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U N I V E R S I T Y O F D U R H A M

A THESIS

entitled

SOME ASPECTS OF AROMATIC FLUORINE CHEMISTRY INVOLVING FUSED HETEROCYCLIC RINGS

submitted by

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(HATFIELD COLLEGE)

A candidate for the degree of Doctor of Philosophy.

1966.

20 OCT 1966

ACKNOWLEDGEMENTS

The work described here was carried out under the supervision of Dr. G.M. Brooke and I would like to express my sincere thanks for his continual help and encouragement. I am also indebted to Professor W.K.R. Musgrave for his interest and advice and Dr. D.T. Clark for some valuable discussions.

Finally I should like to thank the Imperial Smelting Corporation for a maintenance grant, and Mrs. M. Smith for typing this thesis.

MEMORANDUM

Part of this work has been the subject of a publication with Professor W.K.R. Musgrave and Dr. G.M. Brooke in the Journal of the Chemical Society (J. Chem. Soc., C, (1966) 215).

SUMMARY

5,6,7,8-Tetrafluoroquinoline and 2- and 4-methyl-5,6,7,8-tetrafluoroquinoline have been prepared by Skraup reactions of 2,3,4,5-tetrafluoroaniline with glycerol, crotonaldehyde, and methyl vinyl ketone respectively. Similarly 6,7,8- and 5,6,8-trifluoroquinoline have been prepared from 2,3,4- and 2,4,5-trifluoroaniline. Sodium methoxide, potassium hydroxide and ammonia, as nucleophilic reagents, replaced the 7-fluorine atom in 5,6,7,8-tetrafluoroquinoline. Some of the reactions of these derivatives and further reactions of the tetrafluoroquinoline are discussed. Convenient methods for the preparation of 2,4,5- and 2,3,6-trifluoroaniline are described.

Tetrafluoroanthranilic acid and 2,3,4,5-tetrafluorophenylglycine have been prepared and both have been used to synthesise 3,4,5,6-tetrafluorophenylglycine-o-carboxylic acid, from which octafluoroindigo has been prepared in a two stage process.

In attempts to prepare partially fluorinated indole derivatives the reactions between the sodium salts of pentafluoroaniline and perfluoroacetanilide and diethyl acetylenedicarboxylate have been investigated. However only maleic and fumaric acid derivatives were obtained and no cyclised product could be isolated.

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Chapter I

THE PREPARATION OF SOME FLUORINATED HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN

Quinolines and Isoquinolines.

With the exception of 4-fluoroquinoline all the monofluoro-derivatives of quinoline[1] and isoquinoline[2,3] have been prepared by means of the Schiemann reaction on the appropriate amino-compound. The method generally involves two steps: first, the preparation and isolation of a dry diazonium fluoroborate; and second, the controlled thermal decomposition of this salt to yield an aromatic fluoride, nitrogen and boron trifluoride. An excellent review describing the scope, limitation,

$$C_6H_5NH_2 + HNO_2 + BF_4^- \longrightarrow C_6H_5N_2BF_4 + H_2O + OH^- \qquad (1)$$

$$C_6H_5N_2BF_4 \xrightarrow{\text{Heat}} C_6H_5F + N_2 + BF_3 \qquad (2)$$

and mechanism of the reaction has recently appeared[4]. Decomposition of the diazonium fluorosilicate and the diazonium fluoride in anhydrous hydrogen fluoride have been used to prepare 2-fluoroquinoline[5] but the yields obtained (21 and 17% respectively) were less than that from the Schiemann reaction (28%).

Both 2-fluoroquinoline[6] and 1-fluoroisoquinoline[3] have been prepared by halogen exchange with potassium fluoride and the corresponding chloro-compound in dimethyl sulphoxide as solvent. Here the yields (ca 60 and

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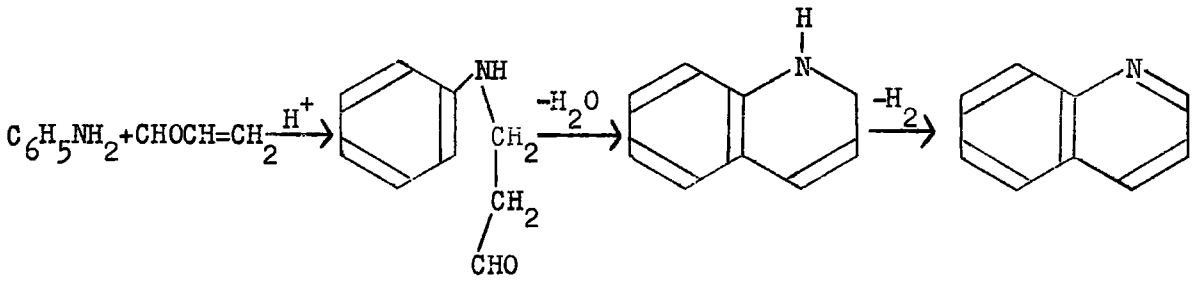
70% respectively) were much better than those obtained from the methods outlined above.

The Skraup reaction has been used to prepare 5-,6-,7- and 8-fluoroquinoline using the appropriate fluoroaniline[7-9]. The synthesis consists of a series of reactions brought about by heating a primary aromatic amine with glycerol, sulphuric acid and an oxidising agent. The mechanism will be discussed later. Meta-fluoroaniline, which theoretically could be

$$CH_2OH \cdot CHOH \cdot CH_2OH \longrightarrow CHO \cdot CH{=}CH_2$$



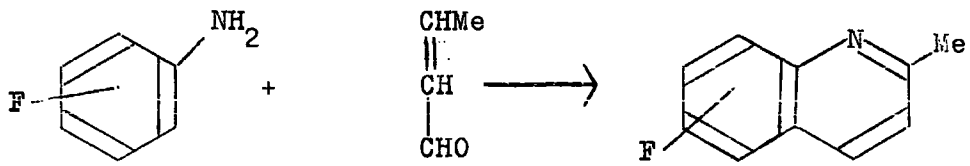
cyclised in two ways, was claimed to give only 7-fluoro- and no 5-fluoroquinoline[8]. The reaction has since been repeated and 25% of the product shown to be 5-fluoroquinoline.

2,4-Difluoroquinoline and 1,3-difluoroisoquinoline have been prepared from 4-hydroxy-2-quinolone and 1,3-dihydroxyisoquinoline respectively by treatment with trifluoro-1,3,5-triazine in an autoclave for one hour at 165-195°C.[10]

A synthesis of heptafluoroquinoline has been claimed by defluorination of perfluorodecahydroquinoline in a nickel vacuum pyrolysis tube packed with iron wire at elevated temperatures[11]. A much more convenient method for the synthesis of heptafluoro-quinoline and -isoquinoline has been

developed in Durham. Halogen exchange between heptachloro-quinoline ~~and~~ or -isoquinoline and anhydrous potassium fluoride takes place readily at elevated temperatures to give the corresponding perfluoro-compounds in excellent yields[12]. This method has previously been successfully used for the preparation of hexafluorobenzene[13] and pentafluoropyridine[14,15].

All the monofluoro-derivatives of 2-methylquinoline (quinaldine) have been synthesised. The Schiemann reaction was used to prepare 3-, 4- and 8-fluoroquinaldine from the corresponding amino-compound[16,17]. 4-Fluoroquinaldine and 2-fluorolepidine (2-fluoro-4-methylquinoline) have been prepared from 4-hydroxyquinaldine and 2-lepidone by fluorination with trifluorotriazine[10]. While the existence of 4-fluoroquinoline is questionable, 4-fluoroquinaldine was obtained as an unstable hydrate. On heating m- and p-fluoroaniline with paraldehyde, concentrated hydrochloric acid and a little zinc chloride, 7- and 6-fluoroquinaldine[16] respectively were formed. It is possible that crotonaldehyde is formed as an intermediate and this reacts with the amine. The method is known



as the Döbner-Miller synthesis. From a modified Skraup synthesis between m-fluoroaniline and crotonaldehyde a high yield of a mixture of 7- and 5-fluoroquinaldine, in the ratio 3:1, was obtained[18].

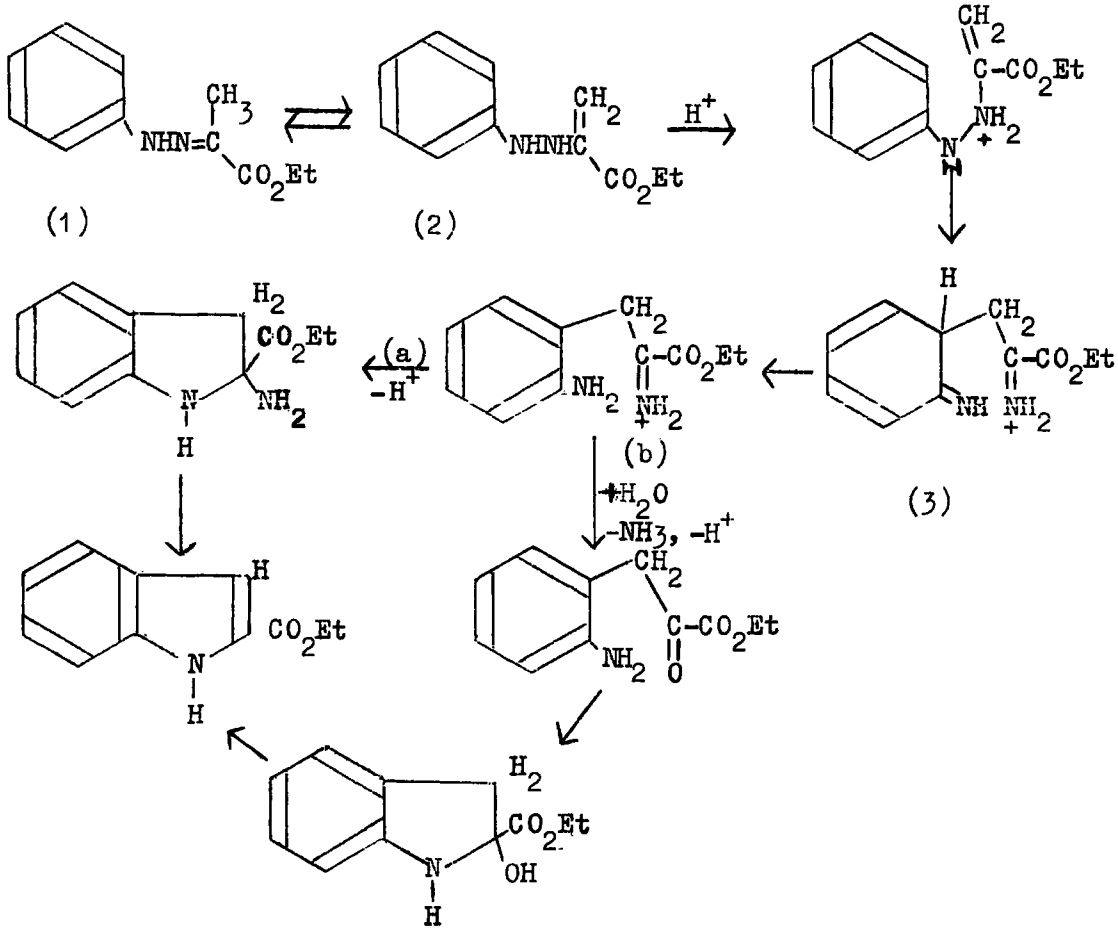
Indoles.

4-,5-,6- and 7-Fluoroindole have been prepared by Fischer cyclisations of ethyl pyruvate o-, m-, and p-fluorophenylhydrazone, followed by hydrolysis and decarboxylation. The Fischer indole synthesis can be regarded as the elimination of ammonia from the arylhydrazone of an aldehyde or ketone, by treatment with an acid or various metal and anhydrous halide metal catalysts, with the formation of an indole nucleus. The probable mechanism is outlined below. It consists of three separate stages.

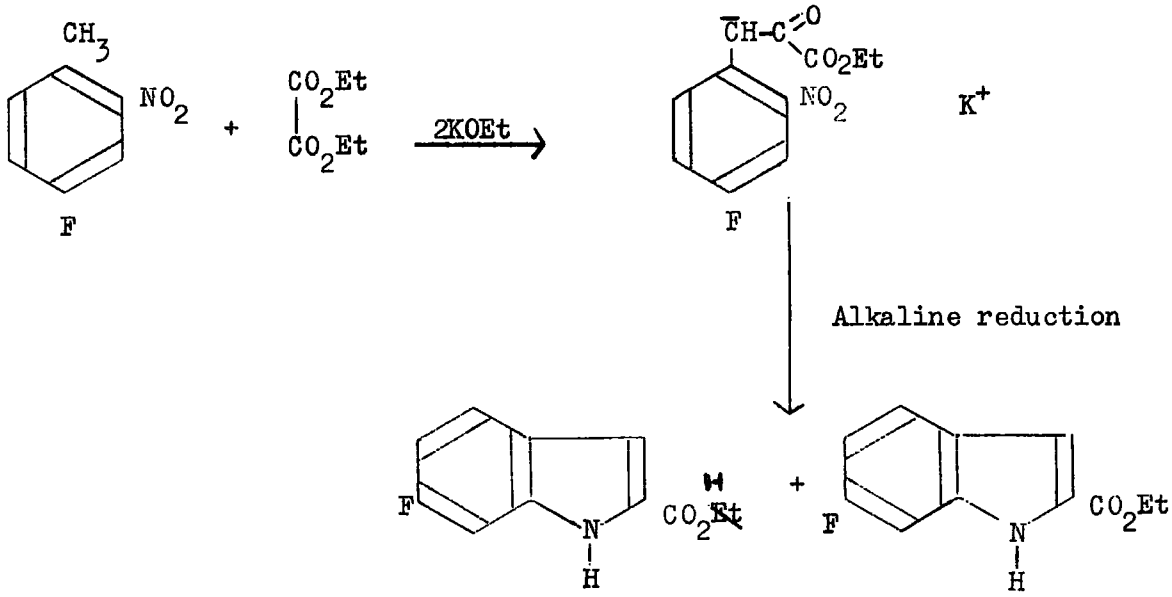
(i) hydrazone-enehydrazine equilibrium (1 $\rightleftharpoons$ 2)

(ii) formation of a new C-C bond (2 $\longrightarrow$ 3)

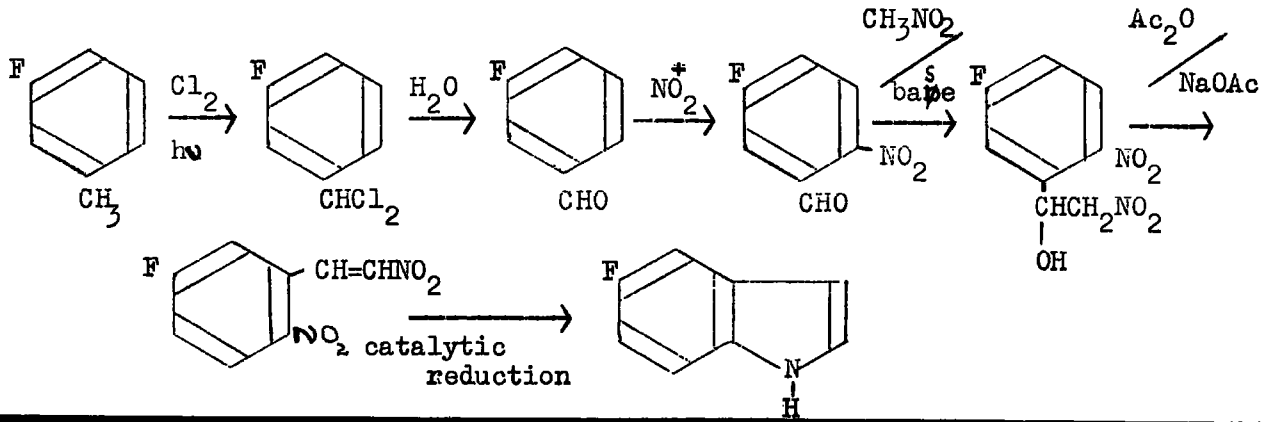
(iii) loss of ammonia by route (a) or (b)



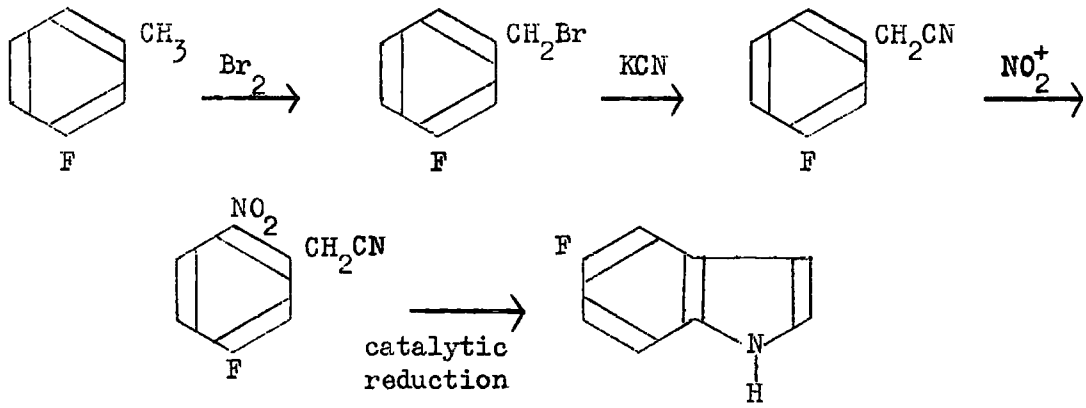
Ring closure of the m-fluorophenylhydrazone led to a mixture of ethyl 4- and 6-fluoroindole-2-carboxylate from which only the latter could be isolated. The presence of the former was inferred from ultraviolet absorption. These two compounds were also obtained by Reissert syntheses.



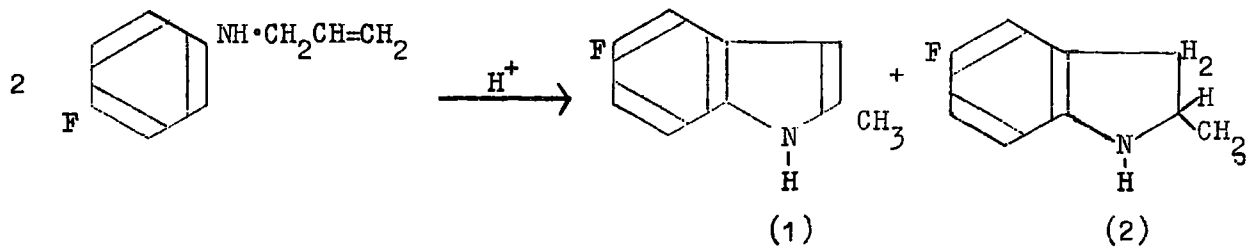
The fluoroindole acids were decarboxylated by heating above their melting points to give the respective fluorindoles[19]. A very similar preparation of 6-fluoroindole has been described in patents[20,21]. This method has also been used to prepare 5-fluoroindole from 5-fluoro-2-nitrotoluene[22]. The sequence represented below was developed to produce 5-fluoroindole on



a large scale,[23] the overall yield was 29%. These same workers have prepared 6-fluoroindole[24] by the same route, starting from 4-fluoro-2-nitrotoluene. A more recent synthesis of 5-fluoroindole[25] claims an overall yield of 46% from m-fluorotoluene. The method is briefly outlined below.

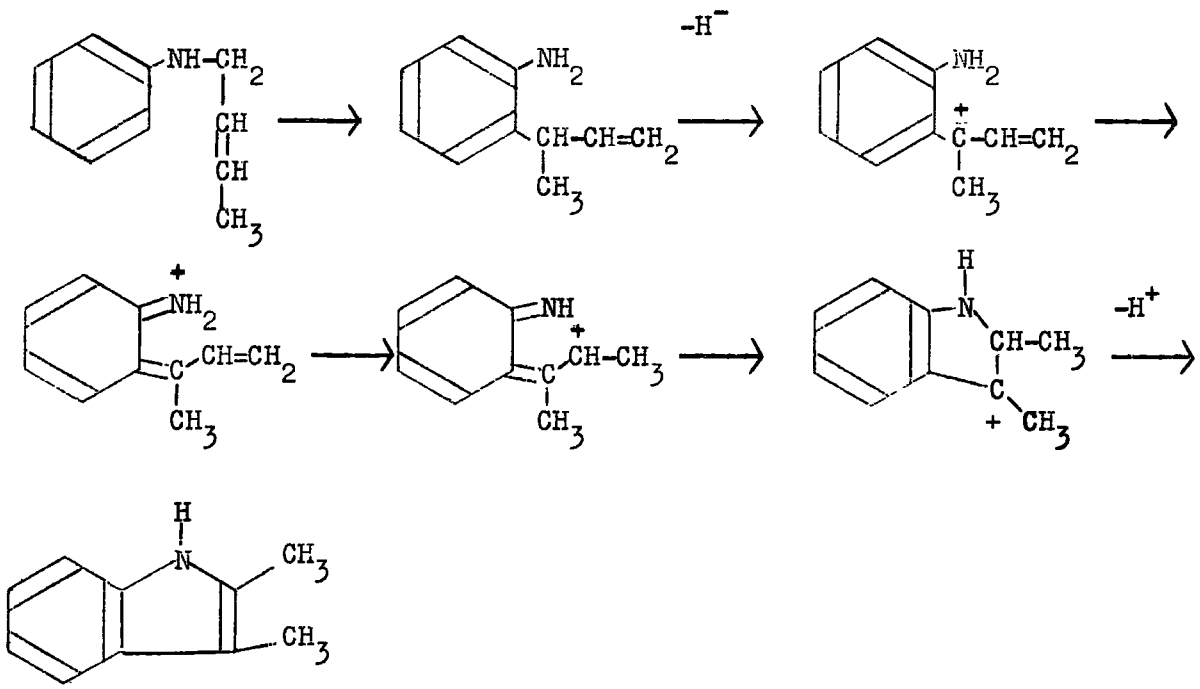


A very interesting preparation of 5-fluoro-2-methylindole (1) and 5-fluoro-2-methylindoline (2) has been reported[26]. These are formed in about equal amounts when N-allyl-p-fluoroaniline is heated to 230° in the presence of concentrated hydrochloric acid. The indoline can be readily dehydrogenated by heating with palladium on charcoal at 200° for 15-20 mins. The method is quite general for N-2-alkenylanilines and substituted anilines,



(1) (2)

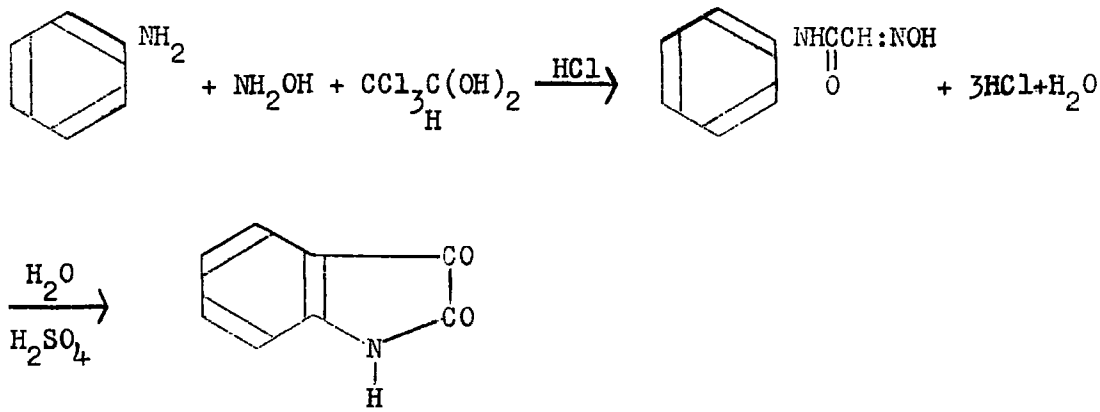
and also those in which the aniline is disubstituted, subject to the conditions mentioned below. One of the advantages of the method is that the N-alkenylaniline can be prepared "in situ" and need not be isolated. The disadvantages include the fact that the N-alkenylanilines are both thermally unstable, and may be cleaved by the strongly acidic conditions of the re-arrangement. In either case allyl moieties may be liberated which will alkalate the indoles further. A reaction scheme by the authors for the re-arrangement of N-crotylaniline to 2,3-dimethylindole is shown below.



Isatins.

The Sandmeyer isatin synthesis has been applied with success to 3-fluoro-, 4-fluoro- and 3,4-difluoroaniline, but 2-fluoro- and 2,4-difluoro-aniline

failed to give the corresponding isatins[27,28]. The synthesis consists of condensing a primary arylamine with chloral and hydroxylamine to give the corresponding isonitrosoacetanilide, and cyclisation of the latter with hot concentrated sulphuric acid. The final stage failed in the cases

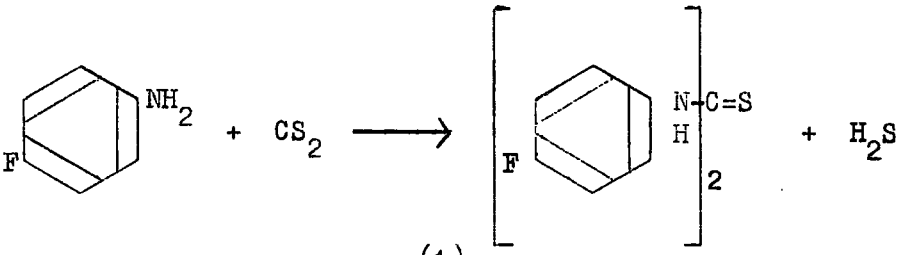


mentioned above. Para-fluoroaniline gave 5-fluoroisatin, and m-fluoroaniline gave 6-fluoroisatin in ca 70% yield with only a trace of 4-fluoroisatin. This was attributed to the inductive effect of fluorine, which strongly deactives the ortho position towards electrophilic attack. Similarly cyclisation of 3,4-difluoroaniline gave a single compound which by analogy was said to be 5,6-difluoroisatin.

