Some sigmatropic rearrangements of polyfluoroaromatic and heteroaromatic compounds

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SOME SIGMATROPIC REARRANGEMENTS OF POLYFLUOROAROMATIC AND HETEROAROMATIC COMPOUNDS

by

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(University College)

A thesis submitted

for the Degree of Doctor of Philosophy

to the University of Durham

1986

To my Parents

Read not to contradict and confute
nor to believe and take for granted
nor to find talk and discourse
but to weigh and consider.

FRANCIS BACON 1561-1626.

MEMORANDUM

The work reported in this thesis was carried out in the Chemistry Laboratories of the University of Durham between October 1983 and July 1986. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by references.

Parts of this work have been the subject of the following publications:

(i) G.M. Brooke and J.A.K.J. Ferguson, J.Chem.Soc. Perkin 1, 1986, 515.

(ii) G.M. Brooke and J.A.K.J. Ferguson, submitted for publication to J.Chem.Soc. Perkin 1.

Aspects of the work have been presented at the following meetings:

(i) XIth International Symposium on Fluorine Chemistry, Berlin, August 1985.

(ii) Graduate Symposium, University of Durham, April 1986.

ACKNOWLEDGEMENTS

I would like to express my thanks to Dr. G.M. Brooke for his considerable encouragement, support and guidance throughout the course of my research.

I am indebted to Dr. R.S. Matthews for allowing me use of the n.m.r. facilities, as well as help in the interpretation of spectroscopic data.

The assistance of the many technical staff was invaluable, especially the efforts of the glassblowers, Mr. R. Hart and Mr. G. Haswell.

I am grateful to Mrs. M. Wilson who typed this manuscript with considerable speed and accuracy.

Finally, I would like to add my thanks to all my friends and colleagues for the good times we shared, in particular Mary, my love and confidante.

SOME SIGMATROPIC REARRANGEMENTS OF POLYFLUOROAROMATIC AND HETEROAROMATIC COMPOUNDS

by

J.A.K.J. FERGUSON

ABSTRACT

This Thesis describes some [3,3] and [2,3]-sigmatropic rearrangements that can occur in a variety of polyfluoroaromatic and -heteroaromatic compounds. The presence of fluorine on the aromatic moiety precludes the normal rearomatization process. The work is conveniently divided into two parts.

Part A concerns the preparation and thermal (Claisen) rearrangement of derivatives of allyl 5-fluoropyrimidin-4-yl ether. These rearrange upon thermolysis to give isomers in which the terminus for the migration of the allyl group is N-3, provided that there is no preceding reaction which localises a double-bond between C-4 and C-5 - in which case C-5 is the migration terminus. Hydrolysis of some of the N-allyl derivatives results in the formation of some new derivatives of 5-fluorouracil.

Part B describes the reactions that occur when polyfluorinated monocyclic, polycyclic and heterocyclic ring systems are treated with dimethylsulphoxide activated by dicyclohexycarbodiimide or by trifluoroacetic anhydride. Fluorinated phenolic type compounds give products which are the result of a [2,3]-sigmatropic rearrangement of the derived sulphonium ylide. Fluorinated anilines and thiophenols behave differently. Dearomatization occurs under very mild conditions. A number of reactions of the fluorinated cyclohexa-2,4-dienone products are described.

The preparation and attempted rearrangement of 2,3,4,5,6-pentafluorobenzylmethylsulphoxide is also discussed.

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INTRODUCTION

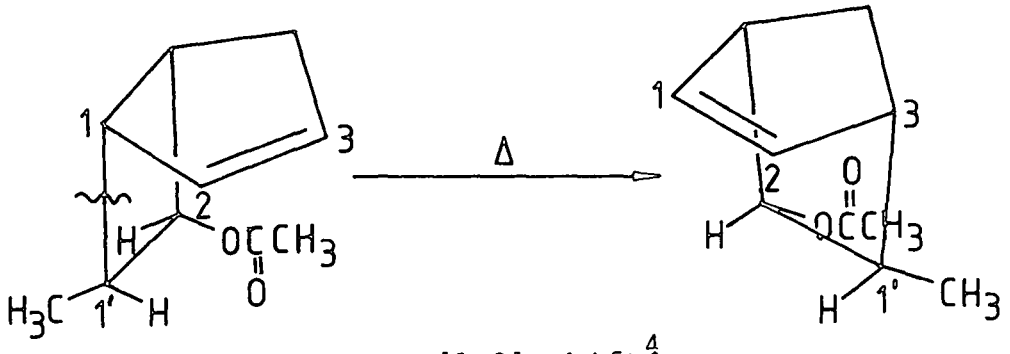
INTRODUCTION

The vast majority of organic reactions involve changes at functional groups in which the carbon framework of the reacting molecules remains unaltered. There are, however, many reactions which involve molecular rearrangements, wherein functional groups migrate within the molecule resulting in a modification of the carbon framework. A number of these rearrangements where reaction is seemingly induced only by the action of heat or light give no evidence for the involvement of intermediates when subjected to the usual mechanistic probes of solvent effects, acid/base catalysis, or the detection of free-radicals by physical or chemical means. This lack of evidence for intermediates led to such reactions being referred to as "no-mechanism thermal reorganizations",[1] although it was concluded that the reactions must be concerted processes, with bonding changes in the transition state occurring simultaneously rather than in two or more steps.

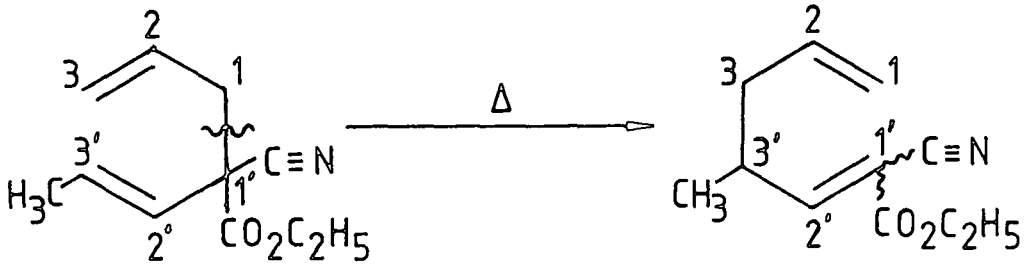
In 1965, Woodward and Hoffmann[2] attempted to rationalize these processes by the simple application of some fundamental principles of orbital theory, suggesting that the reactions were determined by the symmetry properties of the orbitals involved. This, and later studies[3] has revolutionized the understanding of these reactions.

Woodward and Hoffmann subdivided these so called pericyclic reactions into five categories: cycloaddition, electrocyclic, sigmatropic, cheletropic and group transfer reactions. In a sigmatropic rearrangement reaction, a σ-bond migrates over a π-system to a new location, the extent of this migration being defined in the order of the reaction [i,j],

where the termini of the σ-bond are i-1 and j-1 atoms removed from the original position. Some examples are shown in Scheme 1.



A [1,3] shift[4]



A [3,3] shift[5]

Scheme 1

By consideration of the phase relationships of the highest occupied molecular orbitals in both the migrating group and the π-system, and also the mode in which bonds are made and broken in these components, it can be determined whether a sigmatropic reaction is thermally or photochemically allowed. These results are summarised in Table 1.

Any component reacting in such a way that bonds are made and broken on the same face of the π-system is described as suprafacial (supra in Table 1), whereas if the bonds are made and broken on opposite sides it is described as antara-

i + j	Thermally allowed		Photochemically allowed	
	Migrating group	π-electron system	Migrating group	π-electron system
4n	antara	supra	supra	supra
	supra	antara	antara	antara
4n + 2	supra	supra	supra	antara
	antara	antara	antara	supra

n = any integer

TABLE 1

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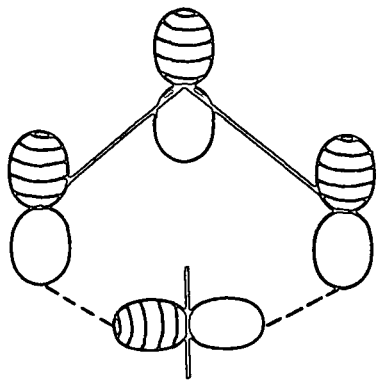
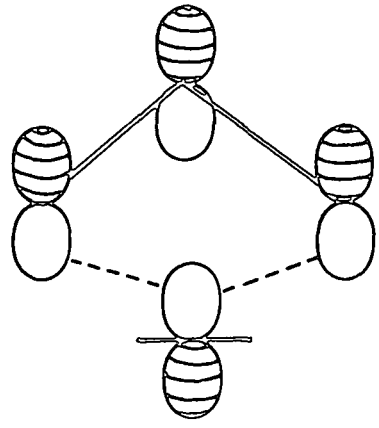
n = 1



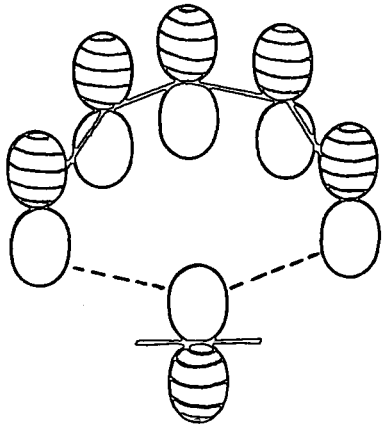
[1,3] supra-antara
thermally allowed



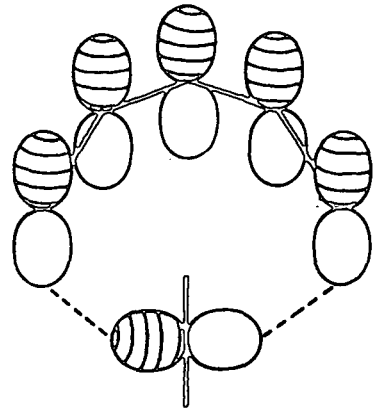
[1,3] supra-supra
thermally disallowed

Scheme 2

n = 2



[1,5] supra-supra
thermally allowed



[1,5] supra-antara
thermally disallowed

facial (antara in Table 1). Some examples of this analysis are illustrated in Scheme 2.

In this thesis some sigmatropic rearrangement reactions of polyfluoroaromatic and heteroaromatic compounds will be described. The work is conveniently divided into two parts. Part A deals with the well known [3,3] sigmatropic rearrangement of allyl phenyl ethers, the Claisen rearrangement, as applied to fluorinated allyl pyrimidyl ethers. Part B, on the other hand, is concerned with some [2,3] sigmatropic rearrangements that can occur in fluorinated phenols, their heterocyclic analogues, naphthols, thiophenols and anilines.

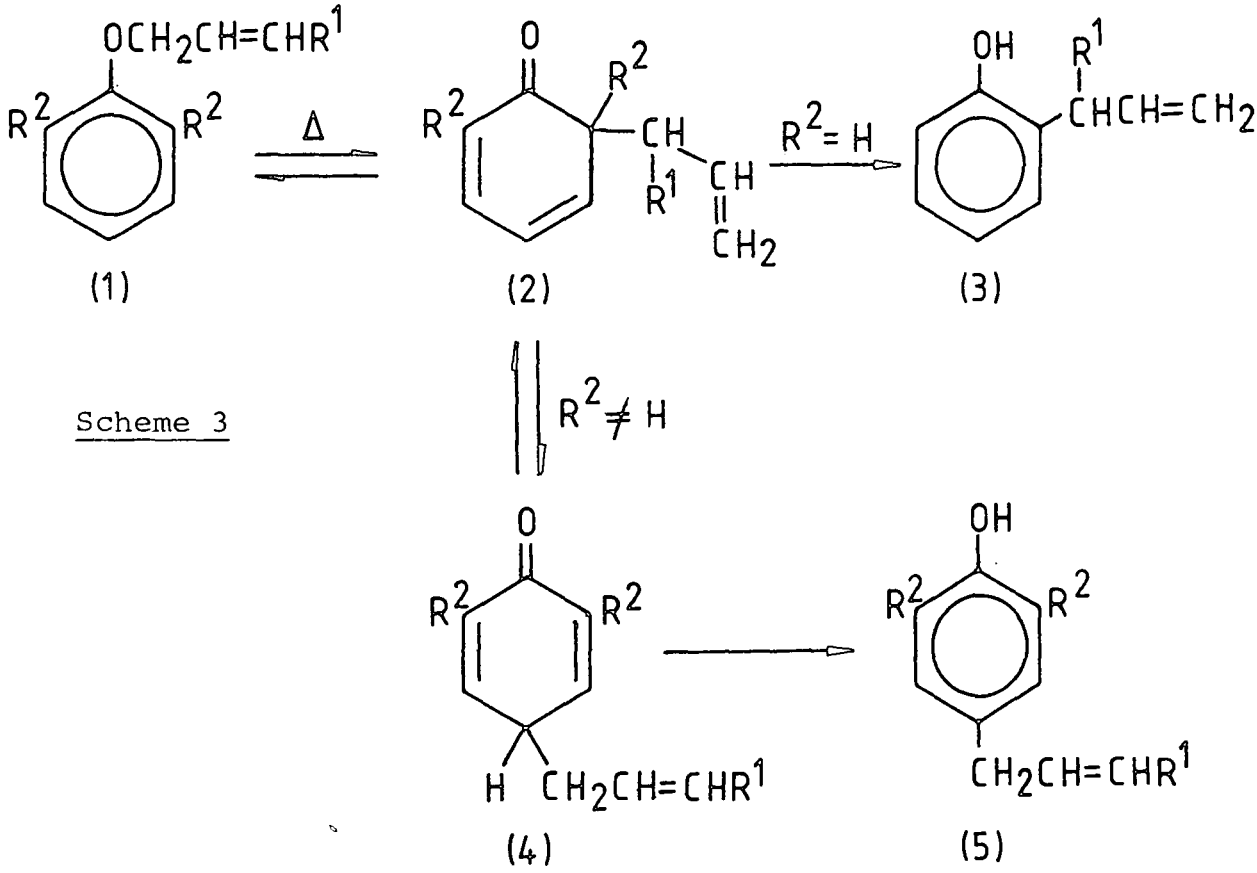
PART A

CHAPTER ONE

THE CLAISEN REARRANGEMENT OF AROMATIC ALLYL ETHERS

1.1 Introduction

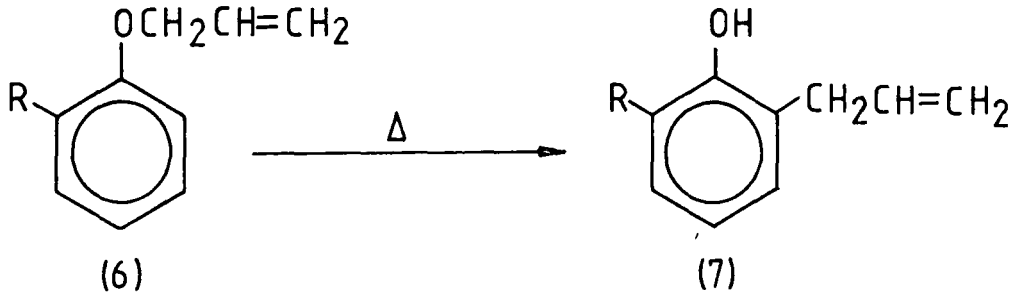
The aromatic Claisen rearrangement, a thermal transformation involving an intramolecular rearrangement *via* a six-membered transition state, is a well-known sigmatropic reaction and has been extensively reviewed.[6] Generally, an allyl phenyl ether (1) undergoes a thermal [3,3] sigmatropic rearrangement into a 6-allyl-cyclohexa-2,4-dienone (2), which can subsequently undergo two main types of reaction, Scheme 3. When R^2=H, the 'ortho-dienone' rapidly tautomerises to the 2-allyl phenol (3), whereas when $R^2 \neq H$, (2) undergoes a further [3,3] rearrangement (a Cope rearrangement) to give the 'para-dienone' (4), which again rapidly tautomerises to give the 4-allyl phenol (5). Such processes are termed the ortho- and para-Claisen rearrangements respectively.



Scheme 3

1.2 The Historical Development

In 1912[7] Claisen reported that the thermal rearrangement of the allyl phenyl ethers (6 a,b) resulted in the formation of their isomeric ortho-substituted phenols (7 a,b). Scheme 4.



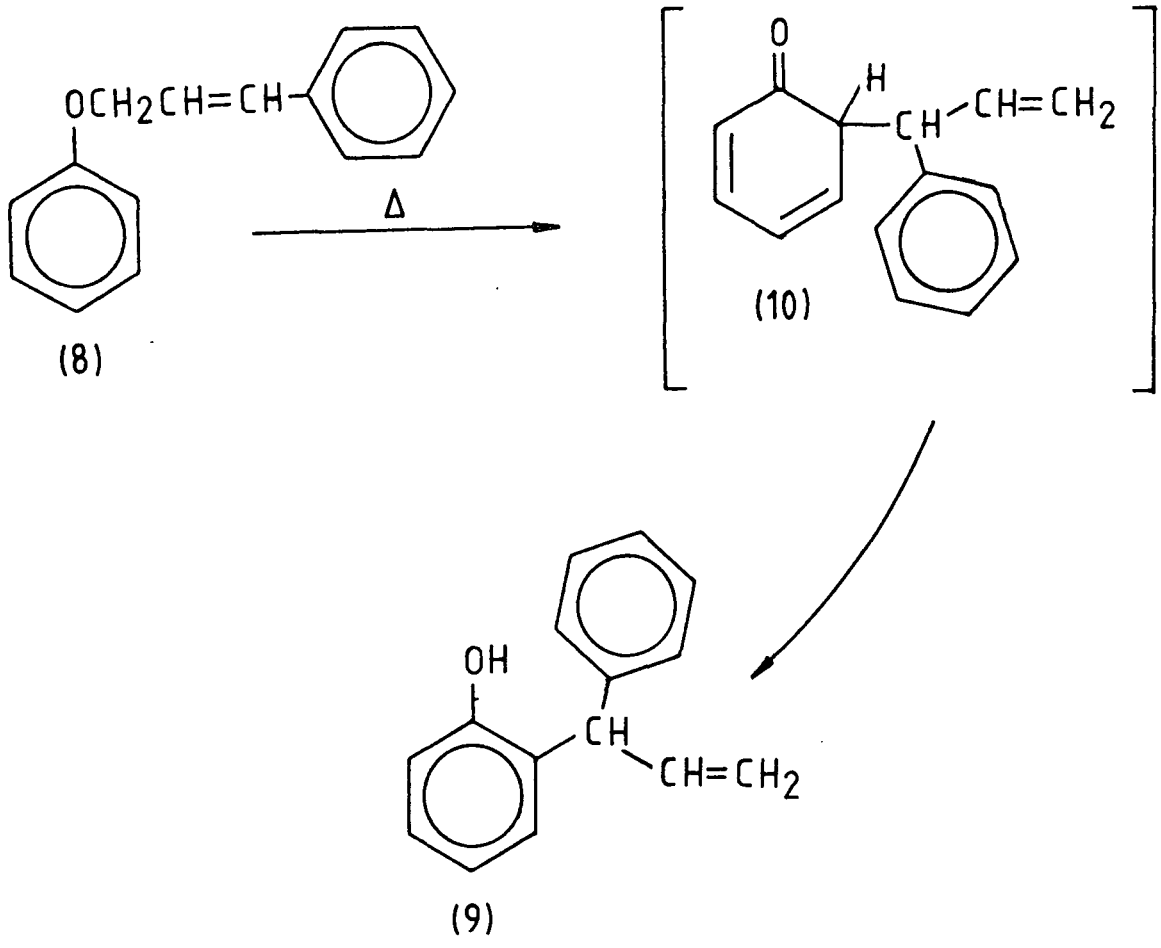
(6) (7)

(a) R = $-OCH_3$ (b) R = $-CO_2C_2H_5$

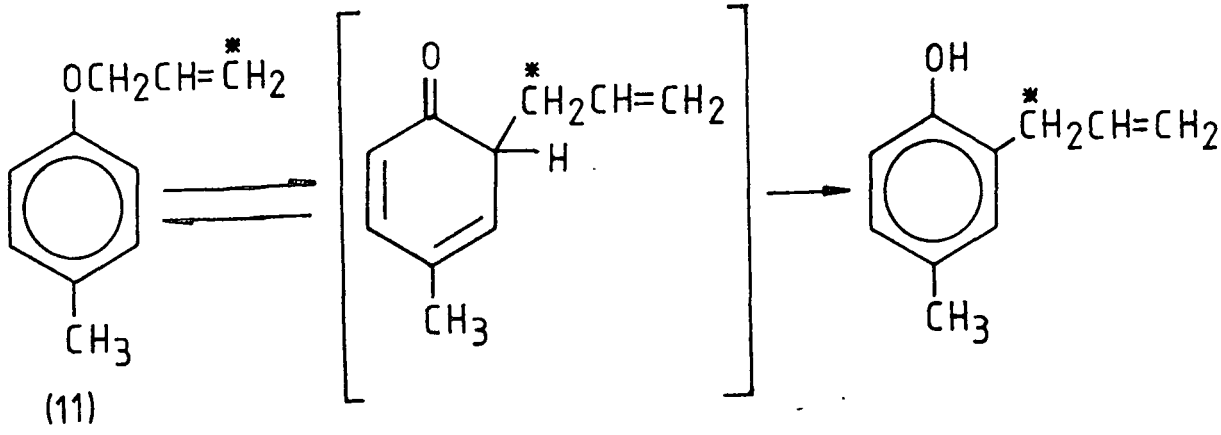
Scheme 4

In a much later study[8] Claisen also observed that upon thermolysis the phenyl 3-phenylallyl ether (8) rearranged to the corresponding 2-(1-phenylallyl)phenol (9), Scheme 5. This inversion of the allyl group on rearrangement of (8) to (9) was also substantiated by other workers.[9] Claisen himself postulated that the reaction involved the intermediate dienone (10).[8]

By a more elegant technique, using ^{14}C-labelled material (11), Schmid[10] was also able to show that inversion of the allyl group had taken place. In this case, a para-methyl substituent was present to prevent the formation of any para-substituted phenols, Scheme 6.

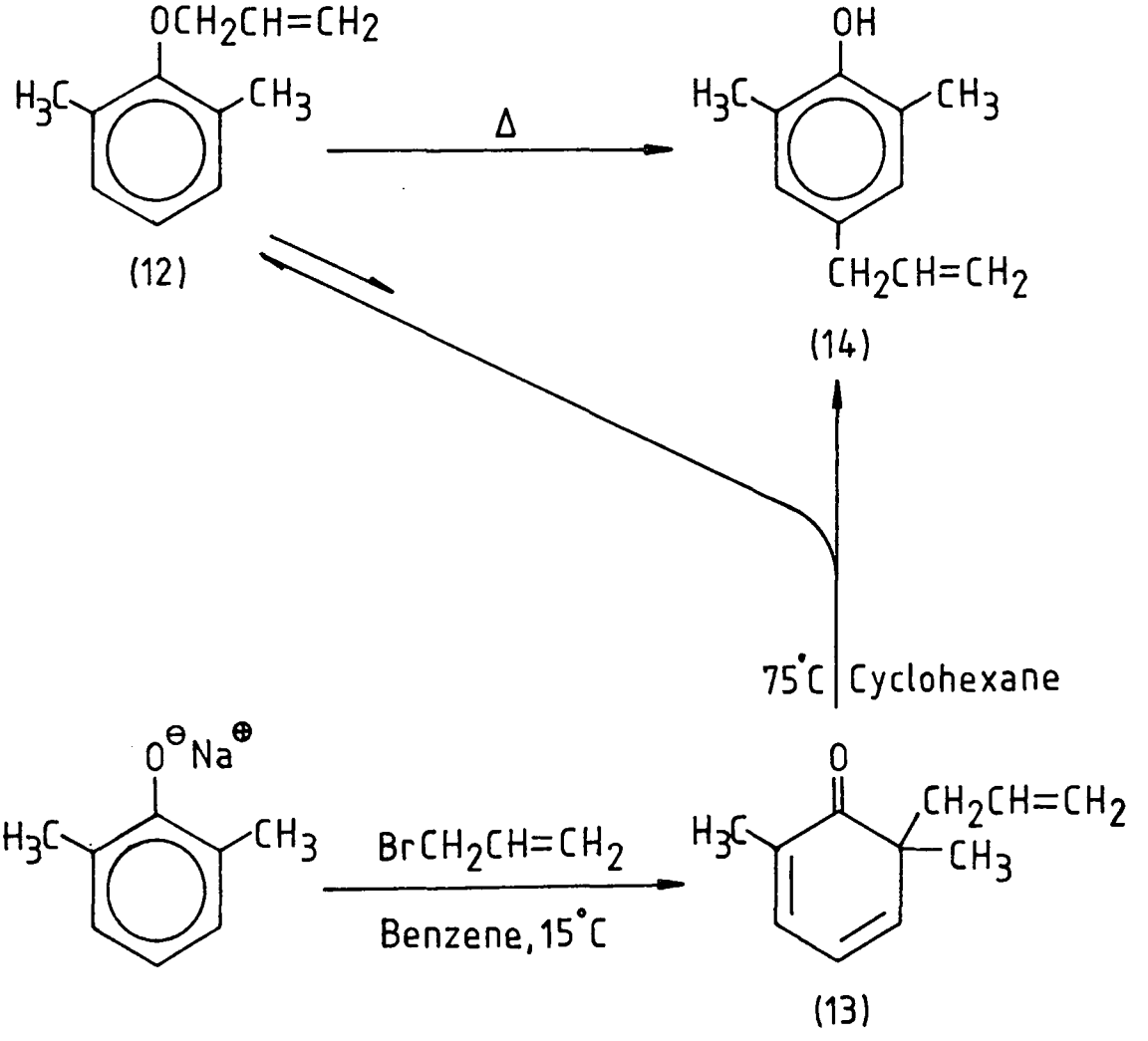


Scheme 5



Scheme 6

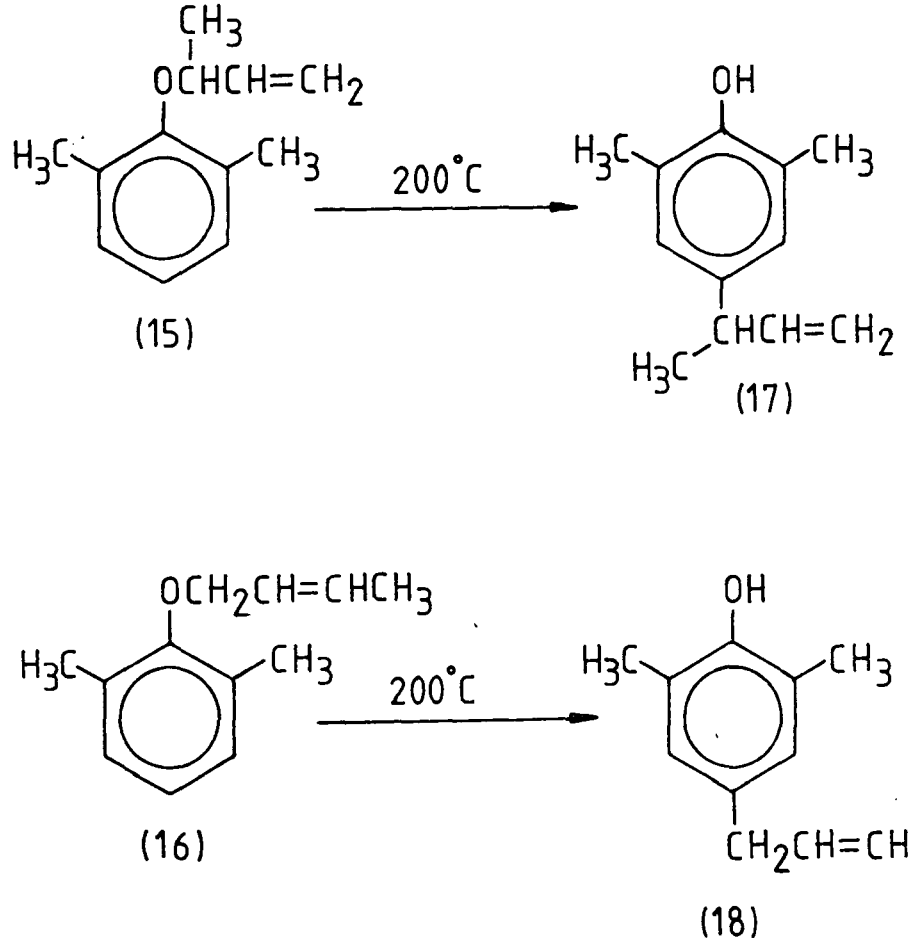
In systems where both ortho-positions were substituted, as in allyl 2,6-dimethylphenyl ether (12), rearrangement did not yield the ortho-dienone (13) as the reaction product, but instead gave the para-substituted phenol (14),[11] Scheme 7. The rearrangement was later shown to involve the intermediacy of the ortho-dienone (13), however, since the reaction of allyl bromide on 2,6-dimethyl phenoxide at 15°C actually resulted in the isolation of (13), which when thermolysed at 75°C gave the para-substituted phenol (14) as well as the ether (12).[12]



Scheme 7

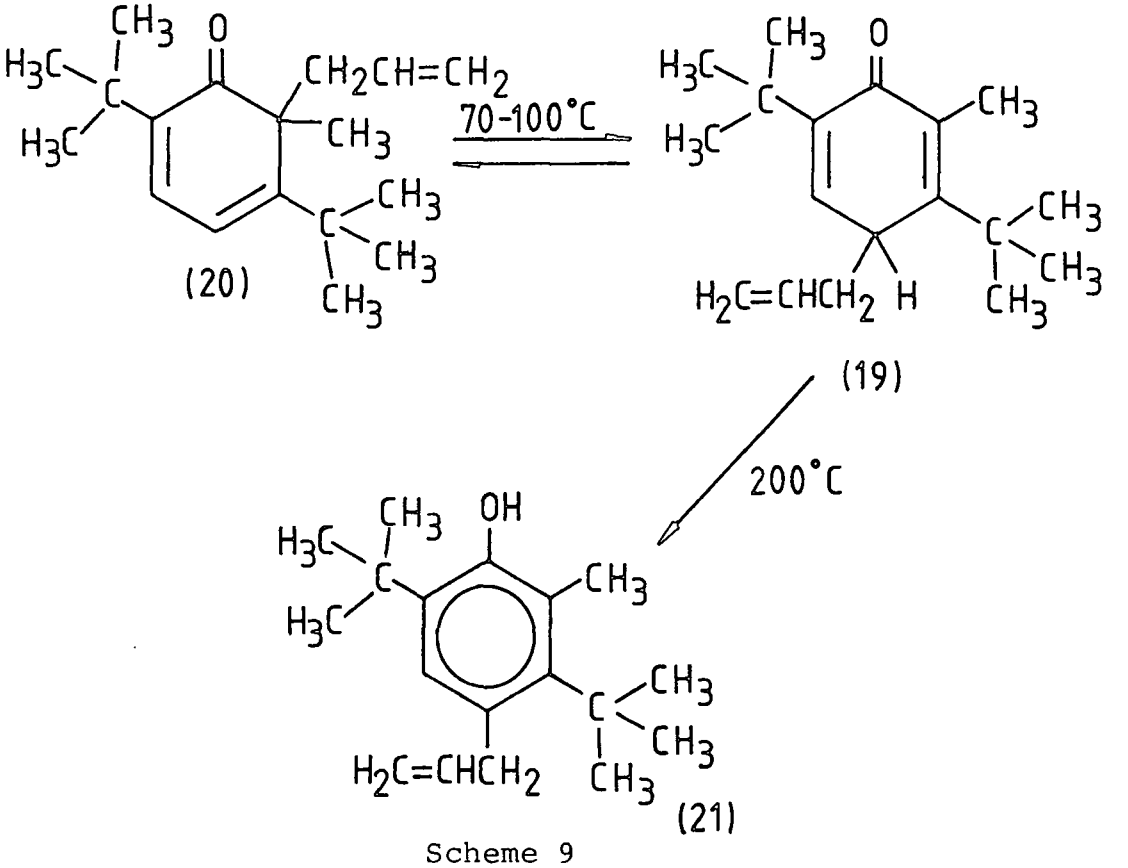
This reaction not only demonstrated that the ortho-dienone must be an intermediate in the aromatic Claisen rearrangement, but also that the reaction occurs reversibly.

Thermolysis of 2,6-disubstituted ethers having 1- or 3-substituents on the allyl group indicated that unlike the ortho-rearrangement, where reaction occurred with inversion of the allyl group, the para-rearrangement proceeded with retention of the configuration.[13] Thus, ethers (15) and (16) rearranged to the para-substituted phenols (17) and (18) respectively, Scheme 8.



Scheme 8

Just as the intermediacy of the ortho-dienones had been established, conclusive evidence for the intermediacy of para-dienones in the para-rearrangement was demonstrated by the formation of the stable compound (19) from thermolysis of the ortho-dienone (20) between 70-100°C,[14] Scheme 9.

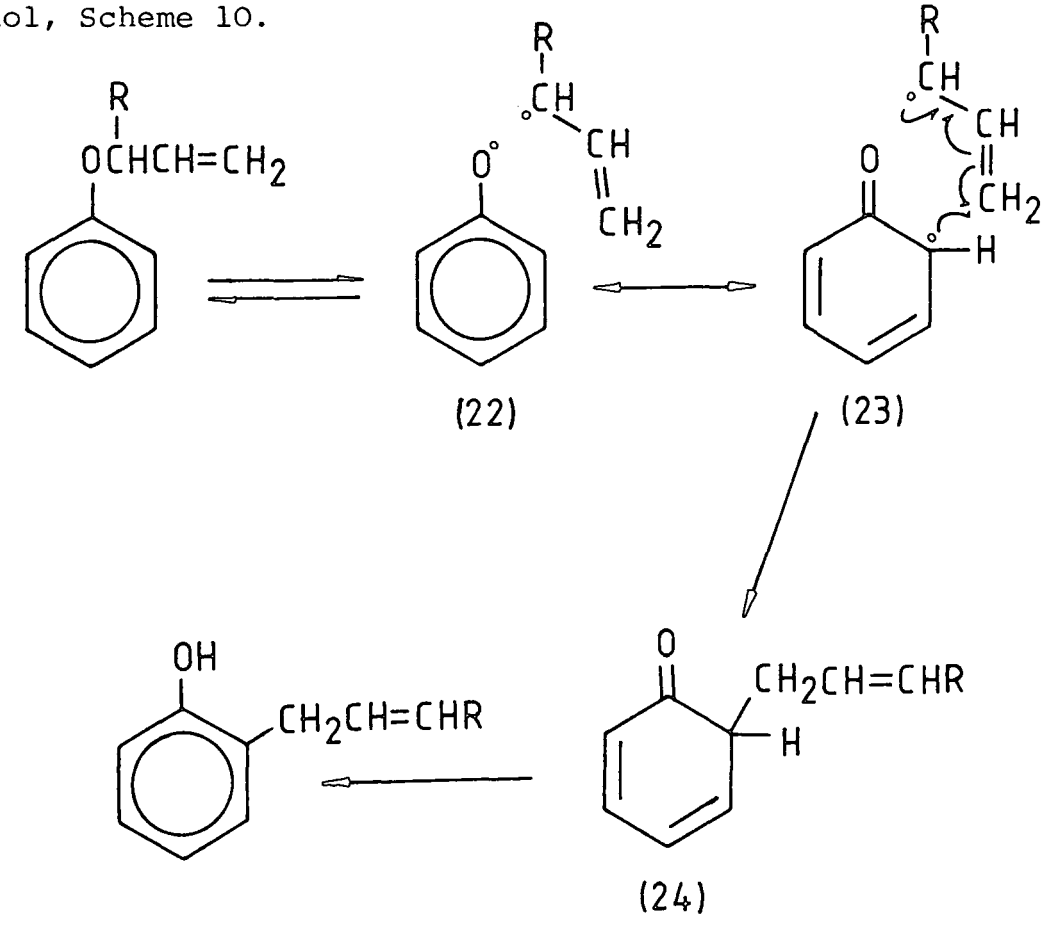


Scheme 9

The large steric strain which would be developed in the aromatized product as a result of having adjacent allyl and *t*-butyl groups in the same plane enabled (19) to remain stable to tautomerism to the para-substituted phenol (21) below 200°C.

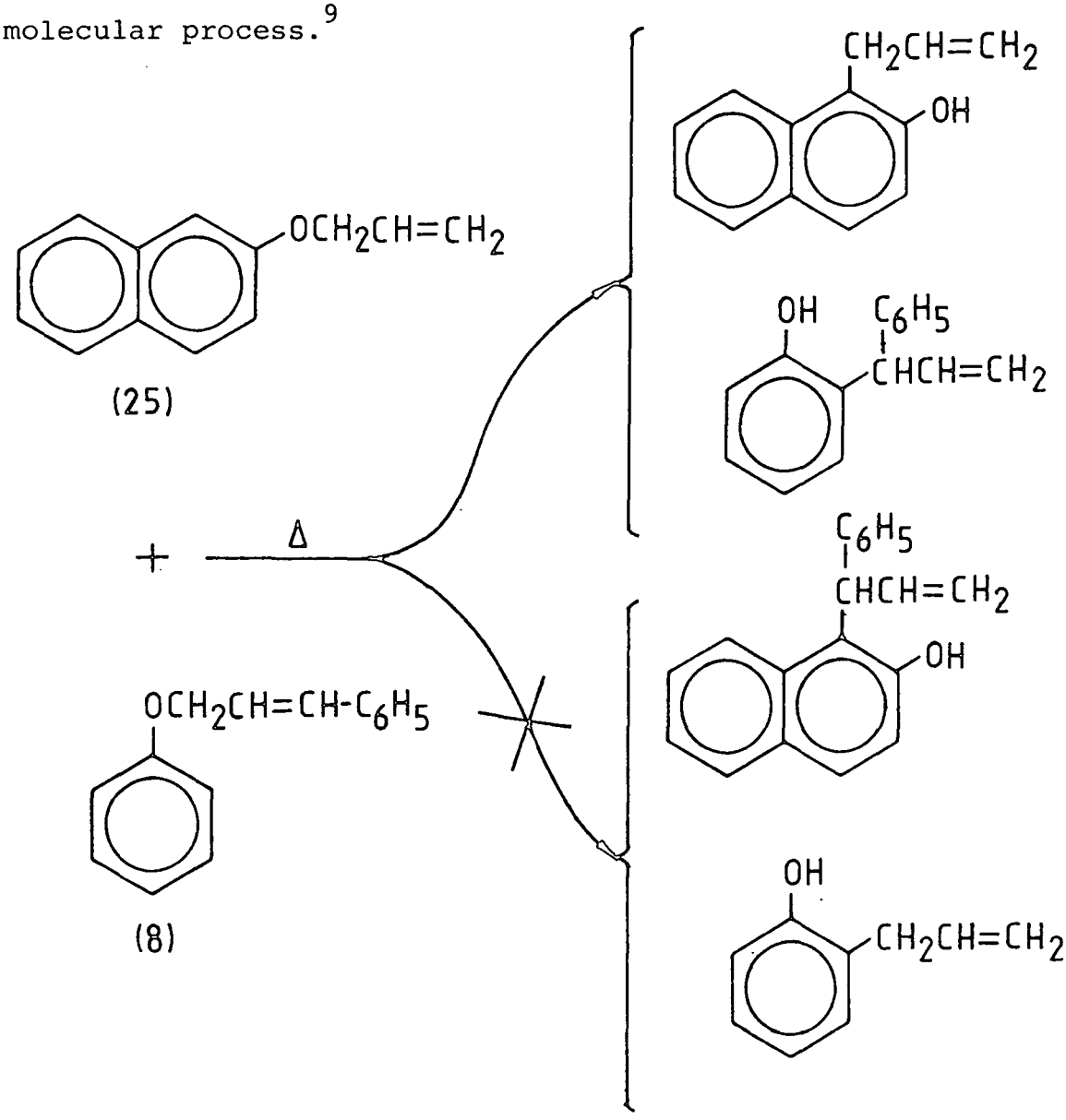
1.3 The Mechanism

Although the intermediacy of dienones was without doubt, there remained the question as to the mechanism of their formation. Claisen had already postulated as early as 1925 that the rearrangement was cyclic, intramolecular, involved a dienone intermediate and proceeded with inversion of the allyl group.[8] For the actual mechanism, however, he suggested that the bond between the allyl group and the oxygen split into radicals. The phenoxy radical (22) thus formed would then resonate to the keto form (23), capture the 3-carbon of the allyl group, since it was considered to be nearest in space, and then tautomerize from the dienone (24) to the phenol, Scheme 10.



Scheme 10

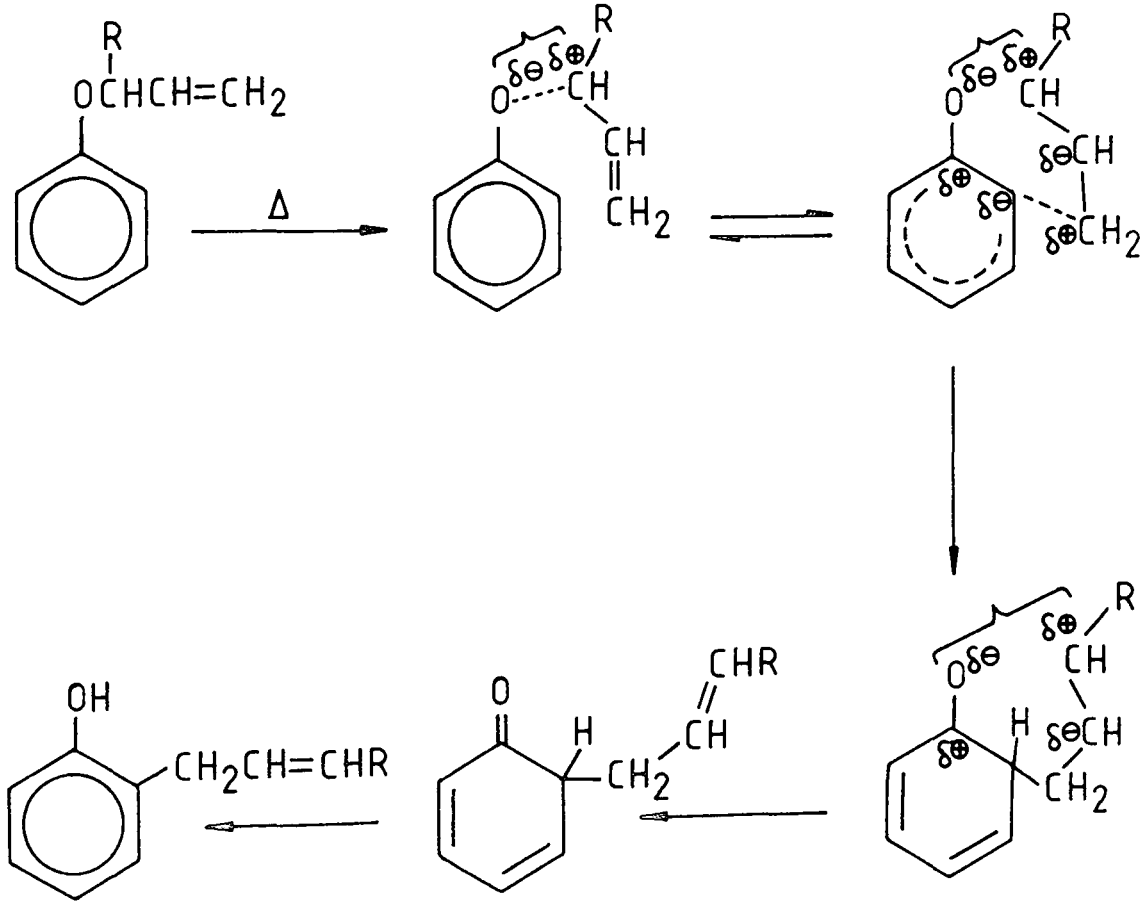
The absence of any by-products resulting from other combinations of the radicals present, such as two phenoxy radicals to give phenyl peroxide[15] and the fact that no cross-over products were obtained when 2-allylnaphthyl ether (25) and phenyl(3-phenyl)allyl ether (8) were heated together, Scheme 11, suggested that the rearrangement was indeed an intramolecular process.[9]



Scheme 11

However, it was unreasonable to expect a radical reaction to have such a degree of intramolecularity,[16] and since the 3-carbon of the allyl group need not necessarily be the nearest atom, Claisen's explanation for inversion, and thus the idea for a radical mechanism was abandoned.

Hurd and Pollack[16] offered an alternative hypothesis wherein rearrangement occurred by an alteration of the position, *i.e.* semi-ionization, of the pair of electrons bonding the allyl group to the oxygen, resulting in other 'ionic disturbances' at the double bonds. The overall effect of this being a resultant concerted cyclic reorganization of the electrons with the migrating group 'cartwheeling' around the ring, Scheme 12.

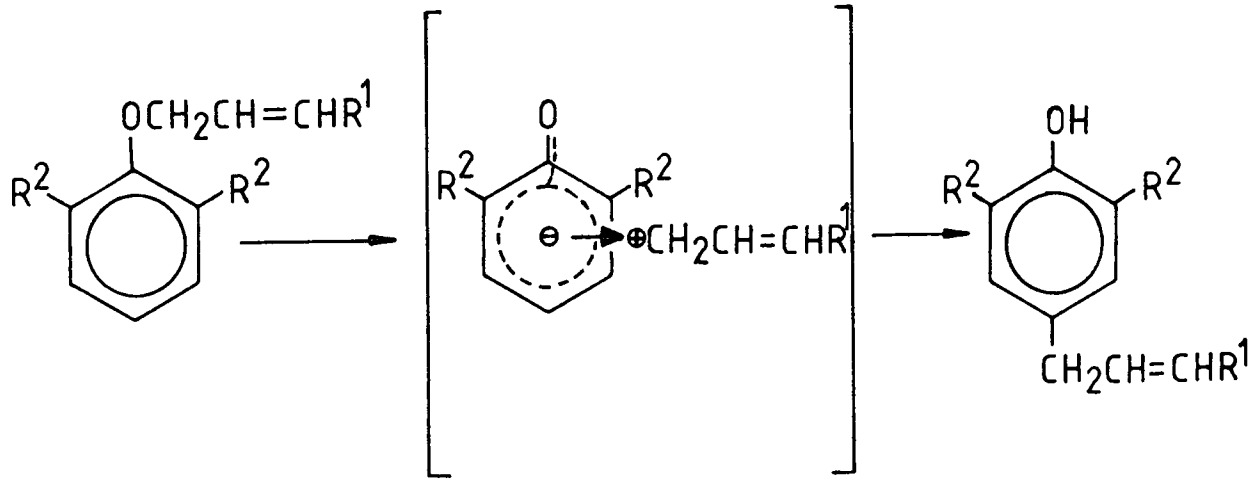


Scheme 12

This mechanism not only provided an explanation for the intramolecular nature of the reaction, but also for inversion of the migrating group.

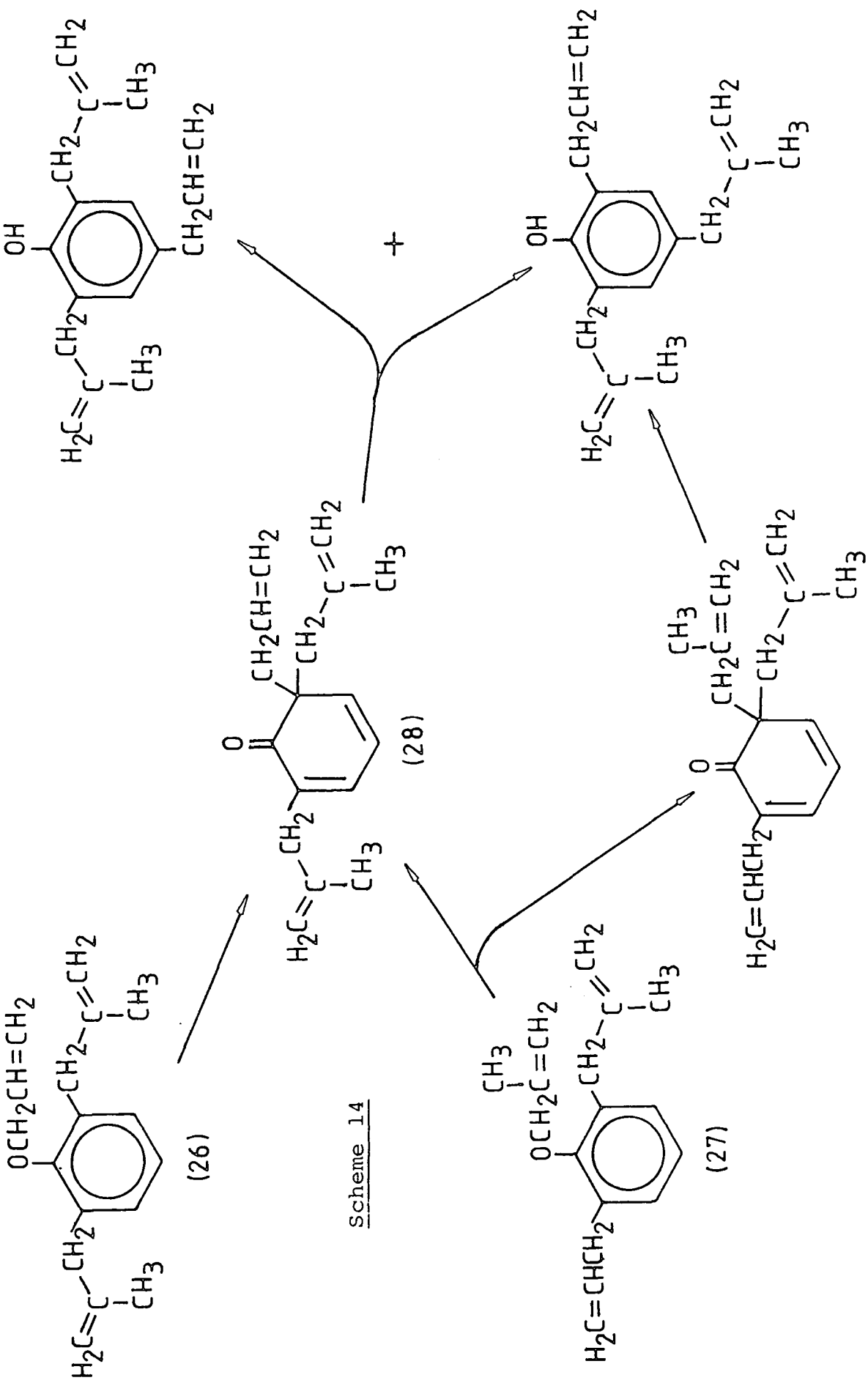
By analogy, Hurd and Pollack also applied the mechanism to the formation of the para-substituted phenols, with the allyl group undergoing two 'cartwheeling' processes to reach the para-position. This again successfully rationalized the observation for retention of configuration of the migrating group.

An alternative mechanism for the para-rearrangement was proposed by Dewar,[17] wherein an ionization occurred, with the allyl group and the aromatic species held together in a form of π-complex, which subsequently collapsed, without resonance of the allyl group, to form the para-substituted phenol, Scheme 13.



Scheme 13

This theory was later shown to be incorrect, however, since it failed to rationalize the intermediacy of dienones, a point demonstrated in the reaction of the isomeric ethers (26) and (27), which rearranged to give an identical product distribution. The migration of the ortho-substituent could only be explained if the ortho-dienone (28) was an intermediate common to both rearrangements,[18] Scheme 14.

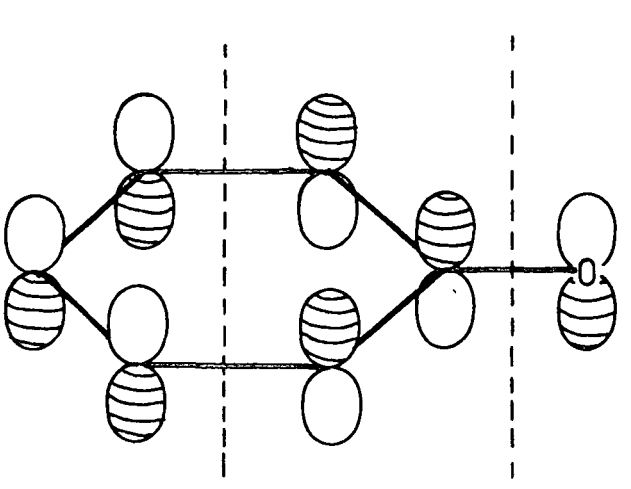


Scheme 14

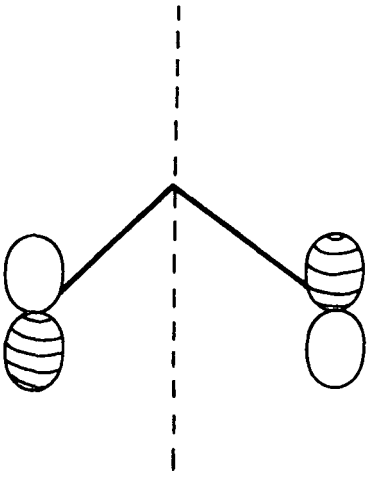
The Hurd and Pollack proposal thus became the accepted mechanism for the rearrangement, and it was not until Woodward and Hoffmann's pioneering work[2] using molecular orbital theory that a more precise description of the mechanism was put forward.

1.4 Stereochemistry and the Transition State

Using the current theory[3] devised by Woodward and Hoffmann,[2] the course of a sigmatropic rearrangement can be analysed by simply regarding the transition state as being constructed from two odd-alternant radicals, an alternant hydrocarbon being a π-system in which all the π-centres can be divided into two non-overlapping sets so that no members of either set are adjacent to a member of the same set. The dominant attractive forces between these two radicals are those of their highest occupied molecular orbitals, which in the case of odd-alternant radicals, is always the singly occupied non-bonding molecular orbital. The transition state for the Claisen rearrangement can thus be constructed as a 'complex' of an interacting quasi-phenoxy radical and a quasi-allyl radical. The non-bonding molecular orbitals are (29) and (30) respectively.

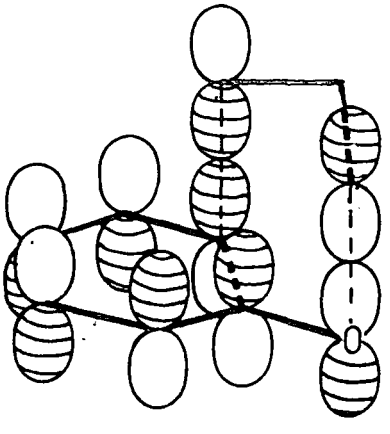


(29)



(30)

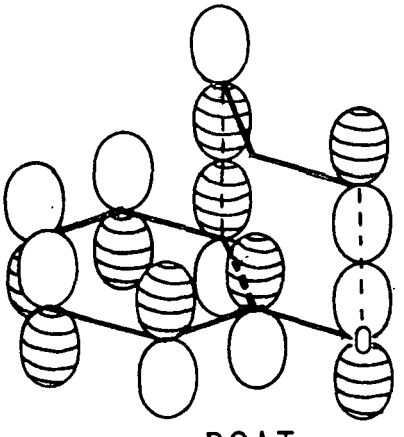
From Table 1, it can be seen that the Claisen rearrangement is thermally allowed (i+j=6, n=2) if migration occurs either suprafacial-suprafacial or antarafacial-antarafacial with respect to both quasi-radicals. Bonding can only occur between molecular orbitals of the same phase, and thus there are various geometries possible for the transition state. Three such transition states are (31), (32) and (33).



CHAIR

(31)

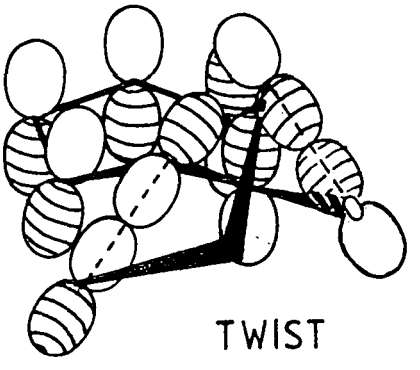
supra - supra



BOAT

(32)

supra - supra



TWIST

(33)

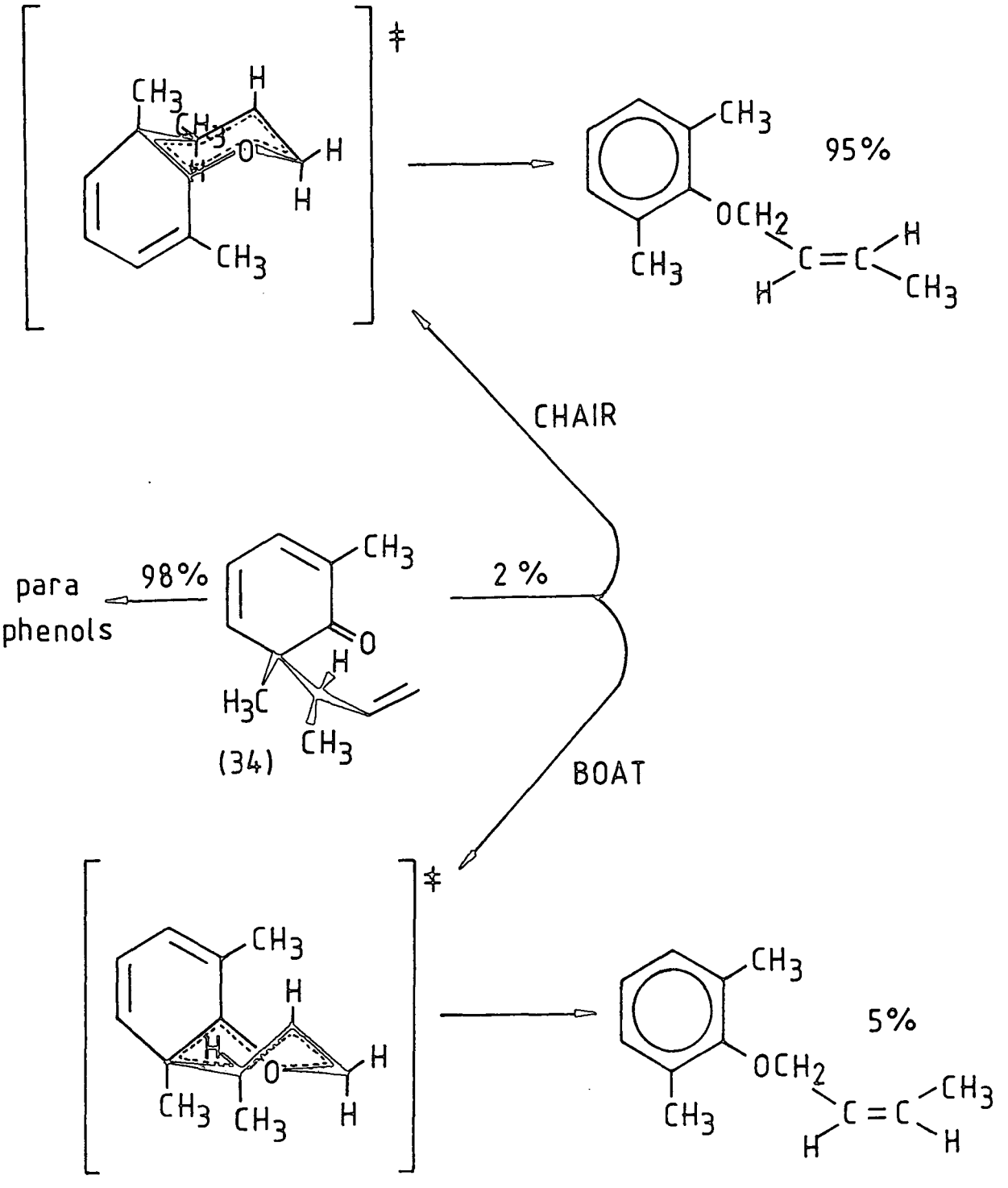
antara - antara

Of these, (33) is much less likely, as it involves twisting of both components. Both supra-supra processes are relatively strain free, and of the two, the chair form (31) might be expected to dominate by consideration of secondary orbital effects.[19]

Normally, in a Claisen rearrangement where the aromatic ring is unsubstituted, enolization of the intermediate dienone results in the loss of the stereochemical information about the [3,3] step, making it impossible to analyse the transition state geometry. However, these can be obtained indirectly from the reaction of 2,6-disubstituted ortho-dienones, which can undergo either a retro-Claisen rearrangement to the ether, or a Cope rearrangement to give the para-phenol. A number of extensive studies on these rearrangements have been made.[20] Erythro 6-(1-methylallyl)-2,6-dimethylcyclohexa-2,4-dienone (34) rearranges to give a mixture of para-phenols (98%) and a mixture of *cis* and *trans* but-2-enyl-2,6-dimethylphenyl ethers (2%), Scheme 15.[20a]

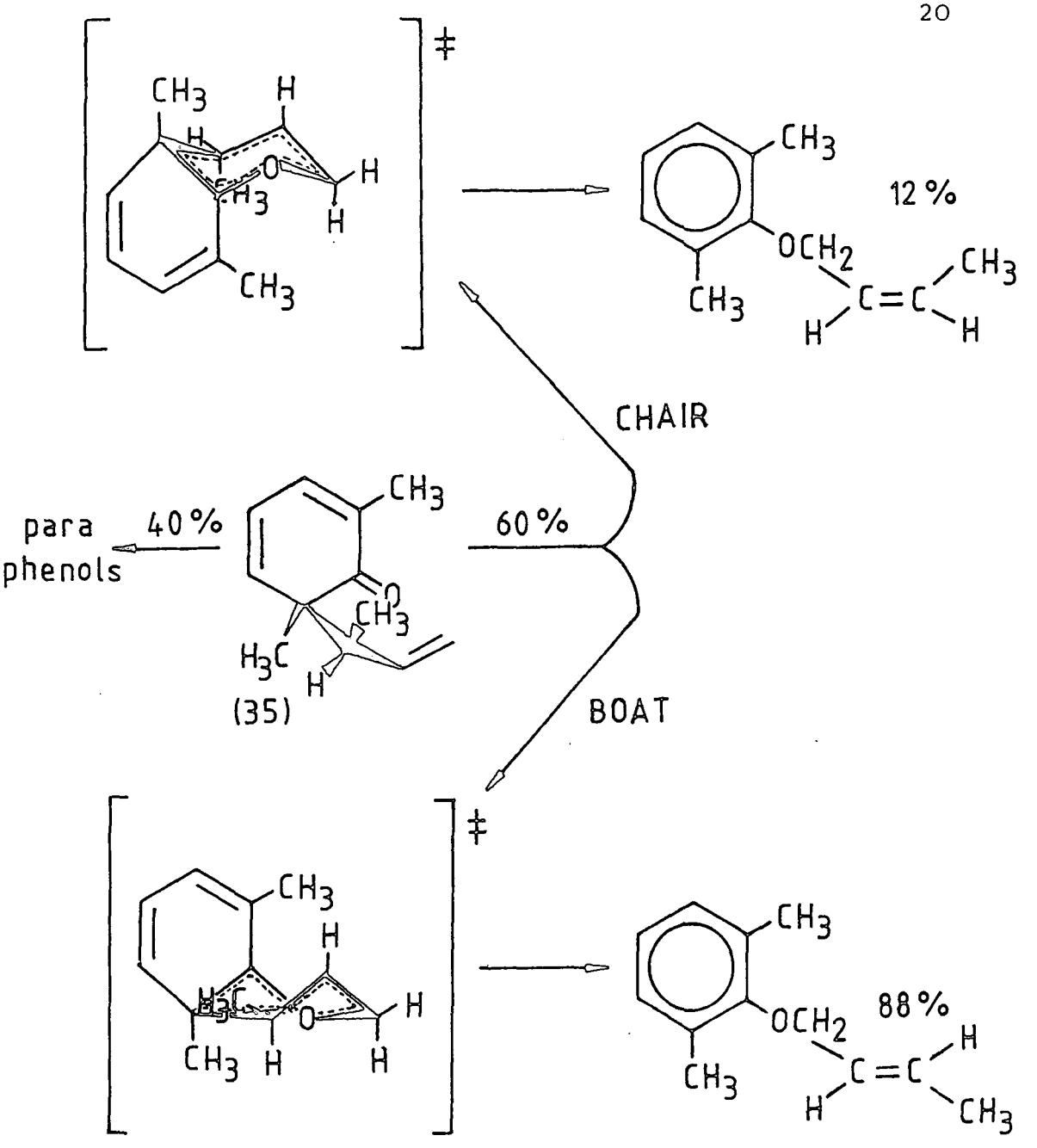
Of the ethers formed, the *trans* one predominates (95%), and this could only have been formed from the transition state having a chair conformation.

Steric interactions imposed on a transition state configuration, especially axial-axial interactions, also play an important rôle in determining the extent of the chair/boat ratio. Normally this has the effect of reducing the amount of product resulting *via* the boat form.[20,c,d] However, in some cases, the chair form may result in larger steric interactions than in the boat form, or it may lead to the thermodynamically less stable product. Threo 6-(1-methylallyl)-



Scheme 15

2,6-dimethyl-cyclohexa-2,4-dienone (35),[20 a,b] for example, rearranges to give a mixture of *cis* and *trans* ethers (60%) in which the *trans* ether predominates (88%), Scheme 16. This could only have been derived from the boat conformer (36).



Scheme 16

1.5 Catalysis

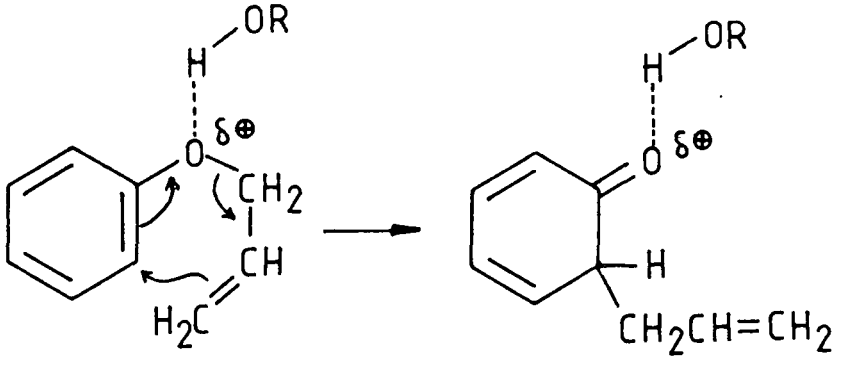
The effect of the variation of solvent upon the rate of the aromatic Claisen rearrangement is shown in Table 2.[21] The figures demonstrate the insensitivity of the rearrangement to variation of the reaction medium.

TABLE 2

Rate Constants for the Rearrangement of Allyl 4-Methylphenyl Ether at 184.85°C in Various Solvents

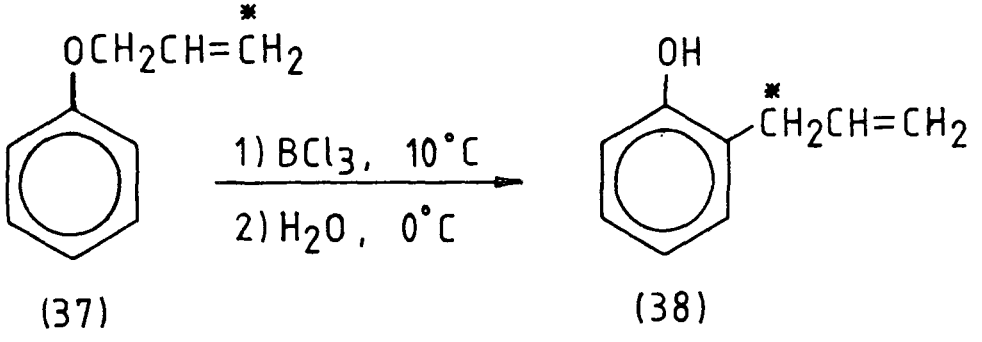
Solvent	k x 10^5 sec^{-1}
Ethylene glycol	18
Benzyl alcohol	9.7
1-Octanol	9
Phenol	45
Methyl salicylate	2.45
Benzonitrile	2.49
N,N-Dimethyl aniline	2.46
Acetophenone	2.41
Diphenyl ether	2.08
Diphenylmethane	2.12
Decalin	1.56

Rate enhancement is most marked when the solvent system is hydroxylic or phenolic in nature and is probably due to partial protonation of the ether oxygen by hydrogen-bonding to the solvent. This enhances the breaking of the oxygen-allyl bond, Scheme 17.



Scheme 17

The effect of added substrates on the rearrangement, especially Lewis acids, is well documented.[22] Considerable rate enhancement of the rearrangements are observed in most cases. Thus, the allyl phenyl ether (37), when treated with BCl_3 at $10^{o}C$ gives the ortho-substituted phenol (38), 89%, with an increase of the reaction rate relative to the thermal rearrangement of the order 10^{10},[23] Scheme 18.

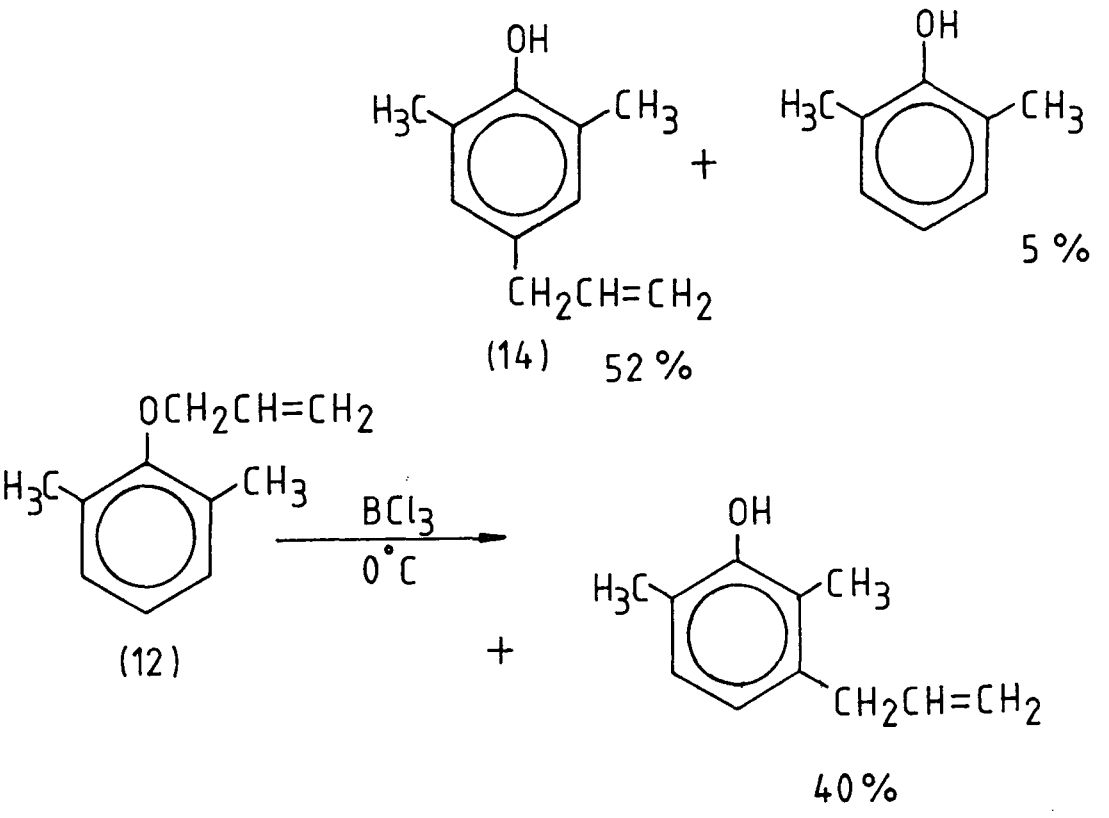


(37) (38)

Scheme 18

High yields of products resulting from [3,3] rearrangements are also observed in other systems, but complications are often observed. Allyl 2,6-dimethylphenyl ether (12) when treated with BCl_3 at $0^{o}C$ gives the expected para-substituted phenol (14), as in the thermal rearrangement, but also yields two other products, one being 2,6-dimethylphenol,[23] Scheme 19.

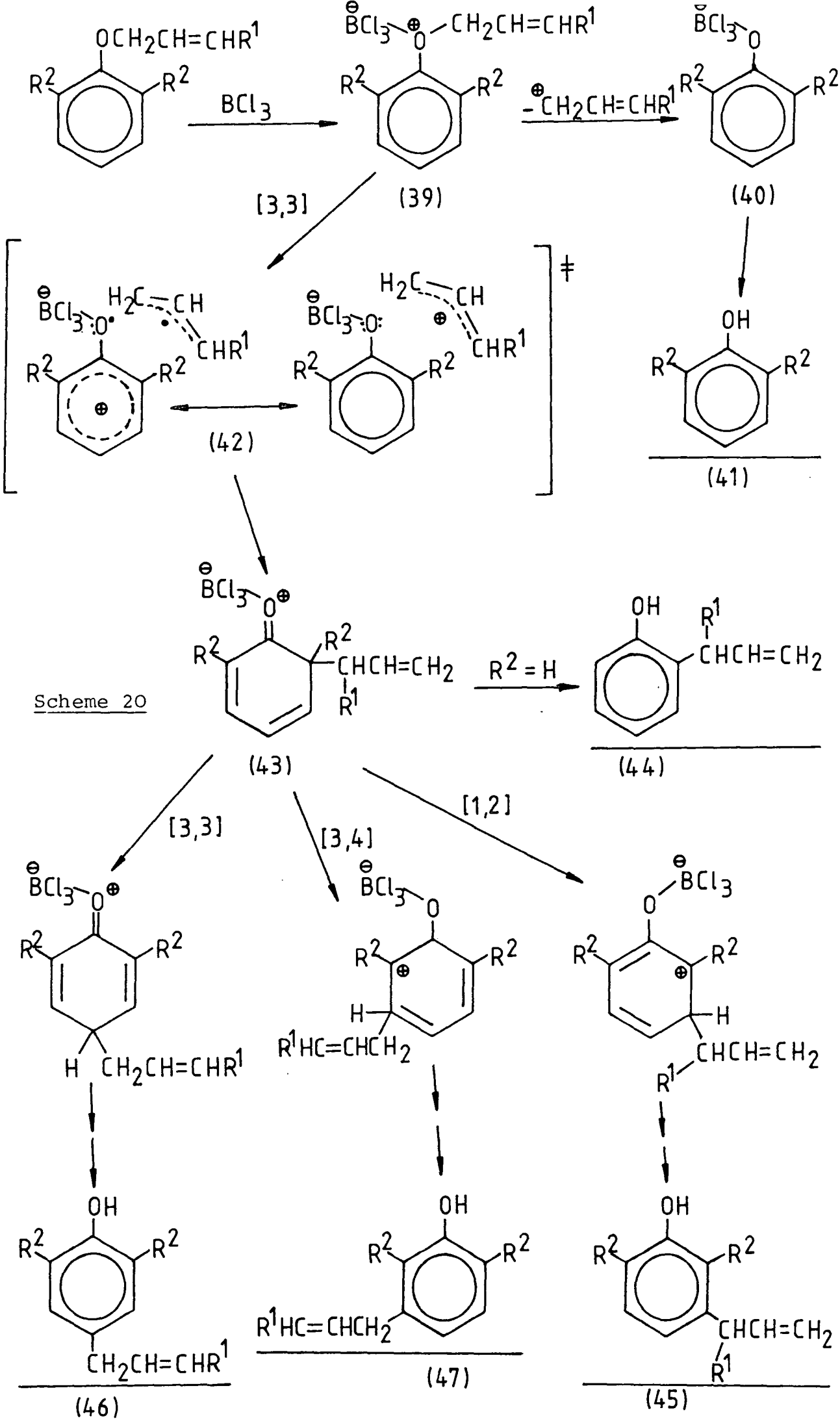
The mechanism proposed for these acid-catalysed 'charge-accelerated' [3,3] reactions, and the rationalization for the formation of the other products observed is shown in



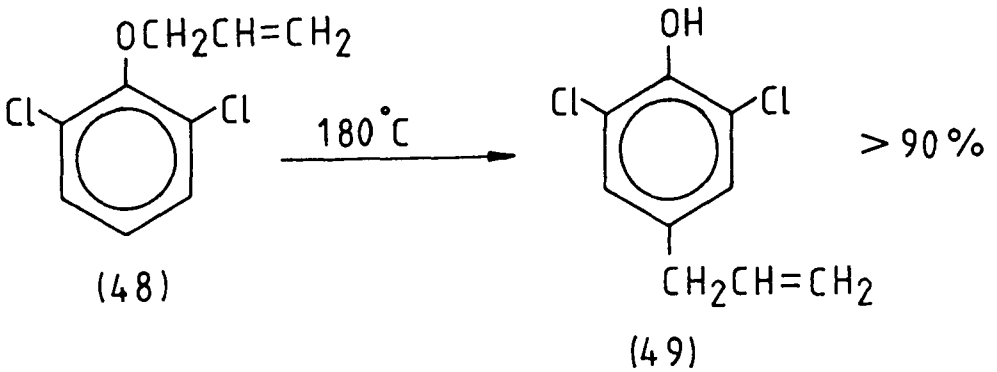
Scheme 19

Scheme 20.[22] The initially formed ether-BCl_3 complex (39) either undergoes cleavage to the species (40) and an allyl cation, which leads to the phenol (41) and products derived from intermolecular allyl transfers,[24] or undergoes a [3,3] rearrangement through a charged-delocalized transition state (42) to the ortho-dienone (43). When R^2=H, this rapidly enolizes to the product phenol (44). When R^2=alkyl, products resulting from subsequent [1,2], [3,3] and [3,4] rearrangements arise, namely (45), (46) and (47) respectively.

Anomalous reactions of another kind occur in the reaction of ethers where the aromatic ring carries chlorine or bromine substituents. Straightforward thermolysis of allyl 2,6-dichlorophenyl ether (48) at 180°C yields the para-substituted phenol (49),[25] Scheme 21.



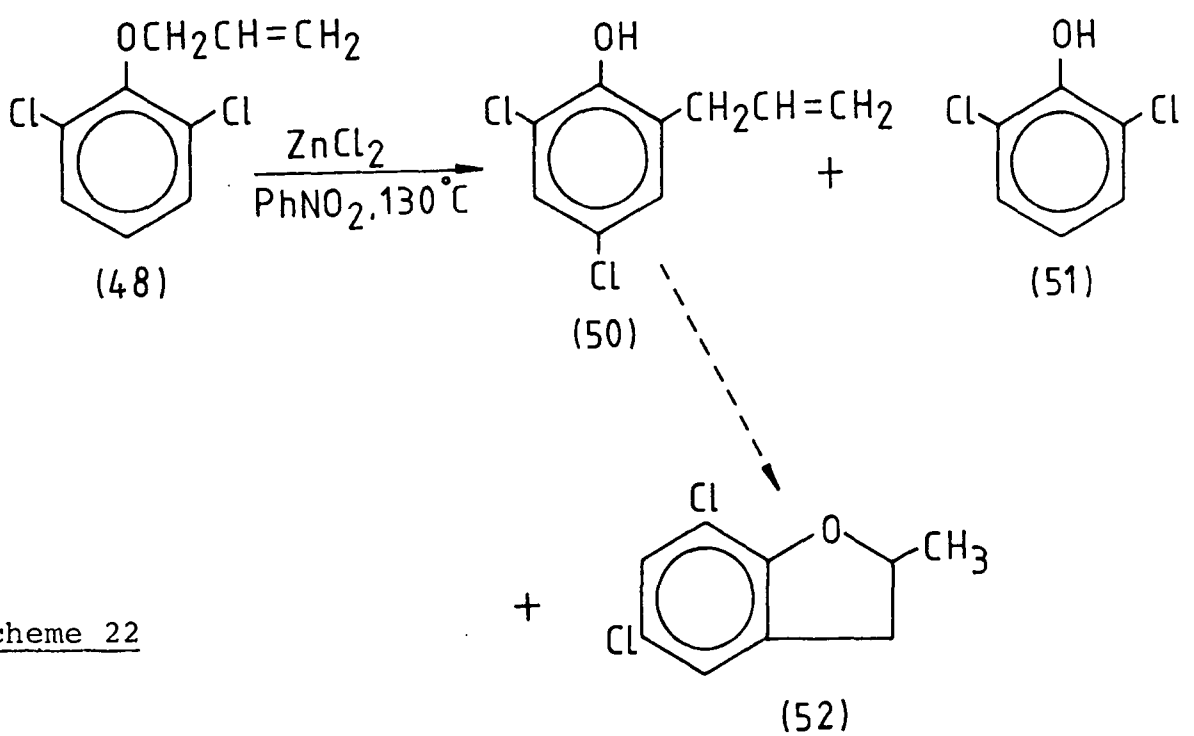
Scheme 20



(48) (49)

Scheme 21

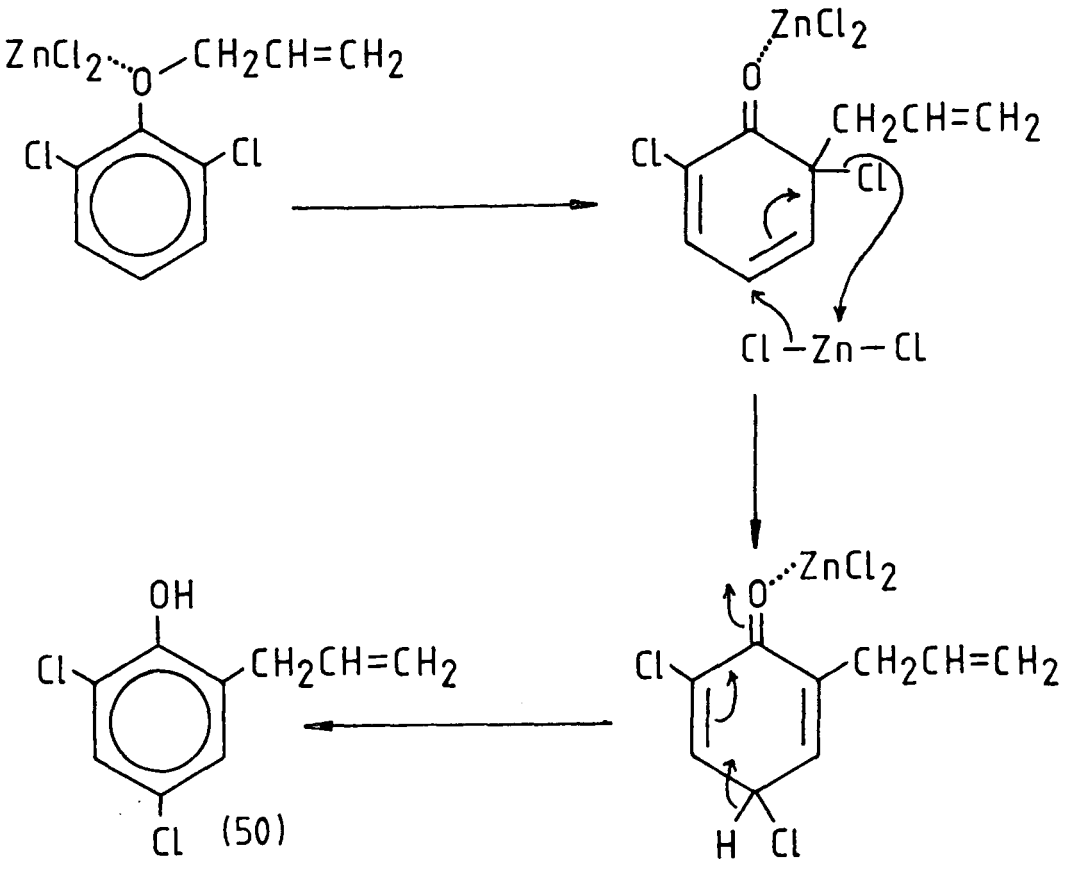
When the reaction is carried out using zinc chloride as the catalyst however, the products obtained are 2-allyl 4,6-dichlorophenol (50), 2,6-dichlorophenol (51) and 2-methyl-5,7-dichlorocourmaran (52), the latter resulting from acid-catalysed cyclization of the rearrangement phenol (50),[25] Scheme 22.



(48) (50) (51) (52)

Scheme 22

Formation of the 4,6-dichlorophenol derivative (50) is the result of a halogen exchange process, occurring in the dienone-intermediate, Scheme 23.



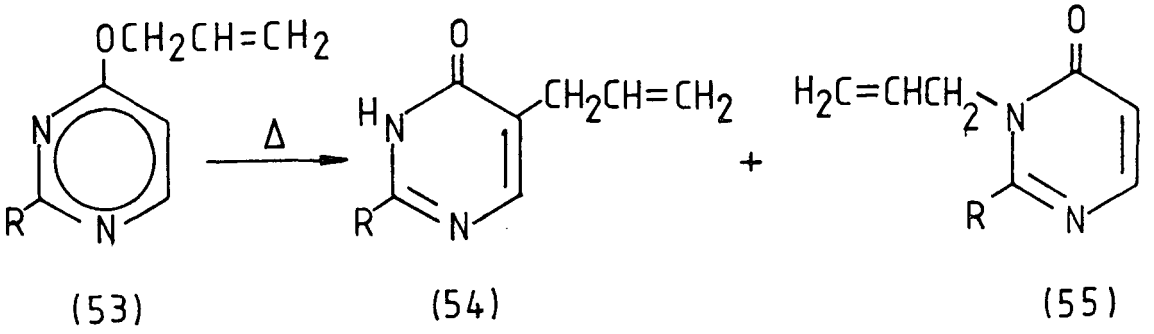
Scheme 23

1.6 Rearrangement in Nitrogen Heterocyclic Systems[26]

From a structural standpoint, compounds similar to allyl phenyl ethers should also undergo Claisen-type rearrangements. In the case of nitrogen heterocyclic systems there exists, for the first time, the possibility for rearrangement of an allyl group not only to an adjacent carbon atom, but also, in some cases, to an adjacent nitrogen atom. Usually when two dissimilar ortho-positions are available, migration of the allyl group takes place predominantly to the position

having the higher electron density,[27] and thus a pattern of nitrogen migration might be expected.

