The synthesis of highly fluorinated pyridine derivatives

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UNIVERSITY OF DURHAM

A THESIS

entitled

THE SYNTHESIS OF HIGHLY FLUORINATED PYRIDINE DERIVATIVES

submitted by

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To JOY and SIMON

MEMORANDUM

The work described in this thesis was carried out in the University of Durham between January 1965 and August 1967. It has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

SUMMARY

The chlorination of pyridine using chlorine in the presence of antimony trichloride at elevated temperature has been shown to give quite good yields of a mixture of di-, tri- and tetra-chloropyridines. This mixture was readily converted into pentachloropyridine on heating to 300° with excess phosphorus pentachloride in a stainless steel autoclave. Halogen exchange between pentachloropyridine and anhydrous potassium fluoride at 480° gave pentafluoropyridine.

A number of possible methods of reducing 3-chlorotetrafluoropyridine to 2,4,5,6-tetrafluoropyridine have been investigated. 3-Lithiotetrafluoropyridine (obtained by reacting 2,4,5,6-tetrafluoropyridine with n-butyl lithium in ether at -65°) reacted with N-methylformanilide to give tetrafluoropyridine-3-aldehyde.

2,4,6-Trifluoronicotinic acid was reacted with phosphorus pentachloride to give 2,4,6-trifluoronicotinyl chloride which gave a mixture of 2,4,6-trifluoronicotinamide and 4-amino-2,6-difluoronicotinamide by reaction with ammonia. Reaction of the acid with thionyl chloride appeared to give 2,4,6-trifluoronicotinic anhydride. This gave 4-amino-2,6-difluoronicotinamide with ammonia.

A number of 4-substituted tetrafluoropyridine derivatives have been prepared starting from tetrafluoroisonicotinic acid. These include tetrafluoroisonicotinyl chloride and fluoride, tetrafluoroisonicotinic anhydride and amide, ethyl and methyl tetrafluoroisonicotinate, N,N'-bis(tetrafluoroisonicotinyl)hydrazine, 2,5-bis(tetrafluoro-4-pyridyl)-

1,3,4-oxadiazole and thiadiazole and perfluoro(4-pyridyl isopropyl)-ketone. Some perfluoro-aromatic secondary amides and hydrazides have been prepared from tetrafluoroisonicotinyl and pentafluorobenzoyl chlorides. The latter was fluorinated to give pentafluorobenzoyl fluoride which was converted into perfluoro-(phenyl isopropyl) and perfluoro(4-isopropylphenyl isopropyl)ketones.

Tetrafluoropyridine-4-aldehyde has been prepared by a new, better method. It has been used to synthesise tetrafluoro-4-pyridyl carbinol, β-(tetrafluoro-4-pyridyl)acrylic acid, bis(tetrafluoro-4-pyridyl)azine, and (tetrafluoro-4-pyridyl pentafluorophenyl) and bis(tetrafluoro-4-pyridyl)carbinols. The latter two compounds have been oxidised to the corresponding ketones. Tris(tetrafluoro-4-pyridyl)carbinol has been prepared by two methods.

Thermal stability measurements have been carried out on the oxadiazole and the bis(tetrafluoro-4-pyridyl)ketone.

CONTENTS

Part I. The Preparation of Fluorinated Pyridines

Chapter 1. Introduction (Part I)

Part I. The Preparation of Fluorinated Pyridines.

Introduction.

Fluorinated pyridines have usually been prepared by methods which have been discovered and developed on the corresponding benzenoid compounds, major advances in the latter being extended fairly quickly to the former. A good example is the Balz-Schiemann[1] reaction,

$$ArNH_2 + NaNO_2 + HCl \xrightarrow{0^\circ} ArN_2^+ Cl^-$$

$$ArN_2^+ Cl^- + HBF_4 \longrightarrow ArN_2^+ BF_4^- + HCl$$

$$ArN_2^+ BF_4^- \xrightarrow[\text{salt}]{\text{heat dry}} ArF + N_2 + BF_3$$

which was used to prepare fluorobenzene from aniline and then later used for the preparation of 2- and 3-fluoropyridine from 2- and 3-amino-pyridine respectively.[2] Further examples of this close relationship in the development of fluoro-benzene and -pyridine chemistry will be found in the following text.

Mono- and di-fluoropyridines.

2-[3] and 3-[4] fluoropyridine were first prepared by diazotising the corresponding amines in 40% hydrofluoric acid and then decomposing the resulting diazonium salt, the yields being 25 and 22% respectively. 2-Fluoro-5-nitropyridine has also been prepared by this method.[5] Diazotisation of 2-aminopyridine in anhydrous hydrogen fluoride and

decomposition of the diazonium salt "in situ" at 40° gave a 20-22% yield of 2-fluoropyridine.[6]

Bart in 1913[7] isolated the stable benzene diazonium fluoroborate but did not attempt to convert it into fluorobenzene. However Balz and Schiemann later showed that good yields of aromatic fluorides could be obtained by the controlled decomposition of diazonium fluoroborates.[1] The reaction is carried out in two stages; first the preparation and isolation of the dry diazonium fluoroborate and second, the controlled decomposition of this salt to yield an aromatic fluoride plus boron trifluoride and nitrogen.

(1) $ArNH_2 + NaNO_2 + BF_4^- \longrightarrow ArN_2BF_4 + H_2O + OH^-$

(2) $ArN_2BF_4 \xrightarrow{heat} ArF + BF_3 + N_2$

The reaction has been carried out on a wide variety of amines and yields as high as 70% are not uncommon. However when Roe and Hawkins[2] applied the method to the three monoaminopyridines it was not so successful because unlike most aromatic diazonium fluoroborates, which are stable, the pyridine ones were unstable. Some modification of the Schiemann technique was necessary but a 34% yield of 2-fluoropyridine and a 50% yield of 3-fluoropyridine were obtained from the corresponding amines. Attempts to isolate 4-fluoropyridine by similar techniques were unsuccessful. The instability of 4-fluoropyridine is hardly surprising in view of the fact that 4-chloropyridine

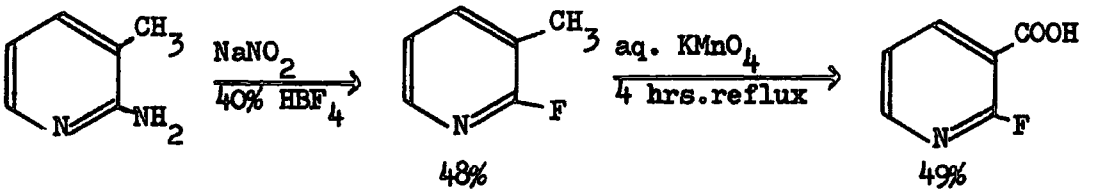
starts to decompose a few hours after its formation and 4-bromopyridine is even less stable. Roe and Hawkings suggest that any 4-fluoropyridine formed reacts with itself to give N-(4'-pyridyl)-4-fluoropyridinium fluoride (I) which is readily hydrolysed to N-(4'-pyridyl)-4-pyridone (II).

I II

A picrate derivative of this ketone was obtained in several of the attempted preparations of 4-fluoropyridine. This is analagous to the reactions of 4-chloro- and 4-bromo-pyridines with themselves, reported by Wibaut and Broekman.[8]

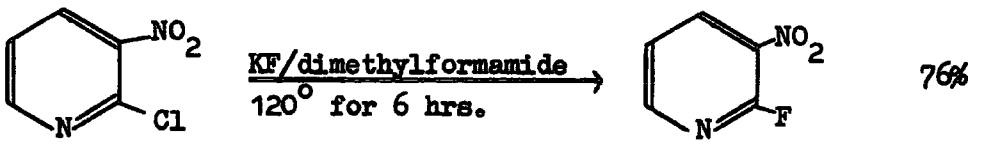
Suschitzky however has isolated pyridine-3-diazonium tetrafluoroborate and has decomposed it to give 3-fluoropyridine in 59% overall yield.[9] The preparation of an impure sample of 4-fluoropyridine by diazotising 4-aminopyridine in hydrogen fluoride and working up the reaction at low temperature has been reported.[10]

Roe and Hawkins have prepared a number of monofluoropicolines, from the corresponding aminopicolines using the Balz-Schiemann technique, which they then oxidised to the corresponding fluoro-acids, e.g.[11,12,13]

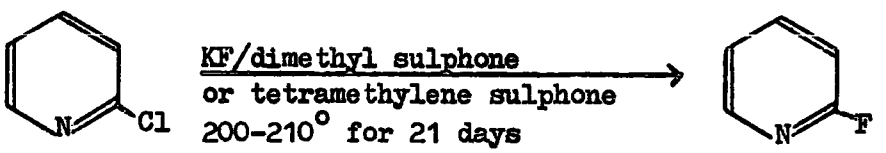


The preparation of fluoro-aromatics using diazonium salts of acids other than fluoroboric or hydrofluoric has been carried out. Acids used were phosphoric and fluorosilicic but the yields were poor although Beaty and Musgrave[6] prepared 2- and 3-fluoropyridine in ~ 40% yield via the diazonium fluorosilicate.

Finger and Starr prepared some 2-fluoronitropyridines by halogen exchange using anhydrous potassium fluoride in dimethylformamide.



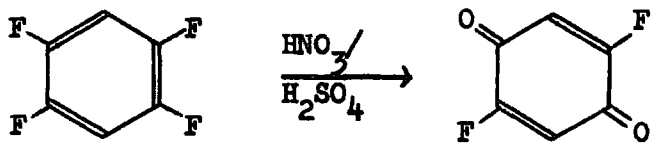
Under these conditions activation of the chlorine atom by a nitro- or bromo-group was necessary since 2-chloropyridine failed to react.[14] However, successful reaction of 2-chloropyridine with potassium fluoride was achieved by using much more vigorous conditions.[15]



2-Fluoro-3-chloropyridine, 2-fluoro-5-chloropyridine and 2-fluoro-3,5-

dichloropyridine have been prepared similarly. 2-Fluoropyridine has been obtained recently in good yield (74%) by heating 2-chloropyridine with potassium bifluoride to 315° for 4 hrs. in an autoclave.[16]

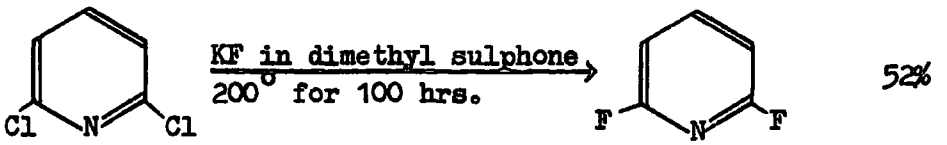
Application of the Schiemann technique in a stepwise manner allowed several fluorine atoms to be introduced into the benzene ring.[17,18,19,20] Fluorobenzene was nitrated and the nitro-group reduced to an amino group which on diazotisation and treatment with fluoroboric acid gave the diazonium fluoroborate. Thermal decomposition of this gave difluorobenzene. This sequence of reactions was repeated to give tri- and tetra-fluorobenzenes. Attempted nitration of 1,2,4,5-tetrafluorobenzene yielded no nitro compound, expulsion of two p-oriented fluorine atoms occurring to give a difluoroquinone.



This shows that penta- and hexa-fluorobenzene cannot be prepared by the Schiemann technique.

Roe attempted the simultaneous introduction of two fluorine atoms into the pyridine nucleus by using the Schiemann technique on 2,6-diaminopyridine but he did not isolate any 2,6-difluoropyridine.[22] Finger and co-workers[22] later showed that two fluorine atoms could be introduced into the pyridine nucleus when they used a stepwise approach

to prepare 2,3- and 2,6-difluoropyridine by the Schiemann reaction. Attempts to prepare 2,5-difluoropyridine by the same method failed. 2,6-Difluoropyridine has also been made by a halogen exchange reaction between 2,6-dichloropyridine and anhydrous potassium fluoride in dimethyl sulphone.[23]



Under the same reaction conditions 2,3,5,6-tetrachloropyridine gave 2,6-difluoro-3,5-dichloropyridine in 33% yield after 24 hrs. This shorter reaction time demonstrates the activating influence of the adjacent chlorine atoms on the halogen exchange reaction.

Highly Fluorinated Pyridines.

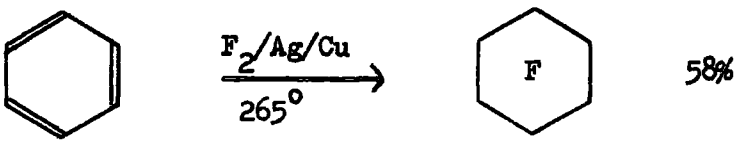
The preparation of highly fluorinated pyridines and benzenes has been carried out by three different routes. Route one involves the replacement of hydrogen atoms by fluorine atoms. Fluorinated precursors are used for direct syntheses in route two and in route three other halogen atoms are replaced by fluorine atoms.

Route 1. Replacement of Hydrogen by Fluorine.

a Fluorination using Elemental Fluorine.

The first major step forward in the direct fluorination of organic

compounds came with Bigelow's work[24] on direct vapour phase fluorination or as it is sometimes called the "catalytic method" of fluorination. In this method the vapour of the organic compound and fluorine diluted with nitrogen are passed through a reactor filled with a divided metal packing, usually copper gauze or copper coated with another metal, at elevated temperature. Although the metal packing could act as a catalyst, by reaction with fluorine to give a metal fluoride which would then be the fluorinating agent, its main function appears to be to dissipate the heat evolved during the reaction since Musgrave and Smith[25] found little variation in overall yield of fluorinated material when using a number of different "catalysts" including gold, silver, nickel, cobalt and steel wool. Cady, Grosse et al.[26] investigated the reaction of fluorine with several hydrocarbons, including benzene and anthracene, using copper turnings coated with silver as "catalyst".



When Haszeldine[27] attempted the fluorination of 2,6-dimethylpyridine with a gold catalyst he obtained a very poor yield (~5%) of the expected perfluoro-(2,6-dimethylpyridine). He suggested that this was due to the formation and subsequent decomposition, by fluorination, of the hydrofluorides of the starting base and of compounds derived

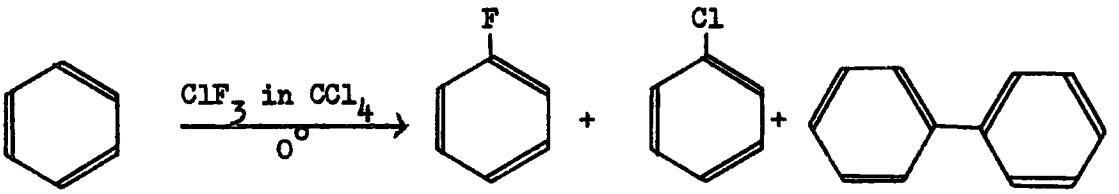
from it by the introduction of one or two atoms of fluorine. Fluorination of pyridine[28] at 280° under similar conditions gave perfluoropiperidine in only 0.3% yield. Breakdown of the pyridine ring was shown to have occurred since a straight chain fluorocarbon C_5F_{12} was isolated. Other compounds in which carbon-carbon bond fission instead of carbon-nitrogen had occurred were present in the reaction product. Haszeldine again reasoned that the low yield was due to formation of a non-volatile hydrofluoride during the critical initial stages of the reaction and he suggested that fluorination of heterocyclic compounds already containing fluorine should give superior yields. However when Banks and Williamson[29] fluorinated 2-fluoro-pyridine using a Bigelow "cool-flame" burner[30] at 150-160° they obtained perfluoropiperidine in less than 0.1% yield, extensive breakdown of the pyridine skeleton having occurred.

Tedder has recently reviewed the fluorination of organic compounds with elemental fluorine.[32]

b Halogen fluorides as Fluorinating Agents.

The use of halogen fluorides for the fluorination of organic compounds is somewhat limited because (a) the reactions are often vigorous and complicated and (b) halogenation as well as fluorination occurs e.g. with chlorine trifluoride chlorination as well as fluorination takes place.

Musgrave and Ellis[32] showed that chlorine trifluoride reacted with benzene in carbon tetrachloride solution to give mainly substitution products although small amounts of addition compounds were also isolated. The yield was rather poor.



7·5% 10·4% 2·5%

+ addition products 2·6%

They extended the reaction to benzene homologues and again found that substitution predominated although twice as much addition compound was obtained as with benzene.[33]

Beaty[34] investigated the reaction of pyridine with chlorine trifluoride in carbon tetrachloride at 0° and obtained fluoro- and chloro-pyridines in poor yield. A number of catalysts including CoF_2, AgF and SbF_3 were tested and were found to increase the yields considerably provided that the hydrofluoric acid produced during the reaction was absorbed by potassium fluoride as it was formed. The ratio of fluoro- to chloro-pyridine produced depended to some extent on the catalyst used.

c Electrochemical Fluorination.

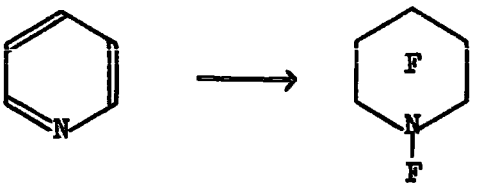
Many organic compounds dissolve in anhydrous hydrogen fluoride to give conducting solutions and when a direct current at low voltage (4-8 v.) is passed through these solutions, or alternatively through a suspension of an organic compound in hydrogen fluoride made conducting by the addition of an electrolyte, hydrogen is evolved at the cathode and the organic compound is fluorinated at the anode. This electrochemical process results in virtually complete fluorination, all hydrogen atoms being replaced by fluorine and unsaturated groups becoming saturated. Functional groups are sometimes retained e.g.

$$CH_3COF \longrightarrow CF_3COF \qquad 85\%$$

$$C_8H_{17}SO_2Cl \longrightarrow C_8F_{17}SO_2F \quad 25\% + C_8F_{18} \quad 21\%$$

Electrochemical fluorination was initially developed and extensively used by Simons and his associates.

The electrochemical fluorination of pyridine[35,36] and its derivatives[37,38] gave fully fluorinated saturated compounds in low yields.

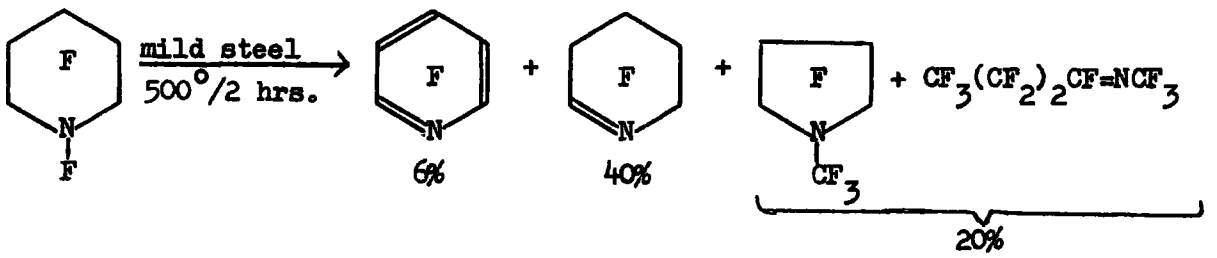


8%

Two groups of workers reported that undecafluoropiperidine, obtained

by the electrochemical fluorination of pyridine or piperidine, could be defluorinated to give pentafluoropyridine,[39,40] the first aromatic perfluoro-heterocyclic compound to be synthesised.

The group at Birmingham passed the undecafluoropiperidine vapour through a nickel tube packed with nickel gauze at 560° under atmospheric pressure, obtaining pentafluoropyridine in 12% yield. The Manchester workers carried out the defluorination over iron wire at 600° under reduced pressure (< 1 mm. Hg) with a contact time of about 1 second. The yield of pentafluoropyridine was 26%. These relatively mild conditions are quite different from those required for the defluorination of alicyclic fluorocarbons which require long contact times (10-30 mins.) at atmospheric pressure.[42] Indeed in the reduced pressure equipment perfluoromethylcyclohexane was recovered quantitatively at 700°. These results show that the N-F bond helps the defluorination. Further evidence for this was obtained when undecafluoropiperidine was heated with mild steel wool at 500° for 2 hrs. at atmospheric pressure.[38] The products were pentafluoropyridine (6%), perfluoro-2,3,4,5-tetrahydropyridine (40%) and a mixture (20% yield) of perfluoro-(1-methylpyrrolidine) and perfluoro-(N-butylidenemethylamine). No compounds containing only C=C bonds were isolated.



d Fluorination with High Valency Metal Fluorides.

One of the general methods for the preparation of fluorocarbons is the direct reaction of hydrocarbon derivatives with high valency metal fluorides.[42] Deep-seated fluorination of the organic structure occurs and all substituents on a carbon skeleton can be replaced by fluorine and unsaturation removed to give highly fluorinated products and eventually fluorocarbons. The metal fluoride, in which the metal exerts its highest valency, is reduced to a lower valency as the reaction proceeds.

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

$$\text{>C=C<} + 2MF_n \longrightarrow \text{>C(F)-C(F)<} + 2MF_{n-1}$$

Regeneration of the fluorinating agent is easily accomplished by reaction of the low valency metal fluoride with elemental fluorine. Members of this group of fluorinating agents which have been used are silver difluoride,[43] manganese trifluoride,[44] cobalt trifluoride, cerium tetrafluoride[45] and lead tetrafluoride.[46] Cobalt trifluoride has been the most widely used of these on account of its easy and economical preparation. With aromatic systems it adds fluorine across the double bonds as well as replacing hydrogen by fluorine.

The fluorinating action of cobalt trifluoride and its subsequent regeneration can be expressed as follows:

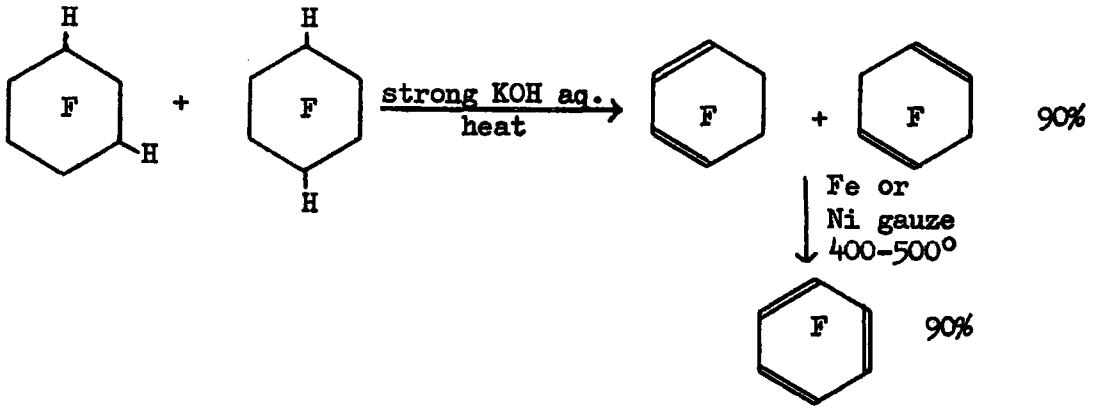
$$\geq C\text{-}H + 2CoF_3 = \geq C\text{-}F + HF + 2CoF_2$$

$$2CoF_2 + F_2 = 2CoF_3 \qquad \Delta H_{473}^{o} = -52 \text{ k.cals/mole}$$

From the experimentally determined value of the heat of the regeneration reaction,[47] it can be calculated that during fluorination of an organic compound with cobalt trifluoride only approximately half of the heat of reaction of the organic compound with elemental fluorine (102-104 k.cals/mole)[47] is liberated and the amount of breakdown is therefore considerably reduced.

$$\geq C\text{-}H + F_2 = \geq C\text{-}F + HF \qquad \Delta H_{298}^{o} = -104 \text{ k.cals/mole}$$

Fluorinations with cobalt trifluoride can be carried out in either the liquid or the vapour phase although the latter method has been more widely and successfully used with aromatic compounds, and is used commercially to prepare highly fluorinated benzenes e.g. hexafluorobenzene is obtained as follows. Fluorination of benzene with cobalt trifluoride at 150-200° gives a mixture of polyfluorocyclohexanes. Dehydrofluorination of decafluorocyclohexanes, obtained from the mixture, gives a mixture of octafluorohexa-1,3- and 1,4-dienes which are then pyrolytically defluorinated to give hexafluorobenzene.[48]

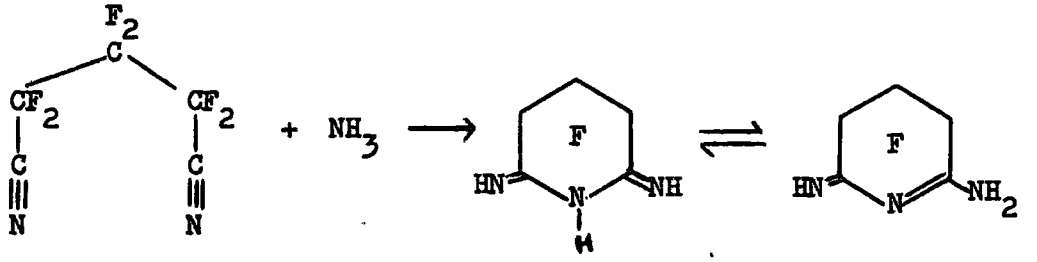


Benzene[49] and its derivatives,[47,50,51] naphthalene,[50] anthracene[52] and biphenyl[53] have all been converted into the corresponding saturated alicyclic fluorocarbons by vapour phase reaction with cobalt trifluoride. Although yields from these reactions were generally good (50-70%), they were poor when the method was extended to heterocyclic aromatic compounds.

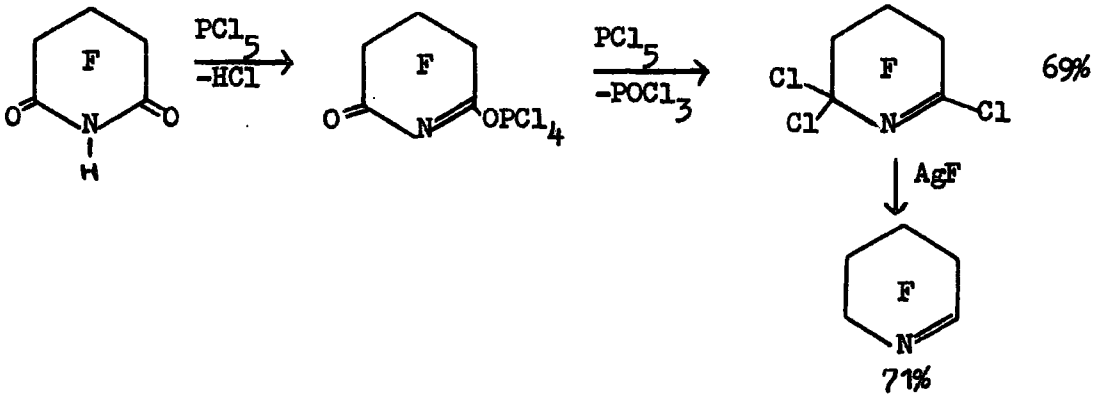
When pyridine vapour, diluted with nitrogen, was passed over cobalt trifluoride at 350°, undecafluoropiperidine was obtained in only 0.2% yield, extensive breakdown of the pyridine nucleus having occurred.[28]

Route 2. Syntheses involving Fluorinated Precursors.

Brown[54] prepared a polyfluoropyridine derivative by the reaction between liquid ammonia and perfluoroglutarodinitrile.

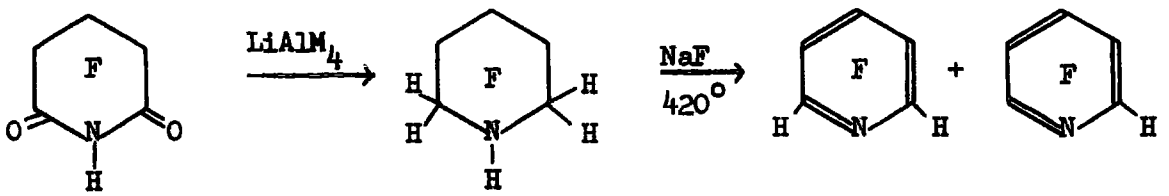


Hexafluoroglutarimide, obtained by cyclising the diamide of hexafluoroglutaric acid,[55] has been used to prepare perfluoro-1-piperideine by the following sequence of reactions



Bigelow et al.[56] showed that the direct jet fluorination of the dinitrile of glutaric acid with fluorine gave decafluorocyclopentane, nonafluoro-1-piperideine and undecafluoropiperidine plus many linear unsaturated and breakdown products.

Workers at Birmingham University[57] have prepared polyfluoropyridines from hexafluoroglutarimide



III IV

The product was 3,4,5-trifluoropyridine (III) containing 2% of 2,3,4,5-tetrafluoropyridine (IV).

Route 3. Replacement of other Halogens by Fluorine.

The methods of replacing halogens in highly halogenated, usually chlorinated, aromatics fall conveniently into two groups. In the first group (A) fluorination destroys the aromaticity and produces chlorofluorocyclohexanes and hexenes which are then dehalogenated to give fluoroaromatic compounds. The second group of methods (B) is more direct and involves halogen exchange between the chloro-compound and a metal fluoride.

Group A.

I. Fluorine or Halogen Fluorides.

The reaction between hexachlorobenzene and fluorine in carbon tetrachloride has been shown to give small quantities of hexachlorotetrafluorocyclohexene and hexachlorohexafluorocyclohexane.[58]

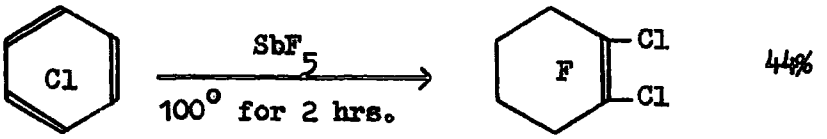
$$C_6Cl_6 + F_2 \longrightarrow C_6Cl_6F_4 + C_6Cl_6F_6$$

Musgrave and co-workers[59] later carried out the same reaction in 1,1,2-trichlorotrifluoroethane and obtained a mixture of chlorofluorocyclohexanes. Dehalogenation of this mixture with iron filings at 330° gave a mixture of hexafluorobenzene and chlorofluorobenzenes in good yield.

Reaction of hexachlorobenzene with chlorine trifluoride at 240° was carried out by Heyes[60] who obtained good yields of chlorofluorocyclohexenes $C_6Cl_nF_{10-n}$ where n = 3 to 6 and tetrachlorotetrafluorocyclohexadiene. With a large excess of chlorine trifluoride saturation was achieved with difficulty giving chlorofluorocyclohexanes, $C_6F_nCl_{12-n}$ where n = 3-7. Bromine trifluoride and hexachlorobenzene at 150° gave a mixture of products, of average composition $C_6Br_2Cl_4F_6$.[61,62]

II. Antimony Pentafluoride.

McBee and his associates[63] in 1947 showed that this reagent was able to add fluorine across double bonds in aromatic systems as well as replacing chlorine by fluorine, by reacting it with hexachlorobenzene



44%

It was later shown that the yield could be increased to 87% by using a reaction temperature of 150°.[64]

III. High Valency Metal Fluorides.

The reaction between hexachlorobenzene and cobalt trifluoride at 350° produced good yields of a large range of chlorofluorocyclohexanes of general formula $C_6Cl_nF_{12-n}$ where n = 1-6.[65] These were dehalogenated over hot iron gauze at 430° to give good yields of hexafluorobenzene.

