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UNIVERSITY OF DURHAM

A THESIS

entitled

THE PREPARATION AND PROPERTIES OF 4,5,6,7-TETRAFLUOROBENZO[b]THIOPHEN

submitted by

MD. ABUL QUASEM, M.Sc.

(THE GRADUATE SOCIETY)

A candidate for the degree of Doctor of Philosophy

1967

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TO MY PARENTS

ACKNOWLEDGEMENTS

The work recorded in this thesis was carried out under the supervision of Dr. G.M. Brooke and I should like to express my thanks to him for his constant help and encouragement. I should also like to thank Professor W.K.R. Musgrave for his interest. Thanks are also due to many laboratory technicians for their help and co-operation.

I wish to extend my gratitude to the Government of East Pakistan for the provision of a scholarship.

Finally, I am most grateful to my wife, Farhad Banu Begum, who inspired and encouraged me constantly throughout this work from thousands of miles away across the ocean.

MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1964 and March 1967. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

The work has provided subject material for three publications: (i) Tetrahedron Letters, 1965, p-2991 (With G.M. Brooke, B.S. Furniss and W.K.R. Musgrave), (ii) J. Chem. Soc., C, 1967, p-865 (With G.M. Brooke) and (iii) Tetrahedron Letters in press (With G.M. Brooke).

SUMMARY

4,5,6,7-Tetrafluorobenzo[b]thiophen has been prepared by two routes:

Route A.

2,3,4,5-Tetrafluorothiophenol was prepared from 2,3,4,5-tetrafluorophenyl-lithium and elemental sulphur. The thiol gave 2,3,4,5-tetrafluoro-6-mercaptobenzoic acid on treatment with butyl-lithium followed by reaction with carbon dioxide. The mercaptobenzoic acid was converted into its ethyl ester, which was reacted with ethyl chloroacetate to give two products, ethyl (6-ethoxycarbonyl-2,3,4,5-tetrafluorophenylthio)acetate and 2-ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl. The former, the major product, was converted to the latter by the treatment with sodium hydride in tetrahydrofuran. The thioindoxyl was converted into 4,5,6,7-tetrafluorobenzo[b]thiophen, in very low yield, by treatment with zinc dust in a mixture of acetic acid, sulphuric acid, and water, which effected ester hydrolysis, decarboxylation and reduction.

Route B.

The reaction of lithium pentafluorobenzenethiolate with diethyl acetylenedicarboxylate gave diethyl 4,5,6,7-tetrafluorobenzo[b]thiophen-2,3-dicarboxylate. Hydrolysis of the diester with acid gave the corresponding dicarboxylic acid (isolated as a monohydrate from water) which was converted into 4,5,6,7-tetrafluorobenzo[b]thiophen using copper powder in quinoline.

4,5,6,7-Tetrafluorobenzo[b]thiophen, when treated with sodium methoxide in methanol gave 6-methoxy-4,5,7-trifluorobenzo[b]thiophen and two unidentified isomers in the ratio of 86:7:7 respectively. 4,5,6,7-Tetrafluoro-

benzo[b]thiophen was also treated with acetyl chloride and anhydrous aluminium trichloride in carbon disulphide to give 3-acetyl-4,5,6,7-tetrafluorobenzo[b]thiophen in good yield. Traces of 2-substituted product might have been formed. When oxidised with hydrogen peroxide (90%) in presence of trifluoroacetic anhydride in methylene chloride, 4,5,6,7-tetrafluorobenzo[b]thiophen gave the corresponding sulphone.

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CHAPTER I

PREPARATION OF FLUORINATED AROMATIC HETEROCYCLIC COMPOUNDS

PREPARATION OF FLUORINATED AROMATIC HETEROCYCLIC COMPOUNDS

The methods of preparation of fluorinated hetero-aromatic compounds are, in most cases, the extensions of those available for the synthesis of aromatic fluorocarbon compounds. These methods may be divided into two broad sections:

A. Overall replacement of hydrogen by fluorine in alicyclic or aromatic hydrocarbons.

B. Replacement of halogens in aromatic compounds by fluorine.

An additional method is also available for fluorinated hetero-aromatic compounds:

C. Ring Synthesis.

A. REPLACEMENT OF HYDROGEN BY FLUORINE

(i) Decomposition of Diazonium Salts

The most common method for the introduction of a single or a small number of fluorine atoms into the aromatic nucleus has been the use of Balz-Schiemann reaction[1]. The method involves two steps: firstly, the preparation of a dry diazonium fluoroborate; and secondly, the controlled decomposition of this salt by heat to yield an aromatic fluoride, nitrogen and boron trifluoride.

$$C_6H_5\overset{+}{N}\equiv\bar{N}\cdot Cl + HBF_4 \longrightarrow C_6H_5\overset{+}{N}\equiv NBF_4^{-}\downarrow$$

$$C_6H_5\text{-}\overset{+}{N}\equiv NBF_4^{-} \xrightarrow{\text{heat}} C_6H_5F + N_2\uparrow + BF_3$$

These fluorine compounds can be nitrated and reduced to give amines and

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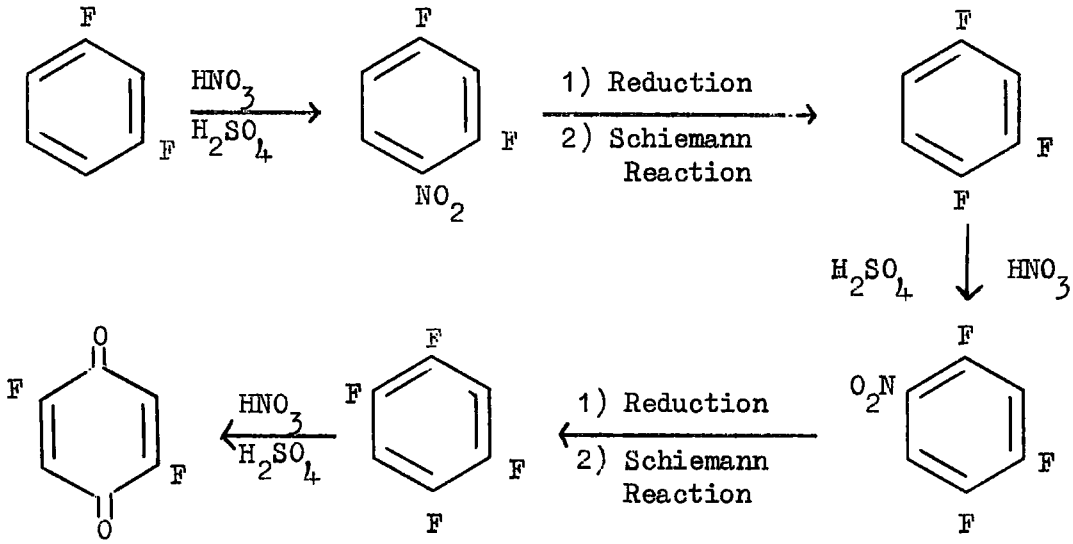
the conversion sequence can be applied again. In this way the reaction has been used to effect stepwise replacement of four hydrogen atoms in benzene by fluorine[2,3]. Extension of this method to give pentafluorobenzene and hence to fully fluorinated aromatic compounds, proved impossible owing to the elimination of two parafluorine atoms during the attempted nitration of 1,2,4,5-tetrafluorobenzene.



The application of Balz-Schiemann reaction in the heterocyclic field, has met with less success. Relatively few fluorine-substituted five-membered heterocyclic compounds have been prepared by means of this reaction. More success has been reported in six-membered heterocyclic systems such as pyridine[4,5,6], and in condensed heterocyclic systems such as quinoline, all the monofluoro derivatives (except 4-fluoroquinoline) have been prepared[7].

Diazonium hexafluorophosphates and hexafluorosilicates have been

used as alternatives to fluoroborates but with no real advantage[8].

A review article on the Balz-Schiemann reaction was published by Roe[9] some time ago and recently the subject has been reviewed by Suschitzky[10].

(ii) Fluorination with Elemental Fluorine

All early attempts at direct fluorination of organic compounds with undiluted elemental fluorine were unsuccessful. The failure was due to the exceedingly high heat of reaction which caused thermal decomposition of both starting material and the products. To avoid this, two techniques were evolved, vapour-phase fluorination in a packed vessel; and a simple liquid-phase reaction in which fluorine, usually diluted with nitrogen, was bubbled through an organic compound normally in a solution[8].

Direct vapour-phase fluorination over a metal packing, usually called the "Catalytic Method", was developed by Bigelow[8] and produced compounds with a high degree of fluorination. Usually, the reaction was carried out by mixing the reactants, both heavily diluted with nitrogen, in a heated metal tube, filled with some form of finely divided metal such as gauze, turnings, or shot. The reaction proceeds via a free radical chain mechanism. Progressive replacement of

$$CH_4 \xrightarrow{F\cdot} HF+CH_3\cdot \xrightarrow{F_2} CH_3F+F\cdot \longrightarrow \text{etc.} \longrightarrow CF_4$$

hydrogen and saturation of any multiple bonds or aromatic systems by fluorine, occurs. The main function of the catalyst is probably to

disperse the heat of reaction, although some fluorination possibly occurs via intermediate formation of surface films of metal fluorides. Musgrave and Smith[11] while studying the fluorination of benzene found little variation in the overall yield of fluorinated material by using various catalysts including silver, gold, nickel, cobalt and steel wool which indicated that these were not true catalysts.

Haszeldine and Smith fluorinated many substituted benzenes using a gold catalyst and obtained high yields of perfluoro alicyclic compounds; no aromatic compounds containing fluorine were isolated. However, Haszeldine had little success when he attempted to fluorinate nitrogen heterocyclic compounds[13,14] e.g. pyridine[14].

Bigelow and co-workers have recently developed unpacked fluorinators with special inlet jets for reactants which promote mild fluorination and this has been considered to be the best method of direct fluorination so far[8].

The liquid phase fluorination has many problems, the principal of which is to find a solvent which has sufficient stability towards fluorine and at the same time, is a good solvent for fluorocarbons. Due to these problems the method has not been used extensively.

A recent review on the fluorination of organic compounds by elemental fluorine has been published by Tedder[15].

(iii) Fluorination by High-valency Metallic Fluorides

The most important member of this group of fluorinating agents is Cobalt trifluoride, Manganese trifluoride, Cerium trifluoride and Lead

tetrafluoride have also been used to a lesser extent. These fluorides react directly with organic compounds at 100 - 400°, and revert to a fluoride of lower valency:

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

$$>C{=}C< + 2MF_n \longrightarrow >CF{-}CF< + 2MF_{n-1}$$

All of this group of fluorides are capable of effecting exhaustive fluorination, hydrogen being replaced by fluorine, and unsaturated groups, including aromatic rings, being saturated.

Reactions between metal fluorides and organic compounds can be carried out with the latter in either the vapour or liquid phase, though the vapour phase process has been by far the more useful[8].

In the liquid phase process the reagent is added to a heated, stirred sample of the material to be fluorinated, which may be dissolved or suspended in an inert diluent, usually a high-boiling fluorocarbon.

In the vapour phase fluorination a stream of the organic compound is swept over a heated stirred bed of the fluoride in a tube. The exhausted metal fluoride is regenerated by passing fluorine through the same apparatus, e.g.,

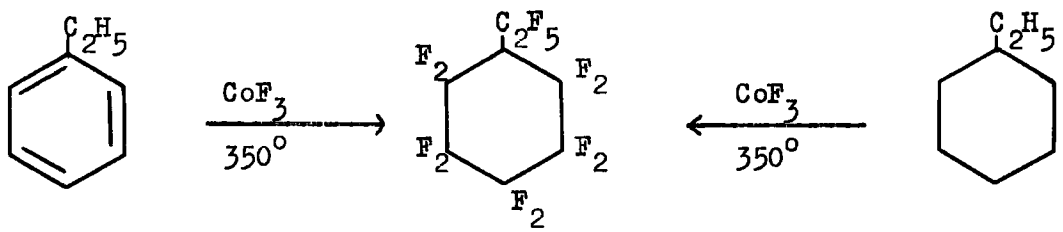
$$-\overset{|}{\underset{|}{C}}H + 2CoF_3 \longrightarrow -\overset{|}{\underset{|}{C}}F + HF + 2CoF_2$$

(ΔH = -58 Kcal/mole
cf. ΔH for Direct fluorination
= -104 Kcal/mole)

$$2CoF_2 + F_2 = 2CoF_3; \quad \Delta H = -52 \text{ Kcal/mole}$$
$$473^\circ$$

Much less heat (almost half) is generated in this process compared with that in the fluorination using elemental fluorine. Thus extensive C-C bond fission is avoided and hence higher yields of fluorinated products are obtained.

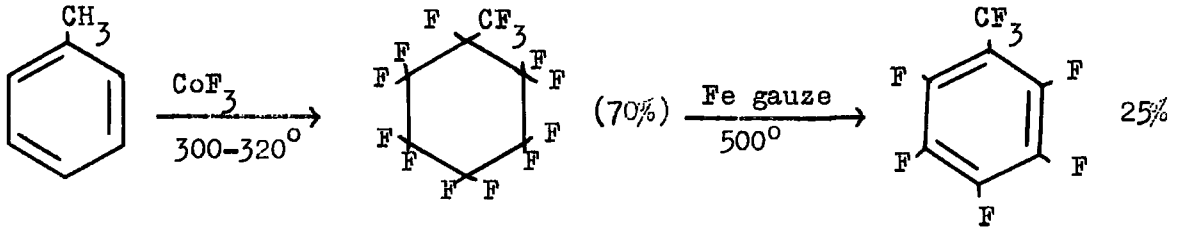
Using cobalt trifluoride at 300 - 350°[16] complete fluorination usually results but at lower temperatures partial fluorination occurs to give hydrogen-containing products. With an aromatic hydrocarbon complete fluorination gives a product which is the same as that obtained from the corresponding cycloparaffin i.e. a fully fluorinated alicyclic compound. (These latter compounds are also formed by electrochemical fluorination, discussed later, and by fluorination using elemental fluorine described earlier).



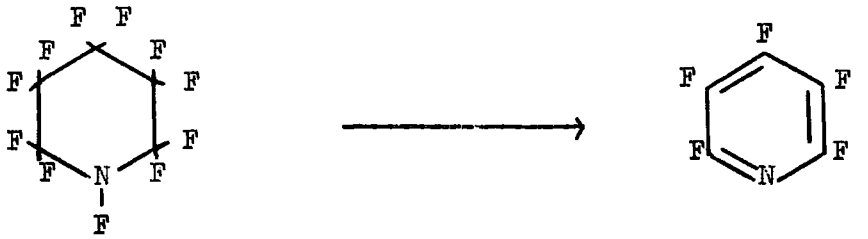
Workers in Birmingham discovered in late 1950's that saturated fluorocarbons could be defluorinated with hot finely divided nickel or iron[17]. This discovery led to the development of a general preparative route to aromatic and heteroaromatic fluorocarbons.

The method of defluorination consists in passing the fluorocarbon in a stream of nitrogen through a metal tube packed with small pieces of iron gauze, heated to a temperature in the range of 400 - 600°. In this

way Tatlow and his co-workers[17] prepared perfluorotoluene from perfluoromethylcyclohexane, perfluoronaphthalene from perfluorodecalin and perfluorobiphenyl from perfluorodicyclohexyl.



This defluorination technique was also successfully applied to perfluoropiperidine both by Tatlow and co-workers[18] and by Haszeldine and co-workers[19], to give among other break-down products pentafluoropyridine:



The starting material for this reaction was obtained by the electrochemical fluorination of pyridine (discussed later).

Aromatization has also been effected by dehydrofluorination of polyfluorocyclohexanes. When benzene is fluorinated over CoF_3 at 150 - 200°[20,21] polyfluorocyclohexanes, $C_6H_nF_{12-n}$ (n = 1-4), are formed. (A small amount of perfluorocyclohexane is also formed. For maximum yield of this compound temperatures of 300 - 350° would be used). Aromatization is then recreated by elimination of hydrogen fluoride with alkaline reagents[22] as shown in the following figures[23].

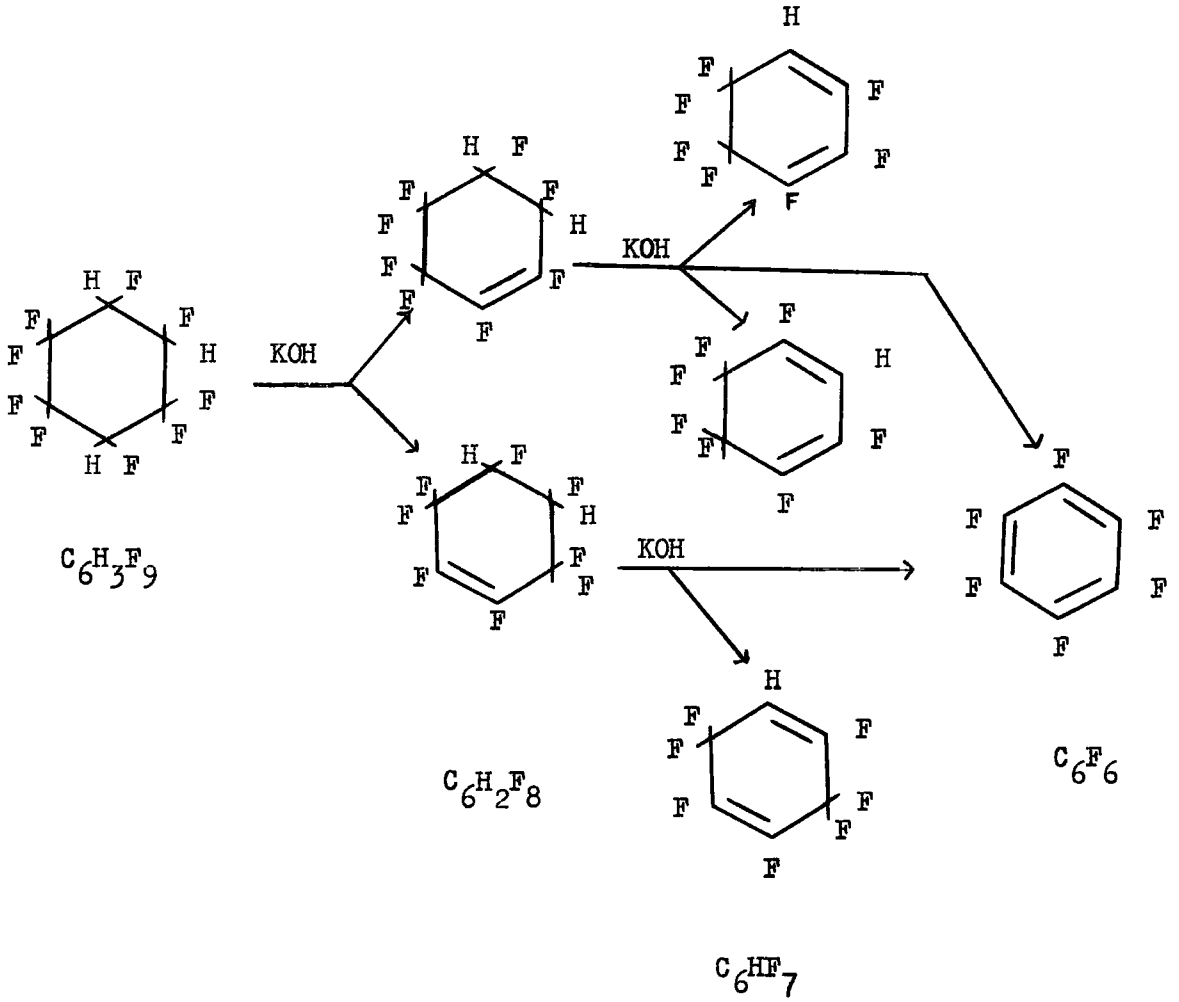


Fig.1

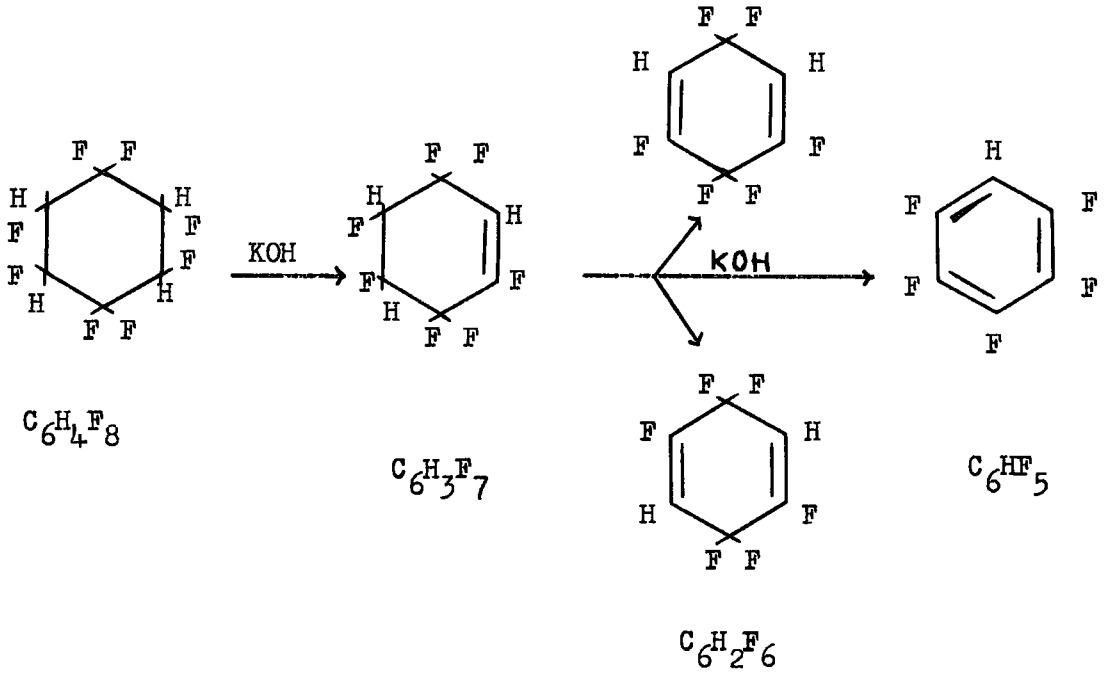

KOH
KOH
$C_6H_4F_8$
$C_6H_3F_7$
$C_6H_2F_6$
C_6HF_5

Fig. 2

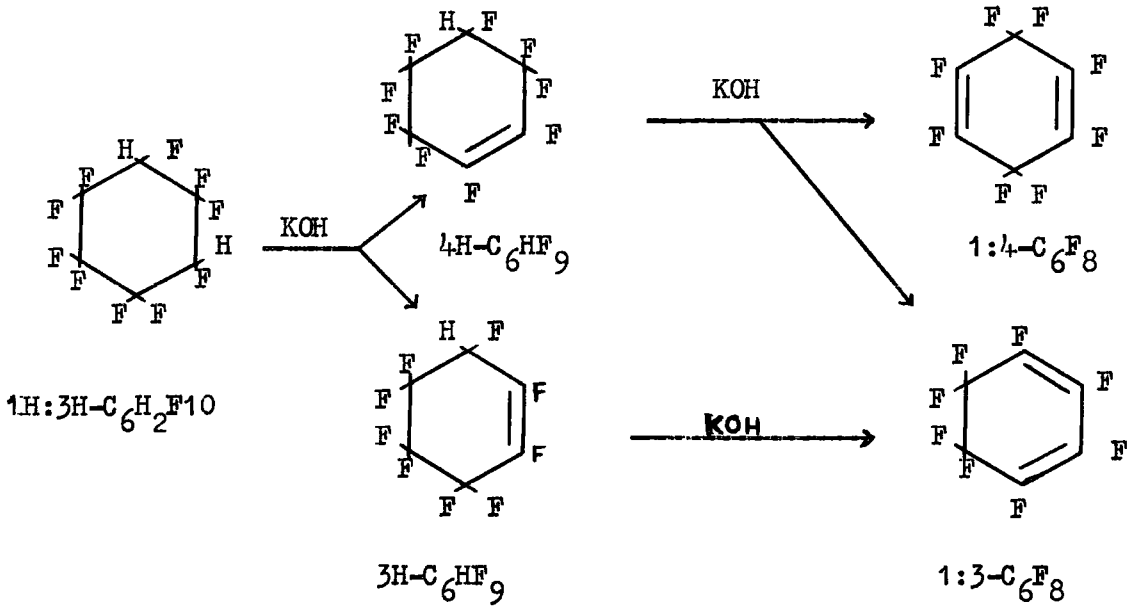
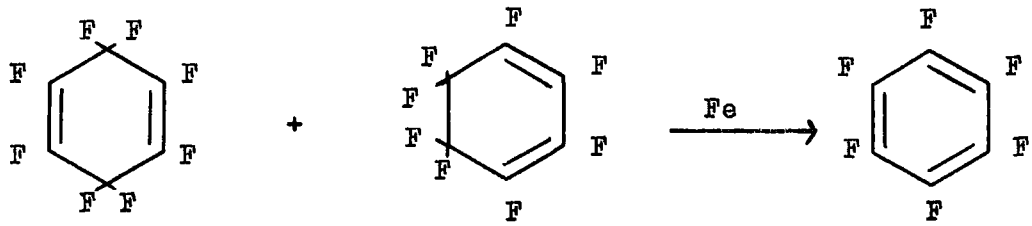
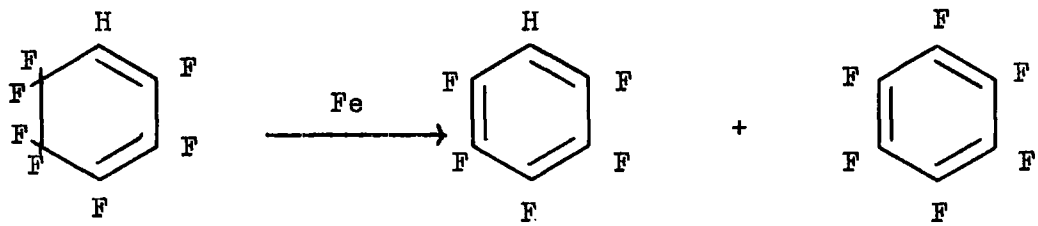

KOH
KOH
KOH
1H:3H-C_6H_2F10
4H-C_6HF_9
3H-C_6HF_9
1:4-C_6F_8
1:3-C_6F_8

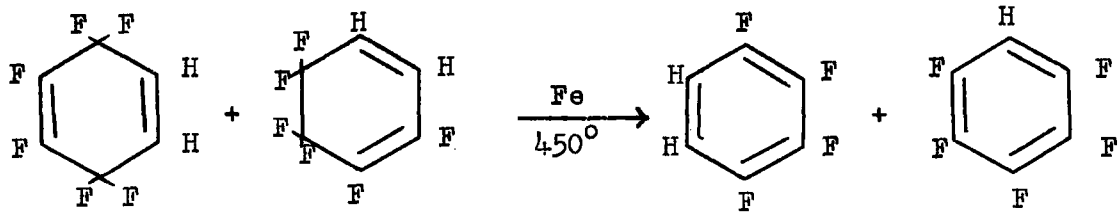
Fig.3

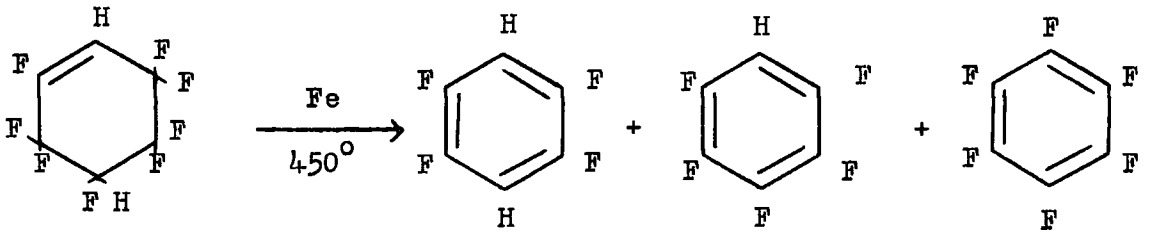
The unsaturated alicyclic fluorides (olefins or diolefins), obtained by dehydrofluorination of polyfluorocyclohexanes (above) can also be defluorinated over heated iron or nickel to effect aromatization.

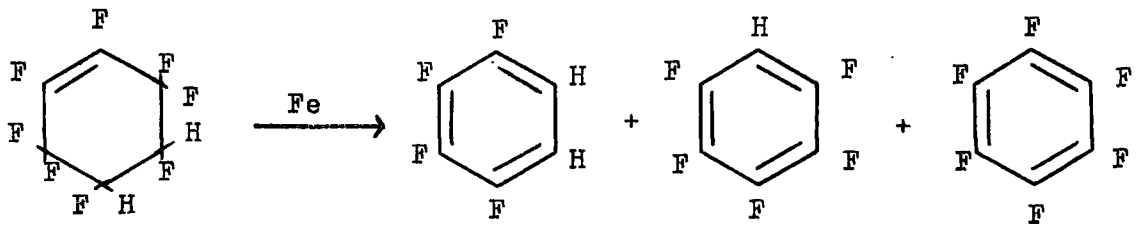


The defluorination procedure is not limited in its application to compounds containing only carbon and fluorine as is shown by the following examples[24]:



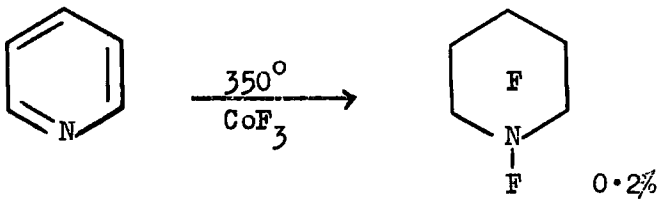






The products from many of these reactions were separated by the use of preparative scale chromatography.

Although the cobalt trifluoride method of fluorination has been a large success in the preparation of fluorocarbons from aromatic hydrocarbons[25,30] (yields generally in the region of 50 - 70%), the success was limited when this method was applied to the heterocyclic compounds[14,29,33] e.g.

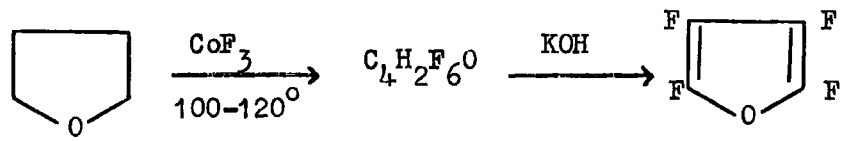


Ref. 14

N.B. All unmarked bonds are attached to fluorine.

When thiophen[32] was reacted with CoF_3 extensive decomposition took place and no fluorothiophens were obtained.

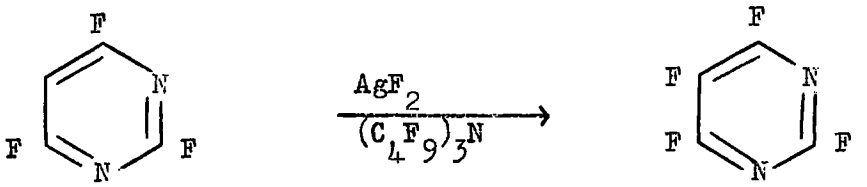
Benzo[b]thiophen[33] has been reacted in the vapour phase with CoF_3 without any success. Complete elimination of sulphur took place and perfluoroethyl cyclohexane was the principal product. The first synthesis of tetrafluorofuran has recently been reported by the workers at Birmingham[34]. The process is outlined below:-



Tetrahydrofuran 15% 25%

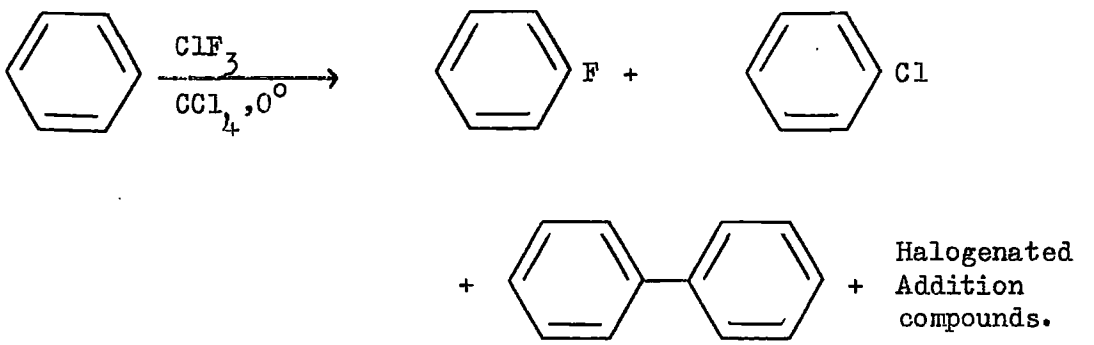
Fluorination over Other High-valency Metal Fluorides

The fluorinations with metal fluorides other than CoF_3 are less common. The reason is that none of the listed fluorides give better results than CoF_3. Silver difluoride is a good fluorinating reagent but it has been displaced in practice by the equally efficient but cheaper CoF_3. One use of AgF_2 is the direct replacement of hydrogen by fluorine in the liquid-phase fluorination of 2,4,6-trifluoropyrimidine. The aromatic ring system is preserved[8]:



A review on fluorination by high-valency metallic fluorides has been published.[16]

Halogen fluorides have also been used as fluorinating agents for organic compounds. Musgrave and Ellis[35] reacted benzene with chlorine-trifluoride in carbon tetrachloride solution, and in the presence of various catalysts.