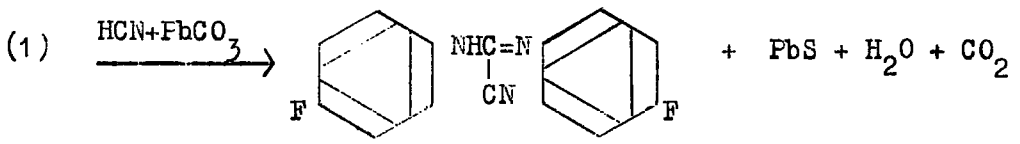
Indigos

The preparation of 5,5'- and 7,7'-difluoroindigo from p- and m-fluoroaniline was first reported by Roe and Teague[29]. The method of Sandmeyer was found to be the most satisfactory for preparing these compounds. The synthesis of 5,5'-difluoroindigo (5) is outlined in the accompanying

equations. An interesting fact was that m-fluoroaniline would not react



(1)



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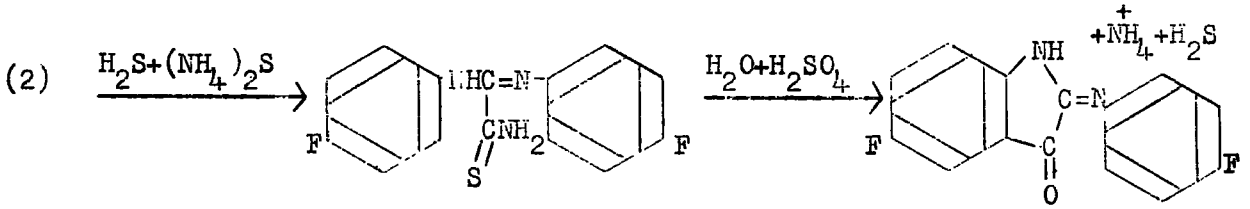

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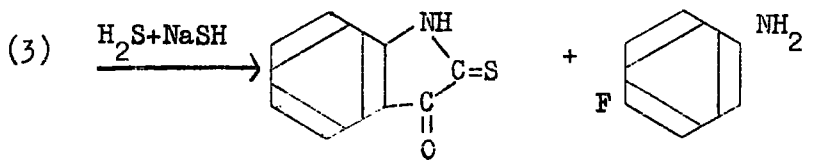

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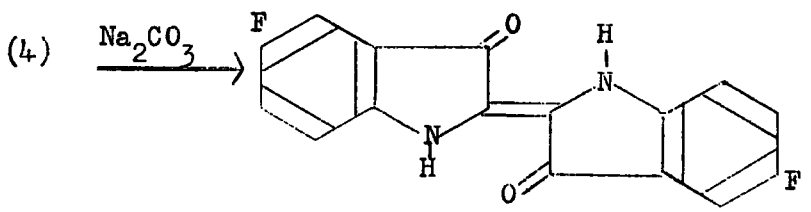
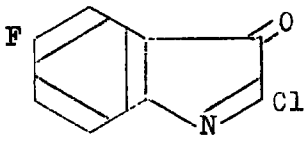


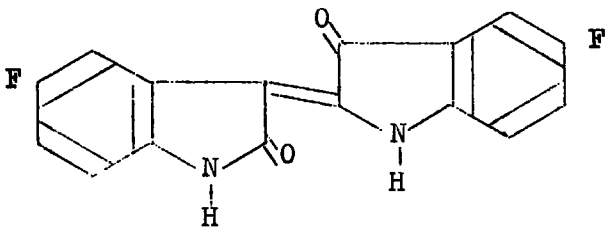
(5)

with carbon disulphide to form a difluorodiphenylthiourea, and hence 4,4'- and/or 6,6'-difluoroindigo could not be prepared by this method.

A small amount of 5,5'-difluoroindigo was obtained by reduction of 5-fluoroisatin α-chloride (6) with zinc and acetic acid, the major product was however 5,5'-difluoroindirubine (7)



(6)

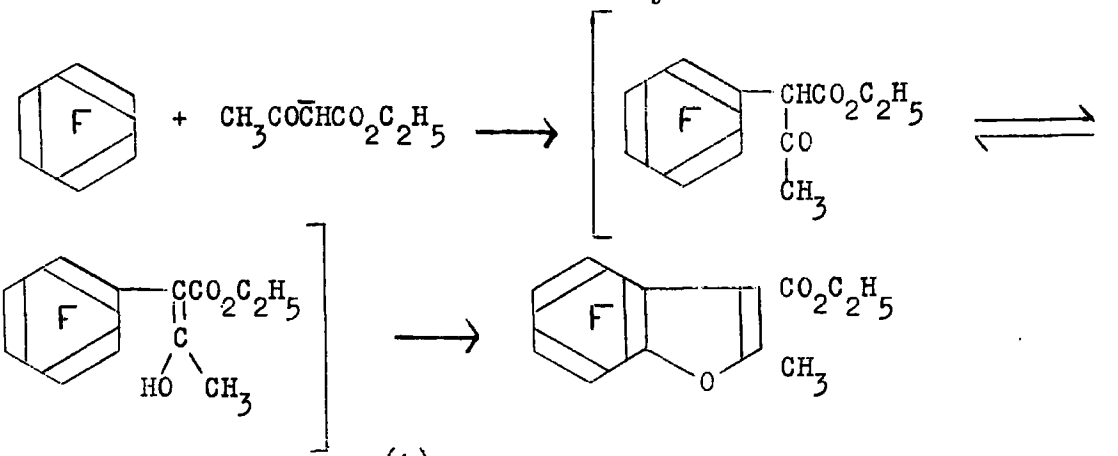


(7)

Chapter II

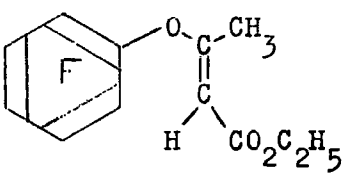
THE PREPARATION OF SOME FLUORINATED HETEROCYCLIC COMPOUNDS FROM HEXAFLUOROBENZENE AND ITS DERIVATIVES

Very few aromatic heterocyclic compounds derived from hexafluorobenzene and its derivatives have been prepared. However Russian workers[30] have found that acetoacetic ester, sodium hydride and hexafluorobenzene in approximately equimolar quantities gave a 30% yield of a benzofuran derivative (1). The reaction mechanism which they suggested is outlined below. The same reaction has been carried out by other workers who believe



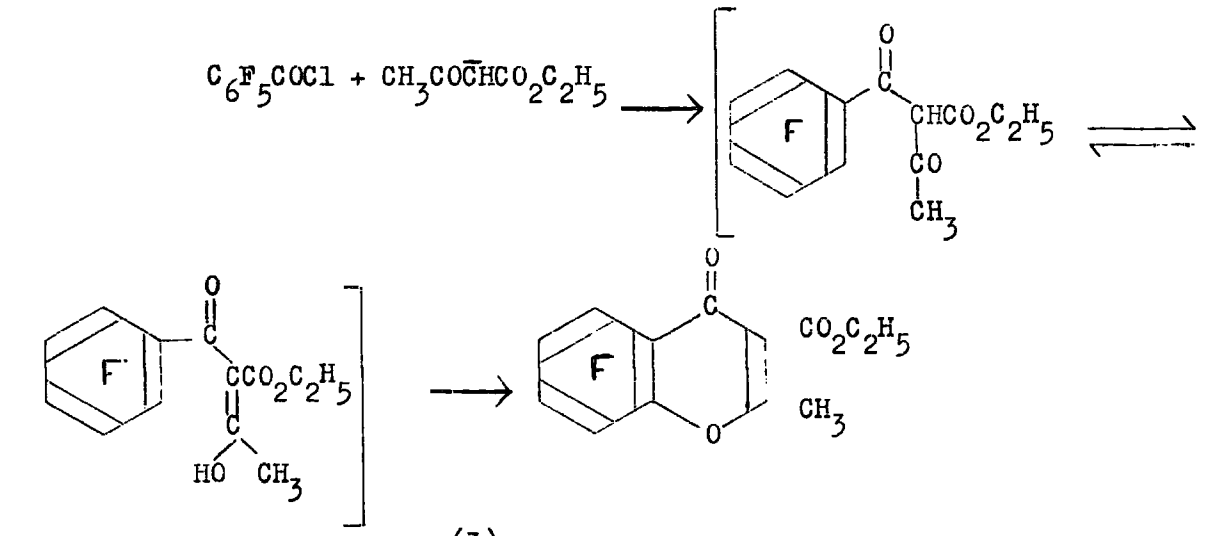
(1)

that the first stage of the reaction is ~~O-alkylation~~ nucleophilic substitution of hexafluorobenzene to give the intermediate (2) which is then cyclised[31]. At the moment insufficient evidence is available to decide which mechanism is correct.



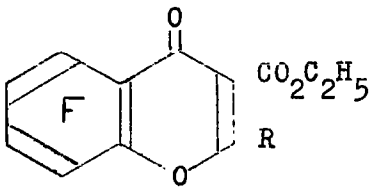
(2)

Russian workers have also synthesised the chromone derivative (3) by condensing pentafluorobenzoyl chloride with the magnesium derivative of acetoacetic ester in benzene. The yield of (3) was so high that O-acylation ~~alkylation~~ must have taken place to a very small extent if at all.



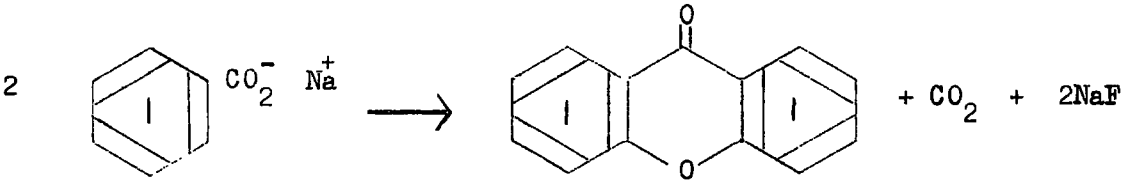
(3)

Similar reactions with pentafluorobenzoyl chloride and the magnesium derivatives of ethyl benzoylacetate and pentafluorobenzoylacetate gave the substituted flavones (4) and (5) respectively, both in excellent yields[32].



(4 : R = C_6H_5)
(5 : R = C_6F_5)

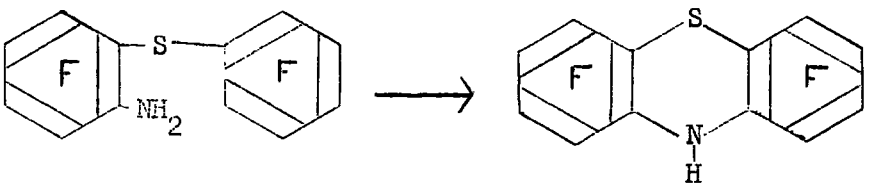
Octafluoro-xanthone (6) has been prepared by means of the thermal decarboxylation of sodium pentafluorobenzoate at 275°. A similar



(6)

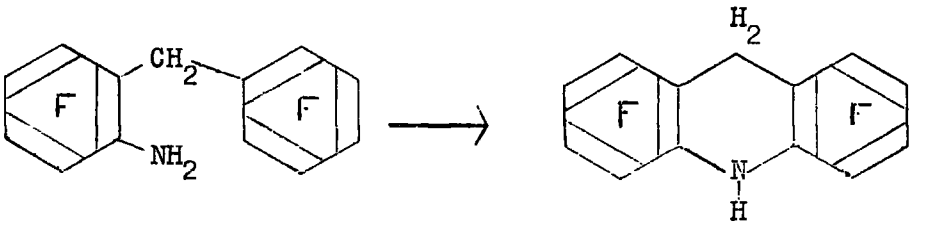
decomposition of silicon tetrakis(pentafluorobenzoate) gave decafluorobenzophenone[33]. In comparison mercuric pentafluorobenzoate decarboxylates smoothly at the melting point (ca. 200°) to give bispentafluorophenylmercury in good yield[34].

2-Amino-3,4,5,6-tetrafluorophenyl pentafluorophenyl sulphide (7) has been cyclised when heated under reflux with sodium hydride to give octafluorophenothiazine (8)[35]. A very similar compound (9) has been cyclised



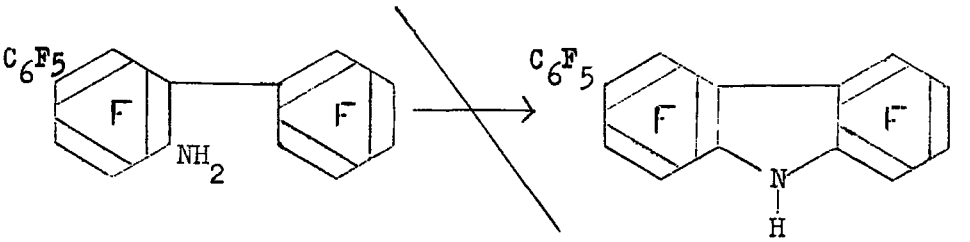
(7) (8)

to octafluoroacridan (10) using the same method[36].



(9) (10)

In contrast attempts to cyclise 2,4-bispentafluorophenyl-3,5,6-trifluoroaniline (11) to the corresponding carbazole (12) with sodamide in liquid ammonia, and with sodium hydride in dioxan at elevated temperature, were unsuccessful[37].



(11) (12)

A cleavage reaction involving sulphur dichloride and o-bromo-tetrafluorophenyl lithium has been used to prepare bis(o-bromo-tetrafluorophenyl) sulphide (13) and this compound undergoes ring closure via intramolecular coupling in an Ullmann synthesis to yield octafluorodibenzothiophene (14)[38]. This is the first report of a fully fluorinated condensed ring compound containing one hetero atom.

(13) (14)

Chapter III

A GENERAL REVIEW OF THE SKRAUP REACTION

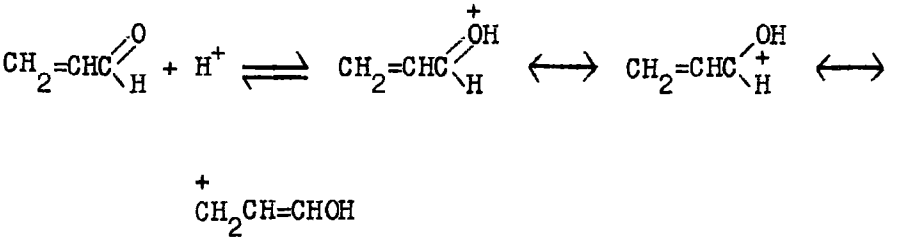
Because of the great utility of the Skraup reaction much effort has been made both in applying the method to an even wider variety of compounds and in improving the general technique. However it is not appropriate to attempt a comprehensive review here and only a general outline of the topic will be given. Much of this discussion is based on a previous review,[39] and since then two important papers have been published which help to elucidate the mechanism of the reaction[40,41].

The product obtained is a quinoline, generally containing those substituents originally present in the amine. Several cases are known in which substituents ortho to the amino group are replaced. Those amines having substituents which may be degraded or hydrolyzed by the hot concentrated sulphuric acid often fail to give the required product. Quinolines substituted in the heterocyclic ring may be obtained by a modified synthesis in which a substituted acrolein or vinyl ketone is used in place of glycerol.

The conditions under which the earlier Skraup syntheses were carried out often resulted in reactions of uncontrollable violence. However the addition of ferrous sulphate and acetic or boric acid has been found to reduce the vigour of the reaction. Originally the corresponding nitroaniline was used as the oxidising agent but various others have been tried

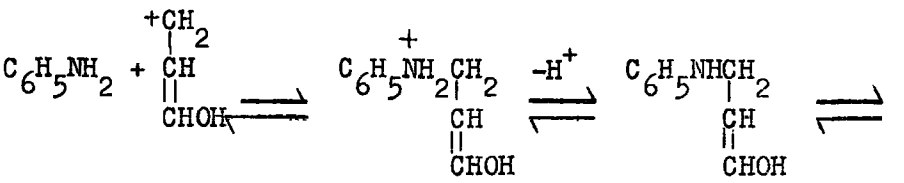
from time to time. A recent publication[42] suggests that the procedure is considerably simplified by using sodium m-nitrobenzenesulphonate instead of nitrobenzene in the synthesis of quinoline itself. Sulphuric acid of various concentrations has been used and recently it has been successfully replaced by polyphosphoric acid[43].

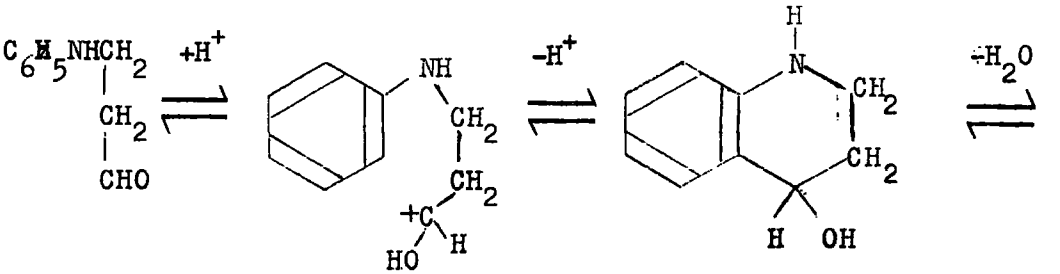
The mechanism outlined below has been postulated for the Skraup synthesis[41]. There is little doubt that the first stage of the reaction is dehydration of the glycerol to acrolein, and it seems possible that under the conditions of the reaction it is the protonated form (1) which condenses with the amine.

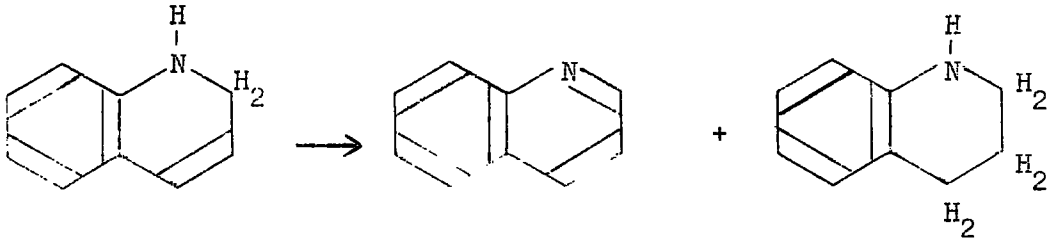


$CH_2CH{=}CHOH$

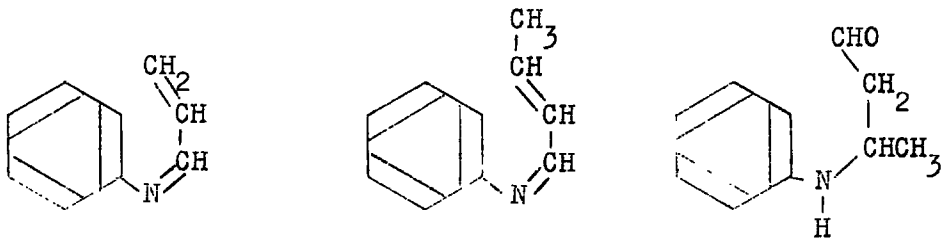
(1)







Skraup suggested originally that the aromatic amine condensed with acrolein to form a Schiff base (2), but this can not be correct. If it were, β-methylacrolein (crotonaldehyde) should yield as an intermediate the Schiff base (3), which on ring closure would give 4-methylquinoline (lepidine). The product, however, is 2-methylquinoline (quinaldine), and therefore the intermediate must be the β-arylaminoaldehyde (4), or a Schiff base derived from it.

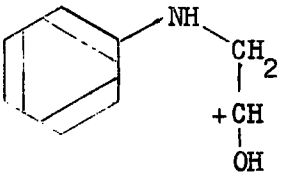


(2) (3) (4)

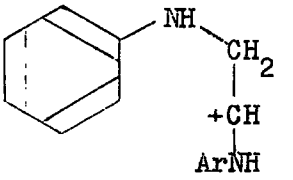
In order to confirm this mode of reaction the Australian workers[41] have isolated and characterized a great number of β-arylaminoaldehydes, a few of which were obtained as Schiff's bases, using conditions a little less vigorous than those needed for cyclisation. In these reactions no compounds corresponding to (2) were obtained. The β-arylaminoaldehydes were then cyclised to give the corresponding quinolines; those derived

from weak bases gave especially good yields.

The question of which carbonium ion (5) or (6) is responsible for the



(5)



(6)

cyclisation has not been satisfactorily answered, neither has the course of the final stage of the synthesis. The intermediate 1,2-dihydroquinoline could be oxidised directly to quinoline, or could disproportionate to give quinoline and 1,2,3,4-tetrahydroquinoline, which would then itself be oxidised to the parent quinoline.

Chapter IV

NUCLEOPHILIC ADDITION TO SOME ACETYLENE COMPOUNDS

A. By Thiolates.

Nucleophilic addition to mono- and di-substituted acetylenes has been carefully studied by Truce and his co-workers at the University of Purdue[44]. In particular the stereochemistry of the products has been thoroughly investigated and kinetic studies have helped to formulate a mechanism for the general reaction. Isomerisation of the reaction products has sometimes made the interpretation of the results difficult.

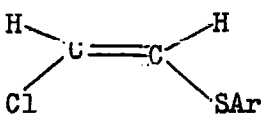
These workers found that base-catalyzed additions of thiols to the acetylenic compounds phenylacetylene[45,46], 2-butyne[45,46], p-tolymercapto-acetylene[45,47], ethyl propiolate[48,49], phenyl ethynyl ketone,[48,49] disodium acetylenedicarboxylate[50], diethyl acetylenedicarboxylate[50], ethyl phenylpropiolate[51,52] and mesitylacetylene[52,53] all gave high yields of a single product. In those cases where a reactive acetylene was used catalytic amounts of base were preferred, since in the reaction of ethyl propiolate with sodium p-toluenethiolate in ethanol for example, some ethyl β,β-diethoxypropionate (ca 20%) was isolated. This was presumably due to the formation of sodium ethoxide

$$HC{\equiv}CCO_2C_2H_5 + ArSNa \xrightarrow{EtOH} \text{cis-}ArSCH{=}CHCO_2C_2H_5 + (C_2H_5O)_2CHCH_2CO_2C_2H_5$$

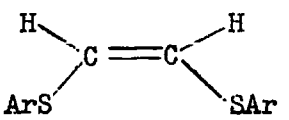
The products obtained from these reactions were all shown to have been formed by trans-addition of the nucleophile. In the reaction of

mesitylacetylene and sodium mesitylenethiolate it was thought that the size of the substrate and nucleophile would increase steric hindrance to such an extent that some cis-addition would occur, but this proved not to be the case.

With butylacetylene[47] and sodium p-toluenethiolate a mixture of olefinic sulphides was obtained consisting of approximately five parts of $C_4H_9C(SC_7H_7)=CH_2$ and one part of $C_4H_9CH=CHSC_7H_7$. Chloroacetylene[45,47] gave cis-bis-(p-tolylmercapto)-ethene (2) and cis-chloro-(p-tolylmercapto)-ethene (1). By varying the ratio of aryl thiol to sodium the relative amounts of each product could be controlled. It was suggested that in the presence of base (1) is dehydrohalogenated to p-tolylmercaptoacetylene which



(1)

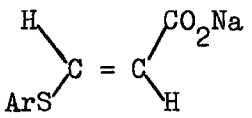


(2)

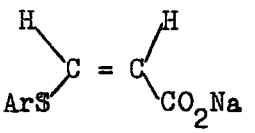
reacts further.

In the reactions of sodium propiolate[48,49,54] with p-toluenethiol in ethanol containing small amounts of sodium p-toluenethiolate two

products were isolated, trans—p-tolylmercaptoacrylic acid (3) in ca 80% yield and cis—p-tolylmercaptoacrylic acid (4) in ca 10% yield. It was originally thought that this was the first recorded example of cis



(3)



(4)

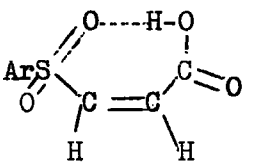
nucleophilic attack at a triple bond. Further work[52] has since shown that (4) undergoes isomerisation to (3) in the presence of p-toluenethiol, and hence the origin of the trans-acid is in doubt. Sodium phenylpropiolate[51] gives similar results.

With ethoxyacetylene[55,56] the adduct formed initially is 1-ethoxy-1-(p-tolylmercapto)-ethene which isomerises on standing to cis-ethoxy-(p-tolylmercapto)-ethene. In the first report the latter was identified as the preliminary adduct.

The last two examples illustrate the care that must be exercised when interpreting these results. A recent article[57] has shown that aromatic thiols react readily with phenylacetylene at room temperature, by a free radical mechanism, to give high yields of cis-disubstituted products. These workers found that isomerisation was catalysed by the presence of benzenethiol, but that isomerisation of the purified products themselves was insignificant at ambient temperatures. There is however on balance sufficient evidence to enable trans-nucleophilic addition to be predicted

from the reaction between thiolate reagents and acetylenes.

