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A STUDY OF THE THERMALLY-INDUCED CYCLISATIONS  
OF SOME POLYFLUOROAROMATIC HYDRAZONES LEADING  
TO FISCHER INDOLE PRODUCTS

by

FRANK DOMINIC BENKE, B.Sc.

(Grey College)

A thesis submitted to the University of Durham for the

Degree of Master of Science

1983



13. APR. 1984

TO MY PARENTS

ACKNOWLEDGEMENTS

The author is indebted to Dr.G.M.Brooke for his constant help and encouragement during the supervision of this work.

Also I would like to thank members of Lab. 25 for many helpful discussions, and to the many laboratory technicians for their help and co-operation.

MEMORANDUM

The work reported in this thesis was carried out in the Chemistry Department of the University of Durham between October 1982 and July 1983. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

NOTES TO THE READER

Throughout this thesis a number of abbreviations have been used regularly, these are : infra-red spectroscopy (i.r.) ; nuclear magnetic resonance spectroscopy (n.m.r.) ; thin layer chromatography (t.l.c.) ; tetrahydrofuran (THF) and N,N-dimethylformamide (DMF).

ABSTRACT

Previously acetophenone 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazone and acetophenone pentafluorophenylhydrazone were reported to react in tetralin at reflux temperature to give among the products 4,5,6,7,8,9-hexafluoro-2-phenylbenz[e]indole and 4,5,6,7-tetrafluoro-2-phenylindole respectively. These are typical Fischer indole products, and yet are formed by the surprising loss of ortho-fluorine rather than ortho-hydrogen.

The work contained in this thesis is concerned with exploring the generality of this reaction : polyfluoroaromatic hydrazones with a variety of substituents have been synthesized, and their response to cyclization investigated.

The thesis is divided into three main sections. Chapters one, two, three, and four deals with the literature on the synthesis of partially fluorinated heterocyclic compounds. Chapter five discusses the synthesis of some new partially fluorinated indoles, whilst chapter six contains the experimental detail for this work.

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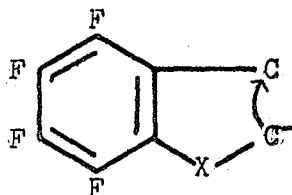
## CHAPTER 1

### THE PREPARATION OF PARTIALLY FLUORINATED BENZO[b]FURAN, BENZO[b]THIOPHEN AND INDOLE DERIVATIVES BY CONVENTIONAL METHODS

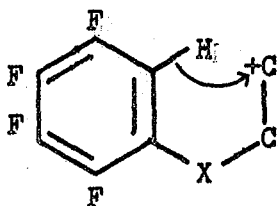
### 1.1 Introduction

There are three main procedures for forming cyclic systems; all have the benzene nucleus already formed with one or more side-chains. Ring closure takes place by either nucleophilic or electrophilic attack with displacement of an ortho-hydrogen. Essentially they can be envisaged as :-

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

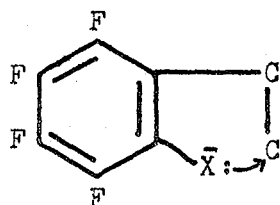


- B. Ring closure between  $C_{(3)}$  and the benzene nucleus by an electrophilic substitution of the hydrogen atom ortho to the heteroatom.



- C. Linkage of the heteroatom to  $C_{(2)}$  by a nucleophilic attack.

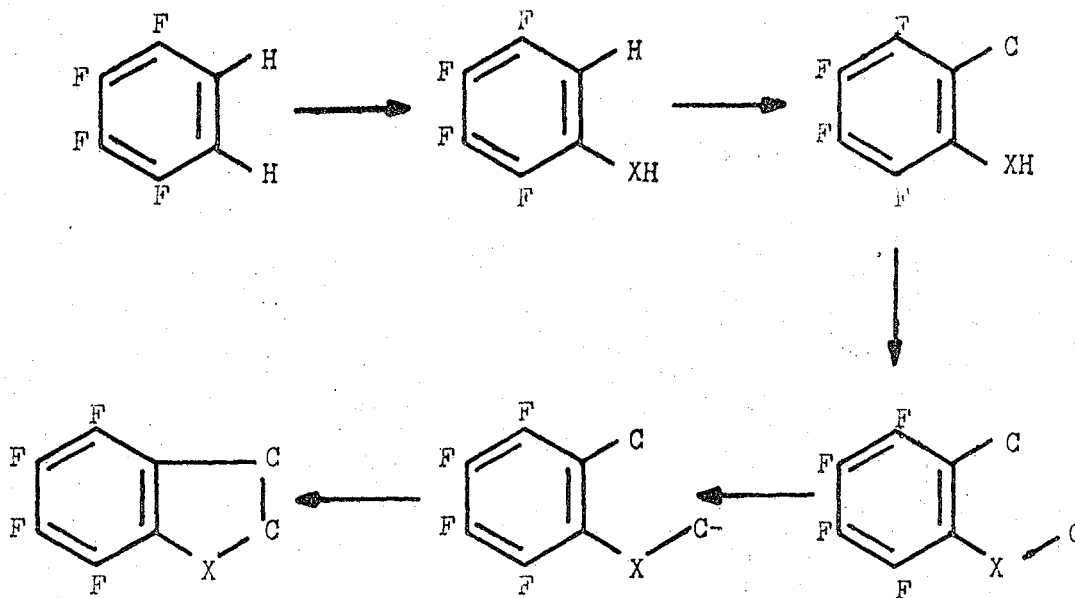




Each of the above synthetic models will be dealt with individually.

## 1.2 ROUTE A Ring Closure Between C(2) and C(3) by a Nucleophilic Attack on C(3)

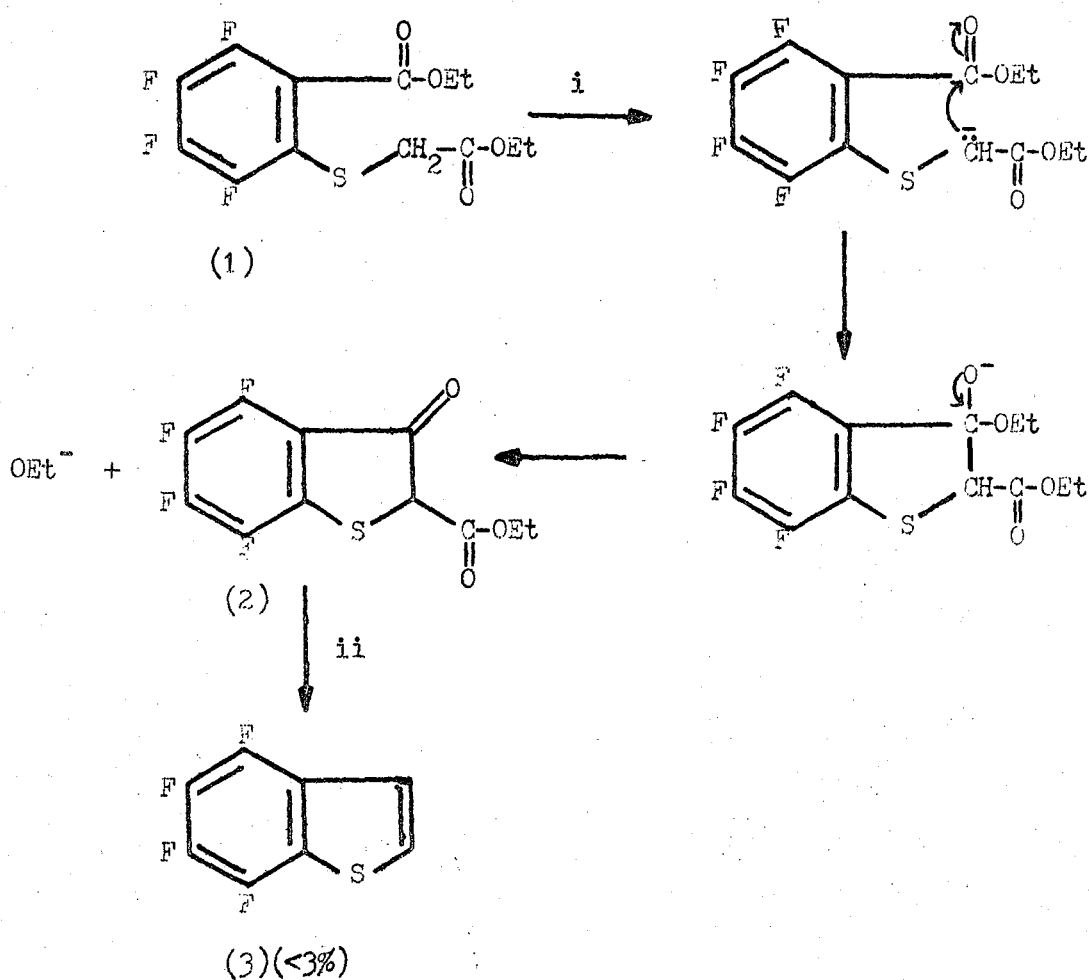
Starting materials which are to be cyclised by this route require two side-chains in positions ortho- to each other and this is one of the most important methods with hydrocarbon compounds. The application of this synthesis to fluorine containing heterocycles suffers from the three step route required to secure cyclisable starting materials (Scheme 1).



Scheme 1

However, a typical starting material is (1) in which an active methylene

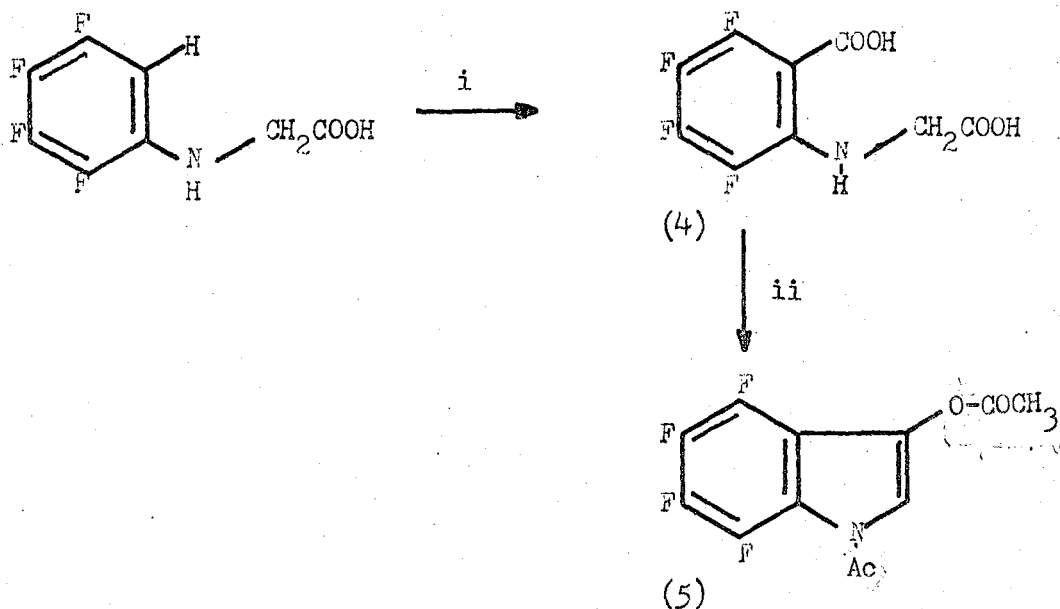
group reacts under base catalysis with a carbonyl group (Scheme 2). Treatment of the cyclized material (2) in acetic acid, sulphuric acid and water afforded the 4,5,6,7-tetrafluorobenzo[b]thiophen (3) in low yield (<3%).<sup>1</sup>



Scheme 2 Reagents : i, NaH, THF  
 ii, Zn, AcOH, H<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>O

Brooke et al.<sup>2</sup> reported the synthesis of crude N-acetyl-3-acetoxy-4,5,6,7-tetrafluoroindole (5) in very low yield from 6-carboxy-N-(2,3,4,5-tetrafluorophenyl)glycine (4) by reaction with sodium acetate in acetic anhydride (Scheme 3).



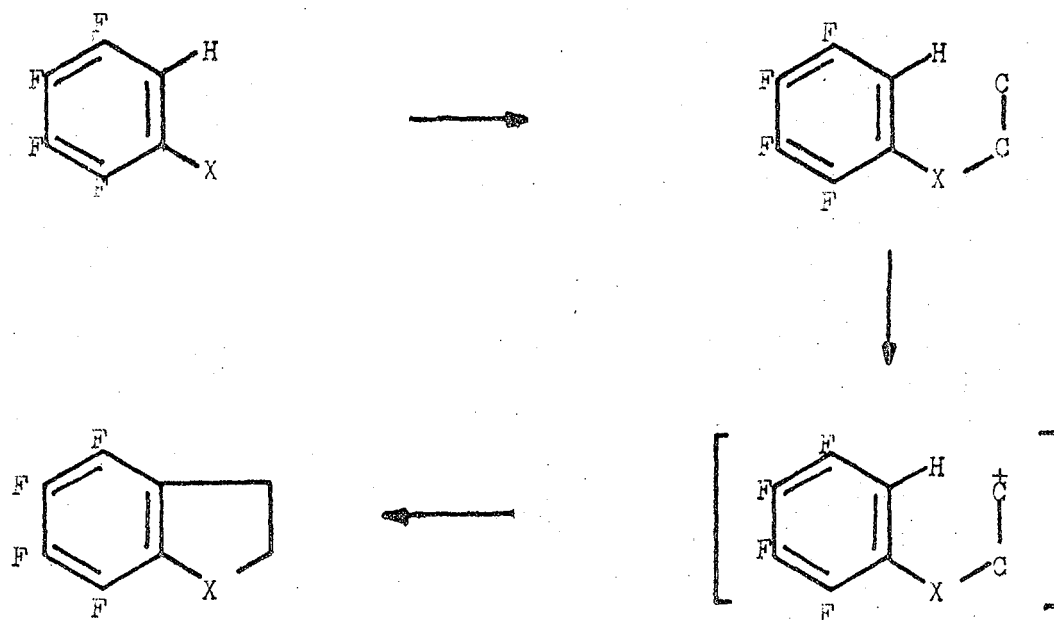


Scheme 3 Reagents : i, n-BuLi/CO<sub>2</sub>  
ii, NaOAc/Ac<sub>2</sub>O

Analogous oxygen compounds also underwent a similar cyclization to give the benzo[b]furan derivatives.<sup>3</sup>

1.3 ROUTE B      Ring Closure between C(3) and the Benzene Nucleus by  
an Electrophilic Substitution of the Hydrogen Atom ortho-  
to the Heteroatom

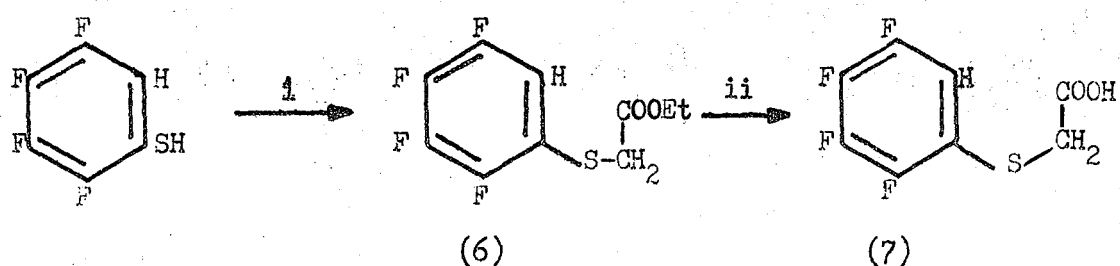
This is another widely used method and can be schematically represented for a partially fluorinated substrate as follows (Scheme 4) :



Scheme 4

The addition of two further carbon atoms onto the heteroatom is required.

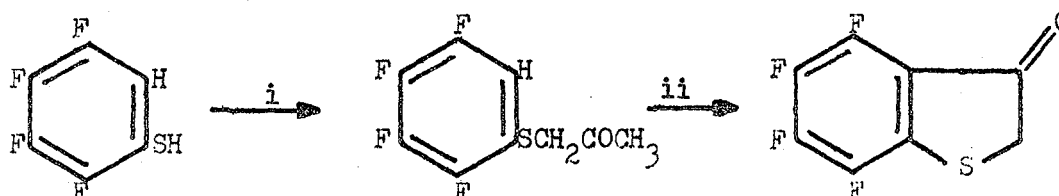
A suitable precursor is (7), formed by the reaction of 2,3,4,5-tetrafluorothiophenol and ethyl chloroacetate in pyridine followed by hydrolysis with 50% sulphuric acid (Scheme 5) :



Scheme 5 Reagents : i,  $\text{ClCH}_2\text{CO}_2\text{Et}$  in pyridine, reflux  
ii, 50%  $\text{H}_2\text{SO}_4$

Cyclization of the thioacetic acid (7) has been attempted<sup>1</sup> using a number of reagents. With polyphosphoric acid, phosphorus pentoxide, anhydrous

hydrofluoric acid, concentrated sulphuric acid, and chlorosulphonic acid; the starting material was recovered in all cases. A successful cyclization using polyphosphoric acid has been reported by Chapman et al.<sup>4</sup> (Scheme 6).



Scheme 6 Reagents : i,  $\text{ClCH}_2\text{COCH}_3$ , pyridine, reflux  
ii, polyphosphoric acid

Brooke et al.<sup>2</sup> attempted a cyclization of 2,3,4,5-tetrafluorophenylglycine by this method, again using polyphosphoric acid, but without success. There are no reported reactions which use precursors containing oxygen as the heteroatom.

#### 1.4 ROUTE C Linkage of the Heteroatom to C(2) by a Nucleophilic Attack

This method of synthesis requires a precursor with a two-carbon atom side chain, ortho- to the heteroatom which carries the negative charge for nucleophilic attack.

An example is the reaction between o-mercapto-2-chlorostyrene and KOH/Ethanol to give benzo[b]thiophene<sup>5</sup> (Scheme 7).



Scheme 7

The reaction probably occurs via an addition-elimination process at the unsaturated carbon. No examples of this reaction have been reported in the case of partially fluorinated fused-ring heterocycles.

## CHAPTER 2

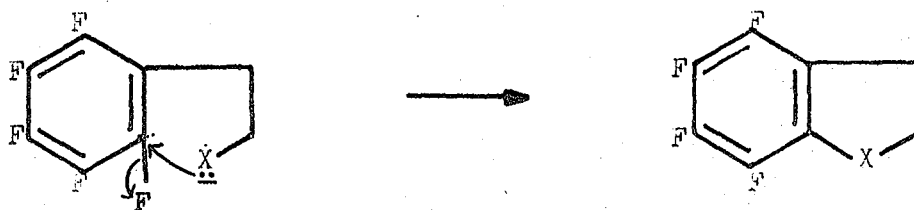
THE PREPARATION OF PARTIALLY FLUORINATED  
BENZO[b]FURAN, BENZO[b]THIOPHEN AND INDOLE  
DERIVATIVES VIA NUCLEOPHILIC AROMATIC  
DISPLACEMENT OF ORTHO-FLUORINE

## 2.1 Introduction

In an attempt to increase the overall yields of partially fluorinated heterocycles prepared by the conventional methods described in the previous chapter ( multistage reactions which essentially required 1,2,3,4-tetrafluorobenzene as the starting material ) special syntheses have been reported, all of which involve the nucleophilic displacement of ortho-fluorine from the aromatic nucleus of a  $C_6F_5$  - derivative.

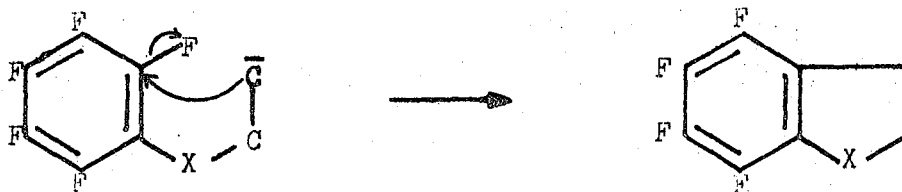
There are two synthetic pathways to fluorinated heterocyclic compounds depending on whether cyclization and displacement is effected by a carbanion or the heteroatom acting as a nucleophile.

- (i) This involves the linkage of the heteroatom to the benzene ring by a nucleophilic replacement of fluorine (Scheme 8) :



Scheme 8

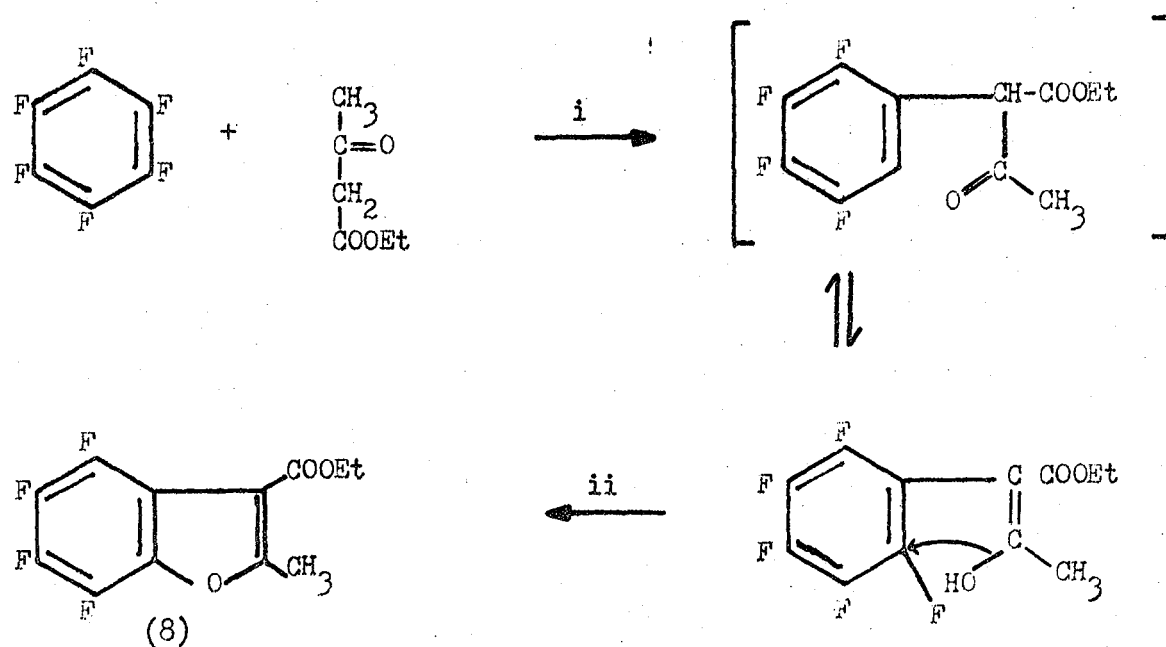
- (ii) A carbanion acts as the nucleophilic attacking species which displaces fluorine from the benzene nucleus (Scheme 9).



Scheme 9

## 2.2 ROUTE D Cyclisations Involving Nucleophilic Replacement of Fluorine by the Heteroatom

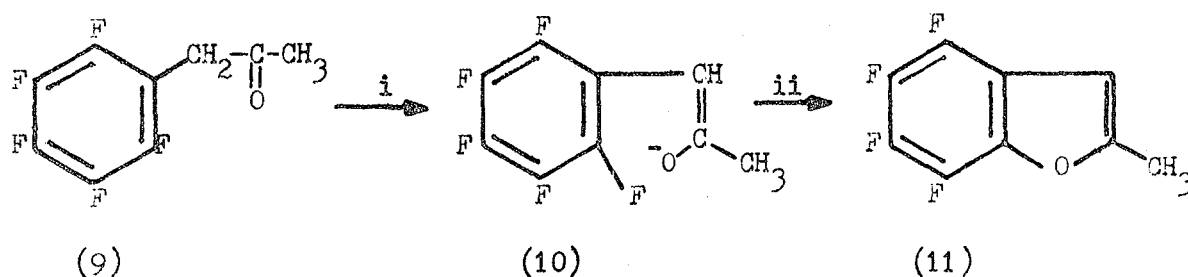
A team of Russian workers headed by Vorozhstov et al.<sup>6</sup> and Young<sup>7</sup> found that heating a mixture of ethyl acetoacetate, sodium hydride and hexafluorobenzene in approximately equal quantities in N,N-dimethylformamide gave a 30% yield of a 4,5,6,7-tetrafluorobenzo[b]furan derivative (8). Scheme 10 shows a plausible mechanism for this reaction in which the heteroatom acts the nucleophile.



Scheme 10 Reagents : i, NaH/DMF  
ii, NaOH/H<sub>2</sub>O

In 1968, Brooke<sup>8</sup> reported two cyclization reactions leading to benzo[b]furan compounds by hydride ion promotion in which the heteroatom definitely acts as the nucleophile. For example, treatment of the ketone (9) with sodium hydride in N,N-dimethylformamide at reflux temperature effected

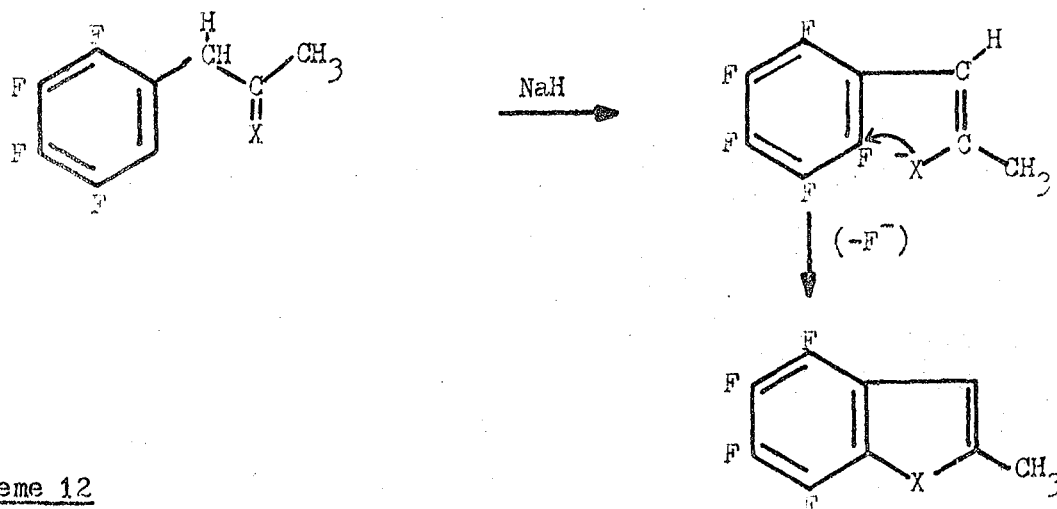
cyclisation to give 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan (11) in 33% yield (Scheme 11).



Scheme 11    Reagents : i, NaH,  $(-H_2)$   
                                  ii,  $(-F^-)$

Cyclisation proceeds through the enolate anion (10) by nucleophilic displacement of fluorine.

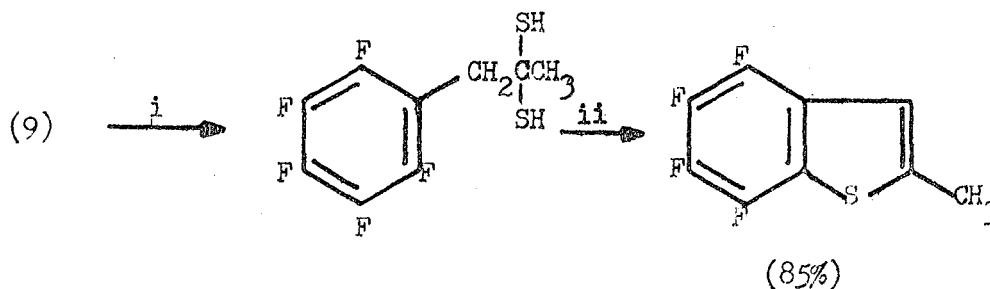
In the light of these hydride ion promoted cyclisations to give benzo[b]furan derivatives, there is a possibility of extending the scope of these reactions to include the preparation of other partially fluorinated heterocycles with sulphur and nitrogen as the heteroatom, to give benzo[b]thiophen and indole derivatives respectively. This is outlined in Scheme 12.<sup>8</sup>



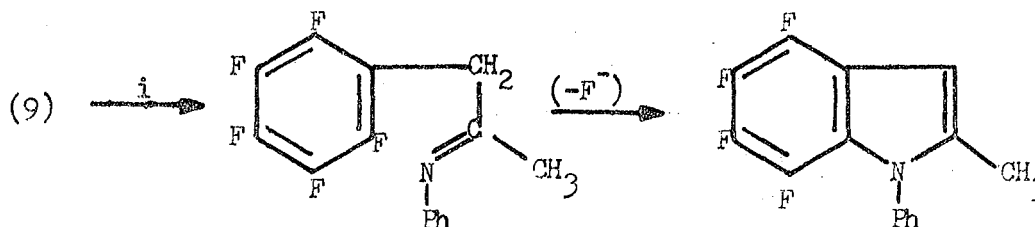
Scheme 12



Further work in this direction was carried out by Brooke<sup>9</sup> in which benzo[b]thiophen and indole derivatives were obtained by cyclizations involving either the sulphur or nitrogen as the nucleophile in displacing the ortho-fluorine as shown in schemes (13) and (14) respectively.

