The synthesis and chemistry of 4,5,6,7 - tetrafluorobenzo [b]furan

Furness, Brian Stanley

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UNIVERSITY OF DURHAM

A THESIS

entitled

THE SYNTHESIS AND CHEMISTRY OF 4,5,6,7-TETRAFLUOROBENZO[b]FURAN

submitted by

BRIAN STANLEY FURNISS, B.Sc.

(Grey College)

A candidate for the degree of Doctor of Philosophy

1967

ACKNOWLEDGEMENTS

The work described in this thesis was carried out under the supervision of Dr. G.M. Brooke and I wish to record my appreciation of his help and encouragement throughout. I should also like to thank Professor W.K.R. Musgrave for his interest.

Thanks are also due to Imperial Smelting Corporation, Avonmouth, Bristol, for the award of a Research Studentship.

MEMORANDUM

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

Part of this work has provided material for two publications: Tetrahedron Letters, 1965, 2991 (with Dr. G.M. Brooke, Professor W.K.R. Musgrave and Mr. M.A. Quasem), and J. Chem. Soc. (C) 1967, 869 (with Dr. G.M. Brooke).

SUMMARY

A method which has been described for the synthesis of phenols from aryl halides has been adapted for the synthesis of 2,3,4,5-tetrafluorophenol and other highly fluorinated phenols. 2,3,4,5-Tetrafluorophenol has been used to prepare 2,3,4,5-tetrafluorophenoxyacetic acid, -acetyl chloride, -acetaldehyde diethylacetal, and 2-(2',3',4',5'-tetrafluorophenoxy)ethanol, and the attempted electrophilic cyclisation reactions of these compounds are described. 4,5,6,7-Tetrafluoro-2,3-dihydrobenzo[b]furan-3-one has been prepared from ethyl 6-ethoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate by a two stage synthesis involving cyclisation, hydrolysis and decarboxylation. The latter compound was obtained from 2,3,4,5-tetrafluorophenol by a three stage synthesis. 4,5,6,7-Tetrafluoro-2,3-dihydrobenzo[b]furan-3-one was also obtained from the reaction of 2,3,4,5-tetrafluorophenoxyacetic acid with butyl-lithium followed by carbonation, and the mechanism of this cyclisation reaction was investigated. Reduction of the benzo[b]furan-3-one followed by dehydration gave 4,5,6,7-tetrafluorobenzo[b]furan.

The reaction of 4,5,6,7-tetrafluorobenzo[b]furan with sodium methoxide gave a mixture of 4-, 6-, and 7-methoxytrifluorobenzo[b]furan compounds. The 6-isomer was synthesised independently starting from 2,3,4,5-tetrafluorophenol and the structures of the remaining isomers were deduced from ^{19}F n.m.r. spectroscopic data, Metalation of 4,5,6,7-tetrafluorobenzo[b]furan with butyl-lithium gave the 2-lithio

compound which was converted to the 2-carboxylic acid and 2-aldehyde; these two compounds were also synthesised from 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan. Acetylation of 4,5,6,7-tetrafluorobenzo[b]furan gave a mixture of 2-acetyl and 3-acetyl derivatives.

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PART I

THE SYNTHESIS OF 4,5,6,7-TETRAFLUOROBENZO[b]FURAN

CHAPTER I

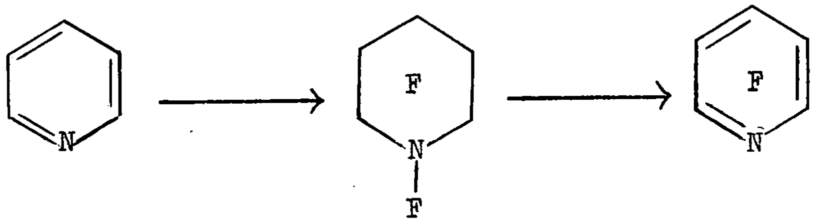
INTRODUCTION

Section 1

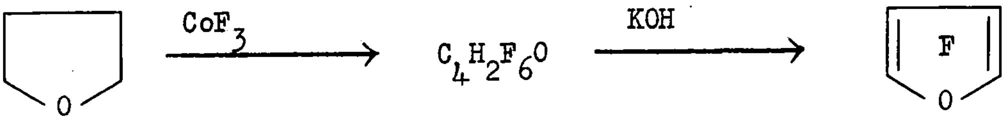
The Synthesis of Polyfluorinated Heterocyclic Compounds from Hexafluorobenzene and its Derivatives

Since the development in the mid 1950's of methods for the preparation of aromatic fluorocarbons in comparatively large quantities, polyfluoro-aromatic chemistry has been extensively developed[1]. In the last few years however, increasing attention has been turned to the synthesis and chemistry of highly fluorinated aromatic heterocyclic compounds. This development has taken place mainly along two well defined routes; route A usually giving rise to perfluorinated heterocycles, and route B leading to fully or partially fluorinated fused ring heterocycles.

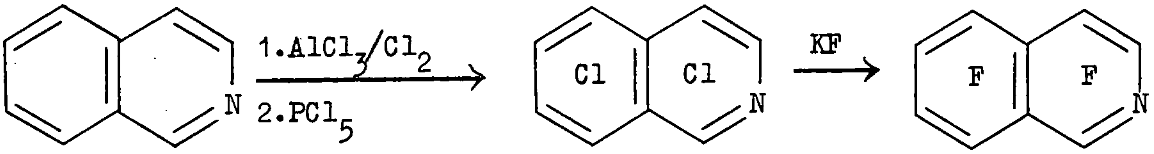
Two synthetic approaches have been employed in route A. The first requires fluorinated saturated heterocyclic compounds as intermediates; these are then aromatised by defluorination or dehydrofluorination. Electrochemical fluorination is a common method for the preparation of such saturated compounds[2]; fluorination of pyridine or 2-fluoropyridine by this method gave undecafluoropiperidine[3], which was defluorinated over iron at 600°[4] or nickel at 560°[5]:



[The following convention will be used throughout this thesis: in all rings with an elemental symbol (e.g. F) inside the ring, all unmarked bonds are to that element (e.g. fluorine); in all rings with no symbol inside, all unmarked bonds are to hydrogen]. The preparation of heptafluoro-quinoline and -isoquinoline has also been claimed by this process[6]. Application of the cobalt trifluoride process[7] to aromatic heterocycles, such as thiophen[8], benzo[b]thiophen and 2-methyl indole[9], was unsuccessful, usually resulting in loss of the heteroatom. Tetrahydrofuran, however, has recently been fluorinated by this method to give a mixture of $C_4H_2F_6O$ isomers, which was dehydrofluorinated to give tetrafluorofuran[10]:



The second route recently developed to give fully fluorinated heterocycles requires the fully chlorinated heterocycles as precursors; halogen exchange reactions, usually with potassium fluoride, then give the perfluorinated compound. An example of this route is the preparation of heptafluoroisoquinoline[11]:

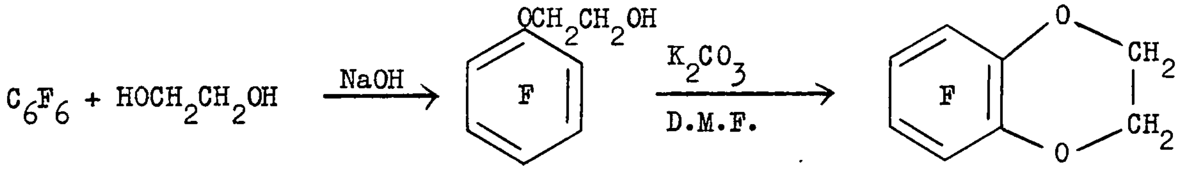


This route has also been used for the preparation of pentafluoropyridine[12,13], heptafluoroquinoline[11], tetrafluoropyrimidine[14],

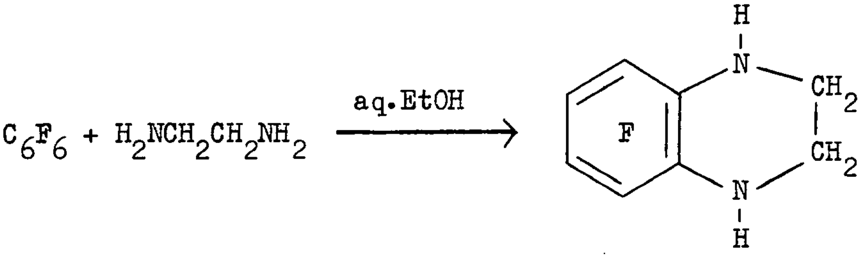
-pyridazine[15], and pyrazine[14].

The second type of approach to highly fluorinated heterocyclic compounds, route B, makes use of the ready availability of highly fluorinated aromatic compounds and the information now accumulated on their chemistry, and necessarily gives rise to compounds in which the heterocyclic ring is fused to one or more fluorinated benzene rings. No compound in which the heterocyclic ring contains a fluorine substituent has yet been synthesised by this route.

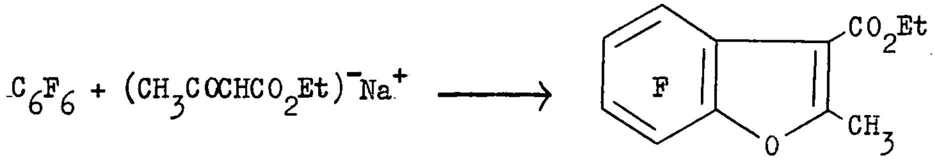
A common method for the synthesis of heterocyclic compounds involves electrophilic displacement of hydrogen from an aromatic nucleus as the ring closure reaction. The counterpart to this reaction in polyfluoro-aromatic chemistry is the nucleophilic displacement of fluorine from an aromatic nucleus, and the majority of heterocyclic compounds obtained from polyfluorobenzene derivatives have been formed in this way. The first report of a reaction of this type concerned the reaction of hexa fluorobenzene with a number of potential bidentate nucleophiles such as ethylene glycol and ethylenediamine[16]:



(I)

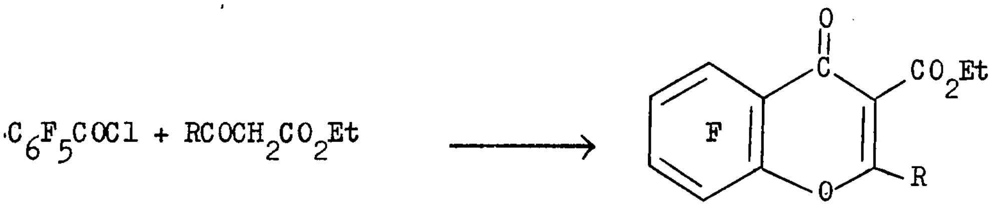


The formation of the dioxin (I) was also reported shortly afterwards by Russian workers, in a paper[17] which also described the synthesis of a benzo[b]furan derivative (II) from hexafluorobenzene and the sodium salt of ethyl acetoacetate (see later):



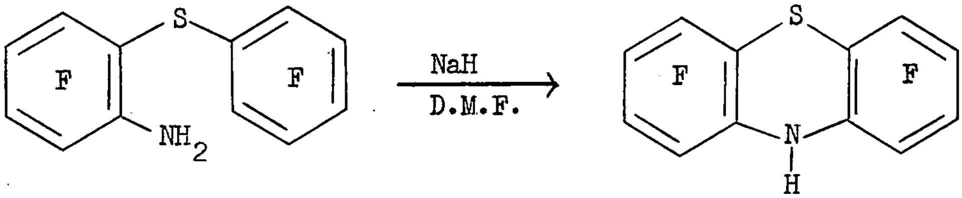
(II)

Vorozhtsov and co-workers have also reported the synthesis of a number of γ-benzopyrone derivatives from the reaction of pentafluorobenzoyl chloride with ethyl acetoacetate, ethyl benzoylacetate and ethyl pentafluorobenzoylacetate[18]:

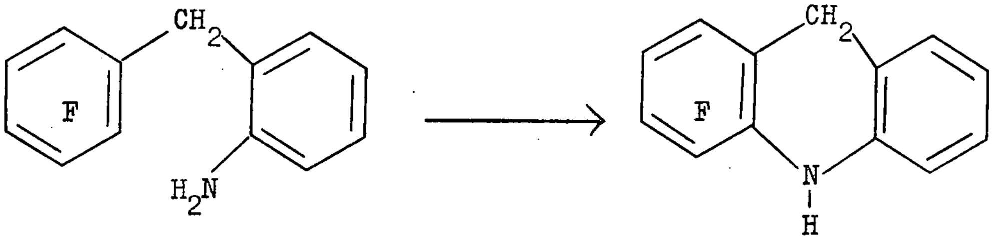


$R = CH_3, C_6H_5, C_6F_5$

The synthesis of octafluorophenothiazine has been reported by a reaction which involves displacement of fluorine by a nitrogen nucleophile[19]:

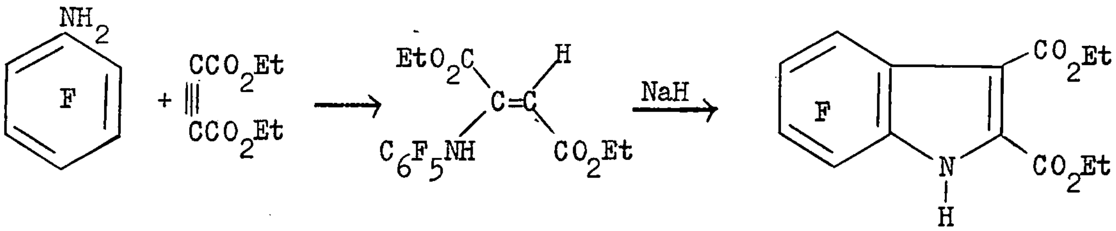


and a similar reaction has been used to synthesise 1,2,3,4-tetrafluoroacridan[20]:



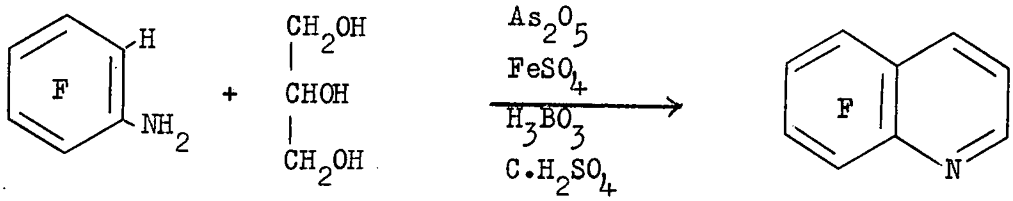
A reaction recently developed for the synthesis of fluorinated benzo[b]thiophens involves the reaction of pentafluorothiophenate anion with ethyl acetylenedicarboxylate[21]. In this case fluorine is displaced by a carbanion:

A closely related reaction has been used for the preparation of fluorinated indoles[22]:

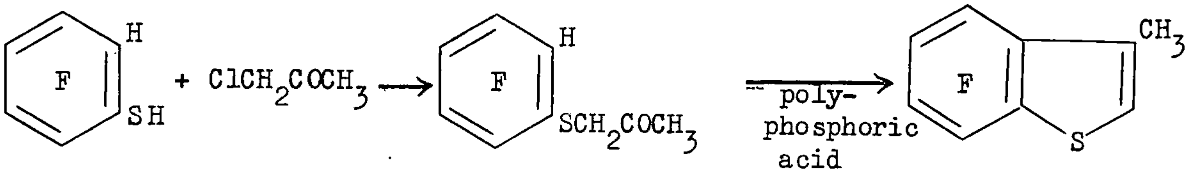


As can be seen from the above survey, a wide variety of heterocycles are available from reactions which involve nucleophilic displacement of fluorine, and it would seem that the full potential of this type of reaction has yet to be realised.

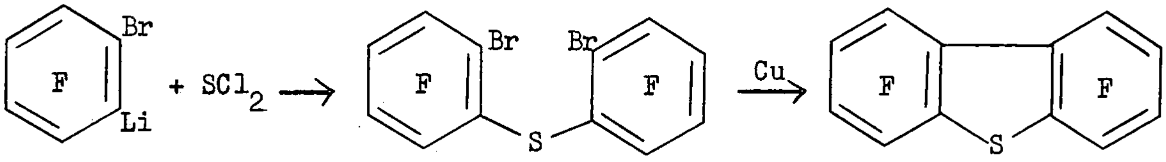
Polyfluorinated heterocyclic compounds have also been synthesised using conventional cyclisation reactions. A number of partially fluorinated quinolines have been prepared using the Skraup reaction[23]:



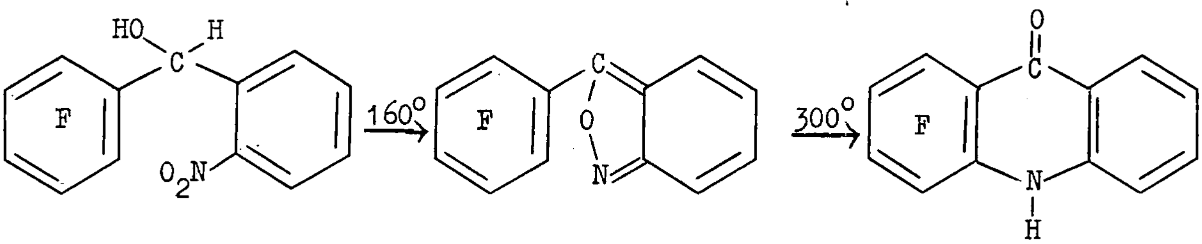
Another conventional electrophilic cyclisation reaction has recently been described for the preparation of fluorinated benzo[b]thiophen derivatives[24]:



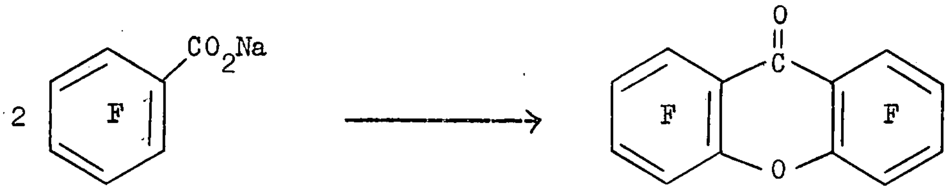
An Ullman reaction has been used to prepare octafluorodibenzothiophen from bis-(o-bromotetrafluorophenyl)sulphide[25]:



Free radical elimination of fluorine by a nitrene intermediate has been postulated to account for the formation of 1,2,3,4-tetrafluoroacridone by the action of heat on 3-pentafluorophenylanthranil[20]:



Octafluoroxanthone has been prepared by pyrolysis of sodium pentafluorobenzoate[26]:

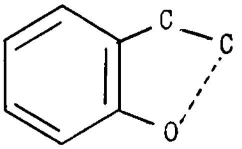


On similar treatment, silicon tetrakis-(pentafluorobenzoate) gave decafluorobenzophenone.

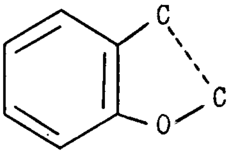
Section 2

The Synthesis of Benzo[b]furan Derivatives

The methods available for the synthesis of benzo[b]furan derivatives have been comprehensively surveyed[27], and this discussion will deal mainly with those methods which are relevant to the present work. The vast majority of methods which have been used to synthesise benzo[b]furan derivatives involve ring closure of the furan ring. These methods can be divided into three groups:



III



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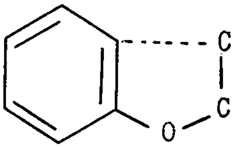
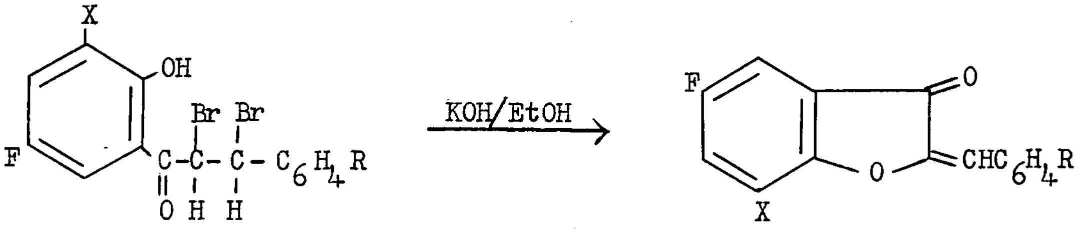


V

Method III has been used to synthesise the only fluoro-2,3-dihydrobenzo[b]furan-3-ones (VII) so far reported in the literature[28]:

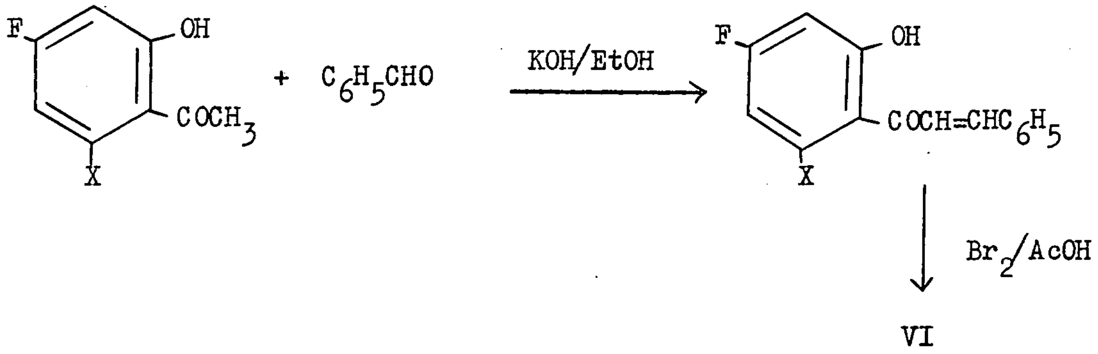


(VI)

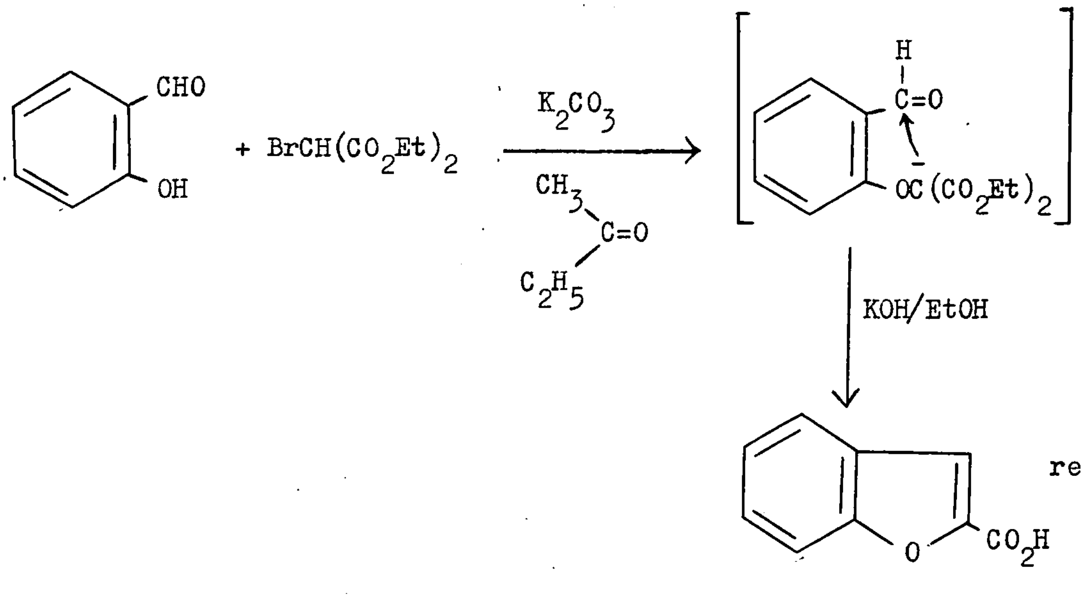
(VII)

X = H, Cl, Br.

The precursors (VI) in the cyclisation reaction were synthesised as follows[29]:

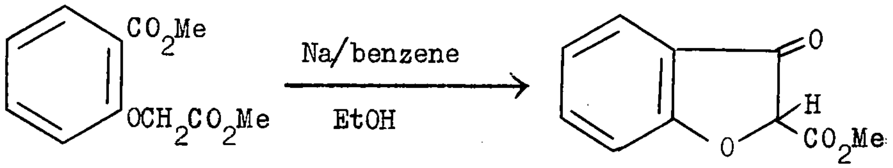


Cyclisation by method IV usually involves an internal Claisen condensation reaction and can give rise to a variety of benzo[b]furan derivatives, depending on the nature of the two carbonyl functions:



ref.30

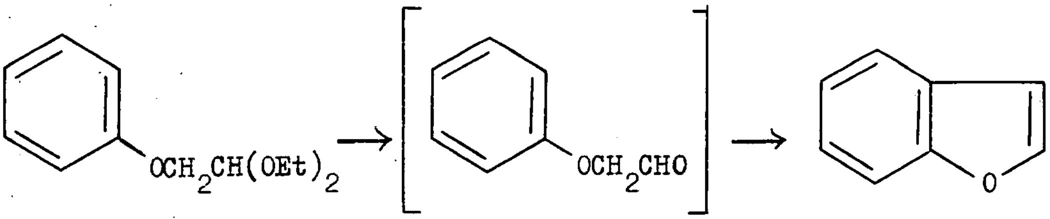
(80%)



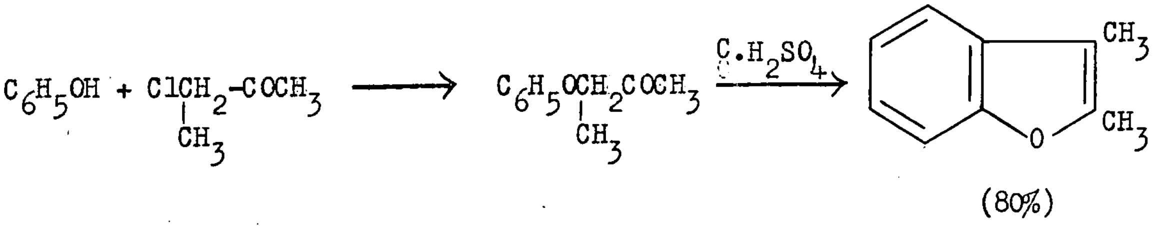
Ref.31

The cyclisation of di-esters has been widely used in recent years for the preparation of substituted 2,3-dihydrobenzo[b]furan-3-ones as intermediates in the synthesis of griseofulvins and related compounds[32]. A large number of benzo[b]furan derivatives have recently been prepared using methods of this general type[33].

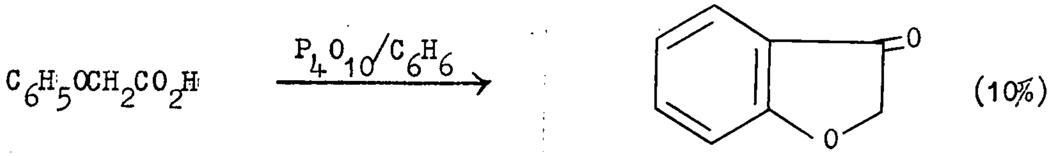
Cyclisation by method V involves electrophilic displacement of hydrogen and has generally been used to synthesise benzo[b]furan derivatives from a range of carbonyl compounds. In acid solution phenoxyacetals are converted to aldehydes which immediately cyclise[34]:

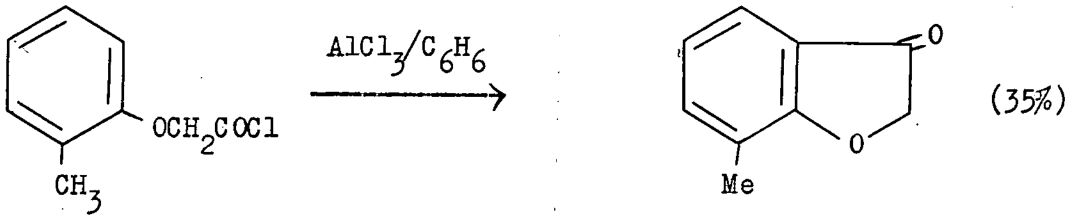


Similarly in strongly acidic media, ketones are cyclised in high yield[35]:

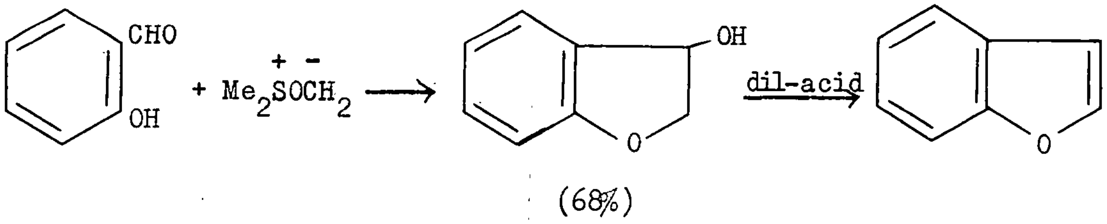


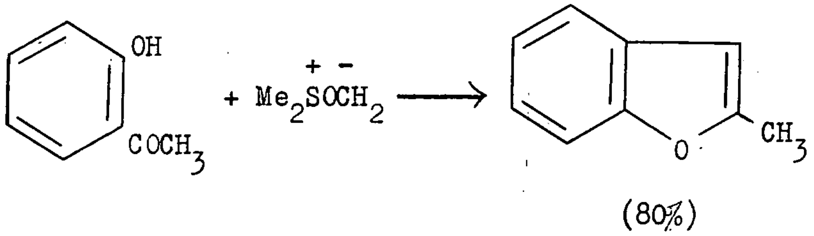
Cyclisation of acids[36] and acid chlorides[37,38] givesrise to 2,3-dihydrobenzo[b]furan-3-one and its derivatives:



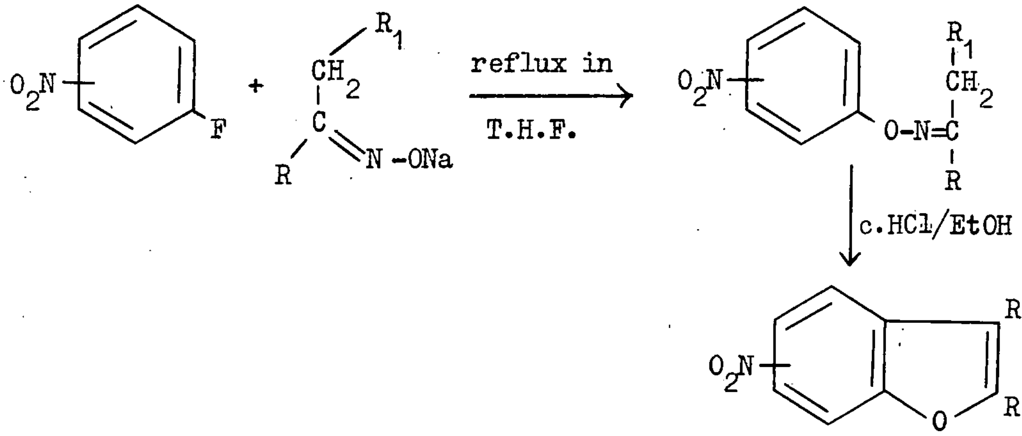


Three interesting new routes to benzo[b]furan derivatives have recently been described in the literature, all of which give high yields. The first involves the reaction of an ortho-hydroxycarbonyl compound with dimethylsulphoxonium methylide[39]:

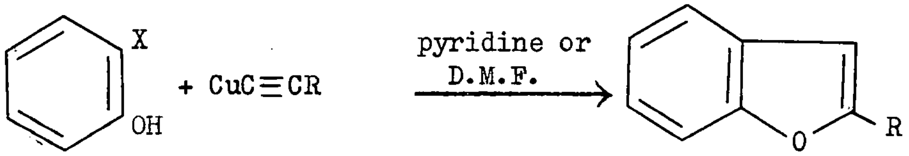




The second new route is an adaptation of the Fischer indole synthesis. The method was initially reported by Sheradsky[40], but has recently been improved[41]:



The third new route involves the reaction of an o-halogeno-phenol with cuprous acetylides[42]:



(50 - 90%)

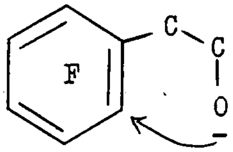
X = Br, I

The route has also been used for the synthesis of indoles using o-halogeno-anilines. This route has obvious applications in the field of polyfluorinated heterocycles since polyfluoroaryl bromides have been shown to react with cuprous salts with replacement of bromine[43]:

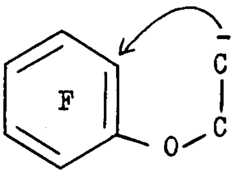
$$CuY + C_6F_5Br \xrightarrow{D.M.F.} C_6F_5Y + CuBr$$

Y = CN, Cl, C_6F_5S, SMe etc.

For the synthesis of highly fluorinated benzo[b]furan derivatives additional methods of ring closure of the furan ring are available:

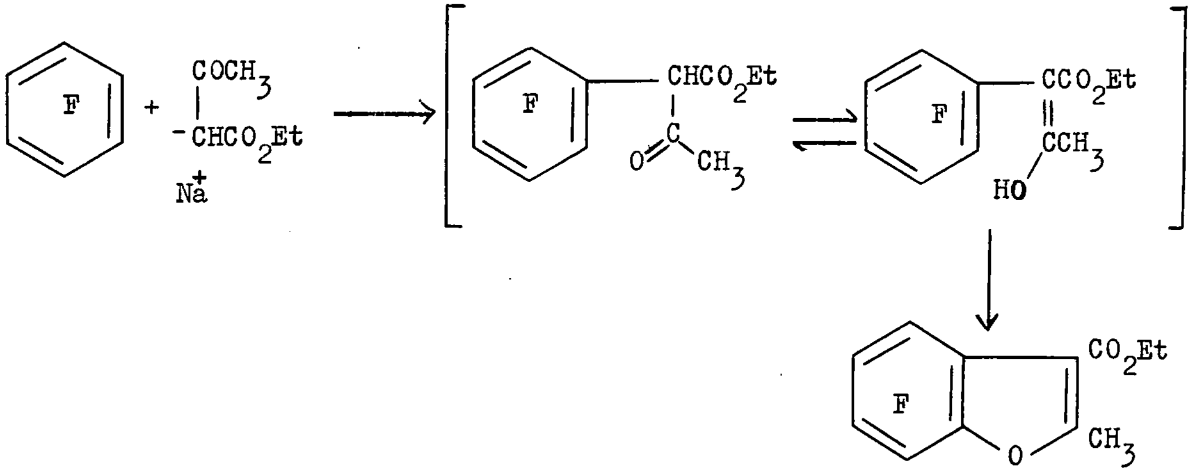


VIII



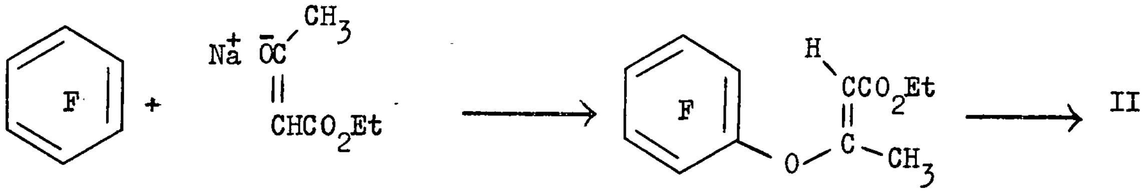
IX

These methods involve nucleophilic displacement of fluorine by an oxygen anion (VIII) or a carbanion (IX). The synthesis of 2-methyl-3-ethoxycarbonyl-4,5,6,7-tetrafluorobenzo[b]furan (II) from hexafluorobenzene and ethyl acetoacetate has been reported by two groups of workers[17,44], who have postulated conflicting mechanisms. The synthesis was first reported by Russian workers[17] who assumed, although with no experimental evidence, that the cyclisation was of type VIII:

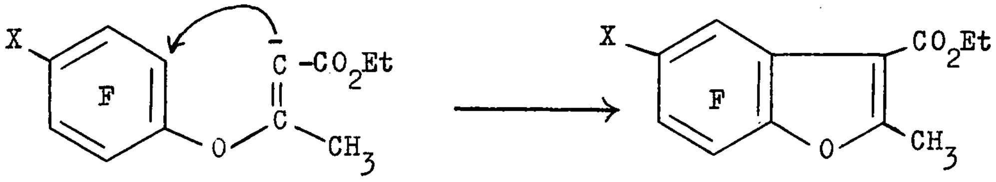


(II)

On the basis of a more detailed study of the reaction, British workers[44] have postulated cyclisation of type IX



These workers carried out the reaction with pentafluorobenzene, chloropentafluorobenzene and pentafluorobenzonitrile as well as hexafluorobenzene, and on the basis of n.m.r. studies on the products (as yet unpublished) decided that the substituents were in the 5-position. Assuming that nucleophilic substitution in the above compounds takes place para to the substituent[45], the initial replacement reaction must have involved the oxygen anion in order to give rise to a 5-substituted trifluorobenzo[b]furan:



X = H, Cl, CN

Initial reaction of the carbanion derived from ethyl acetoacetate, as postulated by the Russian workers, would lead to a 6-substituted trifluorobenzo[b]furan:

Some recent studies on the alkylation of ethyl acetoacetate in dipolar aprotic solvents[46,47] have shown that the extent of O-alkylation can be large but depends on the solvent, temperature, nature of the leaving group and the nature of the base. It would therefore appear to be possible to obtain either 5- or 6- substituted trifluorobenzo[b]furan derivatives from the above reaction by a suitable choice of conditions.

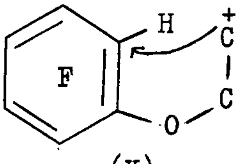
CHAPTER II

DISCUSSION OF EXPERIMENTAL WORK (PART I)

Introduction

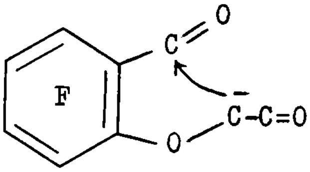
Three routes were investigated for the synthesis of 4,5,6,7-tetrafluorobenzo[b]furan:

1. Electrophilic displacement of hydrogen



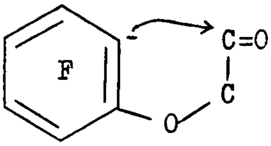
(X)

2. Internal Claisen condensation



(XI)

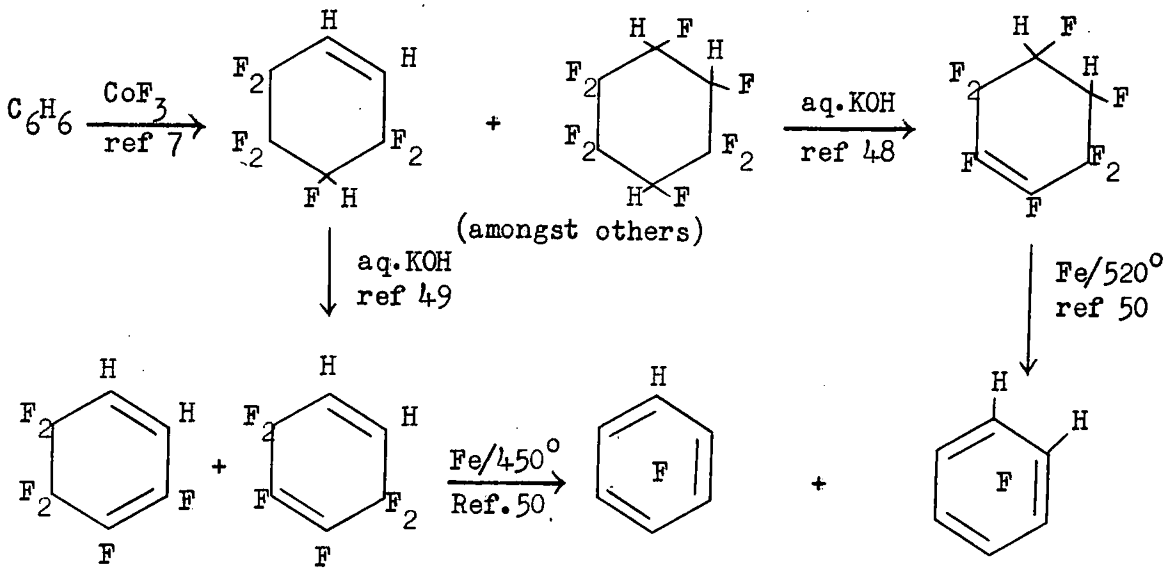
3. A variation of route 2, in which the carbanion was formed in the fluorinated ring



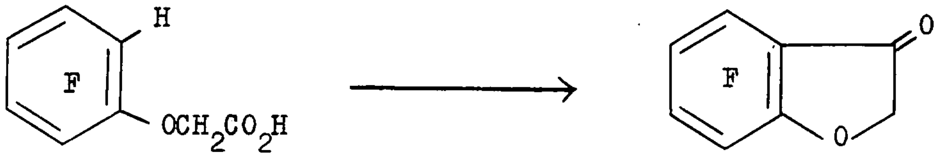
(XII)

The synthesis of compounds with the skeleton structure (X) required 2,3,4,5-tetrafluorophenol as precursor, and since it had not been prepared when this work was started, a known phenol synthesis was adapted as a route to this compound. The starting material used was 1,2,3,4-tetrafluorobenzene which is prepared, as are other highly fluorinated benzenes, by the fluorination of benzene with cobalt trifluoride[7] to give a mixture of polyfluorinated cyclohexanes and cyclohexenes, followed by dehydrofluorination with potassium hydroxide solution,[48,49] and finally defluorination by passage in the vapour phase over heated iron gauze[50], Scheme 1:

Scheme 1



The cyclisation of five compounds of type (X) was investigated under a variety of conditions but all failed to give the desired cyclised product in other than trace amounts. The synthesis of compounds suitable for internal Claisen condensation reactions was investigated and 2,3,4,5-tetrafluorophenol was converted to a di-ester of skeleton structure (XI) which was converted to 4,5,6,7-tetrafluorobenzo[b]furan by a series of high yield reactions. One compound suitable for cyclisation by route 3 was synthesised, but cyclisation could not be effected. 2,3,4,5-Tetrafluorophenoxyacetic acid was unexpectedly converted to 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one:



Investigation of the mechanism of this reaction has shown it to be of type (XI).

