SYNTHESIS AND FLASH VACUUM PYROLYSIS

OF CISOID- AND TRANSOID-

4-THIATRICYCLO[5.2.0.$0^{2,6}$]NON-8-ENE 4,4-DIOXIDE

AND DERIVED SYSTEMS

by

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DOCTOR OF PHILOSOPHY

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December 1987

VOLUME 1

Dedication

"For the crazy child" - Time Will Crawl

Never Let Me Down.

Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr I. Gosney since 1st October 1982, the date of my admission as a research student.

Postgraduate Lecture Courses

The following is a statement of the courses attended during the period of research:

Organic Research Seminars (three years attendance).

Current Topics in Organic Chemistry, various lecturers (10 lectures).

Medicinal Chemistry, Dr R.M. Paton (five lectures).

1,3-Dipolar Intermediates in Heterocyclic Synthesis, Dr J.T. Sharp and Dr R.M. Paton (five lectures).

Synthetic Strategy, Professor R. Ramage (five lectures).

Molecular Electronics, Professor R.W. Munn and Professor J.O. Williams, UMIST (five lectures).

Chemical Technology and Industrial Chemistry, Dr A.J.S. Nicoll, Dr L.H. Mustoe and Dr R.S. Sinclair, Paisley College of Technology (six lectures).

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Finally, I am grateful to the British taxpayer for providing financial support *via* the Science and Engineering Research Council.

ABSTRACT

A number of synthetic routes to the novel *cisoid*- and *transoid*-4-thiatricyclo[5.2.0.$0^{2,6}$]non-8-ene 4,4-dioxides have been investigated. The successful preparation of both isomers permitted a detailed comparison of physical and spectral characteristics to be made. An extensive examination of the reactivity of the *transoid* isomer towards reactions commonly undergone by olefins (including additions of 1,3-dipoles, dienes, a carbenoid, a nitrene and a sulphenyl chloride; photoadditions of an olefin and an azide; epoxidation, bromination and catalytic hydrogenation) is described, a similar spectrum of reactivity to that of cyclobutene being established. Bromination of the *cisoid* isomer resulted in isolation of 5-bromo-1-oxo-10-oxa-1 λ^6-thiatetracyclo[4.3.1.$0^{3,8}$.$0^{4,7}$]decan-1-ylium tribromide *via* an unprecedented intramolecular trapping of a bromonium tribromide intermediate by the sulphone group, functioning as a nucleophile. Thermolysis of the salt appeared to result in formation of the corresponding *exo*-*cis*-8,9-dibromo derivative of the *cisoid* tricyclic olefin.

The FVP of a series of substituted *transoid*, *transoid*-5-thiatetracyclo[7.n.0.$0^{2,8}$.$0^{3,7}$]polyane 5,5-dioxide systems (n = 1-4) - available from reaction of the olefin group of the above *transoid* tricyclic isomer or from manipulation of a precursor to this, *transoid*-4-thiatricyclo[5.2.0.$0^{2,6}$]nonane-*exo*-*cis*-8,9-dicarboxylic anhydride 4,4-dioxide - was undertaken. With those tetracyclic systems for which n = 1 or 2, the presence of terminal ring strain resulted in thermal ring opening to isomeric, unsaturated bicyclic sulphones on FVP at *ca* 500°C; with the comparatively unstrained systems for which n = 3, FVP at *ca* 650°C resulted in thermal extrusion of sulphur dioxide with

generation of cis-1,2-divinylcyclobutane-cyclopentane intermediates which were found to undergo secondary thermal rearrangements to cycloocta-1,5-diene and 4-vinylcyclohex-1-ene based products.

FVP at 400°C of both the cisoid and transoid isomers of 4-thiatricyclo[5.2.0.$0^{2,6}$]non-8-ene 4,4-dioxide was found to result in common formation of cis-8-thiabicyclo[4.3.0]nona-2,4-diene 8,8-dioxide. The Diels-Alder reactivity of this diene towards dimethyl acetylene-dicarboxylate (DMAD) and maleic anhydride was investigated : the stereospecific formation of an exo-adduct in each case was rationalised by consideration of electronic and steric factors. A study of the reactivity of the olefin group(s) of the DMAD adduct and the dimethyl ester derivative of the maleic anhydride adduct is described; a parallel (limited) examination of the derived bridged systems, 4-thiatricyclo[5.2.2.$0^{2,6}$]undeca-8,10-diene 4,4-dioxide and exo-4-thia-tricyclo[5.2.2.$0^{2,6}$]undec-8-ene 4,4-dioxide was also undertaken. The observed variation in olefin reactivities of the four related compounds reflected the operation of differing olefin electron-availabilities [influenced by interactions through-bond and through-space (with the proximate sulphone group)] and steric factors.

FVP of a series of 4-thiatricyclo[5.2.2.$0^{2,6}$]undec-8-ene 4,4-dioxide based compounds demonstrated a marked dependence in the ease and direction of the observed retro-Diels-Alder fragmentations on the level and position of unsaturation in the starting sulphones. A similar directing influence exerted by the presence of olefinic unsaturation upon the thermal (FVP) fragmentation behaviour of cis-8-thiabicyclo[4.3.0]nona-2,4-diene 8,8-dioxide and hydro/dehydro derivatives is also described.

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INTRODUCTION

INTRODUCTION

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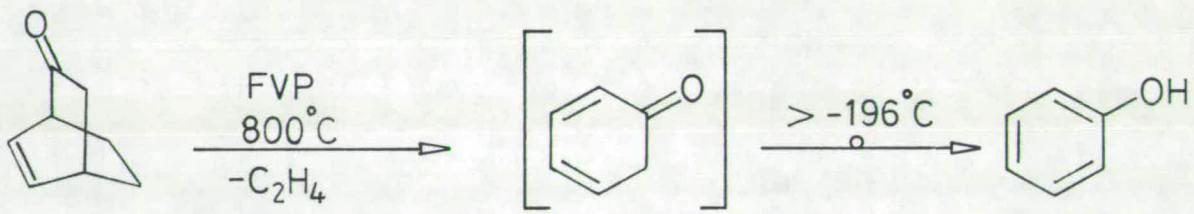
A. Thermal Extrusion Reactions of Cyclic Systems

The thermally-induced fragmentation of a cyclic system with expulsion of a small, thermodynamically stable molecule to give ring-contracted, ring-expanded or acyclic products can be described as a thermal extrusion reaction. Typical extrusion fragments encountered are nitrogen, sulphur monoxide, carbon monoxide, sulphur dioxide, carbon dioxide, acetylene, acetic acid, ethylene and acetone. An estimate[1] of the relative ease of extrusion of such common species furnishes the following order: $N_2 > CO_2 > CO > SO > SO_2 > O_2 > S > O$.

Thermal extrusion reactions are a long established branch of organic chemistry, the subject having made a sizeable contribution to an extensive review of pyrolysis reactions compiled by Hurd[2] in 1929. This publication details the 'traditional' methods of 'pyrolysis' in which the precursor material is heated either in neat form, or in solution, often at temperatures much below 400°C. (In the remainder of this thesis such reactions will be referred to as belonging to the class of 'thermolysis' reactions; the term 'pyrolysis' will be reserved for thermal reactions carried out at temperatures in excess of 400°C, invariably in the gas phase, and often at reduced pressure.) Traditional thermolysis methods often suffer from side reactions which compete with the desired thermal transformation, with the result that in many cases a large number of products are isolated. However, in the last two decades the emergence and increasing application of flash vacuum pyrolytic techniques has greatly enhanced the synthetic and mechanistic utility of thermal extrusion reactions[3].

Flash vacuum pyrolysis (FVP) is a flow method in which the precursor material is volatilised and passed through a hot zone under

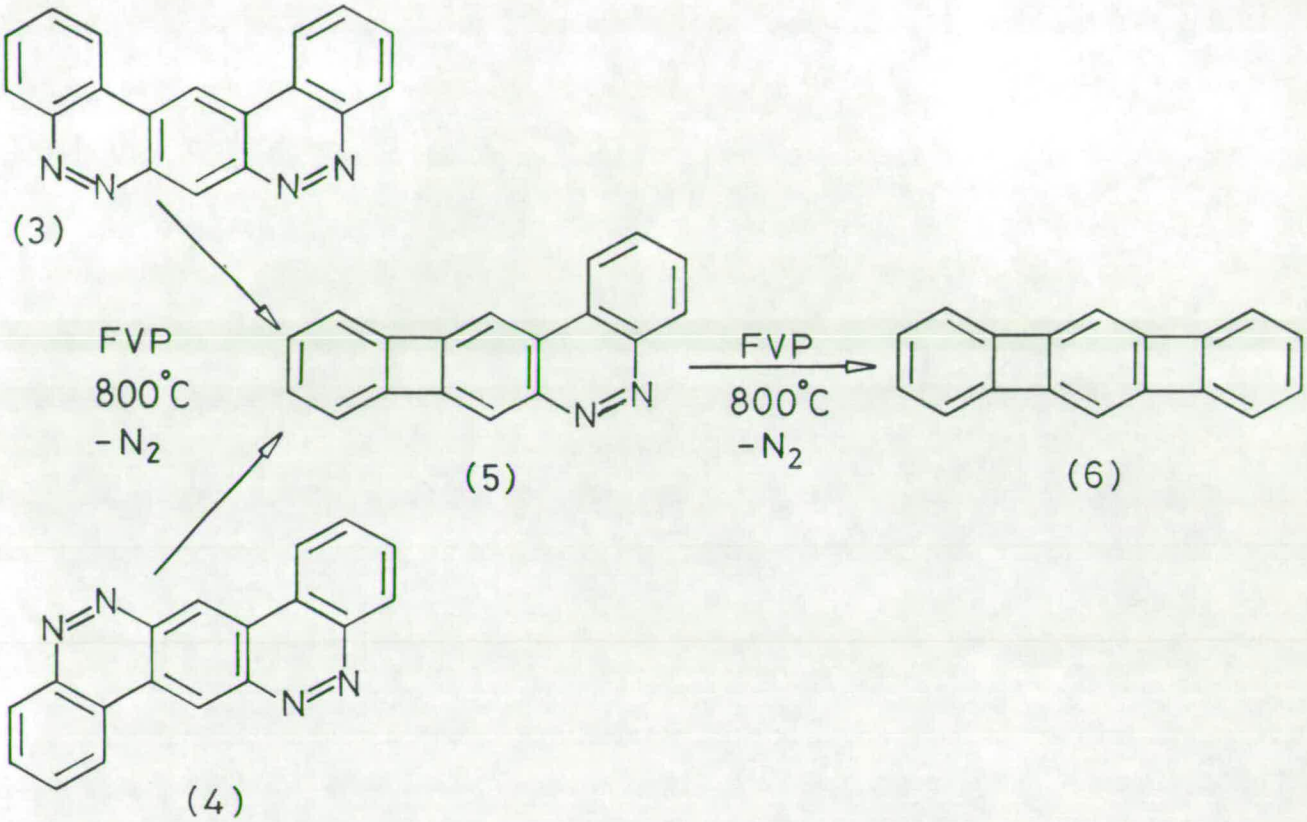
conditions of low pressure (10^{-3} mm Hg) and short contact times (ca 10^{-3}s). [A more detailed description of the technique is included in the Experimental section.] Such conditions favour unimolecular fragmentation of the precursor system, drastically reducing intermolecular interactions and often increasing yield and product selectivity. Application of FVP methods to the generation and examination of unstable compounds, not readily accessible from other routes, demonstrates the value of the technique: the thermal extrusion of ethylene from the bicyclic ketone (1) under FVP conditions (800°C, 5×10^{-5} mm Hg) led to the trapping (at -196°C) and subsequent spectral investigation of the unstable cyclohexadienone (2), which was found to thermally rearrange to phenol on warming[4].



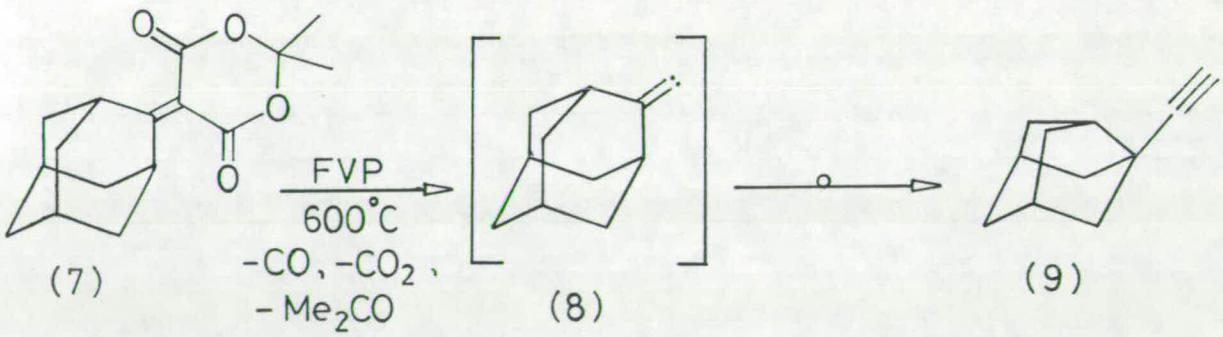
(1) (2)

The thermal expulsion of nitrogen is one of the most easily realised, and therefore one of the most commonly encountered extrusion reactions. An example of the synthetic utility of the extrusion of nitrogen under FVP conditions is furnished by Barton and Rowe[5] who have described the preparation and subsequent study of the aromatic character of the linear sesquibiphenylene (6). This was obtained from FVP of either of the benzodicinnolines (3) and (4) at 800°C, 4×10^{-2} mm Hg *via* the isolated biphenylenocinnoline (5).

Extrusion of more than one thermodynamically stable small molecule on thermal fragmentation of a system is possible. Thus, pyrolysis of the Meldrum's acid derivative (7), with loss of carbon



dioxide, carbon monoxide and acetone, has been found[6] to generate the adamantylidenecarbene (8), which undergoes intramolecular trapping with isolation of 3-noradamantylacetylene (9) as the sole product. This example demonstrates the versatility of the FVP technique, here used in the generation of reactive intermediates.



Since the thermal extrusion of sulphur dioxide from cyclic sulphone precursors, in particular from five-membered sulphone-containing rings, is of especial relevance to the experimental work of which this thesis is a record, the subject is now considered in some detail.

B. Thermal Extrusion of Sulphur Dioxide from Cyclic Sulphones

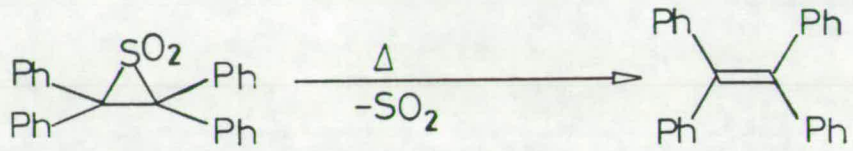
From the historical perspective the contribution to organic chemistry literature made by those extrusion reactions (both thermal and photochemical) involving loss of sulphur dioxide is very much smaller than that found for expulsions of other small gaseous species such as nitrogen, carbon dioxide or carbon monoxide. As evident from the earlier detailed sequence for the ease of extrusion of common fragments, the expulsion of sulphur dioxide is less easily achieved than that of most of the other fragments listed; this, taken in conjunction with the rarity of systems capable of losing sulphur dioxide compared to those from which carbon monoxide, carbon dioxide or nitrogen may be liberated offers an explanation for the relatively modest size of the literature concerning extrusion of sulphur dioxide.

In terms of the process of extrusion, a study[7] of the available literature indicates that for cyclic systems in which the sulphone group is present in an otherwise carbocyclic ring, or present in a ring containing other heteroatoms or functional groups as ring elements, sulphur dioxide may be thermally extruded with the termini of the fragmented ring then able to rearrange to form acyclic products, or products differing in ring size from that of the original sulphone ring. The sulphone group is found to be incorporated in rings of all sizes; the synthetic and mechanistic importance of sulphur dioxide extrusion from cyclic sulphones is now considered.

1. Three-membered rings

The saturated, three-membered sulphone-containing rings, known as the thiirane dioxides or episulphones, are found to be

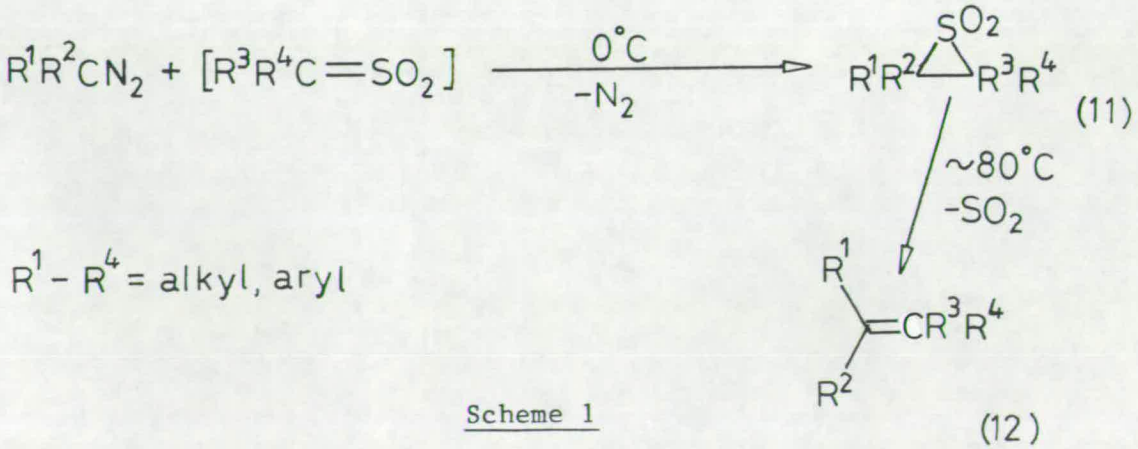
thermally unstable as a result of the ring strain inherent in these structures. For example, the thiirane dioxide (10) was found[8] to extrude sulphur dioxide on heating just above its melting point to generate the corresponding olefin; this represents the earliest reported example of sulphur dioxide extrusion from a thiirane dioxide (dating to 1916), but is typical of the general thermal extrusion of these systems. It is found that as the extent of substitution of the



(10)

episulphone ring is decreased, the temperature required to effect expulsion of sulphur dioxide is correspondingly lowered: thiirane dioxide is found[9] to undergo a slow decomposition at room temperature to generate ethylene and sulphur dioxide.

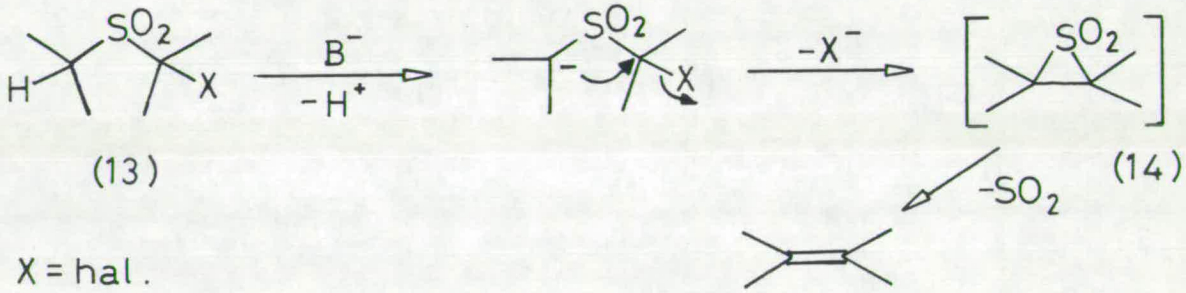
Thermal fragmentation of thiirane dioxides forms the basis of a synthetically useful route to unsymmetrical olefins (12), as shown in Scheme 1. Preparation of the thiirane dioxides (11) themselves may be effected readily <u>via</u> the reaction of sulphenes with diazoalkanes[9,10]. Loss of sulphur dioxide occurs stereospecifically



Scheme 1

to furnish olefins with retention of configuration - doubt remains as to whether this results from a concerted mechanism, or from a sequential bond cleavage mechanism in which sulphur dioxide is released before rotation about the remaining C-C bond can occur[11].

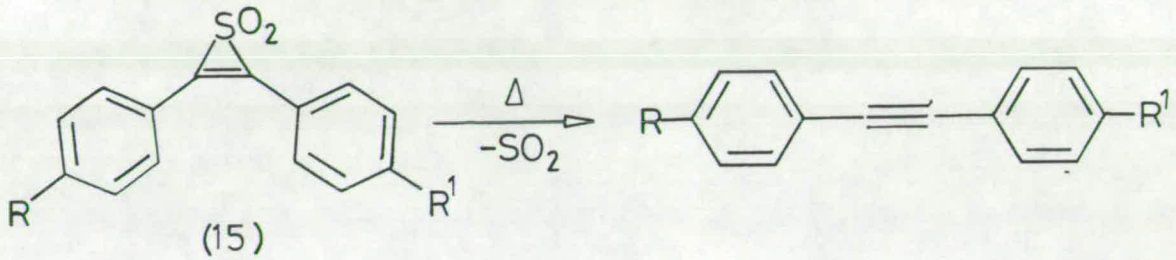
Thiirane dioxides can also undergo base-catalysed elimination of sulphur dioxide, with the use of strong base allowing facile elimination even at room temperature[9]. The Rämberg-Backlund reaction, in which an α-halosulphone (13) is converted into an olefin, is thought to occur via base-induced elimination of hydrogen halide to give an intermediate thiirane dioxide (14) which then undergoes base-catalysed loss of sulphur dioxide with generation of the olefin (Scheme 2)[12].



Scheme 2

The unsaturated analogues of the thiirane dioxides are known as the thiirene dioxides. Thermal elimination of sulphur dioxide occurs from these less readily than in the corresponding thiirane dioxides, generating the corresponding acetylenes. Since thiirene dioxides are not readily accessible systems, and since the acetylene products realised on thermolysis of these can be obtained in more convenient ways, studies of such compounds are rare. However, one such publication[13] describes evidence for the stepwise, rather than concerted, mechanism for extrusion of sulphur dioxide from

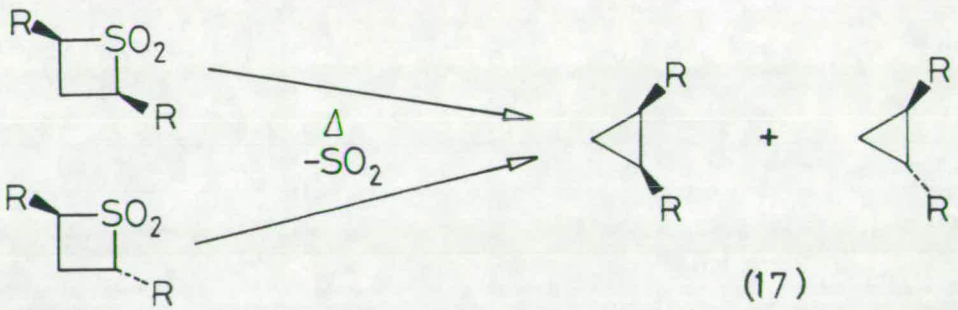
thiirene dioxides (15), resulting from analysis of kinetic data associated with the effect of varying electronegativity of substituents R,R^1 on the extrusion process.



(15)

2. Four-membered rings

Saturated four-membered sulphone-containing rings, thietane dioxides, do not in general undergo ready extrusion of sulphur dioxide. The earliest examples of thermal elimination of sulphur dioxide from thietane dioxides, observed by Dodson and Klose[14], involve the thermolysis of isomeric cis- and trans-2,4-diphenylthietane dioxides (16; R = Ph) at 250°C for a period of one hour, resulting in formation of similar mixtures of isomeric cis- and trans-diphenylcyclopropanes (17; R = Ph) from either isomer. This implies the operation of a common

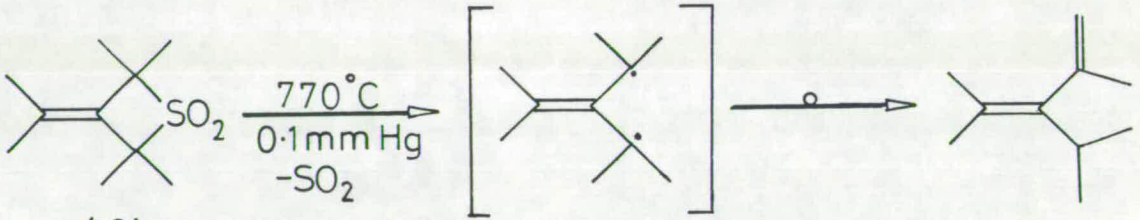


(16) (17)

diradical mechanism for extrusion from either of the thietane dioxides; the extreme conditions required to effect extrusion is also in accord with the absence of a facile, concerted pathway for this to occur. Similar results were obtained from the pyrolysis of cis- or trans-2,4-

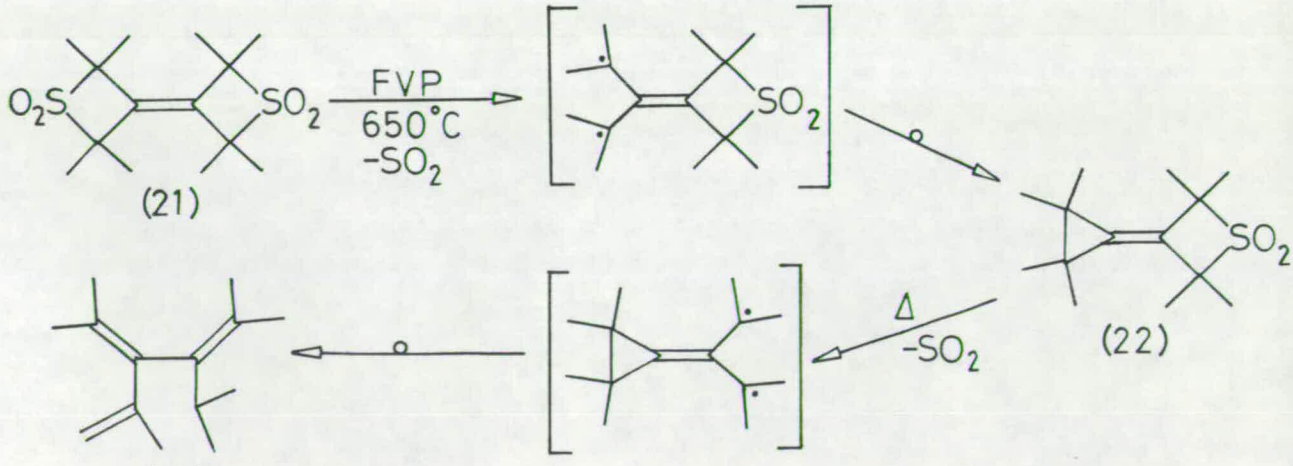
dimethylthietane dioxides (16; R = Me) at 350°C, which in addition to yielding the corresponding cis- and trans-dimethylcyclopropanes (17; R = Me), also formed cis- and trans-pent-2-ene[15].

Thietane dioxide itself has been found[16] to extrude sulphur dioxide under extreme FVP conditions (950°C) to give a high yield of almost equimolar quantities of cyclopropane and propene. As a consequence of the difficulty of preparation of thietane dioxides, and in view of the isomeric mixture of cyclic and acyclic products often obtained, this route to cyclopropane systems has little synthetic utility. However, the pyrolysis of thietane dioxides does have a useful application in the study of diradical rearrangements: the 2-methylenetrimethylene diradical (19) has been proposed[17] as an intermediate in the vacuum pyrolysis of the thietane dioxide (18) following the isolation of hydrocarbon (20). Similarly, FVP of the



(18) (19) (20)

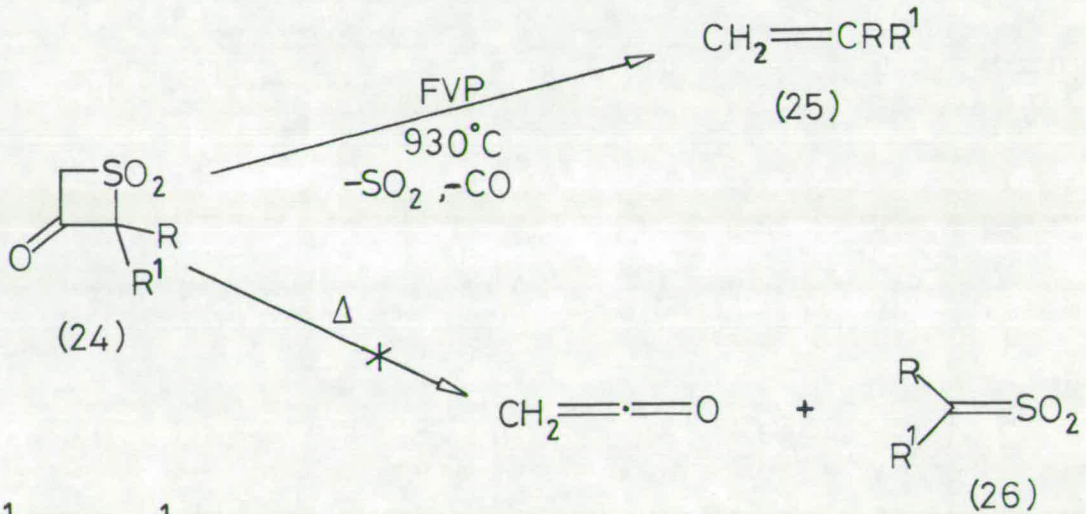
bisthietane dioxide (21) is believed[18] to generate the diradical species shown in Scheme 3 en route to the isolated thietane dioxide (22) and triene (23).



(21) (22) (23)

Scheme 3

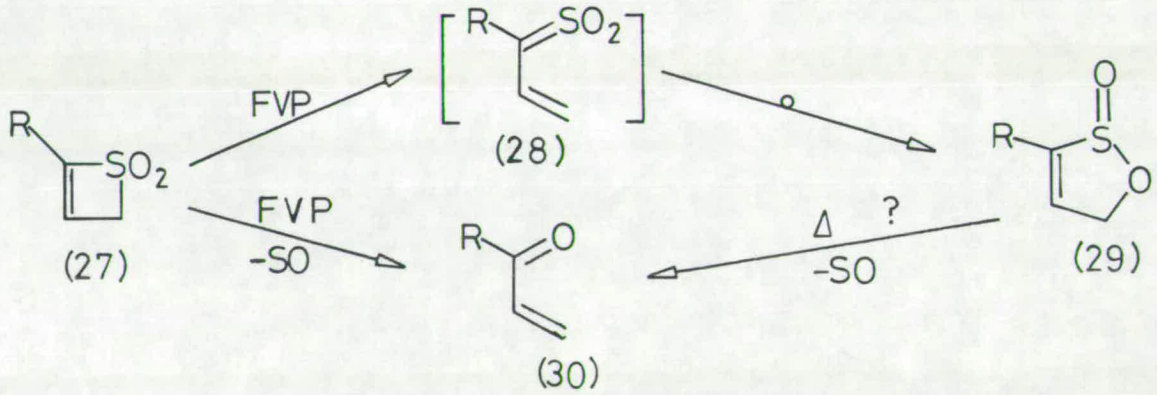
Pyrolysis of the keto-thietane dioxides (24) has been found to result in quantitative formation of the olefins (25) by extrusion of both sulphur dioxide and carbon monoxide[16,19]. The suggested mechanism for this process involves the intermediacy of a three-membered ring formed by initial extrusion of either sulphur dioxide or carbon monoxide; further extrusion from this intermediate of the remaining species (carbon monoxide or sulphur dioxide) would lead to formation of the observed olefin product (25). An alternative fragmentation pathway leading to intermediacy of ketene and a sulphene (26) was completely discounted in view of the quantitative yields of olefin (25) isolated.



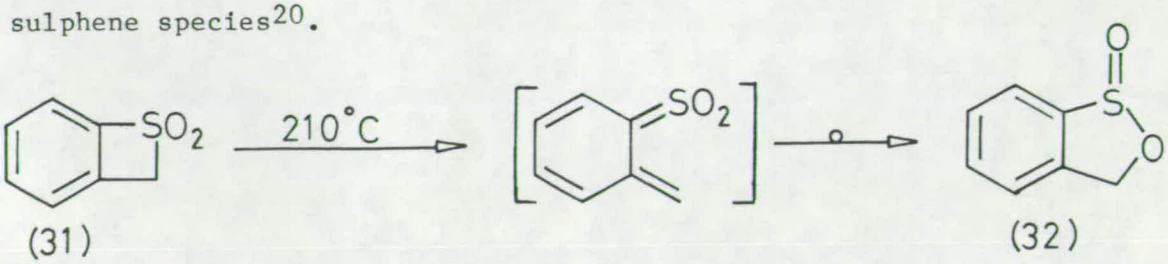
R=R^1=H; R=R^1=Me;
R=H, R^1=Ph

The unsaturated analogues of the aforementioned thietane dioxides, the thiete dioxides, show marked differences in behaviour under pyrolysis conditions to their saturated relatives. Thiete dioxides are not found to thermally extrude sulphur dioxide: the parent compound (27; R = H) on FVP under mild conditions (390°C) gave a high yield of the sultine (29; R = H)[16,19]. Vinyl sulphene (28; R = H) was indicated to be an intermediate in the thermal rearrangement

process following the successful trapping of this species. Formation of (28; R = H) may be attributed to a concerted ring opening, rather than a diradical mechanism operating on thiete dioxide (27; R = H), in consideration of the exceptionally mild pyrolysis conditions required to effect formation of sultine (29; R = H). Upon pyrolysis of (27; R = H) at elevated temperatures, acrolein (30; R = H) was detected in high yield corresponding to a loss of sulphur monoxide, possibly from sultine (29; R = H). The generality of these thermal transformations was demonstrated by similar findings[16,19] following pyrolysis of 2-phenylthiete dioxide (27; R = Ph); the use of comparatively mild FVP temperatures (455°C) resulted in formation of the phenyl-substituted sultine (29; R = H) and the phenyl-substituted vinyl ketone (30; R = Ph). Only the latter was present following FVP under fiercer conditions (at 950°C).



In similar fashion, benzo-fused thiete dioxides are known to form the corresponding sultines on heating. Thus, the neat thermolysis at 210°C of benzothiete dioxide (31) furnished the benzosultine (32) in high yield, via the suspected intermediacy of a sulphene species[20].

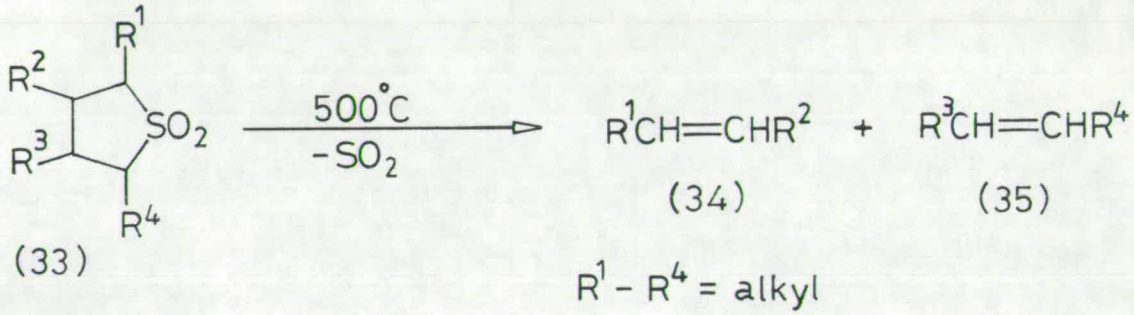


3. Five-membered rings

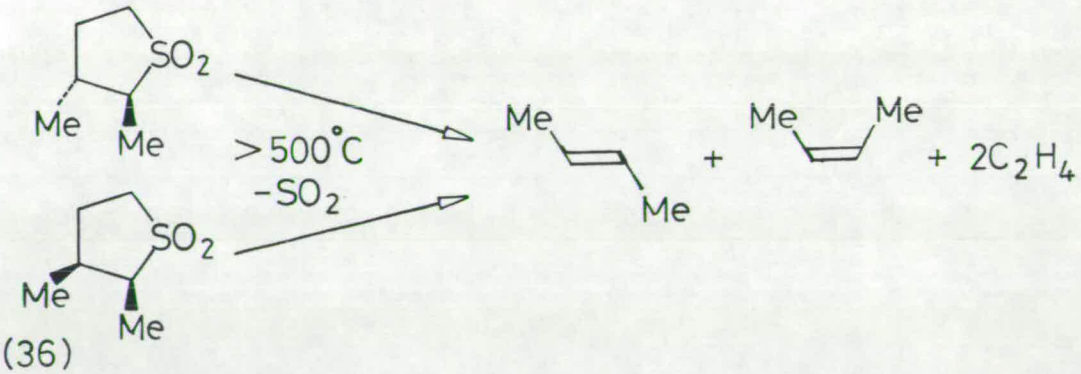
a. Sulpholanes

i. Simple sulpholanes

The saturated five-membered sulphone-containing rings, commonly known as sulpholanes, undergo thermal extrusion of sulphur dioxide only under extremely forcing conditions. Simple alkylated derivatives (33) when subjected to neat pyrolysis at 500°C lose sulphur dioxide with concomitant formation of the substituted olefins



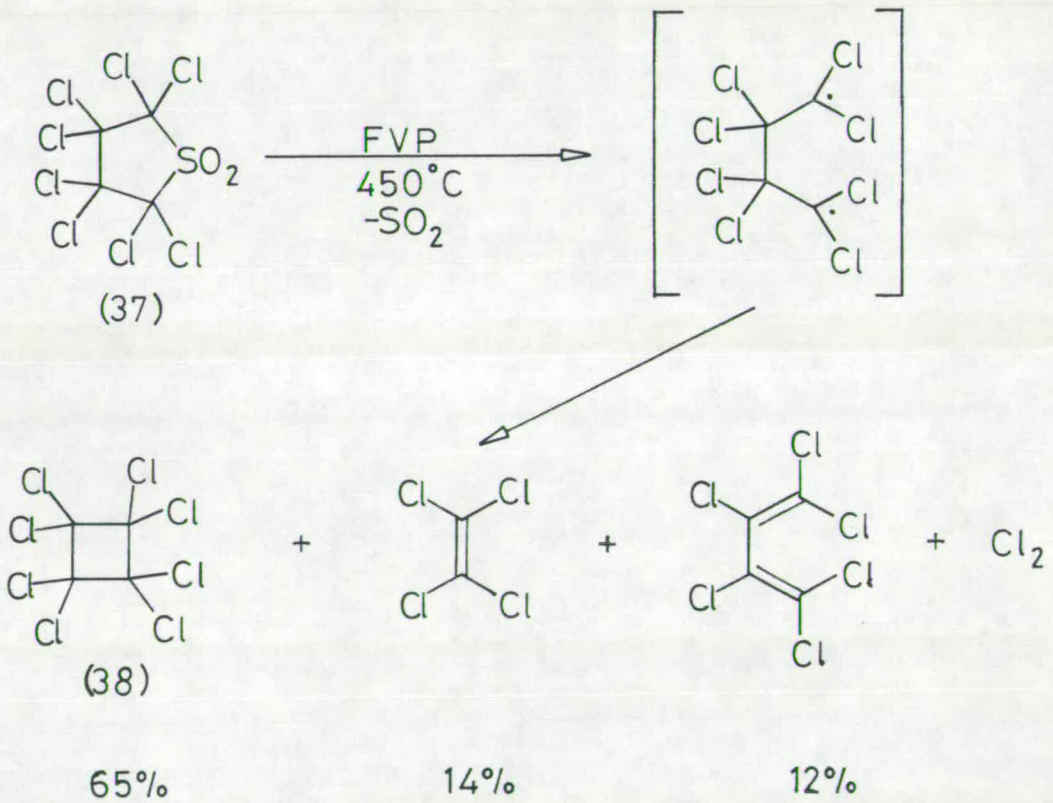
(34) and (35)[21]. A detailed study[22] of the neat pyrolysis of cis- and trans-dimethylsulpholanes (36) revealed that a similar mixture of cis- and trans-but-2-enes was realised starting from either sulpholane isomer. Formation of these products was interpreted as



arising via a radical ring cleavage mechanism, with the intermediate diradical species possessing a sufficiently long lifetime to enable rotation about the C2-C3 bond to occur prior to fragmentation to the olefin products. The extreme conditions generally required to

effect fragmentation of simple sulpholanes is in accord with the absence of ring strain in these systems, and the absence of an alternative (low energy) concerted fragmentation pathway for extrusion of sulphur dioxide to occur.

In contradistinction, FVP of perchlorosulpholane (37) under comparatively mild conditions effected complete extrusion of sulphur dioxide with generation of perchlorocyclobutane (38) as the major product, together with minor amounts of tetrachloroethylene and hexachlorobutadiene[23] (Scheme 4). A mechanism involving the



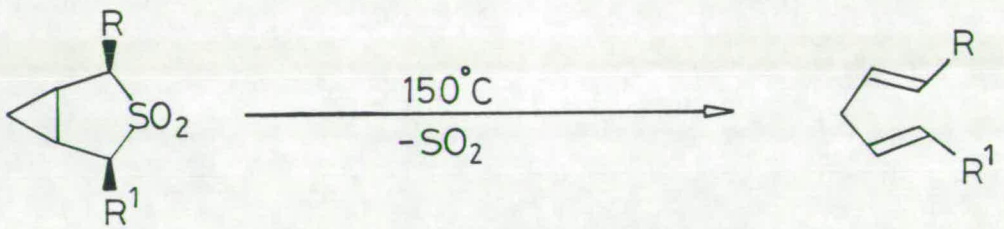
Scheme 4

intermediacy of a stabilised diradical was suspected; formation of the cyclobutane (38) was explained as resulting from a kinetically favourable ring closure of this species.

ii. Bicyclic systems containing a sulpholane ring

α. Thiabicyclo[3.1.0]hexane dioxide systems

A fair number of 3-thiabicyclo[3.1.0]hexane 3,3-dioxide systems (e.g. (39)) have been studied, these systems being of interest with regard to both synthetic and mechanistic extrusion properties. In contrast to simple (monocyclic) sulpholanes, these bicyclic systems are found to thermally extrude sulphur dioxide moderately easily by a concerted process in which the strained ring-fusion bond is cleaved. The evidence for a concerted mechanism for the extrusion process was provided by Mock[24] who established that the cyclopropyl-sulpholane system (39; R = R^1 = Me) underwent a thermal expulsion of sulphur dioxide on thermolysis at 150°C stereospecifically to give (E,E)-hepta-2,5-diene (40; R = R^1 = Me). A concerted ($\sigma_{2s} + \sigma_{2s} + \sigma_{2s}$)

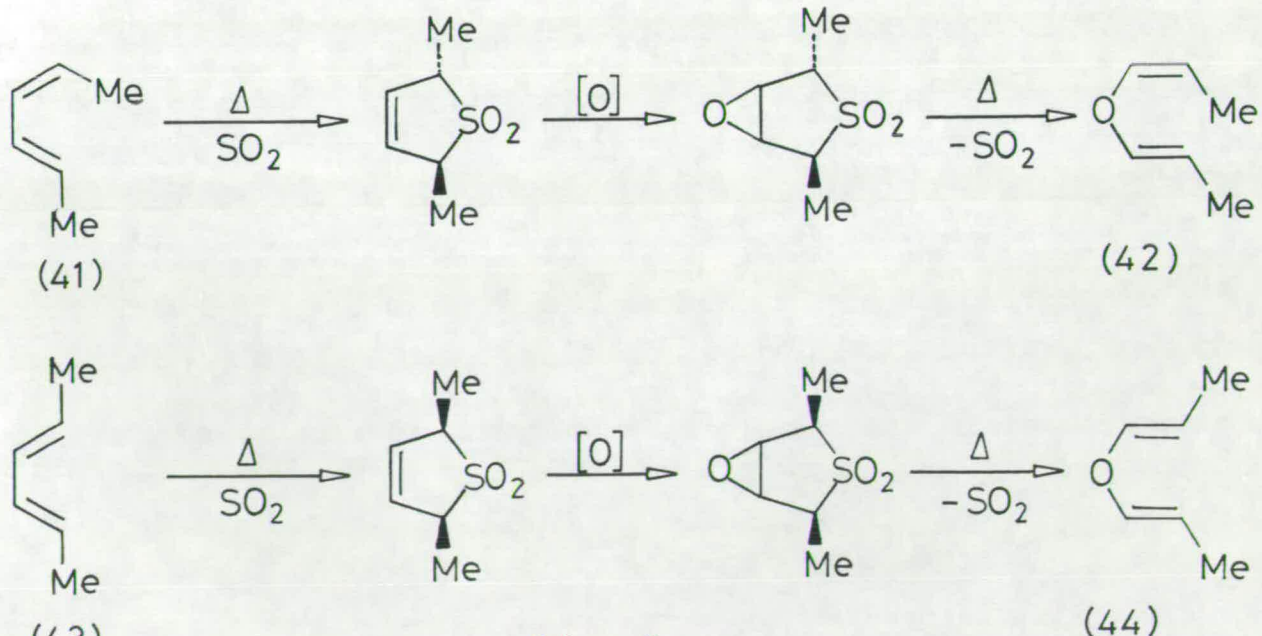


(39) (40)

cycloreversion, as predicted by the Woodward-Hoffmann rules[25], appears to be operating. The absence of (Z,Z)-hepta-2,5-diene, the formation of which is theoretically possible on the basis of a concerted disrotation of the two methyl groups during the extrusion process, was attributed to the presence of destabilising steric interactions between these groups in the transition state leading to formation of this diene. In contradistinction, thermolysis of a bridged analogue (39; R,R^1 = $CH_2CH_2CH_2$) at relatively extreme temperatures (300°C),

failed to cause dislodgment of sulphur dioxide. In this instance, the strain inherent in the two possible products resulting from concerted extrusion of sulphur dioxide, the (E,E)- or (Z,Z)-cycloocta-1,4-dienes, was sufficient to disfavour the concerted extrusion process from occurring.

Following from the ease of extrusion of sulphur dioxide from simple 3-thiabicyclo[3.1.0]hexane 3,3-dioxide systems and the resultant isolation of stereochemically pure 1,4-diene products, this thermal process does possess synthetic utility. An additional attraction in the use of these sulphone systems for this purpose lies in their ready availability *via* reaction of simple electrophilic species with 3-sulpholenes (the adducts of 1,3-dienes and sulphur dioxide). Overall then, the reaction sequence may be regarded as a transformation of 1,3- to 1,4-dienes in which sulphur dioxide acts as a readily removable stereochemical director. This is exemplified[24] by the conversion of (E,Z)-hexa-2,4-diene (41) and the corresponding (E,E)-isomer (43) in good yield to (E,Z)-dipropenyl ether (42) and its (E,E)-isomer (44) respectively, by the stereospecific reaction sequence displayed in Scheme 5. Other substituted 1,4-dienes have

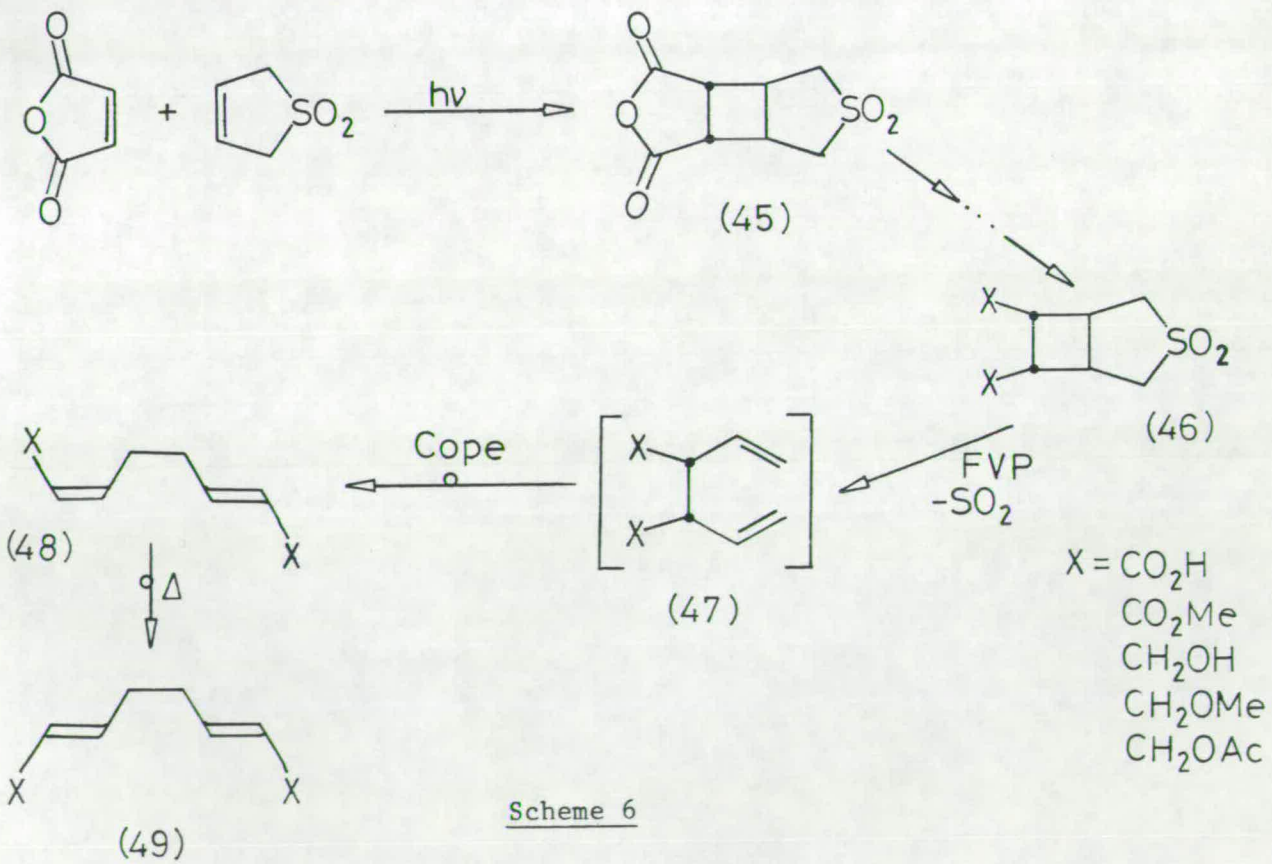


Scheme 5

been prepared similarly by the reactions of carbenes and nitrenes with selected 3-sulpholenes[24,26].

β. Thiabicyclo[3.2.0]heptane dioxide systems

The bulk of published research into the preparation and thermal fragmentation behaviour of the title systems has been carried out within these laboratories. Following the findings of Shaikhrazieva et al[27] that 3-sulpholene and maleic anhydride undergo a facile photochemical [2π + 2π] cycloaddition with formation of the transoid tricyclic system (45), considerable effort has been directed towards the preparation of substituted bicyclic and higher-cyclic derivatives of this compound, containing the basic fused cyclobutane and sulpholane ring assembly. Flash vacuum pyrolysis of the derived cis-6,7-disubstituted-3-thiabicyclo[3.2.0]heptane 3,3-dioxide systems (46) has produced a useful stereoselective synthesis of disubstituted (E,Z)-hexa-1,5-dienes (48) (Scheme 6)[28]. Thermal



Scheme 6

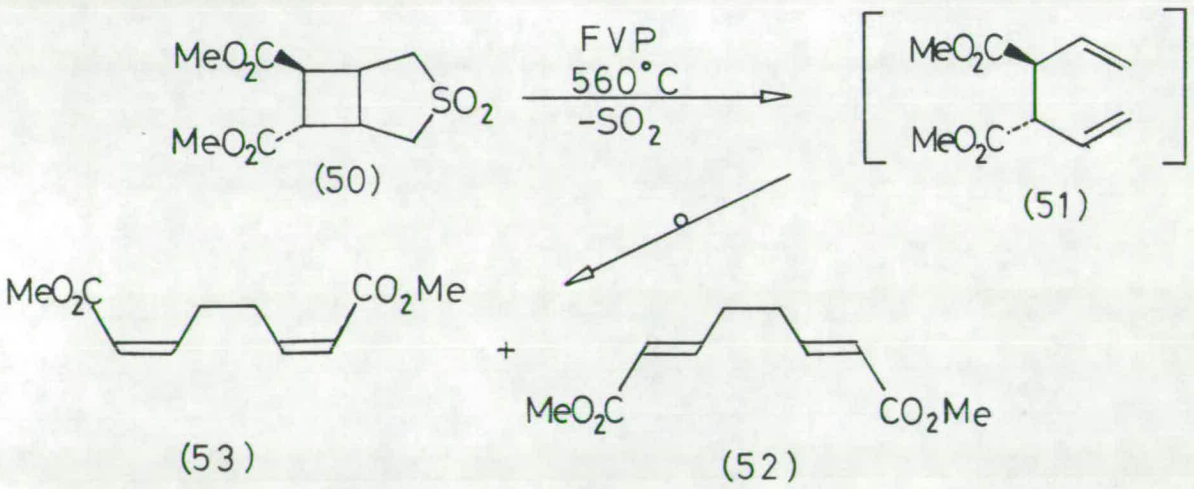
extrusion of sulphur dioxide, possibly *via* a concerted mechanism, was found to occur with initial formation of *cis*-divinyl compounds (47), which were isolated in some cases where a FVP temperature of *ca* 530°C was employed[29]. At higher temperatures (600-650°C), the initially formed divinyl species underwent a Cope rearrangement *via* a chair-like transition state[30,31] to give as isolated products, (*E*,*Z*)-hexa-1,5-dienes (48), together with - in some instances - a minor quantity of the corresponding (*E*,*E*)-isomer (49), formed by a thermally-induced *cis*-*trans* isomerisation of (48).

By way of example, FVP (550°C, 10^{-3} mm Hg) of diester (46; X = CO_2Me) has been reported[28] as realising the (*E*,*Z*)-diene (48; X = CO_2Me) (78%) and the corresponding (*E*,*E*)-isomer (49; X = CO_2Me) (9%). It is theoretically possible, but very unlikely on energetic considerations, that formation of the latter product may arise from Cope cyclisation *via* a disfavoured boat-like transition state of the intermediate *cis*-divinyl species (47; X = CO_2Me). Evidence that this is not the case, and that the minor (*E*,*E*)-isomer arises from a thermal *cis*-*trans* isomerisation process, was furnished by the results of vacuum pyrolysis (500°C, 0.5 mm Hg) - rather than flash vacuum pyrolysis - of (46; X = CO_2Me). This was found[29] to give only the (*E*,*Z*)-diene (48; X = CO_2Me); the absence of the (*E*,*E*)-isomer (49; X = CO_2Me) was rationalised as being due to collisional deactivation of the vibrationally excited (*E*,*Z*)-isomer which consequently possessed insufficient vibrational energy to undergo isomerisation to the more thermodynamically stable (*E*,*E*)-isomer. The intermediacy of the *cis*-divinyldiester (47; X = CO_2Me) was proven by FVP at 580°C of an independently synthesised sample: (48; X = CO_2Me) was obtained as the sole product, in contradistinction to the FVP of (46; X = CO_2Me) under

identical conditions. It appears feasible, therefore, that a thermal isomerisation of (48; X = CO_2Me) to (49; X = CO_2Me) is operating, this being facilitated by generation of the divinyl species (47; X = CO_2Me) in a vibrationally excited state following thermal expulsion of sulphur dioxide from (46; X = CO_2Me).

This example demonstates an oft-encountered drawback of the FVP technique: the use of high vacuum which facilitates sample volatilisation and severely curtails intermolecular interactions (leading to formation of unwanted by-products) also prevents effective collisional deactivation of the initially formed, vibrationally excited species which then lose energy by undergoing complicating secondary intramolecular rearrangements, or fragmentations.

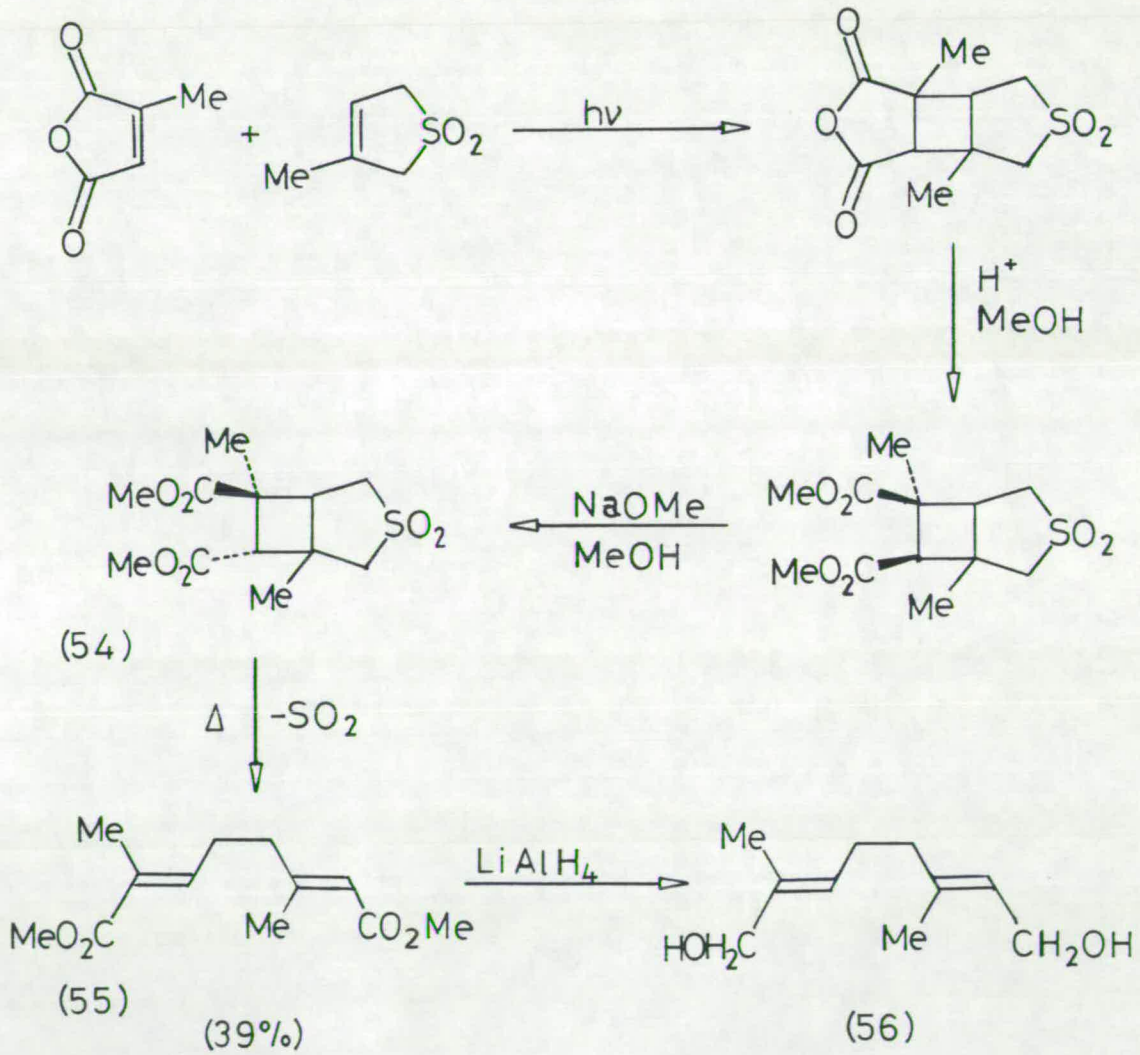
The corresponding trans-diester system (50) has been found[28,29] to thermally extrude sulphur dioxide with formation of two diester



(50) (51) (53) (52)

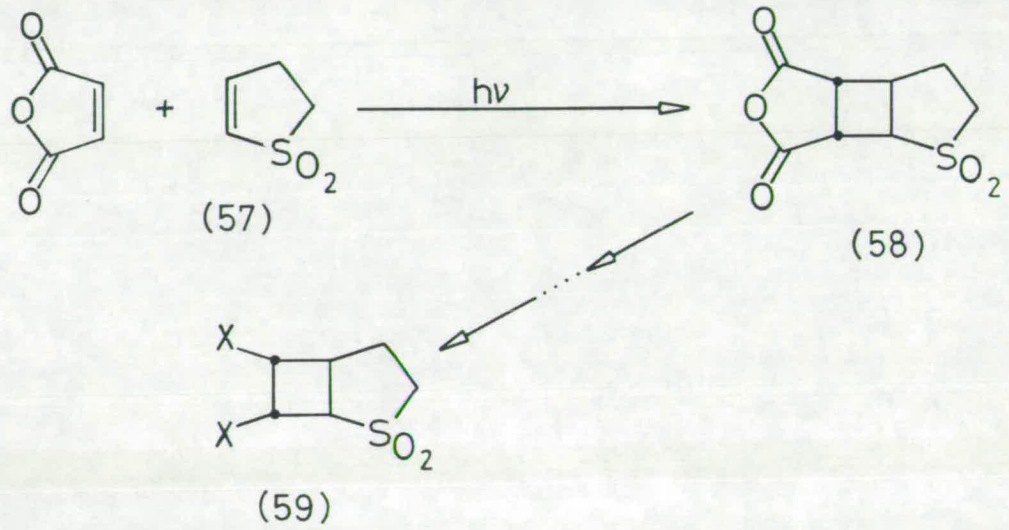
substituted-1,5-dienes, the (E,E)-isomer (52) (54%) and the (Z,Z)-isomer (53) (9%). Both of these products are in accord[30,31] with those expected from Cope rearrangement of the intermediate (d1)-divinyl species (51) via a chair-like transition state. Others[32] have utilised a related trans-6,7-diester system (54) for the synthesis

of the (E,E)-1,5-diene, 10-hydroxygeraniol (56), a biosynthetic precursor of indole alkaloids. The reaction sequence, outlined in Scheme 7, leading to this diene is of little synthetic utility due primarily to the formation of four isomeric 1,5-dienes on pyrolysis of the asymmetric bicyclic sulpholane system (54); chromatographic separation of the (E,E)-diene (55) which possesses the required geometry for reduction to 10-hydroxygeraniol (56) renders the overall synthetic route unattractive.



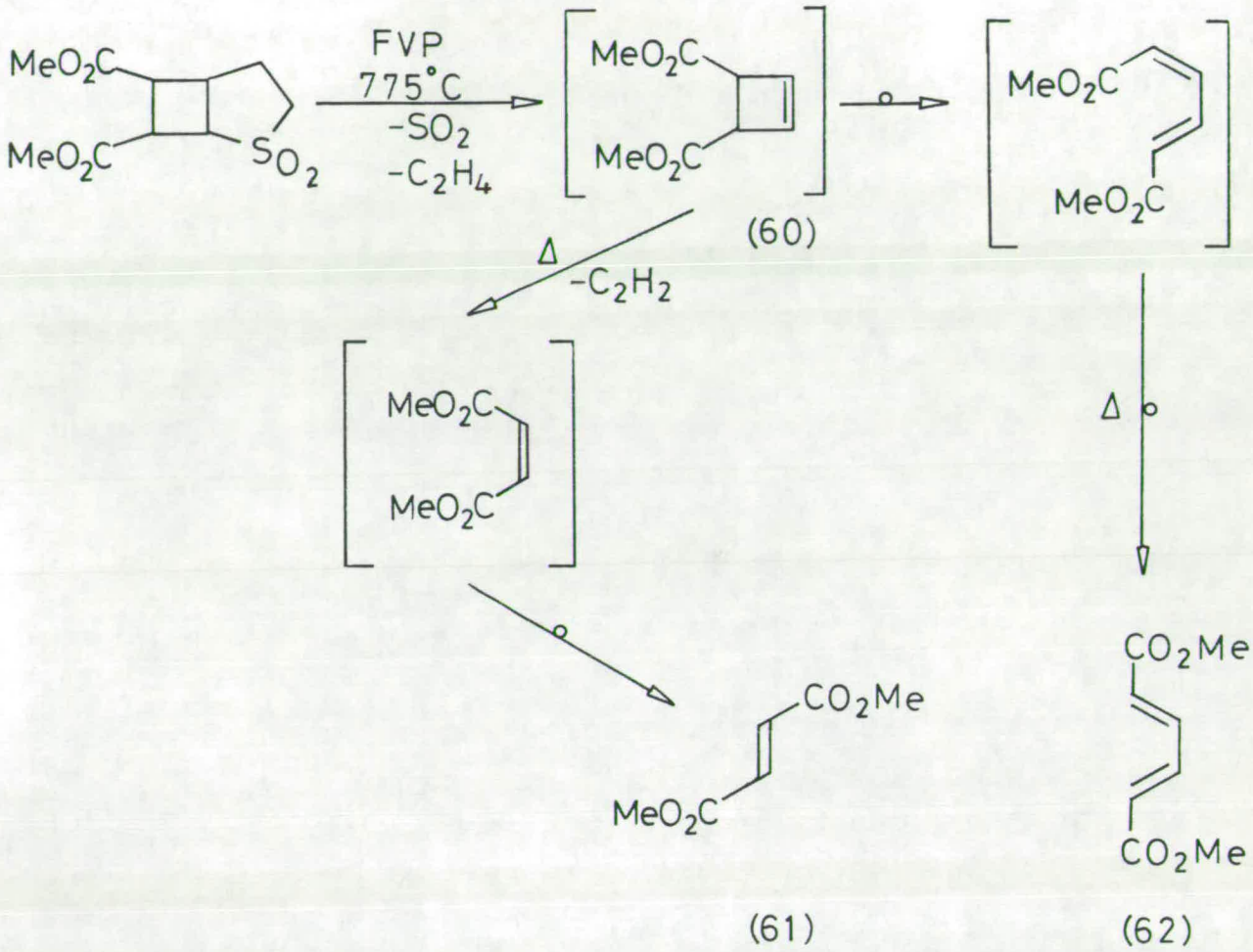
Scheme 7

In addition to the substituted 3-thiabicyclo[3.2.0]heptane 3,3-dioxide derived systems described above, the corresponding 2-thia dioxide analogues have been prepared and their thermal extrusion behaviour studied within these laboratories. These systems were obtained[33] by a parallel route (Scheme 8) to their 3-thia dioxide isomers, replacing 3-sulpholene by 2-sulpholene (57) in the initial photolysis step: 6,7-disubstituted-2-thiabicyclo[3.2.0]heptane



Scheme 8

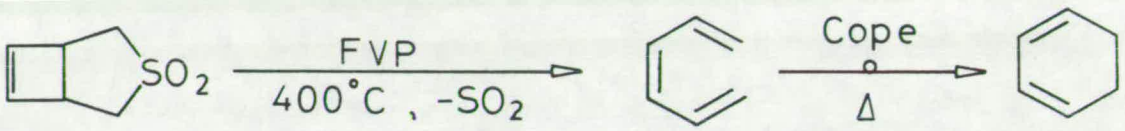
2,2-dioxide systems (59) are obtained by ready chemical manipulation of tricyclic anhydride (58). Such similarity in the synthesis of the 2- and 3-thiabicyclic sulpholane systems is not maintained with respect to pyrolytic behaviour. Whereas the 3-thia dioxide (46; X = CO_2Me) undergoes[28] loss of sulphur dioxide on FVP at 550°C to give high yields of acyclic products, formed by rearrangement of intermediate (47; X = CO_2Me), the corresponding 2-thia dioxide analogue (59; X = CO_2Me) has been found[33] to require much more forcing FVP conditions (775°C) to effect expulsion of sulphur dioxide. As shown in Scheme 9, both sulphur dioxide and ethylene are extruded with formation of



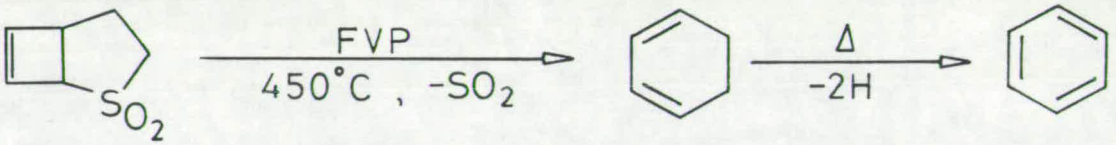
Scheme 9

the intermediate cyclobutene diester (60) leading to generation of the isolated products, dimethyl fumarate (61) and dimethyl (E,E)-hexa-2,4-dienedioate (62) by the rearrangement/fragmentation processes outlined[33]. The low yield of these isolated products, taken in conjunction with the forcing conditions required to cause extrusion, is indicative of a radical mechanism for fragmentation of the 2-thia dioxide system (59; X = CO_2Me). In contradistinction, the milder conditions required for the extrusion of sulphur dioxide from the 3-thia dioxide isomer (46; X = CO_2Me), coupled with the high yields of isolated products is in accord with a lower energy, concerted pathway for this process.

Two unsaturated systems, 3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide (63) and the isomeric 2-thia dioxide analogue (64) have received some attention. FVP of the former at 400°C resulted in facile elimination of sulphur dioxide with isolation of high yields of



(63)



(64)

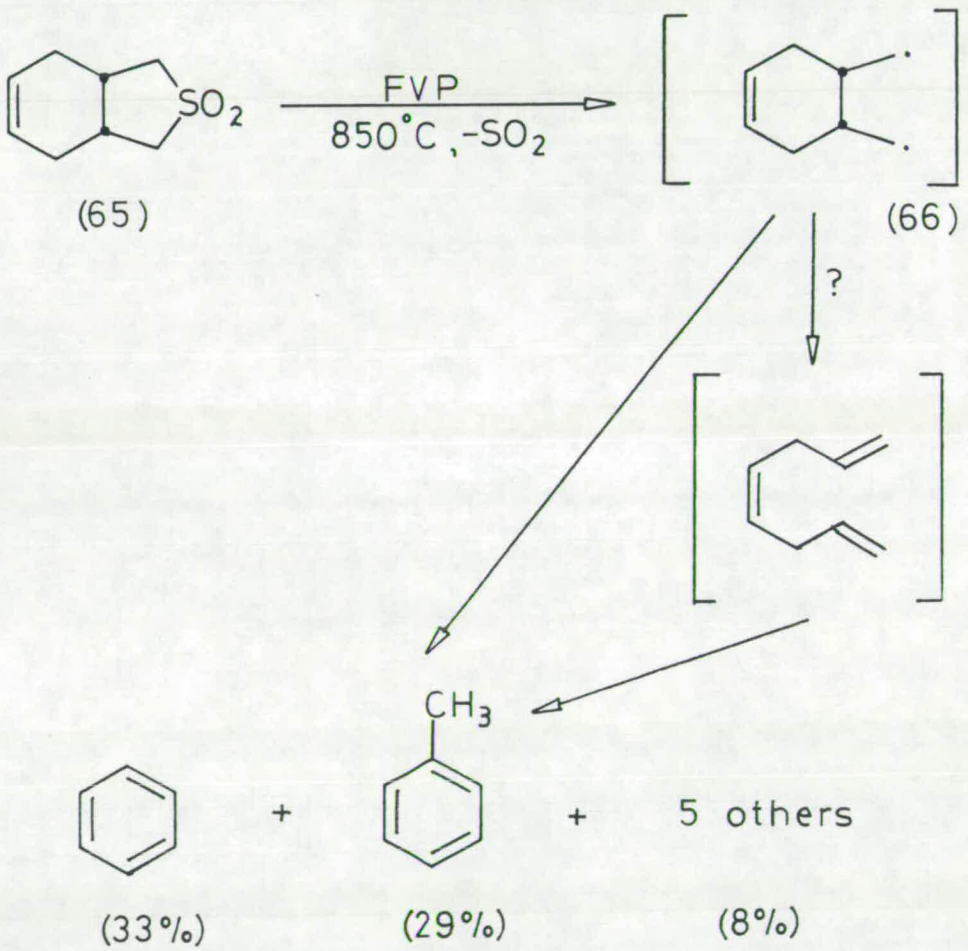
an equimolar mixture of (Z)-hexa-1,3,5-triene and cyclohexa-1,3-diene[34]. Bicyclic sulpholane (63) may be regarded as a masked form of (Z)-hexa-1,3,5-triene, forming the triene under mild pyrolysis conditions, most probably by a concerted extrusion mechanism; rearrangement of the triene to yield cyclohexa-1,3-diene explains the presence of the latter product. Pyrolysis of the isomeric sulpholane (64) also furnished cyclohexa-1,3-diene together with minor quantities of benzene, although only 35% of consumed sulpholane (64) could be accounted for by formation of these products[33]. It would therefore appear that fragmentation of (64) to very volatile, non-isolated products (e.g. acetylene, ethylene) also occurs.

γ. Higher bicyclic systems

Systems derived from fusion of a sulpholane ring with a three- or four-membered ring have been described above. Those bicyclic

systems comprising fused sulpholane and five-membered rings, although known in the literature, have not been studied with respect to thermal extrusion reactions. However, thiabicyclo[4.3.0]nonene dioxide systems (fused sulpholane-cyclohexene systems) have received some attention.

Fragmentation of cis-8-thiabicyclo[4.3.0]non-3-ene 8,8-dioxide (65) required a forcing FVP temperature of 850°C to be applied[33].

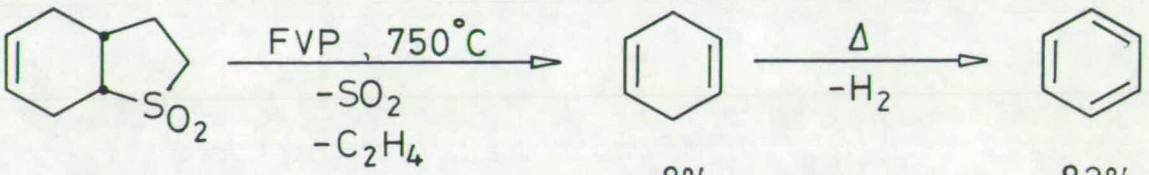


Scheme 10

The mechanism for fragmentation remains unclear, but the high temperature required would imply that a radical mechanism for extrusion of sulphur dioxide is operating. Initial formation of diradical (66)

followed by further fragmentation, rearrangement and dehydrogenation processes operating on this under the extreme conditions employed may account for formation of the observed products, mainly benzene and toluene (Scheme 10).

In contradistinction, the isomeric 7-thiabicyclo[4.3.0]non-3-ene 7,7-dioxide (67) was found[33] to undergo clean expulsion of both sulphur dioxide and ethylene to yield cyclohexa-1,4-diene, and by



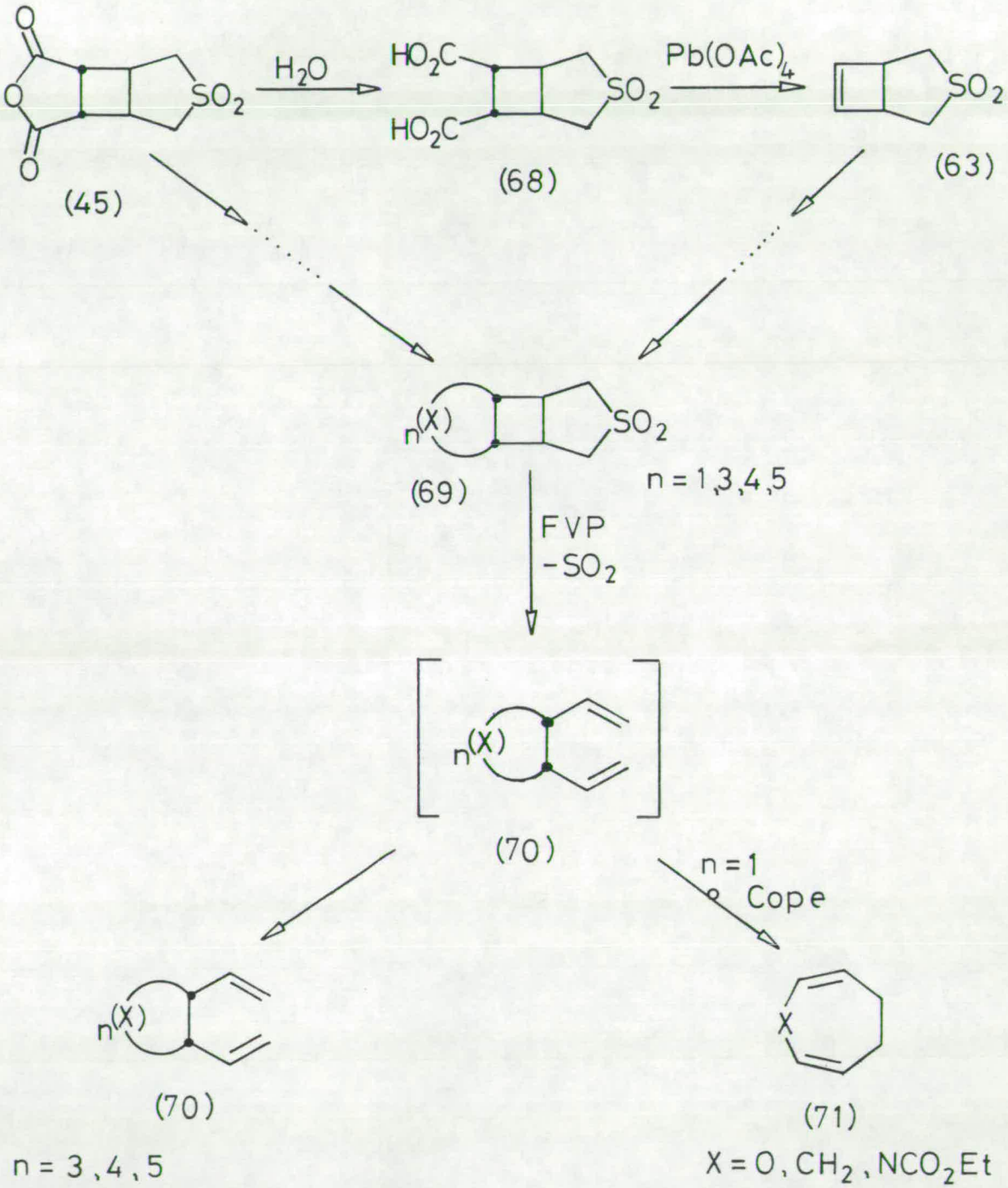
(67)

dehydrogenation of this, benzene. This fragmentation mirrors that of the simple sulpholanes described earlier: the result of extrusion of sulphur dioxide is the formation of two olefins. This parallel and consideration of the rather elevated pyrolysis temperature required form indirect evidence for a radical extrusion process operating in the case of (67).

iii. Tricyclic systems containing a sulpholane ring

Examination of the thermal extrusion behaviour of the title systems has in the main been restricted to these laboratories. A number of tricyclic systems (69) comprising fusion of a central cyclobutane ring to a sulpholane ring, and to a terminal ring of varying size, have been prepared[29,33,35] by manipulation of the tricyclic anhydride (45) as outlined in Scheme 11. Extrusion of sulphur dioxide from the tricyclic systems is generally effected on FVP at 500-600°C

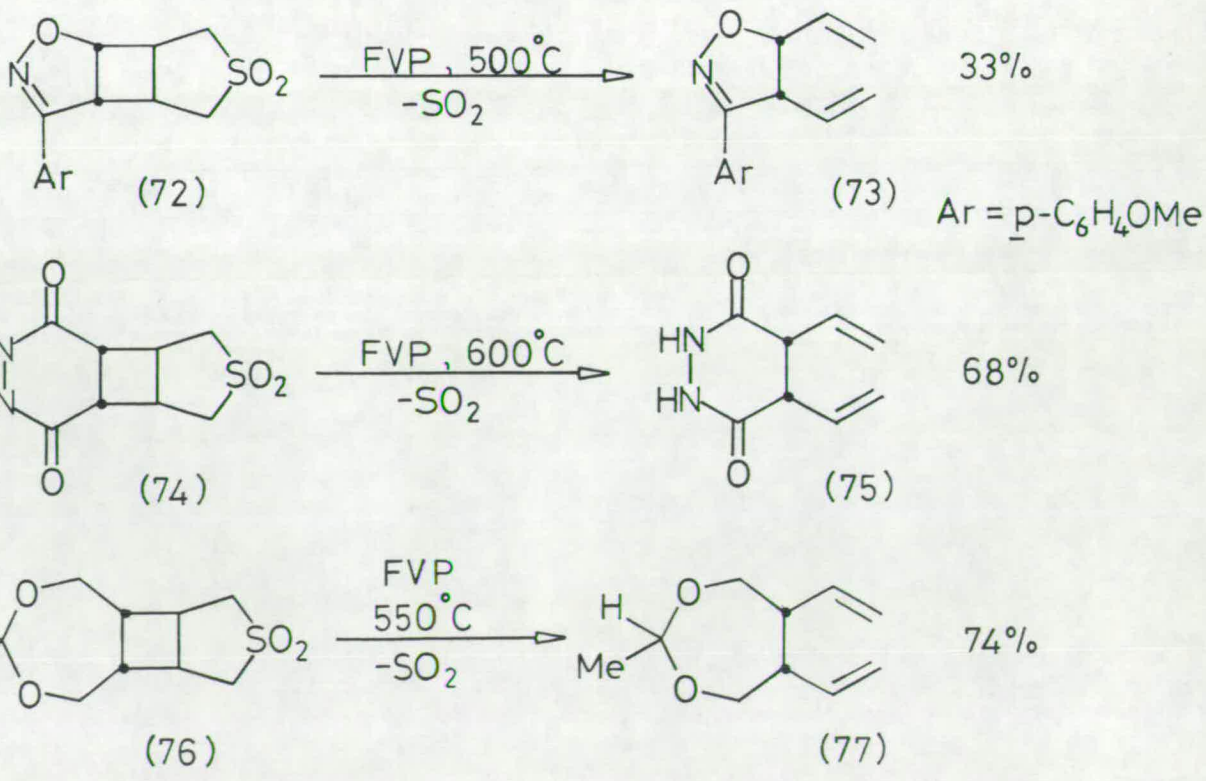
to give initially a cis-divinyl cyclic system (70) in direct analogy to the substituted bicyclic systems (46) whose pyrolyses have been



Scheme 11

already covered (Scheme 6). The stability of the divinyl systems (70) to the pyrolysis conditions employed has been found[34] to depend on the ring size of the cyclic moiety, i.e. on the value of n. For tricyclic systems (69; n = 1), prepared from olefin (63) by reaction with electrophilic species, the divinyl compounds (70; n = 1) are not isolated on extrusion of sulphur dioxide: a facile Cope rearrangement of the intermediate cis-divinylcyclopropyl system to the corresponding cyclohepta-1,4-diene (71) is observed, the driving force being the alleviation of ring strain in accord with precedent[30] for such Cope rearrangements. Thus, pyrolysis of epoxide (69; X = O, n = 1) under flash vacuum conditions (580°C) resulted in complete extrusion of sulphur dioxide and isolation of 4,5-dihydrooxepin (71; X = O) in 55% yield[34].