In nearly all cases chemical evidence was produced to confirm the assignments. The most widely used method was to oxidise the product to the corresponding sulphone and to compare this with an isomer of known configuration. Physical methods[58], in particular the use of infrared absorption spectroscopy, nuclear magnetic resonance spectroscopy, and dipole moments were all used to confirm the assignments when both isomers were available for comparison. An elegant example of the application of infrared data was to distinguish the cis and trans isomers of the sulphones of the corresponding p-tolylmercaptoacrylic acids. The isomer to which was assigned the trans configuration showed a strong absorption at 3118cm^{-1}, corresponding to the O-H stretching mode, while the cis-isomer showed a broad absorption with many submaxima in the region 3000-2500 cm^{-1}. The C=O stretching frequency of the latter was at 1685 cm^{-1}, compared with 1730 cm^{-1} for the trans-isomer. This evidence points to the cis-isomer existing in the form illustrated below. Such intramolecular hydrogen



bonding is impossible for the trans-isomer.

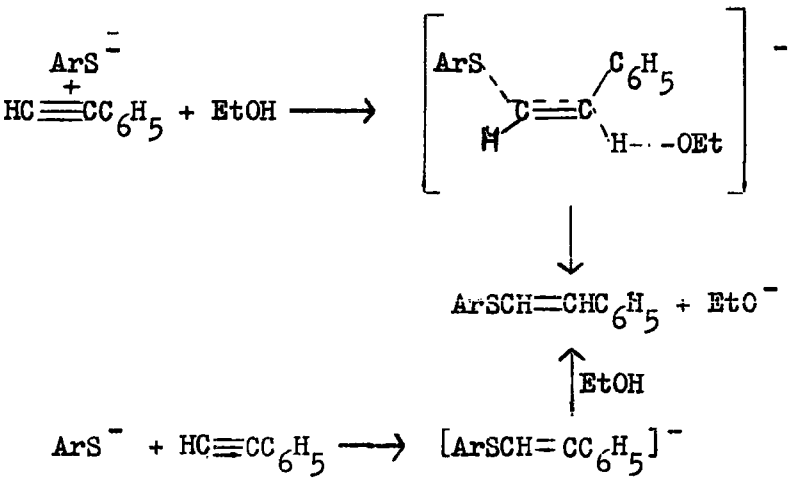
In order to clarify the mechanism of thiolate addition to triple bonds, Truce and Heine investigated the kinetics of the reaction between

sodium *p*-toluenethiolate and phenylacetylene[59]. This had previously been shown to be a high-yield stereospecific reaction[48]. They found that,

(1) the rate of the reaction was faster in deuterioethanol than in ethanol.

(2) the rate was faster in *N*,*N*-dimethylformamide (DMF), containing very small amounts of ethanol, than in absolute ethanol.

The second point is interesting since the rate of reaction between an ion and a neutral molecule is normally predicted to be faster in the medium which has the lower dielectric constant, in this case ethanol. Truce suggested that these results could be most logically explained on the basis that there are two competing mechanisms, one a concerted and the other a stepwise process, e.g., equations (1) and (2) respectively, with (1) having predominance in ethanol and (2) in DMF.



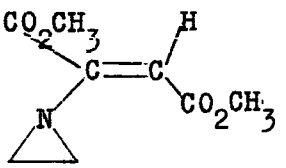
In DMF the probability of a concerted mechanism would be reduced considerably because of the small amount of proton-donor (ethanol)

available. Truce also suggested that the small but definite isotope effect in deuterioethanol was in agreement with a concerted process.

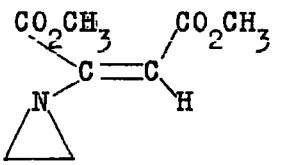
The trans nature of nucleophilic addition to triple bonds was rationalised as follows. As the negatively charged sulphur group initiates attack and displacement of a pair of electrons from the acetylenic bond, these two regions of negative charge would be expected to be separated as far from each other as possible, on the basis of coulombic repulsion. This would entail a trans arrangement leading to overall trans addition.

B By Amines.

The stereospecificity of amine additions to acetylenic esters has been systematically studied. Dolfini[60] found that reaction of equimolar quantities of aziridine and dimethyl acetylenedicarboxylate in methanol at room temperature produced a 76% yield of a semi-solid. Analysis of the product mixture was expedited by examination of the p.m.r. spectrum which revealed that the fumaric acid derivative (1) comprised 67% of the product and the maleic acid derivative (2), 33%. However the reaction product



(1)

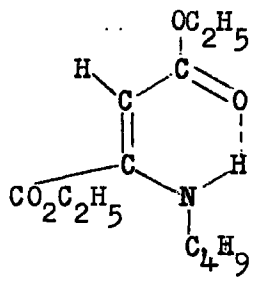


(2)

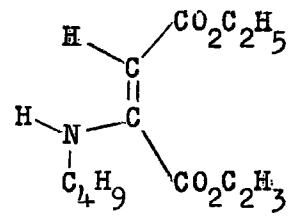
obtained from repeating the reaction in dimethyl sulphoxide under the same conditions, consisted of 95% (2) and only 5% of (1); the product mixture

was obtained in 75% yield. The reaction of aziridine and ethyl propiolate proceeded in a similar fashion. Great care was taken to check that isomerisation did not take place under the conditions used. Other workers have confirmed these observations. In a recent article[61] the reactions of diethylamine, piperidine and aziridine with dimethyl acetylenedicarboxylate and methyl propiolate in ether were investigated. The products obtained were almost exclusively those resulting from cis addition of the nucleophiles. Only in the reactions with aziridine was some (9-17%) of the other isomer, corresponding to trans addition, obtained. In the reactions of diethyl acetylenedicarboxylate with aniline, some mono-substituted anilines,[62] benzylamine[63] and butylamine[64] in ethanol only the corresponding fumaric acid derivatives was isolated.

The identification of the adduct from the reaction of butylamine and diethyl acetylenedicarboxylate provides another informative example of the use of infrared data to determine configuration. The reaction product could have been either of the isomers (3) and (4). The compound obtained



(3)



(4)

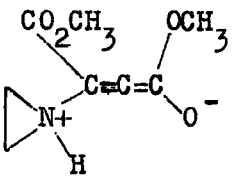
showed absorptions at 1735 and 1667 cm^{-1} indicating that one of the carbonyl groups was taking part in intramolecular hydrogen bonding. This was confirmed when the product was catalytically reduced to the succinic acid derivative (5). Here only one band corresponding to the carbonyl

$$CO_2C_2H_5CH_2CH(NHC_4H_9)CO_2C_2H_5$$

(5)

stretching mode was found, at 1735 cm^{-1}. This indicated that saturation of the double bond had removed the possibility of chelation, as would be anticipated. Study of the N-H stretching mode confirmed the assignment.

The variation of the course of amine addition in dimethyl sulphoxide vs. methanol was attributed to the formation of the zwitterionic intermediate (6). In the absence of an external proton source the



(6)

zwitterion might be expected to undergo a stereospecific collapse via intramolecular protonation leading to the cis disposition of the ester functions. Dolfini went on to suggest that in a hydroxylic solvent protonation of an intermediate by the solvent becomes the favoured path. Whether this is of a kinetic nature concerted with the addition of the nucleophile or is a ~~product~~ thermodynamically controlled process can not be dated categorically,

although either factor would provide a predominance of the fumaric acid derivative, formed by trans addition.

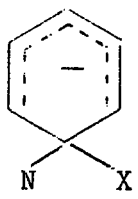
Truce explained cis addition slightly differently[49]. He argued that an uncharged nucleophilic agent would be developing a positive charge in the transition state to addition, and hence tend to bring the displaced electron pair into a cis arrangement relative to itself, on the basis of increased coulombic attraction. This mechanism also would be particularly sensitive to changes in the solvent.

Chapter V

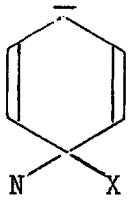
A REVIEW OF THE NUCLEOPHILIC REPLACEMENT REACTIONS OF AROMATIC POLYFLUORO-COMPOUNDS

Nucleophilic replacement of fluorine in C_6F_5X compounds most frequently occurs at the position *para*[65] to the group X (e.g., X = H, CH_3, CF_3, SMe, SO_2Me, NMe_2, Cl, Br, I). However with X = OMe, NHMe, *para* and *meta*[66,67] replacement of fluorine occurs to approximately the same extent , while with X = O^-, NH_2 predominately *meta*-replacement is found[66-68], the nature of the nucleophile has little effect in determining the orientation in these instances. In some cases (X = NO_2, NO, CO_2^-)[69-71] reaction takes place mainly at the *para* position with sodium methoxide in methanol, but gives high *ortho* replacement (> 50% in some cases) with certain amines. It has also been shown that pentafluoronitrobenzene reacts with sodium methoxide in ether containing a little methanol, to give high *ortho* replacement (~ 50%)[72]. These results have been reviewed and rationalisations advanced to explain the orientation and reactivity of aromatic polyhalo-compounds towards nucleophiles[73,74]. To summarise briefly with reference to nucleophilic substitution in a pentafluorophenyl derivative, C_6F_5X, assuming for the moment that both steric and solvent effects are negligible, then the orientation will be governed by the relative magnitudes of the activation energies associated with the various

reaction pathways. Replacement of the substituent X has not been observed in this connection, hence there are three possible products corresponding to ortho, meta and para replacement of fluorine. The transition states leading to these may be discussed in terms of Wheland-type intermediates (1), since they generally provide good guides. It was argued that the resonance



(1)



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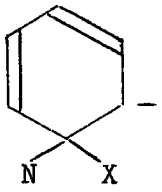


(3)

hybrid (2) was the main contributor to the intermediate, with the two hybrids of type (3) of only secondary importance. Hence the relative energies of the para-quinoid structures are of signal importance in determining the orientation of the product.

A novel feature of the theory is that fluorine is taken as electron repelling in π-electron systems (the I_{π} effect). It has been suggested that this is due to coulombic repulsion between the p-electrons on the halogen and the ring π-electrons on the neighbouring carbon[75].

The nature of X must then be taken into account; three distinct situations arise.

(i) X is electron attracting in π-electron systems.

(ii) X is neutral.

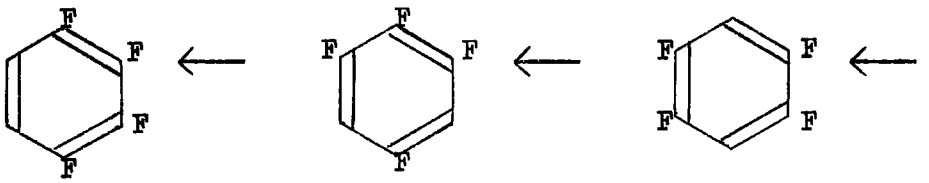
(iii) X is electron repelling.

In the first two cases substitution will take place para to the substituent, since the latter will stabilise the negative charge in (2), relative to fluorine. It follows that the rate of reaction will be much greater in case (i). An excellent example of this is shown in the relative reactivities of pentafluoronitrobenzene (case (i)) and pentafluorobenzene (case (ii)) with sodium methoxide in methanol. Kinetic evidence[76] indicates that the former is more reactive by a factor of $2 \cdot 3 \times 10^6$. There is always an ambiguity in ascribing differences in reactivity between two or more compounds as being due to differences in the energies of the various transition states. This arises from the assumption that the energies of the ground states are comparable, and this is not necessarily so. For present purposes however this refinement has been neglected.

If X is electron repelling but to a less extent than fluorine a mixture of isomers is produced. The more nearly the I_π-repulsive effect of the substituent approaches that of fluorine so does the isomer ratio approach the statistical para:ortho:meta = 1:2:2, from the direction para $>$ ortho $>$ meta. This is illustrated by the increasing amount of ortho-substitution obtained from the reaction of the C_6F_5X (X = Halogen) compounds with nucleophiles[74], as shown below. It has been postulated before[75] that I_π replusion by halogens in π-systems decreases in the order F $>$ Cl $>$ Br $>$ I.

COMPOUND	C_6F_5I	C_6F_5Br	C_6F_5Cl
% ortho-substitution on reaction with $NaOCH_3$ in MeOH	5	12	17

Further evidence in favour of this theory was found in consideration of the orientation and reactivity of the three tetrafluorobenzenes shown below. They react at the positions indicated[77].



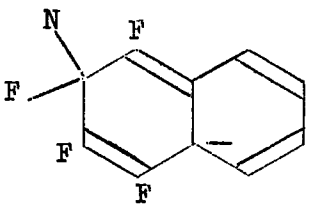
(4) (5) (6)

In (4) and (5) the positions attacked are those which lead to intermediates of type (2) in which the negative charge is localized on a hydrogen bearing carbon atom. Moreover (6) reacts about 10^3 times more slowly with sodium methoxide than do the other tetrafluorobenzenes. In this case the intermediate of type (2) requires that a negative charge be localized on a fluorine bearing carbon. Since it can be assumed that the three tetrafluorobenzenes have comparable ground state stabilities, it was concluded that contributions to the transition state of type (3) are of only secondary importance. If they were equivalent to type (2) then

the tetrafluorobenzenes would react at comparable rates.

These rationalisations are extremely valuable and account very well for almost all of the substitution reactions of polyfluorobenzene derivatives. Apparent anomalies can generally be convincingly explained by consideration of steric and solvent effects or by the reactivity of the substrate or nucleophile.

The theory is readily applied to substitution in 1,2,3,4-tetrafluoronapthalene[78], and octafluoronapthalene[79]. In both cases substitution takes place in the β-position (7); an earlier report suggested α-substitution in the former[80]. Only para-quinoid structures need be



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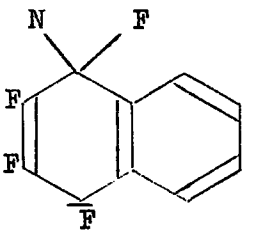


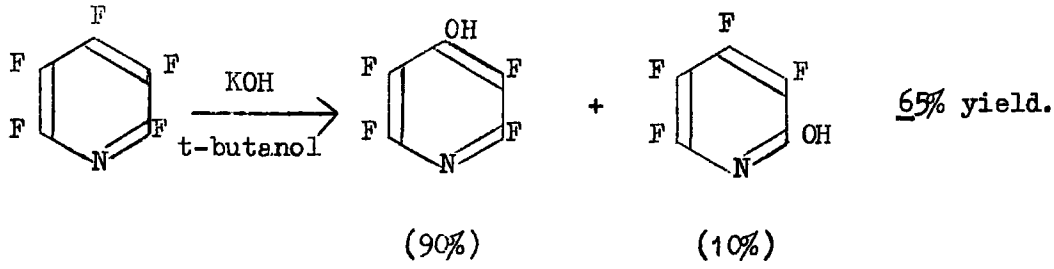
(8)

considered as contributing to the transition state, and it can be quickly seen that α-substitution would involve a para-quinoid structure in which the negative charge is placed on a carbon bonded to fluorine (8).

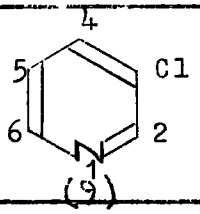
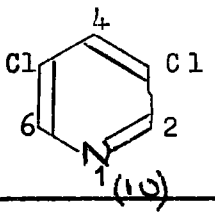
Octafluorodibenzthiophene has been prepared and the orientation of the product obtained from nucleophilic substitution discussed in terms of the relative energies of the possible para-quinoid structures[38]. Here substitution in the 2-position was rationalised by the assumption that in

the transition state the sulphur atom stabilises the negative charge by delocalisation into the sulphur d-orbitals.

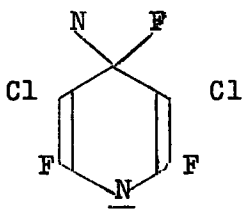
Nucleophilic substitution in pentafluoropyridine has received much attention recently and the results obtained will be briefly summarised. It was quickly established that nucleophiles replaced the 4-fluorine atom first[81,82]. Negligible amounts of isomeric products were detected, except in the reaction with potassium hydroxide[83]. In aqueous solution a single product was isolated, 4-hydroxytetrafluoropyridine. However when t-butanol was used as the solvent a mixture of isomers, with the substituent in the 4- and 2-position was obtained.



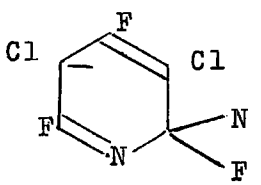
This interesting result prompted an investigation into the reactions of 3-chlorotetrafluoropyridine (9) and 3,5-dichlorotrifluoropyridine (10) with potassium hydroxide. The results are given in the table below. It was suggested that variations in the positions of attack were due to to steric considerations brought about by the solvation of the attacking hydroxyl ion by bulky butanol molecules.

COMPOUND	SOLVENT	% YIELD	% SUBSTITUTION AT POSITION		
			2	4	6
 (9)	H_2O	65		90	10
	t-butanol	80	10	55	35
 (10)	H_2O	85	10	90	
	t-butanol	85	70	30	

Another contributing factor may be that the transition state (11) corresponding to 4-substitution in (10) is more heavily solvated than the corresponding transition state for 2-substitution (12), since in the latter the charge is shielded by the relatively large chlorine atom. Hence a strongly solvating medium would favour 4- at the expense of 2-substitution. Similar arguments apply to substitution in 3-chlorotetrafluoropyridine, where a strongly solvating medium would favour 4- over 6- and 2-substitution.



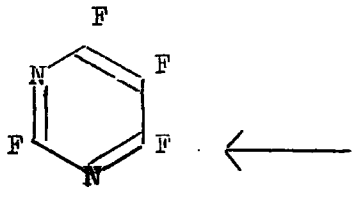
(11)



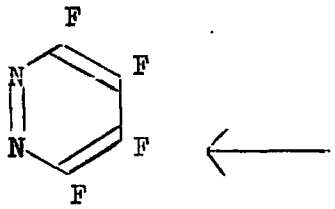
(12)

On further reaction 4-substituted tetrafluoropyridines give 2,4-disubstituted trifluoropyridines[84] with one notable exception[85] — those reactions involving nucleophiles and 4-nitrotetrafluoropyridine. With sodium methoxide 4-methoxytetrafluoropyridine is the major product (~70%), the remainder consisting of 2-methoxy-4-nitrotrifluoropyridine and an even smaller amount of 3-methoxy-4-nitrotrifluoropyridine. This result was compared with the reaction of 2,3,5,6-tetrafluoronitrobenzene and sodium methoxide, which gave exclusively replacement of fluorine ortho to the nitro group. It was concluded that the ring nitrogen was the greatest single factor determining the orientation of nucleophilic attack. This fits in very well with the rationalisations advanced by Burdon to account for nucleophilic substitution in fluorinated benzenes,[73] since nitrogen may be taken as electron attracting in a π-electron system.

Nucleophilic substitution in tetrafluoropyrimidine[86] (13) and tetrafluoropyridazine[87] (14) has been reported. In each case a fluorine atom para to nitrogen was replaced initially, as indicated below. Both



(13)

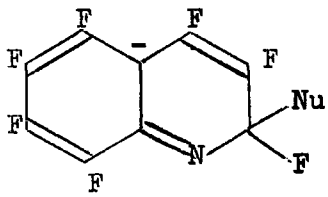


(14)

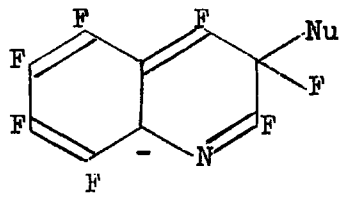
compounds are substantially more reactive than pentafluoropyridine.

Heptafluoro-quinoline and -isoquinoline have been prepared[12] and their properties investigated[12,88]. It was found that the former when reacted

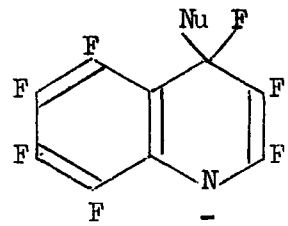
with nucleophiles gave two monosubstituted products, in particular with sodium methoxide the two isomers were formed in the ratio of 3·4:1, which was shown to be the ratio of the 2-:4-substituted compounds, by the use of ^{1}H and ^{19}F n.m.r. On the basis of considering <u>para</u>-quinoid structures only, as indicated below, the major product would be expected to be the 4-isomer, since here the negative charge is placed on the nitrogen atom.



2-substitution



3-substitution



4-substitution

If contribtions from <u>ortho</u>-quinoid structures are included it can readily be appreciated that substitution at position 2 will be favoured relative to position 3. But the theory, as it stands, fails to explain why more 2-substition is actually obtained.

The reaction of nucleophiles with heptafluoroisoquinoline produces a single monosubstituted product, and a single disubstituted product. It has been established that replacement of the 1-fluorine atom takes place first, followed by replacement of the 6-fluorine. Unfortunately the simple qualitative theory breaks down completely, since it would predict preferential replacement of the 3-fluorine atom. The theory fails because it can not predict the relative importance of each hybrid to the transition state. Nevertheless two of the major factors influencing the

energy of the π-electrons have become clear.

(i) Fluorine is electron repelling, thus an increase in the charge on a carbon atom directly bonded to fluorine will increase the energy of the transition state.

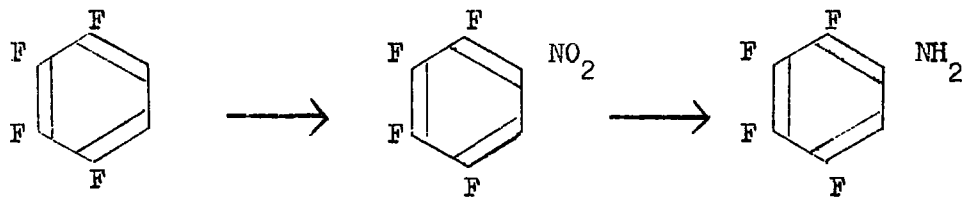
(ii) Nitrogen is electron attracting in these systems and hence stabilises the transition state.

It has become apparent that a more quantitative treatment is required.

Chapter VI

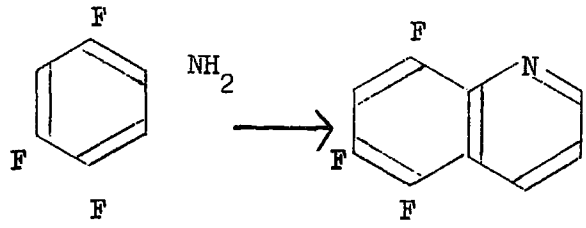
THE PREPARATION OF SOME TETRA- AND TRI-FLUOROQUINOLINES AND SOME REACTIONS OF 5,6,7,8-TETRAFLUOROQUINOLINE

5,6,7,8-Tetrafluoroquinoline was prepared in excellent yield from 2,3,4,5-tetrafluoroaniline[89] by means of the Skraup Reaction. The aniline itself is prepared from 1,2,3,4-tetrafluorobenzene by a two stage process[35]. Nitration with a mixture of concentrated nitric and sulphuric acids at 30° gives 2,3,4,5-tetrafluoronitrobenzene and reduction of the latter with tin and concentrated hydrochloric acid gives the aniline. [An interesting

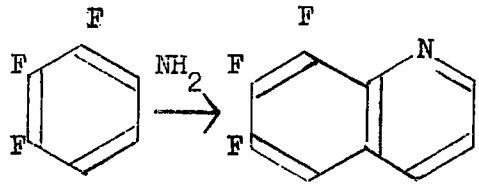


comparison emerges since nitration of 1,2,4,5-tetrafluorobenzene is known to give 2,5-difluorobenzoquinone.[90] Oxidation of hexafluorobenzene[91] and octafluoronapthalene[92] with concentrated nitric acid under suitable conditions gives 2,3,5,6-tetrafluorobenzoquinone (fluoranil) and hexafluoronapthoquinone respectively].

5,6,8-Trifluoroquinoline (1) and 6,7,8-trifluoroquinoline (2) were prepared from 2,4,5-trifluoroaniline and 2,3,4-trifluoroaniline by the Skraup Reaction. Both amines had been prepared previously[93], and a sample



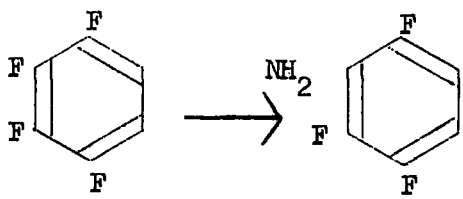
(1)



(2)

of the latter was kindly provided by Dr. Finger. The former has now been prepared in very good yield by treating the commercially available 1,2,4,5-tetrafluorobenzene with aqueous ammonia in a sealed tube at 215° for 12½ hr. Pentafluoroaniline has been prepared in a similar fashion from hexafluorobenzene.[94,95]

In view of the arduous nature of the synthesis of 2,3,4-trifluoroaniline, the reaction between 1,2,3,4-tetrafluorobenzene and ammonia was investigated. A single compound was obtained in excellent yield, but this proved to be the 2,3,6-trifluoroaniline, since an authentic sample of 2,3,4-trifluoroaniline, the only other possible isomer, was available for comparison. Nucleophilic substitution in the tetrafluorobenzenes has since



been reported using other reagents.[77] The orientation of 1,2,3,4-tetrafluorobenzene towards ammonia is consistent with these results.

