Highly fluorinated quinolines

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entitled

HIGHLY FLUORINATED QUINOLINES

submitted by

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TO ELAINE

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I should like to thank Mr. J.D. Dyson for nuclear magnetic resonance measurements and the many laboratory technicians for their help and co-operation. Also, I should like to express my gratitude to the Science Research Council for the award of a Research Studentship.

MEMORANDUM

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

This work has provided subject material for three publications with Professor W.K.R. Musgrave, Dr. R.D. Chambers, Mr. R.A. Storey and (in part) Dr. B. Iddon in the Journal of the Chemical Society (in press).

SUMMARY

Highly Fluorinated Quinolines

Initial direct chlorination of quinoline in the presence of aluminium trichloride, and subsequent treatment of the tetra- and pentachloroquinolines formed with phosphorus pentachloride at elevated temperatures gave heptachloroquinoline in high yield. Earlier attempts to convert quinoline directly to heptachloroquinoline using either a mixture of sulphuryl chloride, aluminium trichloride and sulphur monochloride, or phosphorus pentachloride gave mixtures of highly chlorinated quinolines which were difficult to purify.

Halogen exchange between heptachloroquinoline and anhydrous potassium fluoride in the absence of solvent readily gave chlorofluoroquinolines, and at a temperature of 470-490°C heptafluoroquinoline was obtained in high yield.

Heptafluoroquinoline reacted readily with the nucleophilic reagents sodium methoxide, ammonia and hydrazine monohydrate. Monosubstitution and disubstitution occurred at the 2- and 4-positions and further substitution occurred in the benzene ring at, most probably, position 7. The orientation of nucleophilic attack was deduced from nuclear magnetic resonance spectroscopy.

A number of polyfluorohydroxyquinolines have been prepared by demethylation of the corresponding methoxy derivatives and by reaction of heptafluoroquinoline with potassium hydroxide. The polyfluoro-2-hydroxyquinolines prepared exist as tautomers and react with diazomethane to give a mixture of the O-methyl and N-methyl derivatives. In contrast

4-hydroxyhexafluoro- and 4-hydroxy-2-methoxypentafluoro-quinoline do not tautomerise to any significant extent and react with diazomethane to give only the O-methyl derivative.

Heptafluoroquinoline is a very weak base but is protonated by concentrated acids. The protonated species has been shown to react readily and specifically with the nucleophilic reagents water and methanol at position 2. Reaction of heptafluoroquinoline with a two molar ratio of hydrogen chloride in sulpholane resulted in replacement of fluoride ion at positions 2 and 4 of the protonated species by chloride ion.

CONTENTS

General Introduction

Fluorine, like hydrogen, occupies a special place in chemistry in that it gives rise to a whole system of organic compounds. First efforts were directed towards the study of aliphatic fluorocarbons and their successful development and the discovery of their industrially useful properties led to the establishment of fluorine chemistry as a major field of organic chemistry. Aromatic fluorocarbon chemistry has been developed only relatively recently and it has been almost exclusively limited to homocyclic compounds because of the preparative difficulties in extending the methods of fluorination suitable for homocyclic compounds to heterocycles. The successful extension of the halogen exchange method to the preparation of pentafluoropyridine[1] indicated a possible preparative method for nitrogen-containing heterocycles in general, and the present study was concerned with the extension of the method to the preparation of heptafluoroquinoline and the subsequent development of the chemistry of this new fluorocarbon system. Some of the principal points of interest in this project were the effect of the fluorine substituents on the basic properties of the ring nitrogen and the influence of the latter on the nucleophilic substitution reactions of the fluorocarbon system, especially in comparison with the homocyclic aromatic fluorocarbons which have received considerable attention.[2a,2b,3]

Many compounds containing the quinoline nucleus display biological activity and several halogenated quinolines have been synthesised in the hope that they might display such activity.[4,5,6] The relationship between structure and biological activity is not clear and it is possible that highly fluorinated quinolines could exhibit some unique activity, though the present study was in no way concerned with this aspect.

PART I

THE PREPARATION OF HIGHLY FLUORINATED QUINOLINES

CHAPTER I

HISTORICAL INTRODUCTION

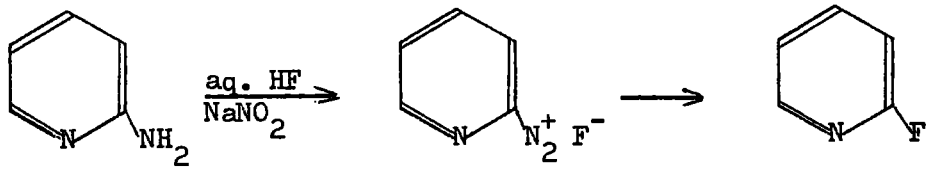
Historical Introduction.

Before the present work was undertaken the nuclear substituted fluoroquinolines that had been prepared were limited to all the monofluoroquinolines and two difluoroquinolines. These had been prepared by either cyclisation methods, employing a fluorinated aniline to give fluoroquinolines containing fluorine in the benzene ring, or by replacement of a suitable functional group in the quinoline nucleus, either directly or indirectly, to give fluoroquinolines with fluorine in either the benzene or heterocyclic ring.

Replacement of Functional Groups by Fluorine.

1.) Replacement of the amino group.

As early as 1870, Schmitt and von Gehren[7] synthesised p-fluorobenzoic acid by diazotising the corresponding amine in aqueous hydrofluoric acid and decomposing the resultant diazonium fluoride "in situ". This method was applied to the preparation of nuclear-substituted fluoroheterocyclic aromatic compounds when Tschitschibabin[8] prepared 2-fluoropyridine.



However a considerable amount of 2-pyridone was formed and the use of an aqueous solution for the decomposition of the diazonium salt is an obvious disadvantage of this method. The use of anhydrous hydrofluoric acid avoids this complication and Beaty[9] diazotised 2-aminoquinoline in this solvent at 0°C and decomposed the diazonium fluoride "in situ" at 60°C to give 2-fluoroquinoline in 17% yield.

An indirect method of converting aminated benzenes to the corresponding fluorides in good yield was discovered by Balz and Schiemann[10] when they found that diazonium fluoroborates could be decomposed to give the aromatic fluoride. The method involves the preparation and isolation of the dry diazonium tetrafluoroborate and its controlled thermal decomposition to yield the aromatic fluoride, nitrogen and boron trifluoride.

$$ArNH_2 + HNO_2 + BF_4^- \longrightarrow ArN_2BF_4 + H_2O + OH^-$$

$$ArN_2BF_4 \xrightarrow{HEAT} ArF + N_2 + BF_3$$

One of the earliest attempts to extend this method to the heterocyclic field for the preparation of fluoroquinolines was by Elderfield,[11] and although he prepared the diazonium tetrafluoroborate from 5-amino-6-methoxyquinoline in 80% yield decomposition of it resulted in tar formation only. Tar formation apparently occurred under all conditions but no experimental details were given. Roe and Hawkins,[12] presumably

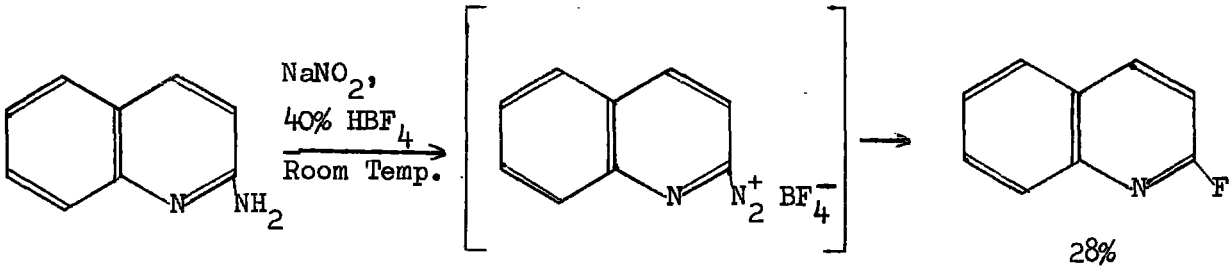
exercising a more careful control of the reaction, successfully applied this method for the preparation of all the monofluoroquinolines with the possible exception of 4-fluoroquinoline.

The diazonium fluoroborates derived from the amino quinolines having the amino group in the benzene ring were quite stable and the usual technique could be used for their conversion to the fluoride. 5-quinoline diazonium tetrafluoroborate was decomposed by heating in toluene to give a 59% yield of 5-fluoroquinoline, 6-quinoline diazonium tetrafluoroborate was decomposed in the absence of solvent to give 6-fluoroquinoline in 58% yield, 7-fluoroquinoline was obtained in 27% yield by decomposition of the corresponding diazonium tetrafluoroborate in hot xylene and a 24.5% yield of 8-fluoroquinoline was obtained by dry decomposition of 8-quinoline diazonium tetrafluoroborate.

In contrast to 3-pyridine tetrafluoroborate,[13] 3-quinoline tetrafluoroborate is quite stable when dry up to 95°C, when it melts with decomposition, and decomposition in hot toluene gave a 73.5% yield of 3-fluoroquinoline. According to Roe 3-pyridine tetrafluoroborate decomposes violently when dry above 10°C but Suschitzky[14] claims that the dry salt is stable at room temperature.

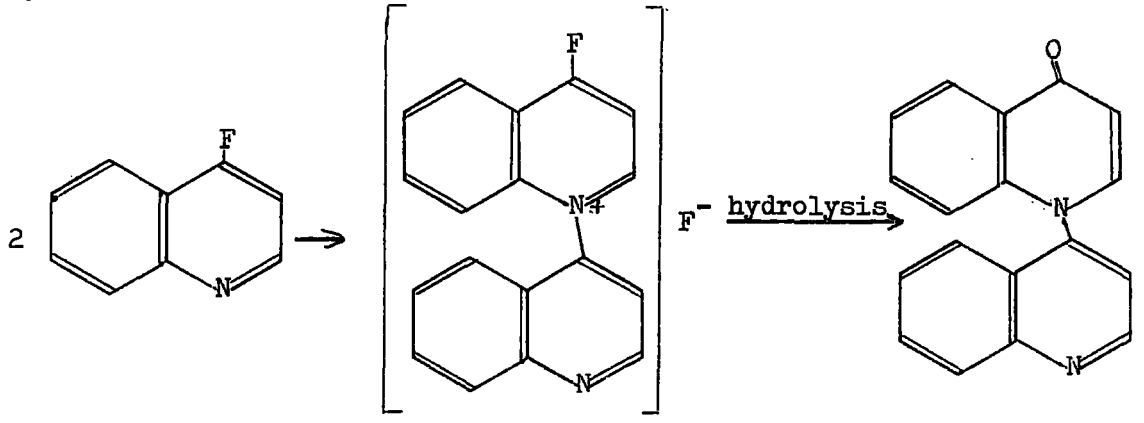
Like 2-pyridine tetrafluoroborate,[13] 2-quinoline tetrafluoroborate is unstable and could not be isolated. Diazotisation of 2-amino-quinoline with sodium nitrite in 40% fluoroboric acid solution at room temperature gave 2-quinoline tetrafluoroborate which decomposed as it was

formed. When the reaction mixture was made alkaline, extracted with ether and the dried ether extract distilled a 28% yield of 2-fluoroquinoline was obtained.



Similar instability of 4-quinoline tetrafluoroborate was found also. Diazotisation of 4-aminoquinoline with sodium nitrite in 40% fluoroboric acid at 0°C to -10°C gave a precipitate of the diazonium tetrafluoroborate which could be filtered off and washed with ether without decomposition occurring if the salt was kept moist and below 10°C. An ethereal suspension of it started to decompose at 10°C and decomposition was rapid at 22°C. After decomposition was complete the reaction mixture was rendered alkaline and extracted with ether. Distillation of the dried ether extract gave a small amount of a colourless liquid (b.pt. 119°C/30 mm.), which was presumed to be 4-fluoroquinoline, and left in the distillation flask was abundant tarry material. The distillate rapidly solidified to a tan solid which melted at 180-195°C. Its analytical data suggested it was impure N-(4'-quinolyl)-4-fluoroquinolinium fluoride. It gave an impure picrate which contained no fluorine and was possibly the picrate of N-

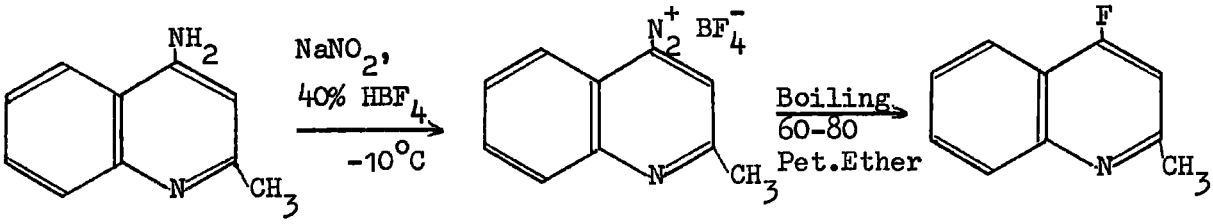
(4'-quinolyl)-4-quinolone. This suggests that 4-fluoroquinoline is analogous to 4-fluoropyridine in its decomposition. 4-Fluoropyridine has been shown[13] to dimerise rapidly by nucleophilic substitution to give N-(4'-pyridyl)-4-fluoropyridinium fluoride which is rapidly hydrolysed to N-(4'-pyridyl)-4-pyridone. Thus the decomposition of 4-fluoroquinoline probably proceeds in the following way



4-Chloropyridine and 4-bromopyridine dimerise in a similar way[15] and must be distilled at reduced pressure to prevent this happening. 4-Chloroquinoline and 4-bromoquinoline can be distilled at much higher temperatures without any such reaction occurring[16] although 4-haloquinolines are more susceptible to nucleophilic attack than 4-halopyridines.[17] The difference must be due to the lower nucleophilic strength of the ring nitrogen in the quinoline derivatives compared with the pyridine derivatives. Pyridine is a stronger base than quinoline[18] and presumably a stronger nucleophile also. For the

same reason 2-haloquinolines and 2-halopyridines do not dimerise because the ortho halogen reduces the nucleophilic strength of the nitrogen sufficiently to prevent it acting as a nucleophile with another molecule of the 2-substituted compound. That 4-fluoroquinoline dimerises as above reflects the greater susceptibility of fluorine to nucleophilic displacement.

Preparation of a homologue of 4-fluoroquinoline was achieved by Bellas and Suschitzky[19] by application of the Schiemann reaction to 4-amino-2-methylquinoline



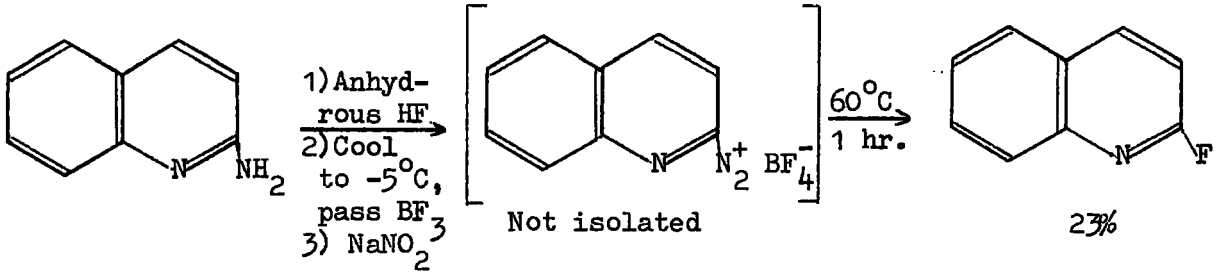
Decomposition Point 52°C

Unstable Hydrate m.pt. 40°C

That nucleophilic self-condensation does not occur in this case is due to the α-methyl group imposing steric requirements that more than offset the increase in base strength.

A modification of the usual Schiemann method was employed by Beaty[9] for the preparation of 2-fluoroquinoline. This involved diazotising 2-aminoquinoline in anhydrous hydrofluoric acid containing fluoroboric acid with sodium nitrite at -5°C. Heating the solution to 60°C for 1 hour resulted in a 23% yield of 2-fluoroquinoline, lower

than that obtained by

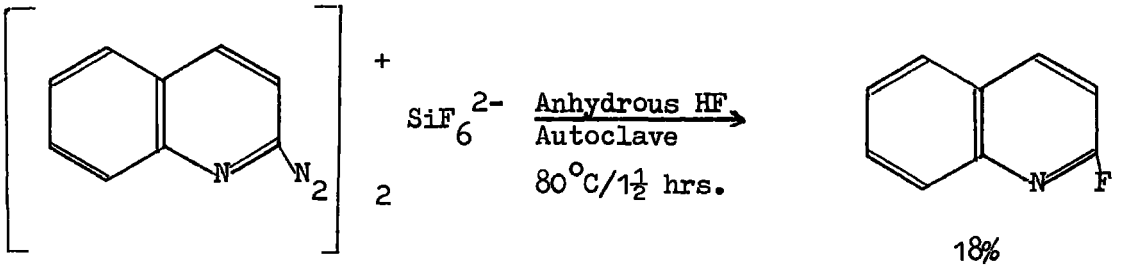


the method employed by Roe.[12]

The Schiemann method has been used to prepare many substituted fluoroquinolines, examples of which include 7-fluoro-8-hydroxyquinoline-5-sulphonic acid,[20] 5-fluoro-8-hydroxyquinoline,[4,21] 3-fluoro-2-methylquinoline[22] and 8-fluoro-2-methylquinoline.[22] In general the usual Schiemann technique can be applied to prepare substituted fluoroquinolines with the fluorine at the 3-position or in the benzene ring, whilst for those with fluorine in the 2-position the method must be modified due to the instability of 2-quinoline diazonium tetrafluoroborates. For the preparation of substituted 4-fluoroquinolines the substituent must be one that prevents nucleophilic self-condensation from occurring.

Other complex fluorine acids besides fluoroboric acid form stable aryl diazonium salts which decompose to give aromatic fluorine compounds.[23,9] These include diazonium fluorophosphates, ($ArN_2^+PF_6^-$) diazonium fluorosilicates [$(ArN_2)_2^+SiF_6^{2-}$] and diazonium fluoro-

antimonates ($ArN_2^+SbF_6^-$). Usually the yields from these salts are much inferior to those from aryl diazonium fluoroborates. 2-Fluoroquinoline[9] was prepared in 18% yield by decomposing quinoline-2-diazonium fluorosilicate in anhydrous hydrofluoric acid at 80°C.

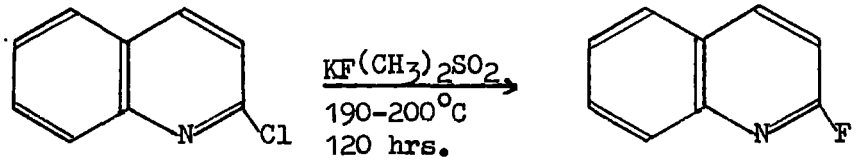


18%

This is a considerably lower yield than that obtained by the Schiemann method[6] (27%) but the use of the aryl diazonium fluorosilicate gave a higher yield[9] (42%) of 2-fluoropyridine then did the Schiemann method[13] (34%).

2. Replacement of Chlorine.

The chlorine of 2-chloroquinoline was found to undergo halogen exchange on heating with potassium fluoride at 200°C in dimethylsulphone to give the corresponding fluoro compound in high yield.[24]

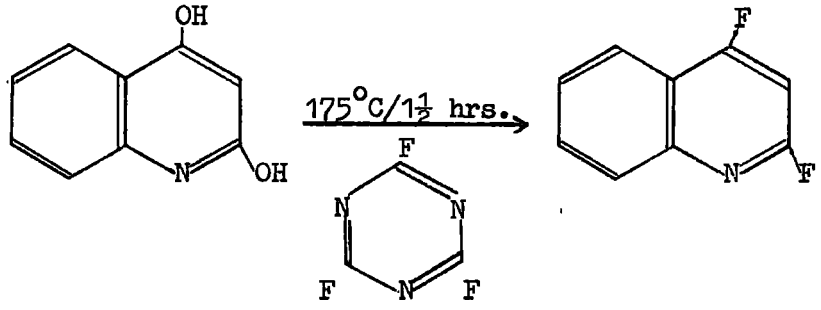


60%

3. Replacement of the hydroxyl group.

Hydroxyl groups in the 2- or 4-positions of the quinoline nucleus were found to undergo replacement by fluorine when heated at 175°C for 1½ hours with 2,4,6-trifluoro-1,3,5-triazine in an autoclave.[25] In this way 2,4-difluoroquinoline, 2-fluoro-4-methylquinoline and 2-methyl-4-fluoroquinoline were prepared from the corresponding hydroxy compounds.

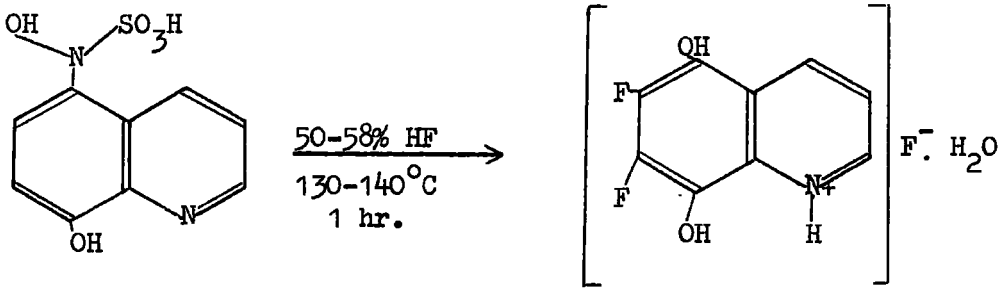
e.g.



Autoclave

4. Replacement of Hydrogen.

Russian workers[26] observed that when 8-hydroxy-5-(N-hydroxy-N-sulphoamino)quinoline was heated with aqueous hydrofluoric acid, hydrolysis and fluorination occurred to give 5,8-dihydroxy-6,7-difluoroquinoline hydrofluoride as the monohydrate.



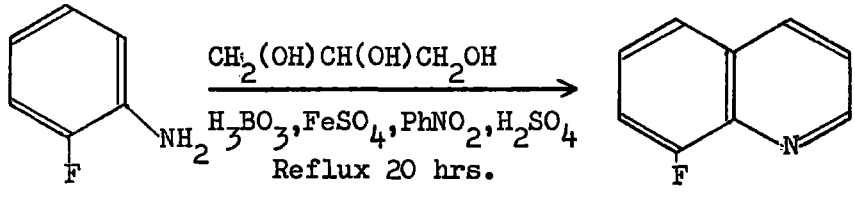
55%

An analogous reaction was found to occur with concentrated hydrochloric and hydrobromic acids. The mechanism of this remarkable replacement of hydrogen by fluorine is not known.

Cyclisation Methods.

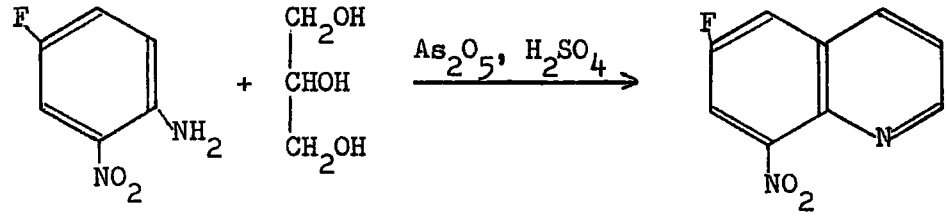
Cyclisation reactions involving a fluorine-containing aniline or aniline derivative have been widely used to prepare quinoline or its derivatives bearing fluorine in the benzene ring. The Skraup reaction[27] is the most widely used method for the synthesis of quinoline and its derivatives and has been used extensively to prepare fluoroquinolines and fluoroquinoline derivatives.[4,28-32] The Skraup synthesis involves the reaction of a primary aromatic amine, with at least 1 position ortho to the amino group unsubstituted, with glycerol, sulphuric acid, and an oxidising agent. The reaction can be modified to produce 2-, 3-, or 4-substituted quinolines by the use of a substituted acrolein or a vinyl ketone.

8-Fluoroquinoline was prepared by Mirek[28] in 72% yield from orthofluoroaniline.



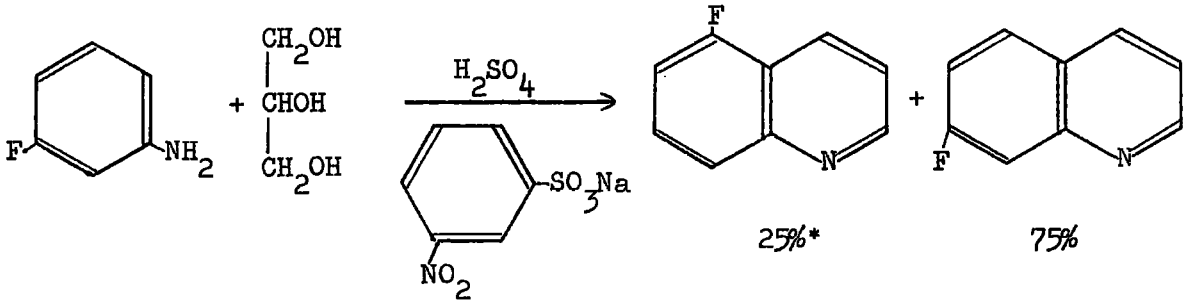
72%

and a 60% yield of 6-fluoro-8-nitroquinoline was obtained from 2-nitro-4-fluoroaniline.[29]



60%

Mirek[28] claimed that the Skraup reaction on metafluoroaniline gave only 7-fluoroquinoline in 98% yield, there being none of the other possible isomer, 5-fluoroquinoline, formed. However, Palmer[30] found that the Skraup reaction on meta-fluoroaniline gave both the 5- and 7-fluoroquinolines, with the 7-isomer present in greater amount.

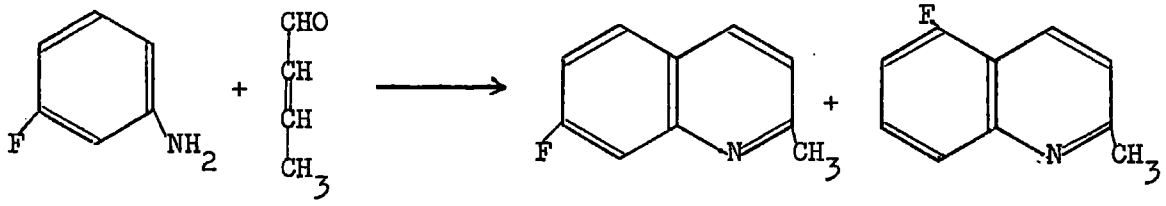


25%* 75%

Reflux 4 hrs.

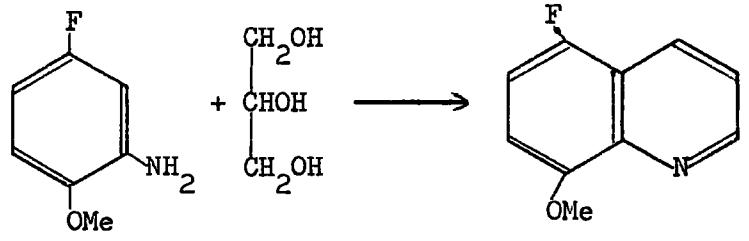
*Percentage composition of the isomeric mixture.

A modified Skraup reaction on meta-fluoroaniline using crotonaldehyde also gave a mixture of the 5- and 7-isomers in 70% yield.[31]



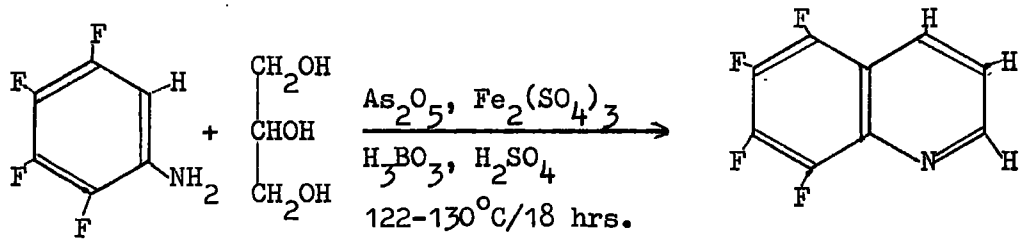
72% 27%

If one of the ortho-positions is blocked there is then no possibility of the formation of isomers. Thus 2-methoxy-5-fluoroaniline gave 5-fluoro-8-methoxyquinoline in 37% yield.[27]



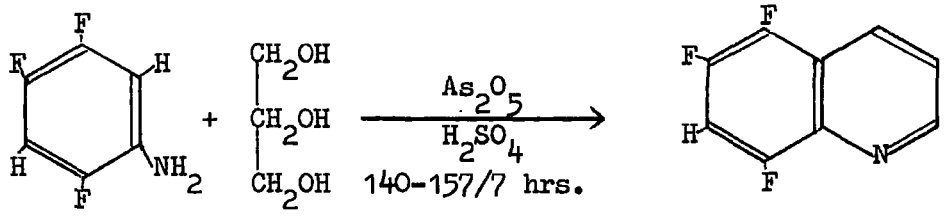
37%

Very recently[32] this method has been successfully extended to highly fluorinated anilines. 2,3,4,5-Tetrafluoroaniline gave 5,6,7,8-tetrafluoroaniline in 53% yield.

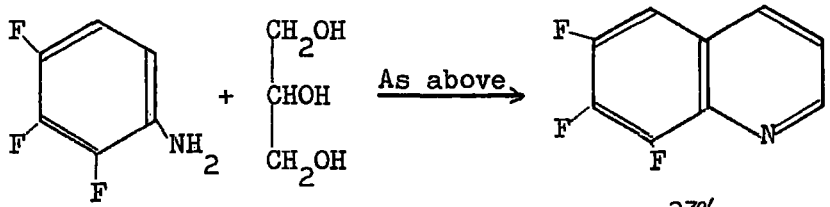


53%

Substitution of crotonaldehyde or vinyl methyl ketone for glycerol gave moderate yields of 2- and 4-methyl-5,6,7,8-tetrafluoroquinolines respectively. 2,4,5-Trifluoroaniline and 2,3,4-trifluoroaniline were also cyclised with glycerol by the Skraup reaction.

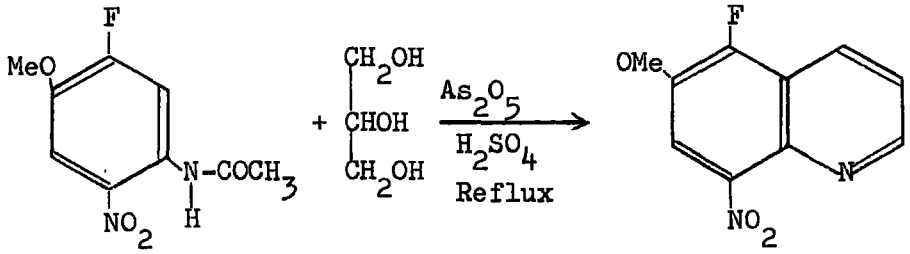


44%



23%

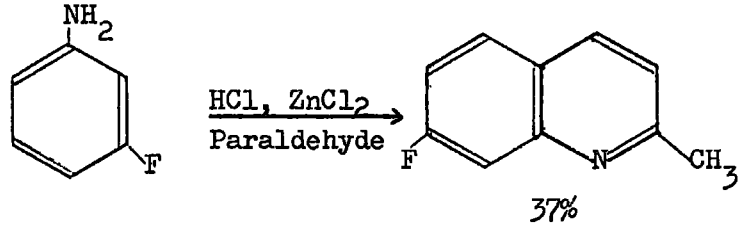
The great utility of this method is limited only by the presence of substituents in the amine which are too reactive to withstand the drastic reaction conditions. Fluorine is not such a substituent unless activated by other substituents, e.g. NO_2, in the amine. The attempted synthesis



gave only traces of the desired fluoroquinoline.[11] The para nitro group activated the fluorine sufficiently to cause extensive hydrolysis under the reaction conditions and the bulk of the product was 5-hydroxy-6-methoxy-8-nitroquinoline. 2-Nitro-4-fluoroaniline, in which the nitro group is meta to the fluorine, cyclised normally.[29]

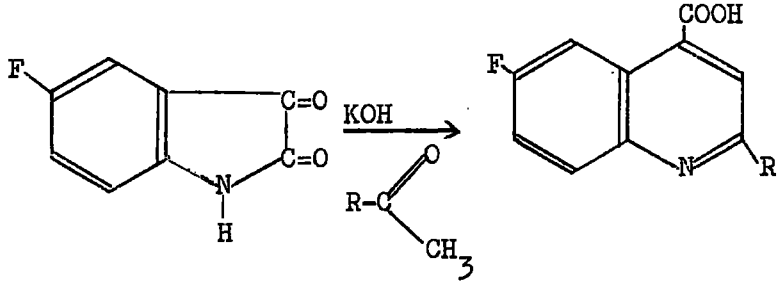
Other methods of synthesising quinolines[33] have been used to a lesser extent to prepare fluoroquinolines in which the fluorine is in the benzene ring and various substituents are present in the pyridine ring.[34-39]

6- and 7-Fluoroquinaldines have been prepared by the Doebner-Miller synthesis.[34]



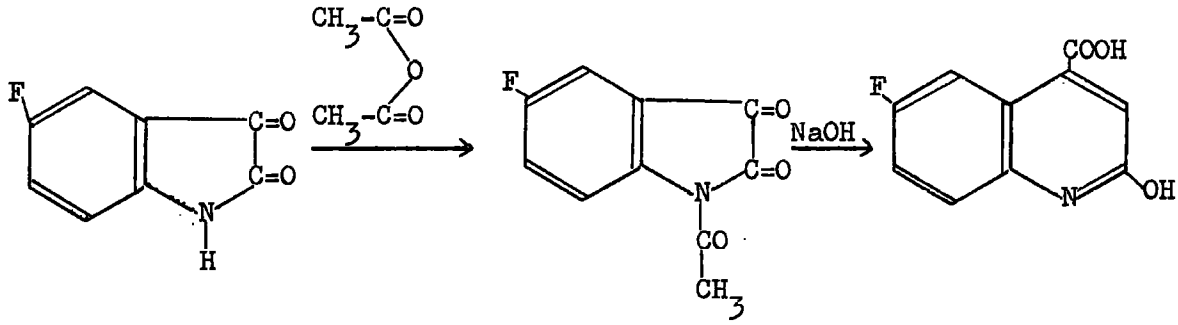
37%

Several 6-fluoroquinoline derivatives have been prepared from 5-fluoroisatin[35] by application of the Pfitzinger and Camps reaction. The Pfitzinger reaction:



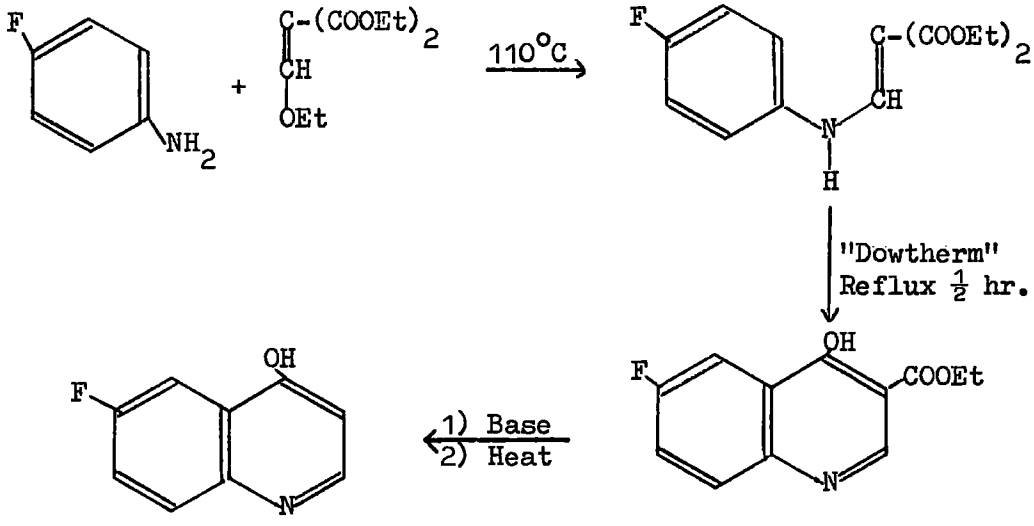
R = CH_3, C_6H_5, p-FC_6H_4

and Camps reaction:

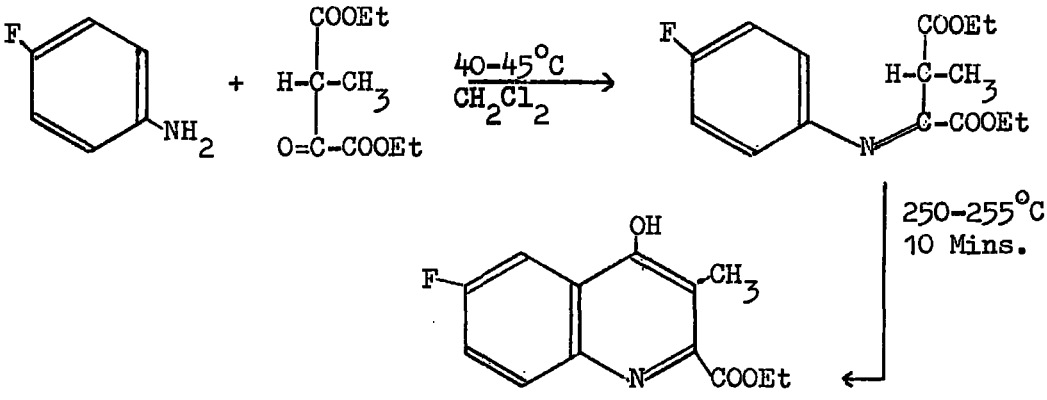


both gave the 2-substituted-6-fluoroquinoline-4-carboxylic acids which were decarboxylated to give the 2-substituted-6-fluoroquinolines.

6- and 7-Fluoro-4-hydroxyquinolines have been synthesised[36-38] by condensation of ethoxymethylenemalonic ester with the appropriate fluoroaniline in the following way:



Metafluoroaniline gave principally 7-fluoro-4-hydroxyquinoline and only very little of the 5 isomer. A variation of the Conrad-Limpach synthesis using ethyl ethoxalylpropionate has been applied to ortho, meta-and para-fluoroanilines.[39]



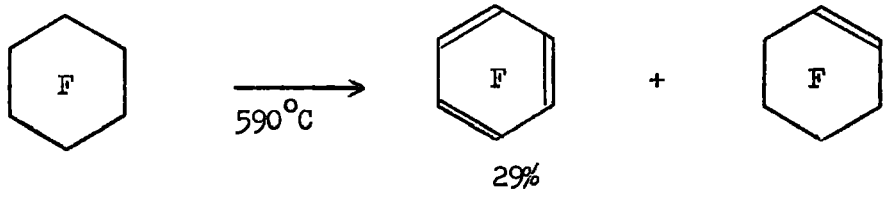
Metafluoroaniline gave a mixture of the 5- and 7-isomers in approximately equal amounts.

Conversion of Aromatic Compounds to Highly Fluorinated Aromatic Compounds.

Until recently the only general method (A) for preparing perfluoroaromatics was by defluorination of the corresponding alicyclic fluorocarbon[40,41] but now the method of halogen exchange (B) has been found to be practicable.[42,1] It will be seen that the second method lends itself better to the preparation of highly fluorinated aromatic heterocyclic compounds than does the first. Method A employs the aromatic hydrocarbon as starting material whilst method B starts with the perchloroaromatic compound.

Method A.

Workers at Birmingham discovered that not only perfluorocyclohexadienes[41,43] and perfluorocyclohexenes[40,41] but also perfluorocyclohexanes[40,41] were defluorinated to give good yields of perfluoro aromatic compounds when they were passed in the vapour state over heated metals. The vapour was passed at atmospheric pressure over the metal, usually iron or nickel, packed in a tubular reaction vessel heated to about 500-650°C. Contact times of between 10-30 minutes were used.



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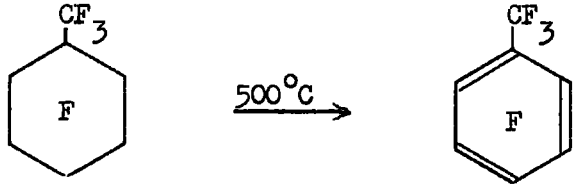

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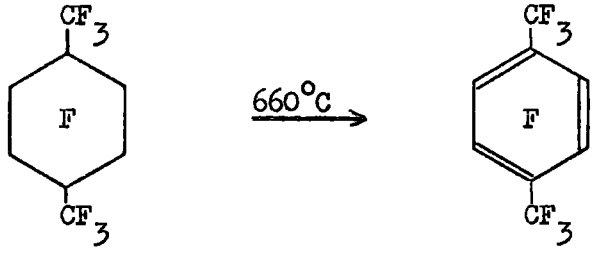
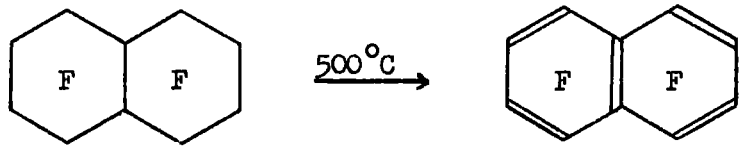


45%

Perfluoropolycyclic aromatic compounds were similarly prepared.[40,44]



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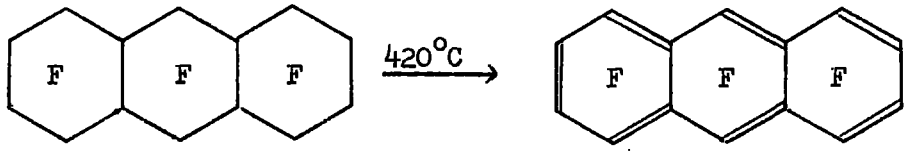

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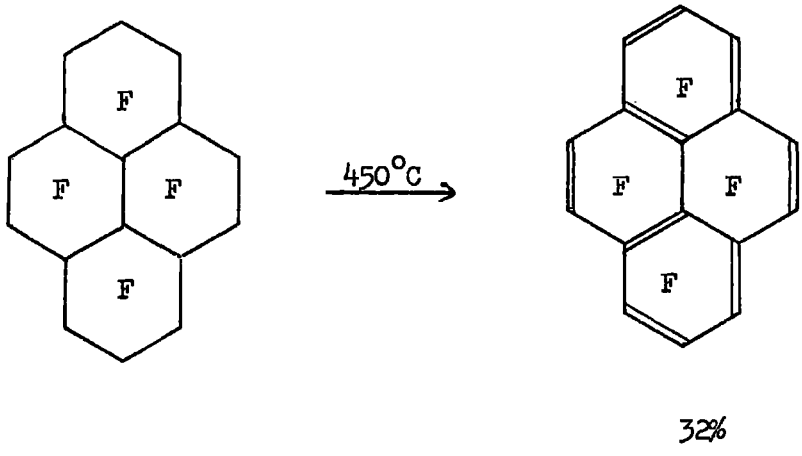
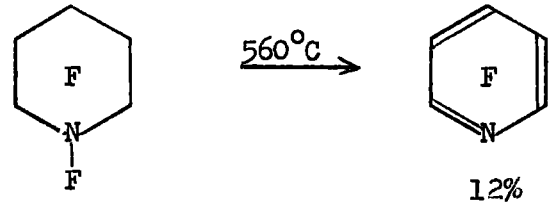


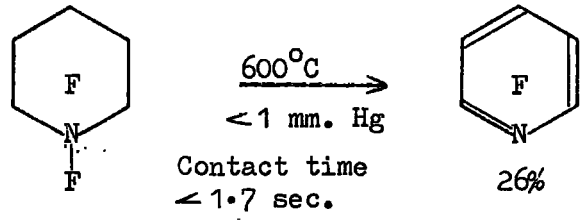
32%

and it was extended to the preparation of pentafluoropyridine.[45]



12%

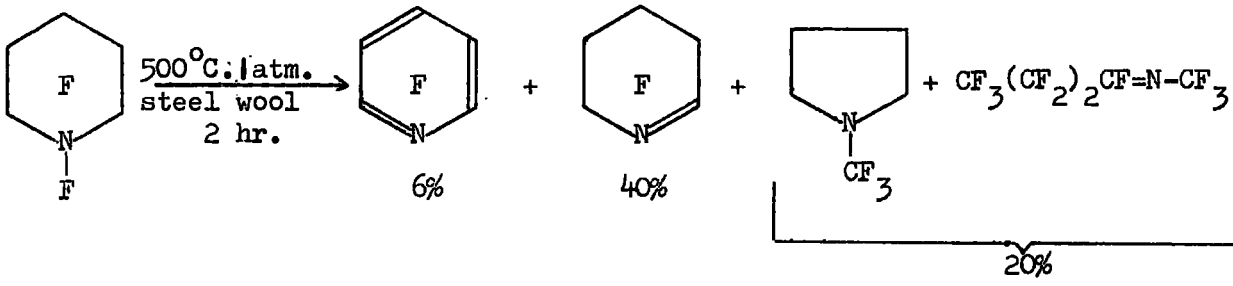
Workers at Manchester[46,47] defluorinated undecafluoropiperidine at reduced pressure using a short contact time to give a higher yield of pentafluoropyridine.



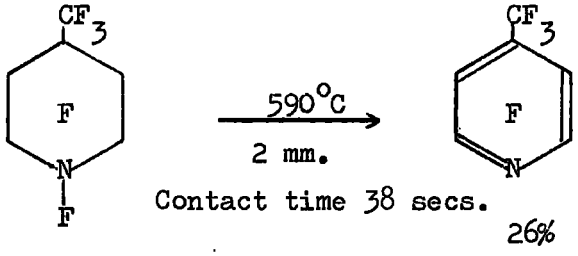
26%

Using similar conditions they found that perfluoro(methylcyclohexane) was recovered unchanged, which suggests that the N-F bond appreciably facilitates defluorination of undecafluoropiperidine. The defluorination

of undecafluoropiperidine at 500°C and atmospheric pressure in the presence of mild steel wool[48]



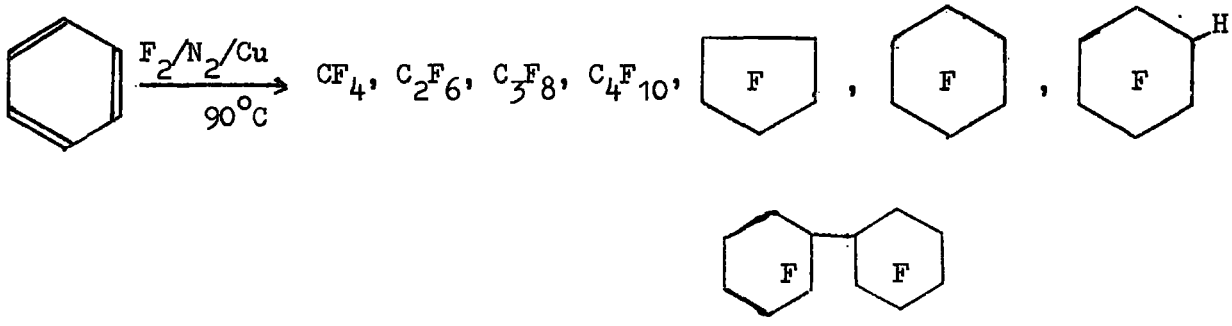
from which no compounds containing only carbon-carbon double bonds were isolated further suggests that the N-F bond facilitates defluorination. Perfluoro-(4-methylpiperidine) was also successfully defluorinated at reduced pressure.[49]



Obviously this method is only of use if the necessary alicyclic fluorocarbon can be prepared easily. The methods by which aromatic compounds have been converted to the desired perfluoro-alicyclic compounds give only very poor yields when applied to aromatic heterocyclic compounds.

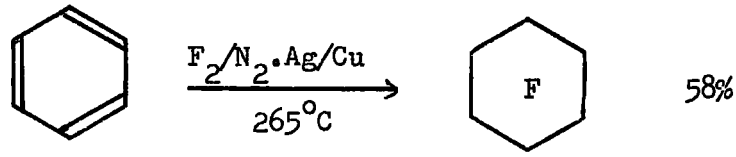
Exhaustive Fluorination using Elemental Fluorine.[50,52]

The reaction of fluorine with organic compounds is a highly exothermic process since the bond dissociation energy of fluorine is low [D(F-F) = 37 kcal./mole] and the heats of formation of C-F and H-F bonds are high[51] (105 and 135 kcal./mole respectively cf. C-H and C-C bond energies are 99 and 83 kcal./mole respectively). The introduction of fluorine causes deactivation of the molecule towards further fluorination and the conversion of aromatic compounds to perfluoro-alicyclic compounds accordingly requires high temperatures.[50] Therefore, the heat of reaction must be effectively and rapidly dispersed, otherwise combustion or fragmentation and polymerisation will be the main reaction. The so called "catalytic"method[53-56] has been developed to convert aromatic compounds to perfluoroalicyclic compounds with considerable success. Benzene was fluorinated in a brass reaction vessel filled with copper gauze.[53]



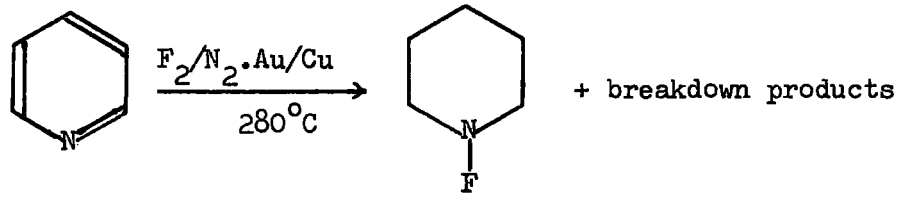
No unsaturated compounds were isolated and considerable breakdown of the carbon skeleton occurred although perfluorocyclohexane was the

major product. Cady[54] used copper turnings coated with silver as the "catalyst" and obtained a higher yield of perfluorocyclohexane



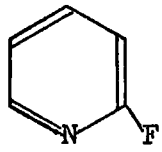
Under these conditions it is likely that silver difluoride is the fluorinating agent. Musgrave and Smith[55] studied the fluorination of benzene with various catalysts, their results indicating that the main function of the catalyst was simply the dissipation of the heat of reaction.

Extension of this method to nitrogen heterocycles gave only very poor yields of the expected product. Haszeldine fluorinated pyridine using gold-plated copper turnings as catalyst.[57] Extensive breakdown of the pyridine ring occurred resulting in only a 0·3% yield of undecafluoropiperidine



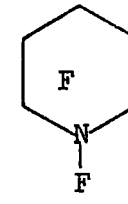
0·3%

Similar fluorination of 2,6-lutidine was reported[58] to give perfluoro-(2,6-dimethylpiperidine) in about 5% yield. Under similar conditions[55] benzene gives a 35% yield of perfluorocyclohexane, and Haszeldine claimed that the low yields from the heterocyclic compounds were due to the formation of non-volatile hydrofluorides in the critical initial stages of the reaction. However, fluorination of the non-basic 2-fluoropyridine[59] resulted in extensive breakdown of the pyridine ring and a lower yield of undecafluoropiperidine than from the fluorination of pyridine itself.



F_2/N_2, 150°C
Bigelow "cool-flame" burner

NF_3, CF_4, C_2F_6, C_3F_8, C_4F_{10},
$n\text{-}C_5F_{12}$, $CF_3\text{-}CHFCF_3$, $C_2F_5CHF_2$,
$(CF_3)_2N\text{-}F$, $(CF_3)_2NH$, $CF_3N{=}CF_2$,
$CF_3\text{-}N{=}CF\text{-}CF_3$, $(CF_3)_2N\text{-}N(CF_3)_2$,
$CF_3(CF_2)_2CF{=}N\text{-}CF_3$, $CF_3(CF_2)_3\text{-}N\text{-}CF_3$

+ 

< 0.1%

The facile cleavage of the C-N bond[57] under the reaction conditions necessary for formation of perfluoroalicyclic compounds renders this

method of no value for the preparation of perfluorinated saturated ring compounds containing nitrogen.

Exhaustive Fluorination using High Valency Metal Fluorides.[60]

It was found[61] that a more controlled fluorination of organic compounds occurred when the organic vapour diluted with nitrogen was passed over certain high valency metal fluorides at elevated temperatures. The most widely used metallic fluoride is cobalt trifluoride. Silver difluoride,[62] manganese trifluoride,[63] cerium tetrafluoride[63] and lead tetrafluoride[63,64] have been used to a lesser extent. In this process substitution by fluorine of substituents on the carbon skeleton occurs and saturation is removed to give highly fluorinated products and finally fluorocarbons. The fluorination of organic compounds with cobalt trifluoride may be expressed[65]

$$\geq CH- + 2CoF_3 \longrightarrow \geq CF- + HF + 2CoF_2$$

$$\Delta H \approx -58 \text{ kcal./mole}$$

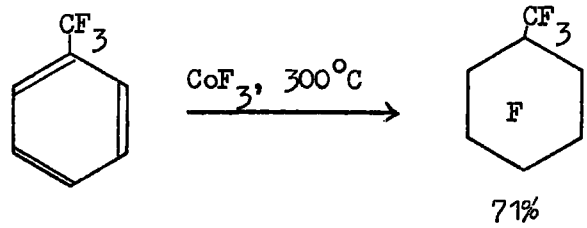
and comparison with fluorination using elemental fluorine[48]

$$\geq CH- + F_2 \longrightarrow \geq CF- + HF$$

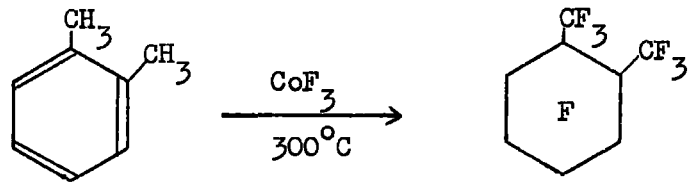
$$\Delta H \approx -104 \text{ kcal/mole}$$

shows that only approximately half as much heat is liberated during fluorination with cobalt trifluoride as with elemental fluorine.

Accordingly fluorination using cobalt trifluoride results in less fragmentation and higher and more reproducible yields. Fragmentation can occur if the temperature is too high - generally this is above 350°C. Between 300-350°C complete fluorination occurs and lower temperatures, 150-200°C, give partially fluorinated products.[66] Fowler[61] and co-workers used cobalt trifluoride in a "static" reactor[67] to fluorinate a number of aromatic compounds and obtained high yields of fluorocarbons

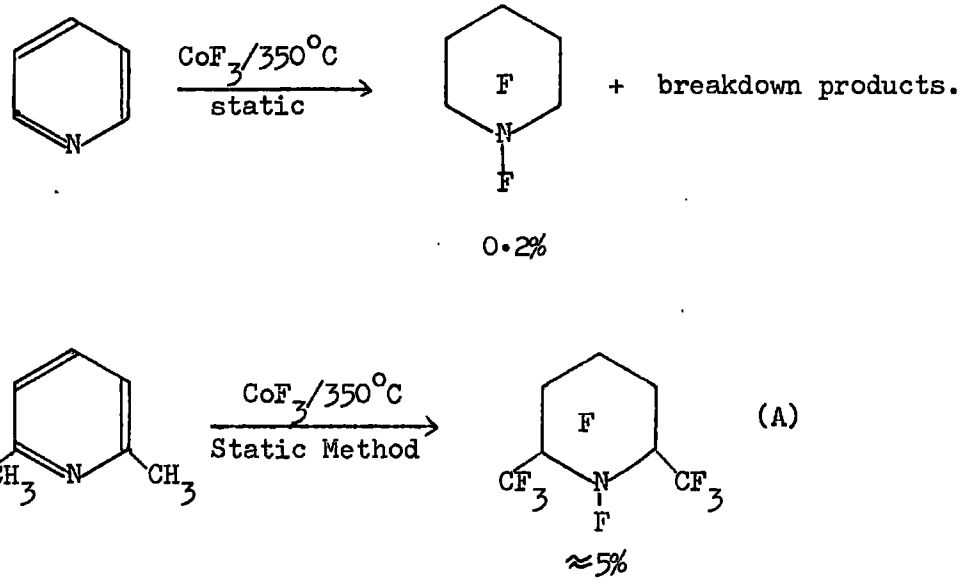


71%



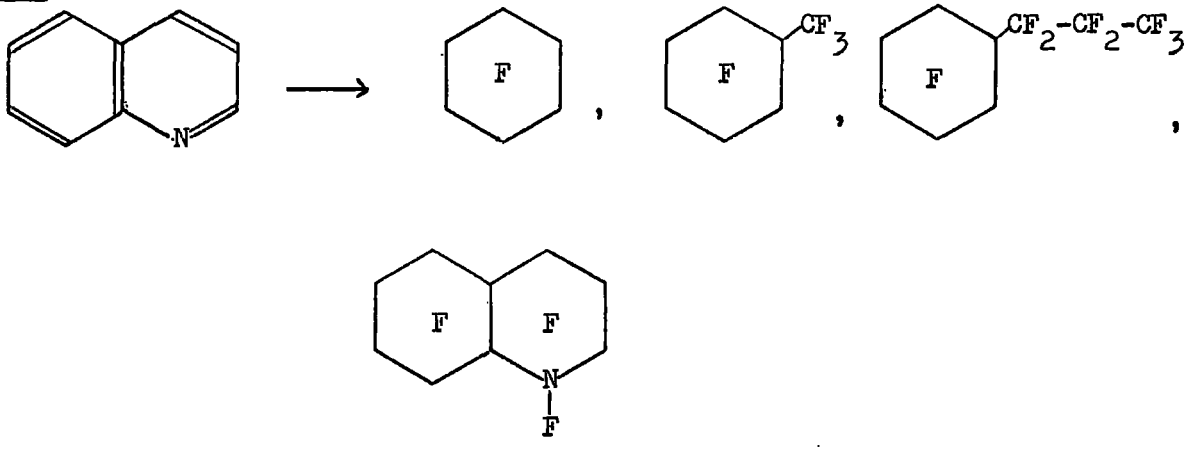
42%

Barbour et al[68] used a stirred reactor and found it gave higher yields than the "static" method. However, fluorination of C-N containing aromatic compounds using cobalt trifluoride was found to be no more successful than direct fluorination. Haszeldine found that aromatic amines[57] suffered extensive C-N fission and so did pyridine and its derivatives.[57,58]



(A) was later[69] shown to contain a small amount of hydrogen. 2-methyl indole[70] similarly suffered extensive C-N fission when fluorinated with cobalt trifluoride at 340-390°C. Apparently the only exhaustive fluorination of quinoline reported in the literature was carried out by Haszeldine and Smith[71] using cobalt trifluoride in a static reactor. Quinoline vapour was passed up a vertical reactor over trays of cobalt trifluoride at 400°C. The crude liquid product so obtained was extracted with ethanol and the insoluble portion distilled to give small amounts of perfluorocyclohexane and perfluoro-(methylcyclohexane) and a fraction boiling between 120 and 135°C. Complete fluorination was effected by treating this fraction with uranium hexafluoride and the product distilled to give a small amount of perfluoro-(n-propyl-cyclohexane) and heptadecafluorodecahydroquinoline in 2% overall yield.

i.e.



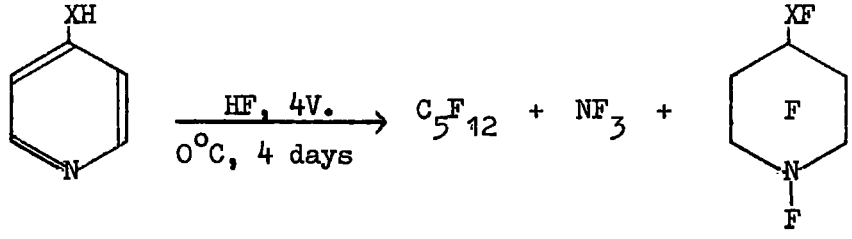
2%

The fact that no decomposition products were isolated which contained nitrogen bonded to the cyclohexane ring suggests that C-N bond fission occurs preferentially at the ring junction. The isolation of perfluorodecalin[67] in 80% crude yield from the cobalt trifluoride fluorination of naphthalene contrasts markedly with the low yield of heptadecafluorodecahydroquinoline. As with direct fluorination, the facile fission of the C-N bond precludes the use of cobalt trifluoride as a practical method for the fluorination of nitrogen-containing aromatic heterocycles.