Tricyclic systems (69; n = 2) have not been described previously and hence the extrusion processes operating on these systems have not been studied. Preparation and FVP of these tricyclic sulpholane systems forms a significant part of the experimental work described later in this thesis. The more readily available tricycles (69; n = 3) have, however, received considerable attention with



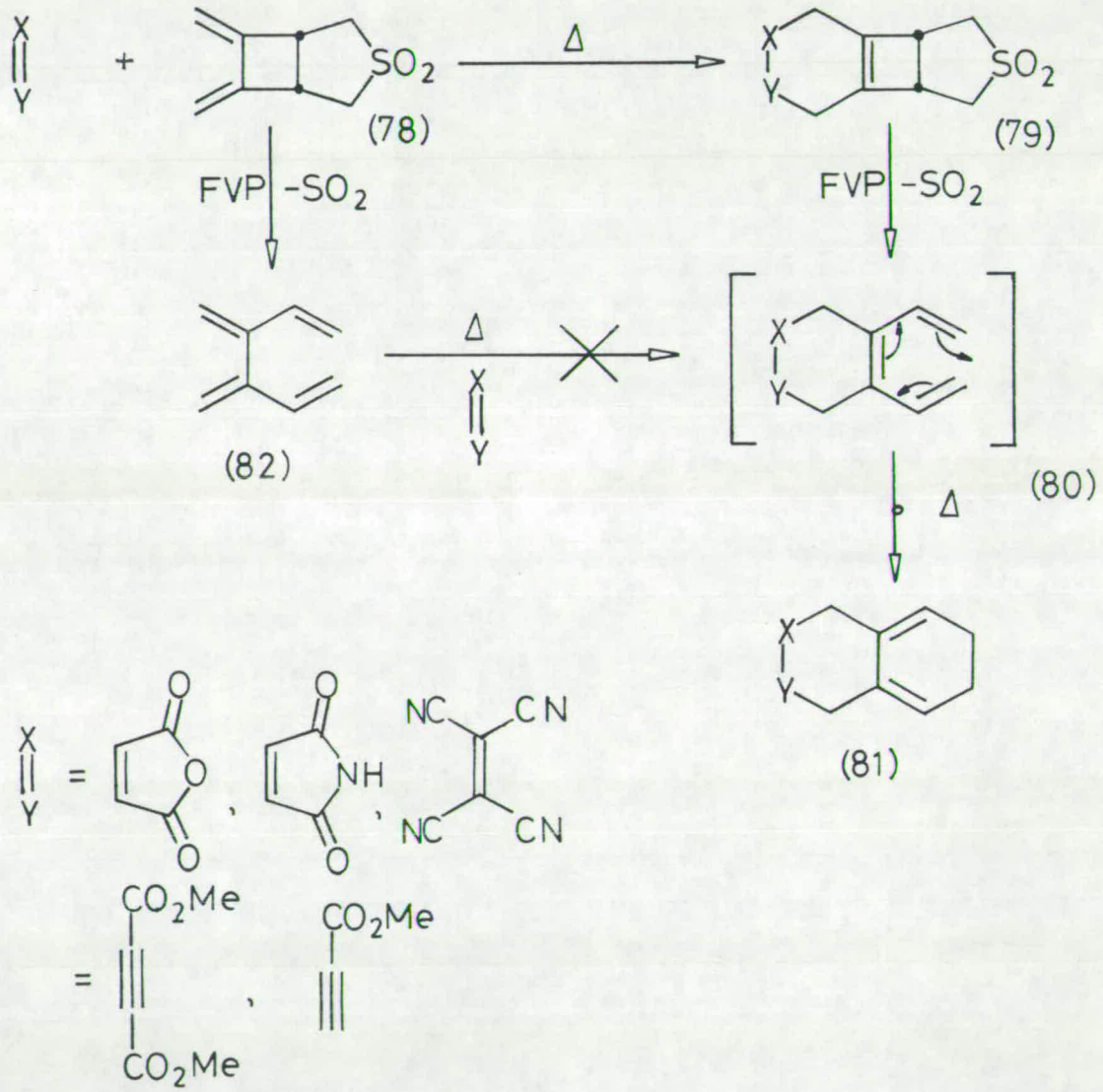
(72) (73) (74) (75) (76) (77)

respect to thermal fragmentation behaviour. Such compounds have been found to extrude sulphur dioxide at moderate temperatures to yield stereospecifically the corresponding cis-1,2-divinylcyclopentane analogues (70; n = 3), known[30] not to undergo Cope cyclisation to cyclononadienes due to the increased ring strain associated with the latter. Consequently, the reaction sequence whereby systems (69; n = 3) are obtained by reaction of olefin (63) with a suitable reagent, followed by FVP of the former, may be considered as a viable synthetic route to cis-divinylcyclopentanes (70; n = 3)[34,36]. These are not easily obtained by other routes - a lack of regiocontrol frustrating straightforward preparation by reaction with the central olefinic bond of hexa-1,3,5-triene - hence the use of olefin (63) as a conveniently masked form of hexa-1,3,5-triene is highly effective. For example, FVP of tricyclic sulpholane (72), the adduct of p-anisonitrile oxide and cyclobutene sulpholane (63), generated the cis-divinyl heterocycle (73) in 33% yield following extrusion of sulphur dioxide[34]. Higher tricyclic systems (69; n = 4,5) are found to behave similarly: FVP of sulpholanes (74) and (76) has resulted in extrusion of sulphur dioxide with formation of the cis-divinyl cyclic systems (75) and (77) respectively[29].

Although pyrolysis of systems (69) has generally been found to result in extrusion of sulphur dioxide at moderate temperatures with generation of clean products in reasonable yields, the mechanism of extrusion has not been established, though this is likely to be concerted in nature. Suitable substitution of both α-sulpholane positions followed by determination of stereochemistry of the unsaturated extrusion products may well establish if loss of sulphur dioxide from (69) proceeds by a concerted or radical mechanism.

A number of unsaturated analogues of tricyclic sulpholanes (69; n = 4) have been reported[37]. These compounds (79), assembled by

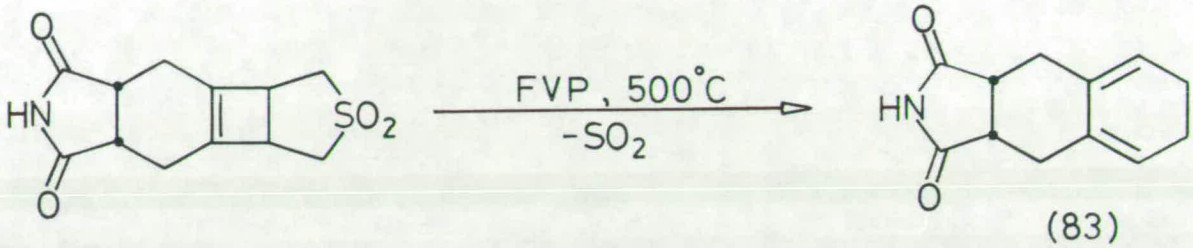
Diels-Alder reaction of the dimethylene sulpholane (78) with various dienophiles, eliminate sulphur dioxide on FVP at temperatures of ca 500°C to form a useful synthesis of annelated six-membered rings (81) via electrocyclisation of suspected intermediate 1,3,5-triene (80) (Scheme 12). This is exemplified by preparation of tricyclic system (83) in good yield by FVP at 500°C of the adduct of diene (78) with maleimide[37].



Scheme 12

In common with cyclobutene-sulpholane (63), the dimethylene-sulpholane (78) may be considered as a sulphur dioxide masked form of a more reactive (less regioselective) unsaturated compound. In the case of (78), the sulpholane is a masked form of [4]dendralene (82),

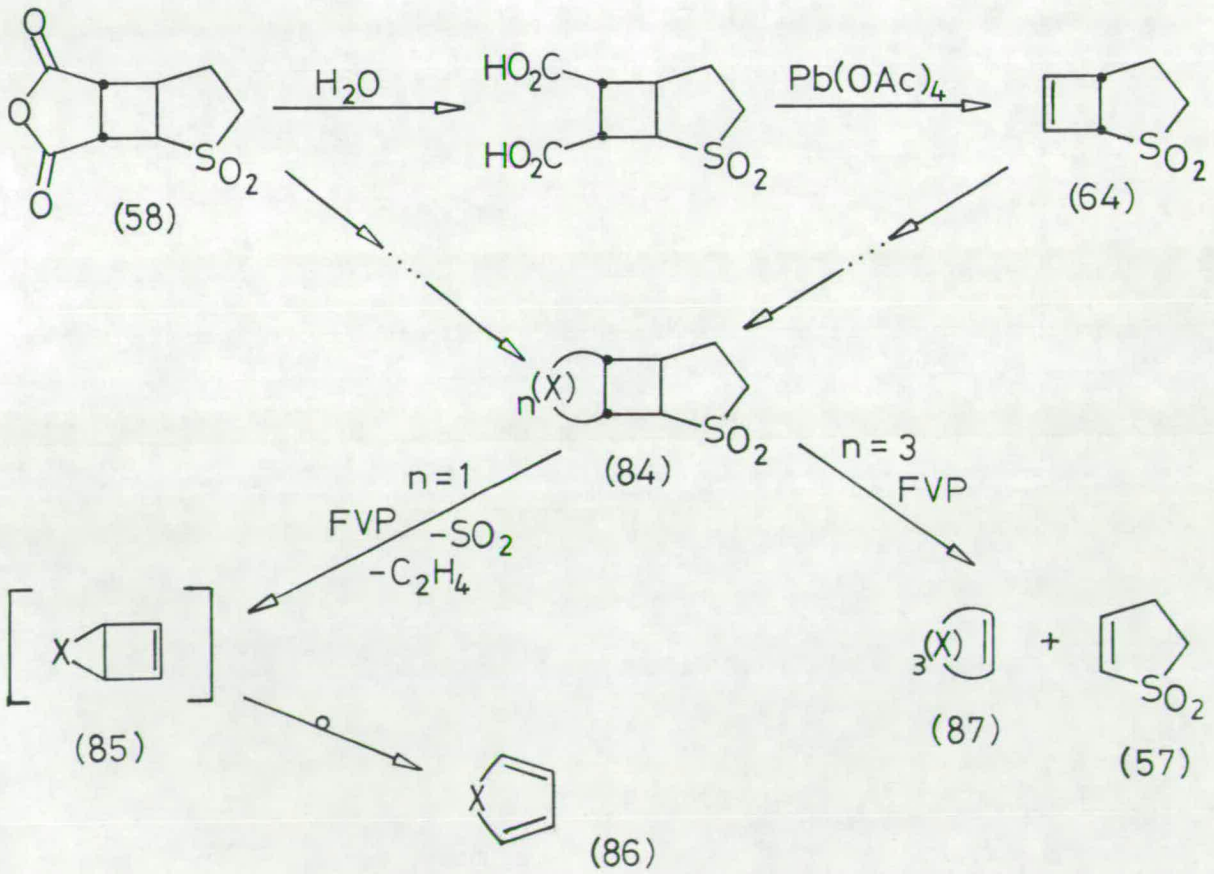
and this has been demonstrated[37] by production of (82) in quantitative yield following FVP of (78) at 550°C. The use of [4]dendralene itself



(83)

in the synthesis of annelated ring systems (81) is frustrated by the indiscriminate reaction of this species with dienophiles in which bis- and possibly higher-Diels-Alder adducts are found[38] to form; the utility of the sulpholane route to systems (81) is thus evident.

Tricyclic systems (84) comprising a central cyclobutane ring fused to a sulpholane ring (α to the sulphone group) and to a three- or five-membered ring have been described[33], these being prepared by direct or indirect (i.e. via olefin (64)) manipulation of anhydride (58) (Scheme 13). In similar fashion to the related



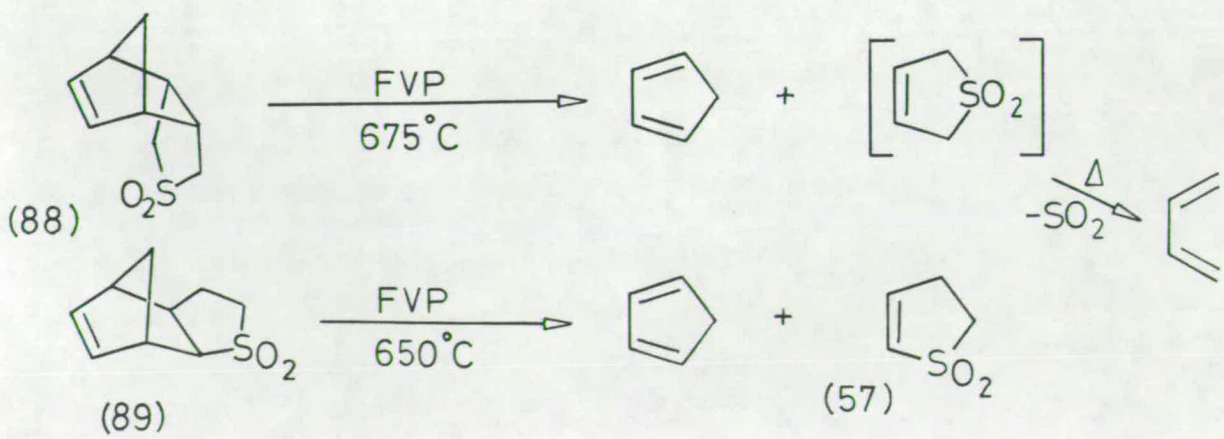
(58) (64) (84) (85) (86) (87) (57)

Scheme 13

tricyclic systems (69), a dependence of fragmentation pathway on terminal ring size (value of n) in (84) has been deduced. Thus, the epoxide (84; X = O, n = 1) has been found to undergo expulsion of both sulphur dioxide and ethylene on FVP at 550°C to generate a high yield of furan (86; X = O) as the isolated product. The intermediacy of Dewar furan (85; X = O) is implicated in this extrusion process. Overall, the reaction sequence involving epoxidation of olefin (64), followed by pyrolysis of the resultant epoxide (84; X = O, n = 1) to generate (85; X = O) demonstrates that cyclobutene sulpholane (64) may be considered to be a cyclobutadiene synthon[33].

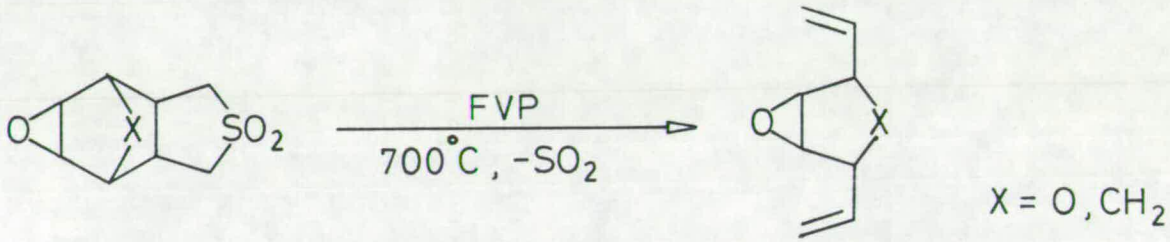
Five-membered terminal ring systems (84; n = 3) have been shown to undergo fragmentation by a completely different route to their smaller ring brethren (84; n = 1). Under extreme conditions, typically 750-800°C, FVP of these systems results in scission of the central cyclobutane ring in a thermally forbidden [$2\pi_s + 2\pi_s$] cycloreversion reaction to generate 2-sulpholene (57) and a cyclopentene-based product (87). Anhydride (58) is typical, undergoing scission to 2-sulpholene (57) and maleic anhydride in ca 65% yield on FVP at 800°C, these two products being the starting materials from which (58) was initially formed by photolysis[33].

Other tricyclic compounds containing a sulpholane ring which have been pyrolysed are restricted to bridged systems such as



(88) and (89). Both of these sulpholanes undergo fragmentation at moderate temperatures to generate cyclopentadiene and the corresponding sulpholene[33]. The extrusion mechanism is known to be a concerted, retro-Diels-Alder reaction for systems based on (88), and possesses synthetic utility in the preparation of dienes, as detailed later (p. 35).

Pyrolysis of saturated tetracyclic sulpholanes (90), derived by epoxidation of bridged olefin precursors, demonstrated the marked difference in extrusion pathway found on removal of the olefinic



(90) (91)

double bond of the unsaturated precursors. Extrusion of sulphur dioxide with formation of the novel 1,3-divinyl bicyclic structures (91) in good yield was noted[33].

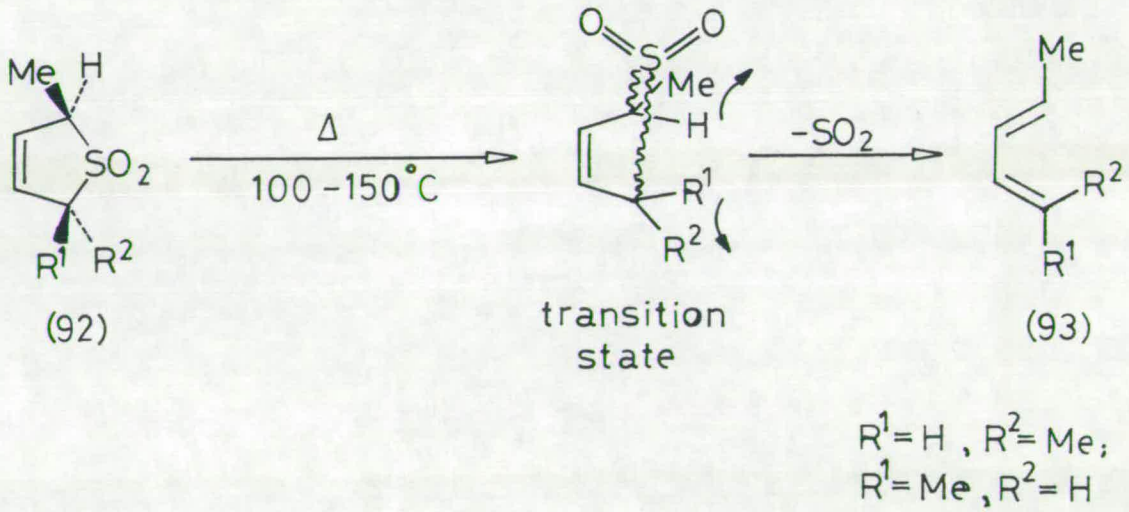
b. Sulpholenes

i. Simple sulpholenes

Sulpholenes are the dehydro analogues of sulpholanes, and they can be subdivided into two categories, the 2- and 3-sulpholenes, the difference arising from the positioning of the olefinic double bond with respect to the sulphone group in the five-membered ring. In terms of synthetic and mechanistic applications, the 3-sulpholenes are by far the more important of the two. This is reflected in the widely encountered but non-specific term in sulphone chemistry of the 'sulpholene reaction' - used to describe the reaction between 1,3-dienes and sulphur dioxide with formation of 3-sulpholenes (but not 2-sulpholenes). It is the facile nature of this reaction - and

its ready thermal reversibility to a 1,3-diene and sulphur dioxide - that have resulted in the predominance of study into 3-sulpholene rather than 2-sulpholene systems. Synthetic applications of the sulpholene - reverse sulpholene reaction sequence in the storage, purification and modification of systems containing a 1,3-diene moiety are legion.

Apart from synthetic applications, the reversible sulpholene reaction has received considerable mechanistic attention and it has been demonstrated to be a cheletropic reaction. Appropriately substituted 3-sulpholenes (92) are found[11] to thermally extrude sulphur dioxide by a concerted, suprafacial (cis elimination) process in which the 1,3-

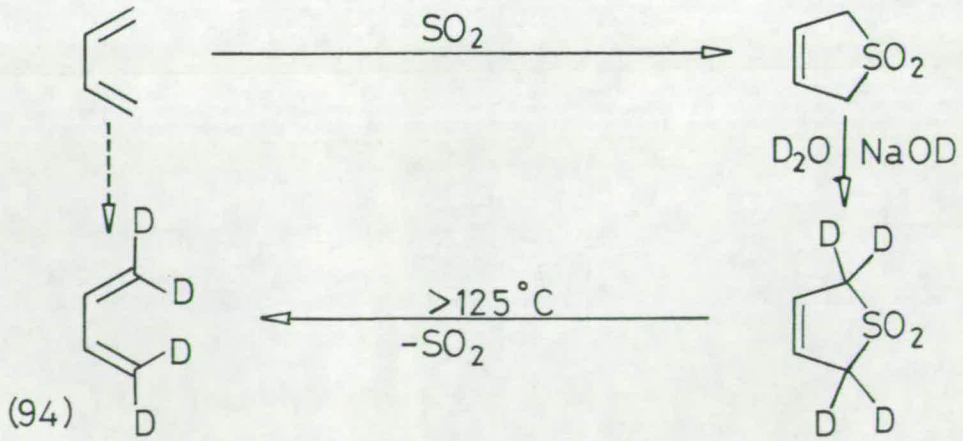


Scheme 14

diene (93) is generated stereospecifically by disrotation of the α -sulphone carbon atoms (Scheme 14). This extrusion - and its reverse - are in accord with orbital symmetry predictions[25] of a [π_{4s} + ω_{2s}] process for the interaction of a diene with sulphur dioxide. Further evidence in support of a concerted mechanism for the reversible sulpholene reaction has been furnished by kinetic studies of the

pyrolysis of suitably isotopically (^{2}H, ^{34}S) labelled 3-sulpholenes[39]. Assessment of kinetic measurements of the rates of thermal extrusion of sulphur dioxide from a number of substituted 3-sulpholenes has concluded that the insensitivity of the reaction to solvent polarity and to electronic variance (provided by substituents of varying electronegativity) is in accord with a concerted extrusion mechanism; acceleration of the extrusion of sulphur dioxide by substituents α- to the sulphone group, and the retardation of this extrusion by β-disposed substituents were ascribed to steric effects[40].

In terms of practical application of the sulpholene/reverse sulpholene reaction sequence, the most simple refers to the storage of 1,3-dienes in a conveniently masked form, circumventing potential problems of volatility and instability. Thus, 3-sulpholene itself has been utilised[41] for the <u>in situ</u> generation of buta-1,3-diene simply by heating to temperatures in excess of 125°C at which point sulphur dioxide is extruded. In addition, the acidity of the α-sulphone protons provides an opportunity for modification of 1,3-dienes <u>via</u> substitution of the 3-sulpholene. Replacement of all the acidic protons of 3-sulpholene by deuterium allows a ready synthesis[42] of [1,1,4,4-$^{2}H_4$]buta-1,3-diene (94) (Scheme 15) following extrusion of

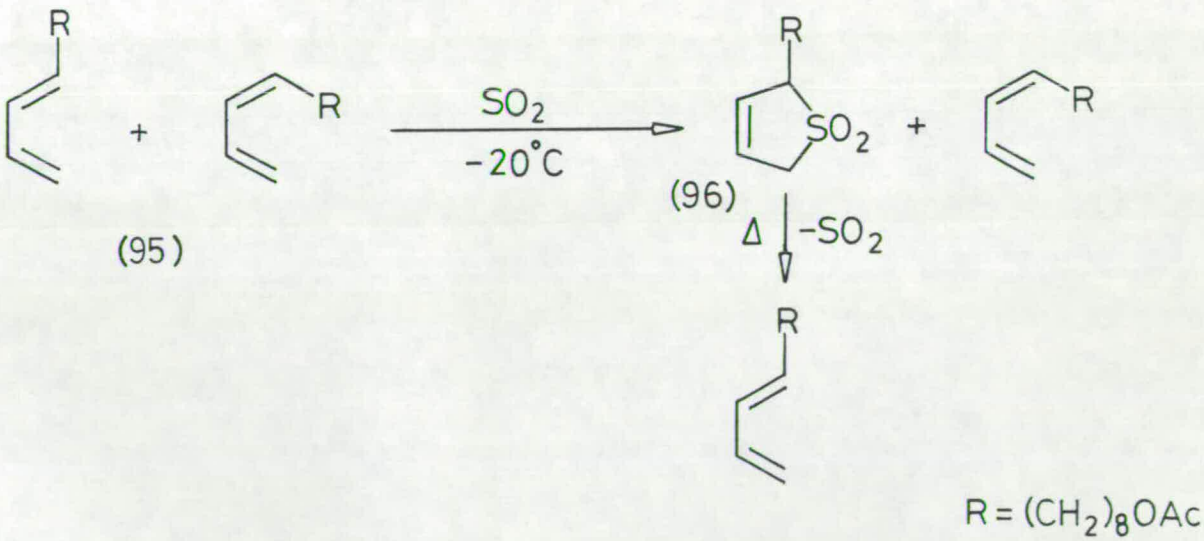


Scheme 15

sulphur dioxide: the tetradeuterated diene (94) has found application[43] in NMR studies of butadiene–methacrylonitrile copolymers.

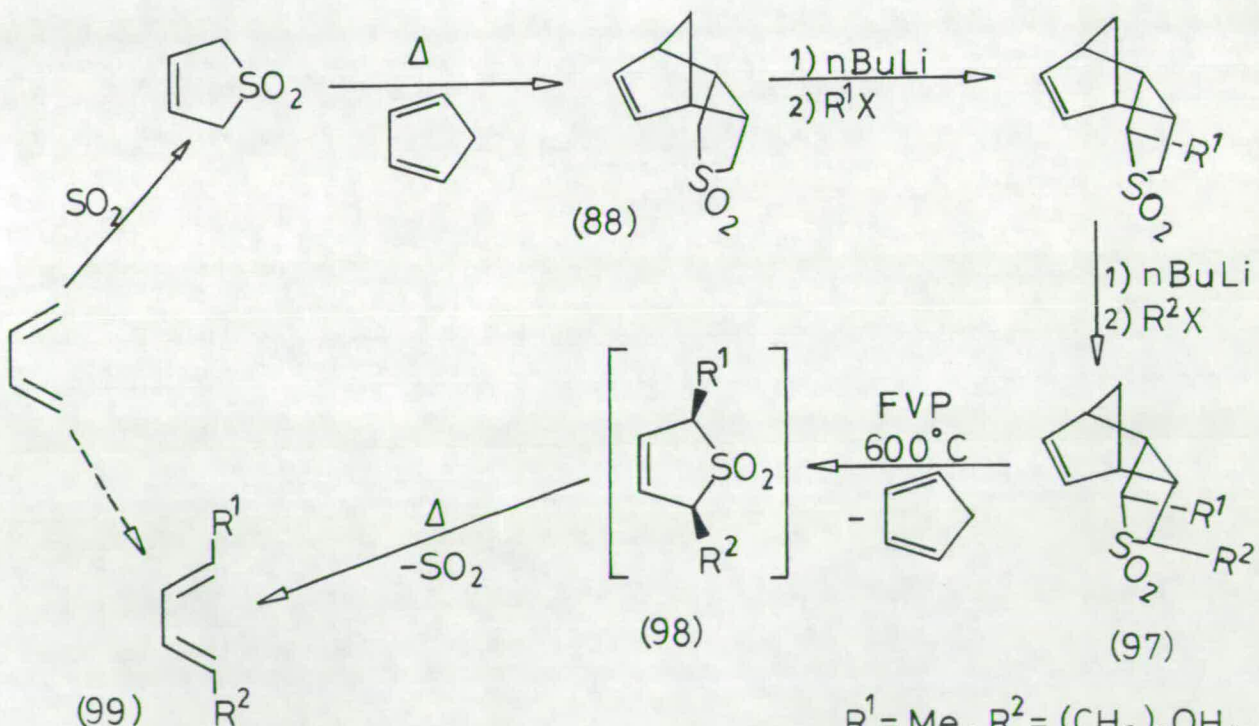
Polymer-bound reversible sulpholene formation as a means of removing sulphur dioxide from waste and flue gases has been investigated[44]: abstraction of undesired sulphur dioxide followed by thermal regeneration of the polymer-bound 1,3-diene on heating, with collection of the sulphur dioxide evolved, may have industrial importance.

Many natural products, in particular insect pheromones, possess a conjugated diene moiety as part of their structure. It is within this area that the reversible formation of 3-sulpholenes as a means of separating or modifying 1,3-dienes has had most utility. Separation of the isomeric (E)- and (Z)-dienes (95) of the red bollworm sex pheromone, prepared via a Wittig reaction, could not be effected easily by chromatographic means. However, on treatment with sulphur dioxide the corresponding 3-sulpholene was formed only from the less hindered (E)-isomer; the unreacted (Z)-isomer was recovered and the (E)-isomer was regenerated by thermal extrusion of sulphur dioxide from sulpholene (96) (Scheme 16)[45].



Scheme 16

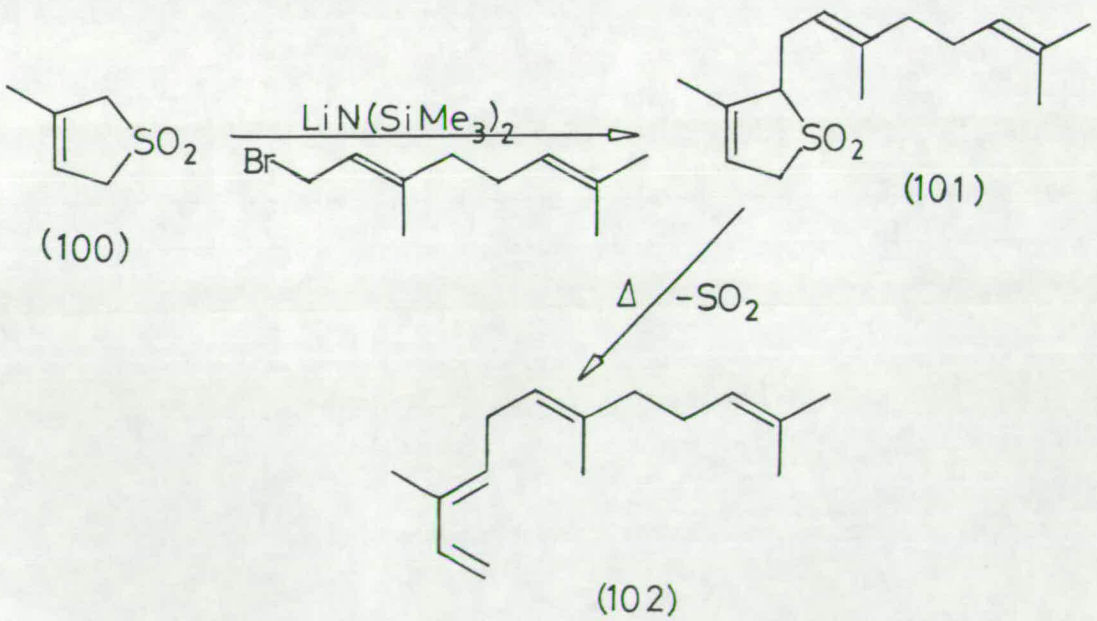
Until recently alkylation at the 2-position of 3-sulpholenes could not be readily achieved due to facile fragmentation of the anionic five-membered ring intermediate with formation of acyclic sulphones and derivatives, frustrating a conceptually attractive route to alkylated 1,3-diene-containing natural products. In order to circumvent these difficulties, a route incorporating a protected sulpholene analogue has been devised[46]. Thus, Diels-Alder reaction of cyclopentadiene with 3-sulpholene furnished the sulpholane (88), a suitable precursor for dialkylation (Scheme 17) to the sulpholane (97). The unique conditions of FVP have been utilised to good effect in the pyrolysis of (97) as both removal of the protecting cyclopentadiene, by a concerted retro-Diels-Alder reaction, and cheletropic extrusion of sulphur dioxide from the resultant intermediate sulpholene (98) occur with stereospecific formation of the (E,E)-diene (99), a known insect sex pheromone. An adaptation of this method has given rise to



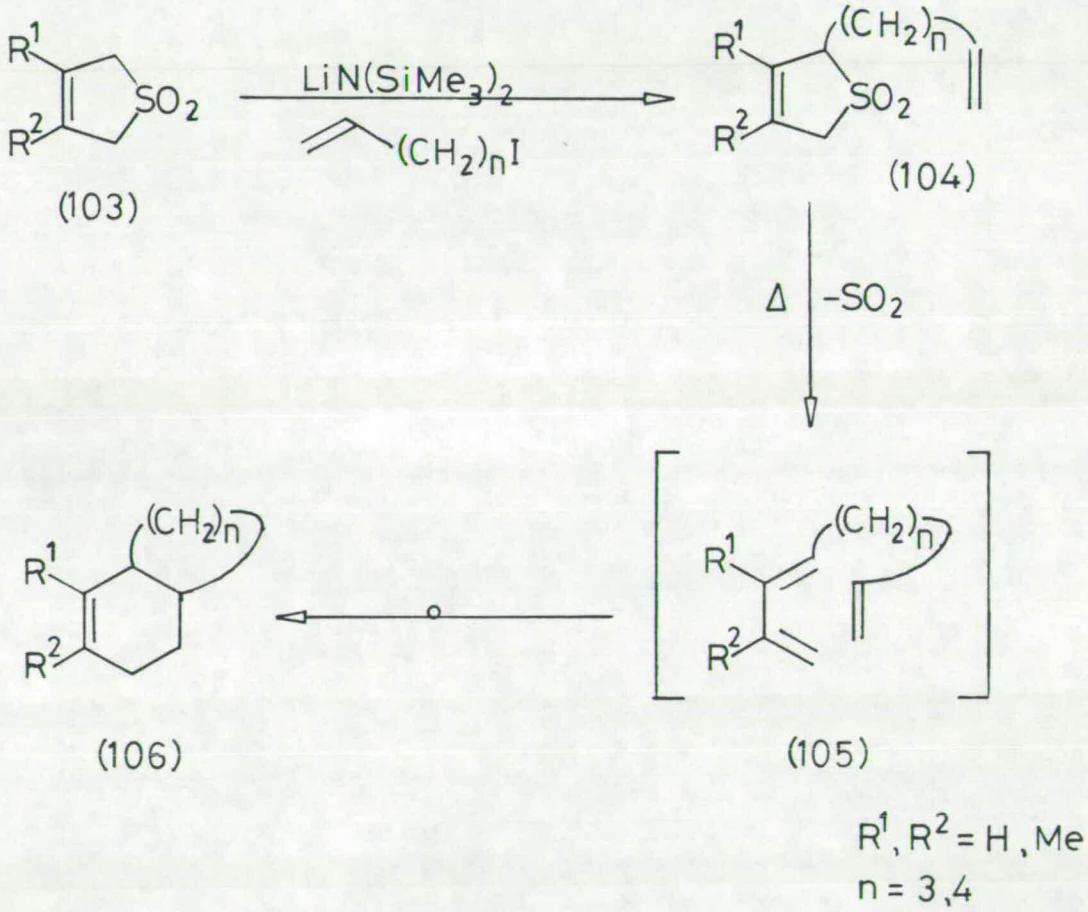
Scheme 17

a stereoselective preparation[47] of terminal 1,3,5-trienes by attachment of an appropriately unsaturated substituent to the tricyclic sulpholane (88) followed by pyrolysis of the resultant product.

The 'protected sulpholene' route (Scheme 17) has recently been superseded as a means of modification of 1,3-dienes by advances in the direct alkylation of 3-sulpholenes utilising hindered (non-nucleophilic) bases as proton-abstracting agents. These bases permit direct alkylation of 3-sulpholenes without adverse ring-opening side-reactions occurring, thus achieving efficient synthesis of the desired substituted 3-sulpholene in fewer steps than is possible using the 'protected sulpholene' route. A novel preparation[48] of the sesquiterpene, α-farnesene, highlights the utility of this route: direct alkylation of sulpholene (100) by treatment with the hindered base lithium bis(trimethylsilyl)amide in the presence of geranyl bromide, followed by thermal extrusion of sulphur dioxide from the resultant substituted sulpholene (101) gave rise to a stereoselective preparation of the sesquiterpene containing a trans C(3)-C(4) geometry, in accord with the stereochemistry associated with α-farnesene (102).



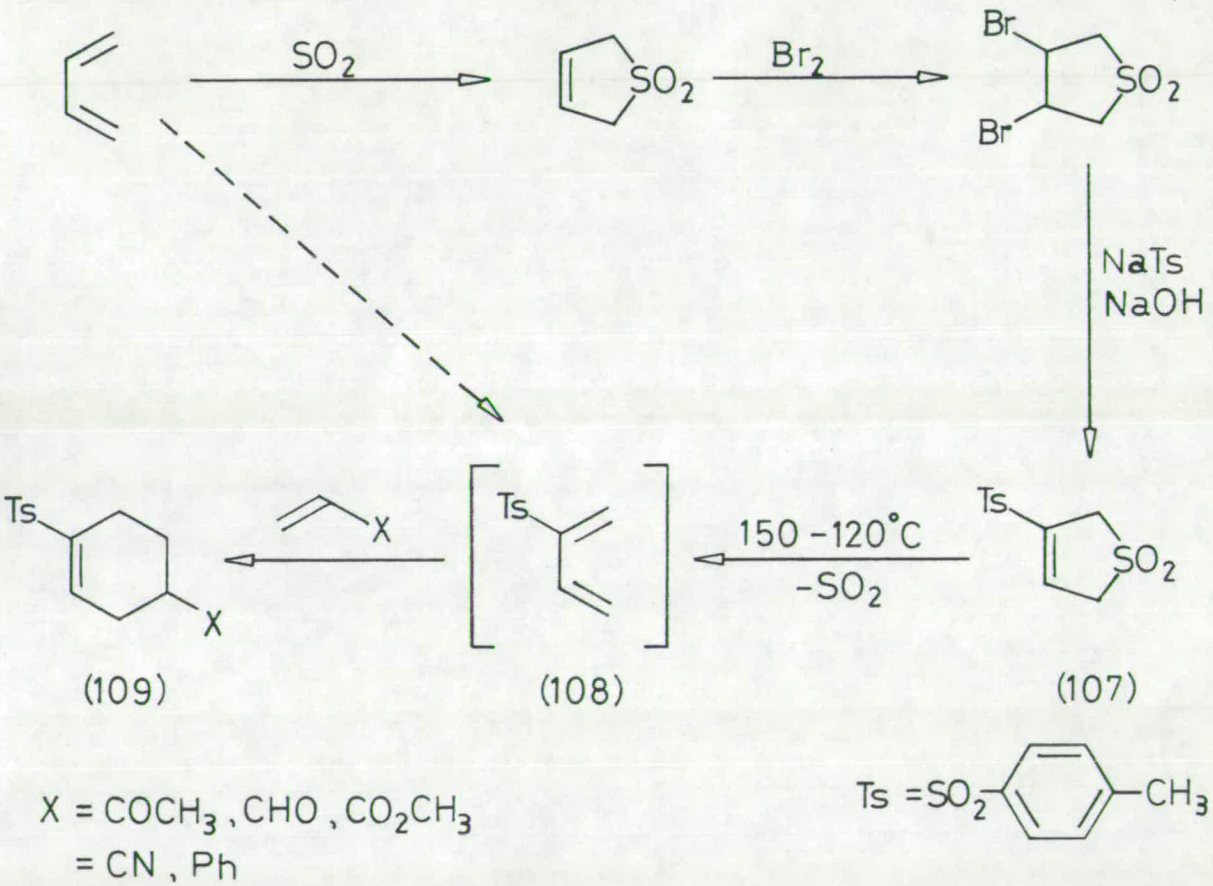
An interesting extension of this procedure has resulted in a convenient synthesis of hydroindans and hydronaphthalenes[49]. As outlined in Scheme 18, alkylation of a 3-sulpholene (103) *via* hindered-base proton abstraction followed by pyrolysis of the resultant 2-(ω-alkenyl)-3-sulpholene (104) is found to result in isolation of *cis*- and/or *trans*-fused bicyclic systems (106) in good yield following Diels-Alder cyclisation of the intermediate triene (105). Thus, the



Scheme 18

unsubstituted 3-sulpholene (104; R^1,R^2 = H, n = 4) realised[49] a 50:50 mixture of the corresponding isomeric *cis*- and *trans*-fused hydronaphthalenes (106; R^1 = R^2 = H, n = 4) in 73% yield on pyrolysis of an n-hexane solution at 580°C.

In addition to providing a means of modification of the terminal positions of 1,3-dienes, the reversible sulpholene reaction may be used to effect a similar transformation of the 2-position. As illustrated by Scheme 19, the 1,3-diene in its masked sulpholene form may be modified by addition reactions of the olefin moiety prior to extrusion of sulphur dioxide and generation of the 2-substituted-1,3-diene (108) from the 3-substituted-3-sulpholene (107). In situ generation of the electron-deficient diene (108) in the presence of a

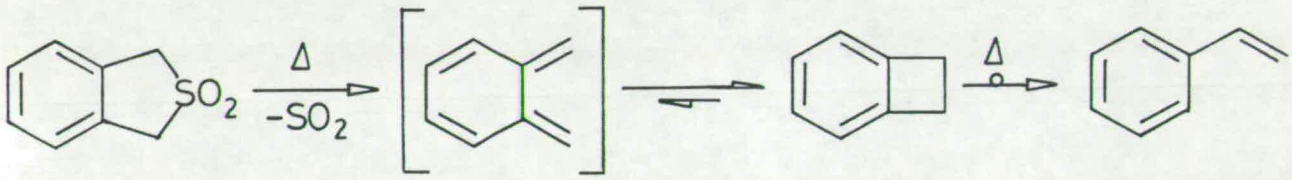


Scheme 19

range of dienophiles has led[50] to an efficient, regioselective synthesis of a number of Diels-Alder adducts (109), not readily available from the free buta-1,3-diene (108) due to a facile dimerisation process associated with this.

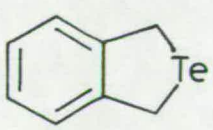
ii. Benzo-fused sulpholenes

The parent 1,3-dihydrobenzo[c]thiophene dioxide (110) was first pyrolysed by Cava and Deana[51] who disclosed that in the gas phase at 770°C, 2 mm Hg of nitrogen, extrusion of sulphur dioxide was effected with formation of benzocyclobutene (112) together with a small quantity of its associated thermal decomposition product, styrene.



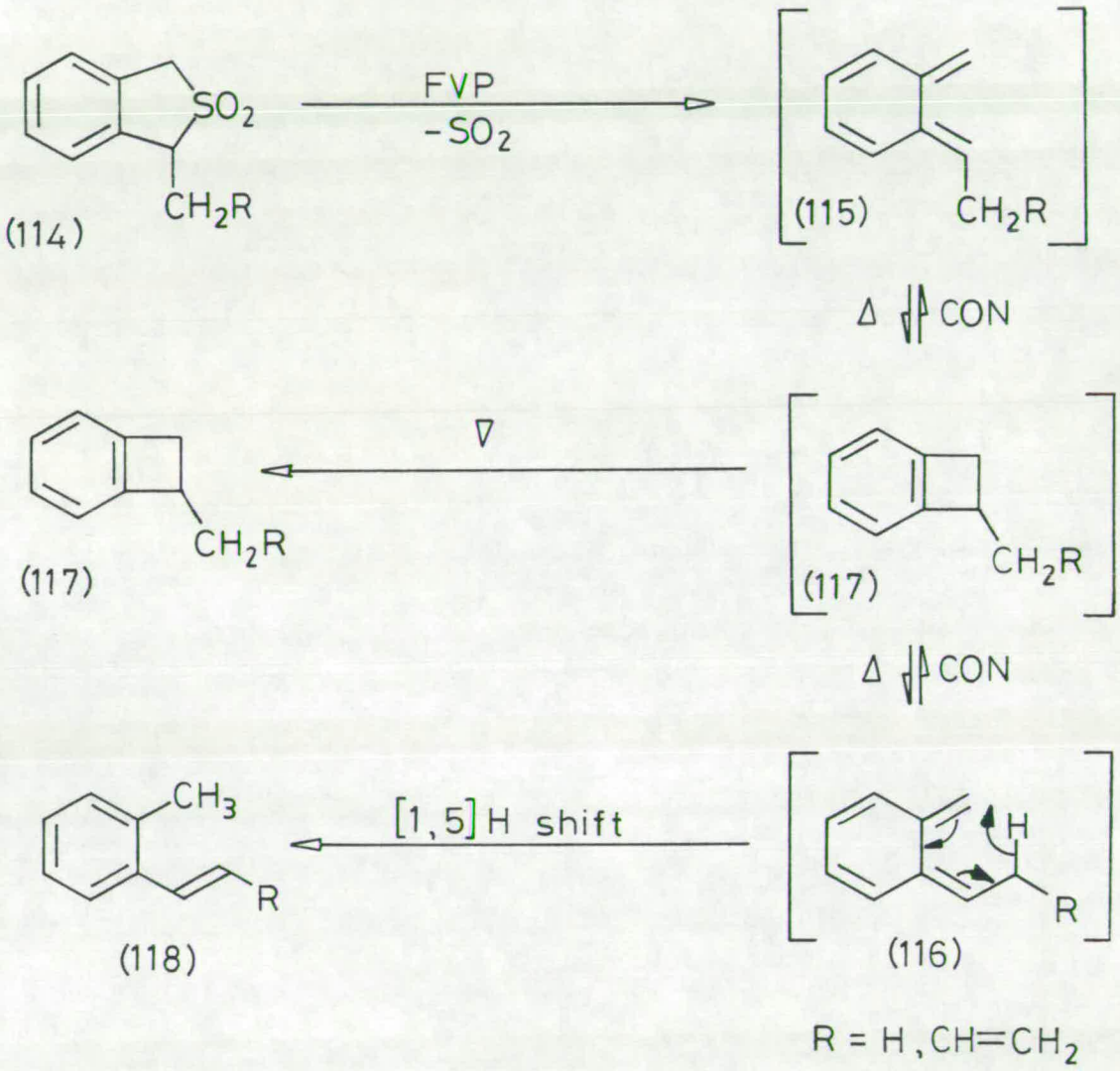
(110) (111) (112)

Verification of the presence of the suspected o-xylylene intermediate (111) was provided by King et al[52] who have reported that under true FVP conditions (500°C, 10^{-3} mm Hg) dideuterated derivatives of (110) formed the corresponding dideuteriobenzocyclobutenes in >95% yield. Determination of the stereochemistry of these products furnished evidence for the formation of o-xylylene (111) by a concerted, disrotatory extrusion of sulphur dioxide from (110), followed by conrotatory ring closure of this intermediate to form benzocyclobutene (112) in accord with the Woodward-Hoffmann rules. Interestingly, benzocyclobutene (112) has also been realised[53] by FVP of the analogous telluride system (113), again via intermediacy of o-xylylene (111) following extrusion of tellurium.



(113)

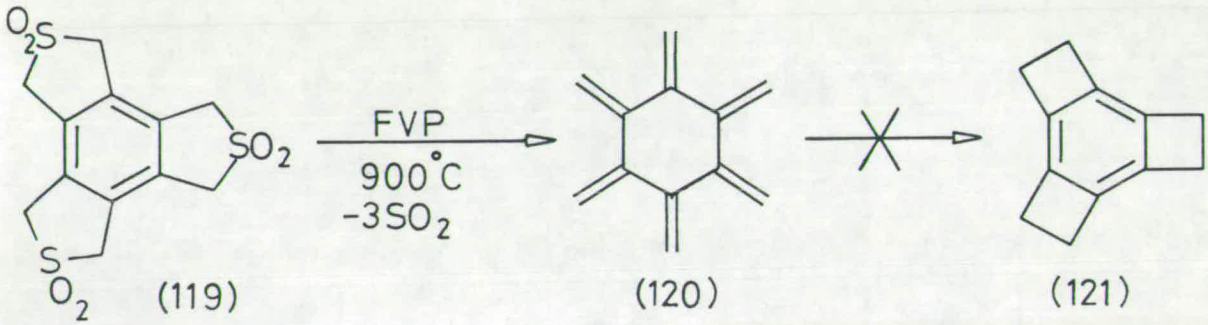
In general, it is found[54] that FVP of mono α-substituted benzo-fused sulpholenes (114) at moderate temperatures (ca 450°C) follows the same pathway as the parent system (110) yielding as



Scheme 20

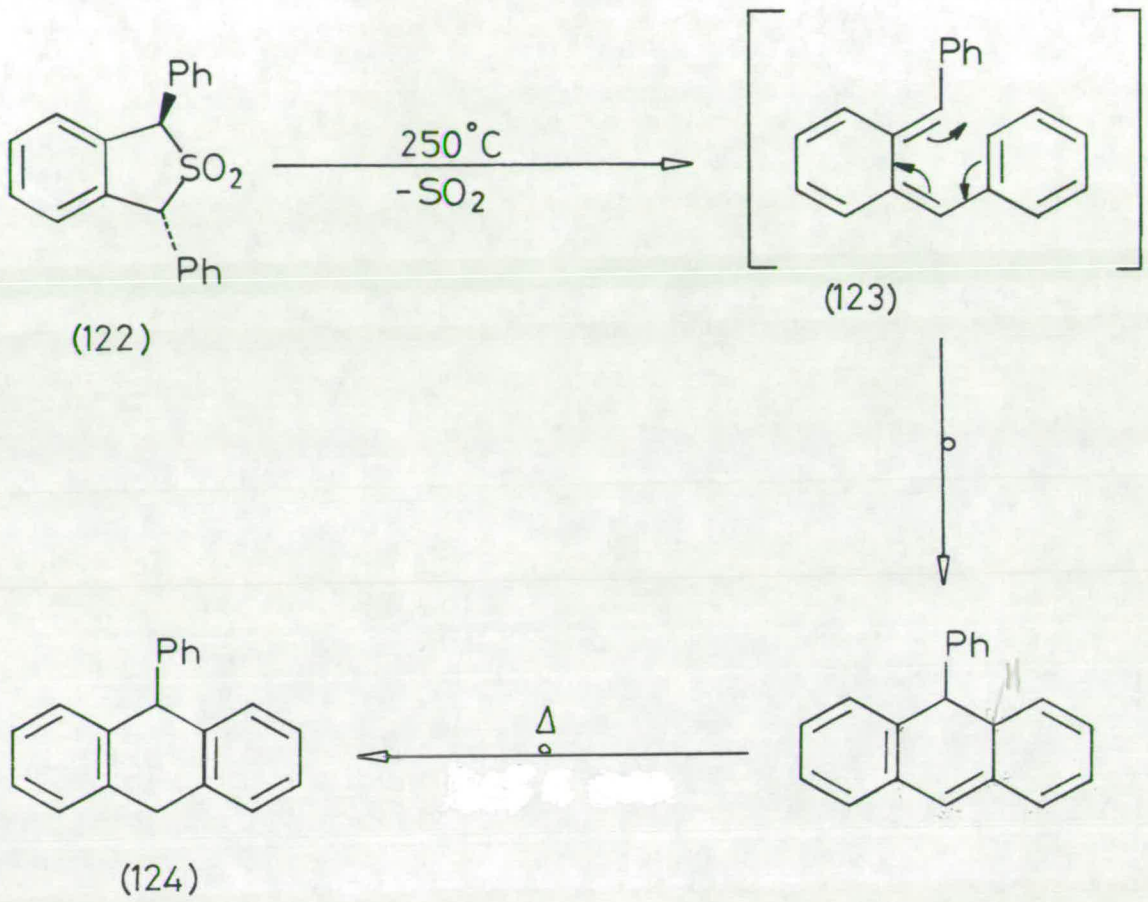
isolated products the corresponding substituted benzocyclobutenes (117) via the intermediacy of the less sterically hindered trans- (rather than cis-) o-xylylene (115). Increasing formation of substituted o-methylstyrenes (118) on FVP of (114) at higher temperatures (540-700°C) has been attributed to a [1,5] hydrogen shift from the more sterically hindered cis-o-xylylene (116), present in equilibrium with the trans-isomer (115) at elevated temperatures (Scheme 20).

An instance of the isolation of an o-xylylene product following thermal extrusion of sulphur dioxide from a benzo-fused sulpholene has been lodged. Boekelheide et al[55] determined that on FVP of the trisulphone (119), elimination of sulphur dioxide resulted in production of [6]radialene (120); cyclisation of this to the tricyclobutene system (121) is disfavoured in this case due to the increase in ring strain which is only partially offset by the aromatic stabilisation gained on forming (121). In the vast majority of cases, however, the o-xylylene is not isolated and the suspected presence of



(119) (120) (121)

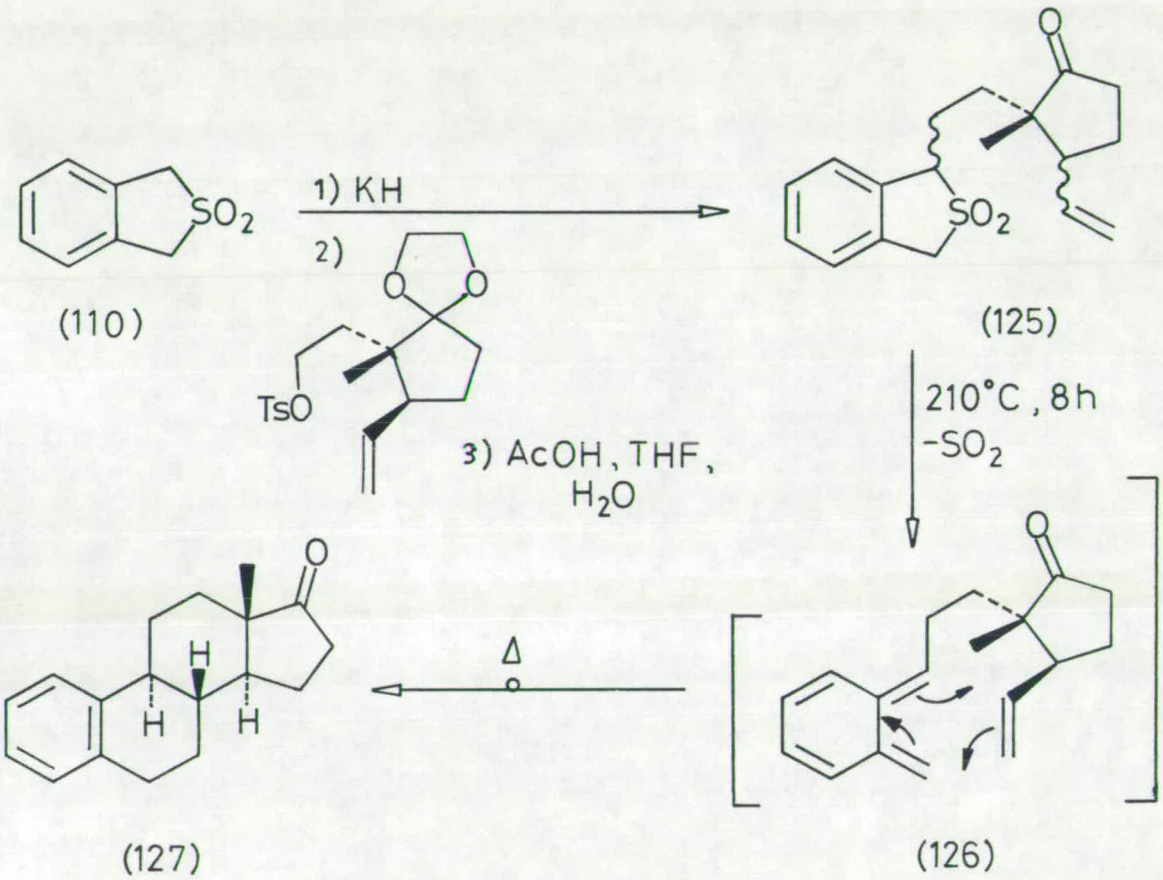
such an intermediate is established by trapping with an appropriate electrophile in classical Diels-Alder tradition. Where an unsaturated side chain can be incorporated in the benzo-fused sulpholene system at the α-sulphone position, the opportunity for intramolecular trapping of the o-xylylene intermediate may be presented. For example, trans-diphenylsulpholene (122) upon solution thermolysis at 250°C has been found[56] to generate the tricyclic hydrocarbon (124) in excellent yield following the efficient intramolecular trapping of the intermediate (E,Z)-o-xylylene (123) (Scheme 21).



Scheme 21

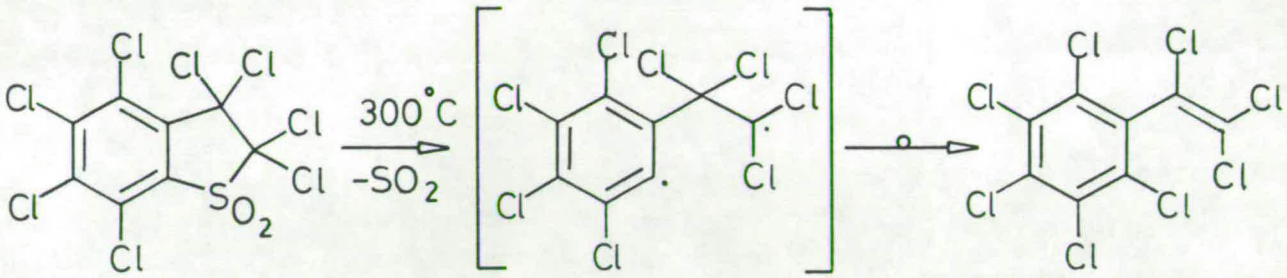
The high yields of products and the stereoselectivity resulting from such intramolecular Diels-Alder reactions has obvious synthetic utility. Many polycyclic structures, including natural products such as steroids, have been synthesised by the intramolecular Diels-Alder reaction of an *in situ* generated *o*-xylylene with an appropriately unsaturated side chain[57,58]. Most of these *o*-xylylene intermediates have been generated by the thermal ring opening of benzocyclobutenes, but a recent synthesis of the steroid (*dl*)-estra-1,3,5(10)-trien-17-one (127) has utilised[59] a benzosulpholene as an *o*-xylylene precursor. As shown in Scheme 22, alkylation of the parent

benzosulpholene system (110) and subsequent solution thermolysis of the resultant isomeric sulpholanes (125) formed the basis of a very acceptable 85% yield of the desired steroid (127) via intermediacy of the less hindered trans-o-xylylene (126). Overall, the reaction sequence presents a short, simple and efficient synthesis of the steroid system.



Scheme 22

In common with the situation regarding 2- and 3-sulpholenes, the 2,3-dihydrobenzo[b]thiophene dioxides have received only a fraction of the attention of their isomeric benzo[c]thiophene analogues, due to a comparative lack of synthetic application. A rare example describes the neat thermolysis of perchlorobenzo[b]thiophene dioxide (128), which was found to extrude sulphur dioxide with formation of perchlorostyrene (130) in 91% yield[23]. A mechanism involving

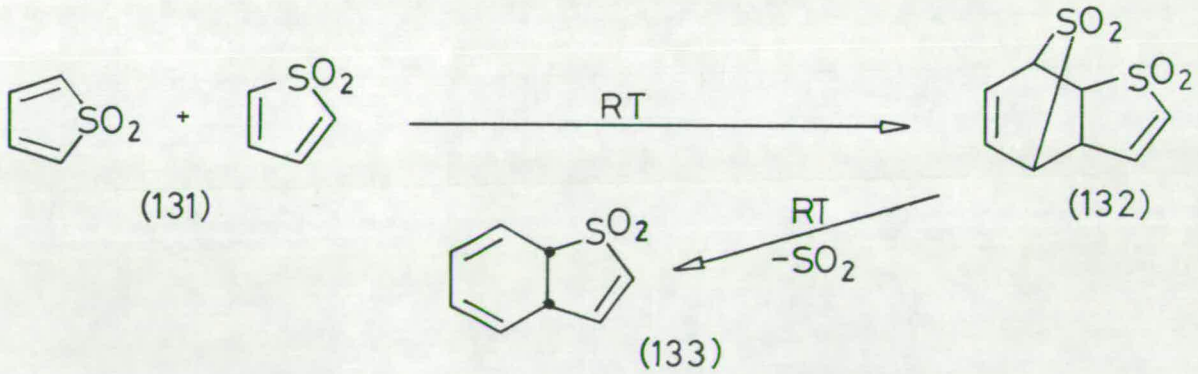


(128) (129) (130)

intermediacy of diradical (129) and associated [1,3] chlorine shift has been proposed. Pyrolysis of these systems does appear to generate only radical species in contrast to the concerted extrusion mechanism determined for the benzo[c]thiophene dioxide analogues, as a result of the direct bonding of the sulphone group to the aromatic ring which precludes a concerted extrusion pathway.

c. Thiophene dioxides

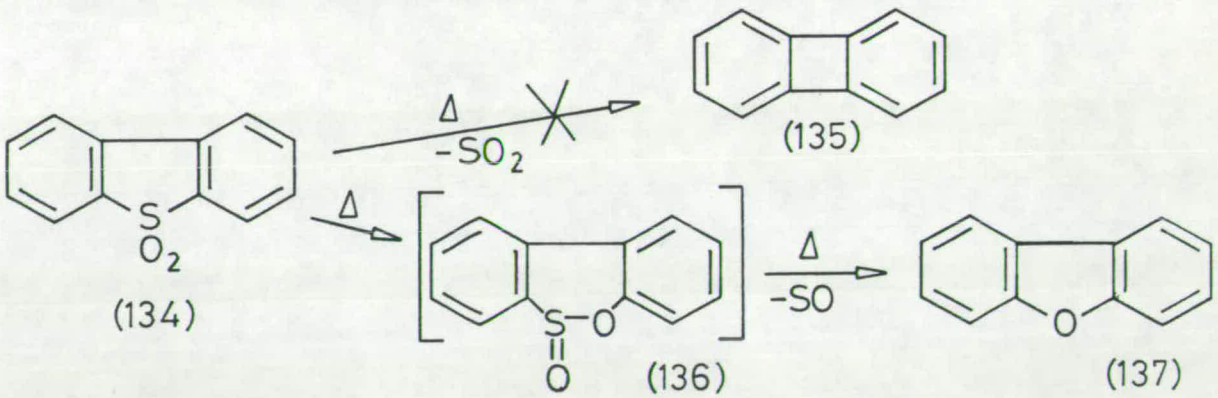
These are the doubly unsaturated five-membered sulphone-containing ring systems. The parent thiophene dioxide (131) is found to be too reactive towards Diels-Alder dimerisation to allow isolation in concentrated form. Extrusion of sulphur dioxide from the sulphone-bridged dimer (132) occurs with ease, generating the bicyclic sulpholene (133) even at room temperature[60]. Reflecting the ease of dimerisation



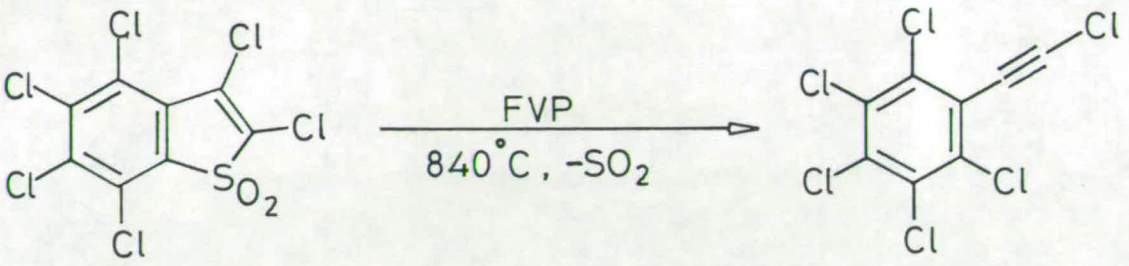
(131) (132) (133)

of the parent thiophene dioxide, the study of extrusion reactions from such structures has been restricted to those cases where dimerisation is disfavoured - namely thiophene dioxides in which the basic ring is heavily substituted, or in which the ring is stabilised

by incorporation into one or more fused aromatic rings. Typical of the latter is the dibenzothiophene dioxide (134). On pyrolysis at 690°C under nitrogen, the expected extrusion of sulphur dioxide with formation of biphenylene (135) was not observed; instead, the major fragmentation pathway was identified[61] as being that of extrusion of sulphur monoxide and formation of dibenzofuran (137). In common with the thiete dioxides discussed earlier, ring expansion to an intermediate sultine (136) from which elimination of sulphur monoxide results, appears most feasible. Mass spectral evidence, corroborated by the work of Bowie et al[62], have indicated a parallel mechanism to occur under electron impact conditions: prominent peaks corresponding to the loss of carbon and sulphur monoxides from the parent ion of (134) were observed. It is often apparent that a strong link exists between mass spectral fragmentation patterns and the corresponding thermal extrusion pathway, as is the case above, and that consultation of mass spectral data may indicate the preferred extrusion course prior to experimental determination. Such parallels are also encountered in the experimental section of this volume, as described later.



Although the mechanism of ring expansion to the sultine followed by extrusion of sulphur monoxide is generally applicable to the pyrolysis of substituted thiophene dioxides, there are notable exceptions. Extrusion of sulphur dioxide on FVP at 840°C of perchlorobenzo[b]thiophene dioxide (138) with isolation of an agreeable yield of perchlorophenylacetylene (139) has been described[63]. In



(138) (139)

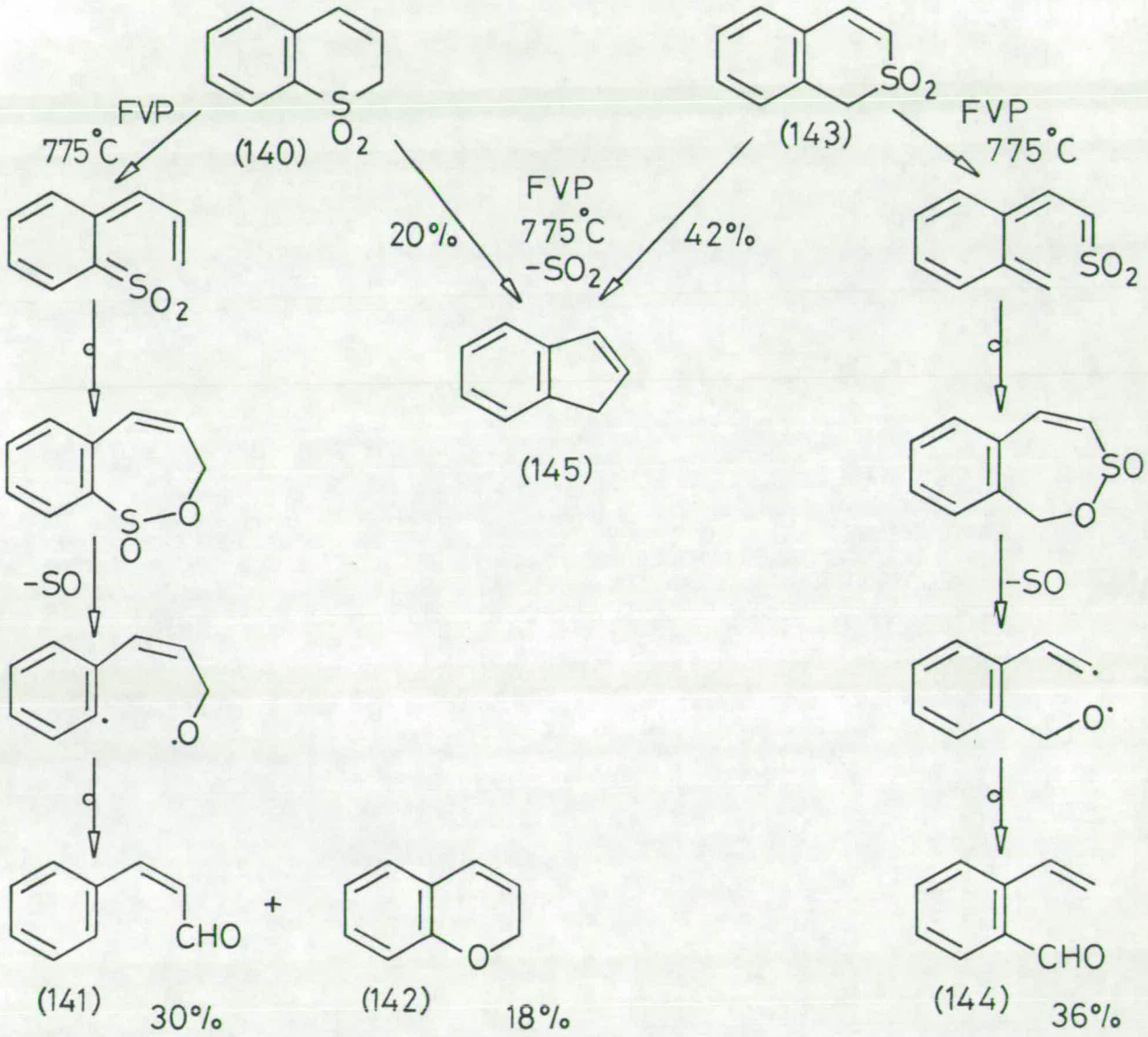
contrast, it has been observed[64] that benzo[b]thiophene dioxide on FVP at 1000°C furnished mainly benzothiete with only a trace of the expected furan product detected. The presence of the sultine intermediate appears feasible and further rearrangement of this to a species capable of extruding carbon dioxide is implicated.

4. Six-membered rings

Compared to the extensive interest in pyrolysis of five-membered sulphone-containing rings, the six-membered systems have been largely overlooked. A general absence of synthetic applicability of thermal extrusions from the latter systems accounts primarily for this situation. The few published examples concerning thermal behaviour indicate the favoured fragmentation pathway to occur by initial ring expansion to a seven-membered sultine intermediate followed by extrusion of sulphur monoxide with concomitant formation of oxygenated products; minor amounts of alternative products are also obtained by direct elimination of sulphur dioxide.

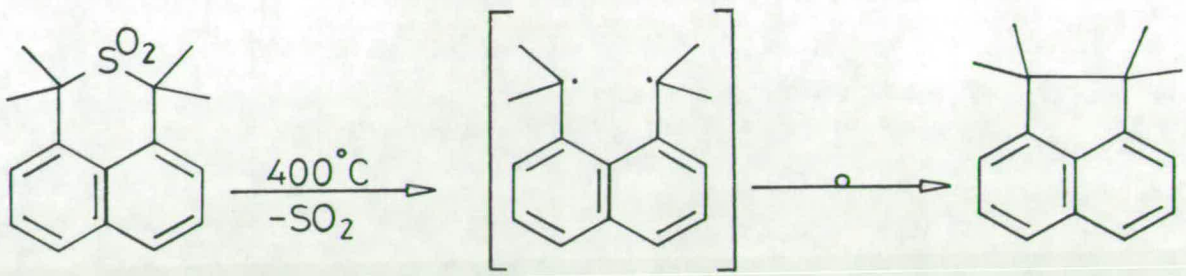
Thus, the isomeric thiopyran dioxides (140) and (143) are found[65] to undergo partial fragmentation on FVP at 775°C to give cinnamaldehyde (141) and benzopyran (142), and o-vinylbenzaldehyde (144) respectively, together with common formation of indene (145). As outlined in Scheme 23, both isomers are thought to undergo initial ring cleavage followed by recyclisation to seven-membered sultine systems, then radical fragmentation with expulsion of sulphur monoxide, and rearrangement of the resultant diradical species to the observed products. For isomer (143), extrusion of sulphur dioxide via a

radical mechanism, to generate indene (145) predominates over the mechanism involving sulphur monoxide extrusion, especially at more elevated pyrolysis temperatures.



Scheme 23

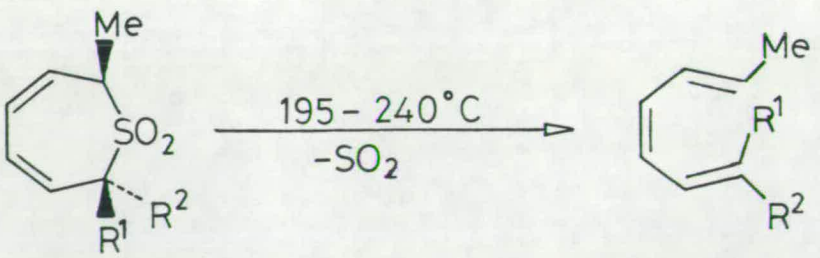
An instance detailing synthetic application of the pyrolysis of six-membered sulphone-containing rings is available[66]: neat thermolysis of tricycle (146) at 400°C for an extended period (six hours) returned a 15% yield of tetramethylacenaphthene (147) which is probably formed via a diradical intermediate generated by elimination of sulphur dioxide. Although no oxygenated hydrocarbons were reported, scope for formation of these is clearly apparent on consideration of the mass imbalance of the thermolysis reaction.



(146) (147)

5. Seven- and higher-membered rings

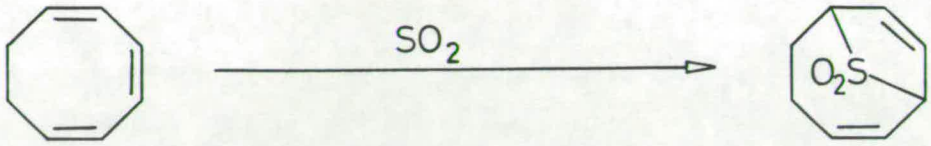
With regard to extrusion processes from seven-membered sulphone-containing rings it may accurately be stated that the saturated (hexahydrothiepine dioxide) systems and singly-unsaturated (tetrahydrothiepine dioxide) systems have received little attention. In contradistinction, the reversible reaction of cis-hexa-1,3,5-trienes and sulphur dioxide to form 2,7-dihydrothiepine rings has benefited from comparatively close scrutiny. This higher analogue of the previously discussed 'sulpholene reaction' is similarly of mechanistic interest, being predicted to follow an antarafacial (conrotatory) pathway. In similar fashion to mechanistic studies pursued on the reversible sulpholene reaction, studies[11,67] of the thermal dissociation of cis- and trans-2,7-dimethyl-2,7-dihydrothiepine dioxides (148) have allowed verification of the predicted concerted cycloreversion reaction, since the requisite triene (149) was formed in >97% stereoselectivity.



(148) (149)

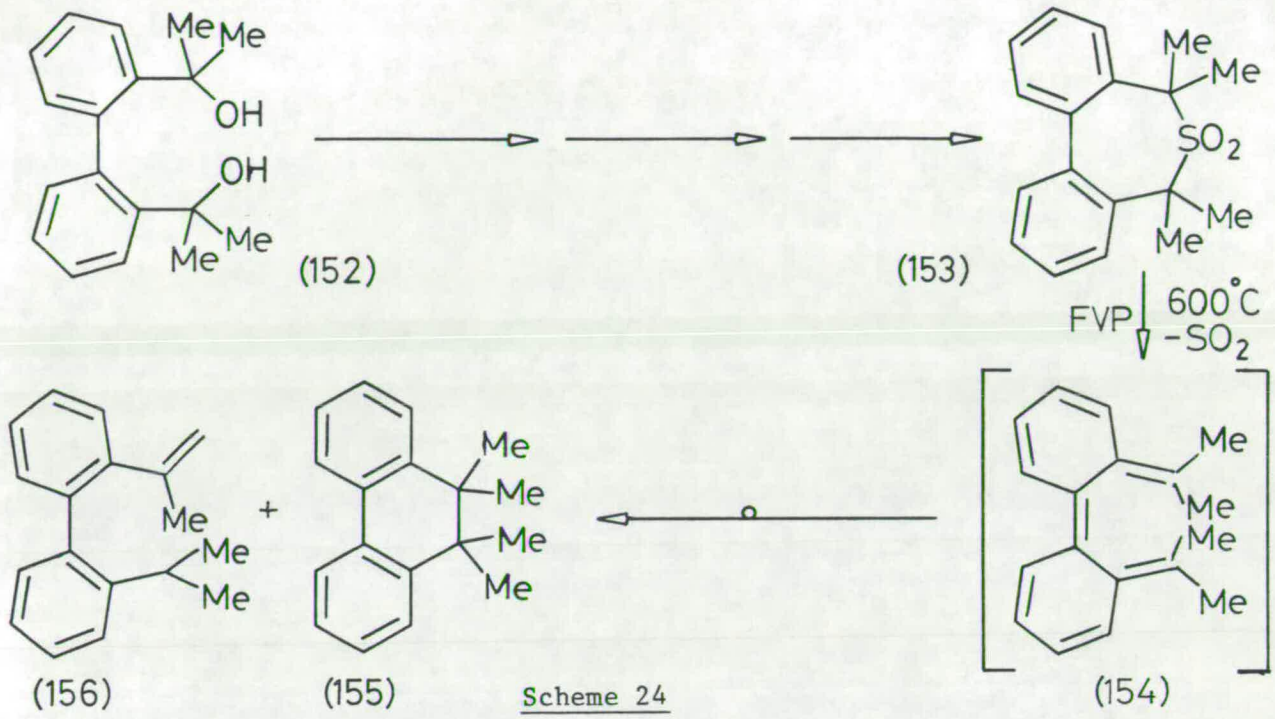
R^1 = Me, R^2 = H;
R^1 = H , R^2 = Me

Although the triene-dihydrothiepine dioxide transformation is reversible - demonstrated[68] by the facile addition of sulphur dioxide to cis-hexa-1,3,5-triene at room temperature and regeneration of the latter on heating to 150°C - there are nonetheless some exceptions to this behaviour. In particular, α-alkylated hexa-1,3,5-trienes are found not to react with sulphur dioxide via 1,6-cyclisation to generate the expected 2-alkylated-2,7-dihydrothiepine dioxides due to steric congestion which prevents approach of the sulphur dioxide to the termini of the triene system. However, it has been reported[69] that in such cases 1,4-cyclisation (the sulpholene reaction) occurs. The presence of a substituent in the β- or γ-position of the triene has been found to offset such inhibitory steric factors, resulting from the presence of substituents in the α-position, towards the 1,6-cyclisation reaction with sulphur dioxide. More facile reaction of β- and γ-substituted trienes with sulphur dioxide compared to the parent cis-hexa-1,3,5-triene has been rationalised as being due to a steric destabilising effect of the transoid-triene conformation relative to the cisoid conformation from which 2,7-dihydrothiepine dioxides are formed[69]. Where the conjugated triene system is incorporated in a cyclic structure, 1,6-cyclisation of the triene with sulphur dioxide may also be disfavoured: such a reaction is not observed on treatment of cycloocta-1,3,5-triene (150) with sulphur dioxide since a concerted mechanism involving conrotation of the termini of the triene system would result in formation of an intolerably strained bicyclic product. Reaction via 1,4-cyclisation resulting in formation of the comparatively unstrained sulphone-bridged cyclooctadiene (151) was recorded; on heating to 100°C, clean reversal of this product to (150) and sulphur dioxide occurred.



