The introduction of fluorine into organic compounds.

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A THESIS

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THE INTRODUCTION OF FLUORINE
INTO
ORGANIC COMPOUNDS.

SUMMARY

It has been shown that fluorinated pyridine derivatives may be obtained by three different methods, namely :-

i) By the application of the Schiemann Reaction using fluoboric acid,

ii) By diazotisation of amine hydrofluosilicates and subsequent decomposition of the diazonium salt in anhydrous HF,

iii) By the reaction of chlorine trifluoride with pyridine in carbon tetrachloride solution.

Further, it has been demonstrated that in some cases, fluoro-pyridines may be obtained in reasonable yield by diazotisation of the amine in anhydrous hydrogen fluoride with sodium or ethyl nitrites.

The reaction whereby the diazonium fluosilicate is decomposed in anhydrous HF cannot be entirely analogous to the decomposition of the diazonium fluoride in HF because the yields in certain cases are quite different.

So far as the reaction between pyridine and chlorine trifluoride is concerned, it has been shown that the main reaction is one of substitution resulting in the formation of fluoro and chloro pyridines. A number of catalysts have been tested and found to increase the yields considerably provided that the hydrofluoric acid produced during the reaction is absorbed by potassium fluoride as it is formed. The ratio of fluoro and chloro pyridines seems to depend to some extent on the catalyst employed.

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I desire to express my indebtedness to Dr. W.K.R.Musgrave under whose supervision this work was carried out, and also to the Department of Scientific and Industrial Research for a maintenance award during the period of this research.

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INTRODUCTION

A survey of the literature of organic chemistry up to 1947 showed that little attention had been paid to the preparation of heterocyclic fluorides. In view of this, the present work, to prepare and characterise some of these compounds, was undertaken.

Two main reactions have been employed, namely, the Schiemann Reaction and certain modifications of this, and halogenation by means of chlorine trifluoride. Using the former reaction fluorides of pyridine, pyridine - carboxylic acids and quinoline have been prepared.

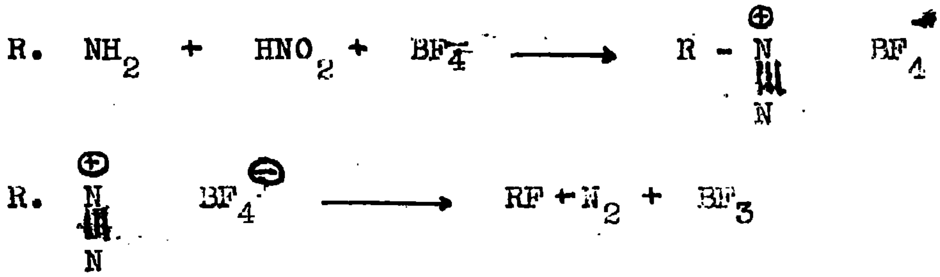
As far as the reaction between chlorine trifluoride and pyridine is concerned, it has been shown that substitution occurs with the formation of fluoro and chloro pyridines. Considerable polymerisation and decomposition takes place and in one instance a dipyridyl derivative was obtained.

The Schiemann Reaction and Modifications

The earliest attempts to prepare aromatic fluorides were based on the decomposition of diazonium salts in aqueous hydrofluoric acid. Thus in 1870, Schmitt and von Gehren synthesised p-fluoro benzoic acid by diazotising the corresponding amine in 40% hydrofluoric acid (J.Prakc. Chem. 1, 394, 1870). In an analogous manner, Tschitschibaben and Rjazancev (J.Russ.Phys.Chem.Soc. 46 1256, 1914) prepared 2-fluoro and 2-fluoro-5-nitro-pyridine. The obvious disadvantage of the method lies in the fact that decomposition of any diazonium salt in aqueous solution leads to the formation of hydroxy compounds with consequent reduction in the yield of the desired fluoro derivative. More recently, anhydrous hydrogen fluoride has replaced the aqueous acid with considerable success.

An alternative method, of limited applicability, was developed by Wallach and Heusler (Ann. 235, 255, 1886; ibid, 243, 219, 1888). This consisted in isolating the diazo-amino compound formed by reaction of a diazonium salt with a secondary amine (usually piperidine) and decomposing this in aqueous hydro-fluoric acid. In this manner a number of aromatic fluorides were prepared including fluoro-benzene itself. The intermediate diazo-amino compounds, however, are not particularly stable and moreover are difficult to perify. Because of this the yields are usually low and the method has passed out of general use.

The first significant advance was made in 1913 when Bart succeeded in isolating benzene diazonium fluoborate (G.P.281,055). He placed on record the peculiar stability of the diazonium fluoborates but did not make use of them for the preparation of aromatic fluorides. It was not until 1927 that Balz and Schiemann (B.<u>60</u> 1186, 1927) published their work on the controlled decomposition of diazonium fluoborates in which they showed that, by this method, good yields of aromatic fluorides could be obtained. The process has now become known as the Schiemann Reaction and consists essentially of two stages, (a) the isolation and purification of the diazonium fluoborate and (b) dry distillation of the salt to yield the aromatic fluoride, nitrogen and boron tri-fluoride.



$$R.\ NH_2 + HNO_2 + BF_4^- \longrightarrow R-\overset{\oplus}{N}\equiv N\quad BF_4^-$$

$$R.\ \overset{\oplus}{N}\equiv N\quad BF_4^{\ominus} \longrightarrow RF + N_2 + BF_3$$

Since the original publication, Schiemann has applied the method to a wide range of aromatic amines including the naphthylamines, amino-di-phenyls (Schiemann and Roselius B. <u>62</u> 1805, 1929) and amino acids (Schiemann et al. B.<u>65</u> 1435, 1932). Later workers have shown that fluoro-fluorenones (B.<u>66</u> 46, 1933) and fluoro-phenanthrenes (Goldberg et.al. J.A.C.S. <u>69</u> 260, 1947) can be prepared by the Schiemann Reaction. Furthermore, the reaction may be used to introduce two fluorine atoms simultaneously, although if the two amino groups are situated in the same nucleus, the yields are poor. This is illustrated by the case of p-phenylene diamine which gives p-difluoro-benzene in 27% yield, whereas p-p^1 diamine diphenyl gives the corresponding di-fluoro compound in 80% yield. More recently, as will be seen, the reaction has been applied to the preparation of fluorinated heterocyclic compounds.

The Mechanism of the Reaction.

The actual mechanism of the thermal decomposition of diazonium fluoborates is still uncertain. Schiemann (Chem. Ztg. 52 754, 1928) supposed the energy liberated when the unstable diazoniumcation decomposed to be sufficient to cause the fluoborate ion to break down into a fluoride ion and boron trifluoride. There are, however, three possible reaction mechanisms by which the process can occur. These are shown schematically below :-

(1) the formation of a carbonium cation and combination of this with a fluoride ion

$$Ar \cdot N_2 \cdot BF_4^1 \longrightarrow Ar^+ + N_2 + BF_4^1$$

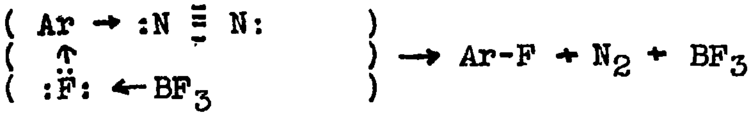
$$Ar^+ + (:F:BF_3)^1 \longrightarrow Ar - F + BF_3$$

(2) The formation of free radicals

$$Ar - N_2 - BF_4^1 \longrightarrow Ar^\bullet + N_2 + BF_3 + :\overset{\bullet}{\underset{\cdot\cdot}{F}}:$$

$$Ar^\bullet + :\overset{\bullet}{\underset{\cdot\cdot}{F}}: \longrightarrow Ar{-}F$$

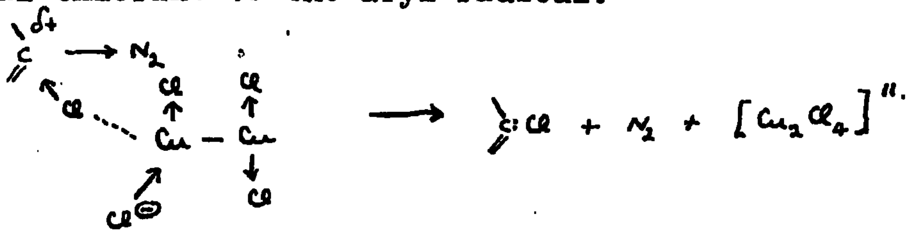
(3) Molecular rearrangement



$$\left(\begin{array}{l} Ar \rightarrow :N \equiv N: \\ \uparrow \\ :\ddot{F}: \leftarrow BF_3 \end{array}\right) \rightarrow Ar\text{-}F + N_2 + BF_3$$

Mechanism (1) was proposed by Bell (J.C.S. 835, 1934) as a result of experiments with optically active 2:2^1 diamino 6:6^1 - dimethyl diphenyl. This amine was converted into the corresponding di-iodo derivative by the Sandmeyer Reaction and found to be optically active. The analogous di-fluoro compound, formed by the thermal decomposition of the bis diazonium fluoborate showed no appreciable activity so that racemisation was presumed to have occurred. This was interpreted as implying the existance of a planar carbonium cation in which there is no longer any restriction to rotation and hence racemisation can occur. The result, however, is really inconclusive, since the di-iodo derivative is prepared in the cold whereas the fluoro compound requires an elevated temperature. Kinetic studies by Kistiakowsky and Smith (J.A.C.S. 58, 1043, 1936) show that 2:2^1 di -amino 6:6^1 dimethyl diphenyl is racemised by heat both in the liquid and vapour phase and that, if the energy of activation of the racemisation process is less than 20.0 K. cals/mol., autoracemisation takes place. Thus, Bell's results may be due to racemisation by heat or to the nature of the difluoro derivative.

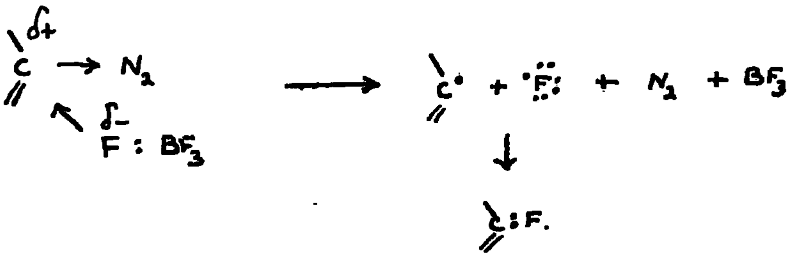
The free radical mechanism is due to Hodgson, Birtwell and Walker (J.C.S. 770, 1941). During an investigation of the Sandmeyer Reaction, they proposed that the process proceeded by way of the complex anion (Cu_2Cl_4) which was attracted to the diazonium cation when the complex decomposed. This involves (a) release of an electron at the carbon and formation of neutral chlorine, followed by (b) evolution of nitrogen and linkage of neutral chlorine to the aryl radical.



The complex was reformed by chloride ias also present in the reaction mixture. This theory was applied to the introduction of fluorine in the following way. In aqueous solutions, hydrofluoric acid is largely dissociated according to the equation :-

$$HF_2 + HO_2 \longrightarrow \overset{\oplus}{H_3}O + HF_2^{\ominus}$$

The stability of the HF_2^- ion apparently prevents complex formation and this accounts for the failure of the Sandmeyer Reaction in the preparation of armmatic fluorides. In the case of the diazonium fluoborates, however, a complex is already present. A mechanism similar to that of the Sandmeyer Reaction is then presumed to occur; a polarised fluorine atom in the BF_4^- ion attacking the cationoid carbon with the resulting evolution of nitrogen and boron trifluoride.



The formation of polymeric material in the Schiemann Reaction would appear to support the concept of a free radical mechanism. So far, there has been no evidence in favour of the third possibility although in the decomposition of nitro compounds it has been suggested that a complex is formed (O.K.Rice - private communication to Roe, Organic Reactions Vol.V.). However, the available experimental evidence does not allow any definite conclusions to be drawn as to the actual reaction mechanism.

Experimental Techniques.

Originally, the diazonium fluoborate was obtained by diazotising the amine in ice-cold HCl with sodium nitrite followed by the addition of 40% fluoboric acid. The precipitated diazonium salt was filtered, washed with alcohol and ether and dried in air. Since the original publication, however, numerous modifications have been introduced to increase the yield of diazonium salt. Chief amongst these is the replacement of hydrochloric acid by fluorboic acid and subsequently carrying out the diazotisation in the presence of fluoborate ions. In this procedure, the diazonium salt precipitates continuously as the diazotisation proceeds. Generally, this results in a purer product and has the advantage of eliminating some of the troublesome side reactions such as coupling and phenol formation. In view of an observation by Meigs (U.S.P. 1, 916, 327) who showed that fluoborates have an appreciable solubility in strongly acid solution, the latter method is to be preferred since the acid concentration is kept to a minimum. Alternatively, in place of fluoboric acid, certain inorganic fluoborates e.g. sodium or ammonium salts, may be used in conjunction with a mineral acid, usually hydrochloric. A further modification is to diazotise the amine in hydrofluoric acid and treat the solution with a stream of boron trifluoride until precipitation of the diazonium salt is complete (Org.React.Vol.V.).

The presence of other substituents in the aromatic nucleus often affects the yield of the diazonium fluoborate. As a general rule, the yields are lowered due to the increased solubility of the salt. In the case of carboxyl and hydroxyl groups, esterification and conversion to the ether increases the yield of diazonium salt appreciably. In all methods, the volume of the solution should be kept as low as possible since diazonium fluoborates are slightly soluble even in the cold.