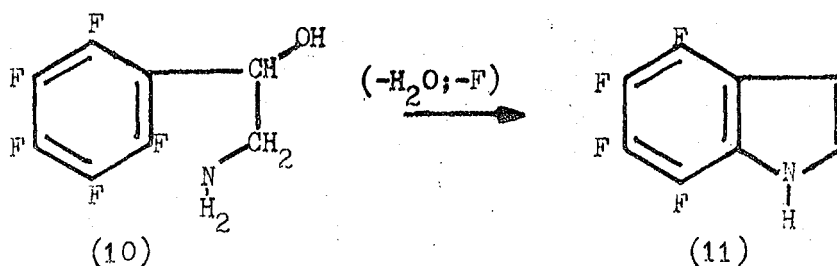


Scheme 13 Reagents : i,  $\text{H}_2\text{S}/\text{HCl}$  at  $0^\circ\text{C}$   
ii, dry pyridine,  $(-\text{F}^-)$



Scheme 14 Reagents : i, Aniline/ $[\text{ZnCl}_2]$

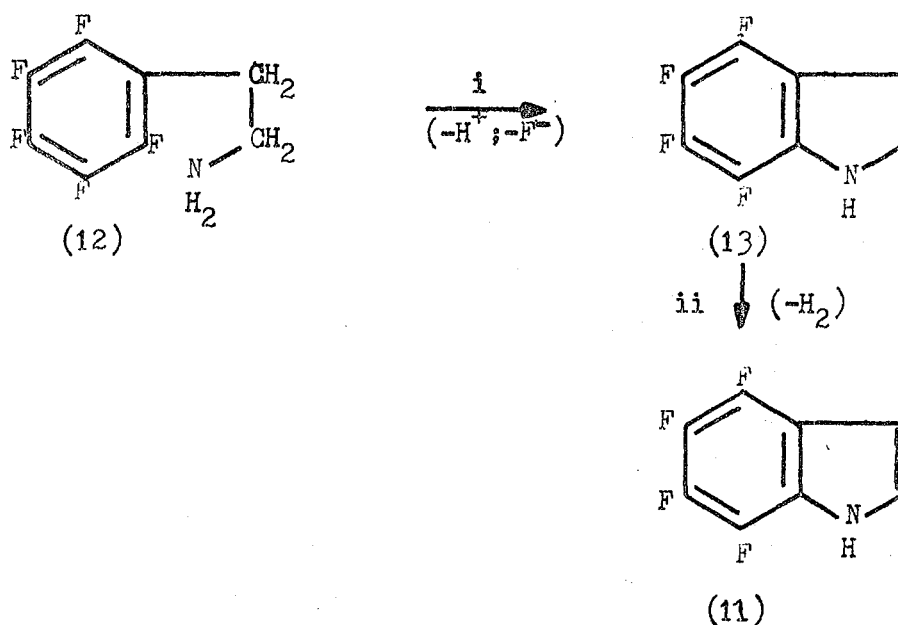
Petrov and coworkers<sup>10</sup> have reported a reaction in which 4,5,6,7-tetrafluoroindole (11) was formed in excellent yield by heating  $\beta$ -pentafluorophenyl- $\beta$ -hydroxyethylamine (10) in refluxing N,N-dimethylformamide (Scheme 15).



Scheme 15

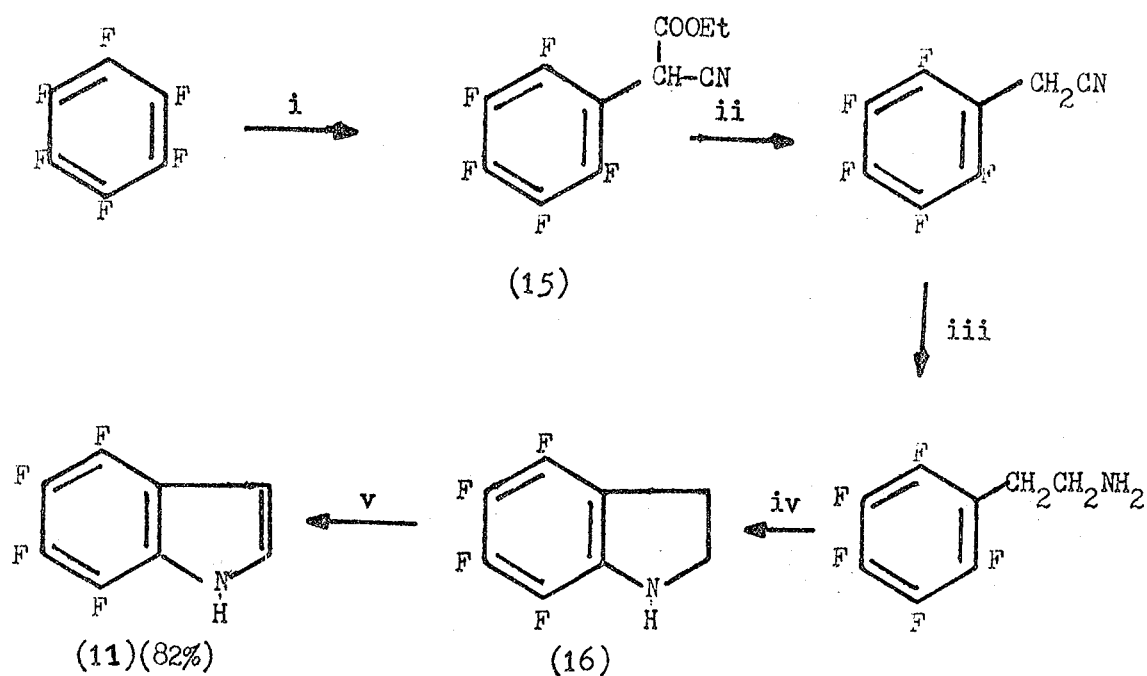
Proton abstraction on the nitrogen produces the nucleophile which attacks ortho-fluorine resulting in cyclization : water is then eliminated. However, as in the cyclization reported by Brooke<sup>9</sup>, an alternative mechanism whereby water is removed before cyclization is equally possible.

An alternative synthesis of (11) by the same Russian group involved the Pd-C dehydrogenation of 4,5,6,7-tetrafluoroindoline (13), obtained by heating  $\beta$ -(pentafluorophenyl)ethylamine (12) with potassium fluoride in N,N-diethylformamide (Scheme 16).



Scheme 16 Reagents : i, DMF, KF  
ii, Pd-C

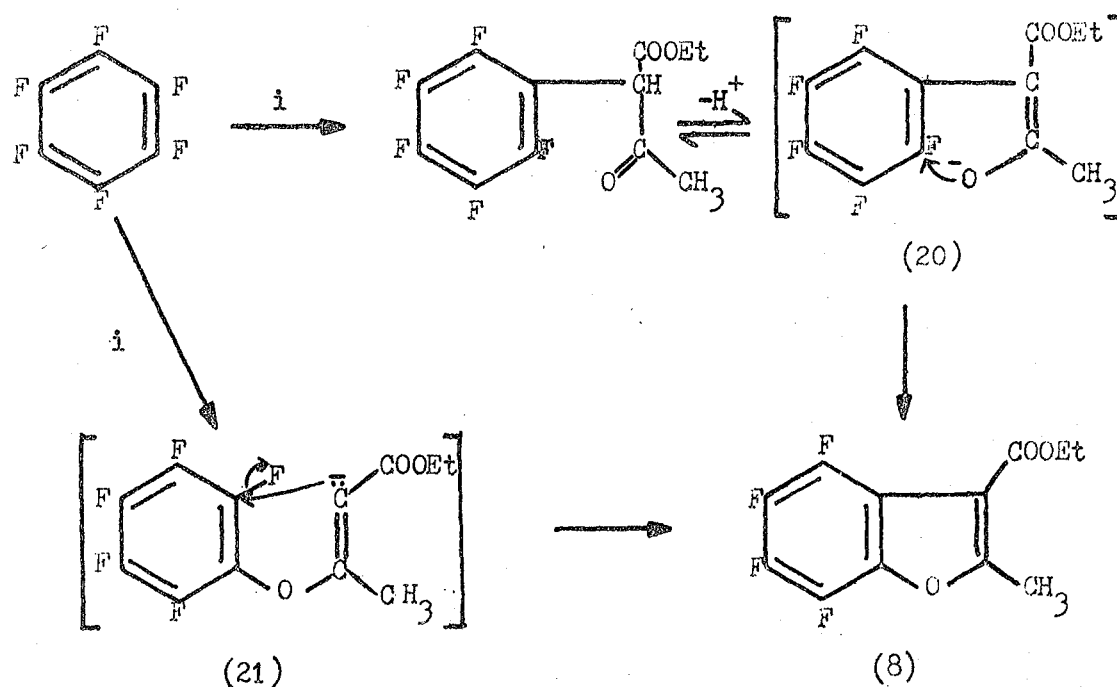
Filler and coworkers<sup>11</sup> in a mechanistically similar reaction were also able to synthesize 4,5,6,7-tetrafluoroindoline derivatives from ethyl cyano(pentafluorophenyl)acetate (15). Aromatization of 4,5,6,7-tetrafluoroindoline (16) gave 4,5,6,7-tetrafluoroindole (11) in 82% yield (Scheme 17).



Scheme 17    Reagents :    i,  $\text{NCCH}_2\text{COOEt}$ , DMF,  $\text{K}_2\text{CO}_3$  at  $110-120^\circ\text{C}$   
                               ii, aq.  $\text{HOAc}^-$ ,  $\text{H}_2\text{SO}_4$   
                               iii,  $\text{H}_2/\text{PtO}_2$   
                               iv, anhyd.  $\text{KF}$ , DMF  
                               v,  $[\text{MnO}_2]$

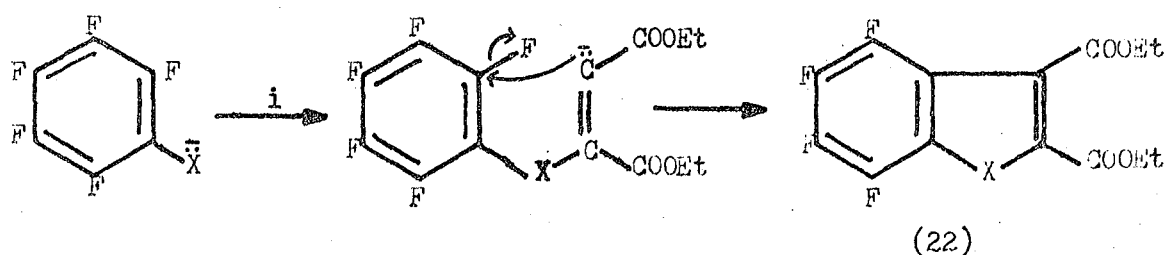
Tatlow et al.<sup>12</sup> have reported the synthesis of a 4,5,6,7-tetrafluoro-benzo[b]thiophen derivative (20) from an intramolecular cyclisation of rhodanine derivatives.<sup>13</sup> Basic hydrolysis of the arylidene-rhodanine (18) afforded the salt of a thioxo-acid which tautomerised to give the enethiol. Proton loss of the enethiol under basic conditions gave the sulphide (19), the sulphur atom of which acted as the nucleophile to displace the fluoride ion (Scheme 18).





Scheme 19 Reagents : i, NaH, DMF

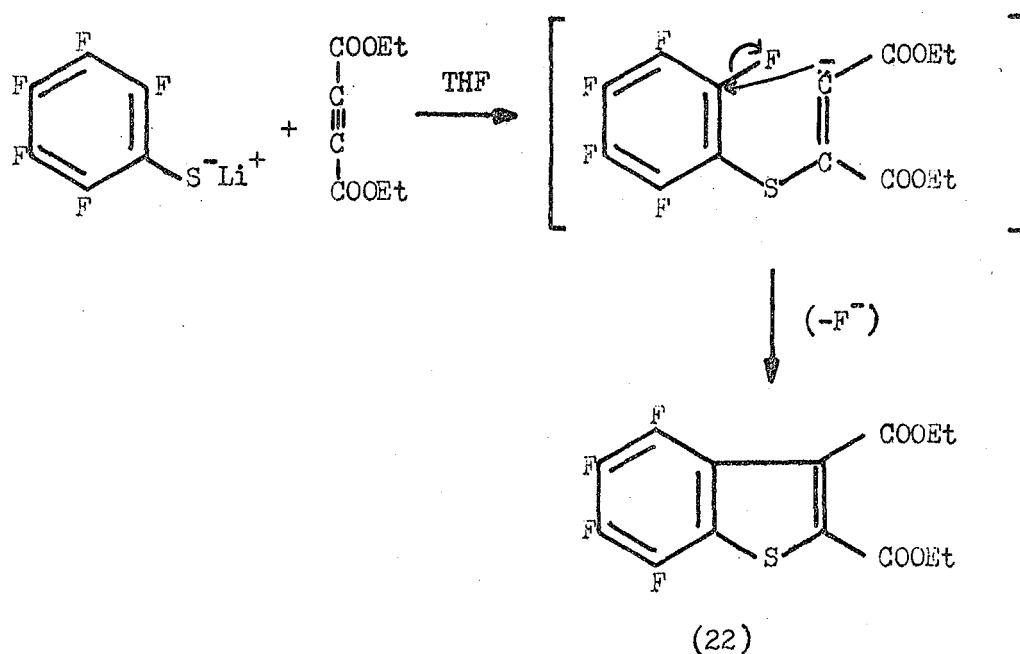
The first reported cyclization which clearly involved a carbanion intermediate as the nucleophile was by Brooke and coworkers.<sup>1</sup> A scheme was envisaged whereby partially fluorinated heterocycles in general could be synthesized via an intermediate similar to (21). The following general mechanistic scheme was postulated in which the intermediate similar to (21) could be synthesized by the addition of a sodium or lithium salt of pentafluoroaniline, pentafluorophenol or pentafluorothiophenol to diethyl acetylenedicarboxylate leading finally to the formation of the corresponding heterocyclic compound (Scheme 20).



Scheme 20 Reagents : i, EtOOC-C≡C-COOEt

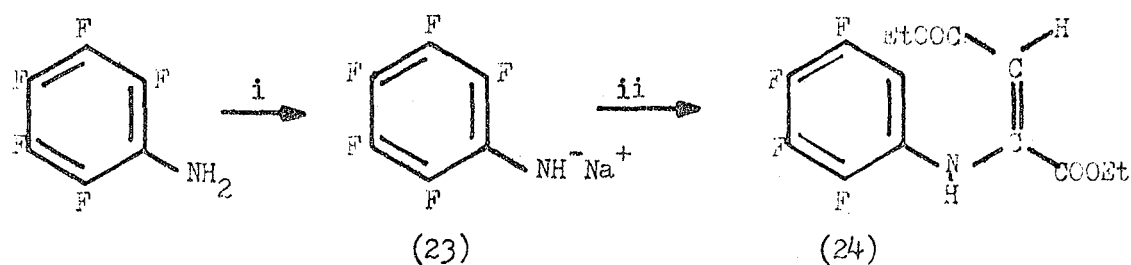
X = NH, O or S

The benzo[b]thiophen derivative (22, X = S) was easily formed<sup>1</sup> when pentafluorothiophenol in dry tetrahydrofuran was treated with n-butyllithium in hexane at  $-70^{\circ}\text{C}$ , followed by slow addition of diethyl acetylenedicarboxylate, the temperature being maintained at less than  $-55^{\circ}\text{C}$  (Scheme 21).



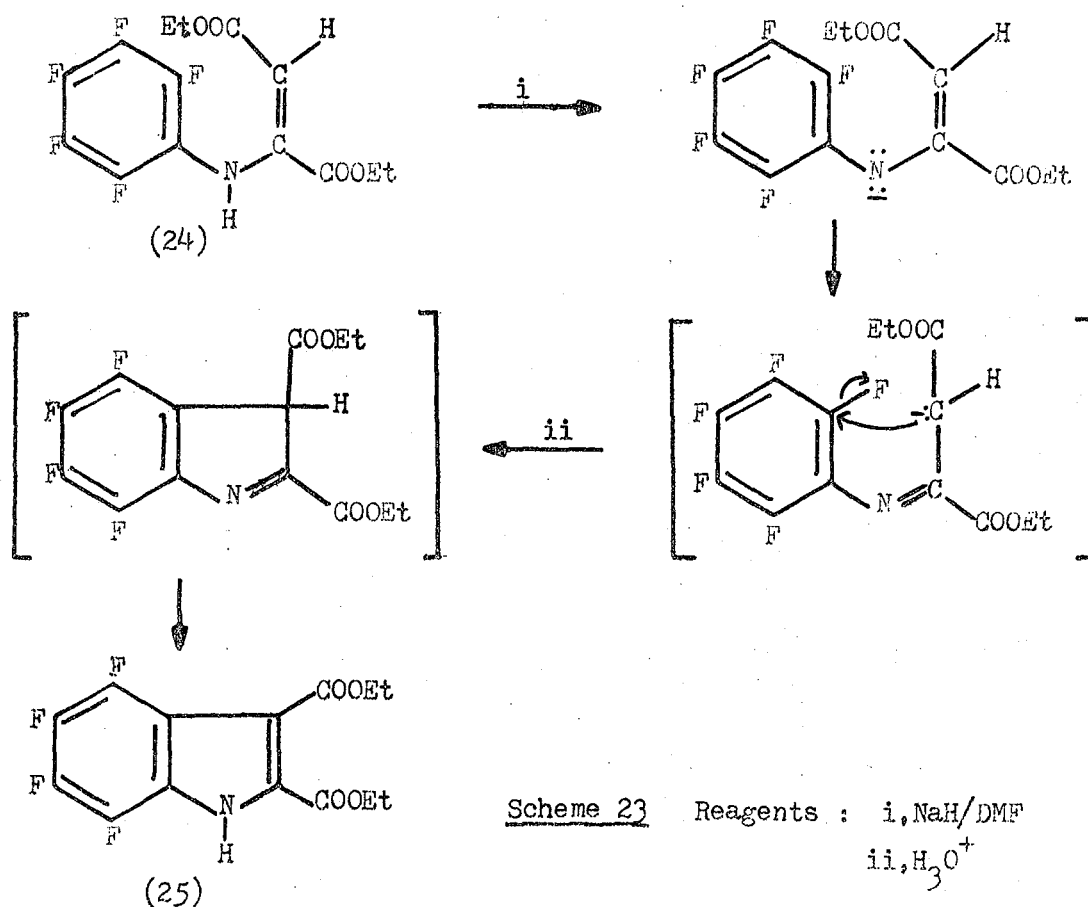
Scheme 21

An attempt was made<sup>14</sup> to expand the general scope of this reaction and so include a synthesis of partially fluorinated indoles. Pentafluoroaniline<sup>15</sup> was treated with sodium hydride in tetrahydrofuran and the resulting sodium salt<sup>16</sup> (23) was treated with diethyl acetylenedicarboxylate, under the same conditions. Trans addition of the amine occurred across the triple bond to give an aminofumarate (24) (Scheme 22).



Scheme 22 Reagents : i, NaH/THF  
ii, EtOOC-C C-COOEt in THF ; H<sub>2</sub>O

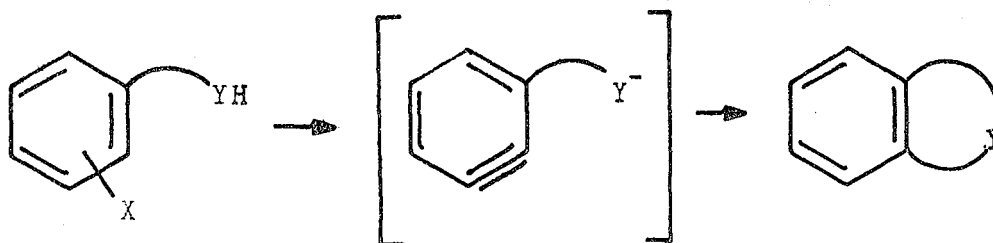
No cyclization product could be detected when even more drastic reaction conditions were employed, viz. in an autoclave at 150°C. Cyclization of the aminofumarate (24) was eventually achieved to afford the indole derivative (25) in low yield (<3%) when treated with sodium hydride in N,N-dimethylformamide at reflux temperature. A plausible mechanism for the reaction is shown in Scheme 23 :



Scheme 23 Reagents : i, NaH/DMF  
ii, H<sub>3</sub>O<sup>+</sup>

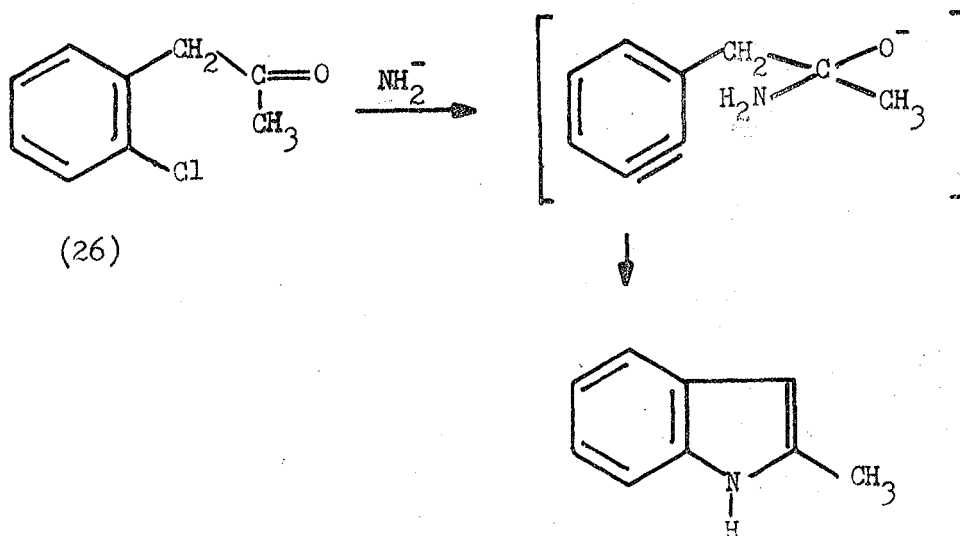
There are no reports of benzo[b]furan synthesis by the possible reaction of  $C_6F_5O^-$  with diethylacetylene dicarboxylate.

The only precedent to these carbanion intermediate cyclisations has been reported by Bunnett,<sup>17</sup> whereby ring closure has been effected by the formation of an aryne (benzyne) intermediate with a side-chain bearing a strong nucleophile which is capable of adding intramolecularly to the benzyne grouping (Scheme 24).



Scheme 24      X = Halogen atom ortho- or meta- to side-chain  
 YH = Functional group, forms the nucleophile  $Y^-$  by loss of a proton

For example, the reaction of o-chlorophenylacetone (26) with sodamide in liquid ammonia gave the 2-methylindole in 31% yield (27) (Scheme 25).



Scheme 25

(27) (31%)



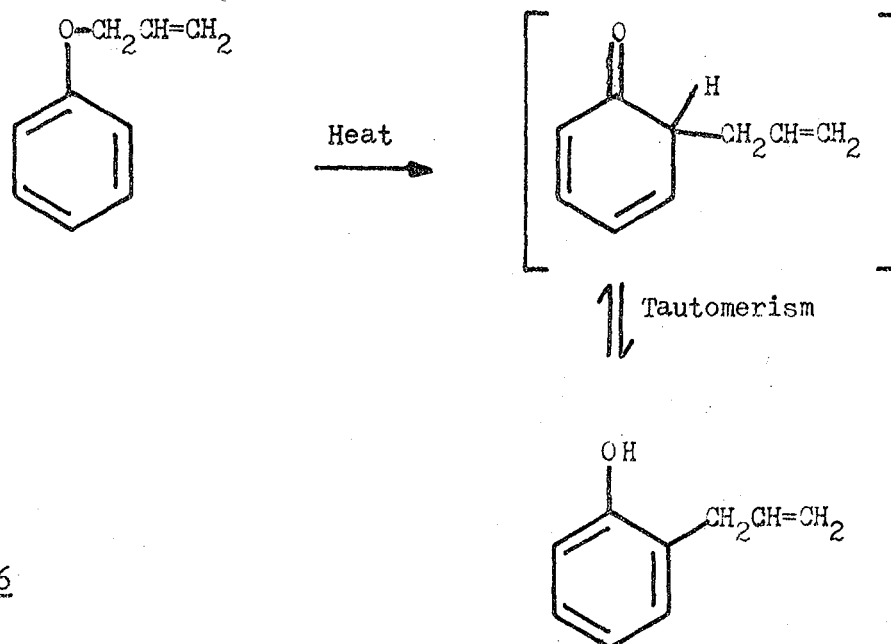
The addition of nitrogen and displacement of the ortho-halogen is contained within an overall elimination-addition type mechanism.

### CHAPTER 3

THE PREPARATION OF PARTIALLY FLUORINATED  
HETEROCYCLIC COMPOUNDS CONTAINING OXYGEN AND SULPHUR  
VIA REACTIONS INVOLVING [3,3]-SIGMATROPIC REARRANGEMENTS :  
ELIMINATION OF ORTHO-FLUORINE

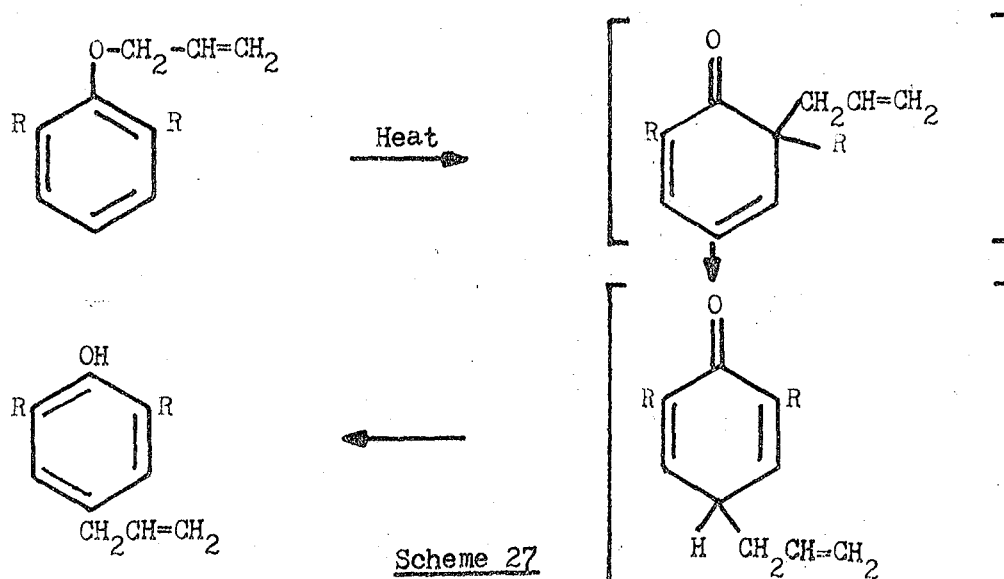
### 3.1 The Claisen Rearrangement

Phenyl prop-2-enyl ether has long been known to undergo a thermally induced [3,3]-sigmatropic rearrangement to give a cyclohexadienone intermediate which rapidly isomerises to 2-(prop-2-enyl)phenol. Overall, this reaction is known as the Claisen rearrangement<sup>18</sup> (Scheme 26).



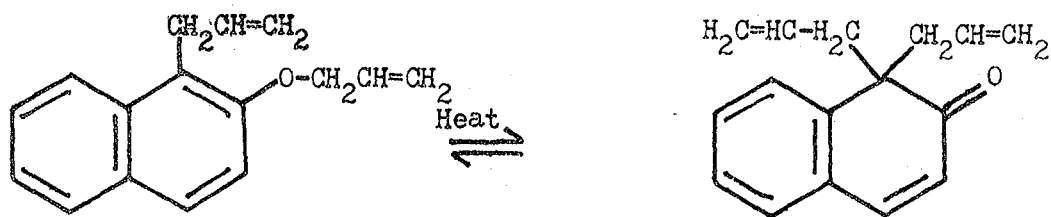
Scheme 26

In ortho-substituted compounds a further rearrangement viz. the Cope rearrangement, can occur via a six-centered transition state to give the 4-(prop-2-enyl)phenol<sup>19</sup> (Scheme 27).



Scheme 27

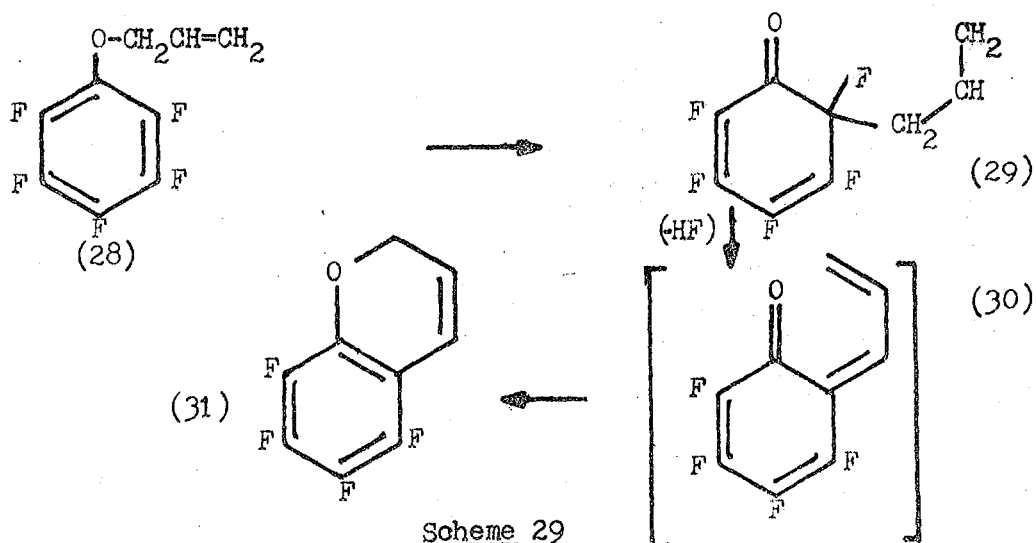
It has been possible to isolate the 2,4-dienone intermediate in the attempted Claisen rearrangement of 1-(prop-2-enyl)-2-(prop-2-enyl)oxynaphthalene. Tautomerism to give the phenolic products was avoided and 1,2-di(prop-2-enyl)oxynaphthalene was recovered in 55% yield (Scheme 28).