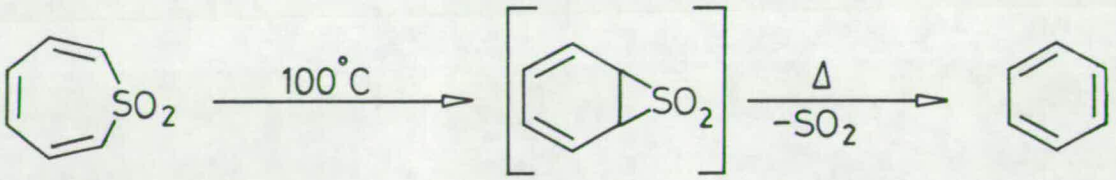
(150) (151)

However, in a substantial number of cases studied the reversibility of the 1,3,5-triene/2,7-dihydrothiepine dioxide relationship has been established[69]. Synthetic application of the reversible reaction appears limited, although like the reversible sulpholene reaction it may be used for storage and manipulation of conjugated trienes in a convenient, masked form. Unlike its lower sulpholene analogue however, regeneration of the triene moiety may occur with concomitant cyclisation of the latter to form a cyclohexa-1,3-diene product. This is apparent in the first reported[70] synthesis of a 9,9,10,10-tetraalkyl-substituted 9,10-dihydrophenanthrene, the tetramethyl system (155). FVP of the dibenzo-2,7-dihydrothiepine dioxide (153), prepared by chemical manipulation of diol (152), led to isolation in good yield of the dihydrophenanthrene (155) together with minor quantities of the vinylbiphenyl (156) (Scheme 24). Intermediate triene (154) was proposed as the species formed on initial cheletropic extrusion of sulphur dioxide from (153) followed by facile cyclisation to the aromatic dihydrophenanthrene; vinylbiphenyl (156) may be formed directly from (154) by a thermally-allowed antarafacial 1,7-hydrogen shift.



Scheme 24

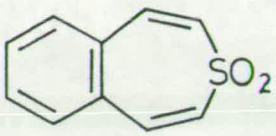
The thiepine dioxides are the fully unsaturated seven-membered sulphone-containing rings. Thiepine dioxide (157), prepared by bromination of 2,7-dihydrothiepine 1,1-dioxide followed by bis-dehydrobromination of the resultant dibromide, is found[68] to undergo thermal extrusion of sulphur dioxide on solution thermolysis at 100°C to produce benzene. In terms of mechanism, cyclisation of (157) to the episulphone intermediate (158) followed by fragmentation of the latter to the stable aromatic species benzene, and to sulphur dioxide, has been proposed.



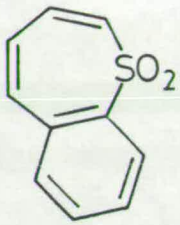
(157) (158)

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Pyrolyses of the corresponding isomeric benzothiepine dioxides (159) and (160) have illustrated a dichotomy in thermal



(159)



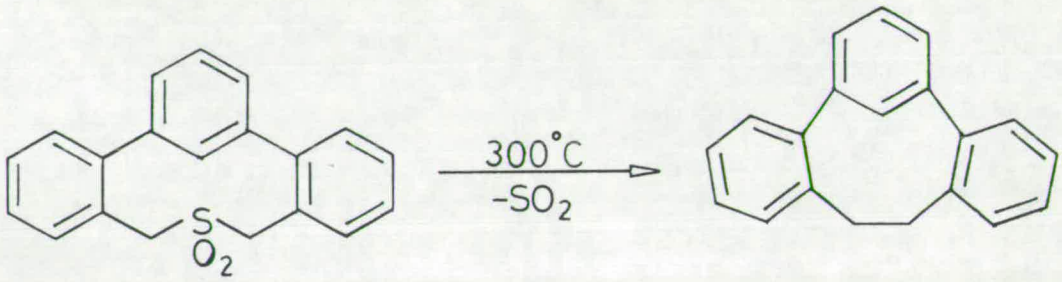
(160)

behaviour. In parallel fashion to the parent system (157), benzo[d]thiepine dioxide (159) thermally fragments to naphthalene and sulphur dioxide in good yield[71]. Benzo[b]thiepine dioxide (160) has been found[72] to be recovered unchanged on heating to 250°C, with a sulphone-containing polymer being formed at higher temperatures. It appears likely that the difference in thermal behaviour between the two isomers results from an inability to form the corresponding strained episulphone intermediate in (160), due to the position of fusion of the aromatic ring. This is a situation not encountered on thermolysis of isomer (159), where the expected low-energy sulphur dioxide extrusion route through an episulphone intermediate is not hindered.

Systems incorporating a sulphone-containing ring greater than seven-membered are almost entirely restricted to those utilised in the synthesis of cyclophanes. The bridged aromatic systems known commonly as cyclophanes are of interest since their rigid structure allows study of steric and electronic factors affecting aromaticity; recent improved synthetic methods to these compounds have resulted in mounting interest over the past two decades[7,73,74]. In particular,

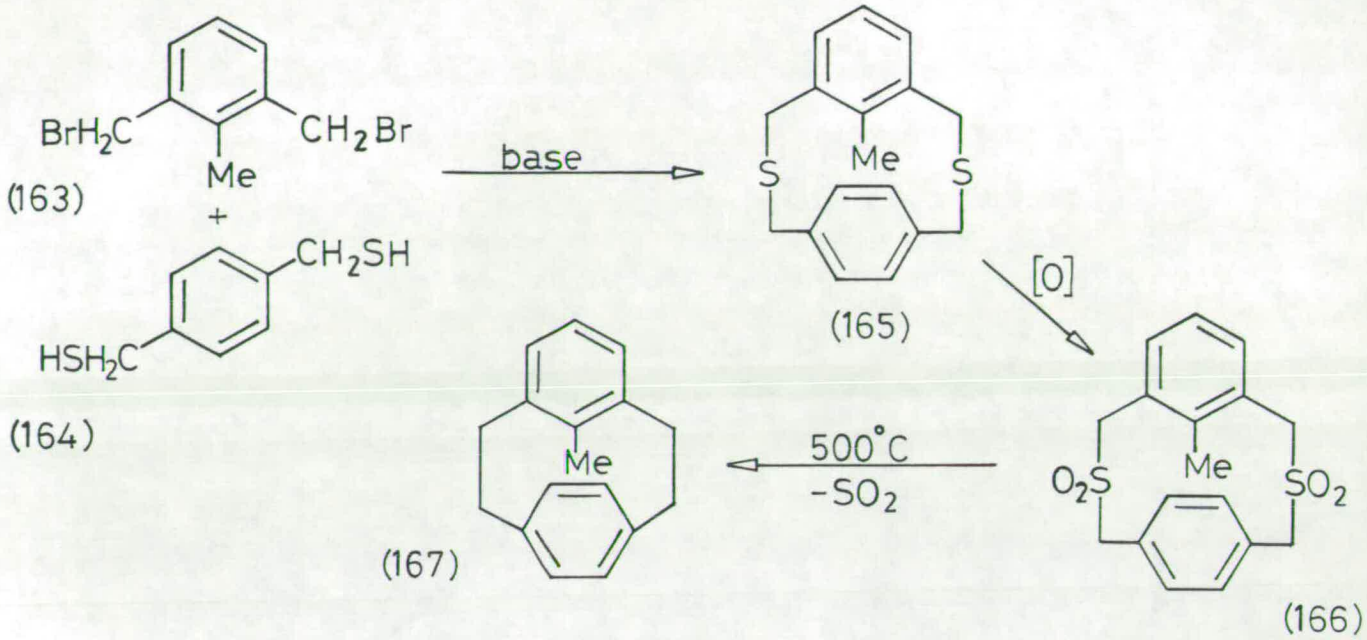
the preparation of even the most strained cyclophanes by thermal extrusion of sulphur dioxide from readily available cyclic sulphone precursors has contributed to this increasing interest in cyclophane chemistry[75].

The first example of the preparation of a cyclophane *via* extrusion of sulphur dioxide was reported by Vögtle[76] in 1969. Quantitative preparation of the terphenyl (162) resulted on thermal extrusion of sulphur dioxide from monosulphone (161), this successful preparation of a cyclophane being the progenitor for a large number of similar syntheses. Perhaps the most advantageous feature of the preparation of



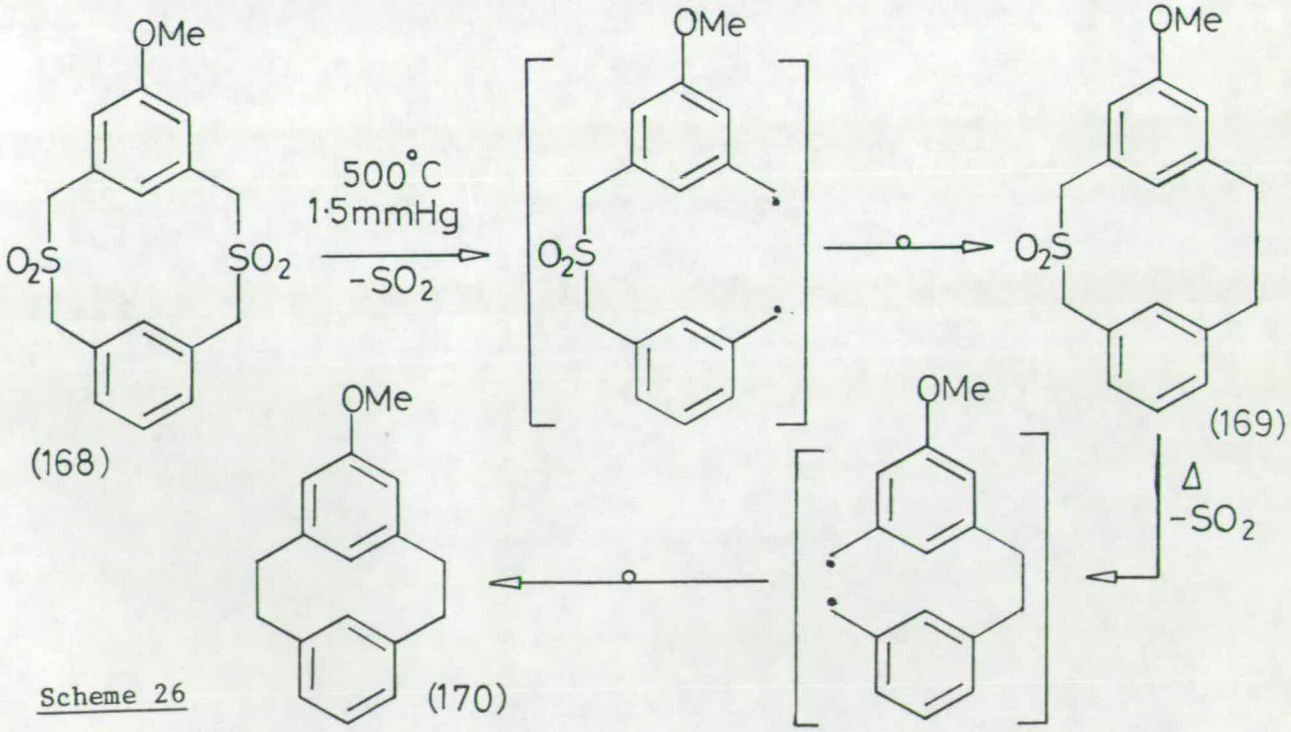
(161) (162)

cyclophanes by such a thermal extrusion method lies in the comparatively large quantities (grams) available, in high yield, from easily synthesised cyclic sulphone precursors. Typically a disulphone such as (166) would be prepared, as outlined in Scheme 25, by reaction of bis(bromomethyl) (163) and bis(mercaptomethyl) (164) precursors followed by near quantitative oxidation of the resultant disulphide (165). Pyrolysis of the disulphone (166) at 500°C led to a 90% yield of the strained cyclophane (167)[77].



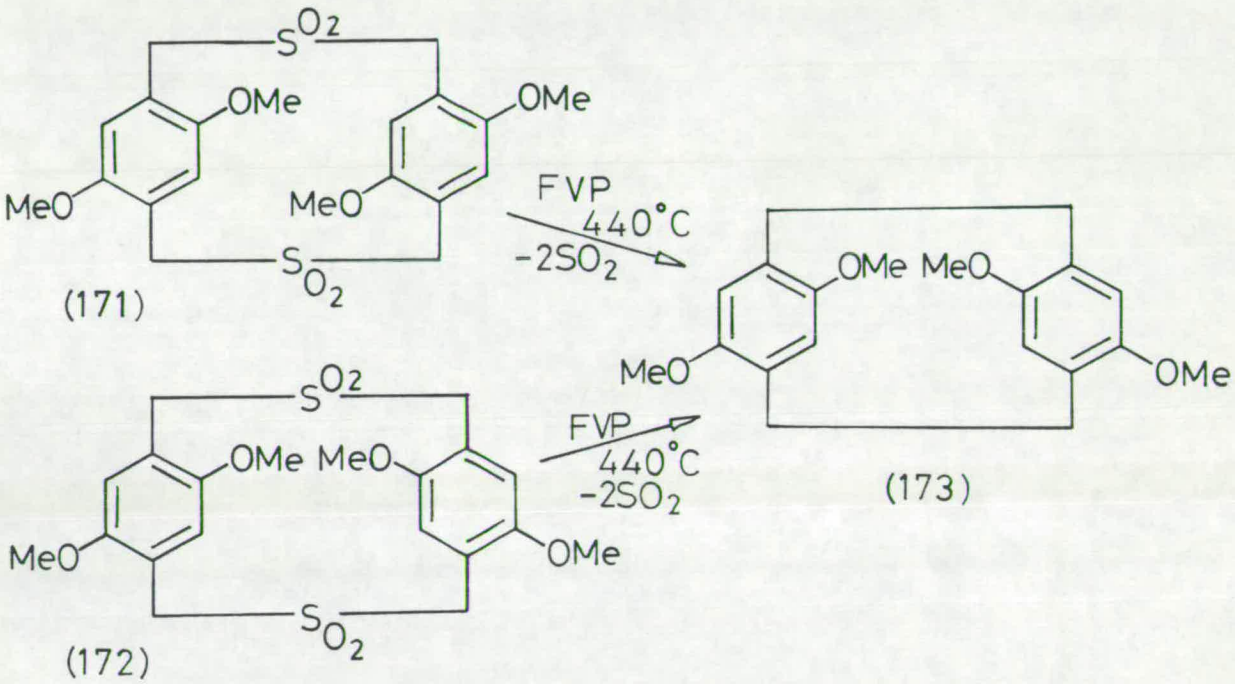
Scheme 25

The mechanism of extrusion of sulphur dioxide from such multi-membered rings, leading to cyclophane formation, is generally regarded as occurring via radical processes. In this respect, the thermal extrusion under conditions of reduced pressure of the disulphone structure (168) gave as products the desired cyclophane (170) together with minor quantities of monosulphone (169)[78]. A mechanism involving the stepwise, radical cleavage of each sulphur dioxide unit (Scheme 26) is implicated. Further evidence for a stepwise loss of sulphur dioxide

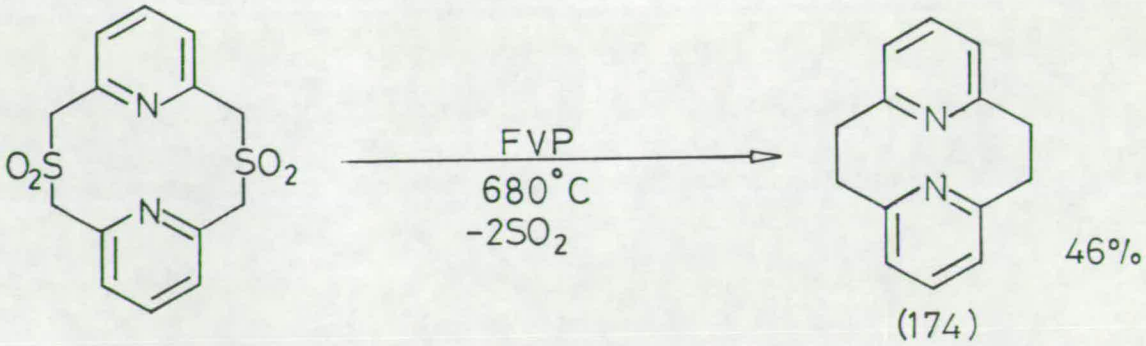


Scheme 26

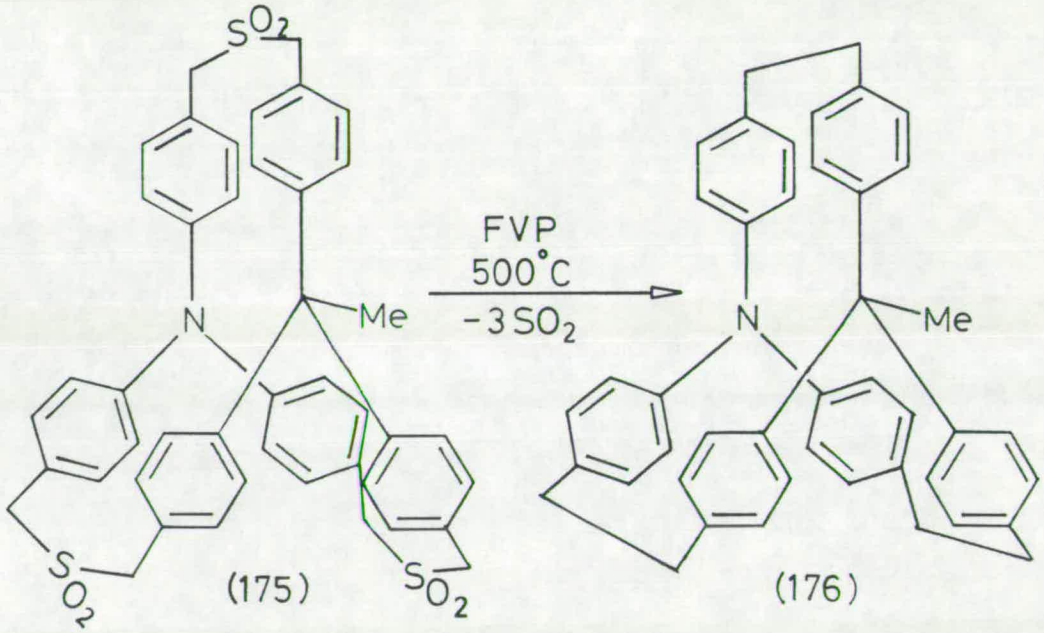
with generation of diradical intermediates has been furnished by the findings of pyrolysis of the isomeric disulphone systems (171) and (172). On FVP of either isomer, or a mixture of both, only a single cyclophane product (173) was realised[79]. A stepwise extrusion of each sulphur dioxide molecule is indicated; rotation of a diradical monobridged intermediate with adoption of the more stable 'staggered' conformation prior to ring closure to (173) is logical.



The applicability of the sulphur dioxide extrusion route to cyclophanes is not restricted to carbocyclic aromatic ring systems. Preparation[80] of the pyridinophane (174) clearly demonstrates the generality of the extrusion reaction towards synthesis of a wide variety of cyclophane systems. In addition, extension of the synthetic



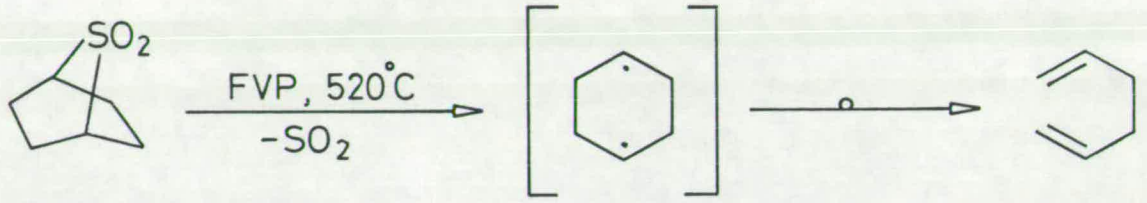
route to cyclophanes possessing three or more hydrocarbon bridges presents no difficulties, as the large number of such examples in the chemical literature attest, making the thermal extrusion of sulphur dioxide from multi-membered sulphone rings with formation of cyclophane systems arguably the most synthetically important of the extrusion processes considered thus far. By way of demonstration of this point, perhaps the most elegant molecule synthesised to date by thermal extrusion of sulphur dioxide is the heterocyclic propeller system (176), prepared albeit in low yield (9%) from FVP at 500°C of the trisulphone (175)[81].



6. Sulphone-bridged ring systems

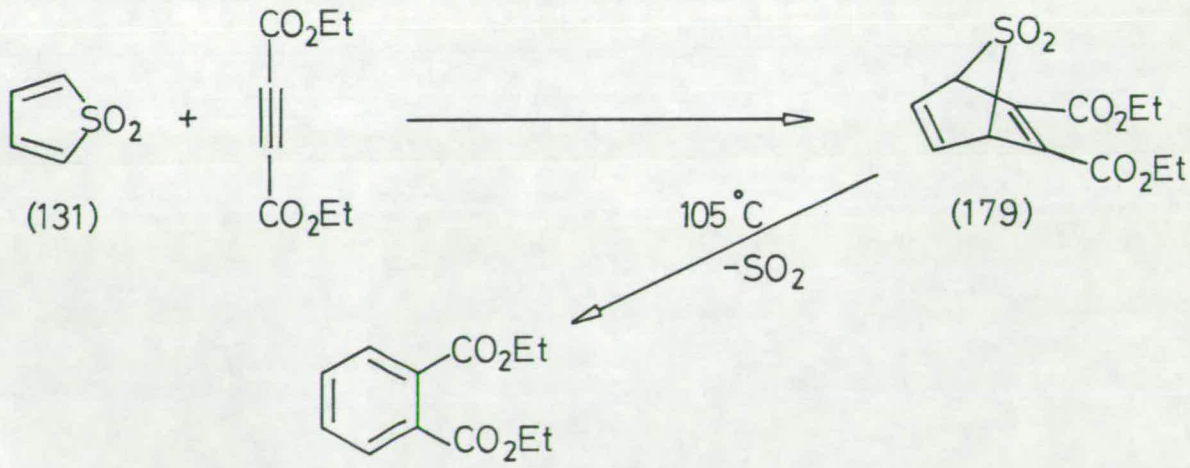
Those cyclic systems in which the sulphone group is present as a bridging ring element are found, in general, to be less thermally stable to extrusion of sulphur dioxide than is the case with typical monocyclic sulphone systems. The additional ring strain often associated with such bridged structures is found to act as an impetus towards ring fragmentation which therefore is effected under comparatively mild pyrolysis conditions. Cleavage of sulphur dioxide from the

saturated sulphone-bridged species (177), by way of example, is achieved[82] on FVP at the low temperature of 520°C giving a good yield of hexa-1,5-diene *via* probable diradical intermediate (178).



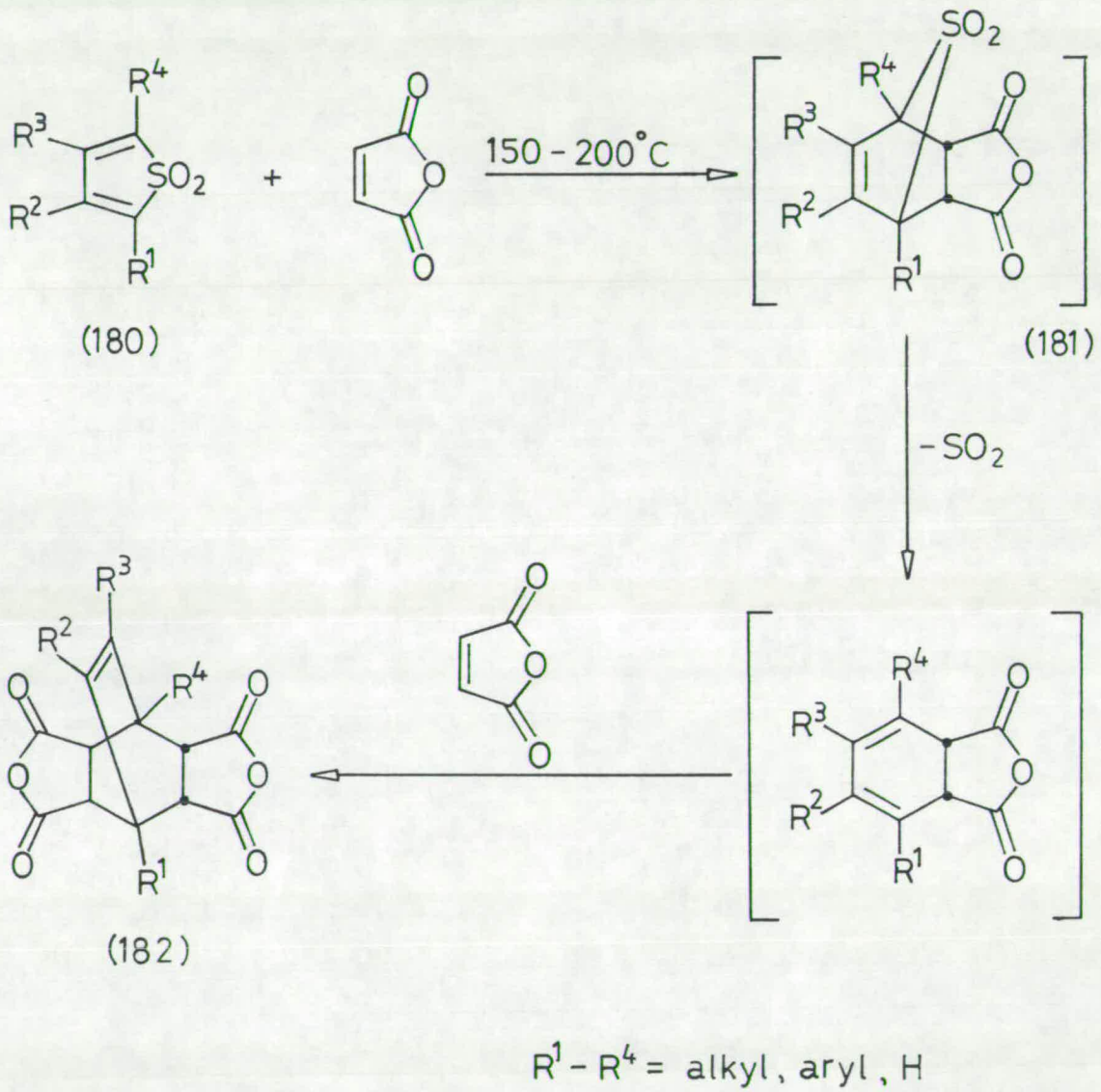
(177) (178)

Unsaturated sulphone-bridged systems often arise from Diels-Alder reaction of a thiophene dioxide with an appropriate dienophile, the dimer of thiophene dioxide (132) itself being a case in point. In common with dimer (132), such bridged unsaturated systems extrude sulphur dioxide under mild thermal conditions. For example, the adduct (179) of thiophene dioxide with diethyl acetylenedicarboxylate undergoes elimination of sulphur dioxide on heating just above its melting point (105°C) to form the thermodynamically stable product, diethyl phthalate[83].



(131) (179)

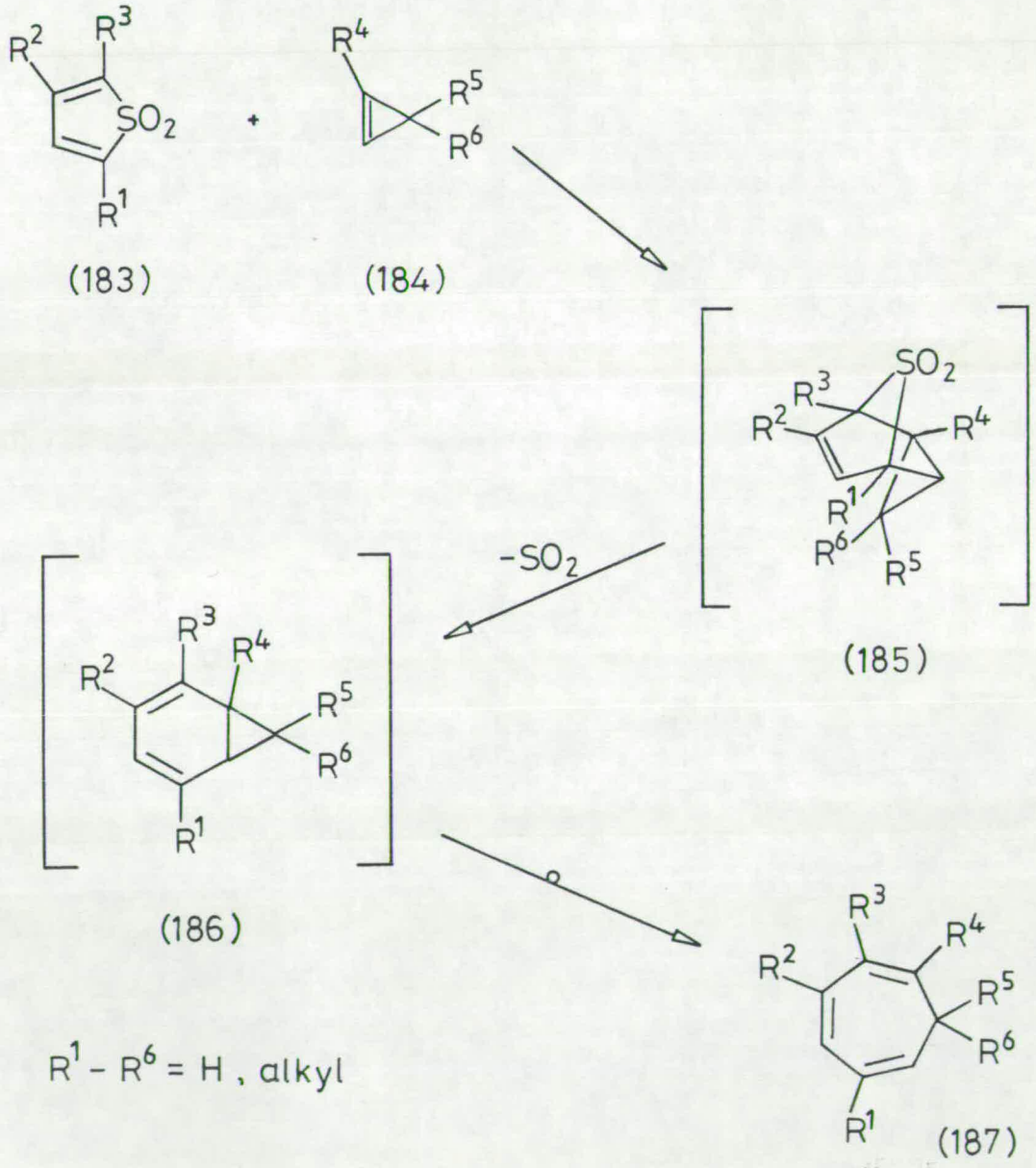
A wide range of substituted thiophene dioxides (180) are readily available from straightforward oxidation of thiophene precursors[84], and reaction of these with maleic anhydride has produced good yields of substituted dianhydrides (182) via bridged sulphone (181) intermediates (Scheme 27)[85]. Further synthetic utility of the



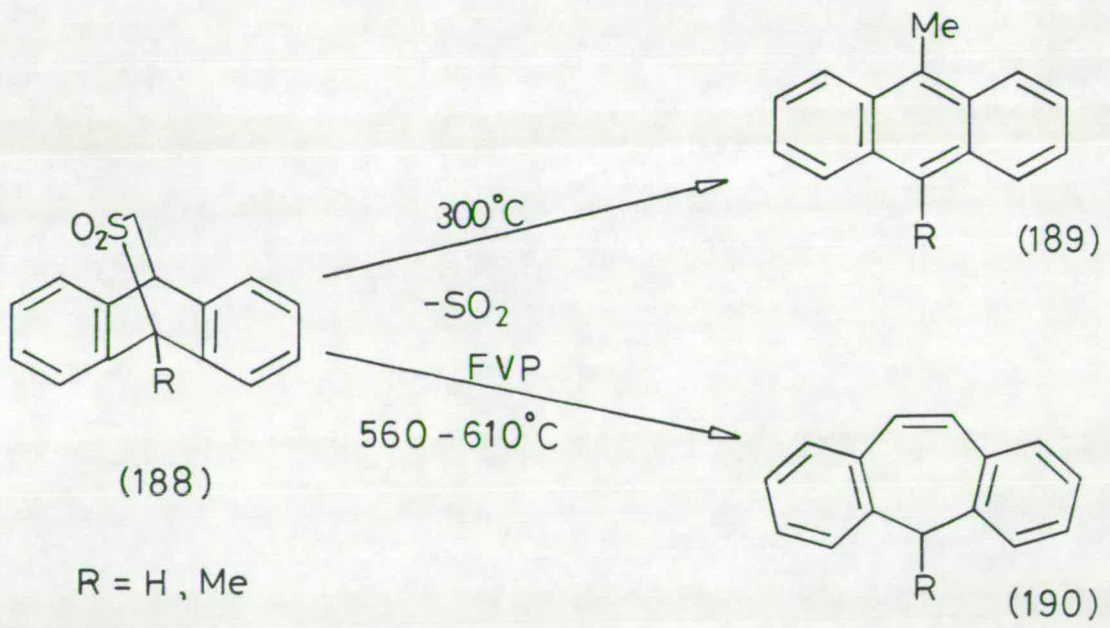
Scheme 27

Diels-Alder reaction between thiophene dioxides and suitable dienophiles has been demonstrated by the facile synthesis of a number of substituted cycloheptatrienes (187). Thus, reaction of thiophene dioxides (183)

with cyclopropene systems (184) at low temperatures resulted in isolation of pure cycloheptatrienes (187) in favourable yields, these compounds being difficult to obtain in comparable purity by other routes[86]. Kinetic studies have indicated the facile elimination of sulphur dioxide from bridged-sulphone intermediates (185) to occur by a thermal, concerted (disrotatory) mode with formation of the unstable diene (186) which then thermally rearranges to the observed cycloheptatriene products.

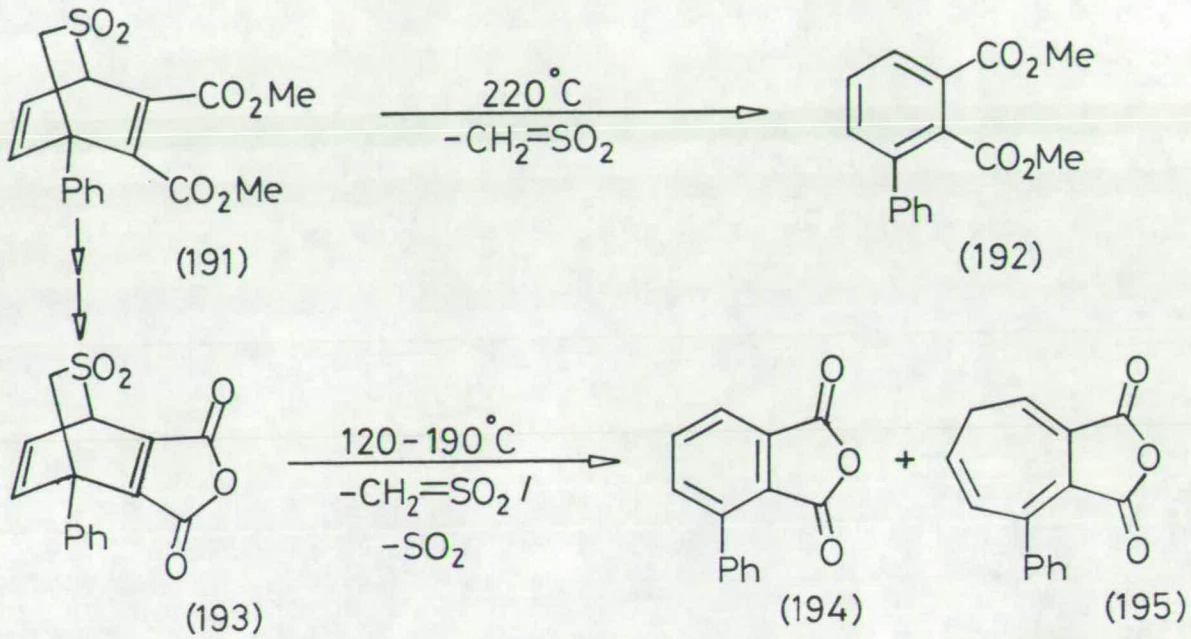


Turning now to consideration of systems incorporating the sulphone group as part of a hetero-ethano bridge, thermal fragmentation of these structures has been shown to be sensitive to slight structural changes in the substrate sulphone, and to the pyrolysis conditions employed. Vacuum thermolysis of system (188) at 300°C effects extrusion of sulphur dioxide with formation of the methylanthracene (189) in high yield; FVP at significantly higher temperatures (560-610°C), however, leads to excellent yields of the dibenzo[a,d]cycloheptene (190) again by thermal dissociation of sulphur dioxide[87]. Both thermal reactions have been considered to occur *via* radical mechanisms, although the marked dependence of these on the pyrolysis conditions are yet to be fully explained. A related bridged system has been described by King *et al*[88,89] as undergoing thermal

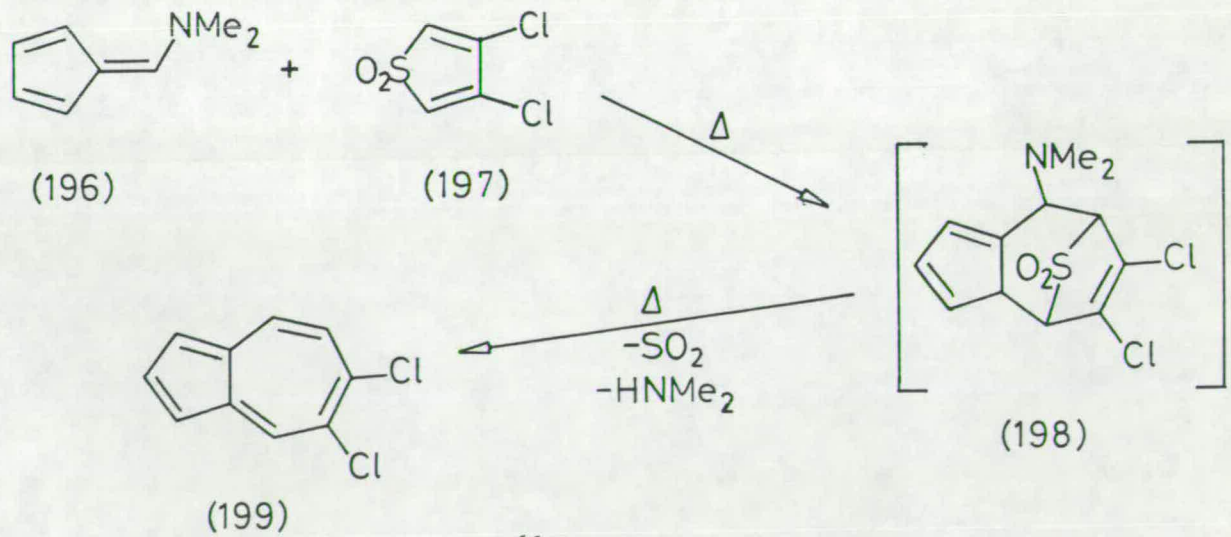


fragmentation by a completely different pathway: bicyclic system (191) upon thermolysis at 220°C extruded sulphene, as evidenced by trapping with an enamine, to generate the stable aromatic diester (192). Conversion of (191) into the corresponding anhydride (193), followed by thermolysis of the latter gave two equimolar products

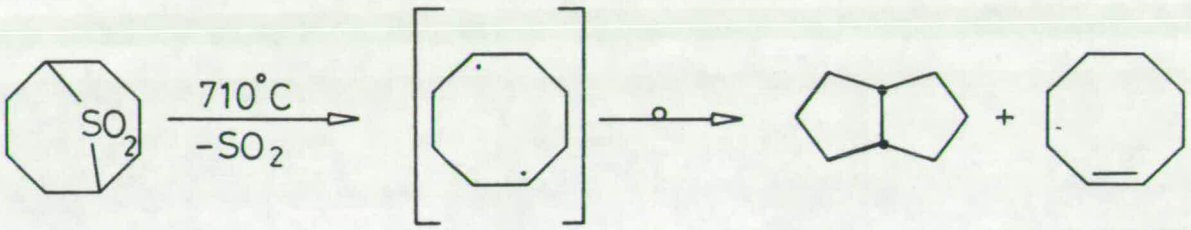
corresponding to competing extrusions of sulphene, and of sulphur dioxide, respectively to form the phenylphthalic anhydride (194) and the cycloheptatriene anhydride (195)[90].



Systems comprising sulphone-bridged seven- and eight-membered rings are known. The synthesis of the blue-coloured azulene (199) from 6-N,N-dimethylaminofulvene (196) and 3,4-dichlorothiophene dioxide (197) is believed[91,92] to involve thermal extrusion of both sulphur dioxide and dimethylamine from the sulphone-bridged seven-membered ring of intermediate (198).

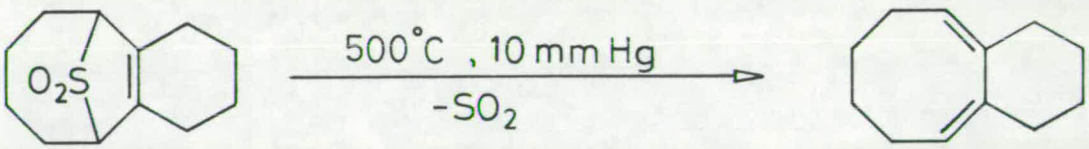


Vacuum pyrolysis of the saturated sulphone-bridged eight-membered ring (200) resulted in extrusion of sulphur dioxide *via* a postulated radical process with isolation of *cis*-bicyclo[3.3.0]octane and minor amounts of cyclooctene[82].

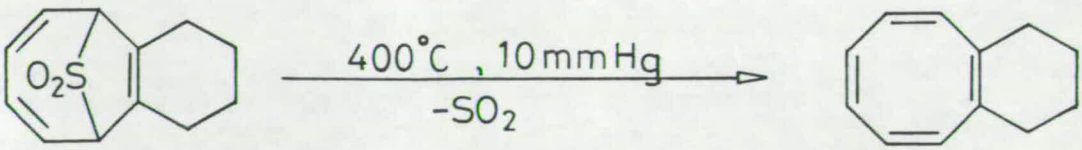


(200)

Sulphone-bridged eight-membered ring systems possessing appropriately located unsaturation have been found to thermally extrude sulphur dioxide under milder conditions than their saturated counterparts. Participation of the cyclic double bond in a low-energy concerted extrusion mechanism may account for these observations. Thus, bridged systems (201) and (203) are found to undergo facile eliminations of sulphur dioxide by proposed concerted pathways, generating higher-unsaturated hydrocarbons (202) and (204), respectively[93].

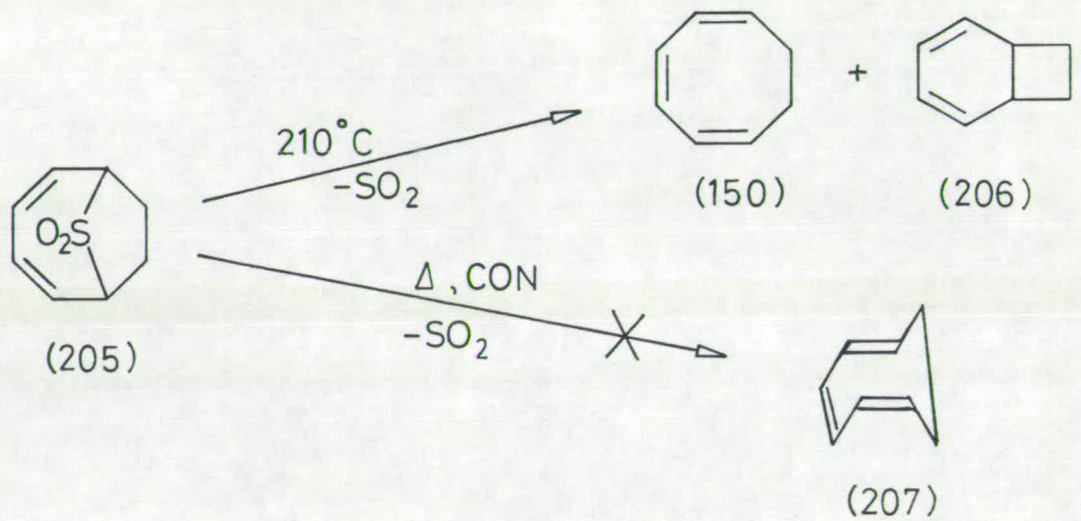


(201) (202)



(203) (204)

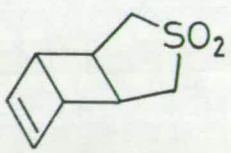
Similarly, the doubly unsaturated system (151), as discussed earlier, undergoes concerted elimination of sulphur dioxide under mild conditions. In contradistinction, elimination of sulphur dioxide from the isomeric system (205) required much more extreme thermolysis conditions, yielding (Z,Z,Z)-cycloocta-1,3,5-triene (150) and bicyclo[4.2.0]octa-2,4-diene (206)[94]. The mechanism for this process may be radical in nature, the predicted conrotatory concerted mechanism being disfavoured due to the ring strain associated with the resultant (E,Z,Z)-cycloocta-1,3,5-triene (207).



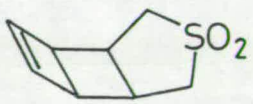
C. Programme of Research

A considerable amount of research has been undertaken within these laboratories into the preparation, reactivity and pyrolysis of 3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide (63) and related tricyclic systems (69), as discussed previously. In particular, a novel through-space orbital interaction was found between the sulphone group and the olefin moiety of sulpholane (63) as evidenced by the unusually high ionisation potential (πI_p = 10.25 eV) of the latter[95]. As a result of the close spacial proximity of the sulphone and olefin groups in (63), bromination of the system generated both cis- and trans-dibromide products[96], again a most unusual occurrence.

In furtherance of research into systems related to (63), it was considered that synthesis of both transoid- and cisoid-4-thiatricyclo[5.2.0.$0^{2,6}$]non-8-ene 4,4-dioxides, structures (208) and (209) respectively, would present the opportunity for a comparative assessment of the effects of a through-space interaction. For the cisoid isomer (209), a strong orbital interaction between the sulphone group and the cyclobutene double bond, with resultant effects on olefin ionisation potential and reactivity, would be anticipated;

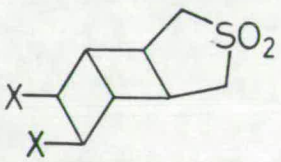


(208)

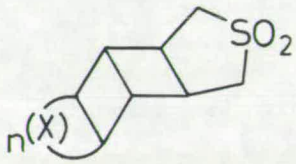


(209)

for the transoid isomer (208), the large spacial separation between the two functional groups would preclude any such effect, with the olefin moiety expected to display typical cyclobutene characteristics. In addition, it was realised that synthesis and pyrolysis of saturated derivatives (210) of the transoid isomer (208) would allow completion of the thermal extrusion study of the tricyclic sulpholane series (69), for which only systems (69; n = 2) in the sequence of n = 0-5 have not been investigated. Examination of the thermal extrusion processes of a parallel series of tetracyclic systems (211) of varying terminal ring size, potentially available by manipulation of (208) or precursor systems, was also considered to be of value.

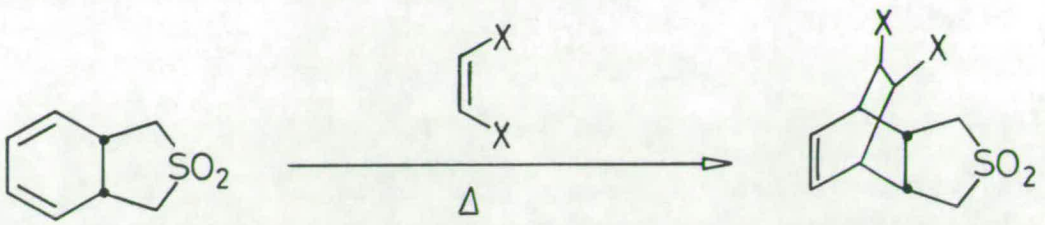


(210)



(211)

Preparation of the novel cyclohexadiene-sulpholane (212) was identified as an initial synthetic target towards realisation (by photochemical ring closure) of tricyclic isomers (208) and (209); however, it was apparent that the bicyclic structure (212) was also of particular synthetic value as a diene template for the construction of bridged tricyclic Diels-Alder adducts (213). Such systems were recognised as potentially possessing spacially proximate sulphone and olefin groups and therefore, in common with (209), to be of interest in the study of orbital interactions through space. The thermal behaviour on FVP of tricyclic sulpholanes (213), and of derivatives formed by manipulation of the olefin portion of this system, was recognised as being worthy of investigation in consolidation of



(212) (213)

research previously conducted on related bridged systems such as (88) and (90; X = CH_2).

D I S C U S S I O N

DISCUSSION

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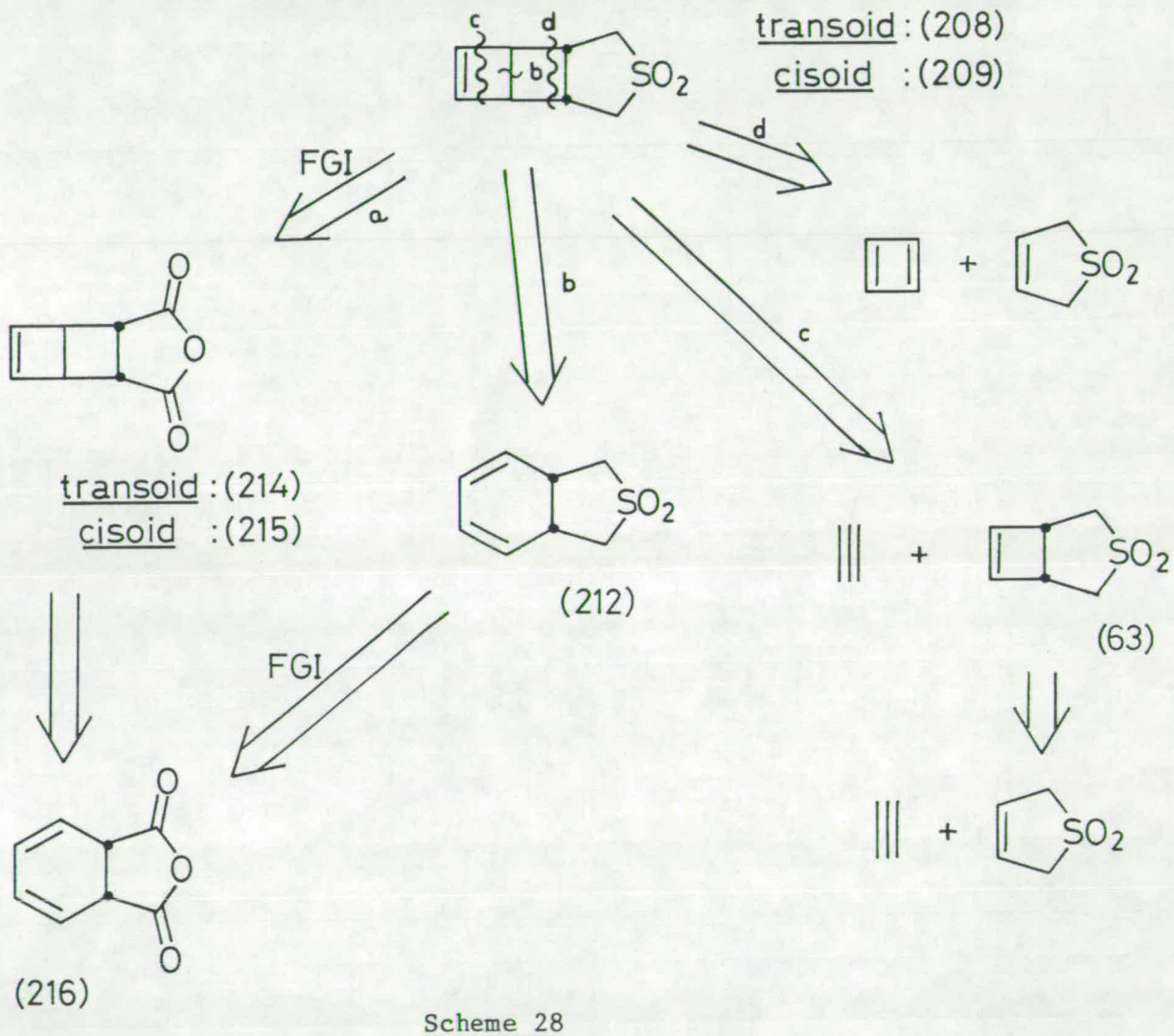
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A. Preparation of (cis-1-transoid-1,2-cis-2)-4-Thiatricyclo-[5.2.0.$0^{2,6}$]non-8-ene 4,4-dioxide (208)

Retro-synthetic analysis of the target tricyclic sulpholane system in its transoid (208) or cisoid (209) forms, as outlined in Scheme 28, indicates four obvious pathways from which such isomers may be constructed. Pathway (a), involving a simple functional



Scheme 28

group interconversion (FGI) of the sulpholane ring to an anhydride precursor (the reverse being a well known reaction sequence for the synthesis of sulpholane systems[97]), yields transoid (214) and cisoid (215) anhydrides as precursors to (208) and (209) respectively. Anhydride (214) has previously been prepared[98] by photolysis of cis-1,2-dihydrophthalic anhydride (216).

Application of disconnection (b) to the target systems generates novel cyclohexadiene-sulpholane system (212) as a potential precursor. This in turn may be available from bicyclic anhydride (216), which is therefore a key compound in the preparation of (208) and/or (209) by two routes involving a photochemical reaction step.

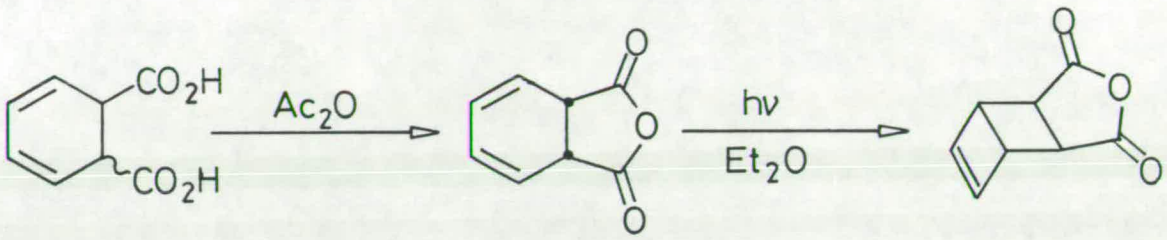
Following application of disconnection (c), synthesis of target molecules (208) and (209) may be achieved by combination of acetylene, or an acetylene synthon, with cyclobutene-sulpholane (63), a known compound[34]. A final possible synthesis of the tricyclic systems (208)/(209) is indicated by pathway (d) to follow from Diels-Alder reaction of cyclobutadiene with butadiene sulphone.

Each of the four possible routes leading to the synthesis of the tricyclic sulpholane system, in its transoid (208) or cisoid (209) forms, indicated by the retro-synthetic analysis outlined in Scheme 28, has been attempted: the results of these are now described in the remainder of this, and in the following section.

1. From cis-1-transoid-1,2-cis-2-bicyclo[2.2.0]hex-5-ene-exo-cis-2,3-dicarboxylic anhydride (214)

The title compound was originally prepared by van Tamelen and Pappas[98] via [2 π_s + 2 π_s] photocyclisation of cis-1,2-dihydrophthalic anhydride (216). Although in theory[25] both transoid (214) and cisoid (215) isomers can be formed by disrotatory photocyclisation of (216), the cisoid anhydride system was not obtained, presumably due to the greater number of eclipsing cyclobutane C-H bonds in this isomer, disfavouring it compared to the transoid alternative. The transoid structure of the sole product obtained was proven following ozonolysis of the anhydride (214) and conversion of the resultant tetraacid to the tetramethyl ester: this was found to be identical to

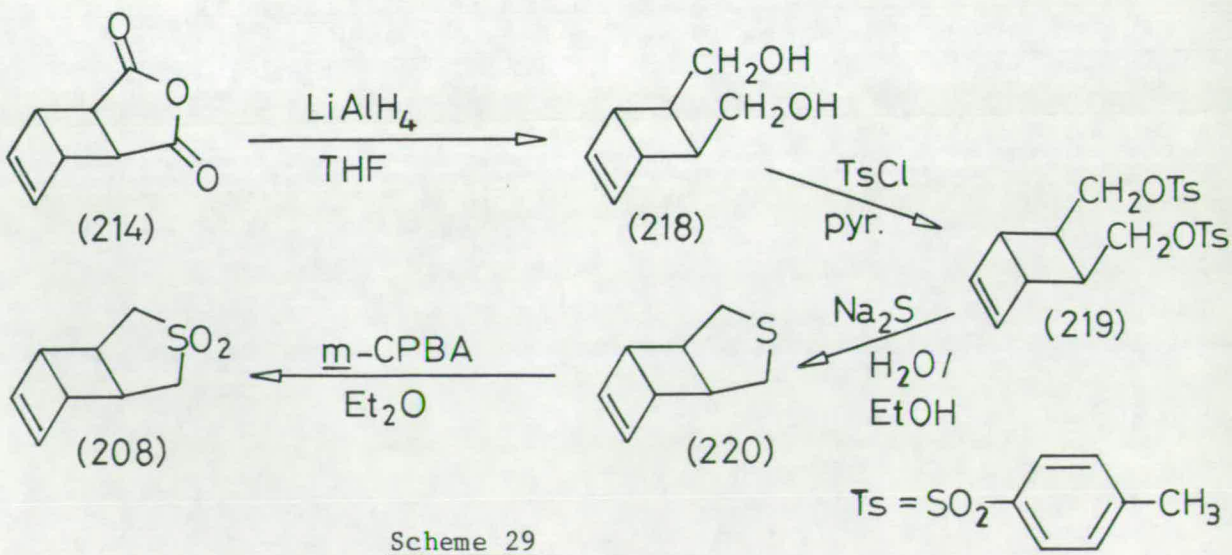
the known cis,transoid,cis-tetramethyl cyclobutane tetracarboxylate, permitting transoid geometry to be assigned to the anhydride (214)[99].



(217) (216) (214)

Preparation of cis-1,2-dihydrophthalic anhydride (216) was effected by acetic anhydride dehydration of a commercially available mixture of cis- and trans-1,2-dihydrophthalic acids (217). Irradiation of a dilute ethereal solution of the diene (216), using a 400W medium pressure mercury lamp through quartz, in a slight variation of the procedure of McDonald and Reineke[100], was monitored by following the decrease with time of diene (216) absorption ($\lambda_{max.}$ 256, 265 nm) in the UV spectrum. After irradiation for five hours, the reaction was found to be complete: standard work-up procedures gave the transoid anhydride (214) in 14% yield (lit.[100] 24%).

Synthesis of the transoid sulpholane (208) was then undertaken by the reaction sequence outlined in Scheme 29. Reduction of



(214) (218) (219) (220) (208)

Scheme 29

transoid anhydride (214) with lithium aluminium hydride gave, following purification by medium pressure liquid chromatography, a 48% yield of the known[101] exo-cis-bis(hydroxymethyl) system (218). Treatment of this with p-toluene sulphonyl chloride in pyridine, following a literature procedure[101], gave the corresponding ditosylate (219) in fair yield as fine colourless needles, m.p. 144-145°C (lit.[101] m.p. 146-147°C).

Analysis of the ^1H NMR spectrum, which compares well with that previously described[101], furnishes supportive evidence for the exo-cis substituent stereochemistry of (219). Thus, triplet signals at δ2.96 (ring fusion protons H_1, H_4) and δ6.24 (olefinic protons H_5, H_6) exhibiting identical coupling constants $J_{1,5}$ ($J_{4,6}$) and $J_{1,6}$ ($J_{4,5}$) of 1.2 Hz require coupling constant $J_{1,2}$ ($J_{3,4}$) to be considerably smaller than this value. Although in general the assignment of cis or trans stereochemistry to substituents on a cyclobutane ring by the use of vicinal coupling constants alone has been demonstrated[102] to be unreliable, there are particular instances where these can be applied with certainty. For systems in which the cyclobutane ring lacks strongly electron-withdrawing substituents and is directly fused to one or more strained rings (ie where complicating electronic and conformational factors are absent), protons exhibit cis vicinal coupling constants in the range 6-11 Hz, and trans vicinal coupling constants of 0-6 Hz[102,103]. Since ditosylate (219) has a cyclobutane ring obeying these criteria, the small value for $J_{1,2}$ ($J_{3,4}$) is indicative of a trans relationship between protons H_1,H_4 and H_2,H_3 in accord with the expected exo-cis substituent stereochemistry of the system.

Returning to the reaction sequence of Scheme 29, treatment of ditosylate (219) with sodium sulphide in boiling aqueous ethanol proceeded smoothly to generate transoid tetrahydrothiophene system (220) as a foul-smelling oil in good yield (74%). The crude product fully satisfied ^{1}H and ^{13}C DEPT NMR, and mass spectral analyses, and was subjected to oxidation without further purification. Reaction of the tetrahydrothiophene (220) with two molar equivalents of m-chloroperoxybenzoic acid (m-CPBA) in ether gave, after chromatographic separation, a crystalline product obtained as colourless prisms m.p. 109-111.5°C on recrystallisation from methylene chloride/diisopropyl ether.

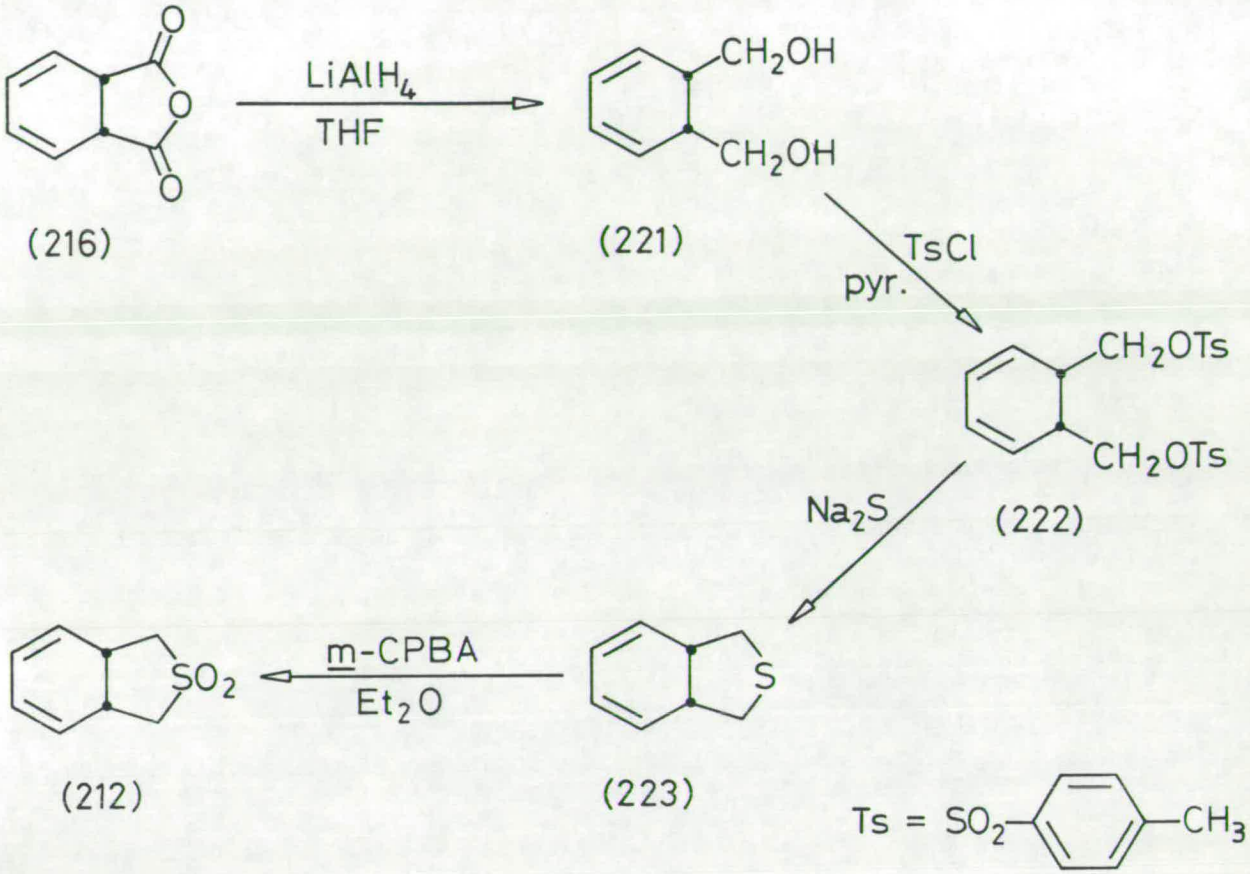
This material displayed elemental composition values for carbon and hydrogen in accord with a compound of empirical formula $C_8H_{10}O_2S$; the presence of a parent ion of m/e 170 in the mass spectrum confirmed the monomeric nature of this product. Examination of the mass spectral fragmentation pattern indicated a major pathway involving loss of sulphur dioxide from the parent ion - the presence of the sulphone group in the infrared spectrum, demonstrated by two intense absorptions at expected values (in the ranges 1320-1300 cm^{-1} and 1160-1140 cm^{-1} characteristic of the asymmetric and symmetric stretching modes of the sulphone group[104]), allowed further confirmation of the sulphone nature of the product. Full ^{1}H and ^{13}C DEPT NMR analyses permitted complete assignment of this product to that of the desired transoid tricyclic sulpholane (208). Finally, X-ray crystallographic examination of suitably grown crystals fully vindicated the transoid geometry assigned to the product (208), demonstrating that no loss of substituent or ring stereochemistry occurred during the reaction sequence displayed in Scheme 29. The detailed crystal structure and

spectral analyses of the transoid isomer (208) are considered in parallel with the spectra of the cisoid isomer (209) in Section D.

Although the reaction sequence outlined in Scheme 29 did culminate in the successful synthesis of transoid sulpholane (208), it is a limited approach to the preparation of this compound in sufficient quantities for extended reactivity studies. The principal drawback of the route lies in the photochemical preparation of the transoid anhydride (214) starting material, since not only is the reaction low yielding, but also requires the use of very dilute solutions of the bicyclic anhydride precursor (216) in order to minimise undesired intermolecular reactions. Using the available photochemical apparatus, anhydride (214) could therefore only be obtained in small quantities; after the four reaction steps required for conversion into the transoid sulpholane (208), each entailing considerable loss in yield of product, synthesis of (208) by this route is clearly logistically undesirable. It was considered that a more advantageous route to (208) (or possibly to (209)) should incorporate the intramolecular photocyclisation reaction as the final, rather than the initial step. In this respect retro-synthetic analysis of the target systems (Scheme 28) indicated synthesis of bicyclic cyclohexadiene-sulpholane (212) to be a suitable vehicle for an improved photochemical route to (208)/(209).

2. From cis-8-thiabicyclo[4.3.0]nona-2,4-diene 8,8-dioxide (212)

The preparation of the title compound (212) was envisaged as being possible by the reactions shown in Scheme 30, a series of transformations directly parallel to those by which transoid sulpholane (208) was prepared (Scheme 29). Reduction of cis-1,2-dihydrophthalic



Scheme 30

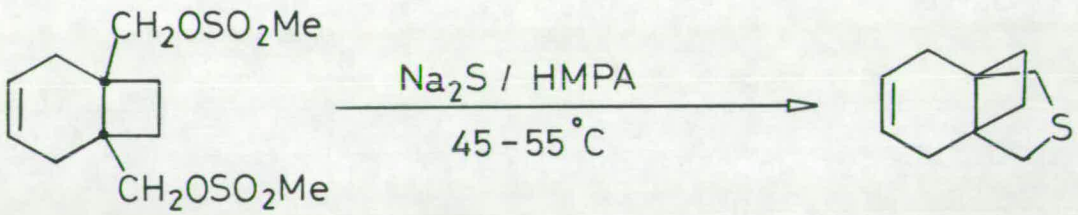
anhydride (216) using lithium aluminium hydride in tetrahydrofuran resulted in isolation, in good yield, of a light yellow oil which was fully characterised by microanalytical and spectroscopic tests as the cis-bis(hydroxymethyl) compound (221).

Following treatment of the diol (221) with p-toluene sulphonyl chloride in pyridine, the corresponding ditosylate (222) was realised as colourless crystals, m.p. 68.5-70°C. Although elemental composition and ^{1}H, ^{13}C NMR and IR data were in full accord with this structure, the mass spectrum displayed no parent ion (m/e 448), and the highest signal detected occurred at m/e 303. The failure to achieve interpretable mass spectra under electron impact (EI) ionisation conditions with the ditosylate system is also found to occur with other related examples, as will be described in later sections.

Mirroring the extensive decomposition of the ditosylate (222) under EI mass spectroscopy, the product was found to degrade to a black tar on exposure to atmosphere over a period of several weeks.

Having prepared the ditosylate (222), the compound was reacted with sodium sulphide in boiling aqueous ethanol in a reaction similar to that by which the tetrahydrothiophene system (220) had been prepared (p. 74). However, rather than formation of the expected product (223) only a small quantity of purely aromatic sulphide products was isolated. In view of the ready decomposition of ditosylate (222) on exposure to moist air, a means of conversion of (222) to the desired tetrahydrothiophene (223) by use of an anhydrous medium, and at ambient temperatures was sought.

Paquette *et al*[97,105] have developed the use of anhydrous solutions of sodium sulphide in hexamethylphosphoramide (HMPA) as an efficient means of preparing tetrahydrothiophenes from dimesylate precursors: use of this reagent has allowed the preparation, at moderate temperatures, of the tricyclic tetrahydrothiophene (225) in 90% yield from dimesylate (224)[97]. The efficiency of the reagent under such

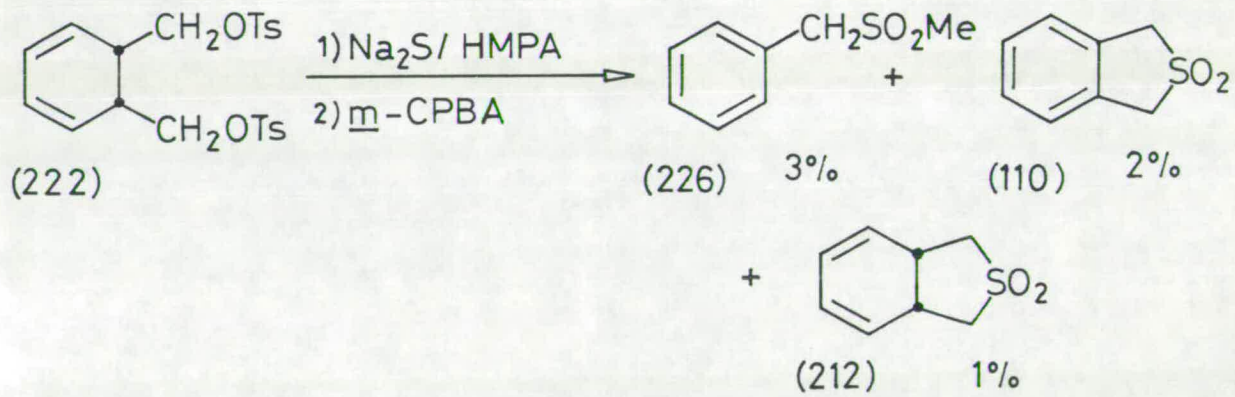


(224) (225)

mild conditions has been proposed[105] to result from the high cation-solvating ability of anhydrous HMPA, which permits the effectively smaller sulphide nucleophile to undergo the displacement-cyclisation

reaction, with formation of the tetrahydrothiophene product, more easily than can occur with the bulkier nucleophile in aqueous media.

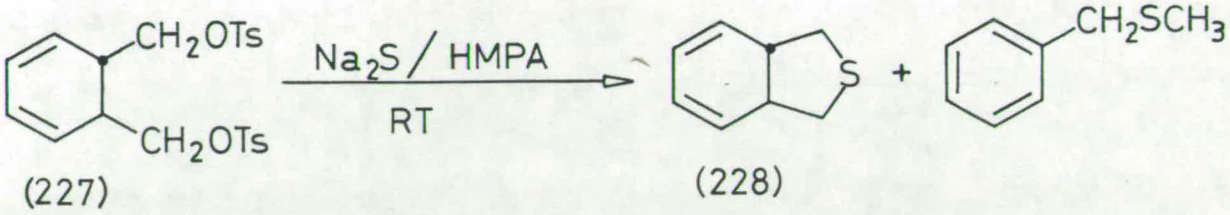
Upon treatment of ditosylate (222) with an anhydrous solution of sodium sulphide in HMPA at room temperature for 70 hours, the starting ditosylate was found to be completely consumed. However, on work-up a mixture of largely aromatic sulphide products was obtained, of which only benzyl methyl sulphide could be identified. In order to facilitate identification of these products the mixture was oxidised with excess m-chloroperoxybenzoic acid in ether. Preparative TLC allowed separation of three component bands, giving low yields of benzyl methyl sulphone (226), the benzosulpholene (110), and an unresolved mixture of olefinic sulphone products containing a small quantity of the desired cyclohexadiene-sulpholane (212), identified



(222) (226) 3% (110) 2% (212) 1%

by comparison of its ^1H NMR spectrum with that of an authentic sample obtained from an alternative route (described later).

In contradistinction, treatment of the isomeric trans-disubstituted cyclohexadiene (227) with an anhydrous solution of sodium sulphide in HMPA, using very similar conditions to those employed on (222), gave the corresponding trans-fused bicyclic tetrahydrothiophene (228), together with minor amounts of benzyl methyl sulphide, in fair yield. Although a commmon feature in the reaction

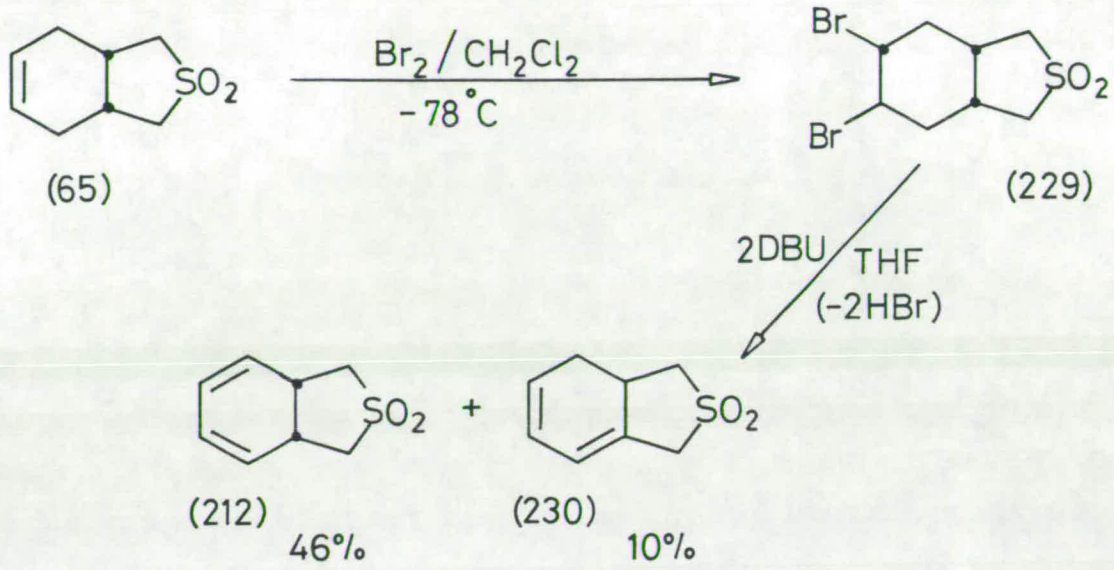


(227) (228)

3 : 1

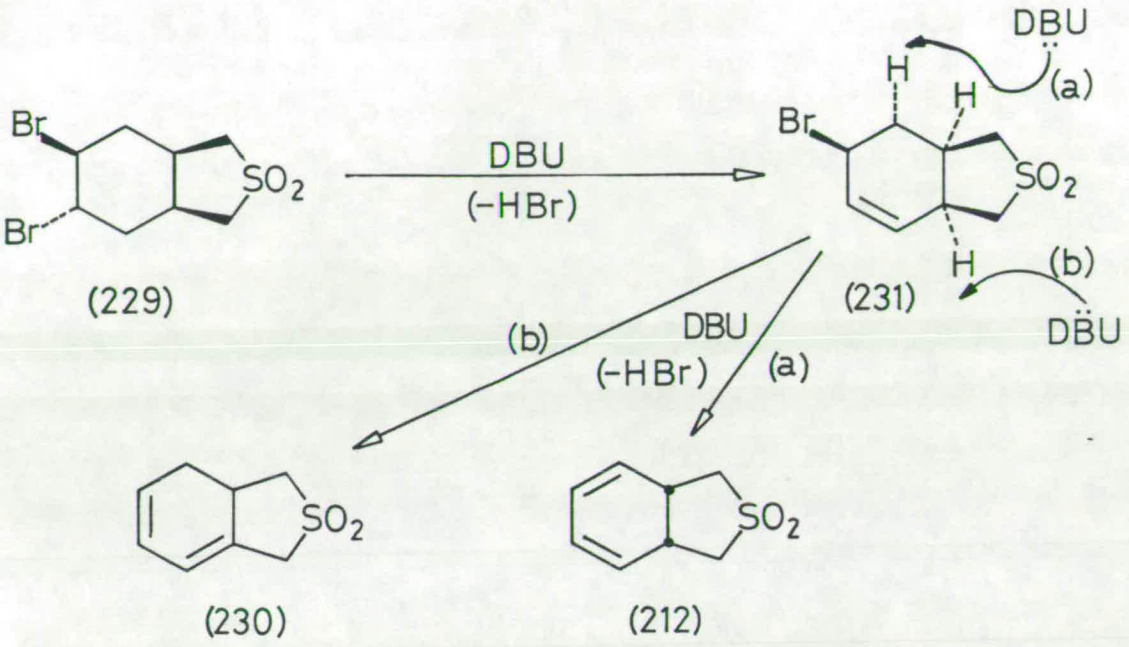
of the isomeric ditosylates (222) and (227) with sodium sulphide is the formation of benzyl methyl sulphide, perhaps due to a similar ring opening process operating on both isomeric tetrahydrothiophenes (223) and (228), the formation of a benzodihydrothiophene (giving rise to (110) on oxidation) in only the case of (222) is surprising. As this product probably arises from dehydrogenation of initially formed cis-fused tetrahydrothiophene (223), the thermodynamic impetus for such a process to occur with the more highly strained trans-fused isomer (228) would be expected to be greater. That, in spite of this, no dehydrogenation is found to occur with (228) may be a reflection of a kinetic requirement for the dehydrogenation process: that the ring fusion hydrogen atoms should be mutually cis, as in the tetrahydrothiophene (223). In any case, the sequence of reactions expressed in Scheme 30 was found to be inadequate with respect to synthesis of the cyclohexadiene-sulpholane (212) in reasonable quantities or purity, and a more efficient route, starting from the known[33] cyclohexene-sulpholane (65), was investigated.

Addition of a solution of bromine in methylene chloride to the olefin (65) at -78°C resulted in almost quantitative isolation of the trans-dibromide (229) as colourless needles, m.p. 190.5-192°C, fulfilling elemental composition and spectroscopic expectations. In particular an eight line ^{13}C NMR spectrum was indicative of a trans,



rather than cis, dibromide stereochemistry for the product. Utilising the general procedure of Warner and Lu[106], bis-dehydrobromination of dibromide (229) using the hindered base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave, after separation by MPLC, two isomeric products. These were identified as being the desired cyclohexa-2,4-diene sulpholane (212) (46% yield), m.p. 35-36.5°C, and the cyclohexa-1,3-diene isomer (230) (10%), m.p. 112-113.5°C, following detailed NMR analyses.

The formation of the undesired side product (230) was initially presumed to have occurred by a base-catalysed isomerisation of the major product (212). However, on treatment of a pure specimen of (212), or of (230), with DBU under identical reaction conditions to those employed in initial formation of the isomeric cyclohexadiene sulpholanes, no isomerisation to the alternative isomer was observed. As isomerisation of one isomer to the other does not occur, a likely mechanism involves formation of both dienes (212) and (230) from a common, mono-dehydrobrominated intermediate (231), as shown in Scheme 31.