In a thorough investigation into the thermal rearrangements of allyl 2-substituted pyrimidin-4-yl ethers (53), Scheme 24, Tieckelman and co-workers[28] found that migration of the allyl group indeed occurred to the ortho-carbon and the ortho-nitrogen to yield (54) and (55) respectively. In each case, however, migration to the ortho-carbon predominated.



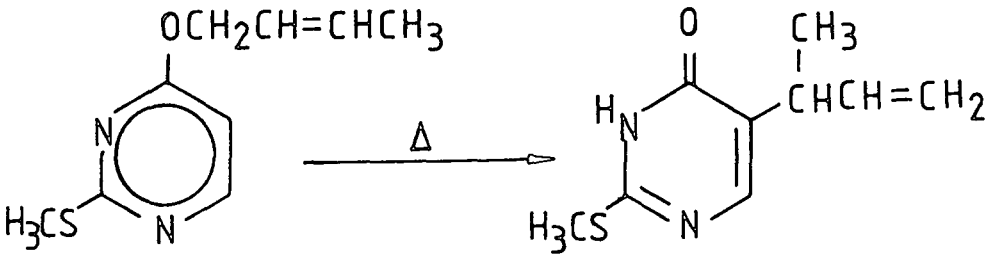
(53) (54) (55)

Scheme 24

R	Ratio N-migration : C-migration
CH_3S-	1 : 1.7
CH_3-	1 : 1.6
$C_6H_5CH_2S$-	1 : 2.4
$C_6H_5CH_2$-	1 : 2.6

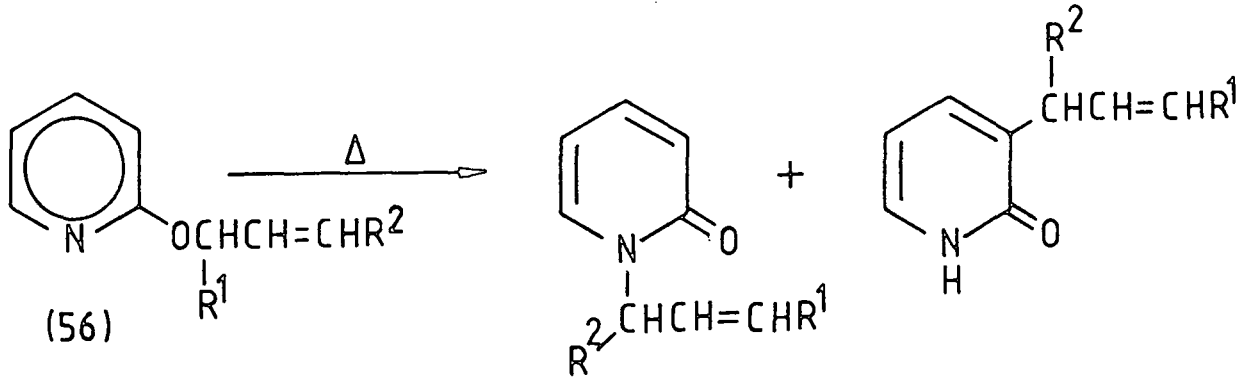
The rearrangement showed the general mechanistic features as found in the benzene systems, reaction occurring with in-

version of the allyl group,[28a] Scheme 25, and no cross-over products being observed when mixtures of ethers were heated together.



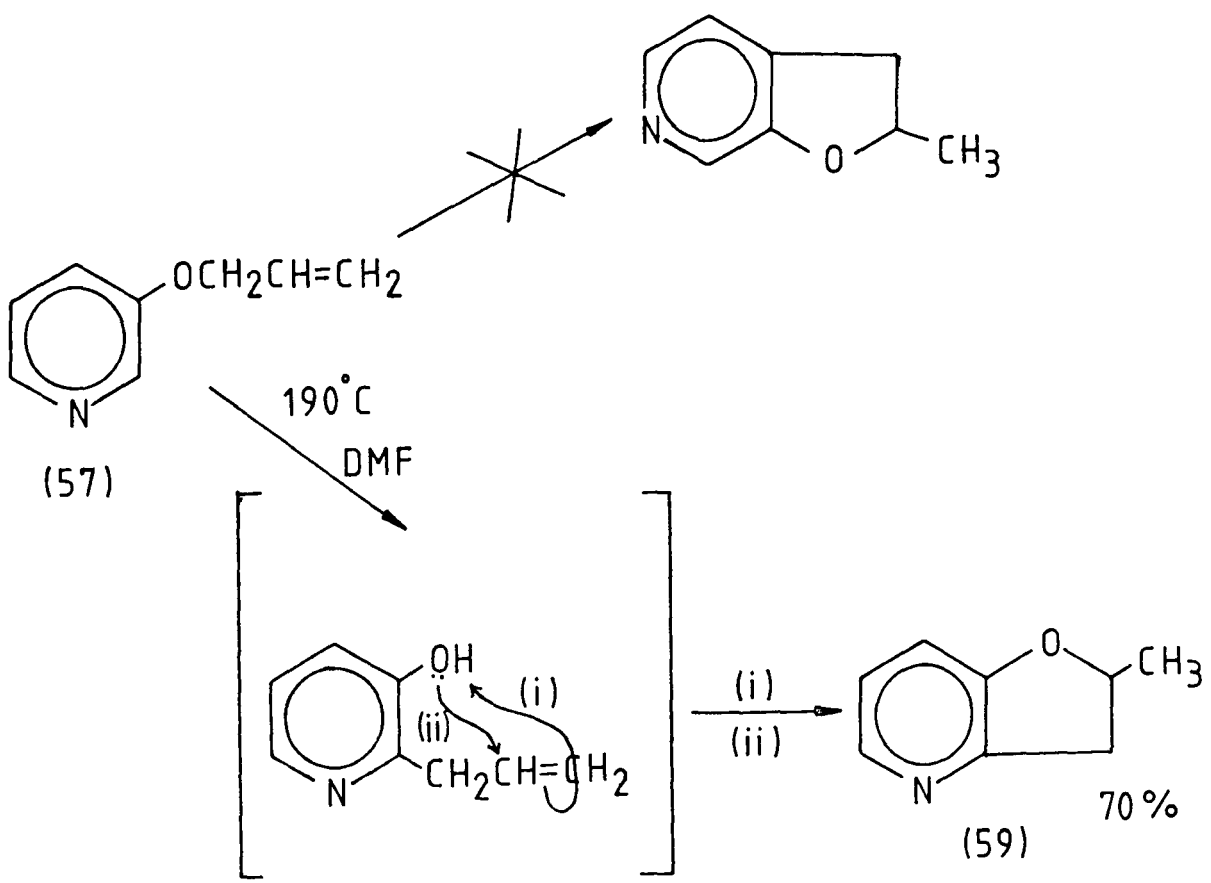
Scheme 25

Dinan and Tieckelman[29] also investigated the thermal rearrangement of some allyl pyridin-2-yl ethers (56), Scheme 26. Reaction proceeded in a similar fashion, both ortho-products being obtained, although in this case in approximately equal amounts.



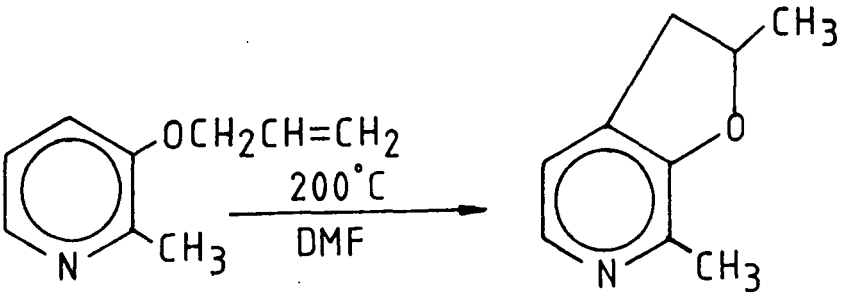
Scheme 26

Attempted thermal rearrangement of allyl pyridin-4-yl ether resulted only in the formation of polymeric materials.[30] The rearrangement of allyl pyridin-3-yl ether (57) and allyl 2-methyl pyridin-3-yl (58) behaved differently again.[31] Thermolysis of the simple ether (57) resulted only in the formation of the cyclized product 2-methyl-2,3-dihydrofuro-[3,2-b]pyridine (59) in which migration of the allyl group had occurred exclusively towards the nitrogen before ring closure, Scheme 27.



Scheme 27

In contrast, the 2-methyl derivative (58) gave only 2,7-dimethyl-2,3-dihydrofuro[2,3-c]pyridine (60) in which the allyl group had migrated only away from the nitrogen, Scheme 28.



(58) (60)

Scheme 28

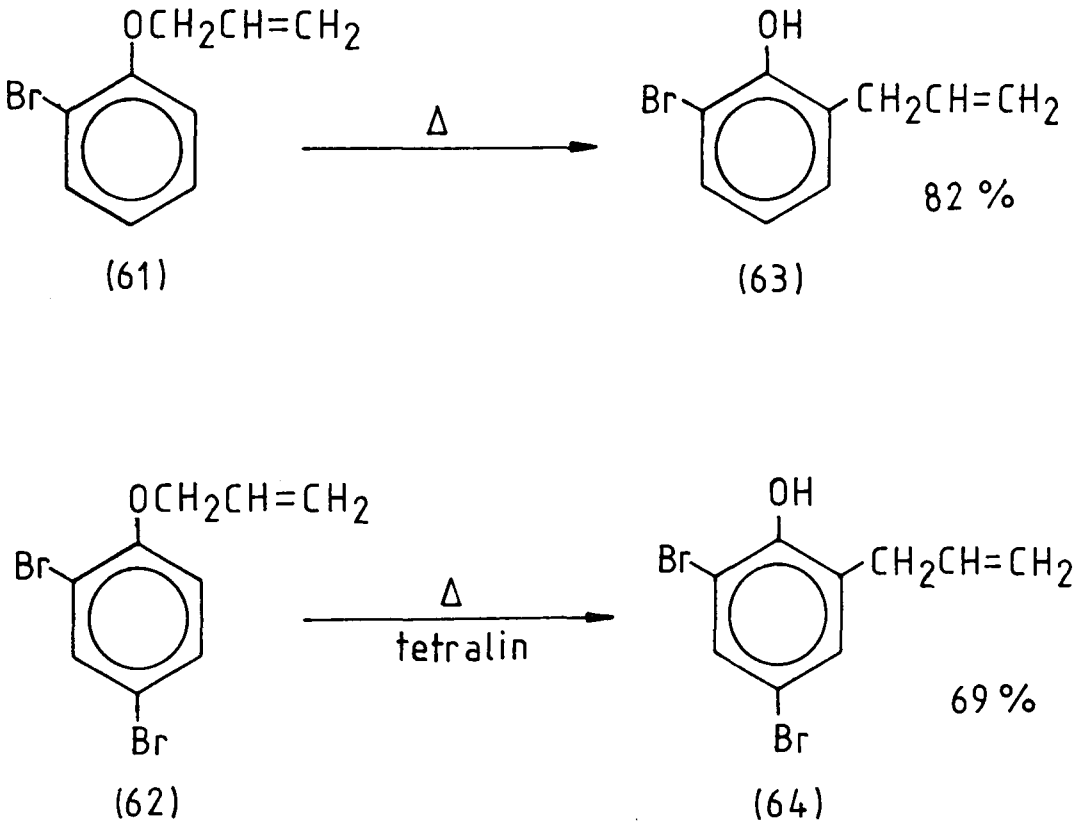
Claisen rearrangements of the allyl ethers of a number of other nitrogen heterocycles have also been established, and with only a few exceptions proceed by the normal Claisen rearrangement mechanism.[26]

1.7 Rearrangement in Halogenated Aromatic Systems

Normally in the course of a Claisen rearrangement of an allyl phenyl ether (1) (see Scheme 3), the dienone intermediates rapidly tautomerise to their respective phenolic compounds (3) and (5), without undergoing further reaction. If, however, the hydrogen atoms on the aromatic moiety are replaced by halogen atoms, the rearomatisation is prevented, opening up the possibility of further reaction pathways normally unavailable for the dienone intermediates.

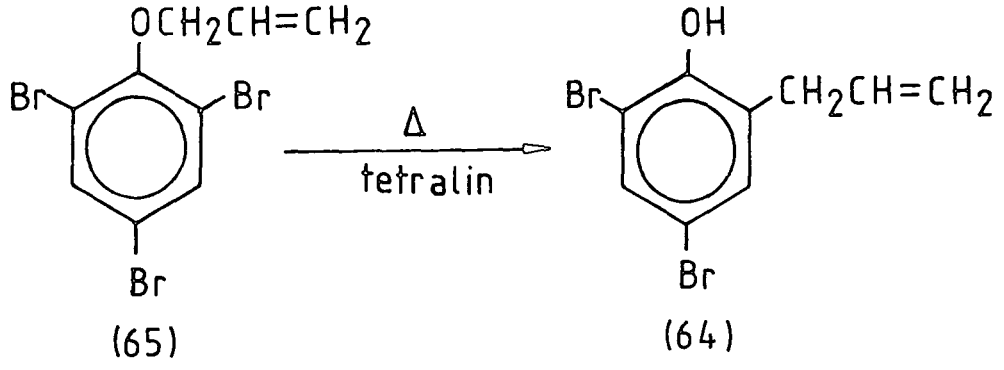
There are a number of examples of rearrangements of allyl phenyl ethers in which some or all of the aromatic protons are replaced by halogen atoms.[25,32-36] When any of

the ortho- or para-positions remain unsubstituted, migration of the allyl group occurs to the available 'open' position. Thus, allyl 2,6-dichlorophenyl ether (48) (see Scheme 21) rearranges to the para-substituted phenol,[25] and the brominated ethers (61) and (62) rearrange to the isomeric ortho-substituted phenols (63) and (64) respectively,[32] Scheme 29.



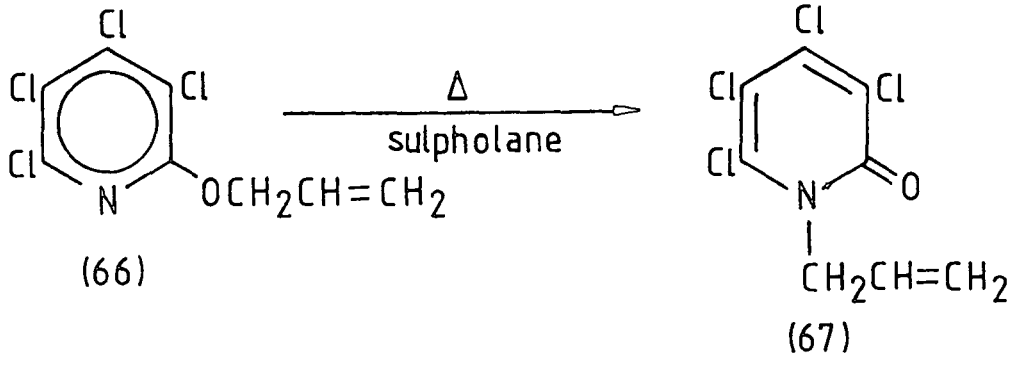
Scheme 29

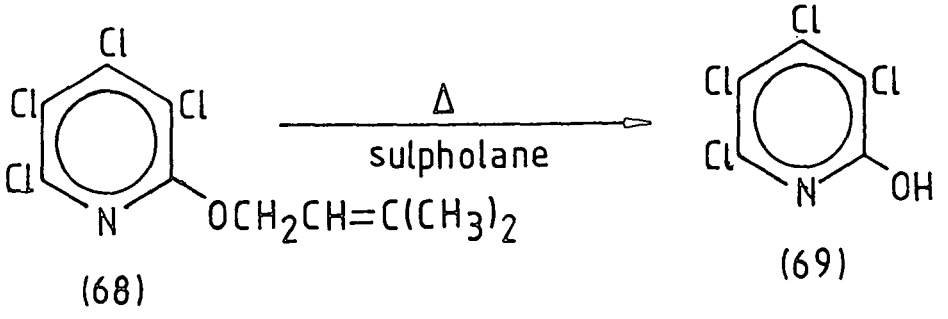
Pentabromophenyl ether, wherein all available positions are blocked, was reported to be inert to rearrangement.[33] Allyl 2,4,6-tribromophenyl ether (65), on the other hand, when thermolysed in tetralin resulted in the migration of the allyl group to the ortho-position with loss of the bromine,[34] Scheme 30.



Scheme 30

In a study on the thermolysis of allyl polychloropyridyl ethers[35] it was observed that allyl pyridin-2-yl ether (66) rearranged to the corresponding N-allyl derivative (67), whereas the dimethylallyl ether (68) gave only the tetrachloro-2-hydroxypyridine (69), Scheme 31.



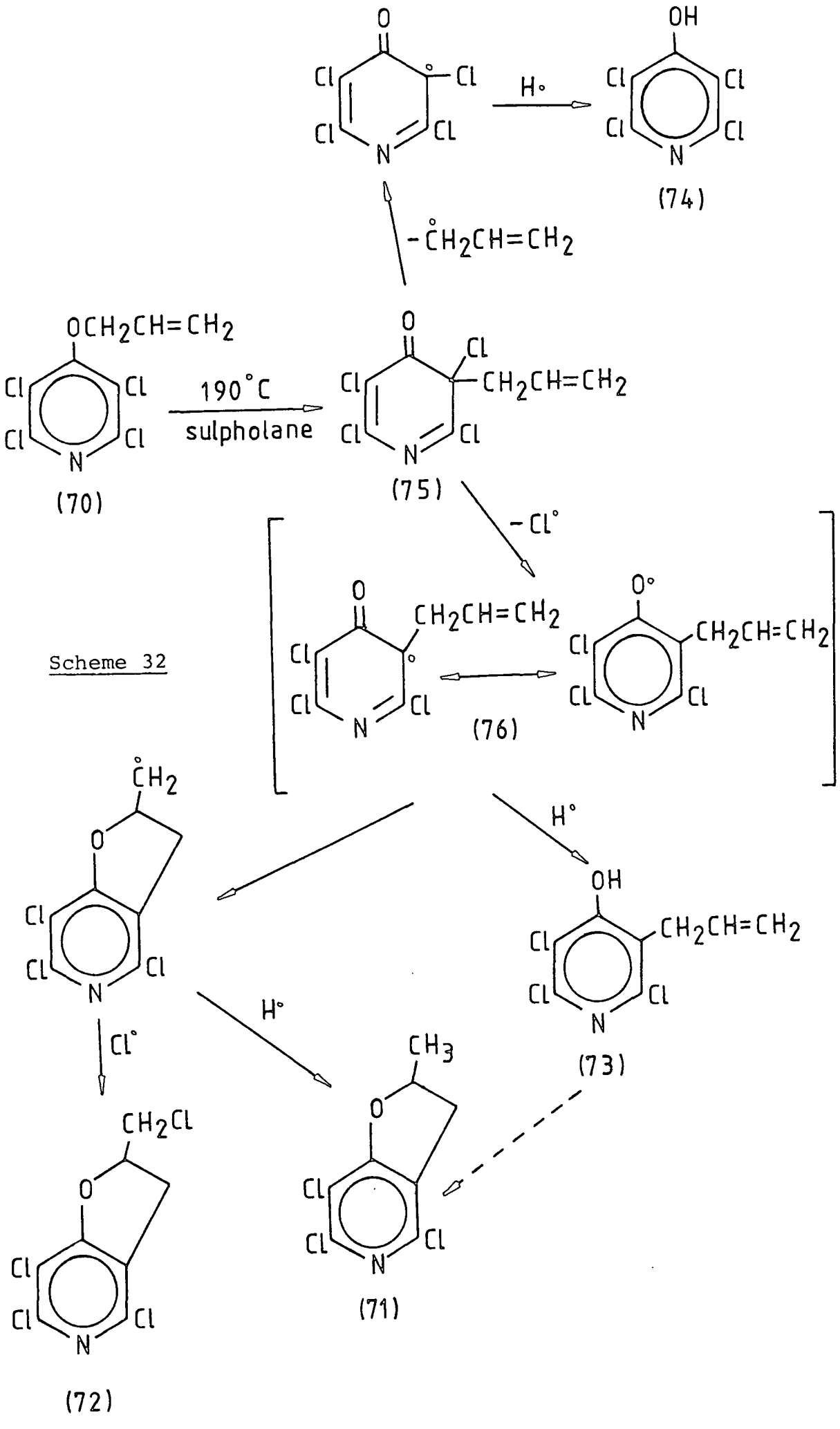


Scheme 31

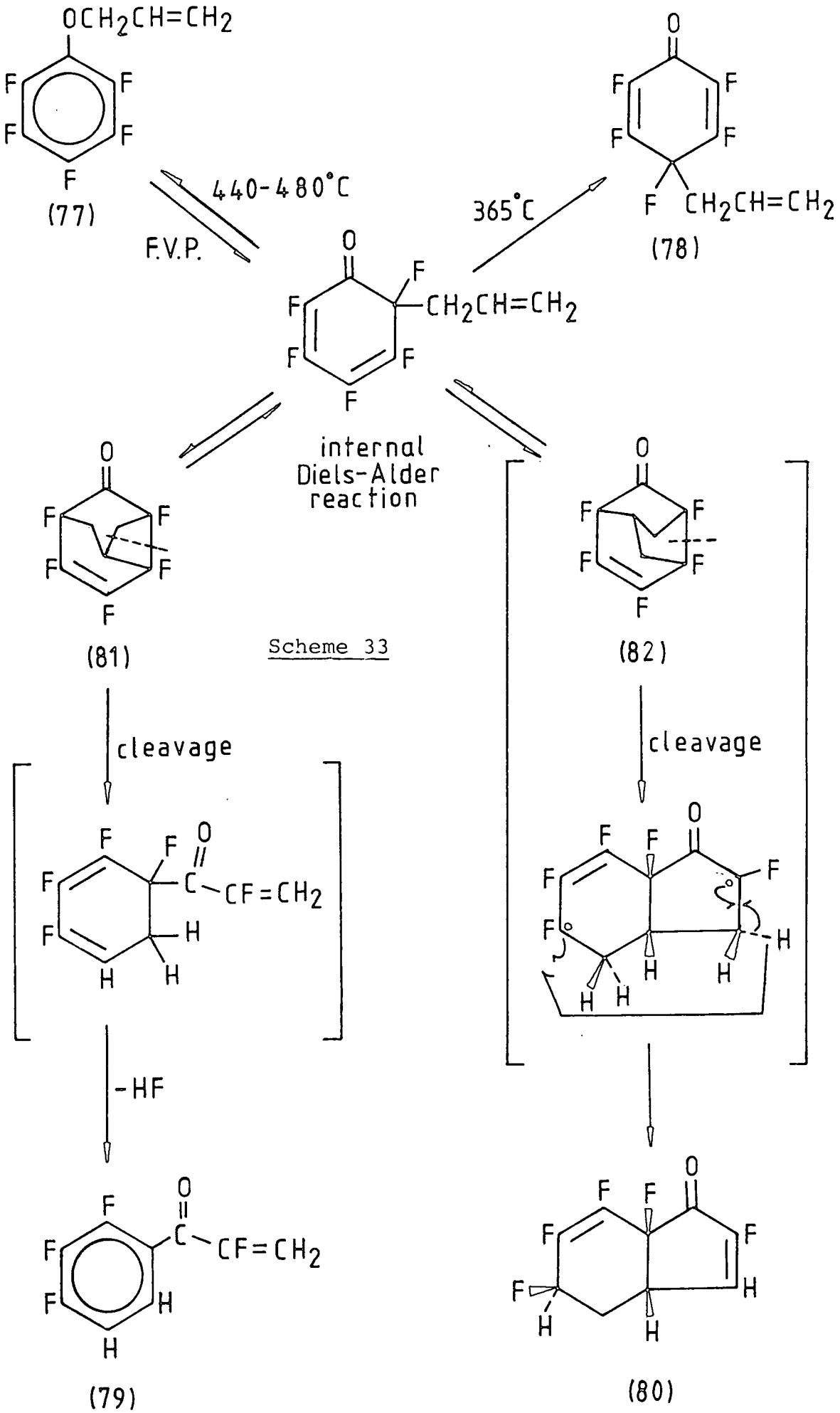
Thermolysis of allyl 2,3,5,6-tetrachloropyridin-4-yl ether (70) in sulpholaneresulted in the formation of a complex product containing 4,6,7-trichloro-2,3-dihydro-2-methylfuro[3,2-c]pyridine (71), the 2-chloromethyl analogue (72), 3-allyl 2,5,6-trichloro-4-hydroxypyridine (73) and the tetrachloro-4-hydroxypyridine (74). This result was rationalised as shown in Scheme 32.

The intermediate dienone (75) undergoes further reaction by loss of an allyl radical, or loss of a chlorine atom. The former route explains the formation of the 4-hydroxypyridine (74). Having lost a chlorine atom the species (76) can either abstract a proton from the solvent to give (73), or cyclize and then abstract either a proton or a chlorine atom to give (71) and (72) respectively. This mechanistic scheme also accounts for the formation of some of the products shown in Schemes 30 and 31.

An extensive investigation has also been made in the thermolysis reactions of various polyfluorinated aromatic and heteroaromatic allyl ethers.[36-39] The vapour phase pyrolysis of allyl pentafluorophenyl ether (77) under various conditions gives a variety of products. Flash vapour phase pyrolysis at 365^{o}C [36a] results in the formation of the para-dienone (78) as the only isolable product, whereas under more vigorous conditions (440-480^{o}C), flow pyrolysis results in a complex mixture containing the vinyl ketone (79)[36b] and the tetrahydroinden-1-one (80). Formation of these products is rationalized in terms of decomposition of the two possible intermediate Diels-Alder adducts (81) and (82), as shown in Scheme 33.

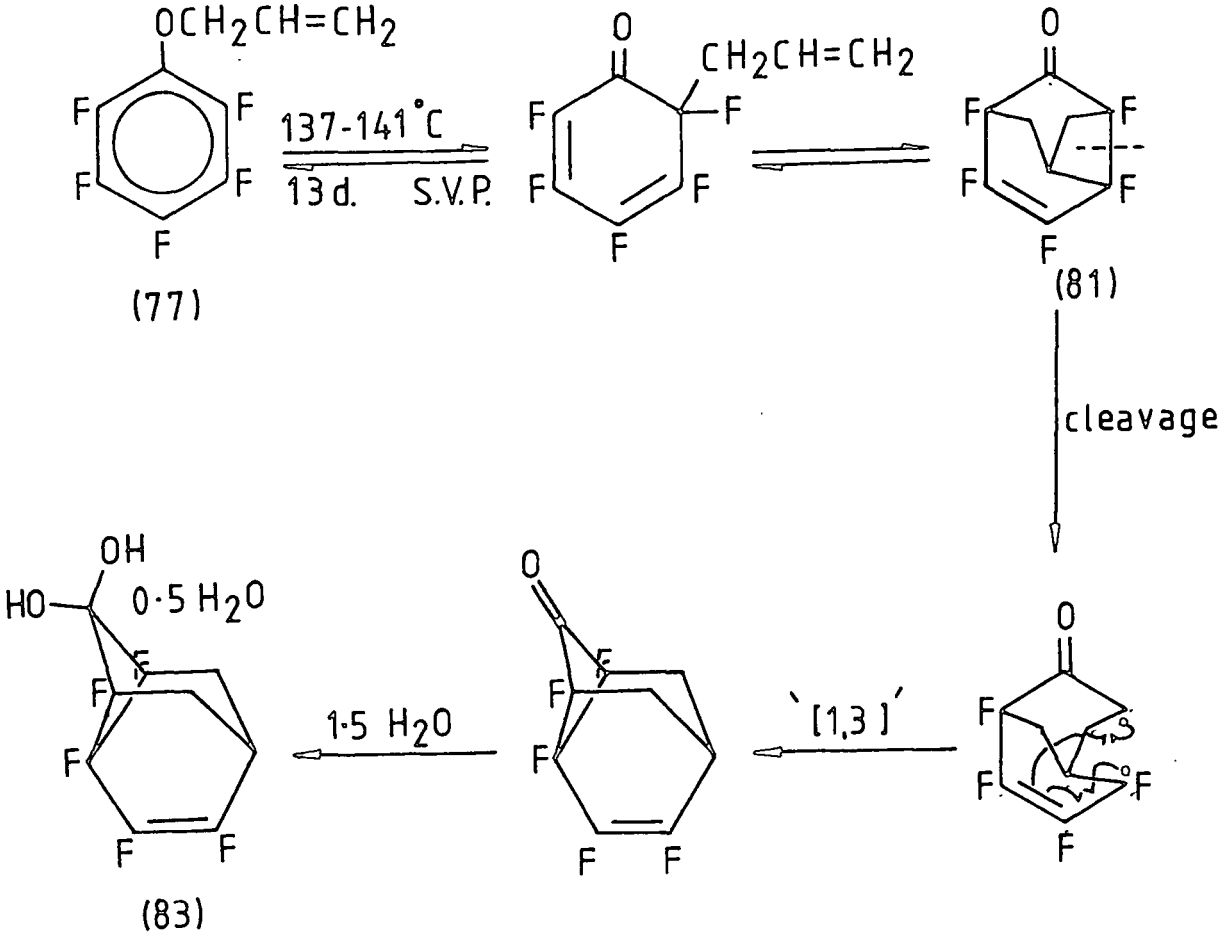


Scheme 32


OCH2CH=CH2
(77)
440-480°C
F.V.P.
365°C
(78)
CH2CH=CH2
internal
Diels-Alder
reaction
(81)
(82)
cleavage
cleavage
CF=CH2
-HF
CF=CH2
(79)
(80)

Scheme 33

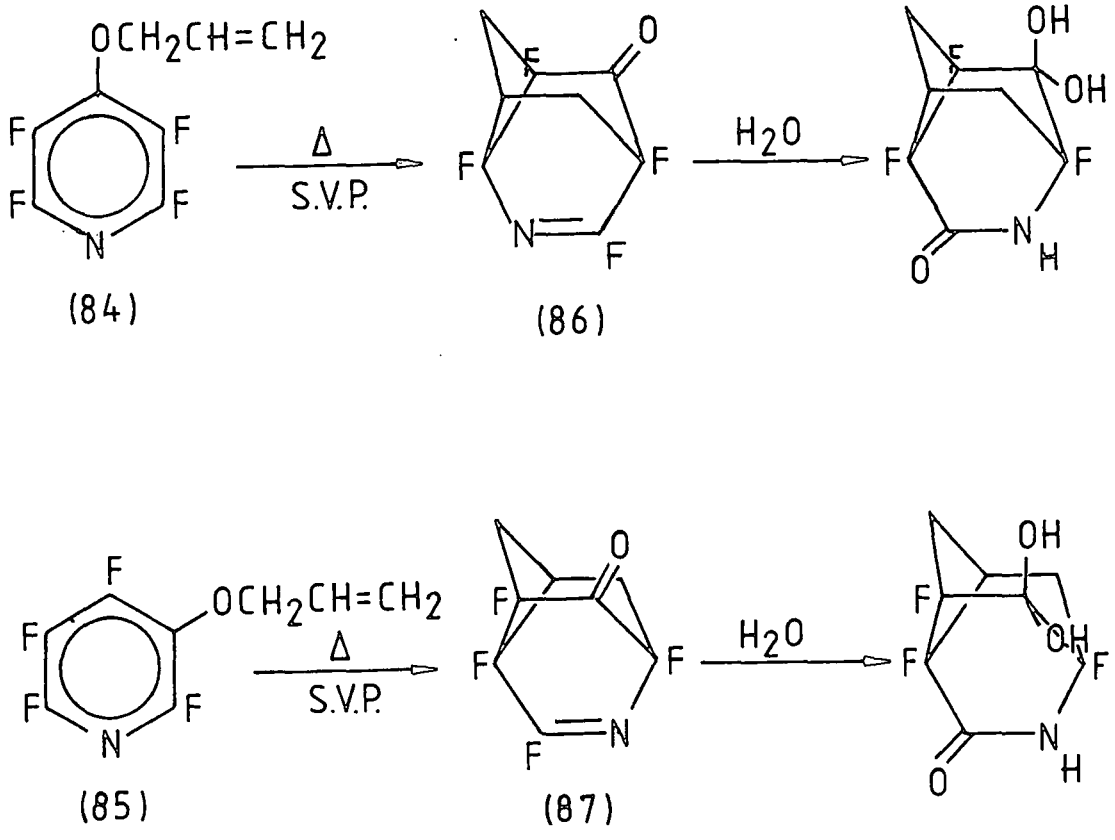
Under milder conditions (137-141°C for 13 days),[37] static vapour phase pyrolysis of the ether (77) gave the hydrated tricyclic compound (83), the formation of which was explained in terms of an overall [1,3] rearrangement of the internal Diels-Alder intermediate (81) (also shown to be present in the product mixture[36e]) by a stepwise process followed by hydration, Scheme 34.



Scheme 34

Work with allyl tetrafluoropyridyl ethers has also given Diels-Alder products and hydrated derivatives of them.[38] Vapour-phase thermolysis of the ethers (84) and (85) both gave internal Diels-Alder products (86) and (87) respectively, but none resulting from the [1,3] rearrangement. These pro-

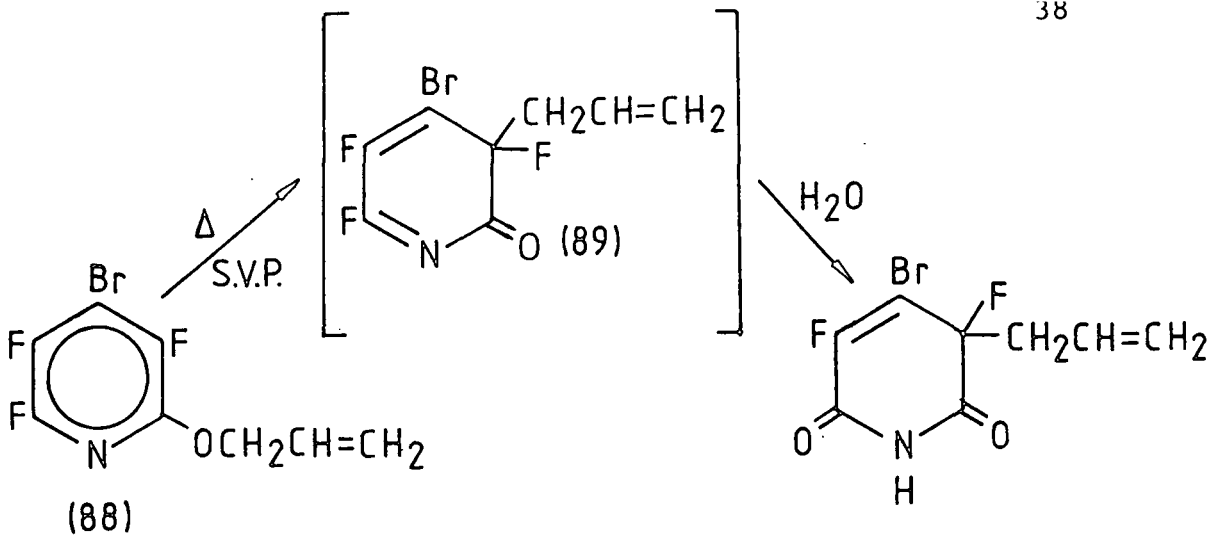
ducts were readily hydrolysed and then converted into their gem-diols with water, Scheme 35.



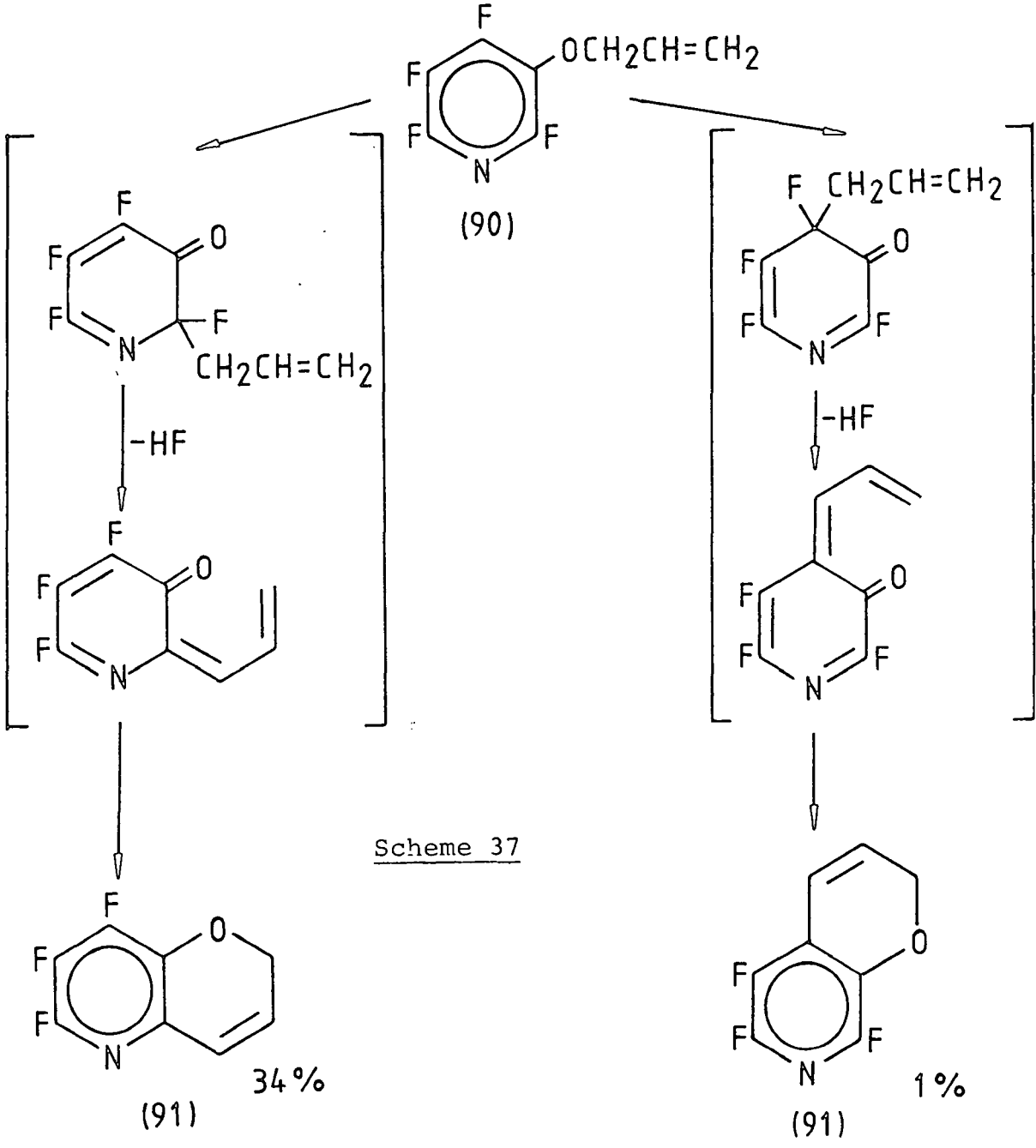
Scheme 35

Interestingly, thermolysis of allyl 4-bromo-2,3,5-trifluoropyridin-6-yl ether (88) gave a product resulting from hydrolysis of the intermediate dienone (89), with no indication of the Diels-Alder adduct, Scheme 36.

Another, more recent report[39] describes the preparation of 2H-pyran derivatives formed by dehydrofluorination of the Claisen rearrangement intermediates produced by the thermolysis of polyfluoroaryl and heteroaryl allyl ethers. Thus, thermolysis of allyl 2,4,5,6-tetrafluoropyridin-3-yl ether (90) in sulpholane with potassium fluoride gave the 2H-pyranopyridines (91) and (92), Scheme 37.



Scheme 36



Scheme 37

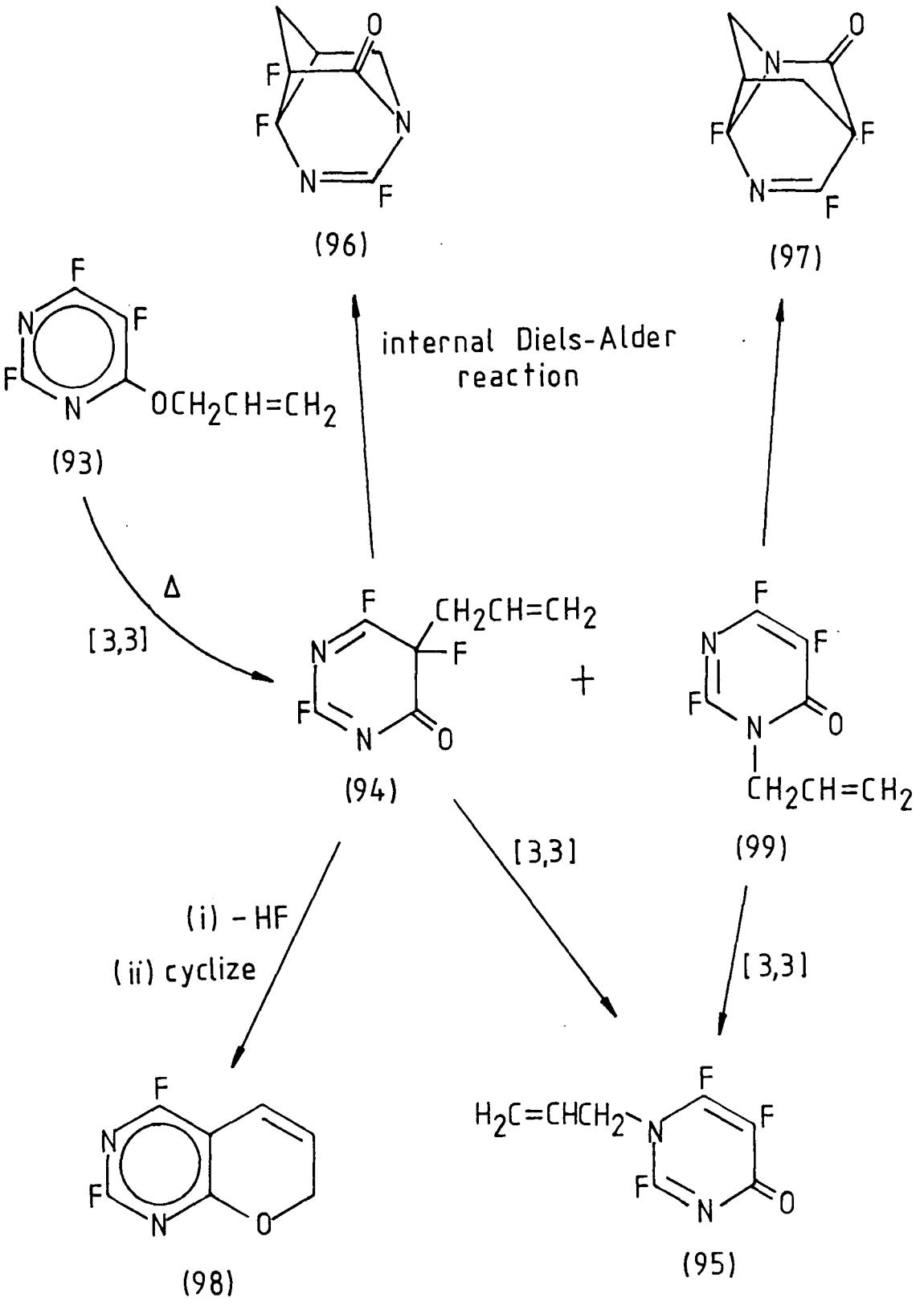
In the chapters that follow (Chapters 2-4), the further generality of the Claisen rearrangement in fluorinated allyl pyrimidyl ethers is demonstrated. Particular attention is paid to the preparations and thermal rearrangements of allyl 2,5,6-trifluoropyrimidin-4-yl ether as well as a number of its substituted derivatives, and the results from this study discussed.

CHAPTER TWO

THE PREPARATION AND THERMOLYSIS OF ALLYL 2,5,6-TRIFLUORO-(93) AND 2,5-DIFLUOROPYRIMIDIN-4-YL (111) ETHERS. FORMATION OF 5-FLUOROURACIL DERIVATIVES

2.1 Introduction

In contrast to the allyl 2-substituted pyrimidin-4-yl ethers (53) studied by Tieckelman and co-workers,[28] in allyl 2,5,6-trifluoropyrimidin-4-yl ether (93), conceivably the most accessible trifluoro ether, all available positions on the aromatic moiety are substituted by fluorine atoms, and are thus effectively blocked. It might be expected therefore, by comparison with Tieckelman's work, and by analogy with the work on other fluorinated aromatic systems[36-39] that thermolysis of the ether (93) could give a variety of products derived from an initial migration of the allyl group to either the ortho-carbon or ortho-nitrogen. Rearrangement of the allyl group to the ortho-carbon would yield the 2,4-dienone (94). This could undergo a further Cope rearrangement to the 2,5-dienone (95), as observed in the thermolysis of allyl pentafluorophenyl ether (Scheme 33),[36a] or from the internal Diels-Alder adduct (96), although the diene component of (94) possesses a 'terminal' nitrogen atom, and in the only case studied where a similar diene component arose [a 1-aza-1,3-diene unit ((89), Scheme 36)], the system proved to be inert to internal Diels-Alder adduct formation.[38] In the presence of potassium fluoride,[39] dehydrofluorination of (94) would be expected to give the 2*H*-pyran derivative (98). Rearrangement of the allyl group to the ortho-nitrogen would yield the 2,4-dienone (99) which could give the 2,5-dienone (95) or the internal Diels-Alder adduct (97). These possibilities are illustrated in Scheme 38.



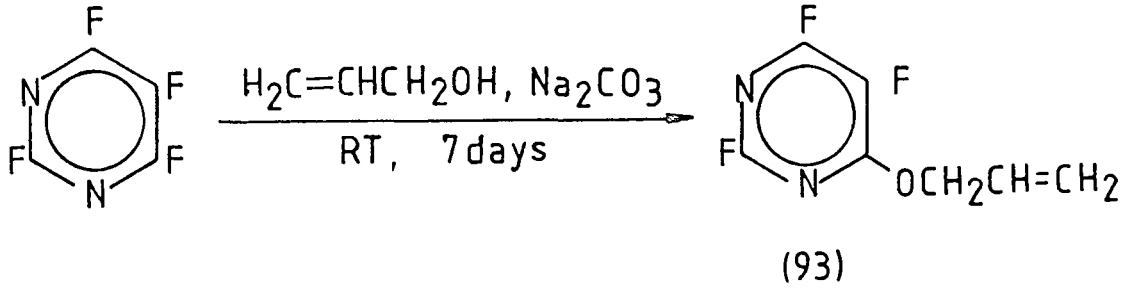
Scheme 38

The preparation of (93) and its thermolysis reactions are described in the following section.

2.2 The Preparation and Thermolysis of Allyl 2,5,6-Trifluoropyrimidin-4-yl Ether (93)

2.2.1 Preparation of the Ether (93)

The ether (93) was prepared in 61% yield by reacting tetrafluoropyrimidine [40] with an excess of allyl alcohol and sodium carbonate at room temperature for 7 days, Scheme 39. The reaction proved to be less facile than expected by comparison with the similar method employed by Banks[40] for the preparation of 4-methoxy-2,5,6-trifluoropyrimidine which required only 30 mins. for 52% conversion. Reactions carried out at reflux temperature without the presence of sodium carbonate shortened the reaction time, but increased the level of minor components present in the reaction mixture. 4-Hydroxy-2,5,6-trifluoropyrimidine was usually recovered from the residues after distillation of the ether (93) and arose due to the presence of water in the reacting system.[40]



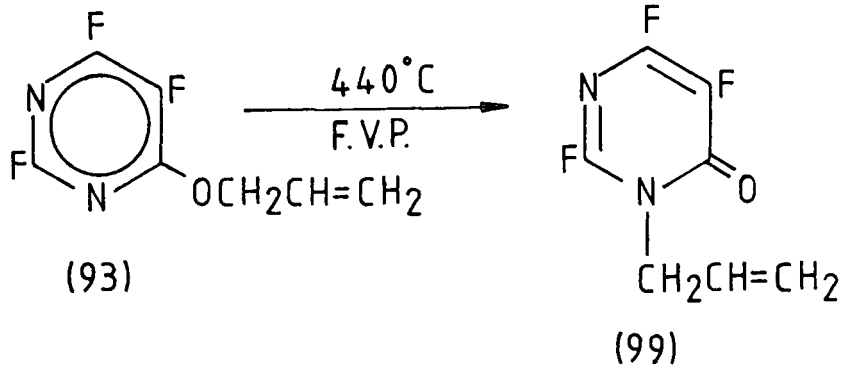
(93)

Scheme 39

2.2.2 Thermolysis of the Ether (93)

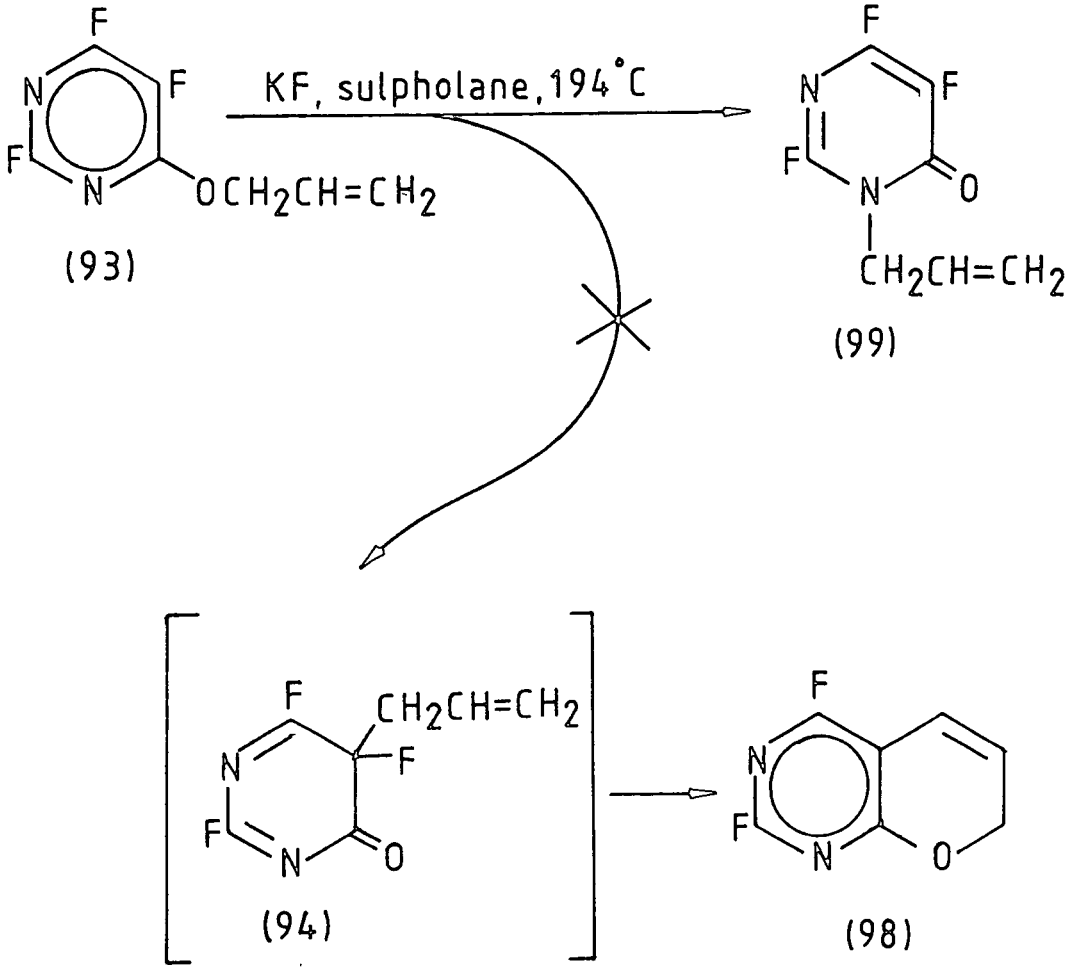
Static vapour phase pyrolysis (S.V.P.) of the ether (93) was attempted using a variety of temperatures (150-220°C) and reaction times (9-158 hours), and in each case the reaction resulted only in the formation of an unidentifiable polymeric material and unreacted starting material (80%). This surprising inertness under these conditions is in direct contrast to the related tetrafluoropyridyl compounds.[38]

A different result was obtained when the ether (93) was distilled under reduced pressure through a quartz tube packed with silica wool at 440°C [flash vapour phase pyrolysis (F.V.P.)]. In this case, thermolysis gave, along with unchanged (93) (12%), the Claisen rearrangement product 3-allyl-2,5,6-trifluoropyrimidin-4(3H)-one (99) (53%) in which the allyl group had migrated exclusively to the ortho-nitrogen, Scheme 40. No products resulting from migration of the allyl group to the ortho-carbon were observed.



Scheme 40

Liquid phase thermolysis of the ether (93) in sulpholane with KF at 194°C was attempted in order to ascertain whether the C-allyl compound (94) could indeed be a thermolysis product of the ether (93), for under these conditions any of compound (94) formed might be expected to undergo dehydrofluorination then cyclization to give the 2H-pyran derivative (98).[39] However, the only product isolated from the polymeric tar produced in the reaction was again the N-allyl compound (99) (22%), Scheme 41.



Scheme 41

2.2.3 Determination of the Structure of the Claisen Rearrangement Product

Although ^{1}H nmr spectroscopy of the product isolated from thermolysis of the ether (93) indicated that the compound

was an N-allyl derivative (an upfield shift of the $-CH_2-$ protons in the allyl moiety in going from $-OCH_2-$ to $-N-CH_2-$) it was not possible to ascertain which of the two possible isomeric N-allyl compounds, the 2,4-dienone (99) or the 2,5-dienone (95), resulting from a further Cope rearrangement of (99) or (94), had been formed.

Previously, Tieckelman[28] had encountered a similar problem with the N-allyl derivatives formed from rearrangement of the 2-substituted pyrimidyl ethers (53). The structural assignments of the rearrangement products here were made by comparison of their ultra-violet and infra-red spectra with those of model compounds which could be prepared with known configuration. These results are summarised in Table 3.

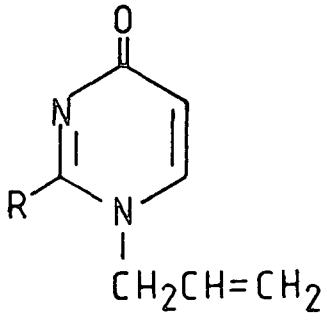
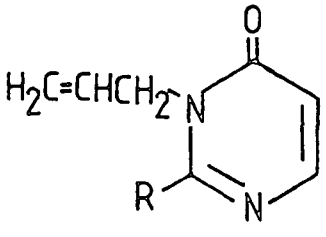
	U.V. Data		I.R. Data
	λ_{max} (nm)	ε_{max}	$\nu_{C=O}$ (cm^{-1})
	∿236	∿23,000	∿1640
	∿274-294	∿6,000-10,300	∿ 1680

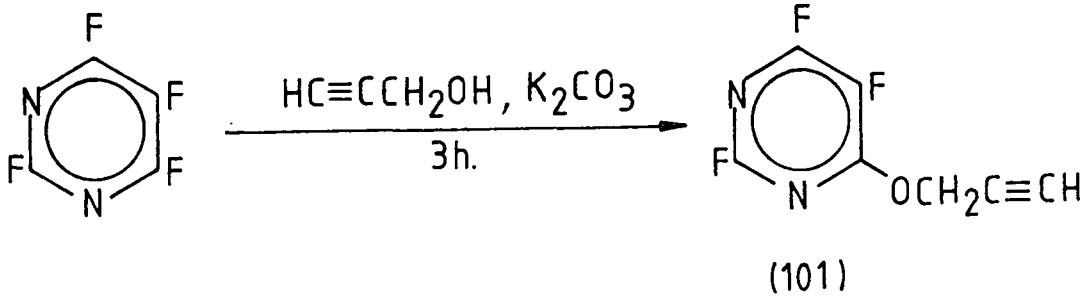
TABLE 3

The comparison of these data with those of the N-allyl product from thermolysis of (93) did not prove to be entirely conclusive since the ultra-violet spectrum showed absorbances at 221nm (ε 4400) and 265nm (ε 3500), and the assignment of $\nu_{C=O}$ could not be made with certainty. Direct physical methods for structural identification thus seemed inappropriate.

It is a characteristic of the Claisen rearrangement that the [3,3] sigmatropic shift occurs with inversion of the allyl group. The ortho-rearrangement product thus has the allyl group inverted compared with the starting ether, whereas the para-rearrangement product has the allyl group in the same configuration. Using a suitably labelled ether, therefore, it should be easy to determine whether an ortho-or para-migration of the allyl group has occurred. For the purposes of this study, the deuterium-labelled allyl ether (100) was synthesised and the nature of its rearrangement investigated.

(a) Preparation of [2,3-$^2H_2$]Allyl 2,5,6-Trifluoropyrimidin-4-yl Ether (100)

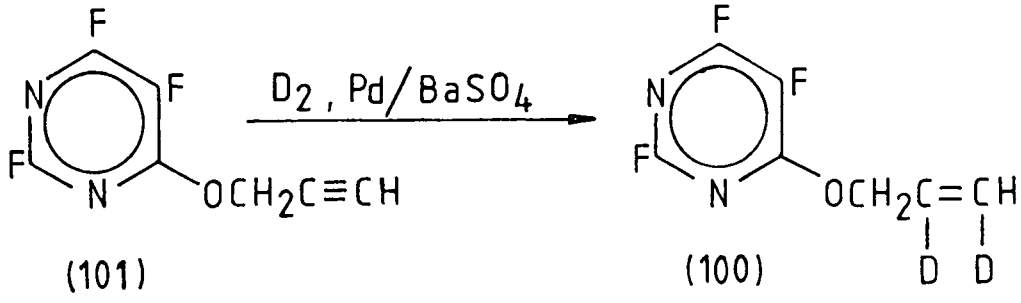
Tetrafluoropyrimidine, an excess of propargyl alcohol and potassium carbonate reacted exothermically to give the propargyl ether (101) (60%), Scheme 42.



(101)

Scheme 42

Reduction of the propargyl ether (101) with 1 mole equivalent of deuterium at atmospheric pressure using $Pd/BaSO_4$ as the catalyst gave the deuterium-labelled allyl ether (100) (62%), Scheme 43.



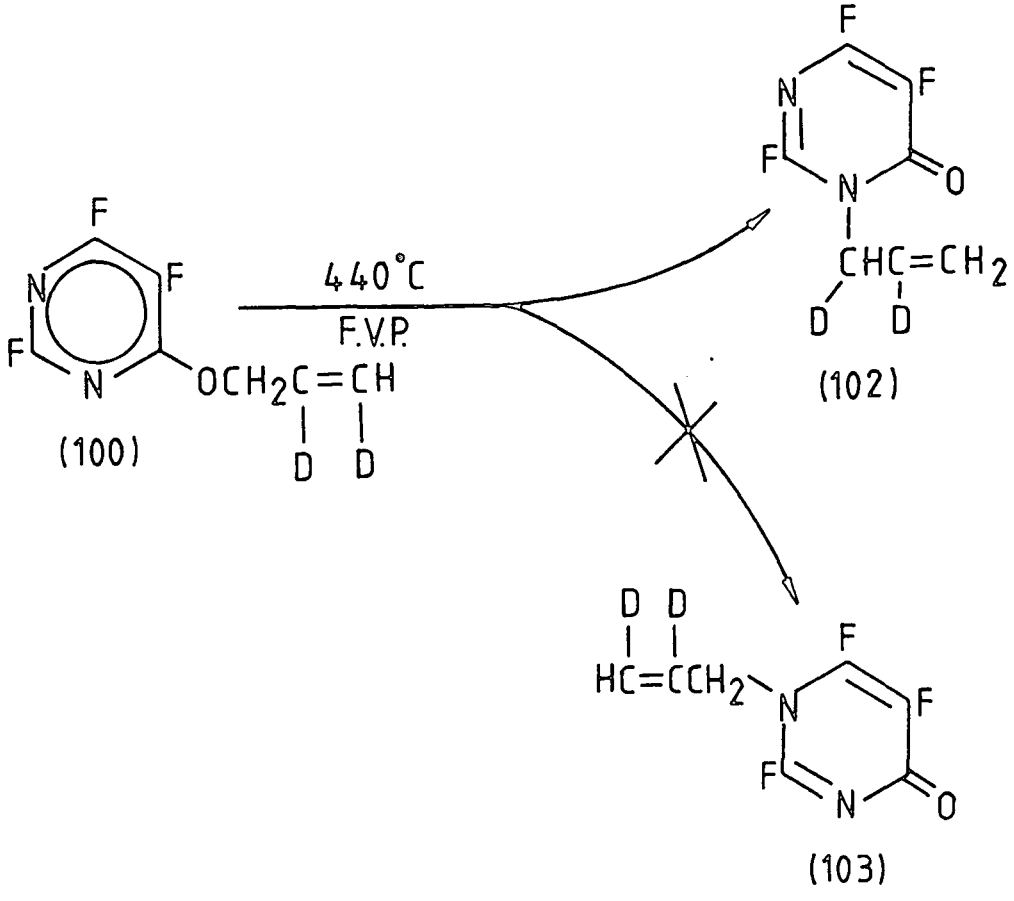
(101) (100)

Scheme 43

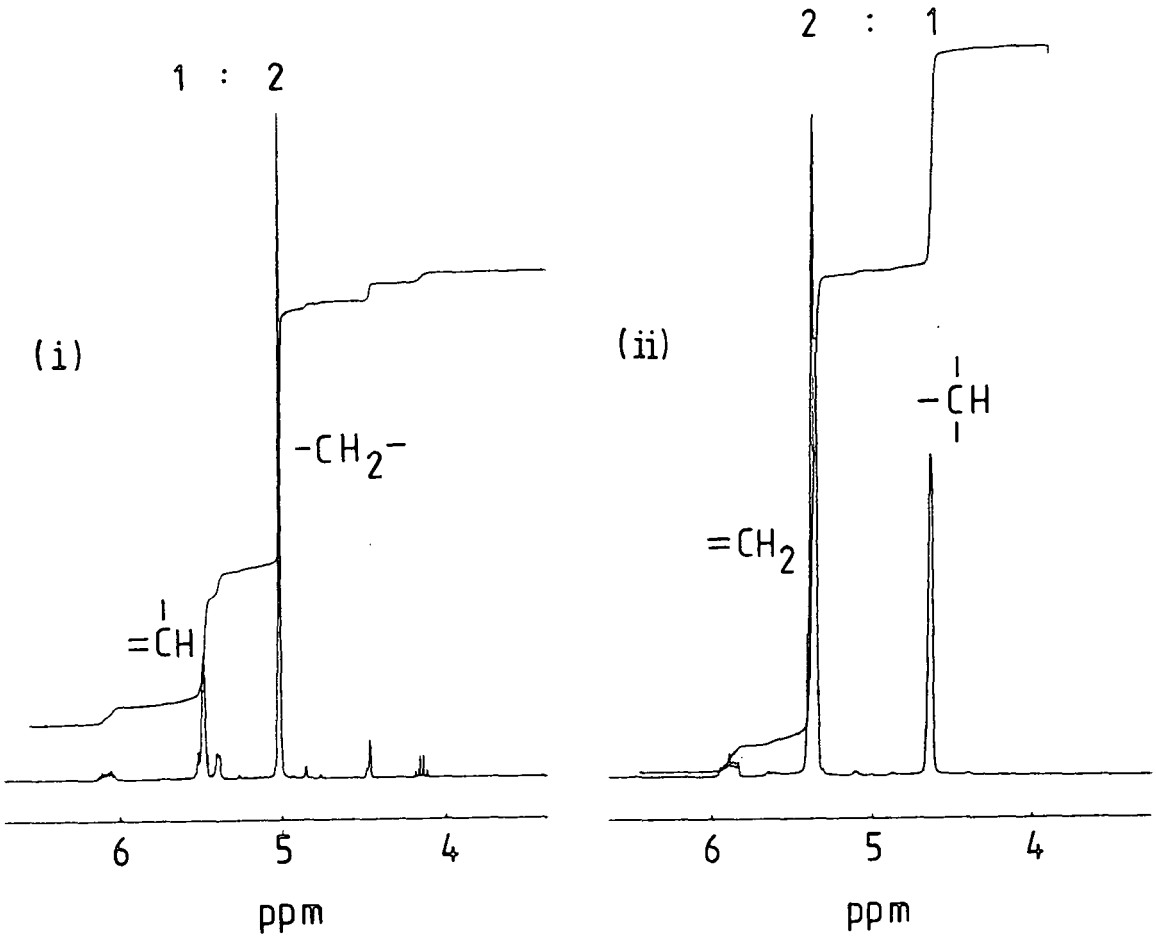
(b) Thermolysis of [2,3-$^2H_2$]Allyl 2,5,6-Trifluoropyrimidin-4-yl Ether (100)

The ether (100) was pyrolysed under identical F.V.P. conditions as that employed for the ether (93). Examination

of the product (45%) by ^{1}H n.m.r. spectroscopy indicated that the integrated intensities of the alkyl to vinyl protons, Diagram 1, had changed from 2:1 in the ether (100) to 1:2 in its thermolysis product, and thus rearrangement had occurred with inversion of the allyl group. The product was thus the N-allyl compound (102) and not the alternative isomer (103), Scheme 44.



Scheme 44



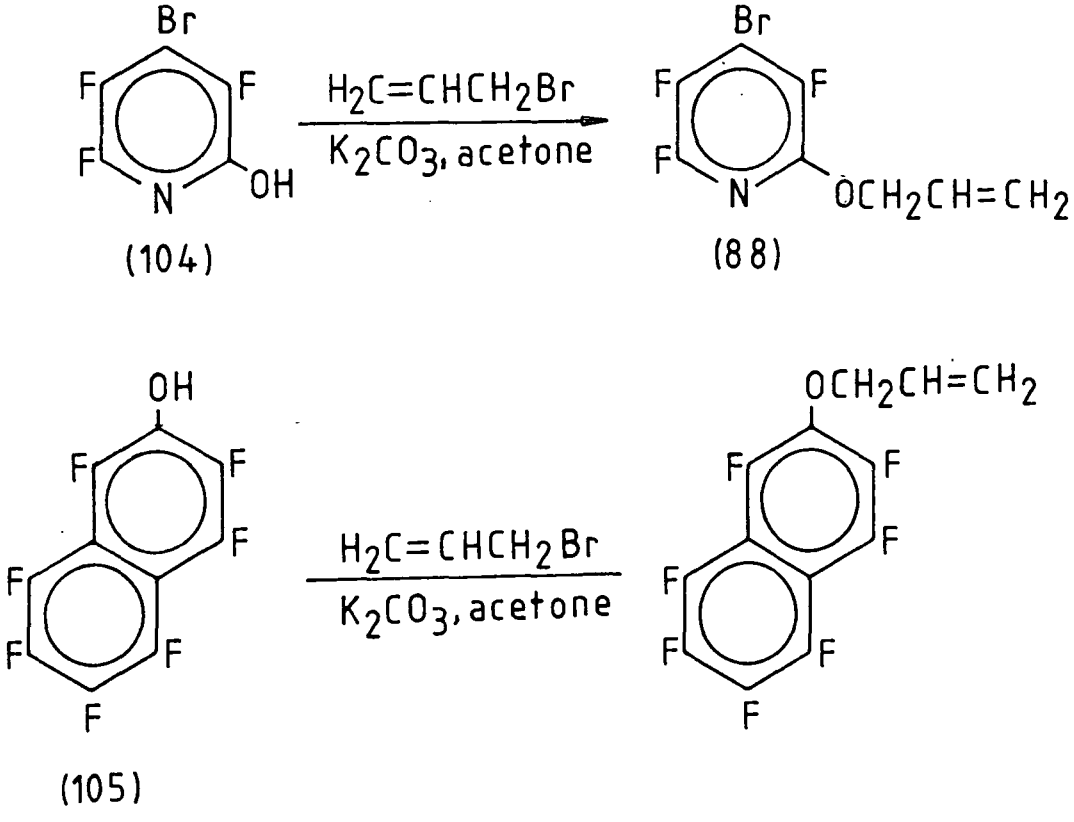
^{1}H n.m.r. spectra of (i) The ether (100) and (ii) The product from F.V.P. thermolysis of (100)

Diagram 1

Having established the structure of (102) it followed that the product from the thermolysis of (93) was the Claisen rearrangement material (99). The ultra-violet spectrum of (99) has served as a model for further structural assignments of related fluorine-containing 2,4-dienone-type heterocycles described in this Thesis.

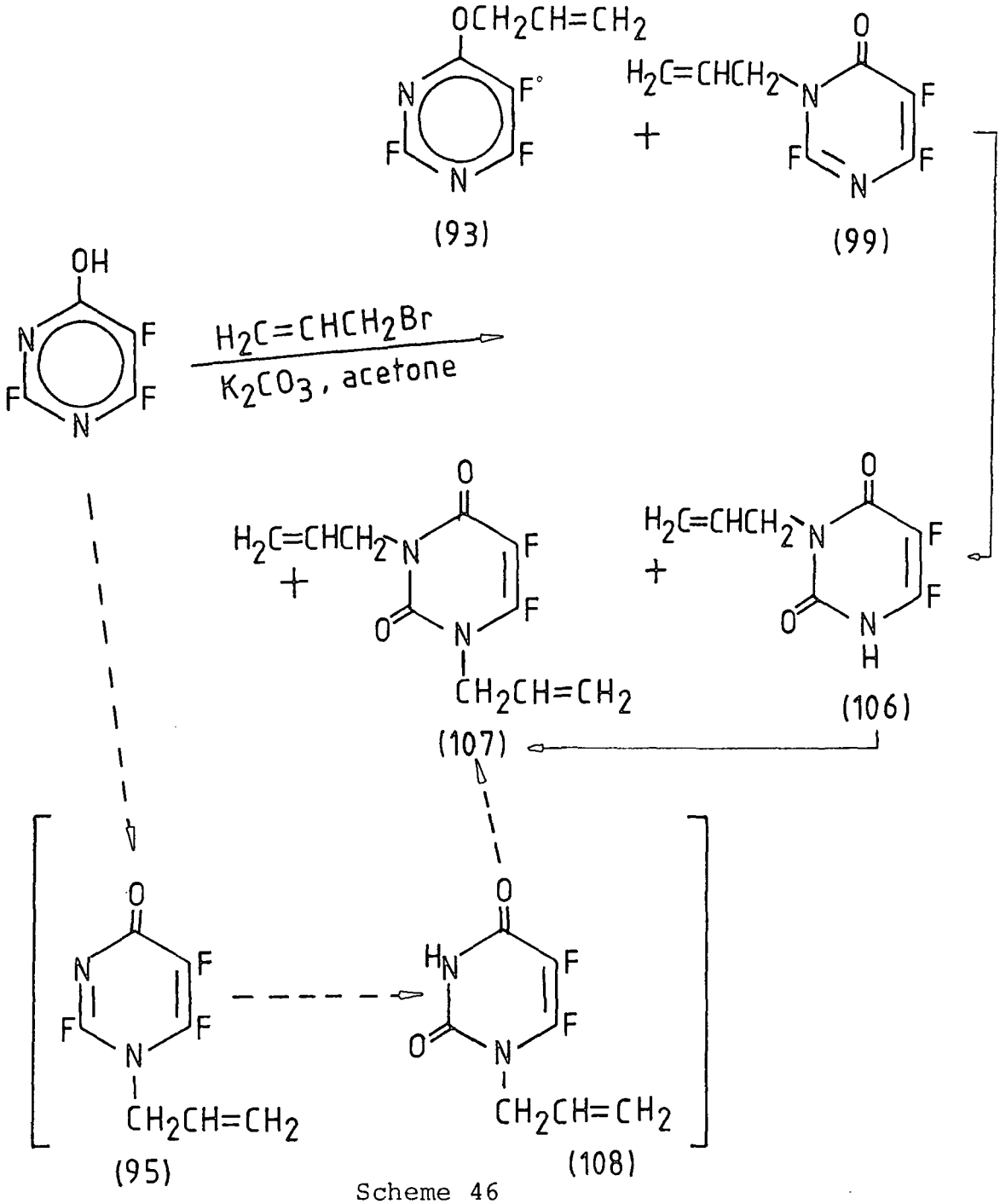
2.2.4 Alternative Preparations of the Ether (93)

The Williamson synthesis[42] is by far the most common method for the formation of ethers and has been extensively used in the preparation of aromatic allyl ethers. Thus, the hydroxy compounds (104) and (105) are readily converted into their corresponding allyl ethers by reaction with allyl bromide in the presence of base,[38,41] Scheme 45.



Scheme 45

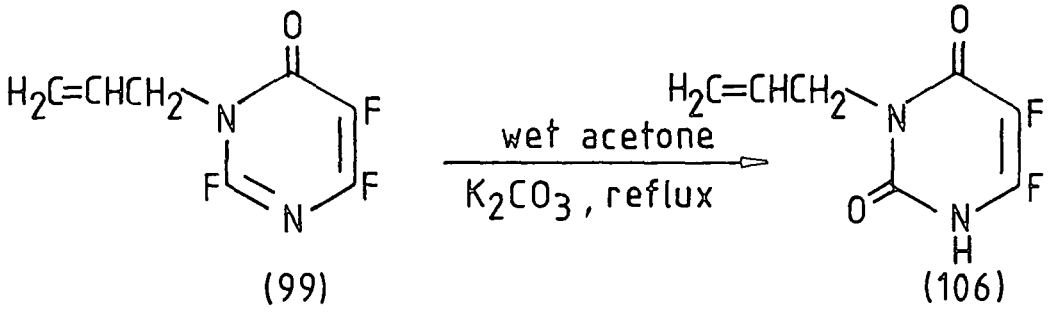
The reaction of 4-hydroxy-2,5,6-trifluoropyrimidine[40] with allyl bromide and potassium carbonate in acetone gave the allyl ether (93) (48%), but was also accompanied by the N-allyl compound (99) (1%), compound (106) (7%) and the di-N-allyl compound (107) (4%), Scheme 46.



Scheme 46

Clearly O-allylation in this case competes with N-allylation, since the mild reaction conditions preclude the Claisen rearrangement of (93) to (99). Once formed, the N-allyl compound (99) undergoes hydrolysis to the compound (106) which is then itself further allylated to give (107). None of the 2,5-dienone (95) or its hydrolysed derivative (108) were observed in the reaction, although these may have been converted through to the di-N-allyl compound (107).

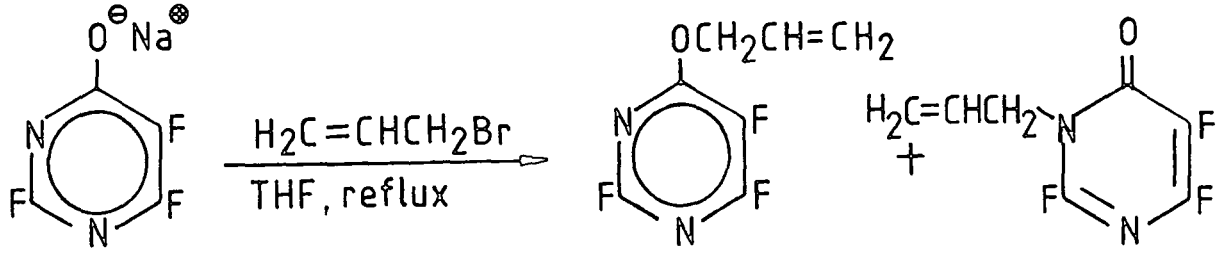
The hydrolysis of the N-allyl compound (99) to (106) was confirmed in a separate experiment by reacting (99) with wet acetone and potassium carbonate at reflux, Scheme 47.



(99) (106)

Scheme 47

In another experiment, under anhydrous conditions in tetrahydrofuran, the preformed sodium salt of the 4-hydroxy-pyrimidine and allyl bromide were reacted at reflux for 3 days. The reaction, which proved to be a very inefficient process, again resulted in a competition between O- and N-allylation, the ether (93) (4%) and the N-allyl compound (99) (12%) being the only products formed, Scheme 48.



(93) (99)

Scheme 48

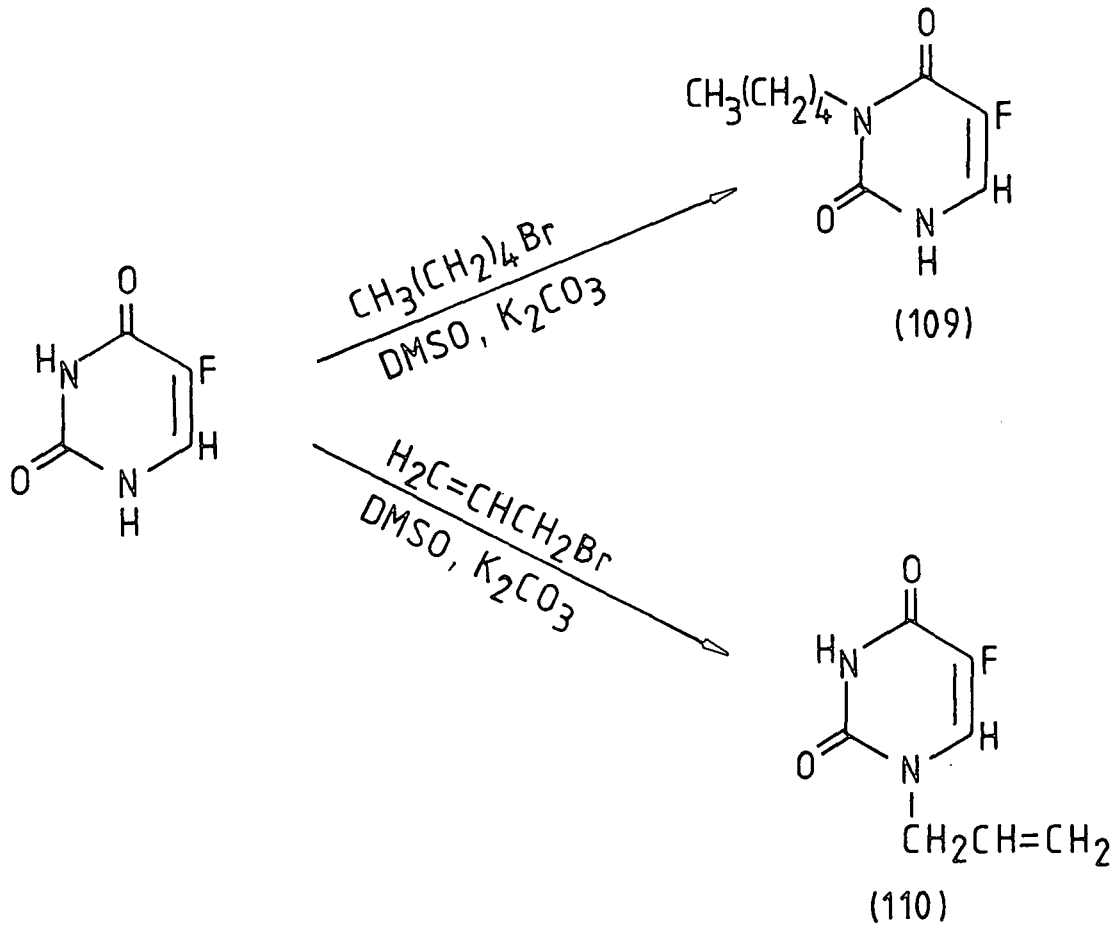
The competition between O- and N-allylation is a common feature in the synthetic approach to allyl ethers in nitrogen heterocyclic systems[26] when using this type of procedure since the heteroaromatic system is capable of acting as an ambident anion. The alternative method using the appropriate haloderivative with allyl alcohol and a base, or the salt of allyl alcohol in allyl alcohol (see Section 2.2.1) provides a far superior route since only an ether can be produced.

2.3 The Preparation and Thermolysis of Allyl 2,5-Difluoropyrimidin-4-yl Ether (111). Formation of a 5-Fluorouracil Derivative

5-Fluorouracil and its derivatives are important drugs in the treatment of specific cancerous diseases,[43] and their synthesis and activity has become a topic of significant interest in recent years.[44]

Normally, alkylation of 5-fluorouracil with unreactive halides, such as 1-bromopentane in dimethyl sulphoxide in the presence of base results in alkylation at the N-3 position, (109), whereas alkylation with the more reactive allylic halides, such as allyl bromide, results only in alkylation at N-1, (110), Scheme 49.[45]

The formation of the compound (106) by hydrolysis of the fluorine at C-2 in (99) is of particular interest since it is a derivative of 5-fluorouracil (the 6-position is substituted with a fluorine atom), but more importantly it has an allyl group at N-3. The specific nature of the Claisen



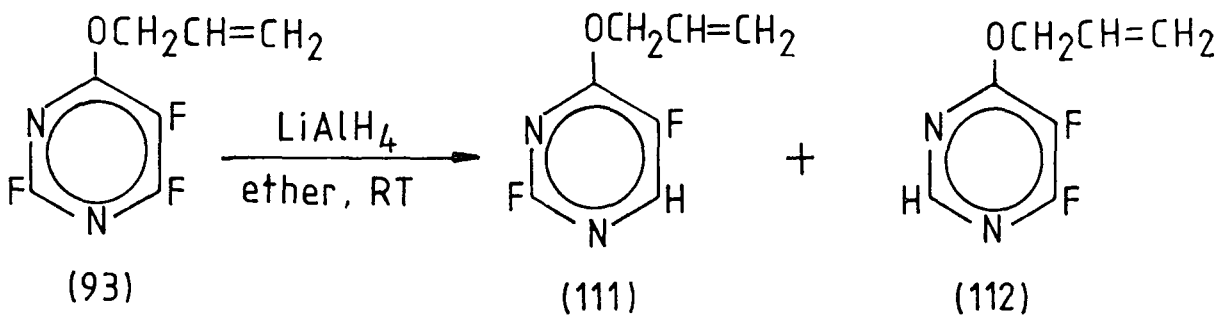
Scheme 49

rearrangement in an ether like (93) and the apparent ease of hydrolysis of the fluorine at C-2 in the product would thus seem to offer a new and valuable route to 5-fluorouracil derivatives in which N-3 is substituted with an allyl group. The synthesis of the N-3 substituted isomer of (110), using this route was thus attempted.

2.3.1 Preparation of the Ether (111)

Reaction of the ether (93) with 1 molar equivalent of lithium aluminium hydride in ether resulted in the formation of a product (96%) which was shown by ^{19}F n.m.r. spectroscopy to be a mixture of the two isomeric mono-hydro substituted ethers (111) and (112) in the ratio 75:25 respectively,

(Scheme 50), a substitution pattern which will be discussed in Chapter Three. These isomers could not be separated, but repeated chromatography on silica gave an enriched mixture of (111) with (112) in the ratio 91:9.

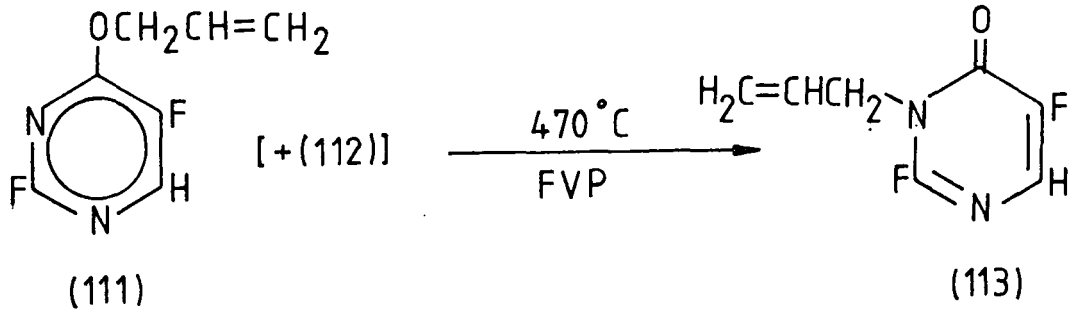


(93) (111) (112)

Scheme 50

2.3.2 Thermolysis of the Ether (111)

Pyrolysis of the enriched mixture of the ethers (111) and (112) under F.V.P. conditions at 470°C gave a product consisting of two components in the ratio 94:6. Only the major component could be isolated from the mixture, and was found to be the N-allyl compound (113) (69%), Scheme 51. Confirmation of structure of (113) was given by its ultraviolet spectrum which was very similar to that of the model 2,4-dienone, (99).



(111) (113)

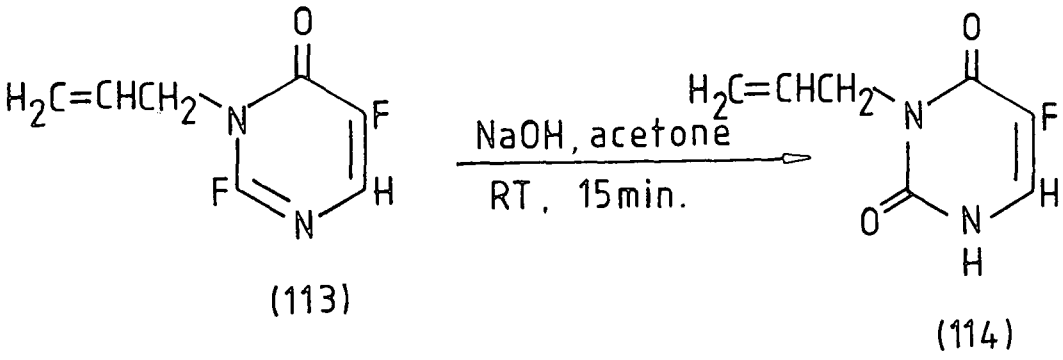
Scheme 51

2.3.3 Hydrolysis of the Claisen Rearrangement Product (113)

Hydrolysis of the N-allyl compound (113) under the same conditions as that employed for the hydrolysis of (99) (wet acetone and potassium carbonate at reflux for 18h), resulted only in the recovery of unreacted starting material (92%).