Electrochemical Fluorination.[72]

The process of electrochemical fluorination involves the passage of a direct current at low voltage (4-8 volts) through a solution of an organic compound, or a suspension rendered conducting by the addition

of an electrolyte if the compound is insoluble, in anhydrous hydrofluoric acid, usually at about $0^{o}C$. Under these conditions fluorine is not liberated but the organic compound is fluorinated at the anode and hydrogen is evolved at the cathode. Fragmentation, cyclisation and polymerisation occur as well as simple fluorination, but the important feature of this method is that less replacement of functional groups by fluorine occurs than in fluorinations using fluorine or a high valency metal fluoride. Thus less C-N bond fission occurs and Simons[73] successfully fluorinated a number of aromatic amines including pyridine and its derivatives[74] to give the fully fluorinated saturated compound.



$$XH = C_nH_{2n+1} \quad (n = 0\text{-}5)$$

No yield was given but the fully fluorinated piperidine derivative was stated as being the principal product. Simmons[75] obtained undecafluoropiperidine in about 11% yield from pyridine and later work[76] showed this could be increased to 13% by using 2-fluoropyridine as starting material, the α-fluorine reducing slightly the extent of C-N bond fission.

Although electrochemical fluorination of nitrogen aromatic heterocycles is much superior to direct fluorination or the use of high valency metal fluorides the yield of the desired fully fluorinated compound is still low. Also the method is difficult to reproduce and yields and ratios of products often vary from experiment to experiment for no apparent reason.

Method B.

The method of halogen exchange[77] was first used by Goltlieb[78] in 1936 for the preparation of an aromatic fluoride from the corresponding aromatic chloride. Very recently it has been developed as a method of producing perfluoroaromatics from perchloroaromatics[42] including perfluoroaromatic nitrogen heterocycles.[1]

Another method of converting perchloroaromatics to perfluoroaromatics has been achieved and has been applied mainly to hexachlorobenzene. This consists of two stages; the first involves conversion to the saturated halofluorocarbon and the second its dehalogenation to give the perfluoroaromatic. The first stage can be achieved using a variety of fluorinating agents, including elemental fluorine,[79,80] halogen fluorides,[81,82] cobalt trifluoride,[83] antimony pentafluoride[82] and sulphur tetrafluoride.[83] Dehalogenation has been effected by passage of the vapour over heated iron gauze[83] or by refluxing with zinc in ethanol[82] and in the first case gave good yields of the perfluoroaromatic. This method is of interest as it was employed by

McBee[82] to give the first reported synthesis of hexafluorobenzene

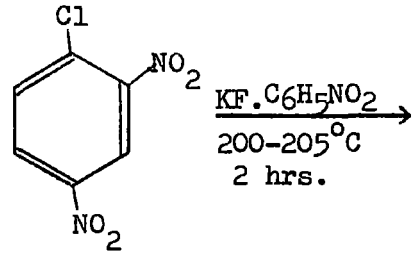
$$C_6Cl_6 + BrF_3 \longrightarrow C_6Br_2Cl_4F_6 \xrightarrow{SbF_5} C_6BrCl_4F_7$$

$$C_6BrCl_4F_7 \xrightarrow{Zn/EtOH} C_6F_6,\ C_6F_5Cl,\ C_6F_8,\ C_6ClF_7,\ C_6Cl_2F_6,\ C_6Cl_3F_5,\ C_6Cl_2F_8,\ C_6Cl_3F_7$$

A survey of the method of halogen exchange shows it to be a much better method for the conversion of perchloroaromatics to perfluoroaromatics.

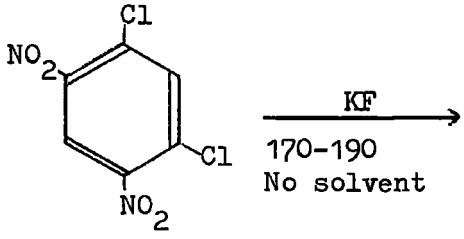
The method of halogen exchange involves reaction under anhydrous conditions of an aromatic halide, usually the chloride, with a metal fluoride, often potassium fluoride, either in a suitable solvent heated to near its boiling-point, or as an intimate mixture at elevated temperatures.

e.g.



30%

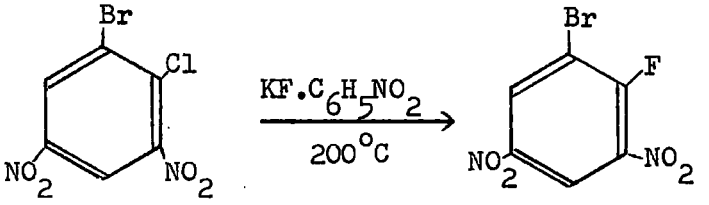
Ref. 78



87%

Ref. 77

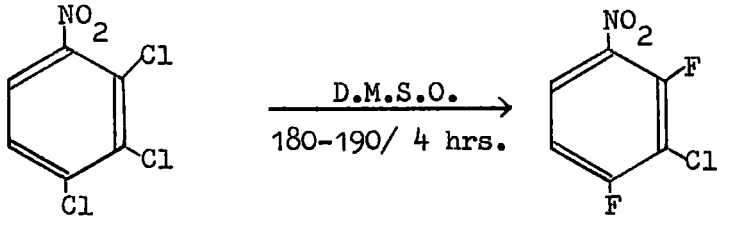
When the reaction is carried out in the presence of a solvent the actual solvent used can greatly affect the extent of halogen replacement observed. Channing and Young[84] found that 3,5-dibromo-4-chloronitrobenzene did not undergo halogen exchange with potassium fluoride at 200°C in nitrobenzene, but 2,4-dinitro-6-bromo-chlorobenzene did.



46%

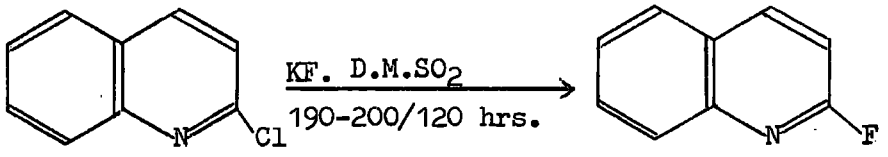
It was therefore thought that activation by at least two nitro groups was necessary for halogen replacement. Finger[85,86] showed that the reaction could be extended to the less activated mono-nitro-aromatic halides by employing the dipolar aprotic solvents dimethyl formamide (D.M.F.) and dimethyl sulphoxide (D.M.S.O.).

40%



23%

He further showed that the reaction did not occur in protic solvents (e.g. glycols) and the presence of moisture resulted in lower yields. Dimethylsulphone (D.M.SO_2) was later found to be more effective as a reaction medium,[87] since it allowed a higher reaction temperature and with this solvent the reaction was extended to halogenated aromatic nitrogen heterocycles.[88,19]



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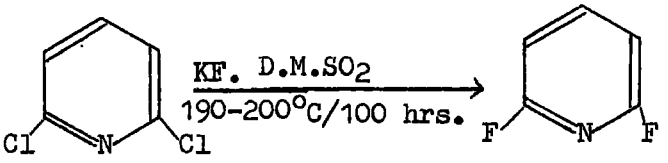

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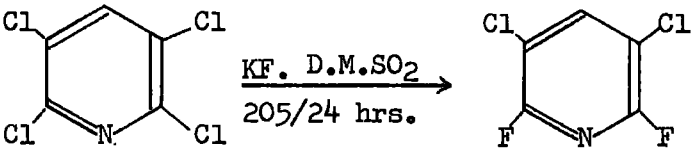
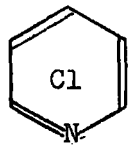
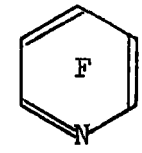


33%

N-methyl-2-pyrrolidone and tetramethylene sulphone (sulpholane) are also very effective media for halogen exchange reactions and have been used very recently to convert perhaloaromatic compounds to perfluoro-aromatics.



KF.N-methyl-2-pyrrolidone
200°C/24 hrs.



5%

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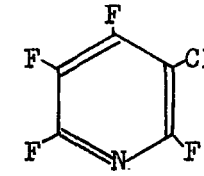

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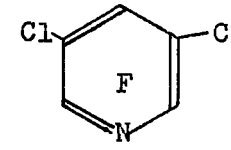
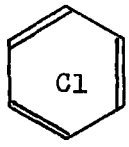


10%

Ref. 89



KF.Sulpholane
230-240°C/18 hrs.

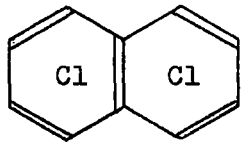
C_6F_6 + C_6F_5Cl, $C_6Cl_2F_4$,

0.4% 25% 24%

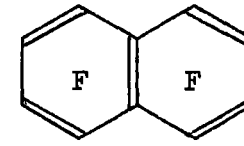
1,3,5-$C_6Cl_3F_3$

30%

Ref. 90



KF.Sulpholane
230-240°C
14 hrs.



50-60%

Ref. 90

The effectiveness of these dipolar aprotic solvents for halogen exchange reactions has been studied by Parker[91,92] and co-workers.

Dipolar aprotic solvents are classed[92] as those with dielectric constants > 15, which although they may contain hydrogen cannot donate

suitably labile hydrogen atoms to form strong hydrogen bonds with an appropriate species. Examples of such solvents include nitrobenzene, benzonitrile, nitromethane, acetone, dimethyl formamide (D.M.F.), dimethyl acetamide (D.M.A.C.), N-methyl-2-pyrrolidone, dimethyl-sulphoxide (D.M.SO), tetramethylene sulphone (sulpholane) and dimethyl sulphone ($D.M.SO_2$). The more important properties of some of these are given in Table A.

In this type of solvent anions are poorly solvated and much less so than cations,[91] solvation increasing with increasing size of the anion.[93] Solvation was found to decrease down the series

$$I^- > SCN^- > Br^- > N_3^-, \quad Cl^- \gg F^-$$

The low solvation appears to be due to a steric resistance to solvation of small anions by the bulky dipoles present in these solvents, with the result that the positive end of the dipole cannot fit closely around the small anion. Also in these solvents there is no significant contribution to solvation by hydrogen bonding, which if it occurred would be more important for the smaller anions. On the other hand when solvation is by the small unshielded proton of protic solvents (e.g. H_2O, MeOH, $HCONH_2$) steric resistance is negligible so that small anions are highly solvated by the close fitting protic solvent dipoles. Furthermore, hydrogen bonding is important in protic solvents and these bonds are stronger the smaller the anion. Consequently, in protic solvents, small anions are more solvated than large anions and solvation

TABLE A

Solvent	M.pt.	B.pt.(76 cm.)	Di-electric Constant	Dipole Moment (Debyes)	Solubility in Water
$C_6H_5NO_2$[a]	5·7	210·8	34·5	4·27	Slight Decomp.
C_6H_5CN[b]	-12·9	191·1	25·2	4·05	Decomposes
CH_3CN[c]	-45	81·6	37·5	3·37	Very
Dimethyl Sulphoxide[c]	18·5	189	48·9	4·3	Soluble
Dimethyl Sulphone[a]	109	233·5		4·49	Soluble
Dimethyl Formamide[c]	-61	152·5	37·6	3·82	Very
Tetra-methylene Sulphone	28·4[d]	280(d)[e]	44[d]	4·69[f]	Soluble
N-methyl-2-pyrrolidone[a]	-17	197-202			Very
Dimethyl Acetamide[c]	-20	165·5	37·8	3·79	Soluble

References to Table A

a Handbook of Chemistry and Physics. 46th Edition. The Chemical Rubber Company.

b Technique of Organic Chemistry, Vol. VII, Ed. Weissberger, Proskauer, Riddick and Troops.

c A.J. Parker, Advances in Organic Chemistry, Vol. 5, p.3, Interscience, 1965.

d E.M. Arnett and C.F. Douty, J. Amer. Chem. Soc., 1965, 86, 409.

e R.D. Chambers, M. Hole and W.K.R. Musgrave, Unpublished Observation. Decomposition becomes appreciable above 240°C.

f A.J. Parker, Quart. Rev. (London), 1962, 163.

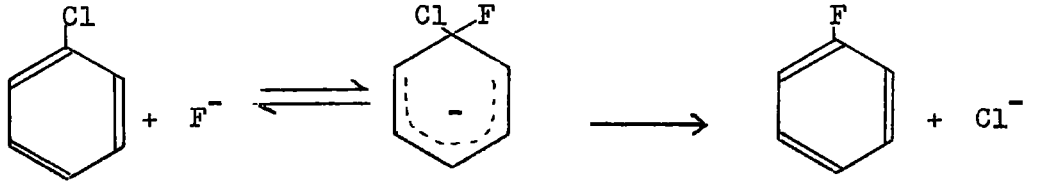
is found to increase through the series

$$SCN^- < I^- < Br^- < N_3^- < Cl^- < F^-$$

That phenyltrimethylammonium hydroxide has a base strength 10^6 times greater in sulpholane than in water,[94] and potassium fluoride in D.M.F. or D.M.SO will abstract a proton from primary alkyl halides and cause dechlorination or dehydrochlorination of highly chlorinated aliphatic compounds,[95] are a consequence of the low solvation of small anions in these solvents.

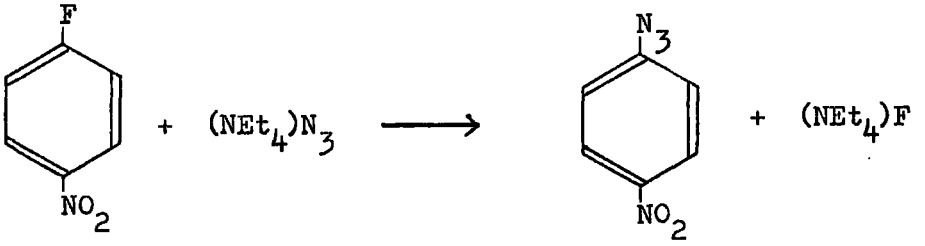
In contrast to the low solvation of anions in dipolar aprotic solvents, cations are highly solvated by these solvents. This is due to them having a region of high electron density, localised usually on a bare oxygen atom, which allows strong interaction with the cation. The type of dipole present is also important. Thus, although alkyl and aryl nitro compounds have high dielectric constants, cations are poorly solvated because the negative portion of the dipole is dispersed. It is this cation solvation that renders electrolytes soluble.

The reaction of an aromatic chloride with potassium fluoride to form the aromatic fluoride most likely proceeds with the fluoride ion as the nucleophile via a bimolecular aromatic nucleophilic substitution mechanism,[96]



(A)

involving a definite intermediate, (A), the formation of which is the rate determining step. The intermediate (A) is a good approximation to the transition state. Thus compared with the attacking nucleophile it is large with its negative charge well disposed. As a result, hydrogen bonding between it and protic solvents will be less important than for small anions and such transition states tend to be similarly solvated in dipolar aprotic and protic solvents.[97] The greater solvation of small anions in protic than in dipolar aprotic solvents coupled with the similarity of solvation, in the two kinds of solvents, of the transition state results in the reaction proceeding faster in dipolar aprotic solvents than in protic solvents.[98] The lower solvation of the anion in dipolar aprotic solvents leads to a lower activation energy for the reaction with subsequent increase in rate. Miller and Parker[93] measured the rates of the bimolecular nucleophilic aromatic reaction



in various dipolar aprotic solvents. They were compared with the rate in methanol (Table B) and show clearly the great increase in the rate of reaction caused by changing from a protic to a dipolar aprotic solvent.

TABLE B

Solvent	Ratio $\frac{k(solvent)}{k(MeOH)}$	Temp.
NH_2CHO	5·6	100°C
NHMeCHO	15·7	100°C
NMe_2CHO	$4·9 \times 10^3$	100°C
NMe_2CHO	$2·4 \times 10^4$	25·1°C
NMe_2COMe	$8·8 \times 10^4$	25·1°C
Me_2CO	$2·4 \times 10^4$	25·1°C

The marked increase in rate as the hydrogen atoms in formamide are replaced by methyl groups shows clearly that hydrogen bonding reduces the rate of the reaction.

The lower yields observed when water is present[85] can be partially attributed to hydrogen bonding by the protic impurity. However, the dipolar aprotic solvent will compete with the anion for the protic impurity and Parker[99] has shown that small amounts of protic impurities do not cause a large reduction in the rate of bimolecular nucleophilic substitution reactions at saturated carbon. A similar effect on aromatic bimolecular nucleophilic substitution reactions will also presumably operate. Chemical reaction of the protic impurity with the substrate was the main reason for the low yields observed by Finger[85]

from halogen exchange reactions carried out in the presence of water.

As regards the relative efficiencies of dipolar aprotic solvents as media for the halogen exchange reaction, Parker[91] has suggested that general cation solvation may decrease in the series of solvents

$$\text{D.M.SO, D.M.A.C.} > \text{D.M.F.} > (CH_3)_2CO, \text{ Sulpholane} \gg CH_3CN, CH_3NO_2 > PhCN, PhNO_2$$

In the absence of any specific cation-solvent interaction, such as complex formation, this would be the expected order of their efficiency for promoting halogen exchange under the same conditions. Maynard[95] found the following order of effectiveness for the reaction between potassium fluoride and hexachloropropene.

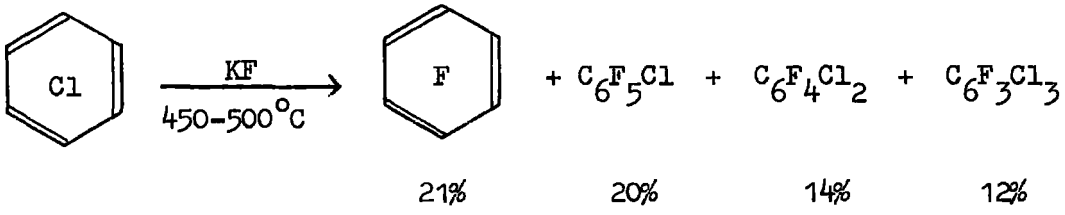
$$\text{Sulpholane} > \text{D.M.F.} > \text{N-methyl-2-pyrrolidone, D.M.SO}_2 > \text{D.M.A.C.} \ggg C_6H_5NO_2$$

The order is somewhat approximate, as the reaction conditions were not standardised for each solvent, but it does show the low efficiency of nitrobenzene, the solvent used for the first aromatic halogen exchange reaction by Gottlieb.[78] Hexachlorobenzene has been reacted with potassium fluoride in a number of dipolar aprotic solvents to give products varying greatly in their fluorine content.[90,95,100] Some of these are tabulated below:-

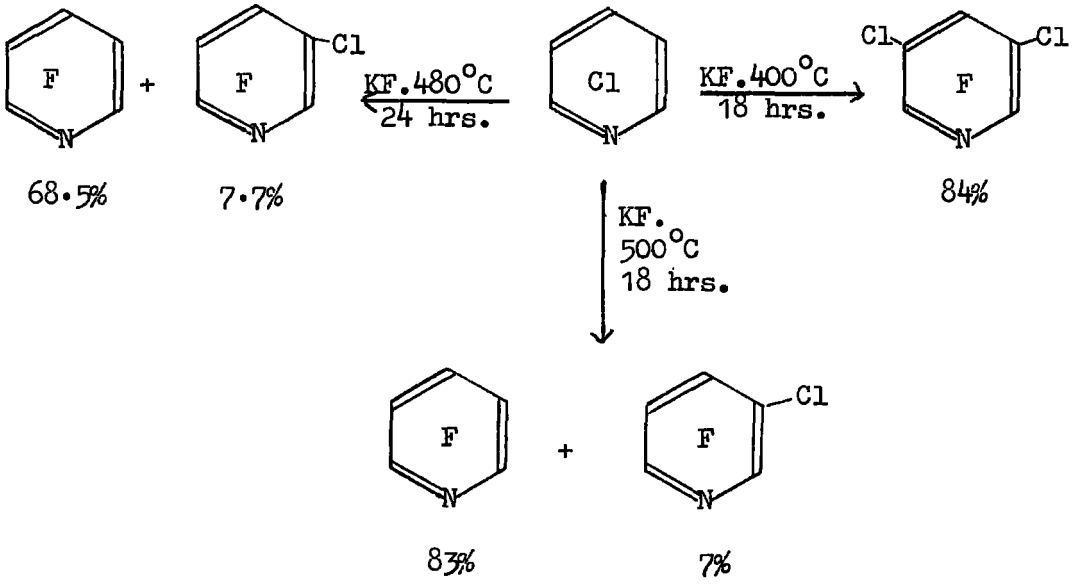
Aprotic Solvent	Temp.	Time (hrs.)	Product (% Yield)
C_6H_5CN	175	18	C_6Cl_6 recovered
$C_6H_5NO_2$	193	20	C_6Cl_6 recovered
D.M.F.	153	36	$C_6Cl_3F_3$(51), $C_6Cl_4F_2$(24)
D.M.SO	180-190	5	C_6ClF_5(0.4), $C_6Cl_2F_4$(3), $C_6Cl_3F_3$(3)
N-methyl-2-pyrrolidone	195-200	3	C_6ClF_5(small), $C_6Cl_2F_4$(34), $C_6Cl_3F_3$(23)
Tetramethylene Sulphone (Sulpholane)	230-240	18	C_6F_6(0.4), C_6ClF_5(25), $C_6Cl_2F_4$(24), $C_6Cl_3F_3$(30)

The reaction conditions varied with each solvent so that no direct comparison of relative efficiencies can be made. The higher reflux temperature possible with sulpholane makes this perhaps the best solvent for the preparation of highly fluorinated aromatics by halogen exchange. It also has good thermal and chemical stability, an absence of side reactions which could form nucleophilic impurities and is miscible with water, allowing ready isolation of the product. The thermal instability of dimethyl sulphoxide and formation of sulphur containing by-products[88] reduces its usefulness. Dimethyl sulphone is rendered less convenient by the fact that it is a high-melting solid.

For the preparation of highly fluorinated aromatic compounds in good yield a higher temperature than is possible with the above solvents is normally required, and reaction in the absence of solvents at elevated temperatures made possible the preparation of perfluoro-aromatic compounds in high yield. Russian workers[42] converted hexachlorobenzene to the perfluoro compound by heating with potassium fluoride at 450-500°C.

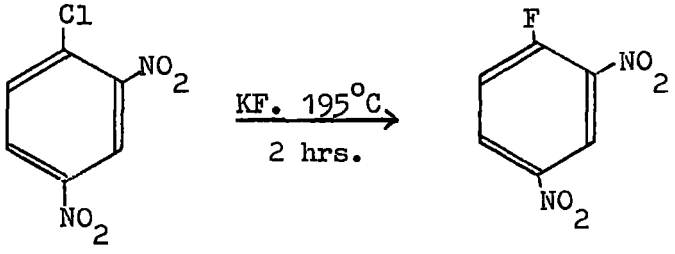


The reaction was extended to the preparation of pentafluoropyridine by workers at Durham[1] and later at Manchester.[89]



Subject to the starting material and product being stable at these elevated temperatures this method appeared the most promising for the preparation of highly fluorinated quinolines although results can not always be predicted in advance because both tetrachloropyrrole[101] and tetrachlorothiophene[102] were found to give only decomposition products when heated with potassium fluoride at temperatures necessary for complete replacement of chlorine by fluorine.

Although potassium fluoride is the most commonly used metal fluoride for the halogen exchange reaction with aromatic halides several others have been used. Finger and Kruse[85] studied the reaction between 2,4-dinitrochlorobenzene and the alkali metal fluorides in D.M.F. They found that lithium and sodium fluorides showed no appreciable reaction under conditions for which potassium, rubidium and caesium fluorides were effective. The same compound was reacted, in the absence of solvent, with a number of alkali and alkaline earth metals by Russian workers[103]



51%

Under the same conditions, lithium fluoride and sodium fluoride were not reactive whilst rubidium and caesium fluorides were more reactive,

giving yields of 88 and 98% respectively. Calcium and barium fluorides were found to be ineffective at 200°C for 5 hours as was zinc fluoride.

The observed order of reactivity of the alkali metals

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

closely resembles their relative crystal lattice energies

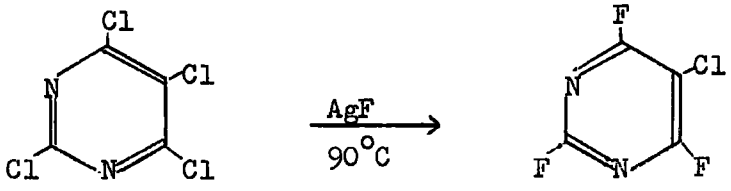
Compound	Lattice Energy (kcal./g. formula wt.)*
LiF	240
NaF	213•4
KF	189•7
RbF	181•6
CsF	173•7

*Taken from Handbook of Chemistry and Physics, 46th Edn., F.129, The Chemical Rubber Company.

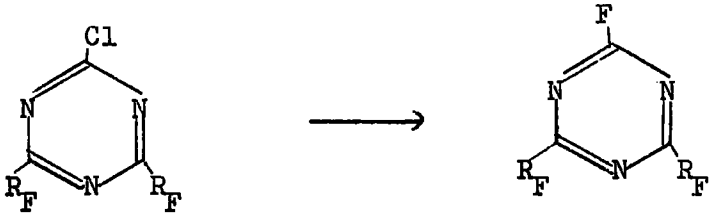
Even in the absence of a solvent it is most likely that the reaction takes place in solution in the molten nitrochloro compound. From a consideration of lattice energies solubility will increase as the size of the cation increases (i.e. from Li to Cs). Also the larger cation results in a higher degree of dissociation of the metal fluoride, with the result that the concentration of fluoride ion in solution increases from lithium to caesium, accounting for the observed order of reactivity. It is possible that an ion-pair of the

alkali fluoride is the reactive species. In this case the increasing degree of polarisation of the ion-pair with increasing size of the cation and the increasing solubility of the metal fluoride from lithium to caesium accounts for the observed order of reactivity. Potassium fluoride is most widely used because of its relative cheapness and availability.

A number of other fluorides have been used to effect halogen exchange, notably with the "active" chlorines of chloropyrimidines and chlorotriazines. Silver fluoride, AgF, was found to exchange the active chlorines in chloropyrimidines[104]

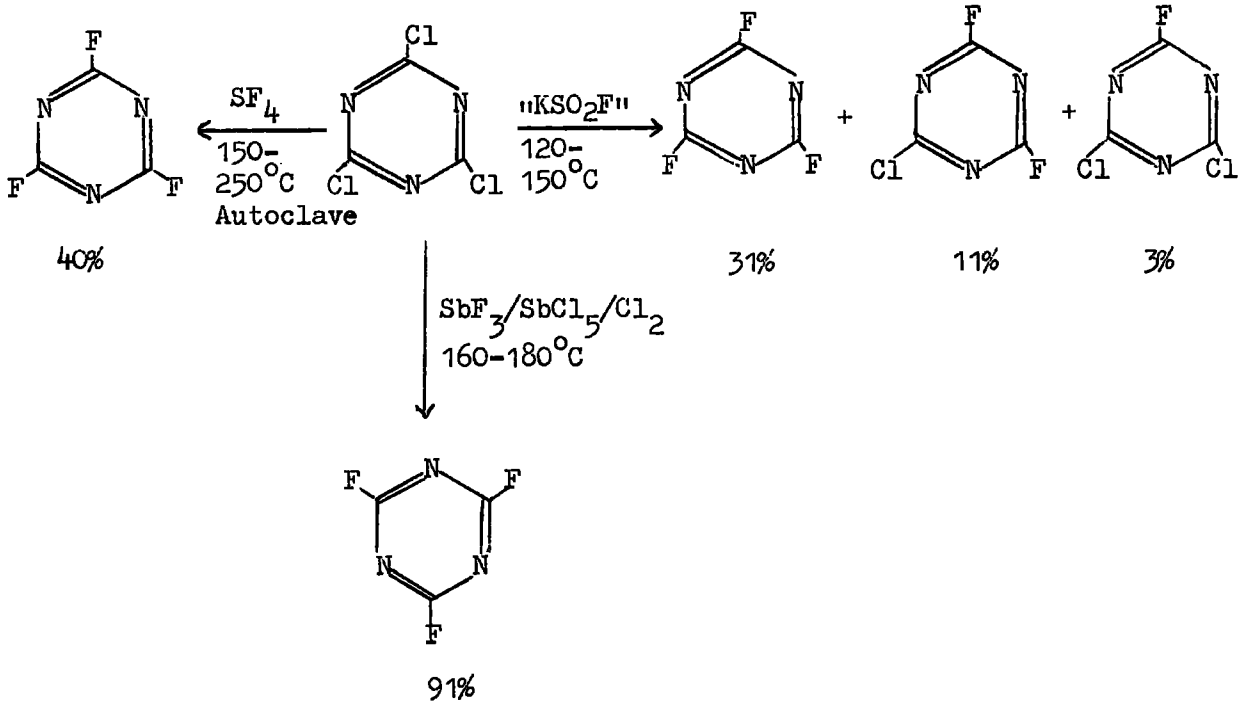


and the exchange reaction of the triazine



was achieved using either silver monofluoride, silver difluoride, mercuric fluoride or antimony trifluoride dichloride (SbF_3Cl_2) but not lead difluoride.[105] Trichloro-1,3,5-triazine has been converted to the perfluoro analogue using sulphur tetrafluoride,[106] potassium fluoro-

sulphinate[107] or Swarts reagent.[108]



The Preparation of Chloro- and Bromoquinolines.

The successful conversion of hexachlorobenzene[42] and pentachloropyridine[1] by means of the halogen exchange reaction to the perfluoro analogue, suggested that this approach might well provide a means of preparing heptafluoroquinoline. The application of this method depended of course upon an efficient method of preparing heptachloro- or heptabromoquinoline being achieved.

A survey of the methods of preparing chloro- and bromoquinolines reveals that, because of the desire to produce compounds of known orientation, cyclisation methods and replacement of functional groups at known positions have been used in preference to direct introduction of the halogen. Consequently, relatively little work has been done on the direct chlorination or bromination of the quinoline nucleus .

Direct Introduction of Chlorine or Bromine into the Quinoline Nucleus.

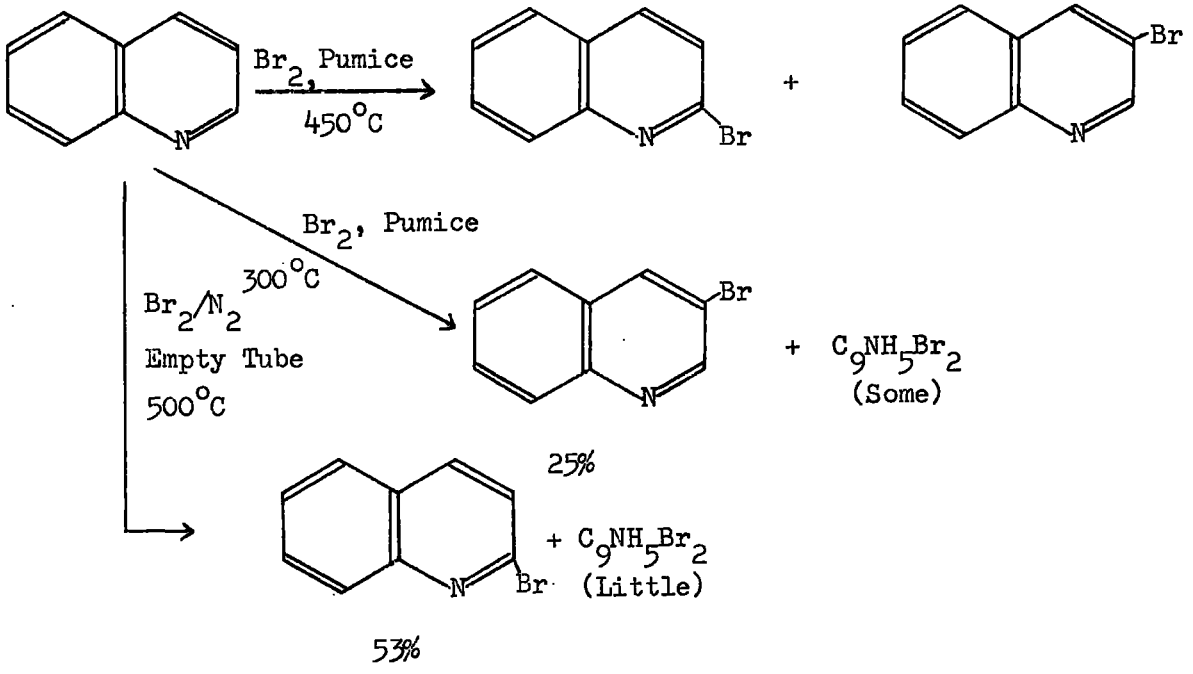
What appears to be the only exhaustive chlorination of quinoline itself reported in the literature was carried out as long ago as 1882.[113] Quinoline was heated with a ten fold excess of antimony pentachloride in a sealed tube for five-hourly periods at temperatures of 170°C, 280°C, 320°C and finally 400°C; the gases formed being vented off after each five-hour period. The brown mass left was saturated with chlorine and heated as above and the process repeated until no more hydrogen chloride was evolved. Only hexachlorobenzene and hexachloroethane were isolated from the residue, showing that under the vigorous conditions

employed the pyridine ring was destroyed. The reaction was formulated as proceeding through heptachloroquinoline, i.e.

$$C_9NH_7 \xrightarrow{SbCl_5\text{-}Cl_2} C_9Cl_7N \longrightarrow C_6Cl_6 + C_2Cl_6 + CCl_4 + N_2$$

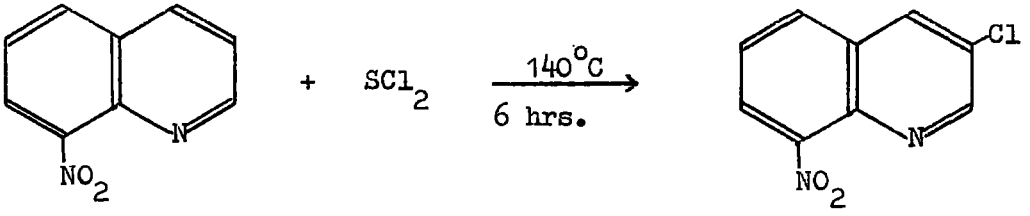
the nitrogen and carbon tetrachloride having been lost on venting to leave the two products isolated. If this is so, then by moderating the conditions it might prove possible to isolate heptachloroquinoline.

Jansen and Wibaut[109] studied the gas phase bromination of quinoline. Quinoline and bromine were preheated to the reaction temperature and passed, with or without nitrogen, through a heated glass tube usually packed with pumice. Below about 300°C little bromination took place whilst at between 300 and 500°C only monobromination occurred to any extent. At these high temperatures carbonisation was appreciable but this could be reduced by dilution of the reactants with nitrogen.



As can be seen, the position of substitution depends markedly on the temperature; substitution occurring at the 3-position at 300°C, whilst at 450°C substitution occurs predominantly at the 2-position. The high temperatures necessary for monobromination and the carbonisation occurring under these vigorous conditions, suggest that this method is unlikely to produce the highly halogenated quinolines required.

Reaction with chlorine or bromine in the presence of sulphur results in substitution occurring at a lower temperature, usually less than 200°C, to give the 3-substituted compound in reasonable yield.[109,110] Presumably the reaction involves a sulphur halide as the active halogenating agent and in fact sulphur dichloride has been used.[111]

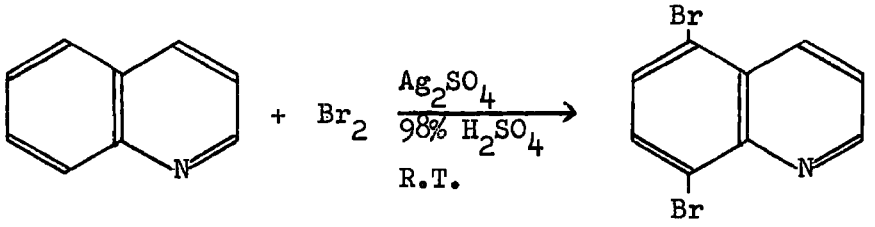


43%

In contrast to the vigorous conditions needed above to achieve substitution, the bromine in quinoline perbromide will substitute in the quinoline nucleus at room-temperature. Thus when an alcoholic solution of quinoline perbromide is allowed to stand at room temperature a mixture of tribromoquinolines is formed, the principal isomer being 3,6,8-tribromoquinoline.[109] Similarly quinoline perbromide hydrobromide

when heated to 200°C gave a small amount of 3-bromoquinoline and larger amounts of more highly brominated quinolines,[121] but no yields were quoted.

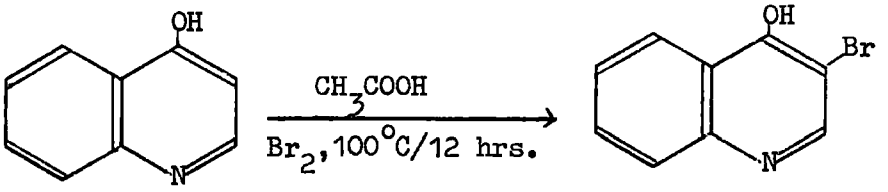
Bromination of quinoline in 98% sulphuric acid in the presence of silver sulphate readily affords the 5-, 8- and 5,8-substituted compounds.[112]



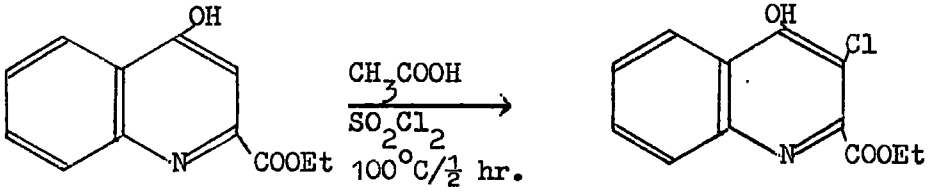
80%

The 5,8-dibromoquinoline reacted only slowly to give the 5,6,8-tribromo-compound.

In contrast, bromination or chlorination in acetic acid results in preferential substitution at the 3-position and the mechanisms of the bromination of quinoline in strong and weak acids have been discussed in some detail.[122,123,124] Quinolines with hydroxyl groups at the 2- and 4-positions are very readily substituted at the 3-position when treated with a suitable halogenating agent in acetic acid as solvent.[125-127]

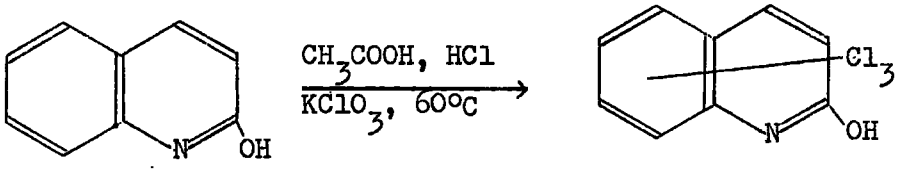


95%

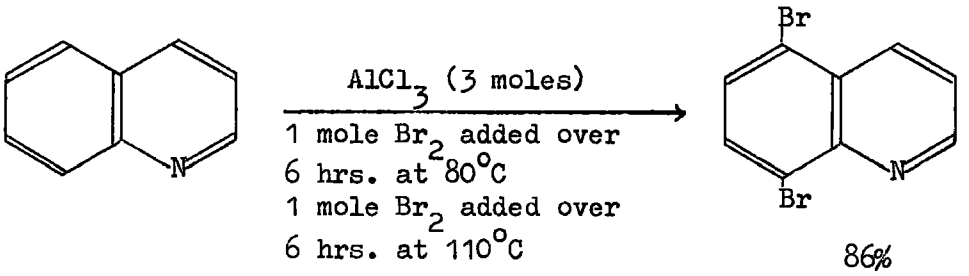


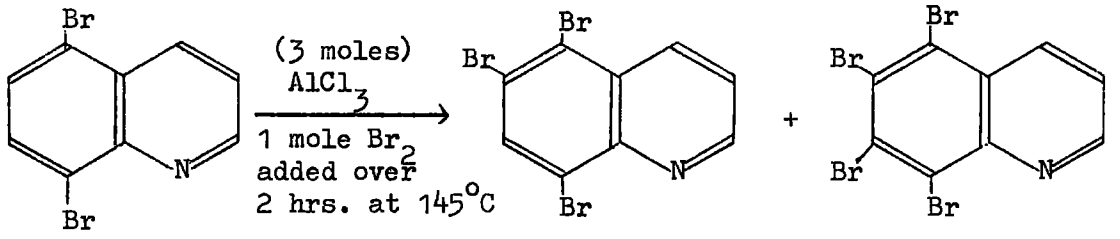
93%

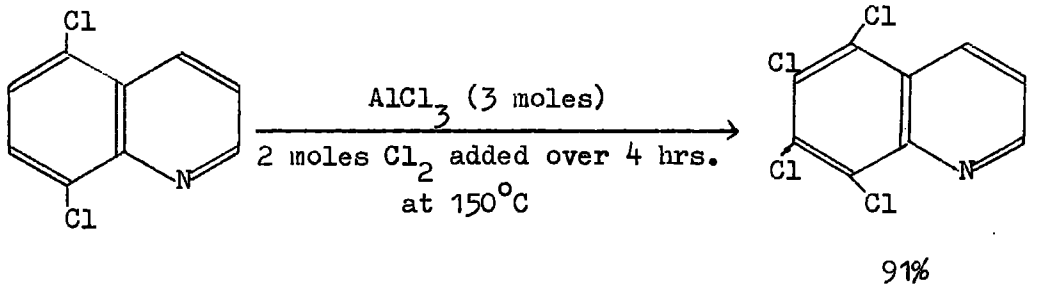
2-Hydroxyquinoline was dissolved in a mixture of glacial acetic acid (2 parts) and concentrated hydrochloric acid (1 part) and the warm solution treated with potassium chlorate to give a trichloro derivative in high yield.[128]



Gordon and Pearson[114] found that the complex formed between quinoline and aluminium trichloride, on treatment with chlorine or bromine at 80-150°C, resulted in good yields of halogenated quinolines. Substitution occurred only in the benzene ring and the tetrahaloquinoline was readily formed at a temperature of about 150°C.

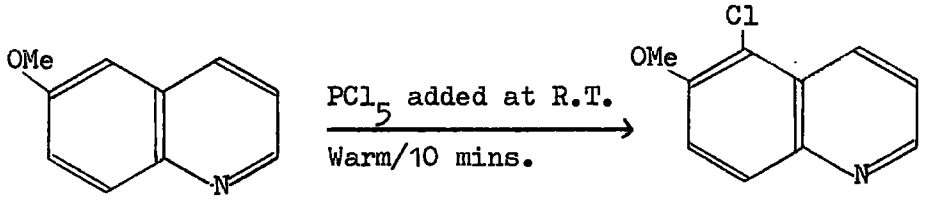




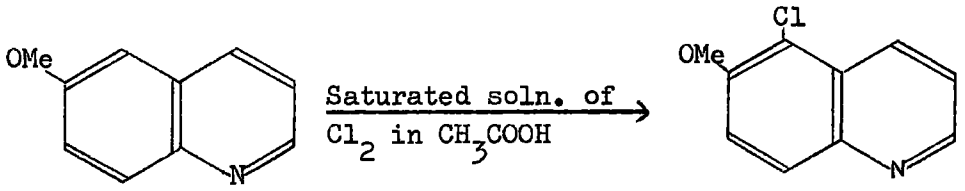


The highly halogenated quinolines were readily isolated by simply decomposing the haloquinoline-aluminium trichloride complex with ice and filtering off the precipitated haloquinoline, thus providing a very convenient preparation of 5,6,7,8-tetrachloro- or 5,6,7,8-tetrabromoquinoline. This method was used in the present work as the first stage of a two stage synthesis of heptachloroquinoline and is discussed in more detail later.

Direct introduction of halogen into the benzene ring of quinoline may also be achieved if suitable ortho, para-orientating groups are present. Thus 6-methoxy quinoline on treatment with phosphorus pentachloride or chlorine gave 5-chloro-6-methoxyquinoline in high yield[115]

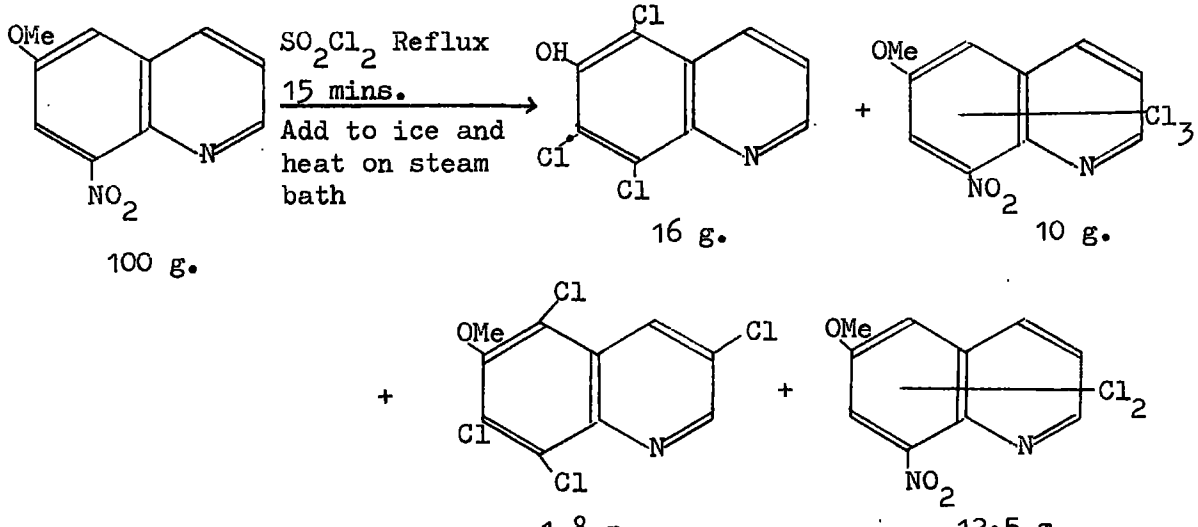


62%



71%

Treatment of 6-methoxy-8-nitroquinoline with sulphuryl chloride gave more extensive chlorination,[116] replacement of the nitro group, as well as hydrogen, by chlorine occurring:-



100 g.

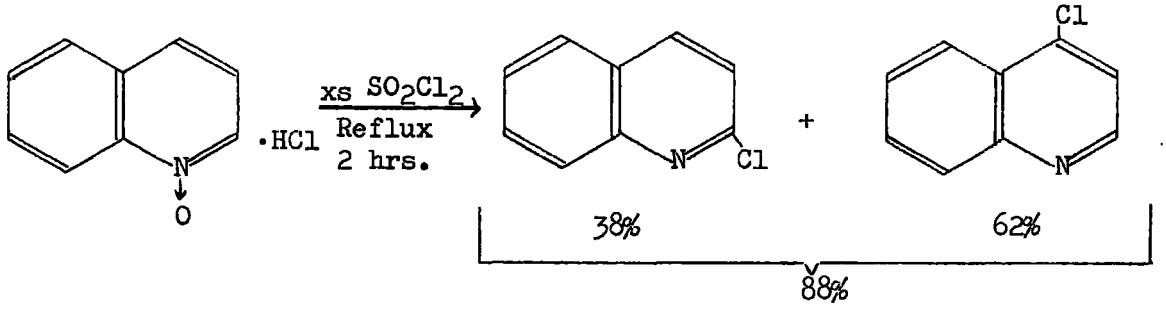
16 g.

10 g.

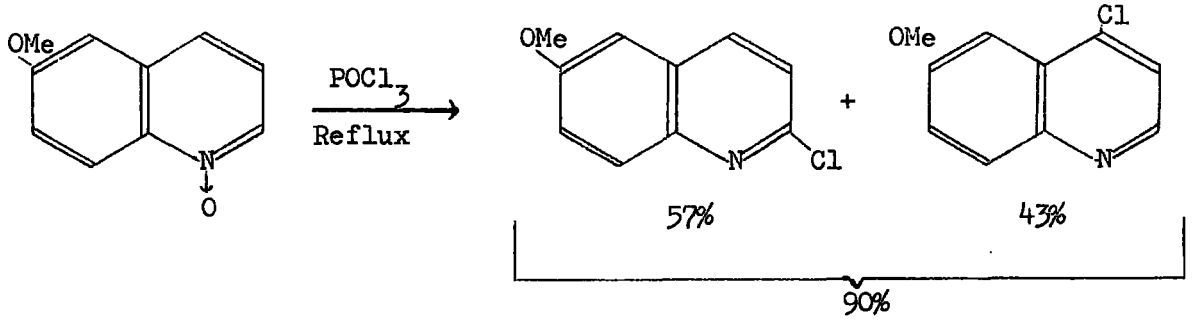
1·8 g.

12·5 g.

Quinoline N-oxides are readily substituted to give 2- and 4-chloroquinolines in high yield when treated with sulphuryl chloride or phosphorus oxychloride. Bobranski[117] reacted quinoline N-oxide hydrochloride with sulphuryl chloride



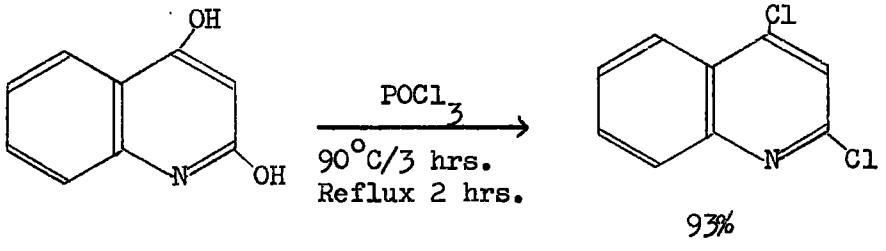
whilst many workers have reacted substituted quinoline N-oxides with phosphorus oxychloride.[118,119,120] Russian workers[120] treated 6-methoxyquinoline N-oxide with this reagent and obtained the 2- and 4-chloro derivatives in high yield



Replacement of Functional Groups and Cyclisation Methods.

Replacement of the hydroxyl group, the amino group and to a lesser extent the carboxyl group by chlorine or bromine has been used to prepare haloquinolines.

Replacement of the hydroxyl group by chlorine or bromine is usually carried out using the corresponding phosphorus oxyhalide or pentahalide or a mixture of the two. Phosphorus oxybromide readily replaces the hydroxyl group in 4-hydroxy-2-phenylquinoline to give the corresponding 4-bromo compound in 83.5% yield.[127] Lower yields were obtained with phosphorus tribromide (39%) and phosphorus pentabromide (65%). 2,4-Dihydroxyquinoline readily affords 2,4-dichloroquinoline on refluxing with phosphorus oxychloride.[129]

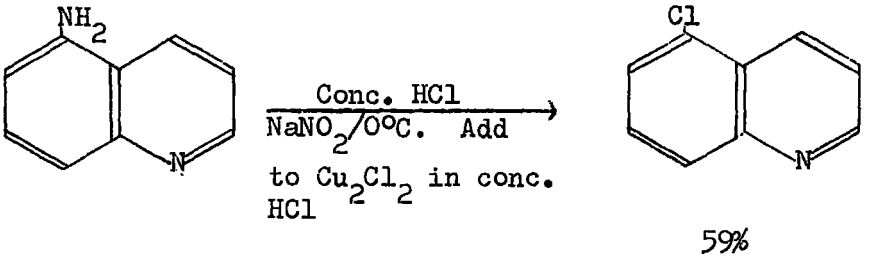


93%

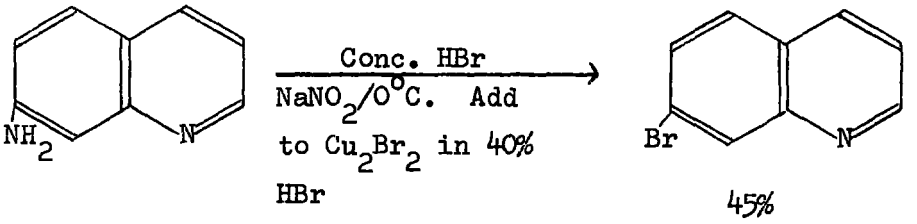
With phosphorus pentachloride at 100°C for 4 hours Koller[130] obtained a trichloroquinoline, whereas phosphorus oxychloride gave only the 2,4-dichloroquinoline under the same conditions, illustrating the more effective nuclear chlorinating properties of the pentachloride.

Replacement of the amino group by chlorine or bromine can be accomplished by either the Sandmeyer or Gattermann method, though the

latter method is the more effective for aminoquinolines. Bradford and co-workers[131] applied the Sandmeyer method successfully to 5- and 8-aminoquinoline



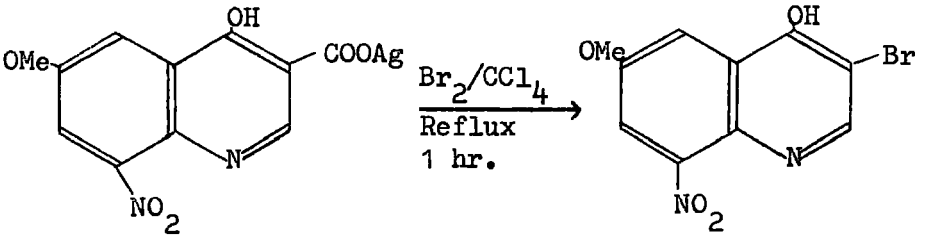
59%



45%

Roberts and Turner[132] found that the Sandmeyer method was unsuccessful when applied to 8-amino-2,4-dimethyl quinoline. However the Gattermann method gave the desired 8-chloro-2,4-dimethyl quinoline though no yield was quoted.

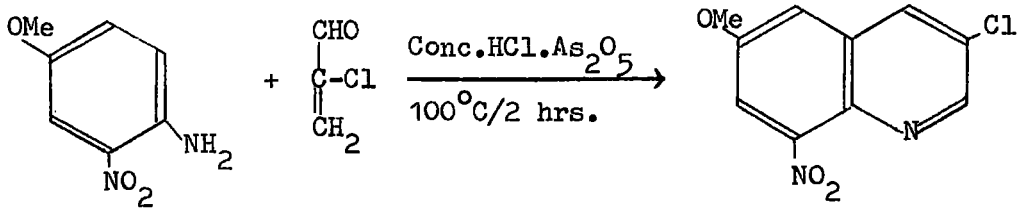
The carboxyl group in 4-hydroxy-6-methoxy-8-nitroquinoline-3-carboxylic acid was successfully replaced by application of the Hansdiecker reaction by Baker et al[135]



35%

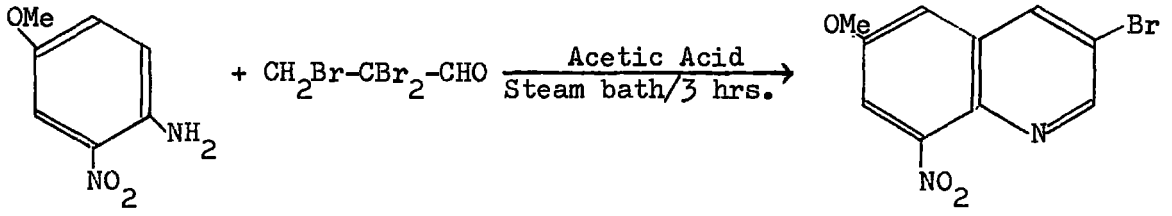
Cyclisation methods have been used to prepare quinolines with halogen in either the benzene or pyridine ring. The preparation of quinolines bearing chlorine or bromine in the benzene ring has been achieved by cyclisation methods similar to those outlined for the preparation of fluoroquinolines (see pages 10 to 16 and references 27, 28, 30, 31, 133, 134).

3-Chloro- or 3-bromoquinoline has also been prepared by cyclisation methods but the success or failure of the reaction depends markedly on the reaction conditions. Yale[136] prepared 3-chloro-6-methoxy-8-nitro-quinoline in moderate yield by cyclising the appropriate aniline with α-chloro-acrolein in concentrated hydrochloric acid.



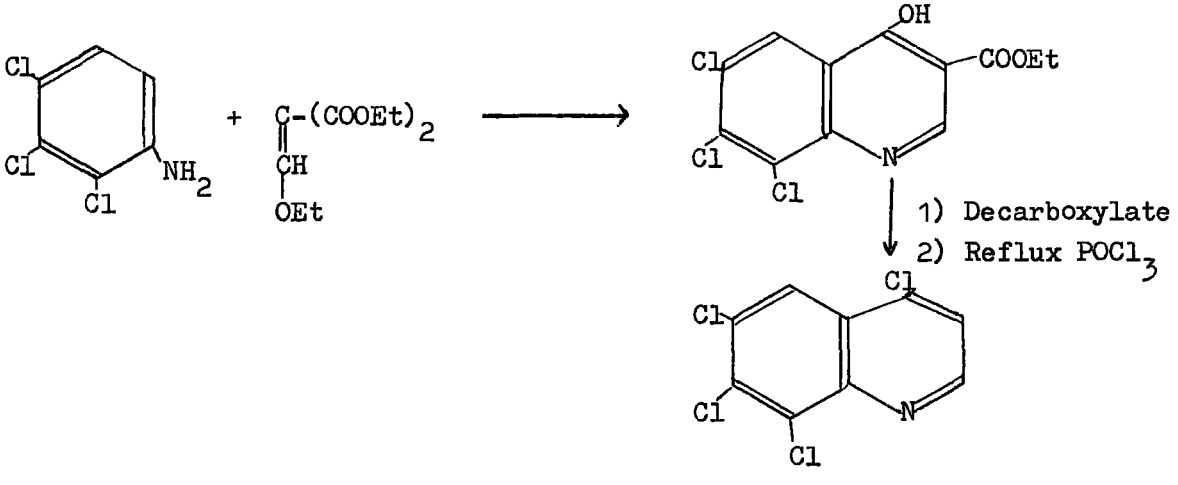
20%

When the reaction was carried out in phosphoric acid[135] the product was 6-methoxy-8-nitroquinoline and none of the desired chloro-compound was formed. Attempted cyclisation of α-bromoacrolein with this amine in either phosphoric acid or 65% hydrobromic acid failed to give the desired bromo-compound in anything but trace amounts.[135] When 1,1,2-tribromopropanal was used instead of α-bromoacrolein and acetic acid was used as solvent, the desired compound was formed in high yield



73%

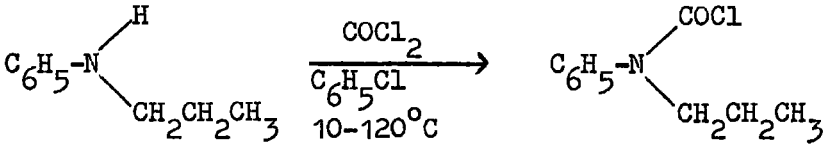
A combination of a cyclisation method and replacement of functional groups by chlorine or bromine is capable of producing highly halogenated quinolines. Such a combination was used by Burckhalter[134] to prepare 4,6,7,8-tetrachloroquinoline



39% (overall yield)

Although such a combination appears capable of producing even more highly chlorinated or brominated quinolines, the many stages involved make such a process very long and tedious and render the overall yield low.

Very recently two new syntheses of heptachloroquinoline have appeared in the patent literature.[137,138] In the first[137] N-propyl-aniline was dissolved in chlorobenzene and treated with phosgene to give N-phenyl-N-propyl carbonyl chloride

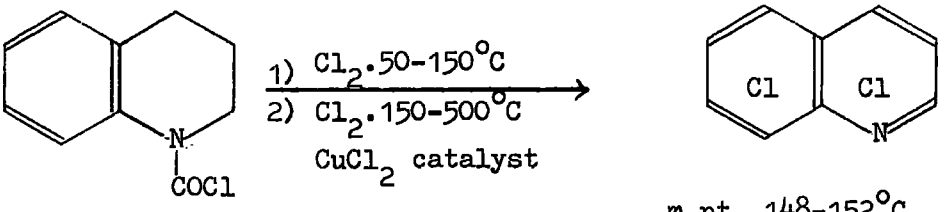


A

A was then dissolved in chloroform and chlorinated in the dark at 50-60°C with chlorine. When the exothermic reaction stopped the reaction mixture was irradiated with ultra-violet light whilst the temperature was raised 5-10°C per hour. The chloroform was replaced by trichlorobenzene and treated with chlorine for five hours at 200-220°C. The solvent was removed under reduced pressure and the residue treated with 2-3% of ferric chloride and chlorinated, without irradiation, at 200°C. After cooling, the residue was extracted with light petroleum and on concentration heptachloroquinoline was precipitated and melted at 150-152°C. No yield was quoted. N-phenyl-N-isobutylaniline was similarly treated to give heptachloroquinoline,

but again no yield was quoted.