Various reagents may be used to effect the diazotisation, the choice depending ultimately on the amine in question. The reagent commonly employed is sodium nitrite. Alternatively, amyl and ethyl nitrites, nitrosyl sulphuric acid and nitrosyl fluoborate (Organic React. Vol.V. Schiemann Reaction) may be employed. The letter reagent possesses the unique property of being both a diazotising agent and a source of fluoborate ions. Its use was first demonstrated by Voznesenkii and Kurskii (J.Chem. Gen. U.S.S.R. 8 524, 1938) who prepared benzene diazonium fluoborate in 90% yield from aniline.

The aryl diazonium fluoborates are on the whole remarkable stable and can be handled safely in large quantities. A few, however, e.g. m-methoxy benzene diazonium fluoborate, are unstable and decompose on standing at room temperature. In the heterocyclic series, the diazonium fluoborates are much more unstable than the corresponding benzene derivatives and, with few exceptions, cannot be isolated as solids. Thermal decomposition of aromatic diazonium salts usually proceeds quite smoothly giving 60 - 70% yields. Those heterocyclic diazonium fluoborates which are capable of isolation are usually decomposed in some inert medium such as toluene or petroleum ether. However, the yield depends to some extent upon the nature and position of other substituents in the nucleus. Generally, the ortho derivative is formed in the lowest yield although the variation in ortho, meta and para is not great. The nature of the substituent has a much more pronounced effect upon the yield. Unsubstituted aromatic compounds yield the best results although the presence of alkyl or halogen groups does not influence the decomposition to any marked extent. Carboxyl, amino, nitro and hydroxyl groups lower the yield in approximately the order given. As was mentioned previously, esterification in the case of an acid or conversion of the hydroxyl group to an ether helps to increase the yield of fluoride. The nitro group is perhaps the most difficult to deal with since it causes unruly decomposition of the fluoborate and the formation of a high percentage of tarry by-products, which decrease the yield considerably. The increased stability of the nitro diazonium fluoborates may be due to the known negative inductive effect of the nitro group which would lower the electron density in the neighbourhood of the diazonium group causing an increased electro-static attraction for the fluoborate ion.

It is difficult, however, to lay down any broad generalisations concerning the effect of structure on the stability of the diazonium fluoborates, and the above considerations must act merely as a guide. Some highly substituted molecules give excellent yields, for example, 2-bromo-3-methoxy-4-6-dimethyl fluoro benzene is formed in 70% yield from the corresponding diazonium salt (Becker and Adams J.A.C.S. 54 2973, 1932). It has been stated that the yield of fluoro compound is somewhat dependent on the decomposition temperature of the diazonium salt, the lower the value of the latter, the higher the yield (Schiemann J.Prakt.Chem.(2) 140 97, 1934). This qualitative relationship is only true for unsubstituted molecules and those containing one or more fluorine atoms. In other cases, the correspondence between temperature and yield is not very evident.

The actual decomposition of the salt is usually carried out in a distillation flask with a wide side arm connected to a condensor, the receiver being cooled in ice. To absorb the boron trichloride evolved, a train of Dreschel bottles half filled with NaOH, may be connected to the receiver. The flask is gently heated until decomposition occurs, heating being continued intermittently as required. Nitro compounds are usually decomposed in successive small quantities (5- 20 grams) the salt being mixed with three to five times its weight of sand or barium sulphate.

Application of the Schiemann Reaction to Heterocyclic Compounds. In applying the Schiemann Reaction to the preparation of heterocyclic fluorides, the amine is diazotised in fluorboric acid solution. The choice of the reagent used to effect diazotisation depends upon the amino position of the group; generally it is either sodium or ethyl nitrite. In the case of pyridine, all the diazonium fluoborates are unstable, pyridine -2-diazonium fluoborate decomposes as it is formed while the diazonium salt prepared from 3-amino pyridine precipitates as a solid which is unstable above 10°C. (Roe and Hawkins, J.A.C.S. 69 2443, 1947). So far, attempts to prepare 4-fluoro pyridine by the Schiemann Reaction have failed.

The stability of the quinoline diazonium fluorborates depends upon the position of the original amino group. If this is situated in the benzenoid nucleus, the diazonium fluoborate is quite stable and can be isolated, dried and distilled in the usual manner. If, on the other hand, the diazonium group is in the heterocyclic ring, the properties of the salt vary widely depending on the position of attachment. Thus, quinoline 2-diazonium fluoborate, like its pyridine analogue, decomposes as it is formed but quinoline-3-diazonium fluoborate is surprisingly stable and decomposes smoothly at 95°C. The yields of fluoroquinolines vary from 74% in the case of the 3-fluoro to 25% for 8-fluoro (Roe and Hawkins J.A.C.S. 71 1785, 1949).

Recently, Ferm and Vander Werf (J.A.C.S. 72, 4809, 1950) have investigated the diazotisation of amines in anhydrous HF and decomposition of the products "in situ". The results obtained by this method are interesting since, as far as aromatic amines are concerned, the yields of fluoro compound obtained are comparable with the Schiemann Reaction and, in some cases, superior. When they applied this method to a heterocyclic amine however, they state that the yields were poor but do not quote any definite figures. It will be shown later, that in the case of the two heterocyclic amines investigated the results obtained by this method were comparable, but slightly lower than those obtained in the normal Schiemann procedure.

During the present investigation, the preparation of fluoro-pyridines by the original method of Roe and Hawkins was repeated with various modifications.

In an attempt to increase the yield of 2-fluoro-pyridine, it was decided to carry out the reaction under different conditions varying the acid strength and the diazotising agent. 2-amino pyridine was diazotised in anhydrous HF and HBF_4 (obtained by passing dry borontrifluoride into anhydrous HF) and also in aqueous fluoboric acid as diazotising agents sodium and ethyl nitrite were employed. The results of these experiments are summarised in Table I; the complete details will be found in the experimental section.

TABLE I.

Solvent.	Ethyl Nitrite.	Sodium Nitrite.
40% aqueous fluoboric acid	-	34%
Anhydrous hydrofluoric acid	6%	20 - 22%
Anhydrous fluoboric acid	26%	30%
Calculate quantity of H_3BO_3 in anhydrous hydro-fluoric acid	22%	25%
Excess of fluoboric acid (200%) - H_3BO_3 in anhydrous hydrofluoric acid.	20%	30%

Inspection of these results shows that sodium nitrite is the most satisfactory diazotising agent in this case. With this reagent, using fluoboric acid, the results are very similar to those obtained by Roe. There is, therefore no increase in efficiency by the above methods. Originally, Roe and Hawkins diazotised in 40% HBF_4 with sodium nitrite and isolated the product by neutralisation followed by steam distillation. In the present investigations the procedure adopted was similar except that ether extraction was used in place of steam distillation. So far as 2-fluoro pyridine is concerned, this is quite satisfactory but 3-fluoro pyridine appears to form anazeotrope with ether so that steam distillation had to be resorted to. The stability of 2-fluoro-pyridine to hydrolysis was also investigated and it was found that in alkaline solution, hydrolysis was fairly rapid. Continuous refluxing in strongly acid solution brings about slowly the complete conversion of 2-fluoro pyridine to 2-pyridone. The following table (II) gives some results of hydrolysis experiments, the time allowed for reaction at any particular temperature being half-an-hour.

TABLE II.

Reagent.	% Hydrolysis		
	15°C	50°C	100°C
N Sodium hydroxide	10%	25%	-
N Hydrochloric Acid	1%	4%	15%

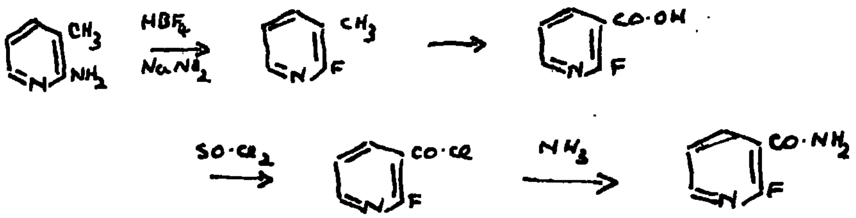
In view of these results it would seem that ether extraction after neutralisation is to be preferred to steam distillation since, if the solution is slightly alkaline, there would be appreciable hydrolysis at the temperature of distillation. In one experiment where steam distillation was used, 2-pyridone was obtained in 25% yield and identified by the N-ethyl and 3:5 dibrono derivatives.

3-fluoro-pyridine was prepared according to the procedure of Roe and Hawkins. Hydrolysis experiments on this compound indicated that it is quite stable behaving like an aromatic halide. This is in agreement with the properites of pyridine derivatives which behave in many respects like those of nitrobenzene. The presence of a positive polar nitrogen in the ring, which appears to behave like an electrophilic substituent, causes substitution in the meta (3) position with resultant stabilisation of the molecule as a whole (Maten-Chemistry of Heterocyclic Compounds Pp 192-4). The two and four positions of the pyridine nucleus are much more reactive. This difference in reactivity of the variohs positions in a heterocyclic ring is further emphasised by the case of the quinoline diazonium fluoborates already referred to.

Neither 4-fluoro pyridine nor 4-fluoro quinoline have been isolated. In the former case, Roe and Hawkins have demonstrated that the fluoro compound is actually formed but rearranges immediately into N (4'-pyridyl)-4-fluoro-pyridine (1). This is readily hydrolysed in acid solution to N-(4'-pyridyl)-4-pyridone (2) which may be identified as its picrate.

(1.) (2.)

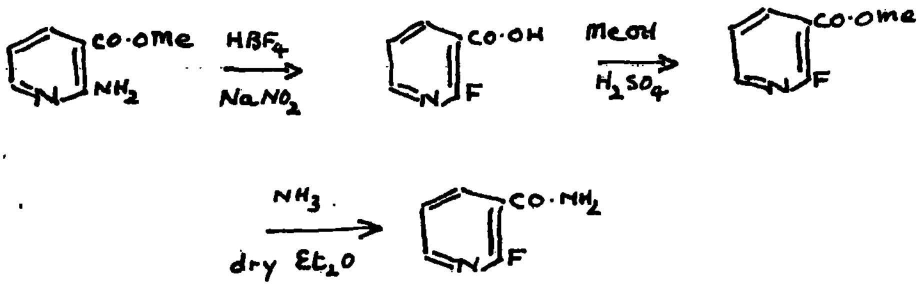
A similar reaction is thought to occur in the case of 4-fluoro-quinoline but as yet there is no definite evidence for this. The preparation of the di-fluoro-pyridine from the corresponding diamines has also been attempted in the present work. Roe (unpublished results) reported that an attempt to prepare 2-6 difluoro pyridine by the Schiemann Reaction had failed. In spite of this further attempts were made here using fluoboric acid of various subsequently treated with ammonia.



A certain amount of interest attaches to the fluorinated nicotinic acids by virtue of their structural similarity to nicotinic acid itself. The latter is an essential metabolite and investigations were carried out to study the effect of the fluorinated acid on metabolic activities. As yet no definite conclusions have been reached.

Before the work of Roe and Hawkins was published some of those acids were prepared directly from the corresponding amino acids as part of the present investigation. 2-amino-nicotinic acid was obtained by a Tschitschibaben Reaction on the sodium salt of nicotinic acid, and was isolated as its methyl ester. A solution of the ester in 40% fluoboric acid was diazotised with sodium nitrite, the resulting diazonium fluoborate being decomposed by gently warming the reaction mixture. After neutralising, the solution was evaporated to dryness and esterified, the ester so obtained being converted to the amide. 5-amino nicotinic acid was prepared by the method of Griess (J.A.C.S. 70 2381. 1948). This was converted to the

5-fluoro nicotinic acid by the above reactions. 3-amino pictotinic acid, obtained by a Hoffmann degradation on quinolinimide (Sucharda Ber. 58 1727, 1925) failed to give a fluorinated acid.



Owing to the fact that no stable diazonium fluoborate is formed in the above reactions and the fact that fluoronicotinic acid has an appreciable solubility in aqueous solutions, the method does not give good yields. 2-fluoro nicotinic acid was obtained in 18% yield as the methyl ester, conversion to the amide being almost quantitative. The method developed by Roe and Hawkins is capable of yields in the order of 60 - 70%.

An attempt has also been made to apply the Schiemann Reaction to a five membered heterocyclic ring system. For this purpose, 2-amino-4-methyl-thiazole was chosen. The amine was diazotised in 40% flueboric acid and the product heated to decompose any diazonium fluorborate. To isolate the product, the solution was extracted with ether. In this way, a low yield of a buff coloured solid was obtained which could be recrystallised from water. Analysis showed that it contained the correct amount of fluorine expected for 2-fluoro-4-methyl thiazole. As before, the low yield is probably due to the solubility of the substance in water, and the fact that there is no stable diazonium fluoborate. The solid itself is freely soluble in the usual organic solvents and has an appreciable solubility in cold water.