Section 1

The Synthesis of 2,3,4,5-Tetrafluorophenol

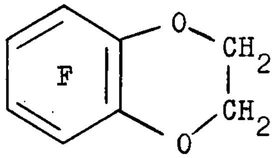
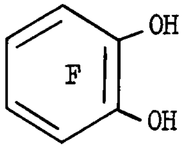
At the commencement of this work two routes were available for the synthesis of highly fluorinated phenols. The first involved the direct introduction of the hydroxyl group into the fluorinated aromatic nucleus by nucleophilic replacement of fluorine, Table 1.

Table 1

Substrate	Reaction Conditions	Product	Yield	Reference
C_6F_6	a) aq.KOH, 175°	C_6F_5OH	84%	51
	b) KOH/t-butanol reflux	C_6F_5OH	71%	52
C_6F_5OH	KOH	$C_6F_4(OH)_2$meta > 90%	80%	53
$C_6F_5CH_3$	KOH/t-butanol	p-$CH_3C_6F_4OH$	32%	51
C_6F_5H	KOH/t-butanol	p-HC_6F_4OH	20%	54
	KOH/pyridine	p-HC_6F_4OH	32%	51
C_6F_5Br	KOH/pyridine	o-BrC_6F_4OH	28%	51
		p-BrC_6F_4OH	62%	

The second route involved initial reaction of the highly fluorinated benzene with alkoxide ion followed by cleavage of the ether thus formed to give the phenol, Table 2.

Table 2

Substrate	Reagent	Ether	Dealkylation Conditions	Product	Reference
C_6F_6	NaOMe/ MeOH	C_6F_5OMe	a) $AlCl_3$/120° b) 47% HI	C_6F_5OH	a) 55 b) 51
C_6F_5H	NaOMe/ MeOH	p-HC_6F_4 OMe	$AlCl_3$/120°	p-HC_6F_4OH	56,54
C_6F_6	$HOCH_2CH_2OH$/ NaOH		$AlCl_3/C_6H_6$		16

These methods of synthesis have limited application however, due to the directional effects of substituents in the fluorinated ring on the position of nucleophilic substitution (see Chapter 4). Hence, in order to prepare 2,3,4,5-tetrafluorophenol, an alternative synthesis was sought which did not involve nucleophilic displacement of fluorine.

A simple procedure for the conversion of aryl halides to the corresponding phenols, in high yield, has been described by Hawthorne[57]:

$$ArX \longrightarrow ArMgX \xrightarrow[2.H_2O/H^+]{1.B(OMe)_3} ArB(OH)_2 \xrightarrow[\text{ether}]{10\%\ H_2O_2} ArOH$$

The method has been adapted for the preparation of high molecular weight phenols, such as 2-fluorenol and 5-acenaphthenol, by using 30% hydrogen peroxide and benzene solvent for the oxidation of the boronic acid[58]. Earlier work on the synthesis of pentafluorophenol from pentafluorophenyl magnesium bromide by reaction with trimethylborate, hydrolysis of the ester with dilute acid and subsequent oxidation of the resulting acid, which was not isolated, by 30% hydrogen peroxide proved unsuccessful[59]. Pentafluorophenylboronic acid has since been isolated by a different route and gave pentafluorophenol in high yield using 85% hydrogen peroxide[60]:

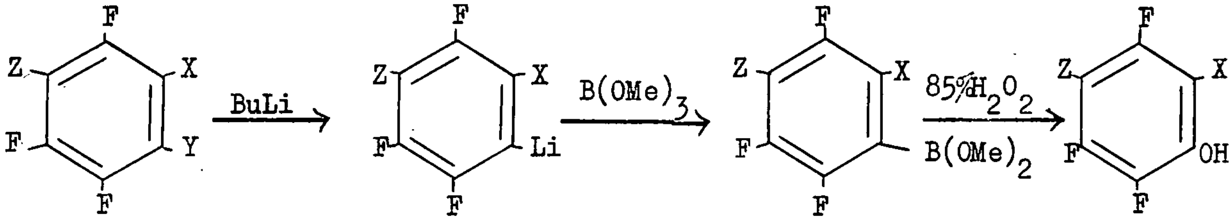
$$\begin{tikzcd}
Me_3SnBr + C_6F_5MgBr \arrow[r] & MeMgC_6F_5 \arrow[r, "BCl_3"] & C_6F_5BCl_2 \arrow[d, "H_2O"] \\
& C_6F_5OH & C_6F_5B(OH)_2 \arrow[l, "85\% H_2O_2"']
\end{tikzcd}$$

Pentafluorophenylboronic acid was also shown to undergo ready hydrolysis to pentafluorobenzene in aqueous solution[60]:

$$\begin{tikzcd}
C_6F_5B(OH)_2 + H_2O \arrow[r] & C_6F_5\overset{-}{B}(OH)_2\cdot\overset{+}{O}H_2 \arrow[r, "-H^+"] & C_6F_5\overset{-}{B}(OH)_3 \arrow[d, "+H^+"] \\
& & C_6F_5H + B(OH)_3
\end{tikzcd}$$

This susceptibility to hydrolysis would account for the failure of the attempted preparation of pentafluorophenol by oxidation of pentafluorophenylboronic acid with 30% hydrogen peroxide[59].

The synthesis of 2,3,4,5-tetrafluorophenol required the use of a 2,3,4,5-tetrafluorophenyl organometallic compound; the lithium derivative was used since Tamborski had already shown that 1,2,3,4-tetrafluorobenzene forms a mono-lithium derivative in high yield when treated with one equivalent of butyl-lithium[61]. The overall synthesis may thus be written:



A X=H, Y=H, Z=F
B X=Br, Y=Br, Z=F
C X=F, Y=Br, Z=F
D X=F, Y=H, Z=H

The method was initially developed using the readily available pentafluorobromobenzene and converting it to pentafluorophenol[51,52], and then extended to the synthesis of other phenols including the required 2,3,4,5-tetrafluorophenol, Table 3.

Table 3

Starting Compound		Phenol	Major Solvent *	Yield
C	C_6F_5Br	C_6F_5OH	Hexane	39%
B	1,2-$Br_2C_6F_4$	2-BrC_6F_4OH	Hexane	54%
A	1,2-$H_2C_6F_4$	2-HC_6F_4OH	Tetrahydrofuran	59%
D	1,4-$H_2C_6F_4$	4-HC_6F_4OH	Tetrahydrofuran	55%

* Butyl-lithium was always used in hexane solvent.

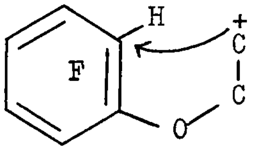
Initially hexane was used as solvent to avoid the possibility of reaction between solvent and the high test peroxide, and this proved satisfactory when the lithium derivative was formed from a bromofluorobenzene, but when this solvent was used with 1,2,3,4-tetrafluorobenzene, no phenolic product was obtained. However, when tetrahydrofuran was used for the reactions of hydrofluorobenzenes, good yields of fluorinated phenols were obtained. This is consistent with the work of Tamborski who has shown firstly, that the reaction of hydrofluorobenzenes with alkyl-lithium is significantly slower in hexane than in ether or tetrahydrofuran[61], and secondly, that bromofluorobenzenes react much more rapidly with alkyl-lithium than do hydrofluorobenzenes[62].

Since the completion of this work, the preparation of 2,6-difluorophenol and 2,3-difluorophenol by an analogous method has been reported[63]. In this case, however, the boronic acids were formed from the esters and oxidised with 30% hydrogen peroxide to give yields of 40% and 60% respectively. Very recently, further work on the preparation of 2,3,4,5-tetrafluorophenol has shown that higher yields (70-80%) can be obtained by carrying out the oxidation with 30% hydrogen peroxide, initially at -70°, and then at room temperature for 16 hr.[64].

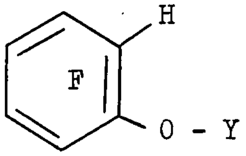
Section 2

Attempted synthesis of 4,5,6,7-tetrafluorobenzo[b]furan derivatives by electrophilic ring closure

This type of synthesis may be generally represented by



The cyclisation of the following five compounds was investigated: 2,3,4,5-tetrafluorophenoxy-acetic acid (XIII), -acetyl chloride (XIV), -acetaldehyde diethylacetal (XV), 2-(2',3',4'5'-tetrafluorophenoxy) ethanol (XVI) and ω-(2,3,4,5-tetrafluorophenoxy)acetophenone (XVII).



XIII $Y = CH_2CO_2H$

XIV $Y = CH_2COCl$

XV $Y = CH_2CH(OEt)_2$

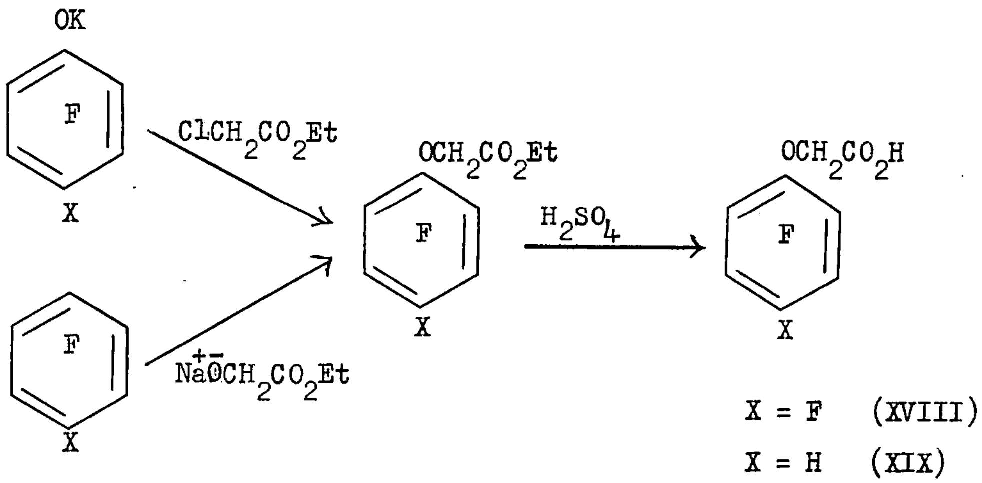
XVI $Y = CH_2CH_2OH$

XVII $Y = CH_2COC_6H_5$

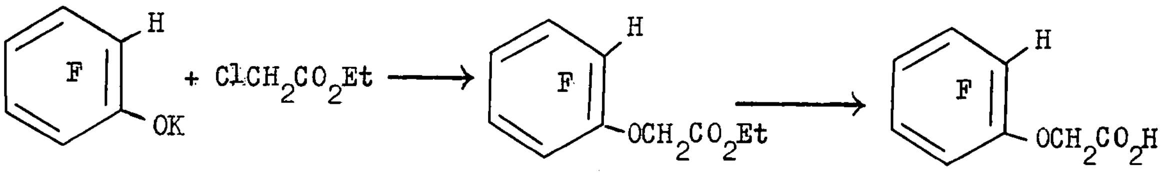
The first four compounds, (XIII), (XIV), (XV), (XVI), were synthesised by standard methods from the potassium salt of 2,3,4,5-tetrafluorophenol. (XVII) was obtained from attempted cyclisation reactions of (XIII) and (XIV).

2,3,4,5-Tetrafluorophenoxyacetic Acid (XIII)

The route used to prepare the acid consisted of reaction of the potassium salt of the corresponding phenol with ethyl chloroacetate followed by hydrolysis of the phenoxyacetic ester. In order to determine the conditions required for these two reactions 2,3,4,5,6-penta-(XVIII), and 2,3,5,6-tetrafluorophenoxyacetic acids (XIX) were first synthesised by the same route from the more readily available pentafluorophenol[51,52] and 2,3,5,6-tetrafluorophenol[51,54] respectively. The ethyl esters of (XVIII) and (XIX) were also synthesised by nucleophilic replacement of fluorine from hexa- and penta-fluorobenzene respectively, using the sodium salt of ethyl glycollate; replacement of fluorine from pentafluorobenzene took place as expected at the 4-position (>90%)[1]:



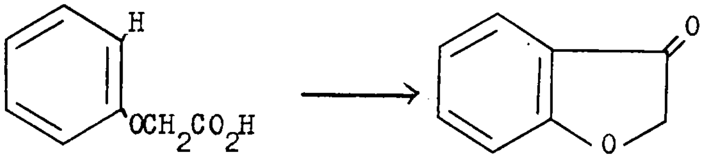
X = F (XVIII)
X = H (XIX)



(XIII)

Attempted alkaline hydrolysis of ethyl pentafluorophenoxyacetate by refluxing in 5N sodium hydroxide solution for one hour gave rise to a mixture of products probably due to nucleophilic replacement of fluorine by hydroxyl ion in addition to hydrolysis of the ester. Acid hydrolysis, however, with sulphuric acid (50% v/v) gave an excellent yield of the acid.

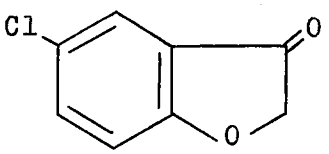
Stoermer and Bartsch[36] carried out the original studies on the cyclodehydration of phenoxy-acetic acids using phosphoric oxide in benzene to give 2,3-dihydrobenzo[b]furan-3-one (XX) in low yield:



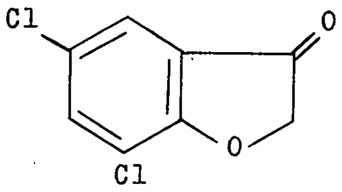
(10%)

(XX)

More recently[65], attempts have been made to synthesise a series of three 2,3-dihydrobenzo[b]furan-3-ones, (XX), (XXI), (XXII), by this and other methods:

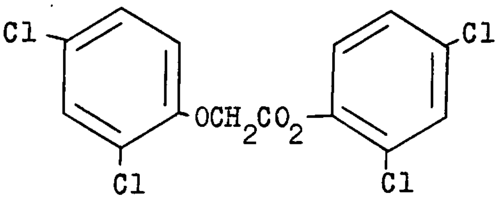


(XXI)



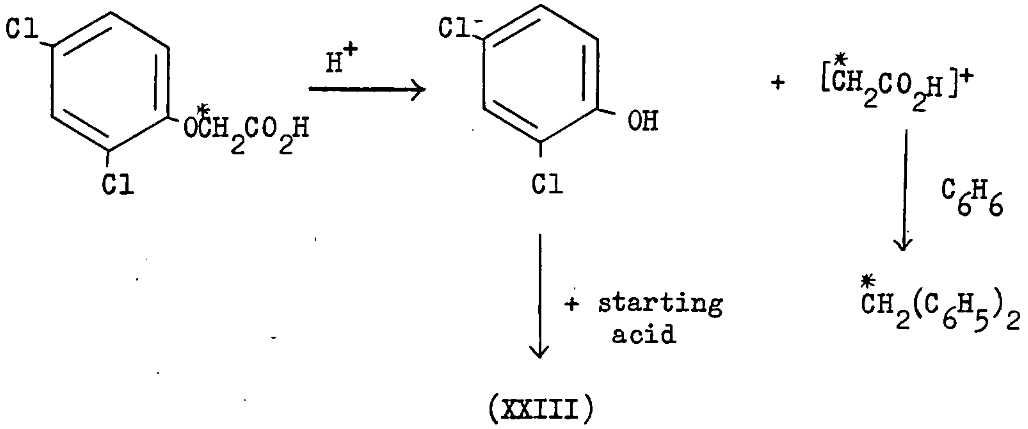
(XXII)

It was found using this method that the yield of cyclic ketone decreased as chlorine substitution increased, (XXI) being formed only in trace quantities, and (XXII) not at all. Since the cyclisation reaction involves electrophilic substitution meta to one chlorine in one case, and meta to two chlorines in the other case, and chlorine is known to direct ortho/para in electrophilic substitution, the failure to obtain good yields in either case is not unexpected. Although (XXII) was not formed from the reaction of 2,4-dichlorophenoxyacetic acid with phosphoric oxide in benzene[65], another compound was isolated and identified as 2,4-dichlorophenyl 2',4'-dichlorophenoxyacetate (XXIII)



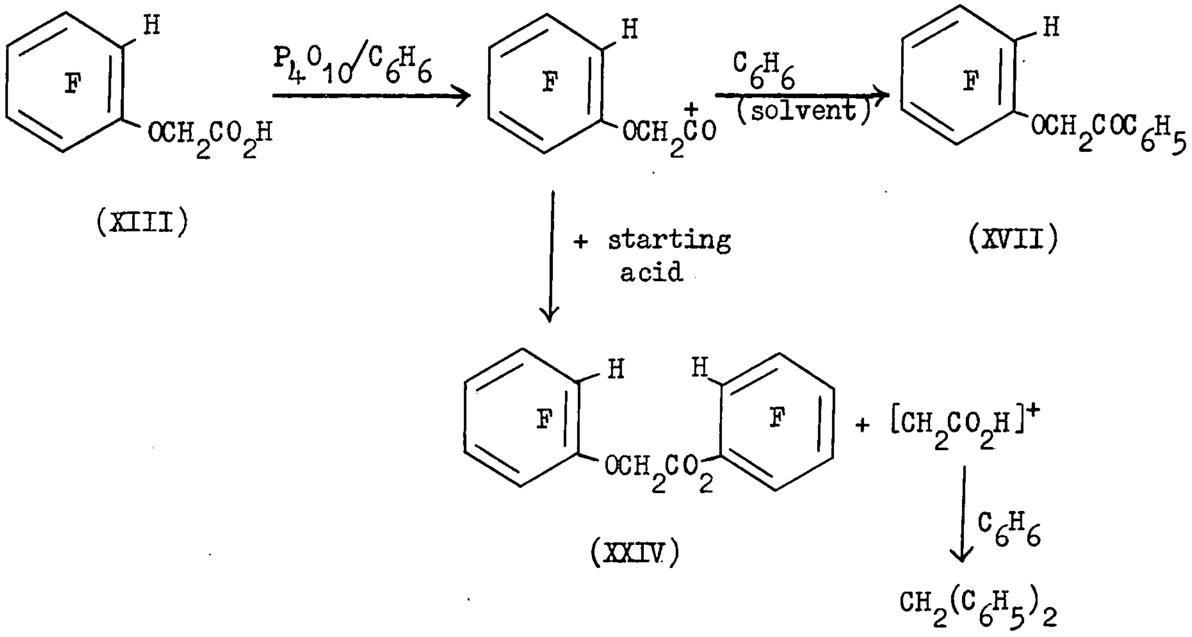
(XXIII)

The mechanism of the formation of this ester has been studied in detail by Armarego[66], who found that diphenylmethane and 2,4-dichlorophenol were formed in addition to the ester (XXIII). On the basis of reactions in which the methylene carbon atom of the phenoxyacetic acid was ^{14}C-labelled, a mechanism was postulated which involved initial cleavage of the ether link in the acid:

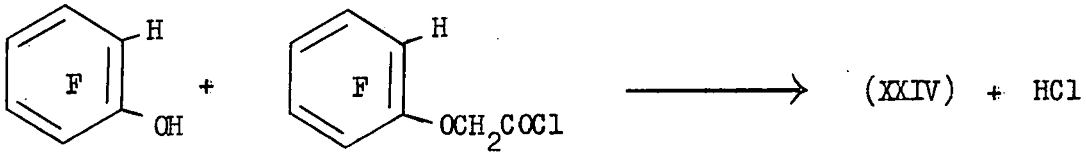


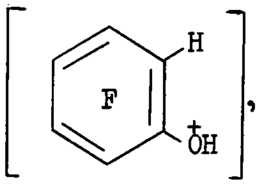
The reaction of 2,3,4,5-tetrafluorophenoxyacetic acid (XIII) with phosphoric oxide in benzene differed from those of the acids mentioned above in that an acetophenone derivative (XVII) was formed in addition to an ester (XXIV) and diphenylmethane, and hence an additional mechanism must be postulated involving reaction of the intermediate acylium cation with the solvent, scheme 2:

Scheme 2



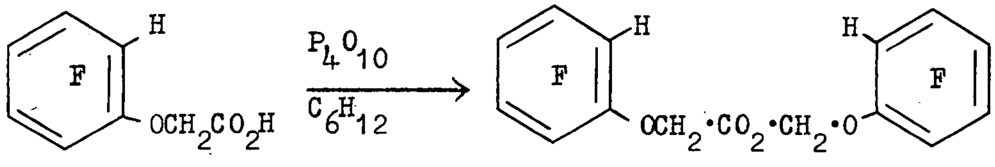
The structure of the ester (XXIV) was confirmed by independent synthesis from the corresponding phenol and acid chloride:



The structure of the acetophenone derivative (XVII) was assigned on the basis of correct elemental analysis, mass spectroscopic molecular weight and fragmentation pattern, ^{1}H n.m.r., and independent synthesis by means of a Friedel Crafts reaction between the corresponding acid chloride and benzene (see later). The ^{1}H n.m.r. spectrum of (XVII) in acetone consisted of four absorptions at τ 1·8, 2·3, 2·6 and 4·1, with relative intensities 2:3:1:2. The first two absorptions were attributed to the hydrogens of the C_6H_5- ring by comparison with the spectrum of acetophenone[67]; the third absorption, a broad complex band was attributed to the hydrogen in the tetrafluorophenyl ring, the complexity being due to coupling with the four fluorine atoms. The absorption at τ 4·1, a singlet, was attributed to the $-CH_2-$ group. The molecular weight by mass spectroscopy was 284 (required 284) and the fragmentation pattern included peaks at 166 

, 119 ($C_6H_5\,CO\overset{+}{C}H_2$), 105 ($C_6H_5\,\overset{+}{C}O$) and 77 ($C_6H_5^+$).

To avoid the reaction of the acylium cation with the benzene solvent, the reaction was carried out in cyclohexane, but in this case a different ester, 2',3',4',5'-tetrafluorophenoxymethyl 2,3,4,5-tetrafluorophenoxyacetate(XXV) was formed:

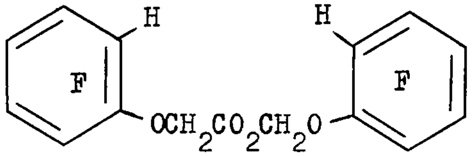


(XXV)

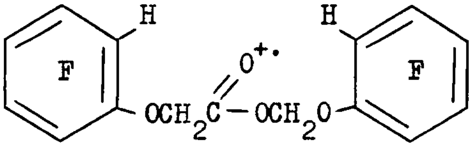
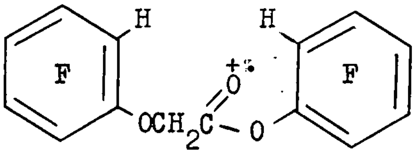
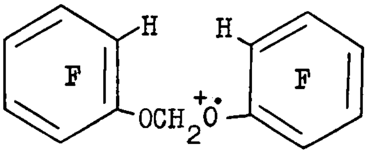
The structure of this ester (XXV) was assigned on the basis of correct elemental analysis, ^{1}H n.m.r., mass spectroscopic molecular weight and fragmentation pattern, and the behaviour on alkaline hydrolysis. The ^{1}H n.m.r. spectrum of XXV in carbon tetrachloride showed three absorptions at τ 3·3, 4·3, and 5·3, all of equal intensity. The last two absorptions were singlets and were attributed to the two methylene groups. The absorption at τ 3·3 was a broad complex band and was assigned to the aromatic hydrogens. The major peaks from the mass spectrum are shown in table 4:

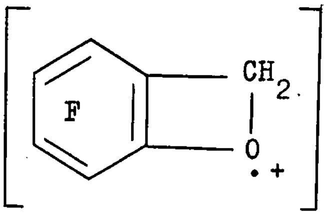
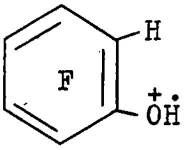
Table 4

Mass Spectrum of



XXV

Mass		Probable Fragment Lost	Probable Ion
402	parent		
372	p-30	CH_2O	
344	p-58	CO	

178	p-224	$C_7H_2F_4O$	
166	p-246		

Metastables at 344 and 318

The two metastable peaks can be used to verify two fragmentations using the formula[68]

$$m_S = \frac{m_2^{\,2}}{m_1}$$

where

m_S = mass of metastable

m_1 = mass of original ion

m_2 = mass of product ion

Metastable at 344:

$$402^{+} \longrightarrow 372^{+} + 30$$

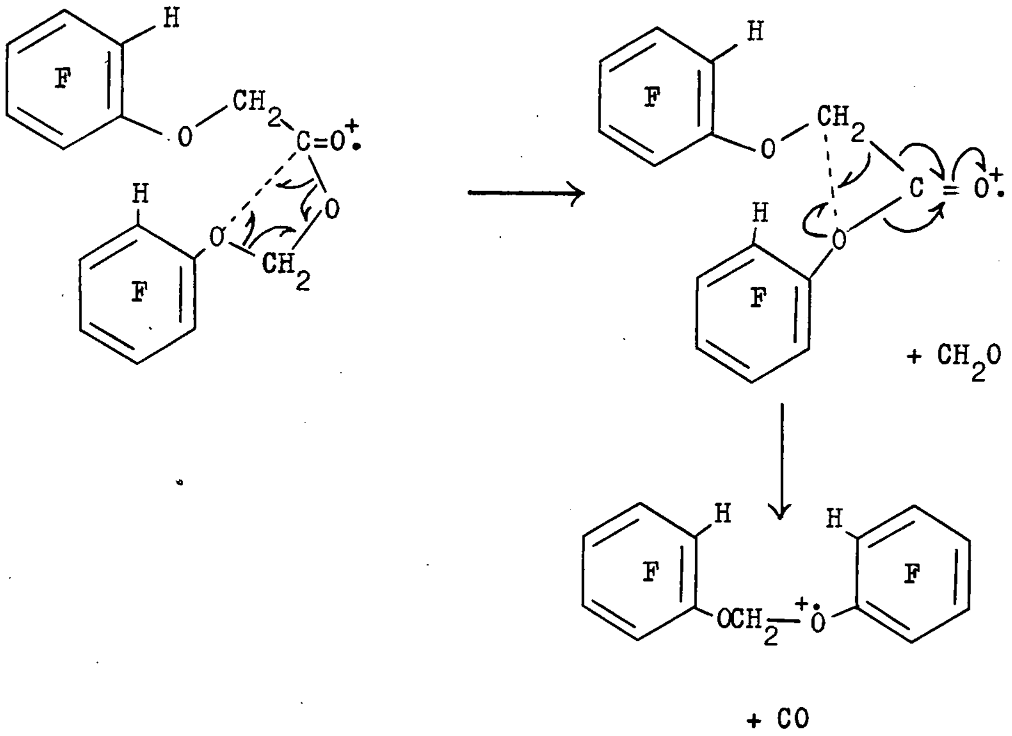
Calculation of mass of metastable from the above formula gives m_S = 344·2

Metastable at 318:

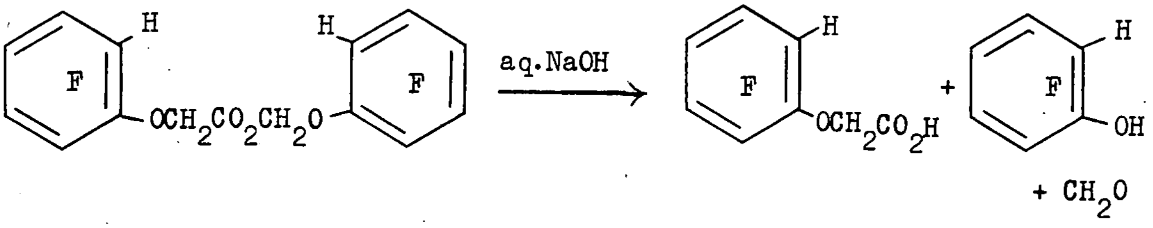
$$372^{+} \longrightarrow 344^{+} + 28$$

Calculation of mass of metastable gives m_S = 318·2

Thus, the probable mechanism of disintegration is:



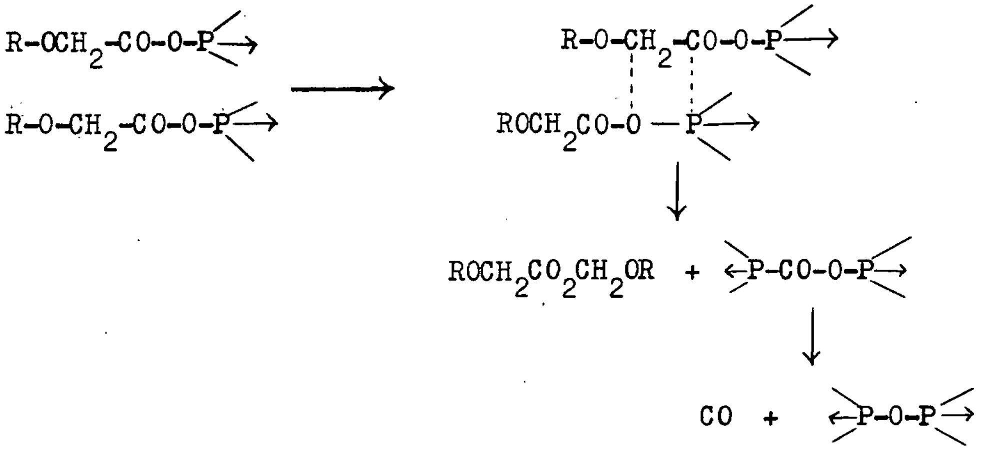
The alkaline hydrolysis of the ester (XXV) was carried out in a similar manner to that used for similar chlorine substituted esters[69]; 2,3,4,5-tetrafluorophenoxyacetic acid (XIII) and 2,3,4,5-tetrafluorophenol were isolated, but the formaldehyde formed in the reaction was not isolated:



(XXV)

(XIII)

A possible explanation of the different course of the reaction in cyclohexane as compared with benzene is the ability of benzene to stabilise the charged species postulated in Scheme 2 by interaction with its π-electron system. Cyclohexane offers no such stabilising effect and hence the reaction is unlikely to involve such charged species. Chlorine substituted esters similar to that formed in this reaction have been synthesised by reaction of the phenoxyacetyl chloride with silver phosphate[69]. The mechanism proposed involves the initial formation of a phosphate ester, two molecules of which form a complex which then decomposes giving the observed products:

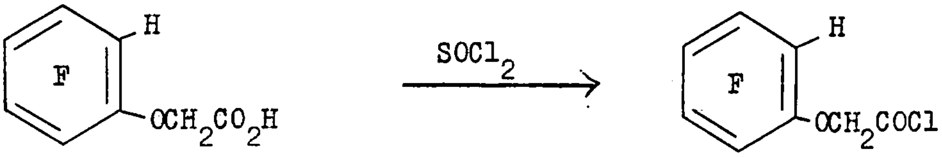


This mechanism would also account for the product (XXV) formed in the reaction of the acid (XIII) with phosphoric oxide in cyclohexane.

Cyclodehydrations of the acid (XIII) were also attempted using in turn concentrated sulphuric acid, polyphosphoric acid and anhydrous hydrogen fluoride, but all were unsuccessful. In concentrated sulphuric acid only starting material and tars were obtained. The reactions with polyphosphoric acid were carried out in a sealed tube with shaking due to the tendency of the acid (XIII) to sublime out of the reagent; again only starting material and tars were obtained. Anhydrous hydrogen fluoride at room temperature and pressure had no effect on the acid.

2,3,4,5-Tetrafluorophenoxyacetyl Chloride (XIV)

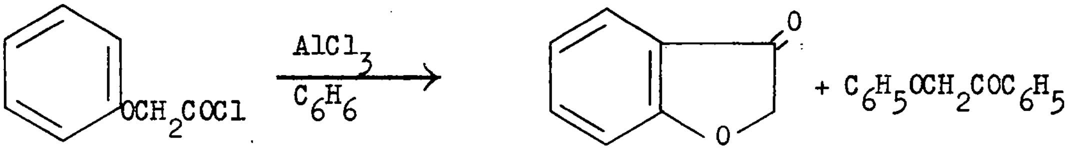
The acid chloride (XIV) was obtained in excellent yield (> 90%) from the reaction of the acid (XIII) with thionyl chloride.



(XIII) (XIV)

94%

Reaction of phenoxyacetyl chloride with aluminium chloride in benzene[70] gave a mixture of 2,3-dihydrobenzo[b]furan-3-one and ω -phenoxyacetophenone:

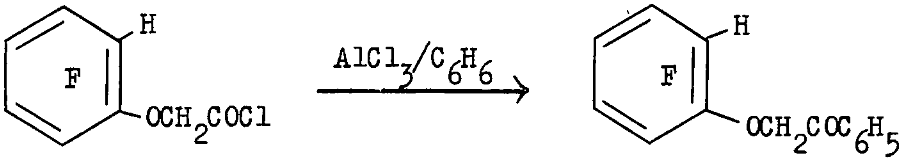


(20%)

Tolyloxyacetyl chlorides, however, gave a higher yield of the cyclic ketone (35-40%) and no acetophenone derivative[37]. Reaction of monochlorophenoxyacetyl chlorides under Friedel Crafts conditions[38,65] gave only low yields of cyclic ketones, and in the reaction of 2,4-dichlorophenoxyacetyl chloride no cyclic ketone (XXII) was isolated at all[65]. When the last reaction was carried out in benzene a 20%

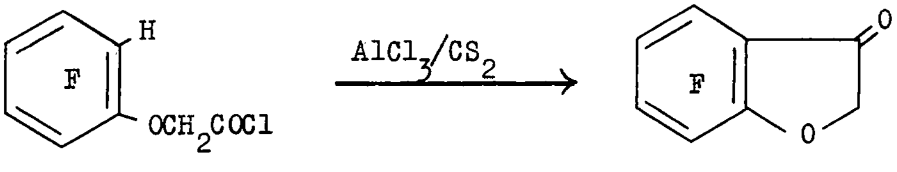
yield of the corresponding acetophenone derivative was obtained[66].

When 2,3,4,5-tetrafluorophenoxyacetyl chloride (XIV) was treated with aluminium chloride in benzene at room temperature, no cyclised product was isolated; ω-(2,3,4,5-tetrafluorophenoxy)acetophenone (XVII) was obtained in high yield (70%):



(XIV) (XVII)

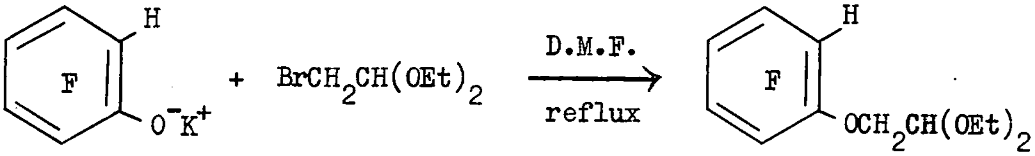
When the same reaction was carried out in carbon disulphide solvent, a reddish brown complex was formed, from which a small amount (<u>Ca</u>.10 m.g.) of white solid product was obtained after acidification. Comparison of the infra-red and mass spectra of this product with those of an authentic sample of 2,3-dihydro-4,5,6,7-tetrafluorobenzo[b]furan-3-one(XXVI), prepared later, showed that the product consisted mainly of this compound:



(XXVI) (trace)

<u>2,3,4,5-Tetrafluorophenoxyacetaldehyde Diethyl Acetal</u> (XV)

The conditions required for the preparation of the acetal (XV) were initially investigated using the more readily available 2,3,5,6-tetrafluorophenol. Reaction of the potassium salt of the phenol with chloroacetaldehyde diethyl acetal in dimethylformamide resulted in poor yields, but when the bromo-acetal was used good yields were obtained:

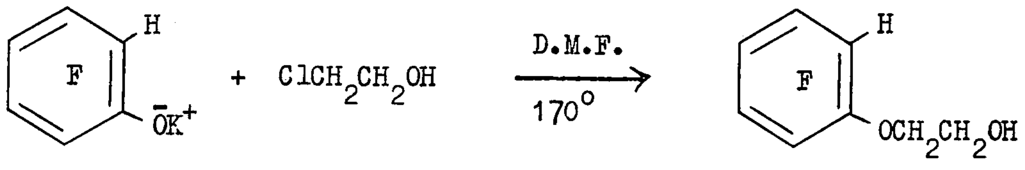


(XV)

Cyclisations of phenoxyacetals were reported by Stoermer at the turn of the century[34,71], but poor yields were obtained. A recent study has been made on the cyclisation of arylthio-acetals[72] and a variety of cyclisation agents were investigated, the best of which was found to be polyphosphoric acid. This reagent has found wide use in recent years in the synthesis of fused ring heterocycles by cyclodehydration reactions [73,74]. When the acetal (XV) was treated with this reagent, no tractable organic product was formed. Reaction of (XV) with adhydrous hydrogen fluoride, another reagent known to effect cyclodehydrations[75], resulted in a mixture of high molecular weight products (350-400 from mass spectrum), probably arising from acid catalysed condensation of the aldehyde before cyclisation could occur.

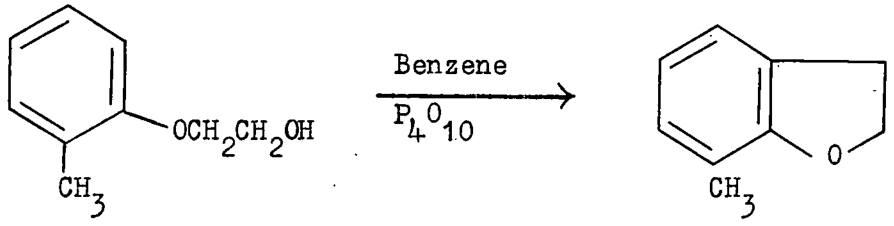
2-(2',3',4',5'-Tetrafluorophenoxy)ethanol (XVI)

Initial investigations of the conditions required for the synthesis of this compound were carried out on the more readily available 2,3,5,6-tetrafluorophenol, and good yields were obtained in both cases from the reaction of the potassium salt of the phenol with 2-chloroethanol in dimethyl formamide in a sealed tube:



(XVI)

Methyl and bromine substituted 2,3-dihydrobenzo[b]furans have been prepared from the reaction of phenoxyethanols with phosphoric oxide in benzene or methyl ethyl ketone[76]:



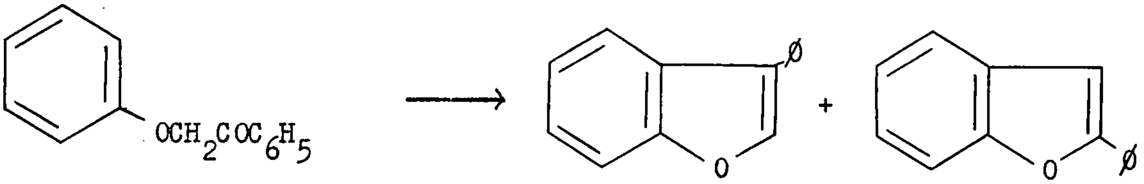
(50%)

The reaction of the alcohol (XVI) with polyphosphoric acid resulted in cleavage of the ether linkage to give 2,3,4,5-tetrafluorophenol. No tractable organic compound was obtained from the reaction of (XVI) with phosphoric oxide in cyclohexane.

