SOME STUDIES IN

CARBOCYCLIC CHEMISTRY

by

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A Doctoral Thesis
Submitted in partial fulfilment of the requirements
for the award of

Doctor of Philosophy of the Loughborough University of Technology

February 1977

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SUMMARY

The work described in this thesis forms part of an attempt to understand some of the factors controlling the acid-catalysed rearrangements of 1-methoxybenzobarrelenes.

A review is presented in chapter one of the important features of the rearrangement-chemistry of dibenzo- and benzo-barrelenes. The commonly observed interconversion of the bicyclo[2.2.2]octadien-2-yl and bicyclo[3.2.1]octadien-2-yl cations is discussed in detail and finally some of the extensive rearrangements of highly substituted benzobarrelenes are presented to illustrate the more subtle aspects of the rearrangements.

Chapters two, three and four deal with the preparation and acid-catalysed rearrangement of 1-methoxy-1-[^{14}C]tetrachlorobenzobarrelene and with the degradation and assay of the major rearrangement product, x-[^{14}C]tetrachlorobenzobarrelenone.

Chapter two describes the synthesis of 1-[^{14}C]anisole; the conventional methods for the synthesis of 1-[^{13}C]- or 1-[^{14}C]-anisole are critically discussed and three alternative procedures are proposed.

Chapter three is introduced by a brief survey of the cycloaddition reactions of arynes with arenes and the contemporaneous conversion of anisoles into both benzobarrelenones and 1-methoxybenzobarrelenes is reviewed in greater detail. The cycloaddition reactions of 1-methoxytetrachlorobenzobarrelenes with 3,6-di-(2′-pyridyl)-s-tetrazine, coumalic acid, or p-nitrophenyl azide, and the reactions of tetrachlorobenzobarrelenones with phenyl Grignard reagent give products which fragment under mild conditions to give naphthalenes and 3,6-di-(2′pyridyl)-pyridazines, benzoic acids, 1-(p-nitrophenyl)-triazoles, or acetophenones respectively. The cycloadditions

of tetrachlorobenzyne to arenes followed by application of the addition-fragmentation sequences to the cycloadducts are proposed as a useful new method for analysis of the isotopic distribution within isotopically labelled arenes.

Chapter four describes the preparation from 1-[^{14}C]anisole of 2-[^{14}C]tetrachlorobenzobarrelenone and 1-methoxy-1-[^{14}C]tetrachlorobenzobarrelene, the rearrangement of this last compound to x-[^{14}C]tetrachlorobenzobarrelenone, and the degradation of the two radiolabelled benzobarrelenones to 1,2,3,4-tetrachloronaphthalene and acetophenone (and subsequently, to benzoic acid and iodoform). The results from this ^{14}C-tracer study of the rearrangement indicate that the C-2 of tetrachlorobenzobarrelenone is derived entirely from C-1 of 1-methoxytetrachlorobenzobarrelene.

The acid-catalysed rearrangements of 2- and 3-methyl- and of 2,5-dimethyl-1-methoxytetrachlorobenzobarrelenes are described in chapter five. The rearrangements of 2- and 3-methyl-1-methoxytetrachlorobenzobarrelenes are governed by the regioselective protonation of the olefinic bonds. Initially, this regioselectivity is dominated by the influence of the methyl-substituents, but as the acidity of the reaction medium increases, the tendency to form cations remote from the (probably protonated) methoxy-group becomes important. Rearrangement of 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene shows that, in addition to these factors, the presence of the extra methyl-group promotes further rearrangement by stabilising additional carbocations formed by secondary rearrangements.

ACKNOWLEDGEMENTS

I would like to thank Dr. H. Heaney for his help and guidance at each stage of this work, and Dr. D. J. H. Smith for his encouragement and understanding during the protracted preparation of this thesis.

I am indebted to the Science Research Council for financial support and for spectroscopic services through the P.C.M.U., and to my wife for financial support and for her forceful insistence that life may be chemistry but chemistry is not life.

Finally, I must record my pleasure and amazement at the success with which Miss. V. Orson-Wright has managed to transform so unusual a manuscript into such an excellent typescript.

CONTENTS

CHAPTER ONE

The Rearrangement Reactions of Benzo- and Dibenzo-bicyclo[2.2.2]octadien-2-yl Cations

Introduction

The chemistry of bicyclo-octanes is bedevilled by skeletal rearrangements[1] which increase in complexity as the degree of unsaturation and the cation lifetime are increased.[2] Some of these rearrangements are extremely subtle and are only detected in optically active[3] or isotopically labelled[2a] compounds, whilst others are immediately apparent by the gross change in molecular structure which they produce.[2b]

The availability of several rearrangement pathways which differ only slightly in the activation energy which they require greatly restricts the range of conditions over which one rearrangement may be studied. An added complication is the difficulty with which product distribution and kinetic data may be disected into their components when more than one mechanism is operating. This difficulty is often compounded by an inability to probe the steric and electronic requirements of the reaction in an unambiguous manner.

However, replacement of one or more of the olefinic linkages by benzene rings removes some of these difficulties. The resistance of the benzene ring to perturbation raises the activation energy of those rearrangement pathways along which its aromaticity would be reduced. Some processes will be completely inhibited inside the normal range of conditions, notably those which give products in which one of the degrees of unsaturation has been converted from an olefinic linkage to a cyclopropane ring.[4] Moreover, those pathways which do remain in operation may be investigated by a study of the effect of varying the benzene ring substitution pattern.

A study of the rearrangements of benzo- and dibenzo-bicyclooctadienyl cations should provide valuable insight into the mechanisms of some of the simpler processes occurring in the various bicyclooctadienyl cations.

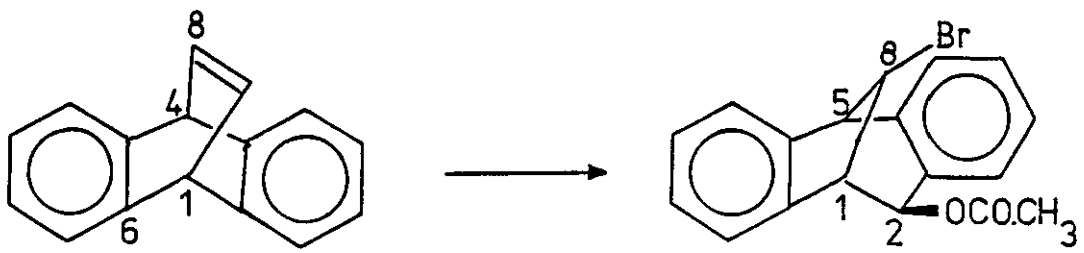
This short review will deal with those cations which are accessible

from benzo- and dibenzo-bicyclo[2.2.2]octadien-2-yl systems or their simple derivatives. The dibenzobicyclo[2.2.2]octadien-2-yl system is comparatively well understood at least at a descriptive level, for which we are indebted almost completely to the extensive work of Cristol's group.[5] The chemistry of this system is relatively simple and serves as an introduction to the more complicated rearrangements encountered in benzobicyclo[2.2.2]octadien-2-yl cation chemistry which have been described by Tanida,[6] Hart,[7] Barkhash,[8] and Heaney[9] and their respective groups. The work of Tanida, Barkhash and Hart will be discussed in the second section of this review; the published results of the Loughborough group are so directly relevant to the work described in chapters four and five, that they are introduced when appropriate in these chapters.

Dibenzobicyclo[2.2.2]octadien-2-yl Cations

Reactions in which dibenzobicyclo[2.2.2]octadien-2-yl cations might be expected to be formed often give products which arise by rearrangement of the carbon skeleton.[5,10]

Addition of some electrophilic reagents to dibenzobicyclo[2.2.2]-octatriene (I-1) under mild conditions gives products with the rearranged dibenzobicyclo[3.2.1]octadien-2-yl system.[5a-d] The reaction exhibits two remarkably stereospecific features: it is the aryl-C-1 bond positioned anti to the attacking electrophile which migrates and it is from the face of the cation which is anti to the migrating aryl-C-1 bond that nucleophilic capture of the cationic intermediate occurs. The reaction is illustrated in Scheme I-1 for the addition of acetyl hypobromite to dibenzobicyclo[2.2.2]octatriene (I-1) to produce exo-2-acetoxy-syn-8-bromodibenzobicyclo[3.2.1]octadiene (I-2).[5b]

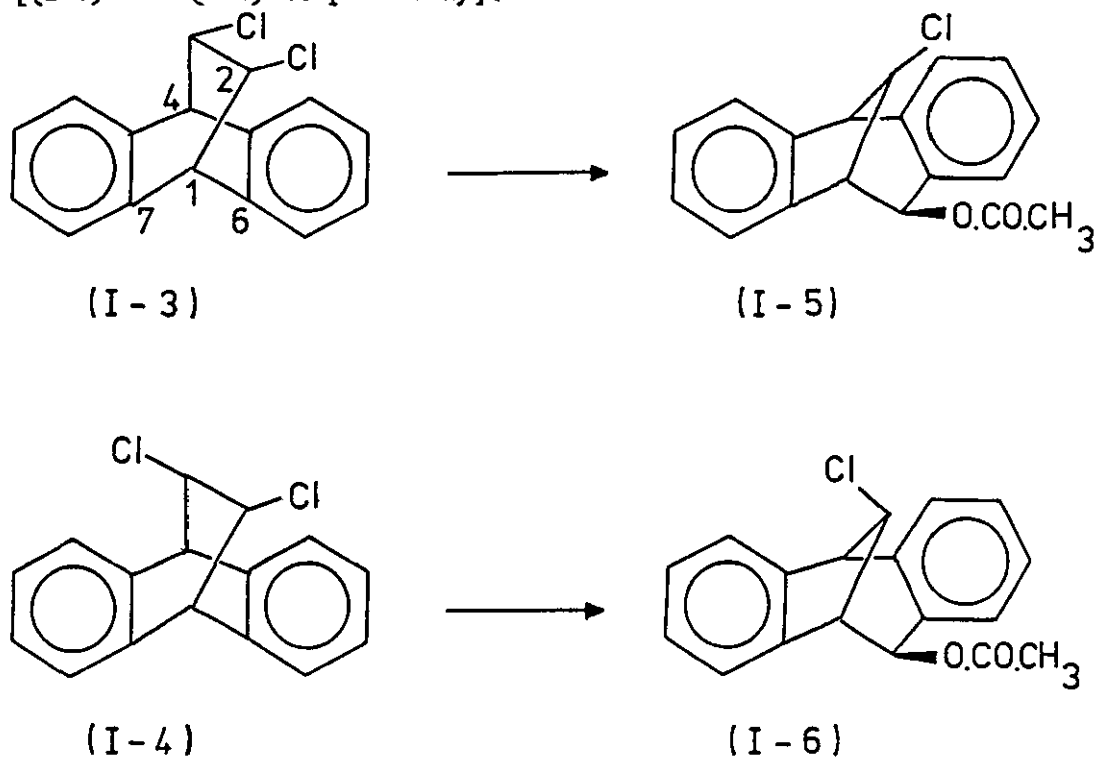


(I-1) (I-2)

Scheme I-1

Solvolysis of dibenzobicyclo[2.2.2]octadien-2-yl derivatives is equally stereospecific: the displaced group departs from and the nucleophile approaches, the face of the cation remote from the migrating aryl-C-1 bond. This is illustrated in Scheme I-2 for the silver acetate induced acetolysis of cis- and trans- 2,3-dichlorodibenzobicyclo[2.2.2]octadiene

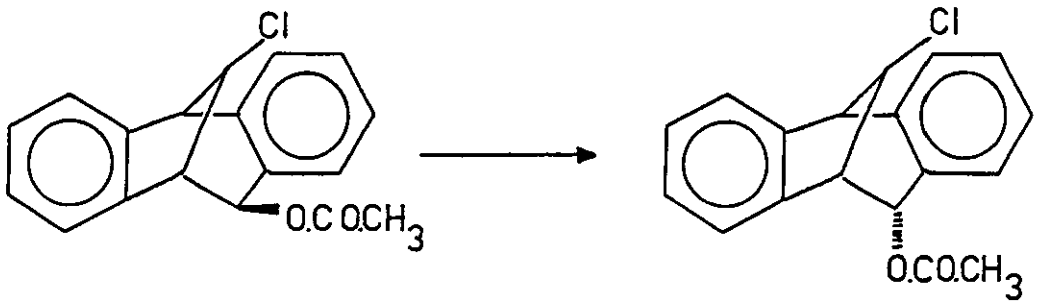
[(I-3) and (I-4) respectively].[5b]



Scheme I - 2

Consideration of similar rearrangements led Vaughan[10a] and co-workers to suggest that the driving force behind the rearrangement of dibenzobicyclo[2.2.2]octadienes to dibenzobicyclo[3.2.1]octadienes might be the presumed greater stability of the latter ring system. The question of whether these rearrangements are proceeding under thermodynamic or kinetic control is easily resolved. Perchloric acid catalysed acetolysis of dibenzobicyclo[3.2.1]octadien-exo-2-yl derivatives results in extensive epimerisation to the corresponding -endo-2-yl derivatives.[5e] This reaction is illustrated in Scheme I-3.

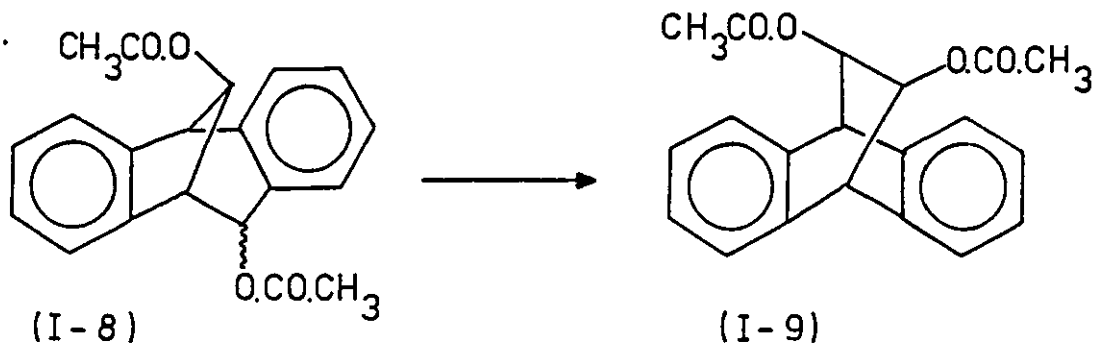
It is apparent that the isolation of dibenzobicyclo[3.2.1]octadien-exo-2-yl derivatives is due to kinetic rather than thermodynamic factors. This observation is reinforced by the results of perchloric acid catalysed



(I-5) (I-7)

Scheme I-3

acetolysis at ca. 80° of several 2-acetoxy-anti-8- or 8-unsubstituted-dibenzobicyclo[3.2.1]octadienes: the acetolysis proceeded with rearrangement to give 2-acetoxy-trans-3- or 3-unsubstituted-dibenzobicyclo[2.2.2]-octadienes,[5e] illustrated in Scheme I-4.



(I-8) (I-9)

Scheme I-4

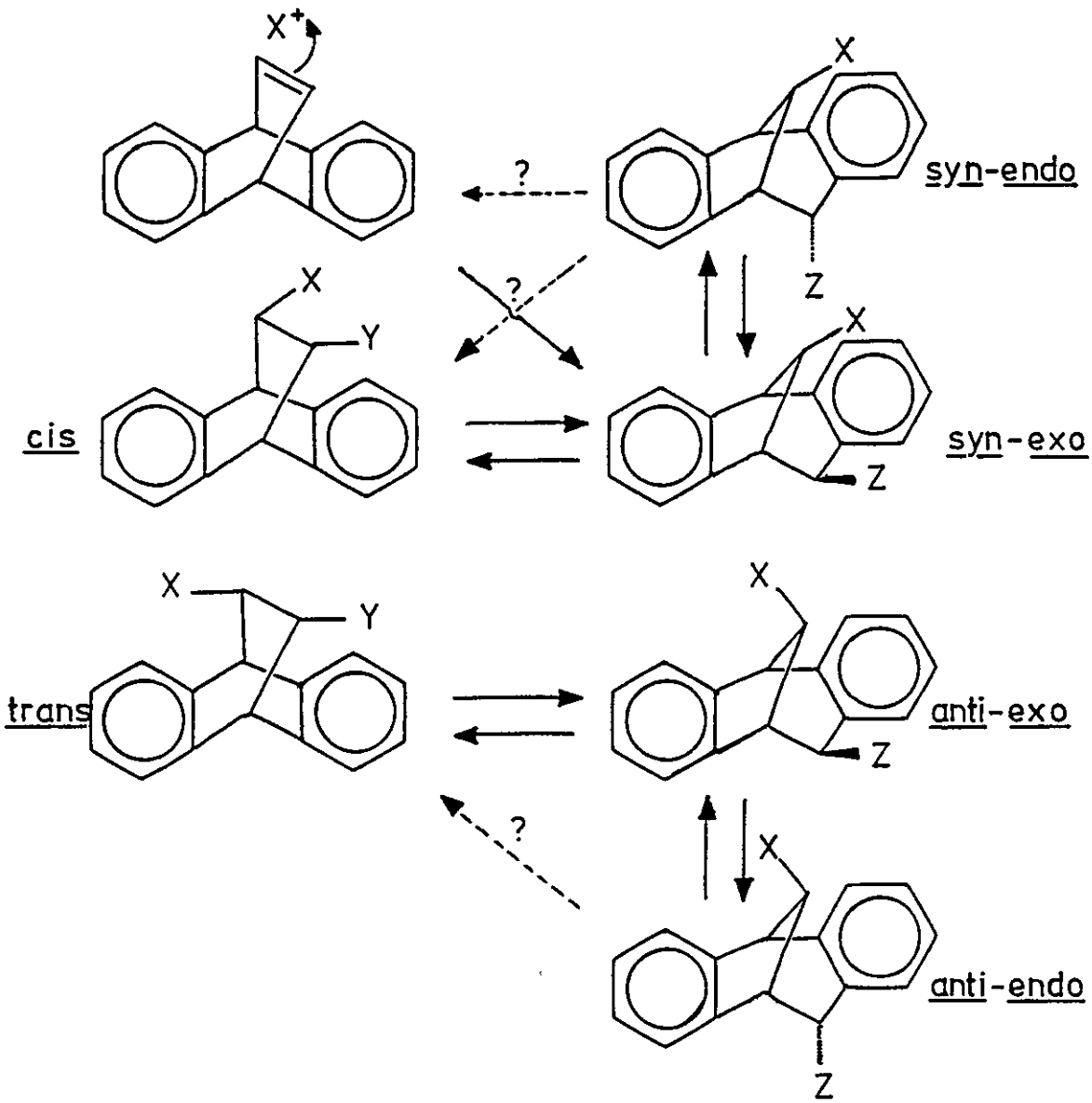
This rearrangement is also stereospecific and is the reverse of the solvolysis reaction illustrated in Scheme I-2. Some syn-8 epimers solvolyse by a different mechanism which will be discussed later.

The solvolysis results may be summarised: trans-2,3-disubstituted-dibenzobicyclo[2.2.2]octadienes solvolyse under kinetic control to give anti-8-exo-2-disubstituted-dibenzobicyclo[3.2.1]octadienes which epimerise

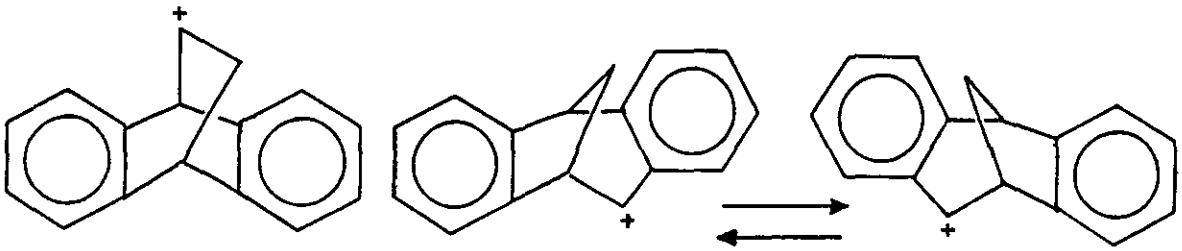
slowly to the more stable anti-8-endo-2-disubstituted-dibenzobicyclo-[3.2.1]octadienes. These in turn rearrange slowly to give trans-2,3-disubstituted-dibenzobicyclo[2.2.2]octadienes. The overall process is one of substitution with retention of configuration, and the steps trans-[2.2.2] → anti[3.2.1] → trans[2.2.2] are characterised by a very high degree of stereospecificity. The analogous cis[2.2.2] → syn[3.2.1] → cis-[2.2.2] pathway is also highly stereospecific, and may also be entered by electrophilic addition to dibenzobicyclo[2.2.2]octatrienes (Scheme I-5).

The stereospecificity of these reactions cannot be understood in terms of a planar dibenzobicyclo[2.2.2]octadien-2-yl cation (I-10). It is clear that no intermediates or transition states with the symmetry of this cation are involved. In this way, the equilibrating benzyl cations [(I-11) and (I-11a)] may be excluded. The presence of a stable benzyl cation is acceptable and provides a plausible intermediate in the interconversion of exo-2- and endo-2-substituted-dibenzobicyclo[3.2.1]octadienes (cf. Scheme I-3). Indeed there is some evidence to suggest that formation of quasiaxial bonds is more rapid than formation of quasiequatorial bonds in collapse of cations of this type,[3] and so the benzyl cation (I-11) could be a precursor of the kinetically favoured dibenzobicyclo[3.2.1]-octadien-exo-2-yl derivatives (cf. Schemes I-1 and I-2).
Moreover, the stereospecific formation of this cation (I-11), by whatever mechanism, requires by the principle of microscopic reversibility that this cation (I-11) could be a stereospecific precursor of the dibenzobicyclo[2.2.2]octadien-2-yl system (cf. Scheme I-4).

The results previously described require the intermediacy of the dibenzobicyclo[3.2.1]octadien-2-yl cation (I-11) but do not require any other cations as intermediates. How is it formed? The stereospecific reaction suggests participation by an aryl ring in the ionisation of



Scheme I-5

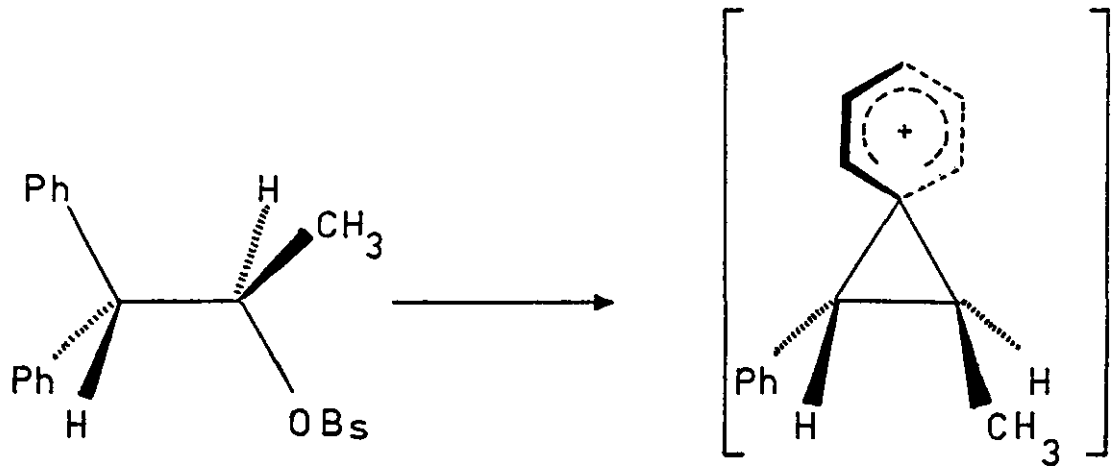


(I-10) (I-11) (I-11a)

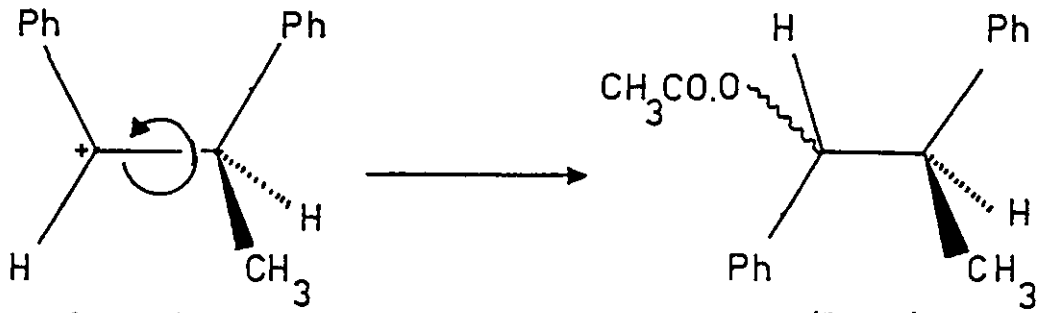
dibenzobicyclo[2.2.2]octadien-2-yl derivatives or in the addition of electrophiles to dibenzobicyclo[2.2.2]octatrienes. This type of behaviour is typical of β-arylethyl systems and leads to bridged phenonium ions.[11] However, whereas the bridged phenonium ions derived from secondary α-alkyl β-arylethyl systems appear in general to be stable product determining intermediates, those from secondary α,β-diarylethyl systems appear in general to be unstable with respect to open (that is, unbridged) benzyl cations.

Thus, although 1,1-diphenyl-2-propyl brosylate (I-12) rearranges on acetolysis by phenyl migration through what is probably a phenonium ion intermediate, the products are derived from the open benzyl cation (I-13): the chiral centre of the brosylate (I-12) undergoes clean inversion of configuration, but the capture of the benzyl cation (I-13) is not stereospecific, and both diastereoisomers of optically pure 1,2-diphenyl-1-propyl acetate (I-14) are obtained (Scheme I-6).[12]

Although the formulation of a bridged phenonium ion (I-15) as an intermediate is attractive in as much as it concisely explains the product stereochemistry, its stability must be in doubt. If, as seems probable,



(I-12)

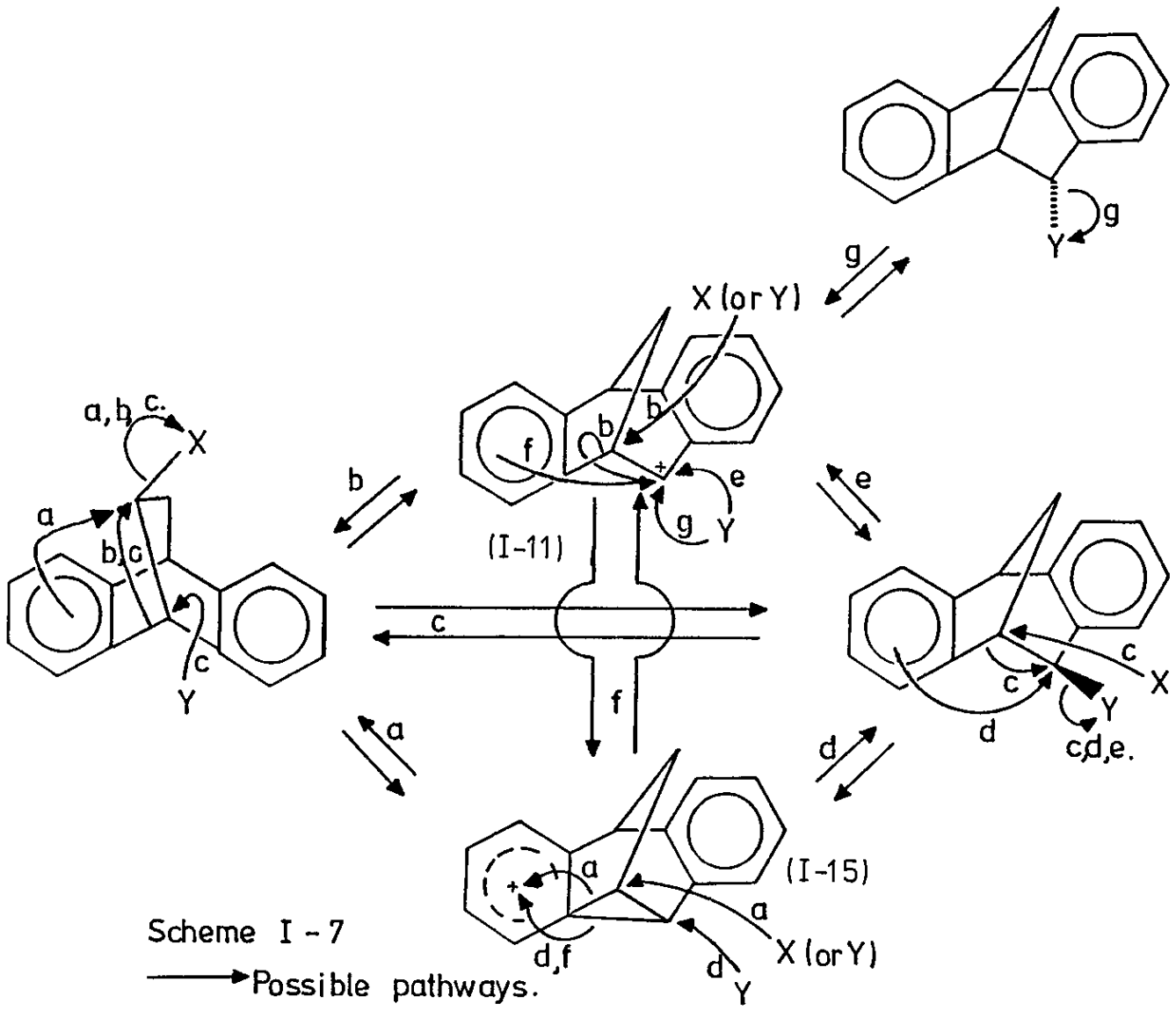


(I-13) Scheme I-6 (I-14)

the nucleophilic capture of the dibenzobicyclo[3,2,1]octadien-2-yl cation (I-11) is kinetically favoured from the exo- or quasiaxial- direction, the presence of this benzylic cation (I-11) adequately explains the rearrangement stereochemistry. The transition state for dibenzobicyclo-[2.2.2]octadien-2-yl derivative formation must be energetically quite close to the dibenzobicyclo[3.2.1]octadien-2-yl cation, for the two systems readily inter-convert.

A summary of the probable mechanistic steps is given in Scheme I-7. The nucleophile assisted bond migration is analogous to the solvent assistance to ionisation which is so important in primary and most secondary systems.[13] Cristol denotes this assisted migration as a geitono-desmic reaction.[14]

An attempt has been made to probe the electronic requirements of the

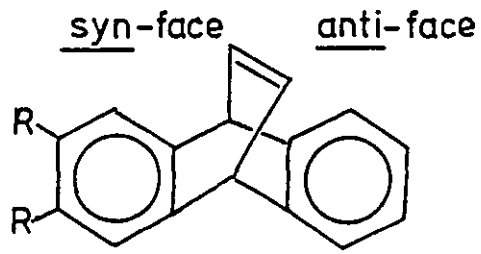


Scheme I - 7

→ Possible pathways.

rearrangement transition state by varying the substitution pattern of one of the aromatic rings.[5d] It was argued that if the transition state resembled an open benzyl cation, the aryl ring which would least stabilise such a cation (i.e. the more electron deficient ring) would migrate preferentially. On the other hand, if the transition state resembled a phenonium ion, the aryl ring which would most readily form such an intermediate (i.e. the more electron rich ring) would migrate preferentially.

This approach would fail however in the case of electrophilic addition to dibenzobicyclo[2.2.2]octatrienes if it were found that the nuclear substitution controlled the direction of approach of the electrophile. The dichloro- and dimethyldibenzobicyclo[2.2.2]octatrienes [(I-16) and (I-17)] were prepared and treated with mild electrophiles under conditions in which skeletal rearrangement is not observed. It was found that treat-



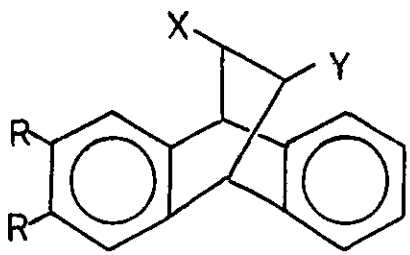
R = Cl ; (I-16)

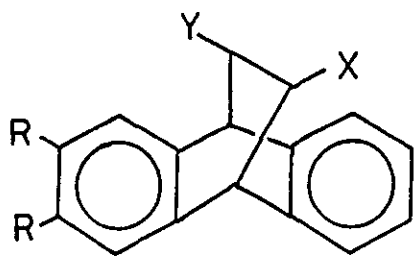
R = CH_3 ; (I-17)

ment of the dichlorodibenzobicyclo[2.2.2]octatriene (I-16) with diborane, followed by oxidation gave equal amounts of the syn- and anti-alcohols [(I-18) and (I-19)]. Similarly, treatment of the dimethyldibenzobicyclo-[2.2.2]octatriene (I-17) separately with diborane followed by oxidation, with benzenesulphenyl chloride, with mercuric acetate followed by reduction, and with the Prevost reagent ("acetyl hypoiodite", from iodine and silver

acetate) gave in each case equal amounts of the products of syn- and anti- electrophilic attack [(I-20) and (I-21), (I-22) and (I-23), (I-24) and (I-25), and (I-26) and (I-27)].

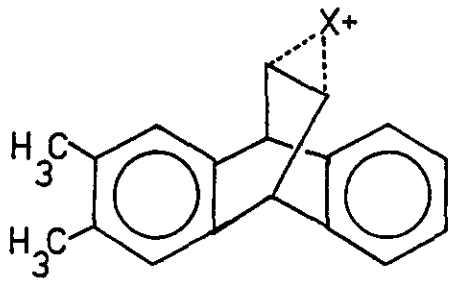
These results indicate that the remote methyl- or chloro- substituents do not influence the direction from which electrophiles approach the olefinic linkage. If this is so, not only are significant steric effects absent, but also the influence of the remote nuclear substituents on the electronic ground state of the double bond appears to be negligible. It is of interest to note that the addition of benzenesulphenyl chloride and "acetyl hypoiodite" to the olefin (I-17) did not lead to rearrangement. These two reactions, which are thought to proceed via cyclic "onium" ions [(I-28) and (I-29) respectively], demonstrate that the C-2 can carry a fair amount of positive charge before aryl migration occurs.





	R	X	Y	
(I-18)	Cl	OH	H	(I-19)
(I-20)	CH_3	OH	H	(I-21)
(I-22)	CH_3	PhS	Cl	(I-23)
(I-24)	CH_3	$OCOCH_3$	H	(I-25)
(I-26)	CH_3	I	$OCOCH_3$	(I-27)

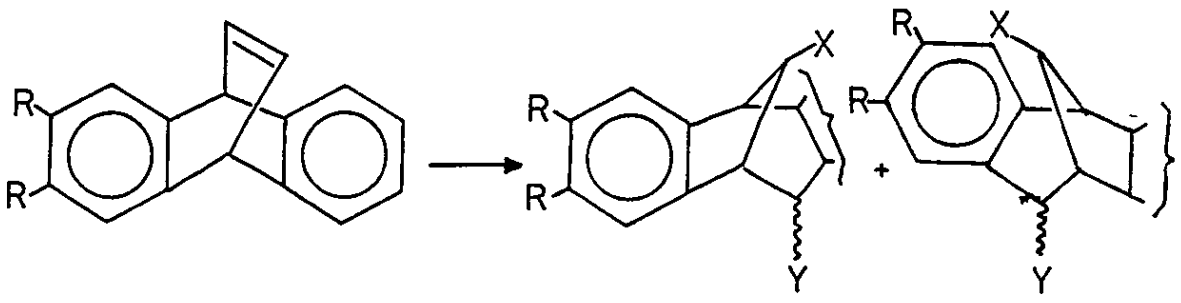
The addition of more powerful electrophiles caused rearrangement. In each case migration of the more electron rich aryl group was preferred. The results obtained by Cristol and co-workers are set out in Table I-1.[5d]



X = PhS ;(I-28)

X = I ;(I-29)

By taking the ratio of the products A and B as the ratio of the rates of migration of the two aryl groups and applying Hammett's linear free energy relationship, a linear correlation between log (rate ratio) and the composite substituent parameter ($\sigma_m^+ + \sigma_p^+$) was obtained. The reaction constants (ρ) were found to be -0.90, -0.67, -0.65 and -0.79 for the addition of bromine, chlorine, hydrogen bromide and acetic acid respectively. These are very low negative values;[11] they have been interpreted to mean that the amount of charge delocalisation into the aryl rings in the transition state is small. Indeed, they are so low as to indicate only a very weak interaction of the carbonium centre and the aryl ring, and to the impartial observer such reaction constants might be regarded as damning evidence that the concept of bridging in the transition state was wrong. There are however two minor criticisms to make of Cristol's treatment of these data. Firstly, it is not always appropriate to regard the sum of the reaction parameters ($\sigma_m^+ + \sigma_p^+$) as a measure of their influence on reactions when they are both present on the aromatic ring, particularly when they are adjacent to one another. Secondly, the reaction constant ρ is a composite reaction constant. It may be treated as a linear combination of ρ_I, which represents the influence on the rate of



A B

Substituents			Structure Type		Ratio
R	X	Y	A	B	A : B
Cl	Br	Br	1-30	1-31	1 : 3.0
Me	Br	Br	1-32	1-33	2.1 : 1
Cl	Cl	Cl	1-34	1-35	1 : 2.3
Me	Cl	Cl	1-36	1-37	1.7 : 1
Cl	H	Br	1-38	1-39	1 : 2.1
Me	H	Br	1-40	1-41	1.8 : 1
Cl	H	OAc	1-42	1-43	1 : 2.5[(a)]
Me	H	OAc	1-44	1-45	2.0 : 1 [(a)]

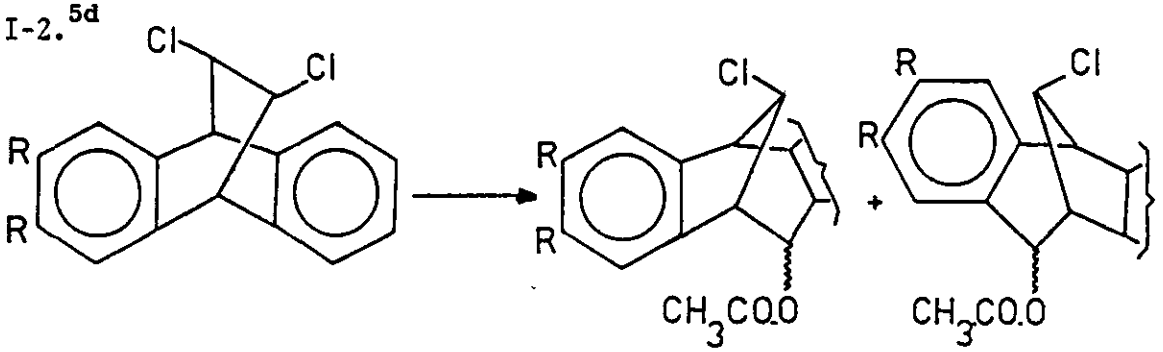
Table I-1

(a) The dibenzobicyclo[3.2.1]octadien-2-ol acetates [(1-42) to (1-45)] are unstable and rearrange to dibenzobicyclo[2.2.2]octadien-2-ol acetates (cf. Scheme I-4). As this rearrangement was reported to be stereospecific the ratio of anti- to syn- dibenzobicyclo-[2.2.2]octadien-2-ol acetates was taken as a good measure of the ratio A:B.

migration of substituents on the migrating benzo-ring, and ρ_2, which represents the influence on the rate of migration of substituents on the non-migrating benzo-ring, (see Appendix I).

This treatment takes into account an enhancement in the rate of migration of the unsubstituted ring caused by the substituents in the non-migrating ring. As the ρ_2 value will also be negative it is clear that the observed reaction constant ρ will be less negative than the true ρ value, ρ_1, for the migration of a substituted as opposed to an unsubstituted benzo-ring. The disection of the composite ρ into its components would be an interesting exercise which should provide more information about the nature of the rearrangement transition state.

Similar results were obtained in the solvolysis of the trans-dichlorides [(I-48), (I-4), and (I-49)]. The results are collected in Table I-2.[5d]



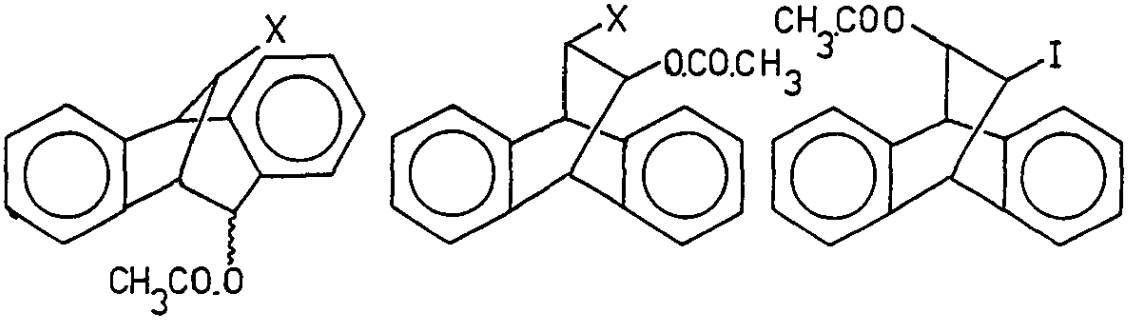
	R	A	B	Ratio A : B
(I-48)	Cl	(I-50)	(I-51)	1 : 8
(I-4)	H	(I-6)+2-epimer		1 : 1
(I-49)	CH_3	(I-52)	(I-53)	5 : 1

Table I-2

Cristol again treated these results by correlating the logarithm of the product ratio with $(\sigma_m^+ + \sigma_p^+)$ and obtained a reaction constant (ρ) of -1.8. This result taken at face value would indicate a small but significant degree of charge delocalisation into the benzo-ring in the

rearrangement transition state; again it would be interesting to resolve this composite constant into its components.

It was noted earlier that the isomerisation of some syn-8-substituted-dibenzobicyclo[3.2.1]octadien-2-yl derivatives to 2,3-disubstituted-dibenzobicyclo[2.2.2]octadienes proceeds anomalously.[5e] The anti-8,2-disubstituted-dibenzobicyclo[3.2.1]octadienes isomerise during perchloric acid catalysed acetolysis to trans-2,3-disubstituted-dibenzobicyclo[2.2.2]octadienes, as shown in Scheme I-4. The syn-8-analogues would be expected to give the corresponding cis-2,3-disubstituted-dibenzobicyclo[2.2.2]octadienes. 2-Acetoxy-syn-8-chlorodibenzobicyclo[3.2.1]octadiene [(1-5) and (1-7)] was not converted to the expected product, cis-2-acetoxy-3-chlorodibenzobicyclo[2.2.2]octadiene (I-54), but was recovered as the endo-2-epimer (1-7). On the other hand, the cis-2,3-chloroacetate (I-54) was also recovered unchanged.



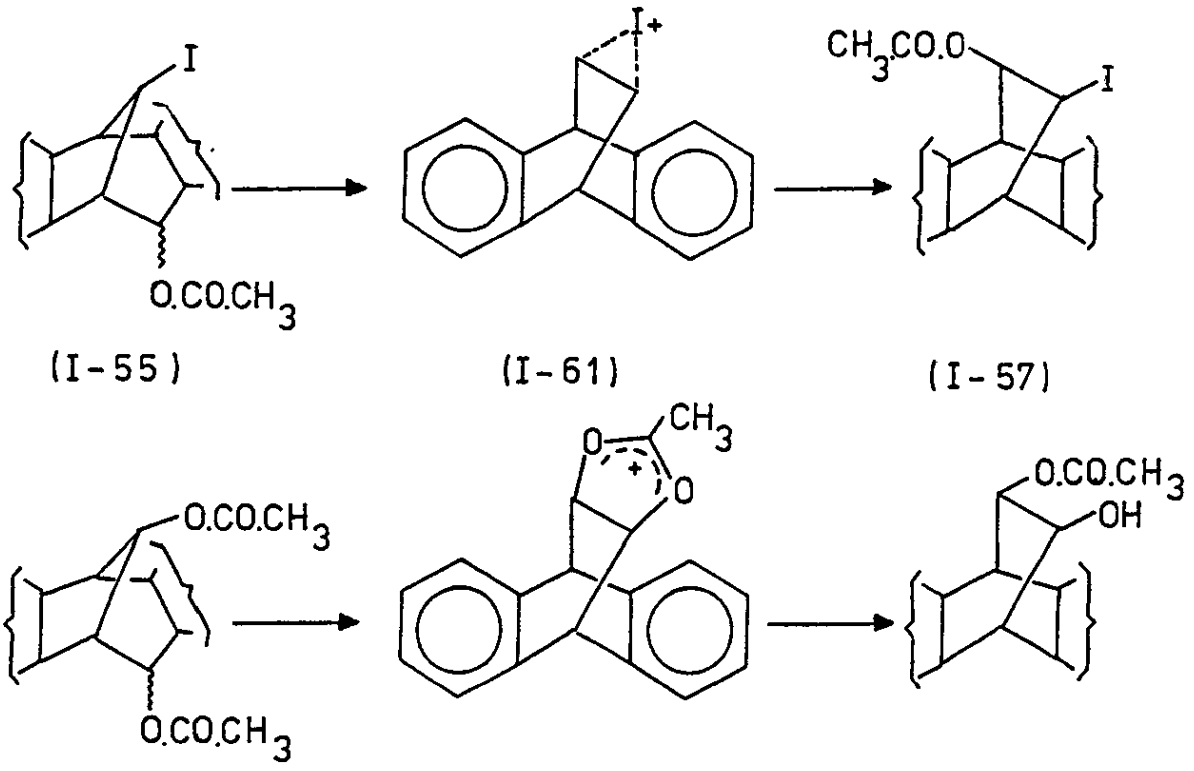
X			
Cl	(I-5)+(I-7)	(I-54)	(I-57)
I	(I-55)	(I-58)	
CH_3COO	(I-56)	(I-59)	
OH		(I-60)	

The inertness of the syn-chloroacetate is probably a kinetic rather than a thermodynamic effect and is attributed to steric hindrance of attack by the solvent on the incipient C-2 cation; an effect best described

as steric inhibition of geitonodesmicity. Support for this interpretation comes from the results of acetolysis of syn-8-iodo-2-acetoxy- and syn-8,2-diacetoxy-dibenzobicyclo[3.2.1]octadienes [(I-55) and (I-56)]. Both rearranged to 2,3-disubstituted-dibenzobicyclo[2.2.2]octadienes, but the products were not those expected by analogy to the anti-series. The syn-iodoacetate (I-55) gave trans-2-acetoxy-3-iododibenzobicyclo[2.2.2]octadiene (I-57) and not the expected cis-chloroacetate (I-58), and although the syn-diacetate (I-56) gave a product with cis-stereochemistry it was not the expected diacetate (I-59), but the monoacetate (I-60). These observations are consistent with product determining attack by the 8-syn-substituent on the incipient C-2 cation to give the iodonium and dioxolanium ions [(I-61) and (I-62)]. Similar iodonium ions are known to be stable with respect to rearrangement to dibenzobicyclo[3.2.1]octadienes,[5d] and it is probable that the dioxolanium ion (I-62) exhibits similar stability (Scheme I-8).

Such anchimeric exhaltation of geitonodesmic behaviour is not observed when the syn-8-substituent is deuterium. The rearrangements of syn-8-[^{2}H] dibenzobicyclo[3.2.1]octadien-2-yl-trifluoroacetate and bosylate [(I-63) and (I-64)] to dibenzobicyclo[2.2.2]octadien-2-yl derivatives proceeded with clean cis stereochemistry (Scheme I-9).[5c] Similarly, addition of deuterio-trifluoroacetic acid to dibenzobicyclo[2.2.2]octatriene (I-1) gives predominantly the cis-deuteriotrifluoroacetate (I-65) by double rearrangement.[5c] (It was not possible to measure the stereochemical purity to better than 80% cis but the trans-isomer was not detected.) The cis-deuterio-trifluoroacetate (I-65) was stable towards cis-trans-isomerisation under the conditions of its formation (ca. 20% trifluoroacetic acid in benzene, 50°).

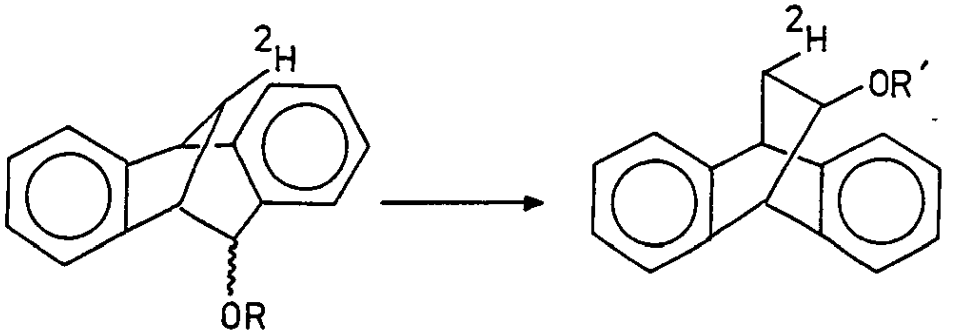
The addition of acetic acid is more difficult, and under the more



(I-55) (I-61) (I-57)

(I-56) (I-62) (I-60)

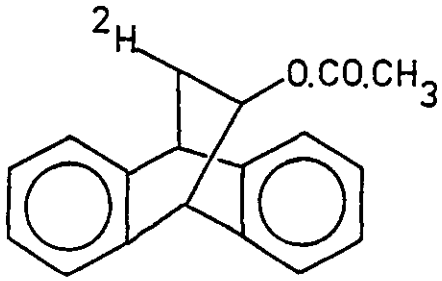
Scheme I-8



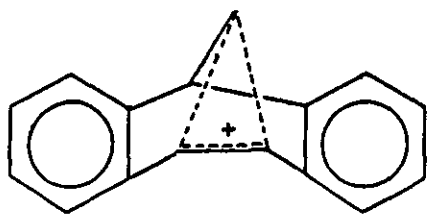
R		R'	
CF_3CO	(I-63)	⟶ CF_3CO	(I-65)
p-$CH_3C_6H_4SO_2$	(I-66)	⟶ CH_3CO	(I-67)

Scheme I-9

forcing conditions used (ca. 10% sulphuric acid in acetic acid, 80°) the stereospecificity was partly lost.[5f] After 10% reaction the product contained both cis- and trans-2-acetoxy-3[^{2}H]dibenzobicyclo[2.2.2]octadiene [(I-67) and (I-68)] in the ratio 86:14.



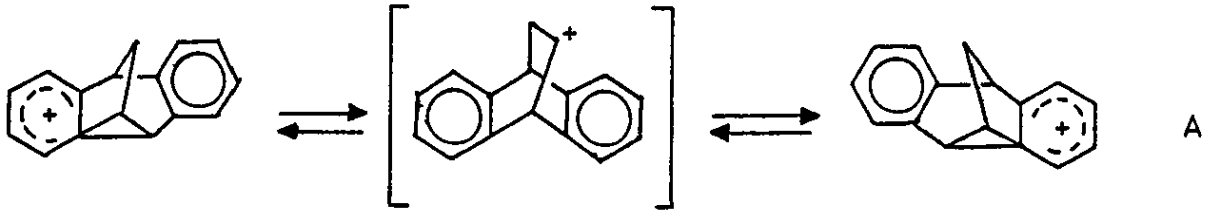
(I-68)



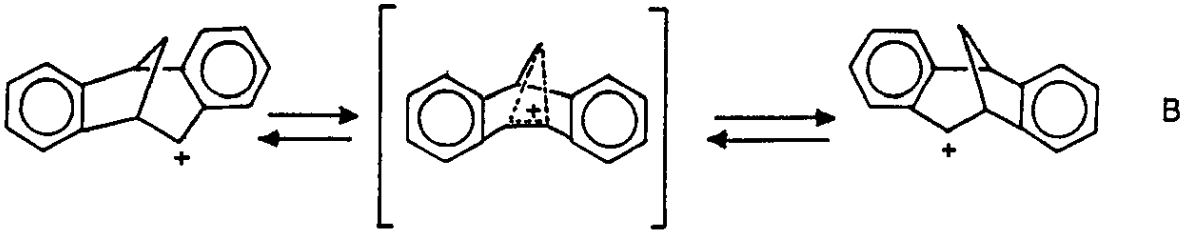
(I-69)

As the reaction proceeded to completion, the ratio decreased to 70:30. There is clearly a pathway by which cis- and trans-isomers of 2,3-disubstituted-dibenzobicyclo[2.2.2]octadienes may equilibrate. With 3-unsubstituted-dibenzobicyclo[2.2.2]octadien-2-yl derivatives this (in this case degenerate) isomerisation must occur through some symmetrical intermediate or transition state. The two likely candidates are the symmetrical dibenzobicyclo[2.2.2]octadien-2-yl cation (I-10) and the bridged cation (I-69). These cations may be transition states in the racemisation of the phenonium and dibenzobicyclo[3.2.1]octadien-2-yl cations [(I-15) and (I-11)] (Scheme I-10). Let the path A (Scheme I-10) or its equivalent in which the bridge changes orientation be called the bridge-flip mechanism, and the path B (Scheme I-10) or its equivalent in which the bridgehead and charge bearing carbon atoms exchange be called the bridgehead switch mechanism.

When racemic 2-acetoxy-2-[^{2}H]dibenzobicyclo[2.2.2]octadiene (I-70)



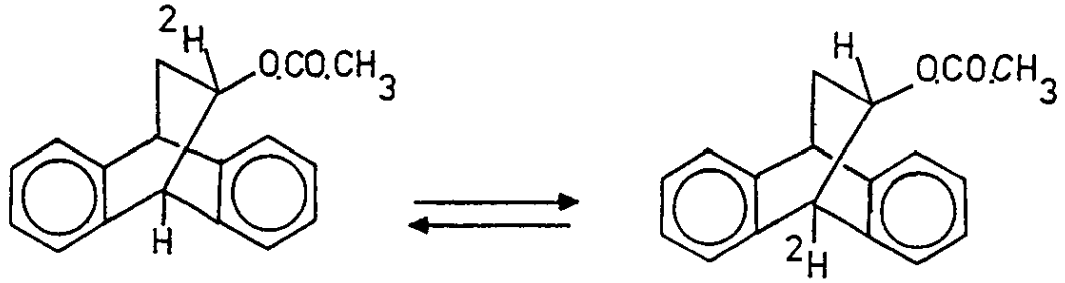
(I-15) (I-10) (I-15a) A



(I-11) (I-69) (I-11a) B

Scheme I-10

was heated at 85° in ca. 15% sulphuric acid in acetic acid it equilibrated slowly with 2-acetoxy-1-[^{2}H]dibenzobicyclo[2.2.2]octadiene (I-71) (Scheme I-10).[5f]



(I-70) (I-71)

Scheme I-11

The bridgehead switch mechanism was operating, but the equilibrium between the 1-[^{2}H]- and 2-[^{2}H]-isomers [(I-71) and (I-72)] was established more

slowly than that between cis- and trans-2-acetoxy-3-[^{2}H]dibenzobicyclo-[2.2.2]octadiene [(I-67) and (I-68)] under comparable conditions, and so another competitive mechanism is also operating.

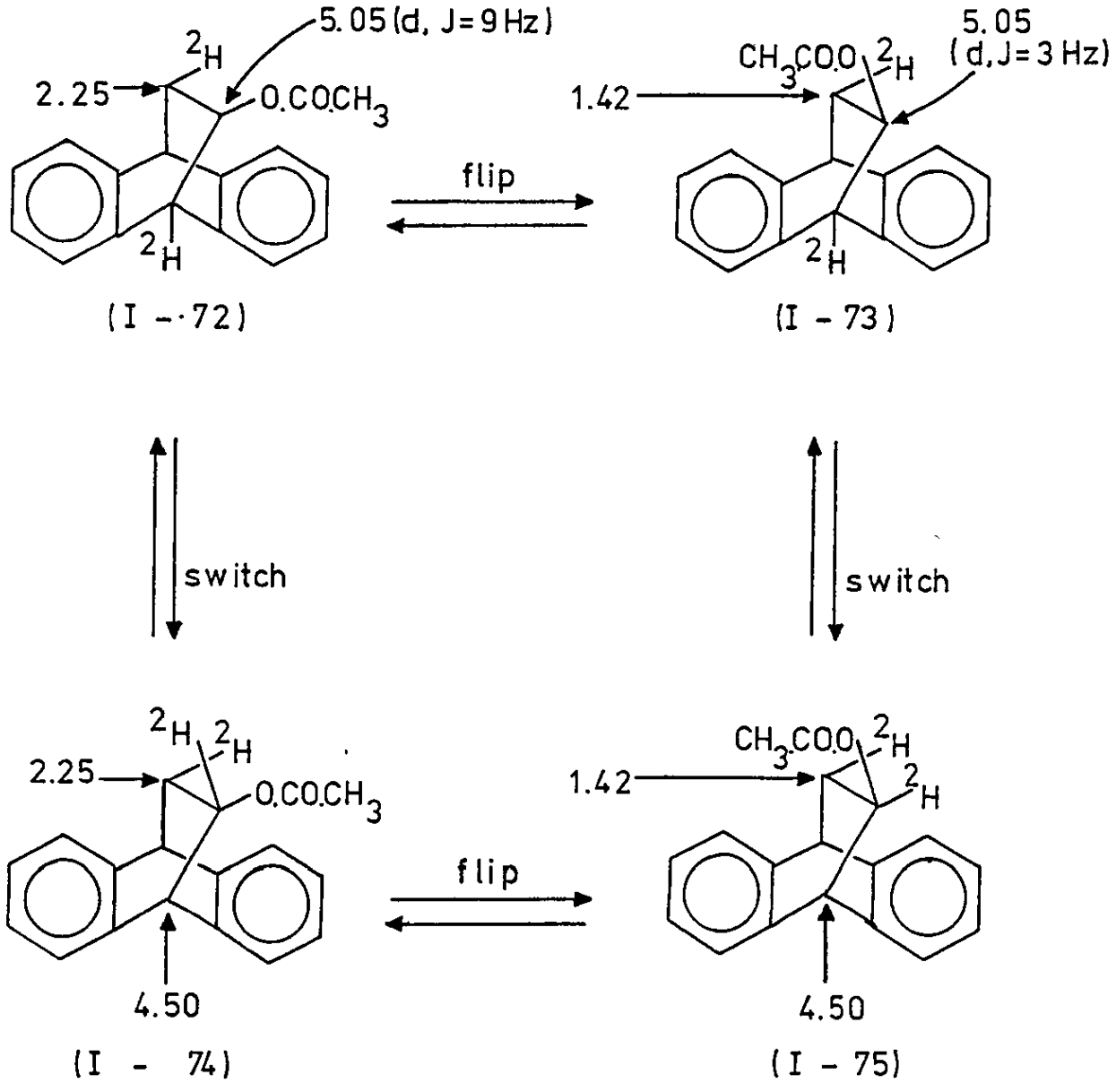
When cis-2-acetoxy-1,3-[$^2H_2$]dibenzobicyclo[2.2.2]octadiene (I-72) was equilibrated with 10% sulphuric acid in acetic acid at 80°, the formation of three additional dideuterioacetates [(I-73), (I-74) and (I-75)] was observed (Scheme I-12).[5f] The reaction was followed by monitoring the growth of signals at δ1.42 relative to δ2.25 and δ4.50 relative to δ5.05 in the ^{1}H n.m.r. spectrum. The results are presented in Table I-3.

Table I-3

Time (hr)	Ratio[(a)] 2.25 : 1.42	Ratio[(a)] 5.05 : 4.50
30	53 : 47	71 : 29
75	50 : 50	56 : 44

(a) Ratio of the intensities of signals at the chemical shifts indicated (δ) in the ^{1}H n.m.r. spectrum.

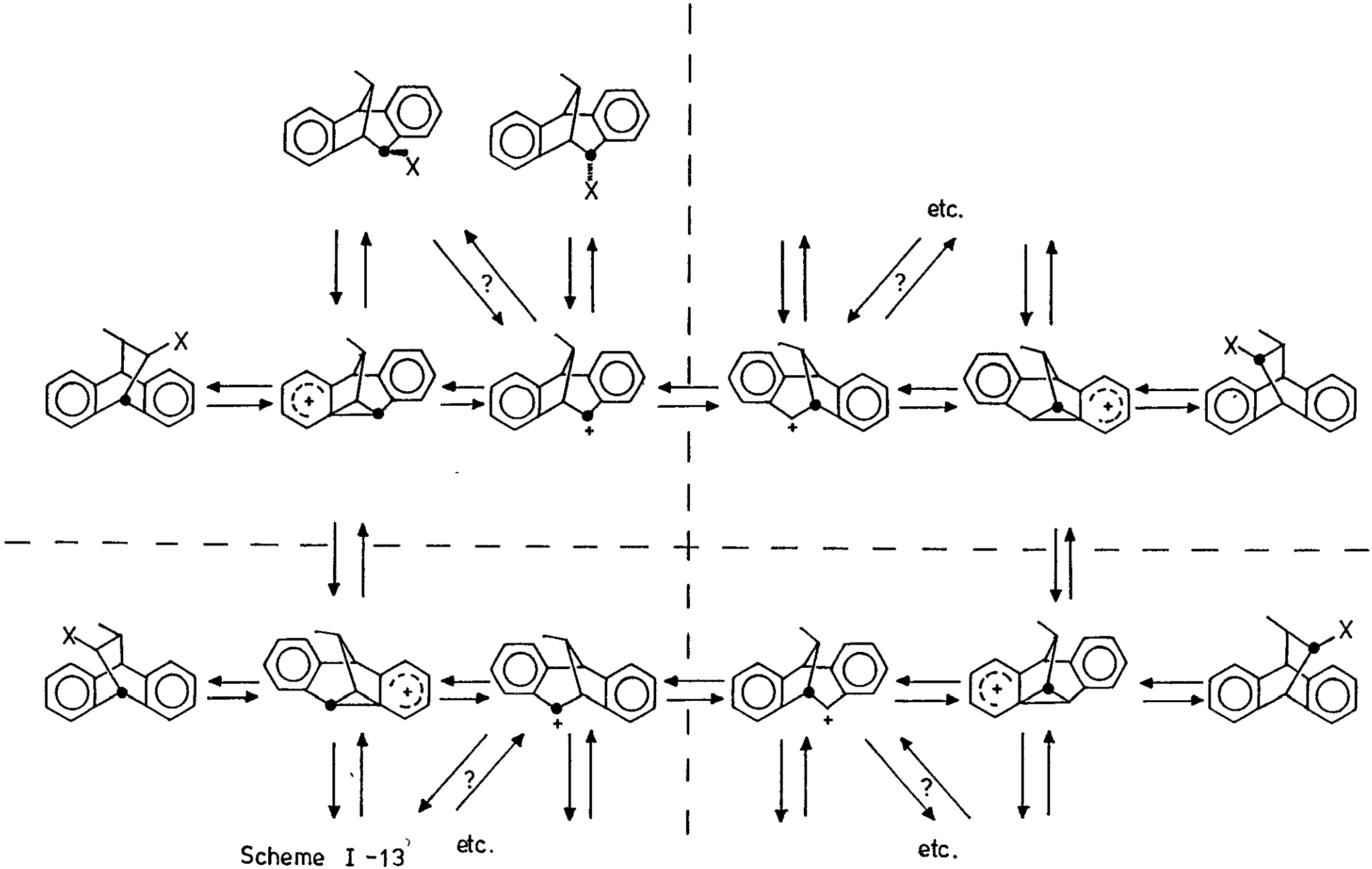
Cristol estimated that the rate of bridge flipping is about three times that of bridgehead switching.[5f] Recalculation of the relative rates for bridge flipping and bridgehead switching shows that bridge flipping occurs 3.28 times as fast as bridgehead exchange at 85° in a molar solution of sulphuric acid in acetic acid. (See Appendix for details of the calculation.)



Scheme I-12

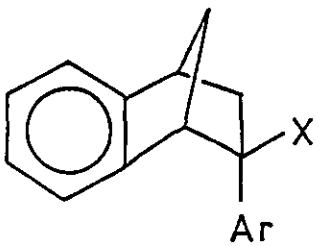
The chemical shifts (δ) of characteristic ^1H n.m.r. signals are shown.

The set of rearrangement pathways is shown in Scheme I-13. The phenonium ion (I-15) and the benzyl cation (I-11) are shown as the most likely intermediates, as they offer the best explanation of the stereochemical features of the rearrangements. The relative stability of these intermediates is difficult to assess. The clean stereochemistry of the rearrangements is consistent with a transition state for dibenzobicyclo-[2.2.2]octadien-2-yl-dibenzobicyclo[3.2.1]octadien-2-yl interconversion with a large degree of benzo-ring participation. Certainly, the incipient dibenzobicyclo[2.2.2]octadien-2-yl cation is sufficiently conformationally locked for stereospecific aryl migration to compete very efficiently with an inversion (racemisation) process. The interpretation of substituent effects on the reaction kinetics is not straightforward when the relative rates are estimated from product ratios. The observed value of ρ in the Hammett plot seems inconsistent with the stereochemical features of the reaction, and is far flatter than values of ρ observed by Tanida in the closely related solvolyses of benzobicyclo[2.2.1]hepten-2-yl[15] and benzobicyclo[2.2.2]octen-2-yl systems.[6b] This is another example of the rate-product quandry which has been such a stumbling block to the universal acceptance of phenonium ions as intermediates, which in this case will not be resolved until the effect of substituents on rates of rearrangement is measured. Whether the aryl participation persists in the first stable cation and, if so, to what extent, or the transition state relaxes without pause to the benzyl cation (I-11) is a subtle question. The phenonium ion (I-15) is an attractive intermediate, both in the stereospecific interconversion of dibenzobicyclo[2.2.2]- and dibenzobicyclo-[3.2.1]octadien-2-yl systems and in the degenerate isomerisation of dibenzobicyclo[2.2.2]octadien-2-yl systems by bridge flipping, but it is not required by the data. If the phenonium ion (I-15) is a stable intermediate

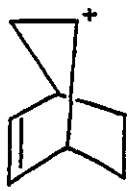


Scheme I -13

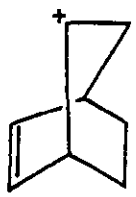
it is not likely to be symmetrically bridged. Results from related systems, particularly the 2-aryl-benzobicyclo[2.2.1]hepten-2-yl system (I-76)[16] indicate that benzo-bridging is not important in the ionisation transition state and so probably not in the ground state of the cation. The amount of bridging in αβ-diarylethyl cations is generally considered to be small.[11] This indicates that the benzyl cation (I-11) is probably the most stable of the intermediates present in the reaction mixture.



(I - 76)



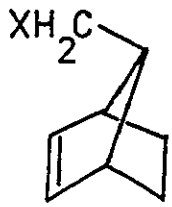
(I - 77)



(I - 78)

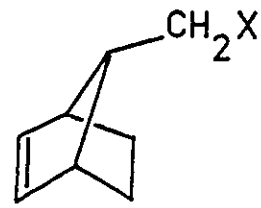
Another explanation of the reaction stereochemistry is possible. Berson has observed that when the bicyclo[2.2.2]oct-5-en-2-yl cation [(I-77) or (I-78)] is generated by rearrangement of syn- or anti-2-norbornenyl-7-carbinyl [(I-79) and (I-80)] derivatives, it is formed in a twisted conformation, and a second stereospecific rearrangement competes efficiently with interconversion of the two conformers through a planar cation.[17] It is possible to explain the stereospecific interconversion of the dibenzobicyclo[2.2.2]- and dibenzobicyclo[3.2.1]-octadien-2-yl systems in terms of a pair of interconverting unbridged cations: the preponderant, relatively stable benzyl cation (I-11) and the relatively unstable, unsymmetrical dibenzobicyclo[2.2.2]octadien-2-yl cation (I-81), which are both captured stereospecifically by nucleophiles. The intermediacy of these species would be consistent with the observed course of

the degenerate isomerisation of the dibenzobicyclo[2.2.2]octadien-2-yl system and the relatively flat Hammett plot. However, because of the high degree of transition state bridging observed in similar systems, the explanation previously offered is preferred.



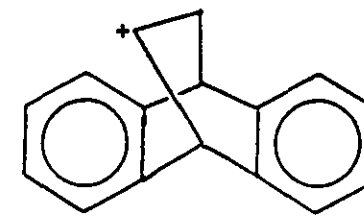
syn

(I-79)



anti

(I-80)



(I-81)

Benzobicyclo[2.2.2]-octen-2-yl and -octadien-2-yl Cations

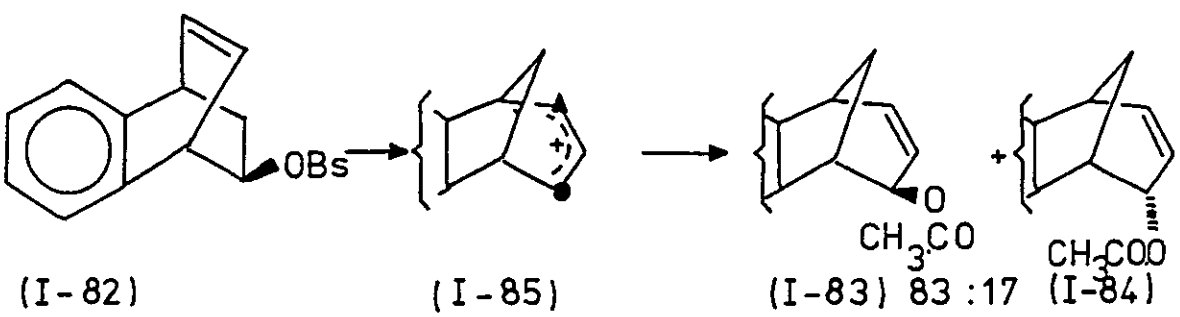
In comparison with dibenzobicyclo[2.2.2]octadien-2-yl systems the monobenzo-analogues would be expected to exhibit a greater variety of rearrangement pathways and products and this greater variety is in fact observed.

Tanida has studied the solvolyses of various benzobicyclo[2.2.2]-octadien-2-yl brosylates and has observed the effect on reaction rates and product composition of reducing the double bond and, in the cases of the benzobicyclo[2.2.2]octen-2-yl systems, the effect of varying the aromatic ring substitution pattern.[6] The reactions were carried out under conditions of kinetic control. Good first order rate constants were observed. Internal return to less reactive isomers was not an important pathway in these systems; slowing down of the solvolyses was only observed in the case of the most reactive brosylate studied. The implication of this is that internal return to more reactive isomers does occur, but this

would not have been detected in Tanida's study. The greater rate of acetolyses compared to ethanolyses in these systems was interpreted as indicating that solvent assisted ionisation was relatively unimportant and that cationic intermediates were involved.

In contrast to dibenzobicyclo[2.2.2]octadien-2-yl derivatives in which the orientation of the substituent is of no consequence unless the aromatic rings are differently substituted, 2-substituents in the monobenzo-analogues may be directed exo- or endo- to the aromatic ring. If the concept of aryl assisted ionisation has any validity, the exo- series of benzobicyclo[2.2.2]-octadien-2-yl derivatives should show the greatest similarity to the dibenzobicyclo[2.2.2]octadien-2-yl derivatives in solvolyses, and this is observed:

The acetolysis of benzobicyclo[2.2.2]octadien-exo-2-yl brosylate (I-82) proceeded with complete rearrangement[6a] to benzo[6,7]bicyclo[3.2.1]-octadien-2-yl derivatives [(I-83) and (I-84)]. The allyl cation (I-85) is captured stereoselectively from the exo-face to give the quasi-axial acetate (I-83) as the major product (Scheme I-14).

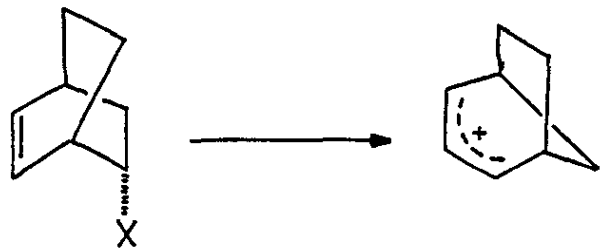


(I-82) (I-85) (I-83) 83 : 17 (I-84)

Scheme I-14

The great stability of the allyl cation (I-85) is probably the important factor in determining the product distribution. The true extent of the rearrangement may be masked by the symmetry of the intermediate allyl

cation; it would be interesting to know whether scrambling of the termini of the allyl system occurs [marked ● and ▲ in (I-85)], and if so whether the extent of scrambling is the same in the two products (I-83) and (I-84). Analogous results obtained by solvolysis of endo-bicyclo[2.2.2]oct-5-en-2-yl derivatives (I-86) indicate that the intermediate cation (I-87) is a symmetrical one (Scheme I-15).[4] The influence of the benzo-bridge in com-



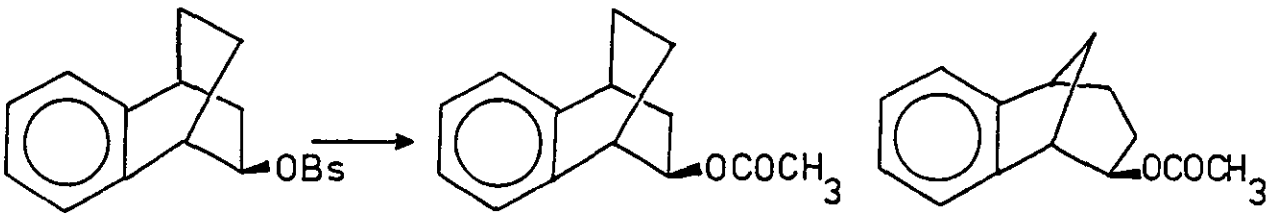
(I-86) (I-87)

Scheme I-15

parison to an ethano-bridge on the rearrangement is difficult to assess; it seems not to influence the product distribution to any great extent, and the overall kinetic influence of the ring is to approximately halve the rate of solvolysis.

In the case of benzobicyclo[2.2.2]octen-exo-2-yl brosylate (I-88) the influence of the benzo-ring is better understood. Acetolysis of the unsubstituted exo-brosylate (I-88) is completely stereospecific.[6a] The major product is exo-2-acetoxy-benzobicyclo[2.2.2]octene (I-89) with retained structure and configuration at C-2; the minor product results from aryl migration followed by nucleophilic capture of the cation from the exo-face to give the axial acetate, exo-2-acetoxy-benzo[6,7]bicyclo-[3.2.1] octene (I-90), as shown in Scheme I-16.

The complete stereospecificity of this reaction suggests extensive



(I-88) (I-89) 83 : 17 (I-90)

Scheme I-16

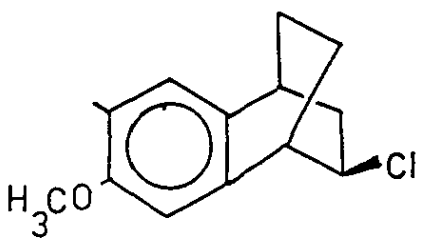
aryl-bridging in the transition state for product formation, and by implication in the transition state for ionisation and in the intermediate cation. An interesting feature of this reaction is the reduced amount of skeletal rearrangement compared to systems where rearrangement forms allyl or benzyl systems (cf. Schemes I-1, I-2 and I-14). It was originally thought that the low exo-endo-rate ratio of the benzobicyclo[2.2.2]octen-2-yl system indicated insufficient rate enhancement to justify the assumption that aryl participation in the ionisation step was an important factor in this reaction.[6a]

It is however not sound practice to assume that the endo-rate is a good measure of what the exo-rate would be without aryl assistance, and to do so will in general lead to an incorrect understanding of the reaction.[11] The correct comparison is with the (usually hypothetical) aryl-unassisted rate. An estimate of this may be obtained from the Hammett log (rate) vs. $\rho\sigma$ correlation. If aryl participation is important, the observed rates show an upward curvature at lower σ (i.e. a rate enhancement with electron rich aryl groups) but with increasingly deactivated aryl groups the correlation becomes linear. Extrapolation of this linear portion of the correlation to the approximate σ gives the contribution to the total rate from factors

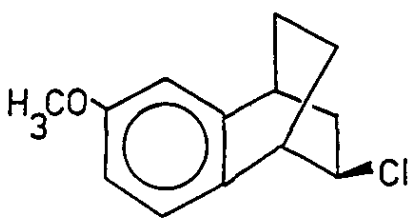
other than aryl assistance. When the total rate is dissected into aryl assisted and other contributions, the proportion of aryl assisted solvolysis is usually found to agree with that deduced from the product distribution. In this way the apparent anomaly of a product distribution which suggests extensive aryl participation in a product controlling intermediate but kinetic measurements which suggest little or no stabilisation of the transition state leading to this intermediate (the so-called rate-product quandry) is often seen to arise from a misconception of the magnitude of the aryl-unassisted solvolysis rate or of the significance of modest rate enhancements: A rate enhancement factor of 5 corresponds to 80% reaction by an aryl assisted pathway. In the solvolysis of benzobicyclo[2.2.2]-octen-2-yl brosylates, the observed exo-endo-rate enhancement of 2.83 would indicate that 65% of the reaction was aryl-assisted even if the unassisted exo-rate were as high as the endo-rate.

Tanida and co-workers have measured solvolysis rates for several nuclear substituted benzobicyclo[2.2.2]octen-2-yl derivatives.[6b] The 2-exo-relative rate logarithms correlate well with σ^+ for the homo-meta-methoxy-, the homo-para-methoxy- and the unsubstituted benzobicyclo[2.2.2]-octen-exo-2-yl derivatives (I-91), (I-92) and (I-88). The observed ρ of -3.25 indicates strong benzo-bridging in the ionisation transition state, and with these compounds [(I-91), (I-92) and (I-88)] the steric course of the solvolysis is entirely controlled by the neighbouring aryl group; it does not differ significantly to that shown in Scheme I-15. With deactivated aryl groups, the reaction becomes increasingly more complicated. The steric course of the solvolysis of the homo-meta-nitrobenzobicyclo[2.2.2]-octen-exo-2-yl brosylate (I-93) is shown in Scheme I-17. Only 47% of the products are those expected by analogy with Scheme I-15, and if this rough correction is applied to the total rate, the point for log (47% of the

total relative rate) is found to fall on the linear correlation line. Extrapolation of this line to the homo-para-homo-meta-dinitrobenzobicyclo-[2.2.2]octen-exo-2-yl derivative (I-94) suggests that the aryl assisted rate should be only 1.7% of the observed rate, and in keeping with this expectation is the observation that solvolysis of this deactivated brosylate (I-94) gives neither of the products associated with aryl participation (Scheme I-18).



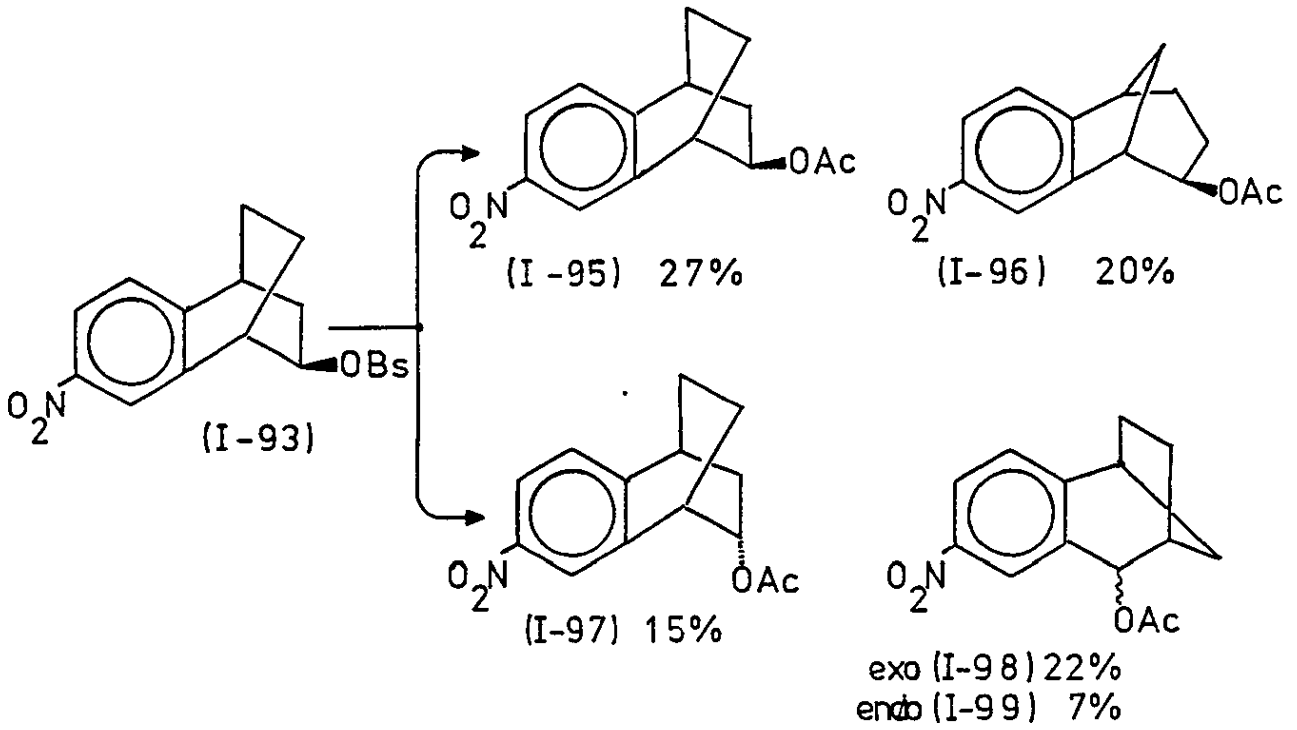
(I-91)



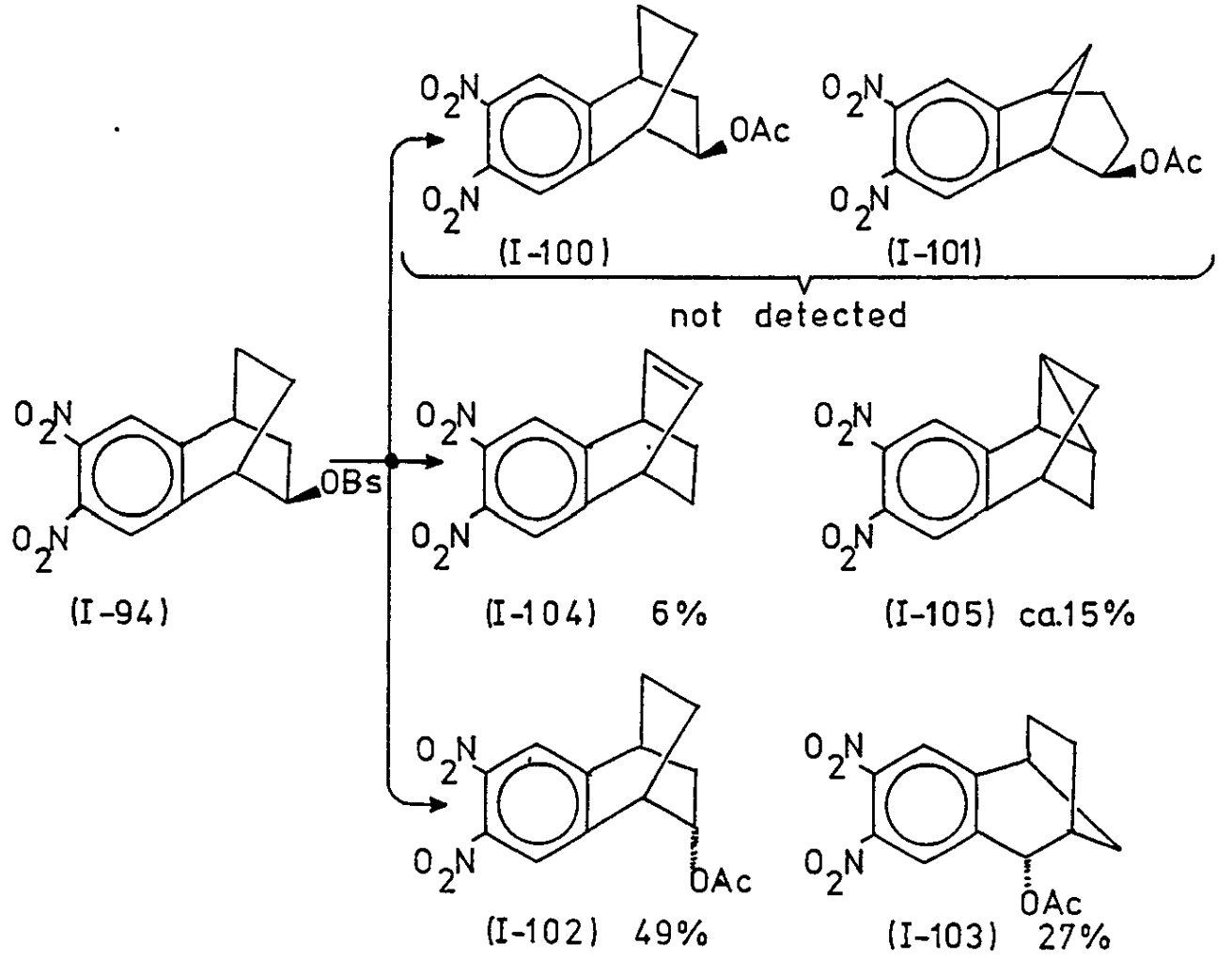
(I-92)

In contrast to the exo-series, the effects of nuclear substitution on the logarithms of the relative rates in the endo-series correlate with σ rather than σ^+, indicating that inductive effects are paramount. The reaction proceeds with ethano-bridge migration to produce a benzyl cation, which is captured by solvent, predominantly from the exo-face. The course of the reaction closely follows that of the solvolysis of bicyclo[2.2.2]-oct-5-en-2-yl derivatives [(I-86) see Scheme I-15] and is illustrated for benzobicyclo[2.2.2]oct-endo-2-yl brosylate (I-106)[6b] in Scheme I-19.