It was considered of interest to investigate whether diazonium salts derived from fluorinated acids other than fluoboric acid were capable of yielding results comparable to those obtained in the normal Schiemann Reaction. Fluoro-phosphoric acid (HPF_6) has been used to prepare 4-4' difluoro-diphenyl by pyrolysis of the corresponding bis diazonium fluophosphate (Lange & Muller B.63 1058, 1930) but the yield obtained was poor. Wiley (U.S.P. 2,423, 359) demonstrated that aromatic amine hydrofluosilicates, obtained by adding aqusous H_2SiF_6 to an alcoholic solution of the amine, could be converted to the corresponding diazonium fluo-silicates by diazotising a suspension of the salt in glacial acetic acid with ethyl nitrite. A number of these diazonium salts were characterised, but apart from the preparation of p-fluoro-benzoic acid in poor yield, no real attempt was made to utilise them for preparative purposes.

Thus, the possibility of using these diazonium salts was considered and preliminary experiments carried out with aromatic amines.

Aniline was converted by Wiley's method (aqueous H_2SiF_6 and alcoholic aniline) to the hydrofluosilicate and the latter diazotised to yield benzene diazonium fluosilicate. Attempts were made to decompose this salt in both polar and non polar solvents. Aqueous hydrofluoric and hydrofluosilicic acids yield phenol only but if the dry diazonium salt was decomposed by refluxing in dry petroleum ether, a 16% yield of fluoro-benzene was obtained. Similarly, o-fluoro-toluene could be prepared in 17% yield. These yields, although poor, were better than the literature leads one to expect and so it was decided to carry on with the application of the method to the heterocyclic series.

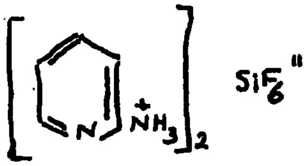
2-amino-pyridine was diazotised in aqueous hydrofluosilicic acid with sodium nitrite. Since the diazonium fluosilicates are soluble in water, no precipitate was formed and the resulting solution was therefore heated to 60°C to decompose any diazonium salt which had formed and finally cooled to 0°C and neutralised. The product was obtained by extraction with ether. In this way, 2-fluoro-pyridine was obtained in 37% yield. This experiment was then repeated using various diazotising agents e.g. amyl and ethyl nitrites and nitrosylsulphuric acid, but there was no improvement in the yield. A similar reaction carried out with 3-amino-pyridine resulted in a 23% yield of the corresponding fluoro-compound. In this case, the isolation was effected by preparing 3-fluoro-pyridine chloride since 3-fluoro pyridine forms an azeotrope with ether. The yield of 3-fluoro-pyridine is considerably lower than that obtained via the borofluoride whereas that for 2-fluoro-pyridine is appreciably greater; hence it was decided to carry out the reaction in stages, and by that means, try to improve the overall yields. The stages decided upon were the obvious ones which may be represented as follows :-

(a) Amine ⟶ amine hydrofluosilicate.

(b) Amine hydrofluosilicate → diazonium silicofluoride

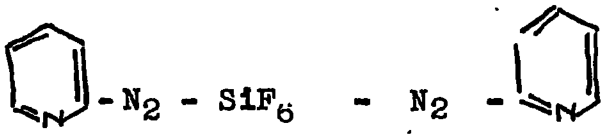
(c) diazonium silicofluoride ⟶ fluoro-compound

The conversion of 2-amino-pyridine to the amine hydrofluosilicate was achieved by passing a stream of dry silicon tetrafluoride into an alcoholic solution of the amine when the required salt precipitated. Determination of the equivalent weight of the dried salt by titration with standard acid indicated that it had the structure shown in (4)



(4)

Diazotisation of this salt was successfully accomplished by Wiley's procedure, although, owing to the relatively unstable nature of the diazonium salt, care had to be taken not to allow the temperature to rise above 20°C. Further, it was found necessary to take great care in ensuring that the acetic acid was really anhydrous, otherwise the diazonium salt reacted with the water present to yield 2-pyridone. During the diazotisation, the amine salt first dissolves and then reprecipitates as the diazonium fluosilicate. Analysis of the salt by liberation and estimation of nitrogen using the method of Schiemann and Pillarsky (B.62, 3035, 1929) showed it to have the following structure (5)



(5)

This diazonium salt is not particularly stable, is water soluble and does not couple with alkaline B-naphthol. Attempts to decompose it in aqueous hydrofluoric and hydrofluosilicic acids led to the formation of 2-pyridone. Howefer, decomposition of the diazonium salt in non-aqueous media e.g. dioxan and trichlor-ethylene, resulted in the formation of 2-fluoro-pyridine in 10-12% yield.

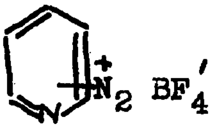
The low yields obtained may be due to the structure of the diazonium salt which, as can be seen from the formula given, has two diazonium residues in the molecule. If a free radical mechanism is postulated for the decomposition of the salt, the two radicals R - will be in close proximity to each other and this may lead to a high degree of polymerisation. In one case, when pyridine-2-diazonium fluosilicate was decomposed in dioxan, a solid was obtained in 10% yield which yielded a picrate and gave a red colouration with ferric chloride; it was 2-2' dipyridyl.

(i) $R.N_2.SiF_6.N_2'R \longrightarrow 2R\cdot + SiF_4 + N_2 + 2\cdot F$

(ii) $R\cdot + \cdot F \longrightarrow RF$

(iii) $2R\cdot \longrightarrow R-R.$

It is significant that, during the decomposition of diazonium fluoborates(6) in which there is only one diazonium residue per molecule, the radicals produced will not be in such close proximity and hence there is less chance of polymerisation.



(6)

(7)

The possibility of isolating a diazonium fluosilicate having the structure indicated in (7) i.e. having only one pyridyl residue was attempted, but the results showed no improvement, presumably because no such salt was obtained.

In an attempt to try and improve these poor yields, it was decided to try the decomposition of the diazonium fluosilicate in anhydrous HF. The reaction was carried out in an autoclave using a large excess of the anhydrous acid, the reaction temperature being in the range 80 - 90°C. On completion of the reaction, the excess acid was removed by distillation and an excess of di-ethyl amine added to decompose any pyridinium salts. The product was then ether extracted. When this technique was applied to 2-amino-pyridine, 2-fluoro pyridine was obtained in yields varying between 26 - 33% of the theoretical. Thus, in this case the yield is about the same as that obtained by the normal Schiemann Reaction, although the procedure is rather more tedious. The reaction was repeated, isolation being effected by neutralisation followed by steam distillation, with similar results to the above. In view of the encouraging nature of these results, other heterocyclic amines were investigated.

3-amino-pyridine hydrofluosilicate was prepared by the same method as that used for the 2-amino derivative and converted to the diazonium salt by diazotisation in glacial acetic acid. The salt so obtained was quite stable and, coupled with β-naphthol in alkaline solution to give a red dye. Attempts were made to decompose the diazonium salt in various solvents e.g. aqueous HF and H_2SiF_6, dioxan and petroleum ether, but only very poor yields of fluoro-pyridine were obtained. Decomposition of the diazonium salt in anhydrous hydrogen fluoride was then studied using a technique similar to that adopted for 2-fluoro-pyridine. Owing to the greater stability of the 3-diazonium derivative, a higher temperature had to be employed (90 - 100°C). Isolation of the fluoro-pyridine was effected by removing the excess acid, neutralising and steam distilling the product. In this way, 3-fluoro-pyridine was obtained in 10 - 14% yield. This result, however, does not compare at all favourably with that reported by Roe for the normal Schiemann Reaction (50%).

Carrying the investigation further, 2-amino-quinoline was converted to the diazonium fluosilicate and decomposed with anhydrous HF in the autoclave. Using the method of isolation given for 2-fluoro-pyridine, a 17 - 18% yield of 2-fluoro-quinoline was obtained. Again, the result is not so good as the Schiemann Reaction (28%), although the discrepancy is less marked than in the case of 3-fluoro-pyridine.

An attempt was also made to apply the method to the preparation of 2-fluoro-4-methylthiazole, the diazonium salt being obtained as previously described. The latter was decomposed in the autoclave with anhydrous HF, the product being extracted with ether. In this way, a compound identical with that obtained in the Schiemann Reaction was isolated in 4% yield. Once more, this is not as satisfactory as the normal Schiemann Reaction, but yields are so poor in both cases that it is impossible to draw a comparison.

In view of the experiments of Ferm and Van der Werf (J.A.C.S. 72, 4809, 1950) on the diazotisation of amines in anhydrous HF with sodium nitrate and subsequent decomposition, it was decided to investigate the straightforward diazotisation of the heterocyclic amines in anhydrous HF and the decomposition of the diazonium salts "in situ". When 2-amino-pyridine was diazotised in anhydrous HF by adding the calculated quantity of $NaNO_2$ and the product decomposed by heating at 40°C, a 20 - 22% yield of 2-fluoro-pyridine was obtained. This experiment was repeated and the results confirmed. To test the method further, 2-amino-quinoline was diazotised in anhydrous HF and decomposed in the same way. The reaction mixture, on completion of reaction, was neutralised and steam distilled. This gave 2-fluoro quinoline in 17% yield. A repeat experiment confirmed the results obtained above.

It can be seen from Table III that while there is no advantage in proceeding via the diazonium

As an alternative method of introducting fluorine into heterocyclic ring systems, the reaction between chlorine trifluoride and pyridine in the liquid phase has been investigated. Previously, little attention has been paid to the possibility of using this reagent although certain other interhalogen compounds have been employed as fluorinating agents. Thus bromine trifluoride BrF_3 and iodine pentafluoride, IF_5 will replace other halogens, but not hydrogen, by fluorine (McBee et.al. Ind.Eng.Chem. 39, 378, 1947, Haszeldine, J.C.S. 2188, 1948). A review of the chemistry of these interhalogen compounds has been published by Sharpe (Quart.Rev. 1950, 4 115 et.seq.).

As far as the reactions of chlorine trifluoride are concerned, Porter, Burnett and Banks (Chem.Soc. Symposium on Fluorine Chemistry) have reported that it introduces both chlorine and fluorine atoms into the organic molecule. Further, Haszeldine, in a private communication to Sharpe, has indicated that in the vapour phase reaction of benzene with chlorine trifluoride, there is evidence for both substitution and addition reactions. Recently, however, Musgrave and Ellis (J.C.S. 712 3808, 1950) have published their observations on the controlled reaction of ClF_3 with benzene in CCl_4 solution. These authors have been able to show conclusively that the main reaction is one of substitution although at the same time small amounts of addition compounds are formed. A number of catalysts were employed which were either (a) salts of transitional elements used in direct fluorination or (b) well known halogen carriers. Cobaltous fluoride appeared to be the most satisfactory of all the catalysts employed.

The formation of the chloro-benzene was attributed to the chlorinating action of chlorine mono-fluoride ClF, which is produced in the reaction according to the following scheme :-

$$\mathrm{ClF_3} + 2\,\mathrm{CoF_2} \longrightarrow \mathrm{ClF} + 2\mathrm{CoF_3} \qquad (1)$$

$$\mathrm{ClF_3} + \mathrm{CoF_3} \longrightarrow \mathrm{F}^{\oplus} + (\mathrm{CoF_4}) \quad \mathrm{ClF} \qquad (2)$$

According to the equation (2), one would expect equimolecular proportions of chloro-and fluoro-benzene, whereas, in practice chloro-benzene is produced in greater yield. The explanation advanced for this result is that chlorine mono-fluoride is produced both in the formation of the trivalent state of the catalyst and the reaction of chlorine trifluoride with the solvent (Emeleus et.al. J.C.S. 1948, 2188).

$$\mathrm{ClF_3} + \mathrm{CCl_4} \longrightarrow \mathrm{CCl_3F} + 2\,\mathrm{ClF}$$

$$\mathrm{ClF_3} + \mathrm{CCl_3F} \longrightarrow \mathrm{CCl_2F_2} + 2\,\mathrm{ClF}$$

An alternative reaction mechanism for the action of $\mathrm{ClF_3}$ on $\mathrm{CCl_4}$ due to Schmitz and Schumacher (Z.Naturforsch, 1947, 2(a) 362) which involves free chlorine was considered unlikely, since the chlorine would react with benzene with the consequent formation of HCl; this gas was never detected during the reaction. The fluorine cation produced in equation (2) is, of course, responsible for the formation of fluoro-benzene by the usual substitution mechanism. Thus, it appears that it is easier to produce a fluorine cation from chlorine trifluoride than from fluorine itself. In direct fluorination an atomic chain mechanism is postulated to account for ring degradation.

Since the results from the reaction of chlorine trifluoride with benzene showed that substitution took place, it was considered to be of interest to investigate the reaction in the case of a heterocyclic ring system, and for this purpose pyridine was chosen. Various reports have appeared recently on the direct fluorination of heterocyclic compounds in the vapour phase. Haszeldine (J.C.S. 1966, 1950) has investigated the action of elementary fluorine on aniline and pyridine and has obtained per-fluoro-pyridine $C_5F_{11}N$ in 0.3% yield, and perfluoro-cyclohexylamine in 0.2% yield. The same author attempted to fluorinate 2-6 dimethyl pyridine (lutidine) in the vapour phase and claimed to have isolated the corresponding per-fluoro derivative. To account for the low yield obtained, Haszeldine assumed the formation of pyridinium salts. Thus, the HF evolved in the initial stages of the reaction is supposed to combine with the basic nitrogen to yield pyridinium fluoride. This then reacts violently with the fluorine resulting in a high percentage of decomposition. Perfluoro pentanil C_5F_{12} and nitrogen trifluoride NF_3 are the principal by-products of the reaction indicating that the ring is ruptured at the $C - N = C$ bonds. This theory, however, is open to the criticism that quaternary salts would in all probability be dissociated at the high temperatures involved and therefore their formation must be considered as unlikely. Some pyridinium salts commence decomposition at their melting points e.g. pyridinium iodide. Further, the ability to form basic salts depends on the nature of any substituents in the nucleus, thus 2-fluoro-pyridine does not form a stable pyridinium fluoride, whereas 3-fluoro-pyridine does. Before any definite conclusions can be reached, more experimental data must be forthcoming. An interesting observation has been recorded by Simons (J.Electrochem. Soc. 95 47, 1949). When pyridine, dissolved in anhydrous HF is electrolysed, some 2-fluoro-pyridine was isolated. The actual experiment is carried out so that the potential difference across the cell never reaches the decomposition potential of HF; in other words, free fluorine is never liberated at the anode. Here again the principal products of the reaction were nitrogen trifluoride and per-fluoro-pentane. In this case, the formation of pyridinium salts cannot be doubted but the reaction was carried out at temperatures below 12°C.