ω-(2,3,4,5-Tetrafluorophenoxy)acetophenone (XVII)

This ketone was prepared from 2,3,4,5-tetrafluorophenoxyacetyl chloride (XIV) as described above.

ω-Phenoxyacetophenone has been reported to give mixtures of 2-phenyl- and 3-phenyl-benzo[b]furans when treated with phosphoric oxide in benzene or polyphosphoric acid[77,78]:



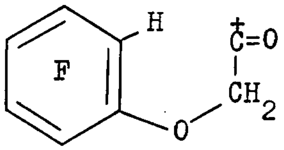
On treatment of the ketone (XVII) with concentrated sulphuric acid only unchanged starting material and tars were obtained.

Conclusions

The information available on the electrophilic displacement of hydrogen from a polyfluorinated aromatic ring shows that fairly severe conditions are required compared with non-fluorinated compounds. Sulphonation, bromination and iodination of pentafluorobenzene all give high yield in the presence of oleum[79]. The Friedel Crafts reaction of pentafluorobenzene gives high yields when carried out in a steel reaction vessel at 150°[80]. The direct nitration of highly fluorinated aromatics in high yield has recently been described using a homogeneous system composed of fuming nitric acid, boron trifluoride and sulpholan[81]. Intramolecular electrophilic displacement reactions have been described in the preparation of 5,6,7,8-tetrafluorquinoline[23] and 3-methyl-4,5,6,7-tetrafluorobenzo[b]thiophen[24]; the former reaction requires 18 hours at 120° whilst the latter requires 2 hours at 160-180°.

In the attempted electrophilic cyclisation reactions described in this section, it would appear that the required electrophilic species were formed in some, if not all, cases. The formation of ω-(2,3,4,5-

tetrafluorophenoxy)acetophenone (XVI) from the reaction of 2,3,4,5-tetrafluorophenoxyacetic acid (XIII) with phosphoric oxide in benzene and from the reaction of 2,3,4,5-tetrafluorophenoxyacetyl chloride (XIV) with aluminium chloride in benzene suggests that the electrophilic species (XXVII) was an intermediate in these reactions:



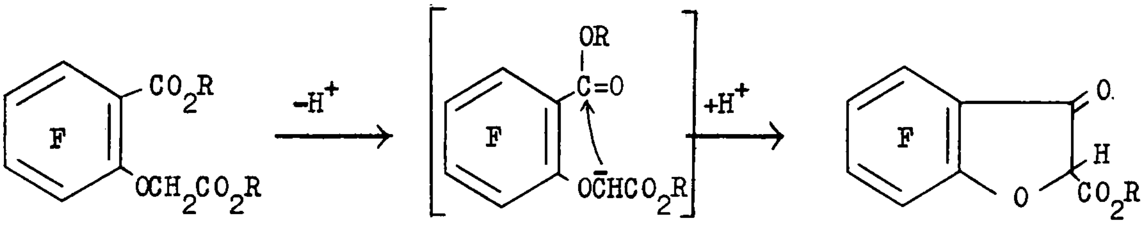
(XXVII)

The formation of 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (XXVI), although only in small quantities, from the reaction of the acid chloride (XIV) with aluminium chloride in carbon disulphide also requires (XXVII) as an intermediate. When more forcing conditions were used, such as reaction in polyphosphoric acid or concentrated sulphuric acid, only decomposition products were obtained. This suggests either that any cyclised product formed is decomposed under these conditions, or that intermolecular reactions take place in preference to the desired intramolecular cyclisation, thus leading to the decomposition products.

Section 3

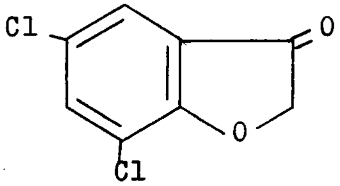
The Synthesis of 4,5,6,7-Tetrafluorobenzo[b]furan

Following the failure of the electrophilic cyclisation reactions described in Section 2, a second conventional synthesis of benzo[b]furan derivatives was investigated:



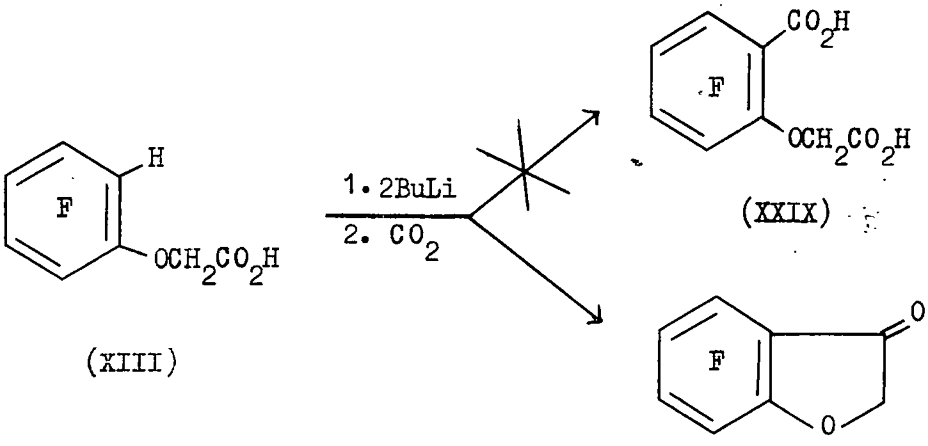
XXVIII

This type of synthesis has been shown to be quite general[31,32,33], and appears to be less dependent on the nature of the ring substituents than the electrophilic cyclisation: 5,7-dichloro-2,3-dihydrobenzo[b]furan-3-one (XXII) could not be obtained by direct electrophilic cyclisation reactions, but has been synthesised via this route[66]. In order to investigate this type of synthesis it was necessary to synthesise a suitable di-ester (XXVIII). A method of synthesis of carboxylic acids has been described by Tamborski[61], by reaction of hydrofluoroaromatic compounds with



(XXII)

butyl-lithium to give highly fluorinated phenyl-lithium compounds, which were then carbonated. An extension of this reaction was applied to 2,3,4,5-tetrafluorophenoxyacetic acid in an attempt to prepare the di-carboxylic acid (XXIX), which could then be converted to the di-ester (XXVIII). Two equivalents of butyl-lithium were used in the reaction, one to react with the carboxylic acid group, and the other to form the required phenyl-lithium. None of the expected di-acid (XXIX) was isolated from this reaction but unexpectedly 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (XXVI) was obtained in low yield (14%):



(XIII)

(XXIX)

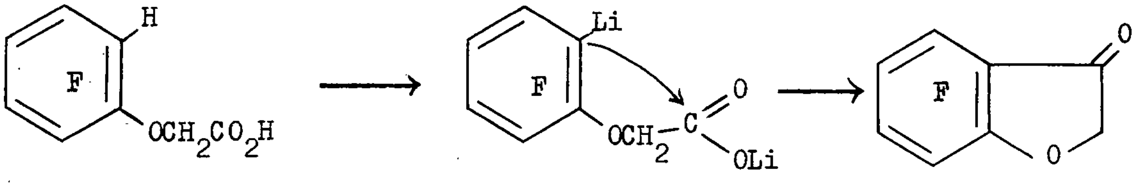
(XXVI)

The mechanism of the formation of (XXVI) was investigated by a number of reactions on the acid (XIII) and the di-acid (XXIX), which was synthesised by an alternative route; the results of these reactions are shown in table 5:

Table 5

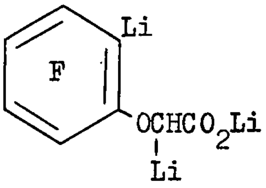
Starting Acid	Moles BuLi	CO_2	Yield of XXVI	Starting Material recovered
XIII	2	No	Trace (ca 1%)	-
XIII	2	Yes	14%	32%
XIII	3	Yes	35%	-
XXIX	3	No	-	-
XXIX	3	Yes	5%	-

The first step was to discover whether cyclisation took place before carbon dioxide was added; only a trace of (XXVI) was formed when carbon dioxide was omitted which indicated that the cyclisation shown was not important:



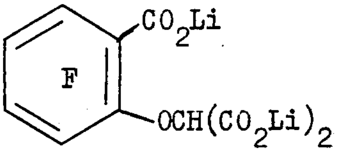
(XXVI)

In the initial reaction, in addition to (XXVI), unchanged starting material (ca 32%) was recovered which indicated the presence of more than two active hydrogen atoms in the molecule. On increasing the proportion of butyl-lithium to three moles, no starting material was recovered and the yield of (XXVI) was greatly increased. This suggested the formation of a tri-lithium compound (XXX):

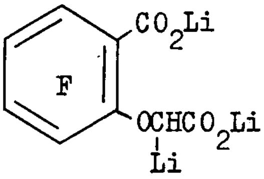


(XXX)

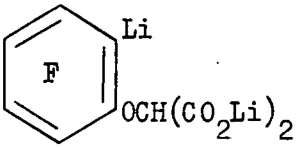
Carbonation of (XXX) could give three possible products, (XXXI), (XXXII), (XXXIII):



(XXXI)



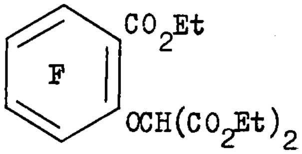
(XXXII)



(XXXIII)

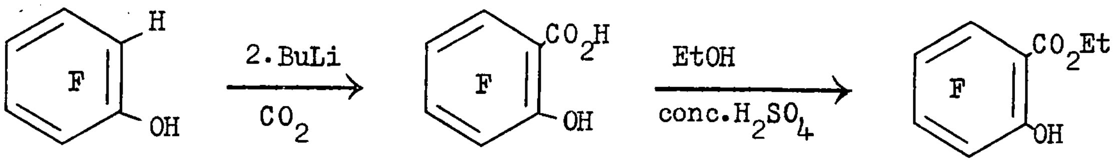
Compound (XXXIII) was discounted since cyclisation would occur by a reaction which was shown above to be unimportant. In order to decide between intermediates (XXXI) and (XXXII) the reaction of the di-acid (XXIX) was studied under the same conditions. Reaction of (XXIX) with three moles of butyl-lithium would be expected to give (XXXII); if this was carbonated, (XXXI) would be formed. It was found that the reaction of (XXIX) with three moles of butyl-lithium without carbonation gave no 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (XXVI); reaction with three moles of butyl-lithium followed by carbonation gave a 5%

yield of (XXVI). The fate of the remaining starting material in these reactions could not be determined since the residues consisted of highly involatile tars. The evidence from the above reaction suggests that (XXXI) was the intermediate which on acidification decarboxylates and cyclises. An attempt was made to prepare the tri-ester corresponding to (XXXI):



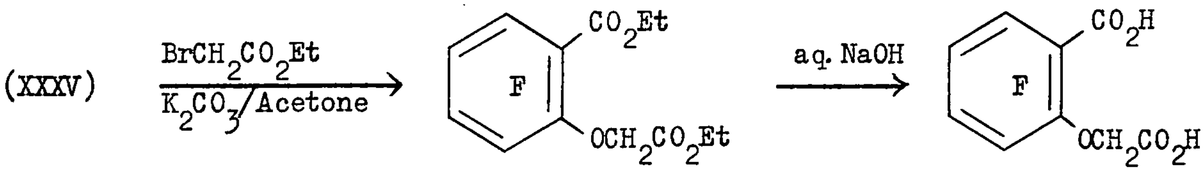
(XIII) was treated with three moles of butyl lithium and carbonated; the solvent was then distilled off and thionyl chloride was added, followed by ethanol; this was unsuccessful giving rise to a complex mixture of high boiling compounds.

The di-acid (XXIX) used in the above reactions was obtained by a sequence of high yield reactions from 2,3,4,5-tetrafluorophenol:



(XXXIV) 84%

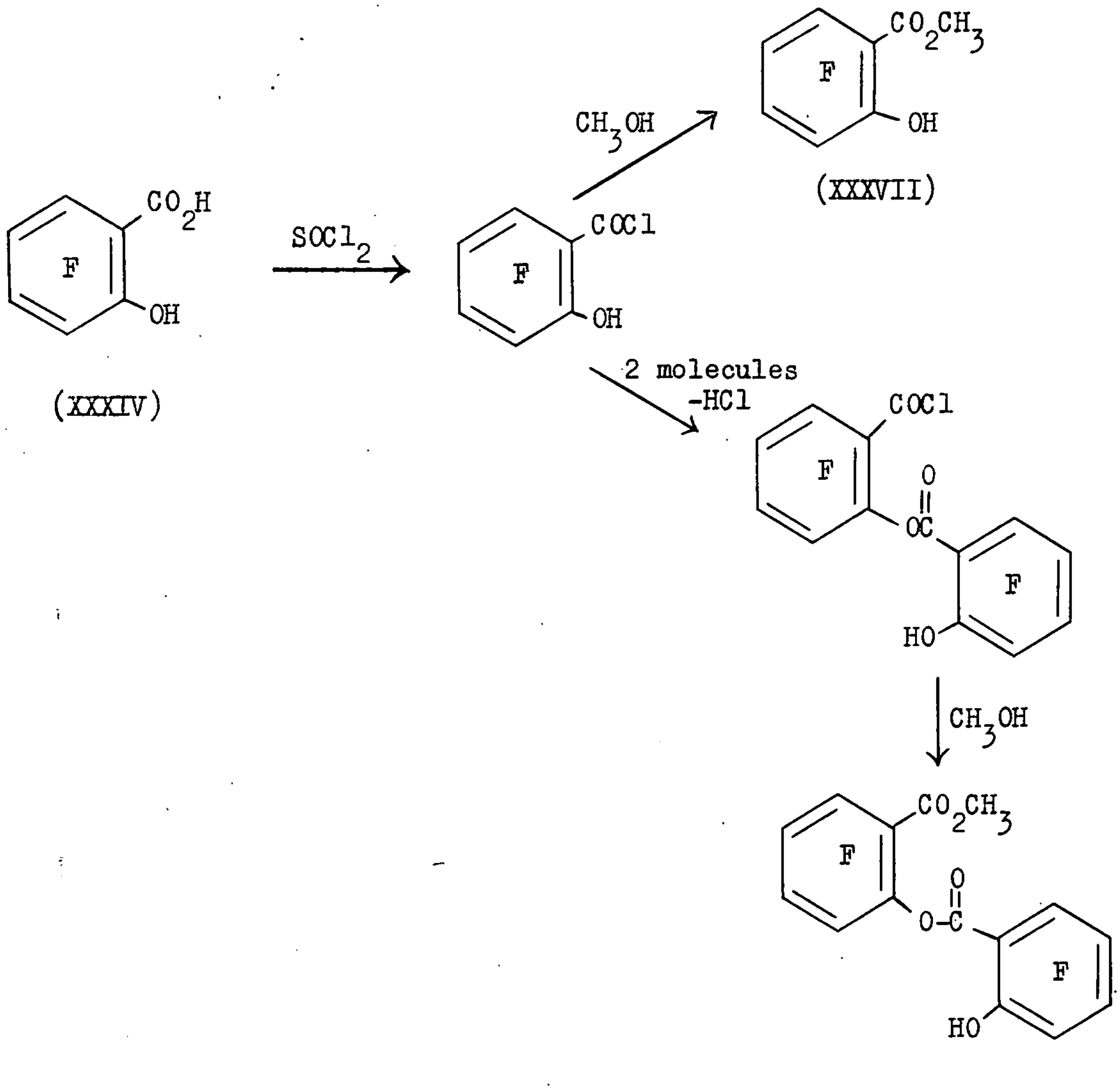
(XXXV) 81%



(XXXVI) 87%

(XXXIX) 51%

Using the method described by Tamborski[61] for the synthesis of carboxylic acids, 2,3,4,5-tetrafluorophenol was treated with two moles of butyllithium followed by carbonation to give the salicylic acid (XXXIV). Tamborski has since reported the preparation of 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid by the same reaction[82]. The salicylic acid (XXXIV) was converted to its ethyl ester (XXXV) by heating under reflux with ethanol and concentrated sulphuric acid. Esterification of (XXXIV) was initially attempted by reaction with thionyl chloride to give the acid chloride, which was not isolated, and then adding methanol; this gave about 35% yield of the methyl ester (XXXVII) but another ester (XXXVIII) was also isolated, which was presumably formed as shown:



(XXXIV)

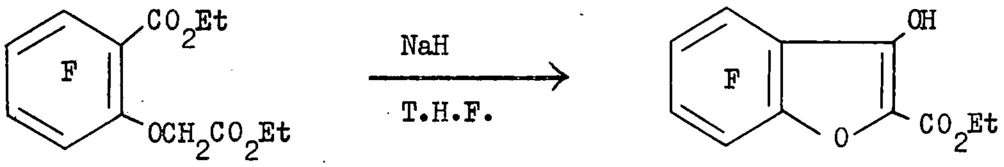
(XXXVII)

(XXXVIII)

This ester (XXXVIII) was not completely characterised, structural assignment being made on the basis of infra-red, ^{1}H n.m.r. and mass spectra. The infra-red spectrum showed two absorptions in the carbonyl stretching region, at 1750 cm^{-1} and 1720 cm^{-1}. The molecular weight by mass spectroscopy was 416 (required M=416). The ^{1}H n.m.r. spectrum of

(XXXVIII) in carbon tetrachloride consisted of two absorptions at τ 2·3 (singlet) and τ 6·2 (singlet) with relative intensities 1:3; these were assigned to the hydroxyl and methyl protons respectively. The di-ester (XXXVI) was obtained by reaction of the ester (XXXV) with ethyl bromoacetate in acetone in the presence of potassium carbonate. Hydrolysis of (XXXVI) in dilute alkali gave the di-acid (XXIX).

The di-ester (XXXVI) was suitable for the internal Claisen condensation reaction described at the beginning of this section; reaction with sodium hydride in tetrahydrofuran gave 2-ethoxycarbonyl-4,5,6,7-tetrafluoro-3-hydroxybenzo[b]furan (XXXIX):

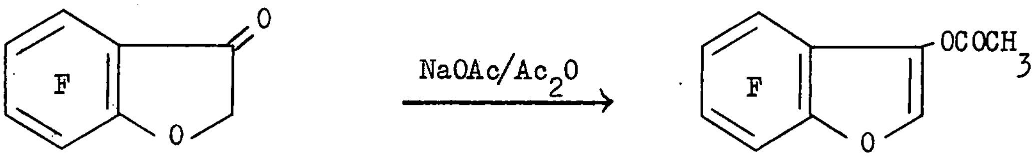


(XXXVI) (XXXIX)

The cyclised ester (XXXIX) is a potentially tautomeric compound and the enol form was assigned to it on the basis of its infra red and ^1H n.m.r. spectra. The infra-red spectrum contained a strong sharp absorption at 3,360 cm^{-1}, attributed to hydrogen bonded -OH, and a strong sharp absorption at 1690 cm^{-1}, attributed to hydrogen bonded carbonyl group. The ^1H n.m.r. spectrum of (XXXIX) in carbon tetrachloride consisted of three groups of peaks: τ 8·5 (triplet); τ 5·5 (quartet); τ 1·8 (broad singlet), with relative intensities 3:2:1. These absorptions were attributed to the methyl, methylene and hydroxyl protons respectively. Hydrolysis of (XXXIX) in both acidic and alkaline media gave 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (XXVI):

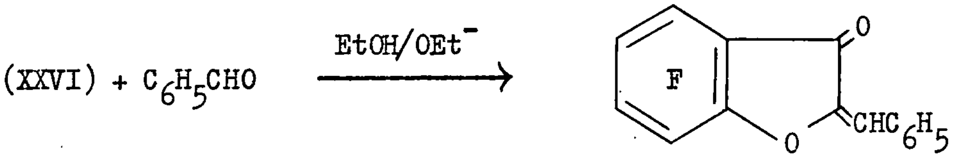
(XXXIX) (XXVI)

Acidic hydrolysis gave a higher yield than hydrolysis in alkaline medium, since (XXXIX) was precipitated out of the alkaline solution, presumably due to the formation of the sodium salt of the -OH group. None of the acid corresponding to the ester (XXXIX) was isolated; presumably decarboxylation took place spontaneously during reaction or work up. The cyclic ketone (XXVI) is also a potentially tautomeric compound; the ketone structure was assigned to this compound on the basis of its infra-red and ^{1}H n.m.r. spectra. The infra-red spectrum showed no absorption which could be attributed to an hydroxyl group but showed a strong absorption in the carbonyl stretching region, at 1740 cm^{-1}. The ^{1}H n.m.r. of (XXVI) in carbon tetrachloride showed a single absorption at τ 5·1 (singlet), well upfield from the position of absorption of the hydrogen in the 2-position of 4,5,6,7-tetrafluorobenzo[b]furan; no absorption due to an hydroxyl proton was observed. Acetylation of the ketone (XXVI) with sodium acetate in acetic anhydride gave 3-acetoxy-4,5,6,7-tetrafluorobenzo[b]furan (XL):

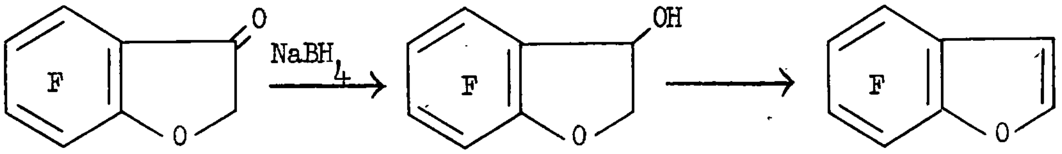


(XXVI) (XL)

The ^{1}H n.m.r. of (XL) in chloroform showed two peaks at τ 2·1 (singlet) and τ 7·7 (singlet) in the ratio of 1:3. The first absorption occurs in the same region as the 2-hydrogen of other benzo[b]furans. Other 2,3-dihydrobenzo[b]furan-3-ones have been acetylated in the same way[83]. The reactive methylene group of the ketone (XXVI) reacted as expected with benzaldehyde in the presence of a base to give a benzylidene derivative:

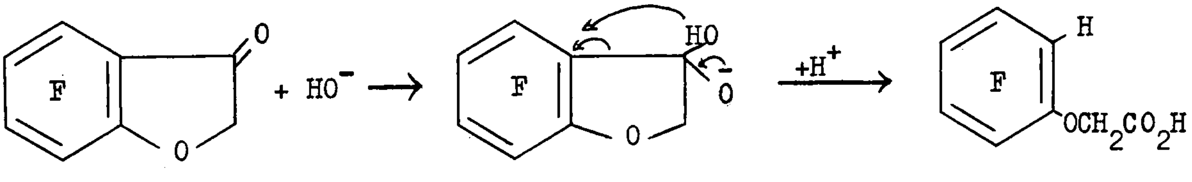


Reduction of 2,3-dihydrobenzo[b]furan-3-ones with Raney nickel under hydrogen has been described in the literature[84]; application of this method to (XXVI) gave small amounts of 4,5,6,7-tetrafluorobenzo[b]furan (XLI), but also other unidentified material. Reduction of (XXVI) with sodium borohydride however, gave a viscous oil, the infra-red spectrum of which was consistent with the alcohol (XLII); dehydration of this oil with phosphoric oxide, or by heating gave a good yield (ca. 70%) of (XLI):



(XXVI) (XLII) (XLI)

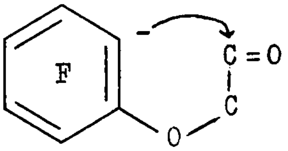
The first stage of the reaction was carried out by dissolving (XXVI) in methanol, cooling to ca 5°, and adding sodium borohydride in small quantities. If, however, the sodium borohydride was first dissolved in methanol to which a few drops of dilute alkali had been added to reduce evolution of hydrogen, a smaller yield of (XLI) was obtained, and some 2,3,4,5-tetrafluorophenoxyacetic acid (XIII) was also isolated:



(XXVI) (XIII)

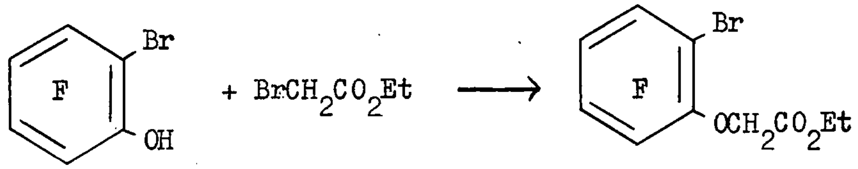
Attempted cyclisation of Ethyl 2-bromo-3,4,5,6-tetrafluorophenoxyacetate(XLIII)

A variation of the above internal Claisen condensation reaction, in which the carbanion was formed in the fluorinated ring, was investigated:



(XII)

Ethyl 2-bromo-3,4,5,6-tetrafluorophenoxyacetate (XLIII), a compound suitable for this type of cyclisation was synthesised by reaction of 2-bromo-3,4,5,6-tetrafluorophenol with ethyl bromoacetate:



(XLIII)

The Grignard reagent appeared to be formed, judged by the disappearance of magnesium, when the ester was treated with magnesium in ether, but no product could be isolated.

CHAPTER III

EXPERIMENTAL WORK (PART I)

2,3,4,5-Tetrafluorophenol. - A solution of butyl-lithium in hexane (30 ml., 2·45M) was added to a stirred solution of 1,2,3,4-tetrafluorobenzene (10 g.) in dry tetrahydrofuran (50 ml.) so that the internal temperature remained between -60° and -75°. The mixture was stirred for 1 hr. at -70° after completion of the addition and then a solution of trimethylborate (6·98 g.) in dry tetrahydrofuran (10 ml.) was added over 0·5 hr. and the mixture stirred for a further hour. Hydrogen peroxide (15 ml., 85% w/w) was added and the mixture allowed to warm to room temperature. Excess sodium hydroxide (2N) was added and a three layer system obtained. The two lower layers were separated, extracted twice with methylene chloride, and then acidified with hydrochloric acid (10 N). The phenol which separated was extracted with methylene chloride and the organic extract was washed with water, dried, and evaporated to small volume. The residue was added dropwise to a stirred solution of potassium hydroxide (10 ml., 6N) and the precipitated potassium 2,3,4,5-tetrafluorophenate dihydrate (9·33 g.) was filtered and dried. The salt crystallised from a small volume of water, m.p. 145-152° (Found: C, 29·7; H, 2·11; F, 31·5. $C_6HF_4KO.2H_2O$ requires C, 30·0; H, 2·08; F, 31·7%). A solution of the potassium salt was acidified, extracted with methylene chloride and then distilled to give 2,3,4,5-tetrafluorophenol, b.p. 143°. (Found: C, 43·5; H, 1·42; F, 45·5. $C_6H_2F_4O$ requires C, 43·4; H, 1·21; F, 45·8%). The p-nitrobenzyl derivative was obtained by heating the potassium salt of the phenol under reflux with p-nitrobenzyl chloride in ethanol for 45 min., m.p. 100-101° (from ethanol) (Found: C, 52·00; H, 2·29. $C_{13}H_7F_4NO_3$ requires C, 51·82; H, 2·33%).

2,3,5,6-Tetrafluorophenol[51,54] - A solution of butyl-lithium in hexane (14·1 ml., 2·37M) was added to a stirred solution of 1,2,4,5-tetrafluorobenzene (5·0 g.) in dry tetrahydrofuran (25 ml.) so that the internal temperature remained between -60° and -75°. The mixture was stirred for 1 hr. at -70° after completion of the addition and then a solution of trimethylborate (3·6 g.) in dry tetrahydrofuran (4 ml.) was added and the mixture stirred for a further hour. Hydrogen peroxide (10 ml., 15% w/w) was added and the mixture allowed to warm to room temperature. Excess sodium hydroxide solution (2N) was added and a three layer system obtained. The two lower layers were separated, extracted twice with methylene chloride, and then acidified with concentrated hydrochloric acid. The phenol which separated was extracted with methylene chloride and the organic extract was washed with water, dried, and the solvent distilled off. The residue (3·02 g.) was added to potassium hydroxide solution and the precipitated potassium 2,3,5,6-tetrafluorophenate dihydrate (2·40 g.) was filtered off and dried. The infra-red spectrum of this compound was identical to that of the product from the reaction of pentafluorobenzene with potassium hydroxide in tertiary butanol.

2-Bromo-3,4,5,6-Tetrafluorophenol[51] - A solution of butyl-lithium in hexane (6·4 ml., 3·2M) was added dropwise over 0·5 hr. to a solution of

1,2-dibromo-3,4,5,6-tetrafluorobenzene (5·85 g., 0·019 mole) in dry hexane (20 ml.) in a cooling bath at -78°. The mixture was stirred for 2 hr. after completion of the addition and then a solution of trimethyl borate (2·2 g., 0·021 mole) in hexane (10 ml.) was added over 0·5 hr. followed by hydrogen peroxide (15 ml., 85% w/w), and the mixture allowed to warm to room temperature. Excess sodium hydroxide solution (2N) was added and the aqueous layer was separated and acidified with concentrated hydrochloric acid until strongly acidic. The phenol which separated was extracted with methylene chloride and the organic extract was washed with water, dried, and evaporated. The residue was distilled to give three fractions: (1) colourless liquid (0·65 g.), b.p. $< 186^{\circ}$; (2) white solid (2·06 g., 44%), b.p. 186-188°, m.p. 28-35°; (3) white solid (0·45 g. 10%), b.p. 188-190°, m.p. 40-43°. <u>2-Bromo-3,4,5,6-tetrafluorophenol</u> was obtained on recrystallisation of fractions 2 and 3 from light petroleum (b.p. 40-60°), m.p. 44-45° (lit.[51] 41-43°). (Found: C, 29·6; H, 0·53; F, 31·0; Br. 33·1. C_6HOF_4Br requires: C, 29·4; H, 0·41; F, 31·0; Br, 32·7%).

<u>Pentafluorophenol</u>[51,52]. A solution of butyl-lithium in hexane (6·6 ml., 3·2M) was added dropwise to a solution of bromopentafluorobenzene (5·0 g.) in dry hexane (20 ml.) in a cooling bath at -78°. The mixture was stirred for 2·5 hr after completion of the addition and a solution of trimethyl borate (2·5 g.) in hexane (10 ml.) was added followed by hydrogen peroxide (15 ml. 85% w/w). The mixture was allowed to warm to room temperature

and heated to 50° for 0•5 hr. After cooling, excess sodium hydroxide solution (2N) was added and the aqueous layer was separated and acidified with concentrated hydrochloric acid until strongly acidic. The phenol which separated was extracted with methylene chloride and the organic extract was washed with water, dried and evaporated. The residue was distilled to give pentafluorophenol (1•74 g.) b.p. $142-144^{\circ}$, with an infra-red spectrum identical to that of an authentic sample.

Ethyl Pentafluorophenoxyacetate. - (a) From potassium pentafluorophenate. Anhydrous potassium pentafluorophenate (8•40 g., 0•038 mole), ethyl chloroacetate (4•73 g., 0•038 mole), and dimethylformamide (50 ml.) were heated under reflux for 1 hr., cooled, poured into water, and extracted with ether. The ether extract was dried, ($MgSO_4$) and evaporated to give a crude residue (8•78 g., 86%) which was distilled in vacuo. Fraction 1.: b.p. $50-56^{\circ}$/0•1 mm. (1•65 g.) consisted of slightly impure ethyl pentafluorophenoxyacetate; fraction 2.: b.p. $56-57^{\circ}$/0•1 mm. (5•34 g.) was ethyl pentafluorophenoxyacetate. (Found: C, 44•6; H, 2•41; F, 34•9. $C_{10}H_7F_5O_3$ requires: C, 44•4; H, 2•59; F, 35•2%).

(b) From hexafluorobenzene. Hexafluorobenzene (5•0 g., 0•027 mole), ethyl glycollate (2•79 g., 0•027 mole), anhydrous potassium carbonate (2•0 g.), and dry dioxan (10 ml.) were heated in a Carius tube for 20 hr. at 170°. The reaction mixture was cooled, poured into ice-water, acidified with concentrated hydrochloric acid, and extracted with ether. The ethereal extract was washed with sodium bicarbonate solution and then with water and dried ($MgSO_4$) and the solvent evaporated. The residue was distilled to give ethyl pentafluorophenoxyacetate (1·74 g., 24%), b.p. 71-72°/0·55 mm., identified by comparison of its infra-red spectrum with that of the sample prepared before.

Pentafluorophenoxyacetic Acid. - Ethyl pentafluorophenoxyacetate (3·72 g.) and sulphuric acid (20 ml. 50% v/v) were heated under reflux for 2·5 hr. On cooling a white solid was precipitated which was filtered off and recrystallised twice from light petroleum (b.p. 60-80°) to give pentafluorophenoxyacetic acid (1·75 g., 52%), m.p. 107·5 - 109°. (Found: C, 39·5; H, 1·28; F, 38·5. $C_8H_3O_3F_5$ requires: C, 39·8; H, 1·24; F, 39·3%). The acid gave a benzylthiouronium salt m.p. 168-169° (from ethanol). (Found: C, 47·0; H, 3·14. $C_{16}H_{13}N_2O_3F_5S$ requires: C, 46·9; H, 3·18%).

Potassium 2,3,5,6-Tetrafluorophenate. - Pentafluorobenzene (5·0 g., 0·030 mole), potassium hydroxide (3·5 g., 0·062 mole), and tertiary butanol (50 ml.) were heated under reflux for 4 hr. Water (50 ml.) was added to the cooled reaction mixture which was then evaporated to approximately 25 ml., and cooled. The potassium salt crystallised and was filtered off. The solution was evaporated further and a second crop of crystals was obtained. The products were combined and heated under reflux with benzene for 3 hr. to give potassium 2,3,5,6-tetrafluorophenate monohydrate (5·58 g., 85%). (Found: C, 31·8; H, 1·34. $C_6H_3F_4O_2K$ requires: C, 32·4; H, 1·35%).

Ethyl 2,3,5,6-Tetrafluorophenoxyacetate. - (a) From potassium 2,3,5,6-tetrafluorophenate. The monohydrate of potassium 2,3,5,6-tetrafluorophenate (3·0 g., 0·0135 mole), ethyl chloroacetate (1·60 g., 0·0133 mole) and dimethylformamide (25 ml.) were heated under reflux for 1 hr., cooled, poured into water and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled *in vacuo* to give ethyl 2,3,5,6-tetrafluorophenoxyacetate (1·90 g., 58%), b.p. 57-59°/ 0·1 mm. (Found: C, 47·6; H, 2·93; F, 30·5. $C_{10}H_8O_3F_4$ requires: C, 47·6; H, 3·17; F, 30·2%). Analytical g.l.c. showed a small amount of impurity (~5%) which was presumably the ortho isomer.

(b) From pentafluorobenzene. Pentafluorobenzene (5·0 g., 0·030 mole), ethyl glycollate (3·2 g., 0·031 mole), anhydrous potassium carbonate (2·0 g.), and dry dioxan (10 ml.) were heated in a sealed tube at 150°C for 16 hr. The reaction mixture was cooled, poured into ice-water, acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with sodium carbonate solution and then with water and dried ($MgSO_4$) and the solvent evaporated. The residue was distilled *in vacuo* to give ethyl 2,3,5,6-tetrafluorophenoxyacetate (0·85 g., 11%), b.p. 56-59°/0·1 mm., identified by comparison of its infra-red spectrum with that of the authentic prepared before.

2,3,5,6-Tetrafluorophenoxyacetic Acid. - Ethyl 2,3,5,6-tetrafluorophenoxyacetate (1·0 g.) and sulphuric acid (10 ml. 50% v/v) were heated under reflux for 1·5 hr., cooled, poured into water, and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to give a crude solid (0·66 g., 74%) which was recrystallised from light petroleum (b.p. 60-80°) to give 2,3,5,6-tetrafluorophenoxyacetic acid (0·24 g., 27%), m.p. 99-101°C. (Found: C, 43·0; H, 1·87; F, 33·6. $C_8H_4O_3F_4$ requires: C, 42·9; H, 1·79; F, 33·9%).

Ethyl 2,3,4,5-Tetrafluorophenoxyacetate.- Potassium 2,3,4,5-tetrafluorophenate (15·0 g., 0·062 mole), ethyl chloroacetate (8·40 g., 0·069 mole), and dimethylformamide (250 ml.) were heated under reflux for 2 hr. The reaction mixture was allowed to cool, poured into water and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$) and the solvent evaporated. The residue was distilled in vacuo to give ethyl 2,3,4,5-tetrafluorophenoxyacetate (13·2 g., 84%) b.p. 58°/0·05 mm., m.p. 29-30°. (Found: C, 47·5; H, 3·31; F, 30·1. $C_{10}H_8O_3F_4$ requires: C, 47·6; H, 3·17; F, 30·2%).

2,3,4,5-Tetrafluorophenoxyacetic Acid. - Ethyl 2,3,4,5-tetrafluorophenoxyacetate (13·2 g.) and sulphuric acid (200 ml. 50% v/v) were heated under reflux for 1·5 hr. and allowed to cool. The reaction mixture was diluted with water and extracted with methylene chloride. The extract was washed with water, dried ($MgSO_4$) and the solvent evaporated. The residue (11·08 g.,94%) was recrystallised from light petroleum (b.p.80-100°) and sublimed in vacuo (70-80°/0·05 mm.)

to give 2,3,4,5-tetrafluorophenoxyacetic acid (8·10 g., 69%), m.p. 109-110°. (Found: C, 43·1; H, 1·76; F, 34·2. $C_8H_4O_3F_4$ requires: C, 42·9; H, 1·79; F, 33·9%).

The reaction of 2,3,4,5-Tetrafluorophenoxyacetic Acid with Phosphoric Oxide in Benzene. - Phosphoric oxide (15 g.) was added to a solution of the acid (5·0 g.) heated under reflux in dry benzene. The mixture was heated under reflux with stirring for 1 hr., poured into ice-water and extracted with ether. The extract was washed with sodium bicarbonate solution, dried ($MgSO_4$), and the solvent evaporated. The yellow solid residue was recrystallised from petroleum (60-80°) to give two fractions: (1) 1·22 g. m.p. 105-113°; (2) 1·90 g. m.p. 77-81°. The first fraction was sublimed *in vacuo* (90°/0·1 mm.) and recrystallised from light petroleum (b.p. 60-80°) to give ω-(2,3,4,5-tetrafluorophenoxy)acetophenone (0·98 g., 16%) m.p. 112-114°. (Found: C, 59·1; H, 2·85; F, 26·2. $C_{14}H_8O_2F_4$ requires: C, 59·2; H, 2·82; F, 26·8%). The infra-red spectrum of the second fraction showed it to be a mixture of the above ketone and 2',3',4',5',-tetrafluorophenyl 2,3,4,5-tetrafluorophenoxyacetate (see below). After five recrystallisations from light petroleum (b.p. 60-80°), a sample (0·22 g.) of the ester was obtained with an infra-red spectrum identical to that of an authentic sample. The mother-liquor from the original recrystallisation was evaporated and distilled *in vacuo* to give diphenylmethane (0·64 g., 17%) identified by comparison of its infra-red spectrum and g.l.c. retention time with that of an authentic sample.

2',3',4',5',-Tetrafluorophenyl 2,3,4,5-Tetrafluorophenoxyacetate. - 2,3,4,5-Tetrafluorophenoxyacetyl chloride (0·5 g., 0·0021 mole) and 2,3,4,5-tetrafluorophenol (0·35 g., 0·0021 mole) were heated at 160° for 1·5 hr., cooled, poured into water and extracted with ether. The organic extract was washed with sodium bicarbonate solution, dried and evaporated. The solid residue was recrystallised from light petroleum (b.p. 40-60°) to give 2',3',4',5'-tetrafluorophenyl 2,3,4,5-tetrafluorophenoxyacetate (0·25 g., 34%) m.p. 88-89·5°. (Found: C, 45·0; H, 1·16; $C_{14}H_4O_3F_8$ requires C, 45·2; H, 1·08%).