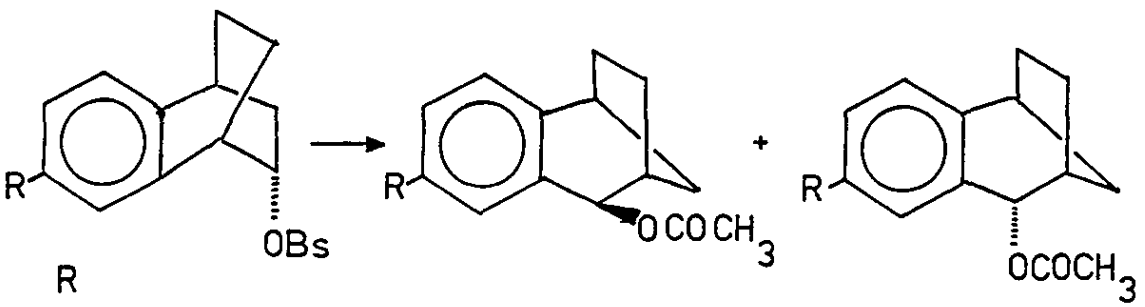
The consequences of deactivating the aryl group with electron withdrawing substituents are not as dramatic as in the exo-series. In going from the unsubstituted endo-brosylate (I-106) to the homo-meta-nitro- and then the homo-meta-homo-para-dinitro-derivatives [(I-109) and (I-110)], a gradual decrease is observed in the exo:endo ratio of the benzo[3,4]bicyclo-



Scheme I-17



Scheme I-18

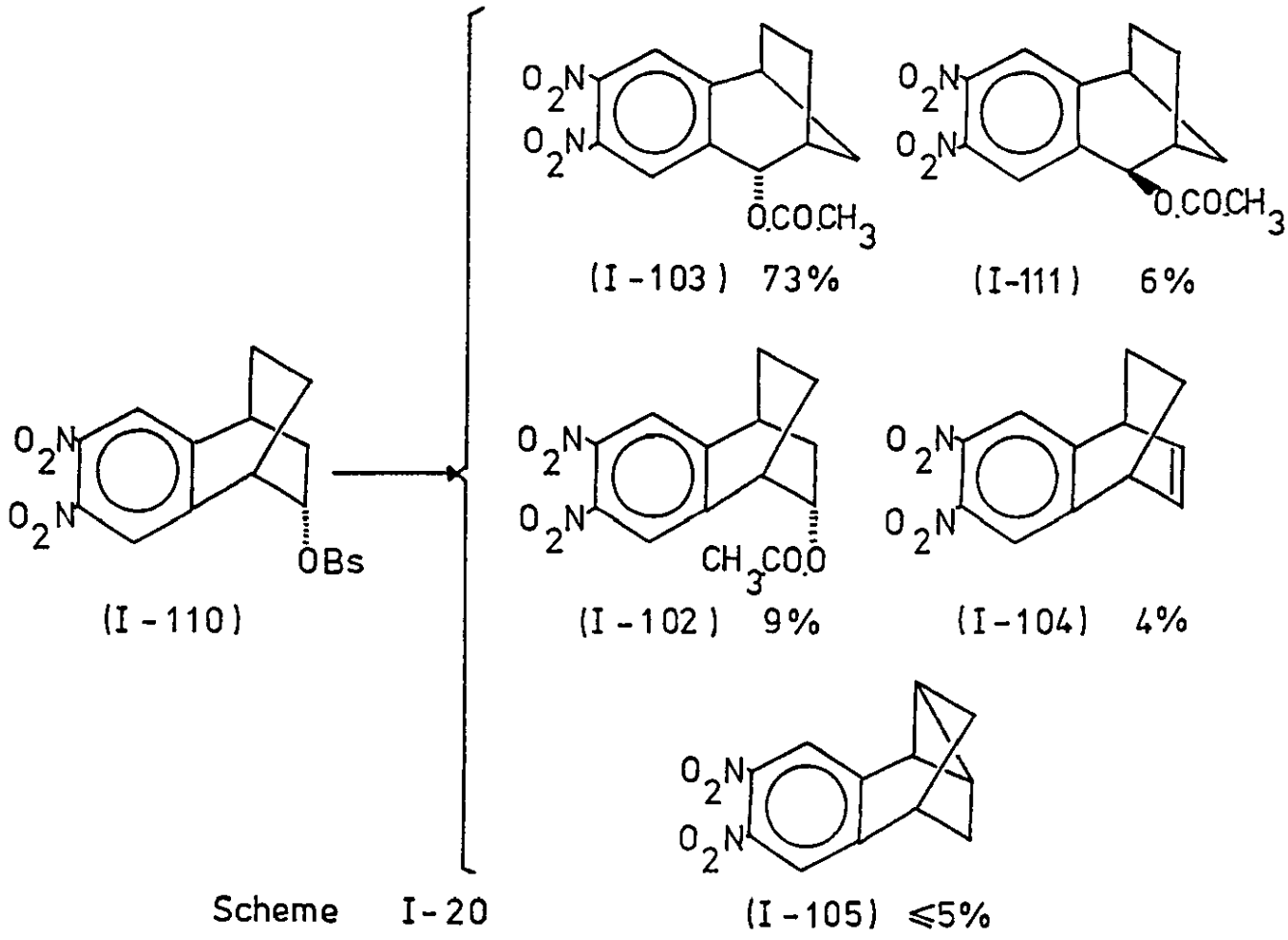


R				
H	(I-106)	(I-107)	2 : 98	(I-108)
O_2N	(I-109)	(I-99)	4 : 92	(I-98)

Scheme I 19

[3.2.1]oct-3-en-2-yl derivatives [e.g. (I-108):(I-107)], from 49:1 through 23:1 to 12:1. In the extreme case, the dinitro-endo-2-brosylate (I-110), a more complex mixture of products is obtained (Scheme I-20). The formation of products which retain the benzobicyclo[2.2.2]octane skeleton is a manifestation of the decreasing stability of the benzyl cation formed by rearrangement as the electron withdrawing substituents accumulate on the arene. The decreasing stability of this benzyl cation is also reflected in the decreasing stereoselectivity of solvent attack. The products formed from the dinitro-endo-brosylate (I-110) are qualitatively similar to those formed from the dinitro-exo-brosylate (I-94), an indication that as aryl participation becomes less important in the exo-series, and bridge migration becomes less favourable in the endo-series then the intermediate cationic species from both series increasingly resemble one another.

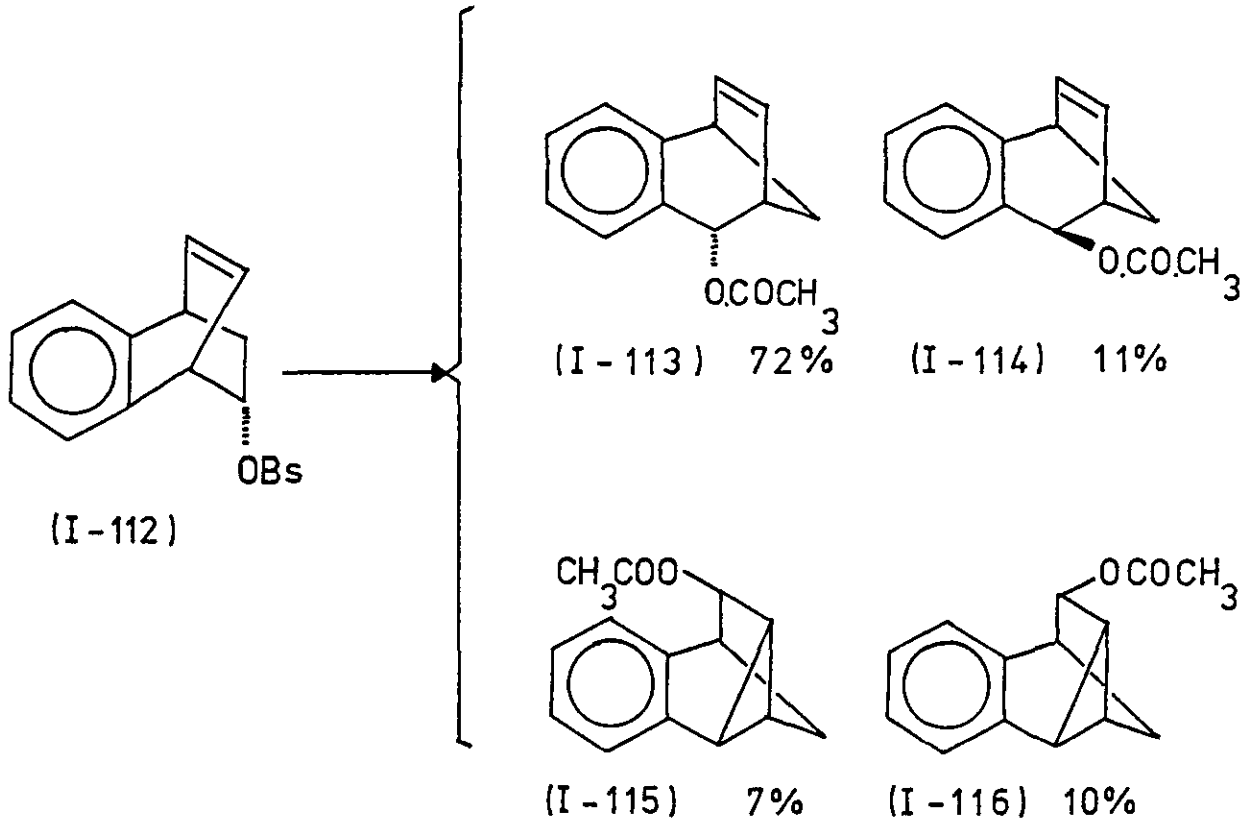
The analogous endo-brosylate, benzobicyclo[2.2.2]octadien-2-yl brosylate (I-112) has been less thoroughly investigated. The principal solvolysis pathway is by rearrangement to exo- and endo-2-acetoxybenzo[3,4]bicyclo-[3.2.1]octadiene [(I-113) and (I-114)], of which the exo- (quasi-axial) epimer predominates.[6b] In this rearrangement, the solvolysis resembles that



Scheme I-20

of 2-endo-hydroxybenzobicyclo[2.2.2]octene brosylate (I-106). The other two products are the cyclopropylcarbinyl derivatives [(I-115) and (I-116)] and they strikingly illustrate the influence of the double bond on the course of the solvolysis (Scheme I-21).

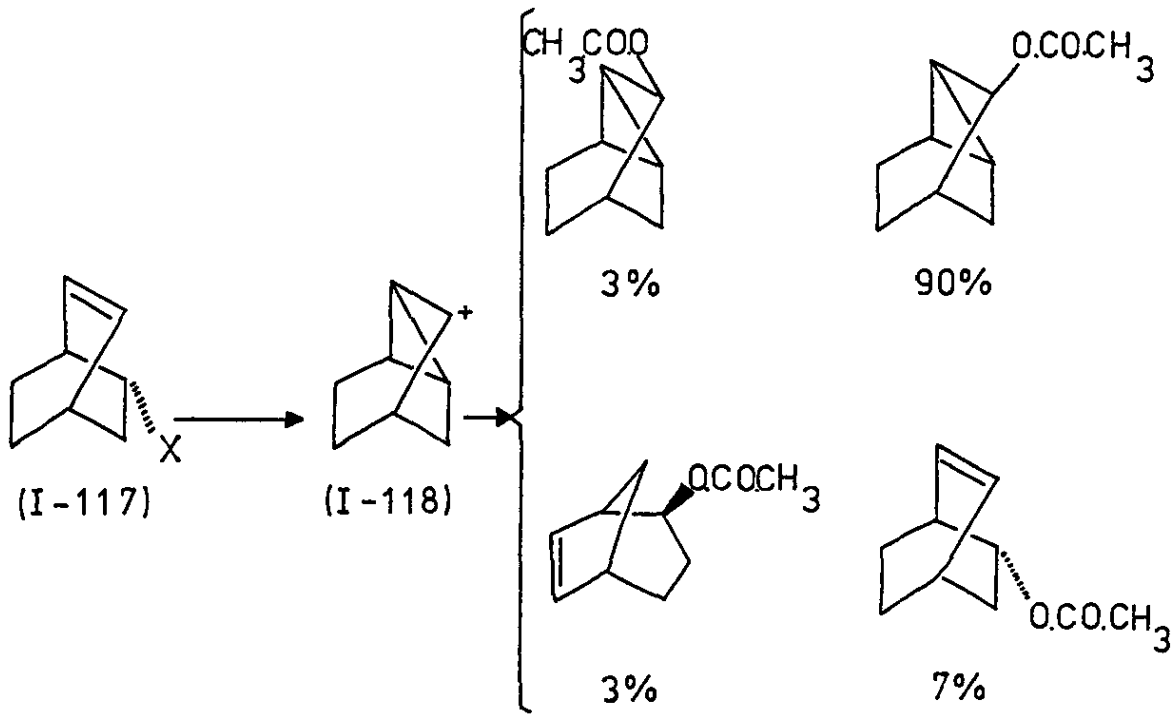
The course of the solvolysis of endo-2-benzobicyclo[2.2.2]octadienyl brosylate (I-112) is similar to that of exo-bicyclo[2.2.2]oct-5-en-2-yl derivatives (I-117), in which the first cationic intermediate is thought to be a homoallyl cation or the cyclopropylcarbinyl cation (I-118), Scheme I-22.[4] The influence of the aryl group of the benzobicyclo[2.2.2]octadien-endo-2-yl systems (e.g. I-112) seems to be largely confined to suppression



Scheme I - 21

of the cyclopropylcarbinyl derivatives [(I-115) and (I-116)] to the benefit of the benzo[3,4]bicyclo[3.2.1]octadien-2-yl derivatives [(I-113) and (I-114)].

What conclusions can be drawn from this substantial body of work? In the exo-series, aryl bridging in the ionisation transition state has been convincingly demonstrated for benzobicyclo[2.2.2]octen-exo-2-yl derivatives and it seems likely that the phenonium ion (I-119) is the most stable cationic intermediate for it leads to a qualitative understanding of the product composition. Aryl bridging in the ionisation transition state of benzobicyclo[2.2.2]octadien-exo-2-yl derivatives seems probable, but the phenonium ion (I-120) is unlikely to be as stable as the allyl cation (I-85), and rearrangement of the phenonium ion (I-120), or relaxation of a similar transition state to the allyl cation (I-85) appears to



Scheme I-22

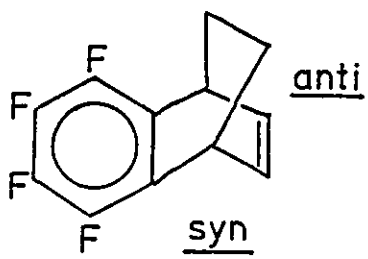
precede product formation.

In the endo-series, the effects of the aryl group on the ionisation transition state appear to be largely inductive. Ionisation of benzobicyclo[2.2.2]octen-exo-2-yl derivatives must be rapidly followed by a [1,2]-bridge shift; there is no evidence that a non-classical bridged cation (I-121) has any stability, though it may resemble the transition state for [1,2]-bridge migration. The driving force for the migration is the relatively great stability of the benzyl cation (I-122). Ionisation of benzobicyclo[2.2.2]octadien-endo-2-yl derivatives is probably assisted by participation of the double bond, for the rate of solvolysis of the brosylate (I-112) is some twelve times faster than the rate of solvolysis of its dihydroanalogue (I-106) despite the expectation that introduction of a non-participating double bond would slow the ionisation by its unfavourable

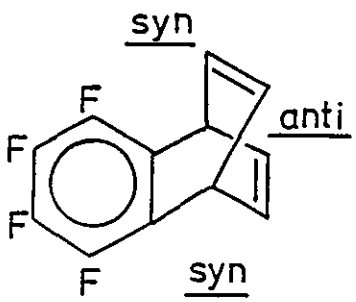
inductive effect. The first stable cation may well be the cyclopropylcarbinyl cation (I-123), in which the cationic centre and the cyclopropyl group are constrained close to the most favourable mutual orientation for cation stabilisation.[18] Although the benzyl cation (I-124) is probably more stable than the cyclopropylcarbinyl cation (I-123), both figure in the reaction as product determining intermediates.

The stereochemistry of attack by nucleophiles on the various benzobicyclo[3.2.1]-octen- and -octadien-2-yl cations is dominated by reaction from the exo-face to form axial or quasi-axial products. These conclusions are illustrated in Scheme I-23.

There are no closely analogous studies of electrophilic addition to benzobicyclo[2.2.2]-octadiene and -triene, but Barkhash has reported some ionic additions to the tetrafluorobenzo-derivatives [(I-125) and (I-126)].[8] Compared to electrophilic addition to dibenzobicyclo[2.2.2]octatriene, the



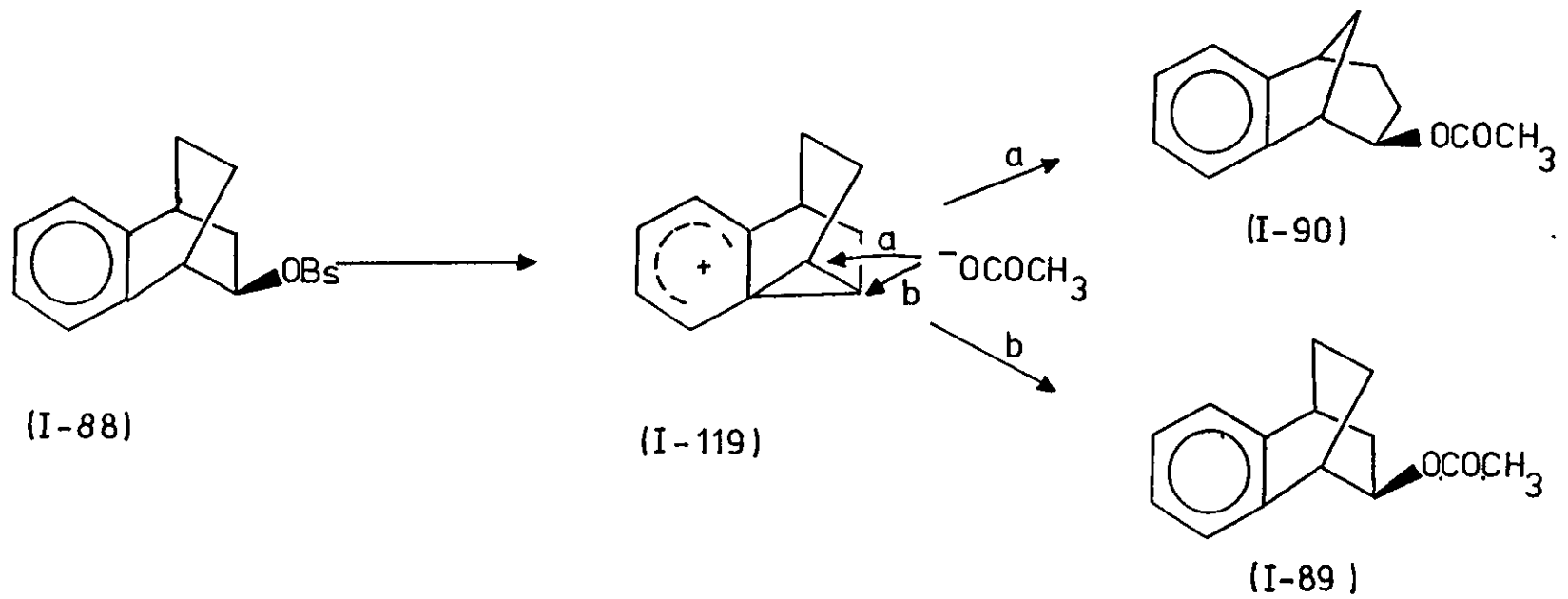
(I-125)



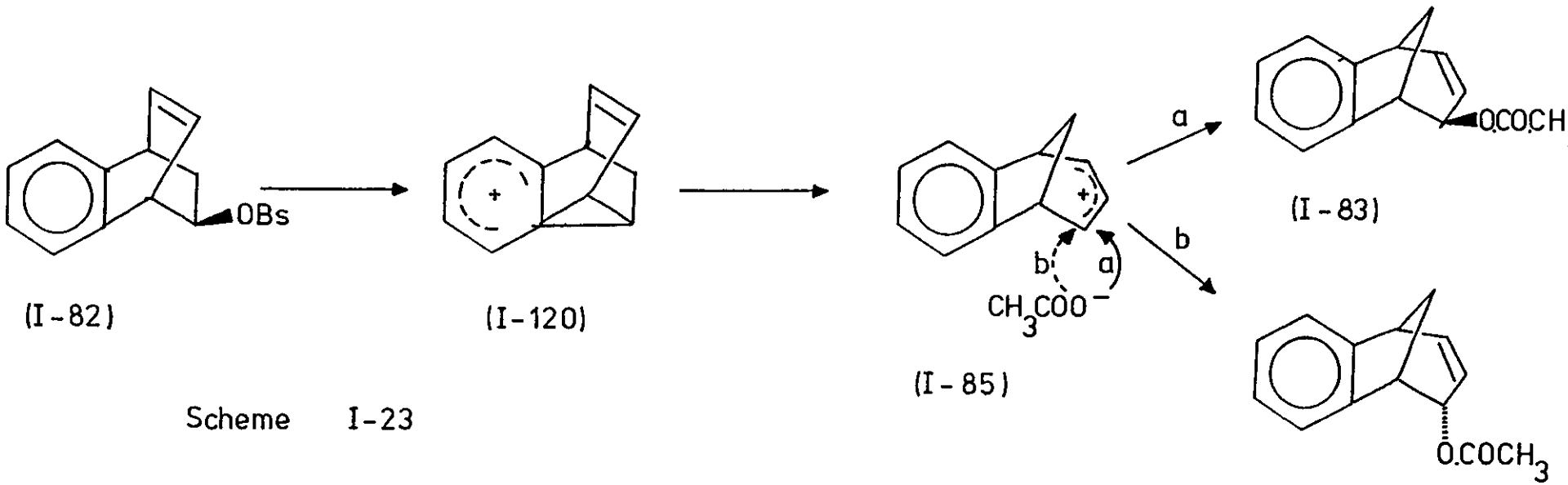
(I-126)

reaction is complicated by two competing modes of addition, syn- and anti- to the benzo-ring.

Addition of bromine to tetrafluorobenzobicyclo[2.2.2]octadiene (I-125) proceeded without rearrangement to give trans-2,3-dibromo-tetrafluorobenzobicyclo[2.2.2]octene (I-127).[8a] In contrast, addition of "acetyl hypochlorite" (as t-butyl hypochlorite in acetic acid) proceeded with complete



(I-88) (I-119) (I-90) (I-89)

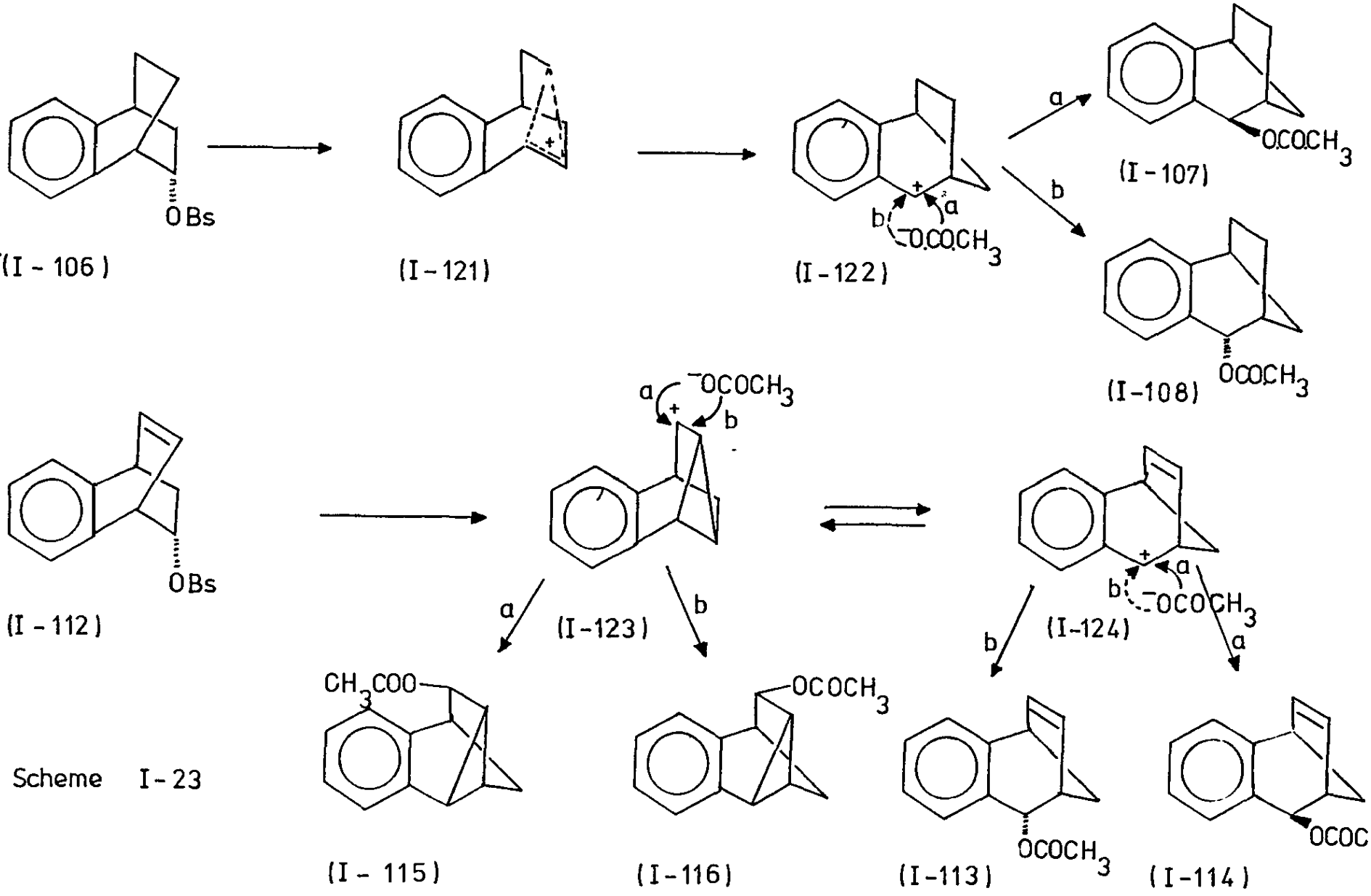


(I-82) (I-120) (I-85) (I-83) (I-84)

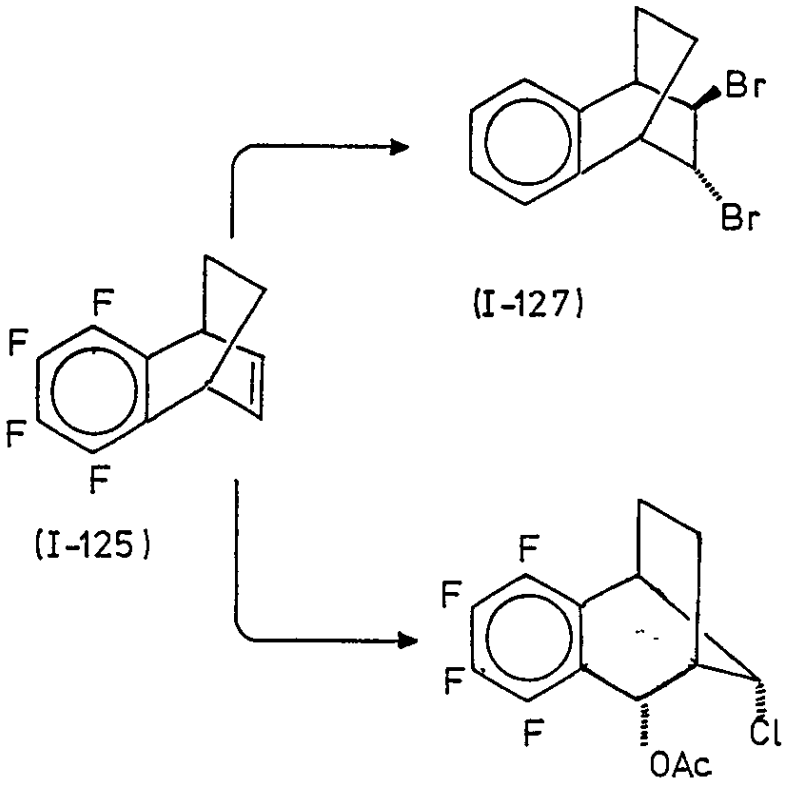
Scheme I-23

continued.

continuation.



Scheme I - 23

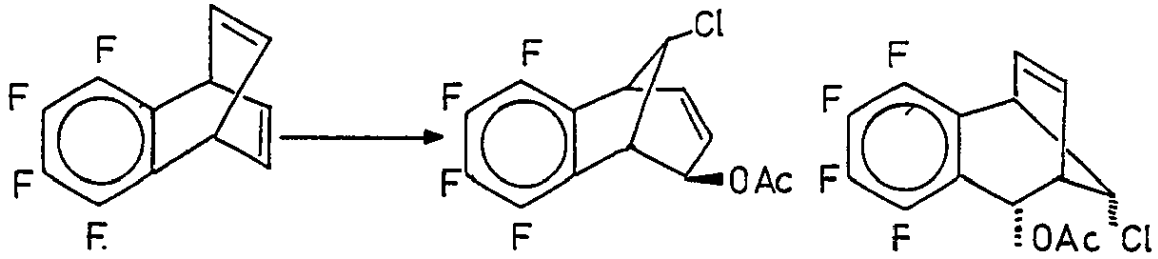


(I-125)

(I-127)

(I-128)

Scheme I-24



(I-126)

1.3 : 1

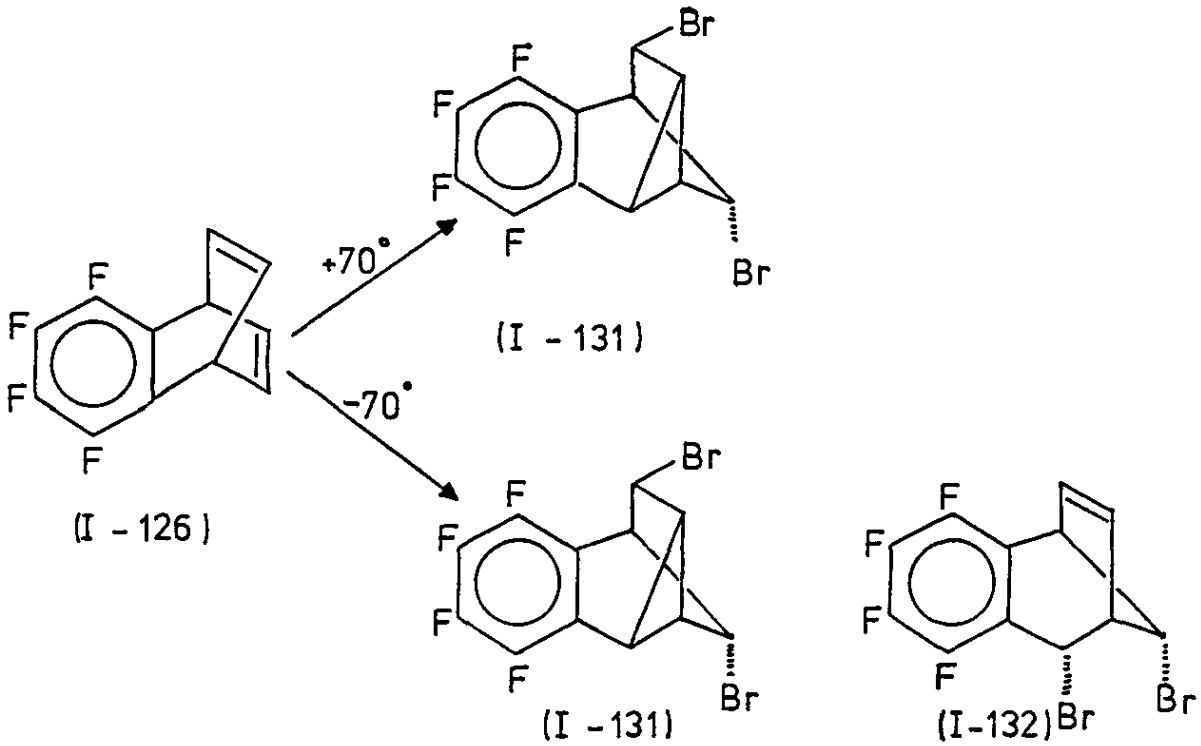
(I-129) (I-130)

Scheme I-25

rearrangement to give exo-2-acetoxy-syn-8-chlorotetrafluorobenzo[3,4]-bicyclo[3.2.1]octene (I-128) (Scheme I-24).[8a]

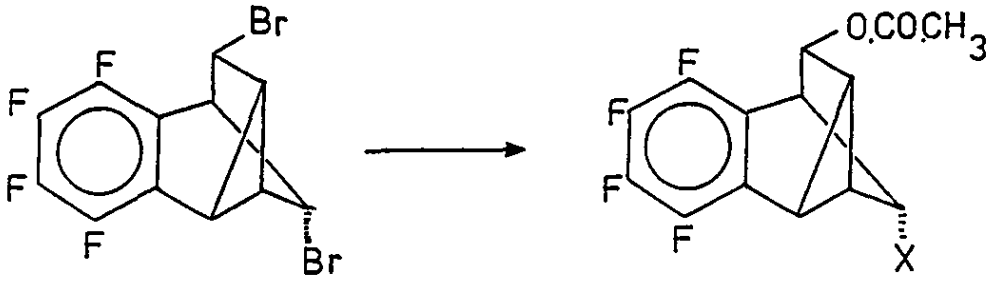
The ionic addition reactions of tetrafluorobenzobicyclo[2.2.2]octatriene (I-126) are more complex. Addition of acetyl hypochlorite (t-butyl hypochlorite in glacial acetic acid "at -10°") takes place from both syn- and anti-face and is accompanied by rearrangement in each case to give exo-2-acetoxy-syn-8-chloro-tetrafluorobenzo[3,4]bicyclo[3.2.1]octadiene (I-129) and exo-2-acetoxy-anti-8-chloro-tetrafluorobenzo[6,7]bicyclo[3.2.1]-octadiene (I-130) (Scheme I-25).[8b]

The course of the addition of bromine to tetrafluorobenzobicyclo-[2.2.2]octatriene is temperature dependent. At +70° only the tricyclic dibromide, trans-6,8-dibromo-tetrafluorobenzo[3,4]tricyclo[3.2.1.$0^{2,7}$]-octene (I-131) forms, but at -70° another dibromide, exo-2, syn-8-dibromo-tetrafluoro[3,4]bicyclo[3.2.1]octadiene (I-132) is formed (Scheme I-26).[8c]



Scheme I - 26

The stability of the bicyclic dibromide (I-132) towards the bromination conditions at +70° was not reported, but treatment of the two dibromides [(I-131) and (I-132)] separately with silver acetate in acetic acid gave significantly different results. The tricyclic dibromide (I-131) reacted with retention of the ring system to give a mixture of trans-bromoacetate (I-133) and trans-diacetate (I-134) (Scheme I-27).



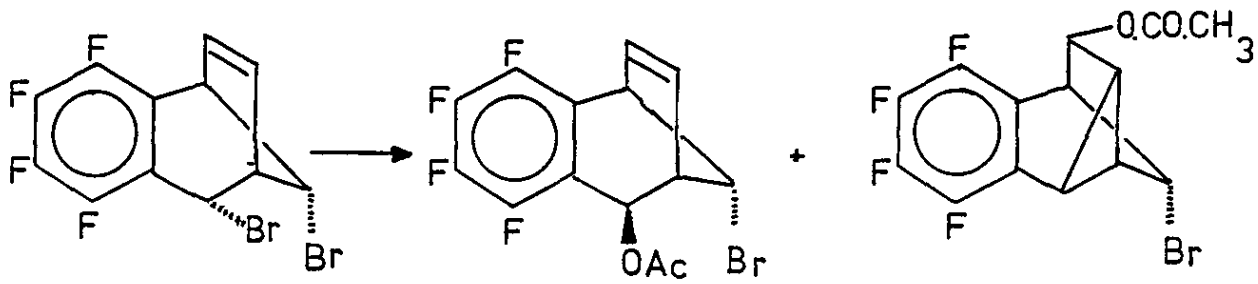
(I - 131)

X = Br (I-133)

X = CH_3COO (I - 134)

Scheme I - 27

The bicyclic dibromide (I-132) reacted with partial rearrangement to the tricyclic ring system, forming the bromoacetate (I-135) and with partial retention of the ring system but inversion at C-2 forming the bromoacetate (I-133), (Scheme I-28).[8c]



(I - 132) (I-135) (I - 133)

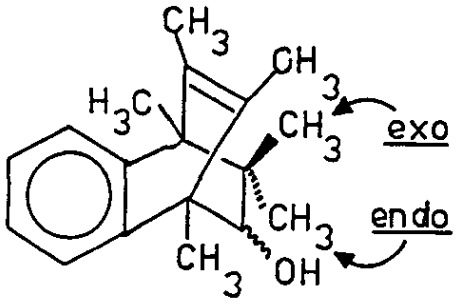
Scheme I - 28

The conclusions which can be drawn from this work about electrophilic additions to benzobicyclo[2.2.2]-octatrienes and -octadienes in general are limited.. The deactivated aryl ring will exhibit less participation during the addition and reduce the extent to which migration of the ethano- or etheno-bridge occurs but the significance of many of the observations will not be clear until a more systematic investigation is carried out.

One further point of interest concerns the relative stability of the benzobicyclo[2.2.2]-octadien- or -octen-2-yl systems and the benzobicyclo-[3.2.1]-octadien- or -octen-2-yl systems. There is little in the work surveyed here to indicate the relative stability of these ring systems, but in one instance Tanida prepared the dinitrobenzobicyclo[2.2.2]octen-2-yl acetates [(I-100) and (I-102)] by nitration of the mononitroacetates [(I-95) and (I-97)] with nitric acid in concentrated sulphuric acid.[6b] The isolation of products with the retained ring system after such severe treatment may indicate that the benzobicyclo[2.2.2]octen-2-yl ring system is more stable than the benzobicyclo[3.2.1]octen-2-yl system, though this is hardly conclusive evidence.

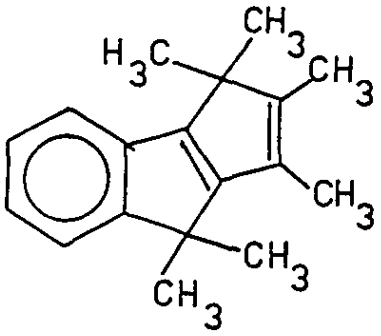
The one other substantial body of work in this system, that of Hart,[7] concerns extensively methylated benzobicyclo[2.2.2]octadien-2-yl or related systems. The great stability and relatively long life of cations in this series leads to much more extensive rearrangements than those already encountered. Although these rearrangements are in many ways atypical of benzobicyclo[2.2.2]octadien-2-yl systems in general, they give a fascinating insight into the type of processes which are possible.

The first of these rearrangements reported was the remarkable transformation of 1,3,3,4,5,6-hexamethylbenzobicyclo[2.2.2]octadien-exo or endo-2-ol [(I-136) or (I-137)] into 2,2,3,4,5,6-hexamethylbenzobicyclo[3.3.0]-octatriene (I-138).[7a] The interpretation of this reaction which is presented



exo (I-136)

endo(I-137)

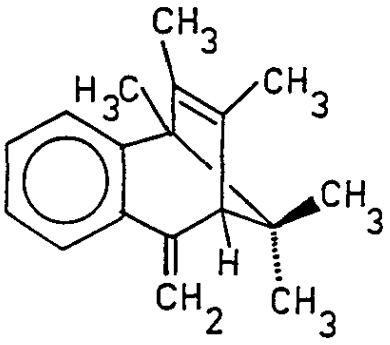


(I-138)

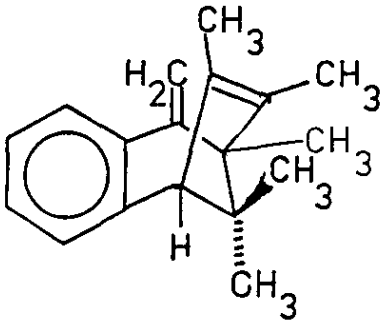
here is based largely on the subsequent results of Hart in related systems,[19] which were of course not available to him at the time of his report of this transformation.

In a careful analysis of the time dependence of the product composition, it was shown that there is a rapid dehydration of either of the epimeric alcohols (I-136) or (I-137) to produce the olefins (I-139), (I-140) and (I-141) or (I-142). The concentration of these olefins [(I-139), (I-140) and (I-141) or (I-142)] rises to a maximum after about 30 min, and then decays as a mixture, of roughly constant proportions after about 60 min, in which the olefin (I-139) is always about 8 times as abundant as each of the olefins (I-140) and [(I-141) or (I-142)]. The rate of formation of the benzobicyclo[3.3.0]octatriene (I-138) is comparatively slow and approximately follows the rate of decay of the concentration of (I-139). These results were interpreted to mean that:

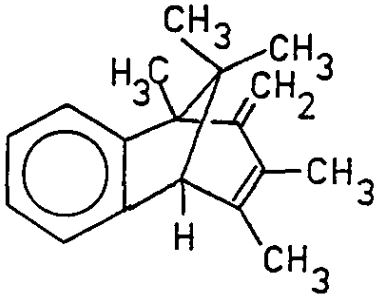
(a) the epimeric alcohols [(I-136) and (I-137)] are rapidly interconverted for the course of the reaction is insensitive to the stereochemistry of the substrate. The conditions of this reaction, a 1:1 mixture of trifluoroacetic and sulphuric acids, are more strongly acidic than those used by Cristol in the epimerisation of dibenzobicyclo[2.2.2]octadien-2-yl acetates.



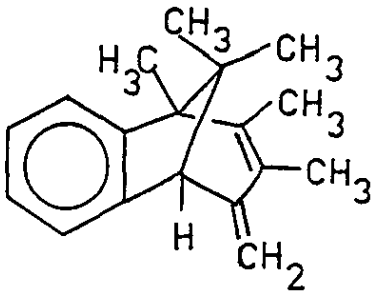
(I - 139)



(I - 140)



(I - 141)

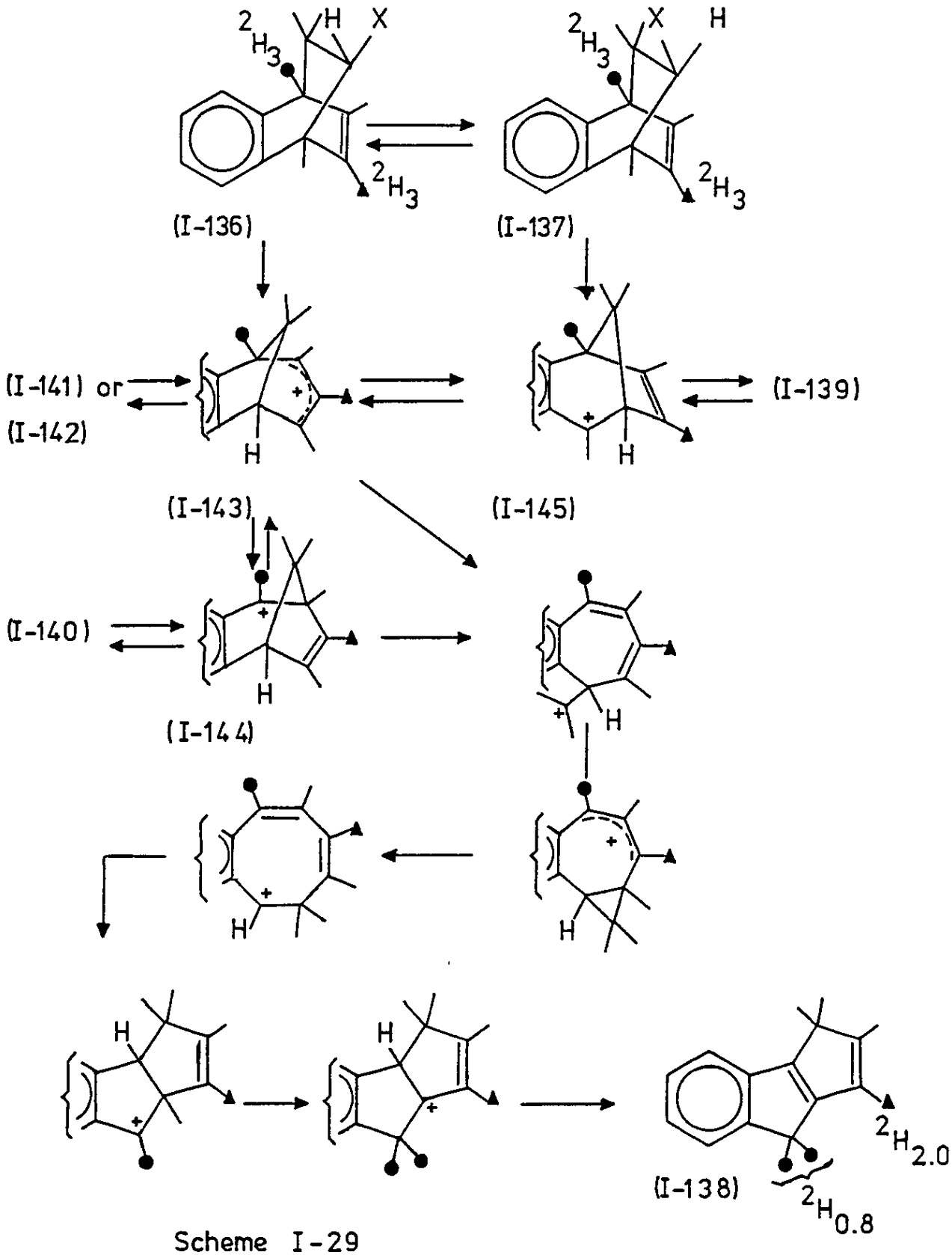


(I - 142)

(b) the epimeric mixture of alcohols [(I-136) and (I-137)] decays by a series of [1,2]-bridge shifts to rapidly form an equilibrium mixture of the cations [(I-143), (I-144) and (I-145)]. These cations, either tertiary benzyl or penta-alkylallyl cations, are very stable and determine the initial products.

(c) the equilibrium mixture of cations [(I-143), (I-144) and (I-145)] is converted in a slow step into a cation which leads to the benzobicyclo-[3.3.0]octatriene (I-138).

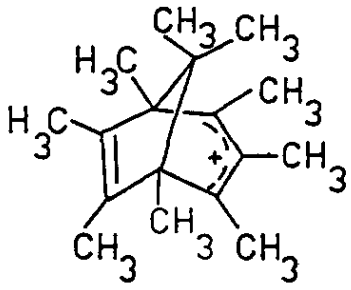
This last, slow process was thought to involve ring opening, ring expansion, and trans-annular ring closure followed by methyl migration and proton loss, as illustrated in Scheme I-29. There are analogies for all of these steps, although some are not close, and the mechanism does correctly predict the result of two labelling experiments (label position


2H3
H
X
2H3
(I-136)
X
H
2H3
2H3
(I-137)
(I-141) or
(I-142)
H
(I-139)
H
(I-143)
(I-145)
(I-140)
H
(I-144)
H
H
H
H
2H2.0
(I-138)
2H0.8

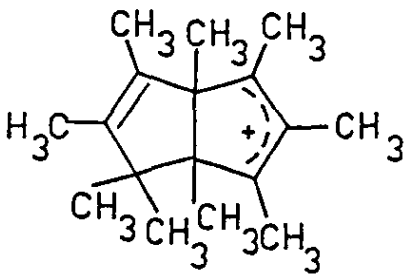
Scheme I-29

marked in Scheme I-29 by ● and ▲), but recent results obtained with the nonamethylbicyclo[3.2.1]octadien-2-yl cation (I-146) suggest an alternative which also accounts for the results of the labelling experiments.

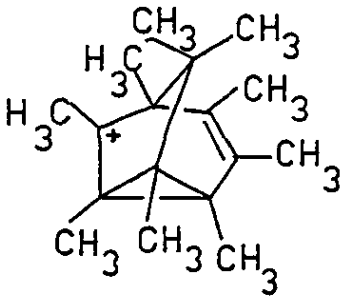
The nonamethylbicyclo[3.2.1]octadien-2-yl cation (I-146) undergoes two separate degenerate rearrangements and an irreversible rearrangement to the nonamethylbicyclo[3.3.0]octadien-2-yl cation (I-147).[19] The first of the degenerate rearrangements scrambles the five carbons o together and



(I-146)



(I-147)

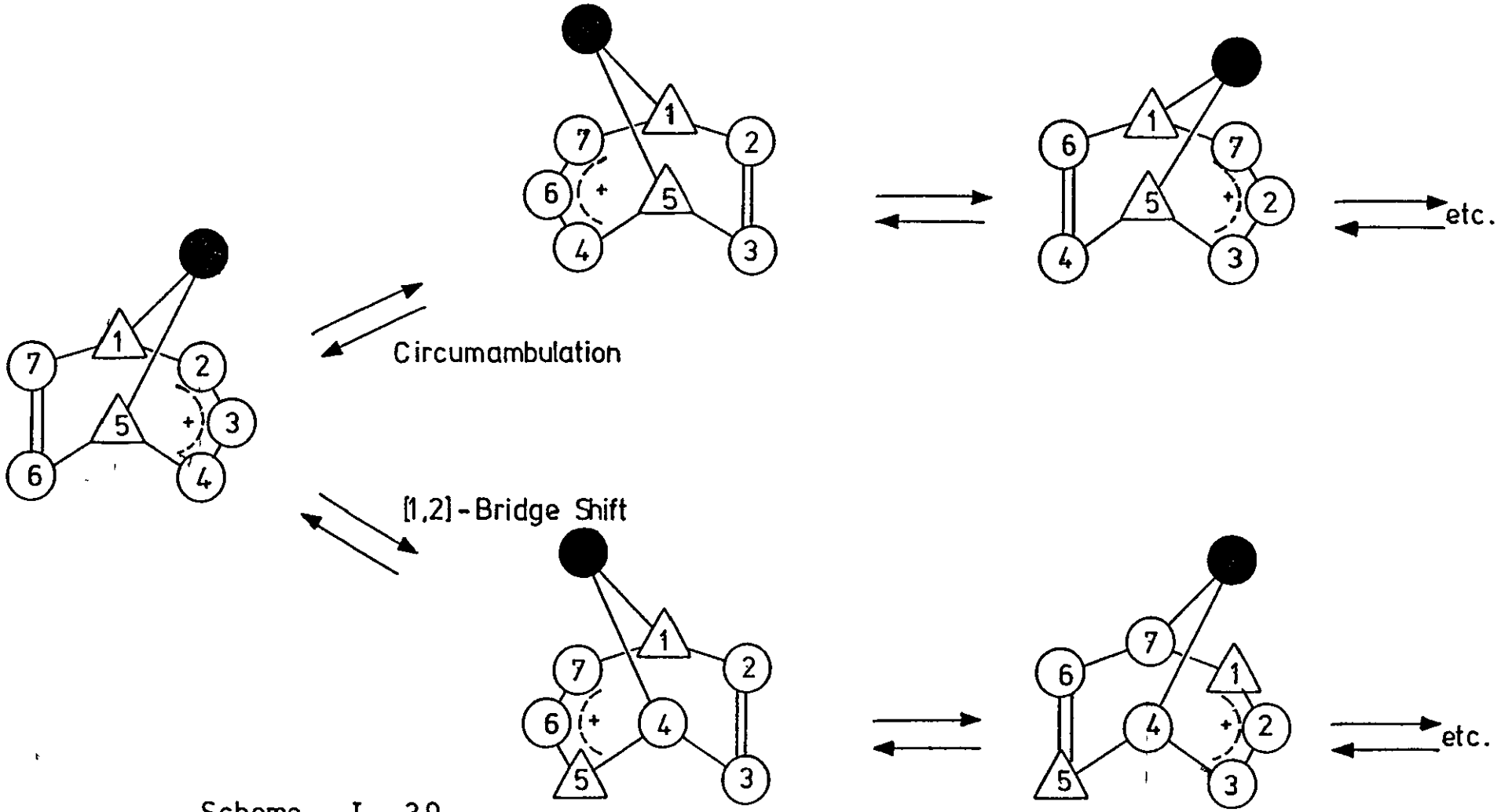


(I-148)

the two carbons Δ together, but leaves the carbon ● unique. The second higher energy process exchanges a carbon o and a carbon Δ, but again leaves the carbon ● unique. The first of these processes is termed circumambulation and the second [1,2]-bridge shift. Both are illustrated for one complete step of each in Scheme I-30. Each cation formed by [1,2]-bridge shift undergoes rapid circumambulation.

The circumambulation process is thought to involve the formation of the cyclopropylcarbinyl cation (I-148) which isomerises degenerately and collapses to another nonamethylbicyclo[3.2.1]octadien-2-yl cation (Scheme I-31). Analogous rearrangements of bicyclo[2.2.1]heptadien-7-yl cations are known.[20]

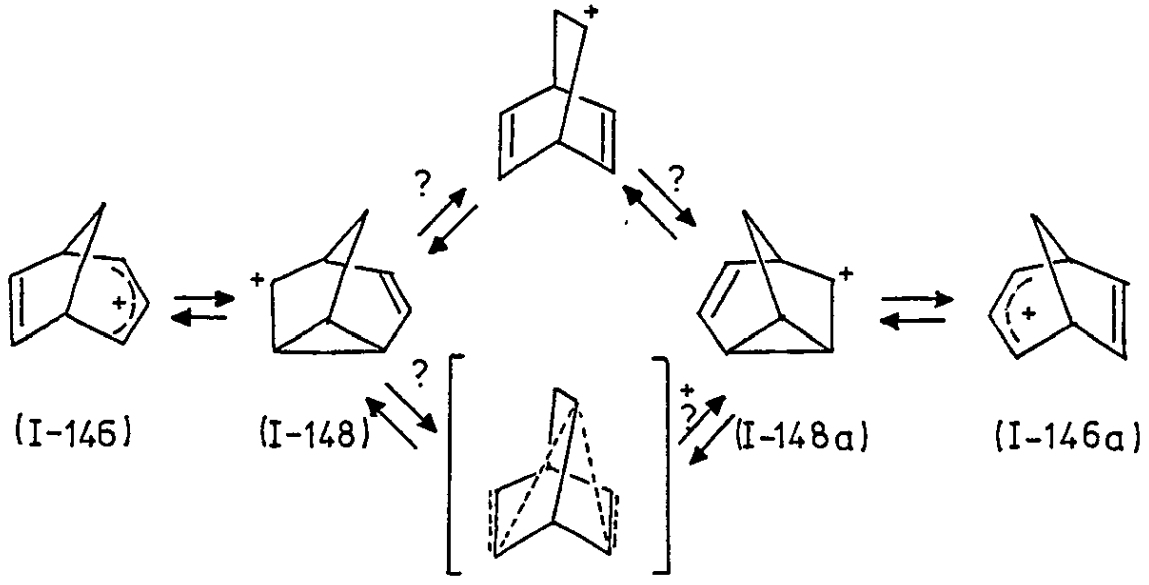
It is clear that these processes of circumambulation and [1,2]-bridge shift are extentions of the bridge flipping and bridgehead exchange



Scheme I - 30

reported by Cristol (see Scheme I-10).[5f] They proceed much more readily and are able to progress much further, but the similarity persists even in the relative ease with which they occur.

The highest energy process, the irreversible formation of the nonamethylbicyclo[3.3.0]octadien-2-yl cation (I-147) is thought to involve the slow non-degenerate isomerisation of a cyclopropylcarbinyl cation (I-148), either by way of a [1,3]-shift or two [1,2]-shifts involving the formation and collapse of a cyclobutyl cation (Scheme I-32). For simplicity,

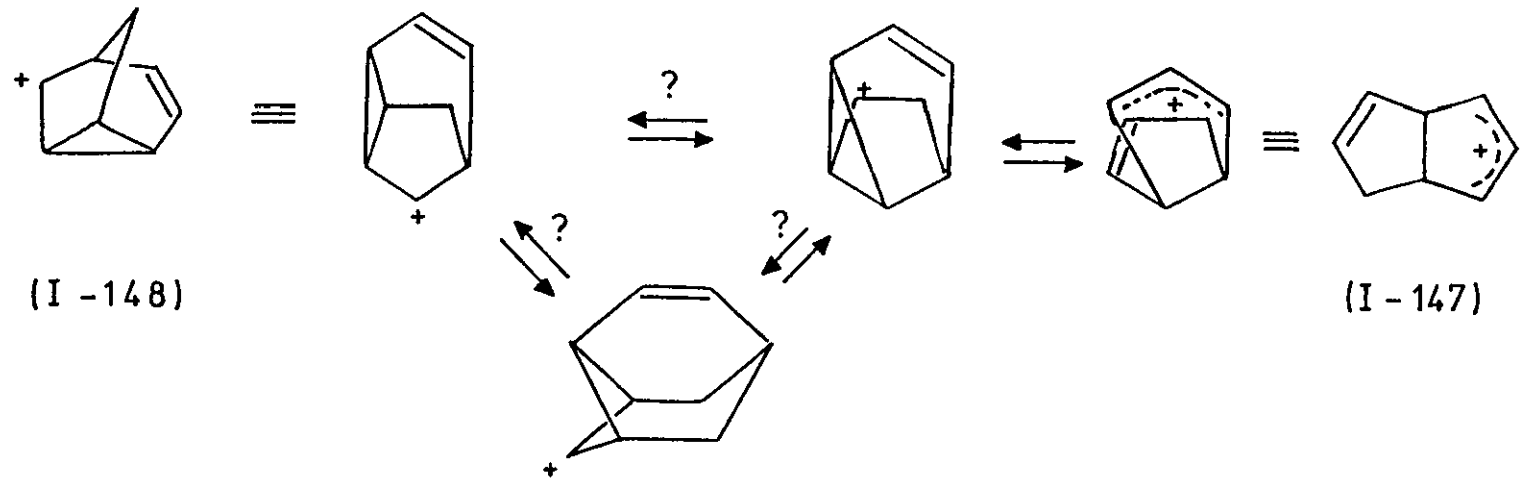


Scheme I-31

Methyl groups not shown.

the rearrangement is usually depicted as a [1,3]-shift. These results are supported by extensive deuterium labelling studies.

The application of these results to benzobicyclo[2.2.2]octadien-2-yl rearrangements is straightforward but the extent to which the rearrangements proceed is restricted by the benzo-ring. The rearrangement of the hexamethylbenzobicyclo[2.2.2]octadien-2-yl cation is further restricted by



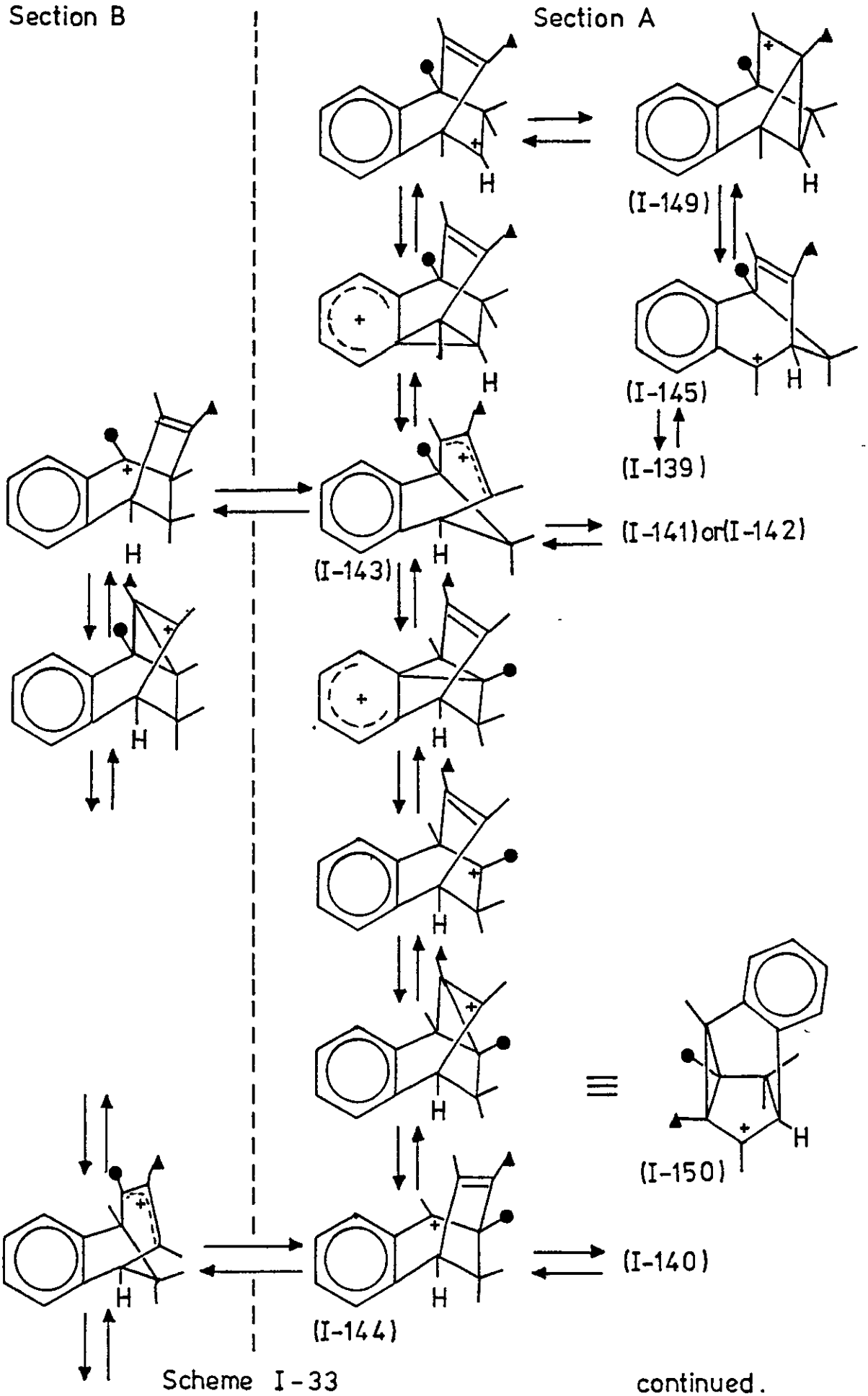
Scheme I - 32

Methyl groups not shown.

the single unsubstituted ring position, the original C-2, which ensures that all rearrangements *via* a secondary cation at this position will proceed relatively slowly.

The proposed course of the rearrangement is shown in Scheme I-33. The intermediates in section A of Scheme I-33 are a set related by circumambulation. The intermediates of section B (not shown in full) are another set of similarly related intermediates, but the sections are closed to each others members with respect to circumambulation. The members of sections A and B may exchange by a [1,2]-bridge shift, occurring in section A at ions (I-143) and (I-144), and this has important consequences for labelling experiments. In particular, a label originally at C-4 of the hexamethylbicyclo[2.2.2]octadien-2-yl system will exchange with the original C-5 substituent. A [1,2]-bridge shift in the ion (I-145) is relatively disfavoured because the secondary allyl cation which would be formed is of relatively high energy. The mechanism of Scheme I-33 correctly predicts that some label placed originally at C-4 in the hexamethylbicyclo[2.2.2]-octadien-2-yl system would appear in the benzylic (C-6) *gem*-dimethyl group, and it is a point in favour of this mechanism that so little of the label does appear at the C-6 dimethyl group (only 0.8D, or *ca.* 25%). The rest of the label should appear at C-3, but is not detected. Why is this? When the hexamethylbenzobicyclo[3.3.0]octatriene (I-138) is treated with sulphuric[$^2H_2$] acid, the C-3 methyl group rapidly exchanges protons with the acid to form a [$^2H_3$]methyl group, and this is highly selective; no other deuterium incorporation is observed. It is clear that any hexamethylbenzobicyclo[3.3.0]octatriene formed with a deuteriated C-3 methyl group would repidly exchange protons with the acid medium to give an undeuteriated C-3 methyl group.

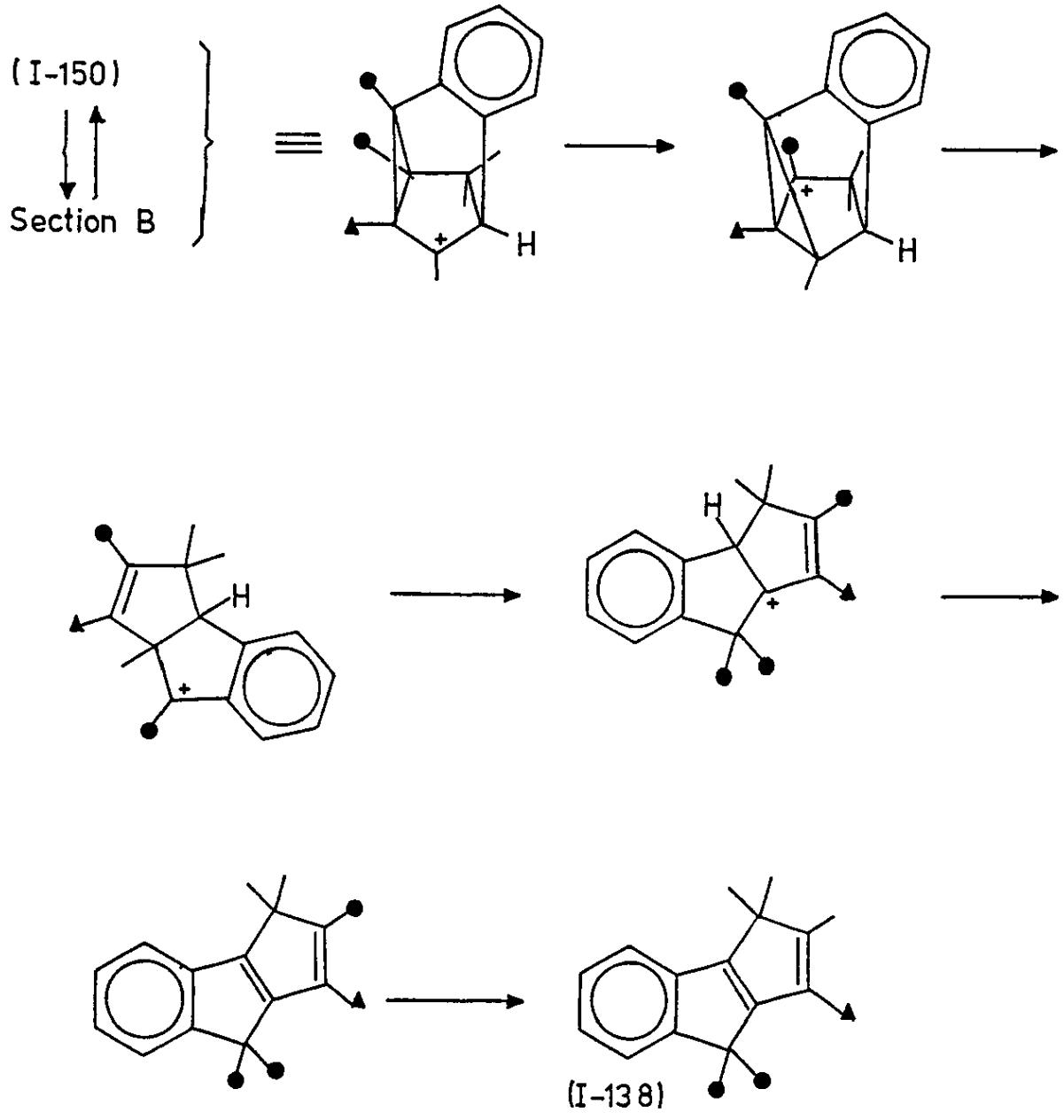
The build up of olefin (I-139) may occur because of its thermodynamic



Scheme I-33

continued.

continuation.

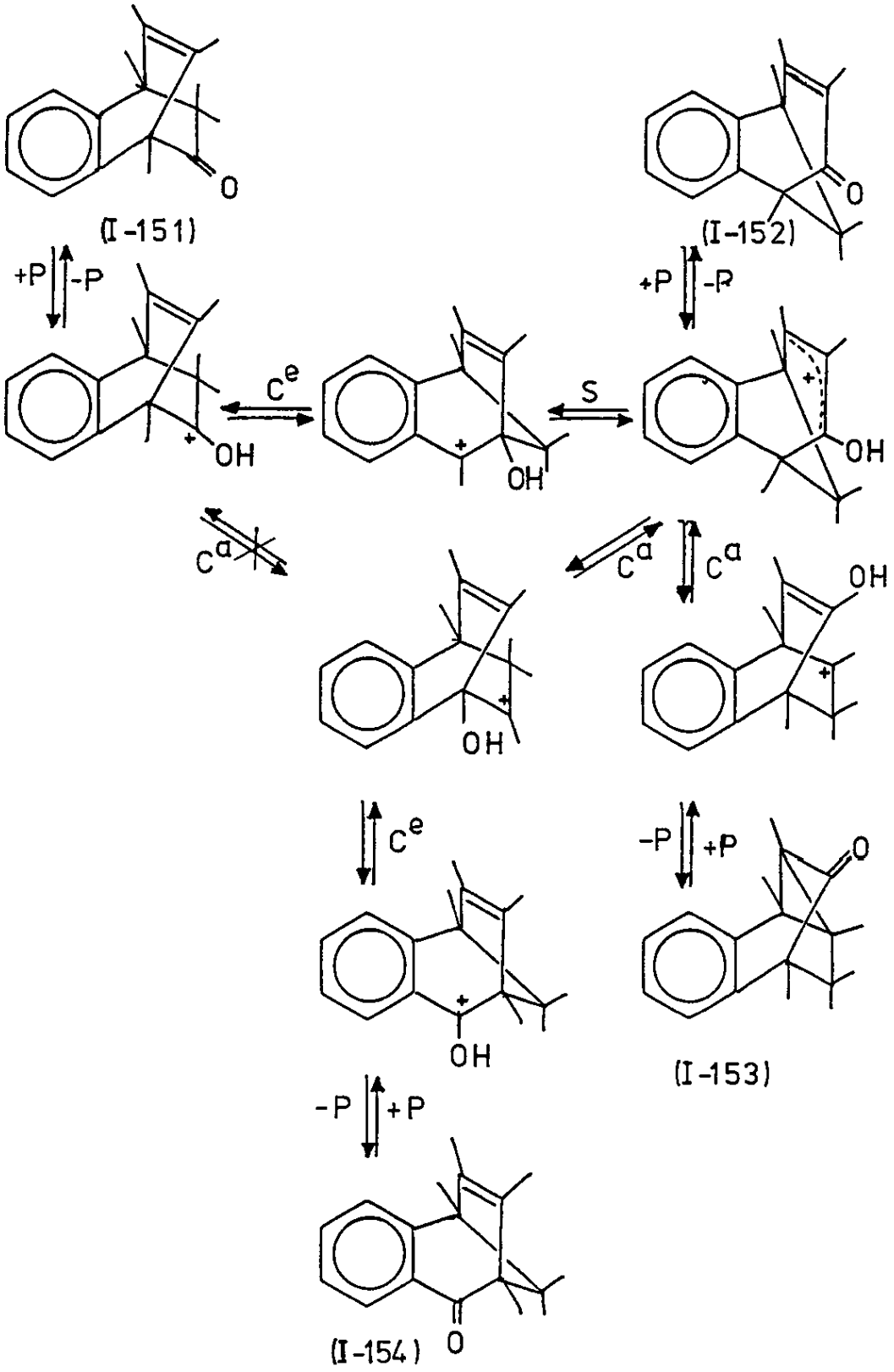


Scheme I-33

stability relative to the olefins (I-140) and (I-141) or (I-142), or because it is trapped in the circumambulation section A on the "wrong" side of a relatively high energy secondary cation. The cyclopropylcarbinyl cation (I-149) does not rearrange by [1,3]-shift in the manner of the cyclopropylcarbinyl cation (i-150) because of the secondary cation which would be formed by the rearrangement.

This interpretation regards the dehydration of the epimeric alcohols [(I-136) and (I-137)] as an extention of the rearrangements to which similar systems are prone, rather than as a fundamentally different process.

A related cation, formed by protonation of 1,3,3,4,5,6-hexamethyl-benzobicyclo[2.2.2]octadien-2-one (I-151), undergoes some similar but less extensive rearrangements.[7b] When the benzobicyclo[2.2.2]octadien-2-one (I-151) was heated in trifluoroacetic acid for several hours, an equilibrium mixture of the substrate (I-151) with the isomeric ketones [(I-152), (I-153) and (I-154)] was formed. The same equilibrium mixture could be obtained from any of the ketones [(I-151), (I-152), (I-153) or (I-154)]. The formation of these ketones is consistent with a circumambulation-[1,2]-bond shift mechanism. The O-protonated benzobicyclo[2.2.2]octadien-2-one [(I-151) $-H^+$] is the most stable cation (and forms the most stable deprotonation product) of one set of cations related by circumambulation; the protonated ketones [(I-152)$-H^+$, (I-153)$-H^+$, and (I-154)$-H^+$] are stable cations leading to stable deprotonation products of another set of circumambulating cations. The two sets of cations are connected by a [1,2]-bond shift (Scheme I-34). Scheme I-34 predicts that the benzo[6,7]bicyclo[3.2.1]octadien-2-one (I-152) should be the first ketone produced from the benzobicyclo[2.2.2]octadienone (I-151), and when this last ketone (I-151) is treated with trifluoroacetic acid at room temperature it is the benzo[6,7]bicyclo[3.2.1]octadien-2-one (I-152) which first accumulates before more slowly forming the equilibrium



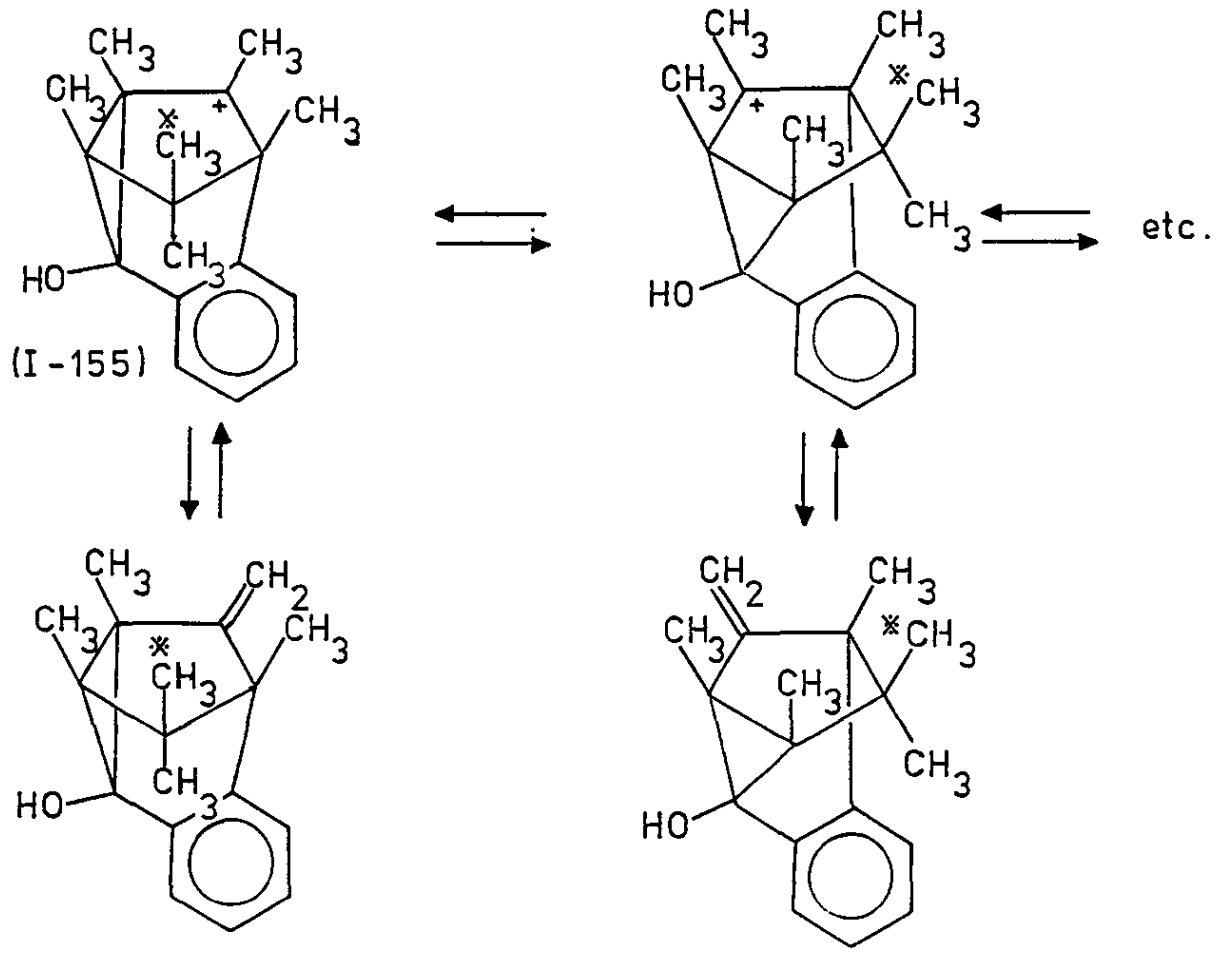
Scheme (I-34)
P : Protonation ; -P : Deprotonation ;
C : Circumambulation [e : etheno- (a : aryl-) participation] ;
S : [1,2]-Bridge Shift.

mixture.

To this point, circumambulation is the lowest energy process which has been discussed. There is some other process which appears to be more rapid in at least one case. The circumambulation which forms the hexamethylbenzo[3,4]bicyclo[3.2.1]octadien-2-one (I-154) involves aryl participation, and this process is probably relatively slow. When an attempt was made to isomerise this ketone (I-154) to the equilibrium mixture [(I-151), (I-152), (I-153) and (I-154)] with trifluoroacetic[^{2}H] acid, five of its six methyl groups underwent rapid [^{1}H]-[^{2}H] exchange.[7c] The exchange was much faster than the formation of the equilibrium mixture. The one methyl group which did not exchange was the anti-8-group (marked with an asterisk).

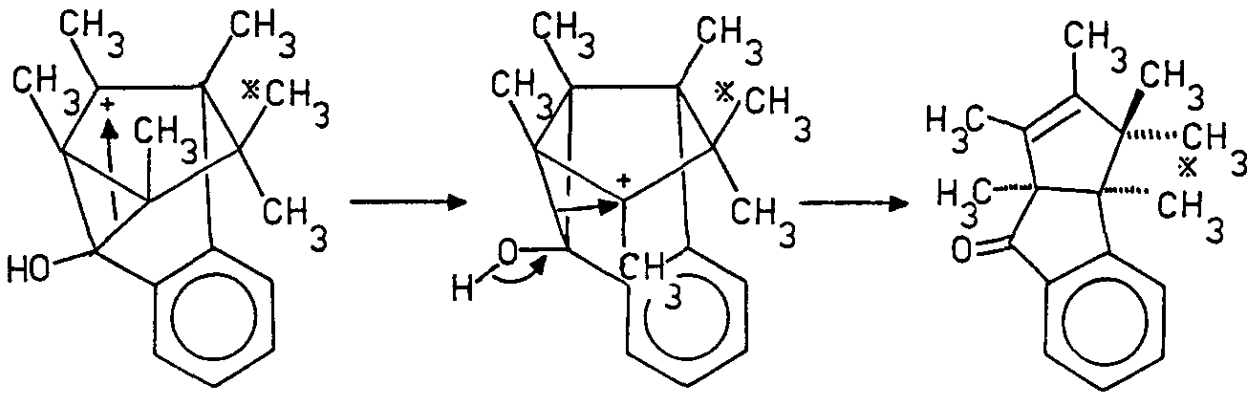
The mechanism of this extraordinary exchange is not known with certainty, but Hart has suggested that a five-fold degenerate rearrangement of the cyclopropylcarbinyl ion (I-155) in which the aryl group, the methyl group (*) and the cyclopropyl group all migrate around the cyclopentane ring in the same direction would account for the observed exchange. This migration (Scheme I-35) would in turn locate the positive charge next to every methyl group except the anti-8-group (marked with an asterisk), and each of these methyl groups which fall adjacent to the positive charge is able to exchange protons with the solvent by equilibration with the corresponding olefin.

In each stage of the degenerate rearrangement three bonds, perhaps four, must migrate. Hart has preferred to depict these migrations as stepwise whilst recognising that they might be "partially concerted". The problem with a stepwise migration is that it produces cations [e.g.(I-156)] which might be expected to collapse to the benzobicyclo[3.3.0]octadien-2-one (I-157) (e.g. by Scheme I-36). Although the benzobicyclo[3.3.0]octa-



Scheme I - 35

dien-2-one (I-157) is known [it is readily available by photoisomerisation of (I-154)] its stability in trifluoroacetic acid was not reported. It would be very interesting to know whether the benzobicyclo[3.3.0]octadien-one (I-157) reverts to benzo[3,4]bicyclo[3.2.1]octadien-2-one (I-154) under acid catalysis. Certainly, molecular models indicate that the double bond and carbonyl carbon of (I-157) are pushed close together and that the isomerising cyclopropylcarbinyl pair [(I-155) and (I-156)] could be formed from the benzobicyclo[3.3.0]octadienone (I-157). If this were in fact the case it would indicate a close similarity between the dehydration of the benzobicyclo[2.2.2]octadien-2-ols [(I-136) and (I-137)] and the equilibra-



(I-155) (I-156) (I-157)

Scheme I-36

tion of the benzobicyclo (or tricyclo) octadienones [(I-151), (I-152), (I-153) and (I-154)].

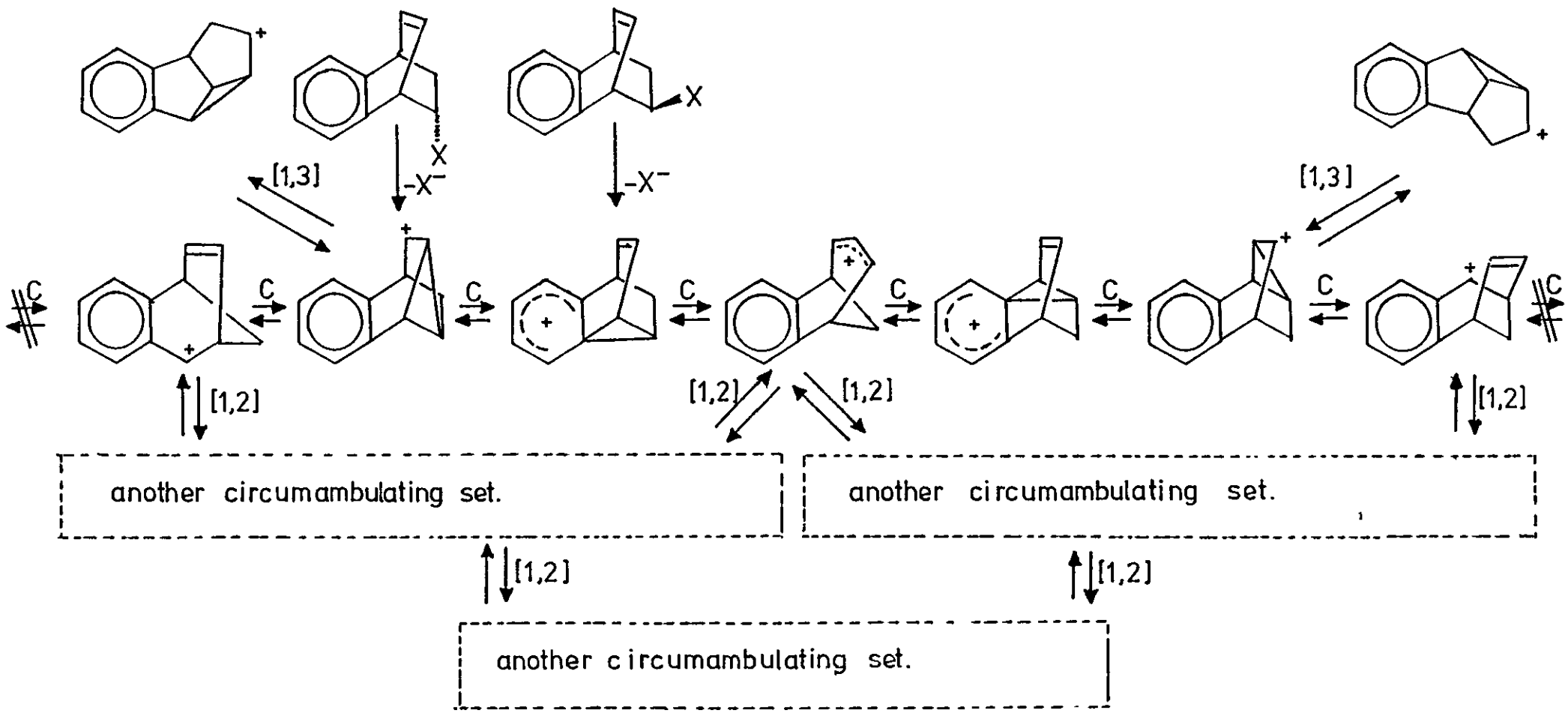
The results obtained so far with the benzobicyclo[2.2.2]octadien-2-yl cations indicate that the reactions are straightforward when the benzo-ring is not strongly deactivated.

When the cation is formed by solvolysis of an exo-2-derivative or by anti-addition of an electrophile it is stabilised by benzo-bridging to give an intermediate or transition state resembling a phenonium ion, which collapses to an allyl cation. Similarly, the endo-2-derivatives give cations stabilised by homo-allylic participation of the double bond, which collapse predominantly to benzyl cations. The allyl or benzyl cations are captured stereoselectively to form axial or quasi-axial products. Under conditions of long-life or repeated formation, the allyl or benzyl cations may isomerise. There are at least three levels on which isomerisation may occur: circumambulation (including "bridge-flipping", see Scheme I-9), [1,2]-bridge shift (including "bridgehead exchange", see Scheme I-9), and

pathways leading from the benzobicyclo[3.2.1]octadien-2-yl manifold. The ease with which these reactions occur is apparently the one given here, but insufficient information is available to allow confident generalisation. These results are summarised in Scheme I-37.

