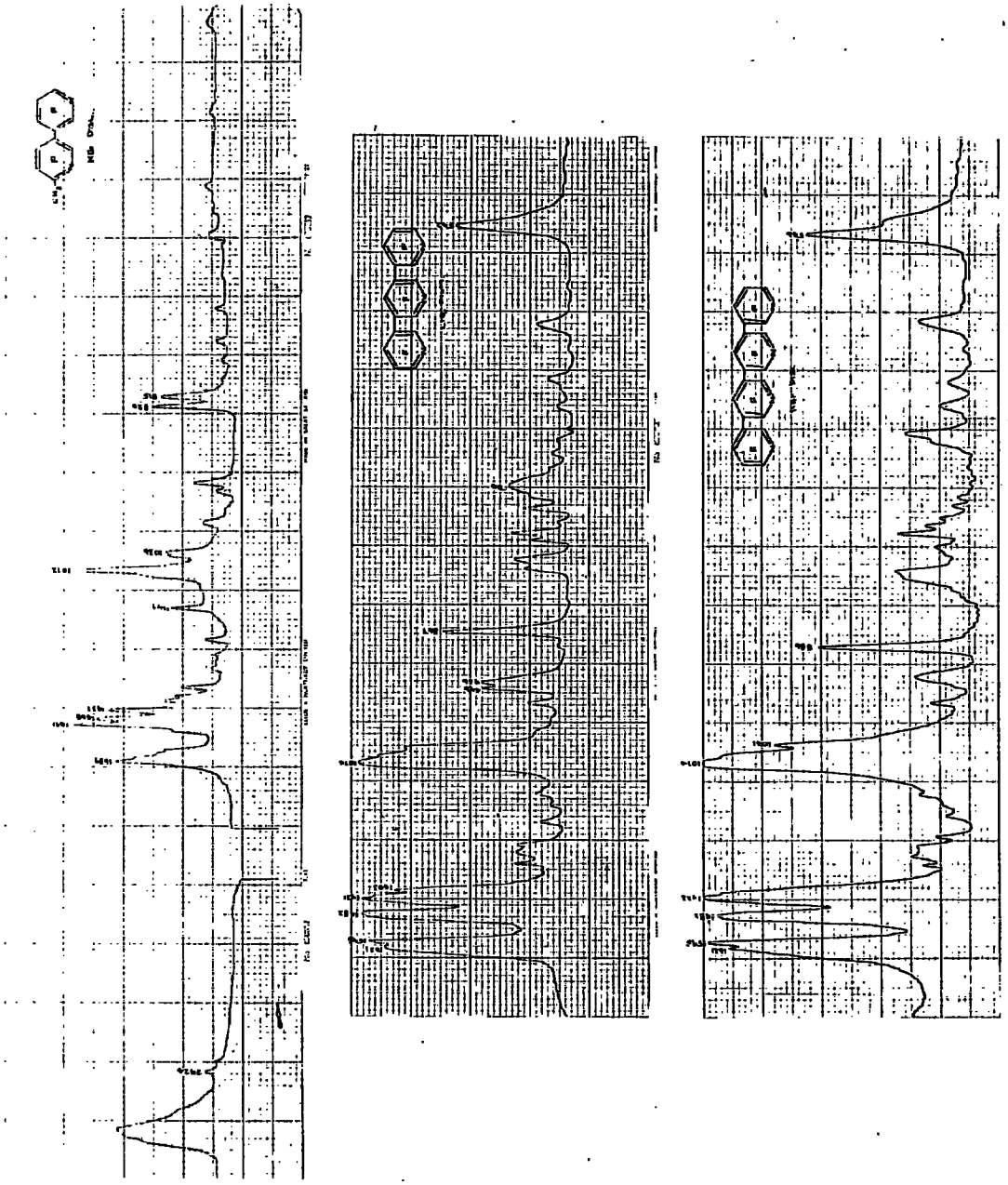


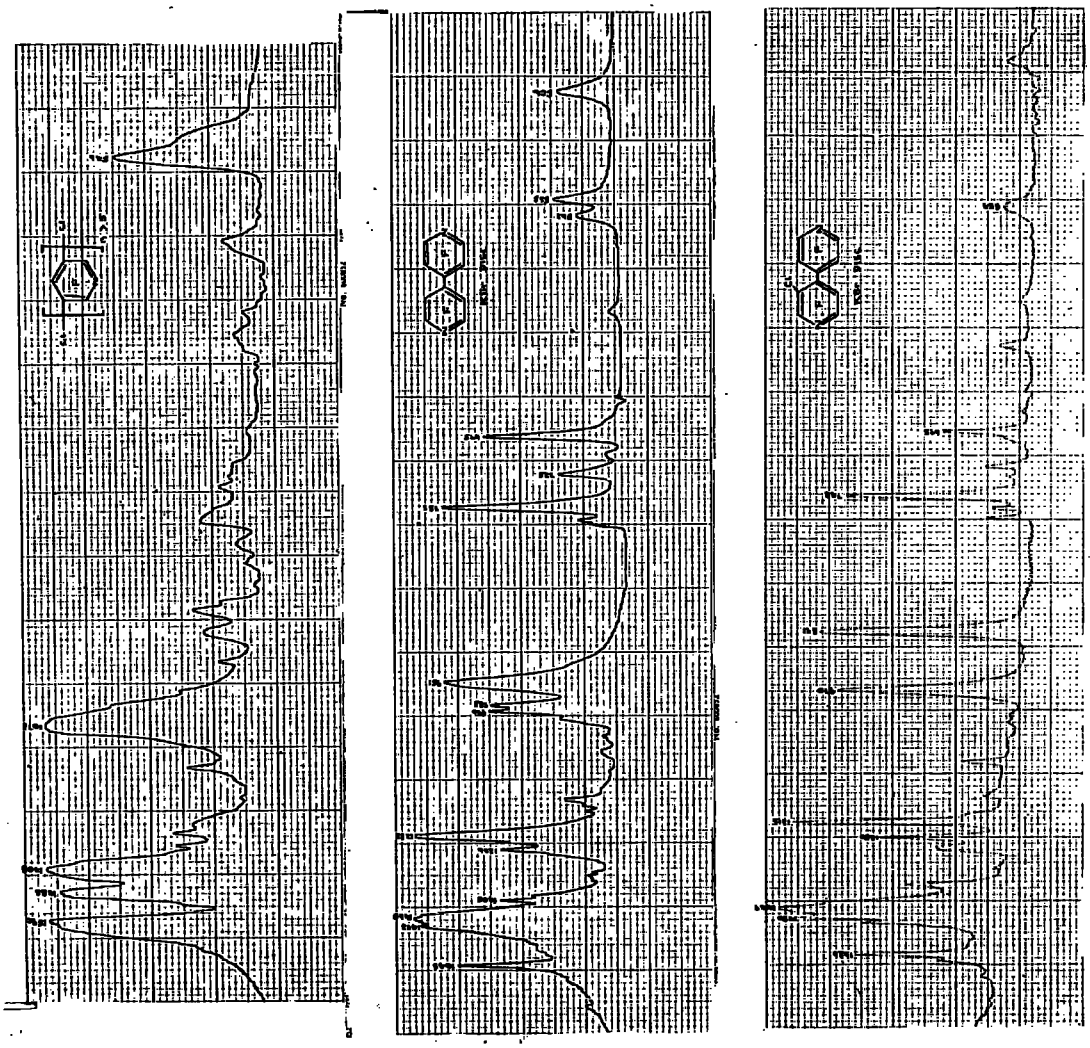