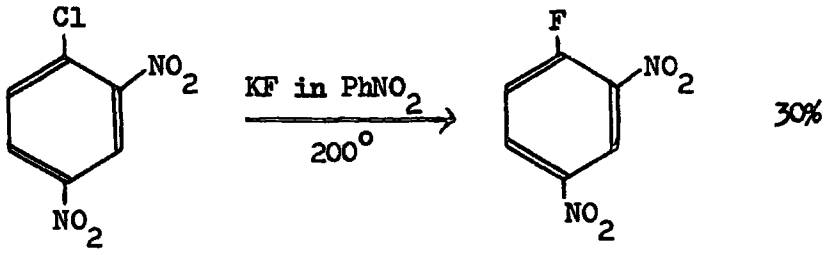
Cerium tetrafluoride and hexachlorobenzene at 275° gave cyclic $C_6Cl_3F_9$ in good yield.[66] This could be converted into cyclic C_6F_{12} by recycling.

Plumbic fluoride at 300° gave cyclic $C_6Cl_3F_9$ in 8% yield.[67]

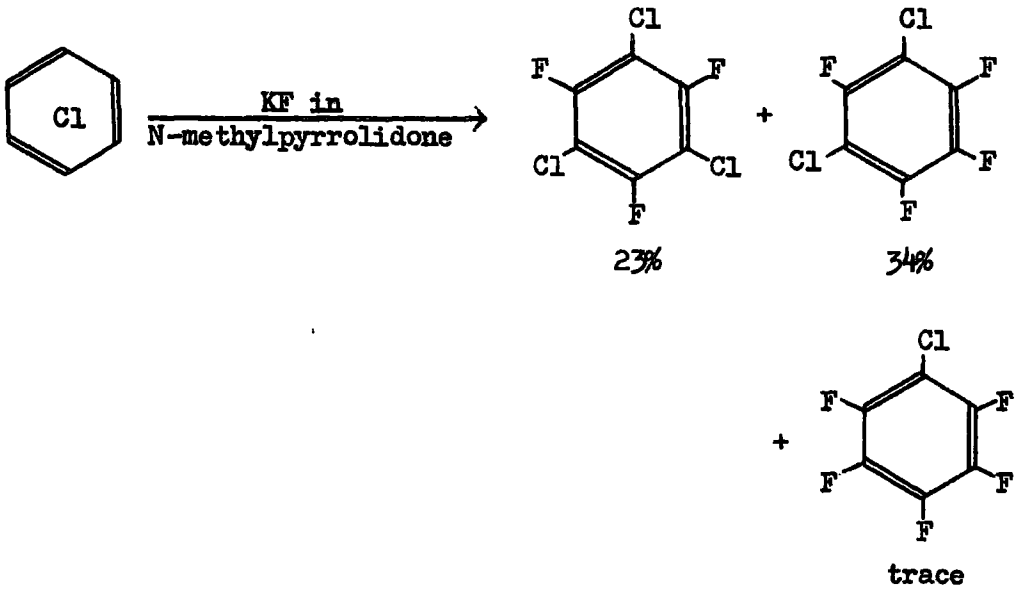
Group B

Halogen Exchange.

This method has been widely used for the preparation of aromatic fluoro compounds and it was shown many years ago that chlorobenzenes, in which the chlorine atom was suitably activated, could be converted into the corresponding fluoro compounds by reaction with potassium fluoride[68] e.g.



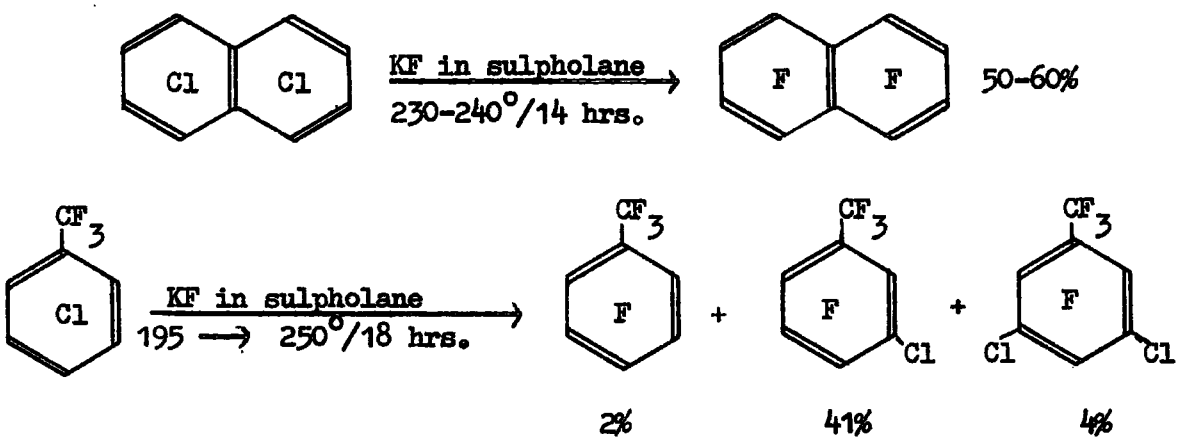
Maynard[69] prepared chlorofluorobenzenes by the reaction between hexachlorobenzene and potassium fluoride in polar solvents at elevated temperatures e.g.



The yields quoted were obtained by retreating all fluid fractions from the initial fluorination of hexachlorobenzene.

Fuller[70] studied the reaction of hexachlorobenzene (0.1 mole) with potassium fluoride (1 mole) in various aprotic solvents and found that sulpholane was the most effective for the preparation of highly

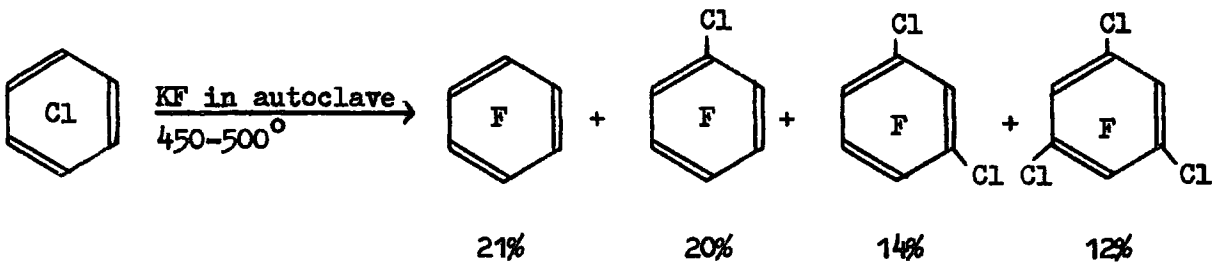
fluorinated aromatic compounds. At 230-240° in sulpholane for 18 hrs. the products were hexafluorobenzene (0.4%), chloropentafluorobenzene (25%), dichlorotetrafluorobenzenes (24%) and sym-trichlorotrifluorobenzene (30%). Hexabromobenzene gave similar results. Chloropentafluorobenzene could be converted into hexafluorobenzene in 42% yield by treatment with caesium fluoride in sulpholane at 160-190° for 18 hrs. Octafluoronaphthalene and octafluorotoluene were prepared using the same technique.



The effectiveness of sulpholane as a reaction medium for this type of reaction was attributed to its high boiling point, good thermal and chemical stability, the absence of side reactions which could produce nucleophilic impurities, and in particular the high cation solvation and low anion solvation of the alkali metal fluoride.

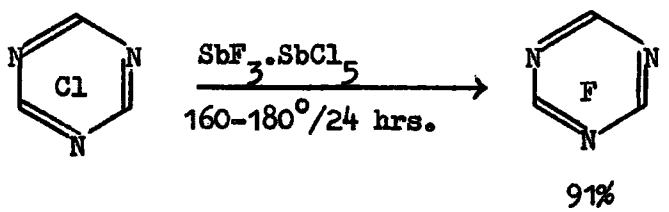
Vorozhtsov and his colleagues[71] carried out the reaction between

hexachlorobenzene and anhydrous potassium fluoride at elevated temperature in the absence of solvent, and obtained good yields of highly fluorinated benzenes.



They later showed that hexabromobenzene behaved similarly.[72] A number of variations of the above method have appeared in the patent literature.

Highly fluorinated heteroaromatic compounds have been prepared from the corresponding chloro compounds by reaction with other metallic fluorides, in cases where the chlorine atoms are activated e.g.



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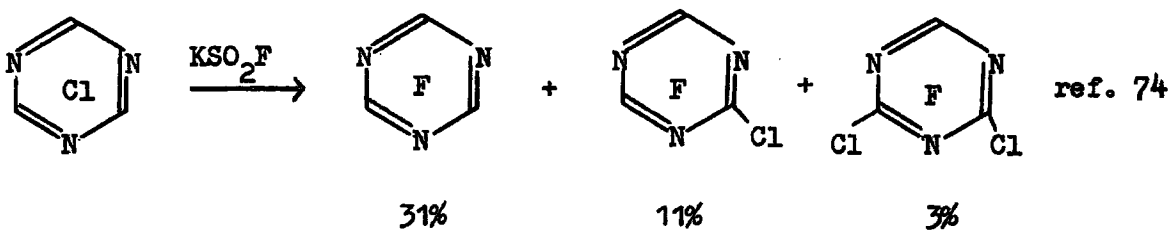

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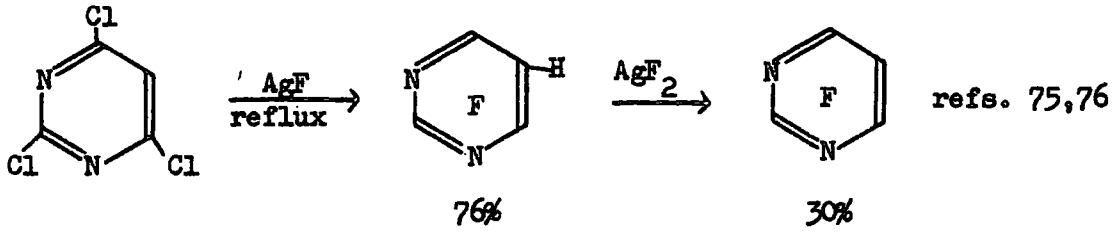
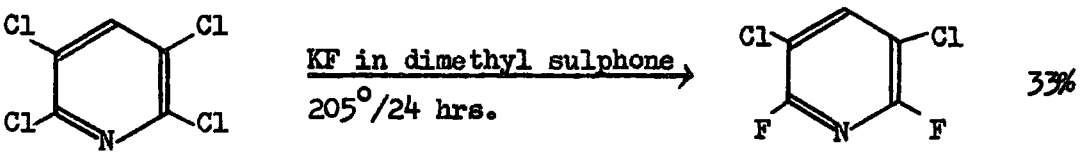
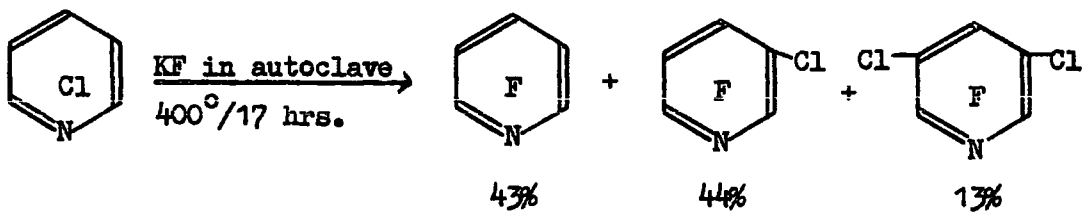


The work of Finger and others on the preparation of lightly fluorinated pyridines by halogen exchange has been described previously.† They were only able to replace the α-chlorine atoms by fluorine in 2,3,5,6-tetrachloropyridine.



By using potassium fluoride at elevated temperature, in the absence of solvent, Chambers, Hutchinson and Musgrave were able to replace all five chlorine atoms in pentachloropyridine by fluorine[77]

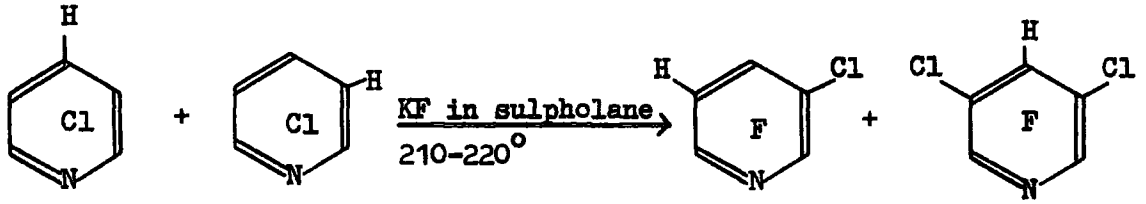


At 480° for 17 hrs. they obtained pentafluoropyridine in 70% yield.

† see p.6

They also found that the 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine could be converted into pentafluoropyridine on further treatment with potassium fluoride. From the same reaction carried out in sulpholane at 190-210° for 36 hrs. they obtained a good yield of 3,5-dichlorotrifluoropyridine together with a small amount of 3-chlorotetrafluoropyridine.

Isomeric tetrachloropyridines (by-products in the preparation of pentachloropyridine) were reacted with potassium fluoride in sulpholane to give an equimolar mixture of 3-chloro-2,4,6-trifluoropyridine and 3,5-dichloro-2,6-difluoropyridine.



The same reaction, carried out in the absence of solvent at various temperatures between 340 and 400° gave a mixture of monochlorotrifluoro-, dichlorodifluoro-, trichloromonofluoro- and tetrachloro-pyridines. The composition of the mixture varied with the temperature of the reaction.

Haszeldine[78] also reported the preparation of pentafluoropyridine by the reaction of potassium fluoride with pentachloropyridine under similar conditions to those described above.

The halogen exchange method described above has been shown to be quite general for the preparation of fluorinated aromatic nitrogen heterocycles since perfluoro-quinoline,[79] isoquinoline,[79] pyridazine[80] and pyrazine[81] have all been prepared from the corresponding perchloro-compound in this way.

Chapter 2. Discussion of Experimental Work (Part I)

Discussion of Experimental.

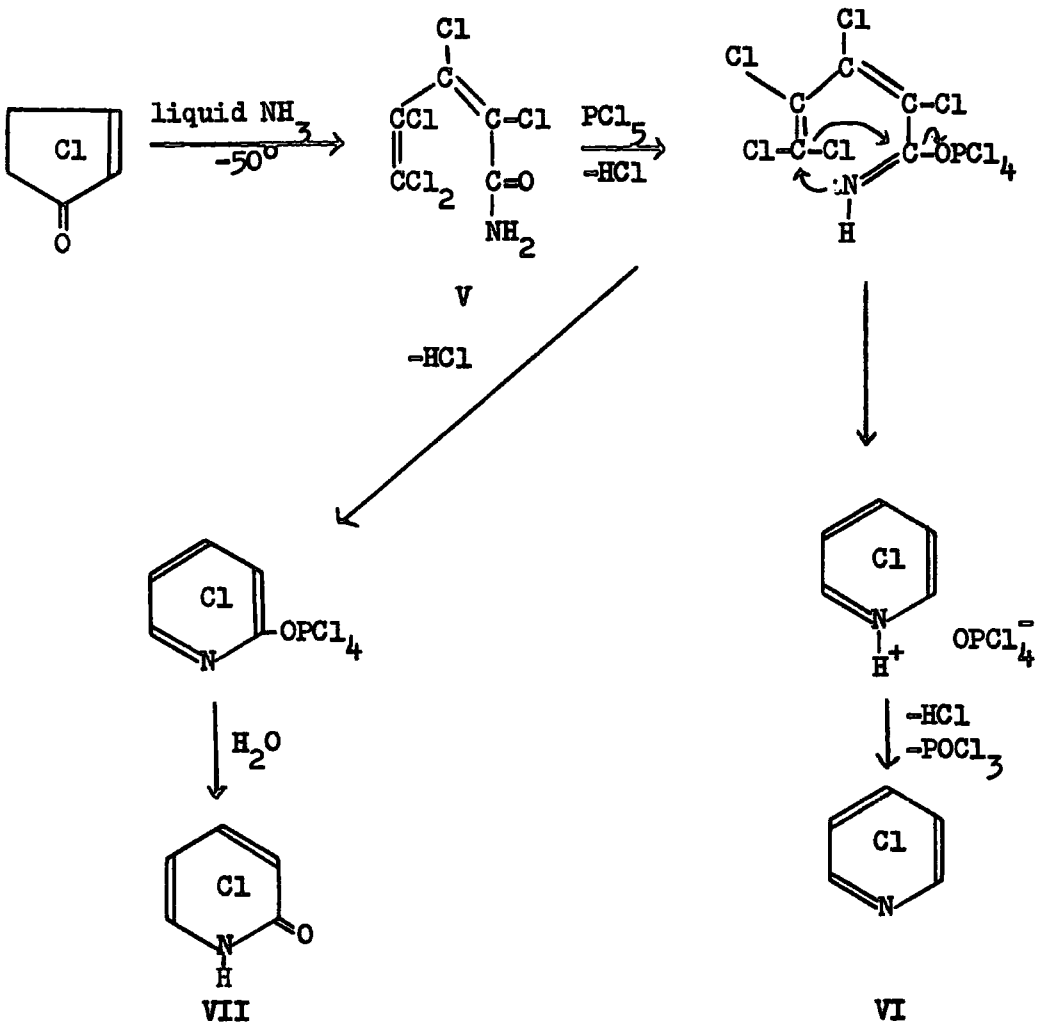
At the start of this work pentachloropyridine was prepared in these laboratories by the reaction of dry pyridine with a large excess of phosphorus pentachloride in a steel autoclave at elevated temperature.[77,82,83] This had occasionally proved to be hazardous due to the phosphorus pentachloride eating away the copper gasket and the autoclave itself, and causing explosions. If, however, the autoclave and gasket are carefully examined after each reaction for signs of corrosion and the corroded parts renewed, then the hazard can be reduced very considerably. Apart from this the main disadvantage with this method is that relatively little pyridine can be used in each reaction since the large amount of phosphorus pentachloride required occupies most of the space in the autoclave. Thus to build up a reasonable stock of pentachloropyridine it was necessary to carry out a large number of reactions.

Since large amounts of pentachloropyridine were required for the present work it was desirable to spend a short time in an attempt to find a better method of preparation. Two authors have reviewed methods of chlorinating pyridine.[82,83]

In view of the successful use of chlorine, with antimony trichloride as catalyst, in converting 2-chlorobenzthiazole into pentachlorobenzthiazole[84] it was decided to investigate the reaction of

these reagents with pyridine. An excess of dry chlorine was bubbled through dry pyridine containing antimony trichloride (2.5% by weight) at temperatures of 160 or 200° (oil bath temperature) and quite good yields of a mixture of di-, tri- and tetra-chloropyridines were obtained. The reaction was rather difficult to carry out since the chloropyridines distilled out of the reaction mixture as they formed and condensed on the cooler parts of the reaction vessel, causing, in particular, blockage of the condenser. In an attempt to overcome this the reaction was carried out at a lower temperature (110°) in carbon tetrachloride solution but the yield of chlorinated material was poor. The whole process was rather time consuming since (a) the chlorine was bubbled through slowly in order to avoid excessive wastage and (b) the chloropyridines were isolated by steam distillation. The results of these experiments are summarised in the table on page 33 The mixture of chloropyridines obtained by this method was readily converted into pentachloropyridine by reaction with an excess of phosphorus pentachloride in a steel autoclave at 300°.

Whilst this work was in progress Roedig and Grohe[85] reported the preparation of pentachloropyridine from hexachloro-2-cyclopentenone as follows:

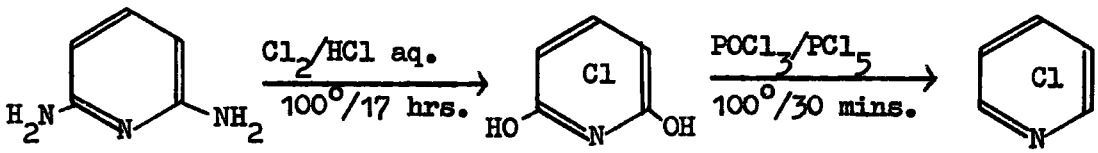


It was reported that, using the theoretical amount of phosphorus pentachloride, the main product was pentachloropyridine(VI) together with a little tetrachloro-2-pyridone (VII). When the author repeated this reaction under these conditions, he found that the main product appeared to be the pyridone since after repeated recrystallisation

from alcohol it had m.p. 190-200°. The m.p. of the pyridone is 224-5° and pentachloropyridine has m.p. 124°. As expected the pyridone was readily converted into pentachloropyridine on heating to 160° for 4 hrs. with phosphorus pentachloride. Alternatively it was found that pentachloropyridine could be prepared in one step by treating the amide (V) with a 120% excess of phosphorus pentachloride.

Pentachloropyridine later became commercially available (Imperial Chemical Industries Ltd.). It is presumably manufactured by the flow method, which has recently been patented by this firm,[86] in which 2-methyl or 2-chloropyridine vapour mixed with nitrogen and chlorine/nitrogen are mixed and passed over coconut carbon at 250-400°.

The preparation of pentachloropyridine from 2,6-diaminopyridine, by the following method, has recently been reported.[87]



57%

almost quantitative

Pentachloropyridine was readily converted into pentafluoropyridine, in good yield, together with 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine by reaction with anhydrous potassium fluoride in a stainless steel autoclave at 480° for 17 hrs.[77] The amount of chloro-compounds obtained could be increased by lowering the temperature.

Chapter 3. Experimental Work (Part I)

Experimental.

The pyridine (analar grade) was dried by heating under reflux over potassium hydroxide pellets for 12 hrs., distilling under dry nitrogen and storing under dry nitrogen until required. Chlorine was dried by bubbling through concentrated sulphuric acid. Potassium fluoride was heated over a "roaring" bunsen burner for 4 hrs. before it was used.

Chlorination of Pyridine with Phosphorus Pentachloride.

Dry pyridine (100 g.) and phosphorus pentachloride (2,500 g.) were placed in a stainless steel autoclave fitted with a nickel liner. The autoclave was heated to 300° for 24 hrs., the temperature being measured by means of a thermocouple inserted into a thermometer well which reached down inside the autoclave. Thus the walls of the autoclave were at a temperature in excess of 300°. After allowing the autoclave to cool to room temperature the hydrogen chloride generated during the reaction was released before the autoclave was opened. Excess phosphorus pentachloride was hydrolysed with ice. When this was complete the organic product was steam distilled. The solid product was filtered off and dried (200 g.). Fractional distillation gave tetrachloropyridines (~60 g.) and pentachloropyridine (~140 g.).

Chlorination of Pyridine with Chlorine.

In a typical experiment a flask fitted with stirrer, water condenser and gas lead was purged with dry nitrogen and then charged with dry pyridine (170 g., 2·15 mole) and antimony trichloride (4·25 g.).

Chlorine gas (756 g., 10·7 mole) was passed through the pyridine, first at 100° and then the temperature of the reaction vessel was gradually raised to 160°. When the refluxing liquid became solid the water condenser was replaced by an air condenser. When the required amount of chlorine had been passed into the reaction mixture it was allowed to cool, water was added and then it was steam distilled. The distillate was extracted with methylene chloride. Removal of the solvent from the dried extracts yielded an oily liquid (257·5 g.) which deposited some white crystals on cooling and whose composition was determined by analytical scale gas liquid chromatography on silicone elastomer at 180° as being

dichloropyridine	19	mole %
trichloropyridine	47	
tetrachloropyridine	34	

Chlorination of Chloropyridines with Phosphorus Pentachloride.

A stainless steel autoclave (1 l.) fitted with a nickel liner was charged with chloropyridines of average molecular formula $C_5H_{2.4}Cl_{2.6}N$ (150 g., 0·85 mole) and phosphorus pentachloride (900 g., 4·3 mole) and was then heated to 270° for 12 hrs., then to 305° for 6 hr. After allowing the autoclave to cool to room temperature, the hydrogen chloride generated during the reaction was released before the vessel was opened. The excess phosphorus pentachloride was then slowly hydrolysed by adding it to crushed ice. When this was complete the

organic product was steam distilled. The solid product was filtered from the distillate, dried by azeotropic distillation of the water with benzene, and fractionated to give tetrachloropyridines (~50 g.) and pentachloropyridine (~100 g.).

Preparation of Pentachloropyridine from hexachloro-2-cyclopentenone(1).

Liquid ammonia (330 cc.) and dry ether (450 cc.) were placed in a flanged glass vessel (2 l.), cooled to -50° and stirred vigorously. Hexachloro-2-cyclopentenone (300 g.) was slowly added and the mixture stirred at -50° for a further hour. The mixture was then allowed to warm to room temperature and the ether distilled off. The solid obtained was washed well with water and dried in an oven (90°) for a short while. 260 g. of the crude amide of pentachloropenta-2,4-dienoic acid were obtained (m.p. 107-108°, lit. 111-112°, yield ~93%).

The crude amide (240 g.) in dry benzene (215 cc.) was cooled to 0° and stirred while phosphorus pentachloride (200 g.) was slowly added. Immediate evolution of hydrogen chloride occurred. After stirring the mixture for 2 hrs. at 0°, it was raised to 80° and maintained at this temperature for 6 hrs. After distilling off the benzene the mixture was heated to 160° for 4 hrs. On cooling to room temperature the excess phosphorus pentachloride was hydrolysed with ice and the solid obtained was filtered off, washed with water and dried in an oven (105 g.). Repeated recrystallisation from meths yielded only solid

of m.p. 190-200°. This solid appeared to be mainly tetrachloro-2-pyridone (lit. m.p. 224-225°).

Some of the above solid (7.3 g.) was heated with phosphorus pentachloride (14 g.) at 160° for 4 hrs. On cooling to room temperature the excess phosphorus pentachloride was hydrolysed with ice. The solid obtained was filtered off, washed with water and dried in an oven (7.0 g.). Recrystallisation from meths yielded almost pure pentachloropyridine (m.p. 118-119°, lit. 124°), identified by comparison of its infra-red spectrum with that of an authentic sample.

Preparation of Pentachloropyridine from Hexachloro-2-cyclopentenone (2).

Liquid ammonia (1 l.) in dry ether (1.28 l.) was placed in a flanged glass vessel (5 l.) fitted with stirrer, condenser, dropping funnel, cooled to -50° and stirred vigorously. Hexachloro-2-cyclopentenone (880 g.) was slowly added, the temperature being maintained at -50°. After 1 hr. the temperature was allowed to rise slowly to room temperature. The ether was distilled off leaving a brown solid which was washed with water and dried to give the crude amide (820 g., 100%; m.p. 105°, lit. 111-112°).

The amide (820 g.) in dry benzene (750 ccs.) was stirred at 0° and phosphorus pentachloride (1 Kg.) slowly added. Immediate evolution of hydrogen chloride took place. The mixture was stirred at room temperature until complete solution occurred (2 hrs.). It was then

heated under reflux for 6 hrs. After the benzene had been distilled off phosphorus pentachloride (500 g.) was added and the mixture heated to 160° for 4 hrs. On cooling to room temperature, the excess phosphorus pentachloride was hydrolysed with ice and the solid obtained filtered off, washed with water and dried by azeotropic distillation with benzene. The hot solution was filtered in order to remove red phosphorus and evaporation of the filtrate yielded a dirty brown solid. Distillation gave almost pure pentachloropyridine (370 g., 48.4%; m.p. 123°, lit. 124°).

Both this and the pentachloropyridine produced in the previous experiment were readily converted into pentafluoropyridine by reaction with potassium fluoride.

Conversion of Pentachloropyridine into Pentafluoropyridine.

In a typical experiment, an autoclave (120 ml.) was charged with pentachloropyridine (20 g., 0.079 mole) and anhydrous potassium fluoride (60 g., 1.04 mole) and evacuated before being heated to 480° for 20 hr. When the reaction vessel was still hot, the product (13 g.) was distilled from it under vacuum. The composition of the product (determined by analytical scale G.L.C. on silicone elastomer at 80°) was pentafluoropyridine 70, monochlorotetrafluoropyridine 25, and dichlorotrifluoropyridine 5 mole %. The products from several reactions were combined and fractionated through a concentric tube column.

TABLE I

	Reactant and experiment number	Temp. °C	Wt. of starting material (gms.)	Wt. of chlorine (gms.)	Wt. of product obtained (gms.)	Composition of Product Mole % Di-chloro	Tri-chloro	Tetra-chloro	Penta-chloro	Average Formula of product	% yield based on average molecular formula
1	Pyridine	160	120 (1·5 moles)	535 (7·5 moles)	137·5	37·5 (31·0)	36·3 (37·1)	26·2 (31·9)	-	$C_5H_{2.1}Cl_{2.9}N$	51·7
2	Pyridine	160	170 (2·15 moles)	756 (10·75 moles)	257·5	19·2 (15·1)	47·0 (45·7)	33·8 (39·2)	-	$C_5H_{1.8}Cl_{3.2}N$	60·6
3	Pyridine	200	180 (2·28 moles)	1222 (17·2 moles)	208·4	61·2 (55·7)	35·9 (40·3)	2·2 (3·1)	0·6 (0·9)		Some product was lost which was relatively richer in tri- and tetra-chloro-pyridines
4	Chloro* pyridines in CCl_4	95	145 (0·725 moles)	197 (2·8 moles)	127·5	30·0 (24·4)	41·9 (42·0)	28·1 (33·6)	-	$C_5H_{1.9}Cl_{3.1}N$	-
5	Pyridine in CCl_4	110	160 (2·0 moles)	781 (11·0 moles)	38·0	31·8 (26·5)	50·7 (52·1)	17·5 (21·4)	-	$C_5H_{2.1}Cl_{2.9}N$	10·7

* The composition of the starting material for this expt. was $C_5H_{1.8}Cl_{3.2}N$

Figures in parentheses are weight %.

Part II. The Preparation of Highly Fluorinated Pyridine Derivatives from Polyfluoropyridines

Chapter 4. Introduction (Part II)

Part II. The Preparation of Highly Fluorinated Pyridine Derivatives from Polyfluoropyridines.

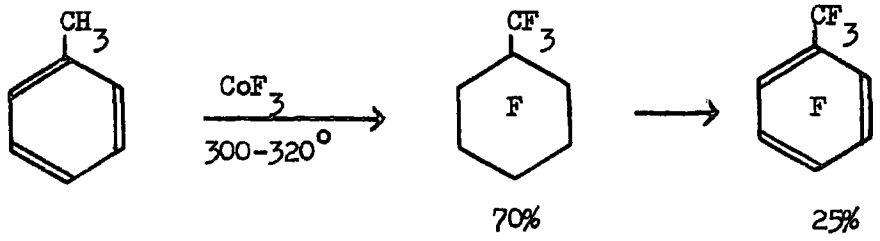
Introduction.

The routes by which highly fluorinated benzene and pyridine derivatives have been prepared can be divided into three parts. The first route involves nucleophilic displacement of fluorine atom(s) by functional group(s). This type of reaction has been extensively studied on hexafluorobenzene and its derivatives, particularly by workers at Birmingham University, and a large number of fluoro compounds have been prepared in this way. A wide variety of 4-mono- and 2,4-di-substituted polyfluoropyridine derivatives have also been prepared by this method.