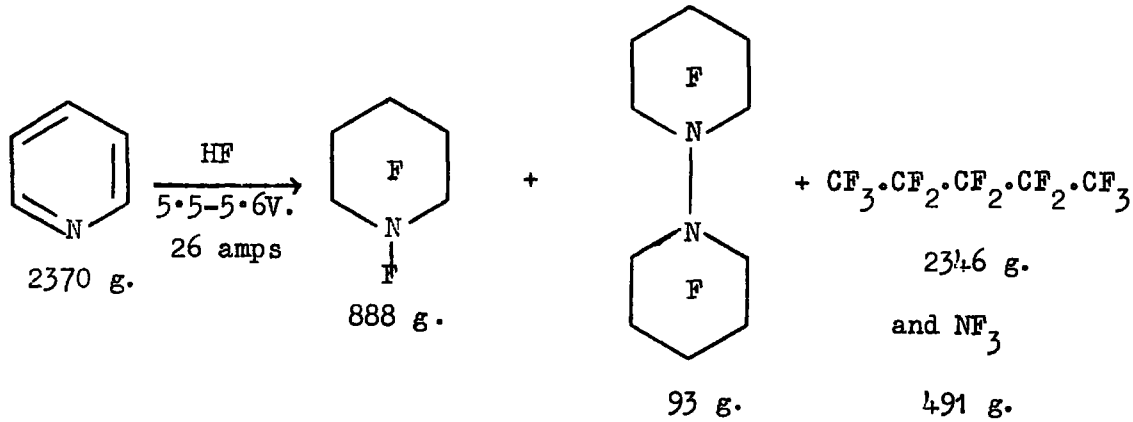
The reaction of pyridine with ClF_3 was investigated by Beaty[5] who obtained low yields (4 - 10%) of 2-fluoropyridine by passing ClF_3, diluted with nitrogen, into a solution of pyridine in carbon tetrachloride at 0°. A review on the subject has been published by Musgrave.[36]

(iv) Electrochemical Fluorination

Many organic compounds, particularly those containing polar groups, dissolve in anhydrous hydrogen fluoride to give conducting solutions. When such a solution is electrolysed at a low voltage (usually 5-6 V) so that free fluorine is not liberated, hydrogen is evolved at the cathode and the organic compound is fluorinated at the anode. This method was discovered by Simons in 1941[37]. It resembles fluorination with elemental fluorine or cobalt trifluoride in that all hydrogen in the organic compound is replaced by fluorine, any multiple bonds or aromatic systems are saturated with fluorine, and partial fragmentation of the carbon skeleton occurs. However, one important feature of the method is that the original functional groups are effectively retained.

Hydrocarbons are difficult to fluorinate electrochemically since they are not very soluble in anhydrous hydrogen fluoride and the solutions are non-conducting. However, suspensions or emulsions can be used, in the presence of a conductivity additive, such as an alkali-metal fluoride.

The method of electrochemical fluorination proved quite successful in the fluorination of heterocyclic bases. Simons and his co-workers[37] obtained along with the required product perfluoropiperidine, perfluorodipiperidyl and several decomposition products (perfluoropentane was the most abundant) starting from pyridine.



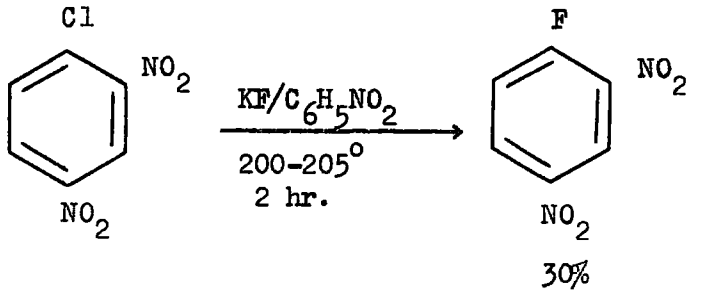
Haszeldine[19] reported an 8% yield of perfluoropiperidine from the electrolysis of pyridine in hydrogen fluoride.

A recent review on electrochemical fluorination of organic compounds has been published[39].

B. REPLACEMENT OF HALOGEN BY FLUORINE

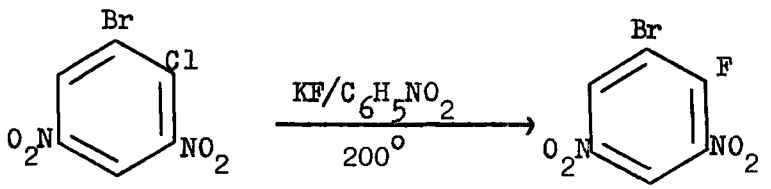
The method of halogen exchange[40] involves reaction under anhydrous conditions of an aromatic halide, usually the chloride, with a metal fluoride, generally potassium fluoride, either in a suitable solvent heated under reflux, or as an intimate mixture at elevated temperatures.

Gottlieb[41] was the first to observe this type of halogen exchange in 1936. The nature of the solvent used in these reactions greatly



Ref.36

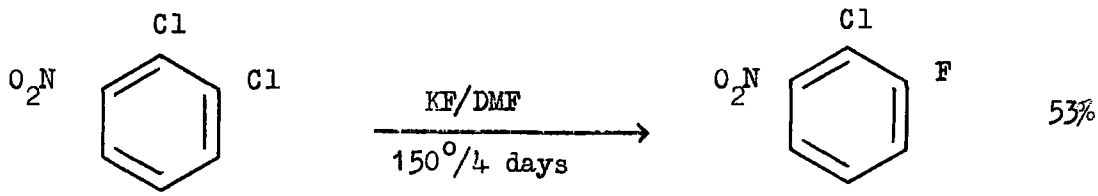
affect the extent of halogen replacement. Thus, using nitrobenzene as the solvent Channing and Young[42] successfully carried out the following reaction

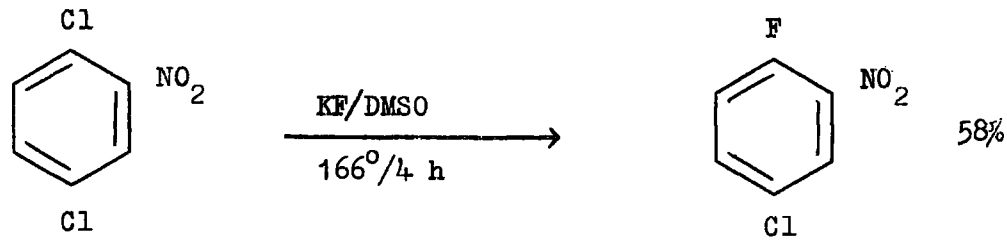


46%

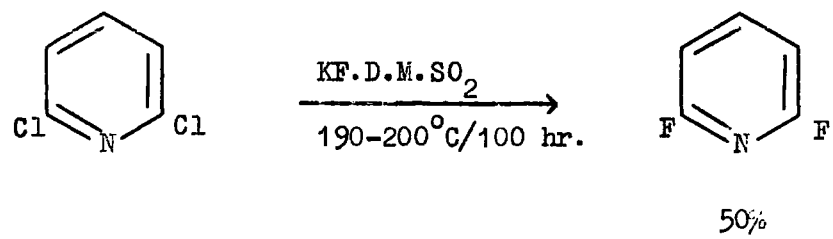
but failed to obtain any halogen exchange between 3,5-dibromo-4-chloronitrobenzene and KF. This illustrated that using nitrobenzene as solvent, activation by at least two nitro groups was necessary for exchange between aryl halide and fluoride ion to occur.

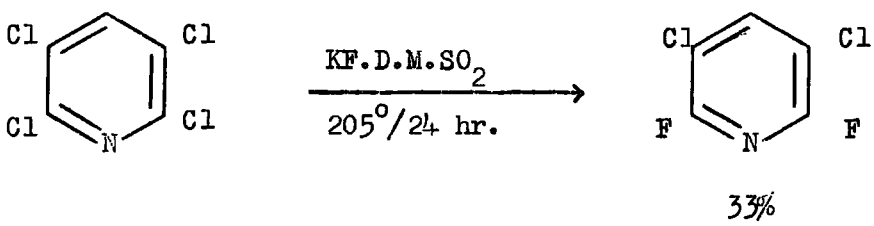
Finger and co-workers[43,44] extended the exchange reactions to less activated mononitro aromatic halides by using KF in the dipolar aprotic solvents dimethylformanide (D.M.F.) or dimethylsulphoxide (D.M.S.O.)





Dimethyl sulphone (D.M.SO_2)has been found to be a more effective reaction medium[45] (it allows a higher reaction temperature). It's use with halogenated aromatic nitrogen heterocycles e.g. pyridine, is illustrated below[46,47];



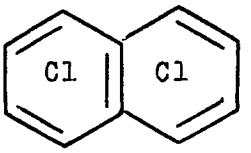


Recently Fuller[48] has reported the use of sulpholane (tetramethylene sulphone) as an effective reaction medium for halogen exchange reactions.

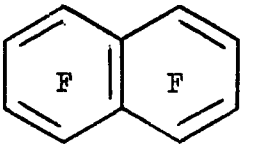
KF/Sulpholane → 230-240°/18 hr

C_6F_6 + C_6F_5Cl + $C_6F_4Cl_2$ + 1,3,5-$C_6F_3Cl_3$

0·4% 25% 24% 30%

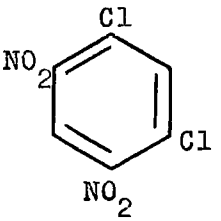


KF/Sulpholane → 230-240°/14 hr

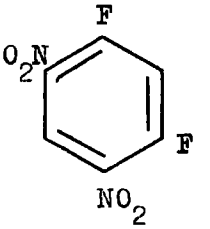


50-60%

Vorozhtsov and Yakobson[40] reported halogen exchange reaction using KF without a solvent and prepared 1,3-difluoro-4-5-dinitrobenzene.

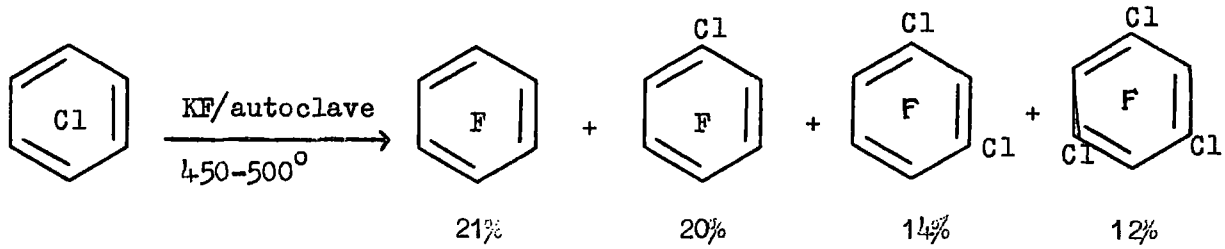


KF → 170-190° No Solvent

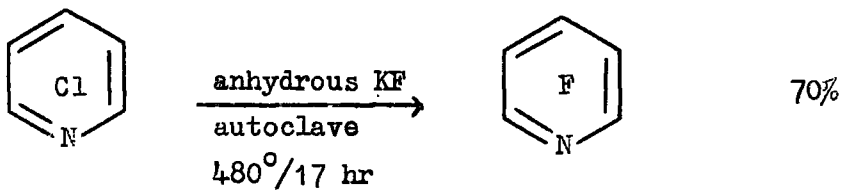


87%

More recently the reaction of hexachlorobenzene with KF in an autoclave to give high yields of highly fluorinated benzenes was reported[49].

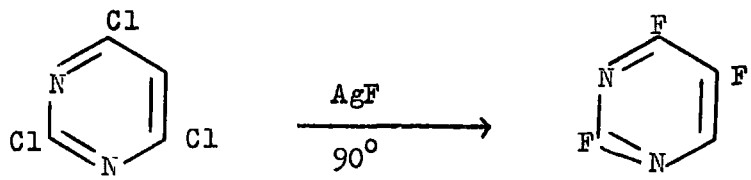


Very recently workers at Durham[50] succeeded in preparing perfluoropyridine from the perchloro derivative in high yields by using similar technique:

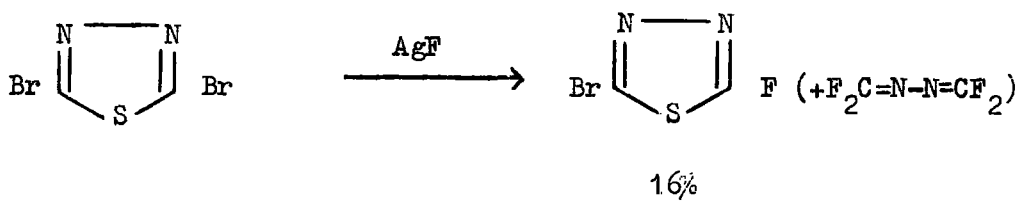


The same reaction has been described by Haszeldine and co-workers[51] and the method has been extended to the preparation of perfluoro-pyrazine,[31] -pyridazine[65] -quinoline[52] and -isoquinoline[52].

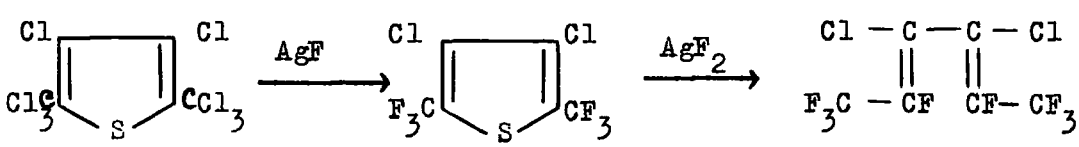
Other fluorides which have been used to effect halogen exchange include those of silver, and antimony; and sulphur tetrafluoride. Silver fluoride, AgF, has been used to synthesise fluoropyrimidines[53] from the chloro-analogue



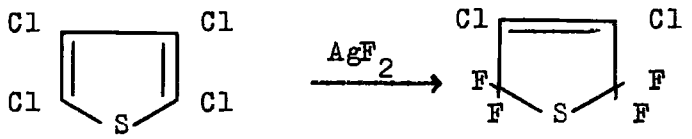
2,5-dibromo-1,3,4-thiadiazole was converted to 2-bromo-5-fluoro-1,3,4-thiadiazole by AgF[54].



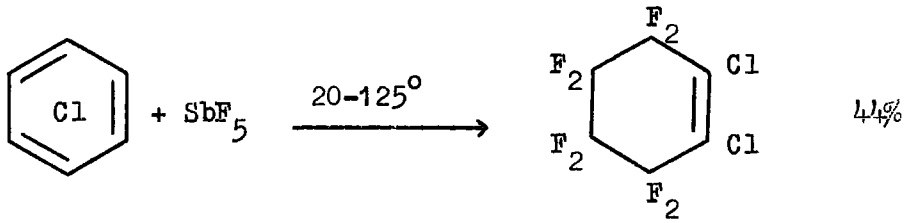
Silver difluoride is much more reactive than the monofluoride. In an attempt to exchange the halogen atoms of fully chlorinated 2,5-dimethyl thiophenes with fluorine by means of silver fluoride, AgF, Grundmann[55] observed the substitution of only those halogen atoms which were attached to methyl groups. Treatment with silver difluoride to force the replacement of the β-bonded chlorine atoms of 2,5-bis(trifluormethyl)-3,4-dichlorothiophen resulted in opening and desulphurization of the thiophen ring.



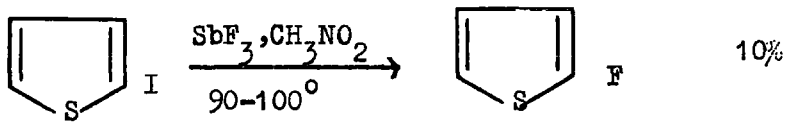
Reaction of tetrachlorothiophen with AgF_2 gave 2,2,5,5-tetrafluoro-3,4-dichlorothiolene-3[55].



MacBee[56] and his co-workers showed that antimony pentafluoride added fluorine to double bonds as well as replaced chlorine by fluorine.



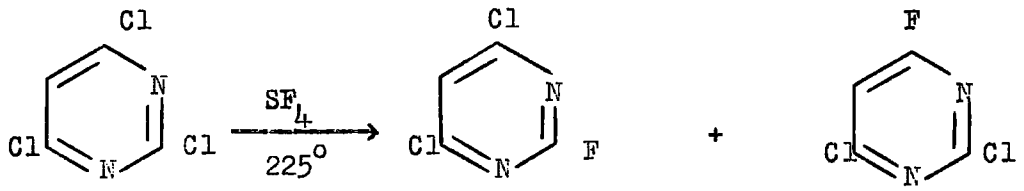
Antimony trifluoride in nitromethane has been used to replace iodine by fluorine in thiophen ring[57].



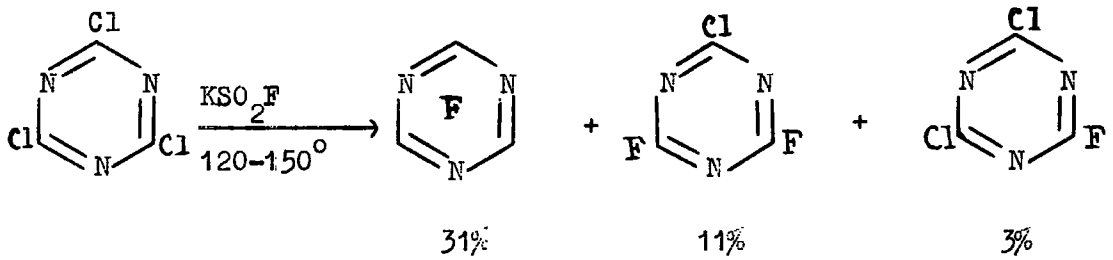
Reactions of antimony trifluoride with either chloro- or bromothiophen were unsuccessful.

Tullock and his co-workers[58] used sulphur tetrafluoride to fluorinate hexachlorobenzene at temperatures ranging from 200-400° and obtained cyclic $C_6Cl_2F_8$ and $C_6Cl_3F_9$. These workers also partially

fluorinated 2,4,6-trichloropyrimidine with the help of this reagent.

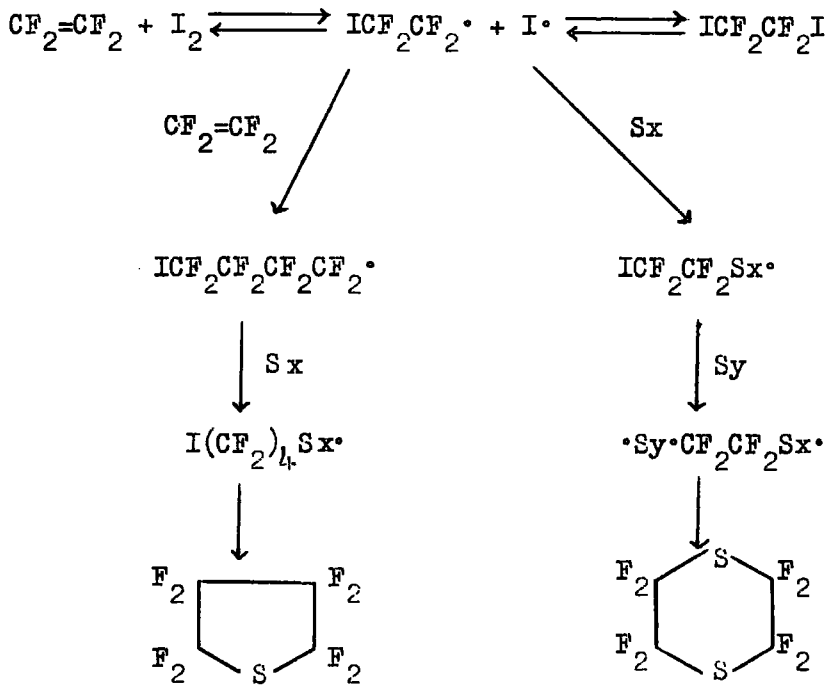


Potassium fluorosulphinate has been reported to be used to fluorinate sym-trichlorotriazine[59].

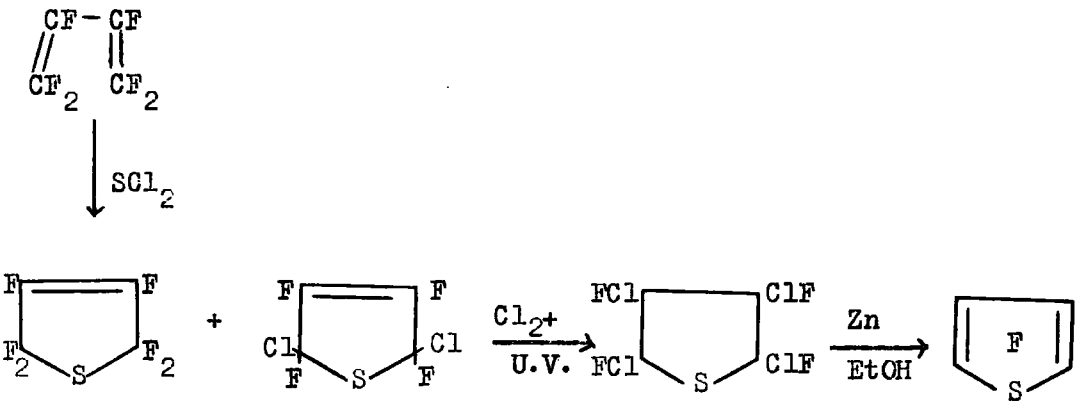


C. RING FORMATION

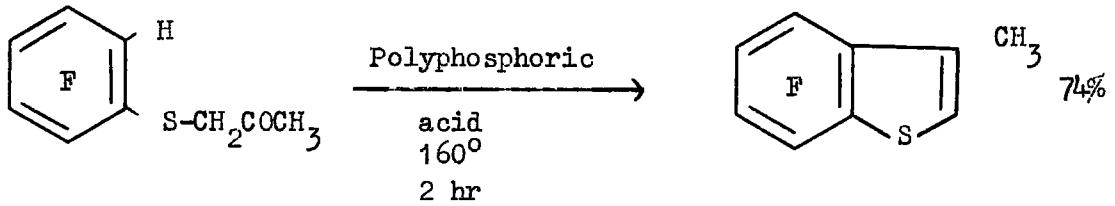
Krispan and Langkammerer[60] reported a one-step synthesis of octafluorothiolane and octafluoro-1-4-dithiane by the reaction of tetrafluoroethylene with sulphur in the presence of iodine at 250-300° under pressure. The reaction courses have been outlined as follows:



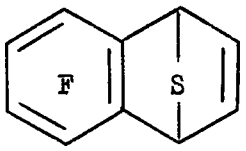
The preparation of perfluorothiophen was reported in 1960[61] and the outline of the synthesis is shown below:



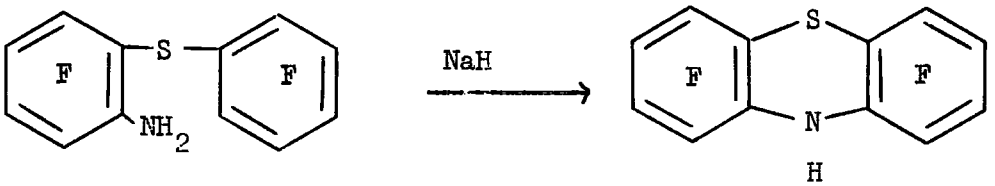
Very recently the preparation of 4,5,6,7-tetrafluoro-3-methylbenzo[b]-thiophen has been published[71].



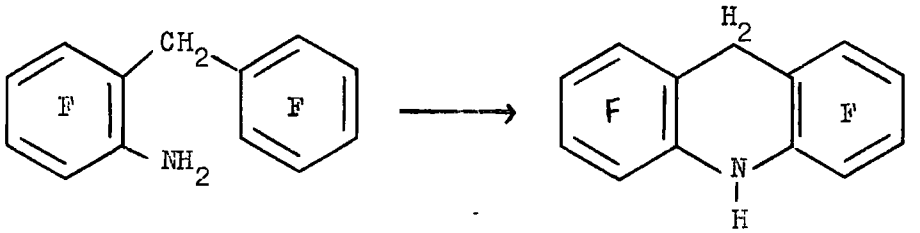
Tatlow and his co-workers[62] reacted thiophen with pentafluorophenyl-lithium and obtained 5% of the following sulphur compound



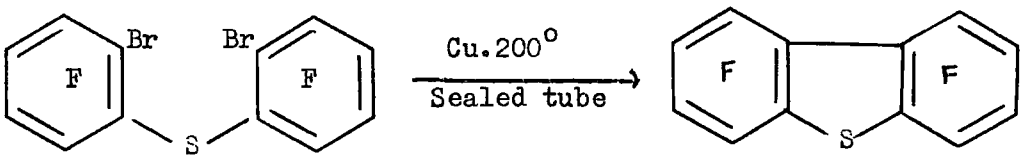
together with 1,2,3,4-tetrafluoronaphthalene (35%) and pentafluoro-thiophenol (1%) [The compound decomposes to give 1,2,3,4-tetrafluoro-naphthalene and sulphur]. The oxygen analogue of this compound had been reported[63] earlier. 2-amino-3,4,5,6-tetrafluorophenyl pentafluorophenyl sulphide gave octafluorophenathiazine[38] when heated under reflux with sodium hydride



Octafluoroacridan was prepared by a similar reaction.[64]

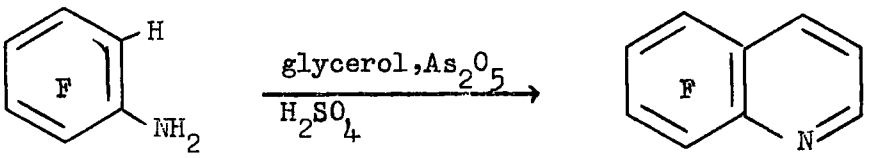


Octafluorodibenzothiophen [66] has been synthesised from bis(o-bromo-tetrafluorophenyl)sulphide which was obtained by the interaction of sulphur dichloride and o-bromotetrafluorophenyl lithium.



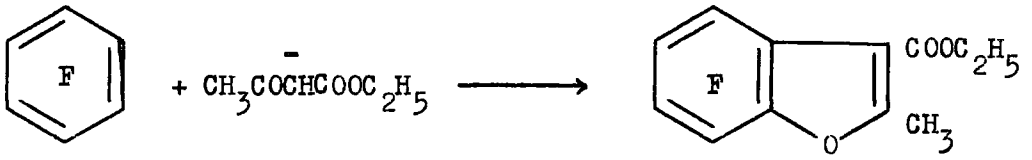
100%

The Skraup synthesis has been applied to prepare fluorinated quinolines[67,68]. Recently in this laboratory[69], 5,6,7,8-tetrafluoroquinoline has been prepared by this method.



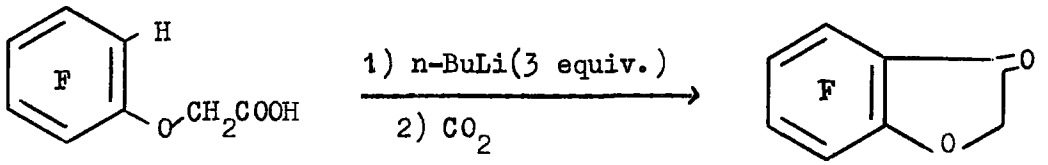
30·1 g. 19·4 g.

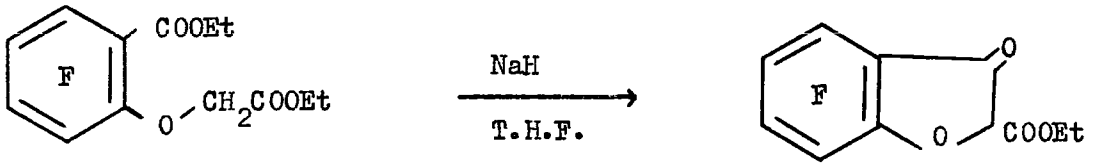
Russian workers[70] have found that ethyl acetoacetate, sodium hydride and hexafluorobenzene in approximately equimolecular quantities gave a 30% yield of the following benzo[b]furan derivative



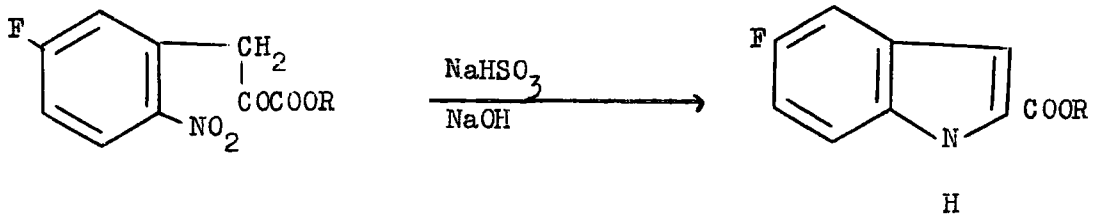
The mechanism of this reaction will be discussed in Chapter IV.

Also 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one derivatives have recently been prepared in this laboratory using methods shown below[73]:

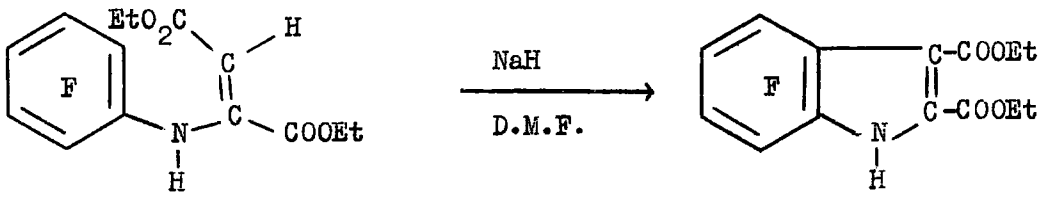




A fluorinated indolecarboxylate was made in almost quantitative yield by the following reaction:[44]



Very recently 2,3-diethoxycarbonyl-4,5,6,7-tetrafluoroindole has been prepared in this laboratory by the cyclization of diethyl N-2,3,4,5,6-pentafluorophenylamino-fumerate with sodium hydride in N,N-dimethyl



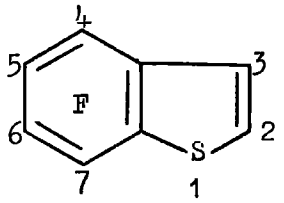
formamide. The starting material was prepared by the reaction of the sodium salt of pentafluoroaniline in tetrahydrofuran with diethyl acetylene-dicarboxylate.

CHAPTER II

CONVENTIONAL METHODS FOR THE PREPARATION OF DERIVATIVES OF BENZO[b]THIOPHEN AND THEIR USE IN THE SYNTHESIS OF 4,5,6,7-TETRAFLUOROBENZO[b]THIOPHEN

CONVENTIONAL METHODS FOR THE PREPARATION OF DERIVATIVES OF BENZO[b]THIOPHEN AND THEIR USE IN THE SYNTHESIS OF 4,5,6,7-TETRAFLUOROBENZO[b]THIOPHEN

The aim of the present work described in this thesis was the synthesis of 4,5,6,7-tetrafluorobenzothiophen (i) and the study of its behaviour towards electrophilic and nucleophilic reagents.

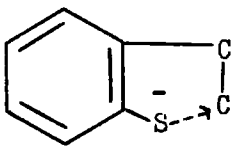


(i)

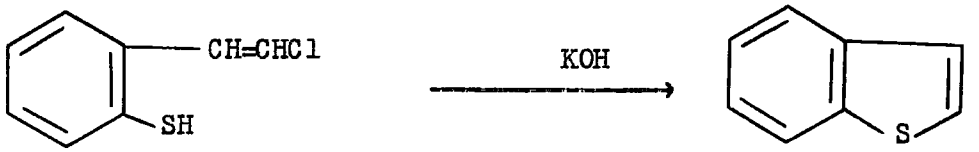
Most methods for the synthesis of benzo[b]thiophen and its derivatives involve closure of the thiophene ring from materials having the benzene nucleus already formed - only in exceptional cases has the benzene ring been built on to an existant thiophene nucleus[74].

In the following pages, various methods of synthesis are given with particular emphasis on the possible mechanisms of the reaction.

