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Some aspects of the chemistry of benzobicyclo systems

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SOME ASPECTS OF THE CHEMISTRY OF BENZOBICYCLO SYSTEMS

by

JOHN HENRY HOLLINSHEAD, B.Sc.

A Doctoral Thesis
Submitted in partial fulfilment of the requirements
for the award of
Doctor of Philosophy of the Loughborough University of Technology

May 1978

Supervisor: H. Heaney, B.A., Ph.D., D.Sc., F.R.I.C.
Department of Chemistry

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SUMMARY

The rearrangement reactions of 1-methoxybenzobicyclo-[2.2.2]-octatriene derivatives in strong acid have been studied. In particular 1-methoxytetrafluoro-, 1-methoxytetrachloro-, and 1-methoxybenzobarrelene have been prepared labelled with ^{14}C at C-4. Rearrangement of these compounds, in strong acid, leads in each case, to three isomeric ketones. The major product in each rearrangement was the corresponding benzobarrelenone, formed, in each case, by two distinct pathways. The ^{14}C label in each benzobarrelenone was scrambled between C-4 and C-5 as a result of the two different mechanisms. A suitable degradation procedure has been devised which allows the ^{14}C activity in C-4 and C-5 of each ketone to be determined, and hence, an evaluation of the percentage rearrangement which proceeds by the two mechanistic pathways previously suggested.

A high yield route to benzobarrelene and certain substituted derivatives was required in order to investigate some of the above processes. The route developed involves dechlorination of the tetrachlorobenzobicyclo-[2.2.2]-octatriene derivatives. The use of sodium-tetrahydrofuran-t-butanol as a self indicating reducing medium allows the removal of chlorine in high yield.

The acid catalysed rearrangement of 1,5,8-trimethoxybenzobarrelene has also been investigated. The two major products are 2,4',5-trimethoxybiphenyl and 5,8-dimethoxybenzobarrelenone. [^{2}H]Labelling studies have been used to investigate the rearrangement further.

ACKNOWLEDGEMENTS

I would like to thank Dr. H. Heaney for his persistent encouragement and guidance throughout this work.

I am indebted to the Science Research Council for financial support and for spectroscopic services through the P.C.M.U.

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CONTENTS

Page No.

SUMMARY I

ACKNOWLEDGEMENTS II

GENERAL INTRODUCTION 1

CHAPTER 1

A High Yield Route to Benzobarrelene and Substituted Derivatives

Introduction 21

Discussion 23

Experimental 47

CHAPTER 2

Mechanistic Studies of the Acid Catalysed Rearrangements of 1-Methoxybenzobarrelene Derivatives

Introduction 63

Discussion 67

Experimental 180

CHAPTER 3

Further Studies in the Preparation and Rearrangement of 1-Methoxybenzobarrelene Derivatives

Introduction 234

Discussion 243

Experimental 290

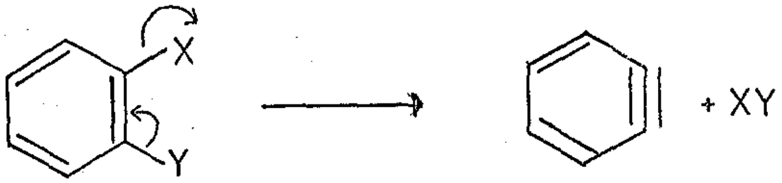
REFERENCES 310

GENERAL

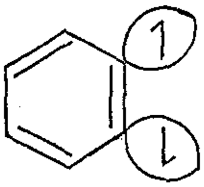
INTRODUCTION

INTRODUCTION

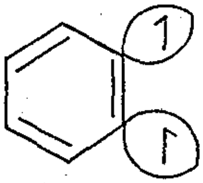
Over the past thirty years the chemistry of orthodehydrobenzene (1, benzyne) has been studied extensively.[1] Although the structure of benzyne has been the subject of much controversy it is now generally accepted that it is a neutral singlet species, derived by the removal of two ortho substituents from the benzene aromatic system. The removal of the two substituents leaves two carbon sp^2-orbitals with two electrons distributed between them, the orbitals being orthogonal to the molecular orbitals of the aromatic ring. The two carbon sp^2-orbitals can interact to give a singlet (2) or a triplet (3) state. Calculations[2] and its reactions show that benzyne exists in a symmetric singlet ground state.



(1)

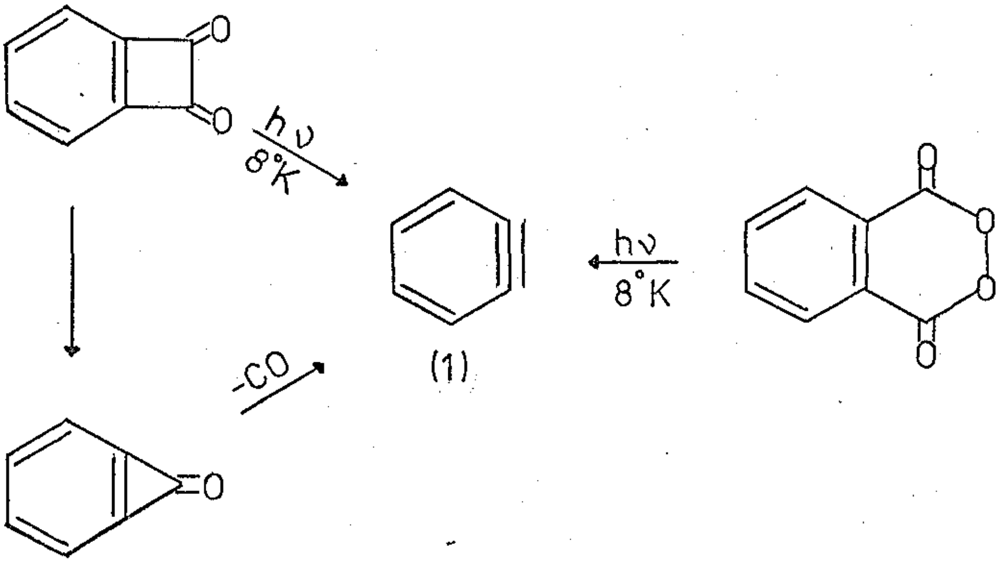


(2)

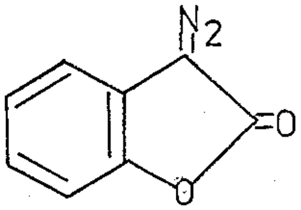


(3)

Although benzyne has never been isolated at normal temperatures, the existence of the intermediate has been justified by time - resolved mass spectrometry.[3] More recently Chapman and his co-workers[4a] have recorded the infra-red spectrum of benzyne generated by the photolysis of phthaloyl peroxide and benzocyclobuten-1,2- dione at 8°K. The various bands observed in the spectrum of benzyne are at 1627,1607, 1451, 1053, 1038, 849, 736 and 469 cm^{-1} and favour the structure (1) for the intermediate.



Matrix photolysis of the diazolactone (4) results in the formation of benzyne with sufficient efficiency for the $C\equiv C$ stretch (2085cm^{-1}) to be observed for the first time.[4b] Laing and Berry[4c] have interpreted the infra-red vibration spectrum of benzyne as reported by Chapman.[4a] Their results show that the infra-red spectrum of benzyne implies that benzyne has alternating bond lengths consistent with the aryne-like structure (1). The analysis predicted a frequency band at 2083cm^{-1} which coincided very well with Chapman's later results [4b] (2085cm^{-1}). Although benzyne has been isolated as a stable entity in rigid matrices at very low temperatures,[4] its lifetime in solution and in the gas

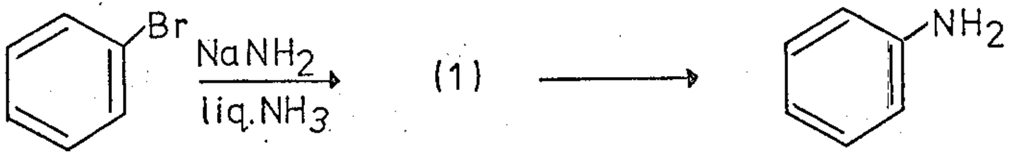


(4)

phase is limited by dimerization to form biphenylene. The process occurs at a rate approaching diffusion control.[3b] Recently Mazur[5] has investigated the effect of polymer immobilisation on the generation of benzyne.

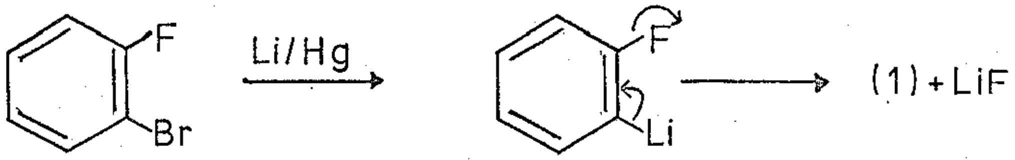
The chemistry of this species is that of a highly electrophilic intermediate. Its half life at room temperature is ca. 10^{-4} sec..

Early methods for the generation of arynes involved the action of very strong bases, such as potassium amide and sodamide in liquid ammonia or lithium alkyls and lithium aryls in ether on aryl halides.

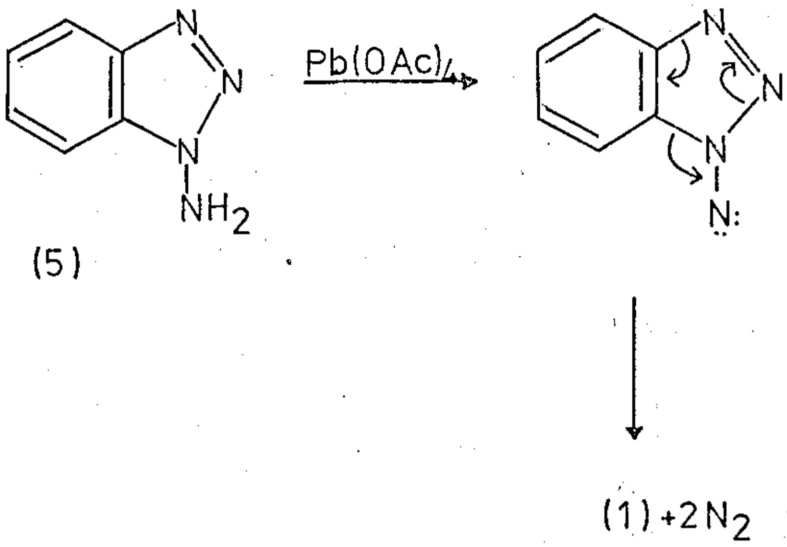


The disadvantage with this procedure is that the strong bases are also strong nucleophiles which will react readily with the benzyne.

Wittig[6] was first to introduce the procedure of trapping benzyne with a diene in a Diels-Alder type reaction. The benzyne was generated from 1,2-dihalogenobenzenes with lithium amalgam or magnesium.

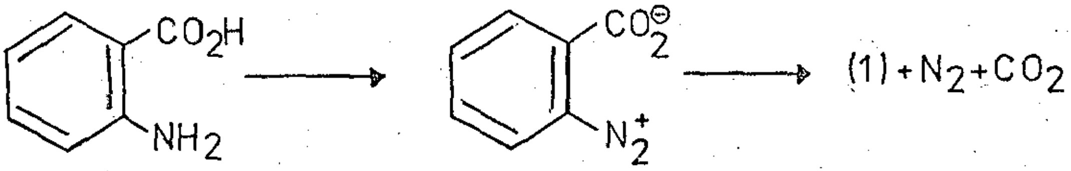

F
Br
Li/Hg
F
Li
(1) + LiF

A method of preparing benzyne under mild conditions involves the oxidation of 1-aminobenzotriazole (5) using lead tetra-acetate or nickel peroxide.[7]


N
N
N
NH2
(5)
Pb(OAc)4
N
N
N
N:
(1) + 2N2

Other reactions, which result in variable yields of benzyne, include the pyrolysis of phthalic anhydride and indanetrione;[8] the photolysis of phthaloyl peroxide and o-diiodobenzene;[9] and flash photolysis of benzenediazonium-2-carboxylate (7).[3]

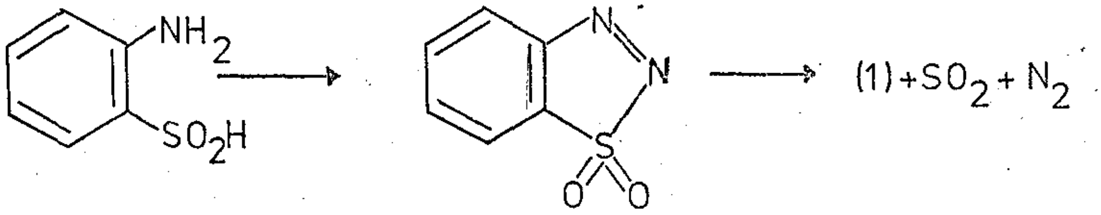
A more widely used and generally higher yield route to benzyne, involves the diazotisation of anthranilic acid (6) to (7) which can, with care, be isolated.[10] On mild pyrolysis (ca.50°) (7) decomposes to benzyne, nitrogen and carbon dioxide.



(6) (7)

Likewise, 1,2,3-benzothiadiazole-1,1-dioxide (9) formed from 2-aminobenzenesulphinic acid (8) fragments readily in organic solvents at ca.20° to give (1), sulphur dioxide and nitrogen.[11]

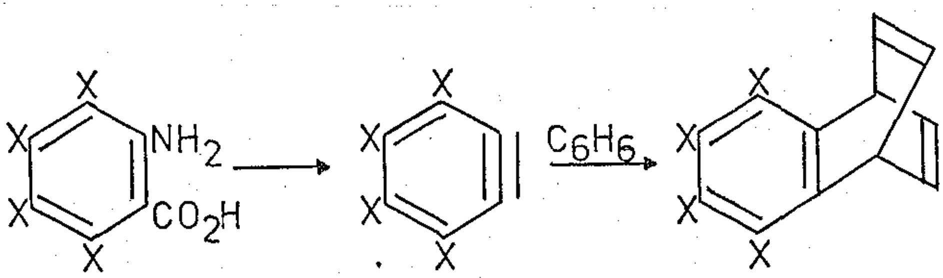
Tetrahalogenated benzynes have been the principal area of study within these laboratories. It had been reasoned[12] that the effect of the four electron withdrawing halogens would cause a significant increase in the electrophilicity of the intermediate, over that of benzyne, and hence affect the reactivity.



(8) (9)

The methods commonly employed for the generation of tetrahalogenobenzynes are similar to those already described for benzyne. Pentafluorophenyl magnesium halides,[13a] pentachlorophenyl magnesium chloride,[13b] pentafluorophenyl lithium,[13c] and pentachlorophenyl lithium[13d] are all good precursors of tetrafluoro- and tetrachlorobenzynes.

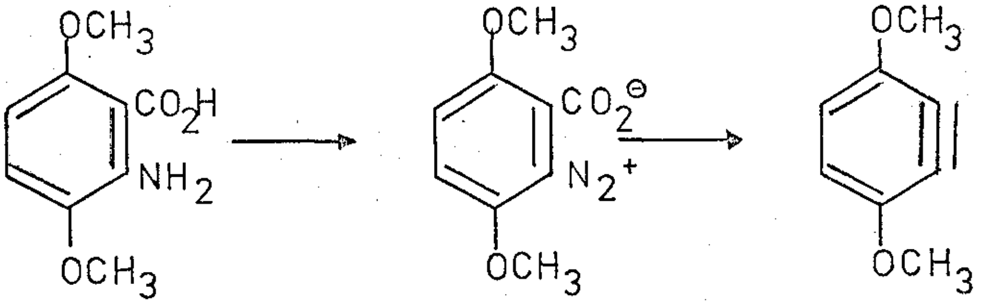
Tetrahalogenobenzynes have also been generated in high yields by the aprotic diazotisation of their corresponding anthranilic acids.



X = F[14a] 35% X = Br[14c] 67%

X = Cl[14b] 55% X = I[14d] 25%

More recently,[15] 2-amino-3,6-dimethoxybenzoic acid (10) has been prepared and like other anthranilic acids has been shown to be an efficient precursor for 3,6-dimethoxybenzyne (11).

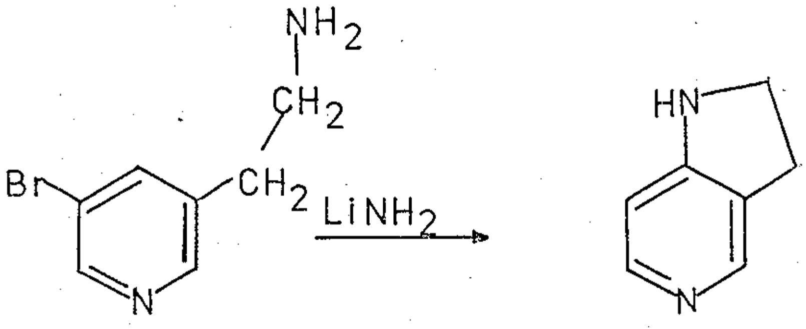


(10) (11)

Cycloaddition reactions of benzynes have been extensively studied.[1] A large number of 1,2-cycloadditions and 1,3-dipolar additions have been reported, but the most useful of all the cycloadditions of arynes are the 1,4-cycloadditions. These are the Diels-Alder type reactions, involving the aryne acting as a powerful dienophile in reactions with a wide variety of dienes.[1]

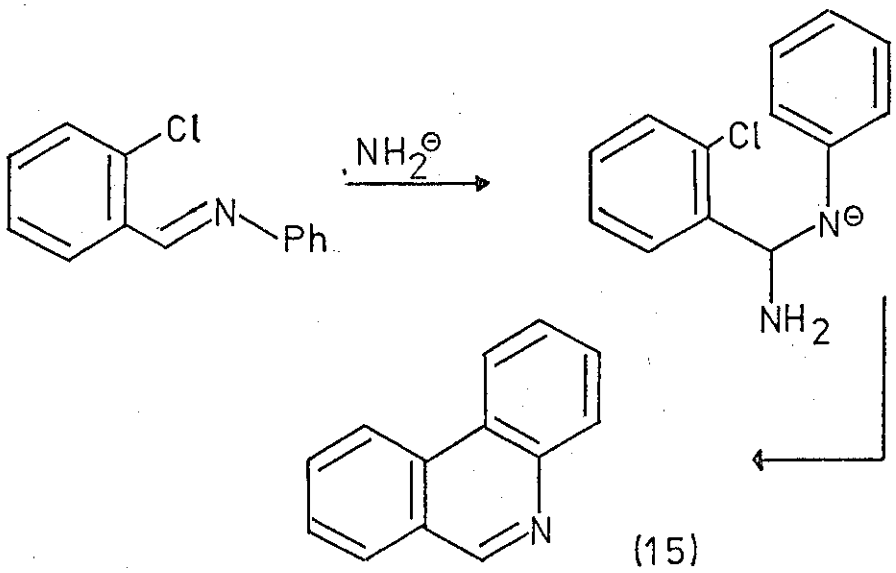
The addition of benzyne to aromatic hydrocarbons affords bridged ring systems, which are otherwise inaccessible; for example Diels-Alder cycloaddition of benzyne to anthracene derivatives is the best known method for preparing various substituted triptycenes. Clearly the aryne must be highly reactive in order to overcome the large resonance energy of many arenes.

Intramolecular nucleophilic addition to the 'dehydro' bond has proved a fruitful source of heterocyclic compounds and similar reactions have been demonstrated for hetarynes, for example (13) from (12) in the presence of lithium amide.[16]



(12) (13)

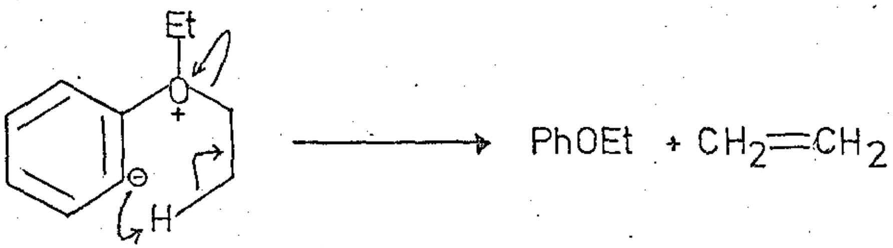
The high yielding synthesis of phenanthridines, e.g. (15) from o-halogenoanils, involves a fast addition of amide ion to the anil to give the anion (14) which is now sterically capable of cyclisation on to the subsequently formed aryne to give (15).[17]



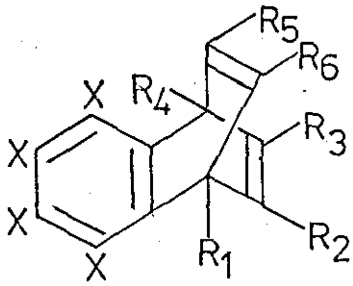
(14)

(15)

Ethers are known to be cleaved by the highly electrophilic tetrahalogenobenzynes and this reaction has now been observed for benzyne itself,[18] giving phenetole in up to 40% yield, but only when the reaction is carried out in a solvent other than the ether itself.



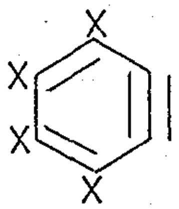
Although benzyne will add to a simple arene,[10] the yield of the 1,4-adduct is usually low. Tetrahalogenobenzynes undergo 1,4-cycloaddition reactions with simple arenes readily and in good yields.[13,14] The products of these reactions are the tetrahalogenobenzobarrelene derivatives (16).



(16)

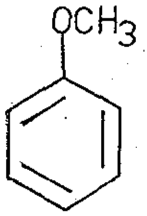
It has been shown that aromatic hydrocarbons form charge-transfer complexes, with highly fluorinated aromatic compounds[19] and such a charge transfer in the case of tetrahalogenobenzyne precursors could be partially responsible for the high reactivity of halogenated arynes towards the aromatic compounds.

Over the past ten years work in these laboratories has been directed at the preparation and reactions of tetrahalobenzobarrelenes.[20] Particular interest has been shown in the formation of the 1-methoxy-tetrahalobenzobarrelenes (19) obtained in good yield from the reaction between a tetrahalobenzyne (17) and anisole (18). This interest came about as a result of studies involving the preparation and re-arrangement of 1-dimethylaminobenzobarrelenes.[20b,21]

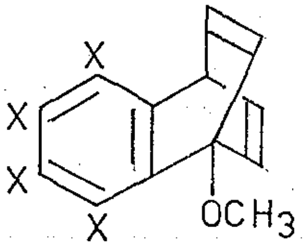


(17)

X = F or Cl



(18)



(19)

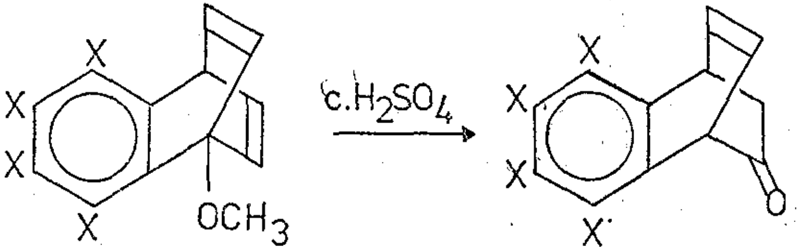
The rearrangement of bicyclic molecules has been studied in some detail.[22] Among these, acid catalysed reactions have become a wide area of study, as a result of the large number of skeletal changes that are possible. Although the rearrangement of benzo- and dibenzobicyclic systems had been studied in depth,[23] no results had been published in which a group was used as an internal nucleophile.

The results from the rearrangement of 1-dimethylaminobenzobarrelenes led to the consideration that the analogous methoxy compounds (19) would prove interesting in their acid catalysed rearrangements, since the methoxy group could exert a directing influence.

It was found[20d] that the rearrangement of the 1-methoxybenzobarrelenes (20-22) only occurred in the presence of strong acids. The rearrangement of (20-22), in concentrated sulphuric acid, gave three isomeric ketones, in each case.

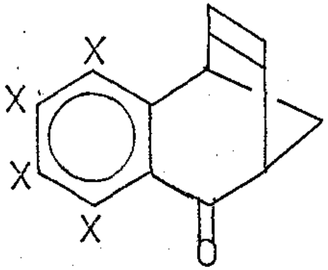
The major product in each rearrangement was the benzobarrelenone (23-25), isolated in yields ranging from 50-70%. The minor products were the aryl ketones (26-28) and the $\alpha\beta$-unsaturated ketones (29-31) isolated in 3-8% and 4.5-5.5% yields respectively.

A rewarding investigation[20d] involving deuterium labelled 1-methoxybenzobarrelenes, deuterated solvents, specifically substituted methyl derivatives and solvolytic reactions of tosylates gave a deep insight into the mechanistic pathways involved in these acid catalysed rearrangements. The results suggested that the aryl ketones (26-28) and the $\alpha\beta$-unsaturated ketones (29-31) were formed from the same carbonium ion (32) obtained by protonation at C-3. This ion could then undergo either aryl- or vinyl-migration to give the $\alpha\beta$-unsaturated and aryl-ketones respectively.

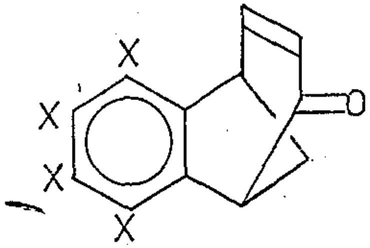

X
X
X
X
OCH3
c.H2SO4
X
X
X
X
O

(20) X = F
(21) X = Cl
(22) X = H

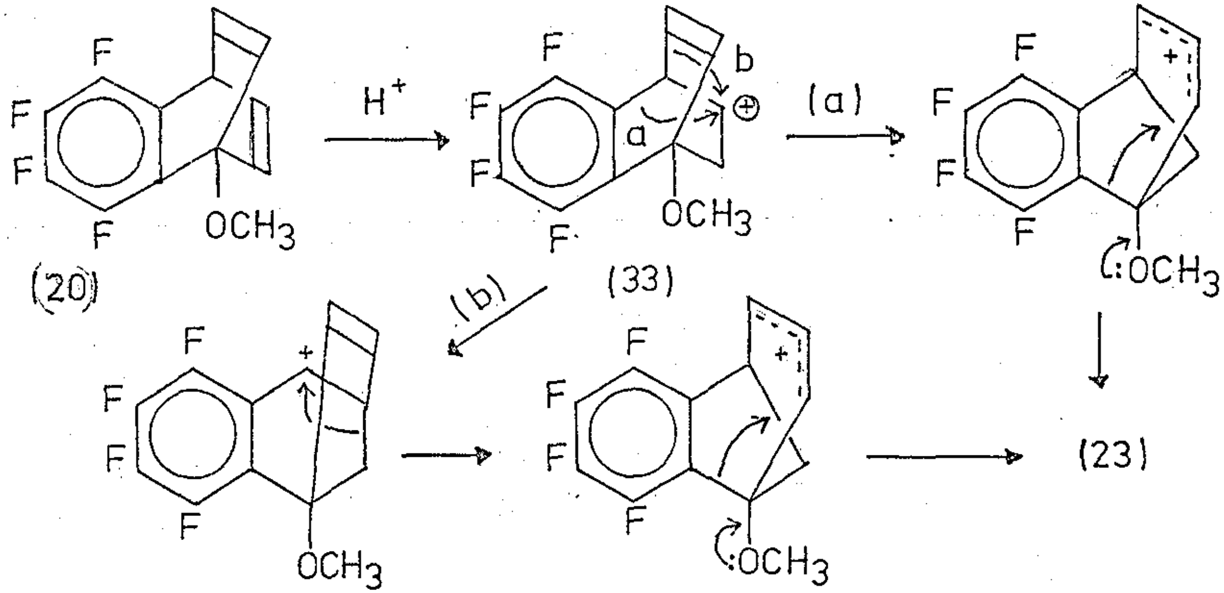
(23) X = F
(24) X = Cl
(25) X = H



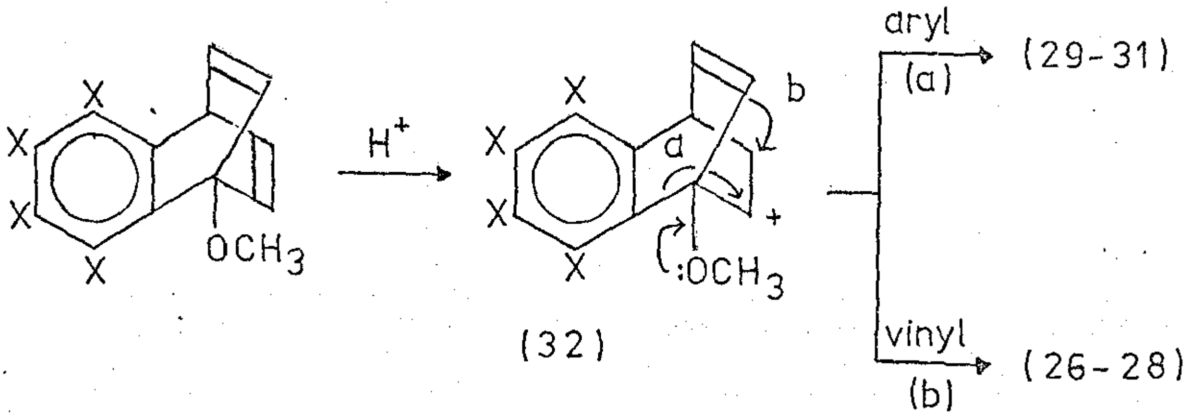
(26) X = F
(27) X = Cl
(28) X = H



(29) X = F
(30) X = Cl
(31) X = H


F
F
F
F
OCH3
(20)
H+
F
F
F
F
b
a
⊕
OCH3
(33)
(a)
F
F
F
F
+
:OCH3
(b)
F
F
F
F
+
OCH3
F
F
F
F
+
:OCH3
(23)

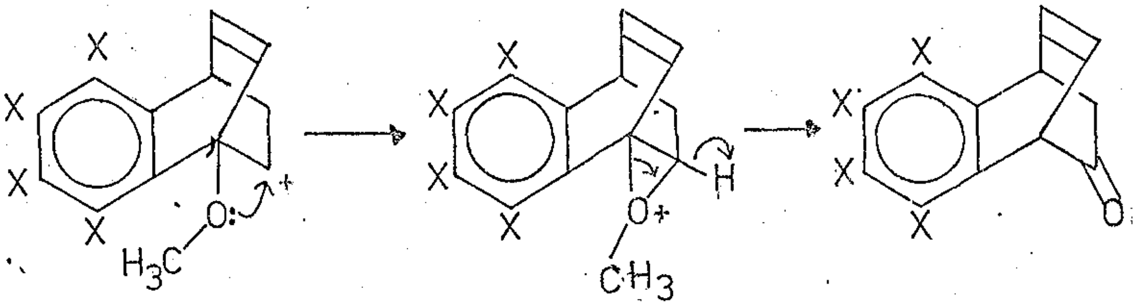
Acid Strength	% (a)	(b)
c. H_2SO_4 at R.T.	80	20
80% H_2SO_4 at 80°	55	45



(32)

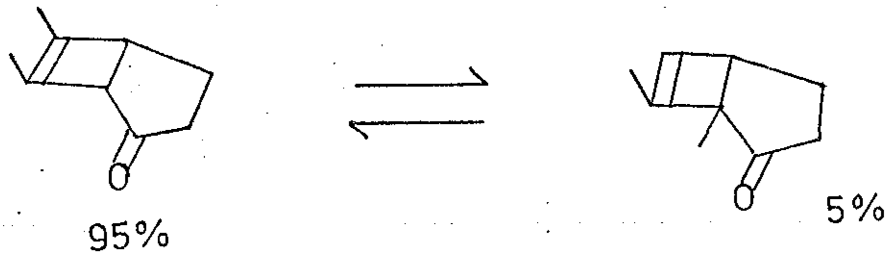
The benzobarrelenones (23-25) were postulated as being formed by two distinct pathways, both involving protonation at C-2 to give the carbonium ion (33). Deuterium labelling results[20d] indicated that the formation of the benzobarrelenones by these two pathways varied according to the concentration of acid used.

Other mechanisms which could account for the formation of the benzobarrelenone have been proposed by Barkhash.[24] They involve anti-Bredt intermediates and hydride shifts and can be readily excluded by the deuterium labelling results.[20d] Further results obtained in this laboratory[20e] also exclude Barkhash's mechanism. It has been shown that in the rearrangement of [1-^{14}C]-1-methoxytetrachlorobenzobarrelene to the benzobarrelenone the carbon attached originally to the methoxyl group becomes the carbonyl carbon in the product. The ^{14}C labelling result also eliminates any mechanism which involves a 1,2-methoxy migration. Similar 1,2-hydroxy shifts are known,[22b] although the strain in the benzobarrelene system is likely to prohibit such rearrangements.

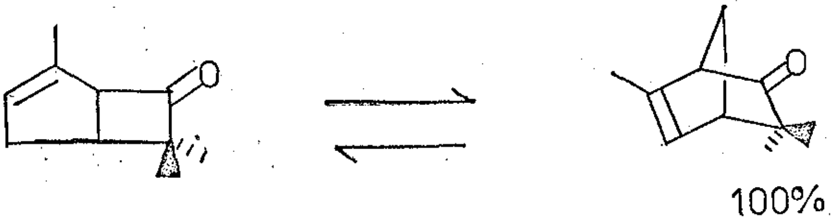

X
X
X
X
H$_3$C
O:
+
X
X
X
X
O+
CH$_3$
H
X
X
X
X
O

In recent years a number of groups have been interested in the acid catalysed isomerisations of $\beta\gamma$-unsaturated ketones. Cargill[25] has investigated isomerisations such as:-

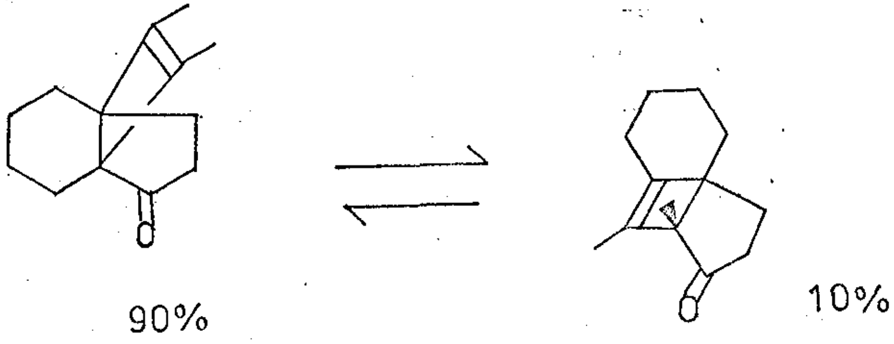
a)



b)

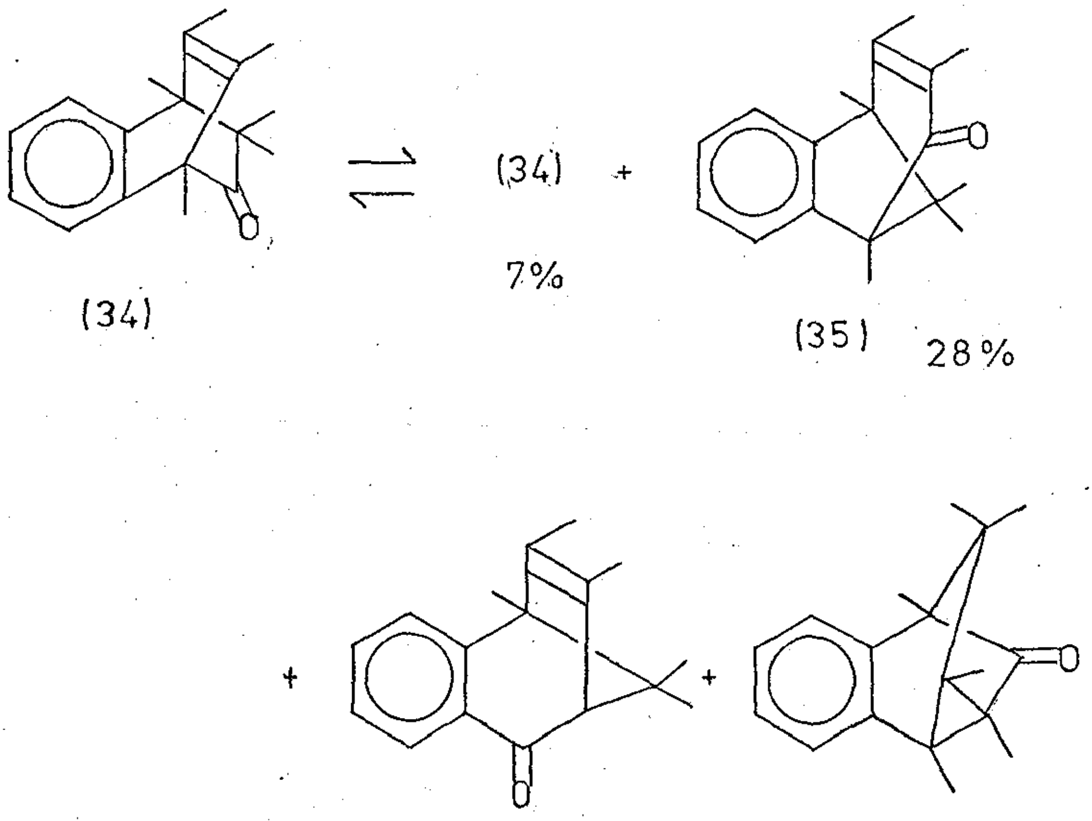


c)



The percentages indicate the concentrations at equilibrium. The most stable isomer is considered to be the one with the lowest enthalpy, due in cases (a) and (c) to the methyl substitution on the double bond.

Hart and Love[26] have discovered a more complex series of isomerisations of βγ-unsaturated ketones contained in bicyclo [2.2.2]- and bicyclo [3.2.1] systems. An equilibrium mixture of ketones (34-37) was obtained when any one of the four was heated in trifluoroacetic acid.

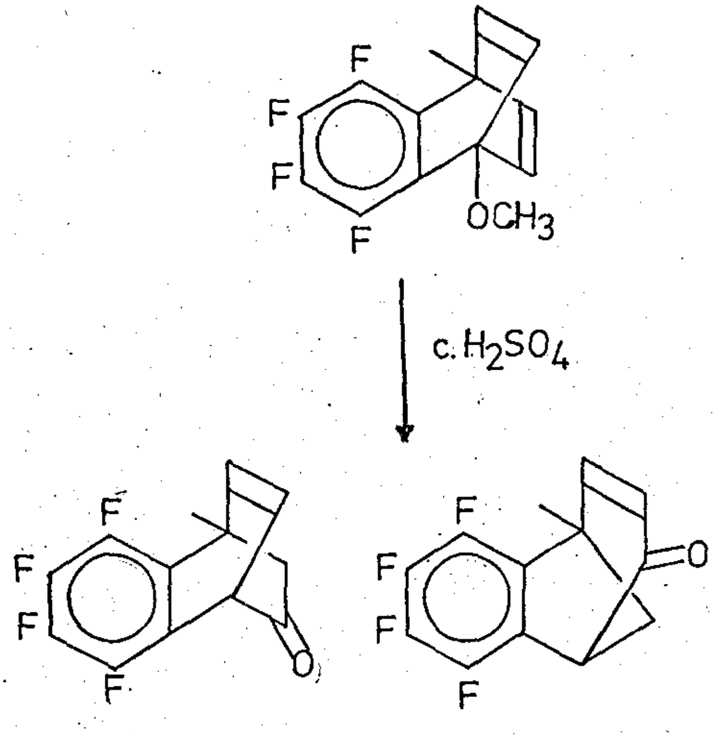

(34) ⇌ (34) 7% + (35) 28% + (36) 59% + (37) 6%

When the starting material was (34), (35) was formed first and then (36) and (37) from (35). These results were particularly disturbing in the light of attempts to equilibrate compounds obtained in this laboratory.[20d] Extensive studies involving the three isomeric ketones obtained from the rearrangement of the 1-methoxybenzobarrelenes (20-22) have shown no equilibration.

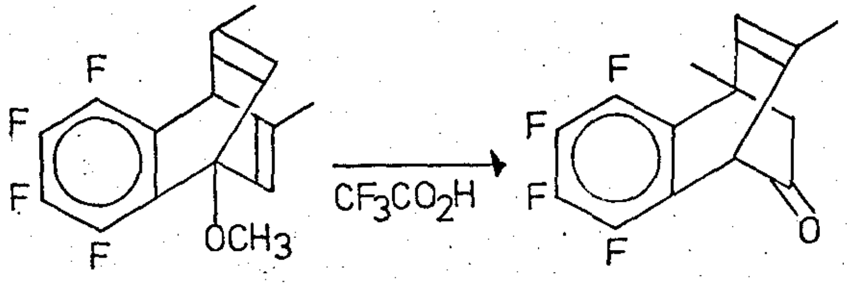
However a study of the acid catalysed rearrangements of substituted 1-methoxyhalogenobenzobarrelenes has produced a number of interesting products.[20d]

As expected, the rearrangement of 1-methoxy-4-methyl-tetrafluorobenzobarrelene gave the three isomeric ketones (38-40) in 11%, 4% and 3% yields respectively, in conc. sulphuric acid. The 3,5-dimethyl- and 2,6-dimethyl-1-methoxybenzobarrelenes, (41) and (42), gave only the ketones indicated. In the rearrangement of (41) the corresponding $\alpha\beta$-unsaturated- and aryl-ketones were not present and in the case of (42) no benzobarrelenone was indicated.

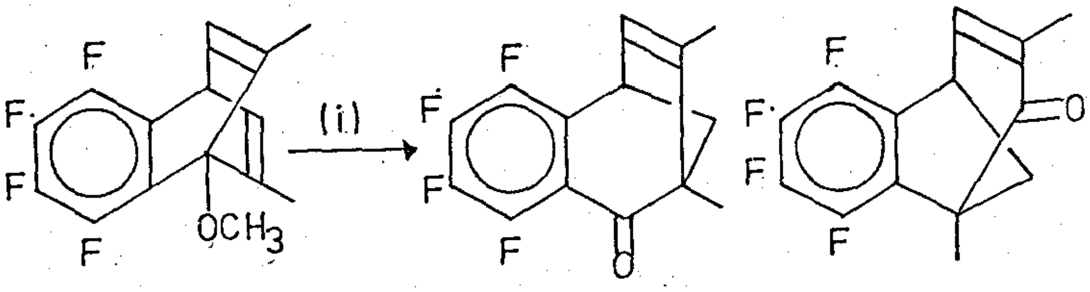
Interestingly the rearrangement of (41) in trifluoroacetic acid gave the benzobarrelenone (43), while (41), in conc. sulphuric acid, rearranged rapidly to afford the lactone (46). When the rearrangement was carried out in a mixture of conc. sulphuric acid and water ($7:3^{v}/_{v}$) at 0° the compounds (43), (46), and the ketone (47) were obtained in 14%, 39%, and 40% yield respectively. The compound (47) was not formed from (43). A mechanism accounting for these results has been proposed.[20b,d]


F
F
F
F
OCH3
c. H2SO4
F
F
F
F
O
F
F
F
F
O
F
F
F
F
O

(38) (39) (40)

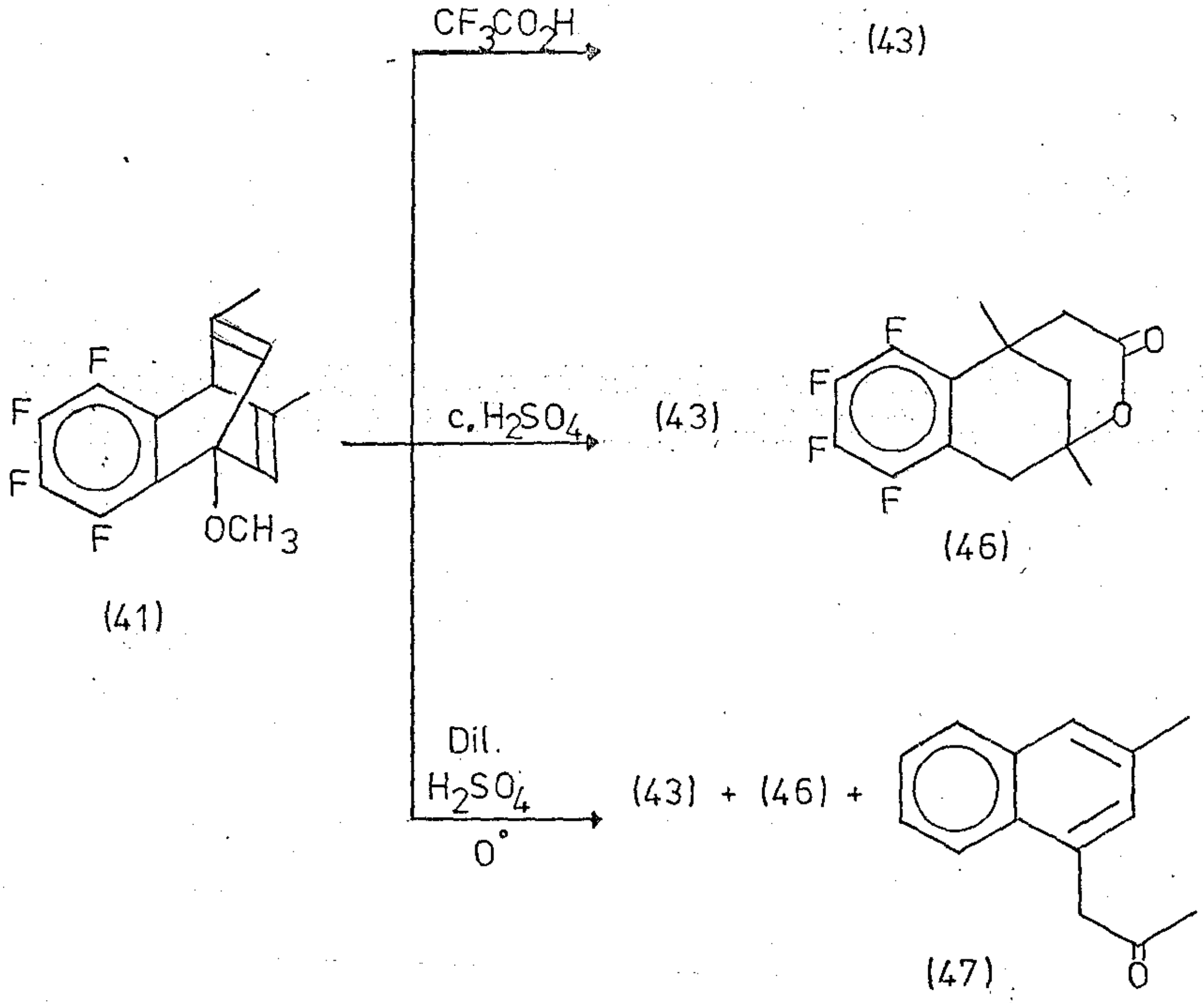

F
F
F
F
OCH3
CF3CO2H
F
F
F
F
O

(41) (43)


F
F
F
F
OCH3
(i)
F
F
F
F
O
F
F
F
F
O

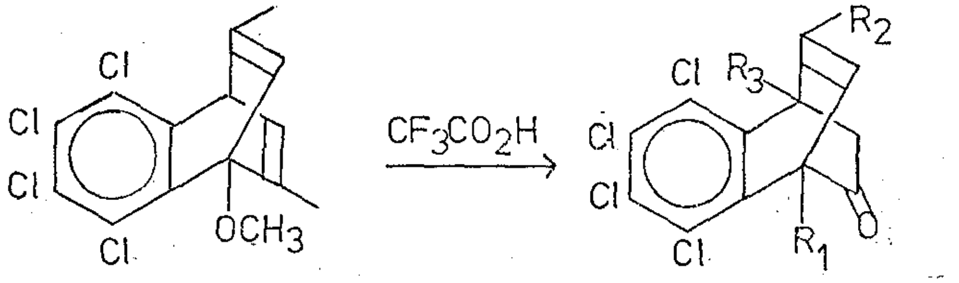
(42) (44) (45)

(i) = CF_3CO_2H



CF_3CO_2H
(43)
F
F
F
F
OCH_3
(41)
c. H_2SO_4
(43)
F
F
F
F
O
O
(46)
Dil.
H_2SO_4
0°
(43) + (46) +
(47)
O

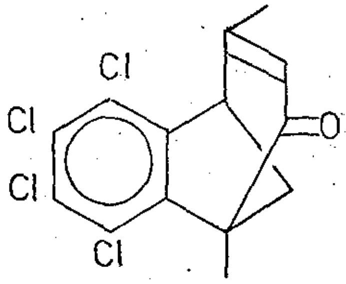
Rearrangement[20g] of (48) in trifluoroacetic acid affords the isomeric ketones (49-52). However, (49) undergoes further rearrangement in the presence of sulphuric acid (98%) or fluorosulphonic acid to the isomer (53) in 70% and 34% yields respectively. In the presence of aqueous sulphuric acid (90%) the ketone (49) was converted into the isomer (54), while in aqueous sulphuric acid (95%) the ketone (53) gave rise to a mixture of (51) and (54) in 5.5% and 43% yields respectively.


Cl
Cl
Cl
Cl
OCH3
CF_3CO_2H
Cl
Cl
Cl
Cl
R_1
R_2
R_3
O

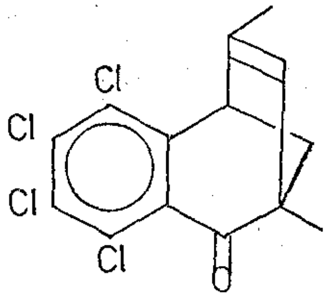
(48)

(49) $R_1 = R_3 = CH_3$ $R_2 = H$

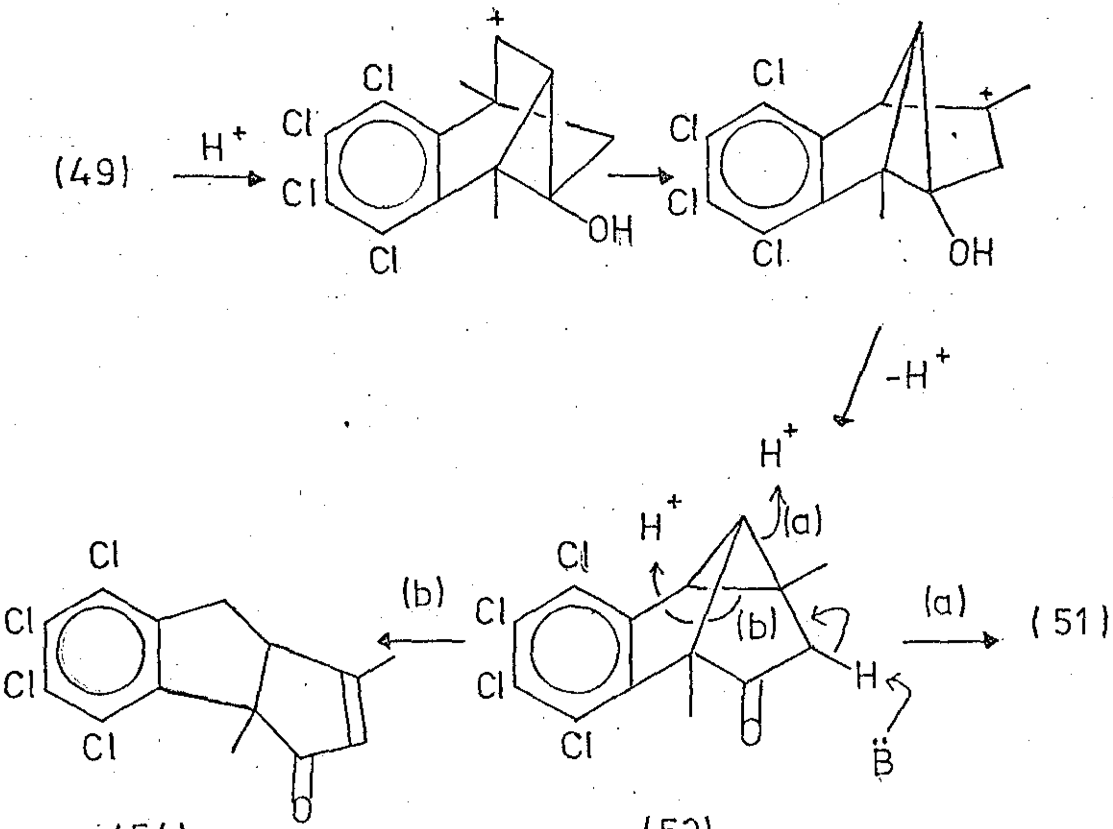
(50) $R_1 = R_2 = CH_3$ $R_3 = H$



(51)



(52)


(49)
H^+
+
Cl
Cl
Cl
Cl
OH
+
Cl
Cl
Cl
Cl
OH
$-H^+$
H^+
H^+
(a)
(b)
(b)
(a)
(51)
H
B̈
Cl
Cl
Cl
Cl
O
Cl
Cl
Cl
Cl
O

(54) (53)

Evidently the precise location of methyl groups affects the eventual outcome of these multi-step rearrangement reactions, in ways which are not thoroughly understood.

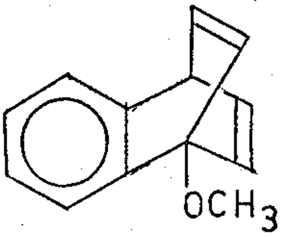
The work described in this thesis deals mainly with the extension of studies into the mechanistic pathways involved in the acid catalysed rearrangement of 1-methoxybenzobarrelenes and their substituted derivatives.

CHAPTER 1

A HIGH YIELD ROUTE TO BENZOBARRELENE AND SUBSTITUTED DERIVATIVES

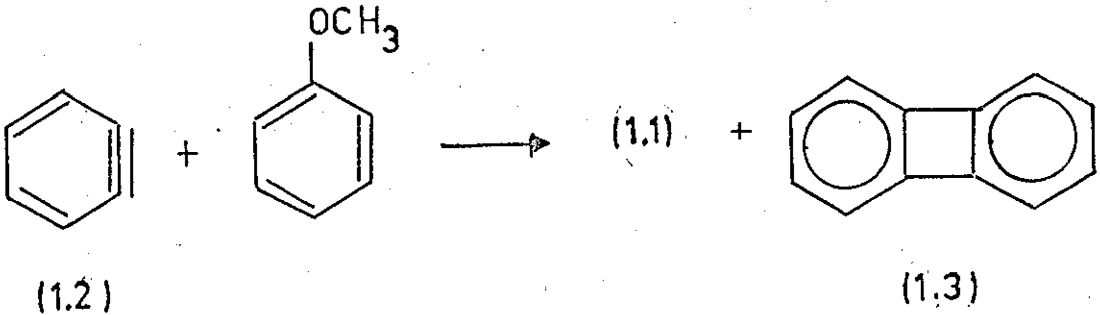
INTRODUCTION

A major disincentive to studies using benzobarrelenes and its simple derivatives is connected with their relative inaccesibility. However, because of our interest in the acid catalysed rearrangements of 1-methoxybenzobarrelenes it was important to find a high yield route to the parent compound (1.1) and its methyl substituted derivatives.

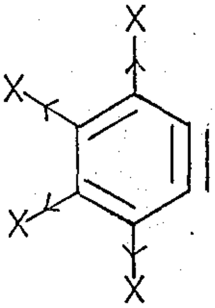


(1.1)

The reactions of tetrahalogenobenzynes with anisole afford tetrahalogenobenzobarrelene derivatives in good yields,[20c] frequently in the range of 55-70%. However, the reaction between benzyne (1.2) and anisole gave 1-methoxybenzobarrelene (1.1) in only 1.5% yield, together with biphenylene (1.3) in approximately 40% yield.[20c]



Obviously this procedure was not suitable for the preparation of 1-methoxybenzobarrelenes in the quantities required for rearrangement studies. The high yields for the analogous tetrahalogenobenzyne reactions are assumed to be due to the presence of the four electron withdrawing substituents which result in a significant increase in the electrophilicity compared with that of benzyne.[12]



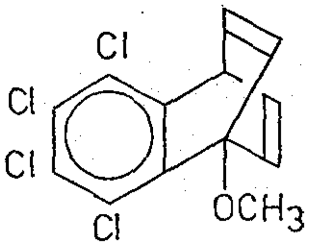
X = F or Cl

Hence it was evident that one should seek an alternative route to produce a high yield of 1-methoxybenzobarrelene (1.1) from a tetrahalogeno-species. The establishment of such a procedure would enable another piece of the complicated picture, surrounding the acid catalysed rearrangements of the 1-methoxybenzobarrelenes, to be fitted. The scope of these rearrangements has already been illustrated in the general introduction to this thesis. However, one question surrounding the rearrangement studies is to what extent do the four electron withdrawing substituents affect the rearrangement mechanisms and the products isolated.

The preparation of 1-methoxybenzobarrelene and its methyl substituted derivatives followed by rearrangement studies should facilitate the answering of this question.

DISCUSSION

As improvement in the yield of 1-methoxybenzobarrelene (1.1) from the reaction between benzyne (1.2) and anisole did not seem feasible. 1-Methoxytetrachlorobenzobarrelene (1.4) was formed in high yield and it was reasoned that this would be a suitable precursor for the 1-methoxybenzobarrelene (1.1), if an efficient procedure for removing the halogens from the aromatic ring could be established.



(1.4)

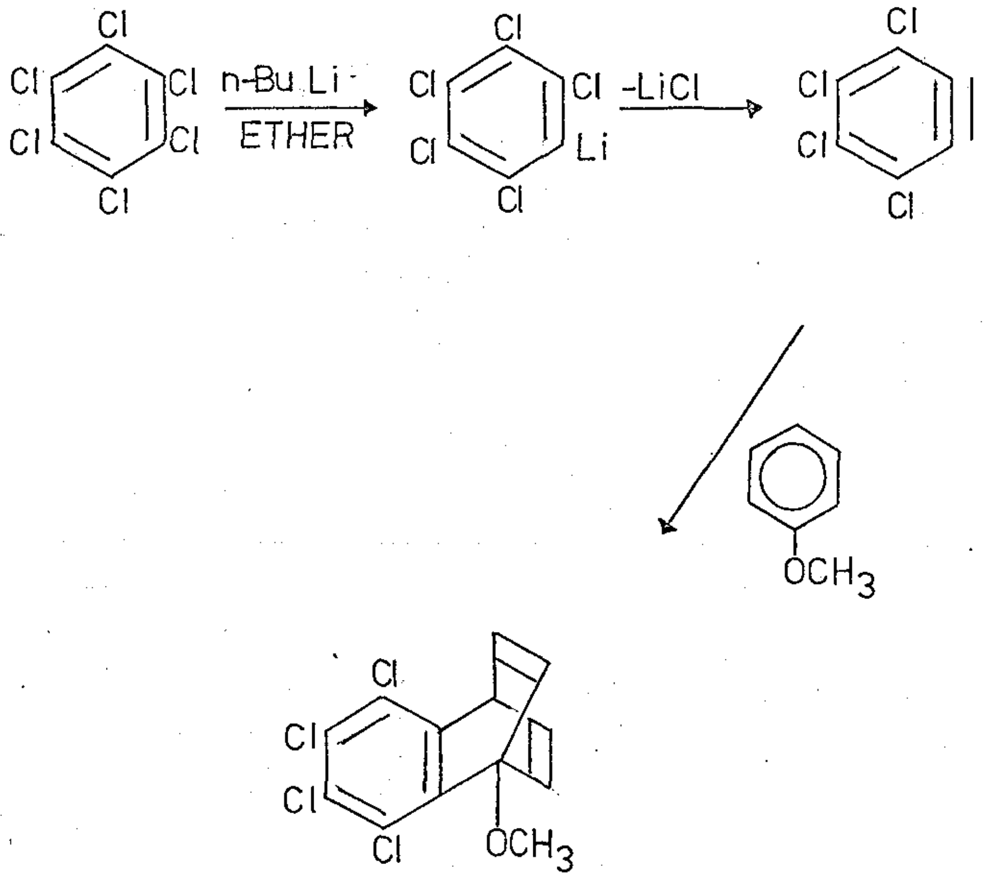
Removal of halogens from aromatic rings can be accomplished by various reducing agents. Among these are: Ph_3SnH,[27a,b] HI, Sn and HBr, Ph_3P,[27c,d] hydrazine and PdC,[27e,f] catalytic hydrogenolysis, and $LiAlH_4$.[27g]

Unfortunately there were a number of problems surrounding the successful dechlorination of the compound (1.4) to 1-methoxybenzobarrelene (1.1):- (i) the possibility of only partial dechlorination, (ii) dechlorination and reduction of the double bonds, and (iii) formation of unwanted side products. Consideration of these points eliminated the majority of the above methods.

The use of radical anions for the production of halide ions from alkyl halides, as a part of the quantitative determination of halogen, has been developed by several workers. Benton and Hamill[28] described the use of sodium naphthalene, and later Liggett[29] developed the use of sodium biphenyl in glyme (1,2-dimethoxyethane) for the quantitative estimation of halogen atoms. For example, Liggett,[29] using the sodium biphenyl reagent, dechlorinated hexachlorobenzene in a quantitative yield, based on halogen analysis. Unfortunately these workers did not concern themselves with the fate of the organic fragments. Warhurst and Mathius[30a] studied the reactivities of various alkyl and aryl halides with a variety of radical anions. Their data led them to conclude that radicals were involved as reaction intermediates from the organic halides, but once again very little was done to learn the fate of the organic radicals. Cristol[30b] has used a solution of sodium biphenyl in glyme to remove chlorine from organic molecules and has shown that the organic product was the one in which the chlorine atom had been replaced by a hydrogen atom.

In the light of these results, a solution of sodium biphenyl in glyme was prepared, according to the procedure of Liggett,[29] and used in accordance with a method described by Cristol,[30c] in an attempt to dechlorinate 1-methoxytetrachlorobenzobarrelene (1.4). The latter was prepared in the normal way by the reaction of *n*-butyl-lithium with hexachlorobenzene in ether at *ca*. -70°, to form the tetrachlorobenzyne precursor, followed by reaction with anisole to yield the required adduct as illustrated in Scheme 1.1.

Scheme 1.1



(1.4)

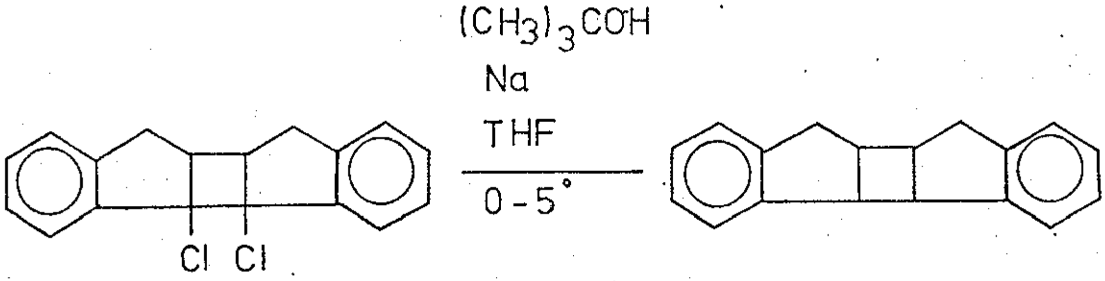
On completion of the dechlorination reaction the aqueous fraction was analysed for the released chloride ion by the addition of nitric acid and silver nitrate. A white precipitate of silver chloride was obtained immediately.

However, attempts to isolate or identify the required 1-methoxybenzobarrelene (1.1) from the large excess of biphenyl present proved impossible. Cristol,[30c] in his procedure, had been able to steam distil the biphenyl, leaving the dechlorinated product as the residue. In the case of 1-methoxybenzobarrelene the low melting point (65°)[31] and high volatility prevented its separation from biphenyl by steam distillation. Analysis of the reaction mixture by ^{1}H.n.m.r., t.l.c., and g.l.c. indicated only biphenyl and no starting material (1.4) or dechlorinated product (1.1).

An alternative procedure uses alkali metals in tetrahydrofuran containing t-butanol. Griffin and Heep[32] had dechlorinated compounds of the type (1.5) using sodium as shown in Scheme 1.2. This method was adapted from a procedure established by Gassman.[33] These conditions were used in an attempt to dechlorinate 1-methoxytetrachlorobenzobarrelene (1.4). On work-up only starting material was obtained, confirmed by ^{1}H.n.m.r., t.l.c., and g.l.c. analysis. The earlier literature[34-37] showed that the use of a refluxing solution, as opposed to a solution temperature of 0-5°, was frequently useful.

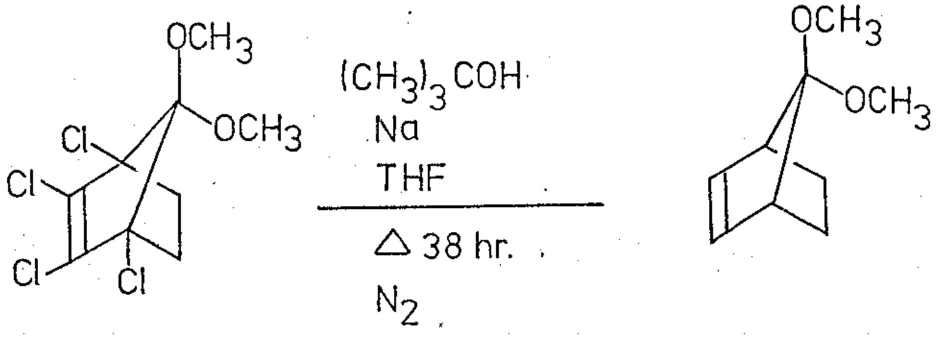
Gassman[35] successfully dechlorinated 7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo - [2.2.1]-hept-2-ene (1.6) to the product (1.7). Other similar dehalogenations have been reported.[36,37] Of particular interest was the comparison between (1.6) and the compound we wished

Scheme 1.2.


$(CH_3)_3COH$
Na
THF
0 - 5°
Cl Cl

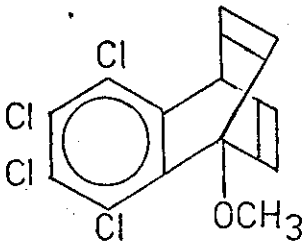
(1.5)

to dechlorinate (1.4). It can be seen that there are a number of similarities in the two structures.


OCH_3
OCH_3
Cl
Cl
Cl
Cl
$(CH_3)_3COH$
Na
THF
△ 38 hr.
N_2
OCH_3
OCH_3

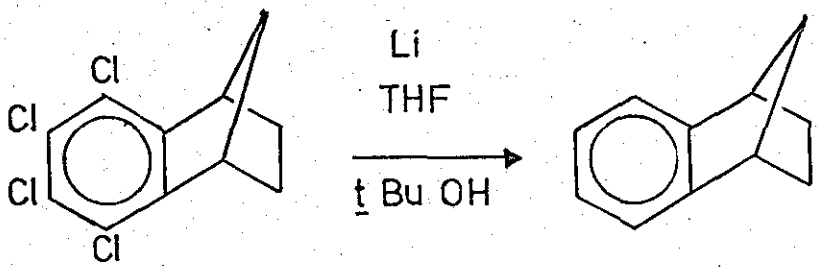
(1.6)

(1.7)


Cl
Cl
Cl
Cl
OCH_3

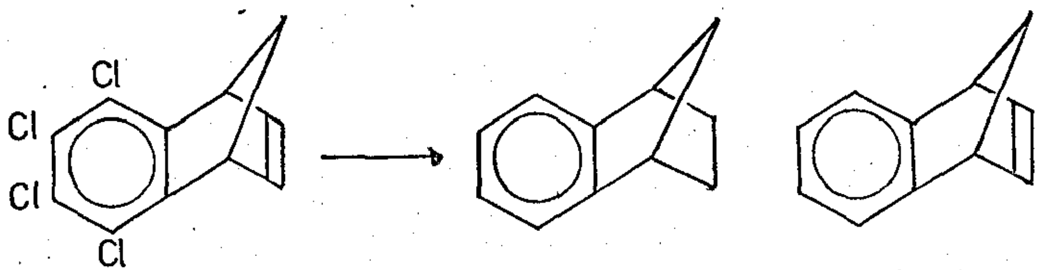
(1.4)

The fact that the double bond remained unreduced in the conversion of (1.6) to (1.7) was particularly significant. Similar investigations by Bruck[36] have shown that tetrachlorobenzonorborene (1.8) can be dechlorinated to benzonorbornene (1.9), in 94% yield, using lithium as opposed to sodium.



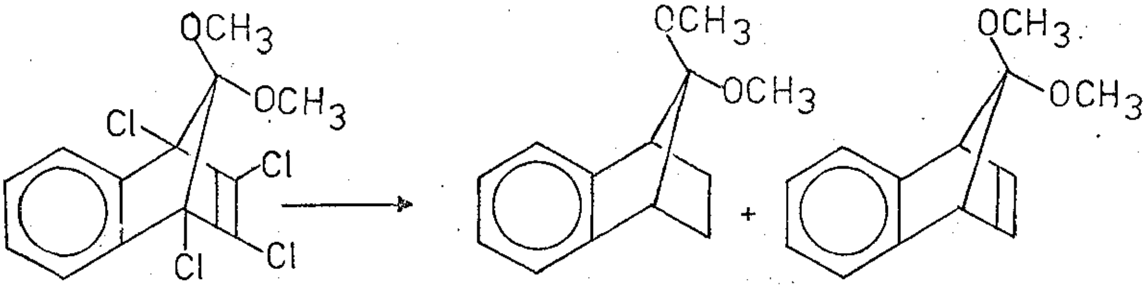
(1.8) (1.9)

One apparent disadvantage of this procedure was that both Bruck[36] and Ranken[37] have shown that under the reaction conditions used, partial reduction of double bonds also occurs. For example, Bruck[36] found that the dechlorination of tetrachlorobenzonorbornadiene (1.10) gave a mixture of benzonorbornene (1.9) and benzonorbornadiene (1.11) in a ratio of 18: 82.



(1.10) (1.9) (1.11)

Similarly, Ranken[37] has dechlorinated (1.12) to give a mixture of (1.13) and (1.14).



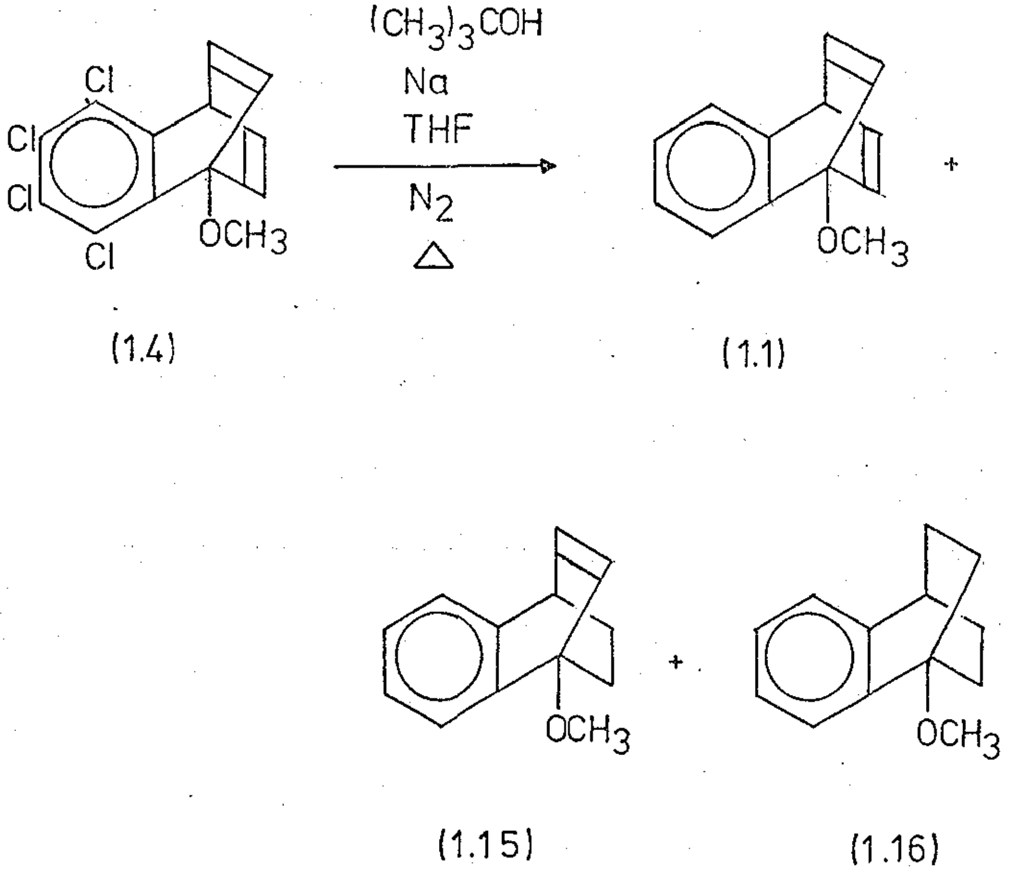
(1.12) (1.13) (1.14)

Further investigations by Bruck[36] have indicated that the ratio of the over-reduced product (1.9) to (1.11) was dependent on how much excess of lithium or sodium was used in the reaction. For example, with a 100% excess of lithium in the dechlorination of (1.10), 76% of (1.9) was obtained in the mixture.

From these results it seemed a reasonable assumption that 1-methoxytetrachlorobenzobarrelene (1.4) could be dechlorinated to 1-methoxybenzobarrelene (1.1), together, if we were unfortunate, with products from reduction of the double bonds, as illustrated in Scheme 1.3.

A series of trial experiments, on a small scale, indicated that the dechlorination of the benzobarrelene (1.4), using the illustrated procedure, was successful and that the best weight ratio of

Scheme 1.3



THF : t-BuOH : Na : Substrate was 40: 3: 1: 1.

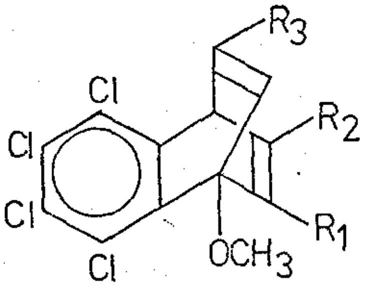
Of major significance was the fact that the only product in these trial experiments, and in all subsequent experiments, involving dechlorination of 1-methoxytetrachlorobenzobarrelene and its substituted derivatives were the dechlorinated products corresponding to (1.1). No compounds corresponding to (1.15) and (1.16) have been detected. These results although completely satisfactory for our investigations were still perplexing considering the results of Bruck[36] and Ranken.[37] Further investigations have also indicated that, unlike Bruck's results,[36] an excess of the metal does not affect the yield of the required product. Other investigations are being carried out, involving dechlorination of various other substrates[38] in order to throw further light on this problem.

Using the above mentioned ratio, reactions carried out on a small scale (1g.), gave an almost quantitative yield of crude 1-methoxybenzobarrelene (1.1). The crude product was isolated as a pale yellow oil, which was found to be pure by g.l.c. and ^{1}H.n.m.r. spectroscopy. Crystallisation of the oil from light petroleum (40:60) gave a white crystalline material, in 86% yield, which was identical[20d] in all respects with 1-methoxybenzobarrelene (1.1) prepared by the reaction of benzyne with anisole.

The scale of the dechlorination of (1.4) to (1.1) was gradually increased from 1g. to 20g. of (1.4) with no reduction in the yield of the required product (1.1).

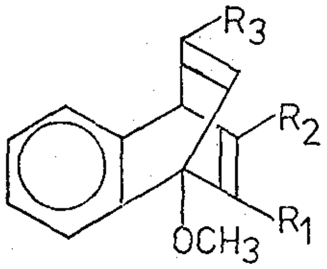
The dechlorination procedure finally adopted involved the addition of sodium wire to dry tetrahydrofuran, which was stirred and heated to reflux temperature under an atmosphere of nitrogen. t-Butyl alcohol and then a solution of substrate in tetrahydrofuran were carefully added to the refluxing mixture. The completion of the reaction was normally indicated by the formation of a deep purple precipitate of sodium chloride. The mixture was then filtered through glass wool (to remove excess of sodium) into methanol. Water was then added and the combined solution extracted with ether. The combined ethereal fractions were washed with saturated sodium chloride, dried ($MgSO_4$) and evaporated to yield an oily solid. This was placed on a column of alumina and eluted with light petroleum to yield the required compound.

In order to check the general application of this procedure and also to obtain potentially useful compounds the adducts (1.17) and (1.18) were prepared and dechlorinated to yield (1.19) and (1.20) respectively, in yields of isolated products around 90%



(1.17) $R_1 = R_3 = CH_3$ $R_2 = H$

(1.18) $R_1 = R_2 = R_3 = CH_3$



(1.19) $R_1 = R_3 = CH_3$ $R_2 = H$

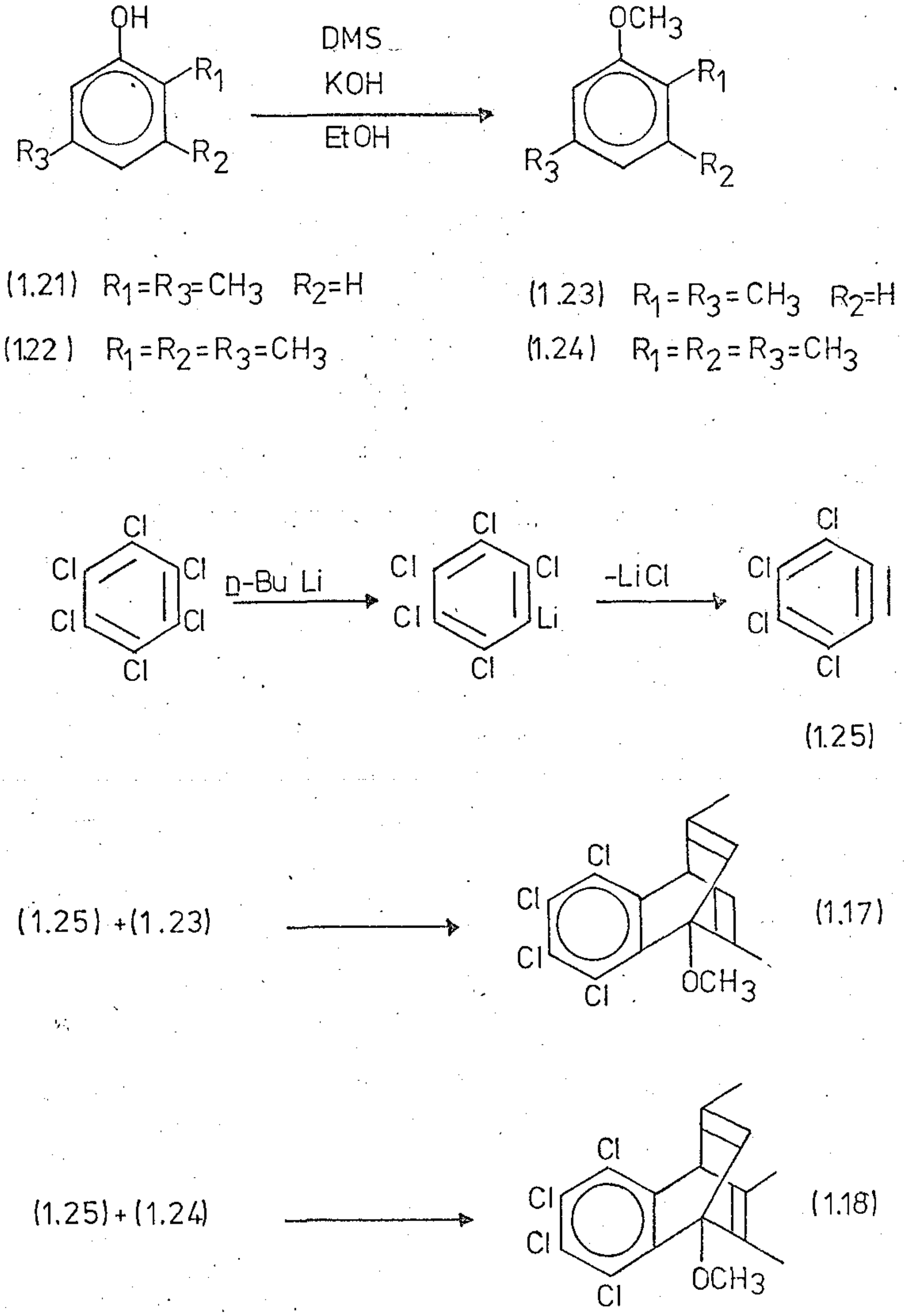
(1.20) $R_1 = R_2 = R_3 = CH_3$

The 1-methoxytetrachlorobenzobarrelenes (1.17) and (1.18) were prepared by the normal procedure reacting hexachlorobenzene with n-butyl-lithium to give pentachlorophenyl-lithium, which in the presence of the required methyl substituted anisole gave tetrachlorobenzyne and hence the products indicated. The methyl substituted anisoles were formed by methylation of the corresponding phenols using dimethylsulphate, in the presence of base. Scheme 1.4 illustrates the complete procedure.

1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (1.17) was identified by comparison of its analytical data with that of a sample previously prepared in this laboratory.[20h] The products (1.18), (1.19) and (1.20) were identified by ^{1}H.n.m.r. and I.R. spectroscopy, mass spectrometry and elemental analysis.

In considering the success of the dechlorination procedure for the preparation, in high yield, of 1-methoxybenzobarrelene our attention was drawn to the difficulty of preparing the parent compound, benzobarrelene (1.26). The best available published route[31] to benzobarrelene uses the Diels-Alder reaction of β-naphthol with maleic anhydride, which affords a mixture of cycloadducts, of which the endo isomer, the required material, is the minor product.[39] Thus, an anhydride function and a ketone function have both to be converted into olefinic functions. The overall published yield, starting with the dicarboxylic acid (1.27) was 2.7%. Scheme 1.5 illustrates the overall route. In this procedure the dicarboxylic acid (1.27) was converted into benzobarrelenone (1.28) in 11% yield, by oxidative decarboxylation using a mixture of lead (IV) acetate and copper (II) acetate. The Kolbé electrolytic method achieves a 51% yield on this step using the mixed dicarboxylic acids.[40] Unfortunately this procedure is restricted to very small scale reactions and only increases the overall yield from β-naphthol to benzobarrelene (1.26) to 6.5%.