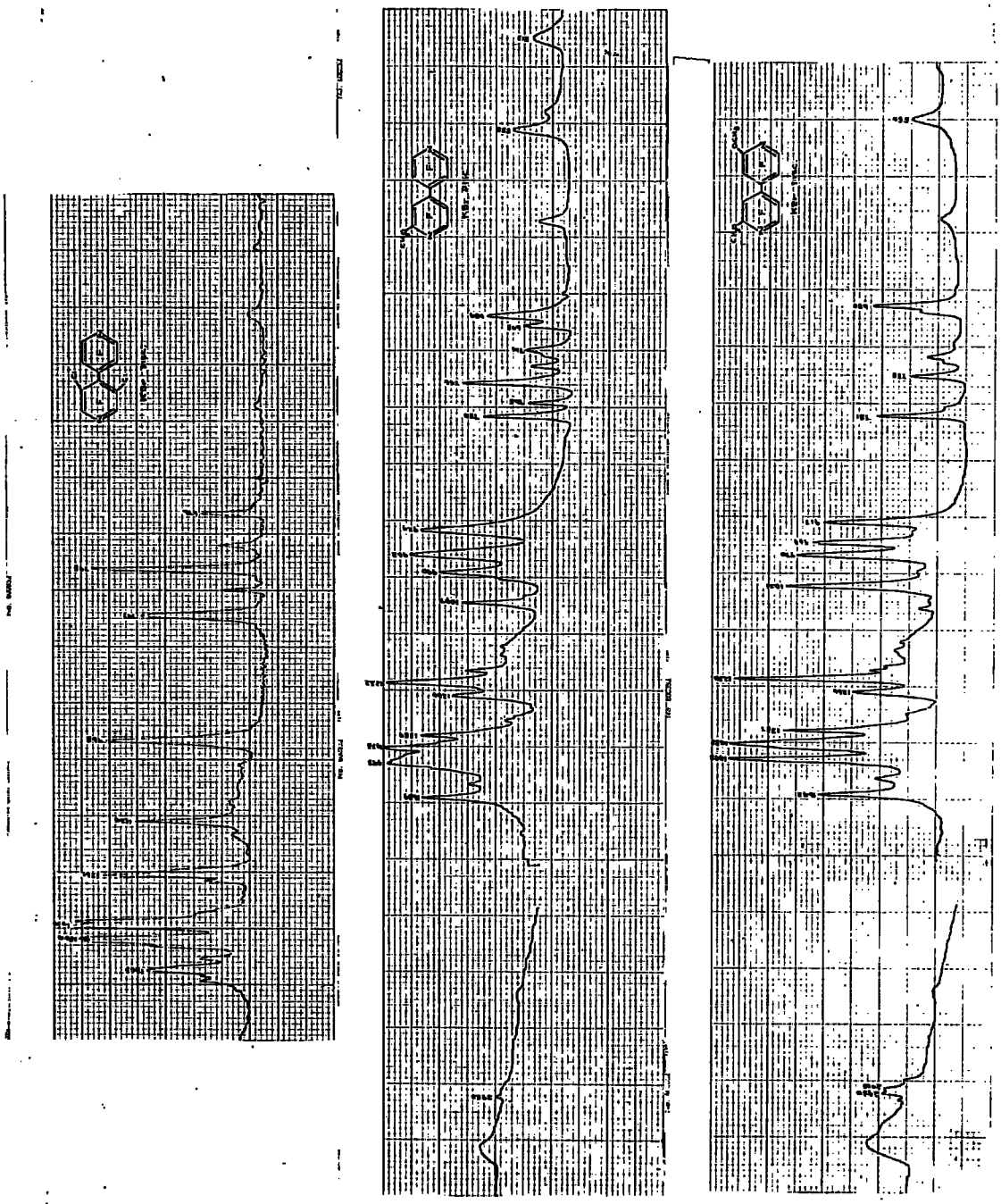


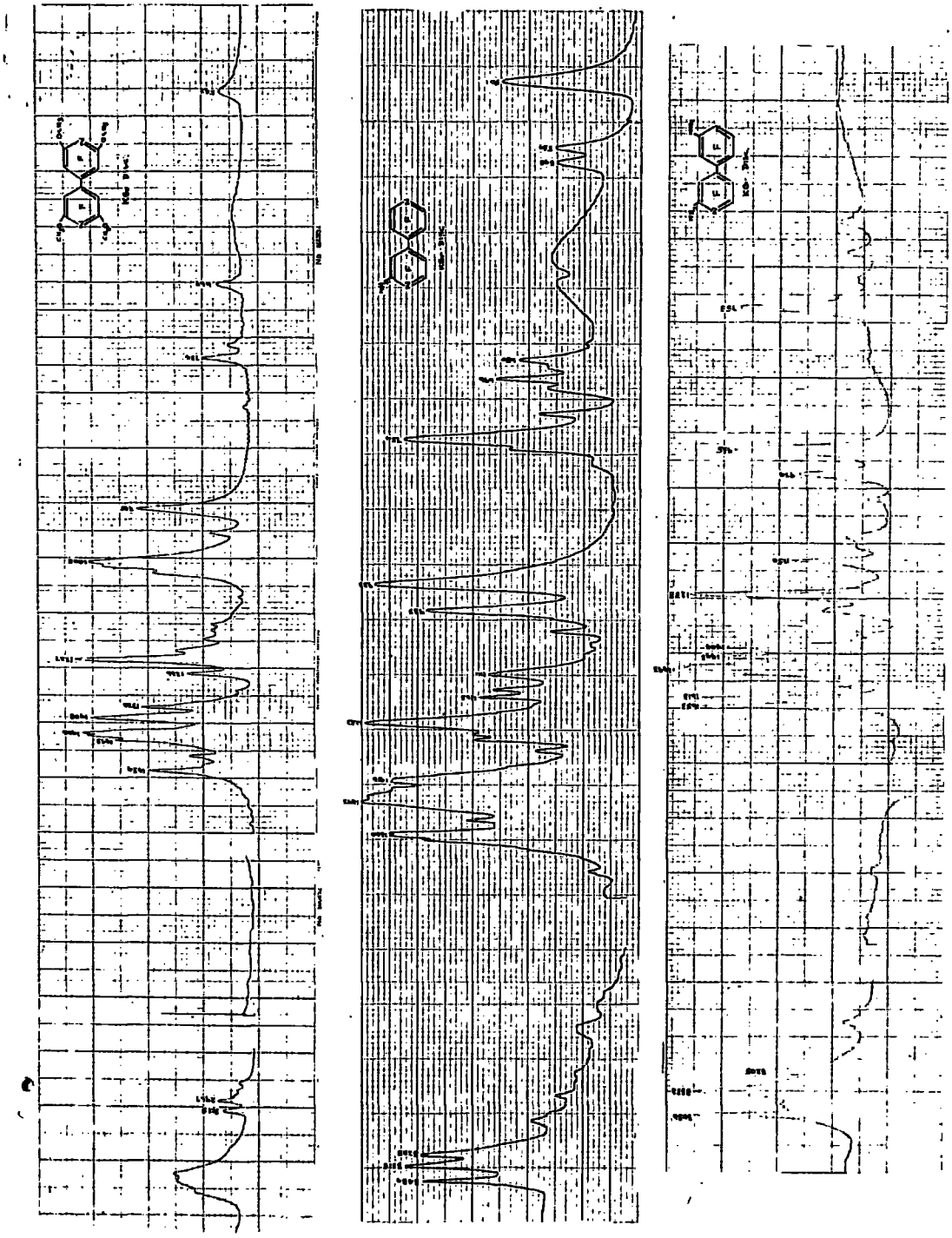