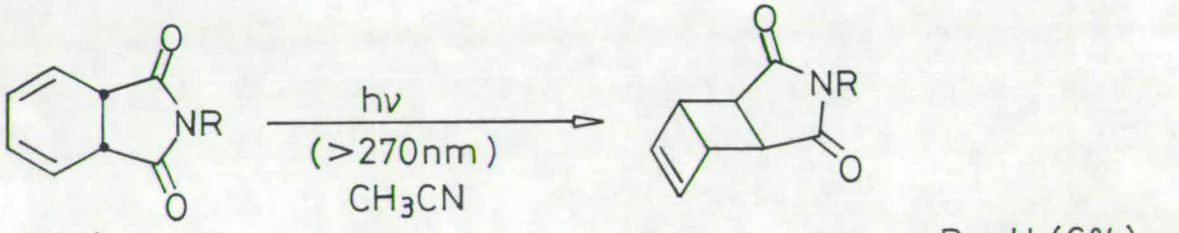


Scheme 31

An alternative to base induced bis-dehydrobromination of (229) is the thermal expulsion of two molecules of hydrogen bromide with generation of the diene (212). FVP of dibromide (229) on a small scale, at a furnace temperature of 650°C, lead to isolation of a pyrolysate containing, by GLC analysis, the volatile hydrocarbons o-xylene (24% yield), ethyl benzene (5%) and styrene (1%). Following chromatographic purification, a single sulphone product was obtained in 42% yield, this being the desired bis-dehydrobrominated product, diene (212). As described in a later section, the volatile hydrocarbons detected arose from extrusion of sulphur dioxide from sulpholane (212) under the pyrolysis conditions employed. Since this thermal route to (212) offered the advantage of simpler purification of the product compared to the base-induced bis-dehydrobromination procedure, the pyrolysis was attempted on a comparatively large scale (using 2.38g of dibromide (229)). Disappointingly, analysis of the pyrolysate indicated this to be a highly complex product mixture in which little

or no cyclohexadiene-sulpholane (212) was present: it would appear that secondary reactions of the liberated hydrogen bromide with the unsaturated sulpholane products in the pyrolysis trap had occurred. In light of this, and the technical difficulties inherent in installing a suitable hydrogen bromide abstraction agent within the FVP apparatus, the base (DBU) bis-dehydrobromination conversion of (229) to diene (212) was retained.

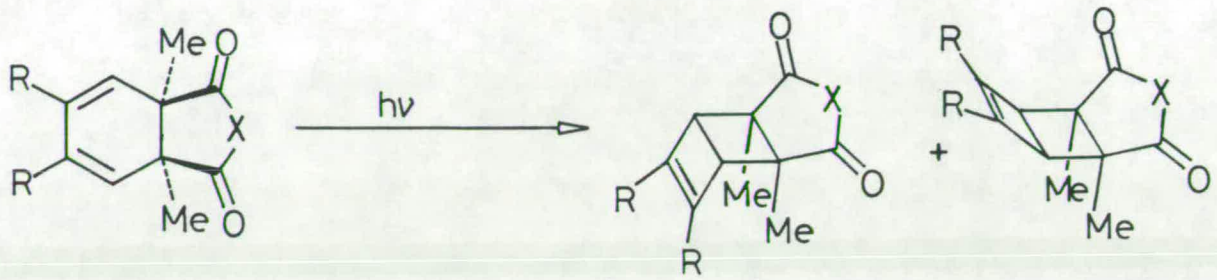
Having obtained the diene (212) in reasonable quantities, the study of its possible [2 π_s + 2 π_s] photocyclisation to the target tricyclic systems (208) and (209) was considered. Although both of these tricyclic isomers may be obtained by a symmetry-allowed disrotatory electrocyclisation process operating on photolysis of diene (212)[25], related examples of irradiation of unsubstituted cyclohexadiene systems such as the anhydride (216)[98] and the imides (232)[107] indicated that only the transoid tricyclic products were formed, albeit in low yield. Formation of the cisoid tricyclic



(232)

R = H (6%)
= Ph (22%)

systems appears to be disfavoured, compared to the transoid isomers, due to the greater ring strain imposed on the former structures resulting from the larger number of eclipsing cyclobutane C-H bonds present. In contradistinction, mixtures of transoid and cisoid isomers are found to result from photolysis of bicyclic systems (233) in which substituents are present on the cyclohexadiene ring[108,109,110].



(233)

X = O ; R = H, Me
X = NH ; R = Me
X = NBu ; R = Me

For these systems, the presence of bulky substituents at the ring fusion positions of the bicyclic system (233) disfavours the formation of the transoid tricyclic product, due to the greater steric interaction between the ring fusion substituents and the cyclobutene ring, compared to the situation in the unsubstituted analogue, resulting in increased formation of the cisoid tricyclic products[107].

Thus, with the expectation that photolysis of (212) would furnish the transoid tricyclic sulpholane (208), irradiation of a dilute solution of the diene in ether was undertaken. Using a 400W medium pressure mercury lamp fitted with a Vycor filter and contained in a quartz immersion well, irradiation of the diene solution, which was submitted to constant nitrogen ebullition, was monitored by following the decrease in diene (212) absorption ($\lambda_{max.}$ 264, 274 nm) in the UV spectrum. Decrease of the diene absorptions to a constant minimum indicated completion of the reaction after 9.5 hours. Analysis of the product indicated the absence of both transoid (208) and cisoid (209) tricyclic isomers; only the benzosulpholene (110) (6%) was

identified. Similar results were obtained on irradiation of dilute solutions of the diene (212) in acetonitrile, and in acetone (containing benzophenone as a photosensitiser) through quartz.

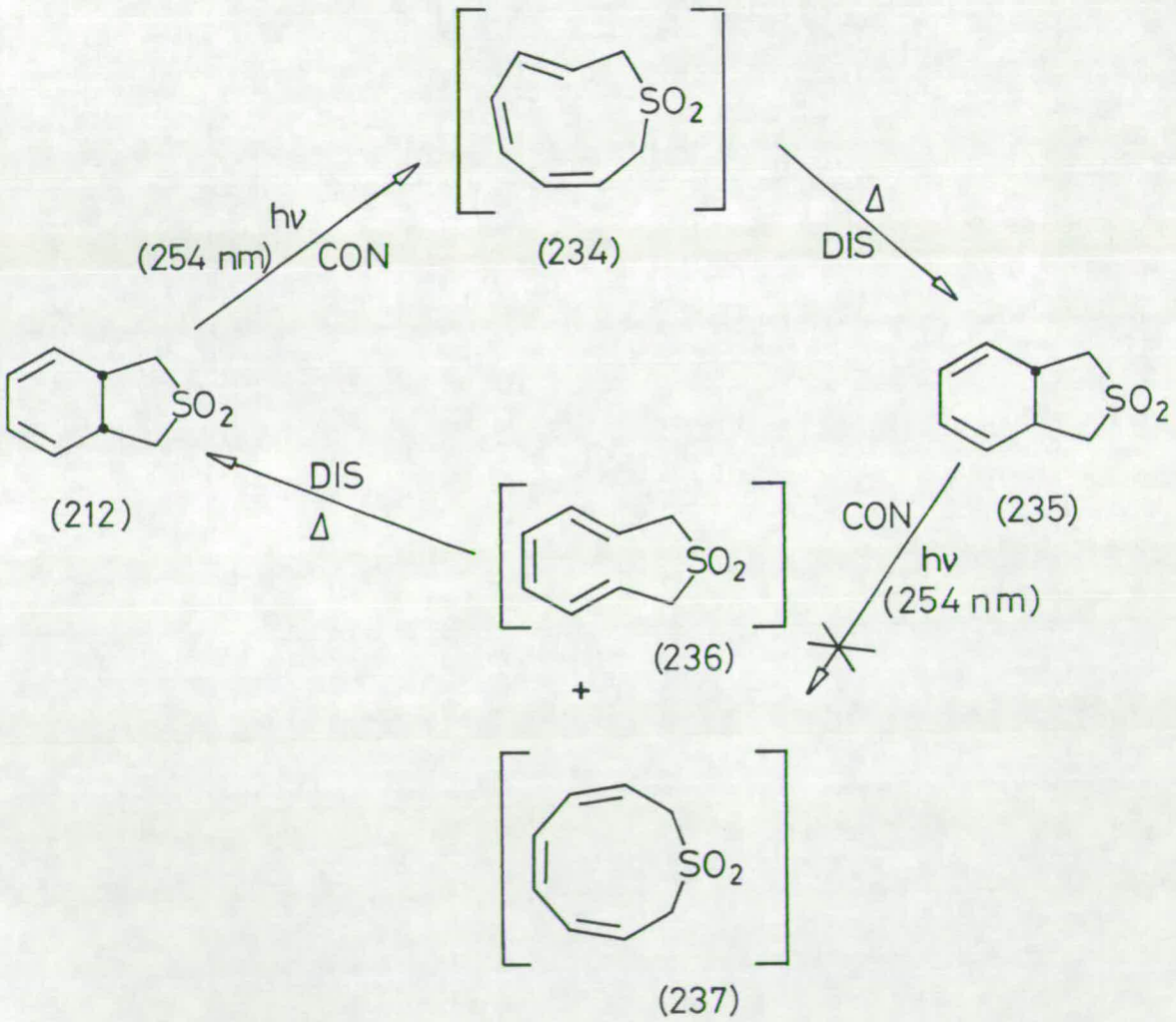
Following failures to generate the desired tricyclic systems on irradiation of (212) at room temperature, the photolysis of this diene, in the form of a dilute ethereal solution, at low temperature (-78°C) was attempted. After irradiation using a 100W medium pressure mercury lamp for eight hours, only recovered diene (212) was isolated in 64% yield.

Irradiation of a concentrated solution of the diene (212) in ether using a 15W lamp (main emission at 254 nm) for an extended period did, however, give surprising results. Analysis of the photolysate indicated that in addition to unchanged cis-fused bicyclic diene (212) (38%), and the product of dehydrogenation of this, benzosulpholene (110) (3%), there also appeared to be present the isomeric trans-fused bicyclic diene (235) (46%). Following chromatographic separation and comparison of the pure product with an authentic sample of (235), prepared by an unambiguous route (described in a later section), this deduction was confirmed.

Mechanistically, two alternative means by which this cis-fused/ trans-fused isomerisation process can occur appear feasible. The first of these is that of a ring junction hydrogen abstraction process, perhaps due to interactions between diene molecules in the concentrated solution employed. However, this mechanism appears remote following irradiation of a dilute solution of diene (212) in ether, under otherwise identical conditions, which returned a cis-fused (212) and trans-fused (235) diene mixture largely unchanged from that obtained on irradiation of the concentrated solution of

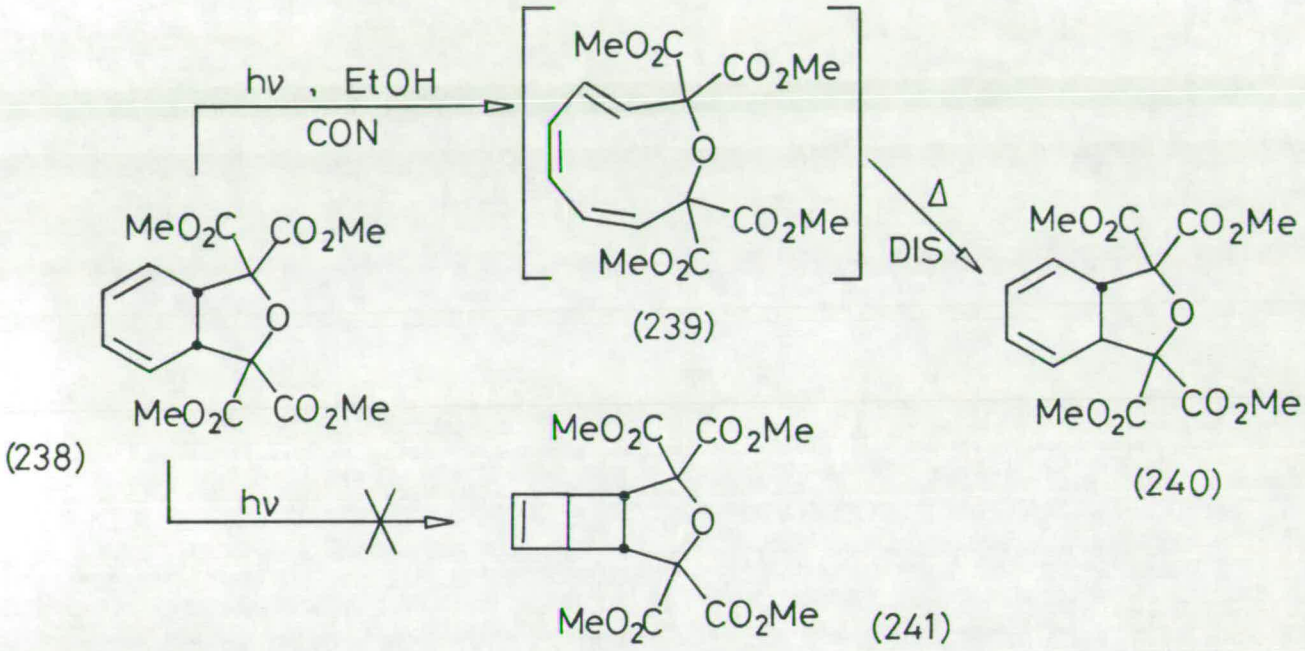
(212) in ether as described above. Furthermore the presence of a small quantity of trans-fused bicyclic diene (235) on irradiation of a dilute solution of (212) in carbon tetrachloride, rather than in ether, disfavours a solvent-diene hydrogen abstraction process as the source of the isomerisation, since this is unlikely to occur with two such diverse solvents.

The second, and much more likely, mechanism is that of a photochemically induced, concerted (conrotatory) ring opening of (212) to an intermediate (E,Z,Z)-cyclononatriene system (234), followed by a concerted (disrotatory) thermal ring closure to the trans-fused isomer (235) as shown in Scheme 32. A related literature example[99]



Scheme 32

concerns the photochemical transformation of the cis-fused diene (238), not to the expected tricyclic product (241), but to the trans-fused isomer (240) via the proposed intermediate (E,Z,Z)-triene (239). Similarly the photochemical isomerisation of cis-bicyclo[4.3.0]nona-



2,4-diene to the corresponding trans isomer, with isolation of the intermediate (E,Z,Z)-cyclonona-1,3,5-triene, has been reported[111].

Since in all the photolyses in which the trans-fused sulpholane (235) was formed, unchanged starting diene (212) was also present, the possibility of an equilibrium existing between the two isomers via intermediate trienes (234), (236) and (237) (Scheme 32) was considered. Should this be the case, the equilibrium mixture of dienes forming this photostationary state may be approached by photolysis of either diene. Thus, a dilute solution of the trans-fused diene (235) in ether was subjected to photolysis under the same conditions as those used on the cis-fused diene (212) and which had previously generated a mixture of the two isomers. However, only the starting diene (235) was observed at all times during irradiation,

indicating that no photoequilibration of the two isomers occurs under these conditions.

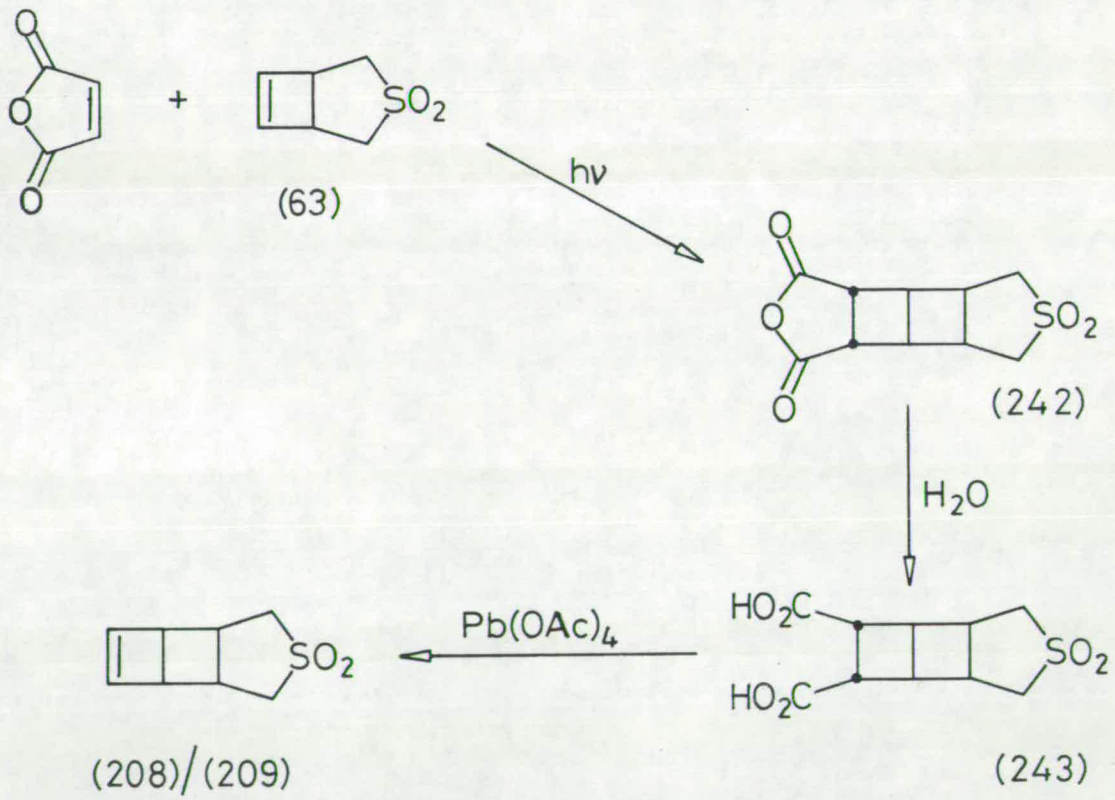
In order to ascertain the reasons for the lack of formation of either of the tricyclic isomers (208) and (209) on irradiation of diene (212), a solution of the transoid sulpholane (208) in acetone was irradiated through quartz using a 100W lamp. Constant monitoring of the course of the reaction by ^1H NMR spectroscopy indicated a steady decrease in concentration of starting material (208), but with formation of only saturated, apparently polymeric, products. No starting diene remained after irradiation for a period of eight hours. This observation may account for the total lack of isolation of (208) under any of the photolysis conditions applied to diene (212), since the demonstrated instability of the tricyclic system to irradiation may serve to destroy this material more quickly than it can form from (212).

The complete failure of the cis-fused diene system (212) to undergo photocyclisation to either of the desired tricyclic sulpholanes (208) and (209) under any of the various photochemical conditions employed resulted in diversion of attention to synthesis of the target molecules by another of the routes suggested by retro-synthetic analysis (Scheme 28), that of reaction of the cyclobutene sulpholane (63) with acetylene.

3. From cis-3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide (63)

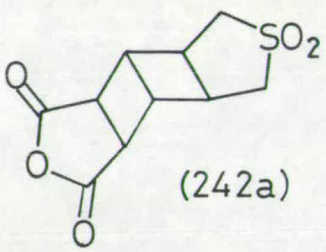
As outlined in Scheme 28, the target systems (208) and (209) are potentially available from a [2 π + 2 π] photoaddition of the known[34] cyclobutene sulpholane (63) and acetylene. Since acetylene is generally poorly activated towards photochemical reactions, and in view of the potentially hazardous nature of reactions involving

inflammable acetylene gas, the use of a more photoactive and conveniently handled acetylene equivalent was considered. Synthesis of cyclobutene sulpholane (63), as outlined in Scheme 11, has been achieved[34] by oxidative decarboxylation of the diacid (68) of the photoadduct (45) of butadiene sulphone and maleic anhydride. In this reaction sequence, it is evident that maleic anhydride acts as a photochemically active acetylene synthon: replacement of butadiene sulphone by the cyclobutene sulpholane (63) in the initial photolysis step in the reaction sequence leading to (63) generates a parallel synthetic route (Scheme 33) to the tricyclic sulpholane systems (208)/(209) which circumvents the use of acetylene gas.

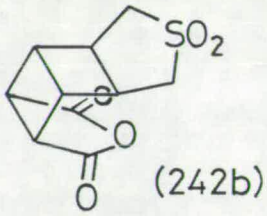


Scheme 33

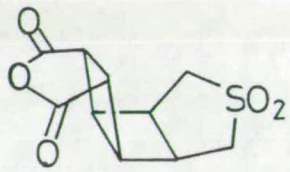
In a variation of the general procedure by which transoid adduct (45) was obtained, a solution of the cyclobutene sulpholane (63)[34] and maleic anhydride in acetone was irradiated through quartz, using a 100W medium pressure mercury lamp, for a prolonged period resulting in formation of a crystalline product, fully characterised, in spite of a ready tendency to undergo hydrolysis to the corresponding diacid (243), as the tetracyclic anhydride (242). Analysis of the ^{1}H and ^{13}C NMR spectra indicated the product to be a single isomer of the four possible tetracyclic structures (242a-d). In general,



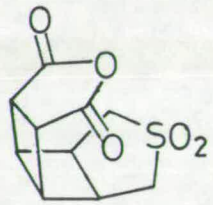
(242a)



(242b)



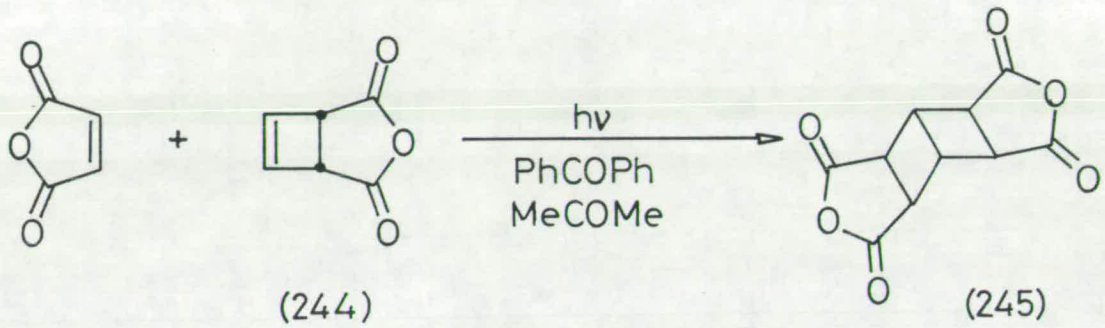
(242c)



(242d)

photochemical reactions between two unsubstituted cycloolefinic systems result in formation of photoadducts with transoid geometry about the central cyclobutane ring[108], these being the structures with minimal steric interactions across the central cyclobutane ring, i.e. the most thermodynamically stable. The demonstrated[28,35] transoid geometry of the adduct (45) of butadiene sulphone and maleic anhydride is one example of this; a more pertinent situation refers to the photoaddition of the cyclobutene anhydride (244) with maleic

anhydride, using benzophenone as photosensitiser, which has been found[112] to generate a single transoid, transoid dianhydride product (245).



(244) (245)

In light of the similarities in the photochemical reactions forming (242) and (245) it might reasonably be expected that the structure of the product of reaction of cyclobutene sulpholane (63) and maleic anhydride would possess the most thermodynamically stable transoid, transoid structure (242a). Detailed analysis of the ^1H NMR spectrum of the product confirms this supposition. A broad singlet resonance at $\delta 2.82$ corresponding to the methine cyclobutane protons H_1 and H_7 indicated that coupling constants $J_{1,2}$ ($J_{6,7}$) and $J_{1,9}$ ($J_{7,8}$) are small (much less than 6 Hz), in accord with trans vicinal coupling constants and hence an overall transoid, transoid stereochemistry for the anhydride product (242a). This assignment of structure is confirmed by findings described later in this section, and by consideration of the symmetry characteristics of the disulphone derived from (242a) by manipulation of the anhydride ring as described in a following section.

In view of the successful photochemical reaction of the cyclobutene anhydride (244) with maleic anhydride resulting in formation of tetracycle (245), it was recognised that sulpholane (242) may also be obtained by photoaddition of anhydride (244) with

butadiene sulphone. Preparation of the cyclobutene anhydride was achieved in 43% yield by a variation of the procedure of Bloomfield et al[113], following photochemical addition of maleic anhydride and acetylene in the presence of benzophenone at low temperature. Photolyses of this compound with butadiene sulphone in acetone solution with irradiation through quartz using a 100W lamp, whether in the presence of benzophenone and acetophenone photosensitisers or not, failed in all instances to generate any of the tetracyclic product (242), with only reduced quantities of starting olefins being recovered.

Returning to the reaction sequence depicted in Scheme 33, hydrolysis of the anhydride (242) by heating in boiling water afforded the corresponding diacid (243) in nearly quantitative yield, this demonstrating expected elemental composition and spectroscopic properties. Heating of the cubic crystals of diacid (243) resulted in decomposition at 225-230°C with expulsion of water and regeneration of anhydride (242), m.p. 286-287°C : such behaviour is typical of cis-diacids derived from five-membered anhydride rings.

Oxidative decarboxylation of diacid (243) was considered next. Lead tetraacetate decarboxylation of diacids and anhydrides is a fairly well known reaction, and the subject of an in-depth review[114]. Such reactions vary a great deal in yield from one case to another, these generally being low and within the range 15-35%. Treatment of diacid (243) with excess lead tetraacetate in oxygen-saturated pyridine at 67°C was observed to cause evolution of gas (carbon dioxide) after a few minutes, indicating that decarboxylation was taking place. On cessation of gas evolution, aqueous work-up followed by sublimation of the crude isolated product gave pure transoid tricyclic sulphone (208) in 35% yield, this being identical in all respects to the product obtained by manipulation of the anhydride ring of (214) as

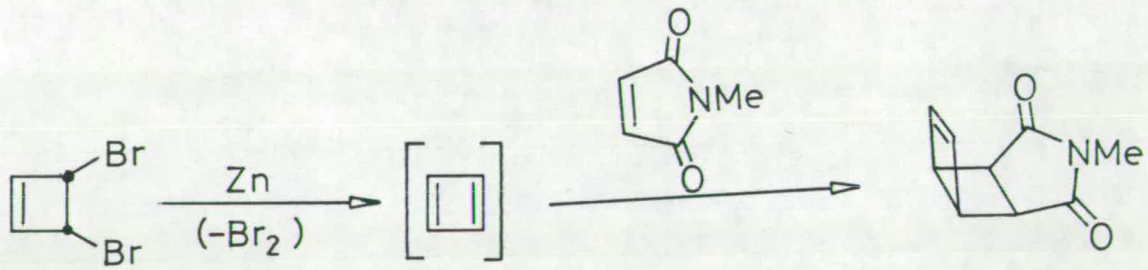
described previously. Following from the identification of the transoid geometry of this product, verification of the transoid arrangement of the sulpholane and two cyclobutane rings, forming part of the structure of transoid,transoid tetracyclic anhydride (242a), was obtained.

As cyclobutene sulpholane (63) was readily available as a starting material for construction of the transoid sulpholane (208) by the reaction sequence shown in Scheme 33, and since this route could be scaled up to realise (208) in appreciable quantities relatively easily, this reaction sequence rather than the alternative successful route (Scheme 29) was the one of choice for synthesis of the transoid tricyclic isomer.

B. Preparation of (cis-1-cisoid-1,2-cis-2)-4-Thiatricyclo[5.2.0.$0^{2,6}$]-non-8-ene 4,4-dioxide (209)

Of the four pathways leading to formation of the transoid (208)- or cisoid (209)-tricyclic sulpholane systems indicated by retro-synthetic analysis (Scheme 28), pathways (a)-(c) have been attempted, as described in the previous section, resulting in preparation of the transoid isomer by two alternative routes. Synthesis of the isomeric tricyclic target systems by the fourth route, i.e. by combination of cyclobutadiene and butadiene sulphone (or synthetic equivalent), was considered next.

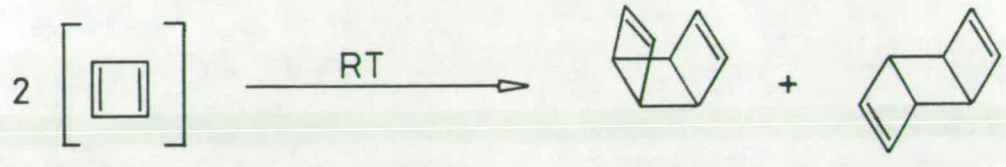
The chemistry of cyclobutadiene and substituted derivatives forms the subject of several in-depth reviews[115-118]. It is apparent from these that the stereospecificity of the product(s) arising from [4 π_s + 2 π_s] cycloaddition of cyclobutadiene with a simple dienophile depends strongly on the rate of reaction of the two. Thus, reaction of cyclobutadiene (formed by treatment of cis-3,4-dibromocyclobut-1-ene (246) with zinc dust) and N-methylmaleimide, considered a moderately activated dienophile, has led to isolation of the cisoid tricyclic system (247) in 34% yield[119]. The stereochemistry of this product is



(246) (247)

in accord with expectations for the Diels-Alder reaction where, in the absence of over-riding steric factors, secondary orbital stabilisation of the relevant transition state leads to sole formation of the cisoid isomer.

In contrast, the dimerisation of cyclobutadiene at room temperature has been found to result in a ca 5:1 ratio of cisoid (248)



(248) (249)

to transoid (249) products. The presence of the transoid isomer (249) in this case has been explained as resulting from the high reactivity of cyclobutadiene as both diene and dienophile which enables reaction to occur before the favoured cisoid geometry can be attained[118,120]. Further evidence in support of this reasoning has been obtained following the generation of cyclobutadiene using low temperature photolysis under matrix isolation conditions[121]: slow warming allowed the reactants to assume the lower energy geometry resulting in formation of the cisoid isomer (248) alone.

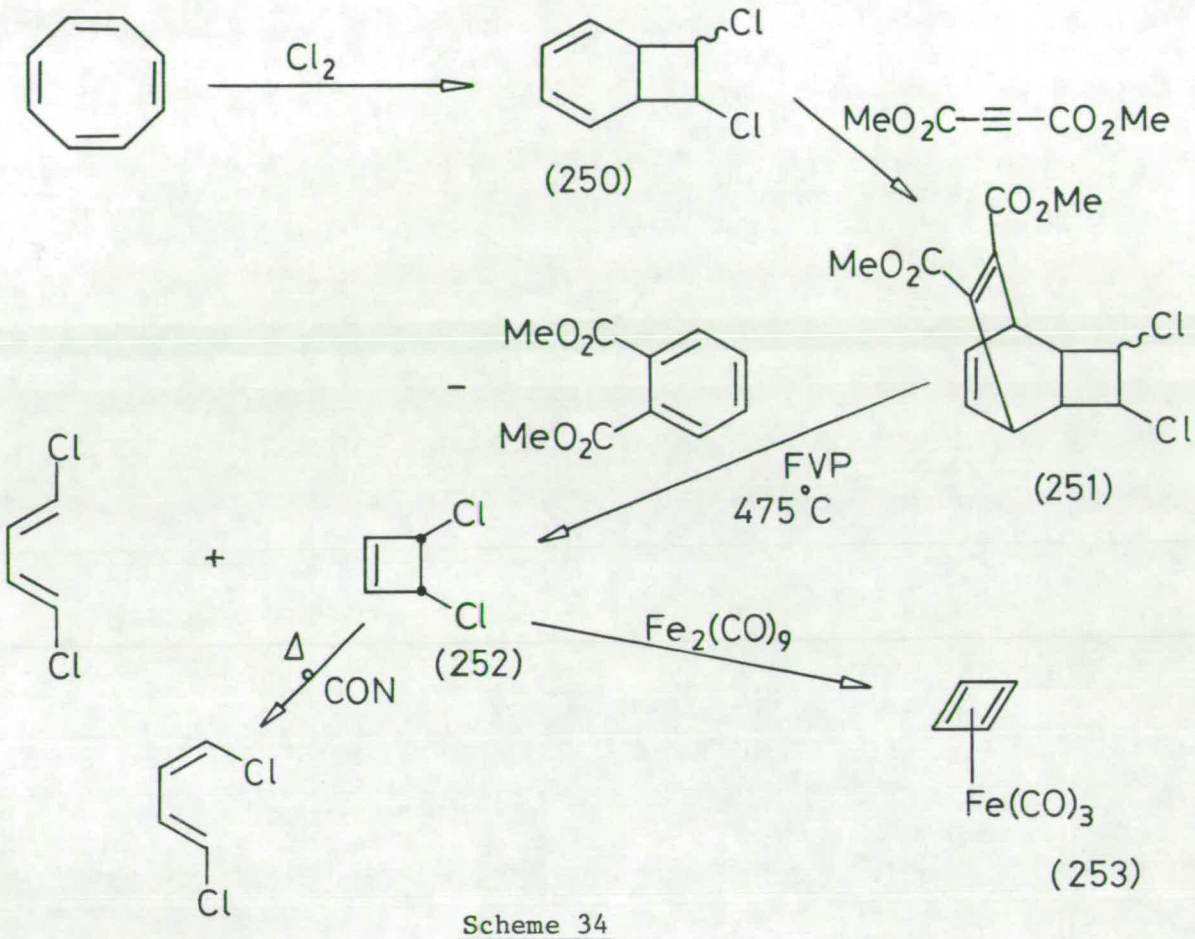
Bearing in mind the favoured endo geometry demonstrated in the reactions of cyclobutadiene and moderately active dienophiles, it would be expected that reaction of cyclobutadiene and butadiene sulphone, should this occur, would result in formation of cisoid product (209) only.

1. Attempted preparation from reaction of cyclobutadiene with butadiene sulphone

The cyclobutene anhydride (244) has been shown[121] to be a cyclobutadiene precursor on irradiation in a matrix at low temperatures under which conditions photochemical extrusion of carbon dioxide and carbon monoxide occurred. Since this anhydride was readily available

from the photochemical reaction of maleic anhydride and acetylene (described in the preceeding section) it was considered to be a viable source of cyclobutadiene under conditions of oxidative decarboxylation, rather than under the experimentally less accessible photolysis conditions described[121] in the literature. Treatment of bicyclic anhydride (244) with lead tetraacetate in oxygen-saturated pyridine at 67°C, in the presence of excess butadiene sulphone, resulted in decarboxylation as witnessed by evolution of gas. However, examination of the isolated products indicated only the presence of butadiene sulphone in high recovered yield. Such a lack of reaction may be rationalised as either resulting from failure to generate cyclobutadiene from anhydride (244), or as a consequence of the low reactivity of butadiene sulphone as a dienophile towards the generated cyclobutadiene. In order to clarify this position the use of an unambiguous source of cyclobutadiene, namely by oxidation of cyclobutadiene iron tricarbonyl (253), for reaction with butadiene sulphone was required.

There are several synthetically useful routes to this cyclobutadiene precursor. Thus, photolysis of ∝-pyrone and treatment of the resulting photopyrone with iron pentacarbonyl and continued irradiation has resulted in isolation of (253) in 10-15% yield[122]. An elegant synthesis of (253) involving reaction of the bicyclic photoadduct of vinylene carbonate and acetylene with diiron enneacarbonyl, described by Grubbs[123], gave a 37% yield of the complex. However, the route utilised here for preparation of (253), displayed in Scheme 34, employs cyclooctatetraene as starting material. Reaction of this with an equimolar quantity of chlorine, followed by heating of the resultant dichlorides (250) with dimethyl acetylene dicarboxylate gave a mixture of diesters (251)[124].



Scheme 34

In an adaptation of the literature method in which thermolysis of the mixture of cis- and trans-dichloro systems (251) at 200°C, 20 mm Hg gave rise to cis-3,4-dichlorocyclobut-1-ene (252) and (E,E)-1,4-dichlorobuta-1,3-diene respectively[124], FVP of the isomeric mixture was attempted in order to increase the yield of (252) by limiting undesired bimolecular interactions. Large scale FVP of the diesters (251) at 475°C gave a mixture of chlorinated products on fractional distillation which comprised of the desired cyclobutene (252) (19% yield) together with both (E,E)- and (E,Z)-1,4-dichlorobuta-1,3-dienes (28%). The low yield of (252) is a result of the thermally-allowed conrotatory ring opening of this cyclobutene system to (E,Z)-1,4-dichlorocyclobuta-1,3-diene. This product was not found on vacuum thermolysis of (251)[124] presumably due to rapid collisional deactivation of the vibrationally excited cyclobutene (252), formed on initial

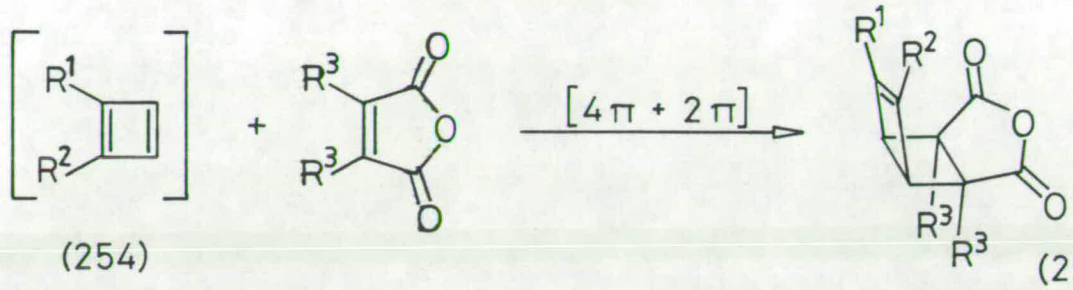
extrusion of dimethyl phthalate, under the comparatively high pressures employed. Collisional deactivation could not occur under the pressures used in FVP.

Treatment of the dichlorocyclobutene (252) (containing minor quantities of both dichlorobutadiene impurities) with diiron enneacarbonyl, according to the procedure of Paquette and Wise[125], resulted in isolation of the pure iron tricarbonyl complex (253) (48%) as a green liquid displaying characteristic spectral properties.

Having obtained a reliable source of cyclobutadiene, the reaction of this with butadiene sulphone in the hope of realising cisoid tricyclic sulpholane (209) was again attempted. Ceric ion oxidation of cyclobutadiene iron tricarbonyl (253) in the presence of an equimolar quantity of butadiene sulphone in ethanol solution at 0°C resulted in brisk evolution of gas, as expected for generation of cyclobutadiene with concomitant evolution of carbon monoxide gas. On work-up, only a high recovery of butadiene sulphone was obtained, indicating therefore that butadiene sulphone is too poor a dienophile to undergo Diels-Alder reaction with the highly active cyclobutadiene. Presumably the liberated cyclobutadiene underwent dimerisation to the volatile, hence non-isolated, hydrocarbons (248) and (249). In light of this failure, a more active dienophilic synthetic equivalent to butadiene sulphone was sought.

2. From dimethyl cis-bicyclo[2.2.0]hex-5-ene-endo-cis-2,3-dicarboxylate (256)

Consideration of the literature examples of reaction between cyclobutadiene and dimethylmaleic anhydride[121], and between the disubstituted cyclobutadiene (254; R^1 = Me, R^2 = Et) and maleic anhydride[126], both of which resulted in sole formation of the

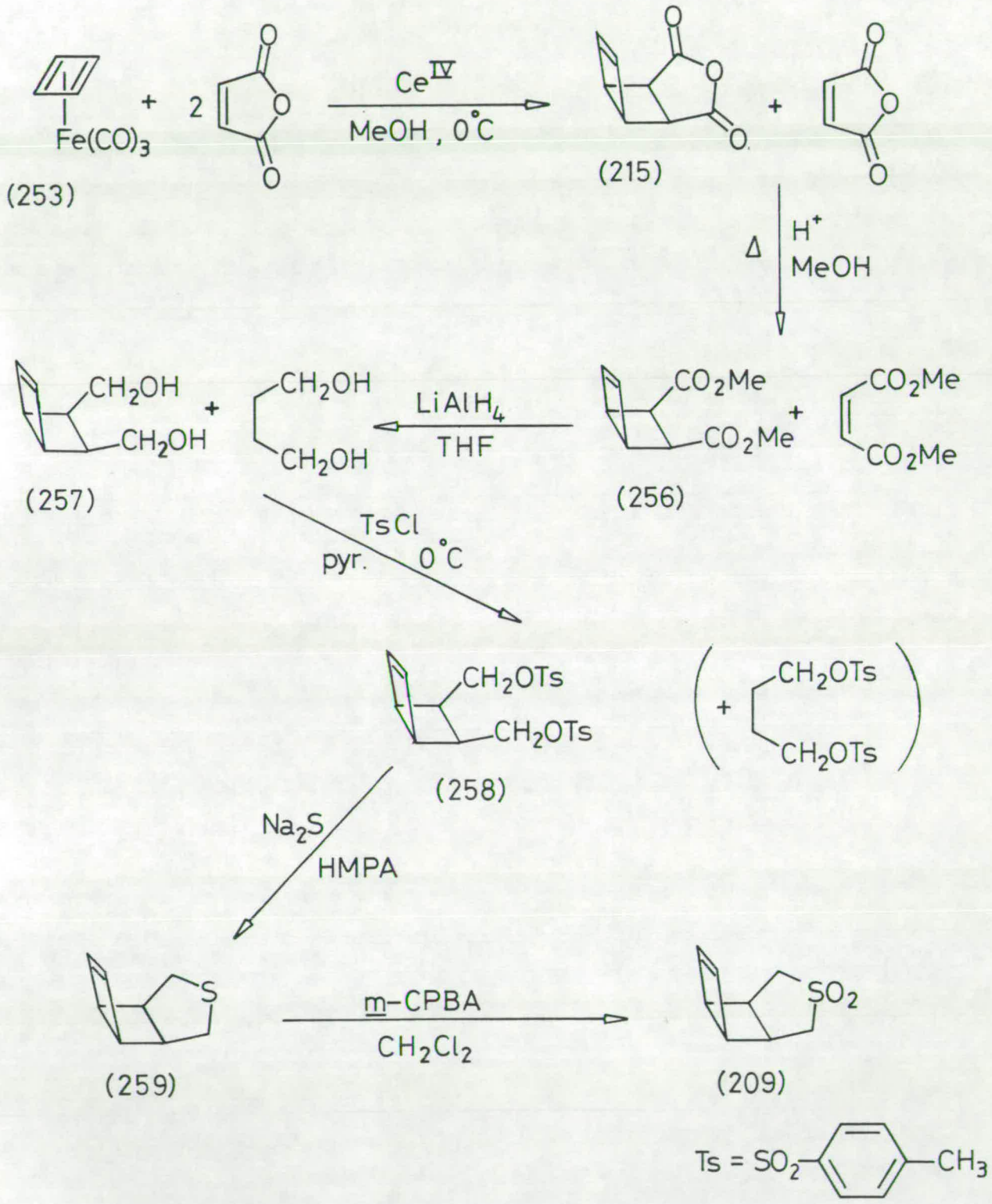


(254) (255)

$R^1 = R^2 = H, R^3 = Me$;
$R^1 = Me, R^2 = Et, R^3 = H$

corresponding cisoid cycloadducts (255), indicated that reaction of cyclobutadiene with maleic anhydride should occur readily with formation of cisoid anhydride system (215). Conversion of this anhydride by a standard reaction sequence paralleling that used to convert the transoid anhydride isomer (214) to the transoid sulpholane (208) (Scheme 29) would yield the desired cisoid sulpholane (209). In this synthetic route (Scheme 35) maleic anhydride performs the role of a more dienophilic butadiene sulphone synthon.

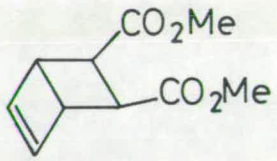
Under similar conditions to those used to prepare the tricyclic system (255; R^1 = Me, R^2 = Et, R^3 = H)[126], a solution of cyclobutadiene iron tricarbonyl (253) in methanol at 0°C, containing two molar equivalents of butadiene sulphone, was oxidised by addition of ceric ammonium nitrate. On completion of reaction, evidenced by cessation of gas evolution, the mixture of anhydride products was not submitted to the customary aqueous work-up (required for separation of the inorganic materials present) in view of the facile hydrolysis of such materials to the corresponding water-soluble diacid systems. Instead the anhydrides were converted to the corresponding diesters by addition of acid to the methanol solution,


Fe(CO)3
(253)
2
Ce IV
MeOH , 0°C
(215)
Δ
H+
MeOH
CH2OH
CH2OH
LiAlH4
THF
CO2Me
CO2Me
(257)
(256)
TsCl
pyr.
0°C
CH2OTs
CH2OTs
(258)
Na2S
HMPA
S
m-CPBA
CH2Cl2
SO2
(259)
(209)
Ts = SO2
CH3

Scheme 35

followed by heating under reflux for one hour. Aqueous work-up at this stage resulted in isolation of equimolar and quantitative yields of dimethyl maleate (formed from esterification of the excess maleic anhydride) and a bicyclic diester displaying spectral properties in full accord with that of a structure such as (256).

At this stage the single bicyclic diester product obtained could have possessed either endo or exo stereochemistry, since both of these isomers would be expected to exhibit spectral features in agreement with those found experimentally. To determine which of the two isomers was present, the exo diester (260) was prepared by an unambiguous route for comparative purposes. Thus, treatment of transoid tricyclic anhydride (214) with boiling acidified methanol gave a high yield (77%) of a diester product fully characterised by ^{1}H and ^{13}C NMR, and by infrared and mass spectroscopy, as exo diester (260).



(260)

Comparison of the NMR spectra and also GLC retention times of the exo diester (260) with that of the product obtained from esterification of the cyclobutadiene-maleic anhydride adduct proved conclusively that the two were different, and therefore that the latter product was indeed the endo bicyclic diester (256). This compound has been previously reported as being formed from reaction of cyclobutadiene with dimethyl maleate[120], although no details of any kind were described pertaining to the product.

With the exception of GLC, no chromatographic technique was encountered which could be used to separate the mixture of dimethyl

maleate and bicyclic diester (256). Therefore the unresolved mixture was used in the next reaction stage, which was reduction with lithium aluminium hydride in tetrahydrofuran. Spectroscopic analyses of the reduced products suggested these to be the corresponding endo diol (257), and butan-1,4-diol, the expected product of reduction of such an α,β -unsaturated carbonyl compound as dimethyl maleate with a strong reducing agent. Once again, no separation of this equimolar two-component mixture of diols could be achieved by available chromatographic techniques and so treatment of the crude diols with p-toluene sulphonyl chloride in pyridine at 0°C was undertaken.

However, in this instance separation of the crude mixture of ditosylate products could be achieved by repeated use of MPLC giving the bis (p-toluenesulphonate) of butan-1,4-diol as finger crystals, m.p. 77-77.5°C (lit.[127] m.p. 83°C), and endo ditosylate (258) as colourless plates m.p. 118.5-120°C [cf. exo ditosylate (219) m.p. 144-145°C] in 33% yield from cyclobutadiene. This material was fully characterised by elemental composition, ^{1}H and ^{13}C NMR, and by other standard spectroscopic determinations as the expected endo isomer (258); comparison of the ^{1}H NMR spectra of the exo ditosylate (219) (Figure 1) and endo isomer (258) (Figure 2) demonstrates that significant differences are present.

Assignment of resonances to protons was made on the basis of selective decoupling studies for the endo ditosylate (258). Irradiation of the olefinic protons H_5, H_6 at δ6.04 resulted in simplification of a broad doublet signal at δ3.24 which was then assigned to the vicinal (ring fusion) protons H_1, H_4. Upon irradiation of the latter signal a noticeable simplification of a multiplet resonance at δ2.78-2.91, corresponding to the neighbouring cyclobutane protons H_2, H_3, was apparent. Following these assignments,

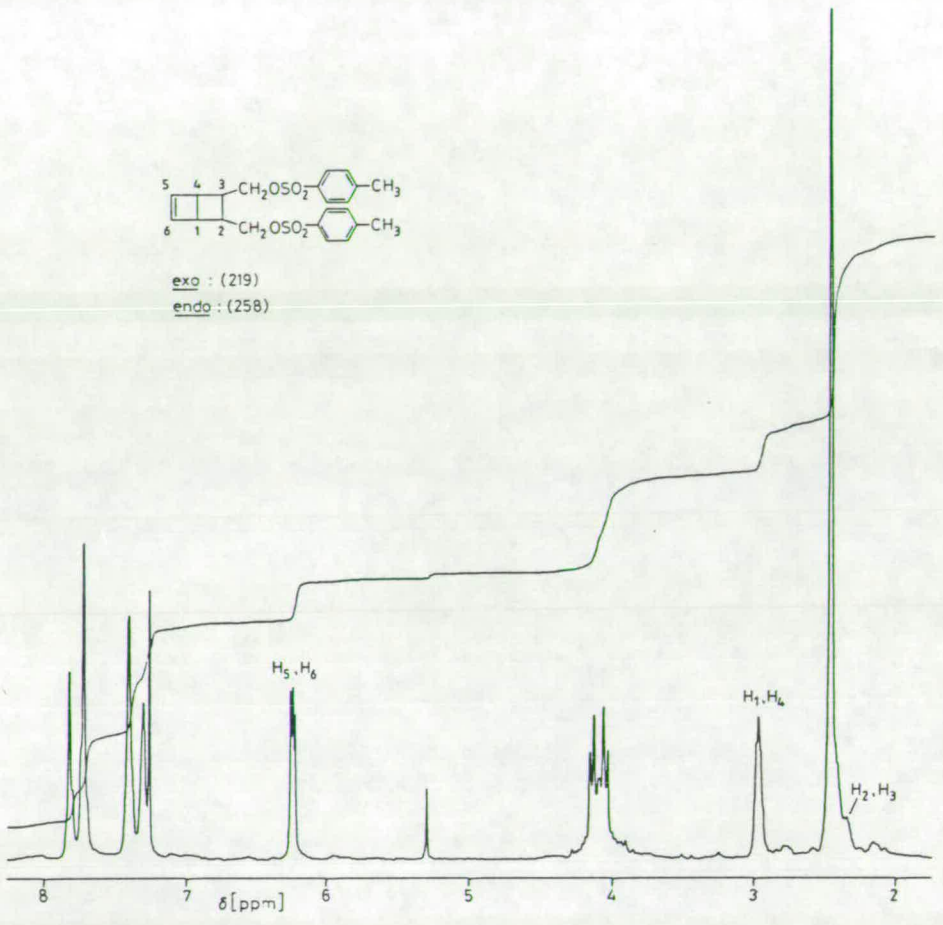


Figure 1 : ^1H NMR spectrum (80 MHz) of (219)

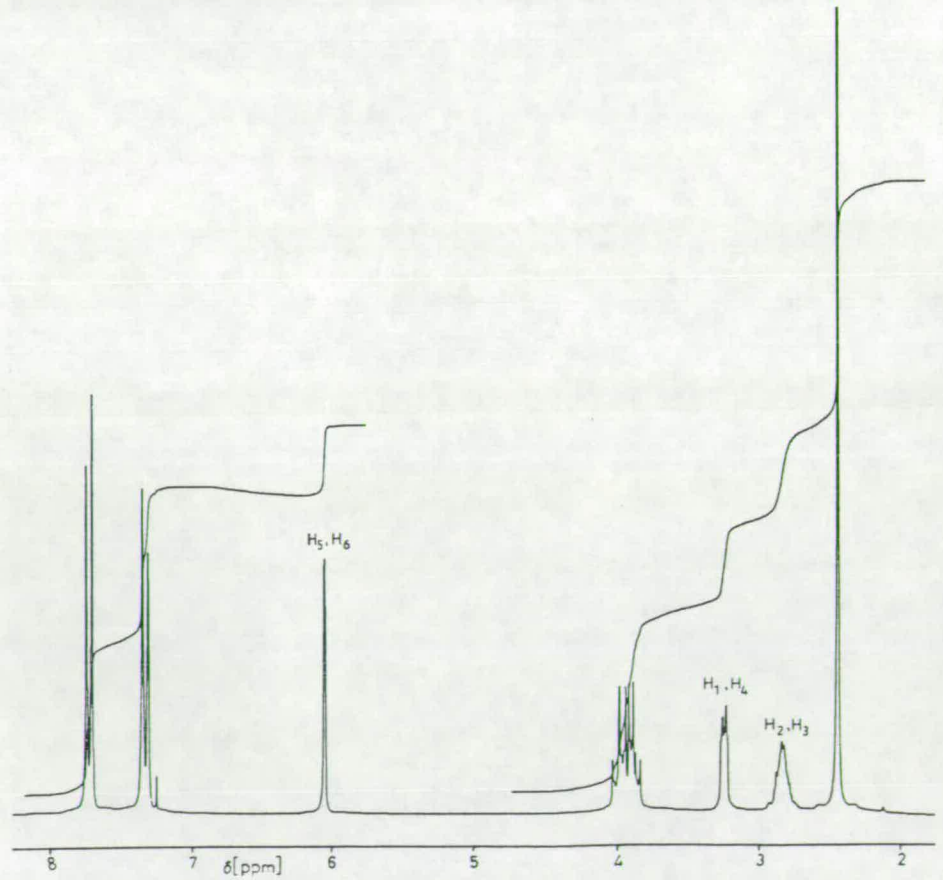


Figure 2 : ^1H NMR spectrum (200 MHz) of (258)

quantification of some of the coupling constants present could be made. Thus, constants $J_{1,5}$ ($J_{4,6}$) = $J_{1,6}$ ($J_{4,5}$) = 1.2 Hz were found to be identical in both exo and endo isomers, in accord with the close similarity in cyclobutene structure of the isomers. A marked difference in the values of cyclobutane vicinal coupling constants $J_{1,2}$ ($J_{3,4}$) was demonstrated : a value of 5.1 Hz in the endo isomer is indicative of a cis vicinal arrangement of these protons, whilst a value of $<<$1.2 Hz in the exo isomer (219) is in accord with a trans vicinal arrangement. Both of these values therefore vindicate the assignment of stereochemistry previously made for each of the two isomers. A final point to emerge from a comparison of the ^{1}H NMR spectra of the ditosylate isomers refers to the relative positions of the signals corresponding to H_1, H_4 and H_2, H_3. For the endo isomer (258) both of these sets of signals are deshielded by 0.3-0.4δ compared to those in the exo isomer (219). This is a result of the close spacial proximity of the H_1, H_4 and H_2, H_3 protons in the endo isomer which leads to van der Waals repulsion between the vicinal cyclobutane protons and hence a mutual deshielding effect. This is not, of course, operational in the exo isomer since the two sets of protons are located on opposite faces of the cyclobutane ring.

Returning to the synthetic sequence of Scheme 35, preparation of the cisoid tetrahydrothiophene (259) was attempted by reaction of the pure endo ditosylate (258) with sodium sulphide in boiling aqueous ethanol. In contrast to the successful generation of the transoid isomer (220) under identical conditions from the corresponding exo ditosylate (219) (described earlier), no identified sulphide products were realised from (258). However, treatment of endo ditosylate (258) with an anhydrous solution of sodium sulphide in hexamethyl-

phosphoramide (HMPA), prepared according to the procedure of Paquette *et al*[105], resulted in isolation of the required tricyclic system (259) which displayed expected spectral features. The crude tetrahydrothiophene (259) was oxidised immediately rather than purified, in consideration of the high losses associated with this procedure carried out on the small quantity of material available. Thus, reaction of sulphide (259) with excess *m*-chloroperoxybenzoic acid in methylene chloride solution at ambient temperatures gave, after work-up and chromatographic purification, a colourless oil. On cooling, this material formed crystals, m.p. 32-36°C, which were found to conform to expectations for a structure of formula $C_8H_{10}O_2S$ in terms of elemental composition and mass spectral determinations. Final characterisation of this product as the *cisoid* tricyclic sulpholane (209) was achieved following detailed analyses of ^1H NMR (including selective decoupling and NOE studies), ^{13}C NMR and infrared spectra. These are considered in-depth in a comparison of spectral characteristics of *transoid* (208) and *cisoid* (209) isomers, as described in a later section.

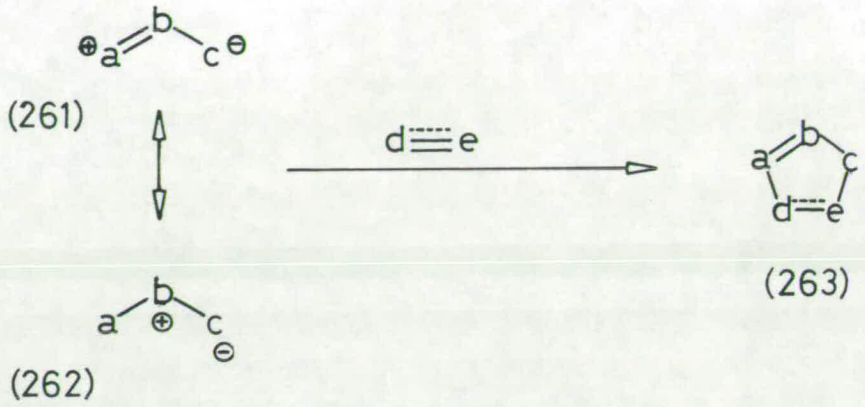
C. Cyclobutene Reactivity of (cis-1-transoid-1,2-cis-2)-4-Thiatricyclo-[5.2.0.$0^{2,6}$]non-8-ene 4,4-dioxide (208)

As described earlier (p. 64), the behaviour of the cyclobutene moiety of the transoid tricyclic sulpholane (208) towards reactions typically undergone by olefins was considered worthy of investigation. The large spacial separation of the sulphone and olefin groups in (208) would be expected to result in no deviation of the latter in terms of electron availability compared to cyclobutene, in contrast to the marked effect on reactivity resulting from a through-space orbital overlap between the sulphone group and the olefin moiety in the related bicyclic system (63). Thus it was anticipated that system (208) would display olefin reactivity rather similar to that cyclobutene, which is an electron-rich olefin. A complicating factor for system (208) is that of the ring strain associated with the fused cyclobutane and cyclobutene rings; the stability of (208) with regard to ring opening reactions under a variety of reaction conditions and reagents was also an important consideration.

A primary reason for the following investigation of cyclobutene reactivity of (208) was the preparation of several tricyclic systems (210) and a series of tetracyclic systems (211) prior to a study of thermal extrusion behaviour of these.

1. Reaction with 1,3-dipoles

The concerted addition of 1,3-dipoles, represented by canonical forms (261) and (262), to multiple bonds is a classical reaction in organic chemistry and has been widely used for the stereospecific synthesis of a large number of heterocyclic systems (263)[128]. In terms of electronic distribution, the majority of 1,3-dipoles may be represented by octet resonance structures in which



4 π electrons are delocalised over the three atoms forming the dipole. The regioselective cycloadditions of the dipole 4 π system with unsymmetrical dipolarophiles, including olefinic (2 π) systems (of particular significance in the context of the work described later) are found to occur with a wide spectrum of reactivity depending on the electronic structure of the two reactants. Houk et al[129] have used frontier molecular orbital theory to explain these findings by considering the interactions between the highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) of dipole and dipolarophile (olefin) with respect to π-frontier orbital energies and coefficients.

In the case of the reaction of a symmetrical olefin with a 1,3-dipole, for which questions of regiospecificity and hence consideration of orbital coefficients do not arise, knowledge of the energy levels of the HOMO and LUMO of both reactants permits a prediction of reaction rate[129]. Thus for cyclobutene, which from photoelectron spectroscopy has a π ionisation potential (πI_p) of 9.43 eV [130], a value of -9.43 eV may be given to the HOMO π level in accord with Koopmans' Theorem[131]. The value of the LUMO π level

can be calculated from a knowledge of the electron affinity[132], but this is not known in the case of cyclobutene which may therefore be given an estimated LUMO π energy of 2 eV, a value typical of an alkyl substituted olefin[132]. Using these values for the cyclobutene HOMO and LUMO levels, and values computed[132] for a range of 1,3-dipoles, an orbital correlation diagram (Figure 3) can be constructed. From this the dominant HOMO-LUMO interaction, which is the one of the two alternatives which has the smallest energy difference, may be used to give an estimate of the relative reaction rate of cyclobutene with a range of 1,3-dipoles: the smaller the energy difference in the dominant HOMO-LUMO interaction then the faster the reaction is predicted to occur.

A parallel correlation diagram may be constructed for the reaction of tricyclic sulpholane (208) with 1,3-dipoles. However, this process requires a value for the olefin πI_p of (208) (in order to quantify the HOMO π energy level) which very unfortunately could not be obtained for this and for related unsaturated sulphone systems due to the unavailability of instrumentation capable of furnishing the necessary photoelectron spectra from which πI_p values could be evaluated. In the absence of πI_p data the HOMO and LUMO values for (208) were accorded the corresponding values found for cyclobutene, the rationale behind this approximation being derived from the similarity in olefin structure of the two compounds. Consideration of the value for the πI_p of bicyclo[2.2.0]hex-2-ene (9.4 eV [130]) further justifies this action with respect to the HOMO level of (208). Figure 3 therefore also represents an approximate correlation diagram for the reaction of tricyclic sulpholane (208) with the five 1,3-dipoles listed. A comparison of predicted reaction rates available

from Figure 3 with those encountered experimentally is now related in turn for each of the dipoles listed.

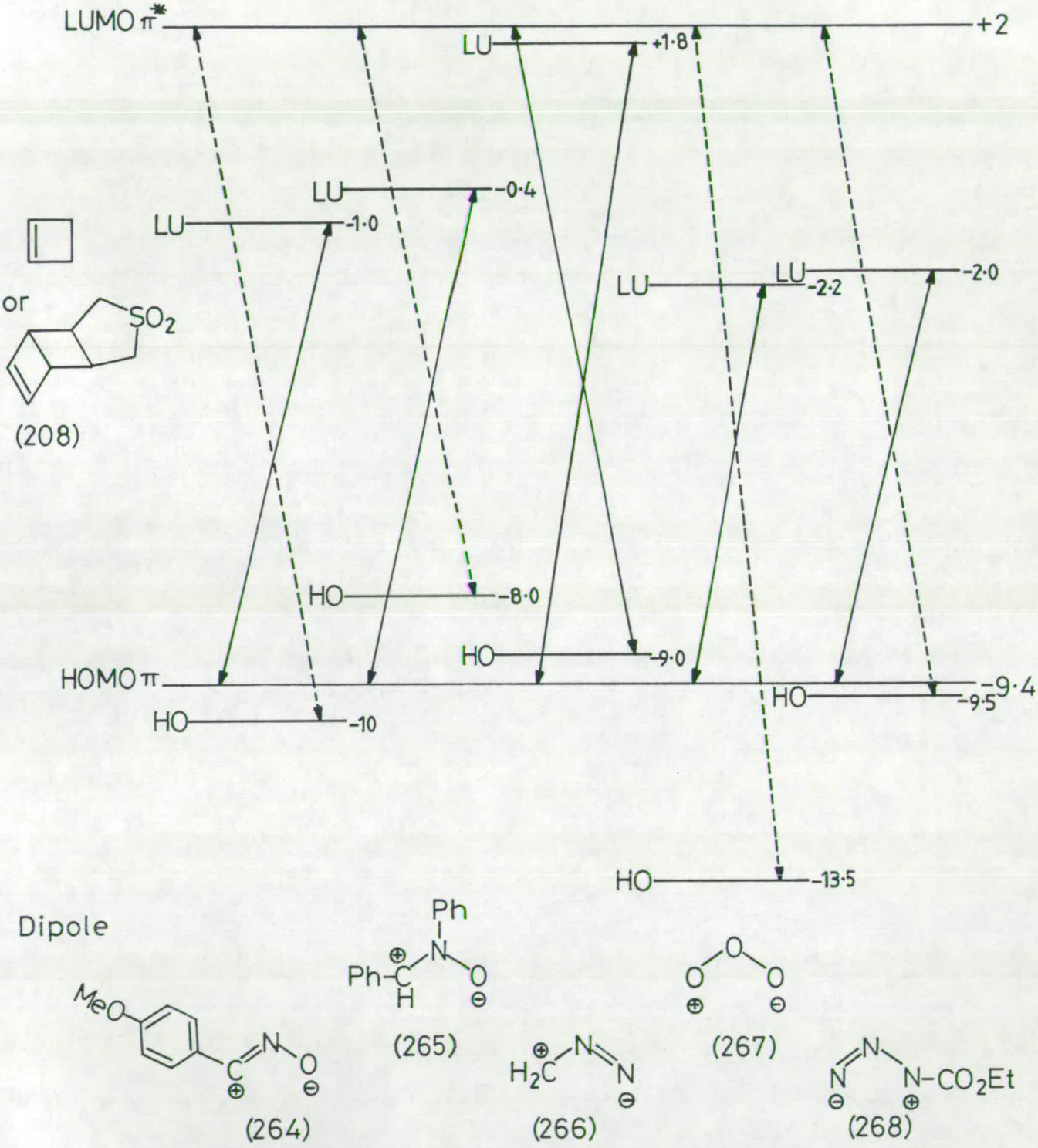
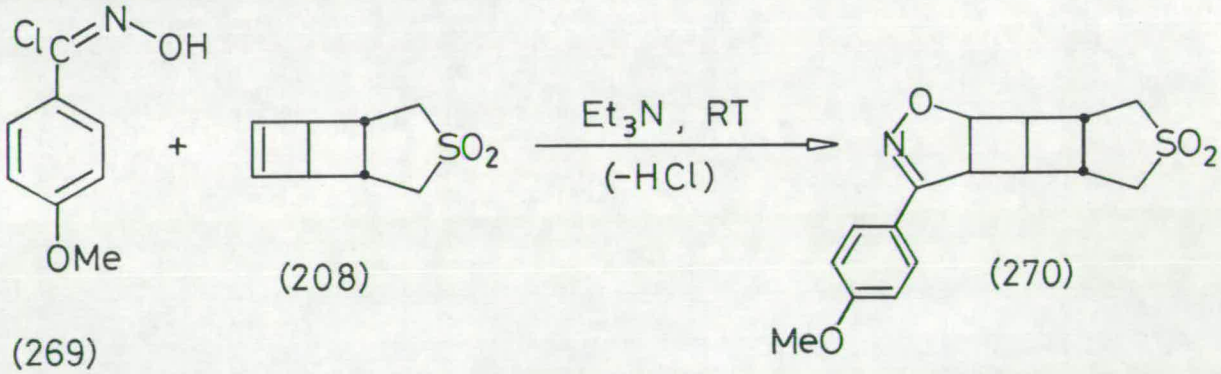


Figure 3: Orbital correlation diagram for reaction of cyclobutene or (208) with various 1,3-dipoles

a. With p-anisonitrile oxide (264)

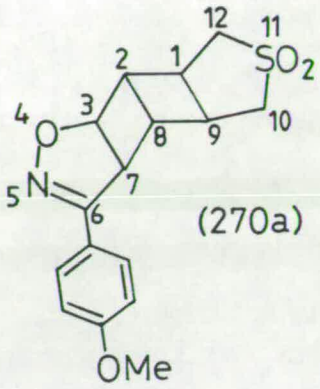
The energy levels for this dipole, which are shown in Figure 3, were assumed to be identical to those of benzonitrile oxide[132]. For reaction of p-anisonitrile oxide (264) with the tricyclic sulpholane (208) the lowest energy interaction is that of the olefin HOMO-dipole LUMO (ca 8.4 eV) and the cycloaddition is therefore under dipole LUMO control, a type III interaction according to the Sustmann terminology[129,133]. This reaction, in view of the fairly large energy difference in the dominant frontier orbital interaction, would be predicted to occur fairly slowly compared to reactions of (208) with ozone (267) or ethyl azidoformate (268) (Figure 3).

Reaction of the transoid tricyclic sulpholane (208) with p-anisonitrile oxide (264), generated in situ by treatment of p-anisohydroxamic chloride (269) with triethylamine at room temperature, gave after 16 hours an 82% yield of a product of molecular formula $C_{16}H_{17}NO_4S$, as evidenced by satisfactory elemental composition and

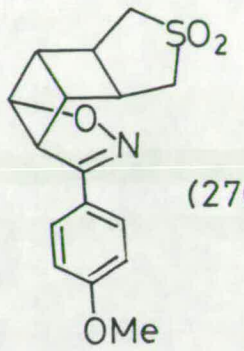


(269) (208) (270)

mass spectral analyses. Examination of ^1H and ^{13}C NMR spectra for this product indicated it to be a single one of the two possible isomers (270a) and (270b), resulting respectively from exo and endo cycloaddition of p-anisonitrile oxide (264) with tricyclic olefin (208).



(270a)



(270b)

In general for reactions of 1,3-dipoles, or for dienes, with olefins the more thermodynamically stable product of the less sterically hindered exo addition predominates in the absence of secondary orbital effects (acting to stabilise the endo transition state). As the reaction of (264) and (208) does not involve secondary orbital considerations, the less sterically congested transoid,transoid system (270a) is the expected product. Detailed examination of the ^1H NMR spectrum of the isolated product does furnish unambiguous evidence that this is the case. Thus the most deshielded saturated signal, a doublet at $\delta 5.19$ corresponding to H_3, exhibits a cis-vicinal cyclobutane coupling constant $J_{3,7} = 6.1$ Hz which is reciprocated in the signal due to H_7, a doublet of doublets at $\delta 4.51$. Also present in the latter is a small coupling constant due to $J_{7,8} = 1.0$ Hz which taken into account with the zero value of coupling constant $J_{2,3}$ is indicative (p.73) of a trans vicinal relationship between H_2 and H_3, and between H_7 and H_8, in accord only with the transoid,transoid structure (270a).

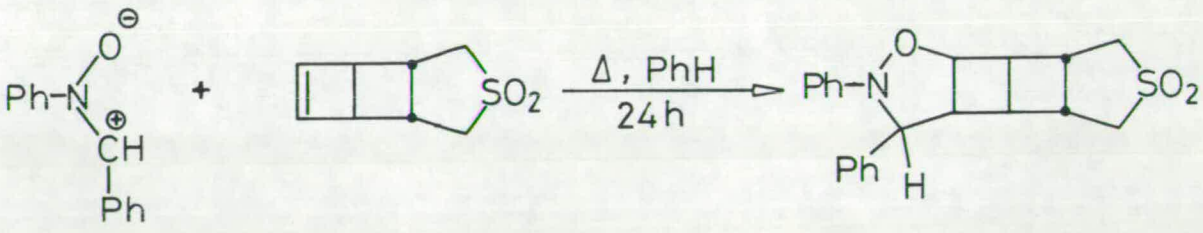
Reaction of olefin (208) with p-anisonitrile oxide (264) generated in situ via the thermal elimination of hydrogen chloride

from the precursor (269) (by heating in boiling toluene for 40 hours) gave the same adduct (270a) in inferior yield (19%) together with recovered olefin (208) (10%) and the product of thermal ring opening of this, cyclohexadiene sulpholane (212) (10%).

b. With C,N-diphenyl nitrone (265)

Cycloaddition of C,N-diphenyl nitrone (265) with olefin (208) would be predicted to be a dipole LUMO controlled (Type III) process occurring more slowly than the reaction of nitrile oxide (264) with (208) since the dominant olefin HOMO-dipole LUMO energy difference (9 eV) is greater (Figure 3).

Heating of equimolar quantities of (208) and (265) in boiling benzene was found to require a 24 hour time period for complete consumption of starting olefin, as indicated by TLC monitoring. The more forcing conditions needed for reaction of the two species compared to that of (264) and (208) is in accord with the expectations described above. Work-up of the reaction gave a fair yield of fine colourless needles, m.p. 158-161°C, which were found to comprise of a single adduct of structure (271) from analysis of ^{1}H NMR (Figure 4) and ^{13}C NMR (Figure 5) spectra. Four possible isomers may be formed from this reaction:



(265) (208) (271)

structures (271a) and (271b) arise from the two exo modes of addition, and structures (271c) and (271d) arise from the two possible endo modes

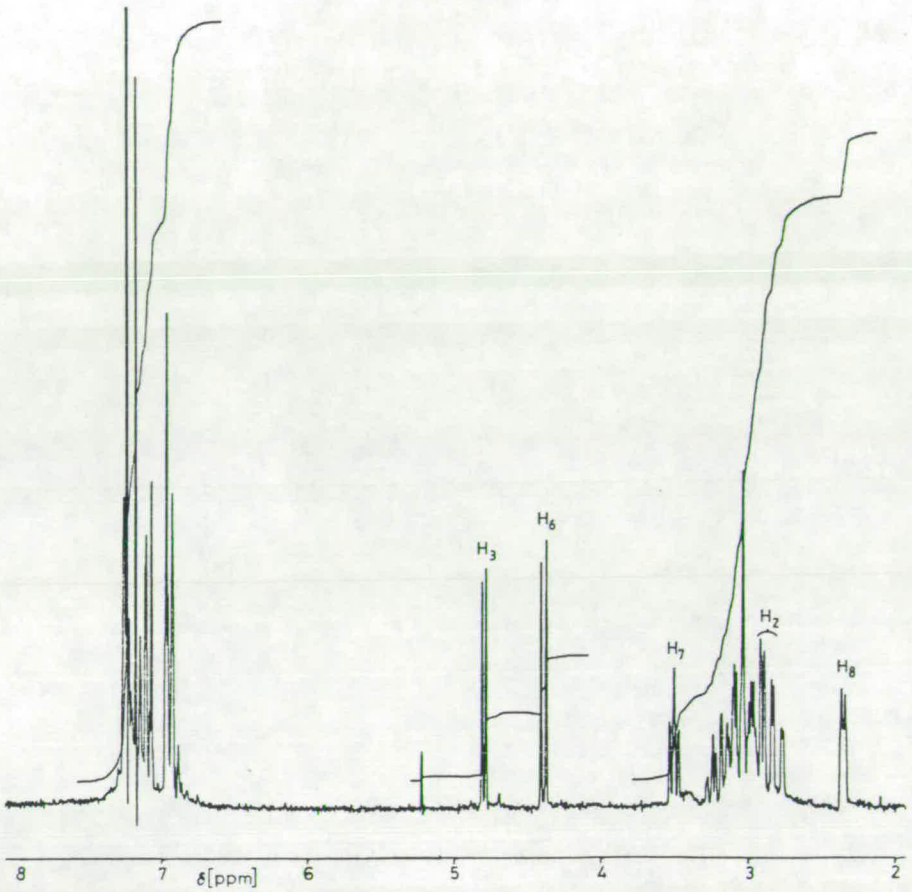


Figure 4 : ^{1}H NMR spectrum (200 MHz) of (271a)

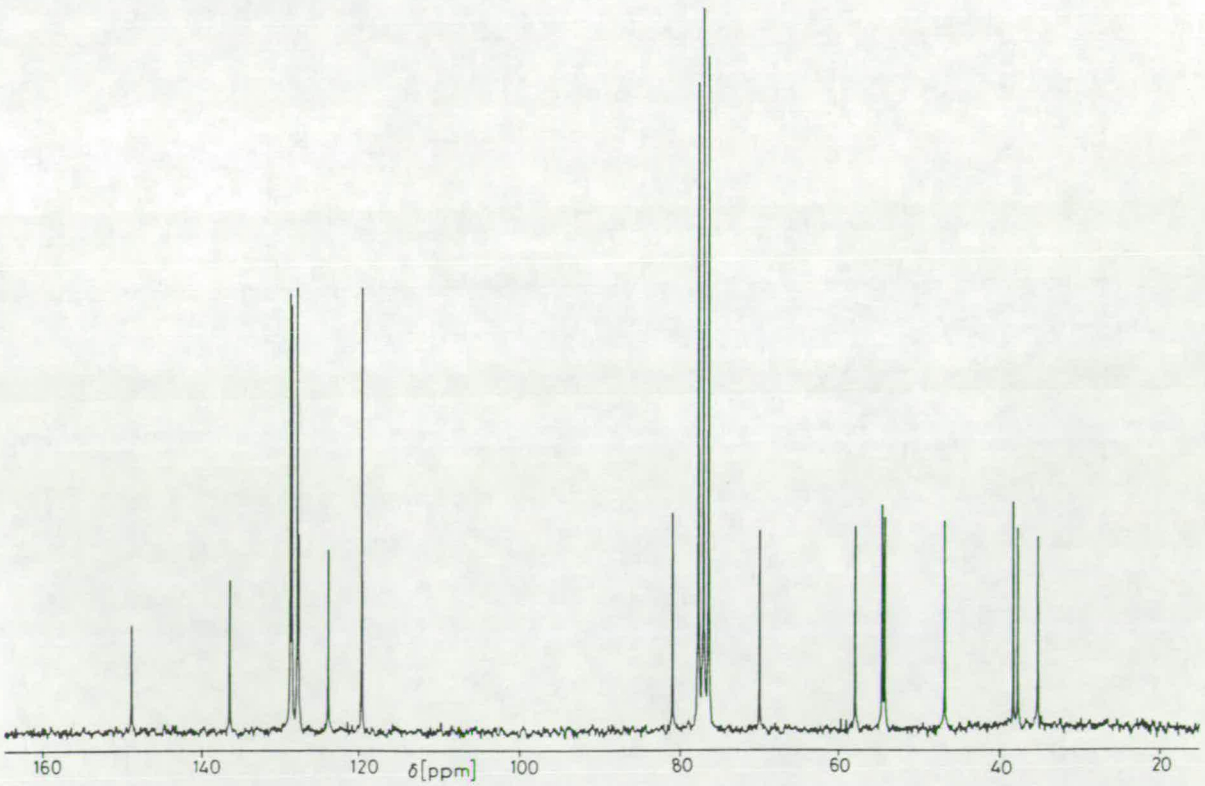
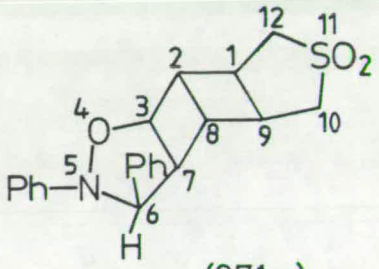
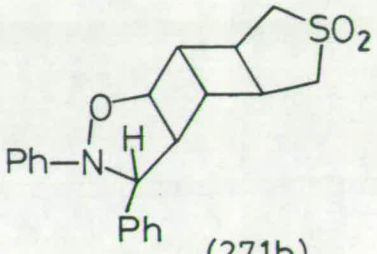


Figure 5 : ^{13}C NMR spectrum of (271a)

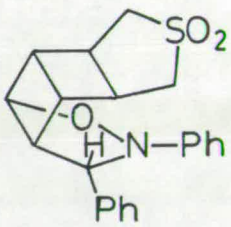
of addition to the tricyclic system (208). However, ^{1}H NMR and nuclear Overhauser enhancement (NOE) studies clearly established that the single product of reaction possesses the stereochemistry of isomer (271a).



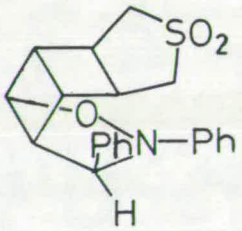
(271a)



(271b)



(271c)



(271d)

Thus, starting from the reasonable assumption that in the ^{1}H NMR spectrum (Figure 4) the most deshielded saturated signals, doublets at δ 4.86 and δ 4.44, correspond to protons H_3 and H_7 respectively on the basis of the relative electron-withdrawing ability of the adjacent ring elements, the couplings evident in these signals may be utilised to assign further signals to protons. In this respect, analysis of the ^{1}H-2D COSY spectrum (Figure 6) of the adduct indicates the presence of large couplings between both H_3 (δ 4.86)

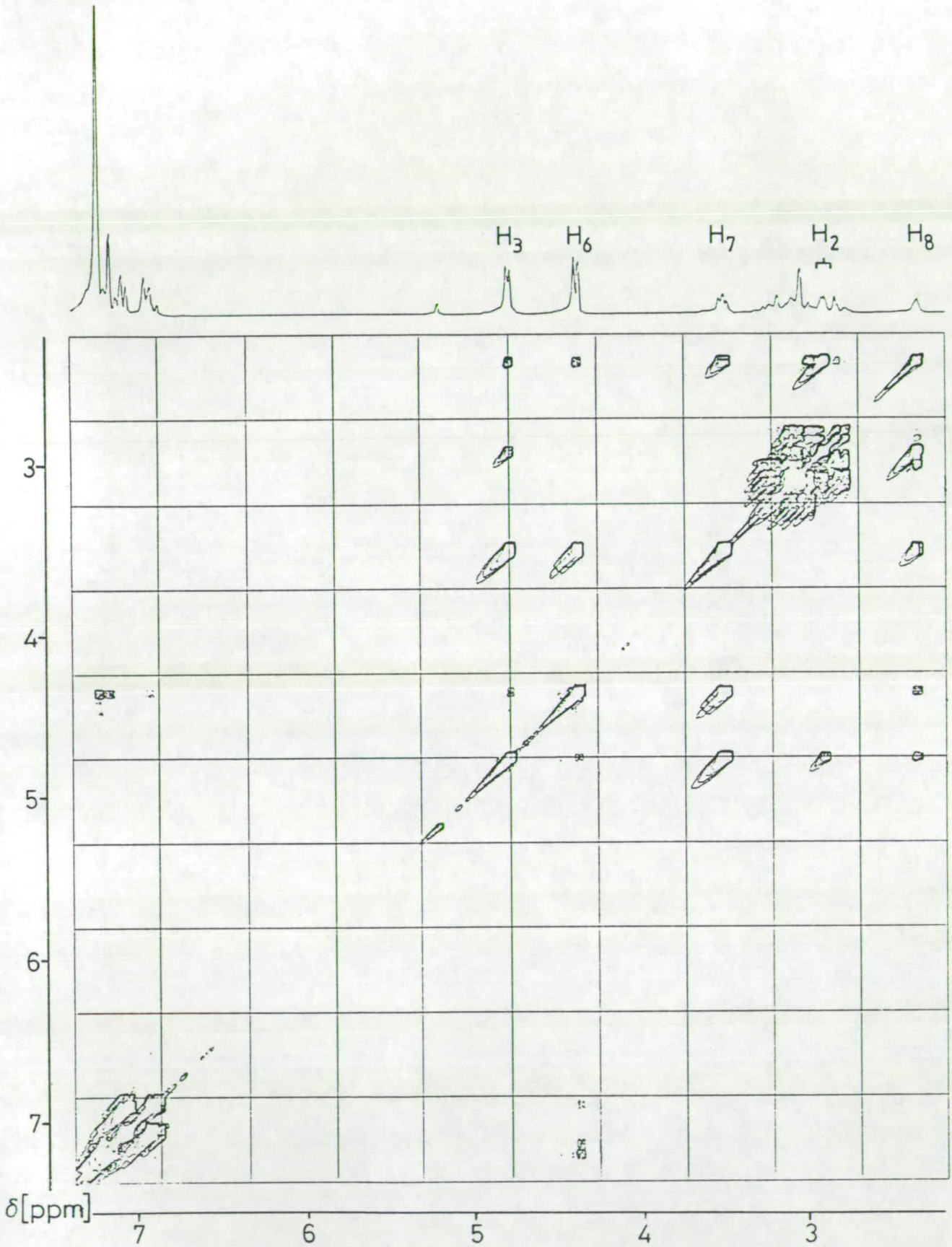


Figure 6 : ^{1}H-2D COSY NMR spectrum of (27la)

and H_6 (δ 4.44) and the signal at δ 3.56, which is therefore assigned to H_7. Observed coupling constants within the latter signal of $J_{3,7}$ = 5.1 Hz (indicative of a cis vicinal coupling between these two protons across the cyclobutane ring) and $J_{6,7}$ = 6.8 Hz (in accord with a cis relationship between H_6 and H_7 on the five-membered heterocyclic ring) limit the possible structures for the product to (271a) or (271d). Also highlighted by the COSY spectrum are the smaller trans vicinal cyclobutane couplings between H_3 (δ 4.86) and H_2 (δ 2.96), and between H_7 (δ 3.56) and H_8 (δ 2.40) [$J_{7,8}$ = 1.3 Hz]; a value of $J_{2,8}$ = 4.7 Hz is confirmation of the cis vicinal relationship between the two protons, and vindicates the assignments of signals to protons made earlier.