The preparation of 2-methyl-5,6,7,8-tetrafluoroquinoline by means of a Skraup reaction with crotonaldehyde using the same conditions as before was not very successful. The yield of product was of the order of 20% and some starting material was recovered. The experimental technique was then altered slightly in that crotonaldehyde and not sulphuric acid was added to the reaction mixture but with little effect on the amount of product formed. The 4-methyl-5,6,7,8-tetrafluoroquinoline was in fact prepared by the Döbner-Miller synthesis, using methyl vinyl ketone, glacial acetic acid, ferrous sulphate and anhydrous zinc chloride.[96] The yield was of the same order as for the 2-methyl isomer.

The reaction of 5,6,7,8-tetrafluoroquinoline with sodium methoxide in methanol[97] gave a monomethoxy derivative in high yield. Gas chromatographic analysis on columns of different polarity indicated that only one product had been formed; no isomer or disubstituted compound was detected.

Reaction with potassium hydroxide in tertiary butanol[98] gave the expected monohydroxy derivative again in high yield. The product did not melt below 180° and was insoluble in non-polar organic solvents (e.g. petroleum, benzene) and only slightly soluble in polar solvents such as water and ethanol, giving a yellow solution. It did however dissolve in glacial acetic acid to give a colourless solution. Careful sublimation gave very small quantities of a white compound but this quickly turned yellow on exposure to air. The compound was identified by the preparation and characterization of its acetate. It has recently been established that

tautomerism occurs in heptafluoro-1-hydroxyisoquinoline and heptafluoro-2-hydroxyquinoline but not in heptafluoro-4-hydroxyquinoline.[99] They were prepared by the reaction of the corresponding perfluoro-compound with aqueous sodium hydroxide or potassium hydroxide in tertiary butanol, and by demethylation of the respective methoxy-derivatives. Those cases in which tautomerism exists are marked by the appearance of a very strong band in the infrared spectrum at 1690-1720 cm^{-1}, which was assigned to the carbonyl stretching vibration. The spectrum of 7-hydroxy-5,6,8-trifluoroquinoline shows no absorption in this region indicating that it is phenolic in nature, as is 7-hydroxyquinoline itself.

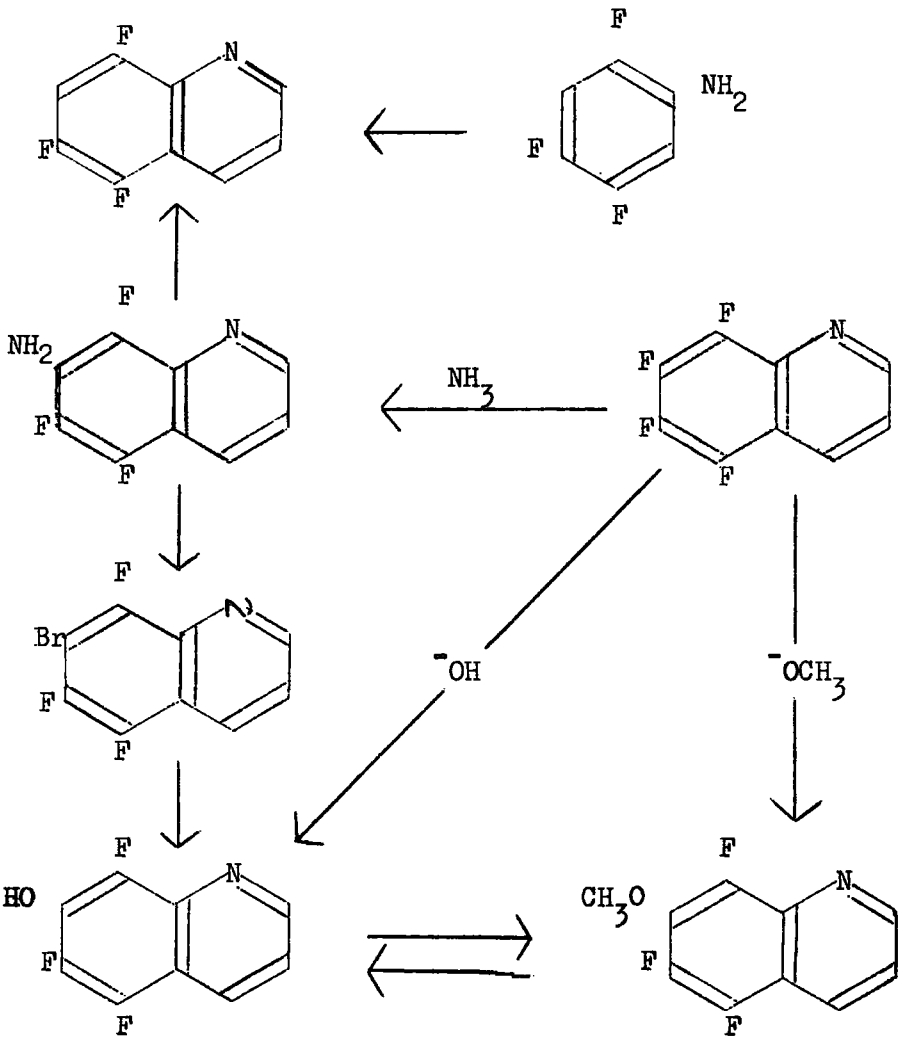
Reaction of the tetrafluoroquinoline with aqueous ammonia in a sealed tube at 150° for 3 hr. gave an estimated 50% yield of an aminotrifluoroquinoline. Little decomposition had taken place and much starting material was recovered. Attempts to increase the yield by heating for a longer period or at a higher temperature gave a product which was difficult, and sometimes impossible, to purify. Reaction of hexafluorobenzene with ammonia under these conditions[95] gives an excellent yield of pentafluoroaniline, while heptafluoroquinoline reacts with ammonia in acetone at room temperature.[88] This suggests that tetrafluoroquinoline is less reactive than the former and certainly much less reactive than the latter.

The orientation of the amino-compound was established by diazotisation in 80% hydrofluoric acid[100] followed by treatment with hypophosphorus acid

to give a trifluoroquinoline, which proved to be 5,6,8-trifluoroquinoline and not 6,7,8-trifluoroquinoline the other most likely isomer. This indicates that ammonia replaces the 7-fluorine atom in 5,6,7,8-tetrafluoroquinoline rather than the 5-fluorine atom.

The amino-compound was diazotised as before and then treated with cuprous bromide in hydrobromic acid to give 5,6,8-trifluoro-7-bromoquinoline. This was converted into the 7-lithium compound by an exchange reaction with butyl lithium and then treated in turn with trimethylborate and 85% hydrogen peroxide, the 5,6,8-trifluoro-7-hydroxyquinoline was formed.[101] The product was identical with that obtained by the direct reaction of tetrafluoroquinoline and potassium hydroxide as described previously.

The 7-hydroxy-compound on treatment with diazomethane gave a methoxy-derivative identical to that prepared previously. The latter could be demethylated using anhydrous aluminium chloride in high yield.[102] The infrared spectrum of the material thus prepared was identical to that of the crude product from the direct reaction of potassium hydroxide on tetrafluoroquinoline. If any isomers had been formed in appreciable amounts ($>$ 10%) the infrared spectra would have been different. These reactions are summarised below. The interconversion reactions indicate conclusively that the nucleophiles $^{-}OCH_3$, ^{-}OH and NH_3 attack 5,6,7,8-tetrafluoroquinoline replacing the 7-fluorine atom. Using gas chromatography



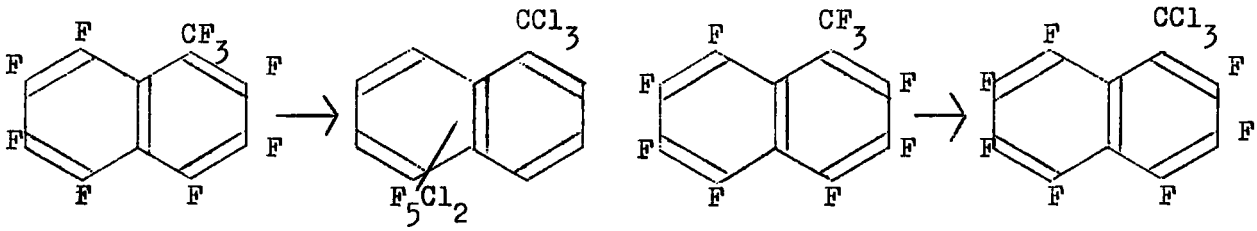
it was only possible to look for isomeric substitution products in the react ion with methoxide ion because the other derivatives made were not sufficiently volatile, and here only one isomer was detected. Infrared evidence suggest that this is also the case when hydroxide ion was used as the nucleophile.

5,6,7,8-Tetrafluoroquinoline formed a hydrochloride only under

anhydrous conditions. The compound was unstable and readily decomposed on standing to give starting materials. Under similar conditions heptafluoroquinoline failed to give the corresponding salt[12].

The successful preparation of pentachloropyridine by the reaction of pyridine and phosphorus pentachloride, and subsequent treatment of the chloro-compound with potassium fluoride to give pentafluoropyridine[103,104] prompted us to try and repeat these reactions using 5,6,7,8-tetrafluoroquinoline with a view to obtaining ultimately the fully fluorinated quinoline. When the tetrafluoroquinoline was treated with phosphorus pentachloride at 235° a hexachloroquinoline of unknown structure was obtained. Not only had two hydrogen atoms been replaced by chlorine but also the four fluorine atoms. The infrared spectrum closely resembled that of a mixture of pentachloro- and hexachloro-quinoline which had been obtained by the direct chlorination of quinoline[12].

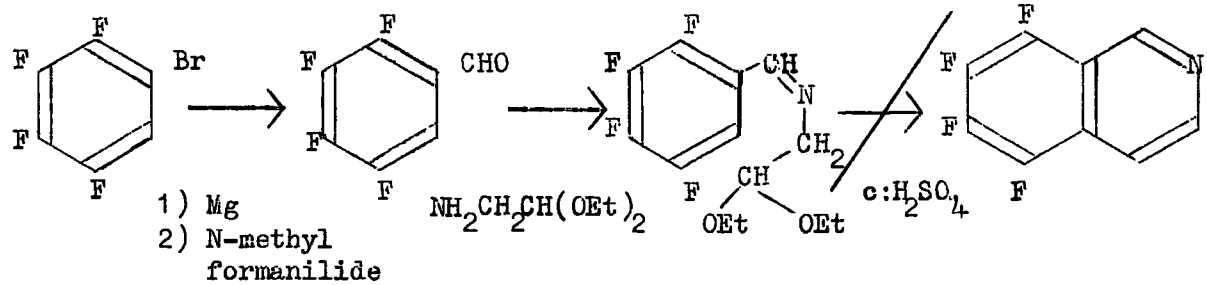
The replacement of fluorine by chlorine in a polyfluoro-aromatic nucleus has been observed previously. Heptafluoro-1-trifluoromethylnapthalene gave a pentachloropentafluoro-1-methylnapthalene on treatment with



aluminium chloride in acetyl chloride. Variation of the reaction conditions did not produce the desired trichloromethyl compound. On hydrolysis with concentrated sulphuric acid a dichloropentafluoro-1-napthoic acid of unknown structure was obtained. Heptafluoro-2-trifluoromethyl napthalene under similar conditions gave heptafluoro-2-trichloromethylnapthalene, which on hydrolysis with sulphuric acid gave heptafluoro-2-napthoic acid[105].

Fluorine replacement also occurred when pentafluorochlorobenzene was reacted with sodium chloride in sulpholane (tetramethylenesulphoxide) at 220-230°; 1,4-dichloro-tetrafluorobenzene was isolated.[106] This is the reverse of one of the better known methods for preparing highly fluorinated chlorobenzenes, that is by the reaction of potassium fluoride and hexachlorobenzene in aprotic solvents.[107,108]

Following the successful preparation of the fluorinated quinolines it was decided to try and synthesise 5,6,7,8-tetrafluoroisoquinoline by means of the Pomeranz-Fritsch synthesis. Thus 2,3,4,5-tetrafluorobenzaldehyde and hence 2,3,4,5-tetrafluorobenzylidineaminoacetal were prepared, and several condensations were attempted on the latter using experimental conditions very similar to those outlined previously.[109] In no case was any of the



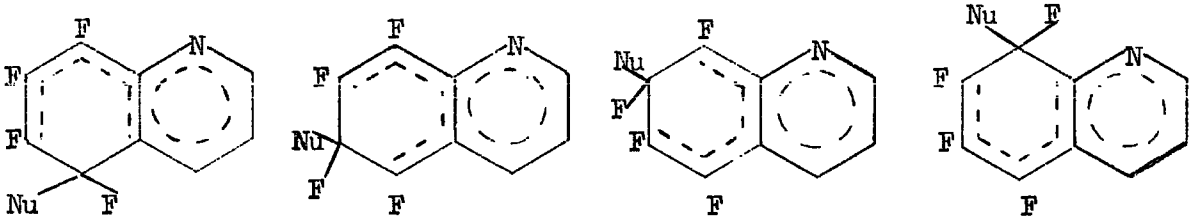
tetrafluoroisoquinoline isolated. Neither o- nor p-fluorobenzylidine-aminoacetal could be cyclised under similar conditions.[3,2]

Chapter VII

A RATIONALISATION OF NUCLEOPHILIC SUBSTITUTION IN 5,6,7,8-TETRAFLUOROQUINOLINE

It has been shown that nucleophilic substitution takes place at position 7, and it is possible to rationalise this using arguments similar to those advanced by Burdon[73]. But since this approach has been shown to be inadequate to meet all cases a different method of more general applicability will be developed here.[110]

In discussing the orientation of compounds resulting from nucleophilic substitution of fluorine in highly fluorinated aromatic systems the factor which determines the nature of the product or products is the rate at which each fluorine atom is replaced. Reaction of 5,6,7,8-tetrafluoroquinoline with a nucleophile Nu can lead to four products. The transition states leading to these are indicated below. Assuming that the Entropy of

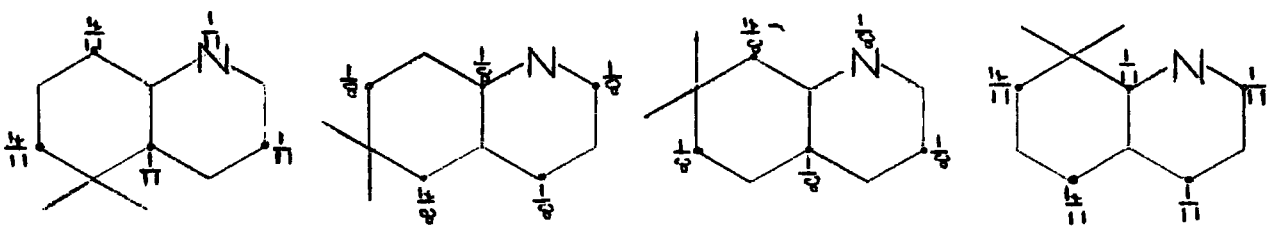


Activation is similar for each reaction the critical factor governing the orientation of substitution will be relative magnitudes of the Activation Energies. The latter reflects the difference in energy between the ground

state of the molecule and the transition state. Differences in energy between transition states reflect differences in the energies of the π-electron systems. The problem resolves into an analysis of the distribution of electrons in the π-electron system and the factors influencing the energy of the electrons therein.

Firstly consider the arrangement of the ten electrons forming the system. The nine $2p_z$ orbitals (eight carbon and one nitrogen atom form the skeleton) are combined to give four bonding molecular orbitals, one non-bonding orbital (N.B.M.O.), and four anti-bonding orbitals. The ten electrons are placed in the bonding and non-bonding orbitals, according to the Aufbau principle.

It has been shown that nine electrons (i.e. arranged as above except that there is only one electron in the N.B.M.O.) are such that the electron density on each atom forming the skeleton at any one time is unity. The distribution of the tenth electron in the N.B.M.O. is of critical importance. To a first approximation the charge can be considered as distributed in the various transition states as shown. The differences in the energies of the various π-electron systems reflect the differences in



energy of the single electron in the N.B.M.O.

What factors will influence the energy of this electron? Firstly because nitrogen is more electronegative than carbon, because of its greater nuclear charge, the greater the charge on the nitrogen the more stable will be the transition state. On this basis substitution would be expected at position 7, followed by position 5. Secondly π-electrons on carbon atoms which are bonded to fluorine atoms are destabilised, this has been ascribed to electrostatic repulsion between negative charge clouds on the adjacent atoms.[75] The total charge on carbon atoms attached to fluorine is given below. Here we predict that substitution will take place

Substitution at Position	5	6	7	8
Total Charge	0·73	0·63	0·63	0·73

equally on carbon atoms 6 and 7. Since we have already seen that position 7 is preferred, the theory clearly points to nucleophilic substitution in 5,6,7,8-tetrafluoroquinoline taking place at position 7, as was found in practice.

This theory can be readily applied with some refinements to rationalise orientation in polyfluoro-aromatic compounds.

Chapter VIII

AN ANALYSIS OF THE ^{19}F NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME FLUORINATED QUINOLINES

These spectra have been analysed using a simple empirical approach. The ^{19}F spectrum of 5,6,7,8-tetrafluoroquinoline shows three groups of peaks centred at 4·0, 6·8 and ca 11·5 p.p.m. downfield from hexafluorobenzene. The absorption at ca 11·5 p.p.m. is twice the intensity of the others and is therefore due to two fluorine atoms with similar chemical shifts. These were calculated as 11·3 and 11·7 p.p.m.[111]

The ^{19}F spectrum of 2-methyl-5,6,7,8-tetrafluoroquinoline shows four absorptions of equal intensity at 2·2, 6·2, 10·3 and 11·2 p.p.m. The introduction of a methyl group in the 2-position seems to have caused a small upfield shift for each fluorine atom.

The ^{19}F spectrum of 4-methyl-5,6,7,8-tetrafluoroquinoline shows four bands centred at 3·0, 6·1, 12·3 and 20·8 p.p.m. The latter must be assigned to the 5-F - the large downfield shift is attributed to the proximity of the methyl group. It follows that in tetrafluoroquinoline the 5- and 8-F's absorb at ca 11·5 and the 6- and 7-F's to higher field.

The chemical shifts of the three fluorine atoms in 7-bromo- and 7-acetoxy-5,6,8-trifluoroquinoline and 5,6,8-trifluoroquinoline are ta

tabulated below. Lawrenson[112] showed that in pentafluorophenyl derivatives (C_6F_5X) the

COMPOUND	Chemical Shift in p.p.m. downfield from hexafluorobenzene	Description of band	Coupling Constants in cycles sec^{-1}	Assignment
$C_9H_3BrF_3N$ (1)	12·3	doublet of doublets	17·5 and 19·1	5F
	30·3	doublet	21·3	6F
	44·6	doublet	16·1	8F
$C_9H_3(OCOCH_3)F_3N$ (2)	10·3	doublet of doublets	17·0 and 19·5	5F
	11·7	doublet	18·2	6F
	21·5	doublet	16·7	8F
$C_9H_4F_3N$ (3)	8·3	doublet of triplets	6·4 and 19·2	5F
	25·0	doublet of doublets	10 and 20	6F
	38·5	doublet of doublets	8·4 and 18·6	8F

two fluorine atoms ortho to the substituent were shifted downfield significantly more than the meta and para fluorine atoms. An exception was pentafluoroaniline where all the fluorine atoms were found upfield from hexafluorobenzene.

Assuming that a substituent in the 7-position shifts the ortho fluorines by a comparable amount then in the three cases mentioned above the 8-F must be that responsible for the absorption at low field. It was possible to distinguish the absorptions due to the 5- and 6-F from the fine structure. The former was coupled to both ortho and para fluorine atoms while the 6-F was only able to couple with one ortho fluorine. For (1) and (3) the analysis can be carried further and tentative values for the changes in chemical shifts for each fluorine atom relative to tetrafluoroquinoline obtained. Lawrenson found that in pentafluorobromobenzene

COMPOUND	Change in Chemical Shift for- (in p.p.m.)
(1)	8-F; 44·6 - ca 11·5 = 33·1 6-F; 30·3 - 4·0 = 26·3 or 30·3 - 6·8 = 23·5
(3)	8-F; 38·5 - ca 11·5 = 27·0 6-F; 25·0 - 4·0 = 21·0 or 25·0 - 6·8 = 18·2

and pentafluorobenzene the ortho fluorines were shifted downfield by 30·2 and 23·8 p.p.m. respectively, relative to hexafluorobenzene. These values are inbetween those found in the cases discussed above.

It is possible to argue that the low field absorbtion in (1), (2) and (3) was due to the 6-fluorine atom in each case. This would mean that the substituent had a widely different effect on each fluorine and it seems less likely that this should be so. N.B. If this were so in (1) the the change in chemical shift for the 6-fluorine, relative to tetrafluoroquinoline, would be 40·6 (i.e. 44.6 - 4·0) or 37·8 (i.e. 44·6 - 6·8) p.p.m. and that for the 8-fluorine ca 18·8 (i.e. 30·3 - 11·5). Similarly for (3) the change in chemical shifts would be 34·5 (i.e. 38·5 - 4·0) or 31·7 (i.e. 38·5 - 6·8) p.p.m. and ca 13·5 (i.e. 25·0 - 11·5) p.p.m. respectively. Assuming that the assignments for (1), (2) and (3) are correct then an interesting point emerges. That is that a substituent in the 7-position in 5,6,8-trifluoroquinolines shifts the 8-fluorine to low field to a much greater extent than the 6-fluorine, relative to the 5,6,7,8-tetrafluoroquinoline. Although data for the acetyl derivative of pentafluorophenol is not available it can be appreciated that here also the above suggestion holds good.

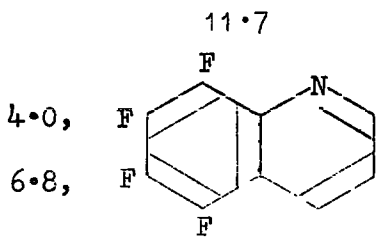
The ^{19}F spectrum of 7-methoxy-5,6,8-trifluoroquinoline shows two groups of peaks centred at 9·8 and 16·4 p.p.m., the latter is half the intensity of the former and because of its position at low field is assigned to the 8-fluorine. As before approximate values of the changes

in chemical shifts due to the methoxy group can be made.

Change in shift at position 8, 16·4 - 11·5 (app) = 4·9 $\pm$ ·2 p.p.m.
Change in shift at position 6, 9·8 - 4·0 = 5·8 or 9·8 - 6·8 = 3·0 p.p.m.

An interesting point arises here, since if the 6-F in the tetrafluoroquinoline absorbs at 4·0, then the change in chemical shift at position 6 on introducing a methoxy group in position 7 will be greater than the corresponding change for the 8-F. But this is contary to experience in the previous compounds examined, and leads us to assign the absorption at 6·8 in the tetrafluoroquinoline to the 6-F. On this basis the shifts are consistent with the previous results.

Returning to 2-methyl-5,6,7,8-tetrafluoroquinoline it seems logical to assign the absorption at 6·2 to the 6-F, and hence at 2·2 to the 7-F. On the basis of the coupling constants the absorption at 10·3 was assigned to the 5-F and at 11·2 to the 8-F. From these figures the assignment of the fluorine atoms in 5,6,7,8-tetrafluoroquinoline follows and is shown below.



11·3

On this basis the ^{19}F spectra of the quinolines can be interpretated and coupling constants and shifts due to substituents calculated. As

COMPOUND	SHIFT in p.p.m. downfield from C_6F_6	DESCRIPTION of BAND	COUPLING CONSTANTS in cycles sec^{-1}
5,6,7,8-Tetrafluoroquinoline	4·0	triplet	17·9
	6·8	doublet of doublets	16·5, 18·5
	11·3		
	11·7	2nd order splitting	
2-methyl-5,6,7,8-tetrafluoroquinoline	2·2	triplet	18·3
	6·2	doublet of doublets	16·3, 18·5
	10·3	triplet	16·3
	11·2	doublet of doublets	15·6, 18·4
4-methyl-5,6,7,8-tetrafluoroquinoline	3·0	triplet	19·0
	6·1	triplet	18·4
	12·3	doublet of doublets	15·1, 18·1
	20·8	doublet of doublets of doublets	6·2, 14·8, 17·9
7-bromo-5,6,8-trifluoroquinoline	12·3	doublet of doublets	17·5, 19·1
	30·3	doublet	21·3
	44·6	doublet	16·1
7-acetoxy-5,6,8-trifluoroquinoline	10·3	doublet of doublets	17·0, 19·5
	11·7	doublet	18·2
	21·5	doublet	16·7
7-methoxy-5,6,8-trifluoroquinoline	9·8	unresolved	
	9·8	unresolved	
	16·4	doublet of doublets	8, 18
5,6,8-trifluoroquinoline	8·3	doublet of triplets	6·4, 19·2
	25·0	doublet of doublets	10, 20
	38·5	doublet of doublets	8·4, 18·6

COMPOUND	SHIFT in p.p.m. downfield from C_6F_6	DESCRIPTION of BAND	COUPLING CONSTANTS $_{-1}$ in cycles sec
6,7,8-trifluoroquinoline	5·6 16·5 29·1	doublet of triplets doublet of doublets unresolved	7, 17 5, 17

Substituent in position 7	Chemical Shifts of some 5,6,8-trifluoroquinolines relative to 5,6,7,8-tetrafluoroquinoline			Corresponding shifts for C_6F_5X compounds		
	5F	6F	8F	oF	mF	pF
Br	1	23·5	32·9	30·2	2·0	8·0
OCH_3	-1·5	3·0	4·7	4·4	-2·0	-1·7
$OCOCH_3$	-1·0	4·9	9·8			
H	-3·0	18·2	26·8	23·8	0·3	8·9

can be seen ortho F-F coupling constants lie in the range 16·3 - 21·3 cycles and para F-F coupling constants in the range 14·8 - 18·6 cycles. In any one compound however ortho coupling was always found to be greater than para coupling.