Analogous results have been obtained with the benzobicyclo[2.2.2]-octen-2-yl system. In the exo-series aryl participation occurs to give a phenonium ion which collapses stereospecifically benzobicyclo[2.2.2]octen-exo-2-yl or benzobicyclo[3.2.1]octen-exo-2-yl derivatives. Solvolysis of benzobicyclo[2.2.2]octen-endo-2-yl derivatives gives benzyl cations by [1,2]-bridge migration and these benzyl cations are captured stereoselectively to give quasi-axial products (cf. Scheme I-23).

When the benzo-ring is strongly deactivated the reaction becomes more complex. Aryl participation is inhibited in the exo-series, and [1,2]-bridge migration is inhibited in the endo-series. Solvent assistance in the ionisation step becomes more important, and the amount of hydrocarbon formed by elimination increases.



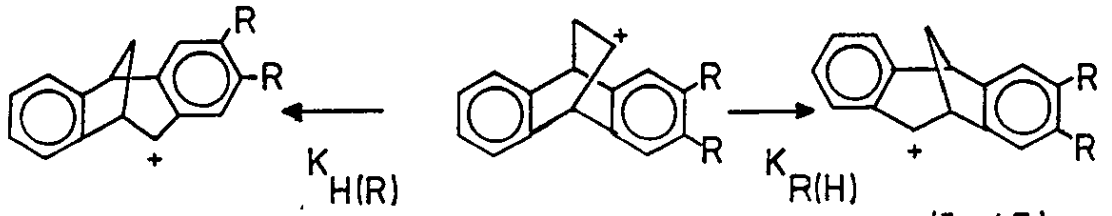
Scheme I - 37

C = Circumambulation.

APPENDICES

I. <u>The Compositite Nature of the Reaction Constant, ρ, Obtained for Reactions of the Dibenzobicyclo[2.2.2]octadien-2-yl Cation.</u>

Consider the following rearrangements:



(I-46) (I-47)

$K_{H(H)}$ is the rate constant for migration of an unsubstituted benzo-ring to leave the "unsubstituted" benzyl cation (I-11).

$K_{H(R)}$ is the rate constant for migration of an unsubstituted benzo-ring to leave the substituted benzyl cation (I-46).

$K_{R(H)}$ is the rate constant for migration of a substituted benzo-ring to leave the "unsubstituted" benzyl cation (I-47).

Applying Hammetts $\rho\sigma^+$ treatment we obtain

$$\log \frac{K_{R(H)}}{K_{H(H)}} = \rho_1[\sigma]^+ , \quad \text{and} \quad \log \frac{K_{H(R)}}{K_{H(H)}} = \rho_2[\sigma]^+$$

(where $[\sigma]^+$ is the appropriate combination of σ_m^+ and σ_p^+.)

which reduces to

$$\log \frac{K_{R(H)}}{K_{H(R)}} = \log \frac{K_{R(H)}}{K_{H(H)}} - \log \frac{K_{H(R)}}{K_{H(H)}} = (\rho_1 - \rho_2)\,[\sigma]^+$$

so that log (product ratio) = $\rho[\sigma]^+$ where $\rho = (\rho_1 - \rho_2)$, a composite reaction constant.

II. Kinetic Analysis of the Isomerisation of cis-2-Acetoxy-1,3-[$^2H_2$]dibenzobicyclo[2.2.2]octadiene (I-72).

See Scheme I-11 for a key to the nomenclature.

Denote the pair (I-72) and (I-73) by US, (= unswitched), their combined concentration by x_{US}, the rate constant for bridgehead switching by k_s, and the half-life for equilibration by bridgehead switching by $t_{\frac{1}{2}}$ (S). Similarly denote the pair (I-72) and (I-74), their combined concentration, the rate constant for bridge flipping, and the half-life for equilibration by bridge flipping by UF (= unflipped), x_{UF}, k_F, and $t_{\frac{1}{2}}$ (F). The initial value of $x_{UF} = x_{US} = a$.

For bridgehead switching:

$$-\frac{d}{dt}(x_{US}) = k_S x_{US} - k_S (a - x_{US})$$

$$= k_S (2x_{US} - a)$$

$$\int \frac{d(x_{US})}{(2x_{US}-a)} = -k_S \int dt$$

$$\tfrac{1}{2}\left[\ln(2x_{US}-a)\right] + C = -k_s t$$

Applying the boundary condition x = a when t = 0

$$C = -\frac{\ln(a)}{2}$$

so that

$$k_S \quad \frac{1}{2t} \cdot \ln\left[\frac{(a)}{(2x_{US} - a)}\right] \qquad (1)$$

As a check that this rate equation has an acceptable form, the limiting concentration of US at infinite time may be found:

(1) rearranges to

$$\frac{(2x_{US} - a)}{(a)} = \exp(-2k_s t) \qquad (2)$$

$$\lim_{t \to \infty} \left| \frac{(2x_{US} - a)}{(a)} \right. = \lim_{t \to \infty} \left| \exp(-2k_s t) \right. = \text{zero}$$

so that

$$\lim_{t \to \infty} \left| (2x_{US} - a) \right. = \text{zero}$$

and

$$\lim_{t \to \infty} \left| (x_{US}) \right. = \frac{a}{2}$$

This is the correct value, the equilibrium boundary condition.

The half-life, $t_{\frac{1}{2}}(S)$, for this equilibration is the time required for x_{US} to drop to $\frac{3a}{4}$. Substitution of this value in (1), and solving for t gives

$$t_{\frac{1}{2}}(S) = \frac{1}{2k_s} \cdot \ln(2) \qquad (3)$$

The corresponding equations for bridge flipping are obtained by replacing k_S, x_{US}, and $t_{\frac{1}{2}}(S)$ by k_F, x_{UF}, and $t_{\frac{1}{2}}(F)$, respectively. Substitution of the data collected in Table I-3 into equations (1) and (3), and the analogous equations for bridge-flipping, gives the values:

$K_S = 1.45 \times 10^{-2}$ h.$^{-1}$; $t_{\frac{1}{2}}(S) = 23.97$ h. (After 30h.)

$K_S = 1.41 \times 10^{-2}$ h.$^{-1}$; $t_{\frac{1}{2}}(S) = 24.52$ h. (After 75h.)

$K_F = 4.69 \times 10^{-2}$ h.$^{-1}$; $t_{\frac{1}{2}}(F) = 7.39$ h. (After 30h.)

so that $\frac{K_F}{K_S} = 3.28$

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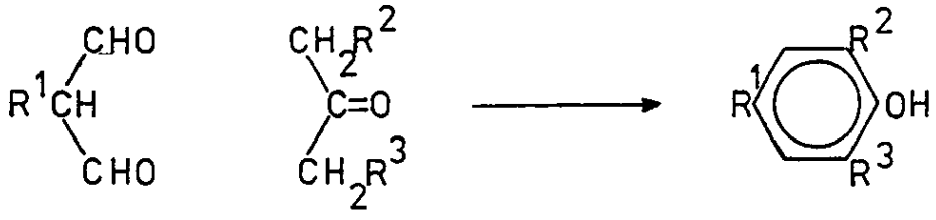
CHAPTER TWO

The Synthesis of 1-[^{14}C]Anisole

Introduction

There are several published syntheses of 1-[^{13}C]- or 1-[^{14}C]-anisole or phenol.[1] Two distinct approaches to the construction of such specifically labelled aromatic compounds may be discerned.

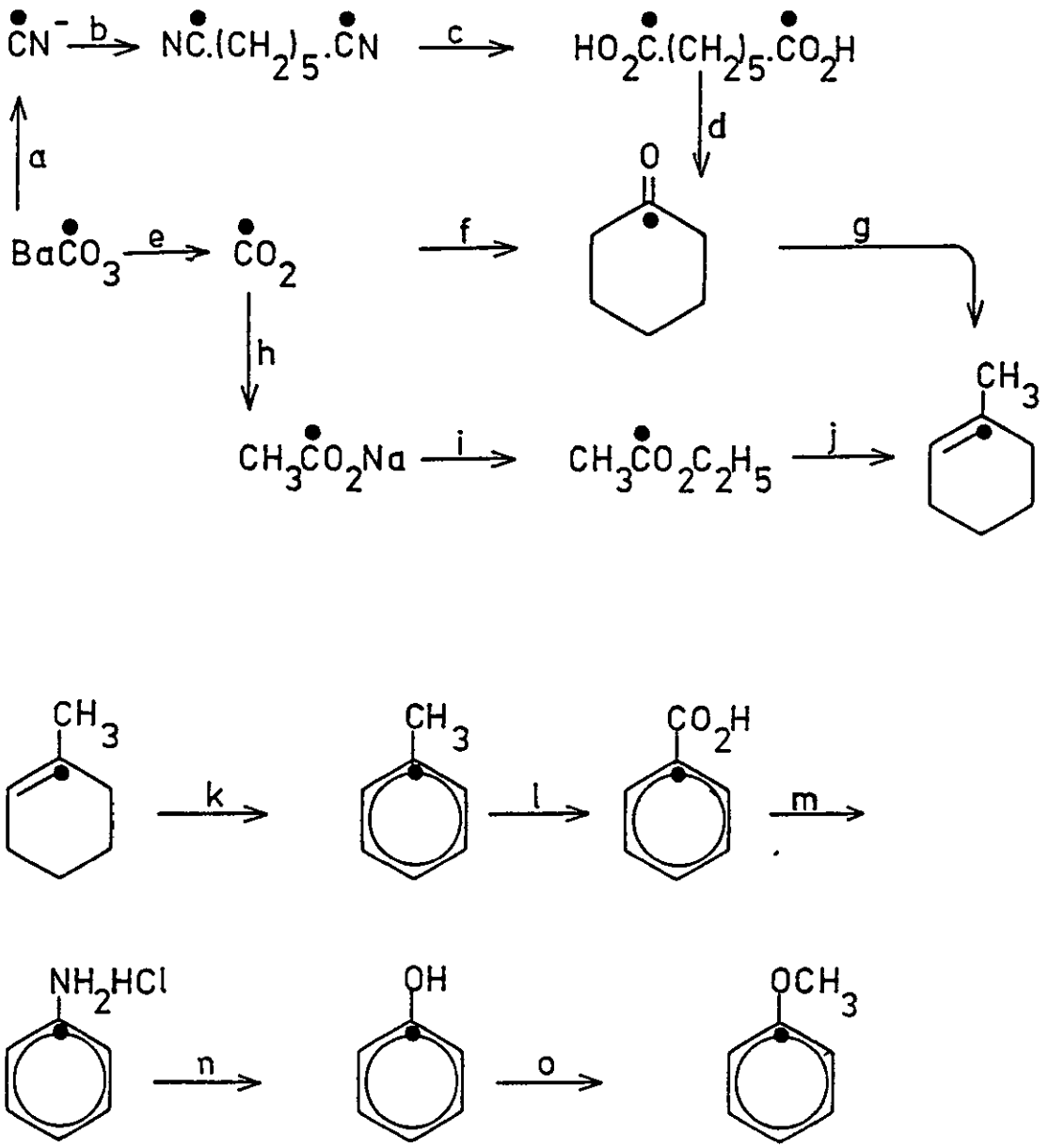
One method (Scheme II-1) involves the condensation of two-three carbon units to produce the aromatic ring in one step. The instability and inaccessibility of most malondialdehyde derivatives and the need for this component to act as an electrophile have restricted the choice of one component to sodium nitromalondialdehyde. This component is not easily labelled and it is the other component which is used to introduce the heavy isotope.



Scheme II-1

In practice the choice of this component is usually restricted to acetone,[1e-i] labelled forms of which are readily available. The key intermediate in syntheses by this route is 4-nitrophenol. We have now developed this method into the most convenient synthesis of 1-[^{14}C]anisole currently available.

The second method (Scheme II-2) has two major variants differing in the nature of the first cyclic product. In both variants the ring is synthesised from a one- and a five-carbon fragment. The one-carbon fragment



Scheme II-2

Reagents (Reference): a) $Zn/NH_3/N_2/650^{\circ}$ (1l,m); b) $Br.(CH_2)_5.Br$/ Aqueous alcohol/Boil(1l-o); c) Conc. HCl/Boil(1l,m,o); d) Ba or Ca salt/Pyrolyse(1l-o); e) H^+ (1d,p); f) $BrMg.(CH_2)_5.MgBr$ (1k); g) CH_3MgI; h) CH_3MgI, then NaOH (1a,d,p,r); i) $(C_2H_5O)_3PO$/Boil(1a,d,p-r); j) f), then boil with I_2 (1a,d,p-r); k) Catalytic dehydrogenation (1a,d,p-s); l) $KMnO_4$ (1a,d,p-r); m) NaN_3/H^+, then HCl (1a,c,d,p,q); n) $NaNO_2/H^+/H_2O$ (1a,c,d); o) $CH_3I/OH^-/CH_3(SO)CH_3$ (11).

carries the label, and the five-carbon fragment may be modified before ring formation to introduce a predetermined substitution pattern.[1j] The key intermediate in these syntheses is 1-methylcyclohexene, the compound at which these variants all converge.

There are several points to note. Firstly, one may choose to enter the synthetic scheme at any of several positions, indeed there is a growing tendency to enter the scheme at 1-[^{14}C]phenol which is now commercially available,[1g,2] and the overall yield will vary accordingly. Secondly, the loss of half of the label as carbon dioxide in the pyrolysis of the barium salt of pimelic acid and the low yield observed in the reaction between carbon dioxide and the bis-Grignard reagent from 1,5-dibromopentane give syntheses via cyclohexanone a poor start. Thirdly, cyclohexanone and phenol differ only in their levels of oxidation and both possess the same carbon skeleton and substitution pattern, but in spite of this structural closeness they are synthetically remote. Fourthly, the implicit use of a methyl group to protect the positional integrity of the label during the aromatisation step generates a large number of additional steps devoted to introducing and removing this group.

Low radiochemical yields have no doubt discouraged syntheses via cyclohexanone although the procedure is widely followed; perversely enough most syntheses by this route then proceed on to 1-methylcyclohexene and so on as shown. Attempts to oxidise cyclohexanone to phenol, avoiding the introduction of a methyl group to locate the labelled carbon atom are rare. The conversions of 3,5-dimethyl-1-[^{14}C]cyclohexanone and 1-[^{13}C]cyclohexanone to the corresponding phenols by catalytic dehydrogenation have been reported,[1j,b] suggesting that syntheses via cyclohexanone could be considerably improved. This suggestion has been confirmed and we have developed a one step conversion of cyclohexanone to phenol and a (different) two step

conversion of cyclohexanone to anisole as alternatives to the five and six step conversions shown in Scheme II-2. It is shown in chapter four that no significant amount of scrambling of the label occurs in the direct oxidation of 1-[^{14}C]cyclohexanone to 1-[^{14}C]phenol, so that the oxygen function may itself be used to locate the labelled carbon atom.

Of prime importance in syntheses which use a methyl group for this purpose is the constancy of the methyl-ring bond; a footloose protecting group is a foolish thing. Ihrig and co-workers have recently reported some scrambling of the label in the catalytic dehydrogenation of 1-methyl-1-[^{13}C] cyclohexene to 1-[^{13}C]toluene.[1s] With ^{13}C-labelling such scrambling may be detected by ^{13}C-n.m.r. spectroscopy, but detection of scrambling with ^{14}C-labelling is more difficult. This result emphasises the importance of the "wet chemical" route to 1-[^{14}C]anisole described in this chapter and highlights the need for a convenient degradative procedure which separates and allows the isolation of the different carbon atoms of an aromatic ring. We have developed such processes, which are described in chapter three.

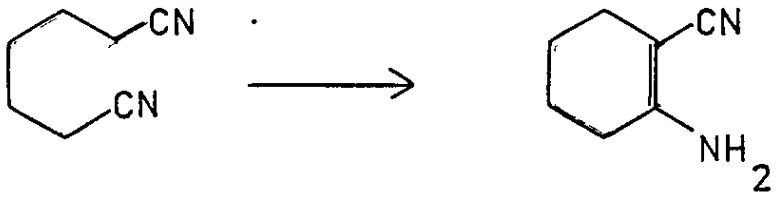
Results and Discussion

There are three distinct objectives on the synthetic pathway to 1-[^{14}C]phenol and anisole. The label must be introduced, the ring system and substitution pattern must be constructed, and the oxidation level must be adjusted. Of these only the last may be performed before the label is introduced, but it might be possible to construct the ring and introduce the label in one step. All other reactions must be regarded as potentially superfluous, if possibly justified by an improvement of the yield relative to those more direct syntheses or by the very probably temporary absence of suitable shorter syntheses. The reactions chosen must be such that the positional integrity of the label is established and maintained.

The choice of syntheses with isotopically enriched reagents is as much directed by the availability of the reagents as by the desire to conserve the enriched isotope. In this case the available source of ^{14}C was sodium [^{14}C]cyanide, suggesting that the successful synthesis would proceed *via* pimelonitrile, cyclohexanone and phenol.

Sodium cyanide was converted to pimelonitrile, pimelic acid and cyclohexanone as in Scheme II-2. The reactions proceeded as reported; no difficulties were encountered and no major improvements were made. Dehydration and decarboxylation of pimelic acid by acetic anhydride during distillation has been reported,[3] but appears to offer no advantages.

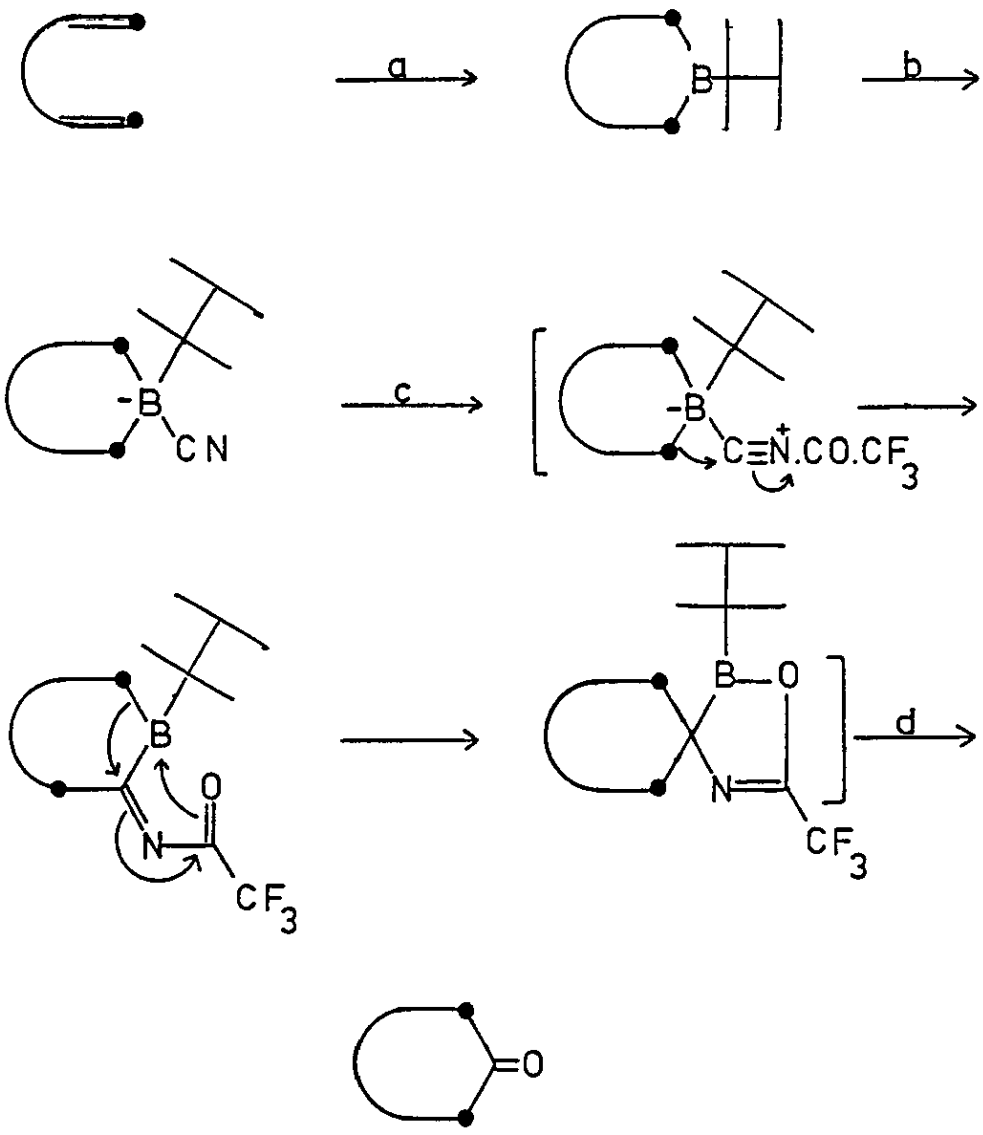
In an attempt to construct the ring system in higher yield, pimelonitrile was subjected to Thorpe-Ziegler cyclisation[4] (Scheme II-3). The



Scheme II-3

product was obtained in excellent yield but the i.r. spectrum differed from that reported; the bands previously observed[4a] at 2212, 3419 and 3509 cm^{-1} were observed at 2180, 3360 and 3450 cm^{-1}. The concordance of melting points[4b] and other i.r. bands (previously 1616, 1647 cm^{-1}, now reported 1610, 1650 cm^{-1}), and the mass and n.m.r. spectra leave little doubt that the structure of the product is correctly assigned.

Attempts to hydrolyse the product to cyclohexanone were unsuccessful; the reasons for this are unclear, but previous attempts have also failed to



Scheme II-4

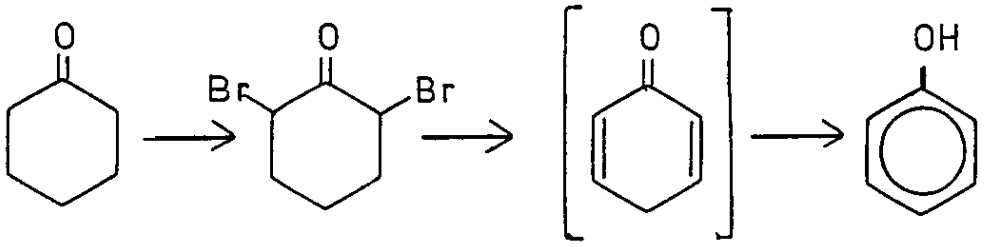
Reagents: a) t-Hexylborane; b) KCN; c) $(CF_3CO)_2O$; d) H_2O_2/OH^-.

produce useful yields,[4c] and the synthesis of cyclohexanone by cyclisation of pimelonitrile was abandoned.

One other synthesis of cyclohexanone which is based on cyanide commends itself: the formation of ketones by rearrangement under the influence of electrophiles of trialkylcyanoborate species has recently been reported in full detail[5] (Scheme II-4). The method is closely analogous to the carbonylation of boranes,[6] but would avoid both the use of radiolabelled carbon monoxide or of some precursor thereof and the forcing conditions associated with the carbonylation reactions. High overall yields are obtained, the label is introduced in the cyclisation step, and a preformed substitution pattern may be easily introduced; the method should become that of choice for the preparation of 1-[^{14}C]cyclohexanone and many of its derivatives. It is unfortunate that this method had not been developed when we were involved in this particular synthesis.

The conversion of cyclohexanone to phenol was considered next.

The sequence bromination-dehydrobromination-spontaneous aromatisation seemed attractive (Scheme II-5). The bromination of cyclohexanone with

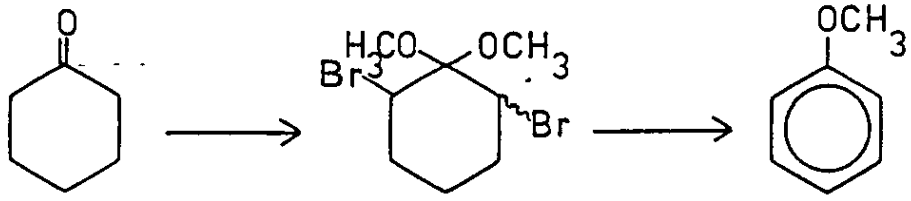


Scheme II-5

bromine in acetic acid gave a lachrymatory oil in 64% yield, but i.r. analysis indicated that the reaction was incomplete. Bromination with pyridinium tribromide in acetic acid gave a similar oil in 86% yield

characterised by i.r. analysis[7] as mixture of cis- and trans- 2,6-dibromocyclohexanone. However, attempts to dehydrobrominate this mixture under a variety of conditions gave disappointing yields of phenol (estimated as the benzoate), and this approach was modified.

Bromination of cycloalkanones in methanol or ethylene glycol has been reported[8] to give α-bromoacetals. Use of two equivalents of bromine results in α,α′-dibromoacetal formation. When cyclohexanone in methanol was treated with two equivalents of bromine a mixture of cis- and trans- 2,6-dibromo-1,1-dimethoxycyclohexane was obtained in better than 86% yield. This product was aromatised with sodium methoxide or sodium t-butoxide in dimethyl sulphoxide to give anisole in overall yields from cyclohexanone of 27 and 52% respectively (Scheme II-6).



Scheme II-6

The catalytic dehydrogenation of cyclohexanone to phenol has been reported.[1b,1j,9] The yields and conversions quoted are excellent, but the conditions are more suited to a continuous flow process than to batch production. The method of Swift[9a] was investigated. Passage of cyclohexanone vapour in a hydrogen carrier gas over a tin-nickel catalyst supported on silica-gel and heated to 380° at such a rate that the catalyst temperature was maintained gave a 60% yield of phenol, estimated as the benzoate. This yield is not as good as those reported by Swift, but com-

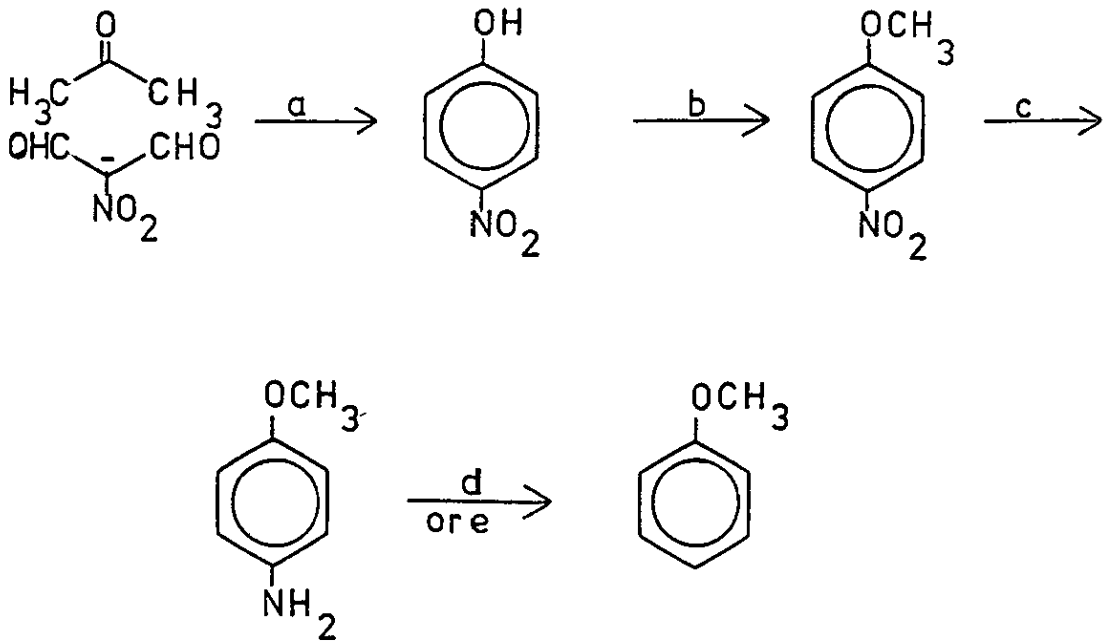
pares favourably with other methods.

The problems of conducting successful batch flow dehydrogenations without specialised equipment should not be underestimated. Difficulties in accurately monitoring carrier gas and particularly cyclohexanone flow rates and in controlling the temperature of the catalyst during the exothermic reaction lend some hit or miss character. The range of conditions under which dehydrogenation occurs in good yield is not great and in a small batch process the time available for "fine tuning" is limited. Nonetheless, careful work will yield reasonable results.

One other synthesis was investigated. Condensation of sodium nitromalondialdehyde with acetone[1e-i,10] gave 4-nitrophenol, the potassium salt of which was methylated with methyl iodide in dimethyl sulphoxide[11] to give 4-nitroanisole. Reduction of this with hydrazine hydrate in the presence of palladised charcoal[12] gave 4-aminoanisole which was deaminated by diazotisation and reduction[13] to give anisole (Scheme II-7).

The reduction of diazotised 4-aminoanisole with alkaline formaldehyde (72%)[13b] and of its acid salt with naphthalene-1,5-disulphonic acid (near quantitative yield)[13c] have been reported. The latter reaction is reported to give unexpected difficulties from time to time.[13d] The available data suggested that dediazoniation with hypophosphorous acid would also proceed in good yield.[13a] The deamination of several aminoanisoles by diazotisation with pentyl nitrite in boiling tetrahydrofuran[13e] and the deamination of some aminoazulenes by diazotisation with pentyl nitrite in dioxan in the presence of hydroquinone[13f] have been reported recently. The latter method, an extention of the work of Orton and Everatt,[13g] has been almost completely neglected since its publication. As the method appeared to have merit, it was reinvestigated with 4-aminoanisole as the substrate.

The method utilises concurrent addition of hydroquinone and pentyl



Scheme II-7
Reagents: a) 25% aqueous NaOH; b) $CH_3I/OH^-/CH_3.SO.CH_3$; c) N_2H_4/ Pd-C, d) C_5H_9ONO/CF_3CO_2H, then urea, then hydroquinone; e) $NaNO_2$/dil. HCl, then 30% H_3PO_2.

nitrite to a solution of the amine in dioxan. Both hydroquinone and pentyl nitrite are taken in twenty-fold molar excess because, it is said,[13f] of their competing self-reaction. This is by any standards an understatement, for the evolution of large volumes of nitrogen oxides occurs immediately. A more satisfactory procedure was found. 4-aminoanisole was diazotised at 0° with pentyl nitrite-trifluoroacetic acid[14] in tetrahydrofuran followed sequentially by the destruction of excess of pentyl nitrite with urea and the addition of one equivalent of hydroquinone. Gas evolution commenced at once and cooling was required to maintain the temperature below 25°. When the reaction was complete, g.l.c. analysis (p-dichlorobenzene as

internal standard) showed the presence of anisole in 55±3% yield. A simple purification procedure has been evolved to complement the reaction (see experimental section). Similarly, diazotisation of 4-aminoanisole with sodium nitrite in hydrochloric acid followed by reduction of the diazonium salt with aqueous hypophosphorous acid[13h] gave anisole in excellent yield (90±5% by g.l.c., p-dichlorobenzene as internal standard, 88% isolated yield). An especially pleasing feature of the last reaction is the absence of tarry by-products. This reaction sequence was not optimised since the source of ^{14}C was sodium [^{14}C]cyanide, but enough data have been collected to show that this sequence is a good alternative to the published syntheses of 1-[^{14}C]anisole. Indeed, the overall yield of over 50%, combined with the simplicity and convenience of the procedure make this synthesis of 1-[^{14}C]anisole the most attractive one currently available.

EXPERIMENTAL SECTION

General Procedures

All reactions involving organometallic reagents were carried out in oven-dried glassware under an atmosphere of dry, oxygen-free nitrogen. All solvents were distilled and dried to the appropriate degree by conventional methods before use.

Analytical t.l.c. was carried out using 0.25mm thick layers of silica-gel (GF_{254} according to Stahl); preparative t.l.c. was carried out using 1.0mm thick layers of silica-gel (PF_{254} according to Stahl).

Analytical g.l.c. was carried out using a Pye 104 series gas chromatograph fitted with a flame ionisation detector.

Infra-red spectra were determined for potassium bromide discs, thin films, or solutions in chloroform, on a Perkin-Elmer 257 spectrophotometer. Ultra-violet spectra were determined on a Pye SP 8000 spectrophotometer.

^{1}H-n.m.r. spectra were determined for approximately 20% w/w solutions containing tetramethylsilane as internal standard at 60MHz or 90MHz on Perkin-Elmer R10 or R32 spectrometers.

Mass spectra were determined on an A.E.I. MS12 mass spectrometer.

Melting points were determined on a Koffler block, and are uncorrected.

Light petroleum refers to the fraction boiling between 60-80° unless otherwise stated.

1. Pimelonitrile, from 1,5-dibromopentane and sodium cyanide in aqueous ethanol.[10,15]

A solution of 1,5-dibromopentane (57.5g, 250 mmol) and sodium cyanide (24.5g, 500 mmol) in ethanol (150 ml) and water (50 ml) was heated under reflux for 12h. Solvents were removed under reduced pressure. The residue was washed thoroughly with ethyl acetate and the washings were evaporated to leave a golden yellow oil, (29.8g, 97% crude yield). Distillation gave pimelonitrile, (20.6g, 80%), b.p. 120° at 0.9 mmHg, (lit.[16] b.p. 149° at 1 mmHg).

2. Pimelonitrile, from 1,5-dibromopentane and sodium cyanide in dimethyl sulphoxide.[16,4f]

A solution of 1,5-dibromopentane (2.30g, 10 mmol) and sodium cyanide (0.98g, 20 mmol) in dimethyl sulphoxide (100 ml) was heated at 90° for 30 min. The reaction mixture was cooled to room temperature and partitioned between brine and chloroform (100 ml). The aqueous phase was extracted with chloroform (2 x 50 ml). The combined organic phases were washed with brine (2 x 25 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure:pimelonitrile, a pale yellow oil, (1.17g, 96%) which distilled as one fraction, b.p. 118° at 0.3 mmHg, (lit.[16] b.p. 149° at 1 mmHg), was obtained.

3. Pimelic acid, by acid hydrolysis of pimelonitrile.[10,15]

An emulsion of pimelonitrile (5.01g, 41 mmol) in hydrochloric acid (concentrated, 15 ml) was heated under reflux for 3h. When the homogeneous reaction mixture was cooled to room temperature it solidified. The reaction mixture was extracted with ether (3 x 20 ml) and the combined ethereal extracts were washed with aqueous sodium hydroxide (2 N, 3 x 20 ml). The

combined basic extracts were acidified (concentrated hydrochloric acid) and extracted with ether (3 x 20 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give pimelic acid, (5.39g, 83%) m.p. 102-105° (lit.[17] m.p. 104-105°).

4. Pimelic acid, by acid hydrolysis of crude pimelonitrile.[1o]

An emulsion of crude pimelonitrile [from 1,5-dibromopentane (6.90g, 30 mmol) and sodium cyanide (2.94g, 60 mmol), prepared by the method described in experiment 1] was hydrolysed with hydrochloric acid [(concentrated, 15 ml), by the method described in experiment 3] to give pimelic acid, (3.74g, 79%), m.p. 102-105°, (lit.[17] m.p. 104-105°).

5. 2-Amino-1-cyanocyclohexene, by cyclisation of pimelonitrile with lithium N-ethylanilide.[4d]

A solution of pimelonitrile (7.32g, 60 mmol) in ether (250 ml) was added dropwise during 96h to the condensate from an ethereal solution of lithium N-ethylanilide [from n-butyllithium in hexane (60 mmol) and N-ethylaniline (7.26g, 60 mmol) in ether (250 ml)] being heated under reflux. The turbid reaction mixture was treated with water (1.19g, 65 mmol), maintained at room temperature for 3h, and filtered. The filtrate was dried ($MgSO_4$) and evaporated to give 2-amino-1-cyanocyclohexene, pale yellow crystals (7.27g, 98%); m.p. 92° (lit.[4b] m.p. 94-95°);
^1H n.m.r. $\tau(CDCl_3)$ 5.57 (broad singlet, 2H); 7.85 (m,4H); 8.39 (m,4H); The singlet at τ5.57 disappeared on addition of deuterium oxide;
ν_{max}(KBr) 3450, 3360, 3260, 2960, 2940, 2900, 2850, 2180, 1650, 1610, 1425, 1405, 1210, and 1150 cm^{-1} (lit.[4g] 3484, 3389, 2188, 1644, and 1615 cm^{-1}) M^+, 122 ($C_7H_{10}N_2$ requires M, 122).

6. 2-Amino-1-cyanocyclohexene, by cyclisation of pimelonitrile with lithium diethylamide.[4a]

A solution of pimelonitrile (1.22g, 10 mmol) in ether (100 ml) was added dropwise during 10h to the condensate from an ethereal solution of lithium diethylamide [from n-butyllithium in hexane (11 mmol) and diethylamine (0.80g, 11 mmol) in ether (500 ml)] being heated under reflux. The reaction mixture was maintained at room temperature for 48h. A solution of water (0.19g, 11 mmol) in tetrahydrofuran (10 ml) was added. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give 2-amino-1-cyanocyclohexene, pale yellow crystals (1.08g, 88%), characterised by comparison with the product of experiment 5.

7. Hydrolysis of 2-amino-1-cyanocyclohexene; attempted formation of cyclohexanone.

Attempts to hydrolyse 2-amino-1-cyanocyclohexene with hot or cold concentrated hydrochloric acid or with cold ethereal hydrogen chloride followed by treatment with hot water gave no cyclohexanone.

8. Cyclohexanone, by pyrolysis of pimelic acid in the presence of barium carbonate.[1o,15]

A finely ground mixture of barium carbonate (0.1g, 0.5 mmol) and pimelic acid (3.0g, 18.75 mmol) in a dry distillation tube fitted with a receiver maintained at -78° was heated to 320° during 2h, and maintained at this temperature for 14h. A clear two-phase oil distilled into the receiver, and a white solid (0.75g) sublimed to the cooler parts of the distillation tube.

The white solid was recrystallised from benzene to give pimelic acid,

white crystals, (0.53g, 17%), m.p. 102-103°, (lit.[17] m.p. 104-105°).

The clear oil was treated with a solution of 2,4-dinitrophenylhydrazine (3.5g, 17.60 mmol) in ethanol (96%, 50 ml) and hydrochloric acid (concentrated, 7 ml), boiled briefly and set aside to cool. A bright yellow solid separated which was isolated by filtration and recrystallised from ethanol to give cyclohexanone 2,4-dinitrophenylhydrazone, bright yellow plates, (3.81g, 73%; 89% based on pimelic acid consumed), m.p. 157-160°, (lit.[15] m.p. 162°).

9. Phenol, by dehydrogenation of cyclohexanone using a silica-gel supported tin-nickel catalyst.[9a]

The catalyst (20g, 8.3 wt%Ni and 3.7 wt%Sn supported on t.l.c. silica-gel), firmly packed into a horizontal pyrex tube and held in place by glass wool plugs, was reduced at 400° for 4h in a stream of hydrogen. The catalyst temperature was lowered to 380±5° and cyclohexanone (9.00g, 92 mmol) was passed through the catalyst in a stream of hydrogen at such a rate that the catalyst temperature did not exceed the limits set out above; about 30 min. was required. The exhaust gases were passed through two traps maintained at -78°. A clear oil condensed on the cooler parts of the exit tube and then solidified. The product was dissolved in ether and extracted with aqueous sodium hydroxide (2 N, 4 x 25 ml). The ethereal phase gave no precipitate with acidified ethanolic 2,4-dinitrophenylhydrazine solution. The combined basic extracts were acidified (concentrated hydrochloric acid) and extracted with ether (4 x 25 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give phenol (5.25g, 60%), identified as the benzoate, m.p. 71-74°, (lit.[15] m.p. 69°).

10. 2,6-Dibromocyclohexanone, by bromination of cyclohexanone with bromine in acetic acid.[7]

A stirred solution of cyclohexanone (37.0g, 385 mmol), hydrogen bromide (45% hydrogen bromide in acetic acid, 0.3 ml), and acetic anhydride (5 ml) in acetic acid (200 ml) was maintained below 20° and treated dropwise during 1h with bromine (123.5g, 772 mmol). The reaction mixture was stirred at room temperature for 18h, poured onto ice-water (1000 ml) and extracted with ether (3 x 200 ml). The combined ethereal extracts were washed with aqueous sodium bicarbonate (saturated, 2 x 50 ml) and water (2 x 50 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give crude 2,6-dibromocyclohexanone, a dark oil, (63.1g, 65%). ν_{max}(film) 1750 (w, cis-2,6-dibromocyclohexanone), 1732 (s, trans-2,6-dibromocyclohexanone), and 1713 cm^{-1} (w, unreacted cyclohexanone), (lit.[7] 1750, cis-2,6-dibromo-, 1732, trans-2,6-dibromo-, and 1732 cm^{-1} 2,2-dibromo-cyclohexanone).

11. 2,6-Dibromocyclohexanone, by bromination of cyclohexanone with pyridinium tribromide in acetic acid.[18]

A solution of cyclohexanone (2.94g, 30 mmol) and pyridinium tribromide (19.20g, 60 mmol) in acetic acid (75 ml) was shaken at room temperature for 20 min. The reaction mixture was diluted with water (400 ml) and extracted with chloroform (4 x 50 ml). The combined chloroform extracts were washed with aqueous ammonium carbonate (saturated, 2 x 25 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual oil was distilled under reduced pressure to give 2,6-dibromocyclohexanone, a golden oil (5.29g, 69%), b.p. 80-85° at 0.3 mmHg, ν_{max} 1750 (w), 1735 (s), and 1720 (w) cm^{-1}.

12. Dehydrobromination of 2,6-dibromocyclohexanone. Attempted formation of phenol.

Attempts to dehydrobrominate 2,6-dibromocyclohexanone did not give useful yields of phenol: (method of dehydrobromination, derivative, yield) (a) boil with 2,4,6-trimethylpyridine for 1h, 3,5-dinitrobenzoate, less than 5%; (b) boil with pyridine in p-xylene for 1h, benzoate, 25%; (c) boil with lithium chloride in dimethylformamide for 1h, benzoate, 24%.

13. Anisole, by methylation of phenol with sodium hydroxide and methyl iodide in dimethyl sulphoxide.[11]

A solution of phenol (0.94g, 10 mmol) and sodium hydroxide (1.60g, 40 mmol) in dimethyl sulphoxide (20 ml) was treated with methyl iodide (2.48g, 20 mmol) and maintained at room temperature for 30 min. The reaction mixture was diluted with water (20 ml) and extracted with light petroleum [(b.p. 40-60°), 3 x 25 ml]. The combined petroleum extracts were washed with aqueous sodium hydroxide (2 N, 3 x 25 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give anisole, a clear oil, (0.98g, 90%), identified by comparison of its i.r. and ^1H n.m.r. spectra with those of authentic anisole.

14. 4-Nitroanisole, by methylation of 4-nitrophenol with potassium hydroxide and methyl iodide in dimethyl sulphoxide.[11]

A stirred solution of 4-nitrophenol (12.9g, 100 mmol) and potassium hydroxide (22.4g, 400 mmol) in dimethyl sulphoxide (100 ml) maintained at room temperature was treated with methyl iodide (56.8g, 400 mmol) in one portion. The reaction mixture was maintained at room temperature for 2h,

then diluted with water (400 ml) and extracted with ether (4 x 50 ml). The combined ether extracts were washed with water (3 x 50 ml) and dried ($MgSO_4$). The solvent was evaporated to give 4-nitroanisole, lemon yellow needles (15.2g, 99%) m.p. 52-54°, (lit.[17] m.p. 54°). The m.p. of the product showed no depression when the product was mixed with authentic 4-nitroanisole.

15. 4-Aminoanisole, by reduction of 4-nitroanisole with ethanolic hydrazine hydrate in the presence of palladised charcoal.[12]

A warm (ca. 60°) solution of 4-nitroanisole (7.61g, 50 mmol) in ethanol (95%, 50 ml) was treated sequentially with palladised charcoal (10% Pd, 0.05g) and hydrazine hydrate (ca. 50% solution, 10 ml, ca. 100 mmol, added dropwise). The reaction mixture was boiled for 2h, then cooled to room temperature and filtered to remove the catalyst. The filtrate was diluted with ether (150 ml), washed with water (4 x 25 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 4-aminoanisole, a crystalline solid with a blue-green lustre, (5.77g, 94%). The product was identified by comparison of its i.r. spectrum with that of authentic 4-aminoanisole and by preparation of a derivative: A portion (0.62g, 5 mmol) of the 4-aminoanisole obtained as described above was treated with a solution of acetic anhydride in pyridine (1 mmol ml^{-1}, 6 ml, 6 mmol) and maintained at room temperature for 24h. The reaction mixture was diluted with water (50 ml) and extracted with ether (3 x 20 ml). The combined ether extracts were dried (Na_2SO_4) and evaporated to give 4-methoxyacetanilide, (0.63g, 77%), m.p. 128-129°, (lit.[17] m.p. 130-132°).

16. Anisole, by deamination of 4-aminoanisole with iso-amylnitrite and hydroquinone in tetrahydrofuran.[13f]

A stirred solution of 4-aminoanisole (12.30g, 100 mmol) and trifluoroacetic acid (0.1g) in tetrahydrofuran (100 ml) maintained at 5° was treated with iso-amylnitrite (14.04g, 120 mmol) dropwise during 5 min. The solution was stirred at 5° for 1h, treated with urea (0.60g, 10 mmol) and allowed to warm to 15°. Hydroquinone (11.0g, 100 mmol) was added. Gas evolution commenced immediately and became vigorous. External cooling maintained the temperature below 25° until the gas evolution had subsided. The solution was warmed to ca. 40° for 1h. Tetrahydrofuran (60 ml) was removed by careful distillation, and the residual dark solution was absorbed onto sufficient alumina to produce a dry free-running powder. The absorbed product was applied to the top of a short (ca. 5 cm) wide (diameter ca. 10 cm) column of alumina and eluted with light petroleum (b.p. 40-60°) until no anisole could be detected in the eluent by g.l.c. analysis (10% SE 30 on celite at 120°). Solvents were removed by careful distillation, finally through a 60 cm heated Vigreux column, to leave anisole, a clear colourless oil, (5.95g, 55%), pure by g.l.c. and n.m.r. analysis.

Note: the product may also be isolated by diluting with ether and washing the product with aqueous sodium bisulphite, concentrated sulphuric acid,and sodium hydroxide (to remove benzoquinone,iso-amyl alcohol,and hydroquinone)[13e,f] followed by drying and evaporating the solvent, but this procedure is distractingly tedious.

17. Anisole, by deamination of 4-aminoanisole with acidified sodium nitrite and hypophosphorous acid.[13h]

A stirred solution of 4-aminoanisole (6.15g, 50 mmol) in hydrochloric acid (concentrated, 11 ml) and water (75 ml) was cooled to 10° and treated dropwise with a solution of sodium nitrite (3.50g, 50 mmol) in water (7 ml) during 10 min. The red solution was stirred at 5-10° for 10 min, filtered (no residue was observed) and the filtrate was added to cool (ca. 10°) hypophosphorous acid (30% aqueous solution, 54 ml, 300 mmol). The resultant yellow solution became opaque and slow gas evolution commenced immediately. The solution was covered with light petroleum (b.p. 40-45°, 25 ml) and stirred at room temperature for 64h, after which time gas evolution had ceased. The phases were separated and the aqueous phase was extracted with light petroleum (b.p. 40-45°, 3 x 25 ml). The combined petroleum phases were washed with brine (2 x 10 ml).

One tenth of the extract was taken and examined by g.l.c. (10% PEGA on celite at 130°, p-dichlorobenzene as internal standard). Anisole was shown to be present (identification by peak enhancement) in 90±5% yield.

The remaining extract was dried ($MgSO_4$) and solvents were removed by careful distillation. The residual golden yellow oil was distilled. After a small forerun containing only traces of anisole by g.l.c. analysis, anisole, a clear oil, (3.90g, 80%), b.p. 150-156°, (lit.[17] b.p. 155°). The small amount of dark residue contained no appreciable amount of anisole by g.l.c. analysis.

18. 2,6-Dibromo-1,1-dimethoxycyclohexane, by bromination of cyclohexanone with bromine in methanol.[8]

A solution of cyclohexanone (9.80g, 100 mmol) in methanol (120 ml) was

treated with bromine (ca. 1g). When the brown colour of the solution had nearly faded, bromine (ca. 31g, total added 32.00g, 20 mmol) was added at such a rate that the colour of the bromine remained just visible. The reaction became ever warmer until gentle boiling occurred. The solvent was removed under reduced pressure to leave a mixture of cis- and trans-2,6-dibromo-1,1-dimethoxycyclohexane, a light orange oil, (26.10g, crude yield 86%).

$\tau(CDCl_3)$ 5.45 (dd, J=6Hz, J=4Hz), 5.70 (m) (These two signals 2H); 6.20 (s), 6.47 (s), 6.66 (s) (These three signals 6H); 7.5 - 8.4 (m, 6H). The signals at τ5.45, 6.20,and 6.66 are assigned to the cis-isomer (ca. 45%). The signals at τ5.70 and 6.47 are assigned to the trans-isomer (ca. 55%) ν_{max} (film). There was no carbonyl stretching band.

lit.[8] $\tau(CCl_4)$ a (cis) 5.77, 6.51, 6.69.

b (trans) 5.69, 6.80.

(C_6H_6) a (cis) 6.03, 6.52, 7.00.

b (trans) 5.70, 6.89, 6.99.

cis:trans = 59:41.

19. Anisole, by elimination of the elements of methanol and hydrogen bromide from 2,6-dibromo-1,1-dimethoxycyclohexane with sodium methoxide in dimethyl sulphoxide.[8]

A solution of 2,6-dibromo-1,1-dimethoxycyclohexane (26.00g, 86 mmol) in dimethyl sulphoxide (120 ml) was treated with solid sodium methoxide (11.30g, 210 mmol). The solution became warm and dark. The reaction was maintained at 20° for 24h. The solution was diluted with brine (100 ml) and extracted with light petroleum (b.p. 40-45°, 3 x 25 ml). The combined petroleum extracts were washed with water (2 x 10 ml) and brine (10 ml)

and dried ($MgSO_4$). Solvent was removed by distillation and the residual dark oil (14.69g) was examined by g.l.c. (10% SE 30 on celite at 120°, with p-dichlorobenzene as internal standard) and shown to contain anisole (identified by peak enhancement) in 31% yield (27% from cyclohexanone). A portion of the product (5.00g) was filtered through alumina (50g) and eluted with light petroleum (b.p. 40-45°) until anisole was not detectable in the eluate by g.l.c. analysis. The solvents were thoroughly removed by distillation to leave anisole, a clear oil, (0.83g, equivalent to 27%, 24% from cyclohexanone).

20. Anisole, by elimination of the elements of methanol and hydrogen bromide from 2,6-dibromo-1,1-dimethoxycyclohexane with potassium t-butoxide in dimethyl sulphoxide,[8]

2,6-Dibromo-1,1-dimethoxycyclohexane [from cyclohexanone (0.98g, 10 mmol) and bromine (3.20g, 20 mmol) in methanol by the method described in experiment 18.] was added dropwise during 5 min. to a solution of potassium t-butoxide [from potassium (1.17g, 30 mg-atoms) and t-butanol (10 ml); excess of t-butanol removed under reduced pressure] in dimethyl sulphoxide (40 ml). The dark solution was maintained at room temperature for 24h. The reaction mixture was diluted with brine (400 ml) and extracted with ether (3 x 30 ml). The combined ether extracts were washed with water (3 x 20 ml) and dried ($MgSO_4$). The solvent was removed by distillation to leave a pale yellow oil. Analysis by g.l.c. (10% SE 30 on celite, 130°, p-dichlorobenzene as internal standard) showed that anisole was present (identified by peak enhancement) in 52% yield (based on cyclohexanone).

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CHAPTER THREE

The Application of the Reaction between Arynes and Arenes to the Assay of Specifically ^{14}C-Labelled Arenes

It was shown in chapter two how 1-[^{14}C]anisole may be synthesised. It remains to be demonstrated that this anisole is specifically labelled, that it may be converted into 1-methoxy-tetrachlorobenzobarrelene, and that the product of acid catalysed rearrangement of this latter compound may be satisfactorily degraded, before the ^{14}C-tracer study of this rearrangement is described in chapter four.

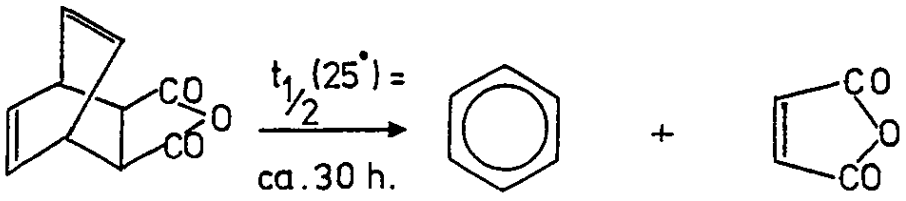
The answers to the first and last of these problems are closely bound up with the well established solution to the second, and so the three apparently diverse topics will be dealt with together in this chapter.

It will be restated how arenes react with certain dehydrobenzenes to yield cycloadducts, exemplified by 1-methoxy-tetrachlorobenzobarrelene. The application of certain addition-fragmentation reaction sequences with these cycloadducts which lead to the isolation of specific atoms of the original arenes or arene derived cycloadducts will be described.

These sequences constitute useful new chemical methods for analysing the substitution pattern of certain arenes. The methods should find use in the determination of ^{14}C distribution patterns which are established only with difficulty using the methods previously available.

Cycloaddition Reactions of Arenes and Arynes[1]

Although a monocyclic arene may be viewed as a cyclic polyolefin containing at least one distinct s-cis-diene group, arenes do not usually behave as dienes in the Diels-Alder reaction.[1c] This inertness is both a kinetic and a thermodynamic effect: not only does the stability of the cyclic 6π electron system which causes a steep rise in the energy of the system as it is perturbed result in a slow reaction rate with conventional dienophiles, it also leads to unfavourable equilibria.



Scheme III-1

In many cases the reverse reaction (e.g. Scheme III-1[2a]) is more useful than the forward one.[2]

The reaction becomes easier as the arenes become more highly (linearly) fused. Naphthalenes react more readily than benzenes, although they are for the most part extremely poor dienes, and anthracenes are sufficiently reactive across the 9,10-positions to be used as standard dienes.[2b,3]

This increasing ease of reaction is parallelled by the decreasing stabilisation energies lost on reaction of the arene ring. (Table III-1)[4]

Substitution of the arene may promote the reaction. 2-methoxynaphthalene reacts with maleic anhydride under much milder conditions than does naphthalene, and even benzenes can be induced to react if they are suitably

substituted.[2b]

TABLE III-1

Arene	Stabilisation Energy[a] (kcal. mole^{-1})	Stabilisation Energy Lost on Reaction[b] (kcal. mole^{-1})
Benzene	38	38
Naphthalene	71	33
Anthracene[c]	104	33
Anthracene[d]	104	28

(a) The amount by which the stability of the arene exceeds the stability expected for a similar structure in which the olefinic linkages are localised, estimated from heats of combustion.

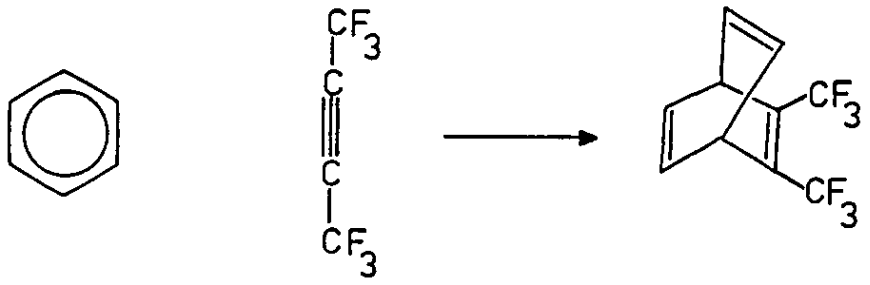
(b) Stabilisation energy of the arene minus stabilisation energies of arenes formed by the reaction.

(c) 1,4-addition.

(d) 9,10-addition.

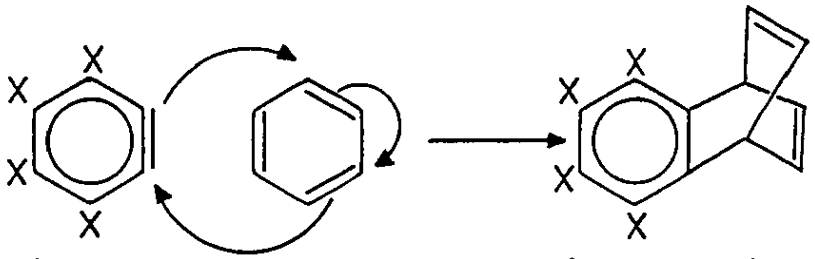
There are some very reactive dienophiles which react with benzenes to give Diels-Alder adducts (Scheme III-2), but the yields are often low. It is clear that even in extreme circumstances benzene derivatives must be regarded as poor dienes.

One class of compounds which does give cycloadducts with simple benzene derivatives is the ortho-dehydrobenzenes,[1a] usually known as benzynes or, in the general case, as arynes. With benzyne (III-1) itself the yields are again often poor, but the reactivity of the aryne may be increased by electron-withdrawing substituents. Two much investigated examples are tetrachloro- and tetrafluoro-benzyne [(III-2) and (III-3)]. These react



Scheme Ⅲ-2

with many arenes to give cycloadducts in better yields than usually obtained in comparable reactions with benzyne itself[1b] (Scheme III-3).



(X=H, III-1)
(X=Cl, Ⅲ-2)
(X=F, III-3)

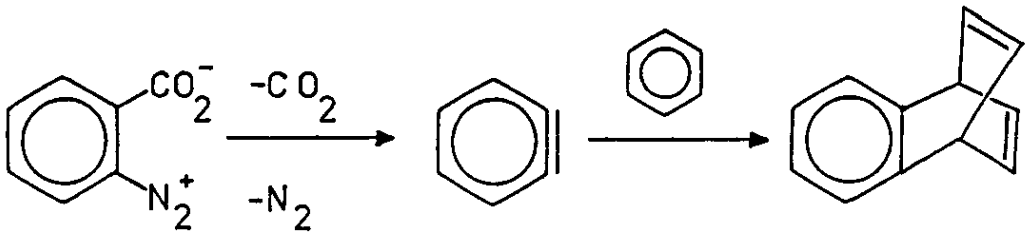
(X=H, III-4)
(X=Cl, Ⅲ-5)
(X=F, III-6)

Scheme III-3

Thus, tetrachlorobenzyne reacts with benzene to give tetrachlorobenzobarrelene (III-5) in ca. 65% yield. This greatly exceeds the useful yields obtained with benzyne. The availability of an efficient reductive dechlorination procedure makes tetrachlorobenzyne a very useful alternative to benzyne.[5]

Arynes are very reactive; the success of their reactions with the normally unreactive arenes is due in part to this property, but this reactivity brings its own problems. Arynes do not persist in solution and the reactions observed will depend on the reactivity and availability of the various potential reaction partners. Arynes react with most nucleophiles, with many common solvents and will dimerise if generated in sufficiently high concentration.[1a] In many "aryne" reactions the product is accompanied by substantial amounts of the ubiquitous tar.

It is possible to manipulate the reaction parameters to good effect. When benzyne is generated from a suspension of benzene diazonium 2-carboxylate (III-7) in the co-reagent benzene in extreme dilution external nucleophiles are absent, reaction with the solvent is the desired reaction and dimerisation is statistically unlikely (Scheme III-4).



(III-7) (III-4)

Scheme III-4

Yields as high as 40% (based on the diazonium salt) have been claimed,[6a] but reactions conducted on a preparative scale using practical amounts of solvent give much lower yields.[6b]

Even when potential co-reagents other than the arene are excluded from the reaction medium, (4 + 2)π cycloaddition does not always take place; there may be other electrocyclic reactions which compete for the available aryne.

A consequence of this reactivity is that the type of substituent which may be tolerated in Diels-Alder reactions of arynes will depend on the reactivity of the arene as a diene component. As this is generally low, the range of compatible substituents is considerably restricted.

Most anionic species will attack arynes[1a] to produce substituted aryl anions. The conjugate acids of many of these anionic species also attack arynes to produce the corresponding substituted arenes. This behaviour is to be expected when there is an appreciable concentration of >NH, >PH, -OH, or -SH groups or hydrogen halide molecules in the reaction medium.

Heteroatoms with lone pairs also attack arynes[1a] to some extent: ethers, sulphides, and tertiary amines are all capable of attacking arynes to give aryl heteronium species. Most nitrogen containing groups, most carbonyl compounds and most sulphoxides also exhibit the sort of reactivity towards arynes which leads to some degree of by-product formation[1a] which is often sufficiently great to inhibit useful amounts of $(4 + 2)\pi$ cycloaddition with unreactive dienes. Even ether, often considered inert, is attacked by arynes if no more reactive partner presents itself.

These complications are not restricted to systems containing heteroatoms; with hydrocarbon dienes many reactions may compete with $(4 + 2)\pi$ cycloaddition.[1a] Arynes have been reported to undergo insertion into C-H bonds to bring about dehydrogenation of dihydro-aromatic compounds and to take part in $(2 + 2)\pi$ cycloadditions with olefins and acetylenes, $(2 + 2 + 2)\pi$ cycloaddition with 1,4-dienes and the "ene" reaction with alkyl substituted olefins.

The intrinsically low reactivity of arenes as dienes results in the incompatibility of many of the above-mentioned groups with successful Diels-Alder reactions of arenes. In the following short survey most of the results are those obtained with tetrahalogenobenzynes. Alkyl and aryl substituents

are usually compatible, but the alkyl group may take part in an "ene" reaction[7a] and the aryl substituent may itself react as a diene component.

Aryl ethers are normally excellent reaction partners with the more active benzynes, although with benzyne itself the reaction proceeds poorly.[8] The increase in diene reactivity more than compensates for the presence of another potential reaction partner. In this context, a notable reaction is the formation of 1-hydroxy-tetrafluorobenzobarrelene from phenol, albeit in poor (11%) yield.[9]

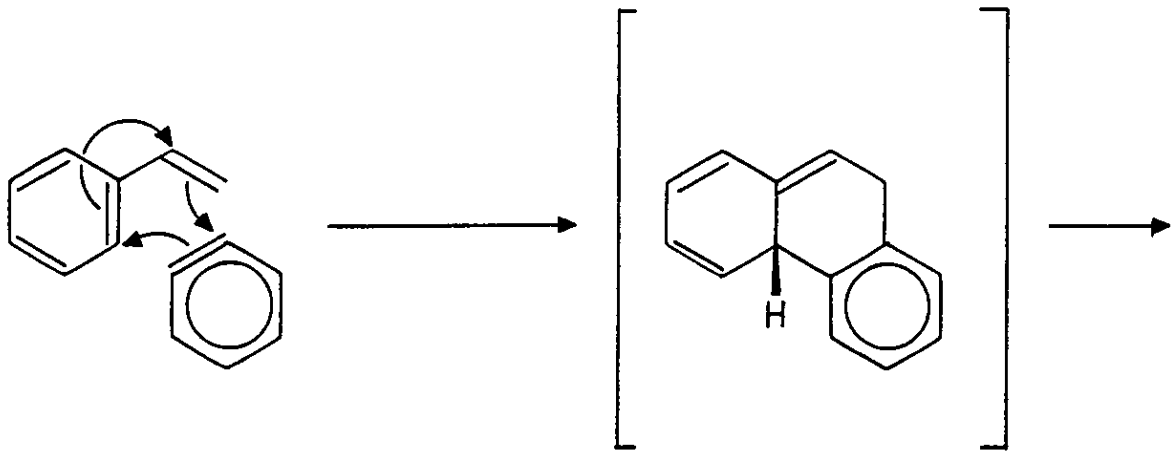
Halogeno-substituents do not interfere with the reaction[10] although they are not able to survive some of the methods used to generate arynes.[1a] Similarly, trialkylsilyl- and trialkylstannyl-substituents are normally unaffected by aryne reactions.[11]

Dialkylamino-substituents may not interfere, particularly if the nucleophilicity of the lone pair is reduced by co-ordination such as to a magnesium halide.[12] Even amide ions do not add to arynes if they are sterically highly hindered.[1a]

Aryl carbonyl compounds tend to react at the carbonyl group[13] and aryl nitroso-compounds give low yields of 1-hydroxycarbazoles.[14] Styrenes undergo (4 + 2)π cycloaddition, but use the olefinic bond as part of the diene component and give dihydrophenanthrenes as primary products (Scheme III-5).[15]

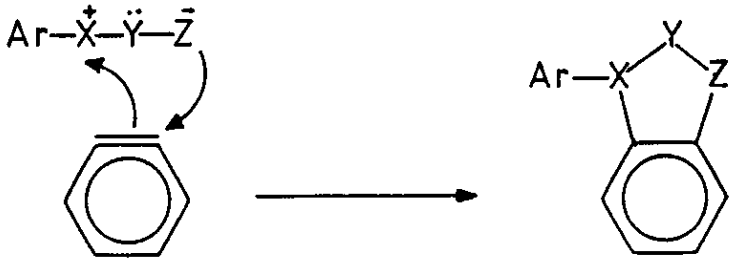
Aryl acetylenes give a complicated mixture of products but formation of ethynyl-benzobarrelenes is not an important pathway.[1a]

In general the aryl-group appears to exert a greater activating effect on conjugating substituents than do the substituents on the aryl-group. With the more reactive substituents the aryl group may be considered as an inert group. A good example of this behaviour is given by the aryl-1,3-dipoles which react with arynes to give good to excellent yields of the



Scheme III-5

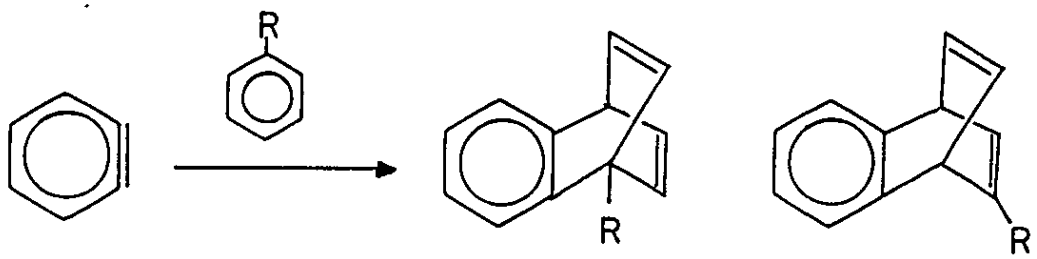
5-membered heterocycles, (Scheme III-6), almost regardless of the nature



Scheme III-6

of the aryl group.[1a]

The reaction of an aryne with a substituted arene can lead in principle to a mixture of isomeric products (Scheme III-7). Where only or predominantly one product is obtained the substituent is exerting a directing effect. Where two or more substituents are present on the arene, the products obtained will depend upon the directing effects exerted by each and upon the effect that each has upon the other. No systematic attempt to understand the relationship between a substituent and its directing effect has been made. Although on the available evidence it is not possible to



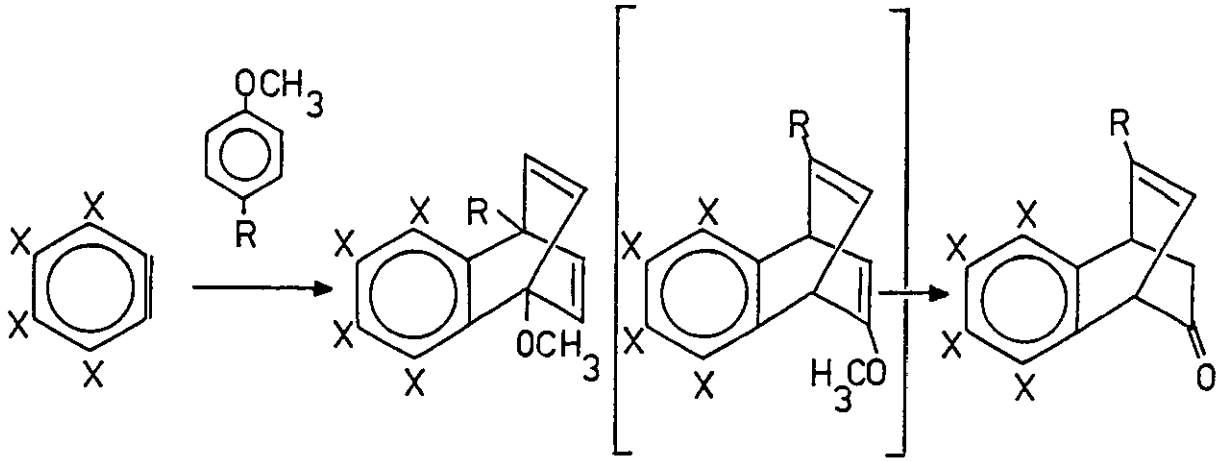
Scheme III - 7

make any sweeping generalisations about this relationship, some trends are clear.

Monoalkyl-benzenes give both possible Diels-Alder adducts. The distribution of adducts is not far from statistical but the product with the more substituted double bond usually predominates. Di- and poly-substitution produces mixtures of products where this is possible, with the reservation that when two alkyl groups stand para- to one another the adduct with two bridgehead substituents is completely avoided if possible. However, even hexamethylbenzene gives an adduct in comparable yield to benzene and the avoidance of di-bridgehead alkylation is clearly a preference rather than a condition of the reaction.[1b]

Ethers[8] and dimethylamino-groups[12] 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 (Scheme III-8).[1b] The enol ethers (e.g: III-10) are usually isolated as their hydrolysis products, the benzobarrelenones (e.g: III-12).

The observation that although cycloaddition of tetrachlorobenzyne to



X=F, R=H	(III-8)	5 : 1 (III-10)	(III-12)
OCH_3		1 : 2*	
CH_3		1 : 2*	
X=Cl, R=CH_3	(III-9)	1 : 15 (III-11)	(III-13)

Scheme III - 8

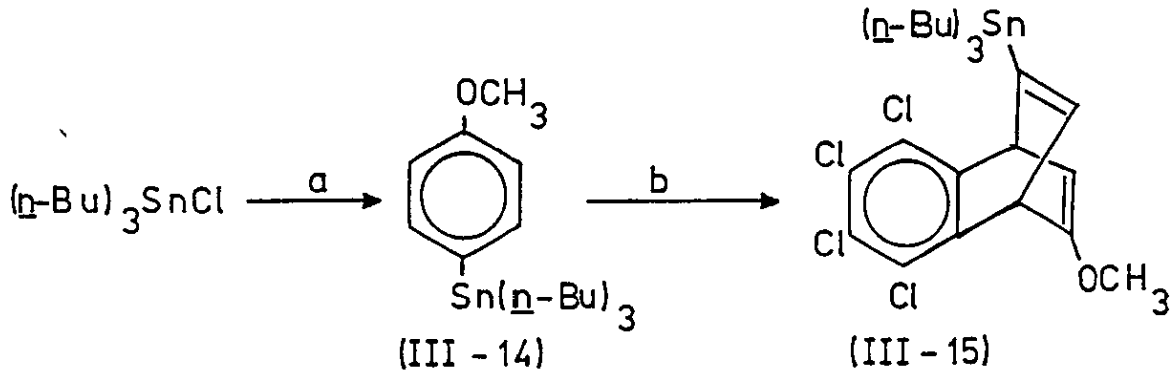
*This is the ratio which would be expected if no directing effect were operating.

anisole proceeds predominantly by 1,4-addition, cycloaddition to 4-methyl-anisole gives the adduct from 2,5(≡3,6)-addition as the major product suggested that if some group (R in Scheme III-8) could be found that would survive the reaction conditions and yet which could be removed from the product, a direct route to benzobarrelenones might be found. The stability of the trialkylstannyl-groups to aryne reaction conditions had been demonstrated, and yet the carbon-tin bond may be cleaved by a variety of electrophilic reagents under mild conditions.[16] The use of this group to

direct the cycloaddition of tetrachlorobenzyne to anisoles was investigated.

Tri-n-butyl-(4-methoxyphenyl)tin (III-14) was prepared from tri-n-butyltin chloride and 4-methoxyphenylmagnesium bromide and reacted with tetrachlorobenzyne prepared by warming a solution of pentachlorophenyllithium in diethyl ether to ca. 35°.[8d] A heavy tan precipitate formed rapidly and after only fifteen minutes the product was isolated under weakly alkaline conditions. This procedure contrasts with the extended reaction times, higher temperatures, and acidic isolation conditions normally used.[8d]

The product was an oil, contaminated with some unreacted tri-n-butyl-(4-methoxyphenyl)tin. It exhibited no ν(C=O) band in the i.r. spectrum, but showed a strong absorbtion at ν(C=C) 1645 cm^{-1}. The ^1H n.m.r. spectrum exhibited peaks at 2,95(d,1H,J=6Hz), 4,69(m,2H), 4,92(m,1H), 6,55(s,3H), and ca. 8,2-9,5, where the butyl groups of the product overlapped with those of the tributylanisyl tin (III-14). These spectral data are consistent with the enol ether structure (III-15).



(III - 14) (III - 15)

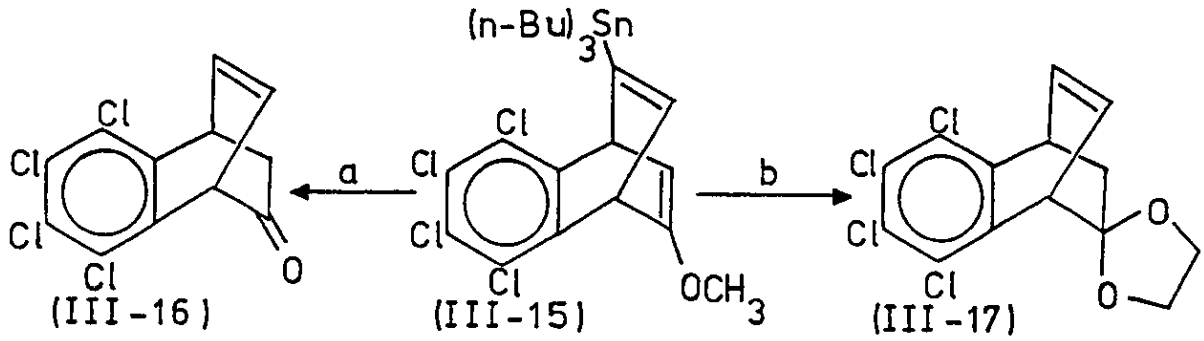
Scheme III-9

Reagents: a) 4-$CH_3OC_6H_4MgBr$; b) C_6Cl_5Li, 35°.

The yield of the adduct (III-15) was estimated from the ^1H n.m.r. spectrum to be ca. 60%, based on hexachlorobenzene.

Although the rapid and alkaline isolation procedure had been undertaken in the hope of obtaining this ether (III-15) its isolation was most unexpected. Such intermediates are not usually detected and there is no need to include a discrete hydrolysis step in reactions which produce benzobarrelenones *via* such enol ethers.[8d,12a]

The enol ether (III-15) was characterised by hydrolysis to tetrachlorobenzobarrelenone (III-16) (75%) with sulphuric acid in aqueous dioxan and by conversion to the ethylene ketal (III-17) (86%) with ethylene glycol and borontrifluoride etherate in dichloromethane (Scheme III-10).



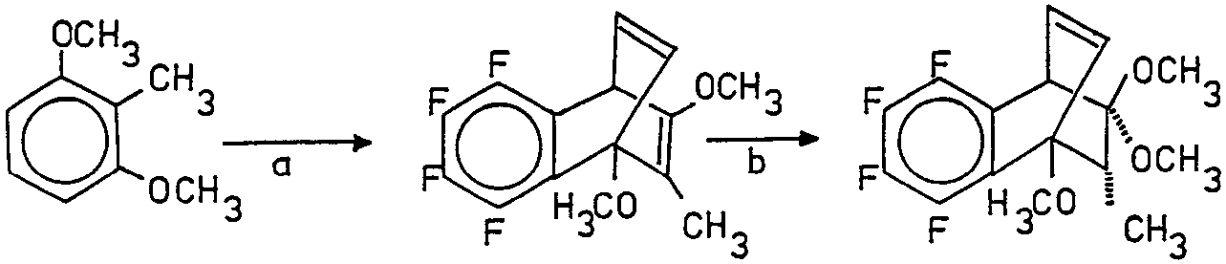
Scheme III-10

Reagents: a) H_2SO_4, H_2O, Dioxan; b) Ethane-1,2-diol, Boron trifluoride Etherate.

These reactions demonstrate the use of trialkylstannyl-groups to direct these cycloadditions from one mode (1,4-addition) to another (2,5 [≡3,6]addition).

The ready isolation and apparent stability of the enol ether (III-15) contrasts with previous reports that the initially formed enol ethers are so unstable that it was usually not possible to obtain evidence for their presence in reaction mixtures.[8d] However, in the reaction of 1,3-dimethoxy-

2-methylbenzene with tetrafluorobenzyne, the enol ether (III-18) was isolated after basic hydrolysis of the reaction mixture. Although this ether was slowly hydrolysed in air and underwent slow methanolysis to give the acetal (III-19) it was stable enough to be purified by rapid preparative t.l.c on silica-gel.[8d]



(III-18) (III-19)

Scheme III-11

Reagents: a) C_6F_5MgCl, 80°; b) Methanol.

Are these enols truly labile? The two which have been isolated so far are certainly stable enough to be kept, purified, and used in subsequent reactions. It seems likely that base hydrolysis of the crude reaction mixtures would permit the isolation of any enol ether present, and that repeated failure to isolate these ethers may be due to habitual use of acidic conditions during product isolation.

An alternative explanation is that the enol ethers do not persist in the reaction mixtures. An intimation that this may be so is given in the report of the reaction of tetrafluorobenzyne with 6-methoxytetralin;[8e] a carbonyl band appeared in the i.r. spectrum of the crude product "within a few minutes" before the usual acid hydrolysis step. If this is the case,

the presumption must be that the enol ethers are cleaved by some nucleophile, either by residual organometallic species or by the anhydrous metal halide, and that the use of more moderate reaction conditions may lead to isolation of the potentially useful enol ethers.

In conclusion, the reaction of arynes and arenes gives benzobarrelenes. The reaction is particularly successful with tetrafluoro- and tetrachlorobenzynes and anisole derivatives. The reaction of tetrachlorobenzyne with anisole can be directed to give predominantly 1-methoxytetrachlorobenzobarrelene (III-20) and some tetrachlorobenzobarrelenone (III-16) or exclusively tetrachlorobenzobarrelenone (III-16) by the appropriate choice of reaction parameters.

The Chemical Degradation of Benzobarrelenes

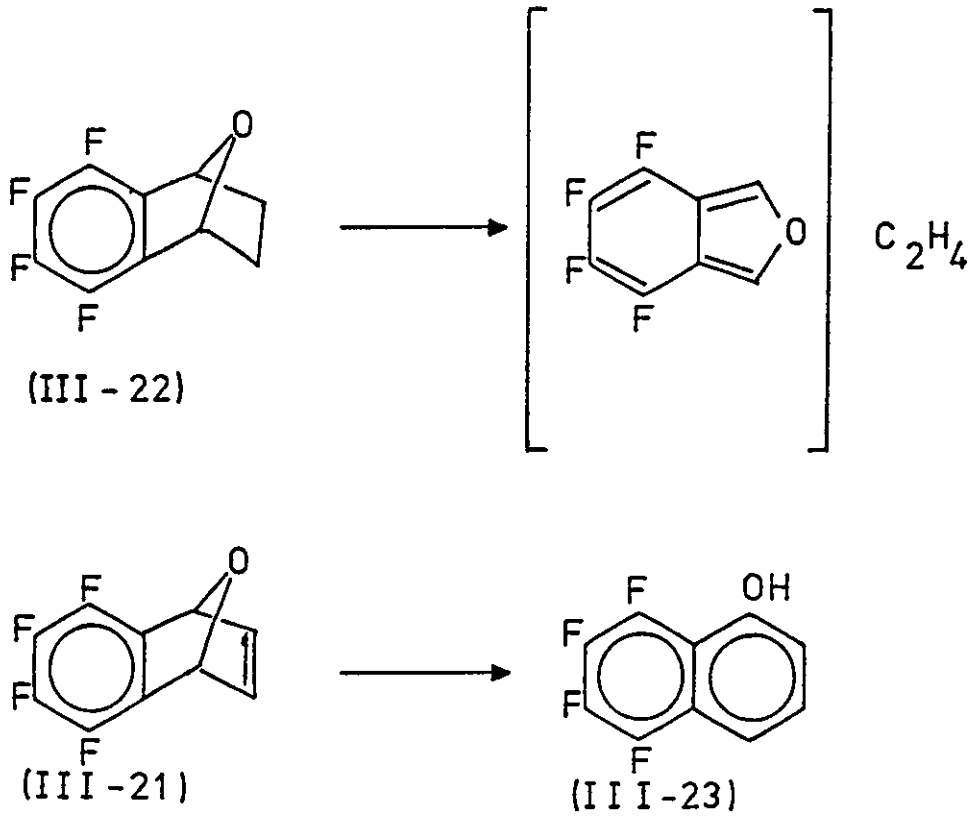
The cycloadducts formed from arynes and arenes constitute 1,4-bridged-1,4-dihydroaromatic bridges systems. The etheno-bridges are the reactive centres in the structure and selective removal of one or other of these bridges appears to be conceptually and practically easier than an attempt to isolate either or both of the bridgehead carbon atoms.

Such systems are known to eliminate the 1,4-bridge with concommitant regeneration of an aromatic system,[2] but the reaction does not usually proceed at ambient temperatures unless there are some special features stabilising the group being eliminated. Thus, the spontaneous decomposition of benzobarrelenes is not observed; the etheno-bridge being eliminated only at elevated temperatures.[17]

The resistance of the bridging etheno-group to elimination is illustrated by the results of the pyrolyses of 5,6,7,8-tetrafluoro,1,4-dihydro-1,4-epoxynaphthalene (III-21) and its hydrogenation product (III-22). Whereas elimination of ethylene from the bridged tetralin (III-22) proceeds smoothly,[18] pyrolysis of (III-21) does not result in extrusion of acetylene, but in isomerisation to produce the naphthol (III-23)[8d] (Scheme III-12).

When the bridging group is itself eliminated as an aromatic fragment the reaction may be expected to occur under much milder conditions. Such an approach has been adopted in syntheses of isobenzofuran, isoindole, and isobenzofulvenes.[20] Pertinent examples are the formation of isobenzofuran (III-24) by elimination of benzene[20a] and 3,6-di-pyridyl-pyridazine (III-25)[20b] as the especially stable groups (Scheme III-13).

The unexpected ease with which such reactions occur may lead to the frustration of apparently sound chemical endeavours: attempted formation of the olefin (III-29) from the quaternary ammonium hydroxide (III-28) by

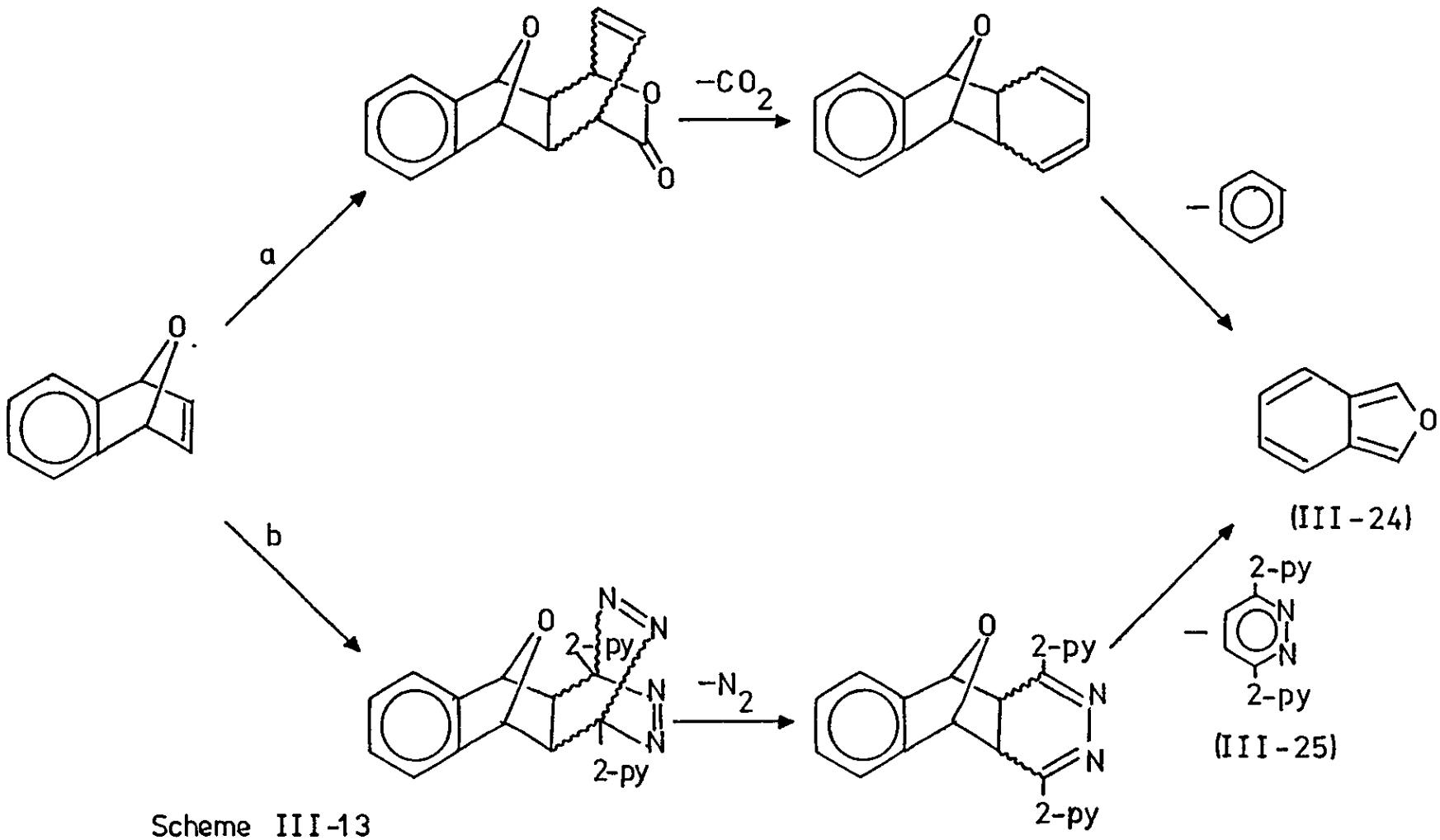


Scheme III-12

pyrolysis gave instead the fragmentation product (III-30), presumably via the desired olefin (III-29)[20c] (Scheme III-14).