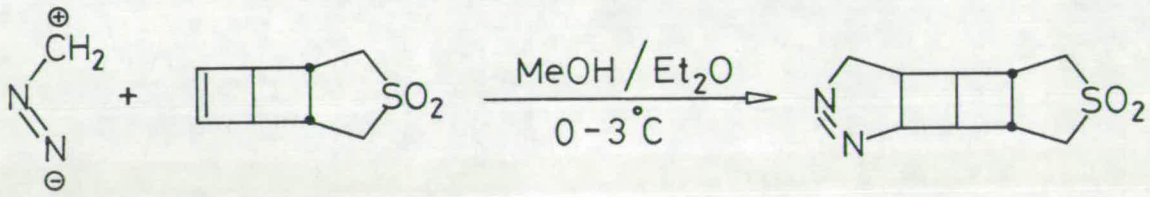
Final assignment of the stereochemistry of the nitrone adduct was achieved following examination of the ^{1}H-2D NOESY spectrum which in addition to confirming the close spacial arrangement of H_3 and H_7, and of H_2 and H_8, also unequivocally established the cis stereochemistry of protons H_6 and H_7 as evidenced by a strong NOE effect between the two signals. Additionally a weak but significant mutual enhancement between H_8 and the C(6)-phenyl ring protons established the product stereochemistry as that of structure (271a). This finding is not unexpected since structure (271a) results from exo addition of C,N-diphenyl nitrone (265) to the less hindered face of the transoid olefin (208), giving the most thermodynamically stable of the four possible isomeric adducts.

c. With diazomethane (266)

The reaction of olefin (208) with diazomethane (266) has almost equally favoured HOMO-LUMO combinations (Figure 3) and is therefore a Type II cycloaddition, according to Sustmann terminology[129,133],

in which neither combination is dominant. Due to the large energy separations of both HOMO-LUMO pairs (ca 11 eV) the reaction is predicted to occur rather slowly.

Treatment of a solution of olefin (208) in methanol with an ethereal solution of diazomethane required a reaction time of several days at a temperature of 0–3°C to complete consumption of the olefin. Large almond-shaped crystals of a single tetracyclic diazomethane-olefin adduct (272) were obtained, in 69% yield, as established by elemental and spectroscopic determinations. Two possible structures for this product, (272a) and (272b) respectively resulting from exo and endo addition modes, are feasible. In order to determine which of the two is actually formed, a detailed analysis of the ^1H NMR



(266) (208) (272)

spectrum (Figure 7) was carried out. Assuming that the most deshielded signal (δ 5.35) arises from the cyclobutane proton H_3 which is adjacent to the azo group, selective decoupling studies carried out on this and the other discrete signals detailed in Figure 8 allowed the assignment of signals to protons shown in Figures 7 and 8 to be made, and also permitted identification and quantification of a sizeable number of coupling constants present within the system. The most important of these in terms of structure elucidation were $J_{2,3}$ = 1.5 Hz and $J_{7,8}$ = 1.4 Hz which proved the trans vicinal arrangement of H_2 and H_3, and of H_7 and H_8, in accord only with the transoid,transoid structure (272a) for the isolated product. This is, of course, the expected product from consideration of steric factors in the exo and

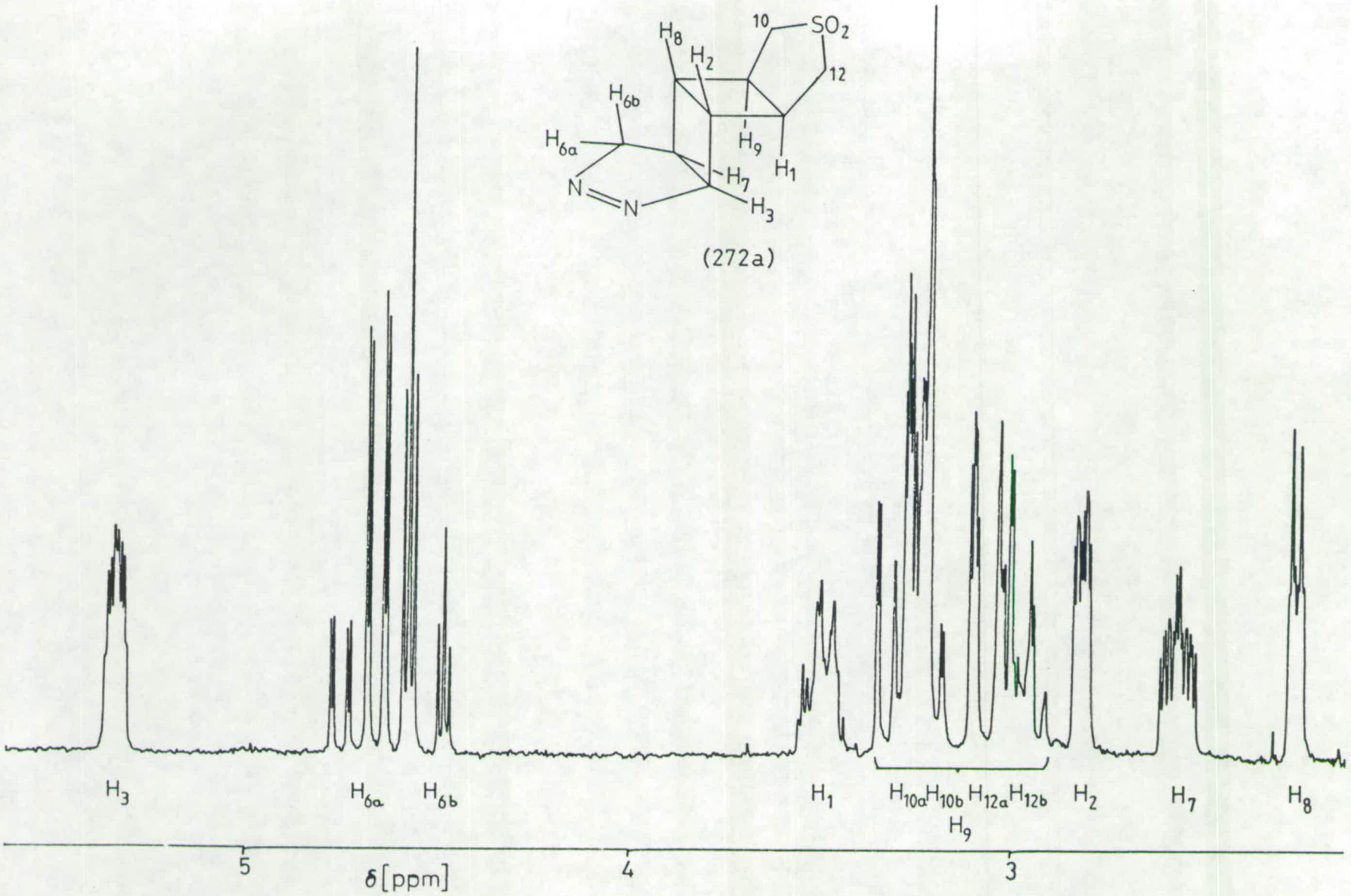


Figure 7 : ^{1}H NMR spectrum (200 MHz) of (272a)

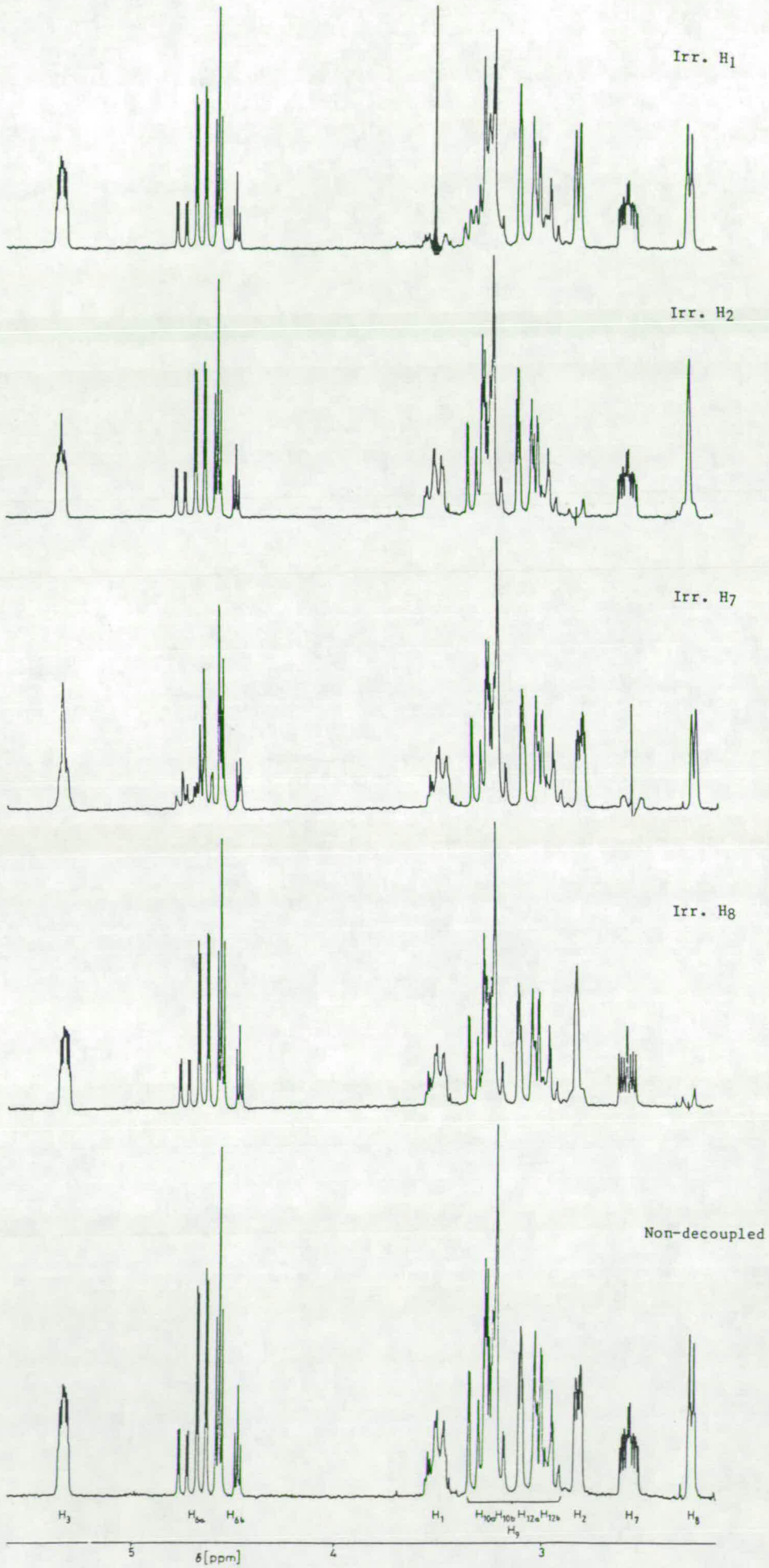


Figure 8 : Selectively decoupled ^{1}H NMR spectra of (272a)

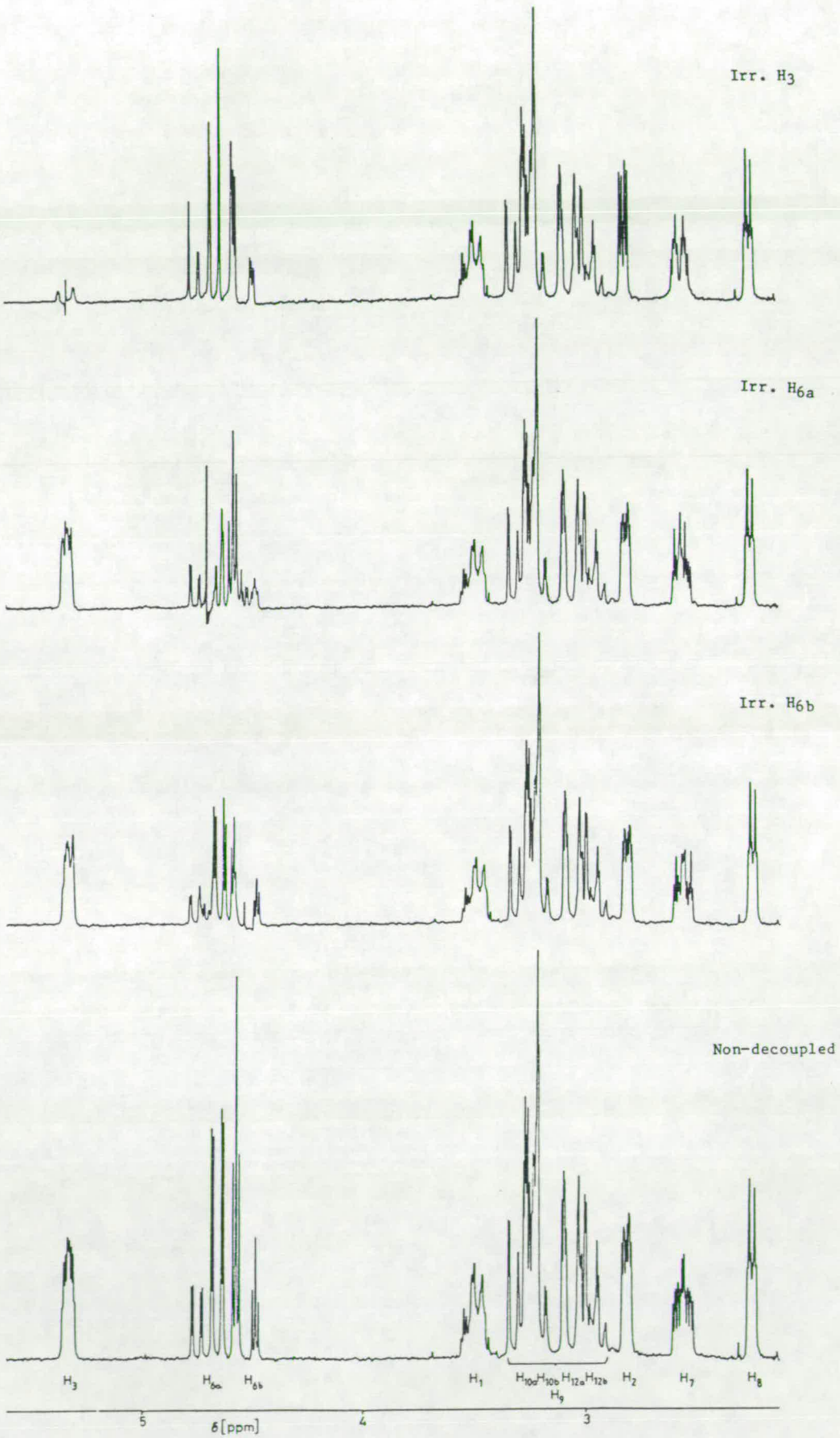
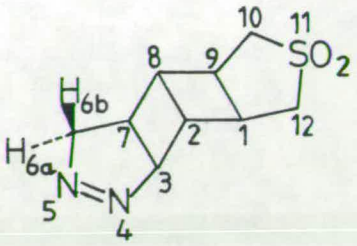
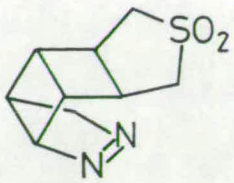


Figure 8 (cont.) : Selectively decoupled ^{1}H NMR spectra of (272a)



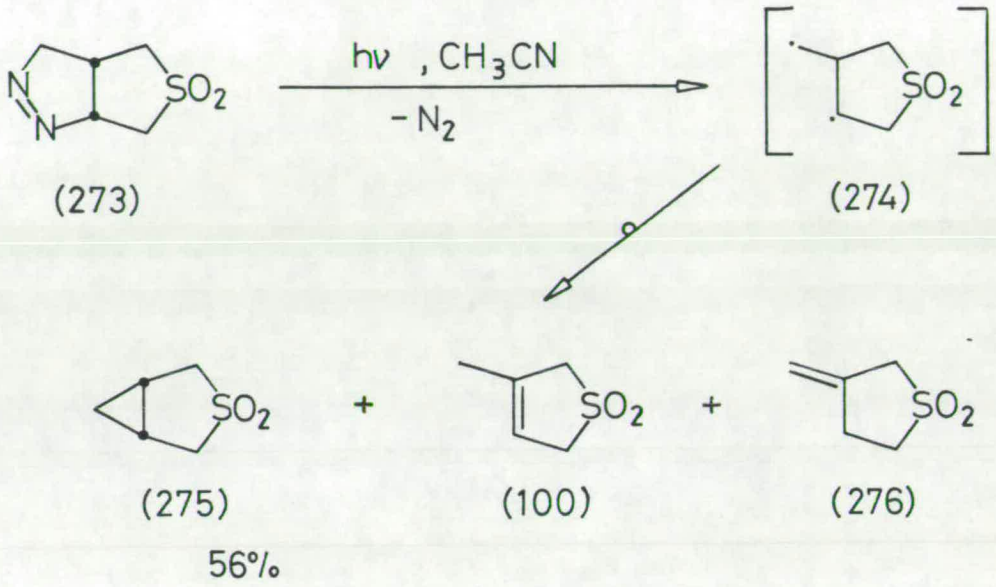
(272a)



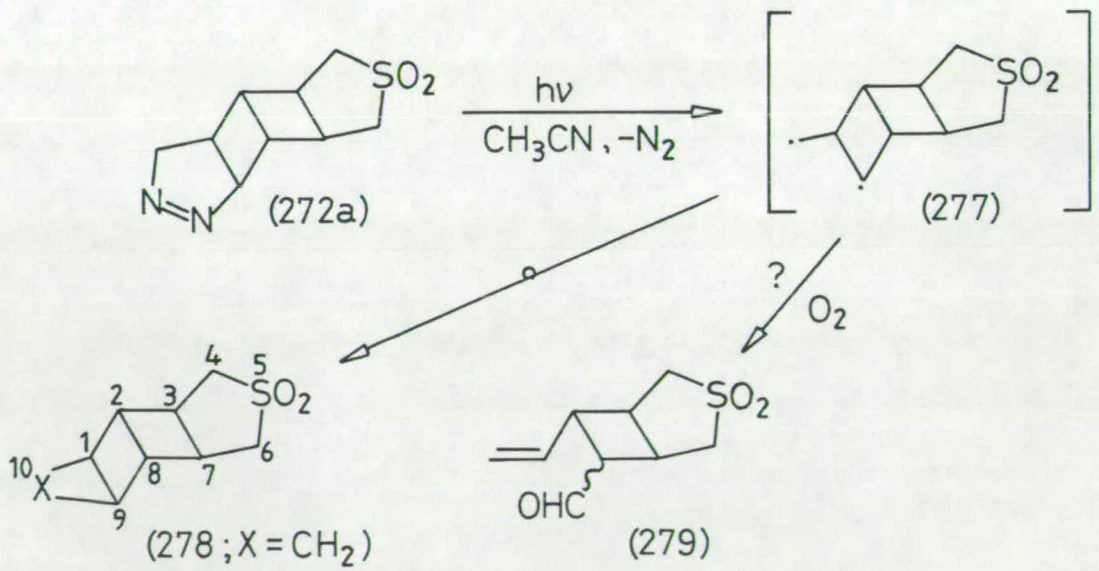
(272b)

<u>endo</u> transition states leading to formation of adducts (272a) and (272b). In passing, the non first-order appearance of the signals corresponding to methylene protons H_{6a} (δ 4.71) and H_{6b} (δ 4.54) are of some interest. The proximity of the signals to each other in frequency terms taken in conjunction with the large geminal coupling constant $J_{6a,6b}$ = 18.3 Hz renders both signals non first-order and hence distorted in appearance; coupling of both protons to H_7 and, through the azo linkage, to H_3 gives rise to an effective ABX_2 pattern for H_{6b}, and to an ABXY pattern for H_{6a}.

As a fundamental reason for examining the reactivity of (208) towards various species was the preparation of tetracyclic sulpholane systems (211), the photochemical extrusion of nitrogen from adduct (272a) with a view to the preparation of the cyclopropyl system (278; X = CH_2) was undertaken. A related literature example[24] describes the preparation of the cyclopropyl sulpholane (275) from photochemical extrusion of the diazomethane-butadiene sulphone adduct (273). The minor products of this photolysis were the monocyclic isomers (100) and (276), thought to arise from intramolecular hydrogen abstraction processes operating on the proposed intermediate diradical (274) formed on initial extrusion of nitrogen from (273).



Using similar conditions to those described[24] for (273), irradiation of a dilute solution of tetracyclic adduct (272a) in acetonitrile using a 100W medium pressure mercury lamp through quartz glassware was carried out for 18 hours. A product mixture comprising two components was established by thin-layer chromatographic analysis and separation of these was achieved by operation of this technique



on a preparative scale. The higher R_f component was fully characterised as the cyclopropyl tetracycle (278; X = CH_2) which was isolated in 32% yield. In particular, structure elucidation was enhanced by the presence, at characteristic shielded positions, of the C(10) methylene cyclopropyl group which was observed at δ 11.69 in the ^{13}C DEPT NMR spectrum and as two discrete resonances at δ 0.43 and δ 0.82 in the ^{1}H NMR spectrum. More detailed analysis of the latter furnished coupling constants $J_{1,2}$ ($J_{8,9}$) = 2.9 Hz and $J_{2,3}$ ($J_{7,8}$) = 0.8 Hz in accord with the expected transoid,transoid geometry of (278; X = CH_2), formed without loss of stereochemistry from transoid,transoid adduct (272a) via the proposed diradical intermediate (277).

The lower R_f component isolated from preparative TLC was obtained as a light yellow oil which demonstrated a tendency to polymerise on standing. Analysis of this by infra-red spectroscopy indicated the presence of both sulphone and aldehyde groups; mass spectroscopy furnished evidence in support of these findings, and a molecular ion at m/e 200 pointed to a molecular formula of $C_9H_{12}O_3S$. The ^{1}H NMR spectrum demonstrated characteristic signals due to vinyl and aldehyde protons which taken in conjunction with a ^{13}C DEPT NMR spectrum displaying two similar sets of nine carbon resonances was indicative of the presence of equimolar quantities of two isomers of structure (279) for this minor product. Separation of the two isomers was not possible, and therefore the relative stereochemistries of the vinyl and aldehyde groups for these structures remains unsubstantiated.

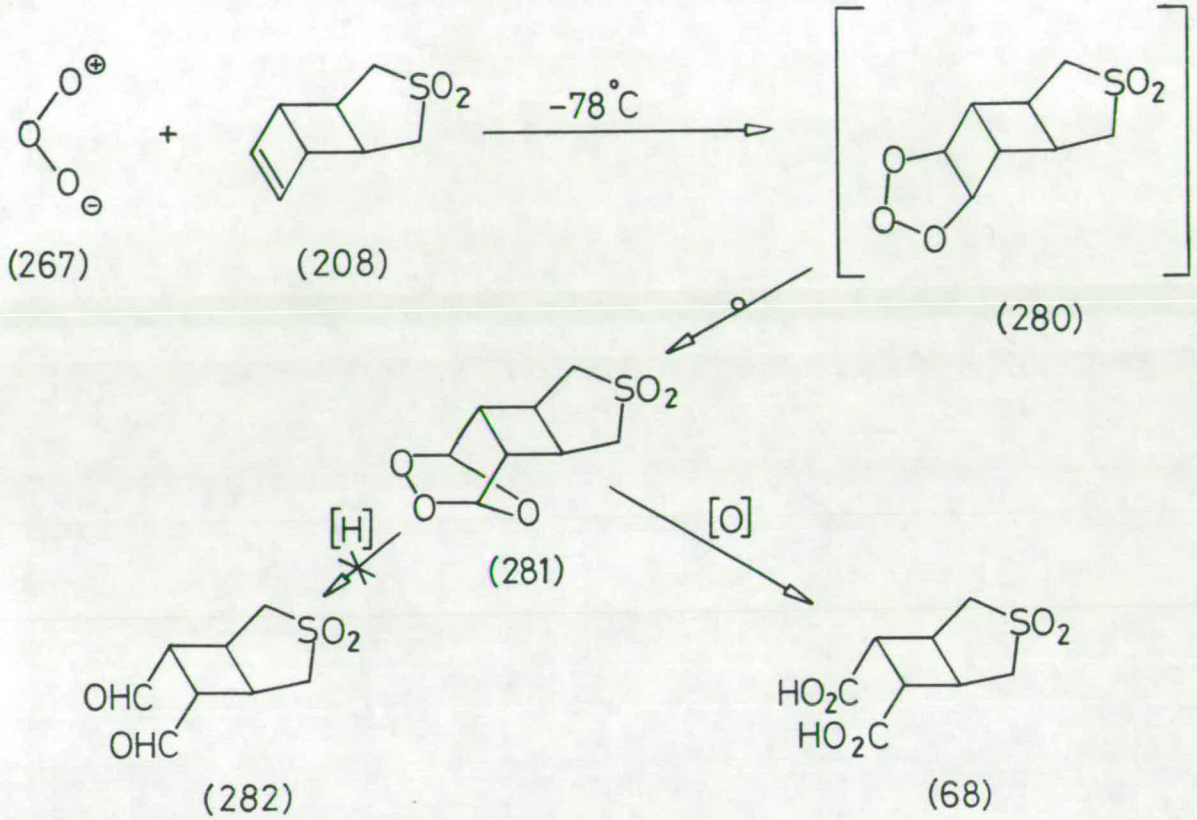
In mass balance terms, the unsaturated isomers (279) are the result of a loss of two nitrogen atoms from, and a gain of one oxygen atom to the diazomethane adduct (272a). The mechanism of formation of the vinyl aldehyde isomers (279) from (272a) remains

unclear, though the presence of dissolved oxygen in the dilute acetonitrile solution of (272a) as the source of the oxygen incorporated in the isolated products (279) appears likely. In this connection, a photolysis experiment conducted using a similarly dilute solution of (272a) in d_3-acetonitrile, thoroughly deoxygenated by nitrogen ebullition prior to irradiation, under a nitrogen atmosphere resulted in no formation of the aldehydic products (279). It would therefore appear that dissolved oxygen plays a vital part in formation of the isomers (279), and the participation of photogenerated, highly-reactive, singlet oxygen is a distinct possibility, though the overall mechanism for formation of (279) remains uncertain.

d. With ozone (267)

Although fairly recent theoretical calculations[134] indicate that ozone (267) exists as a biradical in its ground state rather than the traditional zwitterionic (1,3-dipole) form, its reactivity with an olefin is still amenable to analysis in terms of dipole-dipolarophile frontier orbital interactions. Consideration of the low energy difference (7.2 eV) between the dipole LUMO and the olefin (208) HOMO in the dominant interaction (Figure 3) leads to a prediction that the reaction will proceed much faster than the other dipole-olefin (208) reactions attempted thus far.

Treatment of a methanolic solution of the olefin (208) with a stream of ozone in oxygen at -78°C resulted in uptake of ozone for 15 minutes, after which time excess ozone was present in solution indicating completion of reaction. This high rate of reaction even at reduced temperature was not unexpected in light of the predictions resulting from consideration of frontier orbital interactions.

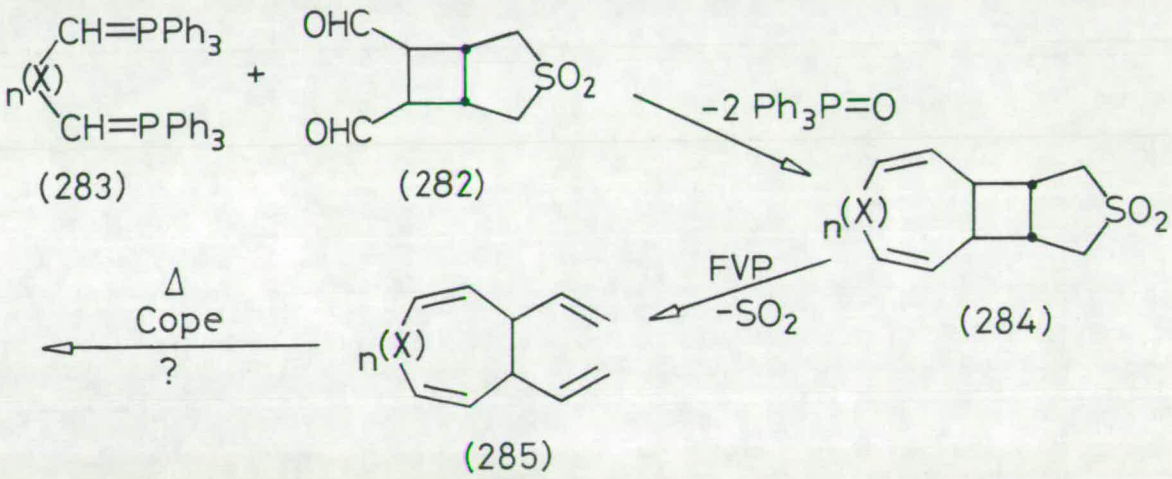


Scheme 36

The ozonide was obtained as a colourless oil expectedly of structure (281), in accord with the Criegee mechanism[135] of olefin ozonolysis, arising from a rearrangement of the initially formed adduct (280) (Scheme 36). The ozonide itself was not characterised, but oxidised immediately by heating with hydrogen peroxide in formic acid to give the exo-cis diacid (68), identical to a sample prepared by hydrolysis of the anhydride (45) (of known[28] transoid stereochemistry). Thus, the ozonolysis of (208) and work-up under standard oxidising conditions[135] furnishes further evidence for the transoid stereochemistry of the tricyclic olefin (208).

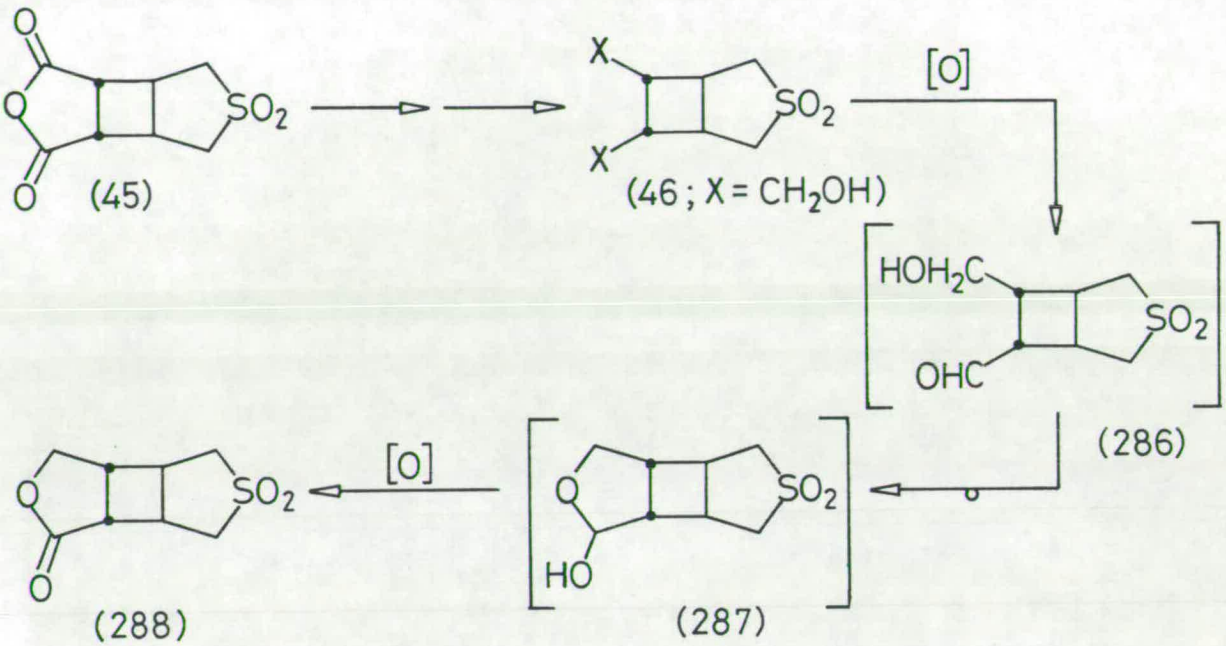
Although oxidative decomposition of the ozonide (281) was of no synthetic utility, since diacid (68) is more easily obtained from anhydride (45), the exo-cis dialdehyde (282), the expected product

of reductive decomposition of (281), was of considerable value in this respect. Reaction of dialdehyde (282) with bis(phosphorus ylide) systems (283) would be expected to generate the unsaturated tricyclic sulpholane systems (284) which are of interest with regard to thermal extrusion behaviour. Complementing the study of thermal extrusion reactions of the related series (69) (p.25), the extrusion of sulphur dioxide from systems (284) would be expected to result in formation



of divinyl monocycles (285) potentially capable of undergoing Cope rearrangement to macrocyclic systems. The influence of ring size of the divinyl cyclic systems (285) upon ease of Cope rearrangement could be conveniently assessed by synthesis and FVP of precursor sulpholanes (284) incorporating unsaturated rings of various sizes.

Previous attempts[29] to prepare the dialdehyde (282) by oxidation of the corresponding exo-cis diol (46; X = CH_2OH) resulted in failure due to facile cyclisation of the product of mono-oxidation, the aldehyde-alcohol (286), to the lactol (287) which was then found to oxidise to the isolated lactone product (288) under the reaction conditions employed.



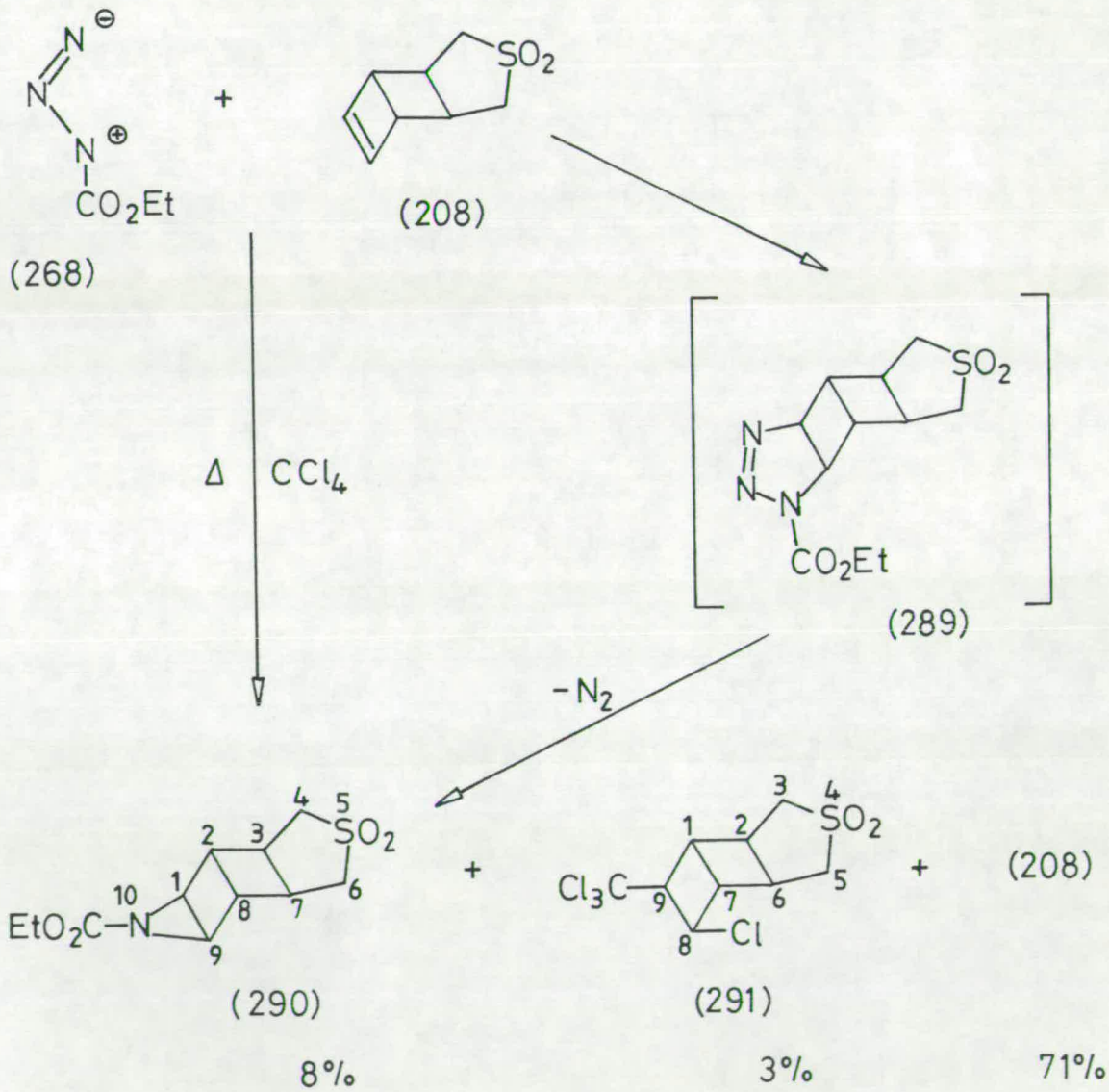
In an effort to prepare the dialdehyde (282), a methanolic solution of the ozonide (281), prepared by reaction of (208) with ozone at -78°C, was treated with a solution of sodium iodide in acetic acid at room temperature. Although reduction occurred, as evidenced by iodine release, it was evident from ^{1}H NMR spectroscopy that a complex mixture of at least five components, containing little aldehydic material, was formed.

A second attempt in which a solution of the ozonide in ethyl acetate was reduced by catalytic hydrogenation using pre-reduced platinum oxide also failed to yield the desired dialdehyde product (282), giving instead two isomeric structures (ca 2:1 ratio) containing no aldehyde groups. These were not identified but from ^{13}C and ^{1}H NMR spectroscopy they appeared to be saturated, asymmetric C_8 (6 x CH, 2 x CH_2) structures. From the infrared spectrum there was evidence for both sulphone and alcohol groups, with a possible molecular weight of 202 ($C_8H_{10}O_4S$) indicated by mass spectroscopy. The reasons for the

failure to generate the dialdehyde (282) from either of the two attempted reductive treatments of the ozonide (281) were not obvious.

e. With ethyl azidoformate (268)

The reaction of olefin (208) with ethyl azidoformate (268) is predicted to occur fairly quickly in consideration of the relatively small energy difference (7.4 eV) between the olefin (208) HOMO-dipole (268) LUMO in the dominant (Type III) frontier orbital interaction (Figure 3).



Heating a solution of the olefin (208) with an excess of ethyl azidoformate (268) in boiling dry carbon tetrachloride for 30 hours gave, after chromatographic purification of the crude reaction mixture, three separate components. Starting olefin (208) was recovered in 71% yield, together with minor quantities of the aziridine (290) and the tetrachloride (291). Full spectral characterisation of the aziridine (290) was achieved and the transoid,transoid geometry was verified by examination of the ^1H NMR spectrum which displayed doublets for the aziridine protons H_1,H_9 at δ 3.23, and for the cyclobutane protons H_2,H_8 at δ 2.69 each containing the trans vicinal cyclobutane coupling constant $J_{1,2}$ ($J_{8,9}$) = 3.3 Hz. This product is formed by facile thermal extrusion of nitrogen from the intermediate adduct (289), resulting from addition of the azide (268) to the olefin (208).

The third separated component, the tetrachloride (291) was obtained in very low yield (3%) as colourless crystals, m.p. 171-173°C. Following confirmation of the molecular formula of $C_9H_{10}Cl_4O_2S$ by elemental and mass spectral determinations, analysis of the nine line ^{13}C NMR spectrum in conjunction with the ^1H NMR spectrum allowed the substituent stereochemistry in structure (291) to be defined. Thus, the most deshielded methine signal (δ70.59) in the carbon spectrum due to the chloromethine C(8)H group was found on examination of the 2D ^1H - ^{13}C correlated NMR spectrum to be associated with a signal at δ3.58 in the proton spectrum which was therefore ascribed to H_8. Analysis of the ^1H - 2D COSY spectrum of (291) indicated H_8 (δ 3.58) to be coupled to the most deshielded signal in the spectrum at δ 4.82, assigned to proton H_9. The low field position of this signal is in agreement with the stereochemistry of (291) in which the H_9 proton

would expectedly be deshielded by a repulsive steric interaction with the spacially proximate H_2 proton and the chlorine substituent. Further couplings of H_8 to protons H_1 and H_7, and couplings between H_9 and H_1, H_7 evident from the COSY spectrum allowed assignment of protons H_7 and H_1 respectively to signals at δ2.81 and to the multiplet (four protons) at δ3.02-3.20.

Further analysis of the COSY spectrum in conjunction with the 2D ^1H - ^{13}C correlated spectrum enabled the location of the signals due to sulpholane ring fusion protons H_2 (multiplet of four protons δ3.02-3.20) and H_6 (δ3.81). Interestingly, the deshielded position of H_6 relative to H_2 is further evidence for the trans disposition of substituents as shown in (291), with H_6 resonating at lower field due to the greater steric interaction of this proton with the chlorine substituent than between H_2 and H_9. In furtherance of this point, examination of the ^1H - 2D NOESY spectrum of the tetrachloride product (291) indicated the close spacial relationship of H_2 and H_9. Although this was expected, an unusual feature of the NOESY spectrum was the lack of enhancement of the rest of the terminal cyclobutane ring protons between themselves, or with other protons in the system. This evidence indicates that the terminal cyclobutane ring of (291) must be considerably distorted from planarity by the presence of the trans disposed substituents.

In light of this, the large numerical values of the trans vicinal cyclobutane coupling constants $J_{1,9}$ = 7.9 Hz and $J_{8,9}$ = 7.0 Hz, and the small values associated with the cis vicinal coupling constants $J_{1,7}$ = 5.1 Hz and $J_{7,8}$ = 3.4 Hz, when compared to those found within a planar cyclobutane ring system (see p.73), can also be accounted for by ring distortion and substituent electronegativity factors.

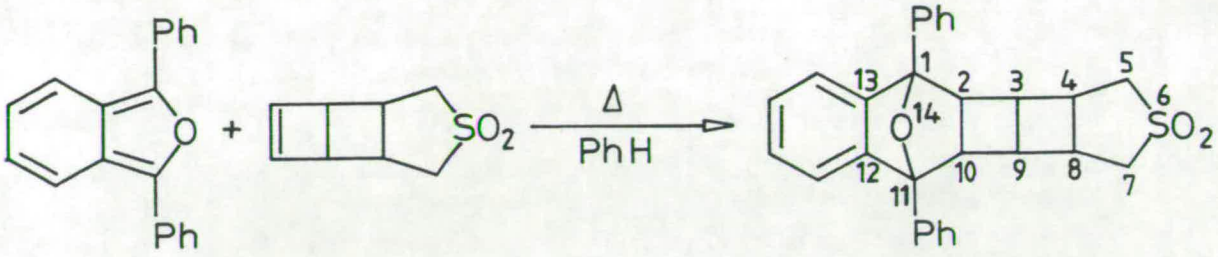
Further evidence for the endo-chloro-exo-(trichloromethyl) geometry of (291) was furnished by the similarity in proton spectra between this and two other trans disubstituted systems derived from olefin (209) which are described later.

As the tetrachloro product (291) appears to result from the addition of the elements of the carbon tetrachloride solvent to olefin (208), a control experiment was conducted in which (208) was heated under reflux in carbon tetrachloride alone (using the same batch of solvent as that used previously) for an extended period. Examination of the reaction mixture revealed the absence of (291) with the olefin (208) being recovered quantitatively. It was concluded that formation of (291) did not occur as a result of thermal decomposition of the solvent, but rather required in addition the presence of ethyl azidoformate. Although the mechanism of formation of (291) has not been unequivocally established, it is probable that thermal decomposition of ethyl azidoformate results in the formation of trichloromethyl and chlorine radicals, with the former then reacting with the olefin (208) to occupy the less sterically hindered exo position, leaving the smaller chlorine radical to fill the more sterically constrained endo position.

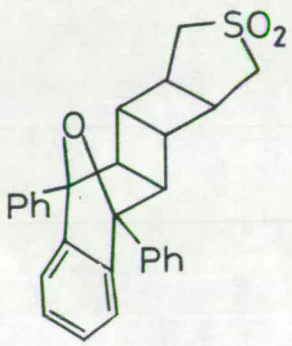
2. Diels-Alder reactions

a. With 1,3-diphenylisobenzofuran (292)

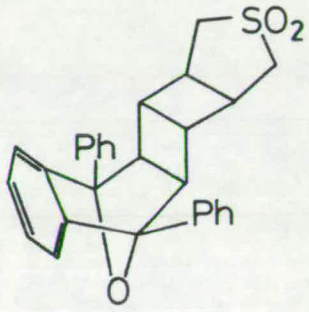
Upon heating a solution of the transoid tricyclic olefin (208) and 1,3-diphenylisobenzofuran (292) in benzene under reflux, the yellow colour due to the diene was observed to have disappeared after five hours. Analysis of the product, obtained as finger-shaped crystals (m.p. 152.5-154.5°C), indicated this to be a single one of



(292) (208) (293)



(293a)

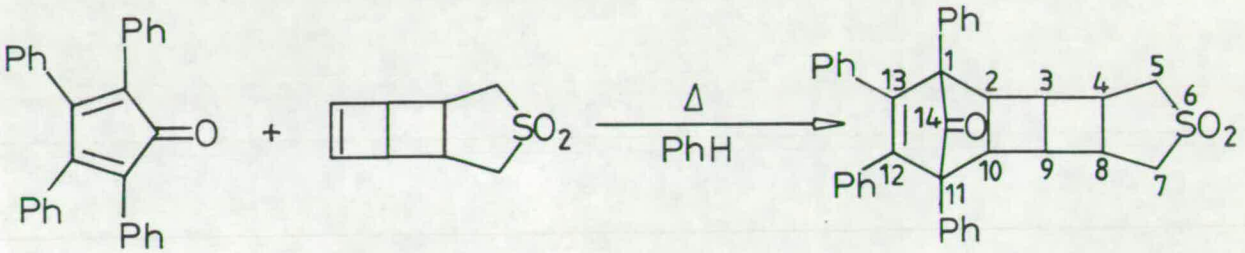


(293b)

the four possible isomeric Diels-Alder adducts (293), isolated in 78% yield. From study of the ^1H NMR spectrum, the signal (δ 2.29) corresponding to protons H_3, H_9 was found not to display appreciable coupling to either of the two sets of vicinal cyclobutane protons H_2, H_{10} and H_4, H_8 in accord with a trans relationship between the neighbouring proton pairs. This information limits the structural possibilities for the product to the two transoid,transoid structures (293a) and (293b), these being the result of exo and endo addition of the diene (292) to the less hindered face of the olefin (208). The stereochemistry of the product could not be further defined, although structure (293a) appears to be the more probable candidate since there is less steric hinderance in the exo mode of addition of the diene (292) to the olefin (208) than in the corresponding endo mode.

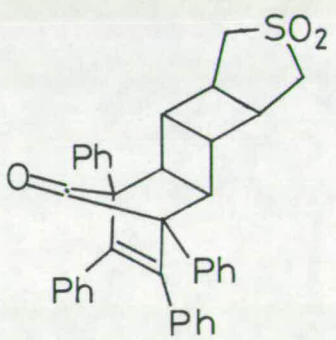
b. With tetraphenylcyclopentadienone (294)

On treatment of the olefin (208) with a slight excess of tetraphenylcyclopentadienone (294) in boiling benzene, reaction was found to have reached completion after 18 hours. A good yield of a crystalline product, m.p. 192-225°C, was obtained which was found to comprise a ca 2:1 mixture of two isomeric Diels-Alder adducts (295)

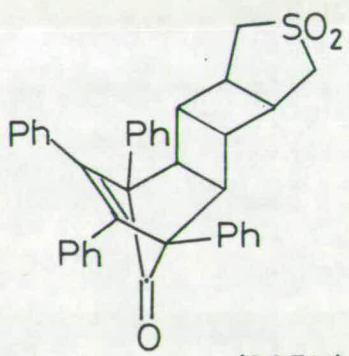


(294) (208) (295)

following spectral examinations. In particular, analysis of the ^1H NMR spectrum gave a singlet signal at δ 2.47 corresponding to protons



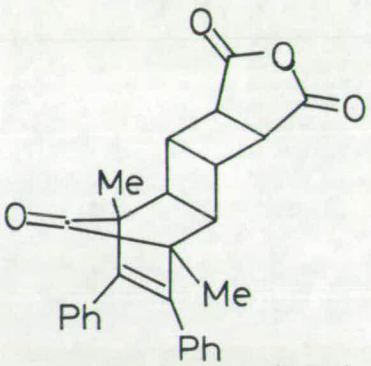
(295a)



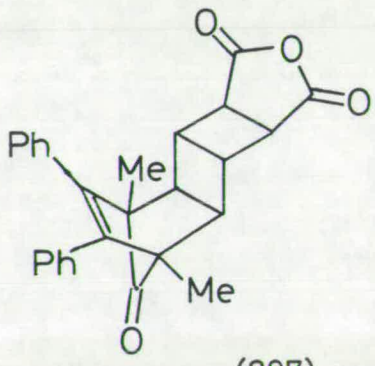
(295b)

H_3, H_9 in both isomers. The lack of coupling between these protons and the two vicinal cyclobutane pairs H_2,H_{10} and H_4,H_8 is in accord only with the transoid,transoid structures (295a) and (295b), the products of exo and endo addition respectively of the diene (294) to the less sterically hindered face of the olefin (208), for the two inseparable isomeric products.

Although not certain, it is likely that the major isomer possesses the stereochemistry of structure (295a) since the exo addition mode suffers less steric hinderance than the corresponding endo mode. A literature precedent furnishes supporting evidence for this proposal: the reaction of the transoid tricyclic anhydride (214) with 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dienone has been reported[136] as yielding the Diels-Alder adducts (296) and (297), the respective products of exo and endo addition of the dienone to the more accessible face of the olefin system, in a 9:1 ratio. By the way,



(296)



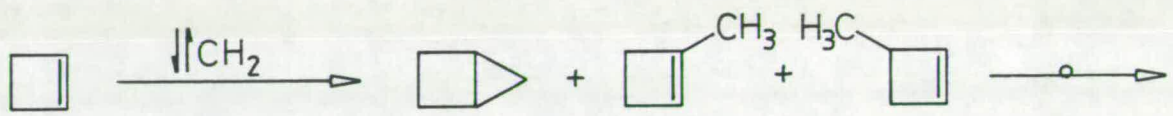
(297)

the formation of two products resulting from both exo and endo addition of olefin (208) and tetracyclone (294) contrasts strongly with the formation of a single adduct (probably via the exo addition mode) on reaction of (208) with 1,3-diphenylisobenzofuran (292). This difference in stereoselectivity may be due to a greater steric destabilisation of the endo transition state for the reaction with the furan (292) since in this transition state (leading to formation of endo adduct (293b)) a greater steric interaction between the oxa bridge and the ring fusion H_2,H_{10} protons would occur than between the oxo bridge and the equivalent protons in the corresponding endo transition state (leading to formation of adduct (295b)) for reaction with tetracyclone (294).

3. Reaction with carbenoids and nitrenes

a. With methylene carbenoids

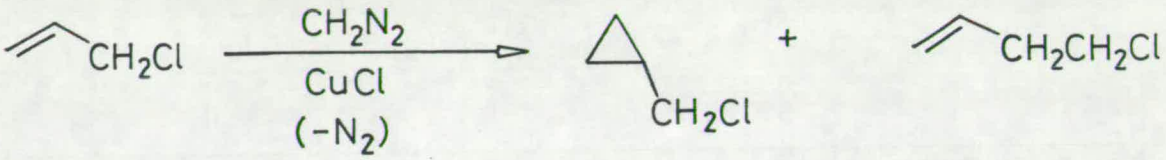
Singlet methylene, generated by solution photolysis of diazomethane, is known to be an electron-deficient carbene capable of undergoing facile stereospecific addition to olefins (particularly electron-rich olefins) with formation of cyclopropane products, and also of undergoing insertion reactions rather indiscriminately into certain σ bonds[137]. The reaction of highly reactive singlet methylene with the electron-rich olefin cyclobutene has been found[138] to result in initial formation of bicyclo[2.1.0]pentane (by a cycloaddition reaction) and 1- and 3-methylcyclobutenes (by insertion reactions) in vibrationally excited forms capable of undergoing rearrangement to more stable isomeric forms or undergoing collisional deactivation (Scheme 37).



Scheme 37

Triplet methylene, formed by photolysis of gaseous diazomethane and spin inversion of the initially formed singlet methylene intermediate by collisional energy transfer, reacts as a diradical undergoing non-stereospecific cyclopropanation reactions with olefins, and also hydrogen abstraction reactions[137]. Additionally the ill-defined 'carbenoid' equivalents of methylene, formed by treatment of diazomethane with inorganic halides or organometallic catalysts, are readily available and synthetically useful species for the preparation of cyclopropane systems. Thus the cuprous chloride catalysed

decomposition of diazomethane in the presence of a solution of the olefin (298) in pentane at ambient temperature has been reported[139] to give the cyclopropane derivative (299) together with minor amounts of an acyclic insertion (into the carbon-chlorine bond) product (300), via a proposed copper-complexed methylene carbenoid intermediate.



(298) (299) 25% (300) 4%

However, this electrophilic carbenoid is known[137] not to insert into carbon-hydrogen bonds, but to readily undergo concerted cycloaddition to electron-rich olefins.

The reaction of the electron-rich olefin (208) with this methylene carbenoid species was therefore attempted with a view to obtaining a more direct synthesis of the cyclopropyl system (278; X = CH_2). Thus, addition of a ten-fold equivalent of diazomethane in ether in portions to a solution of the olefin (208) in methanol containing a catalytic amount of cuprous chloride resulted in instant decolourisation of the added diazomethane with concomitant evolution of gas. Therefore the methylene carbenoid appeared to have formed, although work-up of the reaction gave recovered olefin (208) as the sole sulphone-containing compound present. Upon replacement of the catalyst by rhodium(II) acetate, identical results were achieved.

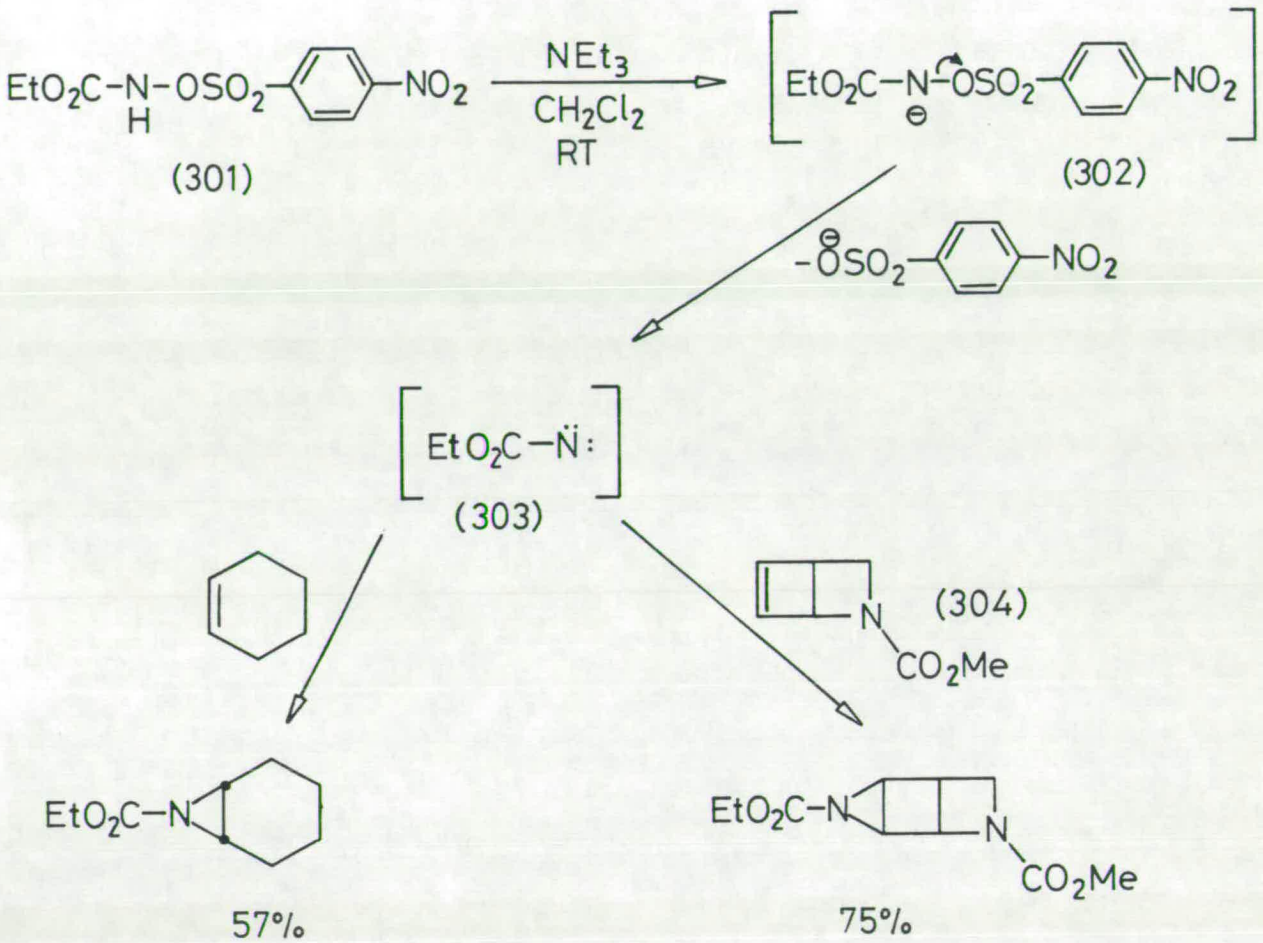
It would therefore appear that the methylene carbenoid species formed in these reactions undergoes insertion into the solvent

(particularly into the methanol O-H bond) with formation of volatile products rather than combining with the olefin (208). This may be a consequence of the indiscriminate reaction of the carbenoid species with surrounding compounds, which in this case is liable to be solvent molecules since dilute solutions of (208) were employed. The contrast in reactivity of olefins (208) and (298) with the cuprous chloride generated methylene carbenoid is perhaps a result of the relative ease of insertion of this species into methanol or ether compared to pentane, these being the solvents employed in each reaction. However, the use of non-polar solvents in the reaction of (208) with a methylene carbenoid (derived from cuprous chloride) was not considered due to the insolubility of the olefin in such solvents.

b. With ethoxycarbonyl nitrene (303)

This nitrene is electron-deficient due to the electron-withdrawing ethoxycarbonyl group, and is therefore highly reactive with respect to addition reactions to electron-rich olefins, forming the corresponding aziridine products[140]. Thus reaction of ethoxycarbonyl nitrene (303), generated initially in the singlet (excited) state by unimolecular decomposition of the anion (302) (formed on treatment of ethyl p-nitrobenzenesulphonoxycarbamate (301) with base in organic solution), with the electron-rich olefins, cyclohexene[141] and the bicyclic system (304)[142], resulted in formation of the corresponding aziridines in good yield (Scheme 38).

Since the transoid tricyclic sulpholane (208) possesses an olefin moiety expected to be as electron-rich as cyclobutene, an improved synthesis of the aziridine (290) (previously prepared in poor yield by addition of ethyl azidoformate to the olefin (208) followed by extrusion of nitrogen from the intermediate triazoline (289))



Scheme 38

might be anticipated on reaction of (208) with ethoxycarbonyl nitrene (303). Under similar conditions to those of Lwowski and Maricich[141], ethoxycarbonyl nitrene (303) was generated in a methylene chloride solution of the olefin (208) by treatment of Lwowski's reagent (301) with triethylamine. However, on work-up the only sulphone-containing material isolated was the starting olefin (208) in 67% recovered yield.

Following this failure, the reaction of (208) with ethoxycarbonyl nitrene (303) generated under phase-transfer conditions was attempted in view of the success of such conditions, in general, with regard to the reactions of reactive intermediates such as carbenes[143]

and nitrenes[144] with olefins. Using conditions based upon those described by Seno *et al*[144], a solution of the olefin (208), Lwowski's reagent (301) and the phase-transfer catalyst, benzyltriethyl ammonium chloride, in methylene chloride was stirred vigorously at room temperature for an extended period with a solution of sodium hydrogen carbonate in water. Analysis of the isolated reaction product indicated the presence of starting olefin (208) (65%) together with the product of ethoxycarbonyl nitrene (303) addition to this, the aziridine (290) (27%).

This observed dichotomy of reaction of the olefin (208) with ethoxycarbonyl nitrene generated under homogeneous (organic phase) and two-phase (phase-transfer) conditions follows a previously established pattern for the reactivity of this nitrene with cyclo-olefinic sulpholane and sulpholene systems, including butadiene sulphone and the cyclobutene sulpholane (63)[95]. A plausible explanation[95] for these findings is that generation of the nitrene in the bulk organic phase is ineffective at reaction with the olefinic sulphone, undergoing insertion reactions with the solvent instead. However, in the two-phase system the olefinic sulphone might be expected to be positioned across the organic-aqueous phase boundary with the polar (hydrophilic) sulphone group protruding into the aqueous phase and the (hydrophobic) olefin group located in the organic phase. Since the nitrene is expected to be generated near to the phase boundary by a phase-transfer process, the nitrene then encounters a much enhanced (compared to the organic phase situation) concentration of the olefin with resultant reaction of the two and formation of the aziridine addition product.

4. Miscellaneous reactions

a. Photochemical reactivity

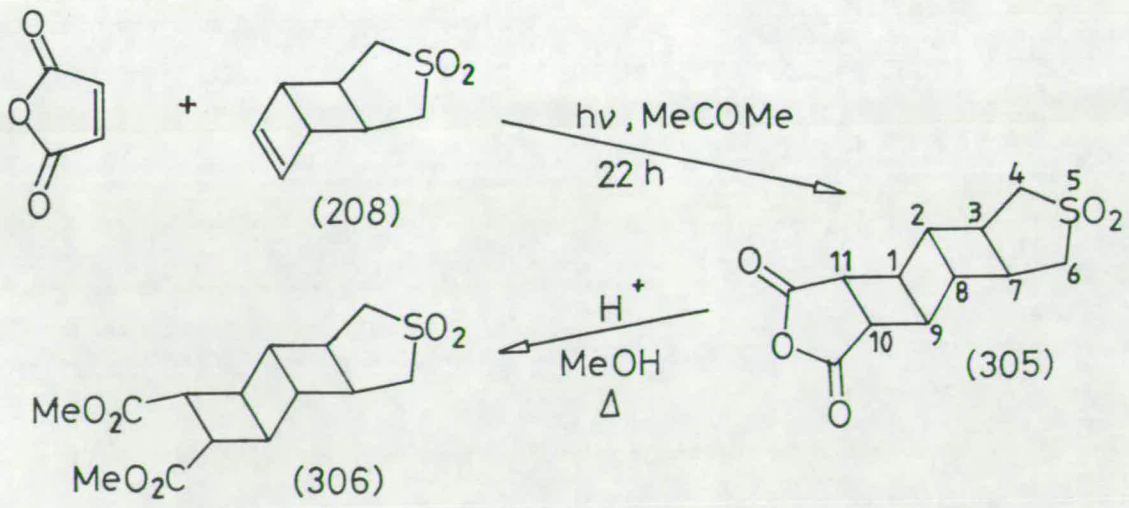
i. With ethyl azidoformate (268)

The photolysis of ethyl azidoformate (268) has in the past been considered[145] to result in formation of ethoxycarbonyl nitrene (303), but more recent evidence[140] indicates that the observed formation of aziridine products in the presence of olefins is more likely to occur *via* cycloaddition of photoexcited ethyl azidoformate (268) to the olefin followed by expulsion of nitrogen. With the aim of synthesis of the tetracyclic aziridine (290) by an alternative route to those described previously, a neat mixture of the olefin (208) and ethyl azidoformate (268) was irradiated through quartz using a 400W lamp. Brisk evolution of gas (nitrogen) was observed: work-up after a three hour irradiation period indicated the presence of starting olefin (208) as the only sulphone-containing material present. Similarly, irradiation of a solution of the two starting materials in carbon tetrachloride/chloroform through quartz using a 100W lamp for almost one day gave parallel results.

These findings are in contrast with the general trend which is that formation of the corresponding ethoxycarbonyl aziridine products from irradiation of neat mixtures of ethyl azidoformate and cycloolefinic sulphones (of various olefin electron availabilities) occurs for those olefins capable of forming the aziridine product by a phase-transfer ethoxycarbonyl nitrene reaction[95]. The reasons for the unreactivity of olefin (208) towards reaction with photochemically excited ethyl azidoformate (268) are not apparent, but this observation is supporting evidence for the lack of generation of ethoxycarbonyl nitrene (303) from the azide (268) under photolysis conditions.

ii. With maleic anhydride

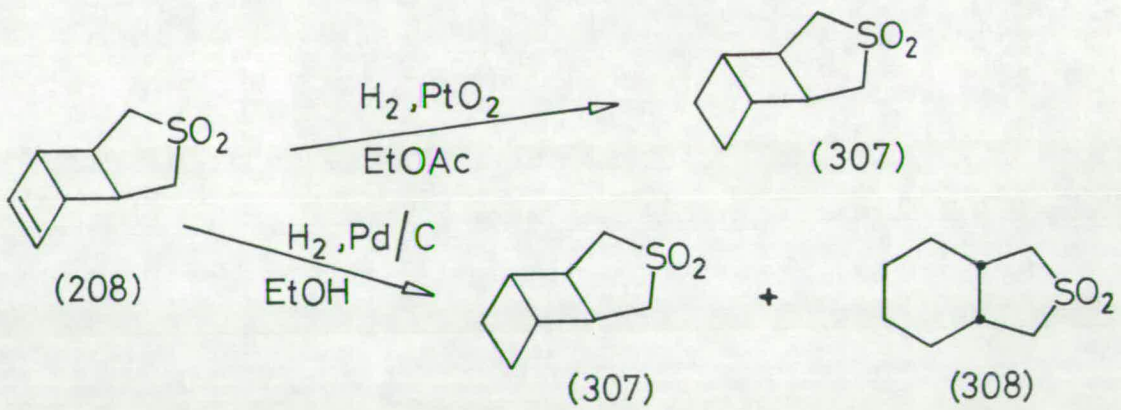
As described previously (p. 89), the photolysis of the related cyclobutene sulphone (63) with maleic anhydride in acetone solution realised the [2 π + 2 π] photoadduct (242a) which displayed transoid stereochemistry of the system about the newly formed cyclobutane ring, a feature commonly observed for the photoaddition of two simple cycloalkenes[108]. In view of this and other successful photoadditions of maleic anhydride to cycloalkenes (e.g. butadiene sulphone, cyclobutene anhydride (244)), the synthesis of a pentacyclic anhydride system (305) from transoid olefin (208) was attempted. Irradiation of a solution of (208) and excess maleic anhydride in acetone, through quartz and using a 100W medium pressure mercury lamp, resulted in complete consumption of starting sulphone after 22 hours. A crystalline photoadduct conforming to structure (305) was isolated in 46% yield. The ^{1}H NMR spectrum displayed two singlets for the central cyclobutane proton pairs H_2,H_8 (δ2.88) and H_1,H_9 (δ3.02) indicating that the single isomer formed (of the four possible pentacyclic products) possessed the transoid,transoid,transoid stereochemistry of structure (305). Such a stereochemistry for the photoadduct is in accord with expectation (see p. 89).



Anhydride (305) was considered to be a viable candidate for a study of the thermal extrusion behaviour of a series of tetra- and higher-cyclic sulpholane systems (211), this being the only example encountered of structure (211; n = 2). The exo-cis dimethyl ester (306) was likewise of value and synthesis of this was achieved by heating anhydride (305) in acidified methanol, giving the desired diester (306) in fair yield as colourless flakes. These fulfilled standard elemental composition and spectral analyses for the transoid, transoid-exo-cis-diester structure (306) of the product.

b. Hydrogenation

Catalytic hydrogenation of cyclic olefins using platinum oxide (Adam's catalyst) has been found to operate very efficiently with the added benefit that this catalyst does not cause hydrogenolysis reactions to occur during the reduction of strained systems[146]. The hydrogenation of the strained olefin (208) was therefore carried out in ethyl acetate using platinum oxide and a pressure of one atmosphere

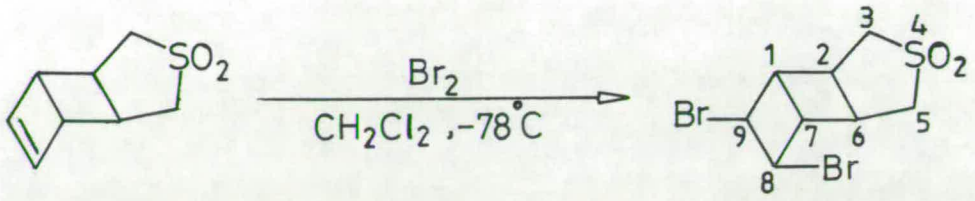


of hydrogen. A near quantitative yield of a completely saturated crystalline product, identified as the transoid system (307), was obtained.

Hydrogenation of a solution of (208) in ethanol under one atmosphere of hydrogen using 10% palladium-on-charcoal as catalyst resulted in isolation of a completely saturated product mixture. Analysis of this by ^{1}H and ^{13}C NMR spectroscopy indicated it to consist of an equimolar mixture of tricyclic sulphone (307) and the saturated bicyclic sulpholane (308), the latter product being identified by comparison with an authentic sample prepared by the palladium-on-charcoal catalytic hydrogenation of cyclohexene-sulpholane (65). Formation of the ring-opened product (308) can be attributed to a palladium-on-charcoal catalysed hydrogenolysis reaction operating on the strained olefin (208). This catalyst is known to cause hydrogenolysis of strained olefin systems with ease[146].

c. Bromination

The olefinic π-bond of tricyclic sulpholane (208) is expected to display the characteristics of an electron-rich olefin, and has done so in the previously described reactions. With respect to bromination, olefin (208) would be expected to demonstrate high reactivity with formation of the classical trans-dibromide product associated with the ionic, anti addition of bromine to an isolated, non-sterically hindered olefin. Slow addition of bromine to a solution of (208) in methylene chloride at -78°C resulted in instant decolourisation of bromine until greater than an equimolar quantity of bromine had been added. Following work-up, a high yield of a single dibromide product resulting from (208) was obtained. This displayed elemental composition and mass spectral data in accord with a compound of molecular formula $C_8H_{10}Br_2O_2S$; ^{1}H and ^{13}C NMR (8 line spectrum) analyses indicated the product to be the trans-dibromide (309), as expected. Scrutiny of the ^{1}H NMR spectrum of (309) indicated the signals due to the



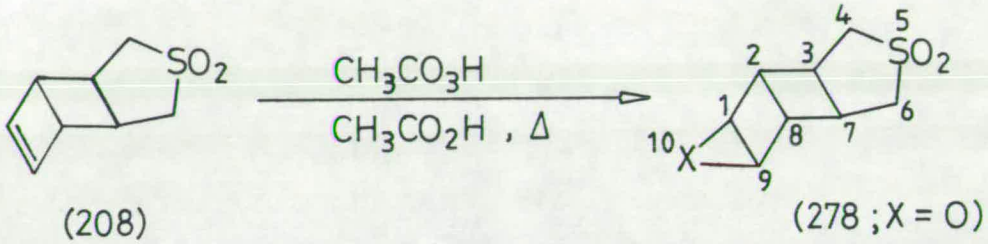
(208) (309)

deshielded bromomethine cyclobutane protons H_8 and H_9 at low field, δ 4.50 and δ 4.99 respectively. These displayed a similar splitting pattern and coupling constants to the related trans-tetrachloro system (291). Thus, values for (309) of $J_{7,8}$ = 2.4 Hz (cis coupling), $J_{1,9}$ = 7.9 Hz (trans) and $J_{8,9}$ = 6.3 Hz (trans) were found to mirror the corresponding couplings in (291). The reversal of the normal situation for planar cyclobutane systems where cis vicinal couplings are larger than the corresponding trans couplings (see p. 73) reflects the gross distortion of the terminal cyclobutane ring of dibromide (309) by the presence of two bulky bromine substituents, in similar fashion to that described earlier (p.128) for the parallel trans-disubstituted cyclobutane system (291).

d. Epoxidation

Since epoxidation of an olefin is a classical electrophilic process, such a reaction is expected to occur very readily with the electron-rich cyclobutene (208). Treatment of (208) with a solution of peracetic acid in acetic acid, prepared in situ by addition of hydrogen peroxide to excess acetic acid, at 55-60°C for slightly more than a day resulted in the preparation in 65% yield of an epoxide product, designated transoid,transoid stereochemistry (278; X = O)

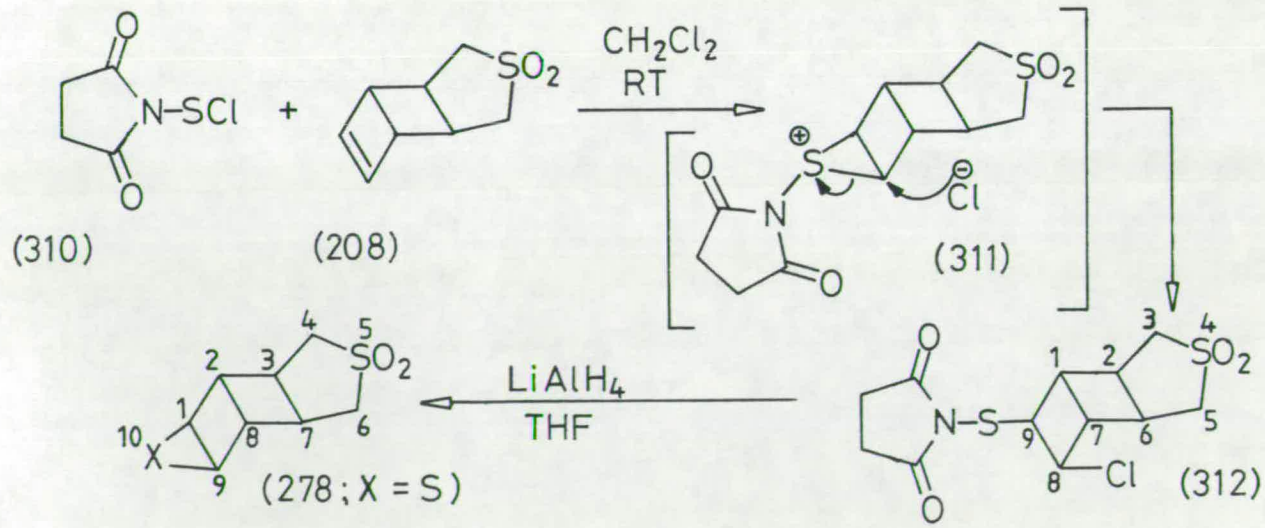
following the identification of the signal due to the epoxide protons H_1, H_9 at δ 3.99 which displayed a trans vicinal cyclobutane coupling constant $J_{1,2}$ ($J_{8,9}$) = 2.9 Hz.



e. Addition of a sulphenyl halide

The addition of sulphenyl halides to simple olefins is believed to occur via an ionic mechanism involving initial electrophilic addition of sulphur to the π double bond to generate an episulphonium intermediate which then undergoes nucleophilic attack by chloride ion with formation of a trans-disubstituted product[147]. Reaction of the electron-rich olefin (208) with a sulphenyl halide would therefore be expected to occur very readily, in light of this mechanism.

The addition of succinimide-N-sulphenyl chloride (310), prepared by the procedure described by Bombala and Ley[148], to a solution



Scheme 39

of the olefin (208) in methylene chloride at room temperature resulted in facile reaction of the two starting materials, which was found to have reached completion after one hour. A single adduct of the correct molecular formula for structure (312) was realised, and detailed examination of the ^1H NMR spectrum furnished evidence for the stereochemistry of the product being that of the trans-disubstituted system (312).

The proton spectrum of the product showed definate similarities in terms of the positions and couplings of the terminal cyclobutane methine protons H_8 and H_9 to those of the related trans-disubstituted tricyclic sulpholanes (309) and (291), and these similarities were especially apparent for the latter system due to the similar nature (electronegativity and steric bulk) of the substituents. It was found for the product (312) that the most deshielded resonance (δ4.78) corresponding to the succinimidothio-substituted methine proton H_9, and the next most deshielded signal (δ3.88) due to H_8 displayed trans coupling constants $J_{1,9}$ and $J_{8,9}$, and cis coupling constants $J_{7,8}$ and $J_{1,7}$ which were almost identical to the known trans-disubstituted system (291), allowing similar endo-chloro substituent stereochemistry to be given to structure (312). Assignments of signals to protons, and hence assigned coupling constants, were verified following a series of selective proton decoupling experiments carried out on product (312).

Having determined the stereochemistry of the adduct (312), formation of this product (Scheme 39) may be rationalised by electrophilic attack of the sulphenyl chloride (310) onto the least hindered face of the cyclobutene (208), followed by nucleophilic attack of chloride ion from the more accessible face of the

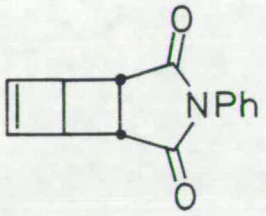
episulphonium intermediate (311) with resultant formation of the trans-disubstituted product (312).

In an adaptation of the general method of Bombala and Ley[148], the addition product (312) was reduced using a suspension of lithium aluminium hydride in tetrahydrofuran. A crystalline product was isolated in fair yield which was identified as the expected episulphide product (278; X = S) following elemental and spectral analyses. Resulting from the identification of the trans vicinal cyclobutane coupling constant $J_{1,2}$ ($J_{8,9}$) = 1.8 Hz in the signals due to H_2,H_8 (δ 2.66) and H_1,H_9 (δ 3.61) in the proton spectrum, the reaction product was accorded the transoid,transoid stereochemistry of structure (278; X = S). The mechanism of reaction of olefin-sulphenyl chloride adducts such as (312) with lithium aluminium hydride is thought to proceed by cleavage of the sulphur-nitrogen bond, deprotonation of the resultant thiol intermediate followed by intramolecular nucleophilic displacement of chloride ion by the resultant thiolate anion with formation of the episulphide product[148]. This mechanism, when taken into account with the transoid,transoid stereochemistry of the episulphide (278; X = S), is confirmatory evidence for the exo-disposition of the succinimidothio substituent in the sulphenyl chloride addition compound (312).