The second synthesis[138] started from 1,2,3,4-tetrahydroquinoline-N-carbonyl chloride. This was prechlorinated with chlorine at 50-150°C and further chlorinated at 150-500°C with chlorine in the presence of Kieselguhr impregnated with a cupric chloride catalyst. Again no yield was quoted.



m.pt. 148-152°C

C H A P T E R 2

DISCUSSION OF EXPERIMENTAL WORK

Discussion of Experimental Work.

Introduction.

The most promising method for the preparation of heptafluoroquinoline appeared to be halogen exchange with potassium fluoride on heptachloroquinoline, and in order to apply this indirect method it was necessary to develop a convenient synthesis of the fully chlorinated compound, which at the time this work was undertaken had not been previously prepared. On account of overall yield and economy it was desirable to try to develop a method of converting quinoline itself directly to the fully chlorinated compound. Since none of the known cyclisation reactions, or chlorination reactions of quinoline derivatives appeared likely to allow a ready synthesis of the desired compound, first efforts were directed towards the chlorination of quinoline itself. Ideally the chlorination would involve the reaction of quinoline with chlorine, both of which are relatively cheap and readily available. The direct bromination of quinoline proceeds with difficulty and decomposition is considerable even under conditions giving only monosubstitution. Similarly direct chlorination would be expected to be equally unsuitable for the preparation of heptachloroquinoline. Pyridine has been reacted with phosphorus pentachloride at elevated temperatures in an autoclave[1] to give pentachloropyridine and it was hoped that this method would achieve the desired conversion when applied to quinoline. A mixture of aluminium trichloride, sulphur monochloride and sulphuryl chloride is a

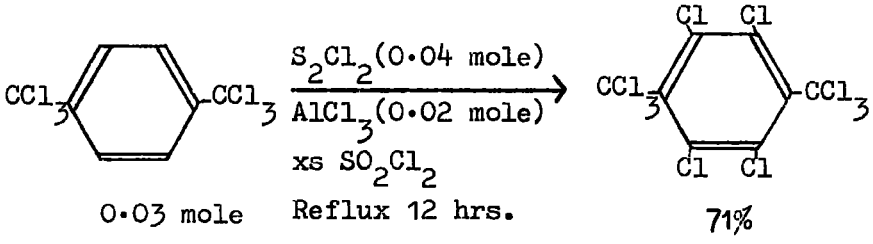
powerful nuclear chlorinating agent for homocyclic aromatic compounds[139,140] (it reacts exothermically with benzene at room-temperature and on gentle reflux gives hexachlorobenzene in high yield) and its effect on quinoline was first studied in the hope of achieving the desired one step preparation of heptachloroquinoline. It was found unsuitable for the chlorination of quinoline, as was the direct reaction with phosphorus pentachloride, and it was decided that the desired one step preparation of heptachloroquinoline in high yield was unlikely to be achieved by either method. Accordingly the direct chlorination of quinoline in the presence of aluminium trichloride,[114] a reaction known to give tetrachloroquinoline in high yield, was investigated and it was found possible to convert the chloroquinolines formed to the desired compound in high yield by treatment with phosphorus pentachloride. It was important that not only should a method be developed to give heptachloroquinoline in high yield, but that the method should allow its complete separation from lower chlorinated quinolines. Tetrachloropyridines[1] decompose when heated with potassium fluoride to the temperature necessary to effect complete replacement of chlorine by fluorine in pentachloropyridine, and by analogy one might expect partially chlorinated quinolines to decompose at the temperature necessary for complete exchange of the chlorines in heptachloroquinoline, with the likelihood of contaminating the fluorination product. Even if such lower chlorinated quinolines underwent exchange without

decomposition, the polyfluoroquinolines produced would be expected to have boiling-points similar to heptafluoroquinoline so rendering the isolation of pure heptafluoroquinoline difficult.

Reaction between Quinoline and Sulphuryl Chloride in the presence of Aluminium Trichloride and Sulphur Monochloride.

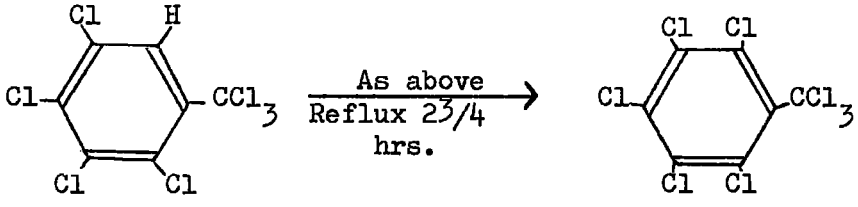
Silberrad[139] in 1922 showed that sulphuryl chloride in the presence of aluminium trichloride and sulphur monochloride was, at least as regards benzene and toluene, a powerful nuclear chlorinating agent. Using this reagent tetrachlorobenzene was converted readily to hexachlorobenzene at the reflux temperature of the mixture, whilst benzene itself could be refluxed indefinitely with sulphuryl chloride alone without any appreciable chlorination occurring. Many other catalysts were studied[141,142] for their effect on the nuclear chlorinating powers of sulphuryl chloride but none proved as effective as a mixture of aluminium trichloride and sulphur monochloride. Silberrad's method was to add the theoretical amount of sulphuryl chloride, as a mixture of sulphuryl chloride and sulphur monochloride in ratio of 100:1 by weight, to a mixture of the substrate (1 or 2 moles) and aluminium trichloride (0·04 - 0·08 moles) and the mixture was warmed, to the reflux temperature if necessary, until gas evolution ceased. Recently Ballester[140] used this mixture, but employed greater concentrations of aluminium trichloride and sulphur monochloride relative to the

substrate, to cause complete chlorination of nuclear- and side-chain-chlorinated alkyl benzenes

i.e. 

0·03 mole

71%



60%.

However 1,3,5-trichloromethylbenzene proved inert to this reagent under the above conditions, and was recovered quantitatively after 12 hours reflux. Despite this the reagent was considered to merit investigation as a possible means of effecting the desired one step conversion of quinoline to heptachloroquinoline. Its reaction with pyridine was studied first since mixtures of mono-, di- and trichloropyridines and of 2,4,5,6- and 2,3,5,6-tetrachloro- and pentachloro-pyridines were available from reactions between pyridine and phosphorus pentachloride carried out in this department,[1] and this would allow the ready characterisation of the chlorination product by analytical-scale v.p.c. analysis. Also it was known that all the chloropyridines were steam

volatile and therefore could be readily isolated by steam distillation. Since it was likely that quinoline would require similar conditions to pyridine for its conversion to the fully chlorinated compound, the initial reactions with pyridine would indicate the conditions necessary for the chlorination of quinoline. The conditions used by Ballester for the less reactive nuclear- and side-chain-chlorinated alkyl benzenes provided the starting point for the investigation of the reagent with pyridine, the susceptibility of which to electrophilic attack is lower than that of benzene.

The procedure initially adopted (reactions R1 and R2, table I) was to add, under an atmosphere of dry nitrogen, an excess of sulphuryl chloride to the finely ground anhydrous aluminium trichloride when the salt disappeared slowly to form an orange solution. On adding sulphur monochloride a white solid precipitated and when pyridine was added a clear, red solution was formed which was refluxed for 16 hours. During the reflux the volume of sulphuryl chloride steadily diminished and fresh reagent was added periodically to maintain the excess. The excess sulphuryl chloride remaining after the period of refluxing was distilled off, water added to the residue and any chloropyridines formed isolated by steam distillation. At this temperature the yield of chloropyridines was extremely low whatever the different concentrations of aluminium trichloride and sulphur monochloride used, but as can be seen (table I) the product contained highly chlorinated material. With

TABLE I

C_5H_5N (mole) [Expt]	$AlCl_3$ (mole)	S_2Cl_2 (mole)	SO_2Cl_2 (mole)	Ratio C_5H_5N/ $AlCl_3$ (molar)	Temp. (°C)	Time (hrs.)	Product (gm.)	Composition of Product in mole-% (% yield in parentheses)				
								C_5ClH_4N	$C_5Cl_2H_3N$	$C_5Cl_3H_2N$	C_5Cl_4HN	C_5Cl_5N
0·25 [R1]	0·037	0·074	3·78	1:0·15	70	16	0·5	-	20(0·27)	-	80(0·75)	-
0·11 [R2]	0·073	0·147	3·15	1:0·68	70	16	0·3	75(1·9)	10(0·18)	-	13(0·15)	2(0·02)
0·342 [R3]	0·057	0·111	2·02	1:0·17	100–105	24	13		5(1·3)		95(16·6)	-
0·361 [R4]	0·063	0·126	2·02	1:0·17	150–155	24	15·3		5(1·4)		90(19·9)	5(0·8)

the lower concentration of the catalysts the bulk of the product was tetrachloropyridines (retention time identical with the mixture of 2,4,5,6-tetrachloro- and 2,3,5,6-tetrachloro-pyridine which were themselves not resolvable) whilst increasing the concentration of the catalysts gave a product which comprised mainly monochloropyridines. The ineffectiveness of the reagent for the chlorination of pyridine under conditions for which benzene is exhaustively chlorinated is most marked and it appeared that a higher reaction temperature would be needed if any appreciable chlorination of pyridine was to be effected. For the reactions at 100°C (R3) and 150° (R4) the red solution was heated in an autoclave. After cooling the autoclave and venting the gases formed, the contents were washed out with carbon tetrachloride, the solvent and excess sulphuryl chloride distilled and any chloropyridines isolated as before. The yields, though still low, were much greater than for the reactions conducted at the reflux temperature and consisted essentially of tetrachloropyridines.

From the exploratory reactions with pyridine it seemed clear that the temperature was more important than the concentration of the catalysts and that a temperature greater than the reflux point of the reagent would be necessary to convert quinoline to heptachloroquinoline. Therefore quinoline and the reagent were heated in an autoclave at 100°C, 150°C and 205-215° (reactions R1, R2 and R3 respectively, table II). The reactions at 100° and 150° were carried out as for pyridine

TABLE II

Expt.	C_9NH_7 gm. (mole)	$AlCl_3$ gm. (mole)	S_2Cl_2 gm. (mole)	SO_2Cl_2 gm. (mole)	Time hrs.	Temp. °C	% C_9NH_7 Recovered	Composition of Product: $C_9NH_5Cl_2$/ $C_9NH_4Cl_3$ gm.	$C_9NH_3Cl_4$/ $C_9NH_2Cl_5$ gm.	$C_9NH_2Cl_5$/ C_9NHCl_6 gm.
R1	36(0·28)	20(0·15)	39·2(0·29)	560(4·15)	24	100	66·7[a]	5[a]	1·9[b]	
R2	32·5(0·25)	21(0·16)	38·8(0·29)	595(4·41)	24	150	55·5[a]	8[a]		2·40[b]
R3[c]	32(0·25)	10·4(0·08)	20·9(0·15)	340(2·52)	90	205-215	Not investigated	Essentially C_9NCl_7 (% Yield in parentheses) (gm.)		
									7·1(7·7)	

[a] Isolated by steam distillation.

[b] Isolated by vacuum sublimation.

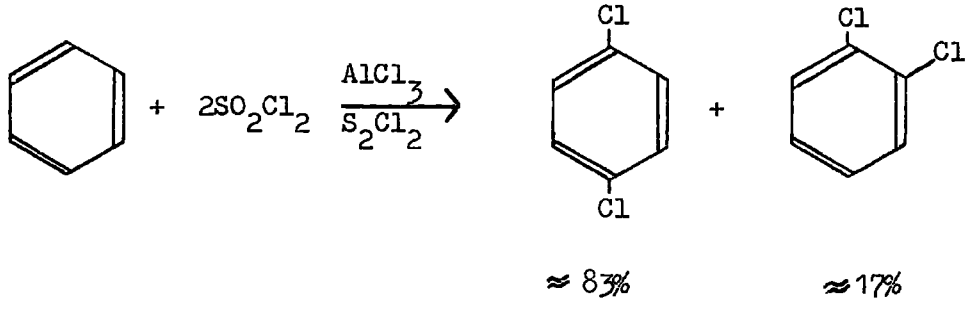
[c] Reaction work-up designed for isolation of highly chlorinated quinolines.

but the crude reaction mixture was made alkaline prior to steam distilling and also the insoluble material remaining in the distillation flask was, after being dried, vacuum sublimed to isolate any higher chlorinated quinolines which were not steam-volatile. The yield of chloroquinolines so obtained was very low (the approximate compositions were based on elemental analysis) and a substantial amount of the quinoline used was recovered. It was evident that much more vigorous conditions would be needed to achieve the desired conversion and that it would not be possible to isolate heptachloroquinoline by steam distillation. A reaction was carried out at 205-215^{o} for 90 hours and the crude product was worked up with the intent of isolating any highly chlorinated quinolines formed. After the autoclave had cooled, the gases formed were released, the contents added slowly to ice-water, the brown precipitate filtered, washed with methanol and vacuum dried at room-temperature to leave a yellow-brown solid. Purification of this proved very difficult and it was only after a laborious and tedious series of solvent extractions, decolourisations with charcoal and recrystallisations that the impurities could be removed to leave what was essentially heptachloroquinoline in 7·7% yield. However it melted over a range and this and its elemental analysis suggested the presence of a small amount of hexachloroquinoline. It was evident that this reagent was capable of fully chlorinating quinoline but on account of the difficulty encountered in removing decomposition products and lower chlorinated material, which rendered the yield of the desired compound very low, this method was not investigated further.

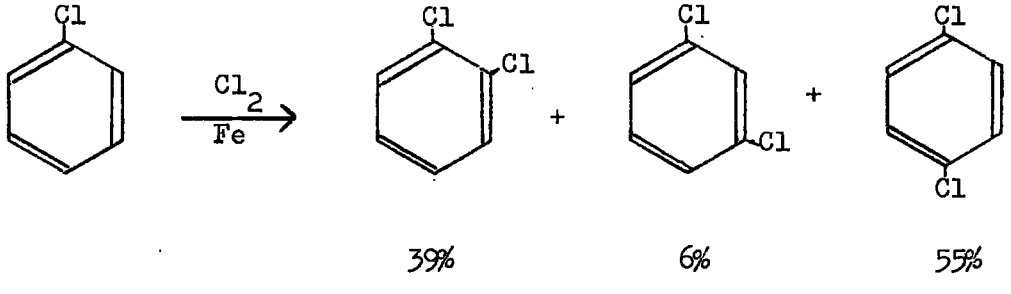
Theoretical Considerations.

Sulphuryl chloride is appreciably decomposed into chlorine and sulphur dioxide on refluxing in the presence of aluminium trichloride and sulphur monochloride[144] and it seems likely that molecular chlorine, rather than sulphuryl chloride itself, serves as the chlorinating reagent in what is undoubtedly an electrophilic reaction. Thus on reacting toluene with this reagent[142] only nuclear substitution occurs, whilst reaction with sulphuryl chloride in the presence of catalytic amounts of benzoyl peroxide, i.e. under free radical conditions, gives only benzyl or benzal chloride.[143] The formation of only para- and ortho-dichlorobenzenes from the reaction of benzene with a two molar ratio of sulphuryl chloride in the presence of aluminium trichloride and sulphur monochloride,[139] and the inertness of 1,3,5-trichloromethyl benzene to this reagent are in accord with an electrophilic mechanism prevailing. Silberrad[139] observed that aluminium trichloride dissolved in sulphuryl chloride to give a solution which with sulphur monochloride gave a precipitate, and this was found also in the present study. The precipitate was isolated by Silberrad and shown to have the composition $Al_2S_2Cl_8$ and it is likely that it is this compound that is the effective catalyst in the chlorination. A remarkable feature of this mixture is its tendency to replace hydrogens in pairs and preferentially those para to each other. Thus on treatment of paradichlorobenzene with a three molar ratio of sulphuryl chloride in the presence of aluminium trichloride and sulphur monochloride, only tetrachloro- (essentially the 1,2,4,5-

isomer) and hexachloro-benzene were formed, and no pentachlorobenzene could be detected. The reaction of benzene with a two molar ratio of sulphuryl chloride



in which the bulk of the product was paradichlorobenzene contrasts with the direct chlorination of chlorobenzene in the presence of an iron catalyst[145]



where orthodichlorobenzene is formed in substantial amount. The above observations suggest that the catalyst ($Al_2S_2Cl_8$) is not acting simply as a "halogen carrier" but is interacting with the aromatic nucleus, in some way which is not understood, to cause preferential replacement of the para hydrogens. A similar effect was found to occur in the chlorination of pyridine where the product consisted essentially of dichloro- and tetrachloro-pyridines. Electrophilic substitution

in pyridine occurs preferentially β to the ring nitrogen so that the tetrachloropyridine formed is likely to be the 2,3,5,6-isomer. The tetrachloropyridine formed did in fact have the same retention time as this isomer but so does 2,3,4,6-tetrachloropyridine.

The most remarkable feature of the reaction of this reagent with pyridine and quinoline is the very low yield of chlorinated material under conditions for which benzene is readily and exhaustively chlorinated. The fact that the white precipitate, presumably $Al_2S_2Cl_8$, dissolved on addition of pyridine or quinoline can probably be attributed to complex formation involving co-ordination of the nitrogen lone pair with the aluminium of this compound. Such complex formation would render the pyridine and quinoline less susceptible to electrophilic attack and at the same time could reduce the effect of the catalyst. The greater reaction observed at elevated temperatures could be due to the breakdown of such complexes, and the catalyst itself may not be stable under these conditions. Toluene when heated with sulphuryl chloride at 130° in a sealed tube forms benzyl chloride,[143] presumably by a free radical mechanism and such a mechanism could well be important for the reactions carried out at elevated temperatures.

Reaction between Quinoline and Phosphorus Pentachloride.

In the hope that a convenient one-step synthesis of heptachloroquinoline could be achieved the reaction between quinoline and phosphorus pentachloride in an autoclave was next studied. In comparison with the

mixture of aluminium trichloride, sulphur monochloride and sulphuryl chloride, phosphorus pentachloride is more convenient to use on a large-scale in an autoclave and is also plentiful and relatively cheap.

The reaction of pyridine and phosphorus pentachloride, originally studied by Sell and Dootson, in 1898,[146] was developed by Chambers, Hutchinson and Musgrave[1] for the preparation of pentachloropyridine in good yields. Reaction at 210-220°C for 72 hours in an autoclave gave only a 1·5% yield of pentachloropyridine but this was increased to 15% by reaction at 280-285° for 50 hours. Mixtures of lower chlorinated pyridines on further treatment with phosphorus pentachloride gave pentachloropyridine in good yield. These reactions were carried out using a mixture of 2·5 moles of pyridine and 12·0 moles of phosphorus pentachloride. Phosphorus pentachloride has been shown to react with aliphatic and aromatic hydrocarbons[147] according to the equation:

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

Presumably pyridine reacts in a similar manner i.e.

$$C_5H_5N + 5PCl_5 \longrightarrow C_5Cl_5N + 5PCl_3 + 5HCl$$

and thus the reactions above were carried out using less than the theoretical amount of phosphorus pentachloride needed for complete conversion to pentachloropyridine. It was hoped that reaction of quinoline with excess of phosphorus pentachloride at approximately 280°C in an autoclave would lead to heptachloroquinoline being formed in good yield.

The results of the reaction between quinoline and phosphorus pentachloride at 285° and at 250-260° are shown in table III where it is seen that mixtures of heptachloro- and hexachloro-quinoline were formed in moderate yield. However, the great disadvantage of this reaction was the difficulty encountered in removing decomposition products from the reaction product. For the reaction with pyridine the chloropyridines formed were readily separated from such decomposition products by steam distillation. However, highly chlorinated quinolines, the desired products, were not steam volatile and isolation of the highly chlorinated quinolines was achieved only by a combination of solvent extractions, recrystallisations, charcoal decolourisations and vacuum sublimation, since no one process gave a direct purification. Such a combination was extremely laborious and time consuming and gave only a mixture of heptachloro- and hexachloro-quinolines and not the desired heptachloroquinoline. Further treatment of the crude reaction product from reaction R2 table III, with phosphorus pentachloride at 235-245° for 80 hours did in fact yield heptachloroquinoline in overall yield from quinoline of 12·5%. However the pure compound was isolated only after a laborious purification process. Bearing in mind that heptachloroquinoline was the starting material for the preparation of heptafluoroquinoline, a more convenient preparation of it than was possible by the above method was required.

TABLE III

Expt.	C_9NH_7 gm. (mole)	PCl_5 gm. (mole)	Time (hrs.)	Temp. (°C)	Crude Product (gm.)	C_9NCl_7/C_9NCl_6H Mixture (gm.)	% Yield (based on C_9NCl_7)	% Yield (based on C_9NCl_6H)
R1[c]	53(0·42)	1,000(4·81)	50	285	132·5[a]	21·4	14	15·5
R2[d]	63·5(0·49)	1,500(7·2)	52	250-260	120[b]	34·8	19·3	22·1

[a] After hydrolysis of the autoclave contents, the insoluble material was filtered off and vacuum dried.

[b] After treatment as in a and then washing with methanol.

[c] Autoclave not evacuated.

[d] Autoclave evacuated.

Theoretical Considerations.

As the reaction between quinoline and phosphorus pentachloride was studied from a preparative stand-point, only a general consideration of the theoretical aspects involved will be given.

Phosphorus pentachloride has been used to chlorinate a number of aliphatic, alicyclic and alkylated aromatic hydrocarbons[147] either in a thermal or benzoyl peroxide catalysed reaction. The reactions were carried out at 90-110°C in a solvent or with the liquid hydrocarbon alone and proceeded according to the equation

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

The thermal reaction of phosphorus pentachloride was found to have an overall behaviour similar to photochlorination which suggests that the attacking species is a chlorine atom or something of similar reactivity. It was suggested that the thermal reaction with phosphorus pentachloride was essentially a free radical reaction involving attack by chlorine atoms produced by thermal fission of the chlorine formed from dissociation of the phosphorus pentachloride. A similar type of reaction scheme could apply to the reaction between quinoline and phosphorus pentachloride

i.e.

$$PCl_5 \rightleftharpoons PCl_3 + Cl_2 \qquad (1)$$

$$Cl_2 \rightleftharpoons 2Cl^{\bullet} \qquad (2)$$

$$RH + Cl^{\bullet} \longrightarrow R^{\bullet} + HCl \qquad (3)$$

$$R^{\bullet} + Cl_2 \longrightarrow RCl + Cl^{\bullet} \qquad (4)$$

$$R^{\bullet} + PCl_5 \longrightarrow RCl + PCl_4^{\bullet} \qquad (5)$$

$$RH + {}^{\bullet}PCl_4 \longrightarrow HPCl_4 + R^{\bullet} \qquad (6)$$

$$HPCl_4 \longrightarrow HCl + PCl_3 \qquad (7)$$

$${}^{\bullet}PCl_4 \rightleftharpoons PCl_3 + Cl^{\bullet} \qquad (8)$$

$$R^{\bullet} + Cl^{\bullet} \longrightarrow RCl \qquad (9)$$

Phosphorus pentachloride is more than 80% dissociated at temperatures above 250°C at atmospheric pressure and at the higher pressure developed in the autoclave the degree of dissociation will be lower but no doubt still significant. It is possible that ${}^{\bullet}PCl_4$ decomposes rapidly to $PCl_3 + Cl^{\bullet}$ so that steps (6) and (7) are unimportant. With toluene assigned a relative reactivity value of 1·0 per replaceable methyl hydrogen, it was found that each hydrogen in cyclohexane was 2·8 times as reactive as regards photochlorination and 3·0 times as reactive for the thermal reaction with phosphorus pentachloride. The similarity to photochlorination implies that step 8 is the important one giving the conclusion that the essential attacking species is the chlorine atom. The reaction between phosphorus pentachloride and pyridine, under similar conditions used for quinoline, was found to be unaffected by a number of transition metals and furthermore positions β to the nitrogen were substituted least readily,[149] suggesting that an electrophilic mechanism was not important. This conclusion presumably applies to the quinoline case also.

When quinoline is phenylated free radically using benzoyl peroxide, attack occurs at all positions and the following order of decreasing

susceptibility is found 8 > 4 > 3 > 5 > 6 ≈ 7 > 2.[150] However the direct bromination of quinoline at 500°C,[109] where the attacking species is most likely the bromine atom, gives 2-bromoquinoline. The mechanism prevailing is by no means clear and it has been tentatively proposed[151] that formation of the 2-bromoquinoline results from initial formation of a complex between quinoline and bromine, involving co-ordination with the nitrogen lone pair to give a complex having similarities to the quinolinium cation, and attack on this complex by a bromine radical. Such a mechanism is supported by calculations of the radical localisation energies for the quinolinium cation and similar reactions might occur with chlorine in the reaction of quinoline with phsophorus pentachloride. Phosphorus pentachloride is a weak Lewis acid and might complex with the ring nitrogen so that reaction then occurs on the quinolinium system so formed, rather than on the free base.

Obviously much work is needed to establish the actual mechanism of the quinoline-phosphorus pentachloride reaction, but it seems most probable that the attacking species is a free radical and possibly the chlorine atom.

Preparation of Heptachloroquinoline by the Two-Stage Process.

The observation[152] that a mixture of dichloro- and trichloropyridines could be converted almost quantitatively to pentachloropyridine by heating with phosphorus pentachloride for 3-4 hours at about 300°C led to the successful development of the two-stage synthesis of hepta-

chloroquinoline in high yield. It was known[114] that 5,6,7,8-tetrachloroquinoline could be prepared in high yield and it was hoped that this could be readily converted to heptachloroquinoline using conditions similar to those employed above for the pyridine case. This has been realised, and the direct chlorination of quinoline in the presence of aluminium trichloride and subsequent treatment of the tetrachloro- and pentachloro-quinolines with phosphorus pentachloride has been developed to give heptachloroquinoline in high yield.

Direct Chlorination of Quinoline in the presence of Aluminium Trichloride.

Gordon and Pearson[114] found that the complex formed between quinoline and excess aluminium trichloride (a molar ratio of quinoline-aluminium trichloride of about 1:3 was used) on treatment with chlorine or bromine gave the halogenated quinoline, in which substitution only in the benzene ring had occurred, in high yield. Their method, termed the "swamping catalyst" method, has been developed to give mixtures of tetrachloro- and pentachloroquinolines in high yield, as shown in table IV.

The complex formed is surprisingly mobile at temperatures greater than about 80°C which permits it to be efficiently stirred as the gaseous chlorine is bubbled through. A large excess of chlorine was passed slowly through the complex in order to achieve a high conversion to the chlorinated quinolines. Gordon and Pearson employed the theoretical amount of chlorine needed to convert 5,8-dichloroquinoline to 5,6,7,8-

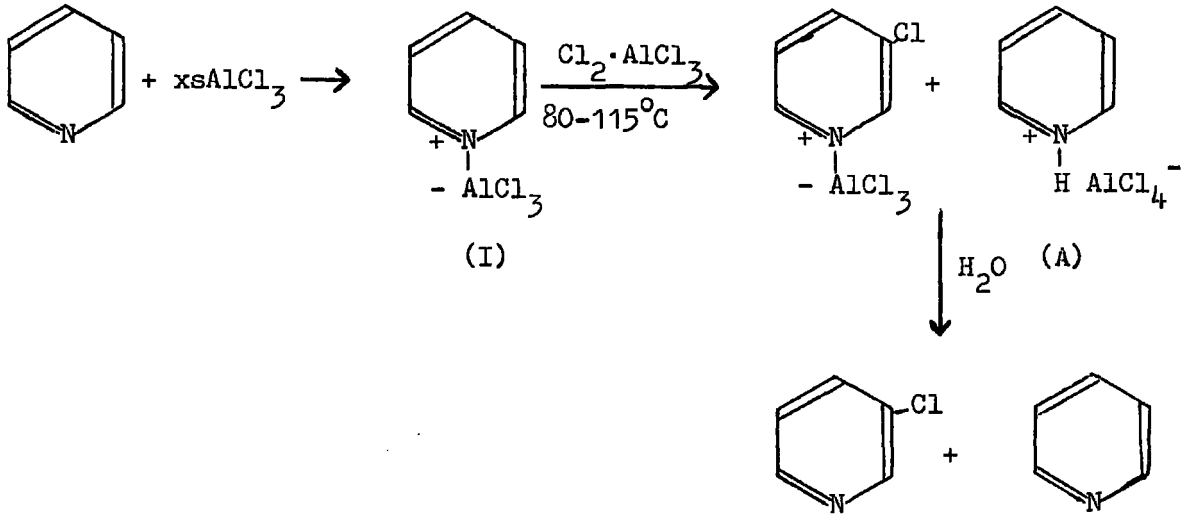
TABLE IV

Expt.	C_9NH_7 gm. (mole)	$AlCl_3$ gm. (mole)	Cl_2 gm. (mole)	Temp.(°C)	Time (hrs.)	C_6H_6-recrystallised Product Approximate composition (% Yield in parentheses) Essentially $C_9NCl_5H_2$ (gm.)	Essentially $C_9NCl_4H_3$ (gm.)	Material Insol. C_6H_6 (gm.)
R1	103(0·80)	320(2·41)	410(5·77)	90-140°C 140-160°C	6½ 123½	152(63)	47·5(22)	23·5
R2	116(0·90)	310(2·32)	1160(16·36)	110-130 170-190	24 24	210(79)	-	69·0
R3	141(1·09)	440(3·30)	480(6·76)	110-140 140-160	2 41		248(87)	-
R4	502(3·81)	1500(11·3)	1830(25·8)	140-150	70		865(83)	-

tetrachloroquinoline at a temperature of 150° but it can be seen (reaction R1, table IV) that slow chlorination at the same temperature with a large excess of chlorine gives more pentachloroquinoline than tetrachloroquinoline. Reaction at a higher temperature and with a greater excess of chlorine (reaction R2, table IV) gave essentially only pentachloroquinoline but the yield was decreased due to the formation of a high-melting, benzene-insoluble by-product which was probably polymeric. Under the milder conditions employed for reaction R3 and R4 (table IV) the formation of this by-product was avoided. Gordon and Pearson suggested that the tetrahaloquinoline was formed in higher overall yield from quinoline by carrying out the reaction in stages, i.e. conversion to the dihaloquinoline and then treatment of this in a separate experiment with aluminium trichloride and the halogen to form the tetrahalo compound. In this way 5,6,7,8-tetrabromoquinoline was formed in 69% overall yield, but the direct conversion of quinoline to the tetrachloro compound was affected in over 80% yield in the present work.

Theoretical Considerations.

The chlorination of pyridine by the "swamping catalyst" method has been shown to proceed in the following way[153]

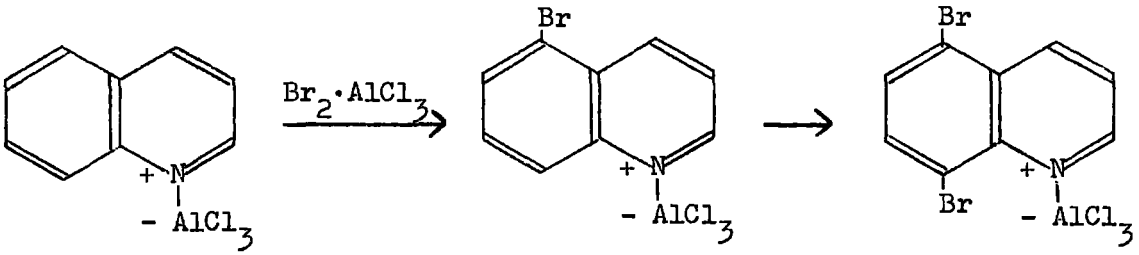


Half of the pyridine was converted to 3-chloropyridine whilst the other half was deactivated by protonation to give A which was shown in a separate experiment to be inert to chlorination under the conditions of the original reaction. It was also shown that in the bromination of 4-methyl pyridine if only one mole of aluminium trichloride were used per mole of the picoline then no bromination occurred, whilst if excess aluminium trichloride were used a 32% yield of 3-bromo-4-methylpyridine was obtained. That substitution occurs at the 3-position is in accord with an electrophilic mechanism and the fact that (I) is more reactive than (A) suggests that the pyridine-aluminium trichloride complex has a more covalent form in which the electrons on the nitrogen are not so firmly held as when the ring nitrogen is protonated. However both are deactivated towards electrophilic attack and it is surprising that halogenation occurs at all. The need for an excess of aluminium trichloride shows that its ability to increase the effectiveness of the attacking

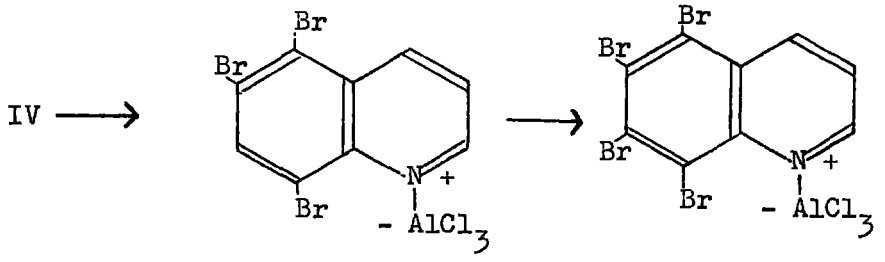
electrophilic species more than compensates for the above deactivation. The increased activity of the attacking species is due to the aluminium trichloride tending to remove one of the halogen atoms from its shared electron

i.e. $Cl_2 + AlCl_3 \longrightarrow Cl^+ + AlCl_4^-$

and the excess aluminium trichloride serves as a medium of high dielectric constant which assists the separation of any such charged species produced. Ferric chloride, either alone or mixed with aluminium trichloride, and boron trifluoride formed complexes with pyridine but no halogenation occurred on treatment with halogen as for the case of aluminium trichloride above. By controlled bromination of the quinoline-aluminium trichloride complex, Gordon and Pearson[114] found the following order of substitution

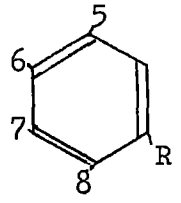


II III IV

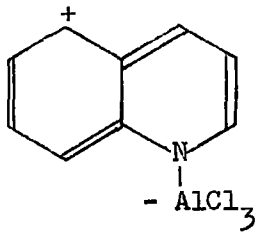


V VI

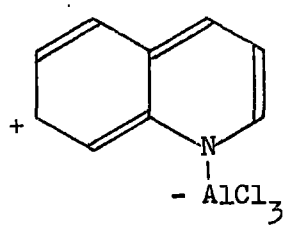
and a similar order no doubt holds also for chlorination. The observed order of substitution can be rationalised by consideration of the charge distribution in the ground state in terms of valence-bond structures. Although one should ideally consider the relative stabilities of the transition states for attack at all the possible positions, the ground state argument readily accounts for the observed orientation. The positively charged nitrogen by a combination of its inductive and mesomeric effects deactivates the pyridine ring more than the benzene ring (in II) so that electrophilic attack occurs preferentially in the benzene ring. II can be regarded as equivalent to VII were R is electron-attracting, inductively and mesomerically, and so deactivates the positions ortho and para to it, i.e. the 6- and 8-positions in II



VII



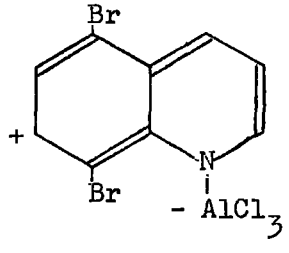
VIII



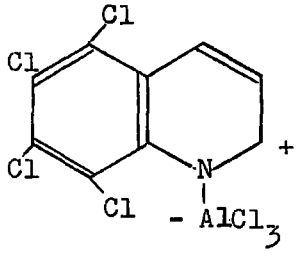
IX

For II, resonance forms such as VIII and IX can be written in which there is a "formal" positive charge at the 5- and 7-positions. Such forms will only make a small contribution to the actual structure of II since they involve a complete rearrangement of the π-electrons of both rings, but IX, with its para-quinonoid structure, is likely to be of greater

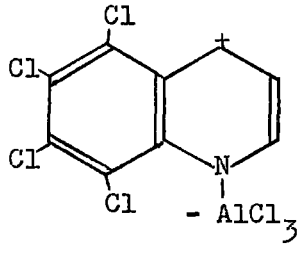
importance than VIII, which has an ortho-quinonoid structure. The apparent greater stability of paraquinonoid forms over orthoquinonoid forms has been noted by several workers[154,159,160] and is discussed later (page 95). Thus position 7 in II will be more electron deficient than position 5 and hence electrophilic attack will occur preferentially at the latter position to give III. Preferential attack on III at position 8 can be ascribed to activation of this position by mesomeric electron release of the bromine in position 5. Apparently no 5,6-dibromoquinoline was formed, although this might have been expected to be formed in small amount by comparison with the bromination of bromobenzene in the presence of aluminium bromide, in which substitution, although occurring mainly (86.5%) in the para position, does take place to a significant extent (13.4%) in the ortho position.[155] Chlorination of chlorobenzene in the presence of an iron catalyst[145] gives a considerable amount (39%) of ortho substitution but the only isomer of dichloroquinoline isolated by Gordon and Pearson was the 5,8 substituted compound. Substitution of further bromine at position 6 in preference to position 7 can be ascribed to the contribution of the resonance form X to the actual structure of IV



X

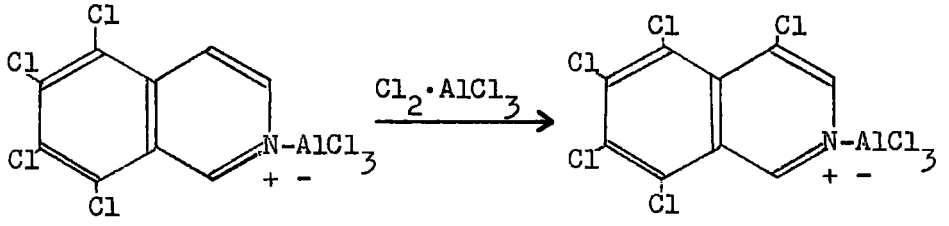


XI



XII

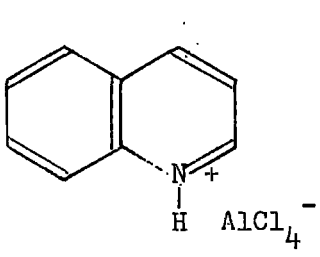
In the 5,6,7,8-tetrahaloquinoline-aluminium trichloride complex, it is seen from XI and XII that the 2- and 4-positions are deactivated relative to position 3. Therefore the pentachloroquinoline isolated is most likely the 3,5,6,7,8-substituted compound. Further chlorination of 5,6,7,8-tetrachloroisoquinoline would be expected, by similar reasoning, to occur meta to the nitrogen, i.e.



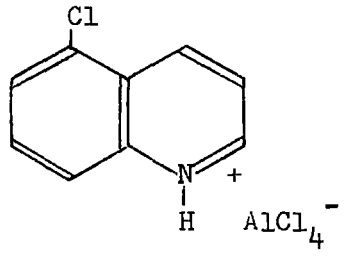
XIII

Mesomeric electron release of the chlorine at position 4 in XIII will activate the 1-position more than the 3-position and under the conditions where quinoline gives only the pentachloro compound, isoquinoline might be expected to form 1,4,5,6,7,8-hexachloroisoquinoline. A hexachloroisoquinoline is in fact formed[156] which has a sharp melting-point suggesting a single isomer of possibly the expected orientation.

The orientation observed in the halogenation has been discussed in terms of the aluminium chloride complex (II), although the hydrogen chloride formed most probably reacts to some extent to form initially the protonated species



and



However, the factors affecting orientation will be the same for both II and the protonated species. The high yields obtained for quinoline contrast markedly with those for pyridine and, since quinoline is a weaker base than pyridine,[157] might be due to the fact that protonation occurs less readily for quinoline. The greater possible delocalisation of the positive charge developed in the transition state for the bicyclic system will also contribute to its greater reactivity.

Chlorination of Penta- and Tetrachloroquinoline with Phosphorus Pentachloride.

The conversion of the partially chlorinated quinolines to heptachloroquinoline in high yield was found to be possible by heating them with phosphorus pentachloride in an autoclave if the reaction conditions were carefully controlled. The dependence of the yield of heptachloroquinoline on the reaction conditions is shown in table V. The autoclave was heated by means of a heating coil which fitted closely around the lower half of the autoclave and the temperature was measured by means of a thermocouple placed into a well in the centre of the autoclave head and which terminated on a level with the top of the heating coil. The lower end of the autoclave was therefore heated to a much higher

TABLE V

Expt.	Partially Chlorinated Quinoline $C_9NCl_5H_2$ gm. (mole)	Partially Chlorinated Quinoline $C_9NCl_4H_3$ gm. (mole)	PCl_5 gm. (mole)	Time (hrs.)	Temp. (°C)	C_9NCl_7 after recrystallisation from benzene (gm.) (% Yield in Parentheses)	
R1	70(0·23)	-	1280(6·15)	2 12	20-290 290-315	Extensive Decomposition	Partially chlorinated quinoline placed in the bottom of the autoclave
R2	80(0·30)	-	514(2·47)	2 7	20-300 300-320	Extensive Decomposition	
R3	-	64(0·24)	946(4·55)	3 2	20-335 335-356	49·5(55)	
R4	-	82·5(0·31)	1,076(5·17)	2 3	20-355 355-390	68·5(60)	PCl_5 placed in the bottom of the autoclave
R5	-	70(0·26)	1,009(4·85)	2 3	20-340 340-372	62·5(66)	
R6	-	95·5(0·36)	1,054(5·05)	2 3	20-315 315-330	103(78)	
R7	-	80·5(0·30)	981(4·72)	2 $3\frac{1}{2}$	20-315 315-330	93·5(84)	

temperature than that actually recorded and in the earlier reactions (R1 and R2 table V) in which the chloroquinolines were placed in the bottom of the autoclave and long reaction times were used extensive decomposition occurred, but a moderate yield of heptachloroquinoline was obtained with a shorter reaction time (R3). This decomposition was greatly reduced by placing the phosphorus pentachloride in the bottom of the autoclave with the chloroquinolines above and on a level with the bottom of the thermocouple well. Thus the phosphorus pentachloride besides acting as the chlorinating agent served as a "thermal shield" between the chloroquinolines and the hot walls of the autoclave, so reducing decomposition. By so placing the phosphorus pentachloride, which was used in large excess, the conditions were most favourable for the production of a high concentration of chlorine radicals, so ensuring complete conversion to the fully-chlorinated compound. Using a tetrachloroquinoline-phosphorus pentachloride ratio of approximately 1:14-18·5, a temperature of 315-330°C for between 3 and $3\frac{1}{2}$ hours was found to produce heptachloroquinoline in yields of around 80% (reactions R6 and R7, table V). As the temperature was increased the yield decreased (reactions R4 and R5, table V). Using the optimum conditions the solid remaining, after the hydrogen chloride had been released, the phosphorus trichloride poured off, and the autoclave contents added to ice-water, was simply filtered off and a single recrystallisation from benzene gave the pure heptachloroquinoline.

This contrasts markedly with the difficulty encountered in purifying the products of the direct reaction of quinoline with phosphorus pentachloride or the mixture of sulphuryl chloride, aluminium trichloride and sulphur monochloride.

The direct chlorination of quinoline in the presence of aluminium trichloride and subsequent treatment of the tetrachloroquinoline produced with phosphorus pentachloride thus afforded a convenient two stage synthesis of heptachloroquinoline. Under optimum conditions (reactions R3 and R4, table IV and reactions R6 and R7, table V) an average overall yield of 69% was achieved.

Fluorination of Heptachloroquinoline.

Of the methods available for the conversion of perchloro-aromatic compounds to the corresponding perfluoro compounds, the method of halogen exchange appeared the most promising for the preparation of heptafluoroquinoline from heptachloroquinoline. In comparison with the single step halogen exchange reaction the other method, involving the addition of fluorine to give the saturated compound followed by dehalogenation, suffers from the fact that being a two stage reaction it is more laborious and there is the likelihood of lower yields on this account, but more important facile cleavage of the C-N bond on fluorination with reagents such as fluorine, high valency metal fluorides or halogen fluorides would be expected to occur resulting in extensive decomposition.

Halogen exchange reactions between potassium fluoride and hexachlorobenzene[42,90] or pentachloropyridine[1,89] were found to require a temperature greater than was possible in a solvent in order to affect total replacement of chlorine by fluorine in good yield. The reaction between heptachloroquinoline and potassium fluoride was therefore studied in the absence of solvent at elevated temperatures in an autoclave. The isolation of any highly fluorinated quinolines formed is also simplified by omission of the solvent, the product being simply distilled from the hot autoclave under reduced pressure. The reaction between an intimate mixture of finely ground anhydrous potassium fluoride and heptachloroquinoline was studied over a range of reaction conditions and the results are contained in table VI. Since the desired product was heptafluoroquinoline, which was expected to have a boiling-point similar to quinoline itself, only the material which distilled from the hot autoclave under reduced pressure (0·2 - 0·4 mm.) was investigated. Under these conditions it was found that heptafluoroquinoline distilled readily. The distillate invariably contained varying amounts of material which boiled off rapidly under reduced pressure (0·2 - 0·4 mm.) at room temperature. This decomposition product was not investigated. Analytical-scale v.p.c. of the product from reaction R3(Fig. 3, p. 120) showed, after recrystallisation from ethyl acetate, a single peak for pentafluorodichloroquinoline, suggesting it was possibly a single isomer, whilst two peaks were given for hexafluoromonochloroquinoline, suggesting the presence of two isomers of this compound, and the isomer with the

TABLE VI

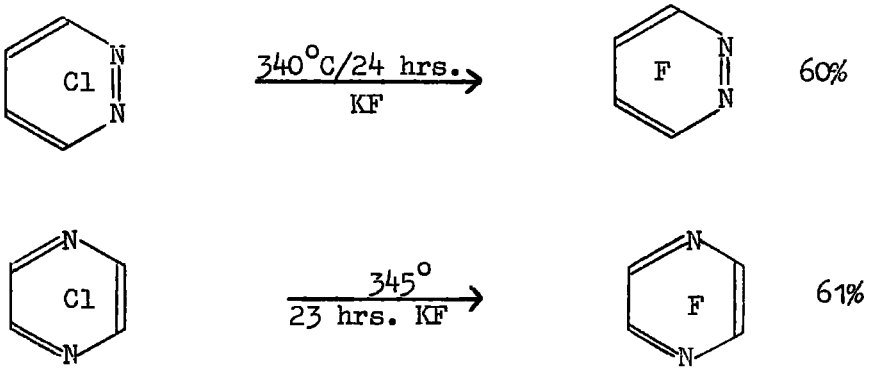
Expt.	C_9NCl_7 gm.(mole)	KF gm.(mole)	Temp. (°C)	Time (hrs.)	Product (gm.)	Composition of Product (mole-%) (% Yield in parentheses)		
						$C_9NCl_2F_5$	C_9NClF_6	C_9NF_7
R1	20·5(0·055)	61(1·05)	320	$9\frac{1}{2}$	-	-	-	-
R2	19·0(0·051)	58(1·00)	415	$7\frac{1}{2}$	-	-	-	-
R3	21·5(0·058)	61(1·05)	460	$6\frac{1}{2}$	6·0	8(2·9)	45(17·2)	47(19·0)
R4	31·0(0·083)	72·5(1·25)	470	17	18·0	-	15(11·9)	85(71·5)
R5	24·5(0·066)	68(1·17)	480	16	13·5	-	10(7·5)	90(71·4)
R6	28·5(0·077)	69·5(1·20)	490	16	16·0	-	10(7·7)	90(73·8)
R7	30·5(0·082)	72·5(1·25)	490	23	13·0	-	7·5(4·4)	92·5(57·3)
R8	20·5(0·055)	60(1·03)	530	12	9·0	-	5(3·0)	95(61·2)
R9	25·0(0·067)	68·5(1·18)	550	$20\frac{1}{2}$	8·5	-	2·5(1·2)	97·5(47·9)

longer retention time was present in smaller amount. For the reactions R4-R9 analytical-scale v.p.c. of the crude distillate (Fig. 4, p.120) showed no pentafluorodichloroquinoline to be present. Two peaks were given for hexafluoromonochloroquinoline but now the isomer with longer retention time was present in greater amount. This was separated, with difficulty, by preparative-scale v.p.c. and its sharp melting-point (89-90°C) suggested it was a single isomer. Fluorine-19 n.m.r. (page 217) showed it to be pure 8-chloro-2,3,4,5,6,7-hexafluoroquinoline within the limits of detection (> 90%). Heptafluoroquinoline, m.pt. 95-95·5°, b.pt. 205°, (756 mm.) was obtained by fractional distillation of the combined products of several reactions.

Reaction Conditions and Extent of Fluorination.

Complete exchange of chlorine by fluorine in heptachloroquinoline only occurred to any extent at temperatures greater than about 460° and at 470-490° for 16-17 hours heptafluoroquinoline was obtained in over 70% yield. By increasing the temperature or time of reaction the percentage of heptafluoroquinoline in the reaction product increased relative to the mixture of the hexafluoromonochloroquinolines but the yield decreased markedly due to increased decomposition. The conditions used in reactions R4 - R6 were therefore optimum conditions for the preparation of the fully fluorinated quinoline in high yield and using these conditions heptafluoroquinoline was consistently obtained in yields of 70% or over.

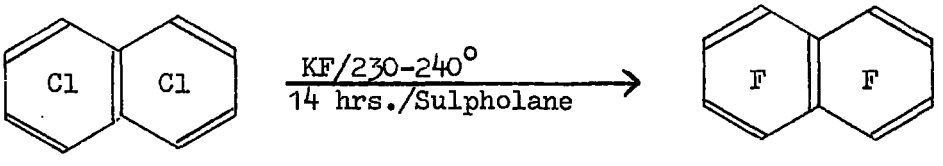
The reaction between potassium fluoride and pentachloropyridine in the absence of solvent has been studied in some detail and it was found that at 480° for 19 hours the fully fluorinated compound was formed in 66% yield,[1] hence showing the slightly greater overall reactivity of heptachloroquinoline towards potassium fluoride (cf. R5). The chlorines at the β-positions in pentachloropyridine were found to be the most resistant to replacement, only 2,4,6-trifluoro-3,5-dichloropyridine being formed at 400°C for 18 hours.[1] The greater reactivity of a chlorine α or γ to a ring nitrogen is clearly shown by the fact that complete replacement of chlorine occurs when either tetrachloro-1,2-diazine[158] or tetrachloro-1,4-diazine[158] is heated to about 340° with potassium fluoride in the absence of solvent.



Although chlorines α or γ to the ring nitrogen in the above compounds are activated towards halogen exchange, chlorine atoms β to the ring nitrogen, on the experimental evidence available, appear to be of comparable reactivity to the chlorine in hexachlorobenzene since the

latter compound undergoes complete exchange at 450-500°C. However, no specific reaction conditions were given for hexachlorobenzene and hence no really valid comparison can be made.

It was thought initially that to obtain heptafluoroquinoline from heptachloroquinoline in good yield a higher temperature than was possible using a solvent would be required. However, the recently reported[90] preparation of octafluoronaphthalene in high yield using potassium fluoride in a solvent,

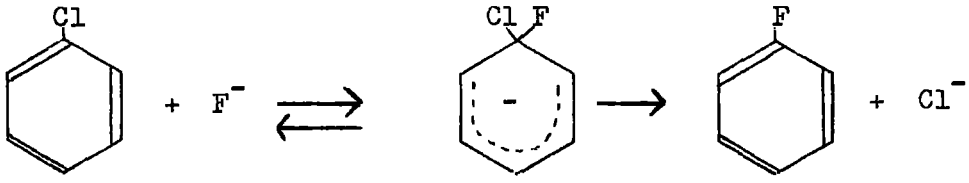


50-60%

and the fact that hexachlorobenzene gives hexafluorobenzene in only 0.4% yield under similar conditions, shows the much greater susceptibility of the bicyclic system to halogen exchange and suggests that it might have been possible to convert heptachloroquinoline to the fully fluorinated compound in high yield by reaction in a solvent.

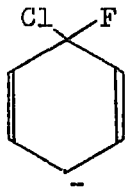
Theoretical Considerations.

The halogen exchange reaction is most likely a bimolecular nucleophilic substitution reaction involving replacement of a chloride anion by a fluoride anion, i.e.

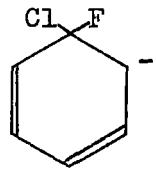


(A)

proceeding via a definite intermediate (A). This Wheland-type intermediate is considered to be a good approximation to the transition state and will be assumed to be so for the following discussion. In his paper rationalising the orientation and reactivity of nucleophilic substitution in homocyclic aromatic polyhalo compounds, Burdon[3] assumes the resonance hybrid (I) to be the main contributor to the intermediate (A), with the hybrid (II) of secondary importance.



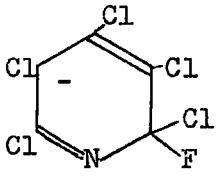
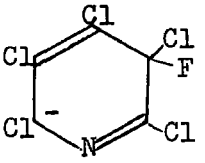
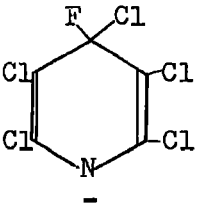
I



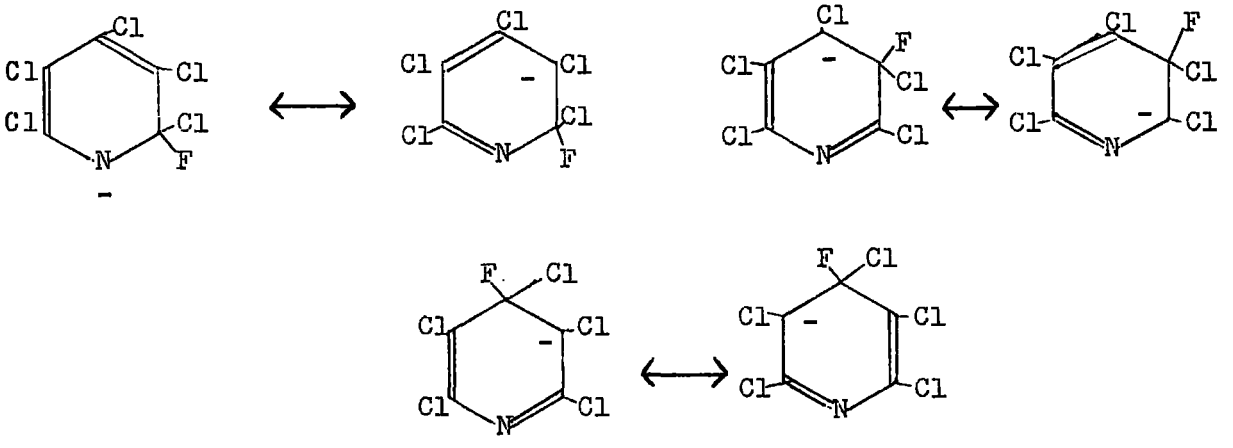
II

As he points out calculations of charge density distributions in such intermediates support this assumption, and many workers have rationalised observed orientations in nucleophilic aromatic substitution reactions on the basis that p-quinonoid structures are more stable (and hence contribute more to the transition state) than o-quinonoid structures.[32,159,160] He then considers the effect of any substituents present on the stability of hybrids of type I for all possible positions of attack by a

nucleophile, and the one which is the most stable will be the preferred position of substitution, since for this position the activation energy will be lowest. This assumes that the entropy of activation is the same for all positions of attack and this assumption applies to the discussion below. The halogens destabilise a negative charge on the carbon atom to which they are attached in the order F > Cl > Br > I. The negative charge in question is in a π-electron system and the destabilisation arises from Coulombic repulsion between the p-electrons on the halogen, which have π-symmetry, and the π-electrons on the neighbouring carbon atom.[161] Such an effect is termed an I_π effect. This approach neglects any possible interaction with the π-electron system to form an extended π-system, and considers that only the change in π-electron energy is important in determining the activation energy. Using these assumptions Burdon was able to rationalise the orientations observed in a great number of nucleophilic reactions of homocyclic aromatic polyhalo compounds, but it was not applied to any heterocyclic polyhalo compounds. As regards nitrogen-containing heterocycles, the ring nitrogen, by virtue of its high electron affinity, will stabilise a negative charge placed upon it. Applying the above rationalisation to the reaction between potassium fluoride and pentachloropyridine, one obtains the following resonance hybrids as the main contributors to the transition states for attack at the α-, β- and γ-positions

with the conclusion that preferential attack will occur at the γ-position. Consideration of the remaining resonance hybrids which contribute to the transition states for attack at the α-, β- and γ-positions



reveal how for attack at the α-position, but not the β-position, the negative charge can be localised onto the nitrogen. Thus the expected order of decreasing ease of replacement is γ > α > β. The order found[162] is α > γ > β. A similar rationalisation when applied to pentafluoropyridine predicts the order of decreasing ease of nucleophilic replacement as γ > α > β which is the observed order.[163] Steric effects are more important for polychloro compounds and possibly the observed

order for pentachloropyridine is a result of greater steric hindrance at the γ-position as compared with the α-position. The low susceptibility towards nucleophilic attack of the β-position reflects the great stabilisation resulting from it being possible to localise the negative charge in the transition state onto the nitrogen, and the greater ease, compared with pentachloropyridine, with which tetrachloro-1,2- and tetrachloro-1,4-diazine undergo total exchange with potassium fluoride can be attributed to such stabilisation.

As mentioned previously the reaction of heptachloroquinoline and potassium fluoride was directed towards the preparation of the fully fluorinated compound and consequently the lower fluorinated compounds were not investigated to any extent, only the isomer of hexafluoromonochloroquinoline with longer retention time being isolated. Consequently a discussion of the course of the reaction can only be speculative. As regards overall reactivity heptachloroquinoline was slightly more reactive than pentachloropyridine but the difference was by no means as marked as that between octachloronaphthalene and hexachlorobenzene. The greater reactivity of the bicyclic systems can be attributed to a greater possible delocalisation of the negative charge in the transition state, with resultant greater stabilisation, than for the monocyclic systems.

Orientation of Nucleophilic Substitution.

In the subsequent discussion of the orientation of nucleophilic

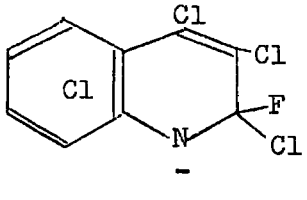
substitution of chlorine in heptachloroquinoline by fluoride anion,

(a) those resonance hybrids in which the negative charge can be localised onto the nitrogen will be assumed to contribute significantly to the transition state whether the hybrid has a para-quinonoid form or not.

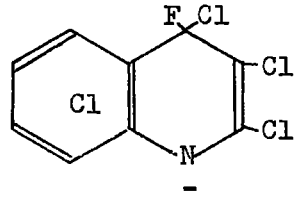
(b) Such resonance hybrids will be more stabilised than those in which the negative charge is localised onto a carbon bearing a halogen or a tertiary carbon atom.

(c) Where localisation of the negative charge onto the ring nitrogen is not possible, those resonance hybrids having a para-quinonoid form and which involve rearrangement of the π-electrons of one ring only will be assumed to contribute most to the transition state for attack at any such position.