The foregoing discussion suggests that the problem of degrading benzobarrelenes reduces to one of converting an etheno-bridge into the dihydroportion of a suitable ortho-dihydroaromatic ring and the brief consideration of some of the factors affecting the ease of fragmentation has illustrated one important approach to this goal.

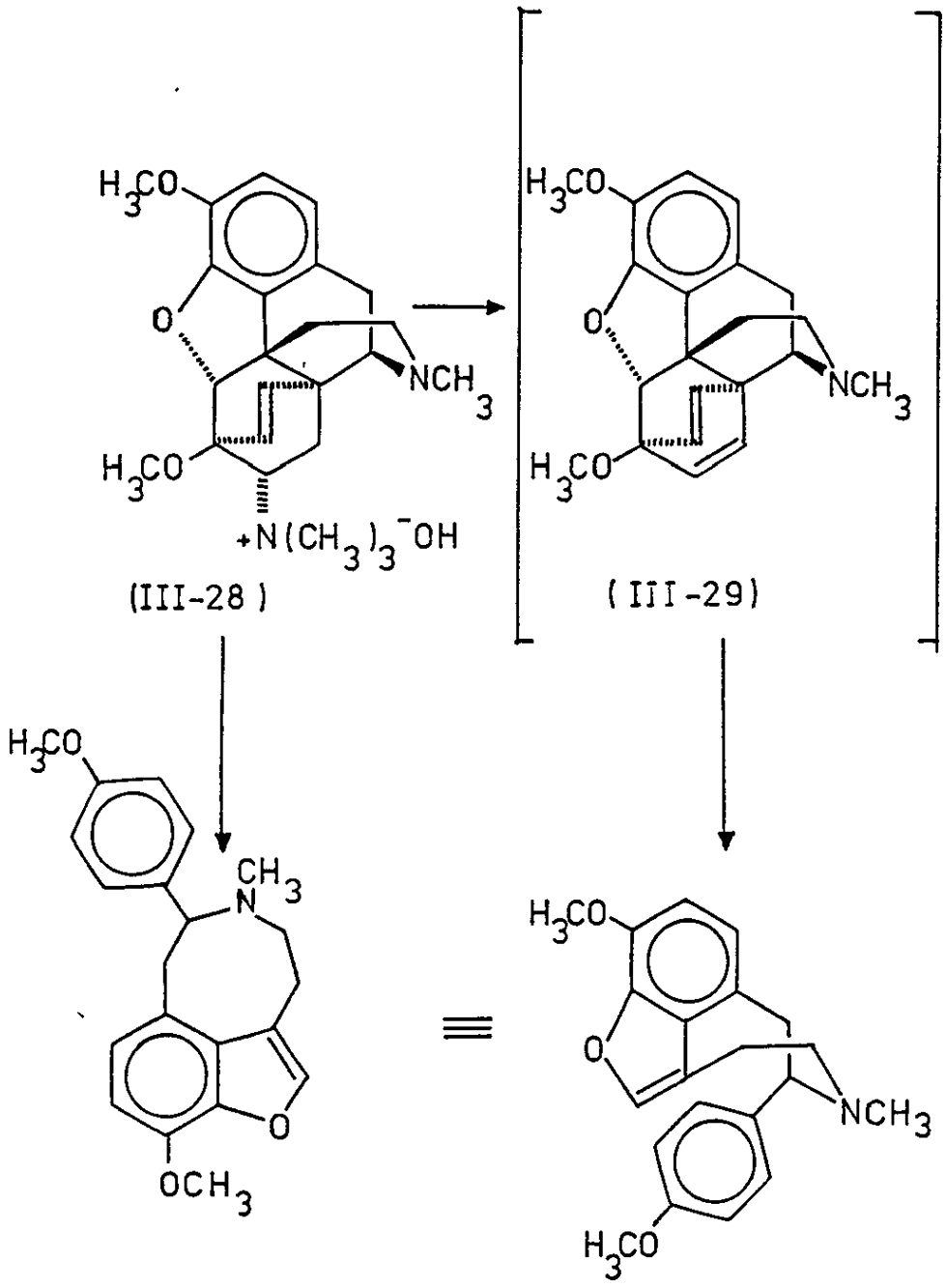
If the etheno-bridge acting as a dienophile is allowed to react with a 1,3-diene which is so constructed that the 1,4-cycloaddition of the etheno-bridge may be followed by a 1,4-elimination then the etheno-bridge



Scheme III-13

Reagents : a) ∝- Pyrone; b) 3,6-Di-(2'-pyridyl)-s-tetrazine.

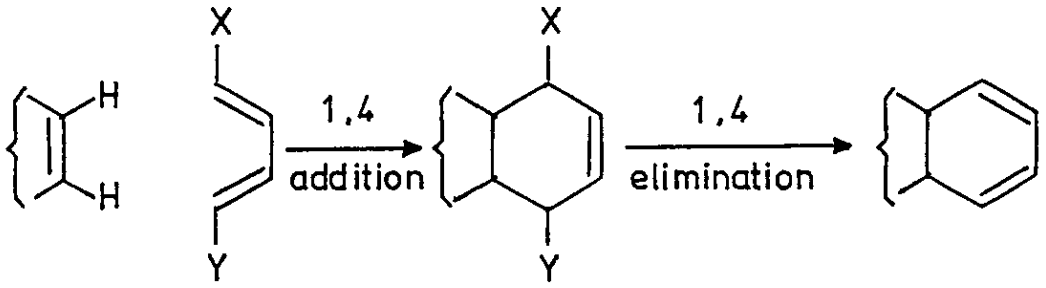
(III-26) (III-27)



Scheme III - 14

Conditions: 215°/0,1mm Hg.

becomes the dihydro-portion of an ortho-dihydroaromatic ring (Scheme III-15).



Scheme III-15

In this approach there are two problems. Firstly, olefins lacking electron withdrawing substituents are generally not recognised as dienophiles, and do not usually take part in the Diels-Alder reaction except under forcing conditions. There are exceptions of course.

Intramolecular cycloadditions between unactivated olefins and 1,3-dienes occur with much greater ease than studies of comparable intermolecular additions would suggest, and double bonds which are bent or twisted away from normal olefin geometry are more reactive than comparable strain-free systems. Although the olefinic bond of the bicyclo[2.2.1] heptadiene structure present in 1,4-dihydro-1,4-epoxynaphthalenes is strained and reacts readily with a variety of simple butadienes,[21] neither of these factors is present to ameliorate the reaction in the case of benzobarrelenes.

There is another, rapidly growing group of reactions for which the generalisation that the only good dienophile is an electron deficient one breaks down. When the diene is electron deficient the diene synthesis often proceeds extremely slowly with conventional dienophiles. This has led some workers to condemn these dienes as inactive in the Diels-Alder

reaction. When such electron deficient dienes are allowed to react with olefins which are relatively electron rich, many do so with great ease.[2b,22] The apparent anomaly of Diels-Alder reactions proceeding with inverse electron demand has been explained as a kinetic effect using Frontier Molecular Orbital treatment of reaction rates.[23]

The second problem lies in the correct choice between the available electron deficient dienes and stems directly from the purpose of the degradation, which is not to practise vandalism on the molecules, but to divide the structure into isolable fragments of unambiguous origin.

If an etheno-bridge is to be excised as some part of an aromatic ring, it is clear that that ring must have at least one substituent to confer the desired crystallinity. The nature of the substituent should be such that it facilitates separation of the excised fragment from the tetrachloronaphthalene residue which will normally be neutral and non-polar.

There are many examples of electron deficient dienes which react with alkenes to give Diels-Alder adducts. The number of these from which a 1,3-diene may be readily regenerated is much smaller.[2b,20] Cyclopentadienones have been popular reagents for this purpose,[24] and recently tetrachloro-o-benzoquinone,[20d] α-pyrone derivatives,[25] and substituted s-tetrazines[26] have all proved useful. Of these reagents, the last would give fragmentation products which could be easily separated and purified. One of the more easily prepared derivatives is 3,6-di-(2′-pyridyl)-s-tetrazine (III-27), which has been widely used[20b,e] and meets the adumbrated criteria. An α-pyrone substituted to produce a crystalline benzene derivative after addition-fragmentation would also be suitable, and coumalic acid (III-31) may be commended in this respect.

The application of cycloaddition-fragmentation schemes similar to those described here to the five-membered heterocyclic aromatic compounds,

notably pyrroles and furans, leads to the separation of the α- and β-carbon atoms. These schemes formally constitute a method for partially assaying these heteroaromatic rings, although their applications have so far been confined to the synthesis of new heteroaromatic rings by exchange of the β-carbon atoms for the carbon atoms of an acetylenic dienophile.[27]

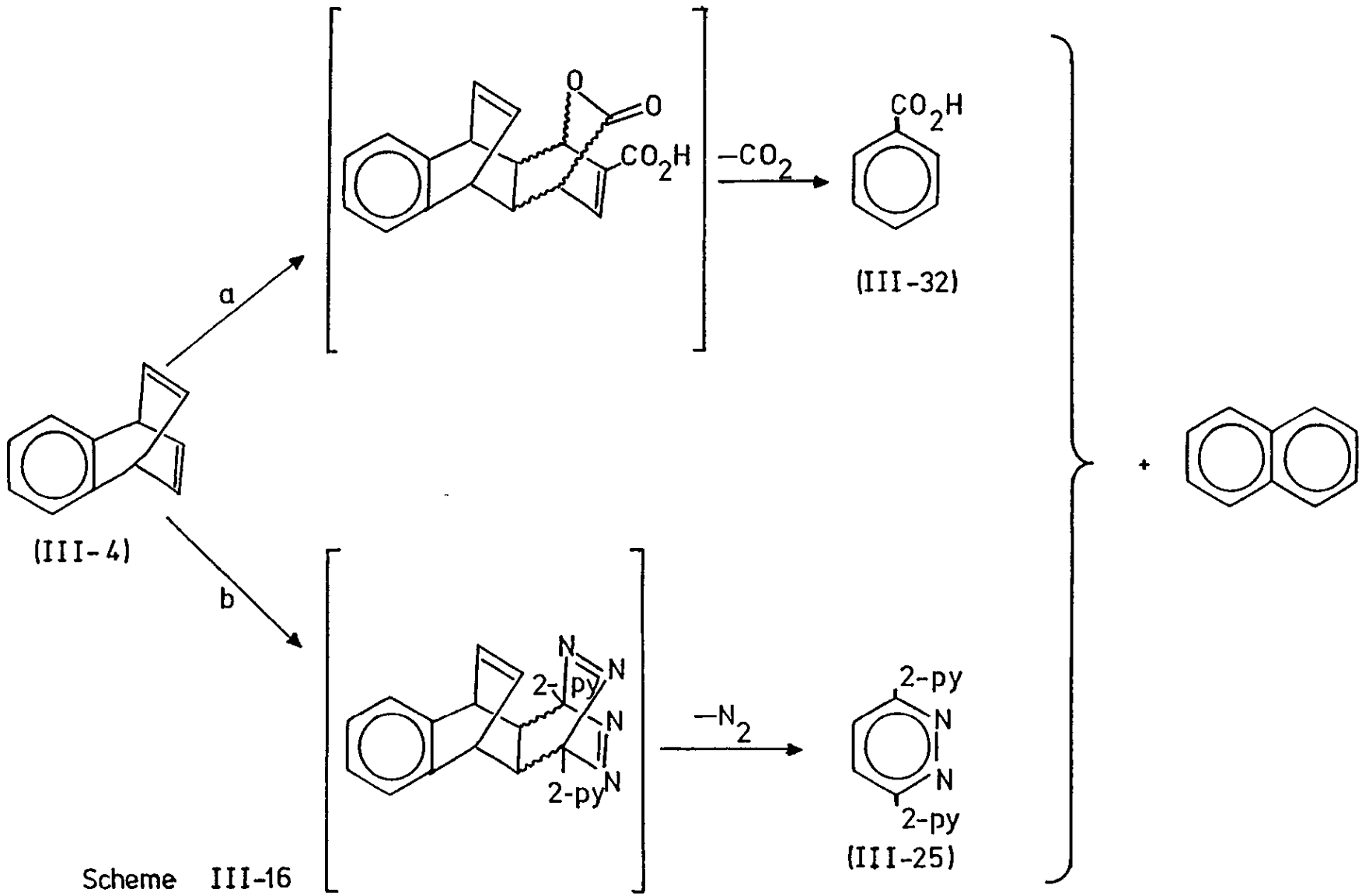
On the basis of these considerations 3,6-di-(2′-pyridyl)-s-tetrazine and coumalic acid were selected as reagents likely to produce fragmentation of the benzobarrelene ring system. The anticipated reactions are shown in Scheme III-16 (cf. Scheme III-13).

Just as not all aromatic rings are six-membered, so not all ortho-dihydroaromatic rings are 1,3-dienes: an important class of aromatic compounds contains the five-membered heterocyclic ring systems, notably the furans, thiophenes and the several azoles. It is apparent that any 1,3-dipole which reacts with acetylenes to give such a heteroaromatic system could also react with the etheno-bridge of a benzobarrelene to produce the desired ortho-dihydroaromatic bridge. One example of a dihydrobenzobarrelene fragmentation in which the bridge was extruded as a furan has already been given, (Scheme III-14, III-28 — III-30).

Barkhash has reacted benzobarrelenes with some 1,3-dipolar species and has found that when the reaction could proceed with aromatisation of both fragments, the initial adducts were unstable under the conditions of their formation, and spontaneous fragmentation occurred.[28]

Of the 1,3-dipoles which might induce this type of fragmentation aryl azides were selected for the ease of their formation, for their relative stability and for the desirable physical properties which they would confer on the heterocyclic fragment.

Although the work of Barkhash had indicated that aryl azides would induce the desired fragmentation, azides are known not to react readily



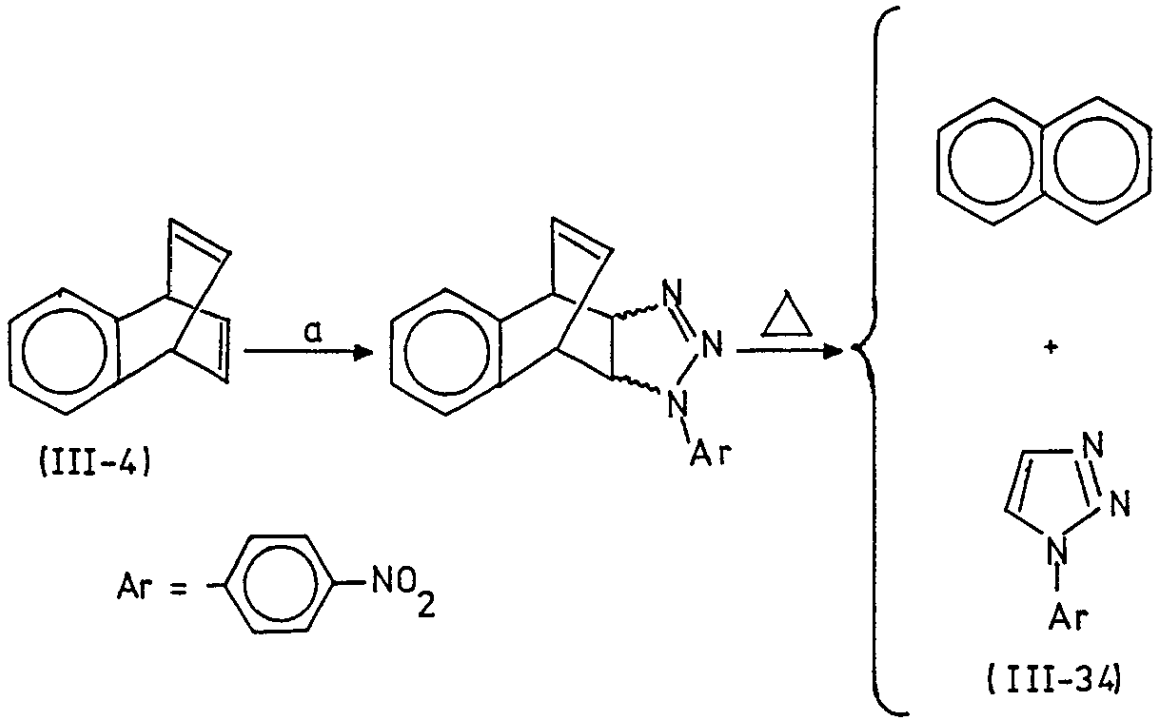
Scheme III-16

Reagents : a) Coumalic Acid , b) 3,6-Di-(2'-pyridyl)-s-tetrazine.

(III-31) (III-27)

with unstrained olefins.[29] Aryl azides behave as electron deficient components in (4 + 2)π cycloadditions and the effect of electron withdrawing aryl substituents is to increase the rate of reaction, if only slightly.[29a]

Accordingly, p-nitrophenyl azide (III-33) was chosen for its enhanced reactivity in 1,3-dipolar cycloadditions. The anticipated reaction is shown in Scheme III-17.



Scheme III-17

Reagent : a) p- Nitrophenyl azide.
(III-33)

Results and Discussion

The reaction of equimolar amounts of 1-methoxytetrachlorobenzobarrelene (III-20) and 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) in boiling di-n-butyl ether for 2½h. gave excellent yields of 5-methoxy-1,2,3,4-tetrachloro-naphthalene (III-35) (96%) and 3,6-di-(2′-pyridyl)-pyridazine (III-25) (83%). The progress of the reaction could be followed by the gradual disappearance of the initial bright red colour which is a sensitive indicator of the presence of 3,6-di-(2′-pyridyl)-s-tetrazine (III-27). The reaction is characterised by the apparent lack of by-product formation.

The conditions under which coumalic acid (III-31) adds to olefinic bonds are not so well documented as are the conditions of many other inverse-electron demand Diels-Alder reactions. The available data[30] indicated that temperatures in the range 150-200° would be required, but a choice of good reaction conditions could not be made until the effect of changing these conditions had been studied.

The benzobarrelene which was of greatest interest at the time of the project was 1-methoxytetrachlorobenzobarrelene (III-20). As this compound was readily available, a series of small scale experiments was carried out with this benzobarrelene in which the effects of varying solvent, reaction time, reaction temperature, and reagent ratio, and of adding catalysts to the reaction were investigated.

The reaction products were separated into acidic and neutral fractions and the progress of the reaction was gauged by the relative proportions of the unreacted benzobarrelene (III-20) and the produced naphthalene (III-35), which were assessed by integration of the O-methyl signals in the ^{1}H n.m.r. spectrum.

The solvents investigated were N-methylpyrrolidone, di-n-butyl ether, p-xylene, and acetic acid. Of these, only N-methylpyrrolidone was truly

unsatisfactory. The dark oily product isolated from this solvent gave every appearance of incomplete reaction coupled with extensive decomposition and its isolation involved a tedious procedure.

This was disappointing, but with hindsight not too surprising. The solvent is the most basic of those investigated. Although the basic character accounts for the fact that this cyclic amide is a considerably better solvent for coumalic acid (III-31) than are the other solvents investigated, the same property may make coumalic acid (III-31) less reactive in cycloaddition reactions by promoting ionisation of the carboxylic acid, so reducing the electron deficiency of the diene. This re-emphasises the characteristic inverse electron demand of the reaction.

In sharp contrast the reaction conducted in acetic acid had progressed the furthest. It is doubtful if this acidic solvent greatly facilitates the reaction by increasing the electron deficiency of the diene through protonation for the reaction in p-xylene had proceeded to nearly as great an extent. Although di-n-butyl ether was the worst of the last three solvents tried, it was by no means unsatisfactory.

None of these last three reactions was attended with appreciable amounts of by-product formation.

Some idea of an appropriate reaction time was gauged by monitoring the progress of the reaction as a function of time: equimolar amounts of 1-methoxytetrachlorobenzobarrelene (III-20) and coumalic acid (III-31) were heated together in p-xylene (each as ca. 0.25 molar solutions) at ca. 205° and the proportions of product naphthalene (III-35) and unreacted benzobarrelene (III-20) were determined after various reaction times by ^{1}H n.m.r. spectroscopy. The ^{1}H n.m.r. spectra of the incomplete reactions did not show the presence of any product other than the naphthalene (III-35) and benzoic acid (III-32).

If it is assumed that the reaction is first order in both 1-methoxytetrachlorobenzobarrelene (III-20) and coumalic acid (III-31) (second order overall) and that the product of this first step decomposes rapidly and irreversibly to the observed products, then the production of 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) should follow second order kinetics. If this is so, then the ratio

$$\frac{[\text{5-methoxy-1,2,3,4-tetrachloronaphthalene}]}{[\text{1-methoxytetrachlorobenzobarrelene}]} = f(C)$$

should be linearly dependent on time. (See experimental section for a derivation of this relationship.)

The results obtained are presented as a plot of f(C) vs. time in fig. III-1. The line shown is a "best straight line" obtained by minimising the root mean square (r.m.s.) deviation of points from the line. In fitting the line to the data the point (f(C),t) = (0,0) was included. Not only is this point incontrovertibly one which would have been observed if such a measurement were possible, but also the linear dependence of f(C) on time was derived assuming that the point (0,0) was a boundary condition of the reaction.

The results displayed in fig. III-1 appear to be presented in remarkably obscure units which can only hinder the extraction of useful kinetic data. This is no bad thing in this case, for it is a deterrent from inferring more from the results than the results can justify. The variation of concentration caused by weighing and measuring errors, and particularly by differential losses of solvent during freeze-thaw degassing cycles would have been greater than should be tolerated in kinetic measurements. Other significant sources of error in this respect would be the initial heterogeneity of the reaction mixture (coumalic acid (III-31) is all but insoluble in cold p-xylene and complete solution would not have occurred until the

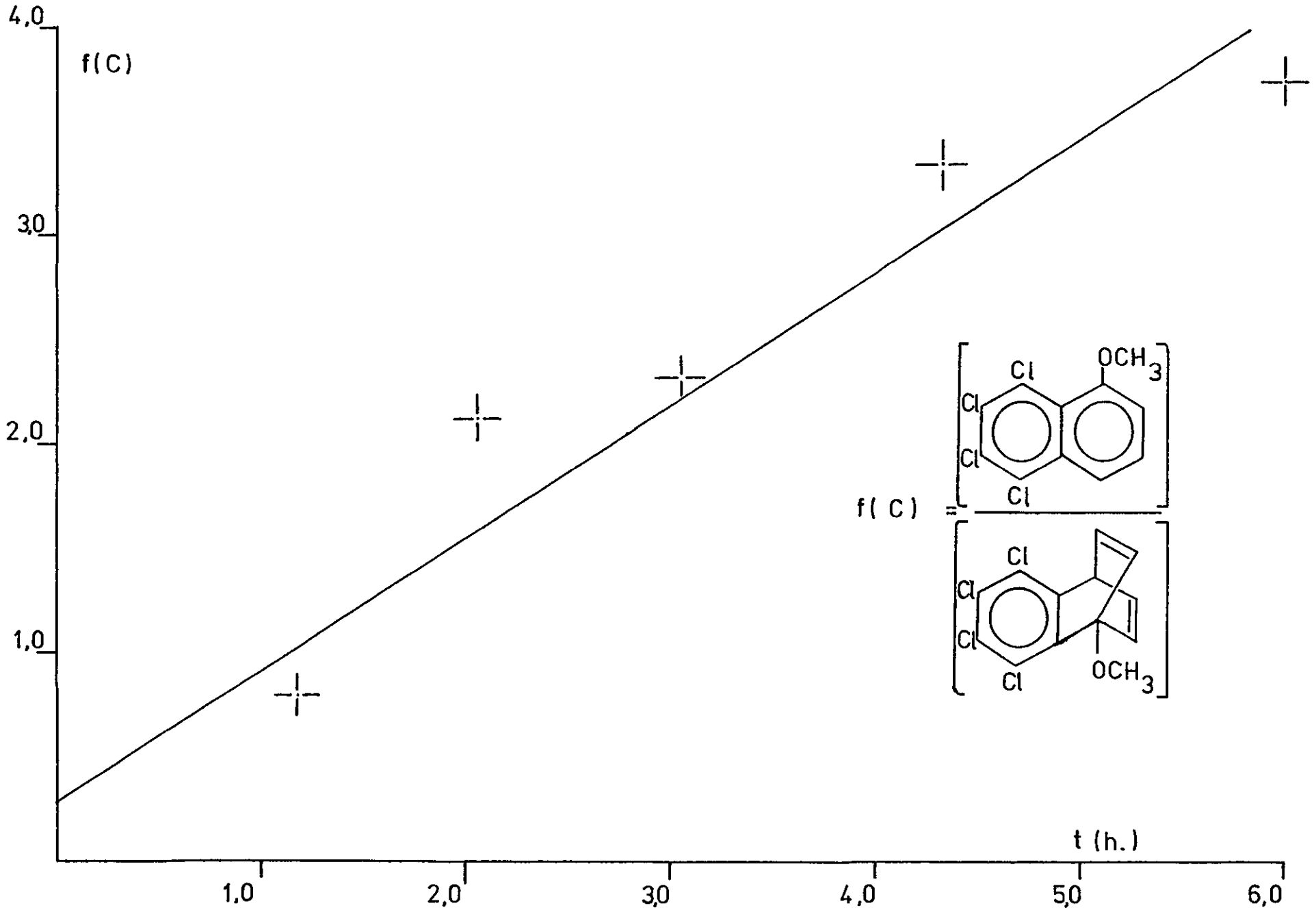


fig III-1

reaction was in progress) and the lack of control over the reaction temperature (the oven used would drift by up to 5° about the pre-set temperature).

With these considerations in mind the linearity of the plot obtained is surprisingly good, and affords clear indication that second order kinetics are being followed. However, the results should not be over-valued.

The effect of changing the reaction temperature was studied. Similar solutions were heated at 160°, 180°, and 220° for 3½h. and the product composition was determined as before. The product composition at 205° after 3½h. was estimated from the best straight line through the points obtained by plotting product composition against time (fig. III-1). A second order reaction would give results which showed a nearly linear dependence of

$$\log_{10}\left\{\frac{[\text{5-methoxy-1,2,3,4-tetrachloronaphthalene}]}{[\text{1-methoxytetrachlorobenzobarrelene}]}\right\} = \log_{10}[f(C)]$$

on $10^3/T$ (where T is expressed in °k; see experimental section for a derivation of this relationship).

The results obtained are presented as a plot of $\log_{10}[f(C)]$ vs. $10^3/T$ in fig. III-2. The line shown is the best straight line, obtained as before.

In agreement with the formulation of the reaction as second order is the increase in rate produced by increasing the amount of coumalic acid (III-31) used. 1-Methoxytetrachlorobenzobarrelene (III-20) was heated at 195° in N-methyl-pyrrolidone for 20h. with various amounts of coumalic acid (III-31) and the product composition was assayed by ^1H n.m.r. spectroscopy. The results are presented graphically in fig. III-3 as a plot of % reaction vs. molar equivalents of coumalic acid (III-31).

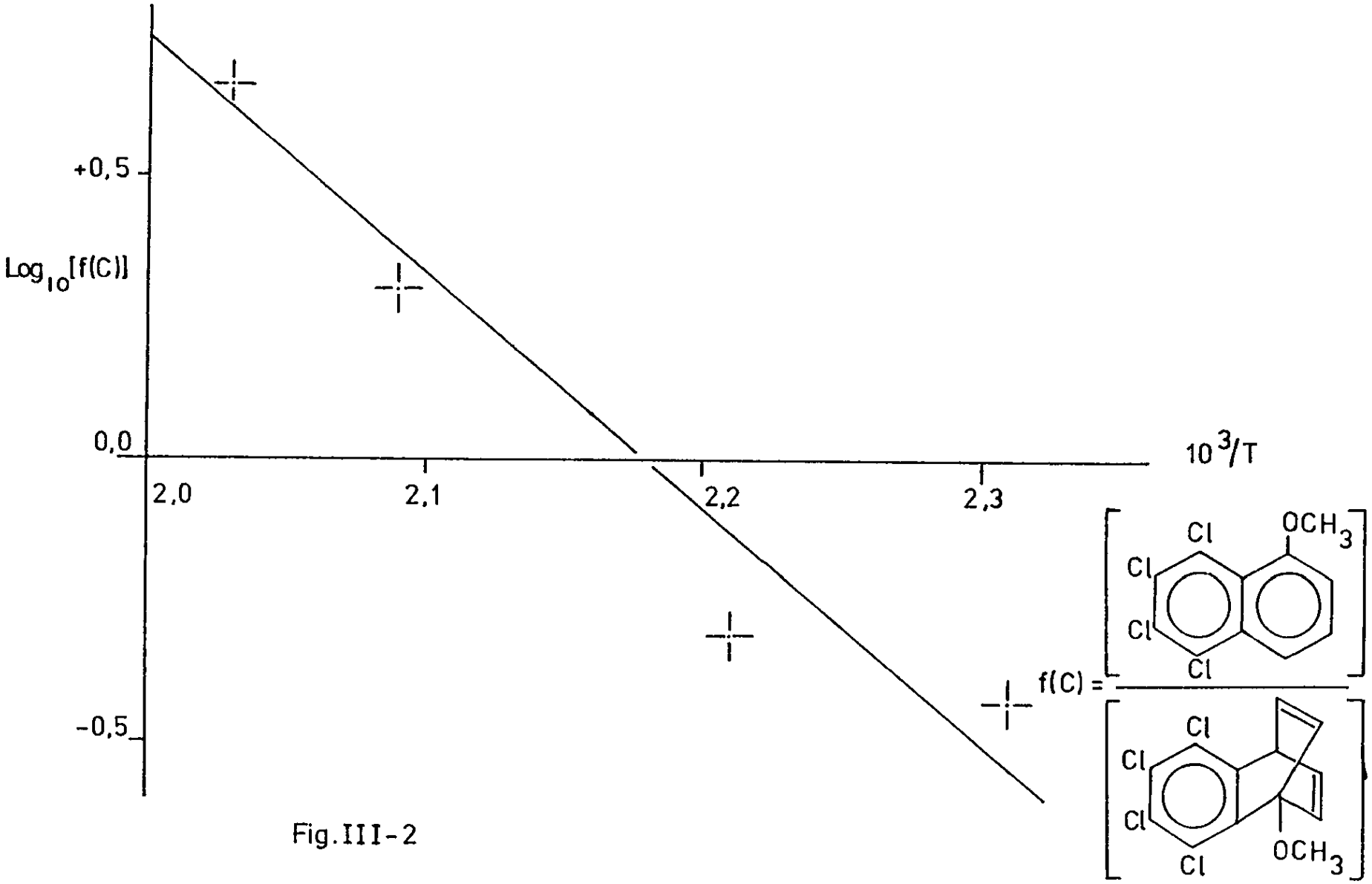


Fig. III-2

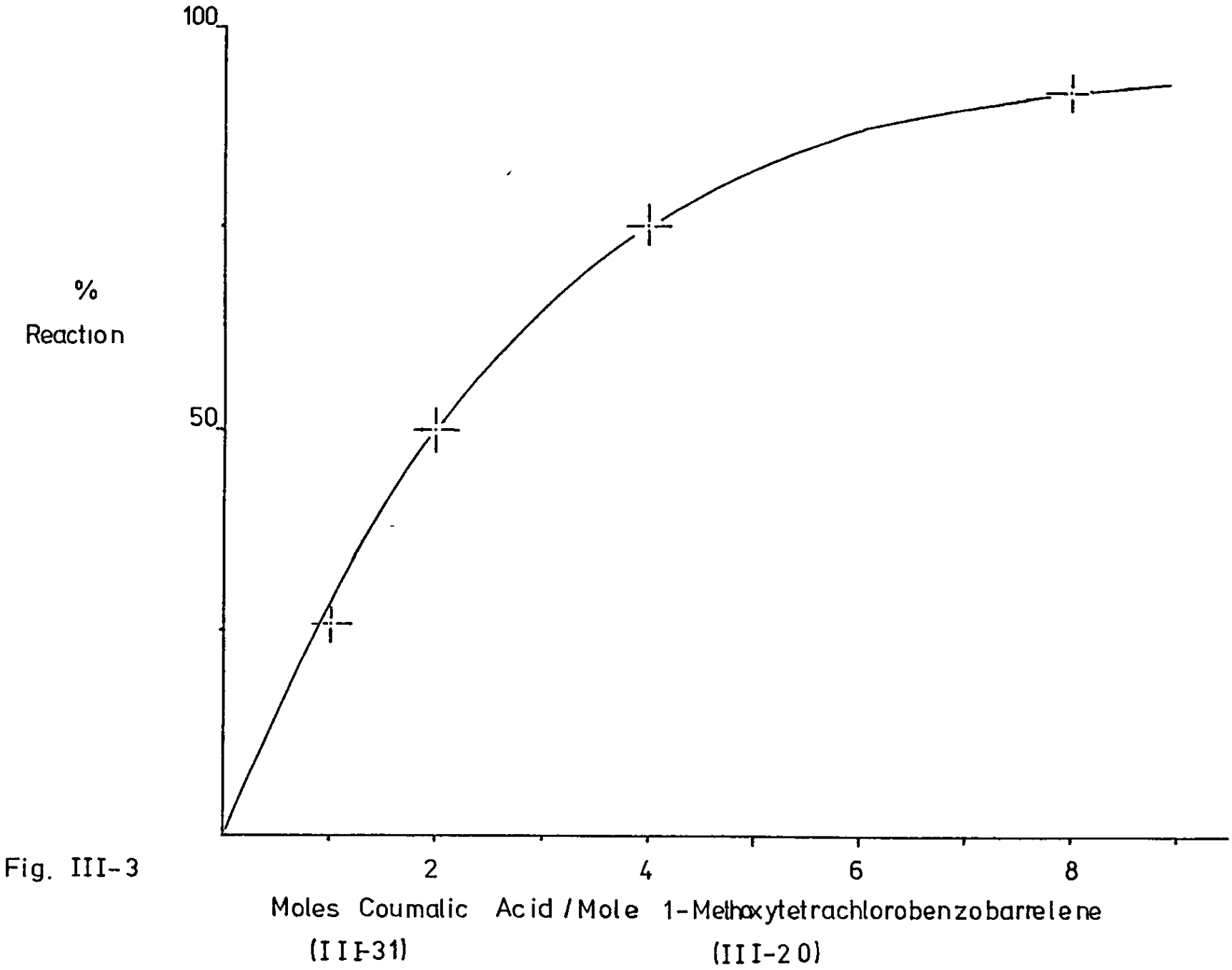

100
50
%
Reaction
2
4
6
8
Moles Coumalic Acid / Mole 1-Methoxytetrachlorobenzobarrelene
(III-31)
(III-20)

Fig. III-3

The benefit of using more than one molar equivalents of coumalic acid (III-31) is apparent, as is the fact that the additional benefit of adding more coumalic acid (III-31) diminishes rapidly once an excess of one or two molar equivalents has been added.

Some Diels-Alder reactions proceeding with "normal" electron demand, particularly those with αβ-unsaturated carbonyl compounds acting as dienophiles are known to be accelerated by the addition of Lewis acids, which are thought to complex with the dienophile and so increase its electron deficient character.[2b] The behaviour of coumalic acid (III-31) as a diene in acidic and basic solvents suggested that increasing the electron deficient character of coumalic acid might greatly facilitate the reaction with benzobarrelenes.

Aluminium bromide and boron trifluoride etherate were selected and their catalytic activity was investigated. Solutions of 1-methoxytetrachlorobenzobarrelene (III-20) (1 part), coumalic acid (III-31) (1 part), and the Lewis acid (3 parts) in p-xylene were heated at 220° for ¾h. The products were compared with those produced in similar experiments conducted without the Lewis acid.

Whereas the uncatalysed reactions had proceeded cleanly to ca. 30% conversion, the "catalysed" reactions had taken an entirely different course. Much by-product had formed, and whereas integration of the O-methyl signals in the ^{1}H n.m.r. spectrum of the aluminium bromide catalysed reaction indicated that less than ca. 10% conversion had occurred, there were no O-methyl signals to be observed in the ^{1}H n.m.r. spectrum of the borontrifluoride etherate catalysed reaction. Aluminium halides are known to O-demethylate 1-methoxybenzobarrelenes,[31] and it is likely that this was a major pathway in both "catalysed" reactions.

As the catalysts appeared to complicate rather than simplify the

reaction, the investigation of catalysis in this reaction was curtailed.

These experiments define conditions under which 1-methoxytetrachlorobenzobarrelene (III-20) may be degraded to 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) by treatment with coumalic acid (III-31). Thus, when 1-methoxytetrafluorobenzobarrelene (III-8) is heated at 200° for 4h. with two molar equivalents of coumalic acid (III-31) the reaction proceeded to completion and 5-methoxy-1,2,3,4-tetrafluoronaphthalene (III-36) (94%) and benzoic acid (III-32) (71%) were isolated.

When a solution of 1-methoxytetrachlorobenzobarrelene (III-20) was boiled in benzene with a 4% excess of p-nitrophenyl azide (III-33) for 24h. the desired reaction occurred, and 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) (84%) and p-nitrophenyl triazole (III-34) (69%) were isolated. In a similar reaction with 1-methoxytetrafluorobenzobarrelene (III-8), 5-methoxy-1,2,3,4-tetrafluoronaphthalene (III-36) (86%) and p-nitrophenyltriazole (III-34) (79%) were produced.

Of the three reactions described in this section, each provides a way in which an etheno-bridge may be removed from a benzobarrelene, and each offers its own advantages and suffers to some extent from individual disadvantages.

Degradation with coumalic acid (III-31) requires more severe conditions than do the other two reagents, and the experimental procedure is by far the most difficult. On the other hand, the separation of the products is particularly easy, requiring only a base extraction to remove the acidic product from the reaction mixture and leave the pure naphthalene.

Degradation with 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) is experimentally very simple, and the end point of the reaction may be readily seen by the discharge of the red colour of the reagent. Purification has been achieved by chromatography so far, but the R_f values of the products are so

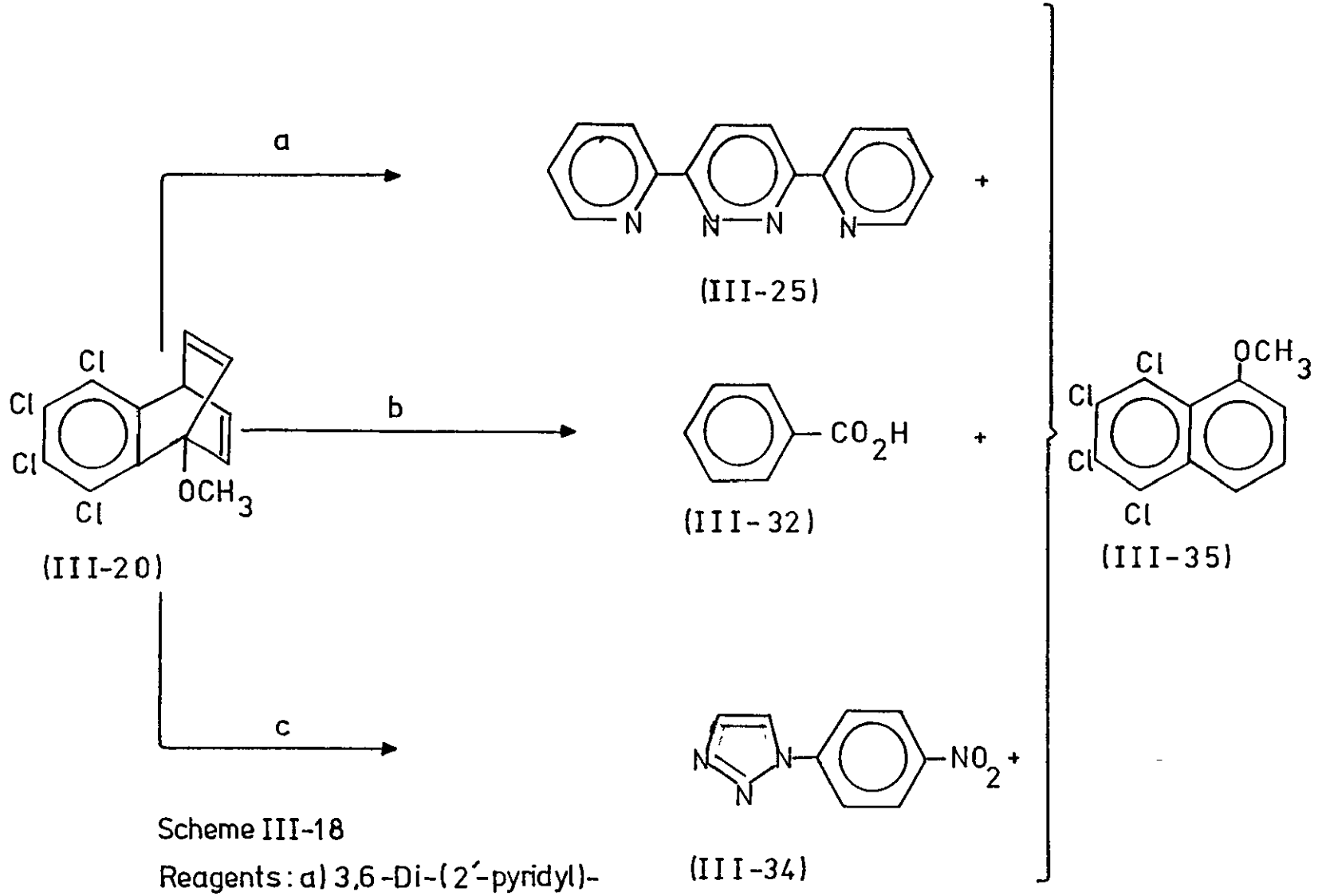
different that a more simple chromatographic separation could hardly be imagined. The basic character of one of the products should allow its isolation by acid extraction, but this has not been attempted.

This reaction gives marginally better yields than the other two, and is held to be the reaction of choice for degrading benzobarrelenes.

Degradation with p-nitrophenylazide (III-33) proceeds under mild conditions and gives good yields of both fragments. One advantage of this reagent is the ease with which it may be prepared, but this is counterbalanced by the darkening of the reagent or its solutions on exposure to light. The degradations are best conducted in the dark. The purification of the products is again simple, the different R_f values of the products makes chromatography both easy and effective.

See Scheme III-18 for a summary of these results.

Benzobarrelenes with unsubstituted etheno-bridges constitute only a small proportion of the products obtained from cycloadding an aryne to an arene. Generally, these bridges will be substituted; very often this substitution will not be symmetrical. In such cases the usefulness of the fragmentation reagents just described will depend largely on the selectivity which they exhibit in the initial cycloaddition reaction. Depending on the application, the preferred reaction may be one which exhibits complete selectivity, or a complete lack of selectivity. Providing the reaction products can be separated, the latter reaction will provide more information about the structure of the benzobarrelene and its arene precursor, but where separation of the products is difficult - which is probably the case with similar naphthalenes - a specific reaction is preferable. This site-selectivity was investigated by comparing the reactivity of various methyl-substituted-1-methoxytetrachlorobenzobarrelenes towards the fragmentation reagents with that already described for 1-



Scheme III-18

Reagents: a) 3,6-Di-(2'-pyridyl)-s-tetrazine (III-27); b) Coumalic acid (III-31), c) p-Nitrophenyl azide (III-33).

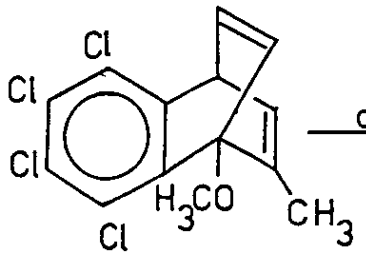
methoxytetrachlorobenzobarrelene (III-20).

Equimolar amounts of 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) and various methyl-substituted-1-methoxytetrachlorobenzobarrelenes [(III-37), (III-38), (III-39), and (III-40)] were allowed to react in boiling p-xylene and the composition of each reaction mixture was determined by ^{1}H n.m.r. analysis followed by product isolation.

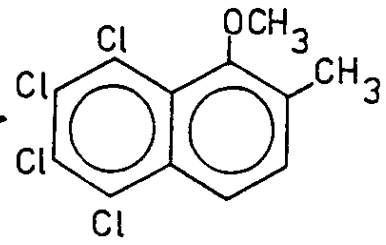
The reaction of 2-methyl-1-methoxytetrachlorobenzobarrelene (III-37) with 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) exhibited considerable selectivity, removing the unsubstituted bridge between five and six times as readily as it removed the substituted bridge. Both 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) (72%) and 6-methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-41) (15%) were isolated. 3,6-Di-(2′-pyridyl)-pyridazine (III-25) (63%) was also isolated, but although the other heterocyclic fragment, 4-methyl-3,6-di-(2′-pyridyl)-pyridazine (III-42) had been formed - its presence as a minor constituent of the reaction mixture was apparent from the ^{1}H n.m.r. spectrum - it was not isolated.

This reaction was the least selective of the four reactions of 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) with methyl-substituted-1-methoxy-tetrachlorobenzobarrelenes studied. The selective removal of the least substituted bridge is a feature which underlies the discussion of the remainder of this section on the fragmentation of methyl-substituted benzobarrelenes.

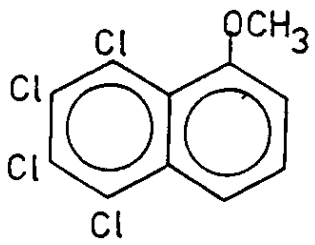
The reactions of 3-methyl-, 2,3-dimethyl-, and 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene [(III-38), (III-39), and (III-40) respectively] with 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) each gave only two products: 7-methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-43) (91%) and 3,6-di-(2′-pyridyl)-pyridazine (III-25) (98%), 6,7-dimethyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-44) (96%) and 3,6-di-(2′-



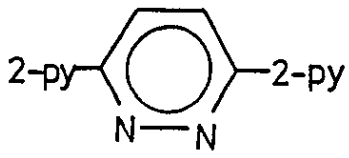
(III-37)



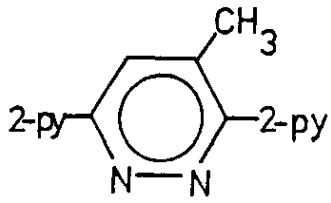
(III-41)(72%)



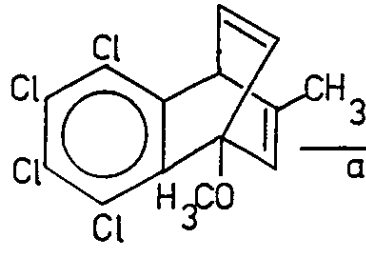
(III-35)(15%)



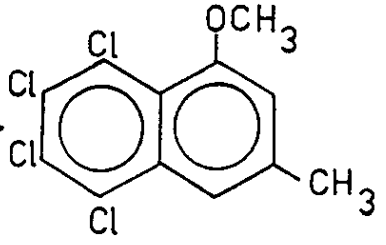
(III-25)(63%)



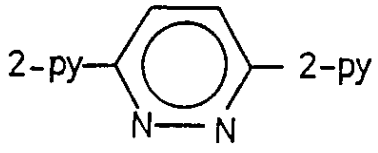
(III-42)(not isolated).



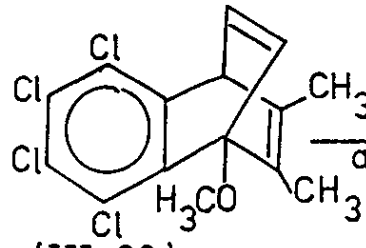
(III-38)



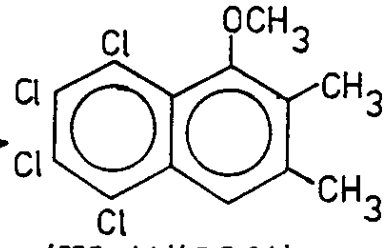
(III-43)(91%)



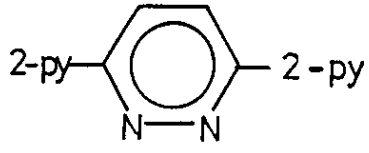
(III-25)(98%)



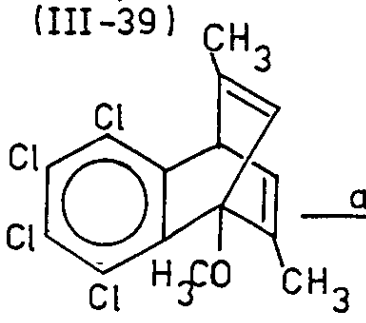
(III-39)



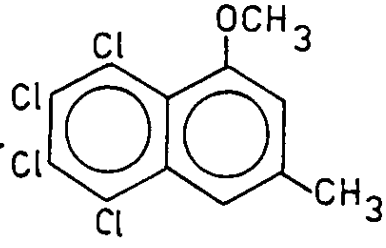
(III-44)(96 %)



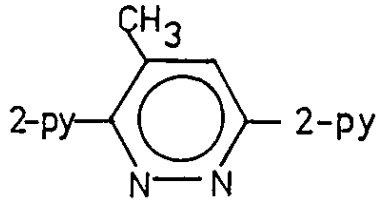
(III-25)(86%)



(III-40)



(III-43)(93%)



(III-42)(93%)

Scheme III-19

Reagent: a) 3,6-Di-(2'-pyridyl)-s-tetrazine (III-27)

-2-py= -2-pyridyl

pyridyl)-pyridazine (III-25) (86%), and 7-methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-43) (93%) and 4-methyl-3,6-di-(2′-pyridyl)-pyridazine (III-42) (93%) respectively.

Of these three reactions the selectivity exhibited in the first two is interesting; that of the last reaction is truly remarkable. The results of all four reactions are summarised in Scheme III-19.

Let us call a substituent in a 2-, or 6- position an α-substituent, one in a 3-, or 5- position a β-substituent. These results show that the preferred order of attack is:

i) unsubstituted > α-substituted ≫ β-substituted

and that

ii) unsubstituted > α,β-disubstituted.

The difference between the reactivity patterns of 2-methyl- and 3-methyl-1-methoxytetrachlorobenzobarrelene [(III-37) and (III-38)] and between the reactivity of the α- and β-substituted bridges of 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (III-40) must be ascribed to the influence of 1-methoxy-substituent. In the absence of this substituent the etheno-bridges which have just been compared and between which such a clear difference exists would be indistinguishable. The nature of this influence is uncertain.

This study was extended to the reactions of coumalic acid (III-31) and p-nitrophenylazide (III-33). The site-selectivity was determined by n.m.r. analysis of the neutral fraction from the coumalic acid (III-31) induced fragmentations and of the whole reaction mixture in the case of p-nitrophenylazide (III-33) induced fragmentations.

The reaction of methyl-substituted-1-methoxytetrachlorobenzobarrelenes with coumalic acid (III-31) under the best conditions found for 1-methoxy-

tetrachlorobenzobarrelene (III-20) itself could not be investigated. 3-Methyl- and 2,3-dimethyl-1-methoxytetrachlorobenzobarrelene [(III-38) and (III-39)] were recovered unchanged after being heated in acetic acid at 200° for 3h. In contrast 2-methyl-1-methoxytetrachlorobenzobarrelene (III-37) was extensively rearranged (ca. 40% reaction occurred), and 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (III-40) was not detected at all in the recovered pyrolysate. The products of the last two reactions resembled those of the trifluoroacetolyses described in chapter five; the principal reaction pathway appears to be aryl or alkenyl-bridge migration to a 2-carbocation.

Because of the demonstrated instability of the substrates under the normal reaction conditions the investigation of the site-selectivity of the reaction of coumalic acid (III-31) with the bridge-substituted benzobarrelenes was confined to reactions conducted in p-xylene.

In spite of this precaution the reactions did not proceed cleanly and starting material rearrangement was a competetive pathway in most cases. Nonetheless, qualitative conclusions may be drawn from the results.

The degradation of 2-methyl-1-methoxytetrachlorobenzobarrelene (III-37) with coumalic acid (III-31) was one of the simpler of the four reactions studied in this context. Although ketonic products were formed and the ^{1}H n.m.r. spectrum of the neutral products indicated that a considerable amount (up to ca. 30% of the neutral fraction) of the αβ-unsaturated ketone (III-45) had been formed, the naphthalene produced was overwhelmingly that resulting from elimination of the unsubstituted bridge. There was no unequivocal indication of the presence of 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) which would result from the elimination of the substituted bridge. Consonant with these observations was the composition of the acidic fraction of the product. The proportion of toluic acids

(III-46) present in the benzoic acid (III-32) produced was not greater than 5%.

The degradation of 3-methyl-1-methoxytetrachlorobenzobarrelene (III-38) with coumalic acid (III-31) gave a neutral fraction composed preponderantly of naphthalenes. 7-Methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-43) resulting from elimination of the least substituted bridge was the major product, but some 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) was also formed (≤25% of total naphthalenes; product analysis by ^{1}H n.m.r. is difficult in this case for the Q-methyl group signals are very nearly coincident). The methyl signals in the ^{1}H n.m.r. spectrum of the acidic fraction also suggested that in this case ca. 25% of the naphthalene formation was proceeding by elimination of the substituted bridge.

Degradation of 2,3-dimethyl-1-methoxytetrachlorobenzobarrelene (III-39) with coumalic acid (III-31) gave a neutral fraction containing no 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) which would result from elimination of the disubstituted bridge. The only naphthalene formed was 6,7-dimethyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-44) resulting from elimination of the unsubstituted bridge, but ^{1}H n.m.r. analysis of the C-methyl signal intensities revealed that this product accounted for only ca. 25% of the neutral fraction. The numerous signals above 8τ (at least nine) in the ^{1}H n.m.r. spectrum and the carbonyl bands (at least 3) observed in the i.r. spectrum suggested that very extensive rearrangement of the benzobarrelene (III-39) had occurred.

The degradation of 2,5-dimethyl-1-methoxy-tetrachlorobenzobarrelene (III-40) with coumalic acid (III-31) did not appear to proceed with any great selectivity; on the other hand, the reaction could not be faulted for any lack of degradation. The extensive by-product formation appeared to have almost completely pre-empted the desired cycloaddition-fragmentation

pathways.

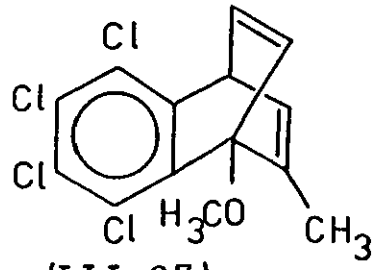
The results are summarised in Schemes III-20 and III-21.

As with 3,6-di-(2′-pyridyl)-s-tetrazine (III-27), coumalic acid (III-31) preferentially attacks the unsubstituted rather than the substituted etheno-bridge, and to a degree which could be synthetically useful were it not for the tendency of the reaction conditions to induce other reaction pathways. Although 2-, and in particular 3-methyl-1-methoxytetrachlorobenzobarrelene [(III-37) and (III-38)] are degraded with good product specificity, the myriad of products and small proportion of naphthalenes produced from 2,3- and 2,5-dimethyl-1-methoxy-tetrachlorobenzobarrelene [(III-39) and (III-40)] make the sequence all but useless for any purpose whatsoever.

Why this should be is not clear. Again the reaction exhibits an interesting site-selectivity which must be due to the presence of the methoxy-group. The acidic character of the diene may be responsible for much of the by-product formation; these molecules have a demonstrated sensitivity to acid catalysed rearrangements. Choice of methyl coumalate (III-47) as the diene component might suppress these reactions, but separation of the products would not be so easy.

The by-product formation is most extensive in those reactions where the 1-methoxybenzobarrelene will readily form a 2-carbocation, and the sequence of reactions might yet be successfully applied to bridge-substituted benzobarrelenes lacking the bridgehead methoxy-substituent.

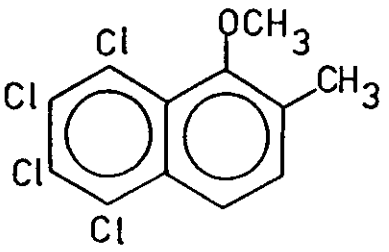
Various bridge-substituted 1-methoxytetrachlorobenzobarrelenes were boiled in dioxan with a 10% excess of p-nitrophenylazide (III-33) for 28h. Under the conditions used the reactions proceeded essentially to completion; greater than 90% conversions were observed. The reactions were free from extensive by-product formation. The reactions were characterised by a



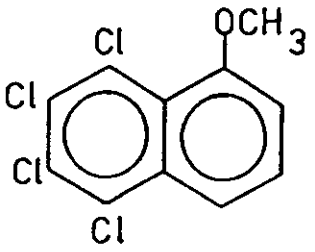
(III-37)

a

Neutral

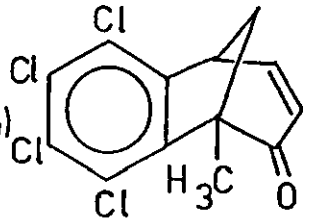


(III-41)(ca.70%)



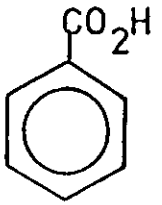
(III-35)(trace?)

Rearrangement Products(ca.30%) Probably:

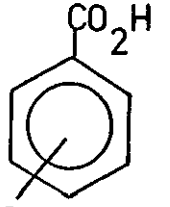


(III-45)

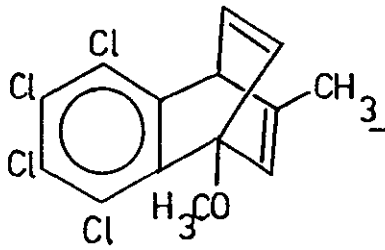
Acid



(III-32)

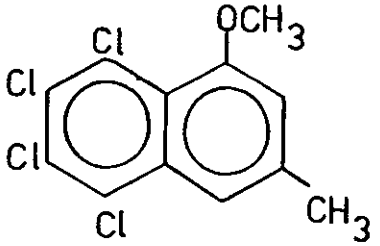


(III-46)(<5%)

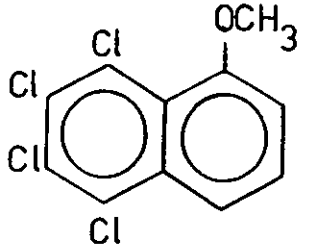


(III-38)

a

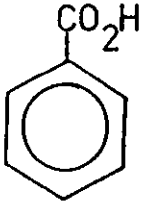


(III-43)(ca.75%)

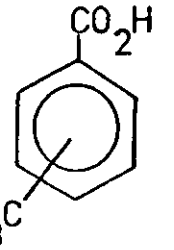


(III-35)(ca.25%)

Rearrangement Products.
(trace)



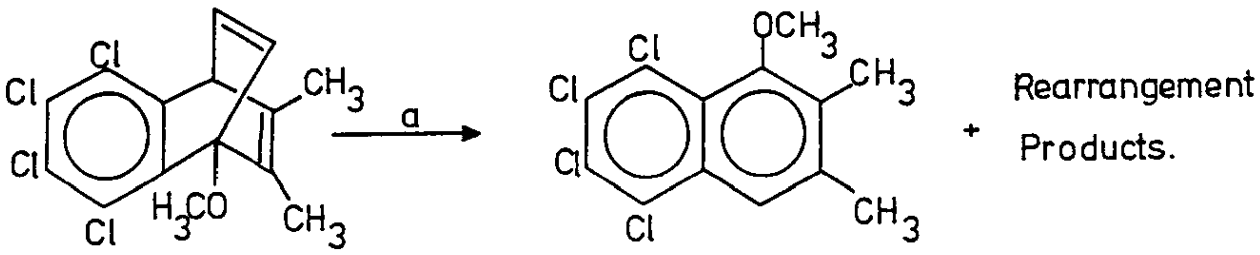
(III-32)(ca75%)



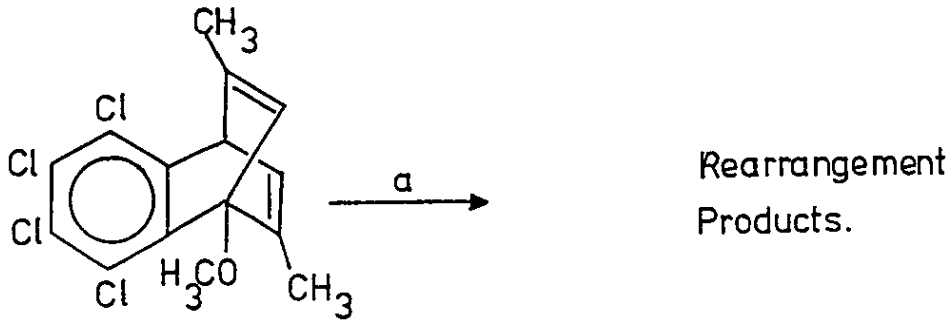
(III-46)(ca25%)

Scheme III- 20

Reagent : a) Coumalic acid.(III-31)



(III-39) (III-44)(ca.25%) (ca.75%)



(III-40) (ca.100%)

Scheme III-21

Reagent :a) Coumalic acid.

(III-31)

smaller degree of site-selectivity in comparison with the reactions of 3,6-di-(2′-pyridyl)-s-tetrazine (III-27).

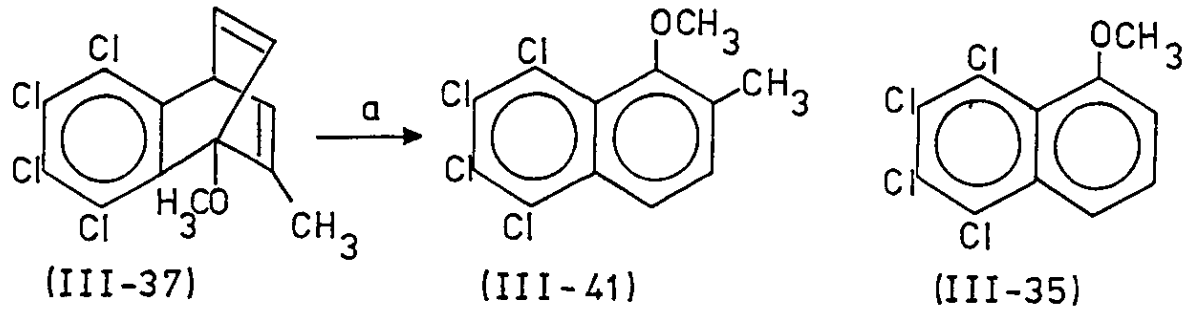
Thus 2-methyl-1-methoxytetrachlorobenzobarrelene (III-37) gave two naphthalenes, with production of 6-methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-41) by elimination of the unsubstituted bridge being slightly favoured over production of 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) (ca. 55% vs. ca. 45%). The degradation of 3-methyl-1-methoxytetrachlorobenzobarrelene (III-38) appeared to be exceptional; only 7-methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-43) produced by elimination of the unsubstituted bridge was detected. The amount of 5-methoxy-1,2,3,4-tetrachloronaphthalene (III-35) produced is estimated as not greater than 10%.

2,3-Dimethyl-1-methoxytetrachlorobenzobarrelene (III-39) gave two naphthalenes. Elimination of the unsubstituted bridge (ca. 80% of the reaction) was strongly favoured over elimination of the substituted bridge (ca. 20% of the reaction).

When the choice was between elimination of a bridge with an α-substituent or one with a β-substituent from a 1-methoxybenzobarrelene, the bridge bearing the α-substituent is preferentially removed. Thus, 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (III-40) gave 7-methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-43) (ca. 80% of the reaction) and 6-methyl-5-methoxy-1,2,3,4-tetrachloronaphthalene (III-41) (ca. 20% of the reaction). These results are summarised in Scheme III-22.

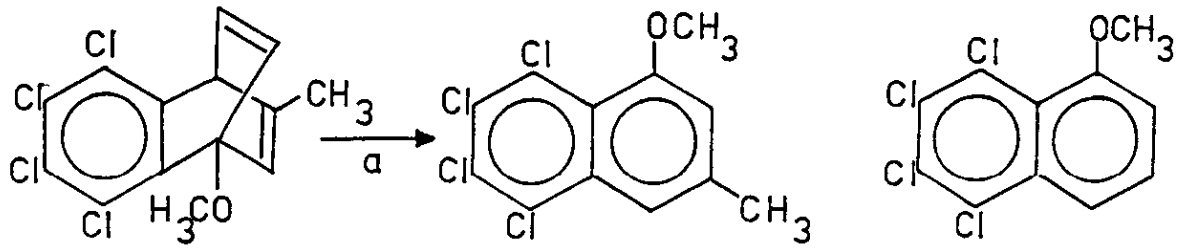
The site selectivity observed in these reactions is similar to that observed with 3,6-di-(2′-pyridyl)-s-tetrazine (III-27), but the degree of selectivity is less.

The main conclusion drawn from these results is that the fragmentation reagents may be used to degrade 1-methoxybenzobarrelenes with a high degree



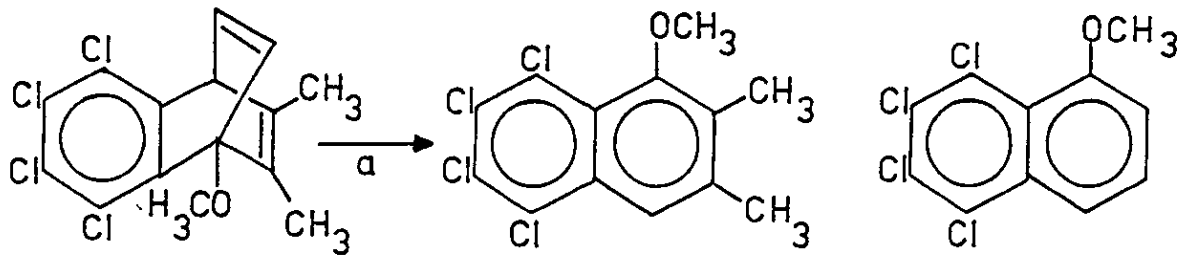
(III-37) (III-41) (III-35)

ca. 55:45



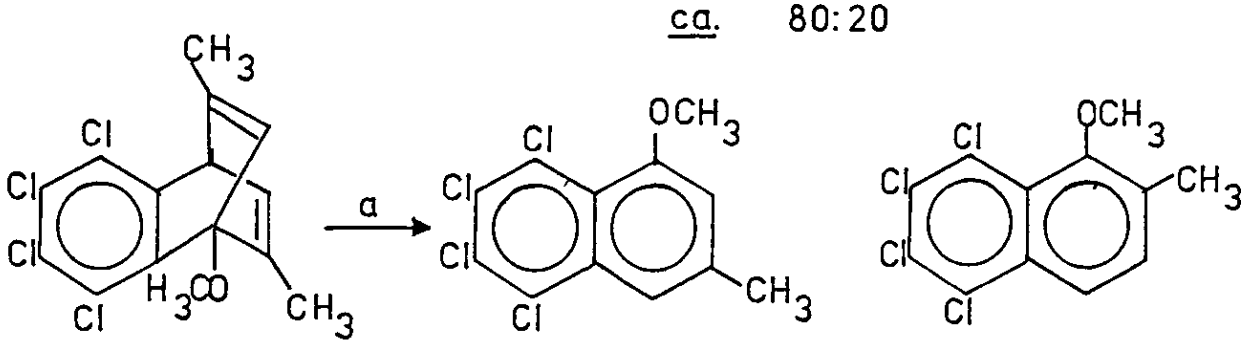
(III-38) (III-43) (III-35)

>ca. 90:10



(III-39) (III-44) (III-35)

ca. 80:20



(III-40) (III-43) (III-41)

ca. 80:20

Scheme III-22

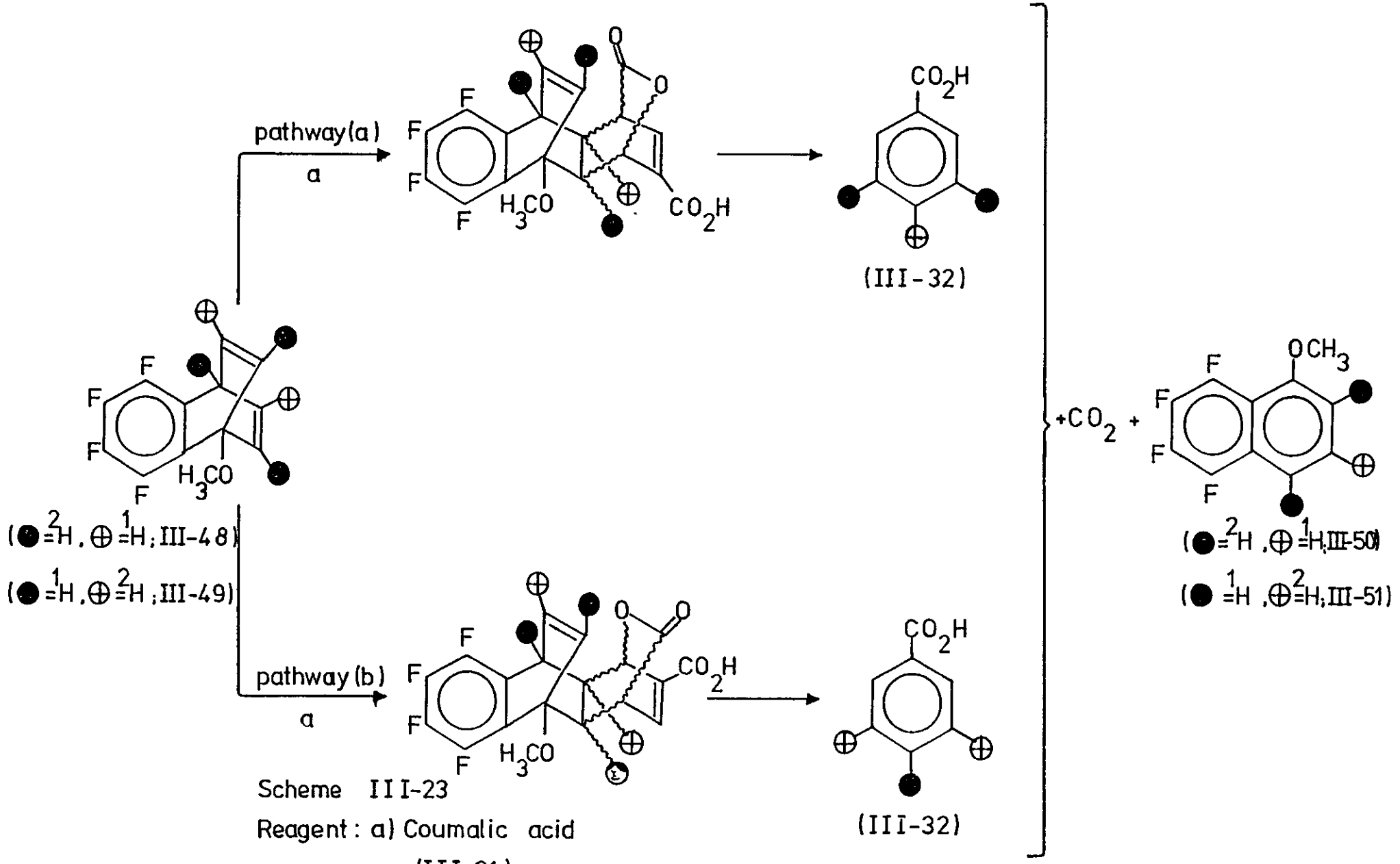
Reagent : a) p- Nitrophenyl azide.(III-33)

of selectivity. The most selective reagent is 3,6-di-(2′-pyridyl)-s-tetrazine (III-27), the least selective is p-nitro-phenylazide (III-33) and, although coumalic acid (III-31) is selective, the extensive by-product formation renders the reagent of little use in the general case. The least substituted etheno-bridge will be preferentially if not exclusively removed. The main exception to this generalisation is that an α-substituted bridge is removed unusually easily in comparison to a β-substituted or an αβ-disubstituted bridge.

The way in which the bridgehead methoxy-group loosens this bridge is obscure but the fact that the effect exists indicates that the remote substituent has a perturbing effect on the cycloaddition. No information about the regioselectivity of addition of p-nitrophenylazide (III-33) or coumalic acid (III-31) in additions to substituted bridges has been obtained, but as the regiospecificity of addition to bridge-substituted benzobarrelenes lacking the bridgehead methoxy substituent is also not known such information could not be used to draw conclusions about the influence of the bridgehead methoxy-substituent. 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) is so symmetrical a reagent that it cannot react in regioisomeric ways.

The regiospecificity of addition of p-nitro-phenyl azide (III-33) or coumalic acid (III-31) to a tetrahalogenobenzobarrelene is known; there cannot be any. The use of specifically deuterated 1-methoxybenzobarrelenes as substrates would enable the influence of the methoxy-substituent on the orientation of cycloaddition to be assessed (neglecting the ^2H isotope effect).

The consequences of both regioisomeric modes of cycloaddition are exemplified in Scheme III-23 for the reaction of a 1-methoxy-2,4,6-[$^2H_3$] benzobarrelene (e.g. III-48; ● = ^2H, ⊕ = ^1H) or a 1-methoxy-3,5-[$^2H_2$]-benzo-



Scheme III-23

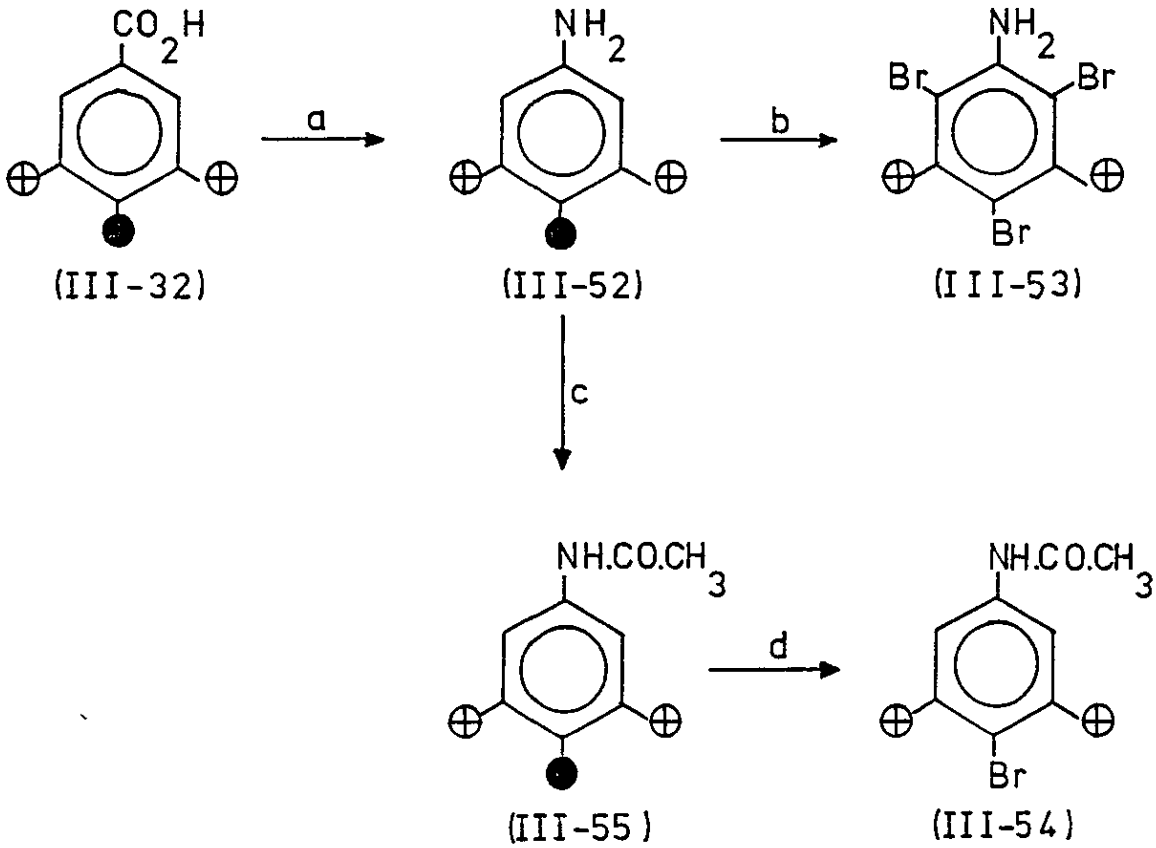
Reagent : a) Coumalic acid (III-31)

barrelene (e.g. III-49; ● = ^1H, ⊕ = ^2H) with coumalic acid (III-31). It may be seen that the different pathways lead to benzoic acids which differ in their patterns of deuteriation. By some good fortune the required labelling patterns were available in 1-methoxy-2,4,6-[$^2H_3$] and 1-methoxy-3,5-[$^2H_2$]tetrafluorobenzobarrelene [(III-48) and (III-49)] which had been prepared for another purpose.[34]

The remaining obstacle to determining the relative importance of each pathway is the problem of ascertaining the distribution of deuterium between the meta- and para- positions of the benzoic acid (III-32) produced. Although the ratio could have been determined by application of the addition-fragmentation sequences described in this chapter, it was considered more straight forward to convert the benzoic acid (III-32) to aniline (III-52), to "wash out" the para-deuterium by electrophilic substitution and then to determine the residual deuterium content by mass spectrometry.

Bromination of aniline (III-52) gives 2,4,6-tribromo-aniline (III-53), and acetylation followed by bromination gives 4-bromo-acetanilide (III-54). Both of these products are stable, crystalline compounds and both show good molecular ions in the mass spectrometer. These two procedures were adopted for the elimination of any para deuterium (Scheme III-24).

Some of the para deuterium may be lost in the conversion of benzoic acid (III-32) to aniline (III-52), for aniline (III-52) exchanges ortho and para hydrogens with acidic media, but this is of no consequence to the deuterium content of the products. A consequence of the possibility that the bridgehead methoxy-group might exert a pronounced directing effect on the cycloaddition is the possibility that the benzoic acid produced might contain almost all of its deuterium in the para position. This deuterium would be removed during subsequent manipulations, which could make the



Scheme III-24

Reagents: a) NaN_3, conc. H_2SO_4 ; b) Br_2, CH_3CO_2H,
c) $(CH_3CO)_2O$, pyridine; d) Br_2, CH_3CO_2H, pyridine.

assessment of the relative importance of the pathways difficult. The degradation of both (III-48) and (III-49) ensures that at least one of the benzoic acid (III-32) products incorporates deuterium at a level significantly above experimental error. This also guards at least partially against any adventitious scrambling or loss of deuterium or any unusually pronounced deuterium isotope effect. In the event this was a wise precaution.

The results of the deuterium labelling experiments are collected in Table III-2.

Concentrating on the results from the 3,5-[$^2H_2$]-labelling pattern, the first conclusion to be drawn is that the results are internally self-consistent. The agreement between deuteriation levels measured on different ions, the identity of deuteriation levels in different compounds in which the deuteriation levels should agree, and the close agreement of the deuteriation level calculated for the methoxybenzobarrelene (III-49) from the deuteriation levels of the methoxynaphthalene (III-51) with the level actually observed (calculated d_0 1.7%, d_1 22.6%, d_2 75.7%; observed d_0 4%, d_1 22%, d_2 74%) are all satisfactory.

An additional point to note is the otherwise unfortunate lack of bromination of the acetanilide (III-55) produced during the preparation of the mass spectrometry samples: the deuteriation level is very close to that measured for the benzoic acid (III-32) which was its immediate precursor. The loss of deuterium from any position cannot total more than 2½% of the total deuterium; the loss from the meta position can safely be taken as being negligible.

The deuteriation levels of the tribromoaniline indicate that 54% of the reaction proceeds through pathway (b), the remaining 46% through pathway (a) (Scheme III-23).

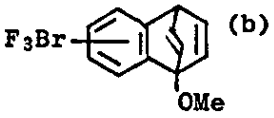
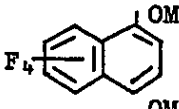
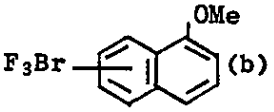
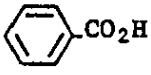
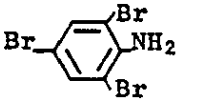
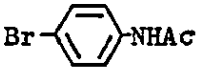
Structure		Source (Benzobarrelene labelling pattern)							
		2,4,6-[$^2H_3$]				3,5-[$^2H_2$]			
		d_0	d_1	d_2	d_3	d_0	d_1	d_2	d_3
	(III-48)	<1	1	5	93				
	(III-49)					4	22	74	0
		<1	1	6	92	4	22	74	0
	(III-50)	3	20	77	0				
	(III-51)					13	87	0	0
		2	28	70	0	13	87	0	0
	(III-32)	5	95	0	0	13	87	0	0
	(III-53)	60	40	0	0	53	47	0	0
	(III-54)	54	46	0	0	15[c]	85[c]	0[c]	0[c]

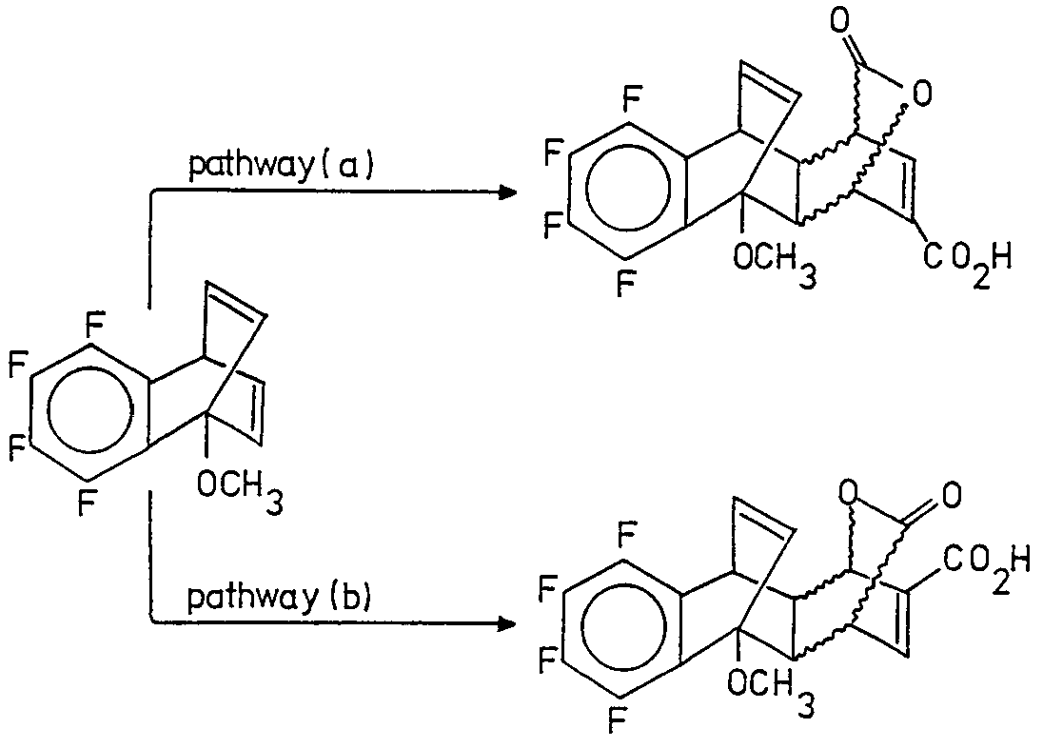
Table III-2

%[^2H][a] in benzobarrelenes and their degradation products.

(a) determined by mass spectrometry.

(b) in the generation of tetrafluorobenzyne from bromopentafluorobenzene some halogen exchange occurs to give bromotrifluorobenzyne, the cycloadducts of which contaminate the product of cycloaddition of tetrafluorobenzyne to an arene. Whilst this would have serious consequences for the determination of specific radioactivities, the happy result for mass spectrometry is to give two molecular ions from which deuterium incorporations may be determined.

(c) no trace of p-bromoacetanilide (III-54) by mass spectrometry. These are the %[^2H] for acetanilide (III-55), which gave the only molecular ion detected.



Part of Scheme III-23

The results from the 2,4,6-[$^2H_3$]-labelling pattern show one glaring anomaly. The deuteriation levels of the naphthalenes are too low by a considerable margin. They do not allow any realistic calculation of the deuteriation levels of the 2-(or 6-) positions of the 1-methoxytetrafluorobenzobarrelene (III-48) used.

If this anomaly is set aside and the deuteriation levels of the benzoic acid (III-32), tribromoaniline (III-53) and p-bromoacetanilide (III-54) are used to calculate the relative importance of the two pathways, the results from tribromoaniline (III-53) indicate that pathway (a)

accounts for 42% of the reaction, and pathway (b) for 58%. The corresponding values calculated from the p-bromoacetanilide deuteriation level are: pathway (a) 48.5%, pathway (b) 51.5%.

These results indicate that pathway (a) accounts for ca. 45.5%, pathway (b) accounts for ca. 54.5% of the reaction of 1-methoxy-tetrafluorobenzobarrelene (III-8) with coumalic acid (III-31). The remote methoxy group obviously exerts some effect, but it is not very great in this case.