Scheme 28

### 3.2 Thermally-Induced Reactions of Pentafluorophenyl Prop-2-enyl Ethers

An attempt was made to convert pentafluorophenyl prop-2-enyl ether (28) into 5,6,7,8-tetrafluoro-2H-1-benzopyran<sup>20</sup> (31) by the "one-pot" reaction shown in scheme 29. The resulting heterocycle could then be oxidised to 6-carboxy-2,3,4,5-tetrafluorophenoxyacetic acid<sup>21</sup>, a precursor that could be used in the synthesis of 4,5,6,7-tetrafluorobenzo[b]furan (Scheme 29).



Scheme 29

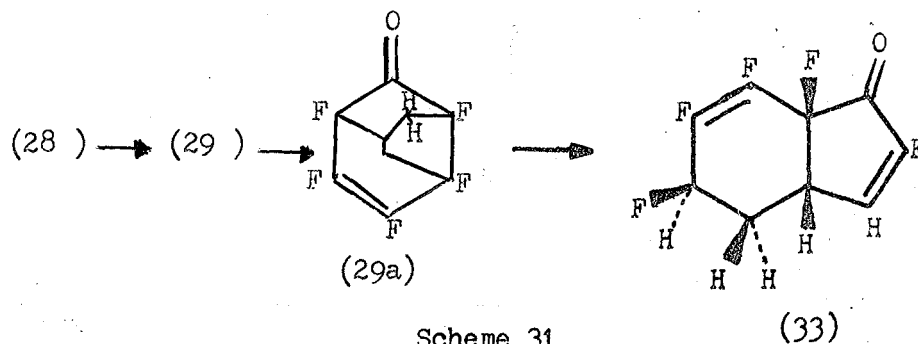
The fluorine on the ortho-positions of (28) act as blocking groups, preventing enolisation which would give the phenolic products. Pyrolytic dehydrofluorination of the initially formed Claisen rearrangement product (29) to give the o-quinomethide (30) would be followed by an electrocyclic ring closure to give the chroman (31).

Flash vapour phase pyrolysis of (28) over silica fibre at 305°C<sup>22</sup> gave the stable 4-(prop-2-enyl)2,3,4,5,6-pentafluoro-2,5-cyclohexadienone (32) in 32% yield, together with unreacted starting material; no cyclised product (31) was isolated (Scheme 30).



Scheme 30

In a further attempt<sup>20</sup> to promote dehydrofluorination of the dienone (32), the ether (28) was subjected to flash vapour phase pyrolysis over silica fibre at 480°C; Compound (33) was isolated (Scheme 31); its formation



Scheme 31

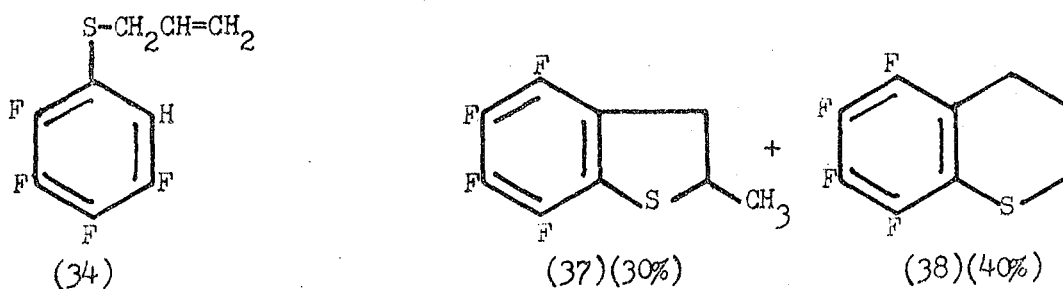
being rationalised from the formation and isomerisation of one of the internal Diels-Alder adducts (29a).

### 3.3 Thermally-Induced Reactions of Polyfluorinated Prop-2-enyl Sulphides: The Formation of some Heterocyclic Compounds Containing Sulphur

The attempts to synthesize polyfluorinated 2H-1-benzopyran derivatives (as a precursor to benzo[b]furan compounds)<sup>20</sup> were extended to include the possible synthesis of the thiopyran analogue. Brooke et al.<sup>23</sup> prepared three different polyfluorinated prop-2-enyl sulphides for thermolysis reactions :

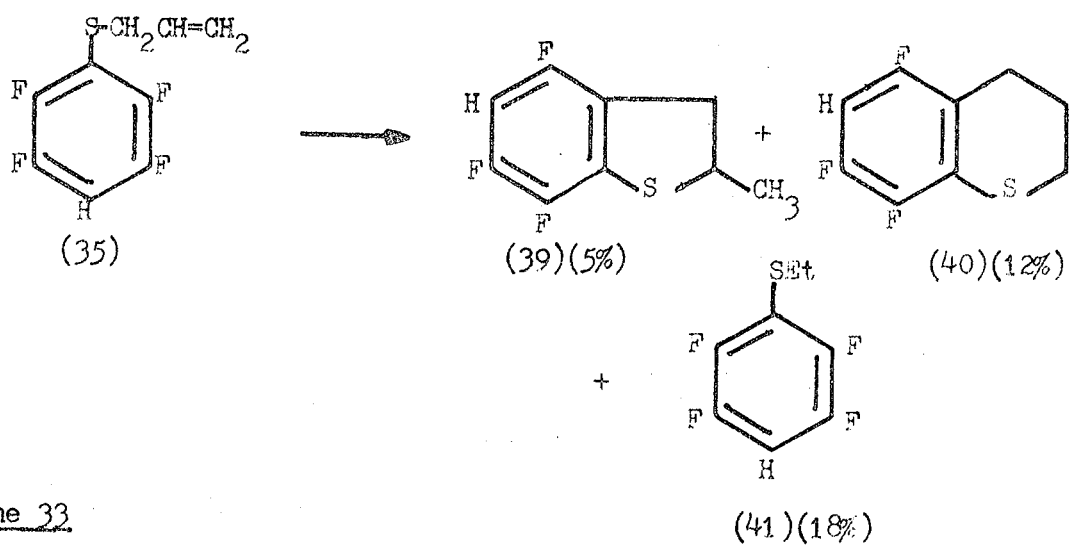
- (i) 2,3,4,5-tetrafluorophenyl prop-2-enyl sulphide (34) ;
- (ii) 2,3,5,6-tetrafluorophenyl prop-2-enyl sulphide (35) ;
- (iii) pentafluorophenyl prop-2-enyl sulphide (36).

When compound (34) was heated under reflux in N,N-diethylaniline for 23 h, the products shown in scheme 32 were obtained.



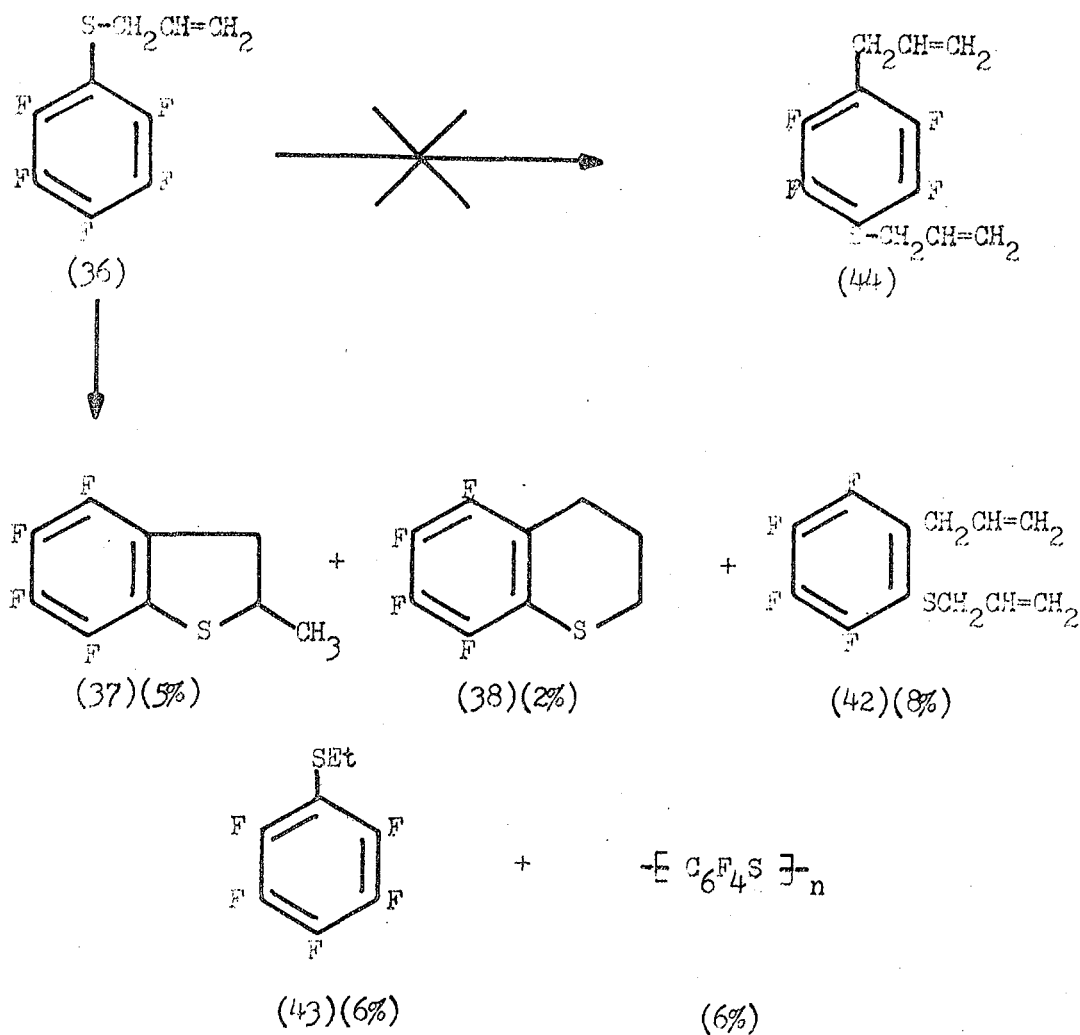
Scheme 32

Compound (35) was heated under reflux in N,N-diethylaniline for 190 h to give the three products shown in scheme 33.



Scheme 33

Finally, compound (36) was heated under reflux in N,N-diethylaniline to give a complex mixture of components shown in scheme 34.



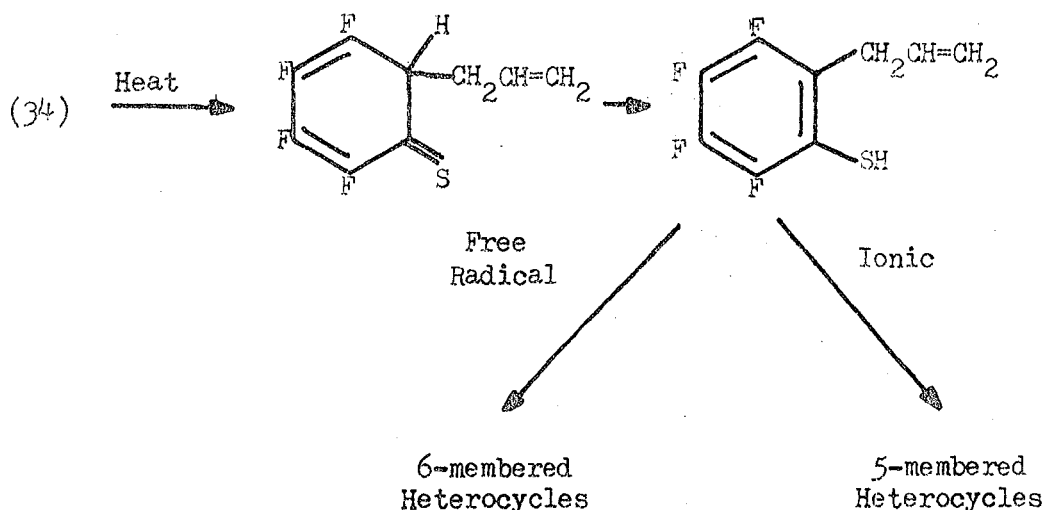
Scheme 34

An attempt was made to explain the formation of other possible products from the reaction of (36) and the solvent N,N-diethylaniline, which is both a base and a nucleophile. As a base the possibility existed for proton abstraction from the prop-2-enylthio- group ( $\rightarrow \text{SCH}=\text{CH}_2 \longleftrightarrow \text{S}-\text{CH}=\text{CH}-\text{CH}_2^-$ ) with the terminal carbon subsequently effecting an intramolecular nucleophilic displacement of fluorine from the aromatic ring to give 5,6,7,8-tetrafluoro-2H-1-benzothiopyran (38). However this product was not formed in the reaction of (36) with the powerful base sodium hydride in refluxing THF over 5 h : the starting material was recovered unchanged.

N,N-Diethylaniline as a nucleophile could possibly displace the 4-fluorine in (36)<sup>28</sup> and the resulting quaternary ammonium salt could be de-N-ethylated by fluoride ion to give 1,4- $\text{PhN}(\text{Et})\text{C}_6\text{F}_4\text{SCH}_2\text{CH}=\text{CH}_2$ . The attempted synthesis of this compound from (36) and  $\text{PhN}(\text{Et})\text{Li}$  in dioxan at reflux temperature over 5 h did not bring about any displacement of fluorine, so it was concluded that N,N-diethylaniline would also be an ineffective nucleophile.

A precedent exists for the formation of compounds (37) and (38) from (34) in an analogous hydrocarbon reaction. Phenyl prop-2-enyl sulphide, refluxed in quinoline gave equal proportions of the non-fluorine containing analogue of (37) and (38) via 2-(prop-2-enyl)thiophenol. This cyclization reaction has been shown to proceed via a competing electrophilic and free-radical mechanism.<sup>89</sup> By analogy the thermolysis of (34) proceeds as shown in scheme 35.

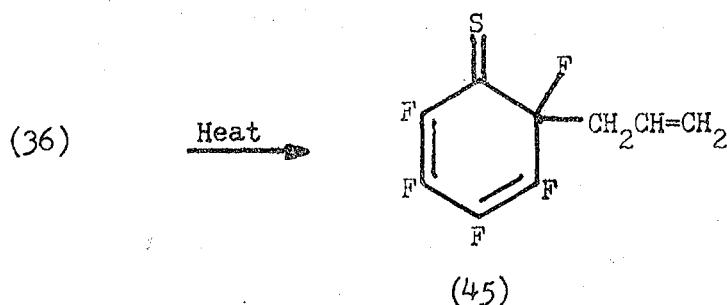




Scheme 35

The conversion of compound (35) into (39) and (40); and compound (36) into (37) and (38) formally require the loss of one fluorine and the gain of one hydrogen in the products, while the formation of (42) from (36) requires the overall replacement of a fluorine by a prop-2-enyl group. These types of reaction, as yet, have no precedent.

The mechanism put forward by Brooke<sup>23</sup>, involves the specific formation of overall ortho-fluorine substitution products. In the reactions of (35) and (36) it would seem that the three carbon side-chain is displaced to a carbon atom ortho to the sulphur by the expected [3,3]-sigmatropic rearrangement as shown in scheme 36.



Scheme 36

The absence of any para-derivative (44) suggests that a Cope rearrangement does not occur after the initial Claisen rearrangement. Nucleophilic displacement of fluorine could not have occurred as this would have resulted in the para-fluorine of (36) being displaced.<sup>24</sup> Hexabromocyclohexa-2,5-dienone has been shown to be an electrophilic brominating agent.<sup>25</sup> The possibility that the  $sp^3$  C-F bond in (45) could be displaced as  $F^+$ , leading to electrophilic substitution of hydrogen in the solvent was considered. However,  $^{19}F$  n.m.r. studies did not detect the presence of any fluorine in the recovered N,N-diethylaniline.

Suschitzky et al.<sup>26</sup> have demonstrated a thermal rearrangement of prop-2-enyl 2,3,5,6-tetrachloro-4-pyridyl ether in sulfolan at  $190^\circ C$  to give amongst other products 4,5,6,7-tetrachloro-2,3-dihydro-2-methyl furo[3,2-c]pyridine which is closely related to the structures of (37) and (39). This was rationalized in terms of an initial [3,3]-sigmatropic rearrangement followed by homolytic cleavage of a  $sp^3$  C-Cl bond, accompanied by the competing loss of prop-2-enyl radical from the same carbon atom to give other products. An analogous mechanism can explain the remarkable formation of ortho-fluorine displacement products from (35) and (36) : homolytic fission of a  $sp^3$  C-F bond from (45) gives rise to the radical (46) which can react in a number of ways :

- (a) Cyclization and hydrogen abstraction from the solvent gives (38) or ;
- (b) abstract hydrogen from the solvent to form the thiol (47) which can then cyclise to give (37) by an electrophilically induced mechanism.

Compound (42) can be formed either by an  $S_N2'$  displacement of  $C_6F_5S^-$

from (36) via the thiolate from (47), or by the related displacement of  $C_6F_5S^+$  from (36) via the free radical (46).  $C_6F_5S^+$  can react further with the solvent to give  $C_6F_5SH$ , then  $C_6F_5S^-$  which in turn would polymerise to perfluoropoly(phenylene sulphide) (Scheme 37).

If this mechanism is correct then homolytic fission of the  $sp^3$  C-F bond occurs at a remarkably low temperature,  $\leq 220^\circ C$ . An explanation could be the considerable stability of the radical formed in this homolysis. This stability, presumably due to extended conjugation, must be adequate in the case of the cyclo-2,4-dieneothione intermediate (45), but insufficient for the corresponding oxygen compound (the cyclohexa-2,4-dienone) where products formed via an internal Diels-Alder adduct are obtained (see Pg. 22). The tetrafluoro- analogue of prop-2-enyl 2,3,5,6-tetrachloro-4-pyridyl ether only gave internal Diels-Alder products due to the C-F bond being stronger than the C-Cl bond.

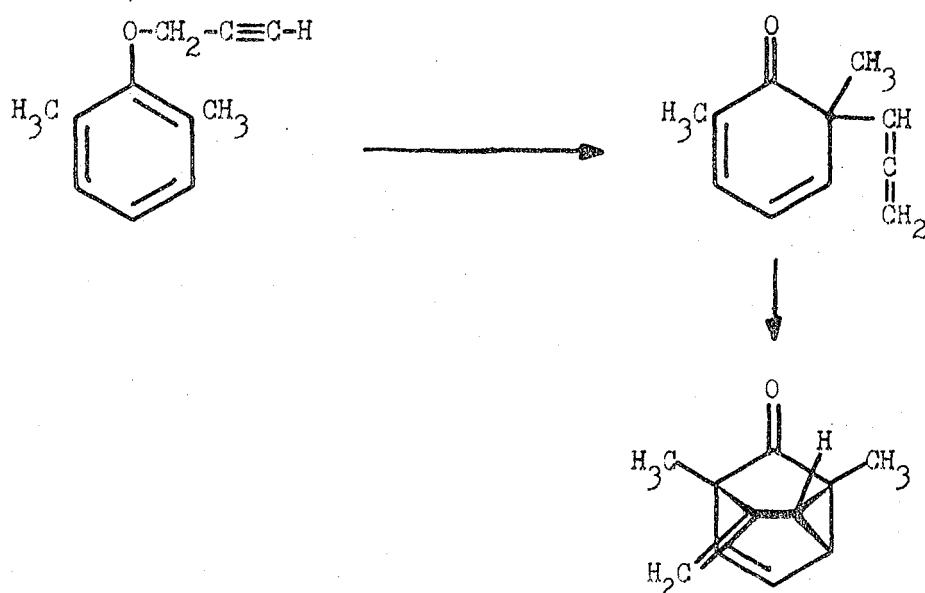
Since the original proposal of a homolytic rupture of the  $sp^3$  C-F bond in (45), it has been conceded that the alternative heterolytic displacement of fluoride ion is a plausible alternative mechanistic route to all the products formed in the reaction.<sup>27</sup> Also it is evident that there is no real evidence to favour homolytic C-Cl cleavage over heterolytic C-Cl cleavage in the case of the intermediate involved in Suschitzkys,<sup>26</sup> and other authors' work.

### 3.4 Thermolysis Reactions of Polyfluorinated Prop-2-ynyl Ethers : The Formation of Benzo[b]furan Derivatives and Related Compounds

Following the successful cyclization reactions of fluorinated prop-2-enyl ethers to give internal Diels-Alder adducts, similar reactions

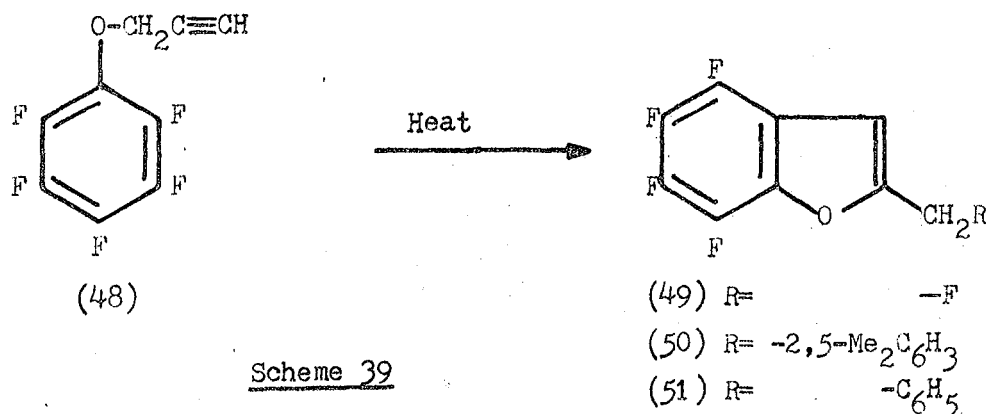


were attempted on related prop-2-ynyl ethers<sup>29</sup> : pentafluorophenyl (48) and 1,3,4,5,6,7,8-heptafluoro-2-naphthyl(52) derivatives. The first internal Diels-Alder adduct ever isolated from a Claisen rearrangement reaction had been reported by Schmid<sup>30</sup> in 1968 (Scheme 38).



Scheme 38

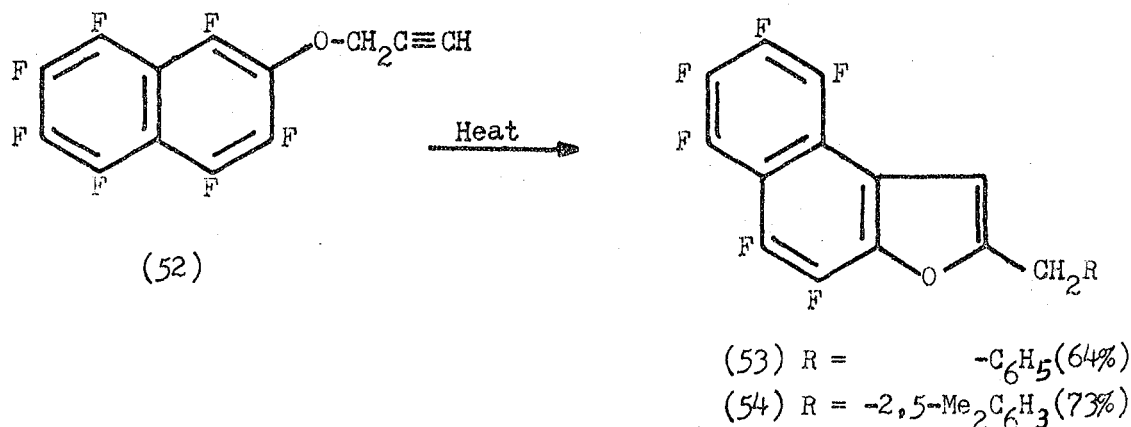
Distillation of pentafluorophenyl prop-2-ynyl ether (48) through a silica tube packed with quartz at 370°C gave 2-fluoromethyl-4,5,6,7-tetrafluorobenzo[b]furan (49) in 8% yield ; no internal Diels-Alder adduct was isolated (Scheme 39).



Scheme 39

When the ether (48) was heated under reflux in p-xylene for 118 h 2-(2,5-dimethylbenzyl)-4,5,6,7-tetrafluorobenzo[b]furan (50)(21%) and HF were recovered, while with benzene at 140°C for 116 h 2-benzyl-4,5,6,7-tetrafluorobenzo[b]furan (51)(28%) was obtained.

Similar reactions were achieved when 1,3,4,5,6,7,8-heptafluoro-2-naphthyl prop-2-ynyl ether (52) was reacted with benzene and with p-xylene to give (53) and (54) respectively (Scheme 40). The yields are given for the reactions at ca. 140°C and over ca. 20 h.



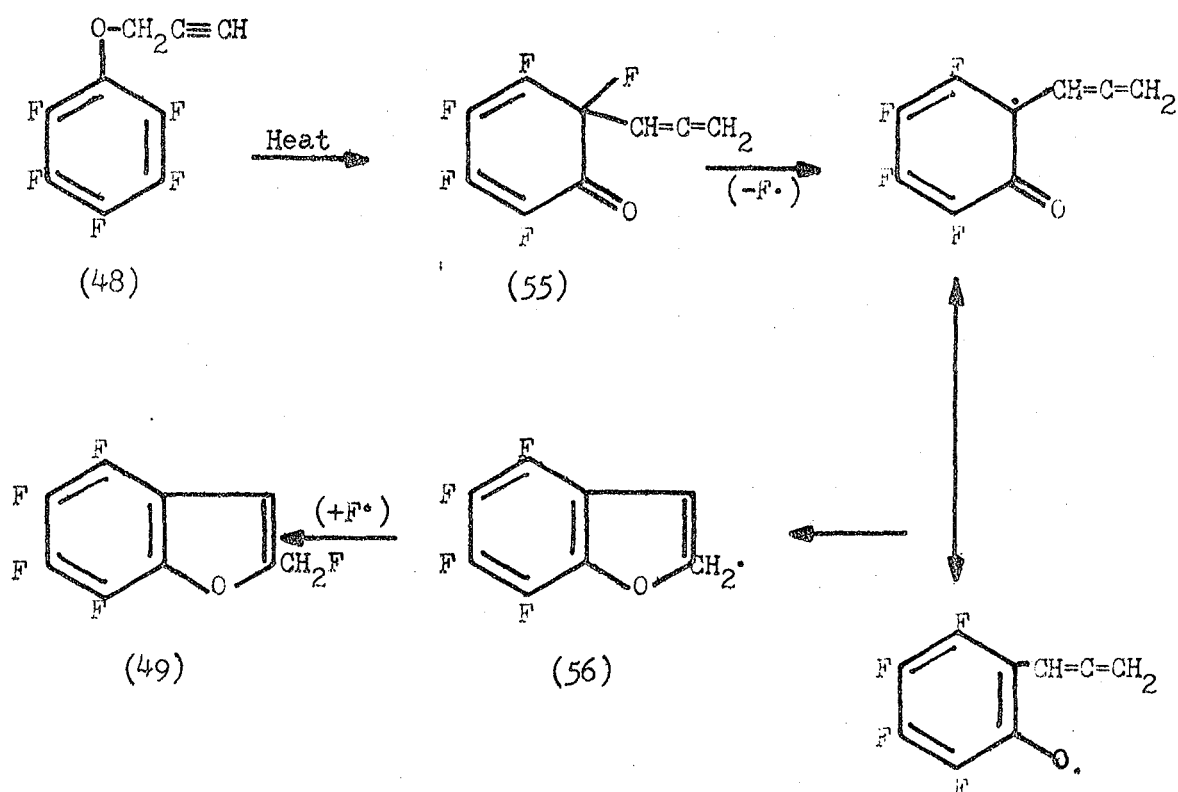
Scheme 40

It is evident from the results of these experiments that the behaviour of prop-2-ynyl ethers and the corresponding prop-2-enyl ethers are quite different. Subsequent reactions of the initial Claisen rearrangement product can take place via two plausible mechanisms :

- (i) homolytic fission of the  $\text{sp}^3$  C-F bond (Scheme 41) ;
- (ii) heterolytic fission of the  $\text{sp}^3$  C-F bond (Scheme 42).