The reaction of (113) with a solution of sodium hydroxide (2M) in acetone at room temperature proved to be a remarkably facile process. Reaction under these conditions for only 15 minutes gave a product shown by ^{19}F n.m.r. spectroscopy to consist of three components in the ratio 70:15:15. The major component was isolated with difficulty to give the 5-fluorouracil derivative (114) (41%), Scheme 52.

Reaction of (113) with sodium hydroxide for longer periods gave only a complex product, presumably due to further hydrolysis of (114), although nothing could be isolated.



(113) (114)

Scheme 52

The successful isolation of (114) suggests that the above procedure is a viable synthetic pathway to the previously inaccessible N-3-allyl substituted isomers of 5-fluorouracil. Nucleophilic substitution of the 6-fluorine in the ether (93) by substituents other than hydrogen would enable a wide variety of these derivatives to be synthesised, and indeed, a number of such compounds will be encountered in later chapters.

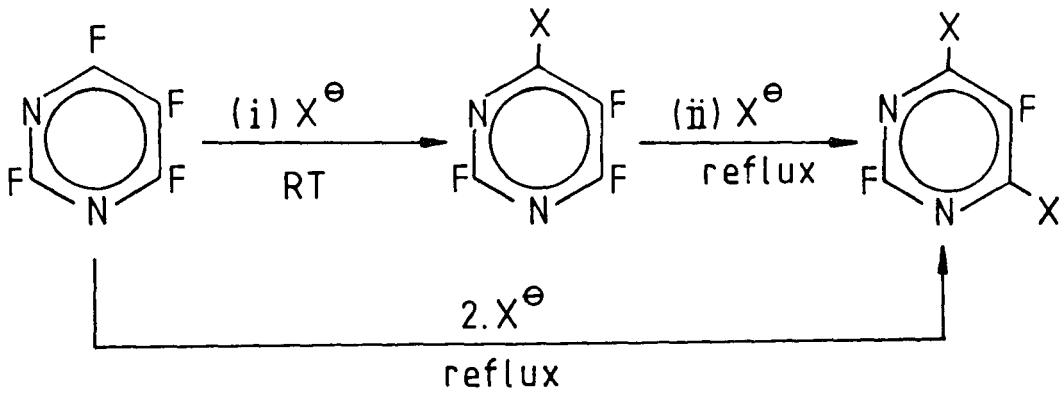
CHAPTER THREE

THE PREPARATION OF SUBSTITUTED DERIVATIVES OF ALLYL 2,5,6-TRIFLUOROPYRIMIDIN-4-YL ETHER(93). NUCLEOPHILIC SUBSTITUTION IN FLUORINATED PYRIMIDINES

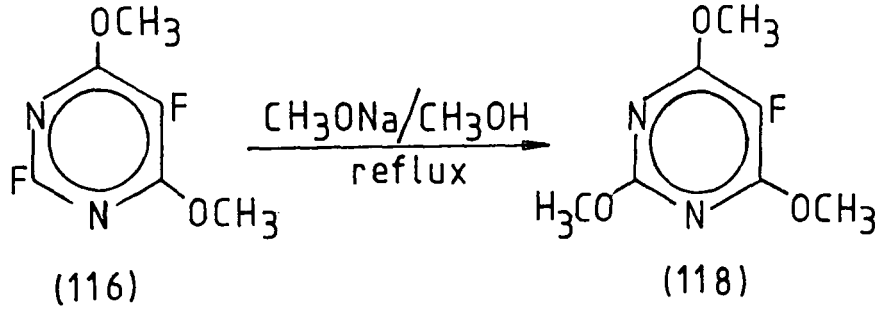
3.1 Introduction

In an early study on nucleophilic substitution in heterocyclic polyfluoro compounds,[40,46] Banks, Haszeldine and co-workers examined the orientation of substitution in tetrafluoropyrimidine.[40] Through the use of a number of nucleophilic reagents they concluded that the ease of displacement of the ring fluorines decreased in the order 4- and 6- > 2- $\gg$ 5-. Thus, the fluorine at the 4-position readily suffered displacement under mild conditions [as already seen in the preparation of the ether (93)], whilst under more drastic conditions further displacement of the fluorine from the 6-position occurred. Substitution of the fluorine from the 2-position to give a trisubstituted compound only occurred when the nucleophile was methoxide. No substitution of the fluorine in the 5-position was observed under any conditions, Scheme 53.

The formation of a significant proportion of a 2-hydro isomer (112) along with the expected 6-hydro compound (111) in the reaction of the ether (93) with lithium aluminium hydride was thus an unexpected result, and this prompted a reinvestigation into the pattern of substitution for the introduction of a second substituent in a 4-substituted trifluoropyrimidine compound. For this purpose, the reaction of 4-methoxy-2,5,6-trifluoropyrimidine (115) with methoxide was studied.



X = $-NHCH_3$, $-N(CH_3)_2$, $-NH_2$, $-OCH_3$, -OH [only for (i)]

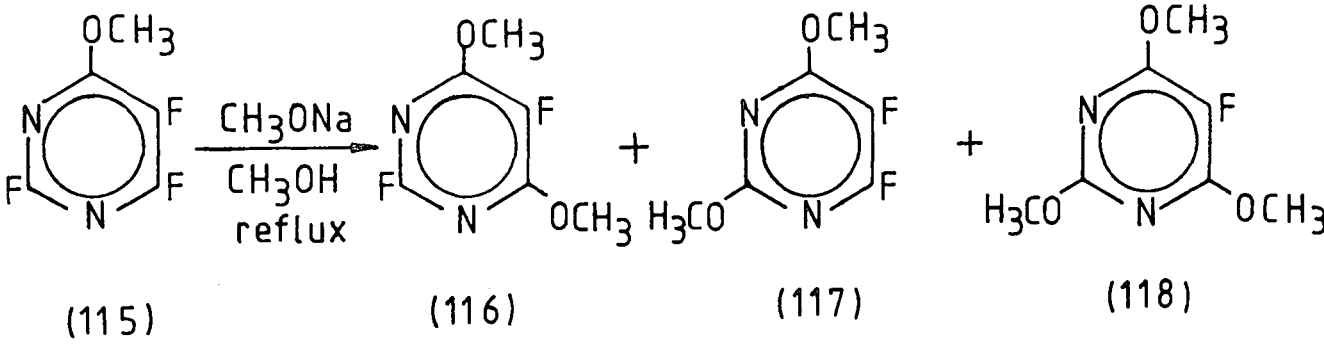


(116) (118)

Scheme 53

3.2 Orientation of Nucleophilic Substitution in 4-Methoxy-2,5,6-Trifluoropyrimidine (115)

The 4-methoxy compound (115) was prepared by the method outlined by Banks and Haszeldine,[40] by reacting tetrafluoropyrimidine with methanol and sodium carbonate at room temperature. Reaction of (115) with sodium methoxide in methanol, under identical conditions as those employed in the original paper,[40] resulted in a product shown by ^{19}F n.m.r. spectroscopy to consist of not one, but three components in the ratio 13:4:1. These were separated to give the 4,6-dimethoxy compound (116) (70%), the 2,4-dimethoxy compound (117) (13%) and the trimethoxy compound (118) (3%) respectively, Scheme 54.



(115) (116) (117) (118)

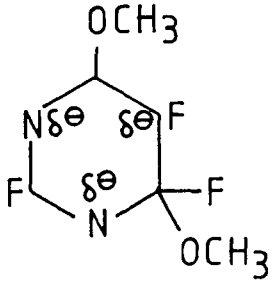
Scheme 54

Clearly then 6-substitution only dominates over 2-substitution (by a factor of ~3:1 both in this case and in the reaction of (93) with $LiAlH_4$), and is not exclusively substituted before reaction at the 2-position.

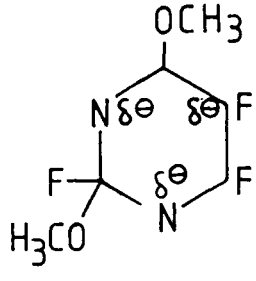
The substitution pattern had previously been rationalized by consideration of the stabilities of the various Wheland-type intermediates in terms of the I_π-repulsive effects of the fluorine atoms, and this would make a rationale for the formation of (117) difficult when the 6-position is 'vacant'. More recently, however, a method for rationalizing the orientation of nucleophilic substitution in polyfluoroaromatic and heteroaromatic compounds has been formulated which considers the influencing effects of the fluorine atoms and the ring heteroatoms (nitrogen in this case), and this is well able to account for the formation of (117).[47] It has been found that fluorine atoms are strongly activating towards nucleophilic attack if they are ortho- and meta- with respect to the position attacked, whereas they are slightly deactivating if they are para-. The meta-influence is the more dominant effect in polyfluoroaromatic compounds whereas in heteroarom-

atic derivatives it is the ortho-influence that predominates. It has also been shown [47b] that the activating influence of ring nitrogen atoms in polyfluoropyridine and -pyrimidines is much larger than fluorine and strongly activates the system at points ortho- and para- to the point of substitution, with the para- influence dominating by a factor of 3.7:1. The meta- influence, although still having a substantial activating effect (8.5 x 10^2:1 relative to hydrogen), is much less marked compared to the other positions (1:266 relative to a nitrogen in the para- position).

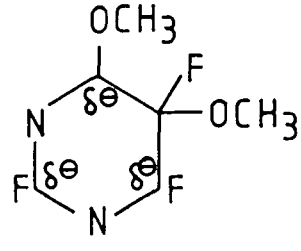
Considering the possible transition states then for attack by methoxide at the 6-, 2- and 5- positions in (115) [(119), (120) and (121) respectively], it can be seen that both (119) and (120) are strongly stabilized and would be expected to form, with (119) dominating due to the influence of para-nitrogen.



(119)



(120)



(121)

Transition state (121), on the other hand is only very slightly stabilized compared with (119) or (120) and would be unlikely to result in the formation of any products.

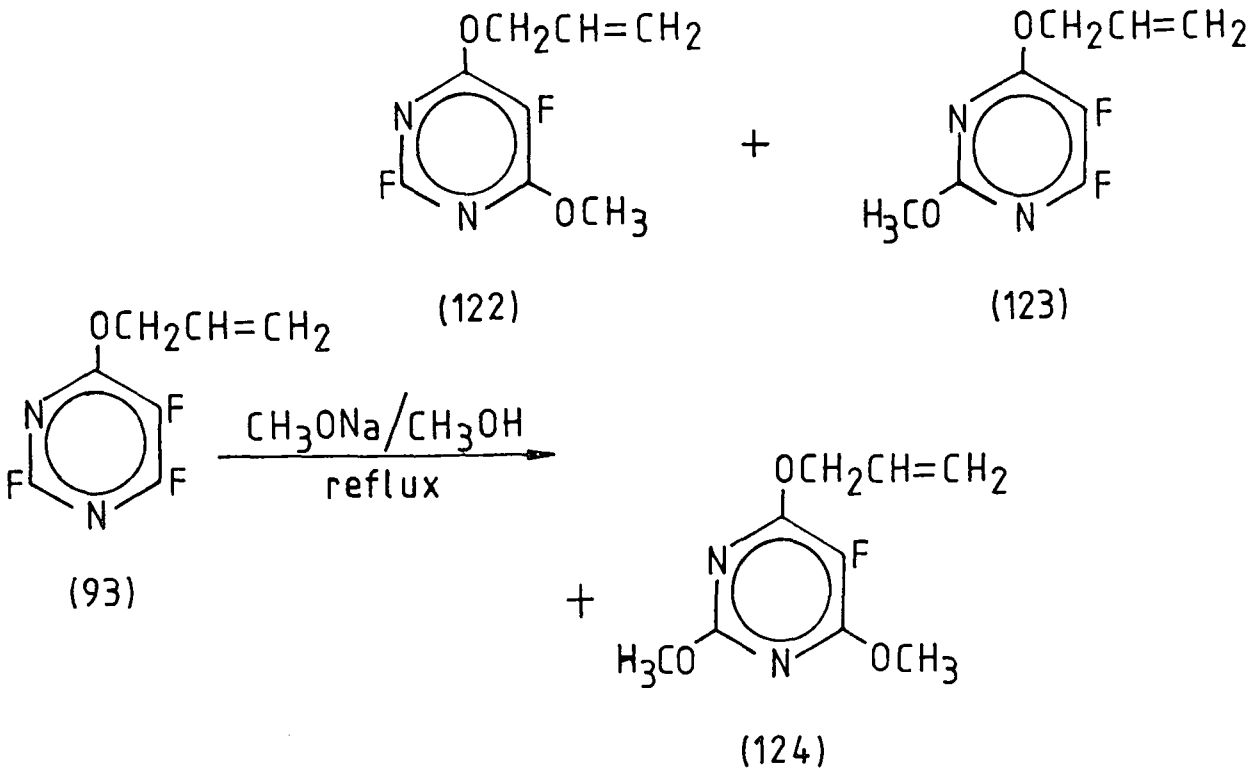
The formation of 2-substituted derivatives from the reaction of the allyl ether (93) with various nucleophilic reagents should therefore not be unexpected. Indeed, their formation, along with the respective 6-substituted isomer, provide some interesting compounds which can be used to investigate the mode of thermal rearrangement in various substituted derivatives of (93).

The following sections outline attempts at the preparation of a number of such derivatives.

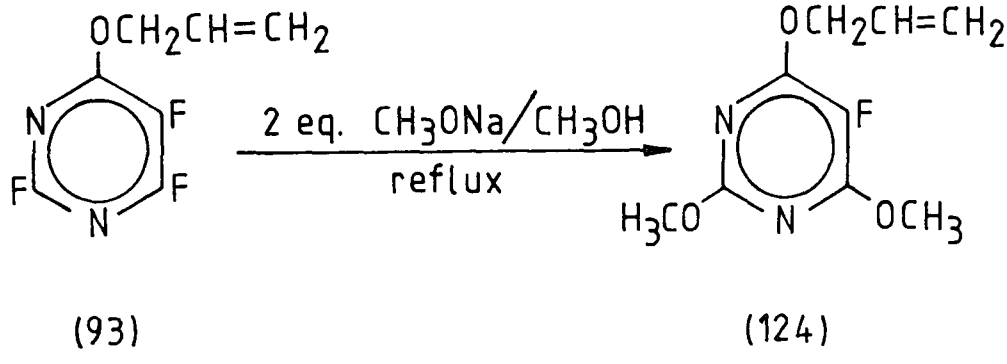
3.3 Preparation of Mono- and Dimethoxy Derivatives of the Ether (93)

Reaction of (93) with 1 molar equivalent of sodium methoxide in methanol under reflux resulted in a similar product distribution as that observed for the reaction of (115) with methoxide, ^{19}F n.m.r. spectroscopy indicating three components in the ratio 74:12:14. These were separated to give the 6- and 2-methoxy derivatives (122) (66%) and (123) (10%) and the dimethoxy compound (124) (14%), Scheme 55.

The dimethoxy compound (124) was also prepared in high yield (96%) from the reaction of (93) with 2 molar equivalents of sodium methoxide in methanol, Scheme 56.



Scheme 55

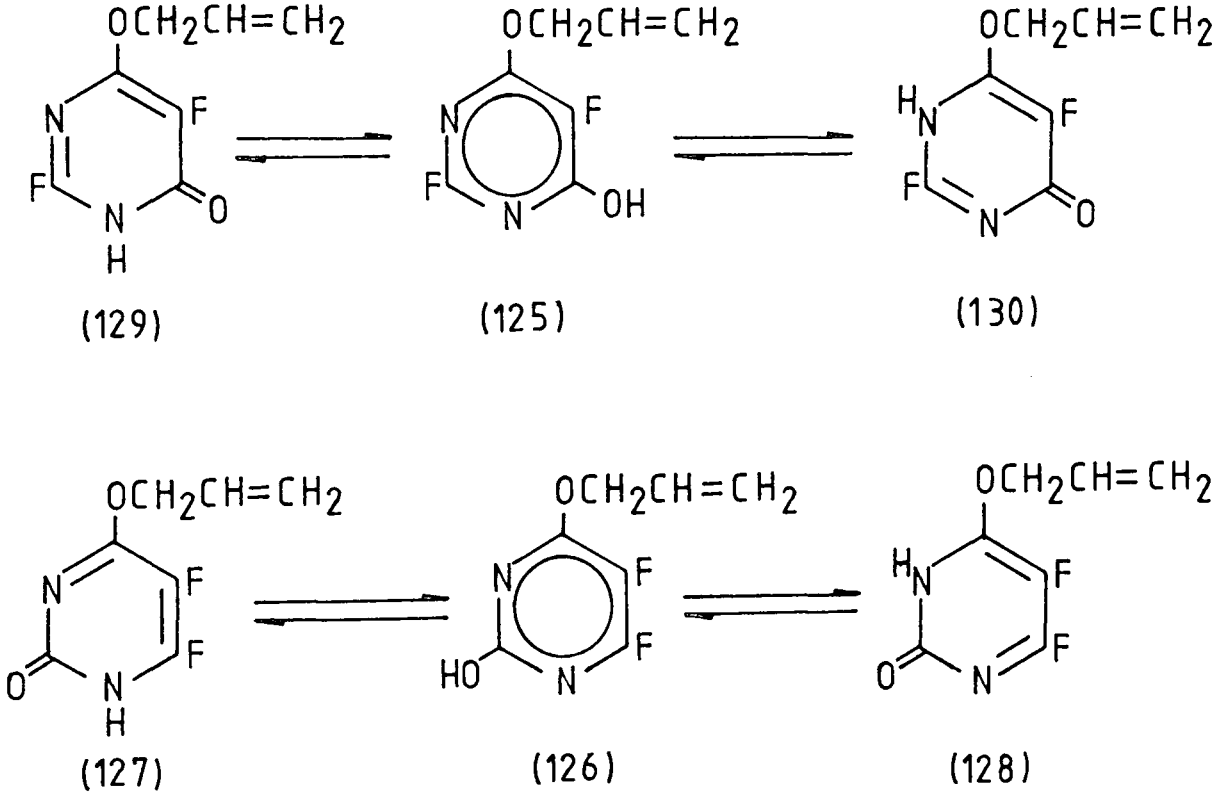


Scheme 56

3.4 Attempted Preparation of Mono- and Dihydroxy Derivatives of the Ether (93). Formation of C-Allyl Rearrangement Products

The introduction of a hydroxy group into the ether (93) proved much less straightforward than for the introduction of a methoxy substituent.

In both of the 2- and 6-hydroxy derivatives of (93), (126) and (125) respectively, the possibility exists for the tautomerism with their lactam forms (127), (128) and (129),(130) respectively, Scheme 57. Such a phenomenon is well established in the 2- and 4-hydroxypyrimidines.[48]



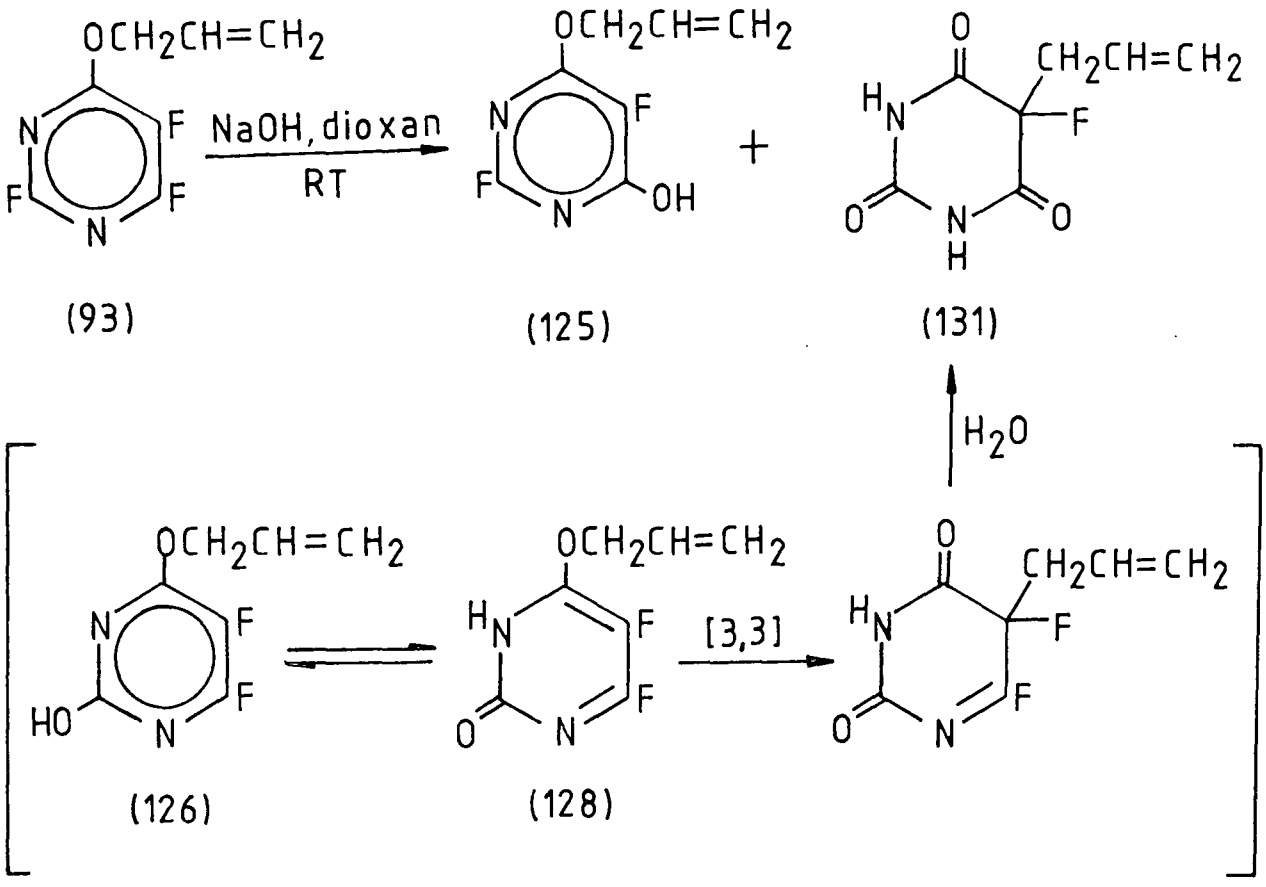
Scheme 57

A consequence of such a tautomeric system with the 6-hydroxy compound is the enhancement of the double-bond character associated with the carbon-carbon bond adjacent to the ether linkage, and this should favour migration of the allyl group in a Claisen rearrangement to the ortho- carbon, in contrast to the mode of rearrangement already observed for the ether (93). In the case of the 2-hydroxy isomer (126), however, the preferred double-bond character adjacent to the ether linkage (C=C *versus* C=N) depends on the position of the equilibrium.

Tautomerism is less marked in highly fluorinated compounds. Indeed, the polyfluorinated analogues of 2- and 4-hydroxypyridine[49] and 4-hydroxypyrimidine[40] exist almost entirely in their hydroxy-form. A hydroxy group in the 2-position in a polyfluoroquinoline, however, results in a tautomeric system, whereas, in the 4-position it does not.[50]

3.4.1 Formation of Mono-Hydroxy Derivatives

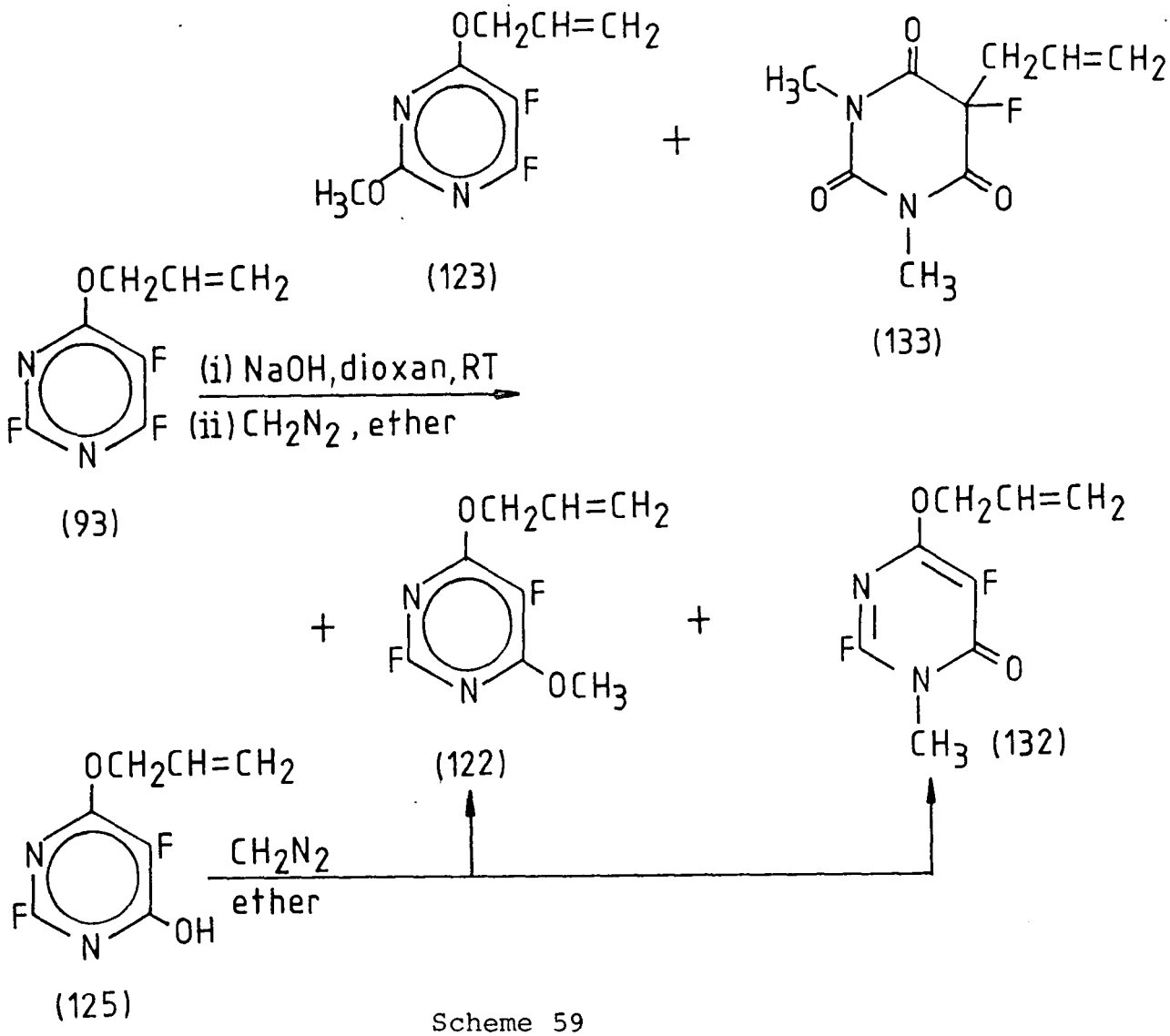
The reaction of the ether (93) with aqueous sodium hydroxide in dioxan resulted in an exothermic reaction giving rise to a product, shown by ^{19}F n.m.r. spectroscopy to consist of 3 components in the ratio 64:27:9. The major component was the 6-hydroxy compound (125) (32%). During the isolation procedure, however, [involving sublimation *in vacuo* at 50°C and fractional recrystallization of the crude product from light petroleum (100-120°C)] the second major component, the 2-hydroxy compound (126), identified by ^{19}F n.m.r. spectroscopy, underwent further reaction resulting in the formation of the barbituric acid derivative (131) (11%). The minor component in the original product was not identified. Formation of (131) can be rationalized in terms of a Claisen rearrangement of (126), or more likely its tautomer (128), since this is the only one to possess the 'locked lactam' required for rearrangement to the ortho-carbon, followed by hydrolysis of the fluorine at the 6-position, Scheme 58. The barbituric acid derivative (131) has previously been prepared by Russian workers, by selective fluorination of its hydrogen analogue using $FClO_3$.[51]



Scheme 58

The presence of the 2-hydroxy compound (126) in the original reaction product was confirmed in a separate experiment by treatment of the crude reaction product with an excess of diazomethane from which the 2-methoxy compound (123) (6%) was isolated. Three further products were also isolated, the 6-methoxy compound (122) (6%), the N-methylated product (132) (3%) [both formed from (125), since in a separate experiment, diazomethane reacted with (125) to give (122) (67%) and (132) (19%)], and the N,N'-dimethyl barbiturate derivative (133) (1%), Scheme 59.

The 2,4-dienone type structure of the N-methyl compound (132) was substantiated by the similarity of its ultra-violet spectrum with that of the model compound (99).



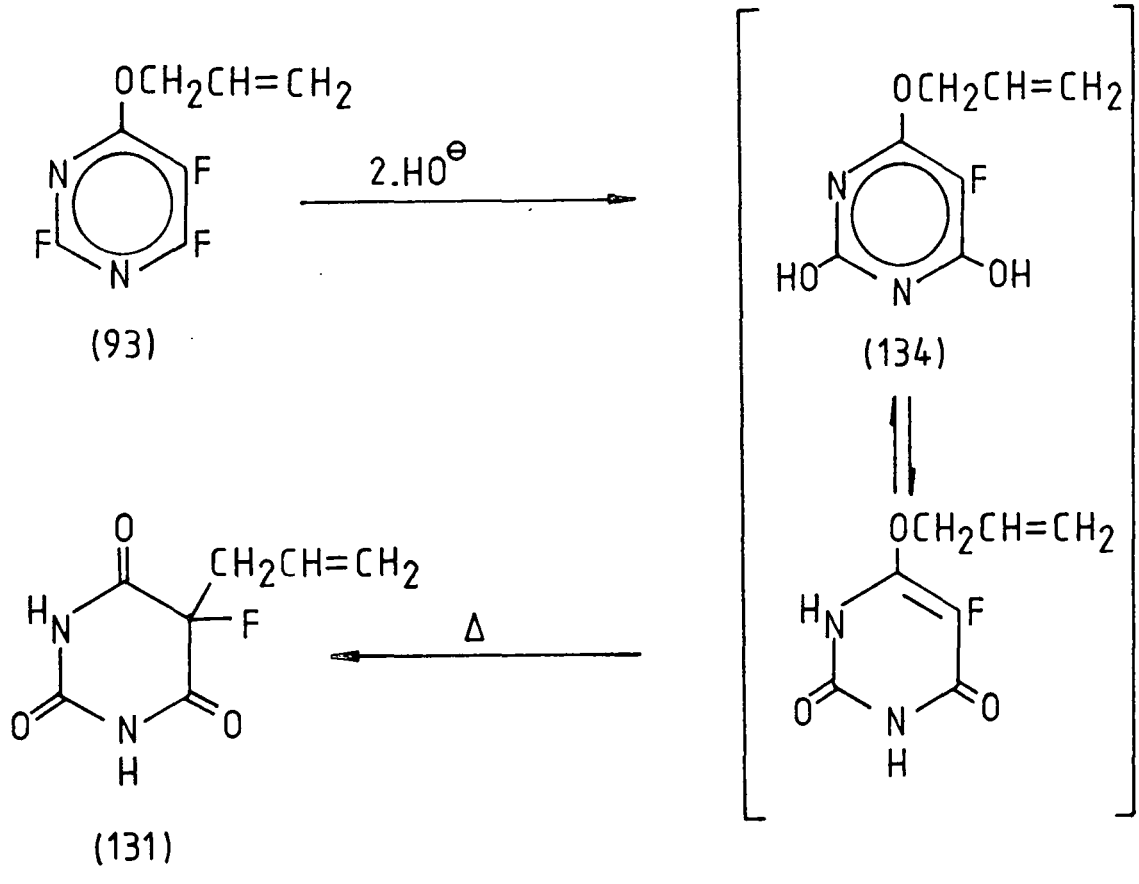
Scheme 59

The reaction of the ether (93) with aqueous sodium hydroxide in tetrahydrofuran, instead of dioxan, resulted in the formation of both the 6- and 2-hydroxy isomers in ratios ranging from 1:1 to 2:1 respectively, but again the 2-isomer (126) could not be isolated. The reaction of the crude product with diazomethane resulted in the formation of (122) (36%), (123) (26%) and the N-methyl compound (132) (12%), but none of the N,N'-dimethyl derivative (133) was observed.

Refluxing the ether (93) with potassium hydroxide in *t*-butyl alcohol[52] resulted in a product from which only the 6-hydroxy compound (125) (67%) was isolated, although ^{19}F n.m.r. spectroscopy did indicate the presence of the isomer (126) in the crude reaction product.

3.4.2 Attempted Formation of the Dihydroxy Derivative

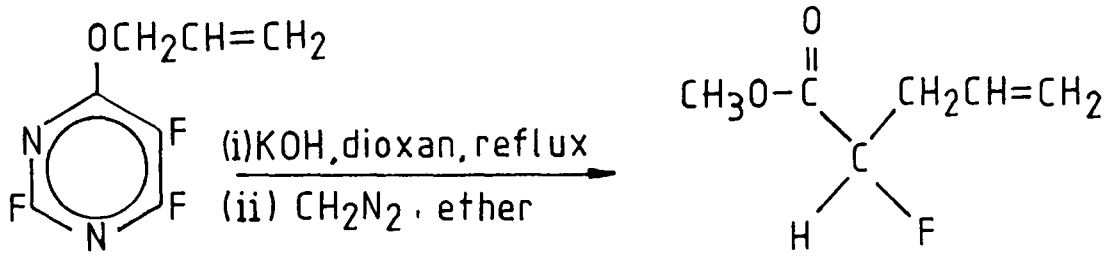
A conceivably simple route to the barbituric acid derivative (131) would be to replace both of the reactive fluorines (6- and 2-) in the ether (93) with hydroxy groups in the same reaction, since simple thermolysis of the dihydroxy compound formed (134) should only give (131), Scheme 60.



Scheme 60

Reaction of the ether (93) using aqueous potassium hydroxide in dioxan at reflux resulted not in the formation of (131), but a ring-opened product, a carboxylic acid which was conveniently handled as the methyl ester (135) (14%) by reaction of the crude product with diazomethane, Scheme 61.

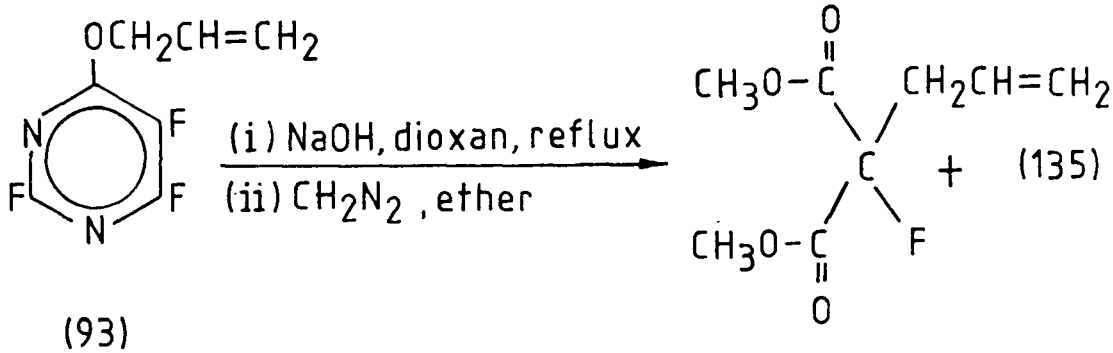
Clearly, under the reaction conditions employed, the ether (93) had followed the pathway outlined in Scheme 60, with migration of the allyl group to the ortho-carbon, but had subsequently undergone ring cleavage and then decarboxylation.



(93) (135)

Scheme 61

Under different reaction conditions using aqueous sodium hydroxide, the product obtained after diazotisation contained two esters, the diester (136) (26%) and the ester (135), in the ratio 85:15 respectively, Scheme 62.



(93) (136)

Scheme 62

Clearly reaction had again involved a Claisen rearrangement of the allyl group to the ortho-carbon before ring cleavage.

In a different series of reactions, the 6-hydroxy compound (125) was recovered unreacted when heated at reflux in wet dioxan for 24 hours. With sodium hydroxide present, however, the reaction again (following treatment with diazomethane) resulted in the formation of the two esters (136) and (135) in the ratio 5.5:1 respectively.

The preparation of the dihydroxy compound (134) by simple treatment of the ether (93) or its 6-hydroxy derivative (125) with hydroxide thus does not seem possible, since the conditions required to form (134) are sufficient to result not only in its rearrangement to the barbituric acid (131), but also further hydrolysis and ring-cleavage. It is interesting to note that Banks and Haszeldine[40] only reported the formation of a monohydroxy derivative of tetrafluoropyrimidine, whereas they were able to prepare disubstituted derivatives for all other nucleophiles studied.

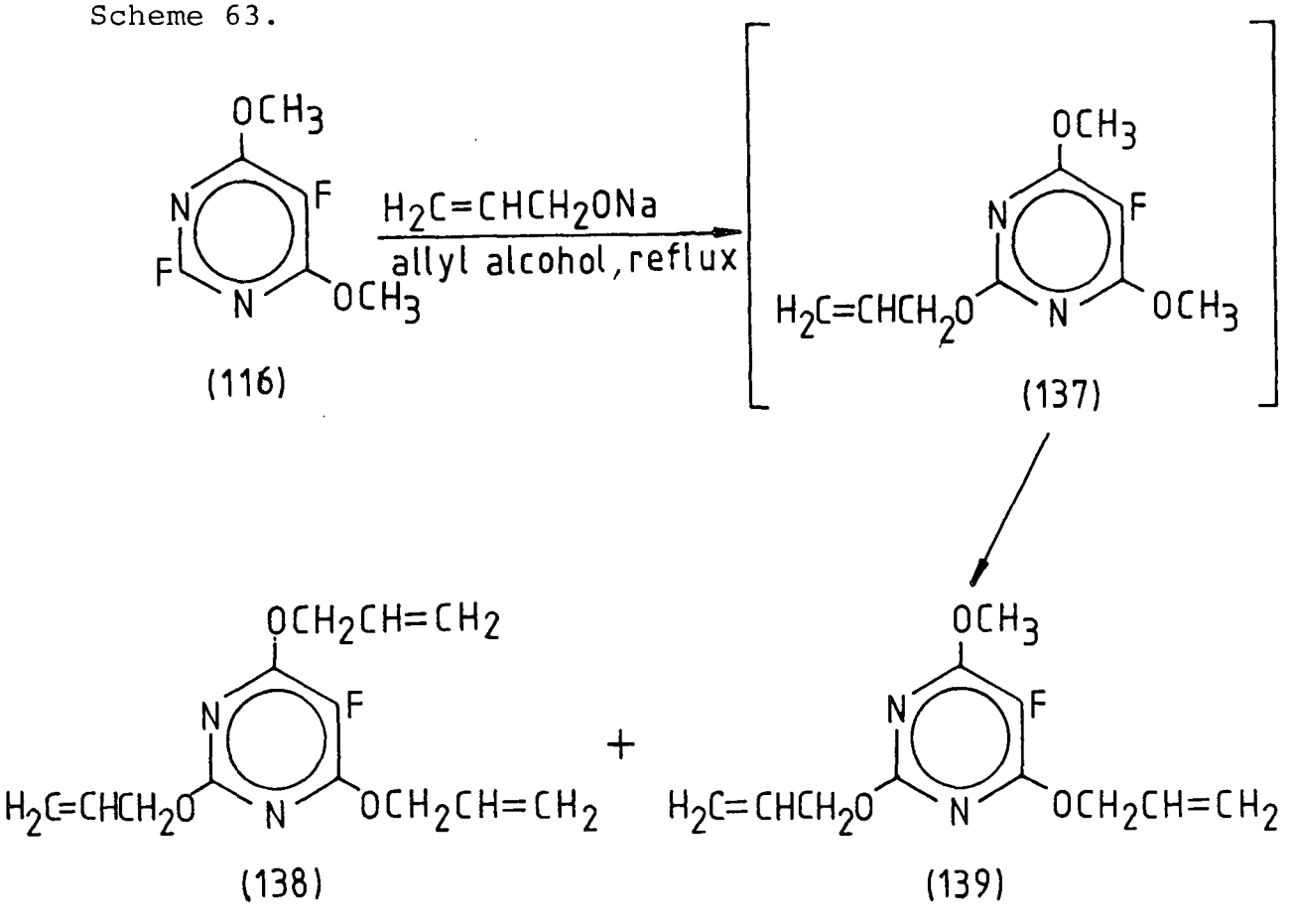
3.5 Preparation of Allyl 5-Fluoro-4,6-Dimethoxypyrimidin-2-yl Ether (137)

Although not a derivative of the ether (93), the allyl ether (137) is an isomer of the dimethoxy compound (124), and is a compound whose thermolytic behaviour would be of particular interest, since the allyl group is sandwiched between the two nitrogen atoms.

Formation of the ether (137) and a number of related compounds are discussed in the following sections. 2,5-Difluoro-4,6-dimethoxypyrimidine (116) was used as the starting material, since this was the most readily available derivative to have only the 2-position 'vacant'.

3.5.1 Reaction of the Dimethoxy Compound (116) with Sodium Allyloxide in Allyl Alcohol

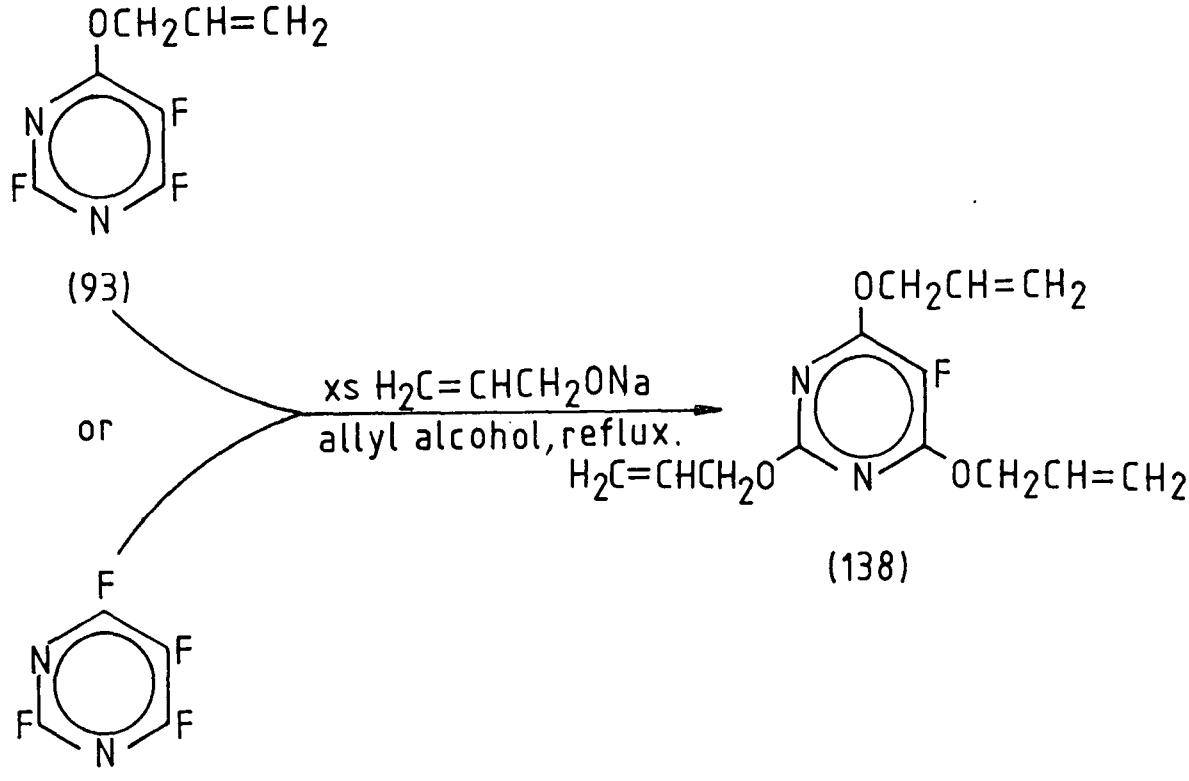
Treatment of the dimethoxy compound (116) with the sodium salt of allyl alcohol in the parent alcohol (1.3 molar equivalents) at reflux gave a product shown by ^{19}F n.m.r. spectroscopy to consist of three components in the ratio 5:2:1. Only the two major components could be isolated, and these were found to be the 2,4,6-triallyloxy compound (138) (29%) and the 2,4-diallyloxy compound (139) (9%), Scheme 63.



Scheme 63

The 2-allyl ether (137) had clearly formed in the reaction (and may well have been the minor component in the product), but under the reaction conditions had undergone further displacement of the methoxy groups *via* transetherification reactions.

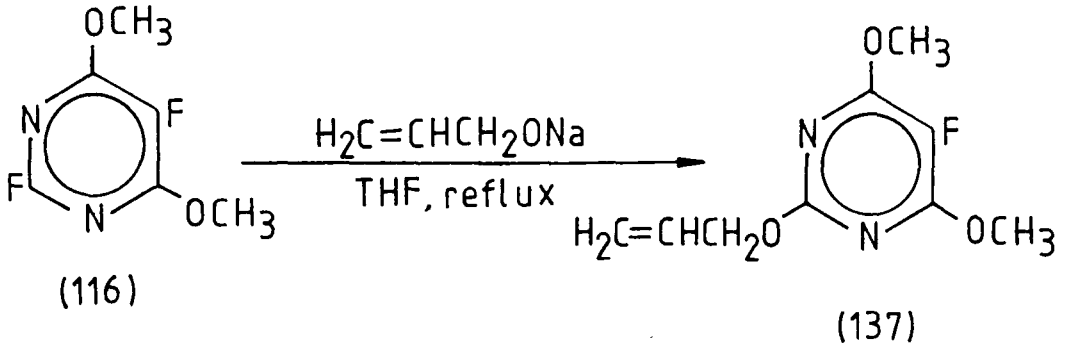
The triallyloxy compound (138) was also prepared by the reaction of excess sodium allyloxide in allyl alcohol on the ether (93) (73%) or on tetrafluoropyrimidine (65%), Scheme 64.



Scheme 64

3.5.2 Reaction of the Dimethoxy Compound (116) with Sodium Allyloxide in Tetrahydrofuran

Under slightly different conditions to those employed in Section 3.5.1, the sodium salt of allyl alcohol in THF (1 molar equivalent), at reflux, reacted with the dimethoxy compound (116) to give the 2-allyl ether (137) (99%) as the only product, Scheme 65.



(116) (137)

Scheme 65

CHAPTER FOUR

THE THERMOLYSIS OF SUBSTITUTED DERIVATIVES OF ALLYL 2,5,6-TRIFLUOROPYRIMIDIN-4-YL ETHER (93) AND ALLYL 5-FLUORO-4,6-DIMETHOXYPYRIMIDIN-2-YL ETHER (137)

4.1 Introduction

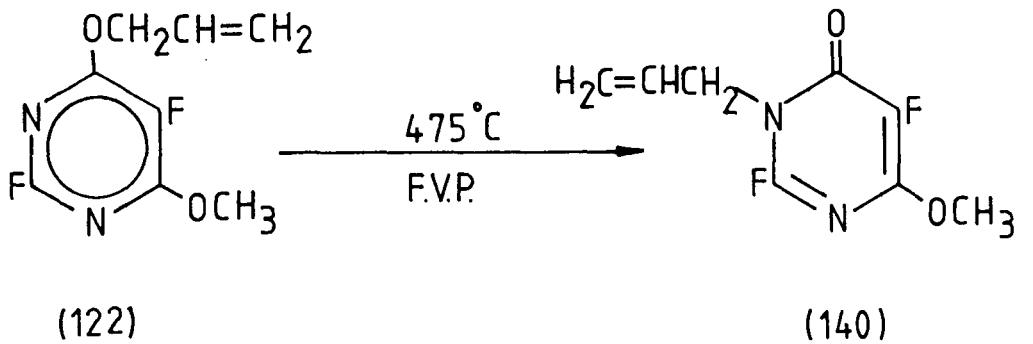
In the preceding two chapters the rearrangement of the allyl group in three fluorinated allyl pyrimidyl ethers, (93), (111) and (126) has been observed. In each case the migration of the allyl group occurred exclusively to one terminus with the formation of an N-allyl or a C-allyl compound only, no competition between the two migration termini (N-3 and C-5) being observed.

Thermolysis of the various substituted derivatives of the ether (93) prepared in Chapter Two was investigated to provide a clearer picture as to what determines this preference for migration of the allyl group to one ortho-position over the other.

4.2 Thermolysis of the Methoxy Derivatives of the Ether (93)

4.2.1 Thermolysis of Allyl 2,5-Difluoro-6-Methoxypyrimidin-4-yl Ether (122)

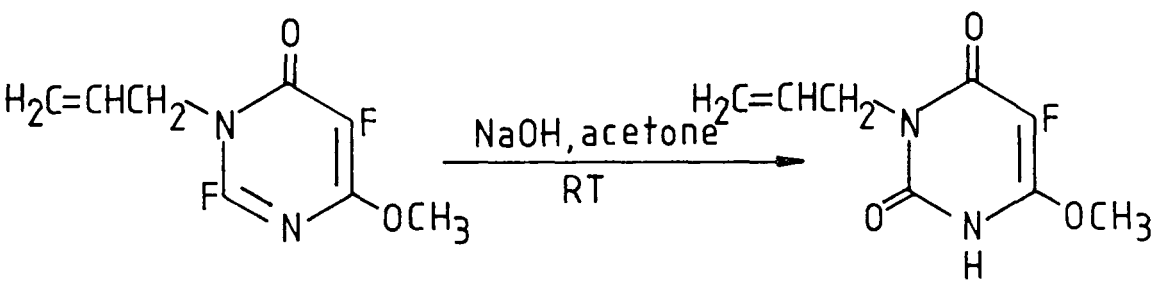
Thermolysis of the 6-methoxy compound (122) under F.V.P. conditions at 475^{o}C resulted in the formation of the N-allyl compound (140) (65%) as the only Claisen rearrangement product, Scheme 66. Unchanged starting material (122) (14%) was also recovered. The structure of the N-ally compound (140) was confirmed by the similarity of its ultraviolet spectrum with that of the model compound (99).



(122) (140)

Scheme 66

Hydrolysis of the fluorine at the 2-position in compound (140), using aqueous sodium hydroxide resulted in the formation of another N-3 allyl-substituted derivative of 5-fluorouracil (141) (89%), Scheme 67.

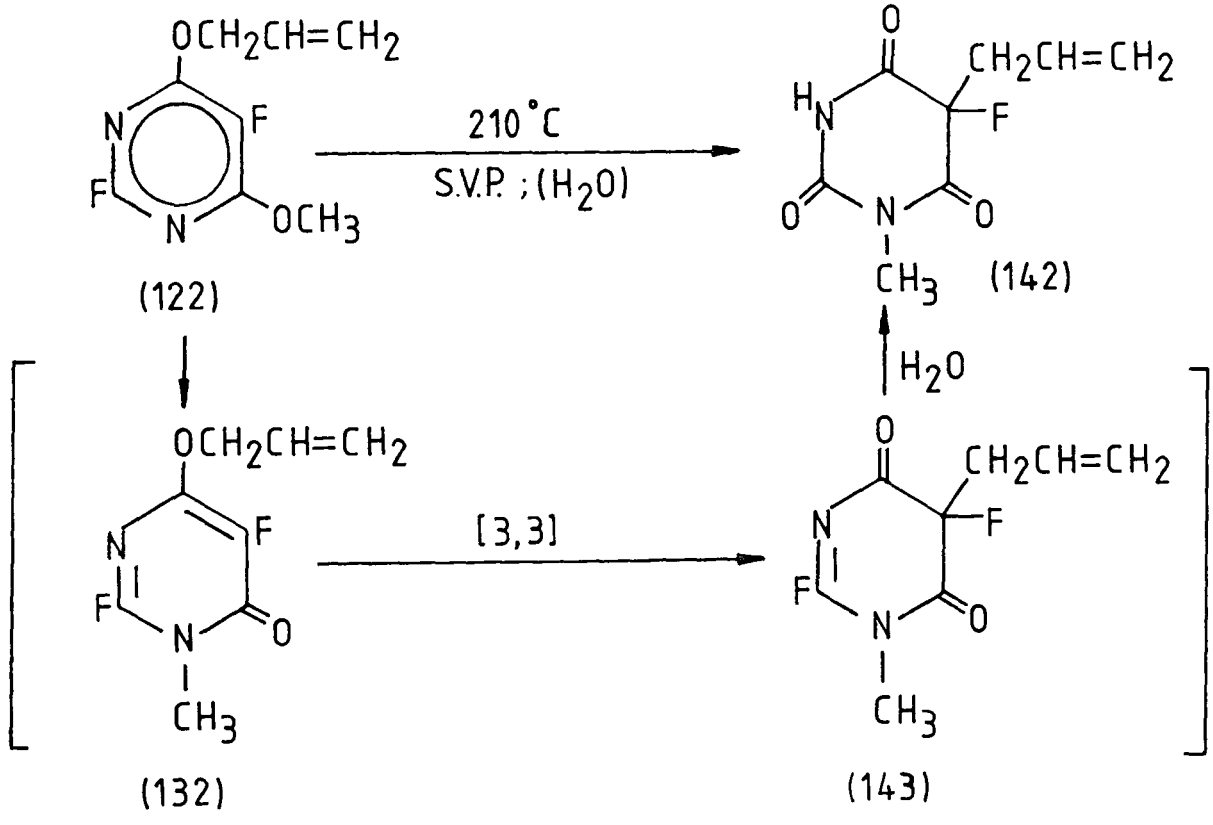


(140) (141)

Scheme 67

In direct contrast to the reaction of the 6-methoxy compound (122) under F.V.P. conditions, thermolysis of (122) under S.V.P. conditions at 210°C for 69h resulted in the

formation of two products (as well as polymeric material) in the ratio 7:4, in which the allyl group had migrated exclusively to the ortho-carbon (triplet resonances for the 5-fluorines, due to an adjacent $-CH_2-$ group). Only the major component from the crude product could be isolated, and was found to be the barbituric acid derivative (142) (6%), Scheme 68.



Scheme 68

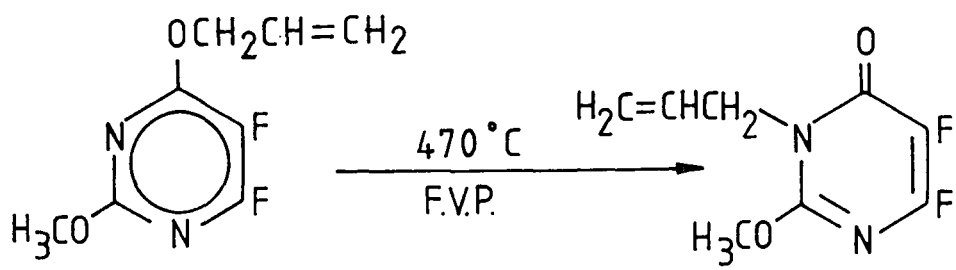
The formation of the C-allyl compound (142) can be rationalized in terms of an initial migration of the methyl from the methoxy group in (122) to the N-1 position giving (132), a well known but unusual thermal reaction of pyrimidine compounds containing the structural feature $-N=C-OCH_3$.[53] A consequence of this methyl migration is a localization of the double bond between the carbons C-4 and C-5 which forces the rearrangement of the allyl group to the ortho-carbon to give

(143). Hydrolysis of (143) (presumably during work-up) then results in the formation of (142).

The S.V.P. of the 6-methoxy compound (122) at 162°C for 17h resulted only in the recovery of unreacted starting material (94%).

4.2.2 Thermolysis of Allyl 5,6-Difluoro-2-Methoxy-pyrimidin-4-yl Ether (123)

Flash vapour phase pyrolysis of the 2-methoxy compound (123) at 470°C gave the N-allyl isomer (144) (65%) along with unchanged (123) (16%), Scheme 69. The structure of (144) was inferred by its ultra-violet spectrum which was very similar to that of the model (99). Pyrolysis of (123) under S.V.P. conditions was not attempted.



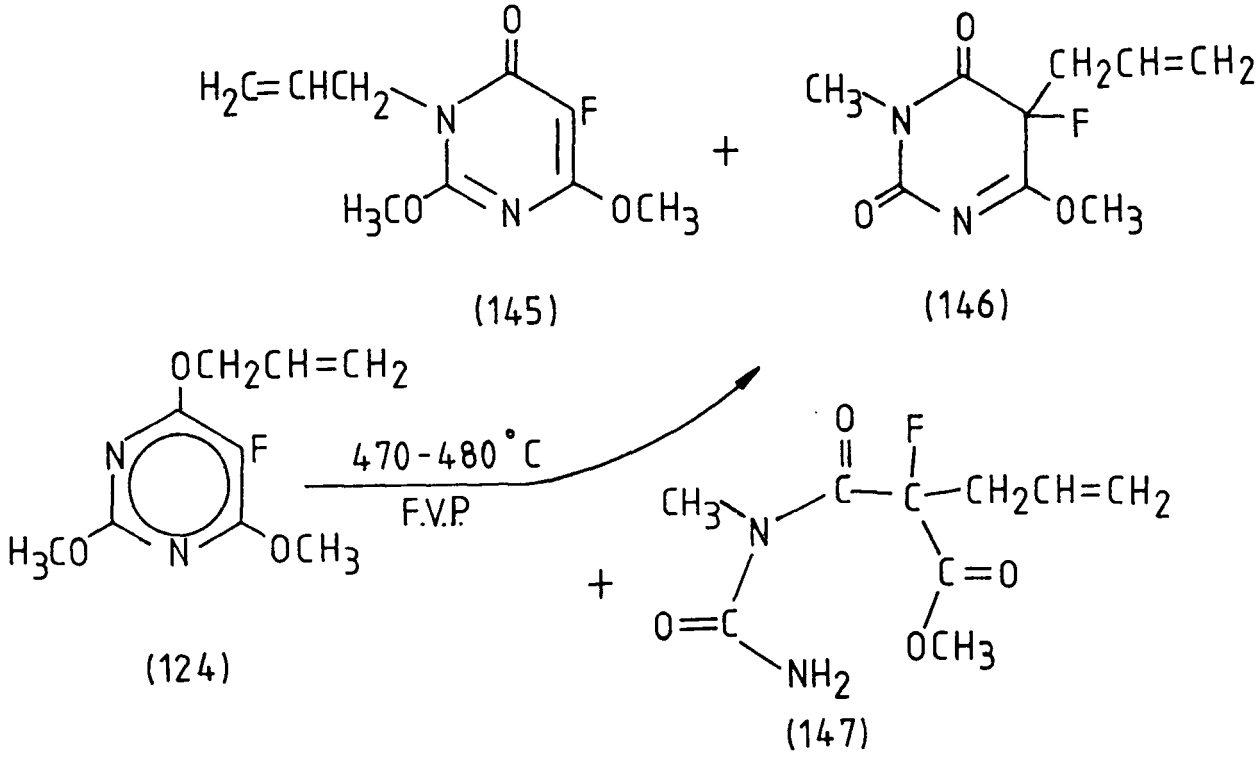
(123) (144)

Scheme 69

4.2.3 Thermolysis of Allyl 5-Fluoro-2,6-Dimethoxy-pyrimidin-4-yl Ether (124)

A complex mixture of products was obtained when the 2,6-dimethoxy compound (124) was subjected to F.V.P. at

470-480°C. Moreover the proportion of the individual components obtained were not reproducible under supposedly identical conditions. In one experiment, three components were identified along with unreacted starting material (124) (11%): the N-migration terminus product (145) (9%), the isomeric C-5 migration terminus product (146) (4%), and the ring-opened hydrolysis product (147) (22%), Scheme 70. Prior to separation, ^{19}F n.m.r. spectroscopy indicated (124), (145), (146), (147) and an unidentified material in the ratio 11:27:5:51:6, giving the overall N:C migration terminus ratio as ∿1:2 [27:(5+51)]. In another reaction this ratio was 1:10.7[7:(52+23)].



Scheme 70

The structure of the N-allyl compound (145) was confirmed by comparison of its ultra-violet spectrum with that of the model compound (99).

Formation of the C-allyl compounds (146) and (147) can again be explained in terms of the localization of the double bond between C-4 and C-5 as a result of the initial migration of one of the methyl groups. In this reaction it is the methyl group from the methoxy group between the nitrogens that migrates to N-3 rather than that from the methoxy group at the 6-position migrating to the N-1. This latter migration would give rise to the structure (148) (Scheme 71) after rearrangement of the allyl group. Assignment of the product as (146) rather than the structure (148) was made on the grounds of the chemical shifts of the methyl groups, as outlined below.

A number of compounds have been prepared in this Thesis having methyl groups at various positions in a pyrimidine ring system, and their ^{1}H n.m.r. shift data are shown in Table 4.

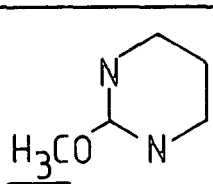
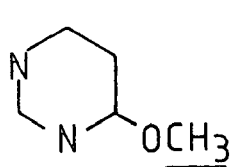
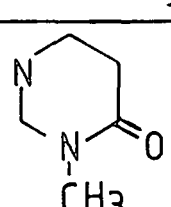
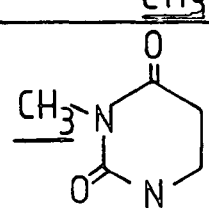
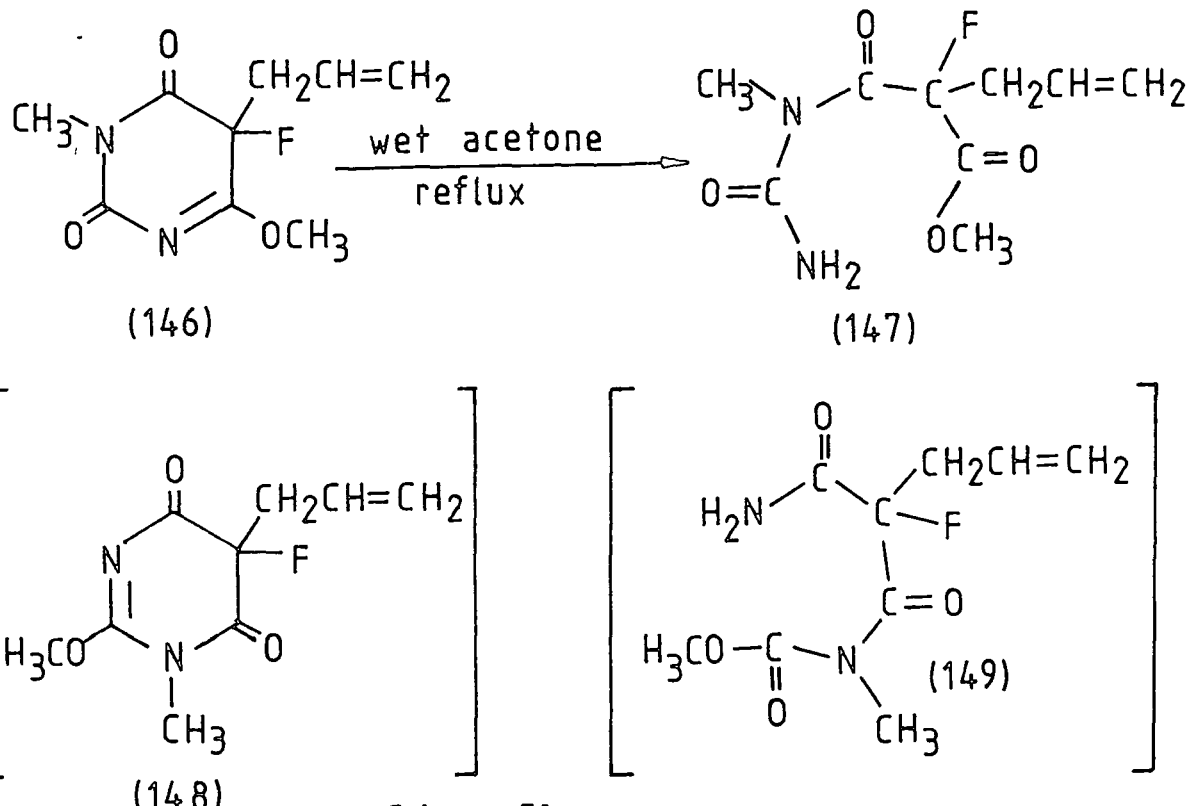
	^{1}H n.m.r. Shift Range (ppm) (shifts relative to TMS)
	3.93 - 4.00
	3.99 - 4.08
	3.51
	3.30 - 3.32

TABLE 4

The ^1H n.m.r. spectrum of the C-allyl product from thermolysis of the dimethoxy compound (124) showed methyl resonances at 3.28 and 4.12 ppm, and clearly, from Table 4, this is only consistent with the product having the structure (146).

Evidence for the ring-opened nature of the compound (147) was shown in its infra-red spectrum, which indicated the presence of $-NH_2$ (3310 and 3410 cm^{-1}) and also an ester functionality (1755 cm^{-1} for $-\overset{O}{\overset{\|}{C}}-$). In a separate experiment it was shown that the ring-opened product (147) was derived from the C-allyl compound (146), since hydrolysis of (146) in wet acetone at reflux resulted in the formation of (147) (99%), Scheme 71.



(146) (147)

(148) (149)

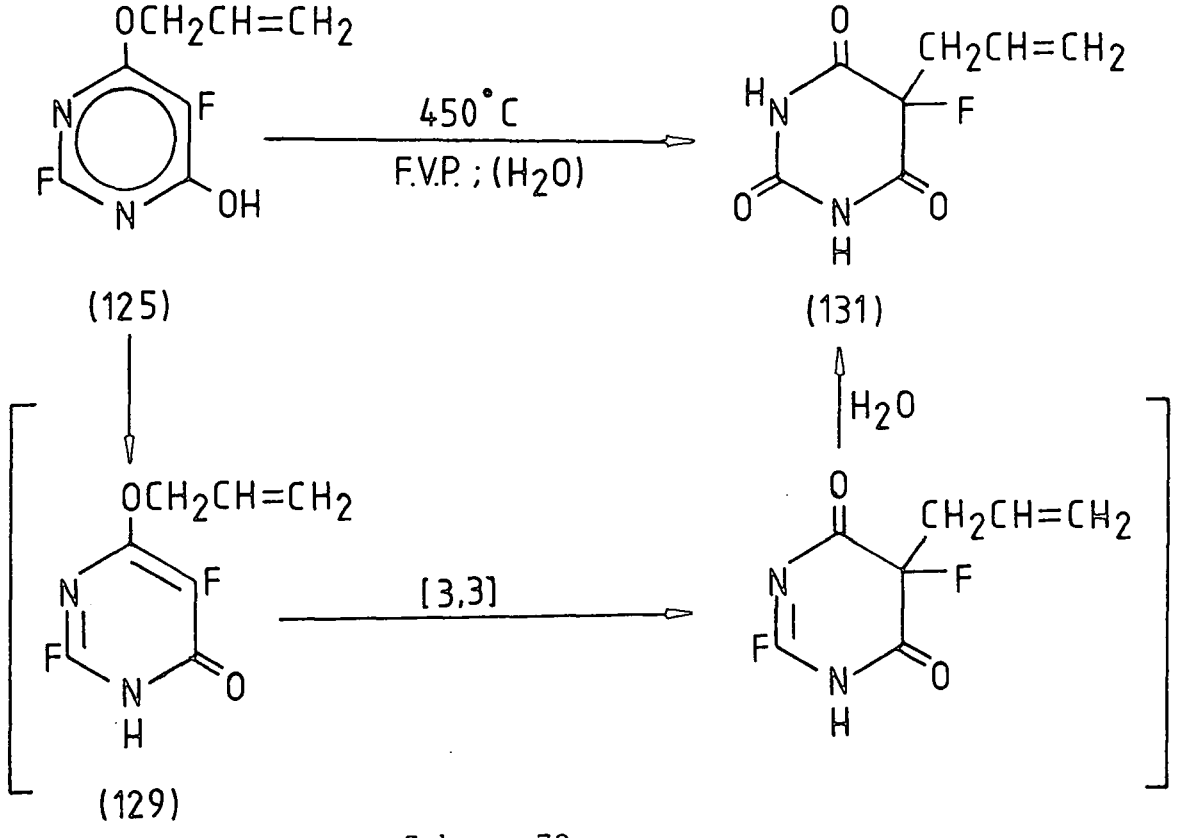
Scheme 71

The mass spectrum of (147) showed M^+ 232, and a significant peak with m/z 101 due to $C_3H_5N_2O_2^+$. The ring-opened product that would result from hydrolysis of the

structure (148) would be (149) and is not consistent with the mass spectral data.

4.3 Thermolysis of Allyl 2,5-Difluoro-6-Hydroxypyrimidin-4-yl Ether (125)

The attempted thermolysis of the 6-hydroxy compound (125) both under S.V.P. conditions at 162°C for 22h and in sulpholaneat 166°C for 6.5h resulted only in the formation of polymeric materials from which nothing could be isolated. When subjected to F.V.P. at 450°C, however, the only product which could be separated and identified from the complex, polymeric product proved to be the previously isolated barbituric acid (131) (11%), Scheme 72.



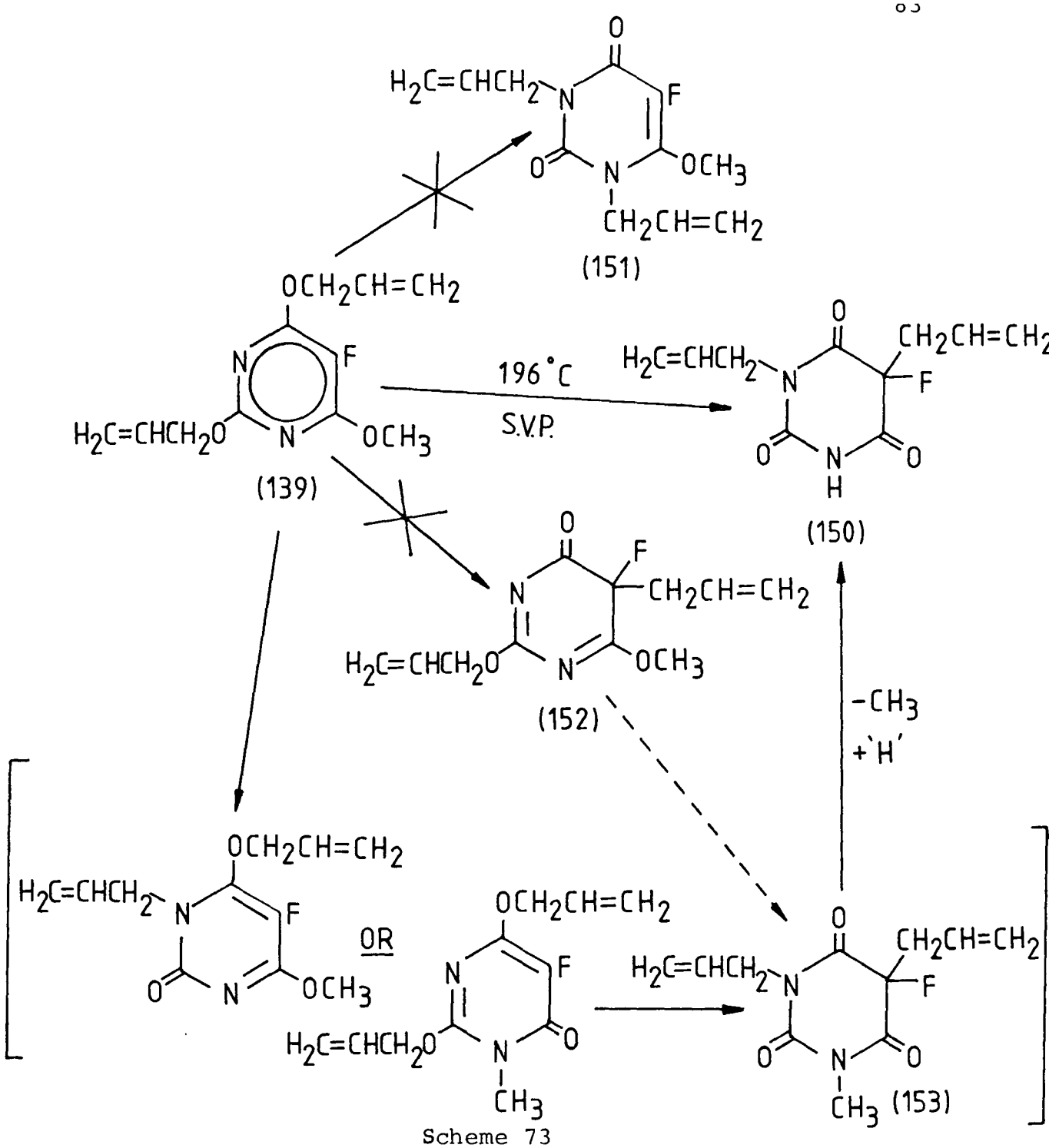
Scheme 72

Rearrangement of the 6-hydroxy compound (125) had thus occurred in a similar manner to that of its 2-isomer (126) *i.e. via* the lactam form which has the double bond localised between C-4 and C-5. In the case of (125), both lactam forms (129) and (130) possess such a 'locked' bond [only (129) is shown in Scheme 72] and would force rearrangement of the allyl group to the ortho-carbon. Hydrolysis of the fluorine at the 2-position during work up then gives the barbiturate (131).

4.4 Thermolysis of 2,4-Diallyloxy-5-Fluoro-6-Methoxypyrimidine (139)

The static vapour phase pyrolysis of the diallyloxy compound (139) at 196°C for 7h gave, along with unreacted (139) (32%), the barbiturate derivative (150) (48%), wherein one allyl group had migrated to the ortho-carbon, the other to the ortho-nitrogen, whilst the methyl group was lost, Scheme 73. None of the product resulting from rearrangement of both the allyl groups to nitrogen (151) was observed.

It is unlikely that the first step in the reaction involves the exclusive migration of the allyl group from the 4-position to the ortho-carbon giving (152), since a migration of this type has never been observed. The only explanation, therefore, for the mode of migration that occurs in this reaction again involves the 'locking' of the double bond between C-4 and C-5. This can be achieved by either the migration of the allyl group at the 2-position to N-3, or more probably by migration of the methyl group to N-1.

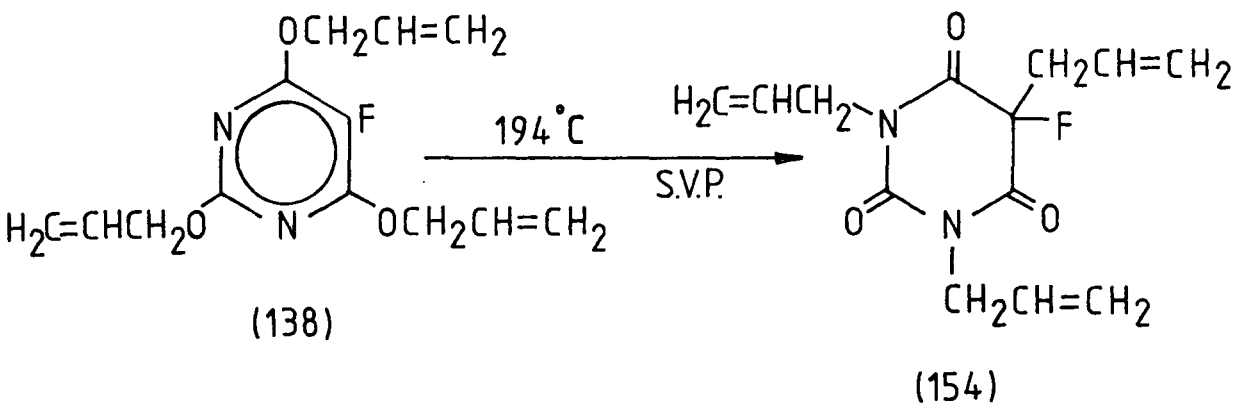


Scheme 73

[The former process is an unlikely one since, as it will be shown in Section 4.6, an allyl group in the 2-position is inert to a Claisen rearrangement if it involves loss of aromaticity in the aromatic moiety]. Rearrangement of the allyl group can then only occur to give (153) which, subsequently, on loss of a methyl group and abstraction of a proton gives (150).

4.5 Thermolysis of the 2,4,6-Triallyloxy-5-Fluoro-pyrimidine (138)

Thermolysis of the triether (138) under S.V.P. conditions at 194°C for 16.5h resulted in the formation of a single product (154) (88%) in which all the allyl groups had undergone rearrangement, Scheme 74.



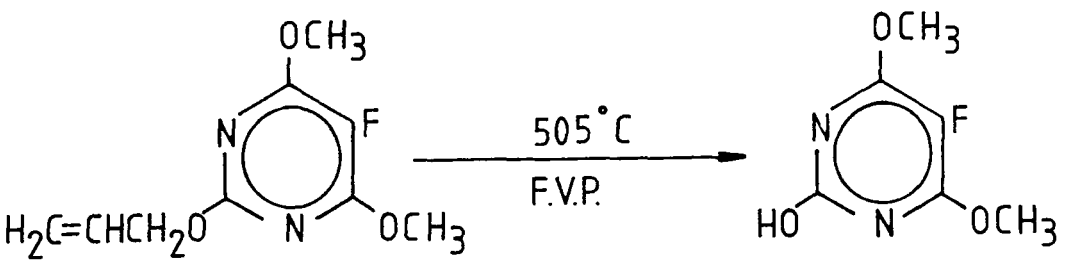
(138) (154)

Scheme 74

A reaction for a shorter period of time (3h) in order to attempt to isolate any of the intermediate rearranged materials that lead to the barbiturate (154) resulted in a product containing only unreacted starting material (138) and the totally rearranged product (154), in the ratio 2:1 (by ^{19}F n.m.r.). Clearly, all subsequent allyl migrations after the first rearrangement, which presumably involves migration of the allyl at the 4- (or 6-) position to the ortho-nitrogen, occur rapidly to give (154).

4.6 Thermolysis of Allyl 5-Fluoro-4,6-Dimethoxypyrimidin-2-yl Ether (137)

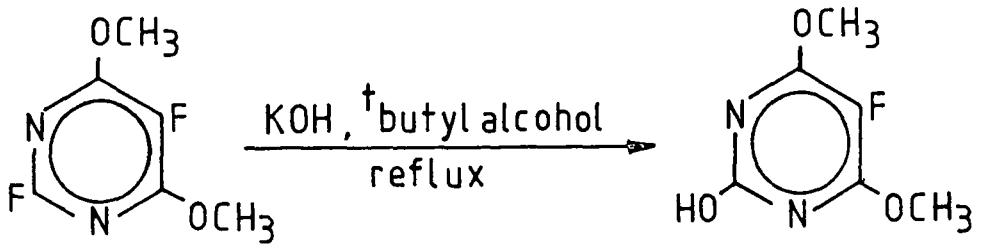
The ether (137) is a symmetrical molecule and is the only example prepared which has just one allyloxy substituent which is between the nitrogen atoms. Surprisingly, this proved to be completely resistant towards the Claisen rearrangement. The static vapour phase pyrolysis of the ether (137) at 196°C for 17h resulted only in the recovery of starting material (90%). It was also recovered unchanged when subjected to F.V.P. at 450°C. At 505°C under F.V.P. conditions, however, the allyl group was lost with the formation of the 2-hydroxy compound (155) (26%), Scheme 75. Unchanged starting material (137) (16%) was also recovered.



(137) (155)

Scheme 75

The hydroxy compound (155) (80%) was also prepared from the reaction of the 4,6-dimethoxy compound (116) with potassium hydroxide in *t*-butyl alcohol at reflux, Scheme 76.



(116) (155)

Scheme 76

4.7 Concluding Remarks

The experiments described in this part of the Thesis show that in a fluorinated pyrimidin-4-yl ether, rearrangement of the allyl group occurs to give an isomer in which the terminus for the migration of the allyl group is exclusively N-3, as seen in compounds (93), (111), (112), (123) and (124), which give the corresponding 3-allylpyrimidin-4(3H)-one derivatives (99), (113), (140), (144) and (145) respectively. The allyl group undergoes inversion when undergoing such a migration, a fact demonstrated in the rearrangement of the deuterated allyl ether (100) to (102). This reaction also nicely establishes that the reaction is cyclic and intramolecular in nature. Rearrangement in which C-5 is the migration terminus is observed, but is only as a consequence of a reaction that precedes migration of the allyl group, localising the double bond between the carbons, C-4 and C-5, adjacent to the ether linkage. Migration of the allyl group can thus only occur to the C-5 position. The compounds (122),

(124), (125), (126) and (139) yield the C-allyl derivatives (142), (146), (131), (131) and (150) because of such an initial reaction.

The mode of the Claisen rearrangement observed is thus in contrast to the pyrimidyl ethers studied by Tieckelman and co-workers, where there is a competition between migration of the allyl group to the two ortho-positions, as well as in contast to the various other fluorinated aromatic systems which result in internal Diels-Alder adducts and products derived from them.

The N-allyl derivatives that have a fluorine at the 2-position have proved to be useful synthetic intermediates in the preparation of some new N-3 allyl substituted 5-fluorouracil derivatives. Thus the N-allyl compounds (99), (113) and (140) have been used to prepare the 5-fluorouracil derivatives (106), (114) and (141) respectively. As far as is known, this is the only method by which such derivatives can be prepared.

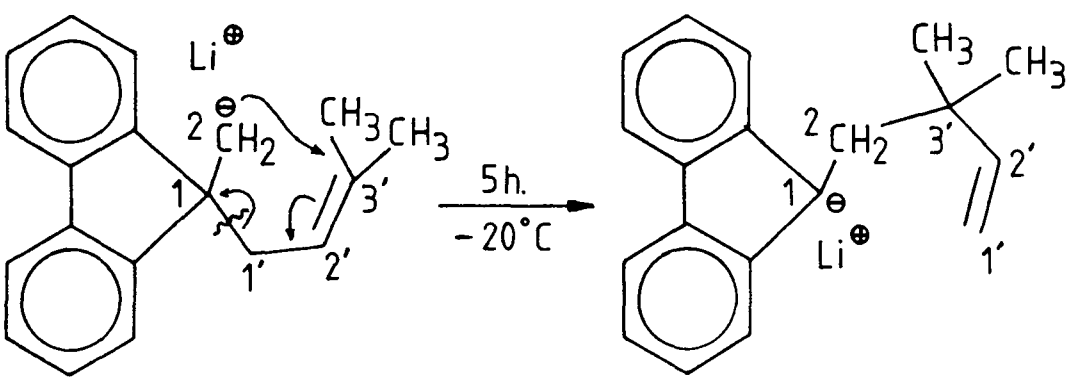
PART B

CHAPTER FIVE

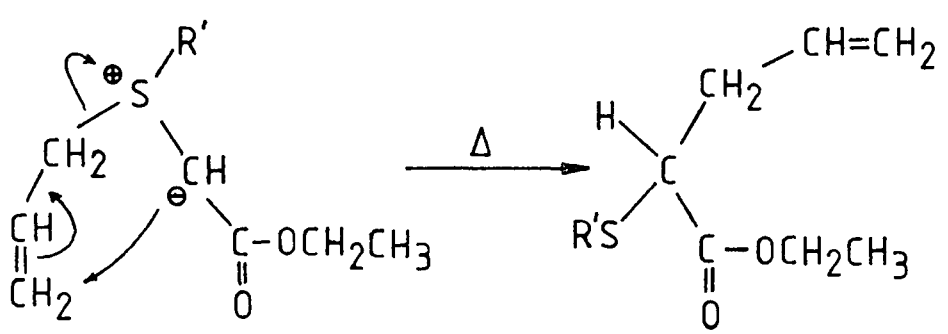
[2,3] SIGMATROPIC REARRANGEMENTS INVOLVING THE RING OF AROMATIC COMPOUNDS

5.1 Introduction

An important class of molecular rearrangements which were recognised much later than the [3,3] shifts described in Part A of this thesis are those designated [2,3] sigmatropic rearrangements. These occur in carbanionic systems such as (156)[55] but more commonly in ylide type compounds,[3b] for example (157),[56] Scheme 77.



(156)

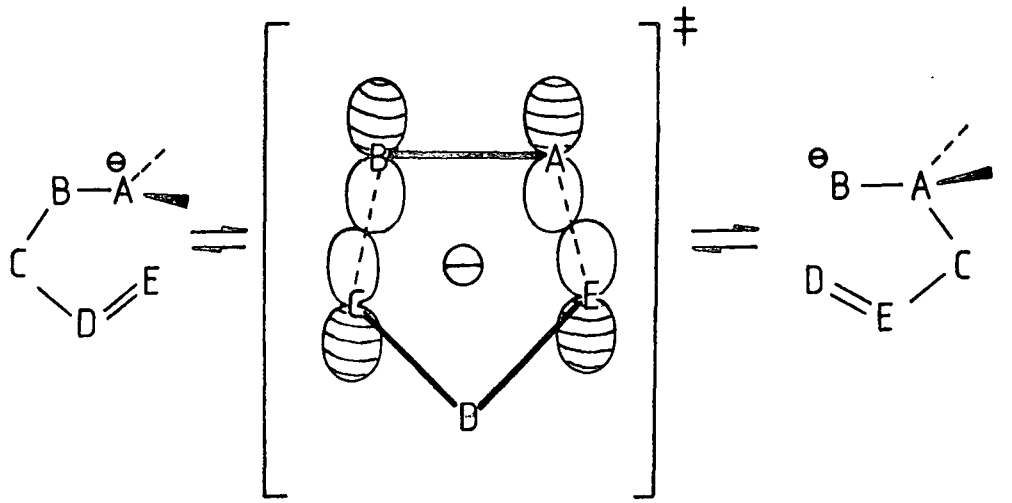


(157)

Scheme 77

In contrast to the Claisen rearrangements previously described, where rearrangement occurs *via* a six-membered cyclic transition state, the transition state for the [2,3] rearrangement consists of only five atoms. The reaction, however, still involves the participation of six electrons,

and thus the selection rules for the rearrangements are the same as those for a [3,3] shift. In a [2,3] rearrangement, therefore, reaction occurs *via* a transition state in which there is a suprafacial-suprafacial interaction of the migrating components,[57] Scheme 78.