D. Comparison of transoid (208) and cisoid (209) Isomers of 4-Thiatricyclo[5.2.0.$0^{2,6}$]non-8-ene 4,4-dioxide

1. Introduction

Examination of the literature indicates that several pairs of transoid- and cisoid-tricyclo[5.2.0.$0^{2,6}$]non-8-ene isomers have been disclosed. These include the N-phenyl imide systems (313), the transoid isomer of which was obtained from photolysis of (232; R = Ph)[107] and the cisoid isomer by reaction of cyclobutadiene with N-phenyl maleimide[119] (in analogy to the preparation of the sulpholanes (208) and (209) described in previous sections).



(313)

Photolysis of the substituted bicyclic cyclohexadiene systems (233) has also generated both transoid and cisoid tricyclic isomers (p.83). However, only scant details of the spectral and reactivity properties of such isomeric tricyclic systems have been reported, and therefore a detailed comparison of the transoid (208) and cisoid (209) sulpholanes in terms of the effect of the two alternative structures on physical form, spectral characteristics and, to a lesser extent, olefinic reactivity was considered a valuable exercise.

2. Physical and structural characteristics

The transoid isomer (208) is a colourless, crystalline material, m.p. 109-111.5°C. Following the slow cooling of a hot, saturated solution of this compound in methylene chloride/ diisopropyl ether, small prisms were obtained which were suitable for X-ray

structural determination. This was kindly performed by Dr R.M. Highcock of the BP Research Centre, Sunbury and the data resulting from this study is collected in Appendix A.

Analysis of the data concluded that the compound was indeed the transoid tricyclic sulpholane (208). The crystals were found to be monoclinic, belonging to space group $P2_1/c$ (No. 14) and a representation of the unit cell is shown in Figure 9. Each unit cell contains four molecules with each of these arranged to maximise intermolecular sulphur-oxygen attractions. The relationship between neighbouring molecules in the crystal can best be observed from the stereoscopic representation of the unit cell displayed in Figure 10: each molecule has two nearest neighbours and the molecules are arranged to minimise the intermolecular sulphur-oxygen(2) distance (3.869Å). It is these strong attractions between molecules, resulting from the highly polar nature of the sulphone group (dimethyl sulphone[149], for example, has a dipole moment of 3.22D) that impart a characteristic crystallinity to sulphone-containing systems : even compounds of comparatively low molecular weight are invariably solid at room temperature, and those that are liquid exhibit high boiling points.

Turning to the molecular geometry of the transoid sulpholane (208), Figure 11 displays a perspective representation of the molecule for which an arbitrary numbering sequence is employed. Selected bond lengths (Å) are also shown, these having estimated standard deviations (e.s.d.) of $\pm 2\text{-}7 \times 10^{-3}$ Å. The three main planes corresponding to the three rings of structure (208) are outlined in Figure 12 with the perpendicular displacements (Å) from the least-squares planes also included.

Considering the data incorporated in Figures 11 and 12, and in Appendix A, a detailed analysis of the molecular structure of (208)

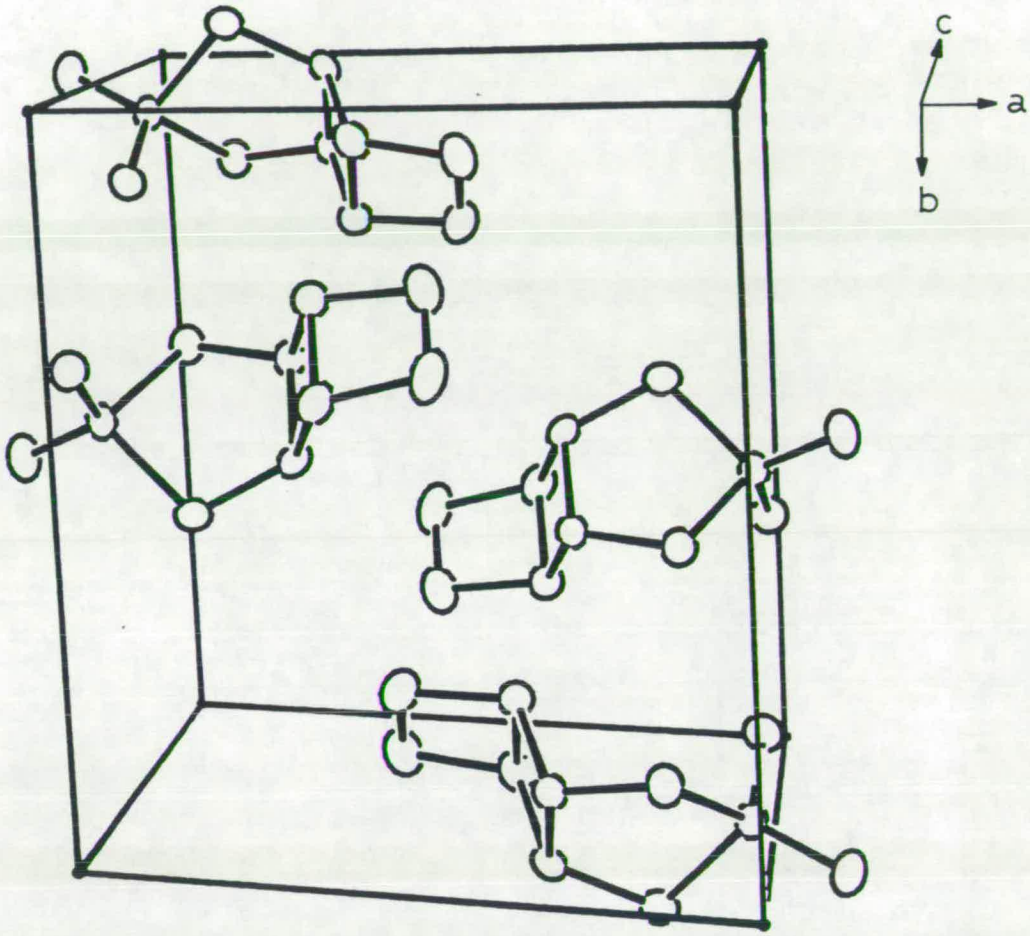


Figure 9 : Unit cell of (208)

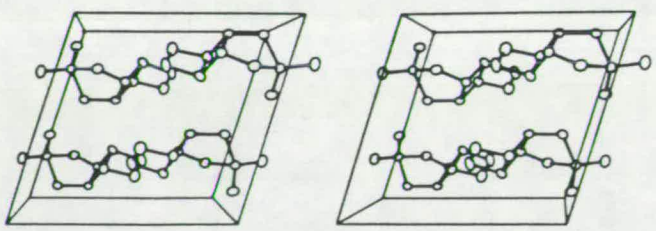


Figure 10 : Stereoscopic representation of unit cell of (208)

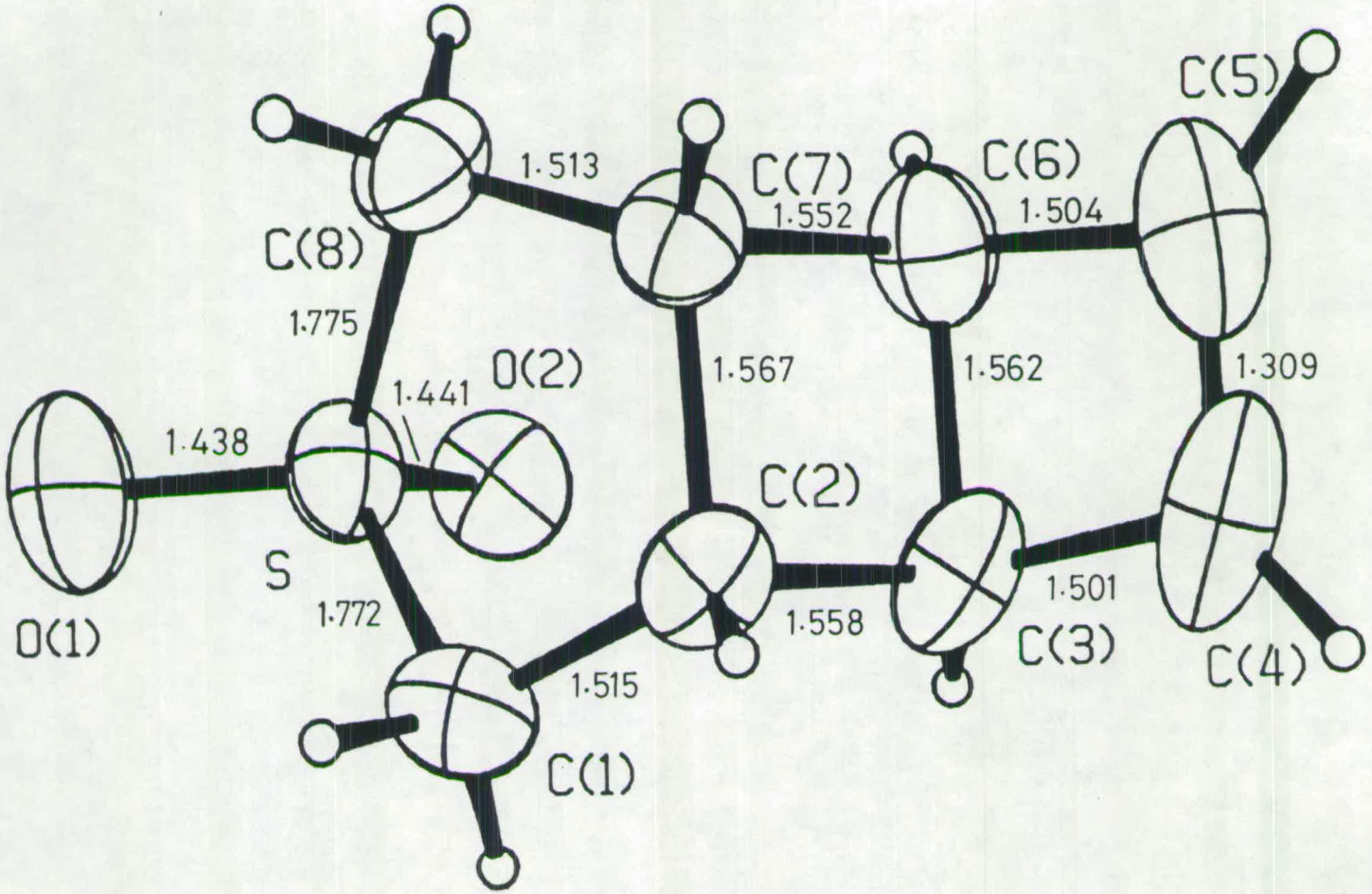


Figure 11 : Perspective drawing of the molecular structure of (208)

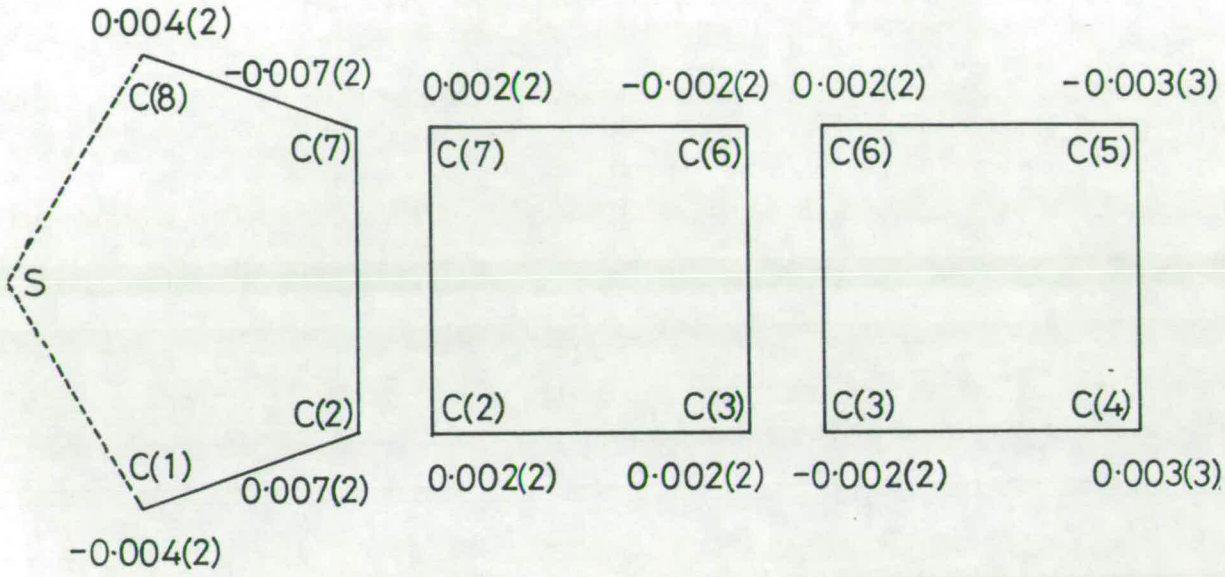
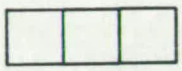


Figure 12 : Principal planes within the molecular structure of (208)

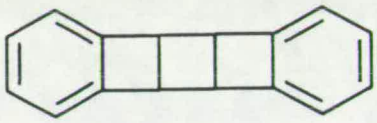
in the crystalline form is possible. The cyclobutane ring (Plane 2) is very slightly puckered in shape and possesses a dihedral angle between the planes through C(2), C(7), C(6) and through C(2), C(3), C(6) of only 0.2°. Taking into account the estimated standard deviations (shown in Figure 12) for the perpendicular displacements from least-squares planes for Plane 2, the cyclobutane ring of (208) may be perfectly square planar in geometry, in accord with the four 90° angles (within e.s.d. - see Appendix A) also found for this ring.

It is known that crystalline cyclobutane systems possessing a crystallographic centre of symmetry are constrained to planarity because of crystal packing forces [150]; however, the transoid structure (208) lacks such a symmetry feature for the central cyclobutane ring

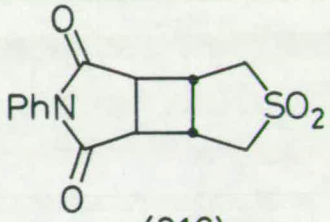
and hence the planarity of this ring can be largely attributed to the constraining effect of cis-fusion to two other strained rings. Although cyclobutane itself is known to exist in the less strained puckered form (displaying a dihedral angle of ca 30°), fusion to two other cyclobutane rings as in the cisoid and transoid isomers of



(314)



(315)



(316)

tricyclo[4.2.0.$0^{2,5}$]octane (314) causes restriction in the puckering of the central cyclobutane ring (dihedral angle of 8-9°) even in the gas phase where, of course, no crystal packing forces can operate[151]. It is therefore not surprising that the related tricyclic sulpholane structure (208) possesses a planar cyclobutane ring when, in addition to the constraining effect of two fused rings, further restriction to puckering imposed by lattice forces are also present.

On comparison of the carbon-carbon bond length of cyclobutane (1.548 Å [152]) with those of the cyclobutane ring of (208) (Figure 11), it is evident that the greater length of these bonds in the latter system is a reflection of the greater strain imposed upon the ring. Such an increase in bond length of a cyclobutane ring fused to two other strained rings compared to the corresponding non-fused counterpart is a general finding[150], occurring in the pentacyclic structure (315)[153], for example.

Examination of the data refering to the cyclobutene ring (Plane 3 in Figure 12) indicates that this is also bowed in shape, and has much in common, as regards bond dimensions (excepting the ring fusion carbon-carbon bond), with the bicyclic analogue (63)

(Figure 13)[154]. Both (208) and (63) exhibit geometries for the cyclobutene moiety not dissimilar to that of cyclobutene[155] itself, apart from a shortening of the olefin bond in the former two systems compared to cyclobutene (1.342 Å) as a consequence of the fusion of the cyclobutene ring to another ring structure.

Comparison of the dimensions of the sulpholane ring of (208) (Figures 11 and 12) with those of the related systems (63) (Figure 13)[154] and the transoid phenyl imide (316)[35] indicates all three to be rather similar. Viewing structure (208) laterally (Figure 14) highlights the puckering of the sulpholane ring, as a consequence of which the intramolecular separation of the two oxygen atoms and the olefinic group are significantly different [O(2)-C(4) separation of 4.652 Å c.f. O(1)-C(4) separation of 6.110 Å].

The alternative cisoid isomer (209) is in physical form a colourless crystalline material, m.p. 32-36°C. As a result of the difficulty of obtaining this isomer in solid form, no crystals suitable for X-ray structural determination could be realised. However, in the absence of comparable crystal structure data for the cisoid isomer some information regarding the relative strengths of packing of molecules within the crystal of each isomer may be deduced from consideration of the respective melting points. Thus, a much lower melting point (by ca 75°C) for the cisoid isomer (209) is a reflection of weaker intermolecular interactions within the crystal lattice compared to the transoid isomer (208). The geometry of the cisoid molecule, in which the sulphone group is forced close to the olefinic double bond (a separation of ca 2.0 Å between the endo oxygen and the olefinic carbons is apparent from an inspection of a Drieding model), may hinder the accessibility of the sulphone groups in neighbouring molecules to one another, resulting in weak intermolecular

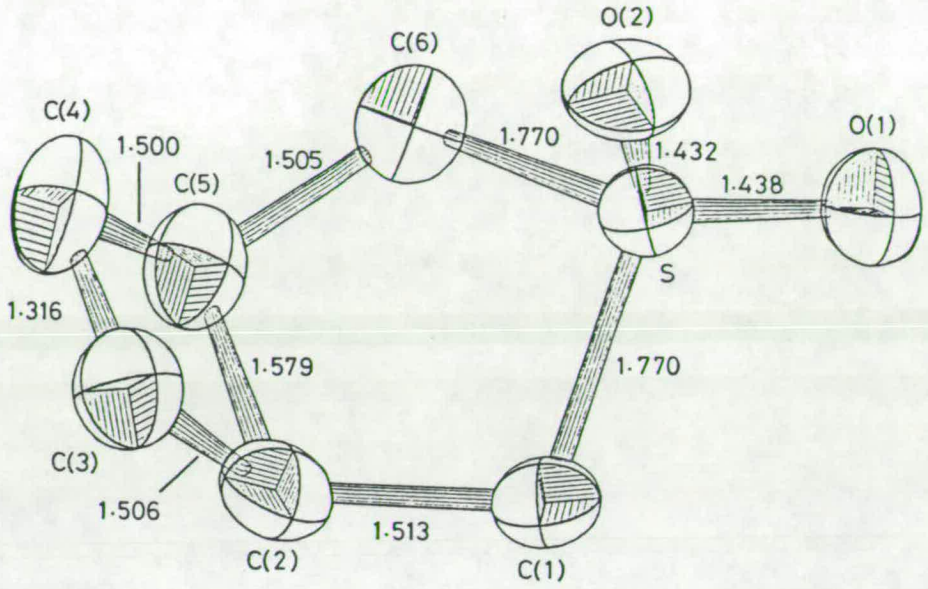
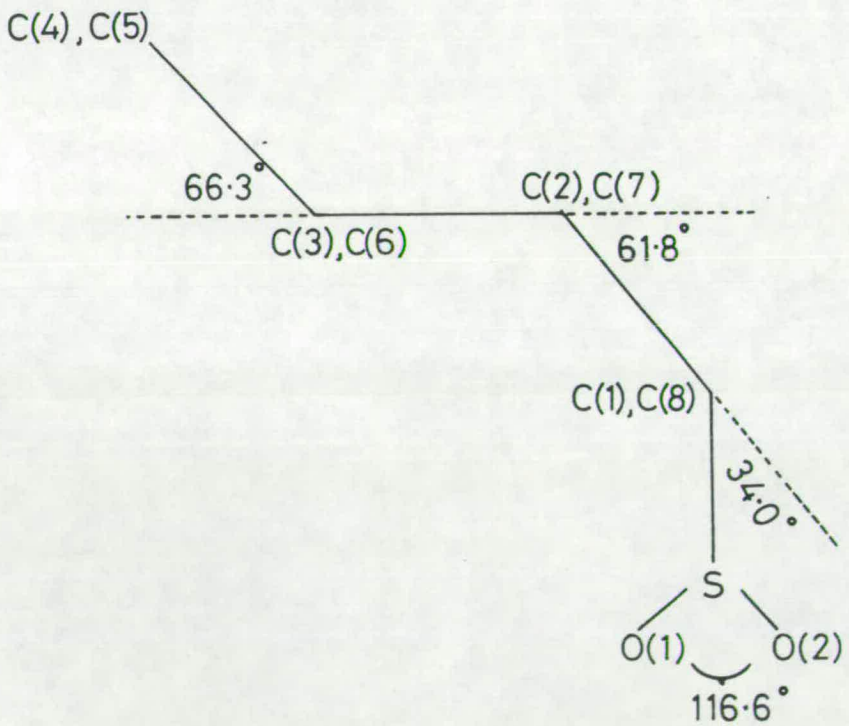


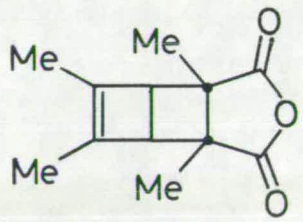
Figure 13 : Perspective representation of (63)

Figure 14 : Lateral view of the molecular structure of (208)



bonding within the crystal. A comparatively small amount of thermal energy would be required to cause the change of state from solid to liquid, by disruption of these weak intermolecular forces, for the cisoid isomer (209) compared to the transoid isomer (208) in which strong intermolecular forces operate.

Literature precedents indicate that in general for isomeric pairs of tricyclo[5.2.0.$0^{2,6}$]non-8-ene systems the cisoid isomer melts at a significantly lower temperature than the transoid isomer. Thus for system (313), the transoid isomer (m.p. 151-152°C [107]) melts at considerably higher temperature than the cisoid isomer (m.p. 136°C [119]); a similarly large differential exists in the reported[109] melting points



(317)

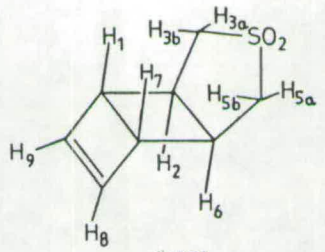
of transoid (317) (150-151°C) and cisoid (317) (100-101°C). Again, these findings indicate that stronger interactions between molecules in the crystal lattice are possible for the more open transoid, as opposed to cisoid, molecular geometry.

3. Spectral characteristics

a. ^{1}H and ^{13}C NMR spectra

i. Of the transoid isomer (208)

As is often found for apparently simple cyclic systems, the ^{1}H NMR spectrum of the transoid sulpholane (208) (Figure 15) is found to be very complicated as a result of the non-equivalence of ring protons, and due to complex couplings between these. In order to



(208)

$J_{1,2}(J_{6,7}) = J_{1,6}(J_{2,7}) =$
$J_{1,9}(J_{7,8}) = 1.2$ Hz
$J_{1,8}(J_{7,9}) = 1.4$ Hz
$J_{2,3a}(J_{5a,6}) = 8.7$ Hz
$J_{2,3b}(J_{5b,6}) = 2.6$ Hz
$J_{2,5a}(J_{3a,6}) = 1.2$ Hz
$J_{3a,3b}(J_{5a,5b}) = 13.9$ Hz

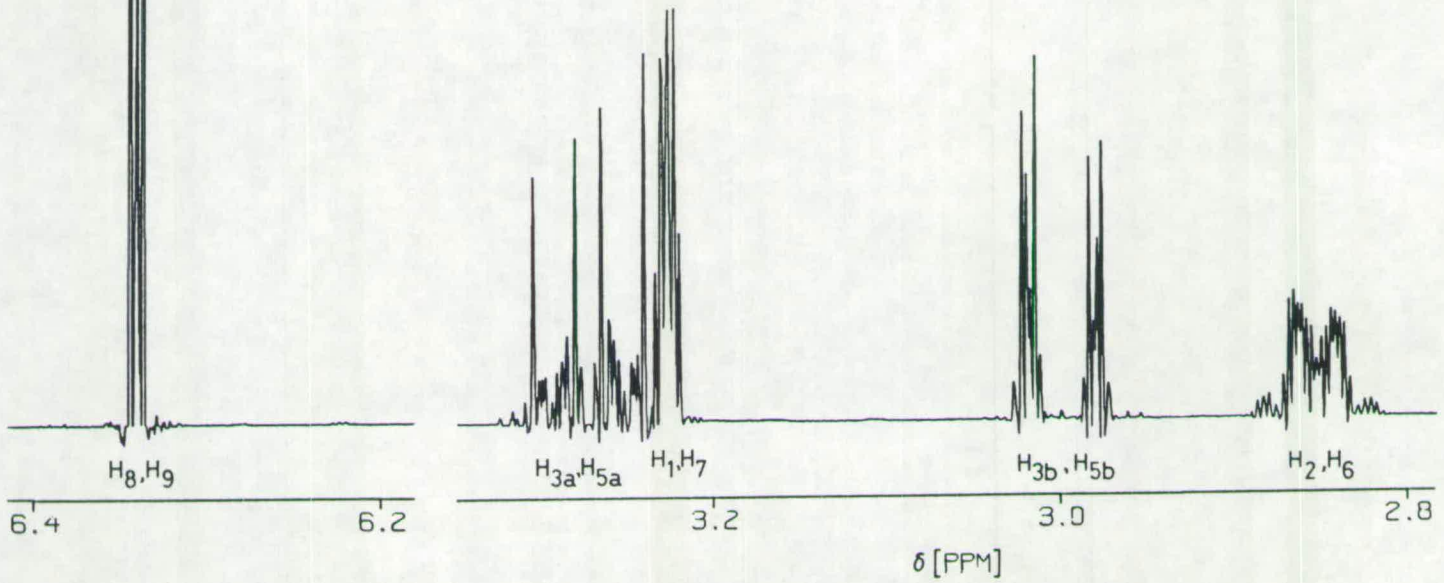


Figure 15 : Expanded ^1H NMR spectrum (360 MHz) of (208)

assign the various signals to protons within (208), and to identify and quantify the coupling constants present, the series of selective ^1H NMR experiments displayed in Figure 16 was carried out. On the basis of these, all of the signals were unambiguously assigned to protons and a large number of coupling constants were evaluated, as shown in Figure 15.

As final confirmation of these assignments, a NOE enhancement study of the proton spectrum was conducted. On irradiation of the signal due to the methylene sulpholane protons H_{3a},H_{5a} (δ3.27) a 13% enhancement of the H_{3b},H_{5b} (δ3.00) signal was observed, in accord with the close spacial arrangement of these geminal protons. Following irradiation of the highest field signal (δ2.85), assigned to methine sulpholane protons H_2,H_6 , enhancements in the signals at δ3.27 due to H_{3a},H_{5a} (4%), and at δ6.34 due to the olefinic protons H_8,H_9 (1%) were found. These observations were in full support of the previous assignments of signal to protons for <u>transoid</u> structure (208).

Having unambiguously assigned each resonance in the proton spectrum, the relationship between the structure of the <u>transoid</u> isomer (208) and the position of each proton signal in the spectrum can be commented upon. The olefinic protons H_8,H_9 resonate at δ6.34, a position which is at lower field than the majority of olefin signals but which falls within the typical range of such protons in strained cyclobutene systems[156]. Protons positioned α to the sulphone group are known to appear within the range δ2.5- δ3.1 [104], and methylene protons present in a sulpholane ring resonate at lower field, typically δ2.7- δ3.4. With respect to the spectrum of (208), the methylene sulpholane proton pairs H_{3b},H_{5b} (δ3.00) and H_{3a},H_{5a} (δ3.27) therefore lie within expected values.

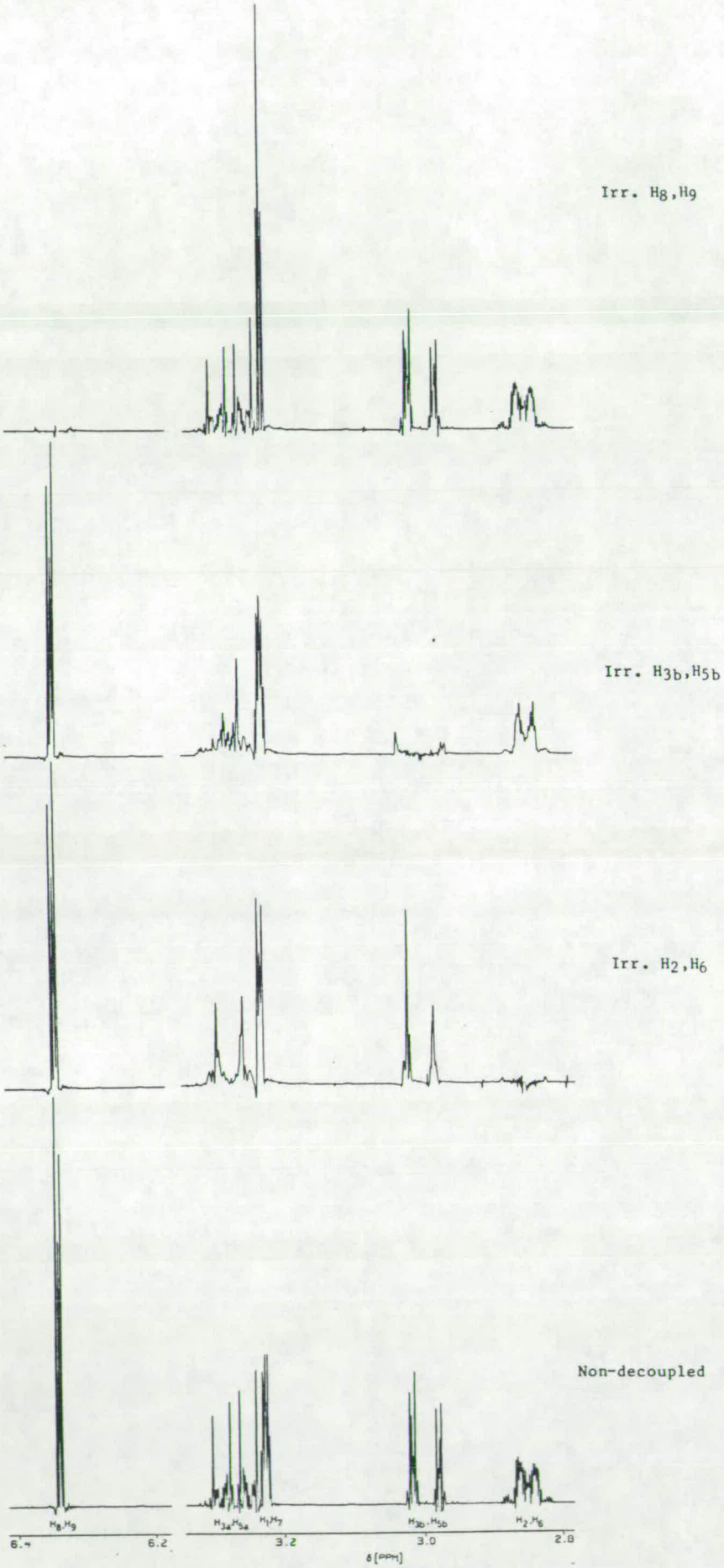


Figure 16 : Selectively decoupled ^{1}H NMR spectra of (208)

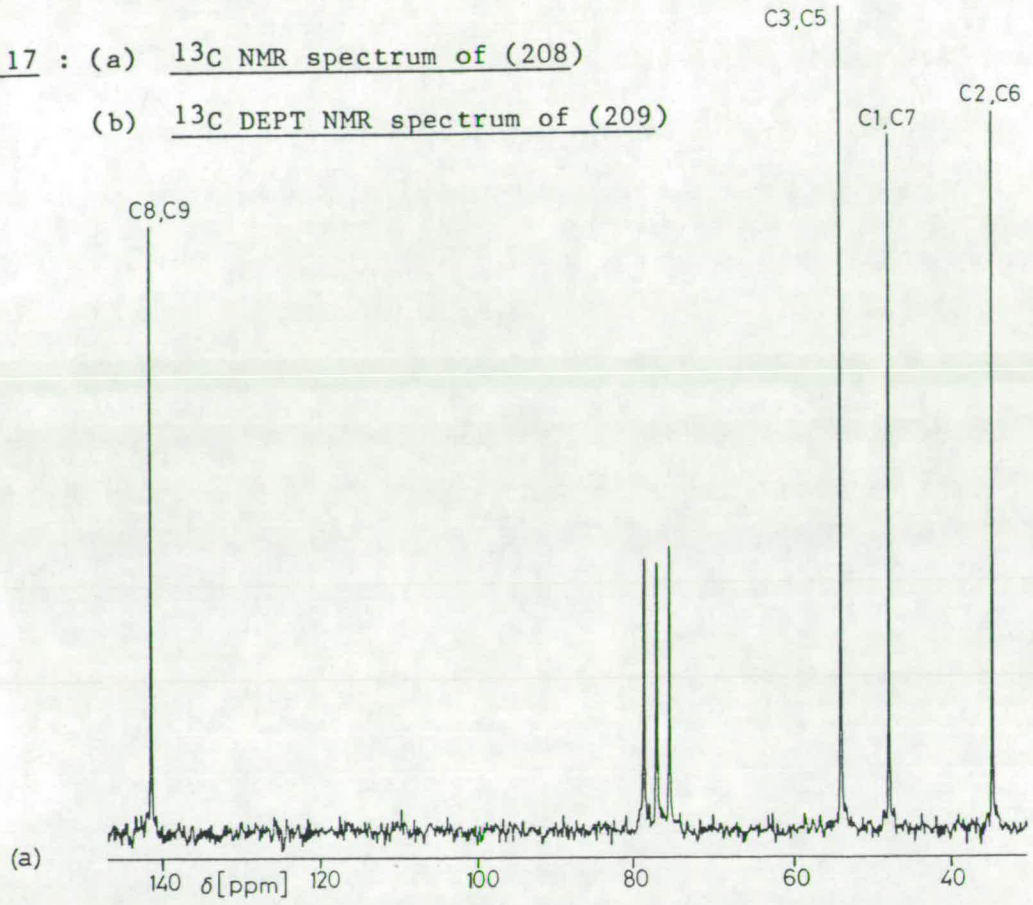
The relative deshielding of the signal due to H_{3a},H_{5a} compared to that of H_{3b},H_{5b} may be accounted for by a repulsive, mutually deshielding, interaction between the spacially proximate H_{3a},H_{5a} and H_2,H_6 protons. Thus, van der Waals repulsion between the electron clouds forming the neighbouring carbon-hydrogen bonds leads to a distortion in the electronic environment of each hydrogen atom, causing an observed shift (compared to expected values) to lower field for both interacting hydrogen atoms. Evidence for the presence of this effect with respect to the positions of H_{3a},H_{5a} and H_2,H_6 can be found in the large value of $J_{2,3a}$ ($J_{5a,6}$) = 8.7 Hz, which implies a small vicinal dihedral angle between these protons; rather convincingly, the significant mutual NOE enhancement (4%) observed on irradiation of either of the H_{3a},H_{5a} or H_2,H_6 signals is in accord with a close spacial relationship between the H_2,H_{3a} and H_{5a},H_6 proton pairs, and hence in accord with the operation of a mutually repulsive deshielding interaction between these.

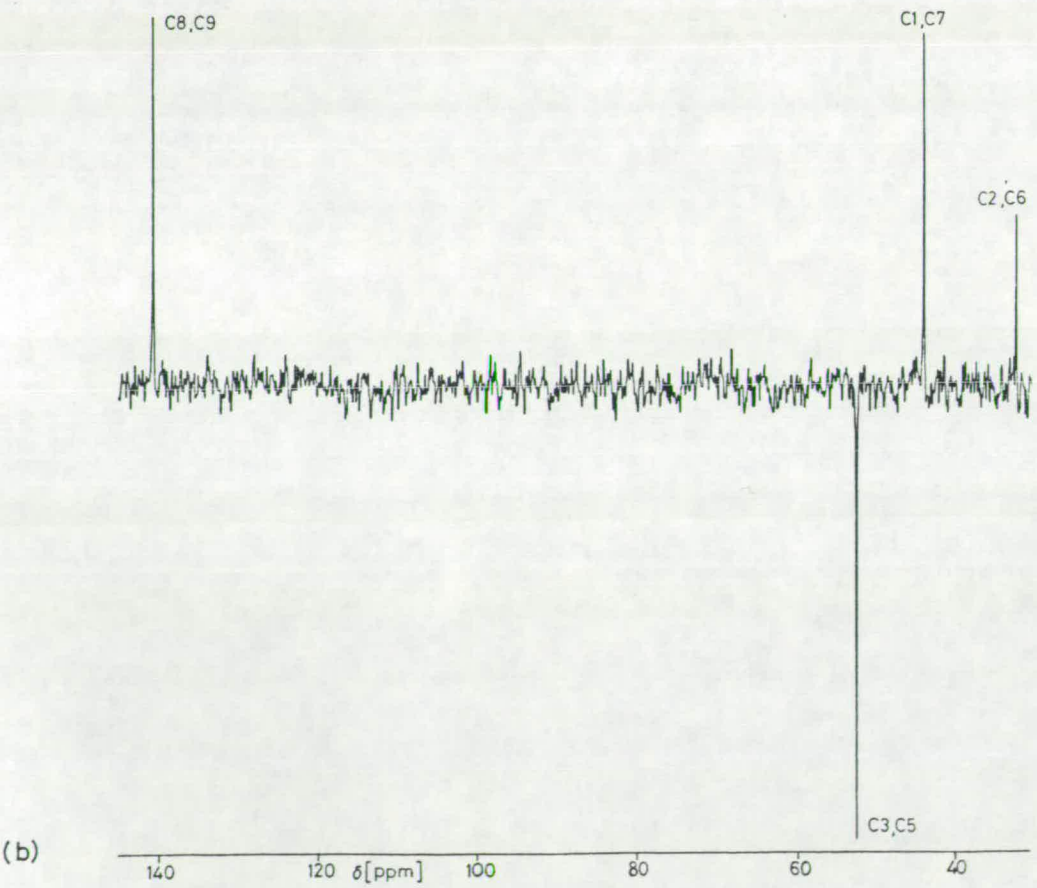
The deshielded position of the cyclobutene ring fusion protons H_1,H_7 (δ 3.22) relative to those of H_2,H_6 (δ 2.85) reflect the allylic position of the former pair within the transoid structure (208). Incidentally, the small value of $J_{1,2}$ ($J_{6,7}$) = 1.2 Hz reflects the trans relationship between the proton pairs H_1,H_7 and H_2,H_6 (since trans vicinal coupling constants across a rigid cyclobutane ring are known to be less than 5 Hz in magnitude - see p.73) expected for the transoid disposition of the three rings in (208).

Consideration of the ^{13}C NMR spectrum of (208) (Figure 17) indicates that the four carbon resonances appear at expected values. Thus, the signal at highest field may be assigned to the cyclobutane-sulpholane ring-fusion carbons C2,C6, with the allylically deshielded cyclobutane carbons C1,C7 resonating at lower field (δ 47.85). The

Figure 17 : (a) ^{13}C NMR spectrum of (208)

(b) ^{13}C DEPT NMR spectrum of (209)



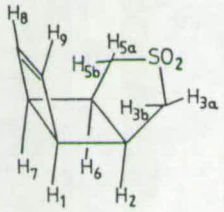


sulpholane methylene carbons C3,C5 at δ 53.96 are typical of such resonances and their deshielded position is a consequence of the strongly electron-withdrawing nature of the sulphone group.

ii. Of the cisoid isomer (209)

Comparison of the ^{13}C DEPT NMR spectrum of the cisoid tricyclic sulpholane (209) (Figure 17) with that of the transoid isomer (208) indicates that the two structures give carbon resonances which are very similar in terms of chemical shifts. The insensitivity of the carbon spectra to the basic structural differences between the two isomers contrasts strongly with the very different ^{1}H NMR spectra of the cisoid (Figure 18) and transoid (Figure 15) isomers.

Selective ^{1}H NMR decoupling studies (Figure 19) carried out on each signal in the proton spectrum of (209) enabled complete assignment of signals to protons to be made, and in addition allowed ready identification and evaluation of the various coupling constants present, as detailed in Figure 18. As a final check on the validity of the signal to proton assignments, NOE enhancement spectra (Figure 20) were obtained. Irradiation of the sulpholane methylene protons H_{3b},H_{5b} (δ 2.86) caused a strong enhancement (17%) in the geminally coupled methylene protons H_{3a},H_{5a} (δ 3.11), as expected. Additionally a significant enhancement (5%) in the olefinic protons H_8,H_9 (δ 6.39) was observed, and this finding supports the folded cisoid structure of this isomer in which the methylene protons H_{3b},H_{5b} are located spacially close to the olefin moiety. Similarly, irradiation of H_{3a},H_{5a} caused a reciprocal strong enhancement for protons H_{3b},H_{5b}. The close proximity of sulpholane methine protons H_2,H_6 (δ 3.28) to methylene protons H_{3a},H_{5a}, and also to cyclobutene ring fusion protons H_1,H_7 (δ 3.48) was



(209)

$J_{1,2}(J_{6,7})$ = 5.0 Hz
$J_{1,6}(J_{2,7})$ = 2.5 Hz
$J_{1,8}(J_{7,9})$ = 1.7 Hz
$J_{1,9}(J_{7,8})$ = 1.4 Hz
$J_{2,3a}(J_{5a,6})$ = 7.2 Hz
$J_{2,3b}(J_{5b,6})$ = 7.2 Hz
$J_{2,5a}(J_{3a,6})$ = 2.2 Hz
$J_{2,5b}(J_{3b,6})$ = 2.3 Hz
$J_{3a,3b}(J_{5a,5b})$ = 13.1 Hz

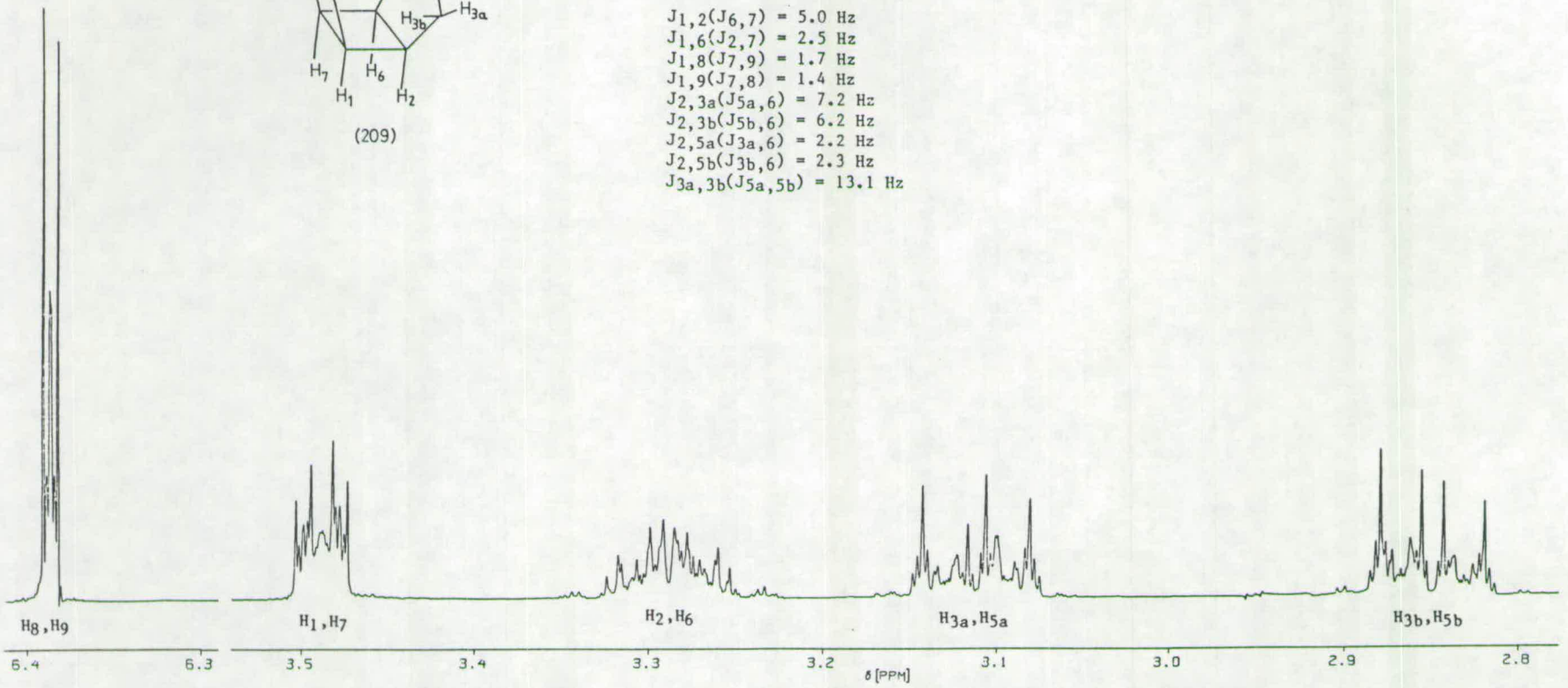


Figure 18 : Expanded ^1H NMR spectrum (360 MHz) of (209)



Figure 19 : Selectively decoupled ^{1}H NMR spectra of (209)

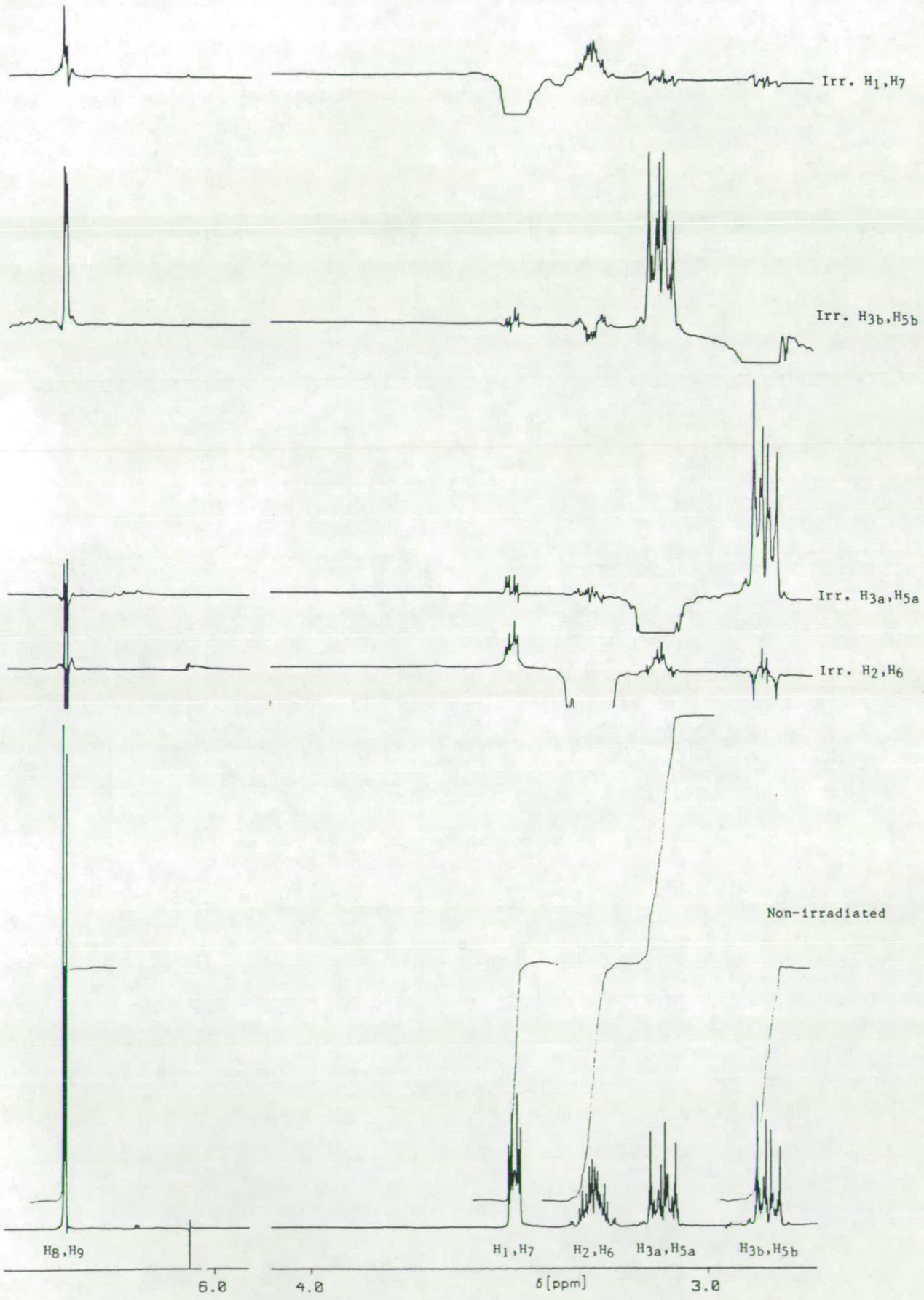


Figure 20 : NOE enhancement ^{1}H NMR spectra of (209)

apparent on irradiation of the H_2,H_6 signal; following irradiation of H_1,H_7 an enhancement of the olefinic protons H_8,H_9 was observed. Taken as a whole, the NOE enhancements completely vindicate the previous signal to proton assignments and support the cisoid geometry of the system (209).

The effect of the cisoid structure of (209) in determining the chemical shifts of the various protons present, and a comparison of these and associated coupling constants with their equivalents in the transoid isomer (208), is now considered. For the cisoid isomer the two pairs of cyclobutane protons H_1,H_7 and H_2,H_6 which both feature the cis vicinal cyclobutane coupling $J_{1,2}$ ($J_{6,7}$) = 5.0 Hz [cf. transoid isomer (208) in which the trans vicinal cyclobutane coupling constant $J_{1,2}$ ($J_{6,7}$) = 1.2 Hz], resonate respectively at ca 0.25 δ and 0.45 δ lower field than the corresponding protons in the transoid isomer. This difference appears largely to result from a mutual deshielding of these proton pairs in the cisoid isomer due to steric interaction of the four cis-disposed protons across the cyclobutane ring, a feature absent in the transoid isomer.

Although a similar magnitude of geminal coupling constant $J_{3a,3b}$ ($J_{5a,5b}$) is present for both isomers, the chemical shifts of protons H_{3a},H_{5a} and H_{3b},H_{5b} with which these are associated are significantly different in the two isomers. It is observed in the spectrum of the cisoid isomer (Figure 18) that H_{3b},H_{5b} and H_{3a},H_{5a} are both relatively shielded, by ca 0.15 δ and 0.20 δ respectively, when compared to their transoid counterparts (Figure 15). The shielding of H_{3b},H_{5b} in the cisoid structure may arise from the protrusion of these protons into the shielding region associated with the anisotropic cyclobutene double bond[157] for this isomer, which obviously cannot occur in the transoid structure. A combination of

this effect and a steric deshielding of H_{3a},H_{5a} due to interaction with H_2,H_6 accounts for the relatively deshielded position of H_{3a},H_{5a} (by ca 0.25 δ) compared to H_{3b},H_{5b} in the spectrum of the cisoid isomer.

The difference in chemical shifts of the H_{3a},H_{5a} protons between the two isomers appears to be a result of a greater steric repulsive interaction between these protons and H_2,H_6 in the transoid isomer. Justification for this reasoning can be found in a comparison of the NOE enhancement strengths found between H_{3a},H_{5a} and H_2,H_6 in each isomer: a larger enhancement (4%) is found for the transoid isomer compared to the cisoid (2%) under similar irradiation conditions, which indicates that the proton pairs are closer in space, and hence will undergo stronger mutual repulsion with consequent effect on chemical shift values, for the transoid isomer. Further evidence in support of these statements emerges following a comparison of $J_{2,3a}$ ($J_{5a,6}$) for each isomer: in the transoid case a value of 8.7 Hz reflects a very small dihedral angle between H_2 (H_6) and H_{3a} (H_{5a}) which in turn indicates that these protons will be closer in space, and hence undergo greater mutual steric deshielding interactions, than in the cisoid isomer where a larger dihedral angle is present [$J_{2,3a}$ ($J_{5a,6}$) = 7.2 Hz].

Interestingly, a much greater value for $J_{2,3b}$ ($J_{5b,6}$) = 6.2 Hz in the cisoid isomer is indicative of a fairly small dihedral angle between these protons compared to the situation in the transoid isomer where $J_{2,3b}$ ($J_{5b,6}$) = 2.6 Hz. This finding may be interpreted as resulting from a steric repulsion between H_{3b},H_{5b} and the olefinic protons H_8,H_9 in the cisoid isomer which forces the methylene protons out of the more favourable geometry exhibited by the corresponding protons in the transoid isomer; the fairly strong NOE enhancement (5%)

between H_{3b},H_{5b} and H_2,H_6 in the cisoid isomer furnishes supporting evidence for this effect. The steric deshielding also expected to occur for H_{3b},H_{5b} in the cisoid isomer as a result of this interaction with the olefinic protons is not realised since it is more than offset by the shielding effect of the olefin system, as discussed earlier.

b. Infrared characteristics

The presence of the sulphone group in a system is immediately obvious from examination of the infrared spectrum which displays two characteristic strong absorptions in the ranges 1300-1320 cm^{-1} and 1140-1160 cm^{-1} due to the asymmetric and symmetric stretching modes, respectively, of this group[104]. For the vast majority of sulpholane ring systems described herein, the sulphone group is found to exhibit bands at slightly altered positions, within the ranges 1290-1315 cm^{-1} and 1110-1145 cm^{-1}. Both the transoid (208) and cisoid (209) sulpholanes conform to these specifications: they both display the asymmetric sulphone stretch at 1297 cm^{-1}, and the symmetric stretch is observed at 1136 cm^{-1} for the cisoid structure, and at 1142 cm^{-1} for the transoid system. Each isomer exhibits weak bands characteristic of the cyclobutene ring, the symmetric and asymmetric olefinic carbon-hydrogen bond stretches of which are known[156] to absorb at ca 3048 and 3126 cm^{-1}, respectively. In accord with these values, the cisoid isomer (209) displays weak absorptions at 3032 and 3100 cm^{-1}, while the transoid system (208) gives these bands at 3023 and 3092 cm^{-1}. With respect to the infrared spectrum as a whole, both isomers show similar positions and intensities for a substantial portion of the spectrum, in accord with their structural similarities, with differences in the spectra most noticeable in the region below 1000 cm^{-1}.

c. Mass spectral characteristics

Isomeric pairs (such as the cisoid and transoid isomers (209) and (208)) are known to give mass spectra which exhibit very similar fragmentation patterns as a consequence of the insensitivity of simple (electron-impact) mass determinations to detection of stereochemical differences between isomers. In agreement with this generality, the tricyclic isomers (208) and (209) demonstrate very similar fragmentation pathways not only to each other, but also to the ring-opened bicyclic isomer (212). The strong links between mass spectral and FVP fragmentation pathways (see p.45) are again substantiated in this case as it is found that on FVP under fairly mild conditions both (208) and (209) undergo thermal ring opening to bicyclic sulpholane (212) (described in greater detail in a later section). An analogous ring opening process operating under mass spectral ionisation conditions upon (208) and (209) would explain the strong similarities between the mass spectra of both of these and that of (212).

In detail, all three isomers exhibit weak parent ions at m/e 170, and higher intensity peaks at m/e 105 and 104 corresponding respectively to loss of $H^{\bullet}$, SO_2 and H_2, SO_2 from the parent ion. Such fragmentations are commonly encountered in the electron-impact mass spectra of sulpholane systems. High intensity peaks corresponding to the formation of aromatic fragments were found in each case: the most intense peak at m/e 91 was accorded to the benzyl cation, and related peaks at m/e 92, 79 and 78 were in accord with aromatic cationic species. Once again, a parallel between mass spectral and FVP behaviour may be drawn: all three isomers (208), (209) and (212) are found on high temperature FVP to form largely aromatic products (including o-xylene, styrene, toluene and benzene) which are also

associated with the electron-impact mass spectral fragmentation patterns of these compounds.

4. Comparison of the olefin reactivities of transoid (208) and cisoid (209) isomers of 4-thiatricyclo[5.2.0.$0^{2,6}$]non-8-ene 4,4-dioxide

a. Background

The effect of the two geometries of (208) and (209) upon the olefin reactivity of the systems is now considered. In the transoid isomer (208), the large separation between the sulphone and olefin moieties would indicate that the reactivity of the latter should be comparable to that of the electron-rich olefin cyclobutene. As described in the preceeding section, the reactivity of (208) towards 1,3-dipoles, dienes and various electrophilic reagents was that typical of an electron-rich olefin; the transoid geometry of (208) was found to direct the stereochemistry of the products towards the most kinetically accessible and thermodynamically stable possibilities.

Consideration of the close proximity of the olefinic double bond and the sulphone group in the cisoid isomer (209) in the light of literature precedents (discussed below) regarding orbital interactions through space indicates that a considerable modification of the electron-availability (and hence reactivity) of the olefin group is feasible. Before discussing this effect in detail with regard to (209), an explanation of the concept of 'through-space' interaction, and the effect of this upon reactivities of cyclic olefins, and in particular of unsaturated cyclic sulphone systems, is now considered.

b. Through-space interactions

i. In cyclic olefins

The concepts of 'through-bond' and 'through-space' (described as 'non-bonding'[158]) interactions between two localised electron pairs separated by several σ bonds was first disclosed by Hoffmann[159] in 1971. Through-bond or inductive interactions concern the non-spacially directive interactions of two localised atoms or groups, containing lone pairs of electrons or a π-system, through the intervening σ bond framework. This relay effect is found to decrease in strength as the number of intervening σ bonds increases, being negligible for situations where there is greater than eight intervening σ bonds[160,161].

Through-space interactions depend upon the direct overlap through space of orbitals associated with lone pairs of electrons or π systems. Consequently, through-space effects are considered[161] to be negligible for systems with interorbital separations in excess of 3 Å. Through-bond and through-space interactions can be stabilising or destabilising with respect to the interacting groups, this being dependent upon the ordering and filling of the mixed orbital set. In addition, Paddon-Row[161] has demonstrated experimentally the operation of the 'parity rule' which states that through-space and through-(nσ) bond interactions will reinforce each other for n even, and be mutually antagonistic for n odd.

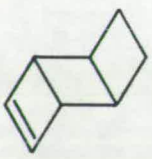
Since both types of interaction arise from mixing of the relevant orbitals either directly through space or relayed through a σ-bond framework, ultra-violet photoelectron spectroscopy (UV-PES), which permits a measurement of orbital energies, is widely used in the quantification of such interactions. Thus, a comparison of the

vertical ionisation potential (Ip), which may be obtained from study of the UV photoelectron spectrum, of a system containing both through-bond and through-space interactions with the Ip of a related non-interacting system may permit a measurement of the combined through-bond and through-space interactions. In the case of butadiene sulphone which is known[95] to possess an olefinic πIp = 10.35 eV (corresponding to the π HOMO energy level), this value can be compared to that of the hydrocarbon analogue, cyclopentene, for which πIp = 9.18 eV [162]. The difference of 1.17 eV is a numerical indication of the effect of the combined through-bond and through-space interactions on the availability of electrons in the olefin group of butadiene sulphone. This is predicted and found to be an electron-deficient olefin and hence less reactive towards electrophilic species than cyclopentene[95]. In the structure of butadiene sulphone only two σ bonds (ie n = 2) separate the interacting olefin and sulphone groups and consequently the through-bond effect is expected to predominate over the (reinforcing) through-space effect.

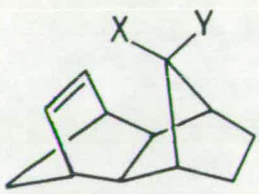
Obviously the above numerical assessment of the effect of through-bond and through-space interactions is at best a rough approximation, and suffers from an inability to quantify the relative contribution of each effect to the total. However, in the situation where two geometrical isomers, such as the cisoid (248) and transoid (249) tricyclo[4.2.0.$0^{2,5}$]nona-3,7-diene isomers, differing only in the absence of a through-space effect in one isomer (249), the relative contributions of each effect in the alternative isomer (248) can be quantified. Since the two isomers have olefin groups separated by a very similar framework of σ bonds (n = 3), the through-bond effect in each can be considered equal, and the measured difference[163] in electron availability between (248) and (249) of 0.12 eV (acting to

stabilise the π systems of (248)) reflects the through-space effect which cannot operate within the transoid structure (249) due to the large spacial separation ($>>3$ Å) of the two π systems. A value for the through-bond interaction in (249) of 0.29 eV (acting to destabilise the olefin system) was available from π Ip data[163] of this system and the mono-olefin (318), thus allowing a reasonably accurate quantification of the mutually antagonistic through-space (+0.12 eV) and through-bond (-0.29 eV) effects operating in the cisoid isomer (248).

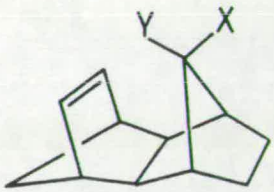
The situation is more complicated than this analysis suggests because the through-bond interactions are not equivalent in the isomers (248) and (249). It is known[161] that the strength of through-bond interactions is dependent on the geometry of the σ-relay between the interacting groups, and this is maximised by an all-trans arrangement (ie 'W' in geometry) of σ bonds between them. This 'trans-effect' predicts a stronger through-bond interaction for the transoid isomer (249) than for the cisoid isomer (248). Incidentally, it is the small value of n for (248) that results in the predominant interaction in the system being through-bond rather than through-space, and the two operate in mutual antagonistic senses since n is an odd number.



(318)



(319)



(320)

X = OMe, OH, H; Y = H or X, Y = O

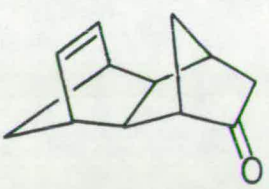
Recent elegant work by Paddon-Row and co-workers[164,165,166] into the correlation of ionisation potentials with reactivity of diastereomeric pairs has contributed much to the understanding of

through-space effects in cyclic olefin systems. A series of related octahydrodimethanonaphthalene structures (319) were prepared with the objective of evaluating the effect of the through-space interaction between the olefinic double bond and the spacially close (though remote in through-bond terms) group X. Comparison of the olefinic πIp of (319) with that obtained from the diastereomeric structure (320), in which the groups X and Y are reversed compared to (319), gave a value for the through-space effect on the π system in (319) as a result of orbital overlap with X. The πIp for system (320) was considered to be influenced only by a through-bond interaction (since the group X, potentially capable of undergoing orbital overlap through space, lies outwith the 3 Å maximum distance over which this effect can operate) and this could be assessed by comparison of the πIp of (320) with the hydrocarbon (319 or 320; X = Y = H). For all cases in which n = 5, the through-bond effect was found to be no greater than 0.03 eV and therefore insignificant compared to the magnitude of the through-space interaction[166].

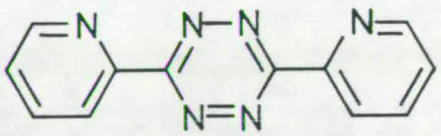
Variation of the nature of the group X resulted in a measured (UV-PES) stabilisation or destabilisation of the olefin group in (319). Thus, for the ether (320; X = OMe, Y = H) a πIp of 8.64 eV when compared to the standard hydrocarbon (320; X = Y = H), πIp = 8.65 eV, allows a value of 0.01 eV to be accorded to the through-bond effect. The diastereomer (319; X = OMe, Y = H), which is expected to also possess a negligibly small through-bond effect, with a measured πIp = 8.28 eV therefore demonstrates a through-space interaction of magnitude 0.36 eV, acting to enhance the electron availability of the π system (ie to destabilise it). As a consequence of the through-space interaction between the π system and the ether oxygen lone pair in (319; X = OMe, Y = H), the resultant mixed molecular orbitals

are found at lower and higher energies respectively compared to the unmixed oxygen lone pair and π olefinic system orbitals of the diastereomer (320; X = OMe, Y = H). As the lower energy mixed orbital associated with the through-space interaction within (319; X = OMe, Y = H) cannot be detected amongst the plethora of orbitals at lower energy, it is the highest energy orbital (most easily identified from an examination of the UV-PES spectrum) that is chosen to form the basis of quantification of non-bonding interactions.

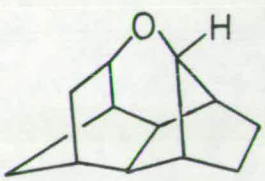
In contradistinction, the alcohol (319; X = OH, Y = H) demonstrated a high πIp = 9.01 eV, which on comparison with the πIp of (320; X = OH, Y = H) gave a through-space interaction of 0.36 eV acting to stabilise the olefin (ie make more electron deficient). The through-bond factor was again found to be negligible (0.03 eV). However, in the ketone (319; X,Y = O) the through-bond effect for this system, in which the olefin and carbonyl π systems are separated by a framework of only four σ bonds (n = 4), was much larger. Following comparison of the ionisation potentials of the olefin moieties of (319; X = Y = H), and (319; X,Y = O) and (321) by Paddon-Row et al[166], values for the reinforcing through-bond (0.1 eV)



(321)



(322)



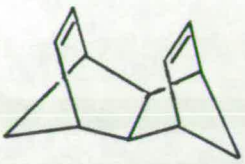
(323)

and through-space (0.24 eV) effects were determined for (319; X,Y = O), these acting to decrease the electron availability of the olefin group in this molecule.

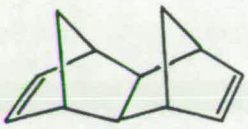
In relation to the reactivity of the olefinic moiety in the series (319) towards the Diels-Alder reaction with inverse-demand (electron-deficient) diene, the tetrazine (322), and towards an electrophilic reaction (epoxidation), a good correlation between electron availability (as measured by πIp values) and reaction rate was established[164,165]. Thus, the ether (319; X = OMe, Y = H), in which a strong through-space interaction resulted in increased electron availability of the olefin, demonstrated an enhanced reaction rate compared to the standard hydrocarbon (319; X = Y = H) towards these reactions with electron-deficient species. Both the alcohol (319; X = OH, Y = H) and the ketone (319; X,Y = O) demonstrated a slower rate in the Diels-Alder reaction with (322) than the hydrocarbon (319; X = Y = H) as a consequence of the electron-deficiency of the olefinic moieties resulting primarily from through-space interactions. Additionally the ketone (319; X,Y = O) displayed an expected slow rate of reaction towards epoxidation, but interestingly the alcohol (319; X = OH, Y = H) gave the bridged ether (323) on oxidation, rather than the expected epoxide. This was rationalised as occurring via a facile acid-catalysed process, and taken as confirmatory evidence for the close proximity of the alcohol group to the double bond in (319; X = OH, Y = H)[165].

The influence of through-space orbital overlap towards the reactivity of other unsaturated cyclic systems has been described. A much increased reaction rate towards Birch reduction of diene (324) compared to the isomeric structure (325) has been rationalised as being due to a through-space interaction in the former[167]. Electrophilic aromatic substitution reactions, notably nitration and bromination, are also demonstrably influenced by through-space effects. In this respect, the methanofluoranthene derivatives (326) were observed to

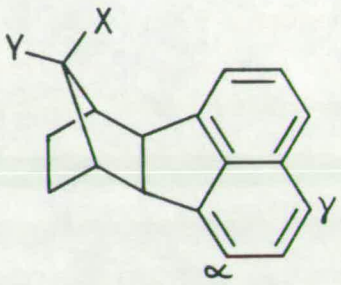
undergo nitration at the α - and β-positions with an ordering of reaction rates dependent upon the nature of the through-space



(324)



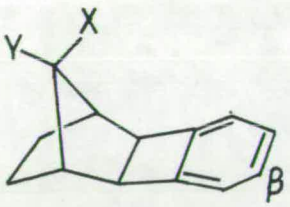
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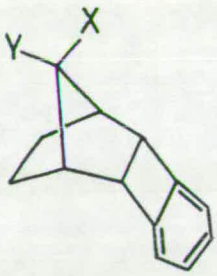
(326)

interaction between group X and the aromatic system[168]. In similar fashion to the order of reactivity of the series (319) to electrophilic species, the following sequence of reaction rates towards nitration was found for systems (326): X = OMe, Y = H > X = Y = H ~ X = H, Y = OMe > X,Y = O.

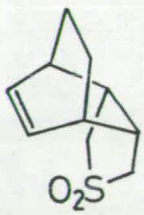
Bromination of a related series of substituted hexahydromethanobiphenyl (327) gave a parallel reactivity sequence to that of (326) towards nitration: for (327), bromination occurred exclusively at the β-position with the <u>syn</u> methoxy derivative (327; X = OMe, Y = H) undergoing reaction <u>ca</u> 10^2 times faster, as a result of a through-



(327)



(328)



(329)

space interaction between the methoxy and aromatic groups, than either the <u>anti</u> methoxy isomer (327; X = H, Y = OMe) or the parent hydrocarbon (327; X = Y = H)[169]. Conversely, the ketone analogue (327; X,Y = O)

was found to brominate ca 2 x 10^3 times more slowly than the hydrocarbon (327; X = Y = H) and ca 10^2 times more slowly than the isomeric ketone (328; X,Y = O) in which no through-space interaction is possible due to the remote disposition of the carbonyl and aromatic groups. Therefore an estimate of the effect on reaction rate of through-space deactivation of the aromatic ring of (327; X,Y = O) towards bromination of ca 2 x 10^2 compared to the parent hydrocarbon (327; X = Y = H) may be calculated[169]. Although the situation is less clear cut for those reactions such as bromination and nitration which involve charged transition states (due to complicating electrostatic factors), the effects of through-space interactions on electron availability and hence reactivity are still very apparent.

Through-space interactions may also manifest themselves as an alteration in the chemical shift of an interacting group compared to a corresponding non-interacting analogue. However, the change in chemical shift is often complicated by concomitant alterations due to changes in steric factors. For example, in the syn alcohol (319; X = OH, Y = H) the olefinic protons are found at 0.22δ lower field in the ^{1}H NMR spectrum than in the corresponding anti isomer (320; X = OH, Y = H)[170]. This appears to be a result of both reduced electron availability (by 0.36 eV) of the olefin system due largely to a through-space interaction with the hydroxy moiety[166], and additionally a steric deshielding effect due to the closer proximity of this bulkier group [compared to hydrogen as in (320; X = OH, Y = H)] to the olefin system. Conversely in the 'syn' methoxy system (319; X = OMe, Y = H) the olefinic protons are located at 0.31δ higher field than in the 'anti' analogue (320; X = OMe, Y = H)[165]. In this case the increased steric bulk of the methoxy substituent over hydrogen, which acts to cause deshielding of the olefinic protons in the 'syn'

isomer compared to the '*anti*' system, is more than compensated for by the large through-space interaction present which acts to increase the electron availability of the olefin system (by some 0.36 eV [166]) and thereby causes a net shielding of the olefinic protons in the ^{1}H NMR spectrum.

ii. *In cyclic unsaturated sulphone systems*

Systems reported to display through-space interactions between the sulphone group and an unsaturated centre are restricted to examples originating from these laboratories[95,171]. A number of cyclic olefinic sulphones have been shown, *via* analyses of their UV-PES spectra and determination of olefinic ionisation potentials, to demonstrate powerful through-bond and through-space interactions between the sulphone and olefin moieties. Sulpholenes such as butadiene sulphone (3-sulpholene) which was discussed earlier (see p.171), and 2-sulpholene (57) demonstrate strong through-bond effects due to the low number of σ bonds separating the interacting groups. However, most effort to date has been applied in connection with olefinic bi- and tricyclic sulpholane systems, in which the number of intervening σ bonds is greater ($n \geqslant 3$) and the sulphone and olefin groups are spacially proximate, encouraging strong through-space interactions.

The cyclobutene sulpholane (63) possesses an olefinic πIp = 10.25 eV which on comparison with cyclobutene (πIp = 9.43 eV [162]) indicates that (63) is in receipt of a combined through-bond and through-space effect of *ca* 0.82 eV. In accord with the parity rule, for system (63) in which n = 3 the two terms act in opposition to one another. Thus, the net stabilisation of the olefinic double bond reflects the difference between the through-space and through-bond

terms and since it is the latter term which is found to alternate with the parity of n, a value of 1.0 eV or more appears likely for the through-space interaction within (63). Analysis of the crystal structure of (63) indicates a closest oxygen - olefinic carbon distance of 3.23 Å [96] which is considerably larger than the previously determined maximum distance over which direct orbital overlap through space is thought to occur[161]. In light of this, the value for the through-space interaction in (63) is still more remarkable.

Other bicyclic and tricyclic sulpholane systems which have been examined include the cyclohexene sulpholane (65) and the bridged analogues (88) and (329). All demonstrate combined and reinforcing (n = 4) through-bond and space interactions resulting in an olefinic electron deficiency found to lie within the range 0.52-0.57 eV [95], on comparison of πIp's of these systems with that of cyclohexene. Since the four σ bond framework between the interacting groups in these systems contains an all cis arrangement of bonds, the through-bond element is liable to be small or zero, and subsequently the $\Delta\pi$Ip's found reflect purely the through-space effect. In terms of the consequences of the through-space interaction in these systems upon olefin reactivity, it has been experimentally demonstrated that (63), (65), (88) and (329) are markedly less reactive towards reaction with electrophilic species than the corresponding non-interacting systems. A trend between olefin ionisation potential, which is a measure of olefin electron availability, and reactivity towards epoxidation and to addition of nitrenes was clearly established[95,171].

c. Olefin reactivities of (208) and (209)

In the literature regarding through-space interactions between the sulphone group and an olefinic centre no isomeric pairs

analogous to the dienes (248) and (249), from which an assessment of the relative contributions of through-bond and through-space interactions upon the electron availability of the olefin moiety, have been described. However, the cisoid (209) and transoid (208) isomers present the first opportunity for such a study: the transoid isomer (208) due to its inherent geometry has a large separation between the interacting groups (a nearest oxygen-olefinic carbon distance of 4.652 Å is apparent from an analysis of the crystal structure of (208)) which precludes any through-space effect, with therefore only an expectedly small (since four σ bonds separate the interacting groups) through-bond interaction present. In contrast the cisoid isomer (209) with a similarly small through-bond interaction to that of (208) would be expected to demonstrate a strong and reinforcing through-space interaction between the sulphone and olefin groups which are estimated to be ca 2.0 Å apart from an inspection of a Drieding model. In consideration of the strong through-space effect operating over a distance of 3.23 Å in the bicyclic system (63) estimated to result in a stabilisation (electron-deficiency) of the olefin group of ca 0.82 eV, a stronger stabilisation of the order of 1.0 eV might reasonably be anticipated for the olefin moiety within the cisoid isomer (209).

Values for the effects of the through-bond and through-space interactions operating in (209) could be obtained, using the previously outlined procedure, from a knowledge of the olefin ionisation potentials of (208) and (209), in turn available from examination of the UV-PES spectrum. Regretfully, due to factors outwith the control of the author, UV-PES spectra for the transoid (208) and cisoid (209) systems, and for a number of other interesting unsaturated cyclic sulphones, could not be obtained. In the absence of ionisation

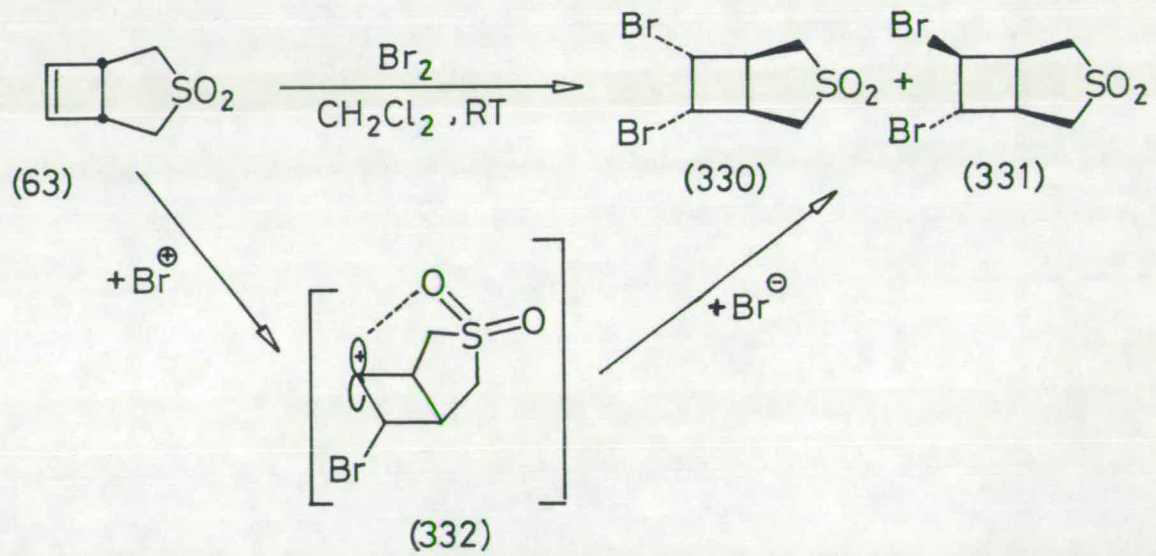
potential data for the tricyclic sulpholanes (208) and (209), the ^1H NMR spectrum of the latter was re-examined for any indication of the operation of a through-space effect. In other systems possessing a through-space interaction, ^1H NMR spectroscopy has proved useful in verifying the presence of such an effect (see p.177).

For the cisoid tricyclic isomer (209), the olefinic protons would expectedly be deshielded by both a steric interaction with the sulpholane methylene protons H_{3b},H_{5b} (as witnessed by a sizeable NOE enhancement observed between these signals) and by the electron-deficiency of the olefin group resulting from a through-space interaction with the sulphone group. However, in actuality a deshielding of only 0.05δ is present in the olefinic protons of (209) compared to those of the transoid isomer (208), in which neither of the above deshielding processes can operate. Similarly, a difference of only 0.01δ has been found[165,170] in the chemical shifts of the olefinic protons of the isomeric ketones (319; X,Y = O) and (321) in spite of a known large through-space deshielding effect operating on the olefinic system in the former. A possible explanation for these findings lies in the presence of a compensating shielding effect on the olefinic protons of (209) and (319; X,Y = O) as a consequence of the proximity of these protons to the shielding region associated with the anisotropic carbonyl[172] and sulphoxonyl groups.

Although no ionisation potential data or NMR evidence for the presence of a through-space interaction in olefin (209) was available, this effect should also be apparent from a study of the reactivity of the olefin group. As detailed in an earlier section, the reactivity of the transoid isomer (208) towards reactions of the olefinic double bond was found to be in accord with those of an electron-rich olefin. However, for the cisoid isomer (209) the presence

of a strong through-space interaction acting to reduce electron availability of the olefin moiety may be detected from a reduced reactivity towards electrophilic reagents compared to (208). As a consequence of the limited quantity of the cisoid isomer (209) available for such a study, only a single electrophilic reaction could be considered for a comparison between the two isomers (208) and (209).

The single comparative reaction chosen was that of bromination. This choice followed from the novel bromination course demonstrated by the through-space deactivated olefin (63) which underwent bromination in methylene chloride at room temperature slowly (due to the electron deficiency of the olefin group) to give an equimolar mixture of both cis (330) and trans (331) dibromide isomers[96]. This departure from the



normal anti mode of bromination is rare and has previously been restricted to olefins bearing α-conjugating substituents[173], or to Dewar benzene[174]. The presence of products resulting from both syn and anti modes of bromination of (63) has been rationalised by invoking the intermediacy of a carbonium ion (as opposed to the traditional cyclic bromonium ion) system (332) stabilised by a through-space

Coulomb interaction with the sulphone group. This intermediate then undergoes nucleophilic attack by bromide ion from either face of the system resulting in formation of both cis (330) and trans (331) dibromide isomers[96]. Interestingly, bromination of (63) in aqueous dimethoxyethane at room temperature gave only the trans dibromide (331) and this finding is believed to reflect removal of the directive influence of the sulphone group due to hydration[96].

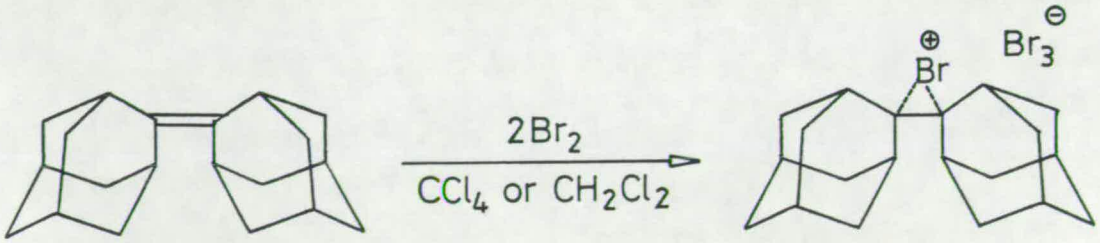
Extrapolation of the bromination behaviour of system (63) in non-aqueous solvents to the cisoid isomer (209), in which a stronger sulphone-olefin interaction is expected to take place, would lead to a prediction of increased syn bromination of the olefin moiety of (209). Prior to this reaction being attempted, the bromination of the transoid tricyclic olefin (208) was carried out (see p.142) and found to occur readily in methylene chloride solution (even at -78°C) to give a high yield of only the trans dibromide product (309), as expected for the reaction of an electron-rich olefin with bromine.