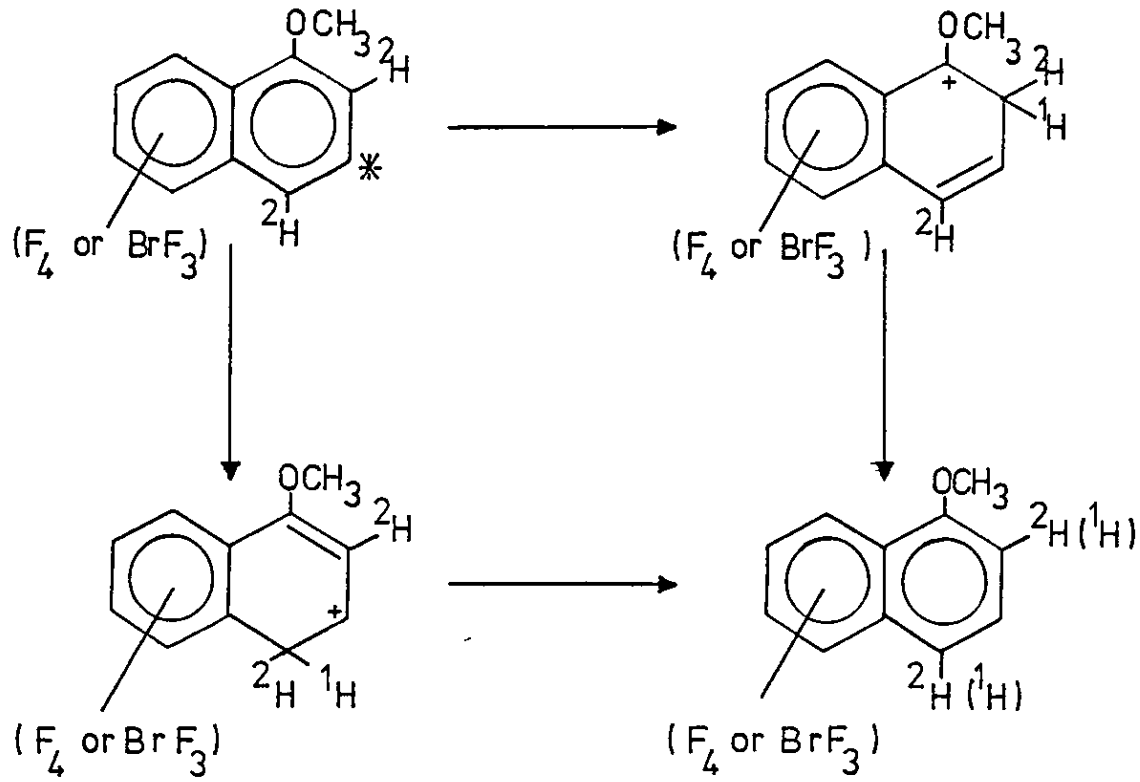
How justified is the assumption that the low deuteriation levels of the naphthalene (III-50) is of no consequence to the subsequent calculation of the importance of the two pathways? Why are the levels low? The obvious, and probably correct reason is because hydrogen exchange has taken place with the reaction medium at some time. If this exchange took place in the 1-methoxy-tetrafluorobenzobarrelene (III-48) the assumption is clearly unjustified; if, on the other hand, the exchange has occurred after the reaction [that is, in the naphthalene, (III-50)] then the assumption is justified.

The results with the 3,5[$^2H_2$]-labelling pattern indicate that 1-methoxy-tetrafluorobenzobarrelene (III-8) does not exchange its β-hydrogen atoms with the reaction medium. It is difficult to believe that the α-hydrogen atoms exchange comparatively much more rapidly than the β-hydrogen atoms in such olefins as the etheno-bridges. Moreover, in a ring system so prone to suffer rearrangement, the exchange of hydrogen would be accompanied by some rearrangement, which is not observed. The ^1H n.m.r. spectra of the neutral fractions indicated that clean conversions had occurred.

The high level of deuteriation of the benzoic acid (III-32) indicates that much, if not all, of this exchange is occurring after the formation

of the benzoic acid (III-32). The markedly greater exchange of deuterium from the bromotrifluoronaphthalene than from the tetrafluoronaphthalene (III-50) indicates that the exchange may have occurred in the naphthalene (III-50) itself.

An explanation which is consistent with these observations is that the exchange occurs in the naphthalene (III-50) by protonation at the deuteriated positions (Scheme III-25). Such a reaction would be easier with the bromotrifluoronaphthalene than with the tetrafluoronaphthalene (III-50), and would not be detected in the case of a naphthalene labelled at the starred position (Scheme III-25).



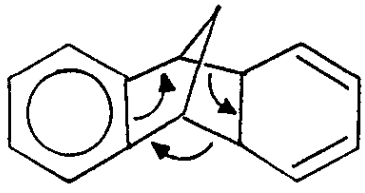
Scheme III-25

There is a note of caution in these results. The reaction medium is obviously quite strongly acidic. Not only does it cause rearrangement of some methyl-substituted 1-methoxybenzobarrelenes, it causes proton exchange with naphthalenes bearing strongly deactivating (as well as activating) substituents. The exchange phenomenon might have caused difficulties if the reaction had been used to determine the amounts of deuterium in the ortho and para positions of the [$^2H_3$]anisole.

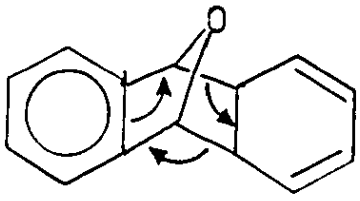
The Chemical Degradation of Benzobarrelenones

The degradation of benzobarrelenes by the cycloaddition-fragmentation pathways discussed earlier provides a means by which many arenes may be degraded. On reaction with tetrachlorobenzyne some arenes form benzobarrelenones alongside or instead of benzobarrelenes,[8d] and a satisfactory degradation of such arenes will in general entail the degradation of a benzobarrelenone.

Any attempt to functionalise and remove the etheno-bridge by extending the scope of the cycloaddition-fragmentation pathways to benzobarrelenones must contend with the extra barrier to fragmentation which the keto-form of a benzobarrelenone presents: cycloaddition to the etheno-bridge may lead to a 1,2-dihydroaromatic system, but this dihydroarene would not be bridging the 1,4-positions of a 1,4-dihydroarene. An interesting comparison is provided by the relative case of fragmentation of the 1,4-methano- and 1,4-epoxy-4a,9,9a,10-tetrahydro-anthracenes, (III-56) and (III-57) respectively.



(III-56)



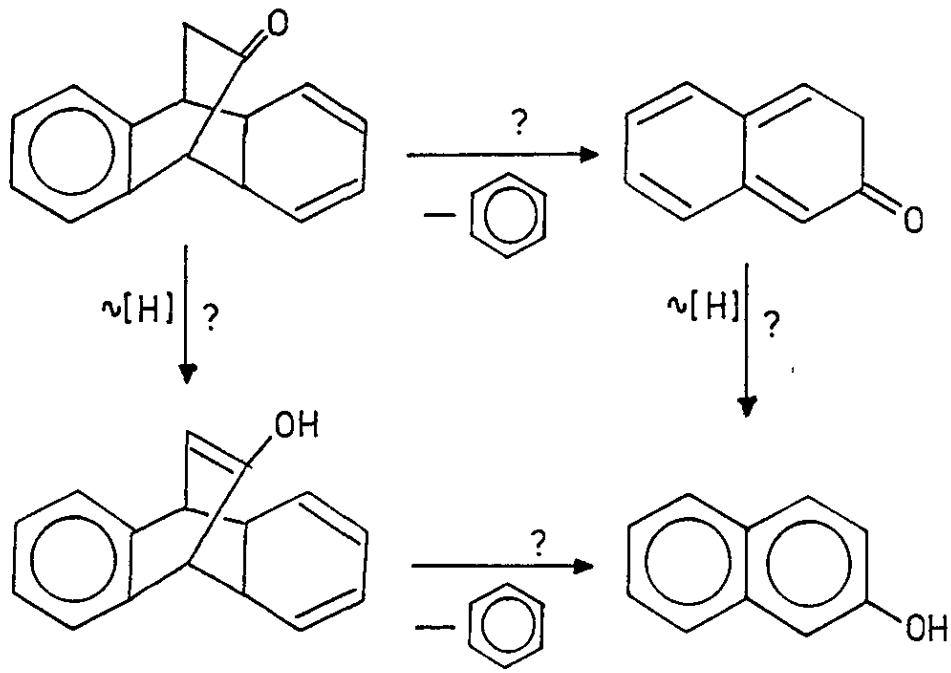
(III-57)

Arrows indicate the bond re-organisation during fragmentation.

Whereas the former compound is stable at temperatures as high as 110°, the latter compound has a transient existence at room temperature and has only been identified from its decomposition products.[20f] The extra activation energy required to form the o-quinodimethane structure (isoindene) relative to that required to form the aromatic structure

(isobenzofuran, which is only weakly aromatic) is seen as a significant factor in such fragmentations. Tetrahalogeno-o-quinonoid compounds exhibit greater stability than their unhalogenated analogues[18] and this effect might facilitate the desired fragmentation of benzobarrelenones despite the non-aromatic character of one of the fragments.

Another way in which this difficulty might be surmounted is through fragmentation of an enol tautomer. Although the proportion of enol would be small, if the ketone-enol equilibrium could be rapidly established, the reaction should proceed to completion by fragmentation of the enol, as outlined in Scheme III-26.



Scheme III-26

With these considerations in mind, an attempt was made to apply the use of 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) to the degradation of tetrachlorobenzobarrelenone (III-16). It was hoped that the products

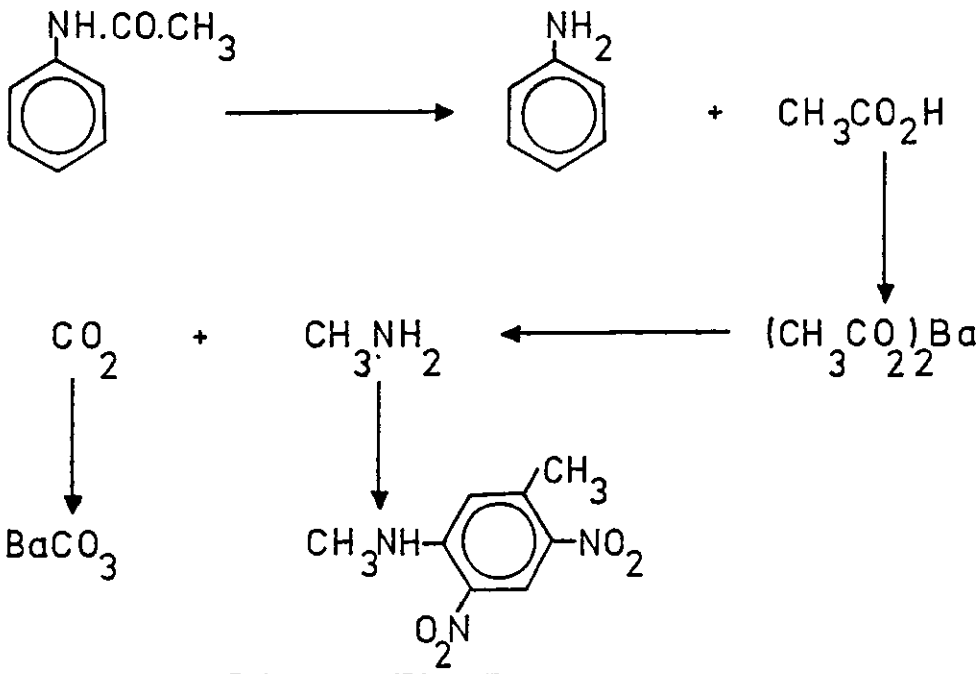
would be 3,6-di-(2′-pyridyl)-pyridazine (III-25) and 1,2,3,4-tetrachloro-6-hydroxynaphthalene (III-57).

In contrast to benzobarrelenes, there are two distinct reactive centres in benzobarrelenones. The other reactive site of a benzobarrelenone is the carbonyl group. Not only would a sequence of reactions which excised the carbonyl group be of use in the assay of arenes, but it would also be the most useful degradative scheme to apply to the [^{14}C]tetrachlorobenzobarrelenone formed by acid catalysed rearrangement of 1-methoxy-1-[^{14}C]tetrachlorobenzobarrelene. It was anticipated that the radioactivity in this ketone would be in the carbonyl group and so the ability to selectively remove this group became a prerequisite to the success of the experiments described in chapter four.

In practice the oxo-ethano-bridge of benzobarrelenones is the more conspicuously reactive of the two bridging groups, and the chemistry of benzobarrelenones is fraught with aromatisation as a consequence. There are reports of reactions conducted under thermal, photochemical, acidic, or basic conditions falling down the $(4n + 2)\pi$ sink.

Pyrolysis of benzobarrelenones gives naphthalene derivatives.[8d,32] The oxo-ethano-bridge is extruded by heating the ketones 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, and there seems little prospect of ever developing direct thermal fragmentation into a useful procedure for excising the carbonyl group.

Photolysis of benzobarrelenones also leads ultimately to extrusion of the oxo-ethano-bridge.[8d,32b] In this case the conditions are milder, and the ketene produced may be trapped as, for example, acetanilide. Degradation of the acetanilide via acetic acid to methylamine and carbon dioxide has been reported (Scheme III-27).[33] This scheme would be better



Scheme III - 27

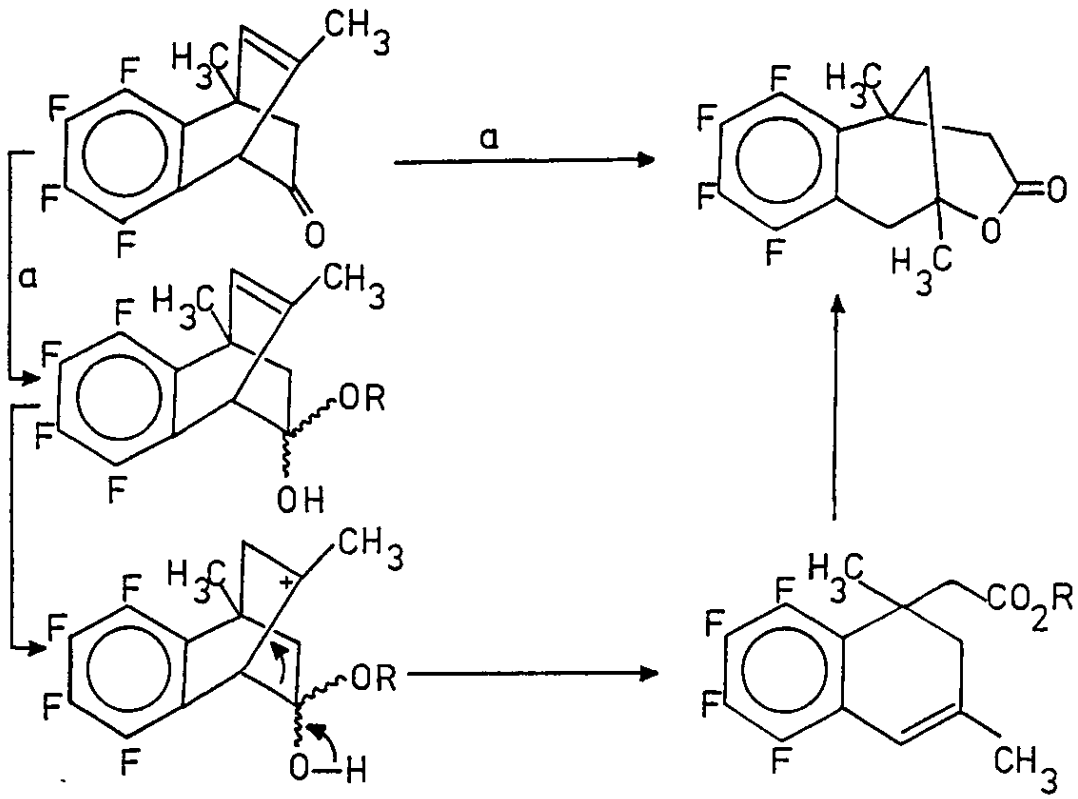
suited to the isolation of the methylene group rather than the carbonyl group of the benzobarrelenone.

Although the cavalier approach is the more exciting, discretion is indeed the better part of valour; a more strategic approach is required.

Acid catalysed reactions of benzobarrelenones have given naphthalene derivatives,[34] but they are probably to be considered as nucleophile induced reactions (Scheme III-28). The alternative fragmentation to an acylium cation which is solvated and then lactonises is another plausible pathway.

The reactions of benzobarrelenones with bases offer more encouragement in this context. The reaction of tetrafluorobenzobarrelenone (III-12) with hydroxide ion at room temperature leads to the formation of 5,6,7,8-tetrafluoro-1,4-dihydronaphth-1-yl acetic acid (III-58); at higher temperatures the conjugated 1,2-dihydro-isomer (III-59) is formed. Alkyl substitution does not seem to hinder the reaction (Scheme III-29).[9,35]

As part of a well conceived synthesis of octamethylnaphthalene the benzobarrelenone (III-60) was treated with the dimsyl anion in dimethylsulphoxide.[32a] The intermediate decomposed under the conditions of its formation and the isolated product was the desired naphthalene (III-61) (Scheme III-30).



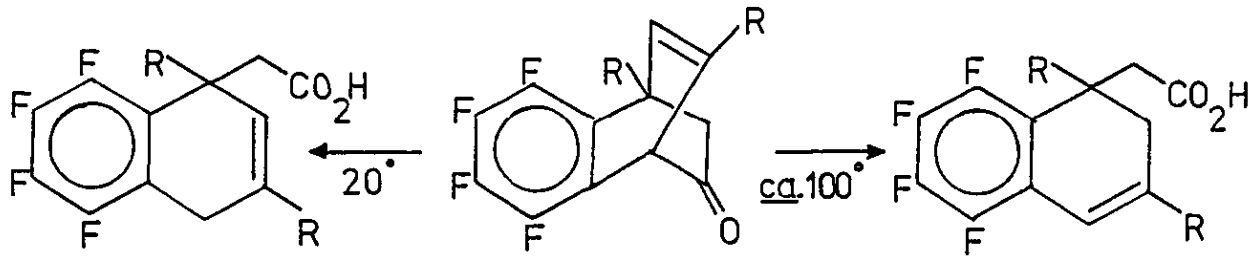
Scheme III-28
Reagent: a) Conc. H_2SO_4

However, at the time of our greatest need, this reaction was as an unopened book.

In a similar reaction, an attempt to form the phenyl carbinol (III-62) by addition of phenyl Grignard reagent to tetrachlorobenzobarrelenone (III-16) in boiling tetrahydrofuran gave tetrachloronaphthalene (III-63) as the only isolated product.[36] This last observation clearly points the way to success; the intermediate is surely the magnesium salt of the carbinol (III-62), the fragmentation very easy, and the other fragment very probably the enolate of acetophenone (III-64).

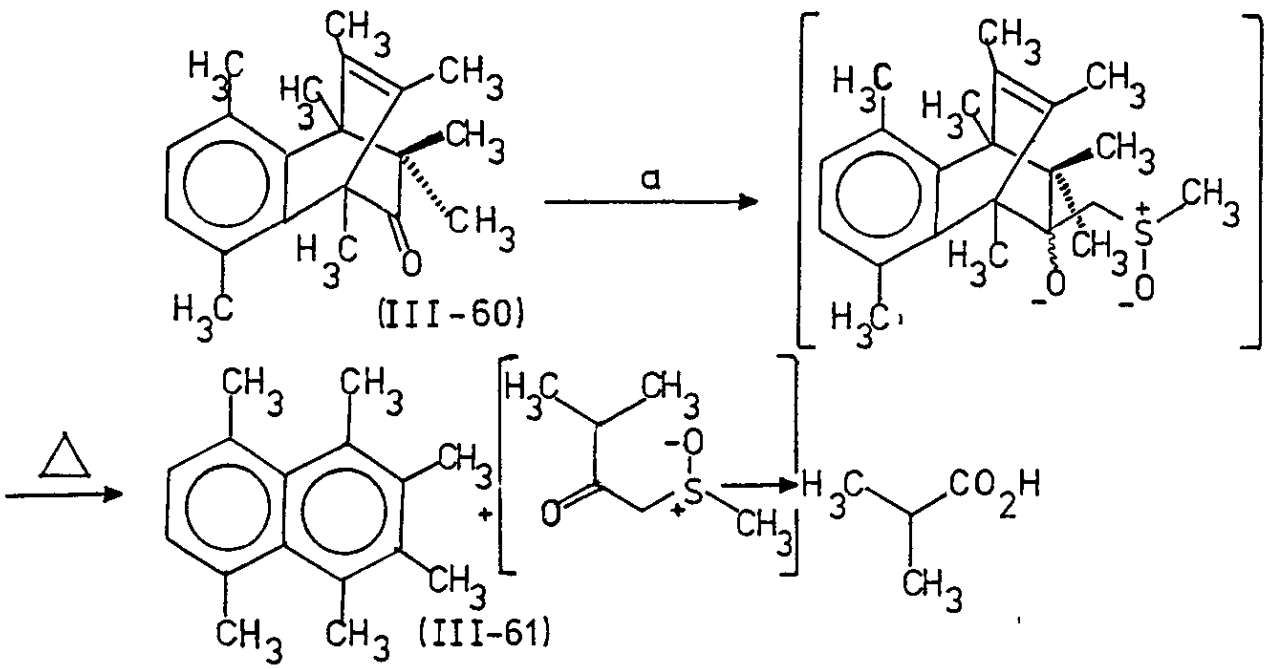
As the degradation of the side chain of acetophenone (III-64) presents a relatively simple problem, this reaction would provide the desired fragmentation if both of the fragments could be isolated.

The second approach chosen to the problem of degrading benzobarrelenones was to isolate the phenyl carbinol derivatives, to thermally fragment these ethano-bridged 1,4-dihydronaphthalenes, to isolate both fragments and then to separate and isolate the carbon atoms of the side chain of the acetophenone (III-64) fragment. This approach was successful.



e.g. R=H (III-58) (III-12) (III-59)

Scheme III-29

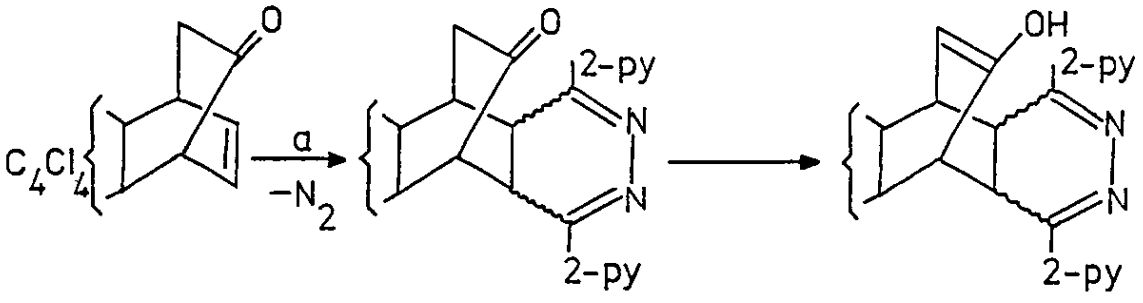


Scheme III-30

Reagent: a) NaH in $CH_3.SO.CH_3$.

When 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) was allowed to react with tetrachlorobenzobarrelenone (III-16) under conditions which cause degradation of benzobarrelenes a complex mixture of products was obtained. Although the products were not fully characterised, it was established that 3,6-di-(2′-pyridyl)-pyridazine (III-25) was not formed although the tetrazine (III-27) had completely reacted.

It is apparent that the proportion of enol present in the reaction mixture is insufficient to allow the partially decomposed cycloadduct (III-65) to fragment before other processes intervene (Scheme III-31).



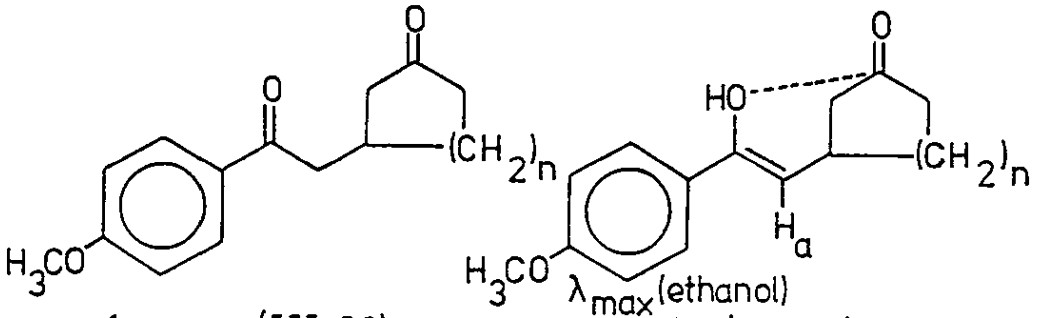
(III-16) (III-65) 2-py = 2-Pyridyl

Scheme III-31

Reagent : a) 3,6-Di-(2'-pyridyl)-s-tetrazine (III-27)

This is not altogether surprising, for enols are high energy species relative to their carbonyl tautomers. When special circumstances permit some enols are sufficiently stable to be isolated but the proportion of enol form present in alicyclic ketones[37] is usually very small and each occasional report of the isolation of such an enol must be carefully considered on its merits.

As an instance which nicely illustrates one of the types of ring opening reaction to which bicyclic molecules are susceptible, consider the report[38] of the irreversible enolisation of the ketones (III-66) and (III-67) by boiling 8% hydrochloric acid. The unexpected stability of these enols [(III-68) and (III-69)] was explained[38] by postulating an interaction (broken line) between the enol oxygen and the ketone carbon presumably an $n \rightarrow \pi^*$ donation.



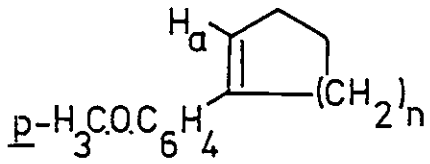
λ_{max} (ethanol)

n = 1 (III-66) 266($\log_{10}\varepsilon$ 4.09)nm (III-68) H_a; τ = 4.05

n = 2 (III-67) 257($\log_{10}\varepsilon$ 4.13)nm. (III-69) H_a; τ = 3.97

In this case the reported data are equally well explained by the alternative structures (III-70) and (III-71). Particularly interesting in this respect are the i.r. and u.v. data. Both "enols" exhibit a carbonyl stretching frequency of 1705 cm^{-1}, unaffected by change of ring size, whereas the change of ring size produces a marked shift in the λ_{max} values observed in the u.v. spectra. The λ_{max} and $\log_{10}\varepsilon$ values are closely comparable to those of cyclopentenyl- and cyclohexenyl-anisole (III-72) and (III-73).[39]

The ^1H n.m.r. spectra also show certain anomalies; the exchangeable protons resonate at τ ca. -1.0 which indicates a moderately acidic environ-



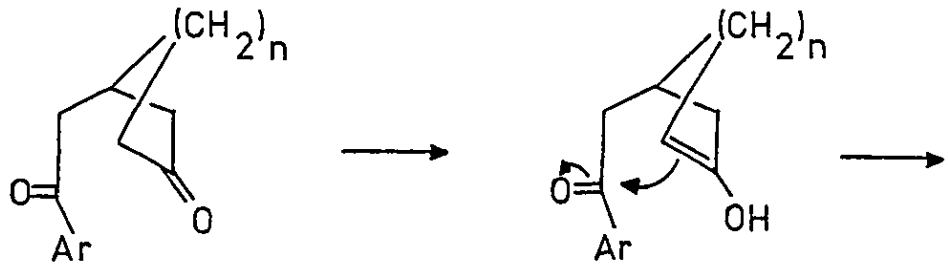
		H_a τ	$\lambda_{max.}^{ethanol}$	$\log_{10}\varepsilon$
n = 1	(III-72)	3.95(t)	~260	~4.15
n = 2	(III-73)		254 254	4.24 4.18

ment and the olefinic protons appear as broad singlets whereas a clearer, fine structure would be anticipated for a compound with structure (III-68) or (III-69).

A sequence of steps which converts the ketones (III-66) and (III-67) to the acids (III-70) and (III-71) is suggested in Scheme III-32. The vigorous enolisation conditions would be sufficient to induce this aldol condensation. Analogous cyclisations to bicycloheptanes - the "π route" - and bicyclooctanes are known,[40] and analogous ring cleavage reactions of norbornenone derivatives have been reported.[41] A similar cleavage of a benzobarrelenone was discussed earlier (Scheme III-28).

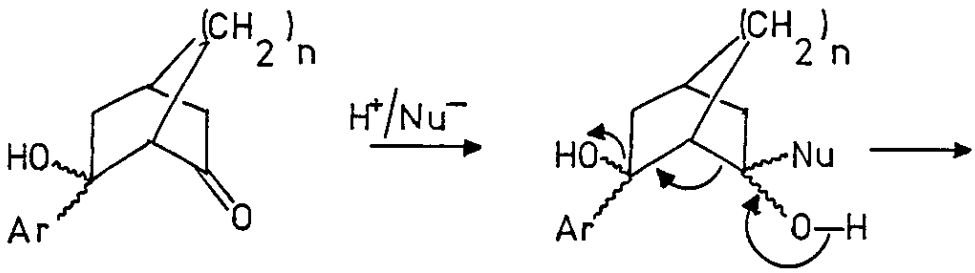
The failure of benzobarrelenones to undergo fragmentation on treatment with 3,6-di-(2′-pyridyl)-s-tetrazine (III-27) was anticipated; although the reaction was intrinsically interesting the prospect of more immediate and more useful progress with the degradation of the phenyl carbinols diverted attention to these latter reactions.

Reaction of the readily available 5-methyltetrachlorobenzobarrelenone (III-13) with a large excess of phenyl Grignard reagent at room temperature for 20h. gave a useful yield of the corresponding phenyl carbinol (III-74) (67%), together with a trace of 1,2,3,4-tetrachloro-6-methylnaphthalene



n= 1 (III-66)

n= 2 (III-67)

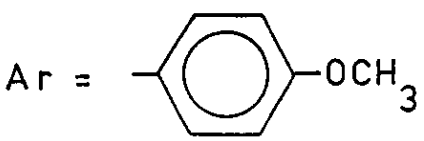


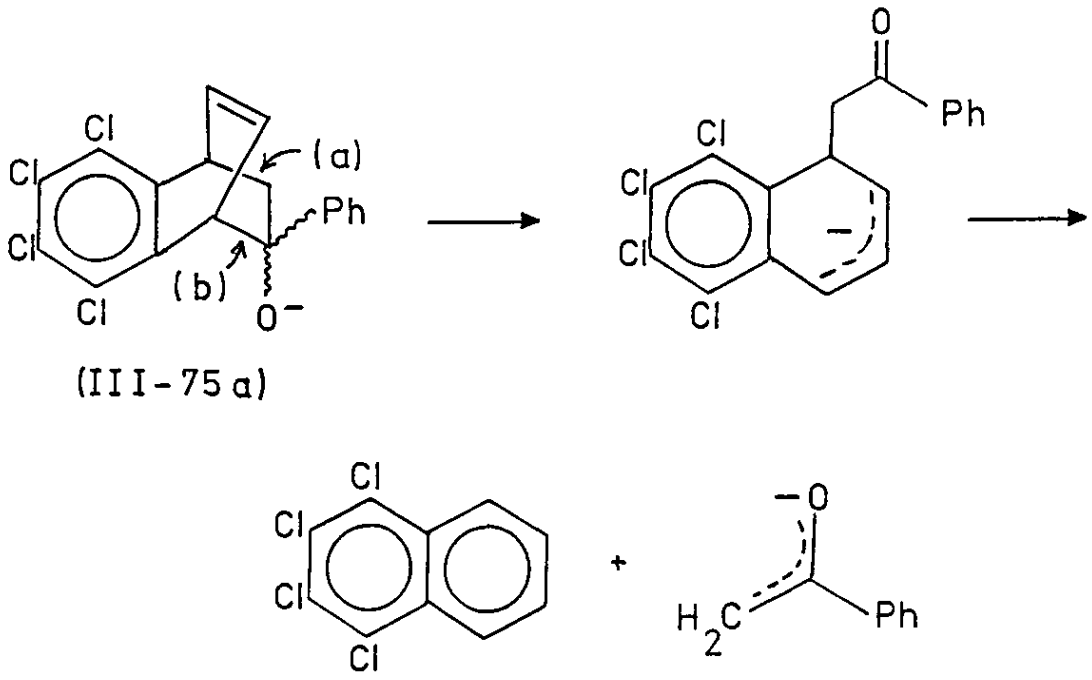
n=1 (III-70)

n=2 (III-71)

Scheme III-32

Reaction medium · Hot, conc. HCl.





Scheme III-33

(III-75) (3%) and some 1-phenyl ethanol (III-76) (20%). No acetophenone (III-64) was isolated, but acetophenone is undoubtedly the precursor of the 1-phenyl ethanol (III-76) isolated. Reduction of ketones by Grignard reagents, particularly when taken in excess, in known.[42] When the reaction time and the excess of phenyl Grignard reagent were reduced and care was taken to maintain the temperature of the reaction at or below 20° during its initial stages, a quantitative yield of the phenyl carbinol (III-74) was obtained after chromatography of the reaction mixture. A high yield of the alcohol (III-62) was obtained from tetrachlorobenzobarrelenone (III-16) by this method.

These crystalline alcohols are stable at room temperature, which contrasts with the fragmentation observed during their attempted formation in boiling THF. The alcohols did decompose at their melting points (ca.

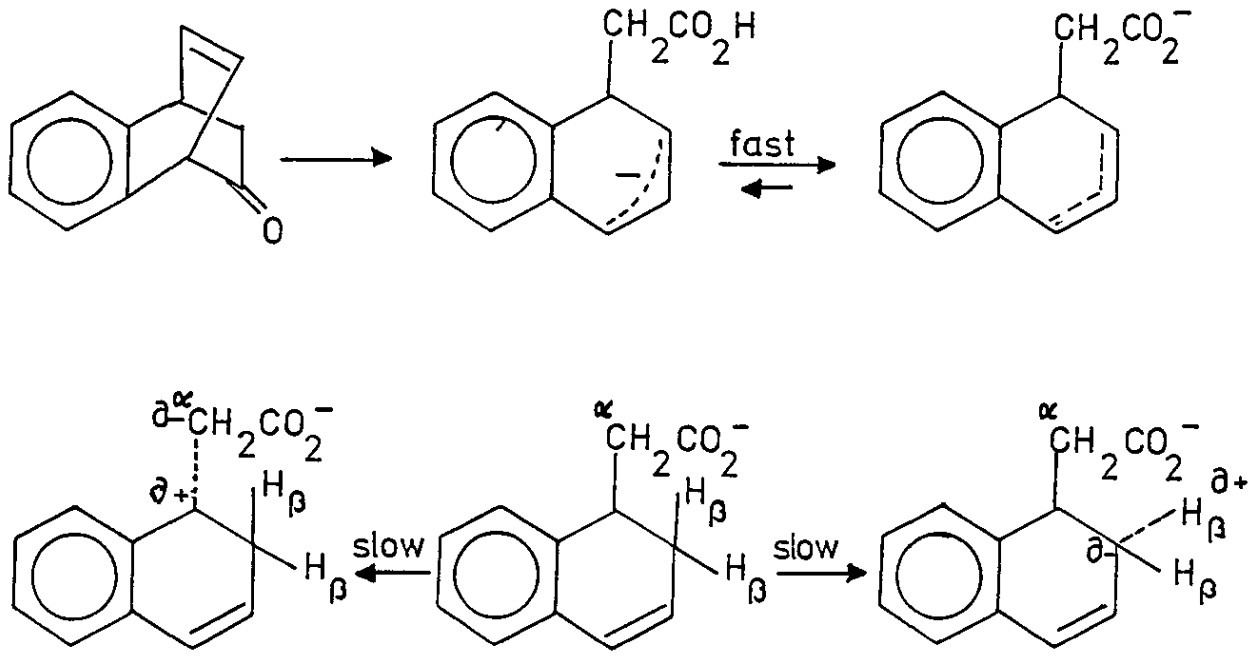
150°) and t.l.c. of the decomposition products after a melting point determination indicated that acetophenone (III-64) and the expected naphthalene (III-75) had been formed.

Pyrolysis of the alcohols [(III-62) and (III-74)] in boiling DMF for 30 minutes gave excellent yields (ca. 90%) of the corresponding tetrachloronaphthalenes [(III-63) and (III-75)] and good yields (ca. 65%) of acetophenone (III-64). The lower isolated yield of acetophenone (III-64) doubtlessly a consequence of its volatility, which problem does not arise to the same extent when the ketone can be handled in solution and degraded further without the need to isolate the compound from residual solvent.

The ease of fragmentation of the alcohol (III-62) relative to its anion is surprising. The alcohol itself is an ethanonaphthalene, and the fragmentation of such molecules at ca. 150° is not unusual. The much easier fragmentation of the anion (III-75a) is anomalous if the reaction is considered as a retrodiene reaction; it is probably to be understood in terms of a stepwise fragmentation producing ever more stable species (Scheme III-33). The degree to which the breaking of bond (b) precedes that of bond (a) is difficult to estimate, but it is unlikely that the fragmentation occurs with synchronous scission of the two bonds.

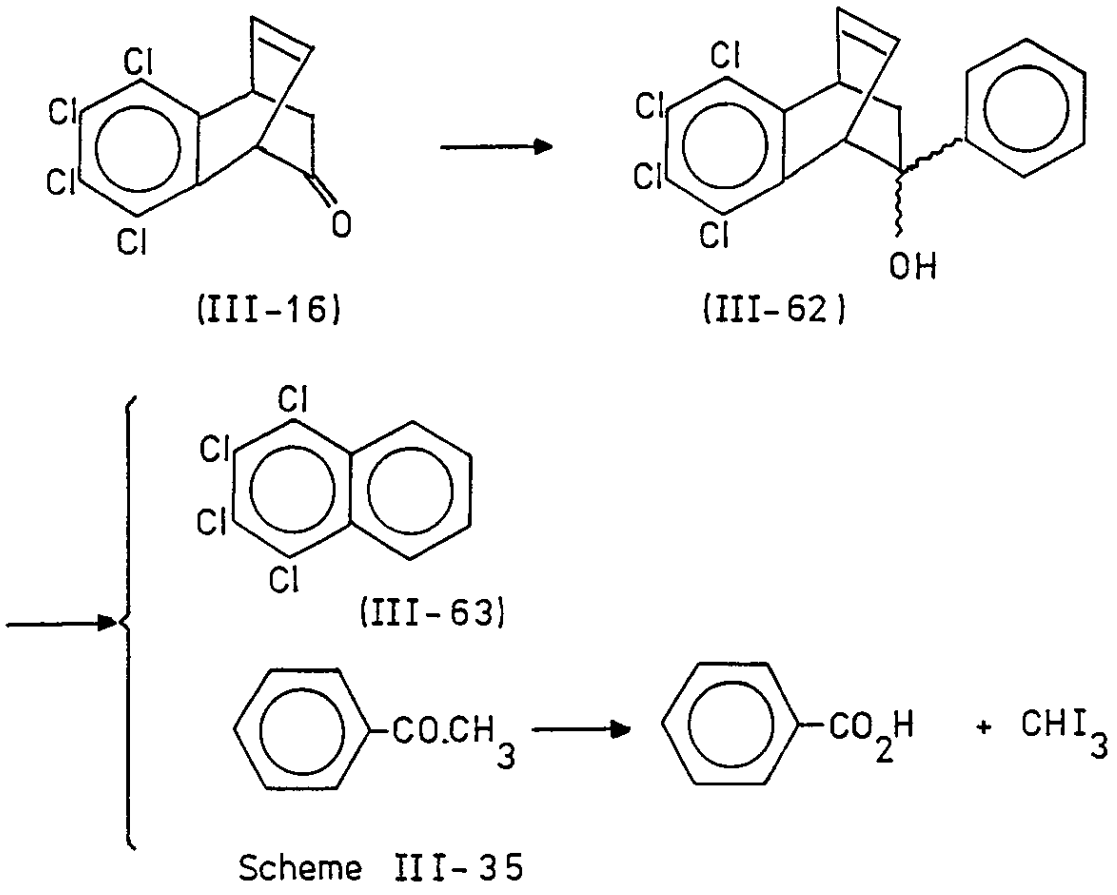
The cleavage of non-enolisable ketones by nucleophiles is well established.[41] The cleavage of benzobarrelenones by hydroxide ion has already been discussed, in which case the reaction does not proceed as far as fragmentation. Why should the difference in behaviour be so marked?

In the cleavage of benzobarrelenones with aqueous sodium hydroxide there are two ways in which the reactions are significantly different to the fragmentation induced by the phenyl Grignard reagent. Firstly the reaction is conducted in a protic solvent; there is a ready supply of protons even though the medium is basic. Secondly the cleavage product is



Scheme III - 34

acidic; it will be rapidly deprotonated. The presence of the ionised carboxyl group hinders the accumulation of negative charge on the cinnamyl portion of the molecule during the transition state for elimination and the presence of a proton source ensures that any dianion formed is rapidly reprotonated. Any elimination in which the breaking of the C-H_β bond is in advance of the breaking of the C-C_α bond is thus inhibited. The prior breaking of the C-C_α bond is suppressed by the instability of the incipient dianion, (illustrated, for the conjugated isomer in Scheme III-34). The rapidity with which the anion is protonated is evident from the preferential formation of the non-conjugated dihydronaphthalene at room temperature and the slowness with which isomerisation to the conjugated form occurs (only on heating). The preferential formation of the 1,2-dihydronaphth-1-yl acetic acid rather than the 1,2-dihydronaphth-4-yl



Scheme III-35

acetic acid shows the importance of electrostatic effects in this system. These factors combine to suppress the fragmentation of benzobarrelenones to naphthalenes and acetic acids in aqueous base.

In the reaction of the phenyl Grignard reagent with a benzobarrelenone the anion will not be protonated and the fragmentation reaction will not be hindered by an unfavourable proto-equilibrium. The pK_a of acetophenone is lower by far than the second pK_a of acetic acid,[37] and the enolate of acetophenone is readily ejected to give the observed naphthalene. The fragmentation observed by Hart[32a] (Scheme III-30) may also be understood in these terms.

The degradation of the side chain of acetophenone may be accomplished by an iodoform reaction. Difficulty was experienced initially in isolating iodoform in a pure state when the reaction was conducted in aqueous solution,

but use of dioxan as a co-solvent gave good yields of both fragments. Care should be taken that the dioxan has been purified; commercial dioxan frequently contains acetaldehyde, the presence of which is clearly deleterious. The sequence of reactions developed to degrade benzobarrelenones is illustrated for tetrachlorobenzobarrelenone (III-16) in Scheme III-35. The isolation of the carbonyl group of benzobarrelenones as benzoic acid is a highly satisfactory solution to the problem of determining the activity associated with the carbon atom of the carbonyl group of [^{14}C]-tetrachlorobenzobarrelenone.

APPLICATIONS

Applications

The applications of the work described in this chapter fall into two well defined categories. There are the analytical uses, in which the reactions are employed to obtain information about the composition of arenes or of their cycloadducts. There are also synthetic uses, although these will often be restricted by the availability of simpler or cheaper alternatives.

(i) Analytical uses.

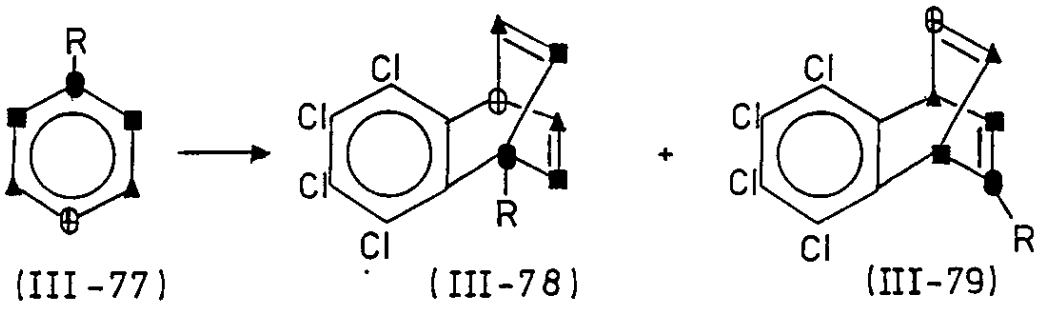
It has been described how many simple arenes react with tetrachlorobenzyne to give two benzobarrelenes. Methods have been reported by which these benzobarrelenes may be degraded by removal of an etheno-bridge. How much information does this provide about the original arene; in particular, how precisely can the distribution of an isotopic label within the arene be determined?

In the general case where the isotope is partially scrambled amongst all of the ring positions the amount of information available is not sufficient to determine value of the activity of each position. Even in the case of an arene with C_{2v} symmetry (Scheme III-36) the amount of information which can be obtained is restricted by the limited number of distinct pairs of carbon atoms which may be removed by the addition-fragmentation sequence. For instance, none of the pairs (● + ▲), (■ + ⊕), and (⊕ + ●) can be isolated by the application of these reactions.

A moment's reflection will show that the number of independent equations which may be derived from these results is insufficient to obtain values for the four unknown activities.

Thus:

Let the total activity be T



(III-77) (III-78) (III-79)

Scheme III-36

● + 2■ + 2▲ + ⊕ = T

We may in general measure the values A, B, C and D where

■ + ▲ = A

● + ■ + ▲ + ⊕ = B

▲ + ⊕ = C

● + 2■ + ▲ = D

However, a knowledge of A and C is sufficient additional information to allow the calculation of B and D from T.

i.e: T—A = ● + ■ + ▲ + ⊕ = B

and T—C = ● + 2■ + ▲ = D

The possibility that the measured and calculated values of B and D may not coincide is of no significance; they are just different estimates of a single pair of activities.

There may be benzobarrelenes (III-79) which fragment in both possible ways. We may then measure E and F

● + ■ = E

■ + 2▲ + ⊕ = F

As before, knowledge of one of the activities allows the calculation of the other from T

$$T-E = \blacksquare + 2\blacktriangle + \oplus = F$$

Note that the results are now summarised in the three equations T—A, T—C, and T—E, and that

$$A + C + E = \bullet + 2\blacksquare + 2\blacktriangle + \oplus = T.$$

In other words, A, C, E, and T are not independent of one another; a knowledge of any three allows the calculation of the fourth. There is not enough information to calculate all of the activities independently.

Is the situation all gloom? If the label is indeed scrambled into the four positions the outlook is not brilliant. If, however, any of the pair-wise measures of activity were zero, the other pair-wise measurements would become estimates of the activities of single positions.

The additional information required to enable the complete evaluation of the activities is the activity of a single position (which is provided in the special case that the activity of a pair of positions is zero). The degradation sequence applied to benzobarrelenones (III-80) gives this information.

We may now measure

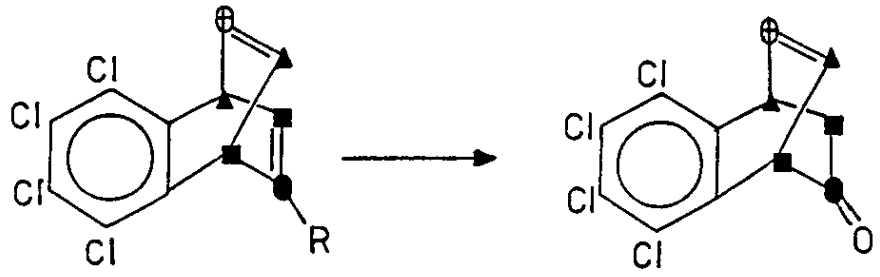
$$\bullet = G$$

$$\blacksquare = H$$

$$\blacksquare + 2\blacktriangle + \oplus = F$$

As before, F may be calculated from T, G, and H.

Knowing the values of T, A, G, and H we may calculate the activities of all positions of an arene (III-77).



(III-78) (III-80)

Scheme III-37

R = OCH_3, $N(CH_3)_2$.

The distribution of activity within an excised etheno-bridge has not been considered. If the two carbon atoms differ in some way other than in their original position in the arene, that is, they remain distinguished in the excised fragment, there is the possibility that this fragment could itself be degraded to provide a measure of the activity of a single position. No attempt has been made to design such a degradation.

In more complicated cases the basic principle remains: in addition to pair-wise values, some estimate must be obtained of the activity of one of the arene carbon atoms.

To which arenes and for what purpose may these sequences be applied?

Arenes with C_{2v} symmetry which form benzobarrelenones are analysed particularly easily. Even those arenes which form only benzobarrelenones may be analysed now that a procedure for removing the etheno-bridge of a benzobarrelenone using the fragmentation reagents has been developed. As a corollary of this, any arene which may be converted to such a benzobarrelenone-forming arene may also be assayed. The numerous methods available for introducing an oxygen function into an aromatic ring make this condition less restrictive than it might at first appear.

In addition arenes lacking the symmetry axis but which form two separ-

able benzobarrelenones may also be completely assayed.

Arenes which form only benzobarrelenes may be completely assayed by the methods described only in the special case that the activity of one of the fragments is zero. Even so it will occasionally be impossible to determine with complete certainty the activities of all atoms; there may remain pairs, the activity of which cannot be partitioned between the constituent atoms.

The method will provide a check against scrambling in many benzobarrelene forming arenes. This gives rise to particular satisfaction, for it was for this purpose that the method was originally devised.

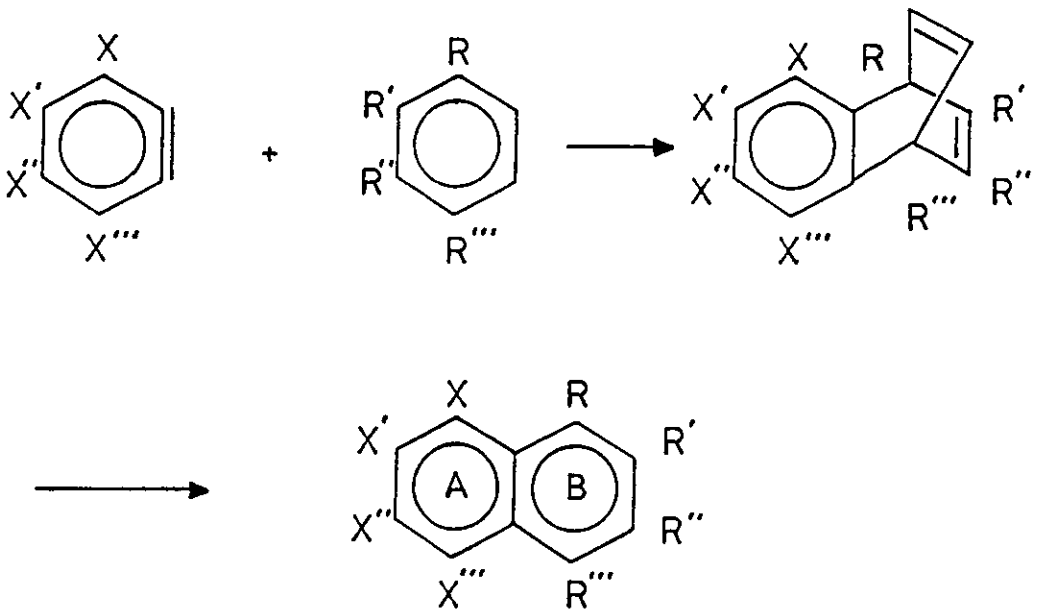
Chemistry is very much a science of special cases, and in this respect the fragmentation sequences are no exception. In the case of complicated molecules, whether or not these sequences can be applied and how much information they can give will depend on the nature of the arene in question.

In spite of the restrictions outlined above, the fragmentation sequences provide a useful new chemical method for assaying arenes.

(ii) Synthetic uses.

The obvious synthetic application of these reactions is in the preparation of naphthalenes (Scheme III-38). Extension of the method to the preparation of anthracenes is straightforward. The success of this sequence depends upon the availability of suitably substituted arenes, and on the selectivity of the addition-fragmentation step.

One of the main advantages is the way in which the B ring of the naphthalene is added in one step with its substitution pattern already complete. The site-selectivity of the fragmentation reactions is of particular importance in this respect. This reaction allows the understanding of



Scheme III-38

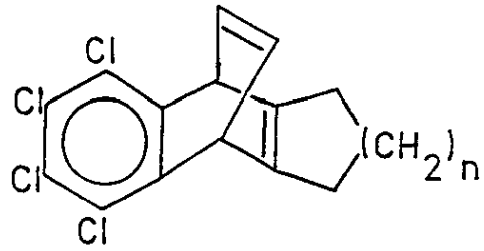
substitution reactions and the control of substitution patterns which has been so painstakingly acquired with benzene derivatives to be transferred to naphthalene synthesis.

Among the disadvantages must be noted that there are many functional groups which are not compatible with benzyne reactions and naphthalenes containing these groups may not be directly prepared. Another disadvantage is the restriction on the substitution pattern which may be introduced with ring A. The range of aryne substituents which permit good yields in the reaction of the aryne with an arene is limited. In general, the aryne should also be symmetrically substituted if difficultly separable isomer mixtures are to be avoided. However, naphthalenes with unsubstituted A rings may be prepared by reductive dechlorination of tetrachlorobenzobarrelenes[5] or the tetrachloronaphthalenes derived from them.[43]

Naphthalenes have been prepared from benzobarrelenes by pyrolysis, but in these reactions it is the more highly substituted etheno-bridge which is preferentially eliminated although the degree of selectivity is low.[17]

These reactions represent an addition to the range of aryne based polycyclic arene syntheses. Although they are not practical general syntheses, there are naphthalenes which are much more difficult to synthesise by any other route, and the reactions should find application in the synthesis of such naphthalenes.

Another aspect of these reactions is the synthesis of the heterocyclic fragment. In these reactions the benzobarrelene functions as a masked acetylene and the reactions could be used to transfer patterns of substitution or isotopic labelling to such heterocycles when the corresponding acetylene is difficult to produce or too reactive to handle conveniently. For instance, the compounds (III-81) and (III-82) are formally masked cyclopentynes and cyclohexynes, although the unsubstituted etheno-bridge would have to be shielded from attack. In these applications aryne-furan adducts might give better results.



n = 1, (III - 81)

n = 2, (III - 82)

In a similar way the oxoethano-bridge of benzobarrelenones is a masked ketene or acetyl group, although useful applications of benzobarrelenones as ketene transfer reagents are probably few and far between.

EXPERIMENTAL SECTION

General Procedures

The general procedures are as described in chapter two with the following additions.

Tri-n-butyl-(p-methoxyphenyl)tin was prepared[44] from p-methoxyphenylmagnesium bromide and tri-n-butyltin chloride and other substituted anisoles were prepared by methylation of the corresponding phenols with dimethylsulphate.[48]

Tetrachloroanthranilic acid was prepared from tetrachlorophthalic anhydride using a published method,[44] but yields varied from excellent to zero. 3,6-Di-(2'-pyridyl)-1,2,4,5-tetrazine,[19] coumalic acid,[49] and p-nitrophenylazide,[44] were made by standard procedures.

1-Methoxy-3,5[$^2H_2$]- and 1-methoxy-2,4,6[$^2H_3$]-tetrafluorobenzobarrelenes were synthesised by S. V. Ley,[8a,b] and obtained by standard procedures. ^{2}H-Isotope incorporations were computed by the P.C.M.U., Harwell, by analysis of the relative abundance of ions in the molecular-ion clusters of the mass spectra.

1. Preparation of 2-Carboxytetrachlorobenzenediazonium Salts[44]

A. Chloride

A stirred solution of tetrachloroanthranilic acid (10.0g, 36.2 mmole) in tetrahydrofuran (50ml) was saturated at room temperature with dry hydrogen chloride gas for 14h. A cream suspension formed. The stirred suspension was treated at -10° with pentyl nitrite (5.0g, 42.7 mmole) during 15 min. and maintained at -10° for 1h. The precipitated product was isolated by filtration, washed at 0° with ether (2 x 5ml) and air dried to give 2-carboxytetrachlorobenzenediazonium chloride, a crumbly pale yellow solid, (6.0g, 52%).

CAUTION! In a similar experiment an explosion occurred during manipulation of the dry diazonium salt causing much loss of yield and composure; attempts to detonate undecomposed portions of the preparation were unsuccessful.

B. Tetrafluoroborate

A stirred solution of tetrachloroanthranilic acid (10.0g, 36.2 mmole) in tetrahydrofuran (50ml) was treated at room temperature with fluoroboric acid (40% aqueous solution, 20ml ca. 91 mmole). The reaction was stirred at room temperature for 10 min. and the solvent was evaporated under reduced pressure. A stirred solution of the solid residue in the minimum volume of dry ether was maintained at -10° and treated with pentyl nitrite (5.0g, 42.7 mmole) during 15 min. The reaction mixture was stirred at -10° for 1h. The precipitated product was isolated by filtration, washed at 0° with ether (2 x 5ml) and air dried to give 2-carboxytetrachlorobenzenediazonium tetrafluoroborate, a crumbly off-white solid (8.3g, 61%).

2. Preparation of 1-Methoxytetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-

1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) and Tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-16)

A stirred solution of pentachlorophenyllithium [prepared and maintained at -55°, from a suspension of hexachlorobenzene (28.48g, 100 mmole) in dry ether (200ml) and n-butyllithium in pentane (2.3 molar, 50ml, 115 mmole)] was treated with anisole (200ml). The reaction mixture was allowed to warm to 0°, at about which temperature it became black, and then heated under reflux for 12h. The clear, black mixture became a khaki suspension at ca. room temperature. The reaction mixture was allowed to cool to room temperature and treated with hydrochloric acid (2N, 100ml). The phases were separated; the organic phase was washed with water (2 x 50ml) and dried ($MgSO_4$). The solvents and excess of anisole were evaporated under reduced pressure and the residue was purified by column chromatography (alumina) to give 1-methoxytetrachlorobenzobarrelene (III-20), (21.46g, 67%) m.p. 123-125° (from ethanol), (lit.[8f] m.p. 122°). Spectral data agreed with those previously reported[8f] and tetrachlorobenzobarrelenone (III-16), (2.33g, 7.5%), m.p. 162° (from ethanol), (lit.[8f] 150°). Spectral data agreed with those previously reported.[8f]

3. Preparation of 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37)

A. From 2-Carboxytetrachlorobenzenediazonium Chloride

A suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium chloride (1.9g, 5.9 mmole) in o-cresol methyl ether (24.5g, 200 mmole) and dry carbon tetrachloride (50ml) was maintained at room temperature for 14h, then heated under reflux for 1h. The solvent and excess of o-cresol

methyl ether were evaporated under reduced pressure. The residue was purified by column chromatography (silica-gel) and crystallisation from ethanol to give 1-methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37), (0.63g, 33%), m.p. 129-131° (from ethanol), (Found: C,49.5; H,3.0; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%).

^{1}H-n.m.r. τ($CDCl_3$) 2.83(dd,1H,J=7Hz, J=1Hz); 3.10(dd,1H,J=7Hz, J=6.5Hz); 3.66(dq,1H,J=6.5Hz, J=1Hz); 4.83(td,1H,J=6.5Hz, J=1Hz); 6.26(s,3H); and 8.23 (d,3H,J=1Hz);

ν_{max}^{KBr} 2970, 2950, 2915, 2835, 1440, 1425, 1370, 1360, 1340, 1325, 1295, 1285, 1230, 1210, 1175, 1115, 1100, 1045, 1025, 1005, 945, 935, 835, 825, 790, 760, 715, 685, and 670 cm^{-1}.

Mass spectrometry: M^+ = 336.

B. From 2-Carboxytetrachlorobenzenediazonium Tetrafluoroborate

A stirred suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium tetrafluoroborate (1.20g, 3.20 mmole) in o-cresol methyl ether (ca. 5ml) and dry carbon tetrachloride (ca. 25ml) was treated at room temperature with a solution of dry pyridine in dry carbon tetrachloride (0.50g, 6.33 mmole in 5ml) during 5 min. The solution became red and warm and effervesced and cast down an unattractive precipitate. The reaction mixture was filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (silica-gel) to give 1-methoxy-2-methyltetrachlorobenzobarrelene (III-37) (0.545g, 51%), characterised by comparison with authentic material.

4. Preparation of 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene)

(III-38) from 2-Carboxytetrachlorobenzenediazonium Chloride

A stirred suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium chloride (3.50g, 10.9 mmole) in m-cresol methyl ether (22g, 180 mmole) and dry carbon tetrachloride (50ml) was heated under reflux for 2h. The solvent and excess of m-cresol methyl ether were evaporated under reduced pressure and the residue was purified by column chromatography (silica-gel) to give 1-methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38), (2.46g, 70%), m.p. 163-165° (from ethanol), (Found: C,50.2; H,3.0; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. τ($CDCl_3$) 3.02(dd,1H,J=7Hz, J=3Hz); 3.17(dd,1H,J=7Hz, J=5.5Hz); 3.57(m,1H); 5.0(dt,1H,J=5.5Hz, J=3Hz); 6.27(s,3H); and 8.08(d,3H,J=1Hz);

ν_{max}^{KBr} 2970, 2915, 2840, 1445, 1375, 1360, 1345, 1315, 1240, 1235, 1205, 1185, 1180, 1135, 1090, 1050, 1015, 760, 685, and 675 cm^{-1}.

Mass spectrometry: $M^{+\bullet}$ = 336.

5. Preparation of 5-Methyltetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-9-methyl-1,4-ethenonaphthalen-2(1H)-one) (III-13) and 1-Methoxy-4-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-4-methyl-1,4-ethenonaphthalene) (III-9) from 2-Carboxytetrachlorobenzenediazonium Chloride

A stirred suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium chloride (8.20g, 25.5 mmole) in p-cresol methyl ether (60ml) and dry carbon tetrachloride (120ml) was heated under reflux for 30 min. The solvent and excess of p-cresol methyl ether were evaporated under reduced pressure and the residue was purified by column chromatography (silica-gel) and recrystallisation from ethanol to give 1-methoxy-4-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-

dihydro-1-methoxy-4-methyl-1,4-ethenonaphthalene) (III-9), (0.302g, 3.7%), m.p. 191-194° (from ethanol), (Found: C,50.1; H,3.1; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. τ($CDCl_3$) 3.00(d,2H,J=7Hz); 3.52(d,2H,J=7Hz); 6.30(s,3H); and 7.78(s,3H).

ν_{max}^{KBr} 3075, 3005, 2980, 2970, 2940, 2915, 2845, 1455, 1445, 1420, 1375, 1355, 1345, 1330, 1320, 1270, 1240, 1235, 1220, 1200, 1190, 1125, 1090, 1075, 1050, 715, 690, and 680 cm^{-1}.

Mass spectrometry: $M^{\dagger\bullet}$ = 336

and 5-methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-9-methyl-1,4-ethenonaphthalen-2(1H)-one) (III-13), (4.68g, 57%); m.p. 172° (from ethanol); (Found: C,48.6; H,2.5; $C_{13}H_8Cl_4O$ requires C,48.5; H,2.5%),

^{1}H-n.m.r. τ($CDCl_3$) 3.80(dq,1H,J=7Hz, J=1Hz); 5.18(d,1H,J=7Hz); 5.65(dd, 1H,J=5Hz, J=2.5Hz); and ca. 7.8-8.2(m,5H);

ν_{max}^{KBr} 2945, 2920, 1735, 1440, 1435, 1415, 1375, 1315, 1300, 1260, 1230, 1225, 1145, 1135, 1085, 1030, 1005, 830, 785, 770, 765, and 680 cm^{-1}.

Mass spectrometry: $M^{\dagger\bullet}$ = 322 (very weak), $[M-42]^{\dagger\bullet}$ = 280.

6. Preparation of 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40)

A. From 2-Carboxytetrachlorobenzenediazonium Tetrafluoroborate

A stirred solution of freshly prepared 2-carboxytetrachlorobenzenediazonium tetrafluoroborate (3.4g, 9.09 mmole) in 2,5-dimethylanisole (4ml) and dry carbon tetrachloride (30ml) was treated at room temperature with a solution of pyridine (1.7g, 20 mmole) in dry carbon tetrachloride (5ml) during 5 min. The reaction mixture was maintained at about room temperature for 5 min,

then filtered through a short column of alumina (60g). The column was washed with ether in light petroleum (20%, 300ml) and the combined filtrate and washings were evaporated under reduced pressure to give 1-methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40), (1.86g, 58%), m.p. 150-153° (from ethanol), (Found: C,51.5; H,3.5; $C_{15}H_{12}Cl_4O$ requires C,51.4; H,3.4%),

^{1}H-n.m.r. τ($CDCl_3$) 3.34(m,1H); 3.65(dq,1H,J=5.5Hz, J=2Hz); 5.10(dd,1H, J=5.5Hz, J=2Hz); 6.28(s,3H); 8.04(d,3H,J=2Hz); and 8.14(d,3H,J=2Hz); ν_{max}^{KBr} 3010, 2975, 2945, 2915, 2835, 1445, 1365, 1340, 1295, 1240, 1205, 1175, 1110, 1100, 1065, 1030, 1020, 990, 930, 840, 800, 755, 745, 685, and 640 cm^{-1}.

Mass spectrometry: $M^{\cdot+}$ = 350.

B. From 2-Carboxytetrachlorobenzenediazonium Chloride

A stirred suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium chloride (6.4g, 19.7 mmole) in 2,5-dimethylanisole (7ml) and dry carbon tetrachloride (30ml) was heated under reflux for 1h. The reaction mixture was filtered through a short column of alumina (30g). The column was washed with ether in light petroleum (20%, 1000ml) and the combined filtrate and washings were evaporated under reduced pressure to give 1-methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40), (3.67g, 53%), identified by comparison with authentic material.

7. Preparation of 1-Methoxy-2,5-dimethyltetrafluorobenzobarrelene (5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) from Pentafluorophenylmagnesium Bromide

A stirred solution of pentafluorophenylmagnesium bromide [from magnesium (1.7g, 70 mg-atoms) and a solution of bromopentafluorobenzene (12.35g, 50 mmole) in ether (100ml), prepared and maintained at ca. 35°] was treated with a solution of 2,5-dimethylanisole (64ml) in cyclohexane (80ml). The reaction temperature was raised to 100° and heated under reflux for 3h. The reaction mixture was cooled to room temperature, hydrolysed with sulphuric acid (1N, 100ml), and extracted with ether (3 x 50ml). The combined extracts were dried ($MgSO_4$) and the solvents and excess of 2,5-dimethylanisole were evaporated under reduced pressure. The residue was purified by column chromatography (alumina) to give 1-methoxy-2,5-dimethyltetrafluorobenzobarrelene (5,6,7,8-tetrafluoro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene), (8.89g, 62%), m.p. 67° (from ethanol), (Found: C,63.2; H,4.2; $C_{15}H_{12}F_4O$ requires C,63.3; H,4.2%), ^{1}H-n.m.r. τ($CDCl_3$) 3.38(m,1H); 3.70(m,1H); 5.35(m,1H); 6.25(d,3H, J_{HF}=3Hz); 8.07(d,3H,J=2Hz); and 8.15(d,3H,J=2Hz); ν_{max}^{KBr} 2985, 2950, 2925, 2840, 1490, 1445, 1375, 1295, 1280, 1270, 1260, 1230, 1205, 1185, 1105, 1075, 1060, 1030, 1020, 995, 965, 920, 810, 795, 755, 750, 675, and 655 cm^{-1}.

8. Preparation of 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39) and 3,4,5,6-Tetrachloro-4′-methoxy-2′,3′-dimethylazobenzene-2-carboxylic acid

A. From 2-Carboxytetrachlorobenzenediazonium Chloride

A stirred suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium chloride (8.0g, 24.9 mmole) in 2,3-dimethylanisole (10ml) and dry carbon tetrachloride (30ml) was heated under reflux for 1h. The solution became red and partially solidified on cooling to room temperature. The solvent

and excess of 2,3-dimethylanisole were evaporated under reduced pressure. The residual dark red solid was washed with chloroform (2 x 25ml) to leave 3,4,5,6-tetrachloro-4′-methoxy-2′,3′-dimethylazobenzene-2-carboxylic acid, orange crystals, (4.14g, 39%), m.p. 224-226° (from anisole), (Found: C,45.6; H,2.9; N,6.8; $C_{16}H_{12}Cl_4N_2O_3$ requires C,45.5; H,2.8; N,6.6%), ^{1}H-n.m.r. τ(DMSO-[$^2H_6$]) 2.40(d,1H,J=9Hz); 3.01(d,1H,J=9Hz); 6.13(s,3H); 7.47(s,3H); and 7.82(s,3H);
ν_{max}^{KBr} 3450 (broad), 2940, 2835, 1770, 1720, 1620, 1605, 1595, 1480, 1460, 1400, 1340, 1320, 1270, 1260, 1250, 1230, 1185, 1105, 1090, 1060, 1050, 1010, 1005, 835, and 770 cm^{-1}.

The red combined chloroform washings were purified by column chromatography (silica-gel) to give 1-methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39), (0.62g, 7%), m.p. 155-156° (from ethanol) (Found: C,51.4; H,3.5; $C_{15}H_{12}Cl_4O$ requires C,51.4; H,3.4%),
^{1}H-n.m.r. τ($CDCl_3$) 2.92(dd,1H,J=7.5Hz, J=2Hz); 3.16(dd,1H,J=7.5Hz, J=5.5Hz); 5.05(dd,1H,J=5.5Hz, J=2Hz); 6.29(s,3H); and 8.23("s",6H);
ν_{max}^{KBr} 3015, 2950, 2915, 2840, 1490, 1365, 1360, 1340, 1320, 1280, 1240, 1215, 1200, 1180, 1110, 1090, 1055, 1015, 925, 815, 760, 715, 680, 670, 645, and 625 cm^{-1}.

B. From 2-Carboxytetrachlorobenzenediazonium Tetrafluoroborate

A stirred suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium tetrafluoroborate (4.0g, 10.4 mmole) in dry carbon tetrachloride (25ml) was treated at room temperature with a solution of 2,3-dimethylanisole (10ml) and pyridine (1.6g, 20 mmole) in dry carbon tetrachloride (40ml) during 5 min. The reaction mixture was stirred at room temperature for 10 min., then heated under reflux for 1h. The solvent and excess of 2,3-dimethylanisole

were evaporated under reduced pressure. The residue was purified by column chromatography (silica-gel) to give 1-methoxy-2,3-dimethyltetrachlorobenzobarrelene (III-39) (0.28g, 8%), identified by comparison with authentic material. No attempt was made to isolate 3,4,5,6-tetrachloro-4'-methoxy-2',3'-dimethylazobenzene-2-carboxylic acid from this preparation.

C. From Pentachlorophenyllithium

A stirred solution of pentachlorophenyllithium [prepared and maintained at -60°, from a suspension of hexachlorobenzene (14.24g, 50 mmole) in dry ether (ca. 250ml), and n-butyllithium in pentane (2.3 molar, 25ml, 57.5 mmole)] was treated with 2,3-dimethylanisole (50ml). The temperature was raised to 80° and the reaction was heated under reflux for 2h. The reaction mixture was allowed to cool to room temperature and hydrolysed with hydrochloric acid (2N, 100ml). The reaction mixture was extracted with ether (3 x 100ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (alumina) to give 1-methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39), (8.8g, 50.5%), identified by comparison with authentic material.

9. Preparation of 1-Methoxy-2,6-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,10-dimethyl-1,4-ethenonaphthalene) and 1,3-Dimethyltetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-1,3-dimethyl-1,4-ethenonaphthalen-2(1H)-one)

A. From 2-Carboxytetrachlorobenzenediazonium Chloride

A stirred suspension of freshly prepared 2-carboxytetrachlorobenzenediazonium

chloride (6.0g, 18.6 mmole) in 2,6-dimethylanisole (6ml) and dry carbon tetrachloride (50ml) was heated under reflux for 1h. The solvent and excess of 2,6-dimethylanisole were evaporated under reduced pressure. The residue was purified by column chromatography (silica-gel) to give 1-methoxy-2,6-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,10-dimethyl-1,4-ethenonaphthalene) (0.69g, 10.5%), m.p. 147-149° (from ethanol), (Found: C,51.2; H,3.6; $C_{15}H_{12}Cl_4O$ requires C,51.4; H,3.4%),

^{1}H-n.m.r. τ($CDCl_3$) 3.60(dq,2H,J=6Hz, J=1.5Hz); 5.01(t,1H,J=6Hz); 6.23 (s,3H); and 8.03(d,6H,J=1.5Hz);

ν_{max}^{KBr} 2975, 2955, 2925, 2850, 1450, 1435, 1365, 1340, 1285, 1240, 1220, 1190, 1165, 1155, 1105, 1030, 1005, 830, 820, 805, 790, 710, and 640 cm^{-1}.

Mass spectrometry: $M^{\cdot+}$ = 350,

followed by an uncharacterised clear oil (0.6g),

followed by 1,3-dimethyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,3-dimethyl-1,4-ethenonaphthalen-2(1H)-one) (0.74g, 12%), m.p. 139-140° (from ethanol), (Found: C,50.0; H,2.8; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. τ($CDCl_3$) 3.22(dd,1H,J=J=10Hz); 3.80(dd,1H,J=10Hz, J=2Hz); 5.37 (ddd,1H,J=10Hz, J=J=2Hz); 7.70(qd,1H,J=10Hz, J=2Hz); 8.0(s,3H); and 9.1 (d,3H,J=10Hz);

ν_{max}^{KBr} 2995, 2975, 2935, 2900, 1735, 1450, 1370, 1355, 1305, 1250, 1215, 1190, 1130, 1085, 965, 920, 895, 860, 785, 745, 695, 685, and 640 cm^{-1}.

Mass spectrometry: $M^{\cdot+}$ = 336 very weak, $[M-42]^{\cdot+}$ = 294.

B. From Pentachlorophenyllithium

A stirred solution of pentachlorophenyllithium [prepared and maintained at -60°, from a suspension of hexachlorobenzene (14.24g, 50 mmole) in dry

ether (ca. 250ml) and n-butyllithium in pentane (2.3 molar, 25ml, 57.5 mmole)] was treated with 2,6-dimethylanisole (40ml). The temperature was raised to 80° and the reaction mixture was heated under reflux for 12h. The reaction mixture was allowed to cool to room temperature and hydrolysed with hydrochloric acid (2N, ca. 10ml). The reaction mixture was dried ($MgSO_4$) and the solvents and excess of 2,6-dimethylanisole were evaporated under reduced pressure. The residue was purified by column chromatography (silica-gel) to give 1-methoxy-2,6-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,10-dimethyl-1,4-ethenonaphthalene) (4.96g, 28%), identified by comparison with authentic material and 1,3-dimethyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,3-dimethyl-1,4-ethenonaphthalen-2(1H)-one), (4.36g, 26%), identified by comparison with authentic material.

10. Preparation of 2-Methoxy-5-tri-n-butylstannyl-tetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-2-methoxy-9-tri-n-butylstannyl-1,4-ethenonaphthalene) (III-15) from Pentachlorophenyllithium

A stirred solution of pentachlorophenyllithium [prepared and maintained at -70°, from hexachlorobenzene (1.43g, 5 mmole) in ether (25ml) and n-butyllithium in hexane (2 molar, 3ml, 6 mmole)] was treated with a solution of tri-n-butyl-p-methoxyphenyltin (9.93g, 25 mmole) in cyclohexane (25ml). The solution was allowed to warm to 20° and then heated under reflux for 15 min. A tan precipitate formed. The reaction mixture was cooled to 20°, diluted with ether (50ml), washed with aqueous sodium hydroxide (2N, 2 x 20ml) and water (2 x 20ml) and dried (Na_2CO_3). The solvents and excess of tri-n-butyl-p-methoxyphenyltin were evaporated under reduced pressure to leave a pale orange oil, 4.28g, containing tri-n-butyl-p-

methoxyphenyltin (ca. 20 mole %) and a new product (ca. 80 mole %) in ca. 65% yield, identified as 2-methoxy-5-tri-n-butylstannyl-tetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-2-methoxy-9-tri-n-butylstannyl-1,4-ethenonaphthalene) (III-15) from its spectra;

^{1}H-n.m.r. $\tau(CDCl_3)$ 2.97(d,1H,J=6Hz); 4.68(m,2H); 4.93(dd,1H,J=6Hz, J=2Hz); 6.55(s,3H); and peaks in the range 8.3-9.5, partially obscured by tri-n-butyl-p-methoxyphenyltin resonances;

ν_{max}(film) 1645 cm^{-1}.

This structural assignment was supported by subsequent reactions of the oily product:

A. Preparation of 2,2-Ethylenedioxy-2,3-dihydrotetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-2,2-ethylenedioxy-1,2,3,4-tetrahydro-1,4-ethenonaphthalene) (III-17) from Crude 2-Methoxy-5-tri-n-butylstannyl-tetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-2-methoxy-9-tri-n-butylstannyl-1,4-ethenonaphthalene) (III-15)

A solution of crude 2-methoxy-5-tri-n-butylstannyl-tetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-2-methoxy-9-tri-n-butylstannyl-1,4-ethenonaphthalene) (III-15) (0.417g, ca. 0.33 mmole) in dichloromethane (5ml) was treated with ethane-1,2-diol (0.5ml) and boron trifluoride etherate (0.5ml) and maintained at room temperature for 72 h. The reaction mixture was diluted with ether (50ml) and washed with water (3 x 20ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (alumina) to give small amounts of uncharacterised products followed by 2,2-ethylenedioxy-2,3-dihydrotetrachlorobenzobarrelene (5,6,7,8-tetrachloro-2,2-ethylenedioxy-1,2,3,4-tetrahydro-1,4-ethenonaphthalene) (III-17) (0.100g, ca. 85%), identified by comparison with authentic material; (see chapter five).

B. Preparation of Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-16) from Crude 2-Methoxy-5-tri-n-butylstannyl-tetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-2-methoxy-9-tri-n-butylstannyl-1,4-ethenonaphthalene) (III-15)

A solution of crude 2-methoxy-5-tri-n-butylstannyl-tetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-2-methoxy-9-tri-n-butylstannyl-1,4-ethenonaphthalene) (III-15) (0.663g, ca. 0.5 mmole) in dioxan (5ml) was treated with water (2ml) and sulphuric acid (98%, 0.5ml) and maintained at room temperature for 72h. The reaction mixture was diluted with ether (50ml) and washed with water (3 x 20ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (silica-gel) to give traces of uncharacterised products followed by tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-15) (0.120g, ca. 75%), identified by comparison with authentic material; (see chapter four).

11. Reaction between 1-Methoxytetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) and 3,6-Di-(2′-pyridyl)-1,2,4,5-tetrazine (III-27)

A solution of 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) (0.080g, 0.25 mmole) and 3,6-di-(2′-pyridyl)-1,2,4,5-tetrazine (0.059g, 0.25 mmole) in di-n-butyl-ether (5ml) was heated under reflux for 2½h. The red colour was discharged and a tan precipitate formed. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (alumina) to give 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35), (0.071g, 96%) characterised by comparison with an authentic sample, and 3,6-di-(2′-pyridyl)-

pyridazine (III-25), (0.048g, 84%), m.p. 180-181° (from ethanol) (lit.[26] m.p. 176-177°).

12. Reaction between 1-Methoxytetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) and Coumalic Acid (III-31)

A. Effect of Varying the Solvent

Solutions of 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) (0.080g, 0.25 mmole) and coumalic acid (III-31) (0.070g, 0.50 mmole) in the solvent (see Table III-3, 1ml) sealed in ampoules (5ml) under nitrogen (0.2mm pressure at -78°) were heated at 195±5° for either (i) 3½h, or (ii) 20h. The ampoules were allowed to cool to room temperature and opened. Reaction d.ii was poured into hydrochloric acid (2N, 20ml) and extracted with ether (4 x 20ml); the combined extracts were washed with hydrochloric acid (2N, 3 x 5ml) then dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to leave the product. The products of reactions a.i; a.ii; b.i; b.ii; c.i; and c.ii were isolated by evaporating the solvent under reduced pressure. The products were studied by ^{1}H-n.m.r. analysis; the results are presented in Table III-4.

B. Effect of Varying the Reaction Time

Solutions of 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) (0.080g, 0.25 mmole) and coumalic acid (III-31) (0.035g, 0.25 mmole) in acetic acid (1ml) sealed in ampoules (5ml) under nitrogen (0.2mm pressure at -78°) were heated at 205±5° for various times (see Table III-5). The ampoules were allowed to cool to room temperature and opened. The solvent was evaporated under

REACTION	SOLVENT	COMMENTS
a.i	Acetic acid	Yellow solution, white crystals on cooling, slight pressure on opening.
a.ii		Orange solution, tan crystals on cooling, slight pressure on opening.
b.i	Di-n-butyl ether	Very pale yellow solution, some crystals on cooling, slight pressure on opening.
b.ii		Pale lemon solution, lemon needles on cooling, slight pressure on opening.
c.i	p-Xylene	Pale yellow solution, some crystals on cooling, slight pressure on opening.
c.ii		Yellow solution, traces of yellow crystals on cooling, slight pressure on opening.
d.ii	N-Methyl-pyrrolidone	Red solution, slight pressure on opening.

TABLE III-3

REACTION	PRODUCT		MOLE RATIO[c]
	Appearance	Wt[b] (mg)	[III-35]/{[III-35]+[III-20]}
a.i	Pale yellow solid. Tan chloroform insoluble solid.[a]	113	0.95
a.ii	Lemon yellow solid. Tan chloroform insoluble solid.	115	>0.97
b.i	Pale yellow solid. Tan chloroform insoluble solid.	118	0.84
b.ii	Lemon yellow solid. Tan chloroform insoluble solid.	117	>0.98
c.i	Pale yellow solid. Tan chloroform insoluble solid.	116	0.88
c.ii	Yellow solid. Tan chloroform insoluble solid.	119	>0.98
d.ii	Yellow oily solid.	92	0.48

TABLE III-4

(a) Coumalic acid (III-31).

(b) Weighed after ^{1}H-n.m.r; some coumalic acid (III-31) lost during filtration.

(c) Mole ratio of 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35) to sum of 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35) and 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20); = % reaction.

reduced pressure and the products were examined by ^{1}H-n.m.r; the results are presented in Table III-6.

REACTION	TIME (h)	COMMENTS
i	1.17	Pale yellow solution.
ii	2.05	Pale yellow solution, tan crystals on cooling, mostly soluble in chloroform.
iii	3.05	Pale yellow solution, tan crystals on cooling, mostly soluble in chloroform.
iv	4.32	Pale yellow solution, tan crystals on cooling, mostly chloroform soluble.
v	6.00	Pale yellow solution, much tan precipitate on cooling, all soluble in chloroform.

TABLE III-5

REACTION	PRODUCT		MOLE RATIO[(a)]
	Appearance	Wt(mg)	[III-35]/{[III-35]+[III-20]}
i	Cream coloured solid	83	0.44
ii	Pale yellow solid	83	0.68
iii	Pale yellow solid	81	0.70
iv	Pale yellow solid	85	0.77
v	Pale yellow solid	85	0.79

TABLE III-6

(a) = Footnote (c), Table III-4.

The data of experiment 12B were plotted graphically (Fig. III-1). The anticipated form of the plot was derived as follows:[45]

Let the concentration of 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20), of coumalic acid (III-31), of their cycloadduct ["(III-31)+(III-20)"], and of 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35), the product of thermal fragmentation of this cycloadduct, be denoted by [A], [B], [C], and [C′] respectively. Assume that the cycloadduct suffers rapid and irreversible decarboxylation and forms 1,2,3,4-tetrachloro-5-methoxy-naphthalene (III-35) quantitatively.

$$A + B \xrightarrow{k_2} C$$

we fix $[A_0] = [B_0]$; $[C_0] = 0$; $[A] + [C] = [A_0]$

$$\frac{d[C]}{dt} = k_2[A][B] = k_2[A]^2 = k_2([A_0]-[C])^2$$

$$\int \frac{d[C]}{([A_0]-[C])^2} = k_2 \int dt$$

so that $$\frac{1}{([A_0]-[C])} = k_2 t + \text{Constant}$$

as $[C_0] = 0$; Constant = $1/A_0$

so $$k_2 t = \frac{[C]}{[A_0]([A_0]-[C])}$$

Chose units such that $[A_0] = 1$

we measure $$\frac{[C']}{([A]+[C'])} \left\{ = \frac{[\text{III-35}]}{([\text{III-20}]+[\text{III-35}])} \right\}$$

$$= [C'] \qquad ([A]+[C'] = 1)$$

$$= [C] \qquad \text{(assumed quantitative conversion)}$$

The rate law becomes

$$k_2 t = \frac{[C']}{1 - [C']}$$

and a plot of t vs. $\frac{[C']}{1 - [C']}$ should be linear. When the data are made to conform to this rate law the best straight line[46] is given by

$$\frac{[C']}{1 - [C']} = 0.645t + 0.27$$

The interpolated value of $\frac{[C']}{1 - [C']}$ when t = 3.5 is 2.53.

C. Effect of Varying the Reaction Temperature

Solutions of 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) (0.080g, 0.25 mmole) and coumalic acid (III-31) (0.035g, 0.25 mmole) in acetic acid (1ml) sealed in an ampoule (5ml) under nitrogen (0.2mm pressure at -78°) were heated for 3.5h at various temperatures (see Table III-7). The ampoules were allowed to cool to room temperature and opened. The products were isolated by evaporating the solvent under reduced pressure and were analysed by ^{1}H-n.m.r; the results are presented in Table III-8.
The data of experiment 12C were plotted graphically (Fig. III-2). The anticipated form of the plot was derived as follows:[45]
Assume that the free energy of activation is independent of temperature over the range of temperatures studied.

$$k_2 = \text{Constant} \cdot \exp(-E_A/RT)$$

REACTION	TEMPERATURE	COMMENTS
a	160 ± 5	Pale yellow solution, some chloroform insoluble solid.
b	180 ± 5	Pale yellow solution, tan solid on cooling, mostly insoluble in chloroform.
c	220 ± 5	Light brown solution. Tan solid on cooling.

TABLE III-7

REACTION	PRODUCT		MOLE RATIO[(a)]
	Appearance	Wt(mg)	[III-35]/{[III-20]+[III-35]}
a	Tan crystalline solid	112	0.27
b	Tan crystalline solid	109	0.33
c	Light brown crystalline solid	116	0.82

TABLE III-8

(a) = Footnote (c), Table III-4.

so that $\ln k_2 = \text{Constant} - \frac{E_A}{RT}$

$$= \text{Constant(1)} - \frac{\text{Constant(2)}}{T}$$

From experiment 12B we know that

$$k_2 = \frac{1}{t} \cdot \frac{[C']}{1 - [C']}$$

at constant t

$$\ln k_2 = \text{Constant(3)} + \ln \left\{ \frac{[C']}{1 - [C']} \right\}$$

Combining the two expressions for $\ln k_2$ we obtain

$$\ln \left\{ \frac{[C']}{1 - [C']} \right\} = \text{Constant(4)} - \frac{\text{Constant(2)}}{T}$$

As $\log_e \propto \log_{10}$, a plot of $\log_{10} \left\{ \frac{[C']}{1 - [C']} \right\}$ vs. $10^3/T$ should be linear.