Reaction of 2,3,4,5-Tetrafluorophenoxyacetic Acid with Phosphoric Oxide in Cyclohexane. - Phosphoric oxide (13 g.) was added to a solution of the acid (5·0 g.) heated under reflux with stirring in dry cyclohexane (70 ml.). After 2 hr. the mixture was poured on to ice and extracted with ether. The organic extract was washed with sodium bicarbonate solution, dried and evaporated. The dark brown oily residue was dissolved in light petroleum (b.p. 40-60°) and the solution cooled to give a solid which was recrystallised from light petroleum (b.p. 40-60°) to give 2',3',4',5'-tetrafluorophenoxymethyl 2,3,4,5-tetrafluorophenoxyacetate (2·98 g., 75%) m.p. 46-48°. (Found: C, 44·9; H, 1·50; F, 38·2. $C_{15}H_6O_4F_8$ requires C, 44·8; H, 1·49; F, 37·8%).

Hydrolysis of 2',3',4',5'-Tetrafluorophenoxymethyl 2,3,4,5-Tetrafluorophenoxyacetate. - The ester (1·50 g.), tetrahydrofuran (20 ml.) and sodium hydroxide solution (25 ml., 0·5N) were heated under reflux for 3 hr. and cooled. The mixture was poured into water, acidified with dilute sulphuric acid and extracted with methylene chloride. The organic extract was washed with water, dried and evaporated. The residue was distilled *in vacuo* to give a liquid distillate (0·63 g.) which was shown to contain 2,3,4,5-tetrafluorophenol by conversion to its potassium salt with potassium hydroxide solution (5N) and comparison of the infra-red spectrum of the salt with that of an authentic sample. The solid residue from the distillation (0·43 g.) was recrystallised from light petroleum (b.p. 60-80°) and sublimed *in vacuo* (60-70°/0·05 mm.) to give 2,3,4,5-tetrafluorophenoxyacetic acid (0·31 g.) m.p. 108-110°C identified by comparison of its infra-red spectrum with that of an authentic sample.

The Reaction of 2,3,4,5-Tetrafluorophenoxyacetic Acid (XIII) in Polyphosphoric Acid. - (a) The acid XIII (0·25 g.) and polyphosphoric acid (10 ml.) were heated in a sealed tube with shaking at 150° for 0·5 hr. After cooling, the contents of the tube were poured into water and extracted with ether. The ethereal solution was dried and the solvent distilled off to give slightly impure starting material.

(b) The acid XIII (0·2 g.) and polyphosphoric acid (10 ml.) were heated in a sealed tube with shaking at 150° for 2 hr. The reaction mixture was worked up as in (a) to give a black tarry residue.

The Reaction of 2,3,4,5-Tetrafluorophenoxyacetic Acid (XIII) in Concentrated Sulphuric Acid. - (a) 2,3,4,5-Tetrafluorophenoxyacetic acid (0·13 g.) and concentrated sulphuric acid (5 ml.) were heated with stirring. At ca 130° the solution became dark brown and a gas was evolved. After cooling, the mixture was poured into water and extracted with ether. The ethereal solution was dried and the solvent distilled off; a small amount of starting material was isolated from the residue by sublimation.

(b) The acid XIII (0·1 g.) and concentrated sulphuric acid (5 ml.) were heated at 95° for 15 min., whilst the solution gradually became brown. The reaction mixture was worked up as in (a), and gave starting material on sublimation.

2,3,4,5-Tetrafluorophenoxyacetyl Chloride. - 2,3,4,5-Tetrafluorophenoxyacetic acid (2·5 g., 0·011 mole) and thionyl chloride (4·0 g., 0·034 mole) were heated under reflux for 2 hr. and then set aside at room temperature for 16 hr. A clear pale yellow liquid was obtained from which excess thionyl chloride was removed. The remaining pale yellow liquid was distilled in vacuo to give 2,3,4,5-tetrafluorophenoxyacetyl chloride (2·59 g., 94%), b.p. $46-48^\circ/0\cdot1$ mm. (Found: C, 39·6; H, 1·27; F, 31·5; Cl, 14·7. $C_8H_3ClF_4O_2$ requires: C, 39·6; H, 1·24; F, 31·3; Cl, 14·7%).

The reaction of 2,3,4,5-Tetrafluorophenoxyacetyl Chloride with Aluminium Chloride. - (a) In benzene:- Anhydrous aluminium chloride (0·4 g.) was added in small portions to a cooled solution of the acid chloride (0·5 g.) in dry benzene (3 ml.) and the mixture was set aside at $20^\circ C$ for 16 hr. The mixture was poured into ice-concentrated hydrochloric acid and extracted with ether. The extract was washed with sodium bicarbonate solution, dried ($MgSO_4$), and evaporated to give a white solid residue (0·46 g.) m.p. 104-112°C. Recrystallisation from light petroleum (b.p. 80-100°) gave ω-(2,3,4,5-tetrafluorophenoxy)acetophenone (0·40 g., 69%) m.p. 112-114°C, with an infra-red spectrum identical to that of the sample prepared before.

(b) In carbon disulphide:- The acid chloride (0·5 g.) in carbon disulphide (2 ml.) was added slowly to a cooled (5°) stirred mixture of anhydrous aluminium chloride (0·4 g.) and carbon disulphide (3 ml.). The mixture was allowed to warm to room temperature and stirred for 1·5 hr. Hydrogen chloride was evolved and a red-brown solid obtained from which carbon disulphide was evaporated under reduced pressure. Ice-concentrated hydrochloric acid was added to the residue and the mixture was stirred for 0·5 hr. and extracted with ether. The ethereal extract was washed with sodium bicarbonate solution and the solvent evaporated. The residue was heated under reflux with light petroleum (b.p. 40-60°) and the solution was decanted from the tarry residue. Removal of solvent and sublimation of the residue (40°/0·1 mm.) gave a white solid (0·01 g.) m.p. 80-100° which was shown to be mainly 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one by comparison of its infra-red and mass spectra with those of an authentic sample.

2,3,5,6-Tetrafluorophenoxyacetaldehyde Diethylacetal. - Potassium 2,3,5,6-tetrafluorophenate (2·0 g., 0·0083 mole), bromoacetaldehyde diethylacetal, (1·65 g., 0·01 mole), and dimethylformamide (20 ml.) were heated under reflux for 3·5 hr., cooled, poured into water and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and the solvent evaporated. The residue (2·04 g., 87%) was distilled under vacuum to give three fractions: (1) 0·65 g., b.p. $<56^\circ$/0·05 mm; (2) 0·60 g., b.p. 56-58°/0·05 mm; (3) 0·31 g., b.p. 57°/0·05 mm. The last two fractions were combined (0·91 g., 39%) and a small amount of impurity of similar boiling point to the main product was removed by preparative scale v.p.c. to give <u>2,3,5,6-tetrafluorophenoxyacetaldehyde diethyl acetal</u>. (Found: C, 51·6; H, 4·35; F, 26·8. $C_{12}H_{14}F_4O_3$ requires: C, 51·1; H, 4·96; F, 27·0%).

<u>2,3,4,5-Tetrafluorophenoxyacetaldehyde Diethylacetal</u>. Potassium 2,3,4,5-tetrafluorophenate (8·0 g., 0·033 mole), bromoacetaldehyde diethylacetal (6·60 g., 0·039 mole), and dimethylformamide (80 ml.) were heated under reflux for 3 hr., cooled, poured into water and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and the solvent evaporated. The residue was distilled <u>in vacuo</u> to give <u>2,3,4,5-tetrafluorophenoxyacetaldehyde diethylacetal</u> (7·03 g., 75%), b.p. 68°/0·1 mm., contaminated with a small amount (<u>ca</u> 5% by g.l.c.) of an impurity with a similar boiling point. This impurity was removed by preparative scale v.p.c. (Found: C, 51·1; H, 4·89; F, 26·6. $C_{12}H_{14}F_4O_3$ requires: C, 51·1; H, 4·96; F, 27·0%).

<u>The Reaction of 2,3,4,5-Tetrafluorophenoxyacetaldehyde Diethylacetal (XV) with Hydrogen Fluoride</u>. - The acetal (XV) (4·0 g.) was stirred for

2 hr. in liquid hydrogen fluoride. Excess hydrogen fluoride was evaporated, sodium bicarbonate solution was added to the residue which was then extracted with ether. The ethereal solution was dried, and the solvent distilled off. The residue (1·78 g.) was distilled *in vacuo* to give a main fraction (0·57 g.), b.p. 150°/0·01 mm. (Found: C, 48·4; H, 1·99; F, 28·8).

2-(2',3',5',6'-Tetrafluorophenoxy)ethanol. - Potassium 2,3,5,6-tetrafluorophenate (2·0 g., 0·0083 mole), 2-chloroethanol (0·68 g., 0·0085 mole) and dimethylformamide (8 ml.) were heated in a sealed tube at 170° for 1·5 hr. The reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled *in vacuo* to give *2-(2',3',5',6'-tetrafluorophenoxy)-ethanol* (1·02 g., 77%), b.p. 55°/0·05 mm., which was contaminated with a small amount of impurity with a similar boiling point which was removed by preparative scale g.l.c. (Found: C, 45·9; H, 2·59; F, 35·8. $C_8H_6F_4O_2$ requires: C, 45·7; H, 2·86; F, 36·2%).

2-(2',3',4',5'-Tetrafluorophenoxy)ethanol. - Potassium 2,3,4,5-tetrafluorophenate (2·0 g., 0·0083 mole), 2-chloroethanol (0·68 g., 0·0085 mole), and dimethylformamide (8 ml.) were heated in a sealed tube for 1 hr. at 170°C. The reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled *in vacuo* to give *2-(2',3',4',5'-tetrafluorophenoxy)ethanol* (0·78 g., 45%), b.p. 63°/0·05 mm. (Found: C, 45·8;

H, 2·77; F, 35·8. $C_8H_6F_4O_2$ requires: C, 45·7; H, 2·86; F, 36·2%).

Attempted Cyclisation of 2-(2',3',4',5'-Tetrafluorophenoxy)ethanol (XVI).- (a) The alcohol (XVI) (0·2 g.) and polyphosphoric acid (5 ml.) were heated at 100° for 0·5 hr, cooled, poured into water and extracted with methylene chloride. The organic extract was washed with water, dried, and the solvent distilled off. The residue was shown to be 2,3,4,5-tetrafluorophenol by comparison of its infra-red spectrum with that of an authentic sample.

(b) The alcohol (XVI) (0·2 g.), phosphoric oxide (0·6 g.) and cyclohexane (10 ml.) were heated under reflux with stirring for 0·5 hr. The reaction mixture was worked up as in (a) to give a tarry residue.

The Reaction of ω-(2,3,4,5-Tetrafluorophenoxy)acetophenone in Concentrated Sulphuric Acid. - The ketone (0·5 g.) was heated on a water bath for 1·5 hr. with concentrated sulphuric acid (5 ml.). The colour of the solution gradually changed from yellow to green to very dark blue. A white precipitate was obtained on diluting with water. Extraction with ether followed by evaporation of ether gave a tarry residue from which unchanged starting material (0·12 g.) was obtained by sublimation.

2,3,4,5-Tetrafluoro-6-hydroxybenzoic Acid. - A solution of butyl lithium in hexane (70 ml., 2·25M) was added dropwise to a stirred solution of 2,3,4,5-tetrafluorophenol (12·0 g., 0·073 mole) in dry tetrahydrofuran (200 ml.) so that the internal temperature remained below -65°. The solution was stirred at -75° for 3·5 hr. and then carbonated, initially with carbon dioxide diluted with nitrogen, so that the internal temperature remained below -65°. When the exothermic reaction was completed the mixture was allowed to warm to room temperature with continued carbonation. The solution was acidified and extracted with ether. After removal of solvent, valeric acid was evaporated off under high vacuum and the residue was recrystallised from light petroleum (b.p. 80-100°) and sublimed *in vacuo* (80-90°/0·01 mm) to give *2,3,4,5-tetrafluoro-6-hydroxybenzoic acid* (12·7 g., 84%) m.p. 168-169·5°; $\nu_{c=o}$ 1675 cm^{-1}. (Found: C, 40·3; H, 1·24; F, 35·7. $C_7H_2F_4O_3$ requires C, 40·0; H, 0·95; F, 36·2%).

Methyl 2,3,4,5-Tetrafluoro-6-hydroxybenzoate. - 2,3,4,5-Tetrafluoro-6-hydroxybenzoic acid (0·8 g.) and thionyl chloride (1·0 ml.) were heated under reflux for 1·5 hr. Excess thionyl chloride was distilled off to give a viscous, pale yellow residue to which was added dry benzene (3 ml.). Dry methanol (2 ml.) was added dropwise to this solution and the mixture was heated under reflux for 0·5 hr. Benzene and excess methanol were distilled off to give a pale yellow semi-solid from which the methyl ester (0·16 g., 19%) was sublimed (100°/15 mm.). Recrystallisation from light petroleum (b.p. 40-60°) gave *methyl 2,3,4,5-tetrafluoro-6-hydroxybenzoate* m.p. 66-67° ($\nu_{c=o}$ 1677 cm.$^{-1}$). (Found: C, 43·0; H, 1·83; F, 33·8. $C_8H_4F_4O_3$ requires C, 42·9; H, 1·79; F, 33·9%). The residue from the initial sublimation was sublimed under high vacuum (60°/0·01 mm.) to give a white solid (0·24 g., 31%, m.p. 75-85°), which was recrystallised from light petroleum (b.p. 60-80°), (0·09 g., m.p. 84-89°). The infra-red spectrum of this compound showed two strong absorptions in the carbonyl stretching region ($\sim$1720 and 1750 cm.$^{-1}$) and the molecular weight determined by mass spectrometry was 416 corresponding to 2'-methoxycarbonyl-3',4',5',6',tetrafluorophenyl 2,3,4,5-tetrafluoro-6-hydroxybenzoate.

Ethyl 2,3,4,5-Tetrafluoro-6-hydroxybenzoate. - 2,3,4,5-Tetrafluoro-6-hydroxybenzoic acid (10·0 g.), ethanol (50 ml.), and concentrated sulphuric acid (20 ml.) were heated under reflux for 17 hr., cooled, poured into water, and extracted with ether. Removal of solvent and sublimation of the residue (60°/15 mm.) gave the ethyl ester (9·18 g., 81%). Further sublimation under high vacuum (80°/0·01 mm.) gave starting material (1·18 g., 12%). Recrystallisation of the crude product from light petroleum (b.p. 40-60°) gave *ethyl 2,3,4,5-tetrafluoro-6-hydroxybenzoate* (8·61 g., 76%) m.p. 45-46°. (Found: C, 45·2; H, 2·47; F, 31·4. $C_9H_6F_4O_3$ requires C, 45·4; H, 2·52; F, 31·9%).

Ethyl 6-Ethoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate. - Ethyl 2,3,4,5-tetrafluoro-6-hydroxybenzoate (8·61 g., 0·036 mole) was dissolved in dry acetone (50 ml.) and heated under reflux for 14 hr. with ethyl bromoacetate (6·60 g., 0·039 mole) and anhydrous potassium carbonate (6g). The acetone solution was filtered from the inorganic salts and the acetone distilled off. Distillation of the residue (106°/0·01 mm) gave the di-ester (10·25 g., 87%) contaminated with a small amount of impurity of similar boiling point which was removed by preparative scale g.l.c. to give an analytically pure sample of ethyl 6-ethoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate. (Found: C, 48·0; H, 3·36. M (mass spectroscopy) 324. $C_{13}H_{12}F_4O_5$ requires C, 48·2; H, 3·70%; M, 324).

6-Carboxy-2,3,4,5-tetrafluorophenoxyacetic Acid. - Ethyl 6-ethoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate (3·70 g.) and sodium hydroxide solution (70 ml., 5%) were heated under reflux for 1 hr., cooled, poured into water and extracted with ether. The aqueous layer was acidified and extracted with ether. Evaporation of ether gave a viscous residue from which 6-carboxy-2,3,4,5-tetrafluorophenoxyacetic acid was obtained (1·61 g., 53%) m.p. 97-99° by sublimation (90°/0·005 mm) and recrystallisation from light petroleum (b.p. 100-120°). (Found: C, 40·5; H, 1·64%, M (mass spectroscopy), 268. $C_9H_4F_4O_5$ requires C, 40·3; H, 1·49%; M, 268). Reaction of a small portion of the acid with diazomethane in ether gave the dimethyl ester. (Found: C, 44·7; H, 2·68. $C_{11}H_8F_4O_5$ requires C, 44·6; H, 2·70%).

2-Ethoxycarbonyl-4,5,6,7-tetrafluoro-3-hydroxybenzo[b]furan. - Ethyl 6-ethoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate (9·3 g., 0·029 mole) in dry tetrahydrofuran (60 ml.) was added dropwise to a stirred suspension of sodium hydride (1·6 g., 50% suspension in oil, 0·033 mole) in tetrahydrofuran (20 ml.). After the initial vigorous reaction had subsided the mixture was heated under reflux for 1 hr., and then cooled, poured into water and extracted with ether. Acidification of the aqueous solution followed by extraction with ether, removal of solvent and sublimation ($60^{o}/0{\cdot}01$ mm) gave 2-ethoxycarbonyl-4,5,6,7-tetrafluoro-3-hydroxybenzo[b]furan (6·90 g., 86%). A sample purified for analysis by recrystallisation from light petroleum (b.p. $80-100^{o}$) had m.p. $142-144^{o}$. (Found: C, 47·4; H, 2·22; F, 26·8. $C_{11}H_6F_4O_4$ requires C, 47·5; H, 2·16; F, 27·3%).

4,5,6,7-Tetrafluoro-2,3-dihydrobenzo[b]furan-3-one. - (a) By alkaline hydrolysis of 2-ethoxycarbonyl-4,5,6,7-tetrafluoro-3-hydroxybenzo[b]furan. Sodium hydroxide solution (5 ml., 30%) was added to the above ester (0·53 g.) dissolved in ethanol (7·5 ml.) to give an immediate precipitate. The mixture was heated under reflux for 15 min. poured into water, acidified and extracted with ether. Evaporation of the solvent and sublimation of the residue ($80^{o}/15$ mm) gave the crude benzo[b]furan-3-one (0·21 g., 53%). Further sublimation under high vacuum ($90^{o}/0{\cdot}01$ mm) gave starting material (0·12 g., 22%). Recrystallisation of the product from light petroleum (b.p. $60-80^{o}$) gave pure 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one m.p. $106-107^{o}$. $\nu_{C=O}=1740\ cm^{-1}$. (Found: C, 47·0; H, 1·09; F, 36·8% M (mass spectroscopy).206. $C_8H_2F_4O_2$ requires C, 46·7; H, 0·97; F, 36·9%; M, 206).

(b) By acid hydrolysis of the above ester. The ester (2·0 g.) and sulphuric acid (20 ml., 30%) were heated in a vigorously shaken sealed tube for

45 min. at 140°. The reaction mixture was diluted and extracted with ether. Sublimation of the residue (90°/15 mm) gave the benzo[b]furan-3-one (1·02 g., 69%). Further sublimation (70°/0·01 mm) gave unchanged starting material (0·37 g., 19%).

(c) From 2,3,4,5-tetrafluorophenoxyacetic acid. - Butyl lithium in hexane (12·5 ml., 2·2M) was added to a stirred solution of 2,3,4,5-tetrafluorophenoxyacetic acid (2·0 g., 0·0089 mole) in dry tetrahydrofuran (60 ml.) so that the internal temperature remained below -63°. The reaction mixture was stirred for 3 hr. at -70° and carbonated and then allowed to warm to room temperature with continued carbonation. On acidification with dilute sulphuric acid a transient violet colouration was observed together with a vigorous evolution of carbon dioxide. The mixture was extracted with ether and the organic extract dried and evaporated to give a brown viscous liquid from which was sublimed (90°/15 mm) the benzo[b]furan-3-one (0·63 g., 35%).

The Reactions of 2,3,4,5-Tetrafluorophenoxyacetic Acid (XIII) and 6-Carboxy-2,3,4,5-tetrafluorophenoxyacetic Acid (XXIX) with Butyllithium and (in some cases) Carbon Dioxide. - The procedure was the same as that described in (c) above, except that carbon dioxide was omitted in two reactions as shown in the table. In all cases the residue from the ether extraction was sublimed at 90°/15 mm., to isolate any 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (XXVI), and then at ~60°/0·01 mm. to isolate any 2,3,4,5-tetrafluorophenoxyacetic acid, and then at 90°/0·001 mm. to isolate any 6-carboxy-2,3,4,5-tetrafluorophenoxyacetic acid. The details of each experiment are shown in the table:

Acid	Solvent T.H.F.	Butyl-lithium (2·4 molar)	Time at -70°	CO_2	Yield of (XXVI)	Recovered (XIII)
XIII, 5·0 g.	150 ml.	20·5 ml,2 equiv.	3 hrs.	Yes	0·55g (14%)	1·6g (32%)
XIII, 2·0 g.	60 ml.	8·5 ml,2 equiv.	3 hrs.	No	0·02g(~1%)	1·1g (55%)
XIII, 2·0 g.	60 ml.	12·5 ml,3 equiv.	3 hrs.	Yes	0·63g(35%)	-
XXIX, 0·95g.	40 ml.	4·6 ml,3 equiv.	3 hrs.	Yes	0·04g(5%)	-
XXIX, 0·90g.	40 ml.	4·4 ml,3 equiv.	3 hrs.	No	-	-

2-Benzylidene-4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one. - 4,5,6,7-Tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (0·5 g.), benzaldehyde (0·5 g.), ethanol (1·5 ml.), and a few drops of sodium ethoxide solution were set aside at room temperature for 2 hr., during which time a solid was gradually precipitated. The mixture was poured into water and extracted with ether. Removal of solvent and recrystallisation from a mixture of light petroleum (b.p. 60-80°) and alcohol gave 2-benzylidene-4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (0·13 g.) m.p. 215-216°. (Found: C, 61·2; H, 1·93; $C_{15}H_6F_4O_2$ requires C, 61·2; H, 2·04%).

3-Acetoxy-4,5,6,7-Tetrafluorobenzo[b]furan. - 4,5,6,7-Tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (0·40 g.), sodium acetate (0·20 g.) and acetic anhydride (4 ml.) were heated under reflux for 0·5 hr., cooled, and poured into water. The solid which separated (0·36 g., 75%) was dried over phosphoric oxide, recrystallised from light petroleum (b.p. 40-60°), and sublimed (50-60°/0·01 mm) to give 3-acetoxy-4,5,6,7-tetrafluorobenzo[b]furan, m.p. 61·5-63°. (Found: C, 48·1; H, 1·62; F, 30·3. $C_{10}H_4F_4O_3$ requires: C, 48·4; H, 1·61; F, 30·6%).

4,5,6,7-Tetrafluorobenzo[b]furan. - Sodium borohydride (0·05 g.) was added in small portions to a solution of 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (0·5 g.) in dry methanol (10 ml.) at 5° and the mixture was stirred for 16 hr. at 20° and then acidified and extracted with ether. The residue after evaporation was distilled in vacuo from phosphoric oxide to give 4,5,6,7-tetrafluorobenzo[b]furan (0·31 g. 67%) b.p. 165-166°. (Found: C, 50·4; H, 1·06; F, 39·5%; M(mass spectroscopy). 190. $C_8H_2F_4O$ requires C, 50·5; H, 1·05; F, 40·0% M, 190).

Reduction of 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (XXVI) with Alkaline Sodium Borohydride Solution. - Sodium borohydride (0·12 g.) was dissolved in methanol (5 ml.) to which a few drops of sodium hydroxide solution (2N) had been added. This solution was added dropwise to a solution of the ketone (XXVI) (1·32 g.) in methanol (15 ml.). The temperature of the solution increased slightly during the addition but remained below 35°. After completion of the addition dilute sulphuric acid was added to the reaction mixture which was then extracted with ether. The ethereal solution was dried and the solvent distilled off. The residue was heated at 120° until no more water distilled over, and then distilled under reduced pressure in a closed system to give 4,5,6,7-tetrafluorobenzo[b]furan (0·52 g.). The residue from the distillation was sublimed (80°/0·05 mm) and recrystallised from light petroleum (b.p. 60-80°) to give 2,3,4,5-tetrafluorophenoxyacetic acid (0·22 g.) with an infra-red spectrum identical to that of an authentic sample.

Reaction of 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one with Raney Nickel. - 4,5,6,7-Tetrafluoro-2,3-dihydrobenzo[b]furan-3-one (0·5 g.), Raney nickel (*ca* 3 g. of a slurry in ethanol), and ethanol (10 ml.) were stirred under an atmosphere of hydrogen at 20° for 4 hr. Nickel was filtered off from the orange solution and washed with ethanol and the washings were combined with the original filtrate. The combined ethanol solution was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed with water, dried, and the solvent was distilled off to give a semi solid residue. The liquid was evaporated off in a closed system under reduced pressure to give a small amount of 4,5,6,7-tetrafluorobenzo[b]furan (0·07 g.) identified by comparison of its infra-red spectrum with that of an authentic sample. The residue was sublimed (60°/15 mm) to give a white solid (0·12 g.); the infra-red spectrum of this product showed it to be partly

4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one.

Ethyl 2-bromo-3,4,5,6-tetrafluorophenoxyacetate. - 2-Bromo-3,4,5,6-tetrafluorophenol (0·5 g.), ethyl bromoacetate (0·35 g.), anhydrous potassium carbonate (1·0 g.) and dry tetrahydrofuran were heated under reflux for 3 hr. After cooling the reaction mixture was poured into water and extracted with ether. The ethereal solution was dried and the solvent distilled off to give the crude product (0·48 g.). Recrystallisation from light petroleum (b.p. 40-60°) gave *ethyl 2-bromo-3,4,5,6-tetrafluorophenoxyacetate* (0·33 g.) m.p. 40-42°. (Found: C, 36·6; H, 2·18; $C_{10}H_7BrF_4O_3$ requires C, 36·3; H, 2·11%).

Attempted Cyclisation of 2-bromo-3,4,5,6-tetrafluorophenoxyacetate. - 2-Bromo-3,4,5,6-tetrafluorophenoxyacetate (0·33 g.) in dry tetrahydrofuran (5 ml.) was added dropwise to a stirred mixture of magnesium turnings (0·1 g.) and dry tetrahydrofuran (3 ml.) at room temperature. After stirring at room temperature for 5 hr. the mixture was heated under reflux for a further hour. After cooling, the reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was washed with water, dried and the ether was distilled off. The residue consisted of a brown tar from which no organic product could be isolated.

PART II

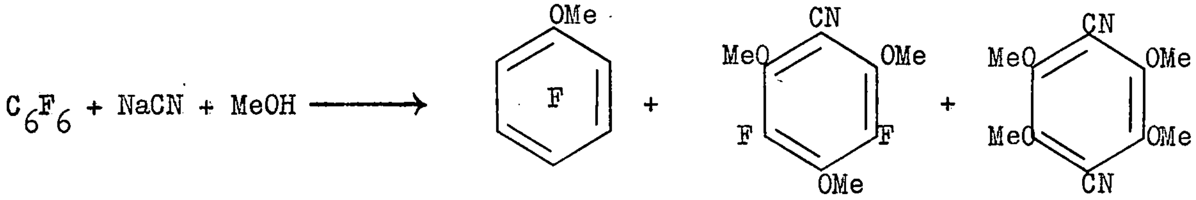
SOME REACTIONS OF 4,5,6,7-TETRAFLUOROBENZO[b]FURAN

CHAPTER IV

NUCLEOPHILIC SUBSTITUTION IN POLYFLUOROAROMATIC COMPOUNDS

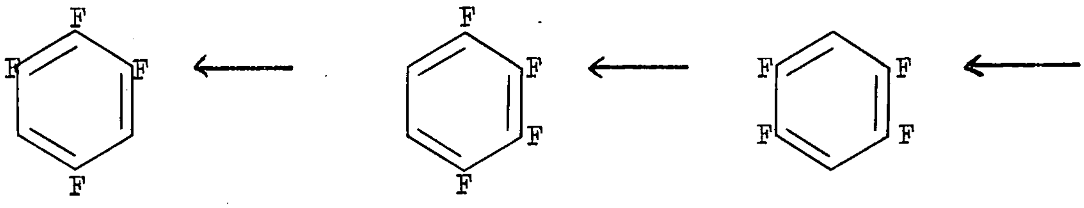
Nucleophilic Substitution in Polyfluoroarenes.

The reactions of hexafluorobenzene with a wide variety of nucleophilic reagents such as $^{-}OCH_3$[55,85], ^{-}OH[51,52], NH_3[86,87], NH_2NH_2[86], H^{-}[1], SH^{-}[88], result in the replacement of a single fluorine under moderate conditions to give a good yield of the corresponding pentafluorophenyl compound. An interesting exception to this general behaviour is the recently reported reaction of hexafluorobenzene with sodium cyanide in methanol[89,90]; one of the products isolated from this reaction resulted from the replacement of all the fluorine atoms from hexafluorobenzene:



A large number of nucleophilic replacement reactions of C_6F_5X compounds have been carried out, mainly by research workers at the University of Birmingham. In most cases the fluorine <u>para</u> to X was replaced (> 90%), for example when X=H[86,91,92], CH_3[53], CF_3[93], SMe[94], SO_2Me[94], NMe_2[95], C_6F_5[96,97], $N(CF_3)_2$[98], OCF_3[99]; when X=O^{-}[51,53], NH_2[95], however, <u>meta</u> replacement predominated, and when X=OCH_3[53], $NHCH_3$[95], replacement of fluorine from the <u>meta</u> and <u>para</u> positions occurred to approximately the same extent. In the case of the halogens[92] (X=Cl, Br,I) <u>ortho</u> substitution occurred to a lesser extent than <u>para</u> substitution and decreased in the order Cl > Br > I. In a few cases (X=NO_2[100], NO[101], CO_2^-[102]) the position of substitution was dependent on the nucleophile; sodium methoxide in methanol giving mainly <u>para</u> replacement but certain amines giving high (> 50%) <u>ortho</u> replacement.

Reaction of the three tetrafluorobenzene compounds with nucleophiles gave substitution at the indicated fluorine atom[103]:



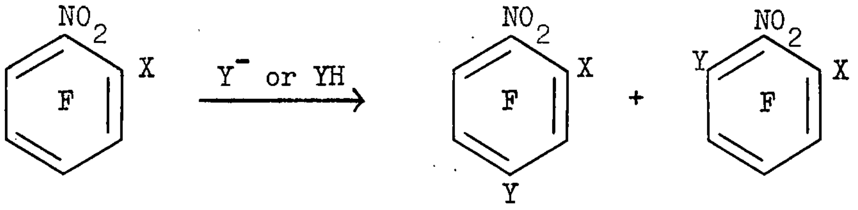
1,2,4,5-Tetrafluorobenzene reacted significantly more slowly with methoxide than did the other two compounds.

The reaction of the six tetrafluorohalogenobenzenes

(X=Cl, Br,I)

with sodium methoxide and with dimethylamine has been studied[104]; with methoxide as nucleophile the fluorine <u>para</u> to hydrogen was the major one replaced, but the fluorine <u>para</u> to X was also replaced, the proportion increasing along the series Cl< Br< I; with dimethylamine as nucleophile reacting with 1,2,3,5-tetrafluoro-4-halogenobenzenes the fluorine <u>para</u> to X was replaced to a much greater extent than with methoxide.

Nucleophilic replacement of fluorine in a number of 2-substituted-tetrafluoronitrobenzenes has been studied[105]:

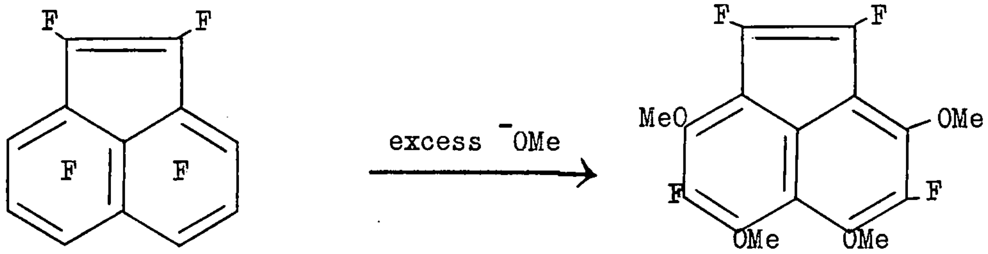


X=NH$_2$,NHMe,NMe$_2$,OMe

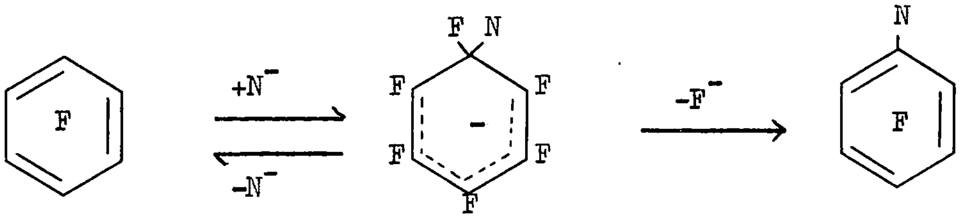
Y=NH$_2$,NHMe,NMe$_2$,OMe

Replacement of the 4-fluorine and the 6-fluorine occurred in varying proportions; the proportion of 6-substitution decreased with the group ortho to the nitro group in the order $NMe_2 > OMe > NHMe > F > NH_2$; the overall reactivities decreased in the reverse order.

The reactions of highly fluorinated polycyclic compounds with nucleophiles have been studied to a much smaller extent than those of the monocyclic compounds. Nucleophilic replacement of fluorine from octafluoronaphthalene[106], 1,2,3,4-tetrafluoronaphthalene[107] and 1,2,3,4-tetrafluoroanthraquinone[108] took place at the 2-position in all three compounds. Replacement of fluorine from octafluoroacenaphthylene[109] occurred sequentially at the 3,8,5 and 6 positions, the tetrafluorotetramethoxyacenaphthylene being formed when four or more equivalents of sodium methoxide were used:

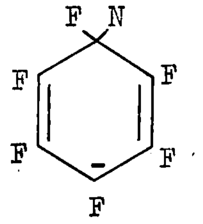


A rationalisation of the observed orientation and reactivity in nucleophilic replacement reactions of aromatic polyhalo-compounds has been advanced by Burdon[45]. The substitution reaction was assumed to involve an addition-elimination mechanism proceeding through a definite intermediate; thus for hexafluorobenzene reacting with a nucleophile N^-:

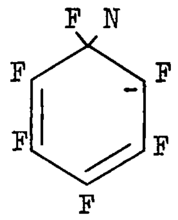


(XLIV)

Recently, kinetic evidence has been published in favour of this type of mechanism[110]. The Wheland type intermediate (XLIV) was used as an approximation to the transition state of the substitution reaction, and the resonance hybrid (XLV) was assumed to be the main contributor to the intermediate, with the hybrid (XLVI) of only secondary importance.



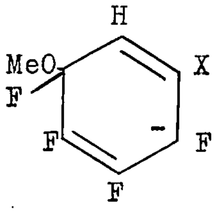
(XLV)



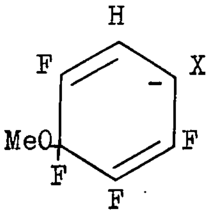
(XLVI)

For C_6F_5X compounds, if solvent and steric effects are neglected the orientation of substitution will be governed by the relative activation energies for substitution <u>ortho</u>, <u>meta</u> and <u>para</u> to the substituent; this resolves into a consideration of the effect of a substituent attached to the carbon atom bearing the negative charge on the stability of the charge. If a substituent X stabilises the negative charge, substitution will take place at the <u>para</u> position and to a lesser extent at the <u>ortho</u> position; if the substituent destabilises the charge more than fluorine, substitution takes place <u>meta</u> to X. If X has exactly the same effect as fluorine on the stability of the negative charge then the <u>ortho</u>: <u>meta</u>: <u>para</u> replacement ratio would be the statistical 2:2:1. The halogens were assumed[45] to destabilise the negative charge in the order $F > Cl > Br > I \sim H$; this order has been determined by spectroscopic measurements[111] and arises because the negative charge is in a π-electron system. The effect ($I\pi$ effect) was attributed to coulombic repulsion between the p-electrons on the halogen and the ring π-electrons on the neighbouring carbon atom[112]. The magnitudes of the $I\pi$ repulsive effects of oxygen and nitrogen are not derivable from spectroscopic measurements[111], but were assumed to be in the order $N > O > F$[45].

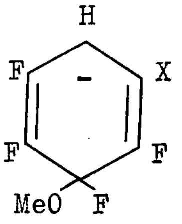
This theory accounts very well for the majority of substitution reactions of aromatic polyfluoro-compounds; of particular relevance to the present work is its application to tetrafluorobenzene derivatives. The predominance of substitution <u>para</u> to hydrogen rather than <u>para</u> to halogen in 1,2,3,4-tetrafluoro-5-halogenobenzenes[104] can be explained by a consideration of the relevant <u>para</u> quinonoid contributing structures (XLVII), (XLVIII), (XLIX), and (L):



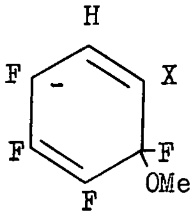
(XLVII)



(XLVIII)



(XLIX)



(L)

From the order of π-electron repulsions given above, (XLIX) would be expected to be more stable than (XLVIII); (XLVII) and (L) would be of approximately the same stability and both would be less stable than (XLVIII). The increase in the proportion of replacement <u>para</u> to halogen along the series $Cl < Br < I$ follows from the decreasing π-electron repulsions in the same order.

Although the above theory accounts satisfactorily for the orientation in the vast majority of nucleophilic substitution reactions of aromatic polyfluoro-compounds, other factors must be taken into account in a number of cases.

None of the arguments just described are directly applicable to reactions in which there is a specific interaction between the nucleophile and the substrate. As mentioned above, the compounds C_6F_5X where $X=NO_2$[100], NO[101], CO_2^-[102], gave large amounts of <u>ortho</u> replacement with amines as nucleophiles, but mainly <u>para</u> replacement with methoxide; this has been attributed to hydrogen bonding between the amine and the substituent which brings the nucleophile into close proximity with the <u>ortho</u> position. That this is not the complete explanation[102] is shown by the fact that dimethylamine gave greater <u>ortho</u> replacement than methylamine in the reaction with pentafluorobenzoic acid, whilst the reverse was the case for pentafluoronitrobenzene and pentafluoronitrosobenzene.

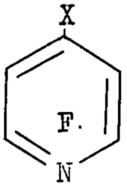
Steric factors must also be taken into account in certain cases; for example, dimethylamine replaced the fluorine <u>para</u> to iodine (92%) from 1,2,3,5-tetrafluoro-4-iodobenzene, whilst with methoxide the fluorine <u>para</u> to hydrogen (i.e. <u>ortho</u> to iodine) was replaced to the extent of 60%[104]. This was explained on the basis of a primary steric effect between the large iodine and dimethylamine groups. Steric interactions can also be used to rationalise the observed orientations in the nucleophilic substitution in the C_6F_5X compounds where $X=N(CH_3)_2$[95], $N(CF_3)_2$[98], $NHCH_3$[95], OCH_3[53], OCF_3[99]. On the basis of $I\pi$ repulsions ($N > O > F$), <u>meta</u> substitution would be expected to predominate; however, steric interaction between the large X substituent and the two <u>ortho</u> fluorine atoms tend to twist the plane of the p-orbitals of the hetero-atom out of the plane perpendicular to the ring and thus reduce the repulsion between the p-electrons of the hetero-atom and the π-electrons of the ring[45]. The extent of para substitution in these cases can thus be roughly correlated with the size of the substituent X.

The nature of the solvent can also play an important part in determining the position of orientation as is shown by the reaction of pentafluoronitrobenzene with sodium methoxide[113]: 3·8% methanol in ether gave 50% ortho replacement as compared with 8% ortho replacement in methanol alone. Another example of the effect of solvent in determining the position of orientation is in the reaction of hexafluorobenzene with excess hydrazine[97]; with dioxan as solvent equal amounts of the 1,3- and 1,4-disubstituted compound were obtained but with tetrahydrofuran as solvent only the 1,4-isomer was formed.