Treatment of a solution of the cisoid olefin (209) in methylene chloride at room temperature with 1.5 equivalents of bromine appeared to result in no immediate reaction on initial addition. However, 30 seconds or so after initial addition an orange solid precipitated. The puzzling insolubility of this product in methylene chloride, in contrast to the comparatively soluble trans dibromide (309) obtained on bromination of (208), was further compounded by its unstable nature, as demonstrated by a tendency to emit white fumes if left at room temperature for short periods. Following evaporation of the methylene chloride filtrate obtained from this reaction, considerable quantities of pure starting olefin (209) were recovered. Taking the weight of (209) recovered and the amount of bromine incorporated in the consumed olefin, it was apparent that the solid product was a

tetrabromide, rather than a dibromide, derived from (209). Although the small scale of the reaction and unstable nature of the brominated product prevented purification of this material, elemental analysis indicated it to be more consistent with a tetrabromide of molecular formula $C_8H_{10}Br_4O_2S$ (though the carbon content was found to be ca 2% lower than theoretical) than the corresponding dibromide.

A structural identification of the tetrabromide product was then sought. Although the product was insoluble in chloroform, it was found to dissolve readily in d_6-acetone to give an orange solution which decolourised after a few seconds. However, on examination of this solution by ^1H NMR spectroscopy the starting olefin (209) appeared to be the only compound present. The implication that the product had decomposed to regenerate olefin (209) and bromine, with the latter then reacting with the acetone solvent and hence decolourising, was vindicated following the identical results found on comparison of the volatile components of the dissolved reaction product in d_6-acetone with a standard sample prepared by addition of neat bromine to d_6-acetone. Addition of a measured quantity of methylene chloride to the 'product' solution allowed calculation of an 89% recovery of olefin (209) on consumed tetrabromide, thus furnishing substantiating evidence for the molecular formula of this material.

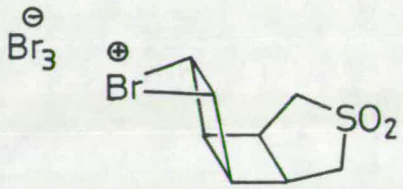
With regard to the bromination literature, only a single reported instance of an isolated and reasonably stable tetrabromide product resulting from bromination of a mono-olefin is available.



(333) (334)

Thus, bromination of adamantylideneadamantane (333) in carbon tetrachloride or methylene chloride solution has been described[175] as yielding the bromonium ion tribromide salt (334) as a yellow solid precipitate, the structure of which has recently[176] been confirmed by an X-ray crystal structure determination. The stability of the bromonium ion salt (334) appears to be a consequence of the severe steric congestion caused by the presence of the two blocking adamantane units. These prevent access of the tribromide counterion to the bromonium ring and hence prevent formation of the conventional dibromide product.

As the salt (334) displays a number of features in common with the tetrabromide derived from bromination of (209), a tentative assignment of this product to structure (335) is justified. In this



(335)

structure the proximity of the sulphone group to the bromonium ring might be expected to provide the same steric hindering effect as found for (334), preventing access of the tribromide counterion and thereby resulting in isolation of the salt (335) rather than a dibromide product. The features which the salt (334) and the tetrabromide derived from olefin (209) have in common are their near complete insolubility in halogenated solvents, their ability to undergo loss of bromine with generation of the starting olefin in bromine-acceptor solvents, and their similar behaviour to mass spectral determinations[175,176].

The electron-impact mass spectrum of (334) has been reported175 as exhibiting a strong peak characteristic of the olefin

(333), with further evidence for the presence of Br^+ and Br_2^+ fragments. Mass spectra for the tetrabromide product obtained from (209), possibly of structure (335), have been determined using a variety of mass spectral techniques, none of which demonstrated peaks corresponding to the molecular weight of a tetrabromide product such as (335). Positive ion fast atom bombardment (FAB) mass spectrometry gave an intense doublet at m/e 251, 249 in accord with the bromonium ion portion of structure (335). Negative ion FAB provided no evidence for the presence of tribromide ion, but did display a low intensity triplet (1:2:1 ratio) at m/e 161, 159, 157 in accord with a dibromide fragment, and a stronger doublet at m/e 81, 79 corresponding to bromide ion.

Chemical ionisation (CI) and electron-impact (EI) mass spectra were also obtained, though it is to be expected that extensive fragmentation of the parent structure would occur under the high temperatures required for sample volatilisation. In accord with this expectation, the CI spectrum furnished evidence for a fragment corresponding to a dibromide of olefin (209), and for the olefin (209) itself. The EI mass spectrum demonstrated fragments for both dibromide and monobromide species, and for olefin (209).

Confirmatory evidence for the tribromide ion portion of the salt (335) was obtained from the solid-state Raman spectrum of the salt, which was kindly run and assigned by Dr J.R. Walton and Miss H.J. Bowley, Project 203, Spectroscopy Branch, BP Research Centre, Sunbury-on-Thames. In addition to a number of weak absorption bands associated with the organic portion of the salt, a strong band at 160 cm^{-1} characteristic of the tribromide ion was observed in the Raman spectrum. This value compares well with the literature value for the tribromide ion of tetramethylammonium tribromide which is

known[177] to absorb strongly at 162 cm^{-1} in the Raman spectrum of this compound in the solid state.

Following examination of the infrared spectrum of the tetrabromide product as a nujol mull (Figure 21) the structure (335), which would have been only the second example of an isolated bromonium tribromide salt, was completely discounted. The most striking feature of this spectrum is the absence of the absorption associated with the symmetric stretch of the sulphone group, expected at 1110-1145 cm^{-1} (see p. 167). Thus the product is not sulphone-containing (ruling out structure (335)) though strong absorptions at 1335 cm^{-1} and in the range 850-950 cm^{-1}, which are not present in the infrared spectrum of the olefin (209), appear to be associated with the functional group resulting from the reaction undergone by the sulphone group upon bromination of olefin (209).

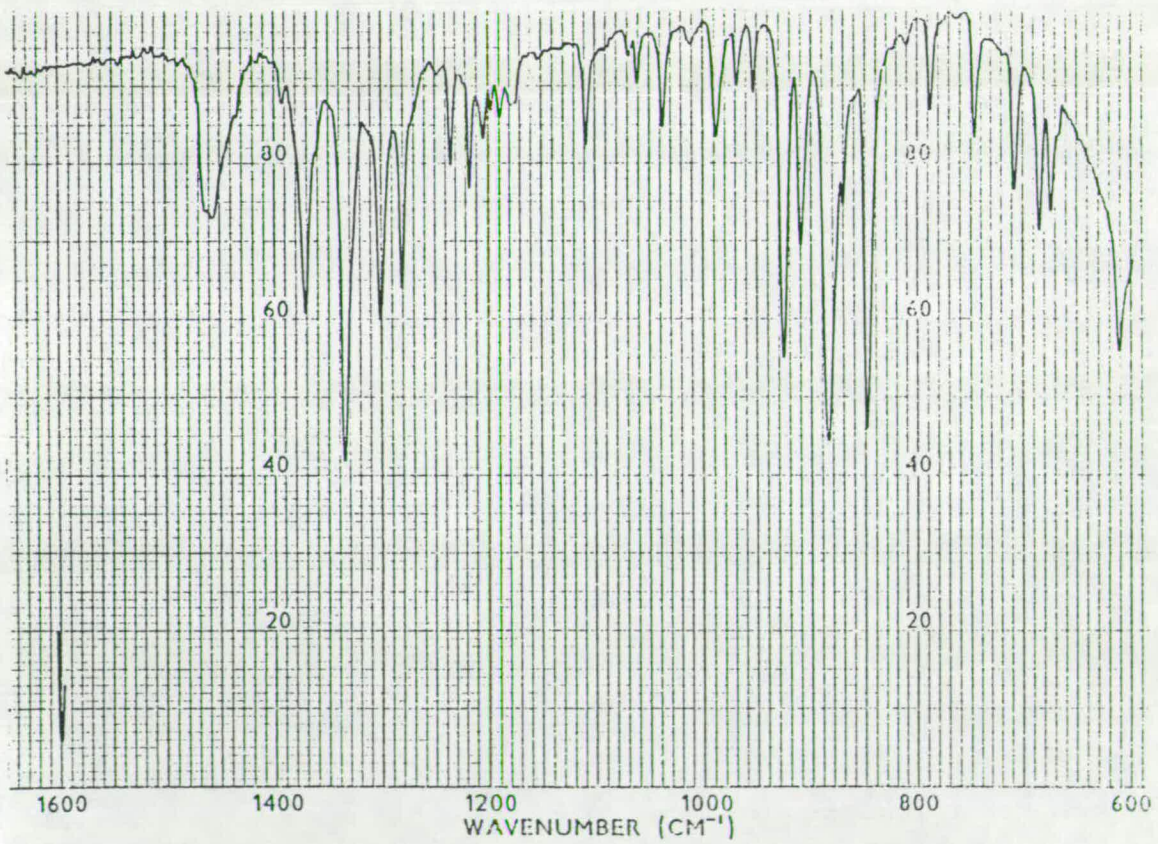
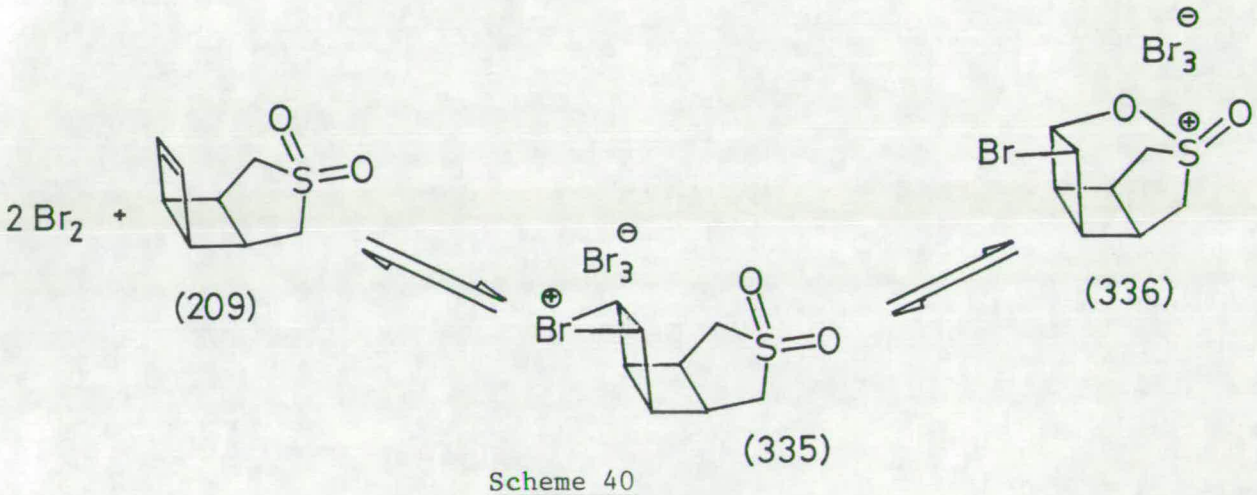


Figure 21 : Infrared spectrum of the tetrabromide product derived from olefin (209)

When taken in conjunction with the previously described evidence pointing to a tribromide salt structure for the tetrabromide derived from olefin (209), the infrared spectrum suggests that the correct structure may be that of the oxysulphoxonium tribromide system (336). Such a structure is even more remarkable than that of (335) since formation of this product entails the intramolecular trapping of a bromonium ion intermediate by the sulphone group, which therefore acts as a nucleophile (Scheme 40). Only one other literature reference to nucleophilic reaction of the sulphone group exists: Whiting et al[178] have found that thermolysis of arenediazonium tetrafluoroborates or hexafluorophosphates in the presence of excess sulpholane (or several acyclic sulphones) led to isolation of the corresponding

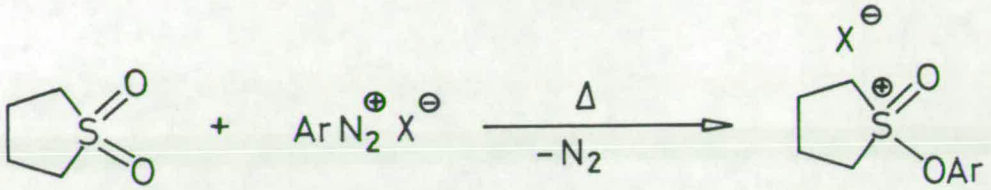


Scheme 40

aryloxysulphoxonium salts (337). This reaction is believed to occur via reaction of the strongly electrophilic aryl cation intermediate with the weakly nucleophilic sulphone group.

Although aryloxysulphoxonium compounds demonstrate one or two strong absorptions ca 1100 cm^{-1} in the infrared spectrum[178] due to the S=O stretch, no such bands were apparent in the spectrum of the brominated product derived from (209) (Figure 21), which instead demonstrates unassigned absorptions in the 1300-1400 cm^{-1} region. One of these may be due to the S=O stretch of an oxysulphoxonium

cation, the position of which in the infrared spectrum for a strained cyclic structure such as (336) would be expected to be significantly different from that in an aromatic, unstrained system such as (337).

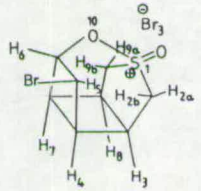


(337)

$X = BF_4, PF_6$

Further evidence for the correctness of structure (336) was sought and the tetrabromide product, in common with the bromonium tribromide salt (334), was found to be readily soluble in d_3-acetonitrile thereby permitting acquisition of the ^1H NMR spectrum. Examination of this spectrum continuously from initial dissolution of the tetrabromide derived from (209) until several hours later indicated that within a few minutes of first dissolving the material an equilibrium consisting of a 40:60 ratio of the olefin (209) and the salt (336) was established, and that this ratio remained unchanged over a 12 hour period. A similar ratio of these two compounds could also be obtained by treatment of a solution of olefin (209) in d_3-acetonitrile with two molar equivalents of bromine; addition of one further molar equivalent resulted in complete suppression of the olefin (209), with only the salt (336) present. These findings of a reversible equilibrium between olefin (209) and the salt (336) in solution are in accord with the equilibrium sequence outlined in Scheme 40.

The ^1H NMR spectrum of the equilibrium mixture of the olefin (209) and salt (336) realised on dissolution of (334) in d_3-acetonitrile (after several days at 0°C during which time minor quantities of unidentified products had formed) is displayed in Figure 22. Analysis



(336)

$J_{2a,2b}$ = 16.2 Hz
$J_{2a,9a}$ = 8.7 Hz
$J_{2a,9b}$ = 1.1 Hz
$J_{2b,9b}$ = 1.9 Hz
$J_{4,5}$ = 3.0 Hz
$J_{4,7}$ = 4.3 Hz
$J_{5,6}$ = 6.0 Hz
$J_{6,7}$ = 4.3 Hz
$J_{7,8}$ = 7.6 Hz
$J_{9a,9b}$ = 15.5 Hz

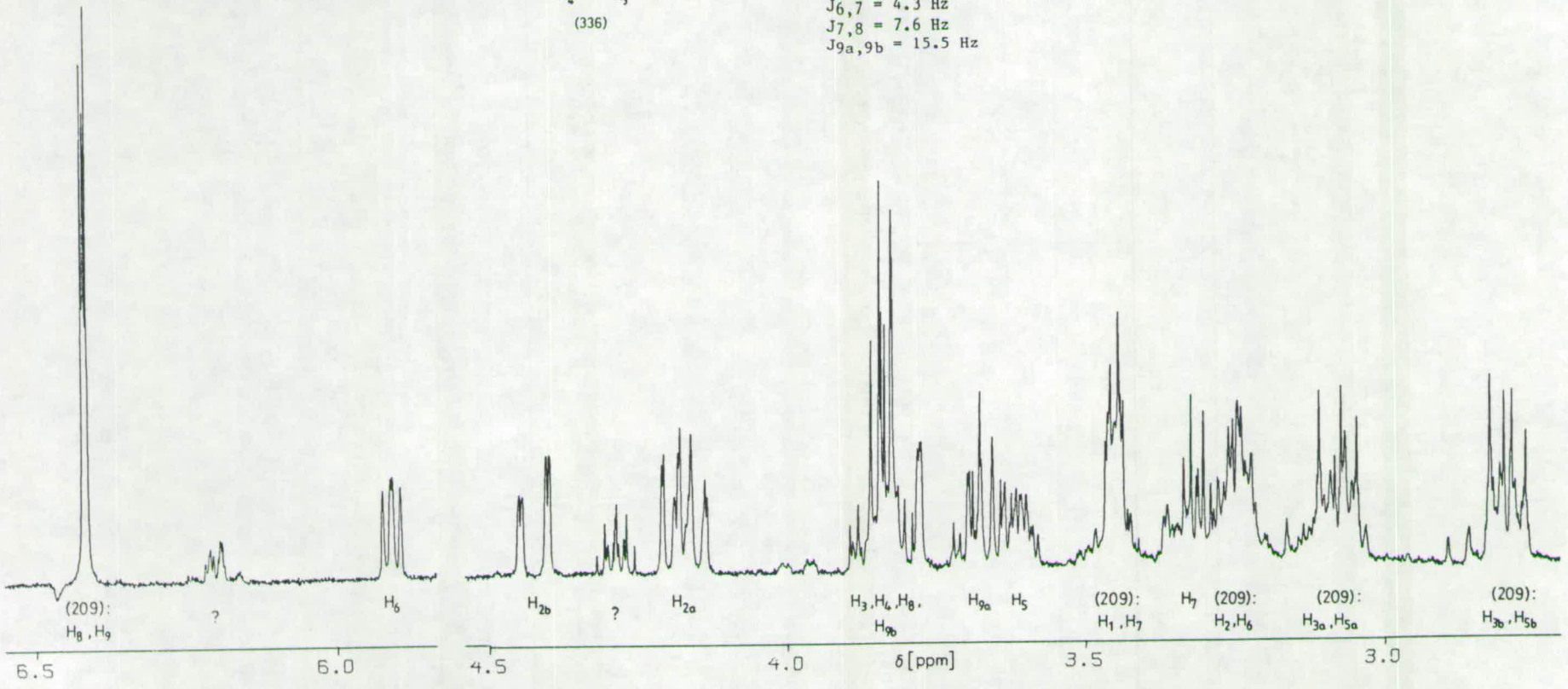
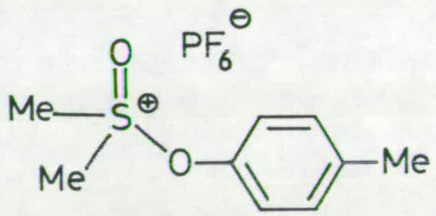


Figure 22 : ^{1}H NMR spectrum (360 MHz) obtained several days after dissolution of (336) in d_3-acetonitrile

of this spectrum after subtraction of the resonances due to olefin (209) generates a spectrum which is fully compatible with expectations for structure (336). Furthermore, no evidence for the presence of structure (335) was observed in this spectrum; cyclic bromonium ion methine protons are known[179] to resonate ca δ 7.5 in the proton spectrum and no such heavily deshielded signals were present in the spectrum of tetrabromide (336) in acetonitrile. However, the presence of (335) in small steady-state quantities, undetected by ^{1}H NMR spectroscopy, in accord with the intermediacy of (335) in the equilibrium between (309) and (336) (Scheme 40) cannot be discounted.

The most striking feature of the proton spectrum of the tribromide salt (336) (Figure 22) is the downfield shift of all the saturated proton signals, particularly the methylene signals, compared to the spectrum of the starting cisoid olefin (209) (Figure 18). As this deshielding action is largely a consequence of the positive charge on the sulphur atom, it is to be expected that the adjacent methylene protons would be effected most. Justification for this is presented by the finding[178] that the methyl resonance of the oxysulphoxonium salt (338) is deshielded by the adjacent positively charged sulphur atom to the extent of 1.25 δ compared to the precursor system, dimethyl sulphone.



(338)

The assignment of signals to protons and the evaluation of a number of coupling constants for the salt (336) which are displayed in Figure 22 followed from a careful analysis of the spectrum in

conjunction with clarifying selective proton decoupling studies. These assignments were made starting from the basis that the most deshielded signal (δ 5.91) was due to the methine proton H_6, and that the low-field position of this signal resulted from the inductive effect of the fused oxa bridge. In the tetracyclic system (271a) encountered previously, the analogous proton H_3 which is adjacent to an oxygen atom (contained within a heterocyclic structure) gave a signal at δ 4.86. For system (336), the corresponding proton H_6 would expectedly be located at lower field than H_3 in (271a) as a consequence of the inductive effect of the positively charged sulphur moiety acting through the oxygen bridge.

With this reasonable assumption in mind, irradiation of the H_6 proton (δ 5.91) was undertaken resulting in simplification of signals at δ 3.61 and δ 3.31, which in view of the structure of (336) were accorded to bromomethine proton H_5 and ring fusion methine proton H_7 respectively. Reciprocal irradiation of either of these signals resulted in collapse of the doublet of doublet signal for H_6 (δ 5.91) to a doublet, thereby allowing assignment and quantification of the two coupling constants present in the latter to $J_{5,6}$ = 6.0 Hz and $J_{6,7}$ = 4.3 Hz. The large value of the trans vicinal coupling $J_{5,6}$, and the small value for the cis vicinal coupling constant $J_{6,7}$ are not in accord with those expected across a rigid cyclobutane ring (see p. 73) and therefore reflect the severe distortion of the relevant cyclobutane ring in system (336) resulting from the presence of the bromine and oxa substituents.

Substantiating evidence for the above proton assignments was obtained from the H_7 signal (δ 3.31), a doublet of triplets incorporating the cis vicinal cyclobutane couplings $J_{7,8}$ = 7.6 Hz and $J_{4,7}$ = 4.3 Hz; similarly the remaining coupling in the doublet of

doublet signal (δ 3.61) due to H_5 was assigned to the trans vicinal cyclobutane coupling constant $J_{4,5}$ = 3.0 Hz. Due to an unfortunate coincidence, the signals due to protons H_3,H_4 and H_8 could not be differentiated and no further coupling constants relating to the central cyclobutane ring of (336) were available.

With regard to the sulphoxonium ring, an obvious geminal coupling constant of 16.2 Hz magnitude in the doublet of doublet signal at δ 4.43 indicates that this signal is due to one of the four methylene protons in (336). The low field position of this resonance by ca 1.3 - 1.6 δ compared to the position of the equivalent methylene protons in the olefin (209) is accounted for by the deshielding action of the positive charge on the adjacent sulphur atom. Irradiation of the methylene signal at δ 4.43 resulted in removal of the geminal coupling present in the signal at δ 4.17, which is therefore the second half of a methylene proton pair. A tentative assignment of these signals to protons H_{2b} (δ 4.43) and H_{2a} (δ 4.17) was made on consideration that of the four methylene protons present in (336), proton H_{2b} would be expected to be located at lowest field due to a deshielding steric interaction with proton H_5.

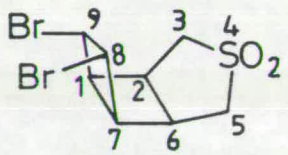
Irradiation of H_{2a} (δ 4.17) in turn resulted in loss of a coupling of 8.7 Hz in a signal at δ 3.67, which was assigned to the methylene proton H_{9a}. The geminal coupling constant $J_{9a,9b}$ = 15.5 Hz present in this signal was similar in magnitude to $J_{2a,2b}$ = 16.2 Hz, in confirmation of this assignment. However, the second methylene proton H_{9b} appeared to coincide with the signals resulting from a number of other protons present in the system, within the multiplet at δ 3.78-3.90. A most unusual feature of the H_{9a} signal is the coupling $J_{2a,9a}$ = 8.7 Hz which represents a strong coupling through four bonds between H_{2a} and H_{9a}, with this being relayed through the

positively charged sulphur atom. Further support for this assignment was available from the related but smaller coupling J_{2b},J_{9b} = 1.9 Hz present in the signal due to H_{2b} at δ 4.43. Considered as a whole, the proton spectrum obtained on dissolution of the tetrabromide product derived from olefin (209) is in broad accord with the proposed structure (336). In particular, the noticeable deshielding effect operating on the methylene protons (of 0.6 - 1.6 δ *cf.* the methylene protons of (209)) is the most obvious evidence for the structure (336), in which a positively charged sulphur atom is responsible for such an effect.

Examination of the ^{13}C NMR spectrum of the tetrabromide product furnished supporting evidence that this material possesses structure (336). Thus, the ^{13}C DEPT NMR spectrum displayed two methylene and six methine resonances: the deshielded position (δ 97.43) of one of the methine carbons was in accord with that expected of C(6) in structure (336), with support for this assignment being found in the similar value (δ 80.75) for C(3) in the related system (271a).

Utilising the same solution of tetrabromide (336) and excess bromine in d_3-acetonitrile from which the ^{13}C NMR spectrum was obtained, the UV spectrum of the salt was determined. This indicated the presence of an absorption for the tribromide ion $\lambda_{max.}$ 270 nm, $\epsilon_{max.}$ *ca* 22,000. By comparison, the UV spectrum of a standard solution of bromine in d_3-acetonitrile of equivalent concentration to that of the excess bromine in the salt (336) solution, was found to display negligible absorption at 270 nm. A favourable comparison between this value for the tribromide ion in acetonitrile solution and published data ($\lambda_{max.}$ 269 nm, $\epsilon_{max.}$ 55,000 [180]) was therefore achieved, furnishing confirmatory evidence for the tribromide salt nature of (336) in solution.

One further result regarding the melting behaviour of product (336) is worthy of comment. Upon heating to 82-84°C, the orange crystallites of (336) were observed to melt with formation of an orange liquid which then quickly evolved a brown/orange gas in the process of changing to a colourless oil. As bromine appeared to be extruded upon melting, the melted material was analysed by ^{1}H NMR spectroscopy in order to establish the identity of the product(s) formed. The chloroform-soluble product (cf. the chloroform-insoluble starting tetrabromide (336)) was found to contain none of the olefin (209), but the symmetric nature and positioning of the signals in the proton spectrum were in accord with expectations for that of the cis-dibromide product (339). Thus, the presence of a doublet (J = 2.2 Hz) at



(339)

δ 5.00, a position characteristic of cyclobutane bromomethine products, was found to bear some relation to the corresponding bromomethine signals of the analogous cis-dibromide (330), known[181] to display a distorted doublet of doublet signal (J_1 = 2.8 Hz, J_2 = 1.3 Hz) at δ 4.87. For structure (339), this small coupling (2.2 Hz) is in accord with a trans vicinal cyclobutane coupling between cyclobutane ring fusion protons H_1,H_7 and the bromomethine protons H_8,H_9. A distorted doublet of doublet signal (δ 3.25) displayed the same coupling constant $J_{1,9}$ ($J_{7,8}$) = 2.2 Hz, and this was assigned to protons H_1,H_7; the presence of a cis cyclobutane coupling constant $J_{1,2}$ ($J_{6,7}$) = 5.7 Hz was supportive of structure (339) as that of the thermolysis product derived from (336).

As a consequence of the small scale on which the debromination of (336) was carried out, no further evidence for structure (339) being that of the product was obtained, and this assignment therefore remains tentative. However, the EI mass spectrum obtained from (336) does lend support for the thermolytic formation of dibromide products on heating of (336).

No literature precedent exists for the isolation of a bromination product which is intermediate between an olefin and the corresponding dibromide product. In light of this, the isolation of the tribromide salt (336) as a stable compound following addition of bromine to the olefin (209) and the subsequent thermal fragmentation of this system to a dibromide product (339), is quite remarkable. Following from the tribromide nature of the salt (336), the implication for the general course of olefin bromination reactions is that many of these may also occur <u>via</u> the intermediacy of tribromide species.

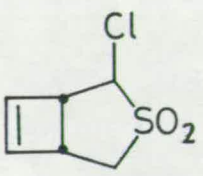
Although only a single electrophilic reaction was carried out on the electron-deficient olefin (209), the unique findings obtained from this clearly indicate the merit of investigation of alternative electrophilic reactions with this interesting system, in spite of the logistical problems in synthesising the olefin in the sizeable quantities required for such an exercise.

E. Preparation of Tricyclic and Higher Systems Containing a 4-Thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide Skeleton

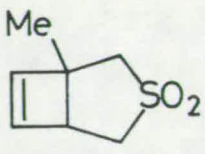
The principal reason for carrying out the reactions described in this section was the preparation of tricyclic systems (210) and tetra- or higher-cyclic systems (211) containing a basic 4-thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide skeleton. These systems were to be used in a comparative study of thermal fragmentation behaviour, as detailed earlier (p.65). In addition, the photochemical behaviour of cyclobutene sulpholane (63) with a range of olefins, and the photochemical reactions of a number of substituted analogues of this sulpholane with maleic anhydride *en route* to the syntheses of systems (210) and (211), were considered to be worthy of investigation.

1. Preparation of substituted derivatives of 4-thiatricyclo[5.2.0.$0^{2,6}$]-nonane-cis-8,9-dicarboxylic anhydride 4,4-dioxide (242)

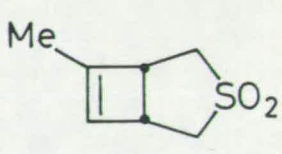
Following the successful preparation of the *transoid*, *transoid* tetracycle (242a) by irradiation of (63) and maleic anhydride in acetone, it was envisaged that a number of analogous systems could be realised by photolysis of (63), and related cyclobutene sulpholanes, with cyclic olefins. In addition to compound (63), the 2-chloro substituted system (340)[182] was available for study (courtesy of Dr S.J. Wyse, University of Edinburgh). To complete a quartet of



(340)



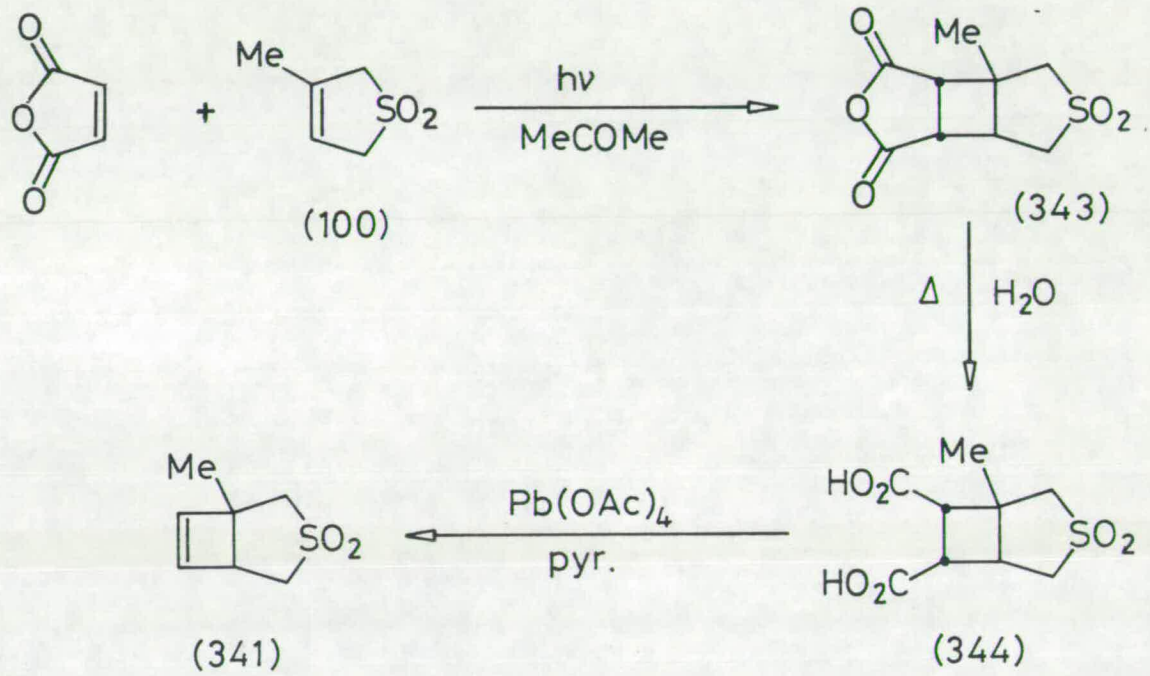
(341)



(342)

cyclobutene sulpholane systems available for a study of the effect of monosubstituent position on photochemical reactivity with maleic anhydride, the novel 1-methyl and 6-methyl analogues (341) and (342) were chosen as synthetic targets.

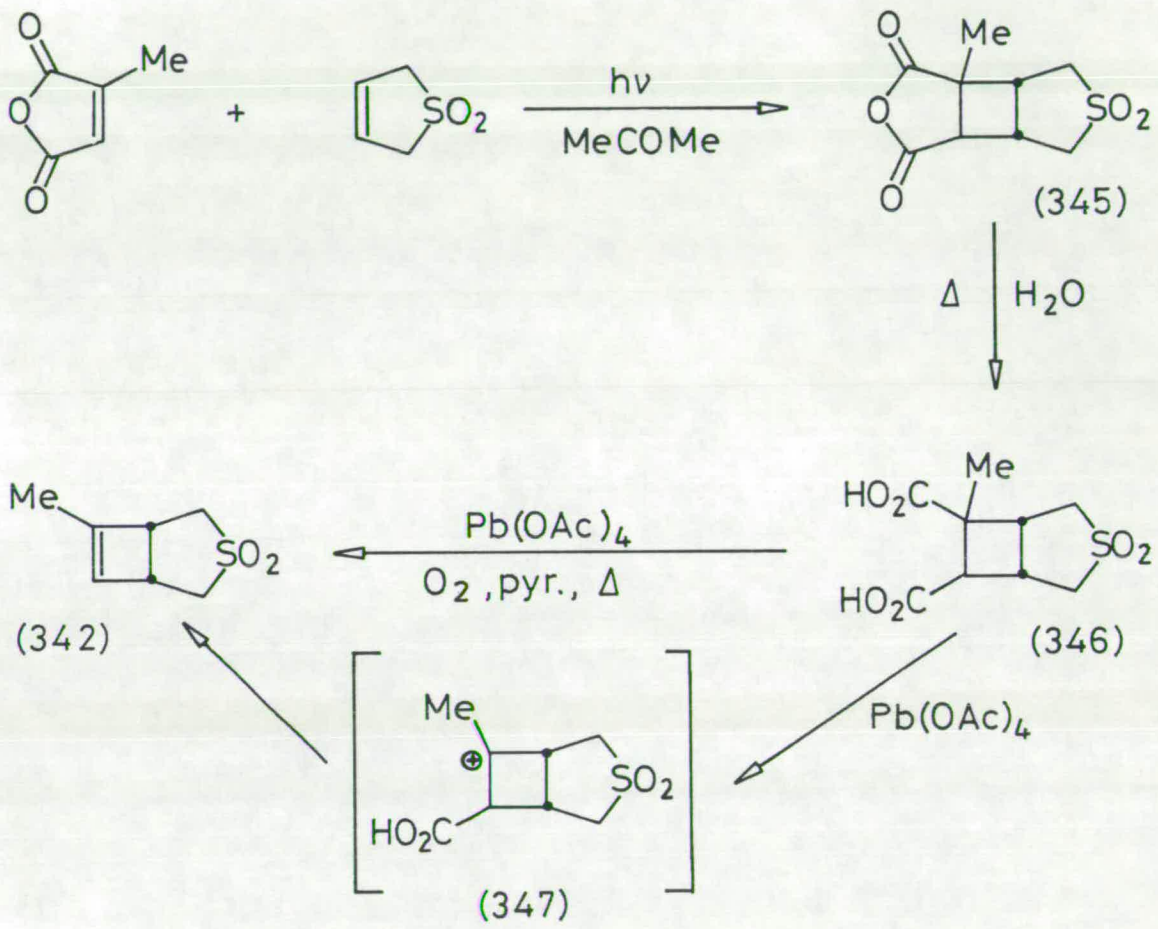
The preparation of the 1-methyl substituted sulpholane (341) was carried out as shown in Scheme 41, a reaction sequence which



Scheme 41

parallels that by which the parent system (63) was prepared. Thus, photolysis of a solution of 3-methyl-3-sulpholene (100) and maleic anhydride in acetone, following the procedure of Buchan[29], gave the photoadduct (343) in 35% yield. The stereochemistry of the anhydride product is not known, but the formation of the adduct (343) in a single one of the possible isomeric forms was confirmed on analysis of the diacid product (344) obtained on hydrolysis. Treatment of diacid (344) with lead tetraacetate under standard bis-decarboxylation conditions gave the expected olefin (341) as colourless needles, m.p. 73.5-75°C, in 24% yield.

Similarly, the trisubstituted olefin (342) was synthesised by a parallel sequence of reactions (Scheme 42), commencing with the photocyclisation of butadiene sulphone and citraconic anhydride with

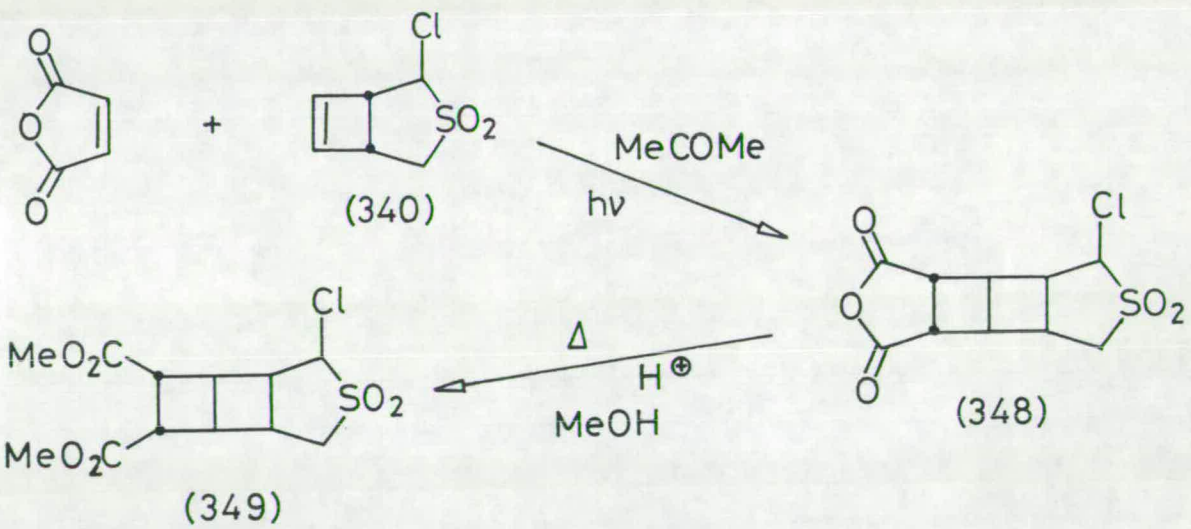


Scheme 42

formation of the known[29] adduct (345) in 43% yield. Hydrolysis of this gave the corresponding diacid (346) monohydrate as verified by elemental composition and spectroscopic analyses. Bis-decarboxylation of the diacid (346) was achieved by treatment with lead tetraacetate in oxygenated pyridine at 67 °C giving the 6-methylcyclobutene sulpholane (342) in 51% yield. The magnitude of the yield of olefin (342) is much higher than found for the analogous systems (63) (17%) and (341) (24%). This may be attributed to the greater stabilisation of the tertiary carbonium ion intermediate (347) formed on initial

decarboxylation of (346) compared to the corresponding secondary carbonium intermediates generated from (63), (341) and other diacid systems lacking an appropriately located alkyl substituent. Although the intermediacy of a carbonium ion species such as (347) is in accord with current belief regarding the mechanism of diacid decarboxylation using lead tetraacetate[114], a radical mechanism involving the intermediacy of a tertiary radical species in the reaction of (346) may account for the empirical results.

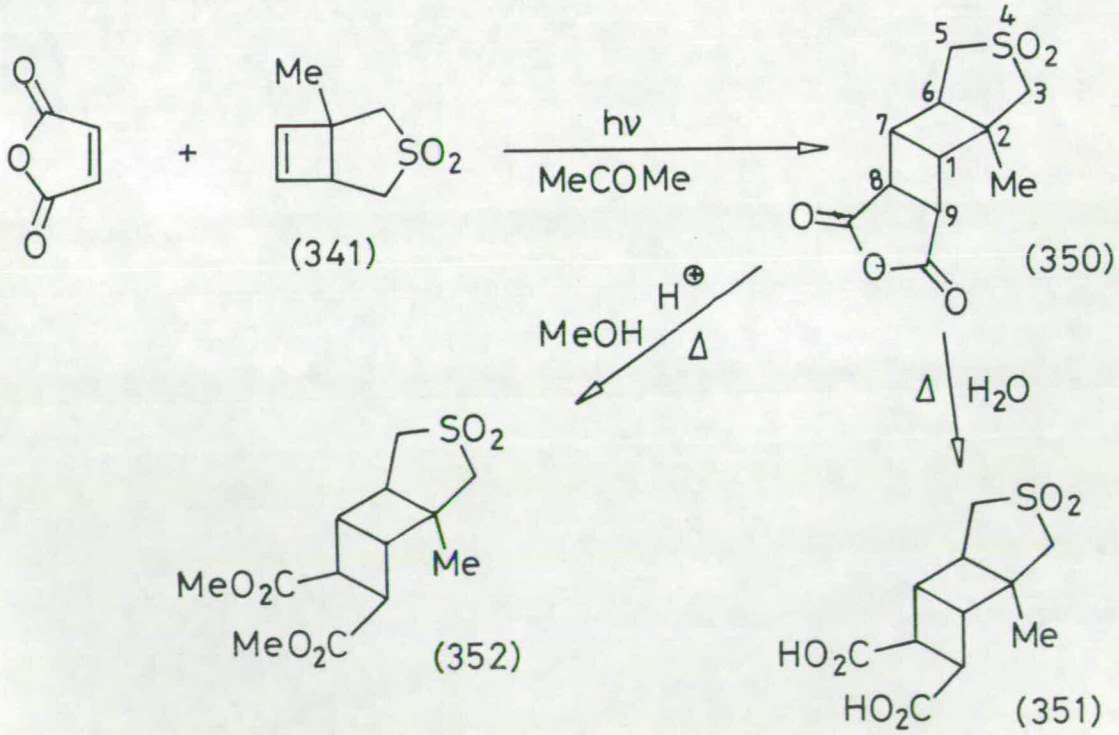
In mimicry of the conditions under which the transoid, transoid tetracycle (242a) had been prepared from cyclobutene sulpholane (63) and maleic anhydride, each of the three analogous systems (340), (341) and (342) was submitted to irradiation with this olefin in acetone solution. Thus, irradiation (100W) of the 2-chloro substituted sulpholane (340) with maleic anhydride resulted in isolation of a crystalline adduct, m.p. 291-292°C, of correct elemental composition



for tetracycle (348) and in fair yield (71%). Conversion of this product to the more conveniently handled dimethyl ester (349) was effected in high yield by heating in acidified methanol. Although fully characterised by elemental and spectroscopic analyses as the diester (349), the stereochemistry of this product, and consequently

that of the precursor anhydride (348), could not be established from the complex ^{1}H NMR spectrum. However, it can be stated that the photocyclisation reaction proceeded to give a single one of the four possible tetracyclic structures (348). In light of this, and the results of photocyclisation of the parent system (63) and the 1-methyl substituted system (341) (described later) with maleic anhydride, the transoid, transoid geometry is the most likely candidate for the ring structure of (348).

Photolysis of an acetone solution of the 1-methyl substituted sulpholane (341) and maleic anhydride, under identical conditions to those employed with (63) and (340), resulted in isolation of a single [2π+ 2π] cycloadduct of the two starting olefins in 24% yield. This product was fully characterised by standard means, and following detailed examination of the ^{1}H NMR spectrum (360 MHz) the adduct was accorded the transoid, transoid geometry of structure (350). In



particular, the magnitude of the two trans vicinal cyclobutane coupling constants $J_{6,7}$ = 2.3 Hz and $J_{7,8}$ = 1.8 Hz were as expected for structure (350), and considerably smaller than the cis vicinal coupling constant $J_{1,7}$ = 4.7 Hz, in accord with previously detailed generalisations regarding cyclobutane coupling constants (p.73).

The anhydride (350), in common with the other systems of this type thus far encountered, displayed an unwelcome tendency to undergo facile hydrolysis to the corresponding diacid (351): this material was prepared in high yield simply by heating in water for a short period. However, on examination of the complex high field ^{1}H NMR spectrum of the diacid (351) no information regarding its stereochemistry could be extracted.

In contradistinction, heating of anhydride (350) in boiling acidified methanol allowed preparation of the corresponding dimethyl ester (352) as rhombic crystals, m.p. 103-105.5°C, which displayed a readily assignable ^{1}H NMR spectrum fully in accord with the expected exo-cis-diester, transoid stereochemistry expected for this system. Thus, analysis of the ^{1}H NMR spectrum of (352) furnished supporting evidence for the transoid, transoid stereochemistry of anhydride (350).

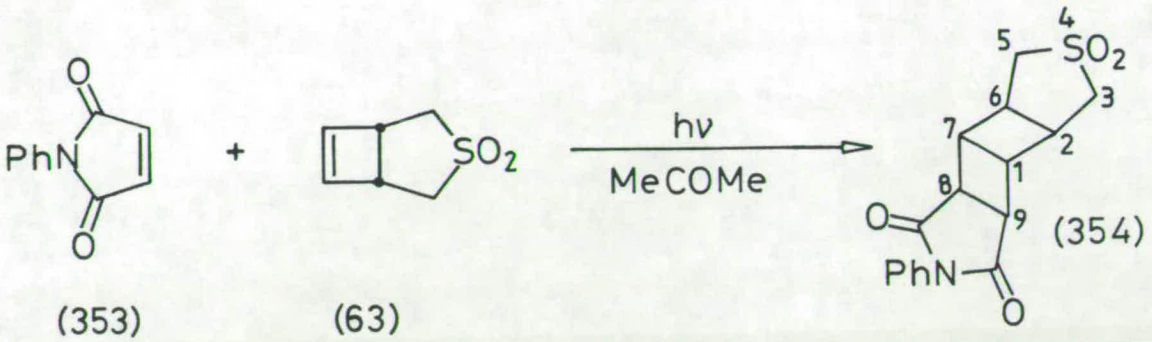
Irradiation of the final member of the cyclobutene sulpholane series, the trisubstituted olefin (342), with maleic anhydride in acetone solution resulted in isolation of a solid product in high yield. However, the physical and spectroscopic properties of this material were not in accord with a tetracyclic adduct of the two starting olefins, but rather reflected those of a polymer derived from the two olefins. In order to determine if any monomeric product was present as an impurity in the bulk of the polymeric product, the crude material was heated in acidified methanol. Examination of the methanol solution by TLC indicated the complete absence of monomeric

diester products, and hence it was concluded that only a polymeric sulphone-anhydride product was formed on irradiation of (342) and maleic anhydride.

Such a result is in contrast to the findings from similar photochemical reactions involving bicyclic sulpholanes (63), (340) and (341) with maleic anhydride, and may therefore reasonably be attributed to the presence of the methyl substituent on the olefin group within (342), a feature absent in the other related sulpholane systems. It is feasible that the availability of a stabilised tertiary site for a radical or cationic intermediate resulting from irradiation of (342) would direct the reaction towards a facile copolymerisation, rather than a [2π+ 2π] cycloaddition reaction mode.

Within the series of four bicyclic sulpholanes whose photochemical reactivity with maleic anhydride has been studied, a definate relationship between proximity of substituent to the olefin group and yield of [2π+ 2π] photoadduct is apparent. Thus, for the unsubstituted system (63) and the 2-chloro analogue (340) the large separation between the substituents (hydrogen and chlorine respectively) and the olefin group result in a very similar yield (ca 70%) of photoadduct in each case. The 1-methyl substituted sulpholane (341) gave a reduced yield (24%) of photoadduct presumably due to complicating steric factors; the 6-methyl system (342) gave no photoadduct as a consequence of a completely altered reaction mode induced by the presence of the methyl substituent on the olefin.

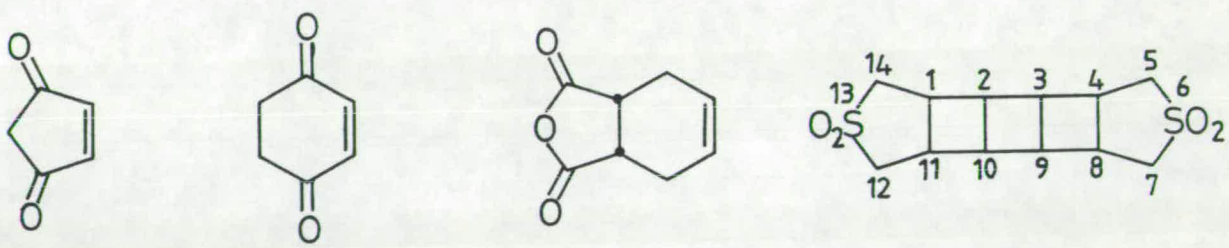
As a means of preparing other tetracyclic systems for FVP studies, the photochemical reactivity of the parent cyclobutene sulpholane (63) with a variety of cyclic olefins was next considered. Irradiation of an acetone solution of (63) and N-phenylmaleimide (353) gave a crystalline precipitate which was found to be a photoadduct of



(353) (63)

the two olefins following satisfactory elemental and spectroscopic analyses. The tetracyclic product was assigned transoid, transoid stereochemistry on examination of the proton spectrum which possessed singlet signals for proton pairs H_1,H_7 (δ 2.82) and H_8,H_9 (δ 3.54). In verification of this assignment, tetracycle (354) was prepared independently from the transoid, transoid anhydride (242a) by a reaction sequence precluding any change in ring geometry and which is described later in this section.

Photolyses of acetone solutions of (63) with cyclopent-4-ene-1,3-dione (355) and cyclohex-2-ene-1,4-dione (356), two olefins expected to be generally responsive towards photochemical [2π+ 2π] cycloaddition reactions, failed to produce the expected

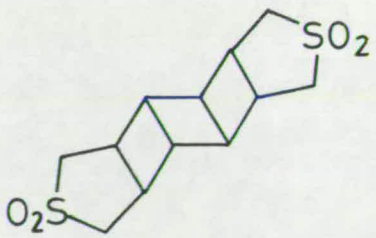


(355) (356) (357) (358)

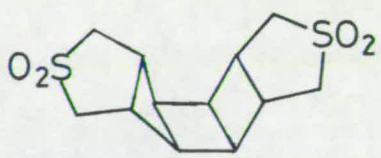
tetracyclic photoadducts in either case. With the former olefin, a small quantity of copolymer was isolated, though the bulk of the two starting materials was recovered unchanged even after a six day irradiation period; the latter olefin was completely consumed in

formation of an acetone-soluble copolymer with the cyclobutene sulpholane (63).

Irradiation of (63) with the cyclohexene anhydride (357) in acetone was conducted until the sulpholane starting material had been completely consumed. However, the small quantity of insoluble crystalline material present on completion of the photolysis reaction was found not to be the expected tetracyclic photoadduct of the two olefins. Following analysis by IR spectroscopy, which demonstrated a complete absence of carbonyl absorptions and the presence of strong sulphone bands, and data from mass spectroscopy it was concluded that this product was a photodimer (358) of cyclobutene sulpholane (63). Supporting evidence from the ^{13}C NMR spectrum, which demonstrated three carbon environments at values expected for a structure such as (358), indicated the C_{12} system to possess two planes of symmetry. Furthermore, analysis of the ^{1}H NMR spectrum confirmed the correctness of proposed structure (358) and allowed additional delineation of stereochemistry to be made. A lack of coupling between H_1 (H_4,H_8,H_{11}) and H_2 (H_3,H_9,H_{10}) in accord with a <u>trans</u> vicinal relationship between the respective pairs restricted the structure of the dimer to either (358a) or (358b). On the basis of available information no further specification of ring geometry could be made, although the all-<u>transoid</u> arrangement (358a) appears the more probable on steric grounds.



(358a)



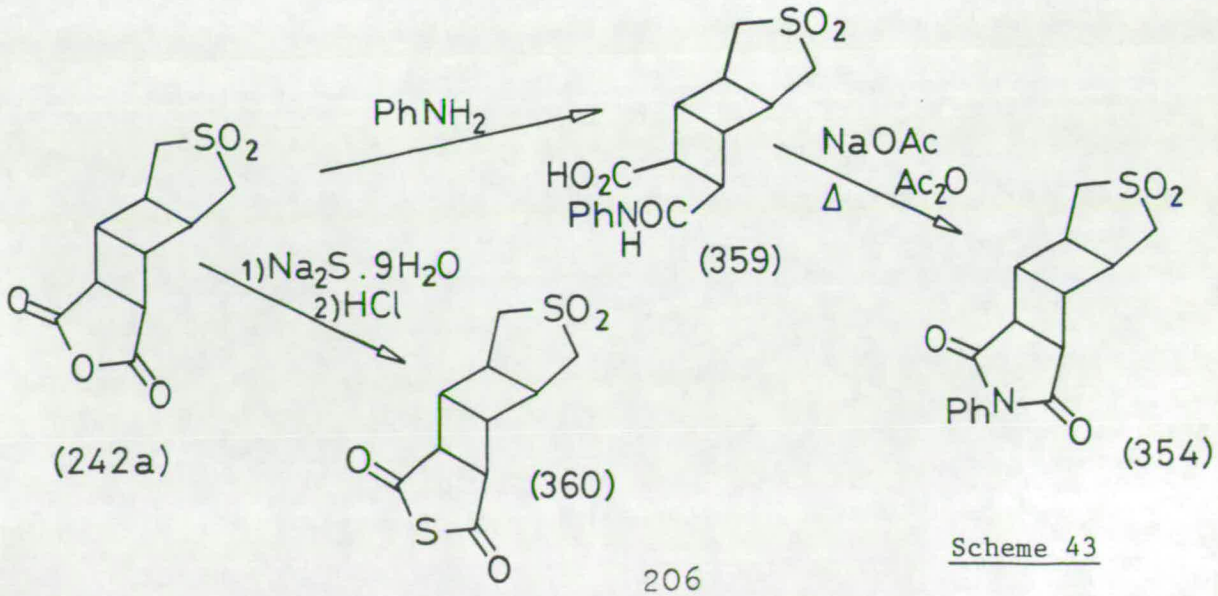
(358b)

A final photolysis reaction involving the irradiation of an acetone solution of sulpholane (63) and butadiene sulphone failed to produce any of the photoadduct of the two olefins. Comparison of the isolated product with pentacycle (358) proved the two to be identical, though this product accounted for just 1% of the consumed olefin (63).

In summary, the cyclobutene sulpholane (63) has been found - under very similar photochemical conditions - to undergo [2 π + 2 π] cycloadditions with maleic anhydride and N-phenylmaleimide, to form copolymers with olefins (355) and (356), and to undergo low-yielding photodimerisation on irradiation in the presence of butadiene sulphone or anhydride (357).

2. Preparation of tetracyclic systems from (cis-1-transoid-1,2-cis-2)-4-thiatricyclo[5.2.0.$0^{2,6}$]nonane-exo-cis-8,9-dicarboxylic anhydride 4,4-dioxide (242a)

Manipulation of the anhydride moiety in the transoid, transoid tetracyclic system (242a) was recognised as a means of producing two related compounds suitable for a comparative study of thermal extrusion behaviour. Both the imide (354), previously prepared by photolysis of (63) and N-phenylmaleimide (353), and the thioanhydride (360) might reasonably be expected to result from the simple reactions performed upon (242a) outlined in Scheme 43.

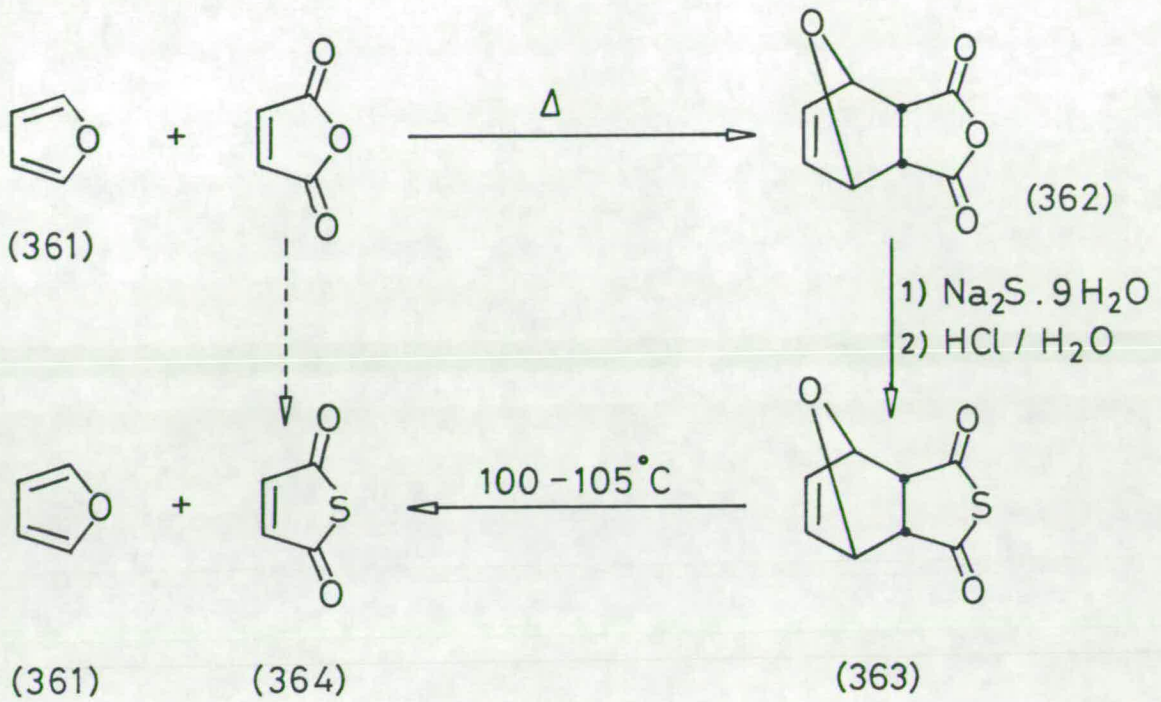


Scheme 43

Reaction of anhydride (242a) with one molar equivalent of aniline in methanol was effected by stirring at room temperature for a short time. A single product was obtained in high yield and was fully characterised by conventional procedures as the acid-amide system (359). In particular, the infrared spectrum was most instructive as it displayed absorptions for the acid (1692 cm^{-1}) and amide (1651 cm^{-1}) carbonyl groups, for the acid hydroxy (3300-2500 cm^{-1}) and amide N-H (3340 cm^{-1}) groups, and also for the sulphone group [asymmetric and symmetric stretches (1312 and 1133 cm^{-1})]. The ready dehydration of the system was illustrated by the electron-impact mass spectrum which displayed a highest peak at the m/e ratio corresponding to loss of water from the parent ion.

In accord with this finding, chemical dehydration of (359) was readily achieved by heating with acetic anhydride in the presence of sodium acetate. The imide (354) was isolated in excellent yield, and the sample proved identical to that obtained previously by photochemical means. Confirmation of the transoid, transoid geometry of the product was available from the ^1H NMR spectrum verifying that no change in ring stereochemistry occurred en route from (242a) to (354).

Turning to the preparation of the thioanhydride analogue (360), a search of the literature revealed that such compounds are readily prepared by a solid-phase reaction between the anhydride precursor and sodium sulphide nonahydrate followed by acidic work-up[183,184]. This procedure is typified by the synthesis of the thioanhydride (363) from the furan-maleic anhydride adduct (362); thermolysis of (363) resulted[183] in a retro-Diels-Alder reaction with formation of thiomaleic anhydride (364), a system which could not be prepared directly from the reaction of maleic anhydride and sodium sulphide nonahydrate[185].



(361) (364) (363)

Treatment of anhydride (242a) with sodium sulphide nonahydrate (by intimate mixing of the two solids) to give a grey paste, followed by acidic aqueous work-up resulted in isolation of a colourless solid. This was found to consist of a 63:37 mixture of the expected thioanhydride product (360) and starting anhydride (242a) from inspection of ^{1}H and ^{13}C NMR spectra. A sample of almost pure thioanhydride (360) was obtained in low yield following a recrystallisation and sublimation purification procedure.

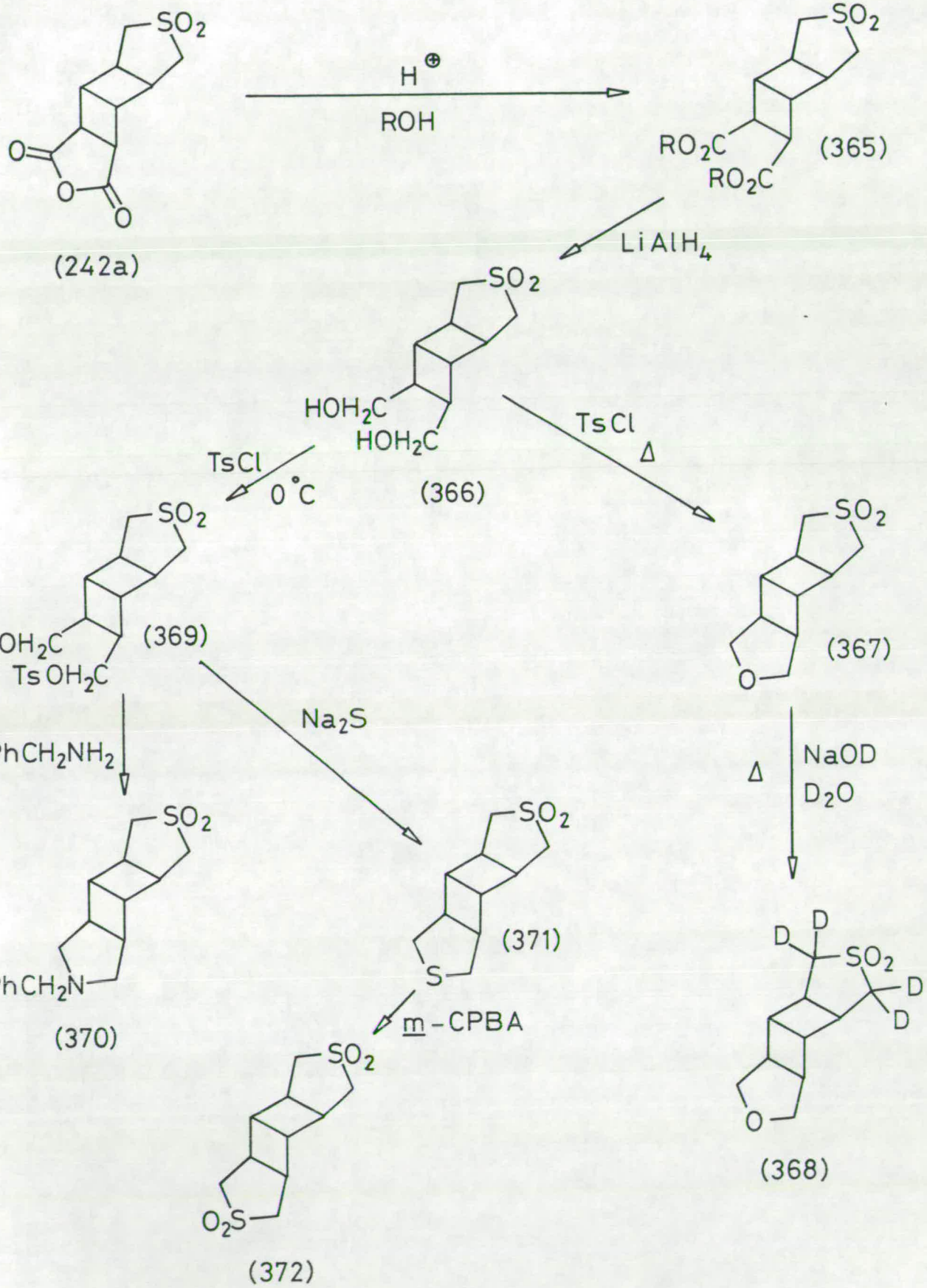
Full characterisation of the thioanhydride (360) was achieved following satisfactory elemental and spectroscopic analyses. The ^{13}C NMR spectrum indicated the presence of five carbon environments including a carbonyl signal (δ 202.09) markedly deshielded relative to that of the starting anhydride (242a) (δ 173.39), as expected for a thioanhydride system. Examination of the proton spectrum indicated that the transoid, transoid structure of starting anhydride (242a) was retained in the thioanhydride product (260) as evidenced by the small trans-vicinal cyclobutane couplings to the cyclobutane-cyclobutane

ring fusion protons H_1,H_7 (δ 2.83). Thioanhydrides generally display two carbonyl absorptions (10-40 cm^{-1} apart) in the infrared spectrum within the range 1730-1690 cm^{-1}, with the more intense band observed at lower frequency[184]: system (363) is typical, displaying[183] coupled carbonyl absorptions at 1710 and 1690 cm^{-1}. The infrared spectrum of (260), with two carbonyl absorptions at 1706 and 1696 cm^{-1}, is therefore in good agreement with literature precedent.

In addition to the two carbonyl-containing tetracycles (354) and (360), manipulation of the anhydride ring in (242a) presented an opportunity to prepare a number of symmetric tetracyclic systems containing a substituted cyclopentane ring for a comparative study of thermal extrusion behaviour with other members of the series (211; n = 3) described earlier. The synthetic routes to these systems starting from (242a) are outlined in Scheme 44.

Heating of a mixture of anhydride (242a) in acidified methanol or ethanol resulted in isolation of the crystalline dimethyl (365; R = Me) or diethyl (365; R = Et) esters in good yield. Reduction of the dimethyl ester was effected by heating with lithium aluminium hydride in tetrahydrofuran giving the corresponding diol (366). When added to a solution of p-toluene sulphonyl chloride in pyridine which was heated under reflux, the diol (366) was dehydrated to generate the tetrahydrofuran derivative (367). This material was isolated in 41% yield as long colourless needle crystals, m.p. 169-171°C, satisfying elemental and spectroscopic tests of composition.

As a potential guide to the mechanism of thermal fragmentation of (367) and as an aid to the identification of the products arising from this, it was considered prudent to synthesise the tetradeuterated analogue (368). This goal was achieved in fair yield by the agitation and heating of a solution of (367) in dioxan with a solution of sodium

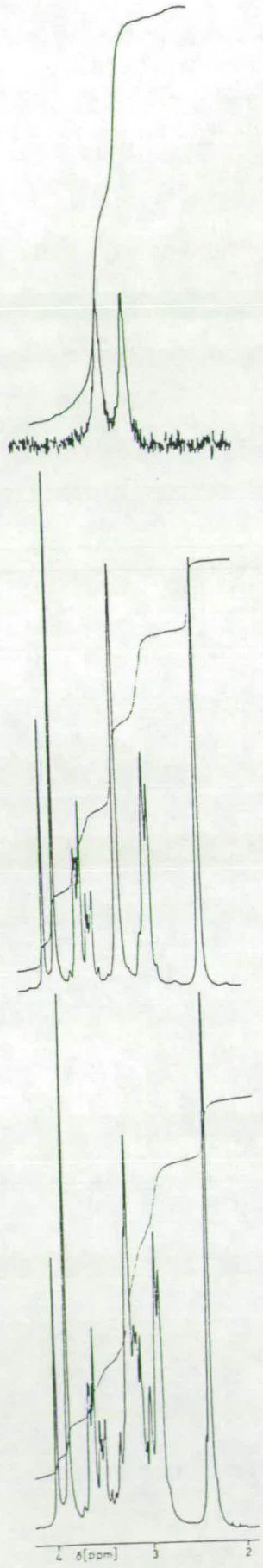

SO2
H⊕
ROH
RO2C
RO2C
(365)
(242a)
LiAlH4
HOH2C
HOH2C
(366)
TsCl
0 °C
TsCl
Δ
TsOH2C
TsOH2C
(369)
(367)
PhCH2NH2
Na2S
Δ
NaOD
D2O
PhCH2N
(370)
(371)
S
m-CPBA
O2S
(372)
D
(368)

Scheme 44

deuteroxide in deuterium oxide. The resultant crystalline product possessed an almost identical melting point to the parent tetracycle and was characterised as a tetradeuterated derivative following elemental and mass spectral analyses. Conclusive proof that the four deuterium atoms had replaced the acidic protons α- to the sulphone group in (367) was furnished from a comparison (Figure 23) of the ^{1}H NMR spectrum of (367) with the ^{1}H and ^{2}H NMR spectra of the deuterated product, which was therefore accorded the structure (368).

The next synthetic target was the tertiary amine (370). Following reaction of the diol (366) with p-toluene sulphonyl chloride in pyridine solution at 0°C, the expected ditosylate product (369) was prepared as a colourless crystalline material in 52% yield. In addition, the tetrahydrofuran (367) was isolated in a minor quantity (5% yield). On heating of a mixture of the ditosylate (369) and benzylamine in ethanol under reflux for an extended period the requisite tertiary amine tetracycle (370) was generated as colourless crystals, m.p. 121.5-123.5°C, in reasonable yield.

A related nucleophilic displacement of the two tosyloxy groups of system (369) was achieved by heating with sodium sulphide in boiling aqueous ethanol for five hours. On work-up, the desired tetrahydrothiophene analogue (371) of the substituted cyclopentane systems (367) and (370) was obtained in 62% yield. Oxidation using excess m-chloroperbenzoic acid in methylene chloride solution gave the corresponding disulphone (372), the final member of the symmetric tetracyclic series displayed in Scheme 44. The disulphone (372) was realised as a colourless solid, m.p. 284-288°C, and was fully characterised by standard means. In particular the ^{13}C DEPT NMR spectrum, which displayed only three environments (two methine and



^{2}H NMR spectrum of (368)

^{1}H NMR spectrum of (368)

^{1}H NMR spectrum of (367)

Figure 23 : ^{1}H and ^{2}H NMR spectra of (368)

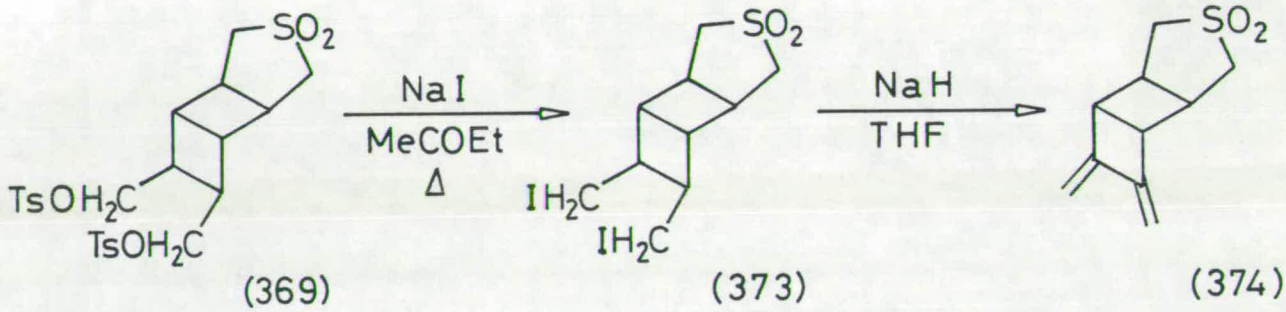
one methylene), has an important bearing upon the assignment of stereochemistry to all of the systems portrayed in Scheme 44.

Since the starting anhydride (242a) is known to possess a basic transoid-4-thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide skeleton (and suspected to possess overall transoid, transoid ring geometry from ^{1}H NMR coupling constants - see p.90), the 3-line carbon spectrum of the disulphone derived from this unequivocally establishes the transoid, transoid geometry of disulphone (372). Incidentally, the latter compound has previously been described by Martin et al[112] as a solid, m.p. 288°C, derived from the known transoid, transoid dianhydride (245) via a standard sequence of reactions similar to those by which disulphone (372) was prepared from anhydride (242a). However, of all the systems containing the 4-thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide structure described in this thesis, disulphone (372) remains the only compound which has appeared in the chemical literature.

Following from the established transoid, transoid ring stereochemistry of the disulphone (372), it follows that all of the other tetracyclic structures (including the starting anhydride (242a)) depicted in Scheme 44 have identical geometry, and it can also be stated that the tricyclic systems present all possess exo-cis-substituent, transoid-tricyclic ring stereochemistry as shown. This is verified by the noticeable lack of coupling to the cyclobutane-cyclobutane ring fusion protons (in accord with the small/zero magnitude of the trans-vicinal cyclobutane coupling constants to each neighbour) for all compounds present in Scheme 44 whose proton spectra permitted inspection of the relevant signal.

3. Preparation of miscellaneous systems containing a 4-thiatricyclo-[5.2.0.$0^{2,6}$]nonane 4,4-dioxide skeleton

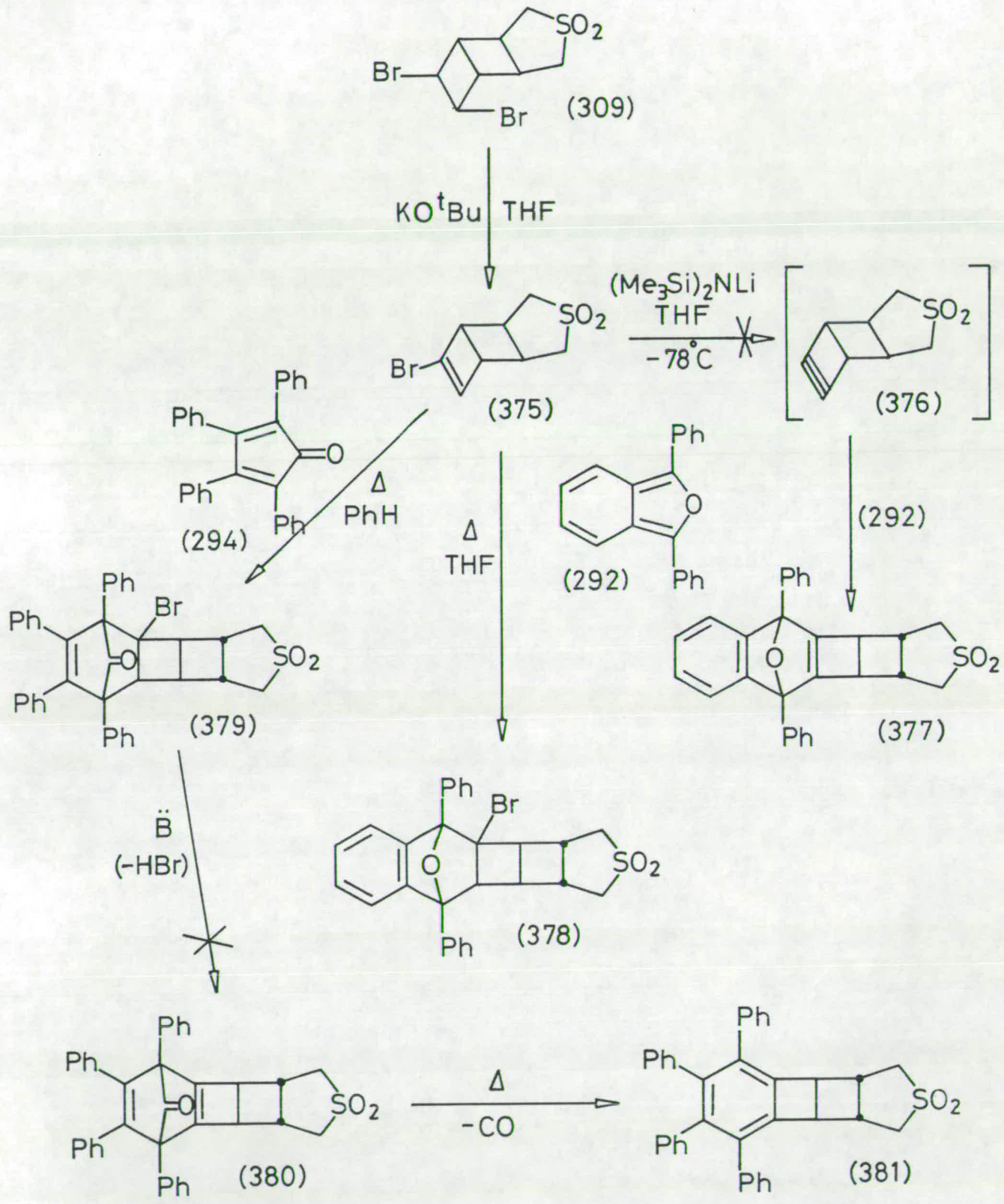
Having prepared the ditosylate compound (369) it was recognised that the novel dimethylene system (374) could be readily prepared from this by a two-step reaction sequence. The thermal fragmentation of (374) was of interest in the light of the thermal extrusion behaviour of the smaller ring analogue (78), found to be a novel source of [4]dendralene (82) on expulsion of sulphur dioxide[37]. It was found that treatment of the ditosylate (369) with sodium iodide in boiling ethyl methyl ketone for 42 hours gave, after chromatographic purification, the desired diiodide product (373) as colourless crystals



(369) (373) (374)

in low yield. Bis-dehydroiodination was achieved by treatment with excess sodium hydride in tetrahydrofuran giving the diene (374) as a colourless solid, m.p. 95-98°C, in agreeable yield. Following full characterisation of this diene by elemental and spectroscopic examinations, a comparison of ^{1}H NMR spectra indicated the two dimethylene systems (374) and (78) to possess very similar olefinic resonances. The similarity in spectroscopic features was continued with respect to physical behaviour: both systems were found to readily polymerise on slow heating.

For the purpose of a comparative study of thermal fragmentation behaviour, the preparation was undertaken of two 4-thiatricyclo[5.2.0.$0^{2,6}$]-non-8-ene 4,4-dioxide based compounds, the hexacyclic (377) and pentacyclic

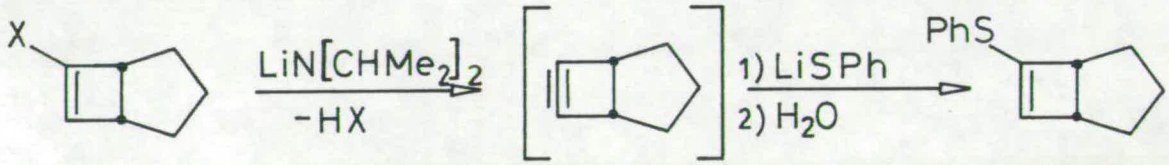

SO2
Br
Br
(309)
KO^tBu
THF
(Me3Si)2NLi
THF
-78°C
SO2
Br
(375)
SO2
(376)
Ph
Ph
Ph
O
Ph
(294)
Δ
PhH
Δ
THF
Ph
O
(292)
Ph
(292)
Ph
Br
O
SO2
Ph
Ph
(379)
Ph
O
SO2
Ph
(377)
B̈
(-HBr)
Ph
Br
O
SO2
Ph
(378)
Ph
Ph
O
SO2
Ph
(380)
Δ
-CO
Ph
Ph
SO2
Ph
Ph
(381)

Scheme 45

(380) systems which are respectively dehydro analogues of the previously prepared systems (293) and (295). It was anticipated that both these and the related benzo-fused system (381) could be obtained by manipulation of the novel transoid bromo-olefin (375), as outlined in Scheme 45.

Towards these objectives, the mono-dehydrobromination of the trans-dibromide (309) was effected by treatment with the hindered base, potassium t-butoxide in tetrahydrofuran at ambient temperature. A sole product, fully characterised as bromo-olefin (375), was isolated in high yield as colourless flakes, m.p. 131-132°C. Preparation of the hexacyclic system (377) appeared possible via a route parallel to that by which the bicyclic thioether (383) was obtained[186] from the precursor halobutene system (382), ie by the trapping of a cyclobutyne intermediate.

Thus, a solution of the bromo-olefin (375) and the Diels-Alder trapping diene, 1,3-diphenylisobenzofuran (292) in dry



(382) (383)

X = Br, Cl, I

tetrahydrofuran at -78°C was treated with the strong hindered base, lithium bis(trimethylsilyl)amide. After stirring at -78°C for 3.5 hours, and then at room temperature for 18 hours, work-up and chromatographic separation gave the recovered bromo-olefin (375) (21%) and a single aromatic-containing sulphone product. However, on detailed spectroscopic examination this material was found not to be the olefin (377), but rather was identified as a Diels-Alder adduct (378) of the two starting materials by comparison with an authentic sample prepared by heating

(375) and (292) in tetrahydrofuran. The failure to prepare system (377) may reflect the inability of the base, strong though it is, to effect dehydrobromination of (375) to generate the high-energy cyclobutyne intermediate (376), or indeed to cause dehydrobromination of the isolated product (378).