A precedent to this series of reactions had also been reported by Schmid et al.<sup>30</sup> who investigated the thermolysis of the prop-2-ynyl ethers of some related ortho-halogenated (chloro- and bromo-) aromatic systems which had given similar results. They proposed a homolytic cleavage

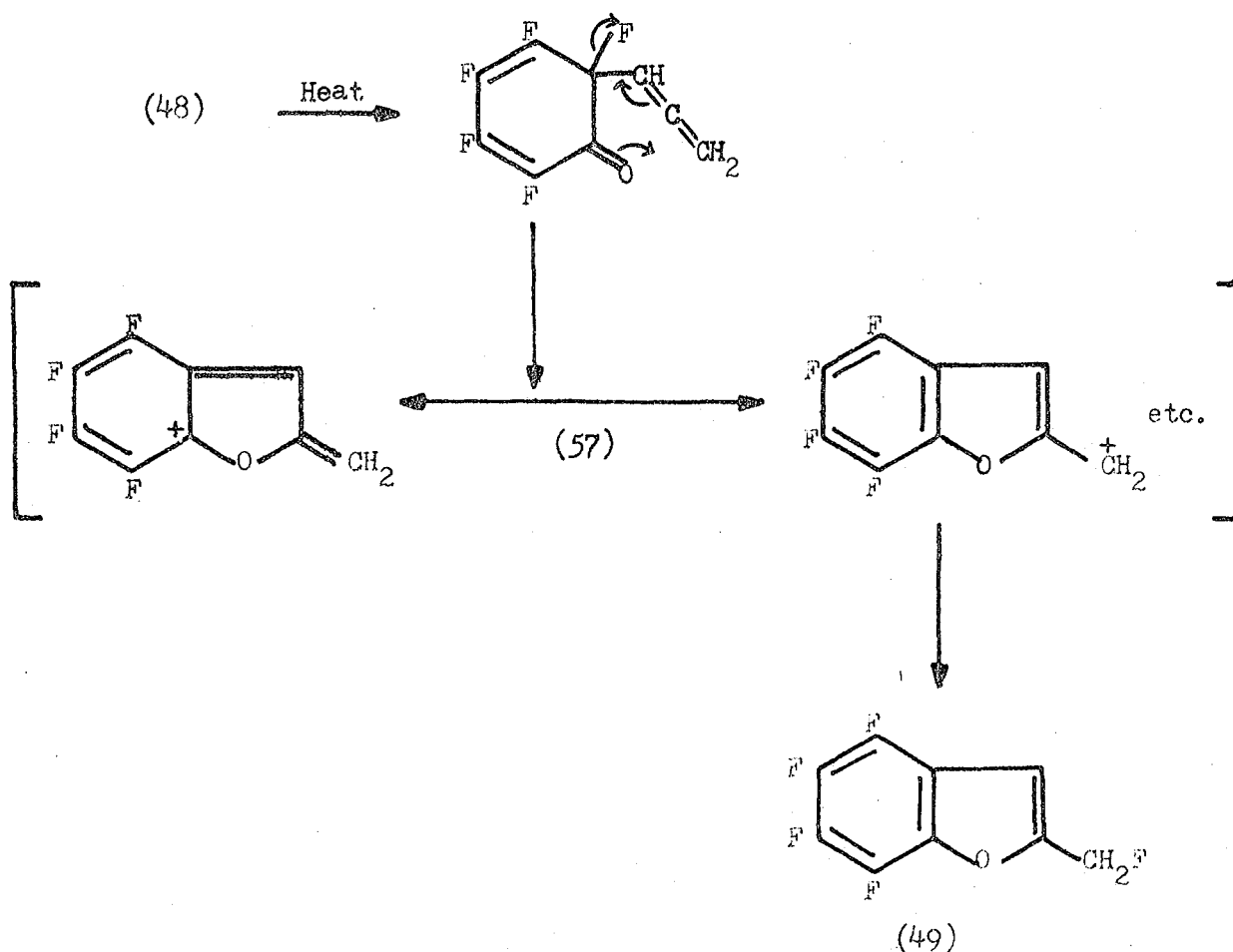
of the C-Halogen bond in the initially formed Claisen rearrangement product to account for the products in their reactions. When translated to these polyfluoroaromatic prop-2-ynyl ethers the following mechanism rationalises the formation of the benzo[b]furan (Scheme 41).



Scheme 41

Following the formation of the Claisen rearrangement product (55), homolytic cleavage of the  $\text{sp}^3$  C-F bond takes place. A requirement is that the fluorine atom is closely related to the accompanying radical during the following cyclization stage. The inclusion of the solvents, benzene and p-xylene onto the furan ring can also be rationalised on the basis of a homolytic substitution mechanism. The cyclized radical (56) attacks the aromatic solvent followed by hydrogen abstraction from the intermediate complex by the fluorine atom.

Scheme 42 shows the alternative heterocyclic process which could be applied equally to the original chloro- and bromo- compounds investigated by Schmid.<sup>30</sup>



Scheme 42

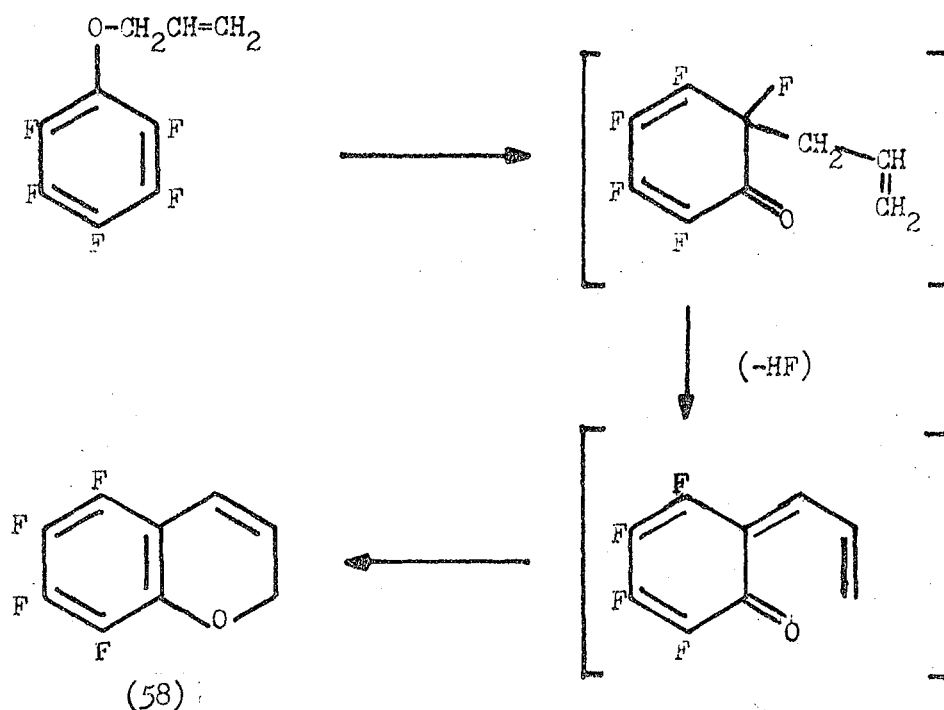
Again there is a requirement for the fluorine (as fluoride ion) and the carbocation (57) to be closely associated in the vapour phase. In the presence of p-xylene and benzene which give compounds (50) and (51) respectively, the cation (57) is simply effecting electrophilic substitution of hydrogen in the aromatic substrate.

At the moment there is insufficient evidence to assign the correct mechanism to this series of reactions.



### 3.5 Reactions of Polyfluorinated Heteroaryl Prop-2-enyl Ethers with KF : The Preparation of 2H-1-benzopyran Derivatives via an o-Quinomethide-Type Precursor

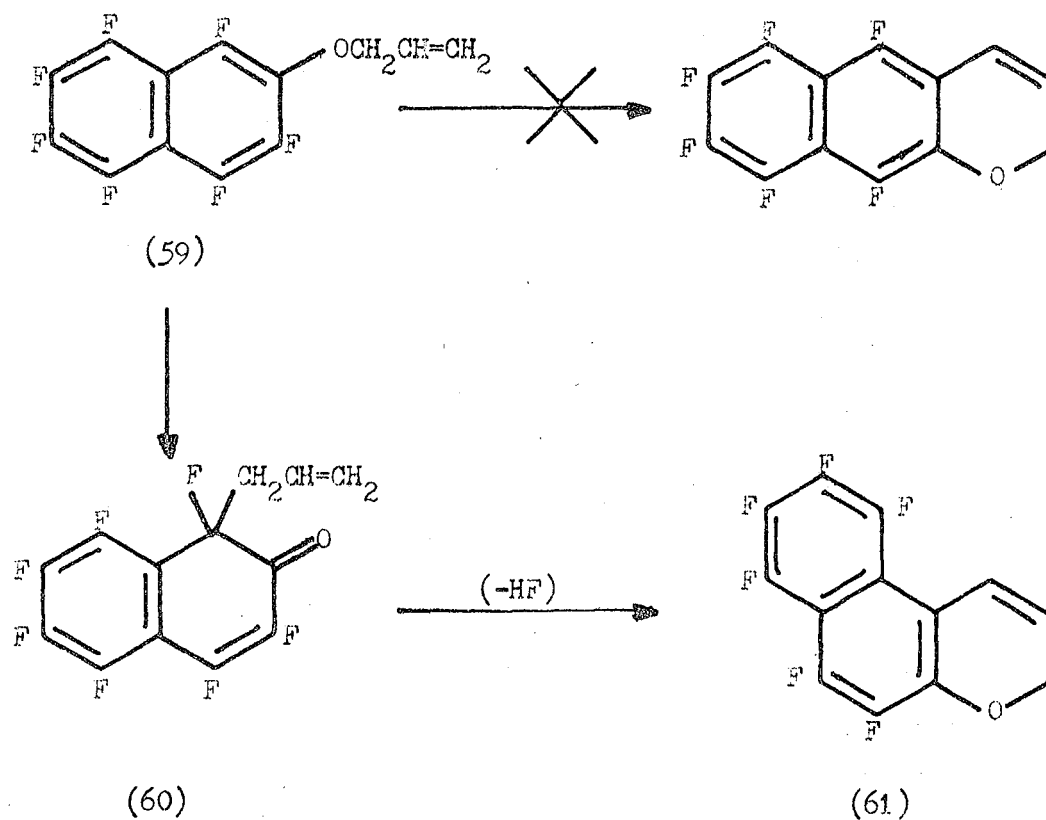
Earlier attempts to synthesize<sup>31</sup> 5,6,7,8-tetrafluoro-2H-1-benzopyran from pentafluorophenylphenyl prop-2-enyl ether by dehydrofluorination of the Claisen rearrangement intermediate, followed by electrocyclization were not successful (see Pg.22). However, the required dehydrofluorination was achieved by treating pentafluorophenyl prop-2-enyl ether with potassium fluoride in N,N-dimethylformamide at reflux temperature for 4 h, resulting in the formation of the 2H-1-benzopyran derivative (58) in 48% yield (Scheme 43).



Scheme 43

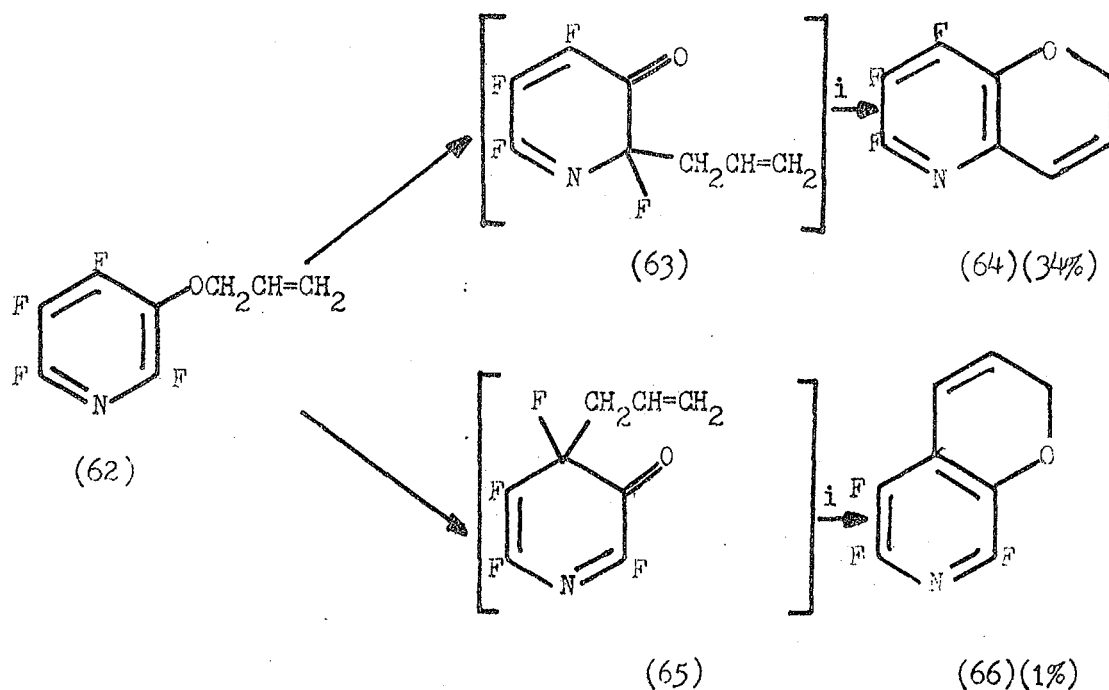
Similar results were obtained from 1,3,4,5,6,7,8-heptafluoro-2-naphthyl prop-2-enyl ether (59)<sup>32</sup> in sulfolane at 155-162°C over 4 h

which gave (61), via the 1-(prop-2-enyl)naphthalene-2-one derivative (60) (Scheme 44).



Scheme 44

Thermolysis of the pyridine compound (62) in a sealed tube at 182<sup>0</sup>C for 4 h, resulted in the formation of the 2H-pyran isomers (64) and (66) in 34% and 1% yields respectively (Scheme 45).



Claisen Rearrangement  
Intermediate

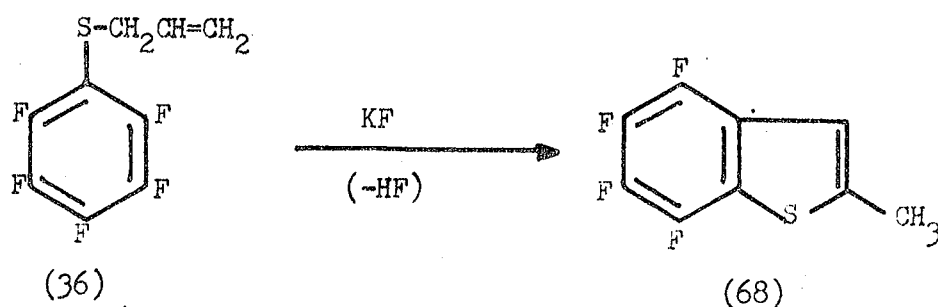
Scheme 45    Reagent : i, KF, (-HF)

An interesting feature of the reaction is the fact that the major product (64) arises from the [3,3]-sigmatropic shift of the prop-2-enyl group onto the adjacent carbon nearest to the nitrogen. However, in the vapour phase reaction at 185°C for 112.8 h the prop-2-enyl group migrated to the adjacent carbon furthest away from the nitrogen,<sup>32</sup> demonstrating the importance of the solvent during the course of the reaction.

3.6    The Reaction of Pentafluorophenyl Prop-2-enyl Sulphide (36)  
with the Formation of a Benzo[b]thiophen Derivative in an Attempt  
to Extend the Scope of Synthesis of 2H-1-benzopyran Derivatives

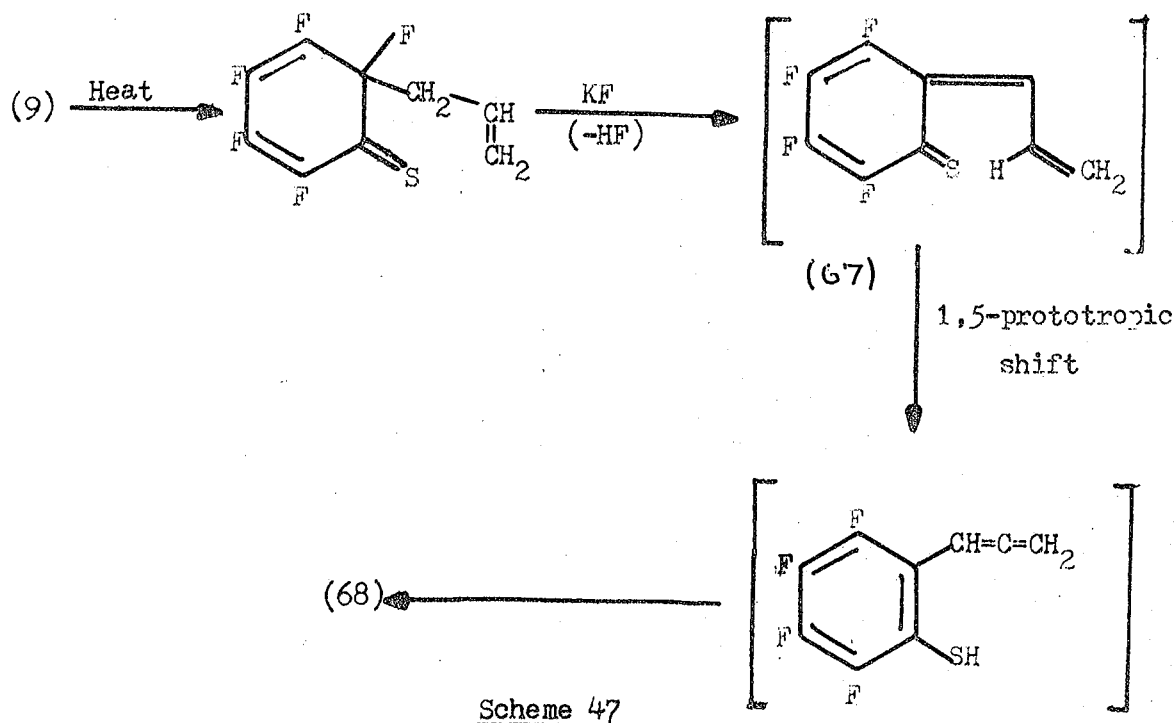
In an attempt to extend the scope of synthesis of 2H-1-benzopyran

derivatives to include the corresponding sulphur heterocycles, the thermolysis of pentafluorophenyl prop-2-enyl sulphide (36) with potassium fluoride in sulpolane was carried out in a nickel tube at 191-192°C for 22 h. The only product isolated from this reaction was 4,5,6,7-tetrafluoro-2-methylbenzo[b]thiophen (68) (Scheme 46).



Scheme 46

The formation of (68) can be rationalized in terms of a novel [1,5]-sigmatropic shift of vinylic hydrogen to the heteroatom in the thio-Claisen intermediate (67) following dehydrofluorination (Scheme 47).



Scheme 47

CHAPTER 4

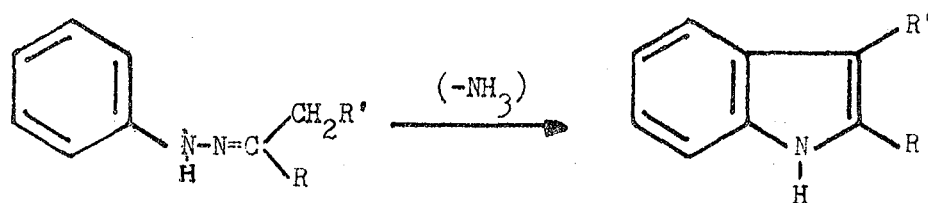
THE FORMATION OF PARTIALLY FLUORINATED

INDOLES VIA REACTIONS INVOLVING

[3,3]-SIGMATROPIC REARRANGEMENTS

#### 4.1 The Fischer Indole Synthesis

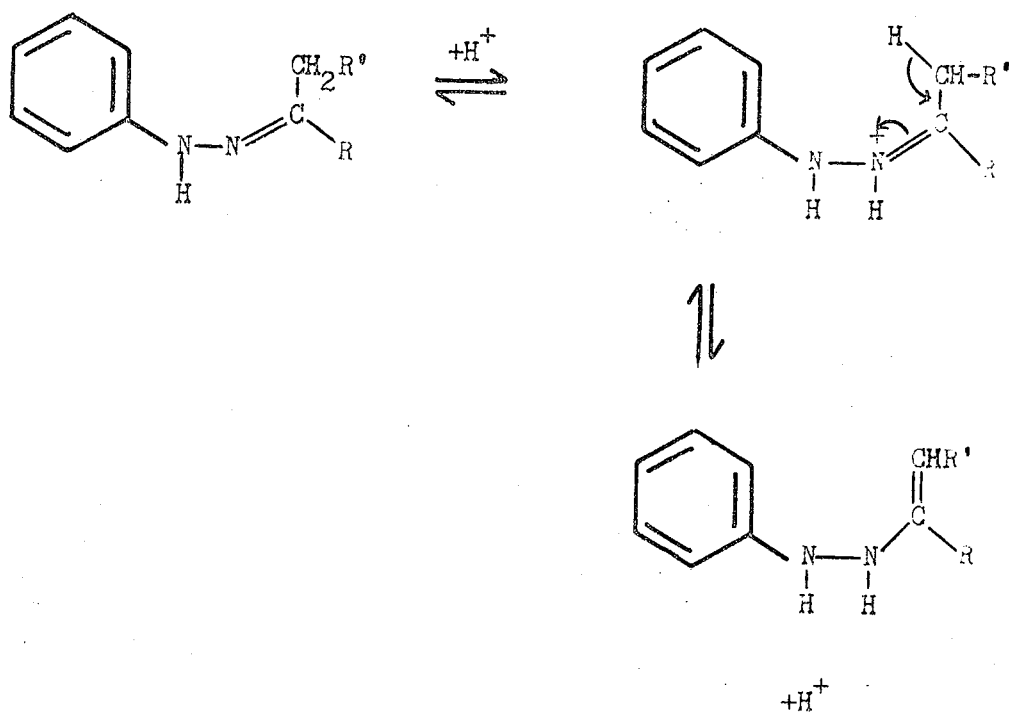
The Fischer indole synthesis is probably the most popular method of synthesizing indoles and has demonstrated almost unlimited flexibility in the preparation of hydrocarbon indoles. Essentially it involves the reaction of an aryl hydrazone with either a cyclizing agent or by a thermally induced reaction (Scheme 48).



Scheme 48

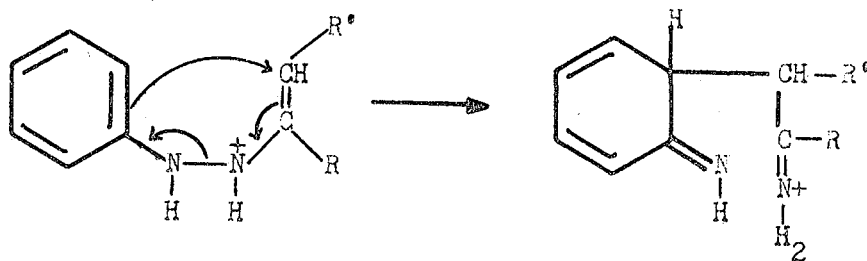
The actual mechanism of the Fischer indole reaction has been best explained by Robinson and Robinson,<sup>33</sup> although at least three other mechanisms have been proposed. The remarkable feature of the Robinson and Robinson mechanism is their realization of the close relationship of the mechanism to both the ortho-benzidine rearrangement and the Claisen rearrangement<sup>34</sup> (a [3,3]-sigmatropic rearrangement in modern terminology). The mechanism can be divided into three stages, which have been emphasised in a more recent review,<sup>35</sup> and are shown in a mechanistic scheme (Scheme 49 a/b/c).

Stage 1 : Hydrazone-enehydrazine tautomerism



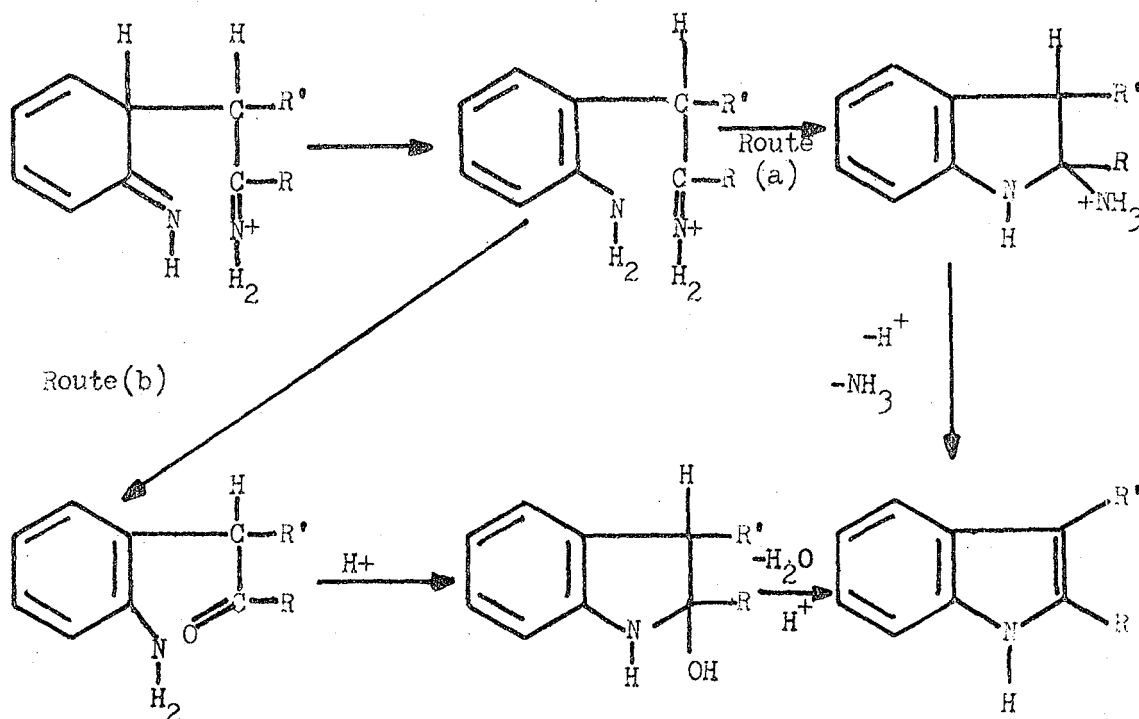
Scheme 49a

Stage 2 : Formation of the new C-C bond ( $\sigma$ -benzidine or [3,3]-sigmatropic rearrangement)



Scheme 49b

Stage 3 Cyclization and loss of ammonia by either of the routes (a) or (b).



Scheme 49c

Tautomerism of the hydrazone to the enehydrazine would seem to constitute the first step in the sequence of reactions. Some inconclusive spectroscopic evidence for the existence of the enehydrazine has been reported,<sup>36-39</sup> and thermodynamic studies by Karabatsos et al.<sup>40</sup> have shown the absence of the enehydrazine due to the greater thermodynamic stability of the hydrazone. A team of Russian workers headed by Suvorov<sup>41,42</sup> have contributed evidence of a more direct nature by isolating various derivatives of the enehydrazine itself.

Stage 2 of the synthesis consists of a [3,3]-sigmatropic shift, resembling the o-Claisen rearrangement. The failure to observe any para-rearrangement has led to some opposition<sup>43,44</sup> that a [3,3]-sigmatropic

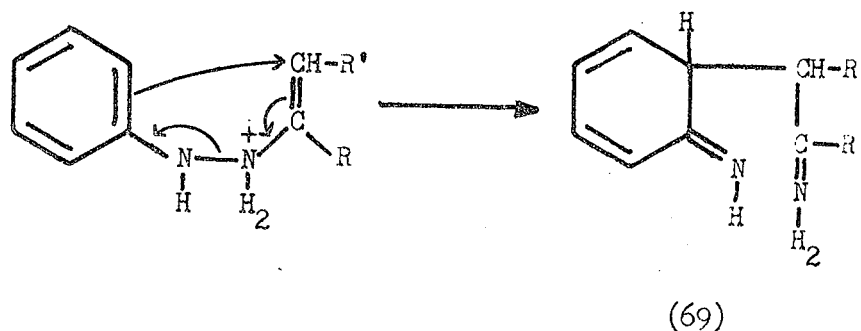


shift is involved (vide infra). Ortho-rearrangement is probably spacially more favoured and so cyclization leading to indole products occurs more easily than para-rearrangement. A para-rearrangement would lead to p-alkylamino acids, p-aminophenylacetaldehyde or p-aminobenzyl ketones which are very reactive species and would form tars under such conditions.<sup>35a</sup> Electron-withdrawing groups on the aromatic ring appear to retard cyclization when judged by yields of product: 1,2,3,4-tetrahydrocarbazole was obtained in 83% yield by thermal indolization, whereas 4,5,6,7-tetrafluoro-1,2,3,4-tetrahydrocarbazole was obtained in 50% yield.<sup>45</sup> Where strongly electron-attracting groups are present on the aromatic nucleus, then more stringent conditions are required for indolization to occur, usually effected by employing a Lewis acid under reflux,<sup>35a,42,46-51</sup> otherwise electron donating groups only require an aprotic acid at room temperature. By selecting carbonyl compounds such as cyclohexanone or deoxybenzoin, where they are known to form indoles relatively easily in hydrocarbon systems, then the ease of cyclization of arylhydrazones containing electron-withdrawing groups can be markedly increased. The nature of substituents on the carbonyl moiety has a much smaller effect on the ease of cyclization.<sup>47</sup>

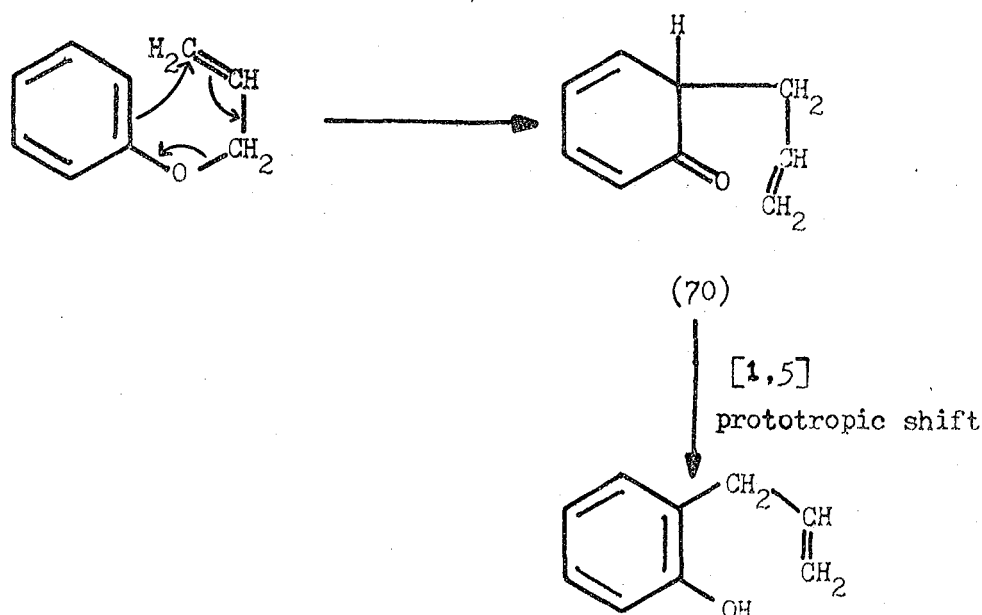
Stage 3 (Scheme 49c) shows the possible ways by which the final step can take place: cyclization can occur either before loss of ammonia (Route a) (thermal reaction) or after loss of ammonia (when an aqueous acid catalyst is present (Route b)).