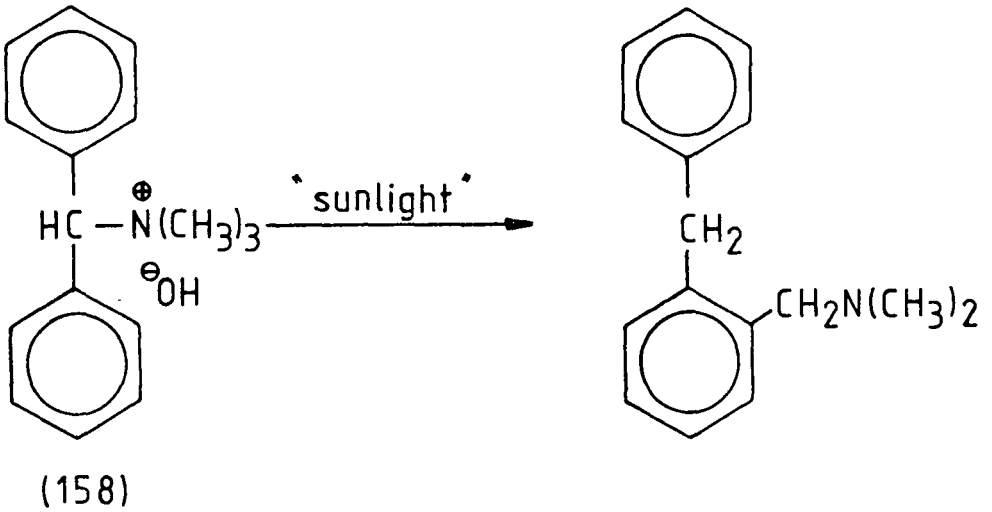
Scheme 78

[2,3] Rearrangements involving the π-electrons of an aromatic ring have also been observed, and a number of such reactions are described in the following sections.

5.2 The Sommelet-Hauser Rearrangement[58-59]

In 1937, Sommelet reported the rearrangement in sunlight, of the trimethylamino group of benzhydryl trimethylammonium hydroxide (158) to an ortho-position in one of the phenyl rings,[60] Scheme 79. (This was later shown to be a base promoted process however, with sunlight being the source of heat[61]).

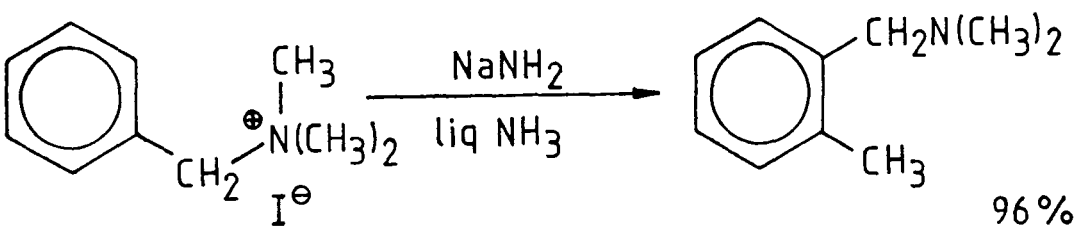
The generality of this 'Sommelet' reaction in other benzyl ammonium salts was extensively investigated by Hauser,[62-66] and the rearrangement now bears both their names.[67] Thus, treatment of the ammonium iodide (159) with sodium amide



(158)

Scheme 79

in liquid ammonia gave a near quantitative yield of the ortho-substituted toluene (160),[62] Scheme 80.

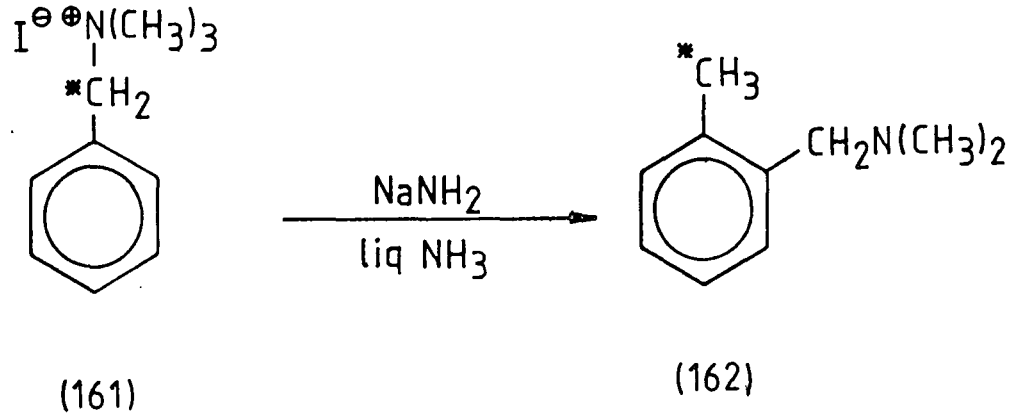


(159) (160)

Scheme 80

Products studies[62] and carbon-14 labelling experiments[66] proved conclusively that the ortho-methyl carbon atom in the product was the methylene carbon of the starting material. Thus the salt (161) resulted in the formation of only the labelled product (162), Scheme 81.

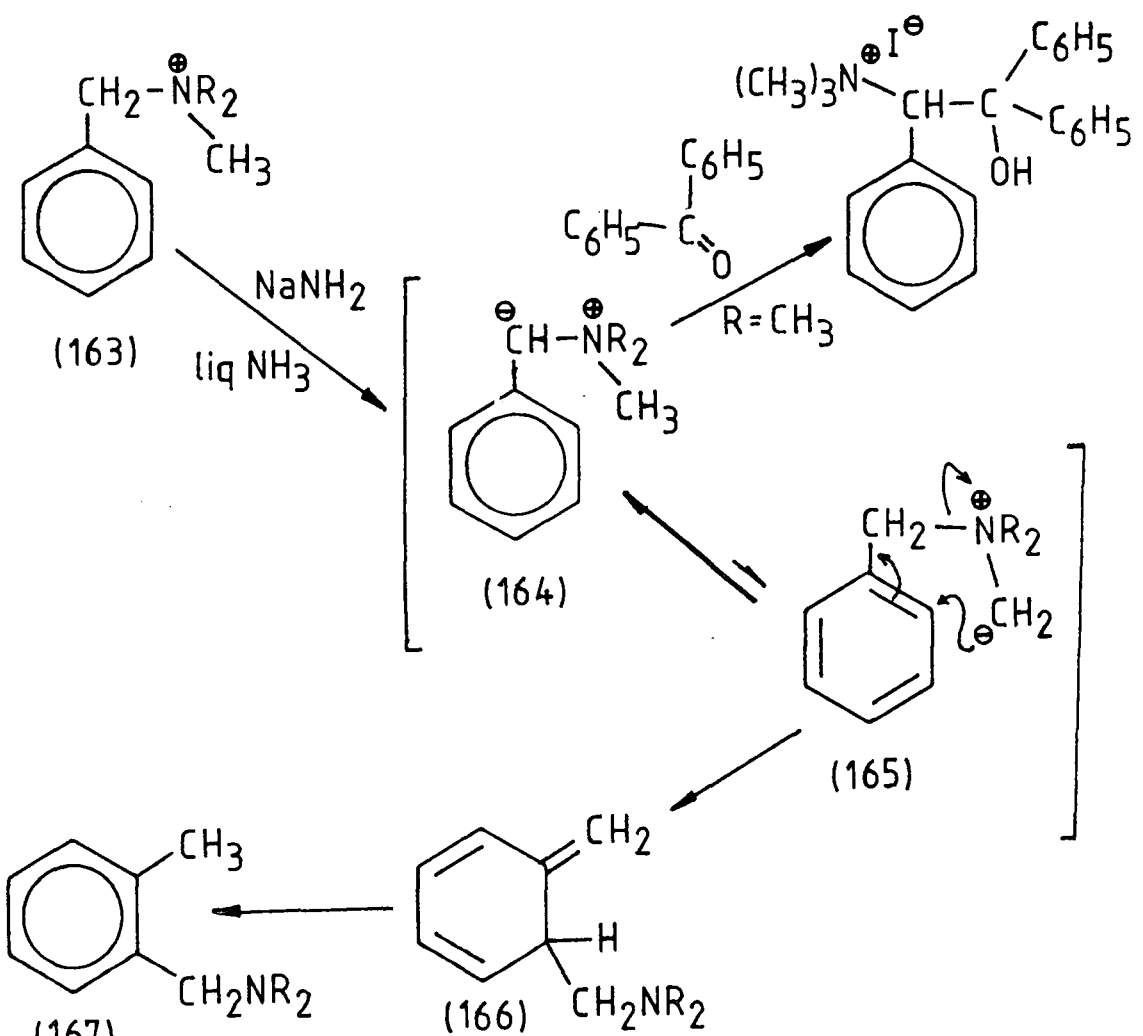
The generally accepted mechanism for the process was proposed by Hauser and involves the initial deprotonation of the salt (163) to give the ylide (164) which in turn is in equilibrium with the less stable ylide (165). The inter-



(161) (162)

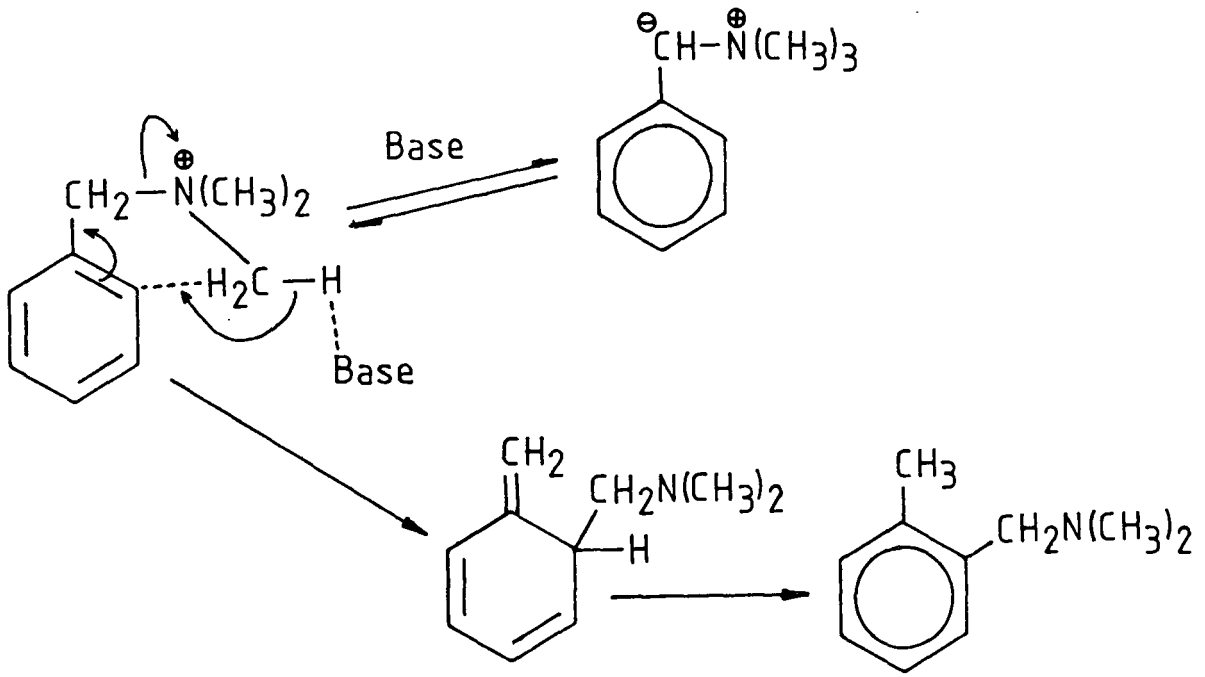
Scheme 81

mediate (165) then rearranges by a [2,3] shift to give the exomethylene derivative (166) which finally rearomatizes to give the ortho-substituted product (167), Scheme 82. The ylide (164:R=CH_3) could be trapped at -80°C with benzophenone.[68]



Scheme 82

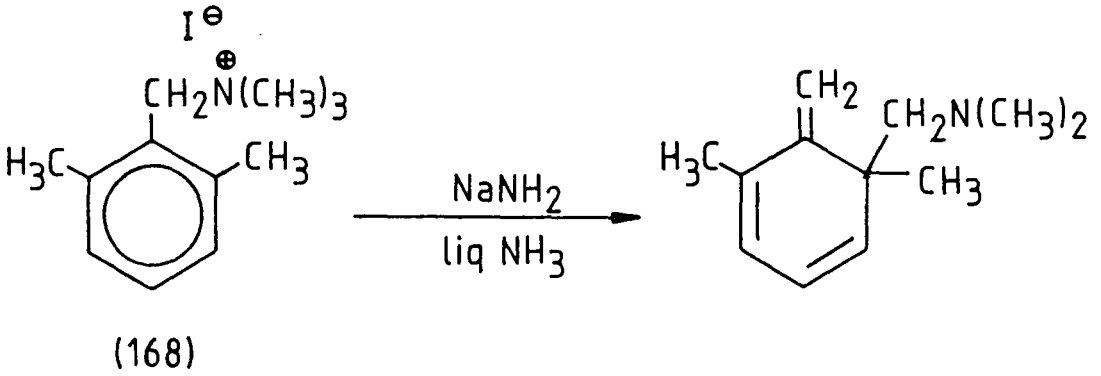
An alternative route for the rearrangement has been put forward on the grounds that no evidence has been obtained for the existence of methyl ylides like (165). Here, the suggested reaction involves a concerted process direct from the starting material and not *via* formation of the methyl ylide, although the equilibrium between the starting salt and the benzyl ylide still occurs,[69] Scheme 83.



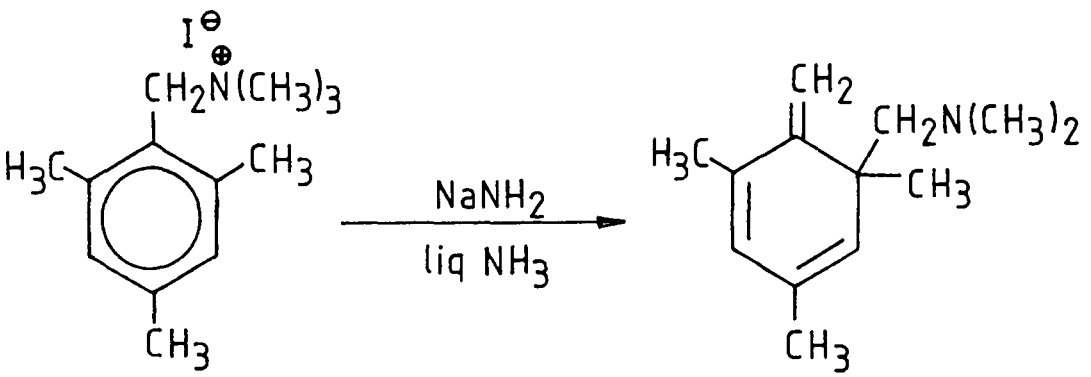
Scheme 83

Support for the intermediacy of exomethylene compounds like (166) was obtained by the actual isolation of such compounds from the rearrangement of the salts (168) and (169), which have the ortho-positions on the aromatic ring blocked by methyl substituents, thus preventing rearomatization,[70-72] Scheme 84.

The existence of the exomethylene compound (170) (166:R=CH_3) has also been demonstrated by the formation of the compound (171) when the rearrangement of the ammonium iodide (159) was carried out using n-butyl lithium as the base,[73] Scheme 85.

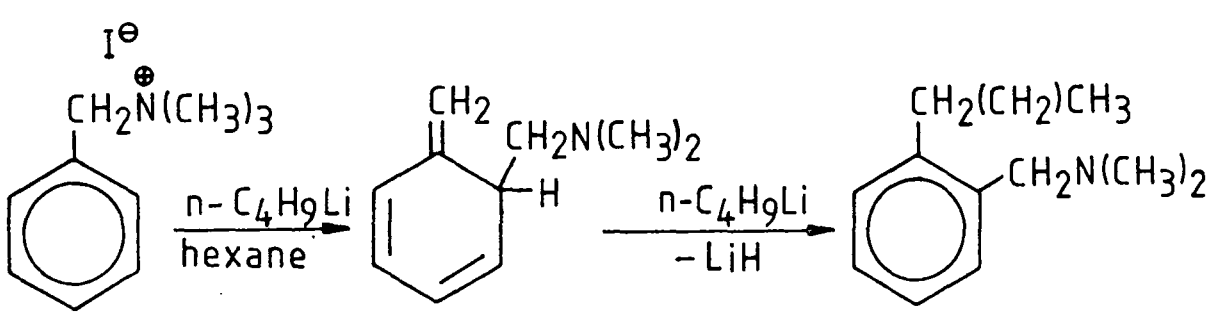


(168)



(169)

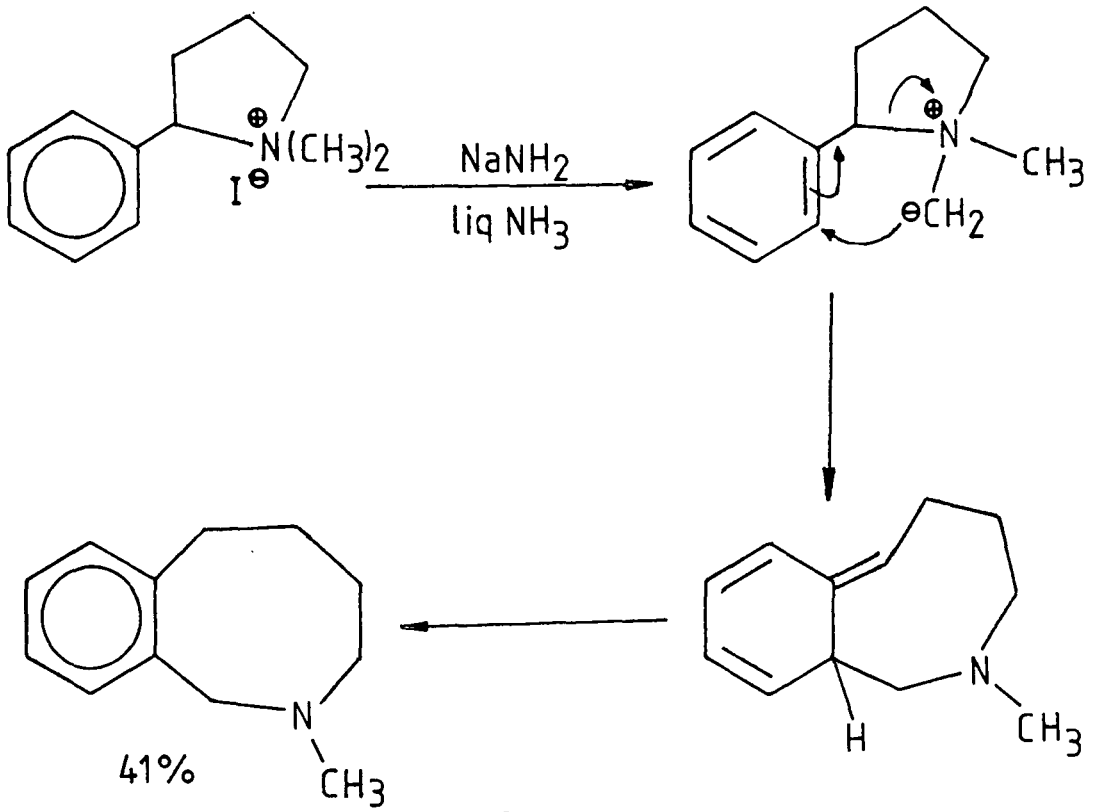
Scheme 84



(159) (170) (171)

Scheme 85

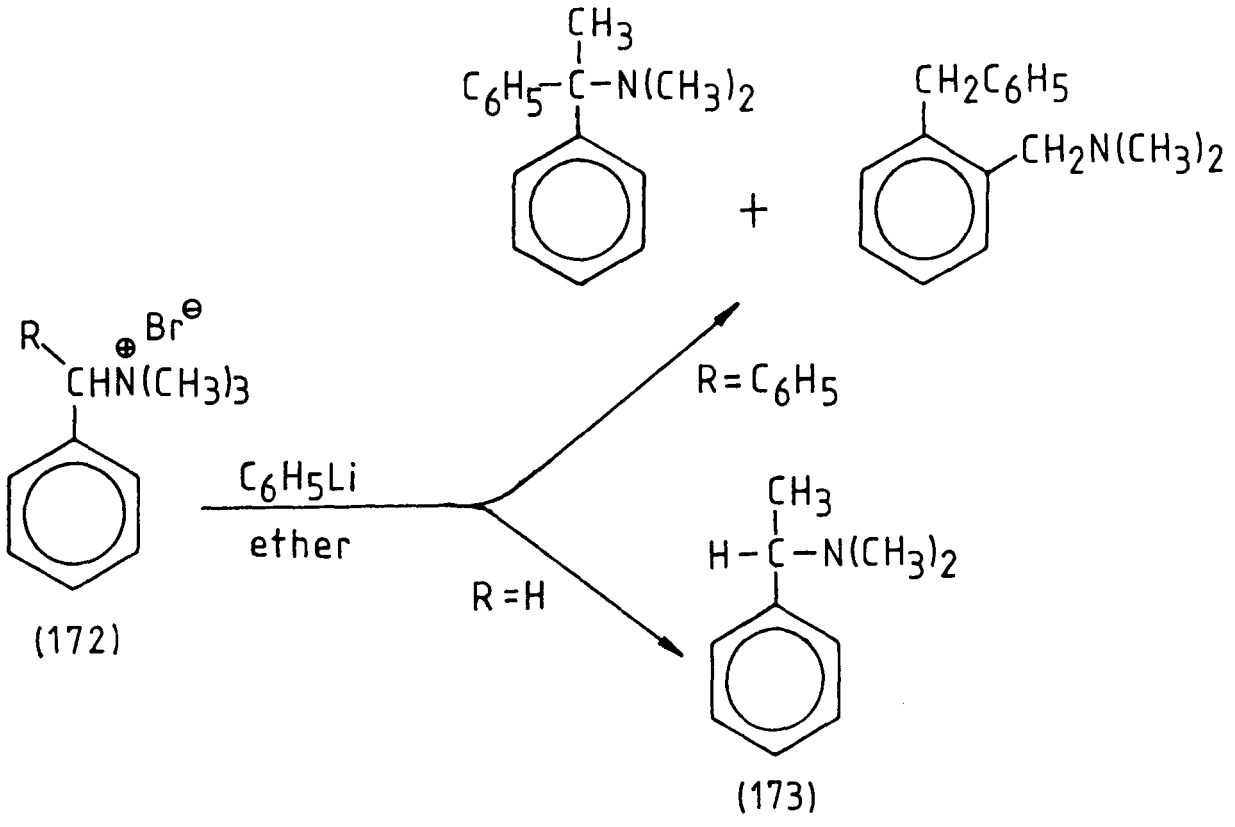
The Sommelet-Hauser rearrangement is usually carried out with three methyl groups on the nitrogen, but other alkyl groups can be used, although competing products may be obtained, the more stable ylide leading to the major product.[67,74] In some cases, where a suitable ammonium salt is used ring expansion occurs.[75] Scheme 86.



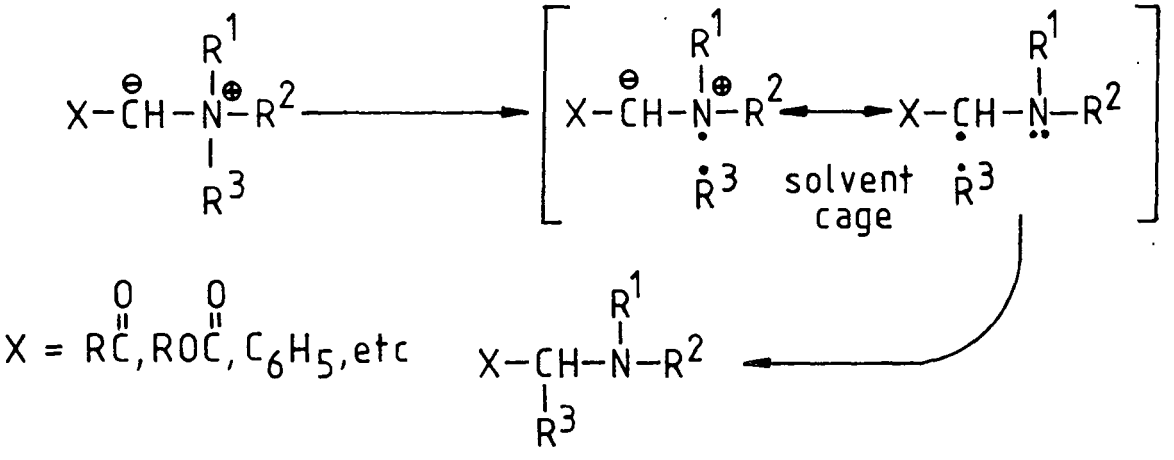
Scheme 86

A number of processes can compete with the Sommelet-Hauser rearrangement, but the most important, and commonly encountered, is the Stevens rearrangement,[58] a reaction involving a '[1,2]' shift of one of the alkyl groups from the quaternary nitrogen atom to the alpha-carbon atom of a second alkyl group upon treatment of the salt with base. Thus, the trimethyl ammonium bromide (172 R=H) with phenyllithium in ether gives only the Stevens product (173),[76] whereas the bromide (172 R=C_6H_5) gives both Stevens and Sommelet-Hauser products,[61] Scheme 87.

The mechanism for this process is believed to involve a radical-pair cage mechanism,[77] as outlined in Scheme 88. Suitable choice of conditions can, however, limit the formation of Stevens rearrangement products since the dissociation pathway is a much higher energy route when compared to the highly ordered transition state pathway for the Sommelet-Hauser rearrangement.[58] Stevens products can thus be limited by using lower reaction temperatures.[78]



Scheme 87

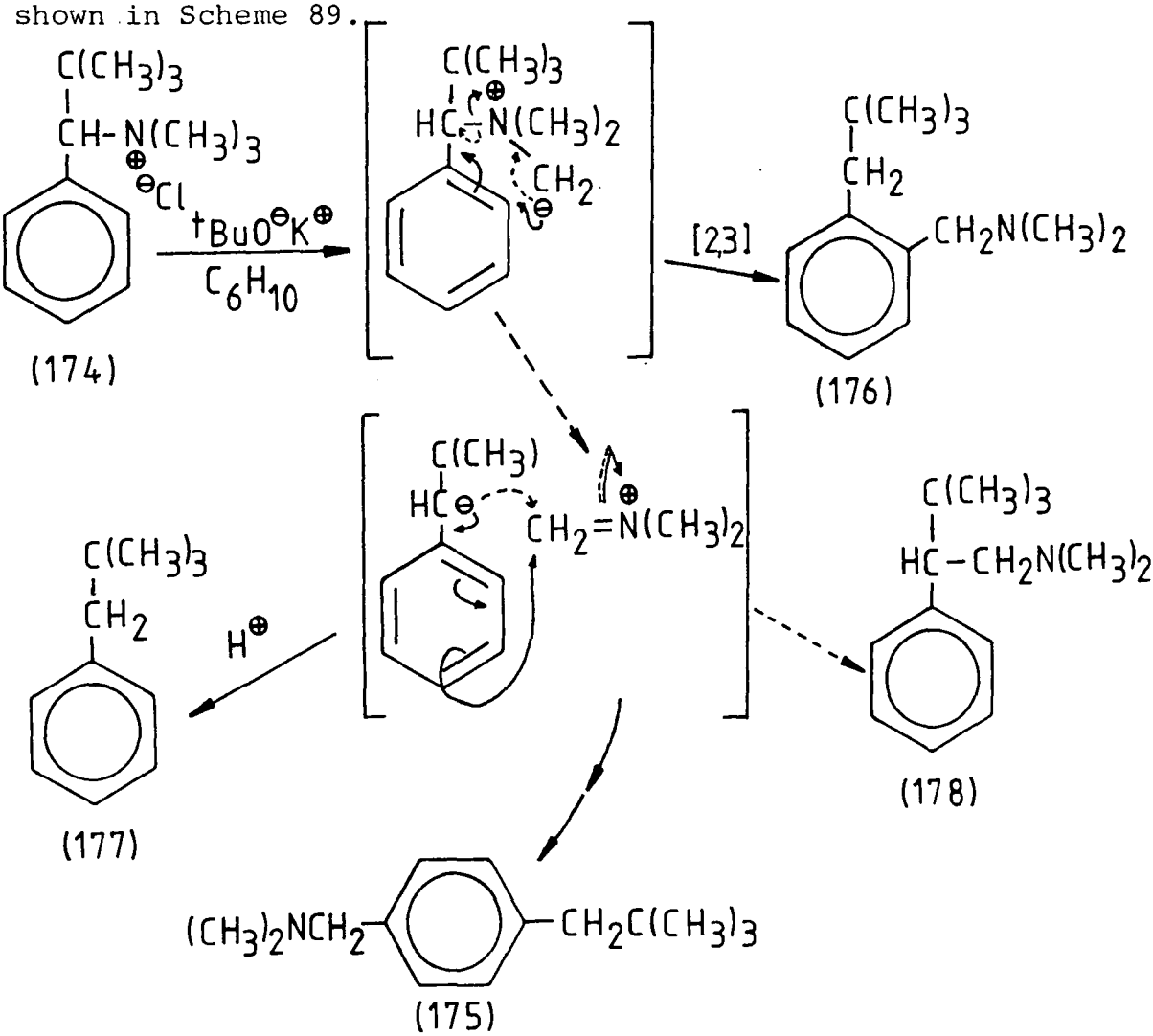


Scheme 88

The reaction medium also plays an important role. Polar solvents like liquid ammonia and dimethyl sulphoxide, where the salts are generally soluble, tend to favour the formation of Sommelet-Hauser rearrangement products, whereas systems such as an alkyl lithium in a hydrocarbon solvent in general yield Stevens rearrangement products.[78]

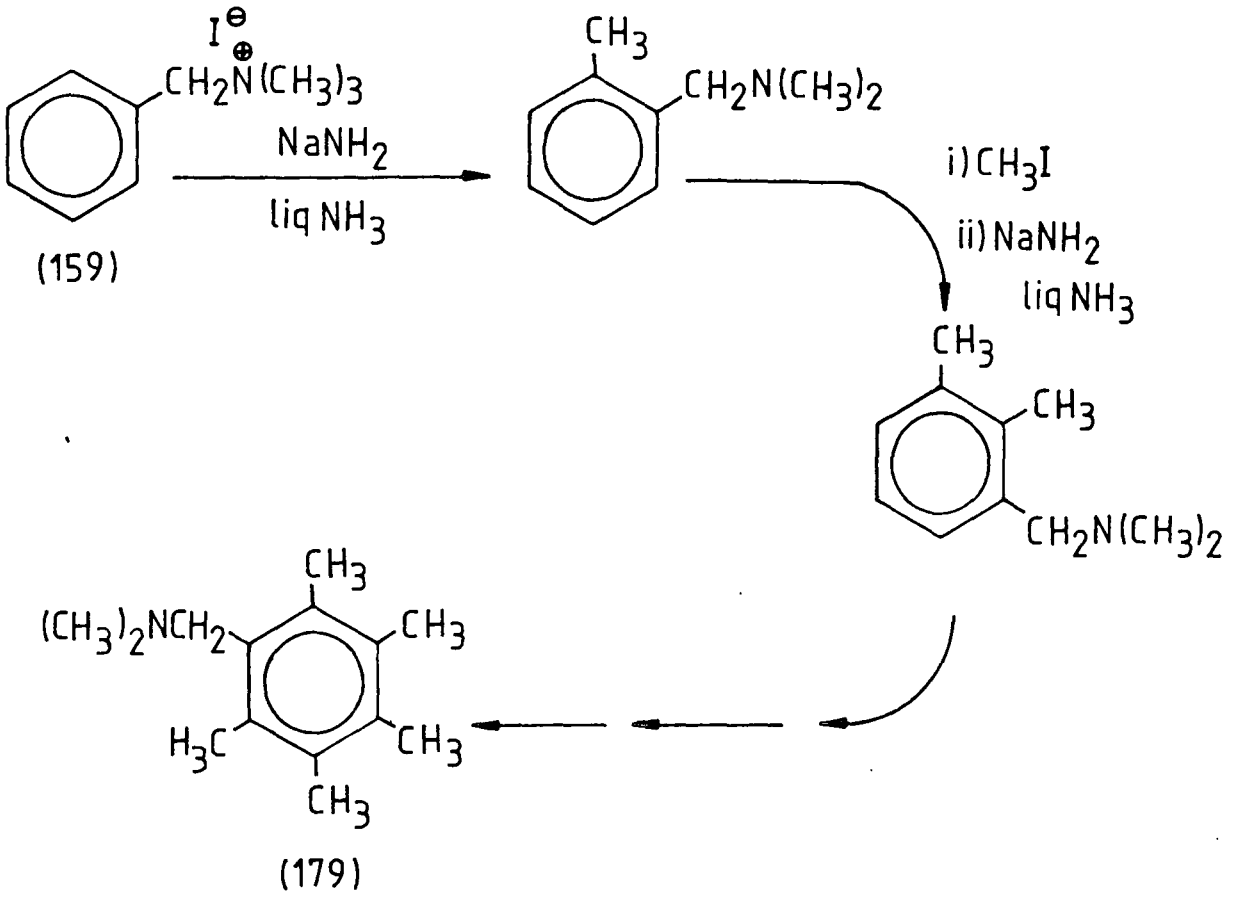
Dissociation-recombination mechanisms involving ion-pairs and radical pairs have also been suggested for the Sommelet-Hauser rearrangement,[62,79] but the general propensity for rearrangement only occuring to the ortho-position

is strong argument against such mechanisms. In some special cases, however, small amounts of para-substituted products are obtained. The hindered ammonium salt (174)[80] reacts with a variety of bases to give small amounts (0-9%) of the para-substituted compound (175) along with the Sommelet-Hauser(176) and other products, (177) and (178). The mechanism for formation of (175) is not certain. It was demonstrated that it does not come from further rearrangement of the ortho-product, and so may well involve a dissociation-recombination mechanism as shown in Scheme 89.



Scheme 89

The rearrangement process can also be used to provide polysubstitution products. This is achieved by successive remethylation of the product followed by treatment with base. This results in another ortho-substitution reaction. Thus

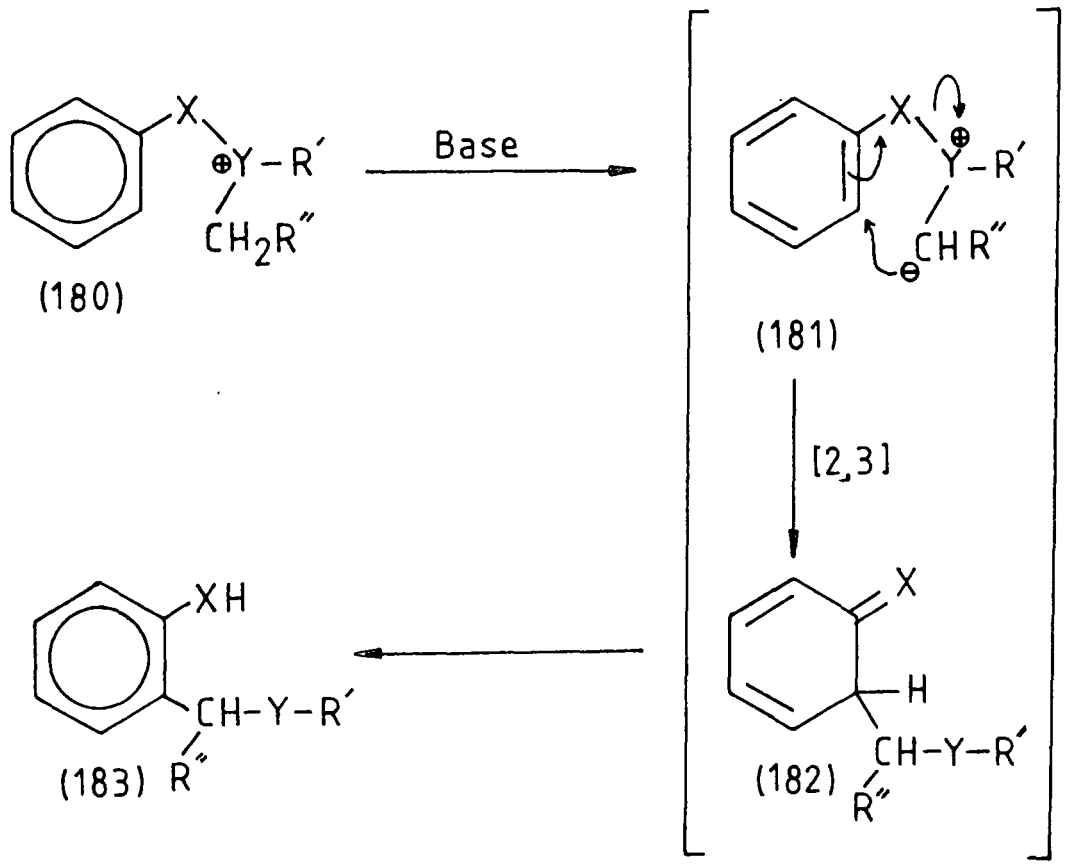


Scheme 90

the ammonium iodide (159) can be converted to the pentamethyl compound (179),[62] Scheme 90.

5.3 Rearrangements involving other Onium Salts

Sommelet-Hauser type rearrangements have also been shown to occur with other ylides derived from the base treatment of a wide variety of onium salts and have been widely used as a selective method for the ortho-substitution of the aromatic substrate. Thus, an onium salt of general formula (180), can be deprotonated to give the ylide (181), which in most cases spontaneously undergoes a [2,3] rearrangement to (182) followed by rearomatization to give (183), Scheme 91.



Scheme 91

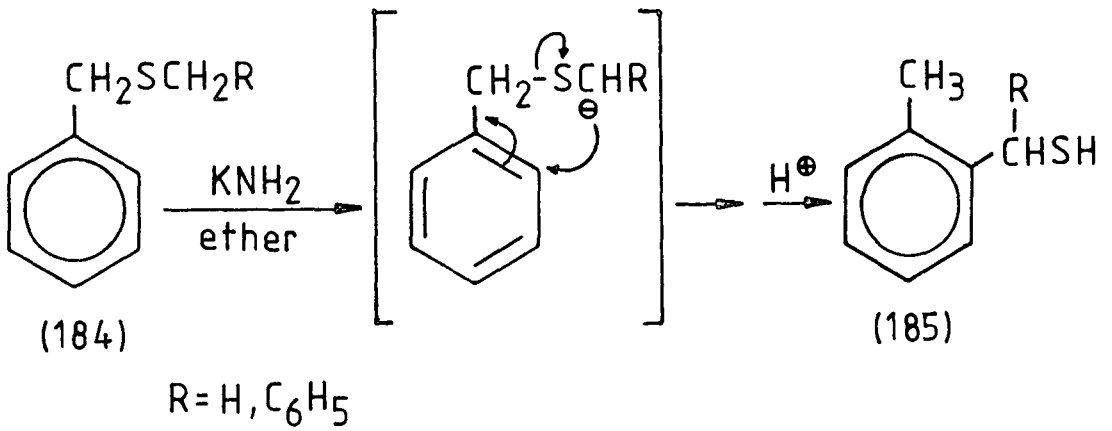
Various combinations of X and Y have been utilized for the rearrangement, and in some cases have been extenisvely studied.

$X = CH_2$,	Y = NR	The Sommelet-Hauser rearrangement
$X = CH_2$,	Y = S	(charged or uncharged on sulphur).
$X = CH_2$,	Y = Se	
X = O,	Y = S	
X = NR,	Y = S	
X = S,	Y = S	

5.3.1 $X=CH_2$, Y=S or Se

Benzylic compounds such as benzyl sulphides[63,81] (No R′ in Scheme 91, *i.e.* uncharged sulphur), benzyl sulphonium ions,[63,81,83-84] and indeed benzylic selenonium ions[82] have all been observed to undergo base promoted [2,3] sigmatropic rearrangements. Thus, treatment of the benzyl methyl sulphides

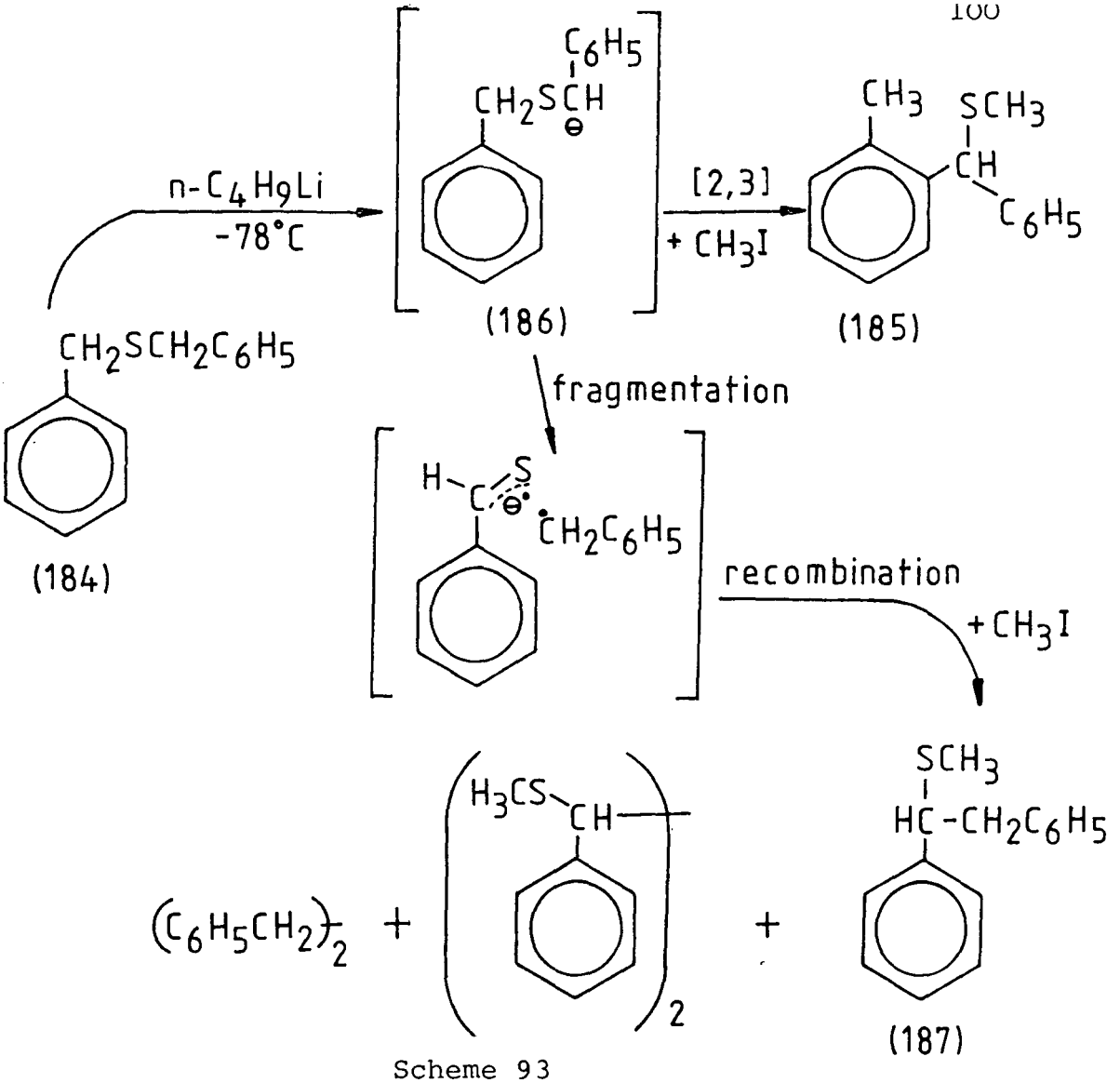
(184) with potassium amide in refluxing ether gives the mercaptans (185), Scheme 92.



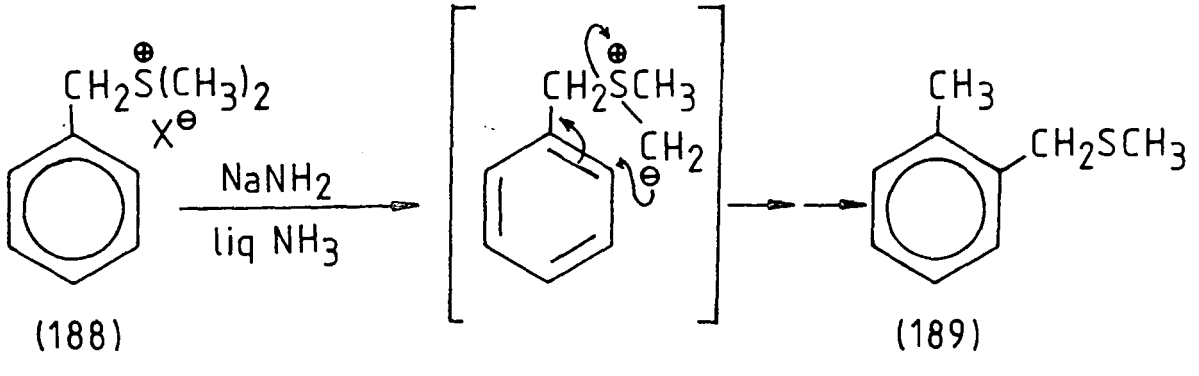
Scheme 92

As in the Sommelet-Hauser rearrangement, the type of rearrangement observed was shown to be dependent on the temperature. Dibenzyl sulphide (184:R=C_6H_5) at low temperature (-78°C) with n-butyl lithium as the base gave the carbanion (186).[81] On increasing the temperature to just above -78°C only the Sommelet-Hauser product (185:R=C_6H_5) was observed (trapped by the addition of methyl iodide). On carrying out the reaction at 11°C, however, dissociation-recombination products, including the Stevens product (187) began to compete, Scheme 93.

Sulphonium ylides bearing aromatic nuclei also undergo Sommelet-Hauser type rearrangements.[63,81,83-84] Treatment of the sulphonium salt (188) with potassium amide in liquid ammonia gave the ortho-substituted compound (189),[63] Scheme 94. As with the sulphides (184), Stevens type rearrangement are also observed for sulphonium ylides and often compete with Sommelet-Hauser products.[85]



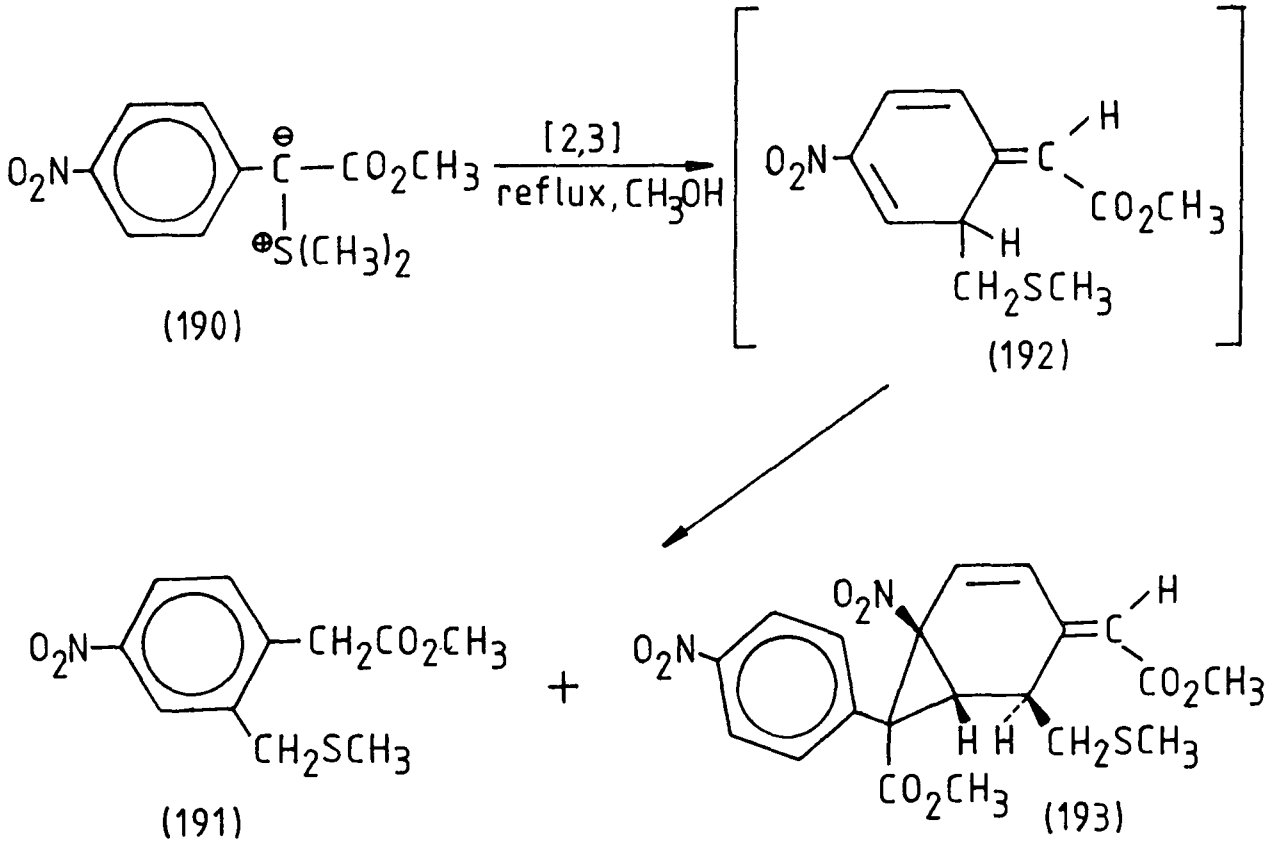
Scheme 93



Scheme 94

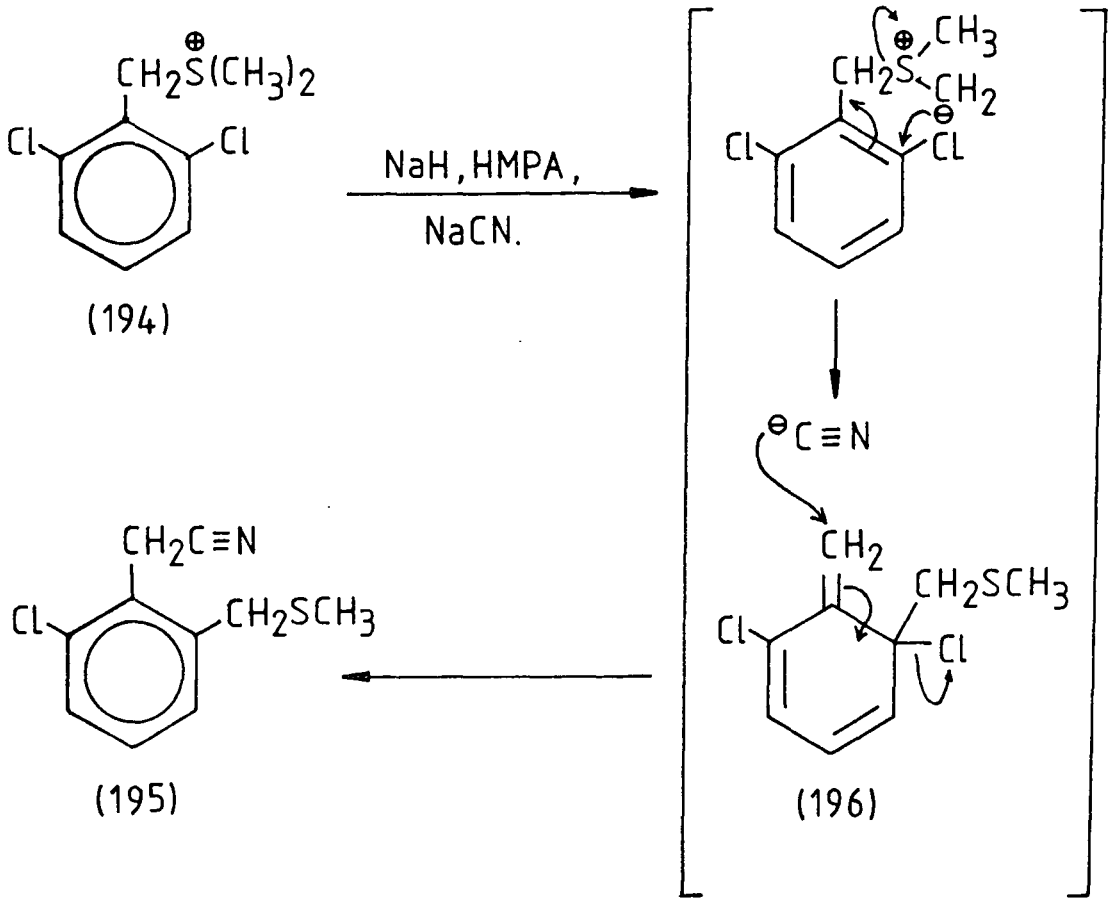
The exomethylene intermediates involved in these reactions have not been isolated, but their existence has been demonstrated in a number of other reactions. Rearrangement of the stabilized methoxycarbonyl sulphur ylide (190),[86] re-

sulted not only in the expected ortho-substituted product (191), but also one which resulted from the reaction of the ylide (190) with the exomethylene intermediate (192): the cyclopropane derivative (193), Scheme 95.



Scheme 95

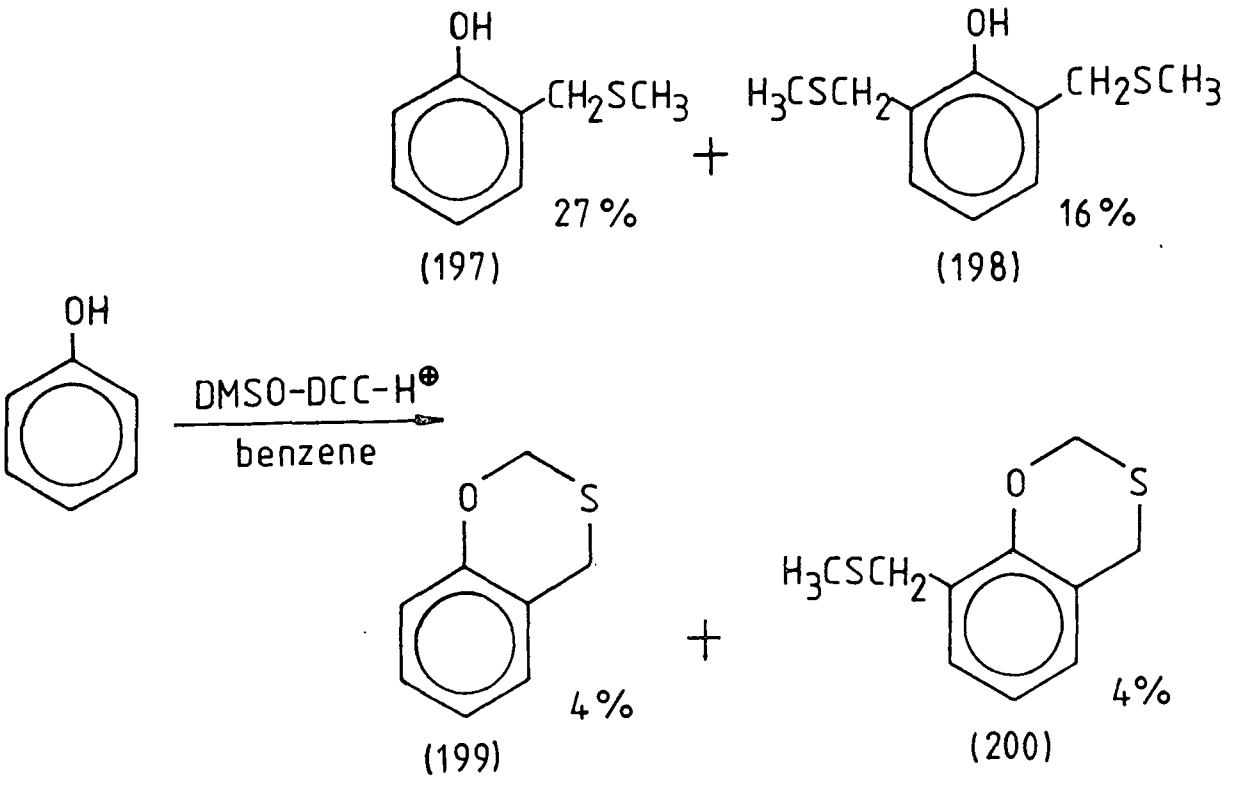
In the reaction of the 2,6-dichlorocompound (194) with sodium hydride in hexamethylphosphoric triamide (HMPA), carried out in the presence of sodium cyanide,[87] the product obtained (195) was one resulting from nucleophilic attack by cyanide on the exomethylene intermediate (196), Scheme 96. Other nucleophilic reagents were successfully reacted in this way and the method thus provides a useful synthetic procedure for the introduction of a functionalized methyl substituent ortho- to the $-CH_2SCH_3$ group.



Scheme 96

5.3.2 X=O, Y=S

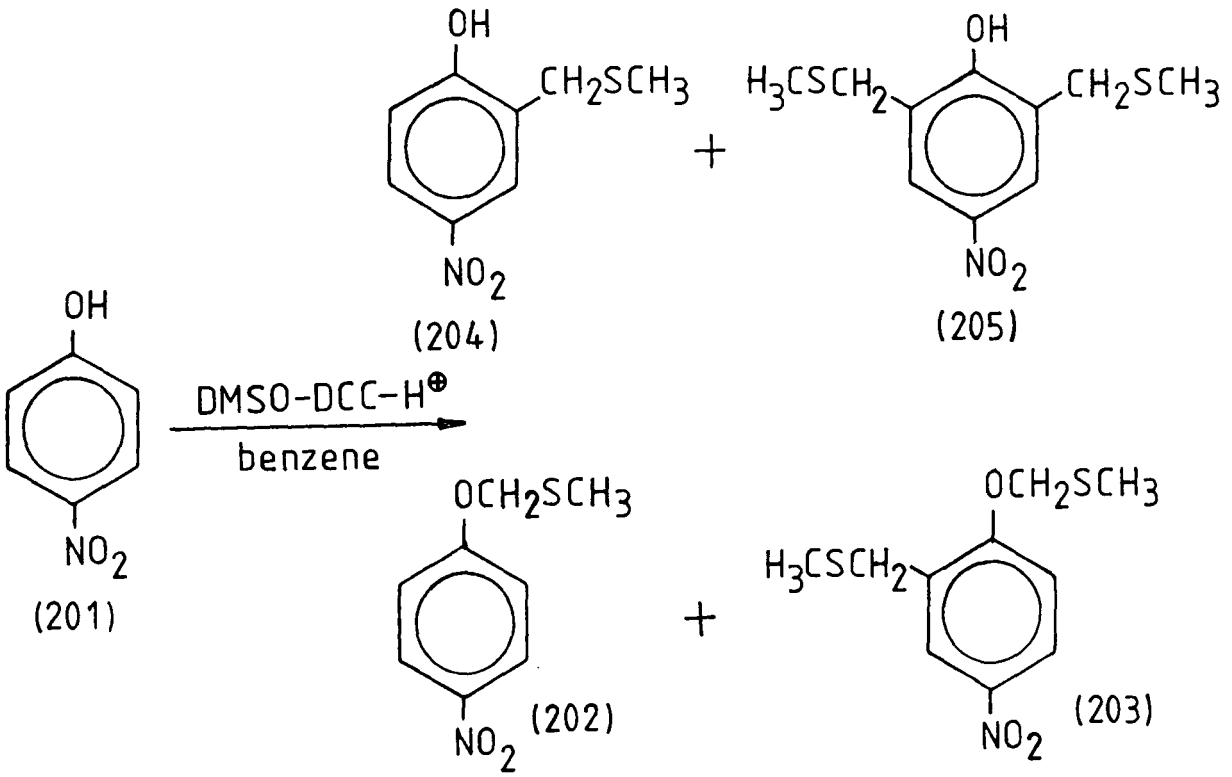
In the early 1960's, Moffatt developed a mild and efficient method for the oxidation of primary and secondary alcohols using dimethyl sulphoxide and dicyclohexylcarbodiimide (DMSO-DCC).[88-89] However, during the attempted acid-catalysed Moffatt oxidation of phenols, the principal products were not the expected quinones but phenols substituted in one or both of the available ortho-positions on the aromatic ring by thiomethoxymethyl groups.[90] Thus the reaction of phenol and DMSO-DCC with anhydrous orthophosphoric acid as the acid catalyst afforded both the mono- (197) and di- (198) substituted phenols, Scheme 97. In addition to these main products, two further minor components were also isolated, (199) and (200), both containing the 5,6-benzo-1,3-oxothian ring structure.



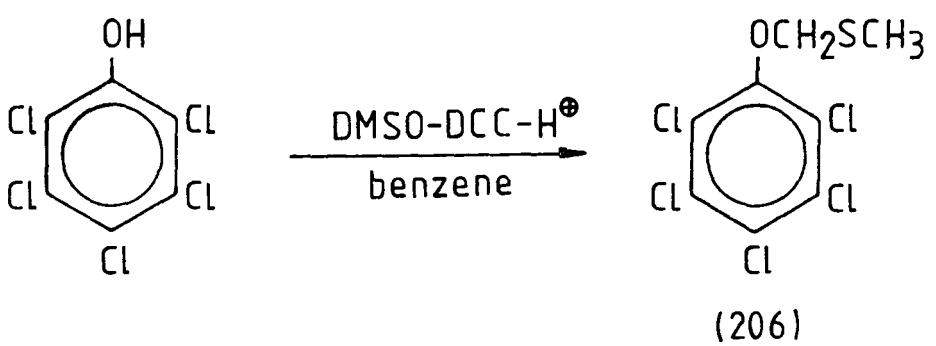
Scheme 97

Similar results were also obtained using pyridinium-trifluoroacetate as the acid catalyst.[91]

With the more acidic phenols the reaction often led to the formation of small amounts of thiomethoxymethyl ethers. Thus 4-nitrophenol (201) gave rise to the two ethers (202) and (203) along with the expected mono- and di-substituted phenols, (204) and (205) respectively,[90] Scheme 98. Of particular significance is the reaction of the even more acidic pentachlorophenol with DMSO-DCC and anhydrous orthophosphoric acid which resulted in the formation of the ether (206) (60%) as the only product,[92] Scheme 99.

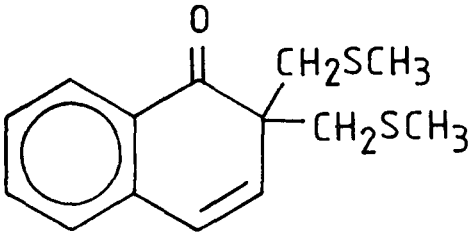


Scheme 98

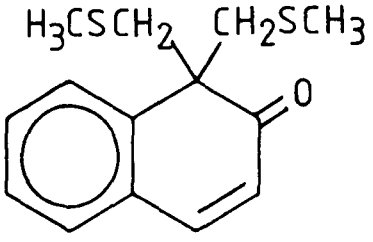


Scheme 99

The reaction of the 1- and 2-naphthols were different again, the major products obtained being the doubly alkylated dihydronaphthalenones (207) and (208) respectively.



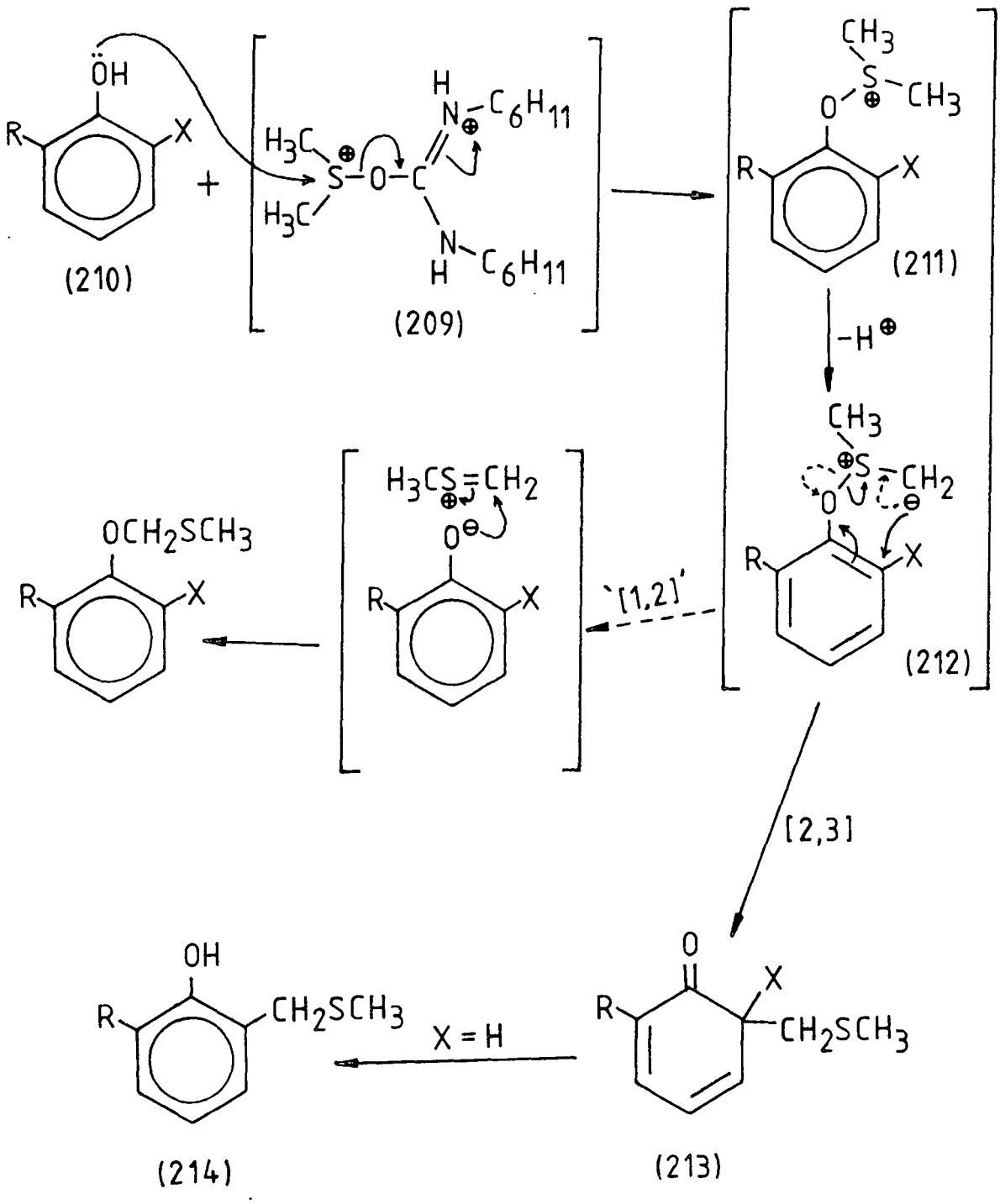
(207)



(208)

The mechanism proposed for the formation of the products observed[91,93] is similar to that already described for the Sommelet-Hauser rearrangement. The DCC is first protonated by the acid and then attacked by the DMSO with the formation of an activated DMSO-DCC complex (209). This then suffers 'backside' displacement on the sulphur atom by the phenol (210) resulting in the generation of the aryloxy-sulphonium cation (211), and the precipitation of the urea derivative dicyclohexyl urea (DCU). Loss of a proton from (211) then gives the ylide (212). A [2,3] sigmatropic rearrangement of (212) then leads to the ortho-dienone (213) which rapidly enolizes (X=H) to give the ortho-substituted phenol (214). The thiomethoxymethyl ethers are also derived from the ylide (212) and it has been suggested that their rearrangement is the result of a fragmentation-recombination mechanism,[91] similar to the Pummerer rearrangement,[94] a reaction resulting in an overall [1,2] shift, Scheme 100.

Obviously, by repeating the same process on the product phenol (214) itself, the disubstituted derivative (214, R=CH_2SCH_3) would be formed. A similar explanation also accounts for the formation of the naphthalenones (207)

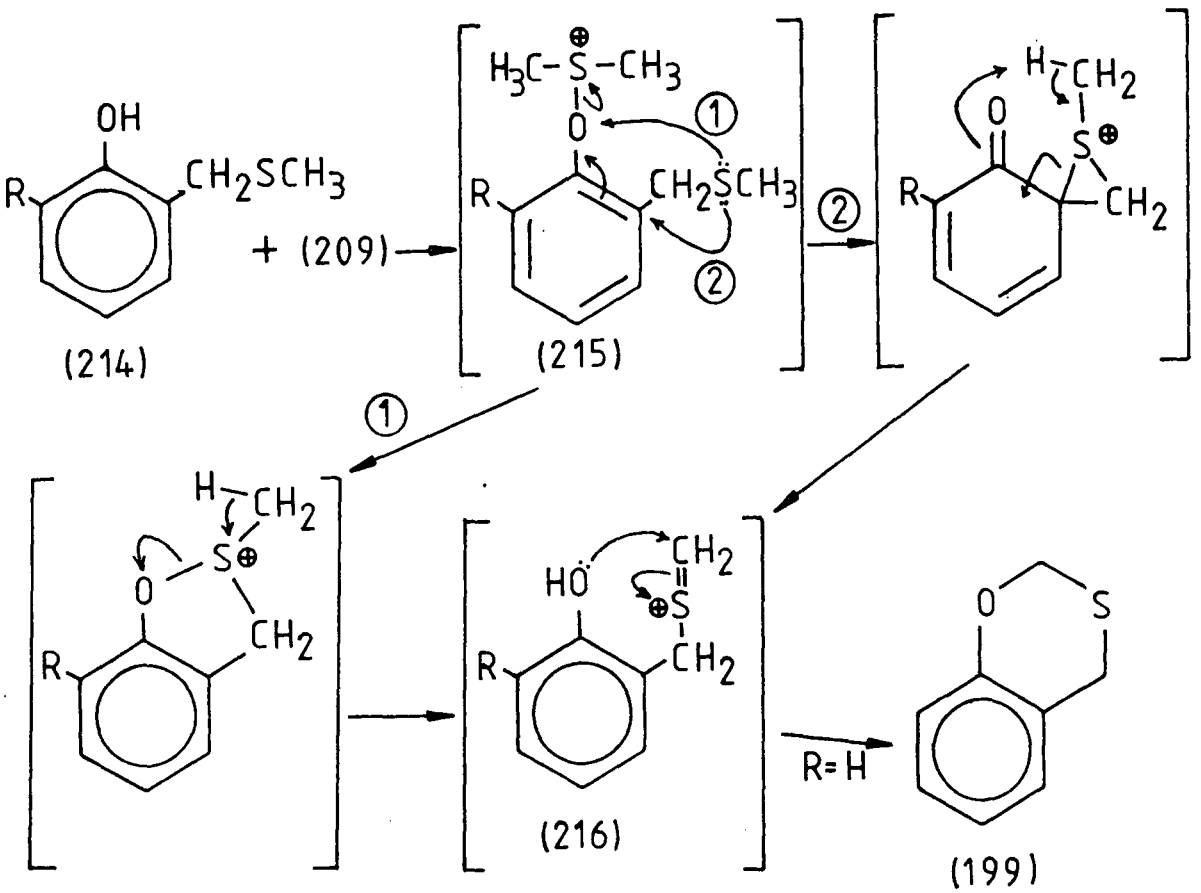


Scheme 100

and (208), where the second thiomethoxymethyl group can only migrate to an already substituted position.

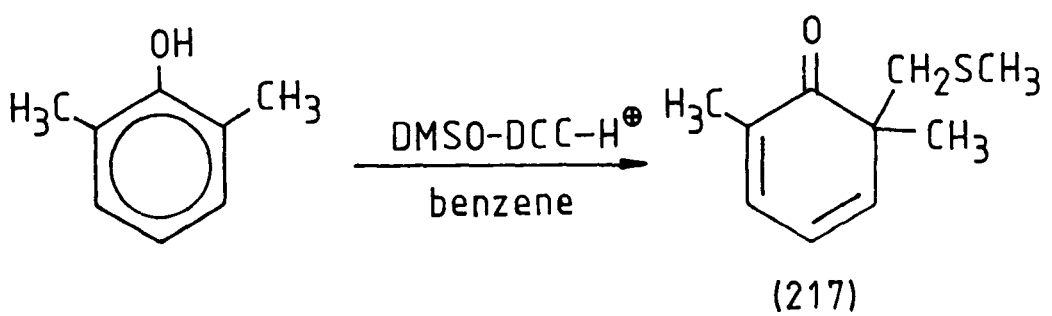
Formation of the 1,3-benzoxathian derivatives was explained[93] by the further attack of the initially formed phenol product (214) on the DMSO-DCC-H^+ adduct (209) giving the sulphonium cation (215). This is then transformed to the cation (216) by loss of dimethyl sulphide by either nucleophilic displacement on oxygen followed by a Pummerer

rearrangement (route (1)) or by a nucleophilic 'ortho' attack (route (2)) as shown in Scheme 101.



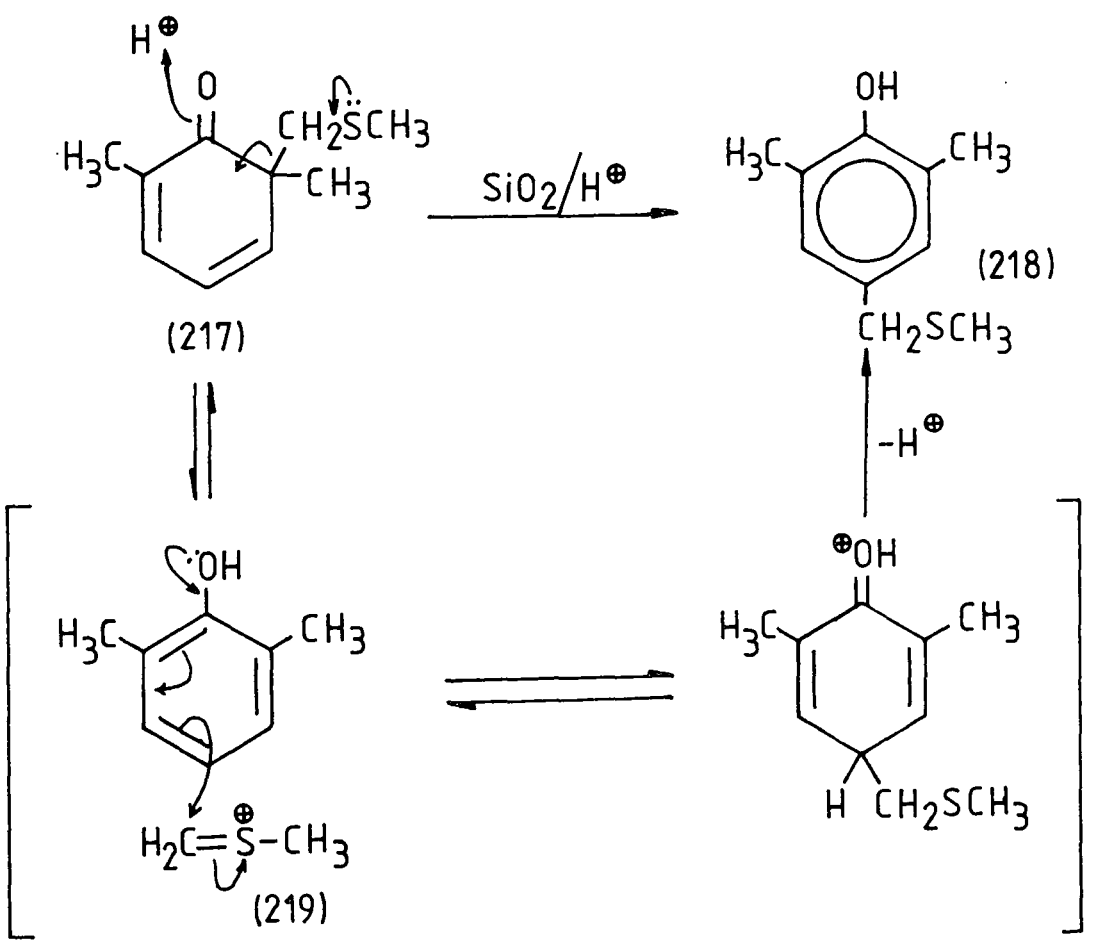
Scheme 101

The intermediacy of dienone type compounds like (213) in the formation of the ortho-substituted products was shown in the reaction of phenols in which both available ortho-positions were substituted therefore preventing re-aromatization. Thus, reaction of 2,6-dimethyl phenol with DMSO-DCC-H^+ gave the dienone (217),[90] Scheme 102.



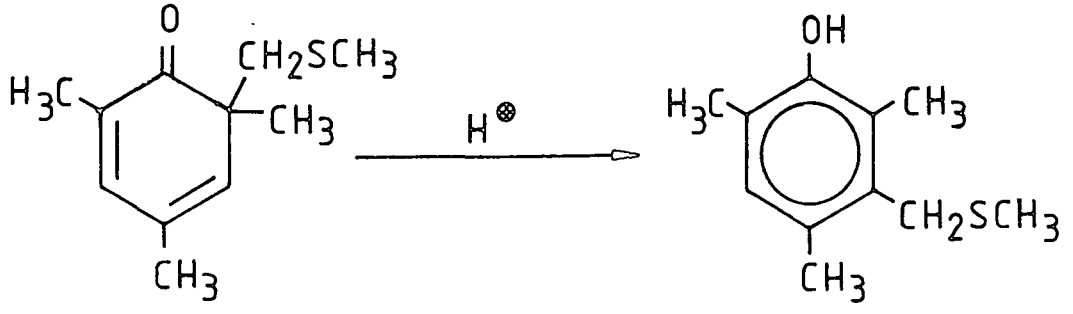
Scheme 102

The dienones like (217) were found to have limited stability, however, undergoing Diels-Alder dimerization on standing.[92] More interesting, chromatography on silicic acid or even storage over silicic acid led to complete rearrangement of the dienones. Thus, the dienone (217) gave the parasubstituted phenol (218). [Other workers using different reaction conditions for the [2,3] rearrangement (using pyridinium trifluoroacetate as the acid catalyst) were only able to isolate the parasubstituted phenol (218), as the reaction product, the dienone (217) not being observed[93]]. The mechanism for the rearrangement[93] is unclear, but would appear to involve a dissociation-recombination mechanism with the involvement of the methylmethylene sulphonium cation (219), Scheme 103.



Scheme 103

In the case of the dienone (220) (resulting from rearrangement of the ylide from 2,4,6-trimethyl phenol) acid catalysed rearrangement gave the meta-substituted phenol (221),[92] Scheme 104.

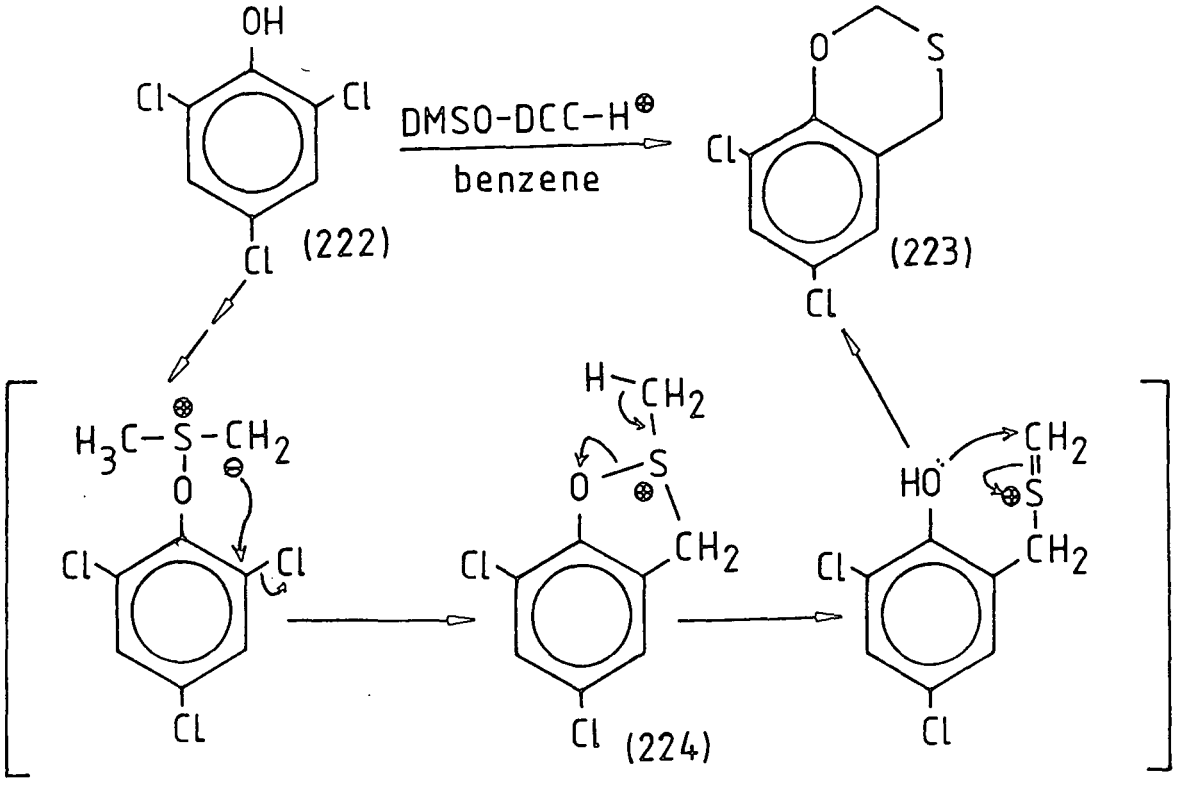


(220) (221)

Scheme 104

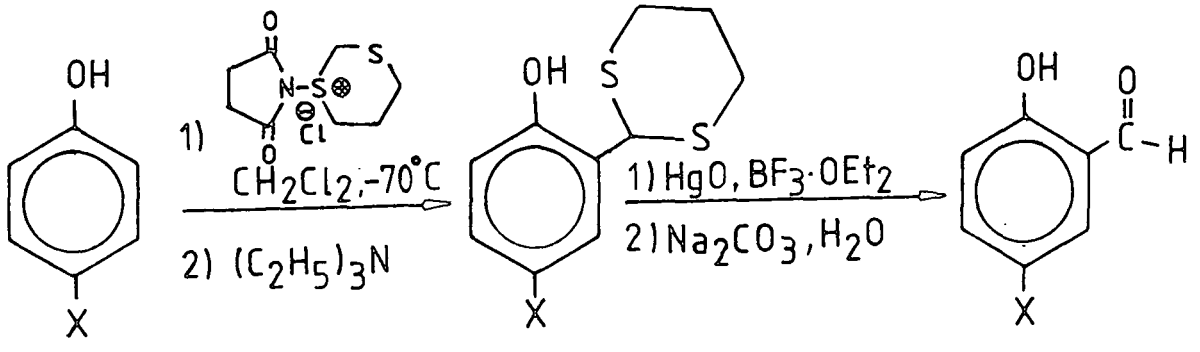
Phenols having chlorine atoms, and not alkyl groups, in the 2- and 6-positions behaved differently, the major products from their reaction with DMSO-DCC-H^+ being chloroderivatives of 1,3-benzoxathians. Thus 2,4,6-trichlorophenol (222) gave the 1,3-benzoxathian (223) (42%),[92] a relatively high yield in contrast to the low yield for the hydrogen analogues. This suggests that displacement of a chlorine ion from one of the ortho-positions to give the sulphonium ion (224) is a considerable driving force for product formation, Scheme 105 . [It is not obvious why pentachlorophenol (see Scheme 99) should behave in such a contrastint manner, only forming a '[1,2]' shift product].

With a view to the synthetic utility of the rearrangement observed in phenolic systems, Gassman and coworkers[95] developed a method for the high yield conversion of phenols to some ortho-substituted derivatives. Considerable success was



Scheme 105

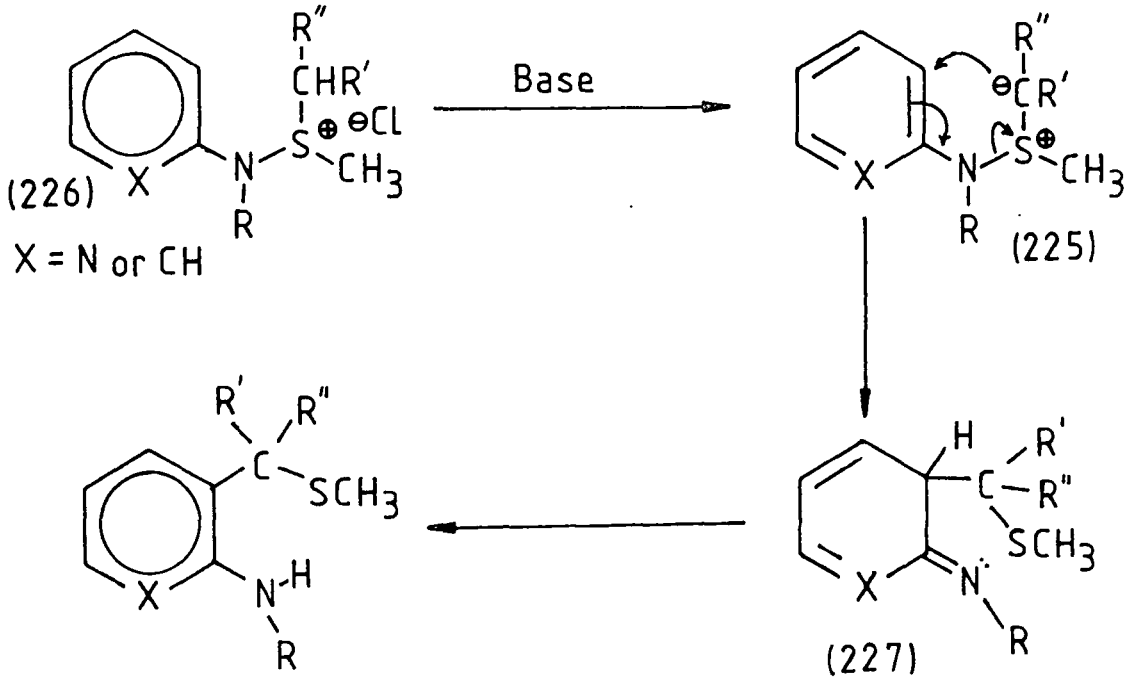
gained by using S-(N-succinimide) sulphonium chlorides instead of DMSO-DCC-H^+. One such synthetic route is shown in Scheme 106.