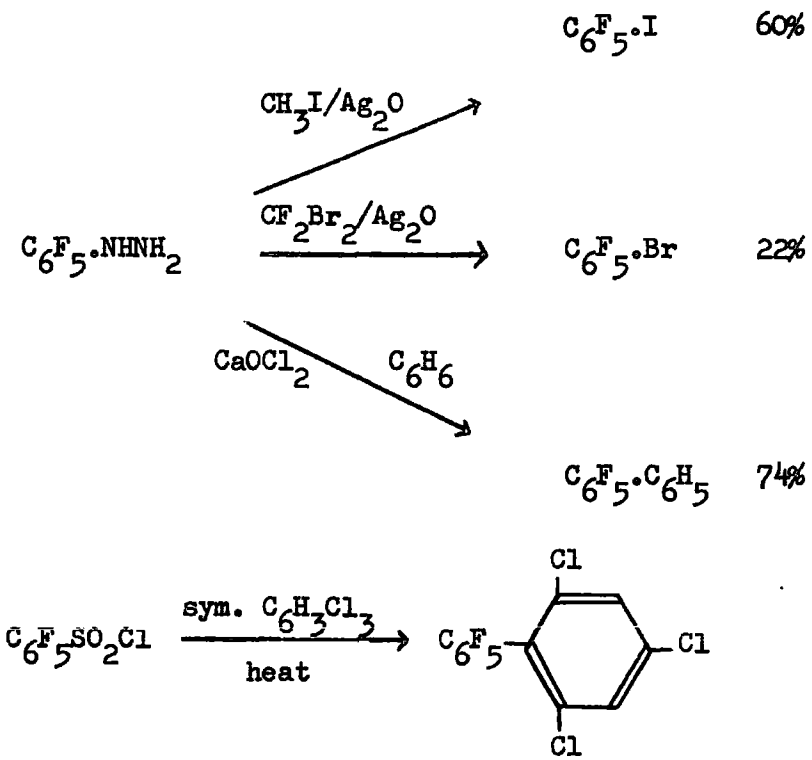
The second route involves preparation of derivatives by reactions of fluorinated Grignard and organolithium compounds with standard reagents. This method has been widely used and has been especially useful for the preparation of 3-substituted tetrafluoropyridine derivatives since they cannot be prepared by other routes.

Two methods which are of minor importance are grouped together in the third route. The first method which has been described previously*, is the exhaustive fluorination of a hydrocarbon derivative, followed by re-aromatisation by controlled defluorination over hot iron gauze, e.g.

* See page 13



Only limited synthetic use of pentafluorophenyl free radicals appears to have been made. These radicals can be generated either by oxidation of pentafluorophenylhydrazine in non-aqueous media[88] or by pyrolysis of pentafluorobenzenesulphonyl chloride.[89] Examples of their use are



Nucleophilic Substitution in Polyfluorobenzenes.

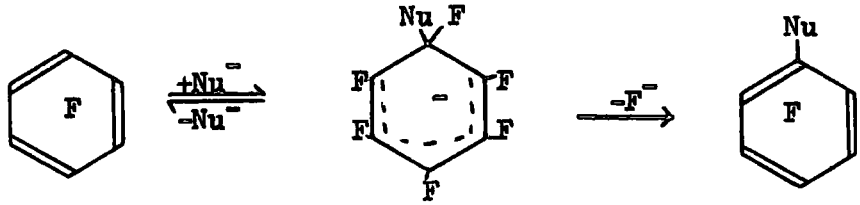
Hexafluorobenzene has been shown to react with a wide variety of

nucleophilic reagents such as OH^-,[90,91] OMe^-[92,93] and NH_3,[94,95] under moderate conditions to give, in good yield, products arising from the replacement of a single fluorine. Two exceptions to this are (a) reaction with thiophenate ion which gives p-di-thiophenoxytetrafluorobenzene and (b) an interesting reaction, with sodium cyanide in methanol, in which multiple replacement of fluorine occurred giving mainly 3,5-difluoro-2,4,6-trimethoxybenzonitrile but also a small amount of 1,4-dicyano-2,3,5,6-tetramethoxybenzene.

Nucleophilic replacement of fluorine in C_6F_5X compounds occurs most frequently at the position <u>para</u> to the group X. In some cases however (X = NH_2[96] or O^-[90,97]) <u>meta</u> substitution predominates and when X = OCH_3[97] or $NHCH_3$[96] comparable amounts of <u>meta</u> and <u>para</u> substitution occur. With the halogens[98] (X = Cl, Br or I) <u>ortho</u> substitution occurs to a significant though lesser extent than <u>para</u> substitution and decreases in the order Cl > Br > I. In a few cases (X = NO_2,[99] NO,[100] or COO^-[101]) the position of substitution depends on the nucleophile e.g. sodium methoxide in methanol gives mainly <u>para</u> replacement whereas certain amines give high (>50%) <u>ortho</u> replacement.

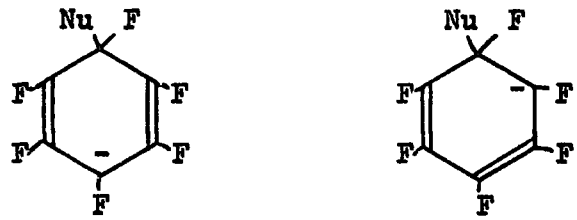
Burdon[102] has rationalised all these results in the following manner. The substitution reaction was assumed to occur through addition of a nucleophile Nu^- to give an intermediate such as (VIII).

Expulsion of a fluoride ion from this intermediate then gave the product,



VIII

The transition state was discussed in terms of the Wheland type intermediate (VIII). The p-quinonoid resonance hybrid (IX) was assumed to be the major contributor to the intermediate with the o-quinonoid form (X) being of only minor importance.

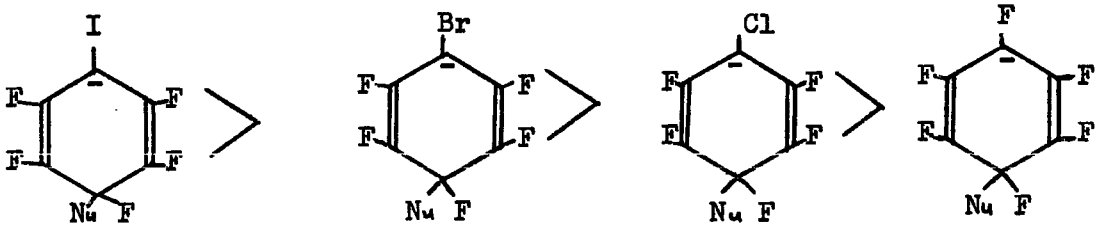


IX X

The effect of substituents in orientating further nucleophilic substitution depends, if solvent and steric effects are neglected, on their effect on the stability of contributors of type (IX) and to a lesser extent type (X). This largely resolves into a discussion of the influence of the group attached to the carbon bearing the negative charge on the stability of the charge. Thus in C_6F_5X compounds if X stabilises the negative charge more than fluorine, then substitution will

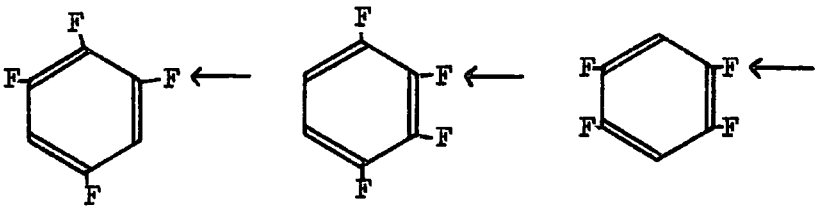
occur at the carbon atom para to X and to a lesser extent ortho to X. If X destabilises the negative charge, relative to fluorine, substitution will occur meta to X. If X is similar to fluorine then the ortho:meta:para ratio should approach the statistical 2:2:1. This approach neglects any interaction between the substituent and the ring π-electrons which could form an extended π-electron system.

Although the halogens are normally electron attracting, they destabilize the negative charge in the order F > Cl > Br > I. This arises because the negative charge is in a π-electron system and in this situation the electron repulsion ($+I_{\pi}$ effect), due to the Coulombic repulsion between the p-electrons on the halogen atom and the π-electrons of the ring, outweighs the electron attraction ($-I_{\sigma}$ effect) expected from purely electronegativity considerations. The above order for the halogens was derived from the U.V. spectra of the halobenzenes.[103] The order of stability of hybrids of type (VIII) is therefore



The magnitude of the I_{π} effect of nitrogen and oxygen cannot be derived from spectroscopic data but they were assumed to be N > O > F.

The above theory accounts quite well for the observed orientation in the majority of nucleophilic substitution reactions of polyfluorobenzenes and is supported by the results obtained with tetrafluorobenzenes which undergo substitution at the positions shown[104] i.e. <u>para</u> to hydrogen if possible



In cases where the theory is unsuccessful in explaining the orientation in substitution of polyfluorobenzenes, the failure can usually be ascribed to the neglect of specific interaction between the substituent and nucleophile and steric effects. Thus $C_6F_5NO_2$,[99] C_6F_5NO[100] and $C_6F_5COO^-$ [101] give large amounts of <u>ortho</u> replacement when amines are the nucleophile but mainly <u>para</u> replacement with methoxide ion as the nucleophile. This has been explained by hydrogen bonding taking place between the amine and the substituent and thus favouring <u>ortho</u> substitution. This is not a complete explanation however because pentafluorobenzoic acid gave more <u>ortho</u> replacement with dimethylamine than with methylamine whereas the reverse was true with pentafluoronitrobenzene.[101]

Steric effects are also important in certain cases since they can

alter the magnitude of the I_π effect. For example nucleophilic substitution in pentafluoro-N,N-dimethylaniline. On the basis of the order of I_π repulsions given previously (N > O > F) this would be expected to produce a meta derivative on reaction with nucleophiles. However, in practice, little meta derivative (~5%) was formed, the main product being the para isomer (> 90%). The reason given for this was that interaction between the N-methyl groups and the ortho fluorines twisted the $-NMe_2$ group out of the plane of the ring, causing a reduction in the magnitude of the I_π effect of the nitrogen. The $-NMe_2$ group thus acts as an inert substituent and para substitution occurs.

The nature of the solvent can also affect the orientation of the products and this is shown by the reaction of hexafluorobenzene with excess hydrazine.[105] In dioxan as solvent equal amounts of meta and para dihydrazinotetrafluorobenzene are produced but in tetrahydrofuran only the para isomer is obtained.

Derivatives from Polyfluorobenzene Grignard and Lithium Reagents.

The hydrogen atom in pentafluorobenzene has been replaced by reaction with a number of electrophilic reagents. Sulphonation with oleum gave pentafluorobenzene sulphonic acid.[106] Nitration with HNO_3/HF gave pentafluoronitrobenzene in 50% yield.[107] Other workers[108] investigated the reaction using all possible combinations of fuming nitric acid and sulphuric acid both with and without solvent and found

that the best yield (82%) was obtained using a mixture of fuming nitric acid, boron trifluoride and tetramethylene sulphone. Friedel-Crafts alkylation of pentafluorobenzene has recently been reported by Beckert and Lowe[109] who obtained excellent yields of bis(pentafluorophenyl)methane (77%) and tris(pentafluorophenyl)methane (92%) by reaction with methylene chloride and chloroform respectively, using aluminium chloride as catalyst.

Chloro-,[110] bromo-[106] and iodo-[106] pentafluorobenzene were prepared by reaction of the appropriate halogen with pentafluorobenzene in sulphuric acid and a route to a large number of pentafluorophenyl derivatives was opened up when it was shown that the chlorine,[59] bromine[106] or iodine[106] atom in these compounds would react with magnesium to give the Grignard reagent. These Grignard reagents underwent standard reactions such as carbonation to give pentafluorobenzoic acid and reaction with ketones to give alcohols. Banks has summarised, in diagrammatic form, the reactions of pentafluorophenyl magnesium bromide, illustrating the scope of this type of reagent.[111]

Later work on bromo- and iodo-pentafluorobenzene showed that the halogen atom underwent an exchange reaction with n-butyl lithium or lithium amalgam to give pentafluorophenyl lithium, the reactions of which were similar to those of pentafluorophenylmagnesium bromide.[112,113] Tamborski has shown that the hydrogen atom, both in pentafluorobenzene[114]

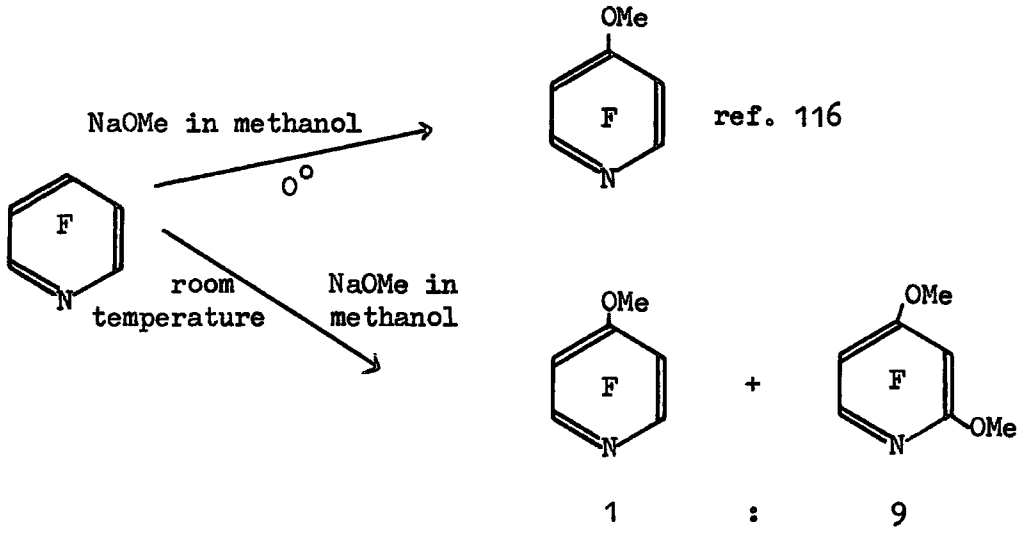
and also in compounds of the type p- x-C_6F_4-H[115] where x = OH, NH_2, SH, CH_3, CF_3, CN or p-H.C_6F_4, is sufficiently acidic to undergo exchange with n-butyl lithium to give lithio derivatives.

Nucleophilic Substitution in Pentafluoropyridine.

This type of reaction has been extensively studied by workers here at Durham and to a lesser extent by workers at Manchester.

The results obtained show that the first nucleophile enters the 4-position exclusively in all but two cases.[116,117] The first of these is the reaction of pentafluoropyridine with phenyl lithium which gave 4-phenyltetrafluoropyridine (> 95%) and a small amount of another isomer, presumably 2-phenyltetrafluoropyridine (< 5%). The other case is the reaction of pentafluoropyridine with potassium hydroxide. In aqueous solution the 4-isomer was formed exclusively, but using t-butanol as solvent gave a mixture of 2- and 4-hydroxytetrafluoropyridines in the ratio 1:9. The difference was attributed to active participation of the t-butoxide ion in the substitution reaction.

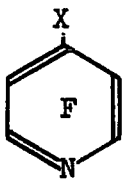
Nucleophiles which have been reacted with pentafluoropyridine are H^-, $C_6H_5^-$, $CH_3CH{=}CH^-$, OH^-, OMe^-, $OC_6F_5^-$, $\bar{O}C_5F_4N$, NH_3, $(CH_3)_2NH$ and NH_2NH_2.[116,117,118] When an excess of the nucleophilic reagent was used, sometimes at a higher temperature, a 2,4-disubstituted trifluoropyridine derivative was also produced e.g.



The greater ease of nucleophilic displacement of fluoride ion from pentafluoropyridine than from hexafluorobenzene is illustrated by their reaction with ammonia. Quantitative reaction of pentafluoropyridine with aqueous ammonia occurs at 80° for 2 hrs., and 2,4-diaminotrifluoropyridine is obtained after 20 hrs. at 140°. A temperature of 167° is required for the preparation of pentafluoroaniline from hexafluorobenzene.

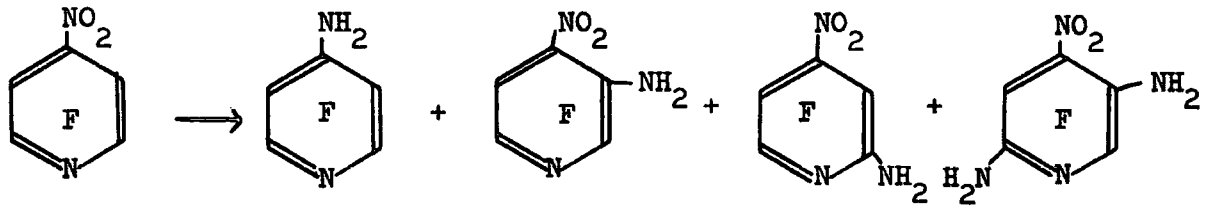
Nucleophilic Substitution in 4-Substituted-Tetrafluoropyridine Derivatives.

Nucleophilic substitution reactions have been carried out on a number of compounds of the type



Where X = OCH_3,[117] Br,[119] NH_2,[120] or Cl[121] replacement of the 2-fluorine occurred and with an excess of sodium methoxide in methanol the former two compounds gave a 2,6-dimethoxytrifluoropyridine derivative.

Some very interesting results have been obtained from the reaction of 4-nitrotetrafluoropyridine (prepared by oxidation of 4-aminotetrafluoropyridine with trifluoroacetic anhydride/hydrogen peroxide in methylene chloride) with nucleophiles.[120] This compound in ethereal solution reacted with gaseous ammonia under very mild conditions (0°) to give the following products:



27 mole % 48 mole % 25 mole % minor product

Using methoxide ion as the nucleophile, the major product (4-methoxytetrafluoropyridine 70 mole %) resulted from the displacement of the nitro-group. Exclusive replacement of the nitro-group occurred with pentafluorophenoxide ion as the nucleophile, only 4-pentafluorophenoxytetrafluoropyridine being isolated.[118] These are the first reported reactions in which a nitro-group is replaced, in preference to fluorine by nucleophiles.

In the reaction of pentafluoronitrobenzene[99] or 2,3,5,6-tetrafluoronitrobenzene[120] with nucleophiles, no replacement of the nitro group has been observed. The fact that large amounts of products resulting from the displacement of the nitro-group in 4-nitrotetrafluoropyridine are formed, suggests that the ring nitrogen is the most important factor in determining the orientation of substitution in polyfluoropyridines, since the nitro-group and fluorine are comparable in their efficiency as leaving groups in nucleophilic aromatic substitution. The preponderance of 3- or ortho-substitution in the reaction of 4-nitrotetrafluoropyridine with ammonia can be ascribed to hydrogen bonding between the nitro-group and ammonia aiding this orientation of attack. This argument was put forward to explain ortho substitution in pentafluoronitrobenzene.[99]

Nucleophilic Substitution in 3-Chlorotetrafluoro- and 3,5-Dichloro-trifluoro-pyridine.

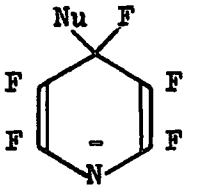
Both these compounds reacted with nucleophiles to give replacement of fluorine, the chlorine atoms being retained. They reacted with ammonia and hydrazine to give exclusive replacement of the 4-fluorine in high yield.[122] 3-Chlorotetrafluoropyridine was reduced by lithium aluminium hydride to give a single isomer 3-chloro-2,5,6-trifluoropyridine.[78] 3,5-Dichlorotrifluoropyridine reacted with methoxide ion to give a mixture of 4-methoxy (80%) and 2,4-dimethoxy (20%) compounds.

As with pentafluoropyridine the reaction of the chlorofluoropyridines with potassium hydroxide gave different ratios of isomers depending on the solvent used. Two patents[123,124] have recently been published listing a very large number of derivatives which have been prepared by nucleophilic substitution in 3-chlorotetrafluoropyridine and 3,5-dichlorotrifluoropyridine.

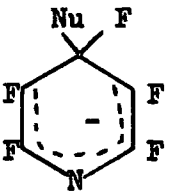
Competition experiments with ammonia have shown that the order of reactivity towards nucleophiles is 3,5-dichlorotrifluoropyridine > 3-chlorotetrafluoropyridine > pentafluoropyridine. This is consistent with the known greater electron withdrawing capacity of chlorine over fluorine in aromatic systems.

Rationalisation of Orientation and Reactivity in Nucleophilic Substitution in Polyfluoropyridines.

The results, given above, obtained in the nucleophilic substitution reactions of 4-nitrotetrafluoropyridine (in which considerable replacement of the nitro-group occurred) show that in polyfluoropyridines the greatest single factor in determining the orientation of the products is the ring nitrogen atom, due to its ability to stabilise a negative charge placed on it. Thus in substitution of pentafluoropyridine by a nucleophile Nu (neglecting solvent and steric effects), the hybrid (XI) will be the most important contributor to the Wheland type intermediate (XII)



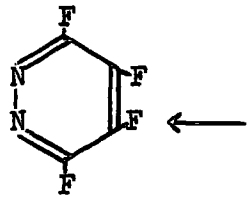
(XI)



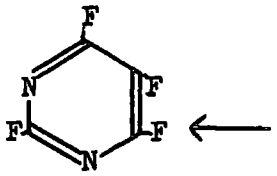
(XII)

Consideration of the o- and p-quinonoid structures for reaction at the other positions shows that only when substitution occurs at positions 2 or 6 can the negative charge be localised on nitrogen. Even then this will occur only in the o-quinonoid form which is less stable than the p-form. Thus mono substitution in pentafluoropyridine would be predicted to occur at the 4-position and further substitution at the 2- and 6-positions and more easily than in hexafluorobenzene since the electron-withdrawing effect of the ring nitrogen will activate the system towards nucleophilic substitution. The latter point is strikingly confirmed by the fact that pentafluorophenylmagnesium bromide reacts with pentafluoropyridine to give 4-(pentafluorophenyl)tetrafluoropyridine but will not react with hexafluorobenzene under the same conditions.[119]

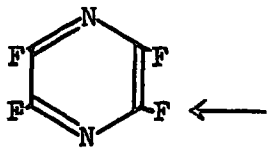
The above type of argument explains the replacement of the nitro-group in the nucleophilic substitution of 4-nitrotetrafluoropyridine and is further supported by the results obtained with the three tetrafluorodiazines, which react with nucleophiles at the positions shown.



(XIII)



(XIV)



(XV)

As expected all three were found to be more reactive than pentafluoropyridine and, significantly, tetrafluoropyridazine (XIII) and tetrafluoropyrimidine (XIV), in which a fluorine <u>para</u> to nitrogen is replaced, were a lot more reactive than tetrafluoropyrazine (XV) in which there is no fluorine <u>para</u> to nitrogen.

The fact that the functional group is not replaced in 4-bromo, -chloro or -methoxy-tetrafluoropyridines may be due to the fact that they are poorer leaving groups than fluorine in aromatic nucleophilic substitution reactions. Substitution does however occur at the 2- and 6-positions, which are predicted by the theory to be the next most reactive positions. This theory fails when extended to perfluorobicyclic heteroaromatic compounds such as perfluoro-quinoline and isoquinoline.[125]

<u>Derivatives from Polyfluoropyridine Grignard and Lithium Reagents.</u>

4-Aminotetrafluoropyridine is a useful intermediate for the synthesis 4-substituted tetrafluoropyridine derivatives. It has been diazotised in 80% hydrofluoric acid and the resulting diazonium salt has been reacted with various cuprous halides to give 4-chloro-,[83] 4-bromo-[119] and 4-iodo-[83] tetrafluoropyridine and it has been coupled with

N,N-dimethylaniline to give 4-(N,N-dimethylphenylazo)tetrafluoropyridine.

4-Bromotetrafluoropyridine formed a Grignard reagent readily in tetrahydrofuran and the reaction had to be carried out at low temperature (-10°) in order to prevent polymer formation. The Grignard reagent[119] reacted with carbon dioxide to give tetrafluoroisonicotinic acid, with ethyl methyl ketone to give 2-hydroxy-2-(tetrafluoro-4-pyridyl)butane and with pentafluoropyridine to give octafluoro-4,4'-bipyridyl, all in good yield.

As indicated at the beginning of this chapter, 3-lithiotetrafluoropyridine is the key intermediate in the synthesis of 3-substituted tetrafluoropyridine derivatives, but its preparation and use will be discussed in the next chapter. 3,5-Dilithiotrifluoropyridine will be treated similarly.

Chapter 5. Discussion of Experimental Work (Part II)

Discussion of Experimental

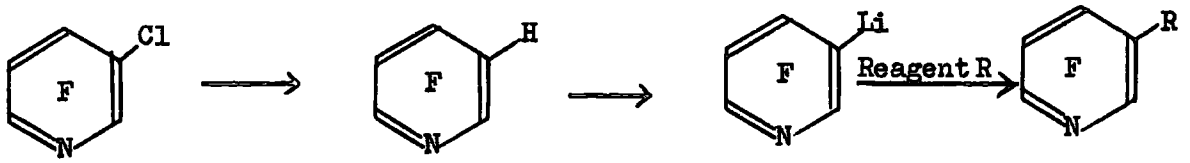
3-Substituted Tetrafluoropyridine Derivatives.

As stated previously 3-substituted-tetrafluoropyridine derivatives cannot be prepared by nucleophilic substitution reactions since it has been shown that this position in pentafluoropyridine is the least reactive towards nucleophiles.

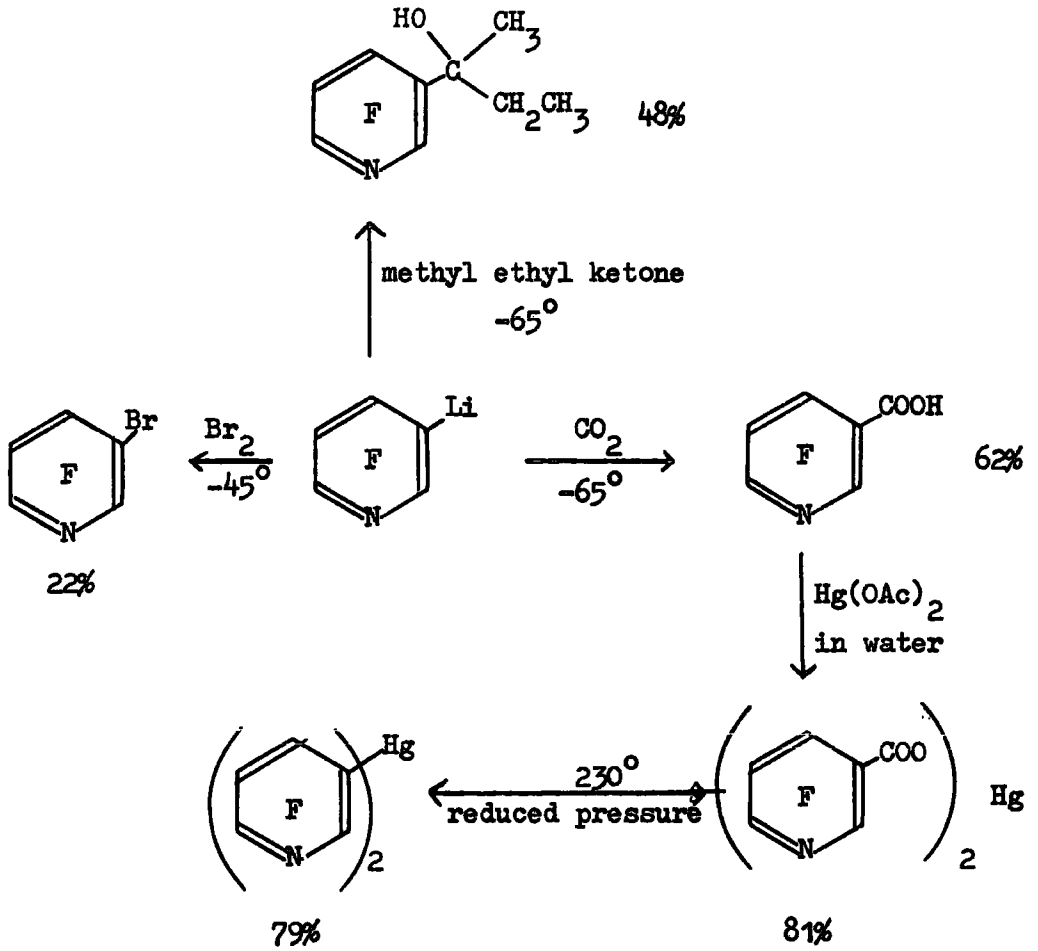
Drakesmith[126] succeeded in replacing the chlorine atom by hydrogen in 3-chlorotetrafluoropyridine, by reducing it (at the rate of 6 g./hour) with hydrogen (flow rate 50 mls./min.) over a 10% palladium on charcoal catalyst at 250°. The pure 2,4,5,6-tetrafluoropyridine was obtained by preparative scale G.L.C. It was shown that the hydrogen atom in this compound was sufficiently acidic to undergo metallation with n-butyl lithium at -65° in ether to yield 3-lithiotetrafluoropyridine. This was carbonated to give tetrafluoronicotinic acid in good yield. 3,5-Dichlorotrifluoropyridine was also reduced (at 280°), and the 2,4,6-trifluoropyridine obtained was metallated and then carbonated to give 2,4,6-trifluoropyridine-3,5-dicarboxylic acid. Similarly at 300° pentafluoropyridine was reduced to 2,3,5,6-tetrafluoropyridine in 30% yield. This gave tetrafluoroisonicotinic acid in 50% yield by reaction with n-butyl lithium at -65° followed by carbonation.

Since 3-chlorotetrafluoropyridine is readily available from the reaction between pentachloropyridine and anhydrous potassium fluoride at elevated temperature, a reasonable route for the preparation of 3-

substituted-tetrafluoropyridine derivatives is available, namely



Derivatives which have been prepared in this way are shown in the following diagram



ref. 82

The preparation of 2,4,5,6-tetrafluoropyridine described above is time consuming because (a) the maximum throughput of 3-chlorotetrafluoropyridine is of the order of 20 g./day since the apparatus needs to be purged with hydrogen for a couple of hours both before and after the experiment, (b) the activity of the catalyst soon becomes diminished with a large throughput, (c) pure 2,4,5,6-tetrafluoropyridine can only be obtained by preparative scale G.L.C. and (d) the overall yield is only moderate. It therefore seemed expedient to investigate other possible methods for converting 3-chlorotetrafluoropyridine into 2,4,5,6-tetrafluoropyridine, since fairly large amounts of the latter might be needed. The choice of methods is rather limited since the fluorine atom, which is attached to the 4-position of the pyridine ring, is very susceptible to replacement by hydride ion or other nucleophiles.