When the data are made to conform to this expression, the best straight line[46] is given by

$$\log_{10} \left\{ \frac{[C']}{1 - [C']} \right\} = 9.04 - 4.15 \frac{10^3}{T} .$$

D. Effect of Varying the Relative Concentration of Coumalic Acid (III-31)

Solutions of 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) (0.080g, 0.25 mmole) and coumalic acid (III-31) (various amounts, see Table III-9) in N-methyl-pyrrolidone (1ml) sealed in ampoules (5ml) under nitrogen (0.5mm pressure

at -78°) were heated at 195±5° for 20h. Each ampoule was allowed to cool to room temperature and opened: its contents were poured into hydrochloric acid (2N, 50ml) and extracted with ether (4 x 20ml); the combined extracts were washed with hydrochloric acid (2N, 3 x 5ml) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to leave the product, which was analysed by ^1H-n.m.r. The results are collected in Table III-10.

REACTION	COUMALIC ACID (III-31)		COMMENTS
	wt(mg)	mmole	
a	35	0.25	Pale pink solution, slight pressure on opening.
b	70	0.50	Red solution, pressure on opening.
c	140	1.00	Dark red solution, pressure on opening.
d	280	2.00	Very dark red solution, much pressure on opening.

TABLE III-9

The date of experiment 12D were plotted graphically (Fig. III-3).

E. Effect of Added Lewis Acids

Solutions of 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) (0.080g, 0.25 mmole) and coumalic acid (III-31) (0.035g, 0.25 mmole) in p-xylene were treated with

REACTION	PRODUCT		MOLE RATIO[(a)] [III-35]/{[III-35]+[III-20]}
	Appearance	wt(mg)	
a	Off-white crystalline solid.	88	0.26
b	Pale yellow crystalline solid.	99	0.50
c	Pale yellow crystalline solid.	118	0.75
d	Yellow crystalline solid.	156	0.92

TABLE III-10

(a) = Footnote (c), Table III-4.

a) aluminium tribromide or c) boron trifluoride etherate and heated at 220±5° for 0.75h under an atmosphere of nitrogen (0.2mm pressure at -78°) in a sealed ampoule (5ml). Blank experiments [b) and d)] were run alongside those containing added Lewis acids (Table III-11). The ampoules were allowed to cool to room temperature and opened. Reaction a) was treated with hydrochloric acid (concentrated, 10ml) and extracted with ether. The extract was dried ($MgSO_4$) and evaporated under reduced pressure to give the product. The products of reactions b), c), and d) were isolated by evaporating the solvent under reduced pressure. The products were analysed by ^{1}H-n.m.r; the results are collected in Table III-12.

REACTION	LEWIS ACID	$\frac{\text{mmole (Lewis Acid)}}{\text{mmole (III-20)}}$	COMMENTS
a	$AlBr_3$	3.0	Pale yellow solution, much black precipitate, pressure on opening.
b	$AlBr_3$	0	Pale yellow solution, some tan solid on cooling.
c	$BF_3.OEt_2$	3.1	Dark red solution, some pressure on opening.
d	$BF_3.OEt_2$	0	Pale yellow solution, some tan solid on cooling.

TABLE III-11

REACTION	PRODUCT	
	Appearance	Wt(mg)
a	Pale yellow solid.	102
b	Pale yellow solid, much chloroform insoluble solid.	109
c	Brown oily solid.	180
d	Pale yellow solid, much chloroform insoluble solid.	106

TABLE III-12

Notes: Whereas the blank experiments b) and d) had proceeded cleanly to 30% conversion, reactions a) and c) gave products containing considerable

by-products. Reaction a) had proceeded to less than ca. 10% conversion (as judged by ^{1}H-n.m.r. analysis of the O-CH_3 peaks; but see discussion). Reaction c) gave a product containing no 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20), yet almost no 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35).

13. Reaction between 1-Methoxytetrafluorobenzobarrelene (5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-8) and Coumalic Acid (III-31)

A solution of 1-methoxytetrafluorobenzobarrelene (5,6,7,8-tetrafluoro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-8) (0.065g, 0.25 mmole) and coumalic acid (III-31) (0.070g, 0.50 mmole) in p-xylene (1ml) sealed in an ampoule (5ml) under nitrogen (0.1mm pressure at -78°) was heated at 200±5° for 4h. The ampoule was allowed to cool to room temperature and opened. The reaction mixture was diluted with ether (to 20ml), extracted with aqueous sodium hydroxide (2N, 4 x 10ml) and dried ($MgSO_4$). The solvents were evaporated under reduced pressure to give 1,2,3,4-tetrafluoro-5-methoxynaphthalene (III-36), (0.055g, 94%), identified by comparison of its ^{1}H-n.m.r. spectrum with an authentic spectrum.[8d]
The combined aqueous extracts were acidified with hydrochloric acid and extracted with ether (4 x 10ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give benzoic acid (III-32), (0.022g, 71%), identified by comparison of its ^{1}H-n.m.r. spectrum with an authentic spectrum.

14. Reactions of 1-Methoxytetrafluorobenzobarrelene (5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-8) and 1-Methoxytetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-

1,4-ethenonaphthalene) (III-20) with p-Nitrophenyl azide

A solution of p-nitrophenyl azide (III-33) (0.017g, 0.104 mmole) and 1-methoxytetrafluorobenzobarrelene (5,6,7,8-tetrafluoro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-8) (0.0256g, 0.10 mmole) in dry benzene was heated under reflux for 24h. The solvent was evaporated under reduced pressure and the residue was purified by preparative t.l.c (silica-gel) to give 1,2,3,4-tetrafluoro-5-methoxynaphthalene (0.0198g, 86%), identified by comparison of its ^{1}H-n.m.r. spectrum with an authentic spectrum.[8d] The m.p. of this naphthalene is an unreliable guide to purity; attempts at purification may enhance the variable amounts of bromotrifluoro-substituted material present, and 1-(4-nitrophenyl)-1,2,3-triazole (III-34) (0.0165g, 84%), m.p. 208-210° (from ethanol) (lit[47] m.p. 203-204), ^{1}H-n.m.r. $\tau(CDCl_3)$ 1.56(d,2H,J=9Hz); 1.89(d,1H,J=1.5Hz); 2.02(d,2H, J=9Hz); and 2.08(d,1H,J=1.5Hz).

A similar reaction between p-nitrophenyl azide (0.017g, 0.104 mmole) and 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-20) (0.0322g, 0.10 mmole) gave 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35) (0.0237g, 79%), identical with material previously prepared and 1-(4-nitrophenyl)-1,2,3-triazole (III-34), (0.0135g, 69%), identical with material previously prepared.

15. Reactions of 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37), 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38), 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39), and 1-Methoxy-2,5-dimethyltetrachloro-

benzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40) with 3,6-Di-(2'-pyridyl)-1,2,4,5-tetrazine (III-27)

General Procedure: A solution of 3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine (III-27) (0.059g, 0.25 mmole) and the substituted 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (0.25 mmole) in p-xylene was heated under reflux until the initial bright red colour of the tetrazine had faded. The solvent was evaporated under reduced pressure. The product was analysed by ^{1}H-n.m.r. and purified by preparative t.l.c. (alumina).

A. 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37) (0.084g, 0.25 mmole) gave:

i) 1,2,3,4-Tetrachloro-5-methoxynaphthalene (III-35) (0.011g, 15%), identified by comparison with authentic material;

ii) 1,2,3,4-Tetrachloro-5-methoxy-6-methylnaphthalene (III-41) (0.056g, 72%) m.p. 120° (from ethanol), (Found: C,46.9; H,2.65; $C_{12}H_8Cl_4O$ requires C,46.45; H,2.6%),

^{1}H-n.m.r. τ($CDCl_3$) 2.00(d,1H,J=9Hz); 2.50(d,1H,J=9Hz); 6.20(s,3H); and 7.50(s,3H):

ν_{max}^{KBr} 2940, 1610, 1535, 1445, 1305, 1295, 1255, 1000, 810, 795, 775, 725, 685, and 655 cm^{-1}.

$\lambda_{max}^{Ethanol}$ 245 (ε4.78 x 10^4) nm.

iii) 3,6-Di-(2'-pyridyl)-pyridazine (III-25) (0.033g, 57%), identified by comparison with authentic material.

B. 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38) (0.084g, 0.25

mmole) gave:

i) 1,2,3,4-Tetrachloro-5-methoxy-7-methylnaphthalene (III-43) (0.071g, 88%) m.p. 170° (from ethanol), (Found: C,46.5; H,2.4; $C_{12}H_8Cl_4O$ requires C,46.4; H,2.6%),

^{1}H-n.m.r. τ($CDCl_3$) 2.73 (broadened s, 1H); 3.16 (broadened s, 1H); 6.04 (s,3H); and 7.48(s,3H).

ν_{max}^{KBr} 2975, 2920, 1625, 1545, 1450, 1385, 1370, 1335, 1315, 1305, 1295, 1260, 1180, 1140, 1025, 830, 800, and 715 cm^{-1}.

$\lambda_{max}^{Ethanol}$ 225 (ε3.71 x 10^4) and 253 (3.88 x 10^4) nm.

ii) 3,6-Di-(2'-pyridyl)-pyridazine (III-25) (0.055g, 94%), identified by comparison with authentic material.

C. 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39) (0.0875g, 0.25 mmole) gave:

i) 1,2,3,4-Tetrachloro-5-methoxy-6,7-dimethylnaphthalene (III-44) (0.078g, 96%), m.p. 169-171° (from ethanol), (Found: C,48.1; H,3.0; $C_{13}H_{10}Cl_4O$ requires C,48.2; H,3.1%),

^{1}H-n.m.r. τ($CDCl_3$) 2.10 (broadened s, 1H); 6.24(s,3H); 7.53(s,3H); and 7.60(s,3H);

ν_{max}^{KBr} 2990, 2950, 1615, 1550, 1535, 1470, 1445, 1380, 1305, 1290, 1280, 1190, 1100, 995, 960, 855, 830, 780, 670, and 655 cm^{-1}.

$\lambda_{max}^{Ethanol}$ 247 (ε1.07 x 10^5) nm.

ii) 3,6-Di-(2'-pyridyl)-pyridazine (III-25) (0.045g, 77%), identified by comparison with authentic material.

D. 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40) (0.0875g,

0.25 mmole) gave:

i) 1,2,3,4-Tetrachloro-5-methoxy-7-methylnaphthalene (III-43) (0.072g, 93%), identified by comparison with authentic material.

ii) 4-Methyl-3,6-di-(2'-pyridyl)-pyridazine (III-42) (0.052g, 84%), m.p. 121-122° (from ethanol), (Found: C,72.4; H,4.8; N,22.4; $C_{15}H_{12}N_4$ requires C,72.6; H,4.9; N,22.6%),

^{1}H-n.m.r. τ($CDCl_3$) 1.1-1.3(m,3H); 1.48(broadened s, 1H); 1.78(d,1H,J=9Hz); 2.10(td,2H,J=9Hz, J=1Hz); 2.60(m,2H); and 7.27(s,3H);

ν_{max}^{KBr} 3075, 3055, 2920, 1585, 1570, 1470, 1430, 1390, 1375, 1245, 1145, 1095, 1075, 1050, 1040, 1010, 990, 895, 790, 745, 725, and 625 cm^{-1}.

16. Stability of 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37), 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38), 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39), and 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40) towards Acetic Acid at 200°

General Procedure: A solution of the substituted 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (0.25 mmole) in acetic acid (1ml) sealed in an ampoule (5ml) under nitrogen (1.0mm pressure at -78°) was heated at 200±5° for 3h. The ampoule was cooled to room temperature and opened. The solvent was evaporated under reduced pressure and the residue was analysed by ^{1}H-n.m.r.

A. 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-

dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37) gave a brown oil which slowly crystallised. ^{1}H-n.m.r. analysis indicated ca. 40% decomposition had occurred to a 1:1 mixture of 1-methyl-tetrachlorobenzo-[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (5,6,7,8-tetrachloro-3,4-dihydro-2-methyl-2,4-ethenonaphthalen-1(2H)-one and 1-methyltetrachlorobenzo[6,7]-bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,8-dihydro-8-methyl-5,8-methanobenzocycloheptен-9-one) (III-45) (these compounds are described in chapter five.

B. 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38) gave a tan crystalline solid. ^{1}H-n.m.r. analysis indicated that only minor changes had occurred; no rearrangement to 4-methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-4-methyl-1,4-ethenonaphthalen-2(1H)-one) (the expected rearrangement product, see chapter five) was detected and decomposition was estimated at less than 20%.

C. 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39) gave a tan crystalline solid. ^{1}H-n.m.r. analysis indicated that no significant changes had occurred.

D. 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40) gave a brown oil. ^{1}H-n.m.r. analysis indicated that complete decomposition had occurred. Amongst several products only 1,6-dimethyltetrachlorobenzo[3,4]-bicyclo[3,2,1]octa-3,6-dien-2-one (5,6,7,8-tetrachloro-3,4-dihydro-2,9-dimethyl-2,4-ethenonaphthalen-1(2H)-one) (This product is described in

chapter five) (ca. 35%) was identified.

17. Reaction of 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37), 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38), 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39), and 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40) with Coumalic Acid (III-31)

General Procedure: A solution of the substituted 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (0.25 mmole) and coumalic acid (III-31) (0.070g, 0.50 mmole) in p-xylene (1ml) sealed in an ampoule (5ml) under nitrogen (0.5mm pressure at -78°) was heated at 208±5° for $4^1/_3$h. The ampoule was cooled to room temperature and opened. The reaction mixture was diluted with ether (to 20ml), extracted with aqueous sodium hydroxide (2N, 4 x 10ml), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to leave a neutral fraction. The combined base extracts were acidified with concentrated hydrochloric acid and extracted with ether (4 x 10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an acid fraction. The fractions were analysed by ^{1}H-n.m.r.

A. 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37) gave:

i) A neutral fraction (0.074g) containing 1,2,3,4-tetrachloro-5-methoxy-6-methylnaphthalene (III-41) and 1-methyltetrachlorobenzo[6,7]bicyclo-

[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,8-dihydro-8-methyl-5,8-methanobenzocycloheptan-9-one) (III-45) in the ratio ca. 3:2. 1,2,3,4-Tetrachloro-5-methoxynaphthalene (III-35) could not be positively identified.

ii) An acid fraction (0.033g) of benzoic acid; toluic acids could not be positively identified.

B. 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38) gave:

i) A neutral fraction (0.071g) containing 1,2,3,4-tetrachloro-5-methoxy-7-methylnaphthalene (III-43) and 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35) in the ratio ca. 3:1.

ii) An acid fraction (0.025g) characterised as benzoic and toluic acids in the ratio ca. 3:1.

C. 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39) gave:

i) A neutral fraction (0.089g) containing 1,2,3,4-tetrachloro-5-methoxy-6,7-dimethylnaphthalene (III-44) (ca. 25%) and several unidentified products. 1,2,3,4-tetrachloro-5-methoxynaphthalene (III-35) was not detected.

ii) An acid fraction (0.027g) containing some benzoic acid but no identifiable amounts of toluic acids.

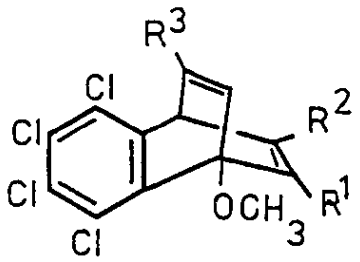
D. 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40) gave:

i) A neutral fraction (0.076g) in which no naphthalenes were identified, containing several ketonic products.

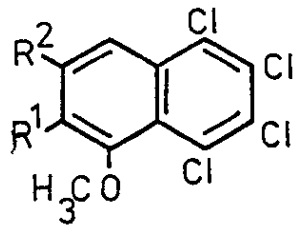
ii) An acidic fraction (0.024g) containing neither benzoic nor toluic acids.

18. Reaction of 1-Methoxy-2-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2-methyl-1,4-ethenonaphthalene) (III-37), 1-Methoxy-3-methyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-3-methyl-1,4-ethenonaphthalene) (III-38), 1-Methoxy-2,3-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,3-dimethyl-1,4-ethenonaphthalene) (III-39), and 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-2,9-dimethyl-1,4-ethenonaphthalene) (III-40) with p-Nitrophenylazide (III-33)

General Procedure: A solution of the substituted 1-methoxytetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (0.1 mmole) and p-nitrophenyl azide (0.018g, 0.11 mmole) in benzene (5ml) was heated under reflux for 28h. The solvent was evaporated under reduced pressure and the residue was analysed by ^{1}H-n.m.r. to determine the composition of the mixture of 1,2,3,4-tetrachloro-5-methoxynaphthalenes produced. The results are collected in Table III-13.



Precursor



Product

Precursor				Product					
				Major			Minor		Ratio[a]
R^1	R^2	R^3	Code	R^1	R^2	Code	R^1	R^2	Code	
CH_3	H	H	III-37	CH_3	H	III-41	H	H	III-35	55:45
H	CH_3	H	III-38	H	CH_3	III-43	H	H	III-35[b]	>90:10
CH_3	CH_3	H	III-39	CH_3	CH_3	III-44	H	H	III-35	80:20
CH_3	H	CH_3	III-40	H	CH_3	III-43	CH_3	H	III-41	80:20

TABLE III-13

(a) Error about 5-10%.

(b) Not positively identified.

19. Acetanilide, by Acetylation of Aniline with Acetic Anhydride in Pyridine

Aniline (0.93g, 10 mmole) was treated with a solution of acetic anhydride in pyridine (1 molar, 11ml, 11 mmole) at room temperature for 24h. The reaction was quenched with ice (50g) and extracted with ether. The extract was dried ($MgSO_4$) and evaporated under reduced pressure to give acetanilide (1.32g, 97.5%) m.p. 110-112° (lit.[48] m.p. 114°).

20. p-Bromoacetanilide, by Bromination of Acetanilide in Acetic Acid

A solution of acetanilide (0.68g, 5.05 mmole) in acetic acid (10ml) was treated with bromine (0.55ml, 1.65g, 10.3 mmole). A precipitate formed. The reaction was quenched with ice (50g) and filtered to give p-bromoacetanilide (1.0g, 93%) m.p. 166-171° (lit.[48] m.p. 167°).

21. p-Bromoacetanilide, by Acetylation and Bromination of Aniline in Pyridine

Aniline (0.93g, 10 mmole) was treated with a solution of acetic anhydride in pyridine (1 molar, 11ml, 11 mmole) at room temperature for 20h. Bromine (0.55ml, 1.65g, 10.3 mmole) was added dropwise to the swirled reaction mixture at room temperature. The reaction mixture was maintained at room temperature for 2h. and then quenched with ice (50g). The resultant aqueous suspension was acidified (to pH4, with concentrated hydrochloric acid) and filtered to give p-bromoacetanilide (1.95g, 91%) m.p. 164-168° (lit.[48] m.p. 167°). A further quantity (0.193g, ca. 1%) of impure p-bromoacetanilide, m.p. ca. 160°, could be isolated by ether extraction of the filtrate.

22. 2,4,6-Tribromoaniline, by Bromination of the Schmidt-Degradation

Product of Benzoic Acid

A solution of benzoic acid (1.22g, 10 mmole) in oleum (20% SO_3, 2ml), sulphuric acid (98%, 3ml), and chloroform (25ml) maintained at 40° was treated with powdered sodium azide (0.75g, 11.5 mmole). Effervescence was observed. The reaction mixture was heated under reflux for 2h. and then maintained at room temperature overnight. The reaction mixture was poured onto ice (ca. 50g), basified ($NaHCO_3$) and extracted with ether (3 x 10ml). The combined extract was dried ($MgSO_4$) and carefully evaporated to leave a mobile brown oil. This product was dissolved in acetic acid (25ml) and treated with bromine (1.6ml, 4.8g, 30 mmole). The solution was maintained at room temperature for 2h, then poured onto ice (ca. 100g). The resultant suspension was neutralised ($NaHCO_3$) and filtered to give 2,4,6-tribromoaniline, (2.89g, 90% crude yield). This product was recrystallised from ethanol to give 2,4,6-tribromoaniline as fine needles (2.30g, 72%) m.p. 122° (lit.[48] m.p. 120°).

23. Regiospecificity of the Addition of Coumalic Acid (III-31) to 1-Methoxytetrafluorobenzobarrelene (5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) (III-8): a Deuterium-labelling Study

A. Degradation of 1-Methoxy-2,4,6-[$^2H_3$]tetrafluorobenzobarrelene (5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-2,4,6-[$^2H_3$]-1,4-ethenonaphthalene) with Coumalic Acid (III-31): 1-Methoxy-2,4,6-[$^2H_3$]tetrafluorobenzobarrelene (5,6,7,8-tetrafluoro-1,4-dihydro-1-methoxy-2,4,6-[$^2H_3$]-1,4-ethenonaphthalene) {[$^2H_3$], 93; [$^2H_2$], 5; [$^2H_1$], 1; [$^2H_0$], < 1%; the bromotrifluoro- contaminant showed [$^2H_3$], 92; [$^2H_2$], 6; [$^2H_1$], 1; [$^2H_0$], < 1%} (0.065g, 0.25 mmole) was reacted with coumalic acid (III-31) by the method of experiment 13.

i) The neutral fraction was purified by sublimation to give 1,2,3,4-tetrafluoro-5-methoxy-6,8-[$^2H_2$]naphthalene {[$^2H_2$], 77; [$^2H_1$], 20; [$^2H_0$], 3%; the bromotrifluoro- contaminant showed [$^2H_2$], 70; [$^2H_1$], 28; [$^2H_0$], 2%}.

ii) The acid fraction was purified by recrystallisation from light petroleum (b.p. 40-45°) to give [^{2}H]benzoic acid { a) [$^2H_1$], 94.4; [$^2H_0$], 5.6%; b) [$^2H_1$], 94.8; [$^2H_0$], 5.2%}.

A solution of [^{2}H]benzoic acid (0.0162g, 0.132 mmole) in concentrated sulphuric acid (95%, 0.5ml) was maintained at 50° and treated with powdered sodium azide (0.010g, 0.154 mmole) during 1h. The reaction mixture was maintained at 60-70° for 1h., then diluted with water (10ml), basified (to pH9, with aqueous potassium hydroxide [50%]), and extracted with light petroleum (b.p. 40-45°, 4 x 5ml). The combined extracts were dried (KOH) and divided into two equal portions, a and b.

a. The solvent was carefully removed at atmospheric pressure and the residue was immediately treated with a freshly prepared solution of bromine in acetic acid (0.64 ml, 50mg/ml, 0.032g, 0.20 mmole). The reaction was diluted with acetic acid (to 5ml) and maintained at room temperature for 2h. The reaction mixture was poured onto ice (ca. 25g), treated with sodium metabisulphite (0.1g) and extracted with ether (4 x 5ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica-gel) and recrystallisation from ethanol to give 2,4,6-tribromo-[^{2}H]aniline {[$^2H_1$], 40; [$^2H_0$], 60%}.

b. The solvent was carefully removed at atmospheric pressure and the residue was treated with a solution of acetic anhydride in pyridine (1 molar, 5ml, 5 mmole). The reaction mixture was maintained at room temperature for 2h., then treated with a freshly prepared solution of bromine in acetic

acid (0.31 molar, 0.22ml, 0.068 mmole). The reaction mixture was maintained at room temperature for 12h., then poured onto ice (ca. 50g), and extracted with ether (4 x 10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica-gel) to give p-bromo-[^{2}H]acetanilide {[$^2H_1$], 46; [$^2H_0$], 54%}.

B. Degradation of 1-Methoxy-3,5[$^2H_2$]tetrafluorobenzobarrelene (5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-3,5[$^2H_2$]-1,4-ethenonaphthalene) with Coumalic Acid (III-31)

1-Methoxy-3,5[$^2H_2$]tetrafluorobenzobarrelene (5,6,7,8-tetrafluoro-1,4-dihydro-1-methoxy-3,5[$^2H_2$]-1,4-ethenonaphthalene) {[$^2H_2$], 74; [$^2H_1$], 22; [$^2H_0$], 4%; the bromotrifluoro-contaminant showed [$^2H_2$], 74; [$^2H_1$], 22; [$^2H_0$], 4%} (0.065g, 0.25 mmole) was reacted with coumalic acid (III-31) by the method of experiment 13.

i) The neutral fraction was purified by sublimation to give 1,2,3,4-tetrafluoro-5-methoxy-7-[^{2}H]naphthalene {[$^2H_1$], 87; [$^2H_0$], 13%; the bromotrifluoro- contaminant showed [$^2H_1$], 87; [$^2H_0$], 13%}.

ii) The acid fraction was treated as described in section A to give:

a. [^{2}H]Benzoic acid { α) [$^2H_1$], 87.7; [$^2H_0$], 12.3; β) [$^2H_1$], 86.8; [$^2H_0$], 13.2%}.

b. 2,4,6-Tribromo-[^{2}H]aniline {[$^2H_1$], 47; [$^2H_0$], 53% .

c. No p-bromo-[^{2}H]acetanilide was isolated. Mass spectrometry showed that the product was [^{2}H]acetanilide {[$^2H_1$], 85; [$^2H_0$], 15%}. The results of experiment 23 are collected in Table III-2, in the discussion.

Note. In the preparation of 2,4,6-tribromoaniline by the bromination of aniline in acetic acid, the acetic acid should be free from acetic anhydride; this is especially important with small scale reactions and it is probable

that acetic acid purified by any procedure involving the addition of acetic anhydride would be less satisfactory as a solvent than unpurified general laboratory reagent grade acid. Traces of the anhydride divert the reaction towards the production of p-bromoacetanilide and other products.

24. Reaction of Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one (III-16) with 3,6-Di-(2'-pyridyl)-1,2,4,5-tetrazine (III-27)

A solution of tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-16) (0.069g, 0.214 mmole) and 3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine (III-27) (0.045g, 0.193 mmole) in dioxan (5ml) was heated under reflux for 19h. The solvent was evaporated under reduced pressure and the residue was examined by t.l.c. (silica-gel) and shown to contain tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-16) and 1,2-dihydro-3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine[19] but neither 3,6-di-(2'-pyridyl)-pyridazine (III-25) nor 3,6-di-(2'-pyridyl)-1,2,4,5-tetrazine (III-27). Preparative t.l.c. (silica-gel) gave tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-16) (0.031g, 45% recovery) and less mobile fractions which were not investigated.

25. Preparation of 2,3-Dihydro-2-hydroxy-5-methyl-2-phenyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-9-hydroxy-2-methyl-9-phenyl-1,4-ethanonaphthalene) (III-74) from Phenylmagnesium Bromide and 5-Methyltetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-9-methyl-1,4-ethenonaphthalen-2(1H)-one) (III-13)

A slurry of 5-methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-9-methyl-1,4-ethenonaphthalen-2(1H)-one) (III-13) (0.644g, 2.0 mmole)

in dry ether (20ml) was added to a solution of phenylmagnesium bromide [prepared from bromobenzene (3.14g, 20 mmole) and magnesium turnings (0.50g, 21 mmole) in dry ether (20ml)]. The reaction mixture was stirred at room temperature for 20h. T.l.c. showed that no starting material remained. The reaction mixture was washed with hydrochloric acid (2N, 50ml) and the washings were extracted with ether (2 x 20ml). The combined ethereal phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica-gel) to give:

i) A white crystalline solid, identified as biphenyl by comparison with authentic material (0.152g, 10% based on bromobenzene).

ii) 1,2,3,4-Tetrachloro-6-methylnaphthalene (0.015g, 3%), identified by comparison with authentic material.[44]

iii) 1-Phenylethanol, a clear oil, [0.048g, 20% based on 5-methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-13)], tentatively identified from its ^{1}H-n.m.r. spectrum.

iv) 2,3-Dihydro-2-hydroxy-5-methyl-2-phenyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-9-hydroxy-2-methyl-9-phenyl-1,4-ethanonaphthalene) (III-74) (0.552g, 67%), m.p. ca. 150° with decomposition (from ethanol), (Found: C,57.1; H,3.6; $C_{19}H_{14}Cl_4O$ requires C,57.0; H,3.5%), ^{1}H-n.m.r. τ($CDCl_3$) 2.65-3.20(m,5H); 3.75(broad d, 1H, J=6Hz); 5.58(m, 2H, $W_{\frac{1}{2}}$=9Hz); 7.52(broad d, 1H, J=15Hz); 7.73(s,1H, exchanged with D_2O); and 7.85-8.25(m including broad s at 7.95,4H);

ν_{max}^{KBr} 3540, 3470 (broad), 3050, 2965, 2945, 2915, 1495, 1450, 1380, 1290, 1270, 1230, 1165, 1090, 1065, 1045, 975, 760, 755, 730, and 695 cm^{-1}.

26. Preparation of 2,3-Dihydro-2-hydroxy-2-phenyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-9-hydroxy-9-phenyl-1,4-ethanonaphtha-

lene) (III-62) from Phenylmagnesium Bromide and Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-16)

A stirred solution of phenylmagnesium bromide [from magnesium (0.122g, 5 mg-atoms) and bromobenzene (just sufficient to react with the magnesium) in ether (ca. 50ml)] maintained at 10° was treated with a solution of tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1H)-one) (III-16) (0.120g, 0.390 mmole) in ether (25ml). The reaction mixture was stirred at room temperature for 4h., then poured into aqueous ammonium chloride (saturated, ca. 50ml) and extracted with ether (3 x 25ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (silica-gel) to give 2,3-dihydro-2-hydroxy-2-phenyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-9-hydroxy-9-phenyl-1,4-ethanonaphthalene) (III-62) (0.152g, 100%), m.p. ca. 145° with decomposition (from ethanol), (Found: C,55.9; H,3.0; $C_{18}H_{12}Cl_4O$ requires C,55.9; H,3.1%),

^{1}H-n.m.r. τ($CDCl_3$) 2.8-3.4(m,7H); 5.25-5.55(m,2H); 7.59(dd,1H,J=16Hz, J=3.5Hz); 7.85(broad s, 1H); and 8.09(dd,1H,J=16Hz,J=3Hz);

ν_{max}^{KBr} 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}.

27. Thermal Decomposition of 2,3-Dihydro-2-hydroxy-5-methyl-2-phenyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-9-hydroxy-2-methyl-9-phenyl-1,4-ethanonaphthalene) (III-74)

A solution of 2,3-dihydro-2-hydroxy-5-methyl-2-phenyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-9-hydroxy-2-methyl-9-phenyl-

1,4-ethanonaphthalene) (III-74) (0.081g, 0.22 mmole) in dry dimethylformamide (25ml) was heated under reflux for 30min. T.l.c. showed that decomposition was complete. The cool solution was poured into brine (150ml) and extracted with ether (4 x 20ml). The combined extracts were dried ($MgSO_4$) and carefully evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica-gel) to give:

i) 1,2,3,4-Tetrachloro-6-methylnaphthalene (III-75) (0.051g, 90%) m.p. 124-125.5° (lit.[44] m.p. 125-127°).

ii) Acetophenone (0.016g, 66%), identified by comparison with authentic material. A portion of the product was converted[48] to its 2,4-dinitrophenylhydrazone, m.p. 229-235° (lit.[48] m.p. 237°).

28. Thermal Decomposition of 2,3-Dihydro-2-hydroxy-2-phenyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-9-hydroxy-9-phenyl-1,4-ethanonaphthalene) (III-62)

A solution of 2,3-dihydro-2-hydroxy-2-phenyltetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-9-hydroxy-9-phenyl-1,4-ethanonaphthalene) (III-62) (0.344g, 0.891 mmole) in dry dimethylformamide (25ml) was heated under reflux for 30min. The cool reaction mixture was poured into water (50ml) and extracted with carbon tetrachloride (ca. 5 x 25ml). 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-gel) to give:

i) 1,2,3,4-tetrachloronaphthalene (0.208g, 88%) identified by comparison with authentic material.[8f]

ii) A solution containing acetophenone, identified by t.l.c.

29. Oxidation of Acetophenone, with Potassium Iodide and Sodium Hypochlorite

A stirred solution of acetophenone, (0.16g, 1.37 mmole) and potassium iodide (0.50g, 3.0 mmole) in water (10ml) and dioxan (10ml) maintained at room temperature was treated with aqueous sodium hypochlorite (5%, ca. 3 mmole). Another portion of potassium iodide (0.30g, 1.8 mmole) was added, and the reaction mixture was treated with sodium hypochlorite (5%, ca. 1.8 mmole). The reaction mixture was filtered to give iodoform (yellow feathery crystals) (0.304g, 57%) m.p. 112-120° (lit.[48] m.p. 119°). The filtrate was treated with sodium thiosulphate (ca. 3g), acidified, and extracted with ether (3 x 25ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give benzoic acid (0.166g, 67%), m.p. 119-121° (from hexane) (lit.[48] m.p. 121°).

Note: Commercial dioxan often contains traces of acetaldehyde. This must be removed before the solvent can be used in this reaction.

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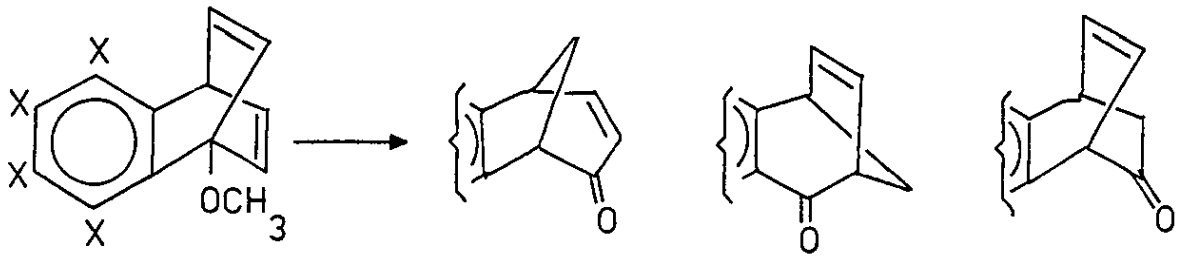
CHAPTER FOUR

A ^{14}C-Tracer Study of the Acid-Catalysed Rearrangement of 1-Methoxytetrachlorobenzobarrelene

Introduction

The acid catalysed rearrangements of 1-methoxybenzobarrelenes have been shown to yield in general three structurally isomeric ketones[1] [e.g: (IV-1) → (IV-2), (IV-3), and (IV-4)] (Scheme IV-1). The mechanisms of



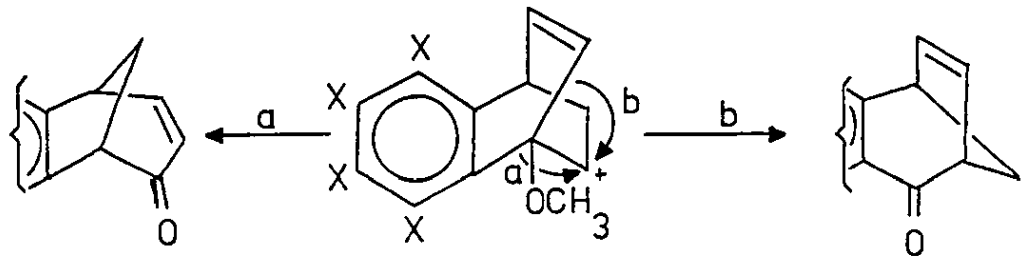
	minor products		major product
$X_4 = H_4$ (IV-1)	(IV-2)	(IV-3)	(IV-4)
$X_4 = Cl_4$ (IV-5)	(IV-6)	(IV-7)	(IV-8)
$X_4 = F_4$ (IV-9)	(IV-10)	(IV-11)	(IV-12)

Scheme IV-1

these transformations have been studied using deuteriated solvents and specifically deuteriated derivatives of 1-methoxybenzobarrelene.[1a,c]

The results of these studies indicate that the αβ-unsaturated ketones [(IV-2), (IV-6), or (IV-10)] arise by a [1,2]-aryl shift and the aryl ketones [(IV-3), (IV-7), or (IV-11)] arise by a [1,2]-alkenyl shift in the 2-carbocations [(IV-13), (IV-14), or (IV-15)] or in some closely related species (Scheme IV-2). No evidence has been found for the direct intervention of the 2-carbocations [(IV-13), (IV-14), and (IV-15)] as

common intermediates in the formation of the αβ-unsaturated ketones [(IV-2), (IV-6), or (IV-10)] and the aryl ketones [(IV-3), (IV-7), or (IV-11)]: the polydeuteriation of product to be expected to arise from an equilibration between the 2-carbocations (IV-15) and the 1-methoxybenzobarrelenes (IV-9) is not observed.[1a]



$X_4 = H_4$ (IV-2)	(IV-13)	(IV-3)
$X_4 = Cl_4$ (IV-6)	(IV-14)	(IV-7)
$X_4 = F_4$ (IV-10)	(IV-15)	(IV-11)

Scheme IV-2

The relative insensitivity reported[1a] for the ratio

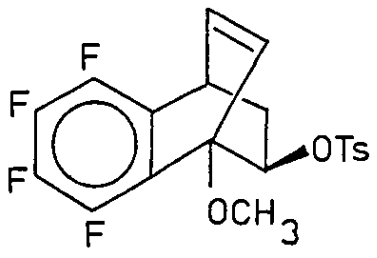
$$\left[\frac{\text{αβ-unsaturated ketone}}{\text{aryl ketone}}\right]$$

to changes of the aryl substituents suggests that the relative migratory propensity of aryl and alkenyl functions in common intermediate ions may have little to do with the determination of the product ratio (Table IV-1). The 2-tosylates [(IV-16) and (IV-17)] are product specific: each tosylate produces only one product [(IV-10) and (IV-11) respectively] and so the

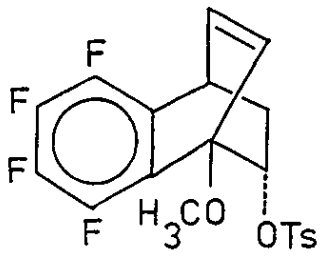
Ratio	αβ-unsaturated ketone / aryl ketone *
(IV-2)/(IV-3)	0.8
(IV-6)/(IV-7)	1.4
(IV-10)/(IV-11)	1.0

Table IV-1

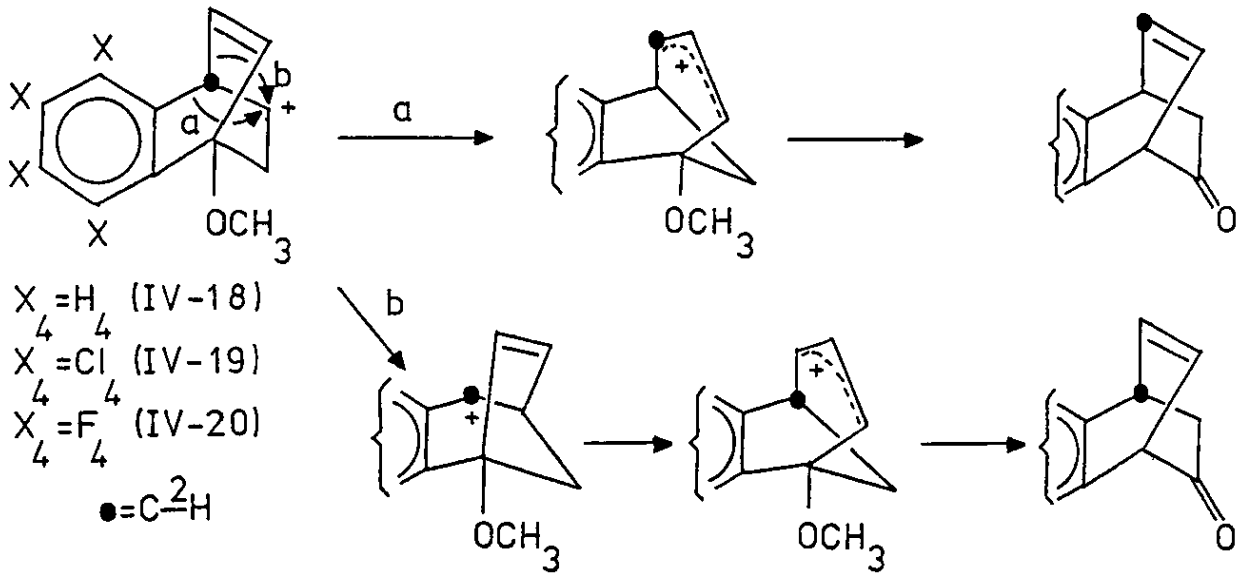
* The absolute values of the yields are very low, and the uncertainties in the ratios are correspondingly high.



(IV-16)



(IV-17)



Scheme IV-3

rearrangement is clearly susceptible to stereoelectronic control. The possibility that the rearrangement is controlled by the direction of proton approach or by solvolysis of products of double bond solvation cannot be discounted and the natures of the intermediates which precede the formation of the aryl ketones [(IV-3), (IV-7), or (IV-11)] and the αβ-unsaturated ketones [(IV-2), (IV-6), or (IV-10)] are still unknown.

The formation of the benzobarrelenones [(IV-4), (IV-8), or (IV-12)] is more complex. The natures of the rearranging species are as little understood in this case as in the formation of the αβ-unsaturated and aryl ketones {[(IV-2), (IV-6), and (IV-10)] and [(IV-3), (IV-7), and (IV-11)]} but deuterium labelling studies have established that the initial rearrangement is from the 3-carbocations [(IV-18), (IV-19), and (IV-20)] or from some closely related species, and that at least two distinct pathways lead to ketones with the benzobarrelenone structure. The two competitive pathways that have been put forward to account for the results of deuterium labelling studies are shown in Scheme IV-3. It is an essential feature of these pathways that the C-1 of the 1-methoxybenzobarrelene becomes the C-2 of the benzobarrelenone.

Two other mechanisms have been seriously proposed:

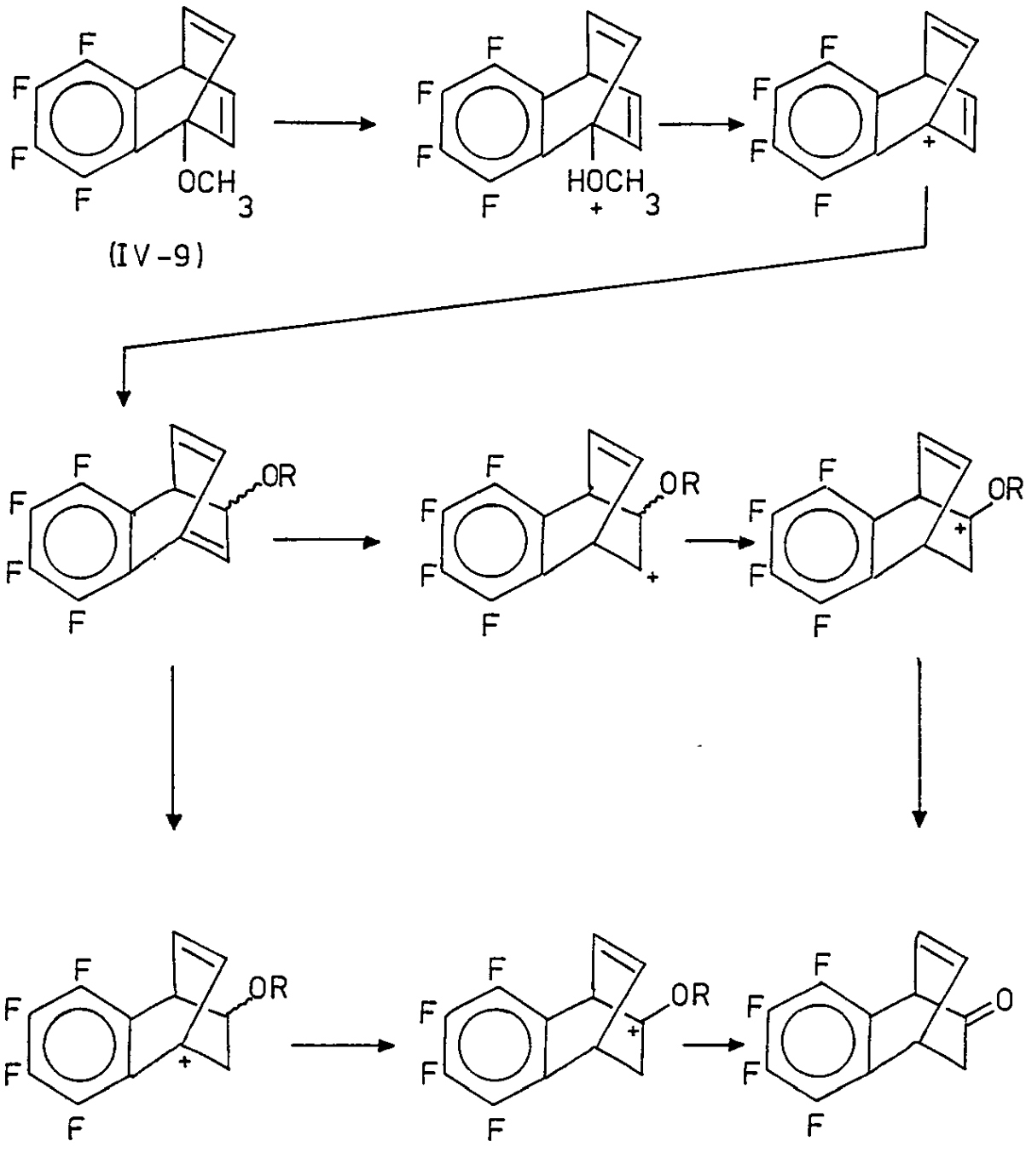
a. Barkhash[2] has suggested a mechanism involving ionisation by loss of an O-protonated methoxy-group, followed by solvolysis of an anti-Bredt allyl cation, protonation and hydride shift to give a benzobarrelenone (Scheme IV-4).

There seems little doubt that the methoxy-group is protonated in strongly acidic media; to this has been attributed the increasing tendency for rearrangements involving 3-carbocations as opposed to those involving 2-carbocations as the acidity of the reaction medium is increased. Ionisation of O-protonated methoxybenzobarrelenes to give a bridgehead cation would be expected to be slow.[3] The influence of the unsaturated bridges would probably be destabilising, with inductive effects outweighing any delocalisation of charge in the twisted allyl systems. This bridgehead cation and the subsequent putative intermediate, the anti-Bredt olefin are expected to be of such high energies that pathways involving them would be relatively unimportant.

This mechanism is excluded by deuterium labelling studies (Scheme IV-3).

b. In the other proposal, the key steps are either a [1,2]-methoxy shift followed by a [1,2]-hydride shift, or the formation and collapse of an O-methyloxiranium ion (Scheme IV-5). This mechanism finds analogies in the rearrangements of epoxides and acyclic ketones,[4] but the great angle strain and the unfavourable stereoelectronic factors render this proposal unlikely. Moreover, this suggestion does not account for the contemporaneous change of the deuterium labelling pattern.

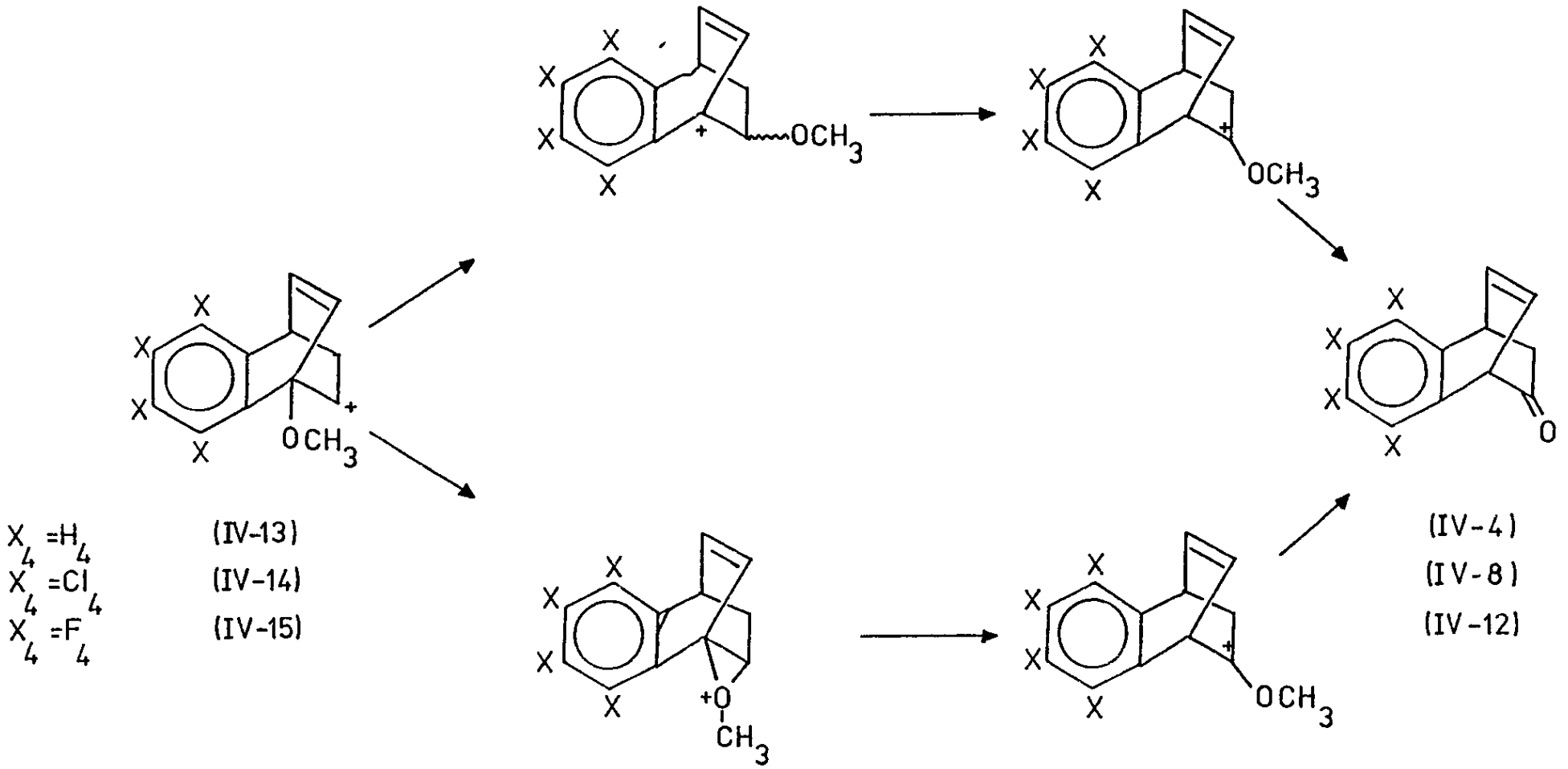
Although the proposals a and b are not easily reconciled with the deuterium labelling results they highlight the uncertainty about the origin of the C-2 of the benzobarrelenones [(IV-4), (IV-8), and (IV-12)] which has so far been the subject of speculation rather than research.



(IV-9)

(IV-12)

Scheme IV-4



$X_4 = H_4$ (IV-13)

$X_4 = Cl_4$ (IV-14)

$X_4 = F_4$ (IV-15)

(IV-4)

(IV-8)

(IV-12)

Scheme IV-5

The work described in this section was designed to distinguish between mechanisms in which the C-1 of a 1-methoxybenzobarrelene migrates to become the C-2 of a benzobarrelenone and those mechanisms in which the C-2 of the benzobarrelenone is derived from some other position(s) of the 1-methoxybenzobarrelene. 1-Methoxy-1-[^{14}C]tetrachlorobenzobarrelene {1-[^{14}C](IV-5)} was prepared and rearranged to x-[^{14}C]tetrachlorobenzobarrelenone {x-[^{14}C](IV-8)} which was degraded; the fragments so obtained were compared with similar fragments obtained by degradation of 2-[^{14}C]tetrachlorobenzobarrelenone {2-[^{14}C] (IV-8)} which was formed as a by-product in the preparation of the [^{14}C] labelled benzobarrelene {1-[^{14}C](IV-5)}.

The synthesis of 1-[^{14}C]anisole was described in chapter two, the conversion of this anisole into 1-methoxy-1-[^{14}C]tetrachlorobenzobarrelene {1-[^{14}C](IV-5)} and the degradation of its rearrangement product {2-[^{14}C](IV-8)} have been described in chapter three.

Results and Discussion

1-Methoxy-1-[^{14}C]tetrachlorobenzobarrelene {1-[^{14}C](IV-5)} and 2-[^{14}C]tetrachlorobenzobarrelenone {2-[^{14}C](IV-8)} were prepared by the reaction of tetrachlorobenzyne with 1-[^{14}C]anisole.[5]

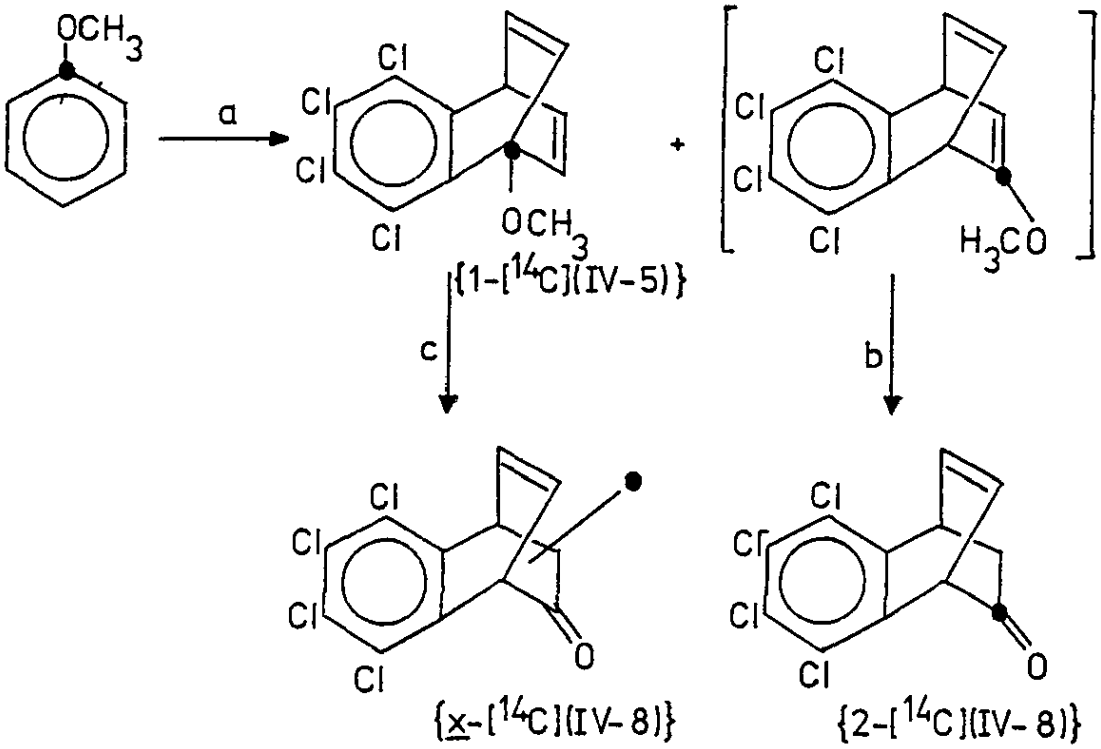
2-[^{14}C]Tetrachlorobenzobarrelenone {2-[^{14}C](IV-8)} is a standard compound: its degradation products are those which would be obtained by degradation of the benzobarrelenone produced by a rearrangement of 1-methoxy-1-[^{14}C]tetrachlorobenzobarrelene {1-[^{14}C](IV-5)} in which all of the benzobarrelenone carbonyl carbon (C-2) atoms are derived from C-1 of the benzobarrelene.

1-Methoxy-1-[^{14}C]tetrachlorobenzobarrelene {1-[^{14}C](IV-5)} was rearranged in concentrated sulphuric acid[1a-c] to give x-[^{14}C]tetrachlorobenzobarrelenone {x-[^{14}C](IV-8)} as the major product (Scheme IV-6).

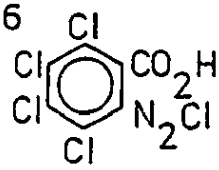
Each benzobarrelenone {x-[^{14}C]- and 2-[^{14}C]-(IV-8)} was degraded to 1,2,3,4-tetrachloronaphthalene (IV-21), benzoic acid (IV-22), and iodoform (IV-23) (Scheme IV-7).

The activities of similar fragments were compared (Table IV-2). Iodoform (IV-23) was not isolated from the degradation products of 2-[^{14}C]-tetrachlorobenzobarrelenone {2-[^{14}C](IV-8)}. An estimate of the maximum activity which could have been observed if the iodoform had been isolated is given by the activity of the corresponding 1,2,3,4-tetrachloronaphthalene (this follows from the symmetry of 1-[^{14}C]anisole: both the iodoform and the 1,2,3,4-tetrachloronaphthalene contain one of the ortho-carbon atoms of the anisole). It is apparent that activity of the iodoform would have been observed to be very low.

The quoted activities of the 1,2,3,4-tetrachloronaphthalene derived from 2-[^{14}C]tetrachlorobenzobarrelenone {2-[^{14}C](IV-8)} and of the 1,2,3,4-tetrachloronaphthalene and iodoform derived from x-[^{14}C]tetrachlorobenzo-

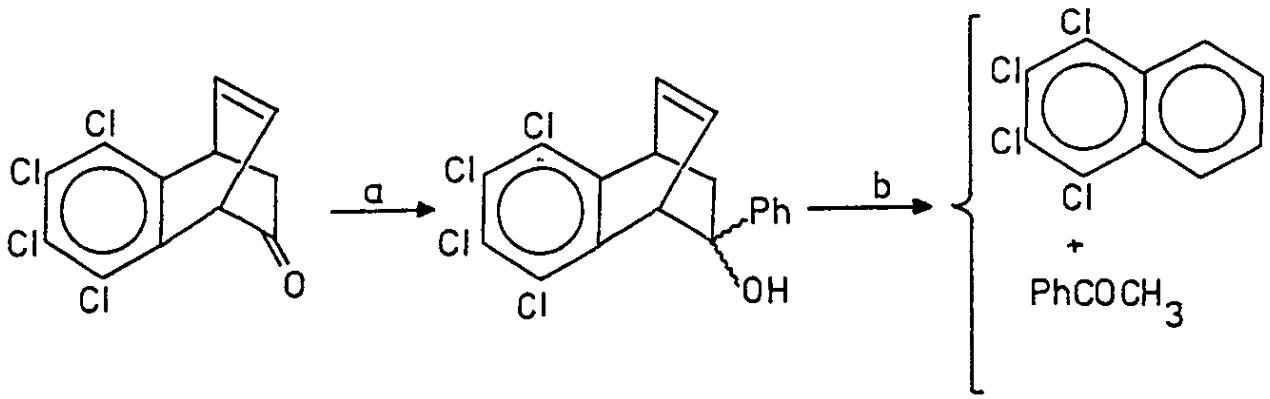


Scheme IV-6

Reagents: a)  , △; b) H^+/H_2O;

c) Conc. H_2SO_4.

barrelenone {x-[^{14}C](IV-8)} are based on observed activities which exceed the level of background radiation by less than ten percent. When these activities are compared[6] with the background activity to assess their significance it is concluded that even inactive samples would exhibit as great or greater an apparent activity about once in fifty or [in the case of 1,2,3,4-tetrachloronaphthalene derived from 2-[^{14}C]tetrachlorobenzobarrelenone {2-[^{14}C](IV-8)}] one hundred determinations. In particular, the activities of the non-benzoic acid fragments derived from 1-methoxy-1-[^{14}C]tetrachlorobenzobarrelene {1-[^{14}C](IV-5)} via x-[^{14}C]tetrachlorobenzobarrelenone {x-[^{14}C](IV-8)} by acid catalysed rearrangement and



$$PhCOCH_3 \xrightarrow{c} PhCO_2H + CHI_3$$

Scheme IV - 7

Reagents: a) PhMgBr, 20°; b) $\triangle$, DMF;

c) $ClO^-/I^-/H_2O$/Dioxan.

degradation do not differ from zero at the 2%-testing level.

The only fragments with significant levels of activity were the benzoic acids. It is not possible to assert with any confidence that the two preparations of benzoic acid have the same specific activity; the difference is about 1¼% and is very significant by the standards of the t-test. However, the difference between the two benzoic acid preparations is less significant than the difference between the measured activities of two samples of the same benzoic acid: the difference between the two preparations has fallen below the difference observed between samples which are known to have identical activities.

FRAGMENT	ORIGIN OF FRAGMENT	
	2-[^{14}C]Tetrachlorobenzobarrelenone {2-[^{14}C](IV-8)}	x-[^{14}C]Tetrachlorobenzobarrelenone {x-[^{14}C](IV-8)}
Iodoform	(a)	1.277 (σ=1.365)
1,2,3,4-Tetrachloronaphthalene	1.048 (0.982)	0.899 (1.069)
Benzoic acid	474.3 (2.89)	468.3 (2.27)

TABLE IV-2

Activities of degradation products (standard deviation of activity)/10^6 dpm/mole.

(a) not obtained pure

In retrospect it seems clear that this discrepancy is due to a failure to purify one or both of the benzoic acid preparations to constant activity. The consequences of this lamentable oversight would have been serious indeed if any significant levels of activity had been found in any of the other fragments.

The statistical insignificance of the levels of activity in both the 1,2,3,4-tetrachloronaphthalene and iodoform derived from x-[^{14}C]tetrachlorobenzobarrelenone {x-[^{14}C](IV-8)} permit the confident assertion that in the rearrangement in concentrated sulphuric acid of 1-methoxytetrachlorobenzobarrelene (IV-5) into tetrachlorobenzobarrelenone (IV-8) there occurs a completely specific skeletal rearrangement in which the C1 of 1-methoxytetrachlorobenzobarrelene (IV-5) becomes the C2 of tetrachlorobenzobarrelenone (IV-8). This conclusion is strongly reinforced by the high level of activity observed in the benzoic acid produced by the degradation of x-[^{14}C]tetrachlorobenzobarrelenone {x-[^{14}C](IV-8)}.

The statistical insignificance of the level of activity in the 1,2,3,4-tetrachloronaphthalene derived from 2-[^{14}C]tetrachlorobenzobarrelenone {2-[^{14}C](IV-8)} and, without rearrangement, from 1-[^{14}C]anisole permits the confident assertion that the activity of the anisole is confined to C1 and that partial scrambling of the activity around the aromatic ring has not occurred. In particular, the partial scrambling of the isotopic label observed by Ihrig and co-workers[7] in the catalytic dehydrogenation of 1-methyl-1-[^{13}C]cyclohexene to 1-[^{13}C]toluene is not important in the catalytic dehydrogenation of cyclohexanone to phenol reported in chapter two.

These results strongly support the proposal[1a-c] that the formation of benzobarrelenones from 1-methoxybenzobarrelenes involves the skeletal rearrangement shown in Scheme IV-3 and demonstrate that the pathways shown in Schemes IV-4 and IV-5 are unimportant under the normal reaction conditions.

EXPERIMENTAL SECTION

General Procedures

The general procedures are those described in the previous chapters with the following additions.

1-[^{14}C]Anisole was prepared from sodium [^{14}C]cyanide (500 μc) via the pimelonitrile, pimelic acid, cyclohexanone, and phenol by the method described in chapter two. The isolation of the cyclohexanone and anisole was facilitated by dilution with inactive material. The [^{14}C]anisole prepared by this method was purified by distillation.

The degradative procedures used are described in detail in chapter three.

Activities were determined using a Beckman Instruments CPM-100 liquid scintillation spectrometer. The scintillator was a solution of 2,5-diphenyloxazole (0.38%) and 1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene (0.02%) in toluene. The efficiency of the scintillator was determined using [^{14}C]hexadecane of known specific activity (obtained from the Radiochemical Centre, Amersham) as a standard. The observed efficiency of the sample of scintillator used (92.2% or 92.6%) is indicated in the text.

Activities were determined for solutions of the sample (ca. 1mg) in dimethylformamide (0.2ml) and the scintillator (5ml).

1. Preparation of 1-Methoxy-1-[^{14}C]tetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-1-[^{14}C]-1,4-ethenonaphthalene) {1-[^{14}C](IV-5)} and 2-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-2-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {2-[^{14}C](IV-8)} from 1-[^{14}C]Anisole and 2-Carboxytetrachlorobenzenediazonium Chloride

A suspension of 2-carboxytetrachlorobenzene diazonium chloride (4.0g, 12.4 mmole) in 1-[^{14}C]anisole (2.05g, 19.0 mmole) and dry carbon tetrachloride (25ml) was heated under reflux for 40min. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography to give:

a. 1-Methoxy-1-[^{14}C]tetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1-[^{14}C]-1,4-ethenonaphthalene) {1-[^{14}C](IV-5)}, (1.58g, 39% based on 2-carboxytetrachlorobenzenediazonium chloride, 26% based on 1-[^{14}C]anisole), characterised by comparison with similar material, followed by

b. A brown oil which was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give 2-[^{14}C]tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-2-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {2-[^{14}C](IV-8)}, (0.114g, 3% and 2%), characterised by comparison with similar material.

2. Degradation of 2-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-2-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {2-[^{14}C](IV-8)}

2-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-2-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {2-[^{14}C](IV-8)} (0.114g, 0.370 mmole) was degraded by the method described in chapter three to give:

a. 1,2,3,4-Tetrachloronaphthalene (0.050g, 51%). The preparation was purified by recrystallisation from ethanol and its activity was determined:

i) 1.104mg exhibited a mean activity of 2.41 cpm above background, with a variance of 6.05 (4 degrees of freedom), equivalent to 0.627×10^6 dpm/mole (scintillator efficiency 92.6%).

ii) 0.666mg exhibited a mean activity of 3.32 cpm above background, with a variance of 8.15 (4 degrees of freedom), equivalent to 1.432×10^6 dpm/mole (92.6%).

b. A yellow precipitate (0.011g) which could not be purified, but which exhibited only a background level of activity.

c. Benzoic-[^{14}C]acid (0.040g). The preparation was purified by two vacuum sublimations and its activity was determined:

i) 0.930mg exhibited a mean activity of 2356.47 cpm above background, equivalent to 333.83×10^6 dpm/mole.

The preparation was re-purified by vacuum sublimation and its activity was determined:

ii) 1.088mg exhibited a mean activity of 3665.63 cpm above background, equivalent to 443.89×10^6 dpm/mole.

iii) 1.023mg exhibited a mean activity of 3474.30 cpm above background, equivalent to 459.06×10^6 dpm/mole.

The preparation was re-purified by vacuum sublimation and its activity was determined:

iv) 1.273mg exhibited a mean activity of 4657 cpm above background with a variance of 1247 (9 degrees of freedom), equivalent to 484.2×10^6 dpm/mole (92.6%).

v) 0.980mg exhibited a mean activity of 3469 cpm above background with a variance of 184.5 (9 degrees of freedom), equivalent to 468.5×10^6 dpm/mole (92.6%).

3. Rearrangement of 1-Methoxy-1-[^{14}C]tetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1-methoxy-1-[^{14}C]-1,4-ethenonaphthalene) {1-[^{14}C](IV-5)} to x-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-x-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {x-[^{14}C](IV-8)} in Concentrated Sulphuric Acid

A suspension of dry, powdered 1-methoxy-1-[^{14}C]tetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1-[^{14}C]-1,4-ethenonaphthalene) {1-[^{14}C](IV-5)} (purified by recrystallisation from ethanol, 0.450g, 1.40 mmole) in concentrated sulphuric acid (98%, 10ml) was shaken at room temperature for 3min. The resultant solution was poured onto ice (50g). The precipitated product was isolated by filtration, washed with water until neutral and air-dried. The product was purified by preparative t.l.c. (silica-gel, 30% ether in light petroleum to give x-[^{14}C]tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-x-[^{14}C]-1,4-ethenonaphthalen-2-(1H)-one) {x-[^{14}C](IV-8)} (0.320g, 74%), identified by comparison with similar material.

No attempt was made to isolate the minor reaction products.

4. Degradation of x-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-x-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {x-[^{14}C](IV-8)}

x-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-x-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {x-[^{14}C](IV-8)} (0.320g, 1.04 mmole) was degraded by the method described in chapter three to give:

a. 1,2,3,4-Tetrachloronaphthalene (0.208g, 75%). The preparation was purified by recrystallisation from ethanol and its activity was determined:

i) 0.741mg exhibited a mean activity of 2.49 cpm above background with a variance of 10.13 (4 degrees of freedom), equivalent to 0.965 x 10^6 dpm/

mole (92.6%).

ii) 0.762mg exhibited a mean activity of 2.21 cpm above background with a variance of 5.37 (4 degrees of freedom), equivalent to 0.833×10^6 dpm/mole (92.6%).

b. Iodoform, the activity of which was determined:

i) 0.623mg exhibited a mean activity of 2.07 cpm above background with a variance of 4.80 (4 degrees of freedom), equivalent to 1.414×10^6 dpm/mole (92.6%).

ii) 0.840mg exhibited a mean activity of 2.25 cpm above background with a variance of 5.80 (4 degrees of freedom), equivalent to 1.140×10^6 dpm/mole.

c. Benzoic acid (0.073g). The preparation was purified by two vacuum sublimations and its activity was determined:

i) 0.668mg exhibited a mean activity of 1996 cpm above background, equivalent to 393.65 dpm/mole.

The preparation was re-purified by vacuum sublimation and its activity was determined:

ii) 1.100mg exhibited a mean activity of 3829 cpm above background, equivalent to 458.58 dpm/mole.

iii) 1.167mg exhibited a mean activity of 4108 cpm above background, equivalent to 463.74 dpm/mole.

The preparation was re-purified by vacuum sublimation and its activity was determined:

iv) 1.076mg exhibited a mean activity of 3757 cpm above background with a variance of 211.5 (9 degrees of freedom), equivalent to 462.0×10^6 dpm/mole (92.2%).

v) 1.021mg exhibited a mean activity of 3662 cpm above background with a variance of 423 (9 degrees of freedom), equivalent to 474.6×10^6 dpm/mole (92.2%).

Statistical Comparisons

The variances of samples which are suspected to be estimates of the same population variance were compared using double-sided F-tests,[6] where

$$F = \frac{\text{larger variance estimate}}{\text{smaller variance estimate}}$$

The date of samples with sufficiently compatible variances were combined.

Means of samples were compared with one another or with standard values using t-tests,[6] where

$$t = \frac{\text{difference between compared values}}{\text{standard error of the difference}}$$

Comparison of 1,2,3,4-Tetrachloronaphthalene Activities.

A. From 2-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-2-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {2-[^{14}C](IV-8)}

2.a.i $\bar{x}_A = 0.627 \times 10^6$; $\sigma_A^2 = 0.41 \times 10^{12}$, $\emptyset = 4$

2.a.ii $\bar{x}_B = 1.432 \times 10^6$; $\sigma_B^2 = 1.52 \times 10^{12}$, $\emptyset = 4$

$$\underline{F} = 3.68; \quad \underline{F}_{20\%}(4,4) = 4.11$$

There is no significant difference in the variances. A better estimate of the population variance is given by combining the two estimates:

$$\hat{\sigma}^2 = 0.965 \times 10^{12}, \quad \emptyset = 8$$

The standard error in the difference of the means is given by:

$$\text{S.E. } (\bar{x}_B - \bar{x}_A) = \hat{\sigma}\sqrt{\frac{1}{5} + \frac{1}{5}} = 0.621 \times 10^6$$

$$\underline{t} = \frac{\bar{x}_B - \bar{x}_A}{\text{S.E. } (\bar{x}_B - \bar{x}_A)} = 1.29; \quad \underline{t}(10\%, \emptyset = 8) = 1.86$$

There is no significant difference in the means; a better estimate of the population mean is given by combining the two sample means:

$$\bar{\bar{x}} = 1.029 \times 10^6$$

B. From x-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-x-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {x-[^{14}C](IV-8)}

4.a.i $\bar{x}_A = 0.965 \times 10^6$; $\sigma_A^2 = 1.523 \times 10^{12}$, $\emptyset = 4$

4.a.ii $\bar{x}_B = 0.833 \times 10^6$; $\sigma_B^2 = 0.763 \times 10^{12}$, $\emptyset = 4$

$\underline{F} = 2.00$; $\underline{F}_{20\%}(4,4) = 4,11$

$\hat{\sigma}^2 = 1.143 \times 10^{12}$; S.E. $(\bar{x}_A - \bar{x}_B) = 0.676 \times 10^6$

$\underline{t} = 0.195$; $\underline{t}(50\%, \emptyset = 8) = 0.706$

$\bar{\bar{x}} = 0.899 \times 10^6$

C. Comparison of Data Sets A and B

A, $\bar{\bar{x}}_A = 1.029 \times 10^6$; $\sigma_A^2 = 0.965 \times 10^{12}$, $\emptyset = 8$

B, $\bar{\bar{x}}_B = 0.899 \times 10^6$; $\sigma_B^2 = 1.143 \times 10^{12}$, $\emptyset = 8$

i) With One Another

$\underline{F} = 1.18$; $\underline{F}_{20\%}(8,8) = 2.59$

$\hat{\sigma}^2 = 1.054 \times 10^{12}$; S.E. $(\bar{\bar{x}}_A - \bar{\bar{x}}_B) = 0.459 \times 10^6$

$\underline{t} = 0.283$; $\underline{t}(50\%, \emptyset = 16) = 0.690$

There is no significant difference between sets A and B.

ii) With Zero

$$\text{S.E. } (\bar{\bar{x}}_B) = \frac{\sigma_B}{\sqrt{10}} = 0.338 \times 10^6$$

$$\underline{t} = \frac{\bar{\bar{x}}_B - 0}{\text{S.E. } (\bar{\bar{x}}_B)} = 2.659$$

$\underline{t}(5\%, \emptyset = 8) = 2.31$; $\underline{t}(2\%, \emptyset = 8) = 2.90$

S.E. $(\bar{\bar{x}}_A) = 0.311 \times 10^6$

$\underline{t} = 3.31$; $\underline{t}(1\%, \emptyset = 8) = 3.36$

Comparison of Iodoform Activity with Zero

4.b.i $\bar{x}_A = 2.07$; $\sigma_A^2 = 4.80$, $\emptyset = 4$

$\bar{x}_B = 2.25$; $\sigma_B^2 = 5.80$, $\emptyset = 4$

$\underline{F} = 1.21$; $\underline{F}_{20\%}(4.4) = 4.11$

$\hat{\sigma}^2 = 5.3$; S.E. $(\bar{x}_B - \bar{x}_A) = 1.46$

$\underline{t} = 0.12$; $\underline{t}(50\%, \emptyset = 8) = 0.76$

$\bar{\bar{x}} = 2.16$ S.E. $(\bar{\bar{x}}) = 0.73$

$\underline{t} = 2.96$, $\underline{t}(2\%, \emptyset = 8) = 2.90$

$\underline{t}(1\%, \emptyset = 8) = 3.36$

Comparison of Benzoic Acid Activities

A. From 2-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-2-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {2-[^{14}C](IV-8)}

2.c.iv $\bar{x}_A = 484.2 \times 10^6$; $\sigma_A^2 = 13.46 \times 10^{12}$, $\emptyset = 9$

2.c.v $\bar{x}_B = 468.5 \times 10^6$; $\sigma_B^2 = 3.36 \times 10^{12}$, $\emptyset = 9$

$\underline{F} = 3.99$; $\underline{F}_{10\%}(9.9) = 3.18$, $\underline{F}_{2\%}(9.9) = 5.35$

$\hat{\sigma}^2 = 8.41 \times 10^{12}$; S.E. $(\bar{x}_A - \bar{x}_B) = 1.297 \times 10^6$

$\underline{t} = 12.41$; $\underline{t}(0.1\%, \emptyset = 18) = 3.92$

B. From x-[^{14}C]Tetrachlorobenzobarrelenone (5,6,7,8-Tetrachloro-3,4-dihydro-x-[^{14}C]-1,4-ethenonaphthalen-2(1H)-one) {x-[^{14}C](IV-8)}

4.c.iv $\bar{x}_A = 462.3 \times 10^6$; $\sigma_A^2 = 3.20 \times 10^{12}$, $\emptyset = 9$

4.c.v $\bar{x}_B = 474.6 \times 10^6$; $\sigma_B^2 = 7.12 \times 10^{12}$, $\emptyset = 9$

$\underline{F} = 2.23$; $F_{10\%}(9,9) = 3.18$

$\hat{\sigma}^2 = 5.16 \times 10^{12}$; S.E. $(\bar{x}_B - \bar{x}_A) = 1.02 \times 10^6$

$\underline{t} = 12.1$; $\underline{t}(0.1\%, \emptyset = 18) = 3.92$

C. Cross-Comparison of the Activities of Sets A and B

2.c.iv and 4.c.iv

$\underline{F} = 4.21$; $F_{2\%}(9,9) = 5.35$

$\hat{\sigma}^2 = 8.33 \times 10^{12}$; S.E. $(\Delta\bar{x}) = 1.29 \times 10^6$

$\underline{t} = 16.97$; $\underline{t}(0.1\%, \emptyset = 18) = 3.92$

2.c.iv and 4.c.v

$\underline{F} = 1.89$; $F_{2\%}(9,9) = 2.44$

$\hat{\sigma}^2 = 10.29 \times 10^{12}$; S.E. $(\Delta\bar{x}) = 1.43 \times 10^6$

$\underline{t} = 6.69$; $\underline{t}(0.1\%, \emptyset = 18) = 3.92$

2.c.v and 4.c.v

$\underline{F} = 2.12$; $F_{10\%}(9,9) = 3.18$

$\hat{\sigma}^2 = 5.24 \times 10^{12}$; S.E. $(\Delta\bar{x}) = 1.02 \times 10^6$

$\underline{t} = 5.96$; $\underline{t}(0.1\%, \emptyset = 18) = 3.92$

2.c.v and 4.c.iv

$\underline{F} = 1.05$; $\underline{F}_{20\%}(9.9) = 2.44$

$\hat{\sigma}^2 = 3.28 \times 10^{12}$; S.E. $(\Delta\bar{x}) = 0.810$

$\underline{t} = 7.65$; $\underline{t}(0.1\%, \emptyset = 18) = 3.92$

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CHAPTER FIVE

The Acid-Catalysed Rearrangements of Some Methyl-Substituted 1-Methoxytetrachlorobenzobarrelenes

Introduction

The acid-catalysed rearrangements of 1-methoxybenzobarrelene and its tetrafluoro- and tetrachlorobenzo-analogues are complex.[1] The structures of the products may be understood as the consequence of a number of [1,2]-alkyl, -aryl, or -alkenyl shifts within the C-protonated molecule. Each shift produces a more stable carbo-cation and eventually the positive charge falls adjacent to the methoxy-group. The methoxy-group so stabilises the carbocation that no further rearrangement occurs; O-demethylation of the cation gives the corresponding ketone as one of the reaction products.

The several products observed are thought to arise from partitioning of both the benzobarrelene between distinguishable cations by non-regio-specific protonation and the initially formed carbocations between distinguishable first-rearrangement ions by competitive migrations. The overall series of rearrangements leading to each product appears to be irreversible. The alternative explanation that one product is formed rapidly, only to equilibrate with the other observed products does not appear tenable: the observed products are all stable with respect to such an equilibration under the conditions of their formation.[1a]

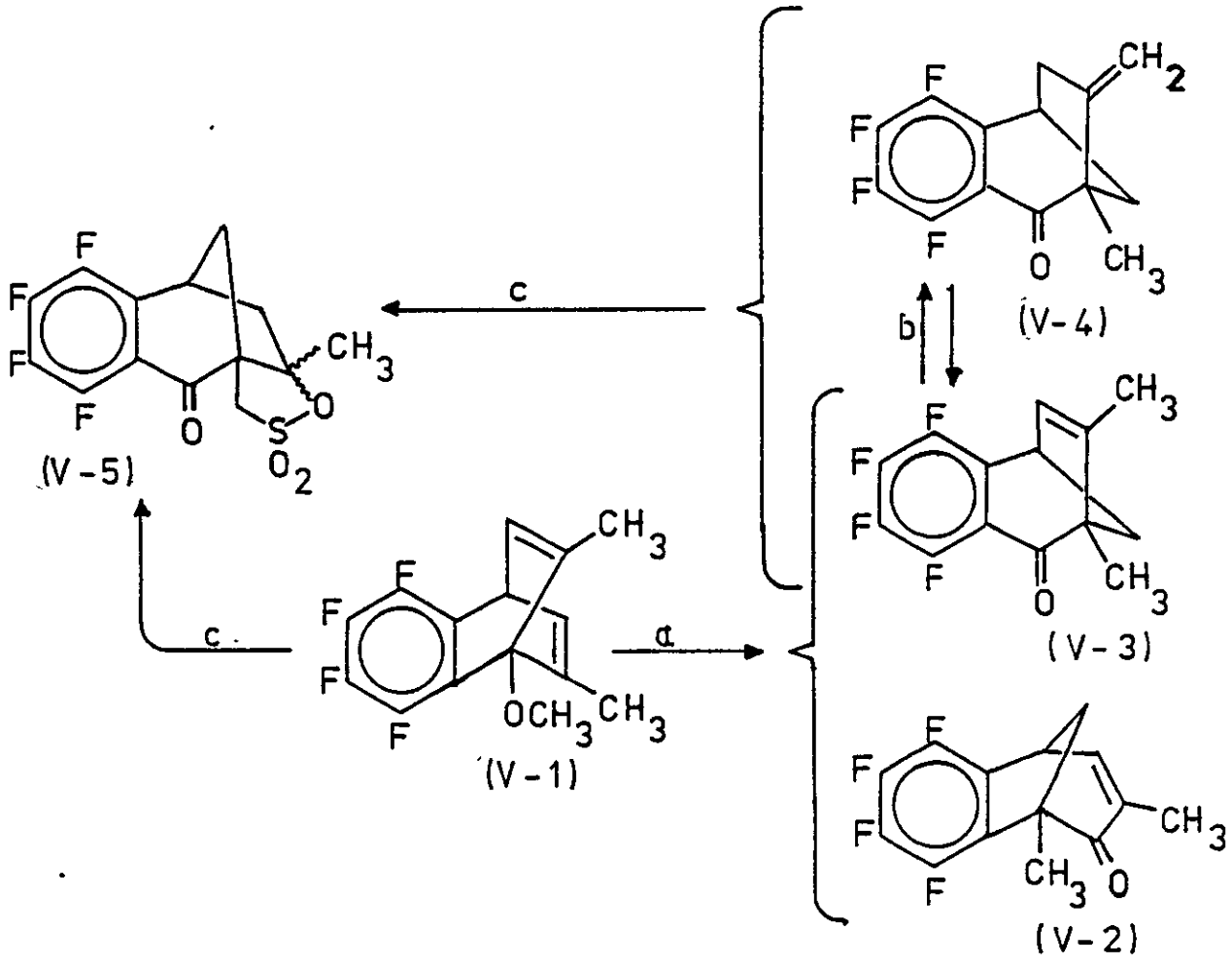
The effect on the rearrangement of alkyl-substitution is dramatic: extensive alkylation stabilises the carbocations to such an extent that equilibrium mixtures of products may be formed from reactions involving degenerate or rapidly interconverting cations.[2] Attempts to study some other aspects of the rearrangement by using less extensively methylated 1-methoxytetrafluorobenzobarrelenes were only partially successful.[1a,3] The primary rearrangement products are subject to secondary reactions under the acidic conditions required to catalyse the rearrangement to 1-methoxy-tetrafluorobenzobarrelene, although under milder conditions their isolation

is possible. Not only do alkyl-substituents enhance the reactivity of the benzobarrelenes, they also increase the lability of the products.

Thus, although rearrangement of 2,6-dimethyl-1-methoxy-tetrafluorobenzobarrelene (V-1) in trifluoroacetic acid gave the αβ-unsaturated ketone (V-2) and the aryl ketone (V-3) only, prolonged reaction caused isomerisation of the aryl ketone [(V-3) ⇌ (V-4)].[1a] Rearrangement of this benzobarrelene (V-1) in concentrated sulphuric acid gave a more complicated mixture of products including the unusual and mechanistically interesting sultone (V-5) (Scheme V-1). The sultone clearly results from sulphonation of a double bond. This type of reaction has many precedents.[4] The stage at which the sulphonation occurs is not known but two distinct mechanistic pathways are suggested by the available data, both entailing sulphonation of an exocyclic methylene group:

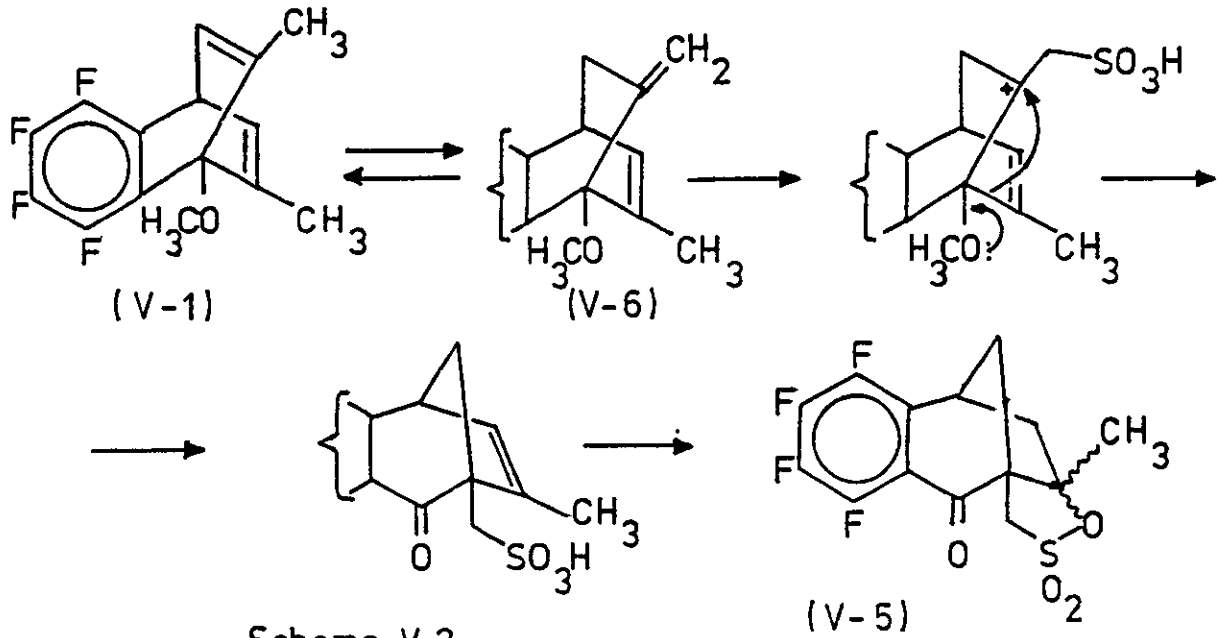
In the first, the benzobarrelene (V-1) is converted to the double bond isomer (V-6) and then sulphonated by the reaction medium. Subsequent rearrangement to the cation produced by sulphonation, and acid-catalysed cyclisation of the unsaturated sulphonic acid would give the sultone (V-5) (Scheme V-2). The absence from the isolated products of a sulphonated αβ-unsaturated ketone (V-7) may be ascribed to the putative water solubility of such sulphonic acids. It is known that the aryl ketones [(V-3) and (V-4)] are also precursors of the sultone (V-5). If these aryl ketones do not revert to 1-"oxy"-benzobarrelenes (a type of rearrangement which is quite reasonable, but which nonetheless has not been observed in several closely related systems)[1a] there must be a direct pathway from these aryl ketones to the sultone (V-5).