Scheme 106

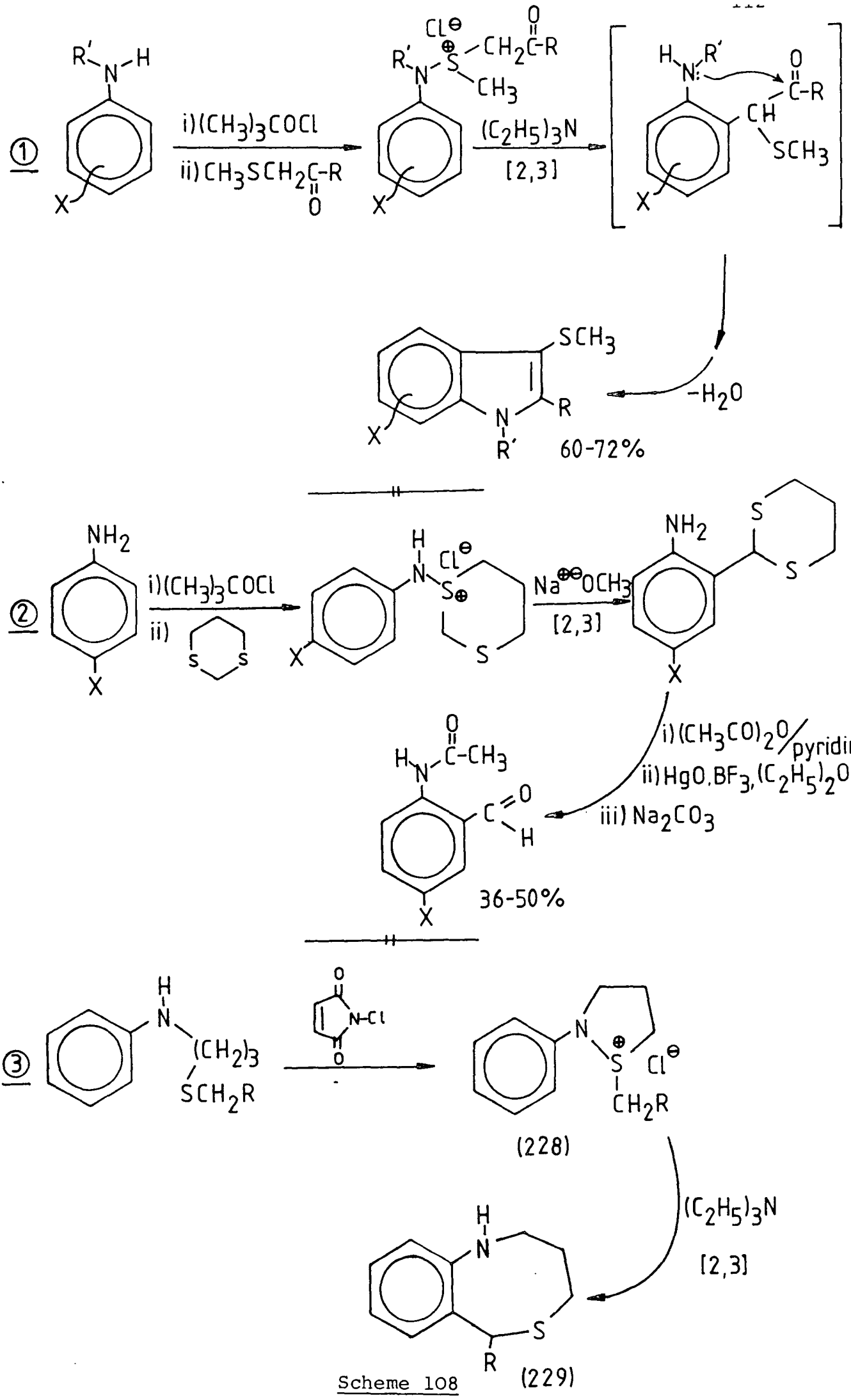
5.3.3 X=N, Y=S

Gassman and coworkers have also made extensive synthetic use of the rearrangement of ylides derived from N-arylazasulphonium salts for the specific ortho functionalization of aromatic amines.[96-106] Mechanistically the key step in the process involves a [2,3] sigmatropic rearrangement of the ylide (225) derived from the base treatment of an azasulphonium salt (226), the key intermediate in the process being the cyclohexadienoneimine (227), Scheme 107.



Scheme 107

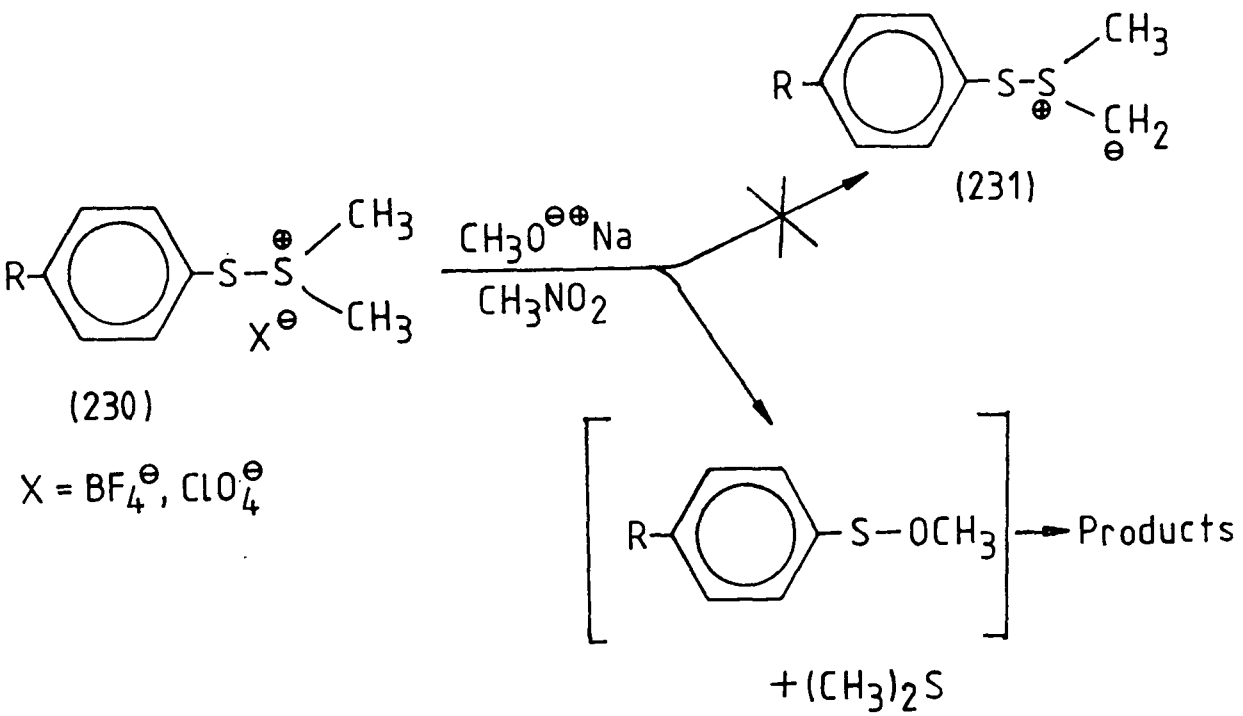
By employing a suitable sulphonium salt, this rearrangement has been used to provide high yield conversions of aromatic amines into ortho-alkylated anilines, indoles and oxindoles. The use of the cyclic azasulphonium salt (228) results in the formation of the thiazocine derivative (229).[107] These reactions are shown in Scheme 108.


①
i)(CH3)3COCl
ii) CH3SCH2C-R
(C2H5)3N
[2,3]
-H2O
60-72%
②
i)(CH3)3COCl
ii)
Na⊕⊖OCH3
[2,3]
i) (CH3CO)2O/pyridine
ii) HgO, BF3, (C2H5)2O
iii) Na2CO3
36-50%
③
(228)
(C2H5)3N
[2,3]
(229)

Scheme 108

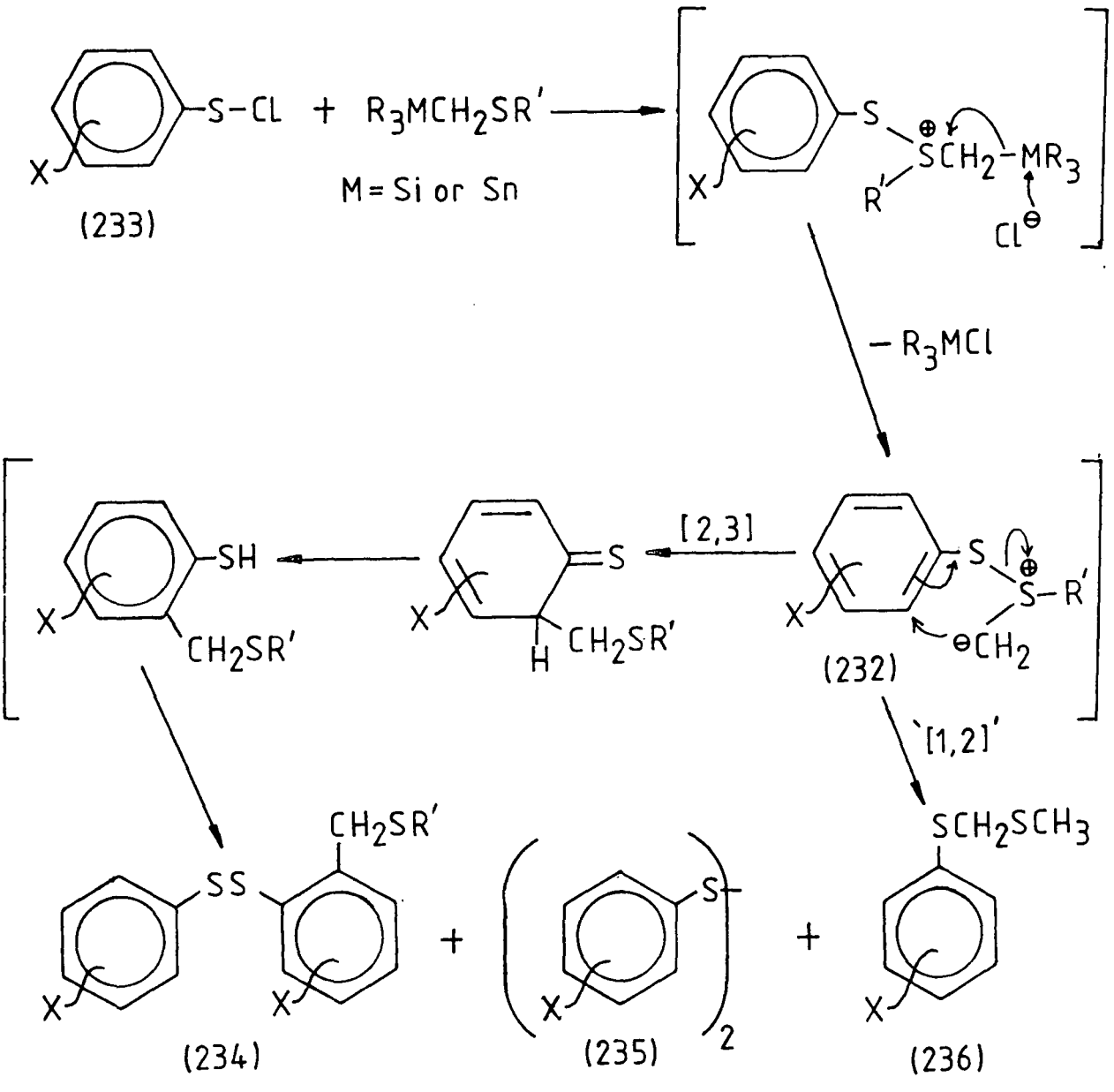
5.3.4 X=S, Y=S

Extending the generality of this type of rearrangement still further, it has now been shown that Sommelet-Hauser type rearrangements occur in S-arylthiosulphonium ylides.[108] The thiosulphonium salts (230) have previously been prepared,[109] but base treatment on them resulted only in attack at neutral sulphur with displacement of dimethyl sulphide, no ylide formation (231) being observed, Scheme 109.



Scheme 109

Ylides of type (231), (232), have now been prepared however by the reaction of arenesulphenyl chlorides with organo tin and silicon compounds. These spontaneously undergo a [2,3] sigmatropic rearrangement under the reaction conditions with the subsequent formation of the disulphide compounds (234),[108] Scheme 110. Compounds (235) and (236) are also formed during the reaction, (236) by a Stevens type rearrangement of (232).



Scheme 110

In the Chapters that follow (Chapters 6-8) the attempted [2,3] rearrangements of ylides derived from a variety of readily accessible derivatives of fluorinated phenols, naphthols, pyridols, pyrimidols, anilines and thiophenols are described. The ylides are formed by deprotonation of the sulphonium salts obtained from the reaction of these fluorinated compounds with activated dimethyl sulphoxide. Similar oxo-, aza-, and thiosulphonium salts and the rearrangements of their respective ylides were described in Sections 5.3.2, 5.3.3 and 5.3.4 respectively and provide the back-

ground to this work. Unless otherwise described, any rearrangements observed are assumed to occur in the same manner as those outlined in this background work. The presence of an ortho-carbon bearing a fluorine or an ortho-nitrogen as the migration terminus for a potential [2,3] sigmatropic rearrangement reaction in these fluorinated ylides again precludes subsequent rearomatization. In Chapter Ten the formation and attempted rearrangement of 2,3,4,5,6-pentafluorobenzyl methyl sulphoxide by the sulphoxide-sulphenate rearrangement[110] and by a base promoted process, similar to that described in Section 5.3.1, are discussed.

CHAPTER SIX

THE REACTION OF FLUORINATED PHENOLS AND NAPHTHOLS WITH ACTIVATED DIMETHYL SULPHOXIDE SYSTEMS

6.1 Introduction

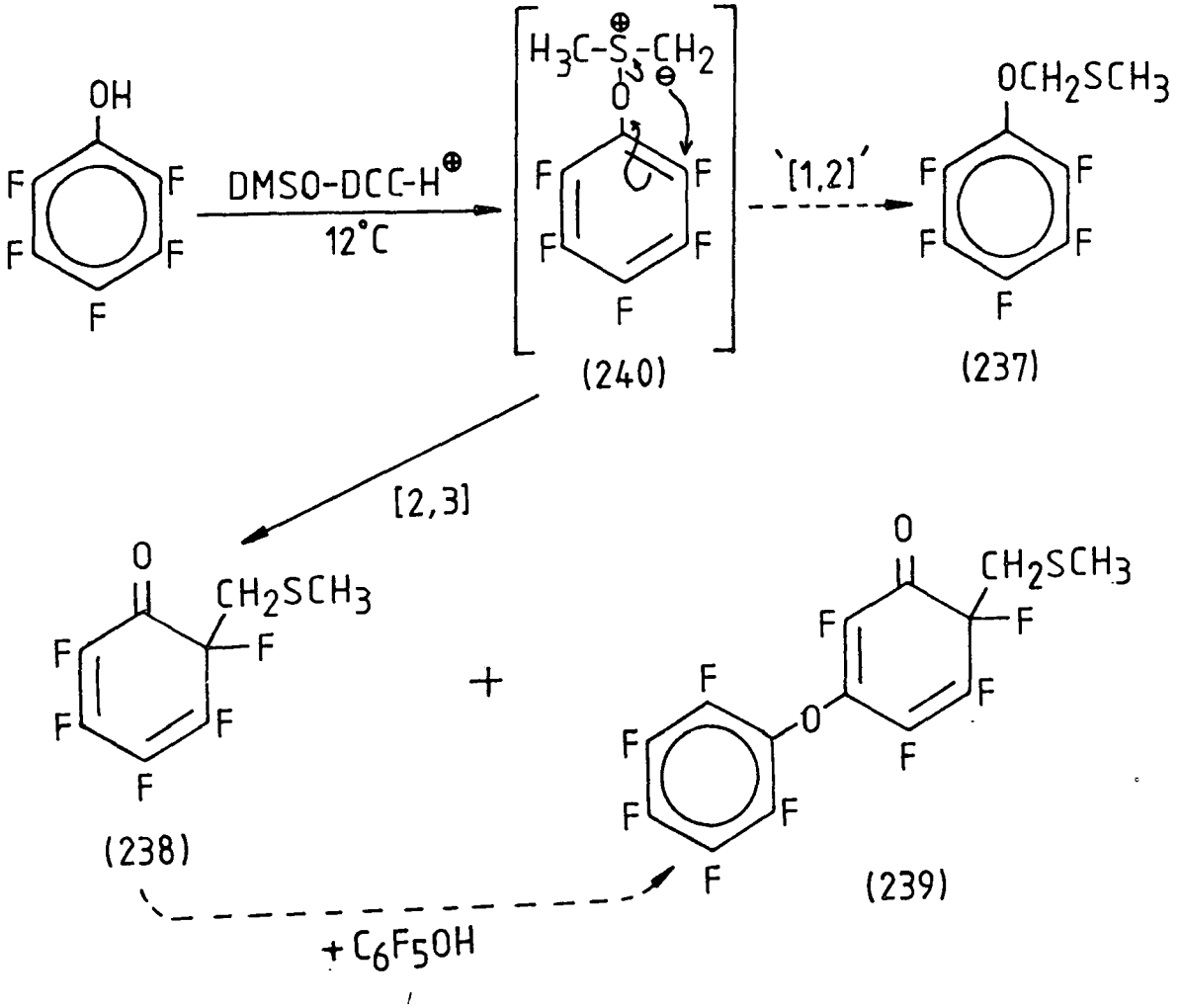
In his pioneering work, Moffatt[92] investigated the reaction of dimethyl sulphoxide activated by dicyclohexylcarbodiimide and anhydrous orthophosphoric acid (DMSO-DCC-H^+) with phenols substituted with chlorine atoms (see Section 5.3.2). These did not give dienone type compounds as products, but instead gave benzoxathians. The only exception to this was the more acidic pentachlorophenol (pk_a=5.2) which resulted only in ether formation, a reaction generally preferred for the more acidic phenols. The acidity of pentafluorophenol[111] (pka=5.5) is very similar to that of pentachlorophenol and on this basis alone it might be expected that its reaction with the DMSO-DCC-H^+ system would result in a similar process. The reactions of various fluorinated arenols with this system are described in the following sections.

6.2 Use of the Dimethyl Sulphoxide-Dicyclohexylcarbodiimide System

6.2.1 With Pentafluorophenol

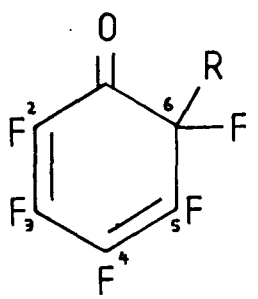
The reaction of pentafluorophenol with DMSO-DCC-H^+ in benzene [1:8 w/v phenol:(DMSO+benzene)] resulted in an uncontrollable exothermic process, the temperature of the reacting mixture rising 40°C above room temperature. A complex product resulted which was shown by analytical t.l.c. using methylene chloride as eluant to consist of at least eight components, none

of which could be isolated. Under more dilute conditions [1:194 w/v] with the temperature being maintained at or below 12°C three products were isolated: the thiomethoxymethyl ether (237) (6%), the cyclohexa-2,4-dienone (238)(13%) and (239) (36%) the pentafluorophenoxy substitution product of (238). These latter two components were both yellow in colour. Formation of the products can be rationalised in terms of the mechanism already described (see Scheme 100), compound (238) and its phenoxy derivative (239) being derived from a [2,3] sigmatropic rearrangement of the ylide (240), the ether (237) resulting from a '[1,2]' shift of (240) by a dissociation-recombination mechanism, Scheme 111.



Scheme 111

All of the fluorines in the dienone (238) have been assigned in the ^{19}F n.m.r. spectrum and are in very close agreement with the chemical shifts of similar compounds (241, R=OC_6F_5,[112] R=F[113]), with the expected exception of the fluorine at C-6. The chemical shift data for these compounds are shown in Table 5. As with the other compounds, the dienone (238) also showed large values of $J_{2F,5F}$ and $J_{5F,6F}$ (22 and 35Hz respectively) (*cf.* 21 and 23.5Hz for 241 R=F).



R = OC_6F_5, F

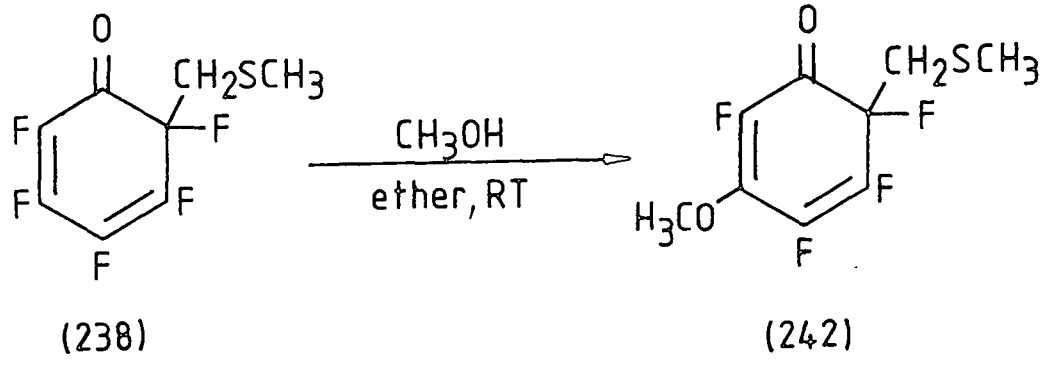
(241)

TABLE 5. Chemical Shifts (p.p.m. relative to $CFCl_3$)

	R=OC_6F_5	R=F	R=CH_2SCH_3
2-F	158.4	159.4	159.4
3-F	131.4	129.7	134.4
4-F	154.7	152.7	156.8
5-F	147.1	150.4	142.2
6-F	123.6	110.9	141.0

The site of substitution of the pentafluorophenoxy group in (239) was indicated by the absence of the lowest absorption at 134.4 p.p.m. (F-3), the chemical shifts for the other fluorines being almost identical to those of the dienone (238). The ease of replacement of the fluorine at C-3 was

also demonstrated in a separate experiment by the addition of methanol to an ether solution of (238) at room temperature which resulted in the formation of the 3-methoxy compound (242) (95%), Scheme 112. Other workers have also noted the



(238) (242)

Scheme 112

lability of the fluorine at the same site in related cyclohexa-2,4-dienone compounds.[113,114]

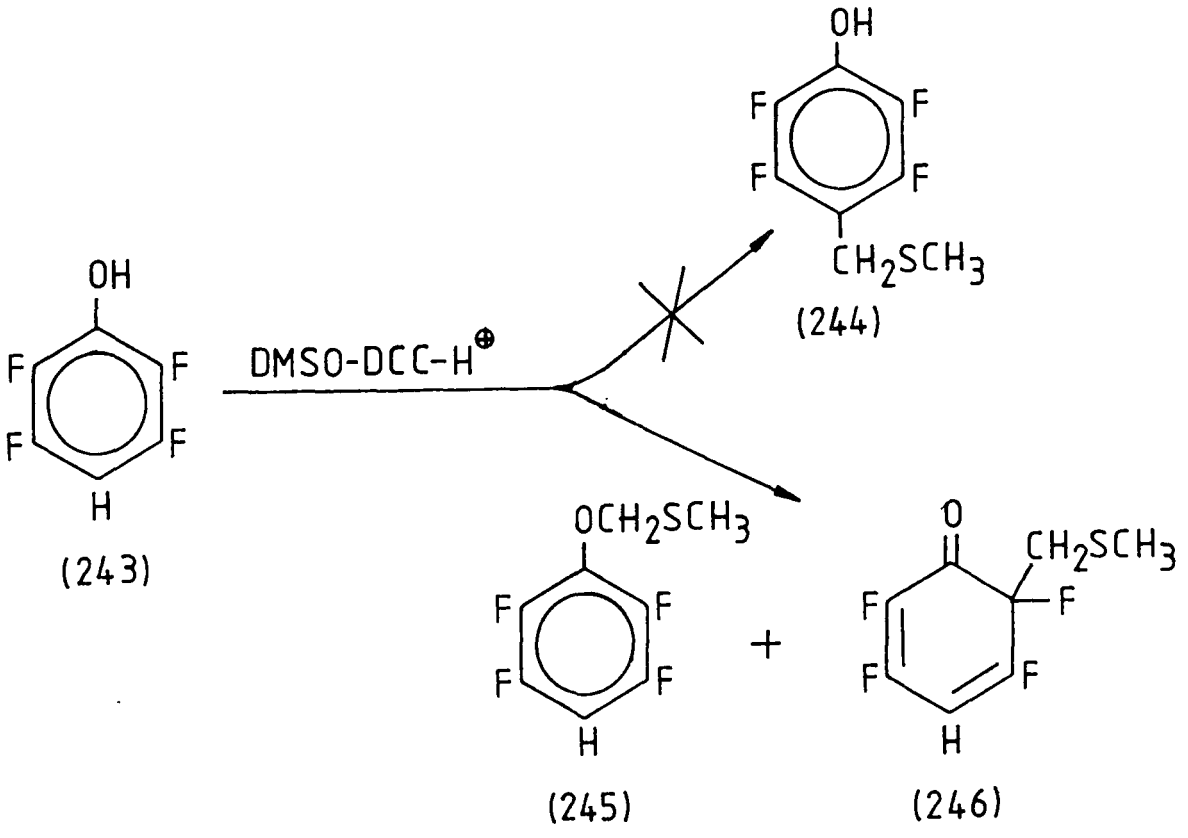
The controlled reaction of pentafluorophenol with DMSO-DCC-H^+ under less dilute conditions than those employed in the previous reaction [1:15 w/v phenol:(DMSO+benzene)] resulted in the formation of the phenoxy-substituted compound (239) as the only major product (45%), none of the dienone (238) being observed. Obviously under these more concentrated conditions, any of compound (238) formed is immediately attacked by unreacted pentafluorophenol to give (239). Two further minor components were isolated: the ether (237) and a bright yellow solid. The mass spectrum of this yellow compound had M^+ 614, the ^1H n.m.r. spectrum indicated twenty-seven protons in the ratio 22:3:2, and the ^{19}F n.m.r. spectrum showed nine fluorines with chemical shifts similar to those found in compound

(239). A 1:1 adduct between a DCC unit and the dienone (239) would account for these data, although the structure has not been investigated further.

The behaviour of pentafluorophenol with activated DMSO is thus in complete contrast to that previously observed using pentachlorophenol and the other halogen containing arenols. Formation of benzoxathians are not observed, and ether formation is only a minor competing process to the major reaction, a [2,3] sigmatropic rearrangement.

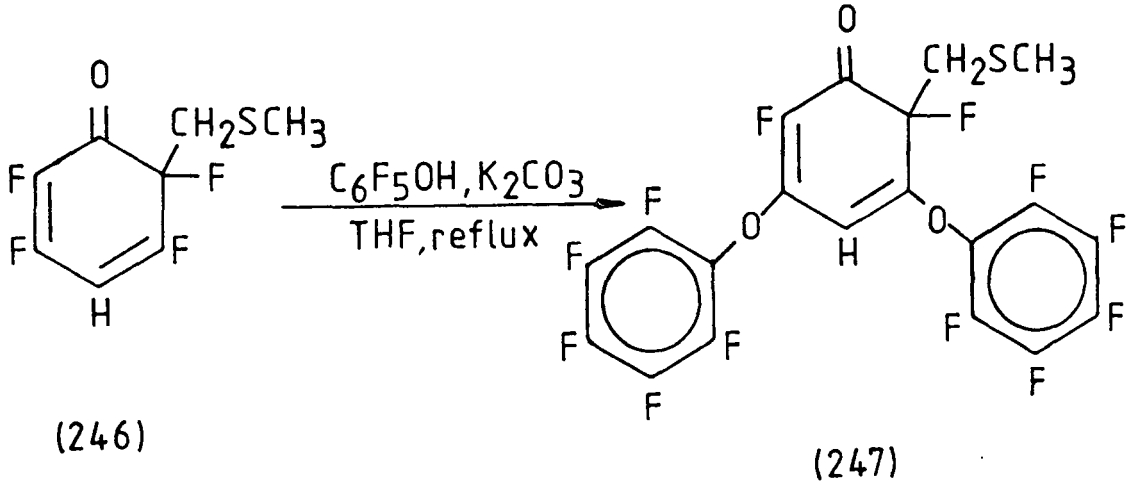
6.2.2 With 2,3,5,6-Tetrafluorophenol (243) [115]

Under moderately acidic conditions,[92] or even under the prevailing acid conditions of the DMSO-DCC-H^+ reagent,[93] dienones of the type (217) (see Scheme 103) rearranged to their isomeric para-substituted phenols. The intermediacy of the methylmethylenesulphonium cation ($CH_2=\overset{\oplus}{S}-CH_3$) was implicated in these processes, and it was of interest to test whether such a related electrophilic substitution product would be obtained from the reaction of the tetrafluorophenol (243), since the product formed would be the 4-thiomethoxymethyl phenol (244). The reaction of (243) with DMSO-DCC-H^+ under the same conditions as those employed for the reaction of pentafluorophenol resulted in the formation of two products: the thiomethoxymethyl ether (245) (8%) and the cyclohexa-2,4-dienone (246) (69%), analogues of (237) and (238) respectively, Scheme 113. None of the phenol (244) nor any of the phenoxy substitution product analogous to (239) were observed. Substitution of the fluorines in the dienone (246) was possible, however, since in a separate experiment (246) reacted with



Scheme 113

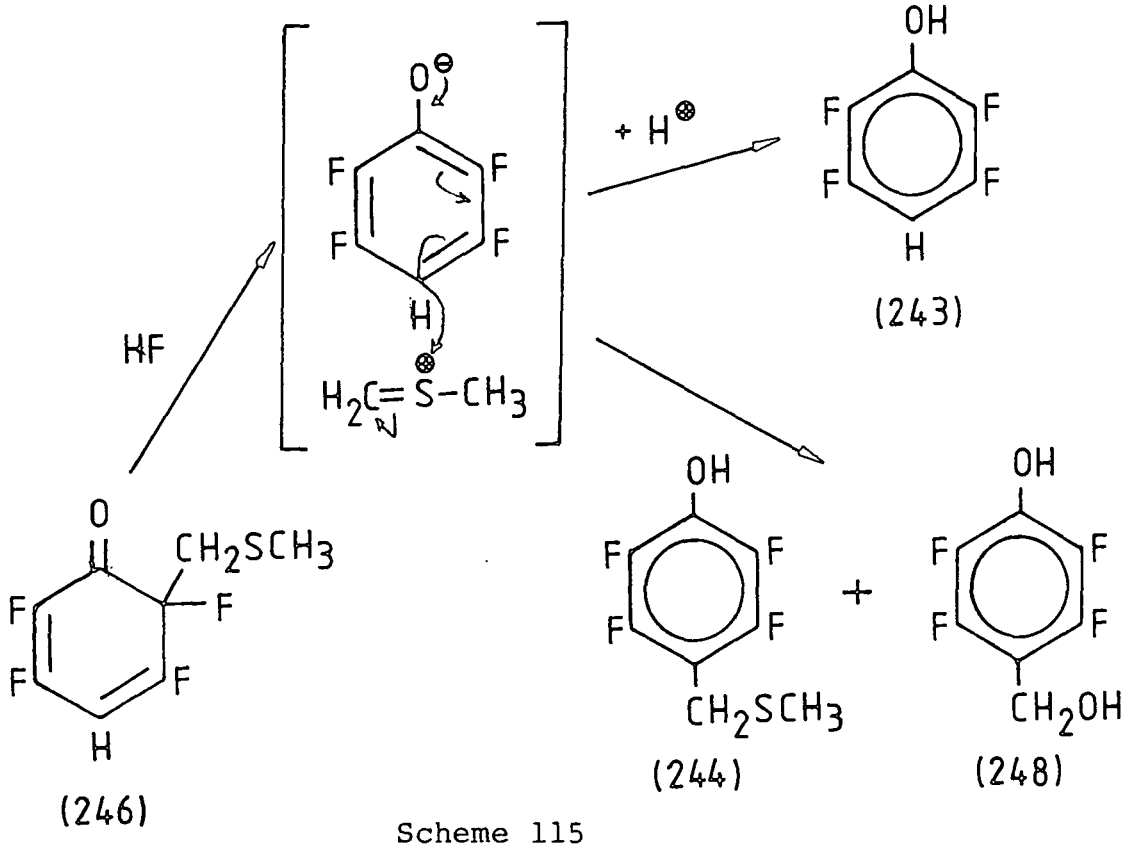
pentafluorophenol and potassium carbonate in refluxing tetrahydrofuran to give the disubstituted compound (247) (66%), Scheme 114.



Scheme 114

In order to attempt to bring about the acid catalysed rearrangement, the dienone (246) was treated with liquid

HF at room temperature. The reaction resulted in the formation of three products, shown by ^{19}F n.m.r. spectroscopy to be in the ratio 2:3:2. These were separated to give the tetrafluorophenol (243) (19%), the 4-thiomethoxymethyl compound (244) (28%) and the methanol derivative (248) (14%) respectively, Scheme 115.

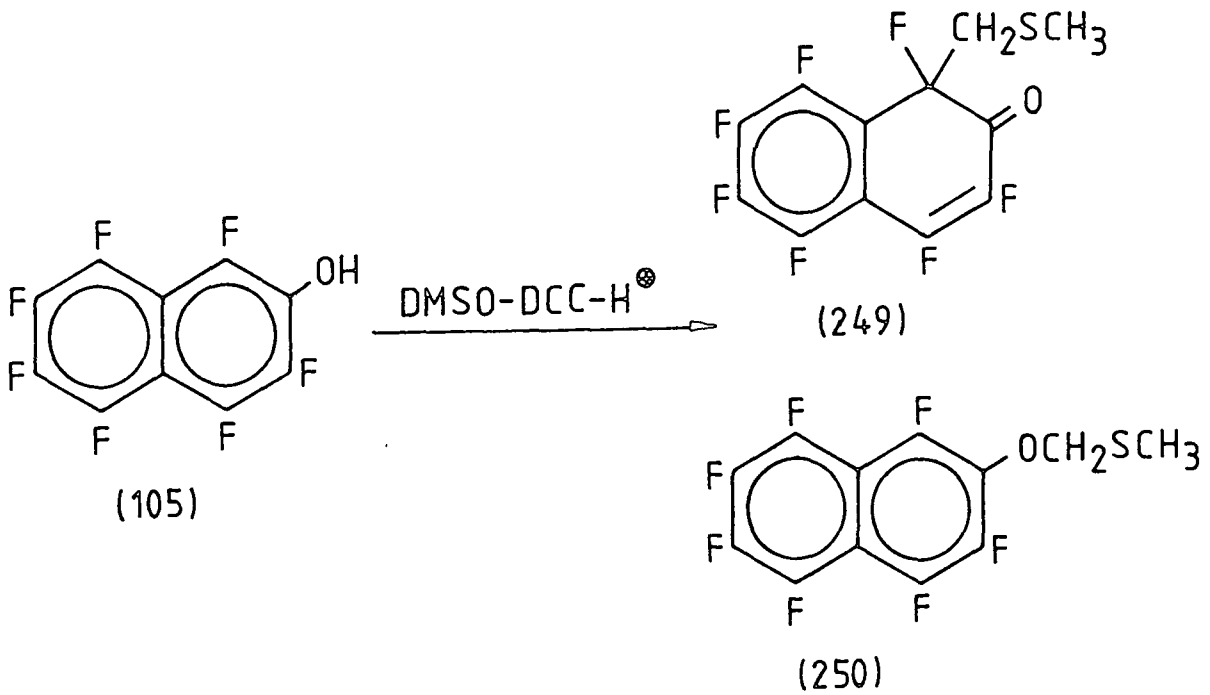


Scheme 115

Isolation of the parent phenol (243), resulting from elimination of a methylmethylene sulphonium cation from the starting dienone (246), and also the para-rearrangement product (244) would seem to demonstrate the formation of $CH_2=\overset{\oplus}{S}-CH_3$ and the fragmentation-recombination mechanism for the process. Presumably the formation of the methanol derivative (248) was as a result of the acid-catalysed hydrolysis of (244).

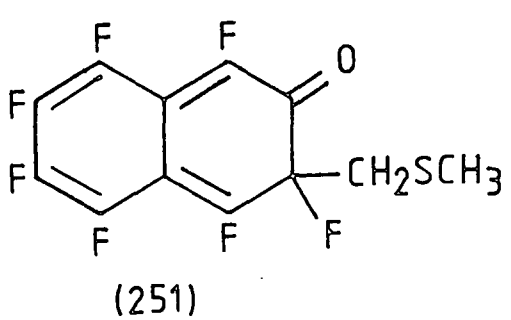
6.2.3 With 1,3,4,5,6,7,8-Heptafluoro-2-Naphthol (105)

Reaction of the naphthol (105) with DMSO-DCC-H^+ resulted in the formation of two major products. These were isolated to give the naphthalen-2(1H)-one (249) (72%) and the thiomethoxymethyl ether (250) (10%), Scheme 116.



Scheme 116

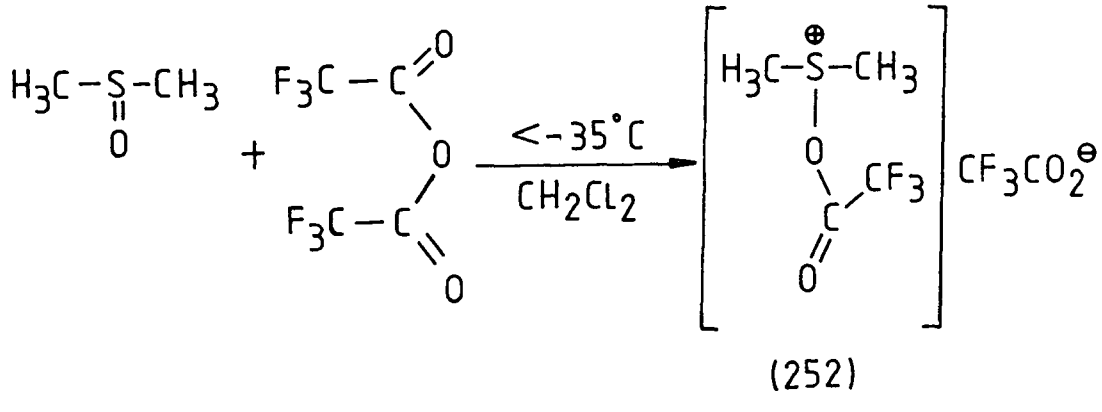
The structure of the naphthalen-2(1H)-one (249) was determined by ^{19}F n.m.r. spectroscopy which showed only one peri J_{F-F} (J_{4F-5F} 77Hz) demonstrating that C-1 rather than C-3 was the migration terminus. The lack of formation of a C-3 migration terminus product was however not surprising, since reaction to give such a product would require the formation of the highly destabilized O-quinoid system (251).



The formation of a naphthalen-2(1H)-one from the naphthol (105) is thus similar to the hydrogen analogue, although bis-compounds like (208) are not formed since (249) is unable to rearomatise to the naphthol for further reaction.

6.3 Use of the Dimethyl Sulphoxide-Trifluoroacetic Anhydride System

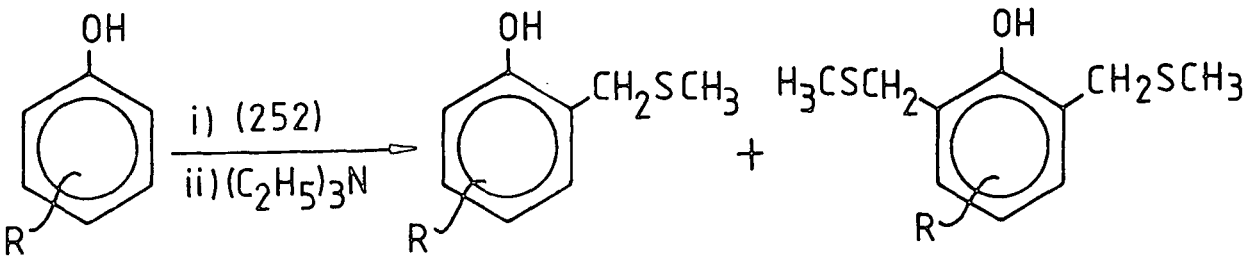
A practical problem with the DMSO-DCC-H^+ reagent is the separation of the products formed in the reaction from the precipitated dicyclohexyl urea. However, dimethyl sulphoxide can be 'activated' with electrophilic species other than dicyclohexylcarbodiimide to produce an intermediate sulphonium complex like (209).[116] A number of these, including acetic anhydride,[117] thionyl chloride[118] and trifluoroacetic anhydride[119] have been successfully reacted with phenols. In the case of trifluoroacetic anhydride (TFAA), the reaction with DMSO [at low temperature (<-35°C)] affords the activated complex (252), Scheme 117.



(252)

Scheme 117

Reaction of this complex (252) with phenols (253) (followed by treatment with triethyl amine to form the ylide) resulted only in the formation of the mono- (254) and di-substituted (255) derivatives, and in higher yields than in the DMSO-DCC-H^+ reactions,[118] Scheme 118.



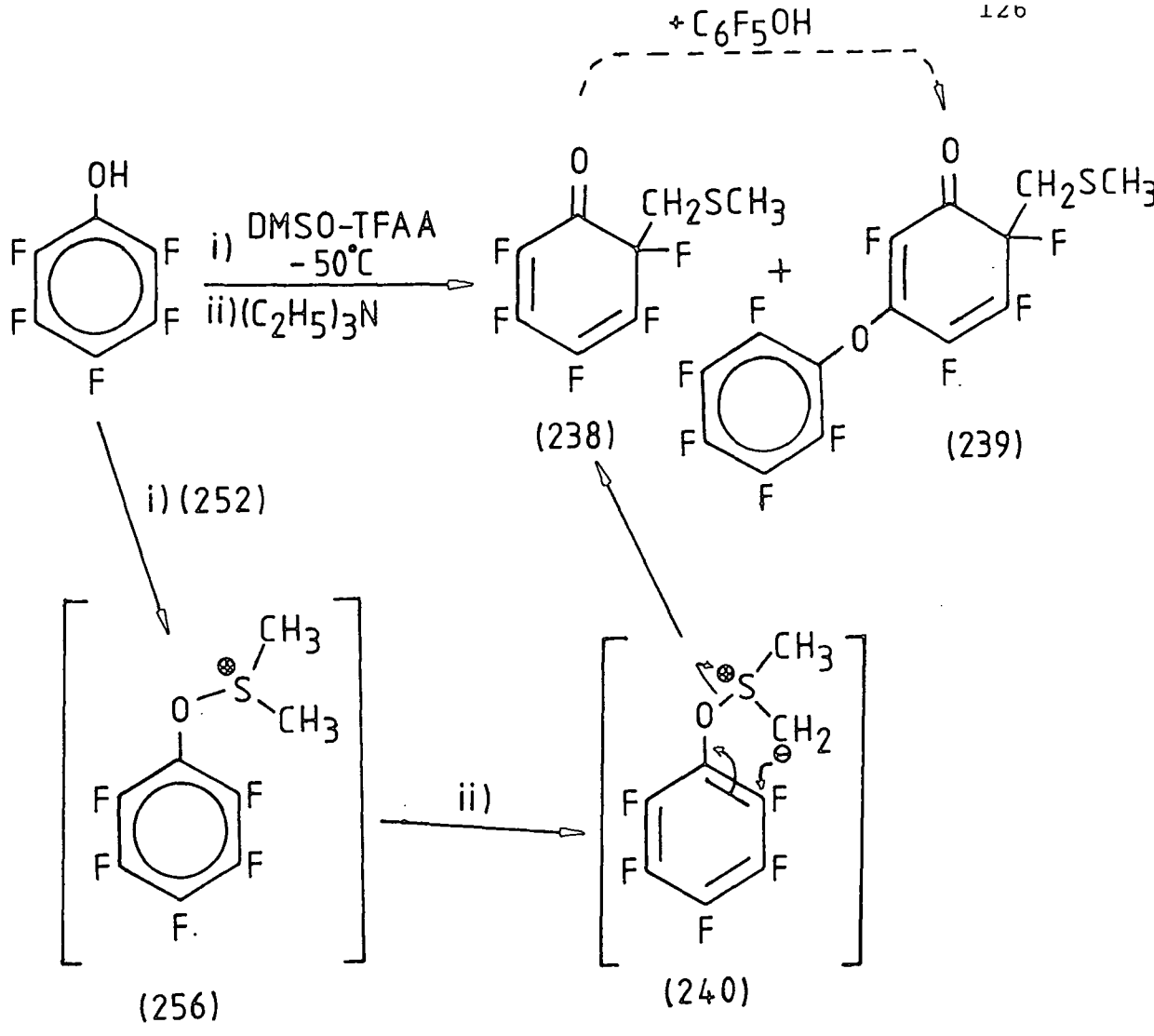
	(253)	(254)	(255)
		%	
R = 4-OCH_3		55	14
R = 4-Cl		43	11

Scheme 118

The reactions of pentafluorophenol and the naphthol (105) with the DMSO-TFAA system are described in the following sections.

6.3.1 With Pentafluorophenol

The reaction of pentafluorophenol with the DMSO-TFAA complex (252) (1:1 molar ratio) at -50°C and subsequent reaction with triethylamine resulted in the formation of the dienone (238) (53%) as the major product. This was accompanied by the phenoxy substituted product (239) (25%), but none of the thiomethoxymethyl ether (237) was observed. Using a reaction ratio of 1:2 (phenol:complex) even more dienone (238) (73%) and less of its substituted derivative (239) (18%) were formed, Scheme 119.



Scheme 119

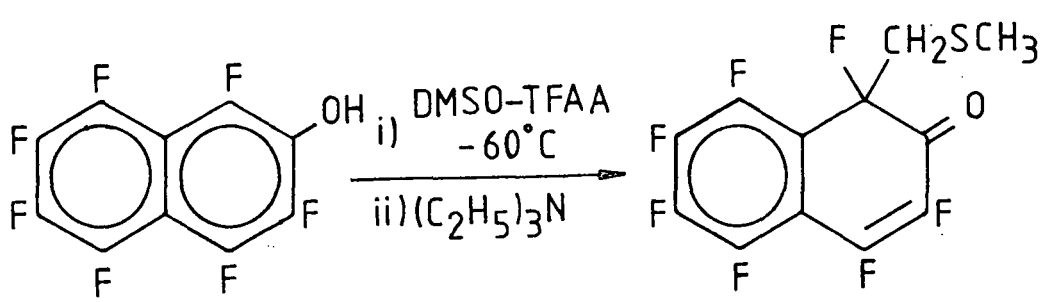
The origin of the reversal in the ratio of (238):(239) [4:1 from <1:3] in changing from the DMSO-DCC-H^+ system to the DMSO-TFAA system is a function of the activated system. In the former case, formation of the activated DMSO complex (209), its reaction with pentafluorophenol, the subsequent formation of the ylide (240) and then rearrangement of (240) to the dienone (238) always occurs in the presence of unreacted pentafluorophenol. This is of particular significance in this case as (238) is particularly reactive towards a nucleophilic species like pentafluorophenol to give (239). In the case of the DMSO-TFAA system however, the course of the reaction relies on the initial formation of the sulphonium salt (256). This is only converted into the ylide (240) on

the addition of triethylamine, when presumably all the pentafluorophenol has undergone reaction with the complex (252). Thus, rearrangement of the ylide (240) to (238) occurs without significant amounts of the phenol being present.

The lack of formation of any of the thiomethoxymethyl ether (237) is not surprising when the low temperature (<-50°C) at which the reaction is carried out is considered. The higher energy dissociation-recombination process in this case is obviously precluded.

6.3.2 With 1,3,4,5,6,7,8-Heptafluoro-2-Naphthol (105)

The reaction of the naphthol (105) with DMSO-TFAA (1:2 molar ratio) in methylene chloride at -60°C followed by the addition of triethylamine resulted only in the formation of the naphthalen-2(1H)-one (249) (78%). Starting material (105) (7%) was also recovered, but none of the thiomethoxymethyl ether (250) was observed, Scheme 120.



(105) (249)

Scheme 120

CHAPTER SEVEN

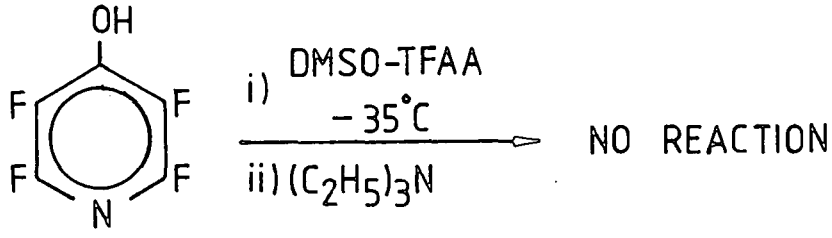
THE REACTION OF FLUORINATED HETEROARENOLS WITH THE DIMETHYL SULPHOXIDE - TRIFLUOROACETIC ANHYDRIDE SYSTEM

7.1 Introduction

The reaction of hydroxypyridines and hydroxypyrimidines with activated dimethyl sulphoxide is an area of chemistry which has not been examined. This is presumably due to the fact that such compounds are tautomeric and exist predominantly in their lactam forms, effectively precluding [2,3] sigmatropic rearrangements of the type observed for the phenolic systems. Tautomerism of this type is, however, less marked in the analogous fluorinated systems (see Section 3.4) and indeed these generally exist predominantly in their hydroxy form. A number of fluorinated monohydroxy-substituted heteroarenols are now readily accessible compounds, and their reaction with the DMSO-TFAA system are described in the following sections.

7.2 With 2,3,5,6-Tetrafluoro-4-Hydroxypyridine[120] (257)

The reaction of the 4-hydroxy compound (257) with the DMSO-TFAA complex (1:2.3 molar ratio) at -55°C followed by treatment with triethylamine resulted only in the recovery of unreacted starting material (257) (90%). In another experiment carried out at -35°C (the temperature above which the activated DMSO-TFAA complex itself decomposes[116]) no reaction was again observed, Scheme 121.



(257)

Scheme 121

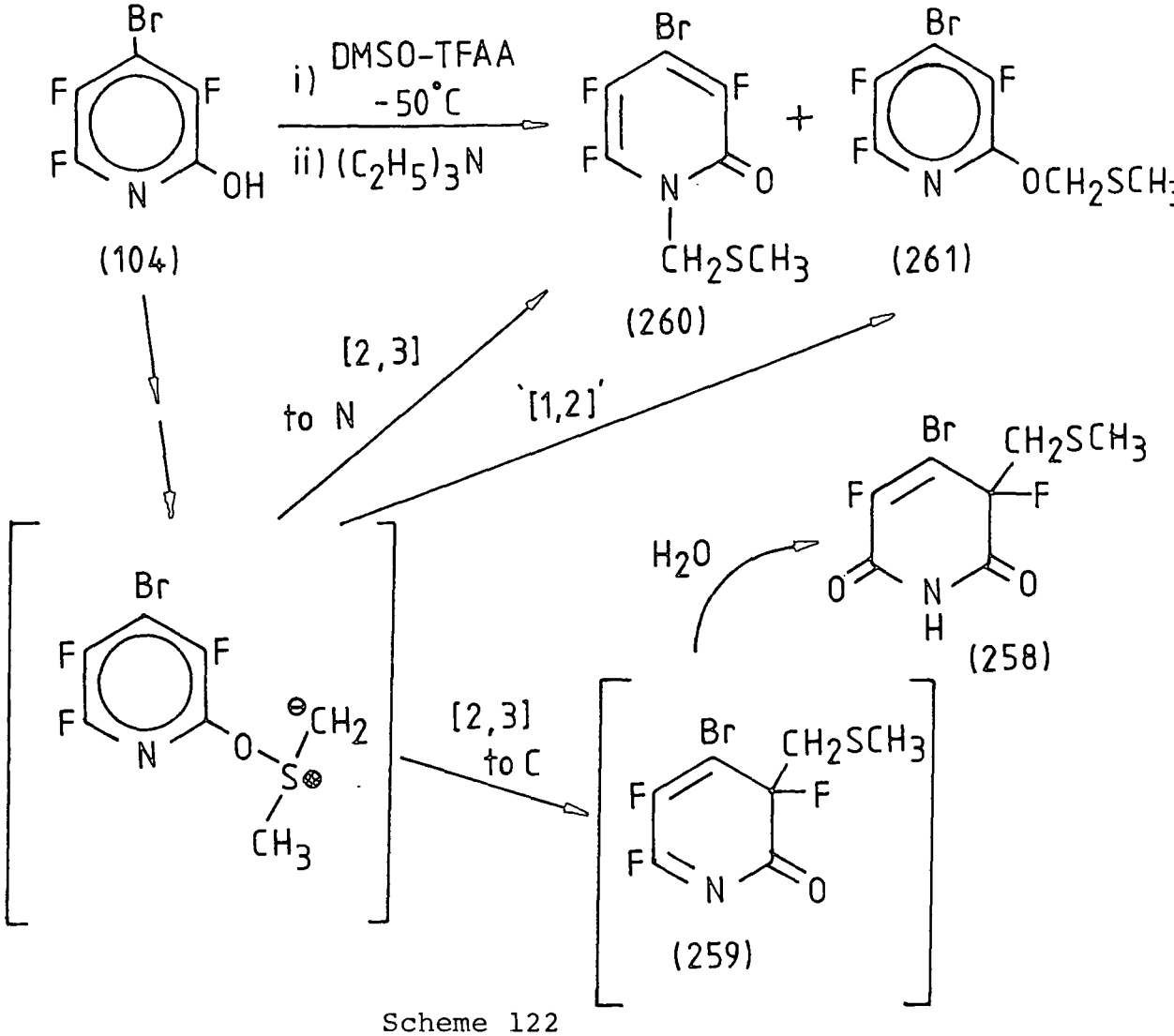
The 4-hydroxy compound (257) was also reacted with the DMSO-DCC-H^+ system at cold temperatures and also at 80°C and 115°C, but only unreacted starting material was recovered in each case.

7.3 With 4-Bromo-2,3,5-Trifluoro-6-Hydroxypyridine[121] (104)

In the 6-hydroxy compound (104) there exists for the first time in this work the possibility for a [2,3] rearrangement to occur to either an ortho-carbon or an ortho-nitrogen. With the corresponding allyl ether[38] (88, Scheme 36) the [3,3] rearrangement reaction resulted only in the formation of a hydrolysis product in which the migration terminus for the allyl group was the ortho-carbon, no products from rearrangement to the ortho-nitrogen being observed.

The reaction of the hydroxy compound (104) with the DMSO-TFAA complex (1:2.2 molar ratio) at low temperature, followed by treatment with triethylamine, gave a product shown by ^{19}F n.m.r. spectroscopy to consist of four components in the ratio 15:43:12:20 which were separated to give the imide

(258) (8%) resulting from hydrolysis of the C-migration terminus product (259), in an exactly similar manner as that of the corresponding allyl ether (88),[38] the N-migration terminus product (260) (44%), the thiomethoxymethyl ether (261) (1.5%) and unreacted starting material (104) (22%) respectively, Scheme 122.



Scheme 122

The formation of a C-migration product (258) in this reaction along with the N-migration product (260), is a result of a genuine competition between migration to the two ortho-positions, and not a result of the prior localization of the adjacent carbon-carbon double-bond as observed for the

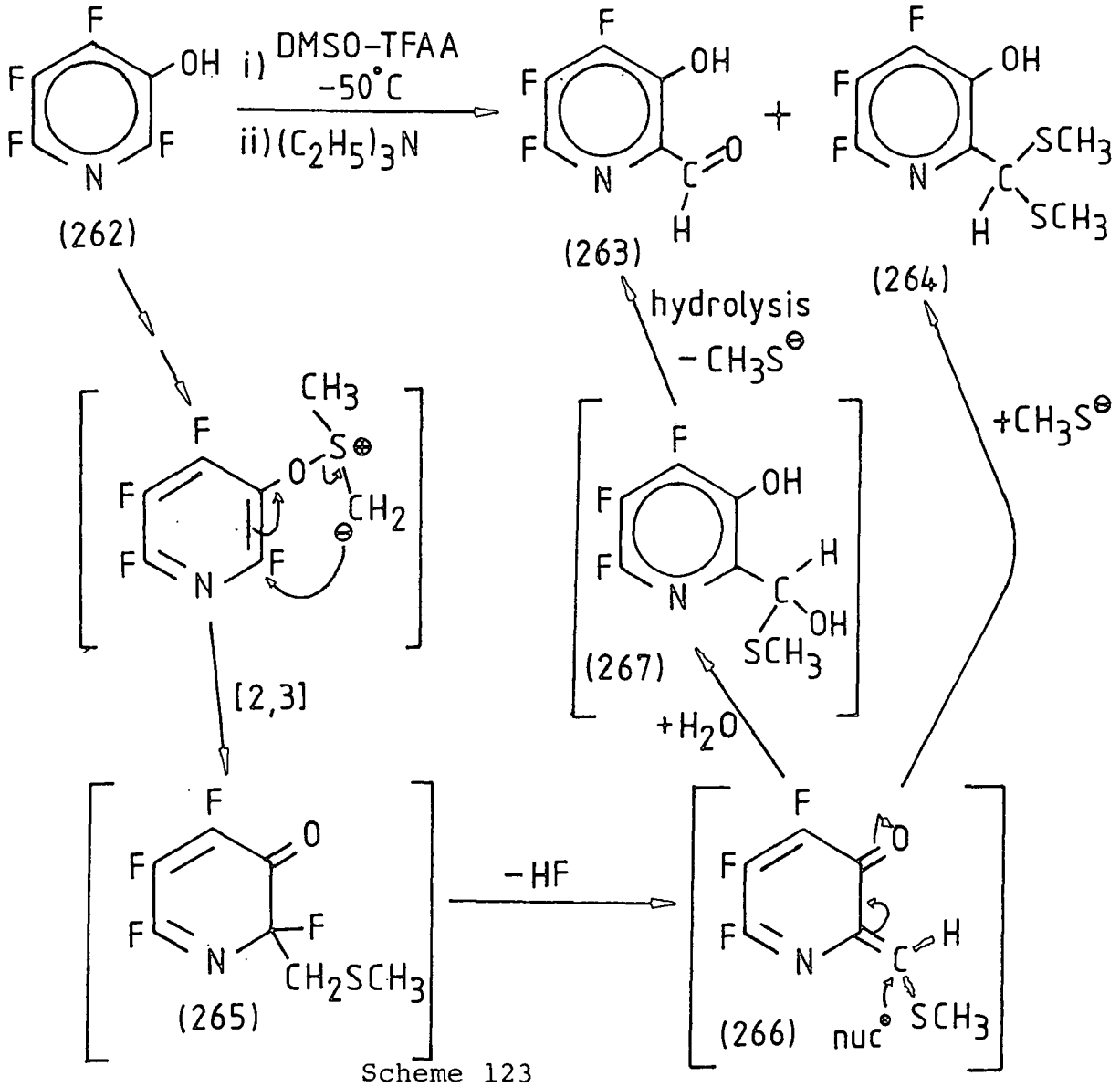
[3,3]-sigmatropic rearrangements of allyl pyrimidyl ethers as seen in Chapter Three since such a process cannot occur in this sytem.

The isolation of the thiomethoxymethyl ether (261) was surprising and is the only instance in the present investigation of such a derivative being formed when using the low temperature DMSO-TFAA system.

7.4 With 2,4,5,6-Tetrafluoro-3-Hydroxypyridine[38] (262)

The reaction of the 3-hydroxy compound (262) with the DMSO-TFAA complex (1:1.9 molar ratio) followed by treatment with triethylamine resulted in the formation of a highly complex mixture of products which often included an unidentified and extremely insoluble material. The proportions of the products were also widely variable under supposedly identical reaction conditions. Only two products could be isolated, and in low yield: surprisingly the hydroxyaldehyde (263) (6%) and its methylthioacetal (264) (6%); starting material (262) (13%) was also recovered, Scheme 123. In another experiment only the hydroxyaldehyde (263) (13%) and recovered starting material (262) (21%) were isolated; though the thioacetal (264) was shown to be present in a trace amount in the crude product by ^{19}F n.m.r. spectroscopy.

Formation of both (263) and (264) can be rationalized as arising from a common origin, the [2,3] rearrangement compound (265), which is a result of a migration occurring towards the nitrogen. Loss of HF from (265) then gives the ortho-quinomethide compound (266) which on rearomatization by



Scheme 123

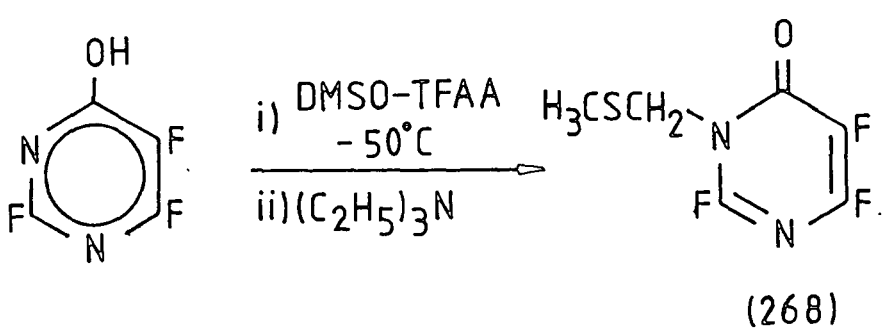
addition of water and then hydrolysis of the resulting hemi-thioacetal (267) gives the hydroxyaldehyde (263). The hydrolysis of (267) results in the release of $CH_3S^{\ominus}$ which is also capable of attacking the ortho-quinomethide (266) to give the methylthioacetal (264). Of course the acetal (264) itself can also undergo hydrolysis to the hydroxy-aldehyde (263) and may explain why the proportions of these two compounds are variable.

It was not possible to ascertain whether any products resulting from rearrangement away from the nitrogen were

formed during the reaction described above due to its complexity and inefficiency. In the [3,3] sigmatropic rearrangement of the corresponding allyl ether (90) in sulpholane (see Scheme 37) only 1% of such a product was isolated, the major process being rearrangement towards the nitrogen,[39] as observed in the DMSO-TFAA reaction.

7.5 With 2,5,6-Trifluoro-4-Hydroxypyrimidine[40]

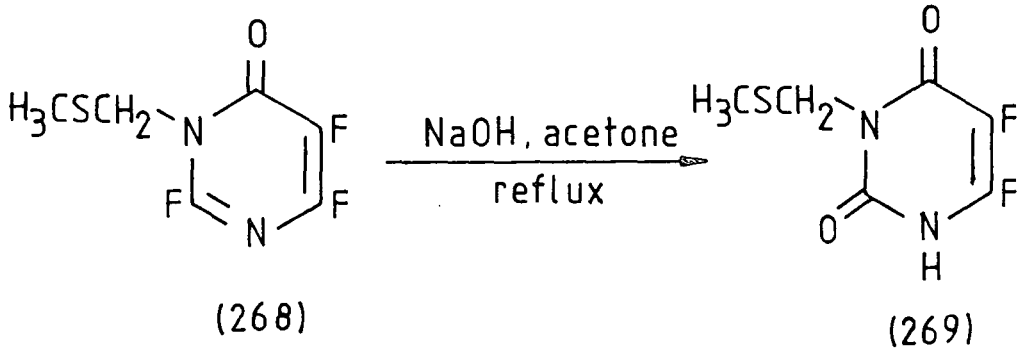
2,5,6-Trifluoro-4-hydroxypyrimidine reacted with the DMSO-TFAA complex (1:2 molar ratio) followed by treatment with triethylamine to give exclusively the [2,3] rearrangement product (268) (71%), Scheme 124, in which the ortho-nitrogen was the migration terminus, the same terminus as observed for the [3,3] sigmatropic rearrangement of the corresponding allyl ether (93) (see Scheme 40). Starting material (19%) was also recovered. The 2,4-dienone type structure of the N-substituted compound (268) was established by the similarity of its ultra-violet spectrum with that of the model compound (99).



(268)

Scheme 124

The hydrolysis of the N-thiomethoxymethyl compound (268) with aqueous sodium hydroxide in acetone resulted in the formation of another 5-fluoruracil derivative (269) (90%), Scheme 125.

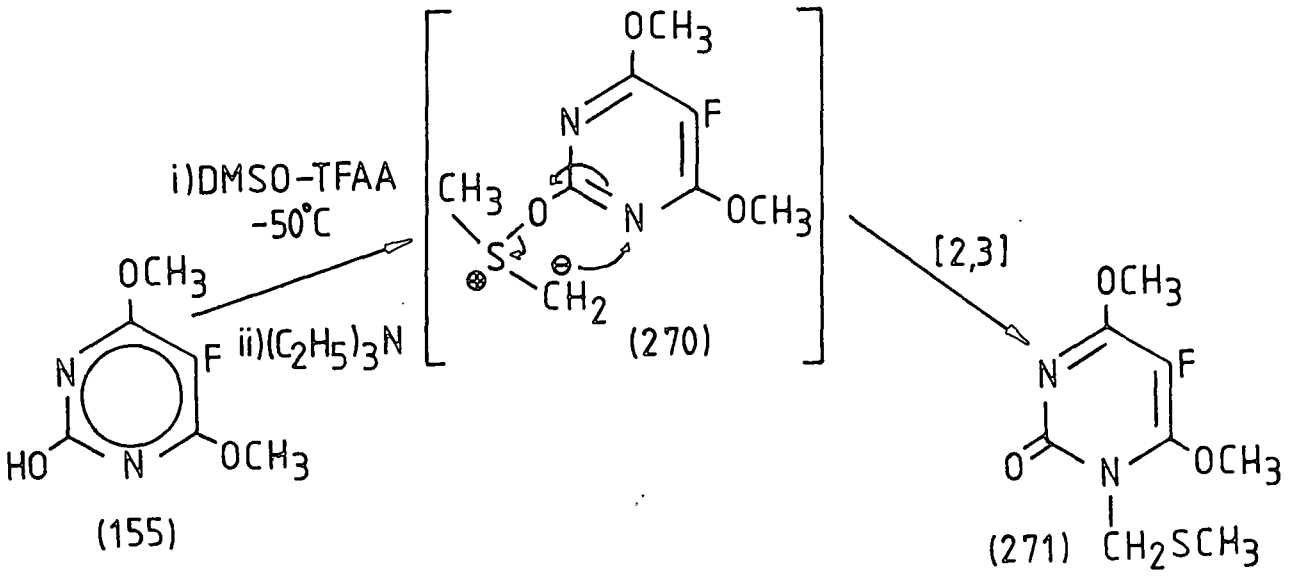


(268) (269)

Scheme 125

7.6 With 5-Fluoro-2-Hydroxy-4,6-Dimethoxypyrimidine (155)

The allyl ether (137) derived from the 2-hydroxy compound (116) proved to be totally inert to a [3,3] sigmatropic rearrangement, the only reaction that occurred being loss of the allyl group (see Scheme 75). In complete contrast, however, the ylide (270), formed from the reaction of the 2-hydroxy compound (116) with DMSO-TFAA complex (1:2.4 molar ratio) followed by treatment with triethylamine readily underwent a [2,3] sigmatropic rearrangement resulting in the formation of the N-thiomethoxymethyl compound (271) (59%), Scheme 126. Starting material (116) (17%) was also recovered.

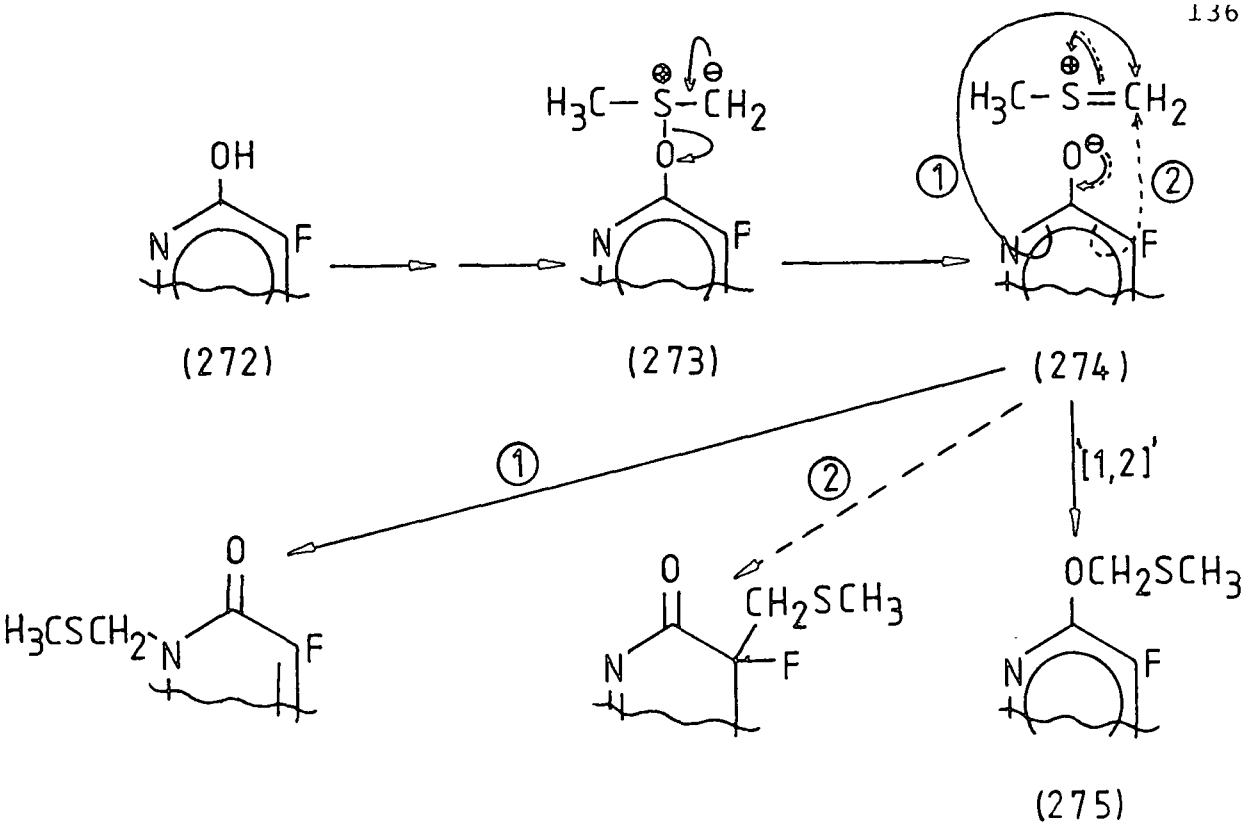


Scheme 126

7.7 Discussion

It is presumed that the mechanism operating in these heteroaromatic systems is exactly similar to that already well established for the phenolic compounds. Certainly the only compounds isolated are those derived from an initial rearrangement to the adjacent ortho-position, whether nitrogen or carbon, as would be expected from a [2,3] sigmatropic rearrangement. It is however worthwhile considering a dissociation-recombination mechanism for the process as outlined in Scheme 127 for a general heteroarenol (272), since this process was used to account for any formation of thiomethoxymethyl ethers.[91]

Following its formation, the ylide (273) may 'decompose' by loss of the methylmethylene sulphonium cation to give the species (274). This can then trap the sulphonium cation at either the nitrogen (1) or the carbon (2), or form the thiomethoxymethyl ether (275); due to the high electronegativity



Scheme 127

of nitrogen over carbon, route (1) is expected to be more favourable than route (2). This type of product distribution was observed for the 6-hydroxy compound (104), yet, in the related process with (104), allyl bromide and potassium carbonate (see Scheme 45) only the O-alkylated product, the allyl ether (88), was formed. Consequently a genuine [2,3] sigmatropic shift accounts for the formation of the ortho-rearrangement products.

The reaction of 2,5,6-trifluoro-4-hydroxypyrimidine with allyl bromide (see Schemes 46 and 48), in contrast to that of the 6-hydroxy compound (104), resulted in the formation of both the allyl ether (93) and an N-allyl compound (99). The reaction of this 4-hydroxy compound with the DMSO-TFAA system did give an N-substituted product (268), but the fact that no 4-thiomethoxymethyl ether compound was formed again indicates the operation of the [2,3] rearrangement process.

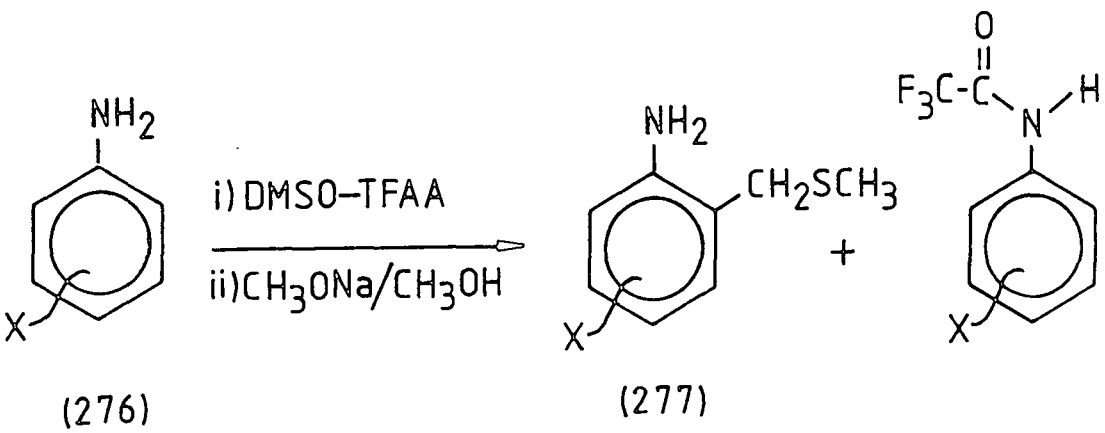
In view of the 'normal' reactions of the 6-hydroxy derivative (104) and the 3-hydroxypyridine (262) with the DMSO-TFAA system, the failure to observe any reactions with 2,3,5,6-tetrafluoro-4-hydroxypyridine (257) is quite unexpected.

CHAPTER EIGHT

THE REACTION OF FLUORINATED ANILINES AND THIOPHENOLS WITH THE DIMETHYL SULPHOXIDE-TRIFLUOROACETIC ANHYDRIDE SYSTEM

8.1 Introduction

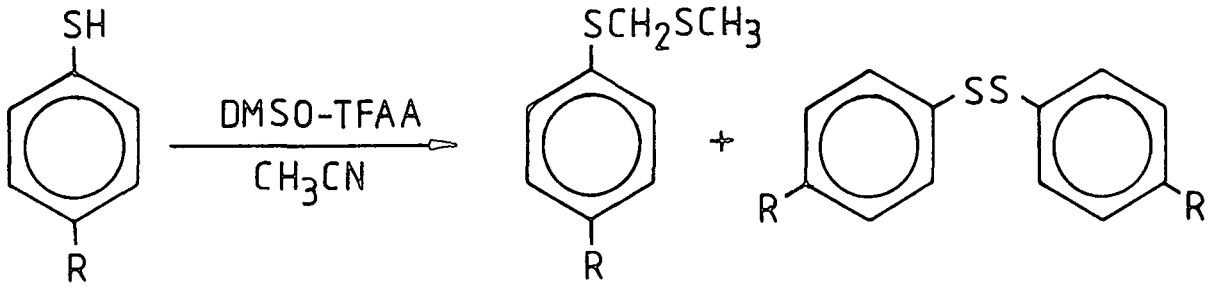
The reaction of thiophenols and anilines with the dimethyl sulphoxide-trifluoroacetic anhydride system has been the subject of a previous investigation.[119] Mono-substituted anilines (276) generally resulted in the formation of the ortho-alkylated products (277), as would be expected from the [2,3] sigmatropic rearrangement process (see Scheme 107). Trifluoroacetylation took place as the sole side-reaction, Scheme 128.



(276) (277)

Scheme 128

In contrast, the reaction of substituted thiophenols (278) with the DMSO-TFAA complex gave the thiomethoxymethyl thioethers (279), accompanied by the oxidation product diphenyl disulphides (280). No [2,3] rearrangement products were observed, Scheme 129.



(278) (279) (280)

Scheme 129

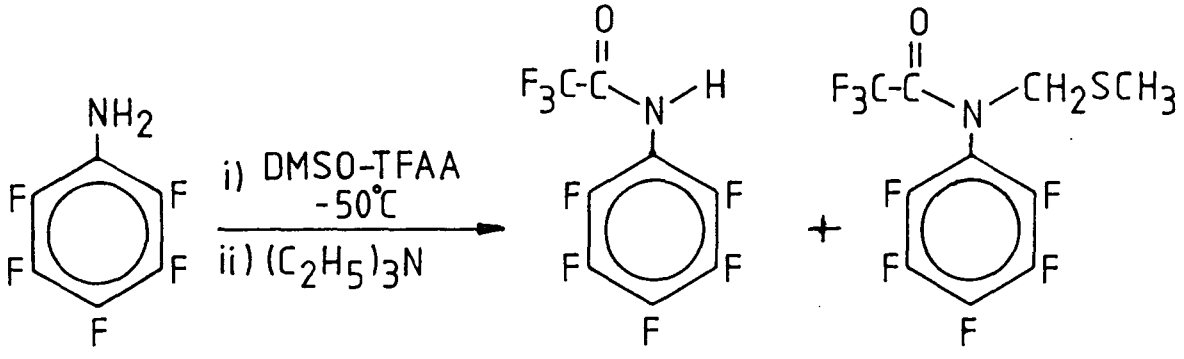
8.2 With 2,3,4,5,6-Pentafluoroaniline (281) and its N-Methyl Derivative (282)[122]

The cyclohexadienoneimine intermediates (227, see Scheme 107) formed as a result of a [2,3] rearrangement of an arylazasulphonium ylide (226) have not been isolated. The presence of fluorine atoms on the aromatic moiety should preclude rearomatization of these intermediates and could facilitate their isolation.

8.2.1 2,3,4,5,6-Pentafluoroaniline (281)

The reaction of pentafluoroaniline (281) with the DMSO-TFAA complex (1:1.9 molar ratio), followed by the addition of triethylamine gave a product shown by ^{19}F n.m.r. spectroscopy to consist of two components in the ratio 59:41. These were separated to give the N-trifluoroacetylated material (283)[123] (37%) and its N-thiomethoxymethylated derivative (284) (54%), Scheme 130.

The formation of (284) can be rationalized by the trapping of the $CH_3\overset{\oplus}{S}=CH_2$ cation formed as a result of the



(281) (283) (284)

Scheme 130

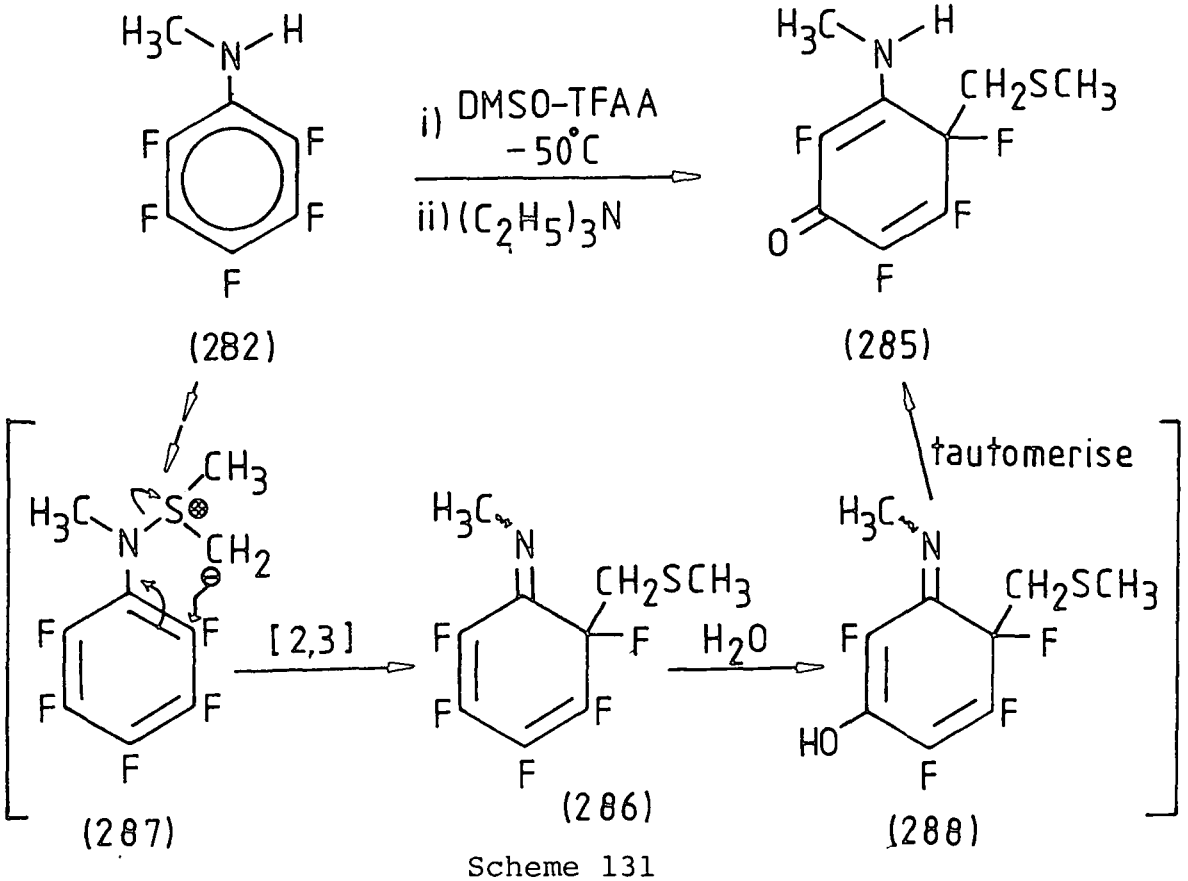
dissociation of the intermediate arzasulphonium ylide, although whether this occurs before or after N-trifluoroacetylation is not certain.

The formation of only the N-trifluoroacetylation product from anilines when using triethylamine as the base had been observed in the previous work,[119] although N-thiomethoxymethyl compounds like (284) were not formed. An effective base for the [2,3] rearrangement was found to be sodium methoxide in methanol (see Scheme 128). The reaction of pentafluoroaniline (281) with the DMSO-TFAA complex (1:2 molar ratio) followed by the addition of sodium methoxide in methanol, however, gave only the N-thiomethoxymethyl compound (284) (8%) and the N-trifluoroacetylated product (283) (91%), no [2,3] rearrangement products being observed. (The significant fall in the amount of the compound (284) formed is presumably as a result of the $CH_3\overset{\oplus}{S}=CH_2$ cation being competitively trapped by methoxide).

8.2.2 N-Methyl 2,3,4,5,6-Pentafluoroaniline (282)[122]

The reaction of the N-methyl substituted aniline (282) with the DMSO-TFAA complex (1:2.1 molar ratio) followed

by the addition of triethylamine gave a product shown by ^{19}F n.m.r. spectroscopy to consist of one major component along with a complex series of minor, and unidentified materials. Only the major component could be isolated and identified, and found to be the 2,5-cyclohexadienone derivative (285) (23%), Scheme 131.

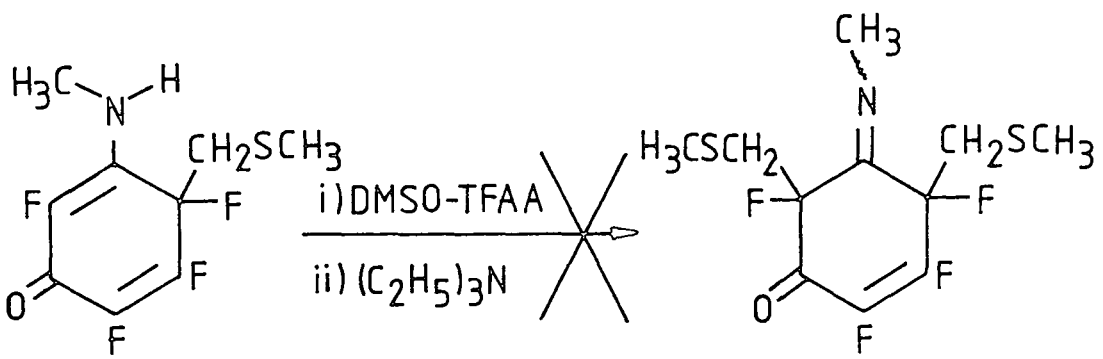


Scheme 131

The formation of the derivative (285) can be rationalized by hydrolysis of the intermediate (286), derived from a [2,3] rearrangement of the ylide (287), presumably during the work-up procedure. Hydrolysis occurs at the 3-position, the same reactive position as that found for the dienone compounds such as (238), although it must be noted that these compounds did not undergo hydrolysis during work-up, indicating the enhanced reactivity of the intermediate (286). The hydrolysis product (288) so formed then tautomerizes to the

product (285). Due to the hydrolytic instability of (286) no further attempts were made of its isolation.