Scheme 1.4


DMS
KOH
EtOH
OH
OCH3
R1
R2
R3
Cl
Li
n-Bu Li
-LiCl
OCH3

(1.21) $R_1=R_3=CH_3$ $R_2=H$

(1.22) $R_1=R_2=R_3=CH_3$

(1.23) $R_1=R_3=CH_3$ $R_2=H$

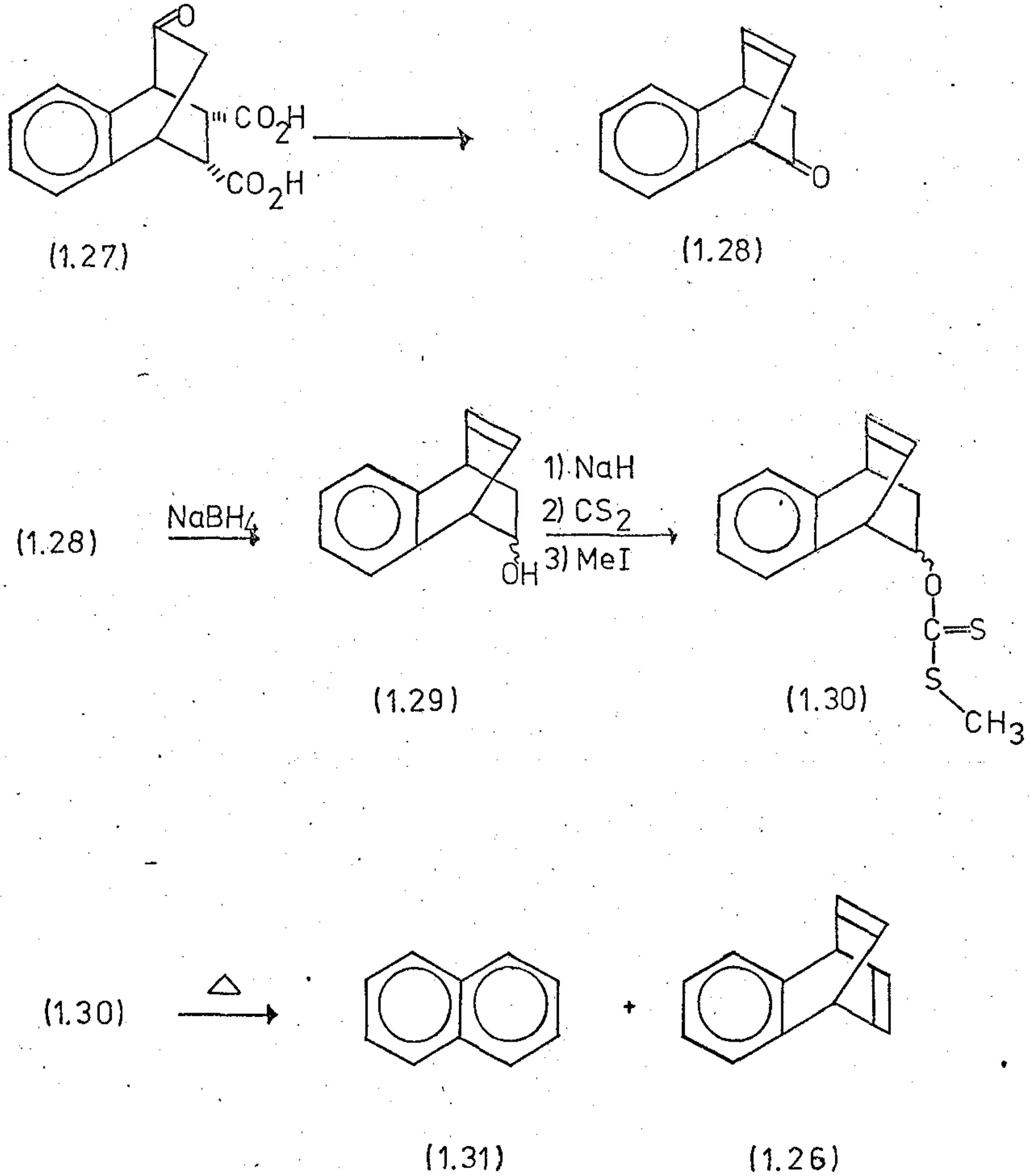
(1.24) $R_1=R_2=R_3=CH_3$

(1.25)

(1.25) + (1.23) → (1.17)

(1.25) + (1.24) → (1.18)

Scheme 1.5


O
CO2H
CO2H
(1.27)
O
(1.28)
(1.28)
NaBH4
OH
(1.29)
1) NaH
2) CS2
3) MeI
O
C
S
S
CH3
(1.30)
(1.30)
Δ
+
(1.31)
(1.26)

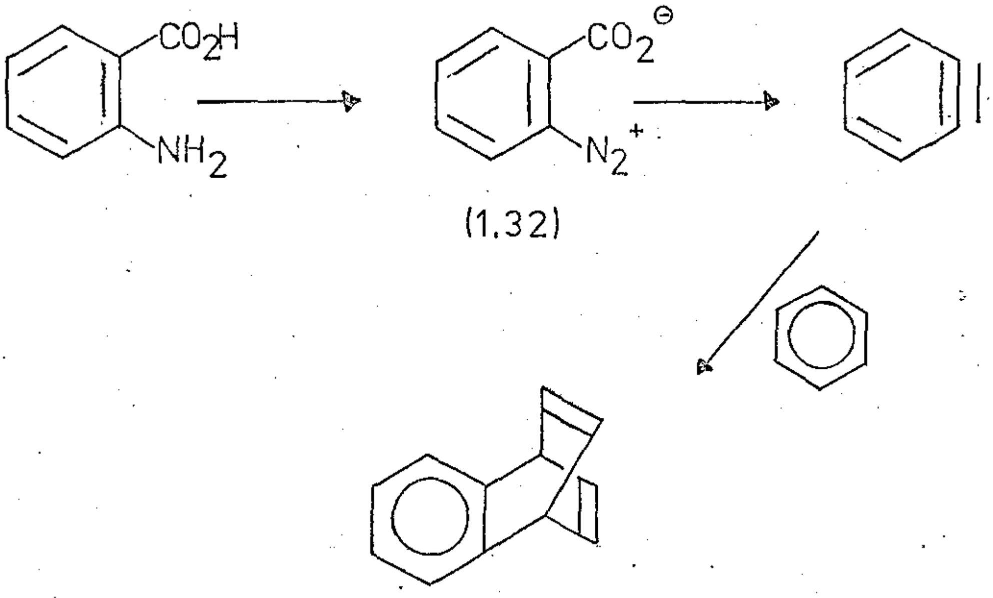
Minor improvements in the conversion of benzobarrelenone (1.28) to benzobarrelene are available.[41] A potential variation of this approach would involve the Diels-Alder reaction of maleic anhydride with naphthalene, which proceeds in 78% yield at 100° and 10,000 atmospheres.[42] The removal of the anhydride function from this product has not been reported, although it is not an unreasonable step.

As illustrated in Scheme 1.5 the published method for the preparation of benzobarrelene (1.26) from benzobarrelenone (1.28) involves the reduction of (1.28) with sodium borohydride to afford a mixture of the epimeric 1,4-dihydro-9-hydroxy-1,4-ethenonaphthalenes (1.29). This mixture was converted to the xanthate esters (1.30) by treatment with sodium hydride, followed by reaction with carbon disulphide and finally methyl iodide. The xanthate esters (1.30), on pyrolysis, yield a mixture of naphthalene (1.31) and the required benzobarrelene (1.26), which can be separated by chromatography.

Benzobarrelene (1.26) has also been prepared by the reaction of benzyne with benzene, but the procedure was restricted to small scale preparations owing to the low yield (∼ 2%) of the desired product.[43] In an unpublished report it was found that in the decomposition of benzenediazonium-2-carboxylate (1.32) [from anthranillic acid (12g)] in benzene (12l.), Scheme 1.6, the yield of the required product was increased to 14%.[44]

All the above routes to benzobarrelene have the disadvantage of low yields and in some instances a long and involved experimental procedure.

Scheme 1.6

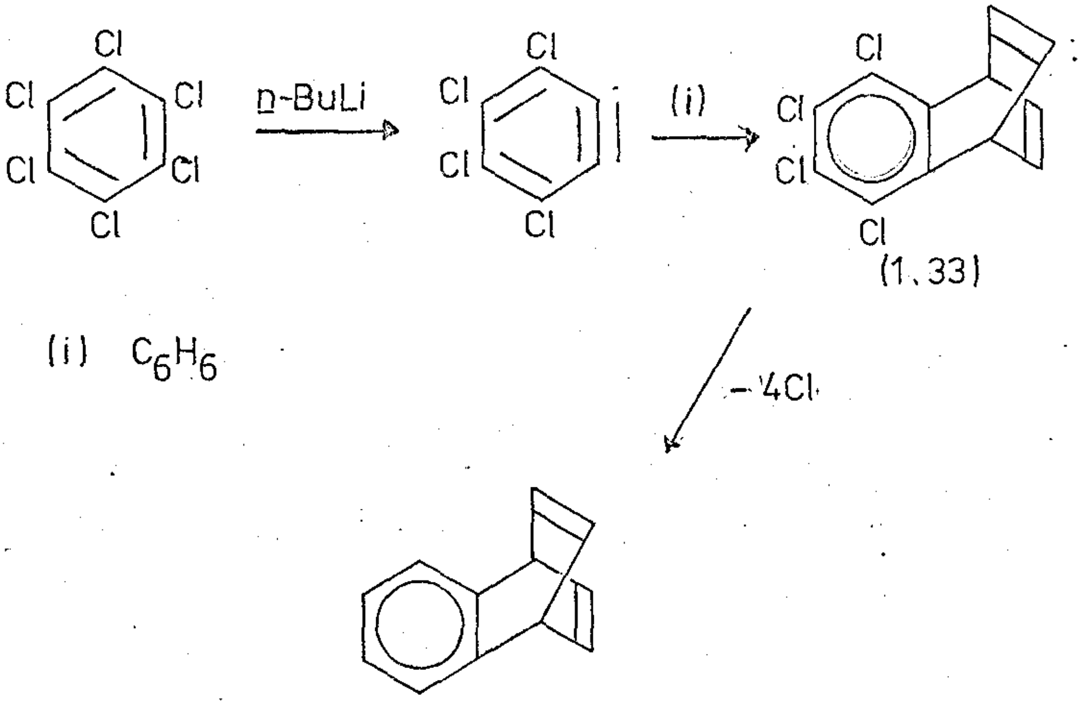


(1.26)

The reaction of tetrachlorobenzyne with benzene to yield tetrachlorobenzobarrelene (1.33) had previously been carried out in this laboratory,[14b] and it was reasonable to assume that (1.33) would dechlorinate to yield (1.26). If this assumption proved correct then it would be feasible to prepare benzobarrelene from hexachlorobenzene in a matter of days, and hopefully in high yield.

A small scale reaction, according to Scheme 1.7, justified the above assumptions, yielding benzobarrelene (1.26) in 40% yield in approximately four days.

Scheme 1.7



(i) C_6H_6

(1.26)

Further investigations into the dechlorination of (1.33) improved the yield of (1.26) to around 90%. This yield was not decreased by increasing the scale of the reaction (1g - 20g) of (1.33). The crude product was obtained as a pale yellow oily crystalline solid, in almost quantitative yield. Analysis by ^{1}H.n.m.r. spectroscopy, g.l.c. and t.l.c. indicated that the crude product was virtually pure. Recrystallisation from light petroleum (40:60) gave a white crystalline solid, yield 98% (mp. 64-65°, lit.[31] 65.5-66°). Spectroscopic data were identical to those previously reported.[31]

The main objective of this particular study was to obtain the highest yield possible of benzobarrelene (1.26) in a quick and straight forward procedure. It was not possible to increase the yield of the dechlorination step, but it was possible to increase the yield of tetrachlorobenzobarrelene (1.33). The major difficulty in the reaction leading to

(1.33) was that tetrachlorobenzyne and benzene react in a Diels-Alder 1,4-cycloaddition. Since benzene is not a particularly good diene, it was necessary to devise a procedure in which tetrachlorobenzyne was formed from its precursor slowly and in the presence of a large volume of benzene to facilitate a maximum yield of the required adduct.

The preparation of tetrachlorobenzyne and its subsequent reactions has been investigated, in some detail by two groups, Rausch[45] and previous workers in this laboratory.[12,14b,20h] Both groups prepared the tetrachlorobenzyne by reacting hexachlorobenzene in ether with *n*-butyl-lithium as shown in Scheme 1.7. The major difference in the two procedures was in the subsequent reaction conditions for the generation of the benzyne intermediate. Rausch,[45] in his study of the reaction with furan, allowed the solution to warm slowly to room temperature and then stirred at room temperature until the completion of the reaction. This was necessary, since it is known that pentachlorophenyl-lithium abstracts a proton from furan at *ca*. 35°. The procedure in this laboratory was to add the diene and then allow the solution to rise quickly to room temperature, followed by a period of refluxing (4-6 hr.). The disadvantage of this latter route was that, although yields of *ca*. 60% had been obtained, the yields were variable and could, in inexperienced hands, be as low as *ca*. 20%.

In order to resolve these problems a detailed investigation of the preparation of the tetrachlorobenzyne precursor and its subsequent reaction was carried out.

Table I, at the end of this section, indicates some of the conditions investigated. The major points which became apparent during the investigation are summarised below:-

a) Hexachlorobenzene recrystallised twice from benzene mp. 227° (lit.[46] 227°) was used. When technical grade was used, some insoluble material remained after the reaction with n-butyl-lithium. This only reduced the yield by a small amount.

b) It was important to completely exclude moisture from the reaction. All of the apparatus was dried overnight in an oven ca. 200° and dry, oxygen-free, nitrogen was passed through the apparatus while it was cooling and during the subsequent steps.

c) Reagent grade diethyl ether was dried first by standing over calcium chloride (to remove water and ethanol) for 1 to 2 days. Filtration and distillation from fresh calcium chloride followed by the addition of sodium wire to the distillate afforded ether which was essentially dry.

d) Analar benzene was dried by the direct addition of small amounts of sodium wire until fresh wire remained clean.

Failure to use absolutely dry apparatus and solvents resulted in low yields of the required product. A low yield was frequently indicated by a coloured solution which normally appeared after addition of the benzene. The colour varied from red to blue with different reactions. It was assumed that these colours appeared due to impurities in the solvents used, since reactions in which the solvents had been carefully purified gave only a pale yellow solution after addition of the benzene. A small scale experiment indicated that the addition of acetone (1 drop) to the pentachlorophenyl-lithium/benzene solution resulted in instant formation of a deep blue colour.

e) It was found advantageous to use a large volume of ether (ca. 600 ml.) in order to facilitate the formation of pentachlorophenyl-lithium and also to prevent the solidification of the benzene during its addition at a later stage.

f) n-Butyl-lithium solution in hexane was transferred to a pressure equalised dropping funnel, using a syringe (50 ml.) which had been carefully dried and flushed with dry, oxygen-free, nitrogen. During the addition of n-butyl-lithium the solution was stirred vigorously to avoid local overheating. It was also important to ensure that the drops of n-butyl-lithium fell directly into the hexachlorobenzene/ether solution. The temperature of the solution was not allowed to exceed -70° during the addition. It was advisable to use an additional 0.1 mole equivalent of n-butyl-lithium to remove adventitous proton sources. Additional amounts of n-butyl-lithium appear to result in the formation of significant amounts of tetrachlorophenylenedi-lithium species. The temperature of the solution after the addition was allowed to rise to ca. -60°.

g) The complete formation of pentachlorophenyl-lithium was indicated by the cloudy suspension becoming clear. Confirmation was obtained by carefully removing an aliquot (ca. 0.5 - 1.0 ml.) of the solution using a dried syringe. The solution, after hydrolysis, was analysed by gas liquid chromatography. Normally it was impossible to obtain a solution of pentachlorophenyl-lithium which was completely free of hexachlorobenzene, although it was not always detected at this stage.

h) The benzene must be added slowly. Fast addition results in localised heating and formation of some tetrachlorobenzyne, which reacts with the precursor rather than with the benzene. Fast addition also resulted in the solution becoming coloured. Since the temperature of the solution was ca. -60° at the beginning of the addition, the benzene tended to solidify. Hence it was important to maintain vigorous stirring during the addition and to ensure that the benzene dropped directly into the solution. If the benzene was allowed to run down the side of the flask, a large lump of solid benzene formed, and again localised heating was a possibility. The large volume of ether, mentioned earlier, helped to keep the benzene as a fine suspension. The temperature of the solution on completion of the addition was ca. -10°. At this stage a clear yellow solution was indicative that a high yield of the required product was likely to be obtained.

The use of a large excess of benzene results in high yields of the desired product, presumably due to the increased opportunity for the aryne to react with benzene rather than with its precursor.

i) On completion of the addition of benzene the solution was allowed to rise slowly to room temperature and then stirred at room temperature until completion of the reaction. Too fast a rise in temperature resulted in lower yields and sometimes highly coloured solutions, again indicative of the aryne reacting preferentially with its precursor. At room temperature the solution should still be clear and pale yellow in colour.

j) Completion of the reaction was checked by g.l.c.. The precise time for the completion of the reaction depended on the ambient temperature. If the laboratory temperature was ca. 18-20° this was as long as ca. 40 hr., while when the laboratory temperature was ca. 29-33° then the time was much shorter.

In the analysis by g.l.c. it was found more convenient to use the ratio of the pentachlorobenzene-hexachlorobenzene peaks, rather than to use the ratio of the peaks due to pentachlorobenzene and tetrachlorobenzobarrelene. The effect of the excess of hexachlorobenzene was to act as an internal standard.

k) Tetrachlorobenzobarrelene could be isolated in a pure crystalline form by column chromatography using alumina and light petroleum (40-60°) as the eluant. A crude product, satisfactory for dechlorination, could be obtained by using a short 'plug' of alumina, again with light petroleum as the eluant. The major impurities in the crude product were pentachloro- and hexachlorobenzene, which on dechlorination give benzene. This can be removed from the benzobarrelene by rotary evaporation.

l) A high yield for the dechlorination step also required the observance of the following points:-

Dry tetrahydrofuran was obtained by refluxing tetrahydrofuran with calcium hydride, followed by distillation under nitrogen onto lithium aluminium hydride, from which it was distilled immediately prior to use. t-Butanol was freshly distilled before use. All apparatus was dried in an oven at 200° overnight, and the reaction was carried out under dry, oxygen-free, nitrogen.

The presence of small amounts of water lowered the yields obtained in the reactions.

m) The procedure devised by Gassman[35] recommended the use of small pieces of sodium. It was discovered that the use of sodium wire, 0.5 mm. diameter reduced the reaction time from ca. 40 hr. to ca. 6 hr.. The increase in surface area would explain this observation.

n) Once again, the completion of the reaction could be determined by g.l.c.. However, an efficient indicator was the appearance of a deep purple colour in the precipitated sodium chloride. This was assumed to be due to the presence of free electrons (sodium atoms) in the crystal lattice.

It was also found[38] that the 'purple sodium chloride' was itself an efficient dehalogenating agent, and hence lends support to the hypothesis that it contains free electrons.

The most efficient conditions found for the conversion of hexachlorobenzene to tetrachlorobenzobarrelene are illustrated in Table II at the end of this section. Using these conditions in conjunction with points (a) to (k) (above) it was found possible to prepare tetrachlorobenzobarrelene in a consistent yield of ca. 65%. This material was suitable for dechlorination to benzobarrelene which was obtained in 90-95% yields.

A typical procedure enabling the preparation of 10g. batches of benzobarrelene, in an overall yield of ca. 50%, in approximately 4 days from hexachlorobenzene has been presented in a short communication.[47]

Since this communication we have received a number of requests, from various parts of the world, for further experimental details of the above reaction. It was therefore considered sensible to present in the experimental section of this chapter a precise and detailed procedure for the above reaction.

TABLE I

Hexachlorobenzene (g)	Benzene (ml)	Ether (ml)	n-BuLi (equiv.)	Temp. °C	%Adduct
25	250	100	1.0	80	34
28.5	1000	100	1.0	80	34
28.5	1000	350	1.1	80	41
28.5	1000	350	1.0	80	45
14.25	1000	400	1.1	20	51
7.13	1000	200	1.1	20	60
28.5	4000	400	1.3	20	35
28.5	4000	600	1.1	20	69
28.5	4000	600	1.1	20	48
28.5	4000	600	1.0	20	63

NOTE:- Temp. °C refers to the temperature that the reaction solution was allowed to reach after addition of the benzene.

TABLE II

Hexachlorobenzene (g)	Benzene (ml)	Ether (ml)	n-BuLi (equiv.)	Temp. °C	%Adduct
28.5	4000	600	1.1	20	ca.65.0

EXPERIMENTAL

GENERAL

All reactions involving organolithium reagents were carefully carried out in glassware dried overnight at 200° and under an atmosphere of dry, "white spot" nitrogen. All solvents were distilled and dried by conventional methods prior to usage. Organic solutions of products were dried over anhydrous magnesium sulphate.

Analytical thin layer chromatography was carried out using silica gel (GF_{254} according to Stahl) for layers of 0.25.mm. thickness. Preparative thin layer chromatography was carried out using silica gel (PF_{254} according to Stahl) for layers 0.75 mm. thick.

Analytical gas chromatography was carried out using a Pye 104 series gas chromatograph with hydrogen flame ionisation detection. The 5ft. columns used were:-

a) 10% S.E.30 on firebrick.

b) 3% S.E.30 on firebrick.

c) 10% Carbowax on Chromosorb W.

d) 10% Diethylene Glycol Succinate on Chromosorb W.

Infra-red spectra were determined for potassium bromide discs in the case of solids, or for thin films in the case of liquids, unless otherwise stated, with a Perkin-Elmer 257 spectrophotometer. Ultra-Violet spectra were determined for solutions with a Unicam SP 8000. ^{1}H.nuclear magnetic resonance spectra were determined at 90M.Hz. for approximately 20% $^w/_v$ solutions using tetramethylsilane as an internal standard. The n.m.r. spectra were recorded with a Perkin-Elmer R32 spectrometer.

Mass Spectra were determined on an A.E.I. M.S.12 mass spectrometer. High resolution mass spectrometry was carried out on an A.E.I M.S.9 at P.C.M.U. by courtesy of S.R.C.

Melting points were determined on a Kofler block and are uncorrected. All compounds were colourless unless stated otherwise.

1. Preparation of 5,6,7,8-tetrachloro-1,4-dihydro-1,4-ethenonaphthalene (1.33) (tetrachlorobenzobarrlene)

A carefully dried 5-litre 3-necked flask containing hexachlorobenzene (28.5g, 0.1 mole) [Note 1] and a magnetic stirrer bar, was fitted with a low temperature thermometer, a liquid paraffin bubbler, and a $\frac{1}{2}$ litre pressure equalised dropping funnel [Note 2] fitted with a T- piece adaptor, topped with a rubber serum cap and acting as a gas inlet tube [Note 3] in the centre neck. Diethyl ether (600ml.) [Note 4] was then added to the flask and the suspension stirred and cooled to *ca*. -78° [Note 5]. A solution of *n*-butyl-lithium (1.1 equivalents) [Note 6] was added over a period of *ca*. $\frac{1}{2}$hr. [Note 7]. After an additional *ca*. 1-1.5hr. an aliquot was removed by means of a syringe [Note 8], added to water and the organic phase was analysed by gas chromatography [Note 9]. Benzene (4l.) [Note 10] was then added at a rate such that the reaction mixture did not solidify [Note 11] and afforded a suspension of benzene in the solution. The stirred reaction mixture was allowed to warm to room temperature slowly and after a further *ca*. 14hr. [Note 12] an aliquot was removed, treated with water and analysed by gas chromatography [Note 13]. When the amount of pentachlorobenzene (after hydrolysis) was no longer decreasing, as shown by gas chromatographic comparison with the relative height of the peak due to hexachlorobenzene [Note 13] solid ammonium chloride (10g.) was added. After *ca*. 15min. the solid materials are removed by filtration through a small quantity of celite (*ca*. 20g.) and the volume of the solvents was reduced to *ca*. 75ml. [Note 14] using a 250ml. flask. Alumina (100g.) [Note 15] was then added and the mixture swirled at 30° for $\frac{1}{2}$hr. under reduced pressure [Note 14].

The freely running product was finally evacuated and pumped at room temperature at low pressure [Note 16] until no more solvent remained [Note 17]. The alumina and product were then placed on top of a column of alumina (1Kg.) [Note 15] and eluted with light petroleum [Note 18] taking fractions of *ca.* 250ml. [Note 19]. The fractions were evaporated and assayed by gas chromatography [Notes 9 and 13]. Fractions 3-11 usually contained essentially pure tetrachlorobenzobarrelene (18-19.5g.,55-67%), mp. 127-131° (from ethanol) (lit.[14b] mp. 125°).

$\nu_{max.}$ 3060, 2995, 2930, 2850, 1585, 1400, 1370, 1330, 1135, 730, 700, 690 and 675 cm^{-1}.

^{1}H.n.m.r. (CDCl$_3$) τ. 3.08 (4H, m) and 4.55 (2H, m).

NOTES:-

1) Hexachlorobenzene (from B.D.H. technical grade) recrystallised twice from benzene mp. 227° (lit.[46] mp. 227°) was used. When technical grade was used some insoluble material remained after the reaction with *n*-butyl-lithium. This only reduced the yield by a small amount.

2) The dropping funnel was fitted with a B34 cone and the dropping tube extended just beyond the bottom of the cone (see Note 6).

3) Dry, oxygen-free, nitrogen was passed through the apparatus while it was cooling and during the subsequent steps. The flow rate could be reduced after the flask had cooled.

4) Reagent grade diethyl ether was dried first by standing the solvent over calcium chloride (to remove water and ethanol) for 1 or 2 days. Filtration and distillation from fresh calcium chloride, followed by the addition of sodium wire to the distillate, afforded ether which was sufficiently dry. In some experiments it was found to be advantageous

to increase the volume of ether to _ca_. 800ml. in order to prevent the solidification of the benzene at a later stage (see Note 10).

5) An acetone - solid carbon dioxide cooling bath allowed an internal temperature of _ca_. -78° to be obtained.

6) _n_-Butyl-lithium solution (2.0-3.0 molar) in hexane obtained from Pfizer (Sandwich) or Alfa (Ventron) was transferred to the pressure equalised dropping funnel using a syringe (50ml.) which had been carefully dried and flushed with dry, oxygen free, nitrogen. The additional 0.1 mole equivalent of _n_-butyl-lithium was used to remove adventitious proton sources. Additional amounts of _n_-butyl-lithium appear to result in the formation of significant amounts of tetrachlorophenylenedi-lithium species.

7) Vigorous stirring of the suspension was maintained in order to avoid local overheating. The temperature was not allowed to exceed -70° during the addition. The suspended hexachlorobenzene slowly went into solution after the addition. The drop-size and rate of addition were adjusted to ensure that the solution of _n_-butyl lithium fell directly into the ethereal suspension of hexachlorobenzene. The temperature of the mixture was then allowed to rise to -60°.

8) A carefully dried syringe(5ml) was flushed with dry, oxygen free, nitrogen and _ca_. 0.5-1.0ml. of the solution was taken. A clear yellow solution may not always be obtained at this stage, some suspended material may be present particularly when using technical grade hexachlorobenzene.

9) Gas chromatography (column b) at 150° gave a satisfactory separation of pentachlorobenzene from hexachlorobenzene. With nitrogen (carrier gas) at 10 p.s.i. (flow rate 45ml. min^{-1}), the retention times of pentachlorobenzene and hexachlorobenzene are ca. 2 and 4 minutes respectively. Normally it was impossible to obtain a solution of pentachlorophenyl-lithium which was completely free from traces of hexachlorobenzene, although it may not be detected at this stage. The addition of a further excess of n-butyl-lithium appears to be disadvantageous (see note 6).

10) Analar benzene (Fisons) was dried by the direct addition of small amounts of sodium wire until fresh wire remained clean. If a reagent grade of benzene was used, it was checked for the absence of thiophene before drying, first with calcium chloride and then with sodium wire. Technical grade benzene was purified by the standard procedure.[48] The rate of addition of the benzene was adjusted so that the drops fell directly into the solution of pentachlorophenyl-lithium. Any benzene falling onto the sides of the flask solidified.

11) The solution of pentachlorophenyl-lithium was at ca. -60° (no solid carbon dioxide was present in the cooling bath at this stage) and the benzene was added slowly at first. The first $\frac{1}{2}$ litre of benzene was added over about 15mins., after which time the temperature in the reaction flask had risen to ca. -20°. The temperature after the second $\frac{1}{2}$ litre of benzene had been added (at the same rate) was ca. -12°. The remaining benzene (3l.) was then added more rapidly ($\sim\frac{1}{2}$hr.) and the final temperature was ca. +10°. The reaction mixture was stirred vigorously during the whole of this stage.

12) The precise time for the completion of the reaction depends on the ambient temperature. If the laboratory temperature was _ca._ 18-20° this could be as long as _ca._ 40hr.. If the laboratory temperature was _ca._ 29-33° then the time falls considerably.

13) A carefully dried syringe (5ml) was flushed with dry, oxygen free, nitrogen and _ca._ 1-2ml. of the solution was taken. Gas chromatography was carried out using the same column as used before [Note 9]. The retention time of the tetrachlorobenzobarrelene was _ca._ 18min.. It was more convenient to use the ratio of the pentachlorobenzene-hexachlorobenzene peaks rather than to use the ratio of the peaks due to pentachlorobenzene and tetrachlorobenzobarrelene. The effect of the excess of hexachlorobenzene was to act as an internal standard.

14) A Büchi rotary evaporator (water pump) and water bath at _ca._ 30° were used.

15) Camag alumina (supplied by Hopkin and Williams) (Brockmann Activity I) was used.

16) A rotary oil pump giving a vacuum of _ca._ 0.2mm. was used.

17) The mixture was pumped at room temperature until the weight remained constant.

18) Light petroleum (boiling range 40-60°) was dried by allowing the solvent to stand over calcium chloride prior to distillation from fresh calcium chloride.

19) The solvent was removed using a Büchi rotary evaporator (water pump) and a water bath temperature of _ca._ 35°. The majority of the distillate was collected and recycled.

2. Preparation of 1,4-dihydro-1,4-ethenonaphthalene (1.26) (Benzobarrelene)

A carefully dried 1-litre 3-necked flask was equipped with a magnetic stirrer bar, combined gas inlet tube and a rubber serum cap [Note 3], a $\frac{1}{2}$ litre pressure equalised dropping funnel and a reflux condenser fitted with a liquid paraffin bubbler. The flask was charged with dry tetrahydrofuran (600ml.) [Note 20] and sodium wire (20g) [Note 21] and the mixture was then heated under gentle reflux before t-butanol (60ml.) [Note 22] was added rapidly. As soon as the operation was completed, a solution of tetrachlorobenzobarrelene (18.5g.) in dry tetrahydrofuran (200ml.) [Note 20] was added over ca. 15min.. The mixture was stirred and heated under reflux and after ca. 4hr. an aliquot was removed, washed with water and assayed by gas chromatography. [Note 23]. The reaction was complete when the precipitate of sodium chloride became deep purple. The reaction mixture was then allowed to cool to room temperature and was filtered through glass wool [Note 24] into methanol (50ml.), contained in a 3-litre beaker. After any small pieces of sodium had reacted with the methanol, water (500ml.) was added [Note 25]. The mixture was then placed in a separatory funnel and extracted with ether (6 x 200ml.). The combined ether layers were washed with a saturated aqueous solution of sodium chloride (2 x 250ml.), dried [Note 26] and evaporated [Note 14] to yield a semi-crystalline product (9-10g, 92-100%) to which alumina (50g.) [Note 15] was added. The mixture was swirled at room temperature under reduced pressure [Note 14] until a freely running product was obtained. This product was placed on a column of alumina (1Kg.) [Note 15] and eluted with light-petroleum [Note 18]. Fractions of ca. 250ml. were collected and evaporated /Note 27/ and assayed by gas chromatography /Note 23/ to afford benzobarrelene (8.3-8.8g, 85-90%), mp. 64-65° (lit.[31] mp. 65.5-66°). $\nu_{max.}$ 3070, 3028, 2990, 1612, 1330, 789, 747, 690 and 655 cm^{-1}. ^{1}H.n.m.r. ($CDCl_3$) τ. 2.75-3.22 (8H, m) and 5.10-5.38 (2H, m).

Notes '(contd.):-

20) Dry tetrahydrofuran /see warning in Org. Synth. Coll. Vol. V, p.976/ was heated under reflux with calcium hydride and distilled under nitrogen onto lithium aluminium hydride from which it was distilled immediately prior to use.

21) Soldium wire 0.5 mm diameter was used.

22) t-Butanol was freshly distilled before use.

23) Gas chromatography using the column and conditions as in Note 9 but at 104° gave a retention time for benzobarrelene of ca. 5min..

24) Glass wool efficiently removed the large knots of sodium wire and a large amount of the "purple sodium chloride".

25) Care was taken to ensure that no pieces of sodium remained before the addition of water.

26) Anhydrous magnesium sulphate was used.

27) A Büchi rotary evaporator (water pump) was used at room temperature.

3. Preparation of 5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene (1.4) (1-methoxytetrachlorobenzobarrelene).

1-Methoxytetrachlorobenzobarrelene (1.4) was prepared in the same manner as tetrachlorobenzobarrelene (1.33) in expt. 1, except anisole (500g.) was added to the pentachlorophenyl-lithium solution instead of benzene. The product was isolated by column chromatography (alumina) using light-petroleum to remove any hexachlorobenzene and pentachlorobenzene remaining, and ether-light petroleum (1:20 - 1:10 $^{v}/_{v}$) to isolate

1-methoxytetrachlorobenzobarrelene (1.4) (22.5g, 70%) mp. 121-122° (from ethanol) [lit.[14b] mp. 122°].

$\nu_{max.}$ 3080, 3060, 3000, 2930, 2840, 1630, 1580, 1450, 1360, 1225, 1175, 1030, 735, 710 and 695 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.8–3.4 (4H, m), 4.5-4.9 (1H, m), and 6.27 (3H, s).

4. Preparation of the Sodium Biphenyl Reagent[29]

In a dry 500ml. 3-necked flask equipped with a sealed stirrer of adjustable speed, an inlet for nitrogen gas and a reflux condenser, was placed toluene (60ml.) and metallic sodium (5.6g). With the stirrer off, and a slow stream of nitrogen passing, the flask was heated until the toluene began to reflux and the sodium was melted. The stirrer was started and the mixture vigorously agitated until the sodium was finely dispersed as small globules. However, on cooling the solution globules tended to coagulate, and re-heating and cooling had to be repeated before a cooled solution was obtained with the sodium still in small globules.

The mixture was cooled to below 10° using a methanol and dry ice cooling bath. Anhydrous ethylene glycol dimethyl ether (125ml.) was added with the stirrer operating at a moderate speed. Biphenyl (39g.) was then carefully added to the solution.

On addition of the biphenyl the solution turned blue-green and then darkened as the reaction proceeded.

Keeping the temperature below 30° the solution was stirred for 1hr. After this period the solution was transferred to a brown bottle [250ml.], stoppered with a rubber serum cap and stored in a refrigerator at below 5°.

5. Attempted dechlorination of 1-methoxytetrachlorobenzobarrelene (1.4) using the Sodium Biphenyl Reagent

1-Methoxytetrachlorobenzobarrelene (0.32g, 1m.mol.) was dissolved in dry toluene (30ml.) and placed in a 3-necked flask (500ml.), including a sealed stirrer, nitrogen inlet and dropping funnel (50ml.). Sodium biphenyl reagent (20ml.) was placed in the dropping funnel and added carefully to the stirred solution, whilst a flow of nitrogen was maintained.

After completion of the addition the reaction was stirred for 5min. and then poured into cold water (100ml.) contained in a separating funnel. The solution was extracted with ether (3 x 50ml.) and the combined ethereal solutions dried over $MgSO_4$. Evaporation of the solvent gave an oily solid with a characteristic odour of biphenyl.

Attempts to identify the dechlorinated product 1-methoxybenzobarrelene (1.1) by gas chromatography, thin layer chromatography and ^1H nuclear magnetic reasonance spectroscopy all met with failure, the large excess of biphenyl masking the identification of the required product.

That the dechlorination had occurred, was shown by analysis of the aqueous fraction from the reaction. Treatment of an aliquot of the aqueous fraction with conc. nitric acid and silver nitrate gave a precipitate of silver chloride. The precipitate darkened on standing.

6. Attempted dechlorination of 1-methoxytetrachlorobenzobarrelene (1.4).

Sodium (0.8g.) was added to a solution of 1-methoxytetrachlorobenzobarrelene (200mg, 0.62m.mol.) in tetrahydrofuran (12ml.) containing t-butyl alcohol (3ml.) at 0°. The mixture was stirred for 50hr. at

0-5° under nitrogen. Additional soldium metal (0.1g.) and t-butyl alcohol (1ml.) were then added, the resulting mixture was then allowed to warm to room temperature. The reaction mixture, after removal of excess of sodium by filtration, was poured onto ice, the aqueous phase extracted repeatedly with ether, and the combined organic phases dried over anhydrous $MgSO_4$. Distillation of the ether gave an oily solid, which from analysis by gas chromatography, thin layer chromatography and ^{1}H.nuclear magnetic reasonance, indicated the presence of starting material (1.4) and no dechlorinated product.

7. Preparation of 1,4-dihydro-1-methoxy-1,4-ethenonaphthalene (1.1) (1-Methoxybenzobarrelene)

1-Methoxybenzobarrelene (1.1) was prepared by the dechlorination of 1-methoxytetrachlorobenzobarrelene (1.4) using the same procedure as described in expt. 2. 1-Methoxybenzobarrelene was isolated by column chromatography (alumina) eluting with light petroleum to give a pale yellow oily solid. Recrystallisation from light petroleum gave 1-methoxybenzobarrelene (90%) as white crystals, mp. 36-37° (lit.[20c] 37-38°).

$\nu_{max.}$ 3070, 2990, 2940, 2840, 1630, 1580, 1495, 1465, 1335, 1290, 1230, 1160, 1135, 1095, 1085, 1030, 1020, 995, 980, 925, 860, 755, 700, 690 and 650 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.9-3.5 (8H, m), 5.2-5.5 (1H, m) and 6.28 (3H, s).

8. Preparation of 2,5-Dimethylanisole (1.23).

Dimethyl sulphate (300ml.) and concentrated aqueous potassium hydroxide (50%, 250ml.) were added alternately in small portions to a solution of 2,5-dimethylphenol (50g, 0.41M.) in ethyl alcohol (100ml.)

and aqueous potassium hydroxide (50%, 50ml.). After completion of the addition the solution was heated to 90-95° and maintained at this temperature for ca. 6hr..

After this period of time the solution was cooled, and the cloudy solution filtered. The filtrate was extracted with ether (4 x 200ml.) and the combined ethereal solution washed with sodium hydroxide (2N, 250ml.). The ethereal solution was dried ($MgSO_4$), filtered and the ether removed by distillation to yield 2,5-dimethylanisole (1.23) (55g, 99%), as a pale yellow liquid, bp. 188-192° (lit.[49] 194°).

$\nu_{max.}$ 3050 - 2850, 1625, 1595, 1520, 1470, 1420, 1290, 1270, 1160, 1140, 1050, 995, 930, 850, 810, and 720 cm^{-1}.

9. Preparation of 2,3,5-trimethylanisole (1.24).

The preparation was as described in expt. 8 but using 2,3,5-trimethylphenol (50g, 0.37M.). 2,3,5-Trimethylanisole (1.24) (52g, 94%) was obtained as a pale yellow liquid, bp. 213-215° (lit.[49] 216°).

$\nu_{max.}$ 3005, 2940, 2870, 2842, 1608, 1593, 1498, 1470, 1320 1285, 1150, 1120, and 840 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 3.4-3.5 (2H, d), 6.25 (3H, s), 7.73 (3H, s), 7.81 (3H, s), and 7.90 (3H, s).

10. Preparation of 5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene (1.17) (1-methoxy-2,5-dimethyltetrachlorobenzobarrelene).

1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (1.17) was prepared by the procedure described in expt. 3, but using 2,5-dimethylanisole (50g.). The product (1.17) was isolated, after removal of the excess of 2,5-dimethylanisole by distillation, by column chromatography (alumina) using light petroleum as the eluant to give a crystalline product (18.0g, 51%), mp. 151-152° (methanol) (lit.[20h] mp. 150-153°).

$\nu_{max.}$ 3000 - 2900, 1450, 1380, 1350, 1300, 1250, 1215, 1185, 1122, 1080, 1030, 1000, 940, 810, 770, 700, and 650 cm^{-1}.

^{1}H.n.m.r. (CDCl$_3$) τ. 3.34 (1H, m), 3.65 (1H, dq, $|J|$=5.5 and 2.0Hz.), 5.10 (1H, dd, $|J|$=5.5 and 2.0Hz.), 6.28 (3H, s), 8.04 (3H, d, $|J|$=2.0Hz.), and 8.14 (3H, d, $|J|$=2.0Hz.).

11. Preparation of 5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,3,9-trimethyl-1,4-ethenonaphthalene (1.18) (1-methoxy-2,3,5-trimethyltetrachlorobenzobarrelene

1-Methoxy-2,3,5-trimethyltetrachlorobenzobarrelene (1.18) was prepared by the procedure described in expt. 3, but using 2,3,5-trimethylanisole (50g.). Excess of 2,3,5-trimethylanisole was removed by distillation, and the residue separated by column chromatography (alumina), eluting with 5% ether-light petroleum. 5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,3,9-trimethyl-1,4-ethenonaphthalene (1.18) (21.8g, 60%), mp. 130-131° (ethanol), was isolated.

$\nu_{max.}$ 3000 - 2840, 1435, 1365, 1345, 1250, 1115, 1095, 785, and 745 cm^{-1}.

^{1}H.n.m.r. (CDCl$_3$) τ. 3.3-3.4 (1H, m), 5.28-5.30 (1H, d, $|J|$= 2.0Hz), 6.28 (3H, s), 8.0-8.05 (3H, d, $|J|$=2.0Hz.) and 8.15-8.30 (6H, m).

Found: C, 52.7, H, 3.8%, M (mass spectrometry), 364.

$C_{16}H_{14}Cl_4O$ requires C, 52.8, H, 3.85%, M, 364.

12. Preparation of 1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene (1.19) (1-methoxy-2,5-dimethylbenzobarrelene).

1-Methoxy-2,5-dimethylbenzobarrelene (1.19) was prepared by the dechlorination of 1-methoxy-2,5-dimethyl-tetrachlorobenzobarrelene (1.17) using the procedure described in expt. 2. The required benzobarrelene (1.19) was isolated by column chromatography (alumina) eluting with light petroleum to yield a pale yellow oil. 1,4-Dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene (1.19) (90%) was obtained by distillation under reduced pressure, bp. 90° (0.5-0.4 mm. Hg).

$\nu_{max.}$ 3060, 2960, 2940, 2910, 2840, 1450, 1370, 1300, 1250, 1230, 1160, 1100, 1080, 1020, 990, 910, 885, 850, 755, 720, 640, and 620 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.6-2.72 (1H, m), 2.8-3.3 (3H, m), 3.4-3.5 (1H, m), 3.6-3.75 (1H, dq, $|J|$ = 6.0Hz. and 2.0Hz.), 5.65-5.8 (1H, dd, $|J|$ = 6.0Hz. and 2.0Hz.), 6.23 (3H, s), and 8.0-8.2 (6H, m).

Found: C, 84.9, H, 8.1%, M (mass spectrometry) 212.

$C_{15}H_{16}O$ requires C, 84.85, H, 7.6%, M, 212.

13. Preparation of 1,4-dihydro-1-methoxy-2,3,9-trimethyl-1,4-ethenonaphthalene (1.20) (1-Methoxy-2,3,5-trimethylbenzobarrelene).

1-Methoxy-2,3,5-trimethylbenzobarrelene (1.20) was prepared by the dechlorination of 1-methoxy-2,3,5-trimethyltetrachlorobenzobarrelene (1.18) using the procedure described in expt. 2. The crude benzobarrelene (1.20) was isolated by column chromatography (alumina) eluting with light petroleum to yield a yellow oil. Recrystallisation gave 1,4-dihydro-1-methoxy-2,3,9-trimethyl-1,4-ethenonaphthalene (1.20) (85%) (light petroleum). mp. 65-67° (softens at 62°).

$\nu_{max.}$ 3000 - 2900, 1450, 1290, 1254, 1162, 1090, 990, 930, 823, 758, 745, 720, and 650 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ 2.6-3.2 (4H, m), 3.42-3.52 (1H, m), 5.9-6.0 (1H, d, $|J|$= 2.0Hz.), 6.22 (3H, s), 8.0-8.1 (3H, d, $|J|$= 2.0Hz.) and 8.15-8.30 (6H, m).

Found: C, 85.0, H, 8.1%, M (mass spectrometry), 226.

$C_{16}H_{18}O$ requires C, 84.9, H, 8.0%, M, 226.

CHAPTER 2

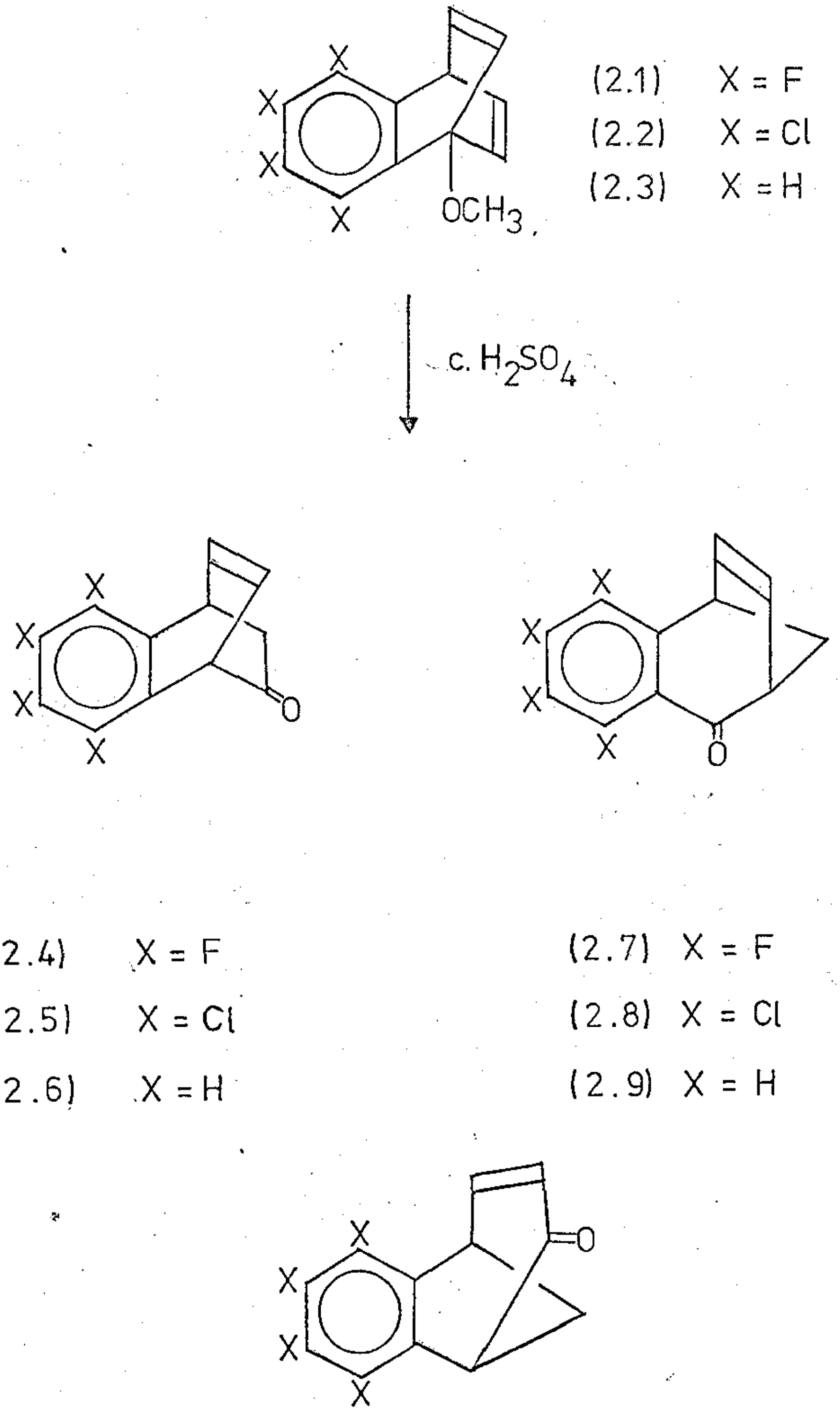
MECHANISTIC STUDIES OF THE ACID CATALYSED REARRANGEMENT OF 1-METHOXYBENZOBARRELENE DERIVATIVES.

INTRODUCTION

Earlier work[20d,c] in this laboratory had established that the 1-methoxybenzobarrelenes (2.1) - (2.3) rearranged in concentrated sulphuric acid (98%), at room temperature, to the three corresponding isomeric ketones (2.4) - (2.12). The major product from each rearrangement was the corresponding benzobarrelenone (2.4) - (2.6) isolated in yields varying from 50 to 76%. The minor products were the aryl ketones (2.7) - (2.9) and the $\alpha\beta$- unsaturated ketones (2.10) to (2.12) isolated in 3.0-8.0% and 4.5-5.5% yields respectively.

Investigations[20d,c,e] involving deuterium labelling, specifically substituted methyl derivatives, solvolytic reactions of certain tosylates, attempted equilibration experiments, and ^{14}C labelling experiments suggested the following mechanisms, illustrated in Scheme 2.1 for the formation of the ketones (2.4) - (2.12). The 1-methoxybenzobarrelenes (2.1) - (2.3) could be protonated at either C-2 or C-3. Protonation at C-3 led to the carbonium ion (2.13) from which the aryl ketones (2.7) - (2.9) and the $\alpha\beta$- unsaturated ketones (2.10) - (2.12) were formed by vinyl and aryl migration respectively.

Protonation at C-2 gave the carbonium ion (2.14), which rearranged to give the benzobarrelenones (2.4) - (2.6) as illustrated. The deuterium labelling experiments indicated that the formation of tetrafluorobenzobarrelenone (2.4) occurred by two pathways, (a) and (b), the ratio of which varied depending on the concentration of acid used.


X
X
X
X
OCH$_3$
c. H$_2$SO$_4$
O
O
O

(2.1) X = F
(2.2) X = Cl
(2.3) X = H

(2.4) X = F
(2.5) X = Cl
(2.6) X = H

(2.7) X = F
(2.8) X = Cl
(2.9) X = H

(2.10) X = F
(2.11) X = Cl
(2.12) X = H

In concentrated sulphuric acid (98%), at room temperature, _ca_. 80% of (2.4) was derived by pathway (a) and _ca_. 20% by pathway (b). In sulphuric acid - water ($4:1^{v}/_{v}$), at 80°, the values obtained were _ca_. 55% for pathway (a) and _ca_. 45% for pathway (b).

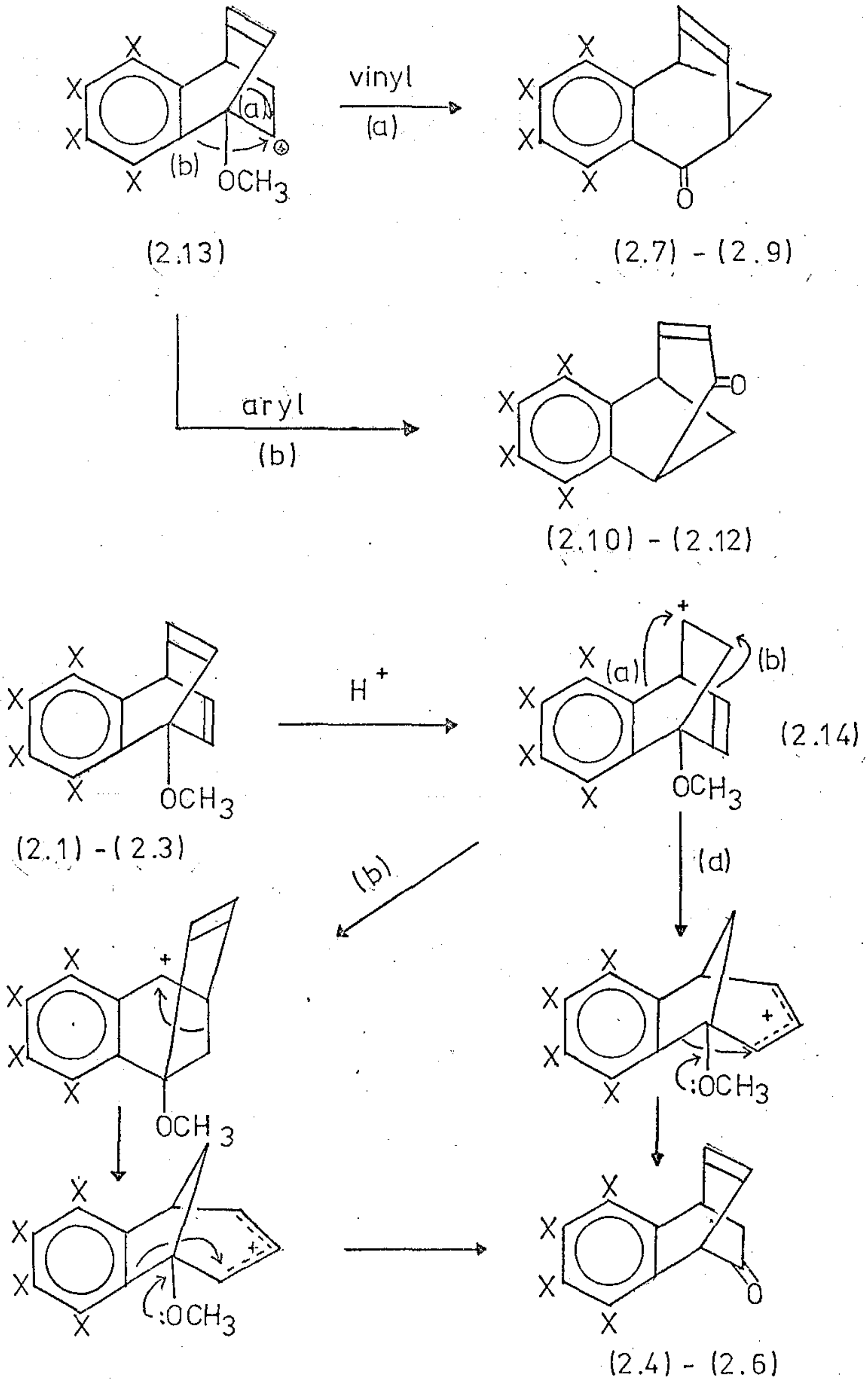
The above results were based on a number of assumptions made in the interpretation of the data obtained.[20d,c] These assumptions were mainly concerned with possible isotope effects. Thus it was assumed that the addition of a deuteron was as easy as that of a proton. Also it was assumed that the orientation of protonation of a double bond was not significantly affected by the presence of deuterium atoms.

We were interested in verifying the accuracy of the deuterium results and also in extending our knowledge of the rearrangement mechanisms.

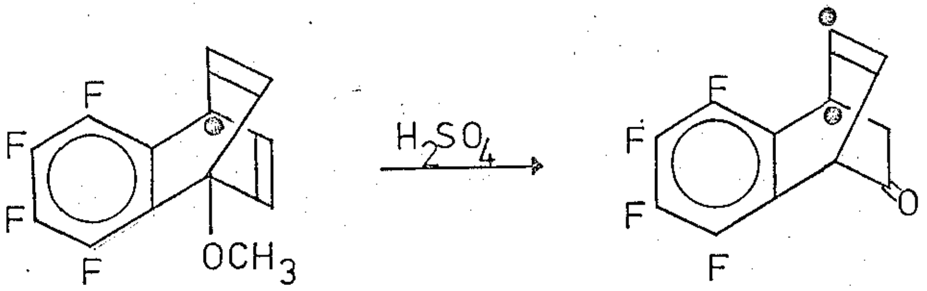
It was reasoned that the preparation of [4-^{14}C]-1-methoxy-tetrafluorobenzobarrelene (2.1), followed by rearrangement in sulphuric acid, would yield tetrafluorobenzobarrelenone (2.4) with the ^{14}C label scrambled between C-4 and C-5. The extent of this scrambling would be dependent on the conditions used for the rearrangement.

Degradation of the benzobarrelenone (2.4) in such a way as to isolate the C-4 and C-5 in separate products would enable an accurate determination of the ratio of the two pathways, (a) and (b), involved in the formation of the ketone (2.4). This method of determination would not be limited by the assumptions made in the deuterium studies.

Scheme 2.1


X
(a)
(b)
OCH3
(2.13)
vinyl
(a)
(2.7) - (2.9)
aryl
(b)
(2.10) - (2.12)
H+
(2.1) - (2.3)
(2.14)
(d)
+
:OCH3
(2.4) - (2.6)

We therefore decided to investigate possible routes for preparing [4-^{14}C]-1-methoxy-tetrafluorobenzobarrelene and then to establish a suitable degradation procedure for tetrafluorobenzobarrelenone.



(2.1) (2.4)

◎ = ^{14}C

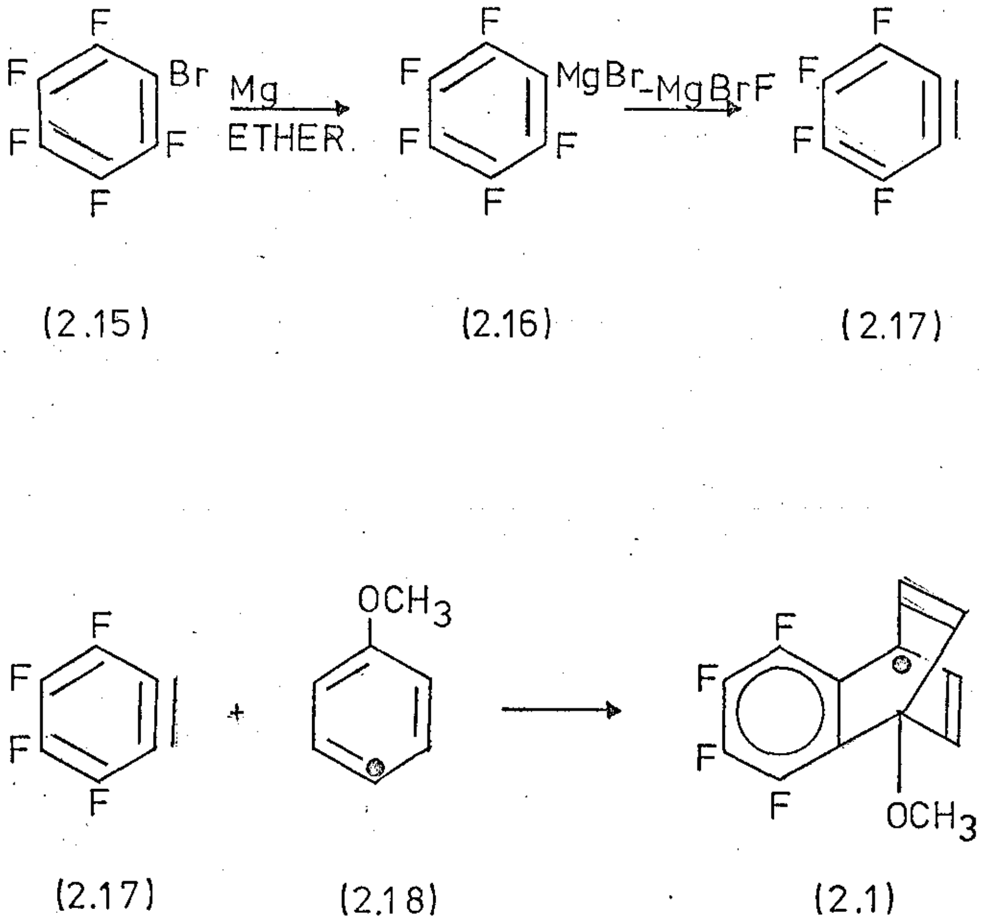
Discussion

All the investigations discussed in this chapter were carried out with unlabelled material until suitable procedures had been established.

The first problem in this investigation was to devise a method of introducing [^{14}C] into C-4 of 1-methoxy-tetrafluorobenzobarrelene (2.1). The normal method of preparation is to react pentafluorophenyl magnesium bromide (2.16), formed by the reaction of pentafluorobromobenzene (2.15) with magnesium in dry ether, with anisole (2.18). The Grignard reagent (2.16) breaks down to form tetrafluorobenzyne (2.17) which reacts with the anisole in a Diels-Alder 1,4-cycloaddition reaction, as illustrated in Scheme 2.2, to give the required product (2.1).

The C-4 in this product originates from the C-4 in the anisole. Hence it was necessary to prepare $[4\text{-}^{14}C]$-anisole (2.18). The reaction between tetrafluorobenzyne and anisole is normally[50] carried out using a large excess of anisole, which facilitates the 1,4-cycloaddition. However, it was not practical to attempt to prepare large quantities of $[4\text{-}^{14}C]$-anisole (2.18), and therefore

Scheme 2.2


F
Br
Mg
ETHER.
MgBr
-MgBrF
OCH3
(2.15)
(2.16)
(2.17)
(2.18)
(2.1)

it was decided to prepare a small volume of high activity anisole which could then be diluted to a suitable volume.

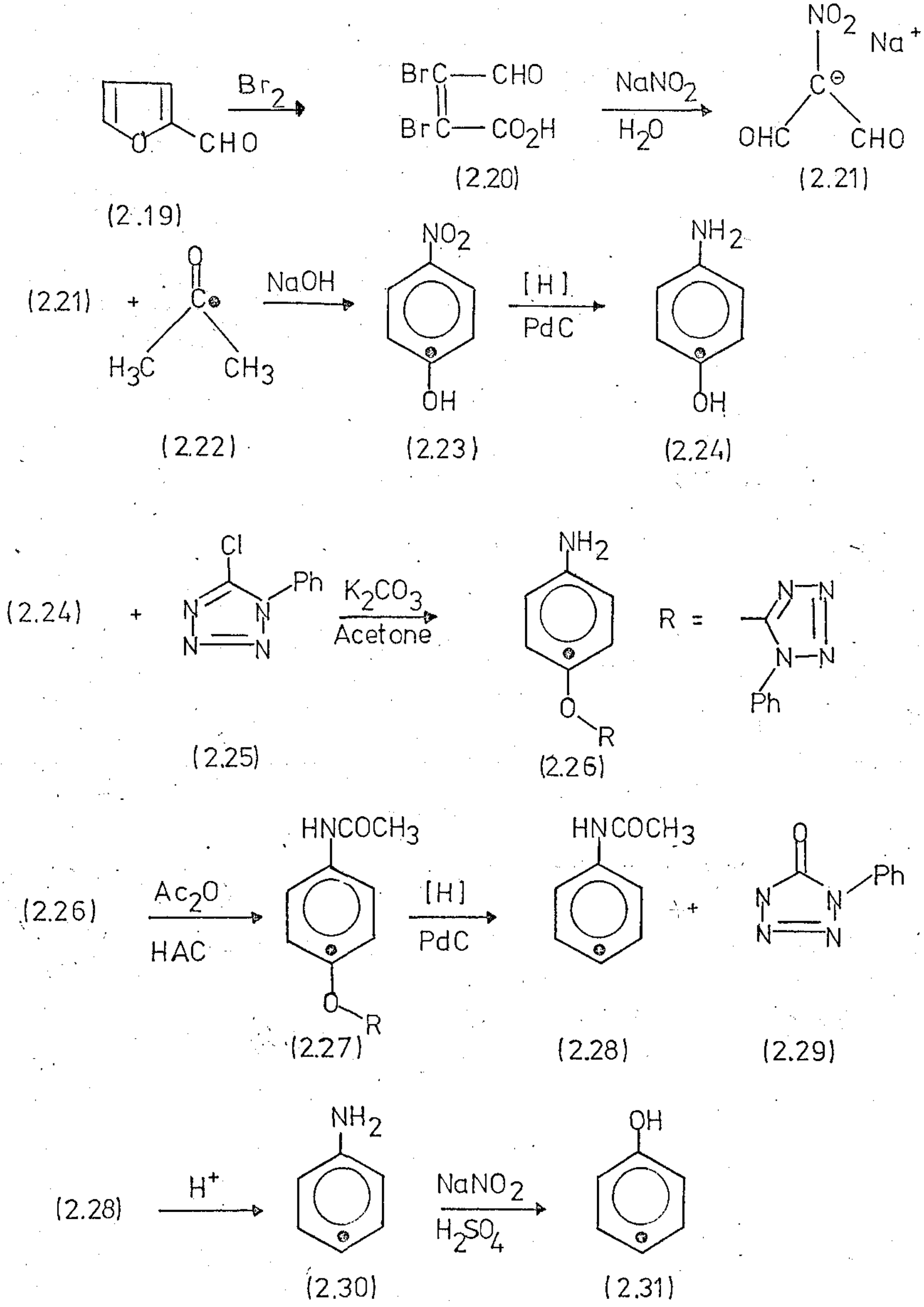
Preparation of /4-^{14}C 7-Anisole (2.18).

No difficulties were foreseen in the synthesis of the labelled anisole (2.18), since a procedure had been published by Kratzl and Vierhapper,[51] which gave a high yield of /4-^{14}C 7-phenol (2.31), as shown in Scheme 2.3. Methylation of the phenol (2.31) would give the required anisole (2.18). Vierhapper's results indicate that the phenol (2.31) can be isolated in an overall yield of ca. 47%. This procedure was carefully investigated.

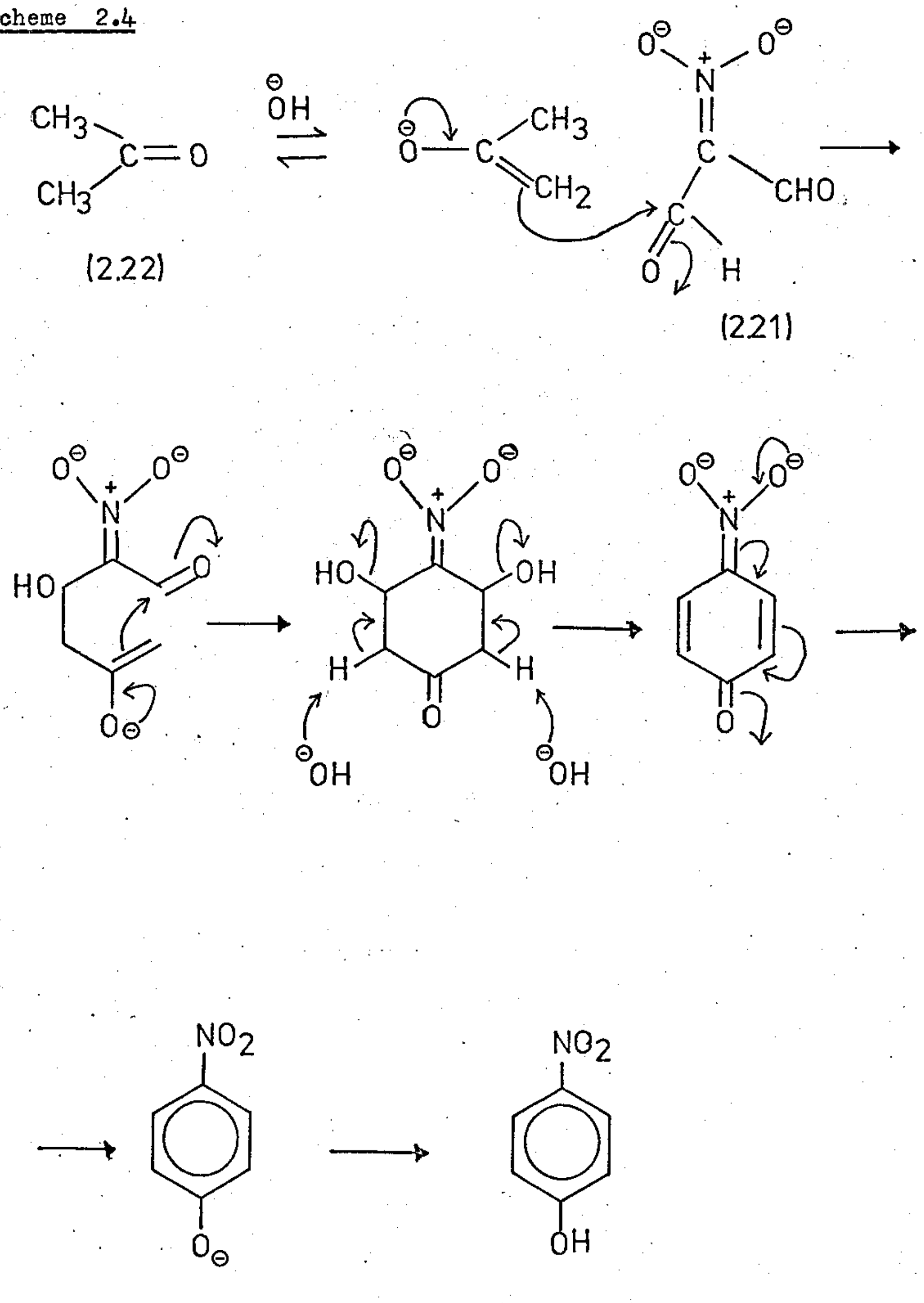
Sodium nitromalondialdehyde monohydrate (2.21) was prepared[52] by the reaction of furfural (2.19) with bromine to yield mucobromic acid (2.20), which upon reaction with sodium nitrite, produced the required dialdehyde (2.21). The following step involved a double aldol condensation between (2.21) and acetone (2.22) to form the aromatic compound, p-nitrophenol (2.23), presumably by a mechanism similar to that shown in Scheme 2.4.

In the reduction of the nitro compound (2.23) to p-aminophenol (2.24) Kratzel and Vierhapper[51] used Raney-Nickel and hydrazine hydrate as their reducing medium. However, in these laboratories we have found that the alternative procedure,[53] using PdC (5 or 10%) and hydrazine hydrate in ethyl alcohol heated under reflux, provides a more convenient method for the reduction of aromatic nitro compounds. Thus p-aminophenol (2.24) was prepared in 97% yield.

Scheme 2.3


(2.19)
Br$_2$
(2.20)
NaNO$_2$
H$_2$O
(2.21)
(2.21)
NaOH
(2.22)
(2.23)
[H]
PdC
(2.24)
(2.24)
(2.25)
K$_2$CO$_3$
Acetone
(2.26)
R =
(2.26)
Ac$_2$O
HAC
(2.27)
[H]
PdC
(2.28)
(2.29)
(2.28)
H$^+$
(2.30)
NaNO$_2$
H$_2$SO$_4$
(2.31)

Scheme 2.4



(2.22)

(2.21)

(2.23)

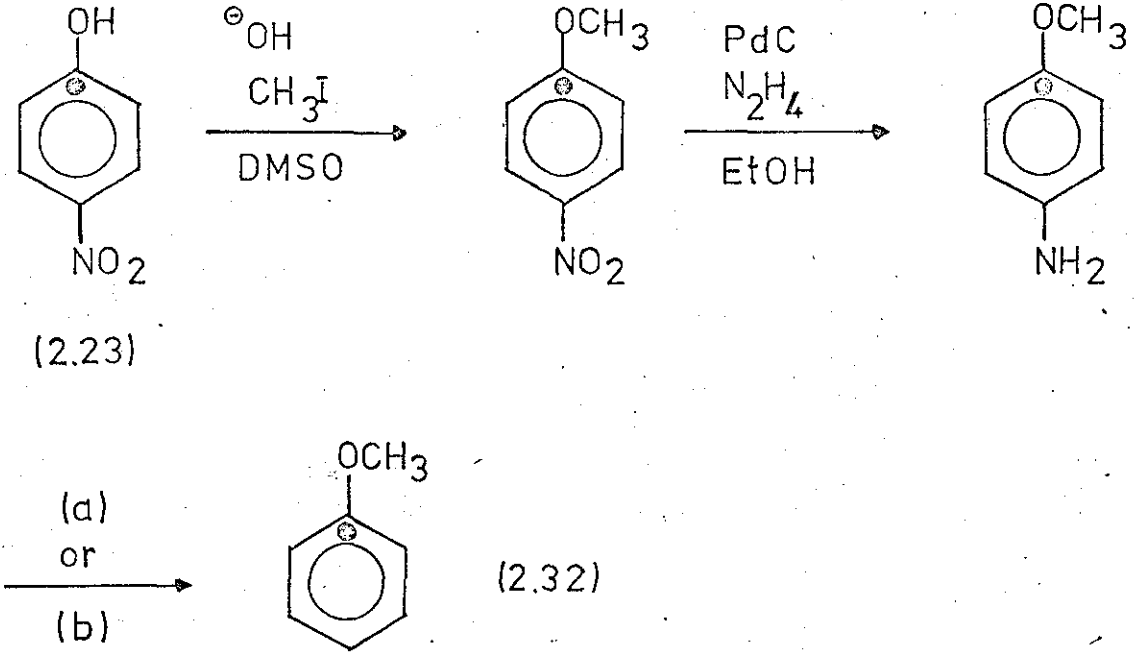
OH
CH3
C
O
CH2
N
CHO
H
HO
OH
NO2

It was interesting to note at this stage that the *p*-nitrophenol (2.23) is a potential intermediate for both [4-^{14}C]-anisole (2.18) and [1-^{14}C]-anisole (2.32). Formation of the anisole (2.18) involves conversion of a nitro group to a methoxy group via a hydroxyl group and the replacement of a hydroxyl group by a hydrogen atom. Scheme 2.5 illustrates the procedure, recently established in this laboratory,[20e] for the synthesis of [1-^{14}C]-anisole (2.32). It is considered that the overall yield of over 50% combined with the simplicity and convenience of the procedure makes this synthesis of [1-^{14}C]-anisole the most attractive one currently available.

The removal of the hydroxyl group from the aminophenol (2.24) to give aniline (2.30) was the most important step in Vierhapper's[51] procedure. A suitable leaving group, which would facilitate the breaking of the aromatic carbon to oxygen bond, had to be attached through the hydroxyl group. The use of 1-phenyl-5-chlorotetrazole (2.25) for this purpose has been well established.[54] 1-Phenyl-5-chlorotetrazole was prepared[55] according to the procedure shown in Scheme 2.6. This involved the reaction of aniline with carbon disulphide and ammonium hydroxide to give the compound (2.33) which on treatment with lead nitrate forms phenyl isothiocyanate (2.34). The required tetrazole (2.25) was obtained by allowing the compound (2.34) to react with chlorine to produce phenylcarbonimidoyl dichloride (2.35) which on treatment with activated sodium azide in glyme forms the tetrazole (2.25).

The reaction of *p*-aminophenol (2.24) with the tetrazole (2.25), in a solution of potassium carbonate in acetone, yielded 1-phenyl-5-

Scheme 2.5


OH
$^{\ominus}OH$
CH_3I
DMSO
OCH_3
NO_2
NO_2
PdC
N_2H_4
EtOH
OCH_3
NH_2
(a)
or
(b)
OCH_3

(2.23)

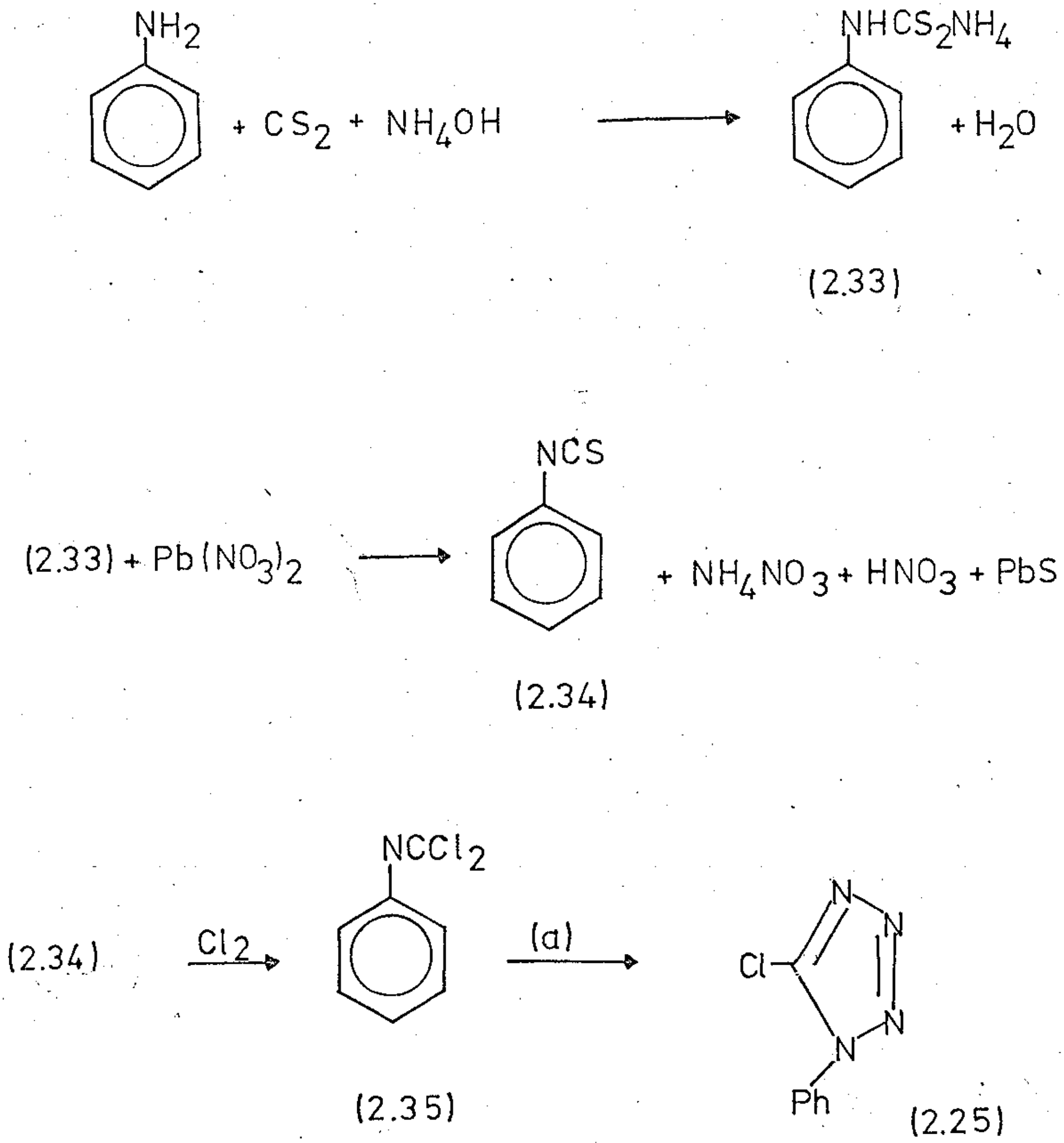
(2.32)

(a) C_5H_9ONO/CF_3CO_2H, then urea, then hydroquinone

(b) $NaNO_2$/dil. HCl, then 30% H_3PO_2

-(4-amino-phenoxy)-tetrazole (2.26). Before reducing the compound (2.26) the amino group was protected by converting (2.26) to the acetyl derivative (2.27). Reduction of the acetyl derivative using PdC (10%) and hydrogen gas at atmospheric pressure gave a mixture of acetanilide(2.28) and tetr$\overset{\text{zo}}{\text{a}}$lone (2.29). The two products could be

Scheme 2.6


NH2
+ CS2 + NH4OH
NHCS2NH4
+ H2O
(2.33) + Pb(NO3)2
NCS
+ NH4NO3 + HNO3 + PbS
(2.34)
Cl2
NCCl2
(a)
Cl
N
N
N
N
Ph

(2.33)

(2.34)

(2.35)

(2.25)

(a) Activated NaN_3/GLYME

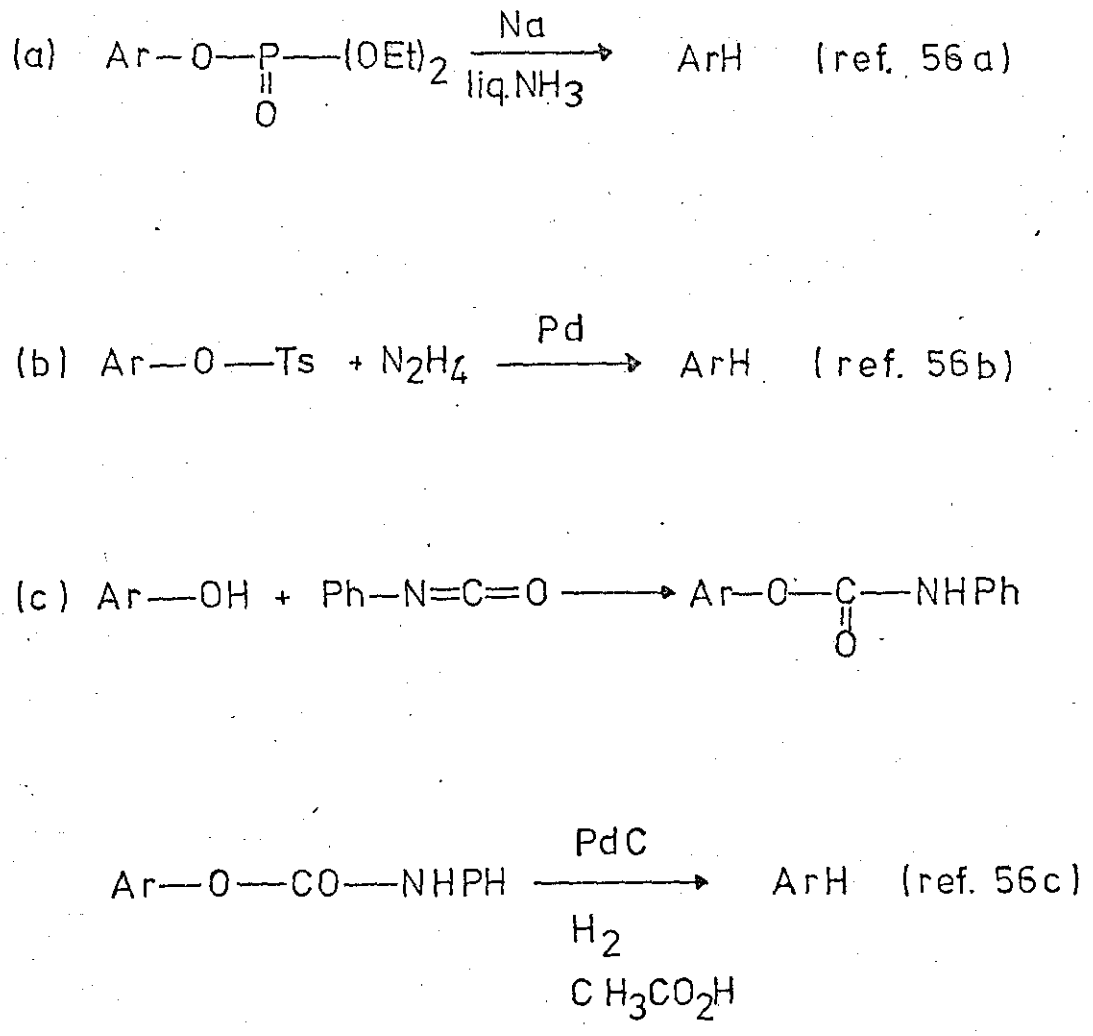
separated by sublimation. Acid hydrolysis of the acetanilide, using dilute sulphuric acid (*ca.* 15%) at reflux temperature for *ca.* 6hr., gave aniline (2.30). Phenol (2.31) was prepared in 67% yield by diazotisation of (2.30), using sodium nitrite and sulphuric acid.

The procedure by Kratzl and Vierhapper[51] was investigated in some detail, since a number of difficulties were encountered. In some of the steps it was not possible to repeat the authors' yields. For instance, the diazotisation of aniline to phenol, according to the authors proceeded in a yield of 95%, and yet the best yield we could obtain was 67%. Differences of this magnitude would alter the authors' overall yield of 47% considerably. By far the major difficulty encountered was the reduction of 1-phenyl-(-4-acetami~~n~~do-phenoxy-)-tetrazole (2.27) to acetanilide (2.28). A number of attempts were made to remove the inconsistency, with results varying from no reduction to a 50 to 60% conversion.

It was reasoned that given sufficient time these difficulties could have been overcome. Unfortunately time was limited, and therefore alternative routes, leading to consistently high overall yields, were sought.

The difficult step was obviously the replacement of the hydroxyl group by a hydrogen atom. A number of alternative procedures[56] were available for accomplishing this step. Three of these procedures are illustrated in Scheme 2.7. Once again the problem with these methods was one of yield.