These assignments are completely self-consistent and in agreement with data already established, as for example with the ^{19}F spectrum of 1,2,3,4-tetrafluoronapthalene (1) and 2-methoxy-1,3,4-trifluoronapthalene (2). These spectra were analysed and the results are given below.[113]

	Shifts	Coupling Constants	Assignments
(1)	ca 2·55 p.p.m. downfield from hexafluorobenzene		2 and 3-F
	ca 11·5		1 and 4-F
(2)	8·2	4 and 18 cycles	3-F
	9·65	16 and 18	4-F
	16·4	15	1-F

They are consistent with the assignments for the quinoline derivatives, in particular

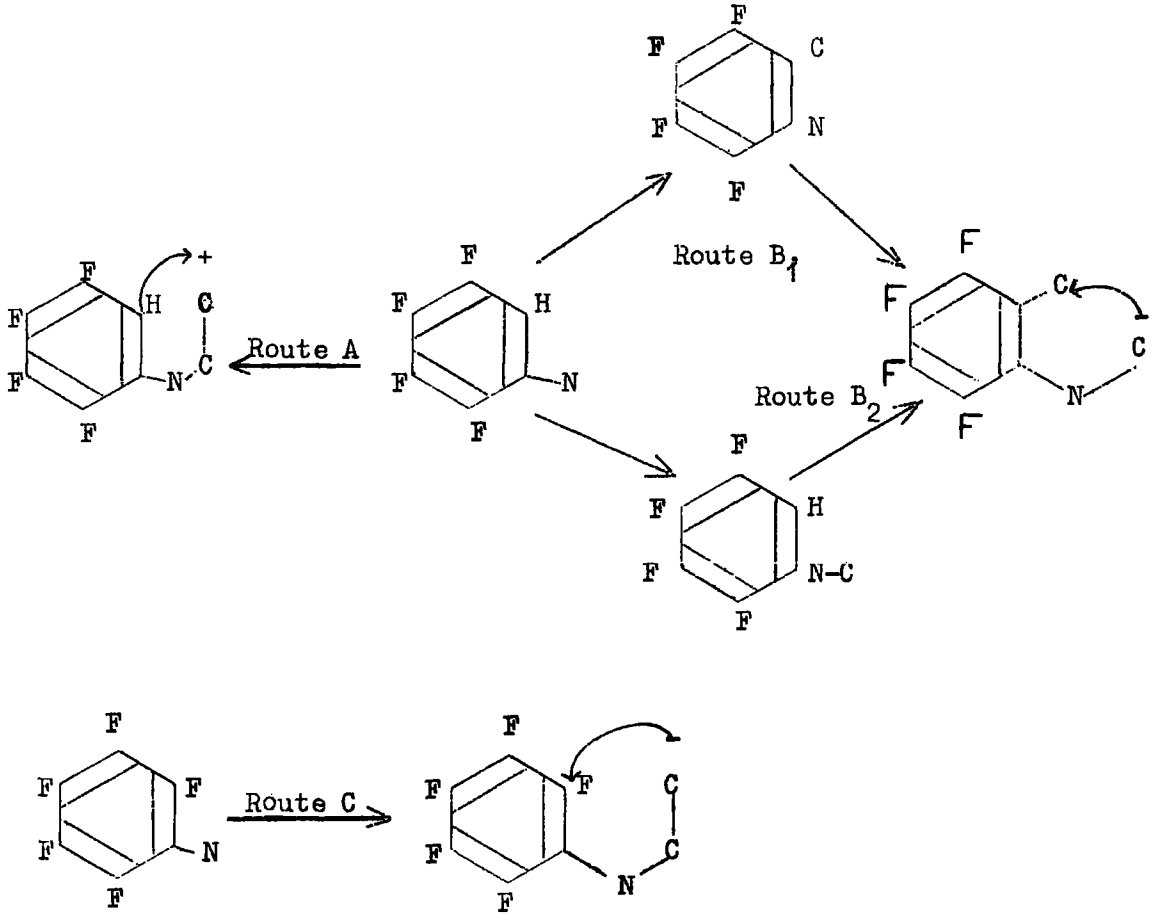
(i) the low field peak in the methoxy-derivative is assigned to 1-F and not the 3-F.

(ii) the ortho coupling constant is greater that the para coupling constant.

Chapter IX

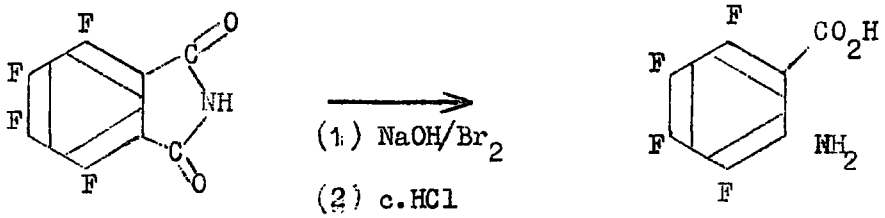
THE ATTEMPTED SYNTHESES OF SOME PARTIALLY FLUORINATED INDOLE DERIVATIVES

Three methods of effecting ring closure to synthesise fluorinated indole compounds were investigated.

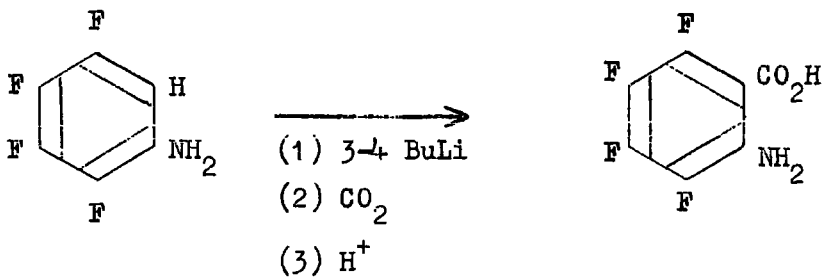


The first method can be classified as electrophilic replacement of a nuclear hydrogen (Route A), the second nucleophilic substitution at an unsaturated carbon atom (Route B) and the third nucleophilic substitution of a nuclear fluorine (Route C).

Before Routes A and B can be discussed the preparation of three important starting materials will be described. Tetrafluoroanthranilic acid has been prepared before by a Hofmann degradation of tetrafluoropthalimide.[114] A more convenient method was developed in which 2,3,4,5-



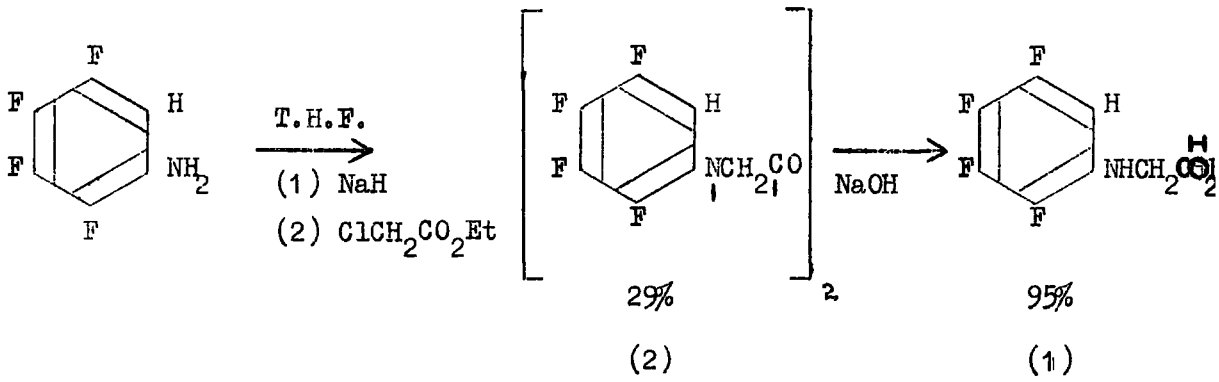
tetrafluoroaniline was treated with ca $3\frac{1}{2}$ moles of butyl lithium at ca -70° in tetrahydrofuran and the salt produced carbonated. The maximum yield



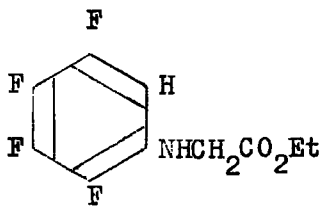
obtained was in the region of 45%, but the valuable tetrafluoroaniline was recovered. A recent publication gives details of the preparation of 4-amino-2,3,5,6-tetrafluorobenzoic acid by an analogous method[115] from

2,3,5,6-tetrafluoroaniline. Tetrafluoroanthranilic acid could be esterified using ethanol in the presence of strong acid as catalyst.

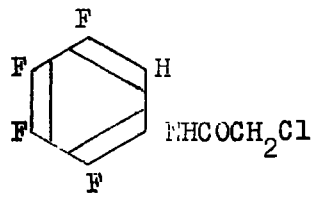
2,3,4,5-Tetrafluorophenylglycine (1) has been prepared previously, using the route outlined below.[116] The diketopiperazine (2) was isolated



and characterized. Two other compounds (3) and (4) were also isolated in small quantities. The method was developed to prepare high yields of (1).



(3)

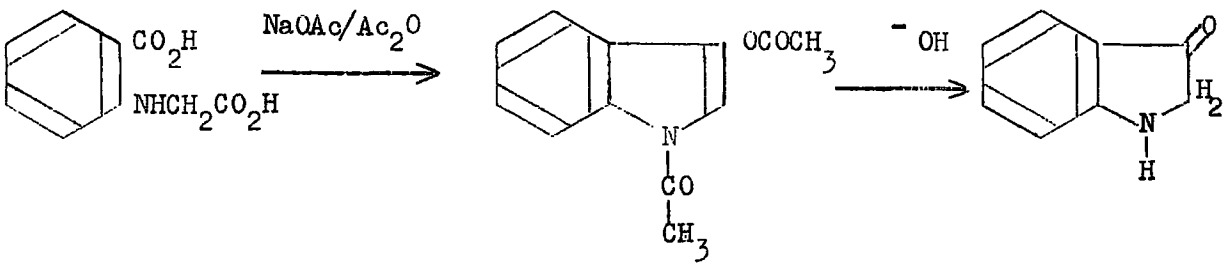


(4)

The major difference being that the products from the first stage of the reaction were not isolated, but hydrolysed immediately with 2N.NaOH. The solution was acidified and the glycine (1) filtered off, the overall yield was ca 60%.

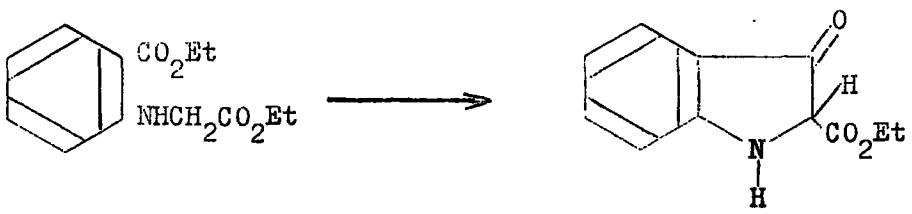
Several attempts were made to cyclise 2,3,4,5-tetrafluorophenylglycine (RouteA) in the presence of polyphosphoric acid,[116] concentrated sulphuric acid, and aluminium trichloride but no cyclised product could be isolated.

In order to carry out the final stage of Route B two methods of cyclisation appeared particularly attractive.[117] The first involved heating o-carboxyphenylglycine (5) with sodium acetate in acetic anhydride. Cyclisation takes place readily to give the N,O-diacetyl derivative (6),



(5) (6) (7)

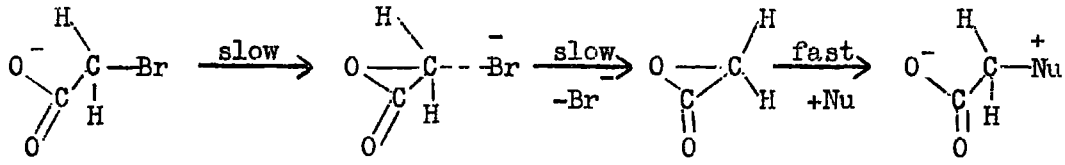
which is hydrolyzed to indoxyl (7) by cold dilute alkali. The second involved the preparation of the diethyl ester of (5) and condensation of the latter in the presence of base (e.g. sodium ethoxide) to give ethyl



(8)

indoxyl-2-carboxylate (8). Hydolysis followed by decarboxylation affords indoxyl.

Although several methods were investigated as potential routes to o-carboxy-tetrafluorophenylglycine only two proved successful, but economically discouraging. The first was based on a method given in the literature for the preparation of the hydrocarbon analogue.[118] It involved heating an aqueous solution of tetrafluoroanthranilic acid, bromoacetic acid and sodium carbonate. In this context the sodium salt of bromoacetic acid is expected to be a very reactive substrate, due to the formation of the α-lactone (9) as a non-isolatable intermediate.[119] From



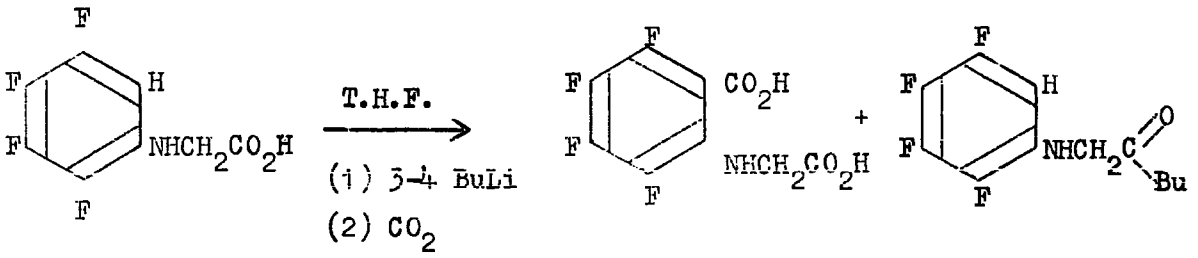
(9)

this reaction o-carboxy-tetrafluorophenylglycine was obtained in ca 30% yield, a similar quantity of tetrafluoroanthranilic acid was recovered. It is well known that the solvent (water) is an efficient nucleophile in the reaction with the intermediate α-lactone, but it seems that anthranilic acid is even more effective. However, the basicity (and hence the nucleophilicity) of tetrafluoroanthranilic acid will be much less than that of the hydrocarbon analogue, on account of the presence of the four electronegative fluorine atoms, and hence relatively the rate of reaction of the

α-lactone with water and tetrafluoroanthranilic acid might be comparable.

In contrast no reaction occurred when tetrafluoroanthranilic acid, bromoacetic acid and benzene were heated under reflux for several days. In a further attempt to prepare the diacid, tetrafluoroanthranilic acid was heated under reflux with two moles of sodium hydride in tetrahydrofuran then bromoacetic ester added. Only starting material was recovered. In this case it is likely that one mole of the sodium hydride reacted to give the acid salt, and this precipitated from solution. This effectively prevented further reaction since both reactants were solids.

The second successful preparation of o-carboxy-tetrafluorophenylglycine involved treatment of 2,3,4,5-tetrafluorophenylglycine with ca $3\frac{1}{2}$ moles of butyl lithium and carbonating the resultant salt. The o-carboxyphenylglycine was obtained in about 30% yield and a similar amount of the glycine was recovered. A third product, in a similar yield, was also

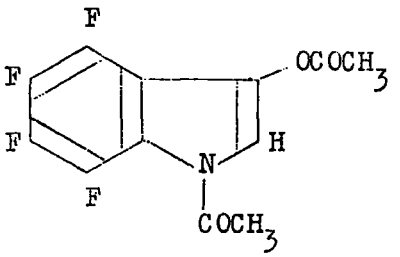


isolated and identified as N-(2,3,4,5-tetrafluorophenyl)aminomethyl n-butyl ketone, on the basis of the following evidence. The mass spectrum gave the correct molecular weight (263), and the infrared spectrum showed strong absorptions near 3410 cm^{-1} (ν N-H); 2960, 2920, 2880 cm^{-1} (ν C-H,

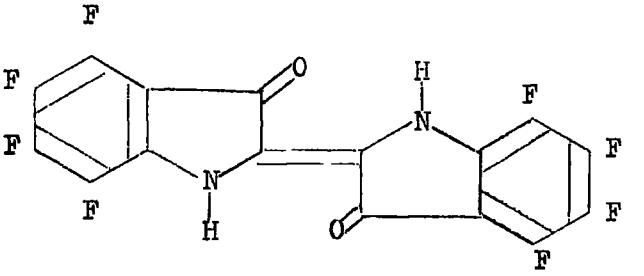
aliphatic); 1730 cm^{-1} (ν C=O); 1490 and 1450 cm^{-1} (skeletal vibrations associated with the aromatic ring). The compound must have been formed by attack of butyl lithium on the carbonyl group. The reaction was repeated in an effort to produce the diacid in increased yield but the major product was the ketone.

Several attempts were made to prepare the diethyl ester of o-carboxy-tetrafluorophenylglycine from ethyl tetrafluoroanthranilate but these proved unsuccessful. The hydrocarbon analogue of the former may be prepared by heating ethyl anthranilate and bromoacetic ester under reflux in benzene.[120] With ethyl tetrafluoroanthranilate only starting material was recovered even though the solution was heated for several days. The anthranilate was also treated separately with both butyl lithium and sodium hydride, and then bromoacetic ester added. In each case a complex mixture of products was obtained. It is possible that the reagents reacted with the carbethoxy group.

Cyclisation of tetrafluoro-o-carboxyphenylglycine seemed to take place readily when it was heated with sodium acetate in acetic anhydride. The crude product melted over a wide range, and because of the small amount of material available it could not be purified. A mass spectrum of the product obtained showed a strong peak at 289; this corresponds to the molecular weight of the N,O-diacetyl derivative (10) which was the product expected. The infrared spectrum was consistent with that expected from (10), but other products were present as evidenced by what



(10)

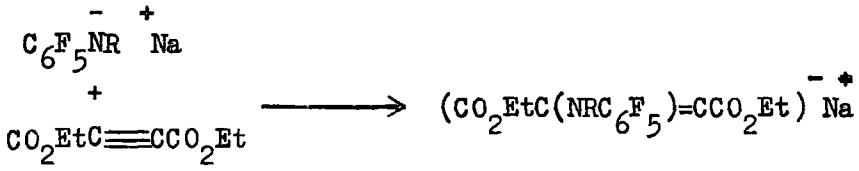


(11)

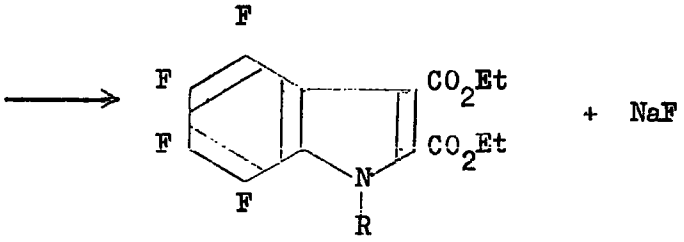
appeared to be a N-H band at 3,290 cm^{-1}. In particular the spectrum showed that no carboxylic acid group were present, i.e. there was no absorption in the region 3000 - 2000 cm^{-1}, which was a further indication that cyclisation had taken place.

The product was hydrolysed with 4N.NaOH, then the solution was acidified and the blue precipitate filtered off. This proved to be octafluoroindigo (11). The compound was identified by a correct molecular weight and a consistent infrared spectrum. In particular absorption bands were found at 3335 cm^{-1} (ν N-H) and at 1680 and 1665 cm^{-1} (ν C=O). The corresponding bands in indigo[121] are at 3270, 1630 and 1615 cm^{-1}. Comparing these figures it seems possible that hydrogen bonding is significantly less in the former. Although some of the shift to shorter wavelengths may be attributable to the effect of the accumulation of negative halogen atoms in the aromatic rings.

Before discussing the reactions involved in Route C a brief introduction will be given as to what we hoped to achieve. It is well established that sodium hydride and pentafluoroaniline give the sodium salt of the latter. This salt and the corresponding salt of perfluoroacetanilide[122] were prepared and then reacted with diethyl acetylenedicarboxylate under various conditions. The first stage of these reactions is addition of a sodium salt across the triple bond to give an intermediate carbanion (12) and it was hoped that this would cyclise by elimination of an ortho fluorine atom to give an indole derivative (13). In fact only adducts of the type (14) were isolated, and a tentative assignment of their



(12)



(13)

(a) R = H,

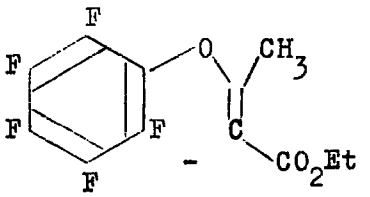
(b) R = $COCF_3$

structures will be suggested. A very similar type of cyclisation has

$$CO_2EtC(NRC_6F_5) = CHCO_2Et$$

(14)

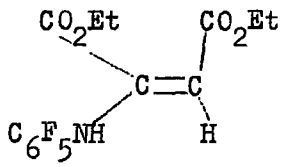
been discussed earlier (chapter II, page 11). From the reaction of hexafluorobenzene, sodium hydride and acetoacetic ester, a derivative of 4,5,6,7-tetrafluorobenzofuran was obtained. Young suggested that O-alkalyation was the first stage of the reaction and that the intermediate ion (15) was formed. This type of intermediate can also be



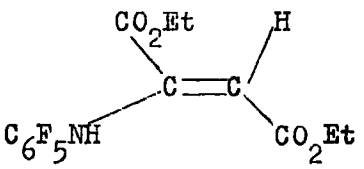
(15)

produced by the addition of the sodium salt of pentafluoroaniline, pentafluorophenol or pentafluorothiophenol to diethyl acetylenedicarboxylate, and these reactions have been investigated with a view to obtaining the corresponding heterocyclic compounds. Attempts to prepare the benzofuran derivative[123] have so far proved unsuccessful, but the benzo[b]thiophene[124] derivative was obtained in excellent yield. In the first experiment the sodium salt of pentafluoroaniline and diethyl acetylenedicarboxylate were

heated under reflux in tetrahydrofuran for 12 hr. The reaction mixture was worked up in the normal way to give an excellent yield of a liquid which was analysed by gas-chromatography (silicone grease-kieselguhr at 200°). One major component (>95%) was found. Elemental analysis and a molecular weight determination showed that ~~the empirical formula of~~ the product was $C_{14}H_{12}F_5NO_4$. It is clear that this compound could be either the maleic (16) or fumaric (17) acid derivatives illustrated below.

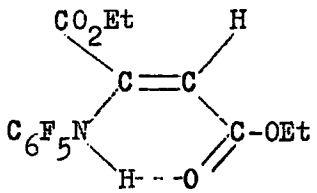


(16)



(17)

An important difference between these two compounds is that intramolecular hydrogen bonding is extremely likely in (17), as shown below, but is impossible in (16). With this in mind the infrared spectrum of



(18)

the compound was examined. Two very strong absorptions were present at 1740 and 1680 cm^{-1}. Both these bands are in the region expected for the

C=O stretching vibration, and are too intense and at too high a frequency to be assigned to either a C=C (conj.) stretching mode or an aromatic skeletal vibration. The appearance of two bands in this region indicates that one of the carbonyl groups is involved in chelation. A broad band centred on 3225 cm^{-1} was assigned to the N-H stretching mode. In general these bands are sharp, and this broadness helps to confirm intramolecular hydrogen bonding. As a further check spectra of the compound were run as a dilute solution in both carbon tetrachloride and methanol to eliminate any effects due to intermolecular hydrogen bonding. These spectra proved to be identical with that obtained previously. On this evidence the adduct may tentatively be said to be the fumaric acid derivative (17).

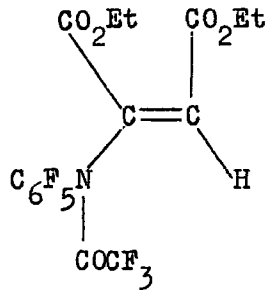
On the basis of the earlier discussion (chapter IV) it was expected that this nucleophile, being negatively charged, would add across the triple bond in a trans fashion to give a fumaric acid derivative, and this seems to have been the case.

At this stage it should be emphasised that before the intermediate carbanion (12) can cyclise, the two carbethoxy groups must be cis-orientated. Hence isomerisation must be promoted before cyclisation can take place. Thus the reaction was repeated adding as a final stage heating in an autoclave at 150° for 8 hr. Although extensive decomposition took place some product (ca 10%) was isolated. This was analysed by gas-chromatography and the major component of the mixture found to be the

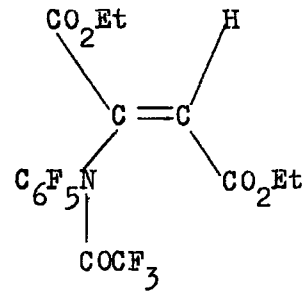
material prepared previously (17). Approximately eight other compounds were present all having retention times less than one third that of the main product. It seems likely that if isomerisation had taken place to give (16) as the final product and/or cyclisation to give the indole (13a), then both would have retention times comparable to that of (17). On this basis neither (13a) nor (16) were formed in detectable amounts. There was no value in repeating the reaction and heating the mixture to an even higher temperature, since extensive decomposition took place under the conditions used.