The 2,5-dienone derivative (285) should, itself, be capable of undergoing a [2,3] rearrangement process to give the substituted imine (289), Scheme 132, but reaction of (285) with the DMSO-TFAA complex followed by treatment with triethylamine resulted only in the recovery of starting material (84%).



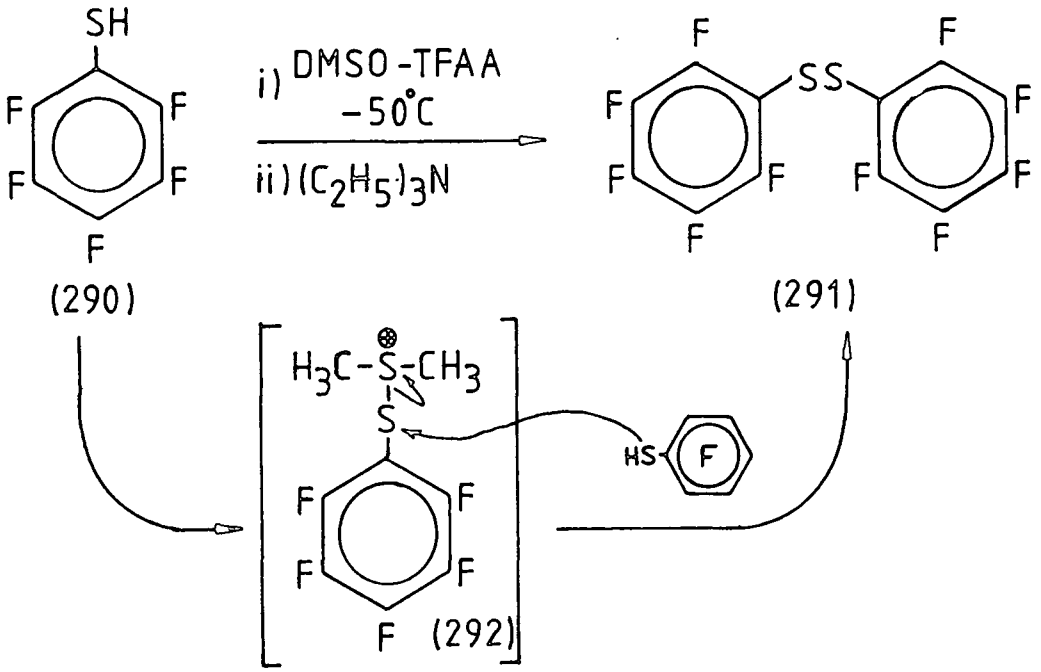
(285) (289)

Scheme 132

8.3 With 2,3,4,5,6-Pentafluorothiophenol (290)

The reaction of pentafluorothiophenol (290) with the DMSO-TFAA complex (1:1.9 molar ratio) followed by triethylamine resulted in the formation of a single product, the diphenyl disulphide[124] (291) (94%), presumably arising from attack by unreacted thiophenol (290) on the initially formed dimethylphenylthiosulphonium salt (292), as shown in Scheme 133. No thiomethoxymethyl thioethers were formed, in contrast to the reaction of the thiophenols (278), although when thiophenol itself was reacted with the DMSO-DCC-$H^{\oplus}$ system only diphenyl disulphide was obtained.[91] No further attempts at

effecting a [2,3] rearrangement in (290) were made.



Scheme 133

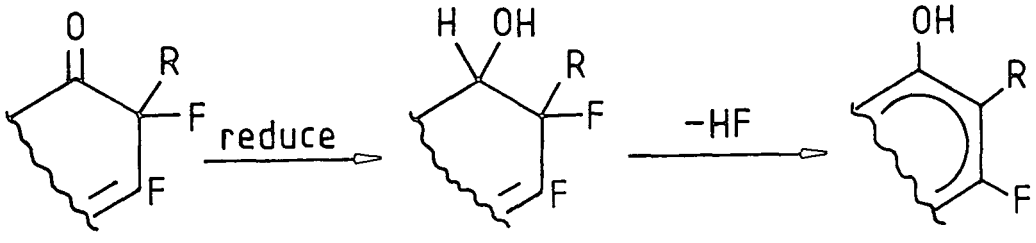
Trifluoroacetic anhydride activated dimethyl sulphoxide is thus not an effective reagent for producing a [2,3] rearrangement process in pentafluoroanilines and thiophenols, in marked contrast to its successful application in fluorinated phenols and their heterocyclic analogues. The promising result obtained for the N-methyl derivative of pentafluoroaniline is therefore a surprise and this and related compounds are worthy of a more extensive investigation.

CHAPTER NINE

SOME REACTIONS OF 2,3,4,5,6-PENTAFLUORO-6-THIOMETHOXYMETHYL-CYCLOHEXA-2,4-DIENONE (238), 1,3,4,5,6,7,8-HEPTAFLUORO-1-THIO METHOXYMETHYLNAPHTHALEN-2[1H]-ONE (249) AND DERIVATIVES OF THEM

9.1 Formation of Ortho-Alkylated Phenols and Naphthols

In the preceding chapters (Chapters Six-Eight) it has been demonstrated that dearomatization of monocyclic, polycyclic and even heterocyclic ring systems can be effected under the mildest of conditions. In the case of the phenolic compounds, such reactions generally resulted in the isolation of cyclohexa-2,4-dienone type ring systems. Rearomatization of these systems *via* the reduction of the carbonyl group to a secondary alcohol followed by loss of HF from the αβ-position would result in the formation of an ortho-substituted polyfluorophenolic compound, as illustrated in Scheme 134. In the absence of powerful overriding substituent effects, only

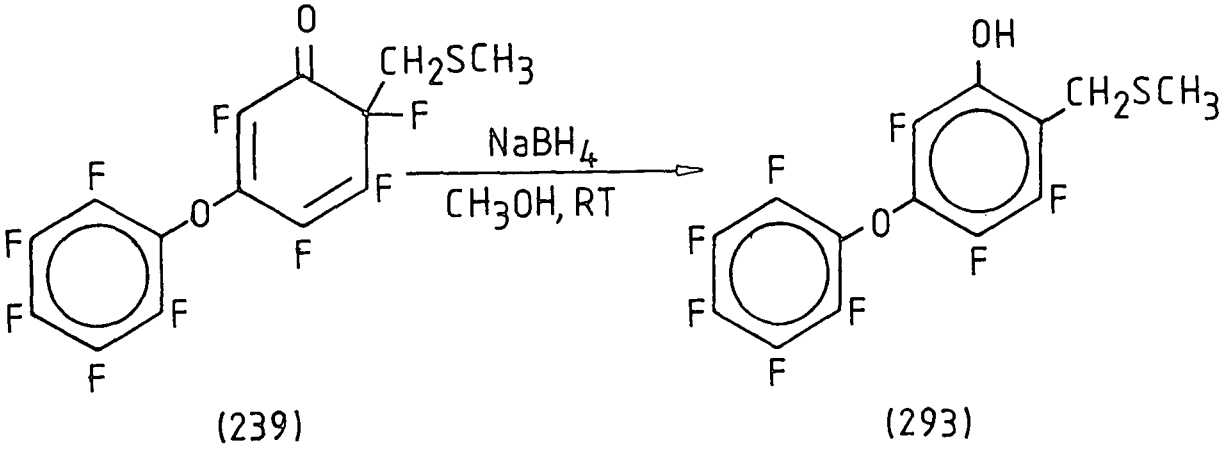


Scheme 134

meta-substituted products are observed by the more direct reaction involving nucleophilic displacement of a fluorine in a fluorinated phenolic compound.[125] The proposed reduction/elimination process would thus provide a novel synthetic route to ortho-substituted compounds.

9.1.1 Using Sodium Borohydride

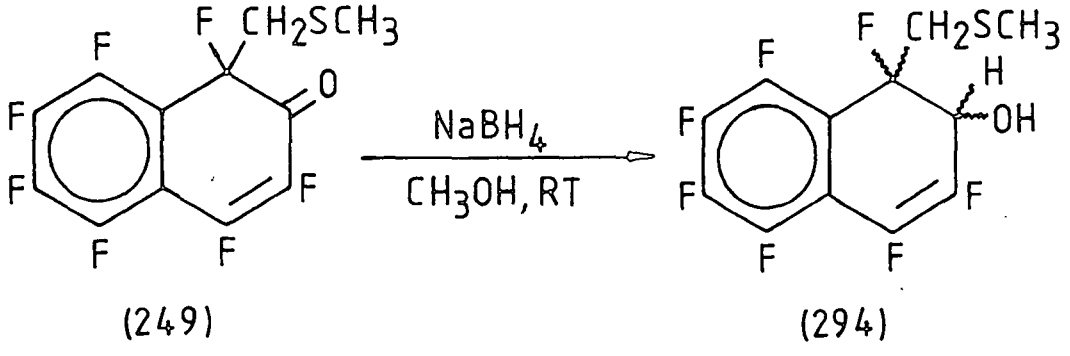
The reaction of the simple 2,4-dienone (238) with sodium borohydride in tetrahydrofuran gave an extremely complex mixture of products, and was not examined further. Treatment of the pentafluorophenoxy substituted derivative of (238), (239) with sodium borohydride in methanol, however, resulted only in the formation of the phenol (293) (97%), Scheme 135.



(239) (293)

Scheme 135

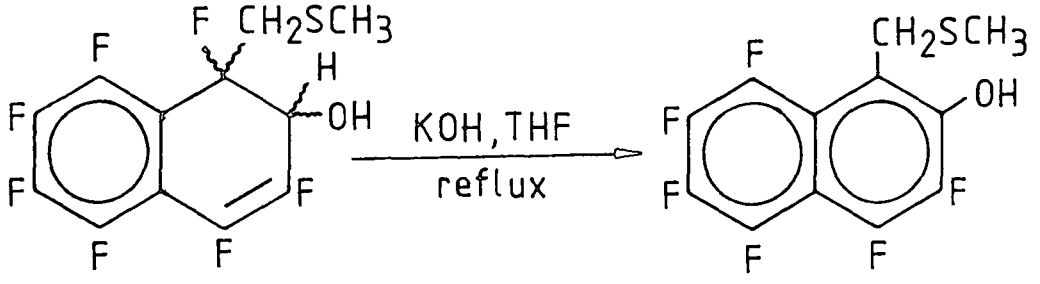
In contrast, the attempted rearomatization of the naphthalenone (249) with sodium borohydride in methanol resulted only in the formation of the secondary alcohol (294) (88%) [shown by ^{1}H n.m.r. spectroscopy to be a mixture of the two possible enantiomeric pairs], Scheme 136.



(249) (294)

Scheme 136

Attempted dehydrofluorination of (294) using potassium fluoride in refluxing tetrahydrofuran resulted only in the recovery of unchanged starting material (81%). Reaction of (294) with KOH under the same conditions, however, brought about the elimination of HF giving the naphthol derivative (295) (86%), Scheme 137.



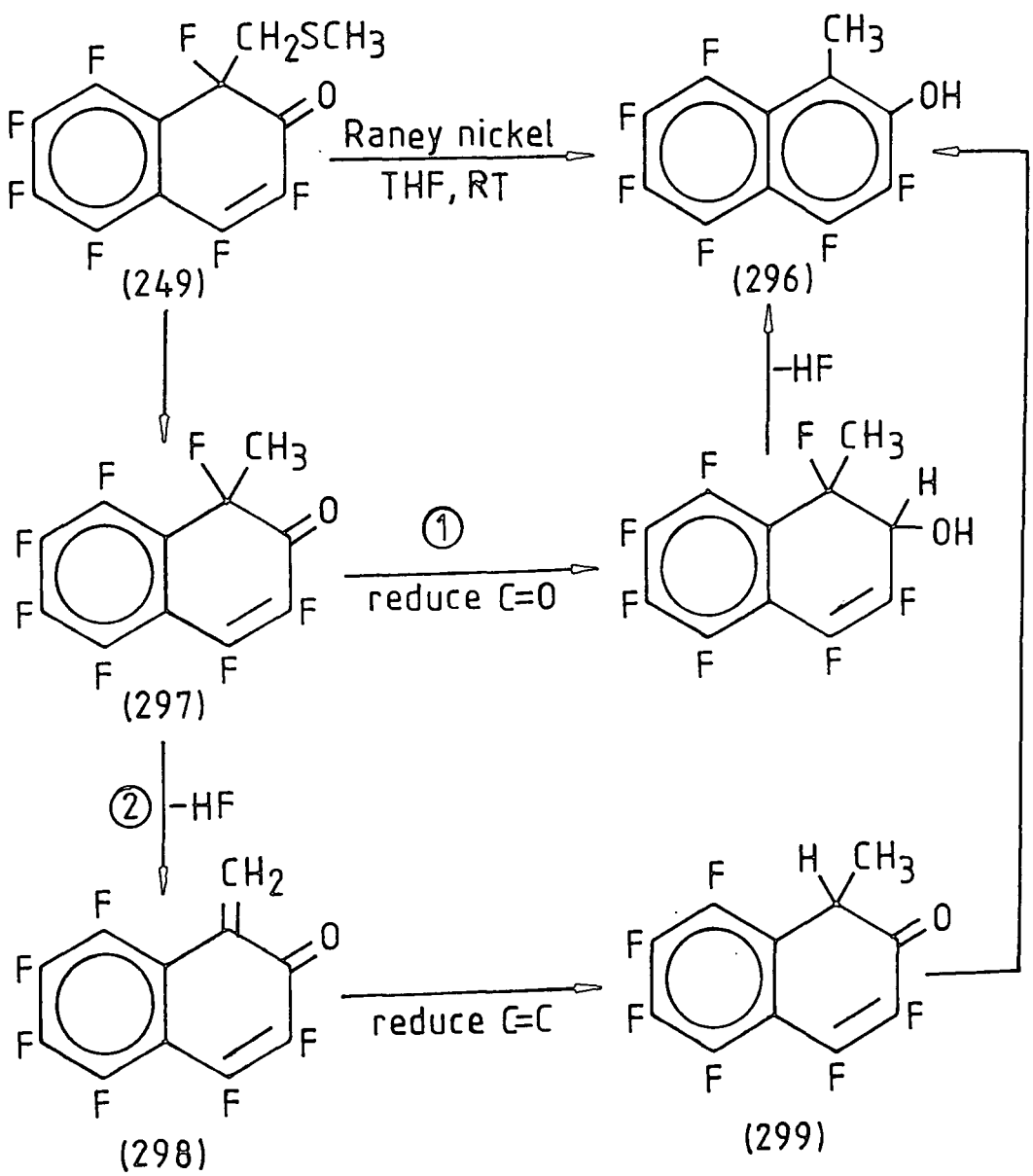
(294) (295)

Scheme 137

9.1.2 Using Raney Nickel

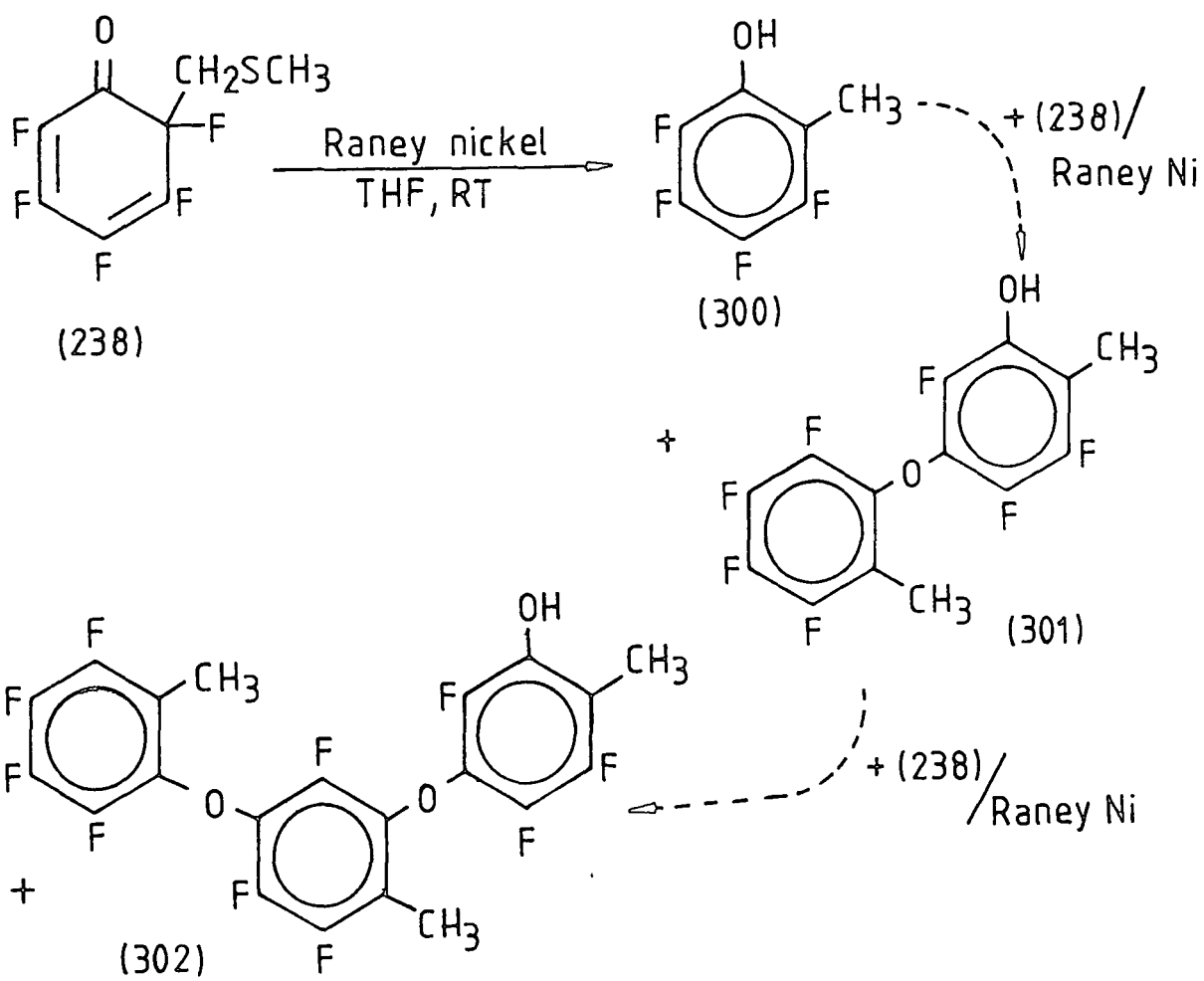
Desulphurization of the thiomethoxymethyl substituent using Raney nickel in some of the 2,4-dienones was always accompanied by reduction and rearomatization *via* dehydrofluorination. Thus, the reaction of the naphthalenone (249) with Raney nickel in tetrahydrofuran at room temperature resulted in the formation of the 1-methyl-2-naphthol derivative (296) (99%), Scheme 138. Formation of (296) can be rationalized in terms of the mechanism shown in Scheme 134 following desulphurization, *i.e.* reduction of the carbonyl group and then subsequent loss of HF with rearomatization (Route (1) in Scheme 138). However, an alternative mechanism can be postulated on the grounds that it might be unexpected for the

carbonyl group to be reduced under the reaction conditions.[126] This is illustrated in Scheme 138, route (2). Following desulphurization the naphalenone compound (297) undergoes dehydrofluorination across the methyl group giving (298). It is then the olefinic double-bond that is hydrogenated to give (299); Raney nickel is known to reduce this functionality much more readily than carbonyl groups.[126] Enolization of (299) then gives (296). It is impossible, however, to differentiate between the two mechanisms in this reaction, though route (2) is probably more likely.



Scheme 138

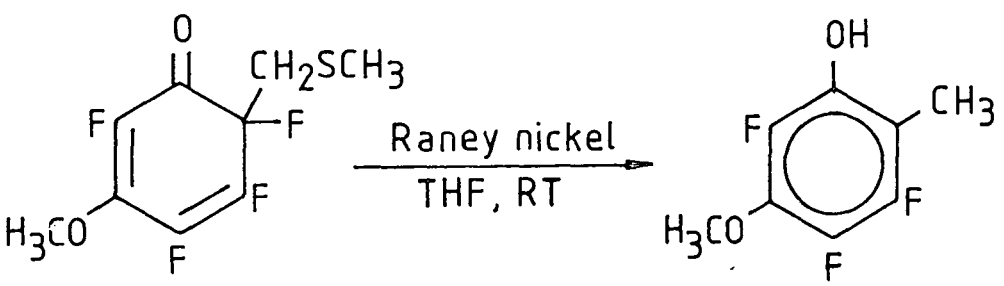
Reaction of cyclohexa-2,4-dienone (238) with Raney nickel in tetrahydrofuran resulted in a complex product shown by ^{19}F n.m.r. spectroscopy to contain three components in the ratio 37:46:17. These were separated to give the simple phenolic compound (300) (22%) accompanied by the mono- and di-ether compounds (301) (33%) and (302) (14%) respectively, Scheme 139. Compound (301) is presumably formed by the reaction of the simple phenol (300) with unreacted dienone (238), followed by the desulphurization/elimination/hydrogenation/enolization sequence of Scheme 138. A similar sequence of reactions of the mono-ether (301) with the dienone (238) would account for the formation of (302). Presumably the reaction of the dienone (238) with Raney nickel under much more dilute conditions, thus limiting such intermolecular processes, would



Scheme 139

result in a better yield of the simple phenol (300), although this particular reaction was not attempted.

When the substituent at C-3 in the dienone (238) was a poorer leaving group than fluorine towards nucleophilic substitution the reaction product was much simpler. Thus the 3-methoxy compound (242) and Raney nickel gave only the phenolic derivative (303) (98%), Scheme 140.

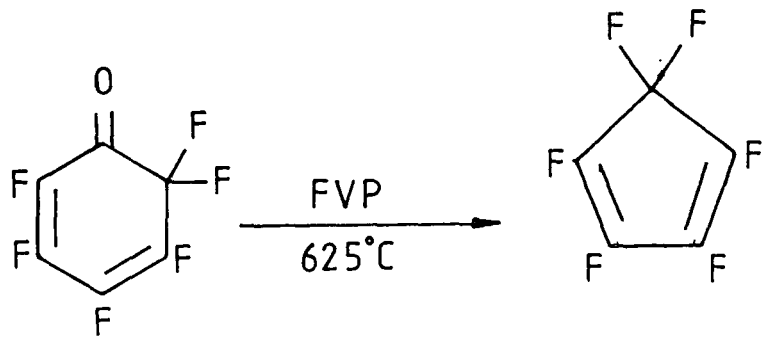


(242) (303)

Scheme 140

9.2 Thermolysis Reactions of the Thiomethoxymethyl Compounds and their Sulphone Derivatives

It has recently been demonstrated[113] that fluorinated cyclohexadienone compounds of the type (304) readily undergo decarbonylation upon flash vapour phase pyrolysis (F.V.P.), resulting in the formation of cyclopentadiene derivatives. Thus, F.V.P. of (304) at 625°C gave (305) (80%), Scheme 141. It was of interest, therefore, to investigate the possible decarbonylation reactions of the title compounds.

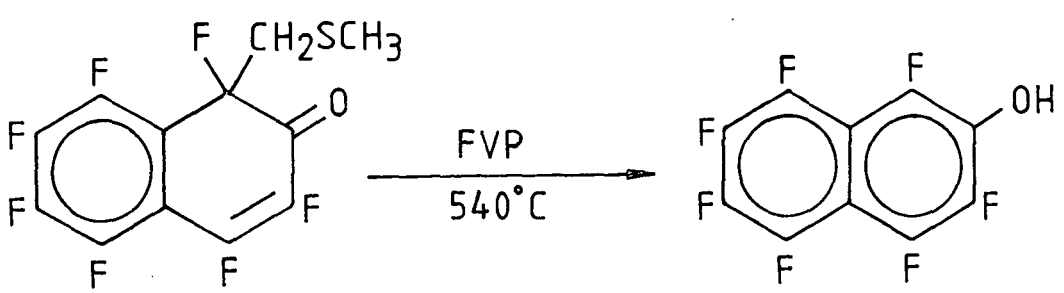


(304) (305)

Scheme 141

9.2.1 1,3,4,5,6,7,8-Heptafluoro-1-Thiomethoxymethyl-naphthalen-2(1H)-one (249)

The readily available naphthalen-2(1H)-one (249) was subjected to pyrolysis under F.V.P. conditions at 540°C. However, the only product isolated was the 2-naphthol (105) (74%), formed as a result of the loss of the thiomethoxymethyl group, Scheme 142.



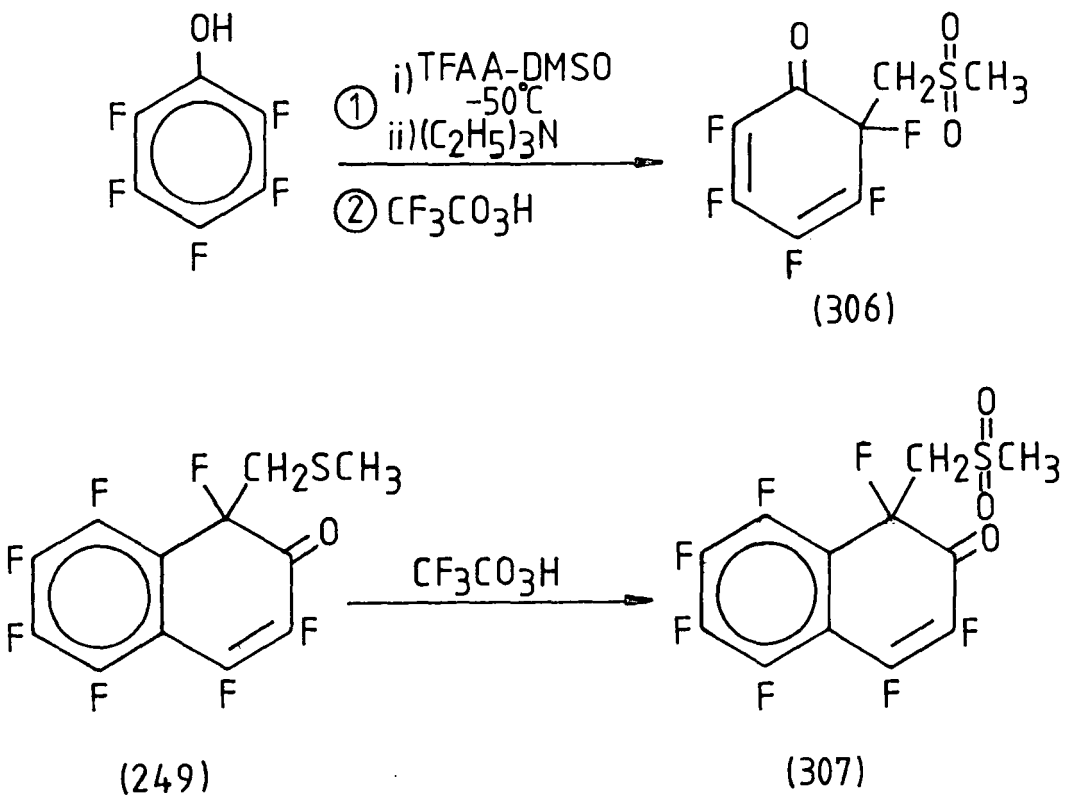
(249) (105)

Scheme 142

9.2.2 Formation and Thermolysis of Sulphone Derivatives

Treatment of both the dienone (238) and the naphthalen-2(1H)-one (249) with peroxytrifluoroacetic acid

readily oxidized the sulphur in these compounds to the sulphone derivatives (306) (39% from starting pentafluorophenol) and (307) (90%) respectively, Scheme 143. (The sulphone (306) was prepared by one continuous process from pentafluorophenol, the dienone (238) being separated as volatile material from its pentafluorophenoxy substituted derivative (239) (11%) before oxidation).

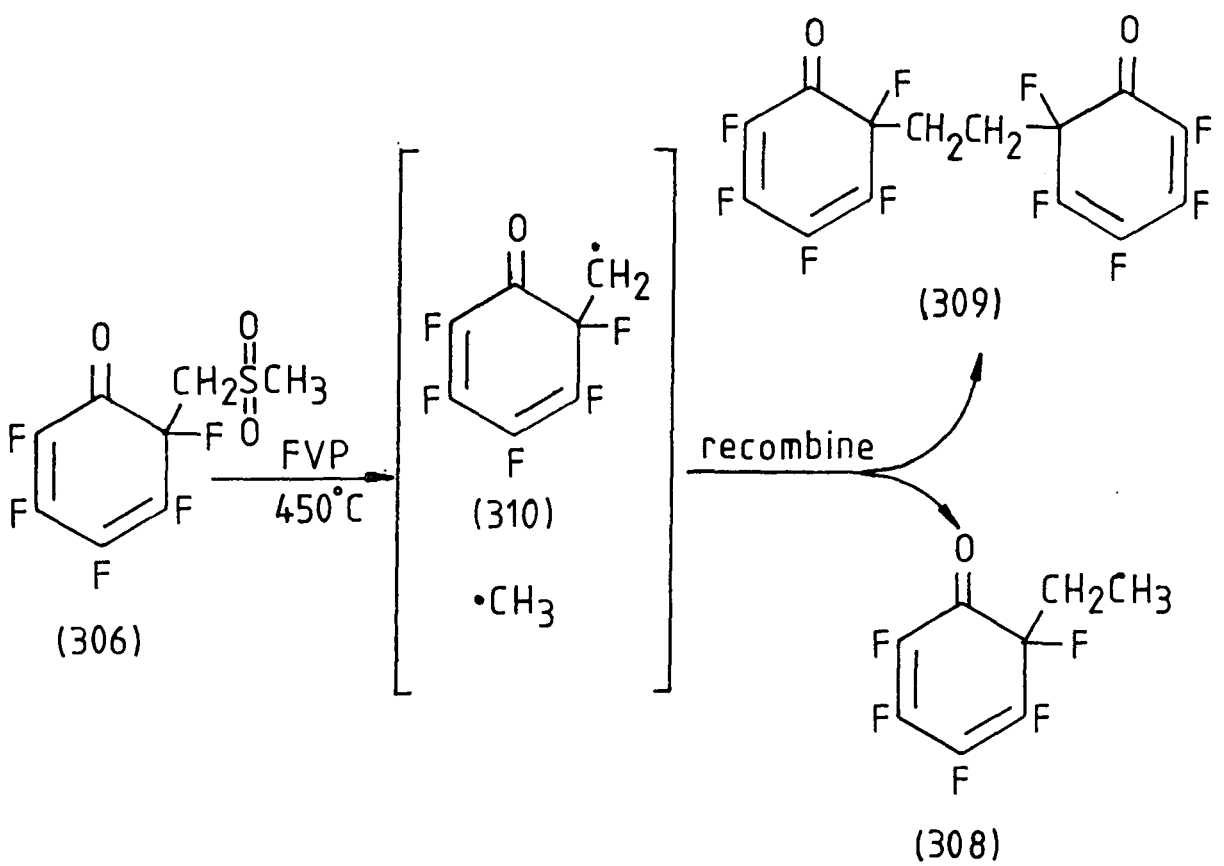


Scheme 143

Flash vapour phase pyrolysis of the naphthalenone sulphone (307) at 540°C resulted in a product containing substantially unchanged sulphone (^{19}F n.m.r.). At 560°C, however, analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated an extremely complex mixture of products from which only

unchanged (307) (21%) could be isolated and identified.

The dienone sulphone (306) was largely recovered unchanged when subjected to F.V.P. at 390°C (^{19}F n.m.r.). At 450°C, a complex reaction product was obtained. Volatile material collected by sublimation of the crude product *in vacuo*/ 0.05mm Hg was shown by ^{19}F n.m.r. spectroscopy to contain one major component, although capillary g.l.c. indicated the presence of at least fifty compounds. Combined g.l.c./mass spectroscopy showed the major component to have M^+, 212, and the infra-red spectrum of the crude volatiles indicated C=O (1710 cm^{-1}). A structure consistent with these data is the ethyl substituted dienone (308), Scheme 144. The involatile material from the crude product also contained only one major component (^{19}F n.m.r.), with a similar set of fluorine resonances as the major volatile component. Although this component could not be isolated for full characterization, mass spectroscopy of a highly enriched sample (obtained by chromatography on silica using CH_2Cl_2 as eluant) showed M^+, 394. A structure consistent with these data is the bis-dienone (309). It would appear, therefore, on the limited data available that thermolysis results in at least cleavage of both C-SO_2 bonds[127] to give the methyl radical, and the radical (310), which subsequently recombine to give (308) and (309). The complexity of the product made it impossible to determine whether decarbonylation had occurred, although it would seem not to be the major process.

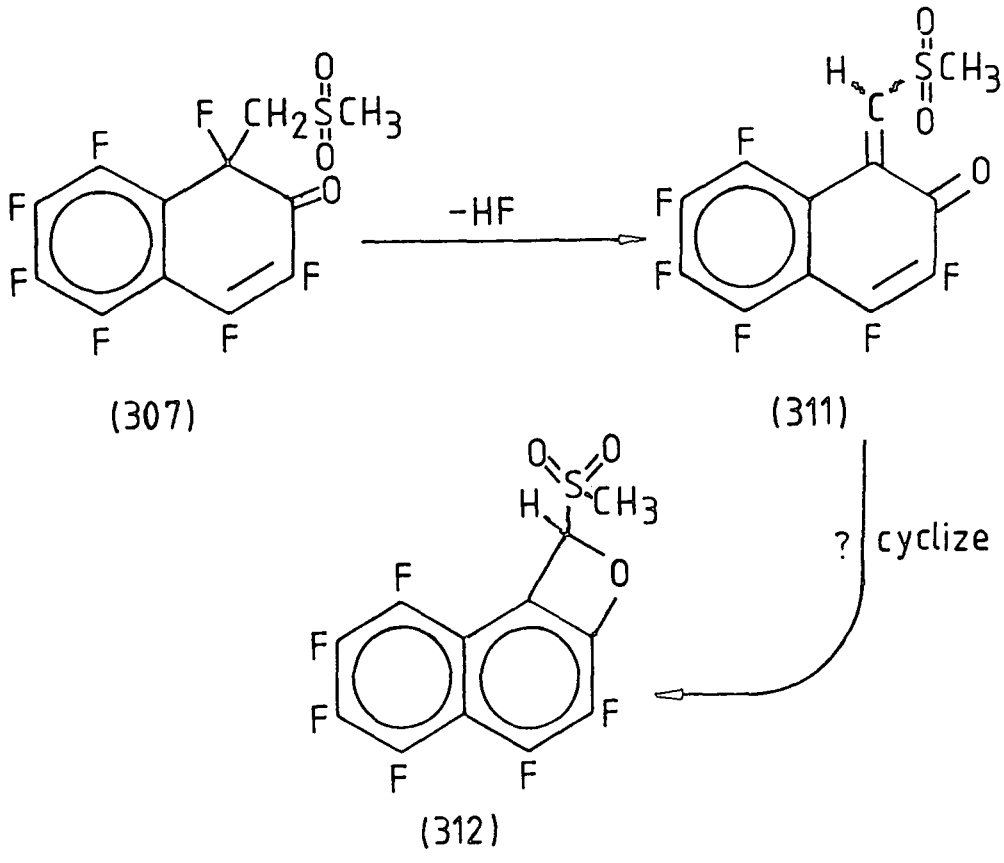


Scheme 144

9.3 Reaction of 1,3,4,5,6,7,8-Heptafluoro-1-Methylsulphonyl-methylnaphthalen-2(1H)-one (307) with Base

An effect of the oxidation of the sulphide group in both (238) and (249) is to increase the acidity of the methylene protons. This should facilitate the elimination of HF across the methylene group, a reaction which would in the case of the naphthalenone sulphone (307), result in the formation of (311), which might undergo an electrocyclization process to give the heterocyclic compound (312), a derivative of 2H-oxete, Scheme 145.

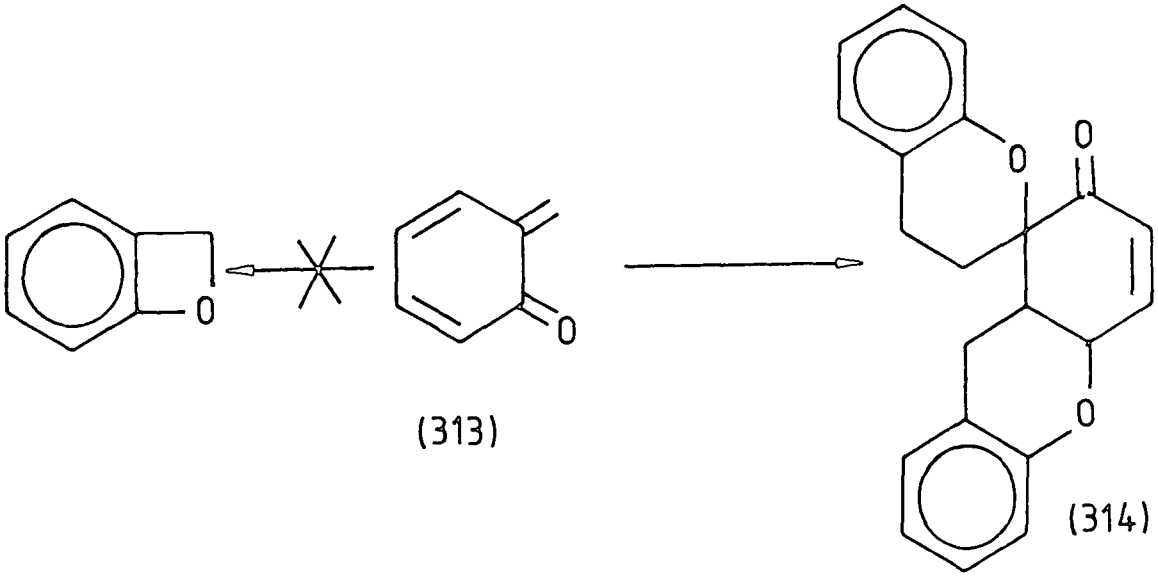
In general 2H-oxete derivatives have limited stability, readily undergoing ring-opening to the αβ-unsaturated enone.[128] Indeed, the parent oxete itself has a half-life in solution at room temperature of only 8h.[129] The fluorinated derivative 2-ethoxy-4,4-bis(trifluoromethyl)-2H-oxete is, however, quite



(307) (311) (312)

Scheme 145

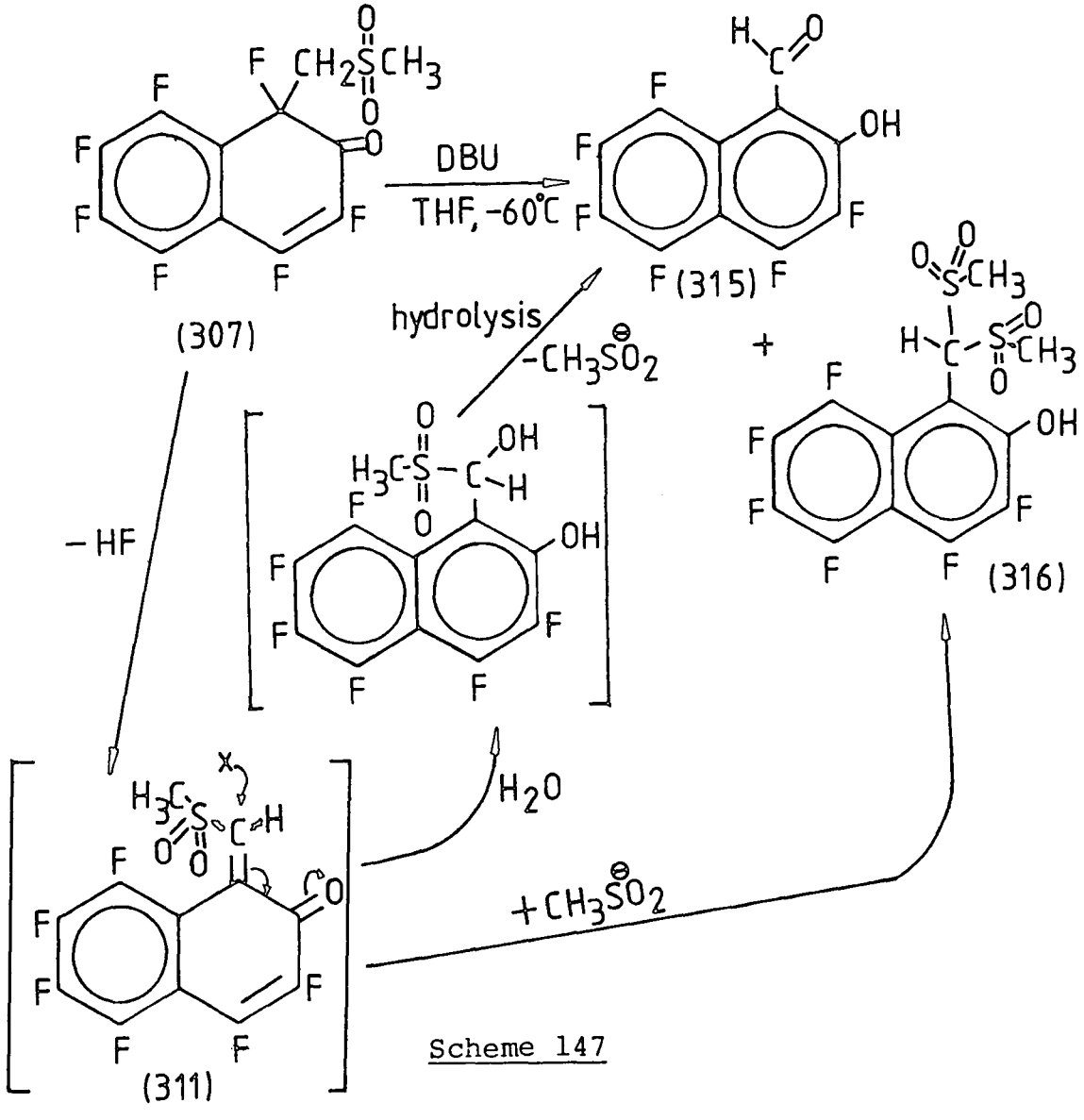
stable,[130] as are other fluorinated oxetes.[130b,c] It might be expected that stabilization of the system would be achieved if the double-bond was part of another conjugated system, since this would reduce the double-bond character, relieving ring strain. However, the ortho-quinomethide (313) has been shown to exist exclusively in the open form (at low temperature) and rapidly undergoes trimerization to (314),[131] Scheme 146.



(313) (314)

Scheme 146

Treatment of the sulphone (307) with potassium fluoride [the same base used in previous dehydrofluorination reactions[39] (see Scheme 37)] at room temperature resulted only in the recovery of unchanged sulphone (98%). At reflux temperature in CH_3CN however, a complex product resulted from which nothing could be isolated. The reaction with the hindered base, 1,8-diazobicyclo[5.2.0]undec-7-ene (DBU), however, was quite different. Addition of DBU to a THF solution of (307) at room temperature resulted in an uncontrollable exothermic process to give an unidentified complex product. Under more controlled conditions at -60°C, the reaction of (307) with DBU gave two compounds: the hydroxy aldehyde (315) (76%) and the bis(methylsulphonyl) derivative (316) (5%), Scheme 147. Neither of the



Scheme 147

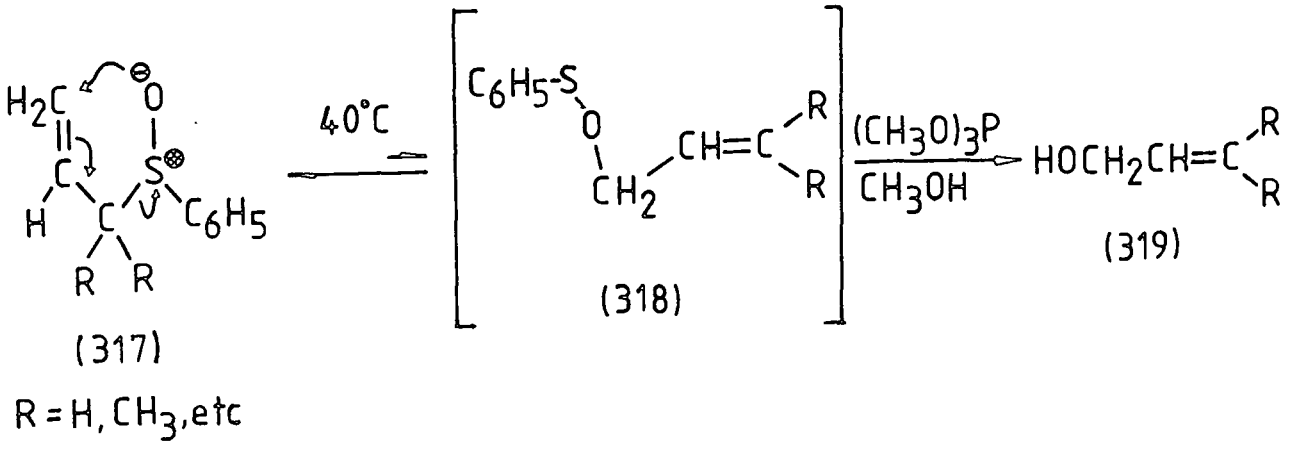
compounds (311) nor (312) were observed, but the existence of (311) is implicated in a rationalization for the formation of the observed products. Thus, addition of DBU results in elimination of HF from (307) to give (311). This then, upon hydration and hydrolysis during work-up, gives the hydroxy aldehyde (315), while the $CH_3SO_2^{\ominus}$ released in the process goes on to attack (311) to give (316). A similar mechanistic process was postulated to account for formation of the hydroxy aldehyde (263) and the bis(thiomethoxy) compound (264) from the reaction of the 3-hydroxypyridine (262) with the DMSO-TFAA complex and triethylamine (see Scheme 123). In the light of these reactions it would seem unlikely that the ortho-quinomethide derivatives (311) and (266) had undergone an electrocyclization. In neither case, however, were attempts made to isolate or trap these proposed 'intermediates', and this area of chemistry may be worthy of further investigation.

CHAPTER TEN

THE PREPARATION AND REACTIONS OF 2,3,4,5,6-PENTAFLUOROBENZYL METHYLSULPHOXIDE (320)

10.1 Introduction

Another type of [2,3] sigmatropic rearrangement, different in character to those described in the previous chapters (Chapters Five-Eight), is the sulphoxide-sulphenate rearrangement.[132] Thus, allylic sulphoxides of the types (317), when heated undergo rearrangement to the isomeric sulphenate esters (318). The process is reversible and the equilibrium highly in favour of the sulphoxide (317). By using a suitable reagent, such as trimethyl phosphite, however, the sulphenate ester (318) can be 'trapped', the overall reaction being conversion of an allylic sulphoxide to an allylic alcohol (319), Scheme 148.



Scheme 148

This type of rearrangement has not been applied to benzylic sulphoxides wherein the olefinic moiety is part of an aromatic ring system, so it was considered interesting to investigate the possibility of such a mode of reaction occurring in the title compound 2,3,4,5,6-pentafluorobenzyl methyl-

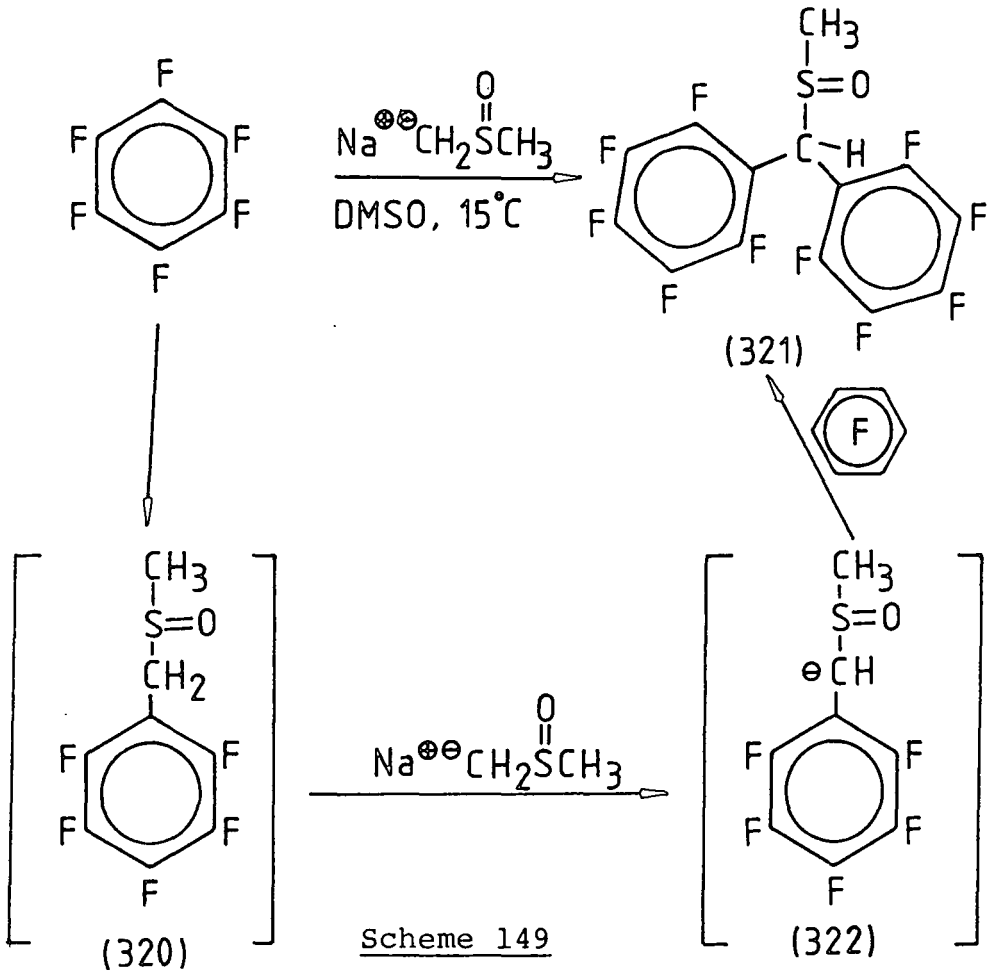
sulphoxide (320).

(A base catalysed rearrangement of the sulphoxide (320), similar to that described in 5.3.1 was also attempted).

10.2 Preparation of the Sulphoxide (320)

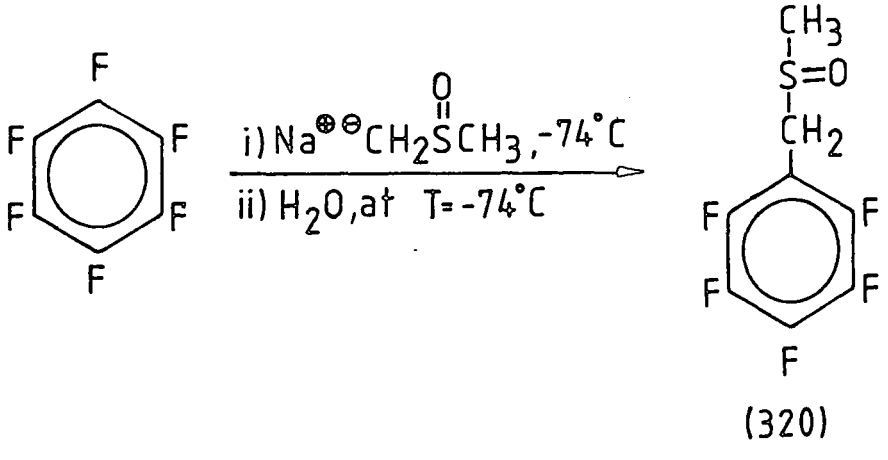
A conceivably simple route to the sulphoxide (320) was one involving simple nucleophilic displacement of a fluorine in hexafluorobenzene with the nucleophilic species derived from treatment of DMSO with sodium hydride; sodium methylsulphinylmethide ($Na^{\oplus\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$).[133] The reaction, however, proved to be more complex than at first envisaged. At a cool temperature (T = 15°C) the reaction of $Na^{\oplus\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$ in DMSO on hexafluorobenzene (1:1 molar ratio) resulted in an exothermic process with the formation of only one major product, the bis(pentafluorophenyl)methyl methylsulphoxide (321) (31%), along with unchanged hexafluorobenzene, Scheme 149. Clearly the expected product (320) had indeed formed, but the $^{\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$ still present had then acted as a base, rather than a nucleophile, removing the acidic benzylic proton of (320) to give (322). This subsequently attacked another molecule of hexafluorobenzene giving the bis-substituted product (321).

The bis-substituted compound (321) (29%) was also obtained when $Na^{\oplus\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$ in DMSO was added to hexafluorobenzene in tetrahydrofuran at -74°C before rapidly warming the reaction mixture to room temperature and quenching with water. A small amount of the expected sulphoxide (320) (6%) was isolated accompanied again by unchanged hexafluorobenzene. By quenching the reaction with water at the low temperature of



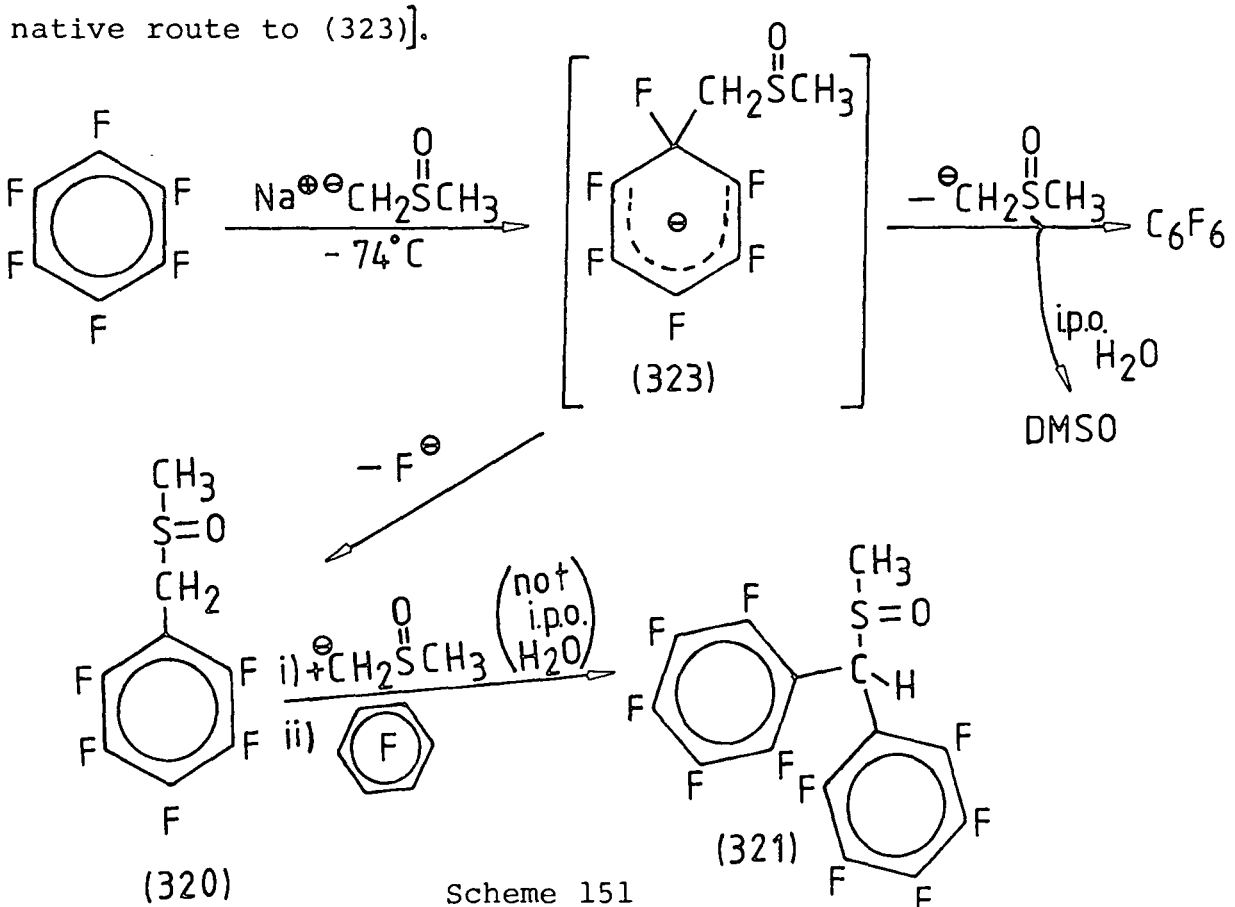
Scheme 149

the reaction, only the expected sulphoxide (320) (37%) was formed along with unchanged hexafluorobenzene, Scheme 150. No increase in the yield of the sulphoxide (320) was achieved when employing a reaction ratio of 2.15:1 ($Na^{\oplus\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$:hexafluorobenzene) rather than 1:1 as used previously, the yield of the sulphoxide still being 37%.



Scheme 150

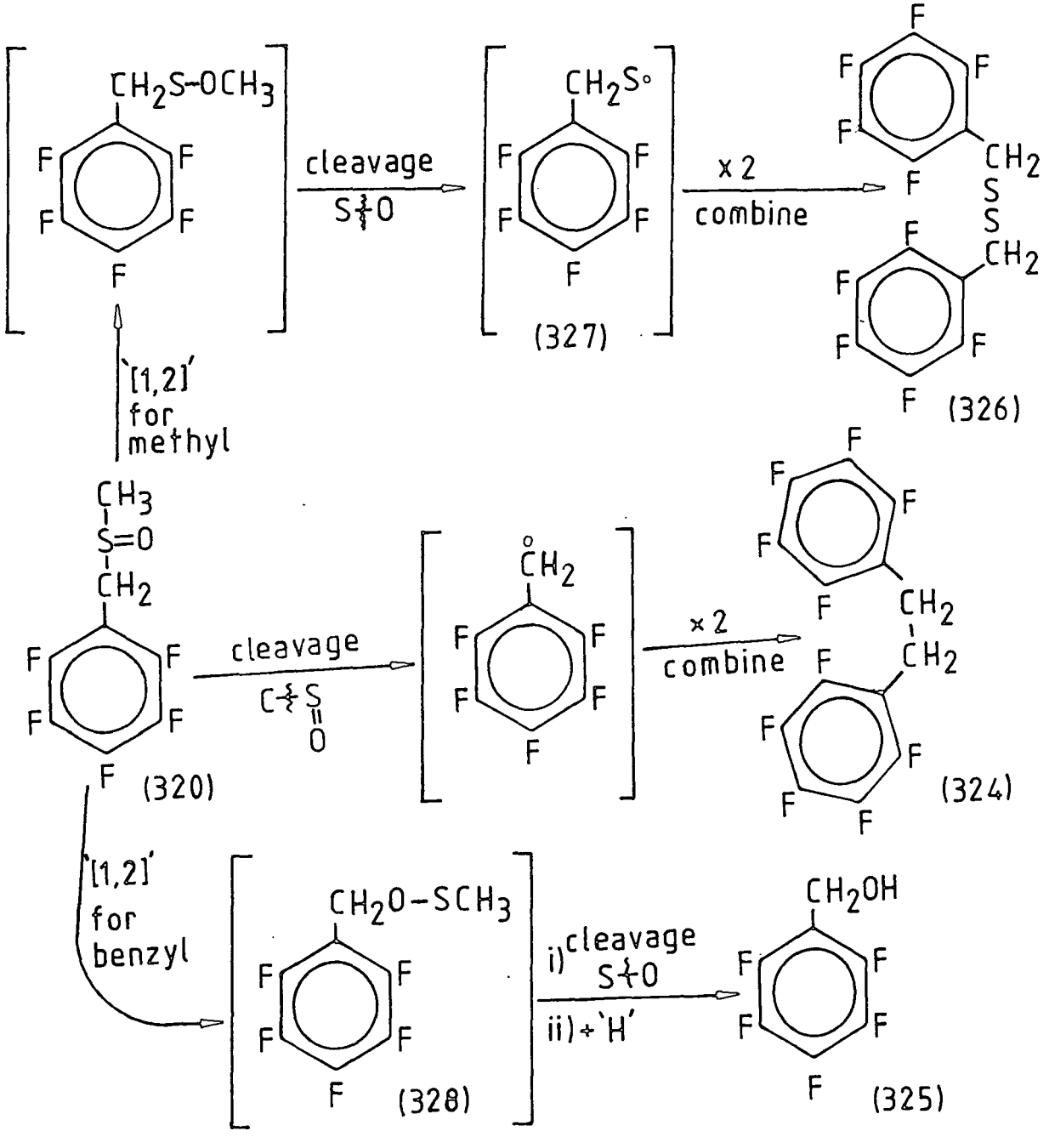
A rationalization for the behaviour observed in this reaction system is shown in Scheme 151. At the low temperature at which the experiment is carried out, attack of $^{\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$ on hexafluorobenzene results in the formation of a 'Meisenheimer' type complex (323).[134] The bright yellow/orange appearance of the reaction mixture is not inconsistent with this. On warming, the complex (323) decomposes by either loss of fluoride <u>or</u> $^{\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$. The former process results in formation of the desired sulphoxide (320), whereas the latter gives hexafluorobenzene and would explain why substantial amounts are always present in the product. The liberated $^{\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$, in the presence of water (see Scheme 150) is immediately quenched forming DMSO, the product then being the sulphoxide (320). However, when water is <u>not present</u> conversion of (320) to the bis-substituted sulphoxide, as shown in Scheme 149, occurs. Formation of the complex (323) also explains why excess $Na^{\oplus\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$, has no effect on the reaction. [Presumably the reaction of CsF with compound (320) would provide an alternative route to (323)].



Scheme 151

10.3 Thermolysis of the Sulphoxide (320)

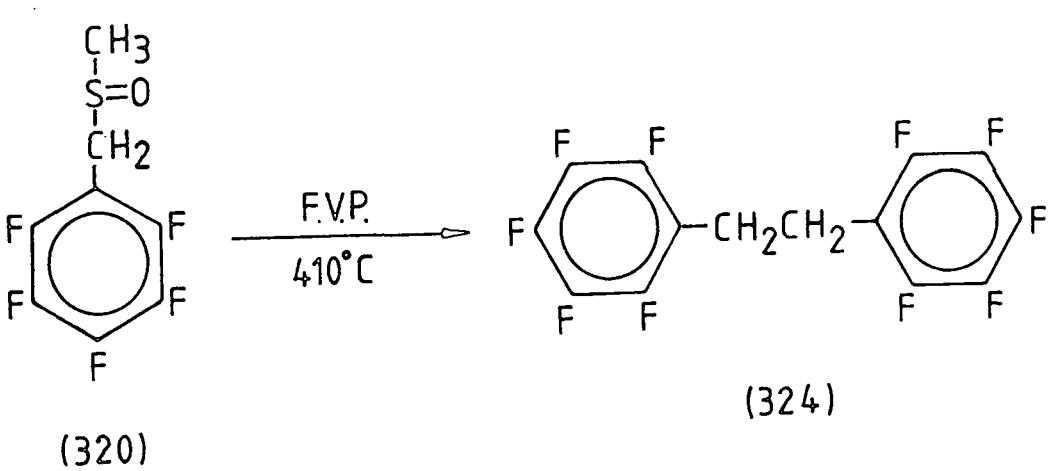
In an attempt to effect a [2,3] rearrangement, the sulphoxide (320) was thermolysed using static vapour phase thermolysis between 140-190°C. A highly complex product resulted, shown by analytical t.l.c. to consist of at least eight components. Only three of these could be isolated and identified; the known decafluorodibenzyl compound (324)[135] (27%) and pentafluorophenylmethanol (325) (22%), accompanied by the decafluorodibenzyl disulphide (326) (7.5%),Scheme 152. A substantial amount of polymeric material was also obtained.



Scheme 152

The mechanism for the formation of the observed products would appear to be one involving the formation of radicals, similar to that found for the sulphone derivatives (306) and (307) (see 9.2.2) and in an exactly similar manner to the thermolysis of the hydrogen analogue of (320) and other similar derivatives.[136] Thus, formation of the dibenzyl compound (324) results from combination of two pentafluorobenzyl radicals formed from cleavage of the C-$\overset{O}{\overset{\|}{S}}$ bond. Formation of both (325) and (326) can be rationalized by an initial '[1,2]' type shift of the methyl or pentafluorobenzyl group onto oxygen before cleavage of the S-OC bond giving (327) and (328) respectively. Combination of two of the radicals (327) then gives the disulphide (326) whilst the radical (328) abstracts a proton to give the methanol derivative (325). A similar explanation is given to account for the formation of PhSSPh and PhOH from the F.V.P. thermolysis of Ph$\overset{O}{\overset{\|}{S}}$Ph.

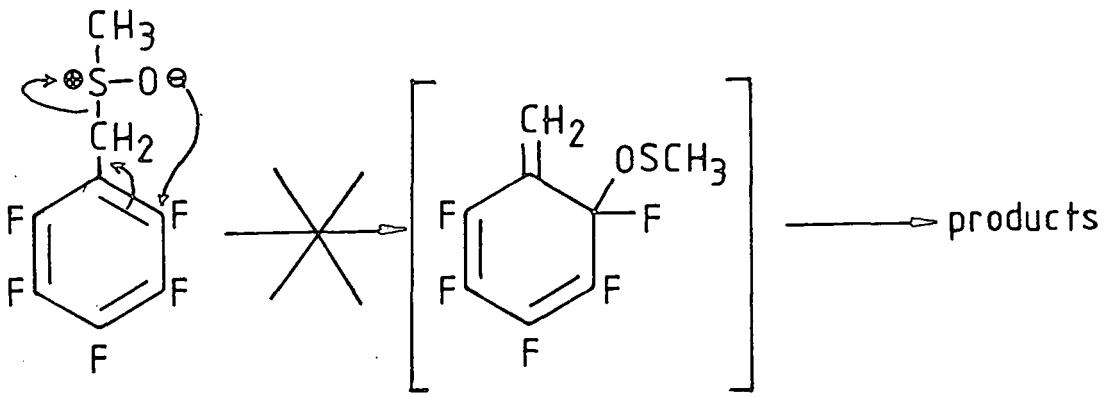
The flash vapour phase thermolysis of the sulphoxide (320) at 410°C resulted in the formation of only a single product, the dibenzyl compound (324) (87%), Scheme 153.



(320) (324)

Scheme 153

It is apparent, therefore, that in the gas phase a [2,3] rearrangement process which would give in the first instance the compound (329) Scheme 154, does not occur, or is not one of the primary modes of reaction. Attempts to rearrange the sulphoxide (320) in the liquid phase using a sulphenate trapping agent were not made, however, so it is still possible that such a rearrangement could be effected.



(329)

Scheme 154

10.4 Reaction of the Sulphoxide (320) with Base

All attempts at producing a base-induced rearrangement in the sulphoxide (320), similar to that observed in 5.3.1, using $Na^{\oplus\ominus}CH_2\overset{O}{\overset{\|}{S}}CH_3$ or sodium hydride as the base resulted only in the formation of an extremely complex, polymeric product from which nothing could be isolated.

EXPERIMENTAL

INSTRUMENTATION

(a) ^{19}F and ^{1}H-nuclear magnetic resonance (n.m.r.) spectra were obtained on either a Bruker AC250 [235MHz (^{19}F), 250MHz (^{1}H)], a Bruker HX 90E [84.7MHz (^{19}F), 90 MHz (^{1}H)], a Varian EM 360L [54.6MHz (^{19}F), 60MHz (^{1}H)] or a Bruker WM 300WB [300 MHz (^{1}H)] situated in the Chemistry Department in Newcastle University). Chemical shifts are expressed in parts per million (p.p.m.) upfield from internal $CFCl_3$ (δ_F) and downfield from internal TMS. All coupling constants are expressed in Hertz (Hz), and the following abbreviations are used in spectral analysis: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad and n=narrow.

(b) Microanalysis were obtained using a Perkin-Elmer C.H.N. 240 Elemental Analyser.

(c) Mass spectra were either determined on an AEI MS9 or Vg Analytical 7070E mass spectrometer both at an ionization beam energy of 70eV.

(d) Ultra-violet spectra were recorded on a Unicam SP800 or Unicam SP8-100 spectrophotometer in 1 cm quartz cells. Extinction coefficients (ε) are given in parentheses after the absorption.

(e) See Appendix A for details of infra-red spectra.

TECHNIQUES AND MATERIALS

(a) Volatile compounds were handled in a conventional glass vacuum system using an Edwards E2M2 two stage high vacuum pump.

(b) Silica gel for column chromatography was Merck Kieselgel 60 (230-400 mesh); preparative thin layer chromatography was performed on plates (20x20x0.1cm) coated with Fluka Kieselgel GF254.

(c) Commercial compounds and solvents were used as received from the supplier. When necessary the solvent was distilled prior to use from an appropriate drying agent according to standard procedures.[137]

CHAPTER ELEVEN

EXPERIMENTAL TO PART A

11.1 Reactions of Tetrafluoropyrimidine

11.1.1 With Allyl Alcohol

Tetrafluoropyrimidine (26.87g), allyl alcohol (65ml) and sodium carbonate (4g) were stirred together at room temperature for 7 days. The mixture was diluted with water, acidified with sulphuric acid (2M), and extracted with ether. The ether extracts were dried ($MgSO_4$), the solvent distilled through a fractionating column (48x1.5cm), and the residue distilled *in vacuo* to give *allyl 2,5,6-trifluoropyrimidin-4-yl ether* (93) (20.4g, 61%), b.p. 74-76°C/17mmHg (Found: C, 43.95; H, 2.65; N, 14.7%; M^+, 190. $C_7H_5F_3N_2O$ requires C, 44.22; H, 2.65; N, 14.74%; M, 190); δ_F ($CDCl_3$), 47.8 (dd, 2-F), 82.1 (dd,6-F), and 176.7 p.p.m. (dd, 5-F); $J_{2\text{-}F,\ 5\text{-}F}$ 25Hz, $J_{5\text{-}F,\ 6\text{-}F}$ 17Hz, $J_{2\text{-}F,6\text{-}F}$ 5Hz; δ_H ($CDCl_3$) ($OCH_2CH_X{=}CH_BH_A$, Z-H_X,H_B), 5.03 (OCH_2), 5.40(H_B), 5.51 (H_A), and 6.10 p.p.m. (H_X), J_{AX} 18Hz, J_{BX}, 10.5Hz, $J_{OCH_2,\ X}$ 6Hz, J_{AB} 1.5Hz.

Sublimation of the residues from the distillation gave 4-hydroxy-2,5,6-trifluoropyrimidine[40] (1.3g, 5%).

11.1.2 With Sodium Allyloxide

Tetrafluoropyrimidine (5.15g) and sodium allyloxide in allyl alcohol (1.25M; 100ml) were heated under reflux for 42h. The mixture was diluted with water, acidified with sulphuric acid (2M) and extracted with ether. The ether

extracts were dried ($MgSO_4$) and the volatiles evaporated. Distillation of the residue *in vacuo* gave *2,4,6-triallyloxy-5-fluoropyrimidine* (138) (5.65g, 63%), b.p. 96-98°C/0.01mmHg (Found: C, 58.9; H, 5.65; N, 10.55%; M^+, 266. $C_{13}H_{15}FN_2O_3$ requires C, 58.64; H, 5.68; N, 10.52%; M, 266); δ_F ($CDCl_3$) 183.8 p.p.m. (s, 5-F); δ_H ($CDCl_3$) 4.73 and 4.85 (2xd, $3xOCH_2$), 5.17-6.00 p.p.m. (m, $3xCH_x=CH_2$), $J_{OCH_2,x}$ 6Hz.

11.1.3 With Prop-2-ynyl Alcohol

Tetrafluoropyrimidine (20.5g), prop-2-ynyl alcohol (10ml) and anhydrous potassium carbonate (10g) reacted exothermically when mixed. After 3h at room temperature, all volatile material was removed *in vacuo*. Recrysatllisation of the residue from light petroleum (b.p. 30-40°C) with external cooling gave *prop-2-ynyl 2,5,6-trifluoropyrimidin-4-yl ether* (101) (17.56g, 69%), m.p. 39.5-40°C (Found: C, 44.95; H, 1.45; N,14.8%; M^+, 188. $C_7H_3F_3N_2O$ requires C, 44.69; H, 1.61; N, 14.89%, M, 188); δ_F ($CDCl_3$) 46.8 (d, 2-F), 80.1 (d, 6-F), and 175.9 p.p.m. (dd, 5-F); $J_{2-F,5-F}$ 24Hz, $J_{5-F,6-F}$ 15Hz; δ_H ($CDCl_3$) 2.37 (t,CH) and 4.85 p.p.m. (d, CH_2); J_{H,CH_2},2Hz.

11.2 Reduction of Prop-2-ynyl 2,5,6-Trifluoropyrimidin-4-yl Ether (101) with Deuterium

The ether (101) (9.7g; 52mmol) and $Pd/BaSO_4$ (0.92g) in ethyl acetate (40ml) was treated at atmospheric pressure, with deuterium (1322 ml; 59mmol). The mixture was then filtered through a drying column ($MgSO_4$) and the solvent removed under reduced pressure. Distillation of the residue

in vacuo gave [2,3-$^{2}H_{2}$] *allyl 2,5,6-trifluoropyrimidin-4-yl ether* (100) (6.13g, 62%), b.p. 74-78°C/17mmHg (Found: M^{+}, 192. $C_7H_3D_2F_3N_2O$ requires M, 192); δ_F as for the ether (93); δ_H ($CDCl_3$) [$OCH_2CD_x{=}CD_BH_A$ (Z-D_x,D_B) and $OCH_2CD_x{=}CH_BD_A$ (Z-D_x,H_B) in the ratio 4.5:1 respectively], 5.00 (CH_2), 5.39 (H_B) and 5.48 p.p.m. (H_A).

11.3 Reactions of Allyl 2,5,6-Trifluoropyrimidin-4-yl Ether (93)

11.3.1 With Sodium Methoxide

(a) The ether (93) (3.7g) and sodium methoxide in methanol (1.3M; 15.5ml) were heated under reflux for 5.75h. The mixture was allowed to cool, then diluted with water, and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvents removed by distillation. Analysis of the crude mixture by ^{19}F n.m.r. spectroscopy indicated a three component mixture in a ratio 74:12:14. Chromatography on silica (20x5cm diam.) using CH_2Cl_2 as eluant gave (as the faster moving and major component) *allyl 2,5-difluoro-6-methoxypyrimidin-4-yl ether* (122) (2.6g, 66%), m.p. 25°C [from light petroleum (b.p. 40-60°C)] (Found: C, 47.45; H, 4.3; N, 13.75%; M^{+}, 202. $C_8H_8FN_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; M, 202); δ_F ($CDCl_3$) 48.8 (d, 2-F) and 178.4 p.p.m. (d, 5-F), $J_{2\text{-}F,\ 5\text{-}F}$ 26Hz; δ_H ($CDCl_3$) 4.03 (s,OCH_3), 4.89 (d, OCH_2) and 5.23-6.07 p.p.m. (m, $CH_x{=}CH_2$), $J_{OCH_2,x}$ 5Hz. The second component eluted from the column was *allyl 5,6-difluoro-2-methoxypyrimidin-4-yl ether* (123) (0.4g, 10%) a liquid obtained by molecular distillation (Found: C, 47.4; H, 4.05; N, 14.25%; M^{+}, 202. $C_8H_8FN_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; M, 202); δ_F ($CDCl_3$) 83.8 (d, 6-F) and

183.1 p.p.m. (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 19Hz; δ_H ($CDCl_3$) 3.93 (s,OCH_3), 4.93 (d, OCH_2) and 5.23-6.03 p.p.m. (m,$CH_x{=}CH_2$), $J_{OCH_2,x}$ 5.5Hz. The component eluted last was *allyl 5-fluoro-2,6-dimethoxypyrimidin-4-yl ether* (124) (0.57g, 14%), m.p. 42-43.5°C [from light petroleum (b.p. 30-40°C)] (Found: C, 50.7; H, 5.4; N, 13.1%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; M, 214); δ_F ($CDCl_3$) 186.2 p.p.m. (s, 5-F); δ_H($CDCl_3$) 3.93 (s, 2-OCH_3), 4.01 (s,6-OCH_3), 4.90 (d,OCH_2) and 5.27-6.03 p.p.m. (m, $CH_x{=}CH_2$), $J_{OCH_2,x}$ 6Hz.

(b) The ether (93) (2.19g) and sodium methoxide in methanol (1.3M, 18ml) were heated under reflux for 30 mins, and then worked up as in (a). Recrystallisation of the crude product from light petroleum (b.p. 30-40°C) gave the dimethoxy compound (124) (2.37g, 96%).

11.3.2 With Lithium Aluminium Hydride

The ether (93) (6.695g; 35mmol) in dry ether (60ml) was cooled in an ice-bath and lithium aluminium hydride in ether (0.233M; 160ml; 37mmol) added. The mixture was then stirred at room temperature for 135 min. before being diluted with water, acidified with sulphuric acid (2M) and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent evaporated to give a product (5.82g, 96%) shown by ^{19}F n.m.r. spectroscopy to be a mixture of two components (111) and (112) in the ratio 75:25 respectively. Chromatography on silica (18x5cm diam.) using $CHCl_3$ as eluant gave a mixture of *allyl 2,5-difluoropyrimidin-4-yl ether* (111) and *allyl 5,6-difluoropyrimidin-4-yl ether* (112) (1.52g) b.p. 74-78°C/11mm Hg in the ratio 91:9 respectively.

(Found: C, 49.05; H, 3.5; N, 16.6%; M^+, 172. $C_7H_2F_2N_2O$ requires C, 48.84; H, 3.51; N, 16.28%; M, 172); compound (111) δ_F ($CDCl_3$) 49.4 (d, 2-F) and 159.8 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 27HZ; δ_H ($CDCl_3$) 4.98 (d, OCH_2), 5.47-6.06 (m,CH_x=CH_2) and 8.18 p.p.m. (s, 6-H), $J_{OCH_2,x}$5Hz; compound (112), δ_F ($CDCl_3$) 86.0 (d, 6-F) and 171.8 p.p.m. (d,5-F), $J_{5\text{-}F,6\text{-}F}$ 19Hz.

11.3.3 With Sodium Allyloxide

The ether (93) (0.622g) and sodium allyloxide in allyl alcohol (1.25M; 7ml) were heated under reflux for 23h. On cooling, the mixture was worked up as in 11.1.2 to give the triallyloxy compound (138) (0.871g, 73%), by comparison with authentic material.

11.3.4 With Sodium Hydroxide

The addition of aqueous sodium hydroxide (2M; 39ml) to a solution of the ether (93) (5.03g) in dioxan (80ml) resulted in a temperature rise of 20°C above room temperature. The mixture was allowed to cool to room temperature over 105 mins. then diluted with water, acidified with sulphuric acid (2M) and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvents evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy revealed the presence of two compounds (125) and (126) in the ratio 70:30 respectively. The attempted sublimation at 50°C/0.05mmHg or fractional crystallisation of the crude product with undried light petroleum (b.p. 100-120°C) resulted in the further reaction of the minor component (126) to give a new compound (131). The mixture was sublimed at 50°C/0.05mmHg to give *allyl 2,5-difluoro-6-hydroxypyrimidin-4-yl ether* (125) (1.57g, 32%),

m.p. 123-124°C [from light petroleum (b.p. 100-120°C)] (Found: C, 44.9; H, 3.2; N, 15.3%; M^+, 188. $C_7H_6F_2N_2O_2$ requires C, 44.69; H, 3.21; N, 14.89%; M, 188); δ_F ($CDCl_3$) 51.7 (d,2-F) and 178.2 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 25Hz; δ_H ($CDCl_3$) 4.92 (d,OCH_2), 5.27-6.17 (m,CH_x=CH_2) and 12.5 p.p.m. (bs,OH) $J_{OCH_2,x}$ 5Hz; continued sublimation at 75-120°C/0.05mmHg and successive crystallization of the sublimate from water followed by toluene gave *5-allyl-5-fluoropyrimidine-2,4,6 (1H,3H,5H)-trione* (131) (0.56g, 11%), m.p. 170-171°C (lit.,[51] 163-164°C) (Found: C, 45.0; H, 3.5; N, 14.65%; M^+, 186. $C_7H_7FN_2O_3$ requires C, 45.16; H, 3.79; N, 15.05%; M, 186); δ_F ($CDCl_3$) 171.9 p.p.m. (t, 5-F), $J_{CH_2,CF}$ 15Hz; δ_H ($CDCl_3$) 2.91 (dd, $CFCH_2$), 5.24-5.62 (m,CH_x=CH_2) and 7.83 p.p.m. (bs, 2xNH) $J_{CFCH_2,x}$ 7.5Hz; the precursor to (131), allyl 5,6-difluoro-2-hydroxypyrimidin-4-yl ether (126), δ_F ($CDCl_3$) 85.3 (d,6-F) and 185.3 p.p.m. (d,5-F), $J_{5\text{-}F,6\text{-}F}$ 18Hz could not be isolated.

11.3.5 With Sodium Hydroxide followed by Diazomethane

(a) In Dioxan: The ether (93) (2.63g), aqueous sodium hydroxide (2M; 20ml) and dioxan (40ml) were allowed to react at room temperature for 1.5h. The mixture was diluted with water, acidified with sulphuric acid (2M) and extracted with ether. The ether extracts were then dried ($MgSO_4$) and some of the solvent evaporated. To this solution was added an excess of diazomethane in ether. Unreacted diazomethane was distilled from the mixture into glacial acetic acid, and the solvents evaporated. Analysis of the crude, methylated product indicated three major products in the ratio 3:1:1 together with a number of minor components. Chromatography

on silica (20x5cm diam.) using CH_2Cl_2 as eluant gave two fast moving components, the 6-methoxy compound (122) (0.18g, 6%) (the major component in the crude product) followed by the 2-methoxy compound (123) (0.17g, 6%). Further development of the column using ether and sublimation at 40°C/0.05mmHg gave as the third major product *6-allyloxy-2,5-difluoro-3-methylpyrimidin-4(3H)-one* (132) (0.08g, 3%), m.p. 42-44°C (Found: C, 47.2; H, 4.0; N, 13.7%; M^+, 202. $C_8H_8F_2N_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; M, 202); δ_F ($CDCl_3$) 56.7 (d, 2-F) and 176.5 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 24Hz; δ_H ($CDCl_3$) 3.51 (d,NCH_3), 4.83 (d,OCH_2), and 5.23-6.02 p.p.m (m,$CH_x{=}CH_2$), J_{F,NCH_3} 2Hz, $J_{OCH_2,x}$ 5.5Hz; λ_{max} (cyclohexane) 233 (ε 3,100) and 272nm (3,300). The component eluted last was one of the minor components, and found to be *5-allyl-1,3-dimethyl-5-fluoropyrimidine-2,4,6(1H,3H,5H)-trione* (133) (0.03g, 1%), m.p. 75-76°C [from light petroleum (b.p. 60-80°C)] (Found: C, 50.5; H, 4.8; N, 12.8%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18, N, 13.08%; M, 214); δ_F ($CDCl_3$) 164.4 p.p.m. (t,5-F), $J_{CH_2,CF}$ 14Hz; δ_H ($CDCl_3$) 2.91 (dd, $CFCH_2$), 3.32 (s,2xNCH_3) and 5.20-5.63 p.p.m. (m,$CH_x{=}CH_2$), $J_{CFCH_2,x}$ 7Hz.

(b) <u>In Tetrahydrofuran</u>: The ether (93) (1.87g), aqueous hydroxide (2M; 9.5ml) and THF (20ml) were stirred at room temperature for 20h and then worked up as in (a). Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated the two compounds (125) and (126) in the ratio 2:1. After treatment with diazomethane three products were present in the ratio 43:28:18. These were separated by chromatography on silica (20x5cm diam.) using CH_2Cl_2 as eluant to give the 6-methoxy compound (122) (0.717g, 36%), the 2-methoxy com-

pound (123) (0.508g, 26%) and the N-methyl compound (132) (0.244g, 12%) in that order.

11.3.6 With Potassium Hydroxide

The ether (93) (0.404g), potassium hydroxide (0.3g) and *t*-butyl alcohol (10ml) were refluxed for 2h. The *t*-butyl alcohol was evaporated, the residue diluted with water, acidified with sulphuric acid (2M) and ether extracted. The ether extracts were dried ($MgSO_4$) and the solvent evaporated. Sublimation of the crude product at room temperature (0.05mmHg) and recrystallization of the sublimate from light petroleum (b.p. 100-120°C) gave the 6-hydroxy compound (125) (0.272g, 68%) by comparison with authentic material.

11.3.7 With Hot Aqueous Alkali followed by Diazomethane

(a) With KOH: The ether (93) (2.45g), potassium hydroxide (1.5g), water (25ml) and dioxan (25ml) were heated under reflux for 64h. The mixture was diluted with water, acidified with sulphuric acid and extracted using continuous ether extraction for 24h. The ether extracts were dried ($MgSO_4$) and some of the solvent evaporated. Excess diazomethane in ether was added to the crude product, the unreacted diazomethane distilled off into glacial acetic acid, and the solvents removed under reduced pressure. Distillation of the residue *in vacuo* gave *methyl 2-fluoropent-4-enoate* (135) (0.236g, 14%), b.p. 54-56°C/13mmHg (Found: C, 54.45; H, 6.75%; M^+-HF, 112. $C_6H_9FO_2$ requires C, 54.54; H, 6.87%; M, 132); δ_F ($CDCl_3$) 192.4 p.p.m. (dt, 2-F), $J_{CH,F}$ 48Hz, $J_{CH_2,CF}$ 24Hz; δ_H ($CDCl_3$) 2.66 (m, CH_AH_BCF), 3.80 (s, OCH_3), 4.98 (ddd, CHF) 5.18-5.82 p.p.m. (m, $CH_X=CH_2$), J_{CHF,CH_AH_B} 7Hz each.