Scheme 2.7



(a) $\mathrm{Ar{-}O{-}\underset{\overset{\|}{O}}{P}{-}(OEt)_2 \xrightarrow[liq.NH_3]{Na} ArH}$ (ref. 56a)

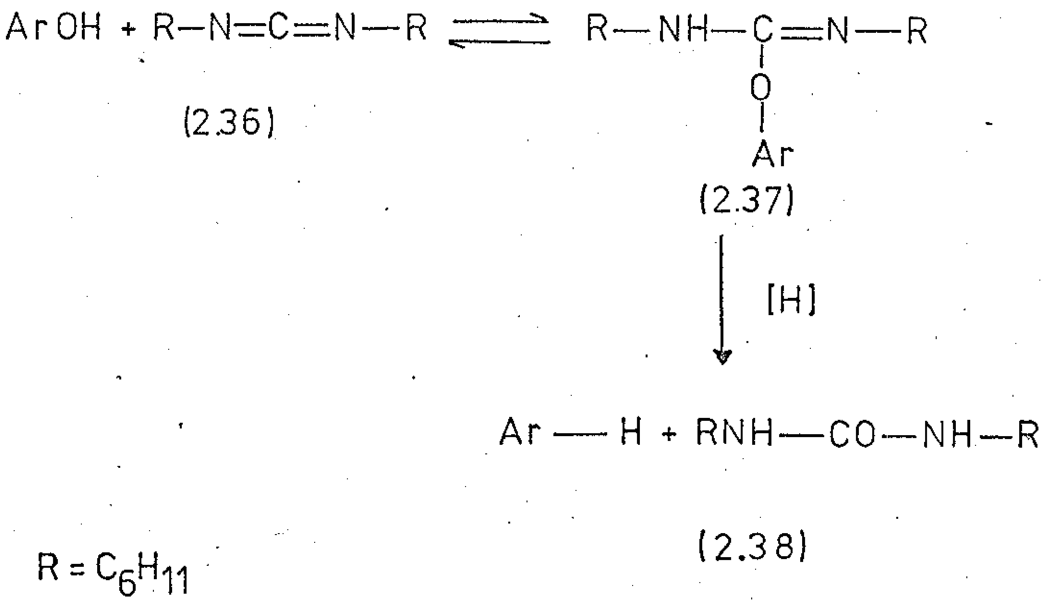
(b) $\mathrm{Ar{-}O{-}Ts + N_2H_4 \xrightarrow{Pd} ArH}$ (ref. 56b)

(c) $\mathrm{Ar{-}OH + Ph{-}N{=}C{=}O \longrightarrow Ar{-}O{-}\underset{\overset{\|}{O}}{C}{-}NHPh}$

$\mathrm{Ar{-}O{-}CO{-}NHPH \xrightarrow[\substack{H_2\\ CH_3CO_2H}]{PdC} ArH}$ (ref. 56c)

Recent results by Vowinkel[57] suggested the possibility of reacting p-nitrophenol (2.23) with dicyclohexylcarbodiimide (2.36) to form an $\overset{O}{\underline{ø}}$-aryl-isourea (2.37). Reduction of the compound (2.37) could possibly lead to aniline. Scheme 2.8 shows this procedure.

Scheme 2.8



*Vowinkel[57] has shown that certain phenols can be dehydroxylated in a two step process. The first step involves a solid phase reaction between the phenol and the carbodiimide to form an $\overset{O}{\underline{ø}}$-arylisourea.

Since this is an equilibrium reaction an excess (ca. 2-3 equivalents) of the carbodiimide was used. The product was isolated by recrystallisation, or the crude mixture used directly in the second step. This involves the hydrogenolysis to the aromatic hydrocarbon and a disubstituted urea (2.38). Steric effects were found to influence the reductive cleavage.[57]

A number of potential difficulties were foreseen before the above procedure was attempted:-

(a) The substituted aromatic phenols used by Vowinkel[57] all contained electron donating groups e.g. OCH_3; CH_3. as opposed to electron withdrawing groups, such as a nitro group. This effect could retard the formation of the C-O bond in the o-arylisourea.

(b) If the reduction of the nitro group was fast, compared to the breaking of the aromatic C-O bond, then the amino group could interfere with the formation of the required product. Since (2.36) and (2.37) are in equilibrium, then during the reduction p-aminophenol could be formed, which could then re-combine with the carbodiimide through the nitrogen to give a C-N linkage instead of a C-O linkage.

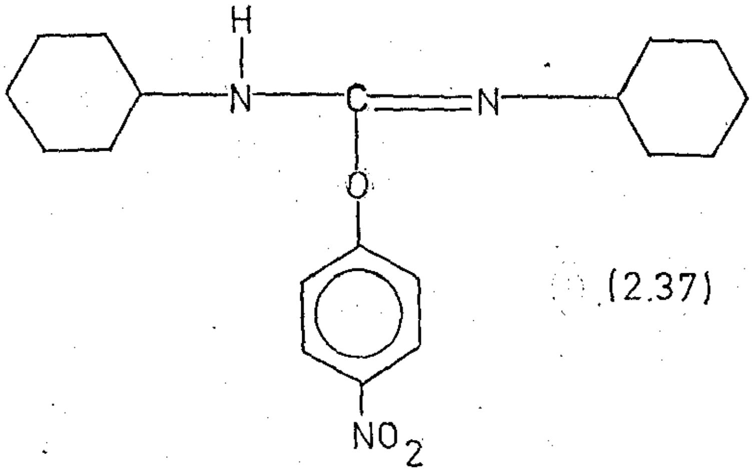
However, one major advantage of this procedure compared with that of Kratzl and Vierhapper,[51] was that a five step synthesis, from p-nitrophenol to aniline Scheme 2.3, would be replaced by only two steps Scheme 2.8.

p-Nitrophenol (2.23) was stirred with N,N-dicyclohexylcarbodiimide (2.36) for 3 days at 50-100°. The resultant green oily solid was recrystallised from benzene and the yellow crystalline material obtained was dissolved in ethyl acetate and treated with PdC (10%) and hydrogen at atmospheric pressure. The hydrogenation was continued until the uptake of hydrogen ceased. The crude product was analysed by gas liquid chromatography and was shown to be p-aminophenol.

This result indicated that either the $\overset{O}{0}$-arylisourea was not being formed in the first stage and the unreacted p-nitrophenol was being reduced, or the $\overset{O}{0}$-arylisourea was cleaving to give either p-aminophenol or p-nitrophenol.

A second reaction involving p-nitrophenol and dicyclohexylcarbodiimide was carried out and the recrystallised product analysed. Thin layer chromatography, using chloroform as an eluant, indicated that the product was a mixture of three compounds. Separation by preparative layer chromatography and identification by spectral and physical methods indicated that the two major products were the starting materials, p-nitrophenol and dicyclohexylcarbodiimide. The third and minor product had a mp. of 135-137°, gave a molecular ion at 345, and a complex ^{1}H.n.m.r. spectrum with peaks at : τ 1.62(m,1H), 1.72(m,1H), 2.55(m,1H), 2.65(m,1H), 6.15-6.6(1H, broad, replaced by deuterium exchange) and 7.90-9.50 (22H, complex). These data would fit the required $\overset{O}{0}$-arylisourea (2.37).

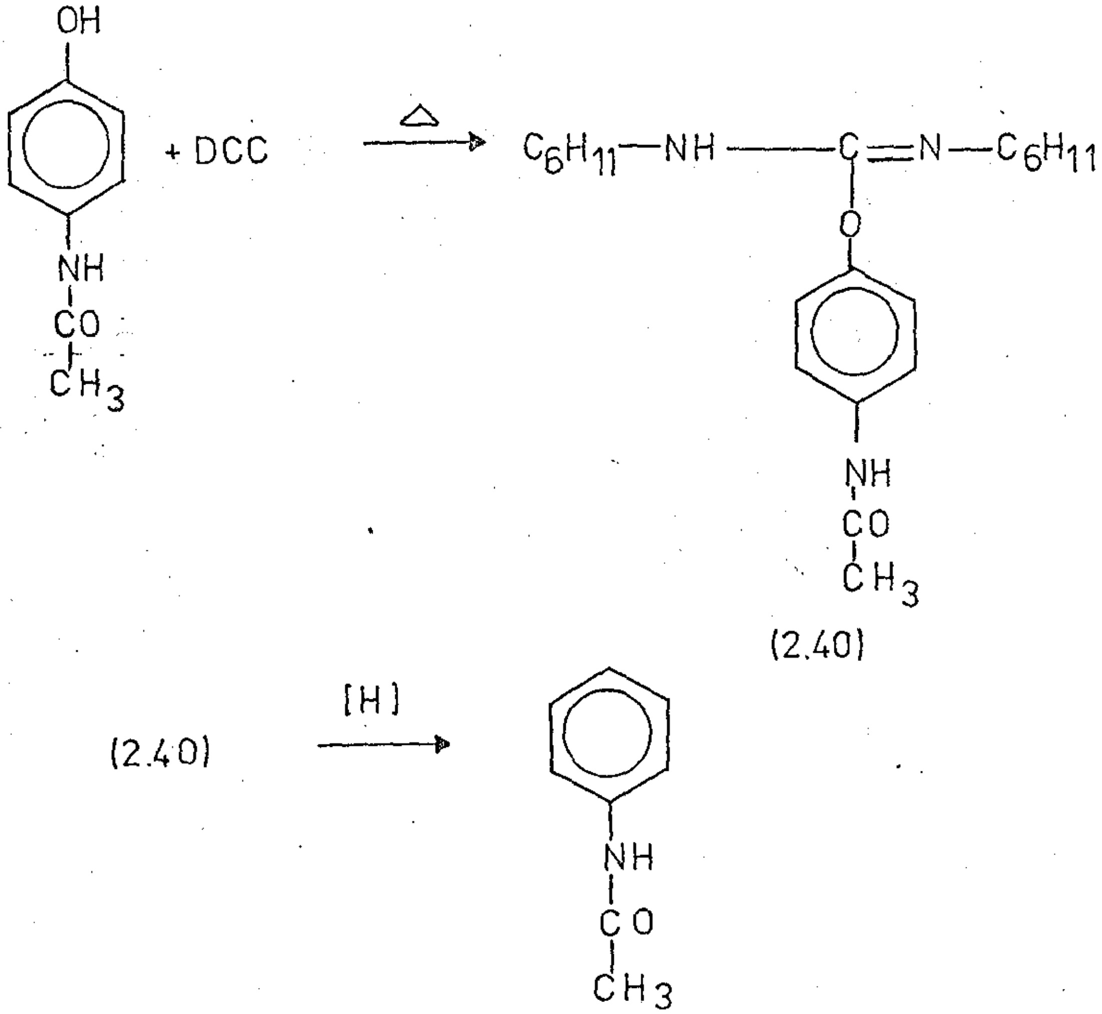
It would seem that the effect of the electron withdrawing nitro group in p-nitrophenol keeps the equilibrium shown in Scheme 2.8 well over to the left. In an attempt to overcome this problem the nitro compound (2.23) was reduced to p-aminophenol and this product converted to p-hydroxyacetanilide (2.39), which was reacted with dicyclohexylcarbodiimide (DCC). It was hoped that the $\overset{O}{0}$-arylisourea (2.40)



(2.37)

would be formed and reduction of this would lead to acetanilide as shown in Scheme 2.9.

Scheme 2.9



OH
NH
CO
CH3
+ DCC
△
C6H11—NH—C=N—C6H11
O
NH
CO
CH3
(2.40)
(2.40)
[H]
NH
CO
CH3

The reaction of the compound (2.39) with DCC led to a black tar which proved impossible to purify or analyse.

The poor yields and difficulty of isolating the required products prevented further investigations into the reactions of p-nitrophenol with DCC.

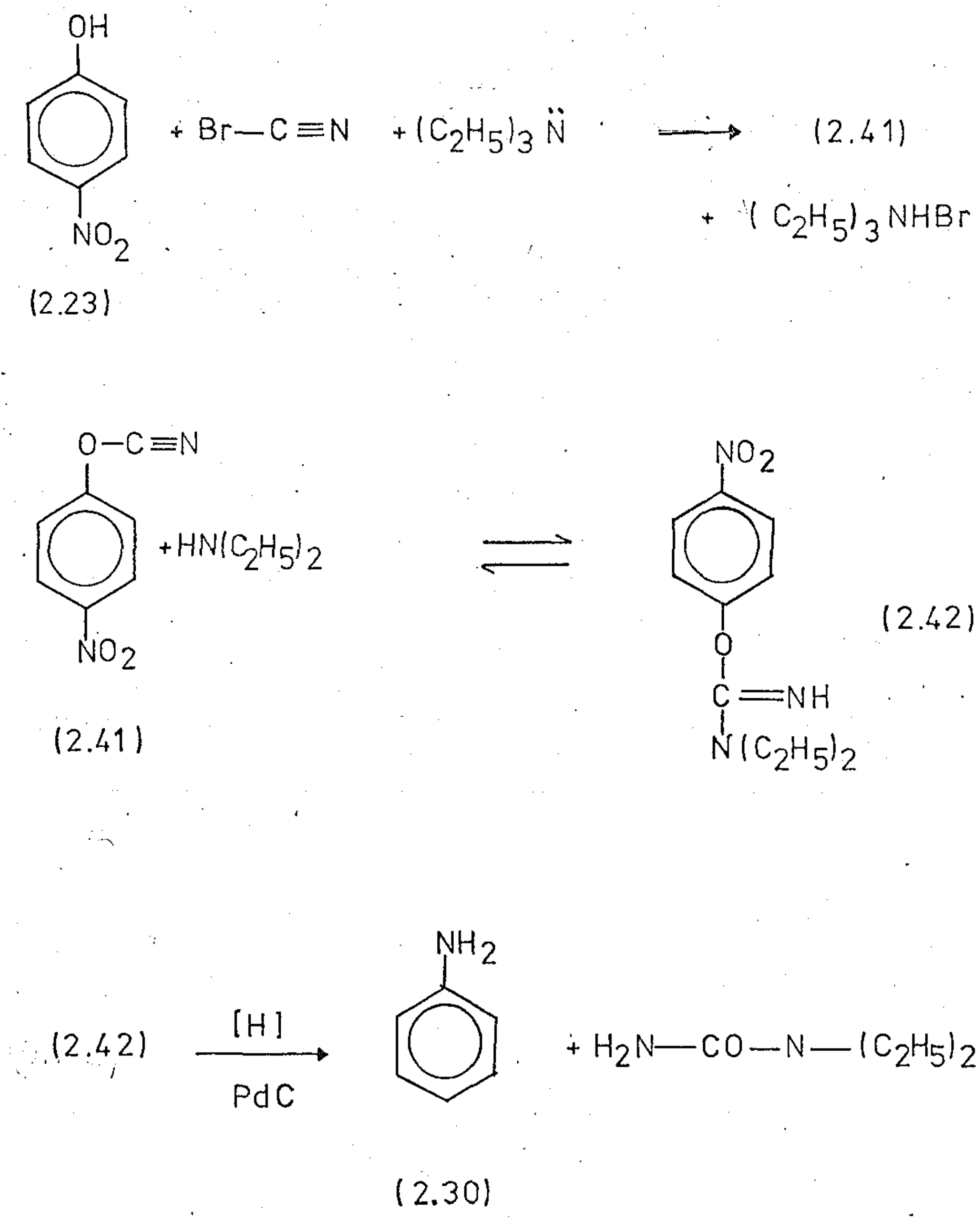
A second procedure used by Vowinkel,[57] illustrated in Scheme 2.10, was rejected on the basis of yield. For the reaction using p-nitrophenol Vowinkel had obtained the compounds (2.41), (2.42) and (2.30) in 92, 57 and 52% yields respectively. Assuming these yields could have been repeated, then the overall yield for conversion of p-nitrophenol to aniline would have been only 27.3%

Finally, after a long period of frustration, a procedure[58] was brought to our attention which ended our anxiety and gave consistently high yields in the conversion of p-nitrophenol to aniline. The method, shown in Scheme 2.11, involves the reaction of p-nitrophenol with methane sulphonyl chloride which gave the aryl sulphonate (2.43) in an almost quantitative yield (97.7%) as a white crystalline compound, mp. 92-94° (ethanol), (lit.[58b] 93-93.5°).

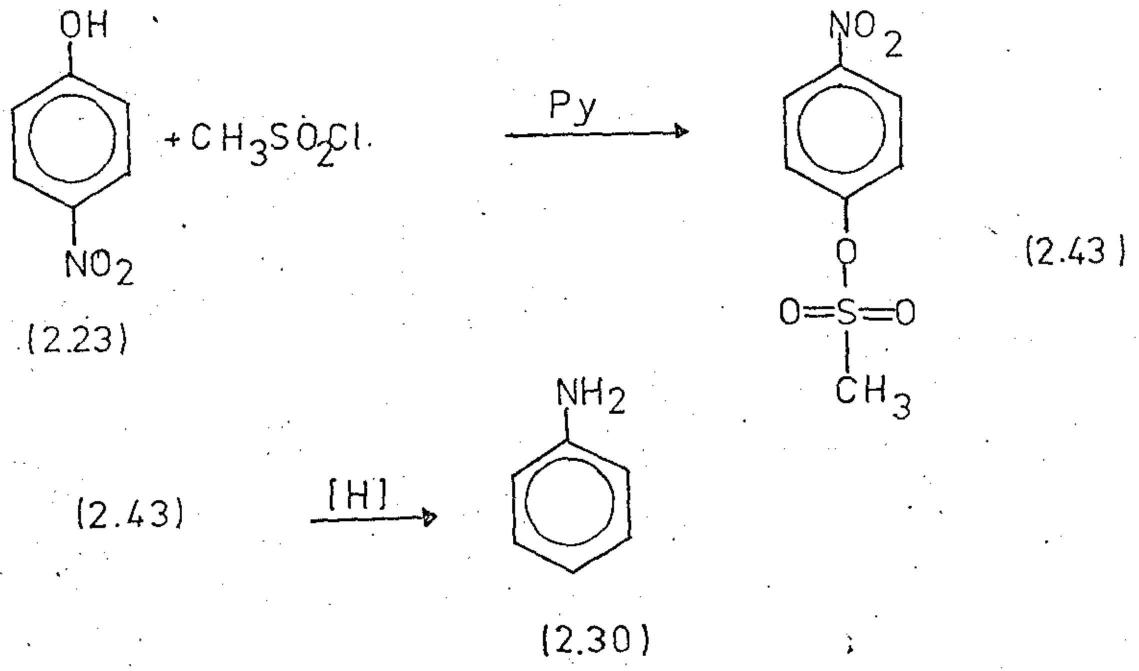
Reduction of the p-nitrophenylmethane sulphonate (2.43) in methanol containing triethylamine, PdC(5%) and hydrogen at atmospheric pressure, gave aniline in 65% yield.

The three routes discussed all involve as the major step a reductive cleavage of an aromatic C-O bond. The ability of this bond to break in the compounds (2.27), (2.38) and (2.43), as opposed to breaking of the bond leading back to starting materials, requires a

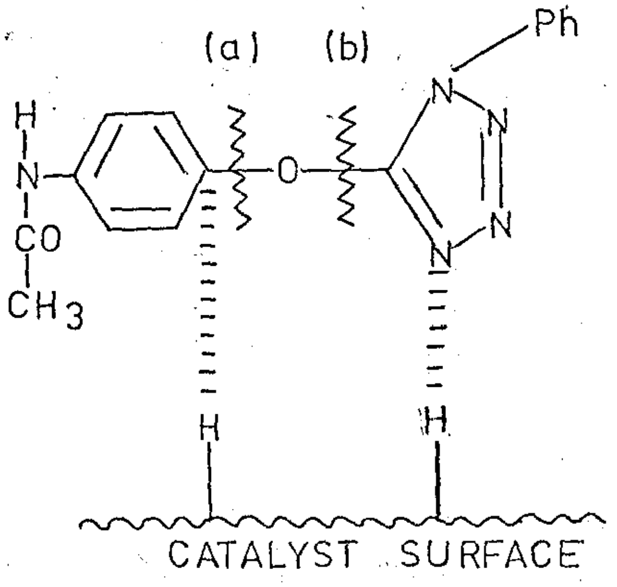
Scheme 2.10

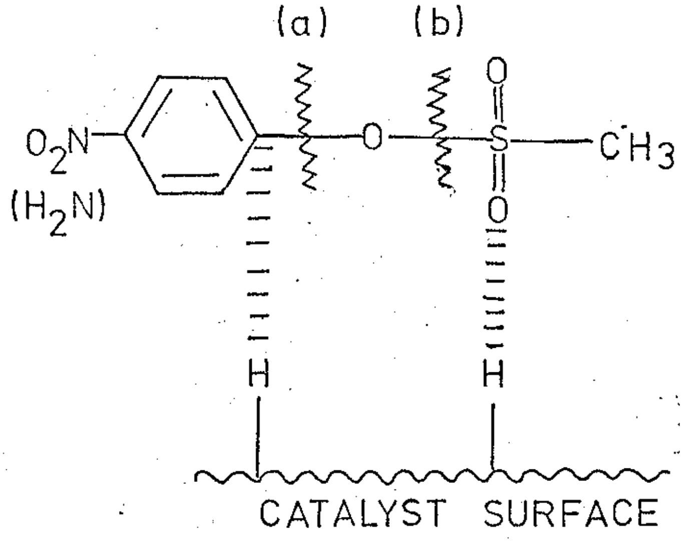

OH
NO2
(2.23)
+ Br—C≡N
+ (C2H5)3 N
(2.41)
+ (C2H5)3 NHBr
O—C≡N
+HN(C2H5)2
NO2
(2.41)
NO2
O
C=NH
N(C2H5)2
(2.42)
(2.42)
[H]
PdC
NH2
(2.30)
+ H2N—CO—N—(C2H5)2

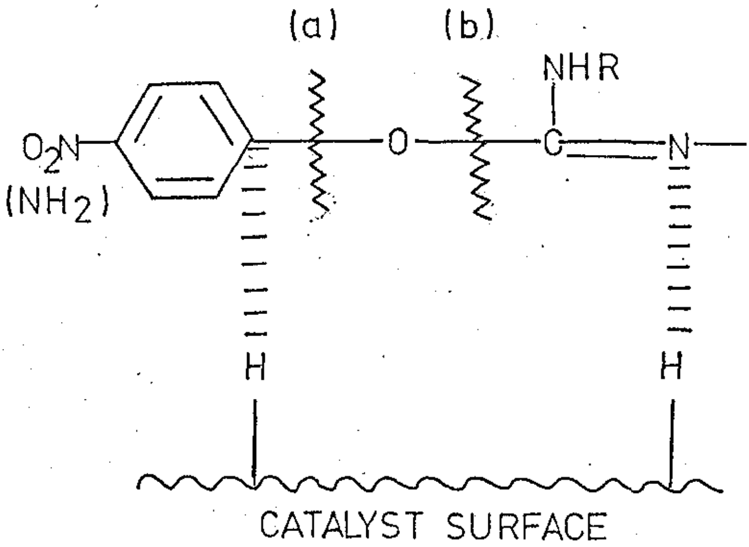
Scheme 2.11


OH
NO2
+ CH3SO2Cl
Py
NO2
O
O=S=O
CH3
(2.23)
(2.43)
(2.43)
[H]
NH2
(2.30)

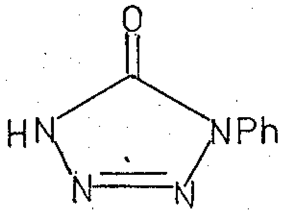
significant driving force. Presumably the reduction can be represented, in all three cases, as proceeding via the six membered transition states illustrated.


(a)
(b)
Ph
H
N
CO
CH3
O
N
N
N
N
H
H
CATALYST SURFACE


(a)
(b)
O_2N
(H_2N)
O
S
O
O
CH_3
H
H
CATALYST SURFACE


(a)
(b)
NHR
O_2N
(NH_2)
O
C
N
R
H
H
CATALYST SURFACE

Which side of the oxygen cleaves, either (a) or (b), in the above three proposed transition states will be dependent upon the stability of the products formed. Previous work[51,57,58] indicates that the compounds illustrated are cleaved to the required product (2.28) or (2.30), and therefore the formation of the other products (2.29), (2.38) and (2.44) must be an important part of the 'driving force' for the respective reactions.

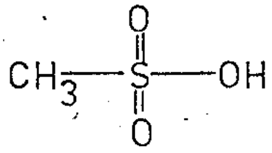


(2.29)

$R{-}NH{-}CO{-}NH{-}R$

(2.38)

$R = C_6H_{11}$



$CH_3{-}S(=O)_2{-}OH$

(2.44)

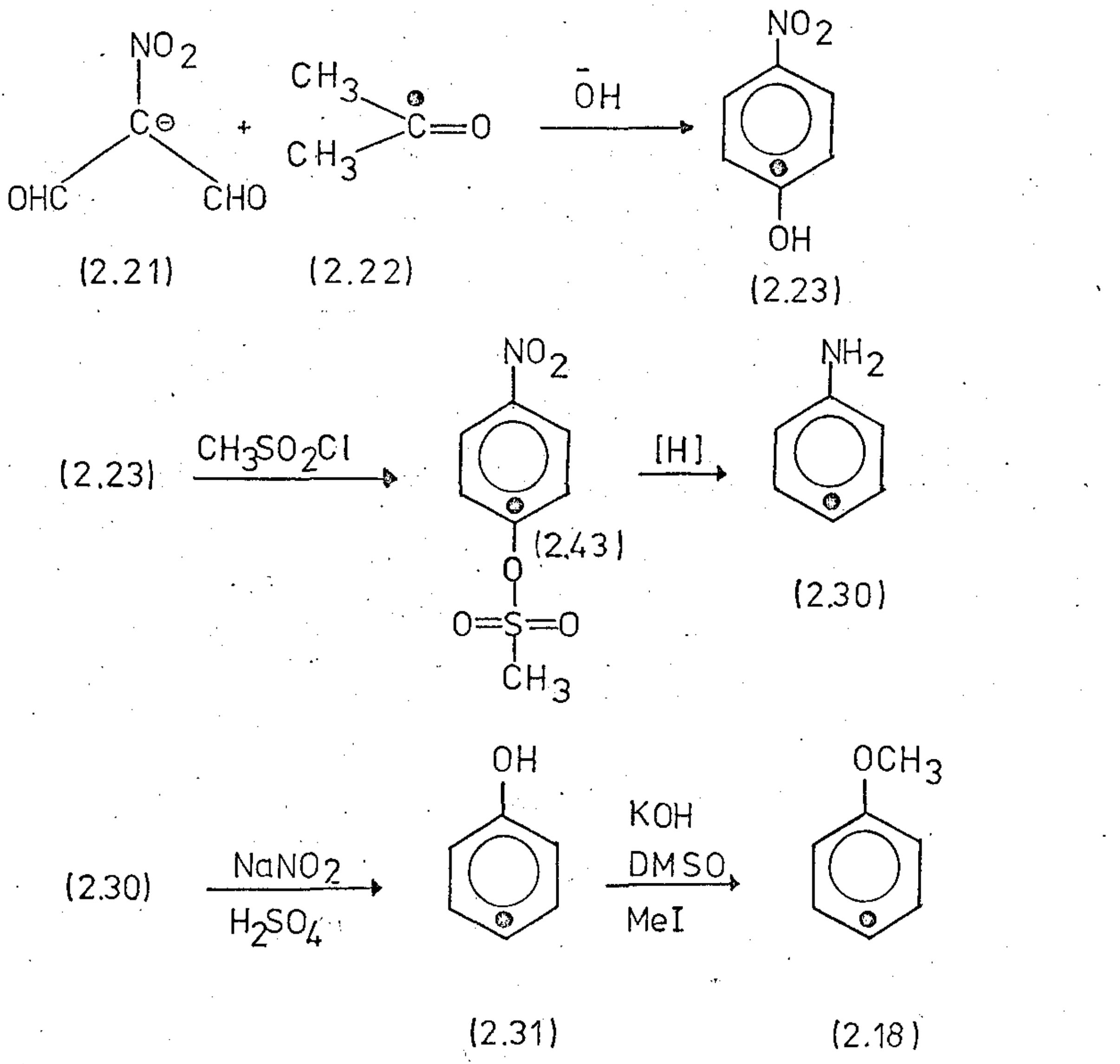
From the results of our investigations, it would appear that the reduction of the compound (2.43) to the two products (2.30) and (2.44) is easier than for the corresponding reductions of the compounds (2.27) and (2.37). The ease of the reduction of the aryl sulphonate (2.43) over the compounds (2.27) and (2.37) may be due to a steric factor. The approach of the aryl sulphonate to the catalyst surface is sterically less hindered, and thus less stringent conditions are required to enable the reduction to proceed.

The most attractive point about this procedure was that it reduced the five step synthesis, as used by Kratzl and Vierhapper[51] for converting p-nitrophenol to aniline to only two simple steps. Not only was there a substantial time saving factor but also a repeatedly consistent yield.

The aniline obtained from the reduction of the aryl sulphonate (2.43) was treated with sodium nitrite and concentrated sulphuric acid, under standard diazotisation conditions, to form phenol (2.31). Methylation using potassium hydroxide, dimethylsulphoxide and methyliodide gave the required anisole (2.18) in 80% yield.

Thus, after a careful investigation, a procedure was now available with which $[2-^{14}C]$-acetone would be converted to $[4-^{14}C]$-anisole in good yield and with a high degree of certainty. The complete procedure is depicted in Scheme 2.12.

Scheme 2.12


NO2
OHC
CHO
CH3
CH3
C=O
OH
NO2
OH
(2.21)
(2.22)
(2.23)
(2.23)
CH3SO2Cl
NO2
[H]
NH2
(2.43)
O=S=O
CH3
(2.30)
(2.30)
NaNO2
H2SO4
OH
KOH
DMSO
MeI
OCH3
(2.31)
(2.18)

During the preparation of [4-^{14}C]-anisole, none of the intermediates were isolated in a pure form. The crude reaction product was always used, in the following step, in order to minimise losses.

Crude [1-^{14}C]-*p*-nitrophenol (2.23) was isolated as a brown crystalline solid, in *ca.* 65% yield. In order to confirm that this product contained the ^{14}C label, a sample was counted. The starting [2-^{14}C]-acetone contained a specific activity of 10 μ.Ci. (micro-curies) per m. mol., and since this value is not affected by yield, it was expected that the *p*-nitrophenol would have a similar value. However, the specific activity of the [1-^{14}C]-*p*-nitrophenol was calculated to be *ca.* 5.78 μ.Ci. per m. mol. This difference could be explained by one or more of the following factors:-

(i) The phenol (2.23) was in a crude form.

(ii) The total activity of the acetone had not been transferred to the unlabelled acetone during the initial dilution procedure.

(iii) The vials obtained from the Radiochemical Centre had not contained the activity specified.

Fourtunately the activity of the phenol (2.23) was still high enough for the purpose for which it was required. Therefore the phenol (2.23) was subjected to the series of reactions shown in Scheme 2.12. [4-^{14}C]-anisole was obtained as a crude orange oil. It was not possible to obtain an accurate measurement of the specific activity of the anisole due to the difficulty of weighing liquids accurately on a microgram scale. A rough estimate of the specific activity indicated that, as expected, the value was similar to that obtained for the crude phenol (2.23).

Disappointingly, the overall yield of $[4-^{14}\mathrm{C}]$-anisole (0.6g, 11.1%) was low, particularly after the long and careful investigations carried out on this aspect. An overall yield, based on the procedure illustrated in Scheme 2.12, of ca. 20% had been expected as a result of the yields obtained using unlabelled compounds to check the possibility of the synthesis.

However, at this stage of the investigation no problems were foreseen, regarding this low yield, since the active anisole was to be diluted to a suitable volume with unlabelled anisole. This dilution factor was to be dependent on the results of the next stage of our investigation, the preparation and rearrangement of $[4-^{14}\mathrm{C}]$-1-methoxytetrafluorobenzobarrelene (2.1) to $[^{14}\mathrm{C}]$-tetrafluorobenzobarrelenone (2.4) and the degradation of this ketone.

Preparation of $[4-^{14}\mathrm{C}]$-1-methoxytetrafluorobenzobarrelene (2.1) and rearrangement.

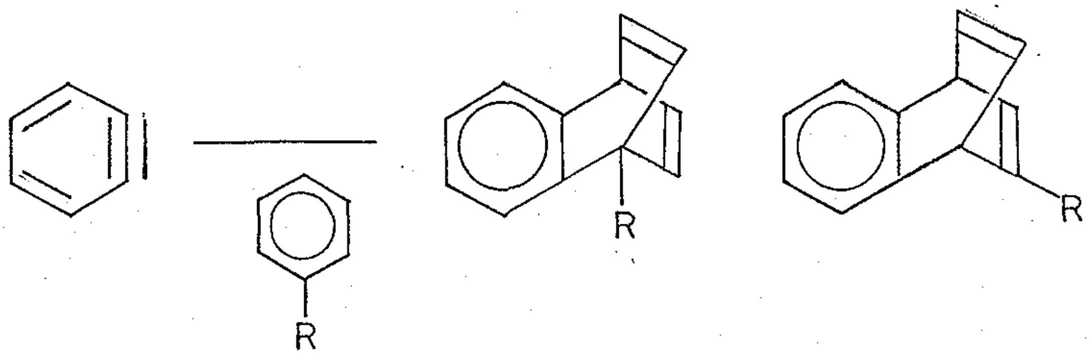
The Diels-Alder reaction between tetrafluorobenzyne and anisole to yield 1-methoxytetrafluorobenzobarrelene (2.1) has been investigated in some detail.[20c] Unfortunately these investigations have always used a large excess of anisole to facilitate a high yield of the required product (2.1). This would not be the case in the experiments using the labelled anisole due to the small volume expected after dilution. Normal procedures use ca. 22M. excess of anisole to attain yields of 50 - 70% of the required adduct.

It was calculated that the maximum dilution of the active anisole would be to a final volume of ca. 15ml. It was also estimated that a minimum weight of ca. 2g. of the 1-methoxytetrafluorobenzobarrelene would be necessary in order to carry out the rearrangements and degradation of the resultent tetrafluorobenzobarrelenones (2.4). We decided to investigate the possibility of using a mole to mole equivalent of anisole to tetrafluorobenzyne precursor and also an excess of the benzyne precursor.

The procedure investigated is illustrated in Scheme 2.2. and involves the reaction of bromopentafluorobenzene (2.15) with magnesium in dry ether to form the Grignard product (2.16). Addition of anisole in cyclohexane followed by a period of reflux causes the compound (2.16) to decompose to tetrafluorobenzyne (2.17) which undergoes cycloaddition with the anisole. Reactions involving a large excess of anisole result in two isolable products from the cycloaddition of the aryne (2.17) and anisole; The major product is the required 1-methoxytetrafluorobenzobarrelene (2.1) and the minor product tetrafluorobenzobarrelenone (2.4) isolated in ca. 5% yield.

It is known that the reaction of an aryne with a substituted arene can lead to a mixture of isomeric products. The ratio of this mixture is normally dependent on the substituent or substituents present. Mono-alkylbenzenes give both possible Diels-Alder adducts but the product with the more substituted double bond usually predominates.[12]

Di- and poly-substitution produces mixtures of products where this is possible, and although the formation of an adduct with two bridgehead substituents is completely avoided if possible, this can be accomplished by the reaction of either tetrafluorobenzyne or tetrachlorobenzyne with hexamethylbenzene.[12]

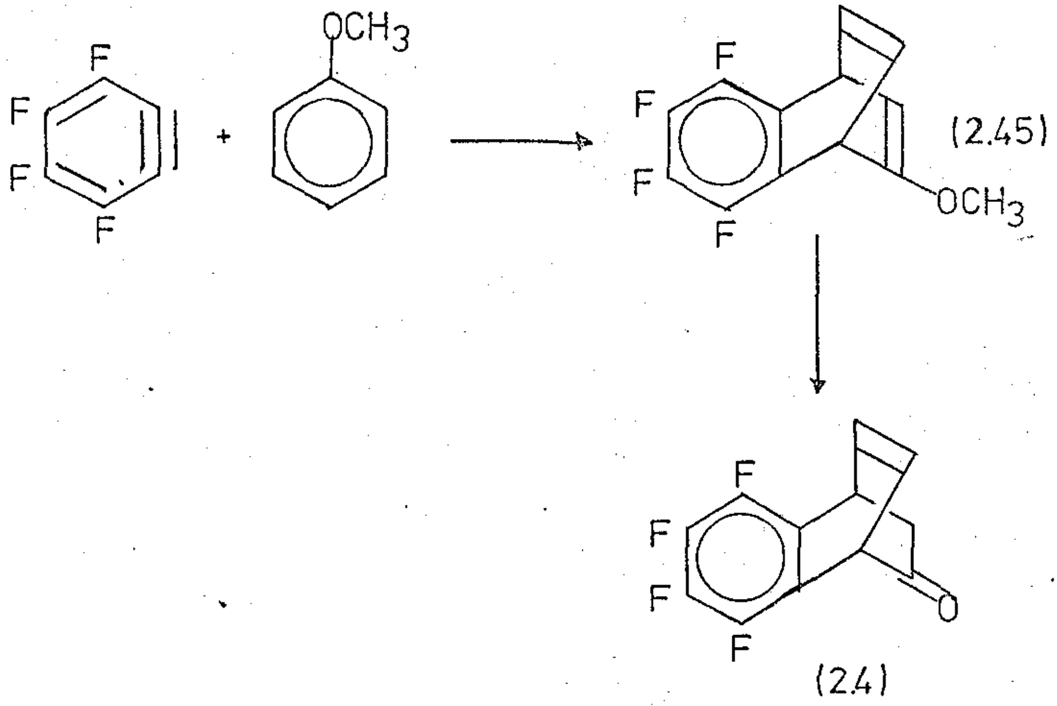


Ethers and dimethylamino-groups[20] direct the addition across the 1,4-positions, but again a para-substituent directs the addition towards the 2,5-(≡ 3,6)-positions whether the para-substituent is an alkyl group or an additional ether group.[12]

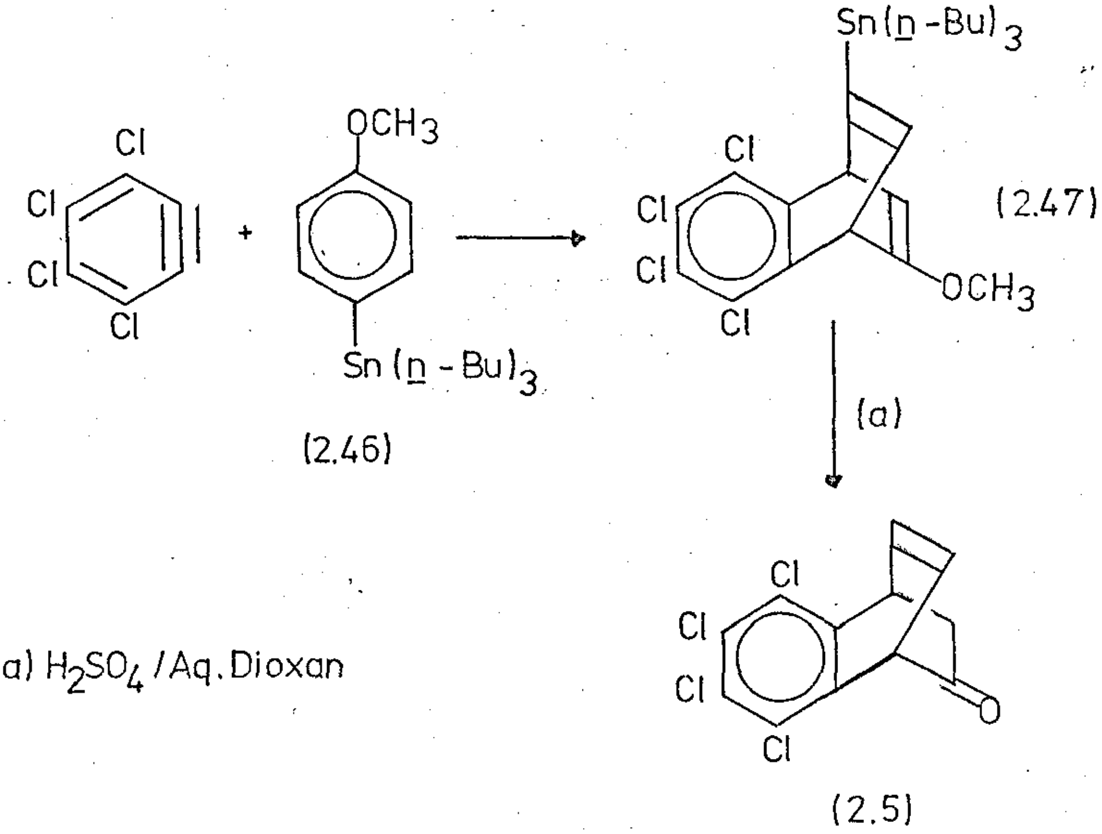
Thus it is reasoned that the minor product, in the reaction between tetrafluorobenzyne and anisole, is formed by cycloaddition across the 2,5-(≡ 3,6)-positions to give the enol ether (2.45) which hydrolyses to the ketone (2.4) during the reaction procedure as shown in Scheme 2.13.

Recently[20e] in this laboratory a stable enol ether (2.47) has been prepared by the reaction of tetrachlorobenzyne and tri-n-butyl-(4-methoxyphenyl) tin (2.46). Hydrolysis of the enol ether (2.47) with sulphuric acid in aqueous dioxan yields the ketone (2.5). Scheme 2.14 illustrates this procedure.

Scheme 2.13

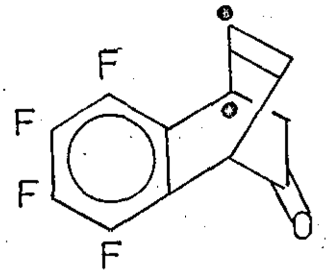

F
F
F
F
+
OCH$_3$
F
F
F
F
(2.45)
OCH$_3$
F
F
F
F
O
(2.4)

Scheme 2.14

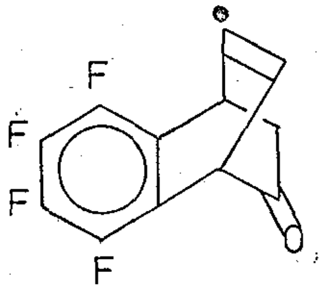

Cl
Cl
Cl
Cl
+
OCH$_3$
Sn(n-Bu)$_3$
(2.46)
Sn(n-Bu)$_3$
Cl
Cl
Cl
Cl
(2.47)
OCH$_3$
(a)
Cl
Cl
Cl
Cl
O
(2.5)

(a) H_2SO_4 / Aq. Dioxan

The reason for our interest in the minor product, tetrafluorobenzobarrelenone (2.4), was that in the proposed reaction between tetrafluorobenzyne and [4-^{14}C]-anisole the ketone (2.4c) would contain the ^{14}C label only in C-5. This was in contrast to the expected scrambling of the ^{14}C label between C-4 and C-5 in the ketone (2.4a) or (2.4b) from the rearrangement of the [4-^{14}C]-1-methoxytetrafluorobenzobarrelene (2.1). Hence, it was desired to isolate and degrade both labelled ketones and analyse the results accordingly.



(2.4a)
or
(2.4b)



(2.4c)

This desire was not to be attained since after a careful investigation of the procedure, shown in Scheme 2.2, on a small scale, only the required 1-methoxytetrafluorobenzobarrelene (2.1) could be isolated and not the ketone (2.4c). Excess of anisole was removed by distillation and the compound (2.1) isolated from the residue by preparative thin layer chromatography. The recovered anisole was used in further reactions until a sufficient quantity of the compound (2.1), ca. 2-3g., had been obtained.

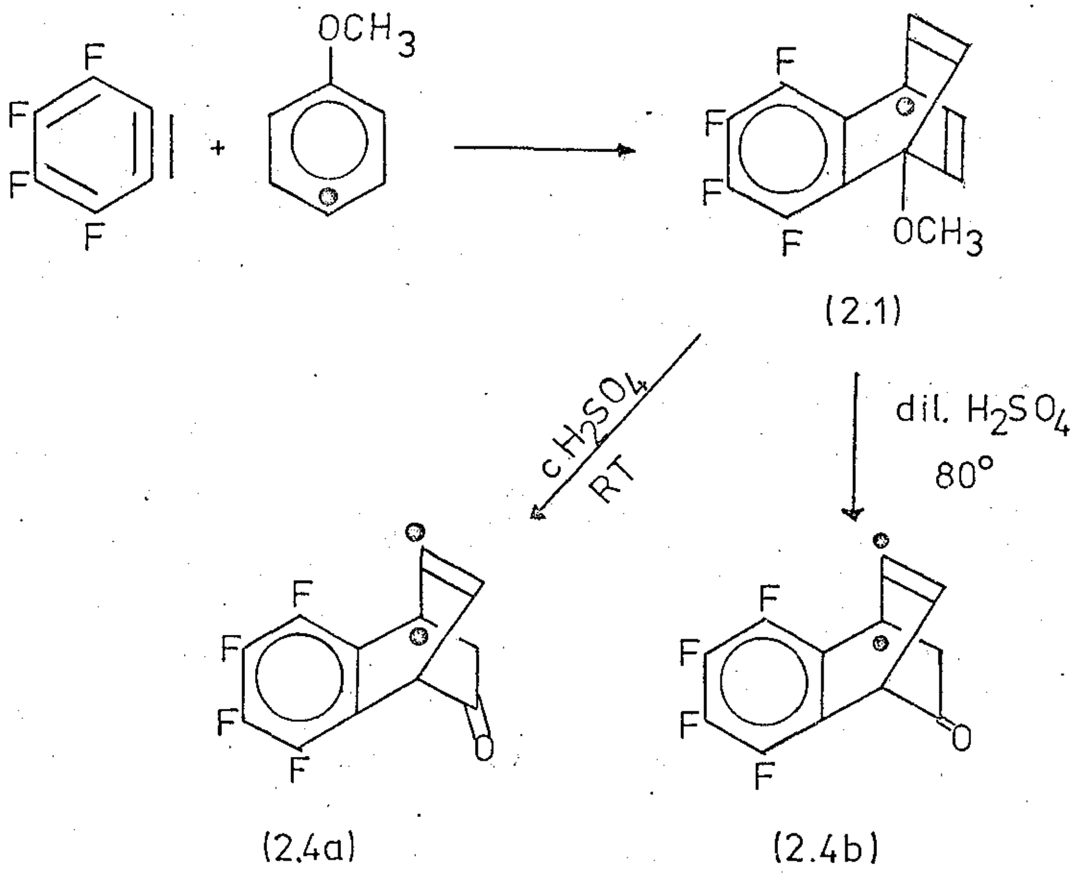
Attention was now directed at the acid catalysed rearrangement of 1-methoxytetrafluorobenzobarrelene to the three isomeric ketones

(2.4), (2.7) and (2.10), as illustrated in Scheme 2.1. The procedure for this rearrangement has been well established.[20c] The compound (2.1) ca. 1g was treated with concentrated sulphuric acid (98%) in one experiment at room temperature and in a second experiment with dilute sulphuric acid (H_2SO_4:H_2O, 4:1, $^v/_v$.) at 80°. In both experiments the mixture was shaken (ca. 3min.) until a clear solution was obtained. The solutions were separately quenched with ice and the tetrafluorobenzobarrelenone (2.4) isolated, in each case, by ether extraction followed by preparative thin layer chromatography. The ketone (2.4) was recrystallised (ethanol) and identified by comparison with authentic material.[20c]

It was now assumed that the [4-^{14}C]-anisole could be converted to the [4-^{14}C]-1-methoxytetrafluorobenzobarrelene (2.1) and this rearranged under the two sets of conditions to yield an acceptable quantity, ca. 500-600mg., of the [^{14}C]-tetrafluorobenzobarrelenones (2.4) for subsequent degradation. The ratio of the ^{14}C label in C-4 and C-5 of the ketone (2.4a) from the rearrangement in concentrated sulphuric acid and the ketone (2.4b) from the rearrangement in dilute sulphuric acid was expected, on the basis of previously discussed work, to be different.

The ultimate step in this investigation was to devise a degradation scheme which would allow the activity in C-4 and C-5 of the two ketones (2.4a) and (2.4b) to be separately calculated.

The investigation of potential degradation routes required substantial amounts of the ketone (2.4) which were not easily obtainable by the rearrangement procedure using sulphuric acid. Fortunately

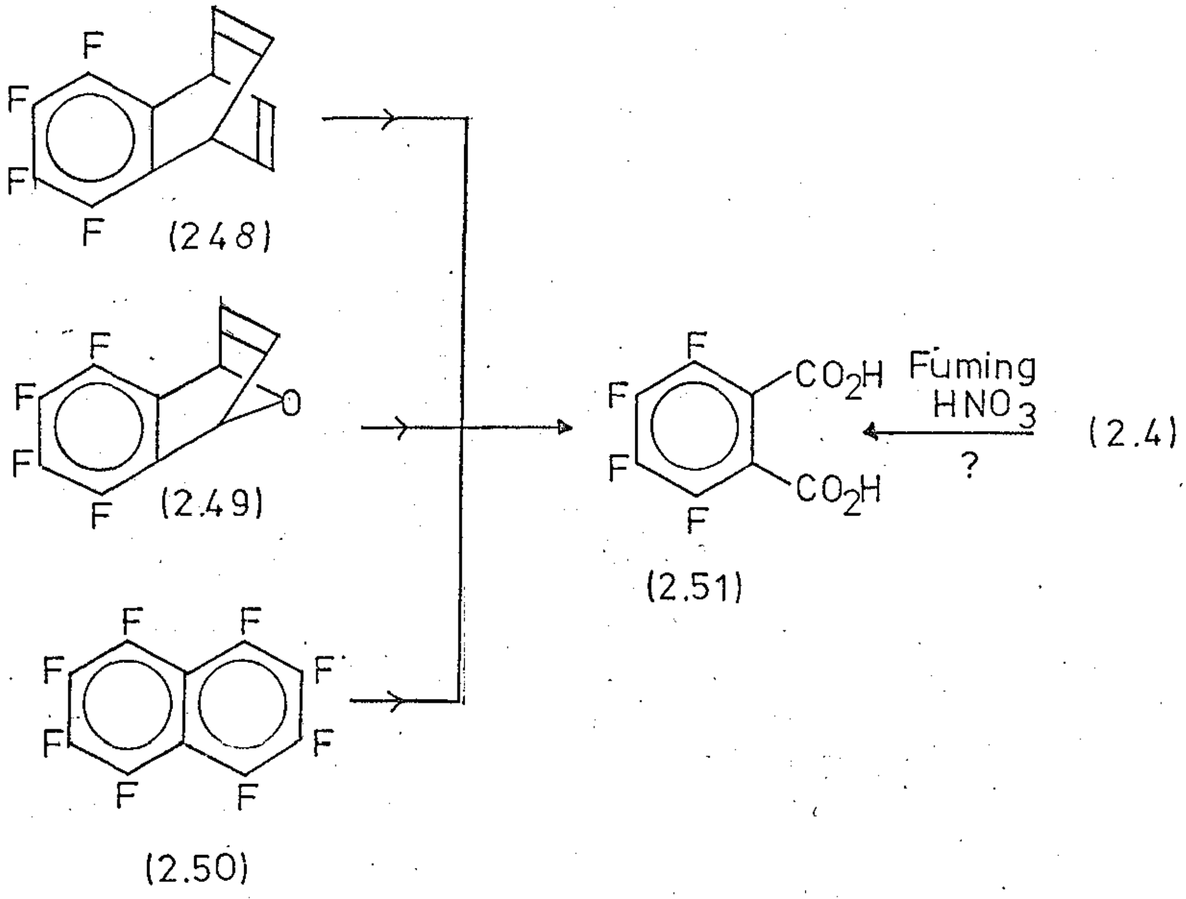


rearrangement of the product (2.1) in fluorosulphonic acid gives tetrafluorobenzobarrelenone (2.4), in ca 90% yield, after recrystallisation of the crude reaction mixture.

Degradation of Tetrafluorobenzobarrelenone (2.4)

The ability[59] of fuming nitric acid to oxidise compounds such as (2.48) - (2.50) to tetrafluorophthalic acid (2.51), as shown in Scheme 2.15, gave high hopes to a quick solution to the degradation problem. It seemed reasonable to assume that under similar oxidising conditions the ketone (2.4) would also be oxidised to the acid (2.51).

Scheme 2.15


(2.48)
(2.49)
(2.50)
(2.51)
(2.4)
Fuming HNO3
?
CO2H
CO2H
F

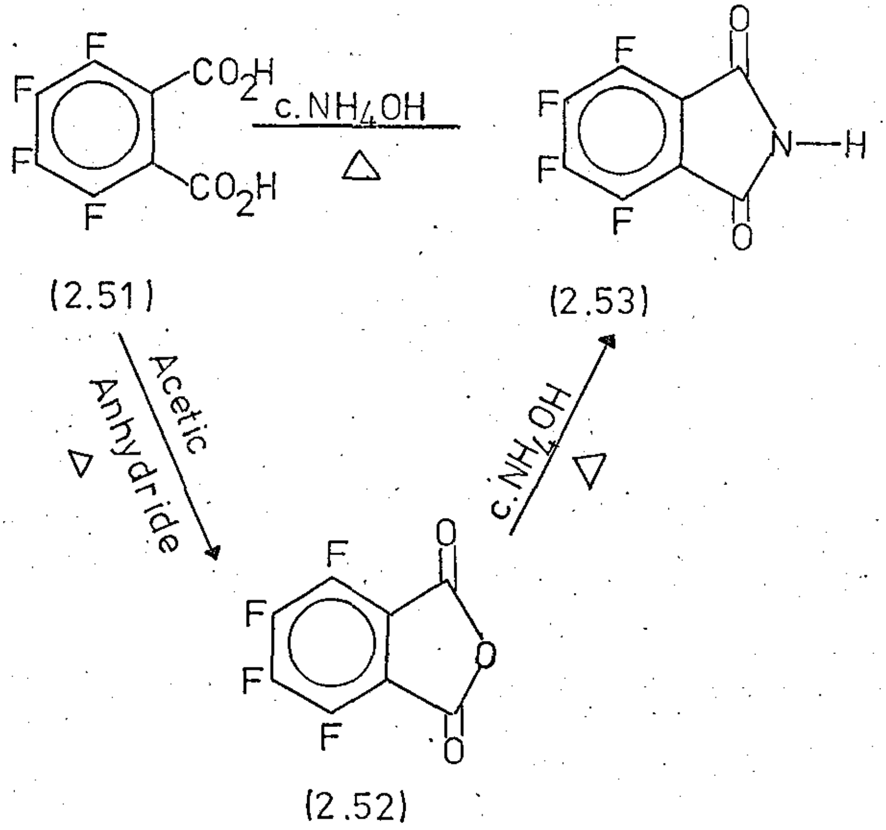
The advantages of using this oxidation procedure were:-

(i) The procedure was normally simple[59] and the isolation of the acid (2.51) easy.

(ii) Although the acid (2.51) was not suitable for accurate ^{14}C counting purposes due to the presence of tetrafluorophthalic anhydride (2.52), it has been shown[59] that the acid (2.51) can be converted either directly or indirectly to the very stable tetrafluorophthalimide (2.53). The two routes are illustrated in Scheme 2.16.

(iii) The imide (2.53) can be easily purified by sublimation.

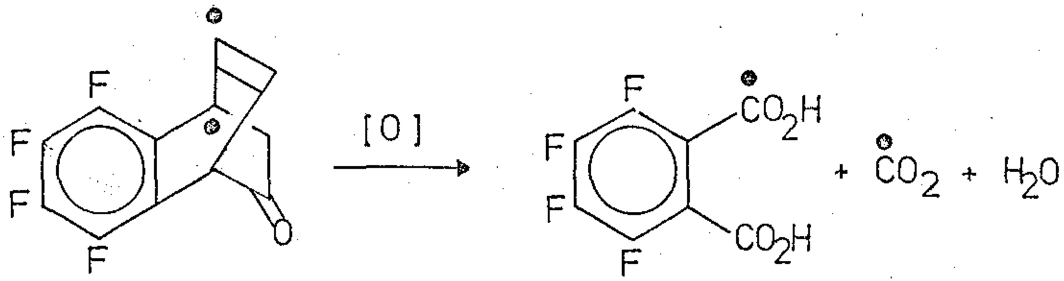
Scheme 2.16



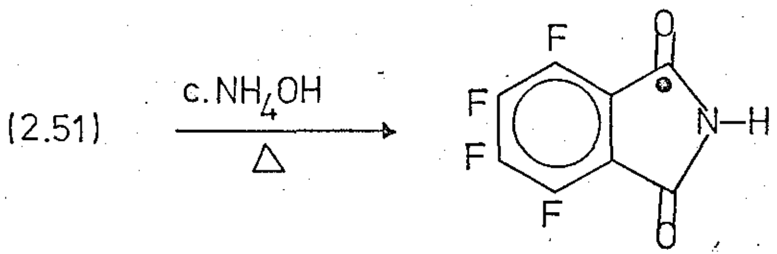
F
F
F
F
CO_2H
CO_2H
(2.51)
$c. NH_4OH$
Δ
F
F
F
F
O
N—H
O
(2.53)
Acetic Anhydride
Δ
$c. NH_4OH$
Δ
F
F
F
F
O
O
O
(2.52)

The major disadvantage with this procedure was that one of the labelled carbons /C-5 in (2.4)/ would be lost during the oxidation step. The deuterium labelling results[20c] predicted that C-5 would contain the major share of the ^{14}C label in both ketones (2.4a) and (2.4b).

However, the imide (2.53) would contain all the original C-4 label and since the activity of this compound and the ketone (2.4) would be known accurately, a simple calculation by difference would furnish the activity in the lost C-5.



(2.4) (2.51)



(2.53)

A number of attempts were made to oxidise the ketone (2.4) with fuming nitric acid. The general procedure involved heating the ketone (2.4) under reflux in fuming nitric acid for one week. Work-up of the reaction mixtures led to varied results. White crystalline compounds were normally obtained, but only on one occasion did the analytical data compare favourably with authentic acid (2.51).[59] The yields ($^{wt}/_{wt}$) of the unknown products varied from quantitative to ca. 10% The melting points of the crystalline products were normally wide range ca. 140-180° (lit.[59] mp. 152-154°). The actual mechanism for oxidations using fuming nitric acid at reflux temperatures is not known, and is presumably complex. The results indicated that in most reactions a mixture was formed, and that perhaps an extended oxidation period would allow a higher proportion of the acid (2.51) to be isolated. The oxidation period was extended from one to two weeks, but once again, on work-up, a similar ill-defined crystalline product was obtained. The compound was not readily soluble in the normal crystallising solvents. Infra-red data were difficult to analyse, since most of the peaks were broad. A broad carbonyl stretching frequency ca. 1690-1730 cm^{-1}. and a broad hydroxyl stretching frequency ca. 3000 cm^{-1} were identified. ^{1}H.n.m.r. spectra indicated that no protons were present.

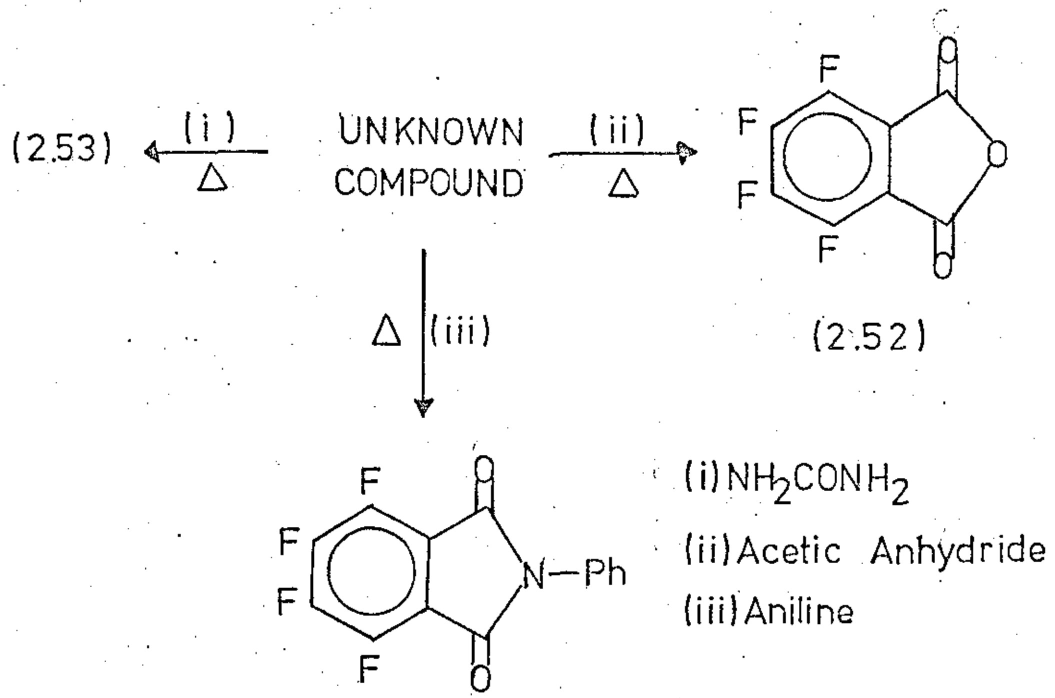
These results suggested that the tetrafluoro substituted aromatic ring was still intact and that a carboxyl group was possibly present.

It was reasoned that if any of the acid (2.51) was present in the unknown mixture then it might be feasible to convert this to the imide (2.53) and remove the latter by sublimation.

The unknown mixture was heated under reflux in concentrated ammonium hydroxide for ca. 3 hr., and the temperature was then allowed to rise slowly to ca. 240°. In a reaction using authentic acid (2.51) the residue after the heating period was sublimed to give the required imide (2.53) as yellow needles, mp. 206-209° (lit[59] mp. 210-211°). The residue obtained from the reaction of the unknown compound always resulted in an intractable tar which would not sublime.

In an endeavour to overcome this difficulty a number of variations of this technique, shown in Scheme 2.17, were tried.

Scheme 2.17



(i) NH_2CONH_2
(ii) Acetic Anhydride
(iii) Aniline

The reactions illustrated all met with failure giving neither a sublimable nor idendentifiable product. The combined results indicated that either the unknown compound/mixture contained very little of the required acid (2.51) or the presence of impurities were interfering with further reaction of the acid (2.51) present. The other compounds could be partially oxidised products, or nitrated products.

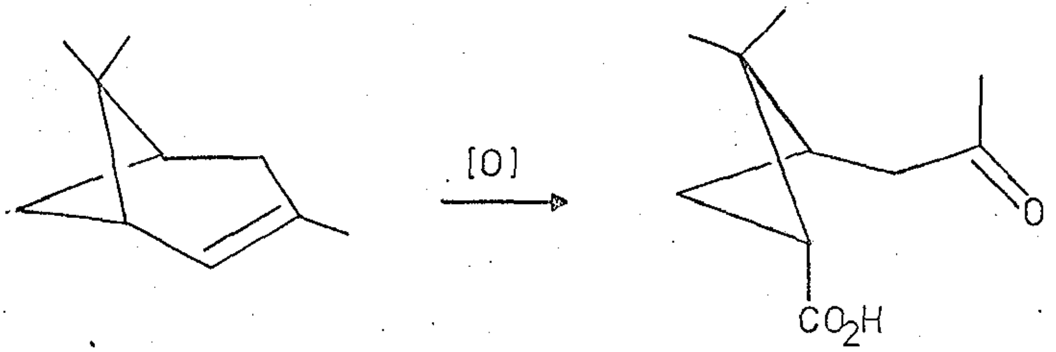
Thus it became obvious that the oxidation procedure using fuming nitric acid was not suitable for the degradation of the ketone (2.4).

Two alternative oxidising procedures were considered. The first involved treating a refluxing acetone solution of the ketone (2.4) with a saturated aqueous solution of potassium permanganate.[14d] This procedure sucessfully oxidises tetrafluorobenzobarrelene (2.48) to the acid (2.51). Treatment of the ketone (2.4) under these conditions resulted in the isolation of the starting ketone (2.4). A variation of this procedure using an alkaline solution (2N.NaOH)of the ketone (2.4) with saturated potassium permanganate solution also gave only recovered starting material.

The assumption that the oxidising agent, potassium permanganate, was not effective enough under the conditions used, diverted our attention to the second procedure in an endeavour to improve the oxidising ability of potassium permanganate.

This method involved the use of the crown ether dicyclohexyl-18--crown 6 (2.54). Since Pedersen's crowning gesture to the chemical world the chemistry surrounding the crown ethers has mushroomed.[60] The use of crown ethers with potassium permanganate has been particularly successful in increasing the yields of a number of oxidations.[60b] For example the aqueous potassium permanganate oxidation of α - pinene (2.55) gives cis-pinonic acid (2.56) in 40-60% yield. The use of the crown ether (2.54) in benzene with potassium permanganate increases the yield of the above oxidation to ca. 90%

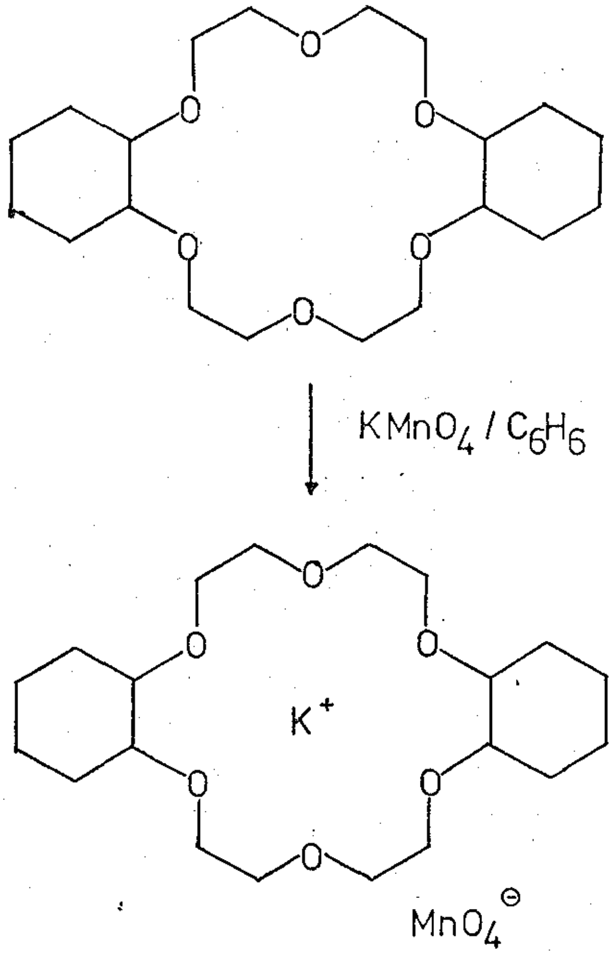
Potassium permanganate can be solubilized in benzene by complexing with the crown ether (2.54), to provide a convenient and efficient



(2.55) (2.56)

oxidant (2.57) for organic compounds under mild conditions. In the absence of the crown ether, potassium permanganate has no detectable solubility in benzene, and no reaction occurs with organic substrates. The products of the oxidation reactions are ketones or potassium salts of carboxylic acids. The potassium salts of the acids are usually insoluble in benzene and this is advantageous not only for product isolation but also because the salts are not subject to further oxidation.

The following procedure was used in an attempt to oxidise the ketone (2.4) to the tetrafluorophthalic acid (2.51). Potassium permanganate was added to a solution of benzene and dicyclohexyl-18-crown 6 (2.54). The solution immediately turned purple, an indication that the complex (2.57) had been formed. A solution of the ketone (2.4) in benzene was then added. The combined solution was stirred overnight, during which time the purple colour disappeared. Isolation



(2.54)

(2.57)

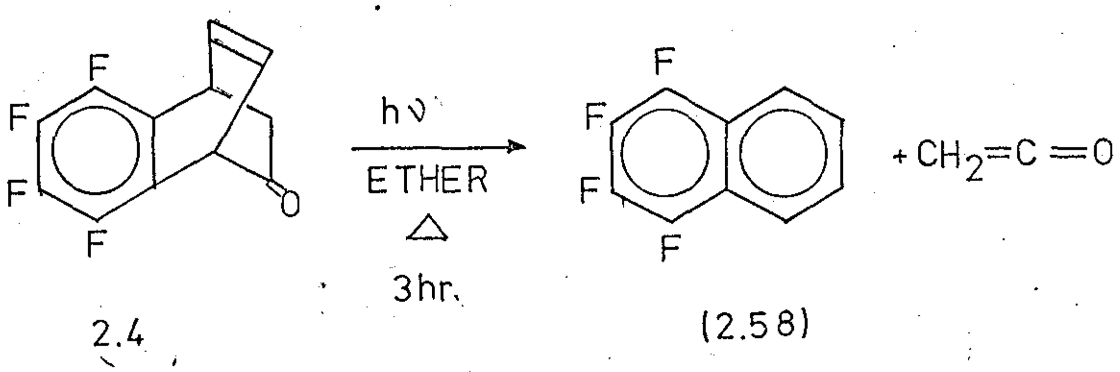
and analysis of the resultant product indicated that only a trace of the starting ketone (2.4) remained. However, it was not possible to obtain a product completely free of the crown ether. The major problem appeared to be the scale of the reaction, *ca.* 500mg. of ketone (2.4), on which we were operating.

The oxidation of tetrafluorobenzobarrelenone (2.4) to the required acid (2.51) was proving more difficult than originally expected. The ease of oxidising the compounds (2.48) - (2.50) and the difficulty of accomplishing the same oxidation with the ketone (2.4), seemed to imply that the presence of the carbonyl group was causing these difficulties.

The carbonyl group can be removed, as ketene, from ketones such as (2.4), by photolysis or thermolysis to the respective naphthalene.[20h] Since octafluoronaphthalene (2.50) had been oxidised to the acid (2.51),[59] it seemed a reasonable assumption that tetrafluoronaphthalene (2.58) would also undergo similar oxidation.

Thus, the ketone (2.4) was dissolved in ether and under dry, oxygen free nitrogen, was heated under reflux whilst being irradiated (Hanovia medium-pressure mercury vapour lamp, quartz flask) for 3hr.. Solvent was removed under reduced pressure to yield tetrafluoronaphthalene (2.58) in 90-100% yield. The procedure is shown in Scheme 2.18. The naphthalene (2.58) was identified by comparison with authentic material.

Scheme 2.18



Treatment of the naphthalene (2.58) with refluxing fuming nitric acid for one week gave, after work-up, a white crystalline solid, mp. 186-188°, infra-red spectra showed the following bands, 3100-2800 (broad), 1740 (broad), 1540, 1350 and 1270 cm^{-1}.

A second reaction gave white crystals, mp. 163-183°, after refluxing for one week. This compound was placed back into refluxing fuming nitric acid for a further week. Again a white solid was isolated, mp. 170-180° and with similar i.r. data to those of the first reaction.

The white solid obtained in these reactions was very similar to that isolated from the attempted oxidations of the ketone (2.4). Once again attempts to convert any of the acid (2.51) present to the imide (2.53), as previously described, met with little or no success.

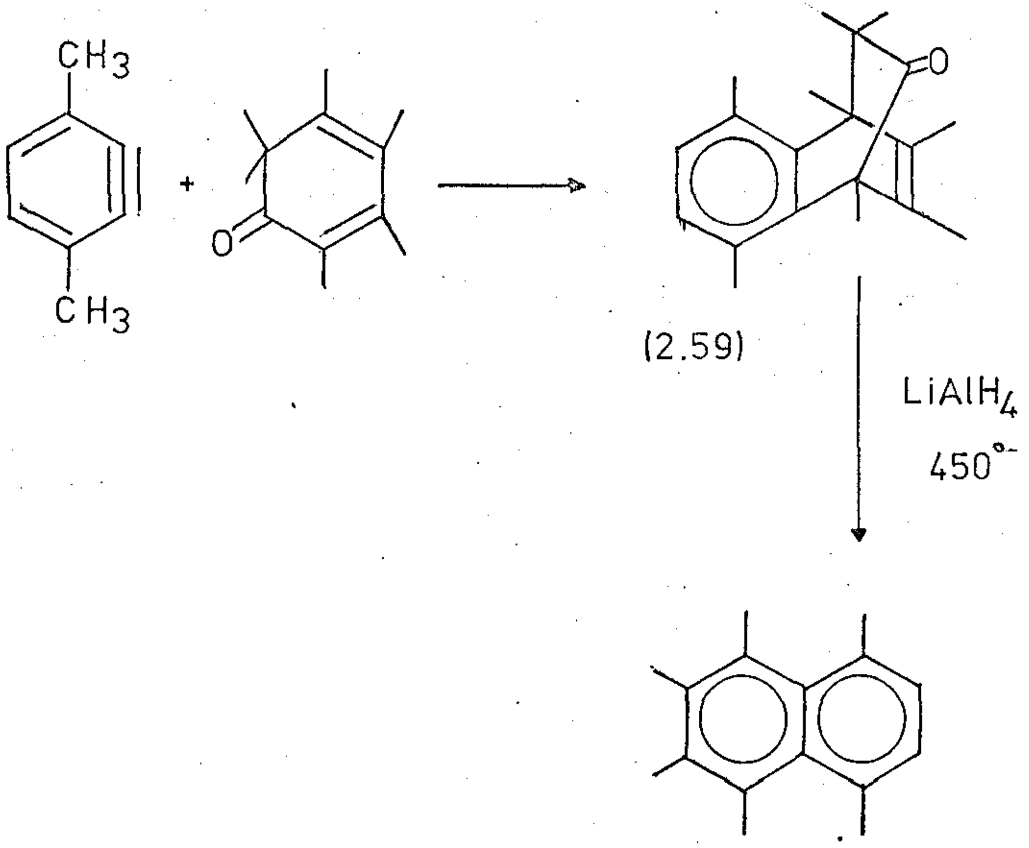
The lack of success of these oxidation attempts was considered to be due to the small scale on which we were operating, since the compounds (2.48)-(2.50) had been oxidised relatively easily. The products isolated from the various oxidations seemed to contain some of the required acid (2.51) but this could not be isolated or reacted further.

The necessity of devising a degradation procedure which gave consistent high yields led us to consider alternative procedures. It was also decided that consideration should be given to a procedure in which both of the labelled carbons in the ketone (2.4) would be isolated.

One consideration was to remove the etheno-bridge containing the labelled C-5, in ketone (2.4), via a cycloaddition - fragmentation process.

Such reactions involving a Diels-Alder or 1,3-dipolar cycloaddition to an active dienophile followed by a reverse Diels-Alder (retrodiene) reaction have been well established.[61,62] Relevant examples are:-

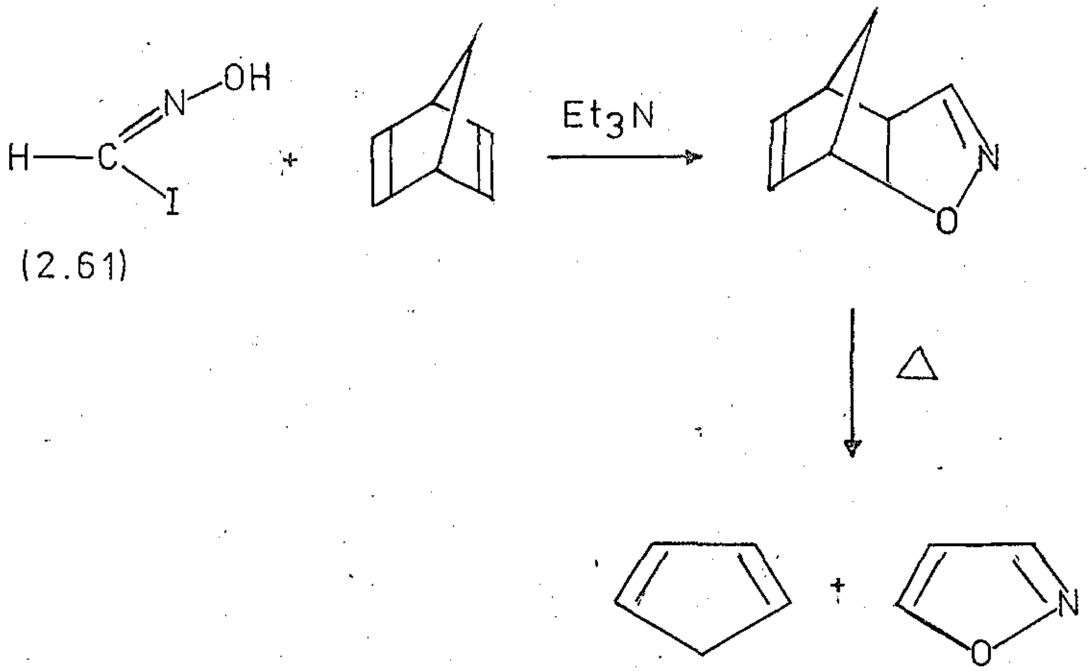
(i) The reverse Diels-Alder reaction of cyclohexadienone adducts may be used to prepare substituted naphthalenes.[62a] Addition of 3,6-dimethylbenzyne to hexamethyl-2,4-cyclohexadienone, prepared by oxidation of hexamethylbenzene,[62b] gave an adduct (2.59) which underwent a reverse Diels-Alder reaction at 450° to give 1,4,5,6,7,8-hexamethylnaphthalene (2.60) (17.8%) and recovered adduct (80%).



(2.59)

(2.60)

(ii) The 1,3-dipolar adduct of norbornadiene and fulminic acid, generated in situ by the dehydroiodination of the compound (2.61), *undergoes reverse Diels-Alder reaction* at 140-160° to give cyclopentadiene (2.62)and isoxazole (2.63) in 90% yield.[62c]

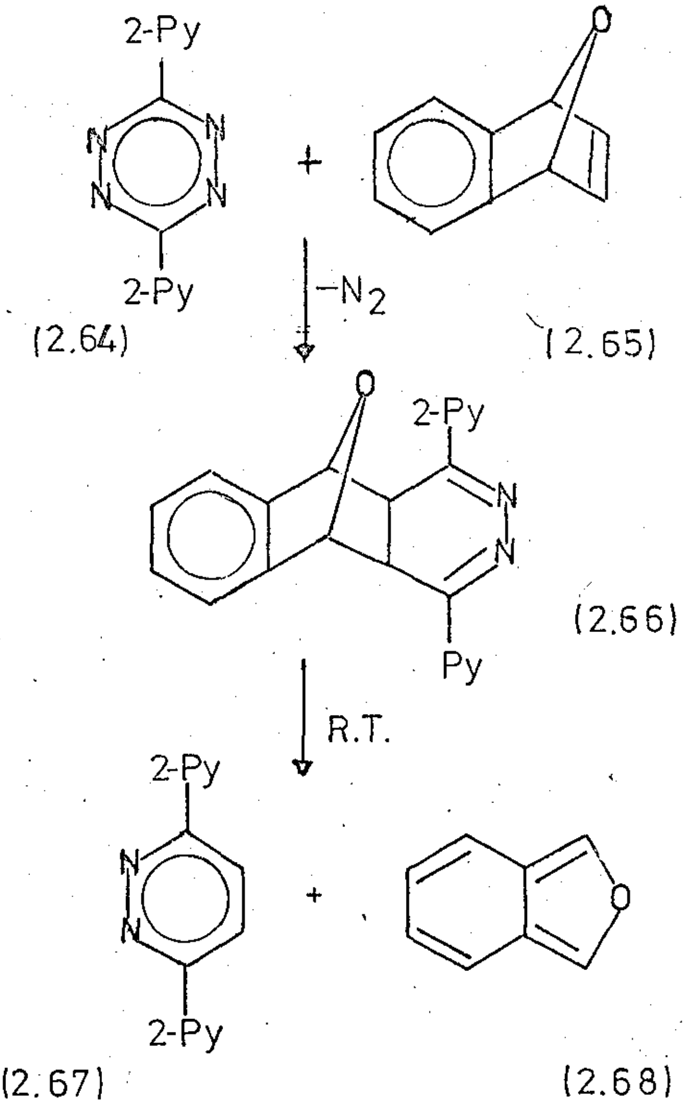


(2.61)

(2.62) (2.63)

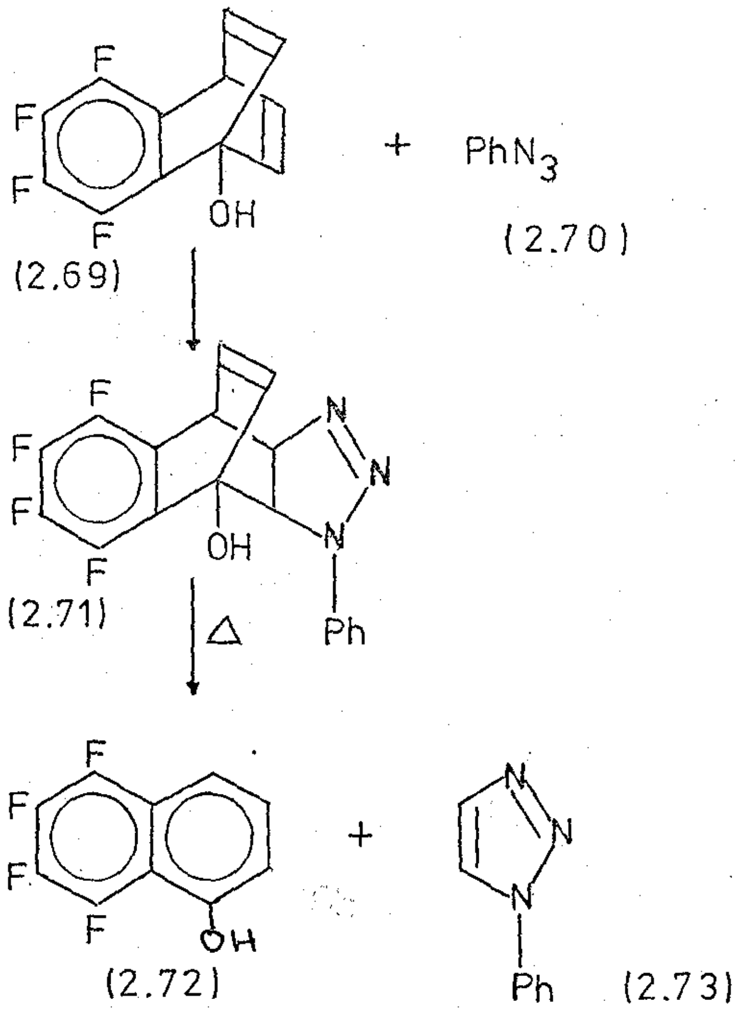
(iii) Reaction[62d] of a suspension of the tetrazine (2.64)[62e,f] with 1,4-dihydro-1,4-epoxynaphthalene (2.65) in dimethyl sulphoxide solution occurred rapidly at room temperature to precipitate the yellow dihydropyridazine derivative (2.66).

The derivative (2.66) decomposes rapidly to yield the pyridazine (2.67) and isobenzofuran (2.68).



(2.64) (2.65) (2.66) (2.67) (2.68)

(iv) Barkhash and Mikhailova[24] have investigated the reaction of 1-hydroxytetrafluorobenzobarrelene (2.69) with phenyl azide (2.70) to give the adduct (2.71). Fragmentation of the adduct (2.71) yields 1-hydroxytetrafluoronaphthalene (2.72) and the phenyl triazine (2.73)



(2.69) (2.70) (2.71) (2.72) (2.73)

There were two problems likely to interfere with this approach to the degradation of the ketone (2.4). Firstly, the etheno-bridge contains no electron withdrawing substituents generally associated with good dienophiles for cycloaddition reactions. However, this problem was not insurmountable as illustrated above (iii)-(iv). Linked with this problem is the correct choice of diene or dipolar species which not only allows the reaction to proceed to completion but also allows easy separation of the two products from the fragmentation.