A possible reason for the reluctance of the intermediate carbanion to isomerise might be that, like the fumaric acid derivative (17) itself, the carbanion is stabilised by intramolecular bonding. With this in mind the trifluoroacetyl derivative of pentafluoroaniline was prepared and similar reactions carried out on this compound. N,N-substituted polyfluoroanilines are also known to be more reactive towards nucleophiles than the corresponding N-substituted compounds.[125]

In the first experiment the reactants were heated under reflux in tetrahydrofuran for 5 hr. A liquid was isolated which was shown by gas-chromatographic analysis to consist of three components, one of which had the same retention time as perfluoroacetanilide. The major component (>90%) was identified as either the maleic (19) or fumaric (20) acid derivative illustrated below, on the basis of the ^{19}F n.m.r. spectrum



(19)



(20)

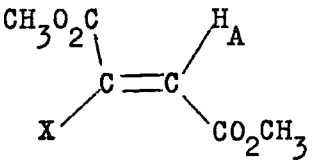
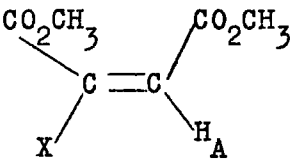
(which indicated five aromatic and three equivalent aliphatic fluorine atoms), ^{1}H n.m.r. spectrum (which indicated two ethoxy groups and one single hydrogen), a correct molecular weight and a consistent infrared spectrum. Unfortunately the other minor component had a very similar retention time and this prevented a completely satisfactory elemental analysis on the major component.

By analogy with the reactions of pentafluoroaniline, the structure was tentatively assigned as the fumaric acid derivative (20). As before the reaction was repeated including as a final stage heating in an autoclave at 120-130° for 3½ hr. Gas chromatographic analysis of the crude product showed the presence of five components. The major component was identified as the proposed fumaric acid derivative (20); another component was perfluoroacetanilide. In each case the retention time was identical with that of an authentic sample. The third component isolated from the mixture was a solid, an elemental analysis indicated that it

was an isomer of (20); possibly the maleic acid derivative (19). The possibility that one of the unidentified products may have been the indole derivative (13b) was ruled out from a close examination of the ^{19}F n.m.r. spectrum of the crude reaction mixture of five components. This clearly showed that only three trifluoroacetyl groups were present and these have been accounted for already.

There is one point that should be cleared up, that is the possibility that isomerisation accurred when the reaction mixture was distilled, i.e. it was (20) which isomerised and not the intermediate carbanion. This prospect was ruled out since when (20) in tetrahydrofuran was heated in a sealed tube at 140° for 8 hr. no isomerisation took place.

Analysis of the p.m.r. of the two olefinic compounds to which the structures (19) and (20) were given confirmed the assignments. The chemical shift of the olefinic proton in a series of substituted fumaric and maleic acid derivatives has been measured by Winterfeldt and Preuss[61] and their results are tabulated below. In those cases where a direct comparison is possible the vinyl proton in the fumarate ester (A) resononates at a lower field than the corresponding proton in the maleate ester (B). It would be expected that the significant diamagnetic anisotropy of the ester carbonyls would lead to a greater deshielding of the vinyl proton in (A) compared with (B), since in the former case the proton is flanked by two carbonyl fields where as in the latter the

	 A	 B
X	H_A (τ)	H_A (τ)
$N(C_2H_5)_2$	-	5·55
$N(CH_3)_2$	-	5·60
NC_5H_{10}	-	5·40
NC_2H_4	3·95	4·80
OCH_3	3·90	4·85
$OCH(CH_3)_2$	3·90	4·90
OC_6H_5	3·55	4·95

the vinyl proton is flanked by a single carbonyl field.[126]

This provides an elegant method of confirming structures when both isomers are available for comparison. The p.m.r. spectra of (19) and (20) were examined and the results are tabulated below. The chemical shifts for the methyl and methylene protons are in the range anticipated for the protons of a carbethoxy group. The chemical shift for the vinyl

COMPOUND	Chemical Shift (τ)	Relative Intensity	Description of peak	Assignment
(19)	5·7	4	two superimposed quartets	methylene protons
	7·9	1	singlet	vinyl proton
	8·8	6	two superimposed quartets	methyl protons
(20)	2·8	1	singlet	vinyl proton
	5·7	4	quartet	methylene protons
	8·6	6	triplet	methyl protons

proton in (20) is at the low field end of the range for olefinic protons (2·0 - 5·5) suggesting that (20) is in fact the fumarate derivative. The chemical shift for the proton in (19) is well outside the accepted range and it is to high field.

The difference between the two chemical shifts is much too great to be attributed to the removal of one carbonyl field. Molecular models of

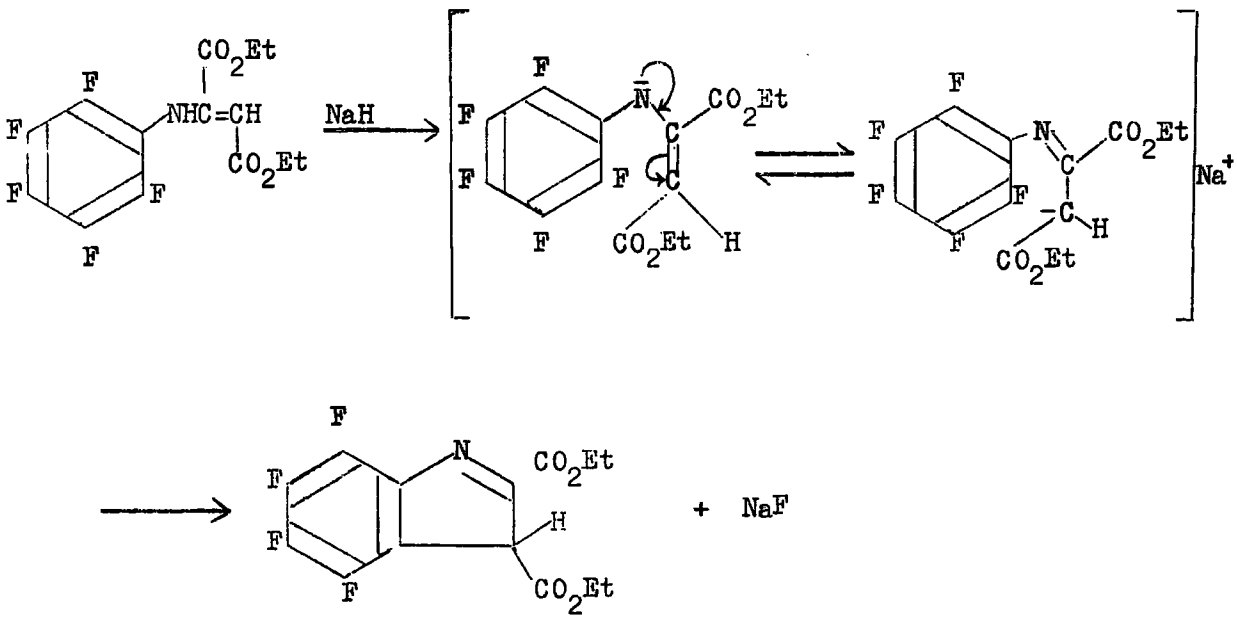
both (19) and (20) were made. In both cases steric hindrance was considerable, and it was only with difficulty that "Courtauld" models could be set up. It was apparent that a favoured conformation of (19) was one in which the vinylic proton was directly above the plane of the ring. This being so it is completely feasible that the large upfield shift is due to diamagnetic shielding provided by the π-electron system— the ring current effect.[126] In the other isomer the vinylic proton can not be placed in a similar environment and hence this shielding effect will not operate. This evidence does much to confirm the structures tentatively assigned to the olefinic products.

Examination of the ^{19}F n.m.r. spectra of the olefins (17), (19) and (20) provided evidence for restricted rotation in the last two compounds. The spectrum of (17) showed three absorptions, corresponding to three magnetically different types of fluorine, i.e. those ortho, meta and para to the substituent.

The spectra of (19) and (20) on the other hand showed four types of magnetically different aromatic fluorine atoms. The low field peak in the spectrum of (17), which was assigned to the ortho fluorines, was split in (19) and (20) in two. This is readily rationalised on the basis of restricted rotation. This evidence is extremely valuable since the absorbtion of the vinylic proton in (19) at such high field could not be explained if free rotation was possible.

It seems doubtful whether this method in its present form can be developed to prepare indole derivates. One of the main problems seems to be the difficulty in isomerising the initially formed trans-adduct. It is probable that isomerisation requires conditions almost as vigorous as those needed to decompose the intermediate carbanion altogether.

The following modification might meet with more success. The cyclised product (21) would be an indolenine derivative. A preliminary



(21)

reaction of this type has been carried out in tetrahydrofuran at reflux temperature, but only the starting material (17) was recovered.

EXPERIMENTAL WORK

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The Preparation of some Tetra- and Trifluoroquinolines

5,6,7,8-Tetrafluoroquinoline.- 2,3,4,5-Tetrafluoroaniline (30·1g.) was stirred with arsenic pentoxide (83·9g.), hydrated ferrous sulphate (7·0g.), boric acid (12·0g.), and anhydrous glycerol (75·4g.) at 120-126°, and sulphuric acid (61·5g., d, 1·84) was added over 35 min. The mixture was heated at 122-130° for 18·25 hr. diluted with water and made alkaline with sodium carbonate. The solution was extracted with ether, the extracts dried ($MgSO_4$) and the solvent evaporated. The residue was sublimed *in vacuo* at 65°, and the sublimate (27·4g.) was recrystallised twice from light petroleum (b.p. 60-80°) to give 5,6,7,8-tetrafluoroquinoline (19·4g.), m.p. 93-93·5°. (Found: C, 54·0; H, 1·6; F, 37·8. $C_9H_3F_4N$ requires C, 53·7; H, 1·5; F, 37·9%).

5,6,8-Trifluoroquinoline.- 2,4,5-Trifluoroaniline (1·3g.) was stirred with arsenic pentoxide (3·7g.) and anhydrous glycerol (5·5g.) at 122°, and sulphuric acid (2·3g., d, 1·84) was added at such a rate that the temperature did not rise above 130°. After diluting the mixture with water and making alkaline with aqueous sodium carbonate, the resulting precipitate was filtered off. Sublimation of this material *in vacuo* gave the crude product (0·7g.), m.p. 82-85°, which was recrystallised from light petroleum (b.p. 60-80°) to give 5,6,8-trifluoroquinoline, m.p. 86-87°. (Found: C, 58·8; H, 2·1; F, 30·7. $C_9H_4F_3N$ requires C, 59·0; H, 2·2; F, 31·1%).

6,7,8-Trifluoroquinoline.- 2,3,4-Trifluoroaniline (1·08g.) was stirred with arsenic pentoxide (3·2g.) and anhydrous glycerol (3·4g.) at 124° and sulphuric acid (1·3g., d, 1·84) was added slowly over 20 min. The mixture was heated for 3 hr. at 140-146° and for a further 2 hr. at 132-168°. It was then diluted with water, made alkaline with aqueous sodium carbonate and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts and sublimation of the residue in vacuo at 70° gave the crude product (0·31g.). This was recrystallised from light petroleum (b.p. 40-60°) to give 6,7,8-trifluoroquinoline, m.p. 101-101·5°. (Found: C, 58·8; H, 2·3; F, 31·4. $C_9H_4F_3N$ requires C, 59·0; H, 2·2; F, 31·1%).

2-Methyl-5,6,7,8-tetrafluoroquinoline.- 2,3,4,5-Tetrafluoroaniline (5·07g.) was stirred with arsenic pentoxide (7·0g.), hydrated ferrous sulphate (1·0g.), boric acid (2·0g.) and sulphuric acid (9·0g., d, 1·84) at 116-119°, and crotonaldehyde (12·6g.) was added over 1·75 hr. The mixture was heated at 120° for 12 hr., diluted with water and made alkaline with sodium carbonate. The solution was extracted with ether, the extracts dried ($MgSO_4$) and the solvent evaporated. The residue was sublimed in vacuo at 60°, and the sublimate (1·2g.), which was shown by infrared spectroscopy to contain some unreacted 2,3,4,5-tetrafluoroaniline, was recrystallised twice from light petroleum (b.p. 40-60°) to give impure 2-methyl-5,6,7,8-tetrafluoroquinoline (0·76g.), m.p. 47·5-49·5°. Sublimation in vacuo at 45°, and further recrystallisation from light petroleum (b.p. 40-60°) gave pure 2-methyl-5,6,7,8-tetrafluoroquinoline, m.p. 51-52°. (Found: C, 56·0; H, 2·2; F, 35·4. $C_{10}H_5F_4N$ requires

C, 55·8; H, 2·3; F, 35·3%).

4-Methyl-5,6,7,8-tetrafluoroquinoline.- 2,3,4,5-Tetrafluoroaniline (4·98g.) was stirred with hydrated ferric chloride (16·3g.), anhydrous zinc chloride (3·0g.) and glacial acetic acid (20 ml.) at 80-90° and methyl vinyl ketone (2·7g.) was added over 30 min. The temperature was gradually increased to 113° over 2·75 hr. and the solution was heated under reflux for 8 hr. The mixture was diluted with water, made alkaline with sodium carbonate and the precipitate which formed, filtered off. Sublimation of this material in vacuo at 70° gave the crude product (1·17g.), m.p. 77·5-79·5°, which was recrystallised from light petroleum (b.p. 40-60°) to give 4-methyl-5,6,7,8-tetrafluoroquinoline, m.p. 80·5-81·5°. (Found: C, 56·0; H, 2·3; F, 35·5. $C_{10}H_5F_4N$ requires C, 55·8; H, 2·3; F, 35·3%).

Some Reactions of 5,6,7,8-Tetrafluoroquinoline

(a) The Reactions with Nucleophiles.

7-Methoxy-5,6,8-trifluoroquinoline.- 5,6,7,8-Tetrafluoroquinoline (2·5g., 0·012 mole) was dissolved in dry methanol (20 ml.) and heated under reflux with sodium methoxide in methanol (0·57N, 27·0 ml., 0·015 mole). After 6·5 hrs., the mixture was poured into water, extracted with ether and the dried ($MgSO_4$) extracts evaporated. The residue (2·3g.) was recrystallised from light petroleum (b.p. 40-60°) to give 7-methoxy-5,6,8-trifluoroquinoline, m.p. 65-66·5°. (Found: C, 56·0; H, 2·6; F, 27·0. $C_{10}H_6F_3NO$ requires C, 56·3; H, 2·8; F, 26·8%).

7-Amino-5,6,8-trifluoroquinoline.- 5,6,7,8-Tetrafluoroquinoline (4·0g.) and aqueous ammonia (12·0 ml., d, 0·88) were heated together in a sealed tube at 148-152° for 3 hr. The mixture was diluted with water and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts and recrystallisation of the crude residue (3·8g.), m.p. 128-162°, four times from benzene-light petroleum (b.p. 60-80°) with one decolourisation with charcoal gave 7-amino-5,6,8-trifluoroquinoline (0·9g.), m.p. 186-187°. (Found: C, 54·4; H, 2·6; F, 28·8. $C_9H_5F_3N_2$ requires C, 54·5; H, 2·5; F, 28·8%).

7-Hydroxy-5,6,8-trifluoroquinoline.- 5,6,7,8-Tetrafluoroquinoline (2·5g.), potassium hydroxide (2·2g.), and t-butyl alcohol (48g.) were heated together under reflux for 12 hr. Water (50 ml.) was added and the mixture was distilled until most of the t-butyl alcohol had been removed. After being washed twice with ether, the aqueous solution which remained was acidified with dilute sulphuric acid and the precipitate which formed was filtered off. The aqueous solution was continuously ether extracted for 72 hr., the extract was dried ($MgSO_4$) and solvent evaporated. The combined reaction product (1·91g.) was recrystallised twice from ethyl acetate and a small portion was sublimed *in vacuo* at 64° to give 7-hydroxy-5,6,8-trifluoroquinoline which began to decompose without melting at 180° (Found: C, 53·4; H, 2·6. $C_9H_4F_3NO$ requires C, 54·3; H, 2·0%). It formed an acetate m.p. 78-79°. (Found: C, 54·6; H, 2·4; F, 23·6. $C_{11}H_6F_3NO_2$ requires C, 54·7; H, 2·5; F, 23·7%).

(b) The reaction with hydrogen chloride.

When dry hydrogen chloride was bubbled through diethyl ether containing the tetrafluoroquinoline, the hydrochloride was precipitated. (Found: Cl, 15·3; $C_9H_4ClF_4N$ requires Cl, 14·9%).

(c) The reaction with phosphorus pentachloride.

The tetrafluoroquinoline (2·91g.) and phosphorus pentachloride (25g.) were heated together in a stainless steel autoclave for 4 hr. at 230-235°. The mixture was diluted with water and the solid filtered off and sublimed in vacuo at 175°. The sublimate (2·67g.) was recrystallised from light petroleum to give a hexachloroquinoline. m.p. 184-185·5°. (Found: C, 31·9; Cl, 62·8; M, 335. C_9HCl_6N requires C, 32·2; Cl, 63·5%; M, 336).

Some Interconversion Reactions

5,6,8-Trifluoroquinoline.- From 7-amino-5,6,8-trifluoroquinoline. Sodium nitrite (6·0g.) was added at 0° during 30 min. to the amine (0·88g.) in hydrofluoric acid (45 ml., 82% w/w). After being stirred for 1 hr. at 0° the solution was added slowly to hypophosphorous acid (80 ml., 50% w/w) at room temperature, and the mixture heated to 80-87° for 1·75 hr. The solution was neutralised with aqueous sodium carbonate and distilled in steam. Ether extraction of the distillate and evaporation of the dried ($MgSO_4$) extracts left a residue (0·28g.) which on sublimation in vacuo at 65° and recrystallisation from light petroleum gave 5,6,8-trifluoroquinoline, m.p. 86-87°, which was not depressed on admixture with the

product obtained previously. The infrared spectra of the two products were identical.

7-Methoxy-5,6,8-trifluoroquinoline.- From 7-hydroxy-5,6,8-trifluoroquinoline. The hydroxy compound (0·30g.) in dry ether (200 ml.) was stirred overnight at room temperature with an excess of diazomethane in ether. The solvent was evaporated and the residue sublimed in vacuo at 50°. The sublimate (0·16g.) was recrystallised from light petroleum (b.p. 40-60°) to give the 7-methoxy compound, m.p. 65-66·5°, which had an infrared spectrum identical to the material prepared before.

7-Hydroxy-5,6,8-trifluoroquinoline.- (1) From 7-methoxy-5,6,8-trifluoroquinoline. The methoxy compound (0·21g.) was heated with anhydrous aluminium chloride (0·6g.) for 19 hr. at 128-130°. The mixture was treated with iced-water, the solution adjusted to pH6 and the precipitate was filtered off. The filtrate was continuously extracted with ether for 72 hr., the extracts dried ($MgSO_4$) and evaporated. The combined reaction product was sublimed in vacuo at 150° to give 7-hydroxy-5,6,8-trifluoroquinoline (0·15g.) which had an infrared spectrum identical with the material from the tetrafluoroquinoline.

(2) From 7-bromo-5,6,8-trifluoroquinoline. The bromo compound (0·42g.) in dry tetrahydrofuran (40 ml.) at -35 to -45° under nitrogen was treated with n-butyl lithium in hexane (0·8 ml., 2·35N) diluted with dry tetrahydrofuran (10 ml.), over 10 min. The mixture was stirred for 40 min., trimethyl borate (0·5 ml.) in dry tetrahydrofuran (10 ml.) was added,

followed 30 min. later by hydrogen peroxide (2 ml., 85% w/w) over 15 min. The mixture was allowed to warm to room temperature over 12 hr., and made alkaline with caustic soda solution (2N). The aqueous layer was separated and was washed with methylene chloride (50 ml.). The aqueous layer was adjusted to pH5 by the addition of dilute sulphuric acid and extracted with methylene chloride (50 ml.). The dried ($MgSO_4$) extract was evaporated to leave 7-hydroxy-5,6,8-trifluoroquinoline (0·06g.) which had an infrared spectrum identical with the material prepared above.

7-Bromo-5,6,8-trifluoroquinoline.- Sodium nitrite (2·0g.) was added at -5 to -10° during 15 min. to 7-amino-5,6,8-trifluoroquinoline (1·1g.) in hydrofluoric acid (28 ml., 85% w/w). After being stirred for a further 2 hr. at the -5 to -10°, a solution of cuprous bromide [from hydrated copper sulphate (12g.) and potassium bromide (13g.) dissolved in boiling water (35 ml.) to which was added hydrated sodium sulphite (7·5g.) and the white precipitate of cuprous bromide filtered off, washed with water and dissolved in hydrobromic acid (40 ml., 48% w/w)] was added over 20 min. After a further 2 hr., during which the temperature was allowed to rise to 14°, the mixture was added to more hydrobromic acid (40 ml., 48% w/w) and heated at 80-92° for 1 hr. After being diluted with water and made alkaline with sodium carbonate solution, the mixture was distilled in steam, and the distillate extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave the crude product (1·4g.) which was sublimed in vacuo at 75° and recrystallised from light petroleum (b.p. 40-60°) to give pure

7-bromo-5,6,8-trifluoroquinoline m.p. 99-99·3°. (Found: C, 41·2; H, 1·3; F, 22·1. $C_9H_3BrF_3N$ requires C, 41·4; H, 1·2; F, 21·8%).

The Preparation of some Trifluoroanilines

2,4,5-Trifluoroaniline.- 1,2,4,5-Tetrafluorobenzene (5·2g.) and aqueous ammonia (10 ml., d, 0·88) were heated together in a sealed tube at 215-219° for 12·5 hr. The mixture was extracted with ether, and the dried ($MgSO_4$) extracts evaporated. The residue (3·5g.) was sublimed *in vacuo* at 45° and the sublimate recrystallised from light petroleum (b.p. 40-60°) to give 2,3,4-trifluoroaniline, m.p. 59-60° (lit. m.p. 60°), (Found: C, 49·2; H, 2·6. Calc. for $C_6H_4F_3N$: C, 49·0; H, 2·7%).

2,3,6-Trifluoroaniline.- 1,2,3,4-Tetrafluorobenzene (5·2g.) and aqueous ammonia (10 ml., d, 0·88) were heated together in a sealed tube at 201-207° for 30 hr. The mixture was extracted with ether, and the dried ($MgSO_4$) extracts evaporated. Further distillation gave 2,3,6-trifluoroaniline (3·3g.), b.p. 81·5°/55 mm. (Found: C, 48·9; H, 2·7; F, 38·5. $C_6H_4F_3N$ requires C, 49·0; H, 2·7; F, 38·8%).

2,3,4,5-Tetrafluorobenzaldehyde.- 2,3,4,5-Tetrafluorobromobenzene (5·15g.) in ether (10 ml.) was added to magnesium (0·6g.) and ether (50 ml.), which had been previously activated with ethylene dibromide, and the mixture was heated under reflux for $2\frac{1}{2}$ hr. It was then cooled to -10 to -15° and N-methyl formanilide (3·4g.) added over 5 min. at such a rate to maintain the temperature in this range. The mixture was stirred for a further hour then heated under reflux for 4 hr. After having been diluted with water and acidified with sulphuric acid, the mixture was distilled in steam. Ether extraction of the distillate and evaporation of the dried ($MgSO_4$) extracts left a residue, which on distillation gave 2,3,4,5-tetrafluorobenzaldehyde (3·27g.), b.p. 151·5-152·5°. (Found: C, 47·3; H, 1·4; F, 42·9. $C_7H_2F_4O$ requires C, 47·2; H, 1·1; F, 42·7).

2,3,4,5-Tetrafluorobenzylidineaminoacetal.- 2,3,4,5-Tetrafluorobenzaldehyde (2·93g.) was condensed with amino-acetal (3·32g.) for 1 hr. at 100°. The mixture was then distilled under reduced pressure to give 2,3,4,5-tetrafluorobenzylidineaminoacetal (3·35g.) b.p. 83-84°/0·008 mm. (Found: C, 53·1; H, 4·7; F, 25·8. $C_{13}HF_4NO_2$ requires C, 53·2; H, 5·1; F, 25·9%).

Attempted Cyclisations of 2,3,4,5-Tetrafluorobenzylidineaminoacetal.

(i) 2,3,4,5-Tetrafluorobenzylidineaminoacetal (0·47g.) and sulphuric acid (2 ml., 76% w/w) were kept at room temperature for 6 hr., then heated at 100° for 1 hr. The solution was made alkaline with

aqueous sodium bicarbonate and the resulting precipitate (0·3g.), m.p. $>170^{\circ}$, filtered off. An infrared spectrum showed absorptions at 1530 cm^{-1} and 1480 cm^{-1} (aromatic ring) and three bands between 1200 cm^{-1} and 1000 cm^{-1}, which were similar in position to bands found on a spectrum of the starting material. The precipitate was heated up to 100° in vacuo but nothing sublimed.