Nucleophilic Substitution in Polyfluoro-heterocyclic Aromatic Compounds

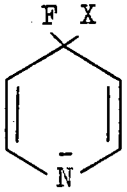
The work on heterocyclic compounds is much more limited than that on homocyclic compounds and has been largely concerned with nitrogen heterocycles.

Nucleophilic replacement reactions of polyfluoro-pyridines have been studied in most detail. The reaction of pentafluoropyridine with a wide range of nucleophiles gave 4-substituted-tetrafluoropyridines[114,115]; the conditions required for these reactions were much milder than for the corresponding reactions of hexafluorobenzene. A number of nucleophilic substitution reactions of compounds of type (LI) have been studied.

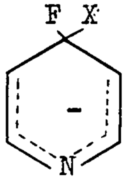


(LI)

When X=OCH_3[115], Br[116], reaction with nucleophiles gave replacement of the 2-fluorine and with excess sodium methoxide a 2,6-dimethoxy compound was obtained. Reaction of 2,3,5,6-tetrafluoro-4-nitropyridine, however, with sodium methoxide and ammonia gave considerable replacement of the nitro group as well as replacement of the 2- and 3-fluorines.[117] The above results were rationalised[117] by assuming that the ring nitrogen is the greatest single factor determining the orientation of nucleophilic substitution due to its ability to stabilise a negative charge placed on it; in other words, that the hybrid (LII) is the most important contributor to the Wheland intermediate (LIII).

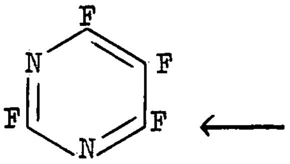


(LII)

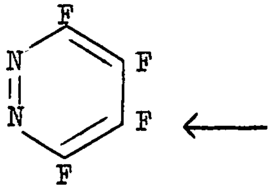


(LIII)

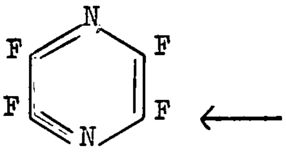
A consideration of the corresponding structures for reaction at the other positions shows that only when substitution takes place at positions 2 or 6 can the negative charge be localised on to nitrogen. The greater stability of an intermediate of type (LIII) is shown by the replacement of the nitro group in 2,3,5,6-tetrafluoro-4-nitropyridine, which is thought to be the only known reaction in which a nitro group is replaced in preference to fluorine by nucleophilic reagents[117]. Further evidence for the effect of a ring nitrogen on the position of substitution is provided by the substitution reactions of the three tetrafluorodiazines which react at the positions indicated:



(LIV)



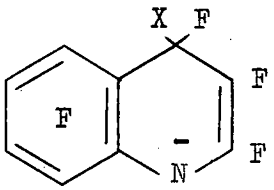
(LV)

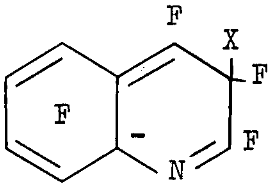


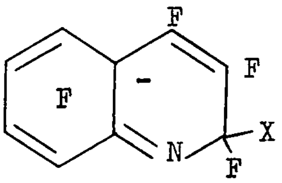
(LVI)

All three compounds were found to be more reactive than pentafluoropyridine, but tetrafluoropyrimidine[118] (LIV) and tetrafluoropyridazine[15] (LV), in both of which the fluorine <u>para</u> to nitrogen was replaced, were substantially more reactive than tetrafluoropyrazine[14] (LVI) in which there is no fluorine <u>para</u> to nitrogen.

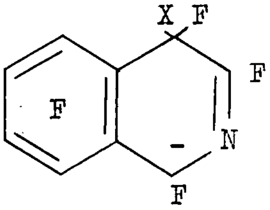
The nucleophilic substitution reactions of heptafluoroquinoline and -isoquinoline demonstrate the first major failure of the simple qualitative theory[45] described in this section. The reaction of heptafluoroquinoline with sodium methoxide[119] gave two monosubstituted products, 2-methoxy- and 4-methoxy-hexafluoroquinolines in the ratio 3·4:1. A consideration of the para quinonoid contributors to the transition states for each position of substitution in the heterocyclic ring indicates that substitution should take place at the 2-position or the 4-position; no choice can be made between these two possibilities on the basis of the simple qualitative theory since the relative stabilising effects of localising the negative charge on the nitrogen (as in pentafluoropyridine[114,115]), or delocalising the negative charge round the fused ring (as in octafluoronaphthalene[106]) are not known.

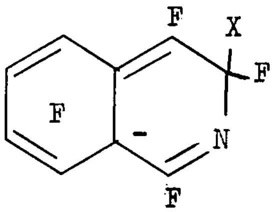


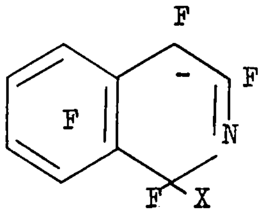




The reaction of heptafluoroisoquinoline with nucleophiles[119] gave exclusively 1-substituted products; further reaction with sodium methoxide gave 3,4,5,7,8-pentafluoro-1,6-dimethoxyisoquinoline. The para quinonoid structures for substitution in the heterocyclic ring of heptafluoroisoquinoline are shown:



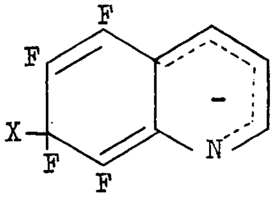




In this case 3-substitution might have been expected to predominate by analogy with octafluoronaphthalene[106].

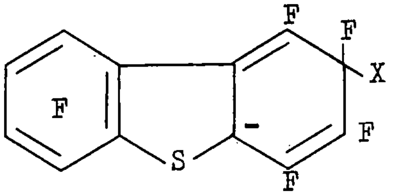
The observed orientations in the substitution reactions of the monocyclic nitrogen heterocycles have been rationalised[14,15,117], mainly by a consideration of two effects: firstly, the destabilisation of a negative charge on a carbon atom bonded to fluorine (Iπ effect), and secondly, the stabilisation of a negative charge by localisation on a nitrogen atom. When these effects reinforce one another, as in the case of pentafluoropyridine, a satisfactory rationalisation can be obtained, but when they are in opposition, as with heptafluoroisoquinoline, the results are ambiguous. It would thus appear that the simple qualitative theory, whilst very satisfactory in explaining the orientation in monocyclic compounds, has definite limitations when applied to fused ring heterocyclic compounds in which substitution occurs in the heterocyclic ring.

Nucleophilic substitution in 5,6,7,8-tetrafluoroquinoline[23], however, has been rationalised satisfactorily by the simple qualitative theory. Substitution took place at the 7-position and (LVII), in which the negative charge can be localised on nitrogen was considered to be the likely transition state:

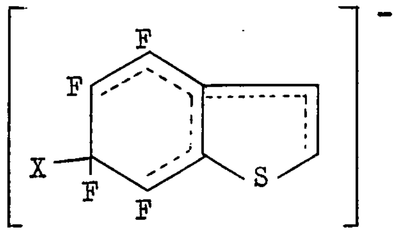


(LVII)

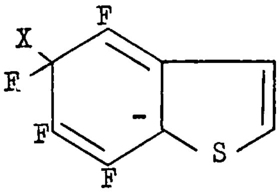
Nucleophilic substitution in octafluorodibenzothiophen occurred at the 2-position[25] (that is, <u>para</u> to sulphur); this orientation was rationalised by assuming that a negative charge on a carbon atom bonded to sulphur is stabilised by the sulphur d-orbitals[120]:



An interesting comparison arises between the orientation in this compound and that in 4,5,6,7-tetrafluorobenzo[b]thiophen[121]. In the latter compound substitution occurred at the 6-position (that is, <u>meta</u> to sulphur); the difference between the two compounds was explained[121] on the basis of charge delocalisation round the thiophen ring of the latter compound (LVIII) which would also place the negative charge on a carbon atom bonded to sulphur and involve greater charge delocalisation than substitution at the 5-position (that is, <u>para</u> to sulphur) (LIX):



(LVIII)



(LIX)

This type of delocalisation was thought to be unlikely in the case of octafluorodibenzothiophen since the aromaticity of the second benzene ring would be disturbed.

Attempted nucleophilic substitution in tetrafluorofuran was unsuccessful[10]. The molecule did not behave like a typical fluoroaromatic compound, as evidenced by the addition of bromine to give a 2,5-dibromo adduct.

CHAPTER V

DISCUSSION OF EXPERIMENTAL WORK (PART II)

Introduction

The reactions of 4,5,6,7-tetrafluorobenzo[b]furan can be conveniently divided into two groups: (i) reactions of the fluorinated benzene ring, and (ii) reactions involving the heterocyclic ring. Section I deals with nucleophilic replacement of fluorine. Only one reaction of this type was studied, that with sodium methoxide, and the orientation of substitution was determined by a combination of chemical and spectroscopic methods. The factors affecting the orientation of nucleophilic substitution in this system are also considered in this section. The reactions of the furan ring which have been investigated are discussed in Section II; these are divided into three groups: firstly, reaction with butyllithium and subsequent reaction of the benzo[b]furyl-lithium; the products from these reactions were related chemically to 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan. Secondly, electrophilic substitution, the orientation in this case being assigned on the basis of nuclear magnetic resonance spectra. Finally, the polymerisation of 4,5,6,7-tetrafluorobenzo[b]furan was briefly investigated.

Section I

Nucleophilic Replacement of Fluorine in 4,5,6,7-Tetrafluorobenzo[b]furan

The reaction of 4,5,6,7-tetrafluorobenzo[b]furan (XLI) with sodium methoxide was the only reaction of this type investigated. The fluorine atoms in (XLI) showed a comparatively low susceptibility to replacement by methoxide; best yields (75%) of trifluoromonomethoxybenzo[b]furan were obtained by reaction in a sealed tube at 95° for about 45 hours, but even under these conditions analytical scale g.l.c. showed small amounts of unchanged (XLI) in the reaction product as well as traces of compounds with longer retention times which were probably difluorodimethoxybenzo[b]furans. Initial reactions were carried out by heating the reaction mixture under reflux in methanol but negligible amounts of the methoxy compound were obtained. When the reaction was carried out in a sealed tube at 150° for 15 hours, the g.l.c. peaks attributed to the dimethoxy compounds increased relative to that of the monomethoxy compound. The trifluoromonomethoxybenzo[b]furan was separated by preparative scale g.l.c., and elemental analysis results indicated the correct empirical formula, but the ^{19}F n.m.r. spectrum showed nine areas of absorption, three groups of three peaks of equal intensity in the ratio A:B:C = 57:27:16, which were attributed to three isomeric trifluoromonomethoxybenzo[b]furans; the mixture was re-examined by analytical scale g.l.c. using a number of columns of different polarity but no separation could be effected. This behaviour is reminiscent of that of the products from the reaction of 1,2,3,4-tetrafluoro-5-halogenobenzenes with sodium methoxide[104] which could not be resolved by g.l.c. Having established that a number of isomeric trifluoromonomethoxybenzo[b]furans were formed in this reaction, the problem of assigning orientations to each isomer was then investigated.

Assignment of Orientation of Trifluoromonomethoxybenzo[b]furans

The methods which were considered for determining the orientations were: (1) n.m.r. spectroscopy; (2) degradation of the furan ring; (3) synthesis of an isomer of known orientation.

1. N.M.R. Spectroscopy

The ^{19}F n.m.r. spectrum of 4,5,6,7-tetrafluorobenzo[b]furan in carbon tetrachloride is shown in Table 6.

Table 6

* Chemical Shift (p.p.m)	Intensity	Multiplicity	Coupling Constants (cps)
148•0	1	doublet of doublet of doublets	19•1, 10•5, 4•2
162•3	2	complex band	
164•8	1	doublet of doublet of doublets	19•6, 13•7, 7•3

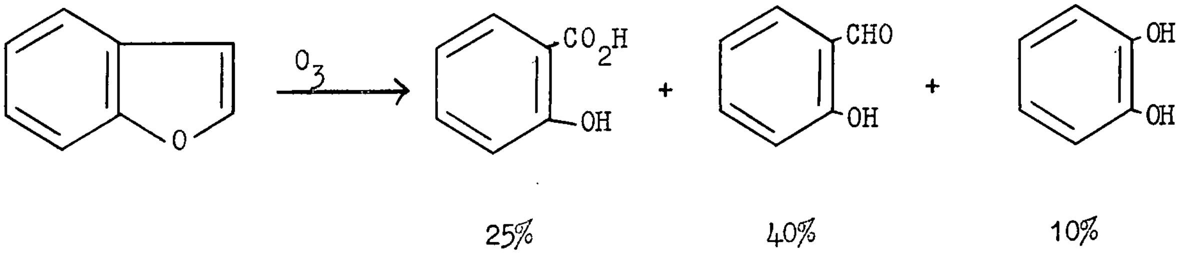
* All fluorine chemical shifts throughout this thesis are p.p.m. upfield from trichlorofluoromethane.

Two of the peaks showed simple first order splitting and the coupling constants were easily measurable. In the case of the remaining two fluorines, the difference in chemical shift was of the same order as the coupling constants and this gave rise to second order splitting; the coupling constants in this case were not calculated. Fluorine-fluorine coupling constants are known to decrease in the order $J_{FF}^{ortho} > J_{FF}^{para} > J_{FF}^{meta}$,[122] and since the two resolved absorptions of 4,5,6,7-tetrafluorobenzo[b]furan have only the largest coupling constant in common, the two fluorines must be ortho to one another. No further information was available from a simple analysis of the spectrum and therefore the method could not be used independently to determine the orientation of the trifluoromonomethoxybenzo[b]furans.

2. Degradation of the Furan Ring

A common method for the determination of orientation in fused ring systems is the degradation of the unsubstituted ring to give a substituted product which is then related to compounds of known structure. In this case oxidative cleavage of the furan ring would be expected to give derivatives of salicylic acid.

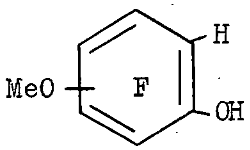
A number of methods for the opening of the furan ring of benzo[b]furan have been reported. Oxidation with concentrated nitric acid gave 2-hydroxy-5-nitrobenzoic acid[123]; potassium permanganate gave complete breakdown of the molecule[124] and ozone gave a mixture of products as shown[125]:



In view of the limited data available on these oxidation reactions of benzo[b]furan, and the known stability of the furan ring in 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan to oxidation[17] (see later) this method of determination of orientation of nucleophilic substitution was not investigated.

3. Synthesis of an Isomer of Known Orientation

The syntheses of 4,5,6,7-tetrafluorobenzo[b]furan described in Part I of this thesis give rise to several possible routes to trifluoromonomethoxybenzo[b]furans. The route investigated necessitated the synthesis of a trifluoromonomethoxyphenol (LX) suitable for ring closure by one of the known methods.



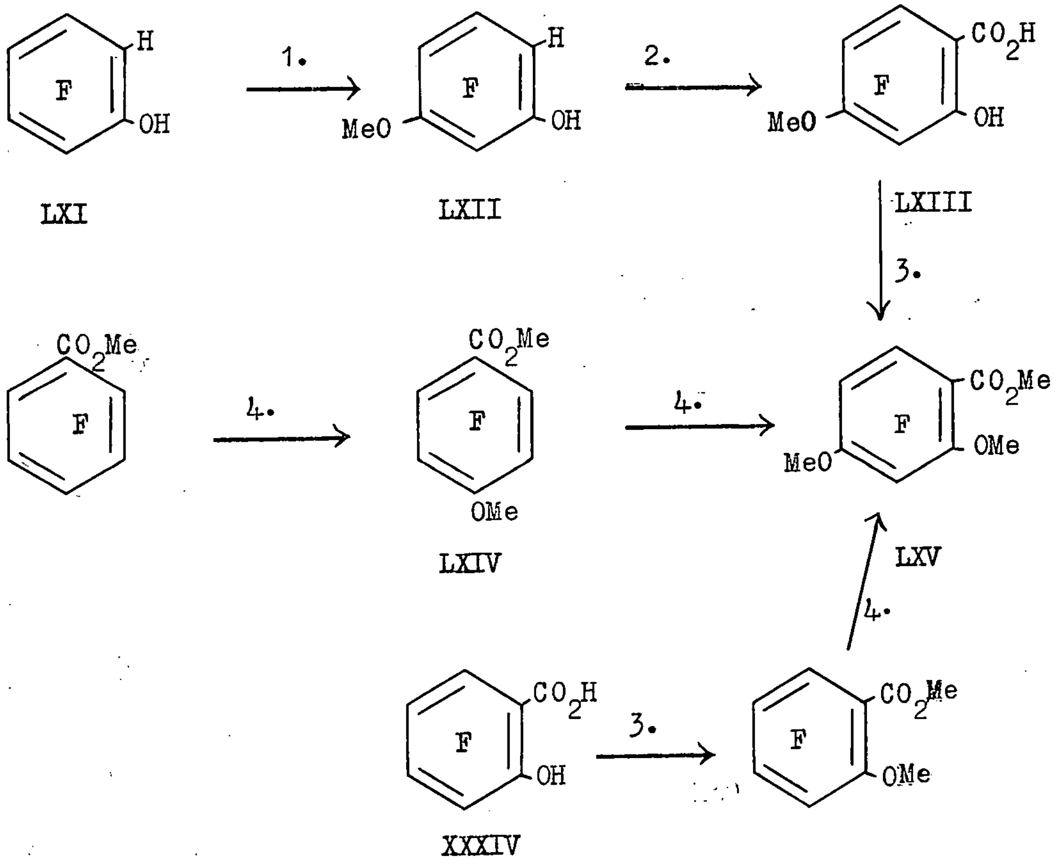
(LX)

The reaction of 2,3,5,6-tetrafluoroanisole with potassium hydroxide in tertiary butanol was initially investigated as a route to 2,4,5-trifluoro-3-methoxyphenol; the phenolic product from the reaction was shown to consist mainly of 2,3,5,6-tetrafluorophenol together with two compounds in approximately equal amounts with longer retention times on analytical scale g.l.c., presumably arising from replacement of the two fluorines (ortho and meta to hydrogen) to approximately the same extent. The demethylation of 2,3,5,6-tetrafluoroanisole in this reaction parallels the behaviour of pentafluoroanisole in nucleophilic reactions[53] in which demethylation also occurs to varying extents depending on the nucleophile. Due to the above unfavourable results this route to a suitable methoxyphenol was abandoned. 2,4,5-Trifluoro-3-methoxyphenol was successfully synthesised by the reaction of sodium 2,3,4,5-tetrafluorophenate with sodium methoxide. The reaction was initially carried out in methanol in a sealed tube at 160°; considerable decomposition occurred and only very small amounts of the required phenol were obtained as indicated by analytical scale g.l.c. However, when the reaction was carried out in sulpholane (tetramethylenesulphone) in a sealed tube at 140° for 12 hours, a 50% yield of 2,4,5-trifluoro-3-methoxyphenol was obtained. The reaction appeared to be susceptible to small changes in temperature, varying amounts (up to 50%) of higher boiling compounds being formed at slightly higher temperatures. These compounds were not investigated but were presumably due to further replacement of fluorine. The marked increase in yield of the methoxyphenol when the reaction was carried out in sulpholane as compared with methanol illustrates the usefulness of dipolar aprotic solvents in nucleophilic substitution reactions;

the greater reactivity (that is, decrease in activation energy) of systems in dipolar aprotic solvents as compared with protic solvents has been attributed[126,127] to the lower solvation of the small anion in the former.

Orientation of Nucleophilic Substitution in 2,3,4,5-Tetrafluorophenol

The orientation of the product from the reaction of 2,3,4,5-tetrafluorophenol with sodium methoxide in sulpholane was confirmed by chemical means and by n.m.r. spectroscopy. The route used for the chemical proof is shown in the scheme:



1. NaOMe/sulpholane; 2. BuLi/CO$_2$; 3. CH$_2$N$_2$; 4. NaOMe/MeOH

The synthesis of methyl 3,5,6-trifluoro-2,4-dimethoxybenzoate (LXV) from 2,3,4,5-tetrafluoro-6-hydroxybenzoic acid (XXXIV) was carried out in another context but is included here for the sake of completion although it is not necessary for the proof of the structure of the methoxyphenol (LXII) The reaction of methyl pentafluorobenzoate with sodium methoxide in methanol gave replacement of the 4-fluorine; the orientation of the product (LXIV) was assigned on the basis of its ^{19}F n.m.r. spectrum which showed only two absorptions of equal intensity. Reaction of (LXIV) with sodium methoxide in methanol gave (LXV). The methoxyphenol (LXII) was converted to the acid (LXIII) by the procedure described in Part I; the acid (LXIII) was converted to the ester (LXV) by reaction with diazomethane. The structure of the methoxyphenol (LXII) follows directly from the two known facts:
(1) the methoxy group in (LXIV) is known to be in the <u>para</u> position;
(2) the hydrogen in the phenol (LXI) is known to be <u>ortho</u> to the hydroxyl group; only if substitution takes place as shown will the same compound (LXV) be obtained from the two routes. The reactions of the esters shown in the scheme illustrate the powerful directive effect of the methoxycarbonyl group on the orientation of nucleophilic substitution; reaction occurred <u>para</u> to this group to the extent of > 90%, except in the case of (LXIV) which has no <u>para</u> fluorine; in this case exclusive ortho substitution occurred.

The structure of 2,4,5-trifluoro-3-methoxyphenol (LXII) was also deduced from n.m.r. data; the chemical shifts and coupling constants for 2,3,4,5-tetrafluorophenol (LXI) and 2,4,5-trifluoro-3-methoxyphenol are shown in Tables 7 and 8.

Table 7

^{1}H n.m.r. Coupling Constants and Chemical Shifts

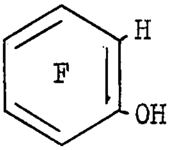
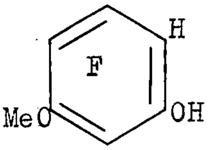
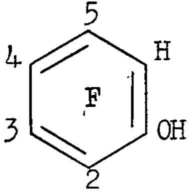
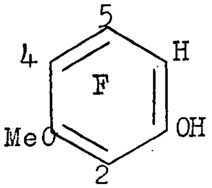
Compound	Chemical Shift (τ)	Coupling Constants (c.p.s.) Aromatic Proton
	3·1 (aromatic H)	J^{ortho}_{HF} 11·3; J^{meta}_{HF} 7·4, 7·4; J^{para}_{HF} 2·6
	3·4 (aromatic H) 5·9 (OCH_3)	J^{ortho}_{HF} 11·5; J^{meta}_{HF} 7·7, 7·7

Table 8

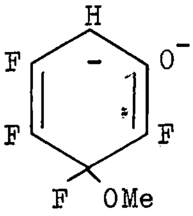
^{19}F n.m.r. Coupling Constants and Chemical Shifts

Compound	Chemical Shift	Assignment	Coupling Constants (c.p.s.)					
			J^{ortho}_{FF}	J^{para}_{FF}	J^{meta}_{FF}	J^{ortho}_{HF}	J^{meta}_{HF}	J^{para}_{HF}
	140·7	5F	21·8	9·1	1·5	11·3	-	-
	156·9	3F	19·2,19·2	-	1·5	-	-	3·0
	163·7	2F	19·2	8·9	3·0	-	7·9	-
	168·1	4F	22·1,19·8	-	3·0	-	7·4	-
	142·0	5F	21·5	10·8	-	10·8	-	-
	160·5	2F	-	8·9*	-	-	8·9*	-
	163·9	4F	21·2	-	-	-	7·1	-

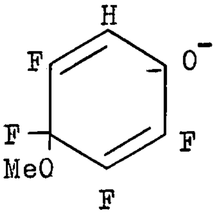
* This value is midway between the expected values for the two coupling constants and is due to an unresolved doublet of doublets appearing as a triplet.

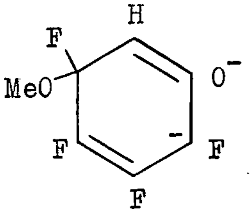
The smallest hydrogen-fluorine coupling constant in the spectrum of 2,3,4,5-tetrafluorophenol (2·6 c.p.s.) was assigned to J^{para}_{HF} in agreement with reported data[104,128]; this small coupling constant is absent from the spectrum of the methoxyphenol (LXII) and hence the fluorine para to hydrogen must have been replaced; the remaining coupling constants are consistent with this structure.

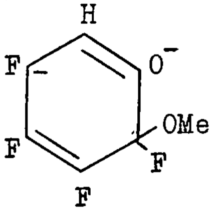
The orientation of substitution in 2,3,4,5-tetrafluorophenol can be rationalised satisfactorily on the basis of the theory described in Chapter IV[45]; the para quinonoid contributors to the four possible transition states are shown:



(LXVI)

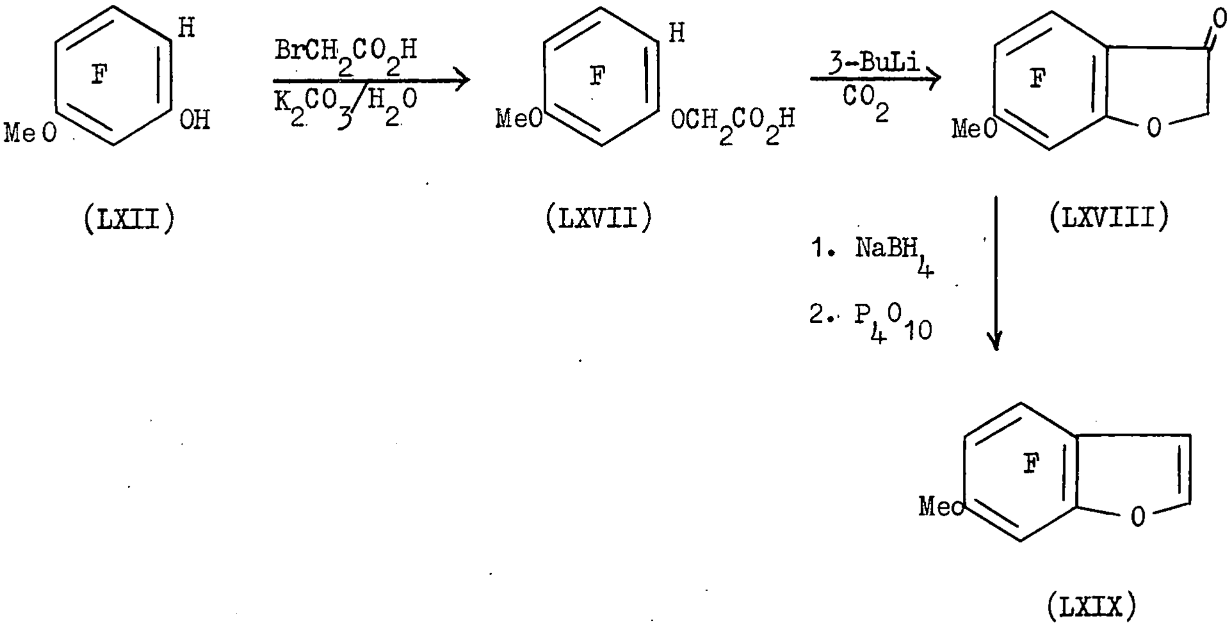






If the $I\pi$ repulsions are assumed to decrease in the order $O^- > F > H$ it can be seen that (LXVI) will be most stable and therefore substitution should occur at the 3-position, as is observed.

2,4,5-Trifluoro-3-methoxyphenol (LXII) was converted to 4,5,7-trifluoro-6-methoxybenzo[b]furan (LXIX) by the series of reactions shown in the scheme:



Reaction of 2,4,5-trifluoro-3-methoxyphenol (LXII) with bromoacetic acid in aqueous solution gave 2,4,5-trifluoro-3-methoxyphenoxyacetic acid (LXVII) in good yield; this proved to be a more convenient route to the phenoxyacetic acid than the two step procedure involving initial formation of the ester followed by hydrolysis described in part I. Cyclisation of the acid (LXVII) with three equivalents of butyl-lithium followed by carbonation, and reduction of the 2,3-dihydrobenzo[b]furan-3-one (LXVIII) with sodium borohydride followed by dehydration with phosphoric oxide were carried out as described in Part I for the corresponding tetrafluoro-compounds.

^{19}F n.m.r. Spectra of Polyfluorobenzo[b]furans

A comparison of the ^{19}F n.m.r. spectrum of 4,5,7-trifluoro-6-methoxybenzo[b]furan (Table 9) with that of the mixture of trifluoromonomethoxybenzo[b]furans obtained from the reaction of 4,5,6,7-tetrafluorobenzo[b]furan with sodium methoxide showed that the major component of the mixture (isomer A) was the 6-isomer. The assignments shown in Table 9 are consistent with reported data on fluorine-fluorine coupling constants of highly fluorinated aromatic systems; some examples are shown in Table 10.

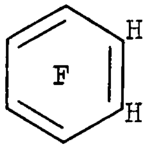
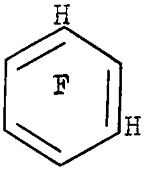
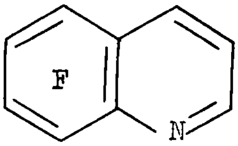
Table 9

^{19}F n.m.r. Spectrum of 4,5,7-Trifluoro-6-methoxybenzo[b]furan (Isomer A)

Chemical Shift	Assignment	Coupling Constants (c.p.s)
149·0	4F	19·8, 17·1
156·8	7F	17·1, 2·6, 1·1
159·4	5F	19·8 (+ smaller splittings)

Table 10

Some Examples of Fluorine - Fluorine Coupling Constants

Compound	Coupling Constants (c.p.s.)			Reference
	J_{FF}^{ortho}	J_{FF}^{para}	J_{FF}^{meta}	
	18-19	12	1-4	129
	19·7-20·1	10	2-6	130
C_6F_5X	18-23	5-9	0-9·5	131, 132
	18-21	15-19	-	133

Thus, the absorption at 149·0 in the spectrum of 4,5,7-tetrafluoro-6-methoxybenzo[b]furan must be due to the 4-fluorine since only this fluorine has fluorines ortho and para to it which give rise to the two large coupling constants. The absorptions at 159·4 and 156·8 must be respectively ortho (5-fluorine) and para (7-fluorine) to the 4-fluorine since the former has the larger coupling constant in common with the 4-fluorine. Confirmation of the assignment of the absorption at 156·8 to the 7-fluorine can be obtained from an examination of the smaller coupling constants derived from this absorption and also from the ^{1}H n.m.r. spectrum of the compound, Table 11.

Table 11

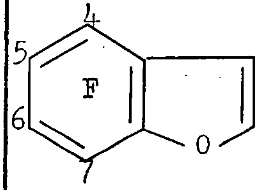
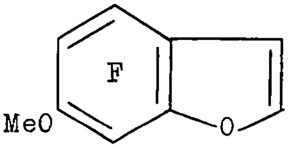
^{1}H n.m.r. Spectrum of 4,5,7-Trifluoro-6-methoxybenzo[b]furan (Isomer A)

Chemical Shift (τ)	Assignment	Coupling Constants (c.p.s)
6·0	OCH_3	1·0
3·3	3H	2·2, 2·8
2·5	2H	2·2

The ^{1}H n.m.r. spectrum of benzo[b]furan[134,135] as a pure liquid shows a doublet (J: 2·3 c.p.s.) for the 2-proton (τ 2·73) and a doublet of doublets (J: 2·3, 0·9 c.p.s) for the 3-proton (τ 3·59); the coupling constant of 2·3 c.p.s. is due to coupling between the 2- and 3-protons and the coupling constant of 0·9 c.p.s. is due to cross-ring coupling between the 3- and 7-protons. The 3-proton of 4,5,7-trifluoro-6-methoxybenzo[b]furan also shows two coupling constants; one (2·2 c.p.s.) is due to coupling with the 2-proton; the other (2·8 c.p.s.) is of the same magnitude as one of the small splittings of the absorption attributed to the 7-fluorine and hence is assumed to be due to cross-ring proton-fluorine coupling. The remaining splitting (1·1 c.p.s.) of the 7-fluorine absorption is due to coupling with the protons of the ortho methoxy group; this type of coupling is observed in many other similar systems[136].

Having determined the chemical shifts of each fluorine of 4,5,7-trifluoro-6-methoxybenzo[b]furan it is now possible to assign the fluorines in the spectrum of 4,5,6,7-tetrafluorobenzo[b]furan and to determine the effect of the methoxy substituent on the chemical shift, Table 12.

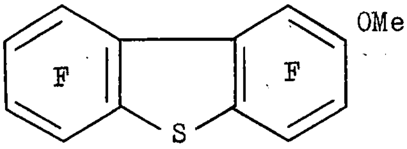
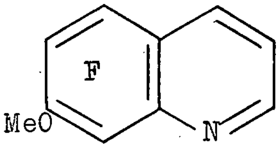
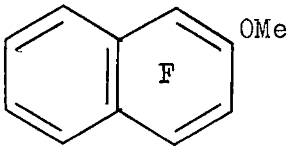
Table 12

Position	Chemical Shifts		Effect of CH_3O (p.p.m)
			
4	148·0	149·0	+ 1·0 (meta)
6	162·3	-	-
7	162·3	156·8	- 5·5 (ortho)
5	164·8	159·4	- 5·4 (ortho)

The most useful feature in the spectrum of 4,5,6,7-tetrafluorobenzo[b]furan is the absorption at 148·0 and the assignment of orientation of the remaining trifluoromonomethoxybenzo[b]furans is dependent on the correct assignment of this absorption. The effect of a methoxy substituent on fluorine chemical shifts for a number of polyfluoroaromatic compounds is shown in Table 13; the substituent effect is obtained by subtracting the chemical shift of a particular fluorine in the unsubstituted compound from the shift in the substituted compound; positive values are upfield shifts, negative values are downfield shifts. The terms ortho, meta, and para are used with reference to the methoxy group.

Table 13

Effect of a Methoxy substituent on ^{19}F Chemical Shifts

Substituted Compound	Effect of MeO			Ref.
	ortho	meta	para	
C_6F_5OMe	-4·4	+2·0	+1·7	131
	-5 and -7	+2	-	137
	-3·0 and -4·7	+1·5	-	133
	-4·9 and -5·7	+1·9	-	138

It can be seen from Table 13 that the methoxy group does not have a large effect on a meta fluorine. Since the low field peak (148·0) of 4,5,6,7-tetrafluorobenzo[b]furan is separated from the remaining peaks by ca 15 p.p.m., the assignment of this peak to the 4-fluorine is justified; if any other absorption was attributed to the 4-fluorine in 4,5,6,7-tetrafluorobenzo[b]furan a meta downfield shift of at least 14 c.p.s. would be required in order to account for the observed spectrum of 4,5,7-trifluoro-6-methoxybenzo[b]furan. From the observed coupling constants (p. 92) the absorption at 164·8 in the spectrum of 4,5,6,7-tetrafluorobenzo[b]furan can now be attributed to the 5-fluorine, and hence the overlapping peaks centred at 162·3 can be assigned to the 6- and 7-fluorines. As can be seen from Table 12 the observed effects of the methoxy substituent, calculated on the basis of these assignments, are in agreement with earlier results shown in Table 13.

The ^{19}F n.m.r. data and assignments for the remaining two isomers (B and C) in the mixture of trifluoromonomethoxybenzo[b]furans are shown in Tables 14 and 15.

Table 14

^{19}F n.m.r. of Isomer B (5,6,7-trifluoro-4-methoxybenzo[b]furan)

Chemical Shift	Assignment	Coupling Constants	Effect of OMe on ^{19}F shift
160·4	5F	18, (+ smaller splittings)	-4·4 (ortho)
163·6	6F	19·5, 18	+1·3 (meta)
165·0	7F	19·2, ~2·8 x 2	+ 2·7 (para)

Table 15

^{19}F n.m.r. of Isomer C (4,5,6-trifluoro-7-methoxybenzo[b]furan)

Chemical Shift	Assignment	Coupling Constants	Effect of OMe on ^{19}F shift
150·8	4F	20·3, 2·4	+2·8 (para)
158·3	6F	19 (+ small splittings)	-4·0 (ortho)
166·4	5F	20·4, 18·5	+1·6 (meta)

The methoxy group in isomer B is assigned to the 4-position since the low field peak assigned to the 4-fluorine in 4,5,6,7-tetrafluorobenzo[b]furan is absent from the spectrum; the absorption at 163·6 can then be assigned to the 6-fluorine on the basis of the two large coupling constants due to two ortho fluorines; the assignment of the remaining peaks is made on the basis of the methoxy substituent effect, the downfield shift being assumed to be due to ortho substitution. The smaller splitting (~2·8 c.p.s.) of the absorption at 165·0, attributed to cross-ring coupling between the 3-proton and the 7-fluorine, gives further confirmation of the assignments in Table 14.

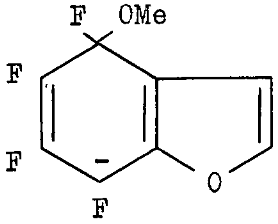
The remaining isomer (isomer C) must be either the 5-methoxy or 7-methoxy compound. The assignment of the methoxy group is made on the basis of the two assumptions which have been used throughout this argument: firstly, that the low field peak, in the region 148-151, is due to the fluorine at the 4-position, and secondly, that $J_{FF}^{ortho} > J_{FF}^{para}$. It can be seen from Table 15 that the 4-fluorine (150·8) couples with the fluorine at 166·4 and that the coupling constant (20·3 c.p.s.) is the largest in the spectrum; it thus follows that these two fluorines must be ortho to one another, that is, that the absorption at 166·4 is due to the 5-fluorine, and hence that the methoxy substituent is in the 7-position. Again the observed effect of the methoxy substituent is in agreement with the values given in Table 13.

Further confirmation of the assignment of fluorines in isomers B and C could be obtained if the smaller splittings observable on some of the peaks could be measured; these splittings could be due to coupling between the protons of the methoxy group and the *ortho* fluorines, or between *meta* fluorines; however, none of these small couplings could be measured with the resolution available.

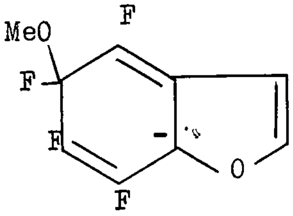
Theoretical Considerations on Nucleophilic Substitution in 4,5,6,7-Tetrafluorobenzo[b]furan

The rationalisation of nucleophilic substitution in 4,5,6,7-tetrafluorobenzo[b]furan is discussed in terms of the arguments which have been used successfully to rationalise the orientation of nucleophilic substitution in many other polyfluoro-aromatic compounds[45] (see Chapter IV). Assuming that the entropy of activation is the same for substitution at each position, the isomer distribution is determined solely by the differences in energy of activation; the lower the energy of a particular transition state, the greater the proportion of that isomer in the reaction product. The following discussion is therefore concerned with the factors affecting the stability of each transition state. The basic assumptions are that a para-quinonoid structure makes a greater contribution to the transition state than an ortho-quinonoid structure, and that the $I\pi$ repulsion of oxygen is greater than that of fluorine[45].