(1) Linkage of the sulphur atom to $C_{(2)}$ by a nucleophilic attack



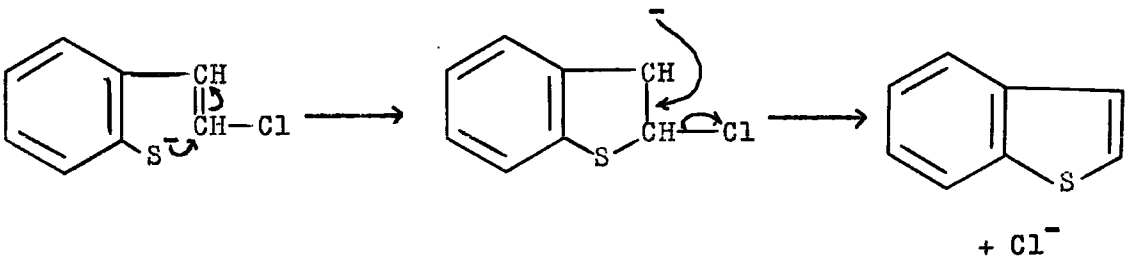
Example: Formation of benzo[b]thiophen from o-mercapto-β-chlorostyrene and alcoholic potash[75]:



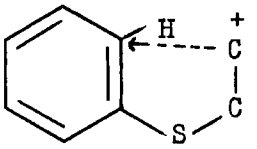
The mechanism can be depicted in two ways:

(i) By a straight forward substitution:

or (ii) by an addition-elimination reaction:

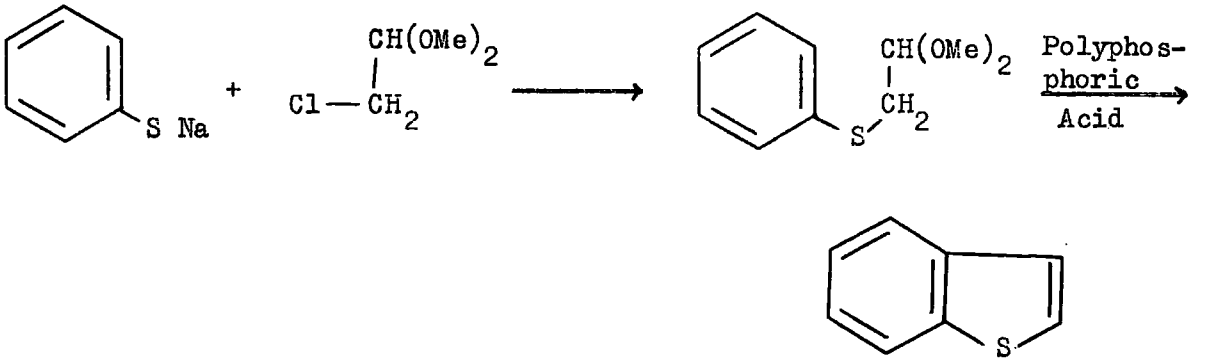


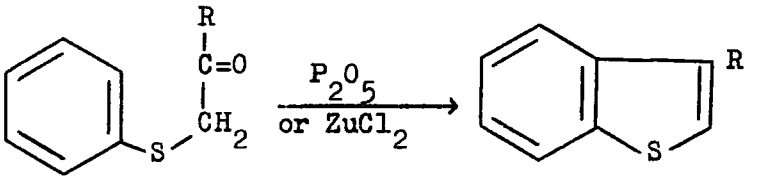
(2) Closure of the ring between $C_{(3)}$ and the benzene nucleus by an electrophilic substitution of the hydrogen atom ortho to the sulphur atom

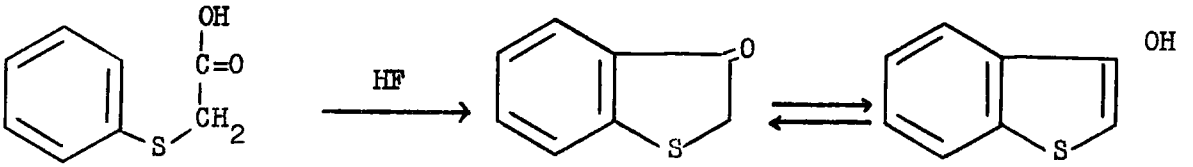


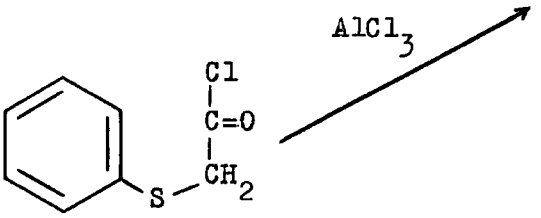
Example:

This method is widely used. Acidic dehydrating agents convert arylthioacetals, arylthioketones and arylthioacetic acids into benzo[b]thiophen derivatives:

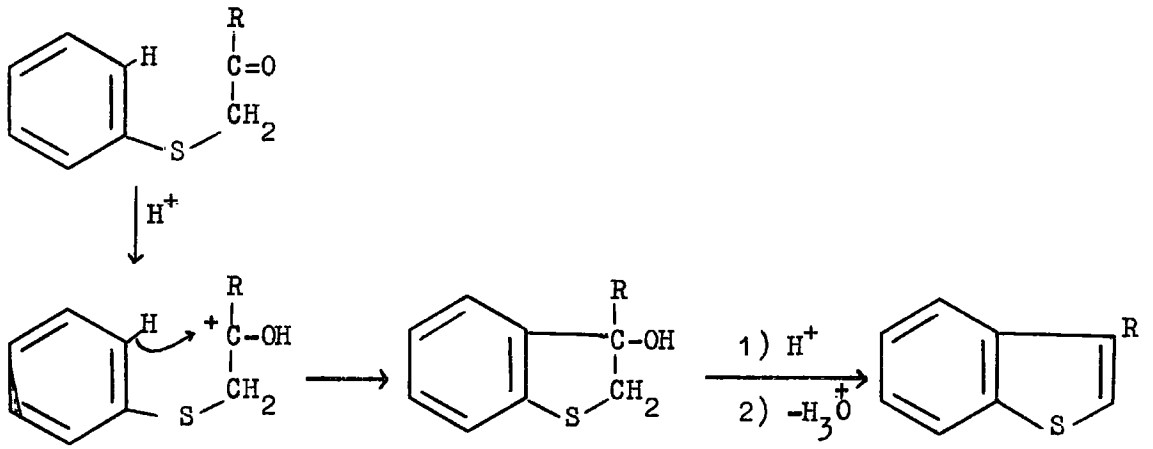




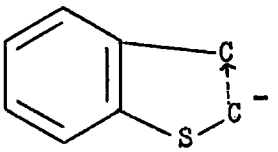




The mechanism of the reaction involving the ketone could proceed as follows:

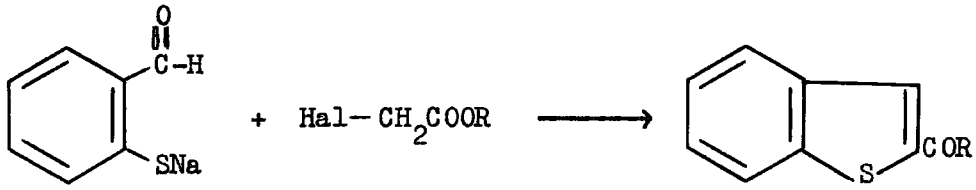


(3) Ring closure between $C_{(2)}$ and $C_{(3)}$ by a nucleophilic attack on $C_{(3)}$.

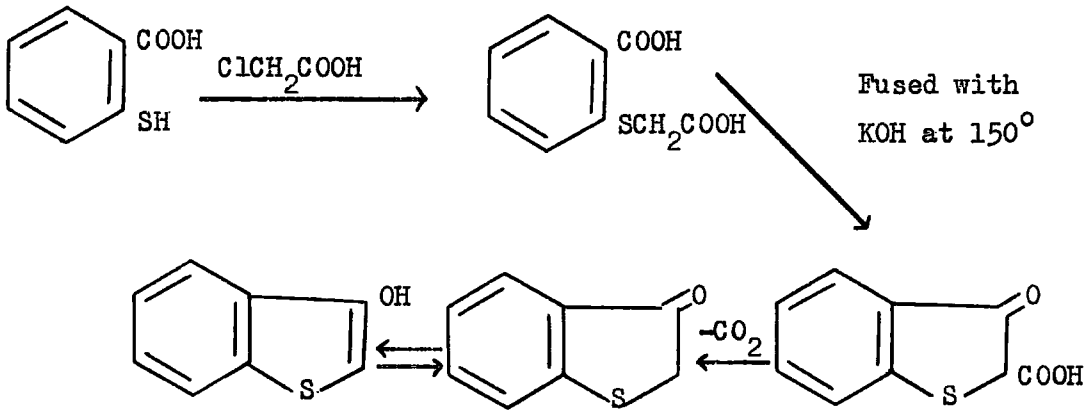


Example:

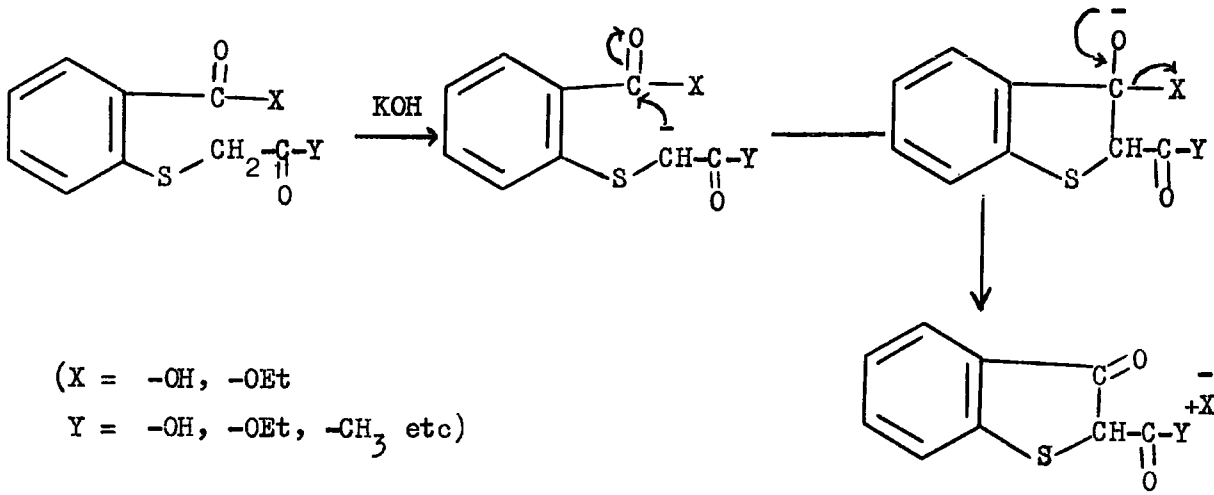
This is usually considered to be the most important method. Reaction can be effected between the carbonyl group of an aromatic aldehyde or ketone, and a reactive methylene group attached to an ortho sulphur atom:



Similar ring closure through a carboxyl function lead to thioindoxyl:



The general mechanism in these reactions isprobably as follows:



(X = -OH, -OEt

Y = -OH, -OEt, $-CH_3$ etc)

Routes (2) and (3) of the above methods have been tried in the preparation of 4,5,6,7-tetrafluorobenzo[b]thiophen(i) as is described below.

The problem of synthesizing 4,5,6,7-tetrafluorobenzo[b]thiophen by methods No. 2 and No. 3 was divided into three parts:

(I) The synthesis of 2,3,4,5-tetrafluorothiophenol.

(II) Conversion of this thiol into materials capable of cyclization by methods No. 2 and No. 3.

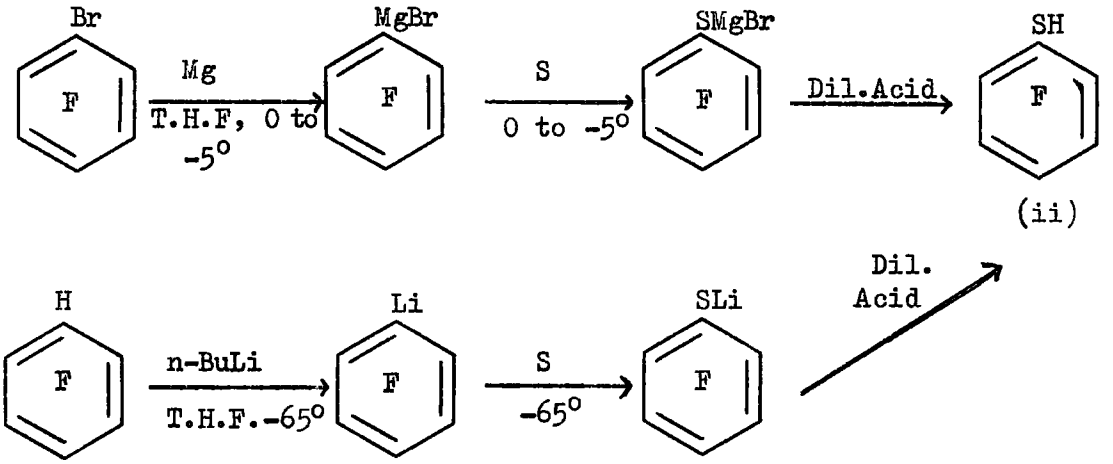
(III) Cyclization and conversion of the cyclized material to the final product, tetrafluorobenzo[b]thiophen.

PART I

Highly fluorinated thiophenols have been prepared by the replacement of fluorine in polyfluoroaromatic compounds C_6F_5X (X = F-,[76] H,[76] CF_3[77]) using sodium hydrogen sulphide in ethylene glycol as nucleophilic reagents. However, in each case where X = H-, CF_3-, the fluorine para to the group X was removed - no ortho substitution products were isolated. It is because of this limitation that the method could not be applied to the present problem of preparing 2,3,4,5-tetrafluorothiophenol.

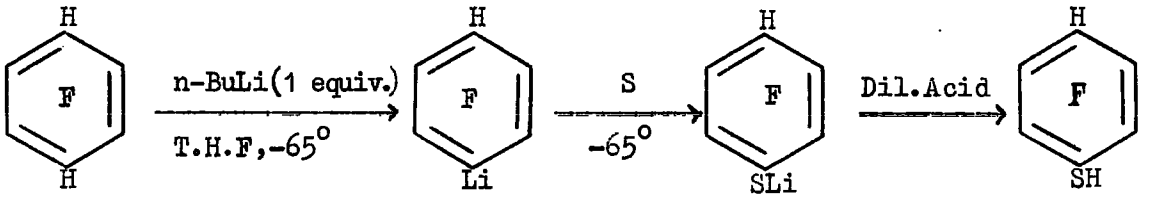
Thiophenols have been prepared by the reaction of elemental sulphur on Grignard reagents[78]. When pentafluorophenylmagnesiumbromide in dry tetrahydrofuran was treated with sulphur at 0°, pentafluorothiophenol (ii)

was obtained in 67% yield. Pentafluorophenyl-lithium[79] when treated with sulphur at -65° gave 46% of pentafluorothiophenol. Similarly the monolithium reagent



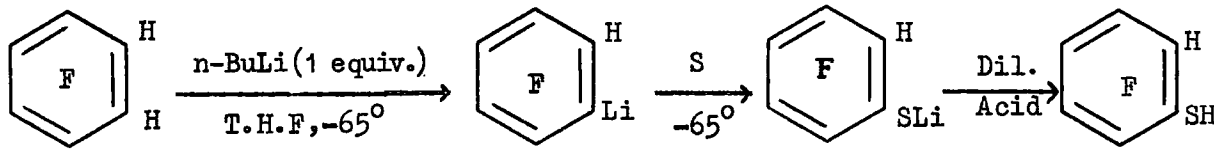
(ii)

derived from 1,2,4,5-tetrafluorobenzene which was recently described by Tamborski[79], gave the known 2,3,5,6-tetrafluorothiophenol (iii) in 69% yield.



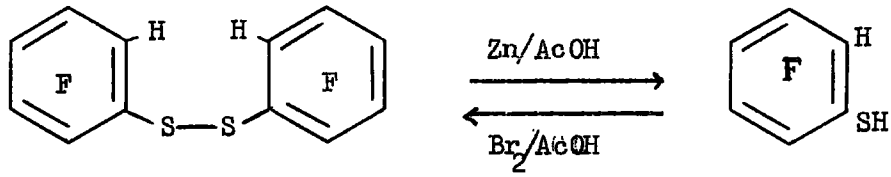
(iii)

Following this method it was possible to synthesise the previously inaccessible 2,3,4,5-tetrafluorothiophenol(iv) in 67% yield, using the monolithium derivative of 1,2,3,4-tetrafluorobenzene in tetrahydrofuran.



(iv)

A small amount of high boiling material was obtained in course of the preparation of 2,3,4,5-tetrafluorothiophenol. This was shown to contain bis(2,3,4,5-tetrafluorophenyl)disulphide(v) by reduction to thiophenol with zinc dust and acetic acid and by synthesis from the parent thiol using the method described previously[76].



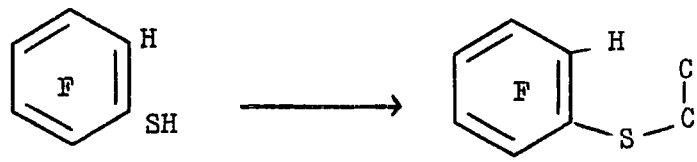
(v)

PART II

2,3,4,5-Tetrafluorothiophenol was reacted with various substances that would lead to the formation of materials capable of cyclization, (a) by route No. 2 and (b) by route No. 3.

(a) Preparation of compounds suitable for cyclization by route No. 2.

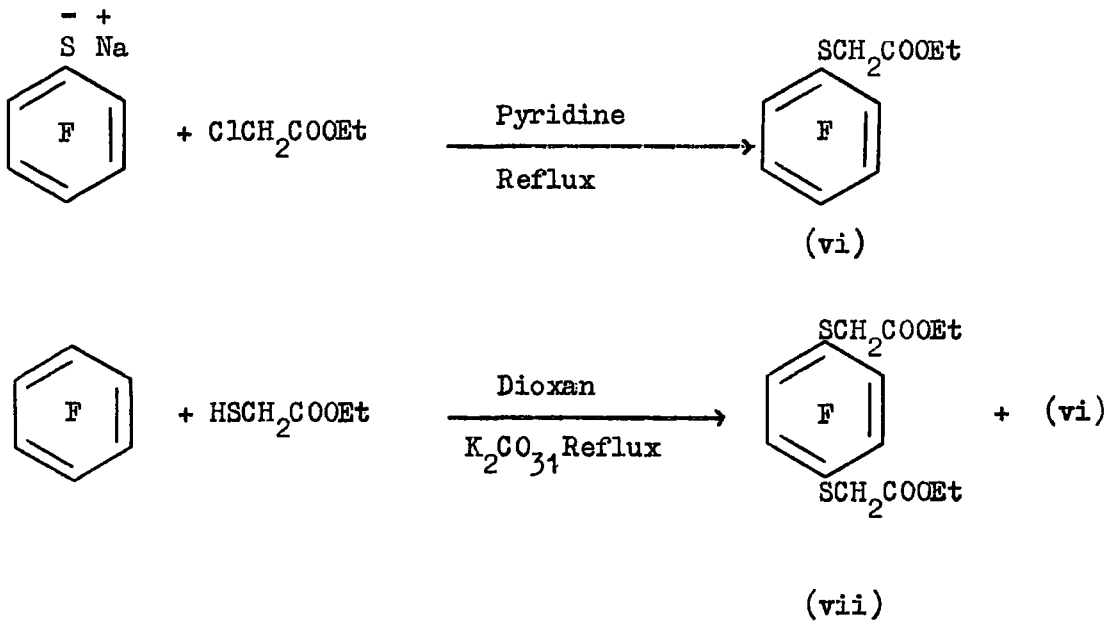
The formation of materials suitable for the synthesis of fluorinated benzo[b]thiophen derivatives by route No. 2 required the addition of two more carbon atoms to the sulphur.



However, before starting on 2,3,4,5-tetrafluorothiophenol, work on readily available pentafluoro- and 2,3,5,6-tetrafluorothiophenol was carried out.

Ethyl(Pentafluorophenylthio)acetate

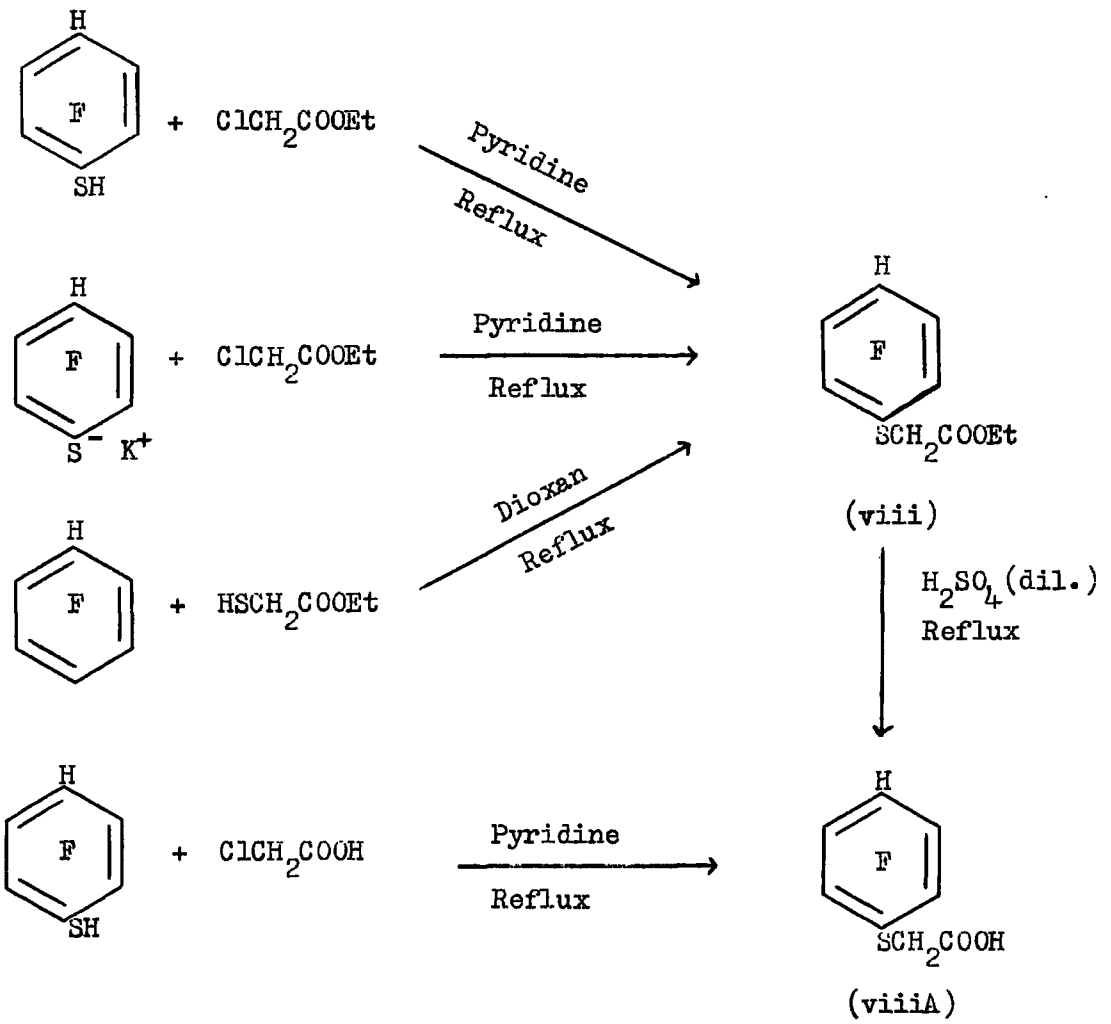
Pentafluorothiophenol was reacted with ethylchloroacetate in pyridine at reflux temperature without any result. However, sodium pentafluorothiophenate (prepared from pentafluorothiophenol and metallic sodium in dry ether) when reacted with ethyl chloroacetate under the same conditions gave ethyl(pentafluorophenylthio)acetate (vi) in 30% yield. This compound was also obtained in small amount when hexafluorobenzene in dry dioxan was heated under reflux with ethyl mercaptoacetate and anhydrous potassium carbonate:



The main product of this reaction was, however, the disubstituted compound[80] (vii). In an earlier report[81] when 2-mercapto ethanol was reacted with hexafluorobenzene, the only product isolated was the para disubstituted product - no monosubstituted product was formed. Ethyl(pentafluorophenylthio)acetate obtained from the two different reactions had identical infrared spectra. Attempts to increase the yield of ethyl(pentafluorophenylthio)acetate by using a smaller proportion of ethyl mercaptoacetate to hexafluorobenzene were unsuccessful. The ^{19}F n.m.r. spectrum showed the compound (vii) to be paradisubstituted: a single peak indicated only one type of fluorine atom in the molecule.

(2,3,5,6-Tetrafluorophenylthio)acetic Acid

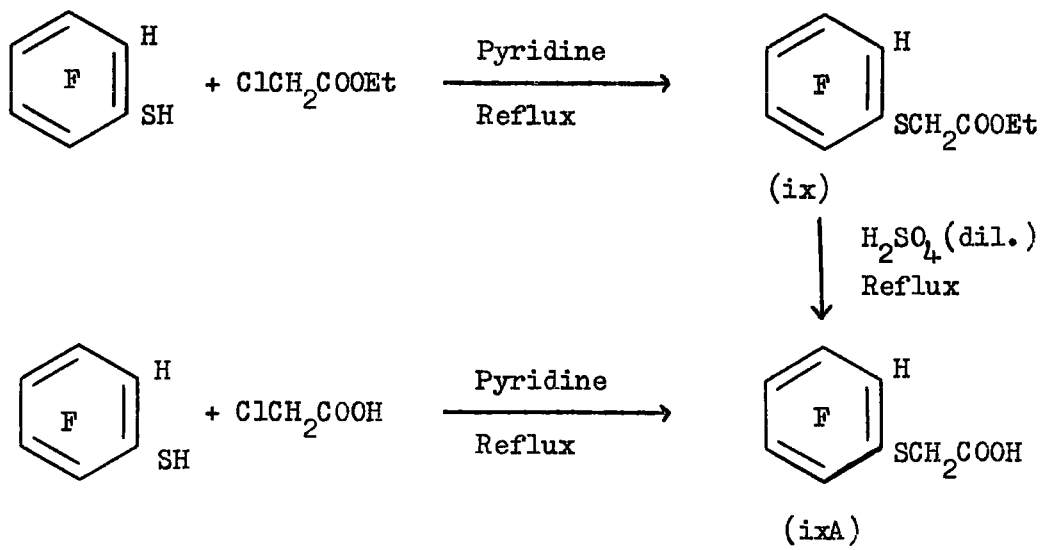
2,3,5,6-Tetrafluorothiophenol as well as its potassium salt were reacted with ethyl chloroacetate in pyridine under reflux. Excellent yields of ethyl(2,3,5,6-tetrafluorophenylthio)acetate (viii) were obtained. The same compound was obtained in 80% yield when pentafluorobenzene was refluxed with ethyl mercaptoacetate and anhydrous potassium carbonate in dry dioxan. This latter reaction provides a further example of the replacement of the parafluorine atom in pentafluorobenzene when undergoing a nucleophilic substitution[23].



The ester (viii) was easily hydrolysed with 50% (V/V) sulphuric acid to (2,3,5,6-tetrafluorophenylthio)acetic acid (viiiA). This acid was also prepared by the interaction of 2,3,5,6-tetrafluorothiophenol and chloroacetic acid in pyridine under reflux, in very good yield. The infrared spectra and the melting points of the two products were identical.

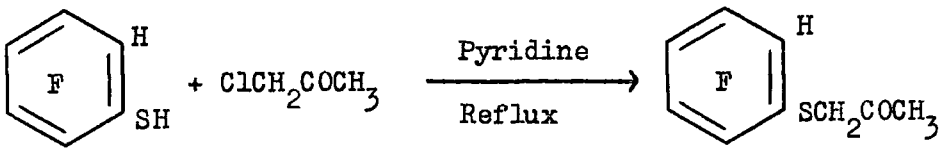
(2,3,4,5-Tetrafluorophenylthio)acetic acid

When 2,3,4,5-tetrafluorothiophenol was heated under reflux with ethyl chloroacetate in pyridine ethyl(2,3,4,5-tetrafluorophenylthio)acetate (ix) was obtained in excellent yield. The ester was hydrolysed with 50%(V/V) sulphuric acid to the corresponding (2,3,4,5-tetrafluorophenylthio)acetic acid. This acid was also obtained in lower yield (25%) when 2,3,4,5-tetrafluorothiophenol was heated under reflux with chloroacetic acid in pyridine. The compounds obtained by two different methods showed identical infrared spectra and had identical melting points.



(2,3,4,5-Tetrafluorophenylthio)acetone

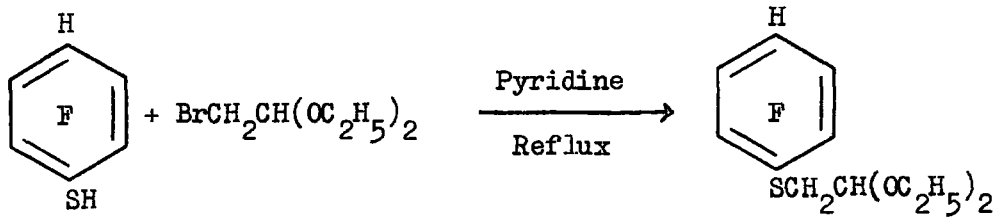
2,3,4,5-Tetrafluorothiophenol was converted into (2,3,4,5-tetrafluorophenylthio)acetone (ixB) in good yield when it was reacted with chloroacetone in pyridine in a similar manner as with ethyl chloroacetate.



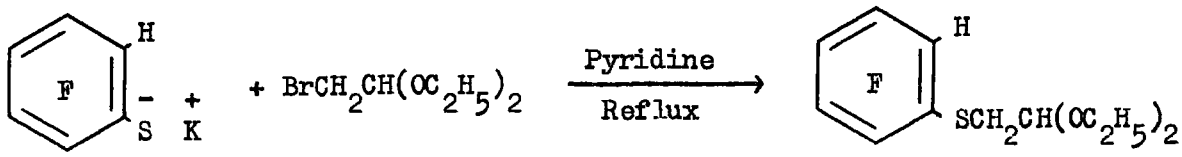
(ixB)

Attempted Preparation of (2,3,5,6- and 2,3,4,5-tetrafluorophenylthio)-acetaldehyde Diethyl Acetal

When 2,3,5,6-tetrafluorothiophenol was heated under reflux with bromoacetaldehyde diethyl acetal in pyridine (2,3,5,6-tetrafluorophenylthio)acetaldehyde diethyl acetal (x) was obtained in good yield. A similar reaction using 2,3,4,5-tetrafluorothiophenol itself was unsuccessful. However, when potassium 2,3,4,5-tetrafluorothiophenate (prepared by adding the thiol to caustic potash dissolved in minimum volume of water) was reacted in a similar manner with the bromoacetal in pyridine (2,3,4,5-tetrafluorophenylthio)acetaldehyde diethyl acetal (xi) was obtained. Both acetals, however, could not be obtained pure.



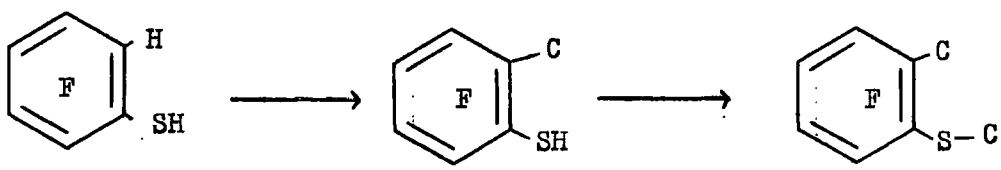
(x)



(xi)

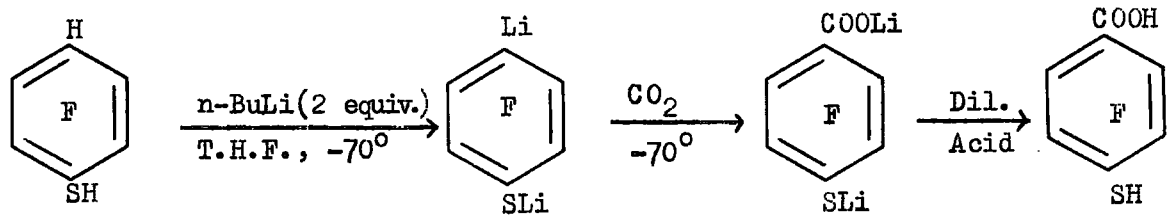
(b) <u>Preparation of compounds suitable for cyclization by route No. 3</u>

Starting materials capable of cyclization by route No. 3 required an extra carbon atom attached to the aromatic ring and also another to the sulphur atom.

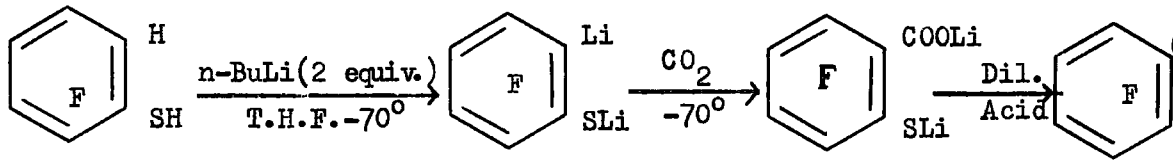


Tamborski[79] reported the preparation of mono- and di-Grignard and mono- and di-lithio reagents of highly fluorinated benzene compounds and their conversion to the corresponding acids by carbonation. In an extension of

these ideas 2,3,5,6-tetrafluoro-4-mercaptobenzoic acid (xii) and 2,3,4,5-tetrafluoro-6-mercaptobenzoic acid (xiii) have been prepared by the treatment of 2,3,5,6-tetrafluorothiophenol and 2,3,4,5-tetrafluorothiophenol respectively with butyl-lithium (2 equiv.) at -70° in tetrahydrofuran followed by treatment with carbon dioxide at this temperature. Tamborski[82] has recently published the preparation of compound (xii) by the same reaction.

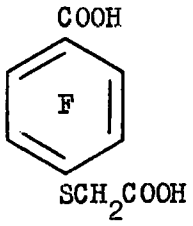


(xii)



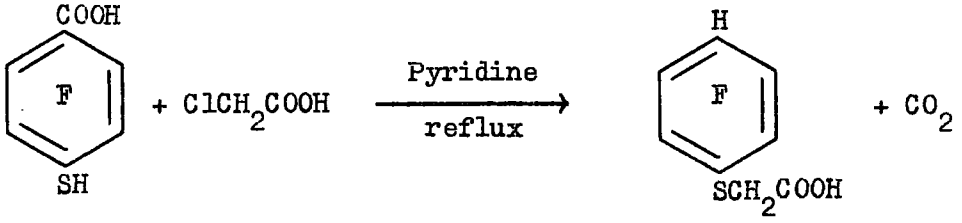
(xiii)

In order to add a suitably reactive carbon atom to the sulphur in (xiii) to act as a substrate for cyclization, a model experiment was carried out by treating the para-mercapto benzoic acid (xii) with chloroacetic acid in pyridine. The product was (2,3,5,6-tetrafluorophenylthio)acetic acid (viiiA), and not the expected diacid (xiiiA).

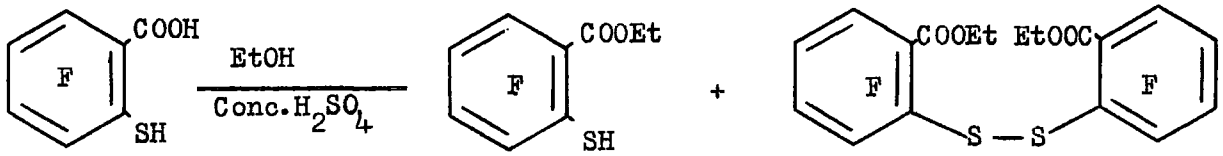


(xiiiA)

Decarboxylation had taken place under the basic conditions of the reaction and it could not be checked even at lower temperatures (60-70°).