(b) With NaOH: The ether (93) (5.546g), aqueous sodium hydroxide (2M, 58.5ml), and dioxan (30ml) were heated under reflux for 22h, and the product worked up as in (a) to give the two products (135) and (136) in the ratio 15:85 respectively. Compound (135) was evaporated at 25°C/12mmHg and the residue was distilled to give *dimethyl 2-allyl-2-fluoropropanedioate* (136) (1.43g, 26%), b.p. 105-110°C/12mmHg (Found: C, 50.75; H, 6.15%; M^+, 190. $C_8H_{11}FO_4$ requires C, 50.52; H, 5.83%; M, 190); δ_F ($CDCl_3$) 166.2 p.p.m. (t,2-F), $J_{CH_2,CF}$ 23Hz; δ_H ($CDCl_3$) 2.92 (dd, $CFCH_2$), 3.83 (s,OCH_3) and 5.07-5.77 p.p.m. (m,CH_x=CH_2), $J_{CFCH_2,x}$ 6Hz.

11.4 Reaction of Allyl 2,5-Difluoro-6-Hydroxypyrimidin-4-yl Ether (125) with Diazomethane

Excess diazomethane was added to the 6-hydroxy compound (125) (0.815g) in ether (20ml), the excess unreacted diazomethane distilled off into glacial acetic acid, and the solvent evaporated. Examination of the crude product by analytical t.l.c. (CH_2Cl_2 as eluant) indicated a three component mixture. These were separated by chromatography on silica (15x5cm diam.) to give as the faster and major component, the 6-methoxy compound (122) (0.585g, 67%). This was followed by the N-methyl compound (132) (0.166g, 19%) on elution of the column with ether. The third component could not be isolated.

11.5 Reaction of 2,5,6-Trifluoro-4-Methoxypyrimidine (115) with Sodium Methoxide

The 4-methoxy compound (115) (3.04g) and a solution of sodium methoxide in methanol (1.1M; 16.6ml) were heated at

reflux for 7.5h. On cooling, the mixture was diluted with water, and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated a three component mixture in the ratio 13:4:1. These were separated by chromatography on silica (20x5mm diam.) using CH_2Cl_2 as eluant to give the major component 2,5-difluoro-4,6-dimethoxypyrimidine[40] (116) (2.3g, 70%). The next component eluted from the column was *5,6-difluoro-2,4-dimethoxypyrimidine* (117) (0.42g, 13%) m.p. 36-38°C [from light petroleum (b.p. 30-40°C)] (Found: C, 41.1; H, 3.7; N, 15.8%; M^+, 176. $C_6H_6N_2O_2F_2$ requires C, 40.92; H, 3.43; N, 15.91%; M, 176); δ_F ($CDCl_3$) 84.2 (d,6-F), and 184.2 p.p.m. (d,5-F), $J_{5\text{-}F,6\text{-}F}$ 19Hz; δ_H ($CDCl_3$) 3.9 (s,2-OCH_3) and 4.1 p.p.m. (s, 6-OCH_3). The last component eluted was 5-fluoro-2,4,6-trimethoxypyrimidine (118) (0.12g, 3%).

11.6 Reactions of 2,5-Difluoro-4,6-Dimethoxypyrimidine (116)

11.6.1 With Sodium Allyloxide in Tetrahydrofuran

Sodium hydride was added to allyl alcohol (0.378g) in THF until the evolution of hydrogen ceased, after which the dimethoxy compound (116) (1.09g) was added, and the mixture heated under reflux for 1h. On cooling, the mixture was diluted with water and extracted with ether. The ether extracts were dried ($MgSO_4$), the solvent evaporated, and the residue recrystallized from light petroleum (b.p. 30-40°C) to give *allyl 5-fluoro-4,6-dimethoxypyrimidin-2-yl ether* (137) (1.32g, 99%), m.p. 41.5-42.5°C (Found: C, 50.4; H, 5.5; N, 12.9%; M^+,214.

$C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; M, 214); δ_F ($CDCl_3$) 185.9 p.p.m. (s,5-F); δ_H ($CDCl_3$) 4.02 (s,2xOCH_3), 4.78 (d,OCH_2), and 5.13-6.00 p.p.m. (m,CH_x=CH_2), $J_{OCH_2,x}$ 5.5Hz.

11.6.2 With Sodium Allyloxide in Allyl Alcohol

A mixture of the dimethoxy compound (116) (2.027g) and sodium allyloxide in allyl alcohol (1.25M, 12ml) was heated under reflux for 17h. On cooling the mixture was diluted with water, acidified with sulphuric acid (2M) and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvents evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated three components in the ratio 5:2:1. These were separated by chromatography on silica (15x5cm diam.) using CH_2Cl_2 as eluant to give as the major product the triallyloxy compound (138) (0.892g, 29%), followed by *2,4-diallyloxy-5-fluoro-6-methoxypyrimidine* (139) (0.24g, 9%), m.p. 23-25.5°C [from light petroleum (b.p. 30-40°C)] (Found: C, 54.95; H, 5.3; N, 11.35%; M^+, 240. $C_{11}H_{13}FN_2O_3$ requires C, 54.99; H, 5.45; N, 11.66%; M, 240); δ_F ($CDCl_3$) 185.1 p.p.m. (s,5-F); δ_H ($CDCl_3$) 4.0 (s,OCH_3), 4.78 and 4.88 (m,2xOCH_2), and 5.18-6.03 p.p.m. (m,2xCH=CH_2). The third component could not be isolated.

11.6.3 With Potassium Hydroxide

The dimethoxy compound (116) (0.066g), potassium hydroxide (0.101g) and *t*-butyl alcohol (5ml) were heated under reflux for 18h. The mixture was diluted with water on cooling, acidified with sulphuric acid (2M) and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent evaporated

to give *5-fluoro-2-hydroxy-4,6-dimethoxypyrimidine* (155) (0.052g, 80%), m.p. 183-185°C (from diethyl ether) (Found: C, 41.75; H, 3.7; N, 16.2%; M^+, 174. $C_6H_7N_2FO_2$ requires C, 41.38; H,4.05; N, 16.09%; M, 174); δ_F ([$^2H_6$]acetone), 187.0 p.p.m. (s,5-F); δ_H ([$^2H_6$]acetone) 4.02 (s, 2xOCH_3) and 7-8 p.p.m. (bs, OH).

11.7 Reaction of 2,5,6-Trifluoro-4-Hydroxypyrimidine and its Sodium Salt with Allyl Bromide

11.7.1 Reaction of the Sodium Salt

The 4-hydroxy compound (2.39g) was dissolved in THF (10ml), and an excess of sodium hydride added. The resulting solution was decanted, and the residue washed with THF (20ml). Allyl bromide (1.65ml) was added to the THF solution, and the mixture heated under reflux for 3d. On cooling, the solvent was evaporated. Volatile material (0.722g) was removed *in vacuo* (0.05mm Hg) and shown by ^{19}F n.m.r. spectroscopy to consist of three components in the ratio 65:20:14. These were separated by chromatography on silica (20x5cm diam.) using CH_2Cl_2 as eluant to give the ether (93) (0.128g, 4%) followed by the major component *3-allyl-2,5,6-trifluoropyrimidin-4(3H)-one* (99) (0.365g, 12%), m.p. 33-34°C [from light petroleum (b.p. 30-40°C)] (Found: C, 44.15; H, 2.5; N, 14.5%; M^+, 190. $C_7H_5F_2N_2O_2$ requires C, 44.22; H, 2.65; N, 14.74%; M, 190); δ_F ($CDCl_3$) 57.1 (dd,2-F), 90.4 (dd, 6-F), and 172.4 p.p.m.(dd, 5-F), $J_{2\text{-}F,5\text{-}F}$ 23Hz, $J_{2\text{-}F,6\text{-}F}$ 8.5Hz, $J_{4\text{-}F,6\text{-}F}$ 13Hz; δ_H ($CDCl_3$) ($CH_2CH_X{=}CH_BH_A$, Z-H_XH_B) 4.64 (NCH_2), 5.35 (H_A), 5.37 (H_B), 5.89 p.p.m. (H_X), J_{AX} 17Hz, J_{BX} 10Hz, $J_{CH_2,X}$ 6Hz; λ_{max} (cyclohexane) 221 (ε4,400) and 265nm (3,900).

11.7.2 Reaction of the Hydroxy Compound

The 4-hydroxy compound (2.23g), allyl bromide (1.90g) and anhydrous potassium carbonate (1.5g) were refluxed in acetone (20ml) for 23h. On cooling the mixture was filtered through a drying column ($MgSO_4$) and the solvent evaporated. Volatile material was removed *in vacuo*: (i) at room temperature /0.05mm Hg to give the ether (93) (1.35g, 48%) and the N-allyl compound (99) (1%); and (ii) at 70°C/ 0.05mm Hg to give a mixture of two components (0.402g) shown by ^{19}F n.m.r. spectroscopy to be present in the ratio 2:1. The major component was isolated by preparative t.l.c. on silica (20x20cm) using CH_2Cl_2 as eluant to give *1,3-diallyl-5,6-difluoropyrimidine-2,4(1H,3H)-dione* (107) (0.128g, 4%), a liquid obtained by molecular distillation (Found: C, 52.75; N, 4.3; N, 12.5%; M^+, 228. $C_{10}H_{10}F_2N_2O_2$ requires C, 52.63, H, 4.42; N, 12.28%; M, 228); δ_F ($CDCl_3$) 116.8 (d,6-F) and 187.8 p.p.m. (d,5-F), $J_{5\text{-}F,6\text{-}F}$ 8.5Hz; δ_H ($CDCl_3$) 4.47 (m,2xNCH_2) and 5.17-5.73 p.p.m. (m,2x$CH{=}CH_2$).

The non-sublimable residue was acidified with sulphuric acid and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent evaporated. Sublimation of the residue gave two fractions: fraction (i) at room temperature/0.05mm Hg gave unchanged pyrimidin-4-ol (0.31g, 14%); and fraction (ii) at 70°C/0.05mm Hg gave *3-allyl-5,6-difluoropyrimidine-2,4(1H,3H)-dione* (106) (0.186g, 7%), m.p. 95-96°C [from light petroleum (b.p. 100-120°C)] (Found: C, 44.55; H, 3.35; N, 14.6%M^+, 188. $C_7H_6F_2N_2O_2$ requires C, 44.68; H, 3.22; N, 14.89%; M, 188); δ_F ($CDCl_3$) 115.8 (d,6-F) and 186.4 (d,5-F), $J_{5\text{-}F,6\text{-}F}$ 8Hz; δ_H ($CDCl_3$) 4.55 (d,NCH_2),

5.26-5.86 (m,$CH_x{=}CH_2$) and 11.13 p.p.m. (bs,NH), $J_{NCH_2,x}$ 6Hz.

11.8 Thermolysis Reactions

11.8.1 Allyl 2,5,6-Trifluoropyrimidin-4-yl Ether (93)

(a) Static Vapour Phase (S.V.P.): The ether (93) (0.5g) was sealed *in vacuo* in a 2*l*. flask and heated at 210°C for 9h. On cooling the flask was opened and washed out with ether, and the ether evaporated to give unchanged ether (92) (0.398g, 80%).

(b) Flash Vapour Phase (F.V.P.): The ether (93) (2.30g) was distilled through a quartz tube [60x1.5cm diam. packed with silica fibre (20x1.5cm)] heated at 440°C, into a trap cooled with liquid air connected to a high vacuum system (0.005mm Hg). Analysis of the crude tarry product by ^{19}F n.m.r. spectroscopy indicated a mixture of the ether (93) (12%) and the N-allyl compound (99) (1.23g, 53%) separated by distillation and recrystallization from light petroleum (b.p. 30-40°C).

(c) Liquid Phase in Sulpholane: The ether (93) (4.95g), anhydrous potassium fluoride (2.5g) and dry sulpholane (20ml) were heated together in a sealed nickel tube (capacity: 90ml) at 194°C for 18h. The mixture was diluted with water, acidified with sulphuric acid (2M), and extracted with ether. The ether extracts were dried ($MgSO_4$), the ether evaporated and the residue distilled *in vacuo* at 106-110°C/8mm Hg and recrystallized from light petroleum (b.p. 30-40°C) to give the N-allyl compound (99) (1.10g, 22%).

11.8.2 [2,3-$^2H_2$]Allyl 2,5,6-Trifluoropyrimidin-4-yl Ether (100)

The ether (100) (1.361g) was pyrolysed by F.V.P.

at 440°C, and the crude tarry product separated by chromatography on silica (10x3.5cm diam.), using CH_2Cl_2 as eluant to give *3-[1,2-$^2H_2$]allyl-2,5,6-trifluoropyrimidin-4(3H)-one* (102) (0.61g, 45%), m.p. 32-34°C [from light petroleum (b.p. 30-40°C)] (Found: M^+, 192. $C_7H_3D_2F_2N_2O_2$ requires M, 192); δ_F ($CDCl_3$) 57.1 (dd, 2-F), 90.4 (dd,6-F), and 172.4 p.p.m. (dd, 5-F), $J_{2\text{-}F,5\text{-}F}$ 23Hz, $J_{2\text{-}F,6\text{-}F}$ 8.5Hz, $J_{5\text{-}F,6\text{-}F}$ 13Hz; δ_H ($CDCl_3$) ($CHDCD_X{=}CH_BH_A$, $Z\text{-}D_X,H_B$), 4.63 (CHD), 5.36 (H_A) and 5.38 p.p.m. (H_B) in the ratio 1:1.05:1.05 respectively; λ_{max} (cyclohexane) 226 (2,800) and 263 nm (3,800)

11.8.3 Allyl 2,5 (and 5,6)-Difluoropyrimidin-4-yl Ether (111) [and (112)]

A mixture of the ether (111) and (112) (91:9 respectively) were pyrolysed by F.V.P. at 470°C. Analysis of the crude product by ^{19}F n.m.r. spectroscopy showed that the product contained two products in the ratio 94:6. These were separated by chromatography on silica (10x3.5cm diam.), using CH_2Cl_2 as eluant, to give the major component *3-allyl-2,5-difluoropyrimidin-4(3H)-one* (113) (0.432g, 67%), m.p. 37-39°C [from diethyl ether - light petroleum (b.p. 40-60°C)] (Found: C, 49.1; H, 3.45; N, 16.25%, M^+, 172. $C_7H_2F_2N_2O$ requires C, 48.84; H, 3.5; N, 16.28%; M, 172); δ_F ($CDCl_3$) 58.7 (d,2-F) and 152.7 p.p.m. (d,5-F), $J_{2\text{-}F,5\text{-}F}$ 24.5Hz; δ_H ($CDCl_3$) 4.65 (d,NCH_2), 5.33-5.89 (m,$CH_X{=}CH_2$) and 7.65 p.p.m. (d,6-H), $J_{F,6\text{-}H}$ 1.5Hz, $J_{NCH_2,X}$ 6Hz; λ_{max} (cyclohexane) 218 (ε2,800) and 266nm (3,900).

11.8.4 Allyl 2,5-Difluoro-6-Methoxypyrimidin-4-yl Ether (122)

(a) Flash Vapour Phase: The ether (122) (0.542g) was pyrolysed by F.V.P. at 475°C to give a crude product shown by ^{19}F n.m.r.

spectroscopy to consist of two components in the ratio 3:1. These were separated by chromatography on silica (10x3.5cm diam.) using CH_2Cl_2 as eluant to give unchanged starting material as the faster moving and minor component (122)(0.77g, 14%). The second component eluted was *3-allyl-2,5-difluoro-6-methoxypyrimidin-4(3H)-one* (140) (0.353g, 65%), m.p. 72-72.5°C [from light petroleum (b.p. 30-40°C)] (Found: C, 47.75; H,4.25; N, 13.6%; M^+, 202. $C_8H_8F_2N_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; M, 202); δ_F ($CDCl_3$) 58.2 (d,2-F) and 176.8 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 24Hz; δ_H ($CDCl_3$) 3.99 (s, OCH_3), 4.61 (d, NCH_2), and 5.30-5.88 p.p.m. (m, $CH_x{=}CH_2$), $J_{NCH_2,x}$ 6Hz; λ_{max} (cyclohexane) 233 (ε3,500) and 272nm (3900).

(b) Static Vapour Phase: The ether (122) (0.56g) was sealed *in vacuo* in a 2*l* flask and heated at 210°C for 69h. The flask was washed out with ether and the ether evaporated. Analysis of the crude product (0.089g) by ^{19}F n.m.r. spectroscopy indicated a two component mixture in the ratio 7:4. Sublimation at 70°C/0.05mm Hg gave an equal mixture of both components (0.028g). Recrystallization of the residue from light petroleum (b.p. 80-100°C) gave the major component *5-allyl-5-fluoro-1-methylpyrimidine-2,4,6 (1H,3H,5H)-trione* (142) (0.036g, 6%) m.p. 116-118°C (Found: C, 48.25; H, 4.35; N, 13.75%; M^+, 200. $C_8H_9FN_2O_3$ requires C, 48.00; H, 4.53; N, 14.00%; M, 200); δ_F ($CDCl_3$) 160.1 p.p.m. (t, 5-F), J_{CF,CH_2} 14.5Hz; δ_H ($CDCl_3$) 2.95 (dd,$CFCH_2$), 3.31 (s,NCH_3), 5.26-5.64 (m,$CH_x{=}CH_2$) and 8.01 p.p.m. (bs, NH), $J_{CFCH_2,x}$ 7Hz. The other component could not be isolated.

11.8.5 Allyl 5,6-Difluoro-2-Methoxypyrimidin-4-yl Ether (123)

The ether (123) (0.673g) was pyrolysed by F.V.P. at 470°C, to give a product shown by ^{19}F n.m.r. spectroscopy to consist of two components in the ratio 4.5:1. These were separated by chromatography on silica (15x3.5cm.diam.), using CH_2Cl_2 as eluant to give the minor component, unchanged ether (123) (0.108g,16%) followed by *3-allyl-5,6-difluoro-2-methoxypyrimidin-4(3H)-one* (144) (0.44g, 65%), a liquid obtained by molecular distillation. (Found: C, 47.65; H, 3.8; N, 13.55%; M^+, 202. $C_8H_8F_2N_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; M, 202); δ_F ($CDCl_3$) 90.3 (d,6-F) and 180.4 p.p.m. (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 14Hz; δ_H ($CDCl_3$) 4.00 (s,OCH_3), 4.62 (d, NCH_2) and 5.23-5.83 p.p.m. (m,$CH_x{=}CH_2$), $J_{NCH_2,x}$ 6Hz; λ_{max} (cyclohexane) 219 (ε4,500) and 266nm (6,200).

11.8.6 Allyl 5-Fluoro-2,6-Dimethoxypyrimidin-4-yl Ether (124)

The ether (124) (2.149g) was pyrolysed by F.V.P. at 480°C. Analysis of the crude polymeric product indicated a multicomponent mixture containing (124), (145), (147), (146) and unknown materials in the ratio 11:27:51:5:6 respectively. These were separated (in the order given) by chromatography on silica (20x5cm diam.) using CH_2Cl_2-ethyl acetate (80:20,v/v) as eluant to give (i) unchanged starting material (124) (0.248g, 11%); (ii) *3-allyl-5-fluoro-2,6-dimethoxypyrimidin-4(3H)-one* (145) (0.196g, 9%), m.p. 71-72°C (from diethyl ether) (Found: C, 50.75; H, 5.4; N, 13.1%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; M, 214); δ_F ($CDCl_3$) 183.3 p.p.m. (s, 5-F); δ_H ($CDCl_3$) 3.99 (s,2-OCH_3), 4.03 (s, 6-OCH_3), 4.58 (d,NCH_2) and 5.19-5.85 p.p.m. (m,$CH_x{=}CH_2$) $J_{NCH_2,x}$ 6Hz; λ_{max} (cyclohexane) 230 (ε3,600) and 271nm (6,400). (iii) *N-methyl-*

N-(2-fluoro-2-methoxycarbonylpent-4-enoyl)urea (147) (0.511g, 22%) a liquid obtained by molecular distillation (Found: C, 46.75; H, 5.3; N, 11.75%; M^+, 232. $C_9H_{13}FN_2O_4$ requires C, 46.55; H, 5.64; N, 12.07%; M, 232); δ_F ($CDCl_3$) 165.6 p.p.m.(t), J_{CF,CH_2} 21Hz; δ_H ($CDCl_3$) 2.98 ($CFCH_2$), 3.81, 3.85 (NCH_3 and OCH_3), 5.18-5.82 ($CH=CH_2$) and 8.82 p.p.n. (NH_2) [Addition of one drop of CF_3COOH resulted in a significant shift of the NCH_3, allowing its identification[54] (due to conversion of the nitrogen to a positively charged species) δ_H ($CDCl_3/CF_3COOH$) 2.99 ($CFCH_2$), 3.87 (OCH_3), 4.30 (NCH_3) and 5.07-5.75 p.p.m. $CH=CH_2$)]; the mass spectrum showed a significant peak with $^m/_z$ 101 due to $C_3H_5N_2O_2^+$; and (iv) *5-allyl-5-fluoro-6-methoxy-3-methylpyrimidine-2,4(3H,5H)-dione* (146) (0.092g, 4%), m.p. 125-126°C (from benzene) (Found: C, 50.7; H, 4.95; N, 12.8%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; M, 214); δ_F ($CDCl_3$) 171.8 p.p.m. (t, 5-F), J_{CF,CH_2} 18Hz; δ_H ($CDCl_3$) 2.81 (dd, $CFCH_2$), 3.28 (s, NCH_3), 4.12 (s,OCH_3) and 5.21-5.70 p.p.m. (m,$CH_x=CH_2$), $J_{CFCH_2,x}$ 7Hz.

The overall N:C migration terminus ratio was 1:2 [27:(51+5)] respectively. In another reaction this ratio was 1:10.7 [7:(23+52)].

11.8.7 Allyl 2,5-Difluoro-6-Hydroxypyrimidin-4-yl Ether (125)

The hydroxy compound (125) (0.585g) was pyrolysed by F.V.P. at 450°C to give a highly polymeric product. Chromatography on silica (10x3.5cm diam.) using ethyl acetate as eluant gave only the barbituric acid derivative (131) (0.062g, 11%).

11.8.8 2,4-Diallyloxy-5-Fluoro-6-Methoxypyrimidine (139)

The diether (139) (0.087g) was sealed *in vacuo* in a 2*l* flask and heated at 196°C for 7h. The flask was washed out with ether and the ether evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated two components in the ratio 74:26. These were separated by preparative t.l.c. on silica (20x20 cm) using CH_2Cl_2 as eluant to give unchanged starting material (139) (0.028g, 32%) as the minor component, and *3,5-diallyl-5-fluoropyrimidine-2,4,6(1H,3H,5H)-trione* (150) (0.042g, 51%), m.p. 87.5-89°C (from benzene) (Found: C, 53.0; H, 5.05; N, 12.2%; M^+, 226. $C_{10}H_{11}FN_2O_3$ requires C, 53.09; H, 4.90; N, 12.39%; M, 226); δ_F ($CDCl_3$) 166.6 (t, 5-F), J_{CF,CH_2} 15Hz; δ_H ($CDCl_3$) 2.90 (dd, $CFCH_2$), 4.40, 4.49 (AB of dd, NCH_AH_B), 5.25-5.75 (m, $2xCH_x=CH_2$) and 8.41 (bs,NH), $J_{NCH_AH_BX}$ 6Hz each and $J_{CFCH_2,x}$ 7Hz.

11.8.9 2,4,6-Triallyloxy-5-Fluoropyrimidine (138)

The ether (138) (2.07g) was sealed *in vacuo* in a 10*l* flask and heated at 194°C for 16.5h. The flask was washed out with ether, the ether evaporated and the residue recrystallized from light petroleum (b.p. 30-40°C) to give *1,3,5-triallyl-5-fluoropyrimidine-2,4,6 (1H,3H,5H)-trione* (154) (1.82g, 88%), m.p. 52-54°C (Found: C, 58.55; H, 5.4; N, 10.2%; M^+, 266. $C_{13}H_{15}FN_2O_2$ requires C, 58.64; H, 5.68; N, 10.52; M, 266); δ_F ($CDCl_3$) 165.5 p.p.m. (t,5-F), J_{CF,CH_2} 15Hz; δ_H ($CDCl_3$) 2.88 (dd, $CFCH_2$), 4.45 (d,$2xNCH_2$) and 5.12-5.72 p.p.m. (m,$3xCH_x=CH_2$); $J_{NCH_2,x}$ 6Hz and $J_{CFCH_2,x}$ 6Hz.

11.8.10 Allyl 5-Fluoro-4,6-Dimethoxypyrimdin-2-yl Ether (137)

The ether (137) (0.096g) was pyrolysed by F.V.P. at 450°C to give only starting material (0.073g, 76%). Pyrolysis of (137) (0.342g) at 505°C resulted in a very polymeric product which gave a crude product (0.153g) on sublimation, shown by ^{19}F n.m.r. spectroscopy to consist of two components in the ratio 1:1. These were separated by chromatography on silica (10x3.5cm diam.) using CH_2Cl_2 as eluant to give unchanged ether (137) (0.056g, 16%) and after elution of the column with diethyl ether, the 2-hydroxy compound (155) (0.073g, 26%), by comparison with an authentic sample.

11.9 Hydrolysis Reactions

11.9.1 3-Allyl-2,5,6-Trifluoropyrimidin-4(3H)-one (99)

The N-allyl compound (99) (0.049g), potassium carbonate (0.033g) and undried acetone (5ml) were heated under reflux for 24h. The mixture was diluted with water, acidified with sulphuric acid (2M) and extracted with ether. The ether extracts were dried ($MgSO_4$) and the solvent evaporated to give the uracil derivative (106) (0.037g, 76%) by comparison with an authentic sample.

11.9.2 3-Allyl-2,5-Difluoropyrimidin-4(3H)-one (113)

The dienone (113) (0.229g), acetone (12ml), and aqueous sodium hydroxide (2M; 1.4ml) were stirred at room temperature for 10 min. The mixture was diluted with water acidified with sulphuric acid (2M) and extracted with ether.

The ether extracts were dried ($MgSO_4$) and the solvent evaporated to give a crude product shown by ^{19}F n.m.r. spectroscopy to consist of 3 products in the ratio 70:15:15. The major component was separated by sublimation at 40°C/0.05mm Hg and chromatography on silica (10x3.5cm diam.) using ethyl acetate as eluant to give *3-allyl-5-fluoropyrimidine-2,4(1H,3H)-dione* (114) (0.092g, 41%), m.p. 78.5-80°C (Found: C, 49.2; H, 4.2; N, 16.8%; M^+, 170. $C_7H_7FN_2O_2$ requires C, 49.41; H, 4.15; N, 16.47%; M, 170); δ_F ([$^2H_6$]acetone) 169.0 p.p.m. (d,5-F) $J_{5\text{-}F,6\text{-}H}$ 5Hz; δ_H ([$^2H_6$]acetone) 4.53 (d,NCH_2), 5.18-5.97 (m, $CH_x{=}CH_2$), 7.74 (m,6-H) and 10.01 p.p.m. (bs,NH), $J_{NCH_2,x}$ 5Hz.

11.9.3 3-Allyl-2,5-Difluoro-6-Methoxypyrimidin-4(3H)-one(140)

The dienone (140) (0.059g), acetone (5ml) and aqueous sodium hydroxide (2M; 0.3ml) were stirred at room temperature for 17h. The mixture was diluted with water, acidified with sulphuric acid (2M) and extracted with ether. The ether extracts were dried ($MgSO_4$), the solvent evaporated and the residue recrystallized from benzene to give *3-allyl-5-fluoro-6-methoxypyrimidine-2,4(1H,3H)-dione* (141) (0.052g, 89%), m.p. 149-151°C (Found: C,48.2; H, 4.25; N, 14.35%; M^+, 200. $C_8H_9FN_2O_3$ requires C, 48.00; H, 4.53; N, 14.00%; M, 200); δ_F ($CDCl_3$) 191.0 p.p.m. (q,5-F), J_{F,CH_3} 4.5Hz; δ_H ($CDCl_3$) 4.22 (d,OCH_3), 4.50 (d,NCH_2), 5.21-5.87 (m,$CH_x{=}CH_2$) and 8.75 p.p.m. (bs, NH), $J_{NCH_2,x}$ 5Hz.

11.9.4 5-Allyl-5-Fluoro-6-Methoxy-3-Methylpyrimidine-2,4-(3H,5H)-dione (146)

The dione (146) (0.197g), acetone (10ml) and water (0.103g) were heated at reflux for 14h. The mixture was filtered through a drying column ($MgSO_4$) and the solvent evaporated to give the ring-opened compound (147), (0.205g, 96%), by comparison with an authentic sample.

CHAPTER TWELVE

EXPERIMENTAL TO PART B

12.1 Reactions of Polyfluoroarenols with Dimethylsulphoxide (DMSO), Dicyclohexylcarbodiimide (DCC) and Orthophosphoric Acid

12.1.1 With Pentafluorophenol

(a) A mixture of pentafluorophenol (1.03g, 5.6 mmol), anhydrous DMSO (100ml), benzene (100ml) and DCC (4.65g, 22.6mmol) was cooled to $0^{o}C$ and anhydrous orthophosphoric acid in DMSO (5M; 0.7ml) was added to the stirred solution. After a short induction period there was a mild exothermic reaction with dicyclohexylurea (DCU) being precipitated. The reaction temperature was maintained at $\leq 12^{o}C$ over 1 h. and after a further 16 h. at room temperature the mixture was diluted with ether, the DCU removed by filtration and the filtrate washed with water. The organic phase was dried ($MgSO_4$), the solvents evaporated and the residue further evaporated *in vacuo* (0.05mm Hg) into a trap cooled in liquid air. The volatile material was separated by chromatography on silica (13 x 5cm diam.) using $CHCl_3/CCl_4$ (1:1 v/v) as eluant to give as the faster moving component, a liquid *pentafluorophenyl thiomethoxymethyl ether* (237) (0.081g, 6%) (Found: C, 39.10; H, 2.35%; M^+, 244 (CI). $C_8H_5F_5OS$ requires C, 39.35; H, 2.06%; M, 244); δ_F (neat liquid, external $CFCl_3$) 151.1 (2-F, 6-F), 158.3 (4-F) and 159.8 p.p.m. (3-F, 5-F); δ_H (neat liquid, external TMS) 1.92 (s, CH_3) and 4.88 p.p.m. (s, CH_2). This was followed by a pale yellow liquid, *2,3,4,5,6-pentafluoro-6-thiomethoxymethylcyclohexa-2,4-dienone* (238) (0.173g, 13%) (Found: C, 39.45; H, 2.05%; M^+, 244. $C_8H_5F_5OS$ requires

C, 35.35; H, 2.06%; M, 244); δ_F (Et_2O) 134.4 (nm, 3-F), 141.0 (bd, 6-F), 142.2 (ddd, 5-F), 156.8 (nm ,4-F) and 159.4 p.p.m. (ddt, 2-F), $J_{2\text{-}F,3\text{-}F}$ 3.5 Hz, $J_{2\text{-}F,4\text{-}F}$ 3.5 Hz, $J_{2\text{-}F,5\text{-}F}$ 22 Hz, $J_{2\text{-}F,6\text{-}F}$ 13 Hz, $J_{4\text{-}F,5\text{-}F}$ 6Hz, $J_{5\text{-}F,6\text{-}F}$ 35 Hz; δ_H ($CDCl_3$) 2.02 (s, CH_3) and 3.18 p.p.m. (m, CH_2).

The residual involatile material from the reaction was crystallized at low temperature from light petroleum (b.p. 40-60°C) to give the yellow *2,4,5,6-tetrafluoro-3-pentafluorophenoxy-6-thiomethylcyclohexa-2,4-dienone* (239) (0.415g, 36%) m.p. 32.5-33.5°C (Found: C, 41.15; H, 1.00%; M^+, 408. $C_{14}H_5F_9O_2S$ requires C, 41.19; H, 1.23%; M, 408); δ_F (Et_2O) 141.3 (bd,6-F), 142.5 (ddd,5-F), 154.1 (dd, 4-F), 156.1 (d, 2´-F, 6´-F), 157.9 (ddd, 2-F), 158.2 (t, 4´-F) and 162.1 p.p.m. (t, 3´-F, 5´-F), $J_{2\text{-}F,4\text{-}F}$ 1.5 Hz, $J_{2\text{-}F,5\text{-}F}$ 20.5 Hz, $J_{2\text{-}F,6\text{-}F}$ 12 Hz, $J_{4\text{-}F,5\text{-}F}$ 4 Hz, $J_{5\text{-}F,6\text{-}F}$ 35 Hz; δ_H ($CDCl_3$) 2.12 (s,CH_3) and 3.25 p.p.m. (m,CH_2).

(b) Under more concentrated conditions pentafluorophenol (2.66g, 14.5mmols), anhydrous DMSO (20ml), benzene (20ml) DCC (9.87g, 48mmols) and orthophosphoric acid in DMSO (5M; 1.75ml) resulted in the formation of the substituted dienone (239) (1.32g, 45%). A bright yellow compound crystallized from the mother liquors from recrystallization of (239) but was not identified. The data, however, indicated a 1:1 adduct between (239) and a DCC unit. m.p. 108.5-110°C [from light petroleum (b.p. 40-60°C)] (Found: C, 55.00; H, 4.65; N, 4.60%; M^+, 614. $C_{27}H_{27}F_9N_2O_2S$ requires C, 52.77; H, 4.43; N, 4.56%, M, 614); δ_F ($CDCl_3$) 139.6, 141.5, 143.6, 146.3, 154.1, 161.0 and 163.8 p.p.m. in the ratio 1:1:1:1:2:1:2 respectively; δ_H ($CDCl_3$) 1.25, 1.63, 1.88, 2.07 and 3.24 p.p.m. in the ratio 10:6:6:3:2 respectively.

12.1.2 With 2,3,5,6-Tetrafluorophenol (243)

A mixture of tetrafluorophenol (243) (1.372g, 8.3mmol), anhydrous DMSO (20ml), benzene (20ml) and DCC (4.46g, 21.6mmol) was reacted with orthophosphoric acid in DMSO (5M; 1.2ml) as in 12.1.1. After 17h the mixture was filtered, the filtrate diluted with ether and extracted with water. The organic extracts were dried ($MgSO_4$) and the solvents evaporated. Analysis of the product by ^{19}F n.m.r. spectroscopy indicated a two component mixture in the ratio 8:1. These were separated by chromatography on silica (15x5cm diam.) using $CHCl_3/CCl_4$ (1:1 v/v) as eluant to give the minor component, *2,3,5,6-tetrafluorophenyl thiomethoxymethyl ether* (245) (0.15g, 8%) (Found: C, 42.70, H, 2.75%, M^+, 226 (CI). $C_8H_6F_4OS$ requires C, 42.48; H, 2.67%; M, 226); δ_F (neat liquid, external $CFCl_3$) 142.3 and 157.6 p.p.m. in the ratio 1:1, δ_H (neat liquid, external TMS) 1.95 (s,CH_3), 5.0 (s,CH_2) and 6.5 p.p.m. (m,4-H). This was followed by the pale yellow *2,3,5,6-tetrafluoro-6-thiomethoxymethylcyclohexa-2,4-dienone* (246) (1.297g, 69%) (Found: C,42.75; H ,2.30%; M^+, 226 (CI). $C_8H_6F_4OS$ requires C, 42.48; H, 2.67%; M, 226); δ_F ($CDCl_3$) 106.0 (ddt, 5-F), 112.6 (m, 3-F), 146.6 (dm,6-F) and 163.6 p.p.m. (m,2-F), $J_{2\text{-}F,3\text{-}F}$ 7.5 Hz, $J_{2\text{-}F,5\text{-}F}$ 23 Hz, $J_{2\text{-}F,6\text{-}F}$ 13 Hz, $J_{3\text{-}F,5\text{-}F}$ 7Hz, $J_{3\text{-}F,6\text{-}F}$ 5 Hz, $J_{4\text{-}H,5\text{-}F}$ 9 Hz, $J_{4\text{-}H,2\text{-}F}$ 5 Hz, $J_{4\text{-}H,3\text{-}F}$ 9.5 Hz, $J_{5\text{-}F,6\text{-}F}$ 36 Hz; δ_H ($CDCl_3$) 2.10 (s,CH_3), 3.21 (m,CH_2) and 6.16 p.p.m. (ddd,4-H).

12.1.3 With 1,3,4,5,6,7,8-Heptafluoro-2-Naphthol (105)

A mixture of the naphthol (105) (1.075g, 4.0mmol), anhydrous DMSO (12m), benzene (12ml) and DCC (3.42g, 16.6mmol) was reacted with orthophosphoric acid in DMSO (5M; 0.4ml) for 21h at room temperature as in 12.1.1. The mixture was then

filtered, the filtrate diluted with ether and extracted with water. The ether extracts were dried ($MgSO_4$) and all volatile material removed *in vacuo* at room temperature (0.05mm Hg). The residue was separated by chromatography on silica (10x5cm diam) using CCl_4 as eluant to give *1,3,4,5,6,7,8-heptafluoro-2-naphthyl thiomethoxymethyl ether* (250) (0.126g, 10%) m.p. 45-46.5°C [from light petroleum (b.p. 40-60°C)] (Found: C,43.70; H, 1.50%; M^+ 330. $C_{12}H_5F_7OS$ requires C, 43.64; H, 1.53%; M,330); $\delta_F(CDCl_3)$ 138.2 (dm), 145.7-148.4 (overlapping m) and 156.4 p.p.m. (overlapping m) in the ratio 1:4:2; δ_H ($CDCl_3$) 2.38 (s,CH_3) and 5.38 p.p.m. (s,CH_2), followed by *1,3,4,5,6,7,8-heptafluoro-1-thiomethoxymethylnaphthalen-2(1H)-one* (249) (0.943g, 72%) m.p. 90.5-91°C [from light petroleum (b.p. 80-100°C)] (Found: C,43.50; H, 1.35%; M^+, 330. $C_{12}H_5F_7OS$ requires C, 43.64; H, 1.53%; M, 330); δ_F ($CDCl_3$) 122.2 (dm,4-F), 135.0 (m,8-F), 138.8 (dm,5-F), 141.5 (dm,1-F), 148.0 and 150.1 (m,m, 6-F,7-F) and 156.5 p.p.m. (m,3-F), $J_{4\text{-}F,5\text{-}F}$ 76 Hz, $J_{1\text{-}F,8\text{-}F}$ 19 Hz; δ_H ($CDCl_3$) 1.96 (s,CH_3) and 3.29 and 3.57 p.p.m. (AB,CH_2), J_{AB} 13 Hz, $J_{1\text{-}F,H_A}$ 7.5 Hz and $J_{1\text{-}F,H_B}$ 6.5 Hz.

12.2 Reactions of Polyfluoroarenols, Heteroarenols, Anilines and Thiophenols with DMSO, Trifluoroacetic Anhydride (TFAA) and Triethylamine (TEA)

12.2.1 With Pentafluorophenol (General Procedure)

A mixture of DMSO (4ml) and dry methylene chloride (30ml) was cooled to -60°C in dry ice-acetone and TFAA (3.9ml, 28mmol) was added dropwise to the stirred solution whereupon a white solid precipitated. Pentafluorophenol (2.438g, 13mmol) in dry methylene chloride (30ml) was added dropwise to the mixture, the temperature being maintained at ≤-50°C. After 2h,

TEA (6.5ml, 47mmol) was added and the solution was allowed to warm to room temperature over 18h. The mixture was diluted with ether, washed with water and with hydrochloric acid (2M) and the organic phase dried ($MgSO_4$). Examination of the crude produce by ^{19}F n.m.r. spectroscopy, following evaporation of the solvent, indicated two products in the ratio 84:16 accompanied by material possessing trifluoromethyl groups as the only fluorine bearing substituents. These latter, unidentified compounds were conveniently removed by rapid distillation *in vacuo* (0.05mm Hg) at room temperature and as baseline material during chromatography of the crude product on silica (10x5cm diam) using $CHCl_3/CCl_4$ (1:1 v/v) as eluant. The faster moving components on chromatography were separated by distillation *in vacuo* at 40°C/0.05mm Hg to give the dienone (238) (2.364g, 73%). Recrystallization of the residue from light petroleum (b.p. 40-60°C) gave the 3-pentafluorophenoxy derivative (239) (0.456g, 8%).

12.2.2 With 1,3,4,5,6,7,8-Heptafluoro-2-Naphthol (105)

The naphthol (105) (0.946g, 3.5mmol) in dry CH_2Cl_2 (15ml) was added dropwise to a mixture of DMSO (1ml), dry CH_2Cl_2 (15ml) and TFAA (1ml, 7.1mmol) at ≤-55°C, as in the general procedure of 12.2.1. After 2h TEA (1.5ml, 11mmol) was added and the mixture allowed to warm to room temperature over 16h at which time it was worked up as in 12.2.1. Volatile material was removed *in vacuo* and shown by ^{19}F n.m.r. spectroscopy to consist of only the unidentified trifluoromethyl compounds (see 12.2.1), whilst the residue consisted of two components in the ratio 88:12. These latter compounds were separated by chromatography on silica (10x3.5cm diam.) using CCl_4 as

eluant to give the naphthalenone (249) (0.898g, 78%) followed by unchanged starting material (105) (0.065g, 7%) on elution of the column with ether.

12.2.3 With 2,3,5,6-Tetrafluoro-4-Hydroxypyridine (257)

The 4-hydroxy compound (257) (0.23g, 1.4mmol) in dry CH_2Cl_2 (5ml) was added dropwise to a mixture of DMSO (0.45ml), CH_2Cl_2 (15ml) and TFAA (0.45ml, 3.2mmol) at $\leq -50^{\circ}C$, as in the general procedure of 12.2.1, followed after 2h by TEA (0.45ml, 3.2mmol). After 17h at room temperature the mixture was worked up as in 12.2.1. Removal of volatile material, shown by ^{19}F n.m.r. to be only the unidentified trifluoromethyl compounds (see 12.2.1), gave a residue which was found to be identical to starting material (257) (0.208g, 90%).

12.2.4 With 4-Bromo-2,3,5-Trifluoro-6-Hydroxypyridine (104)

The 6-hydroxy derivative (104) (0.588g, 2.6mmol) in dry CH_2Cl_2 (10ml) was added dropwise to a mixture of DMSO (0.8ml), dry CH_2Cl_2 (10ml) and TFAA (0.8ml, 5.7mmol) at $\leq -50^{\circ}C$, as in the general procedure of 12.2.1, followed after 2h by the addition of TEA (1.25ml, 9.0mmol). After 18h at room temperature the mixture was worked up as in 12.2.1 to give a crude product shown by ^{19}F n.m.r. spectroscopy to contain the four components (260), (258), (104) and (261) in the ratio 43:15:20:12. The unchanged starting material (104) (0.129g, 22%) was isolated by washing the crude product with dilute $NaHCO_3$ solution, acidification (2M, H_2SO_4) and extraction with ether. Evaporation of the dried ($MgSO_4$) ether solution of the three remaining components and chromatography on silica (15x5cm diam) using CCl_4/ethyl acetate (80:20 v/v) as eluant gave the three remaining

components as they eluted from the column: (i) *4-bromo-2,3,5-trifluoro-6-pyridyl thiomethoxymethyl ether* (261) (0.011g, 1.5%) m.p. 48-50°C (Found: C, 29.40; H, 1.50; N, 4.50%; M^+ 287/289. $C_7H_5BrF_3NOS$ requires C, 29.18; H, 1.75; N, 4.86%; M, 287/289); δ_F ($CDCl_3$) 91.6 (2-F), 134.7 (5-F) and 143.3 p.p.m. (3-F); δ_H ($CDCl_3$) 2.30 (s,CH_3) and 5.48 p.p.m. (s,CH_2); (ii) *4-bromo-3,5-difluoro-3-thiomethoxymethylpyridin-2,6[1H,3H]-dione* (258) (0.061g, 8%), m.p. 139.5-140°C [by sublimation at 100°C/0.05mm Hg and recrystallization from light petroleum (b.p. 100-120°C)] (Found: C, 29.40; H, 2.40; N, 4.60%, M^+, 285/287. $C_7H_6BrF_2NO_2S$ requires C, 29.39; H, 2.11; N, 4.90%; M, 285/287); δ_F ([$^2H_6$) acetone) 114.6 (5-F) and 133.0 p.p.m. (3-F); δ_H ([$^2H_6$] acetone) 2.15 (s,CH_3), 3.35 (m,CH_2) and 6.36 p.p.m. (bs, NH), and (iii) *4-bromo-2,3,5-trifluoro-1-thiomethoxymethylpyridin-6(1H)-one* (260) (0.327g, 44%) m.p. 75-76°C (from diethyl ether) (Found: C, 29.40; H, 1.60;, N, 4.90%; M^+, 287/289. $C_7H_5BrF_3NOS$ requires C, 29.18; H, 1.75; N, 4.86%; M, 287/289); δ_F ($CDCl_3$) 122.3 (ddt, 2-F), 128.5 (dd, 3-F) and 166.3 p.p.m. (dd, 5-F), $J_{2\text{-}F,NCH_2}$ 4 Hz, $J_{2\text{-}F,3\text{-}F}$ 19 Hz, $J_{2\text{-}F,5\text{-}F}$ 9.5 Hz, $J_{3\text{-}F,5\text{-}F}$ 9.5 Hz; δ_H ($CDCl_3$) 2.3 (s,CH_3) and 5.2 p.p.m. (d,CH_2).

12.2.5 With 2,4,5,6-Tetrafluoro-3-Hydroxypyridine (262)

(a) The 3-hydroxypyridine derivative (262) (1.584g, 9.5mmol) in dry CH_2Cl_2 (30ml) was added dropwise to a mixture of DMSO (2.4ml), dry CH_2Cl_2 (30ml) and TFAA (2.6ml, 18.5mmol) at ≤-50°C, as in the general procedure of 12.2.1, followed after 2h by the addition of TEA (4ml, 29mmol). After 19h at room temperature the crude reaction product obtained by work-up as in 12.2.1, was shown by ^{19}F n.m.r. spectroscopy to be a complex mixture.

Evaporation of the mixture at room temperature/0.05mm Hg for 1.5h into a trap cooled in liquid air removed two components, along with the unidentified trifluoromethyl compounds (see 12.2.1). The former compounds were separated by chromatography on silica (10x5cm diam.) using CH_2Cl_2 as eluant to give (i) *5-hydroxy-2,3,4-trifluoropyridine-6-carbaldehyde* (263) (0.102g, 6%) m.p. 63-64°C [from light petroleum (b.p.30-40°C) at low temperature] (Found: C, 40.65; H, 1.05; N, 7.60%; M^+, 177(CI). $C_6H_2F_3NO_2$ requires C, 40.69; H, 1.14; N, 7.91%; M, 177); δ_F ($CDCl_3$) 87.65 (dd,2-F), 138.8 (t,3-F) and 148.6 p.p.m. (dd,4-F), $J_{2\text{-}F,3\text{-}F}$ 16.5 Hz, $J_{2\text{-}F,4\text{-}F}$ 24 Hz, $J_{3\text{-}F,4\text{-}F}$ 16.5 Hz; δ_H ($CDCl_3$) 9.86 (s,CHO) and 10.94 p.p.m. (s,OH); and (ii) unreacted starting material (262) (0.203g, 13%).

The residue (0.801g), involatile at room temperature, was sublimed at 70°C/0.05mm Hg over 2d and the sublimate chromatographed on silica (10x5cm diam.) using CCl_4 initially, followed by CH_2Cl_2 as eluants to give *5-hydroxy-2,3,4-trifluoro-6-di-(thiomethoxy)methylpyridine* (264) (0.139g, 6%), m.p. 70-71°C [from light petroleum (b.p. 40-60°C)] (Found: C, 37.50; H, 3.40; N, 5.50%; M^+, 208. $C_8H_8F_3NOS_2$ requires C, 37.64; H, 3.16; N, 5.49%; M-47 (CH_3S), 208]; δ_F ($CDCl_3$) 90.8 (dd,2-F), 139.3 (t,3-F) and 161.0 p.p.m. (dd,4-F), $J_{2\text{-}F,3\text{-}F}$ 14 Hz, $J_{2\text{-}F,4\text{-}F}$ 23.5 Hz, $J_{3\text{-}F,4\text{-}F}$ 14 Hz; δ_H ($CDCl_3$) 2.19 [s,$(SCH_3)_2$], 5.01 (s,CH) and 7.17 p.p.m. (s,OH).

(b) In another experiment the reaction of the 3-hydroxy compound (262) (2.68g, 16mmol), DMSO (4.5ml), TFAA (4.5ml, 32mmol) in dry CH_2Cl_2 (100ml) at ≤50°C, followed by the addition of TEA (6.8ml, 48mmol) after 2h, resulted in the isolation of the carbaldehyde (263) (0.384g, 13%) and unchanged starting material

262) (0.562g, 21%), the other component (264) being only present as a trace (^{19}F n.m.r.)

12.2.6 With 2,5,6-Trifluoro-4-Hydroxypyrimidine

The 4-hydroxypyrimdine (1.056g, 7.0mmol) in dry CH_2Cl_2 (15ml) was added dropwise to a mixture of DMSO (1.6ml) in dry CH_2Cl_2 (15ml) and TFAA (1.9ml, 13.5mmol) at $\leq -50^{o}C$, as in the general procedure of 12.2.1, followed after 2h by the addition of TEA (1.9ml, 14 mmol), After 22h at room temperature, the crude product, obtained by work-up as in 12.2.1, was separated by chromatography on silica (10x5cm diam.) using $CHCl_3$ as eluant to give (i) *2,5,6-trifluoro-3-thiomethoxymethylpyrimidin-4(3H)-one* (268) (1.051g, 71%) m.p. 66-67°C [from light petroleum (b.p. 40-60°C)] (Found: C, 34.20; H, 2.55; N. 13.15%; M^+, 210. $C_6H_5F_3N_2OS$ requires C, 34.28; H, 2.40, N, 13.33%; M, 210); δ_F ($CDCl_3$) 56.2 (dd, 2-F), 89.6 (dd,6-F) and 172.4 p.p.m. (dd,5-F), $J_{2-F,4-F}$ 9.5 Hz, $J_{2-F,5-F}$ 21 Hz, $J_{4-F,5-F}$ 10.5Hz; δ_H ($CDCl_3$) 2.30 (s,CH_3) and 5.10 p.p.m. (m,CH_2); and λ_{max} (cyclohexane) 216 (ε 4900) and 266nm (3400); and (ii) after elution of the column with ether, the unchanged 4-hydroxypyrimidine derivative (0.198g, 19%).

12.2.7 With 5-Fluoro-2-Hydroxy-4,6-Dimethoxypyrimidine(155)

The 2-hydroxypyrimidine derivative (0.437g, 2.9mmol) in dry CH_2Cl_2 (10ml) was added dropwise to a mixture of DMSO (0.9ml) in dry CH_2Cl_2 and TFAA (0.9ml, 6.5mmol) at $\leq 50^{o}C$, as in the general procedure of 12.2.1, followed after 2h by the addition of TEA (0.09ml, 6.5mmol). After a further 22h at room temperature, the mixture was worked up as in 12.2.1. Volatile material removed *in vacuo* was found to be the unidentified

trifluoromethyl compounds (^{19}F n.m.r.) (see 12.2.1). The residue was separated by chromatography on silica (13x3.5cm diam.) using CCl_4-ethyl acetate (1:1v/v) as eluant into two components: (i) unreacted starting material (0.077g, 18%); and (ii) after elution of the column with ether and sublimation at 90°C/0.05mm Hg, *5-fluoro-4,6-dimethoxy-1-thiomethoxymethylpyrimidin-2(1H)-one* (271) (0.344g, 59%), m.p. 103-105°C (from toluene) (Found: C, 41.20; H, 4.45; N, 11.60%; M^+, 234(CI). $C_8H_{11}FN_2O_3S$ requires C, 41.02; H, 4.73; N, 11.96%, M, 234); δ_F ($CDCl_3$) 191.3 p.p.m. (q,5-F), $J_{5\text{-}F,OCH_3}$ 5 Hz; δ_H($CDCl_3$) 2.25 (s,SCH_3), 4.0 (s, OCH_3), 4.3 (d,OCH_3) and 5.0 p.p.m. (s,CH_2).

12.2.8 With Pentafluoroaniline (281)

(a) Pentafluoroaniline (281) (1.079g, 5.9mmol) in dry CH_2Cl_2 (25ml) was added dropwise to a mixture of DMSO (1.6ml) in dry CH_2Cl_2 (25ml) and TFAA (1.6ml, 11mmol), at ≤50°C, as in the general procedure of 12.2.1, followed after 2h by the addition of TEA (2.5ml, 18mmol). After a further 18h at room temperature the mixture was worked up as in 12.2.1. Following removal of volatile material at room temperature/0.05mm Hg, shown by ^{19}F n.m.r. to be the unidentified trifluoromethyl compounds (see 12.2.1), the residue was separated by chromatography on silica (15x5 cm diam.) to give (i) upon molecular distillation *N-trifluoroacetyl-N-thiomethoxymethyl-2,3,4,5,6-pentafluoroaniline* (284) (1.074g, 54%) (Found: C, 35.20; H, 1.10; N,4.50%; M^+, 339 (CI). $C_{10}H_5F_8NOS$ requires C, 35.41; H, 1.49; N, 4.13%; M, 339); δ_F ($CDCl_3$) 71.7 (s,CF_3), 143.1 (2-F,6-F), 150.0 (4-F) and 161.1 p.p.m. (3-F,5-F); δ_H ($CDCl_3$) 2.25 (s,CH_3) and 4.89 p.p.m.

(s,CH_2); and (ii) N-trifluoroacetyl-pentafluoroaniline (283) (0.612g, 37%) by comparison with an authentically prepared sample.[123]

(b) In another experiment, pentafluoroaniline (281) (1.007g, 5.5mmol) in dry CH_2Cl_2 (25ml) was added dropwise to a mixture of DMSO (1.6ml) in dry CH_2Cl_2 (25ml) and TFAA (1.6ml, 11mmol) at $\leq 50^{\circ}C$, as in the general procedure of 12.2.1, followed after 2h by the addition of a solution of sodium methoxide in methanol (1.6M, 11ml). After a further 19h at room temperature the mixture was worked-up as above to give the N-thiomethoxymethyl derivative (284) (0.144g, 8%) and the N-trifluoroacetylated compound (283) (1.401g, 91%).

12.2.9 With N-Methyl-Pentafluoroaniline (282)[122]

The N-methyl derivative (282) (7.585g, 41mmol) in dry CH_2Cl_2 (100ml) was added dropwise to a mixture of DMSO (12ml) in dry CH_2Cl_2 (100ml) and TFAA (12ml, 85mmol) at $\leq 50^{\circ}C$, as in the general procedure of 12.2.1, followed after 2h by the addition of TEA. After 17h at room temperature the mixture was worked up as in 12.2.1. Analysis of the crude product by ^{19}F n.m.r. indicated a complex mixture of products, with only one distinct series of resonances being observable. Volatile material was removed *in vacuo* and shown by ^{19}F n.m.r. to consist of the trifluoromethyl compounds and some minor components neither of which were identified. Chromatography of the residue on silica (10x5cm diam.) using initially $CHCl_3$ followed by CH_2Cl_2 as eluants gave the major component *2,5,6-trifluoro-3-(N-methylamino)-4-thiomethoxymethylcyclohexa-2,5-dienone* (285) (2.243g, 23%), m.p. 134-135°C (from benzene) (Found: C,42.60;

H, 3.70; N, 5.80%; M^+, 255(CI). $C_9H_9F_4NOS$ requires C, 42.35; H, 3.55; N, 5.49%, M, 255); δ_F ([$^2H_6$]-acetone) 145.8 (dm, 5-F), 150.1 (dm,4-F), 155.5 (nm,6-F) and 171.6 p.p.m. (nm, 2-F) $J_{4\text{-}F,5\text{-}F}$ 30.5 Hz; δ_H ([$^2H_6$]-acetone) 2.16 (s,SCH_3), 3.17 (m, NCH_3), 3.42 (m,CH_2) and 6.55 p.p.m. (bs, NH). None of the minor components could be isolated.

12.2.10 With Pentafluorothiophenol (290)

Pentafluorothipphenol (290) (1.104g, 5.5mmol) in dry CH_2Cl_2 (25ml) was added dropwise to a mixture of DMSO (1.5ml) in dry CH_2Cl_2 (25ml) and TFAA (1.5ml, 10.6mmol) at $\leq$-50°C, as in the general procedure of 12.2.1, followed after 2h by TEA (2.4ml, 17 mmol). The mixture was allowed to warm to room temperature over 19h, then worked up as in 12.2.1 and all volatile material removed *in vacuo* to leave a residue di-(2,3,4,5,6-pentafluorophenyl)disulphide (291) (1.029g, 94%) identical to an authentically prepared sample.[124]

12.3 Reaction of 2,3,4,5,6-Pentafluoro-6-Thiomethoxymethyl-cyclohexa-2,4-dienone (238) with Methanol

A mixture of the dienone (238) (1.271g), diethyl ether (10ml) and methanol (7ml) was stirred at room temperature for 3h, poured into water and extracted with ether. The ether extracts were dried ($MgSO_4$) the solvents evaporated. Molecular distillation of the residue at 50°C/0.05mm Hg gave *2,4,5,6-tetrafluoro-3-methoxy-6-thiomethoxymethylcyclohexa-2,4-dienone* (242) (1.269g, 95%) (Found: C, 41.90; H, 2.85%; M^+, 256. $C_9H_8F_4O_2S$ requires C, 42.19; H, 3.15%; M, 256); δ_F ($CDCl_3$) 142.0 (ddm,6-F), 144.9

(ddd,5-F), 152.6 (nm, 4-F) and 167.2 p.p.m. (m,2-F), $J_{2\text{-F},5\text{-F}}$ 17 Hz, $J_{2\text{-F},6\text{-F}}$ 9.5 Hz, $J_{4\text{-F},5\text{-F}}$ 6.5 Hz, $J_{4\text{-F},6\text{-F}}$ 3 Hz, $J_{5\text{-F},6\text{-F}}$ 34.5 Hz; δ_H ($CDCl_3$) 2.01 (s,SCH_3), 3.18 (m,CH_2) and 4.24 p.p.m. (d,OCH_3), $J_{2\text{-F},OCH_3}$ 6.5 Hz.

12.4 Reactions of 2,3,5,6-Tetrafluoro-6-Thiomethoxymethyl-cyclohexa-2,4-dienone (246)

12.4.1 With Pentafluorophenol

A mixture of the dienone (246) (0.265g), pentafluorophenol (0.310g) and potassium carbonate (0.1g) was heated in tetrahydrofuran (15ml) at 70°C for 5h, diluted with water, acidified (2M, H_2SO_4) and extracted with ether. The ether extracts were dried ($MgSO_4$), the solvent evaporated and the residue purified by chromatography on silica using CH_2Cl_2 as eluant to give *2,6-difluoro-3,5-di(pentafluorophenoxy)-6-thiomethoxymethylcyclohexa-2,4-dienone* (247) (0.395g, 61%) m.p. 108-109.5°C [from light petroleum (b.p. 80-100°C)] (Found: C, 43.60; H, 1.10%; M^+, 554. $C_{20}H_6F_{12}O_3S$ requires C, 43.33; H, 1.09%; M, 554); δ_F ($CDCl_3$) 145.7 (dt,6-F), 152.5 (d,2′-F,6′-F), 155.2 (d, 2″-F, 6″-F), 155.8 (t, 4′-F), 157.6 (t, 4‴-F), 160.1 (t, 3′-F, 5′-F), 161.5 (t, 3″-F, 5″-F) and 165.0 p.p.m. (dd, 2-F), $J_{2\text{-F},6\text{-F}}$ 12 Hz; δ_H ($CDCl_3$) 2.13 (s,CH_3), 3.26, 3.45 (AB,CH_2) and 5.40 p.p.m. (d,4-H), J_{AB} 12.5 Hz, $J_{2\text{-F},4\text{-H}}$ 5 Hz, $J_{6\text{-F},HA}$ 6.5 Hz and $J_{6\text{-F},HB}$ 8 Hz.

12.4.2 With Liquid HF

The dienone (246) (0.809g) was added to liquid HF (*ca.* 20ml) at room temperature in a PTFE beaker. After 17h

the mixture was diluted with water, extracted with ether and the dried ($MgSO_4$) extracts evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated a three component mixture in the ratio 2:3:2. These were separated by chromatography on silica (10x5cm diam.) using CH_2Cl_2 as eluant to give two fractions: (i) a mixture of two components which was separated by evaporation *in vacuo* at room temperature/0.05mm Hg to give 2,3,5,6-tetrafluorophenol (243) (0.111g, 19%), identified by comparison of its i.r. with an authentic sample; the less volatile residue was sublimed at 50°C/0.05mm Hg to give *2,3,5,6-tetrafluoro-4-thiomethoxymethylphenol* (244) (0.252g, 31%) m.p. 77-78°C [from light petroleum (b.p. 60-80°C)] (Found: C, 42.70; H, 2.30%; M^+, 266 (CI). $C_8H_6F_4OS$ requires C, 42.48; H, 2.67%; M, 226); δ_F ($CDCl_3$) at 145.5 and 163.7 p.p.m. in the ratio 1:1; δ_H ($CDCl_3$) 2.14 (s, CH_3), 3.74 (s,CH_2) and 5.86 p.p.m. (s,OH); and (ii) a single component, *2,3,5,6-tetrafluoro-4-hydroxyphenylmethanol* (248) (0.095g, 14%), m.p. 116.5-117°C (from benzene) (Found: C, 42.90; H, 1.8%; M^+, 178. $C_7H_4F_4O_2$ requires C, 42.87; H, 2.06%, M-18 (H_2O), 178); δ_F ([$^2H_6$]acetone) at 148.3 and 164.0 p.p.m. in the ratio 1:1; δ_H ([$^2H_6$]acetone) 4.50 (m,COH), 4.67 (s,CH_2) and 10.0 p.p.m. (s,OH).

12.5 Reactions of some Rearrangement Products with Sodium Borohydride

12.5.1 2,4,5,6-Tetrafluoro-3-Pentafluorophenoxy-6-Thiomethoxymethylcyclohexa-2,4-dione (239)

A solution of the dienone (239) (0.170g) in methanol (5ml) was reacted with sodium borohydride (0.031g) in methanol (2ml) at room temperature for 30 min. The mixture

was acidified (2M, H_2SO_4) and extracted with ether. The dried ($MgSO_4$) extracts were evaporated, and the residue sublimed at 70°C/0.05mm Hg to give *2,4,5-trifluoro-3-pentafluorophenoxy-6-thiomethoxymethylphenol* (293) (0.158g, 97%) m.p. 107-108 [from light petroleum (b.p. 80-100°C)] (Found: C, 43.35; H, 1.20%; M^+, 390. $C_{14}H_6F_8O_2S$ requires C, 43.09; H, 1.55%; M, 390); δ_F (Et_2O) 146.2 (dd,5-F), 157.9 (d,2´-F, 6´-F), 158.9 (dd,2-F), 162.7 (t, 4´-F), 164.4 (t,3´-F, 5´-F) and 166.3 p.p.m. (dd,4-F), $J_{4\text{-}F,5\text{-}F}$ 21 Hz; $J_{2\text{-}F,5\text{-}F}$ 9 Hz; $J_{2\text{-}F,4\text{-}F}$ 4.5 Hz. δ_H ($CDCl_3$) 2.10 (s,CH_3), 3.78 (s,CH_2) and 6.2 p.p.m. (s,OH).

12.5.2 1,3,4,5,6,7,8-Heptafluoro-1-Thiomethoxymethylnaphthalen-2(1H)-one (249)

The naphthalenone (249) (0.128g) was dissolved in methanol (8ml) and sodium borohydride (0.03g) in methanol (2ml) was added. After 25 min the mixture was diluted with water, acidified (2M, H_2SO_4) and extracted with ether. The dried ($MgSO_4$) extracts were evaporated and the residue sublimed at 80°C/0.05mm Hg to give an equimolar mixture of racemic diastereomers, *1,3,4,5,6,7,8-heptafluoro-2-hydroxy-1-thiomethoxymethyl-(1H,2H)-naphthalene* (294) (0.114g, 88%) m.p. 103-104°C [from light petroleum (b.p. 40-60°C)] (Found: C, 43.70; H,1.85%; M^+, 332. $C_{12}H_7F_7OS$ requires C, 43.88; H, 2.12%; M, 332); δ_F ($CDCl_3$) 134.5 (m,8-F), 142.6 (dm,5-F), 144.0 (m,3-F), 147.1 (m,1-F), 151.1 (dm,4-F), 151.2 and 152.7 p.p.m. (both t, 6-F,7-F), $J_{4\text{-}F,5\text{-}F}$ 62 Hz,$J_{1\text{-}F,8\text{-}F}$ 21 Hz; δ_H ($CDCl_3$) 2.24 (s,CH_3) 2.83 and 2.86 (OH), 3.36 and 3.60 (AB of CH_2, J_{AB} 15 Hz), equimolar diastereomer 3.25 and 3.54 (A´B´ of CH_2, $J_{A'B'}$ 16 Hz) and 5.23 (m,CH).

Compound (294) (0.078g) was reacted with KOH (0.1g) in tetrahydrofuran (7ml) under reflux for 18h. to give *3,4,5,6,7,8-hexafluoro-1-thiomethoxymethyl-2-naphthol* (295) (0.063g, 86%), m.p. 125.5-126°C [from light petroleum (b.p. 80-100°C)] (Found: C, 46.40; H, 1.80%; M^+, 312. $C_{12}H_6F_6OS$ requires C, 46.16; 1.94%; M, 312); δ_F ($CDCl_3$) 142.4 (m,8-F), 143.1 (dd,4-F), 146.2 (dt,5-F), 155.8, 159.1 (t and t, 6-F,7-F) and 157.0 p.p.m. (m,3-F), $J_{4\text{-}F,5\text{-}F}$ 67 Hz; δ_H ($CDCl_3$) 2.11 (s,CH_3), 4.26 (d,CH_2) and 6.2 p.p.m. (s,OH), J_{F,CH_2} 3 Hz.

12.6 Reactions of some Rearranged Products with Raney Nickel

12.6.1 2,3,4,5,6-Pentafluoro-6-Thiomethoxymethylcyclohexa-2,4-dienone (238)

The dienone (238) (0.541g), tetrahydrofuran (20ml) and Raney nickel (*ca.* 4g) were stirred under nitrogen at room temperature for 24h. The mixture was filtered through a drying column ($MgSO_4$) and the solvent evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated the three components (300), (301) and (302) in the ratio 37:46:17. Evaporation of the crude product at room temperature/0.05mm Hg gave *2,3,4,5-tetrafluoro-6-methylphenol* (300) (0.087g, 22%), m.p. 22-23°C (Found: C, 46.80; H, 2.40%; M^+, 180. $C_7H_4F_4O$ requires C, 46.68; H, 2.24%; M, 180); δ_F ($CDCl_3$) 144.6 (dd,5-F) 161.8 (t,3-F), 167.3 (dm,2-F) and 169.8 p.p.m. (dt,4-F), $J_{4\text{-}F,5\text{-}F}$, $J_{3\text{-}F,4\text{-}F}$ and $J_{2\text{-}F,3\text{-}F}$ all 21 Hz, $J_{2\text{-}F,4\text{-}F}$ 5 Hz, $J_{2\text{-}F,5\text{-}F}$ 9.5 Hz. δ_H ($CDCl_3$) 2.24 (s,CH_3) and 5.22 p.p.m. (s,OH); the less volatile material was sublimed at 50°C/0.05mm Hg and the sublimate recrystallized from light petroleum (b.p.30-40°C)

to give *2,3,4,5-tetrafluoro-6-methylphenyl-2',3',6'-trifluoro-5'-hydroxy-4'-methylphenyl ether* (301) (0.125g, 33%); m.p. 67-69°C (Found: C, 49.70; H, 2.10%; M^+, 340. $C_{14}H_7F_7O_2$ requires C, 49.42; H, 2.07%; M, 340); δ_F ($CDCl_3$) 143.2 (dm, 3'-F), 144.9 (dm, 5-F), 158.1 (dm, 2-F), 159.8 and 162.4 (both t, 3-F,4-F), 162.0 (nm, 6'-F) and 164.8 p.p.m. (dm, 2'-F), $J_{2\text{-}F,3\text{-}F}$, $J_{3\text{-}F,4\text{-}F}$, $J_{4\text{-}F,5\text{-}F}$ and $J_{2'\text{-}F,3'\text{-}F}$ all 21 Hz; δ_H ($CDCl_3$) 2.18, 2.28 (both s, 2xCH_3) and 5.17 p.p.m. (s,OH). The least volatile material was sublimed at 100°C/0.05mm Hg and recrystallized from light petroleum (b.p. 60-80°C) to give *2,3,6-trifluoro-4-methyl-1-(2',3',4',5',-tetrafluoro-6'-methylphenoxy)-5-(2'',3'',6''-trifluoro-5''-hydroxy-4''-methylphenoxy) benzene* (302) (0.051g, 14%), m.p. 120-125°C [from light petroleum (b.p. 60-80°C)] (Found: C, 50.15; H, 1.75%; M^+, 500. $C_{21}H_{10}F_{10}O_3$ requires C, 50.41; H, 2.01%; M, 500); δ_F ($CDCl_3$) 142.9, 143.4 (both ddd, 3-F,3''-F), 144.8 (ddd, 5'-F), 152.6 (dm,6-F), 157.1 (dd,2-F), 158.3 (dm,2'-F), 159.5, 162.1 (both t, 3'-F, 4'-F), 162.3 (nm, 6''-F) and 165.0 p.p.m. (dm, 2''-F), $J_{2\text{-}F,3\text{-}F}$, $J_{2'\text{-}F,3'\text{-}F}$, $J_{2''\text{-}F,3''\text{-}F}$, $J_{3'\text{-}F,4'\text{-}F}$ and $J_{4'\text{-}F,5'\text{-}F}$ all 22 Hz, $J_{3\text{-}F,6\text{-}F}$, $J_{3'\text{-}F,6'\text{-}F}$ and $J_{3''\text{-}F,6''\text{-}F}$ all 9 Hz; δ_H ($CDCl_3$) 2.27, 2.29 and 2.30 (all s, 3xCH_3) and 5.18 p.p.m. (s,OH).

12.6.2 2,4,5,6-Tetrafluoro-3-Methoxy-6-Thiomethoxymethyl-cyclohexa-2,4-dienone (242)

The substituted dienone (242) (0.311g), tetrahydrofuran (15ml) and Raney nickel (*ca.* 4g) were stirred at room temperature for 4h, after which time the mixture was filtered through a layer of $MgSO_4$ and the solvent evaporated. Sublimation of the residue at room temperature/0.05mm Hg and recrystallization of the sublimate from light petroleum (b.p. 40-60°C)

gave *2,4,5-trifluoro-3-methoxy-6-methylphenyl* (303) (0.228g, 98%), m.p. 72.5-73.5°C (Found: C,50.30; H, 3.45%; M^+, 192. $C_8H_7F_3O_2$ requires C,50.01; H, 3.67%; M, 192); δ_F ($CDCl_3$) 146.3 (dd,5-F), 162.6 (d,2-F) and 165.1 p.p.m. (d,4-F), $J_{2\text{-}F,5\text{-}F}$ 10Hz, $J_{4\text{-}F,5\text{-}F}$ 22 Hz; δ_H ($CDCl_3$) 2.16 (d,CH_3), 4.01 (t,OCH_3) and 5.17 p.p.m. (bs,OH), J_{F,CH_3} 2 Hz; J_{F,OCH_3} 1 Hz.

12.6.3 1,3,4,5,6,7,8-Heptafluoro-1-Thiomethoxymethyl-naphthalen-2(1H)-one (249)

The naphthalen-2(1H)-one (249) (0.894g), tetrahydrofuran (45ml) and excess Raney nickel (*ca.* 4g) were stirred at room temperature for 2h, the mixture filtered through a drying column ($MgSO_4$) and the solvent evaporated. Sublimation of the residue at 80°C/0.05mm Hg gave *3,4,5,6,7,8-hexafluoro-1-methyl-2-naphthol* (296) (0.715g, 99%), m.p. 90-90.5°C [from light petroleum (b.p. 40-60°C)] (Found: C,49.90; H,1.60%; M^+, 266. $C_{11}H_4F_6O$ requires C, 49.64; H, 1.51%; M, 266); δ_F ([$^2H_6$]acetone) 143.4 (m,8-F), 148.15, 148.60 (AB, 4-F,5-F), 154.7 (m,3-F) and 159.8, 162.3 p.p.m.(both t,6-F,7-F), $J_{4\text{-}F,5\text{-}F}$ 64 Hz; δ_H ($CDCl_3$) 2.62 (d,CH_3) and 5.65 p.p.m. (bs,OH), J_{F,CH_3} 7.3 Hz.

12.7 Hydrolysis of 2,5,6-Trifluoro-3-Thiomethoxymethylpyrimidin-4(3H)-one (268)

A mixture of the pyrimidin-4(3H)-one (268) (0.220g), acetone (15ml) and aqueous sodium hydroxide (2M, 1.1ml) was stirred at room temperature for 2.5h, diluted with water, acidified (2M, H_2SO_4) and extracted with ether. The organic extracts were dried ($MgSO_4$), the solvent evaporated and the residue sublimed

at 90°C/0.05mm Hg to give *5,6-difluoro-3-thiomethoxymethyl-pyrimidin-2,4(1H,3H)-dione* (269) (0.197g, 90%), m.p. 103-104°C (from toluene) (Found: C, 34.90; H, 2.80, N, 13.10%; M^+, 208(CI). $C_6H_6F_2N_2O_2S$ requires C, 34.61; H, 2.90; N, 13.46%; M, 208); δ_F ($CDCl_3$) 115.3 (d,6-F) and 187.6 p.p.m. (d,5-F), $J_{5-F,6-F}$ 7.5 Hz; δ_H ($CDCl_3$) 2.30 (s,CH_3), 5.00 (s,CH_2) and 10.7 p.p.m. (bs, NH).

12.8 Oxidation of 1,3,4,5,6,7,8-Heptafluoro-1-Thiomethoxymethylnaphthalen-2(1H)-one (249)

Peroxytrifluoroacetic acid, prepared by the addition of hydrogen peroxide (1ml, 30% w/v) to trifluoroacetic anhydride (7ml), was added dropwise with stirring to the naphthalen-2(1H)-one (0.612g) in CH_2Cl_2 (20ml) at ≤10°C. The reaction mixture was then stirred at room temperature for a further 19h, diluted with water and extracted with ether. The ether extracts were dried ($MgSO_4$), the solvents evaporated *in vacuo*/0.05mm Hg, and the residue sublimed at 100°C/0.05mm Hg to give *1,3,4,5,6,7,8-heptafluoro-1-methylsulphonylmethylnaphthalen-2(1H)-one* (307) (0.602g, 90%); m.p. 127-127.5°C (from chloroform) (Found: C, 39.95; H, 1.15%; M^+, 362. $C_{12}H_5F_7O_3S$ requires C, 39.79; H, 1.39%, M, 362); δ_F ([$^2H_6$]acetone) 125.1 (dm,4-F), 134.9 (m,8-F), 139.4 (dm,5-F), 143.4 (nm, 1-F), 149.7 and 150.4 (m,m,6-F,7-F) and 157.6 p.p.m. (m,3-F), $J_{4-F,5-F}$ 75 Hz; δ_H ([$^2H_6$]acetone) 3.10 (s,CH_3) and 4.50 p.p.m. (m,CH_2).

12.9 Reaction of Pentafluorophenol with DMSO, Trifluoroacetic Anhydride (TFAA) and Triethylamine (TEA) followed by Oxidation with Peroxytrifluoroacetic Acid

Pentafluorophenol (5.09g, 28mmol) in dry CH_2Cl_2 (90ml) was added dropwise to a mixture of DMSO (8ml), dry CH_2Cl_2 (90ml) and TFAA (8ml, 57mmol) at $\leq -50^{\circ}C$, as in the general procedure of 12.2.1, followed after 2h by TEA (13ml, 93mmol). After 24h at room temperature the mixture was worked up as in 12.2.1. Volatile material was removed at $40^{\circ}C/0.05$mm Hg, leaving a residue which was recrystallized from light petroleum (b.p. $40-60^{\circ}C$) to give the phenoxy substituted compound (239) (0.594g, 11%).

Peroxytrifluoroacetic acid, prepared by the addition of hydrogen peroxide (6.5ml, 30% w/v) to trifluoroacetic anhydride (50ml), was added to the volatile material in CH_2Cl_2 (60ml) at $\leq 5^{\circ}C$. The mixture was then stirred at room temperature for 16h, diluted with water and extracted with CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and the solvents removed *in vacuo* (0.05mm Hg). Sublimation of the residue at $70^{\circ}C/0.05$mm Hg gave *2,3,4,5,6-pentafluoro-6-methylsulphonylmethylcyclohexa-2,4-dienone* (306) (3.01g, 39%), m.p. 115-115.5°C (from diethyl ether) (Found: C, 34.80; H, 1.50%; M^+, 276. $C_8H_5F_5O_3S$ requires C, 34.79; H, 1.82%; M, 276); δ_F ($[^2H_6]$acetone) 135.5 (nm, 3-F), 142.2 (ddd,5-F), 150.2 (dm,6-F), 155.3 (nm, 4-F) and 160.0 p.p.m. (ddt, 2-F), $J_{2\text{-}F,5\text{-}F}$ 20.5 Hz, $J_{2\text{-}F,6\text{-}F}$ 14 Hz, $J_{4\text{-}F,5\text{-}F}$ 5 Hz, $J_{5\text{-}F,6\text{-}F}$ 37.5 Hz; δ_H ($[^2H_6]$ acetone) 3.19 (s,CH_3) and 4.42 p.p.m. (m, CH_2).

12.10 Reaction of 1,3,4,5,6,7,8-Heptafluoro-1-Methylsulphonylmethylnaphthalen-2(1H)-one (307) and 1,8-Diazabicyclo-[5.2.0]undec-7-ene (DBU)

A solution of the naphthalen-2(1H)-one (307), 1.029g, 2.8mmol) in dry tetrahydrofuran (40ml) was treated at -60°C with DBU (0.45ml, 3mmol) and maintained at this temperature for 2h. The mixture was diluted with water, acidified (2M,HCl), extracted with ether and the dried ($MgSO_4$) extracts were evaporated. The residue was chromatographed on silica (10x3.5cm diam.) using $CHCl_3$ as eluant to give three components: (i) *3,4,5,6,7,8-hexafluoro-2-hydroxynaphthalene-1-carbaldehyde* (315) (0.602g, 76%), m.p. 90-92°C [from light petroleum (b.p. 40-60°C)] (Found: C,47.35; H, 0.40%; M^+, 280 (CI). $C_{11}H_2F_6O_2$ requires C, 47.16; H, 0.72%, M, 280); δ_F ($CDCl_3$) 128.0 (dd,4-F), 137.9 (tm,8-F), 143.2 (dm,5-F), 151.2, 157.9 (both t, 6-F,7-F) and 156.1 p.p.m. (m,3-F), $J_{4\text{-}F,5\text{-}F}$ 72 Hz; δ_H ($CDCl_3$) 10.74 (s,CHO) and 14.48 p.p.m. (s,OH); (ii) unreacted starting material (307) (0.032g, 3%); and (iii) after elution of the column with diethyl ether and sublimation at 140°C/0.05mm Hg, *3,4,5,6,7,8-hexafluoro-2-hydroxy-1-di(methylsulphonyl)methylnaphthalene* (316) (0.056g, 5%), m.p. 180-181°C (decomp) (from toluene) (Found: C,37.0; H, 1.6%; M^+, 343 (CI). $C_{13}H_8F_6O_5S_2$ requires C, 36.97; H, 1.91%; M-(CH_3SO_2), 343); δ_F ([$^2H_6$]acetone) 139.5 (dd,4-F), 140.1 (dt,8-F), 146.3 (dm,5-F), 153.6 (m,3-F) and 155.3, 160.3 p.p.m. (both t, 6-F,7-F), $J_{4\text{-}F,5\text{-}F}$ 73 Hz; δ_H ([$^2H_6$]acetone) 3.39 (s,2xCH_3), 6.68 (d,CH) and 11.6 (s,OH), $J_{CH,8\text{-}F}$ 19Hz.

12.11 Reaction of Hexafluorobenzene with Sodium Methylsulphinylmethide

(a) Sodium methylsulphinylmethide in DMSO (2.8M; 5.5ml), prepared by the reaction of NaH with dry DMSO, was added dropwise to a stirred solution of hexafluorobenzene (2.877g) in DMSO (20ml) at 15.5°C. An exothermic reaction resulted (T≤20.5°C). After a further 50 min. the mixture was diluted with water, extracted with ether, the ether extracts dried ($MgSO_4$) and the solvents evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated 1 main product along with unchanged starting material, the latter conveniently removed by evaporation *in vacuo*/0.05mm Hg. Recrystallization of the residue from methanol gave *1,1-di(pentafluorophenyl)methyl methylsulphoxide* (321) (0.982g, 31%), m.p. 116-116.5°C (Found: C, 41.30; H, 0.6%; M^+, 347. $C_{14}H_4F_{10}OS$ requires C, 40.99; H ,0.98%; M-CH_3SO, 347); δ_F ($CDCl_3$) 137.1, 138.7 (dm,dm,2-F,6-F, 2′-F,6′-F), 151.3, 152.0 (tm,tm,4-F,4′-F) and 160.2, 161.4 p.p.m. (tm,tm,3-F,5-F,3′-F,5′-F), $J_{3\text{-}F,4\text{-}F}$, $J_{3'\text{-}F,4'\text{-}F}$ 20 Hz; $J_{2\text{-}F,3\text{-}F}$, $J_{2'\text{-}F,3'\text{-}F}$ 26 Hz; $J_{2\text{-}F,5\text{-}F}$, $J_{2'\text{-}F,5'\text{-}F}$ 11 Hz; δ_H ($CDCl_3$) 2.68 (s,CH_3) and 5.42 p.p.m. (s,CH).

(b) In another experiment, sodium methylsulphinylmethide in DMSO (2.8M, 5.8ml) was added dropwise to a solution of hexafluorobenzene (3.056g) in THF (40ml) cooled to -74°C. After 45 min. the reaction mixture was quickly warmed to room temperature, diluted with water, acidified (2M, H_2SO_4) and extracted with ether. The ether extracts were dried ($MgSO_4$) and all volatile material removed *in vacuo*/0.05mm Hg. Chromatography on silica (15x5cm diam.) using ethyl acetate as eluant gave two components: (i) the dipentafluorophenyl compound (321)

(0.983g, 30%), and (ii) *2,3,4,5,6-pentafluorobenzylmethylsulphoxide* (320) (0.236g, 6%), m.p. 96-97°C (from diethyl ether) (Found: C, 39.65; H, 2.15%; M^+, 244. $C_8H_5F_5OS$ requires C, 39.35; H, 2.06%; M, 244); δ_F ($CDCl_3$) 140.5 (dm,2-F,6-F), 153.4 (b,4-F) and 161.9 p.p.m. (tm,3-F,5-F), $J_{3-F,4-F}$ 20 Hz, $J_{2-F,3-F}$ 21 Hz, $J_{2-F,5-F}$ 11 Hz; δ_H ($CDCl_3$) 2.60 (s,CH_3) and 4.1 p.p.m. (s,CH_2).

(c) In a further experiment, sodium methylsulphinylmethide in DMSO (1.73M; 25ml) was added hexafluorobenzene (8.136g) in THF (100ml) at -74°C. After 90 min. excess water was added to the mixture at the low temperature. The mixture was then worked up as in (a) to give a single product, the pentafluorobenzylmethylsulphoxide (320) (3.928g, 37%).

12.12 Flash Vapour Phase Thermolysis Reactions

12.12.1 1,3,4,5,6,7,8-Heptafluoro-1-Thiomethoxymethylnaphthalen-2(1H)-one (249)

The naphthalen-2(1H)-one (249) (1.498g) was distilled through a quartz tube [60x1.5cm diam. packed with silica fibre (20x1.5cm)] heated at 540°C, into a trap cooled with liquid air connected to a high vacuum system (0.05mm Hg). Chromatography of the crude product on silica (7.5x5 cm diam.) using CH_2Cl_2 and the ethylacetate as eluants gave the 2-naphthol (105) (0.909g, 74%), by comparison with an authentic sample.

12.12.2 2,3,4,5,6-Pentafluorobenzylmethylsulphoxide (320)

The sulphoxide (320) (0.508g) was pyrolysed by F.V.P. at 420°C to give a single component 2,2',3,3',4,4',5,5',6,6'-

decafluorodibenzyl (324) (0.328g , 87%), m.p. 104-104.5°C (Lit.,[135] 107-108°C) [from light petroleum (b.p. 40-60°C)] (Found: C, 46.35; H, 0.80%; M^+, 362. $C_{14}H_4F_{10}$ requires C, 46.43; H, 1.11%; M, 362); δ_F ($CDCl_3$) 145.3 (dm,2-F,6-F, 2′-F,6′-F), 157.0 (t,4-F,4′-F) and 163.2 p.p.m. (tm,3-F,5-F, 3′-F,5′-F); δ_H ($CDCl_3$) 3.0 p.p.m. (s,CH_2).

12.13 Static Vapour Phase Thermolysis of 2,3,4,5,6-Pentafluorobenzyl methylsulphoxide (320)

The sulphoxide (320) (1.438g) was sealed, *in vacuo*, in a 10*l* flask and placed in an oven at 190°C. After a short period the oven temperature was reduced to 140°C. After a further 18h at this temperature the flask was washed out with ether and the ether evaporated. Analysis of the crude product by ^{19}F n.m.r. spectroscopy indicated a complex misture shown by analytical t.l.c. [light petroleum (b.p. 40-60°C) as eluant] to contain at least eight components. Volatile material (0.610g) was removed *in vacuo* at room temperature/0.05mm Hg. Chromatography on silica (15x5cm diam.) using light petroleum (b.p. 40-60°C) followed by CH_2Cl_2 as eluants gave two components: (i) 2,3,4,5,6-pentafluorophenyl methanol (325) (0.261g, 22%), by comparison with an authentic sample, and (ii) the decafluorodibenzyl compound (324) (0.150g, 14%).