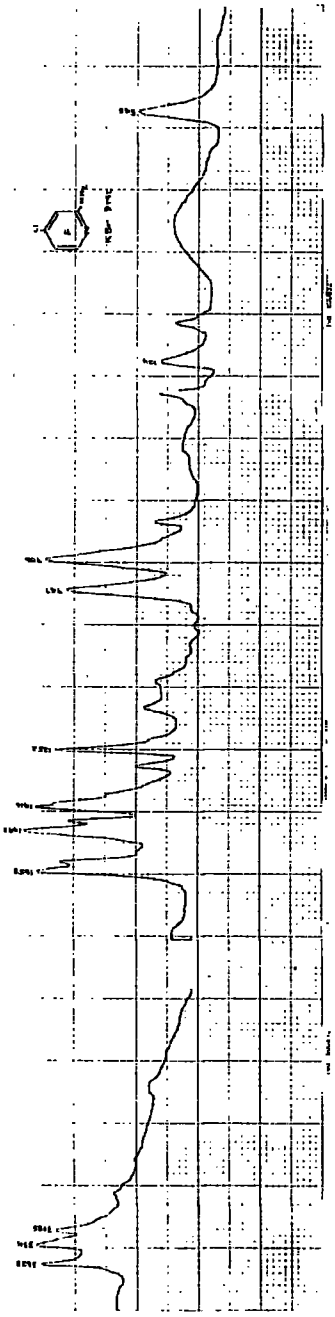


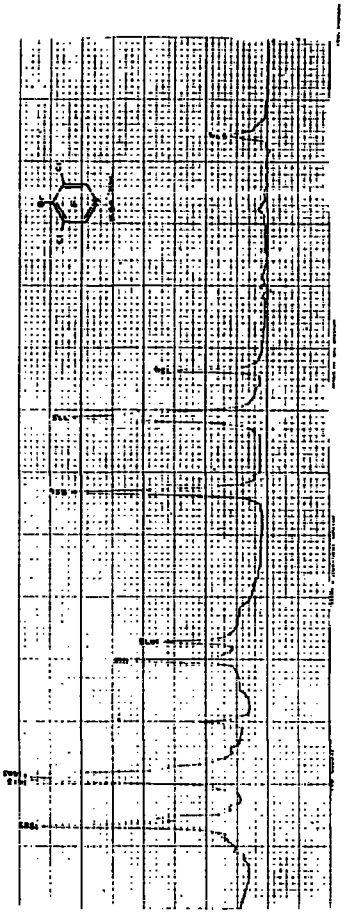


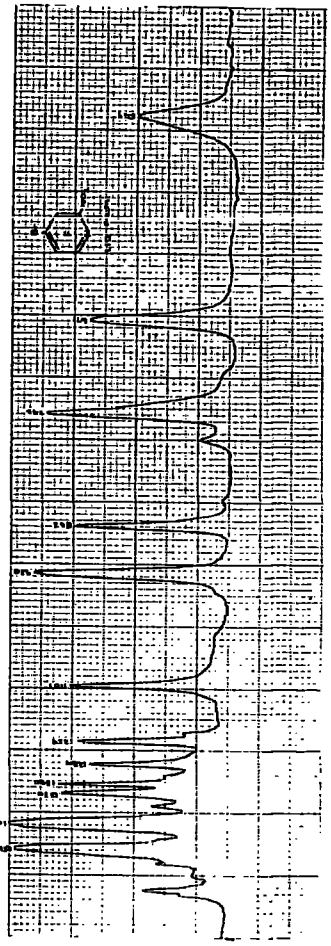












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