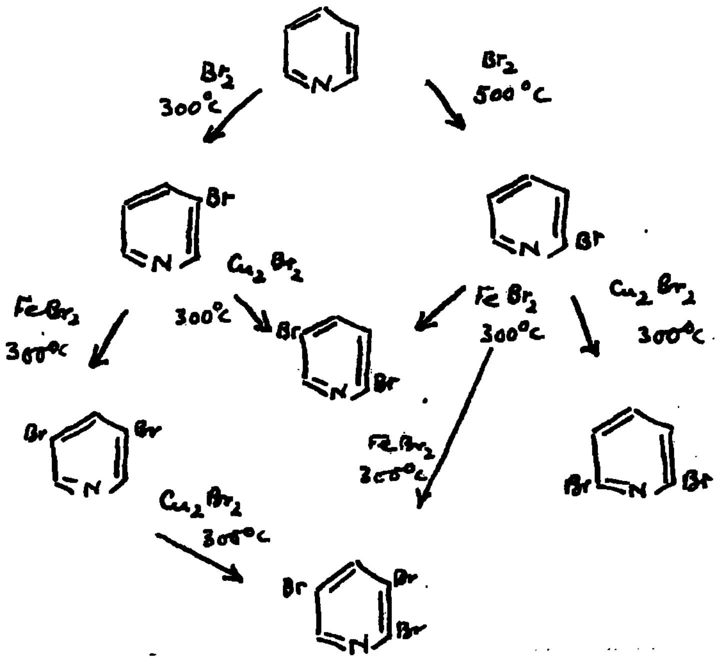
In the present investigation, all the reactions were carried out at 0°C, in a mild steel reaction vessel. Chlorine trifluoride, suitably diluted with dry nitrogen was led into the reaction mixture at a rate of approximately 7 grs/hour. The ratio of chlorine trifluoride to pyridine was 1 mol. to 2 mols, the nitrogen being adjusted to 10 - 12 litres/hour. In the first series of experiments, the products of the reaction were isolated by pouring into saturated brine, washing until free from HF, and drying over $Mg\ SO_4$. The solvent was removed by distillation at atmospheric pressure and the residue fractionated through a short electrically heated column. The products so obtained were analysed for chlorine and fluorine. These results are shown in the table set out overleaf :-

TABLE OF RESULTS (SERIES I)

Catalyst.	Weight of Pyridine	Weight of ClF_3	Tar	Fluoro Pyridine	Chloro-Pyridine
None	100g	57g	8g	5-6g	-
CoF_2 (10g)	100g	57g	10.5g	7.0g	-
CoF_2 (10g)	50g	28g	8.8g	5.4g	-
$CoCl_2$ (10g)	50g	28g	Not Weighed	2.9g	-
AgF (10g)	50g	28g	9g	0.5g	1.2g
TlF (10g)	50g	29.5g	4.5g	-	2.5g
SbF_3 (10g)	50g	26.5g	6.0g	4.6g	-

The chlorinated derivative, an analysis, proved to be 3-chloro-pyridine (B.P.148°C, 750m.m.), whereas the fluoro-compound isolated was, in all cases, 2-fluoro-pyridine (B.P.125°C). Inspection of the above table again shows that substitution has taken place with the formation of both chloro and fluoro derivatives. Further, the proportion of these appears to depend on the catalyst used; thus thallous fluoride yields exclusively the 3-chloro-pyridine whereas cobaltous fluoride and chloride and antimony trifluoride give only 2-fluoro-pyridine. Silver fluoride gives a mixture with the chloro compound in greater yield. As can be seen, the overall yields were poor, the greatest recorded being with an SbF_3 catalyst (8.9%).

A further interesting feature is the position of substitution in these reactions. It is rather surprising that the chlorine and fluorine should substitute in different positions. Normally, however, halogenation of pyridine depends largely on the reaction conditions as illustrated by the following considerations. Direct bromination of pyridine at 300°C yields a mixture of 3- and 3-5 dibromo-pyridine (50%). This is in accordance with the presence of positive polar nitrogen in the ring which is meta (C_3) directing. Further bromination at 500°C yields 2;3,5 tribromo pyridine. The course of the reaction is however influenced by the presence of ferrous or cuprous bromide. If 3-5 dibromo pyridine is treated with Br_2 at 300°C in the presence of cuprous bromide, the product is mainly 2:3:5 tribromopyridine, and 3-bromopyridine, under similar conditions yields 3:6 dibromo pyridine. Thus it appears that cuprous ions cause reaction to occur mainly at the 2 or 2:6 positions. 2-Bromo-pyridine, obtained by the reaction of bromine with pyridine at 500°C, reacts with bromine in the presence of ferrous bromide to yield 2:5 dibromo-pyridine. At higher temperatures, 2-bromo-pyridine yields 2:4:6 tribromo pryidine. The actual mechanism of these reactions is unknown but it has been suggested that at higher temperatures bromine reacts in an atomic form i.e. a free radical mechanism is postulated (Wheland "Theory of Resonance" P.261).



(After Morton "Chem. of Heterocyclic Compounds"
page 193)

A similar scheme is applicable to the direct chlorination of pyridine. Thus, it is seen that although the directive influence is towards the 3 position, at high temperatures substitution in position 2 predominates. The catalysts, it should be noted, are transitional elements in their lowest valency state.

In the reaction between pyridine and chlorine trifluoride the products are 2-fluoro and 3-chloro pyridine. It is not known whether ClF or $F^{\oplus}$

will attack first so it difficult to discuss these results. In any case, the main product was 2-fluoro pyridine.

Further experiments were then carried out with a view to increasing the poor yields obtained in the first series. In the reactions under consideration, the formation of pyridinium salts was considered possible since the temperature was maintained at 0°C. If this should be the case, the salt would precipitate out of the reaction mixture and reaction of this solid with chlorine trifluoride would probably result in violent decomposition with rupture of the ring. It was proposed that the reaction should be carried out in the presence of a large excess of pyridine and without stirring the reaction mixture so that the halogen acids formed during the reaction would be removed by the excess of pyridine and would settle to the bottom of the reaction vessel. The chlorine trifluoride and nitrogen were led in just below the liquid surface. In the actual experiment sufficient chlorine trifluoride was used to react with 40 grams of pyridine. On completion of the reaction, it was worked up in the manner previously described, dried and distilled. The final fractionation yielded 4.8 g. of 2-fluoro-pyridine (9.7%). This was a considerable improvement on the first uncatalysted experiment which a 4.6% yield. It should be noted that no 3-chloro-pyridine was isolated.

This result indicated that pyridinium salts were formed as was thought. To test this hypothesis further, it was decided to carry out the experiment in the presence of anhydrous potassium fluoride. This should remove the HF produced as potassium hydrogen fluoride and also allow the use of a catalyst.

$$KF + HF \longrightarrow KHF_2$$

An initial experiment was carried out with pyridine in the absence of any catalyst but the results were not encouraging. 2-fluoro-pyridine was obtained in 2% yield together with 0.45 g. of a viscous oil (B.P. 160°C 30 m.m.). Analysis of the latter indicated that it was probably a difluoro dipyridyl. A similar reaction was then carried out using antimony fluoride as a catalyst in the presence of potassium fluoride. Here again the result was disappointing since the whole of the product decomposed during the final distillation with the evolution of HF.

These reactions were then repeated but a different method of isolating the product was introduced. At the end of the reaction, the product was transferred to a dry conical flask and thoroughly shaken with anhydrous KF. After being allowed to stand for a while the carbon tetrachloride layer was separated and the solvent removed by rapid distillation under reduced pressure; in this way two fractions were obtained (a) mainly CCl_4 and

(b) the pyridine derivatives. Fraction (b) was then refractionated under reduced pressure through a small 18" electrically heated column. In this way, it was hoped to recover any addition compound before it decomposed. The final fractions were then redistilled at atmospheric pressure, and analysed for both chlorine and fluorine.

The results of these experiments are shown in the following table :-

TABLE OF RESULTS (SERIES II)

Catalyst	Wt. of Pyridine	Wt. of ClF_3	Viscous reaction product.	2-Fluoro pyridine	3-Chloro-pyridine.
None	75.0g	41.0g	40.0g	9.0g (9.6%)	3.0g (2.7%)
SbF_3 (10.0g)	100.0g	55.0g	25.0g	17.8g (14.6%)	3.0g (2.0%)
Co F_2 (10.0g)	50.0g	28.0g	--	12.5g (20.5%)	2.0g (3.0%)
$CoCl_2$ (10.0$_4$)	50.0g	30.0g	20.0g	11.8g (19%)	1.8g (≑ 3%)

In all the experiments 1 gr.mol. of KF per 100g of pyridine was used.

The viscous tarry reaction product separated as an oily upper layer when the solution was poured on to potassium fluoride at the termination of the reaction. This was separated in each case and weighed. Attempts to distil some of this material under reduced pressure led to total decomposition.

Owing to the fact that 2-fluoro pyridine distils in carbon tetrachloride under reduced pressure, each solvent fraction was analysed for free and combined fluorine. The figures in the column headed "2-fluoro pyridine" were obtained in this manner. In order to have some verification of the amount of 2-fluoro pyridine contained in the solvent fraction, a quantity of the latter was carefully fractionated at atmospheric pressure through a column of approximately thirty theoretical plates. The results obtained agreed with the analytical figures within the limits of experimental error. Confirmation of the fact that the dissolved product was 2-fluoro-pyridine was obtained by refluxing a portion of the solvent fraction with concentrated hydrochloric acid. After neutralising the acid layer with NaOH, aqueous bromine was added and the resulting dibromo derivative was identified as 3-5 dibromo 2 hydroxy pyridine.

Examination of the table shows that, as in the case of benzene, cobaltous fluorides gives rise to the greater total yield although cobaltous chloride approximates to it very closely. In all cases, the proportion of chloro pyridine produced was roughly identical. The ratio of the number of gram molecules of 2-fluoro pyridine to the number of gram molecules of 3-chloro-pyridine in the case of the catalysed runs is nearly constant (approximately 7 : 1). The main reaction here is substitution with the production of 2-fluoro pyridine (in benzene the product produced in greater yield was chloro-benzene although the molecular ratio was never as widely diverse in the present case).

The most important point to note however is that in the general yields have risen greatly; these are compared in the following table :-

COMPARATIVE TABLE.

Catalyst.	Yield of 2-fluoro-pyridine.		Yield of 3-chloro-pyridine.	
	No KF	KF	No KF	KF
None	4.6%	9.6%	Nil	2.7%
SbF_3	7.0%	14.6%	Nil	2.0%
CoF_2	6.0%	20.5%	Nil	3.0%
$CoCl_2$	4.7%	19%	Nil	3%

The yield of 3-chloro-pyridine (4%) obtained in the first series of experiments using thallous fluoride is slightly greater than those recorded above although of the same order of magnitude.

The results shown in the table indicate that low yields are due to the formation of pyridinium salts and that the use of KF raises theb yields by preventing salt formation. The fact that 3-chloro pyridine and 2-fluoro-pyridine are the products is not very easily explained. The low yields of chloro pyridine may be due to the fact that the pyridine is relatively stable to the action of chlorine mono fluoride. However, no reference is available on the reaction of pyridine with ClF, so this suggestion is only tentative. Before any conclusions could be reached on the point, it would be necessary to try the reaction out. As has been seen on the section on halogenation of pyridine, the conditions of the reaction govern to a great extent the position of the entering substituent. The formation of 2-fluoro-pyridine should not, therefore, be too difficult to explain. It should be noted that during the course of the reactions conditions were arranged such that no free halogens could be detected in the effluent gases, and thus it is unlikely that the chlorination has proceeded by way of free chlorine. This is further emphasised by the fact that direct chlorination requires rigorous conditions as has been stated previously and therefore, it seems unlikely that chlorination by free chlorine could take place under the reaction conditions employed.

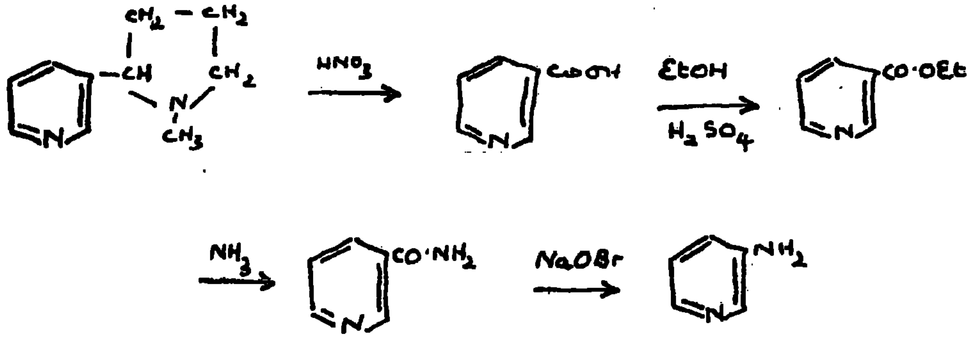
EXPERIMENTAL

The preparation of the amino-pyridines.