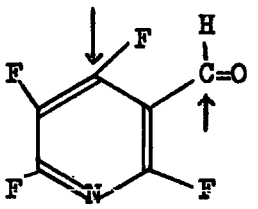
It has been reported that cuprous oxide/acetic anhydride, or the unstable cuprous acetate, in pyridine solution will reduce 1-bromonaphthalene to naphthalene, 5-iodo- or bromo-acenaphthane to acenaphthene, and chloro- or bromo-benzene to benzene, the yields being quite good ($>60\%$ in every case).[127] The attempted reduction of 3-chlorotetrafluoropyridine using this method with milder conditions (100° for 3 hrs. c.f. 115° for 5 hrs.) did not yield any 2,4,5,6-tetrafluoropyridine. The product was a low boiling solid which was shown by G.L.C. analysis (on silicone elastomer at 150°) to be a mixture

of three components. This was not investigated any further but it seems likely that the solid contained polyfluorobipyridyl derivatives since coupling is known to occur together with or instead of reduction with metal catalysts or metal containing reagents.[128]

Bromopentafluorobenzene and 4-bromotetrafluoropyridine are known to form Grignard reagents[106,119] and to undergo exchange of the bromine atom with lithium by reaction with n-butyl lithium.[112,129] Chloropentafluorobenzene also forms a Grignard reagent,[59] though, as expected, less easily than bromopentafluorobenzene. There is no mention in the literature of the attempted exchange reaction between chloropentafluorobenzene and an organolithium reagent. 3-Chlorotetrafluoropyridine has been reacted with n-butyl lithium in diethyl ether at -75° in an attempt to prepare 3-lithiotetrafluoropyridine. A vigorous reaction occurred and, after acidification, a liquid product was obtained. Analysis by G.L.C. (on di-n-decyl phthalate at 100°) showed that the product was a mixture of two components both of which had longer retention times than the required 2,4,5,6-tetrafluoropyridine. These were not separated or investigated any further but one of them could well be 3-chloro-4-n-butyltrifluoropyridine and the other may possibly be 3-chloro-6-n-butyltrifluoropyridine since pentafluoropyridine is known to react with n-butyl lithium in diethyl ether at -75° to give 4-n-butyltetrafluoropyridine.[130]

The reduction method used by Drakesmith for the preparation of 2,4,5,6-tetrafluoropyridine has recently been improved, for large scale work, by employing a higher concentration of catalyst (20% Pd/C).[131] This allows a higher throughput (10 g./hr.), a greater flow rate of hydrogen (100 mls./min.) and gives more consistent results.

3-Lithiotetrafluoropyridine, obtained by reaction of 2,4,5,6-tetrafluoropyridine with n-butyl lithium in ether at -65°, has been reacted with N-methylformanilide to give the lachrymatory tetrafluoropyridine-3-aldehyde in 40.5% overall yield. The aldehyde gave anilide and 2,4-dinitrophenylhydrazone derivatives in the usual way. The results of reactions between the aldehyde and reactive nucleophilic reagents such as hydrazine hydrate and sodium borohydride should be very interesting since the aldehyde has two sites which should be reactive towards nucleophiles, namely the carbonyl carbon atom and the carbon atom at position 4 of the pyridine ring (as shown below)



Unfortunately these reactions could not be carried out in time to be included in this thesis.

It has been stated that 3-chlorotetrafluoropyridine forms a Grignard

reagent in tetrahydrofuran, which can be carbonated to give tetrafluoronicotinic acid in 28% yield.[82] When the author, and others, repeated this reaction they obtained only dark, involatile, presumably polymeric, material. This is hardly surprising since the fluorine atom attached to the 4-position is known to be readily replaced by nucleophilic reagents. Any tetrafluoro-3-pyridyl magnesium chloride which formed (at -15°) would thus readily react with unreacted 3-chlorotetrafluoropyridine to give 3-chloro-4,3'-heptafluorobipyridyl. This could then form a Grignard reagent which would then react with more 3-chlorotetrafluoropyridine leading to the formation of polymeric material.

In order to try and prevent polymer formation the 4-position was blocked prior to Grignard formation. This was accomplished by heating 3-chlorotetrafluoropyridine with potassium pentafluorophenate dihydrate in tetrahydrofuran under reflux for 17 hrs. This gave 3-chloro-4-pentafluorophenoxytrifluoropyridine. Unfortunately even when heated in tetrahydrofuran under reflux for 3 hrs. this ether failed to form a Grignard reagent. This may have been due to the steric effect of the pentafluorophenoxy group.

2,4,6-Trifluoronicotinic acid and phosphorus pentachloride were reacted together at 80° for 1 hr. to give 2,4,6-trifluoronicotinyl chloride in 56.7% yield. When this was reacted with excess anhydrous ammonia in benzene, a mixture of 2,4,6-trifluoronicotinamide and 4-amino-

2,6-difluoronicotinamide was obtained. This result confirms the high reactivity of the 4-fluorine atom towards displacement by nucleophilic reagents. Previously 2,4,6-trifluoronicotinic acid had been reacted with thionyl chloride and the product obtained reacted with excess anhydrous ammonia in benzene to give a single product, namely 4-amino-2,6-difluoronicotinamide. This difference is ascribed to the fact that thionyl chloride probably reacted with 2,4,6-trifluoronicotinic acid to give an anhydride rather than an acid chloride since the author has shown that tetrafluoroisonicotinic acid reacts with thionyl chloride to give the anhydride (see later). Other workers have noted anhydride formation in the reaction of thionyl chloride with fluorinated aromatic acids.[132] Thus in 2,4,6-trifluoronicotinic anhydride the reactivity of the acyl carbon atom and the 4-carbon atom towards ammonia, is about the same and they are equally attacked giving a single product. However in 2,4,6-trifluoronicotinyl chloride, the acyl carbon atom is the more reactive and it reacts preferentially, leading to a mixture of products.

4-Substituted-Tetrafluoropyridine Derivatives.

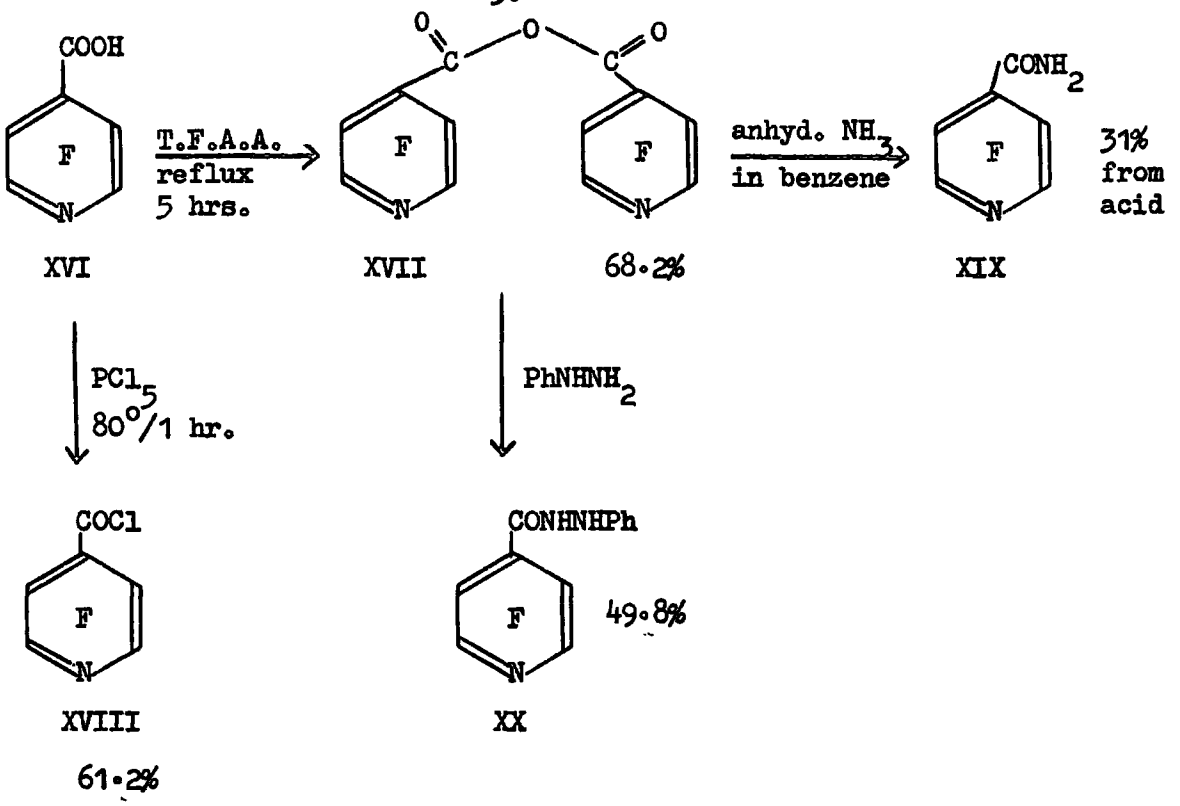
Most of the syntheses to be described have involved 4-lithiotetrafluoropyridine as an intermediate. This was prepared from pentafluoropyridine in the following manner. Reaction of pentafluoropyridine with aqueous ammonia (density = 0.88) in a sealed tube at 80° for a number of hours gave 4-aminotetrafluoropyridine in almost quantitative

yield.[116] This was diazotised in 80% hydrofluoric acid at -20° and then reacted with freshly prepared cuprous bromide dissolved in 40% hydrobromic acid to give 4-bromotetrafluoropyridine in good yield (80%).[119] 4-Lithiotetrafluoropyridine was then obtained by reacting this bromo-compound with n-butyl lithium in ether at -65°.[133] In a large number of cases the 4-lithiotetrafluoropyridine was carbonated to give tetrafluoroisonicotinic acid (XVI) which was then used as the starting material for the syntheses. The syntheses which have been carried out may thus be conveniently divided into two parts (a) those from tetrafluoroisonicotinic acid and (b) other syntheses.

(a) Syntheses from Tetrafluoroisonicotinic Acid.

This acid was made initially, in 60% yield, by carbonation of tetrafluoro-4-pyridyl magnesium bromide in tetrahydrofuran at 0°.[119] It was later prepared in better yield (80%) by carbonation of 4-lithio-tetrafluoropyridine.[133]

Tetrafluoroisonicotinic acid was dehydrated, by heating under reflux for 5 hrs. with trifluoroacetic anhydride, to give tetrafluoro-isonicotinic anhydride (XVII) in 91.8% yield. Unfortunately it was rapidly and exothermically hydrolysed back to the acid on slight exposure to air, and this precluded its use in further syntheses.

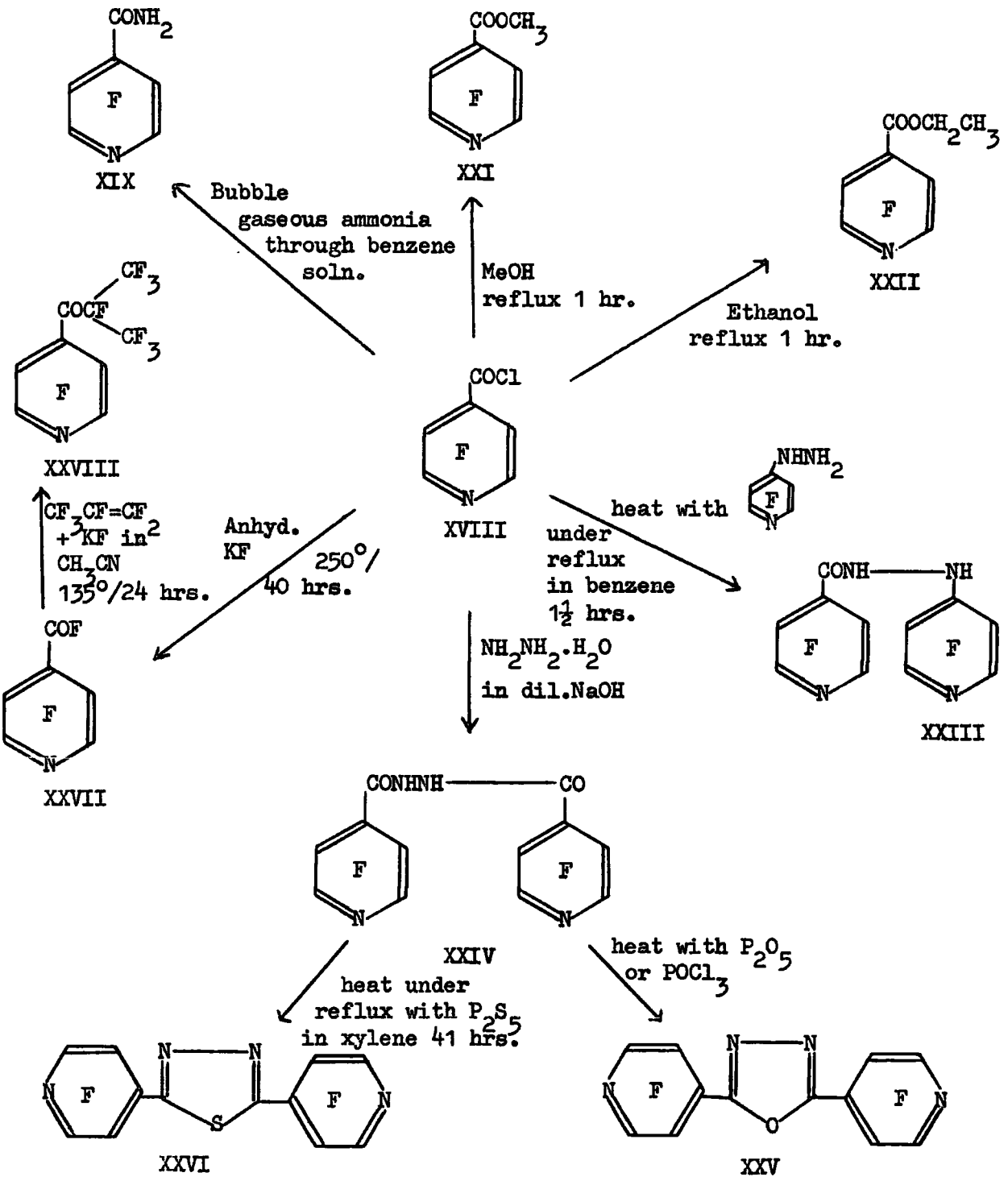


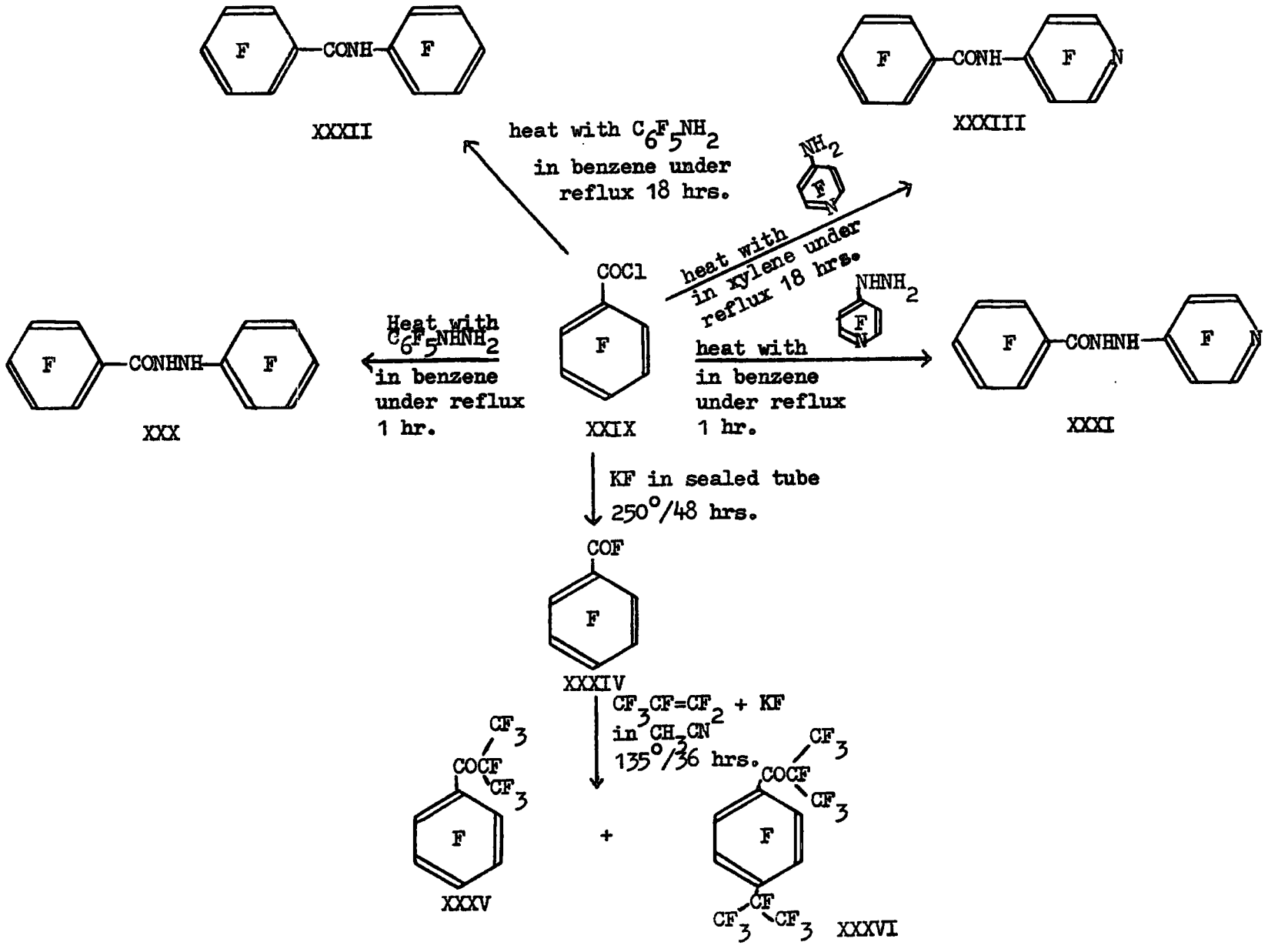
Tetrafluoroisonicotinic acid (XVI) when heated under reflux with thionyl chloride for periods of time ranging from six to seventy two hours, both in the absence and presence of dimethyl formamide in catalytic amounts, failed to react completely. After the removal of excess thionyl chloride, the product was distilled under reduced pressure (0.1 mms.) to give a high boiling liquid (114-118°) contaminated with some solid material (unreacted acid). This liquid was not the expected tetrafluoroisonicotinyl chloride (XVIII) since elemental analysis showed that it contained no chlorine. It was almost certainly tetrafluoroisonicotinic anhydride (XVII) (b.p. 110-110.5° at 0.05 mms.) because of its

similarity in boiling point and the fact that other workers have noted anhydride formation when other fluoroaromatic acids have been reacted with thionyl chloride.[132] It also underwent reactions which are characteristic of anhydrides e.g. reacted with ammonia to give tetrafluoroisonicotinamide (XIX) and with phenylhydrazine in ether to give N-phenyl-N'-tetrafluoroisonicotinylhydrazine (XX). Its reaction with anhydrous (> 95%) hydrazine in ether or tetrahydrofuran, at various temperatures between -50° and room temperature, gave no useful product, only dark brown solid which could not be purified and which rapidly decomposed on heating, being obtained.

Tetrafluoroisonicotinyl chloride (XVIII) has been prepared by the reaction of tetrafluoroisonicotinic acid with phosphorus pentachloride. On mixing these two compounds a vigorous reaction occurred with rapid evolution of hydrogen chloride. When this had subsided the reaction was completed by heating under reflux for 1 hour. It was difficult to obtain pure acid chloride by straight-forward reduced pressure distillation of the reaction product but a 60% yield of analytically pure material was obtained by carrying out the distillation through a short vigreux column. A lower boiling fraction, mainly phosphoryl chloride, was shown to contain more tetrafluoroisonicotinyl chloride from its infra-red spectrum.

Reactions which have been carried out on tetrafluoroisonicotinyl chloride (XVIII) or on pentafluorobenzoyl chloride (XXIX) are shown in the following diagrams




XXXII
heat with $C_6F_5NH_2$ in benzene under reflux 18 hrs.
XXXIII
heat with in xylene under reflux 18 hrs.
COCl
Heat with $C_6F_5NHNH_2$ in benzene under reflux 1 hr.
heat with in benzene under reflux 1 hr.
XXX
XXIX
XXXI
KF in sealed tube 250°/48 hrs.
COF
XXXIV
$CF_3CF=CF_2$ + KF in CH_3CN 135°/36 hrs.
XXXV
+
XXXVI

Tetrafluoroisonicotinyl chloride (XVIII) in dry benzene reacted with anhydrous gaseous ammonia to give tetrafluoroisonicotinamide (XIX) in 70% yield. Two esters, methyl tetrafluoroisonicotinate (XXI) and ethyl tetrafluoroisonicotinate (XXII) were prepared by heating tetrafluoroisonicotinyl chloride under reflux for 1 hour with excess methanol and ethanol. The yields were 80.6% and 74.8% respectively.

A number of secondary amides and hydrazides have been prepared from pentafluorobenzoyl and tetrafluoroisonicotinyl chlorides by heating under reflux, in anhydrous benzene containing sufficient N,N-dimethylaniline to react with all the hydrogen chloride evolved, with the appropriate amine or hydrazine. Prepared in this way, with yields given in square brackets, were

N'-(Tetrafluoro-4-pyridyl)tetrafluoroisonicotinohydrazide (XXIII) [23.3%],

N'-(Pentafluorophenyl)pentafluorobenzohydrazide (XXX) [90.7%],

N'-(Tetrafluoro-4-pyridyl)pentafluorobenzohydrazide (XXXI) [61.5%],

N-(Tetrafluoro-4-pyridyl)pentafluorobenzamide (XXXIII) [80.7%], and

N-(Pentafluorophenyl)pentafluorobenzamide (XXXII) [72.2%].

The low yield of compound (XXIII) is due in part to the fact that it did not precipitate from the benzene solution after acidification, as did the other compounds.

N,N'-bis(tetrafluoroisonicotinyl)hydrazine (XXII) has been prepared

by the reaction between tetrafluoroisonicotinyl chloride and hydrazine hydrate in dilute sodium hydroxide solution, a method which has been used for the preparation of N,N'-bis(pentafluorobenzoyl)hydrazine.[134] The yield was almost 60%. Compound (XXIV) underwent a cyclodehydration reaction on heating to 210° for 5 hrs. with phosphoric oxide, yielding 2,5-bis(tetrafluoro-4-pyridyl)-1,3,4-oxadiazole (XXV). The yield of crude product was almost quantitative but it required considerable purification and the yield of pure material was only poor (21·6%). However a much cleaner product was obtained, in excellent yield (91·3%), by heating the hydrazine (XXIV) under reflux with excess phosphoryl chloride. The N,N'-bis(tetrafluoroisonicotinyl)hydrazine (XXIV) underwent a similar cyclodehydration reaction to give 2,5-bis(tetrafluoro-4-pyridyl)-1,3,4-thiadiazole (XXVI), in poor yield (16%), when heated under reflux in xylene for 41 hrs. with phosphorus pentasulphide.

The oxadiazole (XXV) has been heated with ammonia (density = 0·88) in acetone, in a sealed tube, to 80° for 2 hrs. The product obtained could not be satisfactorily purified but its mass spectrum indicated that it was a diamino-derivative. This result indicates that the oxadiazole ring has an activating effect on the pyridine ring fluorine atoms, towards nucleophilic displacement, since octafluoro-4,4'-bipyridyl gives only a mono-amino derivative under the same conditions.[135]

Considerable difficulty has been experienced in repeating experiments

for the preparation of tetrafluoroisonicotinyl fluoride (XXIII) from tetrafluoroisonicotinyl chloride (XV). Points which had to be borne in mind were (a) it would be advantageous to use the acid chloride as soon as it was made so as to reduce the danger of hydrolysis. Since the only convenient method of assessing the purity of the acid chloride was elemental analysis, which could take up to a few days, this meant that acid chloride of unknown purity would be used. Also it appears (from elemental analysis) that a very narrow boiling range is no indication of purity; (b) the danger of the acid chloride decomposing would be minimised by keeping the temperature as low as possible. Since this would almost certainly lead to a reduction in reaction rate, a compromise would have to be reached.

In the first experiment carried out tetrafluoroisonicotinyl chloride and freshly roasted potassium fluoride (ratio by weight 1:2) were placed in a Carius tube which was evacuated, sealed, and then heated to 210° for 40 hrs. Pure tetrafluoroisonicotinyl fluoride was obtained in 65% yield. However in further attempts to prepare the acid fluoride incomplete reaction occurred, approximately equal amounts of starting material and product being obtained. In an attempt to overcome this the reaction was carried out in a stainless steel autoclave at 190° for 15 hrs., then at 225° for 7 hrs., a greater ratio of potassium fluoride to acid chloride (~5:1) being used. 2,3,5,6-Tetrafluoropyridine was the rather unexpected product which was

obtained from this reaction. It was obtained in 66% yield and was presumably formed by decarboxylation of either tetrafluoroisonicotinic acid or its potassium salt which would be formed by hydrolysis of the acid chloride. This was confirmed by heating together tetrafluoroisonicotinic acid and potassium fluoride in a sealed tube at 190° for 15 hrs. and then at 210° for 5 hrs., 2,3,5,6-tetrafluoropyridine being obtained in 85% yield. It was then decided to try and push the fluorination reaction to completion by carrying it out at a higher temperature, although this would increase the possibility of decomposition. The reaction was carried out in an evacuated, sealed Carius tube at 260° for 40 hrs. Acid fluoride, which contained no detectable amount of acid chloride (by infra-red spectrum), was obtained in 72% yield. Repetition of this experiment using a lower ratio of potassium fluoride to acid chloride (~3:1 instead of 8:1) gave pure acid fluoride in 50% yield. A further preparation using the above conditions but on a larger scale gave only 50% conversion. However the acid chloride used in this reaction had a 4° boiling range and was analytically quite impure whereas that used in the previous two reactions had a narrower boiling range, only 2°.

From the above results it appears that this fluorination reaction can be affected quite profoundly by impurities (e.g. phosphorous oxychloride and phosphorus pentachloride) in the acid chloride. It seems however that if only analytically pure acid chloride is used, then the reaction will go to completion.

Pentafluorobenzoic acid is available commercially and was used to prepare pentafluorobenzoyl chloride (XXIX) which was reacted with anhydrous potassium fluoride at elevated temperature to give pentafluorobenzoyl fluoride (XXXIV) in high yield. The corresponding tetrafluoroisonicotinyl halides are only prepared from the commercially available pentachloropyridine by a multi-stage synthesis. Since it is reasonable to assume that the corresponding chlorides and fluorides will behave similarly, it was decided to use the more readily available pentafluorobenzoyl halides in order to establish experimental conditions for reactions. The corresponding tetrafluoroisonicotinyl halide can then be used under the established experimental conditions. In this way a considerable saving in time and effort can be achieved.

Pentafluorobenzoyl fluoride was prepared by reacting pentafluorobenzoyl chloride and anhydrous potassium fluoride (large excess) together in an evacuated, sealed glass tube at 250° for 48 hrs. The product was isolated by vacuum transfer followed by distillation under reduced pressure. Yields were high, the best being 88.6%. When the process was scaled up however, yields were poor because it became very difficult to free the product from the large amount of potassium fluoride present during the vacuum transfer operation.

It was therefore decided to investigate other possible methods of preparation of the acid fluoride. α-Fluoroamines have been used to convert carboxylic acids to acid fluorides in good yields,[136] and so

1-chloro-1,2,2-trifluorotriethylamine was prepared in order to try the method. In the first reaction the α-fluoroamine was added to the acid at room temperature. Little reaction occurred, so the reactants were heated to 85° for 2 hrs. Distillation under reduced pressure of the liquid obtained yielded only a small amount of pentafluorobenzoyl fluoride. Repetition of the reaction at 100° for 4 hrs. gave no acid fluoride.

Potassium fluoride in sulpholane has been widely used to replace chlorine by fluorine and it was thought that it might be successful in this case. Pentafluorobenzoyl chloride was heated with potassium fluoride (100% excess) in sulpholane to 160° for 24 hrs. Removal of the solid by filtration gave a liquid which, after distillation under reduced pressure, was shown by infra-red spectroscopy to be an approximately 50/50 mixture of pentafluorobenzoyl chloride and fluoride. Since the latter two methods were unsuccessful, the two acid fluorides required were prepared by the method previously established, the reaction product being re-treated with fresh potassium fluoride until the reaction was complete.

A convenient synthesis of perfluoroisopropyl ketones, $(CF_3)_2CFCOR_f$, by the fluoride ion catalysed addition of a fluoroacyl fluoride to hexafluoropropene using acetonitrile as solvent has been described.[137] The group R_f was a perfluoroalkyl group. This reaction has now been

extended to cases where R_f is a perfluoroaryl group. Thus pentafluorobenzoyl fluoride and hexafluoropropene (50% excess) when heated together and shaken in acetonitrile, in the presence of a catalytic amount of potassium fluoride, at 135° for 36 hrs. yield a mixture of perfluoro-(phenyl isopropyl)ketone (35%) (XXXV) and perfluoro(4-isopropylphenyl isopropyl)ketone (65%) (XXXVI). The reaction is thought to proceed via a fluorocarbanion intermediate which is formed by the reversible addition of a fluoride ion to the fluoro-olefin. Reaction between this anion and the acyl fluoride at its highly electrophilic carbonyl group, either by direct displacement or addition-elimination, would yield the fluoro ketone and fluoride ion

$$F^- + CF_3CF{=}CF_2 \rightleftharpoons (CF_3)_2CF^-$$

$$(CF_3)_2CF^- + R_fCOF \longrightarrow (CF_3)_2CFCOR_f + F^-$$

This mechanism explains the formation of two products in the above reaction. Perfluoro(phenyl isopropyl)ketone is formed first. The para fluorine atom in this compound is more susceptible, than the one in pentafluorobenzoyl fluoride, to nucleophilic substitution since the $-COCF(CF_3)_2$ group is more powerfully electron attracting than the -COF group, and is readily replaced by the heptafluoroisopropyl anion giving perfluoro-(4-isopropylphenyl isopropyl)ketone. The above theory is supported by the fact that, under the same conditions pentafluorobenzoyl chloride does not react with hexafluoropropene. Under similar conditions

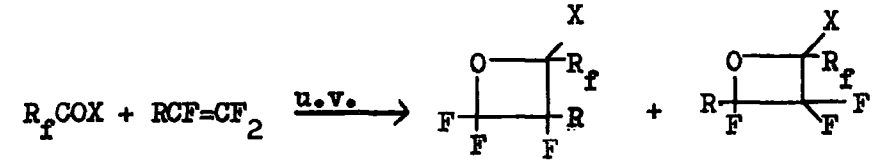
tetrafluoroisonicotinyl fluoride gave a single product, perfluoro-(4-pyridyl isopropyl)ketone (XXVIII). When tetrafluoroisonicotinyl chloride was used as the reactant it was recovered unchanged.

Attempts have been made to extend the above reaction to both cyclic and non-terminal straight chain olefins. Thus pentafluorobenzoyl fluoride, perfluorocyclobutene (in equimolar amounts) and a catalytic amount of caesium fluoride were heated together, in acetonitrile, in a sealed tube with shaking at 160° for 11 hrs. A white solid was obtained by sublimation which after recrystallisation from pet. ether (70-90°) had m.p. 83-88°. G.L.C. analysis (on silicone elastomer at 170°) indicated that it was a single compound. It has not been identified but the analytical figures for carbon and fluorine are inconsistent with those of the ketone expected as the reaction product. A similar reaction using octafluorobut-2-ene as the olefin and potassium fluoride as the catalyst required a temperature of 260° and a reaction time of 8 hrs. The product was shown by G.L.C. analysis (on silicone elastomer at 170°) to be a mixture of two components (one constituting ~90% of the product). Attempted separation of these by preparative scale G.L.C. was unsuccessful due to the inadequacy of the trapping system.