For attack at the 2- or 4-positions the resonance hybrids III and IV will be the main contributors to the transition state

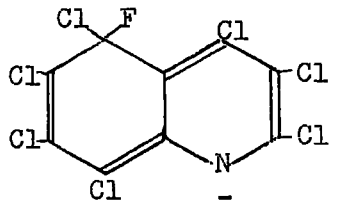


III

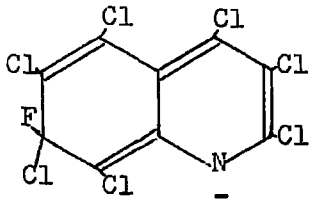


IV

For attack at the 3-, 6- and 8-positions localisation of the negative charge onto nitrogen is not possible and hence the transition states for attack at these positions will be less stable. For attack at the 5- and 7-positions localisation of the negative charge onto nitrogen is possible (V and VI)



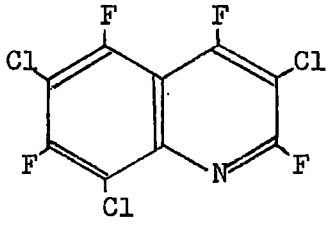
V



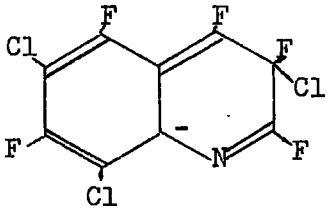
VI

but involves rearrangement of the π-electrons of both rings with subsequent greater loss of aromatic resonance stabilisation than for III or IV. Hence V and VI are of higher energy than III and IV and thus the 2 and 4-positions will be the most reactive towards nucleophilic attack. Consideration of the relative stabilities of ortho- and para-quinonoid structures would suggest that preferential attack would occur at position 4, but bearing in mind the discrepancy between the predicted and observed sites of substitution in pentachloropyridine a similar effect might operate in the quinoline case. Hence the relative reactivity of the 2- and 4-positions is not obvious, but it is clear that these positions will be the most reactive so that 2,4-difluoro-3,5,6,7,8-pentachloroquinoline (A) will be formed. The significant contribution of hybrids equivalent to V and VI for attack at the 5- and 7-positions in (A) will probably result in attack occurring at these positions before at the 3-, 6-, or 8-positions. The hybrid equivalent to VI, with its para quinonoid structure, is expected to be more stable than that equivalent to V so that substitution will occur at position

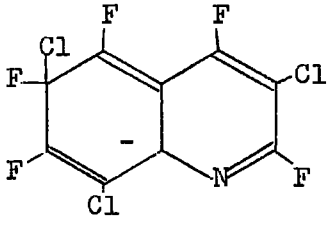
7 in preference to position 5. The tetrafluorotrichloroquinoline formed will therefore probably have the structure (B)



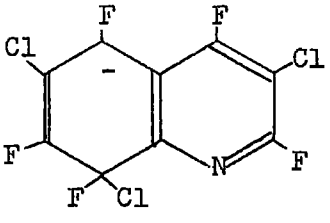
(B)



VII



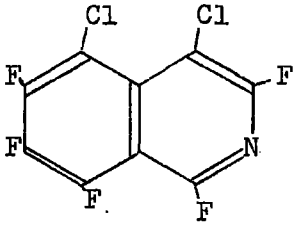
VIII



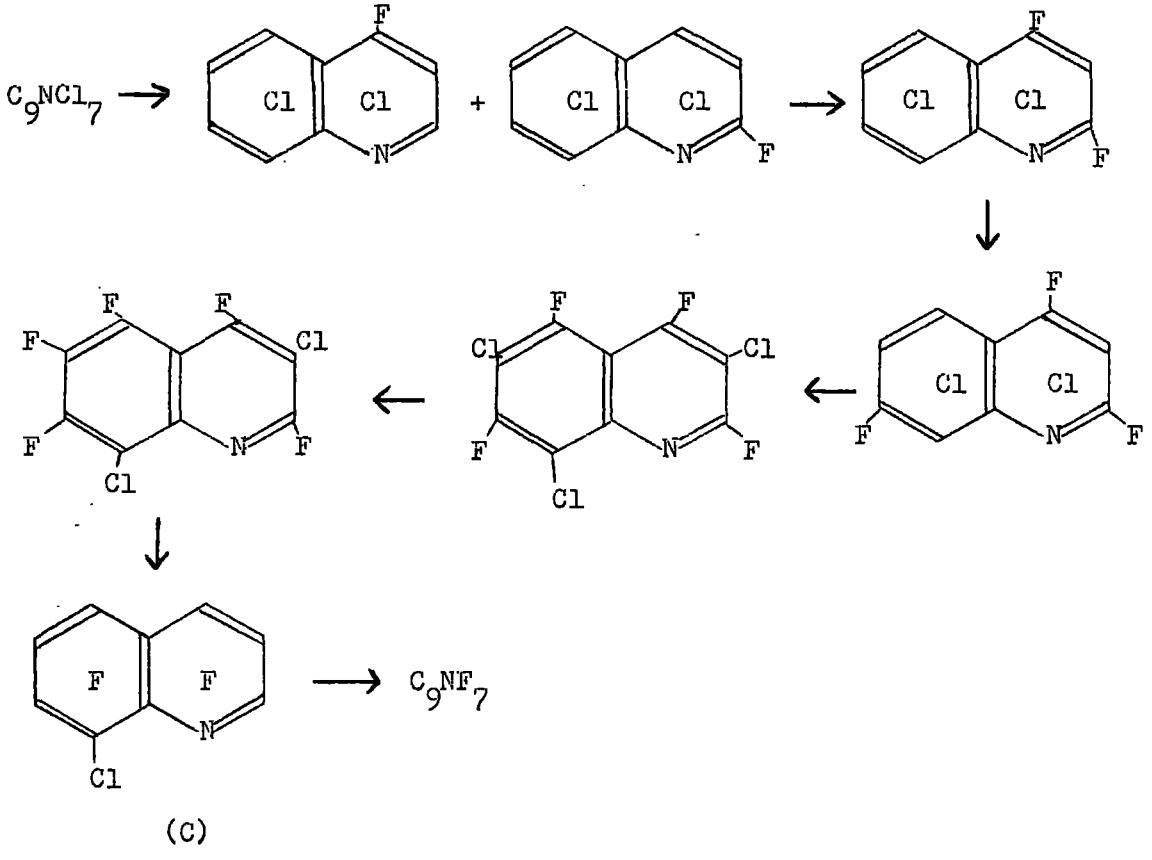
IX

As stated in (c) the resonance hybrids VII - IX are considered to be the main contributors to the transition states for attack at the 3-, 6- and 8-positions respectively in (B). The negative charge will be destabilised most in IX since a fluorine is bound to the carbon bearing the negative charge, whilst in VII and VIII the negative charge resides on a tertiary carbon. Thus attack at position 8 will occur less readily than for positions 3- and 6-, which from a consideration of VII and VIII appear to be of similar reactivity. In the reaction between heptachloroisoquinoline and potassium fluoride a single isomer of hexafluoromonochloroisoquinoline is formed,[156] this being the one with

chlorine at position 4.[164] Application of the above rationalisation to the reaction between potassium fluoride and heptachloroisoquinoline leads to a pentafluorodichloroquinoline having the structure shown.



Why the chlorine at position 5 is replaced in preference to that at position 4 is not clear, but by analogy with this observation one might expect substitution to occur at position 6 before position 3 in (B). The speculative scheme proposed is therefore



In fact two isomers of hexafluoromonochloroquinoline were formed, the major one being (C) in all cases except for reaction R3 (Table VI). Only for this reaction was the product recrystallised prior to analytical-scale v.p.c. analysis and it seems likely that this is the cause of the apparent anomaly.

CHAPTER 3

EXPERIMENTAL WORK

EXPERIMENTAL WORK

PREPARATION OF HIGHLY FLUORINATED QUINOLINES.

Quinoline was exhaustively chlorinated first with the mixture of aluminium trichloride, sulphur monochloride and sulphuryl chloride, secondly with phosphorus pentachloride and finally successful conversion to heptachloroquinoline, in high yield, was achieved by a two-stage process involving the chlorination of a quinoline-aluminium trichloride complex with elemental chlorine and then further chlorination of the mixture of tetra- and pentachloroquinolines so formed with phosphorus pentachloride. Fluorination of heptachloroquinoline by halogen exchange with potassium fluoride has been developed to give heptafluoroquinoline in high yield.

Infra-red (i.r.) spectra were recorded using Grubb-Parsons, type G.S.2A or Spectromaster, spectrometers. Molecular weights were determined using a Mechrolab vapour pressure osmometer. Analytical-scale vapour phase chromatography (v.p.c.) was performed on a Perkin-Elmer 'Fractometer' Model 451 and preparative scale vapour phase chromatography on an Aerograph "Autoprep" A-700 instrument.

CHLORINATION OF QUINOLINE

THE AUTOCLAVES.

Two autoclaves were used, one of 500 ml. capacity (Fig. 2) and a larger one of 1½ litre capacity (Fig. 1).

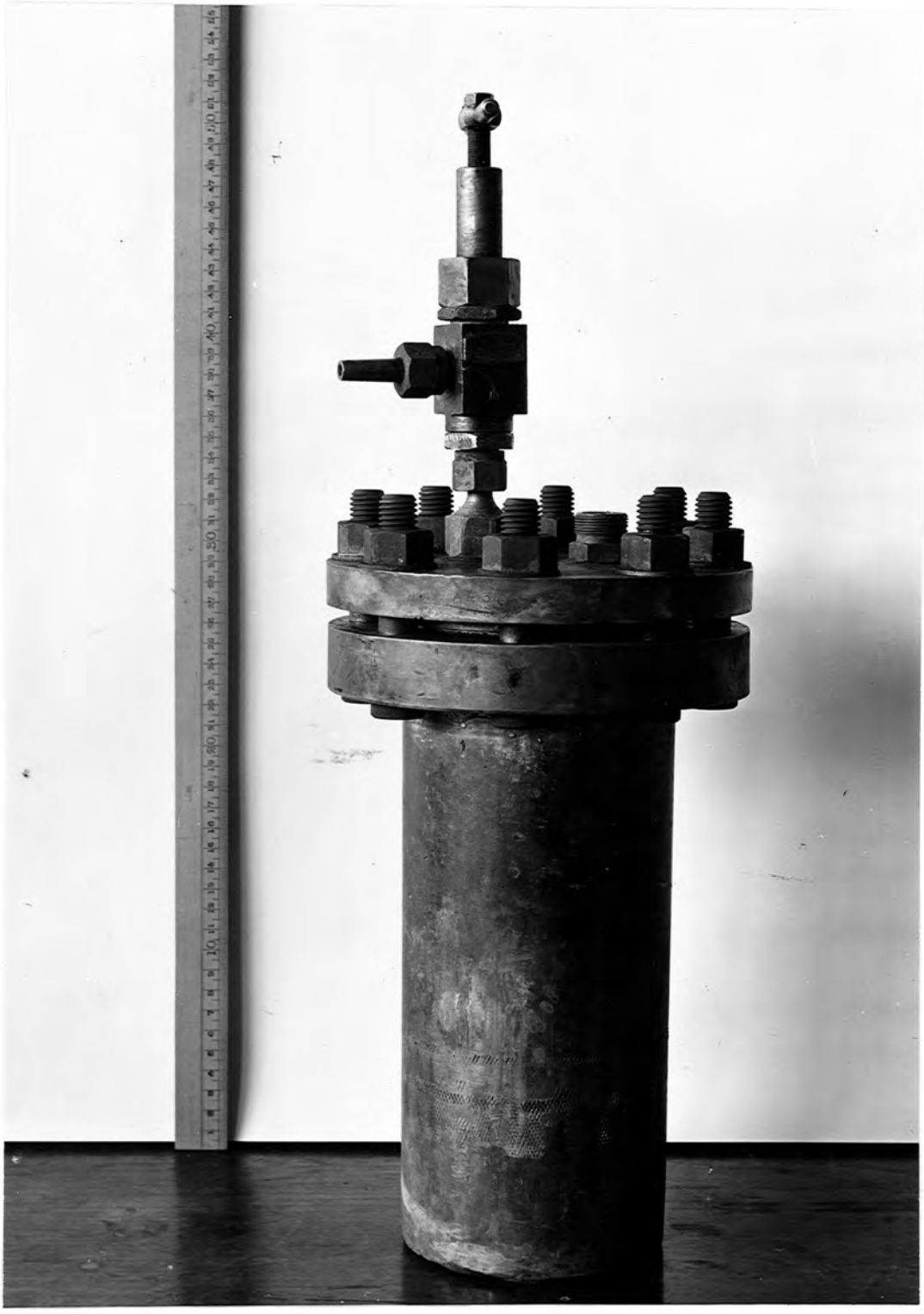


Fig. 1
Chlorination Autoclave (1½ litre)

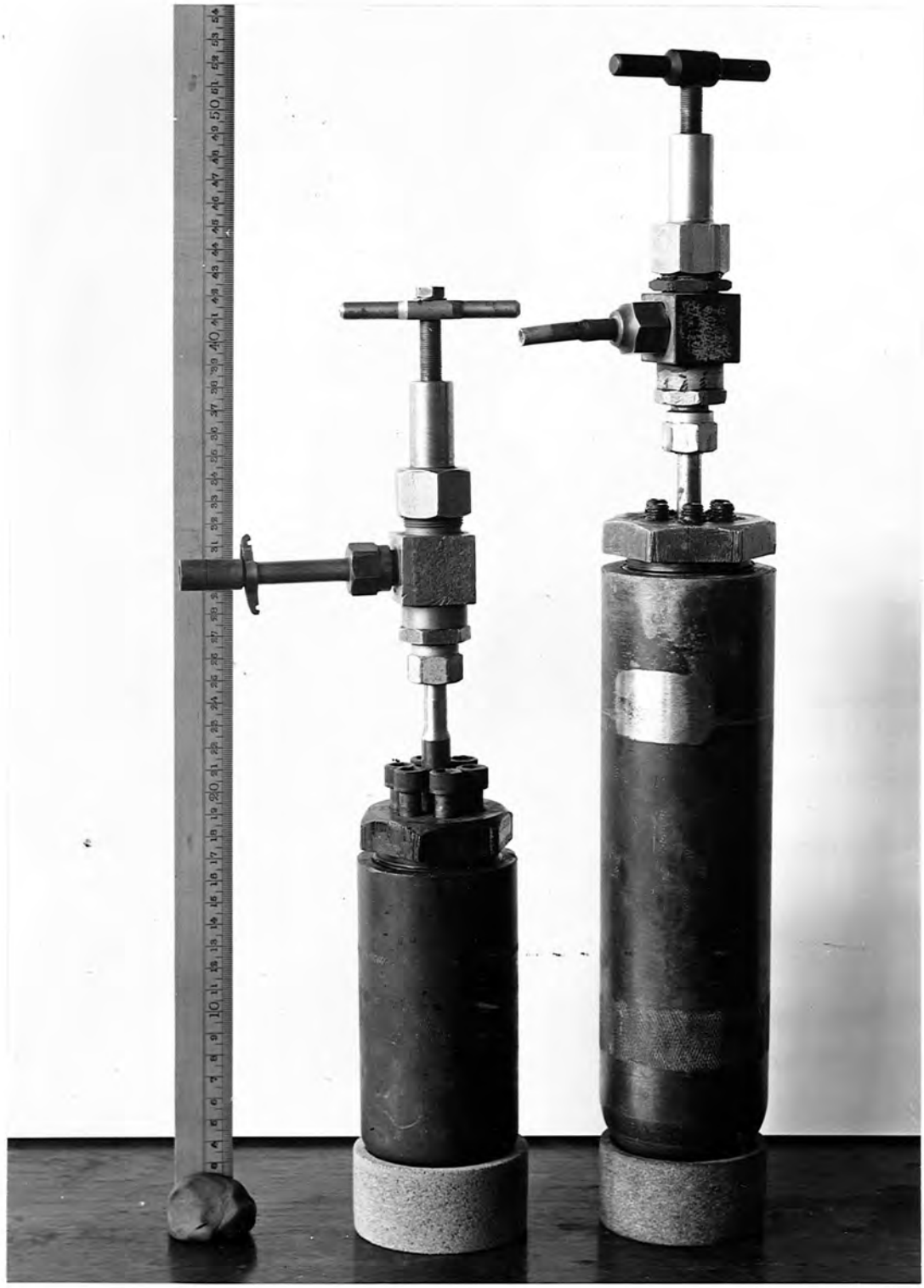


Fig. 2.
Left: Fluorination Autoclave (120 ml.)
Right: Chlorination Autoclave (500 ml.)

The body of the smaller high pressure reaction vessel was constructed by drilling out a solid piece of stainless steel. The autoclave head was fitted with a needle valve and screwed into the body of the vessel to seal by a knife edge on the autoclave head against an aluminium gasket. Final tightening of the seal was effected by Allen screws in the head. The autoclave was placed in a bath of "Lissapol N.X." preheated by an electric immersion heater. The temperature was controlled by means of a precalibrated variable transformer, the temperature being maintained by thermal equilibrium.

The larger autoclave was also constructed of stainless steel with the base and flange welded to the cylindrical body of the vessel. The stainless steel autoclave head was fitted with a needle valve and thermocouple well and was sealed to the flange on the top of the autoclave by a corrugated copper gasket and held in position by steel bolts. Inside the vessel was fitted a nickel liner to prevent corrosion of the inner stainless steel wall. The autoclave was heated by a 9' long, 2 k.watt heating element coiled so that the body of the autoclave fitted snuggly inside. The temperature was controlled by means of a pre-calibrated variable transformer. Initially the full voltage was applied until the temperature, as measured by a thermocouple placed inside the central well, was approximately $30^{\circ}C$ below the required temperature and the transformer was then set to the value required for the desired temperature, the temperature being maintained by thermal equilibrium.

Before a reaction both autoclaves were tested to ensure they were leak proof by charging with solid carbon dioxide and sealing. Immersion in a water bath made obvious any leaks. They were then cleaned and dried at 150-200°C for 2-3 hours before use.

A. Chlorination with Sulphuryl Chloride in the presence of Aluminium Trichloride and Sulphur Monochloride.

The quinoline used was technical grade, made by B.D.H. Ltd., and was dried by heating with potassium hydroxide pellets on a steam bath for 3-4 hours followed by vacuum distillation. It was stored under dry nitrogen in the dark until required for reaction. Pyridine, obtained from May and Baker Ltd., was similarly dried. Aluminium trichloride and sulphur monochloride were supplied by Hopkin and Williams Ltd. and sulphuryl chloride was obtained from B.D.H. Ltd. They were vacuum sublimed and distilled respectively and stored under dry nitrogen until required.

Exploratory reactions with Pyridine.

Initially these were carried out at (i) the reflux temperature of the chlorinating mixture and later (ii) at higher temperatures in an autoclave.

(i) In a typical reaction (Table I, R.1), sulphuryl chloride (340 gm., 2·52 moles) was added under dry nitrogen to aluminium chloride (5 gm., 0·037 moles) contained in a dry, nitrogen-flushed 500 ml., 3-necked flask

fitted with a magnetic stirrer and a condenser equipped with a calcium chloride drying tube. To the orange solution formed sulphur monochloride (10 gm., 0·074 moles) was added under dry nitrogen when a white precipitate was formed. Pyridine (19·8 gm., 0·25 moles) was added over 30 minutes to the stirred suspension at room-temperature. The solution warmed slightly and the suspension went into solution, solution being complete after approximately 5 gm. of pyridine had been added. The solution was now red and was refluxed (bath temperature 70°C) for a total of 16 hours. The volume of sulphuryl chloride diminished steadily and was maintained at 100 ml. by periodic addition of fresh reagent, a total of 170 gm. (1·26 moles) being added. The bulk of the excess sulphuryl chloride was distilled off, water (100 ml.) added to the residue and the acidic mixture steam distilled. The distillate was extracted with methylene chloride, the extracts dried ($MgSO_4$) and the solvent distilled to leave a white solid (0·5 g.). Its composition was shown by analytical-scale v.p.c. (silicone grease at 175°C) to be $C_5H_3Cl_2N$, 20(0·27); C_5HCl_4N, 80(0·75) mole-%. The figures in parentheses are percentage yields.

(ii) In a typical reaction (Table I, R.3) pyridine (27 gm., 0·342 moles) was added to the suspension produced from aluminium trichloride (7·6 gm., 0·057 moles), sulphuryl chloride (275 g., 2·037 moles) and sulphur monochloride (15·1 g., 0·111 moles) as under (i). The red solution was transferred under nitrogen to the dry, nitrogen-flushed 500 ml. autoclave,

the autoclave sealed and heated to 100-105°C for 24 hours. After cooling to room-temperature the gases generated during the reaction were released before the autoclave was opened. The contents of the autoclave were washed out with carbon tetrachloride, the excess sulphuryl chloride and solvent distilled, water (100 ml.) added to the residue and the acidic mixture steam distilled. The distillate was treated as under (i) to give a white solid (13 g.) consisting of $C_5H_3Cl_2N$, 5(1·3); C_5HCl_4N, 95(16·6) mole-%.

Reactions with Quinoline.

Reactions were carried out in an autoclave at temperatures of 100°C and 150°C (Table II, R1 and R2) and the reaction worked up by procedure (a) to give an overall characterisation of the product. The reaction at 205-215°C was worked up by procedure (b) which was directed towards the isolation of any highly chlorinated quinolines formed.

Procedure (a).

In a typical reaction (Table II, R1) quinoline (36 gm., 0·28 moles) was added to the suspension produced from aluminium trichloride (20 gm., 0·16 moles), sulphuryl chloride (560 gm., 4·15 moles) and sulphur monochloride (39·2 gm., 0·29 mole) as under (i). The red solution formed was transferred under nitrogen to the dry, nitrogen-flushed 1½ litre autoclave, the autoclave sealed and heated to 100°C for 24 hours. After cooling to room-temperature the autoclave was vented and then opened. The contents of the autoclave were washed out with carbon tetrachloride,

the excess sulphuryl chloride and solvent distilled, water (100 ml.) added to the residue and the aqueous layer made alkaline with sodium bicarbonate. The alkaline mixture was steam distilled, the distillate extracted with methylene chloride, the extracts dried ($MgSO_4$), the solvent distilled and the residue vacuum distilled to give quinoline (24 g.), identified by analytical v.p.c. and i.r. spectroscopy, and a white solid (5 g.) m.pt. 82-110°C [Found: C, 47·7; H, 2·3; Cl, 41·1. $C_9NH_5Cl_2$ requires: C, 54·5; H, 2·5; Cl, 35·8. $C_9NH_4Cl_3$ requires C, 46·5; H, 1·7; Cl, 45·8%]. The insoluble material in the distillation pot was filtered off and vacuum dried at room-temperature. Vacuum sublimation (up to 135°C/0·01 mm.) slowly gave a white solid (1·9 g.) m.pt. 115-142°C. [Found: C, 38·5; H, 1·2; Cl, 57·1. $C_9NH_3Cl_4$ requires C, 40·5; H, 1·1; Cl, 53·1. $C_9NH_2Cl_5$ requires: C, 35·8; H, 0·7; Cl, 58·8%]. Further vacuum sublimation (up to 205°C/0·01 mm.) gave a negligible amount of a yellow solid.

Procedure (b).

Quinoline (32 gm., 0·25 mole) was added to the chlorinating mixture produced from aluminium trichloride (10·4 gm., 0·08 mole), sulphur monochloride (20·9 gm., 0·15 mole) and sulphuryl chloride (340 gm., 2·52 mole) and the resultant red solution transferred in the usual way to the 500 ml. autoclave which was heated to 205-215°C for 90 hours. After cooling to room-temperature the gases formed were vented off, the autoclave opened and the contents added to ice-water. The brown

precipitate was filtered off, washed with methanol (5 x 100 ml.) at room-temperature and vacuum dried at room-temperature to leave a yellow-brown solid (79 gm.). Fractional Soxhlet extraction with methanol or methylene dichloride, or recrystallisation from ortho-xylene failed to effect any significant purification. A sample (10 gm.) of the crude reaction product was triturated with hot (50-60°C) methanol (5 x 100 ml.) to leave a yellow solid (approx. 5 g.) which was dissolved in acetone, boiled with decolourising charcoal and recrystallised from acetone to yield a pale yellow solid (2·6 g.). This was decolourised by boiling three times with charcoal in iso-propanol and recrystallised from iso-propanol to yield a white solid (0·9 gm.) m.pt. 145-152°C [Found: C, 29·6; Cl, 66·6; M, 376 ± 10. C_9NCl_7 requires C, 29·2; Cl, 67·05%; M, 370·1]. Its melting-range and analysis suggest the presence of a small amount of hexachloroquinoline and a pure sample of heptachloroquinoline prepared later (page 115) melted 155-157°C. The yield, based upon the above sample being pure heptachloroquinoline, is 7·7%.

B. Chlorination with Phosphorus Pentachloride.

The phosphorus pentachloride used was technical grade supplied by Albright and Wilson Ltd., and all reactions were carried out in the 1½ litre autoclave. Quinoline was reacted with phosphorus pentachloride at 285°C and 250-260°C and the mixture of highly chlorinated quinolines thus obtained further reacted with phosphorus pentachloride.

Reaction at 285°C (Table III, R1).

The autoclave charged with phosphorus pentachloride (1000 gm., 4·81 moles) and quinoline (53 gm., 0·42 moles) was sealed, without prior evacuation, and heated to 285°C for 50 hours. After cooling to room-temperature the hydrogen chloride formed was released before the autoclave was opened. The dark brown phosphorus trichloride was poured off and the solid remaining in the autoclave added slowly to ice-water. The insoluble solid was filtered off and vacuum dried at room-temperature to give a black, carbonaceous solid (132·5 g.). Attempted purification by recrystallisation from chloroform or 60-80 petroleum ether, or Soxhlet extraction with methylene dichloride was unsuccessful but Soxhlet extraction with methanol afforded a partial purification. Continuous extraction for a fortnight gave, after evaporation of the solvent, a brown solid (61 g.) but the bulk was non-extractable. A sample (10 g.) of the methanol-extracted material was decolourised by boiling three times with charcoal in methanol and recrystallisation from methanol gave a white solid (3·5 g.) m.pt. 156-172°C. [Found: C, 31·3; Cl, 65·4; M, 356·9 ± 10. C_9NCl_7 requires C, 29·2; Cl, 67·05; M, 370·1. C_9NCl_6H requires: C, 32·15; Cl, 63·35%; M, 335·6]. The yield, based upon the above material being heptachloroquinoline, is 14% and based on hexachloroquinoline is 15·5%.

Reaction at 250-260°C [Table III, R2]

The autoclave was charged with phosphorus pentachloride (1500 gm.,

7·2 mole) and quinoline (63·5 gm., 0·49 mole), the head bolted on and the vessel evacuated (0·25 mm.) via the needle valve before being heated to 250-260°C for 52 hours. After cooling to room-temperature, the hydrogen chloride was released, the autoclave opened and the phosphorus trichloride poured off. The autoclave contents were added slowly to ice-water and the insoluble material was filtered off and washed with methanol at room-temperature to leave a brown solid (120 g.). Attempted purification by recrystallisation from a number of solvents (methanol, 60-80 pet. ether, benzene) was unsuccessful. A sample (10 g.) very slowly sublimed at reduced pressure (135-150°C/0·05 mm.) to give a white solid (2·9 g.) m.pt. 137-150°C. [Found: C, 30·6; Cl, 66·5%; M, 363·4 ± 10]. This mixture of heptachloro- and hexachloroquinolines corresponds to a yield of 19·3%, based on heptachloroquinoline, and 22·1%, based upon hexachloroquinoline.

Reaction of a mixture of highly chlorinated quinolines with Phosphorus Pentachloride.

53 gm. of the crude product from the above reaction (Table III, R2) was heated with phosphorus pentachloride (1000 gm., 4·81 moles) at 235-245°C for 80 hours in the evacuated (0·15 mm.) autoclave. The work-up procedure was analogous to that used for the reaction at 250-260°C above. Trituration with methanol gave a yellow-brown solid (50 g.) and vacuum sublimation of a 10 gm. sample gave, at 130°C/0·01 mm., a pale yellow solid (4·5 g.) m.pt. 148-152°C. Three recrystallisations from

ethyl acetate gave heptachloroquinoline (1·9 g.) as a white solid m.pt. 155-157°C [Found: C, 29·3; Cl, 66·6%] (I.R. spectrum No. 1, page 257)

The overall yield of heptachloroquinoline for the two stages from quinoline is 12·5%.

C. Direct chlorination in the presence of Aluminium Trichloride.

Initially the aluminium trichloride was vacuum sublimed before use but it was later found that the technical grade supplied by Hopkin and Williams Ltd. was perfectly adequate. Cylinders of chlorine were obtained from I.C.I. Ltd. (Runcorn).

Reaction Procedure.

In a typical reaction (Table IV, R2) quinoline (116 gm., 0·90 moles) was added slowly under dry nitrogen and at room-temperature to aluminium trichloride (310 gm., 2·32 moles) contained in a dry nitrogen-flushed 750 ml. flange-head flask fitted with a gas inlet tube, a "Teflon"-bladed stirrer, and an air condenser connected to an outlet gas bubbler containing concentrated sulphuric acid. The finely ground aluminium trichloride was vigorously stirred during the addition of quinoline, which was very exothermic, to prevent local over-heating and the black complex formed became molten, at about 80°C, due to the heat of reaction. With the well-stirred complex heated to 110°C, chlorine (1,160 gm., 16·36 moles) dried by passage through concentrated sulphuric acid was passed into the molten mixture, the inlet tube dipping just below the level of the complex. The temperature was gradually raised to 130°C over 24 hours during which

time about half of the chlorine had been used. The temperature was then quickly raised to 170°C and the remaining chlorine passed into the molten mixture over 24 hours whilst the temperature was slowly raised to 190°C. The black viscous solid formed on cooling was decomposed with ice, the precipitate collected, dissolved in boiling benzene and then the hot solution was filtered to remove the insoluble material (69 gm.). The solution was dried by azeotropic distillation of the benzene, and on concentrating the solution and cooling a white solid (210 gm.) was obtained, whose analysis showed it to be a mixture of tetrachloro- and pentachloro-quinoline with the pentachloro compound present in greater amount. [Found: C, 36·5; H, 0·8; Cl, 57·6. $C_9H_3Cl_4N$ requires C, 40·46; H, 1·13; Cl, 53·1. $C_9H_2Cl_5N$ requires: C, 35·8; H, 0·67; Cl, 58·8%]. Further recrystallisation (benzene) of a small sample of the bulk product gave a pentachloroquinoline, m.pt. 204-206°C, [Found: C, 36·1; H, 0·7; Cl, 58·4. $C_9H_2Cl_5N$ requires C, 35·8; H, 0·67; Cl, 58·8%]. (I.R. spectrum No. 2, page 257). The yield, calculated as pentachloroquinoline, is 79%. The brown insoluble material (69 gm.) did not melt below 360°C. It was presumably polymeric and was not further investigated.

The reaction mixture attacks steel very readily and in one reaction (Table IV, R4) in which a steel-bladed stirrer was used extensive corrosion of the metal occurred and the steel blade was almost entirely eaten away.

Chlorination of Tetrachloro- and Pentachloro-quinoline with Phosphorus Pentachloride.

In a typical experiment (Table V, R6) the 1½ litre autoclave was charged with phosphorus pentachloride (1,054 gm., 5·05 moles) and essentially tetrachloroquinoline (95·5 gm., 0·36 moles), the chloroquinoline being placed on top of the phosphorus pentachloride. The evacuated (0·2 mm.) autoclave was heated from 20° to 315° over 2 hours, maintained at 315-330° for a further three hours and allowed to cool to room-temperature. The hydrogen chloride formed was vented off, the phosphorus trichloride poured off and the solid remaining added slowly to ice and water. The white insoluble material was filtered off, dried on the filter and recrystallised from benzene to give heptachloroquinoline (103 gm., 78%) m.pt. 155-157° [Found: C, 29·1; Cl, 66·8. C_9NCl_7 requires: C, 29·2; Cl, 67·05%]. Its i.r. spectrum was identical with a previously prepared sample (i.r. spectrum No. 1, page 257).

FLUORINATION OF HEPTACHLOROQUINOLINE.

The potassium fluoride used was reagent grade, supplied by B.D.H. Ltd., and was dried by heating in a nickel beaker over a bunsen burner for several hours followed by storage in an oven at 150° until required. Heptachloroquinoline was vacuum dried at room-temperature prior to use.

The Autoclave.

The autoclave (Fig. 2) was a high pressure reaction vessel of 120 ml. capacity. It was of similar construction to the 500 ml. autoclave

(Fig. 2) and was similarly tested and dried before a reaction. In addition it had a thermocouple well brazed onto the lower end of the body of the vessel, and the spout was fitted with a copper B.10 socket which provided a vacuum tight seal with a glass B.10 cone, thus eliminating the need for a pressure tubing connection between the autoclave and the trapping system. This was desirable because the highly fluorinated quinolines tended to solidify and block the connection. The copper-glass joint could be directly warmed with a bunsen to prevent any such solidification. The autoclave was heated electrically via an 8 amp. variable transformer set at a precalibrated value and the temperature, measured by a thermocouple placed in the well on the side of the autoclave, was maintained by thermal equilibrium.

Reaction Procedure.

a) In an earlier reaction (Table VI, R3) the autoclave (120 ml.) was charged with an intimate mixture of heptachloroquinoline (21·5 gm., 0·058 mole) and anhydrous potassium fluoride (61 gm., 1·05 moles), evacuated to 0·5 mm. and heated at 460° for 6½ hours. The product (6·0 gm.) which distilled from the hot autoclave under reduced pressure (0·5 mm.) was recrystallised from ethyl acetate to give a white solid m.pt. 71-77° [Found: C, 40·5; Cl, 9·4; F, 43·4. C_9NF_7 requires: C, 42·4; F, 52·1. C_9NF_6Cl requires: C, 39·8; Cl, 13·05; F, 42·0. $C_9NF_5Cl_2$ requires: C, 37·5; Cl, 24·6; F, 33·0%]. The analytical data and analytical-scale v.p.c. analysis (Fig. 3) showed the molar-%

composition of the product to be $C_9NF_5Cl_2$, 8(2·9); C_9NF_6Cl, 45(17·2); C_9NF_7, 47(19·0). The figures in parentheses represent percentage yields.

b) In a typical experiment (Table VI, R4) for the preparation of heptafluoroquinoline in high yield, the autoclave charged with an intimate mixture of heptachloroquinoline (31 gm., 0·083 mole) and potassium fluoride (72·5 gm., 1·25 mole) was evacuated and heated to 470° for 17 hours. The product (18·0 gm.) was distilled from the hot autoclave under reduced pressure and shown, by analytical-scale v.p.c. (Fig. 4) to comprise C_9NF_6Cl, 15(11·9); C_9NF_7, 85(71·5) mole-%. The figures in parentheses are percentage yields. The products of several reactions were combined and distilled through a short Vigreux column, or a concentric tube column for larger amounts, to give 2 fractions:-

(i) Heptafluoroquinoline b.pt. 205° (756 mm.), m.pt. 95-95·5° [Found: C, 42·2; F, 52·2. C_9NF_7 requires: F, 52·1; C, 42·4%]. I.R. spectrum No.3. The fluorine-19 n.m.r. spectrum is discussed on pages 217 to 244.

(ii) Mixture of two isomeric monochlorohexafluoroquinolines b.pt. 231-239° (756 mm.) [Found: C, 40·0; Cl, 13·0; F, 41·5. C_9NF_6Cl requires C, 39·8; Cl, 13·05; F, 42·0%]. The isomers were present in the ratio of 4:1 and the more abundant one was separated with difficulty by preparative-scale v.p.c. (silicone grease at 155°) and gave [Found: C, 39·6; Cl, 13·1; F, 41·5%] m.pt. 89-90°C. I.R. spectrum No. 4, page 258. Its structure was assigned on the basis of its fluorine-19 n.m.r. spectrum to be 8-chlorohexafluoroquinoline (see page 217).

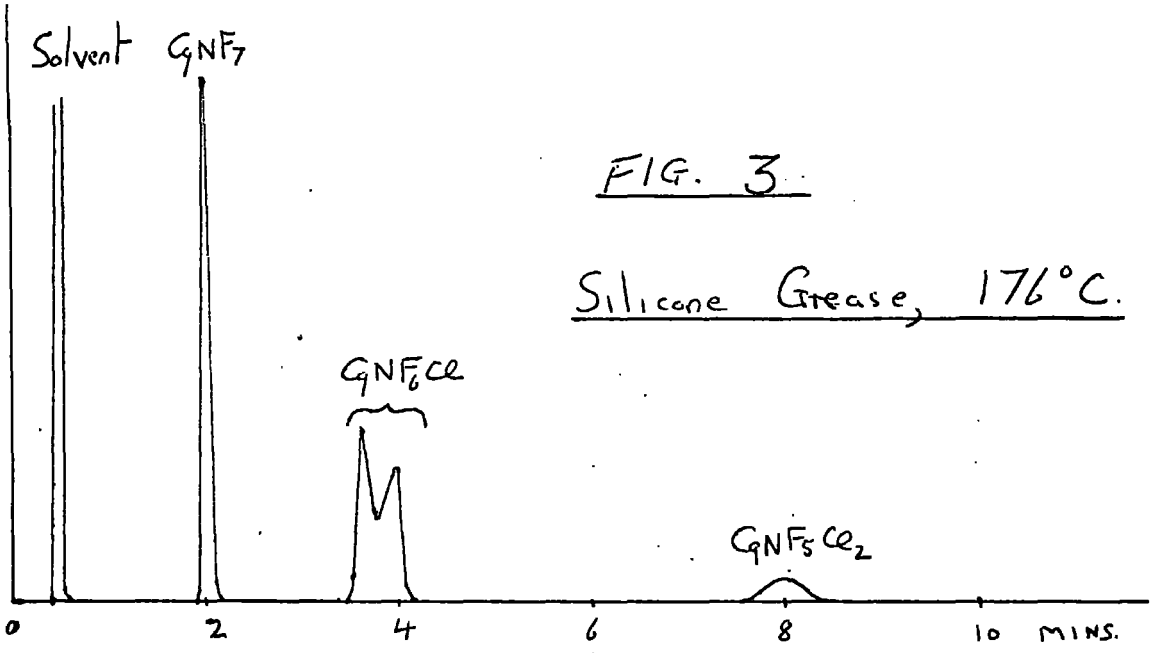


FIG. 3.

Silicone Grease, 176°C.

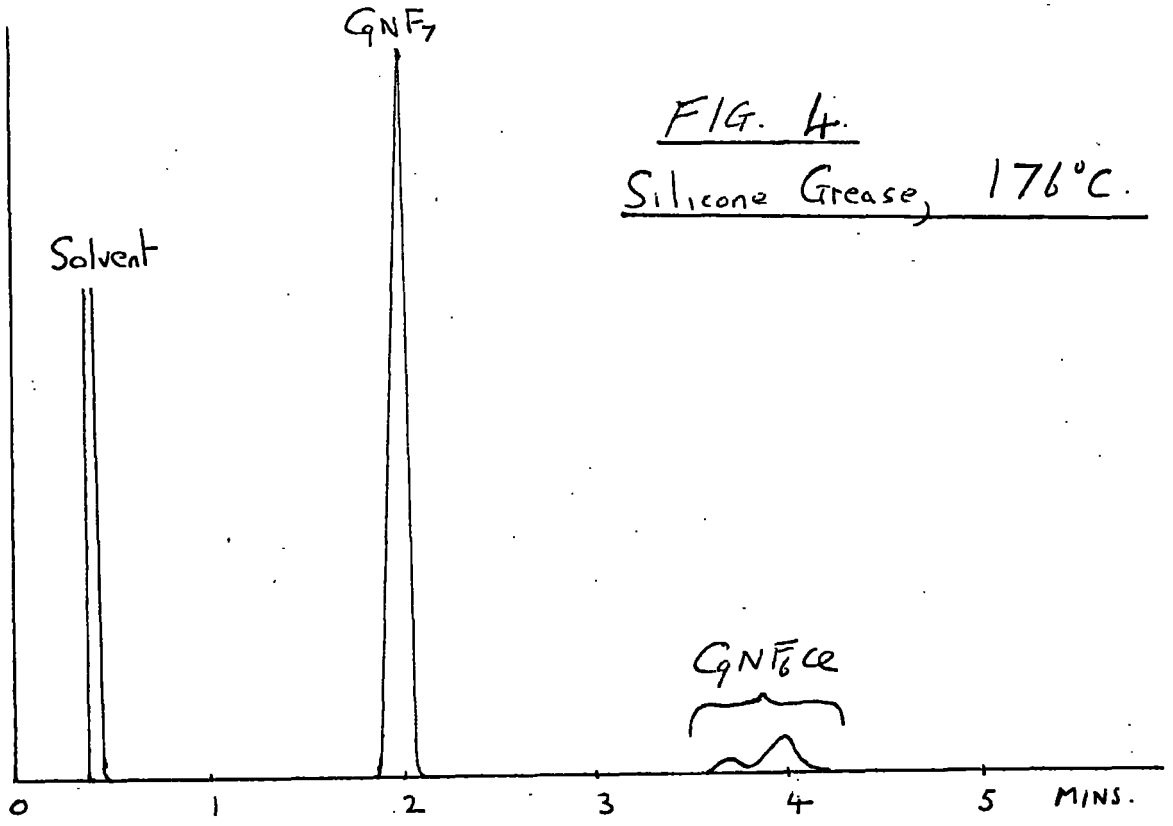


FIG. 4.

Silicone Grease, 176°C.

PART II

SOME REACTIONS OF HIGHLY FLUORINATED QUINOLINES

CHAPTER 4

INTRODUCTION

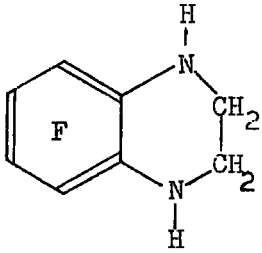
Introduction.

The characteristic reaction of highly fluorinated aromatic compounds is nucleophilic replacement of fluoride ion in contrast to the electrophilic substitution of hydrogen in the parent hydrocarbon. The reactions of highly fluorinated homocyclic aromatic compounds, especially hexafluorobenzene and mono-substituted pentafluorobenzenes, with nucleophilic reagents have been thoroughly investigated but it was not until relatively recently that such an investigation was possible for the heterocyclic series, and before the present work was commenced such an investigation had been confined to pentafluoropyridine.

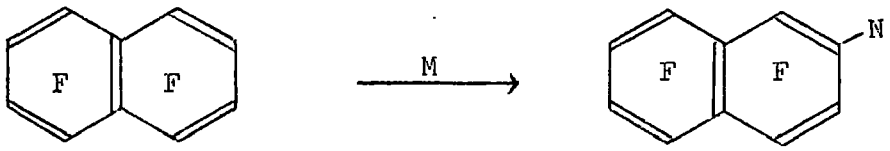
Nucleophilic Reactions of Hexafluorobenzene.[175]

The reaction of hexafluorobenzene with a wide variety of nucleophilic reagents has been studied. In almost all cases reaction occurred under moderate conditions and gave the mono-substituted product in good yield. A representative sample of such reactions are given below in table form:-

Nucleophile		Reaction Conditions	Product	Yield	Reference
$^-OCH_3$	a)	NaOMe, MeOH, Reflux	C_6F_5OMe	72%	165
	b)	NaOMe, MeOH, Pyridine, Reflux	C_6F_5OMe	70%	166
^-OH	a)	Aq. KOH, 175°	C_6F_5OH	83·5%	167
	b)	KOH, t-butanol, reflux	C_6F_5OH	71%	168
^-SH		H_2S, NaOH, $HO(CH_2)_2OH$, Pyridine, Reflux	C_6F_5SH	70%	169

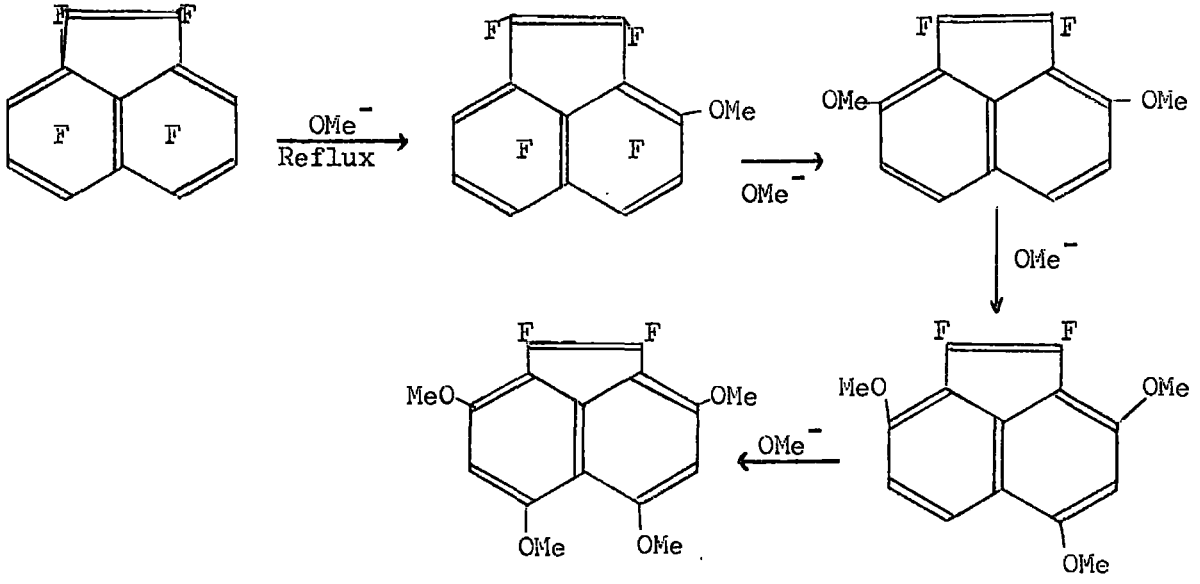
Nucleophile		Reaction Conditions	Product	Yield	Reference
NH_2^-	a)	Aq.NH_3, EtOH, 167°	$C_6F_5NH_2$	60%	170
	b)	$NaNH_2$, liq.NH_3, -70°C	$C_6F_5NH_2$	"High"	171, 170
			$(C_6F_5)_2NH$	3%	
$^-NHNH_2$		$NH_2NH_2.H_2O$, Ethanol, Reflux	$C_6F_5NHNH_2$	73%	170
$^-NHCH_3$		CH_3NH_2, aq.EtOH, 115°	$C_6F_5NHCH_3$	40%	170
			$C_6F_4(NHCH_3)_2$	25%	
^-R	a)	CH_3Li, Ether, -15-20°	$C_6F_5CH_3$	69%	172
	b)	PhLi, Reflux, Ether	C_6F_5-C_6H_5	37%	173
			$C_6F_4(C_6H_5)_2$	15%	
	c)	CH_3CH=$CHLi$, Ether, -15 to 20°	C_6F_5CH=$CHCH_3$	87%	174
H^-		$LiAlH_4$	C_6F_5H		175
^-NH-$(CH_2)_2NH^-$		$NH_2(CH_2)_2NH_2$, aq.EtOH, 110°		27%	176

The reaction of highly fluorinated polycyclic aromatic compounds with nucleophiles has also been studied but much less extensively than for hexafluorobenzene. Octafluoronaphthalene reacts readily with nucleophiles[177], fluorine displacement occurring in the β-position, to give good yields of the heptafluoronaphthalene derivatives.



M = $NH_2NH_2.H_2O$, MeLi, $LiAlH_4$, NaOMe, KOH, giving N = $NHNH_2$, Me, H, OMe, and OH respectively.

Octafluoroacenaphthylene is readily substituted by nucleophiles[178] (reagents used were NaOMe, NH_3, $NH_2NH_2.H_2O$, and $LiAlH_4$). With sodium methoxide in methanol, poly-substitution occurred readily as shown below



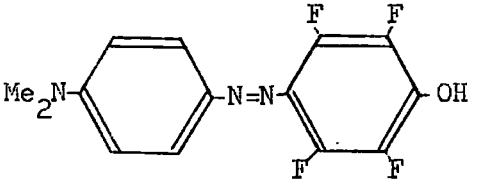
A

A was found to be inert to further attack by methoxide ion.

Nucleophilic Reactions of Mono-Substituted Pentafluorobenzenes.

Further attack by nucleophiles on the mono-substituted products of hexafluorobenzene can be accomplished and is of considerable interest because different positional isomers can be formed. Some examples of such reactions are summarised below.

Pentafluoro-phenyl Derivative	Nucleophilic Reagent	Product and Isomer Ratio	Yield	Reference
C_6F_5H	$LiAlH_4$	$C_6F_4H_2$, o-7,p-92,m-1	90%	179
	NH_2NH_2	$C_6F_4H(NHNH_2)$,o-3,m-0·5, p-96·5	87%	179
	NH_3	$C_6F_4H(NH_2)$,p > 90%	63%	179,170
	NaOMe	$C_6F_4H(OMe)$,p > 90%	47%	180,3
	NaSH	$C_6F_4H(SH)$,p > 90%	70%	181
$C_6F_5OCH_3$	NaOMe	$C_6F_4(OCH_3)_2$,o-16,m-32, p-52	77%	182
	MeLi	$C_6F_4(OCH_3)Me$,o-10,m-34, p-56	92%	182
$C_6F_5CH_3$	NaOMe	$C_6F_4(CH_3)(OMe)$,p > 90%	80%	182
C_6F_5OH	KOH	$C_6F_4(OH)_2$,m > 90%	80%	182
$C_6F_5NH_2$	NaOMe	$C_6F_4(NH_2)OMe$,o-5,m-79, p-16	High	183
C_6F_5NHMe	NaOMe	$C_6F_4(NHMe)OMe$,o-5,m-43,p-52	High	183

Pentafluorophenyl Derivative	Nucleophilic Reagent	Product and Isomer Ratio	Yield	Reference
$C_6F_5NMe_2$	NaOMe	$C_6F_4(NMe_2)OMe$, o-1, m-2, p-97	High	183
C_6F_5-CF_3	NH_3	$C_6F_4(CF_3)NH_2$, p > 90%	82%	184
$C_6F_5N_2^{+\frac{1}{2}}SO_4^{2-}$	NaOH, ($C_6H_5NMe_2$)		50%	185
C_6F_5Cl	NaOMe	C_6ClF_4OMe, o-20, m-4, p-76	70%	186, 187
	NH_3	$C_6ClF_4NH_2$, o-20, m-5, p-75	58%	186, 187
C_6F_5COOH	NaOMe	$C_6F_4(COOH)OMe$, p > 90%	71%	188
	$MeNH_2$	$C_6F_4(COOH)(MeNH)$, o-40, p-60	Some decarboxylation	188
C_6F_5NO	NaOMe	$C_6F_4(NO)OMe$, p > 90%	76%	189
	Me_2NH	$C_6F_4(NO)NMe_2$, p > 90%	45% (much Decomp.)	189
	$MeNH_2$	$C_6F_4(NO)NHMe$, o/p ≈ 2/3	Much Decomp.	189
$C_6F_5NO_2$	NaOMe	$C_6F_4(NO_2)OMe$, o-8, p-92	70%	190
	$NHMe_2$	$C_6F_4(NO_2)NMe_2$, o-19, p-81	75%	190
	NH_2Me	$C_6F_4(NO_2)NHMe$, o-65, p-35	50%	190
	NH_3	$C_6F_5(NO_2)NH_3$, o-69, p-31	85%	190

In general attack occurs mainly para to the substituent for most nucleophiles and under widely different reaction conditions. In the absence of any specific interaction between the nucleophile and substituent group, attack occurs at the para position almost exclusively (>90%) for substituent groups which are strongly electron attracting (CF_3, C_2F_5, N_2^+) or which are neither strongly electron withdrawing or attracting (H, CH_3, NMe_2, SMe, SO_2Me). For strongly electron donating substituents (NH_2, O^-) attack occurs mainly at the meta position. Comparable amounts of attack at the meta and para positions occur for some substituents (OMe, NHMe) and significant amounts of ortho substitution occur when the substituent is chlorine or methoxyl. As previously mentioned Burdon[3] has rationalised these observations by considering the relative stabilities of the Wheland-type intermediates for all possible positions of attack by the nucleophile. However his arguments do not apply where there is a specific interaction between the substituent and nucleophile. Pentafluoronitrobenzene, pentafluoronitrosobenzene and pentafluorobenzoic acid are exceptional in that they give vastly different isomer ratios with different nucleophiles. With sodium methoxide attack occurs predominantly para (>90%) whilst with ammonia and methylamine large percentages of ortho replacement occur. One factor which possibly accounts, at least in part, for this is hydrogen bonding between the amines and substituent group.[190] However

the fact that pentafluorobenzoic acid gives more ortho replacement with dimethylamine (45%) then methylamine (40%)[188] whilst the reverse applies to pentafluoronitrobenzene and pentafluoronitrosobenzene suggests that factors other than hydrogen-bonding are operating. Furthermore the reactions were carried out in different solvents and the discovery that the pentafluoronitrobenzene-sodium methoxide reaction is subject to a solvent effect[191] (50% ortho replacement in 3·8% methanol in ether as compared with 8% in methanol alone) reveals the important effect that the solvent can have on the orientation. In this case the effect of the solvent is sufficiently great to over-ride to a large extent the effect of the substituent ($-NO_2$) on the position of attack by the nucleophile (OMe^-).

Nucleophilic Reactions of Pentafluoropyridine.

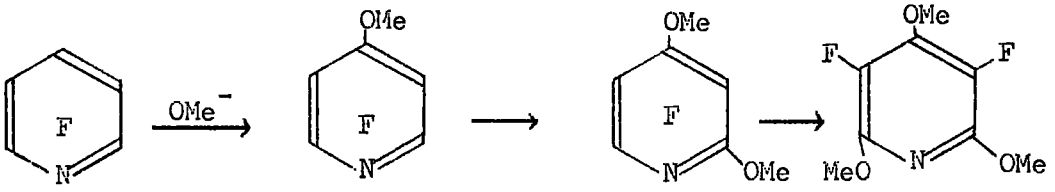
Workers at Durham[163] and Manchester[192] have studied the reaction of pentafluoropyridine with nucleophilic reagents in some detail and two important points emerged from this study. Firstly nucleophilic displacement of fluoride ion from pentafluoropyridine occurred much readily than from hexafluorobenzene. Aqueous ammonia in ethanol reacted exothermically with pentafluoropyridine at room-temperature and quantitative conversion to 4-aminotetrafluoropyridine occurred on heating at 80°C for 2 hours, whereas a temperature of 167° was required for the corresponding production of pentafluoroaniline from hexafluorobenzene.[170] Reaction between sodium methoxide in methanol and pentafluoropyridine occurred

readily at 0°C to give the monomethoxy derivative whereas at least one hour at the reflux temperature was necessary for the analogous preparation of pentafluoroanisole.[165] Secondly preferential substitution took place almost exclusively (≥90%) at the 4-position for the wide variety of nucleophilic reagents used, as seen from the table below

Nucleophilic Reagent	Reaction Conditions	Product	Yield	Reference
NH_3	a) Aq.NH_3, 80°, 2 hrs.	4-$NH_2C_5NF_4$	70%	163
	b) NH_3, EtOH, 110°, 8 hrs.	4-$NH_2C_5NF_4$	81%	192
NH_2NH_2	a) $NH_2.NH_2H_2O$, Dioxan, Reflux 2 hrs.	4-$NH_2NHC_5NF_4$	70%	163
	b) $NH_2NH_2H_2O$, Ethanol, 0°C, 2 hrs.	4-$NH_2NHC_5NF_4$	75%	192
NaOMe	a) NaOMe(1 mole), MeOH, 20°C, 10 mins.	4-$MeOC_5NF_4$	66%	192
	b) NaOMe(2 moles), MeOH, 20°C, 15 mins.	4-$MeOC_5NF_4$	8%	163
		2,4$(MeO)_2C_5NF_3$	72%	
	c) NaOMe($5\frac{1}{2}$ moles), MeOH, Reflux 6 hrs.	2,4,6$(MeO)_3C_5NF_2$	74%	192
Me_2NH	a) Aq.Me_2NH, EtOH, 0°C	4-$Me_2NC_5NF_4$	51%	192
	b) Aq.Me_2NH, EtOH, 100°C, 20 hrs.	2,4$(Me_2N)_2C_5NF_3$	82%	192
$LiAlH_4$	a) $LiAlH_4$, ether, Reflux 4 hrs.	4-HC_5NF_4	74%	192
C_6H_5Li	a) C_6H_5Li, ether, 20°C, 1 hour	4-$C_6H_5C_5NF_4$	26%	163

Nucleophilic Reagent		Reaction Conditions	Product	Yield	Reference
KOH	a)	KOH, water, 85°, 20 hrs.	4-OHC_5NF_4	63%	193
	b)	KOH, t-butanol, Reflux, 90 mins.	4-OHC_5NF_4 2-OHC_5NF_4	58.5% 6.5%	193
NaOH	a)	NaOH, water, Reflux, 2 hrs.	4-OHC_5NF_4	58%	192
NaOH	b)	NaOH(40% aq.), 80°, 12 hrs.	2,4$(OH)_2C_5NF_3$	20%	192

The reaction with sodium methoxide in methanol shows clearly the order in which the fluorines are displaced

i.e. 

and in no case did replacement of the 3-fluorine occur.

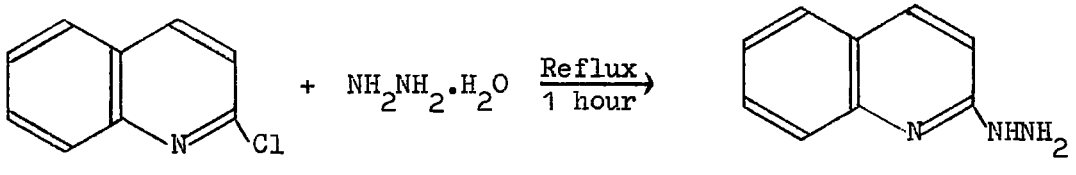
The reaction between pentafluoropyridine and potassium hydroxide in tertiary butanol is interesting as it gave a significant amount of 2-hydroxytetrafluoropyridine. This reaction is discussed in more detail later.

From a consideration of the reactions of the above highly fluorinated compounds one would expect heptafluoroquinoline to be very susceptible to replacement of fluorine by nucleophiles and this has been found to be so. Before the reactions of heptafluoroquinoline are discussed, it is pertinent to consider the susceptibility of the halogen in lowly

halogenated quinolines towards nucleophilic replacement, with special reference to the variation in such susceptibility with the position of the halogen in the quinoline nucleus, and with a view to comparing these results with the orientation of nucleophilic substitution in heptafluoroquinoline.

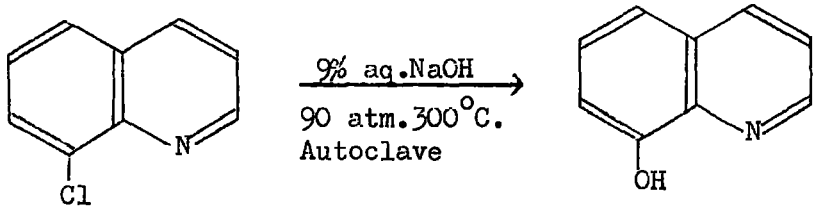
Nucleophilic Reactions of Lowly Halogenated Quinolines.