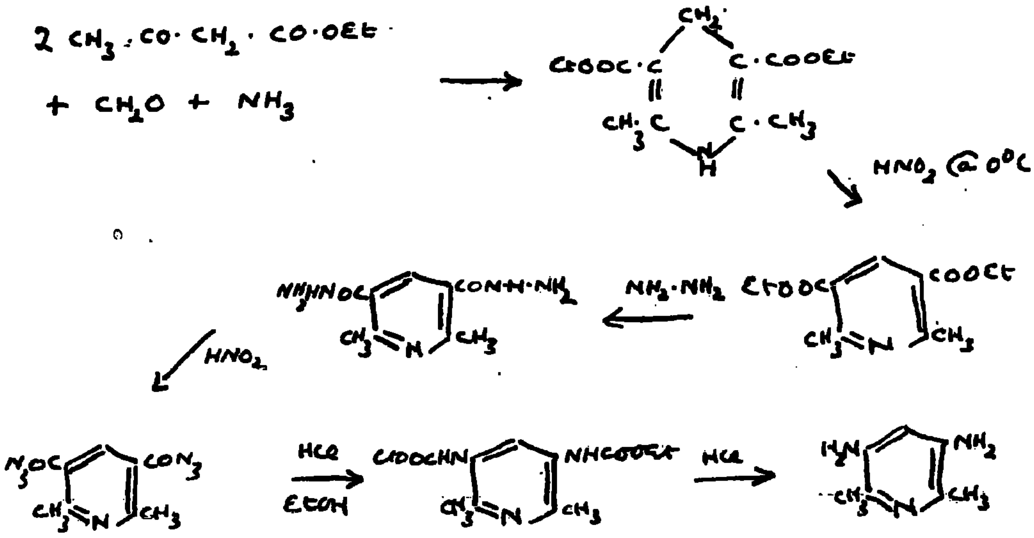
2-amino and 2-6 diamino pyridine.

These were obtained by the Tschitschibaben reaction. Pyridine (1 mol), in dry xylene, was treated with sodamide (1 mol) at 120°C. The product was isolated by the addition of water and NaOH followed by benzene extraction. In the case of the diamine, 3 mols. of sodamide were used and the reaction carried out at 170°C. In both cases, yields were of the order of 50%.

3-Amino-pyridine was synthesised from nicotine by oxidation to nicotinic acid with nitric acid, followed by esterification and conversion to nicotinamide (J.A.C.S. 50 2479, 1928). The amide was then degraded to the amine with alkaline hypobromite (Phillips. Ann. 288, 263). The yields in the last stage were poor, being approximately 30 - 35%, the overall yield from nicotinic acid being 18%.



1:4 Dihydro - 2-6-dimethyl 3:5 - dicarbethoxy pyridine was prepared by condensing aceto-acetic ester with formaldehyde and ammonia (Hantschz B. 35 1788, 1902). Oxidation of this in the cold yield 2-6 dimethyl-3-5-dicarbethoxy pyridine which undergoes a Curtuis' degradation to give 2-6-dimethyl-3-5-diamino pyridine (B. 33 114, 1900).



2. Amino-nicotinic acid

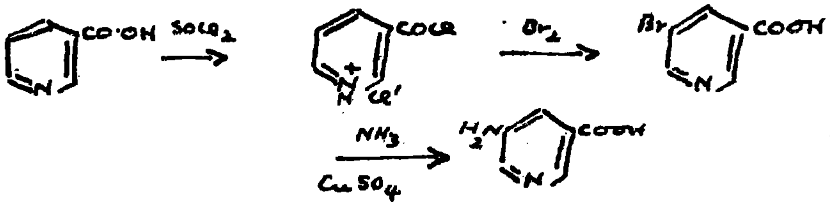
Nicotinic acid (10.0 gr.) was placed in a clean dry flask equipped with a stirrer and reflux condenser. Sodamide (3.5 gr.) was added and the solids covered with dry xylene (50 mls.). The mixture was heated to 150°C until H_2 evolution was negligible (about 3 hours). On cooling, 100 mls. of water were carefully added to decompose the complex. The lower aqueas layer was separated, neutralised and evaporated to dryness. The dried solid was esterified with an excess of 3% methyl alcoholic H_2SO_4, the product was neutralised with sodium methoxide and filtered. The filtrate was then carefully evaporated until crystallisation commenced.

<u>Yield of 2-amino nicotinic acid methyl ester</u>

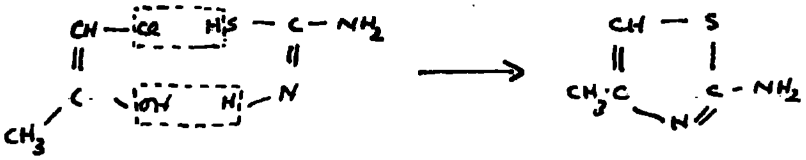
3.0 gr.

M.P. = 83°C

5. Amino nicotinic acid was obtained from nicotinyl chloride hydrochloride. Nicotinic acid was refluxed with Hiconyl chloride for 30 hours, the excess $SOCl_2$ removed, the product sublimed under reduced pressure. The hydrochloride so obtained was brominated and then treated with aqueous ammonia and $CuSO_4$ in a sealed tube (J.A.C.S. <u>70</u>, 2381, 1948).



2-Amino-4-methyl thiazole was prepared from chloracetone and thio-urea (Org.Synthesis. Vol.II).



2-Amino-quinoline was obtained by a Tschitschibaben reaction (Shreve Ind.Eng.Chem. <u>32</u> <u>177</u> 1940).

Replacement of amino groups by fluorine.

2-Fluoro-pyridine (A).

2-Amino-pyridine (5.0g) was dissolved in 40% aqueous fluoboric acid (25.0 mls) and the solution cooled to 0°C. This solution was diazotised by the slow addition of sodium nitrite (4.0 gr). When all the nitrite had been added, the solution was allowed to remain at 0°C for one hour, and was finally warmed to 40°C for half-an-hour to complete the decomposition of the diazonium fluoborate. The product was then cooled to 0°C and neutralised by the addition of solid Na_2CO_3. The oil which separated was extracted with ehter, dried (anhydrous $MgSO_4$) and distilled.

Yield of 2-fluoro-pyridine 1.77 gr. (32%) B.P. 125.5 - 126°C.

Analysis.

Required for C_5H_4NF, F = 19.6%

Found F = 19.4, 19.5%

2-Fluoro-pyridine (B).

2-Amino-pyridine (5.0 g) was dissolved in anhydrous HF (50.0 g) contained in a copper vessel, and cooled to 0°C.

The resulting solution was then diazotised by the slow addition of sodium nitrite (4.0 gr.). When addition of the nitrite was complete, the solution was warmed to 30° - 40°C for one hour. After cooling in ice, the excess acid was neutralised with Na_2CO_3, the product being isolared by ether extraction. Distillation of the dried ethereal extract yielded 1.0 g. of 2-fluoro-pyridine (20%) B.P. 125°C.

2-Fluoro-pyridine (C)

A similar experiment to the above (B) using ethyl nitrite as a diazotising agent gave a 6% yield of 2-fluoro pyridine.

2-Fluoro-pyridine (D)

2-Amino-pyridine (5.0 gr.) was dissolved in anhydrous HF (20.0 g.) contained in a copper vessel. Boron-trifluoride, prepared by heating a mixture of CaF_2, $H_3 BO_3$ and concentrated H_2SO_4 was dried by bubbling through conc. H_2SO_4 and passed into the solution. Sufficient CaF_2 was used to give twice the quantity of BF_3 required to produce HBF_4 from the HF. After cooling 10 - 5°C, the solution was diazotised by passing a slow stream of ethyl nitrite for 1-1½ hours. The temperature was raised to 50°C for half-an-hour to complete the decomposition of the diazonium fluoborate. After cooling to 0°C, the solution was neutralised with sodium carbonate and the product extracted with ether. Distillation of the dried ethereal extract yielded 1.10 gr. of 2-fluoro-pyridine B.P. 125°C (22%).

Analysis :- required for C_5H_4 N.F. F = 19.6%

Found F = 19.5%

2-Fluoro-pyridine (E)

The above experiment (D) when carried out using $NaNO_2$ in place of ethyl nitrite, gave a 25% yield of 2-fluoro-pyridine.

2-Fluoro-pyridine (F)

2-Amino-pyridine (5.0 g.) and boric acid (3.5 g) were dissolved in anhydrous HF (50.0 mls.). The resulting solution, after cooling to 5°C, was diazotised by the slow addition of 4.0 gr. of sodium nitrite, the solution being mechanically stirred. After standing for one hour, the solution was warmed to 30°C for half-an-hour. On cooling, it was neutralised with Na_2CO_3 and extracted with ether. Distillation of the dried ethereal extract yielded 1.56 g. of 2-fluoro-pyridine B.P. 125.5°C (30%).

2-Fluoro-pyridine (G)

In a similar experiment to (F) using ethyl nitrite as the diazotising agent, a 26% yield of 2-fluoro-pyridine was obtained.

Attempted preparation of 2:6 difluoro-pyridine (A)

2:6 Diamino-pyridine (10g) was finely ground with boric acid (10.0g) and introduced into a copper vessel. Anhydrous HF (50 gr) was added and the solution cooled to -5°C. Diazotisation was then effected by the slow addition of sodium nitrite (6.0g), the solution being mechanically stirred. When diazotisation was complete, the solution was allowed to stand for one hour at 0°C. To complete decomposition of the diazonium fluoborate, the solution was heated to 40°C for half-an-hour. After cooling, it was neutralised with Na_2CO_3 and extracted with ether. The dried ethereal extract, on distillation yielded 1.0 g. of a solid (M.P. 44-46°C, B.P.200-208°C 760 m.m.).

Analysis. F = 18.8%. Calculated for difluoro-pyridine $C_5H_3NF_2$.

F = 33.1%. Calculated for $C_{10}H_6N_2F_2$ (difluoro-dipyridyl). F = 19.8%.

The solid yielded a picrate which was recrystallised from aqueous alcohol. (M.P. 156° - 157°).

Analysis. Calculated for $(C_{10}H_6N_2F_2)(C_6H_3N_3O_7)$

F = 8.8%. Found 9.1%.

Thus, the original solid is probably impure difluoro-dipyridyl.

Method (B).

The above method was repeated using anhydrous fluoboric acid.

This was prepared by passing BF_3 into a solution of the amine in anhydrous hydrofluoric acid. Diazotisation was carried out with sodium nitrite as before. The products were isolated by neutralisation followed by ether extraction. Distillation of the dried extract yielded the solid previously reported (A) in 9% yield along with a small quantity of an oil B.P. 160 - 170°C, the yield of the oil being only 2%.

Analysis of the oil.

Calculated for 2-6 difluoro-pyridine $C_5H_3NF_3$

F = 33.1%. Founded F = 27.7%

Further attempts to prepare more of the oil failed.

Attempted preparation of 3:5-difluoro- 2:6-dimethyl pyridine.

2:6 - Dimethyl-3:5-diamino pyridine (3g) and boric acid (5g) were dissolved in anhydrous HF (30 cc). The resulting solution, after cooling to -5°C, was diazotised by the slow addition of $NaNO_2$ (5.0 g). After the diazotisation was complete, the solution was allowed to remain at 0°C for an hour and was finally heated to 40°C to decompose any diazonium fluoborate. On cooling, the solution was neutralised with Na_2CO_3 and extracted with ether. Distillation of the dried ethereal extract a solid which started to distil at 160°C under 14 m.m. pressure. Only a minute quantity was obtained but a qualitative sodium fusion showed the presence of fluorine. Treatment of an alcoholic solution of the solid with picric acid did not yield a picrate. Further attempts at the preparation of this solid have been unsuccessful.

Fluorination of 2-amino nicotinic acid.

The methyl ester of 2-amino-nicotinic acid (3.0g) was dissolved in 40% fluoboric acid (20.0 mls) and the solution cooled to -5°C. Diazotisation was effected by adding slowly sodium nitrite (2.5 g). After the nitrite had been added, the solution was allowed to remain at 0°C for one hour. Finally, to complete the decomposition of the diazonium fluoborate, the solution was raised to 50°C for half-an-hour. After cooling, the reaction mixture was carefully neutralised with Na_2CO_3 and the water removed by distillation under reduced pressure. The residue was then dried at 60°C. This was then refluxed with 50.0 mls. of 3% methyl alcoholic

H_2SO_4 for 2 hours. The hot solution was neutralised with $NaOCH_3$, filtered and evaporated down to about 3 mls. A white crystalline solid was obtained (0.6g) M.P. 74 - 75°C.

When 0.2 gram of this solid was dissolved in absolute alcohol and treated with anhydrous ammonia, a solid was obtained after the solvent had been removed by distillation. The yield was 0.16 gr. (M.P. 124°C).

Analysis $C_6H_5N_2OF$ requires F = 13.5%.
Found F = 13.4%

Fluorination of 5-amino-nicotinic acid.