(ii) 2,3,4,5-Tetrafluorobenzylidineaminoacetal (0·42g.) and sulphuric acid (2 ml., 76% w/w) were mixed then kept at -15° for 42 hr., further diluted with water, and made alkaline with sodium carbonate. A small amount of an involatile precipitate was filtered off. The solution was extracted with ether to give a very dark red viscous liquid, which when analysed by gas chromatography showed no material of similar retention time to tetrafluoroquinoline; however a peak was observed corresponding to 2,3,4,5-tetrafluorobenzaldehyde and the infrared spectrum of the product was very similar to that of the latter.

(iii) 2,3,4,5-Tetrafluorobenzylidineaminoacetal (0·44g.) and sulphuric acid (2·8g., 76% w/w) were mixed at 0° then quickly added to a solution of phosphorous pentoxide (0·04g.) and sulphuric acid (0·53g., 76% w/w) at $160-170^{\circ}$, and the whole heated for 25 min. The mixture was diluted with water and the resulting precipitate (0·18g.) filtered off. Ether extraction of the filtrate gave a liquid which when analysed by gas chromatography showed no material

of similar retention time to tetrafluoroquinoline. But a peak corresponding to 2,3,4,5-tetrafluorobenzaldehyde was observed.

3,4,5,6-Tetrafluoroanthranilic acid.- 2,3,4,5-Tetrafluoroaniline (22·1g.) in dry tetrahydrofuran (150 ml.) at -65 to -70° under nitrogen was treated with n-butyl lithium in hexane (200 ml., 2·35N) over 1½ hr., and the mixture stirred for a further 1½ hr. Dry carbon dioxide was then bubbled through the solution for 1¼ hr. while the temperature was maintained below -50°. The solution was allowed to warm to room temperature over 4 hr., diluted with water, and acidified with sulphuric acid. Extraction with ether gave a liquid, most of which was removed by pumping on a vacuum line through a trap cooled in liquid air. Recrystallisation of the remaining material from light petroleum (b.p. 100-120°) gave the crude product (5·0g.), which was sublimed *in vacuo* at 100° and recrystallised further from petroleum to give 3,4,5,6-tetrafluoroanthranilic acid, m.p. 141·5-142·5° (lit. m.p. 141-142°). (Found: C, 40·1; H, 1·3; F, 36·3. Calc. for $C_7H_3F_4NO_2$: C, 40·2; H, 1·4; F, 36·4%).

The contents of the cold trap were made alkaline and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave a liquid (20·7g.), whose infrared spectrum was almost identical to that of 2,3,4,5-tetrafluoroaniline. Gas-chromatographic analysis of the liquid showed the presence of over 60% of the aniline.

Ethyl 3,4,5,6-tetrafluoroanthranilate.- Tetrafluoroanthranilic acid (3·6g.) ethanol (20 ml.), and concentrated sulphuric acid (8 ml.) were heated at 90° for 16 hr., diluted with water and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts and sublimation of the residue

in vacuo at 50° gave the crude product (2·8g.), m.p. 59-63°. Recrystallisation from light petroleum (b.p. 40-60°) gave ethyl 3,4,5,6-tetrafluoroanthranilate, m.p. 65-66°. (Found: C, 45·4; H, 2·7; F, 31·9. $C_9H_7F_4NO_2$ requires C, 45·6; H, 2·9; F, 32·1%).

2,3,4,5-Tetrafluorophenyl glycine.- A suspension of sodium hydride in oil (2·5g., 50% w/w) was washed twice with dry ether and the solvent decanted off. The sodium hydride was heated under reflux with more ether (50 ml.) and 2,3,4,5-tetrafluoroaniline (10·0g.) in ether (10 ml.) was added over 15 min. The mixture was heated under reflux for a further $7\frac{1}{2}$ hr. then cooled to -70° and ethyl bromoacetate (10·5g.) in ether (15 ml.) was added over 5 min. and the solution allowed to warm to room temperature overnight. The solvent was evaporated and the crude product heated under reflux with 100 ml., 2N. NaOH for 30 min. The solution was acidified with sulphuric acid and the resultant precipitate filtered off and sublimed in vacuo at 130° to give 2,3,4,5-tetrafluorophenyl glycine (7·6g.), m.p. 178-180° (an authentic sample had m.p. 175-178·5°). The infrared spectrum was identical to that of the material prepared before.

3,4,5,6-Tetrafluorophenylglycine-o-carboxylic Acid.- (a) From 2,3,4,5-tetrafluorophenylglycine. The glycine (2·05g.) in dry tetrahydrofuran (90 ml.) at -68 to -73° under nitrogen was treated with n-butyl lithium in hexane (18 ml., 2·35N) over 30 min. The mixture was stirred for 1 hr., then dry carbon dioxide was bubbled through the solution which was allowed to warm slowly to room temperature over 5 hr.

It was made alkaline with caustic soda and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave a liquid (0·38g.), A. The aqueous solution was acidified and extracted with ether. The extracts were then dried ($MgSO_4$), filtered and the solvent evaporated. The residue was sublimed in vacuo to give two fractions. The first (0·78g.), B, sublimed at 130°, the second (0·79g.), C, at 170°.

A was shown to be N-(2,3,4,5-tetrafluorophenyl)aminomethyl n-butyl ketone.

The infrared spectrum of B was identical to that of the starting material, 2,3,4,5-tetrafluorophenyl glycine.

The infrared spectrum of C was completely different to that of B, and recrystallisation from ethyl acetate and light petroleum (b.p. 60-80°) afforded 3,4,5,6-tetrafluorophenylglycine-o-carboxylic acid, m.p. 178-179°. (Found: C, 40·2; H, 1·9; F, 28·7. $C_9H_5F_4NO_4$ requires C, 40·4; H, 1·9; F, 28·5%).

(b) From tetrafluoroanthranilic acid. The acid (1·3g.), bromoacetic acid (1·5g.), sodium carbonate (1·5g.) and water (20 ml.) were heated under reflux for 17 hr., acidified with dilute sulphuric acid and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave the crude product, which was sublimed in vacuo to give two fractions. The first fraction (0·3g.), m.p. 138-140°, sublimed at 100°.

The infrared spectrum of this material was identical to that of tetrafluoroanthranilic acid. The second fraction (0·3g.), sublimed at

160°, was identified as 3,4,5,6-tetrafluorophenylglycine-o-carboxylic acid by its infrared spectrum.

Cyclisation of 3,4,5,6-Tetrafluorophenylglycine-o-carboxylic Acid.- The diacid (0·13g.), anhydrous sodium acetate (0·5g.) and acetic anhydride (15 ml.) were heated under reflux for 15 min. On cooling water was added and the solution heated for a further 15 min. It was then made alkaline with sodium carbonate and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts and sublimation in vacuo at 80° gave the crude product (0·05g.), m.p. 100-132°. Recrystallisation from light petroleum (b.p. 40-60°) and further sublimation in vacuo at 70° gave a purer product (20 mg.), m.p. 105-115°. Most of the sample melted sharply at 105°. The mass spectrum showed a peak at 289, corresponding to N-acetyl-3-acetoxy-4,5,6,7-tetrafluoroindole.

Octafluoroindigo.- A small amount of the product from the previous experiment was shaken with 4N caustic soda for about 15 min., the solution being warmed to 60°. A precipitate formed, the solution was acidified with dilute sulphuric acid and the blue product filtered off. This proved to be octafluoroindigo. The mass spectrum showed a parent peak at 406 ($C_{16}H_2F_8N_2O_2$ requires 406) and the infrared spectrum showed strong absorptions near 3335 cm^{-1} (ν N-H), 1680 and 1665 cm^{-1} (ν C=O), and 1530 and 1480 cm^{-1} (skeletal vibrations associated with the aromatic ring system).

Diethyl N-(2,3,4,5,6-pentafluorophenyl)aminofumarate.- A suspension of sodium hydride in oil (3·0g., 50% w/w) was washed with dry tetrahydrofuran, then the solvent decanted off. The sodium hydride was stirred with tetrahydrofuran (60 ml.) at -10 to -20° and pentafluoroaniline (10·5g.) in tetrahydrofuran (10 ml.) added dropwise over 10 min. The mixture was stirred for a further 4 hr., then cooled to -63 to -70° and diethyl acetylenedicarboxylate (10·7g.) added dropwise over 20 min. The solution was stirred for 2 hr., allowed to warm to 20° over 2½ hr., then heated under reflux for 12 hr. After having been diluted with water and acidified with sulphuric acid, the solution was extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave a dark red liquid which was distilled *in vacuo* to give a pale yellow oil (10·6g.), redistillation gave pure diethyl N-(2,3,4,5,6-pentafluorophenyl)aminofumarate, b.p. 106-108°/0·02 mm. (Found: C, 47·9; F, 27·3; M, 353. $C_{14}H_{12}F_5NO_4$ requires C, 47·6; F, 26·9%; M, 353).

Diethyl N-(2,3,4,5,6-pentafluorophenyl)aminofumarate.- Pentafluoroaniline (9·7g.) in dry tetrahydrofuran (5 ml.) was added dropwise over 15 min. to a stirred suspension of sodium hydride in oil (2·3g., 60% w/w) in tetrahydrofuran (60 ml.) at -10 to -20°. The mixture was stirred for a further 3 hr., then allowed to warm to 20° over 1¼ hr. It was cooled to -60 to -70° and diethyl acetylenedicarboxylate (9·8g.) added over 20 min. The mixture was stirred for 1 hr., allowed to warm to 20° over a further 1 hr., and then transfered to a steel autoclave and heated at 150° for 8 hr.

On cooling the autoclave was opened and the contents poured into water. The solution was acidified with sulphuric acid and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave a thick black oil which was distilled to give the crude product (1·73g.), b.p. 110-146°/0·6 mm., which had an infrared spectrum almost identical with that of diethyl N-(2,3,4,5,6-pentafluorophenyl)aminofumarate. Gas chromatography on silicone grease-kieselguhr at 200° showed that it consisted of about 40-45% of the latter, the remainder being a mixture of about eight materials all having retention times less than one third of that of the main product.

Diethyl N-(trifluoroacetyl)-N-(2,3,4,5,6-pentafluorophenyl)amino-fumarate.- A suspension of sodium hydride in oil (1·3g., 60% w/w) was washed twice with dry tetrahydrofuran and the solvent decanted off. The sodium hydride was stirred with tetrahydrofuran (60 ml.) at -20 to -30° and perfluoroacetanilide (8·4g.) in tetrahydrofuran (20 ml.) added over 20 min. The solution was stirred for 2 hr. during which the temperature rose to 15°. On cooling to -69 to -71° diethyl acetylenedicarboxylate (5·6g.) was added over 15 min. The mixture was allowed to warm to 20° over 1½ hr. then heated under reflux for 5 hr. The solution was diluted with water, acidified with sulphuric acid and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave an oil. Sublimation of this in vacuo at 60° gave a white solid (2·6g.), m.p. 92-93°, whose infrared spectrum was identical to that of perfluoroacetanilide. The

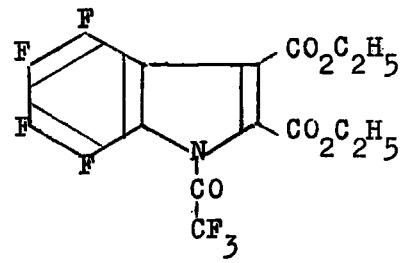
remaining material was distilled in vacuo to give a pale yellow oil (4·7g.). Gas chromatography on silicone grease-kieselguhr at 200° showed one component (>90%) and two minor components. One of which had the same retention time as perfluoroacetanilide, the other a retention time slightly longer than that of the major component.

The oil was redistilled to give diethyl N-(trifluoroacetyl)-N-(2,3,4,5,6-pentafluorophenyl)aminofumarate, b.p. 98-100°/0·02 mm. (Found: C, 43·5; H, 2·4; M, 449. $C_{16}H_{11}F_8NO_5$ requires C, 42·8; H, 2·5%; M, 449).

Reaction of Perfluoroacetanilide, Sodium Hydride and Diethyl Acetylenedicarboxylate in an autoclave.- A suspension of sodium hydride in oil (2·5g., 50% w/w) was washed twice with dry tetrahydrofuran, and the solvent decanted off. The sodium hydride was stirred with tetrahydrofuran (60 ml.) at -20 to -30° and perfluoroacetanilide (12·1g.) in tetrahydrofuran (20 ml.) added over 50 min. The solution was stirred for 3 hr. during which time the temperature rose to 20°. On cooling to -65 to -70°, diethyl acetylenedicarboxylate (7·8g.) was added over 10 min. The solution was stirred for 30 min., then allowed to warm to 20° over 2 hr. The mixture was transfered to a stainless steel autoclave and heated at 120 to 130° for 3½ hr. On cooling the autoclave was opened, and after the contents had been washed out with water and ether, the solution was acidified with sulphuric acid and extracted with ether. The extracts were combined, dried ($MgSO_4$), filtered and the solvent evaporated. The

residues were distilled to give the crude product (7·6g.), b.p. 50-140°/0·015 mm. This was a mixture of a solid and liquid and was recrystallised from light petroleum (b.p. 80-100°) and the crystals obtained (3·5g.) sublimed <u>in vacuo</u> to give two fractions. The first fraction (2·0g.), m.p. 88-90° sublimed at 55°. Recrystallisation from light petroleum (b.p. 80-100°) gave perfluoroacetanilide, identified by its melting point (94-95°, an authentic sample melted at 93-94°), and by its infrared spectrum. The second fraction (1·4g.), m.p. 71-78° sublimed at 70°. Recrystallisation from light petroleum (b.p. 80-100°) gave <u>Diethyl N-(trifluoroacetyl)-N-(2,3,4,5,6-pentafluorophenyl)amino maleate</u>, m.p. 82-83°. (Found: C, 43·3; H, 2·4; F, 33·6; M, 449. $C_{16}H_{11}F_8NO_5$ requires C, 42·8; H, 2·5; F, 33·9%; M, 449).

Gas chromatographic analysis of the original crude material on silicone grease-kieselguhr at 200° showed that it consisted of five products. Three were identified as perfluoroacetanilide, and the fumarate and maleate derivatives. The possibility that another peak corresponded to the cyclised product (I) was discounted by examination of the ^{19}F n.m.r.



I

spectrum of the mixture. Only three bands were observed in the region, corresponding to absorption by aliphatic fluorine atoms, indicating the presence of only three trifluoromethyl groups. These had already been accounted for.

INFRARED SPECTRA

Unless otherwise stated the samples were examined as a potassium bromide disc.

5,6,7,8-Tetrafluoroquinoline 101

5,6,8-Trifluoroquinoline 101

6,7,8-Trifluoroquinoline 101

2-Methyl-5,6,7,8-tetrafluoroquinoline 102

4-Methyl-5,6,7,8-tetrafluoroquinoline 102

7-Methoxy-5,6,8-trifluoroquinoline 102

7-Amino-5,6,8-trifluoroquinoline 103

7-Hydroxy-5,6,8-trifluoroquinoline 103

7-Acetoxy-5,6,8-trifluoroquinoline 103

7-Bromo-5,6,8-trifluoroquinoline 104

A Hexachloroquinoline 104

2,4,5-Trifluoroaniline 104

2,3,6-Trifluoroaniline 105

2,3,4,5-Tetrafluorobenzaldehyde 105

2,3,4,5-Tetrafluorobenzylidineaminoacetal 105

3,4,5,6-Tetrafluoroanthranilic Acid 106

Ethyl 3,4,5,6-tetrafluoroanthranilate 106

2,3,4,5-Tetrafluorophenylglycine 107

N-(2,3,4,5-Tetrafluorophenyl)aminomethyl n-butyl ketone 107

3,4,5,6-Tetrafluorophenylglycine-o-carboxylic Acid 106

Product from cyclisation of 3,4,5,6-Tetrafluorophenylglycine-o-carboxylic Acid 108

Octafluoroindigo 108

Diethyl N-(2,3,4,5,6-pentafluorophenyl)aminofumarate 109

Diethyl N-(trifluoroacetyl)-N-(2,3,4,5,6-pentafluorophenyl)aminofumarate 109

Diethyl N-(trifluoroacetyl)-N-(2,3,4,5,6-pentafluorophenyl)aminomaleate 109

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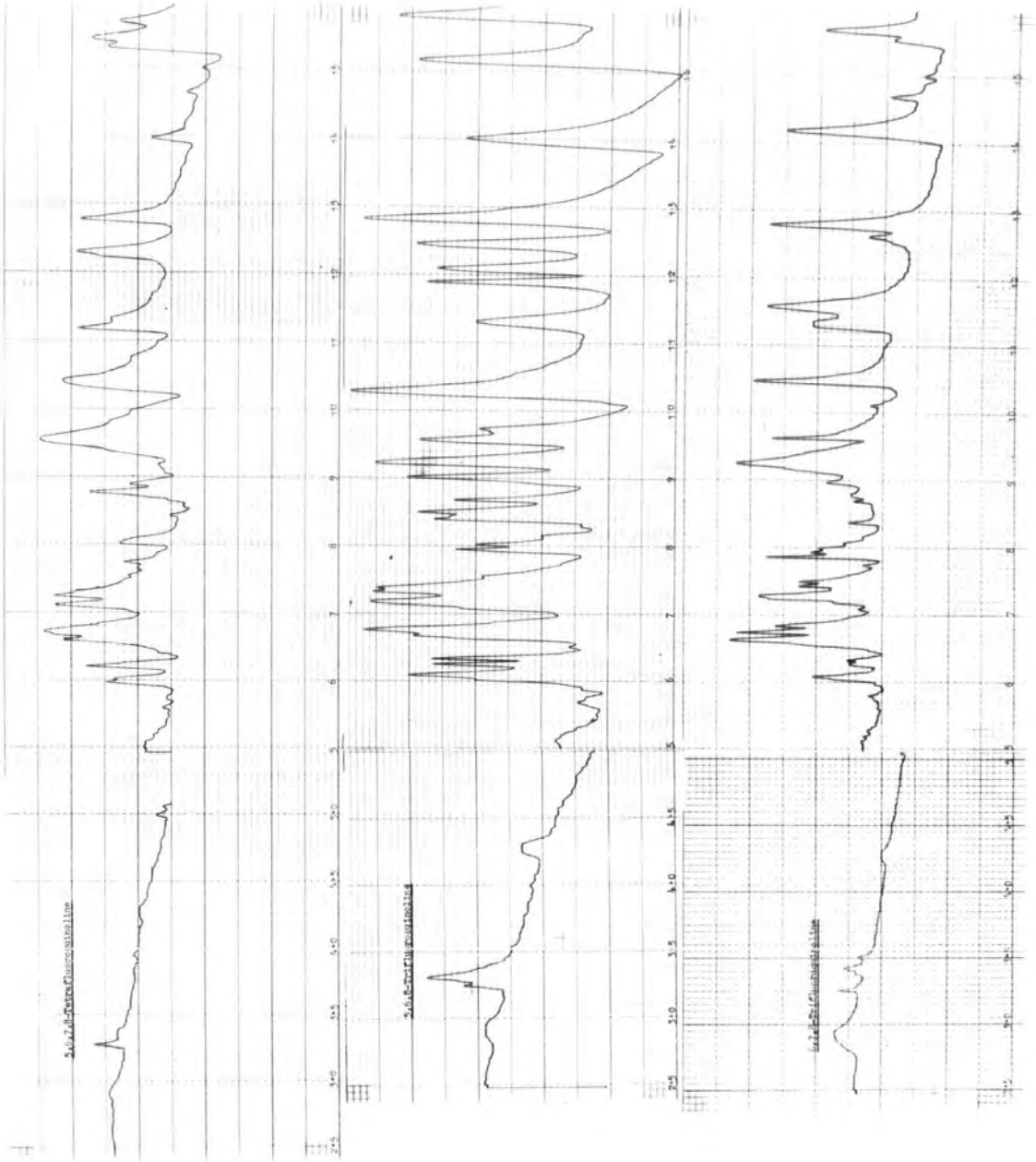