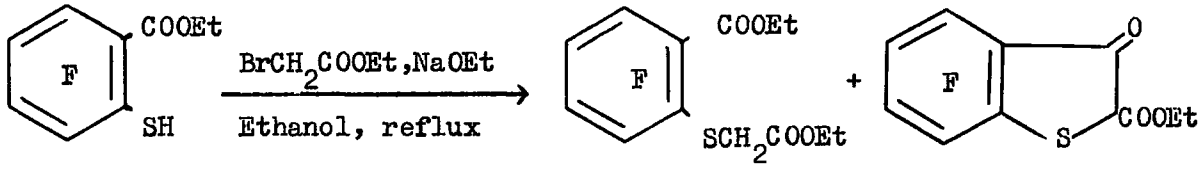


This effect has been observed previously with highly fluorinated aromatic carboxylic acids[83]. This result suggested that 2,3,4,5-tetrafluoro-6-mercaptobenzoic acid (xiii) would decarboxylate under similar treatment. The compound was, therefore, esterified by heating under reflux with ethanol and conc. sulphuric acid to give (xiv) in 60% yield. A small amount of high boiling fraction in the reaction product was found to contain bis(6-ethoxycarbonyl-2,3,4,5-tetrafluorophenyl)disulphide (xivA), the structure of which was determined from elemental analysis and molecular weight (mass spectroscopy).



(xiv) (xivA)

The ester (xiv) was then heated under reflux with ethyl bromoacetate in ethanol in presence of sodium ethoxide to give ethyl 6-ethoxycarbonyl(2,3,4,5-tetrafluorophenylthio)acetate (xv) and 2-ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl (xvi). The latter (solid) was separated from the former by crystallization of the crude mass from ethanol. The mother liquor when distilled under vacuo gave the pure diester (xv) as the major product.

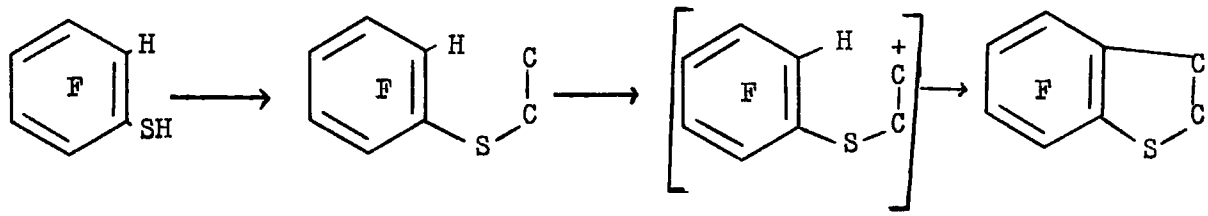


(xv) (xvi)

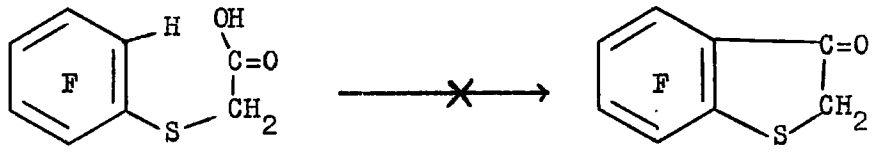
The structure of the cyclized material (xvi) was deduced from its molecular weight (mass spectroscopy) and ^{1}H n.m.r. spectrum; there were three magnetically different protons in the intensity of 1:2:3. The single peak at very low field (τ 0·23), and strong absorption at 3280 cm^{-1}. in the infrared spectrum, indicates that the compound exists largely in the enol tautomeric form.

PART III

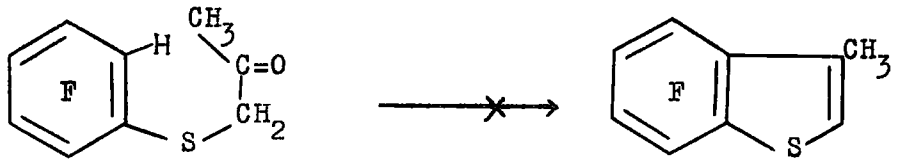
Attempted cyclization by route No. 2



The cyclization of (2,3,4,5-tetrafluorophenylthio)acetic acid (ixA) by a number of standard procedures[84] was attempted. Reactions with polyphosphoric acid, phosphorous pentoxide in cyclohexane, anhydrous hydrofluoric acid, conc. sulphuric acid and chlorosulphonic acid all failed to produce 4,5,6,7-tetrafluorothioindoxyl (xvii); the starting material was recovered in most cases. Similarly attempts to cyclize (2,3,4,5-tetrafluorophenylthio)acetone (ixB), to give 4,5,6,7-tetrafluoro-3-methylbenzo[b]thiophen (xviiA), with polyphosphoric acid and phosphorus pentoxide was unsuccessful, though the same reaction using polyphosphoric acid[71] has now been reported in a successful experiment. With phosphorous pentoxide



(xvii)

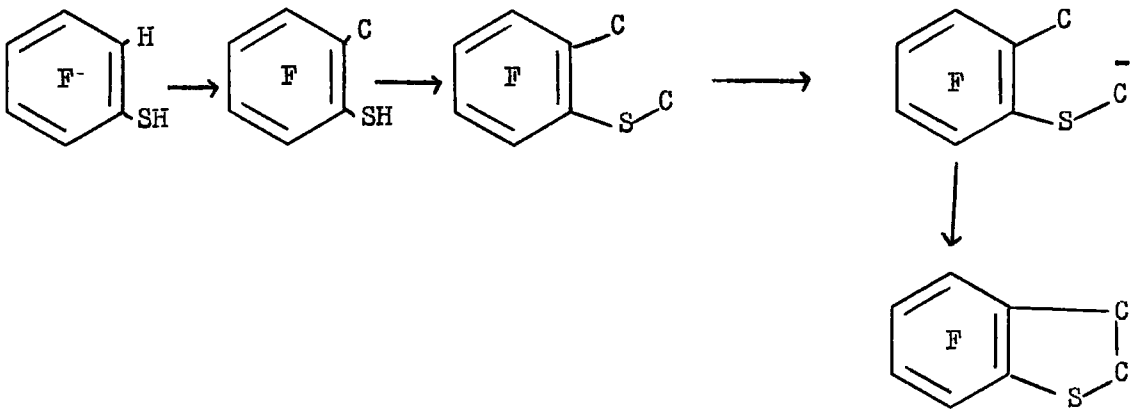


[but see ref.71]

(xviiA)

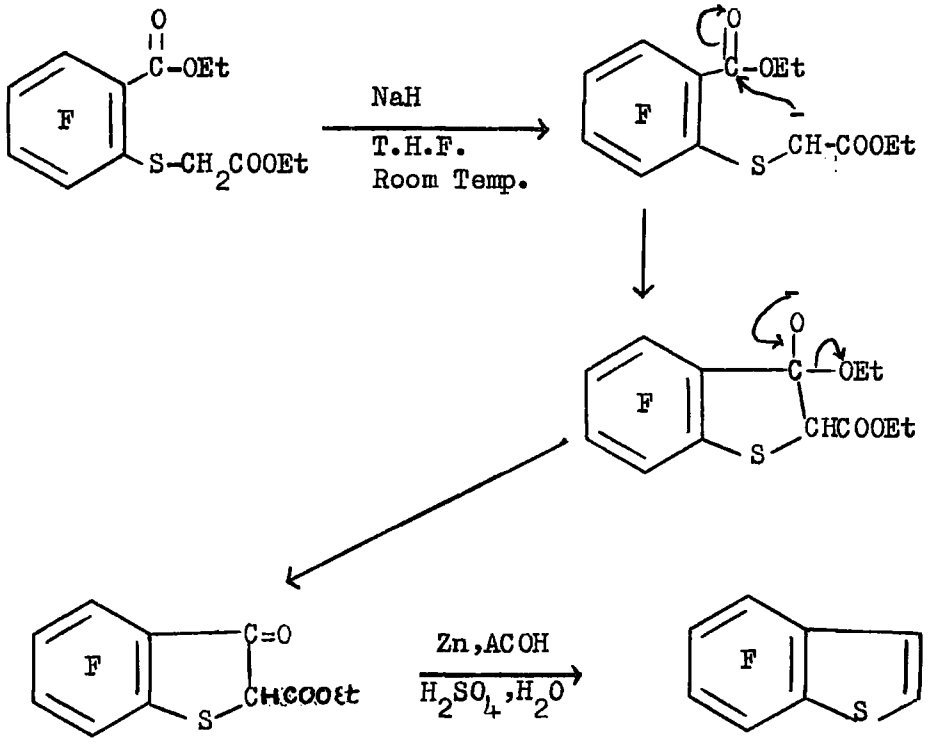
a liquid was obtained which did not show any carbonyl absorption peak in the infrared spectrum. The liquid was, however, shown to contain at least four components by analytical vapour phase chromatography which would have been difficult to separate. Although (2,3,4,5-tetrafluorophenylthio)acetaldehyde diethyl acetal could not be purified attempts were made to cyclize this compound with polyphosphoric acid to give 4,5,6,7-tetrafluorobenzo[b]thiophen. These attempts were unsuccessful.

Ring closure by route No. 3



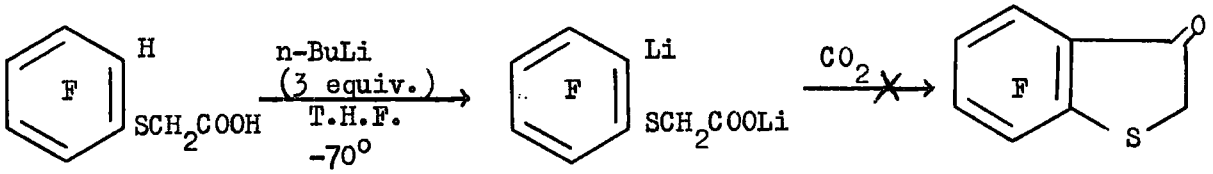
The formation of ethyl (6-ethoxycarbonyl-2,3,4,5-tetrafluorophenylthio)-acetate (xv) has already been described in Part II. Cyclization of this diester to (xvi) by a nucleophilic substitution of ethoxide at the

unsaturated carbonyl group of the aromatic ester was promoted by sodium hydride as follows:



The cyclized compound (xvi), was converted into 4,5,6,7-tetrafluorobenzo-[b]thiophen (i) in very low yield by treatment with zinc dust in a mixture of acetic acid, sulphuric acid and water, which effected ester hydrolysis, dicarboxylation and reduction. Attempts to hydrolyse the ester by acid or base catalysis produced deep red coloured compounds - presumably due to the formation of thioindigo-type dyes. In this procedure sufficient of the benzo[b]thiophen for identification was

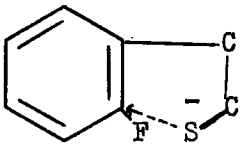
isolated by sublimation. It has been mentioned in Chapter I (p.26) that 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one has been made recently in these laboratories from 2,3,4,5-tetrafluorophenoxyacetic acid[73]. When (2,3,4,5-tetrafluorophenylthio)acetic acid was treated with n-BuLi in dry tetrahydrofuran at -70° followed by dry carbon dioxide only the starting material was recovered.



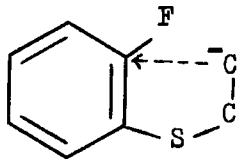
The limited success and unsatisfactory results obtained in the preparation of 4,5,6,7-tetrafluorobenzo[b]thiophen by the conventional methods demanded an exploration of special methods for polyfluoro compounds. A reference to these are made below.

Special Methods for Polyfluoro Compounds

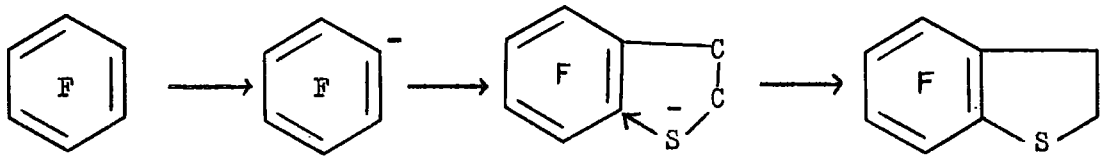
(i) To link S to the benzene ring by a nucleophilic replacement of fluorine



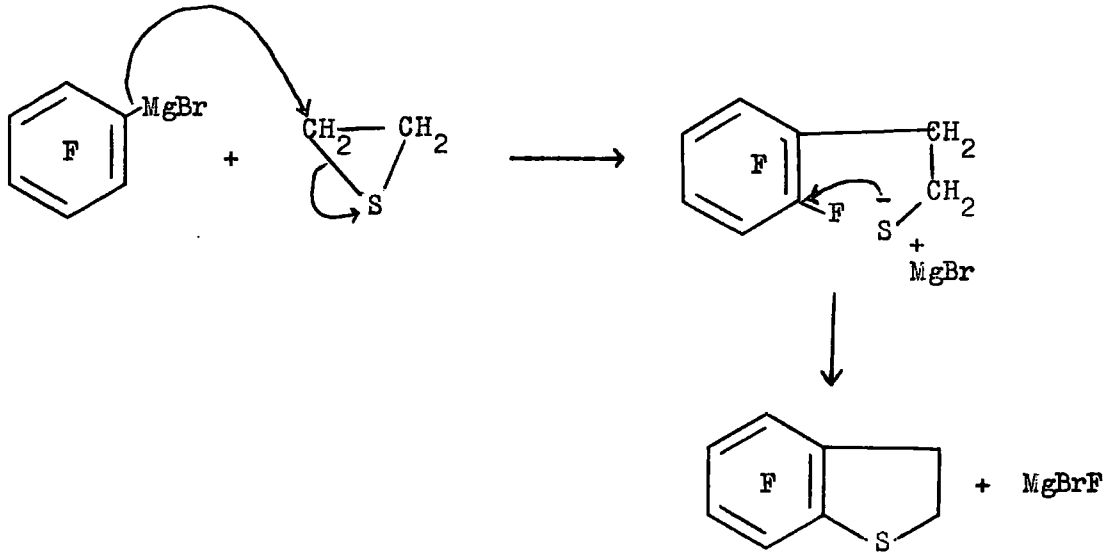
(ii) Attaching $C_{(3)}$ to the benzene ring by a nucleophilic replacement of fluorine



Special Method (i)



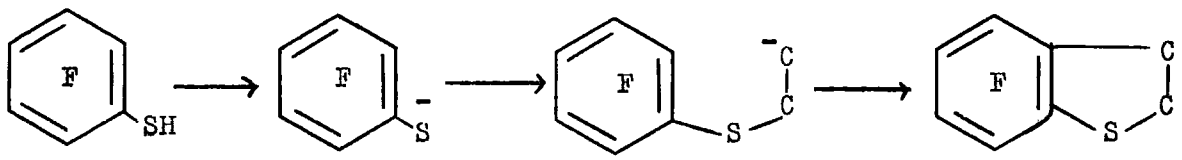
The reaction of pentafluorophenylmagnesiumbromide in tetrahydrofuran with ethylene oxide to give 2-pentafluorophenylethanol has been reported[85]. Pentafluorophenylmagnesiumbromide was similarly reacted with ethylene sulphide in dry tetrahydrofuran at 0 to -5° in an attempt to prepare 2,3-dihydro-4,5,6,7-tetrafluorobenzo[b]thiophen (xviii) as shown in the following scheme:



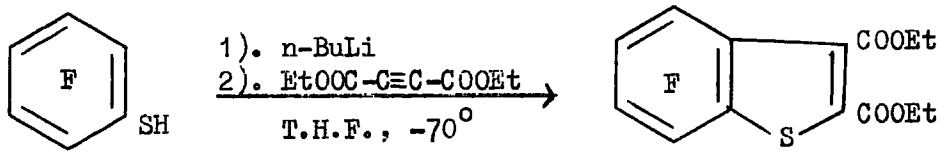
(xviii)

The product of the reaction could not be identified.

Special Method (ii)



The above scheme has been successfully used. When lithium pentafluorobenzene thiolate in tetrahydrofuran was treated with diethyl acetylenedicarboxylate at -70° diethyl 4,5,6,7-tetrafluorobenzo[b]thiophen-2,3-dicarboxylate was formed in good yield.



The potentiality of this reaction between pentafluorobenzenethiolate anion and acetylene compounds as a suitable means of synthesizing 4,5,6,7-tetrafluorobenzo[b]thiophen derivatives became apparent after Russian workers reported the preparation of 2-methyl-3-carbethoxy-4,5,6,7-tetrafluorocoumarone[70] (already mentioned in Chapter I, p.26). Further elaboration of the subject and a detailed discussion on the present reaction will be made in Chapter IV following a brief review in Chapter III on nucleophilic addition to some acetylene compounds.

CHAPTER III

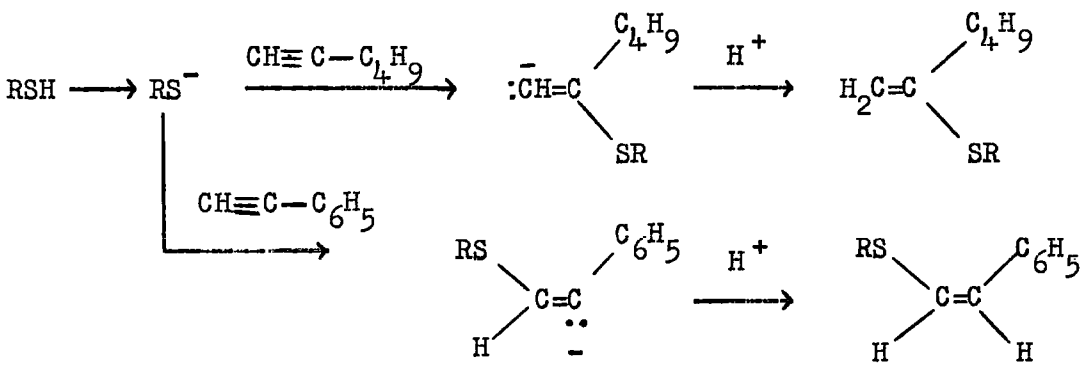
A REVIEW OF NUCLEOPHILIC ADDITION TO SOME ACETYLENE COMPOUNDS

A REVIEW OF NUCLEOPHILIC ADDITION TO SOME ACETYLENE COMPOUNDS

A. Addition of Thiols

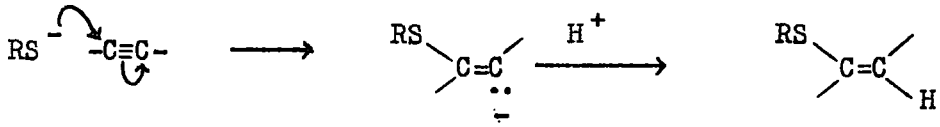
Nucleophilic (anionic) addition of thiols to acetylenes has been known for more than 60 years[86]. Reppe and co-workers[87] extensively studied the reaction with acetylene itself, while Truce[88] investigated the addition to substituted acetylenes.

Truce established that the base catalysed addition of thiols to acetylenes substituted with an electropositive or electronegative group take different courses. For example[89], when started with butylacetylene and phenylacetylene the main reactions were



In an extensive study of nucleophilic additions to mono- and disubstituted acetylenes it was found that thiolates usually react with

triple bonds to give products by an overall trans-addition. These workers



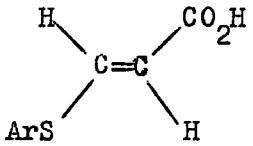
studied the base-catalysed additions of thiols to phenylacetylene[89,90], 2-butyne[89,90], p-tolylmercapto-acetylene[90,91], ethyl propiolate[92,93], phenyl ethynyl ketone[92,93], disodium acetylene dicarboxylate[94], diethyl acetylene dicarboxylate[94], ethyl phenyl propiolate[95,96] and mesityl acetylene[96,97]. They obtained in all these cases high yields of a single product which was shown to have been formed by trans-addition of the nucleophile.

The trans nature of the nucleophilic addition to triple bond was rationalised as follows. As the negatively charged sulphur group initiates attack on an acetylenic carbon atom a pair of electrons begins to be displaced from the triple bond onto an adjacent carbon atom, and 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.

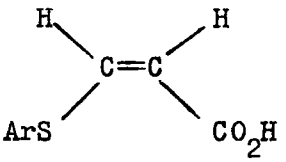
In the reaction of mesitylacetylene and sodium mesitylenethiolate it was thought that the size of the substrate and nucleophile would increase steric hindrance to such an extent that some cis-addition would occur (enabling the two large groups to be in the trans disposition to each other). However, a product of trans-addition was again formed. Apparently any steric effect on the part of the mesityl groups in this

addition was not sufficiently great to violate the rule of trans-nucleophilic addition. In fact no well authenticated examples of violations of this rule for addition of negatively charged nucleophiles to acetylenes were found.

Originally[92,93,98], a partial violation of the rule was claimed for the addition of p-toluene thiolate reagent (p-toluenethiol containing a catalytic amount of sodium ethoxide) to sodium propiolate, which resulted in a mixture of predominantly (85-90%) trans-p-tolylmercaptoaerylic acid(i),



(i)

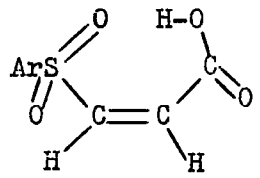


(ii)

the remainder being the cis isomer (ii). It was thought that this was the first record example of cis nucleophilic attack to a triple bond. Truce went on to suggest[92,98] that the cis-addition is associated with the presence of a negatively charged group in the substrate. A competing coulombic repulsion between the negatively-charged carboxylate substituent and the approaching thiolate group would tend to force these groups into a trans relationship and the over-all addition to proceed cis. However since further work[96] has shown that (ii) undergoes isomerization to (i) in the presence of p-toluene thiol and base, the origin of the trans-acid isolated from the reaction mixture is in doubt. Sodium

phenyl propiolate behaved in a similar manner[95]. These results demonstrated the strong driving force for thiolates to add to triple bond in a trans manner so as to overcome even the adverse steric and electronic factors.

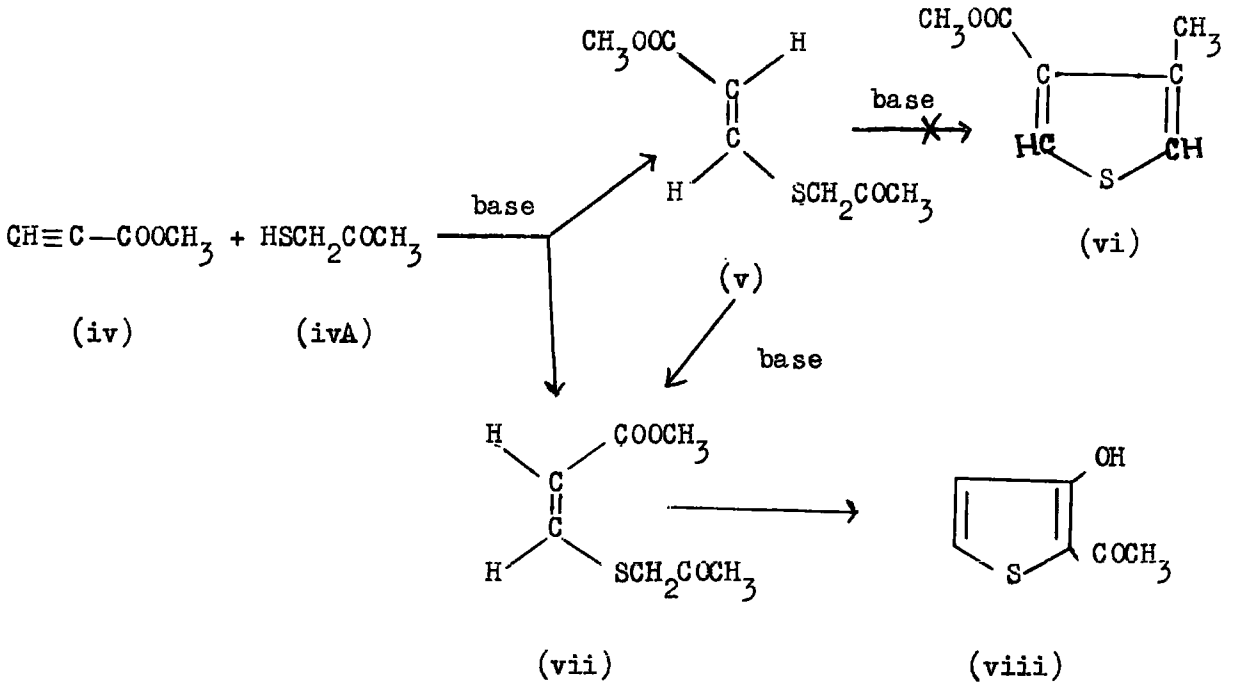
In nearly all cases chemical evidence was produced to confirm the assignments. Physical methods[99], in particular the use of infrared absorption spectroscopy, nuclear magnetic resonance spectroscopy and dipole moments were all used to confirm the assignments when both isomers were available for comparison. An elegant example of the application of infrared data was to distinguish between 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 3118 cm^{-1} corresponding to the O-H stretching mode, while the cis-isomer (iii) showed a broad absorption with many submaxima in the region 3000 - 2500 cm^{-1}. The carbonyl (C=O) stretching frequency of (iii) was at 1685 cm^{-1}, compared with 1730 cm^{-1} for the trans - isomer, a shift of 45 cm^{-1} which was attributed due to the hydrogen bonding in the cis-compound. This evidence points to the cis-isomer existing in the form illustrated below. Such intramolecular hydrogen bonding is impossible for the trans-isomer.



(iii)

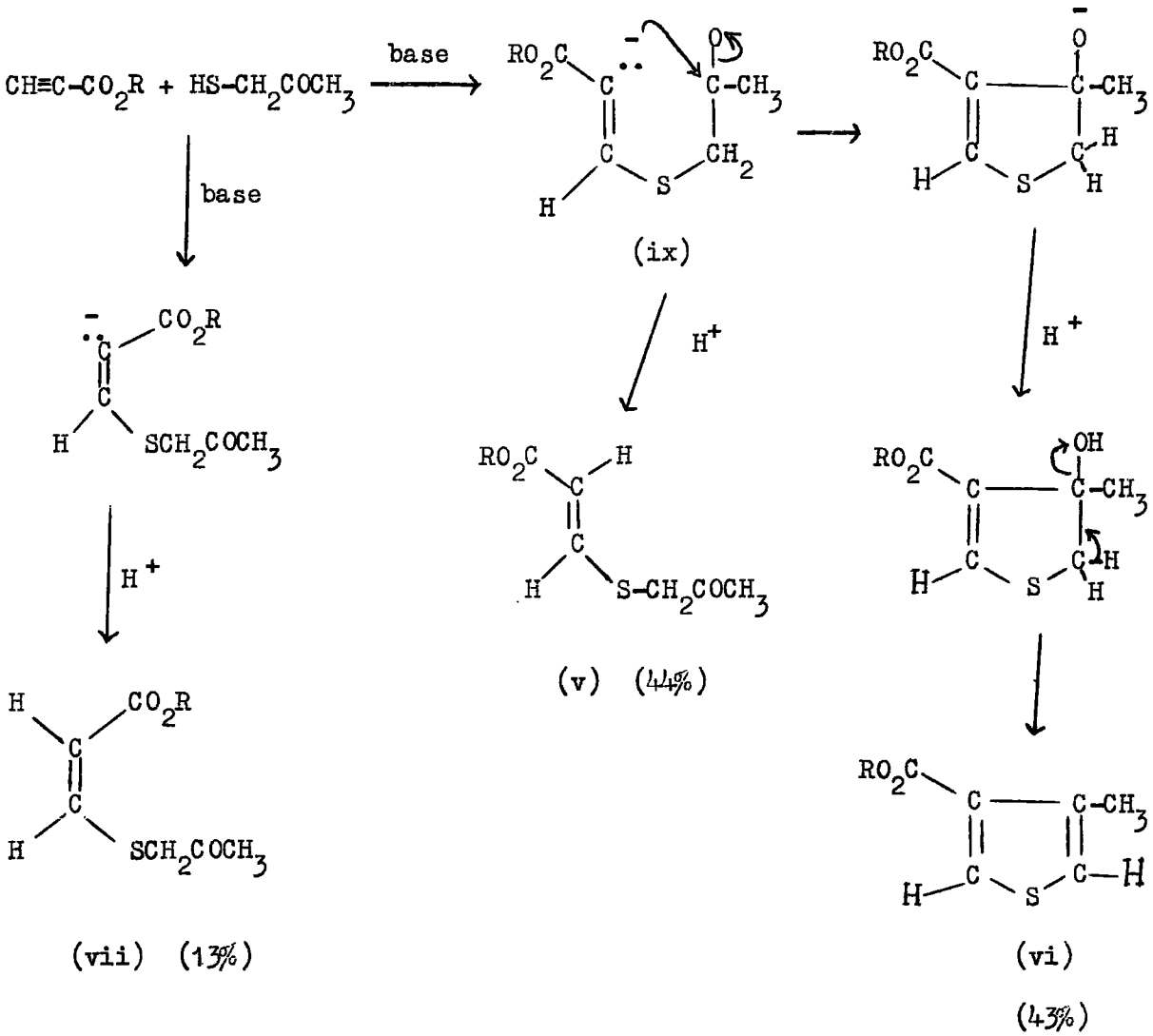
The kinetics of thiolate addition reactions to substituted acetylenes has been investigated[100].

More recently the stereochemistry of the addition of mercaptans to the esters of acetylenic carboxylic acids and their cyclization to substituted thiophens were investigated by Bohlmann and Bresinsky[101]. These authors observed that the reaction of methyl propialate (iv) with mercapto acetone (ivA) could produce under the influence of a base both <u>cis</u>- and <u>trans</u>- addition products.

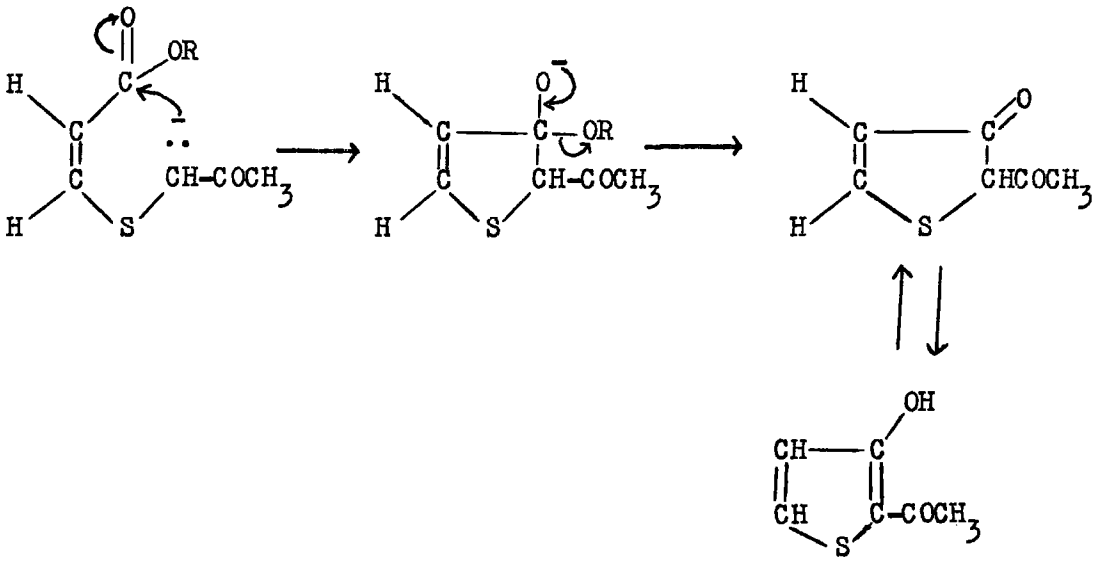


The interation of (iv) and (ivA) in the presence of a molar amount of potassium tertiary butoxide proceeded directly to (viii) without isolation of the intermediate product. With a catalytic amount of tertiary butoxide, however, a mixture of 44% (v), 13% (vii) and 43% (vi) was

obtained. The authors suggested the following mechanism for the formation of (vi) using a catalytic amount of tertiary butoxide:

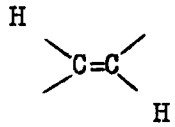


that is the reaction proceeds via a carbanion (ix) which is formed by an overall <u>cis</u>-addition of the thiolate to the triple bonds. To rationalize the direct formation of (viii) by the interaction of (iv) and (ivA) in the presence of a molar amount of t-butoxide it was suggested (1) that under the reaction conditions, (v) is isomerized to (vii) and (2) a proton from the $-S-CH_2-$ group is removed by the base to form a carbanion which then cyclizes in the following way:

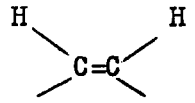


(viii)

The assignment of the isomers was made on the basis of their nuclear magnetic resonance spectra. In 1,2-disubstituted ethylenes the <u>trans</u>-vinyl protons are found to have a larger value of the coupling constant than the <u>cis</u>-vinyl protons[102]:



<u>Trans</u> J_{HH}=11 to 18 cps



<u>Cis</u> J_{HH}=6 to 14 cps

The compound having proton-proton coupling constant of 15 cps was assigned the structure (v) and that having a value of 10 cps was given the structure (vii).

Analogous result was obtained with ethyl propiolate and methyl mercaptoacetate.

The authors found that ethyl tetrolate and thiolates under similar reaction conditions resulted only in <u>cis</u>-additions and several thioethers and substituted thiophen derivatives were isolated.

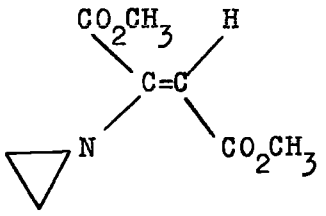
The addition reaction between thiophenol and phenylacetylene has been studied by Yu-Ch'eng Lin and Hsu-K'un Wang[103]. With molar ratio of 1:1 the two reactants were found to add rapidly at 0° to give <u>trans</u> β-phenylthiostyrene in quantitative yield. When the reaction was conducted at -20° or -40°, the adducts consisted of about equal amounts of <u>trans</u>- and <u>cis</u>- β-phenylthiostyrene. The <u>cis</u>-β-phenylthiostyrene was converted to the <u>trans</u> isomer upon heating to 180°. However, <u>cis</u>-β-phenylthiostyrene was obtained as the sole product when sodium thiophenolate was added to phenylacetylene in absolute alcohol. These authors thought

that the direct addition of thiophenol to phenylacetylene probably took place by a free radical chain mechanism.