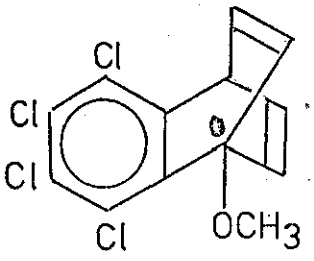
The second problem was of much greater significance and more likely to cause complications. This was the presence of the oxo-ethano-bridge in the ketone (2.4) which has been shown to be the more reactive of the two bridging groups.

Pyrolysis of benzobarrelenones gives naphthalene derivatives.[20h] The oxo-ethano-bridge is extruded by heating the ketone under reduced pressure at *ca.* 350°. The conditions required are if anything more severe than those required to extrude an etheno-bridge to form the same naphthalene.

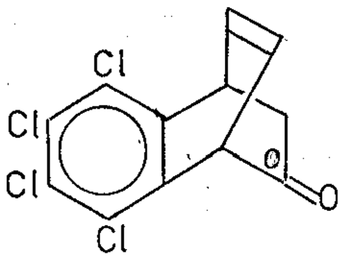
Photolysis of benzobarrelenones also leads ultimately to extrusion of the oxo-ethano-bridge.[20h]

Thus, it seemed most likely that attempts to form a cycloaddition product, with the ketone (2.4), followed by a retrodiene reaction would be greatly affected by the presence of the oxo-ethano-bridge.

The final blow to further considerations of this degradation procedure came from recent studies[20e,63] involving the preparation and potential degradation of $[1-^{14}C]$-1-methoxytetrachlorobenzobarrelene (2.2) and the $[^{14}C]$-tetrachlorobenzobarrelenone (2.5).



(2.2)



(2.5)

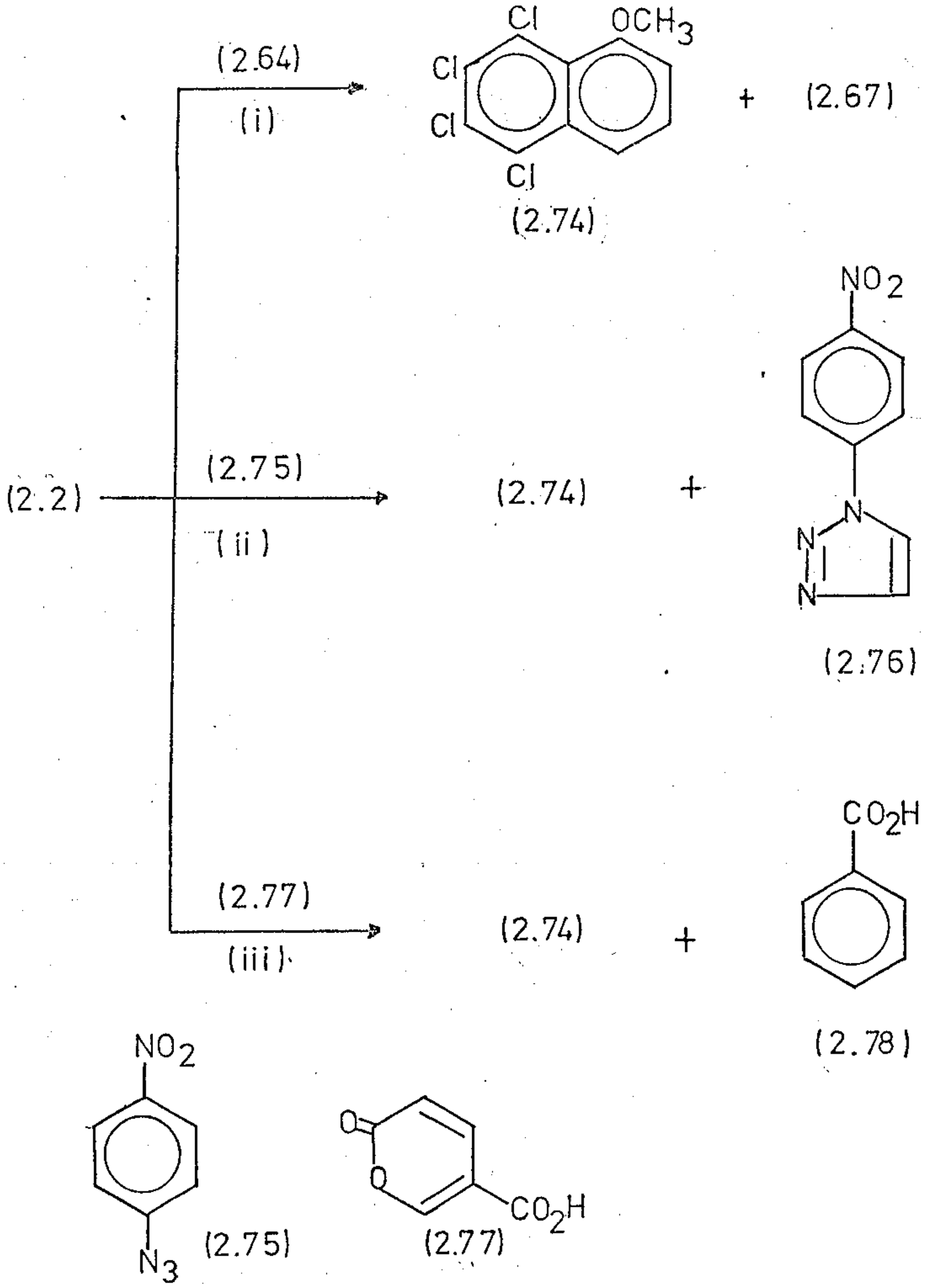
The two labelled products were degraded by an alternative procedure to cycloaddition-fragmentation but this latter procedure was investigated throughly with unlabelled material. The degradation of the unlabelled 1-methoxytetrachlorobenzobarrelene (2.2) was accomplished most successfully by either of the three procedures illustrated in Scheme 2.19. The ketone (2.5) was reacted with 3,6-di-(2'-pyridyl)-*s*-tetrazine (2.64) in the hope of forming the 3,6-di-(2'-pyridyl)-pyridazine (2.67) and the hydroxy-naphthalene (2.7~~1~~2), as illustrated in Scheme 2.20.

A complex mixture of products was obtained and although these products were not fully characterised, it was established, that the pyridazine (2.67) was not formed even though the tetrazine (2.64) had completely reacted. It was assumed that the proportion of the enol (2.79) present was very small and that other processes were intervening before this could fragment to the required products.

The failure of the adduct, formed from the reaction of the ketone (2.5) and the tetrazine (2.64), to fragment to the desired products left little doubt that a similar result would be obtained on using tetrafluorobenzobarrelenone (2.4).

Fortunately, the success of the work by Hales[20e,63] involving the degradation of 1-methoxytetrachlorobenzobarrelene (2.2), Scheme 2.19, gave a second route of attack to the problem of degrading the ketone (2.4). It seemed a reasonable assumption that the methoxy group did not play an important role in the procedure shown in Scheme 2.19 and therefore it was concluded that the related tetrafluorobenzobarrelene (2.80)

Scheme 2.19

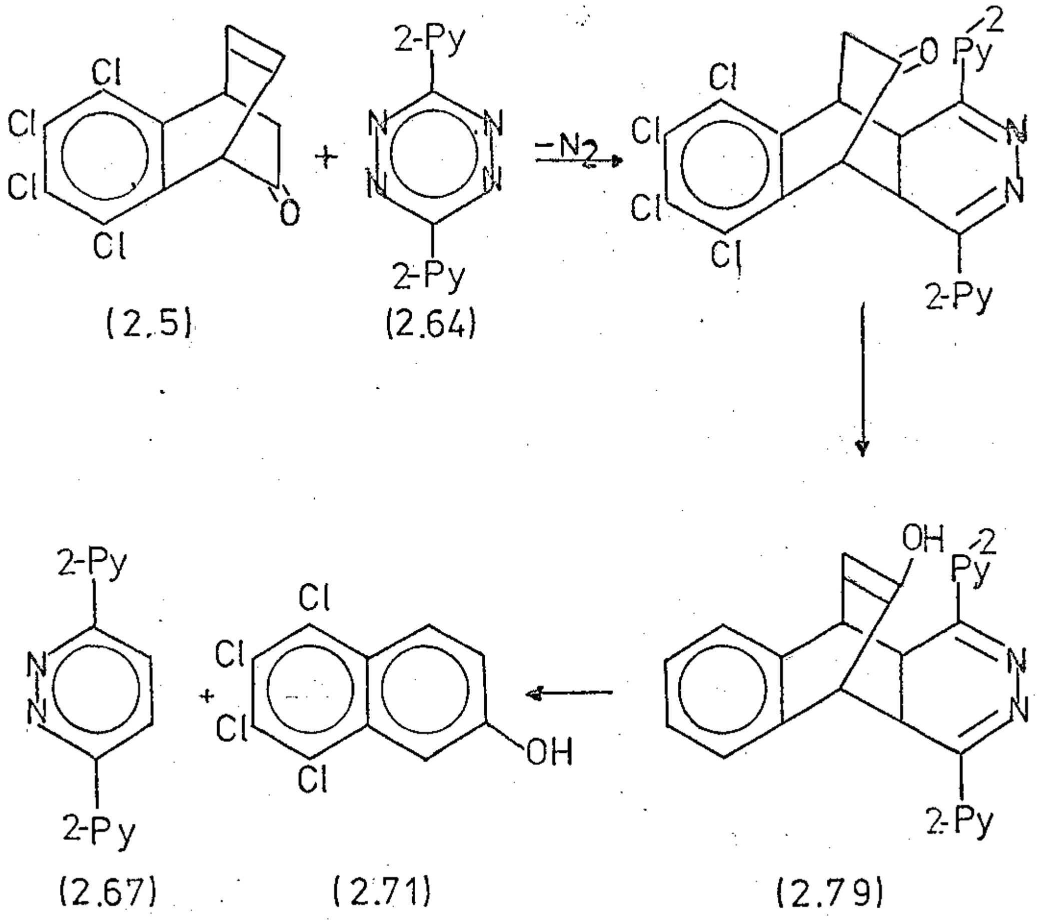

(2.2)
(2.64)
(i)
(2.75)
(ii)
(2.77)
(iii)
Cl
Cl
Cl
Cl
OCH3
(2.74)
+
(2.67)
(2.74)
+
NO2
N
N
N
(2.76)
(2.74)
+
CO2H
(2.78)
NO2
N3
(2.75)
O
O
CO2H
(2.77)

(i) di-n-butyl ether (reflux)

(ii) benzene (reflux)

(iii) acetic acid or p-xylene (200°)

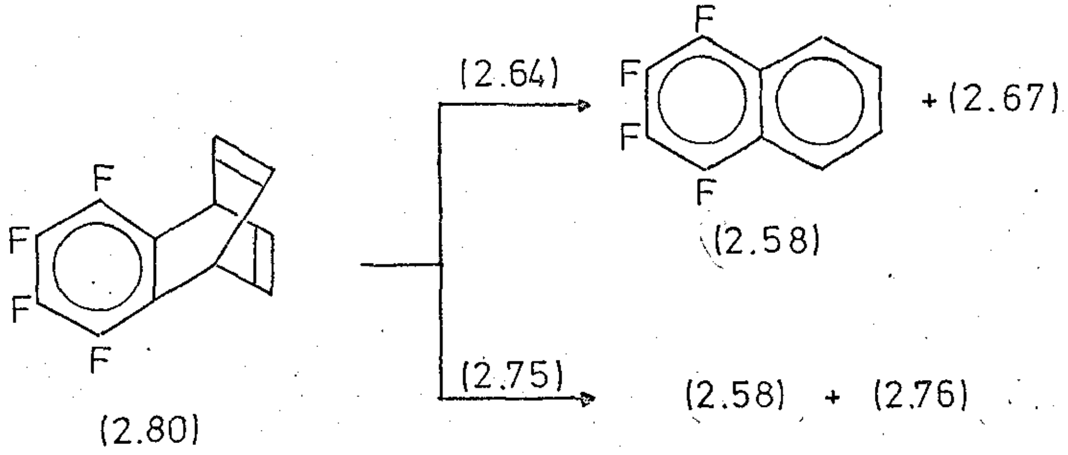
Scheme 2.20


Cl
Cl
Cl
Cl
O
(2.5)
+
2-Py
N
N
N
N
2-Py
(2.64)
$-N_2$
Cl
Cl
Cl
Cl
O
Py
2
N
N
2-Py
OH
Py
2
N
N
2-Py
(2.79)
2-Py
N
N
2-Py
(2.67)
+
Cl
Cl
Cl
Cl
OH
(2.71)

would also undergo a similar cycloaddition-fragmentation as illustrated in Scheme 2.21.

The tetrafluorobenzobarrelene (2.80) could be reacted with either the tetrazine (2.64) or the azide (2.75) to yield on fragmentation, tetrafluoronaphthalene (2.58) plus the pyridazine (2.67) or the triazine (2.76) respectively. The obvious difficulty was the conversion of the ketone (2.4) to the barrelene (2.80). One potential approach to this problem has been investigated by Paquette.[41] This procedure involved the reaction of the ketone (2.6) with toluene-p-sulphonyl hydrazine (2.81)

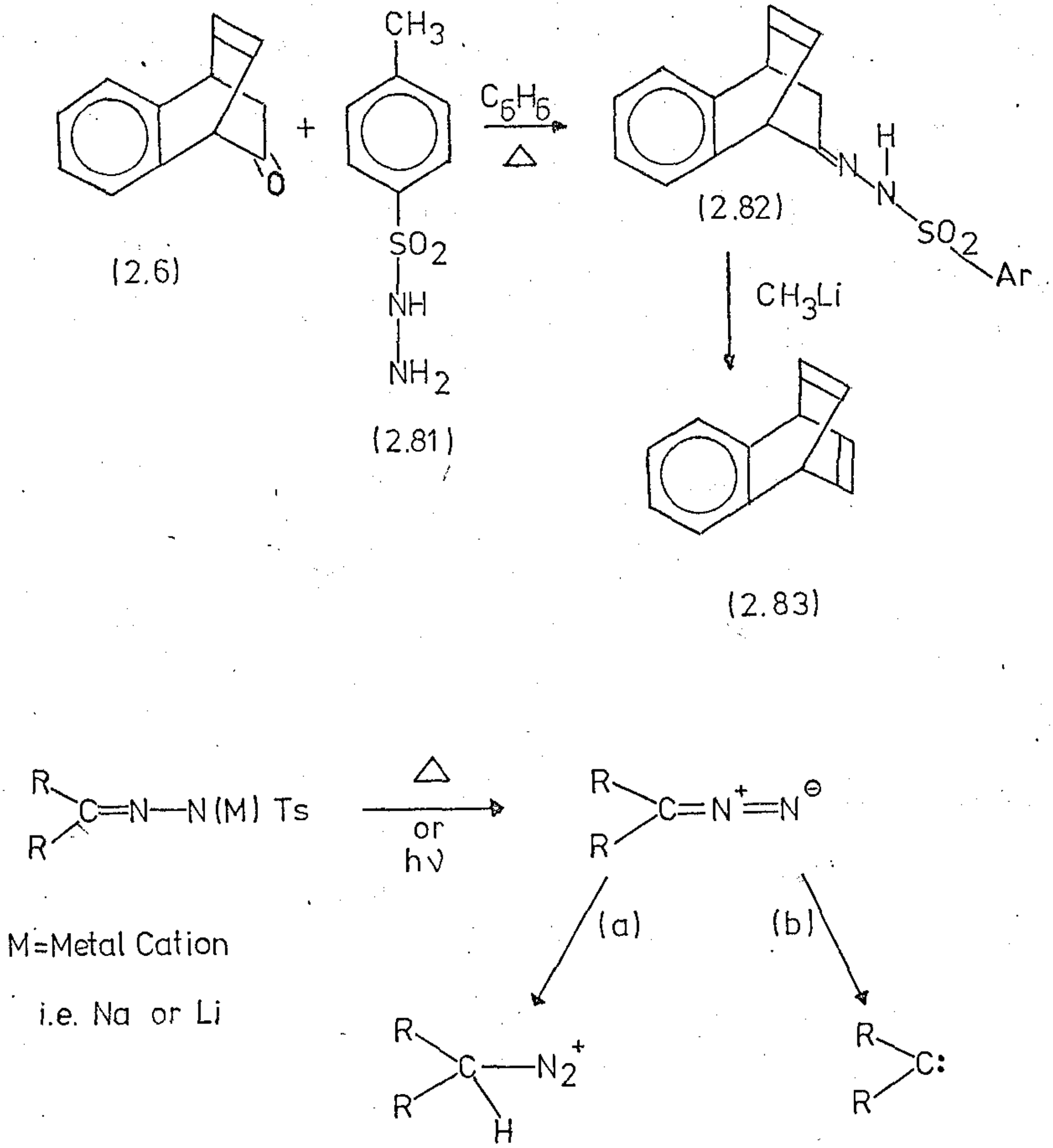
Scheme 2.21



to form the tosyl hydrazone (2.82). Treatment of the hydrazone with methyl lithium resulted in the formation of benzobarrelene (2.83). The complete procedure is depicted in Scheme 2.22.

The course of the thermal decomposition of mono-p-tosyl hydrazone salts has been well established.[64] p-Toluenesulphinate anion is eliminated in an initial step, with resultant formation of a diazo compound. Depending on the choice of reaction conditions the diazo compound may be either isolated [64b,d] or subsequently decomposed in situ via carbenoid or cationoid pathways.[64a,b,e,g] Dauben and Willey[64h] have shown that the decomposition can also be effected photochemically.

Scheme 2.22



(2.6)
CH3
SO2
NH
NH2
(2.81)
C6H6
△
(2.82)
H
N
SO2
Ar
CH3Li
(2.83)
R
C=N—N(M) Ts
△
or
hν
C=N+=N⊖
(a)
(b)
C—N2+
H
C:

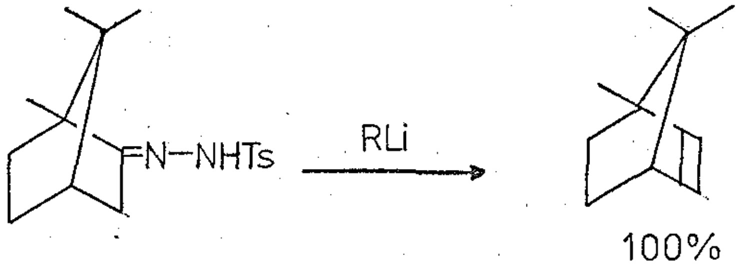
M=Metal Cation

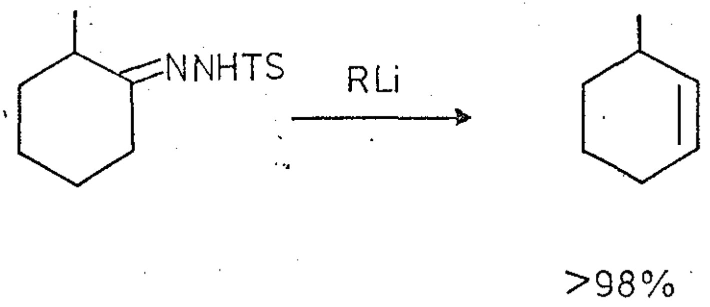
i.e. Na or Li

(a) = Highly protic solvent

(b) = Aprotic solvent

The yield of the olefin from these reactions is normally high, and is typified by the two reactions illustrated.





Paquette's results[41] and the high yields normally associated with these reactions prompted us to investigate the formation of the benzobarrelene (2.80) from the ketone (2.4) by such a route.

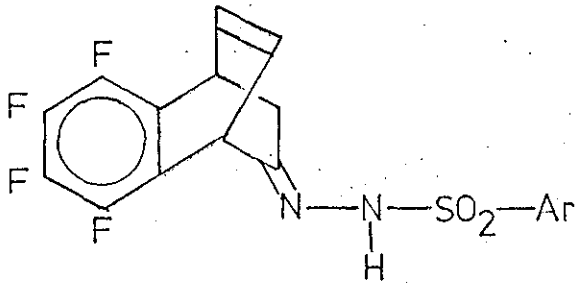
Tetrafluorobenzobarrelenone (2.4) and tosyl hydrazine (2.81) were heated under reflux in dry benzene using a Dean and Stark separator for ca. 5hr. and the reaction was followed by t.l.c.. The infra-red data of the product, a yellow crystalline solid, indicated that the typical carbonyl stretching frequency (νmax ca.1740cm^{-1}) of the ketone (2.4) had disappeared. The product was suspended in dry ether and stirred under nitrogen at room temperature. The solution was treated with n-butyl-lithium (lequiv.) and then stirred overnight. Analysis of the crude product indicated that a complicated mixture of products had been obtained. The mixture was separated by preparative layer chromatography into four major bands. The analysis of each of these bands by gas liquid chromatography indicated that none of the required benzobarrelene (2.80) was formed. This negative result could be explained by one or more of the following points:-

(i) Previous work[64b] has shown that the use of less than two equivalents of base can have an adverse affect on the decomposition of the tosyl hydrazone, resulting in carbon skeleton rearrangements or insertion reactions.

(ii) n-Butyl-lithium is sterically larger than methyl-lithium, the base used by Paquette,[41] and attack by this base may have been hindered.

(iii) The four fluorine substituents may have an effect on the decomposition of the tosyl hydrazone (2.84) as opposed to to the unsubstituted tosyl hydrazone (2.82).

Further investigations of this procedure were curtailed by the successful application of a method devised by Zimmerman[31] during his photochemical studies of benzobarrelene. The method,[31] illustrated in Scheme 2.23, involves the reduction of the ketone (2.6), with sodium borohydride, to an epimeric mixture of alcohols (2.85). This mixture



(2.84)

was converted to the xanthate esters (2.86) by treatment with sodium hydride, followed by carbon disulphide and finally methyl iodide. Pyrolysis of the esters yielded a mixture of naphthalene (2.87) and the required benzobarrelene (2.83). The mixture was separated by column chromatography.

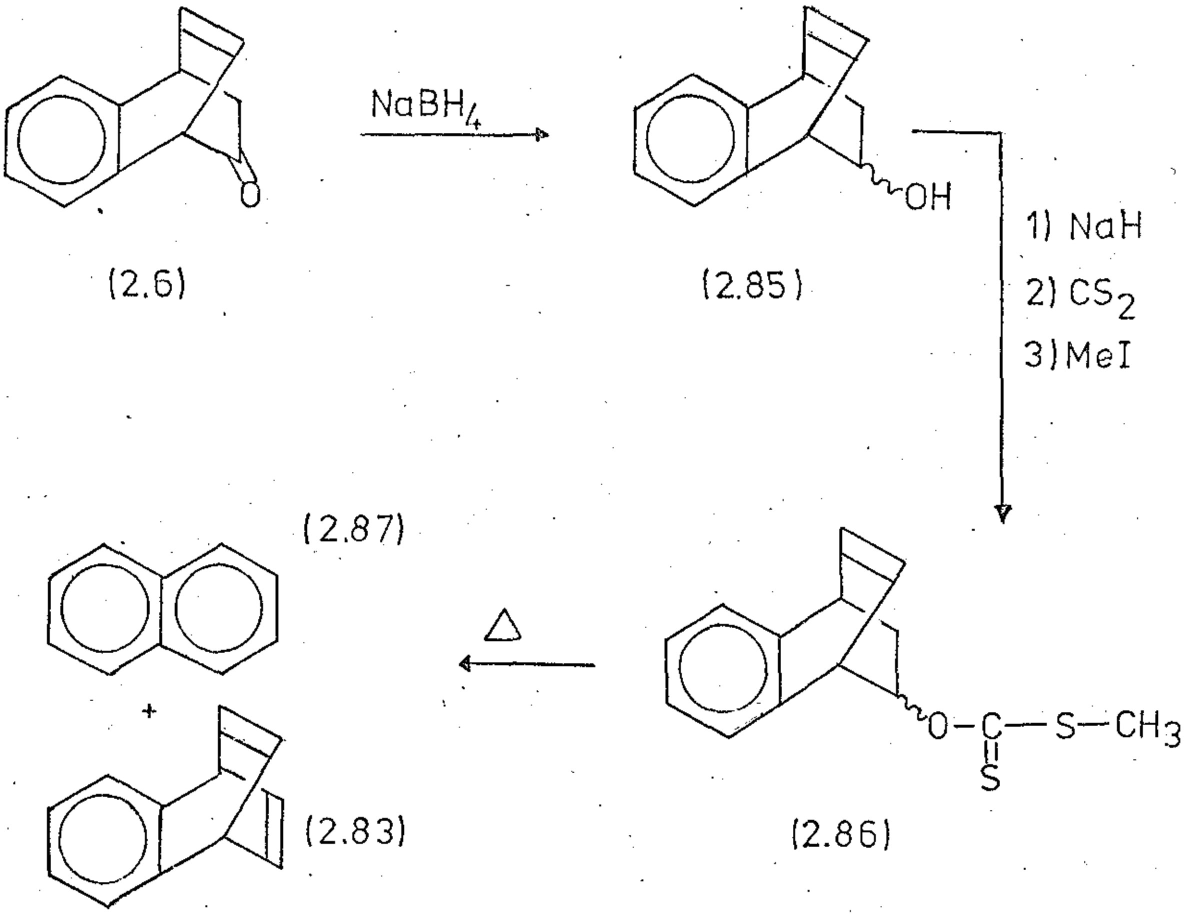
There were a number of potential difficulties with this procedure:-

(i) Would the procedure be adaptable to tetrafluorobenzobarrelenone (2.4).

(ii) What would be the effect of reducing the scale of the reaction. Zimmerman[31] had obtained 1.76g. of benzobarrelene from 7.52g. of benzobarrelenone. Assuming a similar yield then 500mg. of the ketone (2.4) would produce 117mg. of tetrafluorobenzobarrelene (2.80). Such a yield would be satisfactory for the final degradation stage.

(iii) The final step would involve the formation of tetrafluoronaphthalene (2.58) and since this naphthalene is also formed

Scheme 2.23



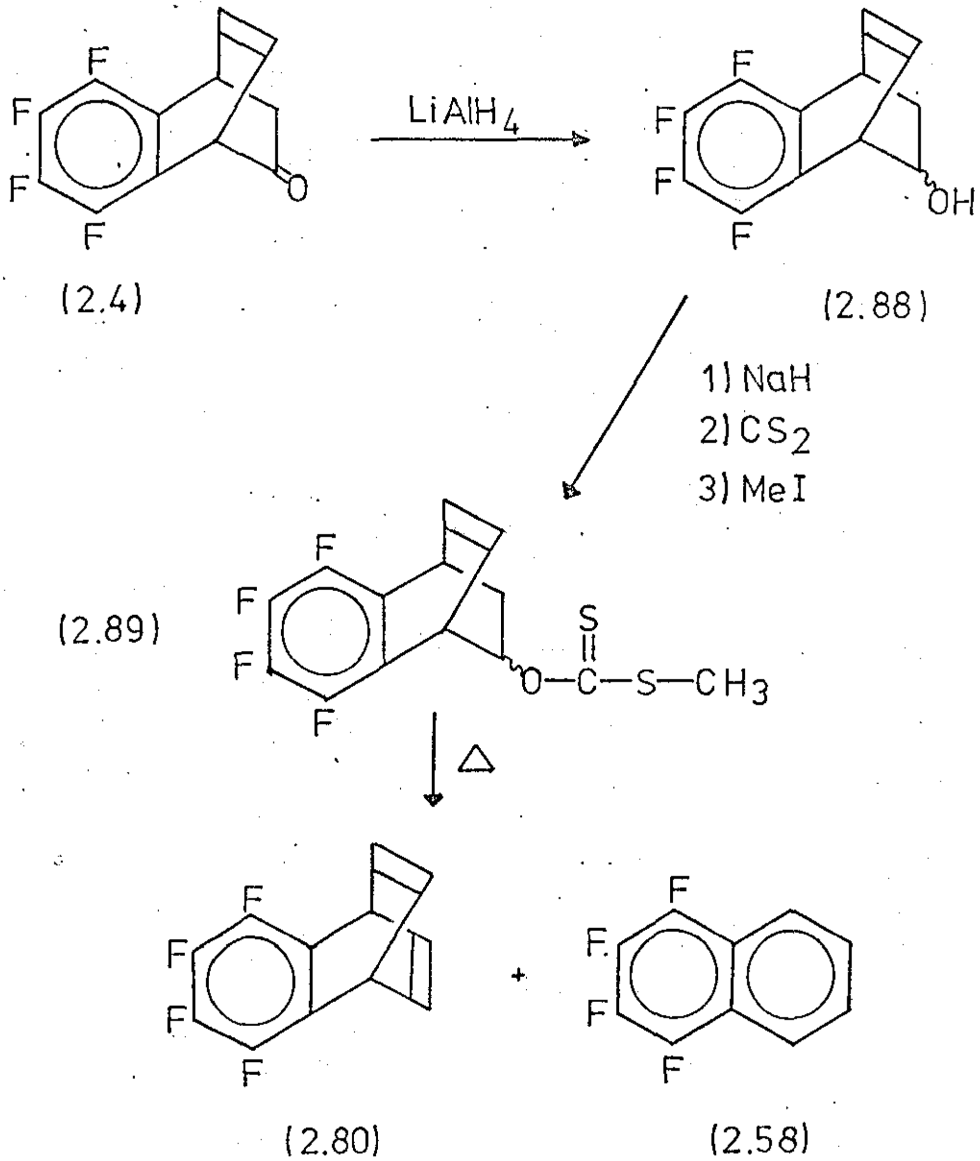
(2.6) (2.85) (2.86) (2.87) (2.83)

in the pyrolysis of the xanthate esters (2.89) it would be obviously important to remove all traces of the naphthalene (2.58) from the benzobarrelene (2.80) : naphthalene (2.58) mixture. The naphthalene obtained in the pyrolysis would, in the case of the ^{14}C labelled xanthate esters, contain a proportion of the ^{14}C label depending on whether the naphthalene was formed directly from the ester or indirectly from the benzobarrelene. The formation of the naphthalene from both sources was also obviously feasible.

Contamination of the benzobarrelene with the naphthelene would yield false results in the analysis of the naphthalene from the degradation of the benzobarrelene.

With the above points in mind, tetrafluorobenzobarrelenone (2.4) was reacted as shown in Scheme 2.24.

Scheme 2.24

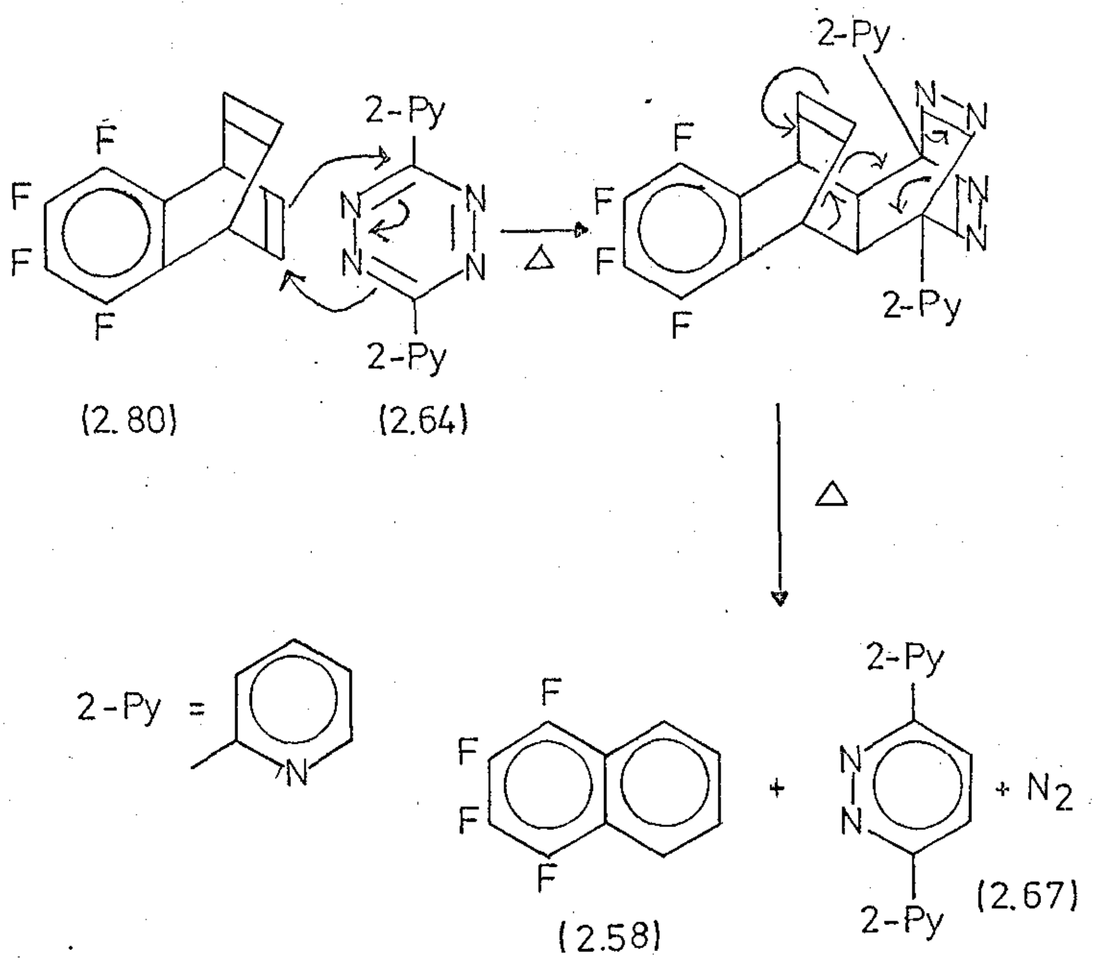

F
F
F
F
(2.4)
LiAlH4
OH
(2.88)
1) NaH
2) CS2
3) MeI
(2.89)
O—C—S—CH3
S
△
(2.80)
+
(2.58)

The epimeric mixture of esters (2.89) was isolated as a crude yellow oil which was sealed in a large pyrolysis tube and heated at ca. 230° for ca. 20-30min. Analysis of the resultant product by g.l.c. indicated a 50:50 mixture of tetrafluorobenzobarrelene : tetrafluoronaphthalene. Careful chromatography on first a column of alumina and then silica-gel allowed the two products (2.80)and (2.58) to be completely separated, as indicated by g.l.c.. The two compounds were identified by comparison with authentic material.

The degradation procedure was completed by reacting tetrafluorobenzobarrelene (2.80) with 3,6-di-(2'-pyridyl)-s-tetrazine (2.64) in refluxing di-n-butyl-ether for ca. 15hr., to form tetrafluoronaphthalene (2.58) and the pyridazine (2.67). Completion of the reaction was signalled by the disappearance of the characteristic red or violet-red tetrazine colour. Scheme 2.25 illustrates this cycloaddition-fragmentation process.

The products from the crude reaction mixture were isolated by removing the excess of di-n-butyl ether by distillation under reduced pressure. Tetrafluoronaphthalene was isolated by preparative chromatography on silica-gel, using petroleum-ether (40:60) as the eluant. The base line containing the required pyridazine (2.67), plus other compounds including unreacted tetrazine (2.64), was re-chromatographed. Repeated elution with chloroform (ca. 4-6 times) was necessary before the required pyridazine (2.67) was sufficiently separated from the remaining tetrazine to be isolated in a pure form. The two products (2.58) and (2.67) were identified by comparison with authentic material.

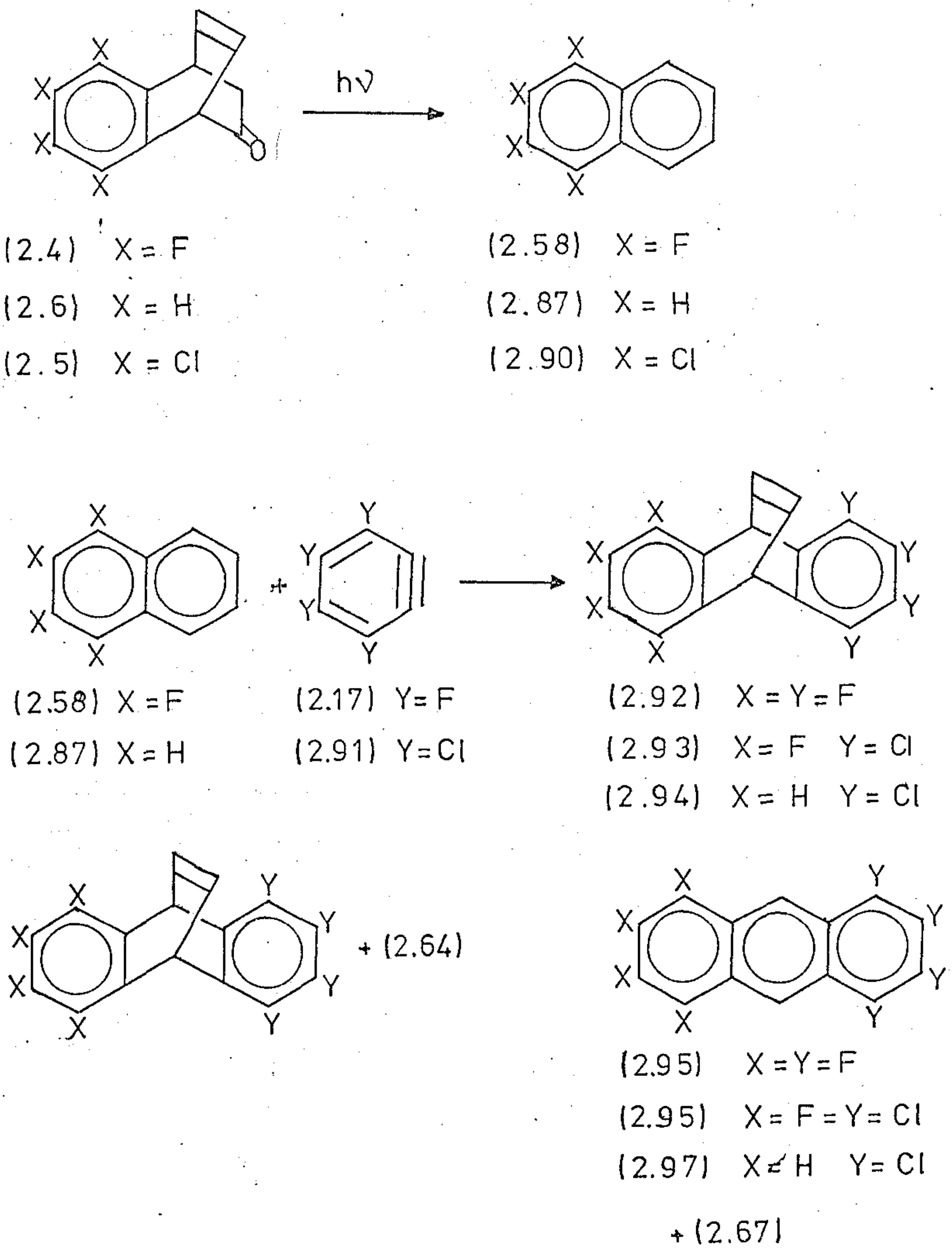
Scheme 2.25



The one danger in this degradation of the ketone (2.4) was the previously mentioned possibility of contamination of the benzobarrelene (2.80) after the xanthate ester pyrolysis. In order to overcome this danger consideration was given to an alternative procedure shown in Scheme 2.26.

Photolysis of benzobarrelenone and its derivatives yields the respective naphthalene[20h] in an almost quantitative yield. Previous workers[14b] had shown that naphthalene (2.87) if present in a large molar excess, would undergo a Diels-Alder 1,4-cycloaddition reaction with tetrachlorobenzyne (2.91) to form 1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene

Scheme 2.26



(2.4) X = F
(2.6) X = H
(2.5) X = Cl

(2.58) X = F
(2.87) X = H
(2.90) X = Cl

(2.58) X = F
(2.87) X = H

(2.17) Y = F
(2.91) Y = Cl

(2.92) X = Y = F
(2.93) X = F Y = Cl
(2.94) X = H Y = Cl

+ (2.64)

(2.95) X = Y = F
(2.95) X = F = Y = Cl
(2.97) X ≠ H Y = Cl

+ (2.67)

(2.94) in 34% yield. The etheno bridge in products such as (2.92)-(2.94) should be susceptible to the previously discussed cycloaddition-fragmenttion process with the tetrazine (2.64) to yield the anthracenes (2.95)-(2.97) and pyridazine (2.67). The following difficulties were envisaged:-

(i) The original work[14b] had involved the use of a large molar excess of naphthalene. This would not be possible in our circumstances.

(ii) Naphthalene is not a particularly good diene and the presence of four electron withdrawing substituents in tetrafluoronaphthalene would further reduce the capability to undergo cycloaddition.

(iii) The difficulty of carrying out an aryne cycloaddition on such a small scale (~500 mg.) was not without its obstacles.

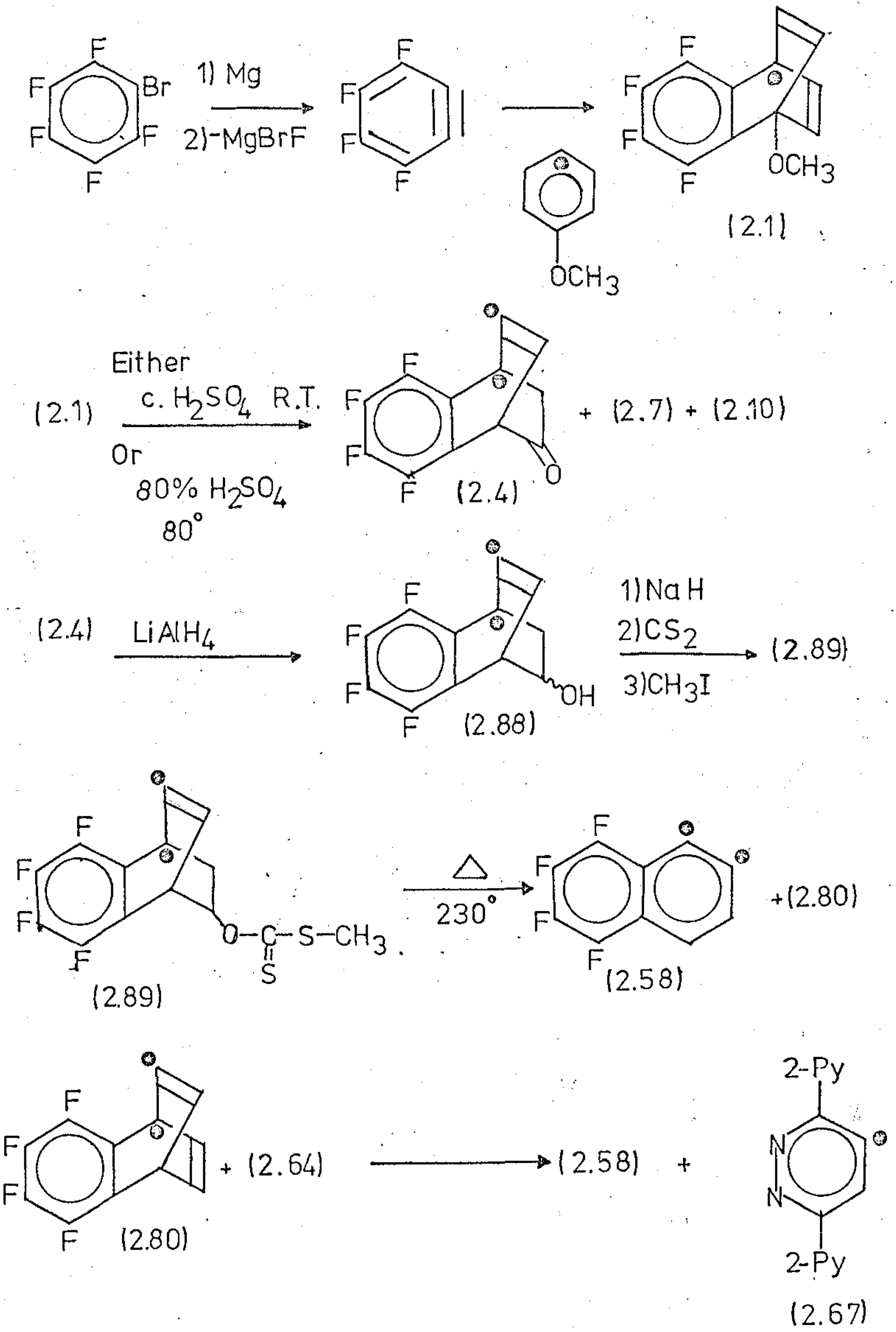
Thus, against the odds a number of reactions were investigated using tetrafluoronaphthalene (2.58) with either tetrafluorobenzyne (2.17) or tetrachlorobenzyne (2.91) in attempts to prepare the compounds (2.92) and (2.93) respectively. The products isolated from all of these reactions were the starting tetrafluoronaphthalene (2.58) and highly coloured materials which were not identified.

The results were not surprising and yet were disappointing because of the advantages that this procedure offered. Not only was the danger of contamination overcome but also the possibility of completely isolating the C-4 and C-5 in the starting ketone (2.4) was lost. Consideration of the degradation procedure shown in Scheme 2.25 indicates that the tetrafluorobenzobarrelene contains two equivalent etheno-bridges, and since the ^{14}C label originally in C-5 of the ketone (2.4) would be in one of these bridges, the resulting pyridazine (2.67) from the degradation would only contain half the ^{14}C label. The other half being contained in the tetrafluoronaphthalene (2.58). On the other hand the degradation shown in Scheme 2.26 indicates that the products (2.92)-(2.94) contain only one etheno-bridge. This bridge must contain all the original C-5 label and hence degradation would give the pyridazine (2.67) also containing all the C-5 label.

However, beggars may not choose and in any event the above disadvantages would not prevent the successful use of the degradation procedure proposed in Scheme 2.25. The possibility of contamination was only a danger if careful separation and purification were not carried out after the pyrolysis step. The fact that the pyridazine (2.67) would only contain half the C-5 label was not a problem since the tetrafluoronaphthalene (2.58) would contain all the original C-4 label plus half of the C-5 label from the ketone (2.4). Hence, a simple calculation would enable the activity in C-4 and C-5 of the ketone (2.4) to be separately determined.

Thus, a suitable procedure was now available, for preparing [4-^{14}C]-1-methoxytetrafluorobenzobarrelene, rearranging this compound to [^{14}C]-tetrafluorobenzobarrelenone and degrading the labelled ketone in such a way as to isolate products which enable the activity in C-4 and C-5 to be calculated. The complete procedure is illustrated in Scheme 2.27.

Scheme 2.27


1) Mg
2) -MgBrF
(2.1)
Either
c. H_2SO_4 R.T.
Or
80% H_2SO_4
80°
(2.4)
+ (2.7) + (2.10)
$LiAlH_4$
(2.88)
1) NaH
2) CS_2
3) CH_3I
(2.89)
230°
(2.58)
+ (2.80)
(2.80)
+ (2.64)
(2.58) +
2-Py
2-Py
(2.67)

At this stage of the investigation the success of the dechlorination work, discussed in Chapter 1, generated further ideas regarding the mechanistic studies of the rearrangement of 1-methoxybenzobarrelenes. It was now possible, to prepare in good yield the three [4-^{14}C]-1-methoxybenzobarrelenes (2.1)-(2.3) rearrange each of the compounds (2.1)-(2.3) in concentrated sulphuric acid at room temperature and in 80% sulphuric acid at 80° to the respective [^{14}C]-benzobarrelenones (2.4)-(2.6) and suitable degradation of each of the ketones (2.4)-(2.6) would allow the effect of the aryl substituent, fluorine, chlorine and hydrogen, on the two rearrangement pathways, Scheme 2.1, to be analysed.

There were two major problems to such considerations:-

(i) The yield of [4-^{14}C]-anisole was low and too high a dilution would affect the accuracy of the results.

(ii) The degradation procedure proposed for [^{14}C]-tetrafluorobenzobarrelenone (2.4) might not be applicable to the ketones (2.5) and (2.6).

It was reasoned that by attempting all three reactions, all might be lost, and therefore, 'safety-first' was the maxim adopted. The decision was made to dilute the [4-^{14}C]-anisole to prepare the compound (2.1) rearrange this under the two different conditions to the ketones (2.4a) and (2.4b) and then degrade each of these ketones as proposed in Scheme 2.27. In the meantime consideration would be given to the preparation and rearrangement of the two compounds (2.2) and (2.3) followed by degradation of the respective ketones (2.5) and (2.6).

The adoption of this procedure would still allow us a crack at the 'glory road' for if the degradation of the [^{14}C]-tetrafluorobenzobarrelenone (2.4) could be completed satisfactory any remaining active anisole could then be used to prepare and rearrange the compounds (2.2) and (2.3). The attitude was taken that the successful completion of the latter would be an added bonus to the original intentions of this work, albeit, a much desired bonus.

Dilution of the [4-^{14}C]-Anisole

After careful consideration and calculations regarding the volume of anisole required, the likely distribution of the ^{14}C label in the ketones (2.4a) and 2.4b), the specific activity of the crude [4-^{14}C]-anisole and the degradation products and route, it was decided to dilute the active anisole to a final volume of *ca*. 15ml.. This was accomplished by adding anisole (5ml.) to the active anisole and then distilling the diluted active anisole. Anisole (5ml.) was added to the residue and the distillation repeated. This latter process was repeated, a third time, using anisole (4ml) to yield a final volume of *ca*. 15ml. of diluted [4-^{14}C]-anisole.

Preparation and Degradation of [^{14}C]-Tetrafluorobenzobarrelenones (2.4a) and (2.4b).

[4-^{14}C]-1-methoxytetrafluorobenzobarrelene (2.1) was prepared as illustrated in Scheme 2.2 but on a smaller scale than originally discussed. A total volume of [4-^{14}C]-anisole (5ml.) was used instead of *ca*. 15ml. The procedure was repeated twice, using the recovered active anisole for each repeat reaction and the required compound(2.1)

(1.32g.) was isolated as a crude crystalline product. The product (2.1) was recrystallised and its activity measured.

The general procedure adopted for preparing and counting all the active products, in this study, was as follows. The products were either recrystallised or sublimed and then a sample (ca. 1-2mg.) of the active compound was accurately weighed into a plastic counting bottle. The sample was then dissolved in dry dimethylformamide (0.5ml.) and a scintillator solution (10ml.). A cap was fitted to the bottle and the bottle shaken to ensure complete solution. Counting was carried out in a Beckmann Scintillation Counter for counting periods of 500min., this long period of counting helped to minimise errors. A blank solution was prepared with each sample in order to estimate background counts. The efficiency of each sample counted was measured using a ^{137}Cs external standard, which was part of the counter used. The efficiency of counting was normally in the region of 90-95%.

The efficiency with which a radioactive sample is counted, in a liquid scintillant, usually varies from sample to sample. The quenching, that is the decrease in the counting efficiency which occurs, is produced by processes which interfere with the production of light in the liquid scintillant and its transmission to the photomultiplier tube of the counter. Quenching may take two forms, chemical quenching and colour quenching. In chemical quenching, compounds in solution in the liquid scintillant interfere with the transfer of energy from the emitted particle or radiation to the organic phosphor, and the energy is degraded by processes which do not produce emission of light. In colour quenching, coloured materials in the liquid scintillant absorb light emitted by the organic phosphor and prevent it being detected by the photomultiplier tube. Many materials, including dissolved oxygen, act as quenchers in the liquid scintillant and it is rarely possible to predict the counting efficiency of a given sample. Some means of determining the counting efficiences of samples is therefore essential to the liquid scintillation counting technique.

Hence, using the external standard ^{137}Cs of the Scintillation Counter, an automatic calculation was made with each sample counted. The value calculated was printed out as a Channel Ratio and was used in conjunction with a calibrated graph (Channel Ratio v Counting Efficiency) to estimate the efficiency of counting.

After counting, the remaining product from the first recrystallisation/sublimation was again recrystallised/sublimed and the product counted again. This procedure was repeated until a constant activity was obtained for each sample.

The crude [4-^{14}C]-1-methoxytetrafluorobenzobarrelene (2.1) (1.32g.) isolated was short of the estimated 2g. necessary to allow the rearrangements to the ketones (2.4a) and (2.4b) to be carried out on a 1g. scale. The activity of the product (2.1), however, was high enough to consider further dilution. Influenced by the knowledge of the ^{14}C split in the ketones (2.4a) and (2.4b), as determined by the deuterium studies,[20d] it was safely decided to dilute the active product with 1-methoxytetrafluorobenzobarrelene (2.1) (1.0g.). The resultant mixture was counted to constant activity and divided into two equal portions. One portion was rearranged to the ketone (2.4a) using concentrated sulphuric acid at room temperature and the other portion to the ketone (2.4b) using 80% sulphuric acid at 80°. Each ketone was isolated as previously described, counted to constant activity and then separately subjected to the degradation procedure shown in Scheme 2.27. Tables I and II indicate the results of this study.

Analysis of the Degradation Results.

Obviously there was no loss in activity during the rearrangement of [4-^{14}C]-1-methoxytetrafluorobenzobarrelene (2.1) to the ketones (2.4a) and (2.4b).

The two samples of tetrafluoronaphthalene (2.58) obtained from the pyrolysis of the xanthate esters (2.89), as shown in Scheme 2.24, were sublimed and counted to constant activity. As previously mentioned the formation of the naphthalene (2.58) can occur by two possible routes during the pyrolysis. The two routes (i) and (ii) are shown in Scheme 2.28. Analysis of the specific activities of the naphthalene (2.58) allows an estimate to be made of the route involved.

Direct formation by route (i) would mean that the specific activity of the naphthalene (2.58) should be the same as the starting ketone (2.4) i.e. $4.37\times10^{-2}\mu$.Ci/m.mol.. Indirect formation by route (ii) involving prior formation of tetrafluorobenzobarrelene (2.80) would have resulted in a 50% loss of the ^{14}C activity in the etheno bridge during the pyrolysis of the barrelene (2.80) to the naphthalene (2.58).

Table I Rearrangement of /4-^{14}C 7-1-methoxytetrafluorobenzobarrelene (2.1) in conc. H_2SO_4 at room temperature.

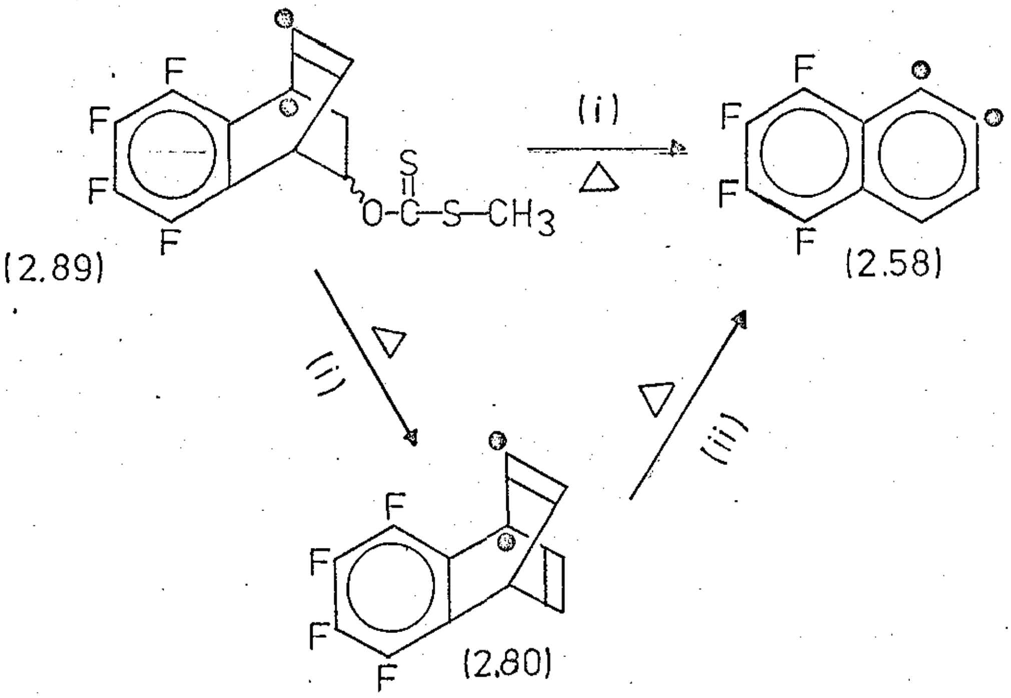
COMPOUND (^{14}C)	Specific Activity μ.Ci/m.mol.
1-methoxytetrafluorobenzobarrelene (2.1)	4.34×10^{-2}
Tetrafluorobenzobarrelenone (2.4a)	4.37×10^{-2}
Tetrafluoronaphthalene (2.58) (from xanthate pryrolysis)	3.67×10^{-2}
Tetrafluoronaphthalene (2.58) (from degradation of (2.80))	/2.70×10^{-2} 7
Pyridazine (2.67)	1.67×10^{-2}

Table II Rearrangement of /4-^{14}C 7-1-methoxytetrafluorobenzobarrelene (2.1) in 80% H_2SO_4 at 80°

COMPOUND (^{14}C)	Specific Activity μ.Ci/m.mol.
1-methoxytetrafluorobenzobarrelene (2.1)	4.34×10^{-2}
Tetrafluorobenzobarrelenone (2.4b)	4.37×10^{-2}
Tetrafluoronaphthalene (2.58) (from xanthate pyrolysis)	3.44×10^{-2}
Tetrafluoronaphthalene (2.58) /from degradation of (2.80) 7	/2.88×10^{-2} 7
Pyridazine (2.67)	1.49×10^{-2}

*/ 7values obtained by subtraction of specific activity of (2.67) from (2.4)

Scheme 2.28



The pyrolysis involves the loss of an etheno-bridge and since the two etheno-bridges are equivalent a 50% loss vould be expected. The total activity in the etheno-bridge would be equal to the activity originally in C-5 of the ketone (2.4). The pyridazine (2.67) isolated in the last step of the degradation of the ketone (2.4) contains 50% of the activity originally in C-5. Hence, if the naphthalene (2.58) had been formed solely by route (ii) the specific activity of the naphthalene (2.58) from the ketone (2.4a) would have been 2.70 x 10^{-2} μ.Ci/m.mol. and that from (2.4b) 2.88 x 10^{-2} μ.Ci./m.mol. The actual values obtained were

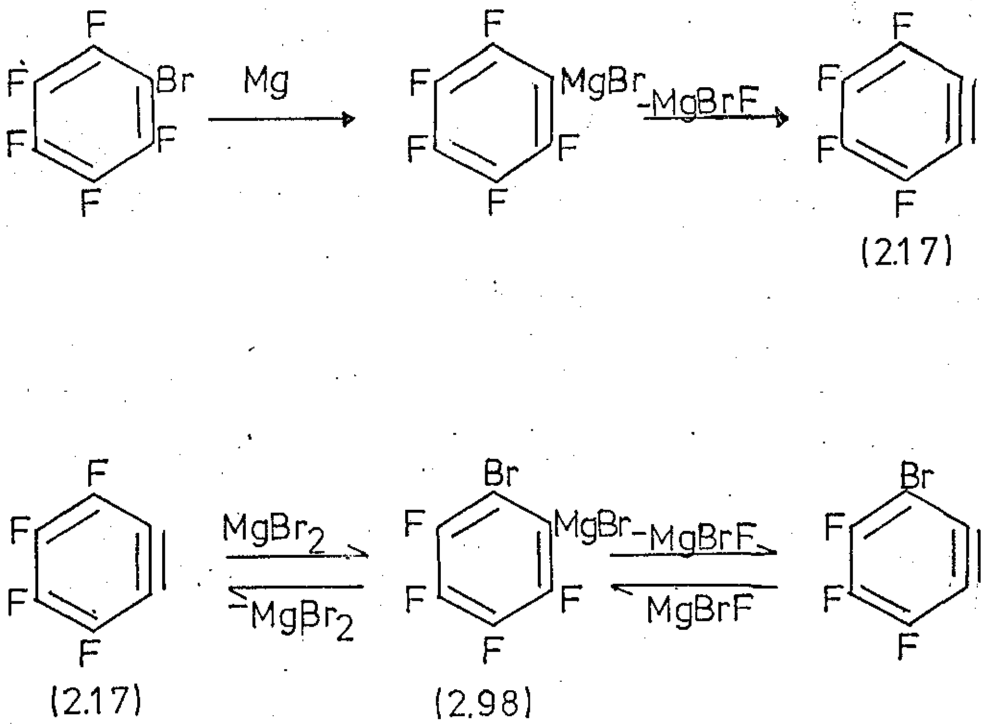
3.67×10^{-2} and 3.44×10^{-2} μ.Ci./m.mol. respectively which are between the values expected for route (i) or (ii). Not unexpectedly the naphthalene (2.58) was being formed by both routes. Further calculations allowed the determination of a percentage ratio of routes (i) and (ii) for the two pyrolysis experiments to be calculated. Tetrafluoronaphthalene derived from the ketone (2.4a) by pyrolysis of the xanthate ester (2.89) gave a ratio of 58% (i) : 42% (ii) and from the ketone (2.4b) 38% (i) : 62% (ii).

Although it was not surprising that both (i) and (ii) were involved in the formation of the product (2.58) what was surprising was the difference in the percentage ratio for the two reactions. This difference presumably occurs due to the extreme difficulty of carrying out the two pyrolysis reactions under exactly the same conditions. Variations in time of pyrolysis, pressure and temperature would account for the above differences.

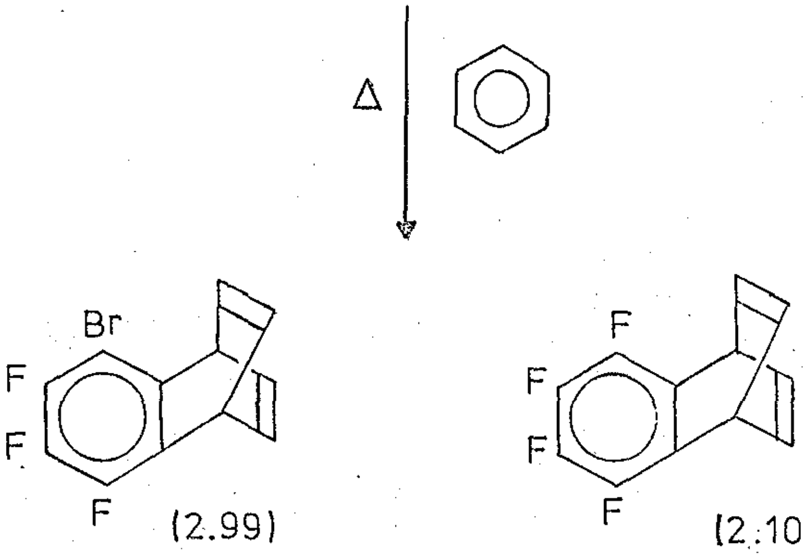
The two samples of tetrafluoronaphthalene (2.58) obtained from the cycloaddition-fragmentation reaction of tetrafluorobenzobarrelene (2.80) and the tetrazine (2.64) could not be counted to constant activity. The samples were sublimed and a portion (ca. 1mg.) counted in the normal way. The procedure was repeated but instead of the activity increasing to an eventual constant value, as the purity increased, the values became lower.

A possible explanation for this spurious result is illustrated in Scheme 2.29. The elimination of metal halides from o-halophenyl Grignard and lithium reagents is known to be reversible[11] as is the reversibility of lithium compounds.[65] The addition of halide ion to benzynes is known to occur in the order $I^- > Br^- > Cl^-$. These considerations suggested to earlier workers[14d] that a similar mechanism to that illustrated in Scheme 2.29, would explain the formation of bromotrifluorobenzobarrelene (2.99), in the reaction of pentafluorophenyl-magnesium-bromide with benzene. When 2-bromo-3,4,5,6-tetrafluorophenyl-magnesium-bromide (2.98) was heated under reflux in benzene solution, the two adducts (2.99) and (2.100) were formed in a ratio of 99:1

Scheme 2.29



(2.98)

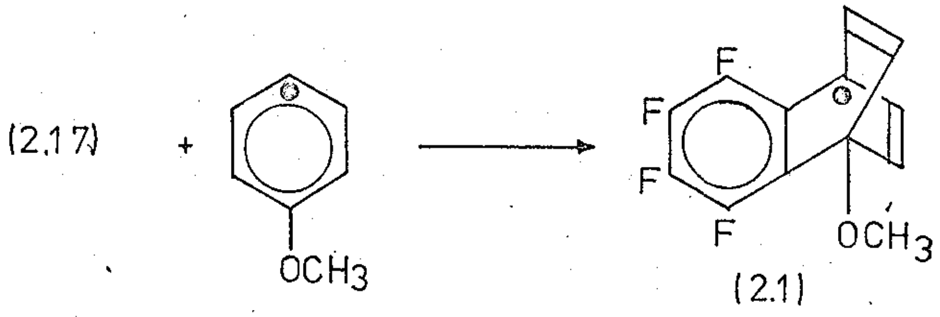


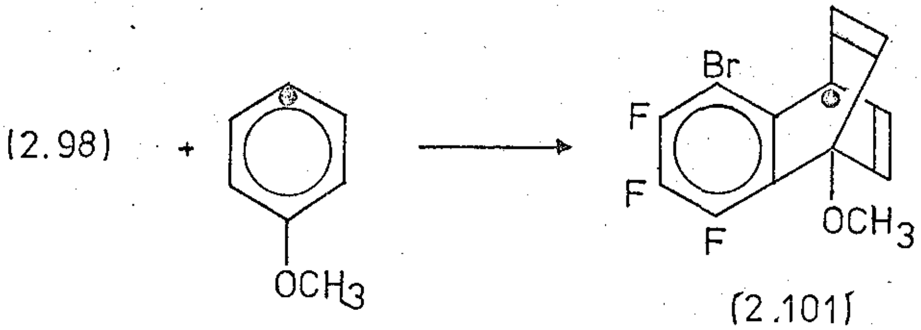
(2.99)

(2.100)

The reaction between pentafluorophenylmagnesium bromide and anisole, under normal conditions, would result in a very high ratio of the product (2.1) to the product (2.101). Normal conditions involve the use of a large excess of anisole but the reaction using [4-^{14}C]-anisole involved the use of equi-molar quantities of pentafluorobromobenzene and [4-^{14}C]-anisole. This may have resulted in a higher proportion of the compound (2.101) being formed. Subsequent rearrangement and degradation of the mixture would have resulted in the isolation of the pyridazine (2.67) and a mixture of the tetrafluoronaphthalenes (2.58) and (2.102). If the repeated sublimations resulted in an increase, in the mixture, of the naphthalene (2.102) then the specific activity calculated would fall due to the higher molecular weight of the product (2.102).

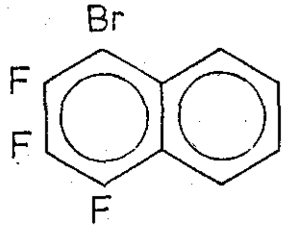
It can be argued that a similar result should have been noticed for the tetrafluoronaphthalene isolated from the pyrolysis of the





xanthate esters. However, at this stage of the degradation, a larger quantity of the tetrafluoronaphthalene was isolated than in the reaction of tetrafluorobenzobarrelene with the tetrazine (2.64). The sublimation of the larger quantity could have resulted in a fractional separation yielding pure tetrafluoronaphthalene (2.58).

In order to overcome this difficulty the specific activity of the tetrafluoronaphthalene (2.58) was calculated by subtraction of the corresponding pyridazine (2.67) activity from the starting ketone (2.4).



(2.102)

The specific activities of the tetrafluoronaphthalenes (2.58) and the pyridazines (2.67) given in Tables I and II, enables the percentage of each of the pathways (a) and (b), proposed in Scheme 2.1, for the rearrangement of 1-methoxytetrafluorobenzobarrelene (2.1) to tetrafluorobenzobarrelenone (2.4), to be calculated.

The $[^{14}C]$ activity is contained in C-4 of the compound (2.1). Rearrangement in acid medium to the ketone (2.4) scrambles the label between C-4 and C-5 depending on the rearrangement conditions. The degradation of the ketone (2.4) is such that the pyridazine (2.67) contains 50% of the activity originally in C-5 of the ketone (2.4) and the tetrafluoronaphthalene (2.58) contains the other 50% plus all the original C-4 activity of the ketone (2.4). Hence, double the activity in the pyridazine equals the total activity in C-5 of the ketone (2.4) and subtraction of the activity in the pyridazine from that in the tetrafluoronaphthalene equals the total activity originally in C-4 of the ketone (2.4). The C-5 activity relates to formation of the ketone (2.4) by pathway (a) and the C-4 activity to formation by pathway (b).

It was thus calculated that in concentrated sulphuric acid (98%), at room temperature, the rearrangement of 1-methoxytetrafluorobenzobarrelene (2.1) to tetrafluorobenzobarrelenone (2.4) proceeded in _ca_. 76.4% by pathway (a) and _ca_. 23.6% by pathway (b). In dilute sulphuric acid (H_2SO_4 (98%) : H_2O, 4:1 $^{v}/_{v}$) at 80° the values were _ca_. 68.2% for pathway (a) and _ca_. 31.8% for pathway (b).

The corresponding values calculated from the deuterium labelling experiments[20d] were in concentrated sulphuric acid _ca_. 80% (a) and 20% (b) and for dilute sulphuric acid at 80° _ca_. 55% (a) and 45% (b).

By comparing the two sets of results it can be seen that the deuterium and ^{14}C labelling results for the rearrangement in concentrated sulphuric acid (98%) compare favourably. The results from the rearrangement in dilute sulphuric acid at 80° vary considerably. This difference may have been due to the difficulty of repeating exactly the physical aspects of the rearrangement. Thus a variation in dilution of the sulphuric acid, the rearrangement time or temperature could cause the differences noted.

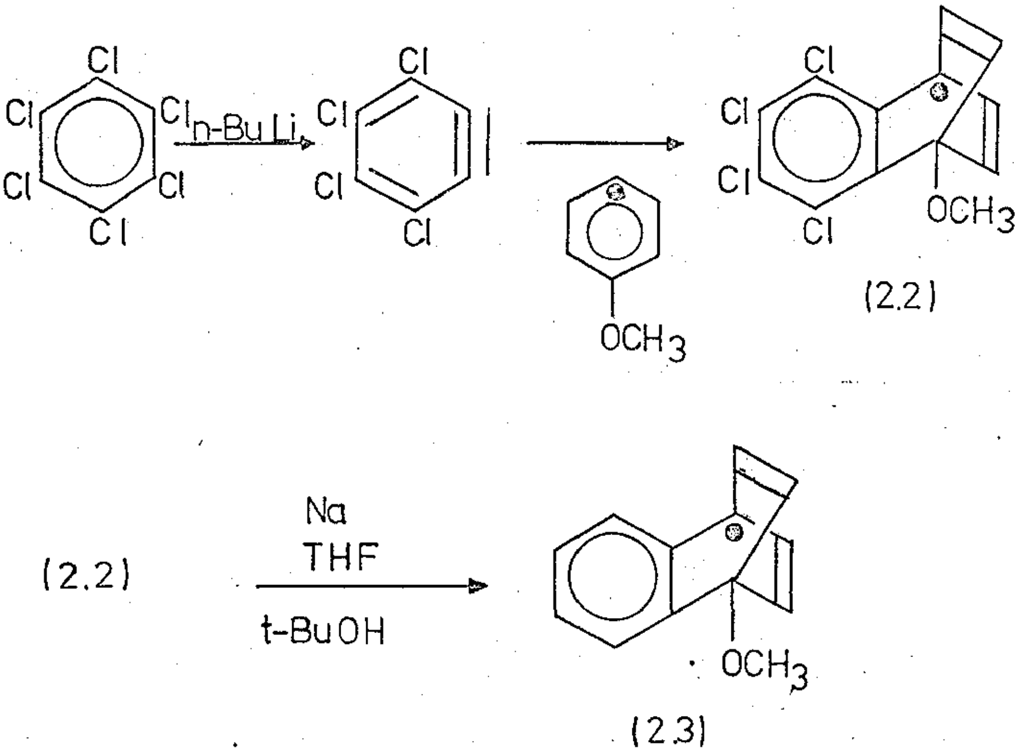
Both sets of results indicate that on decreasing the acid strength the proportion of the ketone (2.4) formed by pathway (b) increases.

The successful completion of this work meant that our attention could be directed at a similar investigation involving [4-^{14}C]-1-methoxy-tetrachlorobenzobarrelene (2.2) and [4-^{14}C]-1-methoxybenzobarrelene (2.3).

Preparation and Rearrangement of the 1-methoxybenzobarrelenes (2.2) and (2.3)

The two compounds (2.2) and (2.3) were prepared as illustrated in Scheme 2.30.

Scheme 2.30


Cl
Cl
Cl
Cl
Cl
Cl
n-BuLi
Cl
Cl
Cl
Cl
OCH$_3$
Cl
Cl
Cl
Cl
OCH$_3$
(2.2)
(2.2)
Na
THF
t-BuOH
OCH$_3$
(2.3)

The investigation was based on the volume of $[4\text{-}{}^{14}C]$-anisole (ca. 10ml.) remaining from the 1-methoxytetrafluorobenzobarrelene (2.1) studies. Reaction of this volume of anisole with tetrachlorobenzyne, formed from an equi-molar quantity of hexachlorobenzene with n-butyl-lithium, gave 1-methoxytetrachlorobenzobarrelene (2.2) in 20-25% yield.

In order to attain this yield it was necessary to recover the unreacted anisole and repeat the reaction a second and even third time when necessary. The product (2.2) was isolated from each reaction by preparative chromatography and the samples combined.

1-Methoxybenzobarrelene (2.3) was prepared by the dechlorination of the product (2.2) by the procedure established in Chapter 1.

There was no difficulty in preparing 2g. quantities, the amount considered suitable for the respective rearrangements, of the compounds (2.2) and (2.3) by the above procedure.

Samples (ca. 1g.) of the two compounds (2.2) and (2.3) were rearranged in concentrated sulphuric acid at room temperature and dilute sulphuric acid (80%) at 80° to their respective benzobarrelenones (2.5) and (2.6). The rearrangement procedure and isolation of the ketones (2.5) and (2,6) was similar to that described earlier for the ketone (2.4). The major difference was that of the rearrangement time as illustrated in the Table below. The longer rearrangement times for 1-methoxytetrachlorobenzobarrelene (2.2) in concentrated sulphuric acid and particularly in dilute sulphuric acid were due to the lower solubility of this compound in the acidic medium. The yield of the tetrachlorobenzobarrelenone (2.5) in both of these rearrangements was higher than the corresponding ketones obtained from the rearrangement of (2.1) and (2.3).

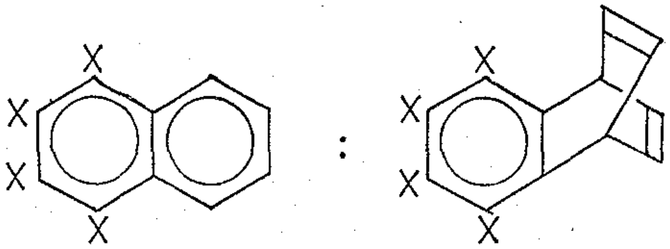
Suitable quantities of the ketone (2.5) for the degradation studies were obtained, as for the ketone (2.4), by rearrangement of the corresponding 1-methoxybenzobarrelene in fluorosulphonic acid.

COMPOUND	Rearrangement Time (min.)	
	CONC. H_2SO_4	80% H_2SO_4
	at R.T.	at 80°
1-methoxytetrafluorobenzobarrelene	3	3
1-methoxytetrachlorobenzobarrelene	8	80
1-methoxybenzobarrelene	2	2

Degradation of the Benzobarrelenones (2.5) and (2.6).

There appeared to be no reason why the procedure established by Zimmerman[31] and used to degrade tetrafluorobenzobarrelenone could not also be applied to the ketones (2.5) and (2.6). Hence the procedure illustrated in Scheme 2.24 was used to convert the two ketones (2.5) and (2.6) to their respective xanthate esters (2.104) and (2.86) via the epimeric alcohols (2.103) and (2.85). Unfortunately the pyrolysis of these xanthate esters gave a different picture to that established for the xanthate ester (2.89). The ratios of the resulting naphthalene and benzobarrelene, as determined by gas-liquid chromatography, are shown in the table below.

These results were particularly disturbing since Zimmerman[31] had obtained a weight ratio of naphthalene (2.87) to benzobarrelene (2.83) of 1.34g. : 1.99g.. The scale of Zimmerman's pyrolysis was obviously larger than our scale i.e. 10.25g. of the xanthate ester (2.86) as compared to *ca.* 1.0g. but the pyrolysis time was similar



X = F	(2.58)	50	:	50	(2.80)
X = Cl	(2.90)	90	:	10	(2.105)
X = H	(2.87)	> 90	:	<10	(2.83)

Pyrolysis at *ca*. 230° for 30 min.

(*ca*. 35mins.). In the light of the evidence presented earlier for the formation of the naphthalene (2.58) by the two pathways (i) and (ii) Scheme 2.28, it was assumed that a shorter pyrolysis time would yield a higher ratio of the benzobarrelene : naphthalene. The reaction time was reduced to *ca*. 20min. but the ratio results were similar to the pyrolysis at *ca*. 30 min.

The results seem to indicate that the two naphthalenes (2.90) and (2.87) are more stable than the corresponding benzobarrelenes (2.105) and (2.83) under the conditions of the pyrolysis. Shorter pyrolysis times or lower temperatures might have resulted in a higher proportion of the required benzobarrelenes but it was considered safer to search for an alternative degradation procedure.

Consideration was given to the oxidation procedures discussed earlier in this chapter, where the main problem seemed to be the four electron withdrawing substituents on the aryl ring of the ketone (2.4) or the naphthalene (2.58). A possible method of degrading the two ketones (2.5) and (2.6) is illustrated in Scheme 2.31. The problem was the oxidation of naphthalene (2.87) to phthalic acid (2.106).

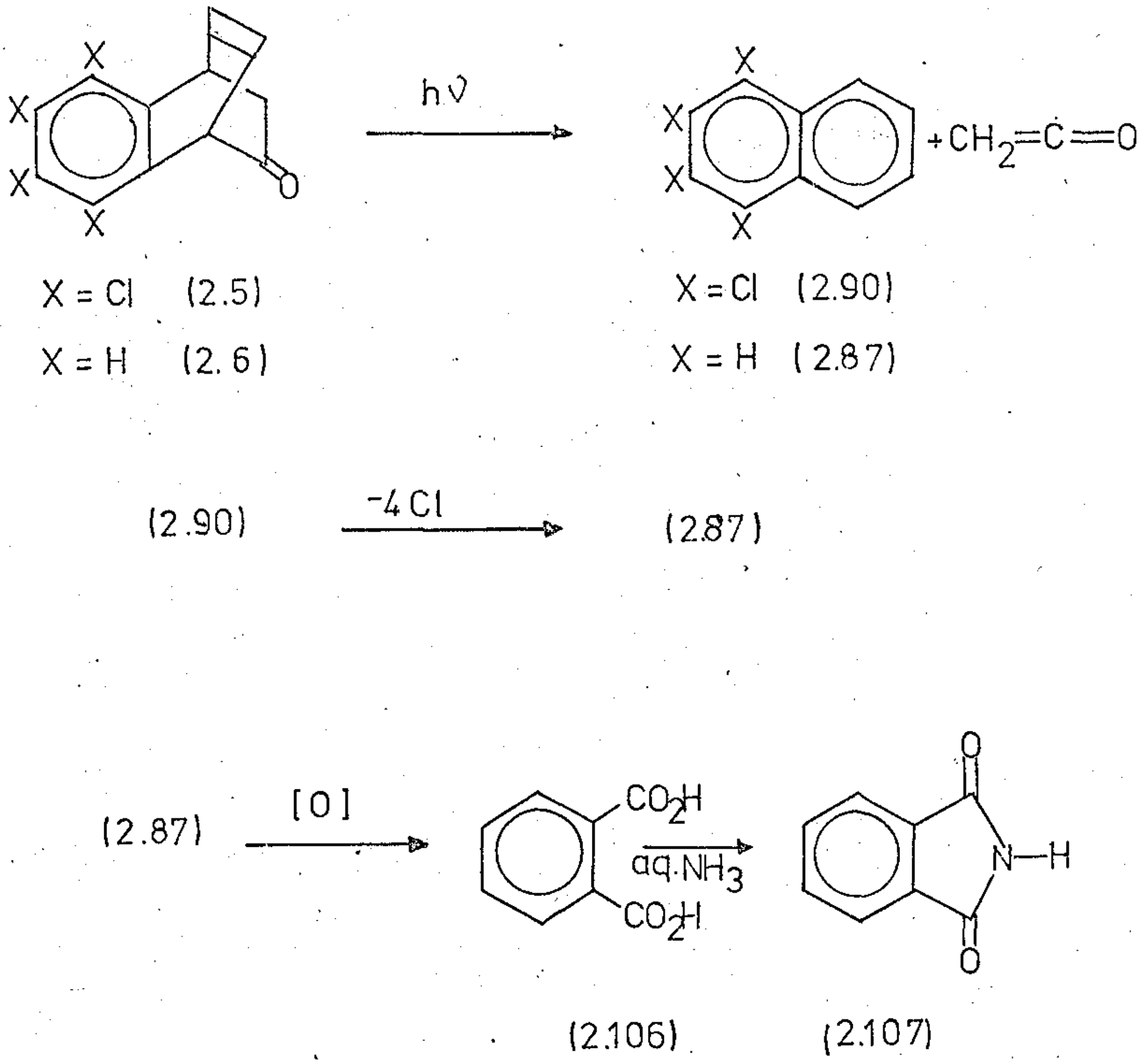
The oxidation of naphthalene can be accomplished by energetic oxidising agents, such as chromic acid, hot fuming sulphuric acid in the presence of a mercury catalyst, or air in the presence of a vanadium or molybdenum catalyst at elevated temperatures. Under moderate conditions, oxidation of naphthalene may result in the formation of intermediate products such as phthalonic acid. Electron releasing substituents such as the amino and hydroxyl groups facilitate the fission of the ring in which they are present.

In an attempt to find a suitable small scale oxidation procedure for oxidising naphthalene to phthalic acid, the following methods were investigated:-

(i) $KMnO_4/H_2O$/Acetone
(ii) $C_6H_6/KMnO_4$/Crown Ether
(iii) $KMnO_4/OH^-$
(iv) $KMnO_4/H^+$

The results of these experiments were inconsistent, in some experiments low yields of impure phthalic acid were isolated and these were

Scheme 2.31


X
X
X
X
hν
X
X
X
X
+CH₂=C=O
X = Cl (2.5)
X = H (2.6)
X = Cl (2.90)
X = H (2.87)
(2.90)
-4 Cl
(2.87)
(2.87)
[O]
CO₂H
aq.NH₃
CO₂H
O
N—H
O
(2.106)
(2.107)

converted, in some cases, to the required phthalimide (2.107). The products (2.106) and (2.107) were identified by comparison with authentic material.