On comparing the [3,3]-sigmatropic rearrangement products (69) and the ortho-Claisen rearrangement product (70), one can visualize more easily the analogy that Carlin first realized<sup>52</sup> (Scheme 50a/b).

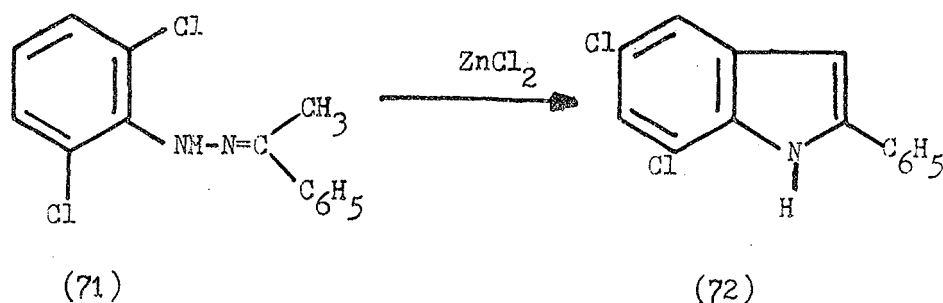
Scheme 50a: Fischer indole, viz. [3,3]-sigmatropic shift reaction mechanism



Scheme 50b: o-Claisen rearrangement reaction mechanism



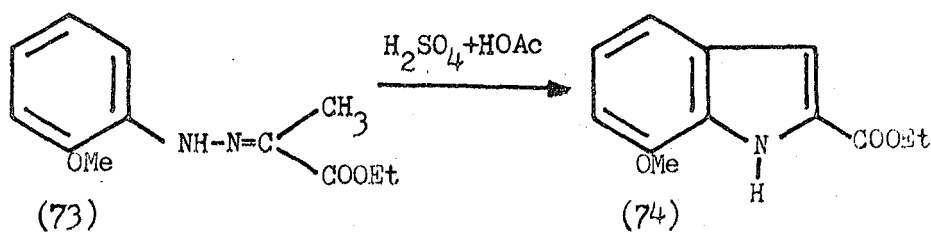
In spite of the very close similarity between the two mechanisms there remains the question : why does para-rearrangement not occur during Fischer indolization ? In 1948, Carlin et al.<sup>83</sup> treated the 2,6-dichlorophenylhydrazone of acetophenone (71) with zinc chloride in order to obtain evidence relating to this problem and obtained a rearrangement product 5,7-dichloro-2-phenylindole (72)(Scheme 51).



Scheme 51

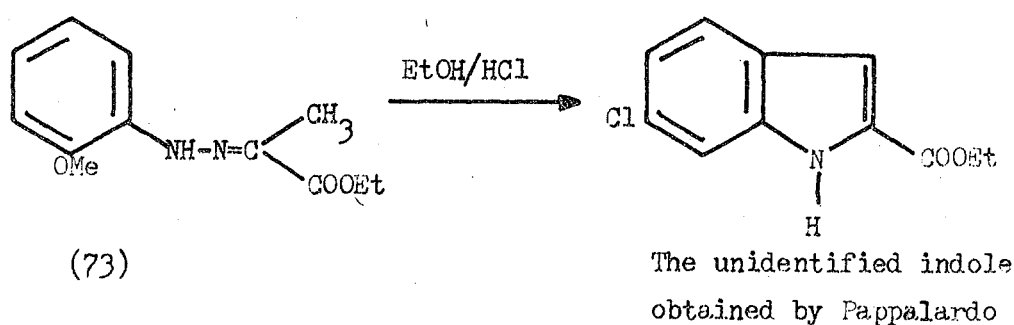
The indolization involved the migration of an ortho-substituent of the starting phenylhydrazone, the first report of such a phenomenon. Later, Carlin et al.<sup>84</sup> also observed either a 1,2- or a 1,4-migration of an o-methyl group when 2,6-dimethylphenylhydrazone derivatives were indolized under Fischer conditions.

Other unusual rearrangements have been reported involving migration of substituents. Dappalardo et al.<sup>85</sup> attempted the indolization of ethyl pyruvate 2-methoxyphenylhydrazone (73) with ethanolic hydrogen chloride and obtained an undefined indole, m.p.  $168^\circ\text{C}$ . (vide infra), and not the expected 7-methoxyindole (74), m.p.  $117^\circ\text{C}$ . which was obtained when the same hydrazone (73) was treated with a mixture of sulphuric and acetic acids (Scheme 52).



Scheme 52

The hydrazone (73) was indolized under varying conditions to give a wide variety of indoles, together with the normally expected 7-methoxy-indole (74). These abnormal reactions can be classified into two major categories, ortho-C6<sup>86</sup> or ortho-C5<sup>87</sup> abnormal Fischer indolizations, according to whether the product is a 6-substituted (e.g. Scheme 53) or a 5-substituted indole.

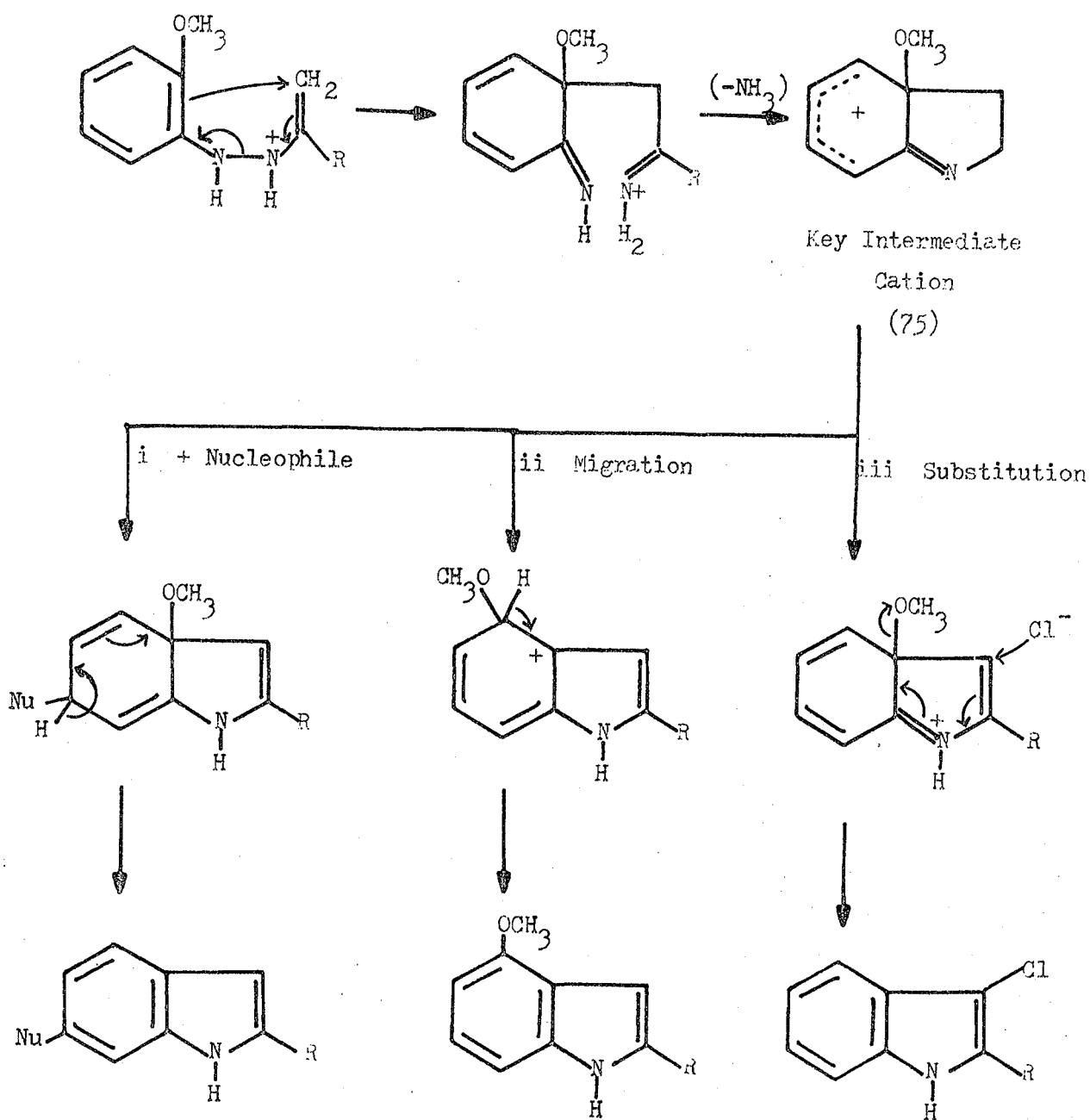


Scheme 53

In a recent paper, Ishii<sup>88</sup> rationalised these unexpected reactions by an expansion of the Robinson and Robinson mechanism (Scheme 54).

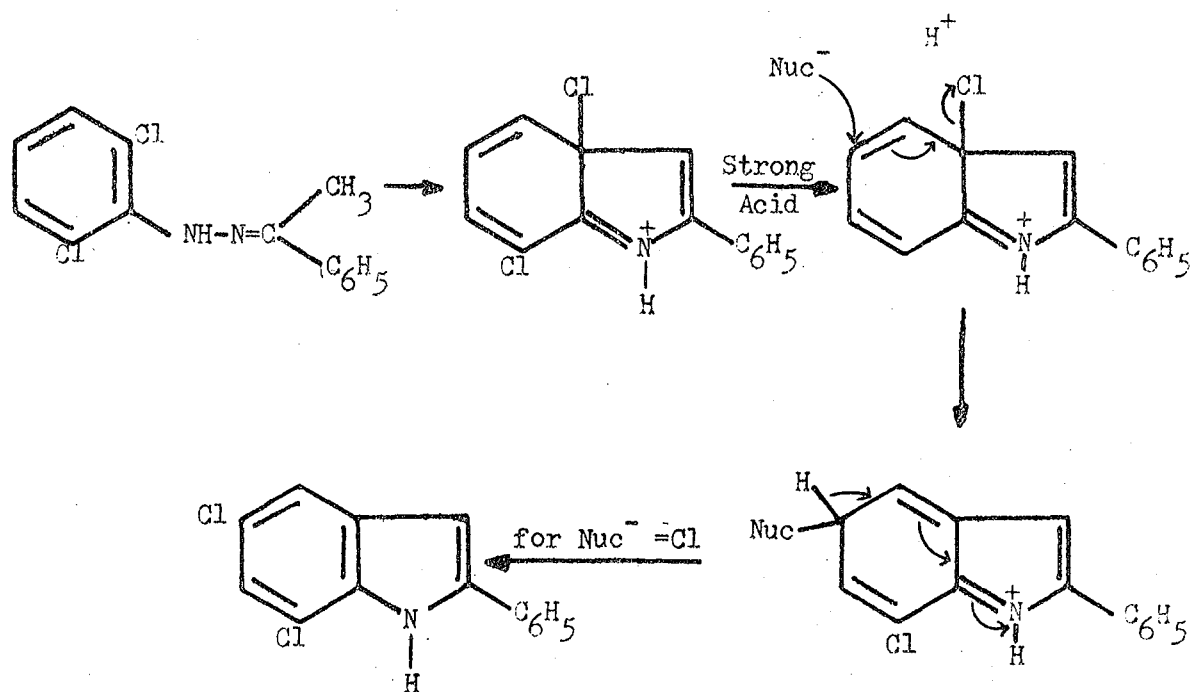
C-C bond formation by the enehydrazine intermediate takes place at the ortho-position occupied by the methoxy groups, thus forming an intermediate with the methoxy group on a tertiary carbon. This is subsequently transformed into the key intermediate (75) by attack of the ring imino nitrogen on the side-chain iminium carbon and expulsion of an ammonia molecule. The intermediate (75) can lead to three different indole products (including the ortho-C6 and ortho-C5 abnormal Fischer indole products), according to the proposed mechanism in scheme 54.

Carlins<sup>83</sup> discovery of the formation of 5,7-dichloroindoles from 2,6-dichlorophenylhydrazone derivatives with zinc chloride would fall into a pathway consistent with that of an ortho-C5 abnormal Fischer



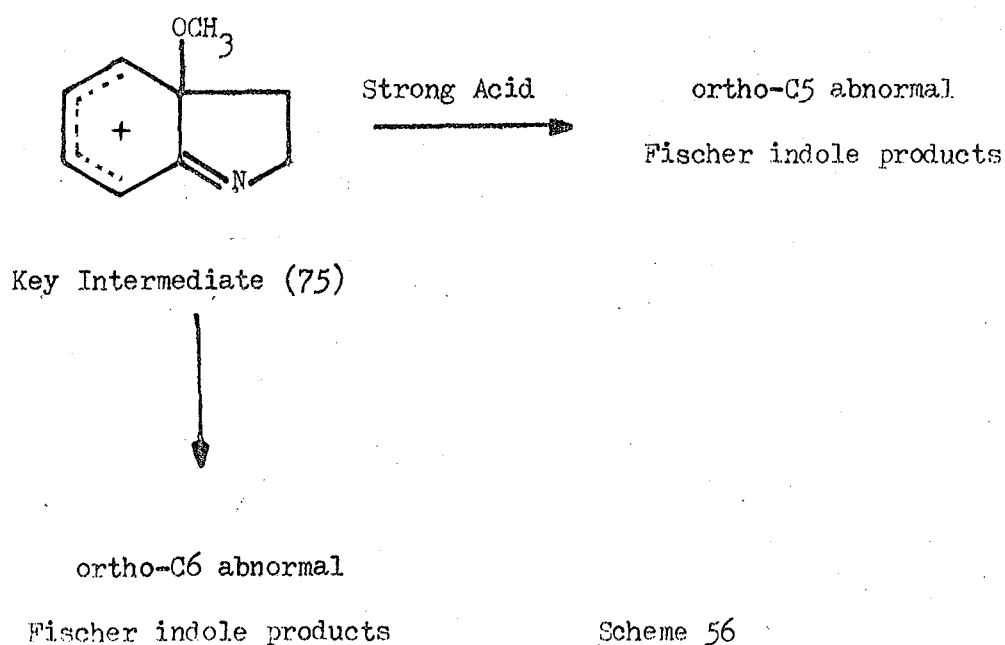
Scheme 54 , R = -COOEt

indolization, involving a 1,3 migration of a chlorine group (Scheme 55).



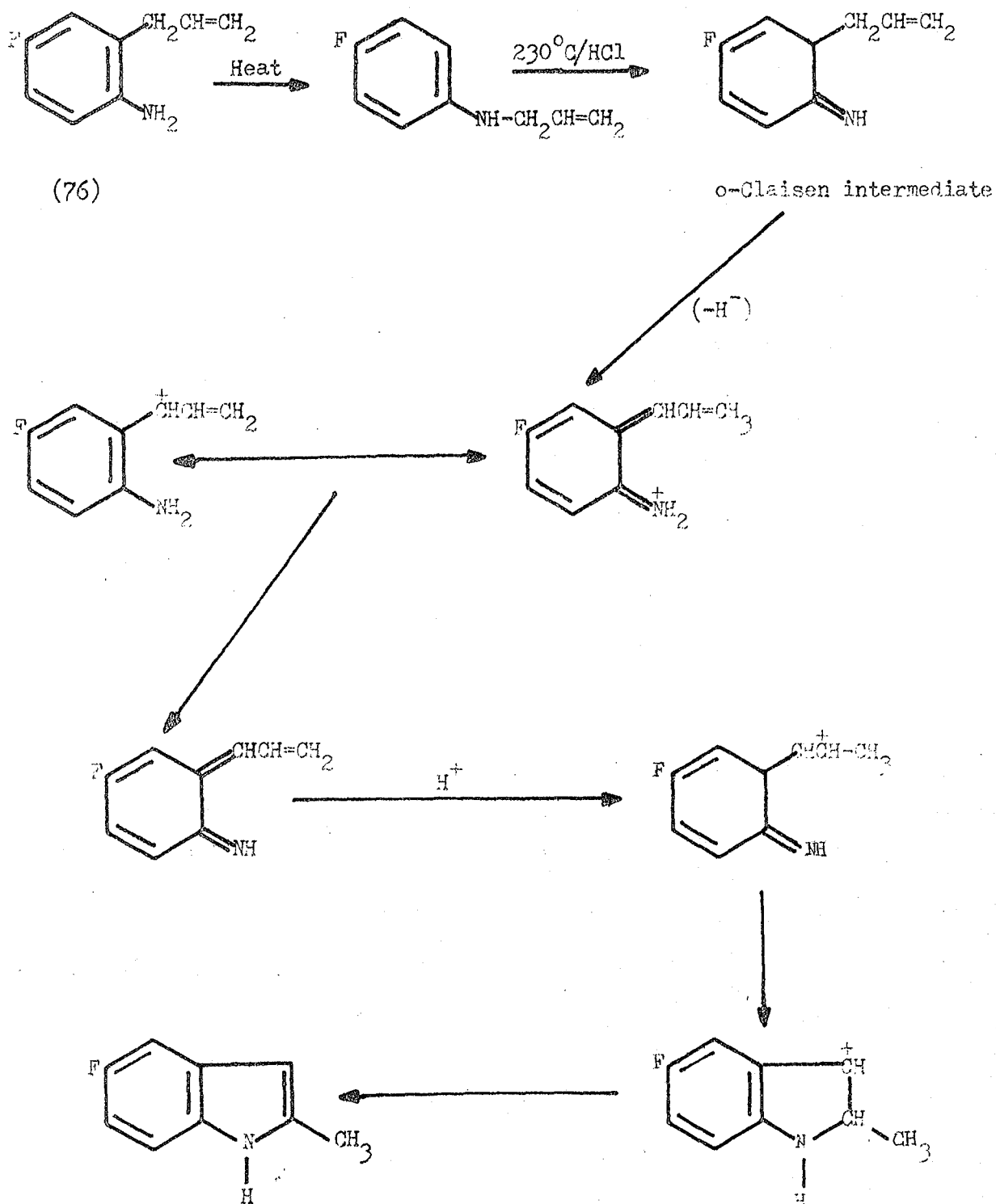
Scheme 55

It would seem that the nature of the reagent is the factor determining the mode of abnormal Fischer indolization (Scheme 56)



Scheme 56

An interesting proton-catalysed amino-Claisen rearrangement of (76) has been reported<sup>53</sup> to give 5-fluoro derivatives of indole (Scheme 57).



Scheme 57

Fischer indolization can be initiated by thermal means alone without the presence of any catalyst.<sup>54-59</sup> Where thermal cyclization takes place only with difficulty such as with cyclohexanone p-nitrophenylhydrazine to give 6-nitro-1,2,3,4-tetrahydrocarbazole,<sup>56</sup> then the addition of acid does enhance the yield.<sup>60</sup>

Aryl hydrazones, the requisite starting material in the Fischer indole synthesis, can be prepared by a wide variety of means.

- (a) A conventional condensation reaction between the arylhydrazine and the corresponding carbonyl compound; usually a ketone or aldehyde. The arylhydrazine being prepared by the reduction of N-nitrosoarylamines.<sup>61-66</sup>
- (b) The reduction of diazonium salts.<sup>64,67-69</sup>
- (c) By nucleophilic attack of hydrazine monohydrate on the aromatic nucleus,<sup>70,71</sup> followed by condensation with the required carbonyl compound.

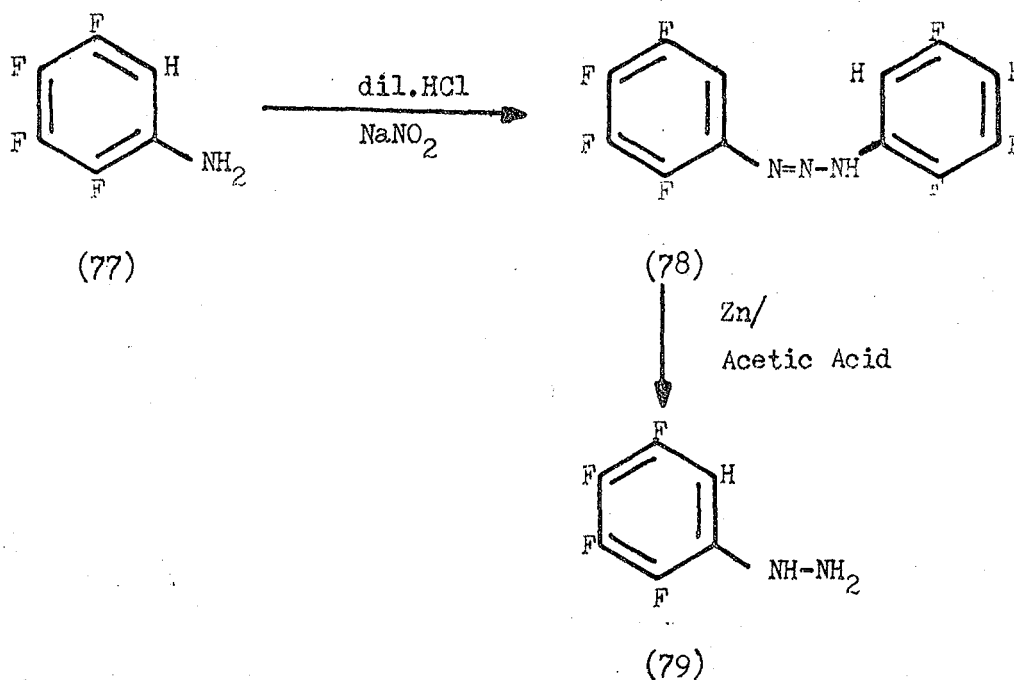
In cases where decomposition of the arylhydrazine readily occurs in solution then cyclisation is effected in situ by addition of the carbonyl compound without isolating the intermediary hydrazone.<sup>64,72</sup> The method was realized as an important means of synthesis when dealing with arylamines which contain an electron-withdrawing group such as the nitro- group and where the indole readily decomposes on exposure to light and heat.

#### 4.2 Preparation of 5,6,7,8-Tetrafluoroindole Derivatives by the Conventional Fischer Indole Synthesis

Petrova et al.<sup>45</sup> have effected the successful synthesis of

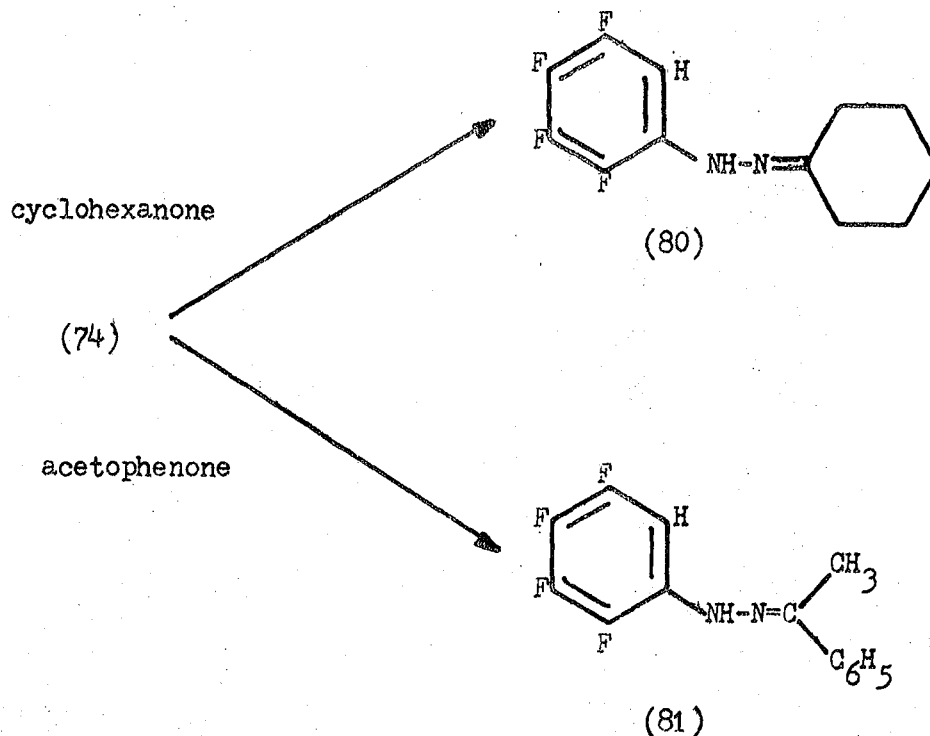


partially fluorinated indole derivatives by a conventional Fischer indole cyclisation reaction. Cyclohexanone and acetophenone are used as the carbonyl moieties. Preparation of a suitable hydrazine (79), viz. containing an ortho-hydrogen, was achieved by the diazotization of 2,3,4,5-tetrafluoroaniline (77) (not a readily available material) to give 2,2',3,3',4,4',5,5'-octafluorodiazaminobenzene (78), followed by reduction with zinc in acetic acid (Scheme 58).



Scheme 58

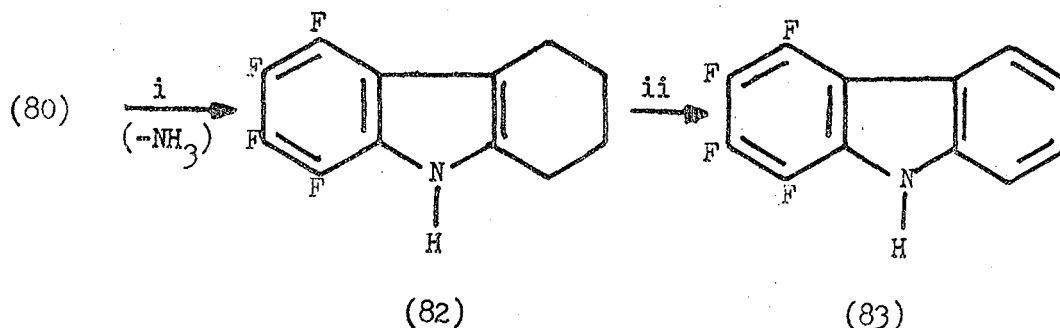
Reaction of (79) with cyclohexanone and acetophenone gave the corresponding hydrazones (80) and (81) respectively (Scheme 59).



Scheme 59

As mentioned in section 4.1, the inclusion of electron-withdrawing groups in the aromatic nucleus appears to reduce the ease of indolization as with the 2,4-dinitrophenylhydrazone of cyclohexanone which requires boiling concentrated hydrochloric acid as a catalyst,<sup>60</sup> compared to cyclohexanone phenylhydrazone which only requires boron trifluoride/benzene.

The use of a strong acid catalyst was employed for the cyclisation of (80) to give 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydrocarbazole (82) in 50% yield. Complete aromatization of (82) was carried with 10% palladium on carbon at 210°C to afford 1,2,3,4-tetrafluorocarbazole (83) (Scheme 60).



Scheme 60 Reagents : i, conc. HCl/reflux  
ii, 10% Pd-C/210°C.