Sulphonation of the aryl ketone (V-4) followed by acyl-migration and cyclisation of the sulphonic acid-carbocation produced would give the sultone (V-5) (Scheme V-3). The relatively uncommon acyl-migration would

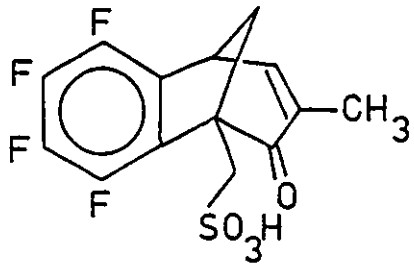


Scheme V-1-

Reagents: a) CF_3CO_2H, 20°, 10 min; b) CF_3CO_2H, reflux, 24h; c) H_2SO_4.

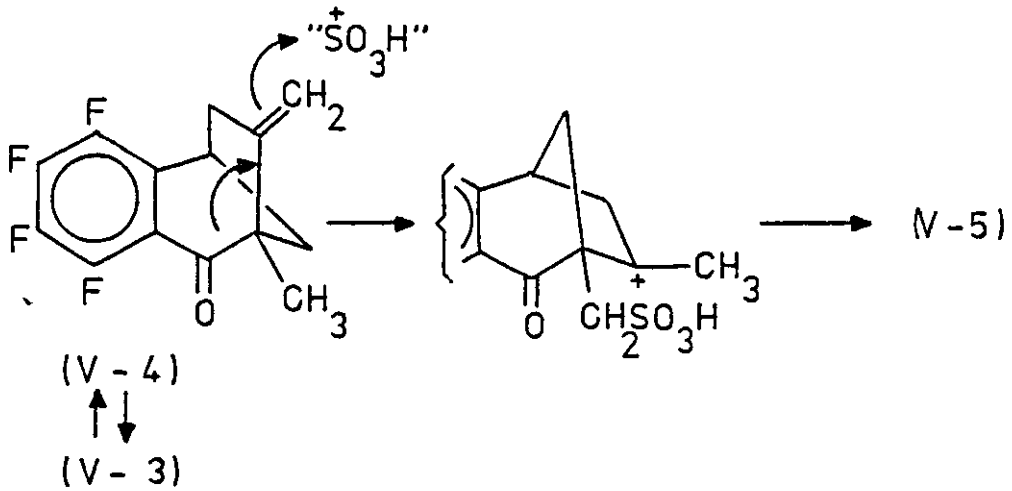


Scheme V-2



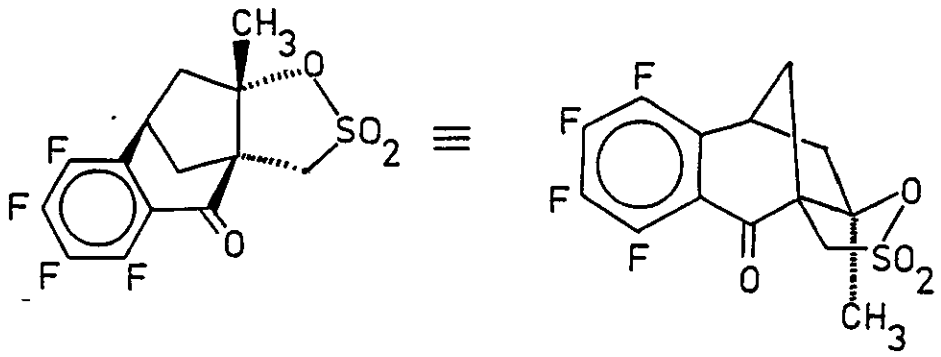
(V - 7)

be favoured by the combination of several factors: Methyl-migration is disfavoured on both stereoelectronic and on product stability grounds. The geometry of the molecule is such that the methyl group could not main-



Scheme V-3

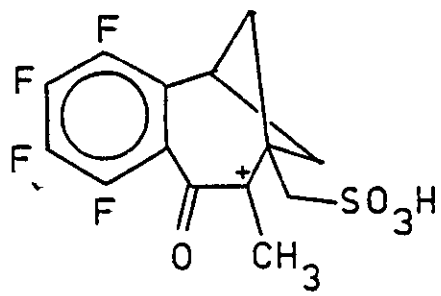
tain a high degree of bonding throughout the migration, but that even if it could migrate, the cation produced would be a bridgehead position, in an unstable state.[5] Although no such geometrical considerations would inhibit migration of the methylene group, the product would be the relatively more strained cyclobutane (V-8) which has an unstable α-keto-carbocation. The intervention of the acylium ion (V-9) in this migration may also be



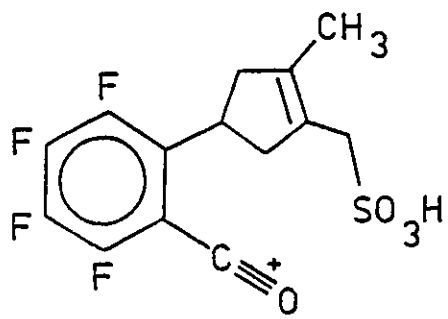
(V - 10)

considered.

The stereochemistry of the sultone (V-5) has not been established, but the probable structure is the all-cis configuration (V-10).[6]

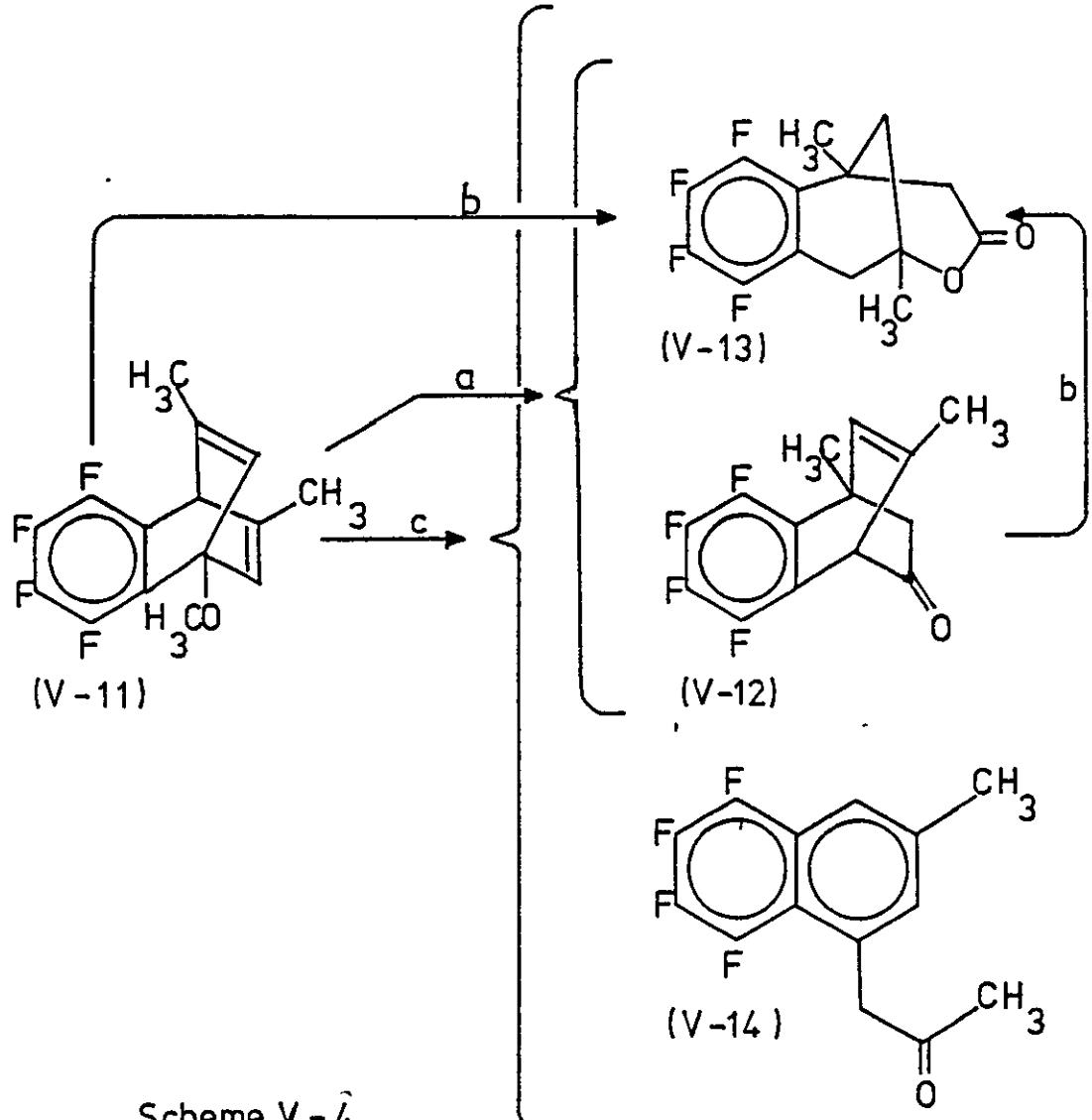


(V - 8)



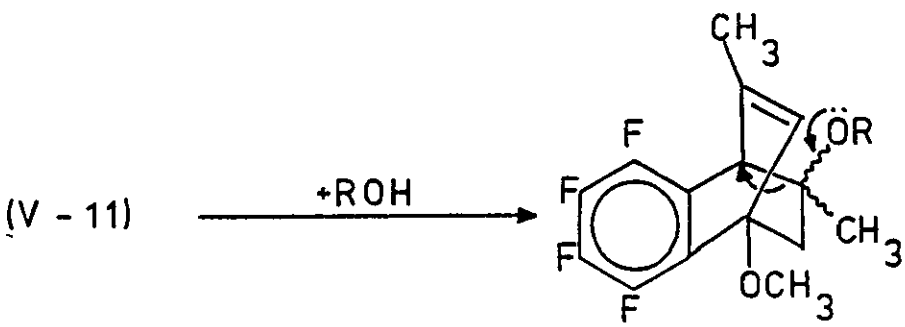
(V - 9)

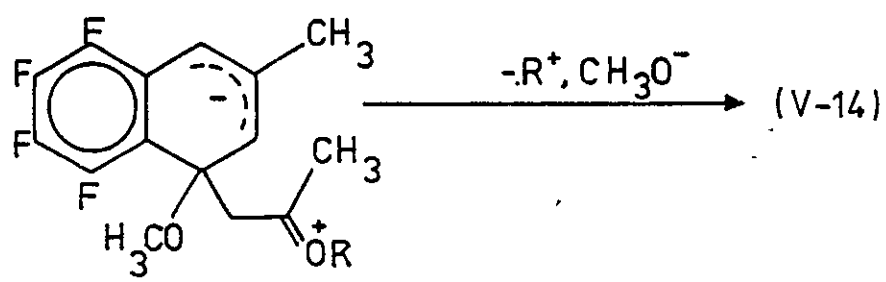
Yet more complex are the rearrangements of 3,5-dimethyl-1-methoxy-tetrafluorobenzobarrelene (V-11), (Scheme V-4).[1a,3] Rearrangement of (V-11) in trifluoroacetic acid gives 4,6-dimethyl-tetrafluorobenzobarrelenone (V-12) and small amounts of the lactone (V-13). Rearrangement of either the benzobarrelenone (V-12) or its precursory benzobarrelene (V-11) in concentrated sulphuric acid gives the lactone (V-13) in high yield. In 70% aqueous sulphuric acid another product is observed in addition to the



Scheme V - 4

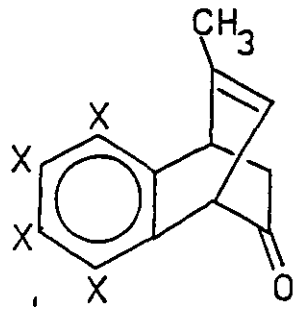
Reagents: a) CF_3CO_2H; b) 98% H_2SO_4; c) 70% H_2SO_4.





Scheme V-5

benzobarrelenone (V-12) and the lactone (V-13) and which is not produced from either of these products. This product, the acetonyl-naphthalene (V-14) illustrates another reaction pathway open to these benzobarrelenes, a nucleophile induced ring opening (Scheme V-5) reminiscent of the cleavage of benzobarrelenones with the phenyl Grignard-reagent, described in chapter three. The formation of the lactone (V-13) may involve a similar fragmentation followed by acid catalysed lactonisation. Base catalysed hydration of the carbonyl-group leads to ring opening (cf. chapter three) and the first step of the lactone formation could be an acid catalysed equivalent. However, benzobarrelenones are usually moderately stable in concentrated sulphuric acid. The labilising factor seems to be the methyl substituent on the etheno-bridge. The other notably unstable benzobarrelenones are the 5-methylbenzobarrelenones (V-15), the fate of which becomes a mystery from the moment that they are dissolved in concentrated sulphuric acid.[1a]



(V-15)

The order in which the steps protonation, solvation, and ring opening occur and the relative importance of each of the pathways corresponding to the different orders are far from clear and may vary with reaction conditions.

It may be seen that the product determining protonation is directed by one of the methyl groups, but that it is the other methyl group which pro-

motes the secondary reactions. Although the choice of symmetrically substituted 1-methoxybenzobarrelenes appears at first sight to simplify analysis of the rearrangement by reducing the number of different processes that may occur, this is not the case. The reactions are complicated by the additional substitution rather than simplified.

In spite of the secondary reactions, an underlying trend is readily discernible: a 3-methyl group promotes rearrangement to a benzobarrelenone, with retention of a bicyclo[2.2.2]octane skeleton, whereas a 2-methyl group promotes rearrangement to aryl and αβ-unsaturated ketones in which the carbon skeleton is changed to that of a bicyclo[3.2.1]octane. This specificity is doubtless due to control of the position of protonation by the methyl substituents.

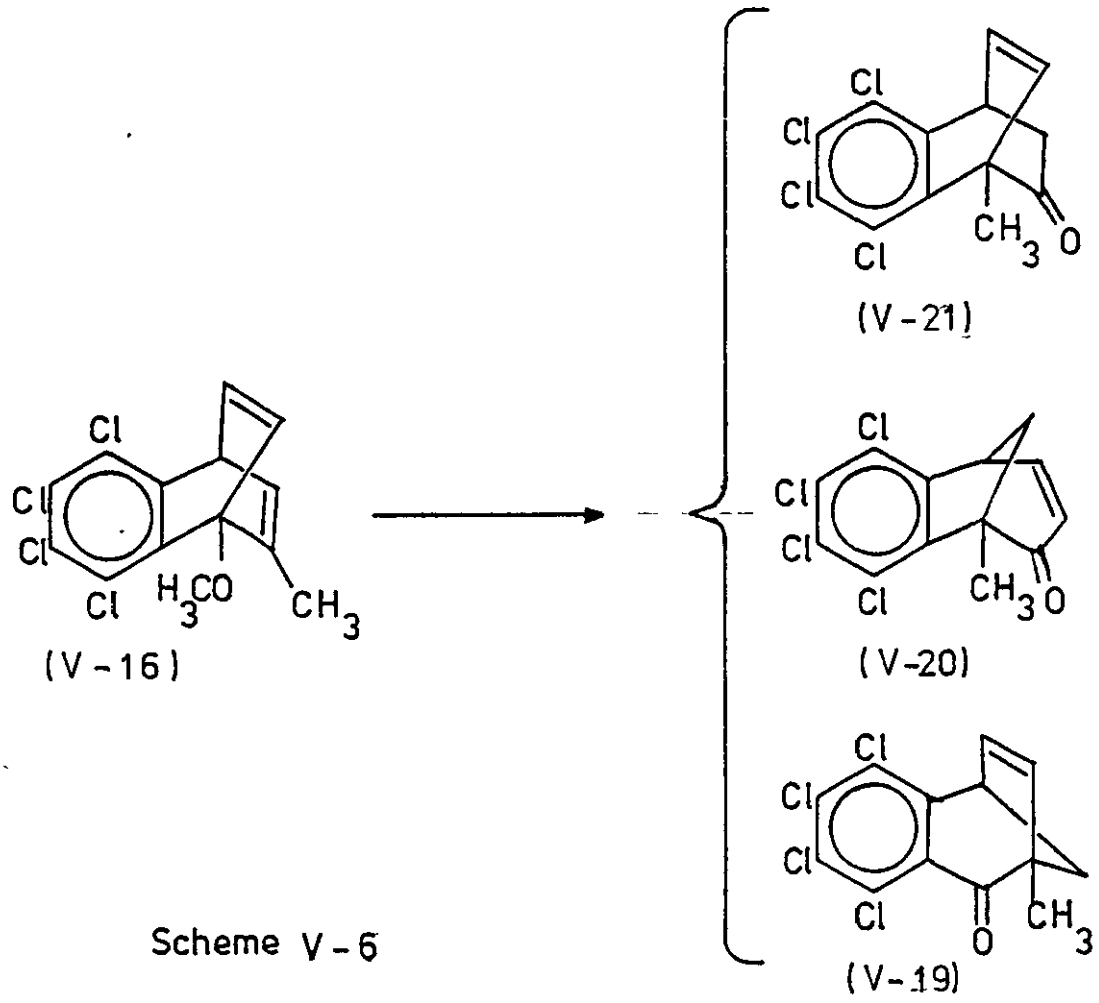
This work has been complemented and extended by a study of the acid catalysed rearrangements of 2-methyl-, 3-methyl-, and 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene [(V-16), (V-17) and (V-18)]. The first two series of rearrangements were designed to confirm the results already described. The exclusion from the molecules of all superfluous substituents suppresses secondary reactions. Amongst such possible reactions must be included protonation or sulphonation of the aromatic ring, two reactions which are effectively hindered by the chloro-substituents. These substituents confer a desirable degree of crystallinity on the products, but also effect the stability of any benzylic carbocations. Even so, the benefits outweigh the disadvantages. The last series was chosen to compare the two modes of rearrangement within one molecule. The benzobarrelenes (V-16) and (V-17) gave the results which were anticipated, but the more substituted benzobarrelene (V-18) underwent an unusual secondary rearrangement in strong acid.

Results and Discussion

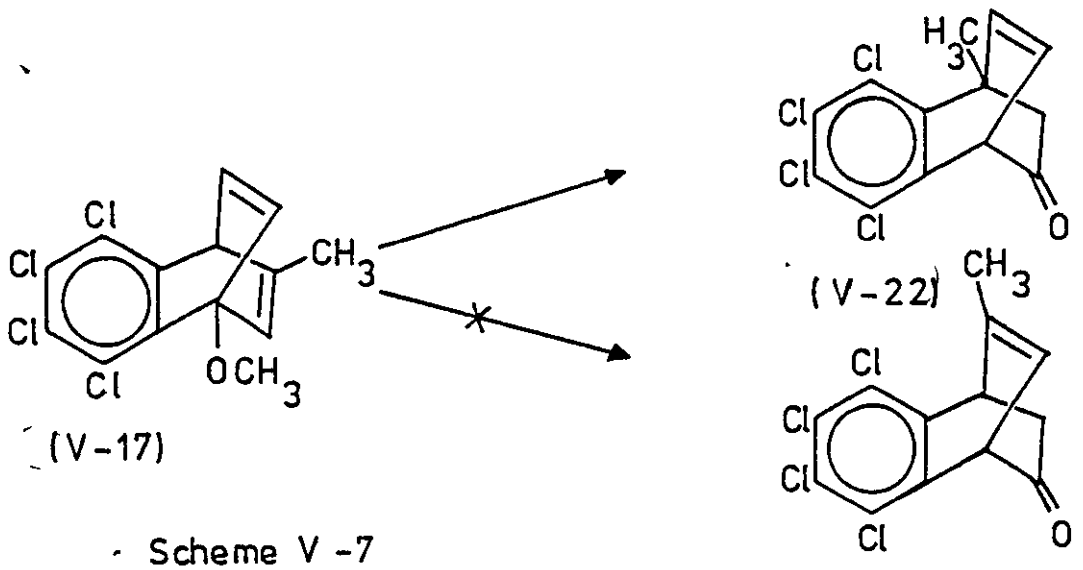
Treatment of 2-methyl-1-methoxytetrachlorobenzobarrelene (V-16) with boiling trifluoroacetic acid for two hours gave the aryl ketone (V-19) (56%), the αβ-unsaturated ketone (V-20) (40%) and a trace of the benzobarrelenone (V-21) (4%). The same products were formed when the rearrangement was conducted in concentrated sulphuric acid at 20° for two minutes, but the relative amounts of the products were different. The aryl ketone (V-19) (4%) and the αβ-unsaturated ketone (V-20) (27%) were formed in yields greatly reduced in comparison with those obtained with trifluoroacetic acid. The yield of the benzobarrelenone (V-21) (28%) was much enhanced. The products were shown not to interconvert under the conditions used (Scheme V-6).

Rearrangement of 3-methyl-1-methoxy-tetrachlorobenzobarrelene under acid catalysis is much simpler. The only product obtained after treatment with either boiling trifluoroacetic acid for two hours or concentrated sulphuric acid at 20° for two minutes was 4-methyl-tetrachlorobenzobarrelenone (V-22) (100% and 90% respectively)(Scheme V-7). This is only one of the pair of isomeric benzobarrelenones which might be expected to be formed on the basis of the mechanistic speculation outlined in chapter four.

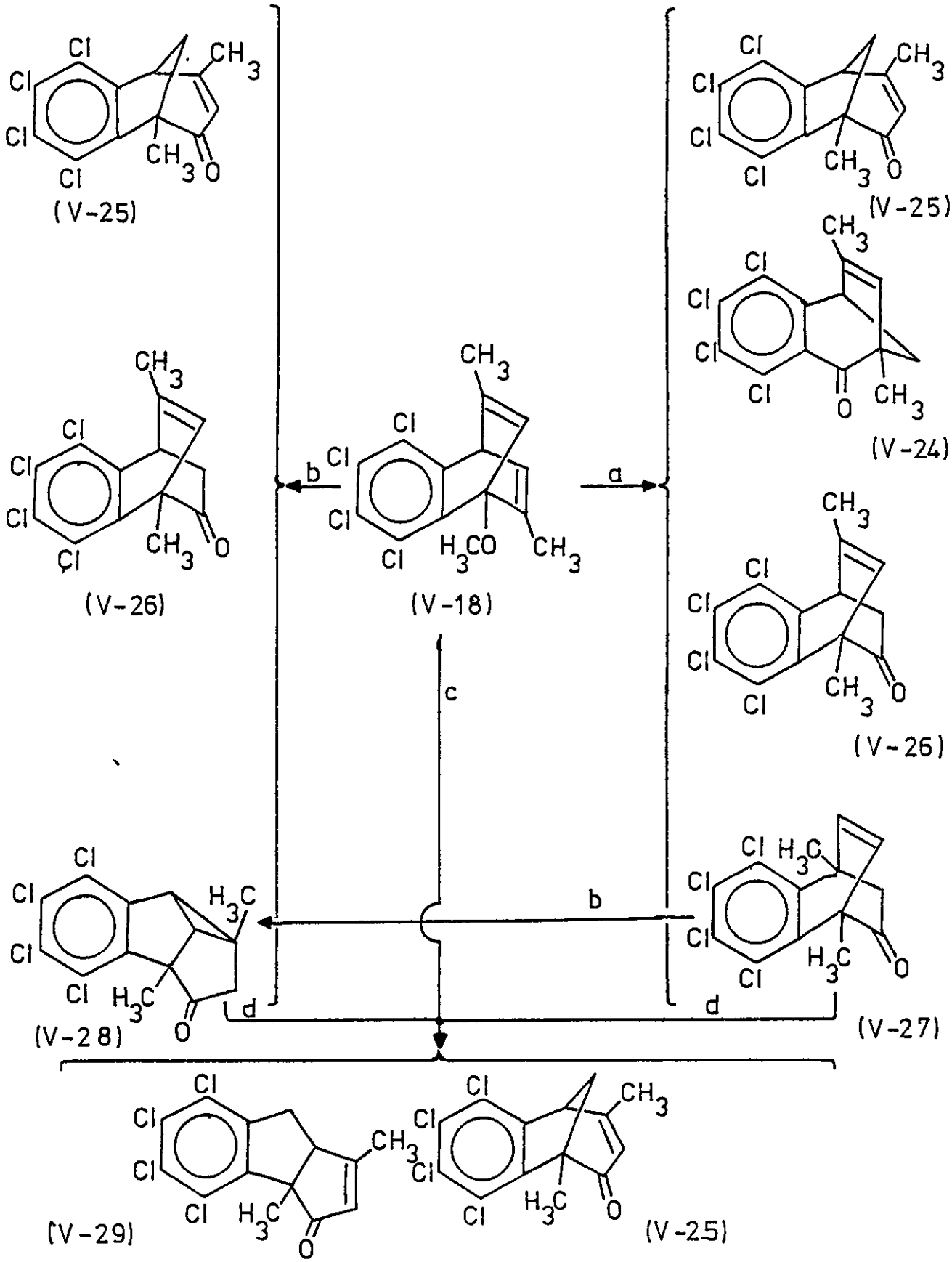
2,5-Dimethyl-1-methoxy-tetrachlorobenzobarrelene (V-18) incorporates the more obvious structural features of 2-methyl- and 3-methyl-1-methoxy-tetrachlorobenzobarrelene [(V-16) and (V-17)] within one molecule, and provides an interesting opportunity for competition between the two types of rearrangement. The analogy is not complete, for neither methyletheno-bridge is now proximate to an etheno-bridge, and the rearrangements will not proceed along independent competitive pathways characteristic on the one hand of a 2-methyl- and on the other of a 3-methyl-substitution pattern.



Scheme V-6



Scheme V-7



Scheme V - 8 Reagents: a) CF_3CO_2H, 30 min., 20°; b) Conc. H_2SO_4 1 min, 20°, or FSO_3H, 1 min., -40°; c) FSO_3H, 1 hour, -40°; d) ca. 95% H_2SO_4, 5 min, 20°.

Rather, each will perturb the other and to an extent which will not be easy to predict or to evaluate in retrospect. This deviation from perfection notwithstanding, the 2,5-dimethyl-substitution pattern offered the prospect of an insight into some of the factors controlling the choice of rearrangement pathway.

The results were unexpected: the product was a complex mixture, the composition of which varied with acid strength, reaction time, and solvent basicity.

Rearrangement of 2,5-dimethyl-1-methoxy-tetrachlorobenzobarrelene (V-18) in trifluoroacetic acid at 20° for three hours gave the aryl ketone (V-24) (52%), the αβ-unsaturated ketone (V-25) (24%), and a mixture of the benzobarrelenones (V-26) and (V-27) (total yield 21%) (Scheme 8). The two benzobarrelenones formed are those which would be expected from the mechanistic speculation of chapter four.

The ratio of these benzobarrelenones to one another and to the other reaction products was not constant, varying considerably from reaction to reaction.

Conducting the reaction in boiling trifluoroacetic acid gave predominantly the benzobarrelenones (V-26) and (V-27), with the ratio (V-27):(V-26):[(V-25) + (V-24)] = 0.4:1.0:1.1, as determined by analysis of the olefinic region of the ^{1}H-n.m.r. spectrum. At room temperature the 1,5-dimethyl-benzobarrelenone (V-26) was observed to preponderate over the 1,4-dimethyl-benzobarrelenone (V-27) (ratio 1:0.75) in dry trifluoroacetic acid, but addition of water (5% v/v) to the reaction medium produced more than an inversion of this ratio (1:1.63) and in the three component chloroform-trifluoroacetic acid-water system (4:8:1 v/v/v), the crude product showed no trace of the 1,5-dimethylbenzobarrelenone (V-26) in the ^{1}H-n.m.r. spectrum.

These results are not a self-consistent and definitive study of the effect of changing the reaction medium, but indicate the sensitivity of the rearrangement to small changes in environment.

Treatment of 2,5-dimethyl-1-methoxy-tetrachlorobenzobarrelene (V-18) with concentrated sulphuric acid at 20° gave a complex mixture of products (see later) but treatment with fluorosulphuric acid at -60° for one hour gave a mixture of the benzobarrelenone (V-26) (18%) and another ketone later shown on the basis of accumulated chemical and spectral evidence to be the benzosemibullvalenone (V-28) (40%) (Scheme V-8).

The four products of the rearrangement in trifluoroacetic acid are the primary rearrangement products which would be expected from 2,5-dimethyl-1-methoxy-tetrachlorobenzobarrelene (V-18). The benzosemibullvalenone (V-28) cannot be rationalised within the accepted mechanisms as a primary rearrangement product, but must be supposed to be a secondary product.

The stability of the αβ-unsaturated ketone (V-25) and the strongly contrastingly rapid degradation of both the aryl ketone (V-24) and the 1,5-dimethylbenzobarrelenone (V-26) to multitudinous uncharacterised products under conditions which favour formation of the benzosemibullvalenone (V-28) led to this conclusion: the elusive 1,4-dimethylbenzobarrelenone (V-27) is the black jasper to prove this supposition. And so it was.

Treatment of the 1,4-dimethyl-benzobarrelenone (V-27) with concentrated sulphuric acid at 20° for one minute gave the benzosemibullvalenone (V-28) (70%) (Scheme V-8).

More surprising yet was the effect of moist concentrated sulphuric acid (ca. 95%) on 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (V-18) at 20° for three minutes. In addition to the 1,5-dimethylbenzobarrelenone (V-26) (22%), the αβ-unsaturated ketone (V-25) (15%), and the benzosemi-

bullvalenone (V-28) (17%) a further product was isolated which was later shown to be the dihydro-benzopentalenone (V-29) (15%).

Not surprisingly, treatment of either the 1,4-dimethylbenzobarrelenone (V-27) which was again conspicuously absent, or the benzosemibullvalenone (V-28) with sulphuric acid containing 5-10% v/v water gave the novel dihydro-benzopentalenone (V-29) (72% and 43% respectively). A significant additional product in the latter reaction was the αβ-unsaturated ketone (V-25) (8.5%). It is clear that the dihydro-benzopentalenone (V-29) could have been formed from the 1,4-dimethylbenzobarrelenone (V-27) by way of the benzosemibullvalenone (V-28) and that this is very probably its provenance.

The correct assignment of the structures of the benzosemibullvalenone (V-28) and the dihydro-benzopentalenone (V-29) is of fundamental importance to any discussion of the place which these molecules occupy in the bicyclooctane manifold. The structure of the benzosemibullvalenone is established later by independent synthesis of the ethylene acetal, but it is instructive to consider the spectral data.

Mass spectrometry and combustion analysis establish that both compounds are isomerous with the ketones previously obtained from the same source. In addition the benzosemibullvalenone (V-28) readily fragments in the mass spectrometer to give a strong $[M-28]^+$ ion, usually associated in similar compounds with loss of ethylene or carbon monoxide.[7]

Infrared spectroscopy confirms that both are ketones: the benzosemibullvalenone (V-28) exhibits $\nu_{max}(CHCl_3)$ 1745 cm^{-1} indicating that the ketone is not conjugated and that it is probably in a five-membered ring. The dihydro-benzopentalenone (V-29) exhibits $\nu_{max}(CHCl_3)$ 1710 and 1625 cm^{-1}. The latter band is strong and suggests the presence of a conjugated double bond; the former, of itself, indicates little about the ketone, but if the

functional group present is an αβ-unsaturated ketone the position of the band implicates a five-membered cyclic ketone as a structural sub-unit.[8] ^{1}H-n.m.r. spectroscopy and the shift of ν_{max} following catalytic hydrogenation strongly indicate that this interpretation is correct.

The ^{1}H-n.m.r. spectra of the two compounds provided no easy answers:

The benzosemibullvalenone (V-28) exhibited two methyl singlets at τ8.55 and τ8.31, the one at higher field being slightly broadened; a two proton multiplet centred at τ7.61 and best described as a broadened singlet ($W_{\frac{1}{2}}$ = 3.5 Hz) with additional fine structure, and an AB system at τ7.46 (d, J = 6.0 Hz) and τ7.15 (d, J = 6.0 Hz). The absence of olefinic or aromatic protons is immediately apparent.

In the presence of tris(dipivaloylmethanato-) europium(III) [Eu(dpm)$_3$][9] the methyl group and the two proton multiplet resonances at τ8.31 and τ7.61 respectively were shifted at similar rates to lower field (3.81 ppm/mole Eu(dpm)$_3$/mole ketone and 3.56 ppm/mole/mole respectively). The methyl group and the AB system resonances at τ8.55 and τ7.15 respectively were also shifted to lower field at rates comparable to one another, but to a much smaller extent than the first mentioned pair of resonances (0.58 ppm/mole/mole and 1.05 ppm/mole/mole respectively); the AB system resonance at τ7.46 was shifted downfield at an intermediate rate (2.11 ppm/mole/mole) (Fig. V-1).

This suggests, though not with absolute certainty that the protons of the τ8.31 methyl group and the protons of the τ7.61 multiplet are spacially close to the carbonyl group, but that the other methyl group and the protons of the AB system are remote from the carbonyl group.

^{13}C-n.m.r. spectroscopy[10] with broad band ^{1}H decoupling of the benzosemibullvalenone (V-28) showed the expected eight resonances in addition to those of aromatic carbon nuclei, and confirmed the absence of an olefinic group. Off-resonance decoupling of the protons indicated that apart from

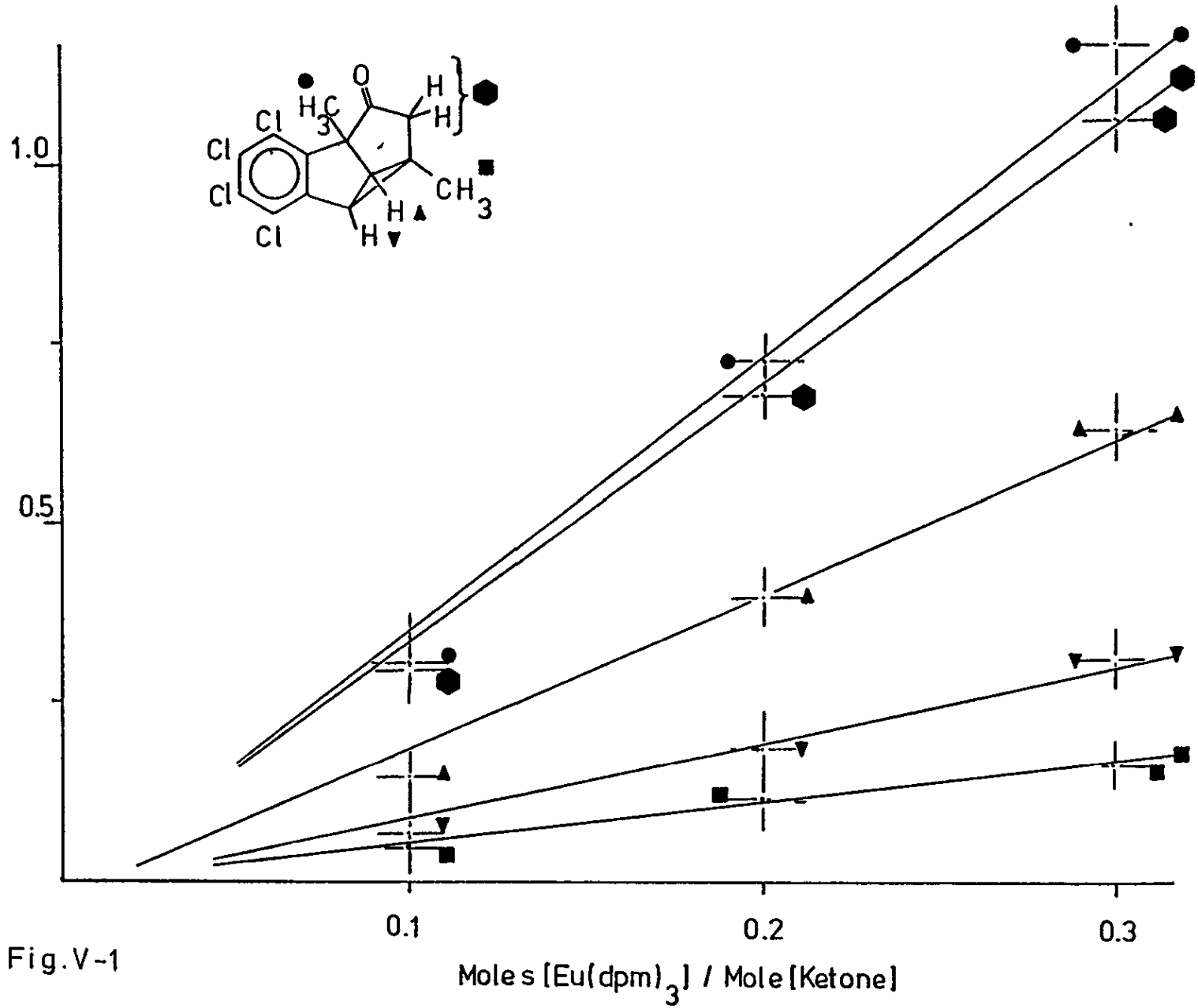

Induced
Shift
(p.p.m.)
1.0
0.5
0.1
0.2
0.3
Moles [Eu(dpm)3] / Mole [Ketone]
Cl
Cl
Cl
H3C
O
H
H
CH3
H
H

Fig. V-1

the carbonyl group, two of the carbon atoms were present as methyl groups, one as a methylene group, two as methine groups, and that there were two other quaternary carbon atoms, that is carbon atoms that bore no hydrogen atoms.

In the absence of an olefinic linkage, the alicyclic part of the structure must be a tricycle in which two carbon atoms of one bridge are fused with a benzene ring. The methyl groups give rise to singlets in the ^{1}H-n.m.r. spectrum and are each connected to quaternary carbon atoms. Their markedly different behaviour in the ^{1}H-n.m.r. experiment in the presence of Eu(dpm)$_3$ strongly suggests that they do not constitute a geminal dimethyl group. The two methine carbon atoms are each connected to one another and to quaternary carbon atoms, one of which may be one of the atoms of the aromatic ring. The structural elements generated by this analysis are shown in Fig. V-2.

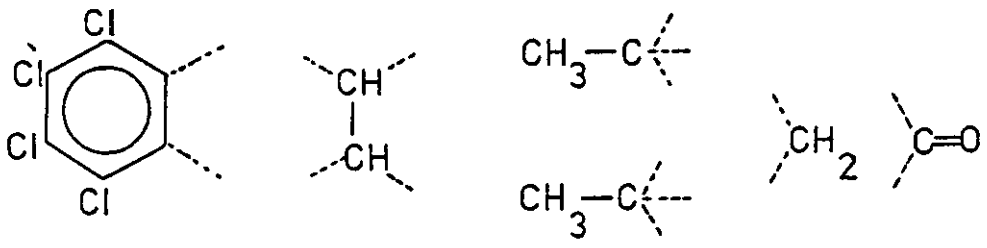


Fig.V-2

The methyl group and the methylene group are close to the carbonyl group and probably flank it, and the methylene group is also connected to a quaternary carbon. If this quaternary carbon is selected from the aromatic ring, the five-membered ring so formed cannot accommodate the remaining fragments within the restrictions, notably that there should be

no olefinic bonds. The methylene group is thus bonded to the other methyl-bearing quaternary carbon atom. The five-membered ring is completed by one of the methine carbon atoms (fig. V-3). The aromatic ring must bridge

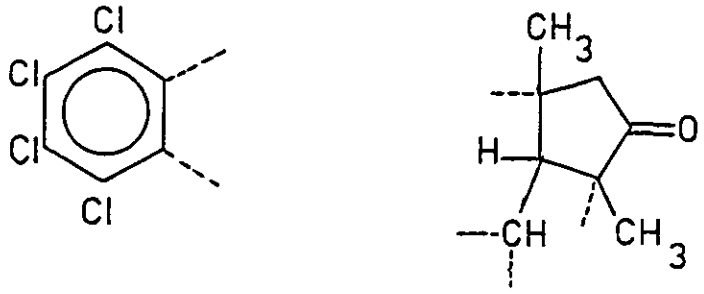
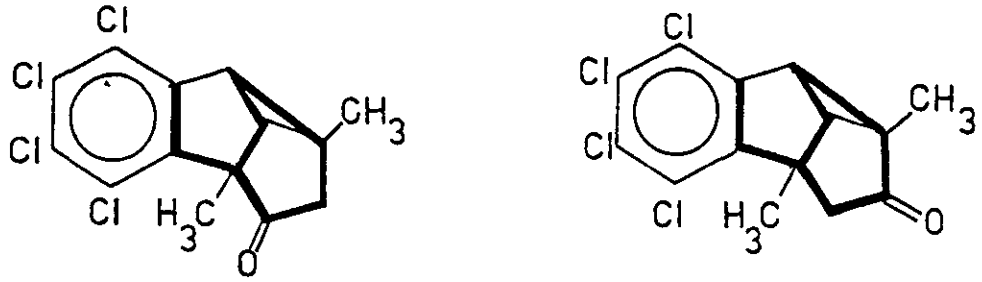


Fig. V-3

the remaining methine and one of the methyl-bearing quaternary carbon atoms; the two unsaturated valences must join to give a cyclopropane ring. The two structures given by this process are shown in fig. V-4. Note that the heavy outline indicates those bonds of the product which would have been present in the bicyclic precursor (V-27) and that formation of these structures does not involve any extensive bond relocation.



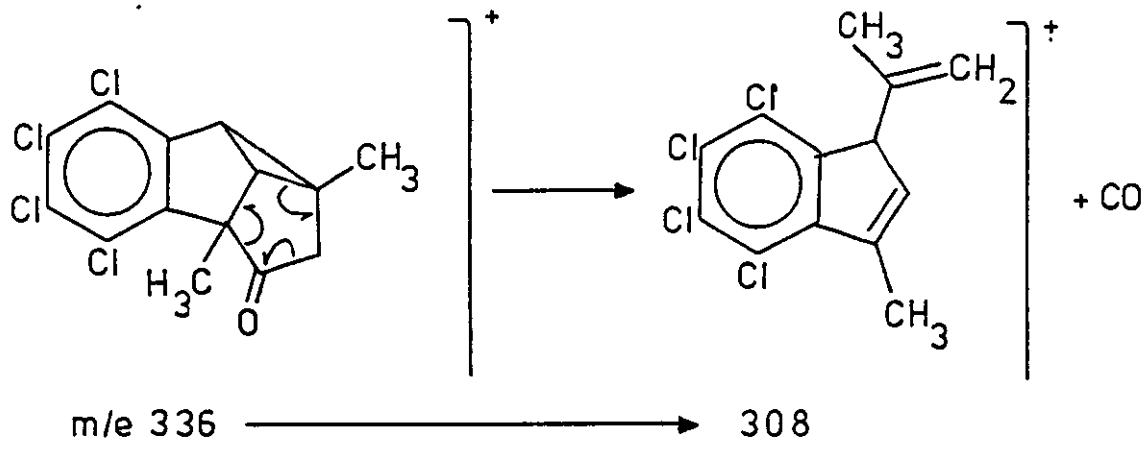
(V-28) A

(V-28a) B

Fig. V-4

Of the two, structure A is preferred on two bases. Firstly, the

ready decarbonylation in the mass spectrometer (Scheme V-9).



m/e 336 ⟶ 308

Scheme V-9

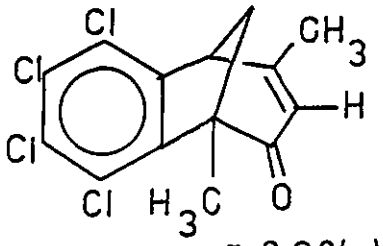
Secondly, in the ^{1}H-n.m.r. spectrum the methyl group resonance at high field which is slightly broadened is also the one which is least affected by the addition of Eu(dpm)$_3$. This slight broadening is attributed to long-range coupling through the cyclopropane ring. The lower field methyl singlet is noticeably sharper than any of the other resonances in the spectrum.

In these structures the ^{1}H-n.m.r. bands at τ7.15 and τ7.46 are to be attributed to the cyclopropane protons. This part of the spectrum is one in which such (cyclopropane) resonances would not normally be expected to appear. In benzosemibullvalenes "abnormally" low field resonances are commonly encounted[11] for some of the cyclopropane protons which effect is to be attributed to a combination of rigid molecular geometry with the magnetic anisotropy of the aromatic ring.

In the ^{1}H-n.m.r. spectrum the dihydro-benzopentalenone (V-29) exhibited a sharp methyl singlet at τ8.33; a weakly coupled methyl doublet at τ7.85 ($J \simeq 1.5$ Hz); a complex three-proton multiplet centred at τ6.85 but spread over 0.6 ppm at 60 MHz; and a one proton multiplet at τ4.18.

The last signal is typical of the α-proton of an αβ-unsaturated ketone,

the methyl resonance at τ7.85 is consonant with that expected of the β-methyl group of an αβ-unsaturated ketone, and the magnitude of the coupling constant (J ≈ 1.5 Hz) is in the range characterising an allylic system. These data should be compared with those of the αβ-unsaturated ketone (V-25) which contains the same structural sub-unit. The sharp methyl resonance



τ 7.85 (d, J≈2Hz)

τ 4.61 (m)

τ 8.28 (s)

(V - 25)

(τ8.33) is nearly isochronous with sharp methyl resonances in the benzo-semibullvalenone (V-28) (τ8.31) and the αβ-unsaturated ketone (V-25) (τ8.28), suggesting that the immediate environments of all of these methyl groups are similar.

From the character of the three-proton multiplet centred at τ6.85 may very little be inferred with any certainty. The complexity suggests the presence of a fully coupled three-spin system of non-equivalent protons. A simple exercise in counting establishes that these protons are distributed between two carbon atoms, that is an in all probability connected methylene and methine grouping. ^{13}C-n.m.r.[10] confirms this.

Addition of Eu(dpm)$_3$[9] produces changes in the ^{1}H-n.m.r. spectrum of the benzodihydropentalenone (V-29) which bear a remarkable qualitative similarity to those produced in similar experiments with the benzosemibull-valenone (V-28): The methine and sharp methyl group resonances at τ4.18

and τ8.33 respectively were shifted at similar rates to lower field (6.13 ppm/mole/mole and 7.70 ppm/mole/mole respectively) whereas the methyl group and three-proton multiplet resonances at τ7.85 and τ ca. 6.85 respectively were shifted to lower field at a much smaller rate (1.93 ppm/mole/mole and ca. 2.76 ppm/mole/mole respectively) (fig. V-5).

The most significant difference between the results obtained with the benzosemibullvalenone (V-28) and the dihydrobenzopentalenone (V-29) is the overall larger magnitude of the shifts induced with the latter compound. This is in accord with the greater propensity to form complexes with Lewis acids (of which the shift reagent is an example) expected of αβ-unsaturated ketones relative to their saturated analogues. The observed difference is not due to a concentration effect. These results strongly indicate the presence of the structural units in fig. V-6. Recalling that the infrared

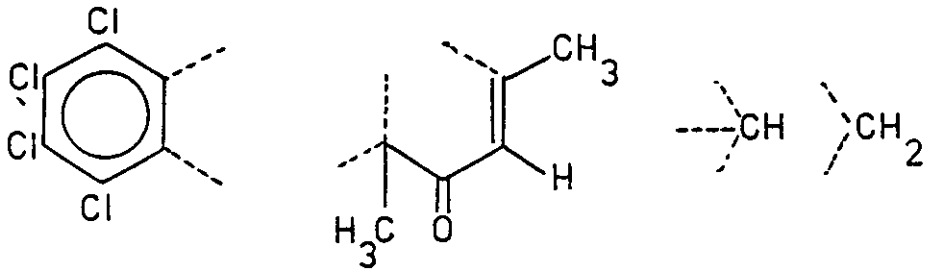


Fig. V-6

spectrum suggests that the αβ-unsaturated ketone is part of a five-membered ring, the two possible structures which follow from completing this ring with a methine group are shown in fig. V-7. This ring may not be reasonably completed by the methylene group.

Of the two structures A and B, the former is preferred, for it fits the ^{1}H-n.m.r. data in a way which would be surprising for structure B. The

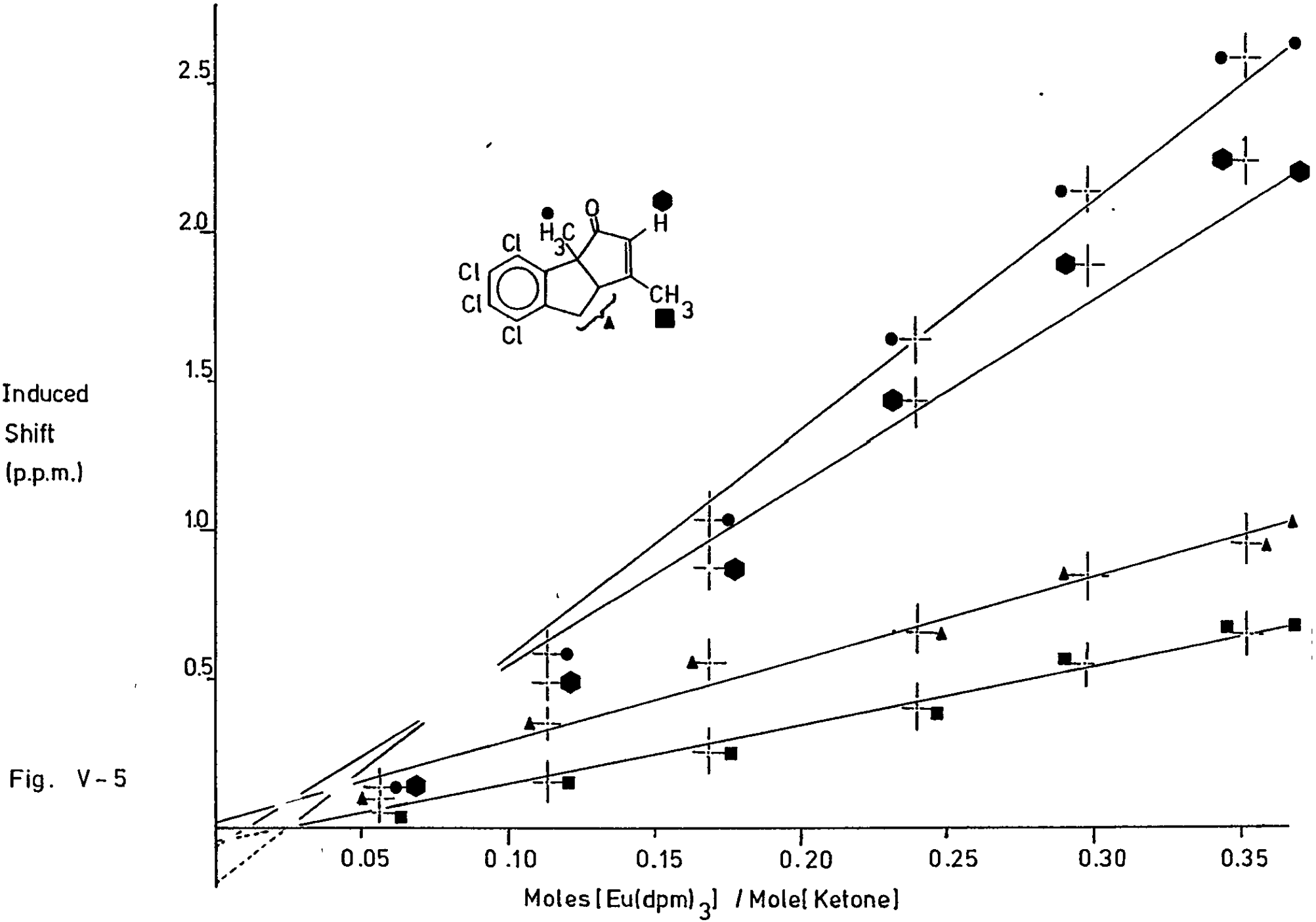
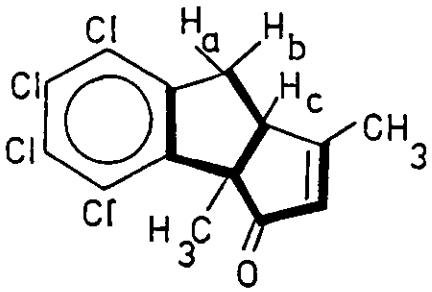
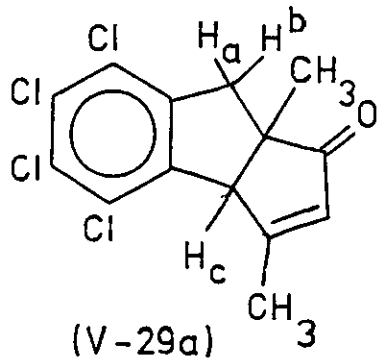

Induced
Shift
(p.p.m.)
2.5
2.0
1.5
1.0
0.5
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Moles [Eu(dpm)3] / Mole[Ketone]
O
H
H3C
Cl
Cl
Cl
CH3

Fig. V-5



(V-29)

A



(V-29a)

B

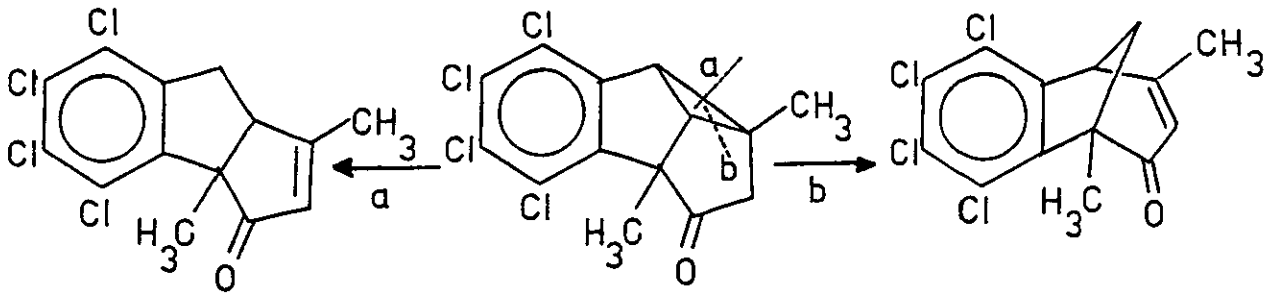
Fig. V-7

complexity of the multiplet at τ6.85 arises from the extensive coupling between protons a, b, and c, which would be expected in structure A, but not in structure B.

Further, the benzodihydropentalenone (V-29) is derived chemically from the benzosemibullvalenone (V-28) and more remotely from the benzobarrelenone (V-27). Structure A contains much of the connectivity present in both of these precursors, indicated by the heavy outline, in a way which structure B never could.

Inspection of the heavy outlines of the benzosemibullvalenone (V-28)A and the dihydrobenzopentalenone (V-29)A discloses that these structures are connected by a cyclopropylcarbinyl-homoallyl relationship. The benzosemibullvalenone (V-28)A is related in a similar way to another αβ-unsaturated ketone (V-25) involving an alternative cyclopropane ring opening (Scheme V-10). The formation of small amounts of the αβ-unsaturated ketone (V-25) in reactions producing the dihydrobenzopentalenone (V-29) is obviously significant in this context, although other pathways for the formation of this αβ-unsaturated ketone (V-25) are available.

The benzosemibullvalenone (V-28), the dihydrobenzopentalenone (V-29) and the αβ-unsaturated ketone (V-25) were reduced catalytically and the

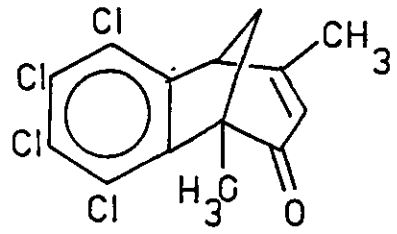


(V-29) (V-28) (V-25)

Scheme V-10

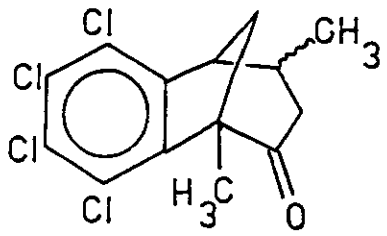
products were characterised by ^{1}H-n.m.r. spectroscopy and elemental analysis. Of principle interest were the changes produced in the carbonyl stretching frequencies by the reduction. The αβ-unsaturated ketone (V-25) gave the epimers (V-30) which were not separated. The carbonyl stretching frequency showed the anticipated change, rising from 1685 cm^{-1} to 1725 cm^{-1} on reduction (Scheme V-11).

The dihydro-benzopentalenone (V-29) was reduced to the epimers (V-31) which were not separated. The carbonyl stretching frequency showed the expected change, rising from 1710 cm^{-1} to 1750 cm^{-1} on reduction. In addition the band attributed to the carbon-carbon double bond stretching mode disappeared (Scheme V-12). This reduction was extremely slow. Models reveal that the hydrogen H_a on the endo-face of the folded bicyclo[3.3.0]-octadiene part of the molecule obstructs approach to the β-carbon of the αβ-unsaturated system, and that whereas approach to the exo-face is relatively unhindered, reduction from this face requires the β-methyl group to move towards the endo-hydrogen H_a generating severe steric compression in the reduction transition state (fig. V-8). Both of these factors are conventionally taken to retard the rate of reactions in which they occur. It was hoped that reduction of the benzosemibullvalenone (V-28) would give



(V-25)

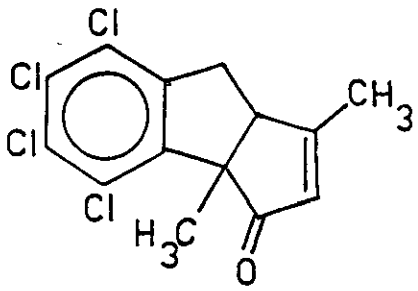
$\nu_{max.}$ 1685 and 1625 cm.$^{-1}$



(V-30)

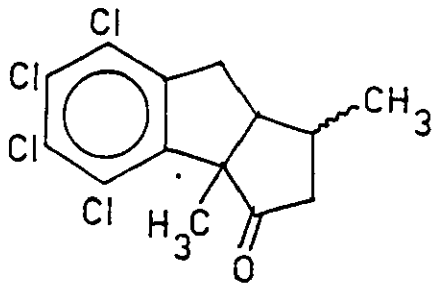
$\nu_{max.}$ 1725 cm.$^{-1}$

Scheme V-11



(V-29)

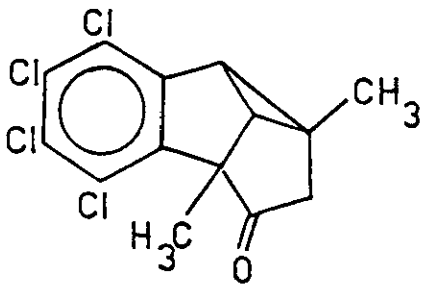
$\nu_{max.}$ 1710 and 1625 cm.$^{-1}$



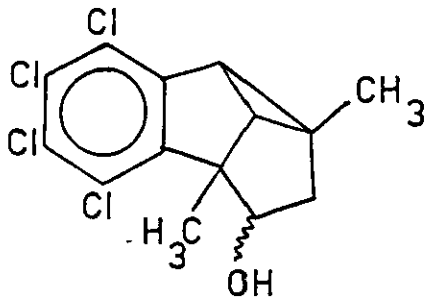
(V-31)

$\nu_{max.}$ 1750 cm.$^{-1}$

Scheme V-12



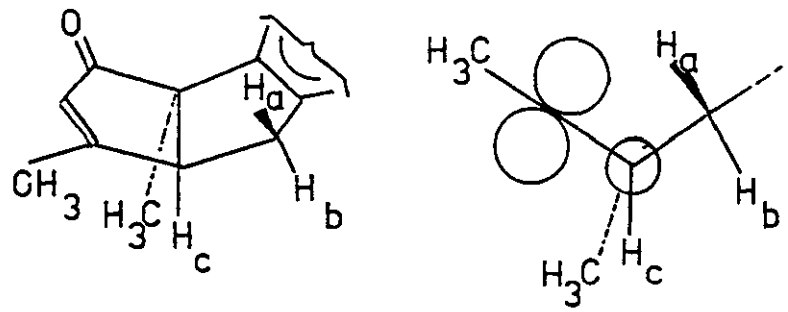
(V-28)



(V-31)

Scheme V-13

Fig. V-8



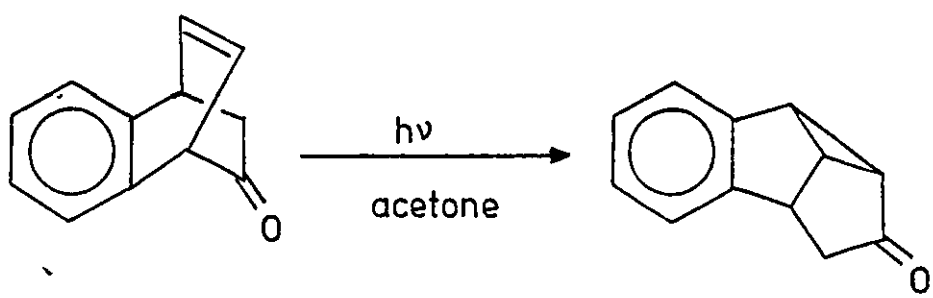
one epimer of either of the ketones (V-30) or (V-31), but the absorbtion of hydrogen by this cyclopropyl-ketone was negligible in the presence of palladised charcoal. The semibullvalenone (V-28) did absorb hydrogen slowly in the presence of platinum black, but the product did not arise from hydrogenolysis of the cyclopropyl ring; the product was an alcohol (V-31), in which the cyclopropyl ring remained intact (Scheme V-13).

These spectral data firmly establish the structures of the benzosemibullvalenone (V-28) and the dihydro-benzopentalenone (V-29). Nonetheless, the conversion of a benzobarrelenone into a benzosemibullvalenone is unusual and no example of this structural interconversion had previously been observed in the course of this and related investigations. The initial uncertainty over the structure of the ketone (V-28) made synthesis of this compound by some unambiguous route a desirable objective; it remains a challenging synthetic problem and valuable addition proof of structure.

The most usual synthesis of benzosemibullvalenes is by photoisomerisation of the appropriately substituted benzobarrelene, if so appropriate a precursor is to be found.[12]

Zimmerman,[12a] and Dauben[12b] have recently reviewed such reactions.

The photochemistry of βγ-unsaturated ketones is widely known, but poorly understood; mindful of the short half-life of a photochemical truth[13] it is prudent to abandon generality and seek guidance amongst the particular, and in particular amongst the work of Ipaktschi[14a] and of Givens and Oettle.[14b] Their work has shown that in these ring systems triplet sensitised photoisomerisation of benzobarrelenones and dihydro-benzobarrelenones proceeds with a [1,2]-acyl shift, the so-called oxa-di-π-methane rearrangement. The product of this rearrangement is a benzosemibullvalenone, but one in which the ketone function is mispositioned for the successful synthesis of ketone (V-28) (Scheme V-14). No trace is observed of the alternative and desired product of [1,2]-aryl shift, the so-called di-π-methane rearrangement.



(V-33) (V-34)

Scheme V-14

Direct photolysis of benzobarrelenone leads to [1,3]-acyl shift and ultimately by expulsion of ketene to naphthalene,[12a] for which other syntheses are available. Again, no di-π-rearrangement is observed: the presence of the carbonyl group provides the molecule with modes of reaction other than that required, and no photolysis of a benzobarrelenone is likely to be a useful synthetic route to ketone (V-28).

In contrast, the di-π-methane rearrangement occurs smoothly in barrel-

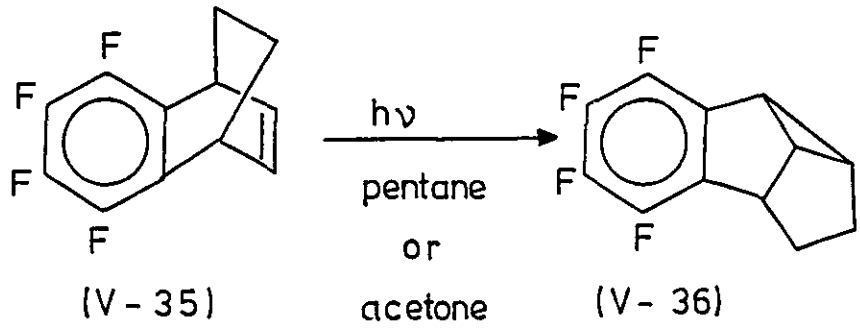
enes and their naphtho- and mono-, di, and tri-benzologues.[12a] Some confusion exists as to the multiplicity of the reaction, for whereas acyclic dienes rearrange most efficiently from a singlet state, those constrained by bicyclic systems are generally most easily rearranged by irradiation in the presence of a triplet sensitiser.

This may be no property of the reaction itself, but a reflection of the changing availability of alternative reaction pathways. Acyclic dienes may dissipate energy from triplet excited states by rapid cis-trans isomerisation, a process often masked by degeneracy. This pathway is not usually available to bicyclic βγ-dienes. Conversely, βγ-dienes in bicyclic systems are often constrained to a geometry which favours intramolecular [2+2] cycloaddition. Such [2+2] cycloadditions may be formulated as [π2s + π2s] pericyclic reactions.[15] That triplet states do not undergo this type of reaction so readily is probably attributable to their rapid relaxation from a geometry in which the π (and π*) orbital lobes are coplanar to one in which the bond is twisted towards a dihedral angle of 90°,[16] thus favouring bonding at one bond terminus rather than concerted formation of bonds at both termini.

There are some dienes, including 2,3-dihydro-tetrafluorobenzobarrelene (V-35) which rearrange smoothly either on direct or on triplet sensitised irradiation (Scheme V-15) and it seems probable that the di-π-methane rearrangement will proceed from either a singlet or a triplet excited state providing that no energetically easier alternatives are available.

Those rearrangements of benzobarrelenes that give benzosemibullvalenes generally employ triplet sensitisation, and such use will be implicit in the subsequent discussion.

Little is known about the influence of substitution patterns on the regiospecificity of the di-π-methane rearrangement of benzobarrelenes, much



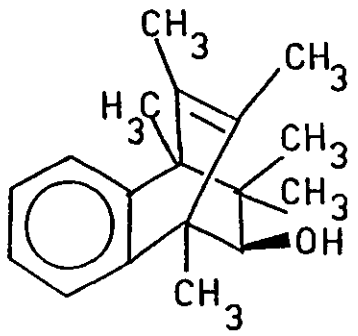
(V-35) (V-36)

Scheme V-15

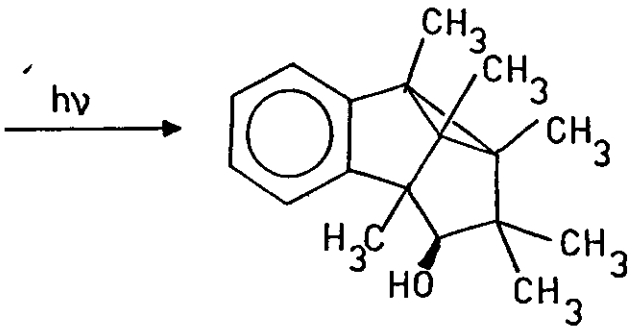
less about such effects in the photolysis of dihydro-benzobarrelenes, but by a rare chance the results of the photolysis of the epimeric 5,6-dihydro-6-hydroxy-1,2,3,4,5,5-hexamethylbenzobarrelenes [(V-37) and (V-38)] are both available and instructive (Scheme V-16).[17] Whereas the exo- (or anti-) alcohol (V-37) produced a mixture of exo- alcohols (V-39) and (V-40) in which the isomer containing the desired functionalised position predominated, the endo- (or syn-) alcohol (V-38) produced only the endo-alcohol (V-41). A similar selectivity was shown by the corresponding acetates. Hart and Murray attribute this effect to the stabilising effect of the endo- C-O bond on a proposed diradical intermediate (V-43) (Scheme V-17).

The rearrangement directing feature of the molecule is probably the σ^*_{C-O} orbital: when the triplet excited state of the olefin twists away from co-planarity, electron density at one end of the bond is twisted into the space occupied by the σ^*_{CO}, and electron density at the other end of the bond is twisted towards the aromatic ring. By stabilising the radical at one end of the whilom olefin the antibonding orbital controls the twisting of the excited state and promotes bonding at the remote end.

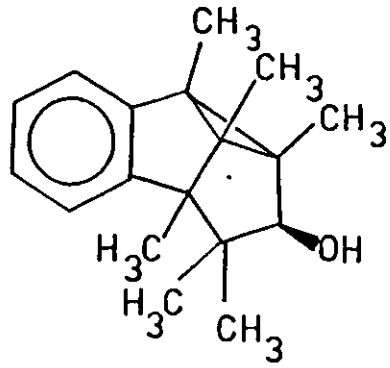
Whatever the factors responsible for the directing effect, they pro-



(V - 37)

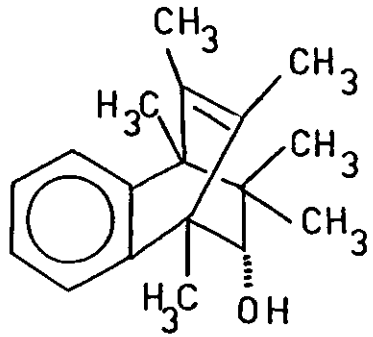


(V - 39)

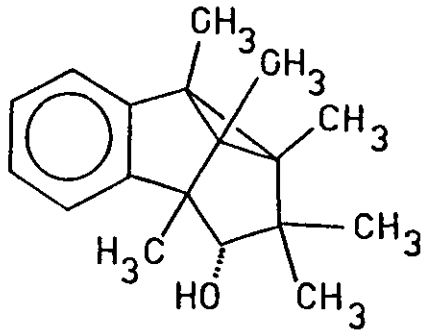


(V - 40)

3 : 2

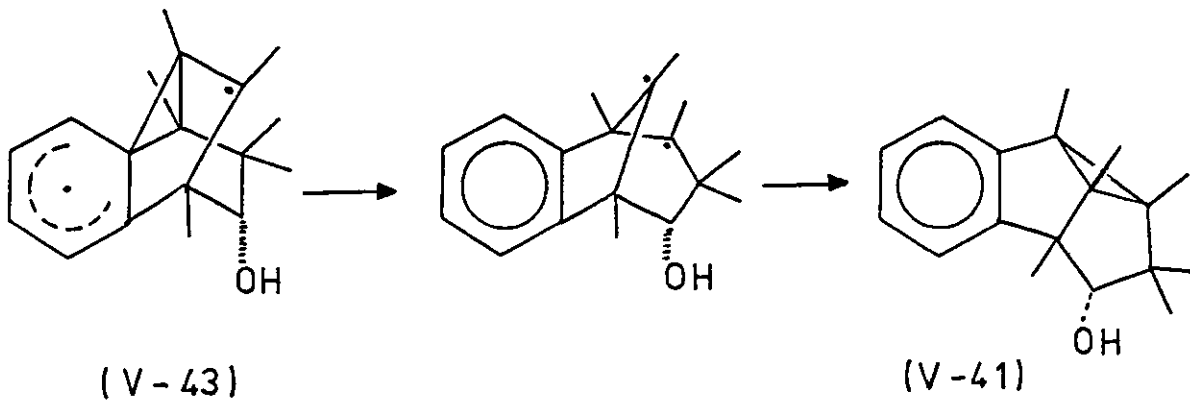


(V - 38)



(V - 41)

Scheme V - 16

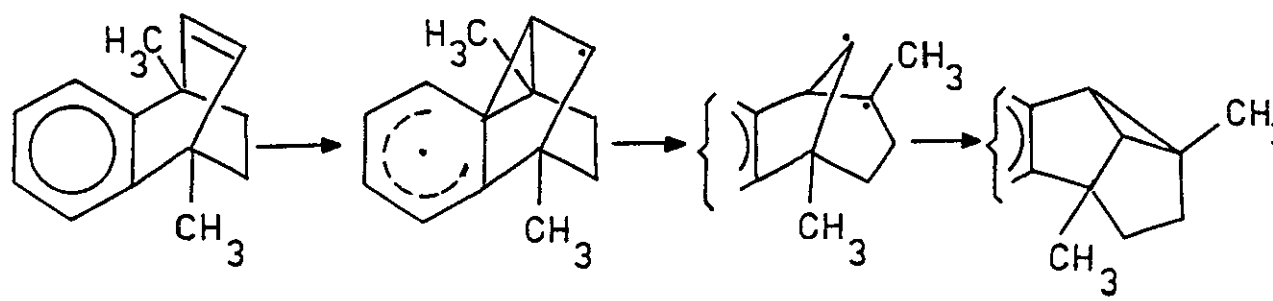


(V-43) (V-41)

Scheme V-17

vide a method of synthesising benzosemibullvalenes with correctly placed functionality; photolysis of a 2,3-dihydro-2-endo-hydroxy-benzobarrelene should provide a suitable approach to the synthesis of the benzosemibullvalenone (V-28).

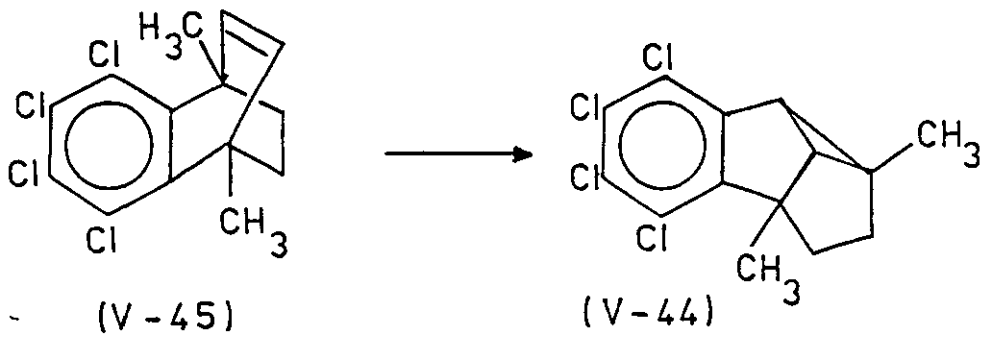
Consideration of the diradical mechanistic algorithm proposed by Zimmerman[12a] to predict the course of the rearrangement suggests that the correct methyl substitution pattern would be obtained by photolysis of a 1,4-dimethyl-2,3-dihydrobenzobarrelene (Scheme V-18).



Scheme V-18

Two approaches to the synthesis of the benzosemibullvalenone (V-28) or of some closely related compound were explored, both of which involved

photoisomerisation of derivatives of 1,4-dimethyl-tetrachlorobenzobarrelenone (V-27). In the first, less ambitious approach, an attempt was made to synthesise the dihydrosemibullvalene (V-44) by photoisomerisation of 2,3-dihydro-1,4-dimethyl-tetrachlorobenzobarrelene (V-45) (Scheme V-19). In this approach, the symmetry of the dihydro-benzobarrelene (V-15) is such that only one dihydrosemibullvalene would be produced; the problem of directing the rearrangement does not apply in this case.

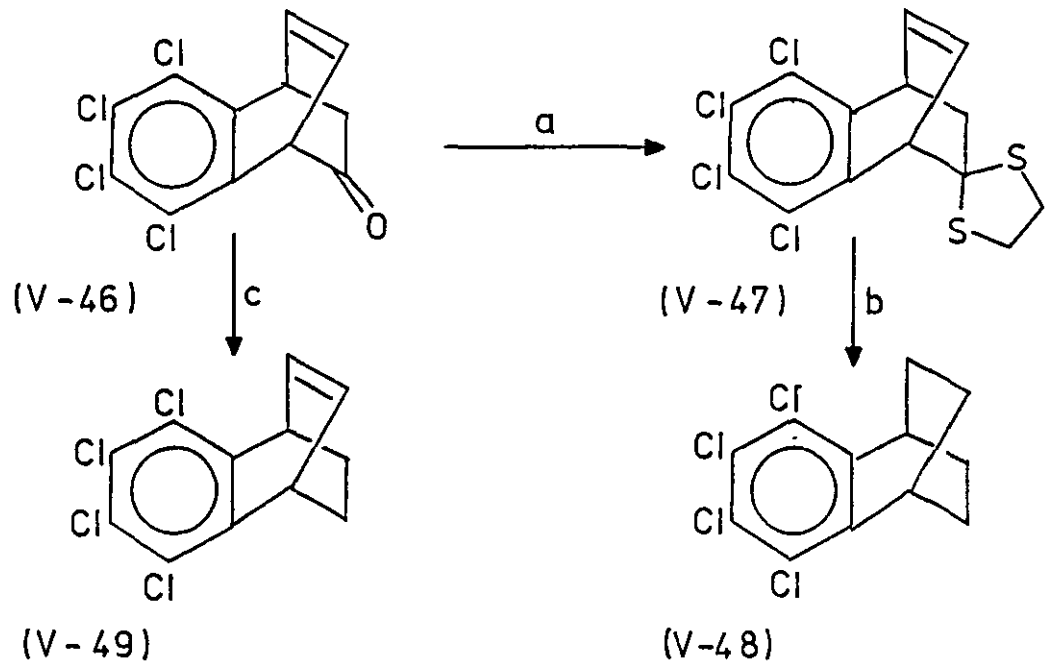


(V-45) (V-44)

Scheme V-19

Trial experiments with tetrachlorobenzobarrelenone (V-46) were carried out to establish a satisfactory method for converting the carbonyl function into a methylene group. Treatment of tetrachlorobenzobarrelenone with ethane-1,2-dithiol and boron trifluoride etherate[18] gave the dithioacetal (V-47) in excellent yield. Desulphurisation of this dithioacetal (V-47) with Raney nickel also caused reduction of the double bond. This over-reduction to give (V-48) persisted even with Raney nickel deactivated by boiling acetone. Another method of reduction was tried: extended Clemmensen reduction[19] using a three-phase system of amalgamated zinc, aqueous hydrochloric acid, and toluene converted tetrachlorobenzobarrelenone (V-46) to 2,3-dihydro-tetrachlorobenzobarrelene (V-49) (Scheme V-20).

When this reaction was applied to 1,4-dimethyl-tetrachlorobenzobarrel-

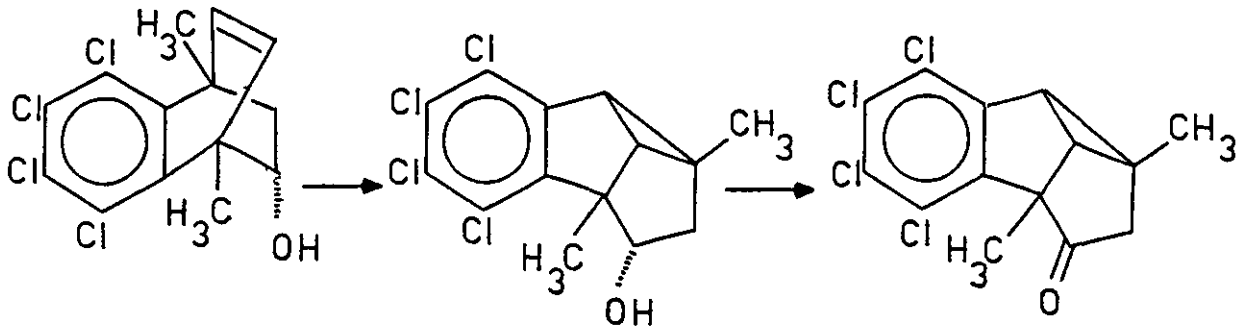


Scheme V - 20

Reagents: a) $HSCH_2CH_2SH$, $BF_3O(CH_2CH_3)_2$;
b) Raney nickel; c) Zn/Hg, HCl, toluene.

enone (V-27) no reaction was observed, although the amount of recovered ketone gradually diminished. The ketone (V-27) is highly hindered, and this disappointing result is not altogether surprising. As the amount of this ketone (V-27) available was strictly limited, attempts to prepare dihydrobenzobarreles suitable for photoisomerisation to analogues of the benzosemibullvalenone (V-28) were abandoned in favour of a more direct synthesis: The photoisomerisation of an oxygenated dihydrobenzobarrelene was reconsidered.

The work of Hart and Murray[17] has indicated that photoisomerisation of 2,3-dihydro-2-hydroxy-1,4-dimethyl-tetrachlorobenzobarrelene (V-50) followed by oxidation of the alcohol (V-51) should give the required benzosemibullvalenone (V-28) (Scheme V-21). Isolation of the pure alcohol (V-50) would give rise to several practical difficulties. Firstly, the



(V - 50) (V - 51) (V - 28)

Scheme V - 21

A Possible Synthetic Approach to Ketone (V-28).

precursory benzobarrelenone (V-27) is isolated in pure form only with difficulty. This problem is likely to attend all photochemical approaches to this synthesis. Secondly, the reduction of this ketone (V-27) produces not only the desired alcohol (V-50) but also its epimer and is a wasteful synthesis in terms of the limiting resource, the ketone (V-27). The unwanted epimer may be oxidised and re-reduced to increase the overall yield but then the third difficulty, the problems often experienced in separating the epimeric alcohols, acquires even greater significance.

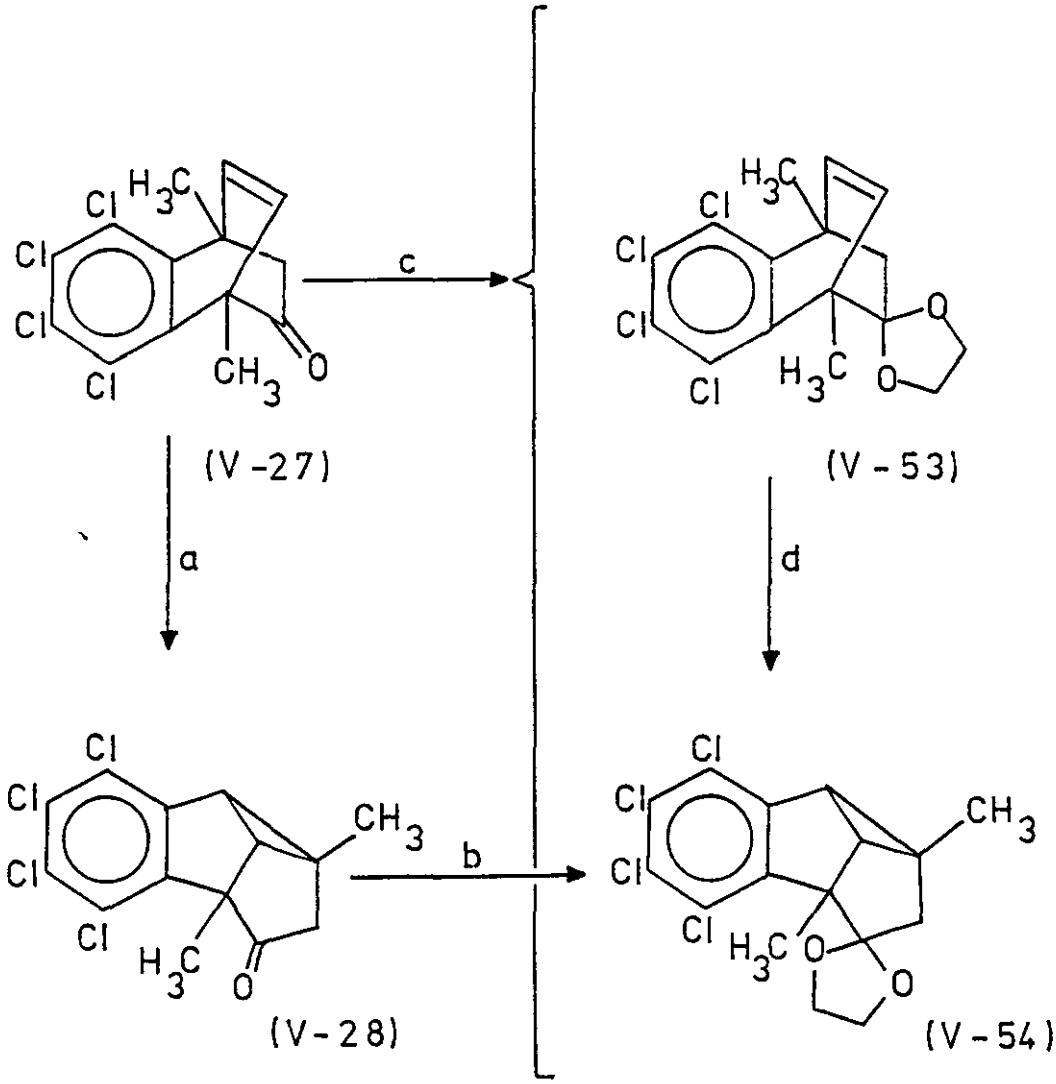
Both of the last two difficulties are removed by converting the carbonyl group of (V-27) into another symmetrical function. The introduction of an endo-C-O bond is a prerequisite of the photoisomerisation step; the need to introduce an exo-C-O bond follows from the symmetry requirement. The hydrate of the ketone (V-27) fulfills these conditions, being at once both the exo- and the endo- alcohol, but from a practical point of view it is easier to isolate and manipulate ketone hydrates as their ethers. The

ethylenedioxy function is one which is readily introduced, is not photolabile, and which possesses the local symmetry required. The group does not mask the region of interest in the ^{1}H-n.m.r. spectrum. This is of particular importance as the ^{1}H-n.m.r. spectrum is the most useful single method of characterising this type of compound; a gem-dimethoxy group would be of even greater use in ^{1}H-n.m.r. studies of the reaction products, but the extra stability of cyclic acetals favours the ethylenedioxy group.