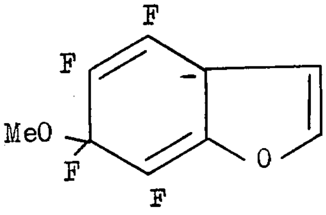
The para-quinonoid contributors to the transition states for substitution at each of the four positions are shown:



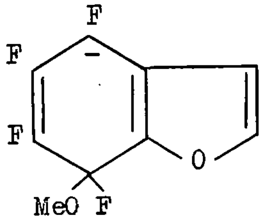
LXX



LXXI



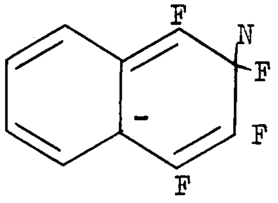
LXXII

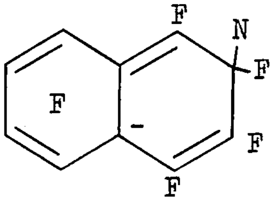


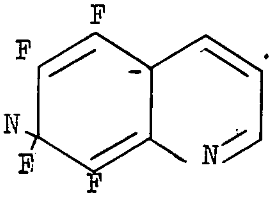
LXXIII

The hybrid (LXXI) would be expected to be least stable since the negative charge is placed on the carbon atom bonded to oxygen; hybrids (LXX) and (LXXIII) would be expected to be of about the same order of stability, and to be more stable than (LXXI), since the negative charge is placed on a carbon atom bonded to fluorine. A negative charge placed on a carbon atom common to two rings has been found to be a comparatively stable arrangement;

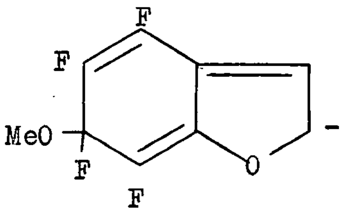
the para-quinonoid contributors to the transition states leading to the observed products from nucleophilic replacement of fluorine in octafluoro-[106] and 1,2,3,4-tetrafluoro[107]-naphthalene, and in 5,6,7,8-tetrafluoroquinoline[23] are shown below:





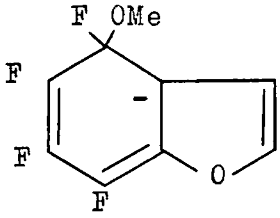


In all three cases the negative charge is placed on the carbon atom which is common to both rings and not on a carbon bonded to fluorine (or a carbon bonded to nitrogen in the case of the quinoline). By analogy, with these results, the hybrid (LXXII), above, in which the negative charge is placed on the carbon atom bonded to the furan carbon atom, would be expected to be most stable; therefore replacement of the 6-fluorine should predominate. The analogy between the three compounds mentioned above and 4,5,6,7-tetrafluorobenzo[b]furan is not completely valid since in the former cases the negative charge can be delocalised round the six-membered rings and, in the case of 5,6,7,8-tetrafluoroquinoline, it can be localised on the nitrogen atom. Delocalisation of the negative charge of hybrid (LXXII) around the furan ring places the negative charge on the carbon atom bonded to oxygen:

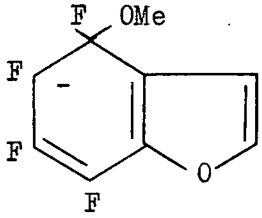


Whether any additional stabilisation results from this delocalisation is questionable.

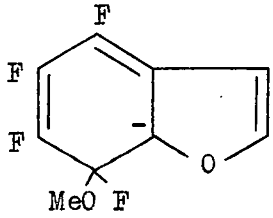
The _para_-quinonoid contributors to the transition states leading to replacement of the 4-fluorine and the 7-fluorine both place the negative charge on a carbon atom bonded to fluorine, and therefore in order to determine the relative stabilities of these transition states it is necessary to consider the corresponding _ortho_-quinonoid contributors:



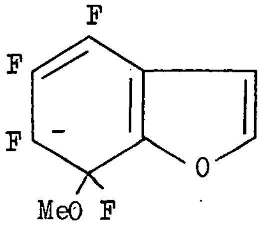
LXXIV



LXXV



LXXVI



LXXVII

The _ortho_-quinonoid contributors to the transition state resulting from reaction at the 4-position place the negative charge on the carbon atom bonded to the furan carbon atom (LXXIV) and on a carbon atom bonded to fluorine (LXXV); the corresponding contributors for replacement of the 7-fluorine place the negative charge on the carbon bonded to oxygen (LXXVI) and on a carbon bonded to fluorine (LXXVII), and hence the transition state leading to replacement of the 4-fluorine should be rather more stable than that leading to replacement of the 7-fluorine. Thus, from the above qualitative considerations, the ease of replacement of fluorine in 4,5,6,7-tetrafluorobenzo[b]furan should decrease in the order 6F > 4F > 7F > 5F, which is the same order as that found experimentally from the reaction with sodium methoxide.

The preceeding discussion gives a reasonable qualitative explanation of the orientation of nucleophilic substitution in 4,5,6,7-tetrafluorobenzo[b]furan; the lower reactivity of the molecule as compared with hexafluorobenzene can best be explained by a consideration of ground state stabilities. It has been suggested[45] that an increase in fluorine substitution decreases the stability of an aromatic compound; stability in this context is used in an absolute sense: one compound is more stable than another if more free energy is required to decompose it into its constituent atoms in their standard states. This decrease in stability was attributed mainly to electron-deficiency caused by the electronegativity of fluorine, and thus C_6F_5X compounds were placed in an approximate order of stability depending on the ability of X to offset this deficiency. Thus, it was suggested that pentafluoroaniline and -anisole are more stable than hexafluorobenzene because some of the electron deficiency caused by the five fluorines can be compensated by mesomeric electron donation by the nitrogen and oxygen. Similarly in 4,5,6,7-tetrafluorobenzo[b]furan, mesomeric electron donation from oxygen will partly compensate the electron deficiency of the fused fluorinated aromatic ring; if the transition state stabilities are considered to be of approximately the same order, the difference in reactivity between 4,5,6,7-tetrafluorobenzo[b]furan and hexafluorobenzene can thus be attributed to the difference in ground state stabilities.

The results from Huckel molecular-orbital calculations[139] on 4,5,6,7-tetrafluorobenzo[b]furan are in general agreement with the conclusions reached above. Calculation of ground state π electron densities at each of the four positions indicate that all are very similar and are of approximately the same order as in benzene; calculation of localisation energies for nucleophilic substitution at each of the four positions shows again that all the positions are very similar.

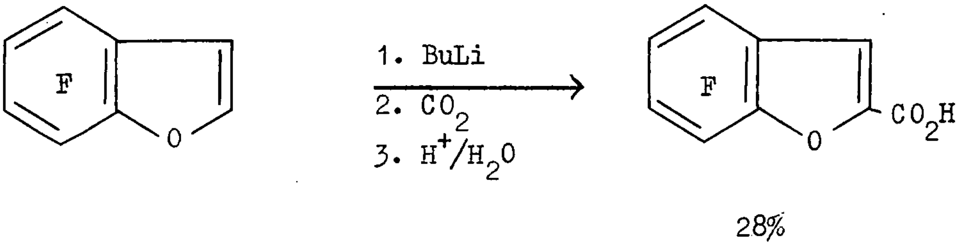
Section 2

Reactions of the Furan Ring of 4,5,6,7-Tetrafluorobenzo[b]furan

(A) Reaction with Butyl-lithium

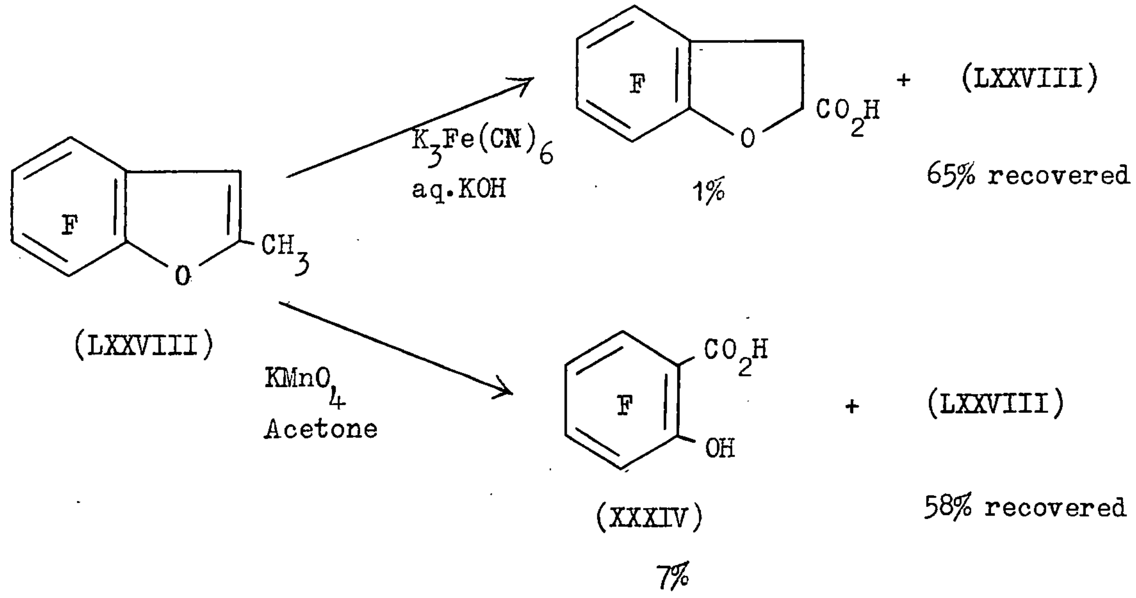
Benzo[b]furyl-2-lithium has been prepared by the reactions of benzo[b]furan[140] and 2-bromobenzo[b]furan[141] with butyl-lithium; carbonation[141] gave benzo[b]furan-2-carboxylic acid and treatment with sulphur dioxide[140] gave benzo[b]furan-2-sulphinic acid which was oxidised with hydrogen peroxide to the corresponding sulphonic acid.

Treatment of 4,5,6,7-tetrafluorobenzo[b]furan in dry tetrahydrofuran with one equivalent of butyl-lithium at -78° followed by carbon dioxide gave 4,5,6,7-tetrafluorobenzo[b]furan-2-carboxylic acid:

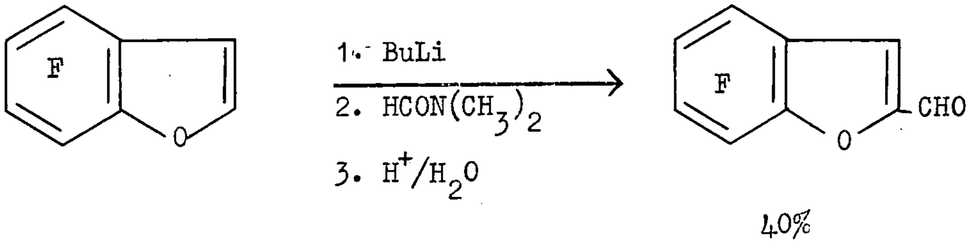


The acid was also prepared by the oxidation of the methyl group of 4,5,6,7-tetrafluoro-2-methyl-benzo[b]furan[17], thus identifying the position of metalation in the reaction of 4,5,6,7-tetrafluorobenzo[b]furan with butyl-lithium. A number of oxidising agents were investigated for the oxidation of the methyl group of 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan (LXXVIII). Selenium dioxide [142] in alcohol has been reported to give 2-formylbenzo[b]furan on reaction with 2-methylbenzo[b]furan[143,144];

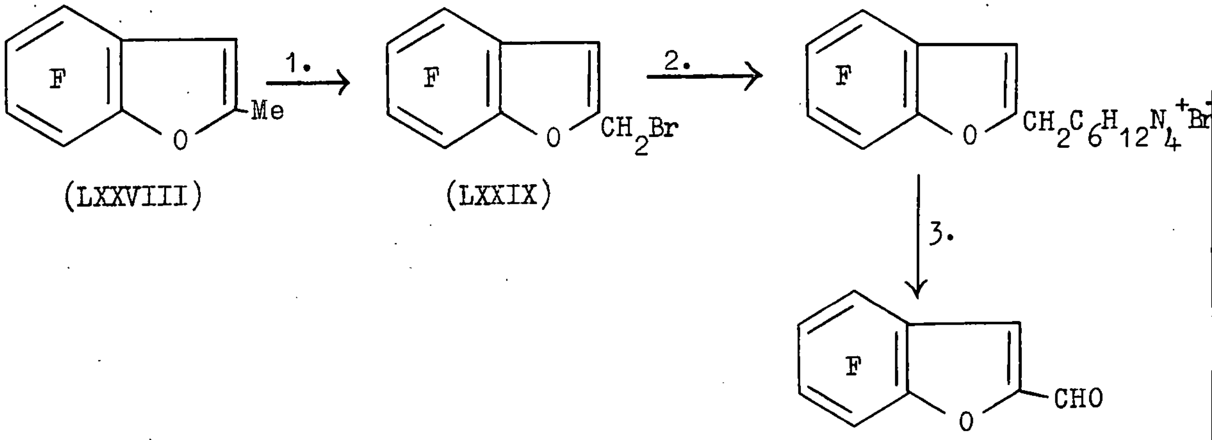
reaction of (LXXVIII) under these conditions gave only unchanged starting material, and similarly in dioxan as solvent no reaction was observed. The oxidation of (LXXVIII) with potassium permanganate was investigated in both aqueous and acetonic solution at several different temperatures and concentrations, but in the majority of the reactions only unchanged starting material or decomposition products were isolated. However, when the reaction was carried out in acetone with a deficiency of potassium permanganate a low yield (ca 7%) of 2,3,4,5-tetrafluoro-6-hydroxybenzoic acid (XXXIV) was isolated. Alkaline potassium ferricyanide[145] has been used for the oxidation of furan compounds without cleaving the furan ring[146]; 2-methylfuran was oxidised to 2-furoic acid in ca 3% yield, but higher yields (up to 50%) were obtained with a number of other furan derivatives. Application of this method to 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan (LXXVIII) gave a low yield (~1%) of 4,5,6,7-tetrafluorobenzo[b]furan-2-carboxylic acid together with a large amount (65%) of unreacted (LXXVIII).



Treatment of 4,5,6,7-tetrafluorobenzo[b]furan with one equivalent of butyl-lithium and reaction of the resulting benzo[b]furyl-lithium with N,N'-dimethylformamide gave 4,5,6,7-tetrafluoro-2-formylbenzo[b]furan:



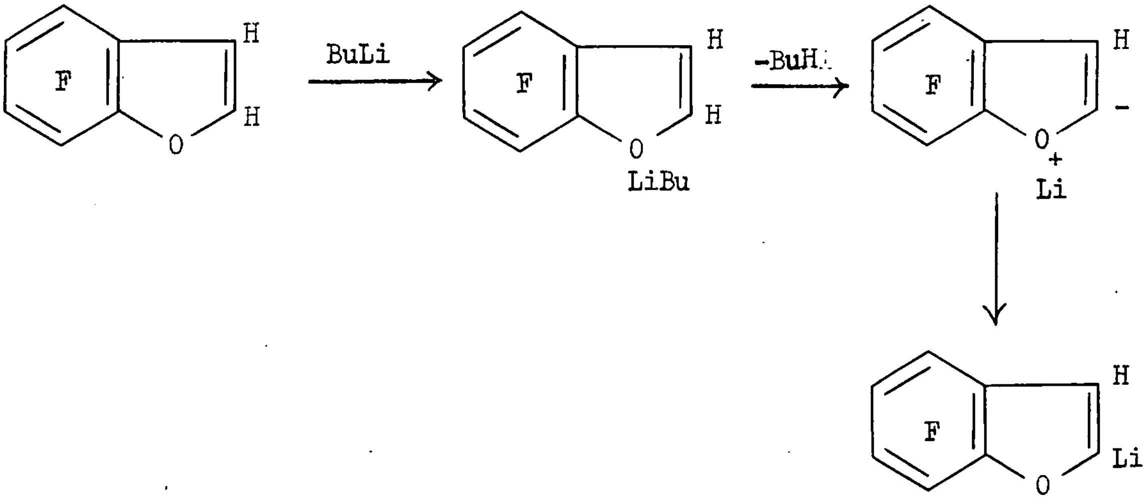
The aldehyde was also synthesised from 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan by the route shown in the scheme.



1. N-bromosuccinimide and trace of peroxide in carbon tetrachloride;
2. hexamine in chloroform; 3. 50% acetic acid.

Free radical bromination of (LXXVIII) with N-bromosuccinimide in the presence of a trace of benzoyl peroxide gave 2-bromomethyl-4,5,6,7-tetrafluoro benzo[b]furan (LXXIX); a correct elemental analysis could not be obtained on this compound but its structure was confirmed by ^{1}H n.m.r. and mass spectra. The ^{1}H n.m.r. spectrum showed two regions of absorption, at τ3·0 (doublet) and τ5·3 (singlet) with relative intensity 1:2, which were attributed to the 3-proton and methylene protons respectively; the mass spectrum showed peaks at 282 and 284 corresponding to the molecular weight of the two bromine isotopes of (LXXIX). On treatment with hexamine in chloroform (LXXIX) gave a 62% yield of the hexaminium salt, but only a low conversion of the salt to the required aldehyde could be effected; the reaction was carried out with and without isolation of the hexaminium salt and with different strengths of acid in the hydrolysis step[147] with no noticeable increase in yield; best yields (~18%) of 4,5,6,7-tetrafluoro-2-formylbenzo[b]furan were obtained by separating the salt and then heating under reflux for 2 hours with 50% acetic acid.

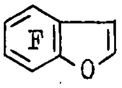
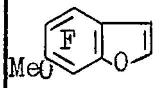
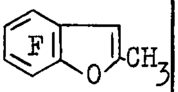
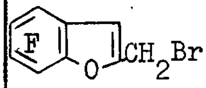
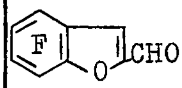
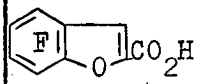
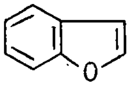
The alternative syntheses of 4,5,6,7-tetrafluorobenzo[b]furan-2-carboxylic acid and -2- carboxaldehyde from 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan demonstrate unambiguously that metalation of 4,5,6,7-tetrafluorobenzo[b]furan with butyl-lithium occurs exclusively at the 2-position, that is, ortho to the hetero-atom. Similar orientations have been observed with benzo[b]furan[140], benzo[b]thiophen[148], dibenzofuran[149], and dibenzothiophen[150]; the probable explanation for these orientations[151,152], is that there is initial co-ordination between the hetero-atom and the lithium of the alkyl-lithium, followed by proton abstraction from the 2-position and subsequent rearrangement of the lithium to the 2-position:



^{1}H n.m.r. Spectra of Polyfluorinated Benzo[b]furan Compounds

The ^{1}H n.m.r. spectra of 4,5,6,7-tetrafluorobenzo[b]furan and a number of its 2-substituted derivatives are shown in Table 16; the data for benzo[b]furan itself[134,135] is also included for comparison. The assignments of the absorptions in 4,5,6,7-tetrafluorobenzo[b]furan are made by analogy with benzo[b]furan[134,135], the low field peak being attributed to the 2-proton. The absorption due to the 3-proton (τ 3·1) is split into a doublet of doublets (J, 2·2, 2·8 c.p.s.) and that due to the 2-proton (τ 2·3) is a doublet (J, 2·2 c.p.s.); again by analogy with benzo[b]furan, these splittings are attributed to coupling between the 2-proton and the 3-proton (2·2 c.p.s.) and between the 3-proton and the 7-fluorine (2·8 c.p.s.). This cross-ring coupling could not be confirmed from the ^{19}F n.m.r. spectrum of 4,5,6,7-tetrafluorobenzo[b]furan (p. 92) since the absorption attributed to the 7-fluorine is part of a complex

Table 16

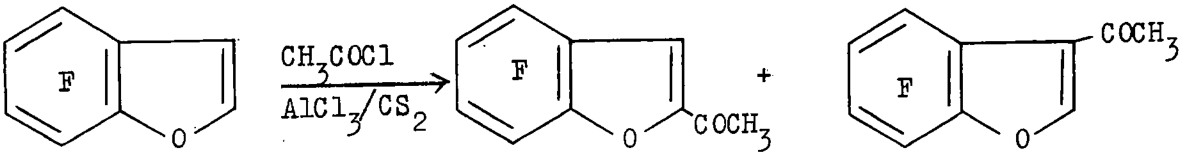
	Chemical Shift (τ)			Substituent Effect	Multiplicity (3-proton)	Coupling Constants (c.p.s.)
	3H	2H	Substituent			
	3·1	2·3	-	-	doublet of doublets	J_{23}=2·2; J_{37}=2·8
	3·0	2·2	-	-	doublet of doublets	J_{23}=2·2; J_{37}=2·8
	3·6	-	7·5(CH_3)	+0·5	not resolved	-
	3·0	-	5·3(CH_2)	-0·1	doublet	2·6
	2·3	-	0·1(CHO)	-0·8	doublet	2·7
	2·4	-	-1·0(CO_2H)	-0·7	doublet	2·8
	3·59	2·73	-	-	doublet of doublets	J_{23}=2·3; J_{37}=0·9

multiplet involving second order splitting. A coupling constant of the correct magnitude (2·8 c.p.s.) is however observed on the absorption attributed to the 7-fluorine in the spectrum of 4,5,7-trifluoro-6-methoxybenzo[b]furan (p. 101) and this is confirmatory evidence for the assignment of the extra splitting of the 3-proton in the compounds listed in Table 16 to cross-ring coupling with the 7-fluorine. The existence of this coupling allows assignment of orientation of the products from substitution reactions of the furan ring since the 3-proton in 2-substituted compounds is a doublet, as seen from Table 16, and the 2-proton in 3-substituted compounds would be expected to be a singlet. The substituent effects shown in Table 16, obtained by subtracting the chemical shift of the 3-proton in 4,5,6,7-tetrafluorobenzo[b]furan from the shift of the same proton in the substituted compound, are of approximately the same magnitude as the effect of the same substituent in substituted furan compounds[153]. This substituent effect can thus give additional evidence for the assignment of unknown orientations.

(B) Electrophilic Substitution in 4,5,6,7-Tetrafluorobenzo[b]furan

The extent of the present knowledge on the electrophilic substitution reactions of benzo[b]furan and its derivatives is rather limited. The probable explanation for this situation is that a wide range of substituted benzo[b]furan compounds are available from ring closure reactions[27]. It has been established that substitution occurs preferentially at the 2-position in the nitration[154], acetylation[140,155], formylation[156,157] and sulphonation[158] of benzo[b]furan, but there appears to be only one recent report[155] of an attempt to determine the presence of any small amounts of other isomers. Most attention in recent years has been directed to the acylation reactions and a survey of substitution in benzo[b]furan and its derivatives in these reactions has recently been published[159]. Aluminium chloride cannot be used in the Friedel-Crafts acylation of benzo[b]furan since it causes polymerisation[159]; stannic chloride has also been reported to cause polymerisation[160], but other workers[155] have obtained moderate yields (~40%) of the 2-substituted product with this catalyst. Benzo[b]furan has also been acetylated using boron trifluoride etherate as catalyst[155], and high yields (~70%) of 2-formylbenzo[b]furan have been obtained using phosphorus oxychloride and N,N -dimethylformamide (Vilsmeyer Reaction)[156,157]. In all these reactions the 2-substituted compound was the only isomer isolated.

Since most information was available on the acylation of benzo[b]furan, the reaction of 4,5,6,7-tetrafluorobenzo[b]furan under similar conditions was investigated as an example of electrophilic substitution. This type of reaction was likely to provide the most effective basis for a comparison between the two systems. Attempted formylation of 4,5,6,7-tetrafluorobenzo[b]furan by the Vilsmeyer Reaction was unsuccessful, giving only unreacted starting material; similarly, attempted acetylation with boron trifluoride etherate and acetic anhydride was unsuccessful. Acetylation of 4,5,6,7-tetrafluorobenzo[b]furan was, however, achieved in 28% yield by reaction with acetyl chloride and aluminium chloride in carbon disulphide at room temperature.



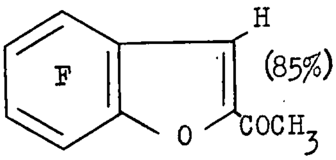
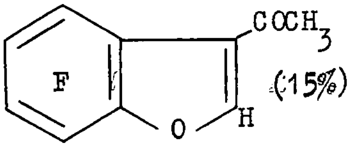
85%

15%

The mixture of isomers from the acetylation reaction melted over *ca* 10° after recrystallisation, but gave correct elemental analysis results; the isomer ratio was determined from the integration of the absorptions due to the furan ring protons in the ^{1}H n.m.r. spectrum, Table 17.

Table 17

^{1}H n.m.r. Spectrum of Product from Acetylation of 4,5,6,7-tetrafluorobenzo[b]furan

	Chemical Shift (τ) Furan ring proton	Multiplicity	Substituent Effect (p.p.m.)
 (85%)	2·4	doublet (J 2·8 c.p.s.)	- 0·7
 (15%)	1·6	singlet	- 0·7

The assignment of orientation shown in Table 17 is based on the criteria described earlier (p.119). The effect of a carbonyl substituent is to shift the position of absorption of the proton on the adjacent carbon atom downfield by 0·6 - 1·0 p.p.m. from the position of absorption in 4,5,6,7-tetrafluorobenzo[b]furan. Thus the 3-proton of a 2-substituted compound would be expected to be a doublet in the region $\tau\,2{\cdot}3 \pm 0{\cdot}2$ and the 2-proton of a 3-substituted compound would be expected to be a singlet in the region $\tau\,1{\cdot}5 \pm 0{\cdot}2$. The assignment of orientation of the acetyl derivatives follows from a comparison of these predictions with the observed spectrum, Table 17.

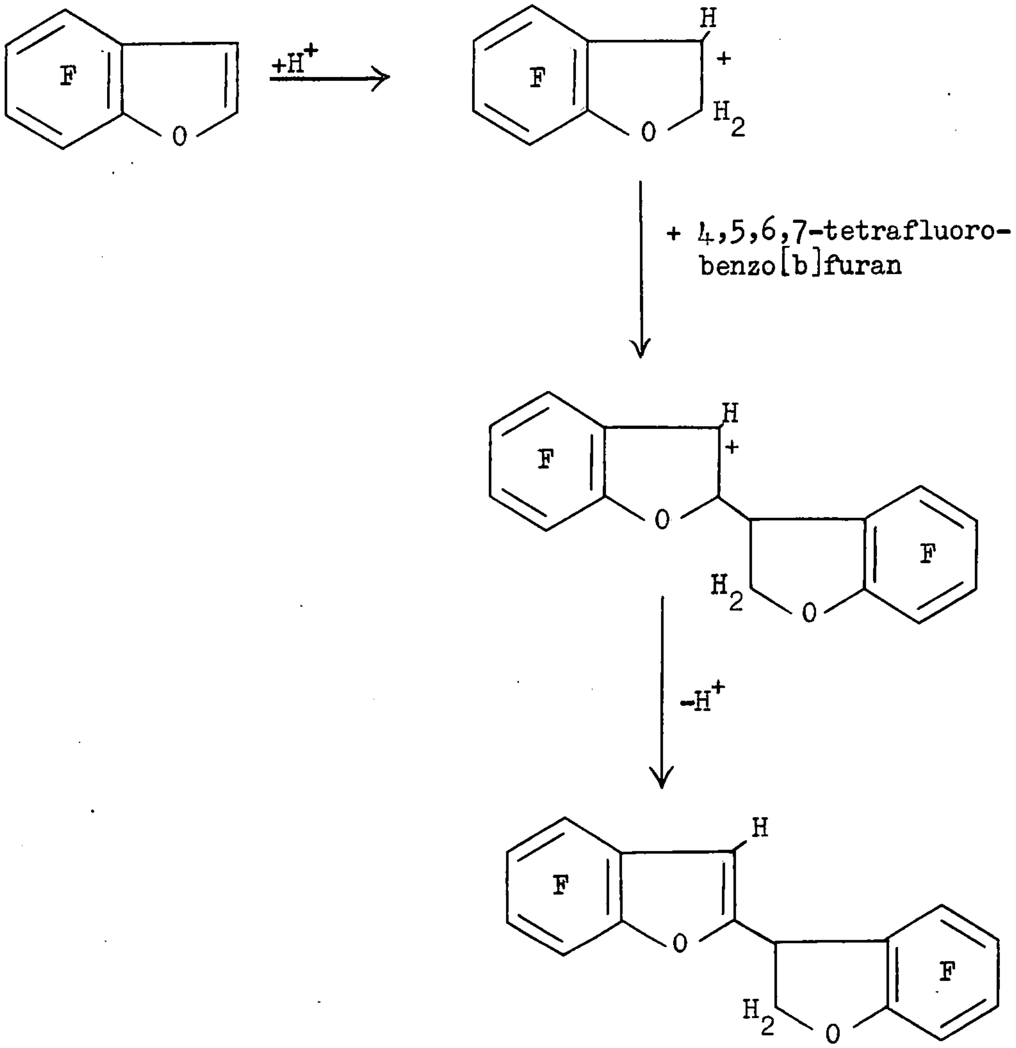
From the above results two differences can be discerned between the behaviour of 4,5,6,7-tetrafluorobenzo[b]furan and of benzo[b]furan in electrophilic substitution reactions: firstly, a difference in reactivity, and secondly a difference in orientation. The lower reactivity can best be explained in the same way as was its lower reactivity in nucleophilic substitution reactions, that is, that the electron deficiency of the fluorinated ring is offset by mesomeric donation of electrons from the heterocyclic ring, thus reducing the electron density in the heterocyclic ring and hence also reducing its susceptibility to electrophilic attack.

The factors affecting the orientation of electrophilic substitution in fused ring heterocyclic compounds are not well understood. Benzo[b]furan gives only 2-substitution whilst benzo[b]thiophen gives mainly 3-substitution, although up to 33% of the 2-isomer is formed in some reactions[155]. Substitution in indole also occurs preferentially at the 3-position[161]. Several authors[151,155,162] have attempted to rationalise these orientations, but with only limited success. In the light of the present theory of the orientation in this type of reaction, a discussion of the possible reasons for the formation of the small proportion of the 3-isomer in the acetylation of benzo[b]furan is not considered to be of any value at this stage.

(C) Polymerisation of 4,5,6,7-Tetrafluorobenzo[b]furan

The polymerisation of benzo[b]furan has been carried out on an industrial scale for many years. The coal-tar fraction boiling between 168° and 175° which is rich in benzo[b]furan and indene is polymerised by sulphuric acid[163] to give the industrially important indene-coumarone resins with molecular weight up to 1000.[164] The stereospecific polymerisation of benzo[b]furan with Ziegler catalysts has also been investigated in recent years[165,166]. 6-Methoxy-3-methylbenzo[b]furan is reported to give a dimer in 87% yield with sulphuric acid but no experimental details could be obtained from this inaccessible paper[167].

4,5,6,7-Tetrafluorobenzo[b]furan gave a deep violet solution in concentrated sulphuric acid. A small amount of white solid was obtained on pouring this solution into water after standing for 3 hr. The mass spectrum of this product showed a major peak at 380 corresponding to a dimer of 4,5,6,7-tetrafluorobenzo[b]furan; other small peaks at 568, 569 and 570 were probably due to a trimer. The extent of polymerisation was found to be critically dependent on the time of contact between the benzo[b]furan and the acid, and on the rate of stirring. Longer reaction time or very vigorous stirring gave tars and time did not permit a sufficiently detailed investigation to determine the optimum conditions for the formation of the dimer. The probable mechanism for the formation of the dimer is shown below:


F
O
+H+
H
+
H2
+ 4,5,6,7-tetrafluoro-
benzo[b]furan
-H+

CHAPTER VI

EXPERIMENTAL WORK (PART II)

The Reaction of 4,5,6,7-Tetrafluorobenzo[b]furan with Sodium Methoxide

(a) 4,5,6,7-Tetrafluorobenzo[b]furan (0·5 g. 0·0026 mole) and a solution of sodium methoxide in methanol (1·0 ml. 2·77N, 0·0028 mole) and methanol (2·5 ml.) were heated in a sealed tube at 95° for 41 hr. After cooling, the contents of the tube were poured into water and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent was distilled off. The residue was vacuum transferred to give a mixture of trifluoromonomethoxybenzo[b]furan compounds (0·36 g.) contaminated with a small amount of 4,5,6,7-tetrafluorobenzo[b]furan and a trace of higher boiling material which were removed by preparative scale g.l.c. to provide an analytical sample, b.p. 224-226°. (Found: C, 53·7; H, 2·54; F, 27·9. $C_9H_5O_2F_3$ requires C, 53·5; H, 2·48; F, 28·2%.)

(b) 4,5,6,7-Tetrafluorobenzo[b]furan (0·2 g., 0·0011 mole) and a solution of sodium methoxide in methanol (1·4 ml. 0·85N, 0·0012 mole) and methanol (1 ml.) were heated under reflux for 16 hr, cooled, poured into water and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent was distilled off. Volatile material (0·15 g.) was removed from the residue by vacuum transfer. Analytical scale g.l.c. and infra-red spectrum showed this to be mainly 4,5,6,7-tetrafluorobenzo[b]furan. A small peak corresponding to trifluoromonomethoxybenzo[b]furan was also observed on the chromatogram.

(c) 4,5,6,7-Tetrafluorobenzo[b]furan (0·2 g., 0·0011 mole) and a solution of sodium methoxide in methanol (1·4 ml., 0·85N, 0·0012 mole) were heated in a sealed tube at 150° for 18 hr. After cooling, the contents of the tube were poured into water and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent was distilled off. Volatile material (ca. 0·05 g.) was removed from the tarry residue by vacuum transfer and was shown by analytical scale g.l.c. to contain three components in approximately equal quantities. The shortest retention time was the same as that of trifluoromonomethoxybenzo[b]furan. The remaining two components had much longer retention times and were presumably due to difluorodimethoxybenzo[b]furans. The mixture was not investigated further.

2,4,5-Trifluoro-3-methoxyphenol:- Sodium (1·7 g., 0·074 mole) was dissolved in methanol and the excess methanol was removed under vacuum. A solution of 2,3,4,5-tetrafluorophenol (6·2 g., 0·037 mole) in sulpholane (40 ml.) was added to the sodium methoxide thus obtained and the mixture was heated in a sealed tube at 140° for 12 hr. After cooling, the reaction mixture was poured into water, acidified, and extracted with ether. After removal of solvent, the residue was distilled under reduced pressure to give three fractions: (1) 0·41 g., b.p. $< 84°$/8 mm., which consisted mainly of 2,3,4,5-tetrafluorophenol; (2) 2·2 g., b.p. 84-88°/8 mm., which was 2,4,5-trifluoro-3-methoxyphenol. (Found: C, 46·9; H, 2·81; F, 32·3. $C_7H_5F_3O_2$ requires C, 47·2; H, 2·81; F, 32·0%). Fraction (3), 2·8 g., b.p. 88-148°/8 mm., was shown by analytical scale g.l.c. to be two compounds in approximately equal amounts: 2,4,5-trifluoro-3-methoxyphenol and a compound of longer retention time which was not investigated further.

The Reaction of 2,3,4,5-Tetrafluorophenol with Sodium Methoxide in Methanol:- 2,3,4,5-Tetrafluorophenol (1·0 g.) and a solution of sodium (0·28 g.) dissolved in methanol (4 ml.) were heated in a steel bomb (25 ml.capacity) at 180° for 30 hrs. After cooling, the contents of the bomb were poured into water, acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic solution was washed with water, dried ($MgSO_4$) and the solvent was distilled off. Volatile material was removed from the residue (0·27 g.) by vacuum transfer and analytical scale g.l.c. and infra-red spectrum showed it to consist mainly of 2,3,4,5-tetrafluorophenol (~90%); the other small component had the same g.l.c. retention time as 2,4,5-trifluoro-3-methoxyphenol.

2,4,5-Trifluoro-3-methoxyphenoxyacetic Acid:- 2,4,5-Trifluoro-3-methoxyphenol (4·34 g., 0·024 mole), bromoacetic acid (5·0 g., 0·028 mole), potassium carbonate (10 g.) and water (60 ml.) were heated under reflux for 20 hr. After cooling, the reaction mixture was acidified with dilute sulphuric acid and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off. The residue (4·81 g.) was recrystallised from a mixture of light petroleum (b.p. 80-100°) and benzene to give 2,4,5-trifluoro-3-methoxyphenoxyacetic acid (3·40 g.) m.p. 103-104°. (Found: C, 45·6; H, 2·7; F, 24·3. $C_9H_7F_3O_4$ requires C, 45·8; H, 3·0; F, 24·2%).

4,5,7-Trifluoro-6-methoxy-2,3-dihydrobenzo[b]furan-3-one:- A solution of butyl-lithium in hexane (2·5 ml., 2·2M, 0·0055 mole) was added to a solution of 2,4,5-trifluoro-3-methoxyphenoxyacetic acid (0·42 g., 0·0018 mole) in dry tetrahydrofuran (10 ml.) at -70°. The mixture was stirred for 4 hr. at -70° and then carbonated so that the temperature remained below -60°. The solution was allowed to warm to room temperature with continued carbonation and then was acidified with dilute sulphuric acid and extracted with ether. After removal of solvent, the residue was sublimed (90°/15 mm.) to give a solid (0·11 g.) contaminated with a small amount of valeric acid. Recrystallisation from light petroleum (b.p. 40-60°) gave 4,5,7-trifluoro-6-methoxy-2,3-dihydrobenzo[b]furan-3-one, m.p. 68-69°. (Found C, 49·0; H, 2·20%. M(mass spectroscopy), 218. $C_9H_5F_3O_3$ requires C, 49·5; H, 2·29%. M, 218).

4,5,7-Trifluoro-6-methoxybenzo[b]furan:- Sodium borohydride (0·1 g.) was added in small quantities to a cooled (*ca* 5°) solution of 4,5,7-trifluoro-6-methoxy-2,3-dihydrobenzo[b]furan-3-one (0·65 g.) in dry methanol (10 ml.). The mixture was stirred for 16 hr. at 22° and then acidified and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent was distilled off. The residue was vacuum transferred from phosphoric oxide to give 4,5,7-trifluoro-6-methoxybenzo[b]furan (0·41 g.), b.p. 225°. (Found: C, 53·2; H, 2·42. $C_9H_5F_3O_2$ requires C, 53·5; H, 2·47%).

3,5,6-Trifluoro-2-hydroxy-4-methoxybenzoic Acid:- A solution of butyl-lithium in hexane (11·5 ml., 2·2M, 0·026 mole) was added dropwise to a solution of 2,4,5-trifluoro-3-methoxyphenol (2·25 g., 0·013 mole) in dry tetrahydrofuran (50 ml.) at -70°. The mixture was stirred for 2·5 hr. at -70° and then carbonated so that the temperature remained below -60°. The solution was allowed to warm to room temperature with continued carbonation and was then acidified with dilute sulphuric acid and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off. The residue was sublimed (80°/0·01 mm.) to give the crude acid (1·23 g.) m.p. 155-160°. Recrystallisation from a mixture of benzene and light petroleum (b.p. 80-100°) gave 3,5,6-trifluoro-2-hydroxy-4-methoxybenzoic acid m.p. 169-171°. (Found: C, 43·3; H, 2·27; F, 25·5. $C_8H_5F_3O_4$ requires C, 43·2; H, 2·27; F, 25·7%).

Methyl 2,3,5,6-Tetrafluoro-4-methoxybenzoate:- Methyl 2,3,4,5,6-pentafluorobenzoate (3·0 g.) and a solution of sodium methoxide in methanol (12·0 ml. 1·17N) were heated under reflux for 7 hr. After cooling, the reaction mixture was poured into water and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent was distilled off. The residue was vacuum transferred to give methyl 2,3,5,6-tetrafluoro-4-methoxybenzoate (2·87 g.) b.p.238-240°. (Found: C, 45·3; H, 2·46; F, 32·2. $C_9H_6O_3F_4$ requires C, 45·4; H, 2·52; F, 31·9%). The ^{19}F n.m.r. spectrum of the pure liquid showed two absorptions of equal intensity at 157·8 p.p.m. and 140·3 p.p.m. upfield from trichlorofluoromethane.

Methyl 2,3,4,5-Tetrafluoro-6-methoxybenzoate:- A solution of diazomethane in ether was added to a solution of 2,3,4,5-tetrafluoro-6-hydroxybenzoic acid (3·20 g.) in ether until the yellow colouration persisted. Excess diazomethane and ether were distilled off and the residue was vacuum transferred to give methyl 2,3,4,5-tetrafluoro-6-methoxybenzoate (3·50 g.)

b.p. 214-215°. (Found: C, 45·5; H, 3·09; F, 31·8. $C_9H_6F_4O_3$ requires C, 45·4; H, 2·52; F, 31·9%).

Methyl 3,5,6-trifluoro-2,4-dimethoxybenzoate

(a) From 3,5,6-trifluoro-2-hydroxy-4-methoxybenzoic acid:- A solution of diazomethane in ether was added to a solution of the acid (0·2 g.) in ether until the yellow colouration persisted. Excess diazomethane and ether were distilled off and the residue was vacuum transferred to give methyl 3,5,6-trifluoro-2,4-dimethoxybenzoate (0·16 g.) b.p. > 250° (Found: C, 48·5; H, 3·30. $C_{10}H_9O_4F_3$ requires C, 48·0; H, 3·6%).