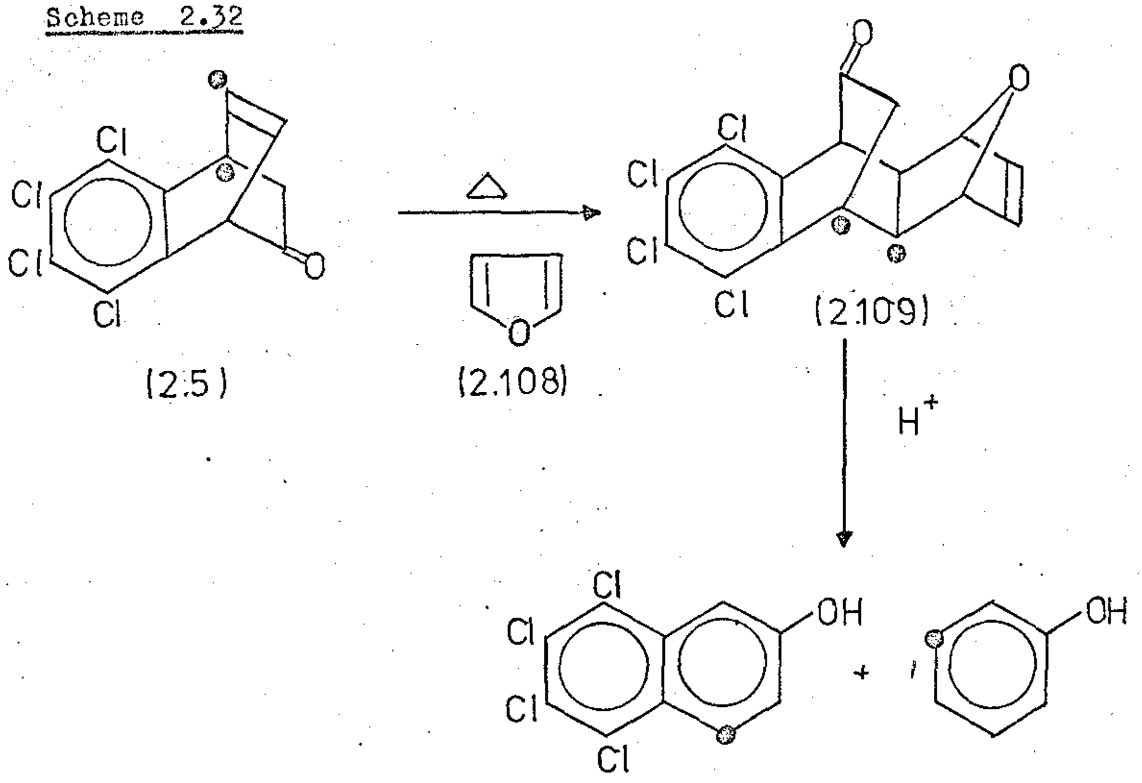
The inconsistency of these results led us back to the possibility of cycloaddition-fragmentation processes and also the work carried out by Paquette[41] involving the formation of tosyl hydrazones.

The failure[20e] to prepare the hydroxytetrachloronaphthalene (2.71) and the pyridazine (2.67) from the reaction of the ketone (2.5) and the tetrazine (2.64) in di-n-butyl ether did not leave much hope for a successful procedure by such a cycloaddition-fragmentation. One alternative, shown in Scheme 2.32, was examined. Tetrachlorobenzobarrelenone (2.5) and an excess of furan (2.108) were sealed in a high pressure tube under vacuum. The tube was heated in a constant temperature water bath, ca. 40°, for two weeks in an attempt to prepare the cycloadduct (2.109). At the end of this period the reaction mixture was analysed by t.l.c., g.l.c., i.r. spectroscopy and ^{1}H.n.m.r. spectroscopy, all of which indicated that only the starting materials were present. This result was not entirely unexpected.

More enthusiasm was generated for the procedure established by Paquette,[41] illustrated earlier in Scheme 2.22, involving the reaction of benzobarrelenone (2.6) with toluene-p-sulphonyl hydrazine to form the tosyl hydrazone (2.82) which on treatment with methyl lithium yielded benzobarrelene (2.83). Investigations involving tetrafluorobenzobarrelenone (2.4) had been curtailed due to the successful application of Zimmerman's[31] procedure. It was therefore, considered worth while investigating the tosyl hydrazine reaction further.

The ketone (2.5) was reacted with tosyl hydrazine under the same conditions as discussed for the ketone (2.4). A white crystalline solid

Scheme 2.32

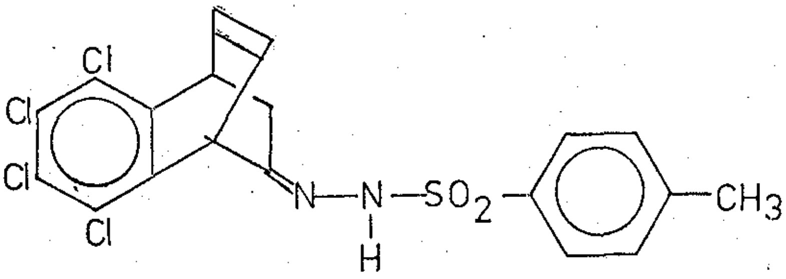


was isolated, mp.227-230° (benzene) in 90% yield. Infra-red spectroscopy indicated that the carbonyl stretching frequencey in the starting material (1740 cm^{-1}) had disappeared. The ^{1}H.n.m.r. spectrum and mass spectral data indicated that the required hydrazone (2.110) had been formed.

A number of different procedures were used in an attempt to degrade the hydrazone (2.110) to the required tetrachlorobenzobarrelene (2.105). The procedures are indicated below:-

(i) (2.110) + 1 equiv. n-butyl-lithium

(ii) (2.110) + 2 equiv. n-butyl-lithium



(2.110)

(iii) (2.110) + 3 equiv. n-butyl-lithium

(iv) (2.110) + Na/T.H.F./t-BuOH

(v) (2.110) + K t-Butoxide

The results of experiments (i)-(iii) indicated a complex mixture of products. The required product (2.105) was present, as indicated by g.l.c., but in very low yield. It was feasible that a side-reaction, dechlorination, was occurring and an attempt was made (iv) to degrade and dechlorinate the hydrazone (2.110) to benzobarrelene (2.83) in one step. The normal purple colour associated with the completion of the dechlorination (chapter 1) was not formed. The product was again a complex mixture. Reaction (v) also failed yielding only starting material.

The hydrazone (2.82) of benzobarrelenone was prepared in a similar manner and subjected to a series of reactions with n-butyl-lithium. Once again mixtures were obtained containing the required benzobarrelene

(2.83) but not in high enough yield to be suitable for further degradation.

It was assumed that given time a solution to the above problem could have been found, particularly in the light of Paquette's[41] success. However, time was running short and the desire to complete this work led us on to greener pastures.

Earlier investigations involving the reaction of tetrafluoronaphthalene with either tetrachloro- or tetrafluorobenzyne had already indicated the reluctance of this naphthalene to undergo 1,4-cycloaddition. This was not the case with naphthalene (2.87) and tetrachlorobenzyne when the former was present in large excess,[14b] as shown in Scheme 2.26. The product (2.94) was isolated in 34% yield.

Our experience, gained in the small scale reactions of tetrachloro- and tetrafluorobenzyne with anisole, enabled us to overcome the necessity of a large excess of naphthalene. Careful investigation of the reaction between tetrachlorobenzyne and naphthalene, in a mole ratio of 2:1 respectively, indicated that the required adduct (2.94) could be obtained, albeit in low yield. Fortunately the yield could be increased to *ca*. 15% by separating the unreacted naphthalene and the product (2.94) by preparative chromatography and subjecting the recovered naphthalene to a second and even third reaction if necessary. The success of this procedure was no mean feat when it is considered that at this stage of the degradation only 100-200mg. of naphthalene was to be expected.

During these small scale preparations an intense blue colour was noted on addition of the naphthalene in ether to the pentachlorophenyl lithium solution. The colour of the solution lightened as the reaction proceeded. The appearance of this colour could be due to similar problems discussed in chapter 1.

The compound (2.94) was isolated as a white crystalline material, and its spectral data compared favourably with that of authentic material.[14b]

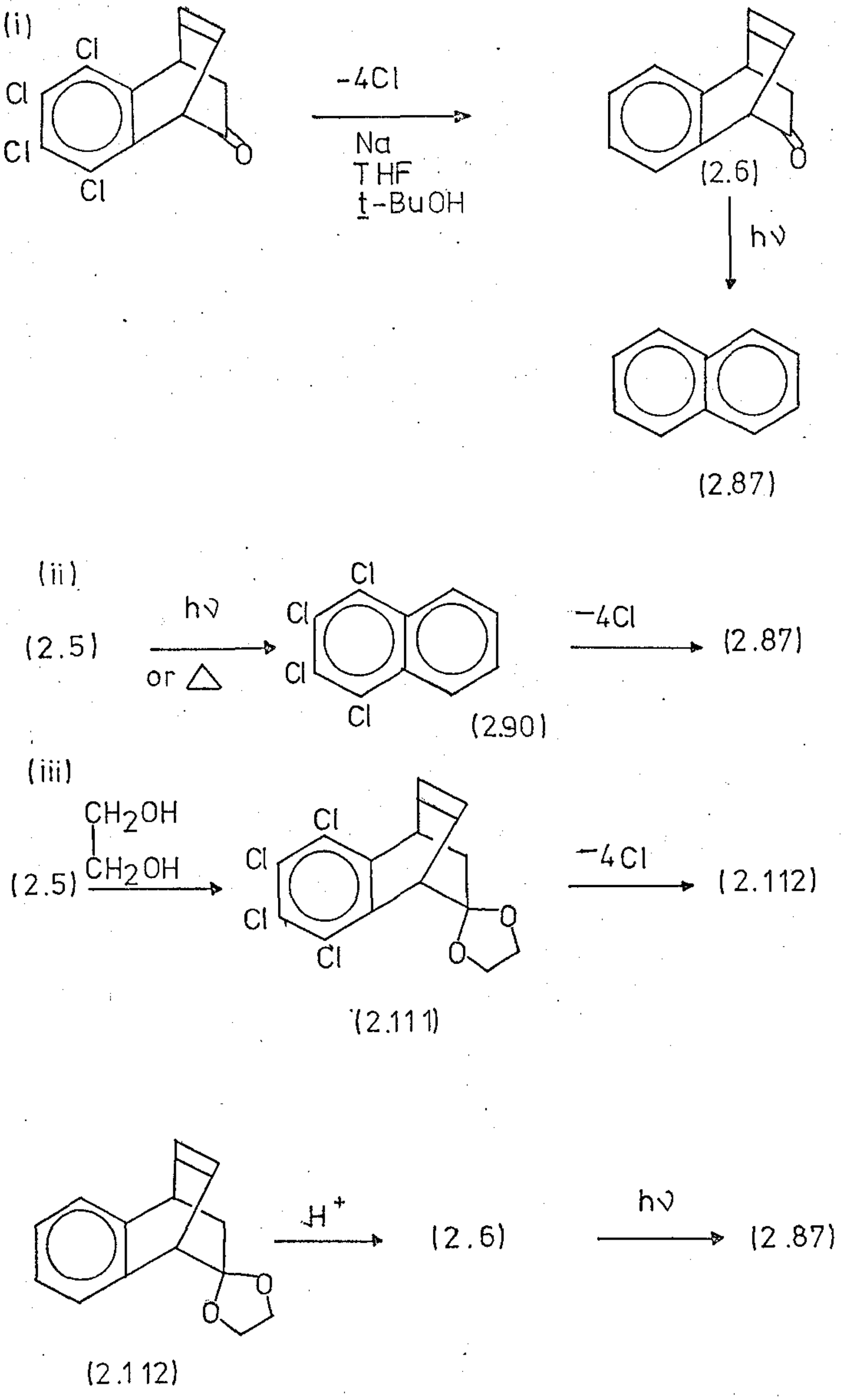
Two cycloaddition-fragmentation procedures were investigated for degrading the compound (2.94). The first, illustrated in Scheme 2.26, involved reaction with the tetrazine (2.64) to yield tetrachloroanthracene (2.97) and the pyridazine (2.67). The second involved p-nitrophenyl azide (2.75) to form the same anthracene (2.97) and p-nitrophenyl-triazine (2.76). Both routes proved successful in the isolation of tetrachloroanthracene by preparative chromatography. However, it was easier to isolate the pyridazine (2.67) from the impurities present, than to isolate the triazine (2.76). Hence, the former reaction was selected to complete the degradation procedure.

Tetrachloroanthracene (2.97) was isolated as a yellow-green crystalline compound, mp. 215-216° (lit.[66a] 217-219°). The i.r. and u.v. spectroscopy data also compared favourably with published values.[66b]

Since it was not feasible to react tetrachloronaphthalene with tetrachlorobenzyne, for the same reasons inhibiting the reaction between tetrafluoronaphthalene and an aryne, it was necessary to devise a procedure of preparing naphthalene from either tetrachloronaphthalene or tetrachlorobenzobarrelenone. Scheme 2.33 illustrates three potential ways of solving this problem.

Dechlorination of the ketone (2.5), using the established procedure

Scheme 2.33



(i)
Cl
Cl
Cl
Cl
-4Cl
Na
THF
t-BuOH
(2.6)
hν
(2.87)
(ii)
(2.5)
hν
or △
Cl
Cl
Cl
Cl
(2.90)
-4Cl
(2.87)
(iii)
CH2OH
CH2OH
(2.5)
Cl
Cl
Cl
Cl
O
O
(2.111)
-4Cl
(2.112)
O
O
(2.112)
H+
(2.6)
hν
(2.87)

(chapter 1), gave the confirmatory purplecolour, but analysis of the product by g.l.c. and ^{1}H.n.m.r. spectroscopy indicated neither the required ketone (2.6) nor the starting ketone (2.5). Further analysis of the data indicated that the product was a mixture of naphthalene (2.87) and tetralin (2.113) with the latter predominating. This result was rather surprising since a similar reaction, mentioned earlier, failed to convert the hydrazone (2.110) to either tetrachlorobenzobarrelene or benzobarrelene in anything but very low yields.

A second dechlorination of the ketone (2.5) was carried out and the reaction followed by g.l.c.. After a reaction time of ca. 1hr., peaks for naphthalene and tetralin were present with the former predominating. Peaks for benzobarrelenone, benzobarrelene or tetrachloronaphthalene were not observed. Analysis after ca. 4hr. showed that the peak for tetralin now predominated over that of naphthalene but also a third peak with a retention time similar to that of tetrachloronaphthalene had appeared. After ca. 6hr. only peaks for naphthalene and tetralin were present and after ca. 12hr. the product was mainly tetralin.

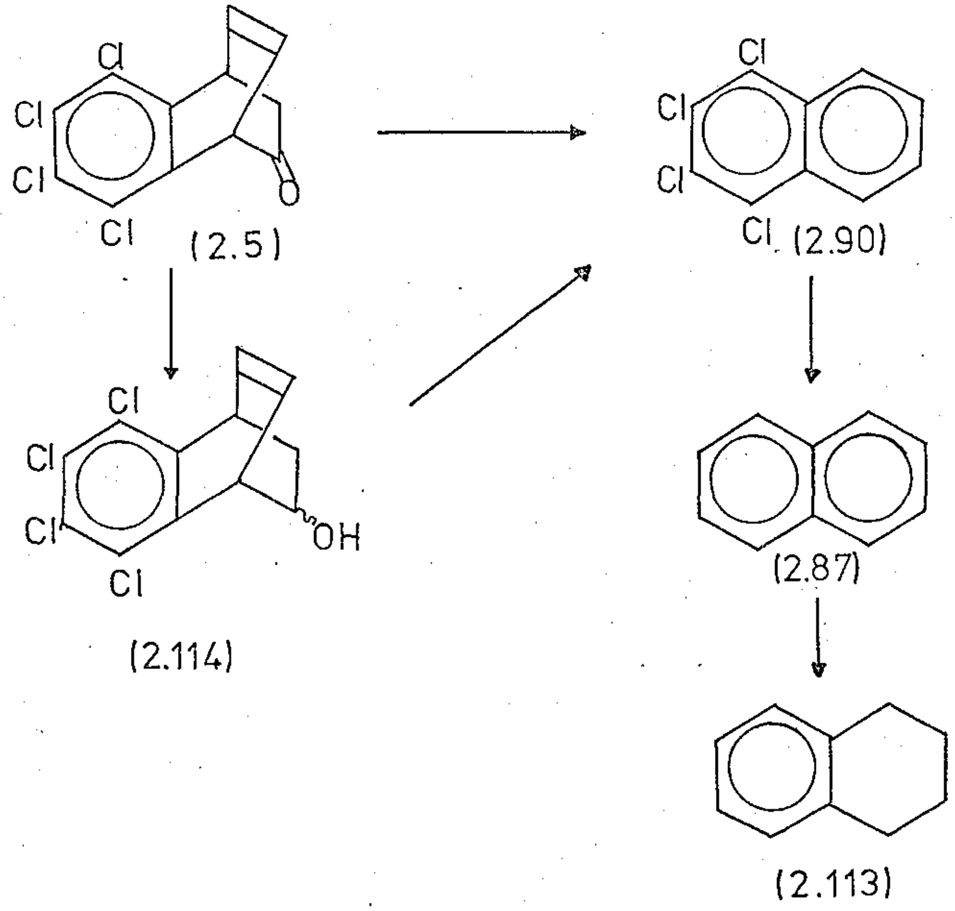
Tetrachloronaphthalene was dechlorinated under the same conditions and after ca. 3hr. g.l.c. indicated no starting material. Tetrachloronaphthalene was prepared in ca. 94% yield by the flash thermolysis of tetrachlorobenzobarrelene at ca. 650°.

The same procedure with naphthalene gave after 24hr. tetralin containing only a trace of naphthalene.

Although the evidence is limited a number of conclusions can be tentatively drawn regarding the conversion of the ketone (2.5) to tetralin

(2.113) as shown in Scheme 2.34.

Scheme 2.34



The fact that no intermediates, other than small amounts of tetrachloronaphthalene, were recorded in the conversion of the ketone (2.5) to naphthalene (2.87) indicates either an intermediate such as the compound (2.114) which would not register on g.l.c. or a fast reaction via tetrachloronaphthalene. The latter compound (2.90) was also shown to dechlorinate very quickly to naphthalene and tetralin. The relative slowness in the reduction of naphthalene to tetralin under the reaction conditions indicates that dechlorination is an easier option than reduction for the tetrachloronaphthalene.

It was decided that the above procedure was not suitable for the preparation of naphthalene from the ketone (2.5) for two reasons:-

(i) The mixture of naphthalene and tetralin was not isolated in a quantitative yield. Minor impurities were present which were not characterised.

(ii) It was feasible to prepare naphthalene from tetralin but it was not easy to isolate tetralin from naphthalene. Also there was a danger of loss of the tetralin due to it being a reasonably volatile liquid.

The second procedure, shown in Scheme 2.33, involved photolysis of the ketone (2.5) to tetrachloronaphthalene followed by dechlorination. The use of sodium, t-butyl alcohol and tetrahydrofuran was obviously out of the question. An alternative method involved the use of PdC(10%) and hydrazine hydrate. A solution of tetrachloronaphthalene, ethyl alcohol, PdC. and hydrazine hydrate was refluxed for ca. 6hr.. Naphthalene (2.87) was isolated in a crude form, in yields varying from 60-90%. Analysis of the product by g.l.c. and ^{1}H.n.m.r. spectroscopy indicated no trace of tetralin.

A third method involving the reaction of the ketone (2.5) with ethylene glycol and boron trifluoride-etherate in dichloromethane was considered. The combined solution was stirred at room temperature for ca. 50hr., and the crude 2,2-ethylenedioxy-2,3-dihydrotetrachlorobenzobarrelene (2.111) was isolated in an almost quantitative yield. The i.r. and

^{1}H.n.m.r. spectra compared favourably with authentic material.[20e]

The ethylene ketal (2.111) was dechlorinated using sodium, *t*-butyl alcohol and tetrahydrofuran under the normal conditions. The product was isolated by preparative chromatography as a white crystalline product mp.115-117°. The infra-red spectrum showed no carbonyl stretching frequency and gave major peaks at 2960, 2855, 1470, 1455, 1435, 1340, 1310, 1265, 1250, 1205, 1115, 1095, 1010, 950, 910, 825, 760, 710 and 670 cm^{-1}. The ^{1}H.n.m.r. spectrum showed a multiplet at τ. 2.7-2.95 for four aromatic protons, a multiplet at τ. 3.2-3.55 for two olefinic protons, a multiplet at τ. 5.9-6.2 for six protons ascribed to two bridgehead protons and four protons of the dioxalanyl-group and finally a quartet of doublets at τ. 7.9-8.35 for two protons of a methylene group. The mass spectrum of the product gave a molecular ion (M^{+}) at 214. The combined data correlates very well with that expected for the required ethylene ketal (2.112), which was isolated in 90% yield.

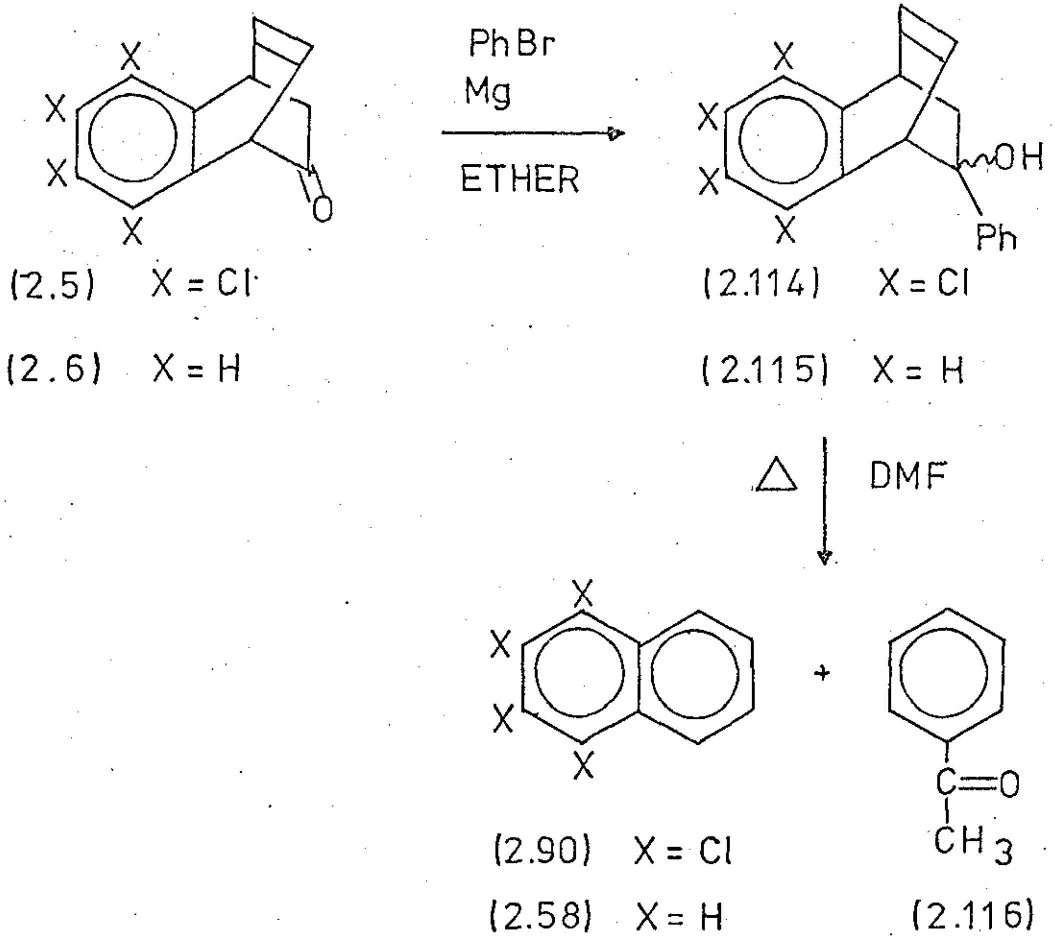
Reaction of the ethylene ketal (2.112) with concentrated hydrocloric acid resulted in the rapid hydrolysis to crude benzobarrelenone (2.6), identified by the re-appearance of a carbonyl stretching frequency at *ca.* 1740 cm^{-1} in the i.r. spectrum. Results discussed earlier indicate that the ketone (2.6) can be converted to naphthalene, in a quantitative yield, by photolysis.

Although it was now possible to prepare and degrade the two ketones (2.5) and(2.6) the procedure involved a photolysis experiment which resulted in the loss of ketene. If the mechanisms for the rearrangement of the 1-methoxybenzobarrelenes (2.1)-(2.3) to the ketones (2.4)-(2.6), as determined by the deuterium labelling studies,[20d] were correct then the two carbons lost as ketene in the photolysis experiments should contain no ^{14}C activity. It was decided to investigate methods of isolating these two carbons in a product which could be counted accurately.

It is possible to trap ketene with primary and secondary amines, to give, respectively, N-substituted and N,N-disubstituted amides, but this did not seem practical on the scale we were operating.

Finally the procedure shown in Scheme 2.35 was established. The ketone (2.5) or (2.6) was reacted with phenyl magnesium bromide in dry ether. The reaction was stirred at room temperature until completion, indicated by t.l.c.. The crude carbinol (2.114) or (2.115) was isolated by preparative chromatography and degraded to the respective naphthalene (2.90) or (2.87) and acetophenone (2.116) by heating under reflux in dimethylformamide for ca. 12 hr.. After hydrolysis of the solution the mixture was extracted with ether and the two products separated by preparative chromatography. The two carbons were thus trapped as acetophenone. Unfortunately acetophenone is a liquid and therefore, not suitable for accurate counting. Therefore, the crystalline derivatives shown in Scheme 2.36 were investigated and the oxime (2.117) identified as the most suitable for small scale preparation. Acetophenone was treated with hydroxylamine hydrochloride and sodium acetate in water. The crude oxime was precipitated from this solution by the addition of ethyl alcohol to give a clear solution which was gently heated, on a steam bath for ca. 10 min., followed by cooling in an ice bath. The crude product was filtered and recrystallised to give the required oxime

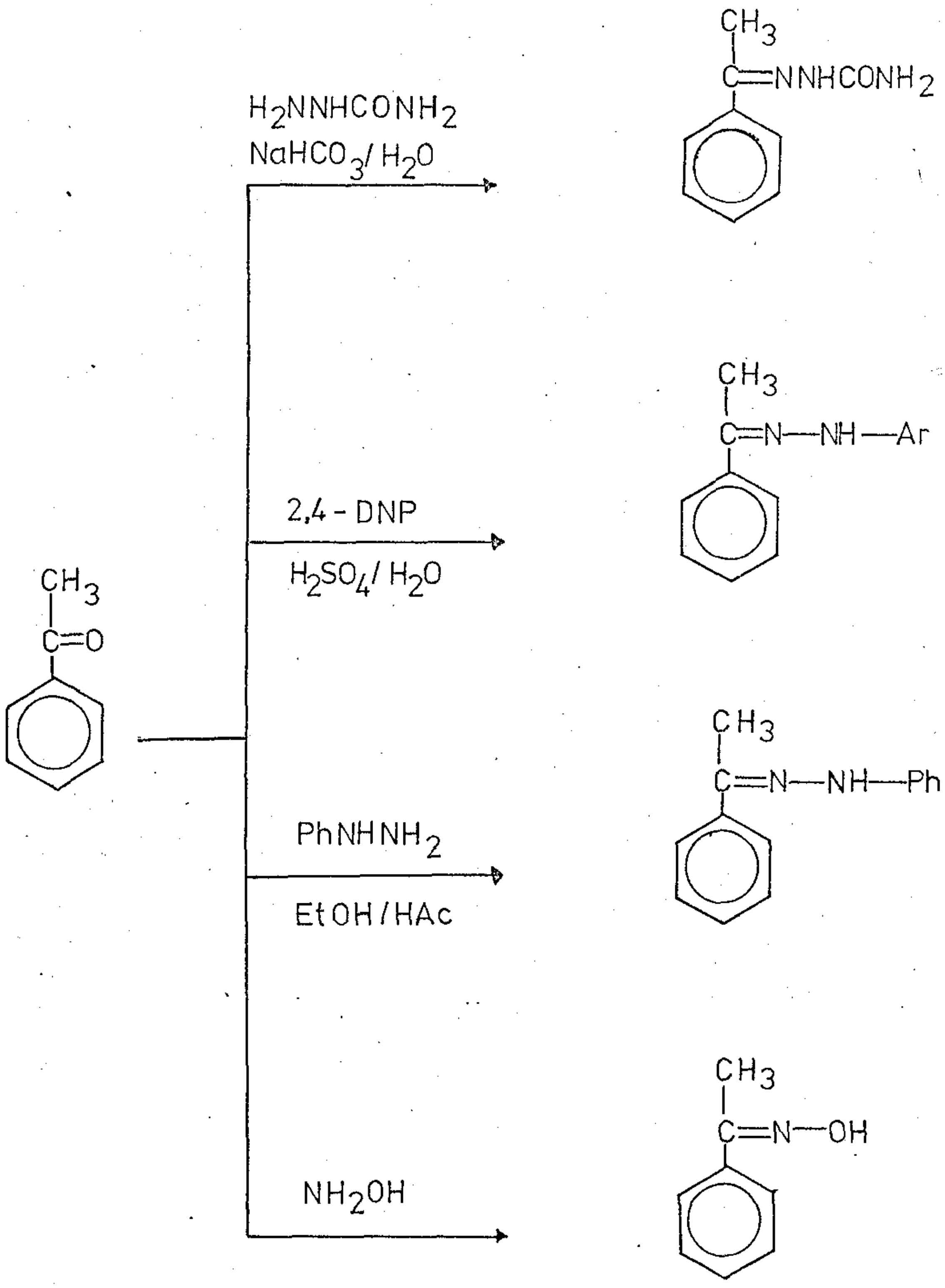
Scheme 2.35


X
PhBr
Mg
ETHER
OH
Ph
(2.5) X = Cl
(2.6) X = H
(2.114) X = Cl
(2.115) X = H
△
DMF
+
C=O
CH3
(2.90) X = Cl
(2.58) X = H
(2.116)

(water) (2.117) as white crystals mp. 59-60° (lit.[67] 60°).

The complete procedures established for the degradation of the ketones (2.5) and (2.6) are illustrated in Schemes 2.37 and 2.38 respectively.

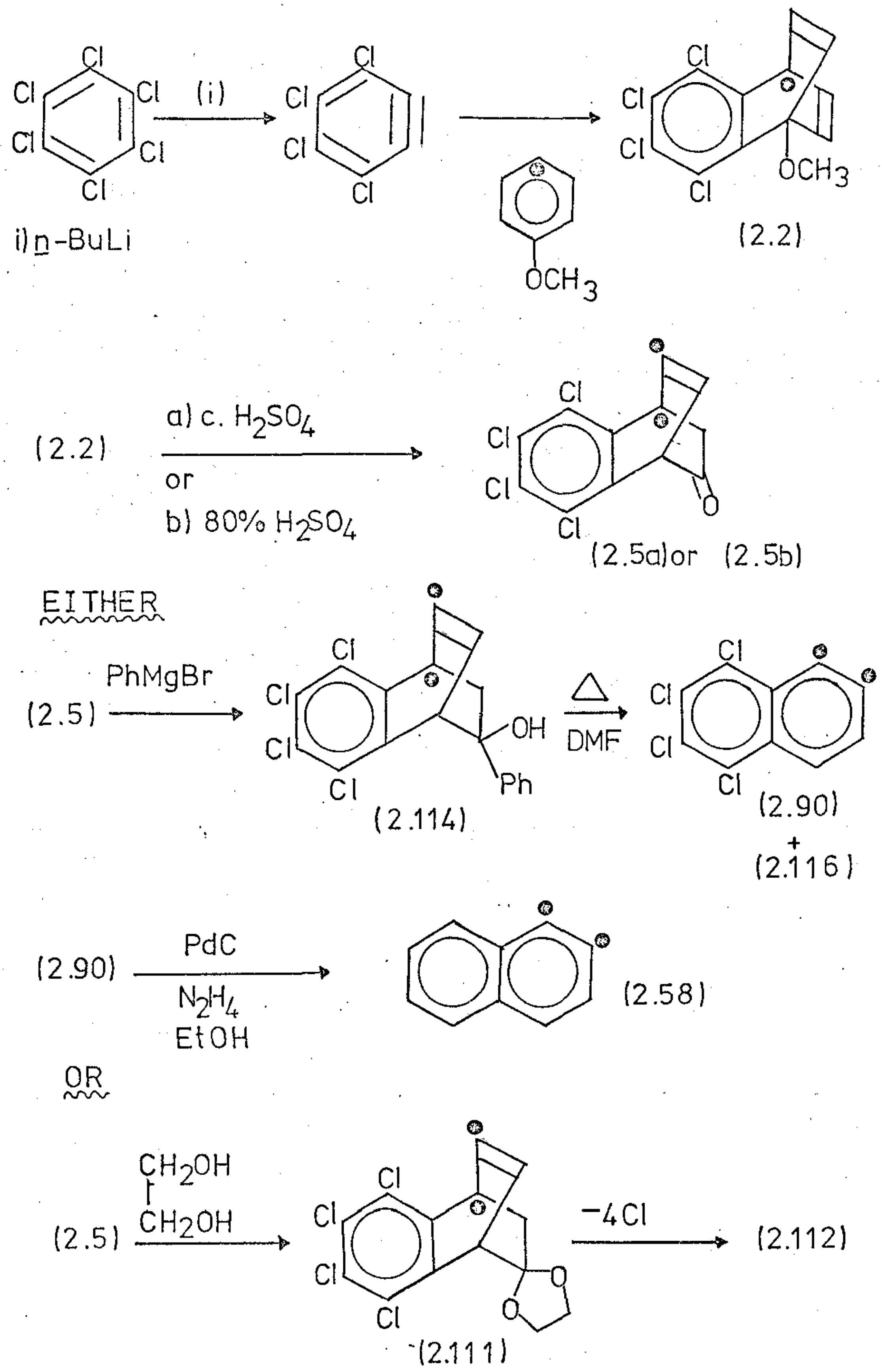
Scheme 2.36



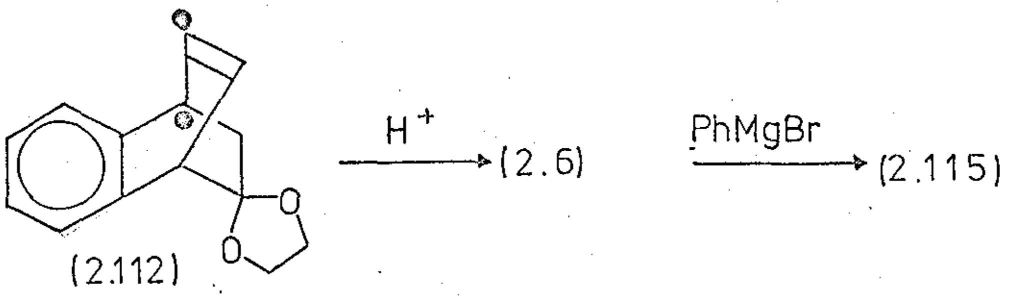
CH3
C=O
H2NNHCONH2
NaHCO3/ H2O
CH3
C=NNHCONH2
2,4 - DNP
H2SO4/ H2O
CH3
C=N—NH—Ar
PhNHNH2
EtOH/HAc
CH3
C=N—NH—Ph
NH2OH
CH3
C=N—OH

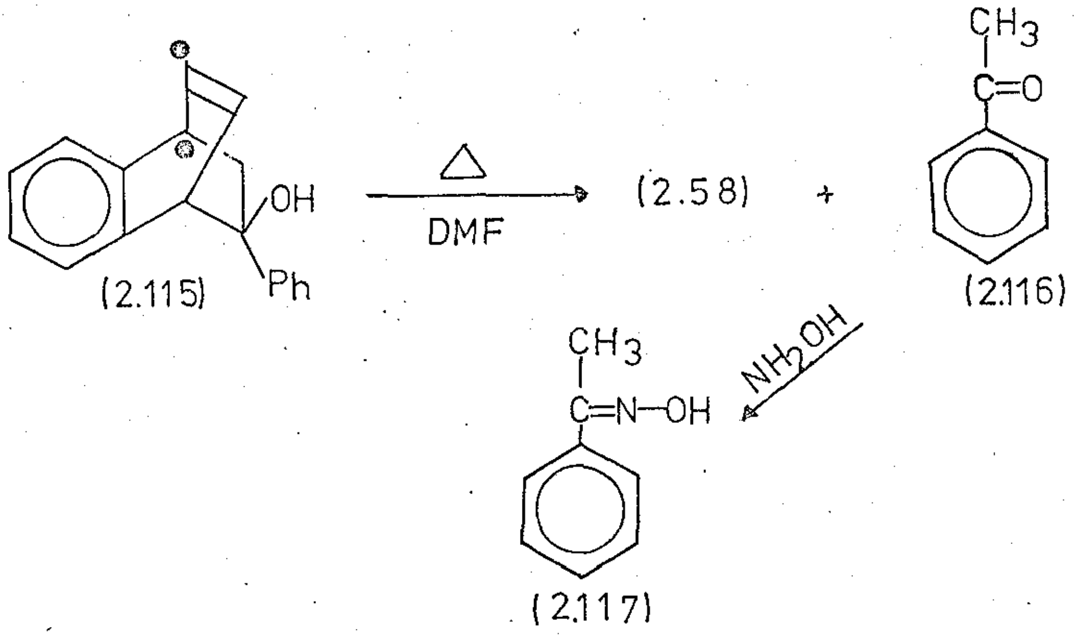
(2.117)

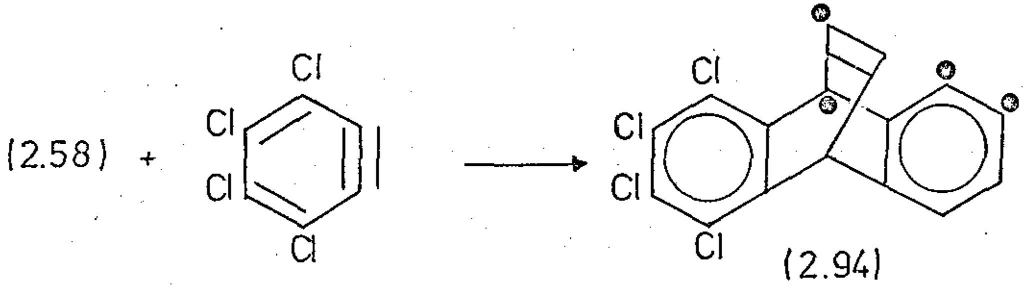
Scheme 2.37

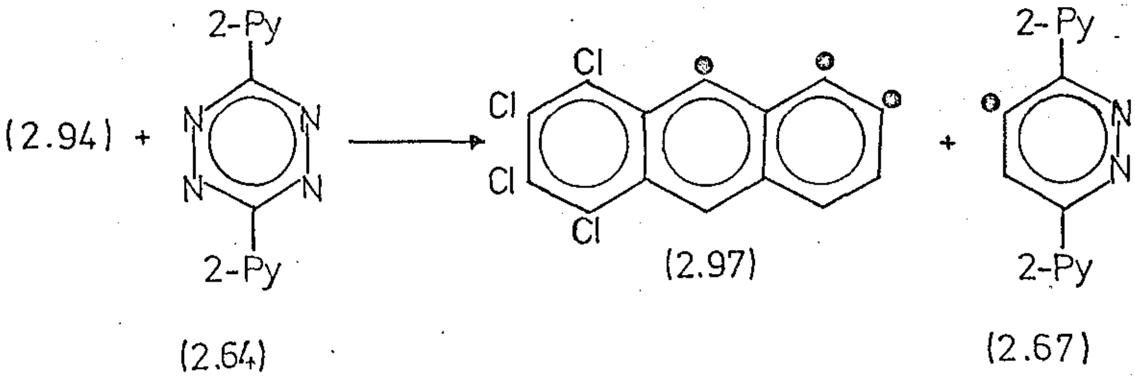


Cl
Cl
Cl
Cl
Cl
Cl
(i)
i) n-BuLi
OCH3
OCH3
(2.2)
(2.2)
a) c. H2SO4
or
b) 80% H2SO4
O
(2.5a)or (2.5b)
EITHER
(2.5)
PhMgBr
OH
Ph
(2.114)
DMF
(2.90)
+
(2.116)
(2.90)
PdC
N2H4
EtOH
(2.58)
OR
(2.5)
CH2OH
CH2OH
O
O
(2.111)
−4Cl
(2.112)

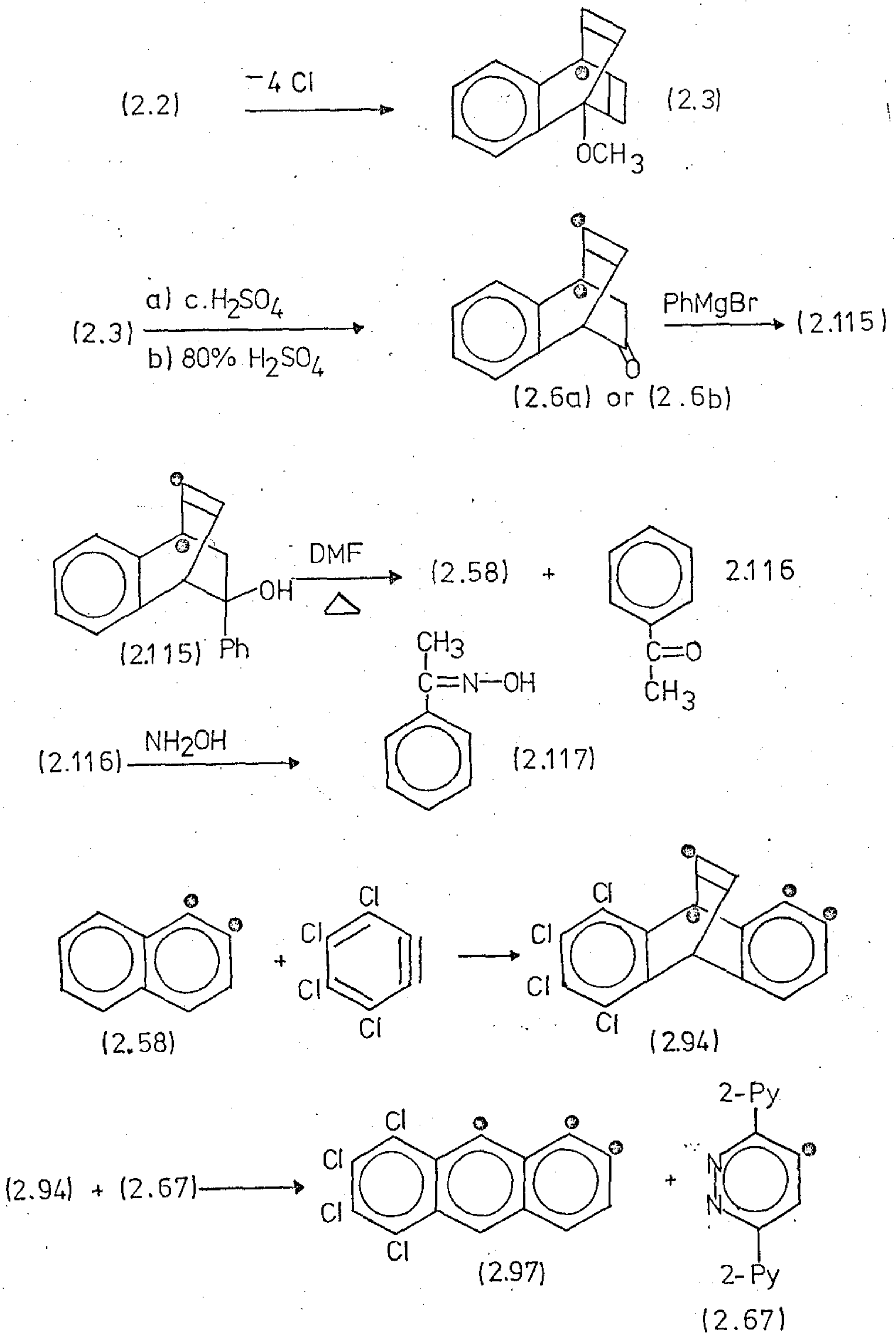

(2.112)
O
O
H+
(2.6)
PhMgBr
(2.115)


(2.115)
OH
Ph
△
DMF
(2.58)
+
CH3
C=O
(2.116)
NH2OH
CH3
C=N—OH
(2.117)


(2.58)
+
Cl
Cl
Cl
Cl
Cl
Cl
Cl
Cl
(2.94)


(2.94)
+
2-Py
N
N
N
N
2-Py
(2.64)
Cl
Cl
Cl
Cl
(2.97)
+
2-Py
N
N
2-Py
(2.67)

Scheme 2.38


(2.2)
−4 Cl
(2.3)
OCH3
(2.3)
a) c.H2SO4
b) 80% H2SO4
(2.6a) or (2.6b)
PhMgBr
(2.115)
OH
(2.115)
Ph
DMF
△
(2.58)
+
2.116
C=O
CH3
CH3
C=N−OH
(2.116)
NH2OH
(2.117)
(2.58)
+
Cl
Cl
Cl
Cl
Cl
Cl
Cl
Cl
(2.94)
(2.94) + (2.67)
Cl
Cl
Cl
Cl
(2.97)
+
2-Py
N
N
2-Py
(2.67)

Preparation and Rearrangement of the [4-^{14}C]-1-methoxybenzobarrelenes (2.2) and (2.3)

Tetrachlorobenzyne was reacted with [4-^{14}C]-anisole to yield the required [4-^{14}C]-1-methoxytetrachlorobenzobarrelene (2.2) (9.44g.) as a crude crystalline product. A portion (ca. 7.5g.) was dechlorinated to [4-^{14}C]-1-methoxybenzobarrelene (2.3) (1.2g.). The remaining sample (1.94g.) was diluted with 1-methoxytetrachlorobenzobarrelene (2.2) (1.0g.) and the combined sample counted to constant activity.

The [4-^{14}C]-1-methoxybenzobarrelene (2.3) (1.2g.) was also diluted with unlabelled compound (2.3) (1,0g.) and then recrystallised to constant activity.

The [^{14}C]- compound (2.2) (1.0g.) was rearranged in concentrated sulphuric acid at room temperature to yield the ketone (2.5a) and in dilute sulphuric acid (H_2SO_4:H_2O, 4:1 $^{v}/v$) at 80° to give the ketone (2.5b).

Similar rearrangments with the compound (2.3) gave the ketones (2.6a) and (2.6b) respectively. Each of the four ketones was isolated by preparative chromatography and recrystallised to constant activity.

The failure of the first attempt to degrade the ketones (2.5a) and (2.5b), discussed in the following section, resulted in the remaining crude compound (2.2) (ca. 0.9g) having to be diluted with 1-methoxytetrachlorobenzobarrelene (2.2) (ca. 1g.) and the counting to constant activity followed by rearrangement to the ketones (2.5a) and (2.5b) repeated.

Degradation of the [^{14}C]-Ketones (2.5a) and (2.5b)

The degradation procedure for the ketones (2.5a), (2.5b) and (2.6a), (2.6b) were as illustrated in Schemes 2.37 and 2.38 respectively. It would be fair to say that the success of these degradations "lay in the laps of the proverbial gods". The degradation of tetrafluorobenzobarrelenone (2.4) had involved only four steps whilst degradation of the ketones (2.5) and (2.6) involved seven and four steps respectively. The pinnacle of the latter degradations was the reaction between naphthalene and tetrachlorobenzyne, it was considered that at this point the scales could be tipped to either success or failure.

The first attempt to degrade the tetrachlorobenzobarrelenones (2.5a) and (2.5b) used the first route shown in Scheme 2.37 involving the reaction with phenyl magnesium bromide, followed by thermolysis of the product (2.114) to yield tetrachloronaphthalene and acetophenone. The reason for the preferential choice of this procedure, over the second method, was purely a practical one. The former required only three steps and the latter five steps to reach the required naphthalene (2.58). It was therefore, judged that the first procedure would give a higher yield of the product (2.58).

The two samples of acetophenone were reacted to give the required oxime (2.117) and the two samples were subjected to the counting procedure.

The two samples of tetrachloronaphthalene were counted to constant activity and then dechlorinated using PdC(10%) and hydrazine hydrate to yield crude naphthalene. Unfortunately the two samples of naphthalene did not react with tetrachlorobenzyne to form the required product (2.94).

A policy had been adopted throughout the degradation studies to always use the crude product in the next step and hence reduce loss in yield. It was a strong possibility that impurities were interfering in the above reaction. Although the naphthalene had been isolated by preparative chromatography (silica gel) it was feasible that an impurity with a similar Rf. value had also been isolated. Such an impurity could have been unreacted tetrachloronaphthalene which had already been shown not to react with tetrachlorobenzyne.

It was not possible to isolate the naphthalene from the crude reaction mixture due to the vast number of bands which appeared in the Rf. region for naphthalene when separation by preparative chromatography was attempted.

The results obtained in the above study are shown in Tables IIIA and IIIB.

The second attempt to degrade the ketones (2.5a) and (2.5b), using the diluted $[^{14}C]$-ketones, involved the second procedure shown in Scheme 2.37. This procedure was more successful than the first but the yields of naphthalene were low ca. 30-50mg. The low yields caused extreme difficulty in the final two steps but eventually samples of the required tetrachloroanthracene (2.97) and the pyridazine (2.67) were obtained. The crude samples of the product (2.97) (ca. 10-20mg.) were sublimed to constant activity, the samples of the crude pyridazine (2.67) (ca. 30mg.) would not crystallise (ethanol) and therefore, it was not possible to measure their activity accurately. The activity of the pyridazines (2.67) was calculated by subtracting the specific activity of the respective tetrachloroanthracene (2.97) from that of the starting ketone (2.5).

Tables IVA and IVB illustrate the results from this degradation.

Degradation of the $/ ^{14}C$ 7-Ketones (2.6a) and (2.6b)

Similar problems to those above were encountered in the degradation procedure, shown in Scheme 2.38, for the ketones (2.6a) and (2.6b). The results are shown in Tables V and VI.

The poor results in the degradation of the ketone (2.6b) resulted in a very low yield of the required tetrachloroanthracene (2.97) (ca. 5mg.) which proved too difficult to sublime. The crude pyridazine (2.67) from this reaction would not recrystallise but a count was made on the crude material. However, the activity was extremely low 2.05×10^{-3} µCi/m.mol.. Such a low result could have been caused by contamination of the active pyridazine (2.67) with an inactive impurity for example the unreacted tetrazine (2.64). It was not possible to draw conclusions from these results and so the degradation of the ketone (2.6b) was disregarded in the final analysis.

Table IIIA. Rearrangement of $/ 4-^{14}C$ 7-1-methoxytetrachlorobenzobarrelene (2.2) in conc. H_2SO_4 at room temperature.

COMPOUND (^{14}C)	Specific Activity µCi/m.mol.
1-methoxytetrachlorobenzobarrelene (2.2)	7.2×10^{-2}
Tetrachlorobenzobarrelenone (2.5a)	7.31×10^{-2}
Tetrachloronaphthalene (2.90)	7.34×10^{-2}
Acetophenone Oxime (2.117)	0

TABLE IIIB Rearrangement of [4-^{14}C]-1-methoxytetrachlorobenzobarrelene (2.2) in dilute H_2SO_4 (H_2SO_4 : H_2O, $^4/_1$, $^v/_v$.) at 80°

COMPOUND (^{14}C)	Specific Activity μ.Ci./m.mol.
1-methoxytetrachlorobenzobarrelene (2.2)	7.2×10^{-2}
Tetrachlorobenzobarrelenone (2.5b)	7.30×10^{-2}
Tetrachloronaphthalene (2.90)	7.22×10^{-2}
Acetophenone Oxime (2.117)	0

TABLE IVA Rearrangement of [4-^{14}C]-1-methoxytetrachlorobenzobarrelene (2.2) in conc. H_2SO_4 at room temperature.

COMPOUND (^{14}C)	Specific Activity μ.Ci./m.mol.
1-methoxytetrachlorobenzobarrelene (2.2)	4.07×10^{-2}
Tetrachlorobenzobarrelenone (2.5a)	4.06×10^{-2}
Tetrachloroanthracene (2.97)	2.21×10^{-2}
Pyridazine (2.67)	[1.85×10^{-2}]

TABLE IVB Rearrangement of [4-^{14}C]-1-methoxytetrachlorobenzobarrelene (2.2) in dilute H_2SO_4 (H_2SO_4 : H_2O, 4:1, $^v/_v$) at 80°

COMPOUND (^{14}C)	Specific Activity μ.Ci./m.mol.
1-methoxytetrachlorobenzobarrelene (2.2)	4.07×10^{-2}
Tetrachlorobenzobarrelenone (2.5b)	4.06×10^{-2}
Tetrachloroanthracene (2.97)	2.35×10^{-2}
Pyridazine (2.67)	[1.71×10^{-2}]

*[ ] Activity value calculated by subtraction of the activity of the product (2.97) from the respective ketone (2.5a) or (2.5b).

TABLE V Rearrangement of [4-^{14}C]-1-methoxybenzobarrelene (2.3) in conc. H_2SO_4 at room temperature.

COMPOUND (^{14}C)	Specific Activity µ.Ci./m.mol.
1-methoxybenzobarrelene (2.3)	4.14×10^{-2}
Benzobarrelenone (2.6a)	4.21×10^{-2}
Acetophenone Oxime (2.117)	0
Tetrachloroanthracene (2.97)	2.17×10^{-2}
Pyridazine (2.67)	1.96×10^{-2}

TABLE VI Rearrangement of [4-^{14}C]-1-methoxybenzobarrelene (2.3) in dilute H_2SO_4 (H_2SO_4:H_2O, 4:1, $^{v}/_{v}$) at 80°

COMPOUND (^{14}C)	Specific Activity µ.Ci./m.mol.
1-methoxybenzobarrelene (2.3)	4.14×10^{-2}
Benzobarrelenone (2.6b)	4.21×10^{-2}
Acetophenone Oxime (2.117)	0
Tetrachloroanthracene (2.97)	[4.01×10^{-2}]
Pyridazine (2.67)	(0.20×10^{-2})

* ( ) Specific activity of the product (2.67) determined on a crude sample.

[ ] Specific activity determined by subtraction of the activity of the product (2.67) from the ketone (2.6b).

Combined Analysis of the ^{14}C results for the degradation of the ketones (2.4) - (2.6)

A similar manipulation of the results in tables IVA, IVB and V, as for the results in tables I and II, allow the percentage ratio of the two pathways (a) and (b) (Scheme 2.1), proposed for the formation of the ketones (2.4) - (2.6), to be estimated for the ketones (2.5a), (2.5b) and (2.6a). The results are shown in the following table:-

Methoxybenzobarrelene	Ketone	%(a)	%(b)
(2.1)	(2.4a)	76.4	23.6
(2.1)	(2.4b)	68.2	31.8
(2.2)	(2.5a)	91.1	8.9
(2.2)	(2.5b)	84.3	15.7
(2.3)	(2.6a)	95.0	5.0

Thus, the rearrangement of $[4-^{14}C]$-1-methoxytetrachlorobenzobarrelene (2.2) in concentrated sulphuric acid (98%), at room temperature, proceeded to the $[^{14}C]$-tetrachlorobenzobarrelenone (2.5a) in the ratio 91.1% pathway (a) and 8.9% pathway (b). Similarly in dilute sulphuric acid (H_2SO_4:H_2O, 4:1, $^v/_v$), at 80°, the formation of the $[^{14}C]$-ketone (2.5b) was in the ratio 84.3% (a) and 15.7% (b).

The corresponding results for the rearrangement of $[4-^{14}C]$-1--methoxybenzobarrelene (2.3) to benzobarrelenone (2.6a) in concentrated sulphuric acid (98%), at room temperature, were 95.0% (a) and 5.0% (b).

The samples of acetophenone oxime (2.117) were counted and within experimental error indicated no activity above that expected for the background count.

ERRORS.

There are three potential sources of error in this type of investigation, (i) weighing errors, (ii) counting errors and (iii) errors due to the presence of impurities.

(i) Weighing:- Each sample was weighed to six decimal places of a gram. The balance used was very susceptible to localised disturbances i.e. temperature and vibration. When possible samples of 1-4mg. were weighed and each sample was allowed to stabilise for 5min.. The readings were normally constant after this period of time. This procedure was accurate to more than ± 0.01mg.. Hence the larger the sample the greater the accuracy of weighing.

(ii) Counting:- If a number of determinations of the count rate from a radioactive sample are made it is unlikely that they will be identical. This is due to the random nature of radioactive decay. If a very large number of determinations were made and the values plotted against the frequency of their occurrence, the curve produced would at least approximate to the Gaussian frequency distribution curve and the mean value could be regarded as the true value of the count rate. In practice, the mean count rate has to be determined from a comparatively small number of observations and so may differ from the true value by an amount which can be assessed by normal statistical methods. This possible error is one of the features which limit the accuracy of radiochemical methods. It is usual to calculate the standard deviation given by the formula:-

$$\sigma = \pm \sqrt{\sum \frac{(x - \bar{x})^2}{n}}$$

$\bar{x}$ = mean of the distribution.

n = number of values in the distribution.

If only one reading is taken then this reading will have to be taken as equivalent to the average count. For a Poisson distribution the standard deviation is equal to the square root of the mean count. This is justifiable since the square root of a large number is small compared with the number.

Using this theory the probability that the result found falls within $\pm 1\sigma$, $\pm 2\sigma$ and $\pm 3\sigma$ of the true value are respectively 68.3, 95.4 and 99.7%.

In our studies counting errors were likely to occur ~~due to~~ because of, the low specific activity of some of the samples and limited quantity of sample for purification and counting.

In an attempt to alleviate these potential sources of counting error each sample was counted for the maximum period of counting time (500min.) and the scintillation counter's preset error was set at its minimum value (0.2%). This latter value meant that when possible each sample was counted for 1×10^6 counts and that this value had an accuracy of $1 \times 10^6 \pm 2000$ (0.2%) with a probability of 95.4%. The efficiency of counting was determined as previously mentioned using a ^{137}Cs external standard. The efficiency was normally in the region of 94% and each value was corrected accordingly.

(iii) Impurities:- Each sample was either sublimed or recrystallised to constant activity whenever possible. Analysis of the degradation products from the unlabelled studies indicated no impurities after purification. However, the low yields and difficulties encountered during the degradation of the ketones (2.5) and (2.6) increased the possibility of contamination. Such a result would obviously affect the accuracy of the ^{14}C activity measurement.

Considering the above sources of error and calculations involving the specific activities of the various products, at constant activity, the following total errors have been estimated.

For the degradation of the [^{14}C]-tetrafluorobenzobarrelenones (2.4a) and (2.4b) the error is less than ± 2%.

In the case of [^{14}C]-tetrachlorobenzobarrelenone (2.5a) and (2.5b) and [^{14}C]-benzobarrelenone (2.6) the average specific activities of the degraded products were calculated from specific activities with a variance of up to ± 6%

CONCLUSIONS

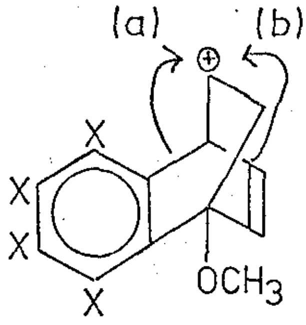
The initial objective of the ^{14}C labelling studies was to establish the accuracy of the deuterium labelling results.[20c,d] The latter results were based on a number of assumptions mentioned in the introduction to this chapter. It has already been indicated that the corresponding ^{14}C results for the rearrangement of the compound (2.1), in concentrated sulphuric acid, to tetrafluorobenzobarrelenone (2.4a) are in good agreement. The variation in the corresponding results for the rearrangement of the compound (2.1), in dilute sulphuric acid, to the ketone (2.4b) could be due to slight variations in the rearrangement procedure.

It is considered that the ^{14}C results reflect the accuracy of the deuterium labelling studies and justify the assumptions made regarding potential isotope effects.[20c,d]

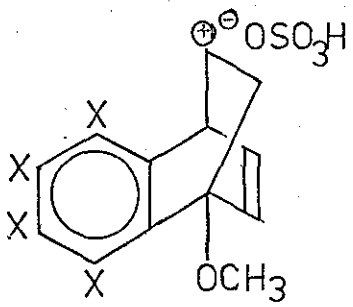
The extension of the ^{14}C studies came about more by good fortune than planning and it was hoped to reap the benefit from such fortune.

Although, it had been established [20c] that the rearrangement of 1-methoxytetrafluorobenzobarrelene (2.1) in strong acid medium gave the ketone (2.4) by the two pathways (a) and (b) [Scheme 2.1] it was only assumed that the similar compounds (2.2) and (2.3) gave the corresponding ketones (2.5) and (2.6) by the same two pathways. This assumption was obviously a reasonable one but more important was the question of the effect of the aryl substituent, in the compounds (2.1) - (2.3), on the ratio of pathways (a) : (b), in the formation of the corresponding benzobarrelenones (2.4) - (2.6).

It was also reasoned that information might be gained regarding the structure of the cation (2.14) postulated as an intermediate ion involved in the formation of the ketones (2.4) - (2.6). Under the conditions of the reaction the cation (2.14) could exist as either a tight ion pair (2.118) or a half sulphate ester (2.119).

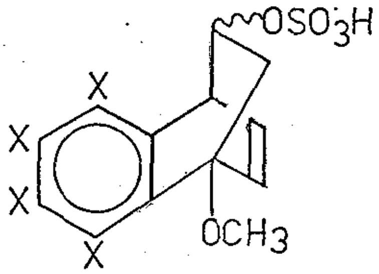


(2.14)



(2.118)

X = F, Cl or H

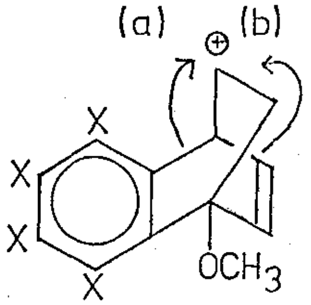


(2.119)

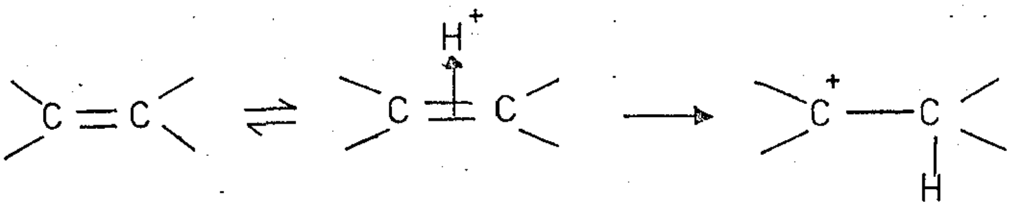
If the ion (2.14) existed as the half sulphate ester (2.119) then in concentrated sulphuric acid the rearrangement would depend on the exo : endo ratio. However, if the ion (2.14) existed as a tight ion pair then in the rearrangments involving dilute sulphuric acid the water molecules could solvate the ion (2.14) and hence affect the rearrangement. The possibility that the electron withdrawing capability of the aryl substituents, in the compounds (2.1) - (2.3), could affect the rearrangement of the solvated tight ion pair was considered.

The actual results make it difficult to draw accurate conclusions regarding the above proposals. However, it is possible to confirm that the two compounds (2.2) and (2.3) rearrange to their respective benzobarrelenones (2.5) and (2.6) by the two pathways (a) and (b), as does the compound (2.1) to tetrafluorobenzobarrelenone (2.4). The rearrangement of the compounds (2.1) - (2.3) to the ketones (2.4a) - (2.6a) show a respective increase in the proportion of pathway (a) involved in their formation; i.e. 76.4 ± 2%; 91.1 ± 6%; 95.0 ± 6%. A similar increase is noted for the formation of the ketones (2.4b) and (2.5b) i.e. 68.2% ± 2% and 84.3% ± 6%.

This increase in the proportion of pathway (a) can be correlated with a decrease in electronegativity of the aryl substituents, X=F, Cl or H [4.10; 2.83; 2.20 respectively (Allred-Rochow values)[68]]

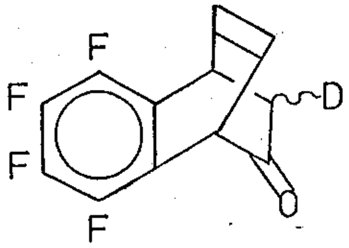


Attempts to interpret the $[^{14}C]$ results lead to many interesting questions. Firstly, in the reaction of strong acids with carbon - carbon double bonds, to form a carbonium ion (2.121), it is not known whether this takes place directly or via the rapid reversible formation of a π- complex (2.120) followed by slow conversion to the ion (2.121).



(2.120) (2.121)

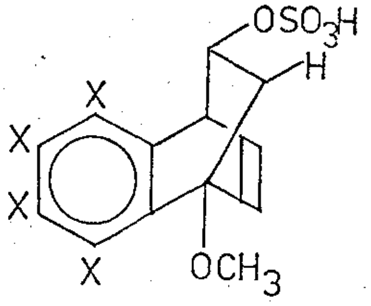
The question then arises - does the bisulphate ion (HSO_4^-) approach from the cis or trans side of the ion (2.121)?. In the formation of the ketone (2.122) by the rearrangement of the compound (2.1) in 80% D_2SO_4, it has been shown,[20d] that the deuterium incorporation was as depicted.



(2.122)

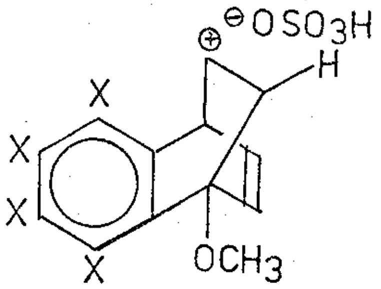
ratio exo D : endo
10 : 7

Consideration of this result coupled with the knowledge that the rearrangement of the cation (2.14) in c. H_2SO_4 is predominantly by aryl migration then it can be concluded that addition to the carbon - carbon double bond of H^+ and HSO_4^- is mainly cis and to the exo side.



(2.119a)

or



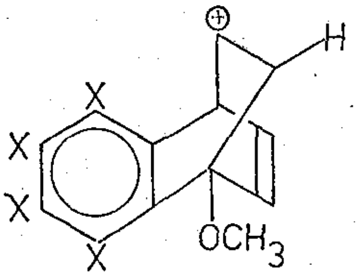
(2.118a)

This preference is probably related to two factors:-

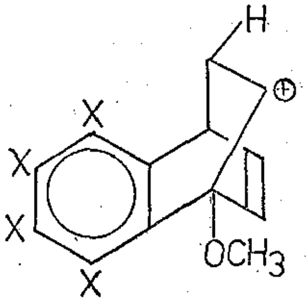
(i) the approach of the bisulphate ion from the exo side is sterically less hindered than from the endo side and (ii) repulsion of the bisulphate ion by the electron density of the aromatic ring on approach from the endo side.

The latter would help to explain the increased aryl migration as the aryl substituent (X) becomes less electronegative. Thus when X = H the electron density of the aromatic ring will be greater than when X = F and therefore, the greater the repulsion of bisulphate ion from endo approach.

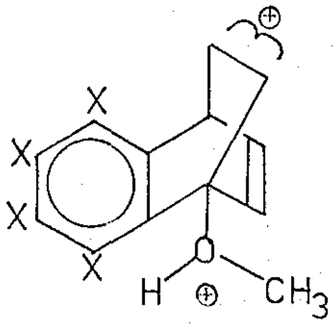
Although it can be concluded that the addition to the ion (2.14) is mainly cis and exo this does not explain the preference for protonation at C-2 over C-3.



(2.14)



(2.13)

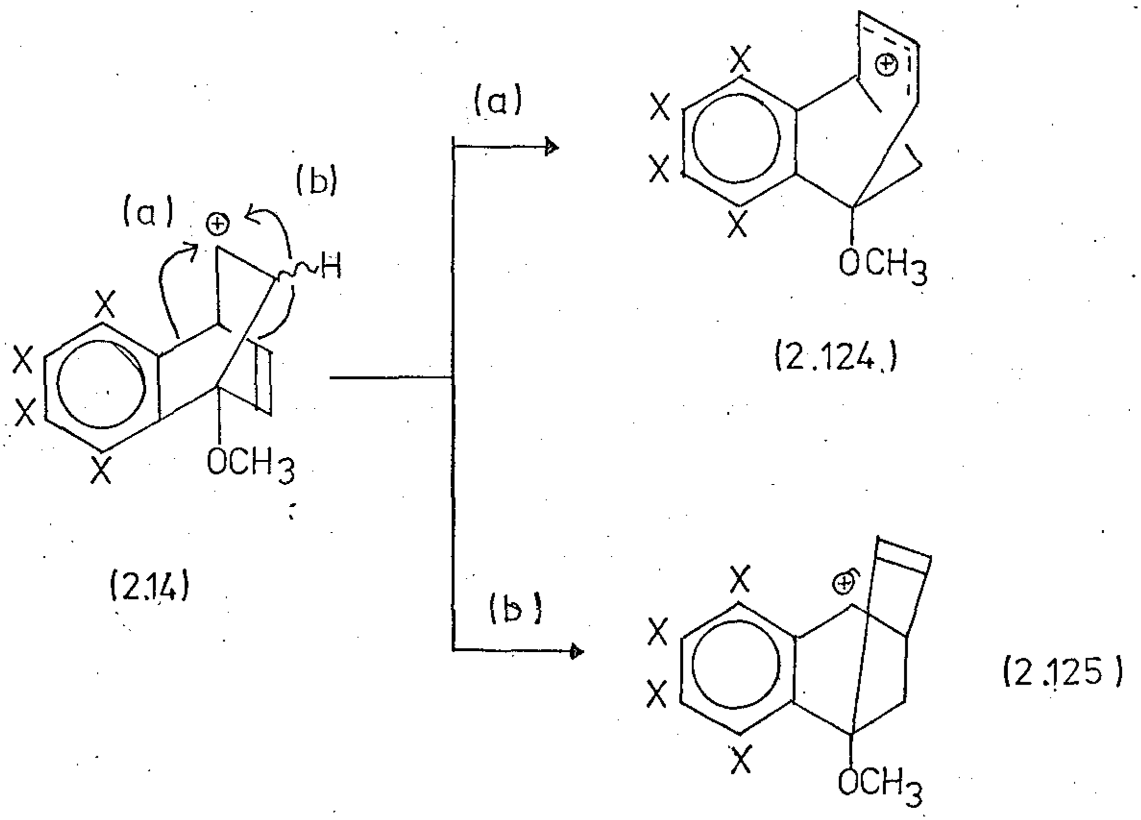


(2.123)

When X = F, Cl or H and the rearranging conditions are either c. H_2SO_4 or 80% H_2SO_4 then protonation at C-2 leading to the respective benzobarrelenone predominates. The explanation probably lies in the stability of the two ions (2.13) and (2.14). Methyl groups have been shown to polarise the initial protonation and thus direct the subsequent rearrangement,[20c,d] confirming that the most stable cation is formed. It is also known that in strong acid media the methoxy group becomes protonated and it is therefore a possibility that the greater stability of ion (2.14) over (2.13) is linked with the greater separation of charge (2.123).

Returning to the question of aryl (a) versus alkenyl (b) migration in the ion (2.14) the preference for aryl migration may be related to the stability of the cations formed in the subsequent rearrangements.

Aryl migration in the cation (2.14) gives the allylic stabilised cation (2.124) whilst alkenyl migration yields the benzyl cation (2.125). There are two points which indicate that the cation (2.124) is of lower energy than (2.125). Firstly, the aryl ring remains intact and does not participate in the stabilisation of the cation (2.124). In the case of cation (2.125) the aryl ring can stabilise the positive charge as shown in structure (2.126) but in doing so forfeits some of the resonance energy associated with the stable aromatic sextet. Secondly, in the proposed mechanism, Scheme 2.1, for the formation of benzobarrelenones (2.4)-(2.6) it is suggested that cation (2.124) rearranges directly to the respective ketone whilst cation (2.125) rearranges first to cation (2.124).

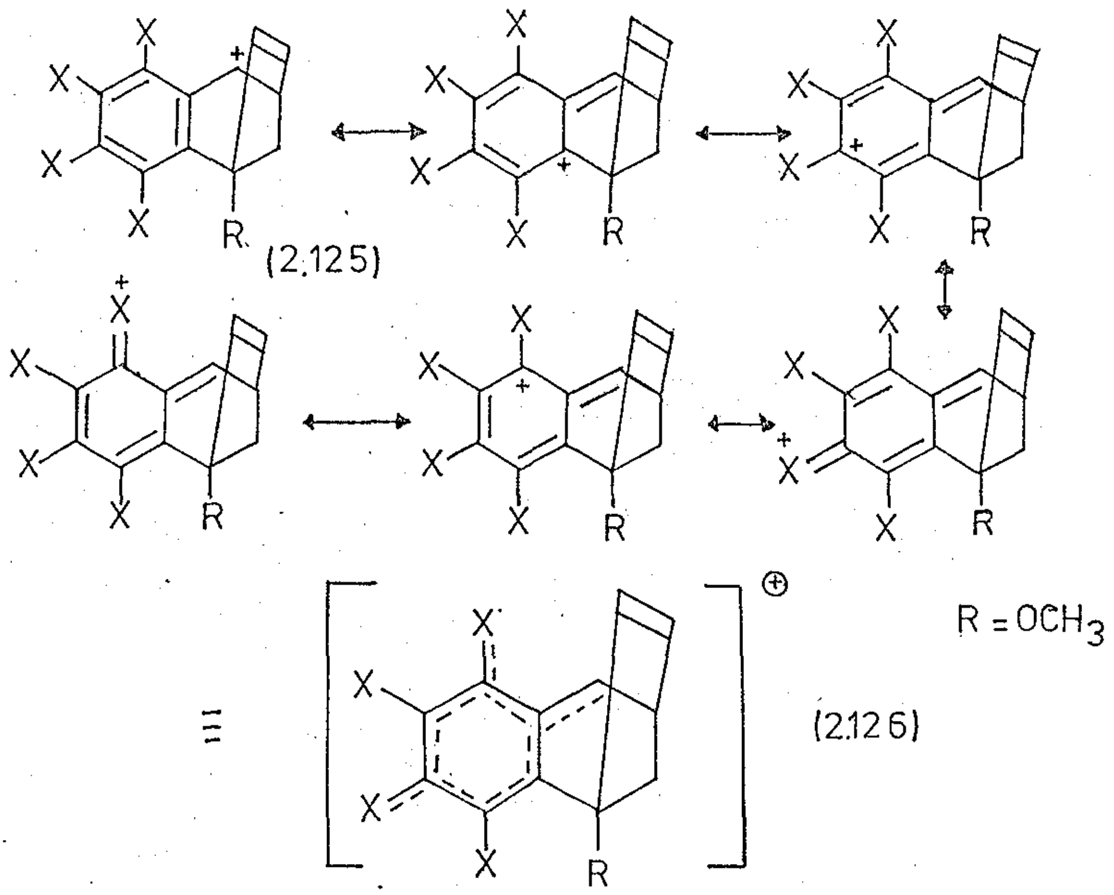


(2.14)

(2.124)

(2.125)

If the cation (2.124) does exist at a lower energy level than cation (2.125) then this would account for the overall preference for aryl

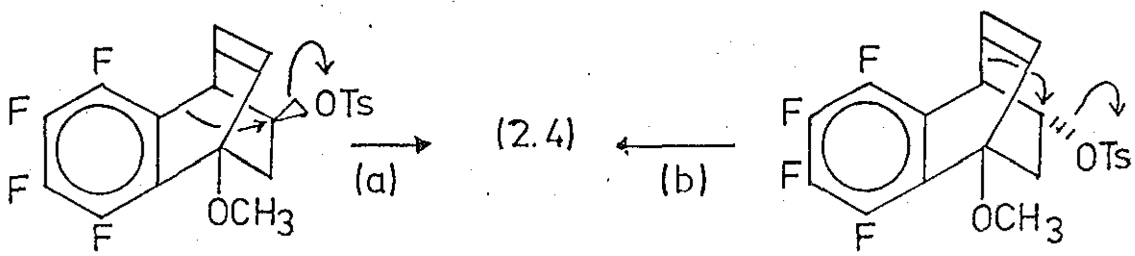


(2.125)

(2.126)

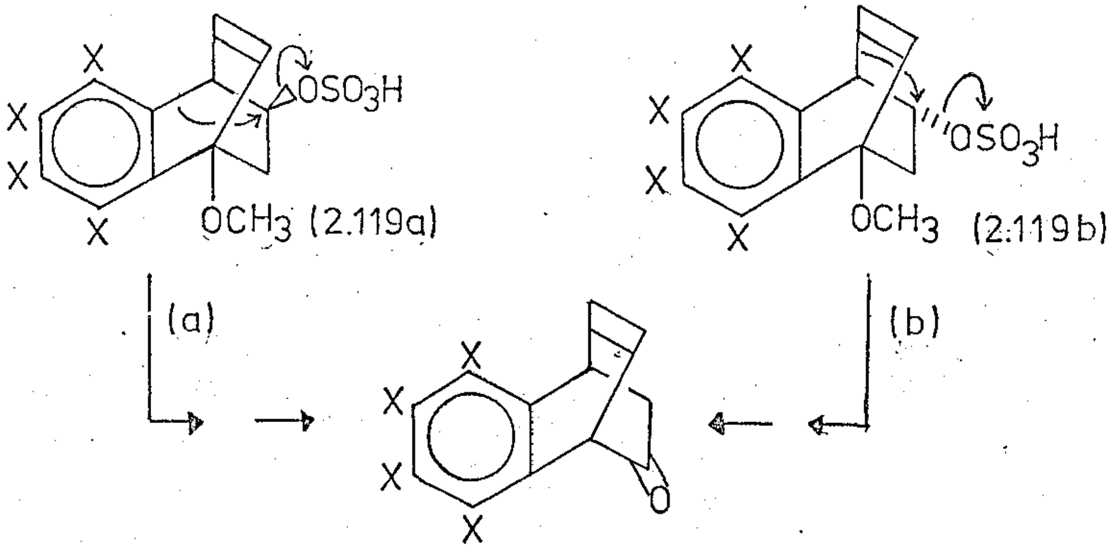
migration.

The question of whether the ion (2.14) exists as the tight ion pair (2.118) or the half sulphate ester (2.119) is more difficult to answer. Earlier studies^{20d} have shown that the 3-exo-tosylate (2.127) and the 3-endo-tosylate (2.128) rearrange in concentrated sulphuric acid to the ketone (2.4). It was suggested that the tosylate (2.127) rearranged purely by aryl migration and the tosylate (2.128) by vinyl migration.

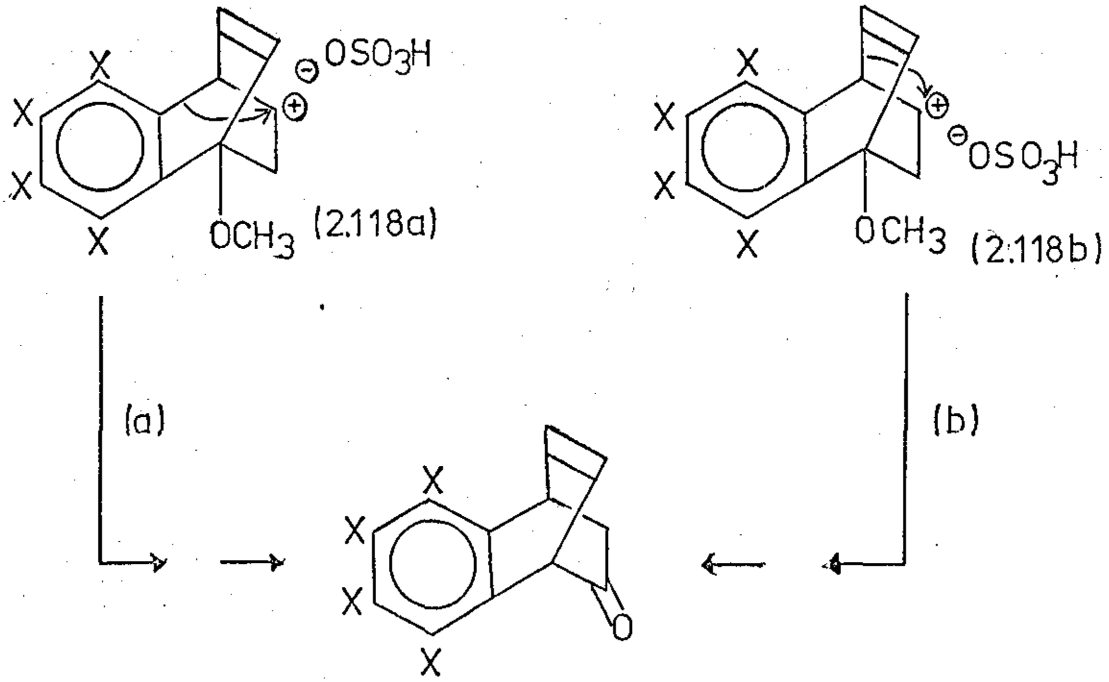


(2.127) (2.128)

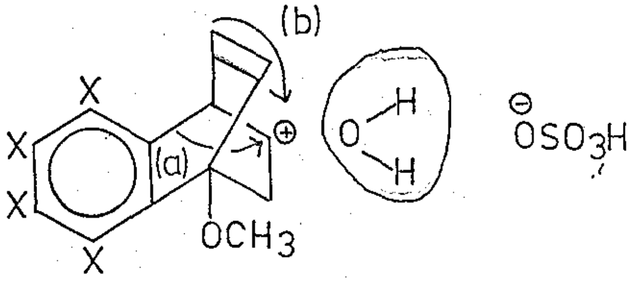
Similarly the ^{14}C labelling results could be explained by the formation of the half sulphate esters (2.119a) and (2.119b)


X
X
X
X
OSO3H
OCH3
(2.119a)
X
X
X
X
OSO3H
OCH3
(2.119b)
(a)
(b)
X
X
X
X
O

Unfortunately such esters would not account for the increased proportion of pathway (b) in dilute sulphuric acid (ca. 80%) for the rearrangement of the two compounds (2.1) and (2.2). The formation of the tight ion pairs (2.118a) and (2.118b) would appear to present a better explanation of the results.


X
X
X
X
⊖OSO3H
⊕
OCH3
(2.118a)
X
X
X
X
⊕
⊖OSO3H
OCH3
(2.118b)
(a)
(b)
X
X
X
X
O

The effect in concentrated sulphuric acid would be as previously proposed but in dilute sulphuric acid the ion (2.118) would be solvated. Such solvation would allow an increase in alkenyl migration (b) at the expense of aryl migration (a).



The failure to obtain the ratio of (a) to (b) for the rearrangement of [4-^{14}C]-1-methoxybenzobarrelene (2.3) in 80% sulphuric acid plus the potential error (± 6%) in the analysis of ketones (2.5a) (2.5b) and (2.6a) make it difficult to extract further information from the results.

Further work is obviously necessary to expand and clarify some of the points which have arisen during these investigations.

EXPERIMENTAL

All general methods and procedures were as described in Chapter 1.

All the experiments involved in the ^{14}C studies were initially investigated using unlabelled material. The results of the unlabelled studies established the feasibility of reaction pathways, yields, m.p., and purity of product.

The counting of the ^{14}C products was carried out according to the following standard procedure:-

A sample of the ^{14}C product (1-3 mg.) was weighed accurately (Stanton Balance, Model MC9, to six decimal places) into a plastic counting bottle. The material was dissolved in dimethylformamide (dry, 0.5ml., pipetted) and a liquid scintillator (10ml., Liquid Scintillator NE250, Nuclear Enterprise Ltd., Sighthill, Edinburgh 11, Scotland. Dioxan base and argon purged). The solution was shaken, ca. 2min., to ensure thorough mixing. The bottle was then placed in a Beckman Liquid Scintillation System (CPM-100) and the solution counted for 500 min.. The system contained an automatic print out which gave the following information for each sample counted:-

(i) Sample N^{o}

(ii) Channel Ratio - used in conjuction with a graph showing Channel Ratio v Counting Efficiency.