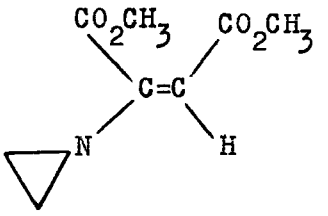
In a recent article[86] free radical addition of aromatic and aliphatic thiols to phenyl acetylene has been described. It has been found that when equimolar amounts of reactants were mixed at ambient temperatures, mainly trans mono addition occurred, yielding cis-1-substituted mercapto-2-phenylethenes. The resulting cis adducts were readily isomerized by thiyl radicals to equilibrium mixtures consisting mainly of the trans isomer.

B. Addition of Amines

The stereochemistry of amine additions to acetylenic esters has also been systematically studied. Dolfini[104] found that reaction of equimolecular quantities of aziridine and dimethyl acetylenedicarboxylate in methanol gave a product (76% yield) comprising 67% of (x) and



(x)

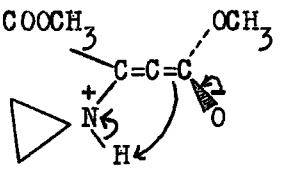


(xi)

33% of (xi). When the reaction was repeated in dimethylsulphoxide under the same conditions the product (75% yield) consisted of 95% (xi) and only 5% (x). The reaction of aziridine with ethyl propiolate proceeded

in a similar fashion.

The variation of the course of amine addition in dimethyl sulphoxide vs. methanol was attributed to the formation of the zwitterionic intermediate (xii).



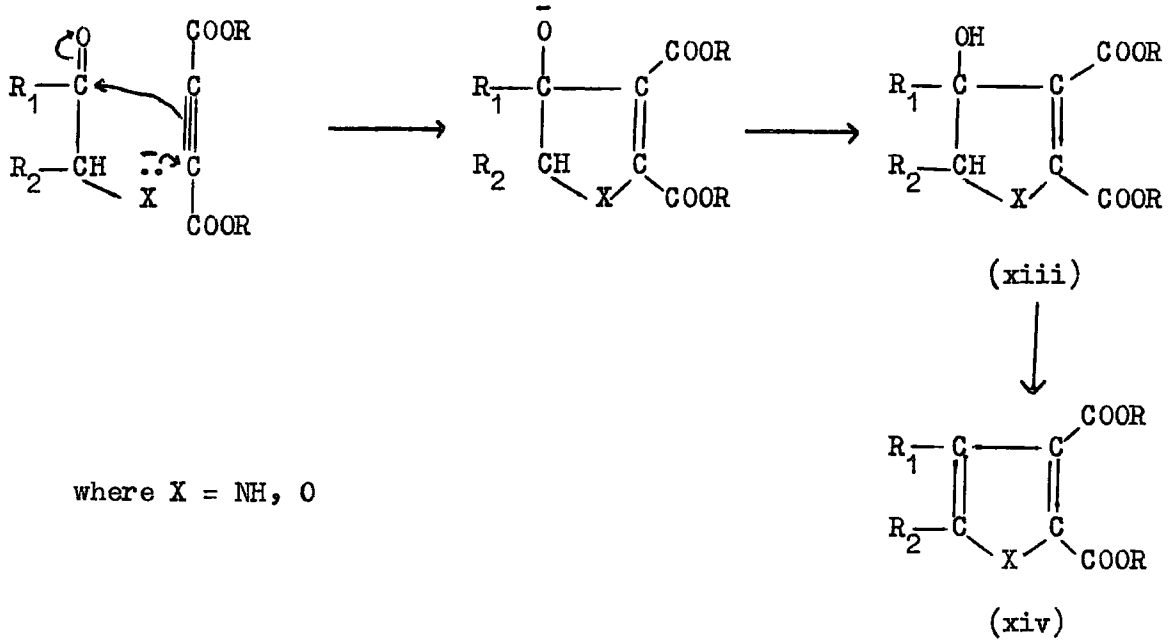
(xii)

In the absence of an external proton source the zwitterion might be expected to undergo a steriospecific collapse via intramolecular protonation leading to the <u>cis</u> disposition of the ester functions.

In a recent paper[105] the reactions of dimethylamine, piperidine and aziridine with dimethyl acetylenedicarboxylate and methyl propiolate in ether were investigated. The products obtained were almost extensively those resulting from <u>cis</u>-addition of the nucleophiles. Only in the reactions with aziridine a small (9-17%) amount of the other isomer, corresponding to the <u>trans</u> addition, was obtained.

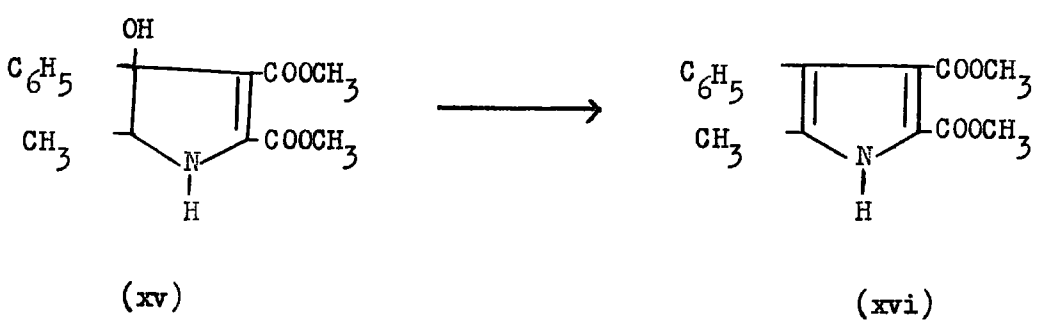
Hendrikson[106,107] and co-workers prepared a number of 5-membered heterocyclic compounds by the reaction of acetylenedicarboxylic esters

with various nucleophiles selected by reference to a general scheme as follows:

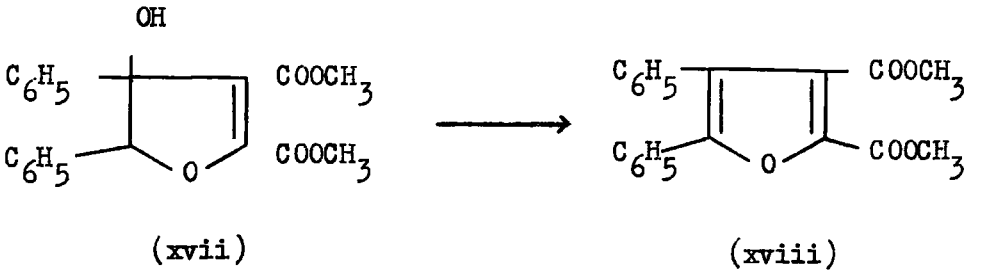


where X = NH, O

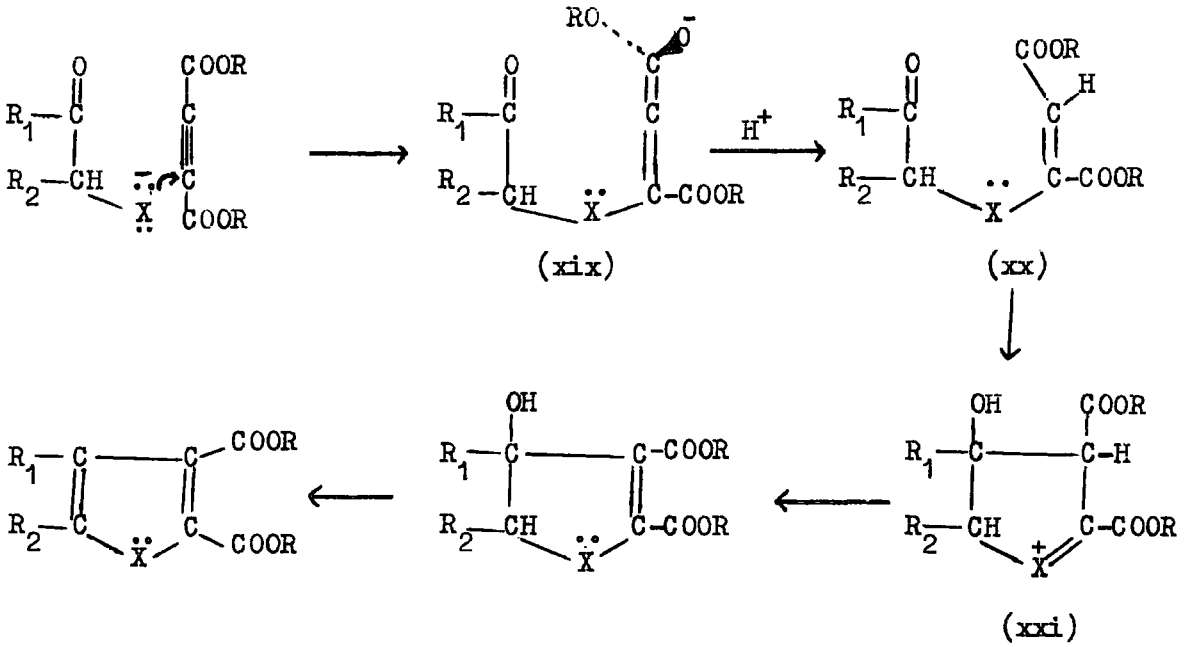
When equimolecular amounts of α-aminopropiophenone hydrochloride, sodium acetate, and dimethyl acetylenedicarboxylate were boiled in methanol a high yield of (xv) was obtained which gave pyrrole (xvi) with a trace of acid. In an analogous reaction with basic catalysis



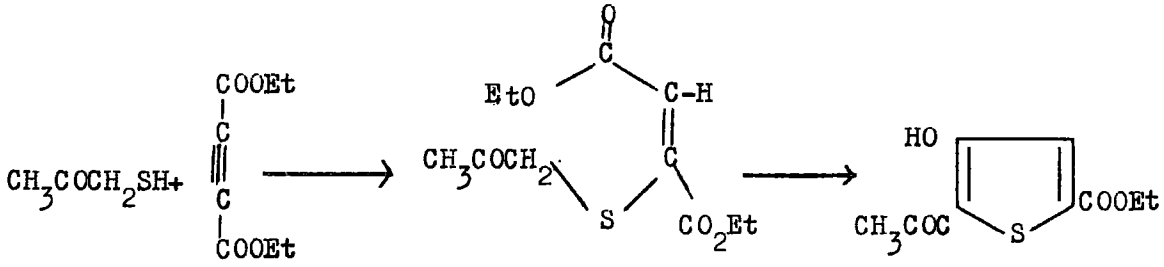
(Potassium carbonate) benzoin yielded the hydrated furan (xvii)



which dehydrated easily in methanolic acid to give the furan (xviii). As to the course of these reactions the authors concluded that instead of the initial attack on the acetylinic carbon by $-\ddot{X}$ and the ring closure being accomplished in a single fast sequence analogous to that for 1,3-dipolar addition (as shown in the above scheme), a simple trans-addition product (xx) is first formed through an intermediate enolate (xix) by protonation. This could in turn cyclize via (xxi) to (xiv).



Evidence bearing on this choice of routes has been derived from the experiments aimed at thiophen syntheses analogous to those above. For example, when mercaptoacetone reacted with diethyl acetylenedicarboxylate in boiling ethanol (xxii) was obtained. The authors argued that



(xxii)

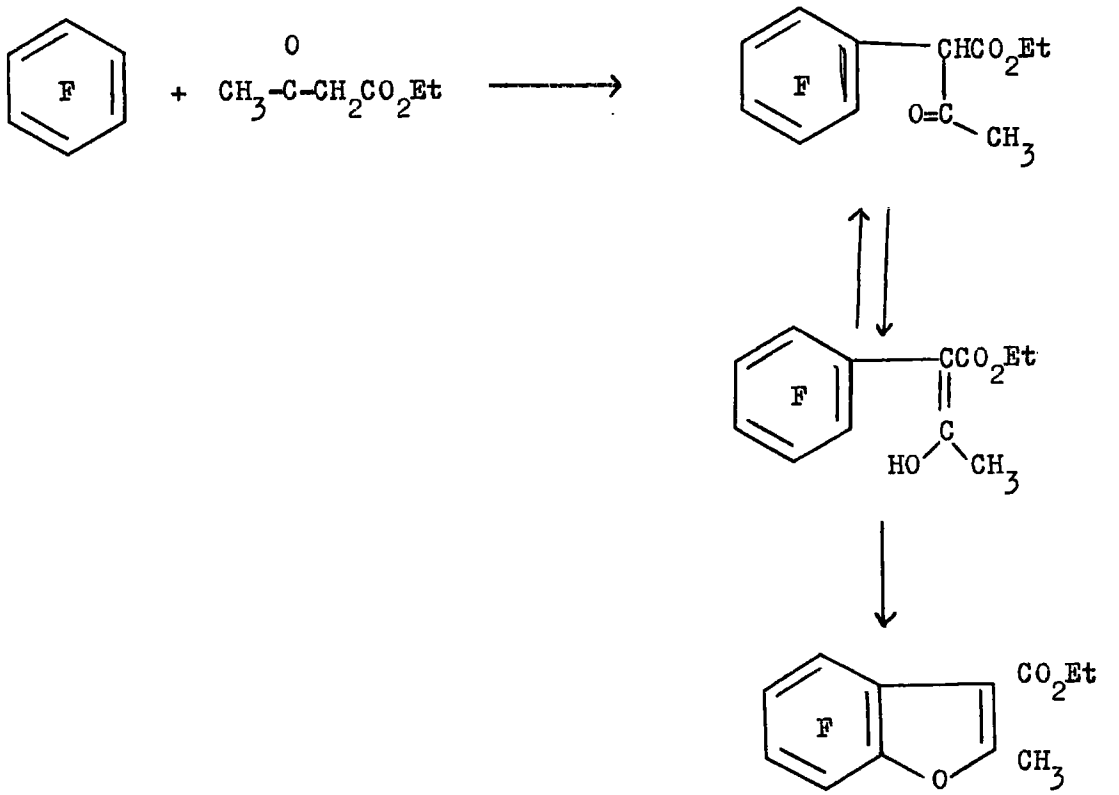
while cyclization of (xx) to (xxi) in the cases of X = O and N is reasonable, it is not so with the sulphur analogue owing to the presence of the unfavourable C=S double bond in (xxi), and conversely the alternative Dieckmann-type cyclization is favoured in sulphur case by the extra stabilization afforded the enolate in such a cyclization by overlap with the d-orbitals of the adjacent sulphur atom.

CHAPTER IV

THE PREPARATION OF DERIVATIVES OF 4,5,6,7-TETRAFLUOROBENZO[b]THIOPHEN BY THE NUCLEOPHILIC ADDITION OF LITHIUM PENTAFLUOROTHIOPHENATE TO DIETHYL ACETYLENE-DICARBOXYLATE .

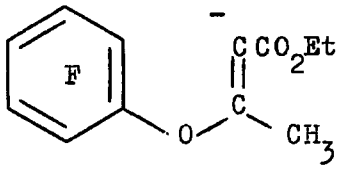
THE PREPARATION OF DERIVATIVES OF 4,5,6,7-TETRAFLUOROBENZO[b]THIOPHEN BY THE NUCLEOPHILIC ADDITION OF LITHIUM PENTAFLUOROTHIOPHENATE TO DIETHYL ACETYLENE-DICARBOXYLATE

Before this work was started, Russian workers[70] had found that ethyl acetoacetate, sodium hydride and hexafluorobenzene when heated together in D.M.F. in approximately equimolecular quantities gave a 30% yield of 4,5,6,7-tetrafluorobenzofuran derivative (i) (also mentioned in Chapter I, p.26 and Chapter II, p. 51). The reaction mechanism which they suggested is outlined below:



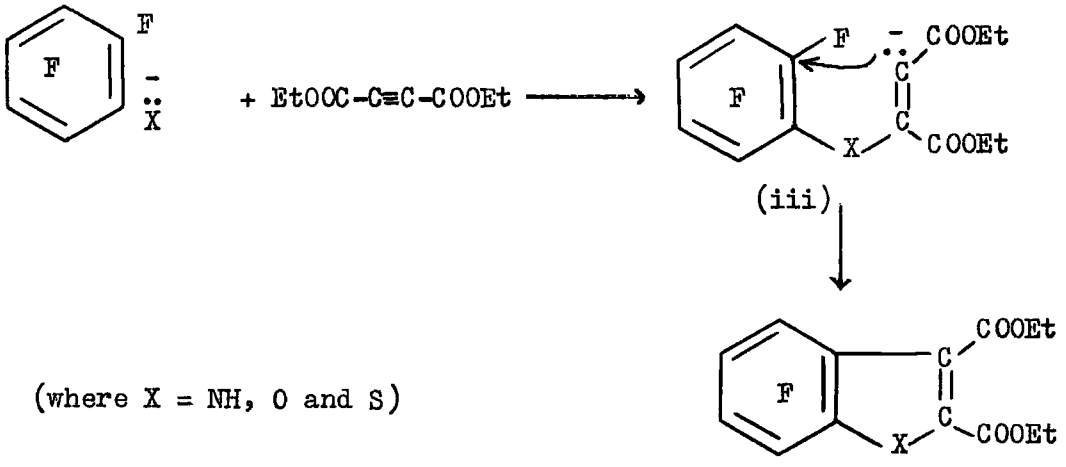
(i)

The same reaction has also been carried out by other workers[108] who believe that the first stage of the reaction is O-alkylation of hexafluorobenzene to give intermediate (ii) which is then cyclized.



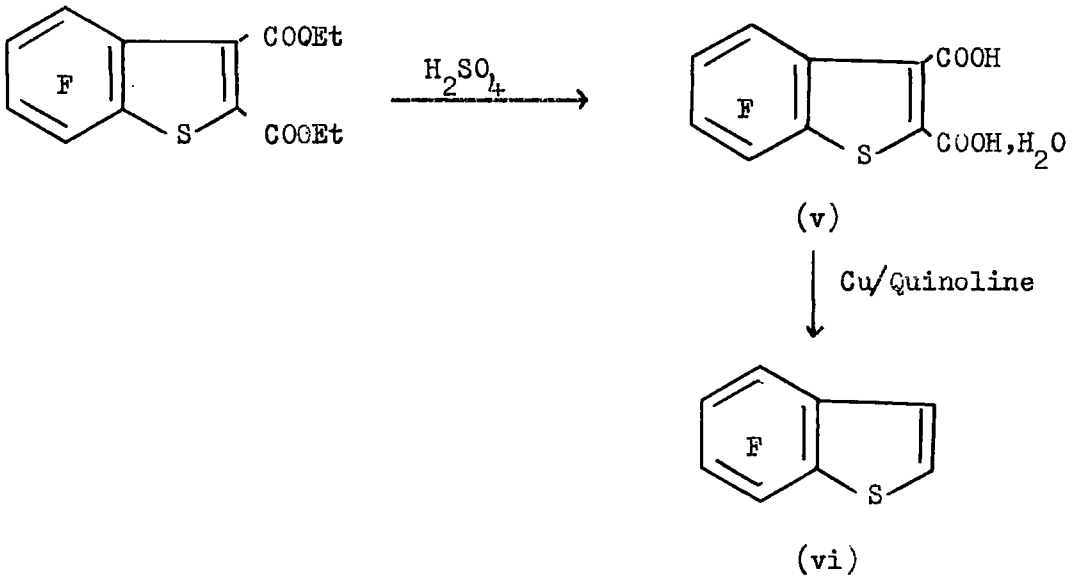
(ii)

In the light of this latter mechanism it was thought that intermediates similar to (ii) could also be produced by the addition of the sodium or lithium salts of pentafluoroaniline, pentafluorophenol and pentafluorothiophenol to diethyl acetylenedicarboxylate leading finally to the formation of corresponding heterocyclic compounds. These possibilities are shown by the following sequences:



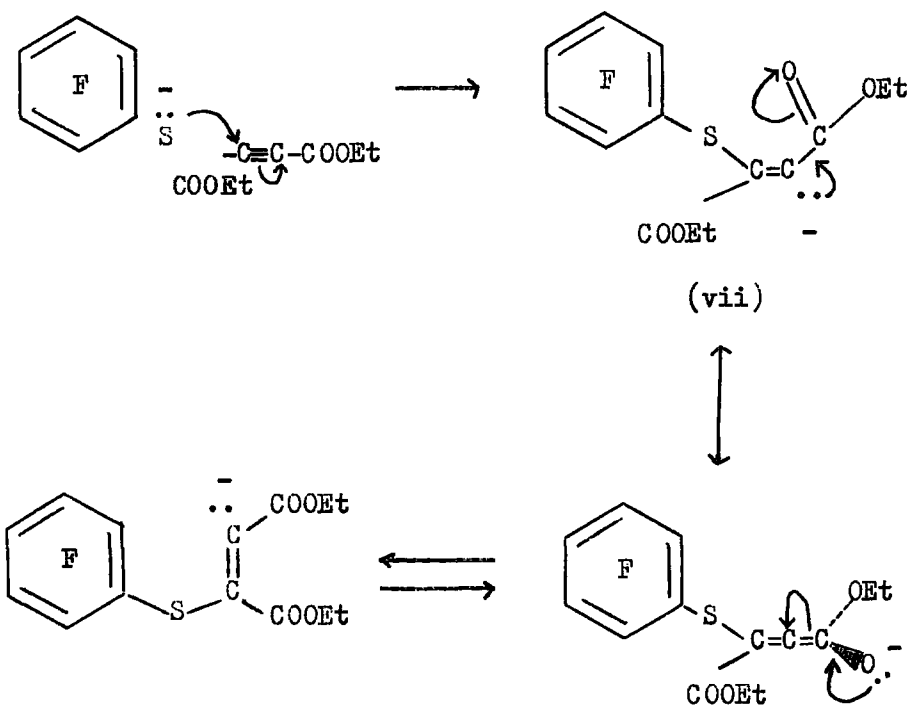
(where X = NH, O and S)

Although attempts to prepare benzo[b]furan[109] and indole[72] derivatives (iv, X=O & NH respectively) according to the above scheme have so far been unsuccessful, olefinic products being isolated in both cases, the benzo[b]thiophen derivative (iv, X=S) was easily formed when pentafluorothiophenol in dry tetrahydrofuran was treated at -70° with n-butyllithium in hexane followed by slow addition of diethyl acetylenedicarboxylate, the temperature being kept at less than -55°. The structure of the product was determined by its molecular weight (mass spectrometry), correct elemental analysis and by its ^{19}F n.m.r. spectrum. There were four magnetically different types of fluorine atom. Hydrolysis of the diester (iv, X=S) with



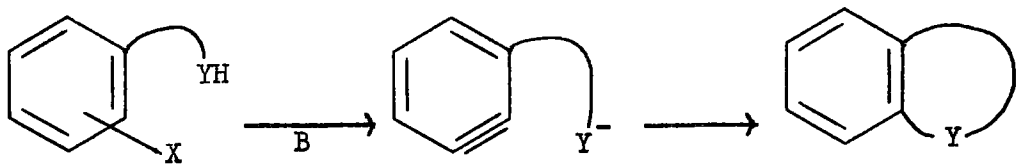
sulphuric acid (50% v/v) gave the corresponding dicarboxylic acid which was isolated as a monohydrate (v) from water. On decarboxylation,

using copper powder in quinoline, this compound gave 4,5,6,7-tetrafluorobenzo[b]thiophen (vi) as a volatile low melting solid (46-48°). In order for the cyclization to occur in the above reaction, the intermediate carbanion (iii, X=S) must be such that a potential <u>cis</u> addition to the triple bond must have occurred. Alternatively, if the addition took place in the expected <u>trans</u> manner, the intermediate carbanion (vii) must have isomerised to (iii, X=S) before it could cyclize. This may possibly occur as follows:



Attempts were made to determine the stereochemistry of the intermediate carbanion by isolating olefinic products.

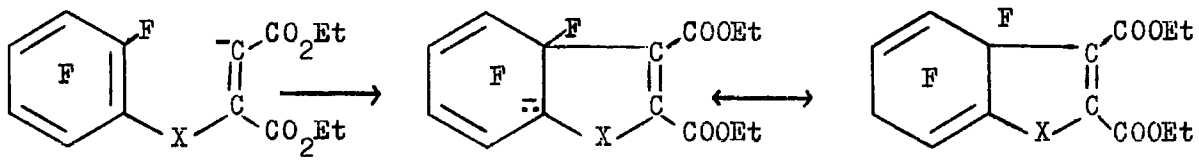
The reaction was repeated at -60°, -90° and -110° respectively, in each case the protonating agent being added at approximately the corresponding temperatures. No olefin was isolated; the cyclised product was formed in each experiment. At the lowest reaction temperature ether was used as co-solvent with tetrahydrofuran in order to prevent solidification. The above results show clearly how strong is the driving force for cyclization. Since it was not possible to isolate an olefin, the mode of addition of pentafluorobenzenethiolate ion to the triple bond of diethyl acetylenedicarboxylate remains obscure. Bunnett[110] has described a general principle of ring closure by the formation of an aryne (benzyne) intermediate having a side chain bearing a strong nucleophile which can add intramolecularly to the aryne structure. The principle has been represented by the generalized equation



in which X is a halogen atom <u>ortho</u> or <u>meta</u> to the side chain and YH is a functional group which, upon loss of proton, forms the nucleophilic group Y^-. This seems to be the closest approach to the reaction of pentafluorobenzenethiolate ion and diethyl acetylenedicarboxylate to give the tetrafluorobenzo[b]thiophen derivative.

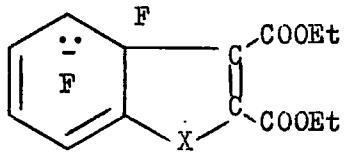
The spontaneous cyclization in the case of pentafluorothiophenol and apparent lack of success in obtaining a cyclized product with

pentafluorophenol and pentafluoroaniline may be rationalized by comparing in each case the relative stability of the transition states (viii, ix, x) in the final cyclization step of the reaction in which nucleophilic replacement of fluorine has to take place.



(viii) (ix)

(X = O, NH & S)



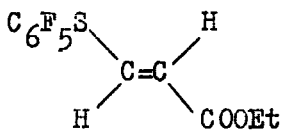
(x)

Although p-quinonoid structures (ix) are considered more important than o-quinonoid (viii) in nucleophilic aromatic substitutions[111], in this particular case the o-quinonoid form (viii) having the lone pair of electrons adjacent to the heteroatom may be the most important one that controls the reaction. In the case when X=S, since the lone pair of electrons are stabilized by overlap with the d-orbitals of the adjacent sulphur atom, this form will have the lowest energy. As a result the reaction is likely to be facilitated in the case where X=S but not in the

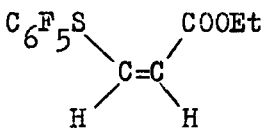
other two cases (X=O and NH) where there is no possibility of similar stabilization of the lone pair of electrons in the transition states.

Polyfluoro aromatic compounds, C_6F_5X with X = -OMe and -NHMe have been found to be deactivated relative to pentafluorobenzene towards nucleophilic substitution whereas with X = -SMe the molecule is activated towards replacement of fluorine.

When lithium pentafluorothiophenate was reacted with ethyl propiolate under the same conditions as with diethyl acetylenedicarboxylate no cyclization product was formed. Instead olefins (xi) and (xii) were obtained.



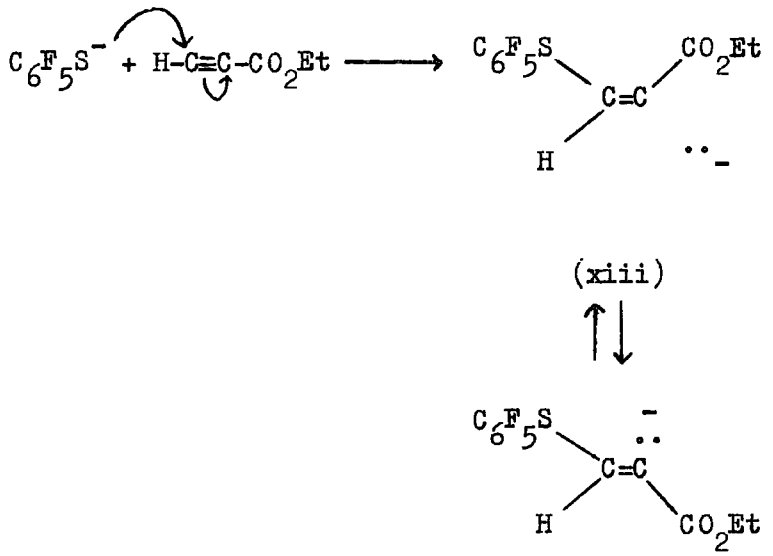
(xi)



(xii)

as a mixture, the proportion of the <u>cis</u> olefin, (xii), being 90% and that of the <u>trans</u>, (xi), 10%. The isomer ratios were determined from the integrated ^1H n.m.r. spectrum.

Drastic conditions were then used in an attempt to induce cyclization but without any success. Thus, after the additions of all the reagents at -60 to -70°, the mixture was heated under reflux for 115 hours and then worked up the usual way. The product obtained was found to contain almost equal proportions of (xi) and (xii). This clearly suggested that the intermediate carbanion (xiii) first formed, when heated, isomerized to (xiv) which is the precursor for cyclization.

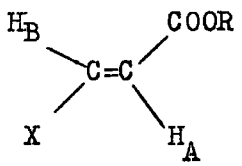


(xiii)

(xiv)

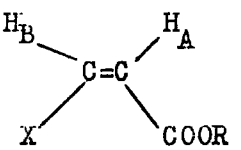
The experiment was repeated in an autoclave at 190° for 5 hr. in the hope of obtaining some cyclized product. The product again consisted of the two isomeric olefins - no cyclised material was isolated.

The assignment of the configurations and the determination of the isomer-ratio was based on ^1H n.m.r. spectra (coupling constants). In a recent article Winterfeldt and Preuss[105] described the chemical shift and the coupling constants in a series of olefinic compounds of type (xv) and (xvi) and



(xv)

Trans-olefin



(xvi)

Cis-olefin

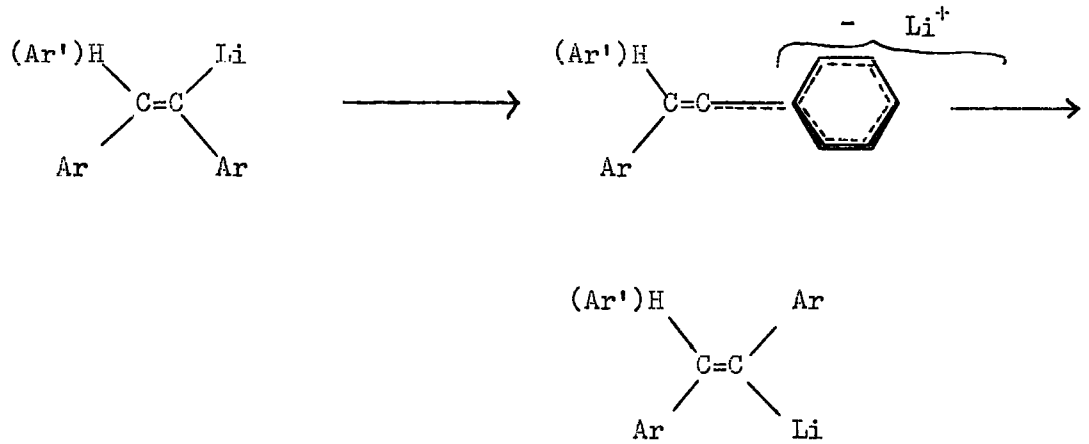
these results are tabulated below.

Chemical shifts and coupling constants of olefinic protons in *cis*- and *trans*-acrylic ester derivatives

X	(xv)			(xvi)		
	H_A	H_B	J	H_A	H_B	J
	τ	τ	c.p.s.	τ	τ	c.p.s.
$-N(Et)_2$	5·55	2·70	13	-	-	-
$-NMe_2$	5·60	2·70	13	-	-	-
$-NC_5H_{10}$	5·55	2·90	13	-	-	-
$-OCH_3$	4·85	2·45	12·5	5·30	3·60	7
$-OCH(CH_3)_2$	4·85	2·55	12·5	5·35	3·55	7
$-OC_6H_5$	4·45	2·25	12·5	4·9	3·15	7

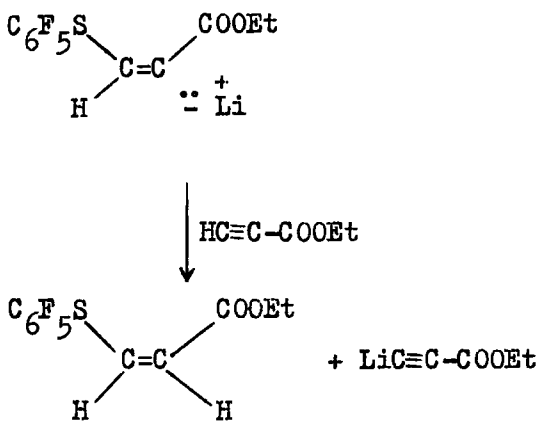
The ^1H n.m.r. spectrum of the pure cis-olefin (xii) obtained by crystallization from light petroleum (b.p. 40 - 60°) showed a triplet for the methyl protons at 8·7, a quartet for the methylene protons at 5·8 and two doublets at 3·1 and 4·1 respectively for the two olefinic protons. The pure *cis*- compound was found to isomerize when exposed to daylight at room temperature for a long time as well as when exposed to u.v. radiation or heated at high temperature (100 - 150°). Thus, a freshly prepared sample containing 90% of the *cis*-olefin when left on the bench for about 4 months was found to contain equal amounts of both the isomers. A sample of pure

cis-compound after being heated to 100° for 127 hr in the absence of light was found to contain 35% of cis- and 65% of trans-compound, whereas heating it at 158° for 72 hr. in the absence of light resulted 27% of cis- and 73% of trans-compound. These results were all based on the results of ^{1}H n.m.r. spectra. The isomerization of vinyl carbanions has been observed and studied previously by various workers[112]. Curtin and co-workers studied the geometric stability of cis- and trans-vinyl-lithium compounds as structure and solvent were varied[30]. They found that the rates of isomerization of arylvinyllithium compounds vary markedly with the solvent polarity, the rate decreasing in the order tetrahydrofuran > 3 to 1 ether-benzene > hydrocarbon solvents. The authors suggested that the isomerization of the arylvinyllithium compounds occurs by ionization of the partially covalent carbon-lithium bond; that the vinyl anion isomerizes through linear transition state or intermediate in which charge is highly delocalized into the benzene ring; and that recapture of the lithium ion occurs to give isomerized organometallic.