Halogen in the 2- or 4-position of the quinoline nucleus is characterised by its much greater susceptibility to nucleophilic displacement than when in the 3-, 5-, 6-, 7-, or 8-positions. Replacement of the chlorine in 4-chloro-8-nitroquinoline occurs on refluxing with sodium methoxide in methanol[194] and 2-chloroquinoline reacts readily with hydrazine hydrate[195]



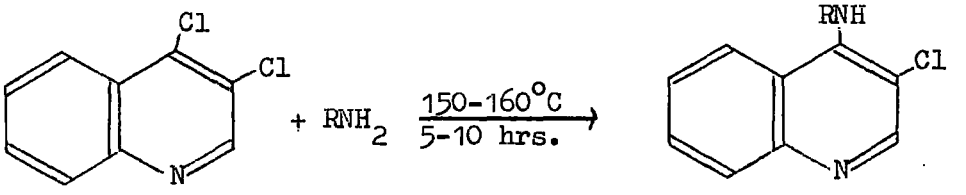
Quantitative

In contrast replacement of the halogen in 7-bromoquinoline by methoxyl required heating with sodium in methanol for 7 hours at 250°C,[196] and only partial replacement of the halogen occurred when 7-chloro- or 7-bromoquinoline was heated with methylamine at 250-290° for 7-8 hours.[196] 8-Chloroquinoline reacted with alkali only under forcing conditions



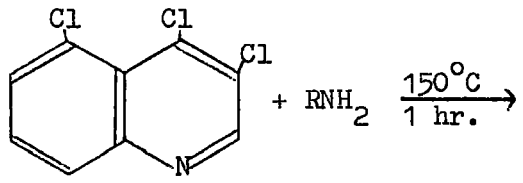
and 6-chloroquinoline was reported to be even less reactive in this reaction.[197] The nucleophilic self-condensation of 4-fluoroquinoline[12] reflects the great susceptibility of fluorine at this position to nucleophilic displacement as does the formation of 4-ethoxy-2-methylquinoline on attempted preparation of the picrate of 4-fluoro-2-methylquinoline in ethanol.[19] Of the remaining monofluoroquinolines, the greater susceptibility of fluorine at position 2 to nucleophilic displacement is shown by the fact that whereas 3-, 5-, 6-, 7- and 8-fluoroquinolines are stable to dilute hydrochloric acid, 2-fluoroquinoline is rapidly converted to 2-hydroxyquinoline.[198]

The greater reactivity of halogen at position 4 compared with that at the 3-, 5-, 6-, 7- or 8-positions is clearly shown by the following reactions, where in all cases 2 moles of amine were used per mole of the quinoline



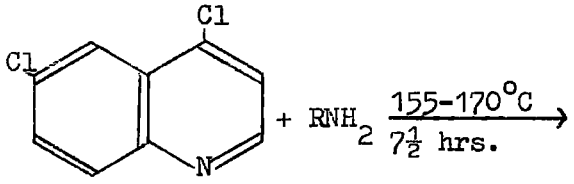
Ref. 199

80-85%



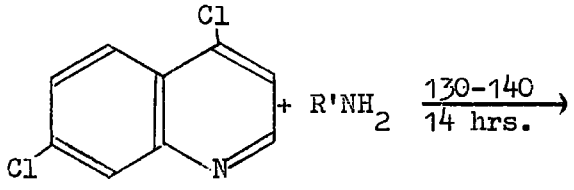
80-85%

Ref.199



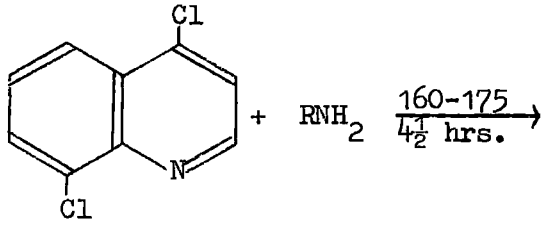
49%

Ref. 200



83%

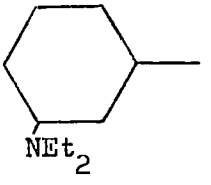
Ref. 200



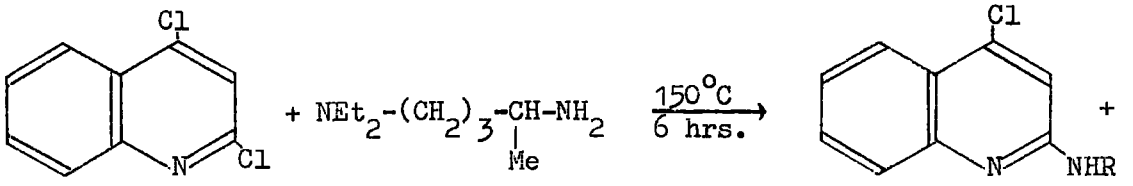
36%

Ref. 200

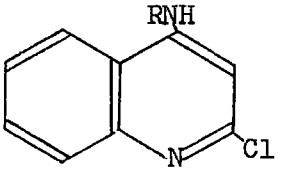
R = $Et_2N(CH_2)_3-CH(CH_3)-$ and R' =



It can be seen that in all cases only replacement of the chlorine at position 4 occurred but a similar reaction with 2,4-dichloroquinoline[200] gave a mixture of products which were not separated



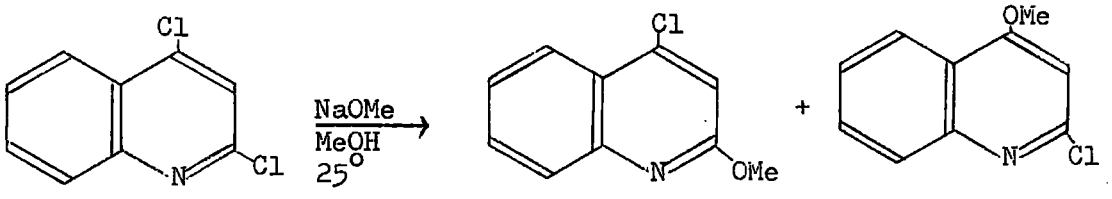
1 mole 2 moles



52% yield of the mixture

The relative reactivities of the chlorines in 2,4-dichloroquinoline towards methoxide ion in methanol have been measured;[201] the reactivity ratio k(4-Cl)/k(2-Cl) being 1·9 at 25°

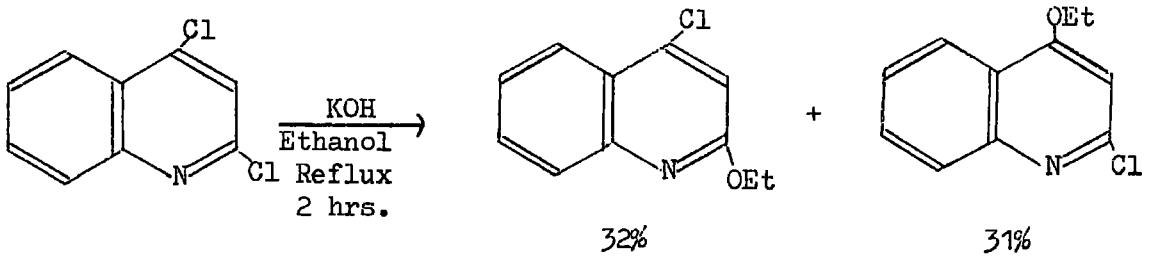
i.e.



35·2% 64·8%

[% composition of product]

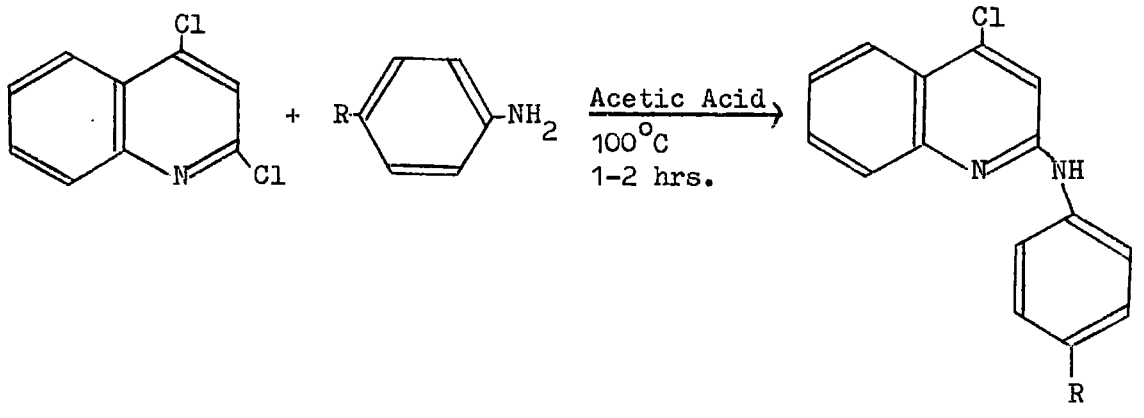
However when refluxed with potassium hydroxide in ethanol, the chlorines were replaced equally readily[202]



32%

31%

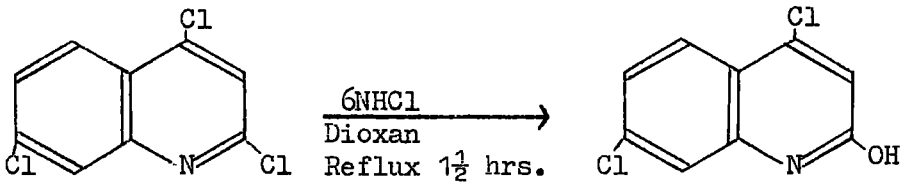
and reaction with a number of para-substituted anilines resulted in preferential replacement of the halogen at position 2[203]



40-50%

R = H, Cl, OMe, Me, NO_2

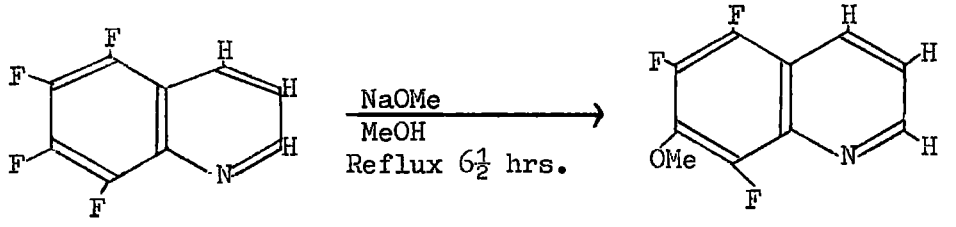
The increase in the amount of 2-substitution with increase in size of the attacking nucleophile suggests that steric factors favour substitution at the 2-position. The reaction[204]



89%

in which replacement of the 2-chlorine occurs preferentially suggests a further factor leading to increased reactivity of halogen at position 2. It is probable that in the acid solution protonation of the nitrogen occurs to a significant extent so that reaction occurs on the quinolinium cation, in which the positively charged nitrogen activates, by its inductive effect, the 2-position more than the 4-position so that nucleophilic attack by water occurs preferentially at the α-position. Preferential attack at the α-position occurs in the reaction of alkali metal hydroxides, Grignard reagents or dialkyl cadmium compounds with N-alkyl quinolinium compounds, but alkali metal cyanides lead to substitution at the 4-position.[205] It is evident that the relative reactivity of halogen at the 2- and 4-positions depends upon the nature of the solvent and attacking nucleophile. As regards 2- and 4-chloroquinoline the rates of their reaction with sodium ethoxide in ethanol were found to be very similar, the relative rates being 1:1·03 respectively.[160]

Nucleophilic attack on 5,6,7,8-tetrafluoroquinoline has been shown to occur preferentially at position 7 with nucleophilic reagents such as ammonia, potassium hydroxide and methoxide ion[32]

e.g. 

90%

Reactions were carried out using a 1:1 ratio of the nucleophile and substrate only so that no information on the relative susceptibility of the remaining fluorines was available. Halogens present in aromatic heterocyclic N-oxides are normally more susceptible to nucleophilic displacement than those in the parent aromatic heterocycle,[206] but the relative susceptibilities towards nucleophilic displacement of halogen at the various positions of the N-oxide will probably be similar to those found in the parent compound. Therefore the relative reactivity towards nucleophiles of the monofluoroquinoline N-oxides will reflect to some extent the relative reactivity of the monofluoroquinolines themselves. 3-, 5-, 6-, 7-, and 8-Fluoroquinoline N-oxides have been treated with a number of nucleophiles and the reactivity of the various fluorines was found to vary markedly with their position.[159] The fluorine in the 6- and 8-substituted N-oxides was unaffected by aqueous sodium hydroxide, sodium methoxide in methanol or piperidine at the reflux temperature of the reagent, that in the 5-substituted compound reacted only on prolonged boiling with aqueous sodium hydroxide or sodium methoxide in methanol whilst 3- and 7-fluoroquinoline N-oxide reacted readily on refluxing with aqueous sodium hydroxide, piperidine or hydrazine hydrate and were qualitatively of similar reactivity.

From the above one can compute, as regards susceptibility towards nucleophilic replacement of halogen in a polyhalogenated quinoline nucleus, the following approximate order of decreasing reactivity

$$2 \approx 4 \gg 3 \approx 7 > 5 > 6 \approx 8$$

However the effect of substituents other than halogen on such an order must be borne in mind.

CHAPTER 5

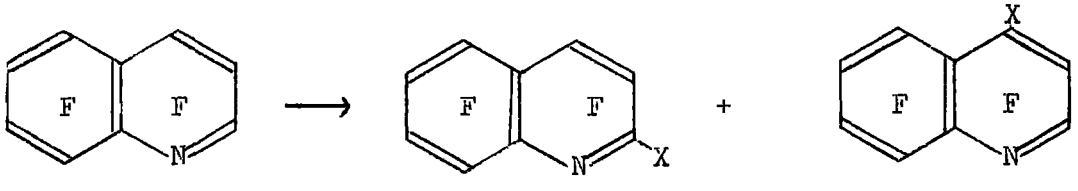
DISCUSSION OF EXPERIMENTAL WORK

Introduction.

The reactions of heptafluoroquinoline and its derivatives which have been carried out can conveniently be divided into three sections. Nucleophilic substitution reactions of heptafluoroquinoline are discussed in Section I whilst the preparation and reactions of some polyfluorohydroxyquinolines are dealt with in Section II. Section III is concerned with nucleophilic substitution in the heptafluoroquinolinium cation. The orientation of the polyfluoroquinolines prepared were assigned on the basis of their nuclear magnetic resonance spectra and this is discussed in Part III.

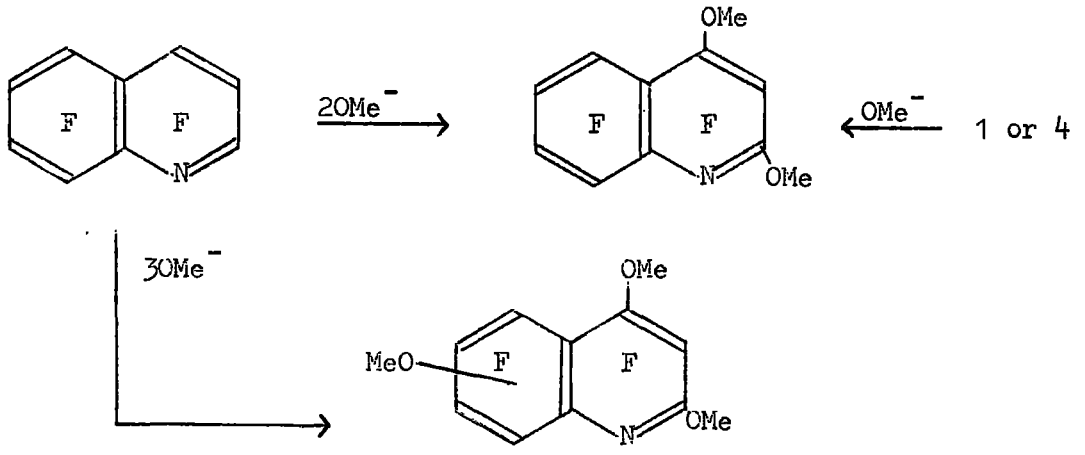
Section I.

The fluorine atoms in heptafluoroquinoline were found to be very susceptible to nucleophilic replacement on reaction with sodium methoxide in methanol, aqueous ammonia in acetone or hydrazine hydrate in dioxan (see diagram below). The reaction with potassium hydroxide in water or tertiary butanol is discussed in Section II.



1. X = OMe
2. X = NH_2
3. X = $NHNH_2$

4. X = OMe
5. X = NH_2
6. X = $NHNH_2$



a) Reaction with sodium methoxide in methanol. Reaction with one molecular equivalent occurred readily at 15°C to give, in high yield, a mixture of 2- and 4-methoxyhexafluoroquinoline in ratio of 3·4:1. The isomeric mixture of the mono-ethers, although clearly resolved by analytical-scale v.p.c., had only slightly different retention times and their separation by preparative-scale v.p.c. was difficult. The 2-isomer, which had the shorter retention time, could be obtained pure relatively easily but the pure 4-isomer could only be obtained in very small amount due to "tailing" of the peak of the 2-isomer into that for the 4-isomer. Also the similarity of retention times was such that only small amounts of the mixture could be injected and this rendered the separation of the two isomers a tedious operation. Refluxing with two molecular equivalents of methoxide ion gave 2,4-dimethoxypentafluoro-quinoline which was also obtained by reaction of either of the mono-ethers

with a one molecular equivalent of sodium methoxide, hence showing the replacement of fluorine to be a sequential process. Refluxing heptafluoroquinoline with three molecular proportions of sodium methoxide gave a 1:1 mixture of 2,4-dimethoxypentafluoroquinoline and a trimethoxytetrafluoroquinoline. The latter compound was shown to be substituted at the 2- and 4-positions by its mode of preparation and n.m.r. spectroscopy showed it to be a single isomer of 2,4,6- or 2,4,7-trimethoxytetrafluoroquinoline. It acquired a glossy appearance before melting suggesting the possible presence of a small amount of another isomer of the trisubstituted compound. The demethylation of the polyfluoromethoxyquinolines is discussed in Section II.

b) Reaction with aqueous ammonia in acetone: Excess aqueous ammonia in acetone reacted exothermically at 20°C to give a high yield of a 1:1 mixture (estimated by n.m.r. spectroscopy) of 2- and 4-aminohexafluoroquinolines. The 2-isomer was obtained pure by recrystallisation, but a series of fractional recrystallisations and sublimations failed to give the pure 4-isomer; the best obtained was a mixture comprising 80% of the 4-isomer and 20% of the 2-isomer. Attempted oxidation of the 2-isomer by refluxing with trifluoroperoxyacetic acid in methylene dichloride, a procedure used to oxidise 4-aminotetrafluoropyridine[207] to the corresponding nitro compound, resulted in decomposition. Carrying out the reaction at room-temperature, under conditions which resulted in 25%

recovery of unreacted amine likewise resulted only in decomposition products being isolated. When heptafluoroquinoline was refluxed with this reagent substantial starting material was recovered but a small amount of 2-hydroxyhexafluoroquinoline was isolated. The mode of formation of the latter is discussed in Section III.

c) Reaction with hydrazine hydrate in dioxan. Refluxing with a two molar equivalent of hydrazine hydrate, as for pentafluoropyridine,[163] resulted in extensive decomposition and 2-hydrazinohexafluoroquinoline was isolated in low (27%) yield. Reaction occurred readily at 20° and the 2-isomer was isolated in 76% yield. The remaining material was extensively decomposed and could not be purified to isolate the 4-isomer. The low solubility and instability of the hydrazino compounds were such that no n.m.r. spectra could be obtained. The orientation of the 2-isomer was shown by reaction with aqueous copper sulphate[208] when only 2-hydrohexafluoroquinoline was obtained. Similar treatment of the total crude reaction product gave a mixture of the 2- and 4-hydrohexafluoroquinolines. Surprisingly the mixture was obtained in only very small amount and consisted of the 2- and 4-isomers in ratio of 1:2. Clearly the hydro compounds isolated are not in proportion to the relative amounts of the 2- and 4-hydrazino compounds formed, since 2-hydrazinohexafluoroquinoline was isolated in 76% yield and gave only a single isomer of 2-hydrohexafluoroquinoline on treatment with aqueous

copper sulphate. Attempts to convert 2-hydrazinohexafluoroquinoline to the corresponding amino compound by refluxing with aqueous hydriodic acid[163] resulted in extensive decomposition. The 2-hydrazino compound condensed with benzaldehyde to give the corresponding hydrazone and this was reduced with zinc in acetic acid in an attempt to obtain the 2-amino compound.[173] A mixture of polyfluoroaminoquinolines was obtained however, the i.r. spectrum of the product being quite similar to that of 2-aminohexafluoroquinoline in the range 4000 - 2000 $cm.^{-1}$ but showed marked differences in the region below 2000 $cm.^{-1}$, possibly arising from substitution of fluorine by hydrogen during the reduction.

Theoretical Considerations.

The reaction of heptafluoroquinoline with nucleophilic reagents can be rationalised in exactly the same way as that described in Part I (page 94) for nucleophilic substitution in heptachloroquinoline.

Reactivity towards nucleophilic attack.

Pentafluoropyridine is markedly more reactive towards nucleophilic attack than hexafluorobenzene[163] (see page 127) and competition reactions between heptafluoroquinoline and pentafluoropyridine show that the quinoline system is of the order of 2·5 times more reactive towards methoxide ion in methanol at 20°. The greater reactivity of the heterocyclic system is readily ascribed to the greater stabilisation of the transition state resulting from the possibility of localising the

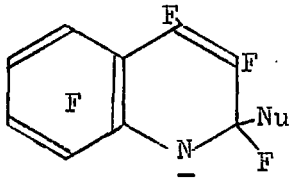
negative charge onto the ring nitrogen. The greater reactivity of the quinoline system compared with pentafluoropyridine can be attributed to the greater possible delocalisation of the negative charge in the transition state for the bicyclic system. The relative reactivities found for the fully fluorinated quinoline and pyridine systems parallel the results found for the monohalogenated systems.[160]

Orientation of nucleophilic attack.

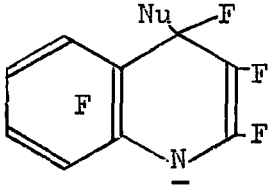
From a consideration of the relative stabilities of the transition states for nucleophilic attack in heptafluoroquinoline, the 2- and 4-positions would be expected to be the most susceptible, as is observed. This parallels the greater reactivity of halogen at the 2- and 4-positions of lightly halogenated quinolines and suggests that the ring nitrogen is the dominant factor in determining the orientation of nucleophilic attack. This has been shown to be so for polyfluoropyridines by the reaction of 4-nitrotetrafluoropyridine[209] with ammonia or methoxide ion. With both nucleophiles substantial replacement of the nitro group (as well as of the 2- and 3-fluorines) occurred, whilst for 2,3,5,6-tetrafluoronitrobenzene fluorine replacement only occurred. This clearly shows the activation, by the ring nitrogen, of the 4-position towards nucleophilic attack. The greater reactivity towards nucleophilic replacement of halogen at the 1-position of the isoquinoline nucleus,[210] and the preferential replacement of the 1-fluorine of heptafluoroisoquinoline by nucleophiles, despite the presence of a fluorine para to

this position, further shows the dominant effect of the ring nitrogen in controlling the orientation of nucleophilic attack.

I and II below are the resonance hybrids considered to be the main contributors to the transition states for nucleophilic attack at the 2- and 4-positions respectively.



I



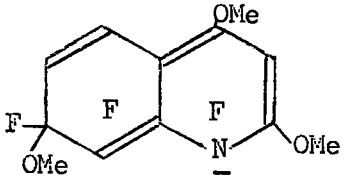
II

Nu^- = nucleophile

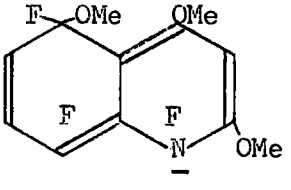
Consideration of the greater stability of a para-quinonoid form would suggest that II should be more stable than I and hence attack should occur more readily at position 4, as is the case for pentafluoro-pyridine. The greater reactivity ratio $\frac{k_2}{k_4}$ for the quinoline system compared with the pyridine system is probably due to some extent to the absence of a fluorine para to the 2-position in the quinoline system. A further possible factor leading to increased 2-substitution is the greater steric hindrance for substitution at position 4. Molecular models show that the peri-fluorines (i.e. those at the 4 and 5 positions) are closer together than two fluorine atoms on adjacent carbon atoms

in the ring systems, and a steric effect is observed in the reaction of heptafluoroquinoline with potassium hydroxide (see Section II) where it was found that the amount of 2-substitution increased on changing the solvent from water to tertiary butanol. This is attributed to an increase in the effective size of the nucleophile due to solvation, the effective size being greater for solvation by the more bulky tertiary butanol molecules.

Further attack by methoxide ion on 2,4-dimethoxypentafluoroquinoline was shown (by n.m.r. spectroscopy) to occur at either the 6- or 7-positions. For attack at the 7-position (as explained earlier) the negative charge can be delocalised onto the ring nitrogen (III) but not for attack at position 6. Hence, the trimethoxy derivative obtained is most like the 2,4,7-trisubstituted compound. The glossy appearance which the trimethoxy compound acquired before melting might possibly be due to the presence of a small amount of another isomer of the trimethoxy compound. This would most probably be the 2,4,5-isomer since for attack at the 5-position the negative charge can also be delocalised onto the ring nitrogen (IV).



(III)



(IV)

Similar considerations account for the greater reactivity towards nucleophilic attack of 7- and 5-fluoroquinoline-N-oxides as compared with the 6- and 8-fluorinated compounds (see page 136).

Section II. Preparation of, and Tautomerism in, Polyfluorohydroxyquinolines.

Preparation of Polyfluorohydroxyquinolines.

Because the reaction of heptafluoroquinoline with nucleophilic reagents (NaOMe, NH_3, $NH_2NH_2.H_2O$) had been found to give mixtures of the 2- and 4-monosubstituted derivatives which were difficult to separate, the polyfluorohydroxyquinolines were prepared by demethylation of the corresponding polyfluoromethoxyquinolines. The polyfluorohydroxyquinolines so formed were methylated with diazomethane in ether and the methylated products characterised. The polyfluorohydroxyquinolines formed by reaction of heptafluoroquinoline and potassium hydroxide were not isolated but the total reaction product was methylated with diazomethane and the methylated products so formed were characterised.

Demethylation of 2,4-dimethoxypentafluoroquinoline.

Because of its ease of preparation 2,4-dimethoxypentafluoroquinoline was the first compound demethylated. It had been found previously[193] that 4-methoxytetrafluoropyridine was readily demethylated using hydriodic acid but that aluminium trichloride gave a mixture of products of unknown identity, in contrast to the ready demethylation of pentafluoroanisole by this reagent.[165] Accordingly the demethylation of

2,4-dimethoxypentafluoroquinoline was attempted using aqueous hydriodic acid (54% w/w). With a reflux time of 5½ hours, 2,4-dihydroxypentafluoroquinoline was obtained in ≈22% yield together with a monomethoxymonohydroxypentafluoroquinoline in ≈42% yield. With a reflux time of 24 hours the yield of the dihydroxy compound was increased to ≈ 71%; the monomethoxymonohydroxypentafluoroquinoline being obtained in 9·5% yield.

Preparation of 4-hydroxy-2-methoxypentafluoroquinoline.

In order to determine the structure of the monomethoxymonohydroxypentafluoroquinoline formed in the demethylation of 2,4-dimethoxypentafluoroquinoline, 2-methoxyhexafluoroquinoline was reacted with aqueous potassium hydroxide to give a monomethoxymonohydroxypentafluoroquinoline. On methylation with diazomethane it gave only 2,4-dimethoxypentafluoroquinoline thus showing it to be 4-hydroxy-2-methoxypentafluoroquinoline. Comparison of the i.r. spectra of this compound and of the monomethoxymonohydroxypentafluoroquinoline (X) formed in the demethylation of 2,4-dimethoxypentafluoroquinoline showed not only that they were different compounds but that (X) contained none of the 4-hydroxy-2-methoxypentafluoroquinoline. Thus 2-hydroxy-4-methoxypentafluoroquinoline is formed along with the 2,4-dihydroxy compound in the demethylation of 2,4-dimethoxypentafluoroquinoline. Further evidence for this structure was obtained from the products formed on its methylation (see below).

Demethylation of Monomethoxyhexafluoroquinolines.

(i) 4-Methoxyhexafluoroquinoline and aqueous hydriodic acid.

In view of the successful demethylation of the 2,4-dimethoxy compound using aqueous hydriodic acid, this reagent was used in an attempt to demethylate the 4-methoxy derivative. It was found however that straightforward demethylation did not occur. From the products formed one, which was soluble in methylene dichloride, was shown to be 2-hydroxy-4-methoxypentafluoroquinoline (by comparison of its i.r. spectrum with an authentic sample) and the remainder of the product, which was insoluble in methylene dichloride, was a mixture whose i.r. spectrum indicated that 2,4-dihydroxypentafluoroquinoline was present. Its analysis could not be correlated with a mixture of 4-hydroxyhexafluoro-,2-hydroxy-4-methoxypentafluoro- and 2,4-dihydroxypentafluoroquinolines, or with any combination of these possible products, hence showing the reaction to be complex. The reaction between heptafluoroquinoline itself and aqueous hydriodic acid was later found to be complex but one of the products was 2-hydroxyhexafluoroquinoline which is considered to arise from nucleophilic replacement by water of fluorine from the protonated species (see Section III). Thus the preparation of 4-hydroxyhexafluoroquinoline cannot be achieved by demethylation of 4-methoxyhexafluoroquinoline with aqueous hydriodic acid due to the facile replacement of the 2-fluorine. The fact that the methylene dichloride-soluble product was 2-hydroxy-4-methoxypentafluoroquinoline and later discovery (see below) that 4-

hydroxyhexafluoroquinoline was soluble in methylene dichloride shows that replacement of the 2-fluorine occurs in preference to demethylation of the 4-methoxyl group.

(ii) 2-Methoxyhexafluoroquinoline and Aluminium Trichloride.

Due to the complex nature of the reaction of aqueous hydriodic acid with 4-methoxyhexafluoroquinoline, the demethylation of 2-methoxyhexafluoroquinoline was attempted using aluminium trichloride. On heating the polyfluoromonomethoxyquinoline with anhydrous aluminium trichloride at 120°C for 3½ hours a 42% yield of 2-hydroxyhexafluoroquinoline was obtained. This contrasts markedly with the reported[193] complex product formed on attempted demethylation of 4-methoxytetrafluoropyridine with aluminium trichloride. A by-product was obtained in trace amount which was non-acidic (i.e. it was extracted from basic solution). Its i.r. spectrum suggested it contained the polyfluoroquinoline nucleus but absorption at 2967 and 2933 $cm.^{-1}$ suggested the presence of hydrogen whilst absorption at 806, 780, and 752 $cm.^{-1}$ might indicate the presence of chlorine.

(iii) 4-Methoxyhexafluoroquinoline and aluminium trichloride.

A further sample of 4-methoxyhexafluoroquinoline was prepared after the 2-methoxy compound had been successfully demethylated using aluminium trichloride and an attempt was made to demethylate the 4-methoxy compound with this reagent. However the product obtained was found to contain

chlorine and methylation of it with diazomethane gave a product which analytical-scale v.p.c. showed to consist of 80% 4-methoxyhexafluoroquinoline together with two compounds of higher retention time in ratio of 1:19. Their composition is unknown but it is likely that they contain chlorine. Thus the reaction of aluminium trichloride with 4-methoxyhexafluoroquinoline gives a complex product (as found[193] also with 4-methoxytetrafluoropyridine) but its methylation shows 80% of it to be 4-hydroxyhexafluoroquinoline. The remainder of the product appears to be essentially one component and the known facile replacement of the 2-fluorine suggests that this might be 2-chloro-4-hydroxypentafluoroquinoline. However the analytical figures obtained do not correlate with such a mixture and the reaction is clearly more complex.

Methylation of Polyfluorohydroxyquinolines with Diazomethane.

The method of methylation employed, i.e. addition of an excess of an ethereal solution of diazomethane to a suspension or solution of the hydroxy compound in ether at room-temperature, has been used to methylate a number of aromatic polyfluorohydroxy compounds[211,32] and in all cases the only product was the o-methyl compound.

(a) 2-Hydroxyhexafluoroquinoline: The methylated product was shown by analytical-scale v.p.c. to consist of 2-methoxyhexafluoroquinoline and another component (A) of higher retention time in the ratio of 2:3 respectively. The compound of higher retention time (A) was found to be

identical with the highest retention time product formed on methylation of the mixture of hydroxy compounds produced by reaction between heptafluoroquinoline and 2 moles of potassium hydroxide (see below). This compound was isomeric with 2-methoxyhexafluoroquinoline.

(b) 2,4-Dihydroxypentafluoroquinoline: The methylated product consisted of two components in ratio of 9:10. The compound present in smaller amount, which had the shorter retention time, was identical with 2,4-dimethoxypentafluoroquinoline. The other compound (B) was separated by fractional sublimation and recrystallisation. Analysis showed it to be isomeric with 2,4-dimethoxypentafluoroquinoline and its sharp melting-point, and ^{19}F and ^{1}H n.m.r. spectra (see Part III) showed it to be a single compound.

(c) 2-Hydroxy-4-methoxypentafluoroquinoline: Methylation gave the same two compounds as obtained on methylation of 2,4-dihydroxypentafluoro-quinoline in ratio of 8:10; 2,4-dimethoxypentafluoroquinoline being present in smaller amount.

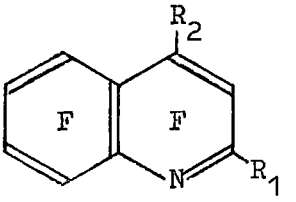
(d) 4-Hydroxy-2-methoxypentafluoroquinoline: As stated above methylation gave only a single compound, shown by analytical-scale g.l.c. and comparison of its i.r. spectrum with an authentic sample to be 2,4-dimethoxypentafluoroquinoline.

(e) Crude 4-hydroxyhexafluoroquinoline (from reaction of 4-methoxyhexafluoroquinoline and aluminium trichloride). As stated above the methylation product consisted of 4-methoxyhexafluoroquinoline (80%) and two other compounds of higher retention time in amounts of 1% and 19%. The compound comprising 1% of the product had retention time slightly greater than that of (A), whilst that comprising 19% had a longer retention time which was slightly greater than that of (B).

(f) Polyfluorohydroxyquinolines formed by reaction between heptafluoroquinoline and potassium hydroxide: Heptafluoroquinoline was reacted with potassium hydroxide using either water or tertiary butanol as solvent and with both two and three molecular proportions of potassium hydroxide. After any unreacted heptafluoroquinoline had been removed, the polyfluorohydroxyquinolines remaining were methylated with ethereal diazomethane and the methylated product analysed by analytical-scale v.p.c. The results obtained are tabulated below:-

		Methylation Product*				
Molar Ratio KOH/C_9NF_7	Solvent	R_1=OMe R_2=F	R_1=F R_2=OMe	(A)	R_1=OMe R_2=OMe	(B)
2	H_2O	30	20	50	-	-
2	Bu^tOH	32	6	62	-	-
3	Bu^tOH	40	2	38	15	5

* (i) R_1 and R_2 refer to the compound



(ii) Numbers are percentages of the methylated product.

Compound (A) was separated from the methylated product obtained from reaction of heptafluoroquinoline with two molecular proportions of potassium hydroxide in tertiary butanol, by fractional sublimation and recrystallisation. Analysis showed it to be isomeric with monomethoxy-hexafluoroquinoline and its sharp melting point and ^{19}F and ^{1}H n.m.r. spectra (see Part III) showed it to be a single compound.

Tautomerism of Polyfluorohydroxyquinolines.

Structure of (A) and (B)

As stated above (A) and (B) were shown to be single compounds and elemental analysis and molecular weight measurements showed (A) to be isomeric with monomethoxyhexafluoroquinoline and (B) to be isomeric with dimethoxypentafluoroquinoline. The i.r. spectrum of (A) (see table T.1.) was characterised by the presence of a very strong absorption at 1686 $cm.^{-1}$ which was not present in 2-methoxyhexafluoroquinoline, and the i.r. spectrum of (B) had a very strong absorption at 1678 $cm.^{-1}$ which was not present in 2,4-dimethoxypentafluoroquinoline. These absorptions are suggestive of the presence of a carbonyl group and together with their mode of preparation and molecular formulae, the only conclusion is that (A) is hexafluoro-N-methyl-2-quinolone and that (B) also has a quinolone structure. The fact that (B) is pentafluoro-4-methoxy-N-methyl-2-quinolone, rather than pentafluoro-2-methoxy-N-methyl-4-quinolone, follows from its preparation from 4-methoxy-2-hydroxypentafluoroquinoline

Table T 1[a,b]

COMPOUND	
2-Methoxyhexafluoroquinoline	1639(s.); 1595(w.)
Hexafluoro-N-methyl-2-quinolone.(A)	1686(v.s.); 1647(m.); 1608(w.)
2,4-Dimethoxypentafluoroquinoline	1661(m.); 1629(v.s.); 1605(m.)
Pentafluoro-4-methoxy-N-methyl-2-quinolone.(B)	1678(v.s.); 1650(s.); 1613(m.)
4-Methoxyhexafluoroquinoline	1669(s.); 1637(s.); 1618(s.)
2-Hydroxyhexafluoroquinoline	1704(v.s.); 1671(v.s.)
Impure 4-hydroxyhexafluoroquinoline	1658(s.); 1603(s.)
2,4-Dihydroxypentafluoroquinoline	Broad band from 1750-1550, centred at 1642 (v.s.) with shoulders at 1675 (v.s.) and 1608 (v.s.)
4-Methoxy-2-hydroxypentafluoroquinoline	1661(v.s.); 1637(s.); 1618(m.)
4-Hydroxy-2-methoxypentafluoroquinoline	1675(sh.(m.)); 1654(s.); 1610(w.)

a) sh. = shoulder; v.s. = very strong; s.= strong; m.= medium; w. = weak. Intensities are relative to the most intense absorption which is assigned as very strong (v.s.).

b) Absorptions in the region 2000-1550 $cm.^{-1}$

with diazomethane. The ^{19}F and ^{1}H n.m.r. spectra of (A) and (B) are consistent with the assigned structures (see Part III). In para-benzoquinone[212] and tetrafluoroparabenzoquinone[211] the carbonyl absorption occurs at 1667 cm.$^{-1}$ and 1674 cm.$^{-1}$ respectively, showing that the presence of α-fluorine causes only a small shift to higher frequency of the carbonyl absorption in contrast to the large high frequency shift (≈75 cm.$^{-1}$) found for α-fluoro aliphatic ketones.[213] In quinol-2-one[214] and 4-methylquinol-2-one[214] the carbonyl absorptions occur at 1660 and 1653 cm.$^{-1}$ respectively and the corresponding N-methyl derivatives might be expected to show similar carbonyl absorption frequencies. The high frequency shift of the carbonyl absorption in (A) and (B) compared with the hydro-analogue is thus greater than that observed for the parabenzoquinone case.

It was found that (A) decolourised a solution of potassium permanganate in acetone much more quickly than did 2-methoxyhexa-fluoroquinoline; the times taken for equally concentrated acetone solutions of (A) and 2-methoxyhexafluoroquinoline to decolourise equal amounts of an acetone solution of potassium permanganate were 1½ and 25 minutes respectively at 21°C. This is consistent with the assigned structure of (A) in which the olefinic double bond (between C3 and C4) would be expected to be oxidised more readily than the aromatic ring in 2-methoxyhexafluoroquinoline.

Ultraviolet Spectra of Hexafluoro-N-methyl-2-quinolone (A) and Pentafluoro-4-methoxy-N-methyl-2-quinolone (B).

Table T.2. contains the u.v. spectra of (A) and (B) together with several other relevant compounds. The presence in (A) and (B) of a conjugated carbonyl group would be expected to cause their spectra to be different from the isomeric o-methyl compounds i.e. 2-methoxyhexafluoroquinoline and 2,4-dimethoxypentafluoroquinoline. A carbonyl group in conjugation with an ethylenic double bond gives rise[215] to a strong $\pi-\pi^{x}$ absorption near the region 215-250 mμ ($\varepsilon_{max} > 10,000$) and a weak $n-\pi^{x}$ absorption near the region 300-350 mμ ($\varepsilon_{max} < 100$). The spectra in table T.2. were recorded over the range 200-350 mμ at dilutions (5-10 mg. per litre of cyclohexane) for which the resolution was insufficient for detection of the weak $n-\pi^{x}$ absorption. Accordingly the spectra were examined in the region 200-250 mμ for evidence of the expected strong $\pi-\pi^{x}$ absorption of the conjugated carbonyl group. Before the u.v. spectra of the polyfluoroquinoline derivatives are discussed the spectra of 1-methoxyhexafluoroisoquinoline and hexafluoro-N-methyl-1-isoquinolone[216] will be compared. The structure of the latter compound follows from its formation, along with the isomeric 1-methoxyhexafluoroisoquinoline, by methylation of 1-hydroxyhexafluoroisoquinoline with diazomethane, the presence of a strong absorption at 1720 $cm.^{-1}$ indicating the presence of the carbonyl group. The strong absorption at 214·3 mμ in the spectrum of 1-methoxyhexafluoroisoquinoline is split to give two strong absorptions

Table T.2. Ultraviolet Spectra.[a] λ_{max}(mμ), ε_{max}(molar) in parentheses.

COMPOUND								
Quinoline	203·0(sh.) (24,800)	221·6 (30,200)	225·0 (33,000)	229·6 (23,700)	270·7 (3,530)	300·8 (212·0)	305·8 (1,750)	313·7 (2,480)
Heptafluoro-quinoline	215·5(inf.) (20,500)		227·6 (28,826)		272·9 (3,367)	281·1(sh.) (3,050)		
4-Methoxyhexafluoro-quinoline	219·6 (32,470)				274·0 (5,160)	283·5 (5,030)	297·0(sh.) (2,462)	
2-Methoxyhexa-fluoroquinoline	225·8(sh.)[b] (32,100)		233·8 (36,000)	258·6 (5,180)	266·2(inf.) (4,830)	301·1 (2,080)	314·9 (2,140)	
(A)	224·6[b] (25,122)		233·8 (22,134)	269·3 (4,471)	279·8 (4,929)	319·8 (2,900)	333·5(sh.) (2,379)	
2,4-Dimethoxy-pentafluoroquinoline	222·0[b] (34,286)			262·8(sh.) (5,221)	271·6 (5,654)	281·7(sh.) (4,411)	314·6 (1,145)	
(B)	213·4(sh.) (17,529)	226·4[b] (29,968)	235·0(sh.) (23,941)	275·0 (5,151)	285·5 (4,995)		318·3 (2,450)	
1-Methoxy-hexa-fluoroiso-quinoline.[216]	214·3 (25,922)			268·6(inf.)	277·3 (7,310)	289·0 (7,361)	330·9 (5,028)	
Hexafluoro-N-methyl-1-isoquinolone.[216]	206·4 (19,190)	225·6 (15,426)	247(inf.)	251·3 (6,508)	283·7 (7,824)	292·8 (8,222)	345·2 (4,968)	

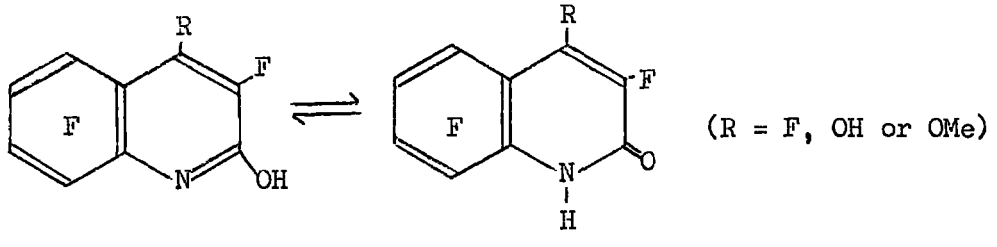
a) Spectra are for solutions in cyclohexane recorded on an Optica C.F.4 spectrophotometer.

b) Very broad bands - see text.

at 206·4 and 225·6 mμ in the spectrum of the isomeric isoquinolone. This is presumably due to the π-π^x transition of the conjugated carbonyl group. Consider now the spectra of the polyfluoroquinoline derivatives. Heptafluoroquinoline itself, like quinoline, shows a strong absorption in the range under investigation (200-250 mμ) but the fine structure shown by quinoline is absent for heptafluoroquinoline. The compounds isomeric with (A) and (B), i.e. 2-methoxyhexafluoroquinoline and 2,4-dimethoxypentafluoroquinoline, both show strong absorption in the range 200-250 mμ but the bands are very broad and lacking in fine structure. For 2-methoxyhexafluoroquinoline this band at half-peak height extends from 200-242 mμ, whilst in the case of 2,4-dimethoxypentafluoroquinoline the band is practically flat-topped extending from 216-237 mμ and at half-peak height extends from 200-245 mμ. Thus it is seen that a broad intense band due to the highly fluorinated quinoline nucleus falls in the range (200-250 mμ) in which the π-π^x absorption of the conjugated carbonyl group is expected to occur. Comparison of the spectra of (A) and 2-methoxyhexafluoroquinoline shows that both show similar broad, diffuse bands in the range 200-250 mμ. It would appear therefore that the strong absorption due to the polyfluoroquinoline nucleus masks the expected absorption due to the conjugated carbonyl group. On comparison of the u.v. spectra of (B) and 2,4-dimethoxypentafluoroquinoline it is found that the very broad band present in the latter

compound, although still broad for (B) showed distinct shoulders at 213·4 and 235·0 and had λ_{max} 226·4 mμ. This could be due to overlapping of the band due to the polyfluoroquinoline nucleus and the π-π^x absorption of the conjugated carbonyl group. However, the broad diffuse nature of the bands found in the region 200-250 mμ for (A) and (B) and the isomeric o-methyl compounds prevents any definite conclusions being formed from the u.v. spectra as regards the structure of (A) and (B).

The formation of hexafluoro-N-methyl-2-quinolone by methylation of hexafluoro-2-hydroxyquinoline and of pentafluoro-4-methoxy-N-methyl-2-quinolone by methylation of either 2,4-dihydroxypentafluoro- or 2-hydroxy-4-methoxypentafluoro-quinoline, together with their i.r. spectra (see below) show that these hydroxy compounds (I) are in equilibrium with their tautomers (II)



(R = F, OH or OMe)

(I) (II)

The infrared spectra (table T.1.) of the hydroxy compounds (I) were all characterised by the presence of a very strong absorption, in fact the most intense peak in the spectrum, in the region 1700-1640 cm.$^{-1}$ This is consistent with the presence of the tautomer (II), the strong

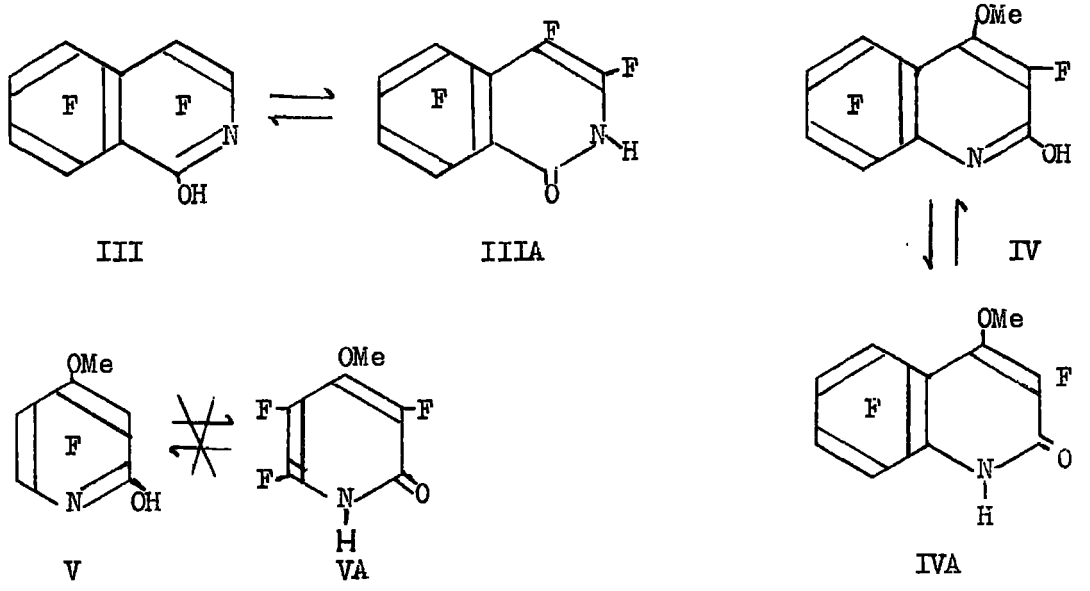
absorption being due to the carbonyl group. The compounds with hydroxyl groups at position 4, i.e. 4-hydroxyhexafluoro- and 2-methoxy-4-hydroxy-pentafluoro-quinoline, which gave only o-methylated products on reaction with diazomethane, had i.r. spectra similar to the corresponding o-methyl compounds in the region 2000-1500 $cm.^{-1}$, showing that the amount of the keto form present was, at least, quite small. Generally all the hydroxy compounds showed a complex, very broad band in the region of 3,300-2,500 $cm.^{-1}$, indicating extensive hydrogen-bonding to be occurring in the solid state and rendering identification of any discrete N-H or O-H absorption impossible. However, one significant exception was 4-hydroxy-2-methoxypentafluoroquinoline which showed a much narrower, though still broad, absorption centred at 3419 $cm.^{-1}$ Pentafluorophenol[168] in the liquid state shows a similar broad band at 3425 $cm.^{-1}$ due to the hydrogen-bonded hydroxyl group, and the band at 3419 $cm.^{-1}$ for the hydroxyquinoline can be similarly assigned, and taken in conjugation with the absence of any absorption due to a carbonyl group indicates the absence of any significant amount of the keto form for this compound. The wide melting range of 2-hydroxyhexafluoroquinoline (196-211°) and the sharp melting-point of 4-hydroxy-2-methoxypentafluoro (151-152°) are in accord with the former compound existing as a tautomeric mixture but not the latter. The relative proportions of the o-methyl and N-methyl compounds obtained on methylation of the tautomeric mixture

(I and II) need bear no relation to the equilibrium proportions of I and II since these are unlikely to react with diazomethane at exactly the same rates, and these may be small compared with the rate of equilibration. An example[217] of this is 2-hydroxypyridine which exists principally as pyrid-2-one but on reaction with diazomethane gives mainly 2-methoxypyridine. Thus the formation of only the o-methyl derivative on methylation of 4-hydroxy-2-methoxypentafluoroquinoline or 4-hydroxyhexafluoroquinoline does not necessarily indicate that these compounds exist entirely in the OH form. However, physical measurements indicate that a hydroxyl group in position 4 does not lead to a tautomeric system containing significant amounts of the keto form, in contrast to a hydroxyl group at position 2 of the polyfluoroquinoline nucleus.

Factors affecting tautomerism in Polyfluorohydroxy-N-hetero aromatic Compounds.

In pyridine, quinoline and isoquinoline a hydroxyl group α or γ to the ring nitrogen gives rise to a tautomeric system in which the keto form predominates.[218] In contrast the evidence available so far indicates that only the polyfluoro-1-hydroxyisoquinoline and polyfluoro-2-hydroxyquinoline systems lead to tautomeric mixtures in which the keto forms are present in significant amounts. An important difference between the above hydroxy-N-heteroaromatic compounds and their polyfluoro derivatives is that the lone pair on the nitrogen is more

readily available in the former compounds (see Section III). The absence of tautomerism in 4-hydroxytetrafluoro-,[193] and 4-methoxy-2-hydroxytrifluoro-pyridine,[219] in contrast to the corresponding hydro analogues, can be attributed to the reduced electron availability on the ring nitrogen. The work on hexafluoro-1-hydroxyisoquinoline[216] and the polyfluorohydroxyquinolines indicates that this is only one of several possible factors involved. The fact that a polyfluoro-2-hydroxy-quinoline gives rise to a tautomeric mixture in which the concentration of the keto form is much greater than for a polyfluoro-4-hydroxyquinoline, indicates two further possible factors. Firstly, the position of the fluorine relative to the ring nitrogen could be important since this will affect the availability of the nitrogen lone-pair and, secondly, the relative positions of the hydroxyl group and ring nitrogen could be important if the mechanism of proton transfer were intramolecular. The latter factor is unimportant in the hydro-analogues, since both 2- and 4-hydroxyquinolines exist predominantly in the keto form, and suggests that the important factor in these systems is the availability of the nitrogen lone pair. The fact that hexafluoro-1-hydroxyisoquinoline (III) and 4-methoxy-2-hydroxypentafluoroquinoline (IV) give rise to a tautomeric system whereas 4-methoxy-2-hydroxytrifluoropyridine (V) does not, suggests that the degree of conjugation possible in the keto form is another factor affecting the extent of tautomerism.



III and V are very similar in that the nitrogen is flanked by fluorine and hydroxyl and in neither compound does the nitrogen have a para-fluorine whilst the hydroxyl group does. In forming IIIA from III and VA from V the loss of aromatic resonance stabilisation is less in the former case and could possibly be the controlling factor in determining the extent of tautomerism. The fusion of a perfluorobenzene ring at the 5,6-positions of V to give IV leads to a tautomeric system for IV and, although the environment of the nitrogen in IV and V is changed by this fusion, the greater degree of conjugation possible in IVA than in VA is probably an important factor leading to tautomerism in IV but not in V. The existence of 2-hydroxy-pyridines and -quinolines in predominantly the keto forms shows that this latter factor is not important

in systems where the nitrogen lone pair is readily available.

Summarising, it would appear that in hydroxy-N-hetero-aromatic compounds the ready availability of the nitrogen lone pair is the controlling factor in determining the formation of a tautomeric system, but that in the polyfluorohydroxy-N-heteroaromatic compounds, where the availability of the nitrogen lone pair is much reduced, the factors discussed above play an important role.

Orientation of Substitution in the reaction between Heptafluoroquinoline and Potassium Hydroxide.

The table on page 152 shows (since (A) is derived from 2-hydroxy-hexafluoroquinoline) that with water as solvent the ratio of 2-substitution to 4-substitution is 80:20 and with t-butanol this ratio is 94:6. Pentafluoropyridine reacts with a large number of nucleophiles to give exclusive replacement of the 4-fluorine[163,192] and this includes the reaction between it and potassium hydroxide in water.[193] In tertiary butanol however the product is a 9:1 mixture of 4- and 2-hydroxytetra-fluoropyridines.[193] The variation in attack at the 4- and 2-positions is much more marked for 3,5-dichlorotrifluoropyridine.[193] This reacts with aqueous ammonia and sodium methoxide in methanol to give exclusive replacement of the 4-fluorine. With potassium hydroxide in water 90% replacement of the 4-fluorine and 10% of the 2-fluorine occurs but with potassium hydroxide in tertiary butanol 70% replacement of the 2-fluorine

occurs and 30% of the 4-fluorine. The results from the pyridine system indicate that in the reaction using potassium hydroxide in tertiary butanol steric requirements are important in determining the position of substitution, and a similar effect appears to occur for heptafluoroquinoline leading to increase substitution at the less hindered 2-position, on changing the solvent from water to t-butanol. This steric effect could possibly arise from replacement of fluorine by the bulky t-butoxide anion and subsequent cleavage of this group by the base. A similar effect had been noted previously by Wall et al.[167] in the reaction between hexafluorobenzene and potassium hydroxide using ethanolic pyridine as solvent. However, it was later found[219] that polyfluoro-t-butoxypyridines did not react with potassium hydroxide in t-butanol under conditions for which the parent compound did. It would therefore appear that the steric affect in t-butanol arises because of solvation of the attacking nucleophile by the bulky solvent molecules.

Section III. Reactions involving the ring nitrogen of Heptafluoroquinoline.

Replacement of hydrogen by the highly electronegative fluorine in the quinoline nucleus would be expected to cause a reduction in base strength, and the reduction has been shown[220] to be greater for substitution of fluorine in the pyridine ring than in the benzene ring. 5,6,7,8-Tetrafluoroquinoline,[32] although a weaker base than quinoline, did form a hydrochloride when the gas was bubbled through a solution

in ether under anhydrous conditions. However, heptafluoroquinoline, like pentafluoropyridine,[163] did not form a hydrochloride under similar conditions, and also did not give a precipitate when boron trichloride was condensed into a solution of it in carbon tetrachloride, in contrast to quinoline itself.[221] The much reduced availability of the nitrogen lone pair in heptafluoroquinoline was shown also by its insolubility in dilute (2N) hydrochloric, sulphuric and nitric acids. However, heptafluoroquinoline did dissolve in sulphuric acid (s.g. 1·84) and the ultra-violet spectrum of this solution showed N-protonation, rather than interaction with the π-electron system, to have occurred. The ultraviolet spectra of heptafluoroquinoline and quinoline in neutral and acid solution are shown on page 167.

Comparison of the spectra of quinoline and heptafluoroquinoline in cyclohexane and sulphuric acid show that similar shifts are produced on changing from neutral to acid solution. In both cases the bands at intermediate wavelength (270-280 mμ) found in neutral solution are absent in acid, and the longer wavelength bands (300-314 mμ) found in quinoline have greater extinction coefficients in acid, whilst for heptafluoroquinoline no long wavelength band is found with a neutral solution but one appears in acid. Knight[222] has studied the effect of increasing acidity on the ultraviolet spectra of a series of monomethylquinolines. He found that as the pH decreased the bands at intermediate wavelength (279-292 mμ) shifted to longer wavelength, finally

Ultraviolet Spectra[a]

Compound	λ_{max} (mμ)	ε_{max} (molar)	Solvent
Quinoline	209·0(sh.)	29,160	Cyclohexane
	222·0	32,480	
	225·5	34,370	
	229·0	26,670	
	269·5	4,980	
	300·3	2,960	
	313·8	3,200	
Heptafluoro-quinoline	215·0(infl.)	18,870	Cyclohexane
	227·0	28,400	
	272·0	3,060	
	282·0	2,550	
Quinoline	193·5	14,700	Sulphuric Acid[b]
	197·0(sh.)	18,800	
	201·8	29,000	
	235·0	39,300	
	238·0(sh.)	38,900	
	310·0(sh.)	10,100	
	314·0	10,900	
Heptafluoro-quinoline	202·5	8,310	Sulphuric Acid[b]
	243·0	37,800	
	314·0	5,920	

[a] Measured using a Unicam S.P. 800 Spectrophotometer.

[b] s.g. 1·84.

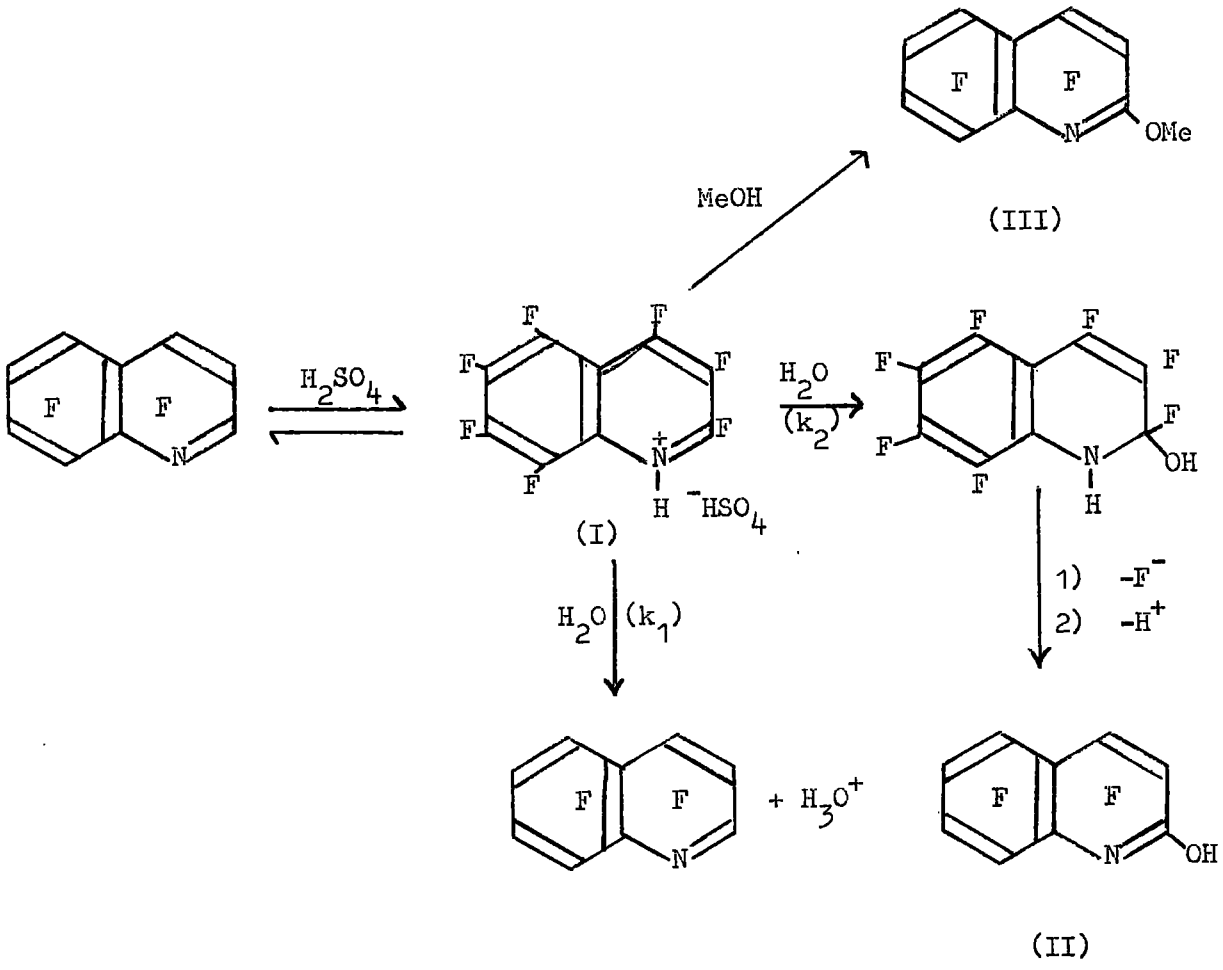
becoming obscured by the bands at longer wavelength (314-318 mμ). These changes were interpreted as arising from N-protonation, the amount of which increased as the pH decreased. That heptafluoroquinoline shows similar spectral changes on changing from neutral to acid solution indicates that it is N-protonated in concentrated sulphuric acid. This is supported by the insolubility of hexafluorobenzene and octafluoronaphthalene in concentrated sulphuric acids. Heptafluoroisoquinoline[156] was similarly found to be N-protonated by concentrated sulphuric acid. Heptachloro-quinoline and -isoquinoline[156] were found to dissolve almost instantly in concentrated sulphuric acid, and much faster than the corresponding perfluoro-compounds probably because of some surface effect. Pentafluoropyridine dissolved readily in sulphuric acid.