(iii) Counting Time (min.)

(iv) Counting Accuracy

(v) Counts per min..

Each batch of labelled counts was accompanied by a blank count, this involved the same preparation as above but with no ^{14}C material included.

The Specific Activity of each sample was calculated as shown in the following example:-

[^{14}C]- Tetrafluorobenzobarrelenone		Blank Sample
c.p.m.	543	36
Accuracy	0.5	3.0
Ch. Ratio	10.99	11.21
Efficiency	94.5%	95.0%
Corrected c.p.m.	$543 \times \frac{100}{94.5} = 575$	$36 \times \frac{100}{95} = 38$
d.p.m.	575 - Blank = 575 - 38 = 537	
Weight Counted	1.337 mg.	
d.p.m./mg.	$\frac{537}{1.337} = 402$	
M.W.	242	

Specific Activity $= \frac{402 \times 242}{2.22 \times 10^{6}} = 4.38 \times 10^{-2}$ μCi/m.mol.

Each of the ^{14}C products counted, when ever possible, was counted to constant activity. This involved either recrystallising or subliming the ^{14}C product and re-counting until a constant activity was obtained.

The samples of 3,6-di-(2'-pyridyl) -*s*-tetrazine and p-nitrophenyl azide were prepared by N. J. Hales.

1. Preparation of Mucobromic Acid[52] (2.20)

Freshly distilled furfural (50g., 0.52M.) and water (500ml.) were stirred vigorously in a 2l. 3-necked flask, equipped with a dropping funnel and thermometer. The mixture was cooled to ca. 0° and bromine (450g., 2.81M.) was added keeping the temperature $<5^{\circ}$. After completion of the addition the mixture was refluxed for ca. 30 min. and then distilled until the distillate was almost colourless.

The mixture was evaporated to dryness and the solid residue cooled and triturated with ice/water (ca. 50ml.). A solution of sodium bisulphite (4.0g.) in water was added in order to discharge a slight yellow colouration.

The remaining crude mucobromic acid was filtered and washed with ice-water (2x25ml.). The crude solid was dissolved in boiling water (110ml.) and decolourising charcoal (4.0g.) was added. After stirring the mixture for ca. 10min. the solution was filtered and the filtrate allowed to crystallise at ca. $0-5^{\circ}$. Mucobromic acid was isolated as colourless crystals (90g., 67%), mp. $121-122^{\circ}$ (lit.[52] $123-124^{\circ}$)

ν_{max}: 3560-3200, 1770, 1630, 1450, 1330, 1270, 1220, 1145, 1090, 1005, 930, 850, 760, and 740 cm^{-1}.

^1H.n.m.r. ($CDCl_3$) τ 1.5-1.9 (1H, broad s.) and 3.94 (1H,s.).

2. Preparation of Sodium Nitromalonaldehyde Monohydrate.[52] (2.21)

Sodium nitrite (258g., 3.74M) and water (250ml.) were stirred in a 2l. 3-necked flask equipped with a thermometer, dropping funnel and stirrer. The solution was heated to ca. 54° and mucobromic acid (258g., 1M.) in ethyl alcohol (95%, 250ml.) was added whilst maintaining the solution temperature at $54 \pm 1^{\circ}$ over a period of ca. 70min..

After stirring for an additional 10min. the solution was cooled to *ca.* 0-5°.

The thick yellow precipitate formed was filtered off through a chilled Buchner funnel and the moist residue transfered to a 1l. flask. A solution of ethyl alcohol-water (400:100) was added and the combined solution heated to boiling point. After filtration the required sodium nitromalonaldehyde monohydrate precipitated from the filtrate as light brown crystals (49.5g., 32%).

3. Preparation of [1-^{14}C]-p-nitrophenol (2.23)

[2-^{14}C]-Acetone (2 x 250μ.Ci., Radiochemical Centre Amersham.) in two separate vials was cooled in liquid nitrogen. The two seals were carefully broken and a mixture of acetone (2.9g., 0.05M.) and water (100ml.) was used to transfer the ^{14}C labelled acetone into a 1l. conical flask. A further volume of water (300ml.) was used to wash the two vials. Sodium nitromalonaldehyde monohydrate (37.2g., 0.24M.) was carefully added to the combined solution. The solution was cooled to *ca.* 0° and sodium hydroxide (9.4ml., 25%.) was slowly added to the solution which was stirred for *ca.* 72hr. at 0-5°. The solution was allowed to warm to room temperature and stirred at this temperature for *ca.* 120hr..

Neutralisation of the solution was effected using solid carbon dioxide. The neutralised solution was extracted with ether for *ca.* 72hr. and the ethereal solution dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude [1-^{14}C]-*p*-nitrophenol as a yellow crystalline solid (4.37g., 63%), mp.112-114° (lit.^{67} mp.114.9 - 115.6^{o}).

$\nu_{max.}$ 3500 - 3300, 1620, 1590, 1500, 1450, 1440, 1330, 1285, 1220, 1170, 1110, 1010, 960, 870, 850, 820, 755 and 690 cm^{-1}.

4. Preparation of p-Aminophenol (2.24)

p-Nitrophenol (2.23g., 0.016M.) was dissolved in ethyl alcohol (30ml.) and heated under reflux with hydrazine hydrate (5ml.) and PdC (5%, 100mg.) for ca. 2hr..

The solution was filtered and the solvents removed on a rotary evaporator. The crude product was recrystallised from methyl alcohol to yield p-aminophenol (1.7g., 97.3%) mp.187-191°, (lit.[67] 186-187°).

$\nu_{max.}$ 3360, 3300, 1620, 1510, 1480, 1390, 1340, 1260, 1240, 1170, 1090, 1010, 970, 920, 825, 750 and 700 cm^{-1}.

5. Preparation of Phenyl Isothiocyanate (2.34)

A mixture of carbon disulphide (54g., 0.71M.) and concentrated ammonium hydroxide (·880, 90ml., 1.3M.) was stirred in an ice cooled 500ml. flask. Aniline (56g., 0.6M.) was added over a period of ca. 20min. keeping the temperature between 0-10°. After the addition the solution was stirred for a further 30min. and then allowed to stand for ca. 30min. during which a heavy precipitate of ammonium phenyldithiocarbamate was formed.

This salt was dissolved in water (800ml.) and transferred to a 5l. flask and lead nitrate (200g., 0.6M.) in water (400ml.) was added. The mixture was steam distilled and the distillate collected in a receiver containing dilute sulphuric acid (10ml., 0.1N.). The distillate (3l.) was extracted with ether (4 x 200ml.), the combined ethereal extract was dried ($MgSO_4$) and evaporated to yield a yellow oil. The oil was distilled to give phenyl isothiocyanate (33.3g., 41%), bp. 66-68° at 1.5m.m., (lit.[55a] bp. 120-121 at 35m.m..) as a pale yellow oil.

$\nu_{max.}$ 3090, 2760, 2575, 2495, 2300 - 1800, 1600, 1495, 1480. 1405, 1290, 1250, 1170, 1160, 1100, 1070, 1030, 1010, 930, 910, 830, 750, and 680 cm^{-1}.

6. Preparation of Phenylcarbonimidoyl)dichloride[55b] (2.35)

Chlorine gas was bubbled through a solution of phenyl isothiocyanate (33.3g., 0.25M.) in carbon tetrachloride (200ml.) cooled in ice, at such a rate as to maintain the solution temperature at *ca.* 3° for a period of 3½hr..

After this time excess solvent and sulphur dioxide was removed by evaporation. The crude product was distilled under reduced pressure to yield the required product (2.35) as a pale yellow oil, (30g., 70%) bp. 78-80° at 7.5mm., (lit.[55b] 103-106° at 31m.m.).

$\nu_{max.}$ 3070, 3040, 3200 - 2000, 1665, 1600, 1590, 1490, 1455, 1210, 1075, 1029, 1000, 920, 885, 760, and 690 cm^{-1}.

7. Preparation of activated Sodium azide[55c]

Commercial sodium azide (10g.) was dissolved in water (30ml.) and treated with hydrazine hydrate (1.0g.). The solution was stirred for 15min. and then filtered into acetone (400ml.). The white precipitate was filtered off and washed with acetone (2 x 100ml.), under a stream of nitrogen to yield the activated sodium azide (5.0g.) which was used immediately in the preparation of 1-phenyl-5-chlorotetrazole.

8. Preparation of 1-phenyl-5-chlorotetrazole (2.25).

Phenylcarbonimidoyl dichloride (12.18g., 0.07M.) was dissolved in 1,2-dimethoxyethane (100ml.) and activated sodium azide (4.9g., 0.077M.) was added and the solution stirred for *ca.* 12hr.. The solution was then poured onto ice/water (500ml.) and the orange precipitate filtered off. The crude product was recrystallised to yield 1-phenyl-5-chlorotetrazole (5.65g., 44.6%), (benzene-petroleum ether) mp. 124-125° (lit.[55c] mp. 123.4-124.6°).

$\nu_{max.}$ 1600, 1510, 1433, 1428, 1412, 1345, 1125, 1118, 1078, 1062, 1019, 978, 769, and 690 cm^{-1}.

9. Preparation of 1-phenyl-5-(-4-amino-phenoxy)-tetrazole. (2.26).

p-Aminophenol (1.69g., 0.016M.) was dissolved in acetone (100ml.) and 1-phenyl-5-chlorotetrazole (2.88g., 0.016M.) added. Potassium carbonate (6.2g.) was also added and the solution was heated under reflux for ca. 72hr..

Filtration and evaporation of the solvent gave a red oily solid which was recrystallised to the required product (2.26), (ethanol), (2.28g., 58%), mp. 173-175°, (lit.[54] mp. 171-173°).

$\nu_{max.}$ 3490, 3390, 1640, 1605, 1555, 1505, 1455, 1435, 1298, 1245, 1170, 1128, 1115, 1073, 1020, 840, 712, and 688 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.1-2.5 (5H., m.), 2.8-3.4 (4H., q.) and 5.4-5.7 (2H., broad s., Exchanged D_2O).

10. Preparation of 1-phenyl-(-4-acetamino-phenoxy)-tetrazole. (2.27).

The compound (2.26) (1.74g., 0.0069M.) was dissolved in glacial acetic acid (60ml.), and acetic anhydride (3ml.), and heated under reflux for ca. 8hr.. Excess of solvent was removed by rotary evaporation and the remaining oil quenched with ice cold water (50ml.). The precipitated product (2.27) (1.75g., 86%) was filtered off and dried, mp. 158-160°, (lit.[51] 159-161°).

$\nu_{max.}$ 3410, 1705, 1620, 1615, 1550, 1510, 1465, 1445, 1412, 1372, 1310, 1295, 1210, 1188, 1170, 1130, 1112, 1075, 1020, 918, 864, 850, 758, and 682 cm^{-1}.

11. Preparation of Acetanilide (2.28)

The compound (2.27) (1.72g., 0.0058M.) was dissolved in glacial acetic acid (100ml.) containing PdC (5% 400mg.). The solution was heated to ca. 60° and reduced using hydrogen gas at atmospheric pressure. Completion of the reaction was indicated by the termination of hydrogen uptake. The solution was filtered and evaporated to yield a red oily solid. This solid was sublimed (110-120° at 0.5m.m. Hg.) to yield acetanilide (500mg., 63.5%) mp.112-114° (lit.[67] 114.3°).

This procedure was carried out on other occasions with varied results for the formation of acetanilide (0-60%).

$\nu_{max.}$ 3440, 1690, 1605, 1520, 1500, 1440, 1370, 1310, 1245, and 1200 cm^{-1}.

12. Preparation of Aniline (2.30) from Acetanilide

Acetanilide (1.83g., 0.014M.) was dissolved in sulphuric acid (75ml., 15%, $^{v}/_{v}$) and heated under reflux for ca. 6hr.. The solution was made alkaline and then extracted with ether for ca. 48hr.. Evaporation of the ether gave an oil which was distilled to give aniline (0.95g., 75.4%) as a pale yellow oil, bp. 74° at 11.5 m.m.Hg., (lit.[67] bp. 184°).

$\nu_{max.}$ 3440, 3360, 3220, 3180, 3140, 1630, 1610, 1500, 1470, 1280, 1180, 1030, 1000, 880, 755, and 695 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.7-3.0 (2H., m.), 3.1-3.55 (3H., m.) and 6.1-6.9 (2H., broad s.).

13. Reaction of N,N-dicyclohexylcarbodiimide with p-nitrophenol

p-Nitrophenol (2.8g., 0.02M.) and N,N-dicyclohexylcarbodiimide (6.24g., 0.03M) was stirred for 3 days at 50-100°. The reaction mixture was cooled and recrystallised from benzene to yield a yellow crystalline compound (2.57g.).

14. Reaction of the product from Expt. 13.

The yellow compound (2g.) in ethyl acetate (50ml.) containing PdC. (10%, 500mg.), at ca. 20° was reduced on a hydrogenator.

Completion of the hydrogenation was assumed when the uptake of hydrogen ceased. Filtration of the solution and rotary evaporation gave a brown solid. The solid was treated with ethyl acetate and two crystalline products were obtained, one insoluble in ethyl acetate (0.75g.), mp. 179-184°, and the other soluble in ethyl acetate (0.80g.) mp. 155-170°.

A second reduction of the yellow compound (0.46g.) was followed by g.l.c.. The major product was identified as p-aminophenol (337mg.), mp. 179-184°, (lit.[67] 186-187°).

15. Second reaction of N,N-dicyclohexylcarbodiimide with p-nitrophenol

The procedure was as described in expt. 13 using N,N-dicyclohexylcarbodiimide (9g, 0.044M.) and p-nitrophenol (3g, 0.022M.). A similar yellow-green crystalline solid (2.8g.) was isolated, mp. 148-152°.

$\nu_{max.}$ 3420, 3340, 3200 - 3100, 2940, 2860, 2120, 1635, 1590, 1515, 1500, 1450, 1395, 1350, 1335, 1290, 1230, 1165, 1115, 890, 860, 850, 750 and 715 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$). τ. 1.6-1.95(m), 2.5-2.7(m), 2.9-3.1(m), 5.5-5.8 (broad band), 6.1-6.6 (broad band) and 7.8-9.4 (v.broad band).

A portion (350mg.) of the above compound was separated by preparative layer chromatography (silica gel, 4 x 1m. x 20cm., 0.75m.m. thickness eluant chloroform) to yield two products:-

Product (1) (higher r.f. value) yellow-green crystals (214 mg.) recrystallised from toluene to give a pale yellow crystalline compound (30mg.) mp. 135-137°.

$\nu_{max.}$ 3420, 2940, 2860, 1680, 1600, 1540, 1500, 1460, 1350, 1325, 1285, 1260, 1230, 1110, 1070, 895, 860, and 720 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$). τ 1.62 (1H., m.), 1.72 (1H., m.), 2.55 (1H., m.), 2.65 (1H., m.), 6.15-6.6 (1H., broad, exchanged by D_2O) and 7.90-9.50 (22H., complex.).

Mass Spectrometry: M^{+} = 345

The above data fits the required o-arylisourea (2.37). The sample was not analysed for C and H.

Product (2) (lower r.f. value) Identified as p-nitrophenol (103mg.) white needles, mp. 110-115° (toluene), (lit.[67] 114.9-115.6°)

$\nu_{max.}$ 3500 - 3200, 2940, 2860, 1635, 1620, 1600, 1520, 1505, 1455, 1445, 1350, 1330, 1290, 1220, 1120, 1115, 860, 850, 755, and 645 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ 1.7-1.9 (2H., m.), 2.9-3.1 (2H., m.) and 5.4-5.6 (1H., broad s.).

16. Reaction of N,N-dicyclohexylcarbodiimide with p-hydroxyacetanilide

p-Hydroxyacetanilide (3g., 0.02M.) and N,N-dicyclohexylcarbodiimide (9g., 0.044M.) was stirred for 3 days at 50-100°. On cooling the solution a black oily tar was obtained which proved intractable.

17. Preparation of $[1\text{-}^{14}C]$-p-nitrophenylmethanesulphonate (2.43)

$[1\text{-}^{14}C]$-p-nitrophenol (4.37g.) was dissolved in pyridine (50ml.)

Methanesulphonyl

and cooled in ice. Methane sulphonyl chloride (5ml.) was added and the mixture was stirred at room temperature for ca. 30min..

The solution was diluted with ether (200ml.) and the ethereal solution washed with hydrochloric acid (2N., 2 x 50ml.). The ethereal solution was dried ($MgSO_4$) and evaporated to yield crude crystals of the required product (2.43) (6.2g.).

Similar reactions using unlabelled p-nitrophenol gave a quantitative yield of the crude p-nitrophenylmethanesulphonate, mp. 92-94°, (lit.[58b] 93-93.5°).

$\nu_{max.}$ 3120, 3090, 3040, 1610, 1595, 1530, 1490, 1360, 1350, 1335, 1315, 1210, 1180, 1160, 1115, 1100, 1010, 980, 880, 865, 830, 795, 750, 725, 685, and 645 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$). τ 1.5-1.8 (2H., m.), 2.4- 2.6 (2H., m.), 3.45-3.65 (1H., m.) and 6.68 (3H.,s.).

18. Preparation of /4-^{14}C 7-Aniline (2.30)

The crude /1-^{14}C 7-p-nitrophenylmethanesulphonate (6.2g.) was dissolved in methanol (150ml.) containing PdC (10%, 1.5g.) and triethylamine (3g.).

The solution was treated with hydrogen, at 25-40°, at atmospheric pressure until the uptake of hydrogen ceased. The solution was filtered and made alkaline with aqueous sodium hydroxide. Extraction with ether and evaporation of the ether gave the crude /4-^{14}C 7-aniline (0.9g.) as an orange-red oil.

Similar reactions using the unlabelled aryl methane sulphonate (4.3g.) gave a 65% yield of crude aniline (1.2g.).

19. Preparation of $[4\text{-}^{14}\mathrm{C}]$-Phenol. (2.31)

$[4\text{-}^{14}\mathrm{C}]$-Aniline (900mg, 0.0097M.) was added to a solution of water (12ml.) and sulphuric acid (98%, 3.5ml.) in a small conical flask. The solution was cooled to ca. 0° and sodium nitrite (0.8g.) in water (10ml.) was added.

The solution was stirred at room temperature for ca. 15 min. and then at 50° on a water bath until the evolution of nitrogen ceased.

Steam distillation followed by ether extraction (3 x 50ml.) of the distillate gave, after removal of the solvent, crude $[4\text{-}^{14}\mathrm{C}]$-phenol (700mg.)

The same procedure with unlabelled aniline (1.2g.) gave, after distillation of the crude product, phenol (0.8g, 66.5%) bp. 85-95° at 15m.m./Hg. (lit.[67] bp. 182°)

$\nu_{\mathrm{max.}}$ 3600 - 3000, 1610, 1500, 1470, 1343, 1250,- 1150, 1070, 1022, 1000, 887, 810 and 687 cm^{-1}.

20. Preparation of $[4\text{-}^{14}\mathrm{C}]$-Anisole. (2.18)

$[4\text{-}^{14}\mathrm{C}]$-Phenol (0.7g.) was added to a solution of potassium hydroxide (2.24g.) in DMSO (100ml.). After stirring for ca. 2 hr. methyl iodide (5.6g.) was added and the solution stirred for a further 2 hr..

The solution was diluted with water (500ml.) and the aqueous solution extracted with ether (4 x 50ml.). The combined ethereal solution was washed with water (2 x 25ml.), dried($MgSO_4$), filtered and evaporated to give crude $[4\text{-}^{14}\mathrm{C}]$-anisole (0.6g.).

Similar reactions with unlabelled phenol gave an almost quantitative yield of crude anisole.

The $[4-^{14}C]$-anisole (0.6g.) was diluted with anisole (5ml.) and the combined anisole distilled, the residue was diluted with anisole (5ml.) and the distillation repeated. The latter procedure was again repeated with anisole (4ml.). The distillates were combined to give the diluted $[4-^{14}C]$-anisole as a pale yellow liquid, bp. 150-160°, (lit.[67] 155°).

$\nu_{max.}$ 3100 - 2900, 2840, 1600, 1500, 1335, 1300, 1170, 1080,
1040, 880, 780, 750, and 640 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ 2.6-2.9 (2H, m.), 3.0-3.2 (3H, m.) and 6.27 (3H, s.).

21. Preparation of $[4-^{14}C]$-1-methoxytetrafluorobenzobarrelene (2.1)

Bromopentafluorobenzene (5g., 0.02M) in ether (20ml.) was added to a stirred slurry of magnesium (0.6g.) at such a rate as to maintain reflux. The reaction was stirred for ca. 45min. under reflux.

A solution of $[4-^{14}C]$-~~A~~anisole (4g., 0.037M.) in cyclohexane (15ml.) was added dropwise and the reflux temperature allowed to rise to ca. 80°. The mixture was refluxed for ca. 3hr..

Dilute hydrochloric acid (1N., 20ml.) was added to the solution and the resultant solution extracted with ether (4 x 50ml.). The ethereal solution was dried ($MgSO_4$) and evaporated to yield a red brown oil.

The crude oil was placed on an alumina column (500g.) and eluted with light petroleum (40:60). Fractions of ca. 200ml. were taken and analysed by g.l.c.. Fractions 1-6 contained recovered crude $[4-^{14}C]$-anisole (5.4g.). Fractions 10-12 contained crude $[4-^{14}C]$-1-methoxytetrafluorobenzobarrelene (180mg.).

The above procedure was repeated twice, each time using the previously recovered anisole. The total yield of the crude [4-^{14}C]-1-methoxytetrafluorobenzobarrelene was (1.32g.). This crude product was diluted with 1-methoxytetrafluorobenzobarrelene (1.0g.) and the combined sample recrystallised (ethanol) to constant activity. [At constant activity:- 2.4mg. gave 882 c.p.m., Accuracy 0.3%, Count time 500min., Ch. Ratio 10.9 ≡ 94% efficiency, blank count 35 c.p.m., d.p.m./mg.376, Specific Activity 4.34 x 10^{-2} μ.Ci./m.mol.]

Similar studies using anisole had given a 32% yield of the product (2.1), mp. 78-81°, (lit.^{14d} mp. 77°).

$\nu_{max.}$ 3015, 2950, 2850, 1635, 1490, 1340, 1227, 1215, 1195, 1077, 1040, 1008, 950, 930, 905, 855, 793, 760, and 680 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$). τ. 2.86-3.35 (4H, 8 lines AB of ABX), 4.68-5.05 (1H, m.) and 6.25 (3H, d, $|J|$ H-F = 2.6Hz.)

22. Rearrangement of [4-^{14}C]-1-methoxytetrafluorobenzobarrelene (2.1) in concentrated sulphuric acid.

The compound (2.1) (0.94g, 0.0037M.) was shaken in concentrated sulphuric acid (20ml.) at room temperature for ca. 3min.. The solution was quenched on ice and extracted with ether (5 x 25ml.). The ethereal solution was washed with water (2 x 10ml.), dried ($MgSO_4$) and evaporated to give an oil (1.0g.).

The oil was separated by preparative layer chromatography (silica, 10 x 1m. x 20cm, 0.75m.m. thickness, eluant 20% ether/light petroleum [60:80] to yield the [^{14}C]-tetrafluorobenzobarrelenone (520mg.) as the major band. The crude ketone was recrystallised (ethanol) to constant activity. [At constant activity:- 1.337mg. gave 543 c.p.m., Acc. 0.5%, Ch. Ratio 10.99 ≡ 94.5% Eff., Blank= 38 c.p.m.; d.p.m./mg. 402, Specific Activity 4.38 x 10^{-2} μ.Ci./m.mol.. Value in Table I is an average of (4.38 + 4.34 + 4.40) x 10^{-2} = 4.37 x 10^{-2} μ.Ci./m.mol..]

Similar rearrangements using 1-methoxytetrafluorobenzobarrelene gave *ca.* 50% yields of the ketone (2.4), mp. 70-72°, (lit.[24] 72.5-73.5°).

$\nu_{max.}$ 3080, 2940, 1738, 1500, 1421, 1386, 1334, 1310, 1130, 1115, 1090, 1080, 1070, 1030, 917, 870, 750, and 717 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$). τ. 3.02-3.48 (2H, m), 5.18-5.55 (2H, m) and 7.94 (2H, octet AB of ABX).

23. Rearrangement of [4-^{14}C]-1-methoxytetrafluorobenzobarrelene (2.1) in dilute sulphuric acid

Dilute sulphuric acid (H_2SO_4:H_2O 4:1 $^v/_v$) was heated to *ca.* 80° on a water bath and the heated solution added quickly to [4-^{14}C]-1-methoxytetrafluorobenzobarrelene (0.98g.). The combined solution was kept at *ca.* 80° and shaken for *ca.* 3min.. The solution was then quenched on ice.

[^{14}C]-tetrafluorobenzobarrelenone (380mg.) was isolated as described in expt. 22. The crude ketone was recrystallised and counted to constant activity. [At constant activity :- 2.06mg. gave 818 c.p.m., Acc. 0.3%, Ch. Ratio 10.5 ≡ 94% Eff., Blank 38 c.p.m., d.p.m./mg. 404, Specific Activity 4.40 x 10^{-2} μ.Ci./m.mol.. Value in Table II is an average value of (4.38 + 4.34 + 4.40) x 10^{-2} = 4.37 x 10^{-2} μ.Ci./m.mol..]

Using 1-methoxytetrafluorobenzobarrelene the ketone (2.4) was isolated in *ca.* 45% yield.

24. Preparation of Tetrafluorobenzobarrelenone (2.4)

The compound (2.1) (3.7g.) was added to a stirred solution of fluorosulphonic acid (9ml.) at *ca.* -70°. The solution was allowed to warm slowly to room temperature and then quenched on ice (100g.). The aqueous solution was neutralised and extracted with ether (4 x 25ml.). The ethereal solution was dried ($MgSO_4$) and evaporated to yield an orange oil (3.1g.). The oil was crystallised to give tetrafluorobenzobarrelenone (2.1g., 60%), mp.70-73° (ethanol), (lit.[24] 72.5-73.5°).

25. Oxidation of tetrafluorobenzobarrelenone (2.4) with fuming nitric acid

(i) Tetrafluorobenzobarrelenone (250mg.) was heated under reflux in fuming nitric acid (10ml.) for one week. The solution was quenched on ice (100g.). The aqueous solution was neutralised with sodium bicarbonate solution and the solution extracted with ether (3 x 20ml.).

The remaining aqueous solution was acidified and extracted with ether (4 x 20ml.). The ethereal solution was dried ($MgSO_4$) and evaporated to give a white crystalline solid (100mg.), mp. 150-165°

$\nu_{max.}$ 1740, 1495, 1385, 1310, 1130, 1115, 1080, 1030, 920, 870, 750, and 715 cm^{-1}.

Similar reactions were attempted with the following results:-

(ii) yellow-white crystals (150mg.) mp. 150-155°.

(iii) yellow crystals (156mg.) mp. 148-151°.

$\nu_{max.}$ 3600 - 3200, 1735, 1615, 1550, 1360, 1300 - 1200, and 1080 cm^{-1}.

26. Attempted preparation of Tetrafluorophthalimide (2.53)

(i) A sample (50mg.), from expt. 25, was heated under reflux in concentrated ammonium hydroxide (.880, 1ml.) for *ca.* 3hr.. The temperature was then allowed to rise slowly to *ca.* 240°. A brown oily residue was left which would not sublime when heated under reduced pressure.

A number of similar reactions were attempted with the following results:-

(ii) yellow-green crystals mp. 175-200°, residue mp. $>$ 300°

$\nu_{max.}$ 1730, 1600, 1540, 1350, 1300, and 1090 cm^{-1}.

(iii) yellow crystals, mp. 160-170°

(iv) yellow crystals, mp. 210-215°

$\nu_{max.}$ 1750, 1550, 1460, 1360, 1350, 1135, and 730 cm^{-1}.

(v) Using a standard sample of tetrafluorophthalic acid, yellow crystals mp. 206-209° (lit.[59] 210-211°)

$\nu_{max.}$ 1790, 1750, 1730, 1650, 1610, 1525, 1510, 1415, 1310, 1150, 1050, 1045, 930, 760, and 660 cm^{-1}.

(vi) yellow crystals, mp. $<$ 100°

(vii) white crystals, mp. 210-215°.

27. Attempted Oxidation of the Ketone (2.4) with Potassium permanganate

Tetrafluorobenzobarrelenone (200mg.) was dissolved in acetone (20ml.). During reflux of this solution a saturated solution of potassium permanganate, in water, was added slowly over a period of *ca.* 3hr. until the purple colour was no longer discharged.

Evaporation of the solvent left a brown residue which was extracted with ether (4 x 20ml.). The ether solution was extracted with sodium bicarbonate solution. The remaining organic phase was dried ($MgSO_4$) and evaporated to yield sample [A] (227mg.) green-brown oil.

Acidification of the sodium bicarbonate solution and extraction with ether (4 x 20ml.) followed by drying ($MgSO_4$) and evaporating the ether gave sample [B] (42mg.) yellow oil.

$\nu_{max.}$ [A] 3600 - 3100, 2920, 2840, 1740, 1510, 1300, and 1130 cm^{-1}.
[B] 3600 - 3100, 2930, 2860, 1745, 1510, 1400, 1130, 1070
865, and 730 cm^{-1}.

28. Attempted Oxidation of the Ketone (2.4) with Dicyclohexyl-18-crown 6 (2.54)

The compound (2.54) (372mg, 1mM.) in benzene (25ml.) was stirred and potassium permanganate (158mg, 1mM.) added. The ketone (2.4) (121mg, 0.5mM.) in benzene (10ml.) was added to the purple solution and the combined solution stirred overnight. The purple colour disappeared after *ca.* 2hr. and the solution turned black.

The solution was centrifuged and the benzene solution removed to leave a black residue. The residue was washed first with benzene and then with water, the latter wash was repeated. Each washing was followed by a centrifuge operation to deposit the residue.

The aqueous fractions were combined, acidified and extracted with ether (4 x 100ml.). The ethereal solution was dried ($MgSO_4$) and evaporated to give a red oil containing white crystals (118mg.).

$\nu_{max.}$ 3600 - 3100, 2920, 2860, 2700 - 2300, 1740, 1510, 1400, 1100
and 760 cm^{-1}.

29. Photolysis of Tetrafluorobenzobarrelenone.

A solution of tetrafluorobenzobarrelenone (170mg.) in ether (100ml.) under dry, oxygen free nitrogen was heated under reflux and irradiated (Hanovia medium-pressure mercury vapour lamp, quartz flask) for *ca.* 3hr.. Solvent was removed under reduced pressure to yield tetrafluoronaphthalene (2.58) (130mg, 92%), mp. 98-106°, (lit.[13c] 110-111°).

^{1}H.n.m.r. ($CDCl_3$) τ. 1.8-2.15 (2H, m) and 2.2-2.6 (2H,m).

30. Oxidation of tetrafluoronaphthalene with fuming nitric acid

(i) The procedure was as described in expt. 25 using tetrafluoronaphthalene (200mg.) and fuming nitric acid (10ml.).

At the end of the reaction an oil (210mg.) was isolated which crystallised to yield a white crystalline solid (100mg.) mp. 186-188° (toluene), (lit.[13c] 152-154°, tetrafluorophthalic acid).

$\nu_{max.}$ 3700 - 3200, 3100, 2920, 1750, 1550, 1480, 1360, 1280 and 920 cm^{-1}.

Similar reactions gave the following results:-

(ii) yellow crystals (1 week at reflux) mp. 163-183°.

$\nu_{max.}$ 3600 - 2700, 1745, 1695, 1620, 1580, 1545, 1440, 1415, 1360, 1255, 1160, 1075, 915, 795, 780, 755 and 690 cm^{-1}.

(iii) yellow crystals, mp. 170-180°.

31. Attempted preparation of tetrafluorophthalic anhydride (2.52)

A sample (100mg.), from expt. 30, was heated under reflux in acetic anhydride (5ml.) for *ca.* 2hr.. Excess of solvent was removed by distillation to give a red oily solid. This material did not sublime.

32. Reaction of the product from expt. 25 with aniline.

A crystalline sample (100mg.), from expt. 25, was heated under reflux in aniline (5ml.) for *ca.* 4 hr.. A black oily residue, insoluble in ether, was isolated, mp. ~ 250°. This product would not sublime under reduced pressure.

$\nu_{max.}$ 1700, 1600, 1500, 1390, 1310, 830, 750 and 695 cm^{-1}.

33. Reaction of the product from expt. 25 with urea

A sample (100mg.), from expt. 25, was heated at *ca.* 165° with urea (100mg.) for *ca.* 10 min.. The residue was sublimed to yield yellow crystals

(15mg.) mp. 95-105°.

34. Oxidation of tetrafluoronaphthalene with potassium permanganate

A saturated aqueous solution of potassium permanganate was added to a refluxing solution of tetrafluoronaphthalene (200mg.) in acetone (20ml.) over *ca.* 4hr.. The dark solution was treated with sulphur dioxide and the resulting clear solution evaporated to remove excess of acetone.

Extraction of the aqueous solution with ether (4 x 20ml.) gave after drying ($MgSO_4$) a crystalline solid (10mg.) mp. 154-156° (lit.[13c] 152-154°, tetrafluorophthalic acid).

$\nu_{max.}$ 3600 - 2800, 1700, 1590, 1410, 1285, 1075, 910, 800, 740, and 670 cm^{-1}.

35. Reduction of the $[^{14}C]$-tetrafluorobenzobarrelenones (2.4a) and (2.4b)

The ketone (2.4a) (290mg.) in dry ether (20ml.) was added to a slurry of lithium aluminium hydride (100mg.) in dry ether (20ml.) and stirred at room temperature for *ca.* 30 min.. Sulphuric acid (2M, 20ml.) was carefully added and the solution extracted with chloroform (3 x 40ml.). The epimeric $[^{14}C]$-alcohols (2.88) (270mg.) wereisolated as a yellow oil after evaporation of the solvent.

The ketone (2.4b) was treated in a similar manner to yield the same product (2.88) (210mg.).

Using unlabelled ketone (2.4) an almost quantitative yield of the crude epimeric mixture of alcohols had been obtained.

$\nu_{max.}$ 3600 - 3100, 3000 - 2900, 1500, 1390, 1325, 1310, 1120, 1115, 1105, 1065, 1035, 1000, 960, 920, 915, 865, 815, 745, and 720 cm^{-1}.

36. Preparation of the $[^{14}C]$-Xanthate esters (2.89) from the $[^{14}C]$-alcohols (2.88).

The alcohol (2.88) (270mg.), derived from the ketone (2.4a), in dry benzene (20ml.) was added to sodium hydride (100mg.) in dry benzene (20ml.) under nitrogen. After the addition of ethyl alcohol (2-3drops, 95%), the solution was stirred for *ca*. 3hr.. Carbon disulphide (6ml.) was added and the solution stirred for *ca*. 4½hr.. Methyl iodide (6g) was added and the solution stirred for *ca*. 12hr..

The organic solution was washed with water (37ml.), dried ($MgSO_4$) and evaporated to yield the crude $[^{14}C]$-xanthate ester (2.89) (330mg.), as a yellow oil.

A similar experiment with the alcohol (2.88), derived from ketone (2.4b) gave the $[^{14}C]$-xanthate ester (2.89) (310mg.).

Similar reactions using the unlabelled alcohol (2.88) gave the required crude ester (2.89) in a quantitative yield.

$\nu_{max.}$ 3095, 3090, 3040, 2960, 2930, 2860, 1500, 1390, 1325, 1215, 1180, 1120, 1080, 1035, 965, 920, 865, 820, 745, 715 and 675 cm^{-1}.

37. Pyrolysis of the $[^{14}C]$-xanthate esters (2.89)

The $[^{14}C]$-xanthate ester (330mg.), derived from ketone (2.4a), was transferred to a pyrolysis tube with ether (2-3ml.) and the solvent removed by evaporation. The pyrolysis tube was sealed under reduced pressure and then heated in a furnace at *ca*. 230° for *ca*. 25min.. The pyrolysis tube was removed and allowed to cool to room temperature. The tube was then cooled in liquid nitrogen and the top carefully opened, using a glass cutter. The resultant oil was separated by column chromatography (alumina, 1Kg., eluant light petroleum ether 40:60), collecting fractions of *ca*. 250ml.. The fractions were checked by g.l.c. analysis and fractions 16-24 contained $[^{14}C]$-tetrafluoronaphthalene (80mg.), fractions

30-39 contained $[^{14}C]$-tetrafluorobenzobarrelene (60mg.).

The $[^{14}C]$-tetrafluoronaphthalene (2.58) was sublimed to constant activity. [At constant activity:- 4.9mg. gave 1932 c.p.m., Acc. 0.3%, Count time 500min., Ch. Ratio 9.99 ≡ 94% Eff., Blank 32 c.p.m., d.p.m./mg. 412, Specific Activity 3.71×10^{-2} μ.Ci./m.mol.. The value in Table I is the average of $(3.71 + 3.62) \times 10^{-2} = 3.67 \times 10^{-2}$ μ.Ci./m.mol.].

A similar reaction involving the $[^{14}C]$-xanthate ester (2.89) (310mg.), derived from ketone (2.4b), gave $[^{14}C]$-tetrafluoronaphthalene (2.58) (50mg.), and the $[^{14}C]$-tetrafluorobenzobarrelene (2.80) (60mg.).

The $[^{14}C]$-tetrafluoronaphthalene was sublimed to constant activity. [At constant activity:- 1.927mg. gave 746 c.p.m., Acc. 0.5%, Count time 500min., Ch, Ratio 10.67 ≡ 94% Eff., Blank 35 c.p.m., d.p.m./mg. 393, Specific Activity 3.54×10^{-2} μ.Ci./m.mol.. The value in Table I is the average of $(3.54 + 3.33) \times 10^{-2} = 3.44 \times 10^{-2}$ μ.Ci./m.mol.].

Similar experiments using unlabelled xanthate ester (700mg.) gave tetrafluoronaphthalene (2.58) (70mg.) mp. 106-109° (lit.[13c] 110-111°). ^{1}H.n.m.r. ($CDCl_3$) τ. 1.8-2.05 (2H, m.), and 2.25-2.5 (2H, m.). and tetrafluorobenzobarrelene (2.80) (60mg.) mp. 75-76°, (lit.[20i] 70-71°). ^{1}H.n.m.r. ($CDCl_3$) τ. 3.0-3.2 (4H, m.) and 4.55-4.75 (2H, m.).

38. Reaction of $[^{14}C]$-tetrafluorobenzobarrelene (2.80) with 3,6-di-(2'-pyridyl)-s-tetrazine (2.64).

The $[^{14}C]$-tetrafluorobenzobarrelene (60mg.), derived from the ketone (2.4a), with the tetrazine (2.64) (80mg.) was heated under reflux in di-*n*-butyl ether (20ml.) for *ca.* 6hr.. Excess of solvent was removed by distillation under reduced pressure and the residue was separated by preparative layer chromatography (silica, 3 x 1m. x 20cm. 0.75mm. thickness, eluant chloroform). [^{14}C]-Tetrafluoronaphthalene (2.58) (65mg.) (highest R.f.) was isolated and the base line plus the two bands just above were also isolated. The latter were extracted and replated. The plates were eluted with chloroform three times to enable the required [^{14}C]-pyridazine (2.67) (27mg.) to be obtained.

It was not possible to sublime the [^{14}C]-tetrafluoronaphthalene (2.58) to constant activity. [Specific Activities obtained were 2.18 and 2.42 x 10^{-2} μ.Ci./m.mol.]. However, it was possible to recrystallise the [^{14}C]-pyridazine (2.67) (ethanol) to constant activity. [At constant activity:- 0.98mg. gave 184 c.p.m., d.p.m./mg.162; Specific Activity 1.71 x 10^{-2} μ.Ci./m.mol. The value in Table I is the average of (1.67 + 1.64 + 1.71) x 10^{-2} = 1.67 x 10^{-2} μ.Ci./m.mol.].

The same reaction was carried out with the [^{14}C]-tetrafluorobenzobarrelene (60mg.), derived from the ketone (2.4b), to give [^{14}C]-tetrafluoronaphthalene (2.58) (85mg.) and [^{14}C]-pyridazine (2.67) (35mg.).

Difficulties were again encountered in attempts to sublime the [^{14}C]-tetrafluoronaphthalene (2.58) to constant activity. [Specific Activities calculated were 2.72 and 2.37 x 10^{-2} μ.Ci./m.mol.]. Once again, it was possible to obtain constant activities for the [^{14}C]-pyridazine (2.67) by recrystallisation. [At constant activity:- 2.376mg. gave 354 c.p.m., Acc. 0.5%, Ch. Ratio 8.65 ≡ 94% Eff., Blank 37 c.p.m., d.p.m./mg. 143, Specific Activity 1.51 x 10^{-2} μ.Ci./m.mol.. The value in Table II is based on the average of (1.51 + 1.47) x 10^{-2} = 1.49 x 10^{-2} μ.Ci./m.mol.].

A procedure using unlabelled tetrafluorobenzobarrelene (100mg.)

gave tetrafluoronaphthalene (30mg., 34%) mp. 105-107° (lit.[13c] 110-111°) and the pyridazine (30mg., 29%) mp. 179-181° (ethanol) (lit.[62] mp. 176-177°). ^{1}H.n.m.r. ($CDCl_3$) τ 1.1-1.3 (6H, m.), 1.95-2.2 (2H, m.) and 2.45-2.70 (2H,m.).

39. Reaction of tetrafluoronaphthalene with tetrachlorobenzyne.

Tetrachloroanthranilic acid (1.17g., 0.0043M.) in tetrahydrofuran (20ml.) was treated with fluoroboric acid (0.8g., 40%) and stirred for *ca.* 5min.. The solution was evaporated, ether (20ml.) added, and cooled to *ca.* 0°. Iso-amyl nitrite (0.5ml.) was added and the solution stirred for *ca*, 30min.. The solution was evaporated and tetrafluoronaphthalene (85mg., 0.0004M.) in carbon tetrachloride (20ml.) added. Pyridine (0.5g., 0.0055M.) was added and the solution stirred for *ca.* 15min..

Work-up yielded a red-oily solid (100mg.) after separation by column chromatography (alumina, 100g., eluant benzene).

Thin layer chromatography (silica, 20% ether/light petroleum ether) and g.l.c. analysis indicated the product was mainly the starting tetrafluoronaphthalene.

40. Reaction of tetrafluoronaphthalene with tetrafluorobenzyne.

Bromopentafluorobenzene (1g, 4mM.) and magnesium (0.2g.) were reacted in dry ether (20ml.) to form pentafluorophenylmagnesium bromide. Tetrafluoronaphthalene (600mg, 3mM.) in dry ether (10ml.) was added.

The reaction procedure and work-up were similar to that described in expt. 21. A white crystalline compound (400mg.) was isolated by column chromatography (alumina), Analysis of the product by t.l.c. and g.l.c. indicated only the starting tetrafluoronaphthalene.

41. Reaction of tetrafluorobenzobarreleneone with toluene-p-sulphonyl hydrazine.

Tetrafluorobenzobarrelenone (0.5g, 0.0021M.) and toluene-p-sulphonyl hydrazine (0.4g, 0.0022M.) were heated under reflux in dry benzene (75ml.) in a Dean and Stark distillation apparatus for *ca*. 5 hr.. The reaction was followed by t.l.c..

Evaporation of the solvent gave the crude tosyl hydrazone (2.84) (950mg.) as pale yellow crystals.

$\nu_{max.}$ 3220, 1595, 1500, 1450, 1400, 1340, 1165, 1120, 1090, 1035, 915, 870, 815, 800, 765, 725, 705 and 680 cm^{-1}.

The crude product was used directly in expt. 42.

42. Reaction of the product from expt. 41 with n-Butyl-Lithium.

The compound (950mg.), from expt. 41, was treated with *n*-butyl-lithium (5ml, 1.3M soln.) and stirred in ether (30ml.) for *ca*. 12 hr.. The solution was quenched with water (20ml.) and extracted with ether (3 x 25ml.) which on evaporation gave a red oil. Separation by preparative layer chromatography (silica, 10 x 1m. x 20 cm, 0.75mm. thickness, eluant light petroleum ether 60:80) gave four major products, (i) (20mg.), (ii) (30mg.), (iii) (10mg.) and (iv) (10mg.) in order of decreasing Rf. values. Analysis of the products by g.l.c. indicated that none of the products (i) - (iv) contained appreciable amounts of the required tetrafluorobenzobarrelene (2.80).

43. Preparation of /4-^{14}C 7-1-methoxytetrachlorobenzobarrelene (2.2).

The basic procedure was as described in Chapter 1 expt. 3 using hexachlorobenzene (28.5g, 0.1M.) and /4-^{14}C 7-anisole (8g, 0.074M.).

At the end of the reaction crude [4-^{14}C]-anisole (7g.) was recovered by distillation under reduced pressure. The residue was separated on a silica column (500g.) eluting with light petroleum (40:60) for fractions 1-11, 5% ether-light petroleum for fractions 12-20 and 10% ether-light petroleum for fractions 21-34. The fractions (ca. 500ml.) were checked by g.l.c.

Fractions 24-31 contained a very crude sample of the required [4-^{14}C]-1-methoxytetrachlorobenzobarrelene (7.5g.). This sample was set aside for dechlorination to [4-^{14}C]-1-methoxybenzobarrelene (2.3) expt. 44.

The procedure was repeated using hexachlorobenzene (14.25g, 0.05M.) and the recovered crude anisole (ca. 7g.). A further quantity of the required product (2.2) (1.94g.) was isolated.

The above sample (1.94g.) was diluted with 1-methoxytetrachlorobarrelene (1.0g.) and the combined sample counted to constant activity. [At constant activity 2.05mg. gave 995 c.p.m., Acc. 0.3%, Ch. Ratio 10.75 ≡ 94.5% Eff., Blank 35c.p.m., d.p.m./mg.497, Specific Activity 7.2 x 10^{-2} μ.Ci./m.mol.]

The diluted sample (2.94g.) was divided into two samples of (1.03g.) for each rearrangement, expt. 45 and 46. The remaining sample (0.88g.) had to be diluted again with 1-methoxytetrachlorobenzobarrelene (1.0g.) for the second attempt at degrading the ketones (2.5a) and (2.5b). This sample was again recrystallised to constant activity. [At constant activity 1.157mg. gave 348 c.p.m., Acc. 0.5%, Ch. Ratio 9.6 ≡ 94% Eff., Blank 44 c.p.m., d.p.m./mg.282, Specific Activity 4.09 x 10^{-2} μ.Ci./m.mol. The value in Table IVA and IVB is an average of (4.09 + 4.04) x 10^{-2}

equals 4.07 x 10^{-2} µ.Ci./m.mol.]

Similar reactions using unlabelled anisole gave a 25.5% yield of the crude 1-methoxytetrachlorobenzobarrelene (2.2) mp. 119-121° (ethanol) (lit.[14b] mp. 122°).

44. Preparation of [4-^{14}C]-1-methoxybenzobarrelene (2.3).

[4-^{14}C]-1-methoxybenzobarrelene was prepared by the dechlorination of the crude [4-^{14}C]-1-methoxytetrachlorobenzobarrelene (*ca*. 7g.), prepared in expt. 43, using the basic procedure described in Chapter 1 expt. 2.

The crude reaction mixture was separated on an alumina column (500g.) using light petroleum ether (40:60) as the eluant. Fractions (*ca*. 250ml.) were taken and checked by g.l.c.. Fractions 35-42 contained the required [4-^{14}C]-1-methoxybenzobarrelene (1.2g.) which was isolated as a pale yellow oil.

The product was diluted with 1-methoxybenzobarrelene (1.0g.) and recrystallised [light petroleum (40:60)] to constant activity. [At constant activity:- 1.049mg. gave 540 c.p.m., Acc. 0.5%, Ch. Ratio 9.45 ≡ 94% Eff., Blank 444 c.p.m., d.p.m./mg. 506, Specific Activity 4.19 x 10^{-2} µ.Ci./m.mol.. The value in Tables V and VI is an average of (4.19 + 4.09) x 10^{-2} equals 4.14 x 10^{-2} µ.Ci./m.mol.].

45. Rearrangement of [4 - ^{14}C]-1-methoxytetrachlorobenzobarrelene (2.2) in concentrated sulphuric acid.

[4-^{14}C]-1-methoxytetrachlorobenzobarrelene (1.03g.) was shaken in concentrated sulphuric acid (20ml.) at room temperature for *ca*. 8min.. The solution was quenched on ice and extracted with chloroform (4 x 40ml.).

The organic extract was dried ($MgSO_4$) and evaporated to yield an oil.

The oil was separated by preparative layer chromatography (silica, 10 x 1m. x 20cm., 0.75m.m. thickness, eluant 25% ether/light petroleum 40:60). Crude [^{14}C]-tetrachlorobenzobarrelenone (2.5a) (1g.) was isolated as the major product.

The ketone (2.5a) was recrystallised (methanol) to constant activity. [At constant activity:- 5.706mg. gave 2859 c.p.m., Acc. 0.2%, Ch. Ratio 9.04 ≡ 94% Eff., Blank 35 c.p.m., d.p.m./mg.527, Specific Activity 7.31×10^{-2} μ.Ci./m.mol.].

The same rearrangement was carried out on the further diluted sample of (2.2) (0.94g.) and the ketone (2.5a) isolated (521mg.) and counted to constant activity. [At constant activity:- 1.571mg. gave 473 c.p.m., Acc. 0.5%, Ch. Ratio 8.2 ≡ 94% Eff., Blank 42 c.p.m., d.p.m./mg.293, Specific Activity 4.06×10^{-2} μ.Ci/m.mol.]

A similar procedure using 1-methoxytetrachlorobenzobarrelene gave the required ketone (2.5) in 56% yield, mp.175-176° (lit.[20c] 166-168).

$\nu_{\text{mas.}}$ 2960, 2930, 1740, 1380, 1270, 1140, 1120, 1070, 740, 710, 690, and 650 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 3.0-3.4 (2H, m.), 4.9-5.1 (1H, m.), 5.1-5.3 (1H, m.) and 7.6-8.2 (2H, octet AB of ABX).

46. Rearrangement of [4-^{14}C]-1-methoxytetrachlorobenzobarrelene (2.2) in dilute sulphuric acid

[4-^{14}C]-1-methoxytetrachlorobenzobarrelene (1.03g.) was shaken with dilute sulphuric acid (H_2SO_4 : H_2O, 4:1, $^v/_v$. 40ml.), at 80° for ca. 80min.. The solution was quenched on ice and the required ketone (2.5b) (450mg.) isolated as described in expt. 45.

The ketone was recrystallised and counted to constant activity. [At constant activity,- 4.447mg. gave 2233 c.p.m., Acc. 0.2%, Ch. Ratio 9.64 ≡ 94% Eff., Blank 35 c.p.m., d.p.m./mg.526, Specific Activity 7.30×10^{-2} μ.Ci./m.mol.].

The same rearrangement was carried out on the further diluted sample of the compound (2.2) (0.94g.) and the ketone (2.5b) (470mg.) was isolated and counted to constant activity. [At constant activity:- 1.571mg. gave 473 c.p.m., Acc. 0.5%, Ch. Ratio 8.2 ≡ 94% Eff., Blank 43 c.p.m., d.p.m./mg.293; Specific Activity 4.06×10^{-2} μ.Ci./m.mol.].

Experiments with the unlabelled compound (2.2) gave a 45% yield of the required ketone (2.5).

47. Rearrangement of [4-^{14}C]-1-methoxybenzobarrelene (2.3) in concentrated sulphuric acid.

The [^{14}C] compound (2.3) (1g.) was shaken in concentrated sulphuric acid at room temperature for *ca.* 2min.. The solution was quenched on ice and extracted with ether (4 x 25ml.). The ethereal solution was dried ($MgSO_4$) and evaporated to give an oil.

The oil was seperated by preparative layer chromatography (silica, 10 x 1m. x 20cm., 0.75m.m. thickness, eluant 20% ether/light petroleum).

Crude [^{14}C]-benzobarrelenone (2.6a) (630mg.) was isolated as the major product. The ketone (2.6a) was recrystallised (light petroleum) to constant activity. [At constant activity:- 1.173mg. gave 639 c.p.m., Acc. 0.5%, Ch. Ratio 9.5 ≡ 94% Eff., Blank 44 c.o.m., d.p.m./mg.542, Specific Activity 4.15×10^{-2} μ.Ci./m.mol.. The value in Tables V and VI is an average of $(4.15 + 4.27) \times 10^{-2} = 4.21 \times 10^{-2}$ μ.Ci./m.mol.].

Experiments with the unlabelled compound (2.3) gave *ca.* 54% of the ketone (2.6), mp.54-56° (lit.[31] 56-58°).

$\nu_{max.}$ 3080, 3015, 2930, 1735, 1470, 1460, 1410, 1334, 1300, 1145, 1120, 1080, 960, and 687 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.55-2.95(4H, m.), 3.05-3.6(2H, m.), 5.57 (1H, q.), 5.6-5.9 (1H, m.) and 7.5-8.3 (2H, octet AB of ABX).

48. Rearrangement of $[4-^{14}C]$-1-methoxybenzobarrelene (2.3) in dilute sulphuric acid.

Dilute sulphuric acid (25ml., H_2SO_4 : H_2O, 4:1, $^v/_v$.) was heated to ca. 80° and added to the $[^{14}C]$-compound (2.3) (1g.). The solution was shaken for ca. 2min. and then quenched on ice.

The crude $[^{14}C]$-ketone (2.6b) (300mg.) was isolated as described in expt. 47. The ketone was recrystallised and counted to constant activity. [At constant activity:- 1.106mg. gave 621 c.p.m., Acc. 0.5%, Ch. Ratio 9.65 ≡ 94% Eff., Blank 44 c.p.m., d.p.m./mg.558, Specific Activity 4.27×10^{-2} μ.Ci./m.mol.. Value in Tables V and VI is an average of $(4.15 + 4.27) \times 10^{-2} = 4.21 \times 10^{-2}$ μ.Ci./m.mol.]

Unlabelled experiments gave ca. 48% yields of the benzobarrelenone (2.6).

49. Attempted preparation of tetrachlorobenzobarrelene (2.105) from tetrachlorobenzobarrelenone (2.5).

The ketone (2.5) (0.5g.) in dry ether (20ml.) was added to lithium aluminium hydride (200mg.) in ether (20ml.) and stirred for ca. 30min.. Dilute sulphuric acid (2M, 20ml.) was carefully added and the solution extracted with chloroform (3 x 40ml.) to yield the mixture of epimeric alcohols (2.103) (490mg.) as a yellow oil.

The oil was treated with sodium hydride (200mg.), carbon disulphide (12ml.), and methyl iodide (6g.) by the procedure described in expt. 36. The xanthate esters (2.104) (0.91g.) were extracted as a crude yellow oil.

$\nu_{max.}$ 2920, 2860, 1380, 1210, 1185, 1160, 1150, 1115, 1070, 1050, 1030, 1010, 960, 870, 860, 820, and 705 cm^{-1}.

Pyrolysis of the xanthate ester at ca. 230° for ca. 30 min. yielded a dark red oil. Column chromatography (alumina, 1Kg., eluant light petroleum - 10% ether/light petroleum) gave 30 fractions (ca. 200ml./fraction). Analysis by g.l.c. indicated fractions 11-17 contained tetrachloronaphthalene (100mg., 23%) mp.186-188° (lit.[69] mp.198°), but only traces of tetrachlorobenzobarrelene were indicated in the remaining fractions.

The procedure was repeated with a shorter pyrolysis time ca. 20min., but again g.l.c. analysis indicated $<$ 10% of the required tetrachlorobenzobarrelene.

50. Attempted preparation of benzobarrelene (2.83) from benzobarrelenone (2.6)

Benzobarrelenone (500mg.) was reduced to the mixture of epimeric alcohols (2.85) (550mg.) as described in expt. 49.

$\nu_{max.}$ 3600 - 3100, 3060, 3020, 2960, 2940, 1475, 1460, 1350, 1315, 1250, 1165, 1145, 1110, 1070, 1005, 990, 940, 830, 755, 700, and 690 cm^{-1}.

The alcohols (2.85) were converted into the xanthate esters (2.86) (900mg.) also as described in expt. 49.

$\nu_{max.}$ 3060, 3020, 2960, 2940, 2860, 1475, 1460, 1420, 1345, 1320, 1225, 1180, 1160, 1145, 1110, 1070, 1040, 1020, 980, 965, 830, 820, 755, and 705 cm^{-1}.

Pyrolysis of the xanthate esters (2.86) at *ca*. 230° for *ca*. 20 min. gave a red oil which on analysis by g.l.c. indicated a ratio of naphthalene : benzobarrelene $> 90 : < 10$.

51. Preparation of tetrachlorobenzobarrelenone. (2.5).

Fluorosulphonic acid (6ml.) was cooled to *ca*. -70° and stirred. The compound (2.2) (3g.) was added and the solution allowed to stir and warm slowly to room temperature.

After quenching in ice (100g.) the aqueous solution was extracted with ether (5 x 50ml.). The ethereal solution was washed with water (100ml.), potassium bicarbonate (100ml., saturated solution), dried ($MgSO_4$) and evaporated to give an orange oil. Recrystallisation of the oil gave tetrachlorobenzobarrelenone (2.0g, 70%), mp. 172-174°, (lit.[20c] 166-168°).

52. Pyrolysis of Tetrachlorobenzobarrelene. (2.105).

Tetrachlorobenzobarrelene (4.2g.) was sublimed through a flash thermolysis apparatus at *ca*. 650° under an atmosphere of dry, oxygen free nitrogen and at a reduced pressure (1m.m.Hg.) for ca. 20 min..

The product was placed on a chromatography column (alumina, 500g.) and eluated with light petroleum (60:80) to yield tetrachloronaphthalene (2.90) (3.6g, 94%) mp. 185-186° (ethanol) (lit.[69] mp. 198°). ^{1}H.n.m.r. ($CDCl_3$) τ. 1.5-1.7 (2H, m.) and 2.1-2.3 (2H, m.).

53. Attempted oxidation of naphthalene.

To a solution of naphthalene (1g.) in acetone (25ml.) heated under reflux was added saturated aqueous potassium permanganate (26.3g/100ml.) drop-wise over a period of ca. 6 hr.. The solution was heated under reflux for *ca*. 12 hr..

The solution was filtered and the filtrate extracted with ether (4 x 25ml.). The ethereal solution was extracted with sodium bicarbonate solution and the remaining ether solution dried ($MgSO_4$) and evaporated to yield a yellow-white crystalline solid (1g.)

$\nu_{max.}$ 3070, 3000, 2970, 2865, 1700, 1600, 1510, 1385, 1265, 1120, 1110, 1005 and 995 cm^{-1}.

Acidification of the sodium bicarbonate solution, extraction with ether (4 x 25ml.) and evaporation gave a yellow oil (100mg.).

$\nu_{max.}$ 3600 - 3400, 3100 - 2900, 1705, 1615, 1375, 1360 and 1170 cm^{-1}.

54. Attempted oxidation of naphthalene.

Dicyclohexyl -18-crown 6 (1g.) in dry benzene (150ml.) was stirred at room temperature. Potassium permanganate (1.9g.) was added followed by naphthalene (1g.). The combined solution was stirred at room temperature for *ca*. 12hr.

The work-up procedure was as described in expt. 28. to give an orange oil (100mg.)

$\nu_{max.}$ 3100 - 2800, 1740, 1500, 1450, 1300, 1200 and 1150 - 1100 cm^{-1}.

55. Attempted oxidation of naphthalene.

Sodium hydroxide (20ml, 0.5N.), dioxan (100ml.), and naphthalene (1g.) were heated under reflux and potassium permanganate (9.89g.) in water (70ml.) was added over *ca*. 1hr.. The solution was refluxed for *ca*. 2hr..

The solution was filtered and the filtrate extracted with ether (4 x 20ml.). The ethereal solution was evaporated to yield recovered naphthalene (0.9g.).

The remaining aqueous fraction was acidified and extracted with ether

(4 x 25ml.) to give an orange oil (200mg.).

$\nu_{max.}$ 3700 - 2000, 1700, 1400, 1275, 1005, 900, 790, 730 and 660 cm^{-1}.

56. Attempted oxidation of naphthalene.

A solution of potassium permanganate (9.89g.) in water (70ml.) was added over a period of ca. 1hr. to a refluxing solution of sodium hydroxide (20ml, 2N.) and naphthalene (1g.). The solution was heated under reflux for ca. 2hr. and then ethyl alcohol (200ml.) added.

Filtration and extraction with ether (3 x 30ml.) gave naphthalene (300mg.).

Extraction of the remaining aqueous fraction with ether (4 x 20ml.) gave a white crystalline compound (600mg.) mp. 135-145°.

$\nu_{max.}$ 3700 - 2700, 1780, 1745, 1690, 1465, 1400, 1280, 1230, 1195, 1155, 1100, 1075, 1000, 925, 790, 760, 730 and 690 cm^{-1}.

57. Attempted oxidation of naphthalene.

The same procedure as expt. 56 was used but under acidic conditions, using naphthalene (1g.), hydrochloric acid (2N, 25ml.) and potassium permanganate/water (10g/70ml.). Normal work-up procedure gave:-

(i) (basic extract) yellow oil (100mg.)

(ii) (acidic extract) pink oily solid (600mg.).

58. Attempted preparation of Phthalimide (2.107).

The products isolated in the oxidation reactions expt. 53-57 were treated with concentrated ammonium hydroxide as described in expt. 26. The following results were obtained:-

Starting Material	PRODUCT
(i) 100mg.	White crystals (20mg.) sublimed at 110-120° at 0.5-0.1m.m.Hg. mp. 210-215°

$\nu_{max.}$ 3200, 3040, 1775, 1740, 1600, 1460, 1380, 1300, 1045 and 705 cm^{-1}.

(ii)	100mg.	yellow-green oily solid. ($<$ 20mg.)
(iii)	400mg.	white crystals (20mg.) sublimed at 120-130° (0.2m.m.Hg.).

$\nu_{max.}$ 3600 - 2800, 1775, 1745, 1690, 1605, 1585, 1465, 1400, 1305, 1280, 1065, 1050, 900, 795, 730, 710 and 665 cm^{-1}.

59. Reaction of tetrachlorobenzobarrelenone with furan.

Tetrachlorobenzobarrelenone (100mg.) and furan (2ml.) were sealed in a Carius tube under vacuum. The tube was placed in a constant water bath at *ca*. 40° for 2 weeks.

Evaporation of excess of solvent yielded a grey crystalline compound (212mg.). Thin layer chromatography (20% ether/light petroleum) and i.r. spectroscopy indicated only the starting ketone (2.5).

$\nu_{max.}$ 1740, 1380, 1310, 1270, 1165, 1145, 1125, 1075, 970, 900, 805, 745, 715, 690 and 655 cm^{-1}.

60. Reaction of tetrachlorobenzobarrelenone with toluene-p-sulphonyl hydrazine (tosyl hydrazine).

Tetrachlorobenzobarrelenone (400mg, 0.001M.) and tosyl hydrazine (240mg, 0.0013M.) were heated under reflux in dry benzene (75ml.) in a Dean and Stark distillation apparatus for *ca*. 5hr.. The reaction was followed by t.l.c..

The solution was evaporated and the yellow solid residue recrystallised (benzene) to give a white crystalline solid (140mg.), mp. 229-230°.

A second reaction using tetrachlorobenzobarrelenone (500mg, 0.0016M.) and tosyl hydrazine (300mg, 0.0016M.) gave a pale yellow solid (700mg.) mp. 227-230°.

$\nu_{max.}$ 3700 - 3300, 3220, 1490, 1400, 1380, 1345, 1295, 1165, 1115, 1085, 1040, 1015, 940, 910, 865, 810, 795, 760, 710, 700, 675, and 655 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 0.1 (s, 1H, D_2O exchange), 2.2-2.3 (2H, d.), 2.64-3.64 (2H, d.), 3.2-3.4 (2H,m.), 5.1-5.25 (1H, m.), 5.3-5.5 (1H, m.) and 7.35-7.9 (5H, m, 7.58 (s) and 7.35-7.9 [AB of ABX]).

The data fits that required for the tosyl hydrazone (2.110).

61. Attempted degradation of the tosyl hydrazone (2.110) to tetrachlorobenzobarrelene (2.105).

A number of procedures were investigated:-

(i) The tosyl hydrazone (2.110) (100mg.) in dry ether (30ml.) was stirred at room temperature under nitrogen. *n*-Butyl-lithium in hexane (0.15ml.) was slowly added and the solution stirred for *ca*. 12hr.. Water (50ml.) was added and the solution extracted with ether (3 x 25ml.). Evaporation of the dried ($MgSO_4$) solvent gave a yellow-orange solid (60mg.).

$\nu_{max.}$ 2900, 2850, 1370, 1330, 1210, 1155, 1090, 1020, 750, and 655 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.1-2.2 (m.), 2.5-2.7 (m.), 3.0-3.2 (m), 3.3-3.5 (m.), 7.62 (s) and 9.0-9.2 (m.)

(ii) The same procedure as (i) was used but an excess of *n*-butyl-lithium (0.3ml.) was used. A similar orange solid was isolated (90mg.).

^{1}H.n.m.r. ($CDCl_3$) τ. 2.18 (s.), 2.26 (d.), 2.65-2.8 (m.), 3.0-3.2 (m.), 3.3-3.5 (m.), 7.62 (s.), 8.73 (s.) and 9.0-9.2 (m.).

(iii) The tosyl hydrazone (100mg.) was reacted with sodium (300mg.), *t*-butyl-alcohol (0.3ml.), and tetrahydrofuran (50ml.) using the standard dechlorination procedure described in Chapter 1 expt. 2. An oily solid was obtained.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.7-3.1 (s.), 3.2-3.4 (s.), 5.4-5.5 (m.) and 7.62 (s.).

(iv) A second reaction involving sodium (1g.), t-butyl-alcohol (2ml.), and tetrahydrofuran (60ml.) and the same procedure as (iii) gave a yellow-orange solid (30mg.).

(v) The tosyl hydrazone (100mg.) was added to a solution of t-butyl-alcohol (25ml.) and potassium (50mg.). The solution was stirred at room temperature for ca. 12hr. and then evaporated. Water (25ml.) was added and the aqueous solution extracted with ether (3 x 25ml.). Evaporation of the dried ($MgSO_4$) solvent gave white crystals (70mg.). The product had a similar ^{1}H.n.m.r. spectra to that of the tosyl hydrazone (2.110).

(vi) The tosyl hydrazone (100mg.) in dry ether (30ml.) was stirred and n-butyl-lithium (0.5ml, 1.3M soln.) was added. After stirring for ca. 1hr. further n-butyl-lithium (0.5ml.) was added and the solution stirred for ca. 12hr.. The solution was quenched and extracted to yield an orange oil (100mg.). The oil was separated by preparative layer chromatography (silica, 2 x 1m. x 20cm., 0.75m.m. thickness, eluant light petroleum 60:80). Three products were isolated, in order of decreasing Rf. value:-

(1) (20mg.) ^{1}H.n.m.r. ($CDCl_3$) τ. 1.9-2.1 (m.), 2.4-2.6 (m.), 2.73 (s.), 7.0-7.2 (m.) and 8.2-9.4 (broad multiple band).

(2) (10mg.) ^{1}H.n.m.r. ($CDCl_3$) τ. 3.0-3.2 (m.), 4.6-4.8 (m.), 7.3-7.5 (m.) and 8.3-9.2 (broad multiple band).

(3) (10mg.) ^{1}H.n.m.r. ($CDCl_3$) τ. 2.6-3.2 (m.), 7.69 (s.) and 8.3-9.2 (broad multiple band).

62. Reaction of Benzobarrelenone with tosyl hydrazine.

Benzobarrelenone (500mg, 0.0029M.) and tosyl hydrazine (528mg, 0.0028M.) were reacted according to the procedure described in expt. 60.

Evaporation of the solvent gave an oily solid which was recrystallised to give a white crystalline solid (0.54g.) mp. 167-168° (aq. ethanol).

A similar reaction using benzobarrelenone (440mg, 0.0026M.) and tosyl hydrazine (460mg, 0.0025M.) gave a crude pale yellow solid (1g.).

$\nu_{max.}$ 3370, 3320, 3060, 3020, 2970, 2920, 2850, 1640, 1595, 1490 1470, 1460, 1400, 1330, 1305, 1290, 1210, 1180, 1160, 1090, 1020, 930, 915, 830, 810, 755, 700, and 655 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.16 (1H, s), 2.25 (1H, s), 2.3-2.5 (1H, broad), 2.65-3.0 (7H, m), 3.3-3.5 (1H, m), 5.35-5.5 (1H, m), 5.75-5.90 (1H, m), 7.59 (3H, s) and 7.83 (2H, s).

The above spectral data would fit the required tosyl hydrazone (2.82) plus a trace of unreacted tosyl hydrazine.

63. Attempted degradation of the product from expt. 62.

The product (100mg.), from expt. 62, was suspended in dry ether (30ml.) and stirred under nitrogen. *n*-Butyl-lithium (0.5ml.) was added. After *ca*. 1hr. further *n*-butyl-lithium (0.5ml.) was added. The solution was stirred for *ca*. 12hr.. Water (25ml.) was added and the aqueous solution extracted with ether (3 x 25ml.). Evaporation gave a yellow oil (t.l.c. indicated 2 products). The oil was separated by preparative layer chromatography (silica, 1 x 1m. x 20cm., 0.75m.m. thickness, eluant light petroleum 40:60) to yield (i) (highest Rf.) 5mg. and (ii) 25mg.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.7-2.9 (m.), 3.0-3.2 (m.) and 4.95-5.15 (m.).

The above reaction was repeated on a larger scale the compound (2.82) (1.05g.) and n-butyl-lithium (2 x 5.0ml.). A crude oil (0.74g.) was isolated which was separated as above to give three products, in order of decreasing Rf. value:- (i) 50mg. (ii) 80mg. and (iii) 130mg.
^{1}H.n.m.r. ($CDCl_3$) τ. 2.7-2.95 (m.), 3.05-3.2 (m.), 5.0-5.2 (m.), 7.7 (s.) and 8.3-9.2 (broad band).

64. Dechlorination of tetrachlorobenzobarrelenone.

The procedure was as described in Chapter 1 expt. 2 using tetrachlorobenzobarrelenone (1g, 3.2m.M.), sodium (1g.), t-butyl-alcohol (3ml.), and tetrahydrofuran (60ml.).

Normal work up gave an orange oil (0.4g.) which was identified by g.l.c. and ^{1}H.n.m.r. spectroscopy to be mainly tetralin (2.113).
^{1}H.n.m.r. ($CDCl_3$) τ. (crude product); 2.98 (s.), 7.1-7.4 (m.), 8.1-8.3 (m.) and 8.7-9.0 (m.).

65. Dechlorination of Tetrachloronaphthalene

The procedure was as described in Chapter 1 expt. 2 using tetrachloronaphthalene (2g, 0.0075M.), sodium (2g.), t-butyl alcohol (6ml.), and THF. (100ml.). The reaction was followed by g.l.c..

The solution turned purple after ca. 2hr.. After refluxing for 24hr., normal work-up procedure gave an orange oil (1.1g.). Separation on a short chromatography column (alumina, 50g.), eluant light petroleum (40:60), yielded a colourless oil (0.7g.)

Analysis by g.l.c. and ^{1}H.n.m.r. spectroscopy showed the oil to be mainly tetralin (2.113).

^{1}H.n.m.r. ($CDCl_3$) τ. 3.03 (4H, s.); 7.1-7.4 (4H, m.) and 8.1-8.4 (4H, m.)

66. Reduction of Naphthalene

Naphthalene (1g, 0.0078M.) was reduced under the conditions used for dechlorination (Chapter 1 expt. 2) with sodium (1g.), *t*-butyl alcohol (3ml.), and THF (50ml.). The solution was heated under reflux 24hr. and the reaction followed by g.l.c..

Normal work-up procedure gave a pale yellow oil (1g.). Analysis by g.l.c. indicated the product was mainly tetralin (2.113).

67. Reaction of the $[^{14}C]$-tetrachlorobenzobarrelenones (2.5a) and (2.5b) with phenyl magnesium bromide.

Magnesium (72mg.) in dry ether (2ml.) was stirred whilst bromobenzene (444mg, 2.8m.M.) in dry ether (5ml.) was slowly added. The solution darkened as the magnesium dissolved.

The $[^{14}C]$-ketone (2.5a) (*ca*. 600mg.) in dry ether (20ml.) was added and the solution stirred for *ca*. 12hr.. The reaction was followed by t.l.c..

A thick slurry was formed and to this water (20ml.) was added. Ether (3 x 25ml.) extraction gave a yellow-green oil (700mg.). The oil was separated by preparative layer chromatography (silica, 10 x 1m. x 20cm., 0.75m.m. thickness, eluant 20% ether/light petroleum 40:60). Two products were isolated, (i) (highest Rf.) 100mg. and (ii) the required $[^{14}C]$-phenyl carbinol (2.114) (630mg.).

A similar reaction using the $[^{14}C]$-ketone (2.5b) (*ca*. 500mg.) with bromobenzene (370mg.) and magnesium (60mg.) gave the same two products (i) 130mg. and (ii) the $[^{14}C]$-phenyl carbinol (2.114) (450mg.).

Experiments using unlabelled tetrachlorobenzobarrelenone also gave the two products (i) and (ii) Product (i) was identified as biphenyl by comparison with authentic material.

Product (ii) was identified as 2,3-dihydro-2-hydroxy-2-phenyltetrachlorobenzobarrelene (2.114) by comparison of its spectral data with authentic material.[20e] The crude product was isolated in a quantitative yield as a yellow-green oil. Recrystallisation (ethanol) gave the product (2.114) as a white crystalline solid.

$\nu_{max.}$ 3550, 3450 (broad), 3080, 2995, 2975, 2945, 1450, 1380, 1345, 1325, 1315, 1280, 1265, 1220, 1195, 1170, 1090, 1060, 1020, 990, 785, 765, 735, 705, and 685 cm^{-1}.

68. Thermal decomposition of the $[^{14}C]$-2,3-dihydro-2-hydroxy-2-phenyltetrachlorobenzobarrelene (2.114).

The crude $[^{14}C]$-phenyl carbinol (2.114) (630mg.) in dry dimethylformamide (50ml.) was heated under reflux for ca. 12hr.. The cool reaction mixture was poured into water (300ml.) and extracted with ether (3 x 75ml.). The combined extracts were washed with water, dried ($MgSO_4$) and carefully evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica, 10 x 1m. x 20cm., 0.75m.m. thickness, eluant 20% ether/light petroleum 40:60) to give:-

(i) $[^{14}C]$-tetrachloronaphthalene (2.90) (370mg.)

(ii) crude acetophenone (220mg.)

The $[^{14}C]$-tetrachloronaphthalene (2.90) was sublimed to constant activity. [At constant activity:- 2.131mg. gave 1265 c.p.m., Acc. 0.5%, Ch. Ratio 10.12 ≡ 94% Eff., Blank 42 c.p.m., d.p.m./mg. 612, Specific Activity 7.34 x 10^{-2} μ.Ci./m.mol.]

A similar reaction was carried out using the [^{14}C]-phenyl carbinol (2.114) (450mg.), derived from the [^{14}C]-ketone (2.5b), to give:-

(i) [^{14}C]-tetrachloronaphthalene (2.90) (300mg.).

(ii) crude acetophenone (130mg.)

The [^{14}C]-tetrachloronaphthalene (2.90) was sublimed to constant activity. [At constant activity:- 1.649mg. gave 973 c.p.m., Acc. 0.3%, Ch. Ratio 10.51 ≡ 94% Eff., Blank 42 c.p.m., d.p.m./mg. 602, Specific Activity 7.30 x 10^{-2} μ.Ci./m.mol.].

Reactions using the unlabelled phenyl carbinol (2.114) (590mg.) gave tetrachloronaphthalene (2.90) (330mg, 81.2%), mp.186-187° (lit.[69] mp.198°) and crude acetophenone (2.116) (280mg., oil).

$\nu_{max.}$ 1690, 1605, 1585, 1450, 1360, 1315, 1300, 1265, 1180, 1075, 1025, 955, 890, 755, and 685 cm^{-1}.

69. Preparation of the acetophenone oxime (2.117)

The crude acetophenone (220mg.), from expt. 68, was added to hydroxylamine hydrochloride (100mg.) and sodium acetate (200mg.) in water (5ml.). Drops of ethyl alcohol (95%) were added until a clear solution was obtained. The solution was heated on a steam bath for *ca.* 5min. and then cooled.

The required oxime (2.117) was isolated by filtration as white crystals (25mg.), mp.50-55°, (lit.[67] 60°).

A similar reaction using the second crude sample of acetophenone (130mg.) gave the same product (2.117) (20mg.).

The two samples of the oxime (2.117) were counted in the normal way and found to contain no activity above that expected for background.

Reactions using a standard sample of acetophenone gave the oxime (2.117) as a white crystalline compound, mp.59-60° (water), (lit.^{67}60°).
$\nu_{max.}$ 3500 - 2500 (broad), 1495, 1440, 1415, 1360, 1310, 1300, 1280, 1155, 1075, 1000, 970, 920, 755, 685, and 645 cm^{-1}.
^{1}H.n.m.r. ($CDCl_3$) τ. 2.25-2.49 (2H, m), 2.52-2.70 (3H, m.) and 7.7 (3H, s.).

70. Dechlorination of the $[^{14}C]$-tetrachloronaphthalenes (2.90)

The crude $[^{14}C]$-tetrachloronaphthalene (370mg.) from expt. 68, derived from the $[^{14}C]$-ketone (2.5a), was heated under reflux in a solution of ethyl alcohol (300ml.), hydrazine hydrate (5ml.), and PdC (10%; 100mg.) for ca. 4hr.. Filtration and evaporation of the solution gave a yellow-green oil. The oil was separated by preparative t.l.c. (silica: 5 x 1m. x 20cm., 0.75 m.m. thickness, eluant light petroleum) to give as the major product an oil (80mg.).

Analysis by t.l.c. and g.l.c. indicated that the oil contained the required $[^{14}C]$-naphthalene (2.87).

The above procedure was repeated for the crude $[^{14}C]$-tetrachloronaphthalene (300mg.), derived from the $[^{14}C]$-ketone (2.5b), to give the same crude $[^{14}C]$-naphthalene (2.87) (40mg.).

Similar dechlorinations using unlabelled tetrachloronaphthalene gave naphthalene as a yellow-green oil in yields of 10-70%. In one reaction the compound (2.90) (200mg.) gave an oily crystalline solid (70mg.).
$\nu_{max.}$ 3050, 3000, 1595, 1505, 1385, 1265, 1125, 1005, and 955 cm^{-1}.
^{1}H.n.m.r. ($CDCl_3$) τ. 2.0-2.7 (broad multiplet).

The product was again separated by preparative t.l.c. to give two products in order of decreasing Rf. value:-

(i) yellow oil (51mg.), ^{1}H.n.m.r. ($CDCl_3$) τ. 1.6-1.8 (m.) and 2.0-2.8 (m.).

(ii) white solid (15mg.), ^{1}H.n.m.r. ($CDCl_3$) τ. 2.0-2.3 (2H, m.) and 2.35-2.6 (2H, m.).

71. Preparation of 1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene (2.94)

Pentachlorophenyl lithium was prepared from hexachlorobenzene (3g, 0.01M.) and *n*-butyl lithium (8ml, *ca*. 2.0M. solution.) as described in Chapter 1 expt. 1.

Naphthalene (1.28g, 0.01M.) in light petroleum (60:80) (10ml., sodium dried.) was added. The solution turned deep-blue instantaneously. The solution was stirred at room temperature for *ca*. 24hr..

The solution was washed with hydrochloric acid (2N., 2 x 100ml.) and evaporated to give an oily red-brown solid. The crude product was separated by column chromatography (alumina, 250g.) collecting fractions (*ca*. 200ml./fraction) by eluting first with light petroleum 60:80 (10 fractions) followed by 10% ether/light petroleum (6 fractions).

The fractions were analysed by g.l.c. and fractions 9-13 were combined to give a white oily solid (1.0g.). Recrystallisation (ethanol) gave the required product (2.94) (300mg, 8.8%), mp.162-167° (lit.[14b] 166°).

A similar reaction using hexachlorobenzene (6g, 0.02M.), *n*-butyl lithium (10ml.), and naphthalene (1.28, 0.01M.) gave a 16.4% yield of the compound (2.94).

Reducing the scale of the above procedure to hexachlorobenzene

(600mg, 2.1m.M.) and naphthalene (200mg, 1.6m.M.) and separating the crude product by preparative t.l.c. (silica, 10 x 1m. x 20cm., 0.75m.m. thickness, eluant light petroleum 60:80), gave a 16.8% yield of the 1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene (2.94).

$\nu_{max.}$ 3060, 3000, 1605, 1470, 1375, 1320, 1255, 1220, 1150, 800, 760, 750, 690, and 650 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.5-3.2 (6H, m.) and 4.25-4.5 (2H, m.)

72. Attempted preparation of $[^{14}C]$-1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene (2.94).

The crude $[^{14}C]$-naphthalene (80mg.) from expt. 70, derived from the $[^{14}C]$-ketone (2.5a) was reacted with pentachlorophenyl lithium as described in expt. 71 (small scale). Separation of the reaction mixture by preparative t.l.c. gave none of the required compound (2.94). A very crude sample of the $[^{14}C]$-naphthalene (62mg.) was recovered.

The reaction was repeated twice each time using the recovered crude $[^{14}C]$-naphthalene. The result was the same for each attempt, none of the required compound (2.94).

A similar series of results were obtained for reactions using the $[^{14}C]$-naphthalene (40mg.) derived from the $[^{14}C]$-ketone (2.5b).

Analysis of all the reaction products by t.l.c. and g.l.c. indicated that the compound (2.94) had not been formed in sufficient quantities to enable its separation from the impurities present.

73. Preparation of $[^{14}C]$-5,6,7,8-tetrachloro-2,2-ethylene-dioxy-1,2,3,4-tetrahydro-1,4-ethenonaphthalene (2.111).

The $[^{14}C]$-tetrachlorobenzobarrelenone (2.5a) (521mg.) was reacted with boron trifluoride-etherate (10ml.), and ethylene glycol (10ml.) in dichloromethane (50ml.) at room temperature for ca. 50hr.. The solution was washed with water (25ml.), sodium bicarbonate (2 x 25ml.), and water (25ml.). Evaporation of the solvent gave an orange oil which was separated by preparative t.l.c. (silica: 5 x 1m. x 20cm., 0.75m.m. thickness, eluant 20% ether/light petroleum 40:60). The [^{14}C]-ethylene ketal (2.111) (810mg.) was isolated as a white oily solid.

The same reaction using the [^{14}C]-ketone (2.5b) (470mg.) yielded the [^{14}C]-ethylene ketal (2.111) (520mg.) as a similar oily solid.

Reactions involving unlabelled tetrachlorobenzobarrelenone gave an almost quantitative yield of the ethylene ketal (2.111) mp. 108-110° (lit.^{20e} 111-112°).

$\nu_{max.}$ 3070, 3000, 2950, 2895, 1480, 1440, 1375, 1345, 1330, 1290, 1275, 1255, 1240, 1155, 1135, 1115, 1055, 1020, 985, 970, 940, 910, 860, 805, 705, 675, and 640 cm^{-1}.