5-amino nicotinic acid (3.0g) was dissolved in 40% fluoboric acid (20.0 mls) and the resulting solution cooled to -5°C. Sodium nitrite (2.5g) was added slowly to diazotise the solution. After allowing to stand in the ice-bath for an hour, it was heated to 50°C for half-an-hour to decompose the diazonium salt. On cooling, the solution was neutralised with sodium carbonate and the water removed by distillation under reduced pressure. The resulting solid, after drying at 60°C, was refluxed with 3% methyl alcoholic sulphuric acid for 2-3 hours. After neutralising the hot solution with sodium methoxide and filtering, the solution was evaporated to about 2 cc. when 0.3 gr. of a solid was obtained (M.P.48°C).

The methyl ester obtained was dissolved in 10 mls. of dry methyl alcohol and saturated with ammonia at 0°C. After standing 24 hours, it was evaporated when

5-fluoro-nicotinamide (0.2g) was obtained (M.P.173-174°C).

Analysis. $C_6H_5ON_2F$ requires F = 13.5%
Found F = 13.3, 13.2%

Attempted preparation of 3-fluoro-picolinic acid.

A similar experiment to the previous one using 3-amino-picolinic acid failed to give any product.

2-Fluoro-pyridine (H).

In this experiment, fluoboric acid was replaced by hydrofluosilicic acid.

2-amino-pyridine (10g) was dissolved in 35cc of pure H_2SiF_6 (approximately 100% excess) and cooled to -5°C in an ice-salt bath. Diazotisation was effected by the slow addition of sodium nitrite (8.0g). After complete addition of the $NaNO_2$, the mixture was allowed to remain at 0°C for one hour. To complete the decomposition of any diazonium fluosilicate, it was heated to 60°C for a further hour. On cooling to 0°C, it was neutralised by the addition of Na_2Co_3 and extracted with ether. Distillation of the dried extract yielded 3.8 g. of 2-fluoro-pyridine (37%) B.P. 125°C.

2-Fluoro-pyridine (I)

The use of ethyl nitrite in place of $NaNO_2$ similarly gave a 37% yield.

2-Fluoro-pyridine (J)

When nitrosyl sulphuric acid was used as the diazotising agent, only an 18% yield of the required

2-fluoro-pyridine was obtained. Amyl nitrite gave 2-pyridone.

3-Fluoro-pyridine (A).

This was first prepared by the Method of Roe and Hawkins (J.A.C.S. 69 2443, 1947). 3-Amino-pyridine (5.0 gr.) was dissolved in 20 cc. of 40% HBF_4 and 50 cc. of 95% alcohol. A slow stream of ethyl nitrite was bubbled through the solution when the diazonium salt precipitated. Cold ether was added to complete precipitation of the diazonium salt which was filtered and transferred immediately to high boiling petroleum ether, since the salt decomposes violently when dry. A few cc. of conc. HCl were added and the ether removed. After making alkaline with NaOH, the solution was steam distilled. Solid NaOH was added to the distillate when an oil separated. This was dried over NaOH and distilled.

Yield of 3-fluoro-pyridine 2.4 g. (48%) B.P. 107°C. Analysis. C_5H_4NF requires F = 19.6%

Found F = 19.3, 19.4%

3-Fluoro-pyridine (B)

3-amino-pyridine (5g) in pure H_2SiF_6 (20 cc) was cooled to 0°C and carefully diazotised by the slow addition of $NaNO_2$ (3.6g). After allowing the solution to stand in the ice-bath for one hour, the solution was raised to 60°C on a water bath. After cooling to 0°C it was neutralised with Na_2CO_3 and steam distilled.

The aqueous distillate was saturated with solid NaOH when an emulsion formed which would not separate into two layers. This was then extracted with ether.

Since 3-fluoro-pyridine forms an azeotrope with ether, it was decided to try and isolate the product as the hydrochloride.

The dried ethereal solution was treated with dry hydrogen chloride at 0°C for one hour. The ether was then removed under reduced pressure, a slow stream of HCl being passed through the solution during the distillation. The crystalline residue was then treated with the calculated quantity of diethylamine to remove the hydrofluoric acid. Distillation of the product yielded 1.2 g. of 3-fluoro-pyridine (24%) B.P. 106° - 107°C.

Attempted preparation of 2-fluoro-4 methyl thiazole.

2-amino-4-methyl thiazole (10.0g) was dissolved in a mixture of 40% fluoboric acid (40.0 mls) and ethyl alcohol (20.0 mls). The solution was cooled to 0°C and diazotised with ethyl nitrite over a period of 1½ hours. When the reaction was complete, the solution was allowed to remain at 0°C for one hour. Finally, to decompose any diazonium fluoborate, it was heated to 60°C for one hour. After cooling to 0°C, the solution was extracted with ether. Distillation of the dried ethereal extract yielded a solid (0.94 g) M.P.66° - 68°C. This solid was recrystallised from water.

Analysis. Required for C_4H_4NFS, F = 16.4%

Found F = 16.6% : 16.5%

Preparation of 2-amino-pyridine hydrofluosilicate.

2-amino-pyridine (4.0 g) was dissolved in 98% alcohol (20.0 mls). A stream of dry silicon tetrafluoride, from calcium chloride, silica and concentrated sulphuric acid, was bubbled through the solution until no more solid precipitated. When precipitation was complete, the solid was filtered, washed with alcohol and ether, and dried in a chloroform dryer. The salt obtained was found to be water soluble. Yield 90%.

NOTE : If the mixture of CaF_2, SiO_2 and H_2SO_4 is heated too strongly, water is driven over which causes precipitation of silica with the amine salt.

Analysis. Equivalent for $(C_5H_6N_2)H\ SiF_6$ = 166

Found 162, 164.

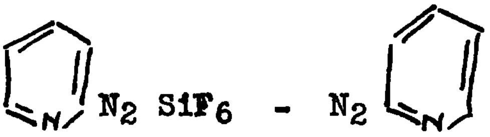
Diazotisation of 2-amino-pyridine hydrofluosilicate (A).

The salt (2.0 g.) was suspended in glacial acetic acid and a stream of ethyl nitrite passed through the solution for about 5 hours. The suspended solid dissolves at first and then reprecipitates as the diazonium salt. When the precipitation appeared to be complete, the solid was filtered, washed with dry ether until acid free, and carefully dried.

Yield 1.8 g. (80%)

Care must be taken that the temperature does not rise above 20°C and further, that the acid used is absolutely anhydrous. The latter is most important since the presence of water causes the formation of 2-pyridone and polymeric material.

Nitrogen analysis, by decomposing the salt in 50% sulphuric acid (Schiemann and Pillarsky B. 62 3035, 1929) showed the diazonium salt to have the formula :-



Diazotisation of 2-amino pyridine hydrofluosilicate (B & C)

As alternative methods of diazotising, nitrosyl sulphuric acid and amyl nitrite were tried, but these were found to be inferior to ethyl nitrite.

Attempts to decompose pyridine-2-diazonium fluosilicate

(A) In Dioxan.

The dried diazonium salt (5.0 gr) was refluxed in dry dioxan (25 mls) for one hour. After cooling to 0°C, the solution was filtered and saturated with dry hydrogen chloride. The solvent was then removed, a continuous stream of HCl being passed through the apparatus. To the residue, diethylamine was added (2 cc) and the product extracted with ether. Distillation of the dried extract yielded 0.35 g. of an oil B.P. 124 - 126° (10%).

(B) In trichlor-ethylene.

A similar experiment, using trichlor ethylene was carried out. After removal of the solvent, a solid remained (0.2 g) which proved to be 2.2' dipyridyl (picrate M.P. 154°C). In addition, 2-fluoro-pyridine was obtained in 5% yield.

Preparation of 3-amino-pyridine hydro-fluosilicate.

3-amino-pyridine (2.0 g) was dissolved in 98% alcohol and treated with dry silicon tetrafluoride. The precipated solid was filtered, washed with ether and dried.

Yield 85%

This salt was also found to be water soluble.

Analysis. Equivalent for $(C_5H_6N_2)_2 \cdot H_2SiF_6$ = 166

Found 160, 163.

Diazotisation of pyridine-3-hydrofluosilicate.

The amine salt (1.6 g) was suspended in glacial acetic acid and diazotised by a slow stream of ethyl nitrite. After 1½ hours, the brown solid was filtered, washed with dry ether and dried. The product was water soluble and coupled with alkaline β naphthol to yield a red dye.

Yield 1.1 g.

Attempts to decompose this diazonium salt in aqueous HF and H_2SiF_6 led to the formation of 3-hydroxy pyridine, identified by the acetyl derivative (M.P. 210°C).

Decomposition of Pyridine-2-diazonium fluosilicate in Anhydrous Hydrofluoric acid.

(a) The diazonium salt (5.0 gr) was dissolved in anhydrous hydrofluoric acid (50.0 g) and the solution transferred to an autoclave. Decomposition was effected by heating the auto-clave to 80° - 85°C, the temperature being maintained for one hour. After cooling in ice, the solution was transferred to a copper distillation apparatus and the excess acid removed. To the residue, an excess of diethylamine was added to decompose pyridinium salts and the whole was extracted with ether. The dried ethereal extract was carefully distilled and yielded 0.78 g. of 2-fluoro-pyridine (B.P. 124 - 125.5°C). Yield 29%.

Analysis. Required for C_5H_4NF, F = 19.6%

Found F = 19.4%

(B) The above experiment was repeated on a larger scale (10.0 g) the procedure being identical with that described above. An oil (1.86 g) was obtained B.P. 125° - 126°C (31%).

(C) Other experiments were carried out using a large excess of HF (up to 200 g) but there was no increase in the yield.

<u>The decomposition of pyridine-3-diazonium fluosilicate in anhydrous HF.</u>

The diazonium salt (6.2 g) was dissolved in anhydrous HF (50.0 gr) and transferred to the autoclave. To decompose the salt, the autoclave was maintained at 90°C for 1½ hours. After cooling in ice, the solution was transferred to a copper distillation apparatus by the use of suction, and the excess acid distilled away. The residue was made alkaline with 2N NaOH and steam distilled. On making the aqueous distillate strongly alkaline with solid NaOH an oil separated which was dried and distilled. Yield 0.34 g. . B.P. 108°C (10%).

Analysis. Required for C_5H_4NF F = 19.6%

Found F = 19.4%

(B) The above experiment was repeated using 100.0 gr. of anhydrous hydrofluoric acid. In this case, the yield of the 3-fluoro-pyridine was 14%.

Preparation of 2-amino-quinoline hydrofluosilicate.

2-Amino-quinoline (3.0 gr) was dissolved in 98% alcohol (20.0 mls). A stream of dry silicon tetrafluoride was passed through the solution until no further precipitation occurred. The yellowish solid was filtered, washed with alcohol and ether and dried at 30°C. The salt was slightly soluble in water. Yield 80%.

Analysis. Equivalent for $(C_9H_8N_2)\ H_2SiF_6$ = 216

Found 210, 214.

Diazotisation of 2-amino-quinoline-hydrofluosilicate.

The salt (2.0 g) was suspended in glacial acetic acid and treated with a slow stream of ethyl nitrite for 2 - 2½ hours. The salt partially dissolved and commenced to reprecipitate as the diazonium salt. This was filtered, washed with ether and dried. The salt is not very stable and, like its pyridine analogue, does not couple with alkaline B naphthol. Yield 80%.

Decomposition of Quinoline-2-diazonium fluosilicate in Anhydrous HF

(A) The diazonium salt (10.0 g) was dissolved in an excess of anhydrous HF (100 g and transferred to the autoclave. The decomposition was carried out at 80°C for one hour. On cooling to 0°C the solution was removed by suction and the excess acid distilled. To the residue, an excess of diethylamine was added and the whole extracted with ether (3 x 20 cc). After drying the ethereal extract, the solvent was removed and the residue distilled under reduced pressure. In this was 1.2 g. of an oil B.P. 132°C 30 mm was obtained.

Yield 18%

Analysis required for C_9H_6NF, F = 12.9%

Found F = 12.7%

(B) This experiment was repeated, but in place of ether extraction, the product was neutralised with Na_2CO_3 and steam distilled. The yield of 2-fluoro-quinoline was the same as in (A).

Diazotisation of 2-amino-quinoline in anhydrous HF.

2-amino-quinoline (4.0 g .) was dissolved in anhydrous hydrofluoric acid (20.0 g) in a copper beaker and the solution cooled to 0°C. Sodium nitrite (1.8 g) was slowly added. When diazotisation was complete, the solution was maintained at 0°C for one hour and finally heated to 60°C to decompose the diazonium salt. On cooling to 0°C the solution was neutralised with solid Na_2CO_3 and steam distilled. The oil which collected in the distillate was separated, dried ($MgSO_4$) and distilled. 2-fluoro-quinoline

(B.P. 132/30 m.m.) was obtained in 17% yield.

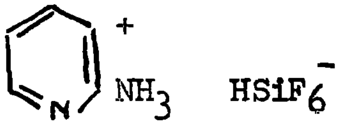
Diazotisation of 2-amino-quinoline in anhydrous fluoboric Acid (A).

2-amino-quinoline (4.0 g) was dissolved in anhydrous HF (20.0 g) and the solution cooled to -5°C. A stream of dry BF_3 was bubbled through the solution, sufficient BF3 being used to react with twice the quantity of HF. The resulting solution was diazotised by the slow addition of $NaNO_2$ (1.8g). After standing for one hour, the reaction mixture was heated to 60°C. The solution was then cooled rapidly to 0°C and carefully neutralised with Na_2CO_3. Steam distillation of the product yielded 0.96 g. of 2-fluoro-pyridine (23%) B.P. 131-133°C 30 m.m. pressure.