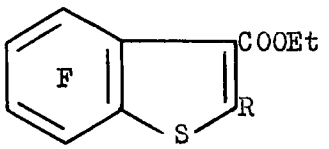
It is clear from the above results that the addition of lithium pentafluorothiophenate to ethyl propiolate is stereospecific, the addition of the thiolate ion taking place almost entirely in the trans-manner. The presence of 10% of trans-olefin (xi), in the product of usual reaction process (without reflux) could be explained by assuming that the cis-compound (xii), isomerizes during the course of distillation. This is supported by the fact that the pure cis-compound was found to isomerize appreciably to the trans-olefin when heated to 158° for 30 minutes in the absence of light.

It was rather surprising that ring closure did not occur in the reaction between lithium pentafluorothiolate and ethyl propiolate even under drastic reaction-conditions while spontaneous cyclization resulted when the former was treated with diethyl acetylenedicarboxylate. One explanation may be that the carbanion (xiii) produced by the initial addition of the thiolate ion to the triple bond of ethyl propiolate is protonated by



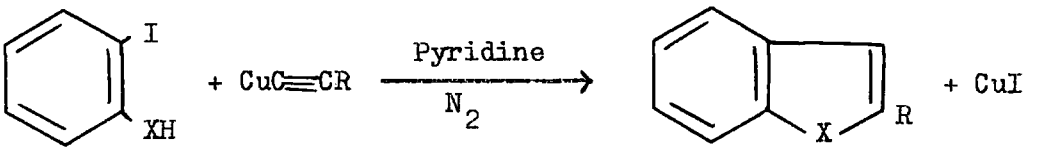
ethyl propiolate itself before cyclization can take place. When diethyl acetylenedicarboxylate is used instead of ethyl propiolate no such intermolecular protonation of the corresponding carbanion can occur and as a result the carbanion remains free to effect a nucleophilic replacement of fluorine at the benzene ring.

If the above explanation is true then lithium pentafluorothiophenate should also react with compounds of the type R-C≡C-COOEt (which have no labile hydrogen atoms; R=Alkyl or Aryl group, -CN etc) to give tetrafluorobenzo[b]thiophen derivatives (xvii) by one-step cyclization. Further work in this direction is merited.



(xvii)

Recently a number of heterocyclic substances containing nitrogen and oxygen have been made in high yields by following a scheme outlined below[113]:



(where X = O, NH; R = C_6H_5, $CH_3CH_2CH_2$-)

This route for synthesizing heterocyclic compounds may conveniently be extended to the preparation of 4,5,6,7-tetrafluorobenzo[b]thiophen derivatives and other polyfluoro heterocyclic compounds, especially as copper salts of a number of organic compounds have been shown to replace a halogen other than fluorine in polyfluoroaromatic compounds[114].

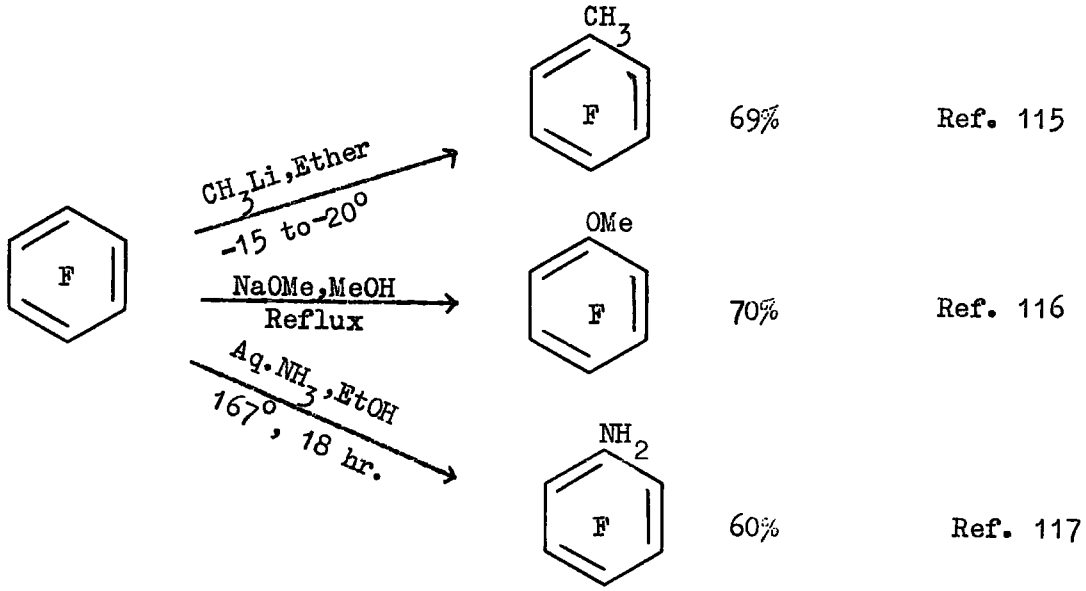
CHAPTER V

NUCLEOPHILIC SUBSTITUTIONS IN POLYFLUORO-AROMATIC COMPOUNDS

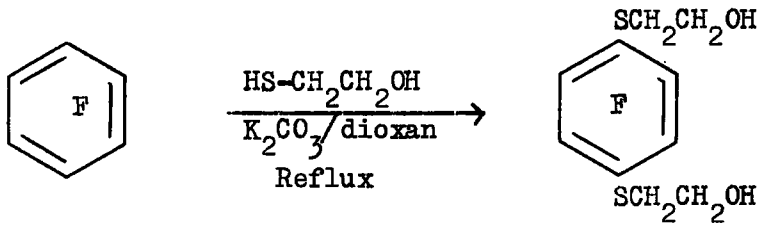
NUCLEOPHILIC SUBSTITUTIONS IN POLYFLUORO-AROMATIC COMPOUNDS

The nucleophilic replacement of fluorine in polyfluoro-aromatic compounds is of general interest in the same way as is the electrophilic substitution of hydrogen in the hydrocarbon analogues.

The nucleophilic substitution reactions of hexafluorobenzene have been thoroughly studied with a wide variety of nucleophiles. In almost all cases the reaction took place under moderate conditions and usually mono-substitution occurred to give good yields of pentafluorophenyl derivatives e.g.,



An example of disubstitution however is the formation of (i) in good yield



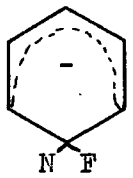
(i)

when hexafluorobenzene was reacted with 2-mercaptoethanol[81]. No mono-replacement product was isolated. It was concluded that the 2-hydroxy-ethylthio-group (an SR group) activates the pentafluorophenyl ring to further nucleophilic attack.

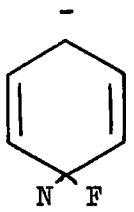
Nucleophilic replacement of fluorine in pentafluorophenyl compounds, C_6F_5X, is of considerable interest because three different positional isomers can be formed. In most cases ($X=H,CH_3,SMe,CF_3,NMe_2,SO_2Me,Cl,Br,I$)[23,118] the fluorine <u>para</u> to X is the one which is usually replaced; <u>meta</u>-replacement[119,121] predominates however when $X=NH_2,O^-$, whereas comparable amounts of <u>meta</u>- and <u>para</u>-replacement[119,120] occur with X=OMe and NHMe.

A rationalization of these results has been put forward by Burdon in a recent article[111] in which it was assumed that fluorine is electron repelling in π-electron system and thus destabilizes a neighbouring negative charge by an effect which is called $I\pi$ repulsion. $I\pi$ repulsion is said to be due to coloumbic repulsion between the negative charge and the lone pairs of electrons on the halogen[122].

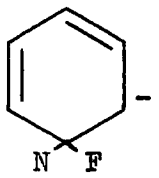
The relative stabilities of the transition states for nucleophilic substitution in a pentafluorophenyl derivative, C_6F_5X, were discussed in terms of Wheland-type intermediates (ii),



(ii)



(iii)



(iv)

and it was assumed that both steric and solvent effects were negligible. The resonance hybrid (iii) (para-quinonoid structure) was taken to be the main contributor to this intermediate, with the two hybrids of type (iv) (ortho-quinonoid structure) of only secondary importance. The substituent attached to the carbon bearing the negative charge in (iii) can now exert an influence on the stability of the charge, the magnitude and direction of which will be determined by the nature of the substituent itself.

If the substituent, X, is electron attracting in π-electron systems it will stabilize the negative charge in (iii) and the substitution will take place at the carbon para to it. If X is neutral it will also stabilize the negative charge in (iii) relative to fluorine and hence para substitution will again take place. However, the rate of reaction in the former case is expected to be much greater than in the latter. This has been found true. Kinetic evidence[123] shows that pentafluoronitrobenzene (NO_2 group strongly electron attracting) is more reactive than pentafluorobenzene (H is neutral in this respect) by a factor of $2{\cdot}3 \times 10^6$.

If X is electron repelling and the effect is very similar to that of a fluorine on the stability of the negative charge in (iii), then the ortho:meta:para replacement ratio will approach the statistical 2:2:1. When the substituent is a less powerful electron-donor than fluorine increased amount of para substitution will take place.

This is illustrated in the reaction of pentafluorohalogenobenzenes[124], C_6F_5X (X=Cl,Br,I) shown below.

Compounds	C_6F_5Cl	C_6F_5Br	C_6F_5I	C_6F_5H
% of Ortho* substitution on reaction with NaOMe in MeOH	17	12	5	3

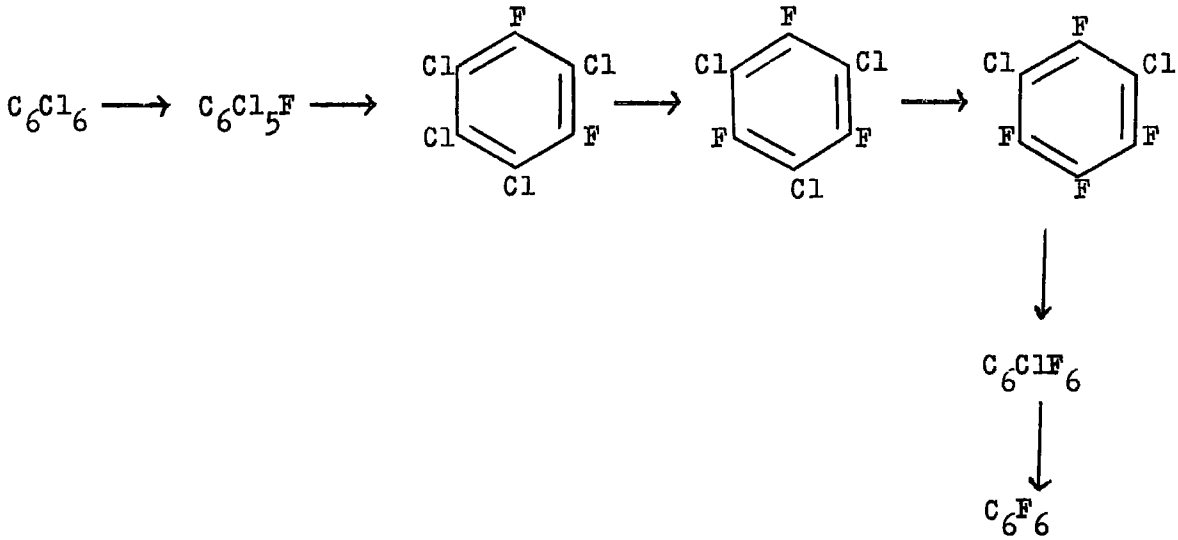
* The rest is para substitution except 3% and 1% meta-replacement in C_6F_5Cl and C_6F_5Br respectively.

Iπ-repulsions of halogens have been postulated to decrease in the order $\bar{C}$-F > $\bar{C}$-Cl > $\bar{C}$-Br > $\bar{C}$-I ~ $\bar{C}$-H and it can be seen in the above table that as the halogen changes from chlorine to iodine ortho replacement decreases with a corresponding increase in the para.

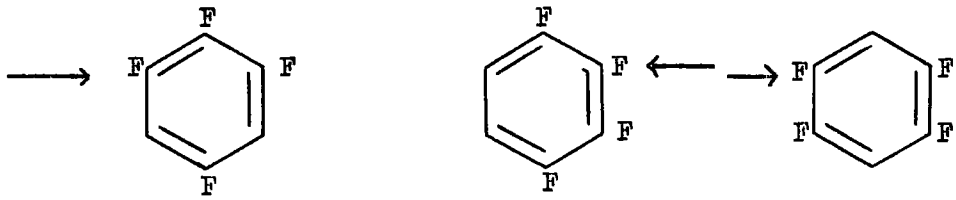
When X, on the other hand, is more electron repelling than fluorine, it destabilizes the negative charge in (iii) more effectively, and meta replacement will predominate. This is examplified in pentafluoroaniline,[117,120] in which replacement of fluorines meta and para to the amine group occurs in the approximate ratio[120] m:p = 7:1. In fact the meta:para replacement ratio should increase with increasing donor power of the substituent X, and at the same time the reaction rate should decrease. This has been shown[119] in the nucleophilic replacement of, (in order of increasing donor capacity of substituent), pentafluorotoluene, -anisole and -phenol. Sodium methoxide, hydrazine, and ammonia reacted with pentafluorotoluene to replace only the fluorine para to the methyl group; both sodium methoxide and methyl lithium give a meta/para replacement ratio of 7:12 with

pentafluoroanisole; whereas only <u>meta</u> replacement occurs in the pentafluorophenol-potassium hydroxide reaction.

A direct consequence of the Iπ-repulsion of chlorine being less than fluorine is illustrated in the path taken by the hexachlorobenzene-alkali fluoride reaction[49].



Excellent evidence in favour of the Iπ repulsion argument mentioned above is obtained from the three tetrafluorobenzenes which react with nucleophiles at the positions indicated[125].



(v) (vi) (vii)

In (v) and (vi) the positions attacked are those which lead to

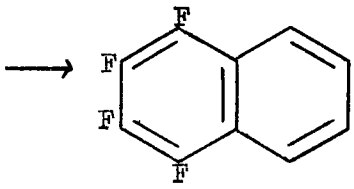
intermediates of type (iii) in which the negative charge is localized on a hydrogen-bearing carbon. With (vii) however there is no orientation problem, but the compound reacts about 10^3 times more slowly with sodium methoxide than the other two tetrafluorobenzenes do. In this case the intermediate of type (iii) requires that a negative charge be localized on a fluorine-bearing carbon. Assuming that the three tetrafluorobenzenes have comparable ground state stabilities, it was concluded that fluorine does destabilize a negative charge in a nearby π-system, and also that contributions to the transition state of type (iv) are only of secondary importance. If they were equivalent to type (iii) then the tetrafluorobenzenes would react at comparable rates.

Although these rationalizations account very well for almost all of the substitution reactions of polyfluorobenzene derivatives, there are a number of apparent anomalies. For example, with pentafluoronitrobenzene[126], pentafluorobenzoic acid[83] and pentafluoronitrosobenzene[118] reaction occurs mainly at <u>para</u> position with sodium methoxide in methanol, but high <u>ortho</u> replacement ($>50\%$ in some cases) results with amines. These latter orientations have been explained by a consideration of hydrogen bonding between the nucleophile and the substituent group already present in the polyfluoroaromatic compound. On the other hand, methoxide can also give high <u>ortho</u> replacement in ether containing a little methanol.[127]

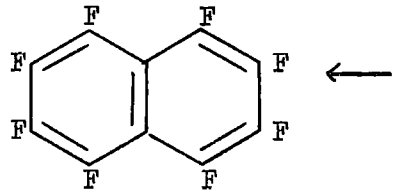
Recently the reactions of 2-substituted-tetrafluoronitrobenzenes, $2\text{-}XC_6F_4NO_2$ ($X=NH_2$, $NHMe$, NMe_2 and OMe) with various nucleophiles[128] have been reported to give mixtures of 2,4- and 2,6-isomers. The results were

rationalised by considering the steric effects of the substituent, X, preventing the adjacent nitro-group from achieving the coplanarity necessary for exerting its full activating effect.

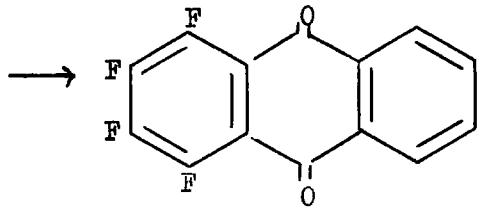
Substitution in 1,2,3,4-tetrafluoro-[129] and octafluoronaphthalene[130] [(viii) and (ix) respectively] was also rationalized on the basis of the theory outlined above. In both the cases the β-fluorine is replaced; it is only by attack at this position that localization of a negative charge on a <u>para</u> carbon bearing a fluorine can be avoided as shown below:



(viii)



(ix)



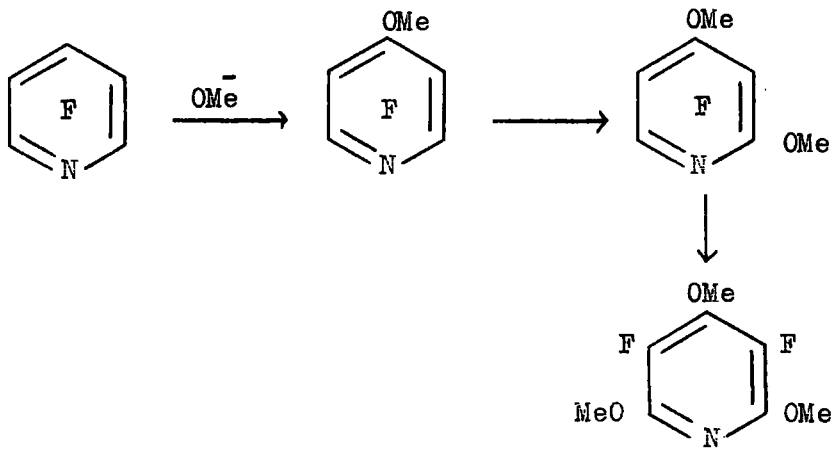
(x)

Similarly, 1,2,3,4-tetrafluoroanthraquinone,[131] (x) has recently been shown to be most susceptible to nucleophilic attack in the 2-position.

Reaction of pentafluoropyridine with nucleophilic reagents has been studied both by workers at Durham[132] and Manchester[133]. It was found that nucleophilic displacement of fluoride ion from pentafluoropyridine occurred

much more readily than from hexafluorobenzene. Aqueous ammonia in ethanol reacted with pentafluoropyridine at 80° for 2 hr. to give a quantitative yield of 4-aminotetrafluoropyridine whereas a temperature of 167° for 18 hr. was required for the corresponding production of pentafluoroaniline from hexafluorobenzene[117]. The same ease of replacement of fluorine in pentafluoropyridine over hexafluorobenzene[116] was observed in the reactions with sodium methoxide. The increased reactivity of pentafluoropyridine over hexafluorobenzene is consistent with the electron-withdrawing power of the ring nitrogen.

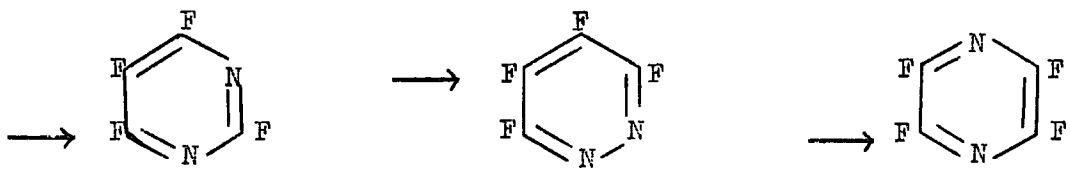
Nucleophilic substitution in pentafluoropyridine takes place almost exclusively at the 4-position followed by substitution at the 2- and 6-positions. The reaction with sodium methoxide in methanol shows clearly that the fluorines are displaced in the following order.[132,133]



The nitro-group in tetrafluoro-4-nitropyridine has been shown to be displaced by nucleophilic reagents[134], but not in pentafluoro- or 2,3,5,6-tetrafluoronitrobenzenes. Since the nitro-group and fluorine are

comparable in their efficiency as leaving groups in nucleophilic aromatic substitution[135], it has been concluded that the ring nitrogen is the greatest factor in determining the orientation of substitution in polyfluoropyridine.

Nucleophilic substitution in tetrafluoro-pyrimidine[53] (xi), -pyridazine[65] (xii) and -pyrazine[31] (xiii) has been reported. Compounds (xi) and (xii) were found to be substantially more reactive than pentafluoro-pyridine (as is expected from the presence of two nitrogen atoms in the ring), a fluorine <u>para</u> to nitrogen being preferentially replaced in each case. However,

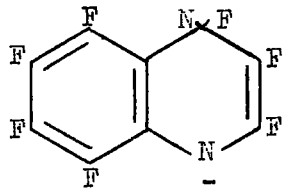


(xi) (xii) (xiii)

unlike (xi) and (xii) the compound (xiii), having no fluorine <u>para</u> to nitrogen, was found to be less susceptible to nucleophilic displacement of fluorine. This was shown by its relatively slow reaction with aqueous ammonia to give 2-amino-3,5,6-trifluoropyrazine. The results illustrated the markedly greater activation of fluorine atoms <u>para</u> rather than <u>ortho</u> to ring nitrogen and that the <u>para</u>-quinonoid structures of the type (iii) are more important than the <u>ortho</u>-quinonoid structures like (iv).

In heptafluoro-quinoline[52,136], nucleophilic attack takes place at 2- and 4-positions to give two monosubstituted products. With sodium methoxide

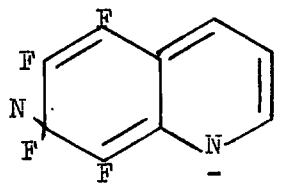
as the nucleophile the major product was hexafluoro-2-methoxyquinoline (2-isomer : 4-isomer = 3·4). On the basis of para-quinonoid structure (xiv)



(xiv)

however, one would expect the 4-isomer to be the major product since in this case the negative charge is placed on the nitrogen atom. The reason why more 2-substitution occurs in this case is difficult to explain on the basis of the present theory. In the reaction of nucleophiles with heptafluoroisoquinoline it has been shown that replacement of the 1-fluorine takes place first, followed by replacement of the 6-fluorine[136]. These results also cannot be explained on the basis of the simple qualitative theory above, since it would predict the preferential replacement of the 3-fluorine atom-analogous to the replacement of β-fluorine in octafluoronaphthalene[130] (ix).

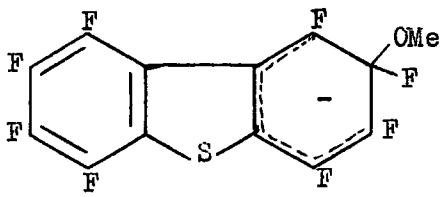
Nucleophilic attack on 5,6,7,8-tetrafluoroquinoline has been shown to take place preferentially at position 7- with reagents such as ammonia, potassium hydroxide and methoxide ion[69]. The transition state in this reaction could involve a para-quinonoid



(xvi)

resonance structure (xvi), in which the negative charge is also delocalised on to the nitrogen atom.

Octafluorodibenzothiophen has been prepared recently[66] and it has been shown that nucleophilic substitution occurs in this compound with the replacement of the 2-fluorine atom. This orientation was explained on the basis of an intermediate (xv) in which



the negative charge is presumably stabilized by the sulphur atom[137].

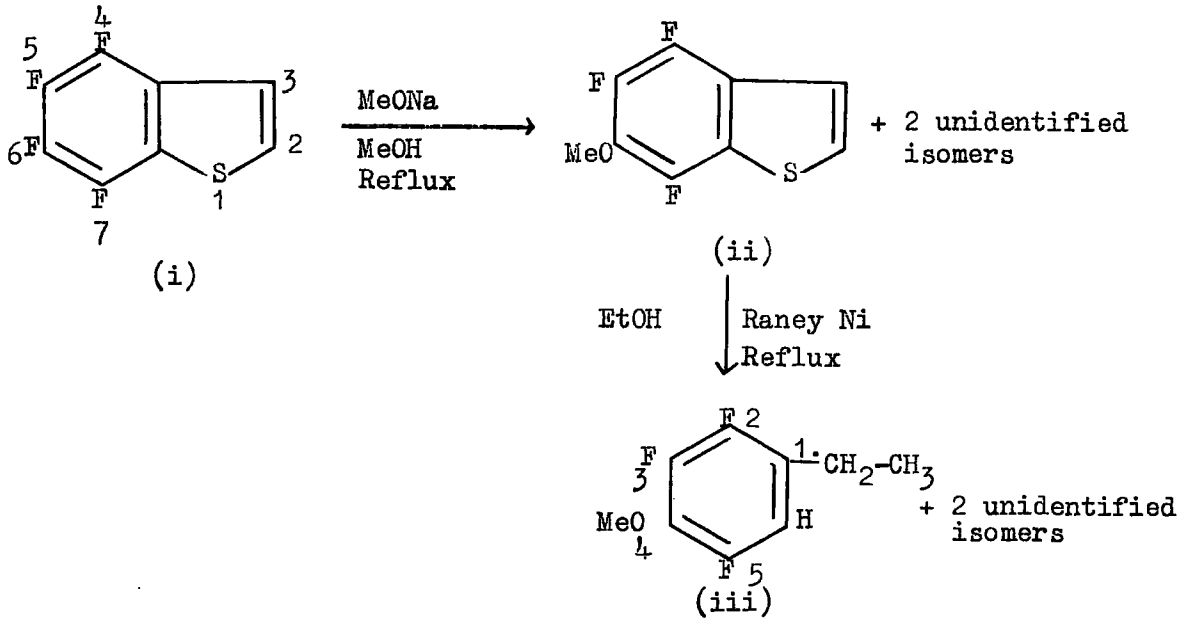
CHAPTER VI

NUCLEOPHILIC AND ELECTROPHILIC SUBSTITUTIONS IN 4,5,6,7-TETRAFLUOROBENZO[b]THIOPHEN

NUCLEOPHILIC AND ELECTROPHILIC SUBSTITUTIONS IN 4,5,6,7-TETRAFLUOROBENZO[b]THIOPHEN

Electrophilic substitution reactions in benzo[b]thiophen have been widely studied[84]. Investigation into the behaviour of polyfluoro benzo[b]thiophens towards nucleophilic replacement of fluorine and electrophilic replacement of hydrogen was of considerable interest.

When 4,5,6,7-tetrafluorobenzo[b]thiophen, (i), was treated with sodium methoxide in methanol 6-methoxy-4,5,7-tetrafluorobenzo[b]thiophen (ii), (m.p. 40-41° from light petroleum [40-60°]) was obtained together with two unidentified isomers in the ratio of 86:7:7 respectively. The structure of the major product and the isomer ratio was determined from an analysis of the ^{1}H and ^{19}F n.m.r. spectra of the mixture of methoxytrifluoro-ethylbenzenes (b.p. 145°) that was obtained from the mixture of methoxytrifluorobenzo[b]thiophen compounds by the treatment with Raney nickel in boiling ethanol. (4,5,6,7-Tetrafluorobenzo[b]thiophen itself gave 2,3,4,5-tetrafluoroethylbenzene with Raney nickel).



The proton spectrum showed four regions of absorption as is shown in the following table:

^{1}H n.m.r. spectrum of 4-methoxy-2,3,5-trifluoroethylbenzene

Chemical Shift (τ)	Relative Intensity	Description of Peak	Assignment
3·4	1	multiplet	aromatic proton coupling with the ring fluorine atoms
6·1	3	triplet	Methoxyl protons
7·4	2	quartet	methylene protons
8·8	3	triplet	methyl protons

The H-F coupling constants obtained from the aromatic proton peak in the ^{1}H n.m.r. spectrum were J^{ortho}_{H-F} = 11·4, J^{meta}_{H-F} = 6·5 and J^{para}_{H-F} = 2·5 cycles/sec.

From the coupling pattern shown in the different absorptions in the proton spectrum it can be easily established that the major isomer in the mixture of methoxytrifluoroethylbenzenes has the structure (iii). Since the methoxy protons appear as a triplet ($J \sim 1^c$/Sec.) it must have two <u>ortho</u> fluorines coupling with it[138]. This shows that the methoxyl group is attached to a carbon atom either <u>para</u> to the aromatic hydrogen, or <u>para</u> to the ethyl group in the methoxytrifluorobenzene concerned. The former

possibility is immediately ruled out since the presence of a fluorine para to the aromatic hydrogen in the ring can be clearly seen from the coupling pattern shown by this latter nucleus. The multiplet at τ 3·4 has a para H-F coupling constant (J^{para}_{H-F} = 2·5 c/sec.) which is easily distinguished from J^{ortho}_{H-F} or J^{meta}_{H-F} values - the former being considerably smaller than any of the latter. This fact has been conveniently utilized previously in determining orientations in polyfluoroaromatic compounds[139]. The conclusion from these results is that the methoxy group in the above compound is attached to the carbon atom para to the ethyl group, that is, (iii) is 4-methoxy-2,3,5-trifluoroethylbenzene.

An analysis of the ^{19}F n.m.r. spectrum of the mixture confirmed the above conclusions. There were three major absorptions of equal intensity for three fluorines as is shown in the adjacent table. The coupling constants are of the magnitude to be expected for a system as (iii)[140].

^{19}F n.m.r. spectrum of 4-methoxy-2,3,5-trifluoroethylbenzene

Chemical shift in p.p.m. downfield from hexafluorobenzene	Coupling Constants derived from the peak cycles/sec.	Assignment
10·1	21, 3·3, 2·6	3-fluorine
15·6	21, 14, 7	2-fluorine
27·7	14·4, 12·1, 4·2, 1	5-fluorine

The coupling constants obtained from the signal at 10·1 p.p.m. downfield from hexafluorobenzene can only arise from the absorption due to the 3-fluorine which is expected to couple only with one nucleus (2-fluorine)

with a large coupling constant (J_{F-F}^{ortho} = 21 c/sec.). The other two small coupling constants were due to 5-fluorine (J_{F-F}^{meta} = 3·3 c/sec.) and the aromatic proton (J_{H-F}^{para} = 2·6 c/sec.) respectively. The coupling due to the adjacent methoxy group was not sufficiently resolved to measure this coupling constant.

The pattern of splitting in the signal at 15·6 p.p.m. (downfield from hexafluorobenzene) gave three different coupling constants: 21 c/sec., 14 c/sec. and 7 c/sec. These coupling constants can only be assigned to the 2-fluorine and arise from its coupling with the 3-fluorine (J_{F-F}^{ortho} = 21 c/sec.), the 5-fluorine (J_{F-F}^{para} = 14 c/sec.) and the aromatic hydrogen (J_{H-F}^{meta} = 7 c/sec.) respectively.

The coupling constants derived from the low field peak at 27·7 p.p.m. (downfield from hexafluorobenzene) fitted very well into the pattern of absorption expected from the remaining fluorine i.e. 5-fluorine. These values were attributed to its coupling with the 2-fluorine (J_{F-F}^{para} = 14·4 c/sec.) aromatic proton (J_{H-F}^{ortho} = 12·1 c/sec.), 3-fluorine (J_{F-F}^{meta} = 4·2 c/sec.) and methoxyl protons (J = ca.1 c/sec.) respectively.

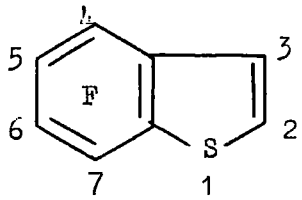
Thus having established the structure of the major isomer in the mixture of methoxyethylbenzenes, the structure of the parent methoxybenzo[b]thiophen immediately follows. 4-Methoxy-2,3,5-trifluorobenzene can only arise from 6-methoxy-4,5,7-trifluorobenzo[b]thiophen on desulphurization. Thus, position 6 in 4,5,6,7-tetrafluorobenzo[b]thiophen was found to be most susceptible to nucleophilic attack.