^{1}H.n.m.r. (CDCl$_3$) τ 3.3-3.52 (2H, m.), 5.4-5.6 (2H, m.), 5.7-6.3 (4H, m.), 8.0 (dd, 1H, $|J|$ = 14Hz, $|J|$ = 3Hz.), and 8.2 (dd, 1H, $|J|$ = 14Hz, $|J|$ = 3Hz.),

74. Dechlorination of the [^{14}C]-ethylene ketal (2.111) to 2,2-Ethylenedioxy-1,2,3,4-tetrahydro-1,4-ethenonaphthalene (2.112)

The [^{14}C]-ethylene ketal (2.111) (810mg.), derived from the [^{14}C]-ketone (2.5a) was dechlorinated by the standard procedure (Chapter 1 expt. 2) using sodium (1g.), t-butyl alcohol (3ml.), and THF (50ml.). The crude [^{14}C]-ethylene ketal (2.112) (510mg.) was obtained as a yellow oil.

The same reaction with the $[^{14}C]$-ethylene ketal (2.111) (520mg.), derived from the $[^{14}C]$-ketone (2.5b) gave the $[^{14}C]$-ethylene ketal (2.112) (395mg.) also as a yellow oil.

The same dechlorination using unlabelled ethylene ketal (2.111) (770mg, 0.0022M.) gave after preparative t.l.c. (silica, 10 x 1m. x 20cm, 0.75m.m. thickness, eluant 20% eher/light petroleum 40:60), 2,2-ethylene-dioxy-1,2,3,4-tetrahydro-1,4-ethenonaphthalene (2.112) (400mg, 85.4%), mp. 115-117° (light petroleum 40:60). (Found: C,78.85, H,6.7%, M (mass spectrometry), 214. $C_{14}H_{14}O_2$ requires C,78.48, H,6.59%, M, 214.

$\nu_{max.}$ 2960, 2855, 1468, 1455, 1434, 1340, 1310, 1265, 1250, 1215, 1115, 1095, 1045, 1010, 965, 950, 910, 860, 825, 785, 760, 710, and 670 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 2.7-3.0, (4H, m.), 3.2-3.55 (2H, m.), 5.9-6.25 (6H, m.), 8.0 (1H, dd, $|J|$ = 14Hz, and 3Hz,), and 8.2 (1H, dd, $|J|$ = 14Hz, and 3Hz.).

75. Preparation of $[^{14}C]$-benzobarrelenone (2.6) from the $[^{14}C]$-ethylene ketal (2.112).

The $[^{14}C]$-ethylene ketal (2.112) (510mg.), derived from the $[^{14}C]$-ketone (2.5a), was dissolved in ether (25ml.) and concentrated hydrochloric acid (3 drops) added. The solution was stirred at room temperature for ca. 30min..

The solution was quenched in water (20ml.) and extracted with ether (2 x 25ml.). The combined ethereal solution was washed with sodium bicarbonate (20ml.), water (20ml.), dried ($MgSO_4$) and evaporated to yield a yellow oil. The oil was separated by preparative t.l.c. (silica, 5 x 1m. x 20cm., 0.75m.m. thickness, eluant 20% ether/light petroleum

60:80) to yield $[^{14}\mathrm{C}]$-benzobarrelenone (2.6) (406mg.)

The same reaction using the $[^{14}\mathrm{C}]$-ethylene ketal (2.112) (395mg.), derived from the $[^{14}\mathrm{C}]$-ketone (2.5b) gave $[^{14}\mathrm{C}]$-benzobarrelenone (2.6) (330mg.).

Reactions using the unlabelled ketal (2.111) gave an almost quantitative yield of benzobarrelenone (2.6), identified by comparison with authentic material.

76. Preparation of $[^{14}\mathrm{C}]$-2,3-dihydro-2-hydroxy-2-phenylbenzobarrelene (2.115).

The four samples of $[^{14}\mathrm{C}]$-benzobarrelenone: (2.6a) (2.6b), (2.6) derived from (2.5a) and (2.6) derived from (2.5b) were reacted with phenyl magnesium bromide as described in expt. 67. The required $[^{14}\mathrm{C}]$-phenyl-carbinol (2.115) was isolated, in each reaction, as a yellow oil by preparative t.l.c. (silica, 5 x 1m. x 20cm., 0.75m.m. thickness, eluant 10% ether/light petroleum 40:60).

$[^{14}\mathrm{C}]$-benzobarrelenone.		$[^{14}\mathrm{C}]$-phenyl carbinol (2.115).
(2.6a)	630mg.	810mg.
(2.6b)	300mg.	420mg.
(2.6 from 2.5a)	406mg.	535mg.
(2.6 from 2.5b)	330mg.	412mg.

Reactions using unlabelled benzobarrelenone yielded *ca.* 85% of the required phenyl carbinol (2.115) as a yellow oil.

$\nu_{\mathrm{max.}}$ 3700 - 3100, 3070, 3030, 2970, 2940, 1495, 1470, 1460, 1450, 1350, 1175, 1110, 1055, 1025, 995, 835, 795, 760, 720, 700, and 685 cm^{-1}.

The crude phenyl carbinol (2.115) was used directly in expt. 77.

77. Thermal decomposition of the $[^{14}C]$-phenyl carbinol (2.115) to $[^{14}C]$-naphthalene and acetophenone (2.116)

The four samples of the $[^{14}C]$-phenyl carbinol (2.115) prepared in expt. 76 were separately heated under reflux in dimethylformamide and the products isolated as described in expt. 68.

$[^{14}C]$-phenyl carbinol	$[^{14}C]$-naphthalene	Acetophenone (crude).
(2.115) derived from (2.6a)		
810mg.	140mg.	112mg.
(2.115) derived from (2.6b)		
420mg.	70mg.	54mg.
(2.115) derived from (2.5a)		
535mg.	340mg.	200mg.
(2.115) derived from (2.5b)		
412mg.	230mg.	150mg.

The same reaction using the unlabelled phenyl carbinol (2.115) (460mg.) gave naphthalene (2.58) (90mg.) and crude acetophenone (2.116) which was converted into the oxime (2.117) (25mg.) mp. 50-55° (lit.[67] 60°).

The four samples of acetophenone derived from the $[^{14}C]$-phenyl carbinols were also reacted to the oxime (2.117). The samples of crude oxime (2.117) were counted by the standard procedure and shown to have no activity above that expected for background.

78. Preparation of $[^{14}C]$-1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene (2.94)

The four samples of $[^{14}C]$-naphthalene (2.58), prepared in expt. 77, were reacted with pentachlorophenyl lithium according to the small scale procedure described in expt. 71. The required [^{14}C]-compound (2.94) was isolated as shown below:-

[^{14}C]-Naphthalene (2.58)	[^{14}C]-Compound (2.94)
(2.58) derived from (2.6a) 140mg.	120mg.
(2.58) derived from (2.6b) 70mg.	65mg.
(2.58) derived from (2.5a) 340mg.	200mg.
(2.58) derived from 2.5b) 230mg.	309mg.

The four [^{14}C]-compounds (2.94) compared favourably by t.l.c. and g.l.c. with authentic material prepared in expt. 71.

79. Reaction of 1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene (2.94) with p-nitrophenylazide (2.75)

A solution of the compound (2.94) (560mg, 1.64m.M.) and *p*-nitrophenyl azide (300mg, 1.83m.M.) in benzene (50ml.) was heated under reflux for *ca.* 48hr.. Analysis by t.l.c. indicated the presence of the starting compound (2.94). Further *p*-nitrophenyl azide (40mg.) was added and the solution heated under reflux for *ca.* 12hr..

The solution was evaporated and the residue separated by preparative t.l.c. (silica: 10 x 1m. x 20cm., 0.75m.m. thickness, eluant 20% ether/light petroleum 40:60) to give three bands (i) to (iii) with high Rf. values and a broad band with a low Rf. value which was isolated and plated a second time (eluant chloroform) to give two bands (iv) and (v).

^{1}H.n.m.r. ($CDCl_3$) τ. :-

(i) (100mg.) 2.6-2.8(m), and 8.72(s)

(ii) (80mg.) 2.5-2.8(m), 2.9-3.1(m), and 4.2-4.4(m).

(iii) (200mg.) 1.65-1.9(m), and 2.7-2.95(m).

(iv) (550mg.) 1.6-2.1(m), 2.4-2.9(m), 4.2-4.32(m), 4.4-4.7(m), 5.3-5.6(m), 7.5-7.8(m), and 8.72(m),

(v) (40mg.) 1.51(s), 1.61(s), 1.85-2.1(m), 2.6-2.8(m), 8.3-8.5(m), 8.72(s), and 9.23(s).

The complicated mixture of products in this reaction and difficulty of isolating the required tetrachloranthracene (2.97) and triazine (2.76) led to the preferential use of the tetrazine (2.64), expt. 80.

80. Degradation of [^{14}C]-1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenonaphthalene (2.94) with 3,6-di-(2'-pyridyl)-s-tetrazine (2.64).

The unlabelled compound (2.94) (200mg, 0.58m.M.) and the tetrazine (2.64) (150mg, 0.73m.M.) were heated under reflux in di-*n*-butyl ether (25ml.) for *ca*. 12hr.. The red colour was discharged and a tan precipitate formed. The solvent was evaporated under reduced pressure and the residue, a oily yellow solid, was purified by preparative t.l.c. (silica, 5 x 1m x 20cm., 0.75m.m. thickness, eluant 10% ether/light petroleum 40:60) to give (i) tetrachloroanthracene (2.97) (166mg, 90%) yellow-green crystals mp. 215-216° (benzene) (lit.[66] 217-219°).

$\nu_{max.}$ 3025, 1600, 1550, 1430, 880, 780, and 730 cm^{-1}.

^{1}H.n.m.r. (CS_2) τ. 1.15(2H, s.), 1.8-2.1(2H, m.), and 2.25-2.5(2H, m.) and (ii) a broad base line which was extracted and the residue re-plated (eluant chloroform) to give two bands very close together near the base line.

Repeated elution (x6) separated the bands to give, in order of decreasing Rf. values:-

(iii) 3,6-di-(2'-pyridyl)-pyridazine(2.67) (100mg, 72.5%) mp.178-180° (ethanol) (lit.[62] 176-177°).

^{1}H.n.m.r. ($CDCl_3$) δ. 1.1-1.4 (6H, m.), 2.0-2.2 (2H, m), and 2.5-2.7 (2H, m.).

(iv) 3,6-di-(2'-pyridyl)-*s*-tetrazine (2.67) (*ca.* 10mg.) identified by comparison with authentic material.

The above procedure was repeated using the four samples of $[^{14}C]$-compound (2.94). The results are shown below:-

$[^{14}C]$-Compound (2.94)	$[^{14}C]$-Tetrachloroanthracene (2.97)	$[^{14}C]$-Pyridazine (2.67)
(2.94) derived from (2.6a)		
120mg.	59mg.	48mg.
(2.94) derived from (2.6b)		
65mg.	10mg.	15mg.
(2.94) derived from (2.5a)		
200mg.	20mg.	36mg.
(2.94) derived from (2.5b)		
309mg.	10mg.	32mg.

Where possible the samples of $[^{14}C]$-tetrachloroanthracene (2.97) were sublimed to constant activity and the samples of $[^{14}C]$-pyridazine (2.67) recrystallised (ethanol) to constant activity.

It was not possible to recrystallise the pyridazine (2.67) derived from the $[^{14}C]$-ketones (2.5a) and (2.5b). This was assumed due to the presence of impurities. Further separation by preparative t.l.c. did not overcome this problem.

The crude yield of the $[^{14}C]$-tetrachloroanthracene (2.97) (10mg.), derived from the $[^{14}C]$-ketone (2.6b), was found too small to sublime accurately.

It was not possible to sublime the $[^{14}C]$-tetrachloroanthracene (2.97) or recrystallise the $[^{14}C]$-pyridazine (2.67) derived from the ketone (2.6b).

The results of the remaining samples are shown in the following table.

$[^{14}C]$ - activity results for Expt. 80

$[^{14}C]$-Compound	Weight (mg.)	c.p.m.	Acc. %	Ch. R	Eff. %	Blank c.p.m.	d.p.m./mg.	Sp. Ac. μ.Ci./m.mol	Av.Sp. Ac. μ.Ci./m.mol
(2.97) from (2.5a)	0.95	180	0.7	7.14	93.5	42	158	2.247×10^{-2} (2.179×10^{-2})	2.21×10^{-2}
(2.97) from (2.5b)	0.67	151	0.5	7.75	94.0	42	175	2.49×10^{-2} (2.21×10^{-2})	2.35×10^{-2}
(2.97) from (2.6a)	1.4	236	0.7	7.44	94.0	42	149	2.12×10^{-2} (2.21×10^{-2})	2.17×10^{-2}
(2.67) from (2.6a)	2.259	427	0.5	6.59	93.5	42	183	1.95×10^{-2} (1.97×10^{-2})	1.96×10^{-2}

c.p.m. - Counts per minute

Acc. - Accuracy

Ch. R. - Channel Ratio

Eff. - Efficiency

d.p.m./mg. - disintegrations per min. per mg.

μ.Ci./m.mol - microcuries per millimole.

Sp.Ac. in ( ) equals a value obtained from a second determination.

CHAPTER 3

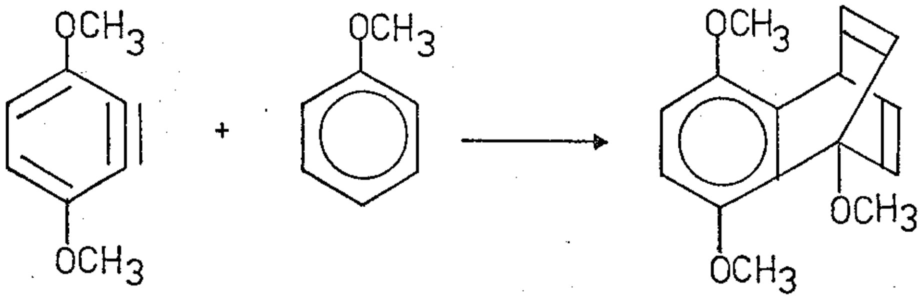
Further Studies in the Preparation and Rearrangement of 1-Methoxybenzobarrelene Derivatives.

INTRODUCTION

In an attempt to broaden our knowledge of the chemistry surrounding the acid catalysed rearrangement of 1-methoxybenzobarrelene and its substituted derivatives, two different approaches were considered.

The first involved the preparation of 3,6-dimethoxybenzyne (3.1) which hopefully would react with anisole to yield 1,5,8-trimethoxybenzobarrelene (3.2) as depicted in Scheme 3.1.

Scheme 3.1

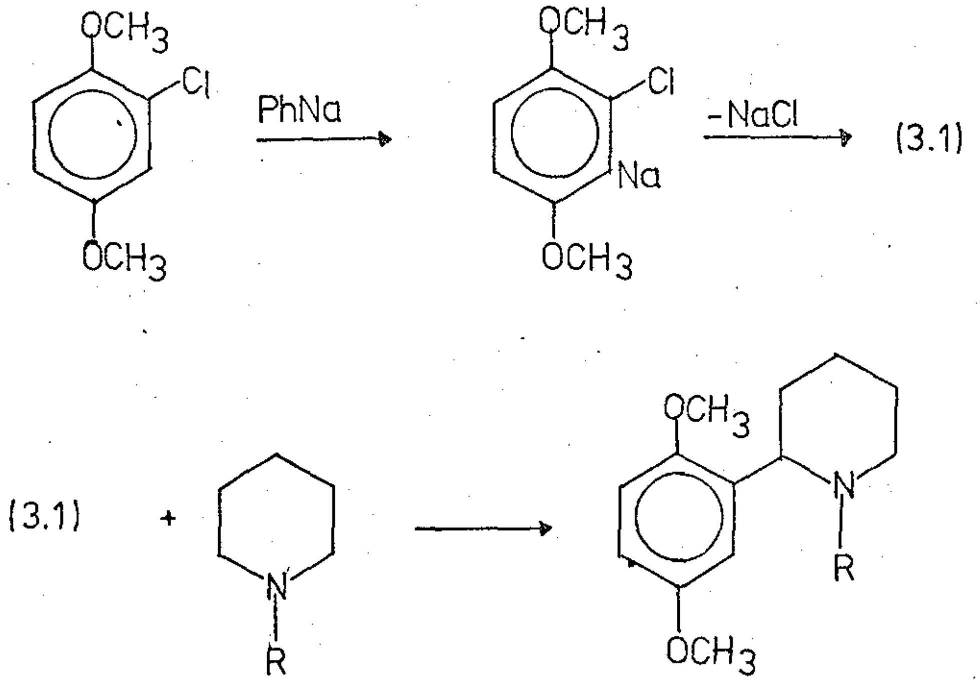


(3.1) (3.2)

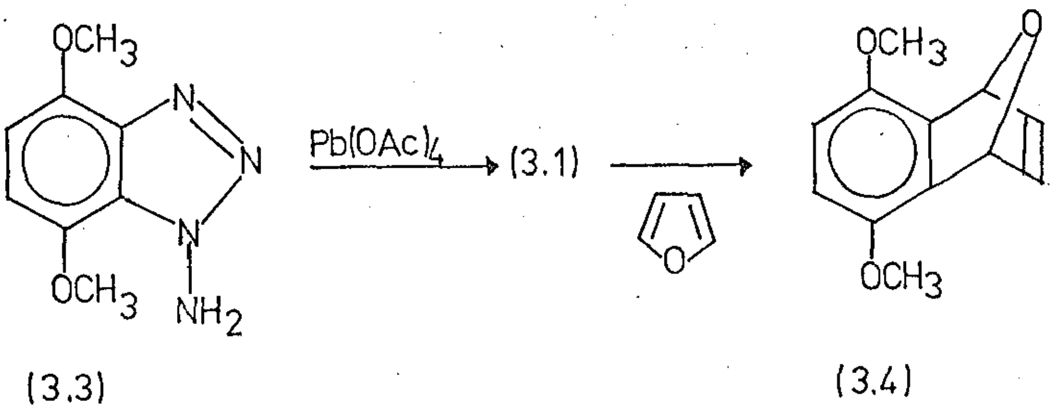
The aryne (3.1) had been prepared previously by Gustav Ehrhart[70] by the procedure shown in Scheme 3.2. More recently, Rees and West[71] had generated the aryne (3.1) by the oxidation of 1-amino-4,7-dimethoxybenzotriazole (3.3), using lead tetraacetate in the presence of furan and obtained the 1,4-cycloaddition product (3.4) in 63% yield as illustrated in Scheme 3.3.

Recent work[15] on the preparation of a model compound for flavothebaone (3.5a) carried out in order to explain the abnormal ultraviolet

Scheme 3.2


OCH3
Cl
OCH3
PhNa
OCH3
Cl
Na
OCH3
-NaCl
(3.1)
(3.1)
+
N
R
OCH3
N
R
OCH3

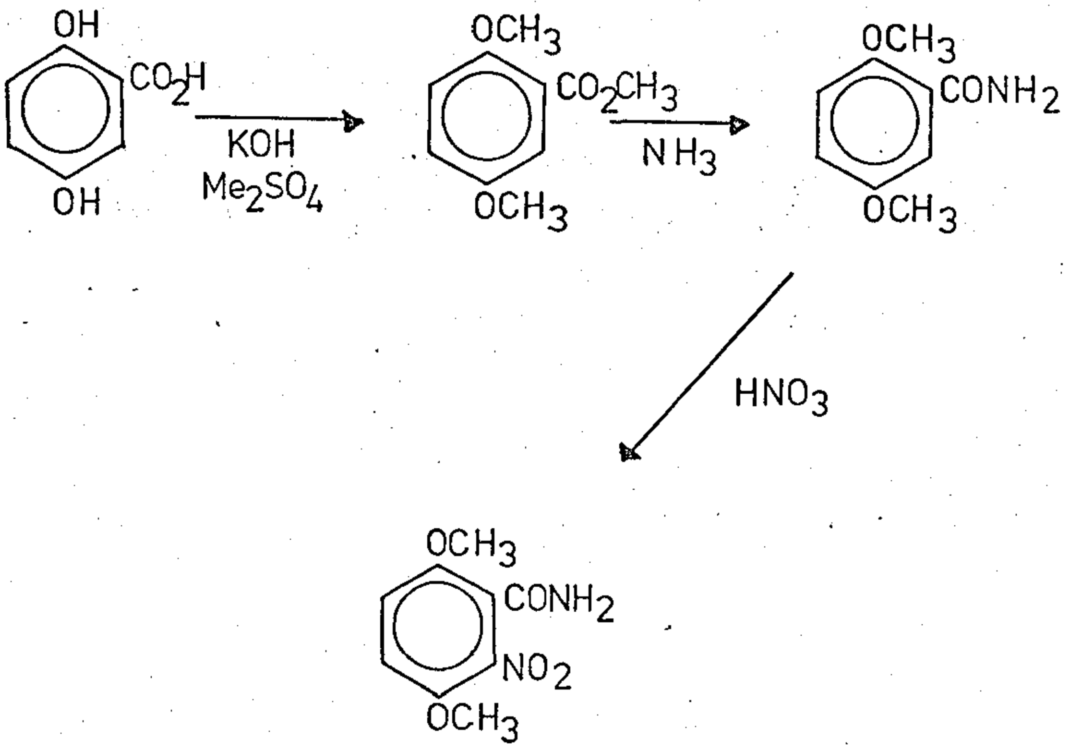
Scheme 3.3


OCH3
N
N
N
OCH3
NH2
(3.3)
Pb(OAc)4
(3.1)
O
OCH3
O
OCH3
(3.4)

spectrum exhibited by this compound and its trimethyl ether,[72] involved the preparation of 3,6-dimethoxybenzyne (3.1). Earlier attempts to prepare such a model had failed.[73]

The precursor for the aryne (3.1), in the above studies,[15] was the anthranilic acid (3.6). The idea of forming the anthranilic acid (3.6) followed from the known abilities of arynes carrying electron withdrawing groups to cyclo-add to arenes when generated from these precursors.[14,20] The route[15] involved the formation of the nitroamide (3.7) according to the established procedure of Rees and West[71] shown in Scheme 3.4.

Scheme 3.4


OH
CO2H
OH
KOH
Me2SO4
OCH3
CO2CH3
OCH3
NH3
OCH3
CONH2
OCH3
HNO3
OCH3
CONH2
NO2
OCH3

(3.7)

A detailed investigation[74] led to a suitable method for converting the nitroamide (3.7) to the required anthranilic acid (3.6). The method involved the diazotisation and hydrolysis of the hindered amide (3.7), using a solution of sulphuric acid and sodium nitrite.[75] The nitro acid (3.8), thus formed, was reduced [53] using hydrazine hydrate and PdC (10%) in refluxing ethyl alcohol.

As anticipated the resultant 2-amino-3,6-dimethoxybenzoic acid (3.6) was found to be an efficient precursor of the aryne (3.1). The aprotic diazotisation in the presence of furan produced the 1,4-cycloadduct (3.4) in ca. 80% yield.[15]

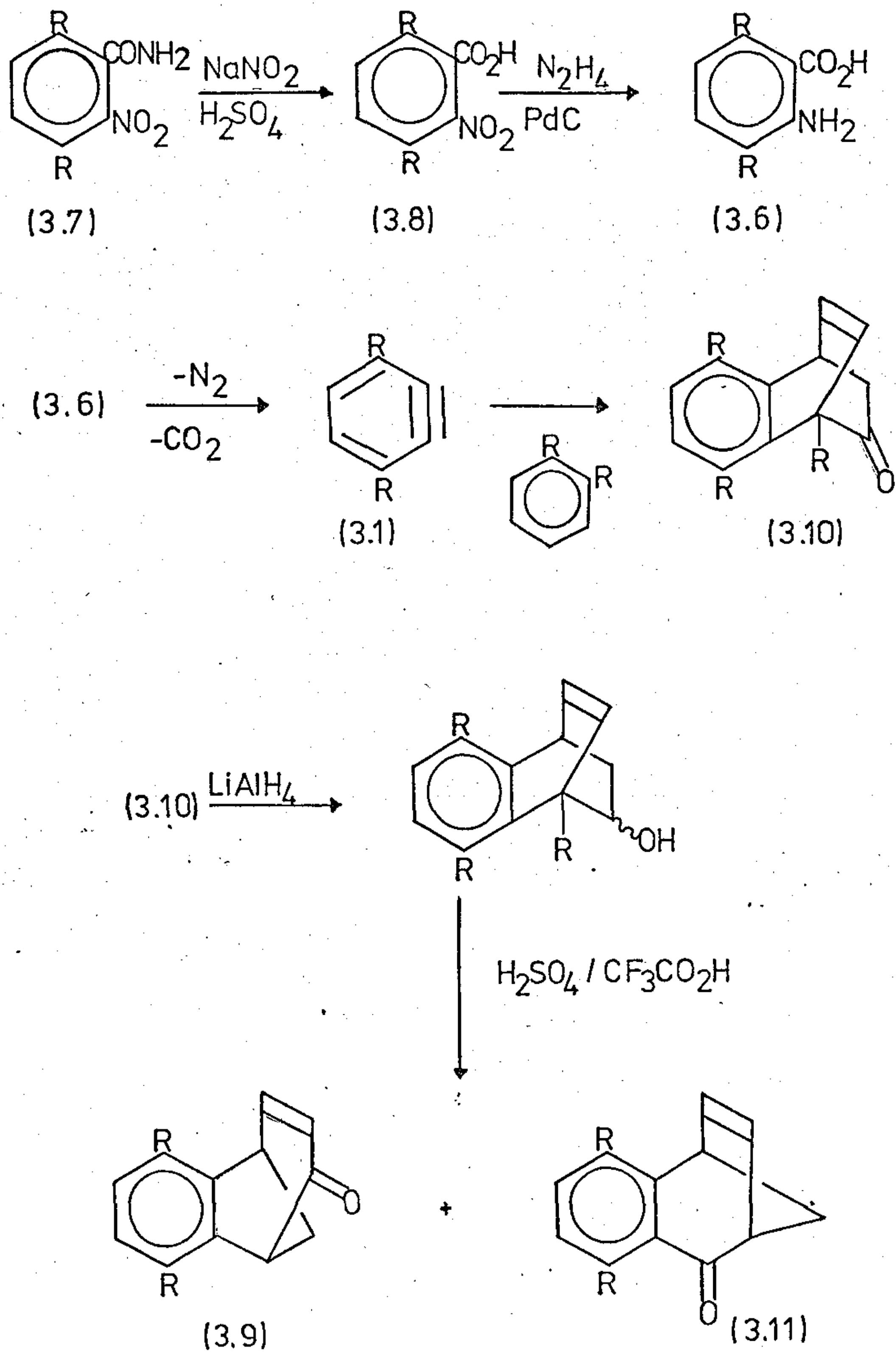
The required model compound (3.9) was generated as illustrated in Scheme 3.5.

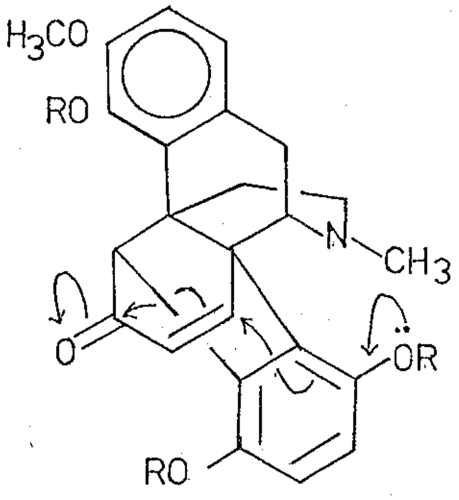
The isolation of the model compound (3.9) and the analysis of its U.V. spectrum, indicated that the abnormal spectrum of flavothebaone trimethyl ether (3.5b) is, as originally suggested,[72a] due to homoconjugation of the alkoxybenzene with the enone function.

The successful reaction between the aryne (3.1) and 1,2-dimethoxybenzene, shown in Scheme 3.5, to yield the ketone (3.10), left little doubt that the similar Diels-Alder cycloaddition, between the aryne (3.1) and anisole, to give the required product (3.2), could also be accomplished. It was reasoned that the rearrangement of the product (3.2), in strong acid, would yield the three isomeric ketones (3.9), (3.11) and (3.12), shown in Scheme 3.6, by comparison with the rearrangement of the similar 1-methoxybenzobarrelenes (2.1) - (2.3) discussed in Chapter 2.

Scheme 3.5

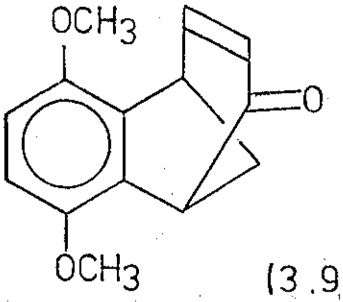
R = OCH_3


R
CONH2
NO2
NaNO2
H2SO4
CO2H
N2H4
PdC
NH2
(3.7)
(3.8)
(3.6)
-N2
-CO2
(3.1)
(3.10)
O
LiAlH4
OH
H2SO4 / CF3CO2H
+
(3.9)
(3.11)



(3.5a) R = H

(3.5b) R = CH$_3$

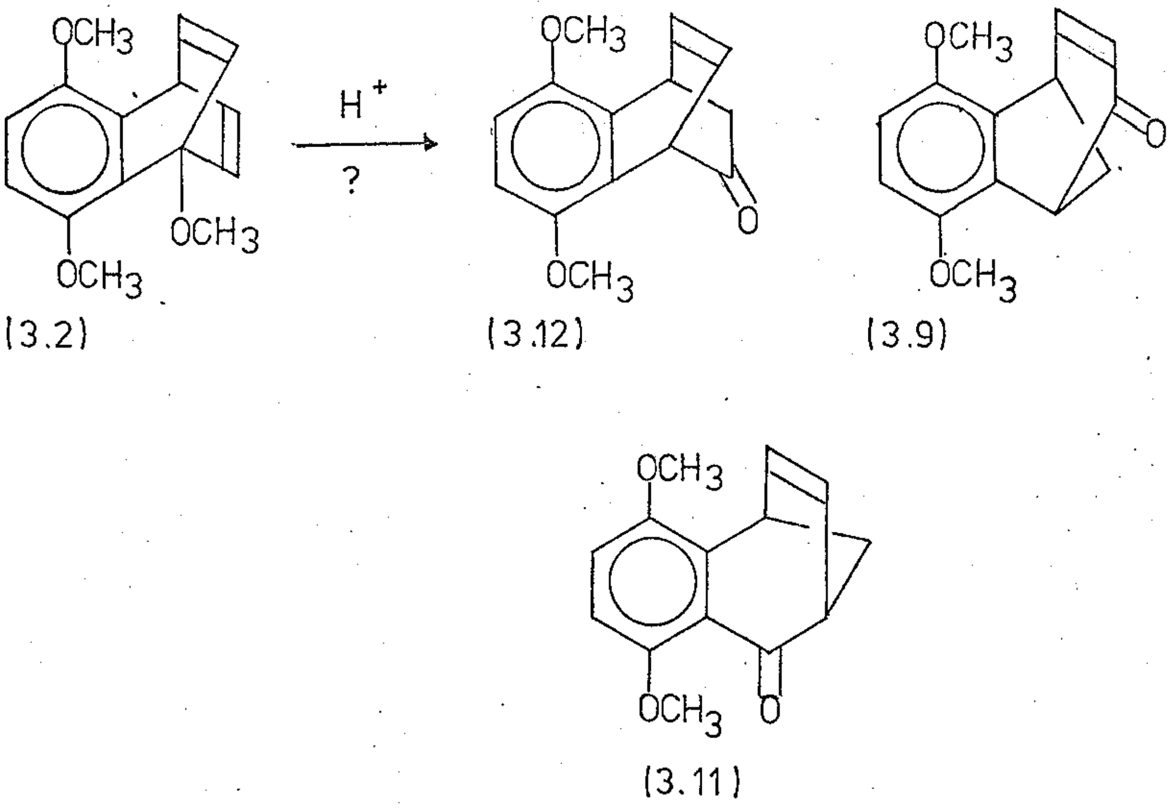


(3.9)

The second line of approach was to consider alternative acid media to sulphuric acid for the rearrangement of the 1-methoxybenzobarrelenes (2.1) - (2.3) discussed in Chapter 2 and to investigate the rearrangement of specifically substituted methyl derivatives of 1-methoxybenzobarrelenes.

The rearrangement of the 1-methoxybenzobarrelenes (2.1) - (2.3) in strong acid medium gave as the major product the respective benzobarrelenone

Scheme 3.6



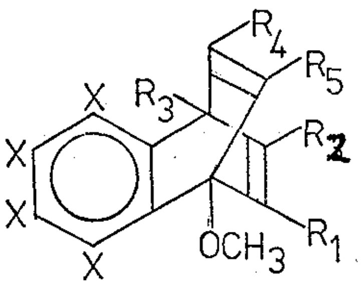
(3.2) (3.12) (3.9)

(3.11)

(2.4) - (2.6) in 50-76% yield. The two minor products were the corresponding αβ-unsaturated Ketone (2.7) - (2.9) and the aryl ketone (2.10) - (2.12) formed in 4.5-5.5% and 3.0-8.0% yields respectively. It was of interest to investigate if these rearrangements would occur in alternative acid media, such as trifluoroacetic acid and perchloric acid, and to analyse the product ratio from such reactions.

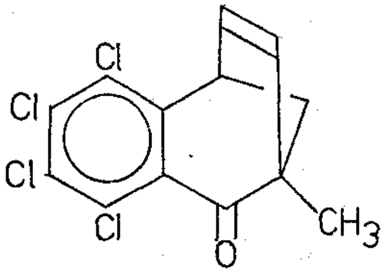
The results of the deuterium labelling studies,[20c,d] previously mentioned, suggested to earlier workers that the presence of alkyl groups, at suitable positions, would polarise the initial protonation and thus direct the rearrangement. This idea initiated a series of investigations[20c,d,e] into the rearrangement of a variety of methyl substituted 1-methoxybenzobarrelenes (3.12) - (3.18).

The presence of methyl substituents in the bicyclic portion of the 1-methoxybenzobarrelenes (3.12) - (3.18) allowed the study of the rearrangement reactions using weaker acids.

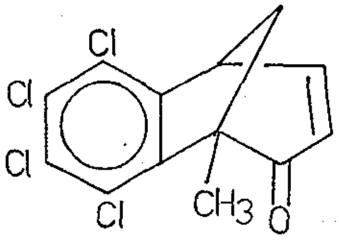


R_1	R_2	R_3	R_4	R_5	X	
H	H	CH_3	H	H	F	(3.12)
H	CH_3	H	CH_3	H	F	(3.13)
CH_3	H	H	H	CH_3	F	(3.14)
H	CH_3	H	H	H	Cl	(3.15)
CH_3	H	H	H	H	Cl	(3.16)
CH_3	H	H	CH_3	H	Cl	(3.17)
CH_3	CH_3	H	H	H	Cl	(3.18)

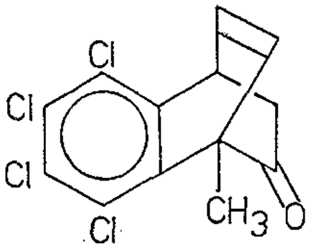
For instance, the compound (3.16) rearranged readily in trifluoroacetic acid to give a mixture of the three isomeric ketones (3.19) - - (3.21) in 56, 40 and 4% yields respectively. In concentrated sulphuric acid the ketones (3.19) - (3.21) were obtained in 3.5, 27 and 28% yields respectively. These results provided further evidence that in strongly acidic media, protonation of the methoxy group in 1-methoxybenzobarrelenes directs the subsequent addition of a proton to a double bond. The product (3.15) gives the benzobarrelenone (3.22) in either trifluoroacetic acid or concentrated sulphuric acid, in 100 and 90% yields respectively.


Cl
Cl
Cl
Cl
O
CH3

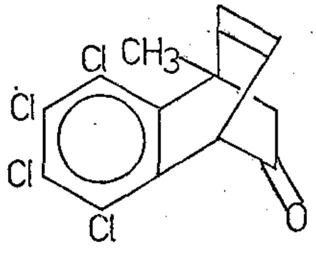
(3.19)


Cl
Cl
Cl
Cl
CH3
O

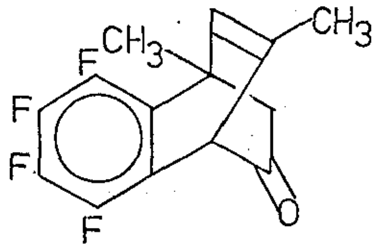
(3.20)


Cl
Cl
Cl
Cl
CH3
O

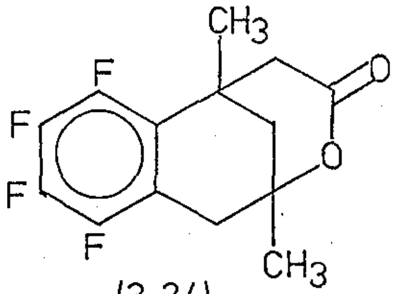
(3.21)


Cl
CH3
Cl
Cl
Cl
O

(3.22)


F
CH3
CH3
F
F
F
O

(3.23)


CH3
F
O
F
O
F
F
CH3

(3.24)

It has also been shown[20b] that the rearrangement can proceed beyond the isomeric ketones. For example, the rearrangement of the compound (3.13) in trifluoroacetic acid gave the ketone (3.23). However, the rearrangement in concentrated sulphuric acid yielded the lactone (3.24).

One further point of interest was that in all our rearrangement studies, so far, the three isomeric ketone products are formed in a non-equilibrating system. On the other hand other workers have shown[26] that the hexamethylbenzobarrelenone (3.25) rearranges in acidic media to afford an equilibrium mixture of four ketones.

Thus our reason for studying further the affect of methyl substitution on the rearrangement of 1-methoxybenzobarrelenes was three fold:-

(i) to study further the competitive nature of protonation at C-2 as opposed to C-3

(ii) the possibility of attaining an equilibrium mixture of isomeric ketones.

(iii) reactions beyond the isomeric ketones to novel systems.

With the above points in mind, 1-methoxy-2,5-dimethylbenzobarrelene (3.26), 1-methoxy-2,3,5-trimethyltetrachlorobenzobarrelene (3:27) and 1-methoxy-2,3,5-trimethylbenzobarrelene (3.28) were investigated.

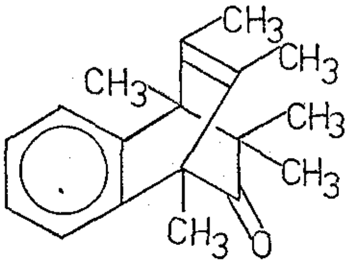
DISCUSSION

Preparation of 3,6-dimethoxyanthranilic acid (3.6)

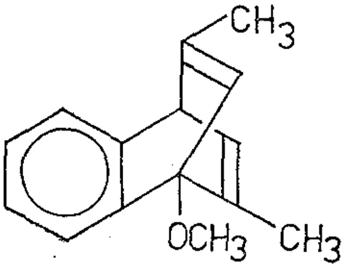
The aryne precursor, 3,6-dimethoxyanthranilic acid (3.6) was prepared as illustrated in Schemes 3.4 and 3.5. A number of modifications were made to the original procedure,[15] based on difficulties experienced by previous workers in this laboratory.

The nitration of 2,5-dimethoxybenzamide, Scheme 3.4, gives a mixture of two nitro amides (3.7) and (3.29). Fortunately the required amide (3.7) is the major product.

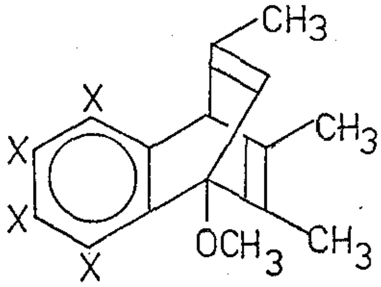
The method adopted by Rees and West[71] for separating the two nitro amides, involved removal of the unwanted compound (3.29) with hot benzene


CH3
CH3
CH3
CH3
CH3
CH3
O

(3.25)


CH3
OCH3
CH3

(3.26)

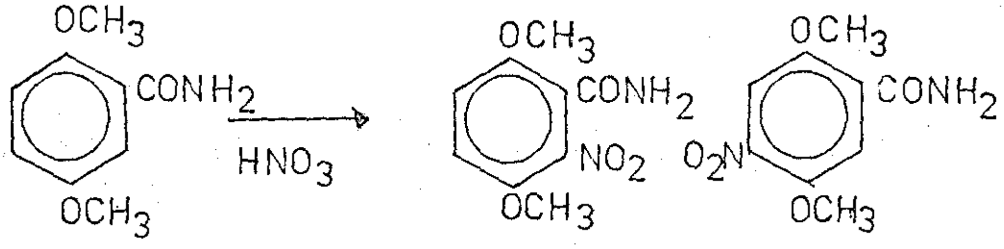

CH3
X
X
X
X
CH3
OCH3
CH3

X = Cl (3.27)

X = H (3.28)

and recrystallising the remaining residue with acetone to yield the required product (3.7).

This procedure was improved by extracting the crude product with refluxing benzene in a soxhlet thimble and recrystallising the residue from acetone. The efficiency of separation was checked by t.l.c., the required nitro amide (3.7) having the lower Rf. value.

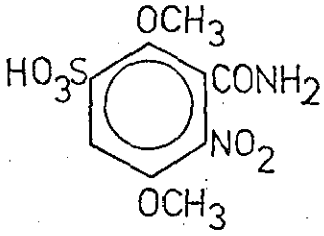


(3.7) (3.29)

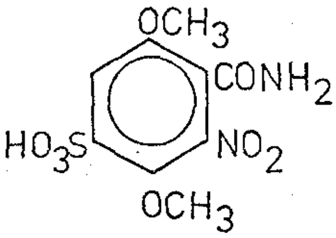
The conversion of the nitroamide (3.7) to the nitro acid (3.8), Scheme 3.5, was accomplished[15] by a procedure established by Sudborough[75] using sulphuric acid and sodium nitrite. However, since the publication of our earlier work[15] a number of workers in this laboratory have encountered difficulties in obtaining consistent results for this reaction. A variety of results were obtained,[76] varying from complete conversion to no conversion, and on occasions no recovered nitroamide (3.7) or nitroacid (3.8) was obtained.

The nitroamide (3.7) is an extremely hindered amide which would account for the difficulties experienced in the earlier hydrolysis studies[74] of this amide. However, steric hindrance was not an acceptable explanation for the variations in yield previously mentioned. The procedure in question involved the diazotisation of the nitroamide (3.7) using sulphuric acid (90%) and sodium nitrite dissolved in a minimum volume of water. One way of explaining the variable results would be to propose the formation of a sulphonic acid, by the reaction of the nitroamide with sulphuric acid to yield a product similar to (3.30) or (3.31).

Generally sulphonation of aromatic compounds with sulphuric acid is slow and requires heat.[77] Electron-withdrawing groups (nitro, carbonyl) are meta directing and make sulphonation difficult, while electron-donating groups (alkyl, alkoxy, hydroxy, amine) render sulphonation easy and are ortho- and para- directing.



(3.30)



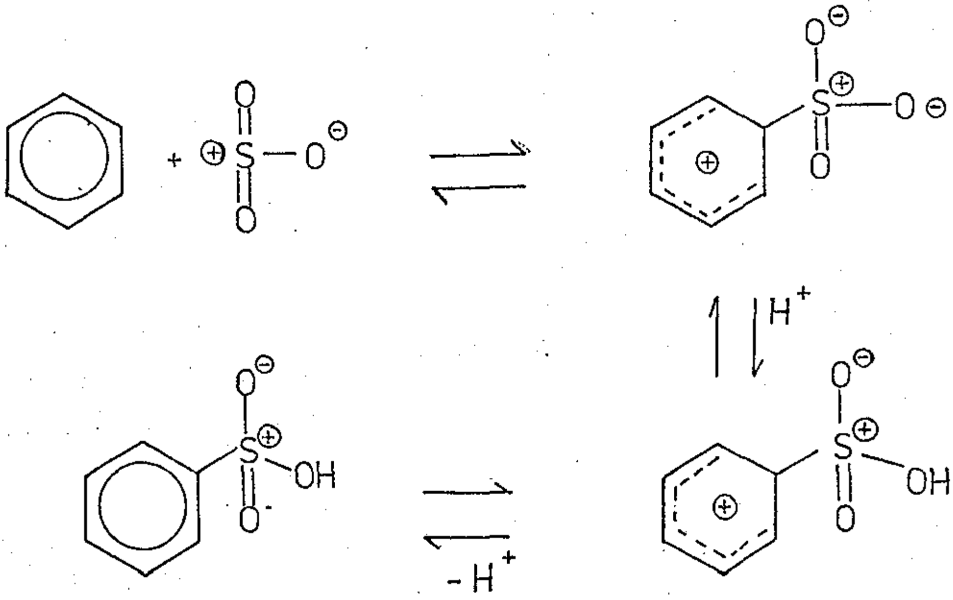
(3.31)

The mechanism for sulphonation of aromatic compounds with sulphuric acid is most probably as shown in Scheme 3.7.

The major resistance to sulphonation using sulphuric acid is the strong affinity of sulphur trioxide for water which must be overcome. Benzene and other aromatic compounds can be sulphonated with concentrated sulphuric acid but as the concentration of water increases, during the reaction, the rate of sulphonation decreases. The reaction ceases

Scheme 3.7

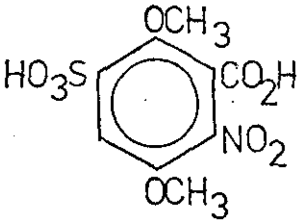
$$2H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^\ominus$$



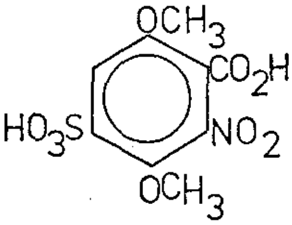
when the acid concentration reaches a level characteristic of each compound. For example, with benzene the concentration is ca. 78% sulphuric acid. This corresponds to an acid concentration at which the rate of sulphonation and desulphonation are approximately equal.

Consideration of the above information would indicate that in the case of the nitroamide (3.7) sulphonation would be directed to a meta position by either the nitro or the amide group and to an ortho position by the methoxy groups. The meta directing groups would reduce the sulphonation rate compared to benzene and the ortho directing groups increase the rate.

If sulphonic acids, such as (3.30) and (3.31), are formed under the conditions of the reaction, then it must be assumed that the ortho directing groups are dominant, and allow the reaction to proceed even at low temperature (ca.0-10°). The presence of such sulphonates would explain the variable yields, since they are normally soluble in aqueous medium and under the conditions of work-up, for the reaction, such sulphonates would be undetected. Also, since sulphonation is a reversible process then the sulphonic acids of the nitroamide (3.30) and (3.31) or of the nitroacid (3.32) and (3.33) could yield the nitroamide (3.7) or the nitroacid (3.8) respectively.



(3.32)



(3.33)

Although the presence of the sulphonic acids (3.30) - (3.33) was not investigated consideration was given to reducing the possibility of their formation. Sorel and Newman[78] had successfully used dilute sulphuric acid (75%) and sodium nitrite for the conversion of hindered amides to acids. This result coupled with the fact that the use of dilute acid reduced the possibility of sulphonation directed our investigation to a similar procedure.

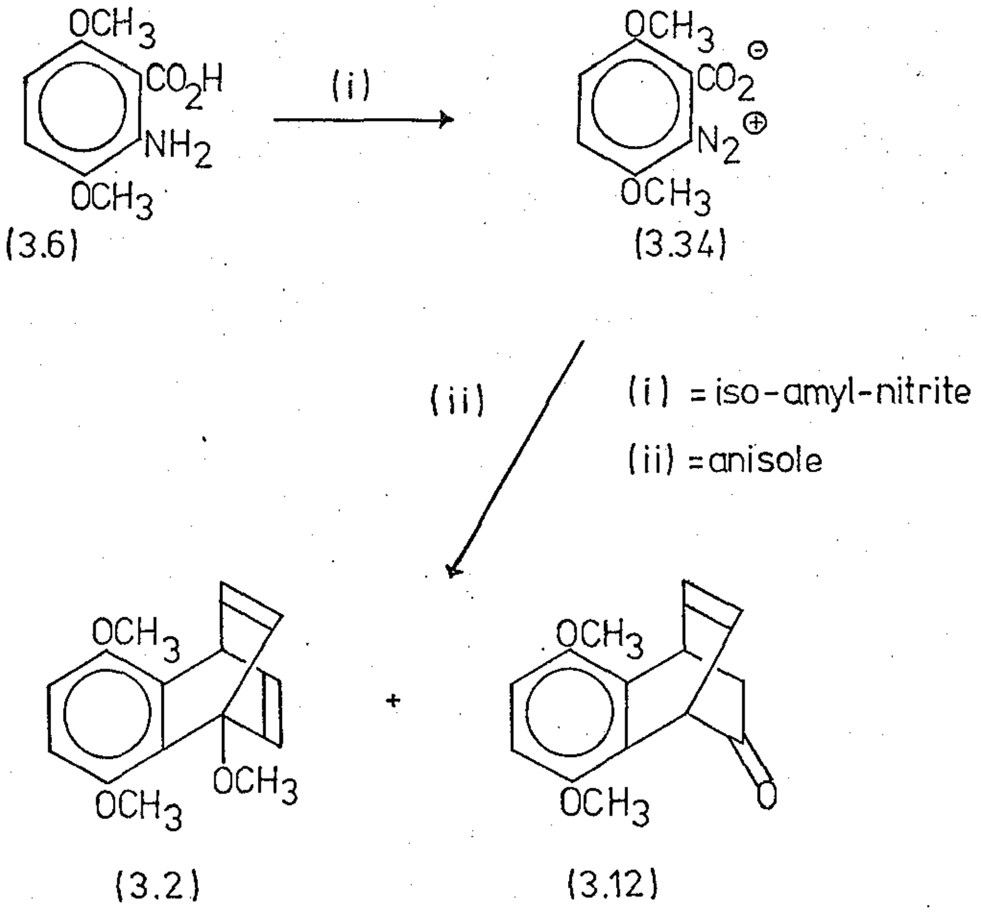
A series of trial experiments involving the nitroamide (3.7) established that a ratio of sulphuric acid to water (2:1, $^{v}/_{v}$) gave the highest yield of the required nitroacid (3.8). Using this method it was possible to consistently obtain a high yield (ca. 90%) of the nitroacid (3.8), mp. 188-189° (lit.[15] 192-194°).

The final step in the preparation of the anthranilic acid (3.6) was to reduce the nitroamide (3.8) using PdC (10%) and hydrazine hydrate in refluxing ethyl alcohol.[15] A variation of this procedure was investigated, due to the interference of unreacted hydrazine in the isolation of the required product. The alternative procedure involved the use of iron powder in concentrated hydrochloric acid with ethyl alcohol as the solvent. The solution was heated under reflux for ca. 2hr. but at the end of this period, normal work-up yielded only the starting nitroacid (3.8).

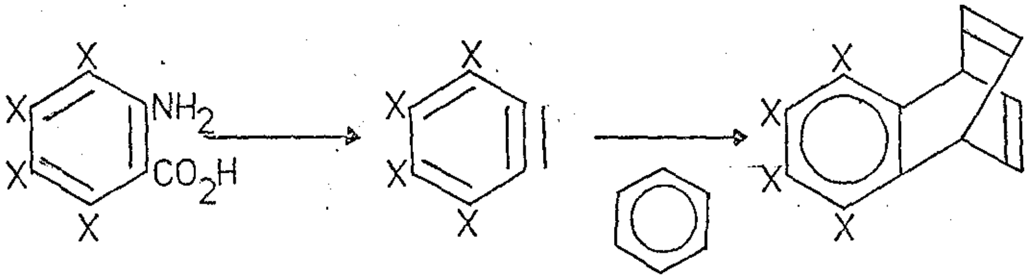
It was found that if, on completion of the reduction of the nitroacid (3.8), using hydrazine, the required aminoacid (3.6) would not crystallise from the reduced volume of solvent, then the following procedure could be adopted. The remaining solvent is removed by rotary evaporation and the crude product quenched in water. The aqueous solution is extracted with chloroform to give 2-amino-3,6-dimethoxyanthranilic acid (3.6).

Preparation and Rearrangement of 1,5,8-trimethoxybenzobarrelene (3.2)

The aprotic diazotisation of the anthranilic acid (3.6), with iso-amyl nitrite, afforded the 3,6-dimethoxy-benzene-diazonium-2-carboxylate (3.34) as a dark red crystalline solid. Decomposition of the diazonium carboxylate (3.34), in an excess of anisole, gave after hydrolysis and normal work-up, the two expected 1,4-cycloadducts 1,4-dihydro-1,5,8-trimethoxy-1,4-ethenonaphthalene (3.2) and 5,8-dimethoxy-1,4-etheno-2-tetralone (3.12). The spectral data for the two compounds compared favourably with authentic material.[79] The two compounds (3.2) and (3.12) were obtained in ~~17~~20% and ~~5~~8% yields respectively. The preference for the methoxy group to be retained at the bridgehead position in the formation of Diels-Alder adducts from arynes and methoxyarenes was noted earlier (Chapter 2).


OCH_3
CO_2H
NH_2
OCH_3
(3.6)
(i)
OCH_3
$CO_2^{\ominus}$
$N_2^{\oplus}$
OCH_3
(3.34)
(ii)
(i) = iso-amyl-nitrite
(ii) = anisole
OCH_3
OCH_3
OCH_3
(3.2)
+
OCH_3
OCH_3
O
(3.12)

The low yield of the required trimethoxybenzobarrelene (3.2) (*ca.* 17%) was disappointing, particularly when earlier work involving the formation of tetrahalobenzynes from tetrahaloanthranilic acids was considered.[14]



X = F[14a] 35%

X = Cl[14b] 55%

X = Br[14c] 67%

X = I[14d] 25%

Presumably the lower yield of the compound (3.2) can be explained in terms of electrophilicity. The fact that the four electron withdrawing substituents in the tetrahalobenzynes result in a significant increase in their electrophilicity compared with that of benzyne, is well established.[12,20] Also the reaction between benzyne and benzene gives benzobarrelene in only ca. 6% yield. Since the electron withdrawing capability of the two methoxy groups in the aryne (3.1) is expected to be between that of the four halogens and the four protons, in tetrahalobenzyne and benzyne respectively, then the yield of the corresponding 1,4-cycloadducts would also be similarly placed.

The low yield of the product (3.2) was not due to a low conversion of the anthranilic acid (3.6) to 3,6-dimethoxybenzyne (3.1), since a high yield of the diazonium salt (3.34) could be isolated and its subsequent decomposition noted by the evolution of a gas.

The crude product at the end of the reaction, after normal work-up,was a dark red solid. This solid was separated on an alumina column using ether-light petroleum as the eluant. For the trimethoxybenzobarrelene (3.2) the ratio was (1:2, $^{v}/_{v}$) and for the ketone (3.12) (5:1, $^{v}/_{v}$). No further products were isolated from the column until a very polar eluant ($CHCl_3$) was used. A crude orange-brown tacky solid was quickly eluted when chloroform was used. The solid appeared to be a complex mixture of products and could not be recrystallised, separated by t.l.c., or positively analysed by spectroscopic methods. It was assumed that this unidentifiable product resulted from various reactions between the aryne (3.1) and its precursor (3.34). Further investigations into the separation and identification of the mixture were not attempted.

In order to determine the most suitable conditions for rearranging the compound (3.2) a number of trial experiments, on a small scale (ca. 10mg.), were carried out involving different acid media and rearrangement conditions. The results are shown in Table I. Each reaction was quenched on ice, extracted with ether and the organic phase analysed by t.l.c.. Each spot on the t.l.c. plate was assumed to represent a product of the rearrangement.

Examination of the results indicated that either perchloric acid (60%) at room temperature or refluxing trifluoroacetic acid gave satisfactory results.

TABLE I

ACID	TEMP. °C	TIME OF REACTION	T.L.C. ANALYSIS
i) $HClO_4$	R.T.	30min.	2P+S.M.
ii) $HClO_4$	R.T.	90min.	3P+S.M.
iii) $HClO_4$	R.T.	4Hr.	3P
iv) CF_3CO_2H	REFLUX	2Hr.	3P
v) CF_3CO_2H 3 drops H_2SO_4	R.T.	30min.	S.M.
vi) CF_3CO_2H $CHCl_3$ 7 drops H_2SO_4	R.T.	30min.	S.M.
vii) $HClO_4$ DIOXAN	REFLUX	2Hr.	2P.

P = Product
S.M.= Starting Material
R.T.= Room Temperature

For the larger scale rearrangements (ca. 1g.) of the compound (3.1), refluxing trifluoroacetic acid was selected as the acid medium, since this gave a cleaner reaction product and also gave the possibility of carrying out deuterium incorporation studies by using deuteriated trifluoroacetic acid.

A number of rearrangements of the trimethoxybenzobarrelene (3.2) (ca. 1g.) were carried out in refluxing trifluoroacetic acid (10ml.) for ca. 6hr.. Normal work-up and extraction gave a crude oil, which on analysis by t.l.c., indicated five to six products.

It was anticipated that three of these products would be the three isomeric ketones (3.9), (3.11) and (3.12) previously mentioned Scheme 3.6.

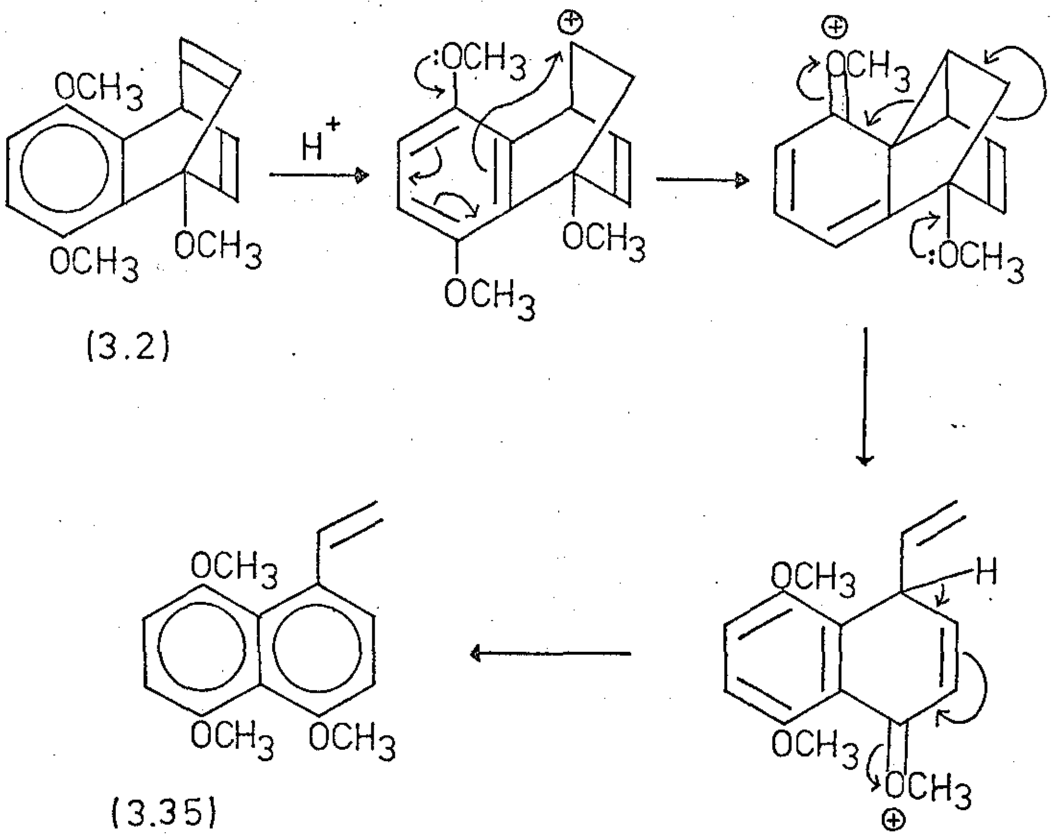
The crude oil from the rearrangement was separated by preparative layer chromatography. The two major products were isolated from the two bands with the highest Rf. values, both of which were formed in ca. 28-37% yields.

Analysis of these two products by i.r. and ^{1}H.n.m.r. spectroscopy and mass spectral data, indicated that the product with the lower of the two Rf. values was the expected dimethoxybenzobarrelenone (3.12) (36%), $\nu_{max.}$ 1740 cm.$^{-1}$, ^{1}H.n.m.r. (CDCl$_3$) τ. 3.2 (m, 4H); 5.13(d.d, 1H), 5.35 (m, 1H), 6.18 (s, 3H), 6.22 (s, 3H) and 7.96 (ABq, 2H), M$^+$ 230, m.p. 104 - 106° (lit.[79] 104 - 106°).

The product with the highest Rf. value showed no carbonyl stretching frequency and could not therefore be one of the two isomeric ketones (3.9) or (3.11). Mass spectral data gave a molecular ion of M$^+$ 244, but although the ^{1}H.n.m.r. spectral data showed three separate methoxy groups, 6.18 (s, 3H), 6.23 (s, 3H) and 6.28 (s, 3H), the remaining spectrum did not correlate with the starting compound (3.2). The remaining spectrum indicated a further seven protons with the following τ. values; 2.50 (m, 2H), and 2.95-3.2 (m, 5H). The product was isolated as a crystalline solid, mp., 62-64° (light petroleum).

One consideration for the structure of the unknown compound was that of the vinyl naphthalene (3.35) formed by the proposed mechanism illustrated in Scheme 3.8.

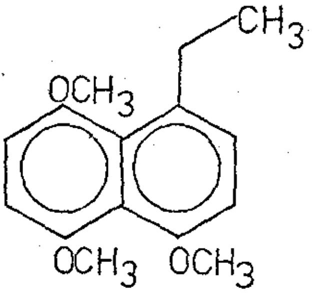
Scheme 3.8


OCH3
OCH3
OCH3
H+
:OCH3
OCH3
OCH3
OCH3
:OCH3
OCH3
H
OCH3
OCH3
OCH3
OCH3
OCH3

(3.2)

(3.35)

However the vinyl naphthalene (3.35) had to be discounted because of two pieces of evidence. Firstly the ^{1}H.n.m.r. data was not satisfied by such a structure and secondly attempted reduction of the new compound using PdC (10%), ethyl alcohol and hydrogen after ca. 12hr. gave only the recovered unknown. The vinyl naphthalene (3.35) would have been reduced to the naphthalene (3.36) under these conditions.

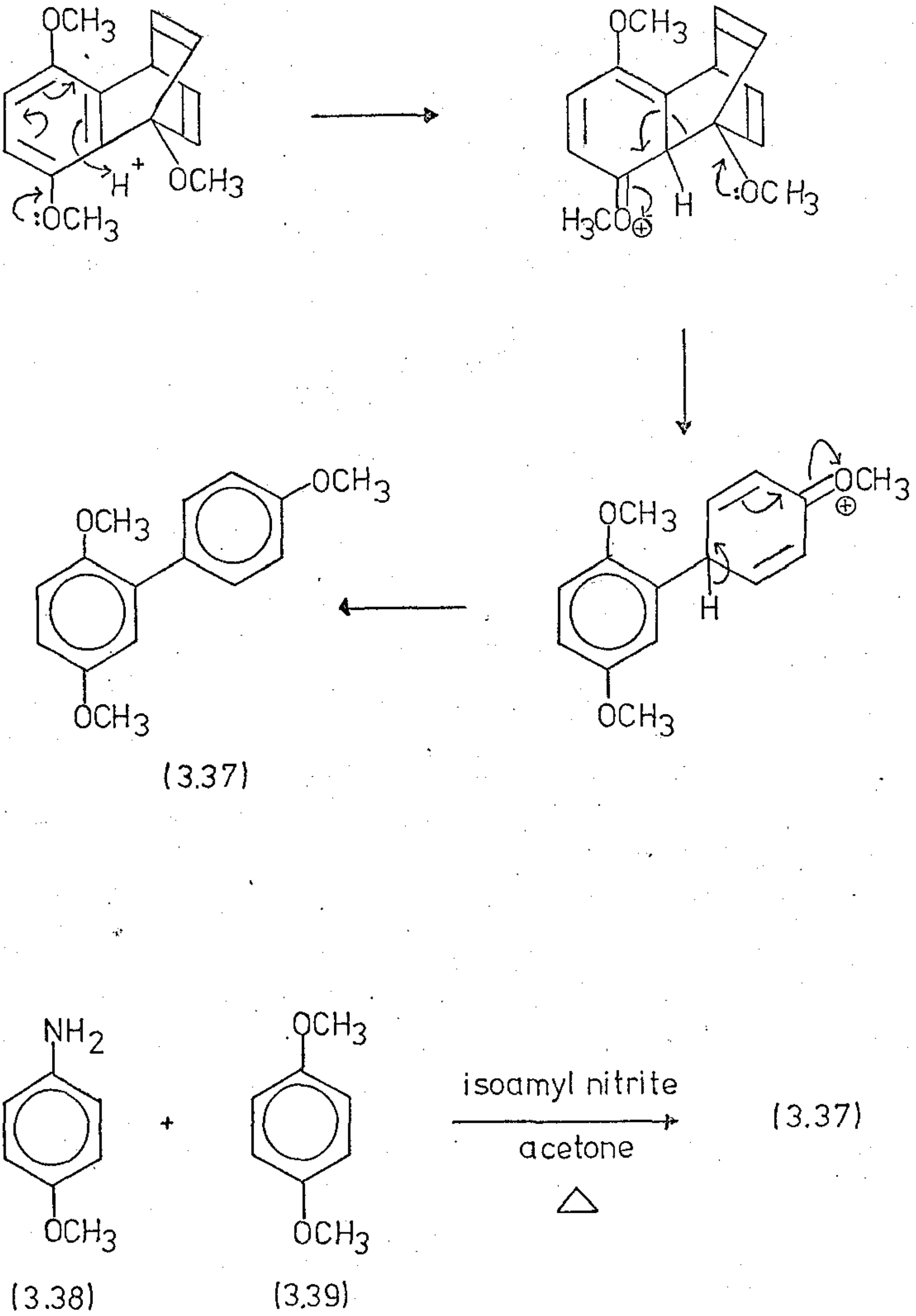


(3.36)

A closer inspection of the spectral data and consideration of potential rearrangement pathways suggested that the structure of the new compound could be that of the substituted biphenyl (3.37), formed by the mechanism illustrated in Scheme 3.9. This type of mechanism is quite unusual involving protonation on the aryl ring. Presumably the high electron density in the aryl residue allows ready protonation. The arenonium ion formed could undergo a retro Friedel-Crafts alkylation to give a new ion, which, by loss of a proton, would result in the formation 2,4′,5-trimethoxybiphenyl (3.37).

The structure of the biphenyl (3.37) was confirmed by a Gomberg-Bachman-Hey Synthesis (5.5%) using 4-amino-anisole (3.38) and 1,4-dimethoxybenzene (3.39). The very low yield in this reaction was undoubtedly due to our inability to use 1,4-dimethoxybenzene as a solvent.

Scheme 3.9

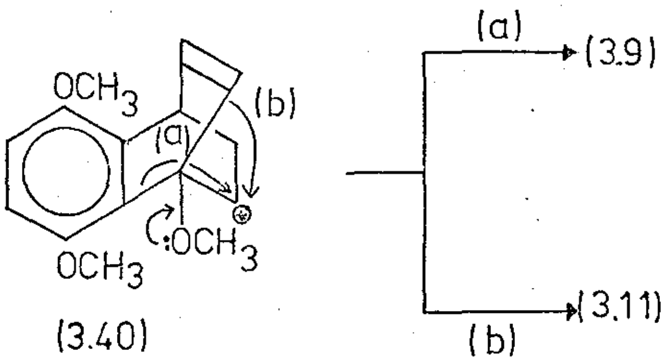

OCH3
H+
OCH3
:OCH3
OCH3
H3CO⊕
H
:OCH3
OCH3
OCH3
OCH3
OCH3
H
OCH3
⊕
OCH3
(3.37)
NH2
OCH3
(3.38)
+
OCH3
OCH3
(3.39)
isoamyl nitrite
acetone
Δ
(3.37)

The biphenyl (3.37) was isolated as a white crystalline solid, mp. 62-63° (lit.[80] 62-64°). A mixed melting point with the unknown compound, from the rearrangement of trimethoxybenzobarrelene (3.2), gave a value of 62-63°. The spectral data of the unknown and the biphenyl (3.37) were identical, thus confirming the unknown structure to be that of 2,4',5-trimethoxybiphenyl (3.37) formed in ca. 31.2% yield.

The two major products, (3.12) and (3.37), from the rearrangement of the compound (3.2) were thus identified and accounted for ca. 67% of the rearranged product. Minor products (approx. 3-4) were also present but these proved more difficult to isolate and identify.

The product, with the third highest Rf. value, was difficult to isolate free of the ketone (3.12). It was necessary to re-chromatograph this mixture and carry out repetitive elution until the mixture separated into two clear bands. The lower band yielded a red-brown crystalline solid, mp. 137-141° (ethanol). The i.r. spectrum indicated a carbonyl stretching frequency at 1675 cm^{-1}. Mass spectral data gave a molecular ion at M^{+} 230 indicating that the product was isomeric with the ketone (3.12). The ^{1}H.n.m.r. spectrum showed the following peaks, (CDCl$_3$) τ 2.58 (q, 1H), 3.4 (m, 2H), 4.55 (q, 1H), 5.92 (m, 1H), 6.15 (s, 1H), 6.2 (s, 6H), and 7.3 (m, 2H). The spectral evidence strongly favoured the structure of the $\alpha\beta$-unsaturated ketone (3.9) and this was confirmed by comparison of the data with that of authentic material.[79]

The ketone (3.9) is formed by the protonation of the compound (3.2) at C-3 to give the ion (3.40). Consideration of the rearrangement of similar systems,[20] discussed in Chapter 2, indicates that there are two pathways by which the ion (3.40) can rearrange. The first involves aryl migration and yields the ketone (3.9). The second involves vinyl migration to yield the isomeric aryl ketone (3.11).



(3.40)

Since the ketone (3.9) had been formed it was therefore logical to assume that the aryl ketone (3.11) should also be present. However, after a careful analysis of the remaining bands the presence of the ketone (3.11) was not detected. This result may be due to either a practical failure or a further reaction involving the aryl ketone. No products were isolated which confirmed the latter suggestion.

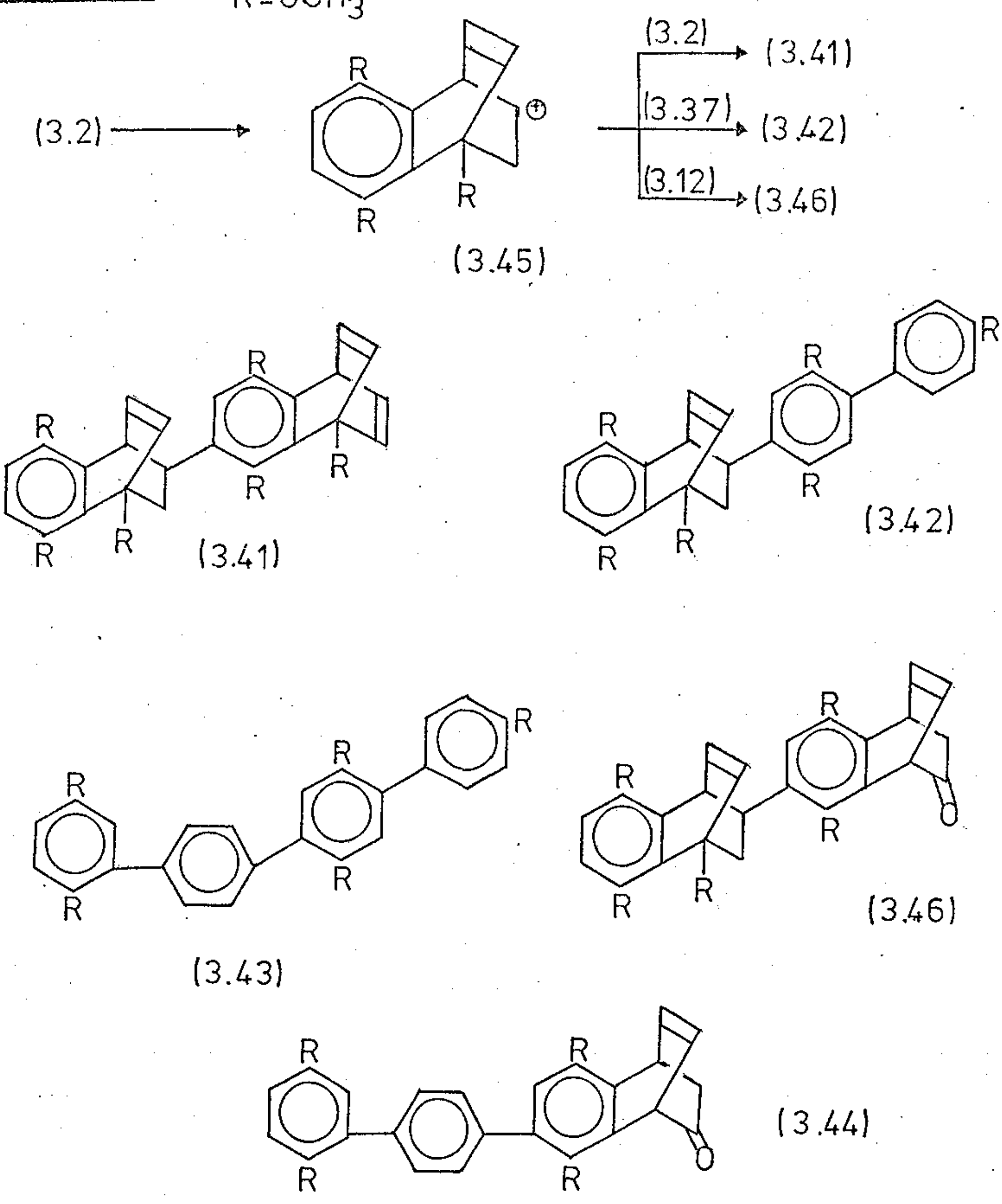
Two bands were isolated, from the rearrangement mixture, which occurred just above the base line on the preparative plates. The band with the lower Rf. value showed a very intense fluoresence under U.V. light.

Extraction of the product from this band gave an extremely low weight ($<$ 5mg.) of a crude yellow oil. Very little evidence was obtained from attempted analysis of the spectral features of this product. The i.r. and ^{1}H.n.m.r. spectra showed only broad uncharacterised peaks. The band with the higher Rf. value on extraction gave a crude yellow crystalline solid, mp. 150-165°. The i.r. spectrum showed a broad carbonyl stretching frequency centered at 1740 cm^{-1}, but no other characteristic peaks. Mass spectral data gave a molecular ion at M$^+$ 488, which indicated a product with double the molecular weight of the starting material (3.2, M.W. 244). The ^{1}H.n.m.r. spectrum was complex with peaks at, ($CDCl_3$) τ. 2.48 (s), 2.58 (s), 2.75 (s), 3.03 (s), 3.13 (s), 3.3 (m), 3.88 (s), 5.0 (m), 6.0-6.7 (complex series of singlets) and 7.7-7.95 (m).

The available data signified a mixture of products and possibly a mixture of dimeric products based on the starting trimethoxybenzobarrelene (3.2). The formation of a dimeric material was a novel experience in our studies of the rearrangement of 1-methoxybenzobarrelenes.[20] A number of potential structures (3.41) - (3.44) were suggested which seemed to fit some, but not all of the available data.

The mass spectral data (M$^+$ 488) indicated a product similar to (3.41) or (3.42). Both of these structures could be formed from the carbonium ion (3.45) as shown in Scheme 3.10.. Similar structures could also have been formed from the carbonium ion (3.40) which would have effected the formation of the $\alpha\beta$-unsaturated ketone (3.9) and the aryl ketone (3.11). None of these structures would explain the broad carbonyl stretching frequency (1740 cm^{-1}).

Scheme 3.10


R=OCH3
(3.2)
(3.45)
(3.2)
(3.41)
(3.37)
(3.42)
(3.12)
(3.46)
R
(3.41)
(3.42)
(3.43)
(3.46)
(3.44)
O

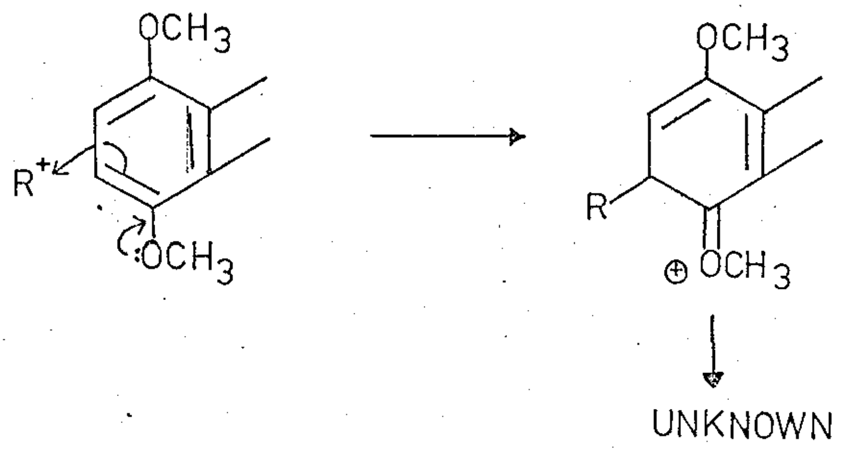
The absorption at 1740 cm^{-1} is typical of the value expected for a carbonyl group in compounds similar to dimethoxybenzobarrelenone (3.12). Structures such as (3.44) and (3.46) would account for the observed $\nu_{max.}$ value, but would not account for the molecular ion M^{+} 488.

Further evidence regarding the structure of the dimeric product was obtained from a comparison of the U.V. spectra of the compounds (3.2), (3.37) and the unknown product. The appearance of the spectra in the region of 225-340~~n.m.~~nm for the biphenyl (3.37), and the unknown, were almost identical. The molar extinction coefficients (ε) at the wavelengths (λmax.), shown in the following table, were calculated for the compounds (3.2), (3.37) and (unknown).

STRUCTURE	λ max. nm (~~n.m.~~)	ε
(3.2)	297	2561
(3.37)	256	13462
	303	7151
(Unknown)	258	16267
	303	14911

The above results indicate that structures similar to (3.41) could be ignored. The fact that the λ max. values for the biphenyl (3.37) and the unknown were almost identical plus the fact that the ε value at 303 n.m. for the unknown was approximately double the corresponding value for the biphenyl (3.37), seemed to indicate that the unknown was formed from two units of the biphenyl (3.37). Such a combination would give a structure similar to (3.43), which again would not account for the M^+ 488.

An attempt was made to trap one of the units leading to the unknown. The compound (3.2) was rearranged under the standard conditions but in the presence of a large excess of p-dimethoxybenzene (3.39). It was considered that the unknown was formed from the reaction of a carbonium ion with a unit containing the dimethoxyaryl ring, as illustrated below.



Thus it was reasoned that the incorporation of a large excess of p-dimethoxybenzene, in the rearrangement, would lead to preferential attack of the compound (3.39) on the carbonium ion yielding a new product, hopefully in high yield.

The compound (3.2), plus a 10M. excess of p-dimethoxybenzene was heated under reflux in trifluoroacetic acid for ca. 6.5hr.. After normal work-up the excess of p-dimethoxybenzene was removed by column chromatography. The fractions were checked by t.l.c. and those containing material with a lower Rf. value than p-dimethoxybenzene were combined and separated by preparative t.l.c.. Analysis of the products indicated that the only compounds present were those normally expected from the rearrangement of trimethoxybenzobarrelene (3.2).

The possibilities that the unknown was formed from the reaction of two units of the biphenyl (3.37), or rearrangement of the ketone (3.12) or a reaction between the biphenyl (3.37) and the ketone (3.12), were not ignored. A number of equilibrium reactions were carried out to determine the stability of the two compounds (3.37) and (3.12), under the rearrangement conditions and other acidic media.

The biphenyl (3.37) was stable to perchloric acid (60%) at room temperature for 12 hr. and refluxing trifluoroacetic acid for 3 hr..

The ketone (3.12) was equally stable to refluxing trifluoroacetic acid for 12 hr. and sulphuric acid (98%) at room temperature for 10 min..

A mixture of the biphenyl (3.37) and the ketone (3.12) was treated with refluxing trifluoroacetic acid for 6 hr.. The two products were recovered unchanged at the end of this period.

The above studies confirmed that the unknown was neither formed from the biphenyl (3.37) nor the ketone (3.12) alone. The fact that the ketone (3.12) was not in equilibrium with the $\alpha\beta$-unsaturated ketone (3.9), or the aryl ketone (3.11), correlated with earlier work[20] on similar systems.

We decided to obtain a more accurate mass spectrum of the unknown and so a sample was sent for analysis to P.C.M.U.. The results of their investigations indicated that the unknown was a mixture of two compounds M^+ 488 and M^+ 474. The molecular ion at 474 was obviously not derived from that at M^+ 488. This result was not surprising and helped to explain some of the conflicting data already mentioned.

Further work is necessary before the two unknown compounds can be isolated and their structures identified. However, the information, so far, would seem to favour a structure formed from two units similar to the biphenyl (3.37) for the M^+ 488, and a structure formed from a unit of M.W. 244 and a unit of M.W. 230 for the M^+ 474. Structures similar to (3.42) and (3.46) respectively seem most likely for the two unknowns.

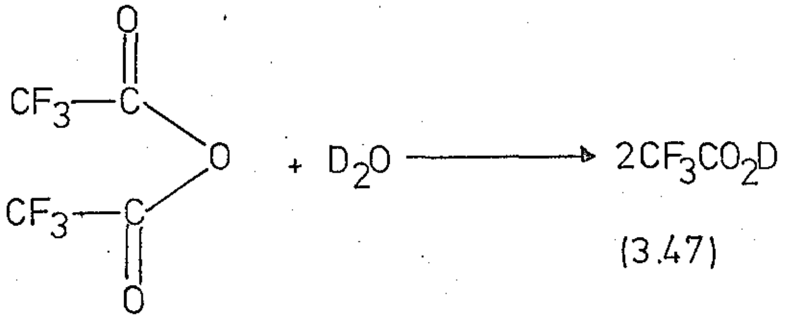
The major disadvantage encountered during the studies of the minor products, from the rearrangement of the compound (3.2), was the low yields and difficulty of isolating such products. Although it would have been interesting to investigate these minor products further, in particular the problem of explaining the apparent absence of the aryl ketone (3.11), the low yields influenced our decision to investigate the two major products (3.12) and (3.37) in more detail. The use of deuterium labelling had already proved profitable in similar rearrangement studies[20] and it was therefore, decided to investigate the incorporation of deuterium, during the rearrangement of trimethoxybenzobarrelene (3.2), in deuteriated trifluoroacetic acid. It was hoped that such studies would enable a deeper insight into the mechanisms for the formation of the ketone (3.12) and particularly the biphenyl (3.37).

Rearrangement Studies Involving Deuteriated Trifluoroacetic Acid.

Deuteriated trifluoroacetic acid (3.47) was prepared by reacting trifluoroacetic anhydride with deuterium oxide. The labelled acid (3.47) was isolated by distillation.

The compound (3.2) was rearranged in the acid (3.47) and the two major products (3.12) and (3.37) plus unreacted (3.2) were isolated ~~as~~ in the ~~normal.~~ usual way. The three samples were recrystallised and analysed by mass spectrometry for deuterium content.