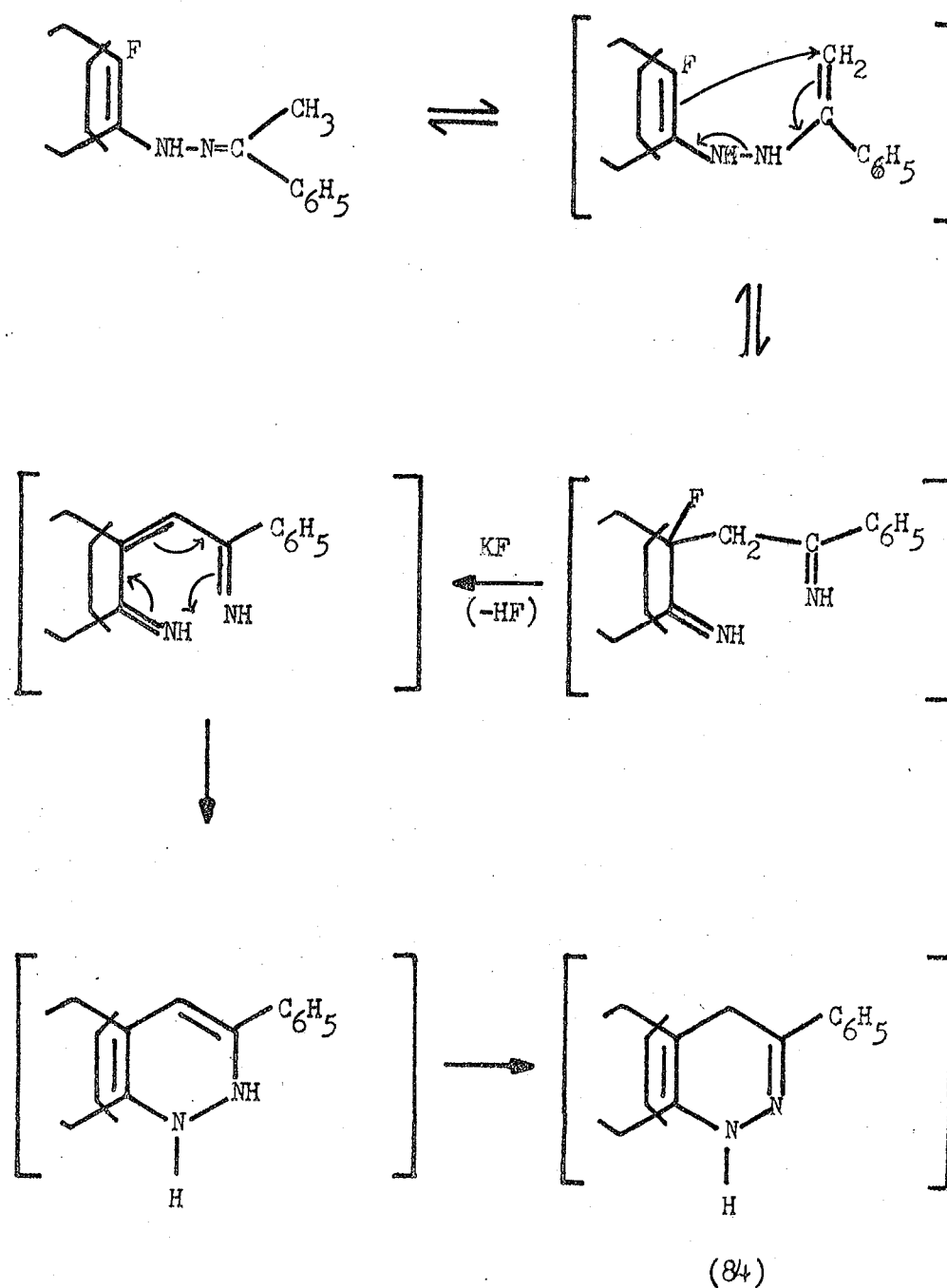
The attempted cyclisation of (81) under identical conditions was not successful : other conventional cyclisation agents such as benzene-BF<sub>3</sub>; CH<sub>3</sub>COOH + conc. H<sub>2</sub>SO<sub>4</sub>; 30% H<sub>2</sub>SO<sub>4</sub>; butanol-H<sub>2</sub>SO<sub>4</sub>; CH<sub>3</sub>COOH saturated with HCl were also unsuccessful. Cyclisation was achieved in 15% yield by using anhydrous zinc chloride.

The conventional Fischer indole synthetic route for the preparation of partially fluorinated products does give a reasonable yield of indole despite the presence of strongly electron-withdrawing substituents on the aromatic nucleus. However, taken in perspective it is the number of steps required to obtain the tetrafluorophenylhydrazine derivative which is the main disadvantage with the method. Until an easier and more efficient synthesis of fluorinated ortho-hydrogen hydrazones can be formulated, then this synthetic route is not very practical.

#### 4.3 The Attempted Synthesis of Partially Fluorinated Cyclic Hydrazones from Polyfluoroarylhydrazones and KF. The Unexpected Formation of Fischer Indole Products<sup>73</sup>

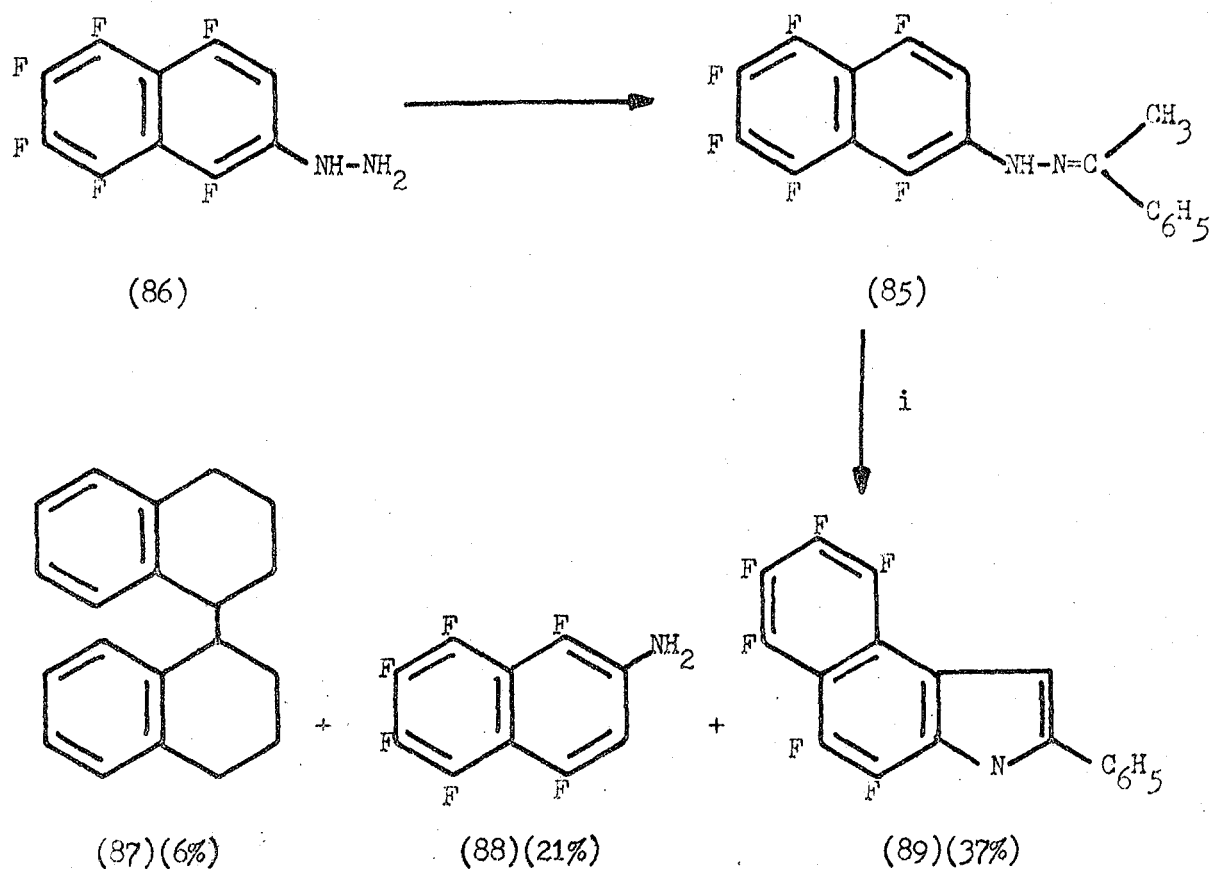
The key step in the Fischer indole synthesis from hydrocarbon

arylhydrazones is generally accepted as involving a [3,3]-sigmatropic shift of the tautomeric enehydrazine.<sup>74</sup> However, in polyfluorinated systems it was envisaged<sup>73</sup> that dehydrofluorination with KF would lead to the novel cyclic hydrazone (84) (Scheme 61).



Scheme 61

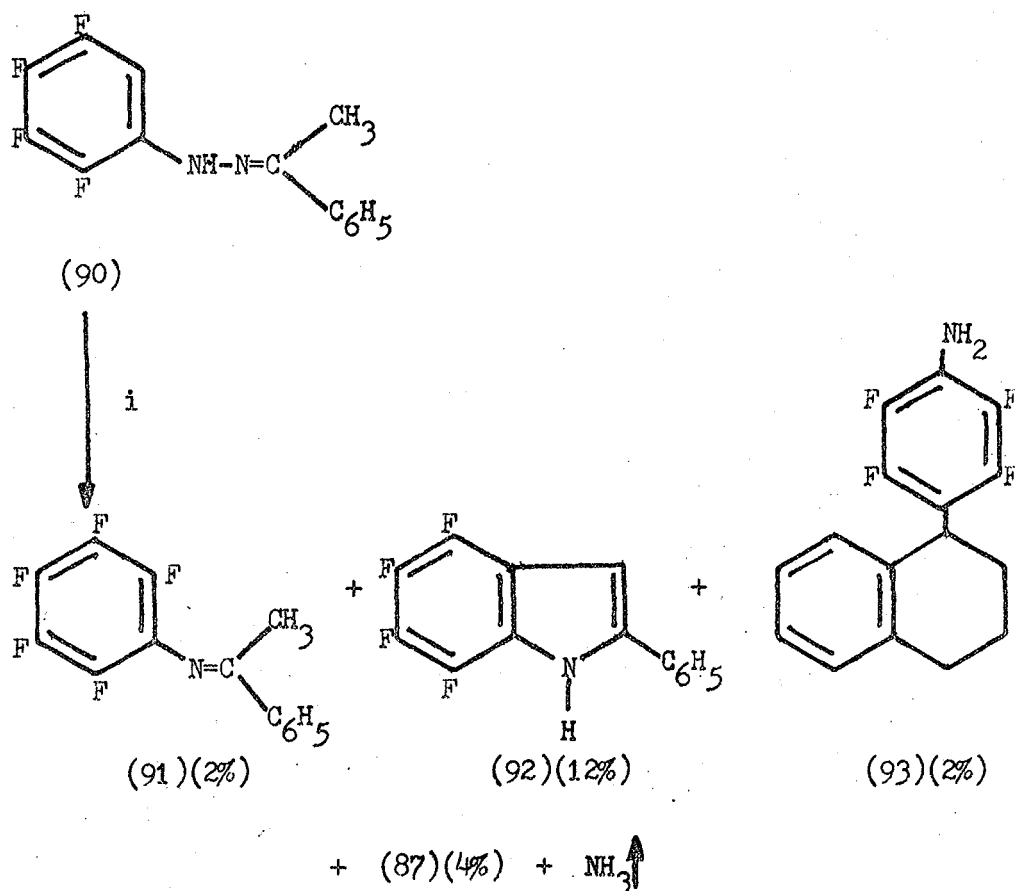
Acetophenone 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazone (85)<sup>73</sup> readily prepared by the condensation reaction of acetophenone with 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazine (86), was heated under reflux in dry tetralin for 24 h in the absence of KF which had been shown in preliminary experiments to have no effect on the course of the reaction. A complex mixture of components was formed from which was isolated the following compounds : 1,1',2,2',3,3',4,4'-octahydro-1,1'-bisnaphthyl (87) (6%); 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine<sup>76</sup> (88) (21%) and 2-phenyl-4,5,6,7,8,9-hexafluorobenz[e]indole (89) (37%)<sup>73</sup> (Scheme 62).



Scheme 62 Reagents : i, Tetralin/Reflux

The complexity of the products and the relative insolubility of the unidentified materials necessitated the requirement of a lower molecular-weight starting material such as acetophenone pentafluorophenylhydrazone<sup>73</sup> (90) from which other products could be identified which would be conducive to the elucidation of the reaction mechanism involved.

The acetophenone derivative of pentafluorophenylhydrazine (90) was heated under reflux<sup>73</sup> in tetralin for 24 h. Ammonia was evolved and the following products isolated from the reaction mixture : 1,1',2,2',3,3',4,4'-octahydro-1,1'-bisnaphthyl (87)(4%); 4,5,6,7-tetrafluoro-2-phenylindole (92)(12%); pentafluoro-N-( $\alpha$ -methylbenzylidene)aniline (91) (2%) and 2,3,5,6-tetrafluoro-4-(1,2,3,4-tetrahydro-1-naphthyl)aniline (93)(2%)(Scheme 63).



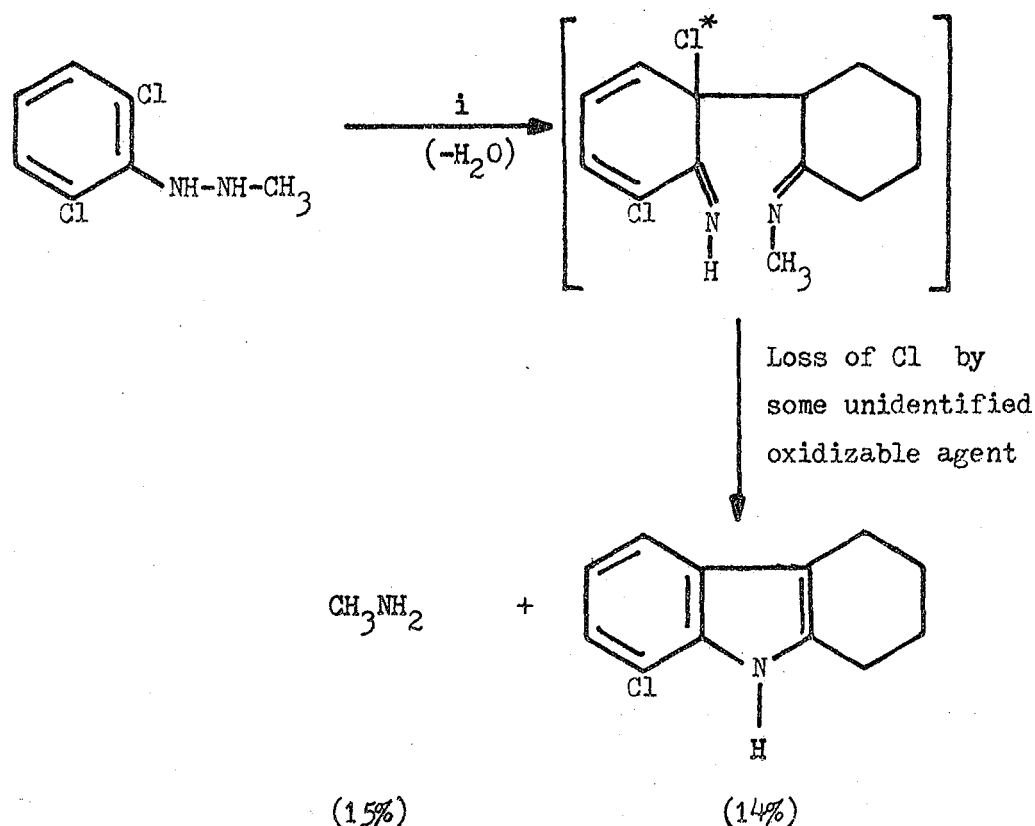
Scheme 63 Reagents : i, Tetralin/Reflux

The indole (92) had been previously prepared by a group of Russian workers<sup>45</sup> (see Pg.51) by a conventional Fischer indole reaction in 15% yield.

Overall, the stoichiometry of both cyclisations [(85)→(89) & (90)→(92)] requires the loss of  $\text{'NH}_2\text{F'}$ .

It is noteworthy that two precedents, both involving cyclisations by displacement of an ortho-halogen atom have been reported.

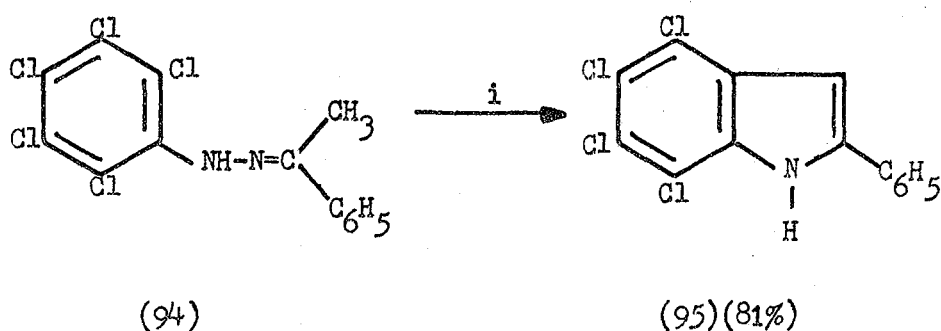
- (i) Loss of ortho-chlorine ( $\text{Cl}^*$ ) during the Fischer indole reactions<sup>77</sup> (Scheme 64).



Scheme 64 Reagents : i, Cyclohexanone in benzene/Reflux

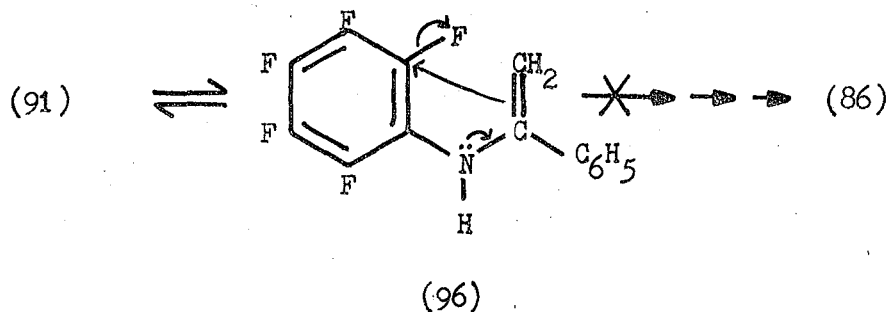
- (ii) The conversion of acetophenone pentachlorophenylhydrazone (94) into 4,5,6,7-tetrachloro-2-phenylindole (95) using

polyphosphoric acid (Scheme 65), a reaction which failed to give the corresponding tetrafluoroindole (92) when compound (90) was used.<sup>75</sup>



Scheme 65 Reagents : i, Polyphosphoric acid/200°C.

An analogous loss of fluorine by an oxidation process could account for the indole formation, although the isolation of the imine (Schiff's base) (91) does suggest another more plausible process. This involves tautomerism of (91) to (96) (Scheme 66).

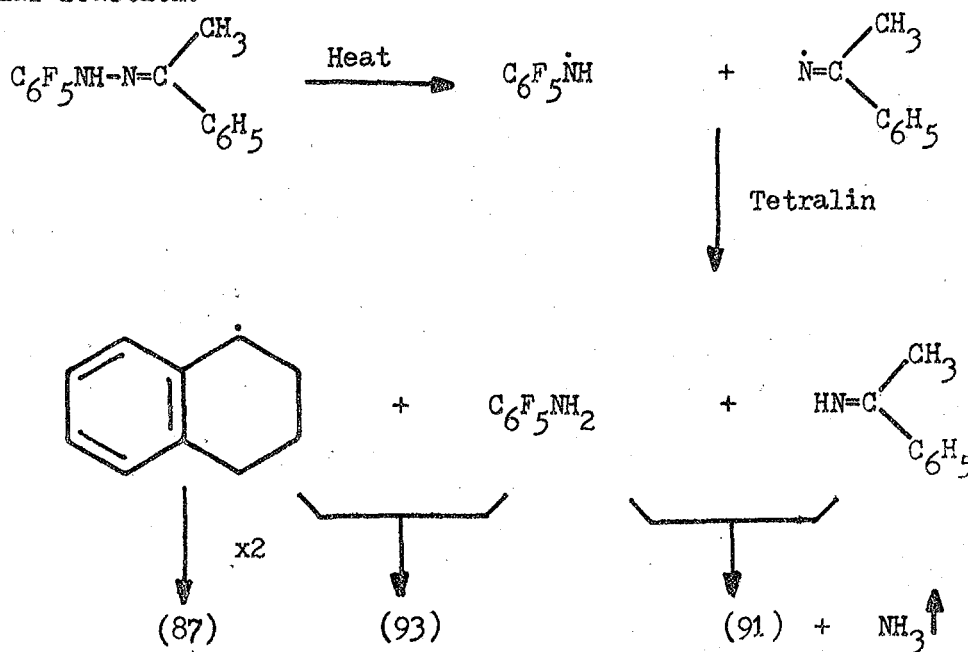


Scheme 66



Previously, the adduct of pentafluoroaniline and diethyl acetylene-dicarboxylate, a substrate closely related to (96), had been converted into the corresponding indole by reaction with sodium hydride in tetrahydrofuran under reflux, although in very low yield (<3%)<sup>14</sup> (see Scheme 23). Blazejewski and Wakesman<sup>78</sup> have had considerable success with the conversion of other enamines with hexafluorobenzene into 4,5,6,7-tetrafluoroindole derivatives. This hypothesis was tested experimentally when both the imine (91) and Heptafluoro-N-( $\alpha$ -methylbenzylidene)-2-naphthylamine were heated in refluxing tetralin with added anhydrous zinc chloride (to catalyse the tautomerism) for 24 h. The crude reaction product contained mainly starting material (83%), but no indole was isolated, even under more rigorous conditions with the inclusion of potassium fluoride.

The remaining products (87), (88), (91), (93) and ammonia could be attributed to the thermal degradation of the arylhydrazone by an initial homolytic fission of the N-N bond (Scheme 67) which has been reported in a similar reaction.<sup>79</sup>



Scheme 67

## CHAPTER 5

### DISCUSSION OF RESULTS

## 5.1 Introduction

The most obvious synthetic route to a partially fluorinated indole derivative would employ the use of the Fischer indole reaction. A poly-fluorinated arylhydrazine precursor is required which has specifically hydrogen in the ortho-position. This conventional synthetic route has been investigated by Russian workers<sup>45</sup> (see section 4.2) who used cyclohexanone and acetophenone-2,3,4,5-tetrafluorophenylhydrazones to form the corresponding indoles with yields of 50% and 15% respectively. Less efficient reactions were expected because of the presence of the electron-withdrawing fluorine substituents in the aromatic nucleus; this was reflected in reduced yields for the cyclisation of cyclohexanone 2,3,4,5-tetrafluorophenylhydrazone (50%), compared with the cyclisation of cyclohexanone phenylhydrazone (80%).

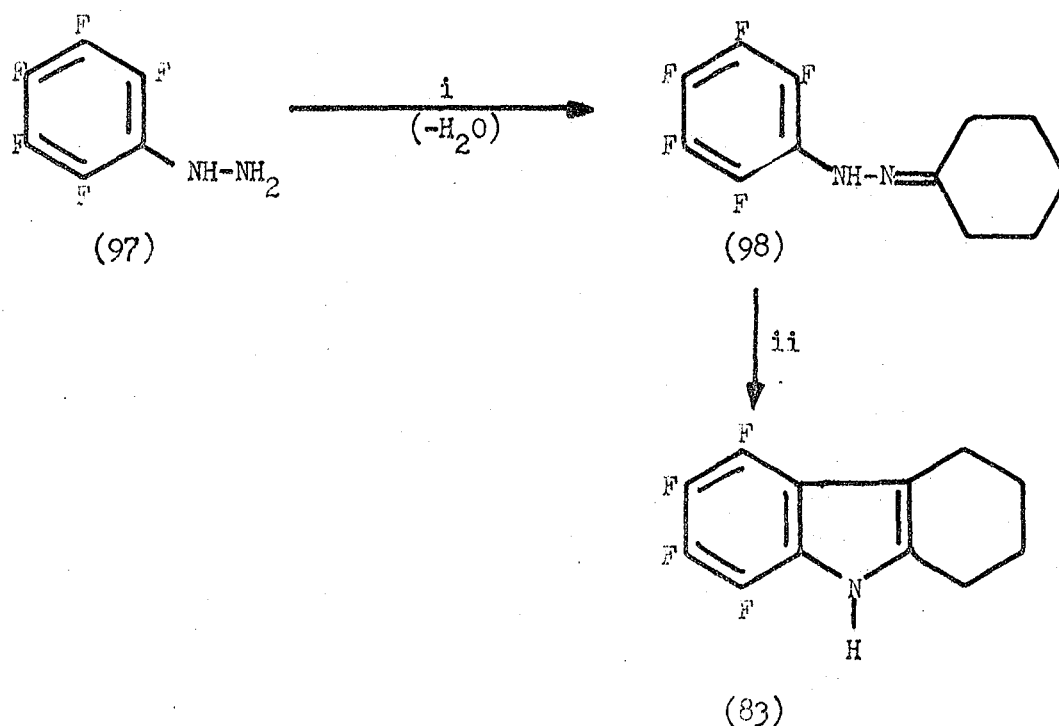
## 5.2 Indolization of Partially Fluorinated Aromatic Hydrazones Bearing an ortho-fluorine

An alternative route was realized in a series of experiments by Brooke,<sup>73</sup> when attempting to synthesize novel polyfluorinated cyclic hydrazones (see section 4.3).

The purpose of the work presented in this thesis was to explore the generality of this reaction further, with various hydrazone derivatives: to ascertain yields and the existence of other possible products which may contribute to an understanding of a plausible mechanism.

The synthesis of 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydrocarbazole (83) from cyclohexanone 2,3,4,5,6-pentafluorophenylhydrazone (98),

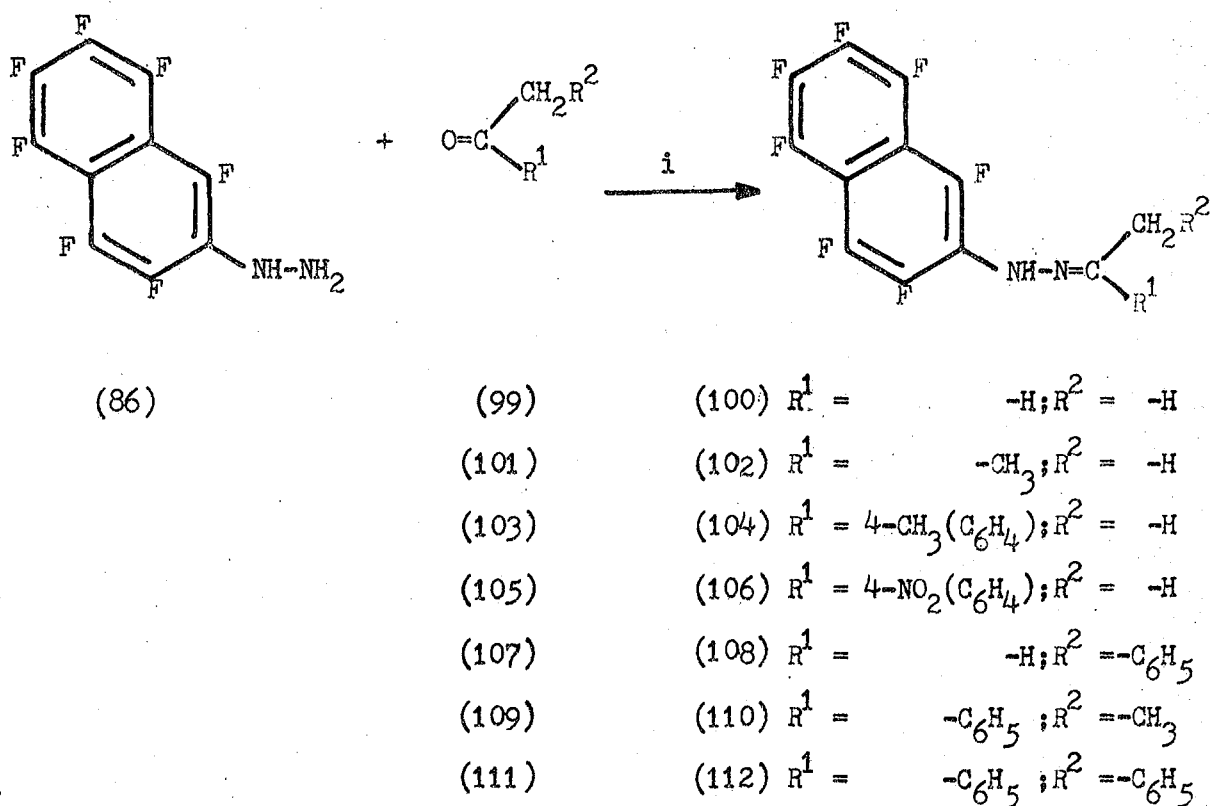
prepared from 2,3,4,5,6-pentafluorophenylhydrazine (97)<sup>70</sup> and cyclohexanone enabled a second direct comparison to be made of the efficiency of this new process and the conventional Fischer indole reaction. Indolization was effected by thermolysis in dry tetralin for 24 h (Scheme 68).



Scheme 68 Reagents : i, cyclohexanone/reflux  
ii, tetralin/reflux

The carbazole (83) was isolated as the major product in 18% yield from a complex mixture, whereas a 50% yield was achieved by the conventional Fischer indole reaction using cyclohexanone 2,3,4,5-tetrafluorophenylhydrazine (80) (see Pg. 50). In spite of the lower yield however, the ease of preparation of the starting material should not be forgotten in this comparison. As acetophenone 1,3,4,5,6,7,8-heptafluoronaphthylhydrazine (85) reacted more efficiently than the corresponding pentafluorophenyl

derivatives, then this justified the use of these naphthylhydrazones in investigating further the effect of various substituents attached to the carbonyl compound precursor. In most cases the hydrazone intermediate was isolable: only those prepared from aldehydic-type carbonyl compounds could not be obtained in a pure enough state for characterization. In such cases the hydrazones [(100) & (108)] were prepared and cyclized in situ, by a "one-pot" reaction. Scheme 69 shows the new hydrazones that were prepared and Table 1 their yields. No attempt was made to isolate (87) which had been found previously.