Since isomer distribution depends only on the stability of the

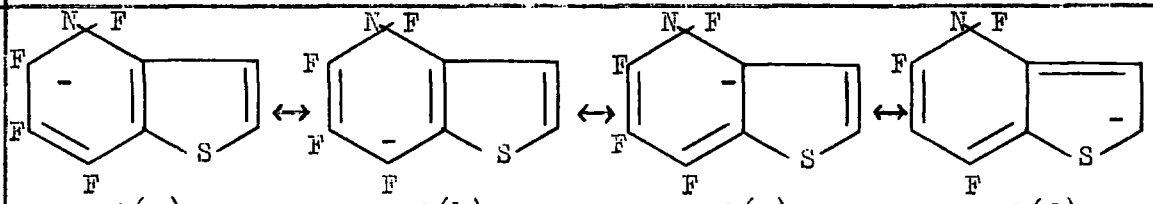
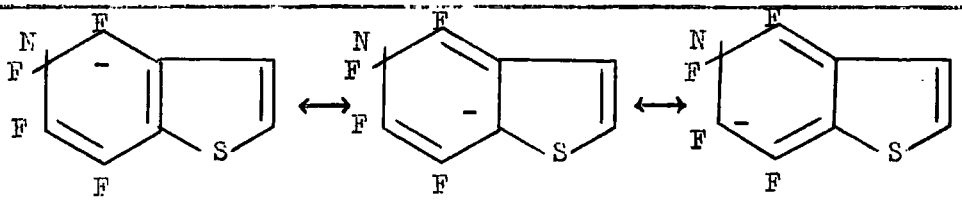
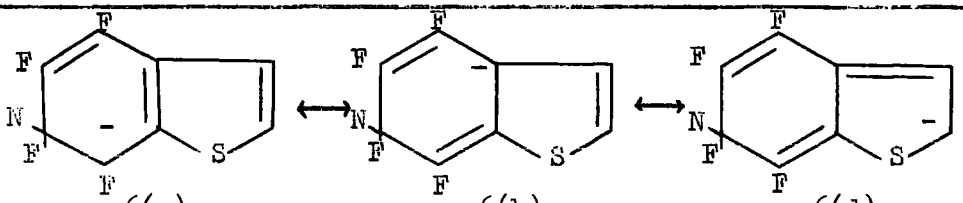
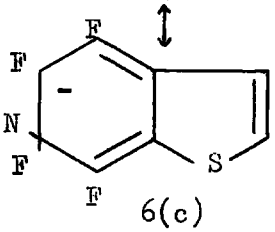
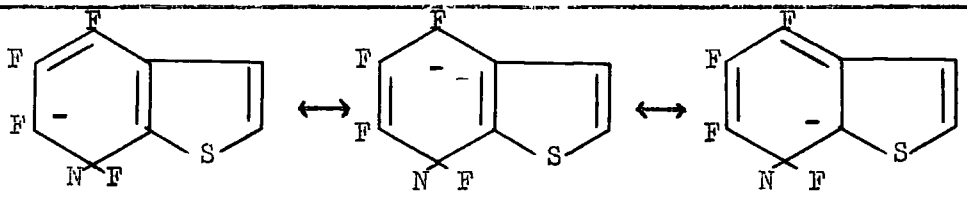
corresponding transition states and not on the ground state stability, a rationalization of the orientation of nucleophilic substitution in 4,5,6,7-tetrafluorobenzo[b]thiophen is possible if the energies of the various transition states leading to the different isomers are considered. Thus from a study of the following possible resonance hybrids approximating to the structures of the transition states for the various positions of attack, it can be seen that the position 6 is the one most likely to be attacked by the nucleophile. This is because in this case the negative charge can not only be delocalized to the maximum extent but also be stabilized by sulphur[137] in a resonance hybrid involving a para-quinonoid structure (Fig.6(d) in the adjacent table). This in turn means that the transition state for an attack at the 6-position will have the lowest energy and, therefore, will cause a preferential substitution at this position leading to 6-methoxy-4,5,7-trifluorobenzo[b]thiophen as the major product.

Similar stabilization of the negative charge by sulphur is also possible for the next most likely position of attack, position 5; but in this case the negative charge is less delocalised than when substitution occurs at position 6. In the transition state of the remaining positions of attack (positions 4 and 7) no such stabilization of the negative charge by sulphur involving para-quinonoid structures is possible, and hence these positions will also be less vulnerable to nucleophilic attack than position 6.

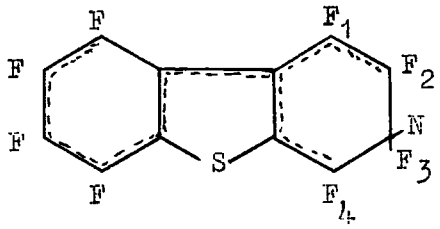
Possible resonance hybrids representing the transition states in the nucleophilic attack on 4,5,6,7-tetrafluorobenzo[b]thiophen,



at various positions.

Position of Attack	Resonance Hybrids
4	 4(a) ↔ 4(b) ↔ 4(c) ↔ 4(d)
5	 5(a) ↔ 5(b) ↔ 5(c)
6	 6(a) ↔ 6(b) ↔ 6(d)  6(c)
7	 7(a) ↔ 7(b) ↔ 7(c)

As has been mentioned earlier (Chapter V, p.88) a similar stabilizing effect by a sulphur atom on negative charge on an adjacent carbon atom has also been noted very recently in the nucleophilic substitution in octafluorodibenzothiophen by methoxide[66] and these results are consistent with the stabilization of carbanions by sulphur which has been observed in other systems[137]. The 2-substitution in octafluorodibenzothiophen has been explained on the basis of an intermediate (Chapter V, p.88) in which the negative charge is stabilized by sulphur atom. Replacement of the 3-fluorine atom, however, would have required an intermediate (iv)



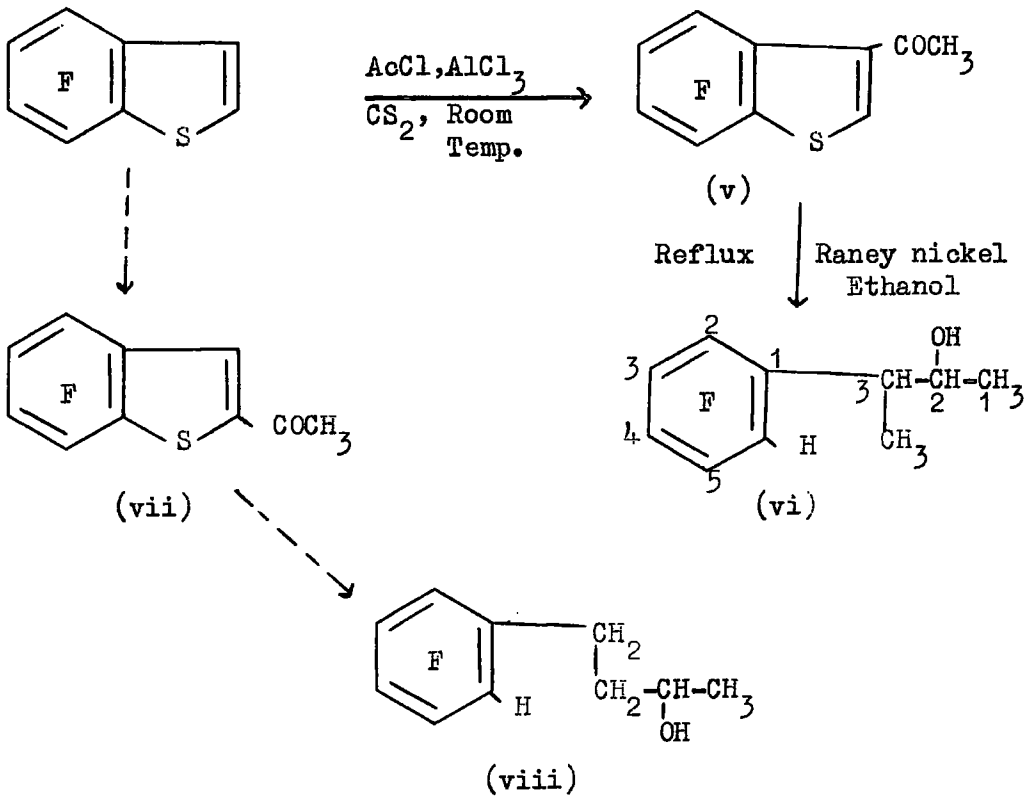
(iv)

in which the aromatic system of the second benzene ring would have been disrupted. Although a greater delocalization of the negative charge is possible in this intermediate, the charge is more likely to be destabilized by the fluorine atoms in the second ring through Iπ repulsion. It would, therefore, be of interest to find out whether nucleophilic substitution in 1,2,3,4-tetrafluorodibenzothiophen takes place in position 3. This might be expected because the hydrogen atoms in the second ring should stabilize the negative charge in the transition state compared to fluorine atoms.

4,5,6,7-tetrafluorobenzo[b]thiophen also gave hydrazino-derivative (m.p. 104-106°) when heated with hydrazinehydrate in dioxane under reflux.

The orientation of the hydrazino group was not, however, determined.

The behaviour of 4,5,6,7-tetrafluorobenzo[b]thiophen towards electrophilic replacement of hydrogen was investigated by the treatment of this compound with acetyl chloride and anhydrous aluminium chloride in carbon disulphide at room temperature. The crude mixture of acetyl compounds was shown to contain at least 85% of one isomer on the basis of a strong singlet at τ 1·15 in the ^{1}H n.m.r. spectrum (in acetone); a weak doublet at τ 1·5 could have been due to the other isomer. The major product was shown to be 3-acetyl-4,5,6,7-tetrafluorobenzo[b]thiophen, (v), (m.p. 132-134°) by treatment with Raney nickel to give an alcohol which was shown to be 3-(2',3',4',5'-tetrafluorophenyl)-butan-2-ol, (vi), (b.p. 128-130°) from its ^{1}H n.m.r. spectrum.



The pattern of absorption obtained in the spectrum described in the table below can only fit in to structure (vi)

Table showing the absorption pattern in the ^{1}H n.m.r. spectrum of (vi)

Chemical Shifts (τ)	Relative Intensity	Description of Peak	Assignment
3·0	1	multiplet	The aromatic proton
6·1	1	multiplet	2-proton
7·0	2	multiplet overlapped by a singlet	3-proton and the hydroxyl proton respectively
8·8	6	two overlapping doublets	Protons of the two methyl groups

The assignment of the multiplate at τ 6·1 to the 2-protons and that at τ 7·0 to the 3-proton is based on the average regions of absorptions quoted in the literature[144] for CH-protons in CH-OH and CH-ϕ compounds respectively. The peak at τ 8·8 which was attributed to the two methyl group protons contributes most to the determination of the structure of the alcohol, which in turn showed the orientation of the substitution reaction. If 2-substitution had occurred to the greater extent in the above acetylation reaction the major product (vii) would have been converted to the alternative isomeric alcohol (viii) on treatment with Raney nickel. This latter alcohol, instead

of showing two overlapping doublets at about 8·8 in the n.m.r. spectrum, would have shown only one doublet in this region representing the protons of the single methyl group present in the compound. Thus, of the two available protons the one at position 3 in 4,5,6,7-tetrafluorobenzo[b]thiophen is clearly the more susceptible to replacement by the acetylium ion. The reaction of benzo[b]thiophen itself under similar conditions with the same reagents gave 88% of the 3-acetyl compound and 12% of the 2-acetyl compound[142].

Electrophilic substitution of benzo[b]thiophen occurs predominantly in the 3-position, although appreciable yields of the 2-substituted product have been obtained[143]. Recently[144] the nitration, halogenation and amination of benzo[b]thiophen and some of its derivatives have been studied. Nitration with a mixture of fuming nitric acid and acetic acid gave among other products, 60-65% of the 3-nitro compound and 10-15% of the 2-isomer. Previously only the formation of the 3-nitro compound had been reported[138]. The authors found that halogenation occurs predominantly in the 3-position. A small amount of 2-substitution and disubstitution was observed in the case of chlorination and bromination but iodination resulted only in the formation of the 3-isomer.

4,5,6,7-tetrafluorobenzo[b]thiophen when oxidised with hydrogen peroxide (90%) in presence of trifluoroacetic anhydride in methylene chloride at the reflux temperature, gave the sulphone, 4,5,6,7-tetrafluorobenzo[b]thiophen 1-dioxide, in good yield (m.p. 82-84° from a mixture of benzene and light petroleum [b.p. 60-80°]). Benzo[b]thiophen itself on oxidation with hydrogen peroxide in acetic acid also gives its sulphone; benzo[b]thiophen 1-oxide is unknown except as derivatives[145].

CHAPTER VII

EXPERIMENTAL

EXPERIMENTAL

Pentafluorothiophenol.- (i) From pentafluorophenylmagnesium bromide. Pentafluorobromobenzene (10·2 g.) was added to magnesium turnings (5·0 g.) in dry tetrahydrofuran (75 ml.) at -5° and the temperature was not allowed to rise above 0° for 2 hr. The solution was decanted from the excess magnesium and added to a stirred suspension of flowers of sulphur (4·0 g.) in dry tetrahydrofuran (25 ml.) at -5°. After 0·5 hr. at -5 to 0°, the mixture was added to excess dilute sulphuric acid and extracted with ether. Distillation of the dried ($MgSO_4$) extracts gave pentafluorothiophenol (5·5 g.) b.p. 143°, identified by its infrared spectrum.

(ii) From pentafluorophenyl-lithium. Pentafluorobenzene (10·0 g.) in dry tetrahydrofuran (75 ml.) was treated at -60° with n-butyl-lithium in hexane (22 ml., 3·0 N) over 10 min., the temperature not being allowed to rise above -50°. Flowers of sulphur (4·0 g.) was added at -60° and the temperature was not allowed to rise above -45° over 15 min. The mixture was added to excess dilute sulphuric acid, and extracted with ether. Distillation of the dried ($MgSO_4$) extracts gave pentafluorothiophenol (5·44 g.), b.p. 143°, identified by its infrared spectrum.

2,3,5,6-Tetrafluorothiophenol.- 1,2,4,5-Tetrafluorobenzene (5·0 g.) in dry tetrahydrofuran (75 ml.) was treated at -60° with n-butyl-lithium in hexane (15 ml., 2·37 N) over 10 min. the temperature not being allowed to rise above -50°. After 3 hr. at -50°, flowers of sulphur (1·06 g.) was added to the stirred solution at -65°, and 1 hr. later the reaction product

was isolated as before to give 2,3,5,6-tetrafluorothiophenol (4·2 g.) b.p. 147° which was identified by its infrared spectrum.

2,3,4,5-Tetrafluorothiophenol.- 1,2,3,4-Tetrafluorobenzene (10·0 g.) in dry tetrahydrofuran (150 ml.) was treated at -67° with n-butyl-lithium (30 ml., 2·37N) over 15 min., the temperature not being allowed to rise above -60°. After 3 hr. at -60°, flowers of sulphur (2·2 g.) was added to the stirred solution at -65°, the temperature not being allowed to rise above -50° over 1 hr. The mixture was added to excess dilute sulphuric acid, and extracted with ether. Distillation of the dried ($MgSO_4$) extracts gave 2,3,4,5-tetrafluorothiophenol (8·08 g.), b.p.150-151° (Found: C, 39·8; H, 1·3. $C_6H_2F_4S$ requires C, 39·6; H, 1·1%).

The crude residue (2·18 g.) was combined with the residue from other experiments and distilled to give bis-(2,3,4,5-tetrafluorophenyl)disulphide b.p. 100°/0·05 mm. (main fraction) (Found: C, 39·7; H, 0·6. $C_{12}H_2F_8S_2$ requires C, 39·8; H, 0·6%).

Oxidation of 2,3,4,5-tetrafluorothiophenol (1·5 g.) in glacial acetic acid (10 ml.) by the dropwise addition of bromine (1·5 g.) to the stirred mixture, and removal of the excess acid *in vacuo* gave the same bis(2,3,4,5-tetrafluorophenyl) disulphide (1 g.) identified by its infrared spectrum.

Reduction of the disulphide (10 g.) with zinc (2 g.) in boiling glacial acetic acid (25 ml.), dilution of the mixture with water, and isolation of the product by ether extraction gave 2,3,4,5-tetrafluorothiophenol (3·1 g.), b.p. 151°, identified by its infrared spectrum.

Ethyl (Pentafluorophenylthio)acetate. (i) From pentafluorothiophenol. The thiophenol was treated with sodium in dry ether to give sodium

pentafluorothiophenate which precipitated from the solution. The thiophenate (1·9 g.), ethyl chloroacetate (1·5 g.) and pyridine (20 ml.) were heated together under reflux for 1 hr. The mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. Distillation of the dried ($MgSO_4$) extracts <u>in vacuo</u> gave the product (0·58 g.), b.p. 66-68°/0·05 mm. (Found: C, 42·0; H, 2·5. $C_{10}H_7F_5O_2S$ requires C, 42·0; H, 2·5%).

(ii) From hexafluorobenzene. Hexafluorobenzene (5·0 g.), ethyl mercaptoacetate (3·5 g.) and anhydrous potassium carbonate (4·0 g.) were heated together under reflux in dry dioxan (25 ml.) for 18 hr. The mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. The dried ($MgSO_4$) extracts were distilled <u>in vacuo</u> to give the product (0·17 g.), b.p. 66-68°/0·05 mm. which had an infrared spectrum identical with the material prepared in the previous experiment, and a higher-boiling fraction (4·31 g.), b.p. 150-175°/0·05 mm. which solidified on cooling. This material was recrystallised from light-petroleum (b.p. 60-80°) to give <u>diethyl 2,3,5,6-tetrafluorobenzene-1,4-bisthioacetate</u>, m.p. 57-58°. (Found: C, 43·4; H, 3·3. $C_{14}H_{14}F_4O_4S_2$ requires C, 43·5; 3·6%). The ^{19}F nuclear magnetic resonance spectrum of this compound in carbon tetrachloride consisted of a single peak at 28·9 p.p.m. downfield from hexafluorobenzene as internal reference.

<u>Ethyl (2,3,5,6-Tetrafluorophenylthio)acetate</u>.- (i) From 2,3,5,6-tetrafluorothiophenol. The thiophenol (5·02 g.) and ethyl chloroacetate (3·62 g.) were heated under reflux in pyridine (25 ml.) for 18 hr. The mixture was diluted

with water, acidified with hydrochloric acid and extracted with ether. The dried ($MgSO_4$) extracts were distilled to give the product (5·97 g.), b.p. 73°/0·01 mm. (Found: C, 44·7; H, 3·0. $C_{10}H_8F_4O_2S$ requires C, 44·8; H, 3·0%).

(ii) From pentafluorobenzene. Pentafluorobenzene (5·0 g.), ethyl mercaptoacetate (3·5 g.) and anhydrous potassium carbonate (4·0 g.) were heated together under reflux in dry dioxan (25 ml.) for 18 hr. Isolation by ether extraction as before gave ethyl (2,3,5,6-tetrafluorophenylthio)acetate (6·32 g.), b.p. 73°/0·01 mm. which was shown by analytical gas chromatography to contain only the one isomer.

(2,3,5,6-Tetrafluorophenylthio)acetic Acid.- (i) From the ester. Ethyl (2,3,5,6-Tetrafluorophenylthio)acetate (1·02 g.) was heated under reflux with sulphuric acid (10 ml., 50% v/v) for 18 hr. The mixture was diluted with water, extracted with ether and the dried ($MgSO_4$) extracts evaporated. The residual oil crystallised slowly, and the crystals were recrystallised from light-petroleum (b.p. 60-80°) to give the acid (0·73 g.), m.p. 74-76° (Found: C, 39·9; H, 1·6. $C_8H_4F_4O_2S$ requires C, 40·0; H, 1·7%).

(ii) From 2,3,5,6-tetrafluorothiophenol. The thiophenol (5·01 g.) and monochloroacetic acid (3·00 g.) were heated under reflux in pyridine (20 ml.) for 4 hr. The mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. The solvent was removed from the dried ($MgSO_4$) extracts and the residue was crystallized from light petroleum (b.p. 60-80°) to give impure (2,3,5,6-tetrafluorophenylthio)acetic acid (6·14 g.).

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Ethyl (2,3,4,5-Tetrafluorophenylthio)acetate.- 2,3,4,5-Tetrafluorothiophenol (8·0 g.) and ethyl chloroacetate (6·0 g.) were heated together under reflux in pyridine (50 ml.) for 6 hr. The mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. The dried ($MgSO_4$) extracts were distilled in vacuo to give the product (10·0 g.), b.p. 75°/0·01 mm. (Found: C, 45·0; H, 3·1%).

(2,3,4,5-Tetrafluorophenylthio)acetic Acid.- (i) From the ester. Ethyl (2,3,4,5-tetrafluorophenylthio)acetate (5·0 g.) was heated under reflux with sulphuric acid (25 ml., 50% v/v) for 18 hr. The mixture was diluted with water, extracted with ether and the dried ($MgSO_4$) extracts evaporated. The crude solid residue (m.p. 48-49°) was recrystallized from light petroleum (b.p. 40-60°) to give the acid, m.p. 48-49° (Found: C, 39·9%; H, 1·6%).
(ii) From 2,3,4,5-tetrafluorothiophenol. The thiophenol (2·02 g.) and chloroacetic acid (1·3 g.) were heated under reflux in pyridine (15 ml.) for 4 hr. The mixture was poured in water, acidified with hydrochloric acid (10 N), extracted with ether and the ether extracts dried with $MgSO_4$. The solvent was removed by evaporation and the residual oil crystallized very slowly to give (2,3,4,5-tetrafluorophenylthio)acetic acid in low yield (25%).

(2,3,4,5-Tetrafluorophenylthio)acetone.- 2,3,4,5-Tetrafluorothiophenol (5·00 g.) and chloroacetone (3·0 g.) were heated under reflux in pyridine (30 ml.) for 5 hr. The mixture was poured in water, acidified with hydrochloric acid (10 N) and extracted with ether. The dried ($MgSO_4$) extracts were evaporated and the residue was distilled in vacuo to give (2,3,4,5-

tetrafluorophenylthio)acetone (5·37 g.), b.p. 75-76°/0·05 mm. (Found: C, 45·3; H, 2·5. $C_9H_6F_4OS$ requires C, 45·3; H, 2·5%).

Attempted Cyclisation of (2,3,4,5-Tetrafluorophenylthio)acetic Acid.- Several attempts were made to cyclise the phenylthioacetic acid with different reagents under different conditions but in most of the cases the starting material was obtained back, as is shown in the following table:

Reagent	Amount of the acid used	Duration of Heating	Reaction Temperature	Result
Polyphosphoric acid, 5 ml.	0·25 g. 0·25 g.	15 min. 1·5 hr.	140 - 150°C 160 - 200°	Starting material recovered "
P_2O_5(1·0 g.) in cyclohexane (10 ml.)	0·26 g.	1 hr.	Heated under reflux	"
P_2O_5(3·0 g.) in cyclohexane (10 ml.)	0·26 g.	3 hr.	"	"
Anhydrous HF	0·35 g. 0·37 g.	2·5 hr. 1 hr.	Allowed to stand in liq. HF	" "
Conc. sulphuric acid (10 ml.)	0·3 g.	3 hr.	200°	Product unidentified
Chlorosulphonic acid	0·35 g.	5 min. (immediate blackening)	200°	"

Attempted cyclisation of (2,3,4,5-tetrafluorophenylthio)acetone.-

(i) Using polyphosphoric acid. The ketone (0·5 g.) was heated in polyphosphoric acid (10 ml.) for 15 minutes at 180-190°C. The mixture was diluted with water and extracted with ether. The dried ($MgSO_4$) ether extracts were evaporated, and the residual was shown by infrared spectroscopy to be the starting material.

(ii) Using phosphorus Pentoxide. The ketone (1·08 g.) was heated with P_2O_5 (4·62 gm.) at 160-180° for 45 minutes with vigorous stirring. The mixture was taken in water and ether-extracted. The dried ($MgSO_4$) extracts were distilled *in vacuo* to give a liquid boiling at 110-122°C/0·01 mm. which did not show any carbonyl absorption peak in the infrared spectrum. The liquid was shown to contain at least four components by analytical vapour-phase chromatography, which would have been difficult to separate.

(2,3,5,6-Tetrafluorophenylthio)acetaldehyde Diethyl Acetal.- 2,3,5,6-Tetrafluorothiophenol (3·0 g.) and bromoacetaldehyde diethyl acetal (3·5 g.) were heated under reflux in pyridine (25 ml.) for 1·5 hr. The mixture was poured in water, acidified with hydrochloric acid (10 N) and extracted with ether. The dried ($MgSO_4$) extracts were evaporated and the residue was distilled in vacuo to give impure product (3·10 g.) b.p. ca. 80°/·01 mm.

(2,3,4,5-Tetrafluorophenylthio)acetaldehyde Diethyl Acetal.- Potassium 2,3,4,5-tetrafluorothiophenate (4·44 g., prepared by the addition of the thiol to a saturated solution of potassium hydroxide in water, filtering off the precipitate and drying it *in vacuo*) and bromo-acetaldehyde diethyl acetal (4·0 g.) in pyridine (30 ml.) were heated under reflux for 1 hr.

The mixture was poured into water, acidified with hydrochloric acid (10 N) and extracted with ether. The dried ($MgSO_4$) extracts were evaporated and the residue was distilled in vacuo to give the impure product (2·68 g.), b.p. 70°/0·01 mm.

2,3,5,6-Tetrafluoro-4-mercaptobenzoic Acid.- n-Butyl-lithium in hexane (30 ml., 2·35N) was added to a stirred solution of 2,3,5,6-tetrafluorothiophenol (5·0 g.) in dry tetrahydrofuran (75 ml.) at -67°C over a period of 15 min., the temperature being kept below -60°C during the addition. After 3 hr. at low temperature (-45°C to -67°C) dry carbon dioxide was passed through the reaction mixture for 1 hr. during which time the temperature rose to room temperature. The mixture was acidified with dil. sulphuric acid (100 ml.), ether-extracted, the extracts were washed with water, dried ($MgSO_4$) and the solvent evaporated. The residue (4·55 g. crude) was crystallized from light petroleum (b.p. 60-80°) to give the product m.p. 148-150°. (Found: C, 37·4; H, 1·01. $C_7H_2F_4O_2S$ requires C, 37·16; H, 0·89%).

2,3,4,5-Tetrafluoro-6-mercaptobenzoic Acid.- n-Butyl-lithium in hexane (30 ml., 2·35N) was added to a stirred solution of 2,3,4,5-tetrafluorothiophenol (5·0 g.) in dry tetrahydrofuran (75 ml.) at -67°C over a period of 15 min. the temperature being kept below -60°C during the addition. After 3 hr., dry carbon dioxide was passed through the reaction mixture for 1 hr. at -67° and the mixture was then allowed to attain the room temperature. It was acidified with dil. sulphuric acid (100 ml.), ether-extracted, and

the extracts were washed with water, dried ($MgSO_4$) and the solvent was evaporated. The residue was recrystallized from light petroleum (b.p. 80-100°) to give the product (4·0 g.), m.p. 125-126°. (Found: C, 37·0; H, 1·14%).

Attempted preparation of 4-carboxy-(2,3,5,6-tetrafluorophenylthio)acetic acid.- The p-mercaptobenzoic acid (1·0 g.) chloroacetic acid (0·6 g.) and pyridine (20 ml.) were heated under reflux for 4 hr. The mixture was diluted with water, acidified with hydrochloric acid (10 N) and extracted with ether. The solvent was evaporated from the dried ($MgSO_4$) ether extracts and the residual solid was sublimed at 60°C/0·01 mm. to give (2,3,5,6-tetrafluorophenylthio)acetic acid (0·72 g. crude) which was identical with an authentic sample of the material prepared before.

The experiment was repeated at a lower temperature using both chloro- and bromo-acetic acids but decarboxylation occurred in each case.

Ethyl 2,3,4,5-Tetrafluoro-6-mercaptobenzoate.- A mixture of 2,3,4,5-tetrafluoro-6-mercaptobenzoic acid (10·16 g.) sulphuric acid (20 ml., 36 N) and ethanol (50 ml.) was heated under reflux for 15 hr., diluted with water and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts and distillation of the residue *in vacuo* gave the product (7·07 g.) b.p. 50-52°/0·01 mm. (Found: C, 42·8; H, 2·59. $C_9H_6F_4O_2S$ requires C, 42·49; H, 2·38%).

A small amount of high boiling fraction in the reaction product was found to contain bis(6-ethoxy-carbonyl-2,3,4,5-tetrafluorophenyl)disulphide. (Found: C, 42·9; H, 1·81, $C_{18}H_{10}O_4S_2$ requires: C, 42·7; H, 1·9%.

2-Ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl.- (i) From Ethyl 2,3,4,5-tetrafluoro-6-mercaptobenzoate.- The o-mercaptobenzoate (2·49 g.), ethylbromoacetate (1·67 g.) and sodium ethoxide (0·23 g. of sodium dissolved in ethanol [30 ml.]) were heated under reflux in ethanol for 3 hr. The mixture was poured into water, extracted with ether and the extracts were washed with water and dried ($MgSO_4$). After evaporating off the solvent, the residue (3·5 g.) which was a mixture of a solid and a liquid, was crystallized from light petroleum (b.p. 40-60°) to give 2-ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl (0·76 g.) m.p. 108-109° (Found: C, 44·8; H, 1·88. $C_{11}H_6F_4O_3S$ requires C, 44·90; H, 2·06%).

The non-crystallizable fraction was distilled in vacuo to give ethyl (6-ethoxycarbonyl-2,3,4,5-tetrafluorophenylthio)acetate (1·61 g.) b.p. 92-94°/0·01 mm. (Found: C, 45·6; H, 3·21. $C_{13}H_{12}F_4O_4S$ requires: C, 45·88; H, 3·5%).

(ii) From ethyl (6-ethoxycarbonyl-2,3,4,5-tetrafluorophenylthio)acetate.- The (o-ethoxycarbonylphenylthio)acetic ester (1·02 g.) dissolved in dry tetrahydrofuran (10 ml.) was slowly added with stirring to sodium hydride (0·1 g., 60% w/w dispersion in oil) suspended in dry tetrahydrofuran (20 ml.). Hydrogen was evolved briskly. After the addition was complete, the mixture heated under reflux for 15 min., then poured into water, acidified and extracted with ether. The dried ($MgSO_4$) ether extracts gave, on removal of the solvent, 2-ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl (0·95 g.) which had infrared spectrum identical with that of an authentic sample.

<u>4,5,6,7-Tetrafluorobenzo[b]thiophen from 2-Ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl</u>.- 2-Ethoxycarbonyl-4,5,6,7-tetrafluorothioindoxyl (0·57 g.), glacial acetic acid (10 ml.) 50% (v/v) sulphuric acid (10 ml.) and zinc dust (0·3 g.) were heated under reflux for 5 hours. The mixture was poured in water and extracted with ether. The ether extract was washed several times with water and then dried over $MgSO_4$. The residue, obtained on evaporation of the solvent, gave 4,5,6,7-tetrafluorobenzo[b]thiophen (0·025 g.) as a sublimate when heated to 50°C/760 mm. The substance melted at 35-40° (m.p. of the pure compound is 46-48°) and gave infrared and mass spectra identical with those of an authentic sample prepared later.

<u>Diethyl 4,5,6,7-Tetrafluorobenzo[b]thiophen-2,3-dicarboxylate</u>.- Pentafluorothiophenol (20·0 g.) in dry tetrahydrofuran (100 ml.) was treated at -70° with n-butyl-lithium in hexane (48 ml., 2·27 N) followed by slow addition of diethyl acetylenedicarboxylate (17·0 g.), the temperature being kept at less than -55°. The mixture was allowed to warm up to room temperature and then was heated under reflux for 4 hr. It was then added to sulphuric acid (120 ml., 4N) extracted with ether and dried ($MgSO_4$). The residue when distilled <u>in vacuo</u> to give the product (17·4 g.), b.p. 130°/0·01 mm. which later solidified; m.p. 37-38° (Found: C, 48·3; H, 3·05. $C_{14}H_{10}F_4O_4S$ requires: C, 48·00; H, 2·87%). The ^{19}F nuclear magnetic resonance spectrum of this compound in carbon tetrachloride had four multiplets of equal intensity at 4·51; 7·45; 20·07; and 21·6 p.p.m. downfield from hexafluorobenzene as internal reference.

<u>4,5,6,7-Tetrafluorobenzo[b]thiophen-2,3-dicarboxylic Acid Monohydrate</u>.- The above ester (8·02 g.) was heated under reflux in sulphuric acid (50 ml., 50% v/v) for 7 hrs. The mixture was poured into water and extracted with ether. The crude solid (6·53 g.) obtained from the dried ($MgSO_4$) ether extract, was boiled in benzene. The impure product (4·57 g.) did not dissolve, and was filtered off and recrystallized from water to give the acid (m.p. 222-225°). (Found: C, 38·7; H, 1·34. $C_{10}H_4F_4O_5S$, requires: C, 38·47; H, 1·29%).

<u>4,5,6,7-Tetrafluorobenzo[b]thiophen</u>.- The above acid (4·80 g.), copper powder (2·13 g.) and quinoline (25 ml.) were heated under reflux for one hour and the product was distilled in steam. The distillate was acidified with hydrochloric acid (11 N) and extracted with ether. The dried ($MgSO_4$) extracts on removal of the ether, gave <u>4,5,6,7-tetrafluorobenzo[b]thiophen</u> (3·00 g.) which was recrystallized from light petroleum (b.p. 40-60°) in the cold, m.p. 46-48°. (Found: C, 46·5; H, 1·04; F, 37·1. $C_8H_2F_4S$ requires: C, 46·59; H, 0·98; F, 36·86%). The ^1H n.m.r. spectrum in carbon tetrachloride showed overlapping signals for the two protons centering at ca. τ 2·6. However, in acetone as the solvent the peaks were well-separated showing a doublet, and a doublet of doublet at τ 2·1 and τ 2·5 respectively. The ^{19}F n.m.r. spectrum showed four absorptions at 20·6, 17·1, 2·2 and 1·8 p.p.m. downfield from hexafluorobenzene. The last two peaks overlapped to give a signal of intensity expected for two fluorines together.

Ethyl β-Pentafluorophenylthioacrylate

Pentafluorothiophenol (9·38 g.) in dry tetrahydrofuran was treated with n-BuLi (25·5 ml; 1·93 N) at -70° followed by ethyl propiolate (4·32 g.) the temperature was not allowed to rise beyond -60°. The mixture was then allowed to attain the room temperature, acidified with dil. sulphuric acid and extracted with ether. The extracts were dried over $MgSO_4$ and distilled to give a 90:10 mixture of cis and trans ethyl β-pentafluorophenylthioacrylate. (3·78 g.) b.p. 87°/0·05 mm. (Found: C, 44·15; H, 2·44, and $C_{11}H_7F_5O_2S$ requires C, 44·33; H, 2·37%).