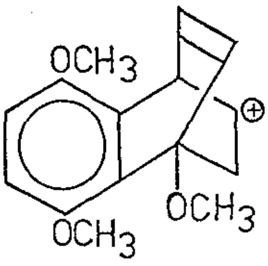
The formation of the trimethoxybiphenyl (3.37) by the mechanism proposed in Scheme 3.9 was of particular interest. The correctness of this mechanism would mean that the rearrangement studies[20] of benzobarrelene substituted derivatives have uncovered a wide spectrum of



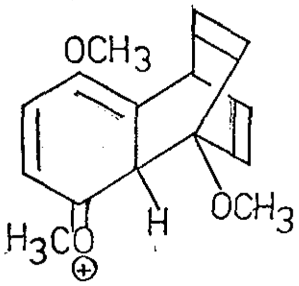
(3.47)

reaction intermediates. Ranging from the dipolar species (3.49) formed during the rearrangement of 1,-*N*,*N*-dimethylaminotetrahalobenzobarrelene (3.48) to the biphenyl (3.50),[20b,j] through the carbonium ion (3.52) present in the rearrangement of 1-methoxytetrahalobenzobarrelene (3.51) to tetrahalobenzobarrelenone (3.53)[20] to the aryl cation (3.54) proposed in the rearrangement of trimethoxybenzobarrelene (3.2) to the biphenyl (3.37). These reactions are illustrated in Scheme 3.11.

It was also interesting to note that in the rearrangement of the compound (3.2) protonation of the olefinic bond to give the ion (3.55) leading eventually to the ketone (3.12) was in competition with the protonation of the aryl ring to yield the ion (3.54)

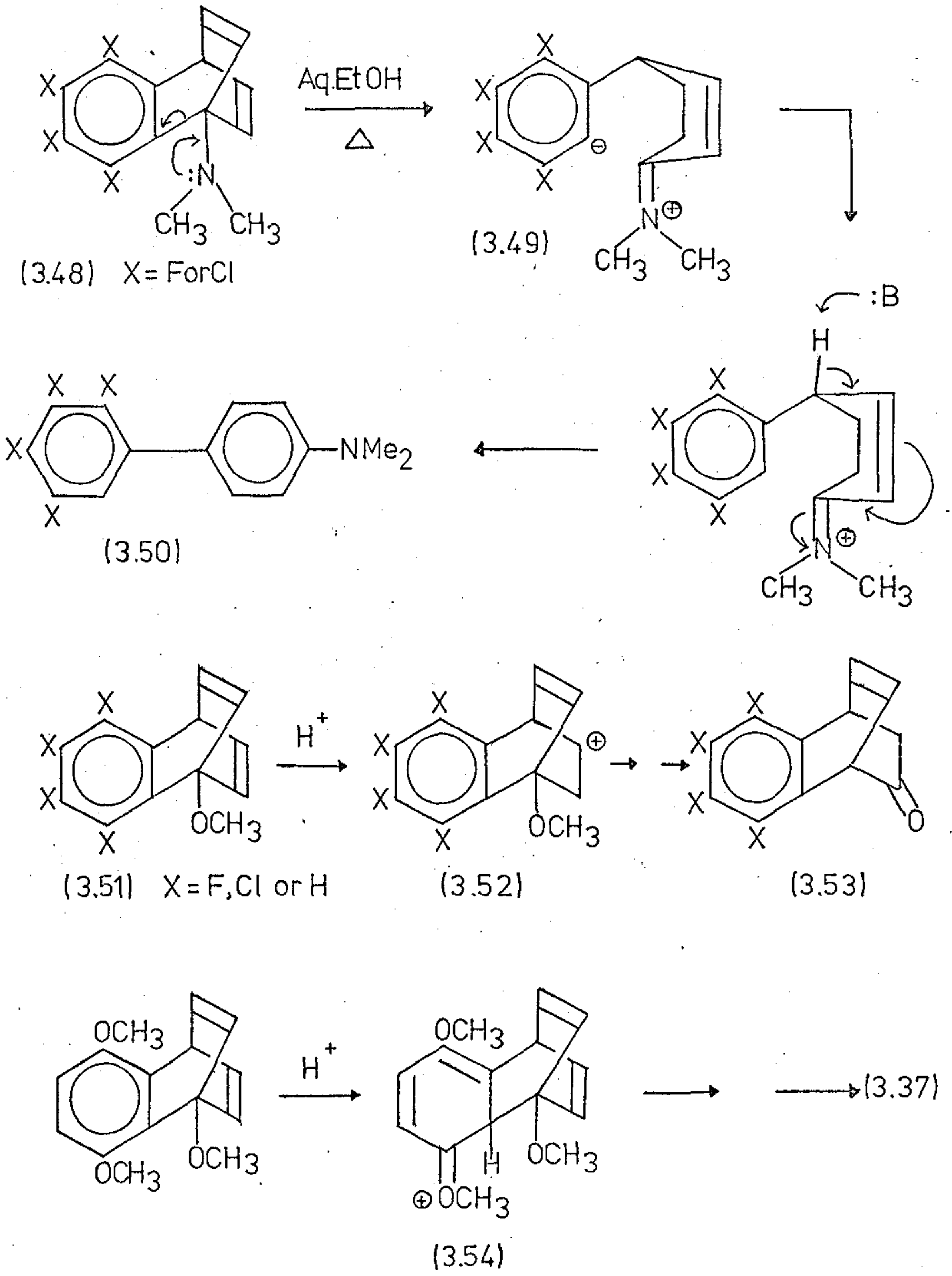


(3.55)

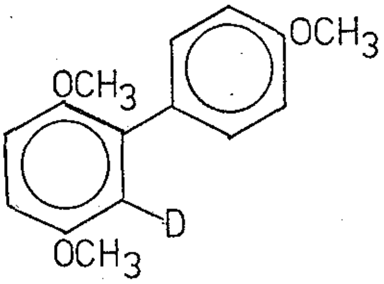


(3.54)

Scheme 3.11


(3.48) X = ForCl
Aq.EtOH
△
(3.49)
:B
(3.50)
NMe$_2$
(3.51) X = F,Cl or H
H$^+$
(3.52)
(3.53)
H$^+$
(3.54)
(3.37)

It was reasoned that the mechanism proposed in Scheme 3.9, for the formation of the biphenyl (3.37), could be justified by the incorporation of one deuterium at C-2 on the dimethoxyaryl ring. The extent of incorporation and position could be determined by mass spectrometry and ^{1}H.n.m.r. spectroscopy respectively.



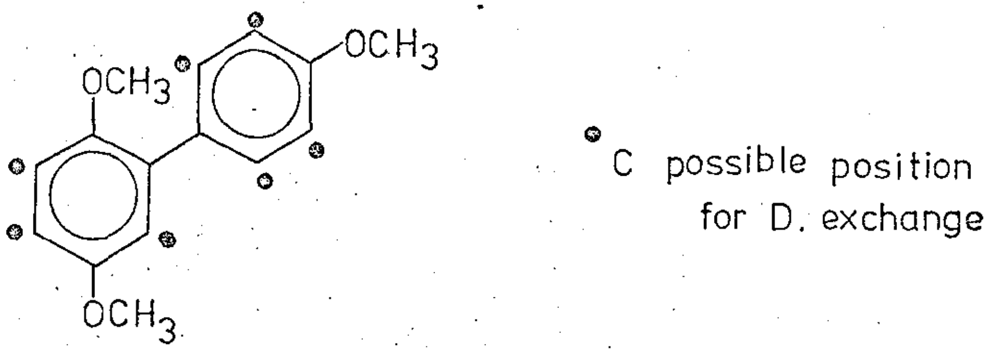
The results of studies involving the biphenyl (3.37) are shown in Table II and, not surprisingly indicate that not one but up to seven deuteriums had been incorporated during the rearrangement. It would seem that a number of proton-deuterium exchange reactions were occurring during the rearrangement.

TABLE II

Molecular Ion (M^+)		244	245	246	247	248	249	250	251
Biphenyl from Rearrangement	%D	0	1.1	5.6	19.2	35.5	36.6	1.0	1.0
Control	%D	0	2.5	13.2	34.5	47.5	1.1	1.2	

Consideration of the biphenyl structure (3.37) indicates that there are seven positions where deuterium could exchange for a proton.

The results in Table II show that all seven positions have deuterium incorporated, but that the incorporation of 3,4 and 5 deuteriums



accounts for 91.3% of the incorporation. The five most likely protons for exchange are those ortho to the three methoxy groups.

A control experiment was carried out to establish the extent of proton-deuterium exchange in the biphenyl (3.37). The biphenyl was heated under reflux in the acid (3.47) for ca. 3hr. and isolated ~~as~~ in the usual way ~~normal.~~ The results (Table II) show that 95.2% of the deuterium is in 2,3 and 4 positions.

Although it is difficult to obtain information from these results, regarding the proposed formation of the biphenyl (3.37), it can be seen that in the control experiment the highest percentage incorporation is at molecular ion 248 and at 249 for the biphenyl from the rearrangement. This result would be expected if the proposed mechanism was correct.

The above results were further complicated by two other considerations. Firstly the possibility of proton-deuterium exchange in the starting material (3.2) prior to rearrangement and secondly, by the possibility of deuterium-proton exchange in the products on quenching the reaction in water.

Analysis of the recovered starting material (3.2) from the reaction mixture indicated that ca. 62.5% had two deuteriums incorporated and ca. 19.8% one deuterium. The fact that ca. 17.7% of the recovered compound contained no deuterium may be due to deuterium-proton exchange during the aqueous work-up.

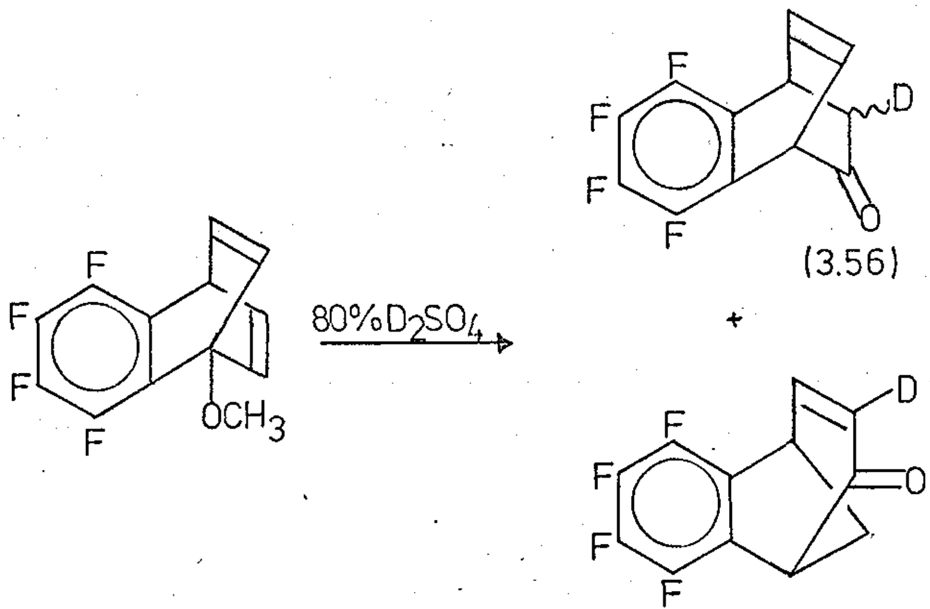
The second consideration was investigated by rearranging the compound (3.2) in the acid (3.47) and quenching the reaction in deuterium oxide, thus preventing deuterium-proton exchange. The products were separated as normal but on this occasion no recovered starting material was isolated. Similar analysis by mass spectrometry showed that ca. 55% of the biphenyl (3.37) contained 5D and 29.5% 4D. The complete results are shown in Table III. Comparison of the results in Tables II and III for the biphenyl indicate that deuterium-proton exchange does occur during the reaction work-up.

TABLE III

Molecular Ion (M^+)		244	245	246	247	248	249
Recovered (3.2)	%D	17.7	19.8	62.5			
Biphenyl D_2O Quench	%D	0.7	0.4	5.6	8.8	29.5	55.0

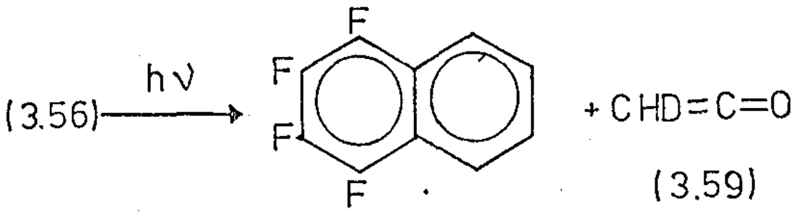
Although the proton-deuterium exchanges in the starting compound (3.2) and the biphenyl (3.37) prevent absolute confirmation of the mechanism proposed in Scheme 3.9, the fact that the biphenyl from the rearrangement contains a high proportion of M^+ 249 and that from the control experiment a high proportion of M^+ 248 strongly favours the proposed mechanism.

Prior to the above work it was assumed that the dimethoxybenzobarrelenone (3.12) would incorporate only one deuterium at C-3. This assumption was based on previous work[20d] involving the rearrangement of 1-methoxytetrafluorobenzobarrelene in 80% D_2SO_4 to form the two deuteriated ketones (3.56) and (3.57). The benzobarrelenone (3.56) was shown by mass spectrometry and ^{1}H.n.m.r. spectroscopy to have the structure (3.56). In order to be sure there was no deuterium in the vinyl positions, the ketone (3.56) was converted to the naphthalene (3.58) by photolysis. The naphthalene was shown by mass spectrometry to be completely undeuteriated.



(3.56)

(3.57)

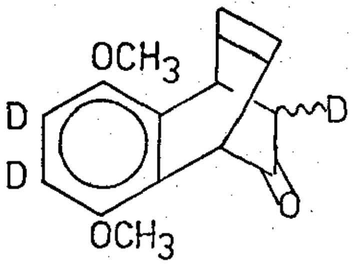


(3.59)

(3.58)

The mass spectra of ketones such as (3.56) and (3.12) show peaks corresponding to their respective naphthalenes and ketene. Thus dimethoxybenzobarrelenone (3.12) gives $^m/_e$ 188 and 42 corresponding to dimethoxynaphthalene and ketene. The original intention was to isolate the deuteriated ketone (3.12) and investigate the peak patterns at $^m/_e$ 230, 188 and 42 and hopefully show a similar result to that of the ketone (3.56).

The previously discussed biphenyl results indicated that more than one deuterium would be incorporated into the ketone (3.12). The most likely number was three as illustrated below.



(3.12)

A control experiment was carried out at the same time as the rearrangement of the compound (3.2), by reacting the unlabelled ketone (3.12) with refluxing deuteriated trifluoroacetic acid for ca. 3hr.. The results of the mass spectral analysis are shown in Table IV.

The results were surprising and difficult to understand. The ketone (3.12) from the rearrangement indicated that ca. 51.4% of the product contained 2D and ca. 32.1% contained 1D. Analysis of the peaks corresponding to dimethoxynaphthalene (MW. 188) and ketene (MW. 42) showed that ca. 70.8% of the naphthalene contained 2D and only ca. 12.5% of the ketene contained 1D. The low incorporation in the ketene was perplexing.

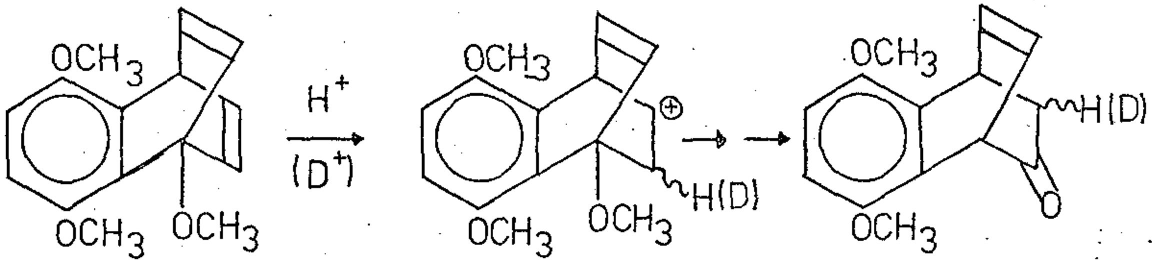
TABLE IV

Molecular Ion M^+	Ketone from Rearrangment (Aq. work-up) %D.	CONTROL EXPT. %D.
230	12.2	3.9
231	32.1	14.7
232	51.4	75.3
233	4.3	2.9
234		3.3
188	7.6	4.1
189	21.6	14.3
190	70.8	81.1
191		0.6
42	87.5	78.3
43	12.5	21.7

The control experiment indicated ca. 75.3% of the recovered ketone contained 2D and ca. 14.7% 1D. The naphthalene portion of the ketone contained ca. 81.1% 2D and 14.3% 1D., whilst the ketene portion showed ca. 21.7% 1D. This latter result was most surprising since it had been assumed that the methylene protons in the ketone (3.12) would not undergo exchange with deuterium.

Barkhash[24] has carried out deuteriation studies on 1-methoxytetrafluorobenzobarrelene during rearrangements and has also shown that when tetrafluorobenzobarrelenone was dissolved in D_2SO_4, then poured into D_2O or when the ketone (3.56) was dissolved in H_2SO_4, then quenched in D_2O, no deuterium exchange occurred.

The results in Table IV indicate that proton-deuterium exchange at the methylene position in the ketone (3.12) can occur. However, this result did not help the explanation of the low deuterium incorporation at C-3 of the ketone (3.12) from the rearrangement. It is impossible to propose a mechanism for the formation of the ketone from the compound (3.2) which does not involve protonation (deuteriation) at C-2 leading to a proton (deuterium) at C-3 in the ketone product.



The fact that the ketone (3.12) was isolated from an aqueous work-up provides the possibility of deuterium - proton exchange as noted in the biphenyl studies. However, it is not a reasonable assumption to suppose that the deuterium at C-3 in the ketone (3.12) would exchange any faster, if as fast, as the two deuteriums ortho to the methoxy groups.

A second control experiment was carried out in which the ketone was heated under reflux in deuteriated trifluoroacetic acid for ca. 3hr.. At the end of this period the majority of excess of acid was removed by distillation. The remaining crude ketone was analysed by mass spectra and the results are shown in Table V.

TABLE V

Molecular Ion M^+	KETONE (CRUDE) % D.
230	8.3
231	34.6
232	51.4
233	5.7
188	8.5
189	36.9
190	54.6
42	88.9
43	11.1

The results do not correlate too well with those obtained for the control experiment involving an aqueous work-up, (Table IV). However, both sets of results show a preference for exchange of two deuteriums, the majority of this exchange takes place in the aryl ring of the ketone (3.12) and a small percentage at C-3.

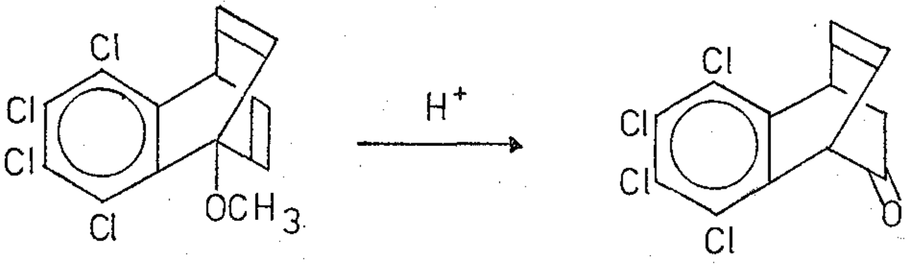
In order to obtain more accurate data a sample of the ketone (3.12), formed in the rearrangement of trimethoxybenzobarrelene (3.2) in deuteriated trifluoroacetic acid, followed by quenching in deuterium oxide was sent for accurate mass determination to P.C.M.U.

Disappointingly their results indicated that the deuteriated ketone (3.12) contained deuteriated trimethoxybenzobarrelene (3.2) as an impurity. The molecular ion of the latter (M^+ 244) gave an ion at 229 (M^+-15) which obviously interfered with the pattern of peaks around the molecular ion of the ketone (M^+ 230). Thus it was not possible to calculate the percentage of deuterium in the ketone (3.12) or the dimethoxynaphthalene and ketene as previously. One significant point rescued from these results was that the ketene ion m/e 42 was much more predominant than the ion m/e 43 expected for the deuteriated ketene.

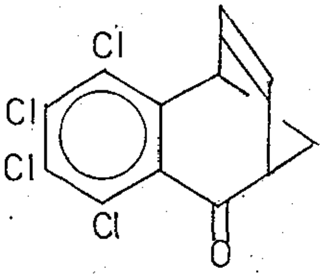
Further work is necessary before the question surrounding the disappearance of the deuterium from C-3 in the ketone (3.12) can be answered. The most likely conclusion is that a deuterium-proton exchange occurs at some stage of the work-up or purification. However, the apparent ease of exchange of a methylene proton (deuterium) of dimethoxybenzobarrelenone (3.12) as compared to the similar tetrafluorobenzobarrlenone remains a perplexing problem.

Rearrangement of 1-methoxytetrachlorobenzobarrelene.

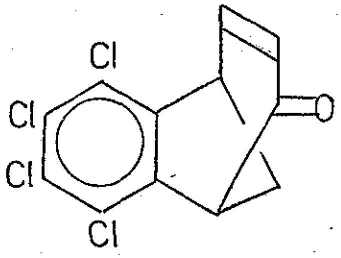
The procedures discussed in Chapter 2 showed that 1-methoxytetrachlorobenzobarrelene (3.60) rearranged in concentrated sulphuric acid to the three isomeric ketones (3.61) - (3.63) in 76, 3.2 and 4.5% yields respectively.


Cl
Cl
Cl
Cl
OCH3
H+
Cl
Cl
Cl
Cl
O

(3.60) (3.61)



(3.62)



(3.63)

We were interested in carrying out this rearrangement under less vigorous conditions, in the hope of identifying alternative products or product ratios. The results of the study are shown in the following table.

Rearrangement Conditions			RESULTS. %			
Acid	Time	Temp.	3.60	3.61	3.62	3.63
$HClO_4$ (60%)	30 min.	R.T.	100%			
$HClO_4$ (60%)	120 min.	R.T.	100%			
$HClO_4$/Dioxan	4 hr.	Reflux.		50	8	12

The three ketones (3.61) - (3.63) were identified by comparison of their spectral data with authentic material.[20c] As expected the compound (3.60) would not rearrange in the milder aqueous perchloric acid, at room temperature but required the more vigorous conditions of reflux. The higher yields of the two minor ketones (3.62) and (3.63) as compared with the results using concentrated sulphuric acid may be due to the difference in acid strength. It is considered [20c] that in strongly acidic media protonation of the methoxy group in 1-methoxybenzobarrelenes directs the subsequent addition of a proton to a double bond. The stronger the acid the more likely protonation will occur at C-2 and hence lead to the ketone (3.61). With weaker acids the probability of protonation at C-3 increases leading eventually to the isomeric ketones (3.62) and (3.63). However, even with perchloric acid-dioxan the major ketone product is the benzobarrelenone (3.61) formed in ca. 50% yield.

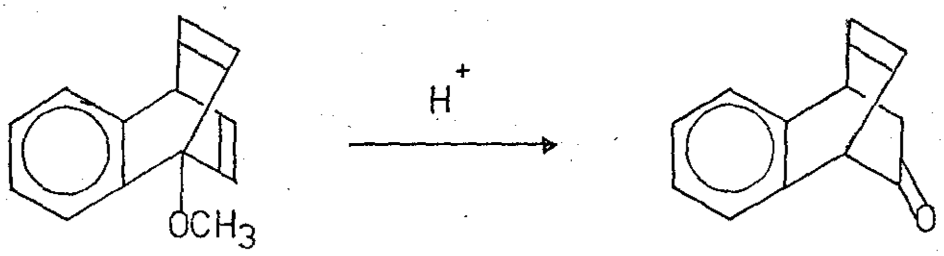
Rearrangement of 1-methoxybenzobarrelene

Earlier investigations[20c] into the rearrangement of 1-methoxybenzobarrelene (3.64) were limited to one reaction in concentrated sulphuric acid, due to the difficulty of preparation of the compound (3.64). Three isomeric ketones (3.65) - (3.67) were isolated in 50, 8 and 6.5% yields respectively.

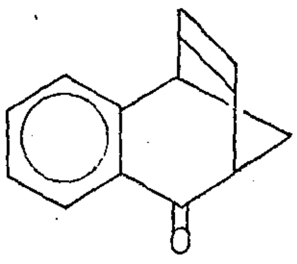
The dechlorination procedure discussed in Chapter 1 provided a high yield route to the compound (3.64) from 1-methoxytetrachlorobenzobarrelene (3.60) and hence the possibility of carrying out a more detailed investigation of the rearrangement of the compound (3.64). The results of this study are shown in the Table below:-

Rearrangement Conditions				PRODUCTS				
Acid	Time	Temp. °C	Wt of (3.64)	(3.64	(3.65)	(3.66)	(3.67)	Unknown
*$HClO_4$ (60%)	120min.	RT.	20mg.	✓	✓	✓	✓	
CF_3CO_2H	5hr.	Reflux	1.01g.	0	440mg. 47.2%	69mg. 7.4%	128mg. 13.7%	310mg.
H_2SO_4 (98%)	2min.	RT.	1g.	0	320mg. 34.6%	28mg. 3.0%	31mg. 3.4%	450mg.
H_2SO_4 (98%)	2min.	RT.	1g.	0	500mg. 54.1%	20mg. 2.2%	50mg. 5.4%	220mg.
H_2SO_4 (80%)	2min.	80°	1.3g.	0	440mg. 36.6%	40mg. 3.3%	20mg. 1.7%	400mg.

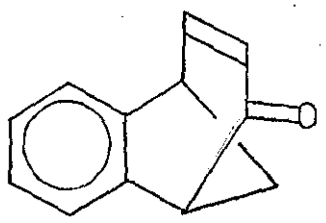
*Reaction in $HClO_4$ (60%) analysed by t.l.c.



(3.64) (3.65)



(3.66)



(3.67)

The fact that 1-methoxybenzobarrelene (3.64) rearranges under milder acidic conditions (perchloric acid 60%) than 1-methoxytetrachlorobenzobarrelene is probably due to the greater solubility of the former.

Rearrangement of the compound (3.64) in CF_3CO_2H, H_2SO_4 (98%) and H_2SO_4 (80% at 80°) yields the three isomeric ketones (3.65)- (3.66) plus an unknown compound, in the yields shown in the above table. The percentage yields of the two minor ketones (3.66) and (3.67) did not appear to be greatly effected by the change in acid medium from con~~d~~c. H_2SO_4 to 80% H_2SO_4. However, the yield of these two ketones did increase when the milder acid CF_3CO_2H was used.

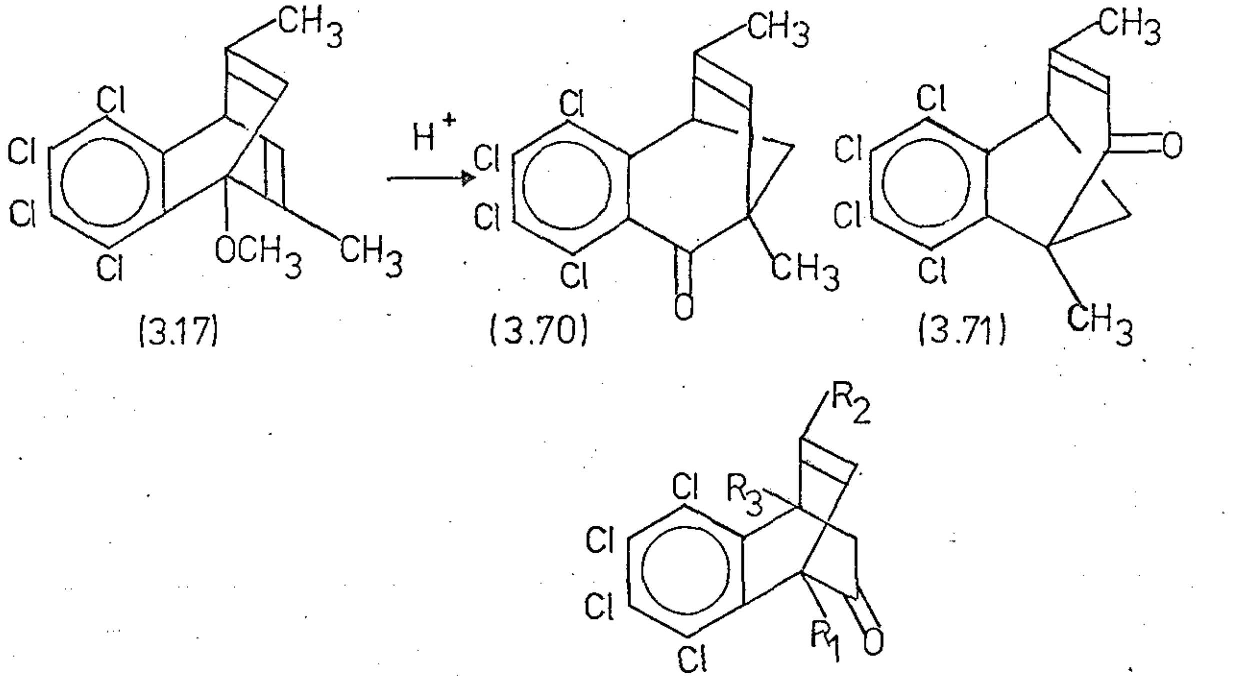
Of particular interest was the apparent increase in yield of the unknown compound at the expense of the yield of benzobarrelenone (3.65). The unknown compound was normally isolated as a white tacky solid, mp. 100-250°. Analysis by i.r. and ^{1}H.n.m.r. spectroscopy gave very little information regarding potential structures. Two broad absorptions at 3700 - 3200 and 1750 - 1650 cm^{-1}, in the i.r. spectrum, could be attributed to O-H and C=O stretching frequencies respectively. The ^{1}H.n.m.r. spectrum was very complex, and although aromatic and olefinic protons were indicated, it was not possible to calculate peak height ratios due to the ill-defined nature of the spectrum. Attempts to separate the unknown by preparative t.l.c., using various solvent systems, met with failure.

The unknown is most likely a mixture of products which are formed from the ketone (3.65) or by the reaction of this ketone with an intermediate of the rearrangement. Owing to the complex nature and difficulty of separating, the unknown was not investigated further.

Rearrangement of 2,5-dimethyl-1-methoxybenzobarrelene

Previous work[20e] had shown that the tetrachlorobenzobarrelene derivative (3.17), in the presence of trifluoroacetic acid, rearranged to the four isomeric ketones (3.68) - (3.71) as illustrated in Scheme 3.12.

Scheme 3.12

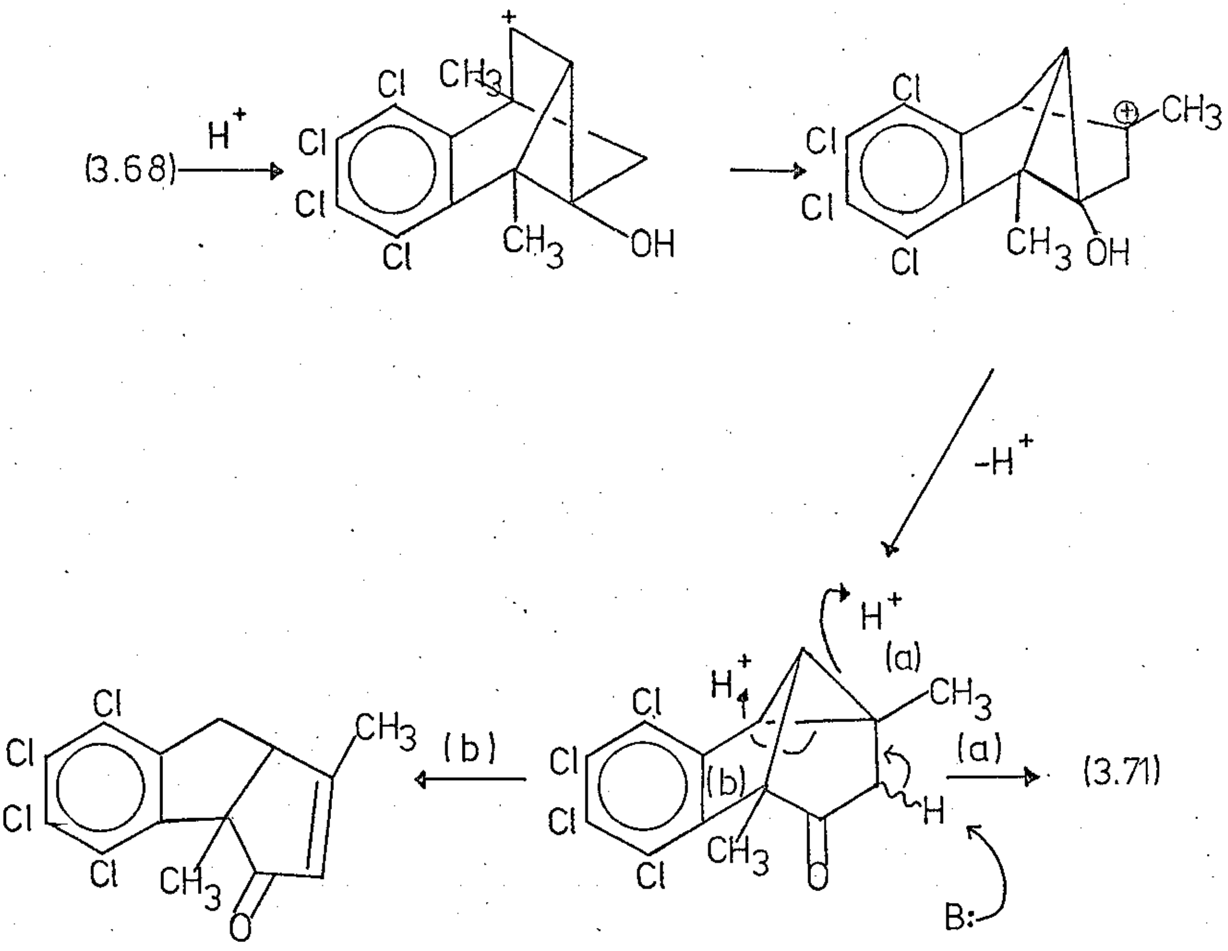

CH3
Cl
Cl
Cl
Cl
OCH3
CH3
(3.17)
H+
CH3
Cl
Cl
Cl
Cl
O
CH3
(3.70)
CH3
Cl
Cl
Cl
Cl
O
CH3
(3.71)
R2
Cl
R3
Cl
Cl
Cl
R1
O

(3.68) $R_1 = R_3 = CH_3$ $R_2 = H$

(3.69) $R_1 = R_2 = CH_3$ $R_3 = H$

It was also established that the ketone (3.68) in the presence of either sulphuric acid (98%) or fluorosulphonic acid rearranged further into the isomer (3.72) which could rearrange to either (3.73) or (3.71) as shown in Scheme 3.13.

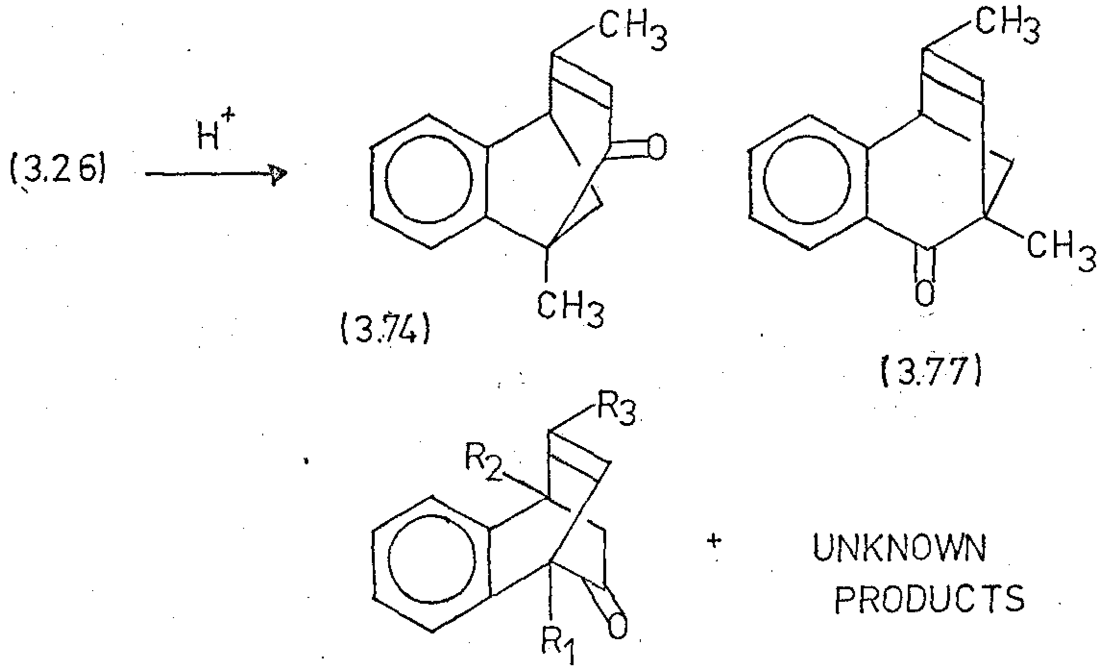
Scheme 3.13


(3.68)
H+
Cl
Cl
Cl
Cl
CH3
CH3
OH
+
CH3
CH3
OH
-H+
H+
(a)
H+
(b)
CH3
CH3
(a)
(3.71)
H
O
B:
(b)
CH3
CH3
O

(3.73) (3.72)

The chlorinated 1-methoxybenzobarrelenes are less soluble and react slower in acid medium than the corresponding 1-methoxybenzobarrelenes. It was therefore considered that the dechlorinated analogue of the compound (3.17) would rearrange under milder conditions with an enhanced possibility of the resultant products reacting further by mechanisms similar to those shown in Scheme 3.13.

Consequently 2,5-dimethyl-1-methoxybenzobarrelene (3.26) was prepared by dechlorination of the compound (3.17) by the procedure described in Chapter 1. The product (3.26) was heated under reflux in trifluoroacetic acid for ca. 4hr.. Analysis of the crude product indicated a complex mixture of products. Separation by preparative t.l.c. gave five bands which on analysis by t.l.c., i.r. and ^{1}H.n.m.r. spectoscopy appeared to be still mixtures of products. A close inspection of the ^{1}H.n.m.r. spectra established that the four isomeric ketones (3.74) - (3.77) had been formed together with other products. Further separation by preparative t.l.c. allowed two of these ketones (3.74) and (3.75) to be isolated and positively identified.



(3.75) $R_1 = R_2 = CH_3$ $R_3 = H$

(3.76) $R_1 = R_3 = CH_3$ $R_2 = H$

The $\alpha\beta$ -unsaturated ketone (3.74) was obtained in 14.8% yield, as a white crystalline solid, mp. 62-64° (ethanol). The i.r. spectrum gave a carbonyl stretch at 1670 cm^{-1} characteristic of an $\alpha\beta$-unsaturated ketone. The ^{1}H.n.m.r. spectrum ($CDCl_3$), τ. showed peaks at 2.65-3.0 (4H, m), 4.74 (1H, broad s), 6.4-6.6 (1H, m), 7.35-7.50 (2H, m), 8.0 (3H, d, $|J|$= ca. 1.5Hz.) and 8.5 (3H, s) which correlates well with the proposed structure (3.74). The mass spectrum gave a molecular ion (M^+) at 198.

The benzobarrelenone (3.75) was also isolated in 38.7% yield, as white crystals, mp. 94-98° (ethanol). The i.r. spectrum showed carbonyl stretching at 1725 cm^{-1}, characteristic of such ketones. The ^{1}H.n.m.r. spectrum, ($CDCl_3$) τ. showed the following peaks 2.5-2.74 (4H, m), 3.4-3.75 (2H, q), 7.83 (1H, s), 7.98 (1H, s), 8.17 (3H, s), and 8.22 (3H, s) which correlates with that expected for the 2,5-dimethylbenzobarrelenone (3.75). The mass spectrum gave a molecular ion (M^+) at 198 with a base peak at 156 (M^+ - 42) corresponding to the loss of ketene.

The other two isomeric ketones (3.76) and (3.77) were not isolated in a pure enough form to be positively identified. Other compounds were also present but little evidence was obtained regarding their structures. Investigations into this rearrangement have been continued.[38]

Rearrangement of the of the 2,3,5-trimethyl-1-methoxybenzobarrelenes (3.27) and (3.28)

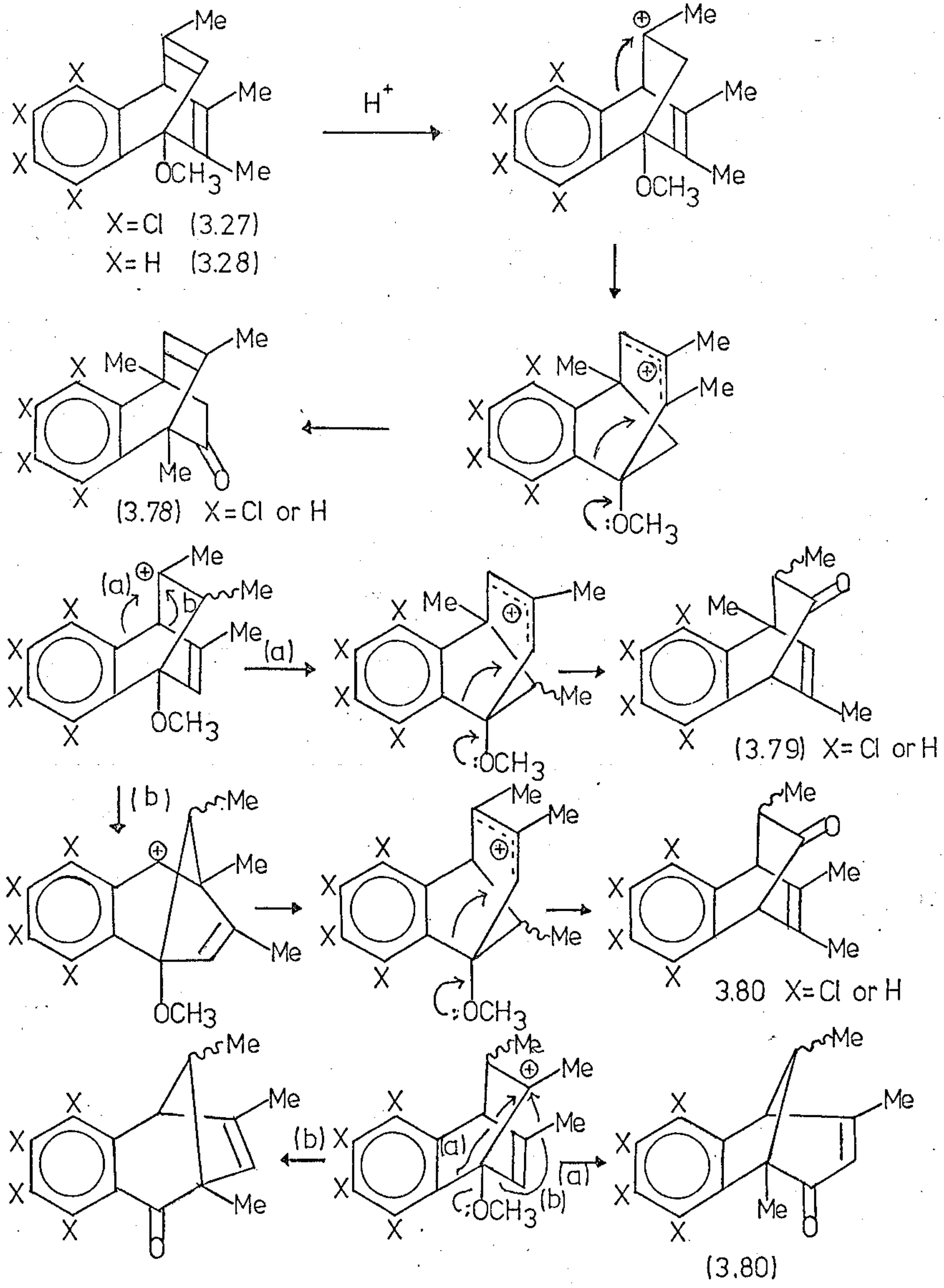
In the acid catalysed rearrangements of 1-methoxybenzobarrelenes, the position of protonation is affected by the strength of the acid used and the presence of substituents which stabilise the carbonium ion formed.

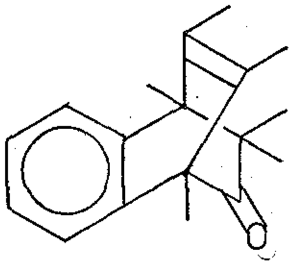
Alkyl groups, and in particular the methyl group, have proved useful in studies of the latter point. The previously discussed rearrangement of 2,5-dimethyl-1-methoxybenzobarrelene (3.26) was of interest, due to the competitive effect of the two methyl groups in different locations with respect to the methoxy-group. The methyl group at C-2 directs protonation to C-3, whilst the methyl group at C-5 directs protonation to C-6. As already discussed this gives alternative modes of rearrangement, which have been shown to react to a complicated mixture of products.

It was reasoned that the two compounds (3.27) and (3.28) would, on rearrangement, result in an even more complicated mixture of products. Some of the possible products are illustrated in Scheme 3.14. It can be seen that most of the expected products (3.78)- (3.82) can exist in two epimeric forms. This picture is further complicated by the possibility of some of the products reacting further. Hart has shown[26] that the related ketone (3.25) can be equilibrated in trifluoroacetic acid with three isomeric ketones. Our studies[20] have, so far, not identified a system which equilibrates under the conditions of the rearrangements. One early explanation for this lack of equilibration had been the presence of four electron withdrawing halogens on the aryl ring of our systems as compared to Hart's ketone (3.25). This was obviously discounted when it was found that the three isomeric ketones (3.65) - (3.67) formed from the rearrangement of the compound (3.64) did not equilibrate.

Hart has established[26] that it is the presence of the six methyl groups which allows the ketone (3.25) to exist in equilibrium with its three isomeric ketones. The presence of these methyl groups enhances the relative stability and lifetime of the cations formed in acidic medium hence allowing equilibration.

Scheme 3.14


X=Cl (3.27)
X=H (3.28)
H⁺
(3.78) X=Cl or H
(a)
(3.79) X= Cl or H
(b)
3.80 X=Cl or H
(b)
(a)
(3.80)
Me
OCH3
X



(3.25)

It was considered that the presence of the three methyl groups in the compounds (3.27) and (3.28) might allow equilibration in the ketone products, formed from their rearrangement.

The two compounds (3.27) and (3.28) were prepared as described in Chapter 1.

A sample of 2,3,5-trimethyl-1-methoxytetrachlorobenzobarrelene (3.27) was rearranged in concentrated sulphuric acid at room temperature. After normal work-up an orange oil was isolated which was separated into 8 bands by preparative t.l.c.. Each of these bands was analysed by i.r. spectroscopy and g.l.c.. The resultant data are shown in the following table.

Bands in order of decreasing RF Value	G.L.C. Results No. of Products	I.R spectra (cm^{-1}.) major peaks.
1	2	2920; 2860; 1450; 1345
2	1	1730
3	2	1730
4	1 major 2 major	3000-2900; 1750; 1450; 1345; 1270; 1230; 1200; 1160; 1055; 940; 800; 770.
5	3	1740; 1670
6	1	1670
7	1	3000-2850; 1705; 1620; 1425; 1360; 1275; 1090; 855; 830; 750
8 Base Line	4	1750-1700 (broad C=0)

The results confirmed the expectation of a complicated mixture of products. The separated bands were not single products but mixtures. It was reasoned that the use of a milder acid, in the rearrangement, might result in a less complicated mixture of products. Thus the compound (3.27) was allowed to rearrange in trifluoroacetic acid. The crude reaction product was separated by preparative t.l.c. to give five bands (A → E). Each band was analysed by i.r. spectroscopy and then separated again by preparative t.l.c.. The results were perplexing, since each of the bands (A → E) was separated into 3-8 bands and analysis of the new bands still indicated mixtures of products. The combined results are given in the experimental section at the end of this Chapter.

The rearrangement was obviously more complicated than originally anticipated. Although a large number of products had been expected, (Scheme 3.14), it seemed unlikely that each of the isolated bands contained mixtures of different products. One explanation of the results was the possibility of individual products rearranging during the chromatographic separation procedure.

Rearrangement of the dechlorinated analogue (3.28), in trifluoroacotic acid, gave a similar complicated mixture of products which could not be separated, by preparative t.l.c., into single products.

As far as the rearrangement of the compounds (3.27) and (3.28) are concerned the tip of the iceberg has only just been scraped. The fact that a number of different ketones are formed during their rearrangement is indicated by the characteristic carbonyl absorbtions noted in the i.r. spectroscopic analysis. The use of ^{1}H.n.m.r. spectroscopy will throw light on the structures of these products and also indicate the possible composition of the isolated bands. The extent of rearrangement or equilibration, if at all, will also be identified by such studies.

Further examination of these rearrangements is under investigation in these laboratories.[38]

EXPERIMENTAL SECTION

General Procedures.

The general procedures are as described in Chapters one and two with the following additions.

The eluant used for the separation of the rearrangement products, by preparative thin layer chromatography, was a mixture of ether and light petroleum. The ratio of this mixture was determined by analytical t.l.c. investigations but was normally either 25 or 50% ether-light petroleum. The plate loading was normally *ca.* 100mg. of product per plate.

The products containing deuterium were examined by mass spectrometry. The spectrum of the molecular ion in question was run six times and average heights of the ion and its deuteriated forms measured. Samples of unlabelled product were subjected to the same analysis in order to determine the correction factors for ^{13}C natural abundance, at the molecular ion concerned.

EXPERIMENTAL

1. Preparation of methyl 2,5-dimethoxybenzoate.

Dimethyl sulphate (500ml.) and aqueous potassium hydroxide (500ml, 50%) were added in small portions to a stirred solution of 2,5-dihydroxybenzoic acid (100g. 0.65M.) in ethanol (200ml.) and potassium hydroxide (100ml, 50%). After the addition was complete the mixture was heated on a water bath (ca. 80°) for about 2 hr., cooled and a brown oil was separated from the aqueous layer. The aqueous phase was extracted with chloroform (2 x 100ml.). The combined organic layer was washed successively with sodium hydroxide (2 x 50ml, 2N.) and distillation of the crude product under reduced pressure gave methyl 2,5-dimethoxybenzoate (72.05g, 56.7%), b.p. 90-95° at 0.5m.m. Hg. (lit.[81] b.p. 95-98° at 1m.m. Hg.).

$\nu_{max.}$ 3000, 2955, 2840, 1737, 1620, 1590, 1470, 1320, 1290, 1250, 1220, 1180, 812 and 735 cm^{-1}.

The basic extract was acidified with hydrochloric acid to give 2,5-dimethoxybenzoic acid (24.2g, 21%) m.p. 72-75° (lit.[82] 76°) after filtration and drying.

2. Methylation of 2,5-dimethoxybenzoic acid.

A solution of 2,5-dimethoxybenzoic acid (31g, 0.16M.), methanol (75ml.) and sulphuric acid (5ml, 98%) was heated under reflux for ca. 15 hr.. Excess of solvent was removed by rotary evaporation and the residue poured into water (100ml.). The aqueous phase was extracted with chloroform (3 x 50ml.) and the combined organic phase was washed and dried as expt. 1. Distillation of the crude product under reduced pressure gave methyl 2,5-dimethoxybenzoate (14.0g, 44.6%).

Acidification of the basic extract, as expt. 1, gave recovered 2,5-dimethoxybenzoic acid (14.2g, 45.8%).

3. Preparation of 3,6-dimethoxybenzamide.

Methyl 2,5-dimethoxybenzoate (120.9g, 0.62M.) was stirred with ammonia solution (650ml.) at room temperature for ca. 15hr.. The white crystalline solid obtained was filtered and washed thoroughly with cold water. Recrystallisation from hot water gave white needles of 2,5-dimethoxybenzamide (117.5g, 97.2%), m.p. 140-141° (lit.[83] m.p. 140°).

4. Preparation of 3,6-dimethoxy-2-nitrobenzamide.

Concentrated nitric acid (700ml.) was cooled in an ice-salt mixture and stirred whilst 2,5-dimethoxybenzamide (117.5g, 0.6M.) was added to it in small portions. After the addition was complete the mixture was stirred for a further period of 1 hr. at 0-5° and then poured onto ice (100g.). The yellow crystalline solid was filtered, washed well with water and dried.

The crude product was extracted with benzene heated under reflux, using a soxhlet thimble, and the remaining solid recrystallised from acetone to afford 3,6-dimethoxy-2-nitrobenzamide (3.7) (100.8g, 70%), m.p. 228-230° (lit.[71] 225-226°).

5. Preparation of 3,6-dimethoxy-2-nitrobenzoic acid.

3,6-dimethoxy-2-nitrobenzamide (76.0g, 0.34M.) was dissolved in sulphuric acid (98% H_2SO_4 : H_2O 800 : 400ml.). The solution was stirred and cooled in an ice-mthanol bath. A thick yellow precipitate was formed on cooling the solution. Sodium nitrite (33g, 0.48M.) was carefully added to the solution in small portions and the solution allowed to warm slowly to room temperature. A brown gas was evolved during this stage of the reaction. The solution was stirred at room temperature for ca. 15hr.. The solution was then quenched in ice-water to yield a yellow solid which was isolated by filtration. The solid was thoroughly washed with water, dried and recrystallised from aqueous ethanol to give 3,6-dimethoxy-2-nitrobenzoic acid (3.8) (70.5g, 92.8%), m.p. 188-191° (lit.[15] 192-194°).

$\nu_{max.}$ 3000, 2855, 1745, 1710, 1620, 1580, 1540, 1495, 1465, 1452, 1435, 1370, 1290, 1250, 1190, 1140, 1055, 935, 810, 800, 790, 760, 720, and 690 $cm.^{-1}$.

6. Preparation of 2-amino-3,6-dimethoxybenzoic acid.

3,6-dimethoxy-2-nitrobenzoic acid (19.6g, 0.086M.) was dissolved in hot ethanol (300ml.) and palladium-carbon (400mg, 10%) was added. Hydrazine hydrate (30ml.) was added to it during 30min.. After the addition was complete the mixture was heated under reflux for 3hr., cooled and the catalyst filtered off. The filtrate was evaporated to a small volume and cooled to give 2-amino-3,6-dimethoxybenzoic acid (3.6) (16.2g, 95.2%), m.p. 94-96° (lit.[15] 96-97°).

$\nu_{max.}$ 3480, 3365, 3100, 2940, 2850, 1700, 1625, 1600, 1550, 1480, 1365, 1270, 1222, 1160, 1115, 1055, 960, 800 and 720 $cm.^{-1}$

7. Attempted reduction of 3,6-dimethoxy-2-nitrobenzoic acid.

3,6-dimethoxy-2-nitrobenzoic acid (0.5g, 2.2m.M.) was dissolved in ethanol (50ml.) and a mixture of iron powder (0.5g.) plus concentrated hydrochloric acid (2ml.) added. The mixture was heated under reflux for *ca*. 2hr., cooled, filtered and evaporated to yield an oily yellow compound. Analysis by t.l.c. and i.r. spectroscopy indicated the presence of only the starting material, 3,6-dimethoxy-2-nitrobenzoic acid.

8. Preparation of 1,4-dihydro-1,5,8-trimethoxy-1,4-ethenonaphthalene (trimethoxybenzobarrelene).

2-Amino-3,6-dimethoxybenzoic acid (9.1g, 0.035M.) was dissolved in tetrahydrofuran (50ml.) and trichloroacetic acid (80mg.) was added. Iso-amyl nitrite (11.5ml.) was added and the mixture stirred at room temperature for *ca*. 2hr.. The dark red diazonium salt was filtered off and washed with dry ether (2 x 10ml.). The semi-dry diazonium salt (9.3g.) was carefully added to preheated anisole (250g, 2.31M.) at 60°. The mixture was maintained at this temperature for a further 4hr.. The solvent and excess of anisole were removed under pressure. The red oil obtained was placed on a column of alumina (1000g.) and elution with ether-light petroleum 40:60 (1:2) afforded 1,4-dihydro-1,5,8-trimethoxy-1,4-ethenonaphthalene (3.2) (1.76g, 20.4%) m.p. 74-76° (lit.[79] 78-79°) (methanol).

$\nu_{max.}$ 3085, 3000, 2965, 2940, 2915, 2840, 1640, 1590, 1500, 1460, 1445, 1345, 1315, 1260, 1240, 1195, 1180, 1150, 1108, 1080, 1065, 1042, 1025, 985, 955, 848, 808, 798, 722, 710 and 678 cm^{-1}.

^{1}H.n.m.r. ($CDCl_3$) τ. 3.10 (m, 4H), 3.49 (s, 2H), 4.72 (t.t., 1H, $|J|$ = 5.8 and 1.8 Hz.), 6.18 (s, 3H), 6.2 (s, 3H) and 6.24 (s, 3H).

Elution with ether-light petroleum 40:60 (5:1) gave crude 5,8-dimethoxy-1,4-etheno-2-tetralone (3.12) (0.66g, 8.1%) m.p. 104-106° (ethanol) (lit.[79] 104-106°).

$\nu_{max.}$ 1740 cm^{-1}.

9. Rearrangement of trimethoxybenzobarrelene (3.2)

(i) The compound (3.2) (10mg.) was stirred in perchloric acid (60%, 10ml.) for ca. 30 min. at room temperature. The solution was quenched in ice and extracted with ether (3 x 10ml.). The combined organic phase was reduced in volume to ca. 5ml. and analysed by t.l.c.. Two products were indicated, one with the same Rf. value as the starting material (3.2).

(ii) A similar reaction to (i) but stirring the mixture for 90min. gave by t.l.c. analysis three products, with one corresponding to the compound (3.2).

(iii) A similar reaction to (i) but stirring the mixture for ca. 4hr. indicated by t.l.c., three products none of which corresponded to the compound (3.2).

(iv) The compound (3.2) (10mg.) was heated under reflux in trifluoroacetic acid (5ml.) for 2hr.. Normal work-up and analysis by t.l.c. indicated three products with similar Rf. values to the products in reaction (iii).

(v) The compound (3.2) (10mg.) was stirred in a mixture of trifluoroacetic acid (3ml.), chloroform (1ml.) and concentrated sulphuric acid (3 drops) at room temperature for ca. 30min.. Normal work-up and t.l.c. analysis indicated only the compound (3.2).

(vi) A similar reaction to (v) but using concentrated sulphuric acid (7 drops) gave only the compound (3.2).

(vii) The compound (3.2) (10mg.) was heated under reflux in a mixture of dioxan (5ml.) and perchloric acid (60%, 5ml.) for 2hr.. Normal work-up and t.l.c. analysis indicated two products and none of the compound (3.2).

The solvent used for the t.l.c. investigations in reactions (i) - (vii) was ether-light petroleum (50:50).

10. Rearrangement of trimethoxybenzobarrelene in trifluoroacetic acid.

Trimethoxybenzobarrelene (3.2) was heated under reflux in trifluoroacetic acid. The acidic solution was poured onto ice and the aqueous solution extracted with ether. Evaporation of the ethereal solution gave an oil which was separated by preparative t.l.c. (silica) to yield the products shown in the table below.

Trimethoxybenzobarrelene wt (mg.)	CF_3CO_2H Vol.(ml).	Hr.	PRODUCTS (Decreasing Rf.) wt (mg.)					
			1	2	3	4	5	6
450	10	4	125	148	32	17	27	5
935	15	4	298	327	38	69	36	42
500	10	6	170	170	20	40	10	

1) 2,4',5-trimethoxybiphenyl (3.37) (28-34%), mp. 62-64° (petroleum ether) (lit.[80] mp. 62-64°) M^+ 244.

^{1}H.n.m.r. ($CDCl_3$) τ 2.50 (AA' of AA'BB', $|J|$ AB= 9Hz, 2H), 2.95-3.2 (m, 5H), 6.18 (s, 3H), 6.23 (s, 3H) and 6.28 (s, 3H).

$\nu_{max.}$ 3000, 2945, 2915, 2840, 1618, 1595, 1580, 1520, 1500, 1465, 1445, 1405, 1300, 1265, 1250, 1220, 1180, 1055, 1027, 882, 835, 798, 745, 720, 692, and 683 cm^{-1}.

$\lambda\cancel{\nu}_{max.}$ (ethanol) 303 (ε 7151) and 256 (ε 13462) n.m.

2) 5,8-dimethoxy-1,4-etheno-2-tetralone (3.12) (35-37%), mp. 108-110° (lit.[79] 104-106°), M$^+$ 230.

^{1}H.n.m.r. (CDCl$_3$) τ 3.20 (m, 4H), 5.13 (d.d, 1H, $|J|$ = 6 and 2Hz), 5.35 (m, 1H), 6.18 (s, 3H), 6.22 (s, 3H) and 7.96 (ABq, 2H, $|J|$ AB = 17Hz).

$\nu_{max.}$ 3080, 3010, 2950, 2840, 1740, 1600, 1500, 1470, 1445, 1337, 1292, 1260, 1150, 1130, 1090, 1010, 970, 770, 715, and 690 cm^{-1}.

3) 1,4-dimethoxy-5,9-dihydro-5,9-methanobenzocyclohepten-6-one (3.9) (4.0-7.1%), red-brown crystals, mp. 137-141° (ethanol) (lit.[79] 140-141°), M$^+$ 230.

^{1}H.n.m.r. (CDCl$_3$) τ 2.58 (q, 1H), 3.40 (m, 2H), 4.55 (q, 1H), 5.92 (m, 1H), 6.15 (s, 3H), 6.20 (s, 3H) and 7.30 (m, 2H).

$\nu_{max.}$ 1675, 1495, 1260, 1155, 1075, 1055, 790, and 710 cm^{-1}.

4) Mixture of two unknowns, M$^+$ 488 and 474.

^{1}H.n.m.r. (CDCl$_3$) τ . 2.48 (s), 2.58 (s), 2.75 (s), 3.03 (s), 3.13 (s), 3.30 (m), 3.88 (m), 5.0 (m), 6.0-6.7 (complex series of singlets) and 7.7-7.95 (m).

$\nu_{max.}$ 1740, 1490, 1480, 1465, 1255, 1205, 1175, 1075, 1035, and 755 cm^{-1}.

5) and 6) - ^{1}H.n.m.r. and i.r. spectroscopy gave only broad and unidentifiable spectra.

11. Preparation of deuteriated trifluoroacetic acid.

Trifluoroacetic anhydride (15.5ml.) and deuterium oxide (1.82ml.) were mixed and allowed to stand at room temperature for ca. 2hr., in a 'dry-box', under an atmosphere of nitrogen. The solution was then distilled and the fraction boiling between 68-70° collected.

12. Rearrangement of trimethoxybenzobarrelene in CF_3CO_2D

A) The compound (3.2) (200mg.) was heated under reflux in CF_3CO_2D (5ml.) for *ca*. 3 hr.. Normal work-up gave a red oil (219mg.) which was separated by preparative t.l.c. (3 x 1m. x 20 cm, 0.75 m.m. thickness; eluant ether-light petroleum (1:1)) to give in order of decreasing Rf. values:-

(i) Deuteriated 2,4',5-trimethoxybiphenyl (43mg.), white crystals (light petroleum).

(ii) A mixture of deuteriated dimethoxybenzobarrelenone and trimethoxybenzobarrelene (96mg.). It was not possible to separate this mixture by preparative t.l.c. but by placing the mixture on a short alumina column and eluting with initially light petroleum followed by ether-light petroleum (1:1), the two products were separated to give:- Deuteriated trimethoxybenzobarrelene (10mg.) pale yellow crystals and deuteriated dimethoxybenzobarrelenone (55mg.) white crystals (ethanol).

The three samples were analysed for deuterium content by mass spectrometry.

B) The compound (3.2) (300mg.) was heated under reflux in CF_3CO_2D (5ml.) for *ca*. 5hr.. The resultant solution was poured into deuterium oxide (6ml.) and then onto ice. The aqueous solution was extracted with ether (3 x 10ml.) and the organic phase dried ($MgSO_4$) and evaporated to yield an oil. The oil was separated by preparative t.l.c. to give six products; (i) 82mg., (ii) 174 mg., (iii) 3mg., (iv) 7mg., (v) 24mg., (vi) 27mg..

(i) Trimethoxybiphenyl - recrystallised from light petroleum and analysed by mass spectrometry for deuterium.

(ii) Mixture of the starting material (3.2) and the ketone (3.12). The mixture was re-plated to give the dimethoxybenzobarrelenone (3.12) (95mg.) which was recrystallised from ethanol and sent for mass spectral analysis to P.C.M.U.. A crystalline sample of the compound (3.2) was not obtained.

Samples (iii) - (vi) were not investigated.

13. Reaction of 2,4',5-trimethoxybiphenyl with CF_3CO_2D.

The biphenyl (3.37) (50mg.) was heated under reflux in CF_3CO_2D (3ml.) for *ca*. 3 hr.. Normal work-up gave a yellow oil which was recrystallised from light petroleum to yield the recovered biphenyl (3.37) (30mg.) as white crystals. The sample was analysed for deuterium by mass spectrometry.

14. Reaction of Dimethoxybenzobarrelenone with CF_3CO_2D.

A) The ketone (3.12) (60mg.) was heated under reflux in CF_3CO_2D (3ml.) for *ca*. 3 hr.. After normal work-up and separation by preparative t.l.c. the ketone (3.12) (50mg.) was recovered.

B) A similar reaction to (A) was carried out but at the end of the reflux period excess of CF_3CO_2D was removed by evaporation under reduced pressure. The ketone (3.12) was recovered as a crude oil.

The recovered ketone from reactions (A) and (B) were analysed for deuterium by mass spectrometry.

15. Attempted reduction of the suspected vinyl naphthalene (3.35).

The suspected vinyl naphthalene (3.35) (100mg.) was dissolved in ethanol (50ml.) and PdC. (10%, 50mg.) added. The mixture was subjected to hydrogenolysis for *ca*. 12 hr.. Filtration and evaporation of the solvent gave an oily solid which on analysis by t.l.c. and ^{1}H.n.m.r. spectroscopy proved to be the starting compound.

16. Preparation of 2,4',5-trimethoxybiphenyl.

p-Methoxyaniline (1.23g, 10m.M.), p-dimethoxybenzene (6.9g, 50m.M), trifluoroacetic acid (2 drops) and isoamyl nitrite (1.3g.) were heated under reflux in acetone (sufficient to form a solution) for ca. 2hr.. Excess of solvent was removed by rotary evaporation and the crude product placed on an alumina column. Elution with ether : light petroleum (0-30% ether) gave a number of fractions which were analysed by g.l.c.. The fractions containing the required biphenyl were combined and evaporated. The resultant oil was separated by preparative t.l.c. to give in order of decreasing Rf. value:-

(i) p-dimethoxybenzene (70mg.) and (ii) 2,4',5-trimethoxybiphenyl (3.37) (120mg, 5.3%) mp. 62-64° (light petroleum) (lit.[80] 62-64°).

17. Reaction of Dimethoxybenzobarrelenone and Trimethoxybiphenyl With CF_3CO_2H.

A mixture of the ketone (3.12) (40mg.) and the biphenyl (3.37) (30mg.) was heated under reflux in CF_3CO_2H (25ml.) for ca. 6hr.. Normal work-up and separation by preparative t.l.c. gave only the ketone (3.12) (30mg.) and the biphenyl (3.37) (25mg.). No other products were isolated.

18. Rearrangement of Trimethoxybenzobarrelene in the presence of an excess of p-dimethoxybenzene.

Trimethoxybenzobarrelene (250mg, 1.03m.M.) and p-dimethoxybenzene (1415mg, 10.3m.M.) were heated under reflux in CF_3CO_2H (10ml.) for ca. 6.5hr.. Normal work-up gave an oil which was separated on an alumina (50g.) column, eluant light petroleum to 30% ether : light petroleum, to give 10 fractions (250ml. per fraction). The fractions were identified by t.l.c. as follows:

Fractions 1-6 p-Dimethoxybenzene

Fractions 7-8 p-Dimethoxybenzene + Trimethoxybiphenyl (3.37)

Fractions 9-10 Mixture of products.

Fractions 9-10 were combined, evaporated and the crude oil separated by preparative t.l.c. to give six products, in order of decreasing Rf. value:-

(i) Trimethoxybiphenyl (3.37) (80mg.).
(ii) Dimethoxybenzobarrelenone (3.12) (66mg.).
(iii) Trimethoxybenzobarrelene (3.2) (10mg.).
(iv) $\alpha\beta$-Unsaturated Ketone (3.9) (11mg.).
(v) Unknown (19mg.).
(vi) Base Line (6mg.).

19. Equilibrium studies on 2,4',5-trimethoxybiphenyl.

The biphenyl (3.37) (50mg.) was stirred in perchloric acid (60%, 10ml.), at room temperature, for ca. 2 hr.. Normal work-up and analysis of the crude product by t.l.c. and ^{1}H.n.m.r. spectroscopy indicated only the biphenyl (3.37).

Similar treatment of the biphenyl for ca. 12hr. gave the same result.

20. Equilibrium studies on Dimethoxybenzobarrelenone.

A) The ketone (3.12) (60mg.) was heated under reflux in CF_3CO_2H (5ml.) for ca. 12hr.. Normal work-up and analysis by t.l.c. and ^{1}H.n.m.r. spectroscopy indicated only the ketone (3.12).

B) The ketone (3.12) (100mg.) was shaken with concentrated sulphuric acid (98%, 20ml.), at room temperature, for 10min.. Normal work-up gave an oil (90mg.) which contained only the ketone (3.12) as shown by t.l.c. and ^{1}H.n.m.r. spectoscopy.

21. Rearrangement of 1-methoxytetrachlorobenzobarrelene (3.60).

1-Methoxytetrachlorobenzobarrelene (10mg.) was stirred in perchloric acid (60%, 10ml.), at room temperature, for ca. 30 min.. The solution was poured onto ice and extracted with ether (3 x 20ml.). Evaporation of the organic phase gave an oil which on analysis by t.l.c. indicated only the starting material (3.60).

The above reaction was repeated but with stirring for ca. 2 hr.. Once again work-up yielded only the starting material (3.60).

A third reaction, using the compound (3.60) (10mg.), was heated under reflux, in a solution of perchloric acid (60%, 5ml.) and dioxan (5ml.) for 2 hr.. Analysis of the crude product by t.l.c. indicated a mixture of three products.

A larger scale reaction, involving the compound (3.60) (500mg, 1.55m.M.), was heated under reflux in a solution of perchloric acid (60%, 25ml.) and dioxan (25ml.) for 4 hr.. The solution was poured onto ice (50g.) and extracted with ether (3 x 30ml.). The ethereal solution was washed (sat. $NaHCO_3$), dried ($MgSO_4$) and evaporated to give a yellow-orange oil. The oil was separated by preparative t.l.c. to give in order of decreasing Rf. value:-

(i) 1,2,3,4-tetrachloro-5,8-dihydro-5,8-methanobenzocyclohepten-9-one (3.62)[20c] (38mg, 7.9%) τ. ($CDCl_3$) 3.27 (q, 1H), 3.77 (q, 1H), 5.5-5.7 (m, 1H), 6.35-6.55 (m, 1H) and 7.1-7.6 (m, 2H), (ii) 5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalene-2(1H)-one(3.61) (238mg, 49.8%) m.p. 168-170° (lit.[20c] 166-168°); and (iii) 1,2,3,4-tetrachloro-5,9-dihydro-5,9-methanobenzocyclohepten-6-one (3.63)[20c] (58mg, 12%, τ. ($CDCl_3$) 2.54 (q, 1H), 4.46 (q, 1H), 5.75-6.2 (m, 2H), and

7.1-7.3 (m, 2H).

22. Rearrangement of 1-methoxybenzobarrelene.

A) 1-Methoxybenzobarrelene (3.64) (1g, 5.4m.M.) was shaken in concentrated sulphuric acid (98%, 25ml.) for *ca.* 15sec.. The solution was poured onto ice and the aqueous solution extracted with chloroform (3 x 75ml.). The organic phase was dried ($MgSO_4$) and evaporated to give a red oil (1.2g.) which was separated by preparative t.l.c.. Four products were obtained which were, in order of decreasing Rf. value:- (i) 5,8-dihydro-5,8-methanobenzocyclohepten-9-one (3.66)[20c] (20mg, 2.2%), a yellow oil, τ. ($CDCl_3$) 2.05-2.3 (1H, m), 2.6-3.1 (3H, m), 3.3 (1H, d.d.), 3.9 (1H, d.d.), 6.3-6.5 (1H, m), 6.5-6.7 (1H, m) and 7.15-7.6 (2H, m), (ii) 3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one (3.65)[20c] (500mg, 54.1%), a yellow oil, τ. ($CDCl_3$) 2.55-2.95 (4H, m), 3.05-3.6 (2H, m), 5.57 (1H, q), 5.60-5.9 (1H, m) and 7.50-8.3 (2H, octet, AB of ABX), (iii) 5,9-dihydro-5,9-methanobenzocyclohepten-6-one (3.67)[20c] (50mg, 5.4%), a yellow oil, τ. ($CDCl_3$) 2.5-3.1 (5H, m), 4.65 (1H, q), 6.15-6.55 (2H, m) and 7.15-7.4 (2H, m) and (iv) base line (220mg.), white oily solid, mp. 100-250°, i.r. and ^{1}H.n.m.r. spectoscopy gave no characteristic absorptions.

B) A similar rearrangement using dilute sulphuric acid (H_2SO_4:H_2O, 4:1, $^v/v.$) at 80°, gave the same products which were separated in the following yields:- (i) (40mg, 4.3%), (ii) (440mg, 47.6%), (iii) (20mg, 2.2%) and (iv) (400mg.).

C) Trifluoroacetic acid.

1-Methoxybenzobarrelene (3.64) (1.01g, 5.49m.M.) was heated under reflux in trifluoroacetic acid (20ml.) for 5hr.. Conventional work-up and separation of the crude product by preparative t.l.c. gave the same four products as reactions A and B, in the following yields:-

(i) (69mg, 7.4%), (ii) (443mg, 47.4%), (iii) (128mg, 13.7%) and

(iv) base line (397mg.), red oil.

D) Perchloric Acid.

The compound (3.64) (20mg.) was stirred in perchloric acid (60%, 8ml.), at room temperature, for 2hr.. Normal work-up and analysis of the crude product by t.l.c. indicated four products with similar Rf. values to the products (i) - (iv) obtained in reactions A,B and C.

23. Rearrangement of 2,5-dimethyl-1-methoxybenzobarrelene (3.26) in trifluoroacetic acid.

The compound (3.26) (1g, 4.7m.M.) was heated under reflux in trifluoroacetic acid (20ml.) for 4hr.. Normal work-up and separation of the crude product by preparative t.l.c. gave four products (i) - (iv) which were analysed by i.r. spectroscopy:-

$\nu_{max.}$ (i) (fluorescent band) 2960, 2930, 2860, 1460 and 1380 cm.$^{-1}$

(ii) 3060, 2970, 2940, 2880, 1780, 1730, 1695, 1600, 1450, 1380, 1220, 1170, 1080, 1050, 750 and 690 cm.$^{-1}$

(iii) 3700 - 3200 (broad), 2980, 2940, 1785, 1750 - 1550 (broad), 1460, 1450, 1380, 1330, 1250 - 1100 (broad), 890, 800, 770, 760 and 680 cm.$^{-1}$

(iv) Base line - no distinct absorptions.

The products (ii) - (iv) were separated again by preparative t.l.c. and the resultant products analysed by t.l.c. and i.r. spectroscopy. Products with the same Rf. value and i.r. spectrum were combined to give four major fractions (v) - (viii). Fractions (v) and (vi) were recrystallised to yield (v) 5,9-dihydro-5,7-dimethyl-5,9-methanobenzocyclohepten-6-one (3.74) (138mg, 14.8%), mp. 62-64° (ethanol), M^+ 198, ^{1}H.n.m.r. ($CDCl_3$) τ 2.65-3.0 (4H, m), 4.74 (1H, broad s), 6.4-6.6 (1H, m), 7.35-7.5 (2H, m), 8.0 (3H, d, $|J|$ *ca.* 1.5Hz.) and 8.5 (3H, s), $\nu_{max.}$ 2980, 2940, 2870, 1670, 1620, 1455, 1375, 1315, 1250, 1195, 1170, 1120, 1110, 1015, 900, 770, 760, and 680 cm^{-1}. and (vI) 3,4-dihydro-1,4-dimethyl-1,4-ethenonaphthalene-2(1H)-one (3.75) (361mg, 38.7%) mp. 94-98° (ethanol), M^+ 198, ^{1}H.n.m.r. ($CDCl_3$) τ. 2.5-2.74 (4H, m), 3.4-3.75 (2H, q), 7.83 (1H, s), 7.98 (1H, s), 8.17 (3H, s) and 8.22 (3H, s), $\nu_{max.}$ 3060, 2980, 2940, 1725, 1450, 1380, 1050, 755, and 690 cm^{-1}.

The remaining two fractions (vii) and (viii) were shown by ^{1}H.n.m.r. to be mixtures of two or more of the ketones (3.74) - (3.77).
(vii) $\nu_{max.}$ 2970, 2940, 1720, 1275, 1170, 1160, 1120, 1105, and 1020 cm^{-1}.
(viii) $\nu_{max.}$ 2970, 2960, 2880, 1730, 1460, 1380, 1280, 1120, 1070, and 750 cm^{-1}. Both (vii) and (viii) were isolated as yellow oils.

The two ketones (3.74) and (3.75) were not analysed for carbon and hydrogen.

24. Rearrangement of 2,3,5-trimethyl-1-methoxytetrachlorobenzobarrelene (3.27).

A. Concentrated Sulphuric Acid.

The compound (3.27) (500mg, 1.37m.M.) was shaken in concentrated sulphuric acid (98%, 10ml.) at room temperature for 5min.. Normal work-up gave an orange oil (0.5g.) which was separated by preparative t.l.c. to yield eight bands. These bands were analysed by g.l.c. and i.r.

spectroscopy. The results are shown in Table A.

B. Trifluoroacetic Acid.

The compound (3.27) (1g, 2.74m.M.) was heated under reflux in trifluoroacetic acid (20ml.) for 4hr.. Normal work-up and separation by preparative t.l.c. gave four bands B1 - B5 which were analysed by i.r. spectroscopy. The five bands were each separated by preparative t.l.c. to yield a complex mixture of products. The results of the analysis of these products are shown in Table B.

25. Rearrangement of 2,3,5-trimethyl-1-methoxybenzobarrelene (3.28).

The compound (3.28) (1g, 4.42m.M.) was heated under reflux in trifluoroacetic acid (20ml.) for 4hr.. Work-up and separation as normal gave a complex mixture of products. The results of the analysis by t.l.c. and i.r. spectroscopy are shown in Table C.

TABLE A

Bands in order of decreasing Rf. value	G.L.C. Results No. of Products	Infra-red spectra. ($cm.^{-1}$)	wt. (mg.)
1	2	2920, 2860, 1450, 1345	40
2	1	1730	10
3	2	1730	10
4	1 major 2 minor	3000-2900, 1750, 1450, 1345, 1270, 1230, 1200, 1160, 1055, 900, 800, 770.	140
5	3	1740, 1670	10
6	1	1670	50
7	1	3000-2850, 1705, 1620, 1425, 1360, 1275, 1090 855, 830, 750	160
8 Base Line	4	1750-1700 (broad C=O)	30

TABLE B

Band	I.R. Data (cm^{-1}) (Major absorptions.)
B1	2930, 2860, 1395
B2	2930, 2860, 1730, 1700, 1450, 1370
B3	3000-2850, 1740, 1460, 1400-1340, 1285, 1260, 1240, 1215, 1150, 1070, 955, 815, 785, 750
B4	3000-3200, 2980, 2940, 2880, 1710, 1625, 1440, 1370, 1290, 1260, 1235, 1170, 1130, 1100, 870, 840, 765, 640
B5	Base Line

Band	T.L.C. No. of Spots	I.R. Data (cm^{-1}) (Major absorptions.)
B1-a	1	3000-2850, 1345
b	1	3000-2850
c	1	3700-3000, 1635, 1345, 1220, 1150
d	1	No distinct absorptions
e	2	No distinct absorptions
f	2	Base Line: 3700-3100, 3050-2850, 1790, 1720, 1450, 1365, 1225, 1175, 1145, 760
B2-a	2	2915, 2870, 1710, 1450, 1345, 1220, 760
b	2	No distinct absorptions.
c	2	1730, 1700
d	2	1730
e	1	1700
f	1	Base Line: 3700-3300, 3050-2850, 1730, 1450, 1380, 760
B3-a	1	No distinct absorptions
b	1	2940, 2860, 1730, 1700, 1450, 1370
c	1	B3-d to B-3i
B3-d	1	3700-3200, 2960, 2940, 2860, 1740, 1650, 1460, 1380, 765

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TABLE B (contd.)

Band	T.L.C. No. of Spots	I.R. Data (cm^{-1}) (Major absorptions.)
B3-e	3	3000-2880, 1740, 1460, 1380, 1360, 1070, 960, 820, 790
f	2	1750
g	3	1780, 1740
h	3	1780-1670 (broad)
i	2	Base Line : 1785, 1730
B4-a	1	1720
b	1	1725
c	3	1785, 1715, 1680, 1630
d	2	No distinct absorptions
e	2	Base Line :- 3700-3200, 1725, 1450, 1370, 760
B5-a	1	No distinct absorptions
b	1	1730
c	1	1785, 1720, 1680
d	2	3010, 2980, 2940, 2880, 1715, 1630, 1465, 1440, 1380, 1370, 1290, 1260, 1105, 870, 845, 765, 665
e	1	1750-1680 (broad)
f	2	1750, 1710
g	1	3700-3200, 1800-1650 (broad).

TABLE C

Band	Weight (mg)	I.R. Data (cm^{-1}) (Major absorptions)
1	160	3080, 3040, 2970, 2940, 2890, 1780, 1730, 1600, 1455, 1380, 1220, 1160, 1070, 1045, 760, 750
2	523	3080, 3040, 2970, 2940, 1780, 1730, 1475, 1455, 1380, 1220, 1160, 1120, 1070, 1045, 820, 765, 745
3	54	3070, 3040, 2970, 2940, 1780, 1730, 1670, 1480, 1455, 1375, 1220, 1170, 760
4	200	3700-3200, 3080, 2980, 2940, 2880, 1780, 1730, 1670, 1450, 1375, 1220, 1170, 755
5	385	Base Line :- 3700-3200, 3070, 2980, 2940, 2880, 1725, 1450, 1380, 1260, 1215, 1655, 1620, 760.

TABLE C (contd.)

Band	T.L.C. No. of Spots	I.R. Data (cm^{-1}) (Major absorptions)
1-a	3	No distinct absorptions
b	3	3050-2850, 1780, 1730, 1455, 1370, 1360, 1220, 1160, 770, 745
c	3-4	Base Line :- 3600-3300, 3000-2850, 1725
2-a	1	3100-2850, 1780, 1730, 1485, 1455, 1320, 1220, 1170, 770, 750
b	3-4	Base Line :- 3700-3300, 3100-2800, 1780, 1725, 1455, 1380, 1215, 1170, 760
3-a	1	1730
b	1	1730
c	1	1730
d	2	No distinct absorptions
e	2	No distinct absorptions
4-a	2	1725
b	1	1780, 1730, 1670, 1455, 1370, 1220, 1165, 755
c	2	1780, 1730, 1670, 1455, 1435, 1325, 1330, 1250, 1220, 1160, 1115, 1010, 885, 830, 755
d	2-3	Base Line :- 3700-3300, 3100-2800, 1725, 1450, 1385, 760.

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