(B). The above experiment was repeated, the product being isolated by ether extraction. This yielded 22% of 2-fluoro-quinoline.

(C) The original experiment of Roe (J.A.C.S. 71, 1785, 1949) was repeated with 40% HBF_4 and their results confirmed (27%)

Attempted preparation of a monobasic pyridine-2-diazonium fluosilicate.



(A) Anhydrous hydrogen fluoride (9.0 gr) was distilled into acetone (10 mls) cooled to 0°C in an ice-bath. 2-amino-(quinoline) pyridine - hydrofluosilicate (5 g) was suspended in this solution. The cold solution was treated with a stream of SiF_4 for half-an-hour. At the end of this time, the solution was diazotised with sodium nitrite (4.0 g.). To decompose the diazonium salt formed, the solution was heated to 40°C. On cooling, the product was neutralised with solid Na_2CO_3 and steam distilled. On making the distillate alkaline an oil separated which was dried ($MgSO_4$) and redistilled.

Yield of 2-fluoro-pyridine 0.6g. (23%)
B.P. 125.5°C.

(B) When ether extraction was employed in place of steam distillation, a 22% yield of fluoro-pyridine was obtained.

These results are much the same as those obtained by diazotising 2-amino-pyridine in anhydrous HF with $NaNO_2$.

Attempted preparation of 2-amino-4-methyl-thiazole hydrofluosilicate.

2-amino-4-methyl thiazole (3.0 g) was dissolved in an excess of 98% alcohol (20.0 mls) and treated with a stream of dry SiF_4. A yellowish solid precipitated which was filtered, washed with ether and dried. The precipitate was found to be water soluble. Yield 2.7 (g) (18%),

Analysis. Equivalent for $(C_4H_6N_2S)_2H_2SiF_6$ = 186.
Found 184.

Diazotisation of the hydrofluosilicate of the 2-amino-4-methyl thiazole.

The amine salt (2.0 g) was suspended in glacial acetic acid (20 mls) and diazotised by a slow stream of ethyl nitrite for 2 hours. During the reaction, the solid changes colour from yellow to reddish-brown. The diazonium salt was filtered, washed with ether and dried.

Analysis. Required for $C_8H_8F_6.N_6.S_2.Si$ N = 21.3%

Found N = 20.6%

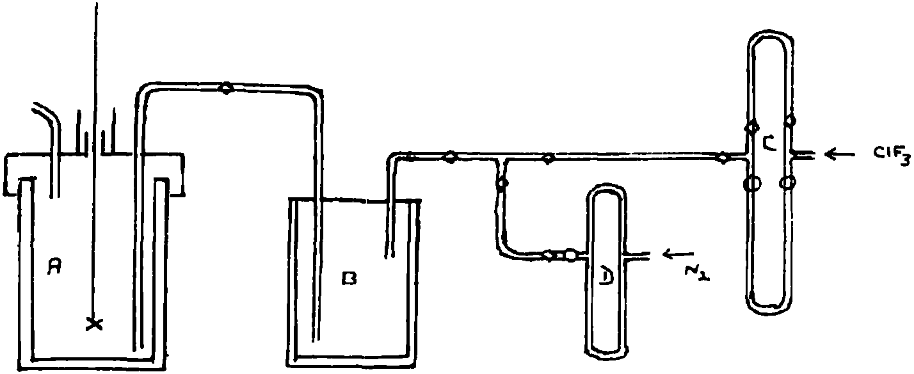
Attempts to decompose this diazonium salt in aqueous HF and H_2SiF_6 were unsuccessful, no fluorinated derivative being isolated.

Decomposition of the diazonium fluosilicate of 2-amino-4-methyl thiazole in anhydrous HF.

The diazonium salt (10.0 g) was dissolved in anhydrous HF (50.0 g.) and the solution transferred to the autoclave. To effect the decomposition, the autoclave was maintained at 80°C for one-and-a-half hours. On completion of the reaction, the autoclave was cooled to 0°C and the reaction mixture transferred to a copper distillation apparatus where the excess acid was removed. An excess of di-ethylamine was added and the product extracted with ether (3 x 20 cc). After drying, the ether was removed leaving a mush of crystals, which were extracted with hot water. Concentration of the aqueous extract yielded 160 m.g. of an orange coloured solid M.P. 65°C.

Analysis. Required for C_4H_4NFS, F = 16.4%

Found F = 16.2%



◇ Compression unions with brass washers.

○ Compression unions with neoprene washers.

EXPERIMENTAL PART II.

The Reaction of Chlorine Trifluoride with Pyridine.

Pyridine, dried by distillation from phosphorous pentoxide, and carbon tetrachloride dried by distillation from anhydrous magnesium sulphate were used in all the experiments. All the reactions were carried out in metal apparatus.

The apparatus (see diagram) consisted of a mild steel reactor (A) of approximately 1 litre capacity equipped with a screw type lid carrying inlet and outlet tubes and having provision for a stirrer; a steel safety trap (B) and two flow meters (C and D) for measuring chlorine trifluoride and nitrogen respectively. The reactor (A) was connected to the trap (B) and thence, through a brass "T" piece, to the flow meters "C" and "D". The flow-meter D and the lower part of C were made of hard glass, the upper part of C consisting of a copper tube terminating in very fine nickel orifices and was connected to the glass by copper tubing. The joints were made with brass compression unions, neoprene washers being used for glass to metal junctions. Carbon tetrachloride was used as the manometric liquid.

The procedure normally adopted was as follows:- Pyridine (1 mol.) was dissolved in dry carbon tetrachloride (500 mls) to which was added the anhydrous catalyst (10.0 g). The reaction vessel was cooled to $0^{\circ}C$ in an ice-bath and the mixture treated with chlorine trifluoride ($\frac{1}{2}$ mol.) at the rate of approximately 7.0g/hr., the solution being mechanically stirred during the reaction. Nitrogen was used as a diluent at the rate of 10 - 12 litre/hr. During the course of the reaction the exit gases were tested qualitatively for free halogen (starch-iodide), hydrogen chloride (silver nitrate on a glass rod) and hydrogen fluoride (etching test) at frequent intervals. In order to check the quantity of chlorine trifluoride that had entered the system, the cylinder was weighed at one or two hourly intervals.

When the required quantity of ClF_3 had been added, nitrogen was allowed to sweep through the apparatus for half an hour. To isolate the reaction products, two methods were used. In the first series of experiments, the reaction mixture was poured into a saturated solution of sodium chloride and washed with this solution until acid free. The organic layer was separated and dried ($MgSO_4$). After removing the solvent by normal distillation, the residue was rapidly distilled under reduced pressure, the receiver being colled in a dry-ice-methanol bath. This reduced pressure distillation was found to reduce tar formation to a certain extent. Finally, the product was carefully fractionated through an 18" electrically heated column packed with Fenske helices.

In the second series of experiments, the reaction mixture was poured on to anhydrous KF to free it from hydrofluoric acid. The acid free product was then all distilled rapidly under reduced pressure, the receiver being cooled in dry ice and methanol. In this manner two fractions were obtained, the first being mainly CCl_4 and the second containing the required pyridine derivatives. The second fraction was refractionated under reduced pressure through an 18" electrically heated column packed with Fenske helices. By carrying out the final distillation under reduced pressure, it was hoped to recover any addition compounds before they decomposed.

Since, in a separate series of experiments, it was shown that 2-fluoro-pyridine distilled in carbon tetrachloride to some extent under reduced pressure, the CCl_4 fraction was analysed for fluorine in all the experiments of the second series.

SERIES I.

(a) The reaction of pyridine with chlorine trifluoride in the absence of a catalyst.

Pyridine (100 g) dissolved in carbon tetra chloride (500 mls) was cooled to 0°C and treated with chlorine trifluoride (56 g) over a period of 7½ hrs, in the presence of nitrogen (10 l/hr).
On completion of the reaction, the product was washed with brine and dried as described previously.

After removing the solvent at atmospheric pressure, the remainder (62 mls) was rapidly distilled under reduced pressure. This yielded 58 mls. of a clean product and 2.0 g. of a tarry residue. Fractionation of the product then gave the following results :-

Fraction	Volume.	Boiling Point
(i)	36.4 mls.	76.8 - 77.5°C
(ii)	12.1 mls.	80.6 - 106°C
(iii)	5.4 mls.	126° - 128°C

Tarry residue 6.0 gr.

Fluorine analysts on fractions (i) and (ii) were negative. Fraction (iii) is 2-fluoro-pyridine B.P. 125.5 - 126°C (J.A.C.S. 2443 69 1947).

Analysis of (iii)

Required for C_5H_4NF F = 19.6

Found F = 19.4

Yield of 2-fluoro pyridine 5.3 g. (4.6%)

No other pyridine derivatives were isolated.

(b) The reaction of ClF_3 with pyridine in the presence of CoF_2 as catalyst.

Pyridine (100 g) was dissolved in CCl_4 (500 mls) containing anhydrous cobaltous fluoride (10.0 g). The solution was stirred vigourously to keep the catalyst in suspension and treated with ClF_3 (56.0g) in the presence of nitrogen (10 l/hr) over a period of 8 hours. After washing with brine and drying, the solvent was removed by atmospheric distillation. Distillation of the residue under reduced pressure yielded a clean product (60.0 mls) and 2.0 g. of residue. When the product was fractionated through a short column, the following fractions were obtained :-

Fraction.	Volume.	Boiling Point.
(i)	45 mls.	76.8 - 78°C
(ii)	5 mls.	80.0 - 100°C
(iii)	7.4 mls.	126°C

Tarry residue 4.5 gr.

Fraction (iii) is 2-fluoro-pyridine, yield 7.2g (6%).

Fraction (ii) gave a positive fluorine test (zirconium-alizarin lake). No quantitative estimations were done however.

The above experiment was repeated on a 50 g . scale using 10.0 gr. of catalyst and 28.0 g. of chlorine-tri-fluoride. After working up the product in the manner described previously and removing the solvent, 27 mls. of clean products were obtained. Fractionation of this yielded the following results :-

Fraction.	Volume.	Boiling Point.
(i)	16 mls.	76° - 77°C
(ii)	5 mls.	79° - 100°C
(iii)	3.4 mls.	124 - 127°C

Tarry residue 4.0 grams.

Fraction (iii) is 2-fluoro-pyridine B.P. 125.5°C. Yield 3.2g. (5.2%)

(c) The reaction of ClF_3 with pyridine in the presence of anhydrous cobaltous chloride.

Pyridine (50.0 g) was dissolved in carbon tetrachloride (500 mls) containing anhydrous cobaltous chloride (10.0g). The cooled solution was treated with ClF_3 (6gr/hr for 5 hrs) in the presence of nitrogen (10 l/hr). After washing the product until acid free, and drying, the solvent was removed and the residue fractionated as before. The following fractions were obtained :-

Fraction.	Volume.	Boiling Point.
(i)	15 mls.	76 - 78°C
(ii)	6 mls.	81 - 95°C
(iii)	2.9 mls.	124 - 126°C

Residue 3.0 g.

Fractions (i) and (ii) were found to be free from fluorine. Fraction (3) is 2-fluoro-pyridine. Yield 2.8 g. (4.7%).

(d) The reaction of ClF_3 with pyridine in the presence of silver fluoride as catalyst.

Pyridine (50.0 g) was dissolved in carbon tetrachloride (500 mls) containing anhydrous silver fluoride (10.0 gms). The solution was treated with chlorine trifluoride (27 gr) over a period of 5 hours.

On completion of the reaction, the product was washed until neutral and dried. After removal of the solvent, followed by distillation under reduced pressure, 16 mls. of a clean liquid were obtained. This was fractionated through the short column, and yielded the following results :-

Fraction.	Volume	Boiling Point
(i)	7.0 mls.	76 - 77.5°C
(ii)	3.0 mls.	80 - 100°C
(iii)	0.5 mls.	124 - 125°C
(iv)	1.15 mls.	145 - 148.5°C
Residue	-	

Fractions (i) and (ii) were found to be fluorine free. Fraction (iii) is 2-fluoro-pyridine, yield 0.95 g [redacted] (0.9%).

Fraction (iv) on qualitative analysis was found to contain chlorine.

Analysis. Required for C_5H_4 N.Cl, Cl = 31.5, N = 12.4

Found Cl = 31.8%, N = 12.6%

This corresponds to chloro pyridine. The liquid was found to be slightly soluble in water and yielded an alkaline solution. On treatment of the hot aqueous solution with mercuric chloride, the addition compound separated on cooling. Recrystallised from water. M.P. 179°C.

A salt was obtained with platinic chloride in HCl M.P. 168°C.

This data shows that the product is 3-chloro-pyridine (B.P. 148° 754 mm).

The products of the reaction are :-

2-fluoro-pyridine 0.5 gr (0.9%)

3-chloro-pyridine 1.15 g (1.7%)

(e) The reaction of ClF_3 with pyridine in the presence of Thallous fluoride.

Pyridine (50.0 g) was dissolved in CCl_4

(500 mls) containing thallous fluoride (10.0 g). The solution was treated with chlorine-trifluoride (29g) over a period of 5 hours, in the presence of a stream of drynitrogen (10 l/hr). After washing the product and drying, the solvent was distilled away and the residue redistilled under reduced pressure; 15 mls of product were obtained. This was then fractionated and the following results were obtained.