The much higher temperature required for the reaction between these symmetrical non-terminal olefins and pentafluorobenzoyl fluoride

compared with the temperature (135°, using potassium fluoride) for an unsymmetrical olefin such as hexafluoropropene is consistent with the known difficulty of forming the intermediate carbanion with symmetrical olefins where no polarisation of the double bond can occur.

Harris and Coffman have reported[138] that U.V. irradiation of a refluxing mixture of a terminal fluoro-olefin and either a fluoro-aldehyde, fluoroacyl fluoride or a fluoroketone resulted in the cycloaddition of the carbonyl function across the olefinic double bond to give a polyfluoro-oxetane, often in excellent yield. The products were colourless liquids which exhibited considerable thermal stability.



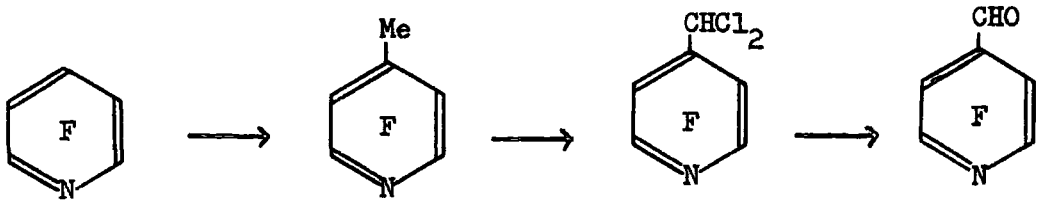
$X = H, R_f, F; R = R_f, Cl$

When an attempt was made to extend the reaction to tetrafluoro-isonicotinyl and pentafluorobenzoyl fluorides with hexafluoropropene under forcing conditions no reaction occurred. Thus tetrafluoroiso-nicotinyl fluoride and hexafluoropropene were placed in a silica tube which was then cooled (in liquid air), evacuated and sealed. It was then heated to 225° whilst being irradiated with U.V. light from a Hanovia lamp placed parallel with it for $4\frac{2}{3}$ days. The liquid obtained

had an infra-red spectrum identical with that of the starting material. Pentafluorobenzoyl fluoride behaved similarly. When the reaction was carried out at room temperature under the influence of γ-radiation from a ^{60}Co source similar results were obtained.

(b) Other Syntheses.

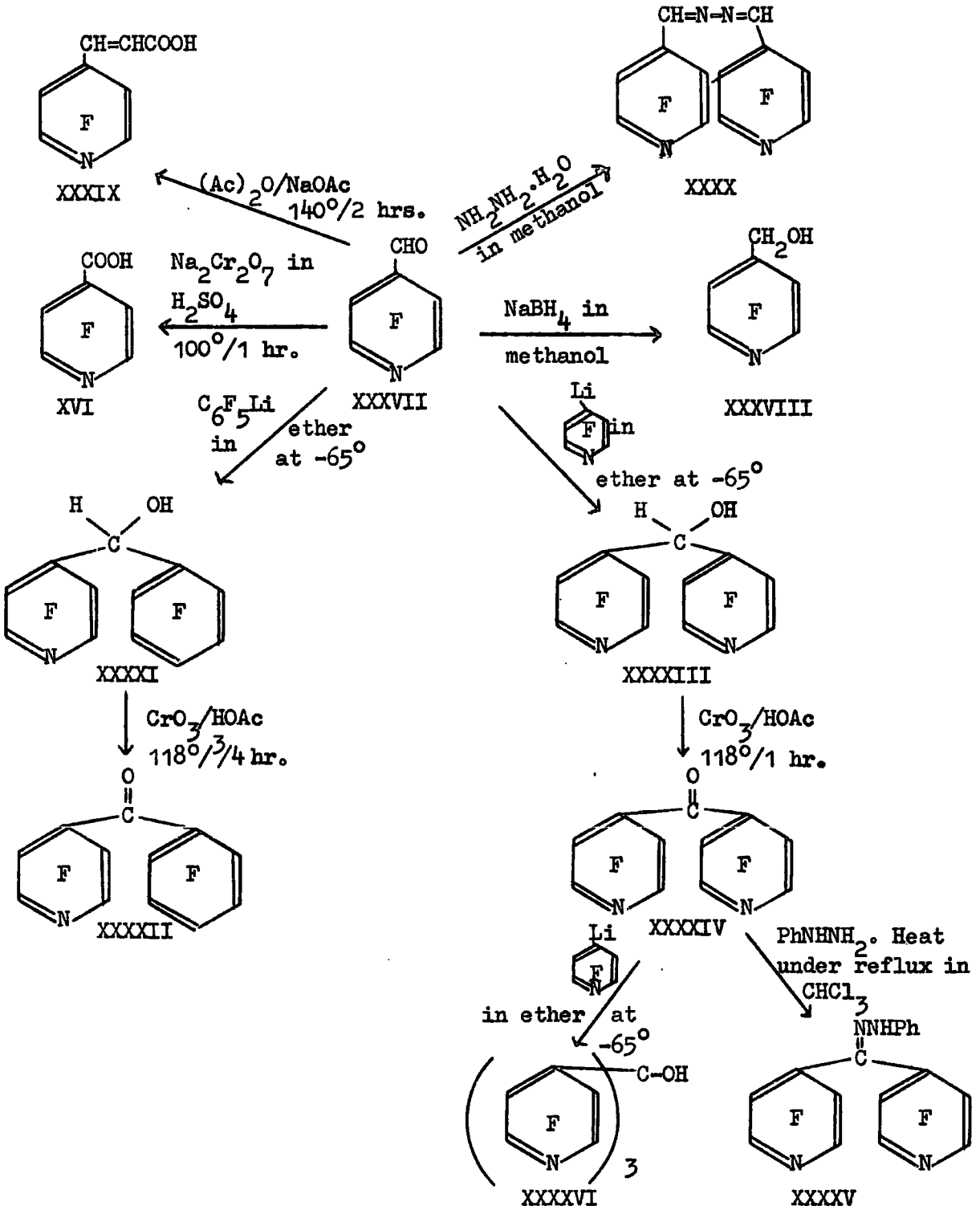
Tetrafluoropyridine-4-aldehyde (XXXVII) was first prepared by the following route[130]



XXXVII

This method had two inherent disadvantages. The 4-Dichloromethyl-tetrafluoropyridine had to be isolated by prep. scale G.L.C. and the overall yield was not very good. A much better method of preparation has now been found. This involved reaction of 4-lithiotetrafluoro-pyridine with N-methylformanilide in ethereal solution at -65°. The aldehyde was obtained in reasonable yield (66%) and was characterised by formation of 2,4-dinitrophenylhydrazone (m.p. 232°, lit.m.p.[130] 232°) and semicarbazone derivatives. The aldehyde could not be obtained by reaction of dimethyl formamide with either 4-lithiotetrafluoropyridine or tetrafluoro-4-pyridyl magnesium bromide.

Reactions which have been carried out on the aldehyde are shown in the following diagram.



Tetrafluoropyridine-4-aldehyde (XXXVII) was readily oxidised to the known tetrafluoroisonicotinic acid (XVI) by heating with sodium dichromate in sulphuric acid to 100° for 1 hr. It was reduced, by excess sodium borohydride in dry methanol at room temperature, to tetrafluoro-4-pyridyl carbinol (XXXVIII) in 65·9% yield.

An attempted Perkin reaction between tetrafluoropyridine-4-aldehyde and acetic anhydride has proved difficult in that the reaction has been accompanied by formation of tarry material which is presumably decomposition product. When the reactants were heated to 140° for 2 hrs. a large amount of tar was formed. A small amount of white solid was isolated which mass spectral analysis indicated was the expected product i.e. β-(tetrafluoro-4-pyridyl)acrylic acid (XXXIX). The carbon analysis was low but the hydrogen analysis was acceptable. The yield was very poor ~15%. Heating at 100° for 1 hr. gave no product, 100° for 2 hrs. gave only a small amount of product but little decomposition. The decomposition may be initiated by some impurity in the aldehyde since even when the aldehyde has been freshly distilled it is slightly yellow (instead of colourless). G.L.C. analysis on silicon elastomer at 120° showed only a single peak. On standing over a period of days the aldehyde progressively darkened until it was a deep red colour. However it still formed derivatives and could be reduced or oxidised.

Hydrazine hydrate (1 mol.) reacted with the aldehyde (XXXVII)

(2 mols.) in ethanol at room temperature to give tetrafluoro-4-pyridyl azine (XXXX).

(Tetrafluoro-4-pyridyl pentafluorophenyl)carbinol (XXXXI) has been prepared by reacting together pentafluorophenyl lithium and tetrafluoropyridine-4-aldehyde in ether at -65°. The yield was 34.7%. The carbinol was, rather surprisingly, a viscous liquid whereas bis-(pentafluorophenyl)carbinol and bis(tetrafluoro-4-pyridyl)carbinol are well defined solids of m.p. 79-80°[139] and 76.5-78° respectively. The carbinol (XXXXI) was readily oxidised, by heating under reflux for 45 mins. with chromic oxide in glacial acetic acid, to (tetrafluoro-4-pyridyl pentafluorophenyl)ketone (XXXXII) in reasonable yield (54%).

Reaction between the aldehyde (XXXVII) and 4-lithiotetrafluoro-pyridine, in ether at -65°, gave bis(tetrafluoro-4-pyridyl)carbinol (XXXXIII) in 56% yield. This was oxidised, by heating with chromium trioxide in glacial acetic acid, to bis(tetrafluoro-4-pyridyl)ketone (XXXXIV). The yield was 62.2%.

Russian workers have very recently reported[140] the preparation of a 2,4-dinitrophenylhydrazone derivative of decafluorobenzophenone by heating the ketone with 2,4-dinitrophenylhydrazine in ethanol containing concentrated sulphuric acid, under reflux for a number of hours. Previously decafluorobenzophenone had been recovered unchanged after heating under reflux for 17 hrs. with 2,4-dinitrophenylhydrazine in ethanol.[139] It was reasoned that this lack of reactivity was due

to the two pentafluorophenyl rings sterically hindering the approach of the attacking nucleophile. Decafluorobenzophenone did however react with pentafluorophenyl lithium in ether at -65° to give tris-(pentafluorophenyl)carbinol. This suggests that the choice of solvent, which can alter the effective size of the nucleophile, is an important factor affecting the reactivity of the carbonyl carbon atom towards nucleophilic reagents. Reactions with normal carbonyl reagents are usually carried out in hydroxylic solvents and this type of solvent can very effectively solvate the attacking nucleophile by hydrogen bonding, giving rise to a bulky, highly solvated molecule, which will be more susceptible to steric hinderance than a smaller, less solvated molecule such as would be found in ethereal solution. The result reported by the Russians shows that even in protic solvents the reduced reactivity of the carbonyl carbon atom towards nucleophiles in decafluorobenzophenone, can be offset by carrying out the reaction in the presence of a strong acid. In the presence of acid protonation of the oxygen atom presumably occurs and this will give rise to a more positive carbonyl carbon atom which will be more susceptible to nucleophilic attack.

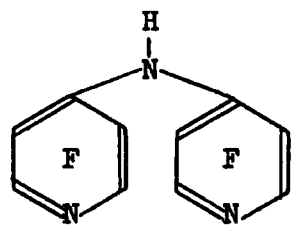
Bis(tetrafluoro-4-pyridyl)ketone (XXXXIV) should be similar, in its degree of steric hinderance towards nucleophiles attacking the carbonyl carbon atom, to decafluorobenzophenone. It did not react with 2,4-dinitrophenylhydrazine in methanol even after heating under reflux

for 16 hrs. A phenylhydrazone derivative (XXXXV) was formed by reaction of the ketone (XXXXIV) with phenylhydrazine in boiling chloroform. The derivative formed rather slowly since after 2 hrs. heating under reflux the yield was only 11·8%. This was increased to 18·4% after 12 hrs. but when the reaction time was further lengthened there was no increase in yield.

The ketone (XXXXIV) also reacted with 4-lithiotetrafluoropyridine in ether at -65° to give tris(tetrafluoro-4-pyridyl)carbinol (XXXXVI) in reasonable yield. This was identified by its mass and infra-red spectra. The carbinol was also prepared by the reaction between 4-lithiotetrafluoropyridine and ethyl tetrafluoroisonicotinate at -65° in ethereal solution.

The above results show that the solvent, which determines the effective size of the attacking nucleophile, has an important effect on the reactivity of the carbonyl carbon atom, in these perfluorinated aromatic ketones, towards nucleophilic reagents.

Bis(tetrafluoro-4-pyridyl)amine (XXXXVII) has been prepared by reaction between the sodio-derivative of 4-aminotetrafluoropyridine and pentafluoropyridine,



XXXXVII

the overall yield being 52·7%. It has not been possible to prepare an N-acetyl derivative of this amine even though the corresponding benzenoid amine (decafluorodiphenylamine) is reported to form one quite readily.[142] This must be due to the reduced basicity of the exocyclic nitrogen atom in the pyridyl amine (XXXXVII) compared with the decafluorodiphenylamine.

Monsanto Chemicals Ltd. have carried out thermal stability determinations on two of the compounds whose preparation is described above. The thermal decomposition points (T_D), where T_D is defined as the temperature at which the vapour pressure of the compound increases at a rate of 0·84 mm. Hg/min. in a nitrogen atmosphere, were determined in an apparatus similar to that described by Blake et al.[141] The results obtained are given below together with those for some related compounds.

Compound	T_D
2,5-Bis(tetrafluoro-4-pyridyl)-1,3,4-oxadiazole	297°
2,5-Bis(pentafluorophenyl)-1,3,4-oxadiazole	327°
2,5-Bis(phenyl)-1,3,4-oxadiazole	304°

Bis(tetrafluoro-4-pyridyl)ketone had too low a boiling point for its thermal stability to be determined by the above method. However

negligible decomposition (as indicated by no increase in vapour pressure) occurred when it was heated to 250° for 5 hrs.

Chapter 6. Experimental Work (Part II)

^{1}H and ^{19}F N.M.R. Spectra.

These were recorded on an A.E.I. R.S.2 or a Perkin-Elmer R10 spectrometer at 60 Mc/sec. Samples were examined as neat liquids or solids dissolved in inert solvents with internal reference compounds.

All ^{1}H spectra are relative to tetramethylsilane.

All ^{19}F spectra are relative to $CFCl_3$. Those marked * were measured using C_6F_6 as internal reference and were converted using the relationship $\delta_{CFCl_3} = \delta_{C_6F_6} + 162{\cdot}24$.

Mass Spectra were recorded on an A.E.I. M.S.9 instrument.

Infra-Red Spectra were recorded using Grubb-Parsons type G.S.2A or Spectromaster instruments.

Drying of Solvents

Diethyl Ether (Ether)

After preliminary treatment with potassium hydroxide this was dried over sodium wire, and then stored over fresh sodium wire until required.

Tetrahydrofuran

This was heated under reflux with potassium (twice), distilled under dry nitrogen and then stored under nitrogen over lithium aluminium hydride. It was freshly distilled off under nitrogen when required.

Methanol

The alcohol (50 mls.) was added to dry magnesium turnings (5 g.) containing a few crystals of iodine and gently warmed until all the iodine had disappeared. Methanol (500 mls.) was then added and the solution heated under reflux for 3 hrs. It was distilled under dry nitrogen and stored under this until required.

Benzene

After preliminary drying, benzene was dried over sodium wire and then stored over fresh sodium wire until required.

Hexane

As benzene.

Temperatures

Unless otherwise stated all reaction temperatures are those of the surrounding heating or cooling baths.

All melting points (m.p.) are uncorrected.

2,4,5,6-Tetrafluoropyridine.[126]

(a) 3-Chlorotetrafluoropyridine (21·1 g.) was flash distilled at 200°, at the rate of 0·15 g./min. and its vapour was carried in a stream of hydrogen (flow rate ~50 mls./min.) over a 10% palladium/charcoal catalyst heated to 250°. The product was condensed out into a trap cooled in liquid air and then dried by distillation in vacuo from phosphoric oxide. 12·87 g. of product was obtained and it was shown by G.L.C. (on di-n-decyl phthalate at 100°) to consist of

3-chlorotetrafluoropyridine	33·5	mole %
2,4,5,6-tetrafluoropyridine	56·5	
2,5,6-trifluoropyridine	10·0	

(b) The experiment was repeated using 3-chlorotetrafluoropyridine (53 g.), a hydrogen flow rate of 100 mls./min. and a 20% palladium/charcoal catalyst. 29 g. of product, which was shown by G.L.C. analysis to contain 76 mole % of 2,4,5,6-tetrafluoropyridine together with 18 mole % of unreacted starting material, was obtained.

Attempted Preparations of 2,4,5,6-Tetrafluoropyridine.

(a) 3-Chlorotetrafluoropyridine (2 g., 11·78 m.mole), acetic anhydride (1·20 g., 11·78 m.mole) and anhydrous cuprous oxide (1·62 g., 11·78 m.moles) in dry pyridine (20 mls.) were heated to 100° for 3 hrs. in an atmosphere of dry nitrogen. It was then poured into 6N hydrochloric acid (125 mls.) and then filtered to give a black precipitate (not investigated)

and a red filtrate which was extracted with ether. The extracts were dried ($MgSO_4$), filtered and the ether distilled off to leave a liquid. This was distilled to give ether and a fraction b.p. 192-6° which rapidly solidified (0·87 g.). The solid was recrystallised from benzene/ pet. ether (40-60) m.p. 118-120°. Analysis by G.L.C. on silicon elastomer at 150° showed it to consist of three components and it was not investigated any further.

(b) A solution of n-butyl-lithium in hexane (3·9 mls., 10·6 m.moles) in ether (5 ml.) was stirred at -75° in an atmosphere of dry nitrogen. 3-Chlorotetrafluoropyridine (2 g., 10·6 m.moles) in ether (5 ml.) was slowly added dropwise. A vigorous reaction occurred and the solution became very dark. It was stirred for a further 30 mins. at -75° and then acidified with dilute sulphuric acid. The solution was extracted with ether, the extracts dried ($MgSO_4$), filtered and the ether distilled off leaving a yellow liquid (0·8 g.). Analysis by G.L.C. (di-n-decyl phthalate at 100°) showed that the liquid contained, as well as solvents, two products both of which had retention times longer than that of the required 2,4,5,6-tetrafluoropyridine. The products were not investigated any further.

Tetrafluoropyridine-3-aldehyde.

2,4,5,6-Tetrafluoropyridine (2·0 g.) in ether (25 ml.) was stirred

at -70° under dry nitrogen. A solution of n-butyl lithium in hexane (10 ml., 2·7M) in ether (5 mls.) was added over 20 mins. and the resulting solution stirred for 30 mins. N-methylformanilide (2 g.) in ether (5 mls.) was added and the mixture stirred for 1 hr. It was then acidified with 25% v/v sulphuric acid (30 ml.) and ether extracted. The extracts were dried ($MgSO_4$), filtered, and the solvent distilled off to leave a viscous liquid from which some solid appeared. Sublimation in vacuo (30°/15 mm.) afforded a white solid (0·96 g., 40·5%). This was recrystallised from pet. ether (40-60) containing a little benzene to give the lachrymatory TETRAFLUOROPYRIDINE-3-ALDEHYDE, m.p. 59-60°.

Calc. for C_6HF_4NO	C:	40·2;	H:	0·56;	F: 42·45
Found:	C:	39·8;	H:	0·75;	F: 40·9

This gave in the usual way an anilide derivative m.p. 186-188° (from aq. methanol).

The aldehyde's mass spectrum showed a strong parent peak at $^m/_e$ 179 and strong peaks at 178 $(C_6F_4NO)^+$ and 150 $(C_5F_4N)^+$

Tetrafluoropyridine-3-aldehyde-2,4-dinitrophenylhydrazone.

Tetrafluoropyridine-3-aldehyde (·05 g.), 2,4-dinitrophenylhydrazine (·075 g.) in methanol (5 ml.) and concentrated hydrochloric acid (3 drops) were heated together under reflux for a few minutes. After cooling the

yellow precipitate was filtered off (0·10 g., 99·7%). It was recrystallised from benzene giving TETRAFLUOROPYRIDINE-3-ALDEHYDE 2,4-DINITROPHENYL HYDRAZONE, m.p. 217-8°.

Calc. for $C_{12}H_5F_4N_5O_4$	C: 40·0;	H: 1·42
Found:	C: 39·8;	H: 1·55

Attempted preparation of tetrafluoropyridine-3-aldehyde from 3-chlorotetrafluoropyridine directly

3-Chlorotetrafluoropyridine (2 g., 10·8 m.moles) in ether (4 ml.)/tetrahydrofuran (1 ml.) was added dropwise to a stirred mixture of magnesium turnings (1 g., 20·5 m.moles) in ether (8 ml.)/tetrahydrofuran (2 ml.) containing ethylene dibromide (3 drops) under dry nitrogen. A vigorous reaction occurred causing the solvent to reflux. After stirring for 15 mins. N-methylformanilide (2 g.) in ether (5 mls.) was added and the mixture stirred for 1 hr. After acidification with dilute sulphuric acid the solution was extracted with ether, the extracts dried ($MgSO_4$), filtered and the solvent distilled off. Sublimation at 15 mms. at 40° yielded no aldehyde. The dark residue was presumably polymeric material.

The experiment was repeated using ether as solvent, refluxing for 3 hrs. for formation of the Grignard and refluxing for 1 hr. after the addition of the N-methylformanilide. No aldehyde was obtained.

3-Chloro-4-pentafluorophenoxytrifluoropyridine.[118]

3-Chlorotetrafluoropyridine (6.0 g.), potassium pentafluorophenate dihydrate (8.38 g.) and tetrahydrofuran (60 ml.) were heated under reflux for 17 hrs. with stirring. The mixture was poured into water, extracted with ether, dried ($MgSO_4$) and the ether removed by distillation. The residue was distilled under reduced pressure (15 mm.) and yielded three fractions:

(1) b.pt. 0-140°, 0.15 g.

(2) b.pt. 140-144°, 4.25 g.

(3) b.pt. 144-182°, 4.10 g.

Fractions 2 and 3 were examined by gas liquid chromatography (silicone grease at 200°). Fraction 2 contained mainly 3-chloro-4-pentafluorophenoxytrifluoropyridine contaminated with a little (~5%) 3-chlorotetrafluoropyridine. Fraction 3 contained approximately equal weights of 3-chloro-4-pentafluorophenoxytrifluoropyridine and bis(pentafluorophenoxy)-3-chlorodifluoropyridine. This was confirmed by the infrared and mass spectra of fractions 2 and 3.

The ^{19}F n.m.r. spectrum of fraction 2 was consistent with its containing mainly 3-chloro-4-pentafluorophenoxytrifluoropyridine.

Attempted Preparation of 4-Pentafluorophenoxytrifluoro-3-pyridyl Magnesium Chloride.

3-Chloro-4-pentafluorophenoxytrifluoropyridine (1 g., 2.86 m.moles) in tetrahydrofuran (2 ml.) containing ethylene dibromide (3 drops) was

added to a stirred mixture of magnesium turnings (·076 g., 3·15 m.mole) in tetrahydrofuran (5 ml.) containing ethylene dibromide (6 drops) under dry nitrogen. There appeared to be no reaction after stirring for 30 mins. so the mixture was heated under reflux for 3 hrs. After acidification with dilute sulphuric acid the solution was extracted with ether, the extracts dried ($MgSO_4$), filtered and the solvent distilled off. Analysis of the liquid remaining by G.L.C. (silicone elastomer at 170°) showed that it consisted of ether, tetrahydrofuran and a component whose retention time was identical with that of the starting 3-chloro-4-pentafluorophenoxytrifluoropyridine.

2,4,6-Trifluoropyridine.[126]

3,5-Dichlorotrifluoropyridine (17·5 g.) was flash distilled at 250°, at the rate of 0·1 g./min., and its vapour carried over a palladium/charcoal catalyst heated to 280° in a stream of hydrogen (flow rate ~ 80 mls./min.). The product was condensed out into a trap cooled in liquid air and then dried by distillation from phosphoric oxide in vacuo (8·77 g., 76%). Analysis by G.L.C. (on silicone elastomer at 80°) showed it to be almost pure (> 95%) 2,4,6-trifluoropyridine.

2,4,6-Trifluoronicotinic acid.[126]

n-Butyl lithium (35·2 m.moles) in dry hexane (10 ml.) was added, under dry nitrogen, over a period of one hour to a stirred solution of 2,4,6-trifluoropyridine (2·33 g., 17·6 m.moles) in dry hexane (30 mls.)

at -70°. The mixture was stirred at -70° for a further half hour and then carbon dioxide was bubbled in for one and a half hours during which the temperature slowly rose to 0°. Water (30 mls.) was added followed by dilute hydrochloric acid (35 mls.). The organic layer was separated and then the aqueous layer was extracted with ether (2 x 20 mls.). The combined organic layers were dried ($MgSO_4$) and the solvent removed by distillation. Sublimation of the resulting product at 50° and 0.05 mms. yielded 2,4,6-trifluoronicotinic acid (0.88 g., 28.4%) which was recrystallised from hexane. The low yield may have been due to the quality of the butyl lithium which was old material.

2,4,6-Trifluoronicotinyl Chloride.

2,4,6-Trifluoronicotinic acid (0.88 g.) and phosphorus pentachloride (1.055 g., 1% excess) were stirred together. On slight warming a vigorous reaction occurred with rapid evolution of hydrogen chloride. When the vigorous reaction had subsided the resulting liquid was heated to 85° for one hour. Distillation of the product obtained under reduced pressure (15 mms.) gave some low boiling material (phosphorus oxychloride) and a main fraction b.p. 73.5 - 74° which was identified by its infra-red spectrum as 2,4,6-TRIFLUORONICOTINYL CHLORIDE, (0.57 g., 56.7%).

Calc. for C_6HF_3ClNO	C: 36.8;	H: 0.51
Found:	C: 35.9;	H: 0.74

Reaction of 2,4,6-Trifluoronicotinyl Chloride with Anhydrous Ammonia.

Anhydrous ammonia was bubbled through a solution of 2,4,6-trifluoronicotinyl chloride (0·42 g.) in benzene (15 mls.) for 15 mins. The benzene was then heated on a water bath and the insoluble white solid filtered off from the benzene solution and washed with ether (15 mls.). The combined organic solutions were then distilled to remove the solvent, leaving behind a white solid which was sublimed at 90° and 0·01 mms. (0·215 g.). The solid was twice recrystallised from benzene to give a white solid, some of which melted at approx. 140° and the remainder at 168°.

Calc. for $C_6H_5F_2N_3O$	C: 41·6;	H: 2·89;	F: 22·0
Calc. for $C_6H_3F_3N_2O$	C: 40·9;	H: 1·70;	F: 32·4
Found:	C: 41·3;	H: 2·60;	F: 26·2

The product thus appeared to be a mixture of 2,4,6-trifluoronicotinamide and 4-amino-2,6-difluoronicotinamide.

Mass spectral analysis confirmed this, the spectrum having peaks at 176 $(C_6H_3F_3N_2O)^+$ and 173 $(C_6H_5F_2N_3O)^+$.

4-Amino-2,6-difluoronicotinamide.

2,4,6-Trifluoronicotinic acid (0·3 g.) was heated with thionyl chloride (6 ml.) under reflux for 12 hrs. The excess thionyl chloride was removed by distillation under reduced pressure. Dry benzene (10 ml.) was then added and anhydrous ammonia bubbled through the

solution for 10 mins. at room temperature. Sublimation under reduced pressure of the brown solid obtained after the benzene had been distilled off, afforded a white solid (0.08 g.) which was thrice recrystallised from water yielding 4-AMINO-2,6-DIFLUORONICOTINAMIDE m.p. 166.5-167.5° identified by its infra-red spectrum.

Calc. for $C_6H_5F_2N_3O$	C:	41.6;	H:	2.9
Found:	C:	41.2;	H:	3.1

SYNTHESIS OF TETRAFLUOROISONICOTINIC ACID.[116,119]

1. Preparation of 4-aminotetrafluoropyridine.

Pentafluoropyridine (10 g., 0·059 mole) and ammonia (20 ml; 0·88 s.g.) were placed in a Carius tube and the tube evacuated and sealed. The tube was heated to 80° for 5 hrs. On cooling to room temperature the organic layer solidified. The tube was opened and water added to the mixture which was then extracted with ether. Distillation of the dried ($MgSO_4$) ether extracts afforded a white crystalline material (8·8 g., 90%). Sublimation under reduced pressure and recrystallisation from light petroleum (b.p. 80-100°) gave 4-aminotetrafluoropyridine m.p. 85-86°.

2. Preparation of 4-bromotetrafluoropyridine from 4-aminotetrafluoropyridine.

4-Aminotetrafluoropyridine (12 g.) was dissolved in hydrofluoric acid (80 ml.; 80% $^{w}/_{w}$), stirred and cooled to -20°. Sodium nitrite (12 g.) was added over a period of 30 mins. Freshly prepared cuprous bromide (made by dissolving the water washed precipitate from 60 g. copper sulphate + 40 g. potassium bromide + 20 g. sodium sulphite, in 40 ml. of hydrobromic acid (48% $^{w}/_{w}$)) was added to the diazotised amine over a period of 30 mins. at a temperature of -20 to -25°. After a further 30 mins. stirring during which the temperature rose to room temperature, the mixture was diluted with water (1 l.). The mixture was extracted with methylene chloride, the extracts dried ($MgSO_4$) and the solvent distilled off. Distillation of the residual liquid from

phosphorus pentoxide yielded 4-bromotetrafluoropyridine (12·3 g., 73·9%, b.p. 138-142°/760 mm. lit. 134-135°/760 mm.).

3. Conversion of 4-bromotetrafluoropyridine to tetrafluoroisonicotinic acid.

(a) Via tetrafluoro-4-pyridylmagnesium bromide.

A three necked flask fitted with stirrer, dropping funnel, condenser and containing magnesium (4 g.) and dry tetrahydrofuran (40 ml.) was purged with dry nitrogen and cooled to -25°. A solution of 4-bromotetrafluoropyridine (20 g.) in dry tetrahydrofuran (10 ml.) was added over 45 mins. After a short time the reaction commenced. The reaction mixture was allowed to warm to -10 to 0° and was then maintained at this temperature for 1·5 hours before dry carbon dioxide was bubbled through the solution for 2 hrs. at -10°. Dilute sulphuric acid was then added and when all the excess magnesium had dissolved the mixture was extracted with ether. The extracts were dried ($MgSO_4$), the solvent was removed by distillation and from the residue a white solid (10·1 g., 62%) was sublimed under reduced pressure. Recrystallisation from hexane afforded tetrafluoroisonicotinic acid m.p. 104-105°.

(b) Via 4-lithiotetrafluoropyridine.

4-Bromotetrafluoropyridine (2 g., 8·75 m.mole) in dry ether (15 ml.) was added over a period of 1 hr. at -75° to a solution of butyl-lithium (3·5 ml., 8·75 m.mole) in ether (15 ml.) under dry nitrogen. The solution was then carbonated for 1 hr. during which the temperature rose to room

temperature. Water was then added in order to dissolve the lithium salt of tetrafluoroisonicotinic acid which had precipitated. The solution was then acidified with dilute hydrochloric acid and ether extracted. The ether extract was dried ($MgSO_4$) and after the solvent had been removed, sublimation under reduced pressure afforded the tetrafluoroisonicotinic acid (1·35 g., 80%).

Tetrafluoroisonicotinic Anhydride.