(b) From methyl 2,3,4,5-tetrafluoro-6-methoxybenzoate:- The ester (1·0 g.) and a solution of sodium methoxide in methanol (3·8 ml., 1·17N) were heated under reflux for 11·5 hr. The reaction mixture was cooled, poured into water and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off. The residue was vacuum transferred to give methyl 3,5,6-trifluoro-2,4-dimethoxybenzoate (0·95 g.), with an identical infra-red spectrum to that of the sample prepared before.

(c) From Methyl 2,3,5,6-tetrafluoro-4-methoxybenzoate:- The ester (1·0 g.) and a solution of sodium methoxide in methanol (3·7 ml. 1·26N) and methanol (7 ml.) were heated under reflux for 14 hr. The reaction mixture was cooled, poured into water and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off. The residue was vacuum transferred to give methyl 3,5,6-trifluoro-2,4-dimethoxybenzoate (0·23 g.), with an identical infra-red spectrum to that of the samples prepared before.

4,5,6,7-Tetrafluorobenzo[b]furan-2-carboxylic Acid

(a) From 4,5,6,7-tetrafluorobenzo[b]furan:- A solution of butyl-lithium in hexane (1·1 ml., 2·4M) was added dropwise to a stirred solution of 4,5,6,7-tetrafluorobenzo[b]furan (0·5 g.) in dry tetrahydrofuran (10 ml.) at -70°. The mixture was stirred at -70° for 45 mins. and then carbonated and allowed to warm to room temperature with continued carbonation. The reaction mixture was acidified with dilute sulphuric acid and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent was distilled off to give the crude acid (0·17 g.). Recrystallisation from light petroleum (b.p. 100-120°) and sublimation (70°/0·01 mm) gave 4,5,6,7-tetrafluorobenzo[b]furan-2-carboxylic acid m.p. 150-151·5°. (Found: C, 46·1; H, 0·90; F, 32·5. $C_9H_2F_4O_3$ requires C, 46·2; H, 0·86; F, 32·5%).

(b) From 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan:- 4,5,6,7-Tetrafluoro-2-methylbenzo[b]furan (0·2 g.) and a solution of potassium ferricyanide (12 g.) and potassium hydroxide (2 g.) in water (30 ml.) were heated in a sealed tube at 100° for 21 hr. After cooling, the contents of the tube were poured into water and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off. The residue was sublimed (50°/15 mm) to give 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan (0·13 g., 65%). The aqueous solution from the ether extraction was acidified with dilute sulphuric acid and extracted with ether. The residue after distillation of the solvent was sublimed (50-60°/0·01 mm.) to give

4,5,6,7-tetrafluorobenzo[b]furan-2-carboxylic acid (0·002 g.). (Found: M(mass spectroscopy) 234. $C_9H_2F_4O_3$ requires M, 234.) The infra-red spectrum of this compound was the same as that prepared above from 4,5,6,7-tetrafluorobenzo[b]furan.

4,5,6,7-Tetrafluoro-2-formylbenzo[b]furan

(a) From 4,5,6,7-tetrafluorobenzo[b]furan:- A solution of butyl-lithium in hexane (1·1 ml., 2·4M) was added dropwise to a solution of 4,5,6,7-tetrafluorobenzo[b]furan (0·5 g.) in dry tetrahydrofuran (10 ml.) at -70°. The solution was stirred at -70° for 2 hr. and then a solution of N,N'-dimethylformamide (0·2 g.) in tetrahydrofuran (2 ml.) was added and the mixture was stirred at -70° for a further hour. After warming to room temperature the reaction mixture was poured into water, acidified with dilute sulphuric acid and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off to give the crude aldehyde (0·23 g.). Recrystallisation from light petroleum (b.p. 40-60°) and sublimation (30°/0·01 mm) gave 4,5,6,7-tetrafluoro-2-formylbenzo[b]furan m.p. 70-71°. (Found C, 49·6; H, 0·83; F, 34·4%. M(mass spectroscopy 218). $C_9H_2F_4O_2$ requires C, 49·5; H, 0·92; F, 34·9%. M,218).

(b) From 2-bromomethyl-4,5,6,7-tetrafluorobenzo[b]furan:- 2-Bromomethyl-4,5,6,7-tetrafluorobenzo[b]furan (1·0 g.) was added to a stirred solution of hexamine (0·55 g.) in chloroform (5 ml.). A precipitate started to form almost immediately and after standing 2 hr. the precipitate was filtered off and washed with a small amount of cold chloroform and then dried (1·05 g.). The salt was dissolved in acetic acid (10 ml., 50%), heated under reflux for 1·5 hr., cooled, poured into water and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, dried ($MgSO_4$), and the solvent was distilled off. The residue was sublimed (50°/0·01 mm.) to give 4,5,6,7-tetrafluoro-2-formylbenzo[b]furan (0·084 g.) with ^1H n.m.r. and infra-red spectra identical to those of the compound prepared from 4,5,6,7-tetrafluorobenzo[b]furan.

2-Bromomethyl-4,5,6,7-tetrafluorobenzo[b]furan:- 4,5,6,7-Tetrafluoro-2-methylbenzo[b]furan (2·0 g.), N-bromosuccinimide (1·7 g.) and a trace of benzoyl peroxide were heated under reflux in carbon tetrachloride (30 ml.) for 1·5 hr. After cooling, the precipitated succinimide was filtered off and the solvent was distilled from the filtrate to give crude 2-bromomethyl-4,5,6,7-tetrafluorobenzo[b]furan (2·20 g.) b.p. 58–62°/0·01 mm. Preparative scale g.l.c. gave a sample which gave elemental analysis results slightly outside the acceptable limits, (Found: C, 37·5; H, 0·95; $C_9H_3BrF_4O$ requires C, 38·2; H, 1·06) but both the ^1H n.m.r. spectrum (τ 3·0, 5·3 with relative intensities 1:2) and the mass spectrum [peaks at 282, 284 ($C_9H_3BrF_4O$) and 203 ($C_9H_3F_4O$)] were consistent with the proposed structure.

Acetylation of 4,5,6,7-Tetrafluorobenzo[b]furan:- A solution of 4,5,6,7-tetrafluorobenzo[b]furan (0·5 g.), acetyl chloride (0·25 g.) and aluminium chloride (0·4 g.) in carbon disulphide (5 ml.) was stirred at 20° for 4 hr. Carbon disulphide was distilled off and a mixture of ice and concentrated hydrochloric acid was added to the dark red viscous residue.

The mixture was diluted with water, extracted with ether and the ethereal solution was washed with sodium bicarbonate solution. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off to give the crude acetyl compound (0·17 g.) which was purified by recrystallisation from light petroleum (b.p. 40-60°) and sublimation (30°/0·01 mm.) to give a mixture of 2-acetyl- and 3-acetyl-4,5,6,7-tetrafluorobenzo[b]furan m.p. 43-51°. (Found: C, 51·9; H, 1·74; F, 33·1. $C_{10}H_4F_4O_2$ requires C, 51·7; H, 1·72; F, 32·8%). The ^1H n.m.r. spectrum showed three areas of absorption at τ 1·6 (singlet), τ 2·4 (doublet) and τ 7·4 (singlet). The intensity of the high field peak (CH_3) was three times the sum of the intensities of the two low field peaks (furan ring protons), and the relative intensity of the two low field peaks was approximately 1(1·6τ) : 6(2·4τ).

Attempted Formylation of 4,5,6,7-Tetrafluorobenzo[b]furan. (Vilsmeyer Reaction). 4,5,6,7-Tetrafluorobenzo[b]furan (0·5 g.), phosphorus oxychloride (0·5 g.), and N,N'-dimethylformamide (2 ml.) were heated at 100° for 3 hr. during which time the reaction mixture became dark brown. After cooling, the reaction mixture was poured into an aqueous solution of sodium acetate and extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off. Volatile material in the residue was separated by vacuum transfer, and analytical g.l.c. and infra-red spectrum showed that this was 4,5,6,7-tetrafluorobenzo[b]furan.

Attempted Acetylation of 4,5,6,7-Tetrafluorobenzo[b]furan:- 4,5,6,7-Tetrafluorobenzo[b]furan (0·5 g.) acetic anhydride (0·3 g.) and boron trifluoride etherate (0·07 g.) were heated at 50° for 10 min. and then stirred at room temperature for 1 hr. Water was added to the reaction mixture which was then extracted with ether. The ethereal solution was dried ($MgSO_4$) and the solvent distilled off. Volatile material in the residue was separated by vacuum transfer and analytical scale g.l.c. and infra-red spectrum showed that this was 4,5,6,7-tetrafluorobenzo[b]furan.

The Reaction of 2,3,5,6-Tetrafluoroanisole with Potassium Hydroxide in t-Butanol:- 2,3,5,6-Tetrafluoroanisole (5·0 g.), potassium hydroxide (1·7 g.) and t-butanol (50 ml.) were heated under reflux with stirring for 17 hr. Water (100 ml.) was added and t-butanol was distilled off. The remaining aqueous solution was extracted with ether, acidified, and the phenol which separated was extracted with ether. The ethereal solution was washed with water, dried ($MgSO_4$) and the solvent distilled off. Volatile material (0·74 g.) was removed from the residue by vacuum transfer. Analytical scale g.l.c. and infra-red spectrum of this material showed it to be mainly 2,3,5,6-tetrafluorophenol; two other peaks, of approximately equal area, with similar retention times (longer than 2,3,5,6-tetrafluorophenol) were shown on the chromatogram; the shorter retention time corresponded to that of 2,4,5-trifluoro-3-methoxyphenol.

Other Oxidation Reactions of 4,5,6,7-Tetrafluoro-2-methylbenzo[b]furan

(a) Potassium Permanganate:- 4,5,6,7-Tetrafluoro-2-methylbenzo[b]furan (0·4 g.) in dry acetone (3 ml.) was added to a solution of potassium permanganate (0·15 g.) in acetone (5 ml.) and the mixture was warmed to ca 40° until the purple colouration had disappeared (ca 20 min.). Water was added to the reaction mixture and acetone was distilled off. The aqueous solution was acidified with dilute sulphuric acid and a stream of sulphur dioxide was passed through the solution until it was decolourised. The solution was extracted with ether, and the ethereal solution was dried ($MgSO_4$) and the solvent distilled off. The residue was sublimed (50°/15 mm) to give 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan (0·23 g.) Further sublimation (60°/0·01 mm.) gave 2,3,4,5-tetrafluoro-6-hydroxybenzoic acid (0·03 g.), identified by comparison of its infra-red spectrum with that of an authentic sample.

(b) Selenium Dioxide. (i) in Ethanol:- 4,5,6,7-Tetrafluoro-2-methylbenzo[b]furan (1·0 g.), selenium dioxide (1·0 g.) and ethanol (16 ml. 95%) were heated under reflux for 18 hr. After cooling, the reaction mixture was poured into water and extracted with ether. The ethereal solution was washed with water, dried ($MgSO_4$) and the solvent was distilled off. Volatile material (1·90 g.) was removed from the residue by vacuum transfer. Analytical scale g.l.c. showed this material to be a mixture of ethanol and 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan.

(ii) In Dioxan:- The reaction was carried out as described in (i), but 95% dioxan was used in place of 95% ethanol. Again, analytical scale g.l.c. showed that no reaction had occurred.

The Reaction of 4,5,6,7-Tetrafluorobenzo[b]furan in Concentrated Sulphuric Acid:- 4,5,6,7-Tetrafluorobenzo[b]furan (0·1 g.) and sulphuric acid

(15 ml. 36N) were shaken together occasionally for 15 min. until a deep violet colour had developed. The mixture was then set aside at room temperature for 3 hr. The mixture was poured into water, extracted with ether, and the ethereal solution was dried ($MgSO_4$) and distilled to give a residue which was sublimed (90°/0·01 mm.). The mass spectrum of the sublimate showed a major peak at 380 corresponding to a dimer of 4,5,6,7-tetrafluorobenzo[b]furan.

INFRA-RED SPECTRA

The spectra of all liquids were measured as contact films in potassium bromide cells, except that of 2-bromomethyl-4,5,6,7-tetrafluorobenzo[b]furan (spectrum No. 40) which was measured using sodium chloride cells. The spectra of all solids were measured as potassium bromide discs, except that of 2'-methoxycarbonyl-3',4',5',6'-tetrafluorophenyl 2,3,4,5-tetrafluoro-6-hydroxybenzoate (spectrum No.39) which was measured as a nujol mull in sodium chloride cells.

Spectrum	Compound
1.	2,3,4,5-Tetrafluorophenol
2.	2-Bromo-3,4,5,6-tetrafluorophenol
3.	Ethyl Pentafluorophenoxyacetate
4.	Pentafluorophenoxyacetic Acid
5.	Ethyl 2,3,5,6-Tetrafluorophenoxyacetate
6.	2,3,5,6-Tetrafluorophenoxyacetic Acid
7.	Ethyl 2,3,4,5-Tetrafluorophenoxyacetate
8.	2,3,4,5-Tetrafluorophenoxyacetic Acid
9.	2,3,4,5-Tetrafluorophenoxyacetyl Chloride
10.	2-(2',3',5',6'-Tetrafluorophenoxy)ethanol
11.	2-(2',3',4',5'-Tetrafluorophenoxy)ethanol
12.	2,3,5,6-Tetrafluorophenoxyacetaldehyde Diethylacetal
13.	2,3,4,5-Tetrafluorophenoxyacetaldehyde Diethylacetal
14.	2',3',4',5'-Tetrafluorophenyl 2,3,4,5-Tetrafluorophenoxyacetate
15.	2',3',4',5'-Tetrafluorophenoxymethyl 2,3,4,5-Tetrafluorophenoxyacetate

16. 2,3,4,5-Tetrafluoro-6-hydroxybenzoic Acid
17. Methyl 2,3,4,5-Tetrafluoro-6-hydroxybenzoate
18. Ethyl 2,3,4,5-Tetrafluoro-6-hydroxybenzoate
19. Ethyl 6-Ethoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate
20. Methyl 6-Methoxycarbonyl-2,3,4,5-tetrafluorophenoxyacetate
21. 6-Carboxy-2,3,4,5-tetrafluorophenoxyacetic Acid
22. 2-Ethoxycarbonyl-4,5,6,7-tetrafluoro-3-hydroxybenzo[b]furan
23. 4,5,6,7-Tetrafluoro-2,3-dihydrobenzo[b]furan-3-one
24. 4,5,6,7-Tetrafluorobenzo[b]furan
25. Ethyl 2-Bromo-3,4,5,6-tetrafluorophenoxyacetate
26. ω-(2,3,4,5-Tetrafluorophenoxy)acetophenone
27. 3-Acetoxy-4,5,6,7-tetrafluorobenzo[b]furan
28. 4,5,6,7-Tetrafluorobenzo[b]furan-2-carboxylic Acid
29. 2-Acetyl (85%) and 3-Acetyl (15%) -4,5,6,7-tetrafluorobenzo[b]furan
30. 4,5,6,7-Tetrafluoro-2-formylbenzo[b]furan
31. 2,4,5-Trifluoro-3-methoxyphenol
32. 2,4,5-Trifluoro-3-methoxyphenoxyacetic Acid
33. 4,5,7-Trifluoro-6-methoxy-2,3-dihydrobenzo[b]furan-3-one
34. 4,5,7-Trifluoro-6-methoxybenzo[b]furan
35. Methyl 2,3,4,5-Tetrafluoro-6-methoxybenzoate
36. Methyl 2,3,5,6-Tetrafluoro-4-methoxybenzoate
37. 3,5,6-Trifluoro-2-hydroxy-4-methoxybenzoic Acid

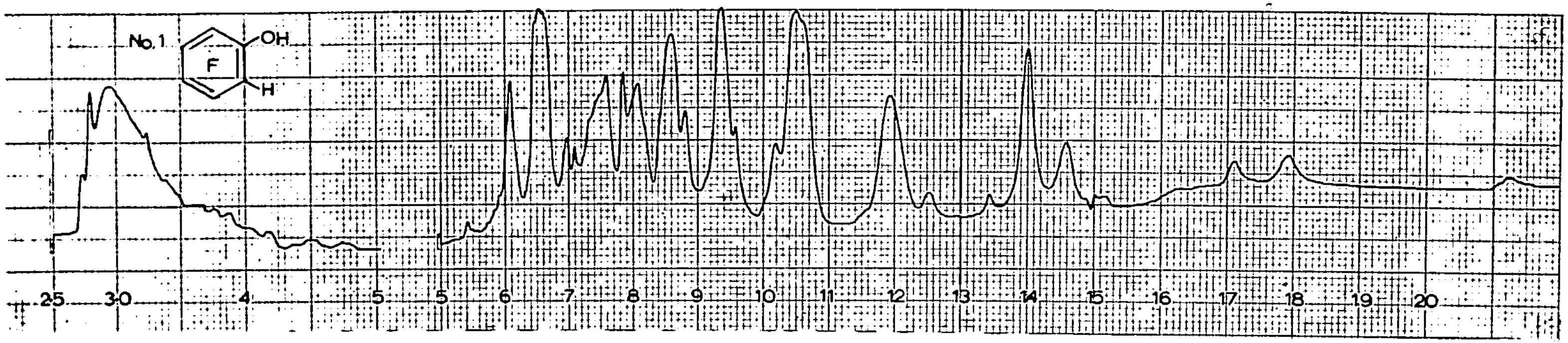
38. 2-Benzylidene-4,5,6,7-tetrafluoro-2,3-dihydrobenzo[b]furan-3-one

39. 2'-Methoxycarbonyl-3',4',5',6'-tetrafluorophenyl 2,3,4,5-Tetrafluoro-6-hydroxybenzoate

40. 2-Bromomethyl-4,5,6,7-tetrafluorobenzo[b]furan

41. Methyl 3,5,6-Trifluoro-2,4-dimethoxybenzoate

42. 4,5,6,7-Tetrafluoro-2-methylbenzo[b]furan[17].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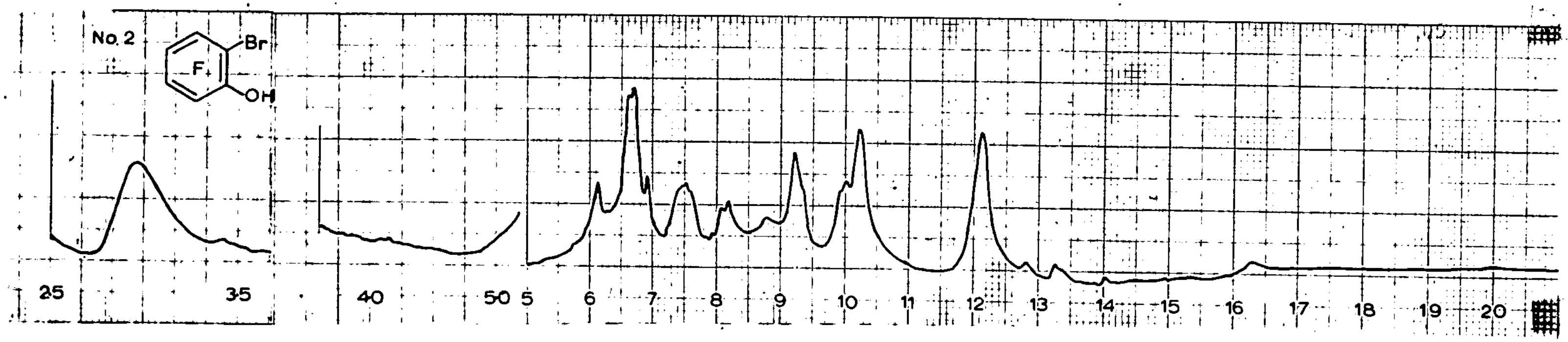
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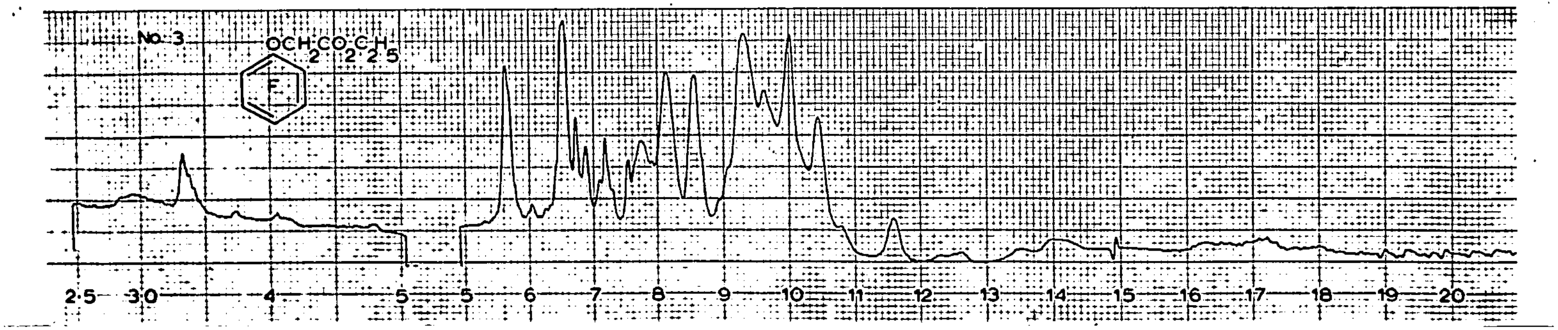
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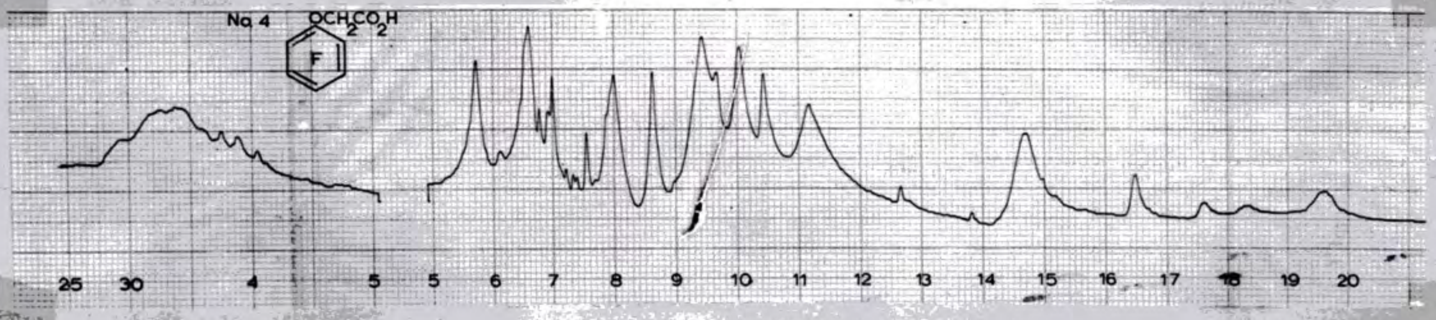
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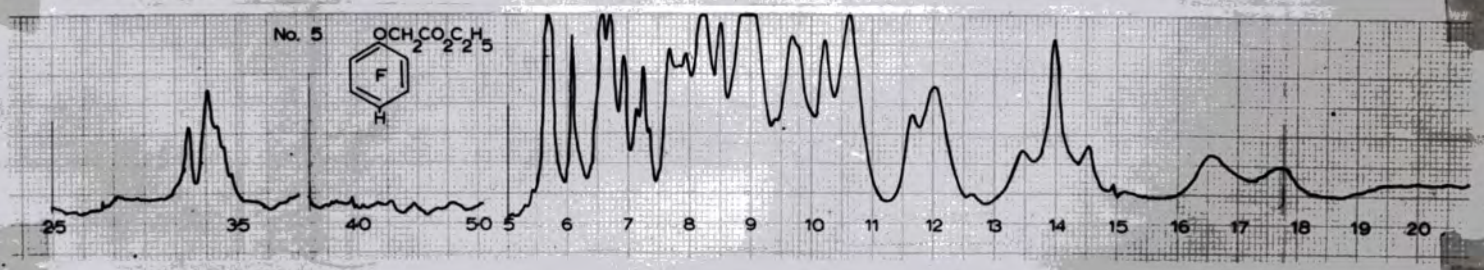
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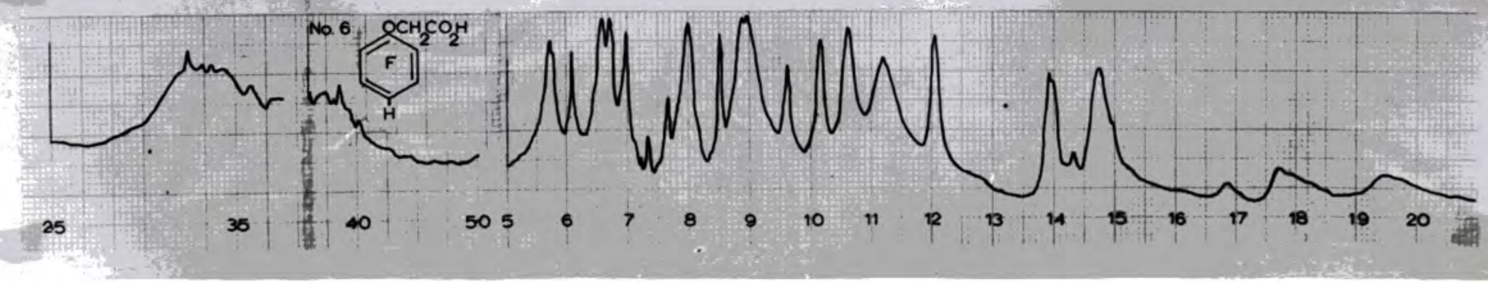
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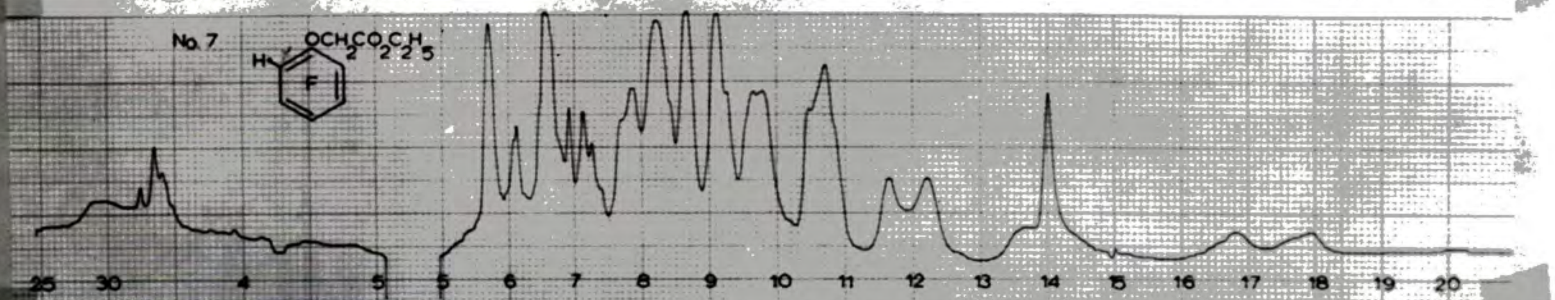
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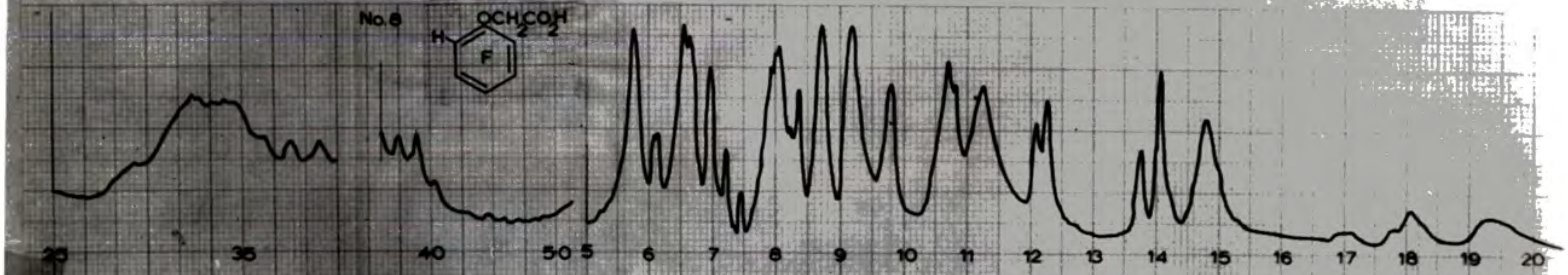
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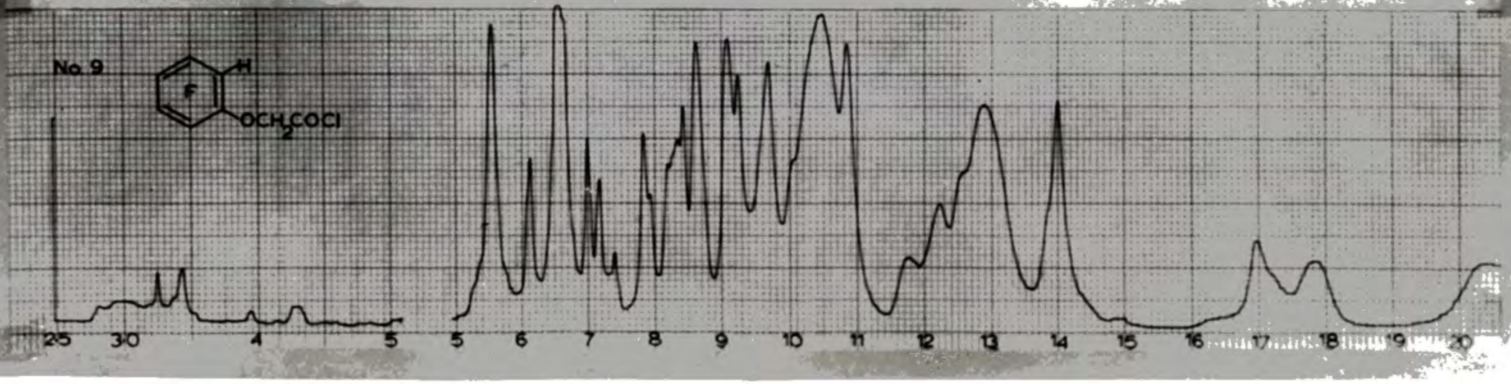
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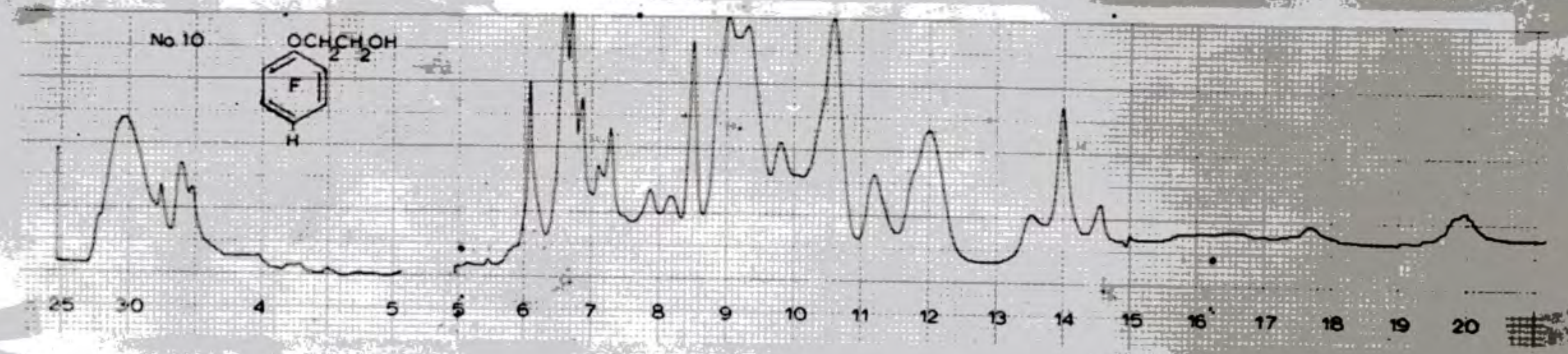

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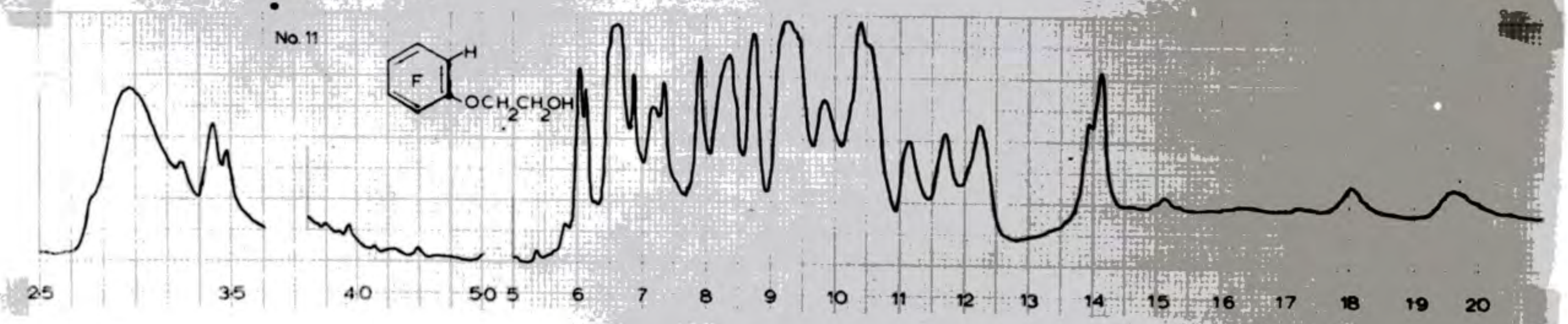

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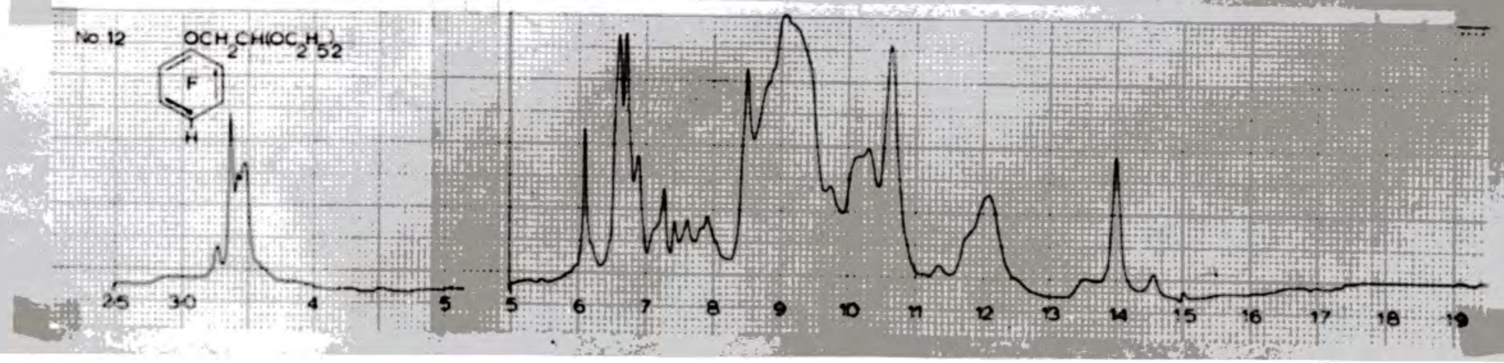

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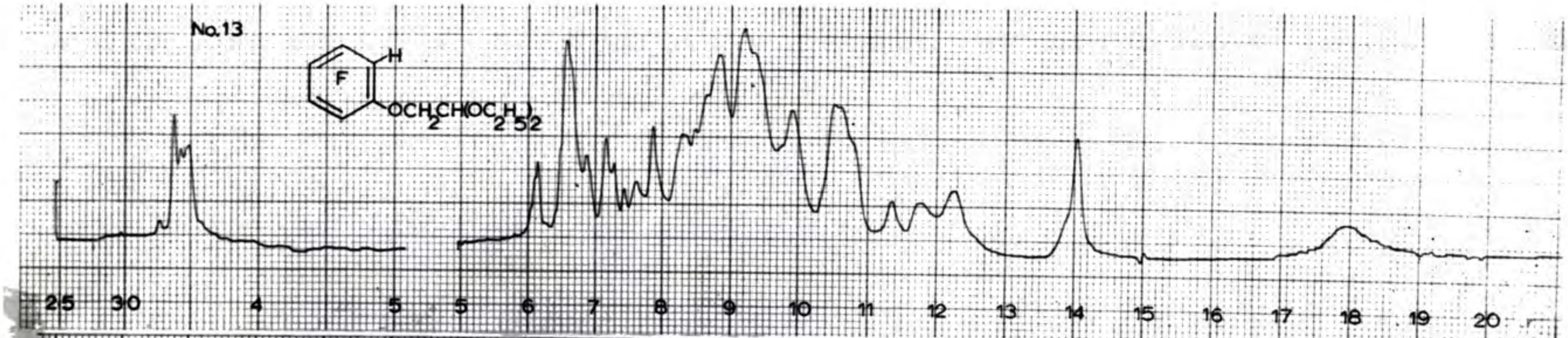

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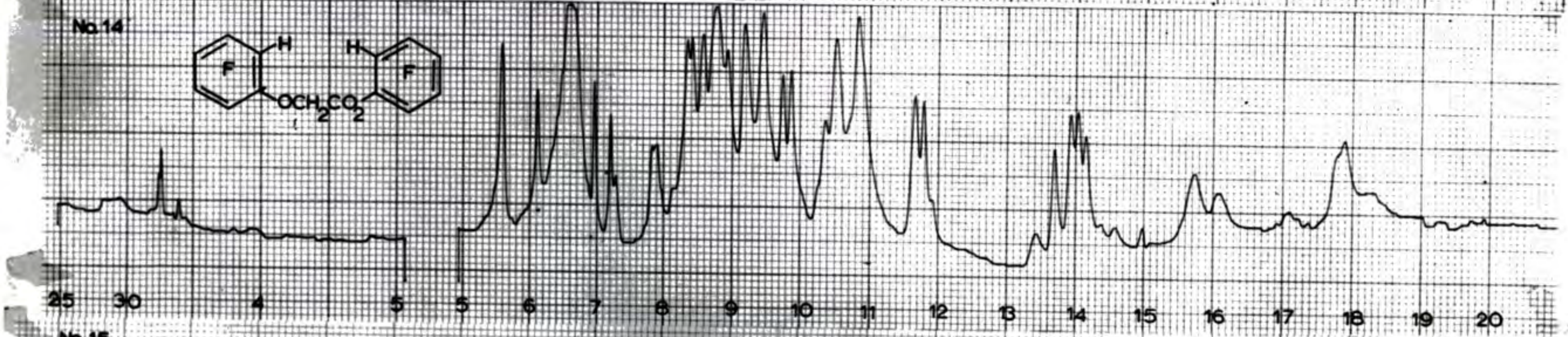

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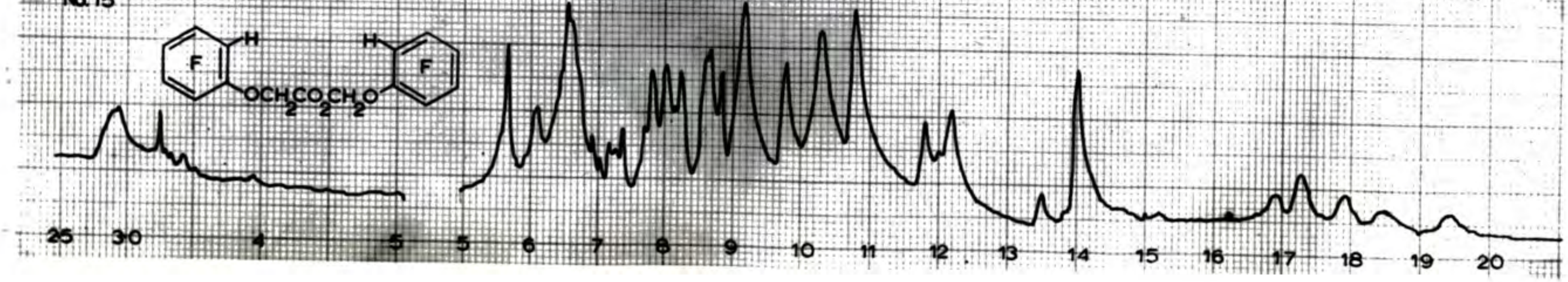