Addition of Water to Solutions of Polyhalo-N-heteroaromatics in Sulphuric Acid.

When a solution of heptafluoroquinoline in sulphuric acid was poured into excess water, the precipitate formed was mainly heptafluoroquinoline but contained a small amount of 2-hydroxyhexafluoroquinoline. When a similar solution was poured into an excess of well-stirred water only heptafluoroquinoline was recovered, whilst slow dilution with water gave only 2-hydroxyhexafluoroquinoline (methylation of the latter compound with diazomethane confirmed the absence of any other isomers). However, using either dilution procedure, corresponding solutions of

heptachloro-quinoline and -isoquinoline,[156] pentafluoropyridine, and heptafluoroisoquinoline[156] gave only precipitated starting material.

Nucleophilic substitution in quinolinium[223,205] isoquinolinium[205,224] and pyridinium salts[225,226] is well known e.g. the formation of nuclear hydroxy derivatives by the reaction of base on N-methyl-quinolinium, -isoquinolinium or -pyridinium iodides, and it appears that the hydroxylation of heptafluoroquinoline is a similar process. The probable reaction scheme is shown below.



In excess water, deprotonation (k_1) of the quinolinium ion (I) must be faster than substitution (k_2) so that the quinoline is mainly recovered but, with gradual dilution, it appears that a stage is reached where the equilibrium condition permits some quinolinium salt (I) and some unprotonated water to be present to allow the substitution (k_2) to occur. It was found that if the amount of water added to the acid solution (this being insufficient to cause precipitation) was decreased prior to rapid dilution, then a stage was reached where only heptafluoroquinoline was recovered. Thus the ratio of water to sulphuric acid is an important factor in determining whether hydroxylation occurs or not, and is consistent with attack on the quinolinium cation by unprotonated water.

That the reaction is not simply dependent upon the production of unprotonated water was evident from treating solutions of heptachloro- and heptafluoro-quinoline with water such that (a) the heptachloroquinoline just remained in solution, and (b) the molar ratio of sulphuric acid to water was the same in both cases. On pouring both solutions into excess well-stirred water the heptachloroquinoline was precipitated unchanged whilst the fluorinated compound was precipitated as 2-hydroxyhexafluoroquinoline. Therefore another controlling factor appears to be the relative reactivities of the protonated species towards nucleophilic attack, which will be related to the relative base strengths and the relative susceptibilities towards nucleophilic displacement of

chlorine and fluorine. In the series considered, the chloroquinolines will be weaker bases than the corresponding fluoroquinolines due to the greater resultant (of inductive and mesomeric effects) electron-withdrawing capacity of chlorine over fluorine in an aromatic system[193] (this is found for monochloro- and monofluoro-quinolines[220]). For the fully-fluorinated compounds, the quinoline will be the stronger base since the isoquinoline and pyridine systems have an additional fluorine ortho to the ring nitrogen. Greater activation of the adjacent positions by positively charged nitrogen is likely to occur in the protonated species arising from the strongest base, i.e. heptafluoroquinoline. In the chloro compounds the reduced susceptibility of the protonated species towards nucleophilic attack arising from their lower basicity will be further reduced by the lower susceptibility of chlorine compared with fluorine towards nucleophilic replacement. Although the authors made no mention of the mechanism involved, similar considerations would appear to apply to the reaction of 2-fluoro- and 2-chloro-quinolines with hydrochloric acid at room temperature,[198] where it was found that the fluoro compound was rapidly converted to the corresponding hydroxy compound, the rate of the reaction increasing with increasing acidity, whilst the chloro compound was unaffected under the same conditions.

It was found also that methanol reacted in a similar manner to water with a solution of heptafluoroquinoline in concentrated sulphuric acid, slow dilution of the solution with methanol, prior to adding water,

giving a substantial amount of 2-methoxyhexafluoroquinoline (III) as well as a small amount of the hydroxy compound (II). The formation of the single isomer of the methoxy compound affords a convenient route to the 2-substituted compound (a mixture of the 2- and 4-substituted compounds is formed by reaction of heptafluoroquinoline with sodium methoxide) and suggests a convenient means of preparing other 2-alkoxyhexafluoroquinolines. The attack by nucleophiles (H_2O, MeOH) at the 2-position of the heptafluoroquinolinium cation parallels the results found for non-halogenated quinolinium cations[223,227] e.g. the N-cyanoquinolinium cation[227] reacts with water and alkoxides preferentially at the 2-position. A notable exception is the cyanide ion where 4-substitution occurs. However recent work[225,226] on the reaction of cyanide ion with various pyridinium cations has shown that initial attack occurs at the 2-position, but the reaction is reversible and rearrangement to give the more stable 4-isomer occurs. A similar effect most probably applies to the quinoline derivatives. Thus, from a comparison with the reactions of the unsubstituted quinolinium cation, one would expect preferential nucleophilic attack at position 2 of the heptafluoroquinolinium cation. The observed results hence afford confirmation of the orientation of 2-methoxyhexafluoroquinoline as deduced from its n.m.r. spectra (see Part III).

Reaction of a solution of pentafluoropyridine in sulphuric acid at elevated temperatures.

Pentafluoropyridine[163] reacts preferentially with nucleophiles at

the 4-position and the reaction between a solution of the compound in sulphuric acid and water was investigated at elevated temperatures in an attempt to find a route to the 2-substituted derivatives. 2-Chloroquinoline, as previously mentioned, does not undergo nucleophilic replacement on treatment with hydrochloric acid (6N) at room-temperature but on refluxing the 2-hydroxy-compound is formed in practically quantitative amount.[198] The reactions with pentafluoropyridine were carried out at 100-110°C and at this temperature the amount of water that could be added to the acid solution without precipitating the pentafluoropyridine was quite small. Thus for a solution of pentafluoropyridine (14·8 m.mole) in sulphuric acid (66·3 m.mole) the maximum amount of water that could be added was 11·1 m.mole. Heating such a solution at 100-110°C for 21 hours followed by slow dilution of the hot solution gave only unreacted starting material. When the time of heating was increased to 160 hours considerable decomposition occurred and only starting material was obtained, the recovery being 20%. Similar decomposition occurred on heating pentafluoropyridine with water itself at elevated temperatures, though some 4-hydroxytetrafluoropyridine was isolated.[163]

It would appear that the factors outlined above which govern the substitution by nucleophiles in the pentafluoropyridinium cation, and which cause it to be unreactive at room-temperature, still apply at elevated temperatures such that decomposition occurs before nucleophilic substitution.

Reaction of Heptafluoroquinoline with aqueous concentrated acids.

Hydrobromic Acid.

Heptafluoroquinoline was insoluble in concentrated hydrobromic acid (50% w/w) at room-temperature and on heating from 50°-80° over ½ hour and maintaining at 80-82° for a further 1 hour a white solid was still present. This solid was filtered off from the hot solution and found to be 2-hydroxyhexafluoroquinoline. The clear hot filtrate on slow dilution with water gave a white precipitate of 2-hydroxyhexafluoroquinoline only.

Hydrochloric Acid.

Heptafluoroquinoline was insoluble in concentrated hydrochloric acid (36% w/w) at room-temperature, but on heating from 45-80°C over ½ hour and maintaining at 80-85°C for a further ¾ hour practically all of it dissolved. Slow dilution of the hot solution with water gave a polyfluorohydroxyquinoline which, however, was found to contain chlorine. This and the fact that none of the reaction product was extracted from basic solution by methylene dichloride indicates the presence of a polyfluorochlorohydroxyquinoline. The i.r. spectrum of the product contained a very strong doublet absorption at 1694 and 1669 $cm.^{-1}$.

Hydriodic Acid.

Heptafluoroquinoline was insoluble in pure (i.e. iodine free) hydriodic acid (54% w/w) at room-temperature. On heating, under nitrogen,

at 75-85°C for 1¼ hours most of the solid dissolved and on slow dilution, with water, of the hot solution a precipitate was obtained which was found to be essentially a pentafluoroquinoline but a small amount of 2-hydroxy-hexafluoroquinoline was also isolated.

The above reactions, which were generally more complex than the reaction of a solution of heptafluoroquinoline in sulphuric acid with water, were similar in that they all gave rise to a 2-hydroxypoly-haloquinoline. 2-Hydroxyhexafluoroquinoline itself was obtained from the reactions involving hydrobromic and hydriodic acids. The product from the reaction with hydrochloric acid contained chlorine but the i.r. spectrum showed a very strong doublet absorption at 1694 and 1669 $cm.^{-1}$ indicative of a carbonyl absorption arising from the tautomer of a 2-hydroxypoly-fluoroquinoline. Heptafluoroquinoline itself was unaffected by heating with water at 80-90°C for 2 hours, i.e. under conditions more vigorous than for the reactions with the halogen acids. It would therefore appear that the hydroxy compounds formed in these reactions arise by a similar mechanism to that involved in the reaction of a solution of heptafluoro-quinoline in sulphuric acid with water at room-temperature, i.e. by nucleophilic attack of water on the heptafluoroquinolinium cation.

The formation of 2-hydroxyhexafluoroquinoline from the reaction with hydriodic acid brings to mind the formation of 2-hydroxy-4-methoxypenta-fluoroquinoline on attempted demethylation of 4-methoxyhexafluoroquinoline by refluxing with hydriodic acid. Similarly its formation can be accounted

for by nucleophilic attack of water at the 2-position of the 4-methoxyhexafluoroquinolinium cation. The reaction between heptafluoroquinoline and a mixture of trifluoroacetic anhydride and aqueous 90% hydrogen peroxide to give 2-hydroxyhexafluoroquinoline can be accounted for in a similar manner. Trifluoroacetic anhydride and hydrogen peroxide react (as in [i]) to form peroxytrifluoroacetic acid instantly, the trifluoroacetic acid formed reacting with more hydrogen peroxide to give the equilibrium[228] ([ii])

$$(CF_3CO)_2O + H_2O_2 \longrightarrow CF_3CO_3H + CF_3COOH \qquad [i]$$

$$CF_3COOH + H_2O_2 \rightleftharpoons CF_3CO_3H + H_2O \qquad [ii]$$

One can envisage N-protonation of heptafluoroquinoline by the trifluoroacetic acid, and subsequent attack at the 2-position of the quinolinium cation formed by water (from the aqueous hydrogen peroxide used or during the work-up when aqueous alkali is added). The formation of a pentafluoroquinoline as the major product from the reaction with hydriodic was most unexpected and its mode of formation is not readily apparent. As described in Part III its n.m.r. spectra (^{19}F and ^{1}H) showed it was most probably 3,5,6,7,8-pentafluoroquinoline. The formation of 2-hydroxyhexafluoroquinoline as one of the products shows that protonation of heptafluoroquinoline occurred under the reaction conditions. It was later found that the reaction between hydrogen chloride and heptafluoro-

quinoline in the dipolar aprotic solvent sulpholane, resulted in nucleophilic replacement of fluoride ion at the 2- and 4-positions of the protonated species by chloride ion. Iodide ion is solvated to a smaller extent by protic solvents (e.g. water) and is consequently a stronger nucleophile in such solvents than the bromide or chloride ion,[229] and it is possible that a similar reaction occurred with aqueous hydriodic acid as with hydrogen chloride in sulpholane to give the 2,4-diiodo compound. Subsequent reduction of the iodo compound by the excess hydriodic acid to give the 2,4-dihydro compound might then occur. Reduction of aromatic iodides by hydrogen iodide in aqueous acetic acid at 30-40°C has been reported,[230] but the introduction of electron-withdrawing groups (e.g. chlorine) or an increase in the concentration of water was found to retard the reduction. Alternatively the formation of the dihydro compound could possibly involve a complicated addition-elimination mechanism. Clearly, further work is necessary in order to establish the mechanism of this reaction.

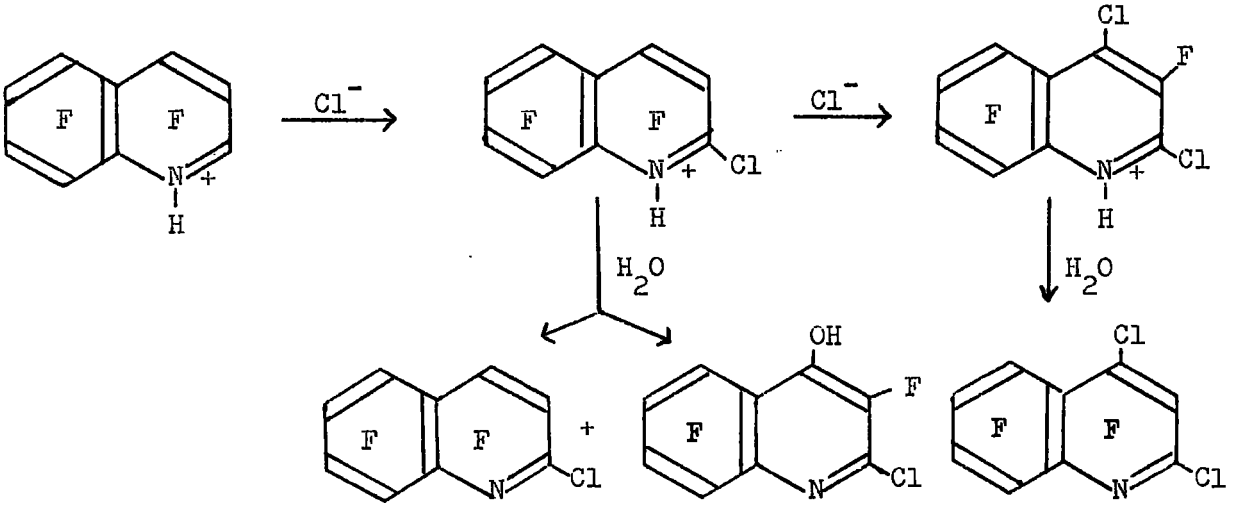
Reaction between heptafluoroquinoline and hydrogen chloride in sulpholane.

It seemed likely that heptafluoroquinoline would react (through its cation) with hydrogen halides, to give replacement of fluorine by halide, if the reaction were conducted in a dipolar aprotic solvent (e.g. sulpholane). As shown previously such solvents solvate anions to only a small extent compared with protic solvents, and a solution of a

hydrogen halide in sulpholane should serve as a source of the strongly nucleophilic halide anion. Due to lack of time this interesting area could only be briefly investigated and only one reaction between heptafluoroquinoline and hydrogen chloride using sulpholane as solvent has been carried out so far. It was found that on heating a solution of heptafluoroquinoline in sulpholane with a two molar ratio of hydrogen chloride, at 90-95°C for 48 hours in an evacuated Carius tube, followed by pouring of the cooled solution into water, a precipitate was formed which consisted of approximately equal amounts of 2,4-dichloropentafluoroquinoline and a monohydroxymonochloropentafluoroquinoline together with a trace of 2-chlorohexafluoroquinoline. In contrast, potassium chloride did not react with heptafluoroquinoline under the same conditions. Thus the reaction can be formulated as one of nucleophilic attack by chloride ion on the heptafluoroquinolinium cation. The detection of 2-chlorohexafluoroquinoline shows that initial attack occurs at position 2, due to greater activation of the ortho position by the positively charged nitrogen. That further attack occurs at position 4, in contrast to the reaction of water with the heptafluoroquinolinium cation, is due to the high reactivity of the chloride anion in the dipolar aprotic solvent and the activation of the system towards nucleophilic attack by the initial chlorine introduced.[193]

The i.r. spectrum of the monohydroxymonochloropentafluoroquinoline showed no strong absorption that could be ascribed to a carbonyl group

and had a sharp melting-point, in contrast to the 2-hydroxypolyfluoroquinolines. Thus it is unlikely that the compound contains a 2-hydroxyl group, and the known greater susceptibility of the 2- and 4-fluorines of heptafluoroquinoline towards nucleophilic attack together with the isolation of 2-chlorohexafluoroquinoline indicates that it is most probably 2-chloro-4-hydroxypentafluoroquinoline. The formation of this undoubtedly occurred when the reaction product was poured into water, probably by nucleophilic attack by water at position 4 of the 2-chlorohexafluoroquinolinium cation, displacement of the 4-fluorine occurring rather than the 2-chlorine because of the greater susceptibility towards nucleophilic attack of fluorine.[207,152] It is unlikely that it was formed by nucleophilic attack by water on the 2,4-dichloropentafluoroquinolinium cation since this would be expected to give replacement of the 2-chlorine. Thus the overall reaction can be formulated in the following way:



This preliminary reaction suggests a convenient direct route from heptafluoroquinoline of 2-chloro-, 2-bromo- and the 2,4-dihalo- polyfluoroquinolines, which, especially the bromo-compounds, will be valuable synthetic intermediates. Such a route would be much more convenient and economical than the indirect route involving the amine, and even this approach is not possible for heptafluoroisoquinoline.[231]

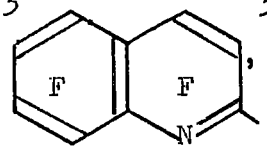
Preparation of 2-chlorohexafluoro- and 2,4-dichloropentafluoro-quinolines from 2-hydroxyhexafluoroquinoline.

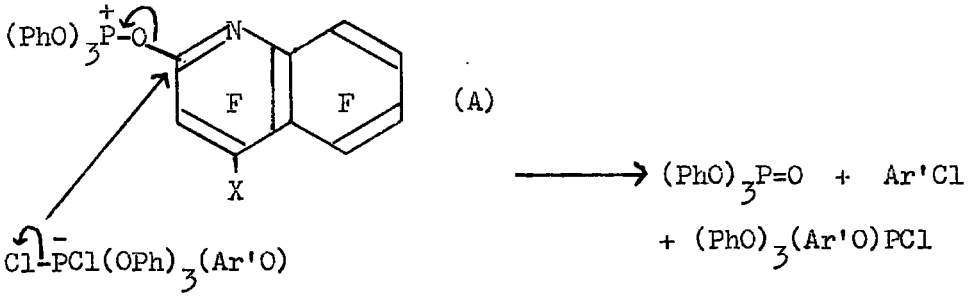
2- and 4-Hydroxyquinolines are readily converted to the corresponding chloroquinolines by reaction with phosphorus oxychloride and/or phosphorus pentachloride.[232] However, it was found that 5,6,7,8-tetrafluoroquinoline[32] reacted with phosphorus pentachloride to give replacement of fluorine by chlorine whilst 1-hydroxyhexafluoroisoquinoline[164] was extensively decomposed by heating with the same reagent. A more likely method of replacing the hydroxyl group of 2-hydroxyhexafluoroquinoline by chlorine appeared to be that developed by Coe, Rydon and Tonge[233] and is outlined below:

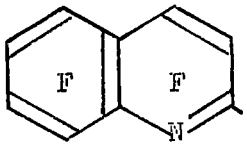
$$3PhOH + PCl_5 \xrightarrow[4\text{-}5 \text{ hrs.}]{100^\circ C} (PhO)_3PCl_2 + 3HCl$$

$$(PhO)_3PCl_2 + Ar'OH \xrightarrow[4\text{-}5 \text{ hrs.}]{100^\circ C} (PhO)_3(Ar'O)PCl + HCl$$

$$(PhO)_3(Ar'O)PCl \xrightarrow[10\text{-}20 \text{ mins.}]{250\text{-}350^\circ C} Ar'Cl + (PhO)_3P{=}O$$

It was found that Ar'Cl was produced in good yield, rather than PhCl, where Ar' contained electron-withdrawing substituents and hence appeared eminently suitable for the desired conversion. However, the product from the reaction with 2-hydroxyhexafluoroquinoline was a mixture of 2-chloro-hexafluoro- and 2,4-dichloropentafluoro-quinolines in 24·3 and 26·6% yields respectively (obtained from analytical-scale v.p.c. analysis of the mixture). The compound $(PhO)_3(Ar'O)PCl$ exists[233] in the dimeric ionic form $[(PhO)_3(Ar'O)P]^+[(PhO)_3(Ar'O)PCl_2]^-$ for Ar' = Ph and probably so for Ar' =  , and the formation of Ar'Cl probably occurs in the following way



where Ar' =  , X = F

i.e. involving nucleophilic attack by chloride ion at the 2-position of the fluorinated quinoline nucleus, most probably by an S_NAr2 mechanism. The reaction, however, is complicated by the great susceptibility of the

4-fluorine towards nucleophilic attack. The replacement of the 4-fluorine by chlorine could occur either by reaction of chloride ion on 2-chlorohexafluoroquinoline, or by attack of chloride ion at either the 2- or 4-positions of the polyfluoroquinoline nucleus in (A). The compound so formed by attack at position 4 (A, X = Cl) undergoing further attack at position 2 to give the 2,4-dichloro compound.

The monochloro- and dichloro-compounds formed were separated with difficulty by preparative-scale v.p.c. The monochloro compound could be isolated pure in reasonable amount but the dichloro compound was obtained pure in only very small amount. Its i.r. spectrum was identical to that of 2,4-dichloropentafluoropyridine obtained by reaction of heptafluoroquinoline with hydrogen chloride in sulpholane.

CHAPTER 6

EXPERIMENTAL WORK. PART II.

Experimental Work.

Some Reactions of Highly Fluorinated Quinolines.

Physical measurements were made as in the experimental for Part I unless otherwise stated. Ultra-violet (U.V.) spectra were recorded using an Optica C.F.4 or Unicam S.P.800 spectrophotometer, and molecular weights were determined mass spectrometrically using an A.E.I. M.S.9 machine.

Reaction of Heptafluoroquinoline with Sodium Methoxide.

(i) Sodium (0·10 gm., 4·48 m.g. atom) was added to dry methanol (5 ml.) and the resulting solution was added slowly to a stirred solution of heptafluoroquinoline (1·14 gm., 4·48 m.mole) in dry methanol (12 ml.) at 15°C; the complete operation being carried out under an atmosphere of dry nitrogen. The mixture was stirred for a further 15 min. after which it was poured into cold (0°C) water. A white solid precipitated and was extracted into methylene dichloride, the extracts dried ($MgSO_4$), and the solvent removed to leave a light yellow solid (0·91 gm.) which was shown by analytical-scale v.p.c. (silicone elastomer on celite at 202°C) to consist essentially (97%, 76% yield) of two isomers of monomethoxy-hexafluoroquinoline in ratio of 3·4:1, together with 2% of heptafluoro-quinoline and 1% of dimethoxypentafluoroquinoline. Separation of the two isomers was achieved by preparative-scale v.p.c. (silicone elastomer at 205°C) and after sublimation at reduced pressure the isomer with lower retention time, which was present in greater amount, being 2-methoxyhexa-

fluoroquinoline was obtained, m.pt. 50·5 - 51·5° (Found: C, 45·2; H, 1·0; F, 42·4. $C_{10}H_3F_6NO$ requires C, 44·9; H, 1·1; F, 42·7%). I.R. spectrum No. 5. Sublimation of the other isomer gave 4-methoxyhexafluoroquinoline, m.pt. 50·5 - 51·5° (Found: C, 44·6; H, 1·0; F, 42·4%). I.R. spectrum No. 6. Carrying out the reaction at 0°C gave a mixture of the two isomers in the ratio 2·2:1 (the 2-isomer being present in greater amount) but more (6%) unreacted heptafluoroquinoline was recovered.

(ii) Sodium (0·19 gm., 8·22 m.g. atom) dissolved in dry methanol (10 ml.) was added to a stirred solution of heptafluoroquinoline (1·05 gm., 4·12 m.mole) in dry methanol (15 ml.) and the mixture refluxed under dry nitrogen for 1½ hr. On cooling a white solid precipitated which was filtered off, washed (H_2O) and recrystallised (MeOH) to give 2,4-dimethoxypentafluoroquinoline (0·73 gm., 64% yield), m.pt. 107·5 - 108·5° (Found: M.W. 279; C, 47·7; H, 2·4; F, 33·6. $C_{11}H_6F_5NO_2$ requires: M.W. 279; C, 47·3; H, 2·2; F, 34·0%). I.R. spectrum No. 7. The filtrate from the reaction mixture on pouring into cold (0°) water gave a white solid which was extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent removed to leave a white solid (0·19 gm.) which was shown by analytical v.p.c. (silicone elastomer at 202°) to consist of 2,4-dimethoxypentafluoroquinoline and 2-methoxyhexafluoroquinoline in ratio of 6:1 respectively. This represents a total conversion to 2,4-dimethoxypentafluoroquinoline of 79%.

(iii) Sodium (0·27 gm., 11·57 m.g. atom) dissolved in dry methanol (15 ml.) was added to a stirred solution of heptafluoroquinoline (1·0 gm., 3·93 m.mole) in dry methanol (25 ml.) and the mixture refluxed for 4 hours under an atmosphere of dry nitrogen. After cooling and pouring into cold (0°C) water, the white solid formed was extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent distilled to leave a white solid (0·90 gm.) which was shown by analytical-scale v.p.c. (silicone elastomer at 202°C) to consist of a 1:1 mixture of 2,4-dimethoxypentafluoroquinoline and a trimethoxytetrafluoroquinoline. Separation of the trimethoxy compound was achieved by preparative-scale v.p.c. (silicone elastomer at 220°C) and after sublimation at reduced pressure gave a white solid (Found: C, 49·3; H, 3·3; F, 25·6. $C_{12}H_9F_4NO_3$ requires: C, 49·5; H, 3·1; F, 26·1%). It acquired a glossy appearance in the range 123-135°C before melting at 135-136°. It showed only one peak on analytical-scale v.p.c. and n.m.r. spectroscopy (see page 233) showed it to be > 90% a single isomer of 2,4,6- or 2,4,7-trimethoxytetrafluoroquinoline. I.R. spectrum No. 8.

Reaction of Heptafluoroquinoline with Aqueous Ammonia.

Aqueous ammonia (1·0 ml., 0·88 s.g.) was added to a stirred solution of heptafluoroquinoline (1·0 gm., 3·93 m.mole) in acetone (10 ml.) at 20°C and the mixture stirred for 45 min. after which it was poured into cold (0°) water. The white solid precipitate was extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent distilled to leave a light yellow

solid (0·90 gm.) which was shown by ^{19}F n.m.r. spectroscopy to be a mixture of 2- and 4-aminohexafluoroquinolines (91% yield) in ratio of 50:50 (± 5). The two isomers were not resolvable by v.p.c. (silicone elastomer at 240°). Recrystallisation (acetone-methylene chloride) followed by sublimation under reduced pressure (125°/0·15 mm.) gave pure 2-aminohexafluoroquinoline, m.pt. 224-225°C (Found: C, 42·5; H, 0·97; F, 45·2. $C_9H_2F_6N_2$ requires: C, 42·9; H, 0·80; F, 45·2%). I.R. spectrum No. 9. Repeated fractional sublimation and recrystallisation failed to give a pure sample of the 4-isomer. The best obtained was a sample containing 20% of the 2-isomer and 80% of the 4-isomer (estimated by n.m.r.), m.pt. 158·5 - 160°C (Found: C, 42·7; H, 0·84; F, 45·6%). I.R. spectrum No. 10.

Reaction of Heptafluoroquinoline with Hydrazine.

Hydrazine hydrate (1·28 gm., 25·64 m.mole) in dioxan (5 ml.) was added to a stirred solution of heptafluoroquinoline (3·09 gm., 12·12 m.mole) in dioxan (20 ml.) at 20°C, the mixture stirred for 45 mins. and poured into cold (0°C) water. The white solid precipitate was extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent distilled to leave a pale yellow solid (2·95 gm.). Recrystallisation (CH_2Cl_2) and sublimation under reduced pressure (110°C/0·15 mm.) gave pure 2-hydrazinohexafluoroquinoline (2·45 gm., 76%) m.pt. 196° (decomp.) (Found: C, 40·5; H, 1·21; F, 42·6. $C_9H_3F_6N_3$ requires: C, 40·46; H, 1·13; F, 42·67%). I.R. spectrum No. 11. The material remaining from the recrystallisation was

an orange-brown colour and could not be further purified by recrystallisation or sublimation. Its i.r. spectrum (No.12) suggested the presence of another polyfluorohydrazinoquinoline. That it was the 4-isomer was confirmed by oxidation to the corresponding 4-hydrohexafluoroquinoline (see below). Initially the reaction between heptafluoroquinoline and hydrazine hydrate was carried out in refluxing dioxan. Under these conditions extensive decomposition occurred and a low (27%) yield of 2-hydrazinohexafluoroquinoline was obtained together with considerable dark brown residue which was not investigated.

Reaction between 2- and 4-methoxyhexafluoroquinolines and Sodium Methoxide.

Sodium (0·063 gm., 2·74 m.mole) dissolved in dry methanol (10 ml.) was added to a stirred solution of 2- and 4-methoxyhexafluoroquinolines (0·73 g., 2·75 m.mole) in dry methanol (10 ml.) at 20°C and the mixture refluxed for $3\frac{1}{2}$ hours. The cooled solution was poured into cold (0°) water, the white solid extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent distilled to leave 2,4-dimethoxypentafluoroquinoline (0·6 gm., 78%), identified by analytical-scale v.p.c. and comparison of its i.r. spectrum with an authentic sample.

Reaction between 2-hydrazinohexafluoroquinoline and aqueous Hydriodic Acid.

(i) In absence of solvent. 2-Hydrazinohexafluoroquinoline (1·02 gm., 3·82 m.mole) and aqueous hydriodic acid (8 ml., 54% w/w) were refluxed together for $2\frac{1}{2}$ hours. The cooled solution was treated with excess

sodium metabisulphite to leave a yellow solution containing an insoluble black solid. The complete reaction product was shaken with methylene dichloride and filtered to leave a black solid. The organic layer was separated, dried ($MgSO_4$) and the solvent distilled to leave a brown solid (0·15 gm.). This was sublimed at reduced pressure (120°C/0·5 mm.) to give a small amount of a pale yellow solid whose i.r. spectrum showed it to be essentially unreacted starting material, but the bulk of it did not sublime. No precipitate was obtained on neutralising the aqueous solution which remained with sodium bicarbonate.

(ii) In tetrahydrofuran. To a solution of 2-hydrazinohexafluoroquinoline (0·92 gm., 3·45 m.mole) in tetrahydrofuran (50 ml.) was added aqueous hydriodic acid (8 ml., 54% w/w) and the mixture refluxed for 2 hours. The cooled solution was treated with excess sodium metabisulphite and the tetrahydrofuran distilled to leave an aqueous suspension of a brown solid. The solid was extracted into ether, the extracts dried ($MgSO_4$) and concentrated to give a light brown solid (0·17 gm.) which was sublimed at reduced pressure (140°C/0·1 mm.) to give 2-hydrazinohexafluoroquinoline (identified by comparison of its i.r. spectrum with an authentic sample). On distilling the remaining ether solution to dryness a dark brown solid (0·4 gm.) remained which on sublimation (140°C/0·1 mm.) gave a small amount of a yellow solid whose i.r. spectrum suggested it was essentially unreacted starting material. Remaining unsublimed was a black viscous liquid.

Reaction between 2-hydrazinohexafluoroquinoline and Benzaldehyde.

To a stirred solution of 2-hydrazinohexafluoroquinoline (0·90 gm., 3·33 m.mole) in ethanol (75 ml.), concentrated hydrochloric acid (1 ml.) was added and then benzaldehyde (0·80 gm., 7·55 m.mole). After stirring at room-temperature for 5 minutes no precipitate formed and further concentrated hydrochloric acid (1 ml.) was added when a faint cloudiness developed. Stirring was continued for a further 2 hours when a slight pale orange precipitate formed. The solution was concentrated to $\approx$ 25 ml. when a pale orange solid precipitated (0·85 gm.). Recrystallisation (ethyl acetate) gave benzaldehyde-3,4,5,6,7,8-hexafluoroquinolylhydrazone as a very pale yellow solid, m.pt. 213·5 - 214·5 (decomp.) (0·57 gm., 47·6%) (Found: C, 54·2; H, 2·03. $C_{16}H_7N_3F_6$ requires C, 54·09; H, 1·99%). I.R. spectrum No. 13. Further concentration of the ethanolic solution (to $\approx$ 5 ml.) gave 2-hydrazinohexafluoroquinoline (0·17 gm.) which was identified by comparison of its i.r. spectrum with an authentic sample.

Reduction of benzaldehyde-3,4,5,6,7,8-hexafluoroquinolylhydrazone.

Benzaldehyde-3,4,5,6,7,8-hexafluoroquinolylhydrazone (0·55 gm., 1·55 m.mole) was added to a suspension of activated zinc dust (1·05 gm., 16·06 m.g. atom) in glacial acetic acid (32 ml.) and the mixture refluxed for 2¼ hours. Water (30 ml.) was added (when a white solid precipitated), the reaction mixture steam distilled, the steam distillate extracted with methylene dichloride, the extracts dried ($MgSO_4$) and the solvent

distilled to leave an off-white solid (0·2 gm.). This was sublimed at reduced pressure (120°C/0·15 mm.) to give a white solid, m.pt. 205-222° (decomp.). Treatment with concentrated hydrochloric acid and filtration of the cloudy solution gave a negligible amount of a white solid. Neutralisation (Na_2CO_3) of the acid filtrate gave a white precipitate, which was extracted (CH_2Cl_2), the extracts dried ($MgSO_4$), the solvent distilled and the residue sublimed (90°C/0·05 mm.) to give a white solid, m.pt. 210-222°C, i.r. spectrum No. 14. Recrystallisation from glacial acetic acid or from acetone gave a product with an i.r. spectrum identical to that above. Its i.r. spectrum was similar to that of 2-aminohexafluoroquinoline in the range 4000-2000 $cm.^{-1}$ but showed some marked differences in the range below 2000 $cm.^{-1}$. However, the overall similarity was consistent with it containing a polyfluoroaminoquinoline.

Reaction of 2-hydrazinohexafluoroquinoline with aqueous Copper Sulphate.

To a suspension of 2-hydrazinohexafluoroquinoline (2·22 gm., 8·31 m.mole) in water (50 ml.) a solution of copper sulphate (3·85 gm., $CuSO_4.5H_2O$ in 70 ml. water) was added slowly over 3/4 hr. Further copper sulphate solution (1·2 gm. $CuSO_4.5H_2O$ in 10 ml. water) was added and the mixture heated under reflux for 1 hour. The mixture was steam distilled, the distillate extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent distilled to leave a pale yellow solid (0·5 gm., 25·4%). Sublimation under reduced pressure (20-30°C/0·1 mm.) gave 2-hydrohexafluoroquinoline, m.pt. 62·5 - 64·5° (Found: C, 45·8; H, 0·42.

C_9NF_6H requires: C, 45·6; H, 0·77%). I.R. spectrum No. 15. It showed only 1 peak on analytical-scale v.p.c. (silicone elastomer at 153°) and ^{19}F n.m.r. spectroscopy showed it to be > 90% the single isomer.

Reaction between aqueous Copper Sulphate and the crude reaction product formed between Heptafluoroquinoline and Hydrazine.

Heptafluoroquinoline (5·0 gm., 19·6 m.mole) was reacted with hydrazine hydrate (2·05 gm., 41·0 m.mole) as previously to give, after removal of methylene dichloride and dioxan, a yellow brown solid (5·18 gm.). To a suspension of this crude product in water (75 ml.) a solution of copper sulphate (8·96 gm. $CuSO_4.5H_2O$ in 25 ml. water) was added over 20 minutes. Further copper sulphate solution (2·85 gm. $CuSO_4.5H_2O$ in 10 ml. water) was added and the mixture refluxed for $1\frac{3}{4}$ hours. The mixture was steam distilled, the distillate extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent distilled to leave a small amount of a viscous yellow liquid. Sublimation under reduced pressure (25°C/ 0·15 mm.) gave a semi-solid white material (≈ 0·1 gm.) and left unsublimed was a small amount of a yellow-orange solid which was not further investigated. Analytical-scale v.p.c. (silicone elastomer at 150°C) showed the sublimed material to consist of two components in the ratio of 2:1. Comparison of retention times showed neither to be heptafluoroquinoline and the component in smaller amount, which had the slightly longer retention time (the two peaks overlapped at their bases),

had identical retention time to 2-hydrohexafluoroquinoline. The other component was presumably another isomer of hexafluoroquinoline and the ^{19}F n.m.r. spectrum of the mixture showed it to be a mixture of 2- and 4-hydrohexafluoroquinolines.

Attempted Oxidation of 2-Aminohexafluoroquinoline with Trifluoroperoxyacetic Acid.

a) A mixture of methylene dichloride (10 ml.), trifluoroacetic anhydride (2·5 ml.) and 90% hydrogen peroxide (1 ml.) was stirred and heated under reflux for 15 mins. A suspension of 2-aminohexafluoroquinoline (1·0 gm., 3·97 m.mole) in methylene dichloride (100 ml.) was added to the cooled solution (15°) and the mixture immediately became yellow. The mixture was then refluxed, after 3/4 hour further hydrogen peroxide (0·5 ml.) was added and again after 2½ hours, together with trifluoroacetic anhydride (0·5 ml.). After a total reflux time of 20 hours the solution was a dark brown. Dilute hydrochloric acid was added to the cooled solution, the methylene dichloride layer separated, washed with further acid, dried ($MgSO_4$) and the solvent distilled through a short Vigreux column to leave a dark brown viscous liquid (0·3 gm.). It dissolved in 40-60° petroleum ether but concentration of the solution gave no precipitate. The solvent was distilled and the residue pumped under vacuum (20°C/1 mm.) to leave a gummy brown solid which on sublimation (60-65°C/0·5 mm.) gave a small amount of an orange gummy material.

b) 2-Aminohexafluoroquinoline (1·0 gm., 3·97 m.mole) in suspension in methylene dichloride (100 ml.) was added to a solution of trifluoroperoxyacetic acid prepared as in a), at room-temperature and the pale-yellow mixture stirred at room-temperature for $2\frac{1}{2}$ hours to give a yellow solution. Dilute hydrochloric acid was added, the methylene dichloride layer separated, washed with more acid, dried ($MgSO_4$) and the methylene dichloride solution concentrated to 10 ml. when a white solid (0·25 gm.) precipitated. It was filtered off, dried and shown by its i.r. spectrum to be unreacted starting material. Removal of the remaining methylene dichloride gave a small amount of an orange gummy solid. The acidic aqueous layer remaining was a red colour.

Reaction of Heptafluoroquinoline with Trifluoroperoxyacetic Acid.

Heptafluoroquinoline (1·0 gm., 3·9 m.mole) was treated as in a) above. The cooled, yellow reaction mixture was made alkaline with excess of a 10% aqueous solution of sodium hydroxide (200 ml.). The colourless methylene dichloride layer was separated, dried ($MgSO_4$) and the solvent distilled to leave heptafluoroquinoline (0·60 gm.). The aqueous basic layer was acidified, extracted with methylene dichloride, the extracts dried ($MgSO_4$) and the solvent distilled to leave a light brown solid (0·1 gm.). Sublimation under reduced pressure (100-110°C/0·1 mm.) gave a white solid, identified by its i.r. spectrum as 2-hydroxyhexafluoroquinoline.

Relative reactivity of Heptafluoroquinoline and Pentafluoropyridine.

Sodium (0·129 gm., 5·61 m.mole) dissolved in dry methanol (10 ml.) was added over 5 minutes to a well-stirred solution of pentafluoropyridine (0·86 gm., 5·09 m.mole) and heptafluoroquinoline (1·298 gm., 5·09 m.mole) in methanol (10 ml.) at 20°. The solution was stirred for 40 minutes, poured in water (100 ml.), extracted with methylene dichloride, the extracts dried ($MgSO_4$), the solvent distilled and the product analysed by analytical-scale v.p.c. (Griffin and George Gas Density Balance, silicone elastomer at 176°C). The v.p.c. apparatus was precalibrated and it was found that for a mixture of compounds the relative ratio $\frac{\text{peak area}}{\text{mol. wt.}}$ for the compounds was proportional to their relative molar concentrations. The peak areas of the product derived from pentafluoropyridine (4-methoxytetrafluoropyridine) and the products from heptafluoroquinoline (2- and 4-methoxyhexafluoro- and 2,4-dimethoxypentafluoro-quinoline) were measured and the relative reactivity of the two compounds towards methoxide ion derived as shown below

Product from C_9NF_7	Peak Area (Relative)	Ratio	$\frac{\text{Peak Area}}{\text{Mol.Wt.}}$
C_9NF_6OMe	509		1·91
$C_9NF_5(OMe)_2$	27		0·095
Product from C_5F_5N			
C_5F_4NOMe	153		0·85

$$\text{Relative reactivity } \frac{C_9NF_7}{C_5NF_5} = \frac{1\cdot91 + (2^* \times 0\cdot095)}{0\cdot85} = \frac{2\cdot5}{1}$$

*The ratio due to $C_9NF_5(OMe)_2$ includes a factor of 2 in order to correlate this with the reactivity of C_9NF_7 towards methoxide ion.

Hence, the relative reactivity towards methoxide ion in methanol of heptafluoroquinoline and pentafluoropyridine at 20° is 2·5:1.

Preparation of Polyfluorohydroxyquinolines and their methylation with diazomethane.

Demethylation of 2,4-dimethoxypentafluoroquinoline with Hydriodic Acid.

2,4-Dimethoxypentafluoroquinoline (1·25 gm., 4·0 m.mole) and aqueous hydriodic acid (15 ml., 54% w/w) were refluxed for 5½ hours and the cooled solution was treated with sodium metabisulphite to remove free iodine. The reaction mixture was treated with excess of 10% aqueous sodium hydroxide when a white precipitate probably consisting of the sodium salts of the fluorinated hydroxyquinolines was obtained. Extraction of this basic mixture with methylene dichloride, separation of the organic layer and distillation of the solvent showed no unreacted starting material to be present. The aqueous, basic suspension was acidified and the resulting suspension of white solid was shaken with methylene dichloride. This dissolved some of the solid and the extract was separated; the undissolved portion filtered off, washed with more methylene dichloride, and the washings added to

the extract. The extract and washings were dried ($MgSO_4$) and the solvent distilled to leave a white solid (0·5 gm., 42·1%) which, after recrystallisation from chloroform/benzene gave 2-hydroxy-4-methoxypentafluoroquinoline. It decomposed over the range 250-263°C to a black viscous liquid. (Found: C, 45·4; H, 1·61; F, 35·8. $C_{10}H_4F_5O_2N$ requires: C, 45·3; H, 1·52; F, 35·8%). I.R. spectrum No. 16. The undissolved portion which had been filtered, was recrystallised (ethyl acetate) to give 2,4-dihydroxypentafluoroquinoline (0·25 gm., 22·2%) which decomposed over the range 245-255°C to a dark brown solid. I.R. spectrum No. 17. The amount of 2,4-dihydroxypentafluoroquinoline formed during the demethylation increased when the time of reflux with hydriodic acid increased. Thus, with a reflux time of 24 hours, 2-hydroxy-4-methoxypentafluoroquinoline was obtained in 9·5% yield whilst the yield of 2,4-dihydroxypentafluoroquinoline was increased to 71·1%.

Methylation of 2,4-dihydroxypentafluoroquinoline.

To 2,4-dihydroxypentafluoroquinoline (2·35 gm., 8·42 m.mole) suspended in dry ether (300 ml.) was added an excess of a solution of diazomethane in ether* at room-temperature. The solution was stirred for 30 minutes with the diazomethane in excess, filtered (to remove a negligible amount of a white flocculent solid) and the solvent distilled

*See reference 234 for preparation of an ethereal solution of diazomethane.

to leave a white solid (2·1 gm.). Analytical-scale v.p.c. (silicone elastomer at 230°C) showed it to consist of two components in ratio of 9:10; the component in smaller amount, which had the shorter retention time, being 2,4-dimethoxypentafluoroquinoline. The other component was separated by fractional sublimation at reduced pressure and re-crystallisation (40-60 petroleum ether-methylene dichloride) and further sublimed (90°C/0·1 mm.) to give pentafluoro-4-methoxy-N-methyl-2-quinolone (0·55 gm.) m.pt. 115-116°C. (Found: C, 47·5; H, 2·12; F, 34·5; M.W. 279. $C_{11}F_5O_2H_6N$ requires: C, 47·3; H, 2·17; F, 34·0%; M.W. 279). I.R. spectrum No. 18.

Methylation of 2-hydroxy-4-methoxypentafluoroquinoline.

Treatment with diazomethane as above gave a product shown by analytical-scale v.p.c. (silicone elastomer at 230°C) to consist of 2,4-dimethoxypentafluoroquinoline and pentafluoro-4-methoxy-N-methyl-2-quinolone in ratio of 8:10 respectively.

Preparation of 4-hydroxy-2-methoxypentafluoroquinoline.

2-Methoxyhexafluoroquinoline (0·62 gm., 2·3 m.mole), potassium hydroxide (0·28 gm., 5·0 m.mole and water (20 ml.) were heated under reflux for 5½ hours. After cooling the basic solution was extracted with methylene dichloride, the extracts dried ($MgSO_4$) and the solvent distilled to leave 2-methoxyhexafluoroquinoline (0·18 gm., 0·67 m.mole, identified by comparison of its i.r. spectrum with an authentic sample).

The basic aqueous solution remaining was acidified (HCl), extracted (CH_2Cl_2), the extracts dried and the solvent distilled to leave a white solid (0·25 gm.). Recrystallisation from petroleum ether (b.pt. 40-60°) gave 4-hydroxy-2-methoxypentafluoroquinoline, m.pt. 151-152° (slight decomp.) (Found: C, 45·1; H, 1·4; F, 35·3. $C_{10}F_5O_2H_4N$ requires: C, 45·3; H, 1·52; F, 35·83). I.R. spectrum No. 19. The yield, based on 2-methoxyhexafluoroquinoline consumed is 56·8%.

Methylation of 4-hydroxy-2-methoxypentafluoroquinoline.

Methylation of 4-hydroxy-2-methoxypentafluoroquinoline (0·15 gm., 0·56 m.mole) was carried out as for 2,4-dihydroxypentafluoroquinoline and gave 2,4-dimethoxypentafluoroquinoline only (0·15 gm., 95% yield, identified by analytical scale v.p.c. (silicone elastomer at 228°) and comparison of its i.r. spectrum with an authentic sample.

Demethylation of 4-methoxyhexafluoroquinoline.

(a) Using Hydriodic Acid: 4-Methoxyhexafluoroquinoline (0·3 gm., 1·0 m.mole) and aqueous hydriodic acid (7 ml., 54% w/w) were refluxed for $3\frac{1}{2}$ hours and the cooled solution was treated with sodium meta-bisulphite. Addition of an excess of 10% aqueous sodium hydroxide gave a clear solution from which nothing was extracted into methylene dichloride. The alkaline solution was acidified (HCl) when a white solid precipitated. The acidic suspension was shaken with methylene dichloride when some of the solid dissolved. The undissolved solid was filtered off, washed with methylene dichloride and the washings combined

with the extracts of the acid solution. The extracts were dried ($MgSO_4$) and the solvent distilled to leave 2-hydroxy-4-methoxypentafluoroquinoline (0·06 gm., i.r. spectrum identical with an authentic sample). The solid insoluble in methylene dichloride was recrystallised from acetone to give a white solid (0·16 gm.) (Found: C, 42·1; H, 1·41; F, 35·5. $C_9NF_6(OH)$ requires: C, 42·7; H, 0·40; F, 45·04. $C_9NF_5(OH)_2$ requires: C, 43·0; H, 0·80; F, 37·83%). It decomposed in the range 260-275°C to a dark brown solid and its i.r. spectrum was consistent with it being mainly 2,4-dihydroxypentafluoroquinoline.

(b) Using Aluminium Trichloride: 4-Methoxyhexafluoroquinoline (0·2 gm., 0·7 m.mole) and anhydrous aluminium trichloride (0·35 gm., 3·0 m.mole) were heated at 120-130°C for $3\frac{3}{4}$ hours, and after cooling the reaction mixture was treated with ice. The insoluble brown solid resulting was extracted into methylene dichloride, the extracts dried ($MgSO_4$) and the solvent distilled to leave a light brown solid (0·2 gm.). Sublimation under reduced pressure (80°C/0·05 mm.) gave a pale yellow solid (0·15 gm.). (The absence of any sublimation at 20-30°C/0·05 mm. showed no unreacted starting material to be present). The sublimate had m.pt. 137·5-139·5° (decomp.) and gave on analysis C, 43·5; H, 0·91; F, 41·0; Cl $\approx$ 0·5%. (C_9NF_6OH requires: C, 42·7; H, 0·40; F, 45·0% . A mixture of C_9NF_6OH (80%) and $C_9NF_5Cl(OH)$ (20%) requires: C, 42·2; F, 43·1; H, 0·4; Cl, 2·6%). I.R. spectrum No. 20.

Methylation of the product from the reaction of 4-methoxyhexafluoroquinoline and Aluminium Trichloride.

Treatment of the product formed in the reaction between 4-methoxyhexafluoroquinoline and anhydrous aluminium trichloride in the usual way and analysis of the products by analytical v.p.c. (silicone elastomer at 202°C) showed 80% of the product to be 4-methoxyhexafluoroquinoline. The remaining product consisted of two compounds of higher retention time in ratio of 1:19; the compound in smaller amount had retention time slightly longer than hexafluoro-N-methyl-2-quinolone (see below) and the other had retention time slightly longer than pentafluoro-4-methoxy-N-methyl-2-quinolone. Their composition is unknown but it is likely that they contain chlorine.

Demethylation of 2-methoxyhexafluoroquinoline.

2-Methoxyhexafluoroquinoline (1·0 gm., 4·0 m.mole) and anhydrous aluminium trichloride (1·1 gm., 8·0 m.mole) was heated at 120° for 3½ hours and the cooled reaction mixture was treated with ice. A brown solid precipitated and was extracted into methylene dichloride, the extracts dried ($MgSO_4$) and the solvent distilled. The residue was treated with 10% aqueous sodium hydroxide and the solution plus suspension of sodium salts formed was shaken with methylene dichloride. The methylene dichloride was separated, dried ($MgSO_4$) and the solvent distilled to leave a small amount of an orange solid ($\approx$ 0·05 gm.) of unknown composition. The alkaline suspension remaining was acidified and

the solid hydroxy-compound formed extracted into methylene dichloride. After drying ($MgSO_4$) the solvent was distilled to leave a pale-yellow solid (0·5 gm.). Recrystallisation (60-80 petroleum ether-methylene dichloride) gave 2-hydroxyhexafluoroquinoline as a white solid (0·4 gm., 42·2%), m.pt. 196-211° (decomp.) (Found: C, 42·4; H, 0·37; F, 45·3. C_9F_6HON requires: C, 42·7; H, 0·40; F, 45·0%). I.R. spectrum No. 21.

Methylation of 2-hydroxyhexafluoroquinoline.

Methylation with excess diazomethane as for 2,4-dihydroxypentafluoroquinoline and analysis of the products by analytical-scale v.p.c. (silicone elastomer at 200°C) showed it to consist of 2-methoxyhexafluoroquinoline and hexafluoro-N-methyl-2-quinolone (see below) in ratio of 2:3 respectively.

Reaction between Heptafluoroquinoline and Potassium Hydroxide.

The polyfluorohydroxyquinolines formed by reaction between heptafluoroquinoline and potassium hydroxide were not isolated, but the total reaction products were methylated with diazomethane in the usual way and the methylated products so formed were characterised.

(i) A mixture of heptafluoroquinoline (3·0 gm., 12·0 m.mole) and potassium hydroxide (1·32 gm., 24·0 m.mole) in tertiary butanol (36 ml.) was refluxed, with stirring, for 2 hours. After cooling, water (45 ml.) was added and the tertiary butanol distilled off. The aqueous basic solution was extracted (CH_2Cl_2), the extracts dried ($MgSO_4$) and the solvent distilled to leave heptafluoroquinoline (0·05 gm., identified by

comparison of its i.r. spectrum with an authentic sample). The aqueous layer was acidified, extracted with ether, the extracts dried ($MgSO_4$) and the ethereal solution treated with excess diazomethane at room-temperature. The usual work-up procedure gave a white solid (2·35 gm.) which analytical-scale v.p.c. (silicone elastomer at 205°C) showed to consist of:- [Figures in brackets are percentages of the reaction product].

2-Methoxyhexafluoroquinoline	(32%)
4-Methoxyhexafluoroquinoline	(6%)
Hexafluoro-N-methyl-2-quinolone	(62%)

Fractional sublimation at reduced pressure (35-50°C/0·1 mm.) removed the bulk of the monomethoxyhexafluoroquinolines and at 80-90°C/0·1 mm. the sublimate (0·5 gm.) was ≈ 98% the quinolone. Recrystallisation (40-60 petroleum ether) gave pure <u>hexafluoro-N-methyl-2-quinolone</u> (0·38 gm.) m.pt. 127·0 - 127·4°. (Found: C, 45·0; H, 1·41; F, 41·7; M.W. 267. $C_{10}F_6H_3ON$ requires: C, 45·0; H, 1·13; F, 42·7%; M.W. 267). I.R. spectrum No. 22.

(ii) Heptafluoroquinoline (2·0 gm., 8·0 m.mole), potassium hydroxide (0·88 gm., 16·0 m.mole), and water (50 ml.) were refluxed, with stirring, for 4¼ hours. After cooling, the solution was extracted with methylene dichloride, the extracts dried ($MgSO_4$) and the solvent removed to leave heptafluoroquinoline (0·01 gm., identified by comparison of its i.r. spectrum with an authentic sample). The aqueous solution was

acidified, extracted with ether, the extracts dried ($MgSO_4$) and methylated in the usual way to give a white solid (1·4 gm.) which was shown by analytical-scale v.p.c. to comprise:-

2-Methoxyhexafluoroquinoline	(30%)
4-Methoxyhexafluoroquinoline	(20%)
Hexafluoro-N-methyl-2-quinolone	(50%)

(iii) Heptafluoroquinoline (2 gm., 8·0 m.mole) was reacted as in (i) but with three molecular proportions of potassium hydroxide (1·33 gm., 24·0 m.mole) and gave a methylated product (1·70 gm.) shown by analytical-scale v.p.c. to comprise:-

2-Methoxyhexafluoroquinoline	(40%)
4-Methoxyhexafluoroquinoline	(2%)
Hexafluoro-N-methyl-2-quinolone	(38%)
2,4-Dimethoxypentafluoroquinoline	(15%)
Pentafluoro-4-methoxy-N-methyl-2-quinolone	(5%)

Relative Rates of Oxidation of 2-Methoxyhexafluoroquinoline and Hexafluoro-N-methyl-2-quinolone.

To 2 ml. of an acetone solution of 2-methoxyhexafluoroquinoline at 21°C (containing 0·014 gm. in 5 ml. dry ($MgSO_4$) acetone) was added 20 µl. of a solution of potassium permanganate in dry acetone, the test-tube stoppered and the time taken (25 min.) for the colour to be discharged noted. Hexafluoro-N-methyl-2-quinolone was treated in exactly

the same way, the colour being discharged in 1½ mins. When 20 µl. of the permanganate solution was added to 2 ml. of acetone at 21°C in a stoppered test-tube, the colour was discharged in 60 mins.

Reactions involving the ring nitrogen of Heptafluoroquinoline.

Reaction between heptafluoroquinoline and gaseous hydrogen chloride.

Gaseous dry hydrogen chloride (great excess) was bubbled through a solution of heptafluoroquinoline (0·32 gm., 1·26 m.mole) in sodium-dried ether (25 ml.) for 10 hours at room-temperature. The solution remained clear at all times and distillation of the solvent left heptafluoroquinoline (0·30 gm.), identified by comparison of its i.r. spectrum with an authentic sample.

Reaction between heptafluoroquinoline and boron trichloride.

Boron trichloride (0·91 gm., 7·78 m.mole) was condensed under vacuum into a cooled (liquid air) 100 ml. B24 single-necked flask containing heptafluoroquinoline (0·96 gm., 3·76 m.mole) dissolved in dry carbon tetrachloride (10 ml., dried by distillation from phosphorus pentoxide). The flask was connected to the vacuum system by a B24/B10 double cone with a tap at its centre. With the tap closed the flask was allowed to warm to 0-10°C (ice-salt bath) and maintained at this temperature for 1½ hours. The solution remained clear and colourless during this period. The solvent and boron trichloride were pumped off at room-temperature

and reduced pressure (0·01 mm.) to leave heptafluoroquinoline (0·95 gm.), identified by comparison of its i.r. spectrum with an authentic sample.

Reactions of solutions in concentrated sulphuric acid of Heptafluoroquinoline and related Polyhalo-N-heteroaromatic Compounds with water.

Heptafluoroquinoline.

a) Heptafluoroquinoline (1·0 gm., 3·9 m.mole) dissolved in sulphuric acid (20 ml., s.g. 1·84) was slowly diluted with water (100 ml.), the water being added dropwise to the cooled (0°) stirred solution over ½ hour. The white precipitate formed (0·8 gm.) was filtered, washed with water and sublimed at reduced pressure (100°/0·05 mm.) to give hexafluoro-2-hydroxyquinoline, identified by comparison of its i.r. spectrum with an authentic sample. The purity of the product was confirmed by methylation of an ethereal solution with excess of an ethereal solution of diazomethane. The methylated product was shown by analytical-scale v.p.c. (silicone elastomer at 199°) to consist of 2-methoxyhexafluoroquinoline and hexafluoro-N-methyl-2-quinolone only.

b) A similar solution of heptafluoroquinoline (1·0 gm., 3·9 m.mole) in sulphuric acid (20 ml., s.g. 1·84) was poured into well-stirred water (200 ml.). The precipitate (0·85 gm.) was filtered off and dried under vacuum (20°C/0·25 mm.) to give heptafluoroquinoline, identified by comparison of its i.r. spectrum with an authentic sample.

Heptachloroquinoline.

Water (100 ml.) was added dropwise over ½ hour to a well-stirred solution of heptachloroquinoline (0·5 gm., 1·35 m.mole) in sulphuric acid (10 ml., s.g. 1·84) at room-temperature. The precipitate (0·4 gm.) was dried under vacuum (30°C/0·1 mm.) to give heptachloroquinoline, identified by its i.r. spectrum.

Controlled addition of water to solutions of Heptafluoro- and Heptachloroquinoline in Sulphuric Acid.

The results of these experiments, which were all carried out at room-temperature, are given in tabular form on the following page. All the products were isolated by filtration, washed well with water, dried under vacuum (20-25°C/0·25-0·01 mm.) and identified by comparison of their i.r. spectra with authentic samples. Product A refers to the first permanent precipitate formed on slow addition of water to the acid solution. This time was much greater for heptafluoroquinoline than for heptachloroquinoline because in the former case a precipitate was formed after the sulphuric acid/water molar ratio exceed 1:1·1 which only slowly redissolved; the precipitate being permanent after 8 hours when the ratio was 1:2·76. After product A had been filtered off, the clear filtrate was added to an excess of well-stirred water and the precipitate (product B) isolated. Solutions of heptafluoroquinoline, equimolar with respect to the above solution, were made up and then varying amounts of water were added, the amounts being insufficient to cause formation of

Dilution of solutions of C_9NF_7 and C_9NCl_7 in Sulphuric Acid with water.

	Compound (moles)	Sulphuric Acid[c] (moles)		Water Added (moles)	Product A	Product B
Heptachloroquinoline	0·001	0·102		0·111	C_9NCl_7	C_9NCl_7
		1	:	1·1	(40 mins.)[a]	
Heptafluoroquinoline	0·004	0·367		1·017	C_9NF_6OH	C_9NF_6OH
		1	:	2·76	(8 hours)[a]	
Heptafluoroquinoline	0·002	0·183		0·183	-	C_9NF_6OH
		1	:	1		(20 min.)[b]
Heptafluoroquinoline	0·002	0·183		0·092	-	C_9NF_7
		1	:	0·5		(20 min.)[b]
Heptafluoroquinoline	0·002	0·183		0·046	-	C_9NF_7
		1	:	0·25		(20 min.)[b]

a) Time from beginning to add water to the appearance of the first permanent precipitate.

b) Time from beginning to add water to rapid dilution.

c) s.g. 1·84.

a precipitate. These solutions were poured into excess, well-stirred water and the precipitate formed (product B) isolated.