Tetrafluoroisonicotinic acid (4·0 g.) and trifluoroacetic anhydride (4 ml.) were heated together under reflux for 5 hrs. Distillation under reduced pressure (0·05 mm.) gave, after removal of excess trifluoroacetic acid and anhydride, a clear liquid (3·24 g., 91·8%). This was re-distilled to give TETRAFLUOROISONICOTINIC ANHYDRIDE, b.p. 110-110·5° at 0·05 mm.

Calc. for $C_{12}F_8N_2O_3$	C: 38·7;	F: 40·9
Found:	C: 38·8;	F: 40·3

The mass spectrum was consistent with the proposed structure.

Reaction of Tetrafluoroisonicotinic acid with Thionyl Chloride.

Tetrafluoroisonicotinic acid (1 g.) was heated under reflux with thionyl chloride (10 ml.) for 16 hrs. The excess thionyl chloride was then removed by distillation under reduced pressure. The residual liquid was then distilled under reduced pressure (0·1 mm.) to give a green liquid (0·7 g., b.p. 114-118°). Some unreacted acid solidified

in the condenser during the distillation. The infra-red spectrum of the liquid obtained showed the presence of a hydroxyl group (due to unreacted acid).

Elemental analysis of what was thought to be a fairly pure sample of green liquid (produced as above) gave:-

	C:	37·6;	F:	43·6;	Cl: nil
Calculated for C_6F_4ClNO	C:	33·7;	F:	35·6;	Cl: 16·6
Calculated for $C_{12}F_8N_2O_3$	C:	38·7.	F:	40·9;	Cl: nil

This liquid reacted as tetrafluoroisonicotinyl chloride would be expected to react e.g. gave an amide by reaction with ammonia, and a phenyl hydrazide by reaction with phenyl hydrazine. An obvious conclusion to draw from this is that the liquid is the anhydride of tetrafluoroisonicotinic acid. This compound would be expected to react in a similar manner to the acid chloride and the carbon analysis is consistent with a 50:50 mixture of anhydride and unreacted acid.

Tetrafluoroisonicotinamide (Method 1).

Tetrafluoroisonicotinic acid (0·66 g.) was heated under reflux with thionyl chloride (11 ml.) for 12 hrs. Excess thionyl chloride was removed by distillation under reduced pressure. Dry benzene (15 ml.) was then added and anhydrous ammonia bubbled through the solution for 10 mins. The benzene was distilled off leaving a light brown solid which was washed with a little water, dried, and sublimed under reduced pressure to give a white solid (0·2 g., 31%). Recrystallisation from

carbon tetrachloride afforded TETRAFLUOROISONICOTINAMIDE m.p. 96-97°.

Calculated for $C_6H_2F_4N_2O$ C: 37·1; H: 1·03; F: 39·15

Found C: 37·0; H: 1·08; F: 38·8

The ^{19}F N.M.R. spectrum was characteristic of a 4-substituted tetrafluoropyridine derivative. It showed only two peaks, at 89·7 p.p.m. (2,6-F's) and 142·1 p.p.m. (3,5-F's)*.

N-Phenyl-N'-Tetrafluoroisonicotinylhydrazine.

The liquid obtained by reacting tetrafluoroisonicotinic acid with thionyl chloride (0·45 g.) in ether (10 mls.) was stirred at room temperature. Phenyl hydrazine (0·5 g.) was added over 15 mins. and then the mixture stirred for a further 30 mins. A white solid soon precipitated from the brown coloured ether solution. The white solid (0·38 g.) was filtered off and recrystallised from propanol/hexane. The solid started to decompose at 130°. Elemental analysis gave

C: 45·4; H: 2·96

It has not been identified.

Concentration of the ether solution gave a red and white solid. This was filtered off and washed with a little ether leaving a white solid which was recrystallised from hexane/meths/carbon tetrachloride affording N-PHENYL-N'-TETRAFLUOROISONICOTINYL HYDRAZINE (0·3 g., 49·8%) m.p. 175-180° (decomposition).

Calculated for $C_{12}H_7F_4N_3O$ C: 50·5; H: 2·35

Found C: 50·5; H: 2·45

The mass spectrum was as expected i.e. parent peak at 285, major peaks at 178 $(C_6F_4NO)^+$ and 107 $(C_6H_7N_2)^+$.

Tetrafluoroisonicotinyl chloride.

Tetrafluoroisonicotinic acid (10 g.) and phosphorus pentachloride (12·2 g.; 10% excess) were stirred together. On slight warming a vigorous reaction occurred with rapid evolution of hydrogen chloride. When the reaction had moderated the solution was heated under reflux for 1 hr. On cooling and standing at room temperature for 1 hr., the excess phosphorus pentachloride crystallised out. The liquid product (19·65 g.) was decanted off and distilled under reduced pressure (13 mms.) through a Vigreux column to yield two fractions

(1) b.p. 16-42°

and (2) TETRAFLUOROISONICOTINYL CHLORIDE b.p. 42-43 (6·70 g., 61·2%).

Calc. for C_6F_4ClNO	C: 33·7;	F: 35·6;	Cl: 16·6
Found	C: 33·4;	F: 35·4;	Cl: 17·1

The infra-red spectrum of fraction (1) showed that it contained some acid chloride.

Pentafluorobenzoyl chloride.

Pentafluorobenzoic acid (4·2 g.) and phosphorus pentachloride (4·7 g.) were stirred together. On warming slightly a vigorous reaction occurred with rapid evolution of hydrogen chloride. When the reaction had

moderated the solution was heated at 100° for one hour. On cooling and standing at room temperature for one hour, the excess phosphorus pentachloride crystallised out. The liquid product was decanted off and distilled under reduced pressure (18 mms.) yielding two fractions,

(1) Phosphorus oxychloride, b.p. 23-40°.

(2) Pentafluorobenzoyl chloride, b.p. 60-61°

The yield of acid chloride (based on the weight of fraction (2)) was 83.9%.

Tetrafluoroisonicotinamide (Method 2).

Tetrafluoroisonicotinyl chloride (6.1 g.) was dissolved in dry benzene (15 mls.) and anhydrous ammonia was bubbled through the solution for 30 mins. After standing overnight, the solid was filtered off and washed with water (1.25 g.). Concentration of the filtrate gave more solid (2.82 g.). The combined solids (4.07 g., 69.8%) were recrystallised benzene/ethanol to give tetrafluoroisonicotinamide m.p. 96-97°.

Methyl tetrafluoroisonicotinate.

Tetrafluoroisonicotinyl chloride (3.8 g.) and anhydrous methanol (12 ml.) were heated under reflux for 30 mins. Excess methanol was distilled off leaving a slightly cloudy liquid (3.0 g.). Distillation gave a clear liquid (2.75 g., 80.6%). This was redistilled to yield METHYL TETRAFLUOROISONICOTINATE b.p. 182-182.5°/760 mm.

Calc. for $C_7H_3F_4NO_2$	C: 40.3;	H: 1.44;	F: 36.4
Found:	C: 40.2;	H: 1.45;	F: 36.0

Its mass spectrum had a strong parent peak at 209, and other prominent peaks at 178 $(C_6F_4NO)^+$ and 150 $(C_5F_4N)^+$.

Ethyl Tetrafluoroisonicotinate.

Tetrafluoroisonicotinyl chloride (3·15 g.) and ethanol (20 ml.) were heated together under reflux for 1 hr. Most of the excess ethanol was distilled off and the residue was then distilled under reduced pressure (18 mms.) to yield ETHYL TETRAFLUOROISONICOTINATE b.p. 92-3° (2·46 g., 74·8%).

Calc. for $C_8H_5F_4NO_2$	C:	43·05;	H:	2·24;	F:	34·1
Found:	C:	43·0;	H:	2·40;	F:	34·2

N-(Tetrafluoro-4-pyridyl)pentafluorobenzamide.

4-Aminotetrafluoropyridine (1 g.) and N,N-diethylaniline (0·94 g.) were stirred in xylene (5 mls.) at room temperature. Pentafluorobenzoyl chloride (1·39 g.) in xylene (5 mls.) was added and the solution heated under reflux for 18 hrs. giving a green solution. The solution was cooled and then stirred at room temperature for 30 mins. with N hydrochloric acid (15 ml.). The green solid which precipitated was filtered off, washed with water and dried (1·75 g.; 80·7%). Sublimation (at 115°) under reduced pressure (0·01 mms.) gave a white solid which was recrystallised from aqueous ethanol yielding N-(TETRAFLUORO-4-PYRIDYL)PENTAFLUOROBENZAMIDE m.p. 170·5 - 1·5°.

Calc. for $C_{12}HF_9N_2O$	C:	40·0;	H:	0·29;	F:	47·5
Found:	C:	39·9;	H:	0·44;	F:	47·0

N-(Pentafluorophenyl)pentafluorobenzamide.

Using the method used in the previous experiment (but with benzene as solvent in place of xylene):- pentafluorobenzoyl chloride (1·1 g.) and pentafluoroaniline (0·86 g.) gave N-(PENTAFLUOROPHENYL)PENTAFLUORO-BENZAMIDE (1·18 g.; 72·2%) m.p. 178·5 - 179·5° from benzene/ethanol.

Calc. for $C_{13}HF_{10}NO$	C:	41·4;	H:	0·27;	F: 50·4
Found:	C:	41·6;	H:	0·55;	F: 49·9

N'-(Tetrafluoro-4-pyridyl)pentafluorobenzohydrazide.

4-Hydrazinotetrafluoropyridine (0·78 g.) and N,N-diethylaniline (0·66 g.) in benzene (5 ml.) were stirred at room temperature. Pentafluorobenzoyl chloride (1 g.) was added and an exothermic reaction occurred. The reactants were then heated under reflux for 1 hr. and on cooling the solution went solid. N hydrochloric acid (5 ml.) was then added and the mixture stirred for 15 mins. The solid was then filtered off, washed with water and dried over phosphoric oxide in vacuo. Two recrystallisations from aqueous ethanol (once in the presence of charcoal) yielded white crystals of N'-(TETRAFLUORO-4-PYRIDYL)PENTAFLUOROBENZO-HYDRAZIDE (1·0 g.; 61·5%) m.p. 184-185·5° (decomp.)

Calc. for $C_{12}H_2F_9N_3O$	C:	38·4;	H:	0·53;	F: 45·6
Found:	C:	38·4;	H:	0·65;	F: 44·9

N'-(Pentafluorophenyl)pentafluorobenzohydrazide.

Method as in previous experiment using:- pentafluorophenylhydrazine (0·5 g.) and pentafluorobenzoyl chloride (0·58 g.) gave N'-(PENTAFLUOROPHENYL)PENTAFLUOROBENZOHYDRAZIDE (0·90 g.; 90·7%) m.p. 194-195·5° (from aqueous ethanol).

Calc. for $C_{13}H_2F_{10}N_2O$	C: 39·8;	H: 0·51;	F: 48·5
Found:	C: 40·1;	H: 0·61;	F: 48·0

N'-(Tetrafluoro-4-pyridyl)tetrafluoroisonicotinohydrazide.

Tetrafluoroisonicotinyl chloride (1·17 g.) was added to 4-hydrazinotetrafluoropyridine (1 g.) and N,N-diethylaniline (1·17 g.) in benzene (3 ml.). A strongly exothermic reaction occurred giving a yellow solution which was heated under reflux for 1½ hrs. After cooling it was stirred for 30 mins. with N hydrochloric acid. No precipitate was obtained. The mixture was extracted with ether, the extracts dried ($MgSO_4$) and the solution concentrated to give a white solid which was filtered off (0·46 g.; 23·3%). It was sublimed at 120° under high vacuum (·001 mm.) giving N'-(TETRAFLUORO-4-PYRIDYL)TETRAFLUOROISONICOTINOHYDRAZIDE m.p. 173-4°.

Calc. for $C_{11}H_2F_8N_4O$	C: 36·9;	H: 0·56;	F: 42·45
Found:	C: 37·0;	H: 0·86;	F: 42·0

N,N'-Bis(tetrafluoroisonicotinyl)hydrazine.

Tetrafluoroisonicotinyl chloride (5 g.) was added to a stirred

solution of N sodium hydroxide (25 ml.) and followed immediately by the dropwise addition of hydrazine hydrate (1·15 ml.) in water (2 ml.). A vigorous exothermic reaction occurred and a white solid appeared. After a further 30 mins. stirring at room temperature the reaction mixture went almost completely solid. Water (10 ml.) was added and the mixture stirred for a further 15 mins. The white solid was filtered off and washed with water. Acidification of the filtrate gave no precipitate. The white solid was dried at 110° for 1 hr. (2·67 g., 59·6%). Recrystallisation twice from aqueous methanol (once in the presence of charcoal) yielded white needles of N,N'-BIS(TETRAFLUOROISONICOTINYL)-HYDRAZINE, decomp. 250-262°.

Calc. for $C_{12}H_2F_8N_4O_2$	C: 37·3;	H: 0·50;	F: 39·4
Found:	C: 37·2;	H: 0·64;	F: 39·4

The ^{19}F N.M.R. spectrum showed peaks at 88·6 p.p.m. (2,6-F's) and 140·8 p.p.m. (3,5-F's)*. The mass spectrum gave a parent peak at 386 and prominent peaks at 178 $(C_6F_4NO)^+$ and 150 $(C_5F_4N)^+$.

2,5-Bis(tetrafluoro-4-pyridyl)-1,3,4-oxadiazole.

(a) An intimate mixture of N,N'-bis(tetrafluoroisonicotinyl)hydrazine (0·20 g.) and phosphoric oxide (0·25 g.) was placed in a Carius tube which was then evacuated, sealed and heated for 4 hrs., during which the temperature rose to 210°, and then five hours at this temperature. On cooling some white and some brown solid were obtained. The tube was

opened, water added and the mixed solid filtered off and washed with water. It was dried at 110° for 15 mins. (0·197 g.; 100%). Two recrystallisations from methylated spirits (once in the presence of charcoal) yielded 2,5-BIS(TETRAFLUORO-4-PYRIDYL)-1,3,4-OXADIAZOLE, m.p. 144-145·5° as a white solid (0·041 g.; 21·6%).

Calc. for $C_{12}F_8N_4O$ C: 39·1; F: 41·3

Found: C: 39·0; F: 40·1

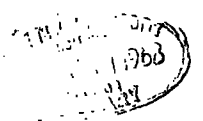
The mass and infra-red spectra were consistent with the proposed structure.

The mass spectrum gave a strong parent peak at 368. The breakdown pattern was rather complicated but accurate mass measurement on the parent peak confirmed that the molecular formula was $C_{12}F_8N_4O$.

(b) Bis(tetrafluoroisonicotinyl)hydrazine (10 g.) and phosphoryl chloride (75 ml.) were heated together under reflux for 40 hrs. After cooling, the resulting solution was slowly poured onto ice to hydrolyse the excess phosphoryl chloride. The white precipitate obtained was filtered off, washed with cold water and then dried over phosphoric oxide in vacuo (8·7 g., 91·3%). Two recrystallisations from aqueous ethanol gave almost pure oxadiazole m.p. 142-3°. Purification by fractional sublimation (120° and 0·02 mm.) gave 2,5-bis(tetrafluoro-4-pyridyl)-1,3,4-oxadiazole m.p. 144-5°.

Calc. for $C_{12}F_8N_4O$ C: 39·1; F: 41·3

Found C: 38·8; F: 40·9



Reaction between the above oxadiazole and ammonia.

Oxadiazole (0·3 g.), ammonia (1 ml., density = 0·88 g./ml.) and acetone (5 ml.) were placed in a Carius tube which was cooled, evacuated and sealed before heating to 80° for 2 hrs. The tube was cooled, opened and its contents poured into water giving a yellow precipitate. This was extracted into ether (2 x 10 ml.), the extracts dried ($MgSO_4$) and the solvent distilled off to leave a yellow solid (0·23 g.). Recrystallisation from aqueous acetone in the presence of decolourising charcoal gave a yellow solid which melted with decomposition at 210-212°. The mass spectrum indicated that this was a di-amino derivative since the parent peak was at 362.

2,5-Bis(tetrafluoro-4-pyridyl)-1,3,4-thiadiazole.

N,N'-bis(tetrafluoroisonicotinyl)hydrazine (0·53 g.) and phosphorus pentasulphide (0·60 g.) were heated together in anhydrous xylene under reflux for 41 hrs. The solution darkened considerably on extensive heating. On completion of the reaction the hot solution was filtered leaving some brown solid. Removal of the solvent (by distillation) from the filtrate yielded a brown green solid which was extracted into boiling ethanol (some brown solid did not dissolve). Charcoal was added and the hot solution filtered. On cooling white needles (0·070 g.; 16%) crystallised out. A further recrystallisation from ethanol yielded white needles of 2,5-BIS(TETRAFLUORO-4-PYRIDYL)-1,3,4-THIADIAZOLE, m.p. 140-1°.

Calc. for $C_{12}F_8N_4S$	C: 37·5;	F: 39·6
Found:	C: 37·6;	F: 39·4

The mass spectrum showed a strong parent peak at 384 and others at 208 $(C_6F_4N_2S)^+$, 194 $(C_6F_4NS)^+$, 176 $(C_6F_4N_2)^+$ and 150 $(C_5F_4N)^+$.

Tetrafluoroisonicotinyl fluoride.

(a) Tetrafluoroisonicotinyl chloride (3·0 g., b.p. 60-66° at 36 mms.) and freshly roasted potassium fluoride (6·0 g.) were placed in a Carius tube which was then evacuated, sealed and heated to 210° for 40 hrs. The tube was allowed to cool, then opened and the product distilled out under vacuum (1·81 g., 65·3%). It was then distilled under reduced pressure (30 mms.) yielding TETRAFLUOROISONICOTINYL FLUORIDE b.p. 55-56°.

Calc. for C_6F_5NO	C: 36·5;	F: 48·2
Found:	C: 36·4;	F: 48·2

Its ^{19}F N.M.R. spectrum showed three peaks, one of which was at very low field in the region characteristic of acyl fluorines. The chemical shifts were 135·7 p.p.m. (3,5-F's), 86·4 p.p.m. (2,6-F's) and -48·8 p.p.m. (acyl fluorine).

The mass spectrum gave the parent peak (197) as the most abundant peak.

(b) Tetrafluoroisonicotinyl chloride (6·95 g., b.p. 58-65° at 25 mm.) and freshly roasted potassium fluoride (12 g.) were reacted as above.

The product was shown (infra-red spectrum) to be a mixture of starting material and product, the relative amounts (estimated by the intensity of the carbonyl group absorption) being ~1·5:1. On heating the product with fresh potassium fluoride (12 g.) to 130° for 40 hrs. further fluorination occurred, the ratio changing to ~0·6:1.

(c) Freshly roasted potassium fluoride (15 g.) and tetrafluoroisonicotinyl chloride (3·21 g., b.p. 54-64 at 23 mms.) were placed in a stainless steel autoclave (120 ml.) which was then sealed and evacuated to a pressure of 10 mms. The autoclave was heated to 190° for 15 hrs., then 225° for 7 hrs. The product, which was distilled out under vacuum (1·5 g.; 66·1%), was 2,3,5,6-tetrafluoropyridine, identified by comparison of its infra-red spectrum with that of an authentic sample.

(d) Tetrafluoroisonicotinic acid (0·5 g.) and freshly roasted potassium fluoride (2·5 g.) were placed in a Carius tube which was then evacuated, sealed and heated to 190° for 5 hrs. and then 210° for 5 hrs. The tube was cooled, opened and the product (0·3 g., 84·8%) distilled out under vacuum and shown to be 2,3,5,6-tetrafluoropyridine.

(e) Freshly roasted potassium fluoride (15 g.) was placed in a Carius tube which was then attached to a vacuum line and evacuated to a pressure of 0·01 mms. at which it was maintained for 4 hrs. Tetrafluoroisonicotinyl chloride (1·83 g., b.p. 50-52° at 11 mms.) was then distilled into the tube under vacuum, the tube sealed and then heated to 260° for 40 hrs. The tube was cooled, opened and the product distilled out under vacuum

(1·22 g., 72·3%). Its infra-red spectrum showed it to be pure tetrafluoroisonicotinyl fluoride.

(f) Repetition of experiment (e) using tetrafluoroisonicotinyl chloride (1·64 g., b.p. 50-52° at 11 mm.) and potassium fluoride (5 g.) gave pure tetrafluoroisonicotinyl fluoride (0·75 g., 49·6%).

(g) Repetition of experiment (e) using acid chloride (6·68 g., b.p. 53-57° at 17 mms.) and potassium fluoride (25 g.) gave a product which consisted of acid chloride and acid fluoride in approx. equal amounts.

Pentafluorobenzoyl fluoride.

(a) Pentafluorobenzoyl chloride (0·85 g.) was distilled under vacuum into a Carius tube containing freshly roasted potassium fluoride (5 g.). The tube was sealed under vacuum and then heated to 250° for 48 hrs. After cooling, the tube was opened and the product distilled out under vacuum (0·70 g.; 88·6%). The liquid product was then distilled under reduced pressure (21 mms.) to yield PENTAFLUOROBENZOYL FLUORIDE b.p. 55-56°.

Calc. for C_7F_6O	C: 39·25;	F: 53·3
Found:	C: 38·9;	F: 53·3

Its ^{19}F N.M.R. spectrum showed four peaks including the characteristic acyl fluorine at very low field. The shifts were 160·7 p.p.m. (m-F's), 143·6 (p-F), 134·9 (o-F's) and -46·9 p.p.m. (acyl fluorine). The

assignments are based on the relative intensities of the peaks and the chemical shifts reported for other C_6F_5X compounds.[143]

The mass spectrum gave a strong parent peak (214) and other prominent peaks at 195 $(C_6F_5CO)^+$, 186$(C_6F_6)^+$, 167 $(C_6F_5)^+$ and 117 $(C_5F_4)^+$.

(b) The above experiment was repeated using pentafluorobenzoyl chloride (16·0 g.) and freshly roasted potassium fluoride (50 g.). The weight of acid fluoride obtained was only 4·3 g.

(c) Pentafluorobenzoic acid (2·0 g.) was stirred and then 1-chloro-1,2,2-trifluorotriethylamine (1·78 g.) was added dropwise. Little reaction occurred so the mixture was heated to 85° for 2 hrs. After cooling the yellow liquid obtained was distilled under reduced pressure (14 mms.) giving three fractions:

(1) 45-60°, 0·14 g.

(2) 96-122, 0·68 g.

(3) 122-124°, 0·80 g.

Fraction (1) was shown by infra-red spectroscopy to be pentafluorobenzoyl fluoride. Some unreacted pentafluorobenzoic acid crystallised from fraction (3).

(d) The above reaction was repeated using a reaction temperature of 100° and a reaction time of 4 hrs. No acid fluoride was obtained.

(e) Pentafluorobenzoyl chloride (8·66 g.), anhydrous potassium fluoride

(7·0 g.; 100% excess) and sulpholane (15 ml.) were heated together to 160° for 24 hrs. with stirring. After cooling the solid was filtered off and the filtrate distilled under reduced pressure (19·5 mms.)

(1) 57-57·5° 1·45 g.

(2) 57·5-59° 4·05 g.

The infra-red spectra showed both fractions to be an approximately 50/50 mixture of pentafluorobenzoyl chloride and fluoride.

Perfluoro(phenyl isopropyl)ketone and perfluoro(4-isopropylphenyl isopropyl)ketone.

Pentafluorobenzoyl fluoride (4·35 g.), hexafluoropropene (5 g.), acetonitrile (5 ml.) and anhydrous potassium fluoride (0·4 g.) were placed in a Carius tube which was evacuated and sealed. It was shaken at 135° for 36 hrs. yielding a dark red liquid which separated into two layers on cooling. The tube was opened and the lower layer separated off (9·0 g.). It was distilled under reduced pressure (16 mms.) yielding some acetonitrile and two other fractions

(1) 62-80° 2·75 g.

(2) 80-86° 2·80 g.

The two fractions were analysed by gas liquid chromatography (on silicone elastomer at 100°) and both contained the same products but the relative amounts of each were different.

	Fraction (1)	Fraction (2)	Average
Component of shorter retention time	62·5	9·0	35·75
Component of longer retention time	37·5	91·0	64·25

The two fractions were combined and the two products separated by prep. scale G.L.C. (on silicone elastomer at 120°). The component of shorter retention time was shown by infra-red, mass and ^{19}F N.M.R. spectra to be PERFLUORO(PHENYL ISOPROPYL)KETONE b.p. 155°/760 mm. (Siwoloboff).

Calc. for $C_{10}F_{12}O$	C: 33·0;	F: 62·6
Found:	C: 33·1;	F: 62·2

The ^{19}F N.M.R. spectrum is summarised below

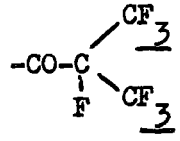
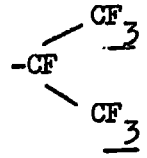
Chemical shift	Assignment
75·0 p.p.m.	CF_3 fluorines
141·0 p.p.m.	ortho fluorines
148·9 p.p.m.	p-fluorine
162·2 p.p.m.	m-fluorines
187·1 p.p.m.	CF- fluorine

The mass spectrum had an intense parent peak (364) and others at 194 $(C_6F_5CO)^+$, 167 $(C_6F_5)^+$, 117 $(C_5F_3)^+$ and 93 $(C_3F_3)^+$.

Similarly the compound of longer retention time was shown to be PERFLUORO(4-ISOPROPYLPHENYL ISOPROPYL)KETONE b.p. 191°/760 mm. (Siwoloboff).

Calc. for $C_{13}F_{18}O$	C: 30·35;	F: 66·5
Found:	C: 30·3;	F: 66·4

The ^{19}F N.M.R. spectrum was as follows

Chemical shift	Assignment
74·8 p.p.m.	
77·1 p.p.m.	
133·7 p.p.m.	ortho fluorines
138·8 p.p.m.	meta fluorines
180·6 p.p.m.	-CF<
186·8 p.p.m.	-CO-CF<

The mass spectrum had an intense parent peak (514) and other prominent peaks at 495 $(C_{13}F_{17}O)^+$, 345 $(C_{10}F_{11}O)^+$, 276 $(C_9F_8O)^+$, 248 $(C_8F_8)^+$ and 198 $(C_7F_6)^+$.

The approximate yields were 27% and 34% respectively.

The above experiment was repeated using pentafluorobenzoyl chloride in place of pentafluorobenzoyl fluoride at 135° for 24 hrs. It was shown by infra-red spectroscopy that no reaction had occurred.

Perfluoro-(4-pyridyl isopropyl)ketone.

Tetrafluoroisonicotinyl fluoride (3·8 g.), hexafluoropropene (3·0 g.), acetonitrile (5 ml.) and anhydrous potassium fluoride (0·5 g.)

were placed in a Carius tube which was then evacuated and sealed. The tube was shaken at 135° for 24 hrs. On cooling the liquid was still homogeneous. The tube was cooled, opened and the liquid obtained distilled under reduced pressure (19 mms.)

(1) 36-46°
(2) 46-60° } 2.88 g.

The infra-red spectra of the two fractions were identical. Analysis by G.L.C. (on silicone elastomer at 100°) showed essentially one peak with a very small peak (< 1%) of much shorter retention time (unreacted acid fluoride). An analytical sample was obtained by prep. scale G.L.C. (on silicone elastomer at 120°). The product was identified by infra-red, mass and ^{19}F N.M.R. spectra as PERFLUORO-(4-PYRIDYL ISOPROPYL)KETONE b.p. 151°/760 mms. (Siwoloboff).

Calc. for $C_9F_{11}NO$ C: 31.1; F: 60.2

Found: C: 31.3; F: 60.2

This experiment was repeated using tetrafluoroisonicotinyl chloride but only starting material was recovered.

The ^{19}F N.M.R. spectrum was as follows

Chemical shift	Assignment
73.6 p.p.m.	CF_3 Fluorines
85.6	2,6-Fluorines
158.5	3,5-Fluorines
183.9	C-F Fluorine

The mass spectrum showed an intense parent peak 347, and other prominent peaks at 178 $(C_6F_4NO)^+$ and 150 $(C_5F_4N)^+$ or $(C_3F_6)^+$.

Attempted preparation of perfluoro(phenyl cyclobutyl)ketone.

Pentafluorobenzoyl fluoride (2 g.), perfluorocyclobutene (1·60 g.), caesium fluoride (0·5 g.) and acetonitrile (10 ml.) were placed in a Carius tube which was cooled, evacuated and sealed. It was heated with shaking to 160° for 11 hrs. After cooling the tube was opened and the solid material filtered off. The solvent was distilled off from the filtrate leaving a brown solid. This was sublimed (40° and 0·3 mms.) to give a white solid (0·44 g.). Analysis by G.L.C. (on silicon oil at 170°) showed it to be a single compound. It was recrystallised from pet. ether (70-90°) to give a white crystalline solid m.p. 83-88°.

Calc. for $C_{11}F_{12}O$	C: 35·1;	F: 60·6
Found	C: 42·8;	F: 51·0

This has not been identified.

Attempted preparation of perfluoro(phenylisobutyl)ketone.

Pentafluorobenzoyl fluoride (2·95 g.), octafluorobut-2-ene (3·2 g., 10% excess), potassium fluoride (0·4 g.) and acetonitrile (10 mls.) were placed in a Carius tube which was cooled, evacuated and sealed. It was then heated with shaking to 100° for 12 hrs. (no reaction), then 160° for 30 hrs. (little reaction) and finally at 260° for 8 hrs. (rapid reaction). The tube was cooled, opened and any volatile material

allowed to escape. Solid material was then filtered off. The solvent was then distilled off leaving a dark coloured liquid (1·8 g.). This was distilled under reduced pressure (9 mms.) giving solvent + a fraction b.p. 122-134° (0·75 g.) which solidified to give a white solid m.p. 79-82°. This was sublimed (60° and 0·35 mms.) to give a white solid which was recrystallised from aqueous methanol m.p. 86·5 - 88·5°. G.L.C. analysis showed it to consist of two components, the major one constituting > 90% of the product. Attempted separation by preparative scale G.L.C. was unsuccessful.

Attempted preparation of Polyfluoro-oxetanes.

(a) Hexafluoropropene (3·0 g., 20 m.moles) and tetrafluoroisonicotinyl fluoride (0·80 g., 4·1 m.moles) were distilled under vacuum into a silica tube which was then sealed. The tube was irradiated with u.v. light whilst being heated to 85° for three days and then 105° for 4 days. The tube was then allowed to cool, opened and volatile material allowed to escape. Infra-red and ^{19}F N.M.R. spectra of the liquid remaining showed that it was unreacted acid fluoride.

(b) Repetition of the experiment at 225° for $4\frac{2}{3}$ days gave acid fluoride plus a trace of higher boiling material.

(c) Pentafluorobenzoyl fluoride gave similar results.

(d) Pentafluorobenzoyl fluoride (2 g., 9·4 m.moles) and hexafluoropropene (1·8 g., 12 m.moles) were placed in a Carius tube under

vacuum. The tube was then sealed and irradiated with γ-rays from a ^{60}Co source for 5 days. Only unreacted acid fluoride (identified by its infra-red spectrum) was isolated.

Reaction between 4-lithiotetrafluoropyridine and dimethylformamide.