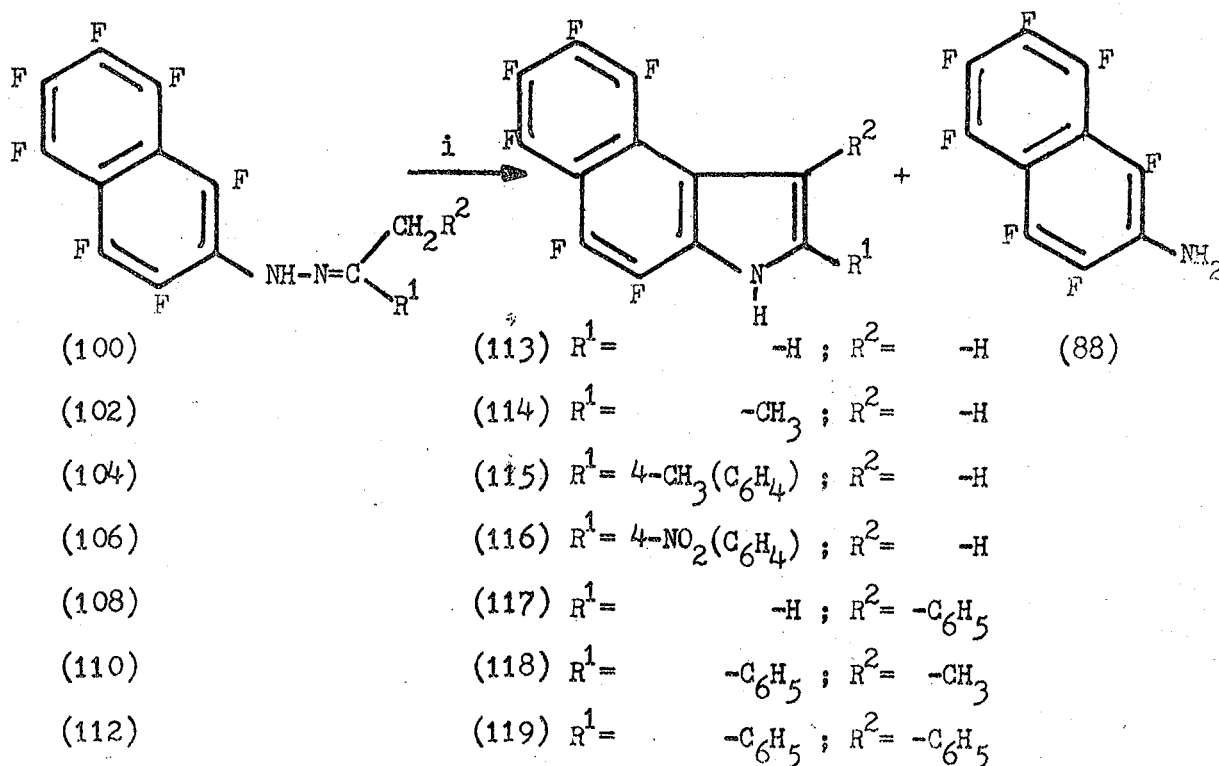
Scheme 69 Reagents : i, EtOH/Reflux

Table 1 : Carbonyl Compounds Used in the Synthesis of Heptafluoronaphthyl-  
hydrazones With Their Respective Yields

Carbonyl Compound	R <sup>1</sup>	R <sup>2</sup>	Hydrazone	Yield
Acetaldehyde (99)	-H	-CH <sub>3</sub>	(100)	Not isolable
Acetone(101)	-CH <sub>3</sub>	-CH <sub>3</sub>	(102)	76%
p-Methylacetophenone(103)	4-CH <sub>3</sub> (C <sub>6</sub> H <sub>4</sub> )	-CH <sub>3</sub>	(104)	90%
p-Nitroacetophenone(105)	4-NO <sub>2</sub> (C <sub>6</sub> H <sub>4</sub> )	-CH <sub>3</sub>	(106)	60%
Phenylacetaldehyde(107)	-H	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	(108)	Not isolable
Propiophenone(109)	-C <sub>6</sub> H <sub>5</sub>	-CH <sub>2</sub> CH <sub>3</sub>	(110)	84%
Deoxybenzoin(111) <sup>†</sup>	-C <sub>6</sub> H <sub>5</sub>	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	(112)	48%

<sup>†</sup> Deoxybenzoin = 1,2-diphenylethanone

Each of the prepared hydrazones was indolized under the same conditions, viz. refluxed in dry tetralin for periods of up to 24 h (Scheme 70), the results are recorded in Table 2.



Scheme 70 Reagents : i, Tetralin/Reflux

Table 2 : Yields of Indole & Heptafluoro- $\beta$ -naphthylamine(88) in the Cyclisation Step

Indole	Yield of Indole	Yield of (88)
(89)	40%	16%
(113)	Trace	13%
(114)	17%	21%
(115)	41%	12%
(116)	-	Not Known
(117)	44% <sup>†</sup>	8%
(118)	34%	19%
(119)	42%	0%

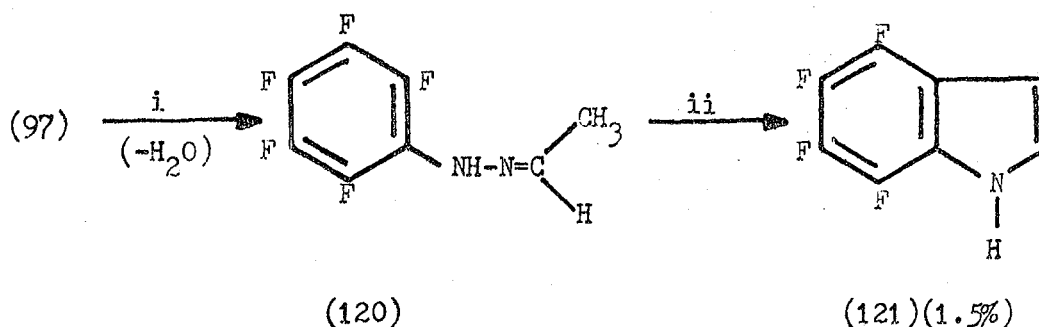
<sup>†</sup> : assuming 100% conversion of hydrazine(86) to hydrazone(108).

The yields in each case were calculated for the cyclisation step from the hydrazone, except in the case of (117) where reaction of 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazine (86) with phenylacetaldehyde gave an overall yield of 24%.

It can be seen that there exists little or no correlation between the yields of indole obtained and the structure of the carbonyl moiety used. Generally speaking, it would seem that hydrazones with aromatic substituents produce the best yields, compared to methyl or hydrogen. An interesting comparison can be made between the two isomers (89) and (117) which are produced in yields of 40% and 44% respectively ; almost identical.

The conventional Fischer indole synthesis is peculiar in that it does not work using the arylhydrazone obtained from acetaldehyde. However, such a synthesis (albeit highly inefficient) has now been achieved

using a polyfluorarylhydrazone by Brooke.<sup>80</sup> Acetaldehyde 2,3,4,5,6-pentafluorophenylhydrazone (120) was prepared from 2,3,4,5,6-pentafluorophenylhydrazine (97) and acetaldehyde. Thermolysis of (120) in dry tetralin gave 4,5,6,7-tetrafluorophenylindole (121) in 1.5% yield (Scheme 71).



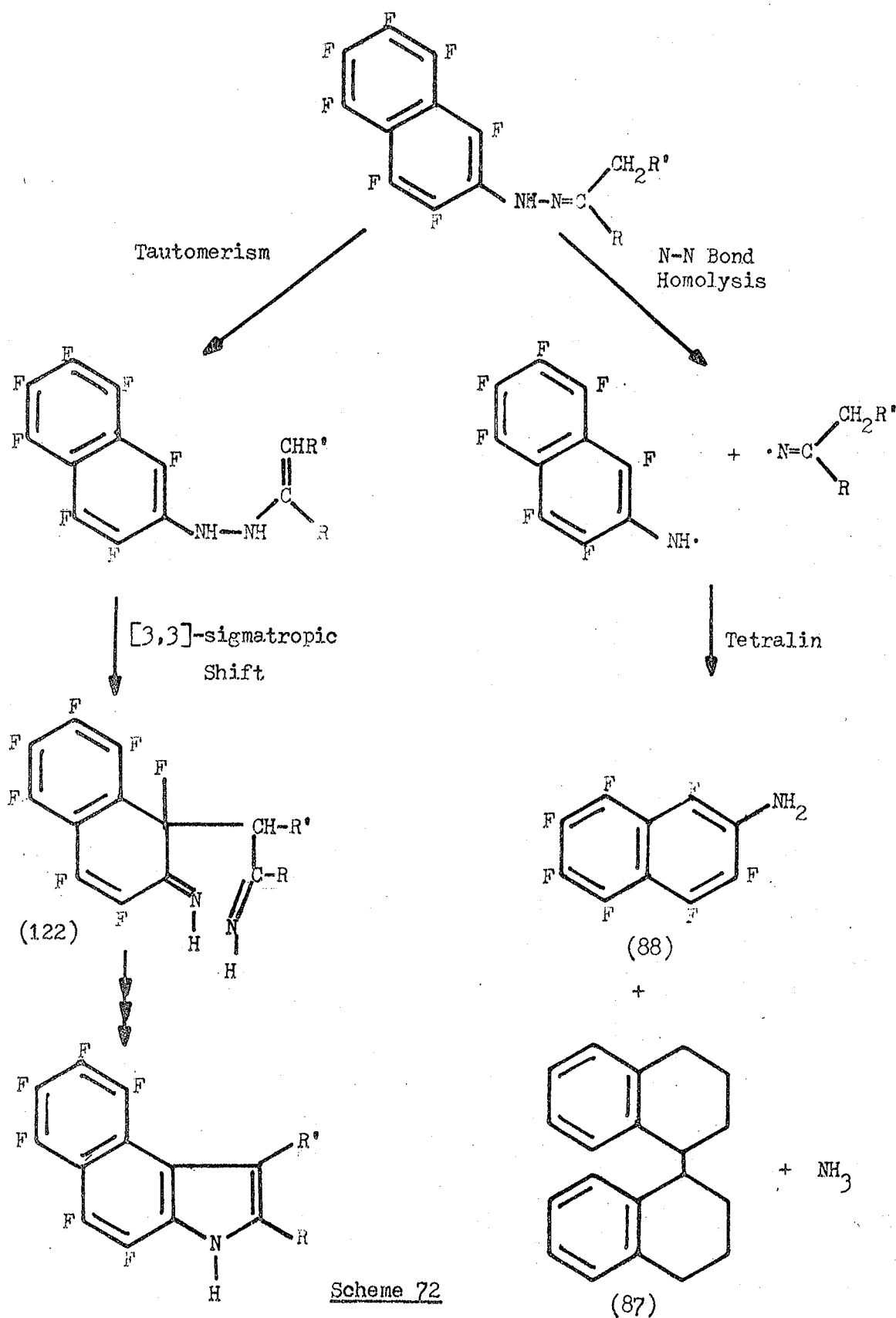
Scheme 71 Reagents : i, EtOH/Reflux  
ii, Tetralin/Reflux

The formation of 4,5,6,7,8,9-hexafluoro-2-(4-nitrophenyl)benz[e]indole (116) could not be established. A yellow solid was obtained (ca. 12%) which failed to analyse correctly, the N-H stretch of the i.r., although in the correct region of the spectrum was too broad. Mass spectroscopy however, did reveal a compound with the required molecular weight for the indole (116).

Thermolysis of these hydrazones not only produced the indole as the major product but, due to an undesirable side-reaction, initiated by homolysis of the N-N bond<sup>79</sup> (see Pg. 57), various other products were found, principally 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88). Compound (88) was produced in significant enough amounts to be recorded alongside that of the indole (see Table 2). Together, they can be seen as a ratio of the extent to which the two competing reactions take place,



i.e. indolization versus N-N bond homolysis (Scheme 72).



It is noteworthy that no 3-fluoroindole derivatives were isolated in any of this work. Moreover, Suschitzky<sup>75</sup> was surprised that no 3-chloro indole material was formed from acetophenone pentachlorophenylhydrazone (Scheme 65). This would imply that there is no free halogen atom or electrophilic halogenating species present during the course of the reactions. Ishii<sup>88</sup> invoked the presence of a key intermediate cation which can undergo a variety of transformations leading to abnormal Fischer indole products (see Pg. 45). Pathway iii involves the attachment of halide anion at the C-3 position of intermediate (75) and gives rise to the 3-haloindole derivative. This mechanism is discounted in the present work for that very reason: no 3-fluoroindole derivative was isolated.

The exact mode of loss of the ortho-fluorine in the indole forming reactions described in this thesis is not understood at the present time.

### 5.3 Conclusion

The work described in this thesis has demonstrated that a variety of 1,3,4,5,6,7,8-heptafluoronaphthylhydrazones can be used as substrates in the formation of indole derivatives by the surprising loss of an ortho-fluorine; the preparation of ortho-hydrogen containing substrates for the classical Fischer indole reaction is unnecessary.

The studies have not contributed to an understanding of the mechanism of the reaction, and further work is required. Of particular interest would be an investigation of the use of different high boiling-point solvents in the reaction, especially those which lack any benzylic hydrogens.

## CHAPTER 6

### EXPERIMENTAL

6.1 Preparation of 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine<sup>71</sup>(86)

Octafluoronaphthalene (31.87g) and hydrazine monohydrate (5.9g) were heated together under reflux in ethanol (180 ml.) for 4 h and then poured into water and extracted with diethyl ether. The extract was dried ( $\text{MgSO}_4$ ), filtered, and the solvent evaporated to leave a brown solid (22.52g). The unreacted octafluoronaphthalene was removed by vacuum sublimation at  $35-40^\circ\text{C}/0.001\text{mmHg}$ . Raising the temperature to  $70-75^\circ\text{C}/0.001\text{mmHg}$  caused the 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazine (86) to be sublimed, and was recrystallised from light petroleum (b.p.  $100-120^\circ\text{C}$ .), lit., m.p.  $118-119^\circ\text{C}$ .

6.2 Preparation of Cyclohexanone Pentafluorophenylhydrazone (98)

Pentafluorophenylhydrazine<sup>70</sup>(97)(8.92g), cyclohexanone (4.64g) and ethanol (250 ml.) were heated together under reflux for 1 h. The ethanol was removed in vacuo leaving a wet orange solid which was dissolved in ether and the solution dried ( $\text{MgSO}_4$ ). Evaporation of the solvent and crystallisation of the solid (13.92g) from ethanol/water required external cooling and gave the pure phenylhydrazone (98) (9.35g, 75%), m.p.  $68-69^\circ\text{C}$  [Found : C, 52.00; H, 4.11; N, 9.70%;  $M^+$ , 278.  $\text{C}_{12}\text{H}_{11}\text{F}_5\text{N}_2$  requires C, 51.80; H, 3.99; N, 10.07%;  $M$ , 278];  $\nu_{\text{max}}$   $3230\text{ cm}^{-1}$  (N-H).

6.3 Attempted Preparation of Acetaldehyde 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (100)

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86)(5.00g), acetaldehyde

(0.77g) and ethanol (50 ml.) were heated together under reflux for 2 h. The mixture was evaporated to give a brown tarry solid (5.34g). Examination by t.l.c. on silica using  $\text{CHCl}_3\text{-CCl}_4$  (50:50 v/v) revealed a multicomponent mixture with no trace of 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazine (86). An attempt to separate the mixture by flash chromatography on silica (160mm x 50mm) using the same eluant was not successful. However, a vacuum sublimation at  $60\text{-}65^\circ\text{C./}0.001\text{ mmHg}$  did give a solid, although this could not be obtained pure due to continual decomposition. The solid was identified as the hydrazone (100) by i.r. spectroscopy;  $\nu_{\text{max}} 3360\text{ cm}^{-1}$  (N-H).

#### 6.4 Preparation of Acetone 1,3,4,5,6,7,8-Heptafluoro-2-Naphthylhydrazone (102)

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86) (5.00g), acetone (2.48g) and ethanol (50 ml.) were heated together under reflux for 2 h, during which time a pink solid (4.35g, 76%) precipitated. Evaporation of the liquid components of the mixture followed by recrystallisation of the residual solid from light petroleum (b.p.  $60\text{-}80^\circ\text{C.}$ ) and vacuum sublimation at  $80\text{-}85^\circ\text{C./}0.001\text{ mmHg}$  gave the pure naphthylhydrazone (102) (2.95g), m.p.  $99.5\text{-}100.0^\circ\text{C.}$  [Found : C, 48.10; H, 1.78; N, 8.24%.  $\text{C}_{13}\text{H}_7\text{F}_7\text{N}_2$  requires C, 48.15; H, 2.18; N, 8.64%; M. 324];  $\nu_{\text{max}} 3370\text{ cm}^{-1}$  (N-H).

#### 6.5 Preparation of (4-Methylacetophenone) 1,3,4,5,6,7,8-Heptafluoro-2-Naphthylhydrazone (104)

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86) (5.01g), 4-methyl-

acetophenone (2.72g), and ethanol (50 ml.) were heated together under reflux for 2 h, during which time a pink-white solid was precipitated. The mixture was filtered and the solid washed with more ethanol. Recrystallisation from toluene-light petroleum (b.p. 100-120°C.) gave the pure naphthylhydrazone (104) (5.72g, 90%), m.p. 192.0-192.5°C. [Found : C, 56.87; H, 2.62; N, 7.07%.  $C_{19}H_{11}F_7N_2$  requires C, 57.00; H, 2.78; N, 7.00%; M, 400];  $\nu_{\max}$  3370  $\text{cm}^{-1}$  (N-H).

#### 6.6 Preparation of (4-Nitroacetophenone)1,3,4,5,6,7,8-Heptafluoro-2-Naphthylhydrazone (106)

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86) (3.98g), 4-nitroacetophenone (2.50g), and ethanol (50 ml.) were heated together under reflux for 1.5 h, during which time a yellow-brown solid was precipitated. The mixture was filtered and washed with ethanol. Analytical t.l.c. on silica using  $\text{CHCl}_3$ - $\text{CCl}_4$  (50:50 v/v) as eluant showed it to be a mixture of the naphthylhydrazone (106) and unreacted p-nitroacetophenone. Separation of the product was achieved by dissolving in diethyl ether the more soluble p-nitroacetophenone. The mixture was filtered and the undissolved material washed with more diethyl ether leaving the naphthylhydrazone (106) behind (3.53g, 60%). Recrystallisation from toluene-light petroleum (b.p. 100-120°C.) and vacuum sublimation at 165-175°C./0.001 mmHg gave the pure naphthylhydrazone (106) m.p. 201.5-202.0°C. [Found : C, 50.11; H, 1.48; N, 9.35%.  $C_{18}H_8F_7N_3O_2$  requires C, 50.13; H, 1.86; N, 9.74%; M, 431];  $\nu_{\max}$  3360  $\text{cm}^{-1}$  (N-H).

6.7 Attempted Preparation of Phenylacetaldehyde 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (108)

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86)(1.56g), phenylacetaldehyde (0.71g), and ethanol (50 ml) were heated together under reflux for 2 h. Evaporation of the solvent in vacuo left a brown tarry residue (2.39g) which was separated on silica by flash chromatography (160mm x 50mm) using  $\text{CHCl}_3$ - $\text{CCl}_4$  (70:30 v/v) as eluant. Analytical t.l.c. revealed a complex mixture of components which were further separated by vacuum sublimation at 130-140°C./0.001mmHg to give a white-yellow sublimate. Successive recrystallisations from light petroleum (b.p. 60-80°C) would not give a constant melting-point sample of (108) due to continual decomposition, but material of m.p. 85.5-86.5°C was submitted for elemental analysis [Found : C, 53.36; H, 2.32; N, 6.74%.  $\text{C}_{18}\text{H}_9\text{F}_7\text{N}_2$  requires C, 55.96; H, 2.35; N, 7.25%; M, 386]. Identified by i.r. spectroscopy,  $\nu_{\text{max}}$  3310  $\text{cm}^{-1}$  (N-H).

6.8 Preparation of Propiophenone 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (110)

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86)(3.79g), propiophenone (1.88g), and ethanol (80 ml.) were heated together under reflux for 2 h. On cooling, pale pink crystals of the naphthylhydrazone were deposited and were filtered with further ethanol to give a solid (1.19g). The remaining naphthylhydrazone was recovered by evaporation in vacuo of the solvents from the mother liquors to give the crude product (5.46g). Recrystallisation from light petroleum (b.p. 100-120°C.) gave the pure naphthylhydrazone (110).

(4.51g, 84%), m.p. 138-139°C [Found : C, 57.03; H, 2.49; N, 6.65%.  $C_{19}H_{11}F_7N_2$  requires C, 57.05; H, 2.78; N, 7.01%; M, 400].  $\nu_{\max}$  3370  $\text{cm}^{-1}$  (N-H).

#### 6.9 Preparation of Deoxybenzoin 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (112)

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86) (1.04g), deoxybenzoin (1,2-diphenylethanone) (0.76g), and ethanol (50 ml.) were heated together under reflux for 2 h. The solid naphthylhydrazone was obtained by evaporation in vacuo of the liquid components. Recrystallisation of the solid from toluene-light petroleum (b.p. 100-120°C) gave the pure naphthylhydrazone (112) (0.81g, 48%), m.p. 173.5-175°C [Found : C, 62.34; H, 2.84; N, 5.73%;  $M^+$ , 462.  $C_{24}H_{13}F_7N_2$  requires C, 62.34; H, 2.84; N, 6.06%; M, 462].  $\nu_{\max}$  3480  $\text{cm}^{-1}$  (N-H).

#### 6.10 Reaction of Cyclohexanone Pentafluorophenylhydrazone (98) in Tetralin

The phenylhydrazone (98) (2.51g) was heated under reflux in dry tetralin (100ml.) for 24 h, during which time ammonia was detected by its smell and by the effect on moist red litmus paper. The solvent was distilled under reduced pressure (0.001mmHg) using an external water-bath at 60°C. Analysis of the black crude residue by t.l.c. on silica using  $\text{CHCl}_3\text{-CCl}_4$  (50:50 v/v) revealed a complex mixture of components and total conversion of the phenylhydrazone. Initial separation was effected by means of flash chromatography on silica (160mm 50mm), using the above as eluant. Sixteen 50 ml. fractions were collected. The fastest moving components were combined (1.151g) as were the next set of mid-range components (0.861g).



Vacuum sublimation of both fractions ( $<30^{\circ}\text{C}$ , 0.001mmHg) gave a white sublimate (0.023g) which was not examined further. Increasing the temperature to  $50^{\circ}\text{C}$ . gave a further sublimate (0.386g, 18%) which was recrystallised from light petroleum (b.p.  $60-80^{\circ}\text{C}$ .) to give 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydrocarbazole (83), m.p.  $136.5-137.0^{\circ}\text{C}$ . (lit.,<sup>45</sup>  $140-143^{\circ}\text{C}$ . (from methanol)) [Found : C, 59.65; H, 3.30; N, 6.15%; M<sup>+</sup>, 243.  $\text{C}_{12}\text{H}_9\text{F}_4\text{N}$  requires C, 59.75; H, 2.93; N, 5.81%; M, 243];  $\delta_{\text{F}}(\text{CDCl}_3)$  155.4(t), 163.7(t), 168.7(t), 171.9 p.p.m. (t), with intensities in the ratio ca. 1:1:1:1;  $\delta_{\text{H}}(\text{CDCl}_3)$  three signals at 7.80 (N-H), 2.73 and 1.83 (Both methylene groups);  $\nu_{\text{max}}$   $3475\text{ cm}^{-1}$  (N-H).

#### 6.11 Reaction of Acetaldehyde 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (100) in Tetralin

The tarry residue (1.06g) from the preparation of the acetaldehyde 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazone (100) (see section 6.3) was heated under reflux in dry tetralin (25 ml.) for 2 h. No ammonia could be detected either by smell or by the effect on moist red litmus paper. The solvent was distilled under reduced pressure (0.005mmHg) using an external water-bath at  $40^{\circ}\text{C}$ . Analysis of the tarry residue on t.l.c. using  $\text{CHCl}_3$ - $\text{CCl}_4$  (50:50 v/v) as eluant revealed a complex mixture of compounds including the presence of a considerable amount of unreacted naphthylhydrazone.

Initial separation was carried out by means of flash chromatography on silica (160mm x 50mm) using the above as eluant. Fourteen 50 ml. fractions were collected, and separated into a fraction of fast components: a fraction of mid-range components, and a fraction of slow components. Analysis of the latter two by t.l.c. on silica using the above as eluant revealed the

presence of both unreacted naphthylhydrazone (100) and 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88). Vacuum sublimation of the mid-range fraction ( $<30^{\circ}\text{C}$ ., 0.01 mmHg) gave a white sublimate identified by i.r. as the 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88). Increasing the temperature to  $70-75^{\circ}\text{C}$ . produced a further sublimate (0.26g) identified by i.r. and molecular weight (mass spectroscopy) to consist of both the naphthylamine (88) ( $\text{M}^+$ , 269) and 4,5,6,7,8,9-hexafluorobenz[e]indole (113) ( $\text{M}^+$ , 251). Final separation was effected by means of thick-layer chromatography on silica (eluant as for the analytical t.l.c.) to give indole as the slow component (0.062g) and naphthylamine as the fast component (0.138g). A pure sample of the indole could not be obtained and its presence has only been established with the evidence based on i.r. (N-H) and molecular weight (mass spectroscopy).

#### 6.12 Reaction of Acetone 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (102) in Tetralin

The phenylhydrazone (102) (0.50g) was heated under reflux in dry tetralin (10 ml.) for 4 h. During the course of the reaction ammonia was evolved as detected by its smell and the effect on moist red litmus paper. The solvent was distilled under reduced pressure (0.001 mmHg) from a water-bath at  $70^{\circ}\text{C}$ . Initial separation of the crude residue was effected by means of flash chromatography on silica (160mm x 50mm) using  $\text{CHCl}_3 - \text{CCl}_4$  (50:50 v/v) as eluant. Twenty-eight 25 ml. fractions were removed from the column and combined to give four fractions of fast ; fast mid-range ; slow mid-range and slow components. Vacuum sublimation of the mid-range components at  $\leq 50^{\circ}\text{C}$ . / 0.001 mmHg afforded 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88)

(0.07g, 21%), identified by comparison with authentic sample on t.l.c. On raising the temperature to 70°C. crude product (0.09g, 17%) was obtained. Recrystallisation of the impure product from light petroleum (b.p. 80-100°C.) gave the pure indole (114), m.p. 193.0-193.5°C. [Found : C, 53.68; H, 1.32; N, 4.74%;  $M^+$ , 289.  $C_{13}H_5F_6N$  requires C, 53.93; H, 1.74; N, 4.84%;  $M$ , 289];  $\delta_F[(CD_3)_2CO]$  145.6 (t), 147.9 (doublet of m, peri-F,  $J_{7,8}$  60Hz.), 155.8 (m), 159.1 (dd; peri-F), 161.1 (triplet of m), and 163.3 p.p.m. (t), with intensities in the ratio 1:1:1:1:1:1;  $\delta_{H(CDCl_3)}$  2.55 (s, methyl), 6.86 (s, 3-H) and 8.61 (N-H) in the ratios of 3:1:1;  $\nu_{max}$  3465  $cm^{-1}$  (N-H).