Pentafluoropyridine.[1]

a) Water (300 ml.) was added dropwise over 1½ hours to a cooled (0°C), well-stirred solution of pentafluoropyridine (3·9 gm., 23·08 m.moles) in sulphuric acid (60 ml., s.g. 1·84). The acid solution was transferred to a separating funnel, further water (200 ml.) added and the solution allowed to stand overnight. The bottom layer of liquid which separated was run and dried ($MgSO_4$) to give pentafluoropyridine (2·7 gm.), identified by comparison of its i.r. spectrum with an authentic sample. The aqueous acid layer remaining was extracted (CH_2Cl_2), dried ($MgSO_4$) and shown by analytical-scale v.p.c. (silicone elastomer at 44°C) to consist of methylene dichloride only. The methylene dichloride was distilled but no solid (i.e. a polyfluorohydroxypyridine) remained.

b) A solution of pentafluoropyridine (2·5 gm., 14·79 m.mole) in sulphuric acid (65 gm., 66·33 m.mole, s.g. 1·84) containing water (2·0 gm., 11·11 m.mole) was heated at 100-110°C for 21 hours. (The amount of water was the maximum amount that could be added without the pentafluoropyridine being thrown out of solution at 100-110°C). Water (100 ml.) was then added dropwise to the hot solution (90-100°C) over 4¼ hours. A colourless, oily liquid readily refluxed on adding water which was washed back into the cooled (room-temperature) reaction flask with water. The reaction mixture, which was a pale brown, was distilled,

the distillate at up to 90°C at atmospheric pressure collected and dried ($MgSO_4$) to give pentafluoropyridine (2·1 gm.), identified by its i.r. spectrum.

c) A solution was made up as in b) and refluxed for 160 hours at 100-110°C to give a clear but brown solution. Addition of water and distillation as in b) gave pentafluoropyridine (0·5 gm.). The acidic solution remaining was extracted with methylene dichloride, the extract dried ($MgSO_4$) and shown by analytical-scale v.p.c. to consist of solvent only. The methylene dichloride was distilled but no solid (i.e. polyfluorohydroxypyridine) remained.

Reaction between Methanol and a Solution of Heptafluoroquinoline in Concentrated Sulphuric Acid

Methanol (150 ml.) was added, dropwise, over a period of 1 hour to a stirred, cooled (0°) solution of heptafluoroquinoline (1·0 gm., 3·9 m.mole) in sulphuric acid (20 ml., s.g. 1·84). The resulting clear solution was shaken with methylene dichloride and then water (150 ml.) was added slowly, over one hour, in order to effect separation of the methylene dichloride. The methylene dichloride layer was separated, dried ($MgSO_4$) and the solvent distilled to leave a light brown solid (0·75 gm.). Sublimation at reduced pressure (20°/0·1 mm.) gave a white solid (0·55 gm.) which was shown by analytical-scale v.p.c. (silicone elastomer at 198°C) to be a mixture of heptafluoroquinoline and 2-

methoxyhexafluoroquinoline in ratio of 15:85 respectively. Fractional sublimation of this mixture (20°C/0·1 mm.) gave 2-methoxyhexafluoroquinoline, identified by comparison of its i.r. spectrum with an authentic sample. The remainder of the crude reaction mixture sublimed at 100°C/0·05 mm., giving 2-hydroxy-hexafluoroquinoline (0·1 gm.), identified by comparison of its i.r. spectrum with an authentic sample.

Reaction of Heptafluoroquinoline with aqueous concentrated solutions of Hydrogen Halides.

Heptafluoroquinoline and Hydrobromic Acid.

Hydrobromic acid (50% w/w, 40 ml.) was added to heptafluoroquinoline (1·0 gm., 3·9 m.mole) and the suspension stirred at room-temperature for 35 minutes. No apparent dissolution occurred and the reaction flask was immersed in a bath at 50°C and the temperature raised to 80°C over 3/4 hour. No apparent dissolution occurred but the suspension appeared to be more flocculent. Further hydrobromic acid (20 ml.) was added and the reaction mixture maintained at 80-82°C for a further 1 hour, the suspension being present at all times. The solid was filtered off, washed with water and vacuum dried (30°C/0·01 mm.) to give 2-hydroxy-hexafluoroquinoline (0·35 gm.), identified by comparison of its i.r. spectrum with an authentic sample. The clear, golden-brown filtrate was maintained at 80-82°C whilst water (100 ml.) was added dropwise over 20 minutes. The white solid precipitated was filtered off, washed

with water and vacuum dried (30°C/0·01 mm.) to give 2-hydroxyhexafluoroquinoline (0·40 gm.), identified by its i.r. spectrum.

Heptafluoroquinoline and Hydrochloric Acid.

Hydrochloric acid (30 ml., 36% w/w) was added to heptafluoroquinoline (1·0 gm., 3·9 m.mole) and the suspension stirred at room temperature for 10 minutes. No apparent dissolution occurred and the reaction flask was immersed in a bath at 45°C and the temperature raised to 80°C over ½ hour when some of the solid dissolved. Further hydrochloric acid (45 ml.) was added and the reaction mixture maintained at 80-85°C for ¾ hour when all but a trace of the solid dissolved. Water (100 ml.) was added dropwise to the hot (70-80°) solution over ¾ hour. After cooling the precipitate was filtered off, washed with water and dried under vacuum (30°C/0·01 mm.) to leave a white solid (0·65 gm.). Sublimation at up to 80°C/0·01 mm. gave a trace of a white solid, which was not investigated, and the remainder all sublimed at 80°C - 110°C/0·1 mm. as a white solid, m.pt. 155-170°C (slight decomp.). Its i.r. spectrum resembled that of 2-hydroxyhexafluoroquinoline but had extra peaks at 1615, 1493, 1339, 1157, 1059, 775, 658 and 629 $cm.^{-1}$ A Lassaigne test showed it to contain chlorine. Treatment with aqueous 10% potassium hydroxide and extraction with methylene dichloride showed no non-acidic material to be present. Acidification of the alkaline layer and extraction with methylene dichloride gave back the original hydroxy compound, (identified by its i.r. spectrum).

Heptafluoroquinoline and Hydriodic Acid.

Purification of Hydriodic Acid:[235] A nearly boiling solution of hydriodic acid (54% w/w) was treated with hypophosphorous acid until the iodine colour was discharged. The acid was then distilled under nitrogen and stored under nitrogen in the dark until required.

Reaction of Heptafluoroquinoline and Hydriodic Acid.

Hydriodic acid (30 ml., purified as above) was added under an atmosphere of nitrogen to heptafluoroquinoline (1 gm., 3·9 m.mole) contained in a 250 ml. flask which was purged with dry nitrogen throughout the experiment. The yellow solution containing a white suspension was stirred at room-temperature overnight (16 hours). The solution was now orange but no apparent dissolution had occurred. The reaction mixture was heated at 75-85°C for 1¼ hours when the reaction mixture turned dark brown and most of the solid dissolved. Water (125 ml.) was added dropwise over 20 minutes to the hot (70-80°C) reaction mixture when a dark brown solid precipitated. Excess sodium metabisulphite was added to the dark brown reaction mixture and left stirring overnight to give a clear pale yellow solution containing a white solid. The solid was extracted into methylene dichloride, the extracts washed with a solution of sodium metabisulphite, dried ($MgSO_4$) and the solvent distilled to leave a pale yellow solid (0·55 gm.). Sublimation at reduced pressure (20-40°C/ 0·25 mm.) gave a white solid (0·4 gm.) shown to be a pentafluoroquinoline,

m.pt. 49·5 - 50·5° (Found: C, 49·2; H, 0·87; F, 42·5; M.W. 219. $C_9NF_5H_2$ requires: C, 49·3; H, 0·92; F, 43·36%; M.W. 219). I.R. spectrum No. 23. Its ^{19}F and ^1H n.m.r. spectra showed it to contain a hydrogen at the 2-position and most probably at the 4-position also. The remainder of the crude reaction product sublimed at 105-115°C/0·25 mm. to give 2-hydroxyhexafluoroquinoline (0·1 gm.), identified by its i.r. spectrum.

Reaction of Heptafluoroquinoline with Water.

Water (30 ml.) was added to heptafluoroquinoline (0·5 gm., 1·95 m.mole) and the stirred suspension heated at 80-90°C for 2 hours. After cooling the insoluble material was filtered off and dried under vacuum (20°C/0·45 mm.). It all sublimed at 30-40°C/0·25 mm. to give heptafluoroquinoline (0·4 gm.), identified by comparison of its i.r. spectrum with an authentic sample.

Reaction between heptafluoroquinoline and hydrogen chloride in sulpholane.

Gaseous hydrogen chloride (0·29 gm., 7·95 m.mole) was condensed under vacuum into a Carius tube containing heptafluoroquinoline (1·0 gm., 3·9 m.mole) dissolved in sulpholane (10 ml.) and cooled in liquid air. After warming to room-temperature the Carius tube, which contained a clear colourless solution, was heated at 90-95°C for 48 hours when the solution was brown and contained a small amount of a white solid in suspension. After opening, the contents of the tube were poured into

water (200 ml.) and the suspension formed stirred for ½ hour. Inadvertently the aqueous suspension was heated to ≈ 60°C during this period. After cooling, the insoluble material was extracted into ether, the ether extract separated, washed well with water, dried ($MgSO_4$) and the solvent removed to leave an off-white solid (0·8 gm.). This was fractionally sublimed to give two distinct fractions. At 20-45°C/0·05 mm. a white solid readily sublimed which was shown by analytical-scale v.p.c. (silicone elastomer at 232°C) to consist essentially (99·5%) of one component, together with a component of shorter retention time which had retention time identical with 2-chlorohexafluoroquinoline (see below). Recrystallisation (benzene) gave pure 2,4-dichloropentafluoroquinoline (0·2 gm.), m.pt. 76·5-77·5°. (Found: C, 37·7; F, 32·3; 34·5; Cl, 23·3; 22·1; $\frac{m}{e}$ = 287(P), 289(P + 2), 291(P + 4). $C_9NF_5Cl_2$ requires: C, 37·5; F, 32·98; Cl, 24·6%; $\frac{m}{e}$ = 287(P), 289(P + 2), 291(P + 4)). I.R. spectrum No. 24. Its orientation was established from its ^{19}F n.m.r. spectra (see Part III). The remainder of the crude reaction product sublimed slowly at 80-85°C/0·05 mm. to give a white solid which was recrystallised (methylene dichloride -60-80 petroleum ether) to give a monochloromonohydroxypentafluoroquinoline (0·2 gm.) m.pt. 164-165° (Found: C, 39·7; H, 0·3; F, 35·7; Cl, 13·5; $\frac{m}{e}$ = 269(P), 271(P + 2). C_9NF_5ClOH requires: C, 40·1; H, 0·4; F, 35·2; Cl, 13·15%; $\frac{m}{e}$ = 269(P), 271(P + 2)). I.R. spectrum No. 25.

Reaction between heptafluoroquinoline and potassium chloride in sulpholane.

Heptafluoroquinoline (0·8 gm., 3·14 m.mole) was dissolved in sulpholane (10 ml.) contained in a 50 ml., 2-necked flask fitted with reflux condenser and purged with dry nitrogen. To the stirred solution anhydrous potassium chloride (0·47 gm., 6·30 m.mole) was added and the stirred reaction mixture heated, under an atmosphere of nitrogen, for 48 hours at 90-95°. After cooling the orange-brown reaction mixture was poured into water, the white precipitate extracted into ether, the ether extract separated, washed well with water, dried ($MgSO_4$) and the ether distilled to leave a white solid (0·7 gm.). It all sublimed readily under reduced pressure (20-30°C/0·01 mm.) to give heptafluoroquinoline, identified by its i.r. spectrum.

Conversion of 2-hydroxyhexafluoroquinoline to 2-chlorohexafluoro- and 2,4-dichloropentafluoro-quinolines.

Phenol (2·20 gm., 23·34 m.mole) and phosphorus pentachloride (1·62 gm., 7·77 m.mole) were heated under an atmosphere of dry nitrogen at 100°C for $5\frac{1}{2}$ hours to give a pale yellow liquid. After cooling 2-hydroxyhexafluoroquinoline (1·95 gm., 7·71 m.mole) was added and the mixture heated (under nitrogen) at 105-100°C for 11 hours and then at 140-145°C for 1 hour. The clear yellow liquid formed was heated to 250° over 20 minutes and maintained at 250-260° for 15 minutes. The cooled reaction product was stirred with aqueous 10% sodium hydroxide and then methylene dichloride. The insoluble material (0·8 gm., presumably phosphate residues) was

filtered off and the methylene dichloride layer separated, dried ($MgSO_4$), the solvent distilled and the residue sublimed at reduced pressure (20-60°C/0·05 mm.) to give a white solid (1·1 gm.) m.pt. 53-61°C. Left unsublimed was a tacky solid (presumably phosphate residues) which was not investigated. The aqueous basic layer remaining after separation of the organic solvent was acidified. No precipitate was formed indicating the absence of any unreacted 2-hydroxyhexafluoroquinoline. The sublimed material was shown by analytical-scale v.p.c. (silicone elastomer at 198°C) to consist of two components in ratio of 46:54, the component in greater amount, having the slightly greater retention time, had retention time identical with 2,4-dichloropentafluoroquinoline. The two components were separated, with difficulty, by preparative scale v.p.c. (silicone elastomer, temperature programmed at 145-200°C). The component in smaller amount, which had the lower retention time, was more readily separated and after sublimation under reduced pressure (55°C/0·05 mm.) gave 2-chlorohexafluoroquinoline (0·1 gm.) m.pt. 57-58° (Found: C, 39·7; F, 41·8; Cl, 13·8; $\frac{m}{e}$ = 271(P), 273(P + 2). C_9NF_6Cl requires: C, 39·8; F, 42·0; Cl, 13·05; $\frac{m}{e}$, 271(P), 273(P + 2)). I.R. spectrum No. 26.

The other component was difficult to obtain uncontaminated with 2-chlorohexafluoroquinoline and could only be obtained pure in very small amount. Sublimation under reduced pressure (50°C/0·01 mm.) gave 2,4-dichloropentafluoroquinoline (≈ 0·005 gm.), identified by comparison of its i.r. spectrum with an authentic sample.

PART III

Assignment of Orientation in Polyfluoroquinolines.

Chapter 7

Discussion

The orientation of the derivatives of heptafluoroquinoline was deduced from their nuclear magnetic resonance spectra. Attempts to obtain direct chemical proof of orientation were unsuccessful.

Nuclear Magnetic Resonance Spectra of Heptafluoroquinoline and its Derivatives.

All ^{19}F n.m.r. spectra were recorded using an A.E.I. R.S.2. spectrometer operating at 60 Mc/sec. and samples were examined as solutions in acetone or methylene dichloride with hexafluorobenzene as internal reference. All chemical shifts are with reference to trichlorofluoromethane (hexafluorobenzene absorbs 162·3 p.p.m. to high field of trichlorofluoromethane).

^{1}H n.m.r. spectra were recorded on the above instrument or on a Perkin-Elmer R10 spectrometer operating at 60 Mc./sec. and samples were examined as solutions in carbon tetrachloride with tetramethylsilane as internal reference.

The resolution available for the measurement of the ^{19}F n.m.r. spectra was insufficient for a complete analysis and the assignment of orientation in the polyfluoroquinolines has been made principally on the basis of the observed chemical shifts. In this way the 2- and 4-fluorines can generally be distinguished and examination of the multiplicity of the peak due to the 2-fluorine, and the appearance of a very large peri F-F coupling provides confirmation of the assignment. Where applicable

further support for the assignment derived from the ^{19}F n.m.r. spectra is provided by examination of the ^{1}H n.m.r. spectra. The structures of the bands in the ^{19}F n.m.r. spectra of some of the compounds examined are given on pages 240 to 244.

Heptafluoroquinoline.

In table N1 the ^{19}F chemical shifts of heptafluoroquinoline are shown together with those for a number of highly fluorinated homocyclic and nitrogen-containing heterocyclic aromatic compounds. The spectrum of heptafluoroquinoline is characterised by the presence of two peaks at much lower field than the remaining five, and their shifts (77·2 and 126·0 p.p.m.) are much smaller than those observed for either hexafluorobenzene, octafluoronaphthalene or 5,6,7,8-tetrafluoroquinoline and can therefore be assigned to the pyridine ring fluorines. Comparison with the shifts observed for the 2- and 4-fluorines in pentafluoropyridine shows that they can be assigned to the 2- and 4-fluorines of heptafluoroquinoline. For all the compounds listed the fluorine ortho to the ring nitrogen shows a shift of $\leqslant 96{\cdot}5$ p.p.m. and hence the peak at 77·2 p.p.m. in the spectrum of heptafluoroquinoline can be assigned to the 2-fluorine. Although the latter spectrum was complex and poorly resolved, the peak at 145·7 showed a large coupling ($J \approx 46$ c/s) which is ascribed to peri F-F coupling (see later). The peak due to the 4-fluorine was complex and broad (width at half peak height ≈ 100 c/s) and could have contained such a large splitting whereas the remaining peaks could not. Thus the peak at 145·7 p.p.m. can be assigned to the 5-fluorine.

TABLE N1

Compound	^{19}F chemical shifts (assignment in brackets)
Heptafluoroquinoline	77•2(2); 126•0(4); 145•7; 148•3; 150•7; 154•4; 160•6.
Pentafluoropyridine[1]	87•6(2); 134•1(4); 162•0(3).
Tetrafluoro-1,2-diazine[158]	82•7(3,6); 144•3(4,5).
Tetrafluoro-1,4-diazine[236]	93•9.
Heptafluoroisoquinoline[231]	61•0(1); 96•5(3); 138•9; 144•5; 145•2; 152•4; 154•6.
5,6,7,8-Tetrafluoro-quinoline[238]	150•6; 150•9; 155•5; 158•2.
Hexafluorobenzene	162•3.
Octafluoronaphthalene[237]	142•6(α); 155•3(β).

Substituent Effects on ^{19}F Chemical Shifts.

The effect of substituents on the chemical shift of fluorines ortho, meta or para to it must be known when assignments of structure are based on the observed chemical shifts. The effects of some relevant substituents are shown in table N2 where ortho, meta, para are with respect to the substituent being considered. A negative shift represents a shift to lower field, a positive shift is one to higher field and the number in [ ] refers to the fluorine shifted where the designation ortho, meta or para is ambiguous. Where there is more than one substituent present the group considered is the one underlined. The effect of the substituent was obtained by comparison of the ^{19}F chemical shifts of the substituted compound and the compound obtained by replacement of the substituent by fluorine. Thus, for example, the effect of a 4-methoxyl group in a polyfluoropyridine was deduced by comparing the ^{19}F chemical shifts of pentafluoropyridine and 4-methoxy-tetrafluoropyridine, and the effect of a 2-amino group by comparison of the ^{19}F chemical shifts of 2,4-diamino-trifluoropyridine and 4-aminotetra-fluoropyridine, since 2-aminotetrafluoropyridine is unknown. In applying these derived substituent effects for the calculation of the chemical shifts of polyfluoroquinolines, the substituent effect used is for the group having a similar environment to that in the polyfluoroquinoline. It can be seen from table N2 that the effect of a substituent in a polyfluoropyridine is not the same as for the same substituent in a polyfluorobenzene, although substituent effects are generally found to be additive when applied to the

TABLE N2

Effect of Substituents on ^{19}F Chemical Shifts.

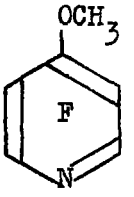
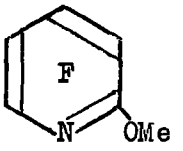
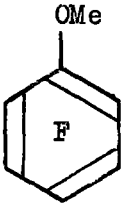
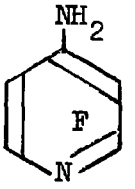
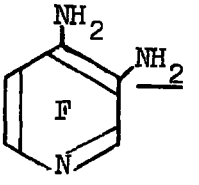
Substituent	Compound	Ref.	Fluorine Shifted		
			Ortho	Meta	Para
OCH_3		209	+0·5	+5	-
		209	0	+7·5[4] +4[6]	+11
		239	-4	+3	+2
NH_2		209	+3	+7	-
		209	+0·5	+5	+10

TABLE N2 (Cont.)

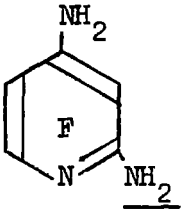
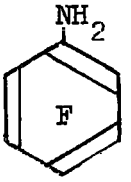
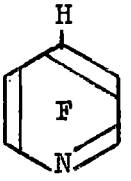
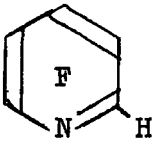
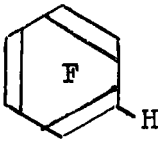
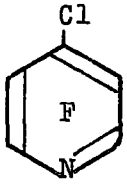
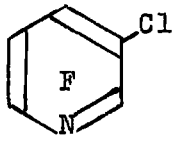
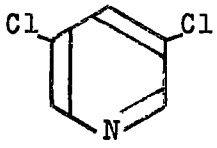
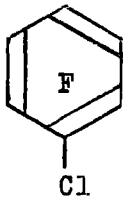
Substituent	Compound	Ref.	Fluorine Shifted		
			Ortho	Meta	Para
NH_2		209	0	+2	+11
		239	+1	+3	+11
		162	-21	+5	-
H		162	-13	-4[6] +6[4]	-4
		239	-24	0	-9

TABLE N2 (Cont.)

Substituent	Compound	Ref.	Fluorine Shifted		
			Ortho	Meta	Para
		152	-20	+1	-
		193	-16[2] -20[4]	+2	-2
Cl		193	-16[2] -20[4]	-	+2
		239	-23	-1	-7

system from which they were derived.[193] Thus it is reasonable to suppose that the substituent effects derived from a polyfluoropyridine will hold for substituents in the pyridine ring of a polyfluoroquinoline, and similarly those derived from a polyfluorobenzene will hold for substitution in the benzene ring of a polyfluoroquinoline. This has been found to be so for a large number of polyfluorobipyridyls[152] using substituent effects derived from the polyfluoropyridine system. Thus to calculate the chemical shift of the 4-fluorine in 2-methoxy-3,4,5,6,7,8-hexafluoroquinoline the shift of the 4-fluorine of pentafluoropyridine caused by the methoxy group in 2-methoxytetrafluoropyridine (+7·5) is added to the chemical shift of the 4-fluorine (126·0 p.p.m.) in heptafluoroquinoline to give a calculated value of 133·5 p.p.m. Since 2-aminotetrafluoropyridine does not exist the effect of this amino group on the chemical shift of the 4-fluorine of pentafluoropyridine cannot be obtained. In this case the substituent effect used to calculate the chemical shift of the 4-fluorine in 2-aminohexafluoroquinoline is the range observed for the effect of an amino group on a meta fluorine in the series of polyfluoropyridines given in table N2. The agreement observed between the ^{19}F chemical shifts calculated in this additive manner and those observed is generally sufficiently accurate to allow a definite assignment of orientation when there is a large difference in chemical shift between the fluorines being assigned[193, 209] and the remaining fluorines, and such a large difference generally occurs

for the 2- and 4-fluorines of polyfluoroquinolines.

Monosubstituted Derivatives of Heptafluoroquinoline.

Table N3 shows the ^{19}F chemical shifts of the monosubstituted derivatives of heptafluoroquinoline.

(a) 2-Substituted-hexafluoroquinolines.

The orientation of the 2-substituted derivatives is readily indicated by the absence of any absorption in the region of 77 p.p.m., where the 2-fluorine of heptafluoroquinoline absorbs, and the known effect of the substituents on the fluorine chemical shifts (table N2). Support for this assignment is provided by the ^1H n.m.r. spectrum of 2-methoxyhexafluoroquinoline which shows a singlet peak at $\tau = 5{\cdot}80$. It has been shown that in methoxy-substituted perfluoro aromatic compounds methoxyl protons couple with the ortho fluorines[240] but an exception is found when the methoxyl group is ortho to ring nitrogen.[163,241] Thus in 2,4-dimethoxytrifluoropyridine[163,241] and 2,4,6-trimethoxydifluoropyridine,[241] the 4-methoxy group shows a triplet indicating coupling with the two ortho fluorines, but the 2- and 6-methoxy groups show only singlets indicating that they do not couple with the orthofluorine. Thus the appearance of only a singlet peak in the ^1H n.m.r. spectrum of 2-methoxyhexafluoroquinoline indicates that the methoxy group is ortho to the ring nitrogen.

From the substituent effects given in table N2 the chemical shift of the 4-fluorine can be calculated and are given below,

TABLE N3

Compound	^{19}F Chemical Shifts (assignments in brackets)
2-X-hexafluoroquinoline	
X = OMe	132·4(4); 147·0(5); 150·2; 154·0; 159·5; 160·5.
X = NH_2[a]	137·1(4); 147·7(5); 152·5; 155·7; 159·8; 164·6
X = H	133·3(4); 146·0(5); 148·2; 151·3; 154·3.≠
4-X-hexafluoroquinolines	
X = OMe	76·0(2); 143·2; 149·6; 153·7; 158·0; 160·1.
X = NH_2[a]	81·9(2); 147·1; 149·8; 155·4; 161·8; 168·0.
X = H[a]	76·3(2); 134·7; 147·8; 149·7; 153·3; 155·8.
8-chlorohexafluoroquinoline	71·8(2); 123·8[b]; 124·8[b]; 141·3(5); 155·4; 161·3.

[a] Spectrum obtained from a mixture of the 2- and 4-isomers.

≠ Intensity twice that of other peaks.

[b] Overlapping of peaks renders peak centre in doubt.

Compound	Chemical Shift of 4-fluorine (p.p.m.)	
2-X-hexafluoroquinoline	Calculated	Observed
X = F		126·0
X = OMe	133·5	132·4
X = H	132	133·4
X = NH_2	128-133	137·2

The calculated values are consistent only with the lowest field peak in the spectra of the 2-substituted hexafluoroquinolines being due to the 4-fluorine. For X = OMe and H the agreement is good, and for X = NH_2 although the agreement between the calculated and observed chemical shifts is poorer, the large difference (10·6 p.p.m.) between the peak at lowest field and the next one to higher field is such that the assignment of the lowest field peak to the 4-fluorine is not invalidated.

The two peaks at lowest field in the spectra of the 2-substituted hexafluoroquinolines were characterised by the presence of a large splitting (Table N4) which is attributed to peri F-F coupling i.e. between the 4- and 5-fluorines.

TABLE N4

Peak Centre	Peak Shape	$J_{4,5}$	$J_{5,4}$
2-Methoxyhexafluoroquinoline			
132·4 p.p.m.	Doublet of doublets of triplets of doublets	50	
147·0	Doublet, showing further complex multiplet splitting		46

Table N4 (cont.)

Peak Centre	Peak Shape	$J_{4,5}$	$J_{5,4}$
2-Hydrohexafluoroquinoline			
133·3	Doublet, showing further complex multiplet splitting	44	
146·0	Doublet of triplets of doublets		47
2-Aminohexafluoroquinoline			
137·1	Doublet, showing further poorly resolved doublet splitting	46	
147·7	Doublet, showing further complex multiplet splitting		48

Although, as stated above, the resolution was insufficient to allow a full analysis of the spectra the coupling was so large (J = 45-50 ± 5 c/s) as to be readily detected. That this large coupling is due to the peri fluorines is deduced in the following way. In a series of pentafluorophenyl derivatives[239] the largest F-F coupling observed is ≈ 23 c/s and that in a series of polyfluoropyridine derivatives[241] is ≈ 32 c/s. The spectra of a number of substituted perfluoroisoquinolines have been examined[231,164] and found to show some very large couplings (J = 50-60 c/s) due to peri F-F coupling. Thus in 1-methoxyhexafluoro-

isoquinoline, the coupling between the peri fluorines (J_{45}) is 49·7 c/s and in 4-chlorohexafluoroisoquinoline the peri F-F coupling constant (J_{18}) is 65 ± 5 c/s. Hence the large coupling observed for the 2-substituted hexafluoroquinolines is attributed to coupling between the 4- and 5-fluorines and allows the assignment of the 5-fluorine.

(b) 4-Substituted hexafluoroquinolines.

The presence of the 2-fluorine is clearly shown by the presence of a peak in the region 76-82 p.p.m. In heptafluoroquinoline the 2-fluorine gives a triplet (J = 21 c/s) due , under the resolution available, to an apparent equivalence of J_{23} and J_{24}, but in the 4-substituted derivatives the 2-fluorine gives a doublet showing the absence of either the 3- or 4-fluorine. The observed coupling constants (J = 28, 27 and 31 c/s for 4-X = OMe, H and NH_2) are of the same order of magnitude as the coupling between the 2- and 3-fluorines and the 2- and 4-fluorines in polyfluoropyridines[241] and hence whether the 3- or 4-fluorine is absent cannot be distinguished from the magnitude of the coupling constant. However, the absence of any large coupling of the order of 40-50 c/s, indicative of peri F-F coupling, shows the 4-fluorine to be absent. The characteristic large shift to lower field of the chemical shift of a fluorine ortho to hydrogen (Table N2), and the absence of any significant change in the chemical shift of the 2-fluorine in 4-hydrohexafluoroquinoline shows the 3-fluorine to be present and hence confirms the orientation. The ^{1}H n.m.r.

spectra of 4-methoxyhexafluoroquinoline, which shows a doublet (J = 5·52 c/s) at τ = 5·61; is in agreement with the assignment deduced from its ^{19}F n.m.r. spectrum. As seen above the ^{1}H n.m.r. of 2-methoxyhexafluoroquinoline shows a singlet, and if the methoxy group were at the 3, 6 or 7 position a doublet of doublets would be expected from coupling between the two ortho fluorines.[240] Thus the appearance of a doublet shows the methoxy group is situated at a peri position and further shows that coupling between it and the peri-fluorine does not occur, or at least is too small to be detected.

c) 8-Chlorohexafluoroquinoline.

The known effect of chlorine on the chemical shifts of fluorines ortho, meta and para to it (Table N2) and the appearance of a peak at 71·8 p.p.m. clearly shows that the 2-fluorine is present, and its appearance as a triplet (J = 27 c/s) shows that the 3- and 4-fluorines are present. The chlorine atom is characterised by its large effect on the chemical shift of a fluorine ortho to it and the fact that the 2-fluorine shows no large downfield shift (i.e. 16 p.p.m.) expected if ortho to chlorine further supports the presence of the 3-fluorine. The overlapping of the two peaks at 123·8 and 124·8 together with the resolution available made it impossible to determine definitely the shape of the peaks and hence to derive coupling constants. However these two peaks are in the region expected for the 4-fluorine and hence one is due to the 4-fluorine. The peak at 141·3 p.p.m. was a doublet (each peak

showing further multiplet splitting) showing a large coupling (J = 50 c/s) indicative of peri F-F coupling and hence showing the presence of the 4- and 5-fluorines. Thus the chlorine must be at the 6, 7 or 8 positions. The fact that the 5-fluorine shows no large downfield shift (i.e. 23 p.p.m.) compared with the chemical shift of the 5-fluorine in the 2-substituted hexafluoroquinolines, which it would if ortho to a chlorine, shows that the 6-fluorine is present. If the chlorine were at position 7, the 6- and 8-fluorines would be shifted downfield by ≈ 23 p.p.m. into the region ≈ 122 - 137 p.p.m. and hence the spectrum would show 4 peaks in the region ≈ 122-141 (since the 4- and 5-fluorines occur in this region also). However, only 3 peaks are observed in this region and hence the chlorine must be at position 8. For this orientation only the 7-fluorine would experience a large downfield shift (due to the ortho chlorine) and hence only 3 peaks would be expected in the region ≈ 122-141, and this is observed.

Polysubstituted Derivatives of Heptafluoroquinoline.

Table N5 shows the ^{19}F chemical shifts of the polysubstituted derivatives of heptafluoroquinoline.

2,4-Dimethoxypentafluoroquinoline.

The orientation of 2,4-dimethoxypentafluoroquinoline follows from its preparation as the only dimethoxypentafluoroquinoline formed from either 2- or 4-methoxyhexafluoroquinoline. As expected the two low field

TABLE N5

Compound	^{19}F Chemical Shifts		
2,4-dimethoxypentafluoro-quinoline	145·1; 157·9;	151·5; 161·8	156·4;
2,4,Y-trimethoxytetrafluoro-quinoline	146·2; 159·9	147·0;	156·4;
2,4-dichloropentafluoro-quinoline	116·7; 151·4;	144·2; 152·7	147·3;
2,Z-dihydropentafluoro-quinoline	123·7;	150·7*;	155·8*

* Intensity twice that of other bands.

peaks (at 77·2 and 126·0 p.p.m.) present in the spectrum of heptafluoroquinoline and due to the 2- and 4-fluorines are absent, and the absence of any large coupling of the order of 40-50 c/s shows that a peri fluorine has been replaced. The ^{1}H n.m.r. spectrum shows a singlet at τ = 5·89, due to the methoxyl group at position 2, and a doublet (J = 3·75 c/s) at τ = 5·79, due to the methoxyl group at position 4.

2,4,Y-Trimethoxytetrafluoroquinoline.

The presence of methoxyl groups at the 2- and 4-positions follows from its mode of preparation and the absence of any peak below 146·2 p.p.m. or a large coupling of the order of 40-50 c/s is as expected from replacement of the 2- and 4-fluorines. The ^{1}H n.m.r. spectrum shows a singlet at τ = 5·95, due to the methoxyl group at position 2, a doublet (J = 4·46 c/s) at τ = 5·81, due to the methoxyl group at position 4, and a doublet of doublets (J = 1·88 and 0·81 c/s) at τ = 5·89. The appearance of a doublet of doublets shows that the third methoxyl group has two ortho fluorines and must therefore be at position 6 or 7.

2,4-Dichloropentafluoroquinoline.

The absence of the 2-fluorine is clearly shown by the absence of any peaks below 116·7 p.p.m. If the other chlorine were at position 3, the 4-fluorine would absorb near the region 108-107 p.p.m. and would show a large splitting (40-50 c/s) due to coupling with the 5-fluorine. The

presence of the lowest field peak at 116·7 p.p.m. and its appearance as a singlet (width at half peak height = 12 c/s) shows that the 3-fluorine is present. If the compound were 2,5-disubstituted peri F-F coupling could not occur but the 4-fluorine would occur near to the region 126-127 p.p.m. (due to it being meta to two chlorine atoms) and be a doublet with a coupling constant of 16-17 c/s, by comparison with the coupling observed between the 3 and 4 fluorines in polyfluoropyridines.[241] Also the 3- and 6-fluorines would occur in the region 123-141 p.p.m. and hence the spectrum would show 3 peaks in the region 123-141 but this is not observed. For the compound to be 2,6-, 2,7-, or 2,8-disubstituted, the absence of any large coupling on the peak at 116·7 p.p.m. (showing that it is not the 4-fluorine) would require that the 4-fluorine be shifted to higher field by $\geqslant$ 18 p.p.m. and this is clearly incompatible with the known effect of chlorine on ^{19}F chemical shifts. Thus the compound is 2,4-disubstituted. The effect of the two ortho chlorines on the chemical shift of the 3-fluorine would be to shift it to lower field by between $\approx$ 36 and 40 p.p.m. i.e. into the region 106-121 p.p.m. which is observed. Also it would be expected to be a singlet since coupling between fluorine and chlorine does not occur. No large downfield shift of the benzene fluorines would occur for chlorine at the 2- and 4-positions and no such shift is observed.

2,Z-Dihydropentafluoroquinoline.

That the 2-fluorine is not present is clearly shown by the absence of any peak below 123·7 p.p.m. and the known effect of hydrogen on fluorine chemical shifts (table N2). If the compound were 2,3-di-substituted the 4-fluorine would occur in the range 119-111 p.p.m. and show a large splitting of ≈ 40-50 c/s due to coupling with the 5-fluorine. The peak at 123·7 p.p.m. is a singlet (width of half-peak height = 17 c/s) showing that the 3-fluorine is present. The peaks at 150·7 and 155·8 p.p.m. (each twice the intensity of the lowest field peak) were complex and asymmetric due to overlapping of peaks but their widths at half-peak height (35 and 40 c/s respectively) showed that they did not contain a large (> 40 c/s) coupling constant. For the 2,6-, 2,7- or 2,8-disubstituted compound the 4-fluorine would absorb in the range 132-123 p.p.m. and show the large (> 40 c/s) peri F-F coupling. Thus the compound is either 2,4- or 2,5-disubstituted. For 2,4-dihydropenta-fluoroquinoline the 3-fluorine would occur in the range 112-127 p.p.m. whilst the range of chemical shifts of the 5-, 6-, 7- and 8-fluorines would be 146-161 as found in heptafluoroquinoline. The observed spectrum is in accord with that expected for the 2,4-disubstituted compound and furthermore the range of shifts attributed to the 5-, 6-, 7- and 8-fluorines is very similar to the range of shifts shown by the fluorines in 5-, 6-, 7-, 8-tetrafluoroquinoline (table N1). For 2,5-dihydro-pentafluoroquinoline, the 4-fluorine would occur in the range 136-128

p.p.m., the 3-fluorine in the range 133-148 p.p.m. due to the hydrogen at position 2 and might be expected to occur at even lower field due to the 5-hydrogen with which it is effectively para. However the desired reference compounds are not available to determine whether the effect would be an appreciable downfield shift as it is for the para-fluorine in pentafluorobenzene. The 6-fluorine, being ortho to a hydrogen atom, would be shifted into the region 122-137 p.p.m. The observed spectrum is clearly not in accord with that expected for 2,5-dihydropentafluoroquinoline.

The ^{1}H n.m.r. spectrum showed, (a) Doublet (J = 2·5 c/s) at τ = 1·13; (b) Doublet of doublets of doublets (J = 8·1, 2·5 and 1·1 c/s) at τ = 1·98. For 2,4-dihydropentafluoroquinoline the ^{1}H n.m.r. spectra can be accounted for as follows:

(a) Doublet at τ = 1·13 due to the 2-hydrogen coupling with the 4-hydrogen but not the 3-fluorine, i.e. J_{24} = 2·5 c/s, $J_{2,3}$ = 0 c/s.

(b) Peak at τ = 1·98 due to 4-hydrogen coupling with the 3-fluorine ($J_{4,3}$ = 8·1 c/s), the 2-hydrogen ($J_{4,2}$ = 2·5 c/s) and the 5-fluorine ($J_{4,5}$ = 1·1 c/s)

The coupling constants observed for this assignment are in agreement with those expected (Table N6) but the unexplained feature is the apparent non-coupling of the 2-hydrogen and 3-fluorine. However a similar unexplained feature occurs for 3,5-dihydrotrifluoropyridine[162] where the 3-hydrogen couples with the 4- and 6-fluorines but not with the 2-fluorine.

TABLE N6

Observed Coupling Constants (c/s).

	H-F[a]	H-H[b]
ortho	6-10	4-10
meta	5-7	1-3
para	2-3	0-1

[a] For a series of fluorobenzenes[239,243] and fluoropyridines.[162]

[b] For pyridine,[242] quinoline,[244] benzene[242] and fluoropyridines.[162]

For 2,5-dihydropentafluoroquinoline the expected ^{1}H n.m.r. spectrum is,

a) Doublet ($J_{2,4}$ = 5-7 c/s, $J_{2,3}$ = 0) or doublet of doublets ($J_{2,4}$ = 5-7, $J_{2,3}$ = 6-10 c/s)

b) Doublet of doublets of doublets ($J_{5,6}$ = 6-10, $J_{5,7}$ = 5-7, $J_{5,8}$ = 2-3, $J_{5,4}$ = 0 c/s) or further split if $J_{5,4} > 0$.

The observed ^{1}H n.m.r. spectrum is clearly more in accord with the 2,4-disubstituted compound, but the unexplained non-coupling between the 2-hydrogen and the 3-fluorine renders this assignment, although most probable, open to doubt.

Polyfluoro-1-methyl-2-quinolones

The ^{19}F chemical shifts of the two polyfluoro-1-methyl-2-quinolones are shown below,

Compound	^{19}F Chemical Shifts
3,4,5,6,7,8-hexafluoro-1-methyl-2-quinolone (A)	134·0; 144·5; 146·3; 150·7; 152·3; 162·4
3,5,6,7,8-pentafluoro-4-methoxy-1-methyl-2-quinolone (B)	142·3; 148·9; 151·9; 152·9; 163·6

The orientation of (A) and (B) follows from the evidence given on pages 153 to 155 and is consistent with their ^{19}F and ^{1}H n.m.r. spectra.

Compound	^{1}H n.m.r. Spectrum
(A)	Doublet (J = 9·8 c/s) at τ = 6·18
(B)	Doublet (J = 5·0 c/s) at τ = 5·80 Doublet (J = 9·0 c/s) at τ = 6·21

The similarity of the ^{19}F chemical shift of the olefinic fluorines of octafluoro-1,4-cyclohexadiene (155·2 p.p.m.) to the aromatic fluorine in hexafluorobenzene (162·3 p.p.m.) suggests that the effect of ring currents on the shielding of aromatic ring fluorine nuclei is small[245] and this would appear to be so for (A) and (B) since their spectra are very similar to those of 2-methoxyhexafluoroquinoline and 2,4-dimethoxy-

pentafluoroquinoline respectively. The two lower field peaks in the spectrum of (A) show very large couplings (J = 80 and 76 ± 2-3 c/s for the peaks at 134·0 and 144·5 p.p.m. respectively) which can be ascribed to peri F-F coupling, and the similarity in chemical shift of the 4-fluorine in 2-methoxyhexafluoroquinoline (132·4 p.p.m.) with the lower field peak suggests that this is due to the 4-fluorine in (A). Similarly the absence of any similar large splitting in (B) is consistent with the 4-position being substituted. In hexafluoro-N-methyl-1-isoquinolone,[216] however, the 3- and 4-fluorines are shifted by ≈ 20 p.p.m. to high field from their positions in 1-methoxy- and 1,6-dimethoxy-perfluoroisoquinoline. Apparently no such effect occurs for (A) since if the peak at 144·5 p.p.m. were due to the 4-fluorine, this would require that the peak due to the 5-fluorine be shifted <u>downfield</u> by 13 p.p.m. from its position in 2-methoxyhexafluoroquinoline.

The ^{1}H n.m.r. spectra of (A) and (B) are also consistent with the assigned structures. The doublets at τ = 6·18 for (A) and at τ = 6·21 for (B) can be assigned to the N-methyl group which couples with the peri (8) fluorine in contrast to the non-coupling of a methoxyl group at position 4 with the 5-fluorine of (B) or a polyfluoro-4-methoxyquinoline. The absorption of the N-methyl protons at higher field than the O-methyl protons in (A) and (B) is in agreement with the relative shifts observed for the protons of the dimethylamino and methoxyl groups when attached to a polyfluorohomocyclic aromatic nucleus.[240]

^{19}F n.m.r. Spectra of Polyfluoroquinolines.

For the spectra given below the coupling constants are generally accurate to ± 2-5 c/s, due to the poor resolution available and the limited solubility of some of the compounds.

Heptafluoroquinoline Peak Centre (p.p.m.)	Peak Shape
77·2	Triplet (J = 21 c/s)
126·0	Complex Multiplet (width at half-peak height = 100 c/s)
145·7	Doublet, showing further complex, poorly resolved splitting (J = 46 c/s)
148·3	Triplet (J = 12 c/s)
150·7	Poorly resolved, possibly triplet of doublets (J = 14-17 and 6-8 c/s)
154·4	Triplet (J = 21 c/s)
160·6	Singlet (Width at half-peak height = 40 c/s)

2-Methoxyhexafluoro-quinoline Peak Centre (p.p.m.)	Peak Shape
132·4	Doublet of doublets of triplets of doublets (J = 50, 15, 4, 2 c/s).
147·0	Doublet, showing further complex multiplet splitting (J = 46 c/s)
150·2	Triplet, showing further complex multiplet splitting (J = 18 c/s)

2-Methoxyhexafluoroquinoline Peak Centre (p.p.m.)	Peak Shape
154·0	Triplet of doublets, showing further complex multiplet splitting (J = 19 and 8 c/s)
159·5	Triplet, showing further complex multiplet splitting (J = 19 c/s)
160·5	Complex Multiplet (Width at half peak height = 23 c/s
2-Hydrohexafluoroquinoline	
133·3	Doublet, showing further complex multiplet splitting (J = 44 c/s)
146·0	Doublet of triplets of doublets (J = 47, 17 and 6 c/s)
148·2	Triplet (J = 15 c/s)
151·3	Doublet, poorly resolved (J = 15 c/s)
154·8[*]	Complex and Assymetric (Width at half-peak height ≈ 60 c/s)

[*] Intensity twice that of other peaks

2-Aminohexafluoroquinoline	
137·1	Doublet, showing further poorly resolved doublet splitting (J = 46 and ≈ 12 c/s)
147·7	Doublet, showing further complex multiplet splitting (J = 48 c/s)
152·5	Poorly resolved triplet (J = 16 c/s)
155·7	Complex (Width at half-peak height ≈ 35 c/s)

2-Aminohexafluoroquinoline Peak Centre	Peak Shape
159·8	Singlet showing further complex multiplet splitting (Width at half-peak height $\approx$ 30 c/s)
164·6	Triplet (J = 20 c/s)
4-Methoxyhexafluoroquinoline	
76·0	Doublet (J = 28 c/s)
143·2	Triplet, poorly resolved (J = 18 c/s)
149·6	Triplet (J = 19 c/s)
153·7	Triplet, showing further poorly resolved doublet splitting (J = 20 and $\approx$ 6 c/s)
158·0	Triplet of doublets, showing further complex multiplet splitting (J = 19 and 7 c/s)
160·1	Doublet (J = 28 c/s)
4-Hydrohexafluoroquinoline	
76·3	Doublet (J = 27 c/s)
134·7	Doublet (J = 28 c/s)
147·8	Triplet, showing further complex poorly resolved multiplet splitting (J = 16 c/s)
149·7	Complex (Width at half-peak height $\approx$ 35 c/s)
153·3	Triplet of doublets (J = 19 and 9 c/s)
155·8	Triplet of doublets (J = 18 and 8 c/s)

4-Aminohexafluoroquinoline

Peak Centre	Peak Shape
81·9	Doublet (J = 31 c/s)
147·1	Triplet, poorly resolved (J ≈ 17 c/s)
149·8	Triplet, showing further unresolved splitting (J = 16 c/s)
155·4	Triplet of doublets, poorly resolved (J = 19 and 6 c/s)
161·8	Triplet of poorly resolved doublets (J = 20 and ≈ 5 c/s)
168·0	Doublet (J = 26)

8-Chlorohexafluoroquinoline

71·8	Triplet (J = 27 c/s)
123·8	Appears to consist of overlapping of a doublet of doublets (J = 47 and
124·8	17 c/s) and a doublet (J = 21 c/s)
141·3	Doublet, showing further complex multiplet splitting (J = 50 c/s)
155·4	Triplet, poorly resolved (J = 20 c/s)
161·3	Singlet, showing complex multiplet splitting (Width at half-peak height = 50 c/s)

2,4-Dichloropentafluoroquinoline

116·7	Singlet (Width at half-peak height = 12 c/s)
144·2	Triplet of doublets, poorly resolved (J = 16 and ≈ 9 c/s)

2,4-Dichloropentafluoroquinoline

Peak Centre	Peak Shape
147·3	Triplet, showing further complex multiplet splitting (J = 16 c/s)
151·4	Complex (Width at half-peak height = 40 c/s)
152·7	Doublet (J = 19 c/s)

Attempts to assign, by chemical methods, the orientation of the products of nucleophilic substitution in heptafluoroquinoline.

Unsuccessful attempts were made to degrade by oxidation hexafluoro-2-methoxy- and pentafluoro-2,4-dimethoxy-quinoline to the substituted pyridine-2,3-dicarboxylic acids (whose structure could then be assigned by fluorine-19 n.m.r. spectroscopy). An unsuccessful, exploratory attempt was made to synthesise pentafluoro-2,4-dihydroxyquinoline by a cyclisation method.

Oxidative Degradation.

Both potassium permanganate in acetone solution and nitric acid were employed as oxidising agents.

A solution of potassium permanganate in acetone readily oxidises fluoro-olefins[246] (the reaction occurring much more readily than with hydrocarbon olefins) and preferentially oxidises the fluorinated aromatic ring of 1,2,3,4-tetrafluoronaphthalene[247] to the corresponding acids. These facts and the stoichiometry of the reaction (1 mole of the permanganate per double bond) suggests that the reaction is nucleophilic, involving possibly the permanganate ion (MnO_4^-).[246] The general experimental procedure was to add the required amount of the solid permanganate to a stirred acetone solution of the substrate, and stirring was continued until the colour was discharged. Water was then added, the acetone removed under vacuum, the aqueous solution acidified and decolourised with sulphur dioxide. Any insoluble material was filtered off and the

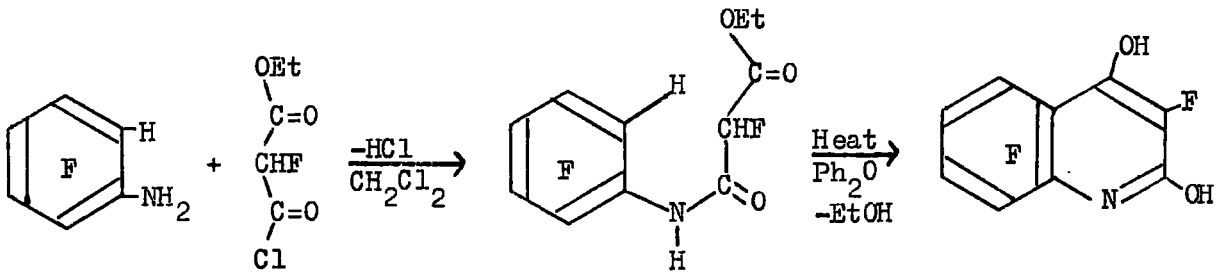
filtrate continuously extracted with ether. Using a 2 molar ratio of permanganate heptafluoroquinoline was readily and completely degraded at 20°C, and at 0°C and -22°C only minute amounts of a brown solid were isolated. Introduction of methoxyl groups into the pyridine ring of heptafluoroquinoline will render this ring less susceptible to nucleophilic attack. In accordance with this 2-methoxyhexafluoroquinoline reacted only slowly at 30-35°C with a two molar ratio of permanganate. Decolourisation of the reaction mixture before acidification gave a small amount of an insoluble solid whose i.r. spectrum indicated the presence of a fluorine-containing aromatic acid. It also showed sharp absorptions at 3521 and 3401 $cm.^{-1}$ suggestive of the N-H stretching frequency and indicating cleavage of the pyridine ring. The ether extracted material decomposed on attempted recrystallisation to a brown oil. 2,4-Dimethoxypentafluoroquinoline reacted only slowly on refluxing and with a 2 or 3 molar ratio of permanganate considerable unreacted starting material was recovered and only traces of acidic products were isolated. Using a 5 molar ratio of permanganate 71% reaction occurred, and a mixture of fluorine-containing aromatic carboxylic acids was obtained in small amount.

2,4-Dimethoxypentafluoroquinoline was not attacked by heating with nitric acid (2N) at 80°C for 2 hours. A slow reaction occurred on heating with nitric acid (7·4 N) at 150-160° for 16 hours but only a trace of organic material was isolated; its i.r. spectrum indicating it to be

essentially a fluorine-containing aliphatic carboxylic acid. It would appear that although the initial reaction is slow the initial oxidation products are readily further degraded.

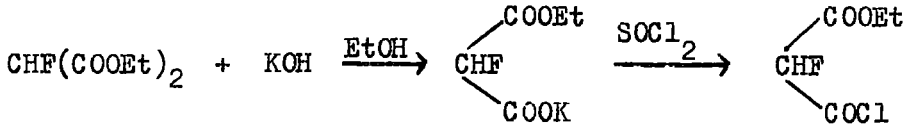
Attempted synthesis of 2,4-dihydroxypentafluoroquinoline.

The attempted synthesis is outlined below



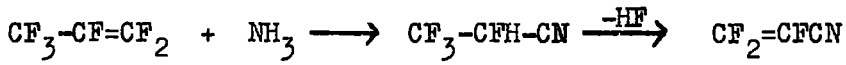
(A)

The preparation of (A) from diethylfluoromalonate was attempted as shown below



Two methods were investigated as routes to diethylfluoromalonate.

(a) Fluoromalonic acid has been prepared by acid hydrolysis of perfluoroacrylonitrile[248] and an attempt was made to prepare the latter compound from perfluoropropene by the scheme



α-Hydroperfluoropropionitrile was readily prepared using the procedure described by Knunyants.[249] Dehydrofluorination of it was attempted by passage of the vapour over heated sodium fluoride,[250,251] since perfluoroacrylonitrile is readily degraded on treatment with base.[248] However, the percentage recovery was very low and under conditions where appreciable dehydrofluorination occurred extensive decomposition took place.

(b) The second method, outlined below, was reported by Bergmann[252] to give diethyl fluoromalonate in 20-25% yield.

$$CH_2FCOOEt + NaOMe \xrightarrow[\text{Ether}\ 15\text{-}25^{\circ}C]{\text{Petroleum}} Na^{+}\bar{C}HFCOOEt + MeOH$$

$$Na^{+}\bar{C}HFCOOEt + \underset{\text{I}}{C(=O)(Cl)(OEt)} \xrightarrow[\text{Shake 1 hr. at } 20^{\circ}C\ \text{Reflux 10 mins.}]{\text{Add(I) at } -10 - 25^{\circ}C} CHF(COOEt)_2 + NaCl$$

On fractionation of the crude reaction product considerable decomposition occurred (due presumably to the presence of moisture[253]) and only a small amount of material was obtained with the correct boiling-point. Analytical-scale v.p.c. analysis showed it to consist of two components and its ^1H n.m.r. spectrum (see page 253) showed it to be a mixture of diethyl- and monoethylmonomethylfluoromalonates in ratio of 3:2. The procedure used differed from Bergmann's (see above) in that the reaction mixture was refluxed for $1\frac{3}{4}$ hours instead of 10 minutes. The longer reaction time presumably allowed trans esterification to occur to a

considerable extent. The mixture so obtained was used for a preliminary study of the desired synthesis although the amount obtained was insufficient to allow the isolation and characterisation of the intermediates. Reaction with ethanolic potassium hydroxide and treatment of the solid product obtained with thionyl chloride gave a liquid with an i.r. spectrum consistent with a monoester monoacid chloride of malonic acid. On treatment of this with a methylene dichloride solution of 3,4,5,6-tetrafluoroaniline a white precipitate (presumably the anilide) was formed which dissolved on refluxing the solution. The solvent was replaced by diphenyl ether and the solution quickly heated to 200°C for 25 minutes. The solution rapidly turned black and on removal of the solvent a black viscous tar remained. It would appear from this exploratory survey that the anilide was in fact formed but decomposed on attempted cyclisation. Lack of time prevented a more thorough study of this synthetic method.

CHAPTER 8

Experimental Work. Part III

Experimental

Oxidation using a solution of potassium permanganate in acetone

General Procedure.

To a well-stirred solution of the substrate (1-3 gm.) in acetone (200 ml., dried over $MgSO_4$) potassium permanganate was added in small portions over 2-4 hours at such a rate that there was never a large excess (as deduced from the colour of the solution) and stirring was continued until the colour was discharged ($\frac{1}{2}$ - 2 hrs.). Water (100-200 ml.) was added, the acetone removed under vacuum, the solution acidified (HCl) and decolourised with sulphur dioxide. Any insoluble material was filtered off, the filtrate continuously extracted with ether, the ether separated, dried ($MgSO_4$) and the solvent distilled under vacuum to leave the acidic product.

Heptafluoroquinoline: Potassium permanganate (1·3 gm., 0·008 mole) was reacted with heptafluoroquinoline (1·0 gm., 0·004 mole) at 0°C to give a brown solid (0·02 gm.). Recrystallisation (CH_2Cl_2) gave a pink solid m.pt. 147-150°C (decomp.) [ν_{max}, broad band from 3636-2353 (showing ν_{max} 3330, 3257, 2915, 2597), 1704, 1639, 1520, 1493, 1435, 1361, 1255, 1220, 1010, 991 $cm.^{-1}$]

2-Methoxyhexafluoroquinoline: Potassium permanganate (3·8 gm., 0·024 mole) was reacted with the methoxy compound (3·0 gm., 0·011 mole) at 30-35°C. Decolourisation, before acidification, gave a brown solid which on

recrystallisation (benzene) gave a yellow solid (0·05 gm.) m.pt. 135-147 (decomp.) [ν_{max}; 3521, 3401, broad band 3330-2105 (showing ν_{max} 2941, 2755, 2667, 2584, 2500), 1675, 1580, 1520, 1473, 1429, 1333, 1276, 1247, 1172, 1124, 1106, 954, 913, 901, 762, 714 cm.$^{-1}$].

Ether extraction gave a yellow solid which decomposed to a brown oil on attempted recrystallisation (chloroform).

2,4-Dimethoxypentafluoroquinoline: Potassium permanganate (9·1 gm., 0·058 mole) and the dimethoxy compound (3·1 gm., 0·011 mole) were reacted under reflux. 0·9 gm. (29%) of starting material was recovered and an orange-yellow solid (0·6 gm.). Recrystallisation (chloroform-acetone) gave two crops:-

(i) Pale yellow solid (0·1 gm.) [Found: C, 41·6; H, 3·26%; N present. ν_{max}, broad band 3660-2105 (showing ν_{max} 3413, 3003, 2976, 2667, 2639), 1709, 1605, 1493, 1479, 1416, 1385, 1282, 1190, 1116, 1038, 954, 917, 751, 680 cm.$^{-1}$].

(ii) Yellow solid (0·2 gm.) [Found: C, 32·4; H, 2·54; N present. ν_{max}, broad band 3745-2222 (showing ν_{max} 3448, 3030 (inf.), 2841, 2667) 1681, 1597, 1490, 1471, 1429, 1379, 1242, 1189, 1111, 1035, 926, 912, 749, 719 cm.$^{-1}$].

Attempted dehydrofluorination of α-hydroperfluoropropionitrile. General procedure.

α-Hydroperfluoropropionitrile[249] was flash distilled and the vapour carried in a stream of nitrogen through a heated silica tube packed with a

mixture of sodium fluoride powder and asbestos wool. The material emerging was condensed and analysed by analytical-scale v.p.c. (silicone grease, 20°C) and i.r. spectroscopy.

Reaction at 350°C: α-Hydroperfluoropropionitrile (1·0 gm.) gave a mixture (0·5 gm.) of unreacted starting material and perfluoroacrylonitrile in ratio of 85:15 [ν_{max}, 2941, 2262, 1764, 1370, 1361, 1299 (sh), 1282, 1274, 1220, 1183 (sh), 1176 (sh), 1140, 1136, 1129, 1125 (sh), 980, 851, 719, 714 cm.$^{-1}$].

Reaction at 410°C: The saturated nitrile (1·2 gm.) gave 0·1 gm. of condensate and considerable brown tar was present just beyond the furnace. The condensate consisted (v.p.c. analysis) of starting material and perfluoroacrylonitrile in equal amounts together with two compounds of higher retention time which comprised 20% of the total product.

Preparation of diethyl fluoromalonate.

Ethyl fluoro-acetate[253] (32·2 gm., 0·301 mole) was added, under nitrogen, in small portions over 20 minutes to a vigorously shaken suspension of sodium methoxide (16·3 gm., 0·30 mole) in dry petroleum ether (200 ml., b.pt. 40-50°) at 18°C. The yellow mass formed was cooled to -10°C and ethyl chloroformate (32·6 gm., 0·30 moles) quickly added, the temperature rising to +8° during the 3 minute addition. The mixture was shaken for 1 3/4 hours at room-temperature, refluxed (1 3/4 hours), water (200 ml.) added, the organic layer separated, washed with 1% sodium hydrogen carbonate (2 X 100 ml.), dried ($MgSO_4$) and the solvent distilled

at atmospheric pressure. Distillation of the residue at reduced pressure gave a fraction (13·6 gm.) boiling at 95-110°C/12 mm. which was redistilled through a short (6 in.) Vigreux column at atmospheric pressure and a fraction (4·85 gm.) boiling at 204-205°/744 mm. collected (lit. b.pt. $CHF(COOEt)_2$ 204-205/760 mm.) [ν_{max}, 3003, 1783, 1764, 1475, 1447, 1399 (sh), 1377, 1355(sh), 1294 (broad), 1253 (broad), 1199 (broad), 1172 (sh), 1116 (broad), 1027 (broad), 859 $cm.^{-1}$]. Analytical-scale v.p.c. (silicone grease, 200°C) showed two components in ratio of 60:40.