4-Bromotetrafluoropyridine (2 g.) in tetrahydrofuran (10 ml.) was stirred at -70° under dry nitrogen. N-butyl lithium (3·7 ml., 2·4M) was added dropwise and the solution stirred for 1 hr. Dimethyl formamide (1·0 g.) in tetrahydrofuran (2 ml.) was then added and the solution stirred for 30 mins. at -70° and for a further 30 mins. whilst the temperature rose to room temperature. Ether and water were added and the ether layer separated. The aqueous layer was washed with more ether. The ether extracts were combined, dried ($MgSO_4$) and the solvent distilled off to leave a dark coloured solid. This was not investigated further.

Reaction between tetrafluoro-4-pyridyl magnesium bromide and dimethyl formamide

Magnesium turnings (0·4 g.) in dry tetrahydrofuran (15 ml.) containing ethylene dibromide (2 drops) were stirred under dry nitrogen. 4-Bromotetrafluoropyridine (2 g.) in tetrahydrofuran (5 ml.) was added and the mixture immediately cooled to -20°. The reaction commenced after a few minutes. The mixture was stirred at -10° for 30 mins. and then added slowly to dimethylformamide (0·53 g.) in tetrahydrofuran (5 ml.) at -20°. It was stirred for 20 mins. whilst the temperature rose

to room temperature and then for a further 1 hr. Acidification with dilute sulphuric acid followed by ether extraction, drying of the extracts ($MgSO_4$) and removal of the solvent by distillation gave a brown solid which was not investigated.

Preparation of Tetrafluoropyridine-4-aldehyde.

4-Bromotetrafluoropyridine (14 g.) in dry ether (35 ml.) was stirred under dry nitrogen at -70°. N-Butyl lithium (25 ml., 2·4M) in ether (10 ml.) was added dropwise and the solution stirred for 1 hr. N-methyl formanilide (14 g.) in ether (10 ml.) was added followed by more ether (10 ml.) and stirred for 1 hr. The solution obtained was acidified with 25% v/v sulphuric acid (50 mls.) and the temperature allowed to rise to room temperature. It was then ether extracted, the extracts dried ($MgSO_4$) and the solvent distilled off to leave a yellow liquid. This was distilled under reduced pressure (12 mins.)

(1) b.p. 28-64 1·1 g.

(2) b.p. 67-80 6·1 g.

(3) b.p. 80-100

Analysis by G.L.C. (silicon oil at 120°) showed that - fraction (1) was a single compound containing a small amount ($< 1\%$) of impurity, fraction (2) contained the same single compound only and fraction (3) contained a mixture of two compounds one being the same as the single compound in the other two fractions. The infra-red spectrum of fraction (2) was

identical with that of an authentic sample of tetrafluoropyridine-4-aldehyde. The yield (based on the weights of fractions (1) and (2)) was 66·1%.

Preparation of tetrafluoropyridine-4-aldehyde semicarbazone.

The aldehyde (0·3 g.) was added to a solution of semicarbazide hydrochloride (0·5 g.) and sodium acetate (0·7 g.) in water (5 ml.). Heating on a water bath for a few mins. gave a white precipitate. After cooling the precipitate was filtered off and washed with cold water (5 ml.). The last traces of water were removed under high vacuum (0·25 g., 63·0%). Recrystallisation from ethanol/benzene gave the white solid, TETRAFLUOROPYRIDINE-4-ALDEHYDE SEMICARBAZONE m.p. 248·5-250° (decomp.)

Calc. for $C_7H_4F_4N_4O$	C: 35·6;	H: 1·70;	F: 32·2	
Found	C: 35·3;	H: 1·7;	F: 32·0	

Preparation of tetrafluoropyridine-4-aldehyde-2,4-dinitrophenylhydrazone.

The aldehyde (2 drops) was added to a solution of 2,4-dinitrophenylhydrazine in methanol (10 ml.). The precipitate which formed was filtered off and recrystallised from benzene to give tetrafluoropyridine-4-aldehyde-2,4-dinitrophenylhydrazone m.p. 232° (lit. m.p. 232°).

Calc. for $C_{12}H_5F_4N_5O_4$	C: 40·1;	H: 1·38	
Found	C: 40·3;	H: 1·53	

Oxidation of tetrafluoropyridine-4-aldehyde to tetrafluoroisonicotinic acid.

The aldehyde (0·22 g.), concentrated sulphuric acid (1 ml.), sodium dichromate (0·7 g.) and water (2 ml.) were heated to 100° for 1 hr. After cooling the product was poured into water (25 ml.). The aqueous solution was extracted with ether and the ether extracts washed with 10% sodium carbonate solution (2 x 10 ml.). The sodium carbonate solution was acidified with dilute sulphuric acid and then ether extracted. The extracts were dried ($MgSO_4$) and the solvent distilled off to leave an almost white solid. This was sublimed (60° and 0·1 mm.) to give tetrafluoroisonicotinic acid m.p. and mixed m.p. 101-3° (lit. 104-5°).[119]

Preparation of Tetrafluoro-4-pyridyl carbinol.

Tetrafluoropyridine-4-aldehyde (1·5 g.) in methanol (10 ml.) was stirred and sodium borohydride (0·15 g., 50% excess) was slowly added giving an exothermic reaction. After stirring for 20 hrs. the solution was acidified with dilute hydrochloric acid and then ether extracted. The extracts were dried ($MgSO_4$), filtered and the solvent removed. The liquid obtained was distilled under reduced pressure (15 mm.) to give TETRAFLUORO-4-PYRIDYL CARBINOL b.p. 102-4° (1·0 g., 65·9%).

Calc. for $C_6H_3F_4NO$	C:	39·8;	H:	1·66;	F: 42·0
Found	C:	40·0;	H:	1·74;	F: 41·6

The mass spectrum had an intense parent peak at 181 and other peaks at 164 $(C_6H_2F_4N)^+$, 160 $(C_6HF_3NO)^+$, and 151 $(C_5HF_4N)^+$.

Preparation of β-(tetrafluoro-4-pyridyl)acrylic acid.

Tetrafluoropyridine-4-aldehyde (0·5 g.), acetic anhydride (0·4 g.) and freshly fused sodium acetate (0·16 g.) were heated to 140° for 2 hrs. The resulting dark solution was poured into water (50 ml.) and made alkaline with sodium carbonate giving a tar in addition to the aqueous solution. The solution was decanted off and acidified with concentrated hydrochloric acid. The precipitated solid was filtered off, washed with water and dried under high vacuum (0·09 g.). It was recrystallised from aqueous methanol and then sublimed in vacuo (75°/0·001 mm.) to give β-(TETRAFLUORO-4-PYRIDYL)ACRYLIC ACID m.p. 171·5 - 172·5° identified by its mass and infra-red spectra.

Calc. for $C_8H_3F_4NO_2$	C: 43·4;	H: 1·36
Found:	C: 42·2;	H: 1·51

The mass spectrum showed a parent peak at 221. Other prominent peaks were at 177 $(C_7H_3F_4N)^+$, 176 $(C_7H_2F_4N)^+$, 175 $(C_7HF_4N)^+$, 174 $(C_7F_4N)^+$ and 164 $(C_6H_2F_4N)^+$.

Tetrafluoro-4-pyridyl azine.

Tetrafluoropyridine-4-aldehyde (0·5 g.) and hydrazine monohydrate (0·07 g.) in ethanol (2·5 ml.) were stirred together for 6 hrs. The

yellow solid which crystallised was filtered off (0·1 g.) and recrystallised from hexane to give TETRAFLUORO-4-PYRIDYL AZINE m.p. 138-9°, identified by its infra-red and mass spectra.

Calc. for $C_{12}H_2F_8N_4$	C: 40·7;	H: 0·56	
Found:	C: 40·8;	H: 0·38	

Dilution of the mother liquors with water yielded more crude azine (0·2 g.).

The mass spectrum had a strong parent peak at 354, and prominent peaks at 177 $(C_6HF_4N_2)^+$ and 150 $(C_5F_4N)^+$.

Preparation of (tetrafluoro-4-pyridyl pentafluorophenyl)carbinol.

Bromopentafluorobenzene (5 g.) in ether (30 ml.) was stirred at -65° under dry nitrogen. n-Butyl lithium in hexane (7·4 ml., 2·7M) in ether (5 ml.) was added dropwise and the solution stirred for 30 mins. Tetrafluoropyridine-4-aldehyde (3·75 g.) in ether (5 ml.) was added and stirred for 1 hr. The solution was then acidified with 25% v/v sulphuric acid (30 ml.), ether extracted, the extracts dried ($MgSO_4$), filtered and the solvent distilled off. The almost colourless liquid obtained was distilled under reduced pressure (12 mms.) giving (TETRAFLUORO-4-PYRIDYL PENTAFLUOROPHENYL)CARBINOL b.p. 146-149° (2·45 g., 34·7%).

Calc. for $C_{12}H_2F_9NO$	C: 41·5;	H: 0·58;	F: 49·3		
Found:	C: 42·0;	H: 0·58;	F: 48·5		

Its mass spectrum had prominent peaks at 347 (parent ion), 197 $(C_7H_2F_5O)^+$, 180 $(C_6H_2F_4NO)^+$, 178 $(C_6F_4NO)^+$ and 167 $(C_6F_5)^+$.

Preparation of (Tetrafluoro-4-pyridyl pentafluorophenyl)ketone.

(Tetrafluoro-4-pyridyl pentafluorophenyl)carbinol (1 g.) chromic oxide (2 g.) and glacial acetic acid (10 ml.) were heated under reflux for 45 mins. The resulting solution was poured into water (100 ml.). The white solid which precipitated was filtered off and washed with water. The last trace of water was removed under high vacuum (0.53 g., 54%). The solid was recrystallised from aqueous methanol yielding (TETRAFLUORO-4-PYRIDYL PENTAFLUOROPHENYL)KETONE m.p. 65.5-66°.

Calc. for $C_{12}F_9NO$	C: 41.75;	F: 49.6
Found:	C: 42.1;	F: 50.0

Intense peaks occurred at 345 (parent ion), 195 $(C_7F_5O)^+$, 178 $(C_6F_4NO)^+$, 167 $(C_6F_5)^+$ and 150 $(C_5F_4N)^+$.

Bis(tetrafluoro-4-pyridyl)carbinol.

4-Bromotetrafluoropyridine (2.6 g.) in ether (10 ml.) was stirred at -75° under dry nitrogen. N-Butyl lithium in hexane (4.7 ml., 2.4M) in ether (10 ml.) was added dropwise and the solution stirred for 30 mins. Tetrafluoropyridine-4-aldehyde (2 g.) in ether (10 ml.) was added and stirred for 1 hr. at -75°. After acidification with 25% v/v sulphuric acid (20 ml.) the temperature was allowed to rise to room temperature. The solution was extracted with ether, the extracts dried ($MgSO_4$) and the solvent distilled off to give a brown liquid.

The experiment was repeated using the same quantities of reactants at a temperature of -65°. The two products were combined and distilled under reduced pressure (10 mms.)

(1) b.p. 40 - 100 0·8 g.

(2) b.p. 100 - 152 0·2 g.

(3) b.p. 152-156° mainly 152-3° m.p. 75-7° 3·81 g.

Part of fraction (3) was redistilled (0·25 mms.) to give BIS(TETRAFLUORO-4-PYRIDYL)CARBINOL, b.p. 118-120° m.p. 76·5 - 78°.

Calc. for $C_{11}H_2F_8N_2O$ C: 40·0; H: 0·61; F: 46·05

Found C: 39·7; H: 0·66; F: 45·7

Expected peaks at 330 (parent ion), 180 $(C_6H_2F_4NO)^+$ and 178 $(C_6F_4NO)^+$ were observed in the mass spectrum.

Oxidation of bis(tetrafluoro-4-pyridyl)carbinol to bis(tetrafluoro-4-pyridyl)ketone.

The alcohol (0·5 g.), chromium trioxide (2 g.) and glacial acetic acid (10 ml.) were heated together under reflux for 1 hr. and then poured into water (200 ml.) giving a white solid. This was filtered off, washed with water and the last traces of moisture removed under high vacuum (0·25 g., 50·3%). Recrystallisation from ethanol gave BIS(TETRAFLUORO-4-PYRIDYL)KETONE m.p. 94-94·5°

Calc. for $C_{11}F_8N_2O$ C: 40·25; F: 46·3

Found C: 40·5; F: 46·4

The mass spectrum was characterised by an intense parent ion at 328.

Preparation of Bis(tetrafluoro-4-pyridyl)ketone phenylhydrazone.

Bis(tetrafluoro-4-pyridyl)ketone (0·3 g.) and phenylhydrazine (0·20 g.) in chloroform (5 ml.) were heated together under reflux for 12 hrs. After cooling, the yellow solid was filtered off and washed with pet. ether (60-80°) giving a white solid (0·07 g., 18·4%). This was recrystallised from methanol giving BIS(TETRAFLUORO-4-PYRIDYL)-KETONE PHENYLHYDRAZONE which decomposed without melting on heating.

Calc. for $C_{17}H_6F_8N_4$	C: 48·7;	H: 1·44
Found:	C: 51·2;	H: 1·77

Tris(tetrafluoro-4-pyridyl)carbinol (Method 1).

4-Bromotetrafluoropyridine (0·545 g., 2·4 m.mole) in ether (5 ml.) was added dropwise to a stirred solution of n-butyl lithium in hexane (2·4 m.mole) in ether (15 ml.), under an atmosphere of dry nitrogen at -65°. After a further 30 mins. stirring bis(tetrafluoro-4-pyridyl)ketone (0·8 g., 2·4 m.mole) in ether (10 ml.) was added, followed by more ether (10 ml.). The cooling bath was removed and stirring was continued for a further 40 mins. After acidification with dilute sulphuric acid the solution was extracted with ether. The extracts were combined, dried ($MgSO_4$) and the solvent distilled off to leave a white solid (0·82 g., 70·2%). This was sublimed under reduced pressure (0·5 mms.) at 110° and then recrystallised from carbon tetrachloride to give TRIS(TETRA-FLUORO-4-PYRIDYL)CARBINOL m.p. 189-190·5°.

Calc. for $C_{16}HF_{12}N_3O$	C: 40·1;	H: 0·21
Found	C: 39·0;	H: 0·00

The mass spectrum had an intense parent ion peak (479) and other prominent peaks at 329 $(C_{11}HF_8N_2O)^+$, 178 $(C_6F_4NO)^+$, 151 $(C_5HF_4N)^+$ and 150 $(C_5F_4N)^+$.

Tris(tetrafluoro-4-pyridyl)carbinol (Method 2).

4-Bromotetrafluoropyridine (2·1 g., 9·0 m.moles) in ether (10 ml.) was slowly added to a stirred solution of n-butyl lithium in hexane (9·0 m.moles) in ether (15 ml.), under an atmosphere of dry nitrogen, at -70°. The solution was stirred for 30 mins. after the addition was completed. Ethyl tetrafluoroisonicotinate (1 g., 4·5 m.mole) in ether (5 ml.) was added and the solution stirred for a further 1½ hrs. The cooling bath was then removed and after a further 30 mins. stirring it was acidified with dilute hydrochloric acid (35 ml.). The resulting solution was extracted with ether, the extracts dried ($MgSO_4$), and the solvent distilled off to leave solid material (1·65 g., 76·8%). This was sublimed under reduced pressure (0·05 mms.) at 110° to give tris(tetrafluoro-4-pyridyl)carbinol whose infra-red spectrum was identical with that of the compound produced in method 1 above.

Bis(tetrafluoro-4-pyridyl)amine.

To a stirred solution of 4-aminotetrafluoropyridine (1 g.) in T.H.F. (8 ml.) was added sodium hydride (0·316 g.; 50% dispersion in oil).

After the vigorous reaction had subsided the mixture was heated under reflux for 45 mins. Pentafluoropyridine (1·02 g.) was added and the solution heated under reflux for 12 hrs. After cooling, the yellow solution obtained was poured into a mixture of water (40 ml.) and concentrated hydrochloric acid (4 ml.) yielding a yellow oil which was extracted into ether, the extracts dried ($MgSO_4$), and the solvent distilled off. Sublimation under reduced pressure (·001 mm.) at 70° gave a white solid (1·0 g.; 52·7%). This was purified by recrystallisation from benzene/pet. ether (80-100) followed by sublimation at 70° (0·01 mm.) yielding BIS(TETRAFLUORO-4-PYRIDYL)AMINE m.p. 147·5 - 149°.

Calc. for $C_{10}HF_8N_3$	C:	38·1;	H:	0·32;	F: 38·25
Found:	C:	37·9;	H:	0·59;	F: 38·2

Attempted preparation of an N-acetyl derivative of bis(tetrafluoro-4-pyridyl)amine.

Bis(tetrafluoro-4-pyridyl)amine (0·2 g.), acetic anhydride (5 ml.) and concentrated sulphuric acid (2 drops) were heated together under reflux for 45 mins. The dark solution was poured into water and a brown solid was obtained. This was filtered off, washed with cold water and dried over phosphoric oxide in vacuo (0·1 g.). Sublimation (90° and 0·1 mm.) afforded a white solid whose infra-red spectrum was identical with that of the starting amine.

Infra-Red Spectra

Infra-Red Spectra.

The spectra of liquid samples were recorded as contact films on potassium bromide cells. Those of solid samples were recorded as potassium bromide discs.

Spectrum No.	Compound
1	Tetrafluoropyridine-3-aldehyde
2	Tetrafluoropyridine-3-aldehyde-2,4-dinitrophenylhydrazone
3	2,4,6-Trifluoronicotinyl chloride
4	4-Amino-2,6-difluoronicotinamide
5	Tetrafluoroisonicotinic anhydride
6	Tetrafluoroisonicotinamide
7	N-Phenyl-N'-tetrafluoroisonicotinylhydrazine
8	Tetrafluoroisonicotinyl chloride
9	Methyl tetrafluoroisonicotinate
10	Ethyl tetrafluoroisonicotinate
11	N-(Tetrafluoro-4-pyridyl)pentafluorobenzamide
12	N-(Pentafluorophenyl)pentafluorobenzamide
13	N'-(Tetrafluoro-4-pyridyl)pentafluorobenzohydrazide
14	N'-(Pentafluorophenyl)pentafluorobenzohydrazide
15	N'-(Tetrafluoro-4-pyridyl)tetrafluoroisonicotinohydrazide
16	N,N'-Bis(tetrafluoroisonicotinyl)hydrazine