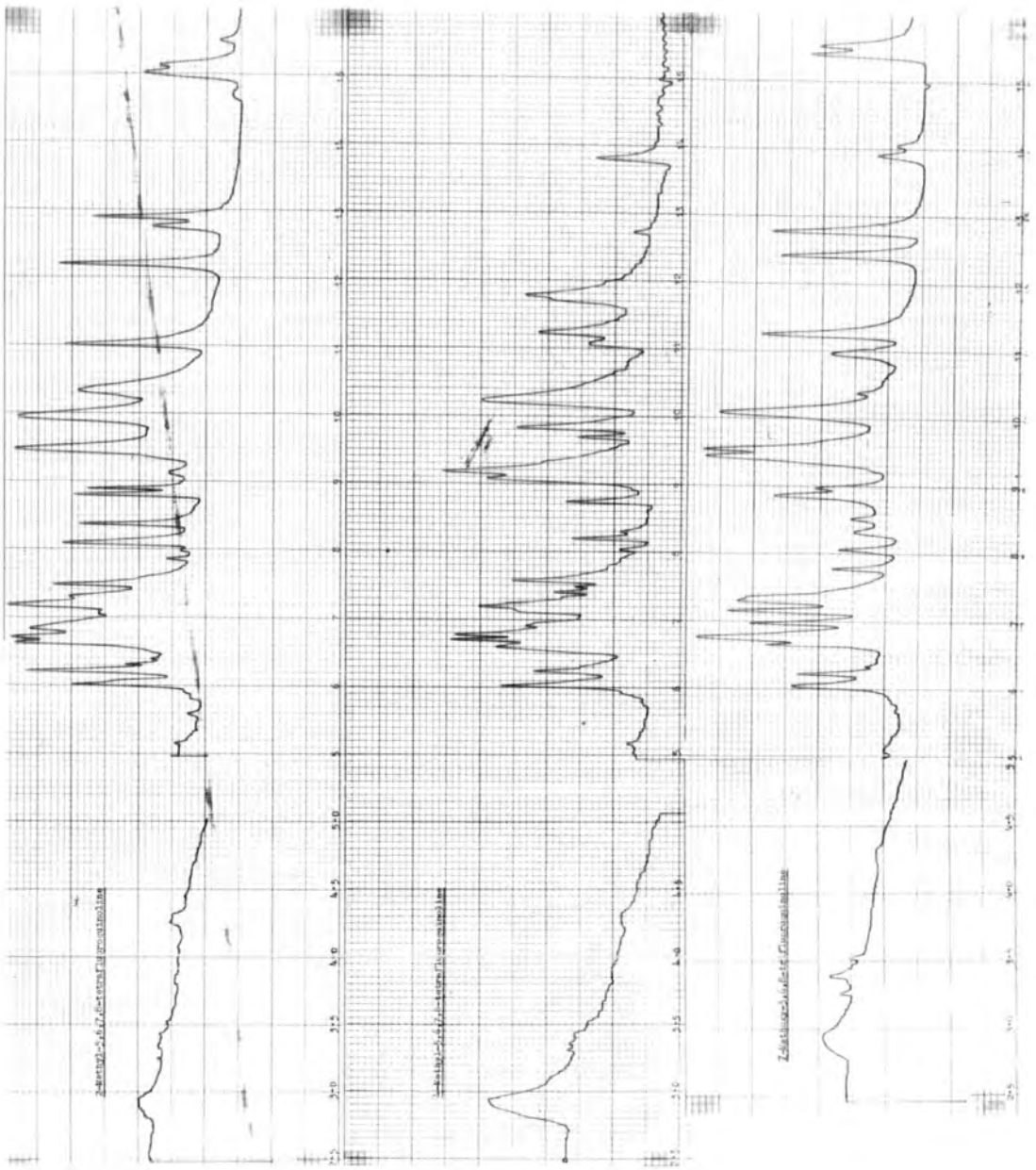

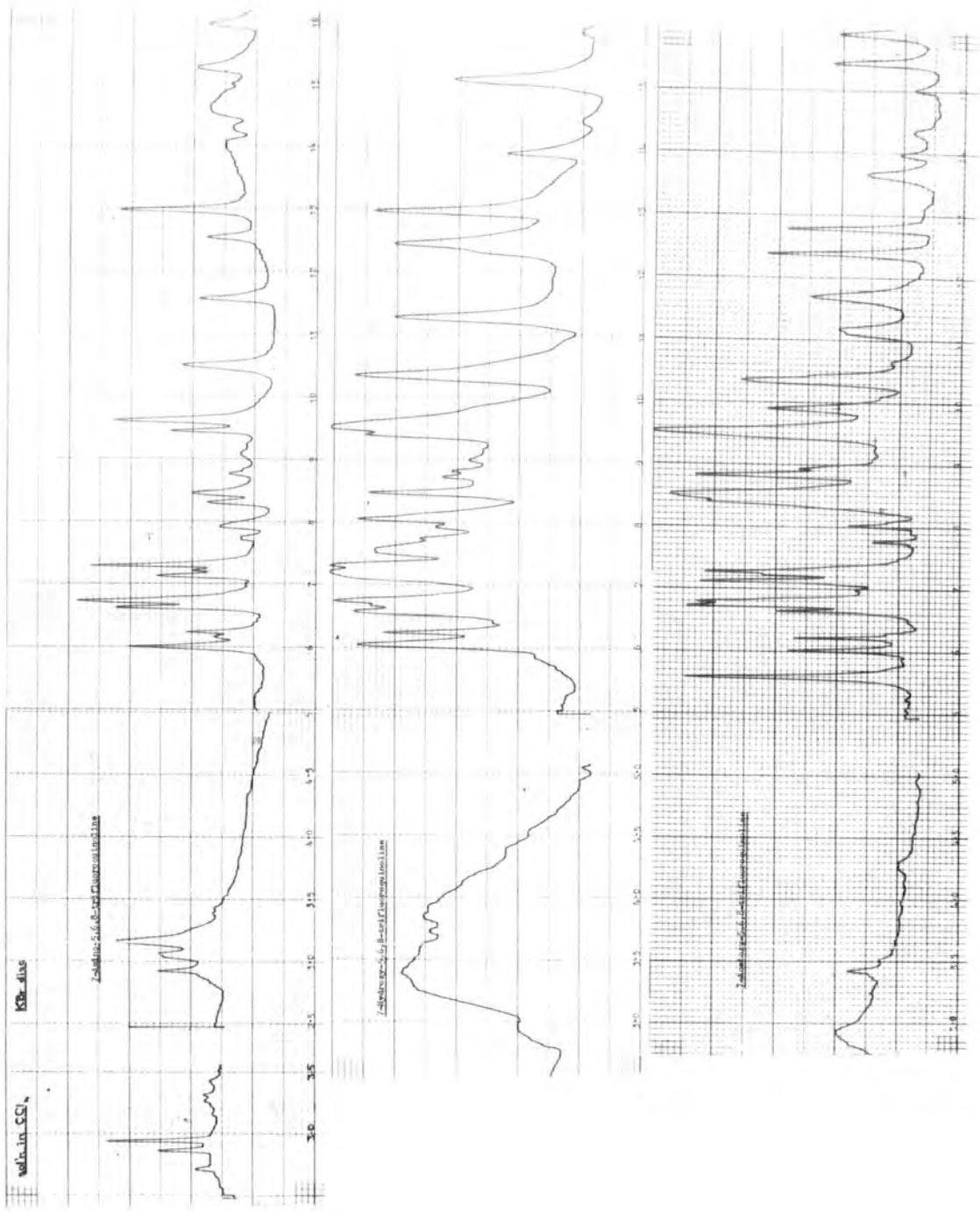

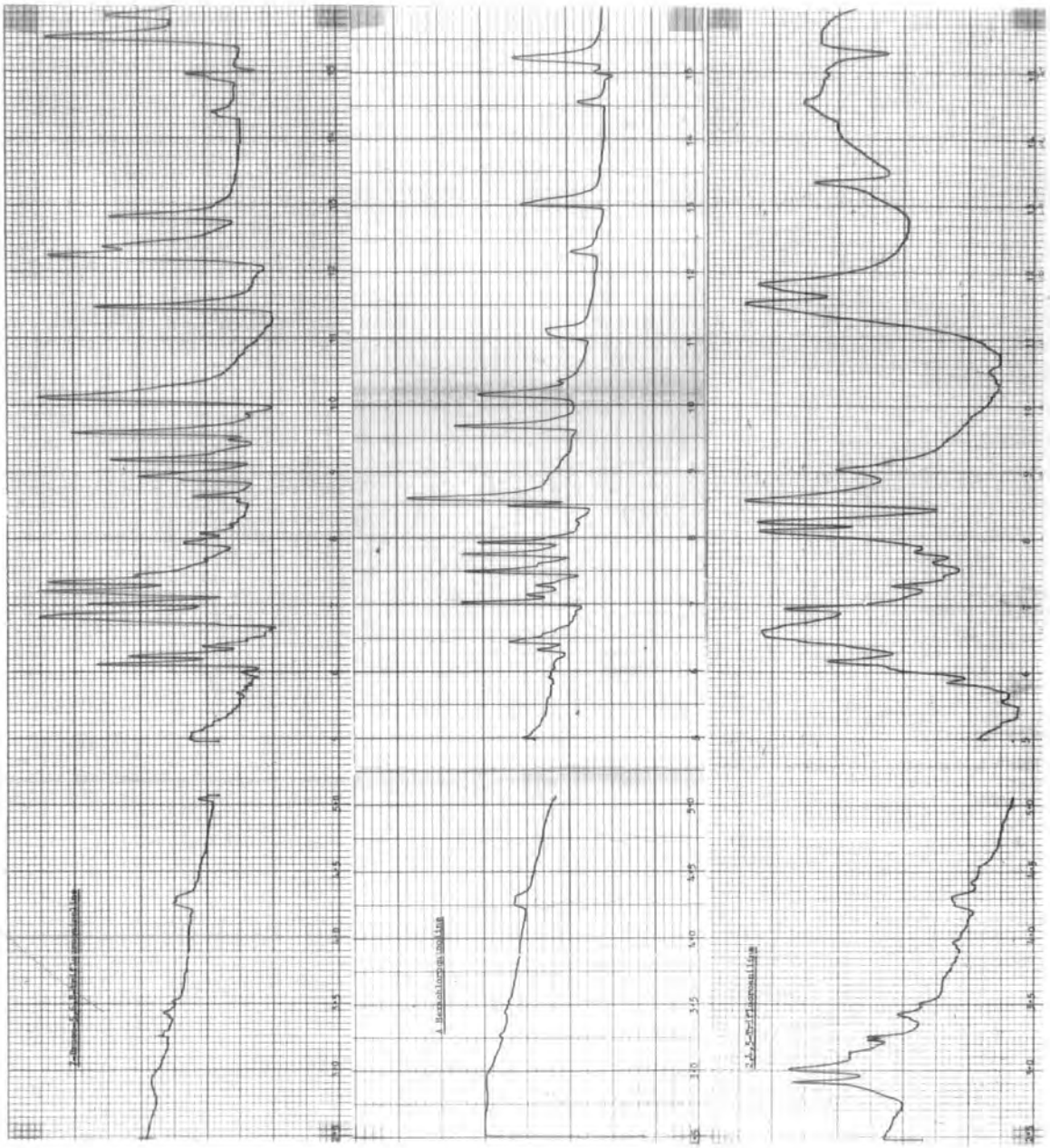

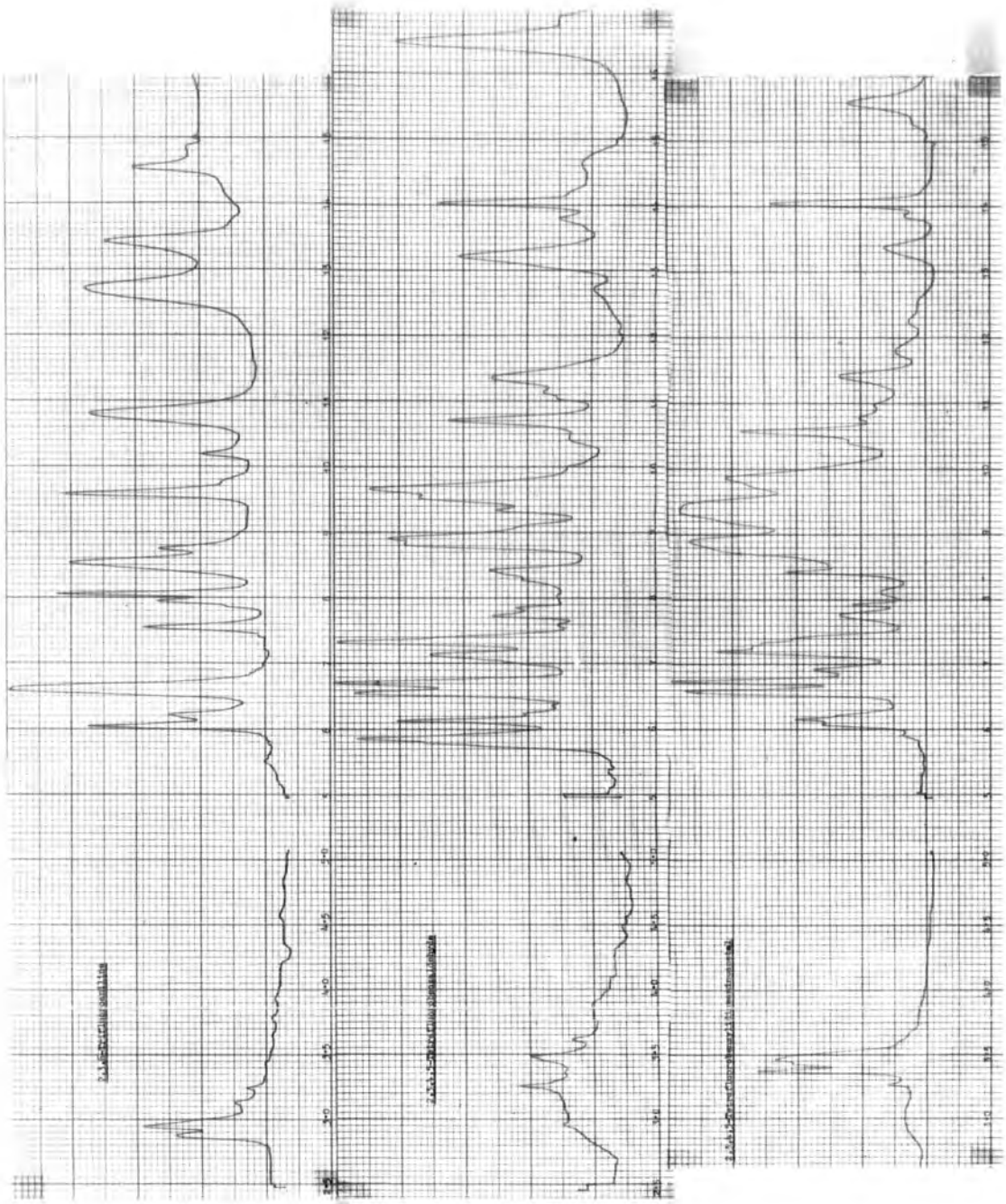

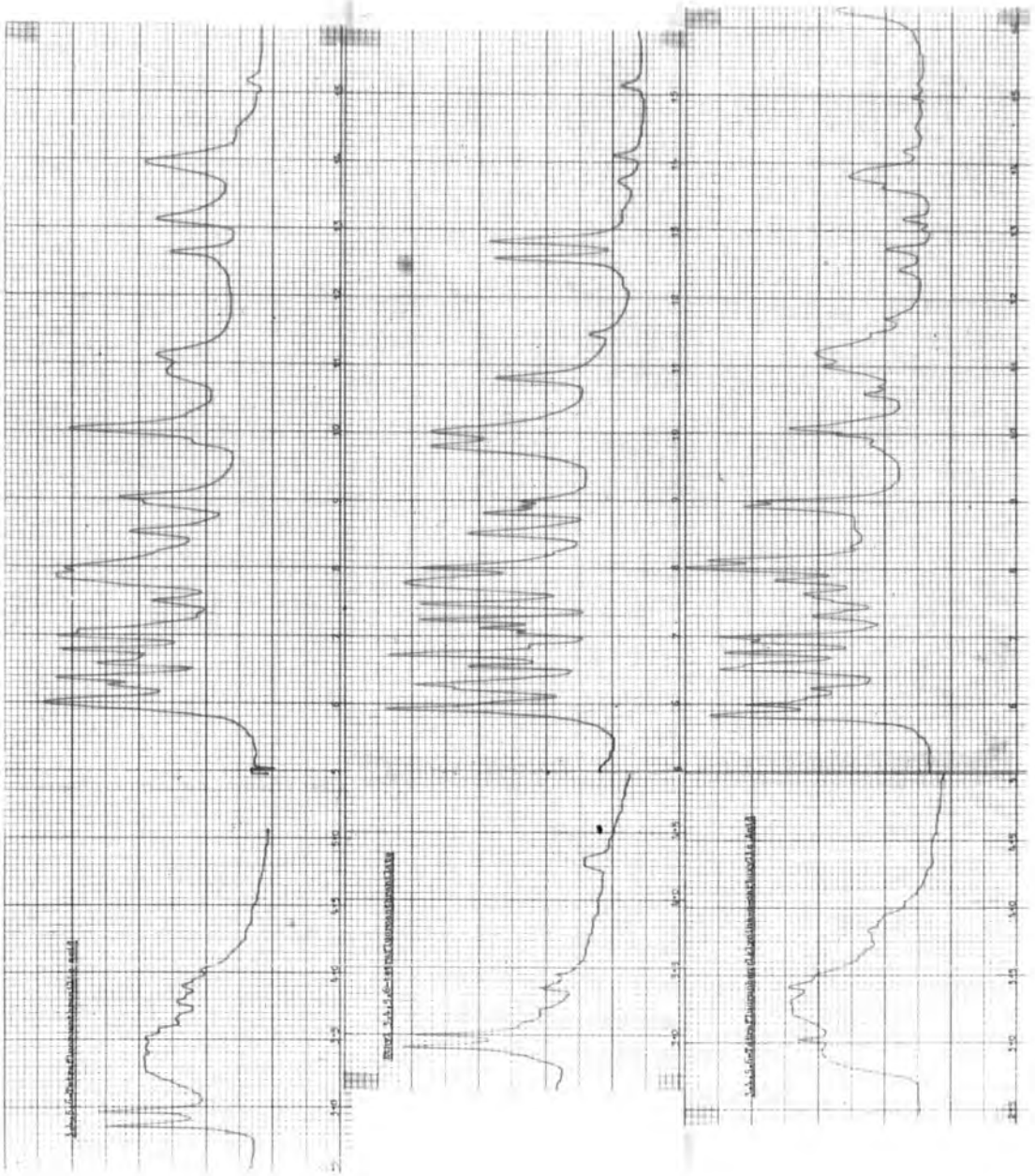

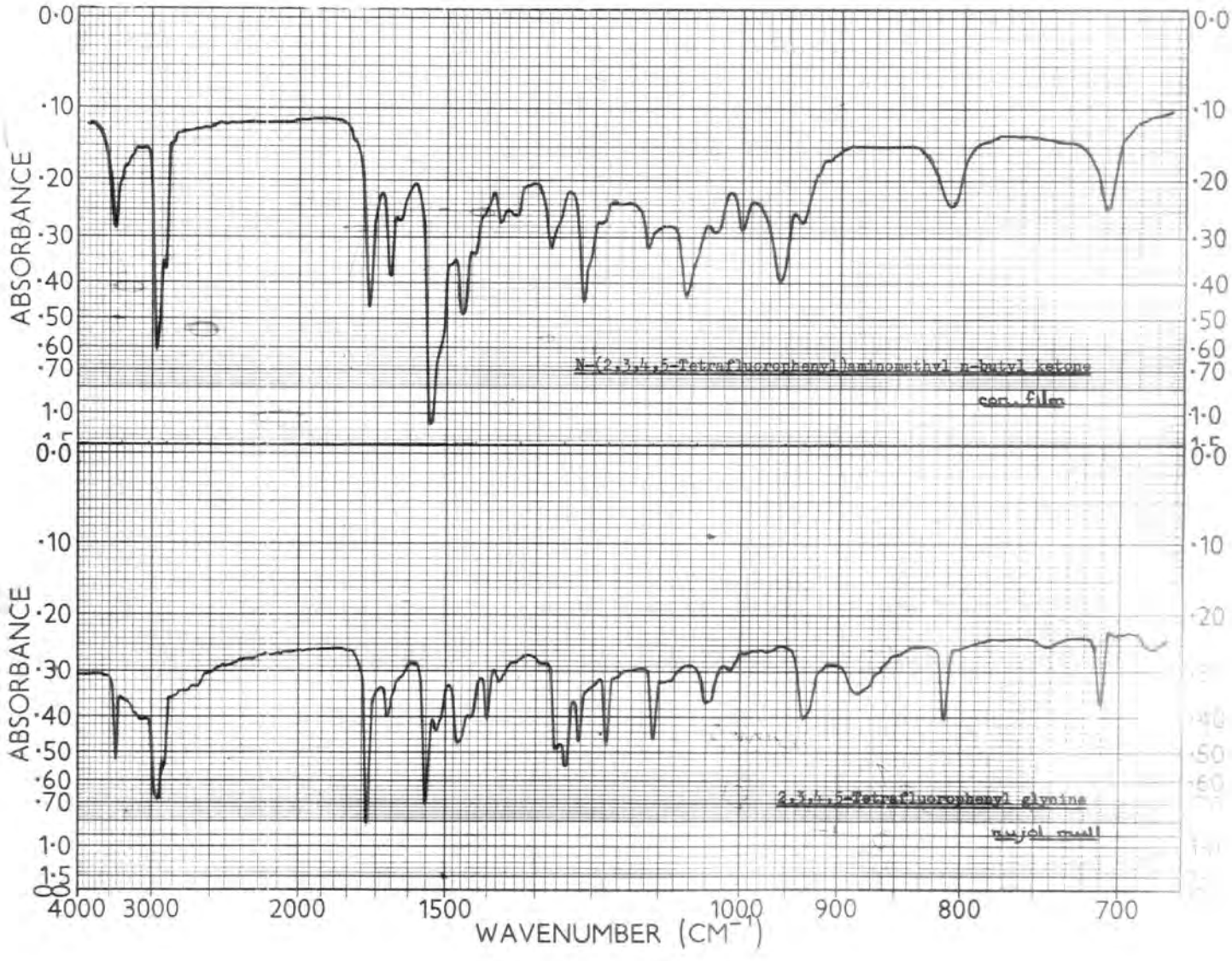
ABSORBANCE
0·0
·10
·20
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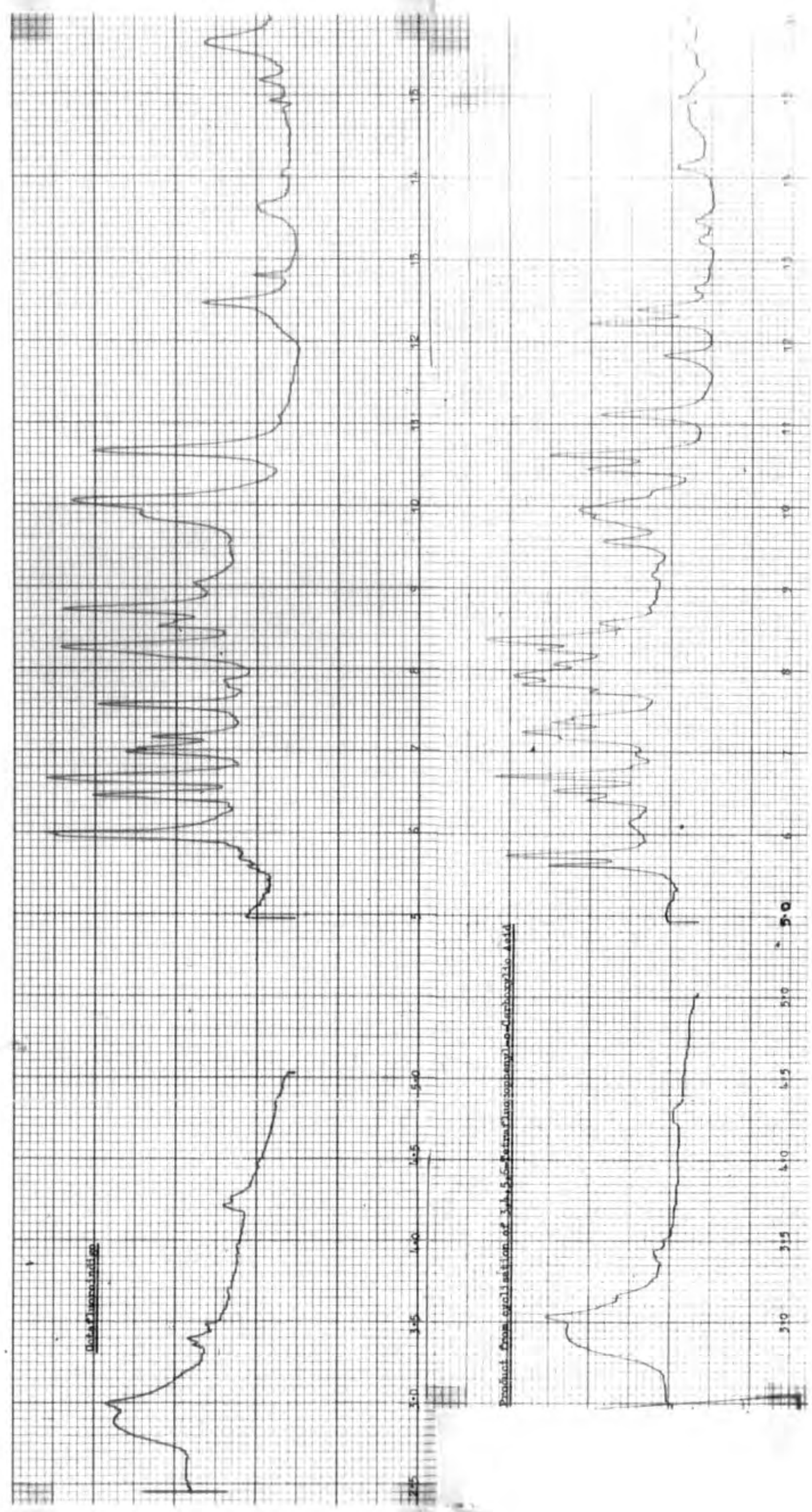
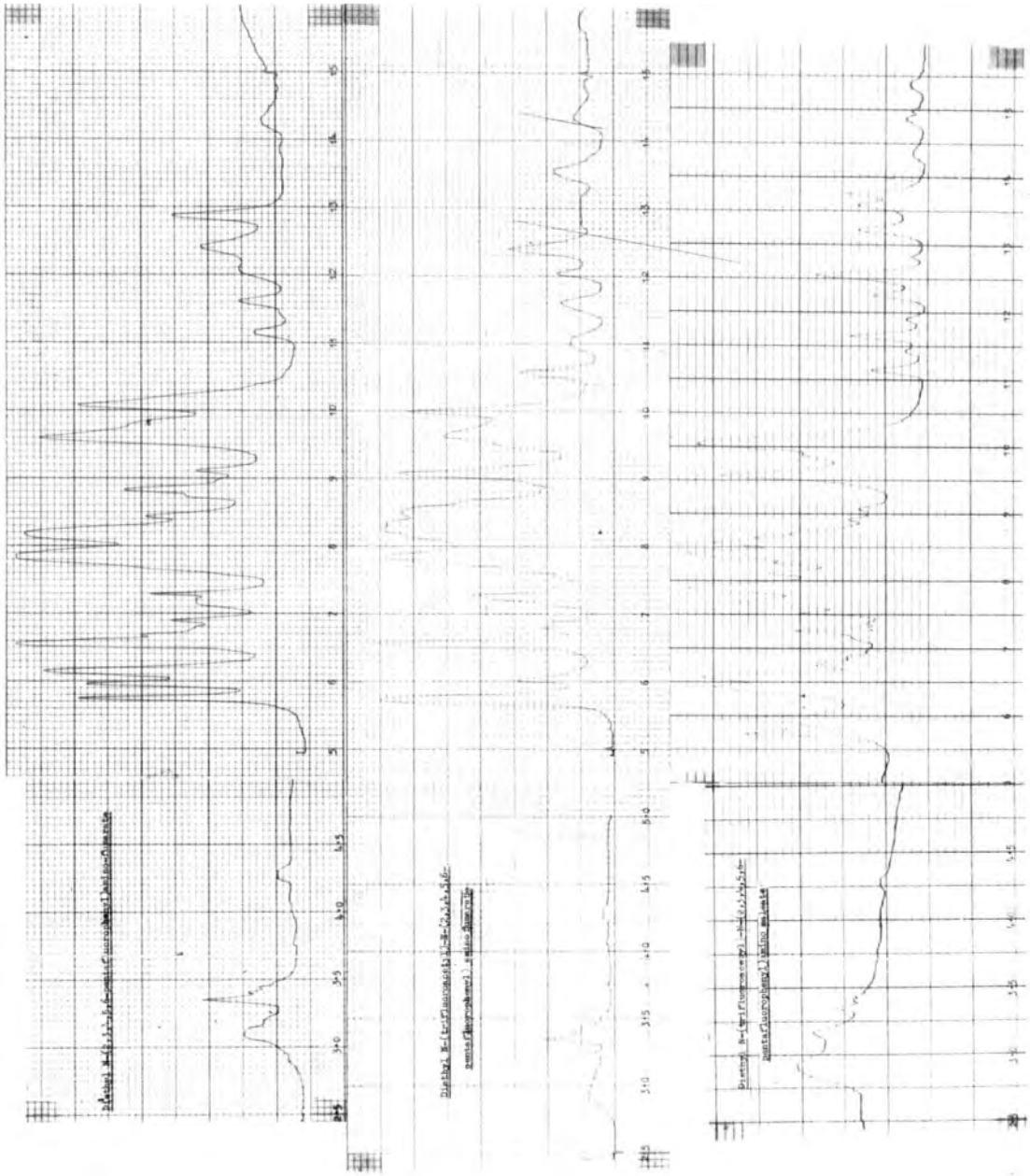
1·0
1·5
N-(2,3,4,5-Tetrafluorophenyl)aminomethyl n-butyl ketone
cap. film
ABSORBANCE
2,3,4,5-Tetrafluorophenyl glycine
nujol mull
4000
3000
2000
1500
1000
900
800
700
WAVENUMBER (CM⁻¹)


Octafluoroindigo
Product from cyclisation of 3,4,5,6-Tetrafluorobiphenyl-o-carboxylic Acid



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