The ^1H n.m.r. spectrum (solution in carbon tetrachloride, benzene as internal reference) showed

Peak	Assignment
(i) triplet (121) at τ = 8·66, J = 7·0 c/s	C_2H_5-
(ii) quartet (1331) at τ = 5·72, J = 7·0 c/s	C_2H_5-
(iii) singlet at τ = 6·20	CH_3-
(iv) "doublet of doublets" at τ = 4·85, J = 48·0 and 2·5 c/s	CHF [near equivalence of CHF in CHF(COOEt)(COOR), R = Et or Me, gives rise to apparent doublet of doublets].

Ratio of $\frac{\text{ethyl protons}}{\text{methyl protons}}$ = 6·4:1, correlating with a mixture of diethylfluoromalonate and monoethylmonomethylfluoromalonate in ratio of 3:2.

Reaction of the mixed fluoromalonic esters with potassium hydroxide and thionyl chloride.

Potassium hydroxide (0·64 gm., 11·4 m.mole) in ethanol (3·7 ml.) was added to the mixed esters (2·0 gm., 11·6 m.mole) at room-temperature. The initial white precipitate redissolved on adding further alcoholic potassium hydroxide and no precipitation occurred on cooling to 0°C overnight. The ethanol solution was washed with petroleum ether, and the ethanol distilled under reduced pressure (90°C/0·01 mm.) to leave a yellow solid (1·2 gm.). Excess thionyl chloride (4·0 gm.) was added at room-temperature, the mixture heated (50°/22 hours), the excess thionyl chloride distilled and the residue distilled at reduced pressure to give a clear yellow liquid (0·8 gm., b.pt. 65-67/12 mm.) [ν_{max}, 3000, 1805, 1770, 1470, 1450, 1375, 1335, 1270, 1215, 1137, 1065, 1015, 990, 935, 863, 754].

Reaction of 3,4,5,6-tetrafluoroaniline with the monoester monoacid chloride of fluoromalonic acid

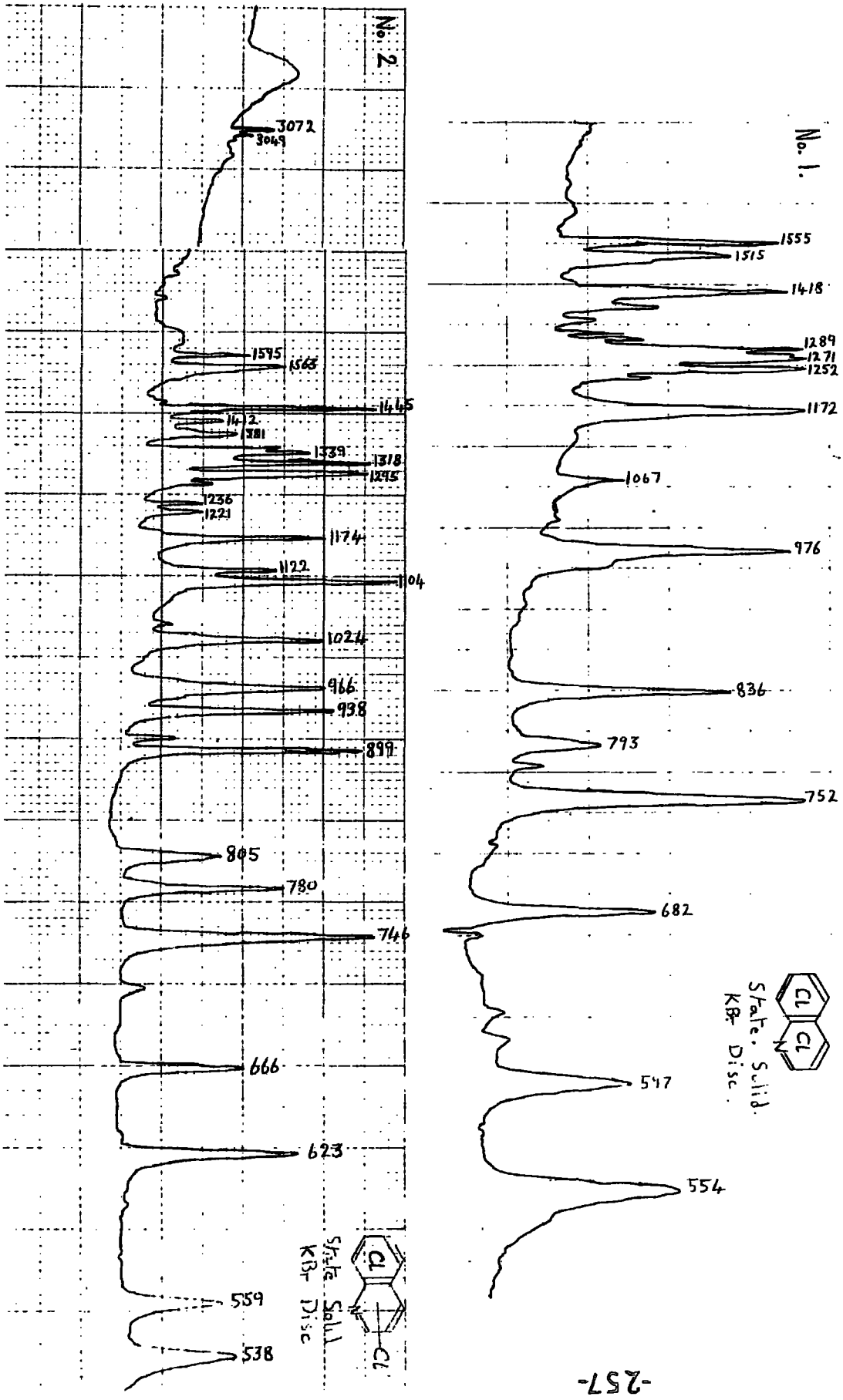
A solution of the fluoroaniline (0·4 gm., 2·4 m.mole) in dry methylene dichloride (2 ml.) was added, at room temperature, to the acid chloride (0·8 gm., 5·0 m.mole). The initial white precipitate dissolved on refluxing and after 1 hour's refluxing, diphenyl ether (6 ml.) was added. The methylene dichloride was distilled and the solution remaining quickly heated to 200°C. The solution rapidly darkened becoming black after 25 minutes. No precipitate was formed on cooling or on addition of light petroleum (b.pt. 40-60°). The solvent and unreacted starting material were distilled (180°C/12 mm.) to leave a black viscous tar ($\approx$0·5 gm.).

INFRARED SPECTRA

Infra-red Spectra

COMPOUND	Number
Heptachloroquinoline	1
Pentachloroquinoline	2
Heptafluoroquinoline	3
8-Chlorohexafluoroquinoline	4
2-Methoxyhexafluoroquinoline	5
4-Methoxyhexafluoroquinoline	6
2,4-Dimethoxypentafluoroquinoline	7
2,4,7 (or 6), -Trimethoxytetrafluoroquinoline	8
2-Aminohexafluoroquinoline	9
4-Amino- (80%) + 2-amino- (20%) hexafluoroquinolines	10
2-Hydrazinohexafluoroquinoline	11
2- and 4-Hydrazinohexafluoroquinolines	12
Benzaldehyde-3,4,5,6,7,8-hexafluoroquinolylhydrazone	13
Reduction product of compound no. 13	14
2-Hydrohexafluoroquinoline	15
2-Hydroxy-4-methoxypentafluoroquinoline	16
2,4-Dihydroxypentafluoroquinoline	17
4-Methoxypentafluoro-N-methyl-2-quinolone	18
2-Methoxy-4-hydroxypentafluoroquinoline	19
4-Hydroxyhexafluoroquinoline (≈80% pure)	20
2-Hydroxyhexafluoroquinoline	21
Hexafluoro-N-methyl-2-quinolone	22

COMPOUND	Number
2,4 (or 5), Dihydropentafluoroquinoline	23
2,4-Dichloropentafluoroquinoline	24
2-Chloro-4-hydroxypentafluoroquinoline	25
2-Chlorohexafluoroquinoline	26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1595
1563
1445
1412
1381
1339
1318
1295
1236
1221
1174
1122
1104
1024
966
938
899
805
780
746
666
623
559
538
Solid KBr Disc
No. 1.
1555
1515
1418
1289
1271
1252
1172
1067
976
836
793
752
682
547
554
Solid KBr Disc

No. 4
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1621
1515
1471
1418
1379
1339
1258
1174
1124
1075
1050
1029
999
965
925
806
781
772
748
720
708
689
F
CL
F
F
N
Solid
KBr Disc.

No. 5
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1616
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1494
1473
1395
1355
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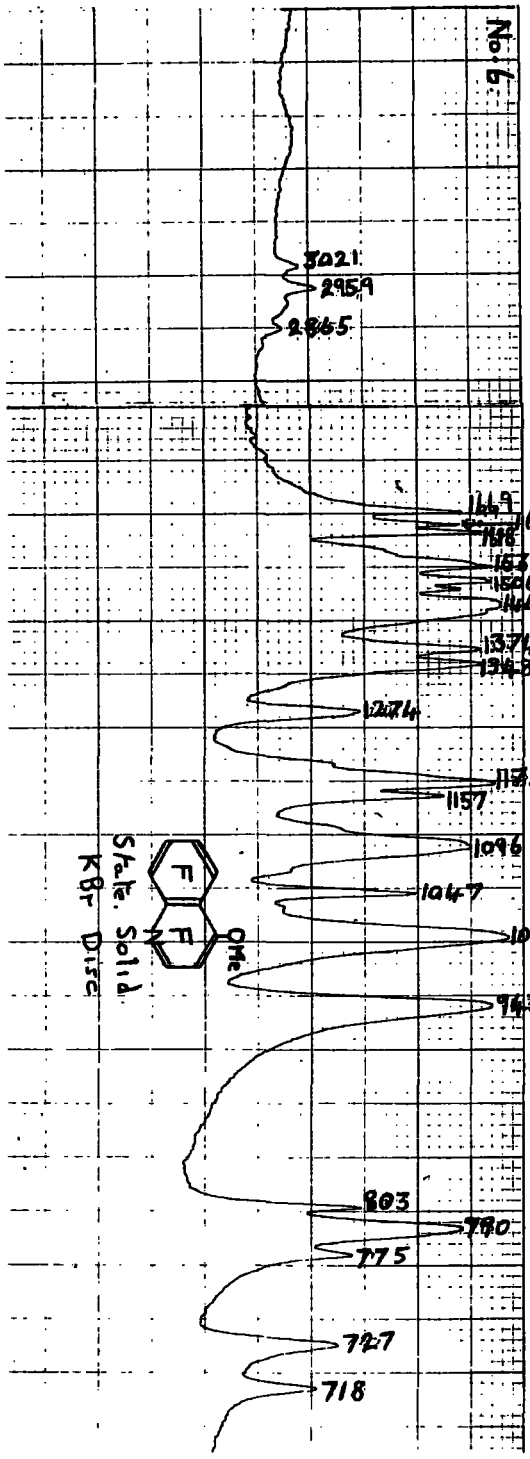
Solid
KBr Disc.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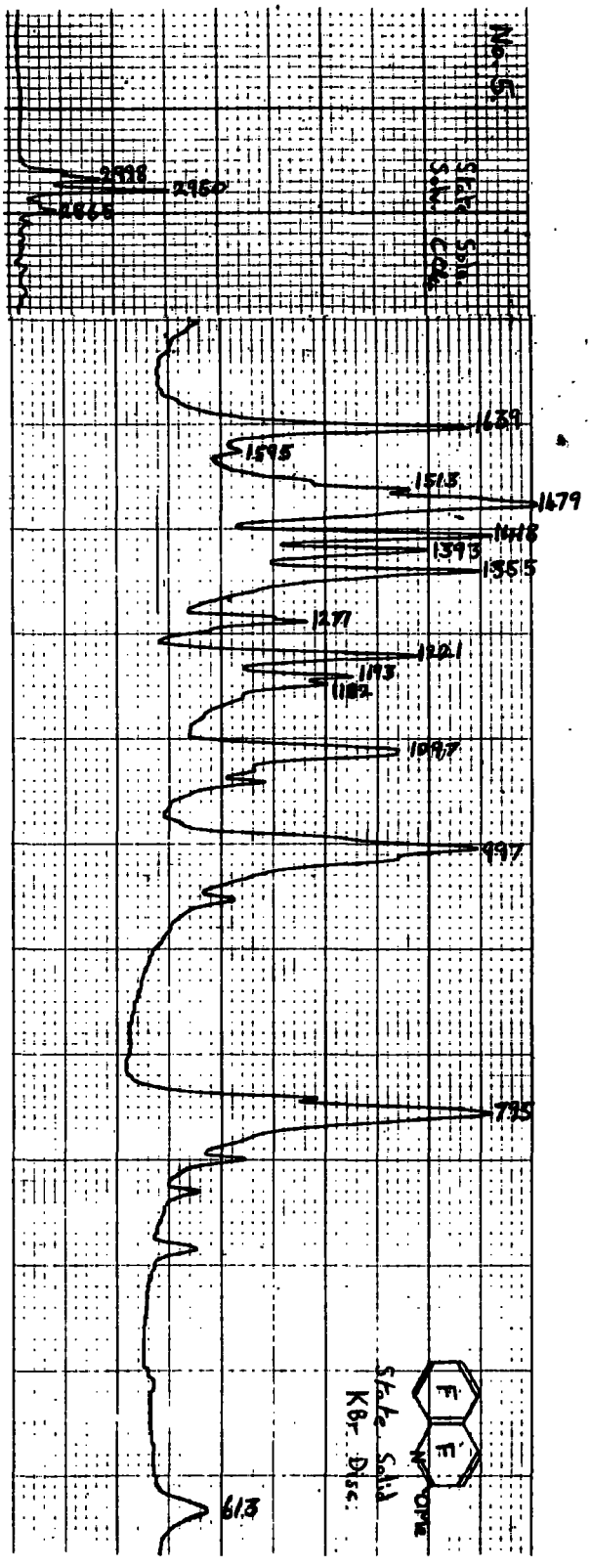
State. Solid
KBr Disc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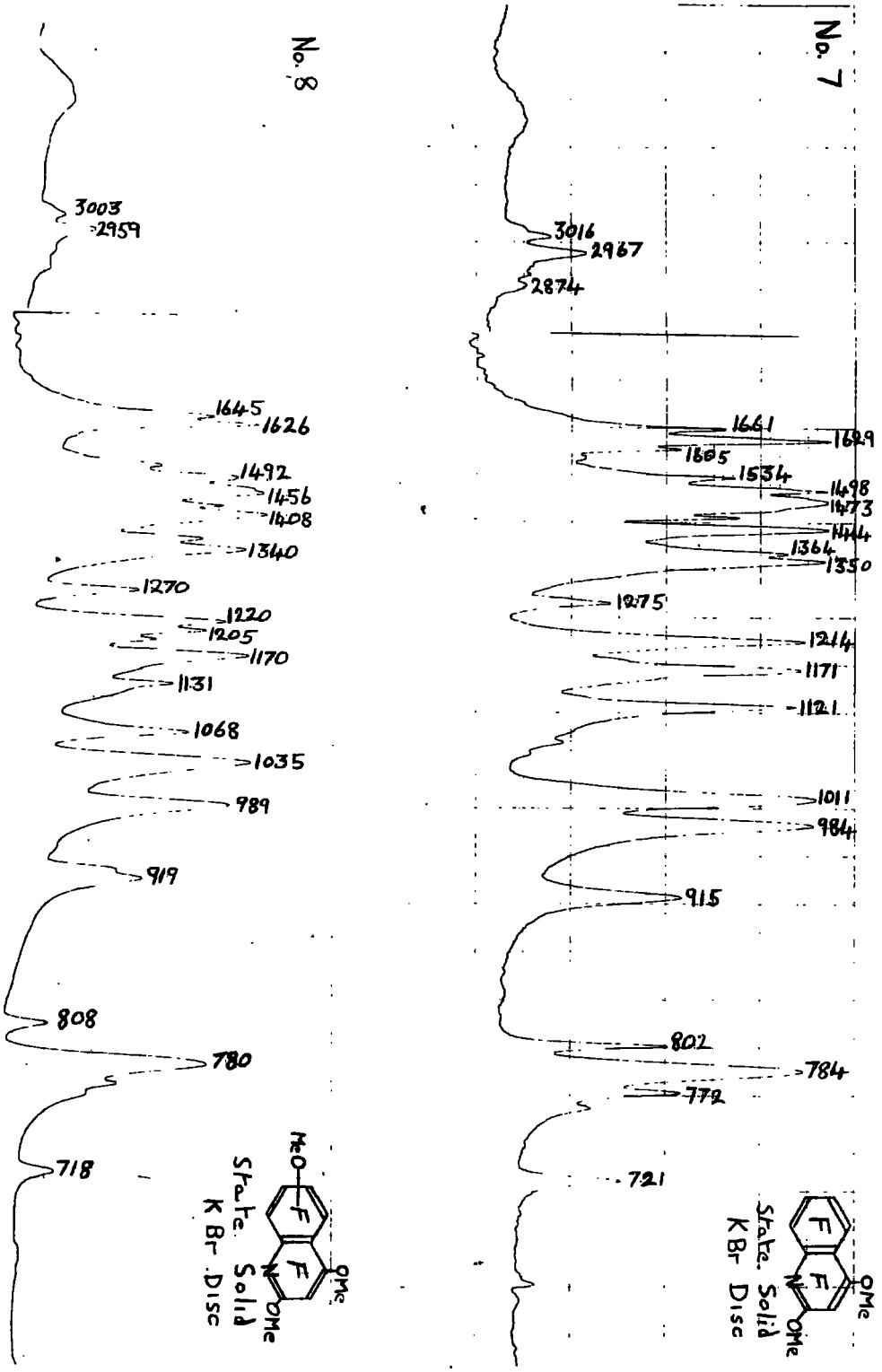
State Solid
KBr Disc.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1171
1121
1011
984
915
802
784
772
721
F
F
N
OMe
OMe
State. Solid
KBr Disc
No. 8
3003
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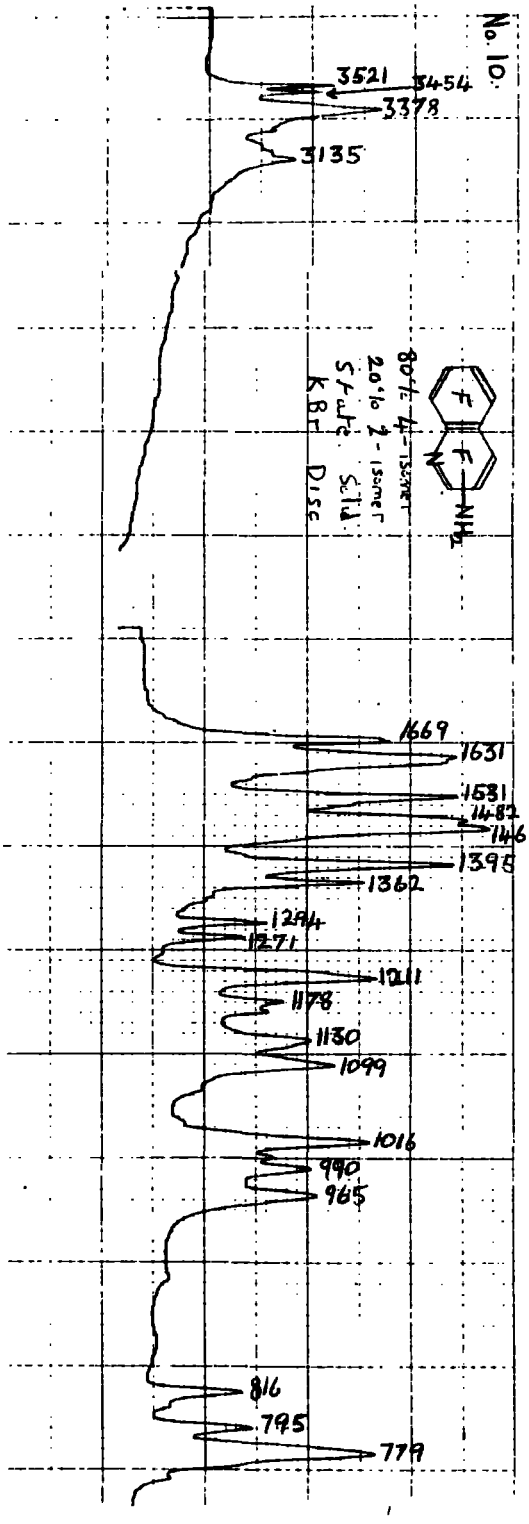
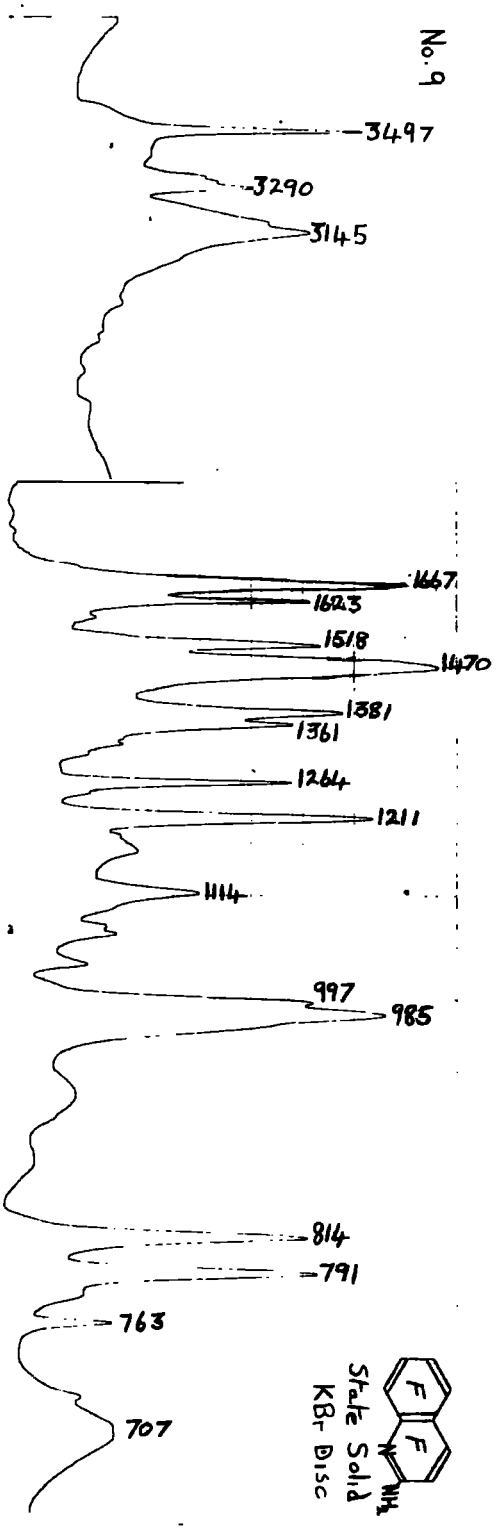
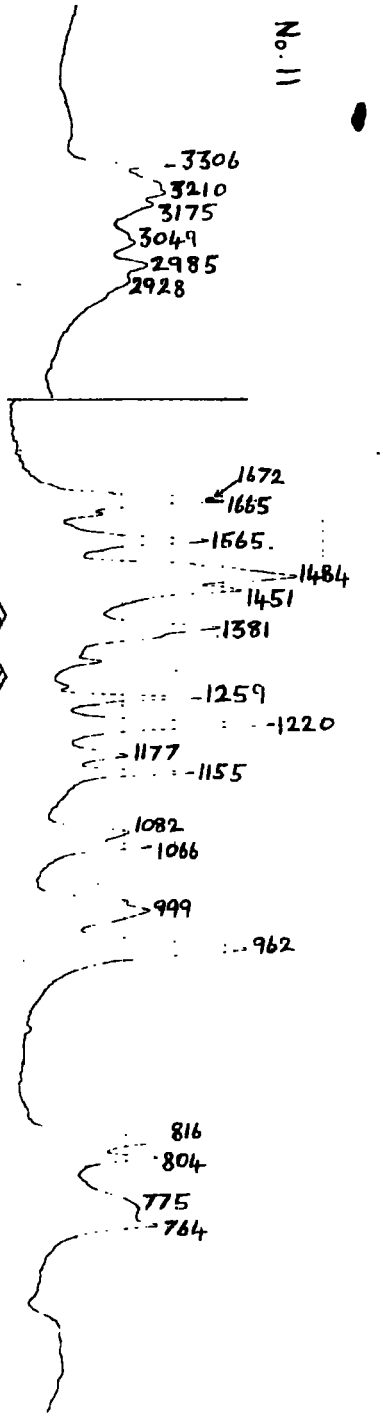
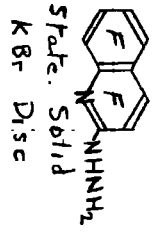
1645
1626
1492
1456
1408
1340
1270
1220
1205
1170
1131
1068
1035
989
919
808
780
718
MeO
F
F
N
OMe
OMe
State. Solid
KBr Disc


No. 10.
3521
3454
3378
3135
80% 4-Isomer
20% 2-Isomer
Solid
KBr Disc
1669
1631
1531
1482
1462
1398
1362
1294
1271
1211
1178
1130
1099
1016
990
965
816
795
779


No. 9
3497
3290
3145
1667
1623
1518
1470
1381
1361
1264
1211
1114
997
985
814
791
763
707
Solid
KBr Disc

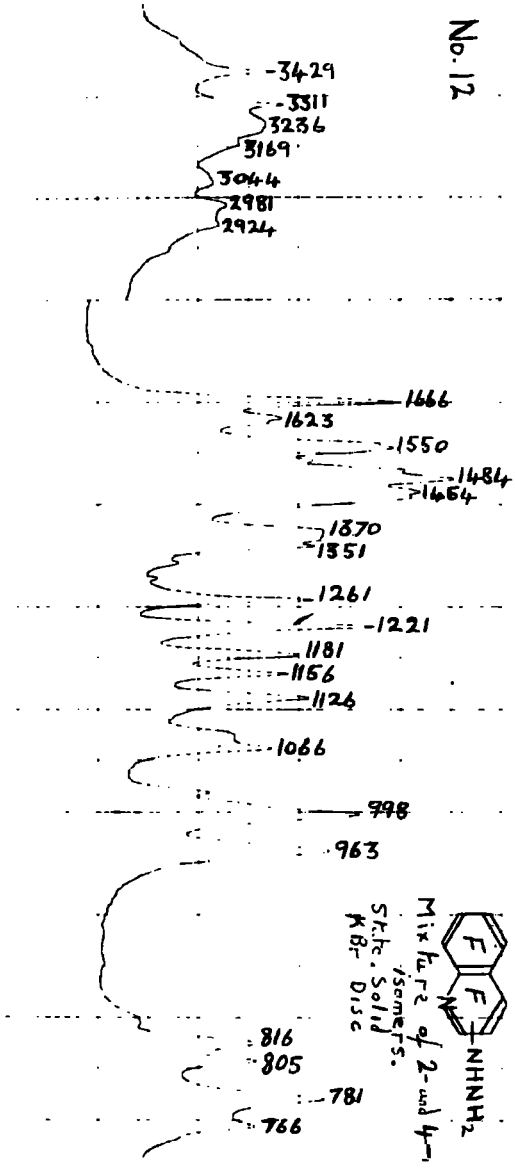
No. 11



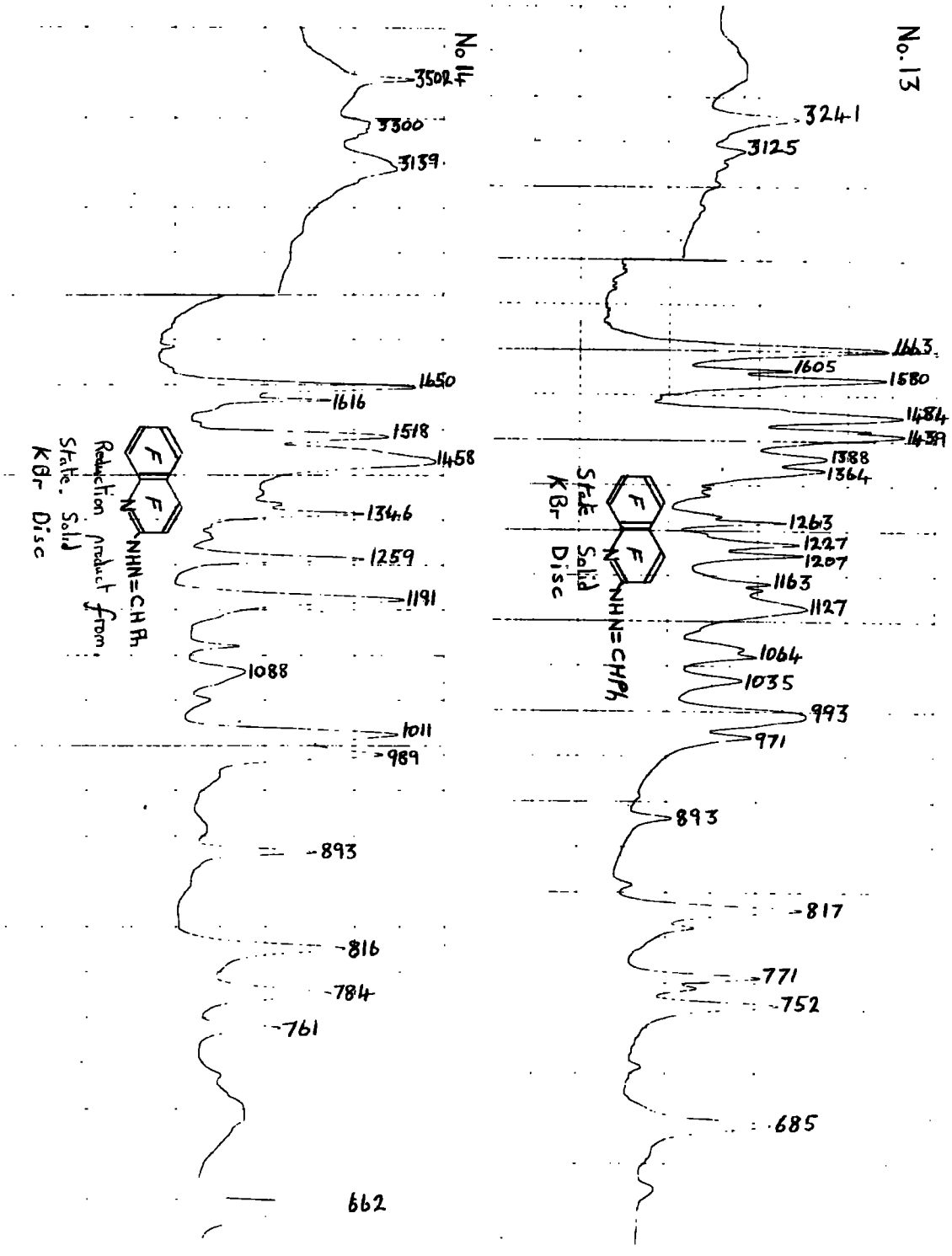


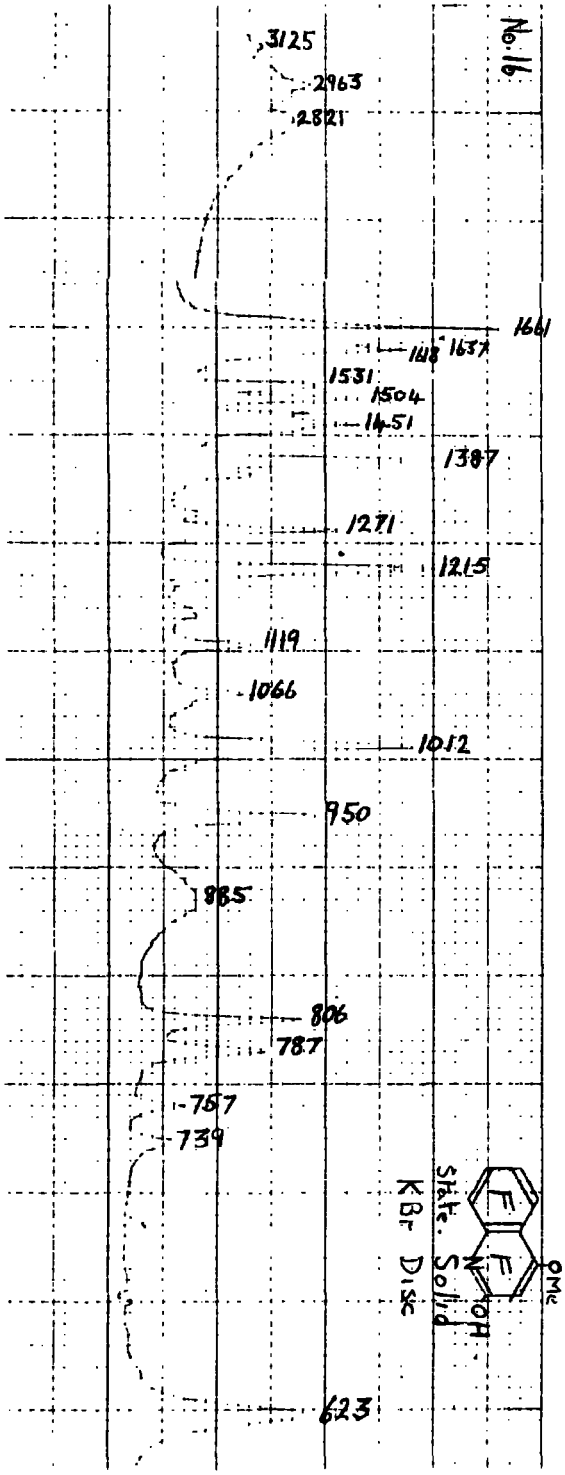
State. Solid
KBr Disc

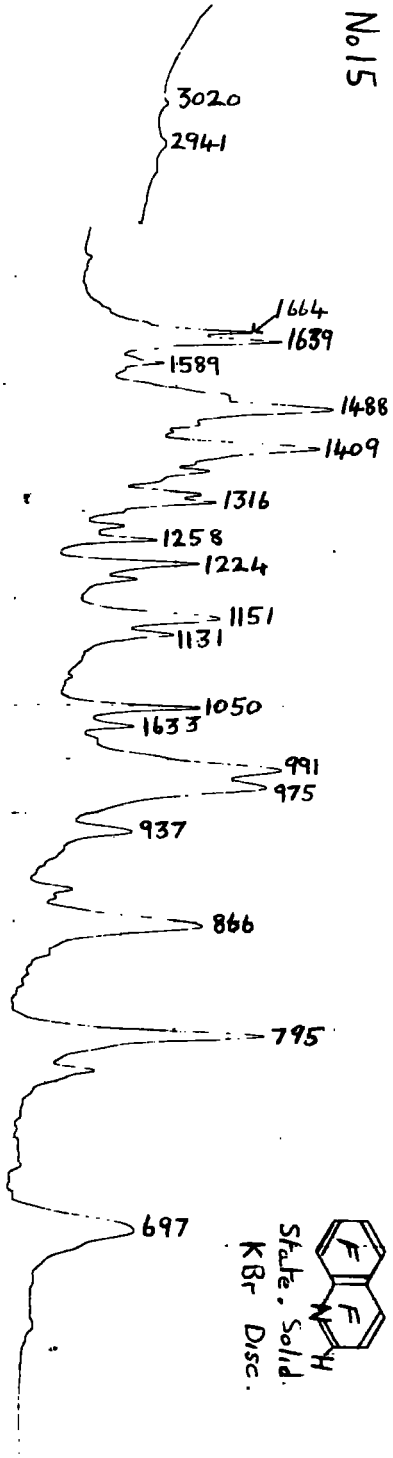
No. 12

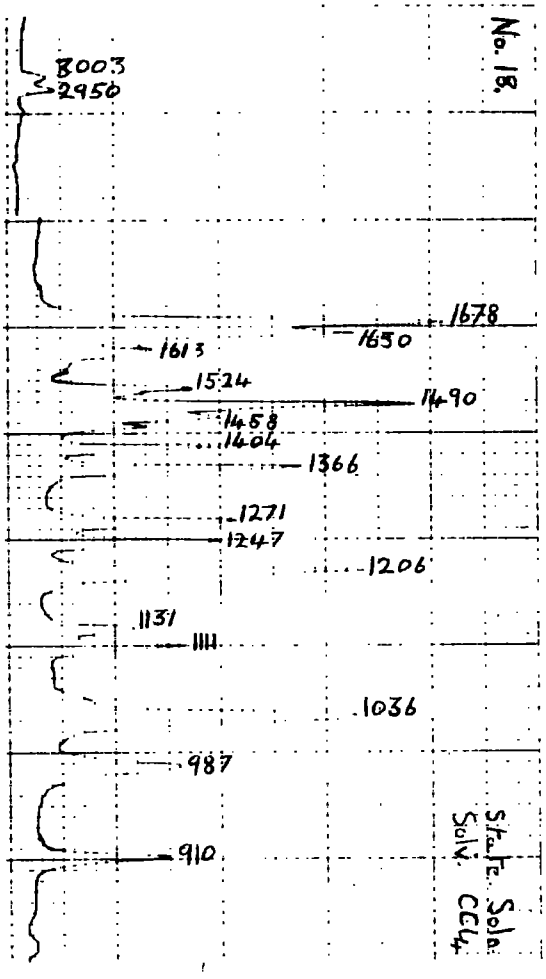


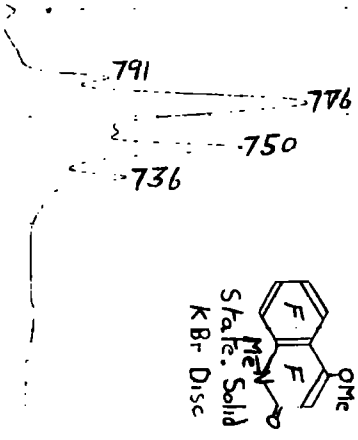
Mixture of 2- and 4- isomers.
State. Solid
KBr Disc


No. 11
3502
3300
3139
1650
1616
1518
1458
1346
1259
1191
1088
1011
989
893
816
784
761
662
F
F
N
NHN=CHR
Reduction product from
State. Solid
KBr Disc
No. 13
3241
3125
1663
1605
1580
1484
1439
1388
1364
1263
1227
1207
1163
1127
1064
1035
993
971
893
817
771
752
685
F
F
N
NHN=CHPh
State
Solid
KBr
Disc

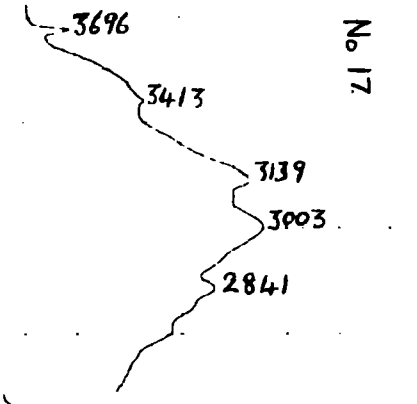

No. 16
3125
2963
2821
1661
1637
1531
1504
1451
1387
1271
1215
1119
1066
1012
950
885
806
787
757
739
623
KBr Disc
Solid
State.

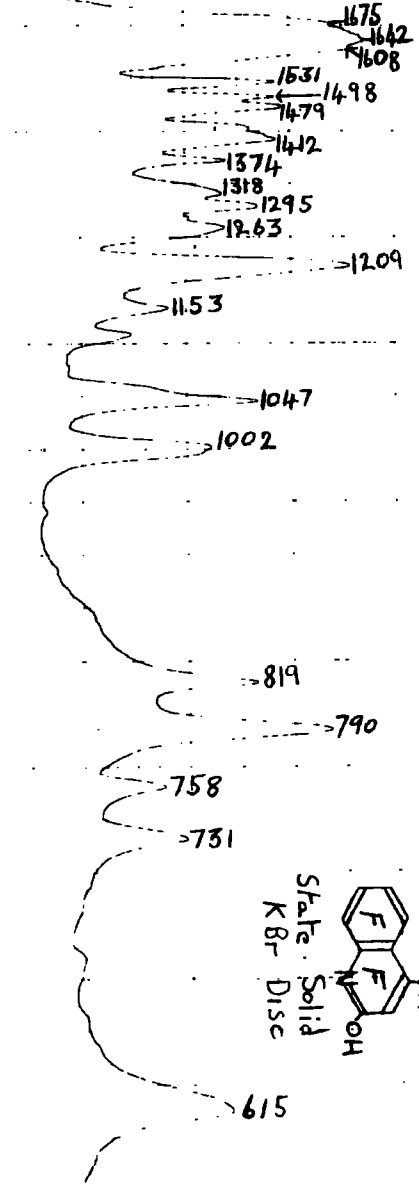

No 15
3020
2941
1664
1639
1589
1488
1409
1316
1258
1224
1151
1131
1050
1033
991
975
937
866
795
697
KBr Disc.
Solid.
State.


No. 18.
8003
2950
1678
1650
1613
1524
1490
1458
1404
1366
1271
1247
1206
1131
1111
1036
987
910
State. Soln. CCl4

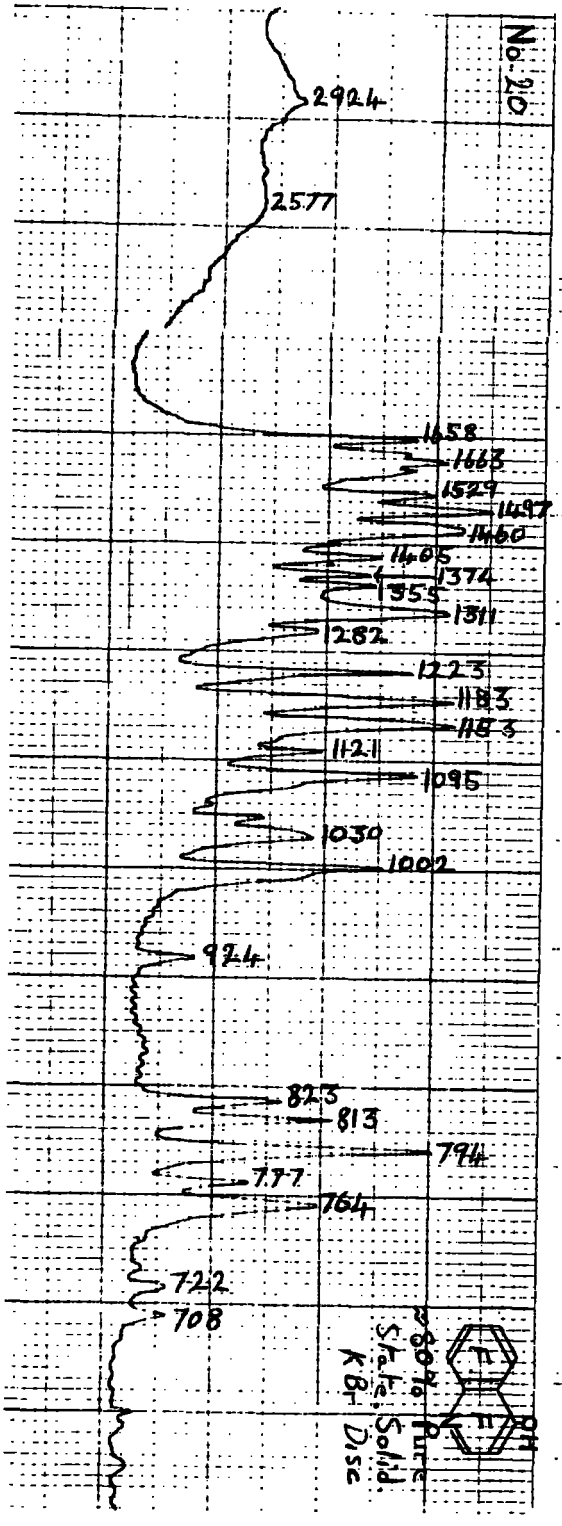

791
776
750
736

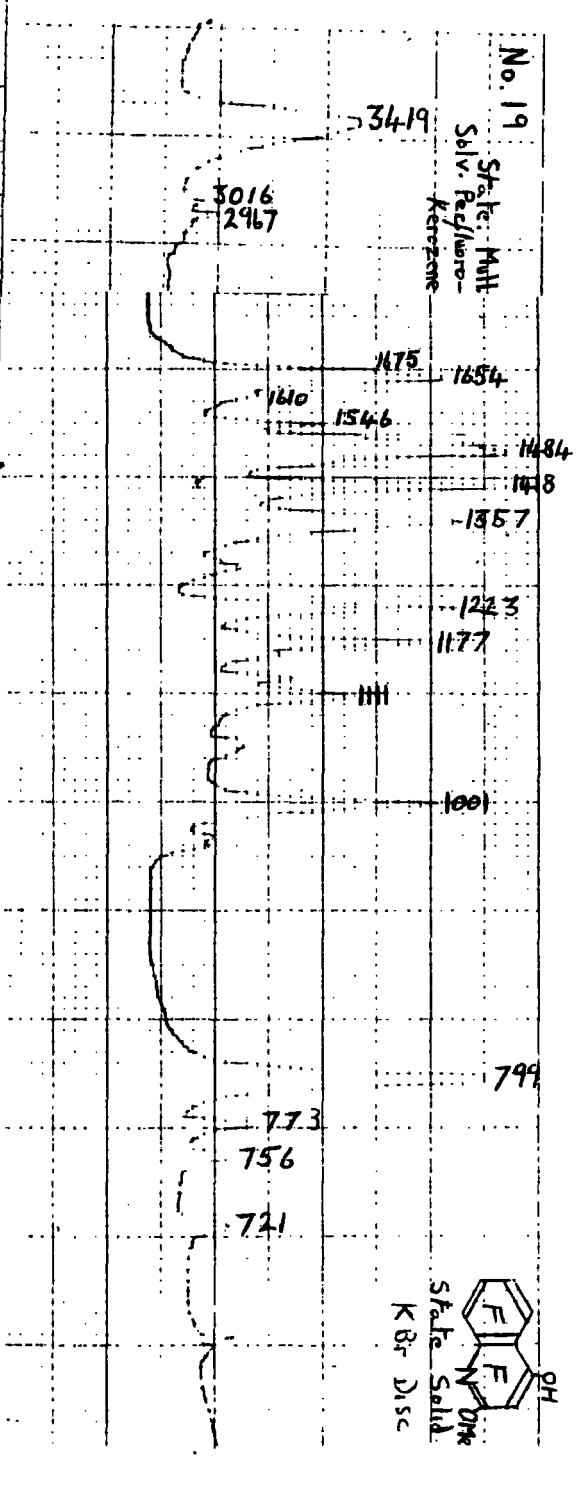
F
F
N
Me
O
OMe
State. Solid
KBr Disc

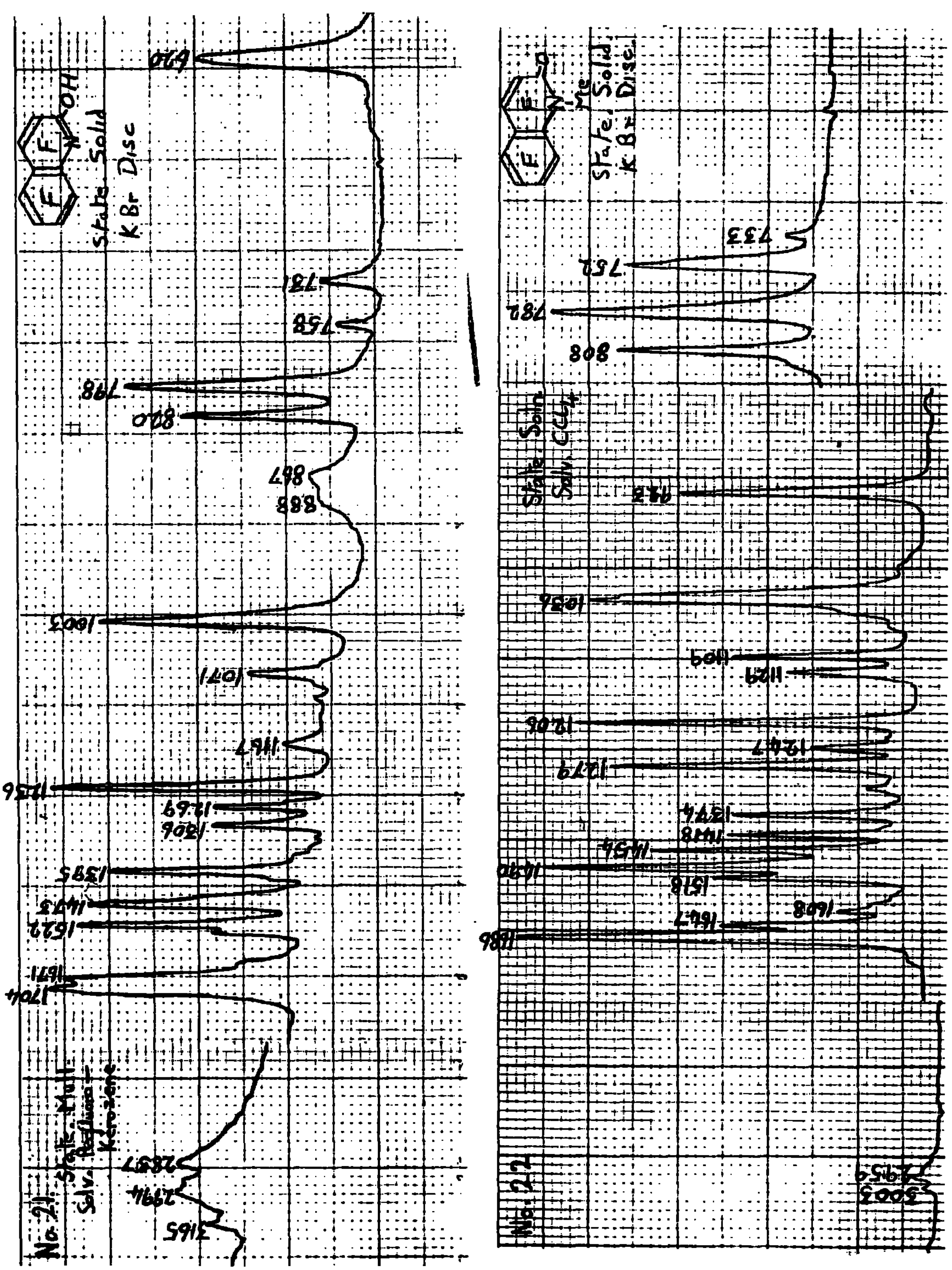

No. 17.
3696
3413
3139
3003
2841

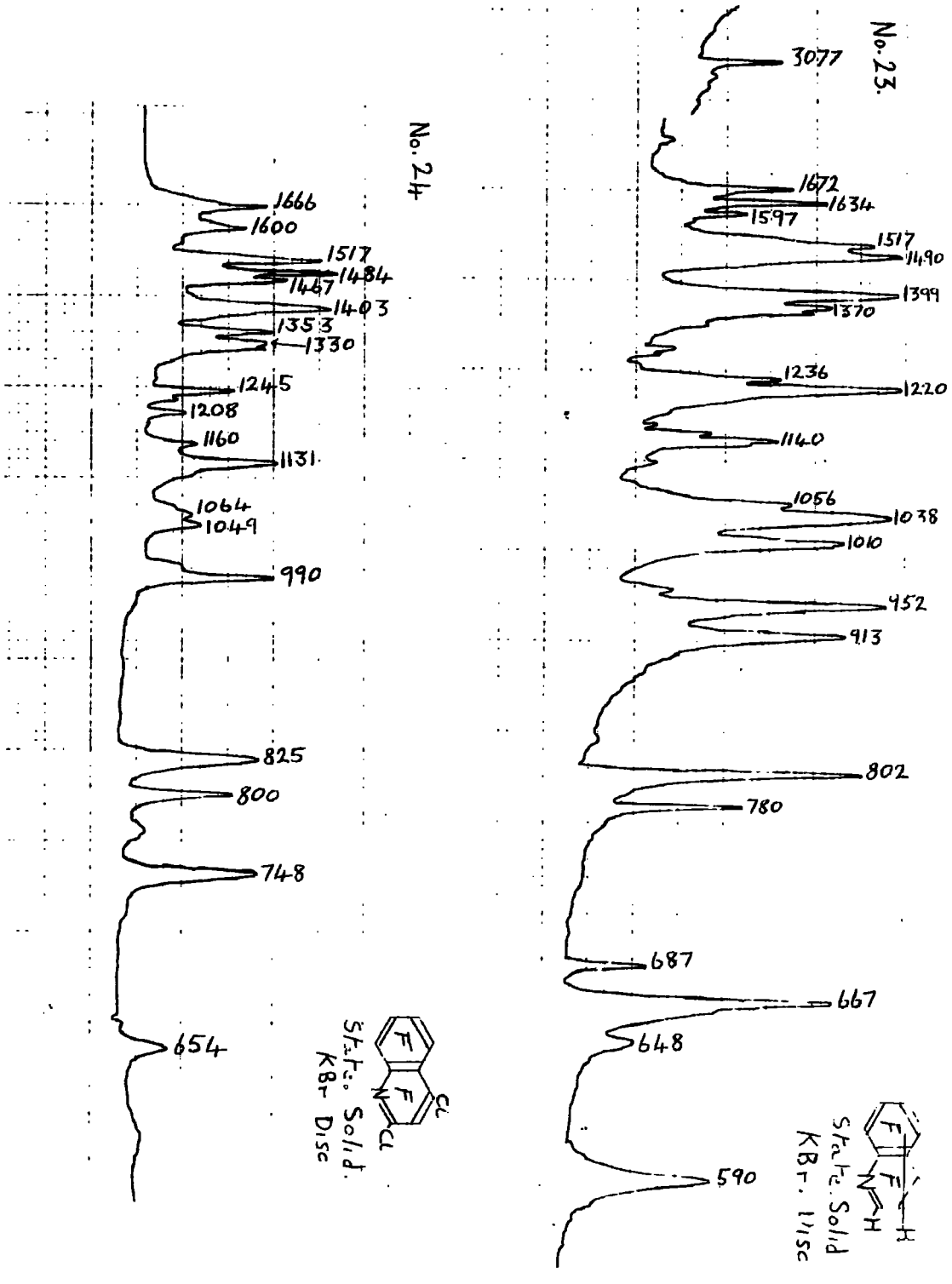

1675
1642
1608
1631
1498
1479
1412
1374
1318
1295
1263
1209
1153
1047
1002
819
790
758
731
615

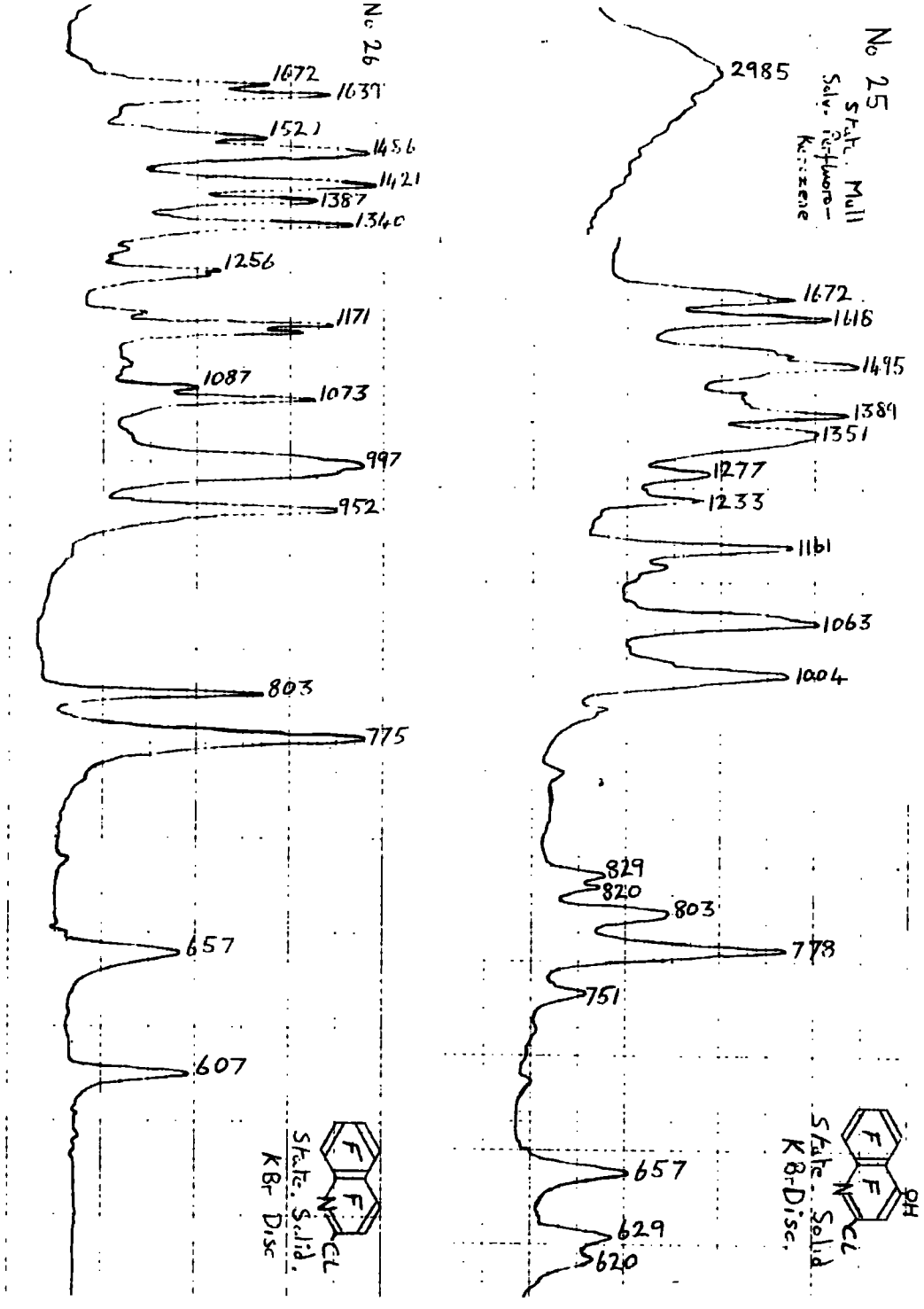
F
F
N
OH
OH
State. Solid
KBr Disc


No. 20
2924
2577
1658
1623
1529
1497
1460
1405
1374
1355
1311
1282
1223
1183
1153
1121
1095
1030
1002
924
823
813
794
777
764
722
708
~100% Purity
State: Solid
KBr Disc
F
F
F
OH


No. 19
3419
3016
2967
1675
1654
1610
1546
1484
1418
1357
1223
1177
1111
1001
799
773
756
721
State: Mull
Solv. Perfluoro-
kerosene
F
F
F
OH


No. 21
State Mull
Solv. Paraffin - Kerosene
State Solid
KBr Disc
690
731
758
798
820
867
888
1003
1071
1167
1256
1269
1306
1385
1473
1522
1671
1704
2857
2914
3165
No. 22
State Soln.
Solv. CCl4
State Solid
KBr Disc
733
752
782
808
982
1086
1109
1129
1206
1247
1279
1374
1418
1454
1490
1518
1608
1667
1686
2959
3005


No. 23.
3077
1672
1634
1597
1517
1490
1399
1370
1236
1220
1140
1056
1038
1010
952
913
802
780
687
667
648
590
State: Solid
KBr. Disc
No. 24
1666
1600
1517
1484
1467
1403
1353
1330
1245
1208
1160
1131
1064
1049
990
825
800
748
654
State: Solid.
KBr Disc


No 25
State. Mull
Solv. Perfluoro-
kerosene
2985
1672
1618
1495
1389
1351
1277
1233
1161
1063
1004
829
820
803
778
751
657
629
620
F
F
F
N
CL
OH
State. Solid
KBr Disc.
No 26
1672
1639
1521
1456
1421
1387
1340
1256
1171
1087
1073
997
952
803
775
657
607
F
F
F
N
CL
State. Solid.
KBr Disc

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