17 2,5-Bis(tetrafluoro-4-pyridyl)-1,3,4-oxadiazole

18 2,5-Bis(tetrafluoro-4-pyridyl)-1,3,4-thiadiazole

19 Tetrafluoroisonicotinyl fluoride

20 Pentafluorobenzoyl fluoride

21 Perfluoro(phenyl isopropyl)ketone

22 Perfluoro(4-isopropylphenyl isopropyl)ketone

23 Perfluoro(4-pyridyl isopropyl)ketone

24 Tetrafluoropyridine-4-aldehyde semicarbazone

25 Tetrafluoro-4-pyridyl carbinol

26 β-(Tetrafluoro-4-pyridyl)acrylic acid

27 Tetrafluoro-4-pyridyl azine

28 (Tetrafluoro-4-pyridyl pentafluorophenyl)carbinol

29 (Tetrafluoro-4-pyridyl pentafluorophenyl)ketone

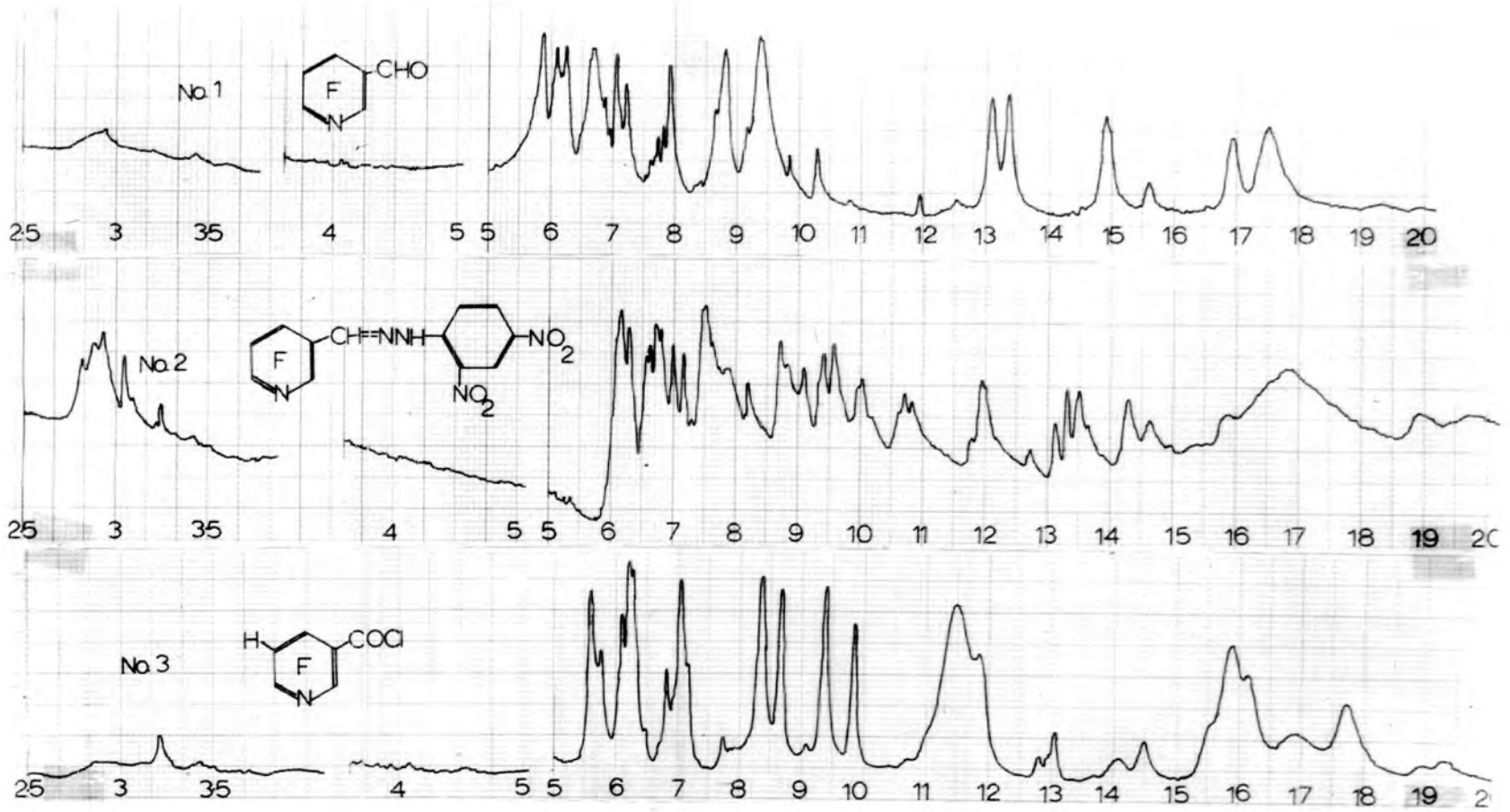
30 Bis(tetrafluoro-4-pyridyl)carbinol

31 Bis(tetrafluoro-4-pyridyl)ketone

32 Bis(tetrafluoro-4-pyridyl)ketone phenylhydrazone

33 Tris(tetrafluoro-4-pyridyl)carbinol

34 Bis(tetrafluoro-4-pyridyl)amine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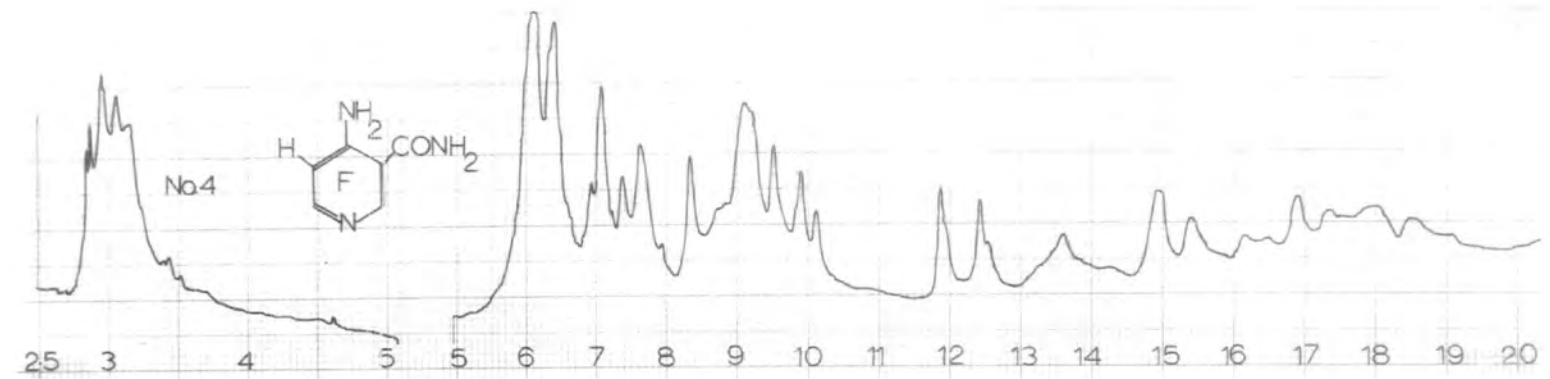
CH=NNH
NO2
NO2
2.5 3 3.5 4 5 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
No. 3
H
F
N
COCl
2.5 3 3.5 4 5 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19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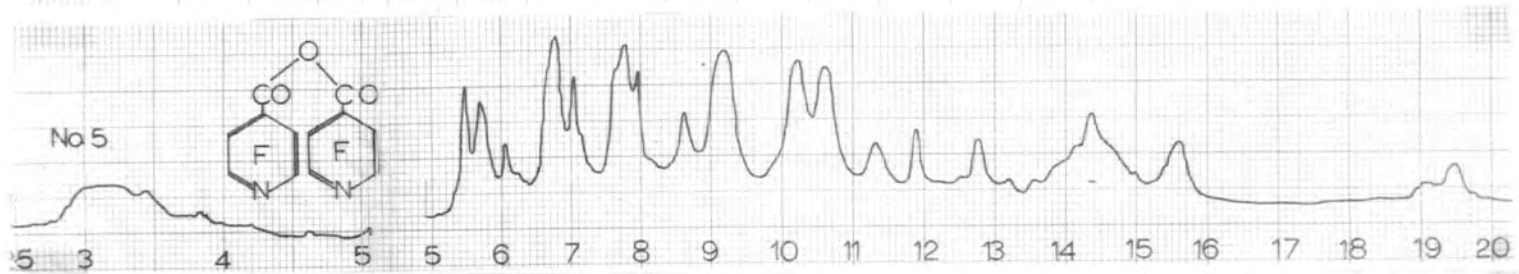
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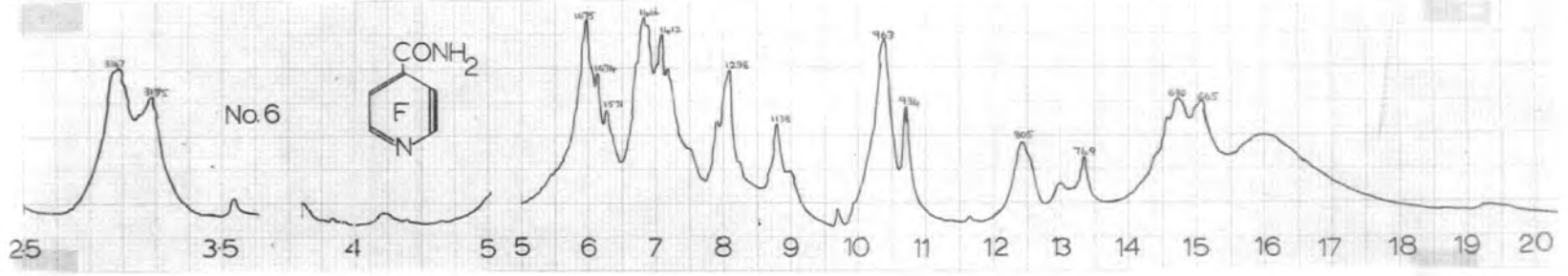
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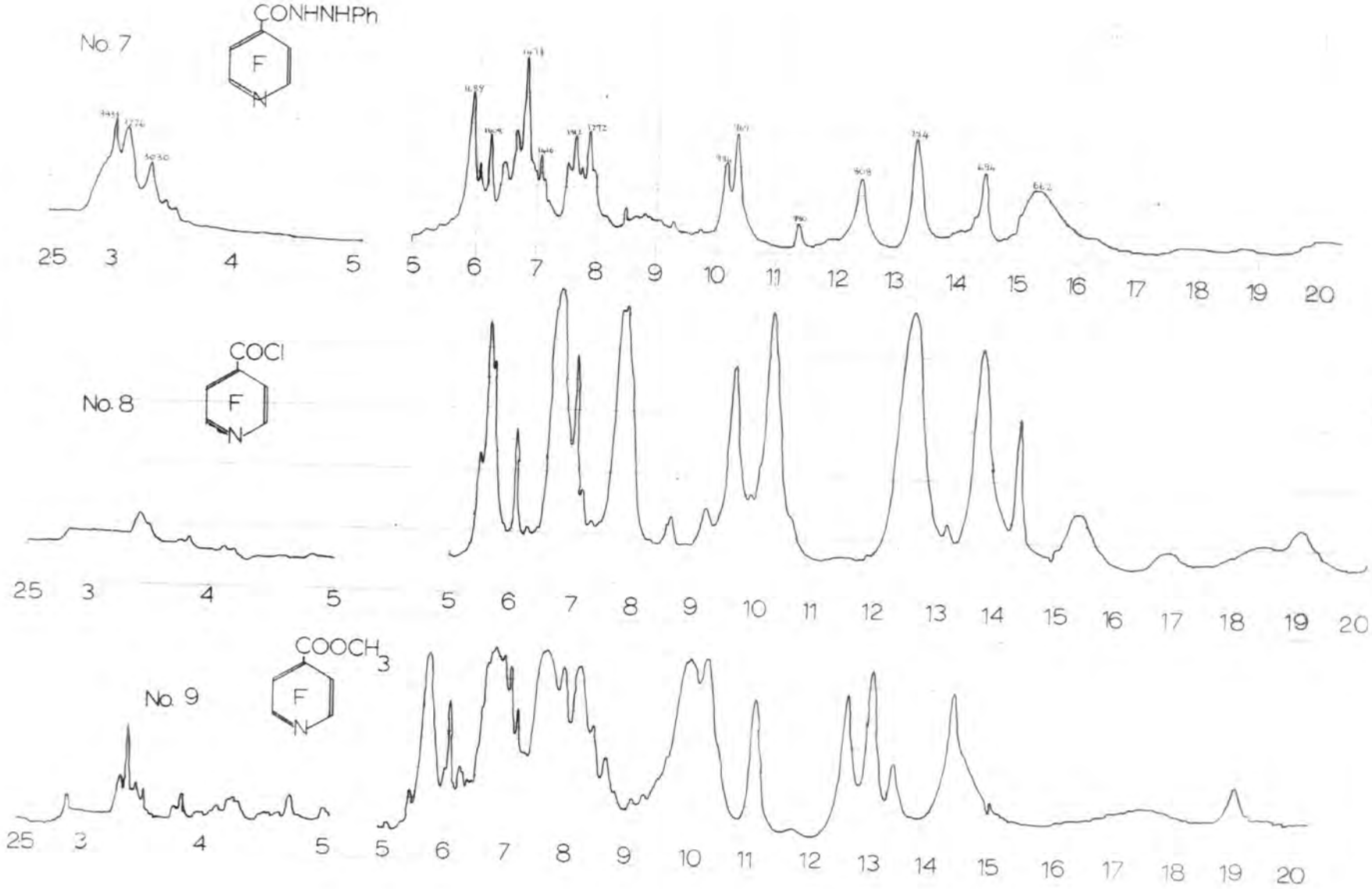
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5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
COOCH3
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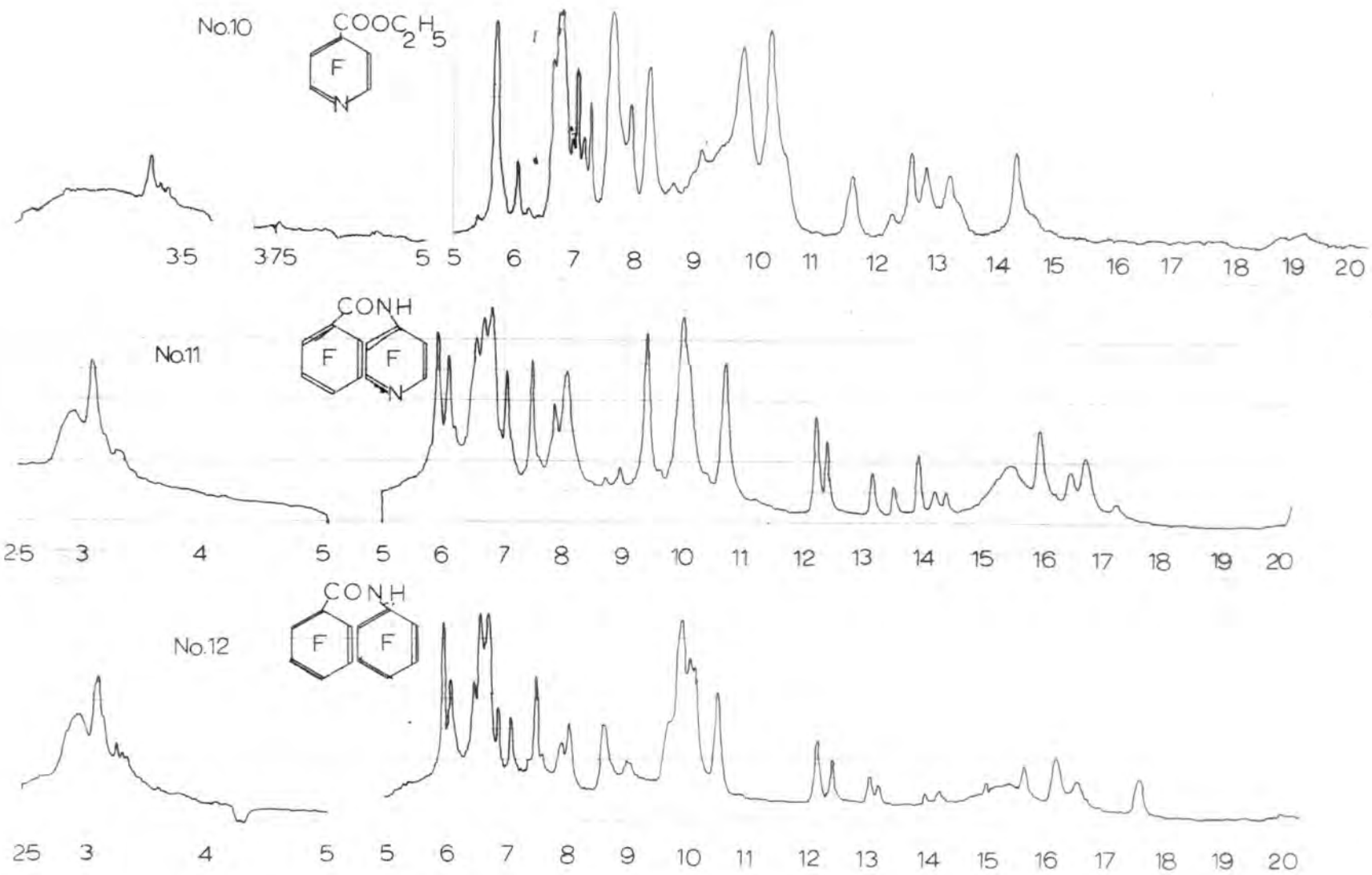
F
N
25 3 4 5
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20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15
16
17
18
19
20
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CONH
F
F
N
2.5
3
4
5
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
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CONH
F
F
2.5
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18
19
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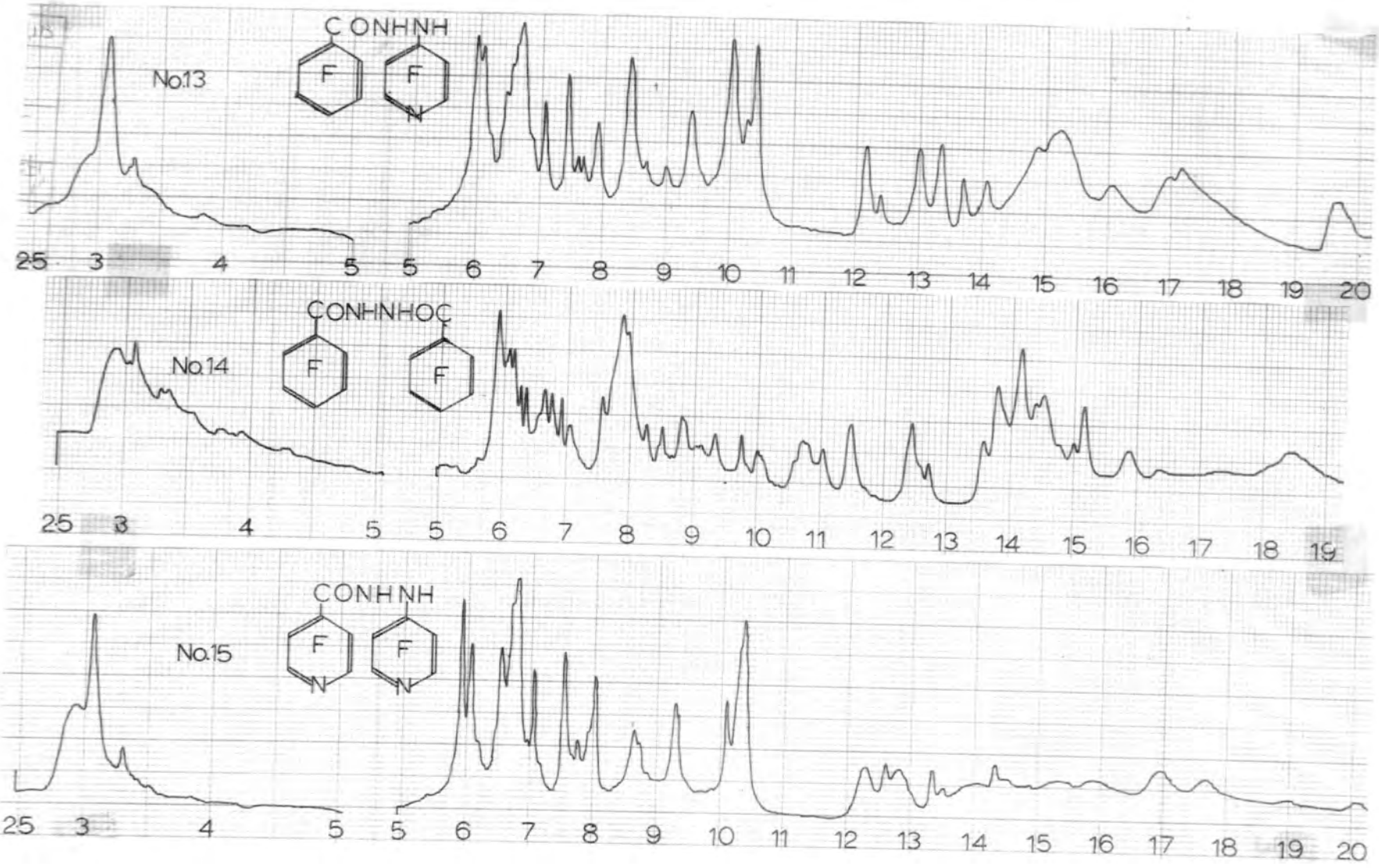
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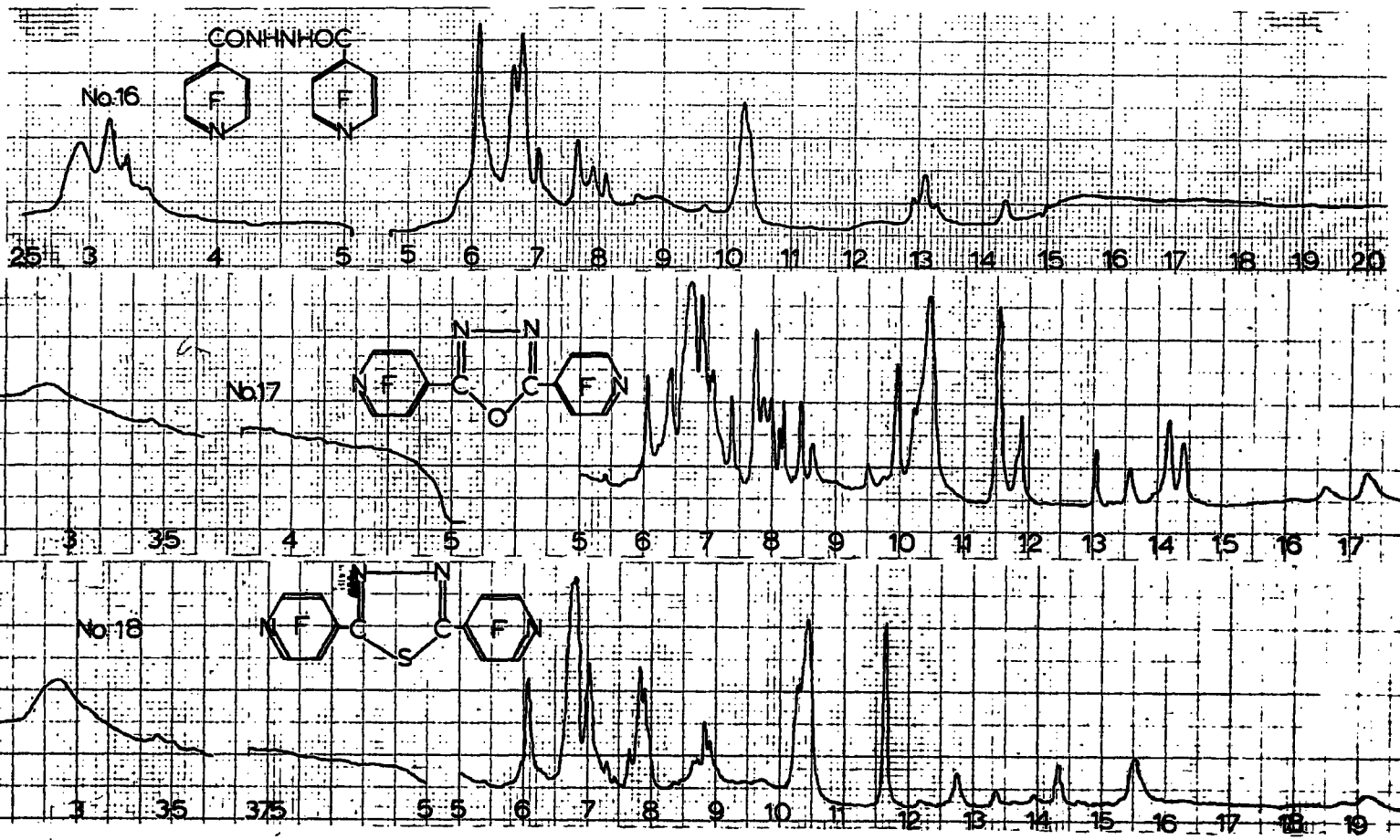
N
N
25 3 4 5 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20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O
25 3 35 4 5 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
No.18
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S
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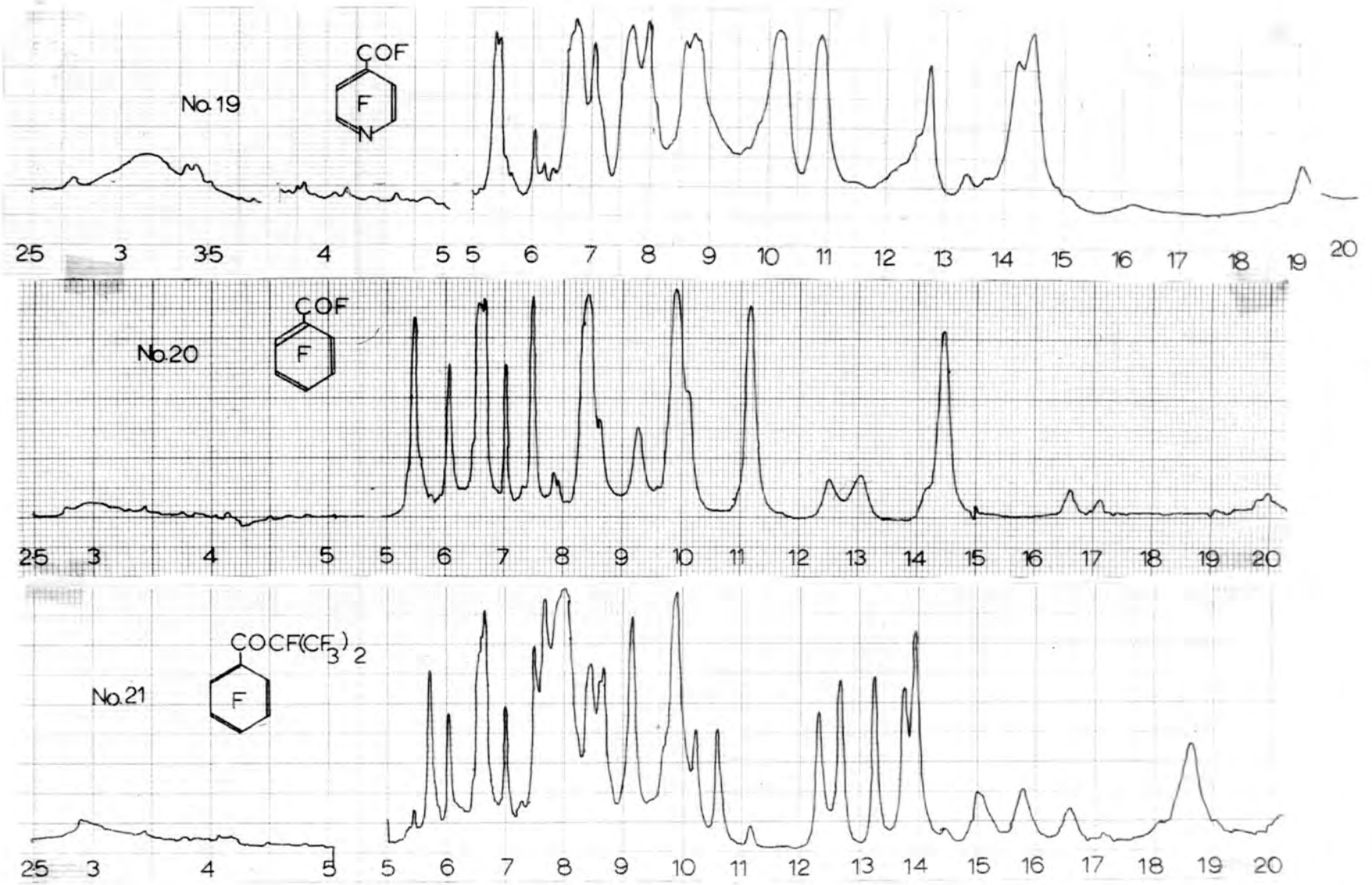
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F
N
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No.20
COF
F
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No.21
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F
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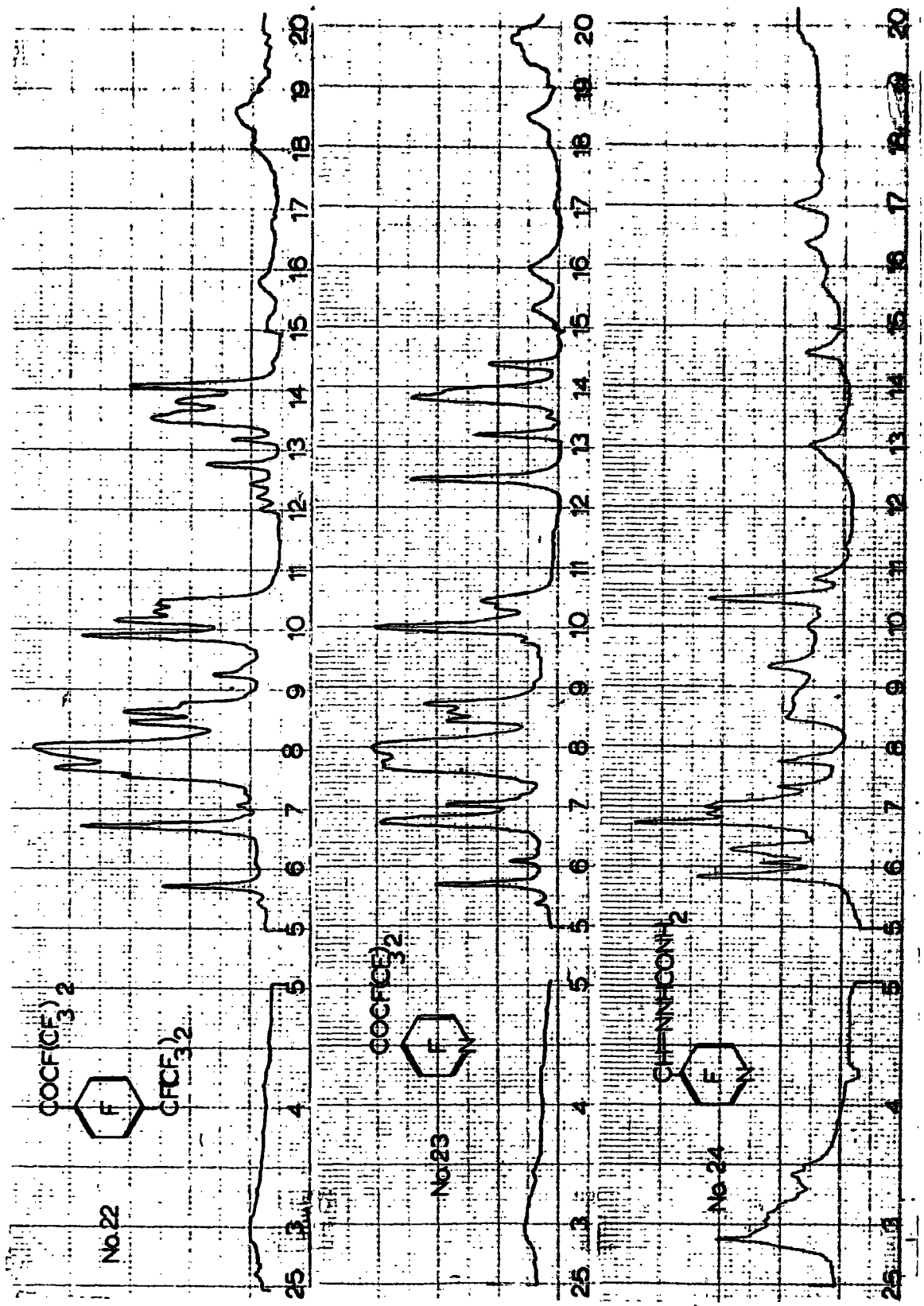
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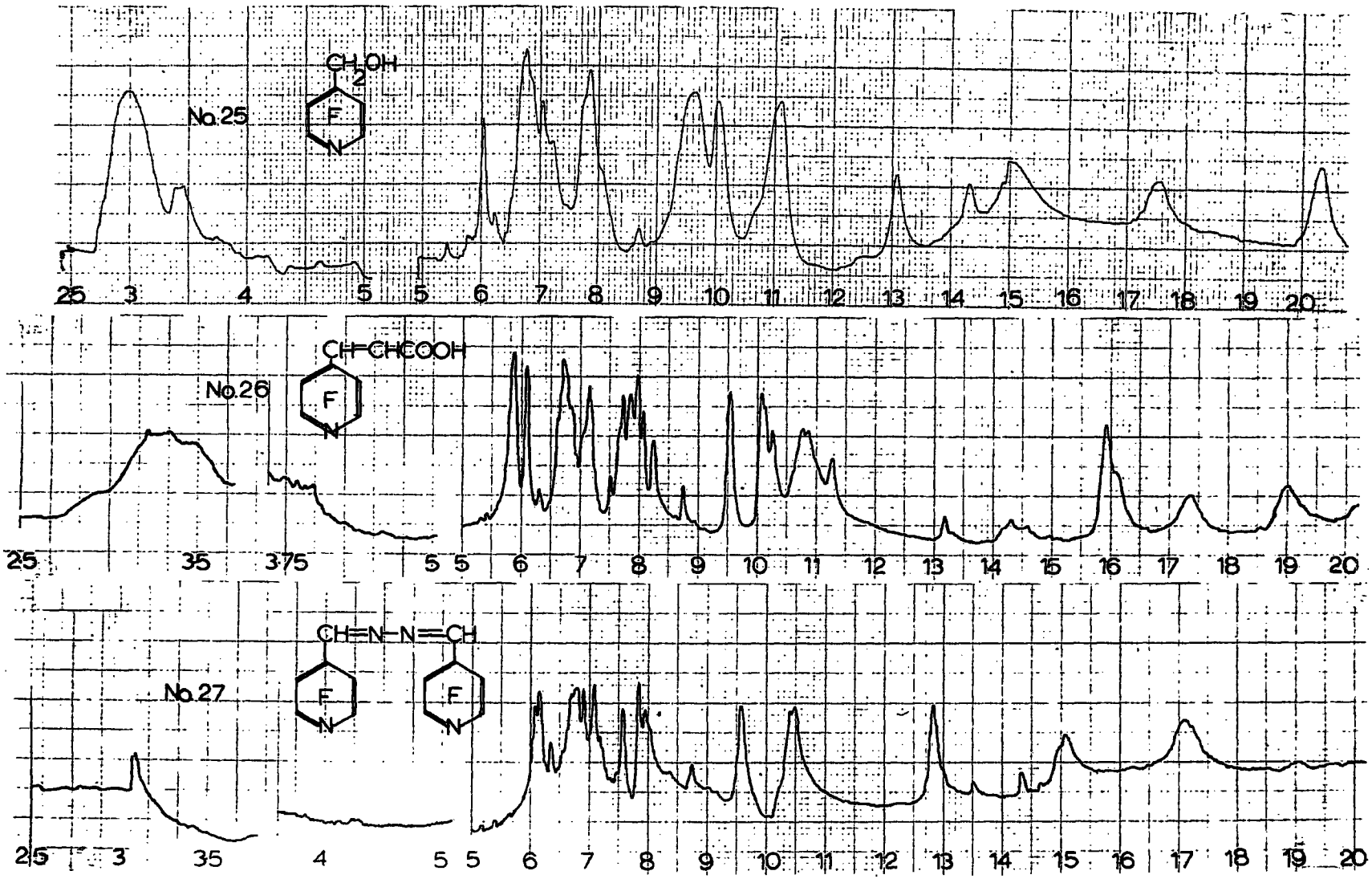
N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F
N
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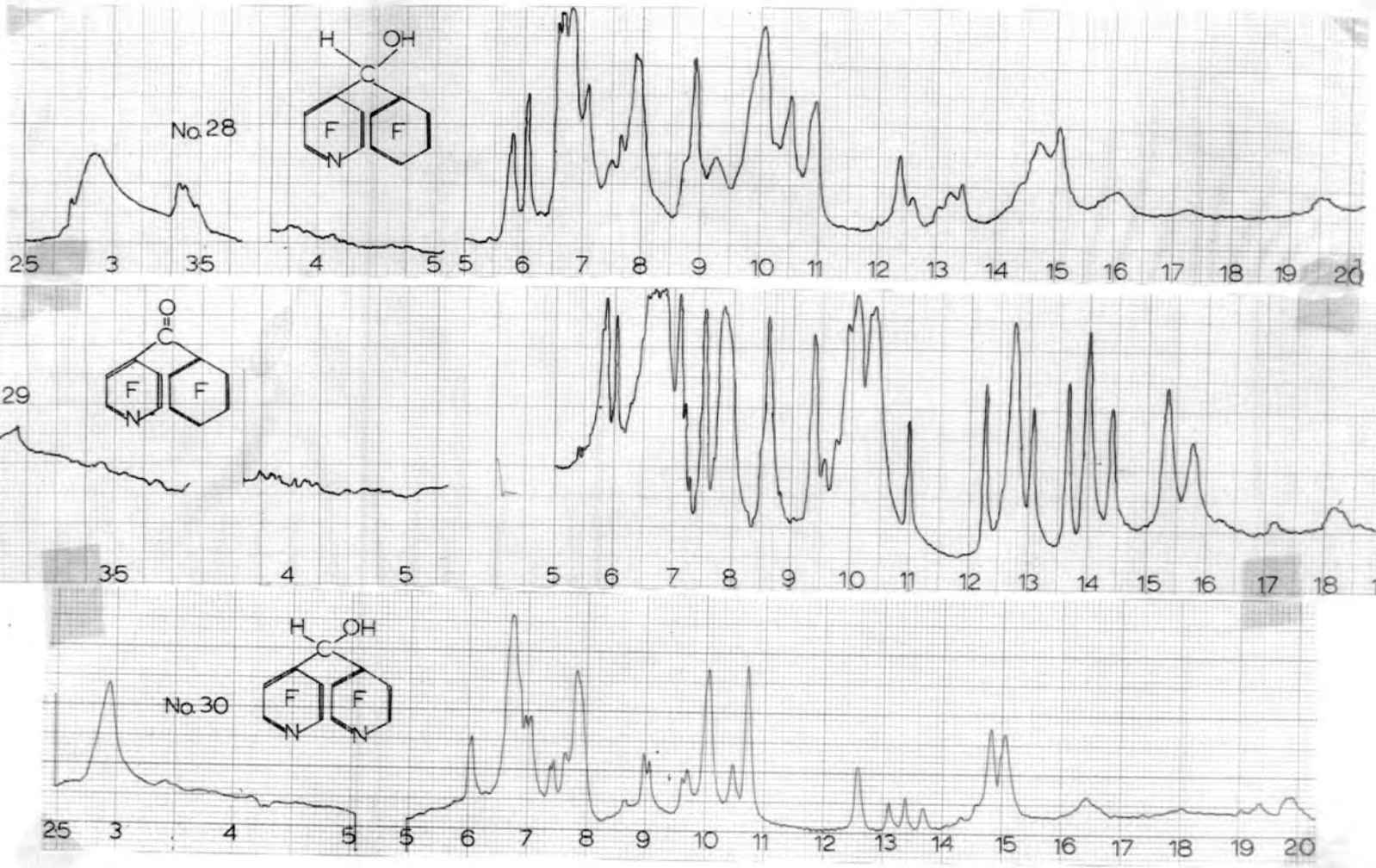
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15
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17
18
19
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O
C
F
F
N
25
35
4
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18
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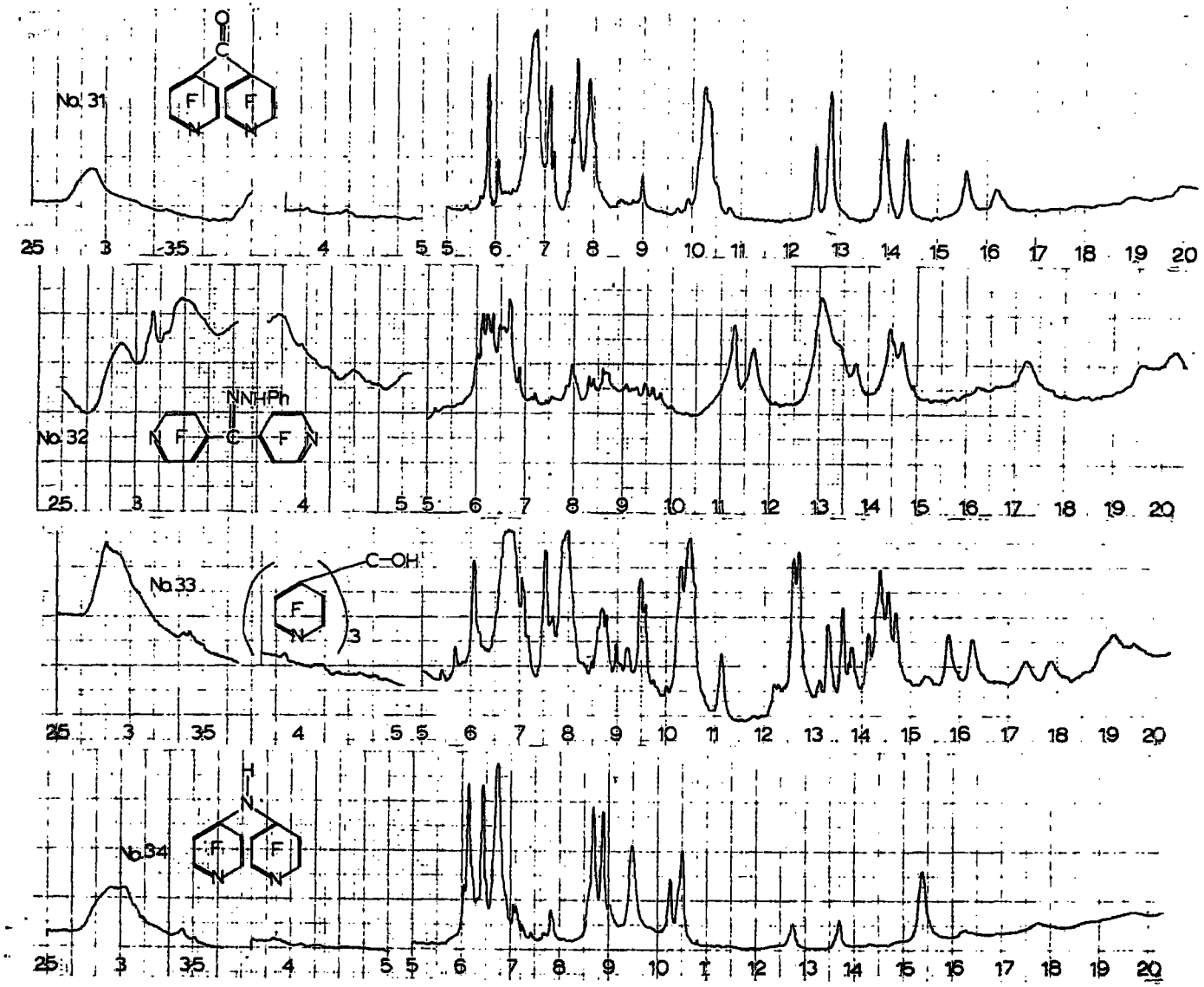
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No. 33
C-OH
F
N
3
25 3 35 4 5 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
No. 34
H
N
F
F
N
N
25 3 35 4 5 5 6 7 8 9 10 1 12 13 14 15 16 17 18 19 20

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