The reaction of 4,5,6,7-tetrafluorobenzo[b]thiophen with methoxide: 6-Methoxy-4,5,7-Trifluorobenzo[b]thiophen

4,5,6,7-Tetrafluorobenzo[b]thiophen (2·66 g.) and sodium methoxide in dry methanol (13·5 ml., 1·6N) were heated under reflux for 41 hr. The mixture was poured in water, extracted with ether and the extracts were washed with water to remove alcohol. The solvent was removed from the dried ($MgSO_4$) extracts to obtain crude 6-methoxy-4,5,7-trifluorobenzo[b]thiophen (2·73 g.) containing traces of starting material and other isomers. Recrystallization of the material from light petroleum (b.p. 40-60°) at low temperatures gave a solid (m.p. 40-41°) which gave a correct analysis for a monomethoxy compound. Found: C, 48·9; H, 2·16. $C_9H_5F_3SO$ requires C, 49·08; H, 2·31%. The ^1H n.m.r. spectrum showed a triplet at τ 5·9 for the methoxyl group and an overlapping multiplet centred at ca. τ 2·6 for the 2- and 3-protons. The chemical shifts and coupling constants for the three absorptions (equal intensity) for the three fluorines are shown in the following table.

^{19}F n.m.r. spectrum of 6-methoxy-4,5,7-trifluorobenzo[b]thiophen

Chemical Shifts in p.p.m. downfield from hexafluorobenzene	Coupling constants derived from the peak c/sec.	Assignment
6·5	18·8, ca 1	5-fluorine
15·5	18·8, 16	4-fluorine
25·8	16	7-fluorine

3-Acetyl-4,5,6,7-tetrafluorobenzo[b]thiophen

A solution of 4,5,6,7-tetrafluorobenzo[b]thiophen (2·01 g.) and acetyl chloride (1·0 g.) in carbon disulphide (8 ml.) was added dropwise to a suspension of anhydrous aluminium chloride (1·6 g.) in carbon disulphide (12 ml.). The mixture was stirred at room temperature for 5 hr. after which it was warmed on water bath to remove carbon disulphide. A mixture of hydrochloric acid (10 N) and ice was added to the brown viscous residue. The mixture was extracted with ether, the extracts washed with sodium bicarbonate, dried ($MgSO_4$) and the solvent evaporated off to give a mixture (2·30 g.) estimated by ^1H n.m.r. to contain 85% of 3-acetyl-4,5,6,7-tetrafluorobenzo[b]thiophen and 15% of the 2-acetyl compound. The mixture was purified by recrystallization from a mixture of light petroleum and benzene to give the pure compound m.p. 132-134°. Found: C, 48·1; H, 1·54. $C_{10}H_4F_4SO$ requires: C, 48·39 and H, 1·62%.

2,3,4,5-Tetrafluoroethylbenzene.- 4,5,6,7-Tetrafluorobenzo[b]thiophen (2·5 g.), ethanol (150 ml.) and Raney nickel (25 spatula-full ca. 38 g.) were

heated under reflux for 5 hr. The mixture was filtered and the nickel was washed thoroughly with a mixture of alcohol and ether. The filtrate and the washings were washed several times with water and the dried ($MgSO_4$) ether solution was evaporated. The residual liquid (2·05 g.) was distilled to give the product (1·35 g.) b.p. 125-127°/760 mm. Found: C, 54·0; H, 3·34. $C_8H_6F_4$ requires C, 53·9 and H, 3·39%.

De-sulphurisation of the mixture of monomethoxytrifluorobenzo[b]thiophens

The product from the reaction of 4,5,6,7-tetrafluorobenzo[b]thiophen with methoxide was separated from unchanged starting material by vapour phase chromatography on kieselguhr-silicone grease at 190°, and a sample of it (1·7 g.), ethanol (100 ml.) and Raney nickel (20 spatula-full, ca.35 g.) were heated together under reflux for 5 hr. The nickel was filtered off and the catalyst was thoroughly washed with a mixture of alcohol and ether. The filtrate and the washings were washed with water. The residual ether-solution was dried ($MgSO_4$) and the solvent was evaporated. The residual liquid on distillation was shown by ^{19}F n.m.r. spectroscopy to contain 86% 4-methoxy-2,3,5-trifluoroethylbenzene and two unidentified isomers (1·18 g.) b.p. 145°/760 mm. Found: C, 56·7; H, 4·6. $C_9H_9F_{30}$ requires, C, 56·8 and H, 4·77%.

3-(2',3',4',5'-tetrafluorophenyl)-butane-2-ol

3-Acetyl-4,5,6,7-tetrafluorobenzo[b]thiophen (0·43 g.), Raney nickel (5 spatula-full, ca. 8 g.) and ethanol (20 ml.) were heated under reflux for 3 hr., filtered and the catalyst was washed thoroughly with a mixture

of alcohol and ether. On removal of the solvent from the dried ($MgSO_4$) filtrate and washings the residual liquid (0·35 g.) was distilled in vacuo to give 3-(2',3',4',5'-tetrafluorophenyl)-butane-2-ol (0·26 g.) b.p. 128-130°/760 mm. (Found: C, 54·05; H, 4·5. $C_{10}H_{10}F_4O$ requires C, 54·3; H, 4·47%).

4-Methoxy-2,3,5,6-tetrafluorothiophenol

n-Butyl lithium in hexane (16·5 ml. of 1·93 N) was added to a stirred solution of 2,3,5,6-tetrafluoroanisole (5 g.) in tetrahydrofuran (70 ml.) at -70°. After 3 hr. at this temperature sulphur (1·0 g.) was added and the mixture was stirred for a further hour at -70°. The mixture was acidified with sulphuric acid (4 N), extracted with ether and the extracts were washed with water and dried ($MgSO_4$). The solvent was evaporated and the residual liquid was distilled to give 4-methoxy-2,3,5,6-tetrafluorothiophenol (3·75 g.) b.p. 200°. (Found: C, 39·9; H, 1·9. $C_7H_4F_4SO$ requires C, 39·62; H, 1·90%). This thiol when reacted with diethyl acetylenedicarboxylate did not produce the expected 5-methoxy-4,6,7-trifluorobenzo[b]thiophen, the preparation of which was originally planned in order to help solve the orientation of nucleophilic substitution in 4,5,6,7-tetrafluorobenzo[b]thiophen.

Trifluoro-hydrazinobenzo[b]thiophen

4,5,6,7-Tetrafluorobenzo[b]thiophen (0·41 g.) hydrazine hydrate (1·0 g.) and dioxan (3 ml.) were heated together under reflux for 19 hr. The mixture was poured into water and extracted with ether. The extracts were washed with water, dried ($MgSO_4$) and the solvent was evaporated. The residue (0·4 g.) was crystallized from a mixture of light petroleum (60-80°) and

benzene to give the hydrazino derivative (0·25 g.), m.p. 104-106°. (Found: C, 44·2; H, 2·11. $C_8H_5F_3N_2S$ requires C, 44·3; H, 2·31%).

4,5,6,7-Tetrafluorobenzo[b]thiophen 1-dioxide

Hydrogen peroxide (3 ml. 90%) was added to trifluoroacetic anhydride (10 ml.) in methylene chloride (30 ml.). 4,5,6,7-Tetrafluorobenzo[b]thiophen (1·0 g.) dissolved in methylene chloride (5 ml.) was added to it drop by drop, the mixture being stirred throughout. The mixture was heated under reflux for 2 hr. and then washed with water. The organic layer was separated, dried ($MgSO_4$) and the solvent evaporated. The residue was crystallized from a mixture of benzene and light petroleum (b.p. 60-80°) to give the sulphone of 4,5,6,7-tetrafluorobenzo[b]thiophen (0·83 g.) m.p. 82-84°. (Found: C, 40·1; H, 0·89. $C_8H_2F_4SO_2$ requires C, 40·37; H, 0·85%).

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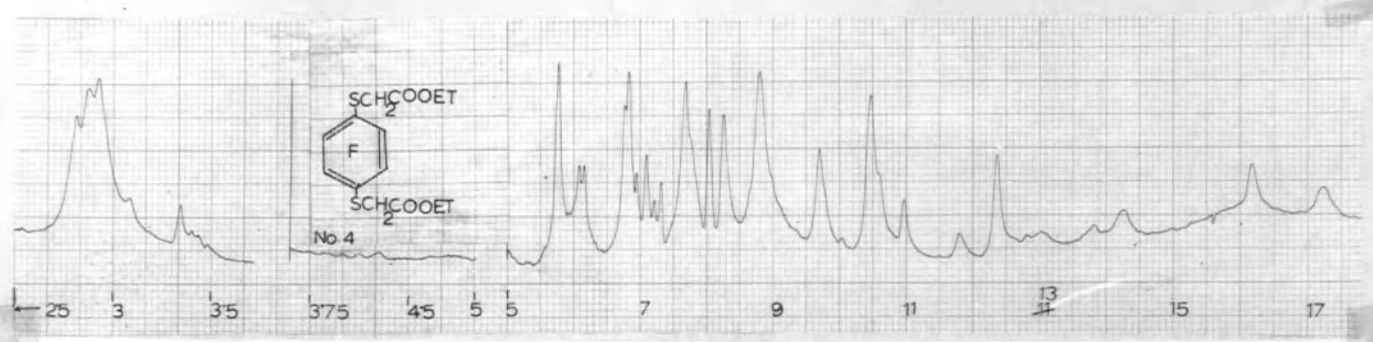
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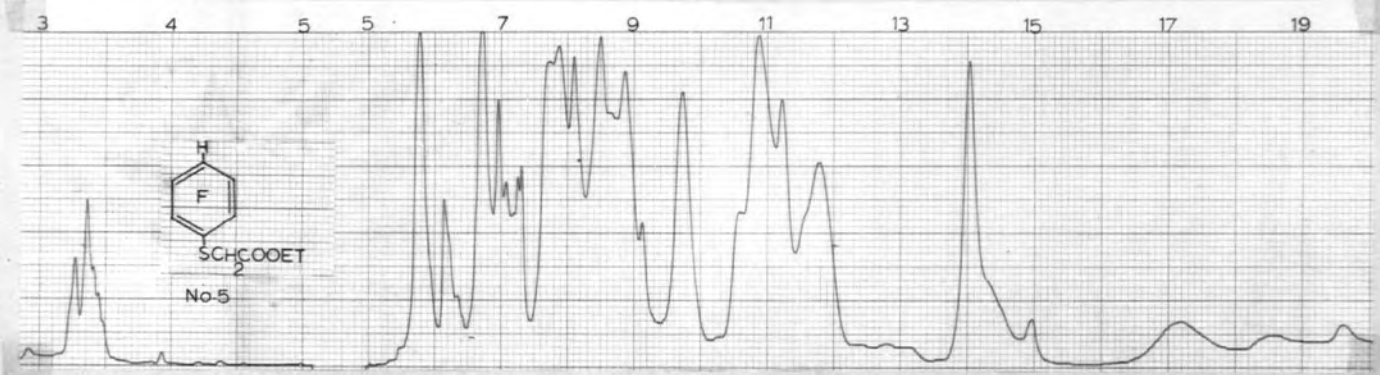
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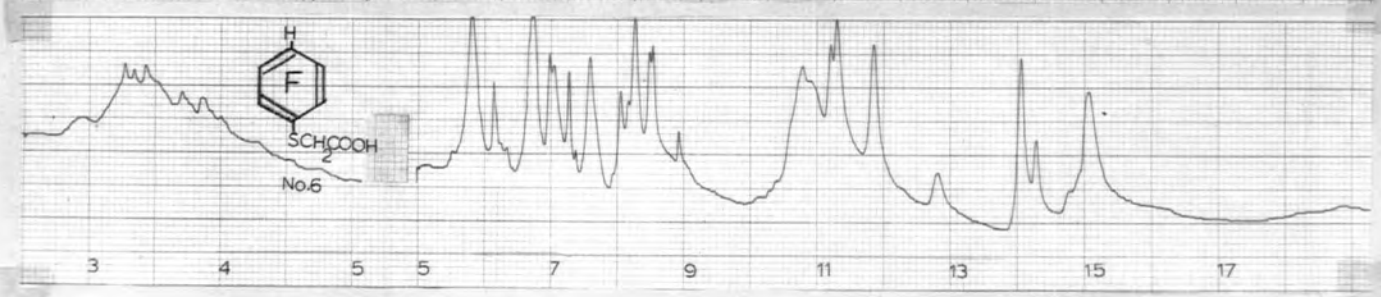
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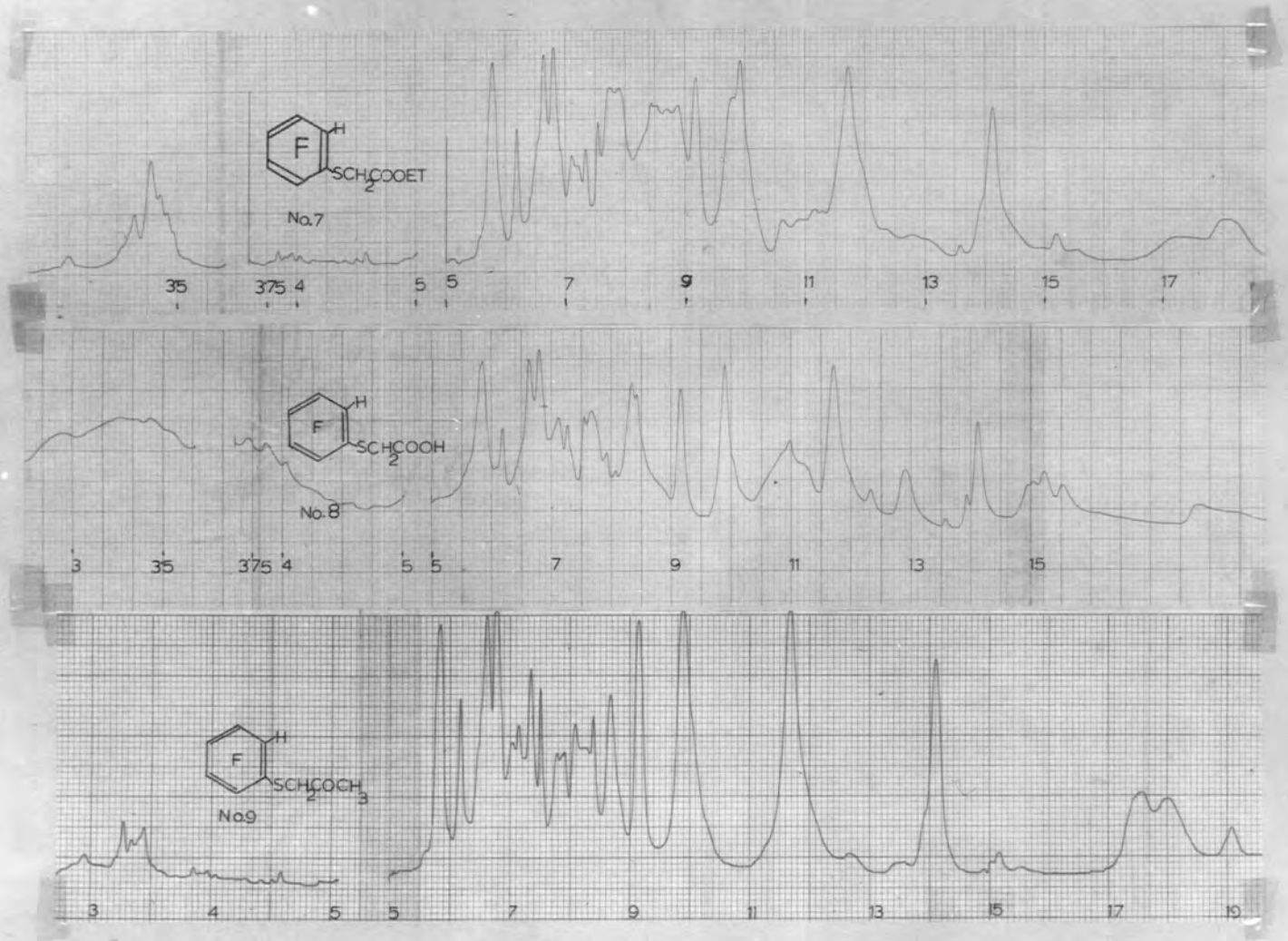
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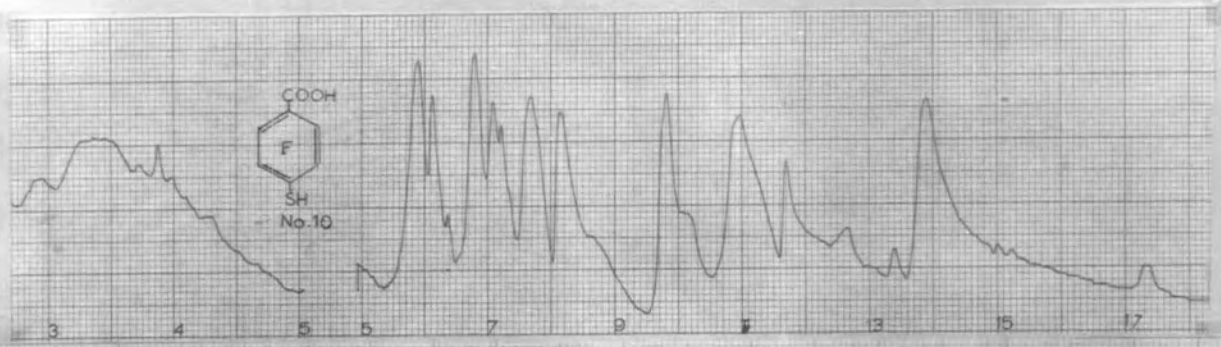
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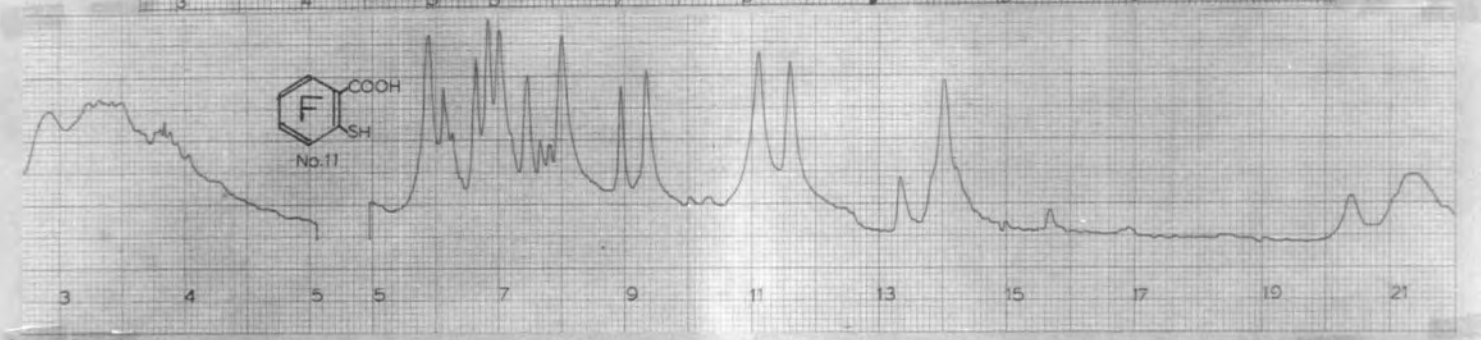
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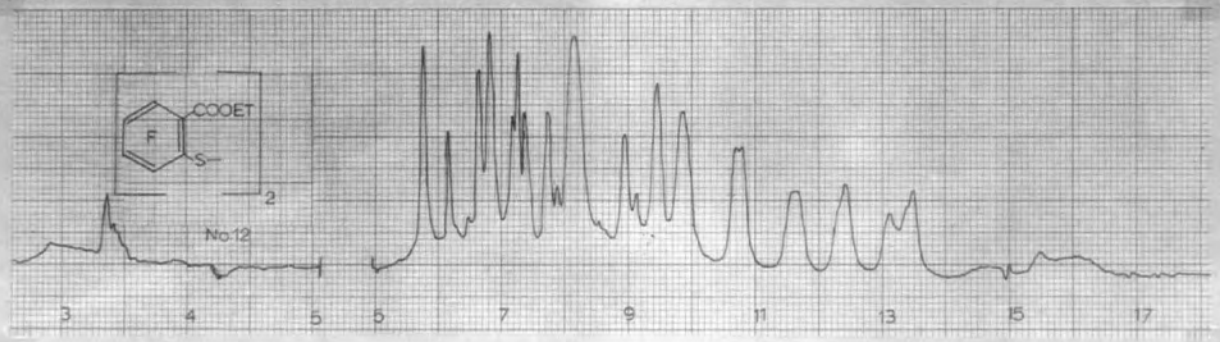
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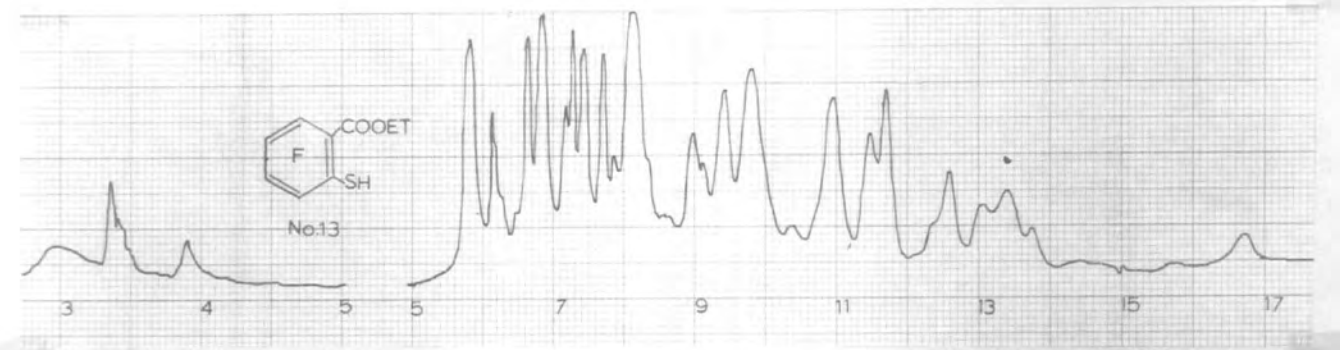
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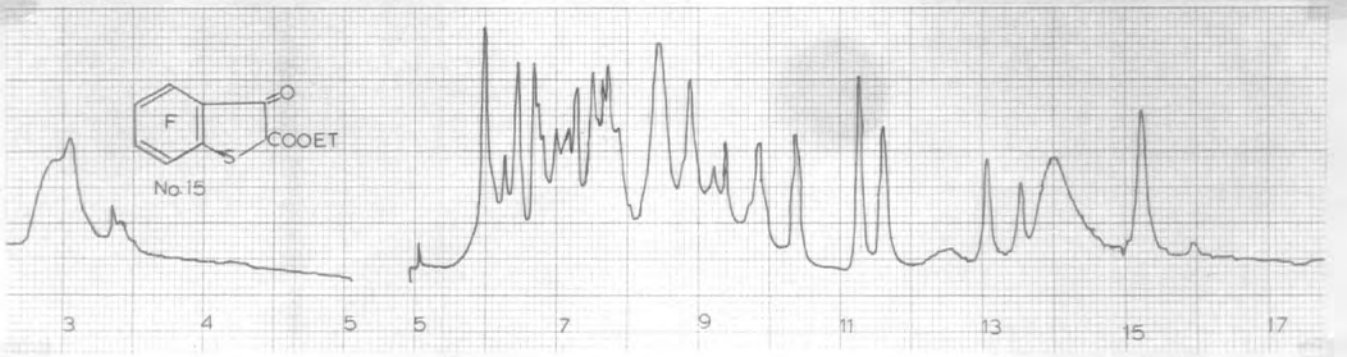
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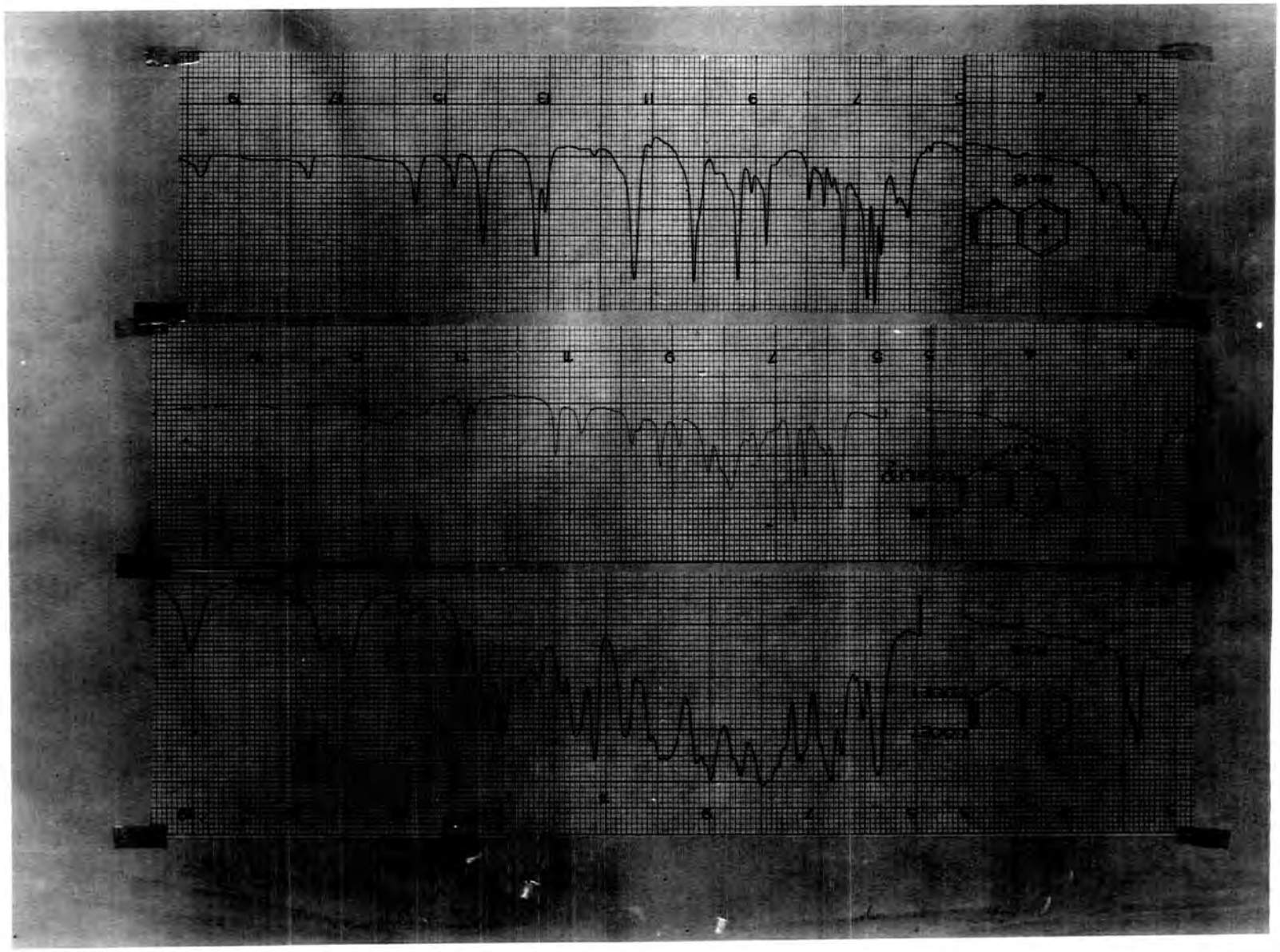

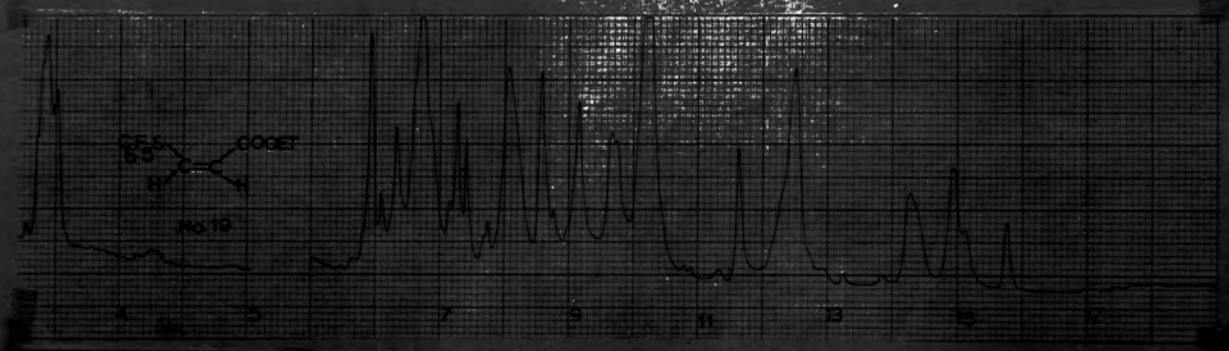
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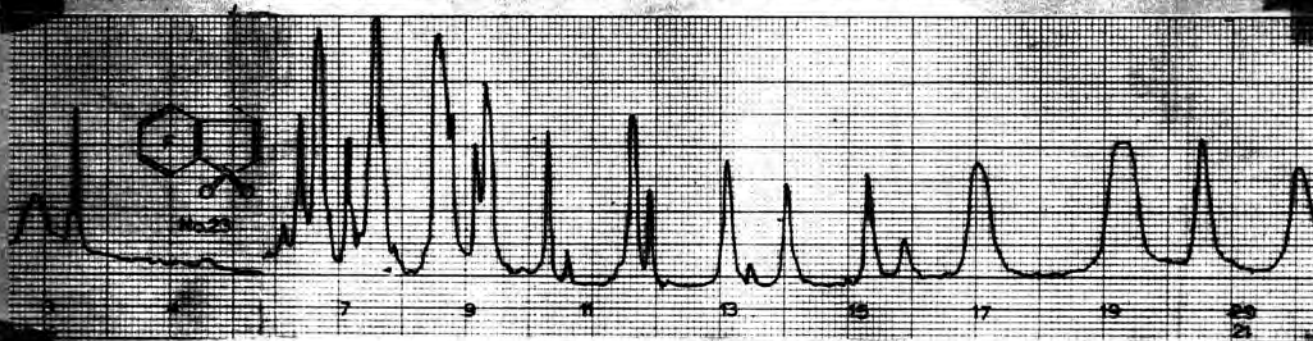
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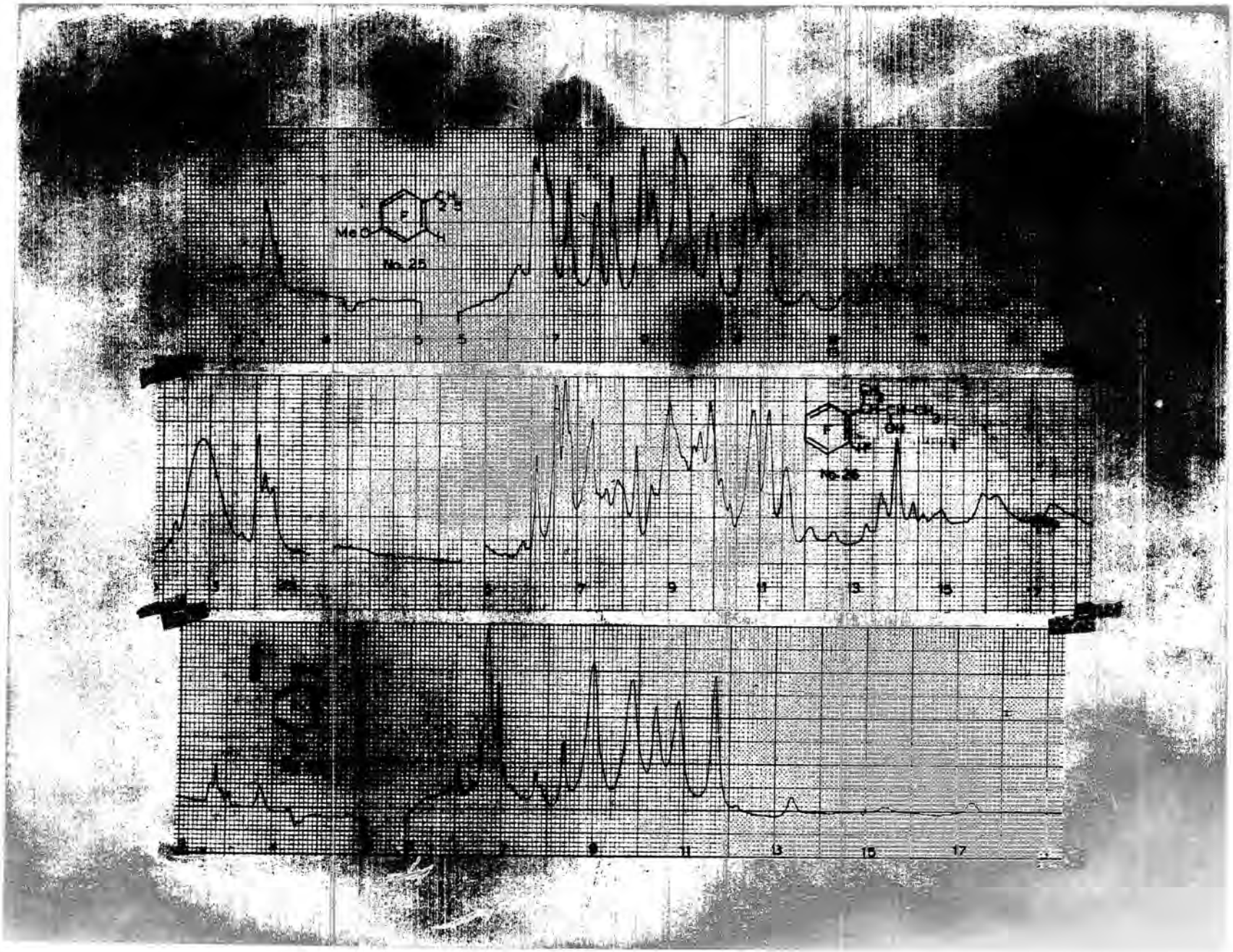
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