The residue from evaporation of the volatiles was separated by chromatography on silica (15x5cm diam.) using light petroleum (b.p. 40-60°C) as eluant to give: (i) the decafluorodibenzyl compound (324) (0.138g, 13%); (ii) *2,2′,3,3′,4,4′,5,5′,6,6′-decafluorodibenzyl disulphide* (326) (0.094g, 7.5%), m.p. 145.5-146°C [from light petroleum (b.p. 40-60°C)] (Found:

C,39.71; H, 1.10%; M^+, 426. $C_{14}H_4F_{10}S_2$ requires C, 39.44; H, 0.09%; M, 426); δ_F ($CDCl_3$) 142.9 (dm,2-F,6-F,2′-F,6′-F), 154.6 (t,4-F,4′-F) and 162.0 p.p.m. (tm,3-F,5-F,3′-F,5′-F); δ_H ($CDCl_3$) 3.92 p.p.m. (s,CH_2); followed by (iii) polymeric material (0.326g), obtained by eluting the column with ether.

APPENDICES

APPENDIX A

INFRA-RED SPECTRA

The spectra were recorded using a Perkin-Elmer 457 or 577 grating infra-red spectrophotometer and were run either as a liquid film using KBr cells (L), from a KBr disc (D), or as a nujol mull (NM).

Spectra for Part A

Compound Number	Name of Compound
I	Allyl 2,5,6-trifluoropyrimidin-4-yl ether (93) (L)
II	2,4,6-Triallyloxy-5-fluoropyrimidine (138) (L)
III	Prop-2-ynyl 2,5,6-trifluoropyrimidin-4-yl ether (101) (L)
IV	[2,3-$^{2}H_{2}$]Allyl 2,5,6-trifluoropyrimidin-4-yl ether (100) (L)
V	Allyl 2,5-difluoro-6-methoxypyrimidin-4-yl ether (122) (L)
VI	Allyl 5,6-difluoro-2-methoxypyrimidin-4-yl ether (123) (L)
VII	Allyl 5-fluoro-2,6-dimethoxypyrimidin-4-yl ether (124) (L)
VIII	Allyl 2,5-difluoropyrimidin-4-yl ether (111) and Allyl 5,6-difluoropyrimidin-4-yl ether (112) (ratio 91:9 respectively). (L)
IX	Allyl 2,5-difluoro-6-hydroxypyrimidin-4-yl ether (125) (D)
X	5-Allyl-5-fluoropyrimidine-2,4,6(1H,3H,5H)-trione(131) (D)
XI	6-Allyloxy-2,5-difluoro-3-methylpyrimidin-4(3H)-one (132) (L)

Compound Number	Name of Compound
XII	5-Allyl-1,3-dimethyl-5-fluoropyrimidine-2,4,6(1H,3H,5H)-trione (133) (D)
XIII	Methyl 2-fluoropent-4-enoate (135) (L)
XIV	Dimethyl 2-allyl-2-fluoropropanedioate (136) (L)
XV	5,6-Difluoro-2,4-dimethoxypyrimidine (117) (L)
XVI	Allyl 5-fluoro-4,6-dimethoxypyrimidin-2-yl ether (137) (L)
XVII	2,4-Diallyl-5-fluoro-6-methoxypyrimidine (139) (L)
XVIII	5-Fluoro-2-hydroxy-4,6-dimethoxypyrimidine (155) (D)
XIX	3-Allyl-2,5,6-trifluoropyrimidin-4(3H)-one (99) (L)
XX	1,3-Diallyl-5,6-difluoropyrimidine-2,4(1H,3H)-dione (107) (L)
XXI	3-Allyl-5,6-difluoropyrimidine-2,4(1H,3H)-dione (106) (D)
XXII	3-[1,2-$^{2}H_{2}$]Allyl-2,5,6-trifluoropyrimidin-4(3H)-one (102) (L)
XXIII	3-Allyl-2,5-difluoropyrimidin-4(3H)-one (113) (L)
XXIV	3-Allyl-2,5-difluoro-6-methoxypyrimidin-4(3H)-one (140) (D)
XXV	5-Allyl-5-fluoro-1-methylpyrimidine-2,4,6 (1H,3H,5H)-trione (142) (D)
XXVI	3-Allyl-5,6-difluoro-2-methoxypyrimidin-4(3H)-one (144) (L)
XXVII	3-Allyl-5-fluoro-2,6-dimethoxypyrimidin-4(3H)-one (145) (D)
XXVIII	N-Methyl-N-(2-fluoro-2-methoxycarbonylpent-4-enoyl)-urea (147) (L)
XXIX	5-Allyl-5-fluoro-6-methoxy-3-methylpyrimidine-2,4-(3H,5H)-dione (146) (D)

Compound Number	Name of Compound
XXX	3,5-Diallyl-5-fluoropyrimidine-2,4,6(1H,3H,5H)-trione (150) (D)
XXXI	1,3,5-Triallyl-5-fluoropyrimidine-2,4,6(1H,3H,5H)-trione (154) (L)
XXXII	3-Allyl-5-fluoropyrimidine-2,4(1H,3H)-dione (114) (D)
XXXIII	3-Allyl-5-fluoro-6-methoxypyrimidine-2,4(1H,3H)-dione (141) (D)

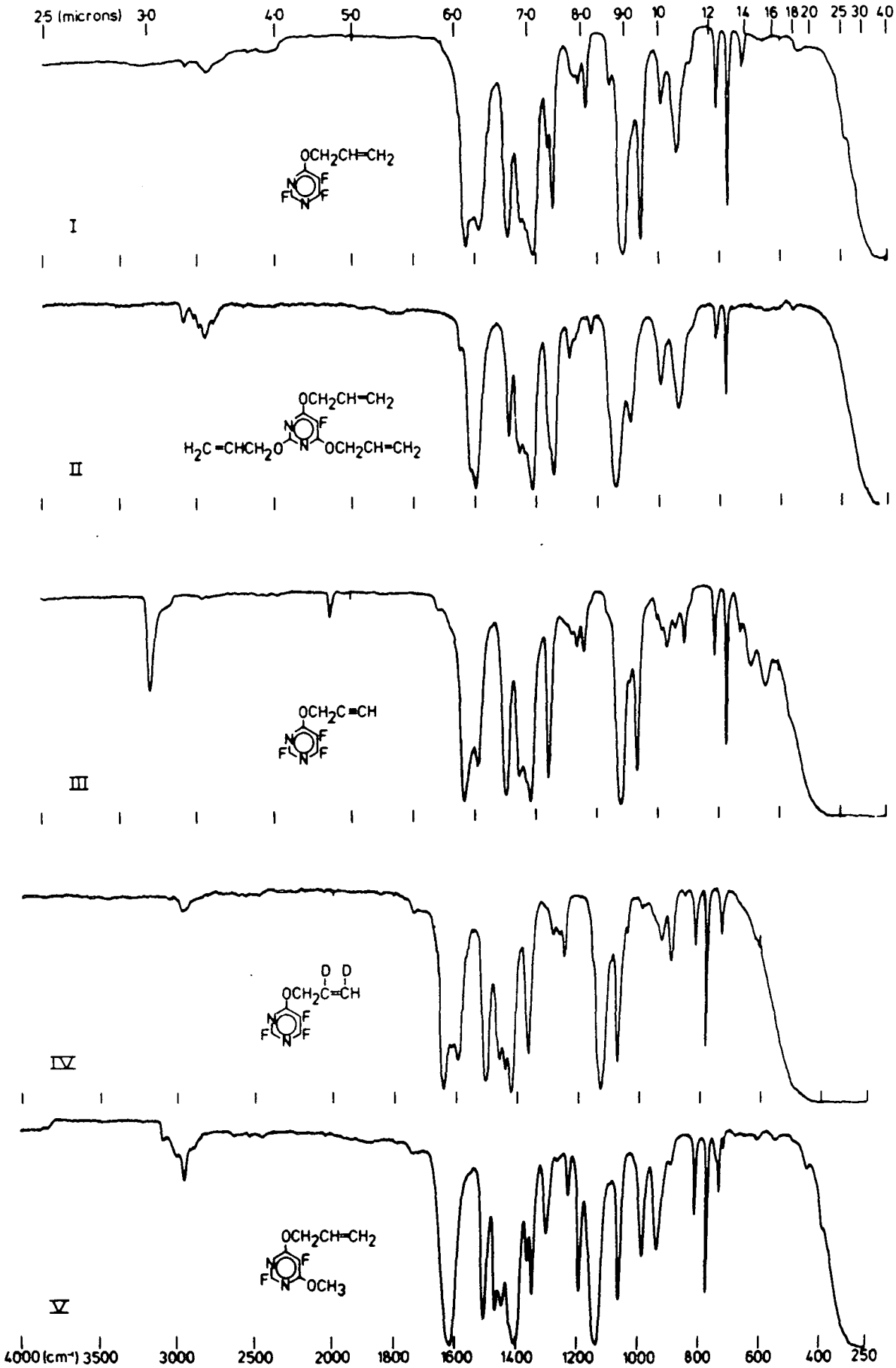
Spectra for Part B

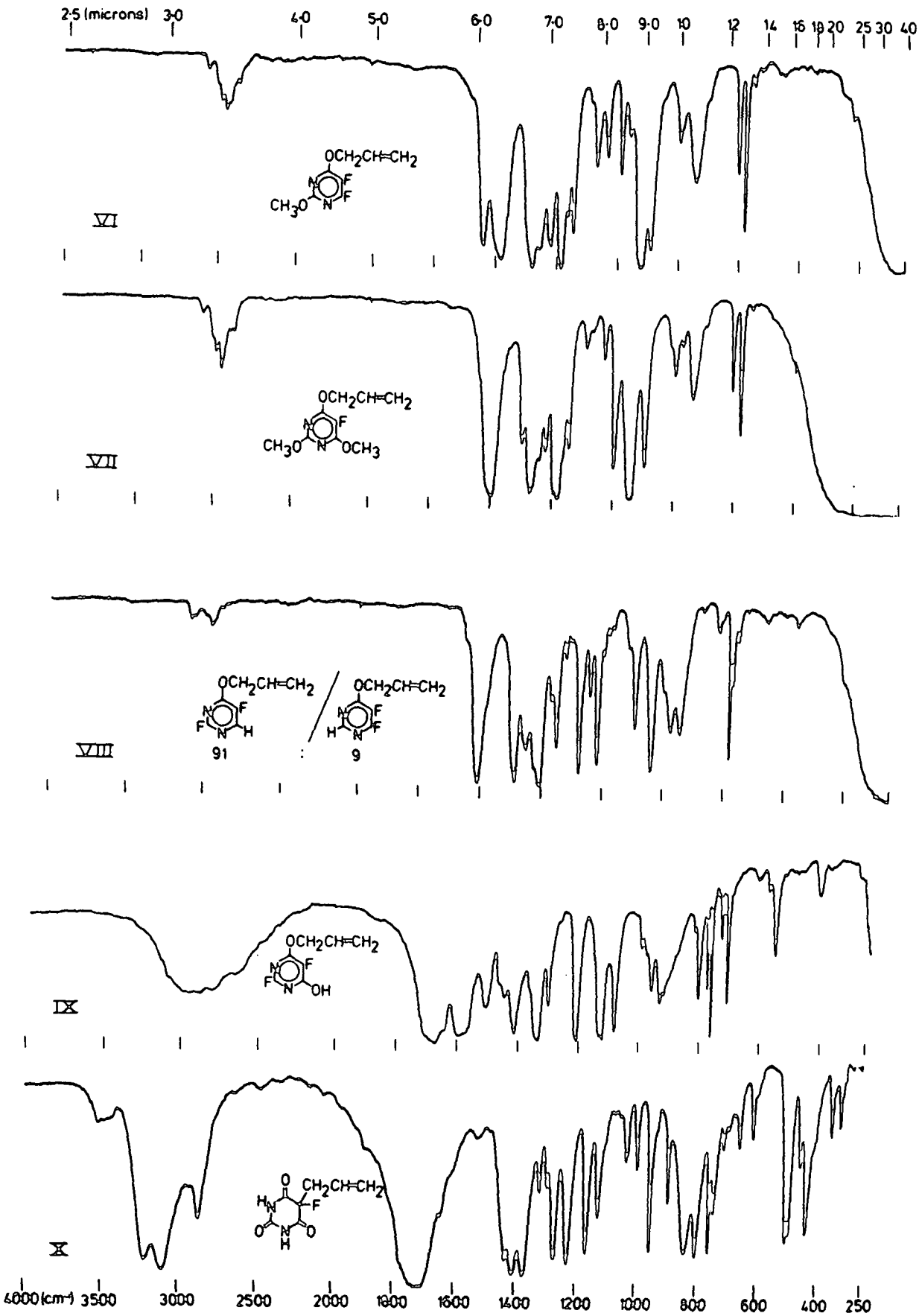
Compound Number	Name of Compound
XXXIV	Pentafluorophenyl thiomethoxymethyl ether (237) (L)
XXXV	2,3,4,5,6-Pentafluoro-6-thiomethoxymethylcyclohexa-2,4-dienone (238) (L)
XXXVI	2,4,5,6-Tetrafluoro-3-pentafluorophenoxy-6-thiomethoxymethylcyclohexa-2,4-dienone (239) (L)
XXXVII	2,3,5,6-Tetrafluorophenyl thiomethoxymethyl ether (245) (L)
XXXVIII	2,3,5,6-Tetrafluoro-6-thiomethoxymethylcyclohexa-2,4-dienone (246) (L)
XXXIX	1,3,4,5,6,7,8-Heptafluoro-2-naphthyl thiomethoxymethyl ether (250) (D)
XL	1,3,4,5,6,7,8-Heptafluoro-1-thiomethoxymethylnaphthalen-2(1H)-one (249) (D)
XLI	4-Bromo-2,3,5-trifluoro-6-pyridyl thiomethoxymethyl ether (261) (NM)
XLII	4-Bromo-3,5-difluoro-3-thiomethoxymethylpyridin-2,6(1H,3H)-dione (258) (D)

Compound Number	Name of Compound
XLIII	4-Bromo-2,3,5-trifluoro-1-thiomethoxymethylpyridin-6(1H)-one (260) (D)
XLIV	5-Hydroxy-2,3,4-trifluoropyridine-6-carbaldehyde (263) (NM)
XLV	5-Hydroxy-6-di(thiomethoxy)methylpyridine (264) (D)
XLVI	2,5,6-Trifluoro-3-thiomethoxymethylpyrimidin-4(3H)-one (268) (D)
XLVII	5-Fluoro-4,6-dimethoxymethylpyrimidin-2(1H)-one (271) (D)
XLVIII	N-Trifluoroacetyl-N-thiomethoxymethyl-2,3,4,5,6-pentafluoroaniline (284) (L)
XLVIX	2,5,6-Trifluoro-3-(N-methylamino)-4-thiomethoxymethyl-cyclohexa-2,5-dienone (285) (D)
L	2,4,5,6-Tetrafluoro-3-methoxy-6-thiomethoxymethyl-cyclohexa-2,4-dienone (24) (L)
LI	2,6-Difluoro-3,5-di(pentafluorophenoxy)-6-thiomethoxymethylcyclohexa-2,4-dienone (247) (D)
LII	2,3,5,6-Tetrafluoro-4-thiomethoxymethylphenol(244) (D)
LIII	2,3,5,6-Tetrafluoro-4-hydroxyphenylmethanol (248) (D)
LIV	2,4,5-Trifluoro-3-pentafluorophenoxy-6-thiomethoxymethylphenol (293) (D)
LV	1,3,4,5,6,7,8-Heptafluoro-2-hydroxy-1-thiomethoxymethyl-(1H,2H)-naphthalene (294) (D)
LVI	3,4,5,6,7,8-Hexafluoro-1-thiomethoxymethyl-2-naphthol (295) (D)
LVII	2,3,4,5-Tetrafluoro-6-methylphenol (300) (L)
LVIII	2,3,4,5-Tetrafluoro-6-methylphenyl-2′,3′,6′-trifluoro-5′-hydroxy-4′-methylphenyl ether (301) (D)

Compound Number	Name of Compound
LIX	2,3,6-Trifluoro-4-methyl-1-(2′,3′,4′,5′-tetrafluoro-6′-methylphenoxy)-5-(2″,3″,6″-trifluoro-5″-hydroxy-4″-methylphenoxy)benzene (302) (D)
LX	2,4,5-Trifluoro-3-methoxy-6-methylphenol (303) (NM)
LXI	3,4,5,6,7,8-Hexafluoro-1-methyl-2-naphthol (296) (D)
LXII	5,6-Difluoro-3-thiomethoxymethylpyrimidin-2,4-(1H,3H)-dione (269) (D)
LXIII	1,3,4,5,6,7,8-Heptafluoro-1-methylsulphonylmethyl-naphthalen-2(1H)-one (307) (D)
LXIV	2,3,4,5,6-Pentafluoro-6-methylsulphonylmethylcyclo-hexa-2,4-dienone (306) (D)
LXV	3,4,5,6,7,8-Hexafluoro-2-hydroxynaphthalene-1-carbaldehyde (315) (D)
LXVI	3,4,5,6,7,8-Hexafluoro-2-hydroxy-1-di(methylsulphonyl)-methylnaphthalene (316) (D)
LXVII	1,1-Di(pentafluorophenyl)methyl methylsulphoxide (321) (D)
LXVIII	2,3,4,5,6-Pentafluorobenzylmethylsulphoxide (320) (D)
LXVIX	2,2′,3,3′,4,4′,5,5′,6,6′-Decafluorodibenzyl (324) (D)
LXX	2,2′,3,3′,4,4′,5,5′,6,6′-Decafluorodibenzyl disulphide (326) (D)

SPECTRA FOR PART A

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CH3O
OCH3
F
VII
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F
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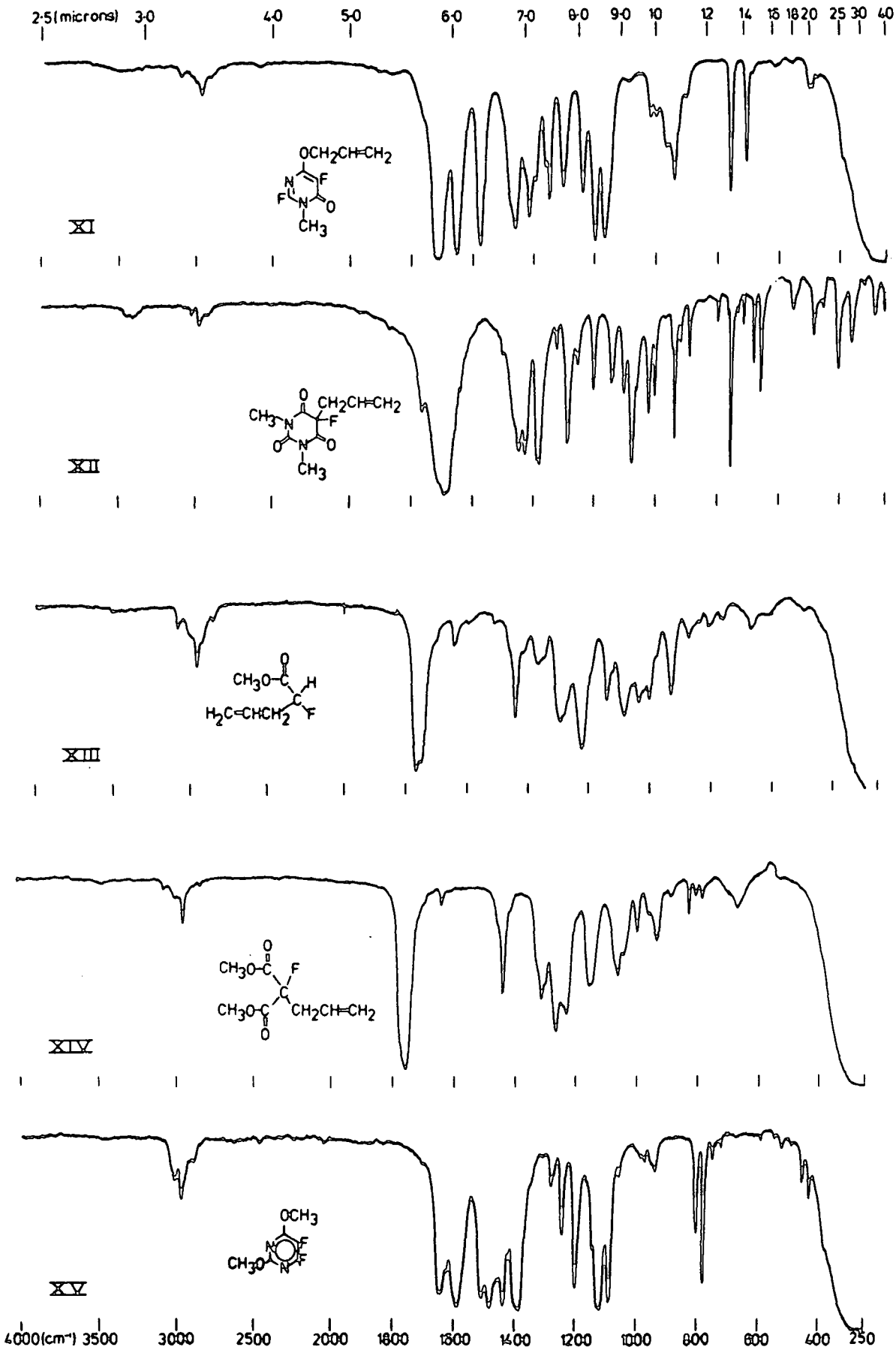
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O
N
O
CH3
XII
CH3O C
O
H
C
H2C=CHCH2
F
XIII
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O
F
C
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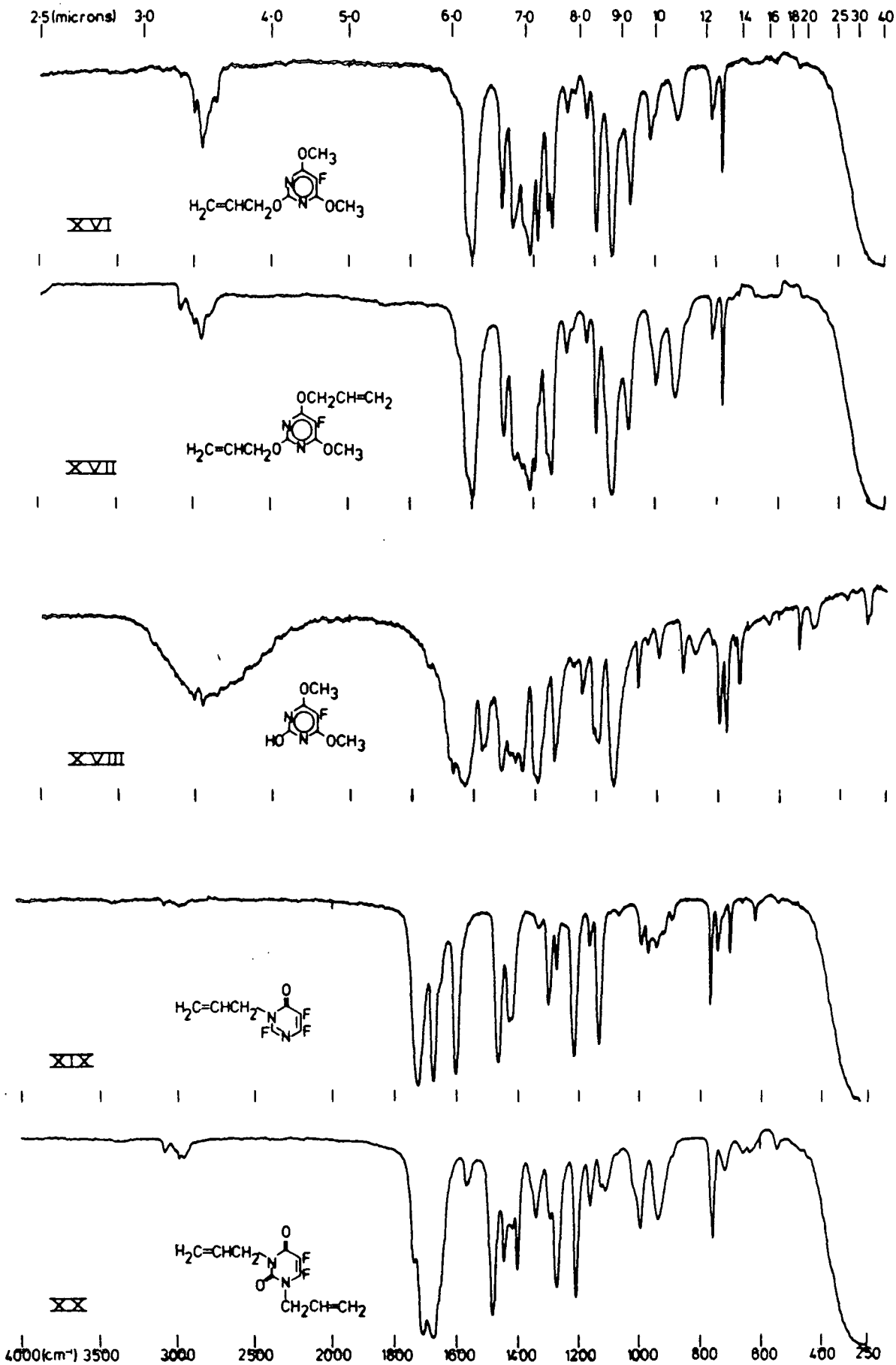
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XVI
XVII
XVIII
XIX
XX
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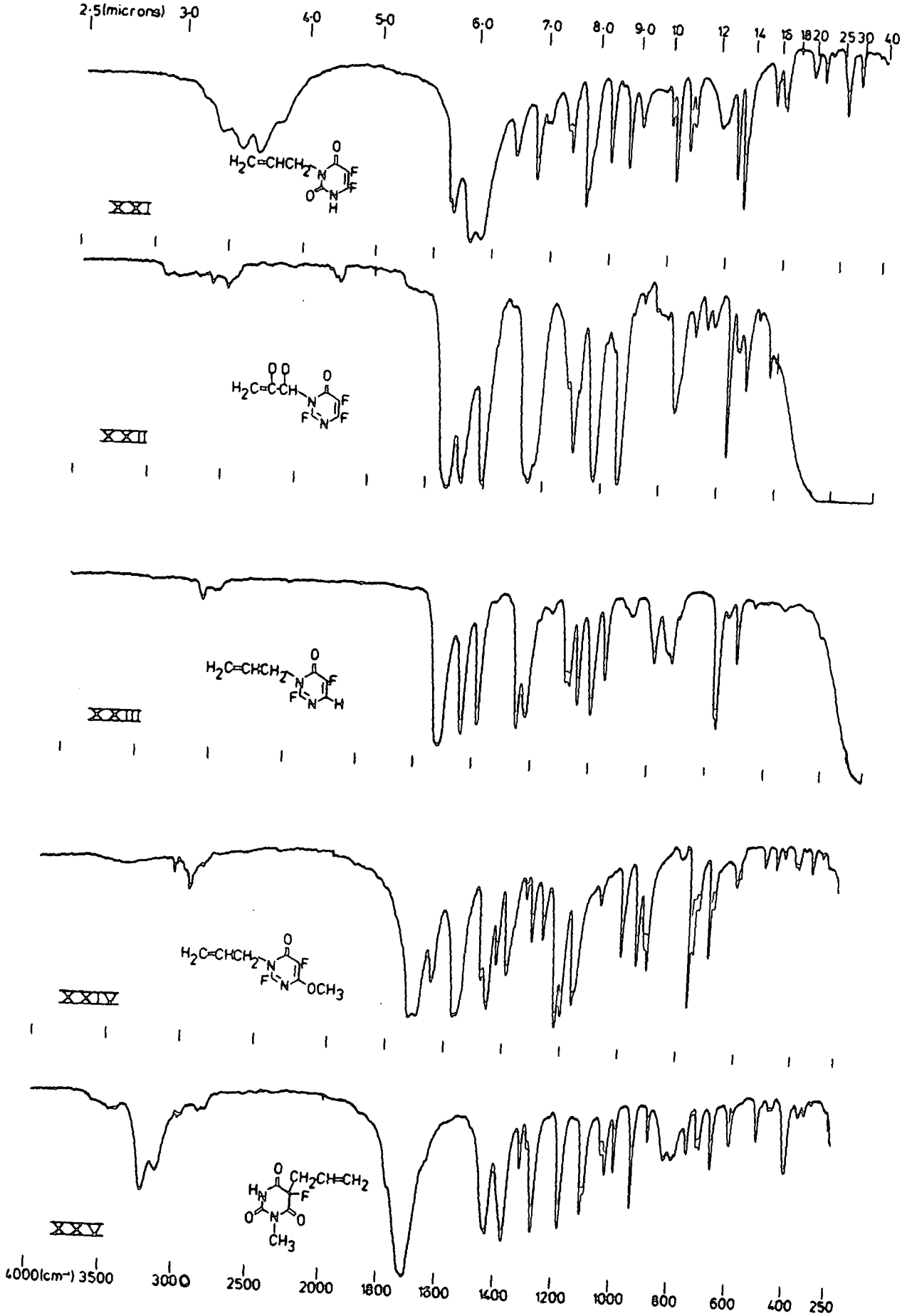
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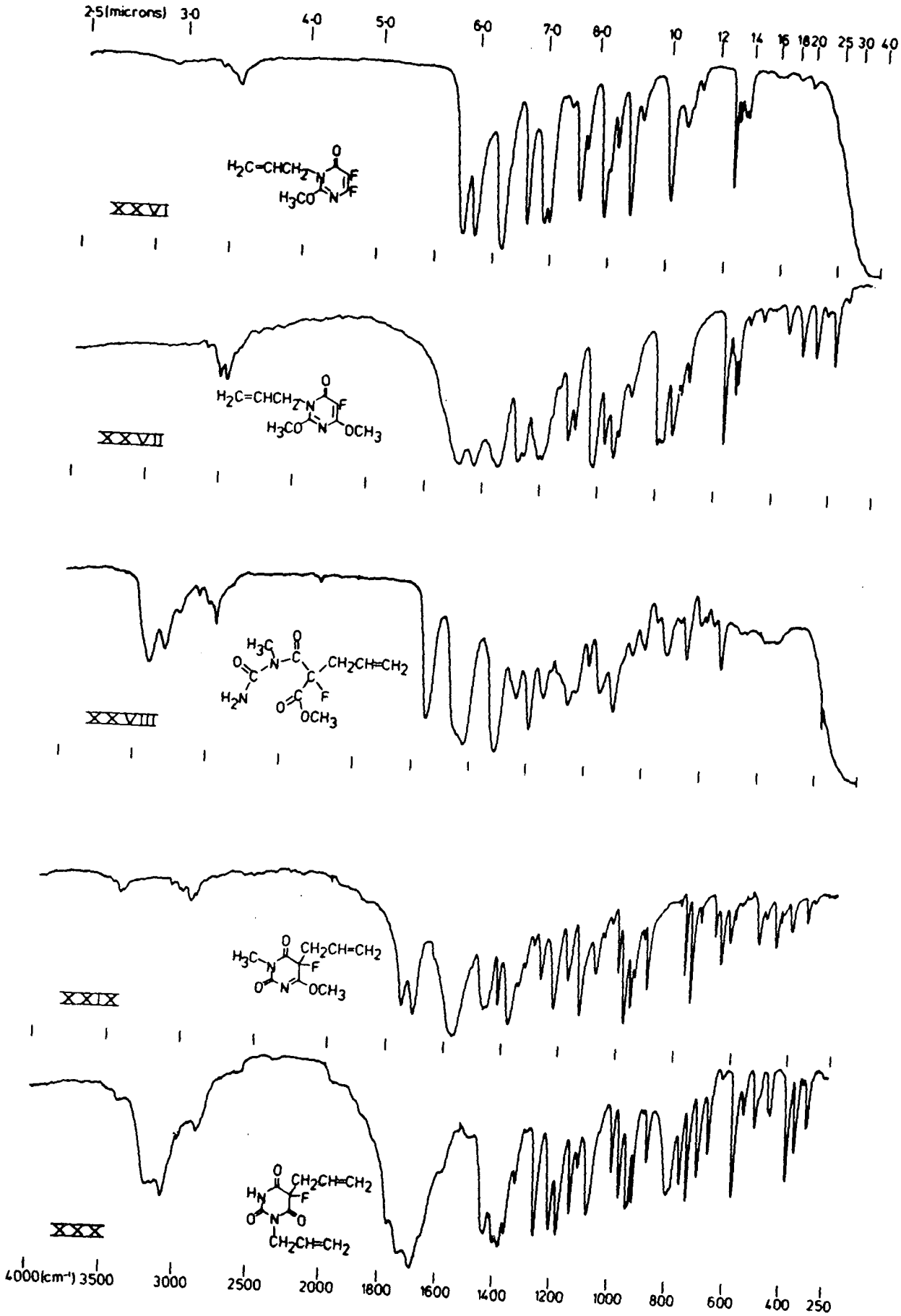
XXI
XXII
XXIII
XXIV
XXV
4000(cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250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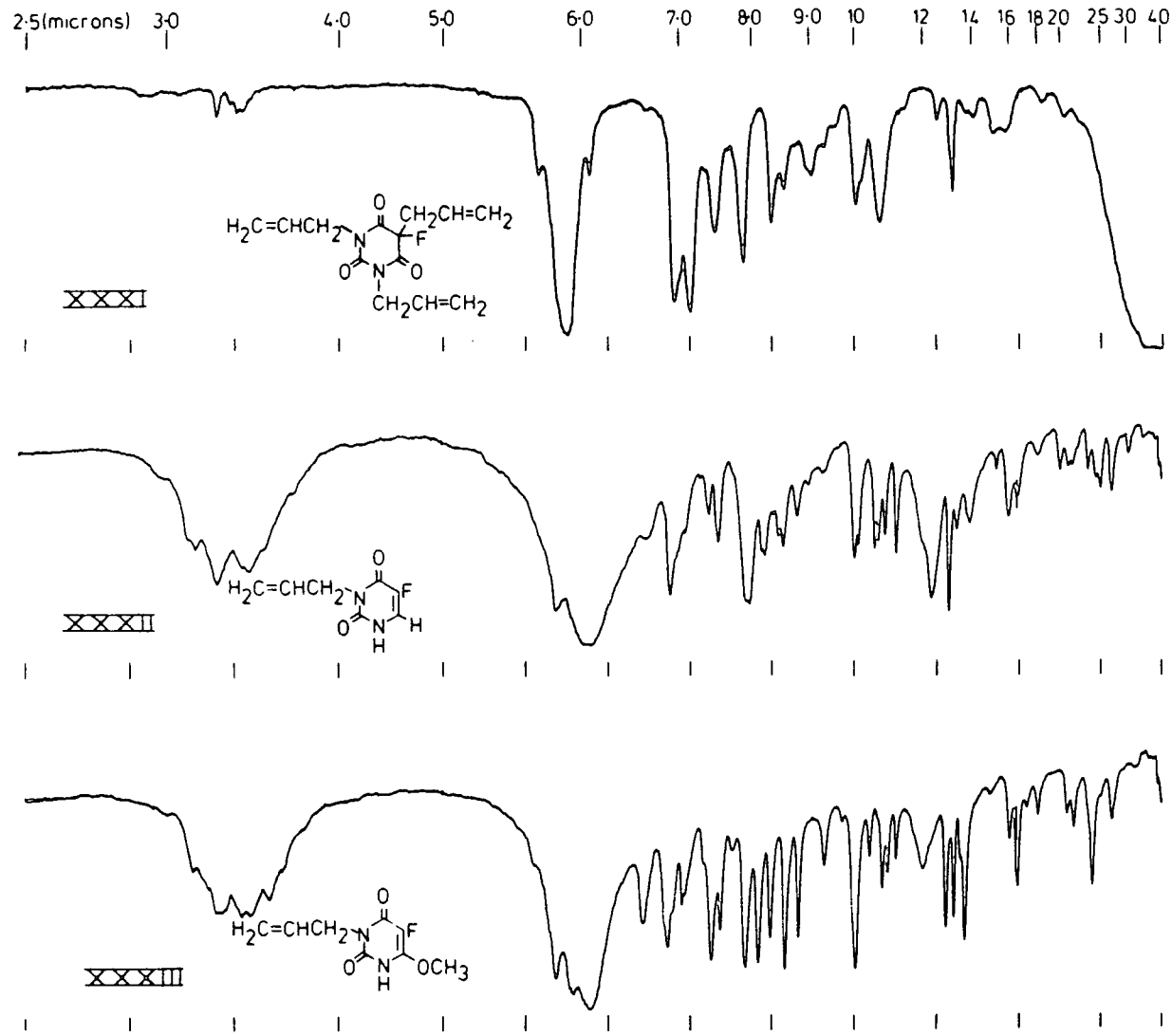
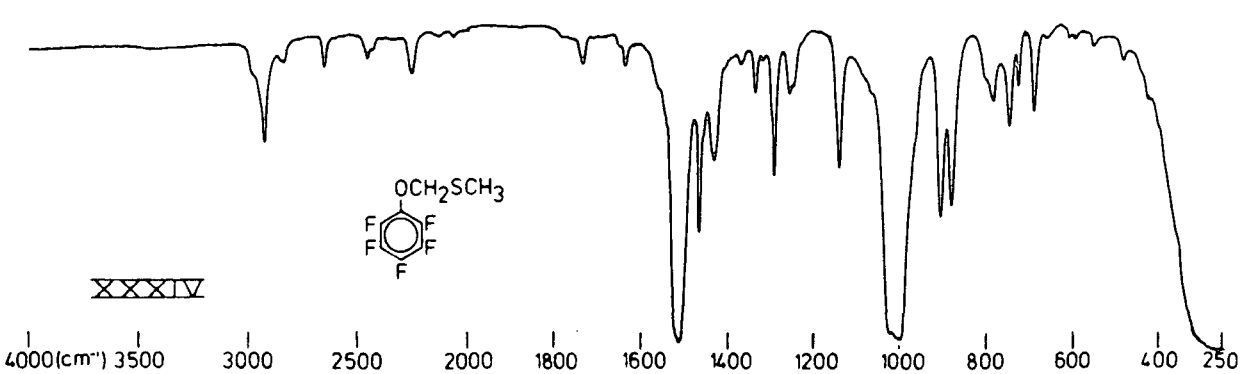
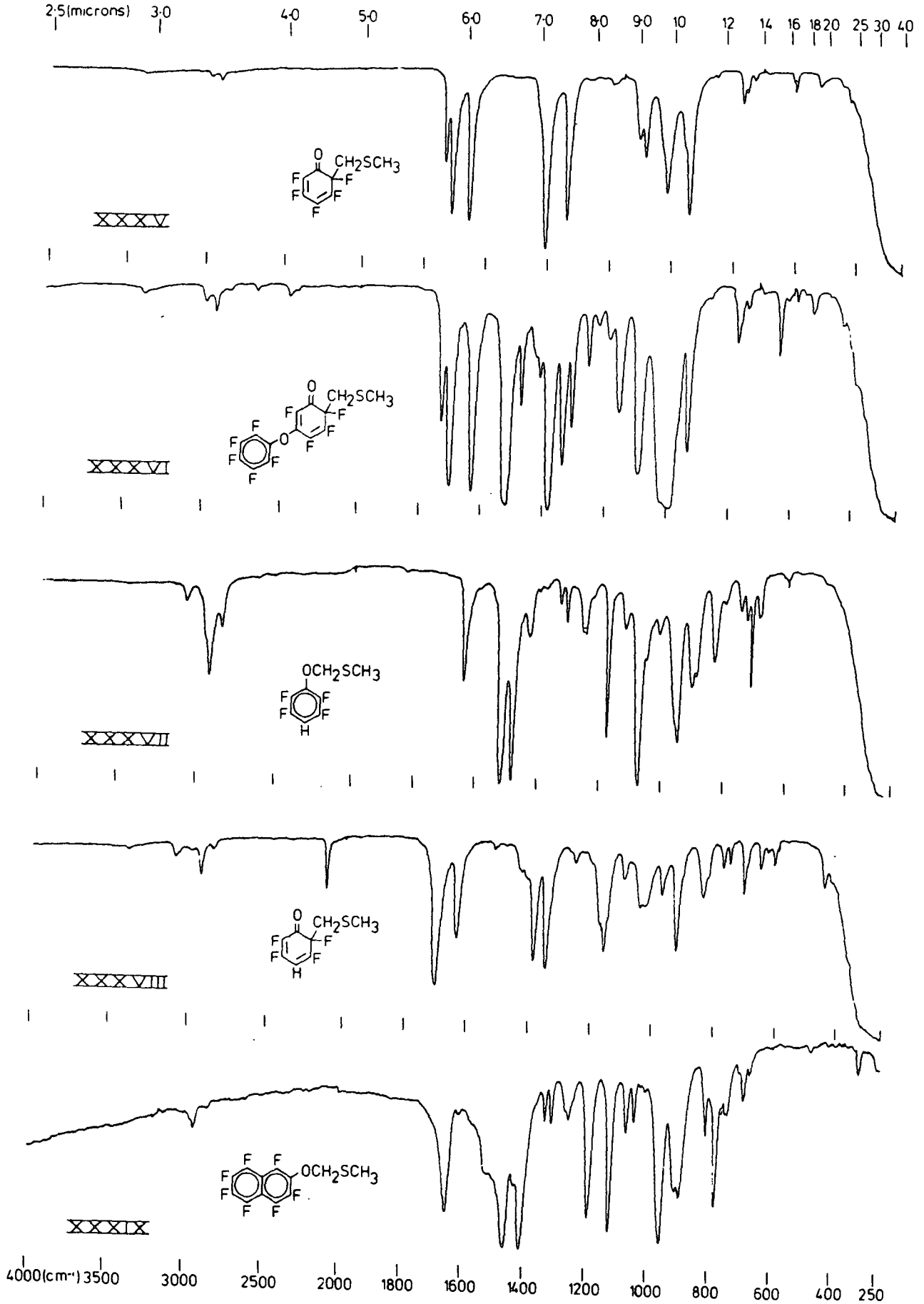
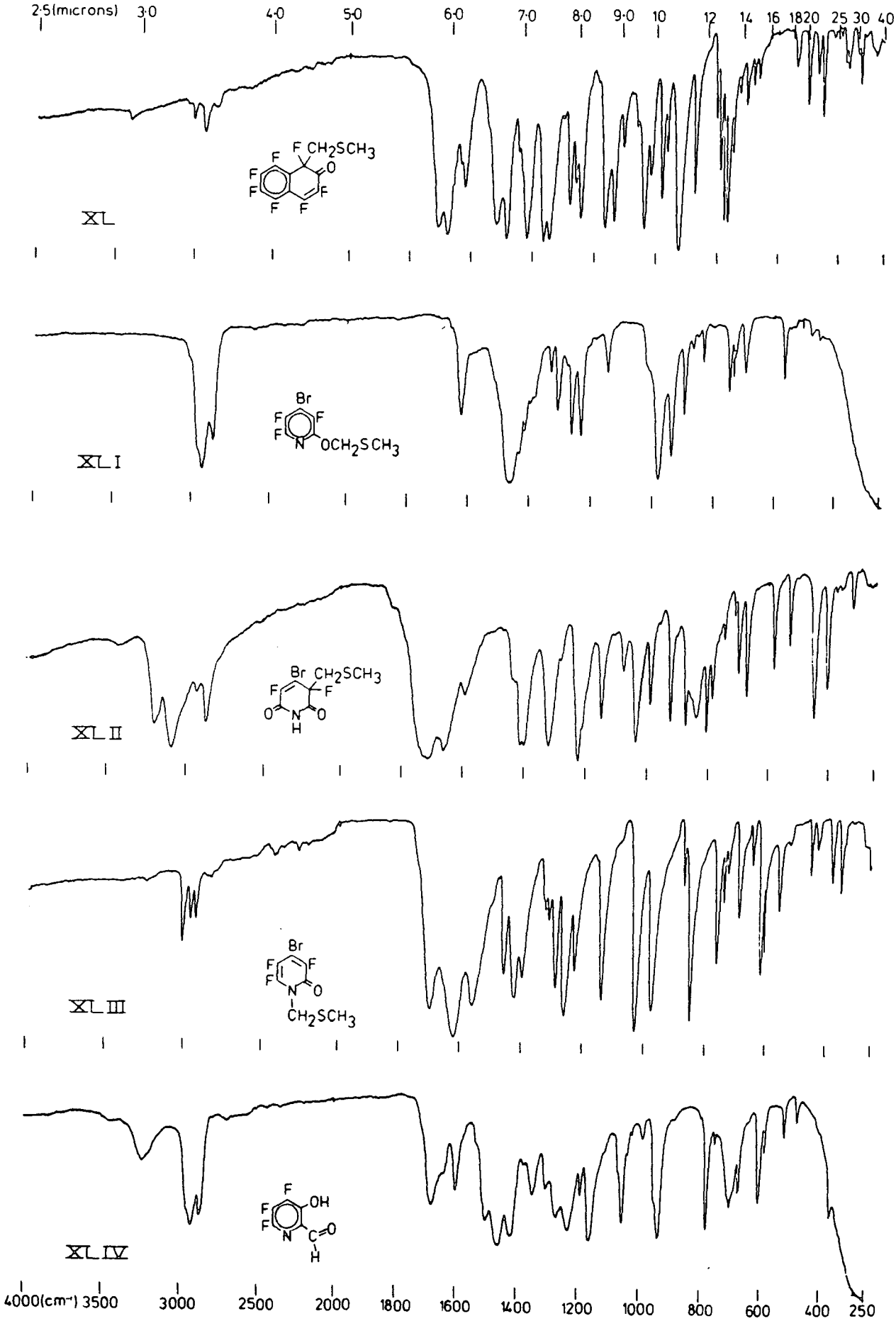
XXVI
XXVII
XXVIII
XXIX
XXX
4000(cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250



SPECTRA FOR PART B




2·5(microns) 3·0 4·0 5·0 6·0 7·0 8·0 9·0 10 12 14 16 18 20 25 30 40
XXXV
XXXVI
XXXVII
XXXVIII
XXXIX
4000(cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250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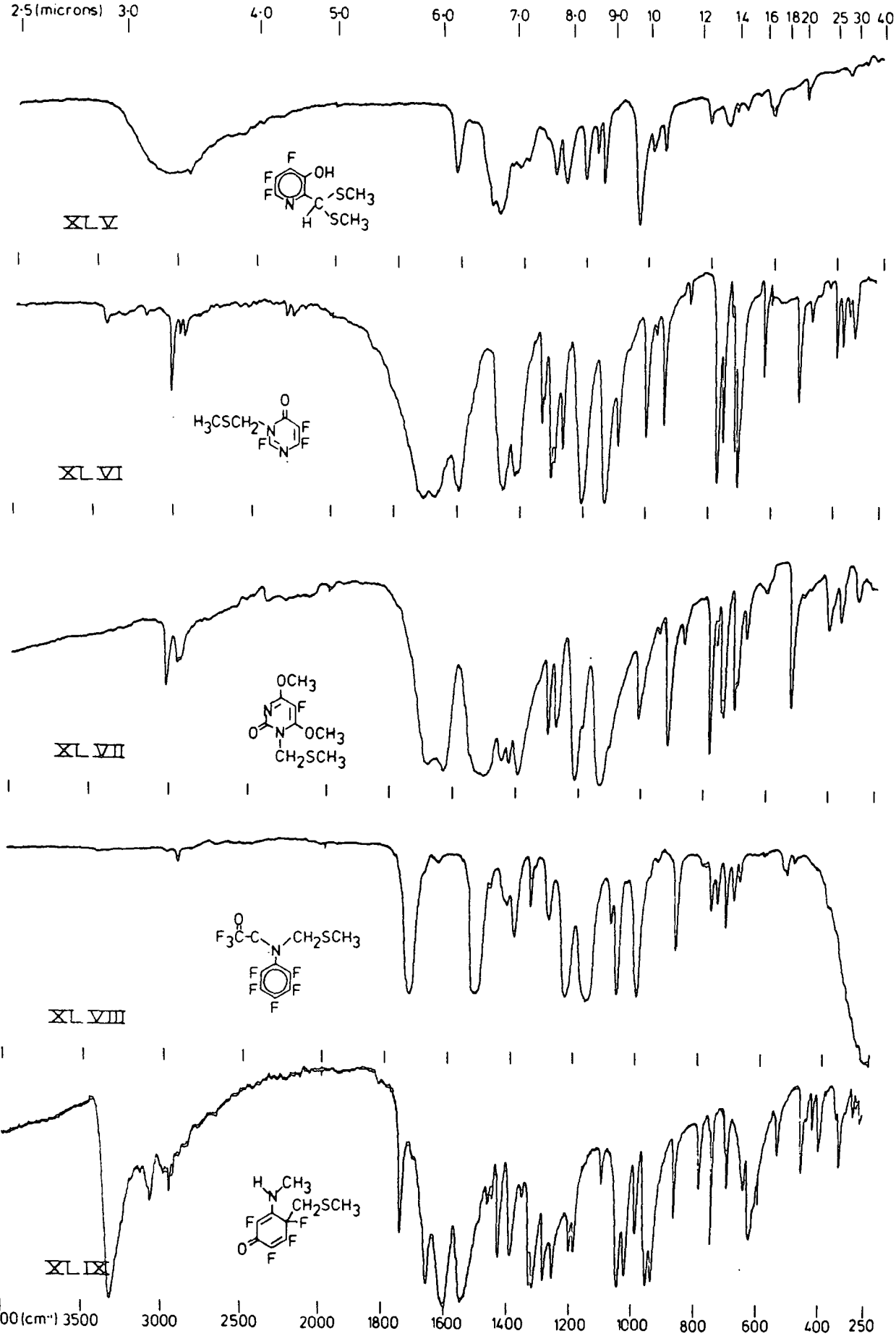
XL
XLI
XLII
XLIII
XLIV
4000(cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250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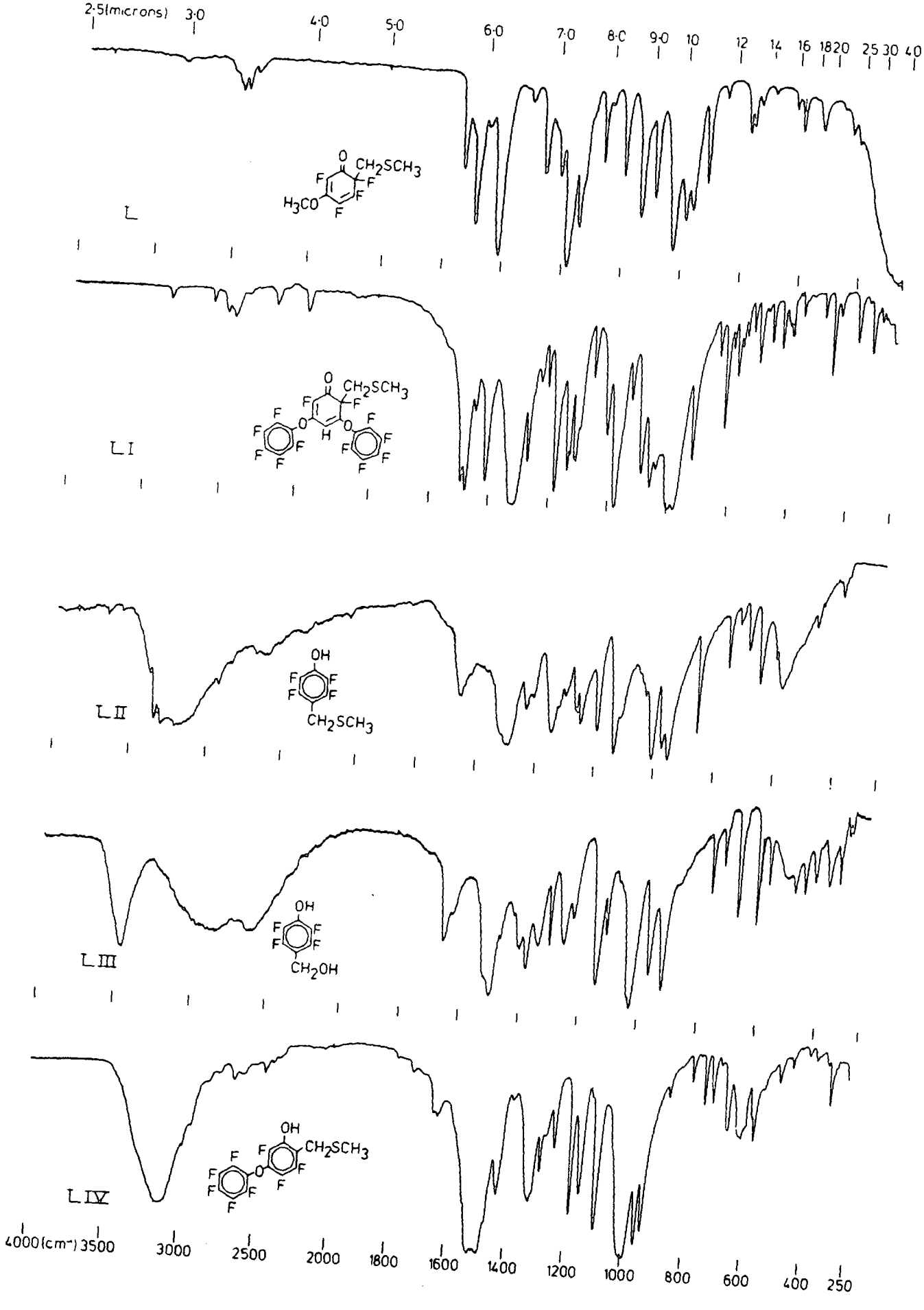
XLV
XLVI
XLVII
XLVIII
XLIX
4000 (cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250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L
LI
LII
LIII
LIV
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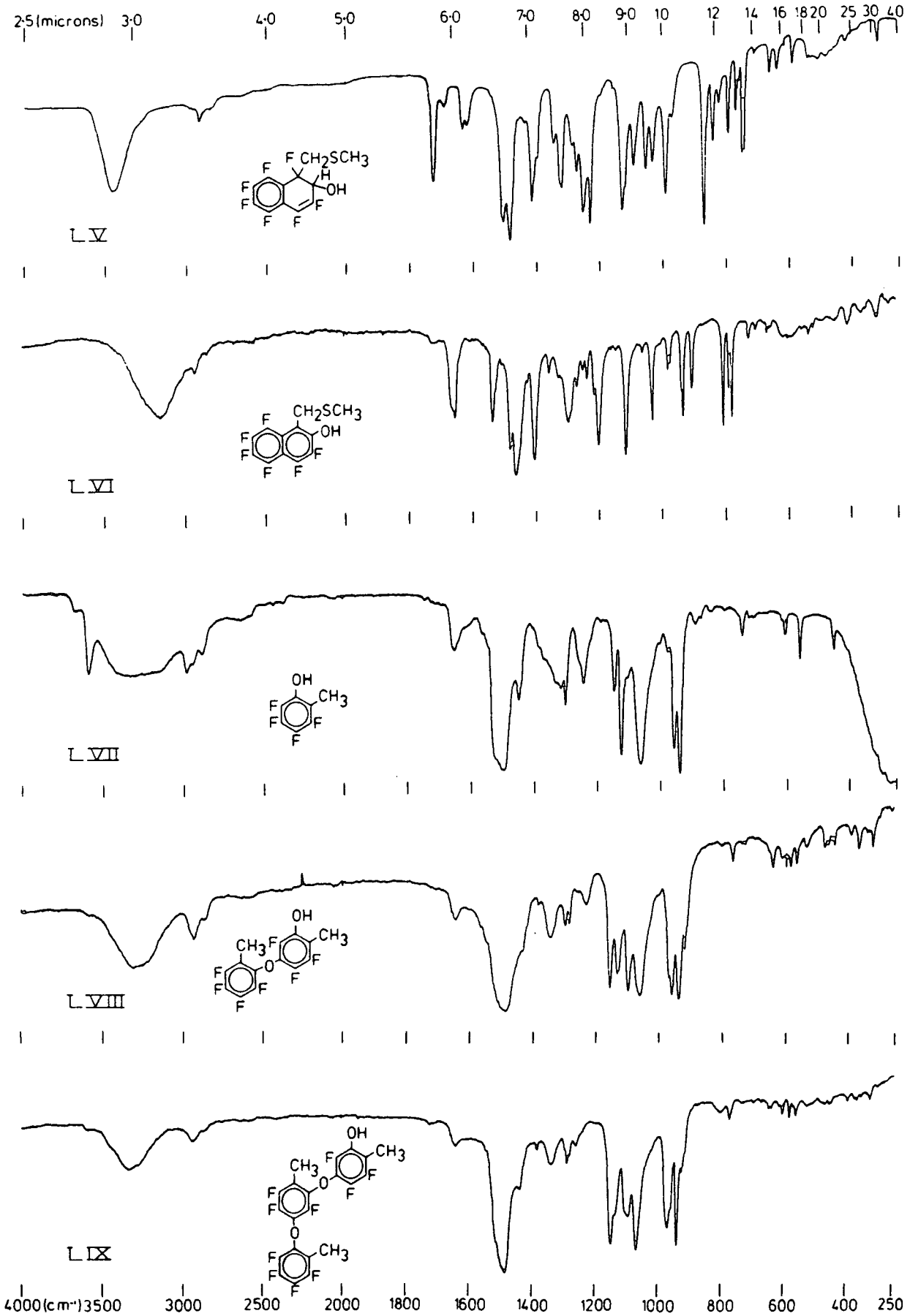
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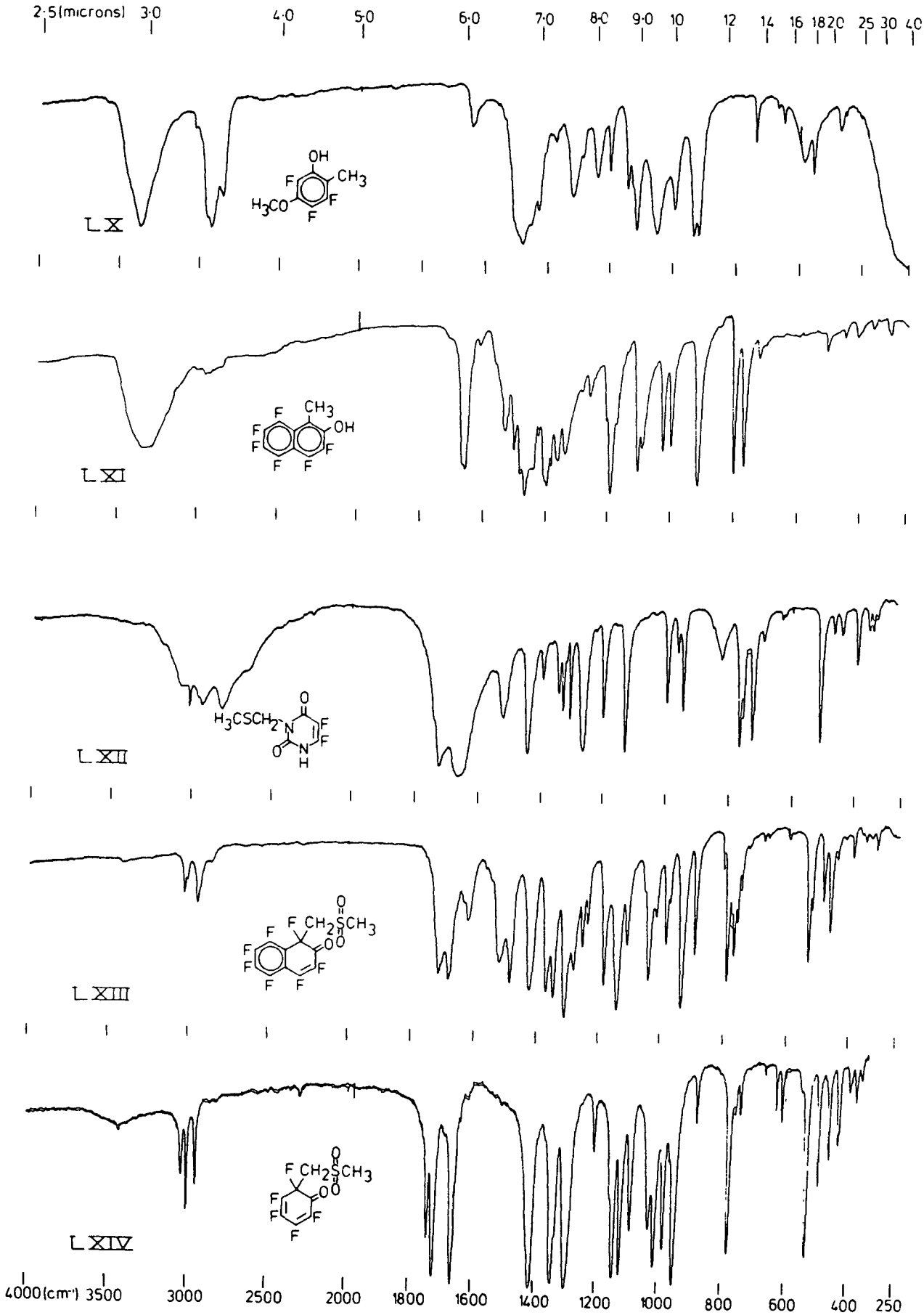
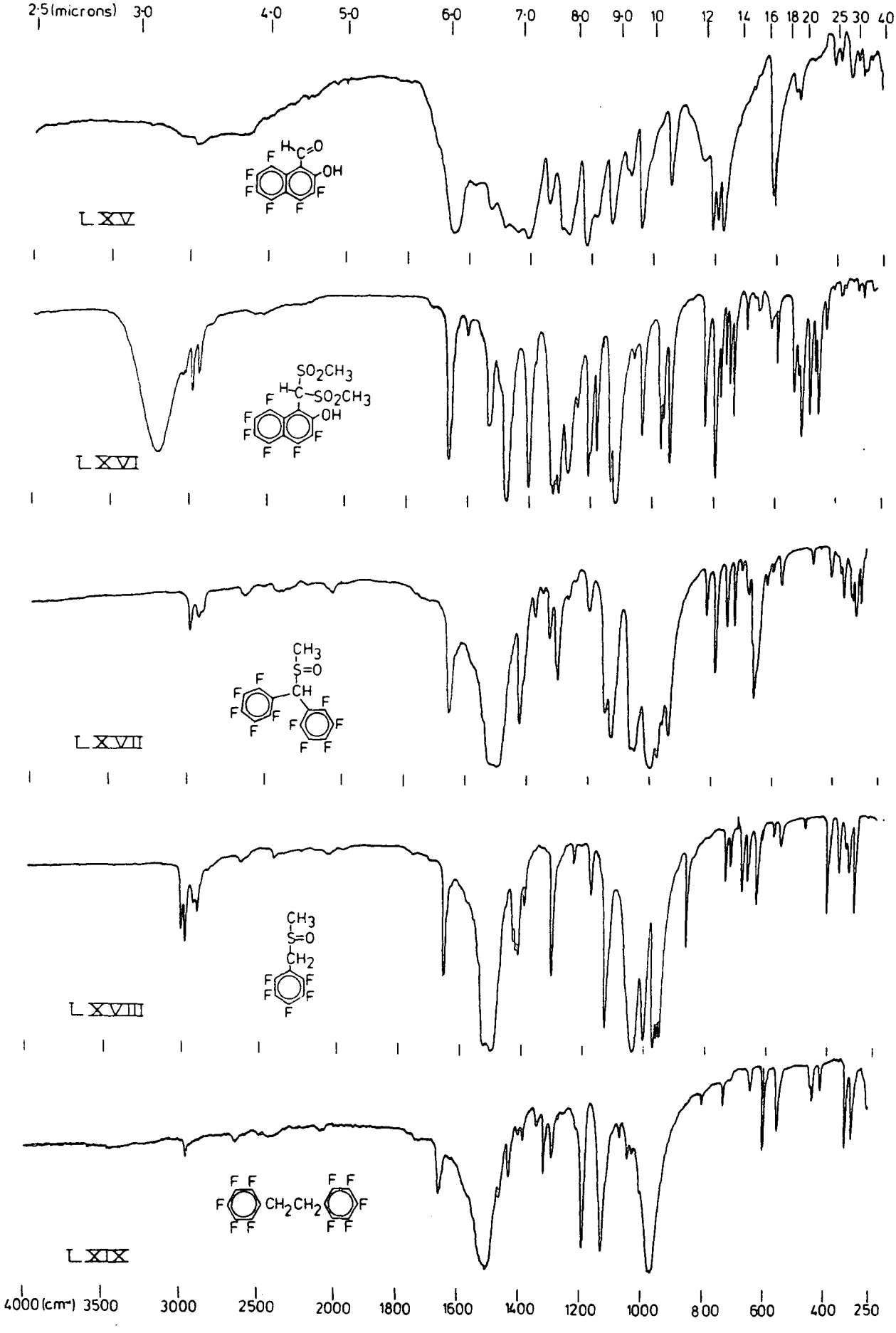
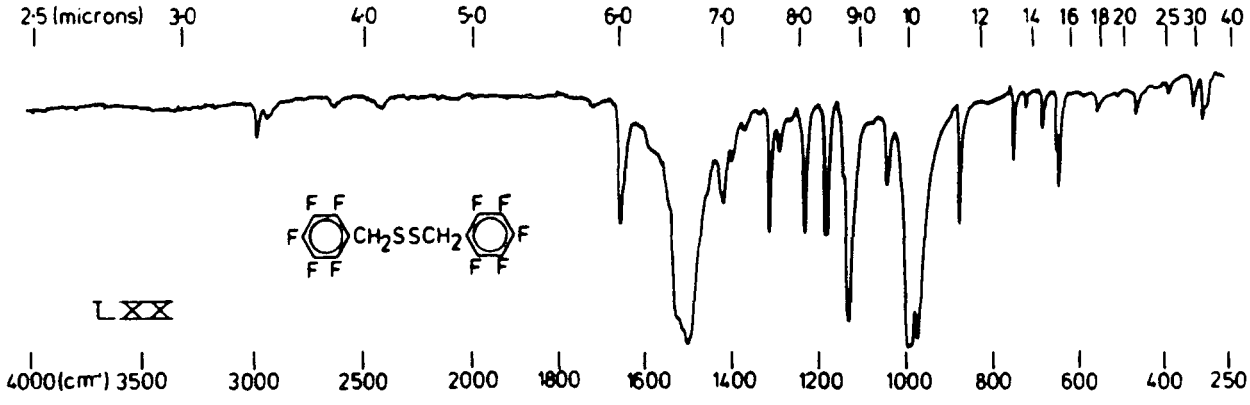
LV
LVI
LVII
LVIII
LIX
4000 (cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250


2·5(microns) 3·0 4·0 5·0 6·0 7·0 8·0 9·0 10 12 14 16 18 20 25 30 40
LX
LXI
LXII
LXIII
LXIV
4000(cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250


2·5 (microns) 3·0 4·0 5·0 6·0 7·0 8·0 9·0 10 12 14 16 18 20 25 30 40
LXV
LXVI
LXVII
LXVIII
LXIX
4000 (cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250


2·5 (microns) 3·0 4·0 5·0 6·0 7·0 8·0 9·0 10 12 14 16 18 20 25 30 40
F F
F CH2SSCH2 F
F F F F
LXX
4000(cm⁻¹) 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250

APPENDIX B

RESEARCH COLLOQUIA, SEMINARS, LECTURES AND CONFERENCES

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix, listing:

(A) all research colloquia, research seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student;

(B) Lectures organised by Durham University Chemical Society;

(C) all research conferences attended and papers presented by the author during the period when research for the thesis was carried out;

(D) details of the postgraduate induction course.

(A) LECTURES ORGANISED BY DURHAM UNIVERSITY - 1983-1986.

5.10.83 Prof. J.P. Maier (Basel, Switzerland) "Recent approaches to spectroscopic characterization of cations".

12.10.83 Dr. C.W. McLeland (Port Elizabeth, Australia), "Cyclization of aryl alcohols through the intermediacy of alkoxy radicals and aryl radical cations".

19.10.83 Dr. N.W. Alcock (Warwick), "Aryl tellurium (IV) compounds, patterns of primary and secondary bonding".

26.10.83 Dr. R.H. Friend (Cavendish, Cambridge), "Electronic properties of conjugated polymers".

30.11.83 Prof. I.M.G. Cowie (Stirling), "Molecular interpretation of non-relaxation processes in polymer glasses".

2.12.83 Dr. G.M. Brooke (Durham), "The fate of the ortho-fluorine in 3,3-sigmatropic reactions involving polyfluoro-aryl and -hetero-aryl systems".

14.12.83 Prof. R.J. Donovan (Edinburgh), "Chemical and physical processes involving the ion-pair states of the halogen molecules".

10. 1.84 Prof. R. Hester (York)
"Nanosecond Laser Spectroscopy of Reaction Intermediates"

18. 1.84 Prof. R.K. Harris (UEA)
"Multi-nuclear solid state magnetic resonance"

8. 2.84 Dr. B.T. Heaton (Kent)
"Multi-nuclear NMR studies"

15. 2.84 Dr. R.M. Paton (Edinburgh)
"Heterocyclic Syntheses using Nitrile Sulphides"

7. 3.84 Dr. R.T. Walker (Birmingham),
"Synthesis and Biological Properties of some 5-substituted Uracic Derivatives; yet another example of serendipity in Anti-viral Chemotherapy"

21. 3.84 Dr. P. Sherwood (Newcastle)
"X-ray photoelectron spectroscopic studies of electrode and other surfaces"

21. 3.84 Dr. G. Beamson (Durham/Kratos)
"EXAFS: General Principles and Applications"

23. 3.84 Dr. A. Ceulemans (Leuven)
"The Development of Field-Type models of the Bonding in Molecular Clusters"

2. 4.84 Prof. K. O'Driscoll (Waterloo)
"Chain Ending reactions in Free Radical Polymerisation"

3. 4.84 Prof. C.H. Rochester (Dundee)
"Infrared Studies of adsorption at the Solid-Liquid Interface"

25. 4.84 Dr. R.M. Acheson (Biochemistry, Oxford)
"Some Heterocyclic Detective Stories"

27. 4.84 Dr. T. Albright (Houston, U.S.A.)
"Sigmatropic Rearrangements in Organometallic Chemistry"

14. 5.84 Prof. W.R. Dolbier (Florida, USA)
"Cycloaddition Reactions of Fluorinated Allenes"

16. 5.84 Dr. P.J. Garratt (UCL)
"Synthesis with Dilithiated Vicinal Diesters and Carboximides"

22. 5.84 Prof. F.C. de Schryver (Leuven)
"The use of Luminescence in the study of micellar aggregates" and
"Configurational and Conformational control in excited state complex formation"

23. 5.84 Prof. M. Tada (Waseda, Japan)
"Photochemistry of Dicyanopyrazine Derivatives"

31. 5.84 Dr. A. Haaland (Oslo)
"Electron Diffraction Studies of some organometallic compounds"

11. 6.84 Dr. J.B. Street (IBM, California)
"Conducting Polymers derived from Pyrroles"

19. 9.84 Dr. C. Brown (IBM, California)
"New Superbase reactions with organic compounds"

21. 9.84 Dr. H.W. Gibson (Signal UOP, Illinois)
"Isomerization of Polyacetylene"

19.10.84 Dr. A. Germain (Languedoc, Montpellier)
"Anodic Oxidation of Perfluoro Organic Compounds in Perfluoroalkane Sulphonic Acids"

24.10.84 Prof. R.K. Harris (Durham)
"N.M.R. of Solid Polymers"

28.10.84 Dr. R. Snaith (Strathclyde)
"Exploring Lithium Chemistry: Novel Structures, Bonding and Reagents"

7.11.84 Prof. W.W. Porterfield (Hampden-Sydney College, USA)
"There is no Borane Chemistry (only Geometry)"

7.11.84 Dr. H.S. Munro (Durham)
"New Information from ESCA Data"

21.11.84 Mr. N. Everall (Durham)
"Picosecond Pulsed Laser Raman Spectroscopy

27.11.84 Dr. W.J. Feast (Durham)
"A Plain Man's Guide to Polymeric Organic Metals"

28.11.84 Dr. T.A. Stephenson (Edinburgh)
"Some recent studies in Platinum Metal Chemistry"

12.12.84 Dr. K.B. Dillon (Durham)
"^{31}P N.M.R. Studies of some Anionic Phosphorus Complexes"

11. 1.85 Emeritus Prof. H. Suschitzky (Salford)
"Fruitful Fissons of Benzofuroxanes and Isobenzimic azoles (umpolung of o-phenylenediamine)"

13. 2.85 Dr. G.W.J. Fleet (Oxford)
"Synthesis of some Alkaloids from Carbohydrates"

19. 2.85 Dr. D.J. Mincher (Durham)
"Stereoselective Synthesis of some novel Anthracyclinones related to the anti-cancer drug Adriamy and to the Steffimycin Antibiotics"

27. 2.85 Dr. R. Mulvey (Durham)
"Some unusual Lithium Complexes"

6. 3.85 Dr. P.J. Kocienski (Leeds)
"Some Synthetic Applications of Silicon-Mediated Annulation Reactions"

7. 3.85 Dr. P.J. Rodgers (I.C.I. plc. Agricultural Division, Billingham)
"Industrial Polymers from Bacteria"

12. 3.85 Prof. K.J. Packer (B.P. Ltd./East Anglia)
"N.M.R. Investigations of the Structure of Solid Polymers"

14. 3.85 Prof. A.R. Katritzky F.R.S. (Florida)
"Some Adventures in Heterocyclic Chemistry"

20. 3.85 Dr. M. Poliakoff (Nottingham)
"New Methods for detecting Organometallic Intermediates in Solution"

28. 3.85 Prof. H. Ringsdorf (Mainz)
"Polymeric Liposomes as Models for Biomembranes and Cells?"

24. 4.85 Dr. M.C. Grossel (Bedford College, London)
"Hydroxypyridone dyes - Bleachable one-dimensional Metals?"

25. 4.85 Major S.A. Shackelford (U.S. Air Force)
"In Situ Mechanistic Studies on Condensed Phase Thermochemical Reaction Processes: Deuterium Isotope Effects in HMX Decomposition, Explosives and Combustion"

1. 5.85 Dr. D. Parker (I.C.I. plc. Petrochemical and Plastics Division, Wilton)
"Applications of Radioisotopes in Industrial Research"

7. 5.85 Prof. G.E. Coates (formerly of University of Wyoming, U.S.A.)
"Chemical Education in England and America: Successes and Deficiencies"

8. 5.85 Prof. D. Tuck (Windsor, Ontario)
"Lower Oxidation State Chemistry of Indium"

8. 5.85 Prof. G. Williams (U.C.W. Aberystwyth)
"Liquid Crystalline Polymers"

9. 5.85 Prof. R.K. Harris (Durham)
"Chemistry in a Spin: Nuclear Magnetic Resonance"

14. 5.85 Prof. J. Passmore (New Brunswick, U.S.A.)
"The Synthesis and Characterisation of some Novel Selenium-Iodine Cations, aided by ^{77}Se N.M.R. Spectroscopy"

15. 5.85 Dr. J.E. Packer (Auckland, New Zealand)
Studies of Free Radical Reactions in aqueous solution using Ionising Radiation"

17. 5.85 Prof. I.D. Brown (McMaster University, Canada)
"Bond Valence as a Model for Inorganic Chemistry"

21. 5.85 Dr. D.L.H. Williams (Durham)
"Chemistry in Colour"

22. 5.85 Dr. M. Hudlicky (Blacksburg, U.S.A.)
"Preferential Elimination of Hydrogen Fluoride from Vicinal Bromofluorocompounds"

22. 5.85 Dr. R. Grimmett (Otago, New Zealand)
"Some Aspects of Nucleophilic Substitution in Imidazoles"

4. 6.85 Dr. P.S. Belton (Food Research Institute, Norwich)
"Analytical Photoacoustic Spectroscopy"

13. 6.85 Dr. D. Woolins (Imperial College, London)
"Metal - Sulphur - Nitrogen Complexes"

14. 6.85 Prof. Z. Rappoport (Hebrew University, Jerusalem)
"The Rich Mechanistic World of Nucleophilic Vinylic Substitution"

19. 6.85 Dr. R.N. Mitchell (Dortmund)
"Some Synthetic and NMR - Spectroscopic Studies of Organotin Compounds"

26. 6.85 Prof. G. Shaw (Bradford)
"Synthetic Studies on Imidazole Nucleosides and the Antibiotic Coformycin"

12. 7.85 Dr. K. Laali (Hydrocarbon Research Institute, University of Southern California)
"Recent Developments in Superacid Chemistry and Mechanistic Considerations in Electrophilic Aromatic Substitutions: A Progress Report"

13. 9.85 Dr. V.S. Parmar (University of Delhi),
"Enzyme Assisted ERC Synthesis"

30.10.85 Dr. S.N. Whittleton (University of Durham),
"An Investigation of a Reaction Window"

5.11.85 Prof. M.J. O'Donnell (Indiana-Purdue University),
"New Methodology for the Synthesis of Amino acids"

20.11.85 Dr. J.A.H. MacBride (Sunderland Polytechnic).
"A Heterocyclic Tour on a Distorted Tricycle-Biphenylene"

28.11.85 Prof. D.J. Waddington (University of York),
"Resources for the Chemistry Teacher"

15. 1.86 Prof. N. Sheppard (University of East Anglia),
"Vibrational and Spectroscopic Determinations of the Structures of Molecules Chemisorbed on Metal Surfaces"

29. 1.86 Dr. J.H. Clark (University of York),
"Novel Fluoride Ion Reagents"

12. 2.86 Prof. O.S. Tee (Concordia University, Montreal),
"Bromination of Phenols"

12. 2.86 Dr. J. Yarwood (University of Durham),
"The Structure of Water in Liquid Crystals"

19. 2.86 Prof. G. Procter (University of Salford), "Approaches to the Synthesis of some Natural Products"

26. 2.86 Miss C. Till (University of Durham), "ESCA and Optical Emission Studies of the Plasma Polymerisation of Perfluoroaromatics"

5. 3.86 Dr. D. Hathway (University of Durham), "Herbicide Selectivity"

5. 3.86 Dr. M. Schroder (University of Edinburgh), "Studies on Macrocycle Complexes"

12. 3.86 Dr. J.M. Brown (University of Oxford), "Chelate Control in Homogeneous Catalysis"

14. 5.86 Dr. P.R.R. Langridge-Smith (University of Edinburgh), "Naked Metal Clusters - Synthesis, Characterisation and Chemistry"

9. 6.86 Prof. R. Schmutzler (University of Braunschweig), "Mixed Valence Diphosphorous Compounds"

23. 6.86 Prof. R.E. Wilde (Texas Technical University), "Molecular Dynamic Processes from Vibrational Bandshapes"

B. Lectures Organised by Durham University Chemical Society during the period 1983-1986

20.10.83 Prof. R.B. Cundall (Salford) "Explosives

3.11.83 Dr. G. Richards (Oxford) "Quantum Pharmacology"

10.11.83 Prof. J.H. Ridd (U.C.L.). "Ipso-Attack in Electrophilic Aromatic Substitution"

17.11.83 Dr. J. Harrison (Sterling Organic), "Applied Chemistry and the Pharmaceutical Industry" "Joint Lecture with the Society of Chemical Industry)

24.11.83 Prof. D.A. King (Liverpool), "Chemistry in 2-Dimensions"

1.12.83 Dr. J.D. Coyle (The Open University), "The Problem with Sunshine"

26. 1.84 Prof. T.L. Blundell (Birkbeck College, London) "Biological Recognition: Interactions of Macromolecular Surfaces"

2. 2.84 Prof. N.B.H. Jonathan (Southampton), "Photoelectron Spectroscopy - A Radical Approach"

16. 2.84 Prof. D. Phillips (The Royal Institution), "Luminescence and Photochemistry - a Light Entertainment"

23. 2.84 Prof. F.G.A. Stone F.R.S. (Bristol), "The Use of Carbene and Carbyne Groups to Synthesise Metal Clusters" (The Waddington Memorial Lecture)

1. 3.84 Prof. A.J. Leadbetter (Rutherford Appleton Labs.), "Liquid Crystals"

8. 3.84 Prof. D. Chapman (Royal Free Hospital School of Medicine, London) "Phospholipids and Biomembranes: Basic Science and Future Techniques"

28. 3.84 Prof. H. Schmidbaur (Munich, F.R.G.), "Ylides in Coordination Sphere of Metal: Synthetic, Structural and Theoretical Aspects" (R.S.C. Centenary Lecture)

18.10.84 Dr. N. Logan (Nottingham), "N_2O_4 and Rocket Fuels"

23.10.84 Dr. W.J. Feast (Durham), "Syntheses of Conjugated Polymers. How and Why?"

8.11.84 Prof. B.J. Aylett (Queen Mary College, London), "Silicon - Dead Common or Refined?"

15.11.84 Prof. B.T. Golding (Newcastle-upon-Tyne), "The Vitamin B_{12} Mystery"

22.11.84 Prof. D.T. Coark (I.C.I. New Science Group), "Structure, Bonding, Reactivity and Synthesis as revealed by EXCA" (R.S.C. Tilden Lecture)

29.11.84 Prof. C.J.M. Stirling (University College of North Wales "Molecules taking the Strain"

6.12.84 Prof. R.D. Chambers (Durham), "The Unusual World of Fluorine"

24. 1.85 Dr. A.K. Covington (Newcastle-upon-Tyne), "Chemistry with Chips"

31. 1.85 Dr. M.L.H. Green (Oxford), "Naked Atoms and Negligee Ligands"

7. 2.85 Prof. A. Ledwith (Pilkington Bros.), "Glass as a High Technology Material" (Joint Lecture with the Society of Chemical Industry)

14. 2.85 Dr. J.A. Salthouse (Manchester), "Son et Lumiere"

21. 2.85 Prof. P.M. Maitlis, F.R.S. (Sheffield),
"What Use is Rhodium?"

7. 3.85 Dr. P.W. Atkins (Oxford),
"Magnetic Reactions"

17.10.85 Dr. C.J. Ludman (University of Durham)
"Some Thermochemical aspects of Explosions"
"A Demonstration Lecture)

24.10.85 Dr. J. Dewing,(U.M.I.S.T.),
"Zeolites - Small Holes, Big Opportunities"

31.10.85 Dr. P. Timms,(University of Bristol),
"Some Chemistry of Fireworks"
(A Demonstration Lecture)

7.11.85 Prof. G. Ertl, (University of Munich),
"Heterogeneous Catalysis",
(R.S.C. Centenary Lecture)

14.11.85 Dr. S.G. Davies (University of Oxford),
"Chirality Control and Molecular Recognition"

21.11.85 Prof. K.H. Jack, F.R.S. (University of Newcastle/Tyne),
"Chemistry of Si-Al-O-N Engineering Ceramics"
(Joint Lecture with the Society of Chemical Industry)

28.11.85 Dr. B.A.J. Clark (Research Division, Kodak Ltd.)
"Chemistry and Principles of Colour Photography"

23. 1.86 Prof. Sir Jack Lewis, F.R.S. (University of Cambridge),
"Some More Recent Aspects in the Cluster Chemistry
of Ruthenium and Osmium Carbonyls"
(The Waddington Memorial Lecture)

30. 1.86 Dr. N.J. Phillips,(University of Technology, Loughborough)
"Laser Holography"

13. 2.86 Prof. R. Grigg (Queen's University, Belfast),
"Thermal Generation of 1,3-Dipoles"
(R.S.C. Tilden Lecture)

20. 2.86 Dr. C.J.F. Barnard,(Johnson Matthey Group Research),
"Platinum Anti-Cancer Drug Development - From
Serendipity to Science"

27. 2.86 Prof. R.K. Harris, (University of Durham),
"The Magic of Solid State NMR"

6. 3.86 Dr. B. Iddon (University of Salford),
"The Magic of Chemistry"
(A Demonstration Lecture)

(C) Research Conferences attended

April 1984	Graduate Symposium, Durham.
July 1984	International Symposium on "Chemistry of Carbanions", University of Durham.
April 1985	Graduate Symposium, Durham.
April 1986	Graduate Symposium, Durham.

(D) First Year Induction Course, October 1983

This course consists of a series of one hour lectures on the services available in the department.

1. Departmental organisation
2. Safety matters
3. Electrical appliances and infrared spectroscopy
4. Chromatography and Microanalysis
5. Atomic absorptiometry and inorganic analysis
6. Library facilities
7. Mass spectrometry
8. Nuclear magnetic resonance spectroscopy
9. Glassblowing technique.

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REFERENCES

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3(a) R.B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry', New York, 1970.

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6(a) D.S. Tarbell, Organic Reactions , 1944, 2, Chap. 1.

(b) N.R. Raulins and S.J. Rhoads, Organic Reactions , 1975, 22 Chap. 1.

(c) H.J. Hansen and H. Schmid, Chem.Brit., 1969, 5, 111.

(d) A. Jefferson and F. Scheinmann, Quart,Rev. (London), 1968, 22, 391.

(e) S. Patai, 'The Chemistry of the Ether Linkage', 1967,Chap.14.

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7. L. Claisen, Chem.Ber., 1912, 45, 3157.

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13(a) J.P. Ryan and P.R. O'Connor, ibid, 1952, 74, 5866.

(b) L.Friedman, R.W. Ledeen, A.V. Longan and E.N. Marvell, ibid, 1954, 76, 1922.

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