#### 6.13 Reaction of Acetophenone 1,3,4,5,6,7,8-Heptafluoro-2-Naphthylhydrazone (85) in Tetralin.<sup>73</sup>

The naphthylhydrazone (85) (1.26g) was heated under reflux with dry tetralin (25 ml.) for 24 h. Ammonia was detected by its smell and its effect on moist red litmus paper. The solvent was distilled under reduced pressure at <65°C/0.001 mmHg to leave a tarry residue and was shown to be a complex mixture by analytical t.l.c. on silica using  $CHCl_3-CCl_4$  (50:50 v/v), was partially separated by flash chromatography on silica (160mm x 50mm) using the same eluant as before. Twenty-six 25 ml. fractions were removed from the column and combined to give three fractions of fast; mid-range and slow components. The slow components were identified as a mixture of 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88) and 4,5,6,7,8,9-hexafluoro-2-phenylbenz[e]indole (89) by analytical t.l.c. on silica using the above as eluant. Separation of the primary amine (88) was effected by vacuum sublimation at  $\leq 95^\circ C$ , 0.001 mmHg (0.14g, 16%) and the indole (89) sublimed at 160°C. (0.46g, 40%). Characterisation was achieved by comparison with available data.<sup>73</sup>

6.14 Reaction of (4-Methylacetophenone)1,3,4,5,6,7,8-Heptafluoro-2-Naphthylhydrazone (104) in Tetralin

The phenylhydrazone (104)(1.00g) was heated under reflux in dry tetralin (50 ml.) for 24 h. Ammonia was detected by its smell and by the effect on moist red litmus paper. The solvent was distilled under reduced pressure, 0.001 mmHg, from a water-bath at  $\leq 60^{\circ}\text{C}$ ., and the tarry residue was shown to be a complex mixture by analytical t.l.c. on silica using  $\text{CHCl}_3$ - $\text{CCl}_4$  (50:50 v/v) as eluant, was partially separated by flash chromatography on silica (160mm x 50mm) using the same eluant as before. Seventeen 50 ml. fractions were removed from the column. The mid-range components were identified by  $^{19}\text{F}$  n.m.r. as the benz[e]indole (six fluorine atoms were observed). After crystallisation from light petroleum (b.p.  $100$ - $120^{\circ}\text{C}$ .)-toluene (50:50 v/v) the solid was vacuum sublimed at  $140$ - $150^{\circ}\text{C}$ ./0.005 mmHg. T.l.c. analysis revealed two compounds, the faster was the naphthylamine (88) and the slower the benz[e]indole (115) was identified by i.r. spectroscopy. A controlled vacuum sublimation at  $40^{\circ}\text{C}$ ./0.005 mmHg gave the 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88)(0.079g, 12%) and at  $140$ - $150^{\circ}\text{C}$ ./0.005 mmHg gave the benz[e]indole (115)(0.378g, 41%). Further recrystallisation from light petroleum (b.p.  $100$ - $120^{\circ}\text{C}$ .) afforded the pure 4,5,6,7,8,9-hexafluoro-2(4-methylphenyl)benz[e]indole (115), m.p.  $216.5$ - $217.5^{\circ}\text{C}$ . [ Found : C, 62.36; H, 2.54; N, 3.94% ;  $\text{M}^+$ , 365.  $\text{C}_{19}\text{H}_9\text{F}_6\text{N}$  requires C, 62.65; H, 2.21; N, 3.85%; M, 365] ;  $\delta_{\text{F}}[(\text{CD}_3)_2\text{CO}]$  145.4 (t), 147.9 (doublet of m, peri-F,  $J_{7,8}$  64 Hz.), 155.3 (m), 157.5 (dd; peri-F), 160.9 (triplet of m), and 162.9 p.p.m. (t), with intensities in the ratio 1:1:1:1:1:1 ;  $\delta_{\text{H}}(\text{CDCl}_3)$  2.15 (methyl), 6.97 (phenyl), 7.31 (3-H) and 8.04 (N-H) with intensities in the ratio ca. 3:4:1:1 ;  $\nu_{\text{max}}$   $3455\text{ cm}^{-1}$  (N-H).

6.15 Reaction of (4-nitroacetophenone)1,3,4,5,6,7,8-Heptafluoro-2-Naphthylhydrazone (106) in Tetralin

The phenylhydrazone (106)(3.611g) was heated under reflux with dry tetralin (180 ml.) for 24 h. Ammonia was detected by its smell and by the effect on moist red litmus paper. The solvent was distilled under reduced pressure (0.001mmHg) using an external water-bath at 50°C. and the tarry residue was shown to be a complex mixture by analytical t.l.c. on silica using  $\text{CHCl}_3$ - $\text{CCl}_4$  (50:50 v/v) as eluant. The addition of chloroform caused a black precipitate to form (0.55g) which was removed by filtration and shown by analytical t.l.c. on silica using the above as eluant to be a single component. Purification was attempted by means of flash chromatography on silica (160mm x 50mm) using  $\text{CHCl}_3$  as eluant. Twenty 50 ml. fractions were removed from the column and the fractions containing the mid-range components were combined to give an impure sample of the suspected indole (116). Vacuum sublimation of the material at  $\leq 120^\circ\text{C}$ ., 0.001mmHg gave a yellow sublimate (0.391g). Mass spectrometry gave the required molecular weight ( $M^+$ , 396) for the 4,5,6,7,8,9-hexafluoro-2-(4-nitrophenyl)benz[e]indole, but i.r. showed  $\nu_{\text{max}}$  at  $3345\text{ cm}^{-1}$  (N-H) to be very broad and must cast some doubt on the authenticity of this suspected indole.

6.16 Reaction of 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86) With Phenylacetaldehyde in Tetralin

1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine (86)(1.107g), phenylacetaldehyde (0.483g), and tetralin (40 ml.) were heated together under reflux. The water produced in the initial condensation reaction was

azeotropically removed, and the reflux continued for a total of 24 h. Ammonia was detected by its smell and by the effect on moist red litmus paper. The solvent was distilled under reduced pressure at 50°C/0.001 mmHg and the tarry residue shown to be a complex mixture by analytical t.l.c. on silica using  $\text{CHCl}_3\text{-CCl}_4$  (50:50 v/v) as eluant, was partially separated by flash chromatography on silica (160 mm x 50 mm) using the same eluant as before. Eighteen 25 ml. fractions were removed from the column and analysed by t.l.c. on silica using the above eluant. The fast mid-range and slow components were obtained in three fractions. The mid-range component (0.101 g) was vacuum sublimed at 40-50°C./0.001 mmHg to give a sublimate, identified by i.r. as 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88) (0.084 g, 8%). The slow fraction (0.384 g) was vacuum sublimed at 160-165°C./0.001 mmHg to give a sublimate (0.322 g, 24%), identified by i.r. as the 4,5,6,7,8,9-hexafluoro-3-phenylbenz[e]indole (117), m.p. 253.0-253.5°C. [from toluene-light petroleum (b.p. 100-120°C.)] [Found: C, 61.59; H, 1.99; N, 3.83%;  $M^+$ , 351.  $\text{C}_{18}\text{H}_7\text{F}_6\text{N}$  requires C, 61.54; H, 1.99; N, 4.00;  $M$ , 351];  $\delta_{\text{F}}[(\text{CD}_3)_2\text{CO}]$  132.2 (t), 148.4 (doublet of m, peri-F,  $J_{7,8}$  68 Hz.), 156.4 (m), 157.6 (dd; peri-F), 160.9 (triplet of m), and 163.0 p.p.m. (t), with intensities in the ratio 1:1:1:1:1:1;  $\delta_{\text{H}}[(\text{CD}_3)_2\text{CO}]$  7.6 (2-H and phenyl), 12.0 (N-H);  $\nu_{\text{max}}$  3400  $\text{cm}^{-1}$  (N-H).

#### 6.17 Reaction of Propiophenone 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (110) in Tetralin

The phenylhydrazone (110) (2.001 g) was heated under reflux in dry tetralin (80 ml.) for 24 h. Ammonia was detected by its smell and by its effect on moist red litmus paper. The solvent was distilled under reduced

pressure (0.001mmHg) using an external water-bath at  $\leq 60^{\circ}\text{C}$ . Analysis of the black tarry residue by t.l.c. on silica using  $\text{CHCl}_3\text{-CCl}_4$  (50:50 v/v) as eluant revealed a complex mixture of components. Initial separation was effected by flash chromatography on silica (160mm x 50mm) using the above as eluant. Thirteen 50 ml. fractions were removed from the column and analysed on t.l.c. The mid-range fractions (1.237g) were separated by vacuum sublimation at  $\leq 180^{\circ}\text{C}$ , 0.001mmHg into a sublimate consisting of two components when analysed by t.l.c. on silica using the same eluant as before. The slower component was identified as the 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88) and separated by vacuum sublimation at  $40\text{-}45^{\circ}\text{C}/0.001\text{mmHg}$  (0.258g, 19%) (i.r. identical to that of an authentic sample). Raising the temperature to  $120\text{-}140^{\circ}\text{C}/0.001\text{mmHg}$  gave the indole (0.628g, 4%). Crystallisation from light petroleum (b.p.  $100\text{-}120^{\circ}\text{C}$ .) afforded 4,5,6,7,8,9-hexafluoro-2-phenyl-3-methylbenz[e]indole (118), m.p.  $169.0\text{-}169.5^{\circ}\text{C}$  [ Found : C, 62.63; H, 2.21; N, 4.01% ;  $\text{M}^+$ , 365.  $\text{C}_{19}\text{H}_9\text{F}_6\text{N}$  requires C, 62.47; H, 2.49, N, 4.84% ; M, 365] ;  $\delta_{\text{F}}[(\text{CD}_3)_2\text{CO}]$  137.0 (t), 144.3 (doublet of m, peri-F,  $J_{7,8}$  68 Hz), 152.4 (m), 153.9 (dd; peri-FO), 157.2 (triplet of m), and 159.5 p.p.m. (t), with intensities in the ratio 1:1:1:1:1:1 ;  $\delta_{\text{H}}[(\text{CD}_3)_2\text{CO}]$  2.50 (methyl), 7.53 (phenyl), 7.53 (phenyl), and 11.50 (N-H) in the ratios 3:5:1 ;  $\nu_{\text{max}}$   $3395\text{ cm}^{-1}$  (N-H).

#### 6.18 Reaction of Deoxybenzoin 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (112) in Tetralin

The naphthylhydrazone (112) (2.212g) was heated under reflux with dry tetralin (50 ml.) for 24 h. Ammonia was detected by its smell and by the effect on moist red litmus paper. The solvent was distilled under reduced

pressure (0.001mmHg) using an external water-bath (50-60°C) and the tarry residue shown to be a complex mixture by analytical t.l.c. on silica using  $\text{CHCl}_3\text{-CCl}_4$  (70:30 v/v) as eluant, was partially separated by flash chromatography on silica (160mm x 50mm) using the same eluant as before. Thirteen 25 ml. fractions were removed from the column and analysed by t.l.c. on silica using the above as eluant to show that no 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (88) was present. Vacuum sublimation of the solid at 160-170°C./0.001mmHg gave a pale-yellow sublimate (0.899g) which was identified by i.r. as the naphthylindole (presence of N-H stretch). Crystallisation of this solid from toluene-light petroleum (b.p. 100-120°C.) afforded the pure 4,5,6,7,8,9-hexafluoro-2,3-diphenylbenz[e]indole (119) (0.868g, 42%), m.p. 223.5-224.0°C [ Found : C, 67.58; H, 3.00; N, 2.95% ;  $\text{M}^+$ , 427.  $\text{C}_{24}\text{H}_{11}\text{F}_6\text{N}$  requires C, 67.58; H, 2.60; N, 3.29% ; M, 427] ;  $\delta_{\text{F}}[(\text{CD}_3)_2\text{CO}]$  132.1 (t), 148.4 (doublet of m, peri-F,  $J_{7,8}$  68Hz.), 156.3 (m), 157.3 (dd; peri-F), 161.1 (triplet of m), and 163.1 p.p.m. (t), with intensities in the ratio of 1:1:1:1:1:1 ;  $\delta_{\text{H}}[(\text{CD}_3)_2\text{CO}]$  7.33 (phenyl), and 11.93 (N-H) in the ratio ca. 10:1 ;  $\nu_{\text{max}}$  3465  $\text{cm}^{-1}$  (N-H).



## Appendix A      Apparatus and Instrumentation

This is a summary of the instruments and apparatus used for obtaining the results throughout the Experimental Section.

### Infrared Spectra

Spectra were recorded on Perkin-Elmer 377, 457 and 577 spectrophotometers.

### Mass Spectra

A.E.I. MS9 Spectrometer.

### N.M.R. Spectra

Proton ( $^1\text{H}$ ) and fluorine ( $^{19}\text{F}$ ) nuclear magnetic resonance spectra were recorded either on a Varian EM 360L spectrometer, operating at 60.0 and 56.46 MHz respectively or a Brüker HX 90 E spectrometer operating at 90.0 and 84.67 MHz respectively.

The chemical shifts have been quoted in p.p.m. ; downfield with respect to the reference TMS for proton n.m.r. and  $\text{CFCl}_3$  as internal reference for fluorine n.m.r.

### Thick-Layer T.L.C.

20g of GF 254 kieselgel (incl. 17% gypsum and 3% fluorescer) in 50 ml. water onto 20 x 20 cm. plates.

### Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution <sup>82</sup> (Flash Chromatography)

This is a simple absorption chromatography technique for the routine purification of organic compounds. Long column chromatography offers

satisfactory results although is often time consuming. The main advantage afforded by flash chromatography is speed, giving a resolution of the order of ( $\Delta R_f \geq 0.15$ ).

The technique employs the use of a short column, packed with silica and eluted by driving the solvent through with a positive air pressure through a flow controller at the top of the column. The column is then loaded with the sample and topped with eluant in the normal manner. The pressure is then used to rapidly push the eluent through at an optimum rate of 2 ins./min. at the solvent head. Small fractions are collected early in the elution with larger ones being collected toward the end of the elution (Plate 1 shows an eluted column).

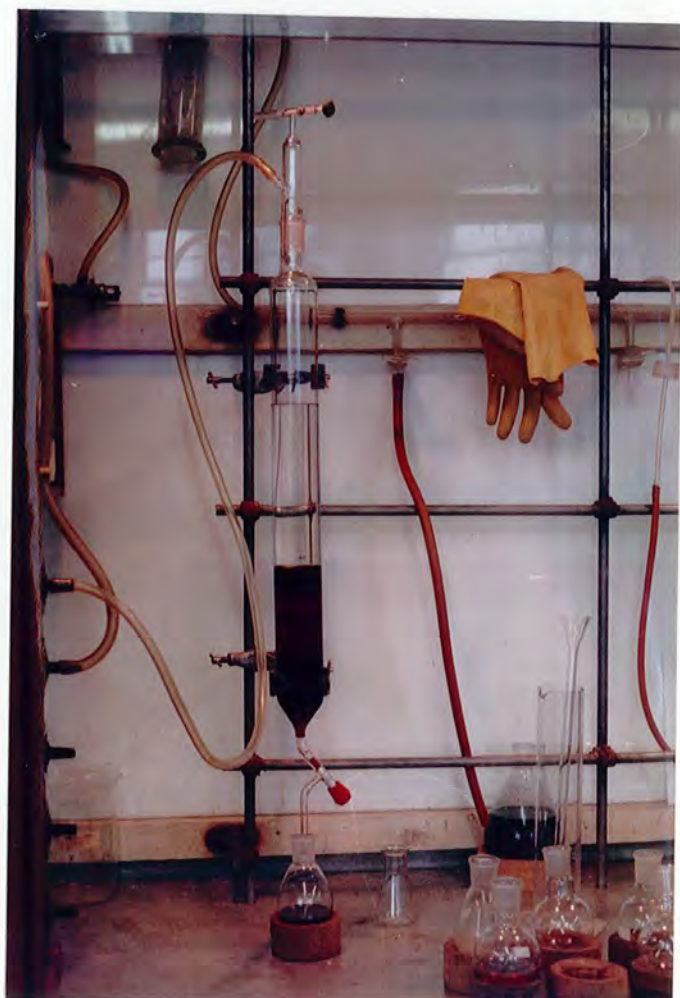


Plate 1:  
Flash Chromatography  
Column

Separated components are conveniently detected by spotting  $\sim 5 \mu\text{L}$  of each fraction on an analytical 20cm x 20cm t.l.c. plate which can take up to 20 samples, and then the plate developed by the ascending method.

The optimum conditions were used throughout this experimental section which include :-

- (i) use of silica gel 60 (230-400 mesh) and an
- (ii) eluant flow rate of  $2.0 \pm 0.1$  in./min.

In each case the use of a 50 mm diameter column was employed which allowed between 1.00 and 2.50g to be loaded on the column. Samples were collected in 50 ml. fractions unless otherwise stated.

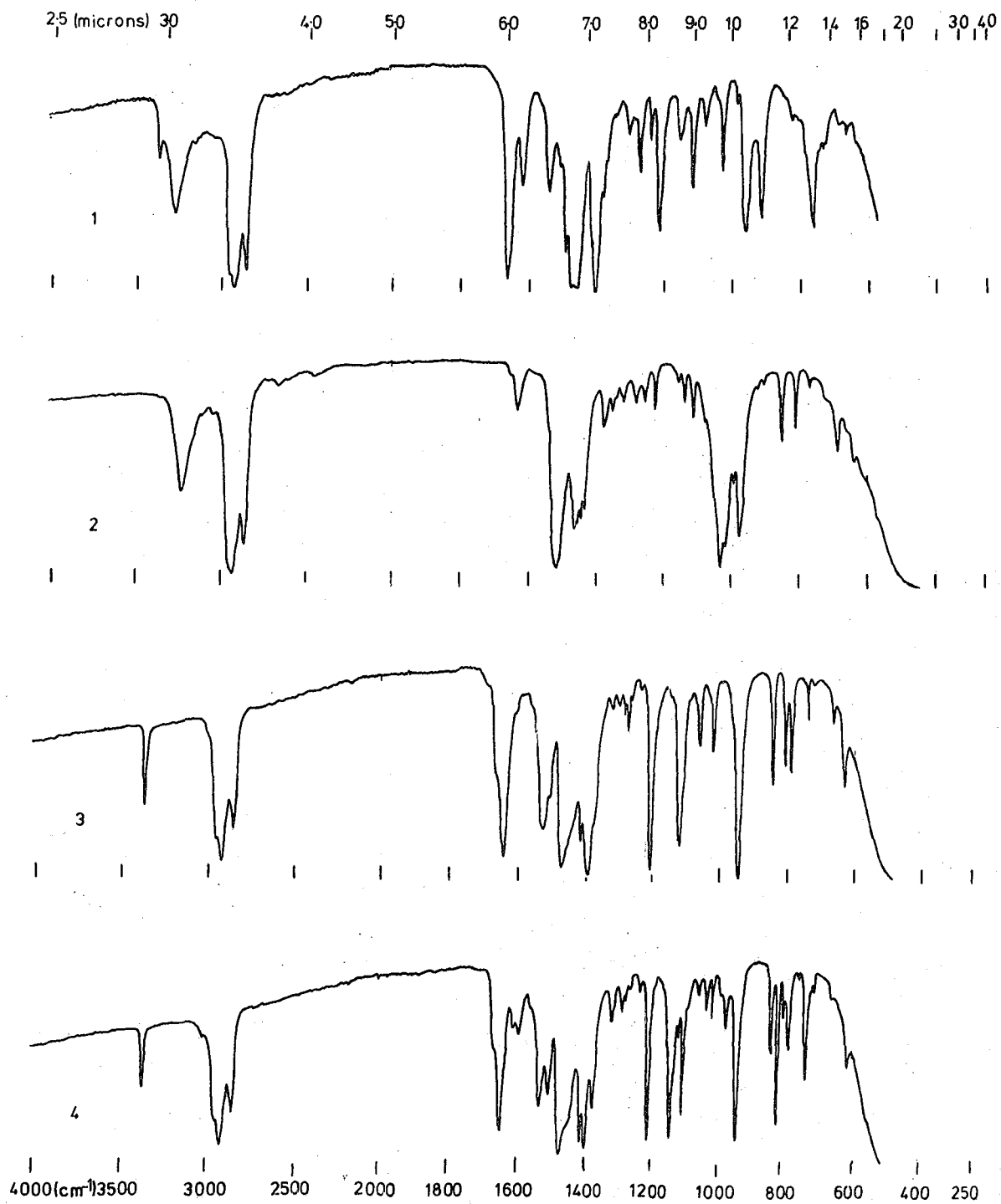
Appendix B      Infra-red Spectra

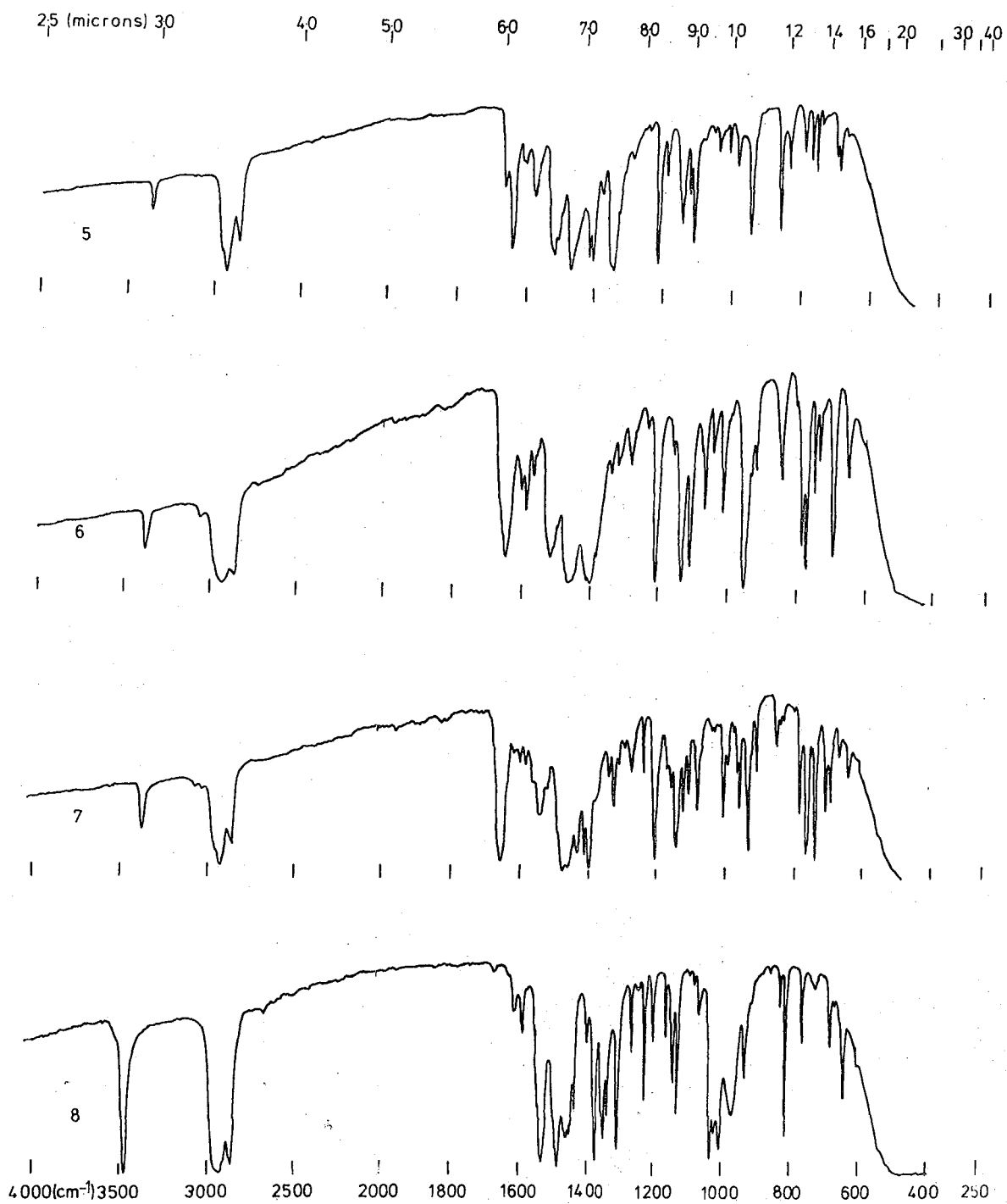
All spectra were measured as a mull prepared with nujol in the form of a thin-layer using NaCl plates.

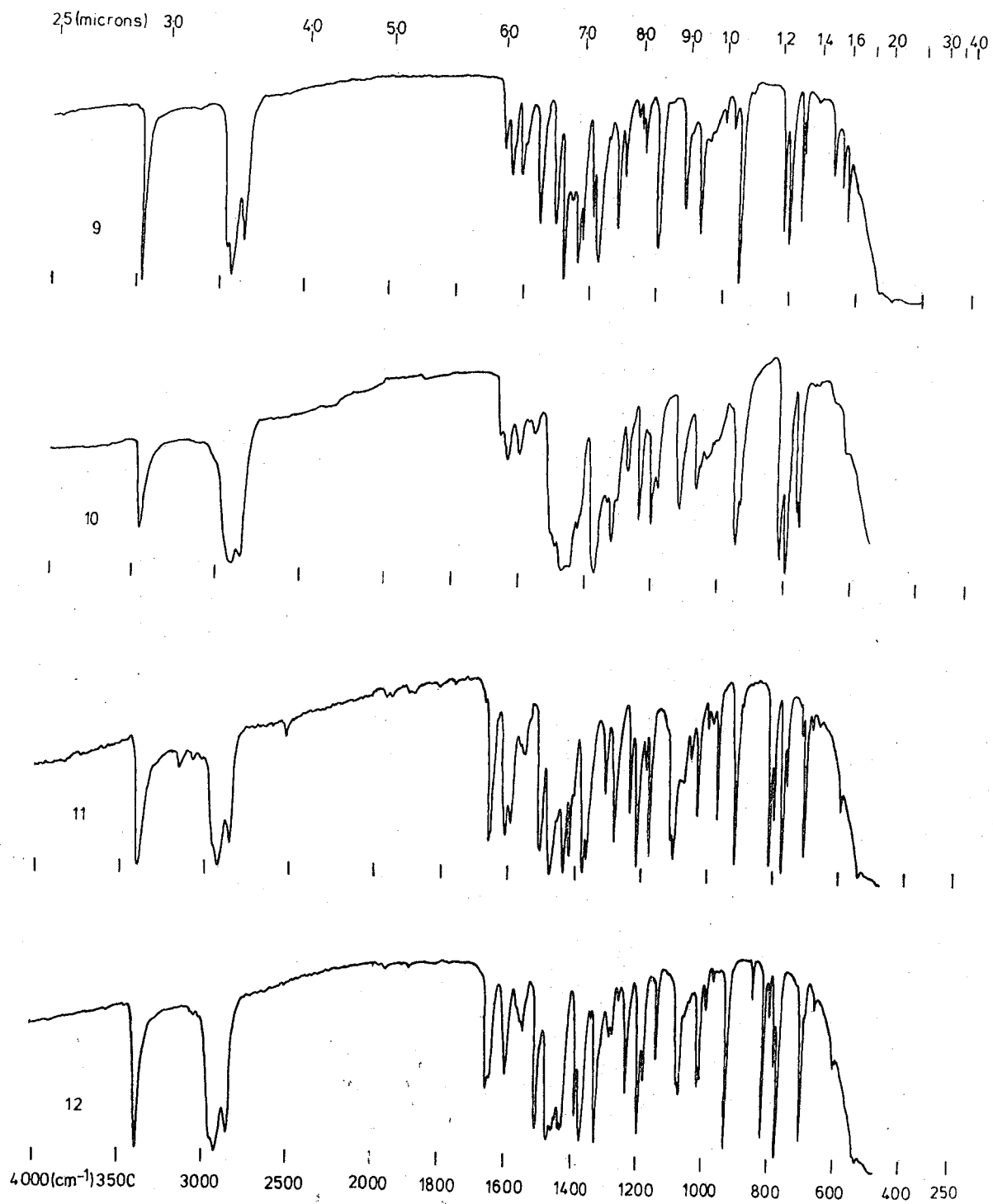
All compounds are new except 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazine<sup>71</sup> (86) and 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydrocarbazole<sup>45</sup> (82).

<u>Spectrum Number</u>	<u>Name of Compound</u>
1	1,3,4,5,6,7,8-Heptafluoro-2-Naphthylhydrazine (86)
2	Cyclohexanone Pentafluorophenylhydrazone (98)
3	Acetone 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (102)
4	(4-methylacetophenone) 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (104)
5	(4-nitroacetophenone) 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (106)
6	Propiophenone 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (110)

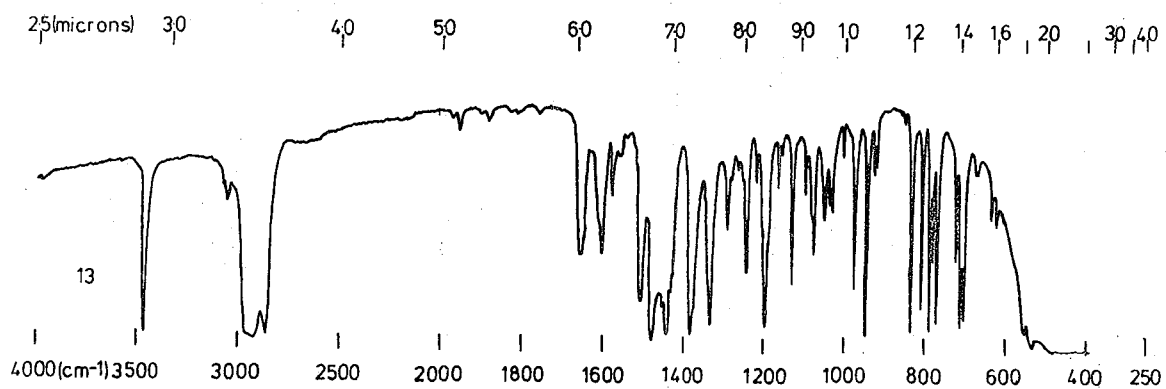
- 7                    Deoxybenzoin 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (112)
- 8                    5,6,7,8-Tetrafluoro-1,2,3,4-Tetrahydrocarbazole (83)
- 9                    4,5,6,7,8,9-Hexafluoro-2-methylbenz[e]indole (114)
- 10                   4,5,6,7,8,9-Hexafluoro-2-(4-methylphenyl)benz[e]indole (115)
- 11                   4,5,6,7,8,9-Hexafluoro-3-phenylbenz[e]indole (117)
- 12                   4,5,6,7,8,9-Hexafluoro-2-phenyl,3-methylbenz[e]indole (118)
- 13                   4,5,6,7,8,9-Hexafluoro-2,3-diphenylbenz[e]indole (119)











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