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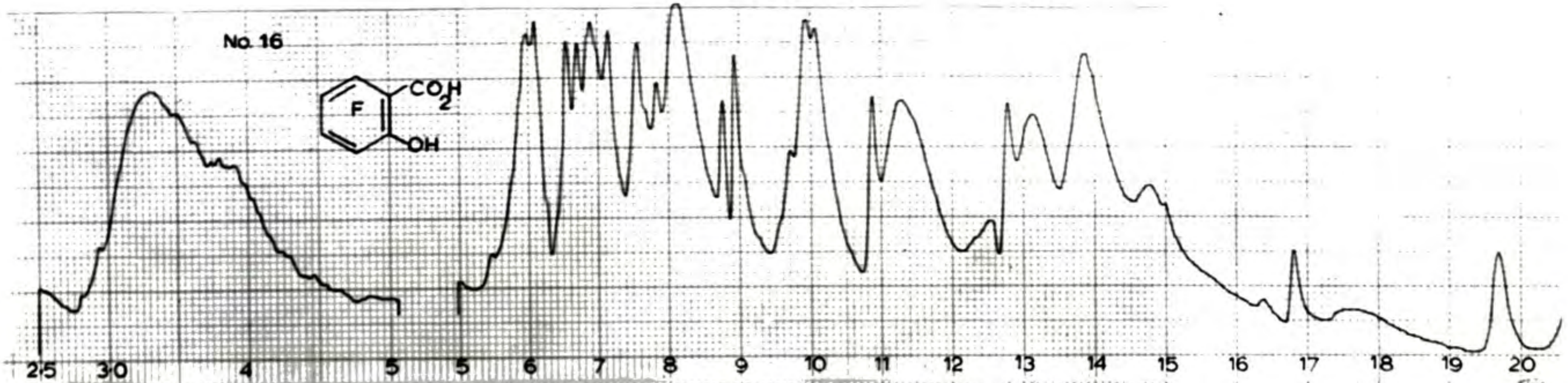

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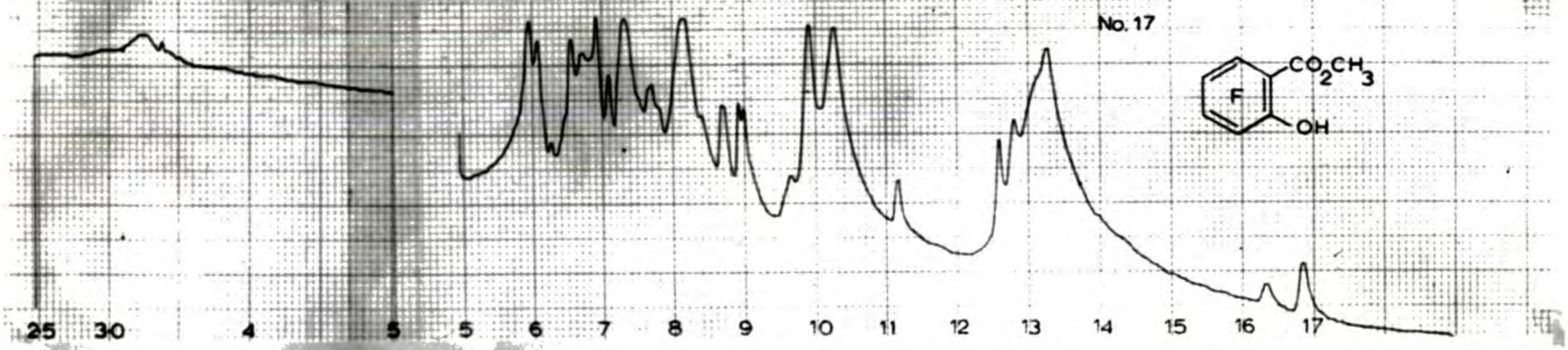

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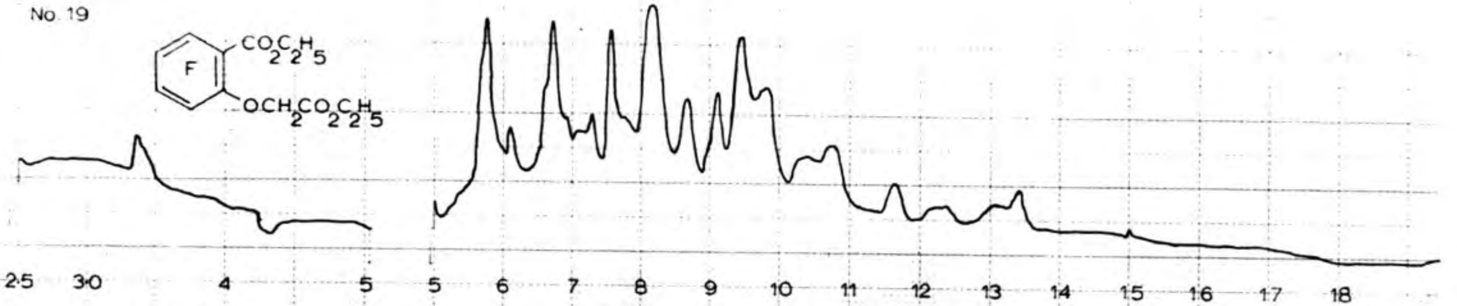

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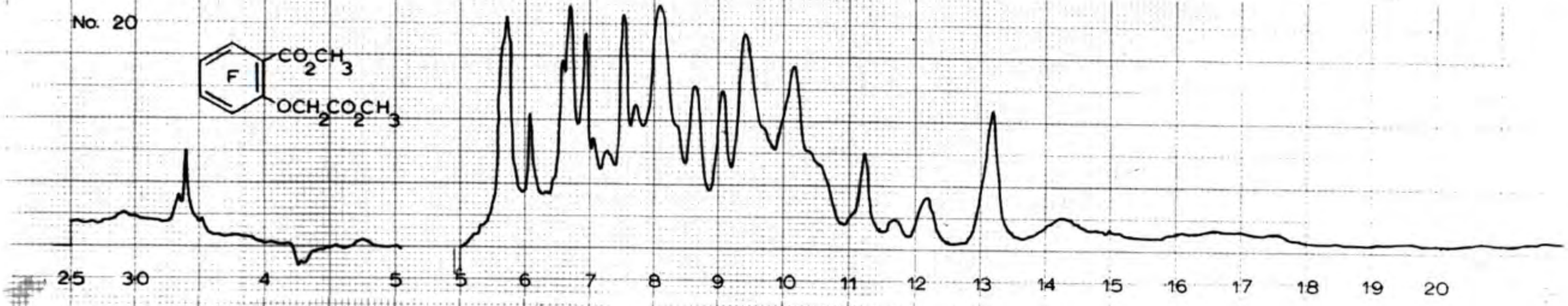

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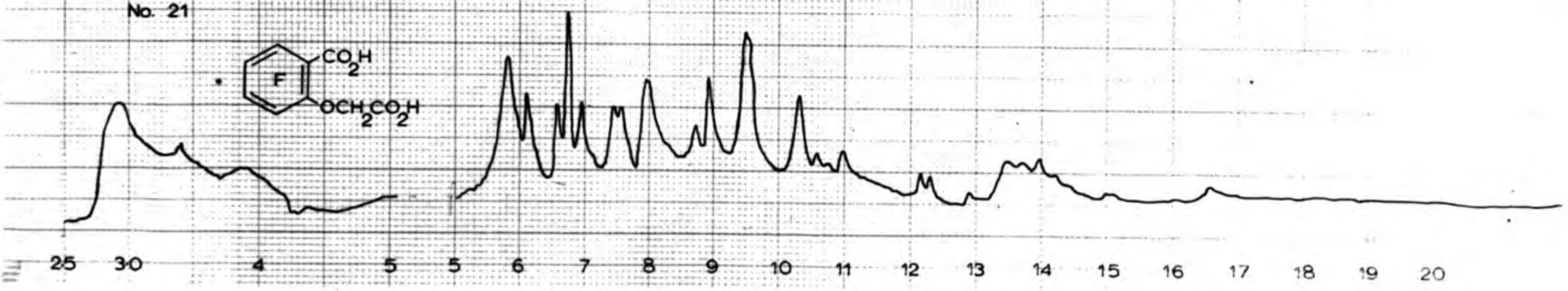

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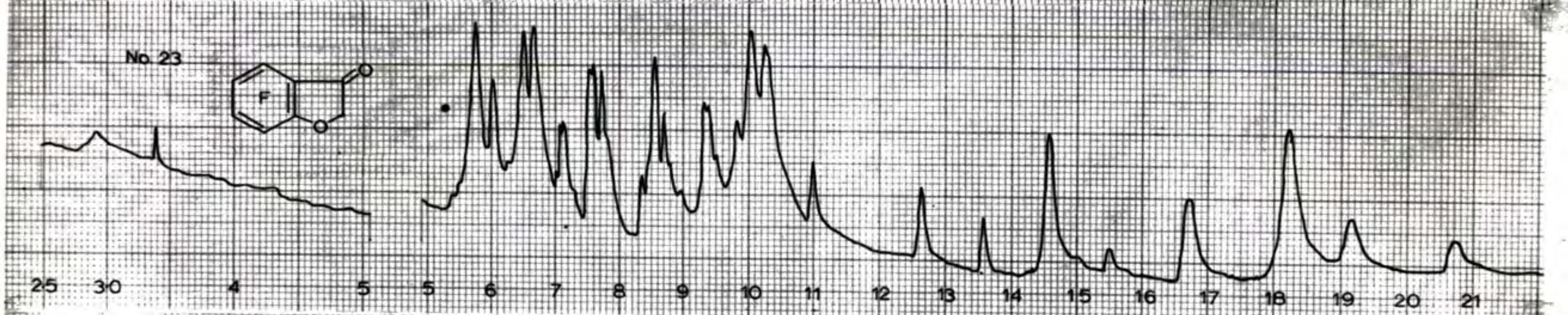

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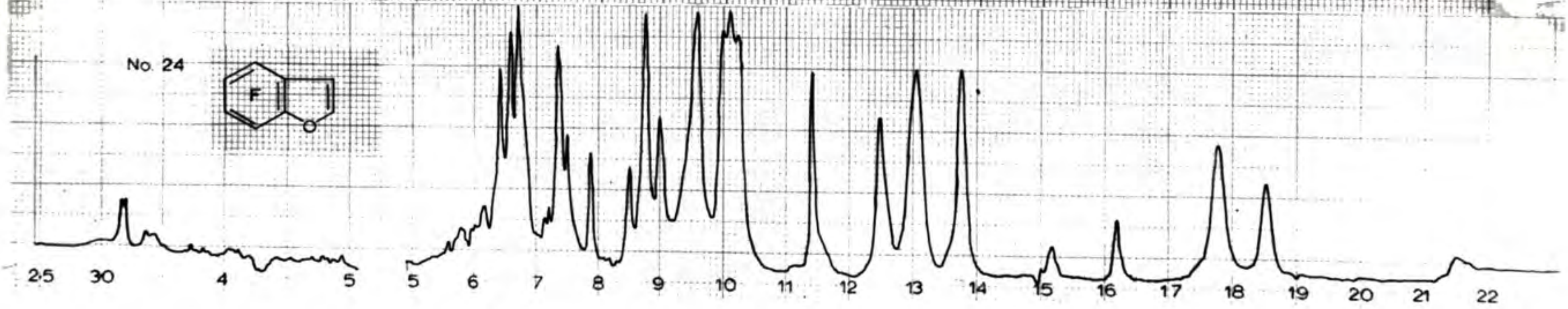

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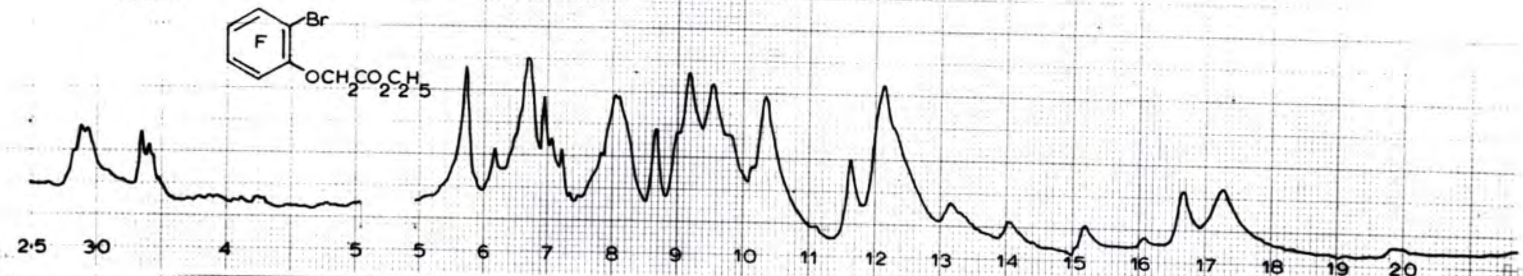

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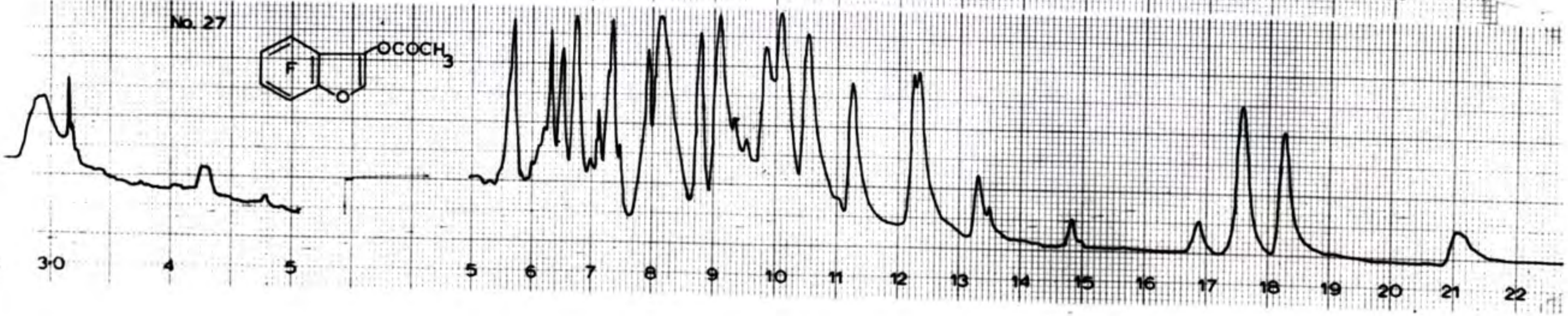

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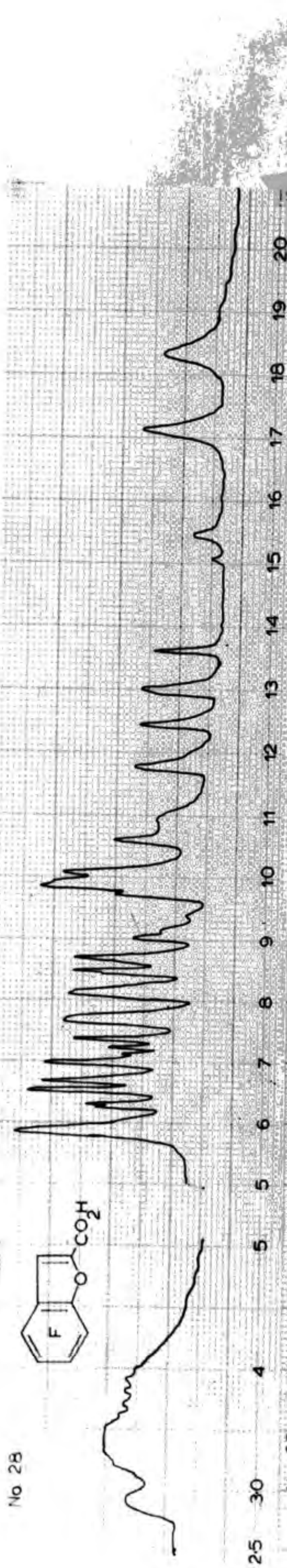

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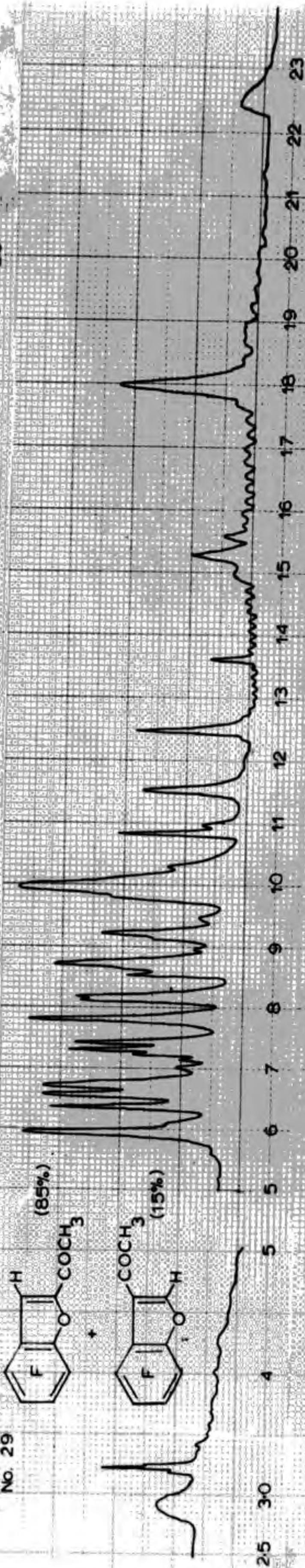

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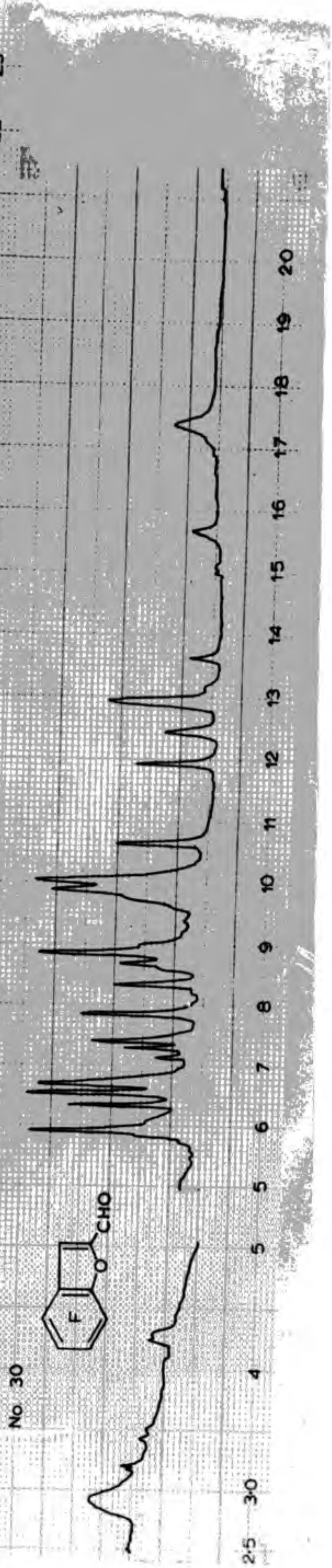

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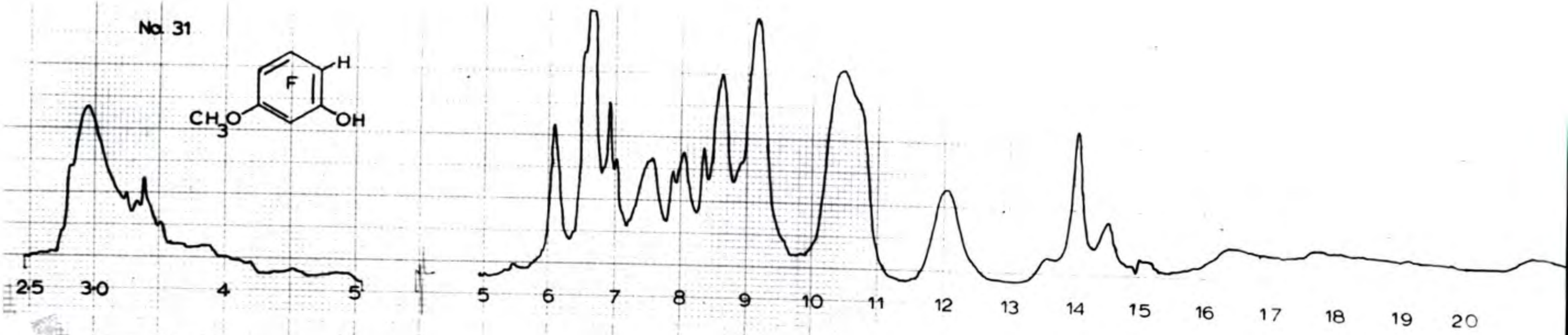

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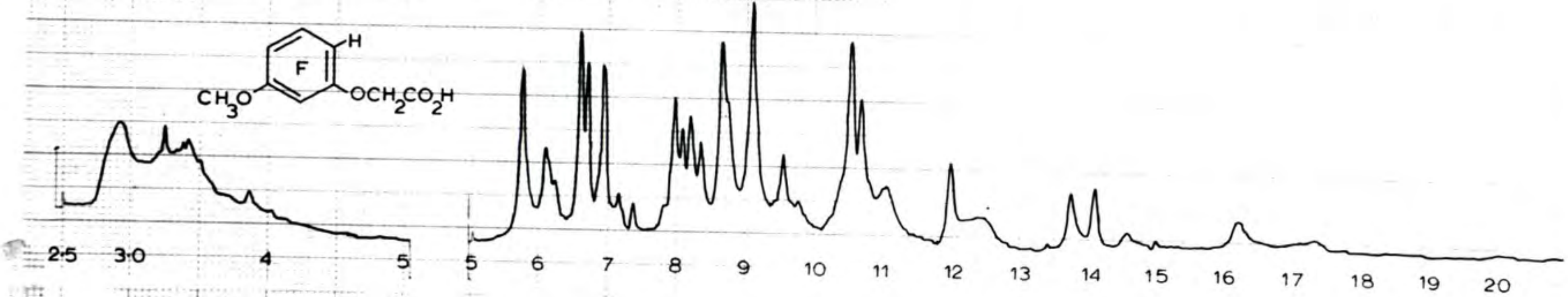

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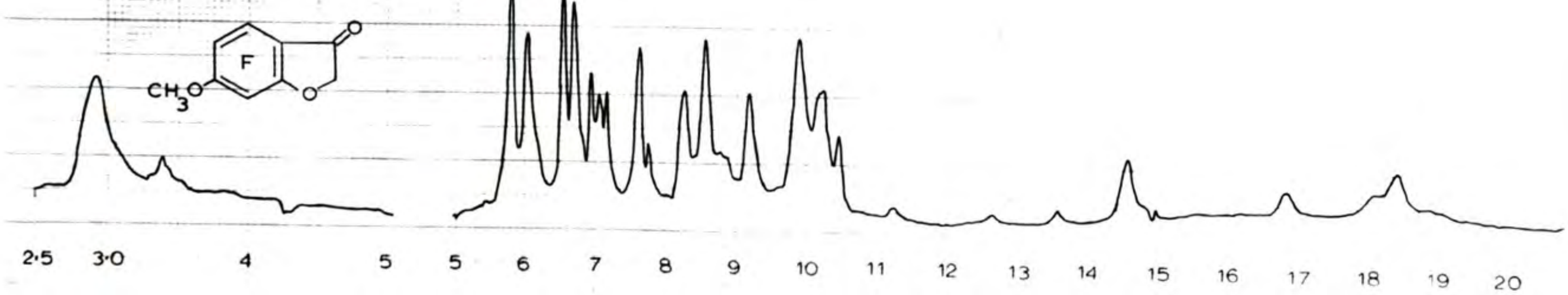

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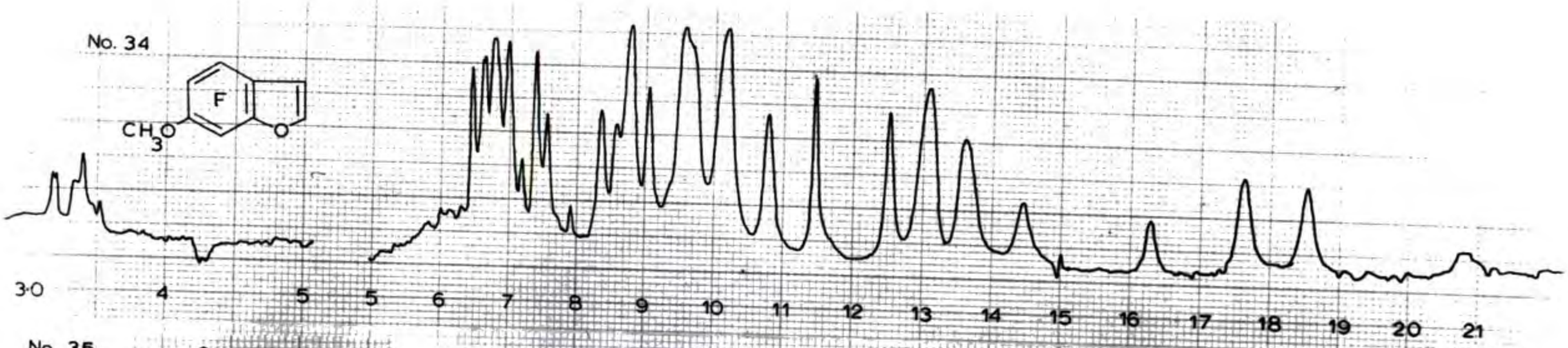

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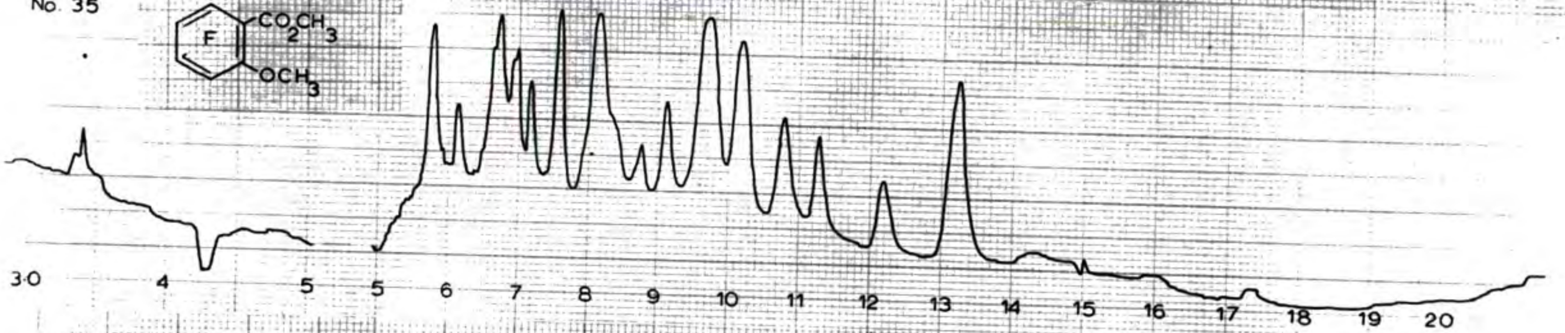

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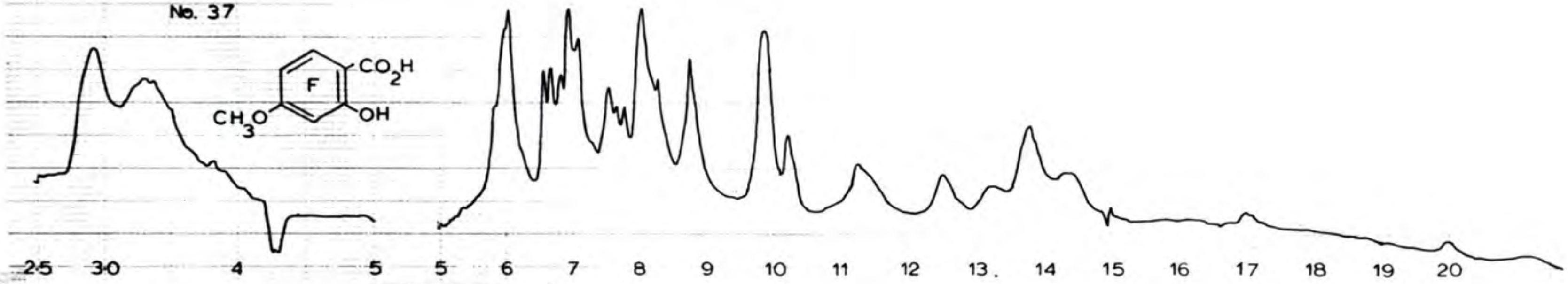
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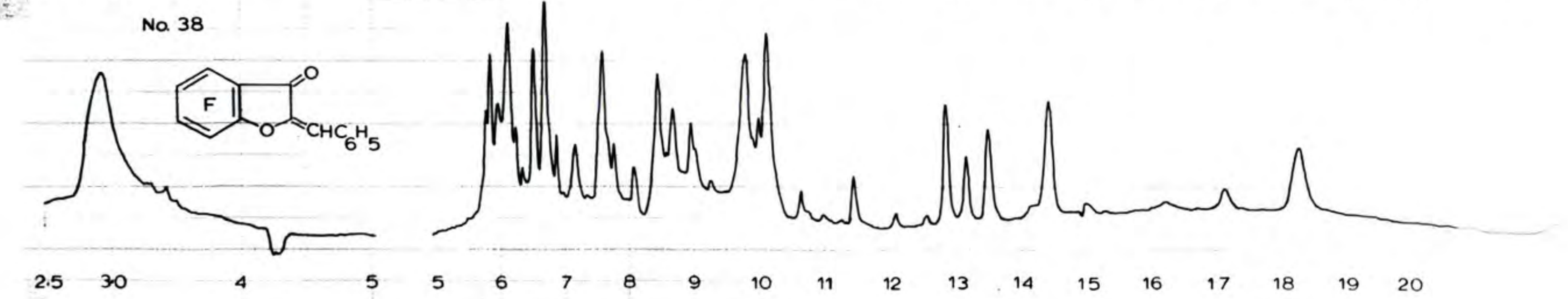
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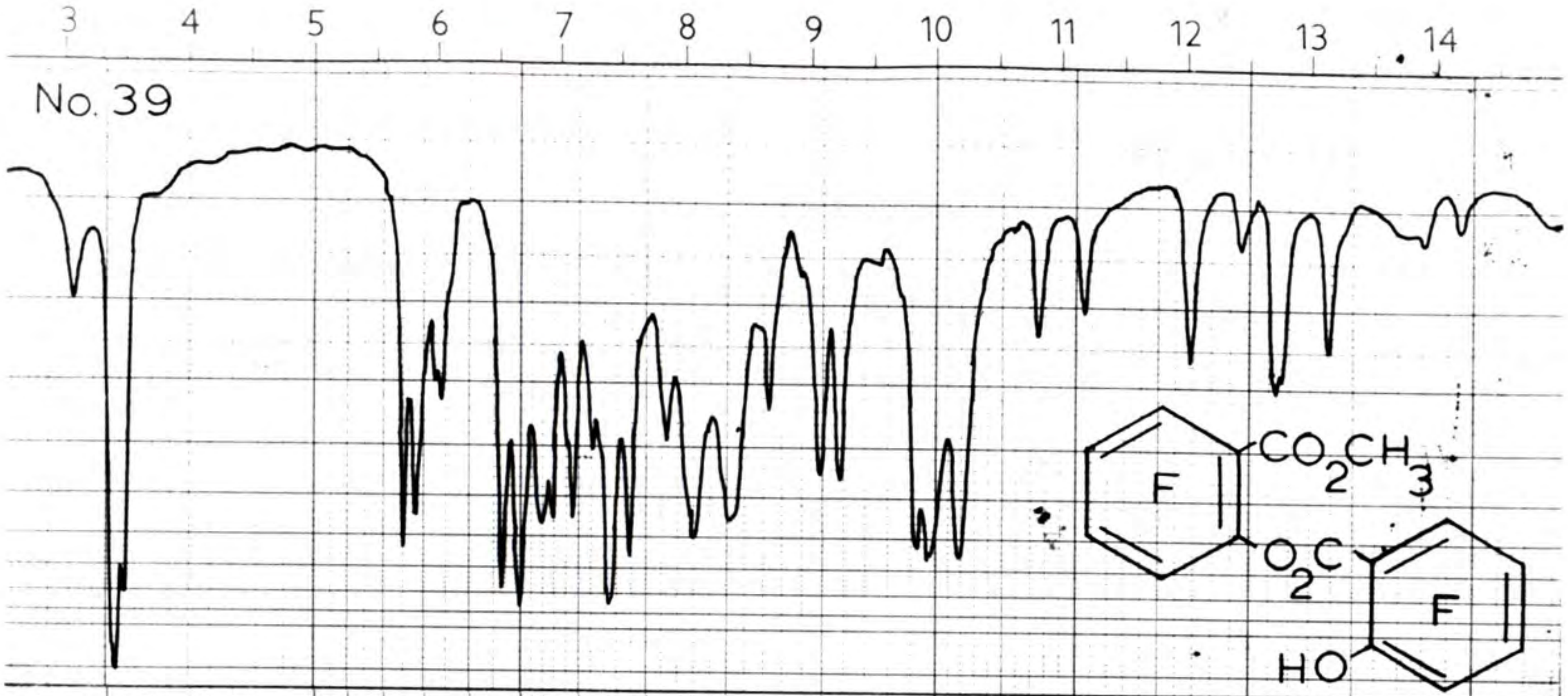

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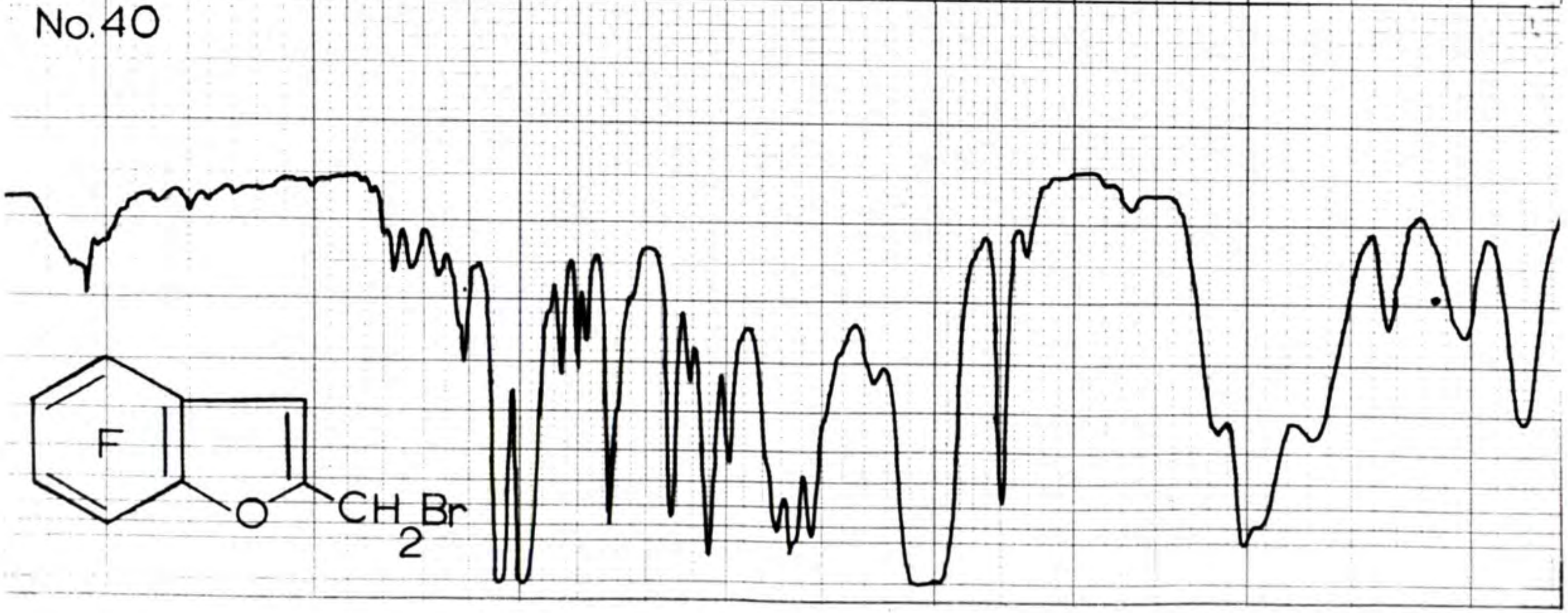

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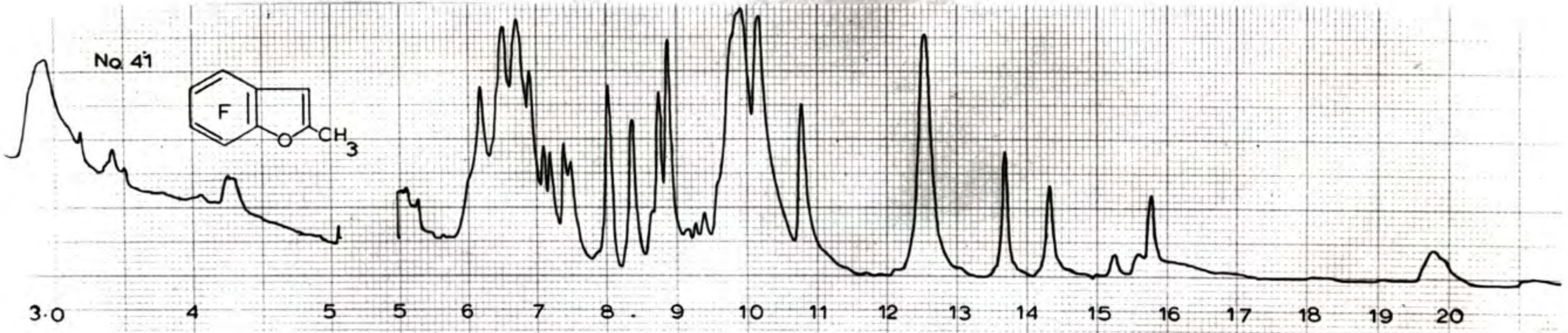
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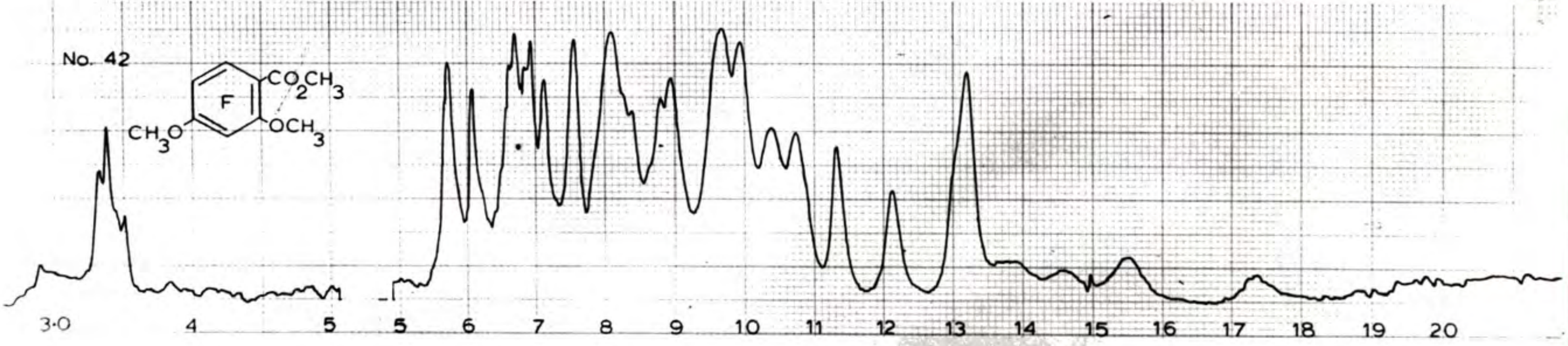
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1. J.C. Tatlow, Endeavour, 1963, 13, 95.
2. J. Burdon and J.C. Tatlow, Adv.in Fluorine Chem., 1960, 1, 129.
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