Fraction.	Volume.	Boiling Point.
(i)	11 mls.	76 - 77°C
(ii)	2.5 mls.	146 - 150°C

Residue 1.5 grams.

Fraction was analysed for chlorine, fluorine and nitrogen.

Calculated for $C_5H_4 \cdot N \cdot Cl$ N = 12.4% Cl = 31.5%

Found N = 12.6% Cl = 31.6%

The product yielded a chloro-platinate M.P. 168°C and a mercuric chloride derivative M.P. 169°C. Thus, the product is 3-chloro-pyridine (B.P. 148°C).

Yield of 3 chloro-pyridine 2.5 g. (4%)

(f) The reaction of pyridine with ClF_3 using antimony trifluoride as catalyst.

Pyridine (50g) was dissolved in CCl_4 (500 mls) containing antimony trifluoride (10.0 g). This solution was treated with ClF_3 (27 g) over a period of 5 hours. After washing and drying the product, the solvent was distilled and the residue distilled under reduced pressure;

this yielded 20 mls. of a clear liquid. Fractionation of this yielded the following results :-

Fraction.	Volume.	Boiling Point.
(i)	12.0 mls.	76 - 78°C
(ii)	2.0 mls.	80 - 100°C
(iii)	4.0 mls.	124 - 126°C
Residue	3.0 grms.	

Fractions (i) and (ii) were found to be free of fluorine; fraction (iii) is 2-fluoro-pyridine. Yield 4 gr (7.0%). No chloro pyridine was isolated with this catalyst.

From these experiments, antimony trifluoride appears to be the best catalyst for fluorination whilst thallous fluoride is successful in promoting chlorination. Attempts were made now to increase the low yields.

(g) The reaction between a large excess of pyridine and ClF_3 in the absence of a catalyst.

This reaction was carried out in the presence of a large excess of pyridine, the purpose being to control the amount of HF present in the system. Further, the inlet tube of the reactor was adjusted so that it only projected to a depth of 4 cms. beneath the surface of the reaction mixture. This was to enable any pyridinium salts formed to precipitate out of the reaction mixture. For the same reason, the experiment was carried out without stirring. The reaction was carried out in three sections, two using 100.0 gs. of pyridine and the other 50.0 gs. A total of 22.0 g. of ClF_3 was used.

	Wt. of pyridine.	Wt. of ClF_3.	Vol. of CCl_4
Run (a)	100 g.	10.0 g.	500 mls.
(b)	100 g.	6.0 g.	500 mls.
(c)	50 g.	6.0 g.	500 mls.

The products were combined, washed with brine and finally dried ($MgSO_4$). Sufficient chlorine trifluoride was used to react with 40.0 g. of pyridine. The solvent was distilled away at atmospheric pressure and the residue distilled under reduced pressure. The product (27 mls) was then fractionated through the short column when the following results were obtained :-

Fraction.	Volume.	Boiling Point.
(i)	20.0 mls.	76.5° - 77.5°C
(ii)	4.8 mls..	125 - 127°C

Fraction (ii) is 2-fluoro-pyridine yield 4.8g (9.7%).

This is an appreciable increase on the first non-catalysed experiment (a) (4.6%).

Experiments were then undertaken using KF to remove the hydrogen fluoride produced during the reaction.

SERIES II.

(1) The reaction between pyridine and chlorine trifluoride in the presence of potassium fluoride.

Pyridine (50.0 g) was added to a suspension of KF (60 g. 1 mol) in carbon tetrachloride (500 mls). After cooling to 0°C the solution was stirred vigorously and treated with ClF_3 (50.0 g). The time of the experiment was 5 hours. On completion of the reaction, the product was poured into brine and washed until acid free. After drying ($MgSO_4$), the solvent was removed and the residue distilled under reduced pressure. In this distillation a small quantity of a yellow syrup was obtained (0.45g B.P. 160°C 30 m.m.). Fractionation of the product yielded 2-fluoro-pyridine (1.5 g. 2%).

Analysis of syrup :-

Found N = 13%, F = 19.2%.

Required for a difluoro-dipyridyl N = 14.4%, F = 19.7%

Thus, the priduct is probably a difluoro-dipyridyl. It had no reaction with permanganate or bromine water.

(2) The reaction between pyridine and chlorine trifluoride in the presence of potassium fluoride and with antimony trifluoride as catalyst.

Pyridine (50g) was added to a suspension of KF (60g, 1 mol) and antimony trifluoride (10 g) in carbon tetrachloride (500 mls). This solution was treated with ClF_3 (27 g). After washing with brine and drying, the solvent was removed and the residue fractionated. No fluoro-pyridine was obtained and the material in the distillation flask underwent total decomposition.

(3) The reaction between pyridine and chlorine trifluoride in the presence of KF.

Pyridine (75.0g) was dissolved in CCl_4 (500 mls) containing KF (60g, 1 mol) and the solution treated with ClF_3 (41.0g) over a period of 7 hours. On completion of the reaction, the product was poured into a beaker when it separated into two layers, an upper viscous layer and lower CCl_4 layer.

The lower layer was separated and shaken with KF, the upper viscous layer was retained (40.0 g).

The whole of the CCl_4 solution was distilled rapidly under reduced pressure. In this way two fractions were obtained :-

(i) 350 mls. - mainly CCl_4

(ii) 24 g. - pyridine products plus CCl_4

The second fraction was then fractionated under reduced pressure through the 18" column. The product was split into two fractions.

Fraction.	Volume.	Boiling Point.
(i)	20 mls.	42° 150 m.m.
(ii)	3.2 mls.	56° - 60° 30 mm.

Fraction (ii) corresponds to 3-chloro-pyridine.

Analysis. Calculated for $C_5 H_4 NCl$, N = 12.4%

Cl = 31.5%.

Found N = 12.2%, Cl = 31.3%

Boiling Point 148°C, mercuric chloride derivative M.P.180°C.

Since it had been shown that 2-fluoro-pyridine distils in CCl_4 under reduced pressure, the CCl_4 was analysed for fluorine.

Analysis. 350 mls. of CCl_4 contain 9.0 grams of 2-fluoro-pyridine (test of CCl_4 for free HF was negative). Further, on standing, the whole of the CCl_4 layer turned an orange-yellow colour - a typical reaction of solutions of 2-fluoro pyridine.

Summarising the results.

2-fluoro-pyridine (by titration) 9.0 g . (9.6%)

3-chloro-pyridine (B.P.148°C) 3.0 g.. (2.7%)

Viscous layer 40.0 g..

This result compares with the experiment in which a large excess of pyridine was used (9.7%)

4. Reaction of pyridine with ClF_3 using SbF_3 as catalyst in the presence of KF.

Pyridine (100.0 g .) in CCl_4 (500 mls) containing KF (60 g) and SbF_3 (10.0 g) was treated with ClF_3 (55.0 g .) in the presence of nitrogen (10 lit/hr). On pouring the product into a beaker two layers separated. The lower CCl_4 layer was run on to anhydrous KF while the upper layer was weighed and retained (weight 25.0 gr). The CCl_4 was rapidly distilled under reduced pressure and divided into two fractions.

(i) CCl_4 - 380 mls. (ii) 27 mls.

Fraction (ii) was then fractionated under reduced pressure when the following results were obtained :-

Fraction.	Volume.	Boiling Point.
(a)	5 mls.	44°C 150 m.m.
(b)	12 mls.	50 - 60°C 80 m.m.
(c)	3 mls.	60°C 30 m.m.

Fraction (c) is 3-chloro-pyridine (B.P.148°C).

Fraction (b) contains fluorine.

Analysis of (b)

0.153 gr. of (b) = 0.75 mls. of 0.05 $N.Th(NO_3)_4$

This corresponds to 0.33 g. of 2-fluoro-pyridine in the

12 mls. of liquid.

Analysis of carbon tetrachloride layer (380 mls).

Test for free HF - negative.

0.2349 g. ≡ 1.4 mls. of 0.05 N thorium nitrate.

This corresponds to 17.5 g. of 2-fluoro-pyridine.

The products of the reaction are then :-

(1) 2-fluoro-pyridine 17.8 g. (14.6%)
(2) 3-chloro-pyridine 3.0 g. (2.0%)
Residual viscous oil 25 g.

An attempt was made to distil a portion of the viscous oily material under reduced pressure but it decomposed rapidly with the evaluation of HF.

5. Reaction of pyridine with ClF_2 in the presence of KF using cobaltous fluoride as catalyst.

Pyridine (50.0 g) in carbon tetrachloride (500 mls) containing kF (1 g . mol) and CoF_2 (10.0 g), was treated with ClF_3 (28.0 g) at 0°C. On pouring the product into a dry beaker, no separation occurred. kF was added and the product allowed to stand overnight. The product was rapidly distilled under reduced pressure, two fractions being obtained.

(a) CCl_4 310 mls. (b) 24 mls.

Fraction (b) was then redistilled through the short column under reduced pressure; three products were obtained in this way.

(1) 10 mls. B.P. 40°C. 150 m.m.

(2) 2 mls. B.P. 55-60°C 30 m.m. (3-chloro-pyridine)

(3) Tar 9.0 g.

Analysis of the CCl_4 layer.

Test for free HF - negative.

0.1917g ≡ 1.1 mls. of 0.05 N thorium nitrate.

This corresponds to 12.5 g. of 2-fluoro-pyridine in 310 mls.

The final products are then :-

(1) 2-fluoro-pyridine 12.5 g. (20.5%)

(2) 3-chloro-pyridine 2.0 g. (3.0%)

Tar 9.0 g.

(6) Reaction of pyridine with ClF_3 using anhydrous, cobaltous chloride as catalyst in the presence of kF.

Pyridine (50 g) in CCl_4 (500 mls) containing kF (1 mol) and $CoCl_2$ (10g) was treated with chlorine trifluoride (30g) in the presence of N_2 (10 l/hr). The reaction product separated into two layers, an upper tarry layer and a lower CCl_4 layer. The latter was separated and poured onto KF (the upper layer was found to weigh 20 g). Rapid distillation under reduced pressure yielded two fractions (a) CCl_4 360 mls, and (b) 2 mls. Fraction (b) was redistilled at atmospheric pressure and yielded 1.8 g. of 3-chloro-pyridine (B.P.149°C). Mercuric chloride derivative M.P.180°C.

Analysis of carbon tetrachloride.

Test for free HF - negative.

0.157g of CCl_4 ≡ 0.8 mls. of 0.05 N thorium nitrate.

This corresponds to 11.8g. of 2-fluoro-pyridine in 360 mls.

Total yield.

2-fluoro-pyridine 11.8 g. (19%)
3-chloro-pyridine 1.8 g. (3%)

Fractionation of the CCl_4 layer from Exp.4 (Series II).

This experiment was carried out in order to make certain that the figures obtained, by titration, for the amount of 2-fluoro-pyridine in the foregoing experiments were correct. Carbon tetrachloride (250 mls) was carefully fractionated at atmospheric pressure through a column of approximately 30 theoretical plates. The purity of the distillate was checked by refractive index measurements. It was found that the volume in the still pot could be reduced to 16 mls before there was any appreciable change in the refractive index. The residue was then distilled from a small flask. Two fractions were obtained, the first, B.P. 78° - 100°C (7 mls) was mainly carbon tetrachloride, the second B.P. 124° - 126°C was 2-fluoro pyridine (7g). There was a small amount (1.0 g) remaining in the flask.

This experiment affords confirmation, within the limits of experimental error, of the results obtained volumetrically, when one allows for a certain amount of decomposition of the fluoro-pyridine which had been standing for several days.

Acid hydrolysis of the carbon tetrachloride (Exp.4.Series II).

Carbon tetrachloride (20 mls) was refluxed with 10 mls of concentrated HCl for 4½ hours. At the end of this time, the yellow acid layer was separated, cooled and neutralised (NaOH). To a portion of the neutralised solution, bromine water was added when a precipitate resulted. This was filtered and dried. The product corresponded to 3:5-dibromo-2-hydroxy pyridine (M.P. 206°C), thus confirming again the presence of 2-fluoro-pyridine. The method of analysis of fluorine used in this work was that described by Willard and Winter (Ind.Eng.Chem. (Anal. Ed.) 5, 7, 1933), and modified by Musgrave, Smith and Tatlow (J.C.S. 1949). This consists of titration of a sodium fusion solution with $\frac{N}{20}$ thorium nitrate solution in the presence of sodium alizarin sulphonate.

To analyse the products for nitrogen the following method was employed.

About 0.1 gr. of the product was fused with sodium in the nickel bomb and the product made up to 100 mls. Aliquot portions of this solution (10 mls) were made faintly acid with N/2 HNO_3 using 2 drops of phenolphthalein as indicator and then 1.0 mls of 16 HNO_3 was added. A known excess of N/20 silver nitrate was then added and the solution heated to 60°C to coagulate the precipitate. The precipitate was filtered whilst hot and the filtrate made up accurately to 50 mls. Aliquot portions of this solution were then titrated against N/40 standard potassium bromide using Rhodamine B.S. as indicator.

The end point was indicated by a blue colouration. This gave total CN^1 and Cl^1.

10 mls. of the fusion solution were treated with 1 ml. of 2N $NaOH$ and the solution titrated against N/100 silver nitrate until a permanent turbitity was obtained. Potassium iodide may be used as indicator, the end point being a yellow precipitate. This yielded total CN^1, whence the chloride was obtained by difference.