It has been previously reported that benzobarrelenones do not readily form acetals.[20] Whilst adventitious acetal formation is never likely to be a hazard of benzobarrelenone chemistry, the introduction of the group is not difficult. Treatment of tetrachlorobenzobarrelenone (V-46) with ethylene glycol and p-toluene sulphonic acid in boiling di-n-butyl ether with provision for removal of water from the condensate gave 2,2-ethylenedioxy-2,3-dihydro-tetrachlorobenzobarrelene (V-52) in fair yield.

Preparation of the ethylene acetal (V-53) of 1,4-dimethyl-tetrachlorobenzobarrelenone (V-27) was attended with an amusing complication. One of the reasons for this approach to the synthesis of the ketone (V-28) was to economise on the amount of 1,4-dimethyl-tetrachlorobenzobarrelenone (V-27) required; the formation of by-products was to be reduced by careful planning. Nonetheless only a moderate yield of 2,2-ethylenedioxy-2,3-dihydro-1,4-dimethyl-tetrachlorobenzobarrelene (V-53) was obtained, and for all the careful planning an additional product was isolated. Now while we labour on as elegantly as we may, nature moves serenely and imperturbably forwards: with a perversity bordering on dumb insolence the by-product was revealed to be the ethylene acetal (V-54) of the benzosemibullvalenone (V-28). This acetal (V-54) could arise by rearrangement of the benzobarrelenone (V-27) followed by acetal formation, or by rearrangement of the acetal (V-53).

Photoisomerisation of the benzobarrelenone acetal (V-53) gave the benzosemibullvalenone acetal (V-54). The same acetal was formed by treating the benzosemibullvalenone (V-28) with ethylene glycol and boron trifluoride etherate in dichloromethane. When the physical properties (m.p., mixed m.p., and spectroscopic data) of the acetals (V-54) prepared by the different methods were compared, they were found to be identical. The synthesis of the benzosemibullvalenone (V-28) as its ethylene acetal confirms the structure assigned on the basis of spectral data (Scheme V-22).



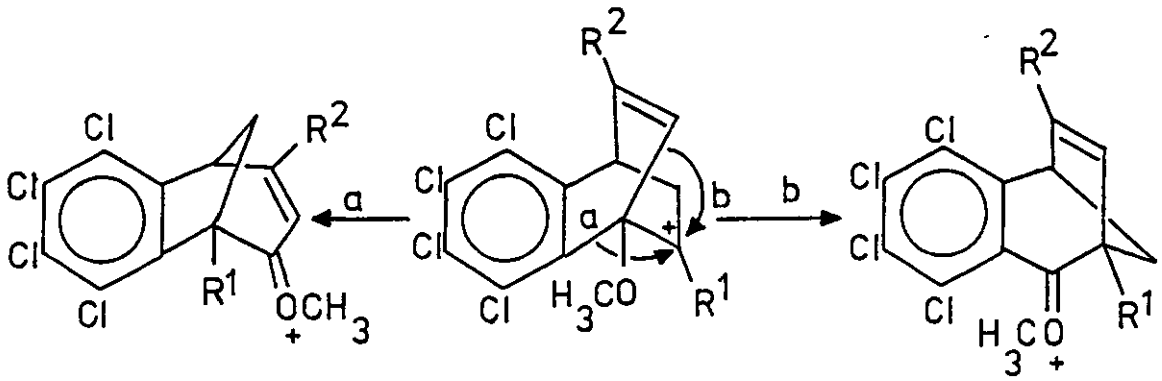
Scheme V-22

Reagents: a) FSO_3H 1 min., -40°; b) $HOCH_2CH_2OH$, $BF_3.O(CH_2CH_3)_2$ cat. p-$C_6H_4SO_3H$, $HOCH_2CH_2OH$. d) hν, acetone.

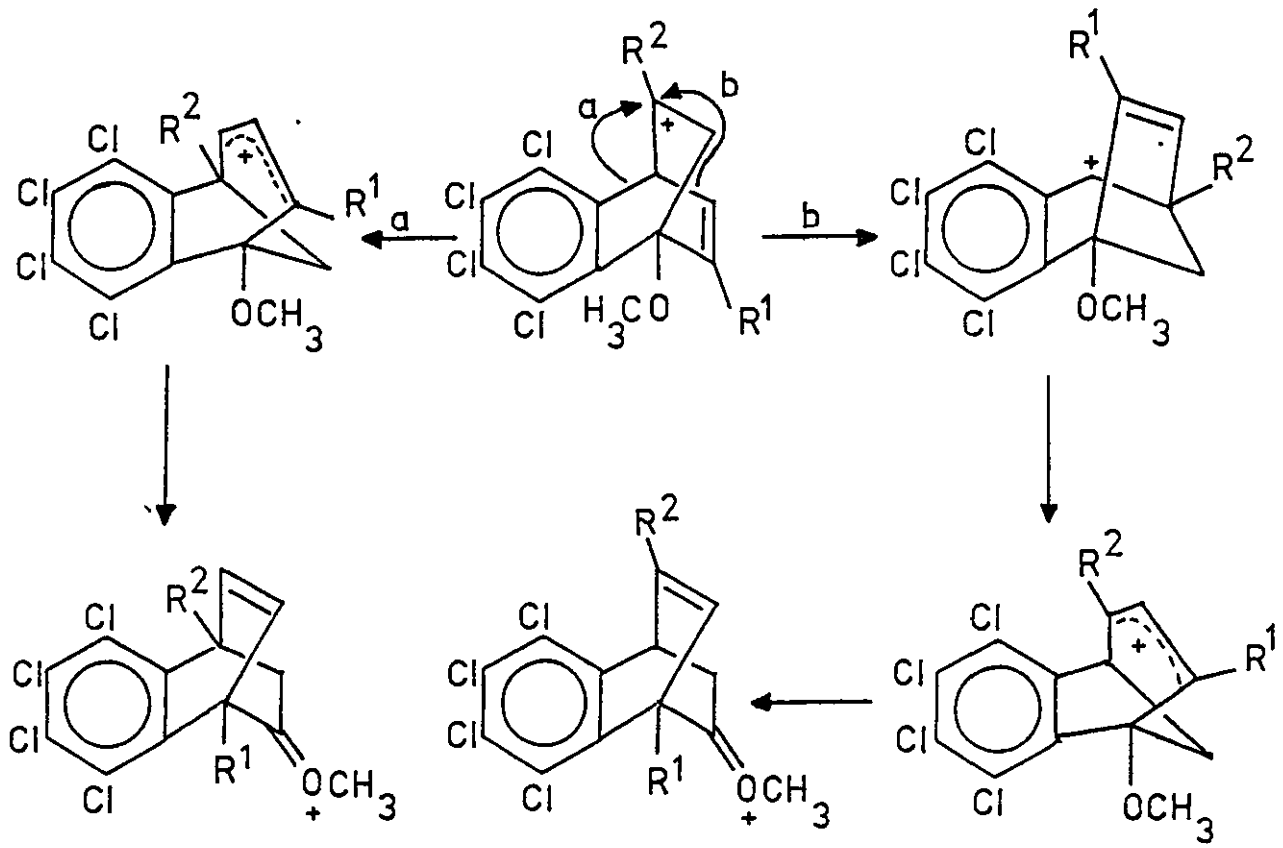
Primary Rearrangements

It is possible to discuss the rearrangements described in this chapter in terms of series of unrelated [1,2]-alkyl, -alkenyl, and -aryl shifts which proceed until the positive charge falls adjacent to the methoxy-group, which freezes the rearrangement at that (those) point(s). The problem with this approach is that the rearrangement steps are introduced *ad hoc* to account for the products observed. The use of this approach for predicting products of untried rearrangements is limited. However, in chemistry as in politics, excuses are every bit as acceptable as reasons, and this empirical approach has the apparent success reserved for *post facto* reasoning.

The majority of products from 2-methyl-1-methoxytetrachlorobenzobarrelene (V-16) arise from rearrangement to a 2-carbocation. The anticipated reaction was protonation at C-3 followed by competitive aryl- and alkenyl-migrations to C-2 (Scheme V-23, $R^1 = CH_3$, $R^2 = H$), and the products predicted by this scheme are found. The formation of small amounts of 1-methyltetrachlorobenzobarrelenone (V-21) in trifluoroacetic acid is more difficult to explain and was unexpected. Protonation at C-6 of the less substituted double bond to give a C-5 cation stabilised by homoallylic participation of the substituted bridge would lead ultimately to the observed minor product, 1-methyltetrachlorobenzobarrelenone (V-21) (Scheme V-24, $R^1 = CH_3$, $R^2 = H$). The increase in the amount of the benzobarrelenone (V-21) formed as the reaction mixture is changed from trifluoroacetic to concentrated sulphuric acid suggests that O-protonation is an important factor in destabilising 2- relative to 3-carbocations. It is not possible to assess the relative importance of the pathways (a)



Scheme V - 23



Scheme V - 24

and (b) using unlabelled 2-methyl-1-methoxytetrachlorobenzobarrelene (V-16).

The rearrangement of 3-methyl-1-methoxytetrachlorobenzobarrelene (V-17) does offer this possibility. In sharp contrast to the results observed with deuteriated 1-methoxytetrafluorobenzobarrelenes[1a,d] no evidence was observed for the operation of the two pathways shown in Scheme V-24 (R^1 = H, R^2 = CH_3). The only product observed in the trifluoroacetic- or sulphuric-acid catalysed rearrangements of 3-methyl-1-methoxytetrachlorobenzobarrelene (V-17) was 4-methyltetrachlorobenzobarrelenone (V-22), corresponding to path (a) but not (b) (Scheme V-24, R^1 = H, R^2 = CH_3). The product from path (b), 5-methyltetrachlorobenzobarrelenone (V-23) was not observed even though an authentic sample of this ketone (V-23) was available for comparison.

The two possible reaction modes are illustrated within one molecule for 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (V-18). Protonation at C-3 followed by rearrangement to C-2 would give the aryl- and αβ-unsaturated ketones [(V-24) and (V-25)] (Scheme V-23, R^1 = R^2 = CH_3) and protonation at C-6 followed by rearrangement to C-5 would lead to the two benzobarrelenones [(V-26) and (V-27)] (Scheme V-24, R^1 = R^2 = CH_3). These are the products observed after rearrangement of 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (V-18) in trifluoroacetic acid. These results indicate that rearrangement to a 2- rather than a 3-carbocation is favoured.

The rearrangements of 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (V-18) in strong acids implicate 1,4-dimethyltetrachlorobenzobarrelenone (V-27) as the important intermediate, again indicating that rearrangement to a 3-carbocation is much more important than rearrangement to a 2-carbocation in strong acids.

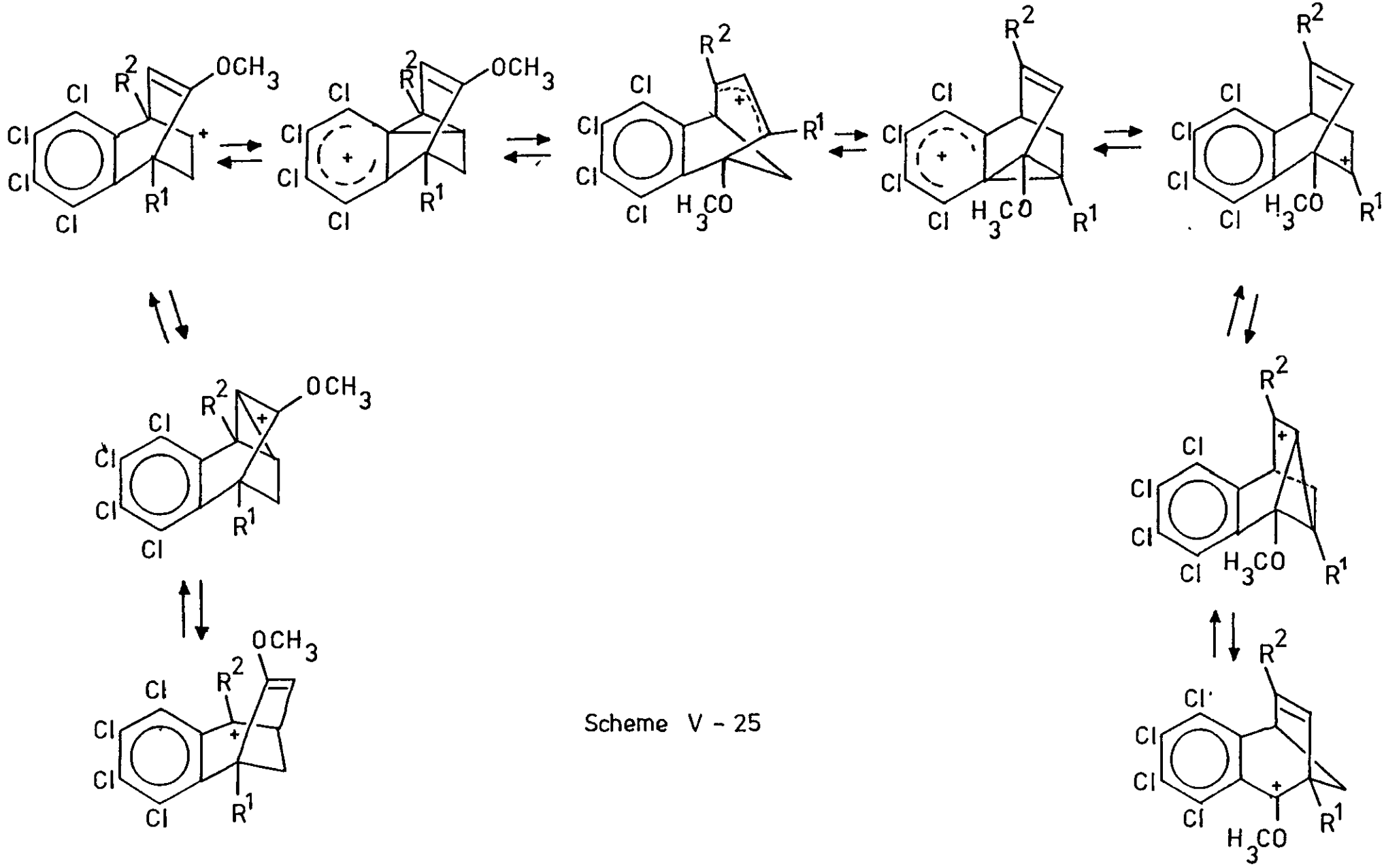
Hart[23] and Cristol[24] have shown that the circumambulation process is of lower energy than processes involving [1,2]-bridge shifts in bicyclo-[3.2.1]octadienyl cations (see chapter one); products arising from the circumambulating set of intermediates formed by the initial protonation should be relatively more common than those products which require a [1,2]-bridge shift before their formation.

Application of the circumambulation mechanism to these three rearrangements is instructive. The circumambulating set of intermediates (Scheme V-25, $R^1 = CH_3$, $R^2 = H$) correctly predicts both major products [(V-19) and (V-20)] of the rearrangement of 2-methyl-tetrachlorobenzobarrelene (V-16) in trifluoroacetic acid and indicates that if the intermediates of the set are sufficiently long lived, a benzobarrelenone should also be formed. The benzobarrelenone predicted to arise from 2-methyl-1-methoxytetrachlorobenzobarrelene (V-16) is 1-methyltetrachlorobenzobarrelenone (V-21) and this is the benzobarrelenone observed; whether or not this ketone (V-21) actually forms from the circumambulating set of intermediates of Scheme V-25 ($R^1 = CH_3$, $R^2 = H$) is another question.

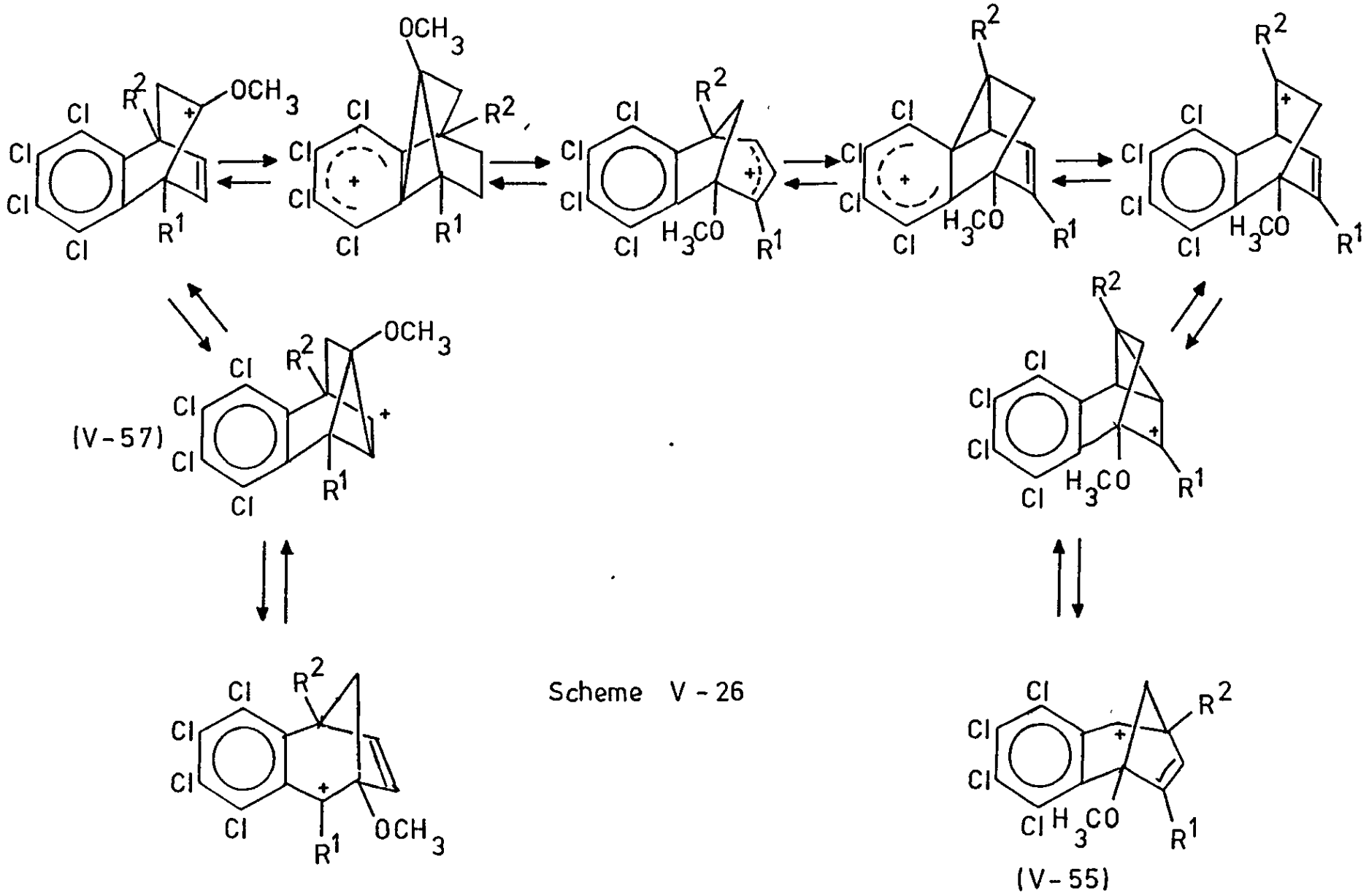
An alternative pathway by which 1-methyltetrachlorobenzobarrelenone (V-21) may be formed is by circumambulation from the C-5 carbocation produced by protonation of the 2-methylbenzobarrelene (V-16) at C-6 (Scheme V-26, $R^1 = CH_3$, $R^2 = H$).

Similarly, Scheme V-26 ($R^1 = H$, $R^2 = CH_3$) predicts that rearrangement of 3-methyl-1-methoxytetrachlorobenzobarrelene (V-17) should give 4-methyltetrachlorobenzobarrelenone (V-22) and this is the observed product. 5-Methyltetrachlorobenzobarrelenone (V-23) is not predicted to occur by the lowest energy process, but would have to be formed after a [1,2]-bridge shift from ion (V-55, $R^1 = H$, $R^2 = CH_3$).

A [1,2]-bridge shift from ion (V-55, $R^1 = R^2 = CH_3$) is required to



Scheme V - 25



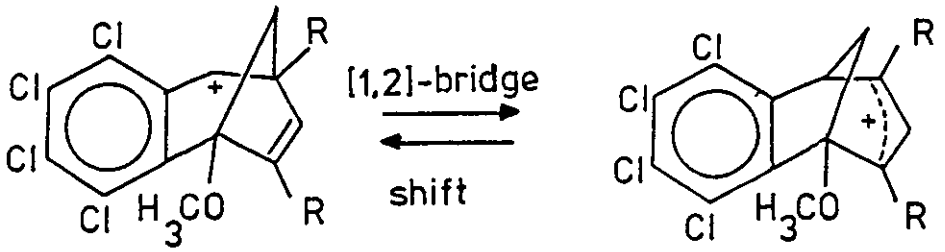
(V-57)

(V-55)

Scheme V - 26

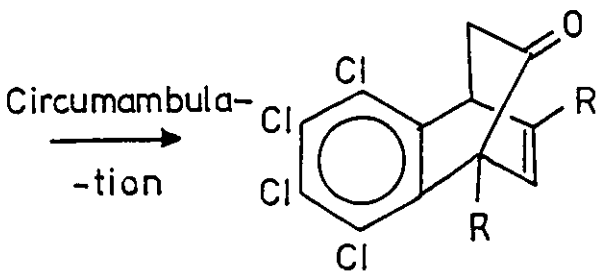
account for the formation of 1,5-dimethyltetrachlorobenzobarrelenone (V-26) alongside the "expected" benzobarrelenone, 1,4-dimethyltetrachlorobenzobarrelenone (V-27, $R^1 = R^2 = CH_3$). The factors which make [1,2]-bridge shift competitive with circumambulation in this case are probably the greater ease of formation of the ion (V-55, $R^1 = R^2 = CH_3$) relative to the ion (V-55, $R^1 = H$, $R^2 = CH_3$) and the greater stability of the ion (V-56, $R^1 = R^2 = CH_3$) relative to the ion (V-56, $R^1 = H$, $R^2 = CH_3$) formed by the [1,2]-bridge shift (Scheme V-27). Both of these effects are due to the introduction of the extra methyl-group. The circumambulation pathway shown in Scheme V-25 ($R^1 = R^2 = CH_3$) predicts formation of the major products of trifluoroacetic acid-catalysed rearrangement of 2,5-dimethyl-1-methoxytetrachlorobenzobarrelene (V-18), which are the αβ-unsaturated- and aryl-ketones [(V-25) and (V-24)].

The explanations advanced in the first part of this conclusion are similar in detail to sections of the circumambulation mechanism. It is proposed that Hart's concepts[23] of low energy circumambulation and relatively difficult [1,2]-bridge shift provide a basis for understanding the products formed in the acid-catalysed rearrangements of benzobarrelenes and related compounds. The relative importance of each of the intermediates must be assessed according to the ease with which it is interconverted with the adjacent intermediates and the stability of the product which is formed from any given intermediate. The first of these influences will take on additional importance in cases where equilibration of all of the intermediates does not occur. The natures of the aromatic- and olefinic-substituents, and the degree of protonation of oxygen functions are clearly important factors to be taken into account in the assessment of the relative importance of each intermediate.

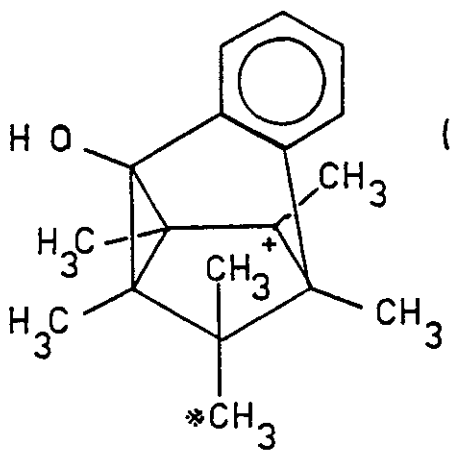


(V - 55)

(V - 56)



Scheme V - 27



(V - 58)

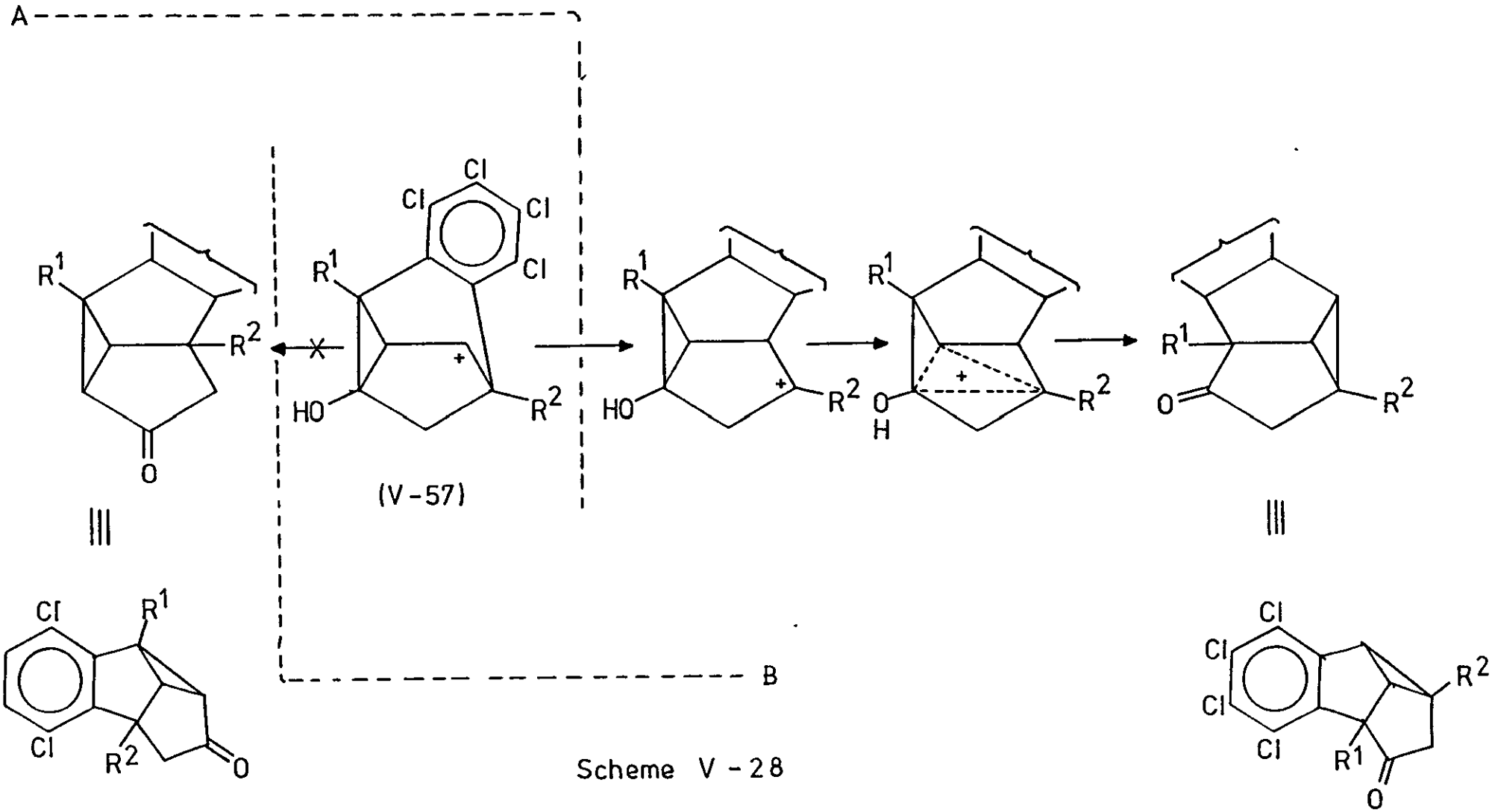
Secondary Rearrangements

These present an interesting problem. When the rearrangement of 1,4-dimethyltetrachlorobenzobarrelenone (V-27) is conducted in [$^2H_2$]-sulphuric acid, the only significant incorporation of deuterium (as judged by ^{1}H-n.m.r.) was in the 5-methyl-group (i.e. adjacent to the carbonyl-group) of the benzosemibullvalenone (V-28). This strongly suggests that 1,4-dimethyltetrachlorobenzobarrelenone (V-27) is protonated on the carbonyl-group to give an intermediate which fits into the circumambulating set illustrated in Scheme V-26 ($R^1 = R^2 = CH_3$, "OCH_3" = OH). Only the protons of the methyl-group R^1 would be expected to undergo ^1H - ^2H exchange.

The next step is the crucial one: a [1,3] shift (see chapter one) is required to form the product carbon-skeleton, but such a rearrangement of an ion of Scheme V-26 [particularly, of ion (V-57, $R^1 = R^2 = CH_3$)] produces the wrong substitution pattern (Scheme V-28, $R^1 = R^2 = CH_3$, section A).

In a similar situation, Hart has observed[25] a five-fold degenerate rearrangement of the ion (V-58) and suggested that the steps in the rearrangement are [1,3]-shift of a cyclopropyl-bond, [1,2]-shift of the methyl-group (*), and [1,2]-aryl-shift (cf. Scheme I-35). Hart suggests that rapid [1,3]-shift is the initial step.

In the present case, the hydroxy-group of the ion (V-57, $R^1 = R^2 = CH_3$) might be expected to accelerate this [1,3]-shift. However, the acidity of the reaction mixture required to initiate this rearrangement of 1,4-dimethyltetrachlorobenzobarrelenone (V-27) is much greater than that used by Hart, so that the oxygen function of the ion (V-57, $R^1 = R^2 = CH_3$) is probably diprotonated for much of the rearrangement. The positive charge carried by the oxygen will inhibit the rearrangement shown in Scheme V-28



Scheme V - 28

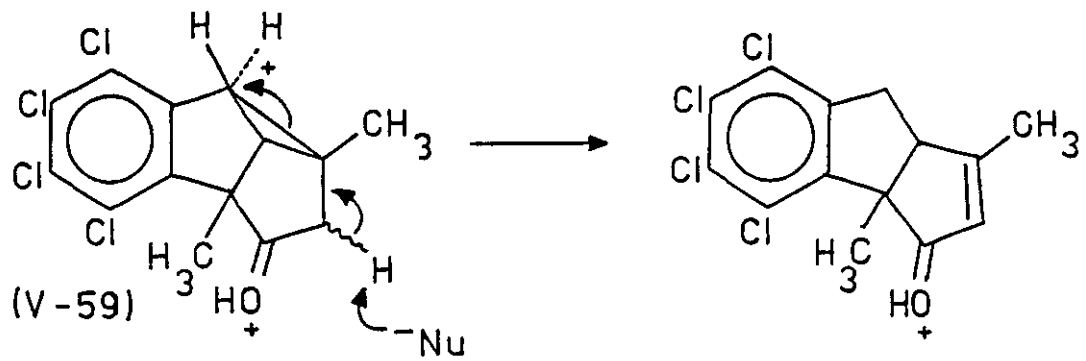
($R^1 = R^2 = CH_3$, section A), and thus prevent the rearrangement from proceeding in the "forward direction".

It is unimportant to an ion (V-58) which is undergoing the five-fold degenerate rearrangement whether or not the reaction proceeds in the "forward-" or "reverse-direction" - the ion does not know whether it is coming or going - and it is just as probable that the first step in the system studied by Hart is a [1,2]-aryl migration rather than a [1,3]-cyclopropyl shift.

In the present case a [1,2]-aryl shift generates a tertiary- from a secondary-carbocation, and a bishomocyclopropenium ion from a cyclopropylcarbinyl cation. The bishomocyclopropenium ion can collapse directly to the observed product, (Scheme V-28, $R^1 = R^2 = CH_3$, section B).

The subsequent rearrangement of this benzosemibullvalenone (V-28) into the dihydrobenzopentalenone (V-29) is less complicated. The reaction proceeds best in the presence of a little water, which probably acts as a nucleophile. The mechanism suggested is the nucleophile induced ring-opening of the corner-protonated cyclopropane (V-59) (Scheme V-29, $R^1 = R^2 = CH_3$).

A similar mechanism accounts for the isolation as a by-product of traces of the αβ-unsaturated ketone (V-25) from this reaction.

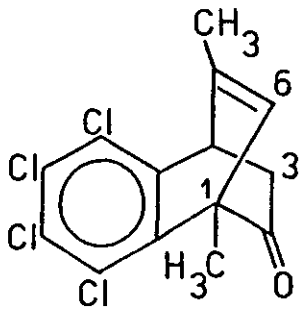
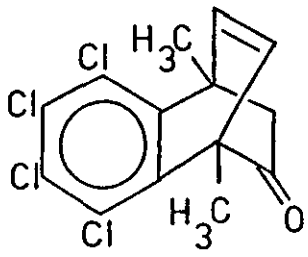
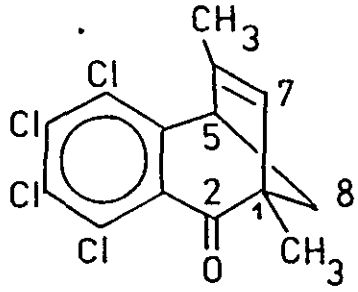


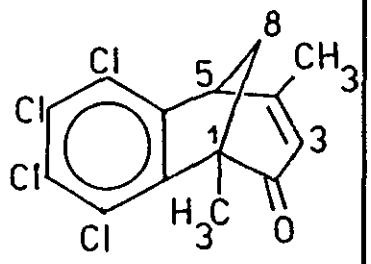
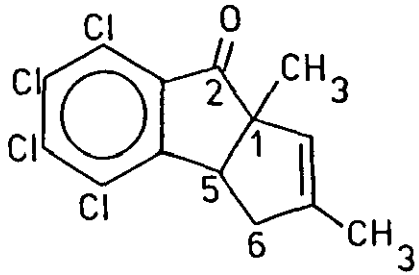
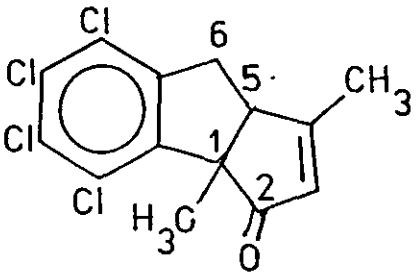
Scheme V - 29

EXPERIMENTAL SECTION

General Procedures

The general procedures are as described in previous chapters.

Compound	Carbon Atom (Multiplicity in Off-Resonance Experiments), Chemical Shift/ppm Downfield from TMS, Relative Intensity							
 (V-26)	C-1(s) 59.82 205	C-2(s) 204.42 129	C-3(t) 34.56 994	C-4(d) 43.74 789	C-5(s) 146.65 207	C-6(d) 130.75 1000	Methyls at C-1(q), C-5(q) 17.89 / 977 and 19.53 / 974	
 (V-27)	C-1(s) 60.75 52	C-2(s) 204.42 35	C-3(t) 44.61 252	C-4(s) 46.25 61	C-5(d) and C-6(d) 142.97 / 263 and 138.58 / 261		Methyls at C-1(q), C-4(q) 19.18 / 192 and 25.38 / 196	
 (V-24)	C-1(s) 58.59 102	C-2(s) 192.96 37	Methyls at C-1(q), C-6(q) 16.08 / 421 and 18.19 / 498		C-5(d) 49.47 520	C-6(s) 153.44 108	C-7(d) 130.22 496	C-8(t) 51.22 553

 (V-25)	C-1(s) 60.87 377	C-2(s) 195.30 206	C-3(d) 120.46 1000	C-4(s) 165.77 304	C-5(d) 47.48 922	Methyls at C-1(q), C-4(q) 18.13 881 and 23.62 843		C-8(t) 55.08 984
 (V-60)	C-1(s) 65.32 215	C-2(s) 202.90 37	Methyls at C-1(q), C-7(q) 16.37 527 and 21.11 671		C-5(d) 48.83 620	C-6(t) 41.57 721	C-7(s) 154.25[b] 101	C-8(d) 127.06 655
 (V-29)	C-1(s) 64.38 133	C-2(s) 205.30 71	C-3(d) 128.70 550	C-4(s) 174.43 110	C-5(d) 56.37 519	C-6(t) 34.03 471	Methyls at C-1(q), C-4(q) 17.43 384 and 19.94 473	

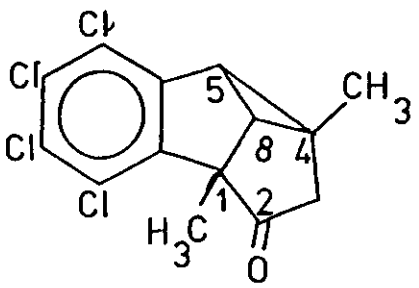
 (V-28)	C-1(s) 64.85 164	C-2(s) 208.05 97	C-3(t) 39.94 616	C-4(s) 26.20 149	C-5(d) and C-8(d) 48.59 and 40.35 533 and 653	Methyls at C-1(q), C-4(q) 16.20 and 22.04 418 and 449

TABLE V-1 ^{13}C-n.m.r. Data[a]

[a] Not including signals attributed to aromatic carbon nuclei .

[b] This assignment might alternatively be made to the signal at 140.8 ppm (intensity 165).

[c] Assignments based on the data reported in reference 10.

1. Acid Catalysed Rearrangements of 1-Methoxy-2-methyltetrachlorobenzobarrelene (V-16)

A. In Trifluoroacetic Acid

A solution of 1-methoxy-2-methyltetrachlorobenzobarrelene (V-16) (0.181g, 0.538 mmole) in trifluoroacetic acid (10ml) was heated under reflux for 2h. The solvent was removed under reduced pressure to leave an orange oil which was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give:

i) 1-Methyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,8-dihydro-8-methyl-5,8-methanobenzocycloheptenone-9-one) (V-19), (0.098g, 56%), m.p. 129-130° (from ethanol), (Found: C,48.4; H,2.6; $C_{13}H_8Cl_4O$ requires C,48.5; H,2.5%),

^{1}H-n.m.r. τ($CDCl_3$) 3.40(dd,1H,J=5Hz, J=3.5Hz); 4.14(d,1H,J=5Hz); 5.60 (dt,1H,J=3.5Hz, J=3.0Hz); 7.53(d,2H,J=3Hz); and 8.60 (s,3H);

ν_{max}^{KBr} 2980, 2940, 1710, 1535, 1360, 1345, 1330, 1300, 1230, 1215, 1195, 1155, 1140, 1010, 1005, 985, 870, 735, and 695 cm^{-1}.

λ_{max} (Ethanol) 253(ε=7100), 270(4600), 317(1580) and 326(1547) nm.

Mass spectrometry: $M^{+\bullet}$ = 322.

ii) 1-Methyltetrachlorobenzobarrelenone (1-Methyltetrachlorobenzo[5,6]-bicyclo[2.2.2]octa-5,7-dien-2-one; 5,6,7,8-tetrachloro-3,4-dihydro-1-methyl-1,4-ethenonaphthalen-2(1H)-one) (V-21) (0.007g, 4%), m.p. 164-165° (from ethanol), (Found: C,48.4; H,2.6; $C_{13}H_8Cl_4O$ requires C,48.5; H,2.5%),

^{1}H-n.m.r. τ($CDCl_3$) 3.18(dd,1H,J=J=7Hz); 3.77(dd,1H,J=7Hz, J=2Hz); 5.19 (ddt,1H,J=7Hz, J=2Hz, J=2.5Hz); 7.65(dd,1H,J=18Hz, J=2.5Hz); 7.89(dd,1H, J=18Hz, J=2.5Hz); and 7.95(s,3H);

ν_{max}^{KBr} 3030, 3020, 3000, 2950, 1735, 1455, 1420, 1390, 1375, 1360, 1335, 1310, 1285, 1260, 1230, 1200, 1170, 1130, 1070, 990, 830, 775, 710, 700, and

675 cm^{-1}.

Mass spectrometry: $M^{+\bullet}$ = 322 (very weak), $[M-42]^{+\bullet}$ = 280.

iii) 1-Methyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,9-dihydro-5-methyl-5,9-methanobenzocyclohepten-6-one) (V-20)(0.070g, 40%), m.p. 140-142° (from ethanol), (Found: C,48.4; H,2.5; $C_{13}H_8Cl_4O$ requires C,48.5; H,2.5%),

^{1}H-n.m.r. $\tau(CDCl_3)$ 2.55(dd,1H,J=9.5Hz, J=6Hz); 4.41(d,1H,J=9.5Hz); 6.01 (m,1H); 7.36(m,2H); and 8.26(s,3H);

ν_{max}^{KBr} 2975, 2935, 1690, 1680, 1460, 1370, 1360, 1355, 1320, 1280, 1255, 1210, 1140, 1110, 1095, 945, 850, 805, 775, 755, 710, and 640 cm^{-} .

λ_{max} (Ethanol) 243(sh)(ε=18.100), 292(4640), 305(4300), 339(2780), 350 (3320), and 359(2450) nm.

Mass spectrometry: $M^{+\bullet}$ = 322.

B. In Concentrated Sulphuric Acid

A suspension of 1-methoxy-2-methyltetrachlorobenzobarrelene (V-16)(0.145g, 0.432 mmole) in sulphuric acid (98%, 5ml) was shaken at room temperature until dissolution was complete. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with ether (4 x 10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residual tan powder was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give:

i) 1-Methyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,8-dihydro-8-methyl-5,8-methanobenzocyclohepten-9-one) (V-19) (0.005g, 3.6%), characterised by comparison with authentic material.

ii) 1-Methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1-methyl-1,4-ethenonaphthalen-2(1H)-one) (V-21) (0.038g, 28%), characterised

by comparison with authentic material.

iii) 1-Methyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,9-dihydro-5-methyl-5,9-methanobenzocyclohepten-6-one) (V-20) (0.036g, 27%), characterised by comparison with authentic material.

2. The Stability of 1-Methyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-Tetrachloro-5,8-dihydro-8-methyl-5,8-methanobenzocyclohepten-9-one) (V-19)

Towards Trifluoroacetic Acid

A solution of 1-methyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (V-19) (0.020g, 0.062 mmole) in trifluoroacetic acid (10ml) was heated under reflux for 24h. The solvent was removed under reduced pressure and the residue was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give: 1-Methyltetrachlorobenzo[3,4]bicyclo[3.2.1]-octa-3,6-dien-2-one (V-19) (0.018g, 90% recovery), characterised by ^{1}H-n.m.r. comparison with authentic material. No other products were detected. Prolonged treatment of 1-methyltetrachlorobenzo[3,4]bicyclo-[3.2.1]octa-3,6-dien-2-one (V-19) with boiling trifluoroacetic acid resulted in gradual decomposition to a complex mixture of many products: after *ca.* 300h. the amount of 1-methyltetrachlorobenzo[3,4]bicyclo[3.2.1]-octa-3,6-dien-2-one (V-19) was reduced to *ca.* 10-15% of its initial value.

3. The Stability of 1-Methyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-Tetrachloro-5,9-dihydro-5-methyl-5,9-methanobenzocyclohepten-6-one (V-20)

Towards Trifluoroacetic Acid

A solution of 1-methyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-

2-one (V-20) (0.061g, 0.190 mmole) in trifluoroacetic acid (10ml) was heated under reflux for 80h. The solvent was removed under reduced pressure to give 1-methyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-20), characterised by ^{1}H-n.m.r. comparison with authentic material. No other products were detected. Prolonged treatment of 1-methyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-20) with boiling trifluoroacetic acid caused a slow change in the substrate to unidentified products: after a further 72h. the amount of the substrate was reduced by ca. 40%, and after a further 150h., by ca. 60% of its initial value as determined by ^{1}H-n.m.r. analysis. The reaction mixture was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give: 1-Methyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-20) (0.028g, 39% recovery) characterised by comparison with authentic material. No other products were isolated.

4. Acid Catalysed Rearrangements of 1-Methoxy-3-methyltetrachlorobenzobarrelene (V-17)

A. In Trifluoroacetic Acid

A solution of 1-methoxy-3-methyltetrachlorobenzobarrelene (V-17) (0.251g, 0.747 mmole) in trifluoroacetic acid (25ml) was heated under reflux for 2h. The solvent was removed under reduced pressure to leave a tan powder which was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give: 4-Methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-4-methyl-1,4-ethenonaphthalen-2(1H)-one) (V-22) (0.241g, 100%), m.p. 138-140° (from ethanol), (Found: C,48.6; H,2.6; $C_{13}H_8Cl_4O$ requires C,48.5; H,2.5%),

^{1}H-n.m.r. τ($CDCl_3$) 3.32(dd,1H,J=7Hz, J=6.5Hz); 3.56(dd,1H,J=7Hz, J=2Hz); 4.95(dd,1H,J=6.5Hz, J=2Hz); and 7.93(m,5H);

ν_{max}^{KBr} 3005, 2990, 2940, 2905, 2885, 1740, 1455, 1405, 1400, 1385, 1370, 1365, 1355, 1330, 1275, 1235, 1200, 1165, 1135, 1100, 1080, 805, 705, 680, and 635 cm^{-1}.

Mass spectrometry: $M^{\cdot+}$ = 322 (very weak), $[M-42]^{\cdot+}$ = 280.

B. In Concentrated Sulphuric Acid

A suspension of 1-methoxy-3-methyltetrachlorobenzobarrelene (V-17) (0.214g, 0.638 mmole) in sulphuric acid (98%, 5ml) was shaken at room temperature until dissolution was complete. The reaction mixture was quenched with ice (ca. 40g) and filtered to give: 4-Methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-4-methyl-1,4-ethenonaphthalen-2(1H)-one) (V-22) (0.184g, 90%), characterised by comparison with authentic material. The ^{1}H-n.m.r. of the crude reaction product did not show signals characteristic of the known 5-methyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-9-methyl-1,4-ethenonaphthalen-2(1H)-one) (V-23).

5. The Stability of 4-Methyltetrachlorobenzobarrelenone (V-22)

A. Towards Trifluoroacetic Acid

A solution of 4-methyltetrachlorobenzobarrelenone (V-22) (0.080g, 0.249 mmole) in trifluoroacetic acid (5ml) was maintained at room temperature for 80h. The solvent was removed under reduced pressure to give: 4-Methyltetrachlorobenzobarrelenone (V-22), characterised by comparison with authentic material. No other products were detected by ^{1}H-n.m.r. or t.l.c. A solution of this material in trifluoroacetic acid (10ml) was heated under reflux for 220h. The solvent was removed under reduced pressure to give: 4-Methyltetrachlorobenzobarrelenone (V-22), characterised by comparison with authentic material. No other products were detected by ^{1}H-n.m.r. and t.l.c.

B. Towards Concentrated Sulphuric Acid

A solution of 4-methyltetrachlorobenzobarrelenone (V-22) (0.078g, 0.242 mmole) in sulphuric acid (98%, 5ml) was maintained at room temperature for 1h. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with chloroform (4 x 20ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give: 4-Methyltetrachlorobenzobarrelenone (V-22) (0.068g, 87% recovery) characterised by comparison with authentic material. A solution of this material in sulphuric acid (98%, 5ml) was maintained at room temperature for 92h. The product was isolated as before to give a yellow oil (0.031g, 40% recovery), characterised by t.l.c. and ^{1}H-n.m.r. as an approximately 1:1 mixture of:

i) 4-Methyltetrachlorobenzobarrelenone (V-22) and

ii) an unidentified product with the approximate ^{1}H-n.m.r. $\tau(CDCl_3)$ 4.66 (m,1H); 5.90(m,1H); 6.15(m,1H); 7.25(m,2H); and 7.85(d,3H).

6. Acid Catalysed Rearrangements of 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (V-18)

A. In Trifluoroacetic Acid

A stirred solution of 1-methoxy-2,5-dimethyltetrachlorobenzobarrelene (V-18) (1.20g, 3.44 mmole) in trifluoroacetic acid (50ml) was maintained at room temperature for 3h. The solvent was removed under reduced pressure and the residue was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give:

i) 1,6-Dimethyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,8-dihydro-6,8-dimethyl-5,8-methanobenzocyclohepten-9-one) (V-24) (0.601g, 52%), m.p. 132-135° (from ethanol), (Found: C,49.9; H,2.7; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. τ($CDCl_3$) 4.66(m,1H); 5.85(m,1H); 7.56(m,2H); 8.17(d,3H, J=2Hz); and 8.66(s,3H);

ν_{max}^{KBr} 2980, 2935, 1700, 1590, 1525, 1370, 1360, 1345, 1325, 1235, 1220, 1205, 1175, 1160, 1155, 1140, 1005, 990, 875, 820, 785, 755, and 640 cm^{-1}.

λ_{max} (Ethanol) 227(ε33066), 258(9282), 264(s)(8121), 308(s)(1508), 318(1972), and 328(s)(1276) nm.

Mass spectrometry: $M^{+\cdot}$ = 336

ii) A mixture of two isomeric ketones (0.246, 21%) in the ratio ca. 1:1. Repeated preparative t.l.c. (silica-gel, 20% ether in light petroleum) gave:

a. 1,5-Dimethyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,9-dimethyl-1,4-ethenonaphthalen-2(1H)-one) (V-26) m.p. 172-173° (from ethanol), (Found: C,50.0; H,3.1; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. τ($CDCl_3$) 4.20(m,1H); 5.47(q,1H,J=3Hz); 7.60(dd,1H,J=18Hz, J=3Hz); and 8.0(m,4H);

$\nu_{max}^{CHCl_3}$ 2950, 1735, 1455, 1445, 1415, 1360, 1320, 1300, 1280, 1265, 1140, 1110, 1085, 1070, and 885 cm^{-1}.

Mass spectrometry: $[M-42]^{+\cdot}$ = 294

b. 1,4-Dimethyltetrachlorobenzobarrelenone (5,6,7,8-tetrachloro-3,4-dihydro-1,4-dimethyl-1,4-ethenonaphthalen-2(1H)-one) (V-27) m.p. 165-167° (from ethanol), (Found: C,50.2; H,3.2; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. τ($CDCl_3$) 3.60(d,1H,J=7Hz); 3.80(d,1H,J=7Hz); and ca. 7.9 (m,8H);

$\nu_{max}^{CHCl_3}$ 2980, 2950, 1735, 1465, 1410, 1390, 1370, 1355, 1275, 1170, 1145, 1085, 1070, 925, 885, and 875 cm^{-1}.

Mass spectrometry: $[M-42]^{+\cdot}$ = 294

iii) 1,4-Dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (1,2,3,4-tetrachloro-5,9-dihydro-5,8-dimethyl-5,9-methanobenzocyclohepten-6-one) (V-25) (0.275g, 24%), m.p. 140-143° (from ethanol), (Found: C,50.1; H,2.9; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%), ^{1}H-n.m.r. τ($CDCl_3$) 4.61(m,1H); 6.13(m,1H); 7.39(m,2H); 7.85(d,3H,J=2Hz); and 8.28(s,3H).

$\nu_{max}^{CHCl_3}$ 2980, 2950, 1685, 1625, 1450, 1435, 1375, 1360, 1310, 1285, 1250, 1160, 1115, and 875 cm^{-1}.

λ_{max} (Ethanol) 209(ε=3702), 232(s)(2536), 290(s)(515), 332(333), 344(363), 356(333), and 376(s)(151) nm.

Mass spectrometry: $M^{+\cdot}$ = 336

B. The Effect on Product Distribution of Varying Trifluoroacetolysis Conditions

1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (V-18) (0.10g, 0.3 mmole) was treated with trifluoroacetic acid under various conditions (Table V-2)

REACTION	CONDITIONS
1	Trifluoroacetic acid at room temperature for ten minutes.
2	Trifluoroacetic acid at room temperature for three hours.
3	Trifluoroacetic acid under reflux for ten minutes.
4	5% Water in trifluoroacetic acid at room temperature for three hours.
5	A two-phase mixture of chloroform-trifluoroacetic acid-water (4:8:1) at room temperature for three hours.

TABLE V-2

The solvents were evaporated under reduced pressure and the residues were examined by ^{1}H-n.m.r. The approximate product ratios were determined from the integrations by comparison of the product spectra with spectra of authentic ketones. The results are collected in Table V-3.

Reaction	Total benzobarrelenone (V-26) : (V-27)	Total benzobicyclo-[3.2.1]octadienone (V-25) : (V-24)
1	1.75 1 : 0.75	6.5 1 : 1
2	2.35 1 : 1.35	4.60 1.2 : 1
3	1.4 1 : 0.4	1.1 1.9 : 1
4	2.65 1 : 1.65	5.0 1.45 : 1
5	1 0 : 1.0	5.45 1 : 1.5

TABLE V-3

C. In Fluorosulphuric Acid

A stirred solution of 1-methoxy-2,5-dimethyltetrachlorobenzobarrelene (V-18) (0.450g, 1.29 mmole) in fluorosulphuric acid (5ml) was prepared and maintained for 1h. at -60°. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with ether

4 x 25ml). The combined extracts were washed with water (2 x 10ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica-gel, 25% ether in light petroleum) to give traces of several uncharacterised products and a yellow oily solid (0.252g, 58%), characterised by t.l.c. and ^{1}H-n.m.r. as a 0.45:1 mixture of the isomeric ketones:

i) 1,5-Dimethyltetrachlorobenzobarrelenone (V-26) (18%), and

ii) 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (3,4,5,6-tetrachloro-2a,2b,6b,6c-tetrahydro-2a,6b-dimethylbenzo[a]cyclopropa[cd]pentalen-1-(2H)-one) (V-28) (40%), a pure sample of which was isolated by recrystallisation of the crude product from ethanol, m.p. 172-174° (from ethanol), (Found: C,49.9; H,2.9; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. $\tau(CDCl_3)$ 7.15(d,1H,J=6Hz); 7.46(d,1H,J=6Hz); 7.61(m,2H); 8.31(s,3H); and 8.55(s,3H);

$\nu_{max}^{CHCl_3}$ 2970, 2935, 1750, 1455, 1415, 1395, 1375, 1350, 1300, 1265, 1235, 1220, 1070, and 815 cm^{-1}.

λ_{max}^{EtOH} 223(ε33022); 295(1431), and 306(1262) nm.

Mass spectrometry: $M^{\cdot+}$ = 336, [M-28] = 308.

D. In Concentrated Aqueous Sulphuric Acid

A suspension of 1-methoxy-2,5-dimethyltetrachlorobenzobarrelene (V-18) (0.801g, 2.30 mmole) in concentrated sulphuric acid (95%, 9ml) was shaken at room temperature until dissolution was complete. The reaction mixture was quenched with ice (ca. 300g) and the resultant suspension was extracted with chloroform (3 x 100ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give:

i) 1-Methoxy-2,5-dimethyltetrachlorobenzobarrelene (V-18) (0.078g, 10% recovery), characterised by comparison with authentic material.

ii) A yellow oily solid (0.254g, 39%), characterised by t.l.c. and ^{1}H-n.m.r. as a 1.3:1 mixture of the isomeric ketones:

a. 1,5-Dimethyltetrachlorobenzobarrelenone (V-28) (22%), and

b. 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.0^{2,8}]oct-6-en-4-one (V-28) (17%).

iii) 1,2,3,4-Tetrachloro-5,9-dihydro-5,8-dimethyl-5,9-methanobenzocyclohepten-6-one (V-25) (0.116g, 15%), characterised by comparison with authentic material.

iv) 1,3-Dimethyltetrachlorobenzo[7,8]bicyclo[3.3.0]octa-3,7-dien-2-one (4,5,6,7-tetrachloro-8,8a-dihydro-1,3a-dimethylcyclopent[a]inden-3(3aH)-one) (V-29) (0.111g, 15%), m.p. 139-140° (from ethanol), (Found: C,50.4; H,3.1; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. τ($CDCl_3$) 4.18(m,1H); 6.85(m,3H); 7.85(d,3H,J=1.5Hz); and 8.33(s,3H);

$\nu_{max}^{CHCl_3}$ 2980, 2940, 1710, 1630, 1440, 1375, 1300, 1280, 1270, 1195, 1095, and 865 cm^{-1}.

λ_{max}^{EtOH} 225(s)(ε32200); 236(s)(20200); 248(s)(10700); 284(506); 294(547); 318(313); and 335(s)(235) nm.

Mass spectrometry: $M^{+\bullet}$ = 336.

7. The Stability of 1,4-Dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]-octa-3,6-dien-2-one (V-25)

A. Towards Trifluoroacetic Acid

A solution of 1,4-dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-25) (0.069g, 0.206 mmole) in trifluoroacetic acid (10ml) was maintained at room temperature for 24h. The solvent was removed under

reduced pressure to give unchanged 1,4-dimethyltetrachlorobenzo[6,7]-bicyclo[3.2.1]octa-3,6-dien-2-one (V-25), characterised by comparison with authentic material. This product was redissolved in trifluoroacetic acid and heated under reflux for 72h. The solvent was removed under reduced pressure to give unchanged 1,4-dimethyltetrachlorobenzo[6,7]-bicyclo[3.2.1]octa-3,6-dien-2-one (V-25), characterised by comparison with authentic material.

B. Towards Concentrated Aqueous Sulphuric Acid

The product of experiment 7.A. was dissolved in concentrated sulphuric acid (95%, 5ml) and maintained at room temperature for 1h. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with chloroform (3 x 10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give unchanged 1,4-dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-25). This product was redissolved in concentrated sulphuric acid (95%, 5ml) and maintained at room temperature for 21 days. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with chloroform (3 x 10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give unchanged 1,4-dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-25) (0.020g, 29% from experiment 7.A.), characterised by comparison with authentic material. No other products were detected.

8. The Stability of 1,6-Dimethyltetrachlorobenzo[3,4]bicyclo[3.2.1]-octa-3,6-dien-2-one (V-24)

A. Towards Trifluoroacetic Acid

A solution of 1,6-dimethyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (V-24) (0.118g, 0.352 mmole) in trifluoroacetic acid (10ml) was maintained at room temperature for 24h. The solvent was evaporated under reduced pressure to give a dark brown oil, characterised by ^{1}H-n.m.r. as a complex mixture containing some 1,6-dimethyltetrachlorobenzo[3,4]-bicyclo[3.2.1]octa-3,6-dien-2-one (V-24), but none of the other primary rearrangement products 1,4-dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]-octa-3,6-dien-2-one (V-25), 1,4-dimethyltetrachlorobenzobarrelenone (V-27), and 1,5-dimethyltetrachlorobenzobarrelenone (V-26), and neither of the secondary rearrangement products 2,5-dimethyltetrachlorobenzo[6,7]tricyclo [3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) and 1,3-dimethyltetrachlorobenzo[7,8]-bicyclo[3.3.0]octa-3,7-dien-2-one (V-29).

B. In Concentrated Aqueous Sulphuric Acid

A solution of 1,6-dimethyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (V-24) (0.155g, 0.46 mmole) in chloroform (1ml) was shaken for 4min. at room temperature with concentrated sulphuric acid (95%, 5ml). The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with chloroform (4 x 10ml). The combined extracts were washed with aqueous sodium carbonate (saturated, ca. 20ml) and water (until neutral). The extract was dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oily solid (0.037g, "24%"), characterised by t.l.c. as a four component mixture and by ^{1}H-n.m.r. as containing 1,4-dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-25) as the only identified component. The mixture was not further investigated.

9. The Stability of 1,5-Dimethyltetrachlorobenzobarrelenone (V-26)

A. Towards Trifluoroacetic Acid

A solution of 1,5-dimethyltetrachlorobenzobarrelenone (V-26) (0.058g, 0.256 mmole) in trifluoroacetic acid (5ml) was heated under reflux for 4h. The solvent was removed under reduced pressure to give unchanged 1,5-dimethyltetrachlorobenzobarrelenone (V-26), characterised by comparison with authentic material.

B. Towards Fluorosulphuric Acid

A solution of 1,5-dimethyltetrachlorobenzobarrelenone (V-26) (0.083g, 0.248 mmole) in fluorosulphuric acid (5ml) was prepared at -40° and maintained at -50° for 40min. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow oil (0.091g). Attempted purification of this oil by preparative t.l.c. (silica-gel, 50% ether in light petroleum) gave four fractions, all less than 0.002g. The mixture was not further investigated.

10. The Stability of 1,4-Dimethyltetrachlorobenzobarrelenone (V-27)

A. Towards Concentrated Sulphuric Acid

A suspension of 1,4-dimethyltetrachlorobenzobarrelenone (V-27) (0.105g, 0.312 mmole) in concentrated sulphuric acid (99%, 1ml) was shaken at room temperature until dissolution occurred. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with ether (3 x 10ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give: 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo [3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) (0.074g, 70%), characterised by comparison with authentic material.

B. Towards Concentrated Aqueous Sulphuric Acid

A solution of 1,4-dimethyltetrachlorobenzobarrelenone (V-27) (0.115g, 0.343 mmole) in concentrated sulphuric acid (95%, 3ml) was maintained at room temperature for 2min. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with ether (3 x 25ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give: 1,3-Dimethyltetrachlorobenzo[7,8]bicyclo[3.3.0]octa-3,7-dien-2-one (V-29) (0.083g, 72%), characterised by comparison with authentic material.

11. The Stability of 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]-oct-6-en-4-one (V-28)

A. Towards Concentrated Aqueous Sulphuric Acid

A solution of 2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) (0.058g, 0.173 mmole) in concentrated sulphuric acid (95%, 5ml) was maintained at room temperature for 5min. The reaction mixture was quenched with ice (ca. 50g) and the resultant suspension was extracted with ether (3 x 25ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give:

i) 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) (0.010g, 17% recovery), characterised by comparison with authentic material.

ii) A yellow solid (0.004g, 7%), tentatively identified as 1,4-dimethyl-tetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-25), by t.l.c. and i.r. comparison with authentic material.

iii) 1,3-Dimethyltetrachlorobenzo[7,8]bicyclo[3.3.0]octa-3,7-dien-2-one (V-29) (0.021g, 36%, 43% based on 2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) consumed), characterised by com-

parison with authentic material.

B. Towards Trifluoroacetic Acid

A solution of 2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) (0.058g, 0.173 mmole) in trifluoroacetic acid (5ml) was heated under reflux for 2.5h. The solvent was removed under reduced pressure to give unchanged 2,5-dimethyltetrachlorobenzo[6,7]tricyclo [3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28), characterised by comparison with authentic material. No other products were detected.

12. The Stability of 1,3-Dimethyltetrachlorobenzo[7,8]bicyclo[3.3.0]-octa-3,7-dien-2-one (V-29)

Towards Trifluoroacetic Acid

A solution of 1,3-dimethyltetrachlorobenzo[7,8]bicyclo[3.3.0]octa-3,7-dien-2-one (V-29) (0.050g, 0.149 mmole) in trifluoroacetic acid (5ml) was heated under reflux for 3h. The solvent was removed under reduced pressure to give unchanged 1,3-dimethyltetrachlorobenzo[7,8]bicyclo[3.3.0]octa-3,7-dien-2-one (V-29), characterised by comparison with authentic material.

13. Catalytic Hydrogenation of 1,4-Dimethyltetrachlorobenzo[6,7]bicyclo-[3.2.1]octa-3,6-dien-2-one (V-25)

A suspension of palladised charcoal (10% Pd, 0.011g) in a solution of 1,4-dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-one (V-25) (0.193g, 0.575 mmole) in ethyl acetate (25ml) was stirred under one atmosphere of hydrogen for 50h. at room temperature. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residual pale yellow solid was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give 1,4-dimethyltetrachlorobenzo[6,7]bicyclo[3.2.1]-

oct-6-en-2-one (1,2,3,4-tetrachloro-5,7,8,9-tetrahydro-5,8-dimethyl-5,9-methanobenzocyclohepten-6-one (V-30) (0.177g, 91%) m.p. 153-158° (from ethanol as a mixture of epimers), (Found: C,49.9; H,3.5; $C_{14}H_{12}Cl_4O$ requires C,49.9; H,3.6%),

^{1}H-n.m.r. τ($CDCl_3$) 6.45(m,1H,$W_{\frac{1}{2}}$=10Hz); 7.30-8.30(m, ca. 5H); 8.42(s,3H); and 9.00(d,3H,J=6Hz);

$\nu_{max}^{CHCl_3}$ 2955, 2935, 2900, 2875, 1725, 1455, 1415, 1380, 1375, 1365, 1335, 1310, 1275, 1260, 1125, 1105, and 1090 cm^{-1}.

14. Catalytic Hydrogenation of 1,3-Dimethyltetrachlorobenzo[7,8]bicyclo-[3.3.0]octa-3,7-dien-2-one (V-29)

A suspension of palladised charcoal (10% Pd, 0.015g) in a solution of 1,3-dimethyltetrachlorobenzo[7,8]bicyclo[3.3.0]octa-3,7-dien-2-one (V-29) (0.058g, 0.173 mmole) in ethyl acetate (25ml) was stirred under one atmosphere of hydrogen for 100h. at room temperature. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residual solid was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give 1,3-dimethyltetrachlorobenzo[7,8]bicyclo-[3.3.0]oct-7-en-2-ol (4,5,6,7-tetrachloro-1,3a,8,8a-tetrahydro-1,3a-dimethylcyclopent[a]inden-3(2H)-one (V-31) (0.051g, 87%), m.p. 76-104° (from cyclohexane as a mixture of epimers), (Found: C,49.9; H,3.5; $C_{14}H_{12}Cl_4O$ requires C,49.7; H,3.6%),

^{1}H-n.m.r. τ($CDCl_3$) 6.5-8.4(complex multiplets); 8.57(s); and 8.7-8.9(m);

$\nu_{max}^{CHCl_3}$ 2960, 2935, 2875, 1750, 1455, 1370, 1295, 1275, and 1120 cm^{-1}.

15. Preparation of Raney Nickel[21]

Nickel-Aluminium alloy (63g) was added to warm stirred aqueous sodium hydroxide (21% w/w, 380g) at such a rate that the temperature was maintained

at 50±2°. This temperature was maintained for a further 50min. The precipitated Raney nickel was washed by decantation with water (3 x 500ml), transferred to centrifuge tubes and washed with ethanol (95%, 3 x 75ml, then absolute, 3 x 75ml). The product was stored under nitrogen at 0° as an ethanolic sludge.

16. Preparation of 2,2-Ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (5′,6′,7′,8′-Tetrachloro-3′,4′-dihydrospiro[1,3-dithiolane-2,2′(1′H)-[1,4]ethenonaphthalene]) (V-47) by Condensation of Tetrachlorobenzobarrelenone (V-46) and Ethane-1,2-dithiol

A solution of tetrachlorobenzobarrelenone (V-46) (0.072g, 0.234 mmole) in ethane-1,2-dithiol (0.2ml) was treated with boron trifluoride etherate (0.2ml, ca. 1.5 mmole). The reaction mixture was maintained at room temperature for 2h. The reaction was quenched by the addition of methanol (1ml) and the precipitated product was isolated by filtration to give 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (5′,6′,7′,8′-tetrachloro-3′,4′-dihydrospiro[1,3-dithiolane-2,2′(1′H)-[1,4]ethenonaphthalene (V-47) (0.083g, 92%), m.p. 176-178° (from ethanol), (Found: C,43.6; H,2.7; $C_{14}H_{10}Cl_4S_2$ requires C,43.8; H,2.6%), ^{1}H-n.m.r. τ($CDCl_3$) 3.34(m,2H); 5.30(m,1H); 5.50(m,1H); 6.62(s,4H); 7.48(dd,1H,J=14Hz, J=3Hz); and 7.82(dd,1H,J=14Hz, J=3Hz), ν_{max}^{KBr} 2920, 1435, 1370, 1335, 1270, 1230, 1215, 1180, 1150, 1115, 1025, and 705 cm^{-1}.

17. Attempted Preparation of 2,3-Dihydrotetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1,4-ethanonaphthalene)(V-49) by Raney-Nickel Reduction of 2,2-Ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47)

A. A solution of 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) (0.075g, 0.195 mmole) in ethanol (absolute, 50ml) was treated with Raney nickel (4ml of settled ethanolic slurry). The reaction mixture was heated under reflux for 2h. (T.l.c. analysis after 1.25h. showed that no 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) remained.) The reaction mixture was filtered through celite and the retained solids were washed with hot benzene (2 x 25ml).

CAUTION! Spontaneous ignition of the retained solids occurred during their disposal.

The combined filtrates were evaporated under reduced pressure. The residue was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give 2,3,5,6-tetrahydrotetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,2,3,4-tetrahydro-1,4-ethanonaphthalene) (V-48) (0.030g, 52%), m.p. 147-150° (from ethanol), (lit.[22] 135-136°)

^{1}H-n.m.r. $\tau(CDCl_3)$ 6.4(m,2H); 8.0-8.9(m,8H); [lit.[22] 6.4(m); 8.0-8.95(m)]

B. When the reduction was conducted at room temperature for 20min., but otherwise by the method of 17.A., over-reduction to 2,3,5,6-tetrahydrotetrachlorobenzobarrelene (V-48) was again observed.

C. A suspension of Raney nickel (4ml of settled ethanolic slurry, deactivated by boiling acetone for 3h.) in a solution of 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) (0.080g, 0.208 mmole) in ethanol-acetone (1:1 v/v, 50ml) was heated under reflux for 3h. The reaction mixture was diluted with ether (50ml) and treated with concentrated hydrochloric acid. The aqueous phase was separated and extracted with ether (1 x 25ml). The combined ethereal phases were dried ($MgSO_4$) and evaporated to give 2,3,5,6-tetrahydrotetrachlorobenzobarrelene (V-48)

(0.029g, 47%) characterised by comparison with material previously isolated. Note: Destruction of excess of Raney nickel with concentrated hydrochloric acid after desulphurisation is a notably malodorous procedure and should be carried out in an efficient fume cupboard.

D. A suspension of Ranel nickel (4ml of settled ethanolic slurry, deactivated by boiling acetone for 4h.) in a solution of 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) (0.080g, 0.208 mmole) in ethanol-acetone (4:1 v/v, 50ml) was stirred at room temperature for 15min. The reaction mixture was diluted with ether (50ml) and treated with concentrated hydrochloric acid. The aqueous phase was separated and extracted with ether (1 x 25ml). The combined ethereal phases were dried ($MgSO_4$) and evaporated under reduced pressure to give unchanged 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) (0.080g, 100% recovery), characterised by comparison with authentic material.

E. When the reaction time was prolonged to 20h, but the reduction was otherwise conducted by the method of 17.D., 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) was quantitatively recovered.

18. Hydrolysis of 2,2-Ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) with Methyl Iodide in Aqueous Acetone

A solution of 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) (0.065g, 0.169 mmole) and methyl iodide (1ml) in aqueous acetone (90% v/v, 25ml) was heated under reflux for 80h. The reaction mixture was diluted with water (to 125ml) and extracted with ether (3 x 25ml). The combined extracts were washed with brine (saturated, 2 x 5ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by

preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give:

i) 2,2-Ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) (0.015g, 23% recovery), characterised by comparison with authentic material.

ii) Tetrachlorobenzobarrelenone (V-46) (0.029g, 56%, 72% based on 2,2-ethylenedithio-2,3-dihydrotetrachlorobenzobarrelene (V-47) consumed).

19. Preparation of 2,3-Dihydrotetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1,4-ethanonaphthalene) (V-49) by Clemmensen Reduction of Tetrachlorobenzobarrelenone (V-46)

A. Preparation of Amalgamated Zinc

Zinc powder (3.5g, 53.5mg-atom) was washed with concentrated hydrochloric acid (2 x 20ml) then twice by a solution of mercuric chloride (0.40g, 1.47 mmole) in hydrochloric acid [concentrated (0.5ml) and water (5ml)], and dried by decantation.

B. Reduction of Tetrachlorobenzobarrelenone (V-46)

A suspension of amalgamated zinc [from zinc powder (3.5g, 53.5mg-atom)] in a solution of tetrachlorobenzobarrelenone (V-46) (0.065g, 0.21 mmole) in the two phase solvent system acetic acid (2ml) — water (2ml) — concentrated hydrochloric acid (3ml) — toluene (3ml) was boiled vigorously under reflux for 6h. T.l.c. analysis showed that no tetrachlorobenzobarrelenone (V-46) remained. The reaction mixture was diluted (to ca. 50ml) with water and extracted with ether (3 x 25ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give 2,3-dihydrotetrachlorobenzobarrelene (5,6,7,8-tetrachloro-1,4-dihydro-1,4-ethanonaphthalene) (V-49) (0.045g, 74%), m.p. 126-128° (from ethanol), (Found: C,49.1; H,2.9; $C_{12}H_8Cl_4$ requires C,49.0; H,2.7%), ^{1}H-n.m.r. τ($CDCl_3$) 3.45-3.68(m,2H); 5.40-5.60(m,2H); and 8.30-8.60(m,4H);

ν_{max}^{KBr} 3060, 2995, 2950, 2875, 1525, 1445, 1405, 1395, 1375, 1350, 1340, 1320, 1310, 1285, 1270, 1255, 1245, 1225, 1200, 1155, 1140, 910, 845, 825, 780, 695, and 635 cm^{-1}.

20. Attempted Preparation of 2,3-Dihydro-1,4-dimethyltetrachlorobenzobarrelene (5,6,7,8-Tetrachloro-1,4-dihydro-1,4-dimethyl-1,4-ethanonaphthalene)(V-45) by Clemmensen Reduction of 1,4-Dimethyltetrachlorobenzobarrelenone (V-27)

A suspension of amalgamated zinc [from zinc powder (10.0g, 152.9mg-atom) by the method of 19.A.] in a solution of 1,4-dimethyltetrachlorobenzobarrelenone (V-27) (0.200g, 0.6 mmole) in the two phase solvent system acetic acid (4ml) — water (4ml) — concentrated hydrochloric acid (6ml) — toluene (6ml) was boiled vigorously under reflux for 3h. The reaction mixture was diluted with water (to ca. 100ml) and extracted with ether (3 x 25ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a clear oil (0.196g), which exhibited a strong carbonyl stretching band at ν_{max} 1740 cm^{-1}. When the reaction was conducted for 6h. under otherwise unchanged conditions and the product was isolated as above, it again exhibited a strong carbonyl stretching band at ν_{max} 1740 cm^{-1}. The attempted reduction was abandoned.

21. Preparation of 2,2-Ethylenedioxy-2,3-dihydrotetrachlorobenzobarrelene (5′,6′,7′,8′-Tetrachloro-3′,4′-dihydrospiro[1,3-dioxolane-2,2′(1′H)-[1,4]ethenonaphthalene](V-52) by Condensation of Tetrachlorobenzobarrelenone (V-46) and Ethane-1,2-diol

A solution of tetrachlorobenzobarrelenone (V-46) (1.87g, 6.05 mmole) and p-toluene sulphonic acid (0.5g) in ethane-1,2-diol (5ml) and benzene (100ml) was heated under reflux for 5 days. Water was removed as formed by azeo-

tropic distillation into a Dean-Stark trap packed with molecular sieves (4A). Sodium acetate (freshly fused, 3g) was added. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure; the residue was dissolved in ether (100ml), washed with aqueous sodium carbonate (10% w/v, 2 x 25ml) and water (2 x 25ml) and dried (Na_2CO_3). Evaporation of the solvent under reduced pressure gave 2,2-ethylenedioxy-2,3-dihydrotetrachlorobenzobarrelene (5',6',7',8'-tetrachloro-3',4'-dihydrospiro-[1,3-dioxolane-2,2'(1'H)-[1,4]ethenonaphthalene])(V-52) (1.35g, 64%) m.p. 111-112° (from hexane) (Found: C,47.6; H,2.7; $C_{14}H_{10}Cl_4O_2$ requires C,47.7; H,2.8%),

^{1}H-n.m.r. τ($CDCl_3$) 3.30-3.52(m,2H); 5.40-5.60(m,2H); 5.70-6.30(m,4H); 8.00(dd,1H,J=14Hz, J=3Hz); and 8.20(dd,1H,J=14Hz, J=3Hz);

$\nu_{max}^{CHCl_3}$ 2895, 1380, 1350, 1335, 1280, 1245, 1225, 1160, 1140, 1125, 1065, 1030, 990, 950, 680, and 650 cm^{-1}.

22. Preparation of 2,2-Ethylenedioxy-2,3-dihydro-1,4-dimethyltetrachlorobenzobarrelene (5',6',7',8'-Tetrachloro-3',4'-dihydro-1',4'-dimethylspiro[1,3-dioxolane-2,2'(1'H)-[1,4]ethenonaphthalene]) (V-53) by Condensation of 1,4-Dimethyltetrachlorobenzobarrelenone (V-27) and Ethane-1,2-diol

A solution of 1,4-dimethyltetrachlorobenzobarrelenone (V-27) (0.270g, 0.80 mmole) and p-toluene sulphonic acid (0.005g) in ethane-1,2-diol (2ml) and di-n-butyl ether (50ml) was heated under reflux for 3 days. Water was removed as formed by azeotropic distillation into a Dean-Stark trap. The solvent was evaporated under reduced pressure; the residue was purified by preparative t.l.c. (alumina, 20% ether in light petroleum) to give:

i) A clear oil (0.067g), characterised by ^{1}H-n.m.r. as a ca. 0.67:1 mixture of:

a. 1,4-dimethyltetrachlorobenzobarrelenone (V-27) and

b. 4,4-ethylenedioxy-2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-ene (V-54), the isolation of pure samples of which is described in 23.A. and 23.B.

ii) 2,2-Ethylenedioxy-2,3-dihydro-1,4-dimethyltetrachlorobenzobarrelene (5′,6′,7′,8′-tetrachloro-3′,4′-dihydro-1′,4′-dimethylspiro[1,3-dioxolane-2,2′(1′H)-[1,4]ethanonaphthalene) (V-53) (0.060g, 20%) m.p. ——— (from ethanol). This compound was not analysed.

^{1}H-n.m.r. τ($CDCl_3$) 3.60(d,1H,J=8Hz); 3.73(d,1H,J=8Hz); 3.90-4.20(m,4H); and 8.00(s,6H);

$\nu_{max}^{CHCl_3}$ 2960, 2940, 2895, 1415, 1360, 1340, 1305, 1265, 1180, 1140, 1110, 1080, 1055, 1025, and 950 cm^{-1}.

23. Preparation of 4,4-Ethylenedioxy-2,5-dimethyltetrachlorobenzo[6,7]-tricyclo[3.2.1.$0^{2,8}$]oct-6-ene (3,4,5,6-Tetrachloro-2a,2b,6b,6c-tetrahydro-2a,6b-dimethylspiro[benzo[a]cyclopropa[cd]pentalene-1(2H),2-[1,3]dioxolane]) (V-54)

A. By Photoisomerisation of 2,2-Ethylenedioxy-2,3-dihydro-1,4-dimethyl-tetrachlorobenzobarrelene (V-53)

A solution of 2,2-ethylenedioxy-2,3-dihydro-1,4-dimethyltetrachlorobenzobarrelene (V-53) (0.040g, 0.105 mmole) in acetone (40ml) maintained at room temperature under one atmosphere of nitrogen was irradiated with a Hanovia medium pressure mercury lamp (125W) for 40min. The solvent was evaporated under reduced pressure and the residue was purified by preparative t.l.c. (alumina, 20% ether in light petroleum) to give 4,4-ethylenedioxy-2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-ene (3,4,5,6-tetrachloro-2a,2b,6b,6c-tetrahydro-2a,6b-dimethylspiro[benzo[a]-cyclopropa[cd]pentalene-1(2H),2′-[1,3]dioxolane]) (V-54) m.p. 169-171°

(from ethanol).

(Found: $M^{+\bullet}$ = 377.9734; $C_{16}H_{14}Cl_4O_2$ requires $M^{+\bullet}$ = 377.9750), ^{1}H-n.m.r. τ($CDCl_3$) 5.76-6.15(m,4H); 7.50(d,1H,J=7Hz); 7.65(d,1H,J=7Hz); 8.20(m,2H); 8.38(s,3H); and 8.63(s,3H);

B. By Condensation of 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo-[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) and Ethane-1,2-diol

A solution of 2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) (0.057g, 0.17 mmole) in ethane-1,2-diol (1ml) and dichloromethane (10ml) was treated with freshly distilled boron trifluoride etherate (1ml) and maintained at room temperature for 60h. The reaction mixture was diluted with dichloromethane (to 40ml), washed with water (1 x 5ml), aqueous sodium bicarbonate (saturated, 2 x 5ml) and water (1 x 5ml), and dried (Na_2SO_4-Na_2CO_3). The solvent was evaporated under reduced pressure and the residual solid was purified by preparative t.l.c. (alumina, 20% ether in light petroleum) to give:

i) 4,4-Ethylenedioxy-2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]-oct-6-ene (V-54) (0.032g, 56%, 73% based on 2,5-dimethyltetrachlorobenzo-[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) consumed) m.p. 170-171° (from ethanol). The m.p. was not depressed by admixture of authentic 4,4-ethylenedioxy-2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-ene (V-54) prepared by the method of 23.A. The ^{1}H-n.m.r. spectra of samples of the acetal (V-54) prepared by this method and by the method of 23.A. did not differ significantly.

ii) 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) (0.013g, 23% recovery), characterised by comparison with authentic

material.

24. Preparation of 1,7-Dimethyltetrachlorobenzo[3,4]bicyclo[3.3.0]-octa-3,7-dien-2-one (4,5,6,7-Tetrachloro-3a,8a-dihydro-2,8a-dimethylcyclopent[a]inden-8(3H)-one (V-60) by Photoisomerisation of 1,6-Dimethyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (V-24)

A stirred solution of 1,6-dimethyltetrachlorobenzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-one (V-24) (0.298g, 0.89 mmole) in methanol (200ml) at room temperature was irradiated with a Hanovia medium pressure mercury lamp (125W) for 2h. under an atmosphere of nitrogen. The solvent was evaporated under reduced pressure and the residue was purified by preparative t.l.c. (silica-gel, 20% ether in light petroleum) to give: 1,7-Dimethyltetrachlorobenzo[3,4]bicyclo[3.3.0]octa-3,7-dien-2-one (4,5,6,7-tetrachloro-3a,8a-dihydro-2,8a-dimethylcyclopent[a]inden-8(3H)-one)(V-60) (0.203g, 68%) m.p. 150° (from ethanol), (Found: C,50.1; H,3.2; $C_{14}H_{10}Cl_4O$ requires C,50.0; H,3.0%),

^{1}H-n.m.r. $\tau(CDCl_3)$ 4.80(m,1H); 6.47(dd,1H,J=9Hz, J=3Hz); 6.60-7.20(m,1H); 7.40-7.85(m,1H); 8.35(d,3H,J=1.5Hz); and 8.65(s,3H);

$\nu_{max}^{CCl_4}$ 2975, 2935, 1730, 1440, 1375, 1295, 1250, 1220, 1165, 1155, 1025, 1005, and 840 cm^{-1}.

λ_{max} (Ethanol) 227(ε=45900), 248(11500), 254(13100), 260(14800), 268(13900), 309(1940) and 318(2360) nm.

Mass spectrometry: $M^{+\bullet}$ = 336.

25. Catalytic Hydrogenation of 2,5-Dimethyltetrachlorobenzo[6,7]-tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28)

A suspension of palladised charcoal (10%; 0.020g) in a solution of 2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28) (0.102g, 0.304 mmole) in ethyl acetate (50ml) was stirred at room temperature under one atmosphere of hydrogen for 100h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was examined by ^{1}H-n.m.r. and shown to be unchanged 2,5-dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28). A suspension of palladised charcoal (10%; 0.020g) in a solution of this product in ethyl acetate and acetic acid (25ml and 25ml) was stirred at room temperature under one atmosphere of hydrogen for 74h. The catalyst and solvents were removed as before. The residue was examined by ^{1}H-n.m.r. and shown to be unchanged 2,5-dimethyltetrachlorobenzo[6,7]tricyclo-[3.2.1.$0^{2,8}$]oct-6-en-4-one (V-28). A suspension of platinum black (from platinum dioxide, 0.015g) in a solution of this product in ethyl acetate and acetic acid (25ml and 25ml) was stirred at room temperature under one atmosphere of hydrogen for 72h. The catalyst and solvents were removed as before to give: 2,5-Dimethyltetrachlorobenzo[6,7]tricyclo[3.2.1.$0^{2,8}$]-oct-6-en-4-ol (3,4,5,6-tetrachloro-1,2,2a,2b,6b,6c-hexahydro-1-hydroxy-2a,6b-dimethylbenzo[a]cyclopropa[cd]pentalene) (V-32) (0.105g, 100%), m.p. 170-172° (from cyclohexane) (Found: C,50.2; H,3.6; $C_{14}H_{12}Cl_4O$ requires C,49.7; H,3.55%),

^{1}H-n.m.r. τ($CDCl_3$) 5.70(dd,1H,J=8Hz, J=10Hz); 7.46(d,1H,J=6.5Hz); 7.76 (d,1H,J=6.5Hz); 7.95(dd,1H,J=8Hz, J=13Hz); ca. 8.15(broad s, 1H); 8.27 (s,3H); 8.70(s,3H); and 8.77(dd,1H,J=10Hz, J=13Hz);

$\nu_{max}^{CH_2Cl_2}$ 3605, 3180(br), 2970, 2930, 2880, 1455, 1405, 1385, 1325, 1300, 1220, 1100, 1120, 1090, 1070, 1030, 1015, 975, 900, 875, 830, and 790 cm^{-1}.

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