Synthesis of the second olefin target, the pentacyclic system (380), was undertaken by initial preparation of the precursor adduct (379) expected from a Diels-Alder combination of the bromo-olefin (375) and tetracyclone (294). Reaction of the two starting materials was conducted in boiling benzene, but even after a period of 125 hours some of the initial reagents remained. However, the desired adduct (379) was isolated in moderate yield as a slightly purple solid, m.p. (decomp.) 177-179°C, displaying expected elemental composition and spectroscopic features.

In contrast to the reaction of the parent transoid tricyclic olefin (208) with tetracyclone (294) (p.132) only a single one of the possible isomeric products resulted from reaction of the latter with (375). It would therefore appear that the effect of the bulky bromine substituent in system (375) is to increase the steric destabilisation of all the transition states leading to products (379), as evidenced by the slow rate of reaction of (375) compared to (208), with one transition state (leading to the isolated product) being less disfavoured than the others. Although the full stereochemistry of the tetracyclone adduct (379) is not known (in common with the 1,3-diphenylisobenzofuran adduct (378)), it is likely on steric grounds to be the structure formed on exo addition of the diene (294) to the less hindered face of olefin (375). A similar lowering of reaction rate was noted on reaction of the bromo-olefin (375) with 1,3-diphenylisobenzofuran (292) compared to the corresponding

reaction carried out on the unsubstituted olefin (208), lending weight to the above considerations.

Having obtained the adduct (379), the dehydrobromination of this was attempted with a view to preparing the system (380), a dehydro analogue of structure (295). Treatment of a solution of the bromide (379) with the hindered base, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran at 45°C for an extended period resulted in quantitative recovery of the starting sulphone. On progressing to the use of the stronger base, potassium t-butoxide in order to effect dehydrobromination, it was found that the starting sulphone (379) was consumed fairly quickly at room temperature in tetrahydrofuran solution. However, upon work-up neither the desired product (380) nor any other sulphone-containing product was isolated, frustrating a conceptually attractive synthesis of the benzo-fused system (381) by thermal extrusion of carbon monoxide from the diene (380).

F. Flash Vacuum Pyrolysis (FVP) of Systems Containing a transoid-4-Thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide Skeleton

The synthetic procedures described in earlier sections have been directed in part towards the preparation of a series of compounds containing the transoid-4-thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide nucleus. Resulting from this work, a number of tricyclic compounds (210), substituted members of the series (69; n = 2), were available for completion of a study of pyrolytic fragmentation behaviour for systems (69), for which examples of compounds where n = 1, 3, 4, 5 had previously been examined (see p.26).

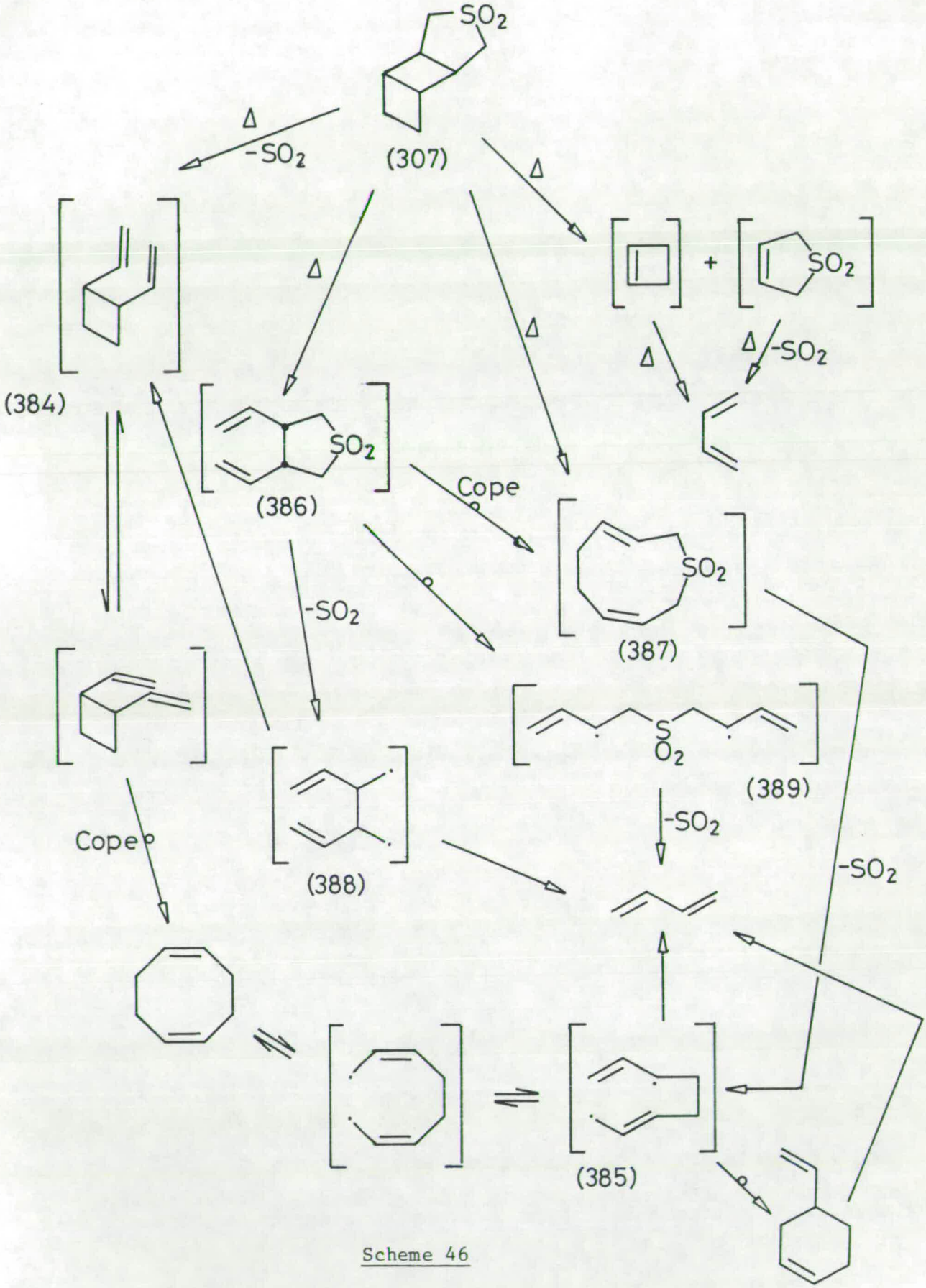
In addition to compounds (210), which may be regarded as systems (211; n = 0), a range of transoid, transoid tetracycles (211; n = 1, 2, 3, 4) were available for a study of the effect of ring size and composition of the terminal ring upon thermal fragmentation behaviour within the series (211). In order to facilitate the communication of the results of these studies, the remainder of this section is categorised into sub-sections each covering the pyrolysis of compounds (211) of a specific terminal ring size (n value), with the sub-sections arranged in order of increasing terminal ring size.

1. FVP of tricyclic systems containing a transoid-4-thiatricyclo-[5.2.0.$0^{2,6}$]nonane 4,4-dioxide skeleton

FVP at a furnace temperature of 650°C of the parent tricyclic system (307) was found to result in complete extrusion of sulphur dioxide. In addition to a small quantity of unidentified polymeric solid, the pyrolysate was found from GLC and ^{1}H NMR spectroscopic analyses to consist of 4-vinylcyclohex-1-ene (42% yield), (Z,Z)-cycloocta-1,5-diene (17%) and buta-1,3-diene (not quantified).

As detailed in Scheme 46, several mechanisms may be proposed for the formation of these products. Of the various possibilities, the thermal extrusion of sulphur dioxide [possibly *via* a concerted ($\sigma_{2s} + \sigma_{2s} + \sigma_{2s}$) cycloreversion] with formation of the intermediate *cis*-1,2-divinylcyclobutane (384) appears the most feasible in terms of formation of the observed products. In addition, this mechanism is fully compatible with that found for the thermal fragmentation of the members of the series (69; n = 1, 3, 4, 5) in which extrusion of sulphur dioxide to initially give a *cis*-1,2-divinylcyclic system (70) was observed (Scheme 11).

As demonstrated by Vogel[187] and verified by the kinetic studies of Hammond and deBoer[188], *cis*-1,2-divinylcyclobutane (384) undergoes a thermal Cope cyclisation within the temperature range 65-120°C to generate solely (*Z*,*Z*)-cycloocta-1,5-diene. The (*Z*,*Z*) geometry of this product is in contrast with the (*E*,*Z*) geometry normally encountered in Cope rearrangement products and which is associated with the generally lower energy chair (four-centre) transition state. In the case of *cis*-1,2-divinylcyclobutane (384) (and similarly for *cis*-1,2-divinylcyclopropane) the preferred chair transition state cannot be attained due to the steric constraints imposed upon the vinyl groups by attachment to the small ring, restricting Cope cyclisation to occur *via* the higher energy boat (six-centre) transition state to generate the more thermodynamically stable (*Z*,*Z*) [*cf.* (*E*,*Z*)]-cycloocta-1,5-diene product. The relief of ring strain on cyclisation of (384) promotes the Cope rearrangement *via* the higher energy boat transition state to such an extent that only comparatively mild thermal conditions are required for rearrangement.


SO2
Δ
-SO2
(307)
Δ
(384)
Δ
Δ
Δ
+
SO2
Δ
-SO2
SO2
(386)
Cope
SO2
(387)
-SO2
S
O2
(389)
-SO2
-SO2
Cope
(388)
(385)

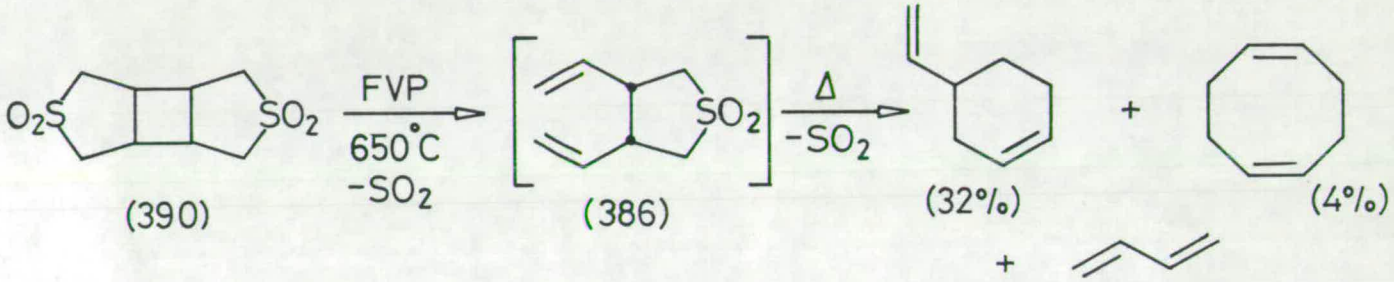
Scheme 46

With respect to the FVP of (307), the isolation of (Z,Z)-cycloocta-1,5-diene is therefore evidence for the intermediacy of cis-1,2-divinylcyclobutane (384). Furthermore, the presence of 4-vinylcyclohex-1-ene may be attributed to a thermal rearrangement of (Z,Z)-cycloocta-1,5-diene under the pyrolysis conditions employed: gas-phase pyrolysis (360°C, 1.5 mm Hg) of (Z,Z)-cycloocta-1,5-diene is known[189] to result in almost complete conversion to 4-vinylcyclohex-1-ene (ca 75%) - stable to FVP at 650°C [29] - and to buta-1,3-diene (ca 25%). Further kinetic studies by Benson[190] demonstrated that the mechanism of this rearrangement and of the dimerisation of buta-1,3-diene was compatible with the intermediacy of the allylically-stabilised diradical (385). Thus, all of the isolated volatile products arising from pyrolysis of (307) can be attributed to a mechanism involving initial formation of cis-1,2-divinylcyclobutane (384) and subsequent rearrangement of this intermediate.

Other possible mechanisms for the thermal fragmentation of (307) include ring opening, via a concerted[25] ($\sigma_{2s} + \sigma_{2a}$) or a diradical mechanism, to generate cis-3,4-divinylsulpholane (386). However, subsequent Cope cyclisation of this species to the (E,Z)-cyclonona-1,5-diene analogue (387) appears unlikely in consideration of the stability of comparable cis-1,2-divinylcyclopentane systems (e.g. (73)) to such cyclisations; direct formation of (387) by concerted ring opening of (307) is also disfavoured in consideration of the ring strain inherent in the (E,Z)-diene. Extrusion of sulphur dioxide from the divinylsulpholane (386) with generation of the intermediate diradical (388) does present a feasible route to the isolated products: fragmentation of (388) to yield buta-1,3-diene, and ring closure to cis-1,2-divinylcyclobutane (384) (and hence to (Z,Z)-cycloocta-1,5-diene and 4-vinylcyclohex-1-ene) is possible. Homolytic cleavage of the

divinyl intermediate (386) to form the bis-allylic radical species (389) may be discounted as a primary fragmentation route on the grounds that extrusion of sulphur dioxide from the latter would generate solely buta-1,3-diene.

The divinyl sulpholane (386) may also act as an intermediate in the thermal fragmentation of the transoid disulphone (390), following extrusion of one sulphur dioxide unit. FVP of (390) at

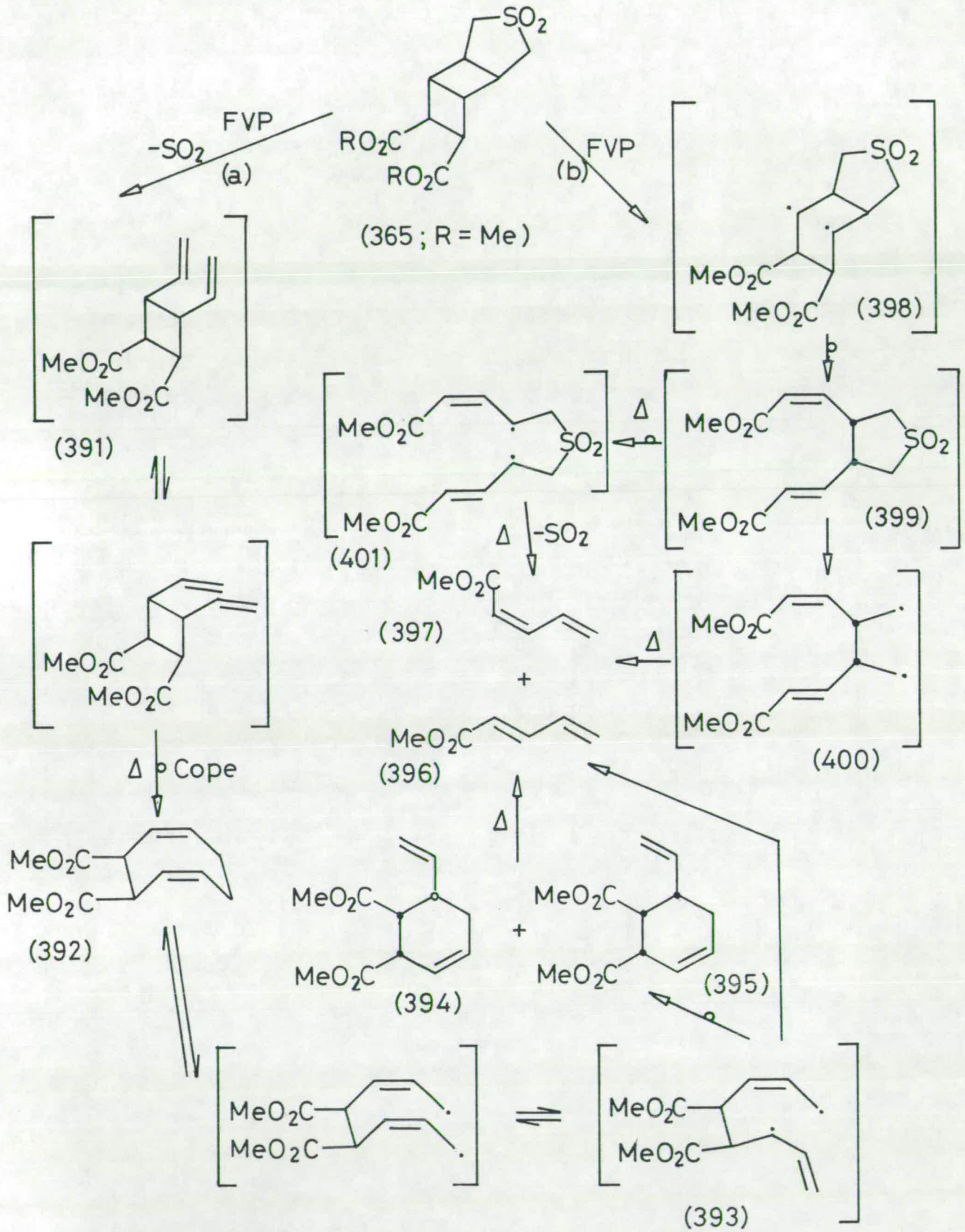


650°C, following the previously established conditions of Buchan[29], confirmed the formation of 4-vinylcyclohex-1-ene (32% yield), (Z,Z)-cycloocta-1,5-diene (4%) and buta-1,3-diene (not quantified). Although these products are the same as those obtained from FVP of (307) under identical conditions, the relatively low yield of the two C_8H_{12} hydrocarbons from (390) (presumably at the expense of an increased formation of buta-1,3-diene) taken in conjunction with the highly probable intermediacy of (386) tends to support the absence of this species in a major pyrolytic fragmentation pathway open to (307). Thus, there is indirect evidence for the thermal decomposition of (307) occurring via the initial intermediacy of cis-1,2-divinylcyclobutane (384) which forms the basis of the most feasible fragmentation pathway available to the system (307). This reasoning is far from conclusive since it is conceivable that the greater fragmentation of the carbon skeleton of (390) compared to that of (307) may reflect the greater vibrational effect of the stepwise loss of two sulphur dioxide molecules in the former compound.

A final fragmentation pathway open to tricyclic sulpholane (307) is the symmetry-forbidden cycloreversion to cyclobutene and butadiene sulphone, both of which would fragment to buta-1,3-diene under the pyrolysis conditions employed. Such a route should be disfavoured compared to others involving concerted ring opening of (307) [e.g. those leading to (384) and (386)] and in addition the inability of this mechanism to explain the formation of the principal pyrolysis products, 4-vinylcyclohex-1-ene and (Z,Z)-cycloocta-1,5-diene, restricts it to at best a minor role in the thermal decomposition of (307).

Turning to the pyrolysis of the exo-cis dimethyl ester analogue (365; R = Me), FVP at 650°C resulted in isolation of the (E)-(396) [77% yield] and (Z)-(397) [16%] isomers of methyl penta-2,4-dienoate. The two isomers were separated by preparative GLC and their structures verified by spectroscopic means. As shown in Scheme 47, two possible pathways (mirroring those shown in Scheme 46 for the parent tricycle (307)) to these products are outlined.

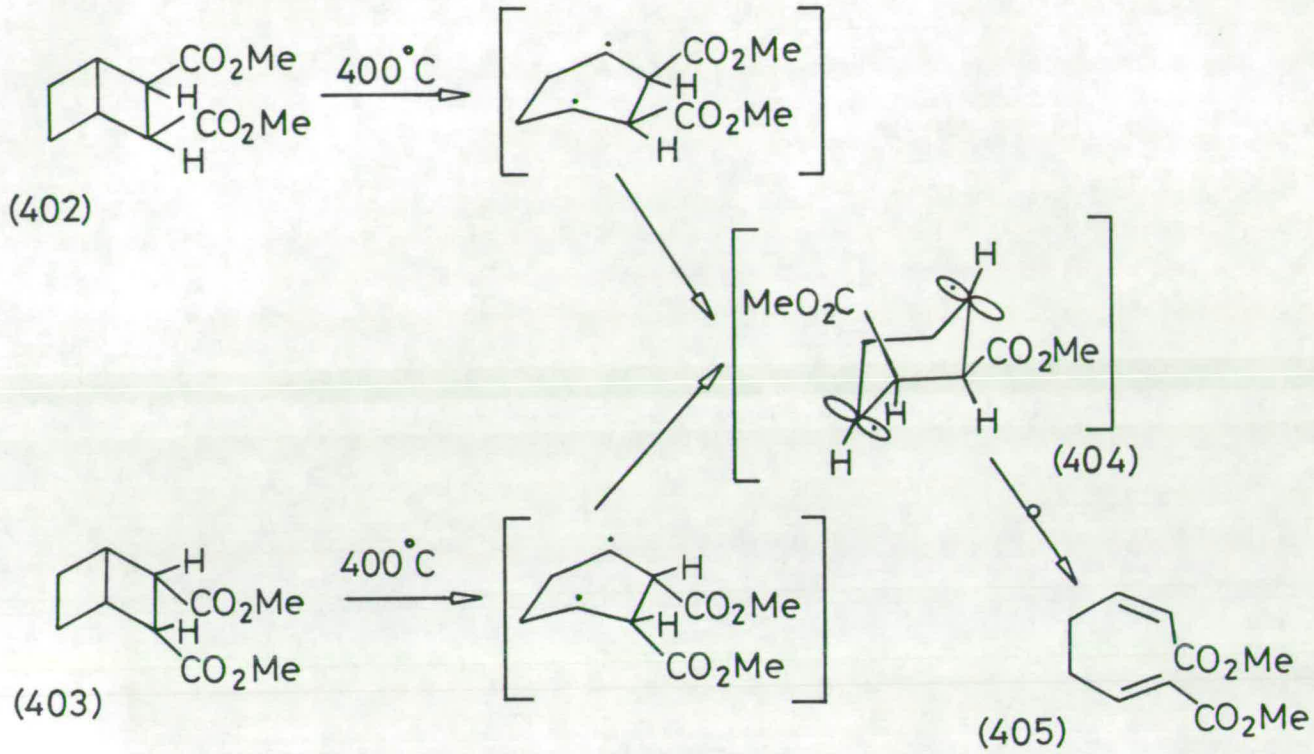
In analogy to the parent system (307), the diester (365; R = Me) may undergo thermal extrusion of sulphur dioxide (pathway (a)) with formation of the cis-3,4-divinylcyclobutane (391), an intermediate expected to cyclise via a Cope rearrangement to the (Z,Z)-cycloocta-1,5-diene (392). Homolytic cleavage of the latter to give the allylically stabilised diradical (393) followed by a dissociation would account for the formation of the isolated diene products (396) and (397). Alternatively, ring closure of diradical (393) to yield the 4-vinylcyclohex-1-ene systems (394) and (395) - intermediates capable of undergoing retro-Diels-Alder fragmentation to the two isolated products (396) and (397) - would also explain the outcome of the pyrolysis of (365; R = Me).


FVP
-SO2
(a)
RO2C
RO2C
SO2
(365 ; R = Me)
FVP
(b)
MeO2C
MeO2C
(391)
MeO2C
MeO2C
SO2
(398)
Δ
MeO2C
SO2
(401)
Δ
-SO2
MeO2C
SO2
(399)
MeO2C
(397)
+
MeO2C
(396)
Δ
MeO2C
(400)
MeO2C
MeO2C
Δ Cope
MeO2C
MeO2C
(392)
Δ
MeO2C
MeO2C
(394)
+
MeO2C
MeO2C
(395)
MeO2C
MeO2C
MeO2C
MeO2C
(393)

Scheme 47

Strong supporting evidence for the operation of pathway (a) involving the intermediacy of the cyclooctadiene (392) and isomeric 4-vinylcyclohex-1-enes (394) and (395) in the thermal fragmentation of (365; R = Me) was found following pyrolysis of a 5:70:25 mixture of (392), (394) and (395) (synthesis described later in this section). Under identical pyrolysis conditions to those employed with (365; R = Me) the mixture of the three isomers underwent fragmentation to the dienes (396) (66% yield) and (397) (13%). Following from the similar ratio (ca 5:1) of the diene products (396) and (397) arising from both pyrolyses, there is a high probability that a similar ratio (ca 2.8:1) of the 4-vinylcyclohex-1-ene isomers (394) and (395) are also involved in both cases. Such a ratio would not be unexpected for the cyclisation step involving rearrangement of the diradical (393) to the 4-vinylcyclohex-1-ene isomers, and thus the results of the pyrolysis of the three component mixture of (392), (394) and (395) furnish confirmatory evidence for the thermal fragmentation of (365; R = Me) as occurring via pathway (a).

The alternative decomposition route outlined in Scheme 47 (pathway (b)) is unlikely to occur in practice. A strong resemblance between the fused cyclobutane ring structure of (365; R = Me) and the bicyclic dimethyl esters (402) and (403) is apparent. Paquette and Schwartz have reported[31] that gas phase pyrolysis of these bicyclic isomers at 400°C (low pressure of nitrogen) gave almost identical mixtures of products containing ca 80% of the (E,Z)-diene (405), the product expected to result from a concerted ($\sigma_{2s} + \sigma_{2a}$) thermal cyclobutane ring opening. However, since (403) could not adopt the configuration necessary for a concerted ring opening mechanism due to steric factors, and both bicyclic isomers were found to require extreme pyrolysis conditions to effect fragmentation, Paquette



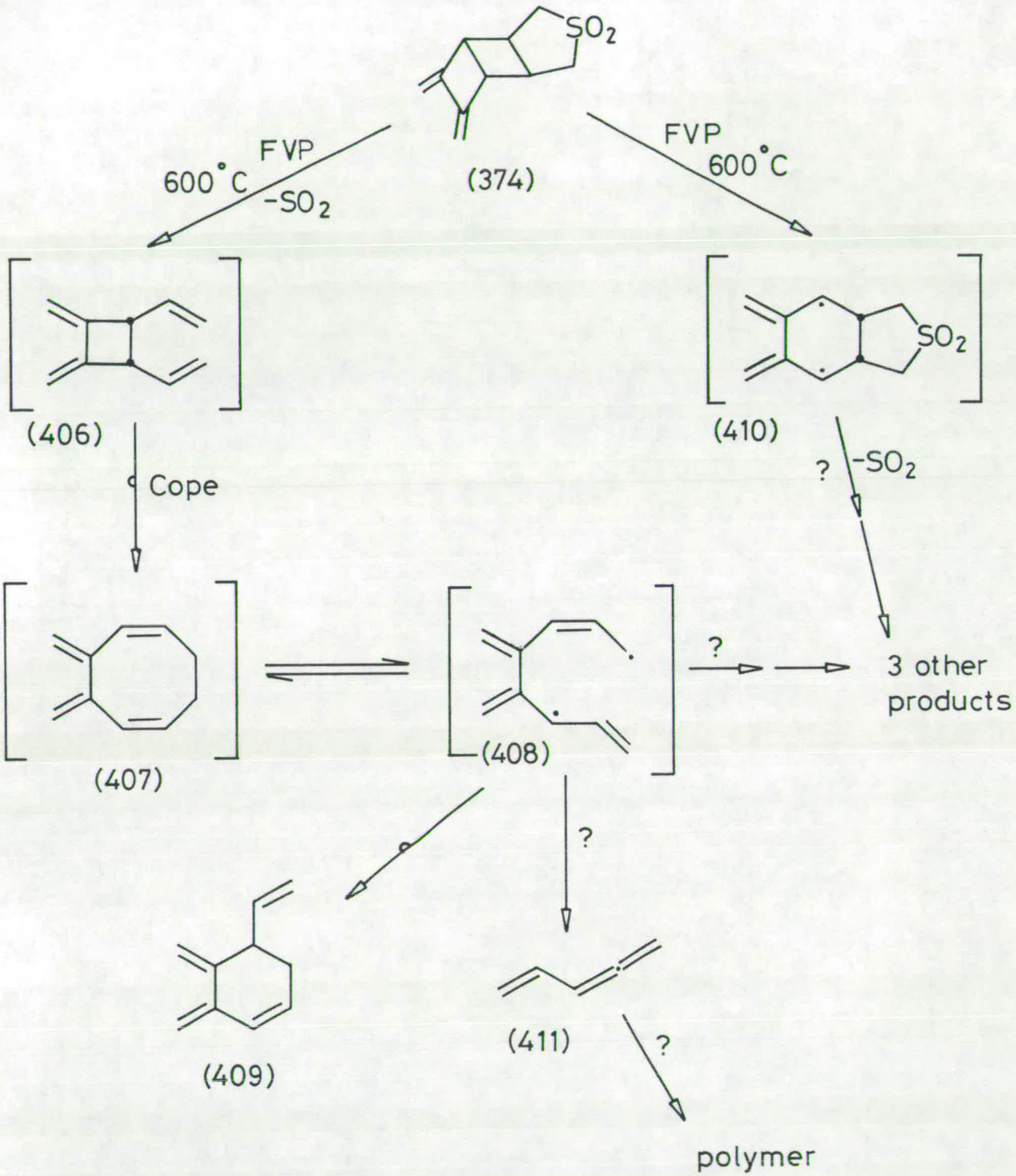
and Schwartz[31] concluded that both isomers dissociate *via* a common, chair-like diradical intermediate (404) to give the very similar product mixtures in which diene (405) is the predominant component.

Extending this literature precedent to the related sulphone system (365; R = Me) would suggest that fragmentation to the (*E*,*Z*)-diene (399) *via* intermediate diradical (398) is more feasible than the concerted ($\sigma_{2s} + \sigma_{2a}$) ring opening mechanism to the same species. Subsequent extrusion of sulphur dioxide from (399) to generate the diradical (400), or homolytic scission of the sulpholane ring of (399) to form the acyclic sulphone (401) affords two intermediates which are capable of fragmenting to the observed diene products (396) and (397). However, consideration of the (*E*,*Z*)-diene geometries of (400) and (401), assuming that the short lifetime of the latter restricts *cis*-*trans* olefin isomerisation, would predict that fragmentation of either would lead to an approximately equimolar mixture of the product dienes (396) and (397). This is obviously far removed from the experimental situation in which a *ca* 5:1 ratio of

(396) to (397) was obtained, and even allowing for a modest isomerisation of the cis-diene (397) to the trans isomer (396) under the pyrolysis conditions, fragmentation pathway (b) must be much less likely to operate than pathway (a) in the thermal decomposition of (365; R = Me).

A third compound containing the transoid-4-thiatricyclo-[5.2.0.$0^{2,6}$]nonane 4,4-dioxide skeleton which was available for pyrolysis was the 8,9-dimethylene system (374). In common with the bicyclic analogue (78), the tricyclic compound (374) displayed a ready tendency to polymerise on heating: thus, the majority of the sample placed in the FVP inlet was found to have polymerised on heating with only a small quantity volatilised for subsequent pyrolysis. Upon FVP at 600°C complete extrusion of sulphur dioxide was achieved to give a mixture of a yellow liquid and colourless polymeric solid.

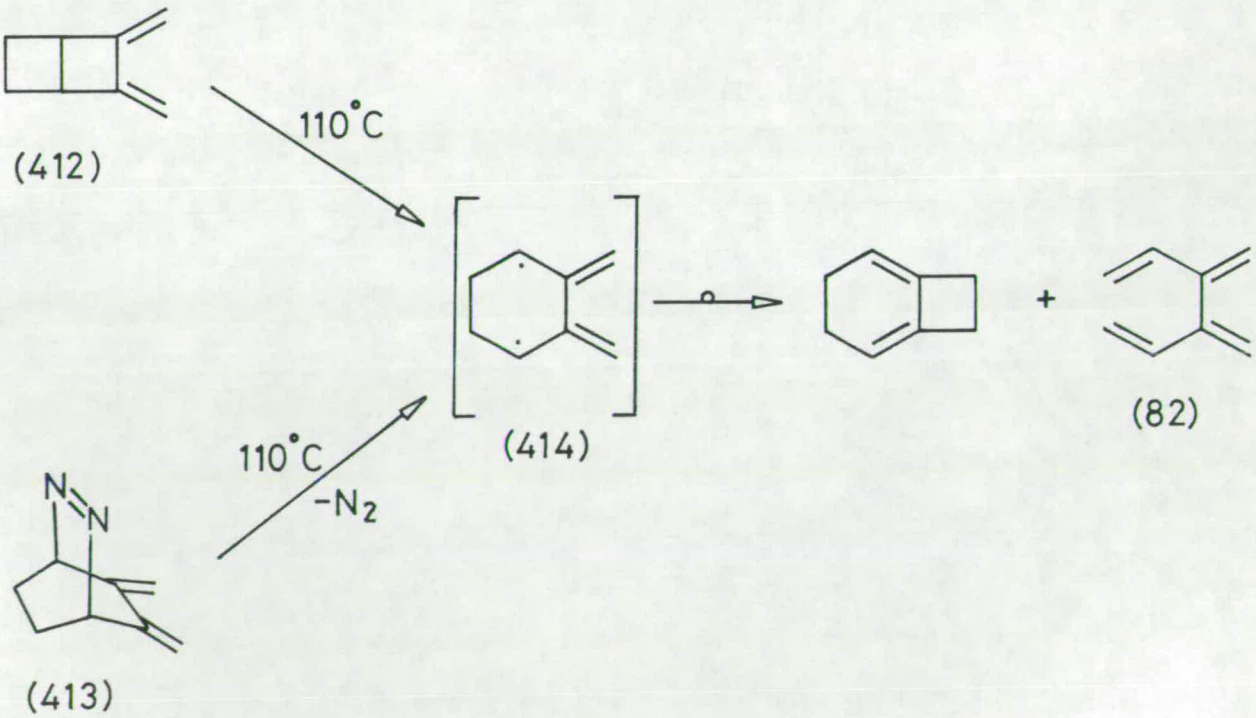
GLC analysis of the liquid product indicated the presence of four volatile components, and GC-MS data demonstrated that the predominant component was a $C_{10}H_{12}$ hydrocarbon (41% yield). The minor species were found to be of formula $C_{10}H_{12}$ (8%, 8%) and $C_{10}H_{10}$ (2%) and while these remain unidentified the major product was tentatively assigned the vinylcyclohexene structure (409) on the basis of ^{1}H NMR and GC-MS fragmentation data. Full confirmation of this structure was not possible due to material limitations, although further support for the vinylcyclohexene nature of the major product may be drawn from the pyrolyses of the sister compounds (307) and (365; R = Me) which generated 4-vinylcyclohexene structures as products or suspected intermediates. In parallel with these related tricyclic sulphones, the fragmentation of (374) appears most likely to occur via initial extrusion of sulphur dioxide with subsequent Cope cyclisation of the cis-divinylcyclobutane intermediate (406)


SO2
FVP
600°C
-SO2
(374)
FVP
600°C
(406)
Cope
(410)
SO2
?
-SO2
(407)
(408)
?
3 other
products
?
(409)
(411)
?
polymer

Scheme 48

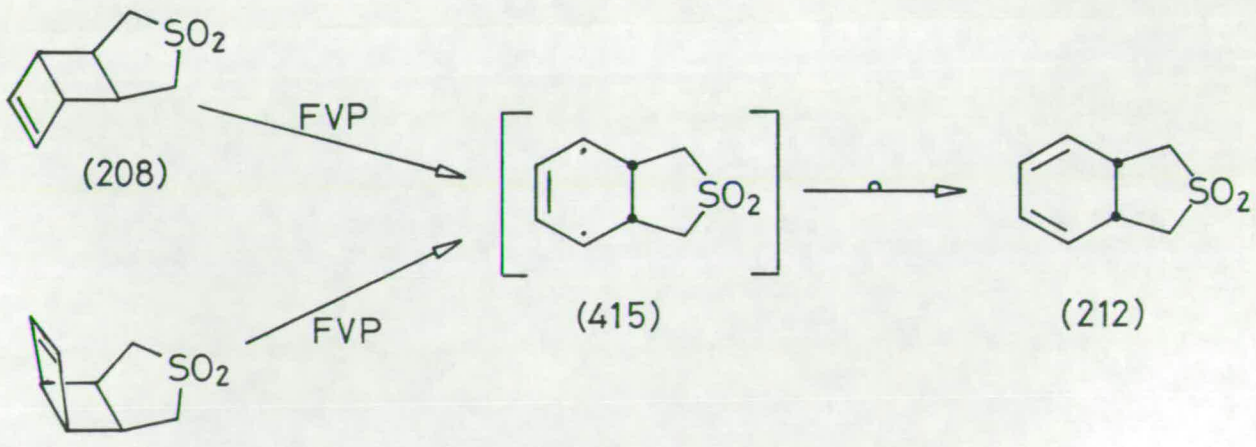
and rearrangement of the resultant cyclooctadiene (407) to the isolated vinylcyclohexene product (409) *via* the allylically stabilised diradical (408) (Scheme 48).

One of the minor $C_{10}H_{12}$ products obtained may correspond to the (*Z*,*Z*)-cycloocta-1,5-diene (407) if a direct parallel between the pyrolysis of (307) (which yielded 4-vinylcyclohex-1-ene and (*Z*,*Z*)-cycloocta-1,5-diene) and (374) is upheld. The remaining volatile components may originate from rearrangement/ dehydrogenation processes operating upon the highly unsaturated diradical (408) in competition to the radical coupling reaction giving rise to the product (409). Alternatively, the minor products may be formed *via* fragmentation of the diradical sulpholane system (410). The formation of (410) is feasible in consideration of the diradical (414) proposed[191] to explain the common products resulting from gas-phase thermolysis of the bicyclic dimethylene systems (412) - structurally very similar to the fused cyclobutane-cyclobutane portion of the sulphone (374) - and (413).



In contrast to the pyrolyses of (307) and (365; R = Me) in which buta-1,3-diene based products were formed in significant quantities, no such products were isolated from the pyrolysis of (374). This may be accounted for by the highly reactive nature of the allene product (411) which would be formed in the latter case from fragmentation of diradical (408) or product (409). Should the high-energy allene species (411) be formed during pyrolysis, dimerisation in the FVP trap upon warming giving rise to one or both of the $C_{10}H_{12}$ minor products, or polymerisation with other available unsaturated species generating the isolated polymeric solid, would not be unexpected.

Two remaining tricyclic sulpholane systems, which may be regarded as 8,9-dehydro analogues of the saturated systems (307), (365; R = Me) and (374), are the transoid and cisoid isomers (208) and (209). FVP at 400°C of the transoid compound (208) resulted in isolation of a mixture of starting sulphone (22%) and the cis-fused (Z,Z)-cyclohexadiene sulpholane (212) (73% yield). Upon raising the furnace temperature to 650°C, complete consumption of starting material was achieved to give the bicyclic system (212) in high yield. Similarly, FVP at 400°C of the cisoid isomer (209) resulted in formation of a mixture of starting sulphone (6%) and bicyclic sulpholane (212) (94% yield).



The common formation of product (212) starting from either (208) or (209) emphasises the isomeric nature of these tricyclic compounds, and the thermal ring-opening behaviour observed is in accord with literature precedent for such isomeric pairs. Thus, the cisoid and transoid isomers of tricyclic anhydride (317) have been found[109] to undergo thermal ring opening to the common cyclohexadiene anhydride (233; R = Me, X = O).

A common mechanism for the ring opening of (208) and (209) is indicated, though this is unlikely to be concerted in nature since strict application of orbital symmetry considerations[25] to the thermal fragmentation of the cyclobutene moiety would predict the formation of an impossibly strained (E,Z)-cyclohexa-1,3-diene rather than the (Z,Z)-diene product (212) actually formed. Homolytic cleavage of the cyclobutane-cyclobutene fusion bond in (208) and (209) with formation of the common allylically stabilised diradical (415) is likely, with the latter then undergoing facile rearrangement to the isolated (Z,Z)-diene product (212).

In accord with this mechanism, the much higher ratio of diene (212) to starting tricyclic sulphone found for the cisoid isomer (209) compared to the transoid isomer (208) following FVP at 400°C reflects a greater tendency for thermal dissociation to diradical (415) in the former case. This may be attributed to the greater steric destabilisation of the cisoid isomer (209) by interactions within the system (discussed in detail in Section D) which results in a smaller activation energy barrier to be thermally overcome in the homolytic cleavage to the diradical (415).

In summary, of the five tricyclic sulpholane systems whose pyrolyses have been described in this section, the unsaturated isomers (208) and (209) have been found to undergo ring opening, by virtue of

the position of the olefin moiety, to give an isomeric bicyclic system (212); at similar pyrolysis temperatures the saturated tricyclic systems (307), (365; R = Me) and (374) extrude sulphur dioxide and rearrange *via* a *cis*-1,2-divinylcyclobutane intermediate to cycloocta-1,5-diene, 4-vinylcyclohex-1-ene and derived fragmentation products. The pyrolyses of these last three compounds (which belong to the class of compounds (69; n = 2)) complete the study of the thermal fragmentation behaviour of the tricyclic series (69; n = 1, 2, 3, 4, 5). It can be concluded that all of these systems undergo extrusion of sulphur dioxide upon FVP at 500-650°C to generate *cis*-1,2-divinylcyclic species (70). These were isolated in the cases (70; n = 3, 4, 5); for the examples (70; n = 1, 2) Cope cyclisations occurred to generate cyclohepta-1,4-diene and cycloocta-1,5-diene (with rearrangement of these in part to 4-vinylcyclohex-1-ene products) systems respectively.

2. FVP of transoid,transoid-10-hetero-5-thiatetracyclo[7.1.0.$0^{2,8}$.$0^{3,7}$]decane 5,5-dioxide systems (278)

As described previously, the *transoid*, *transoid* tetracyclic compounds (278; X = O, CH_2, S) were prepared in quantities sufficient to allow a comparative study of thermal fragmentation to be undertaken. It was desired to establish the mechanism of fragmentation of these compounds, which conform to the class (211; n = 1), as part of the series (211; n = 1, 2, 3, 4). In this respect, it was recognised that the systems (278), being the most strained class of compounds within the tetracyclic series (211; n = 1, 2, 3, 4) due to fusion of the highly angle strained three-membered ring to the basic 4-thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide skeleton, would present the greatest opportunity for a dichotomy of thermal fragmentation behaviour. Thus, in addition to direct extrusion of sulphur dioxide the possibility

of competing ring-opening reactions (in relief of ring strain) with formation of isomeric unsaturated sulphone products was believed to be most relevant to the series (278; X = O, CH_2, S). Within this series, the effect of replacement of the methylene unit (X = CH_2) by the heteroatoms oxygen or sulphur upon the course of thermal decomposition was considered worthy of investigation.

FVP of the epoxide (278; X = O) was carried out initially at 400°C and yielded, as shown by inspection of the ^1H NMR spectrum of the pyrolysate, a mixture of starting epoxide (60% recovered) and two isomeric unsaturated sulphones (27%, 13%). Upon increasing the furnace temperature to 500°C, FVP of (278; X = O) resulted in complete consumption of starting olefin to give a ca 2:1 mixture of the same two unsaturated sulphone products encountered on FVP at 400°C.

These were separated by preparative TLC to give the major component (at lower R_f) as colourless crystals, m.p. 78-78.5°C, which exhibited elemental composition and mass spectral data in accord with those of an isomer of the starting epoxide (278; X = O). The symmetric and unsaturated nature of product is evident from the ^1H and ^{13}C DEPT NMR spectra [Figure 24(a)]. Since the ^{13}C DEPT spectrum displayed only four carbon environments including a methylene signal at a position characteristic of the sulpholane α-methylene unit together with two dissimilar olefinic methine signals, a tentative assignment of this product to the cis-fused bicyclic structure (416; X = O) was made. Further evidence in support of this assignment was derived from the proton spectrum. This indicated the most deshielded signal at δ6.27 (corresponding to protons H_3,H_5 - deshielded by the adjacent oxygen atom) and the next most deshielded signal at δ4.76 (H_2,H_6) to each display a common cis-vicinal olefinic coupling constant $J_{2,3}$ ($J_{5,6}$) = 7.8 Hz. Comfortable accord exists between this spectrum and

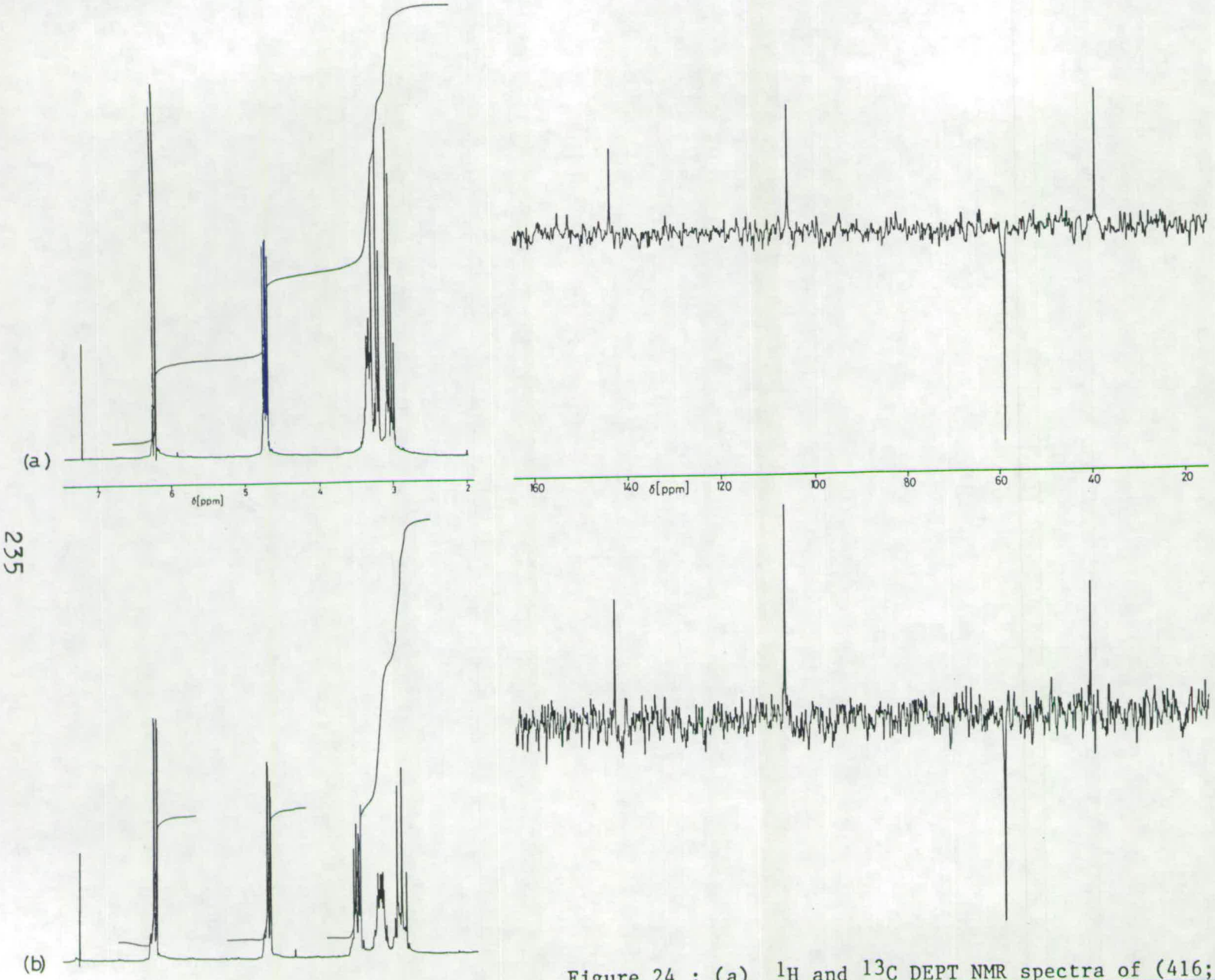
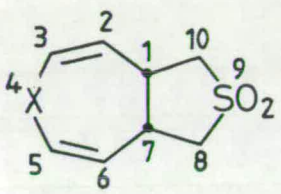


Figure 24 : (a) ^{1}H and ^{13}C DEPT NMR spectra of (416; X = O)

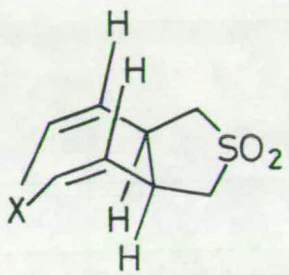
(b) ^{1}H and ^{13}C DEPT NMR spectra of (418; X = O)

that reported[192] for the related bicyclic structure (417), described as containing signals at δ 6.15 (H_3,H_5) and δ 4.61 (H_2,H_6) each displaying a cis-vicinal olefinic coupling constant $J_{2,3}$ ($J_{5,6}$) = 8.5 Hz.

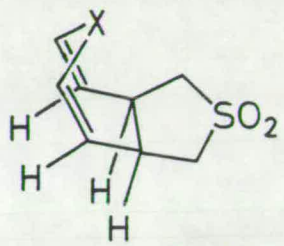
The signal at δ 4.76 (H_2,H_6) in the proton spectrum of (416; X = O) also displays the coupling constant $J_{1,2}$ ($J_{6,7}$) = 5.1 Hz.



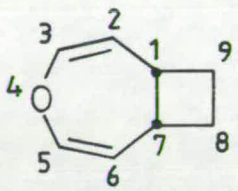
(416)



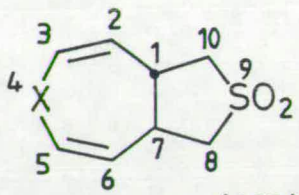
(416a)



(416b)



(417)



(418)

Following examination of Dreiding models of the two cis-fused conformers (416a; X = O) and (416b; X = O) and of the trans-fused isomer (418; X = O), the magnitude of $J_{1,2}$ ($J_{6,7}$) was found only to be compatible with the cis-fused isomer (416; X = O), confirming the earlier structural assumption. With regard to the two cis-fused conformers (416a; X = O) and (416b; X = O), which may possibly interconvert at room temperature, the dihedral angle $\phi_{1,2}$ ($\phi_{6,7}$) for the latter of ca 20° is in greater accord with the observed value of $J_{1,2}$ ($J_{6,7}$) than the corresponding dihedral angle of ca 130° in (416a; X = O). This implies that (416b; X = O) is the major - possibly the sole - contributing conformer within the NMR timescale at ambient temperature.

Returning to the separation of the two unsaturated products realised on pyrolysis of (278; X = O), preparative TLC allowed separation of the minor component (at higher R_f) to give a pure specimen of colourless crystals, m.p. 125-126°C. Microanalytical and mass spectral data verified that this product was isomeric with the starting epoxide, and determination of the ^1H and ^{13}C DEPT NMR spectra [Figure 24(b)] further established it as structurally very similar to the cis-fused bicyclic dihydrooxepin (416; X = O) earlier described.

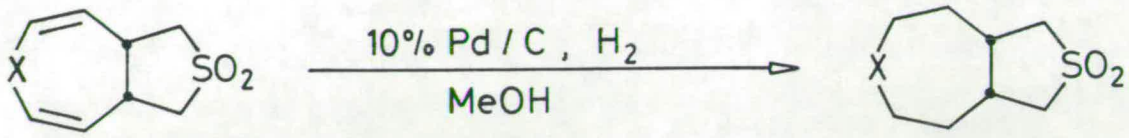
From the NMR data, a cis-vicinal olefinic coupling constant $J_{2,3}$ ($J_{5,6}$) = 7.4 Hz taken in conjunction with the obvious two-fold symmetry of the system suggests that the minor pyrolysis product could be either the trans-fused bicyclic dihydrooxepin (418; X = O) or, more unlikely, the 'frozen' cis-fused conformer (416a; X = O). The latter alternative was rejected for reasons described later in this section, but good accord was found between the observed value of $J_{1,2}$ ($J_{6,7}$) = 1.9 Hz for the minor product [Figure 24(b)] and that predicted from measurement of dihedral angles of a Dreiding model of the trans-fused dihydrooxepin (418; X = O). Inspection of the model indicated that two identical conformers were possible and that should a rapid interconversion (compared to the NMR timescale) occur between the two at room temperature then the time-averaged structure, possessing an almost planar dihydrooxepin ring and dihedral angle $\phi_{1,2}$ ($\phi_{6,7}$) $\simeq$ 95°, would account for the observed value of $J_{1,2}$ ($J_{6,7}$).

Circumstantial evidence in support of the structure elucidations made with respect to the two pyrolysis products obtained from epoxide (278; X = O) can be inferred from a comparison of the physical properties of the isomeric cis- and trans -fused cyclohexadiene-sulpholanes (212) and (235). For this pair, the trans-fused isomer (235)

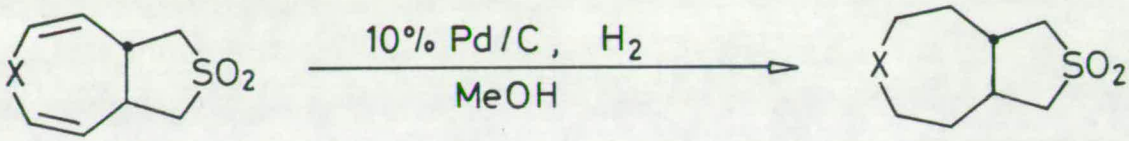
is found to melt at a considerably higher temperature (129-132°C) and to exhibit less polar characteristics (demonstrated by a higher R_f value on TLC (silica; ether)) than the corresponding cis-fused isomer (212), m.p. 35-36.5°C. These differences parallel the melting point and polarity differences (as measured by R_f values on TLC (silica; ether)) found for the cis-fused (416; X = 0) and trans-fused (418; X = 0) dihydrooxepin-sulpholanes.

In order to finally and unambiguously relate the isomeric nature of the two dihydrooxepin pyrolysis products to a difference in ring fusion stereochemistry rather than to a difference in dihydrooxepin ring conformation or olefin stereochemistry, the separated isomers were submitted to catalytic hydrogenation. Thus, hydrogenation of the major (expectedly cis-fused) pyrolysis product in methanol solution using one atmosphere of hydrogen in the presence of palladium-on-carbon resulted in isolation of a colourless oil which refused to crystallise. This material was fully characterised as a single, saturated bicyclic compound of structural type (419; X = 0).

In contradistinction, hydrogenation of the minor (expectedly trans-fused) pyrolysis product gave a high yield of a single, fully-saturated bicyclic compound as colourless crystals, m.p. 95-97°C. These were again fully characterised and found to be isomeric, but not identical, to the hydrogenation product realised on hydrogenation of the major dihydrooxepin pyrolysis product. The findings of exhaustive hydrogenation of the two unsaturated isomers resulting from pyrolysis of the epoxide (278; X = 0) therefore vindicate the initial assignments of cis-fused (416; X = 0) and trans-fused (418; X = 0) geometries since two different products, namely the cis-fused (419; X = 0) and trans-fused (420; X = 0) hexahydrooxepin-sulpholanes were obtained. If the differences in structure of the two isomeric



(416) (419)



(418) (420)

dihydrooxepin starting materials had been based upon conformational or olefin-geometry factors only a single identical product would have been obtained upon hydrogenation of each diene.

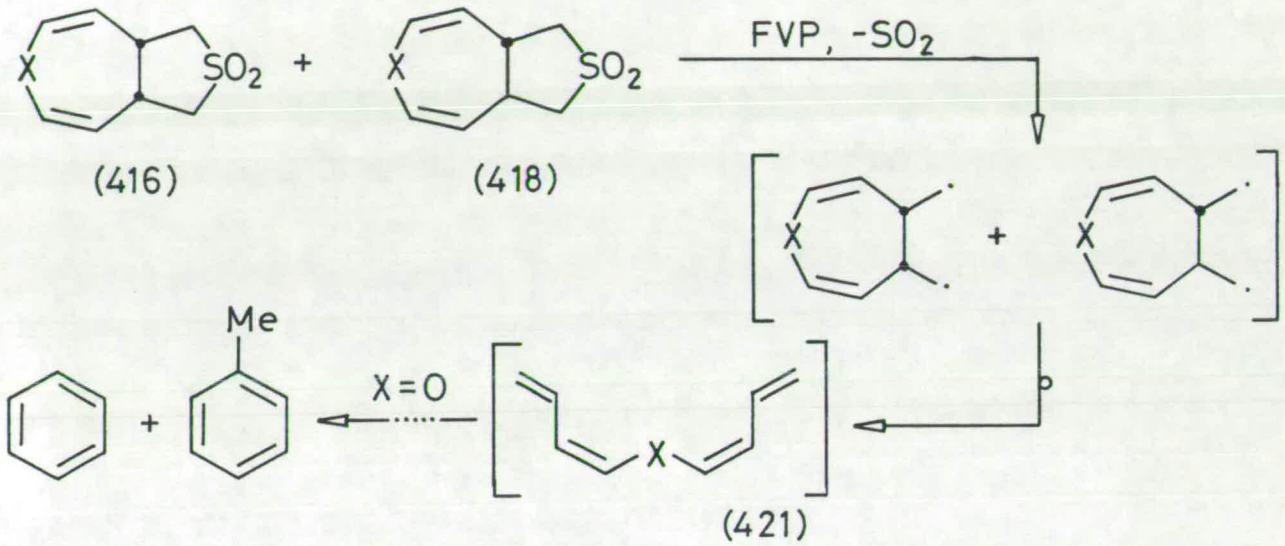
Having established the structures of the unsaturated products derived from FVP of epoxide (278; X = O) at 500°C, the mechanism of formation of these remains to be addressed. In order to establish if - under the pyrolysis conditions employed - one of the two isolated isomeric products rearranged to generate the other, each isomer was separately pyrolysed at 500°C (ie under the conditions from which these were formed from the epoxide (278; X = O)). In fact, FVP of the cis-fused isomer (416; X = O) and of the trans-fused isomer (418; X = O) at 500°C resulted in quantitative isolation of starting material in each case. The lack of isomerisation between the two products under the conditions at which these formed on fragmentation of (278; X = O) suggests that both are derived from a common intermediate. The mechanism of formation of the products (416; X = O, CH_2, S) and (418; X = O, CH_2, S) from (278; X = O, CH_2, S) is discussed in collective detail later in this section.

FVP of the epoxide (278; X = O) was investigated at higher temperatures. At 650°C, analysis of the pyrolysate (after removal of a colourless polymeric product) demonstrated the presence of a single sulpholane product, the cis-fused bicyclic dihydrooxepin system (416; X = O) in 22% yield, together with toluene (13%) and benzene (6%). The absence of the trans-fused product (418; X = O) is indicative either of an alteration in fragmentation mechanism to the detriment of formation of this product, or reflects a relative thermal instability of the trans-fused isomer compared to the cis-fused product (416; X = O) under the more extreme conditions. Consideration of the greater ring strain inherent in the trans-fused bicyclic system (418; X = O) would countenance the latter of the two options.

FVP of the epoxide (278; X = O) at the still higher temperature of 750°C resulted in isolation of toluene (21% yield) and benzene (19%) only. Evidence that these volatile hydrocarbons were generated by extrusion of sulphur dioxide from an intermediate mixture of the dihydrooxepins (416; X = O) and (418; X = O) was obtained following FVP at 750°C of a 2:1 respective mixture of these isomers, after which a similar mixture of toluene (21% yield) and benzene (13%) was obtained.

Although the mechanism of formation of these aromatic species remains undetermined, the forcing pyrolysis conditions required are in accord with a radical cleavage of the sulpholane ring of the dihydrooxepin intermediates with the possible subsequent intermediacy of the dibutadienyl ether (421; X = O) (Scheme 49). The latter clearly has a number of potential rearrangement pathways and the formation of the two thermodynamically stable aromatic hydrocarbons found would not be unexpected in view of the harsh pyrolysis conditions employed. However, the low isolated yields of toluene and benzene on

pyrolysis at 750°C does suggest that other fragmentation pathways are available to the dihydrooxepin intermediates which result in the formation of very volatile, hence undetected, products.



Scheme 49

Pyrolysis of a second member of the tetracyclic series (278), the cyclopropyl system (278; X = CH_2) was next attempted. On consideration of angle strain factors[193], the cyclopropyl compound would be expected to be the most easily ring opened of the series (278; X = O, CH_2, S). In fact this was found to be the case. Following FVP at 400°C, the cyclopropyl tetracycle (278; X = CH_2) was partially ring opened to give a mixture of recovered starting material (37%) and a single isomeric unsaturated product (62%). Thus, the cyclopropyl system is clearly more susceptible to thermal ring opening (in relief of angle strain) than the corresponding epoxide (278; X = O) which was recovered unchanged under identical pyrolysis conditions.

FVP of (278; X = CH_2) at 500°C resulted in complete consumption of starting sulphone giving a single isomeric product in quantitative yield. The semi-solid product was tentatively assigned the cis-fused (Z,Z)-cyclohepta-1,4-diene-sulpholane structure (416;

X = CH_2) on the basis of ^1H and ^{13}C DEPT NMR spectra, and by analogy to the predominant unsaturated sulphone product resulting from FVP of the epoxide (278; X = O) at similar temperatures. No corresponding trans-fused isomer (418; X = CH_2) could be observed, although GLC analysis established the presence of a very small quantity of a single volatile product, found by GC-MS to be a C_9H_{12} hydrocarbon. In accord with the fragmentation pathway displayed in Scheme 49, this hydrocarbon may be the acyclic compound (421; X = CH_2), formed by extrusion of sulphur dioxide from (416; X = CH_2). This assignment remains speculative.

Increasing the pyrolysis temperature still further (600°C) resulted in conversion of (278; X = CH_2) to the bicyclic system (416; X = CH_2) in almost quantitative yield. The difference of ca 4% in yield was accounted for by the formation of nine C_9H_{12} products (established by GC-MS) with the sole C_9H_{12} compound detected on lower temperature pyrolyses present predominantly. Following FVP of (278; X = CH_2) at 700°C, the same nine hydrocarbons were obtained in approximately equimolar amounts but accounted for a much higher proportion of the starting sulphone (278; X = CH_2): the sole sulphone-containing product (416; X = CH_2) was therefore present in much reduced yield (ca 45%). The volatile components possibly arise directly by extrusion of sulphur dioxide from (416; X = CH_2) or indirectly via rearrangement processes operating on the single volatile component found on pyrolysis at lower temperature (500°C), possibly of structure (421; X = CH_2). Incidentally, the isolation of significant quantities of (416; X = CH_2) on FVP of (278; X = CH_2) at 700°C contrasts with the situation previously encountered with the epoxide (278; X = O) in which FVP at the slightly higher temperature of 750°C resulted in the absence of the corresponding product (416; X = O). It is therefore apparent that (416; X = CH_2) is considerably more thermally stable than the

oxygen analogue (416; X = O). Furthermore, this demonstrated thermal stability of the bicyclic product derived from pyrolysis of the cyclopropyl system (278; X = CH_2) furnishes indirect supportive evidence for the provisional assignment of cis-fused geometry previously made, by analogy to the greater thermal stability of the cis-fused dihydrooxepin (416; X = O) over the trans-fused isomer (418; X = O).

Pyrolysis of the third and final member of the series (278), the episulphide system (278; X = S), was next undertaken. Following FVP of this compound at 600°C, a pyrolysate consisting of a colourless polymeric solid and yellow oil was obtained. Examination of the latter by ^{1}H and ^{13}C DEPT NMR indicated the presence of the cis-fused cyclohexadiene-sulpholane (212) (3% yield) and an unsaturated system, isomeric with the starting episulphide, which was provisionally assigned structure (416; X = S) (18%). Capillary GC-MS analysis of the product mixture confirmed the presence of only these two sulphone products, although a fairly involatile product of formula $C_8H_{10}S$ displaying a fragmentation pattern in expectation with that of the acyclic sulphide (421; X = S) was also detected. A number of resonances found solely within the olefinic region of the carbon spectrum and not due to the two sulphone products were taken as further evidence for this tentative assignment of structure. Finally, examination of the product mixture for volatile components by GLC established the presence of minor quantities of benzene, toluene, o-xylene and styrene which are the thermal degradation products found (described later) on pyrolysis of bicyclic system (212) at elevated temperatures.

Unfortunately, the two sulphone products (212) and (416; X = S) could not be resolved by TLC, although a 1:5 (respectively) ratio of the two was separated by preparative TLC from the other components of the product mixture and found to satisfy microanalytical requirements.

Upon reduction of the pyrolysis temperature to 500°C, FVP of (278; X = S) gave a pyrolysate containing less polymeric product, with starting episulphide (10% recovered), the bicyclic sulphide (416; X = S) (28%) and the sulphur-extrusion product (212) (5%) together with reduced quantities of the four aromatic hydrocarbons and the $C_8H_{10}S$ product (possibly of structure (421; X = S)) found on FVP of (278; X = S) at 600°C all being detected.

The presence of significant quantities of starting episulphide (278; X = S) in the 500°C pyrolysate is in marked contrast to the complete consumption of starting materials (278; X = O, CH_2) on FVP at the same temperature. This finding is in agreement with known[193] angle strain factors which indicate episulphide rings to be less strained and hence less liable to undergo thermal ring-opening reactions than the corresponding epoxide and cyclopropane systems. Although the episulphide system (278; X = S) is more resistant to thermal ring opening, the range of products obtained upon ring opening at 500°C differs strongly from the situation found upon pyrolysis of the two related structures (278; X = CH_2, O) which fragmented to give respectively one and two bicyclic unsaturated products, isomeric with the starting sulphone.

It is therefore apparent that in addition to the ring-opening process resulting in formation of the bicyclic sulpholane systems (416; X = S) and possibly (418; X = S), other competing thermal fragmentation pathways are operating on the starting episulphide (278; X = S) or on the above two isomeric species. With respect to the thermal fragmentation of the episulphide, the relative lack of angle strain in the three-membered ring acts to disfavour the predominant formation of the ring-opened isomers (416; X = S) and (418; X = S) compared to the epoxide and cyclopropyl systems. This

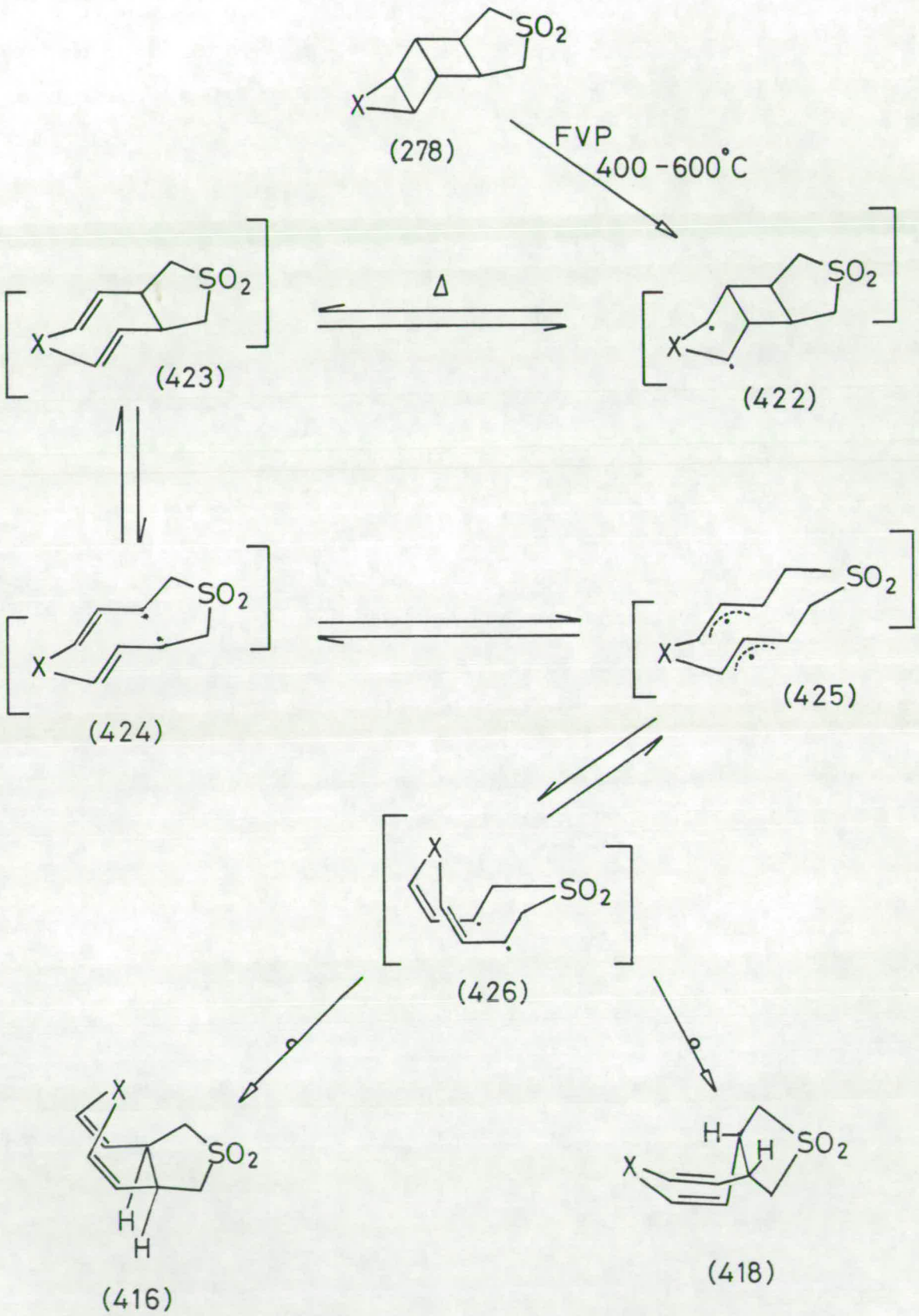
factor, taken into account with the relative weakness of the carbon-sulphur bond (cf. carbon-oxygen or carbon-carbon bonds) and the ease of extrusion of sulphur, explains the presence of the bicyclic system (212), formed by loss of sulphur from (278; X = S) followed by (the previously described) ring opening of the resultant tricyclic sulphone intermediate (208) under the pyrolysis conditions employed (500°C). Fragmentation of the vibrationally excited cyclohexadiene-sulpholane (212) to the four aromatic hydrocarbons observed is in accord with the thermal decomposition of (212) at elevated temperatures (described later, p.328). Incidentally, the formation of (212) and derived hydrocarbon extrusion products on pyrolysis of (278; X = O, CH_2) at 500°C was not observed due to the extremely high activation barrier required to be overcome in the extrusion of monatomic oxygen or methylene.

Formation of the single $C_8H_{10}S$ product which was detected in significant quantities on FVP of (278; X = S) at 500°C, and in higher amounts on FVP at 600°C, may be due to thermal extrusion of sulphur dioxide from (416; X = S) which was isolated in low yield at 500°C, and lower yield at 600°C in keeping with this reasoning; the trans-fused isomer (418; X = S), which although not isolated upon FVP of (278; X = S) may nonetheless be present as a pyrolysis intermediate, could also be a source of this product, thought to be of structure (421; X = S). A less likely alternative is that the sulphide product is derived by direct extrusion of sulphur dioxide from the episulphide (278; X = S) with formation of an intermediate cis-1,2-divinylbicyclo-[2.1.0]pentane based system. However, the lack of an equivalent fragmentation pathway for the two related tetracycles (278; X = O, CH_2) under identical pyrolysis conditions furnishes evidence against this mechanism for the episulphide system (278; X = S); the effect of the

substituent X upon fragmentation of the remote sulpholane ring would be minimal in all three members of the series (278) and therefore such a mechanism if operational in one case would be operational in all three.

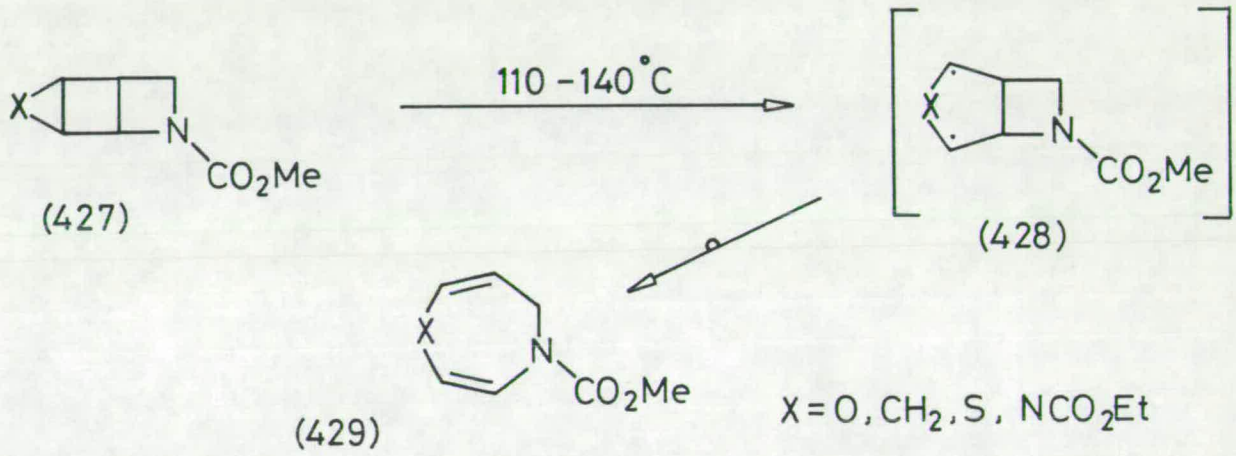
Having pyrolysed all three members of the series (278; X = O, CH_2, S) it is apparent that each compound on FVP within the range 400-600°C principally undergoes a thermal ring opening to form as an isolated product, the cis-fused bicyclic system (416; X = O, CH_2, S) and in the case of (278; X = O) to generate the trans-fused isomer (418; X = O). In view of these facts, a common mechanism may be proposed for the ring opening of the series (278). The results of pyrolysis of this series are strongly dependent on the substituent X, the empirically determined order of ease of ring opening being : X = CH_2 > X = O > X = S. This order mirrors that of the ring strain energy inherent in the corresponding parent three-membered rings (due largely to angle strain) found[193] to be : cyclopropane (105 kJ mol^{-1}) > ethylene oxide (54 kJ mol^{-1}) > ethylene sulphide (38 kJ mol^{-1}). Assuming that fusion of each of the three-membered rings to the transoid-4-thiatricyclo[5.2.0.$0^{2,6}$]nonane 4,4-dioxide skeleton retains the same order of ring strain in the resultant tetracyclic series (278), it can be seen that the more strained the three-membered ring in (278) then the more easily will the system undergo thermal ring opening to the bicyclic structures (416) and (418).

Mechanistically, the implication of such ring strain factors is that initial fragmentation of (278) occurs at the most strained bond in the system which is affected by the presence of the three-membered ring. Thus, a mechanism involving initial cleavage of the fusion bond between the three-membered and cyclobutane rings is implicated, as outlined in Scheme 50. In terms of literature precedent,



Scheme 50

this initial stage in the fragmentation pathway of (278) would be expected to occur *via* a homolytic cleavage of the fusion bond by analogy to the reported[142] thermolytic ring opening of the related 3-azatricyclo[4.1.0.$0^{2,5}$]heptane systems (427) to the (*Z*,*Z*)-diheterocycloheptadiene products (429) *via* the postulated diradical intermediate (428).



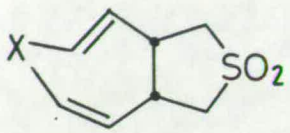
Homolytic cleavage then of (278) with formation of diradical (422) appears the most likely initial step of the mechanism by which products (416) and (418) are derived from (278). Thereafter, a reversible ring opening of diradical (422) with formation of the highly strained (hence intermediate) (*E*,*E*)-diene system (423) may be expected at elevated temperatures; facile fragmentation of the remaining ring fusion bond in order to alleviate ring strain would result in the formation of a comparatively stable bis-allylic radical (424), capable of adopting the more thermodynamically stable (*Z*,*Z*)-diene geometry of (426) prior to intramolecular radical coupling to form both *cis*-fused (416) and *trans*-fused (418) bicyclic (*Z*,*Z*)-diene products.

This mechanism is the most obvious one in accord with the available information. It is in accord, for example, with the previously detailed finding that no isomerisation was found between

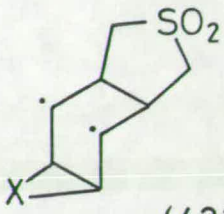
the cis-fused and trans-fused bicyclic isomers (416; X = O) and (418; X = O) under the conditions of formation of these from (278; X = O) since both products are formed from a common, comparatively high-energy diradical intermediate (426). A point remaining to be clarified is the dichotomy in the number of bicyclic sulpholane products formed which exists between (278; X = O) and the other two class members (278; X = CH_2, S). In this respect, it is apparent that a substituent X which can inductively stabilise either or both of the diradical intermediates (422) and (425) would encourage the formation of both the cis- and trans-fused bicyclic products and so the explanation clearly does not lie in the radical-stabilising ability of the group X. Nonetheless, the isolation of both bicyclic isomers (416) and (418) only in the case of FVP of the epoxide (278; X = O) is dependent upon the nature of the group X. Since this moiety can affect a cyclic system both in terms of ring strain and thermal stability, it may be that of the three systems (418; X = O, CH_2, S) only in the case of (418; X = O) is formation both energetically favourable from cyclisation of (426; X = O), and is the resultant trans-fused product stable to the pyrolysis conditions employed.

Although the intermediacy of the allylically stabilised diradical generally represented by structure (425) appears very likely in the transformation of systems (278) to the observed bicyclic products, there are alternative routes to the formation of (425) other than the one outlined in Scheme 50. Concerted ($\sigma_{2s} + \sigma_{2a}$) ring opening of (278) could generate this species by homolytic cleavage of the ring-fusion bond in the resultant highly strained (E,Z)-diene intermediate (430). Alternatively, thermal homolysis of the cyclobutane-cyclobutane ring-fusion bond of (278) may prevail with formation of the diradical (431) which would then be expected to rearrange to the (E,E)-diene (423), the precursor to (425) discussed previously.

Since the presence of angle strain in three-membered rings



(430)



(431)

is known[194] to result in formation of 'bent' or 'banana' bonds rich in p-orbital character (and hence may be regarded as partially olefinic in character), the formation of (E,E)-diene (423) via intermediate (431) would be analogous to the formation of the cis-fused cyclohexadienesulpholane (212) from the transoid olefin (208). Although this point furnishes some support for the initial homolytic cleavage process operating on (278) as occurring via diradical (431) rather than (422), the variation of ease of thermal ring opening with angle strain induced by the presence of the group X is more in accord with the intermediacy of the latter diradical, and the sequence of rearrangements shown in Scheme 50 appears the most feasible route to the observed products.

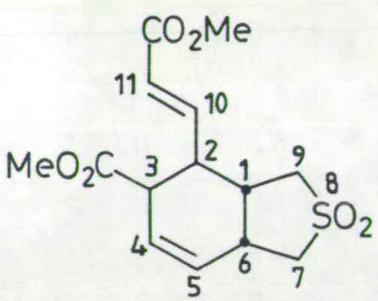
3. FVP of a transoid, transoid-5-thiatetracyclo[7.2.0.$0^{2,8}$.$0^{3,7}$]-undecane 5,5-dioxide system

The dimethyl ester (306) was the only example of the class (211; n = 2) whose pyrolysis was undertaken. In similar fashion to the smaller ring series (211; n = 1), the diester (306) was believed to offer the possibility of competing ring-opening reactions of the strained portion of the system in addition to extrusion reactions upon pyrolysis.

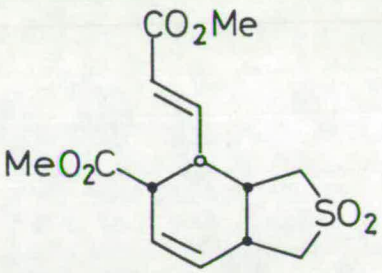
FVP of diester (306) at 300°C resulted solely in recovery of starting material in high yield. Upon increasing the furnace temperature to 400°C, FVP gave a pyrolysate found by ^{1}H NMR analysis to consist of recovered starting sulphone (306) (39%) together with at least two unsaturated sulphone-containing products (believed to be isomeric with starting sulphone (306) (ca 40% combined yield). TLC (silica; ether) analysis indicated these two unidentified products to possess R_f values of 0.37 and 0.48, although material limitations prevented chromatographic separation and subsequent identification of these. Analysis of the pyrolysate by GLC indicated that seven volatile components were present in minor quantities, although none of these were identified.

A comparatively large scale (100 mg) FVP of the diester (306) at 500°C resulted in isolation of a pyrolysate consisting of a yellow oil and polymeric solid. Analysis of the former component by TLC indicated the absence of starting sulphone (confirmed by ^{1}H NMR analysis) and the presence of the two sulphone product spots observed in the 400°C pyrolysate together with an additional, major sulphone product spot at lower R_f. Separation of the three sulphone-containing fractions was achieved by preparative TLC. The lowest R_f component was isolated in the highest yield, and analysis of the resultant colourless oil by means of elemental composition and mass spectral determinations confirmed this substance to be isomeric with the starting tetracyclic sulphone (306). Following examination by ^{1}H, ^{1}H-2D COSY and ^{13}C NMR spectroscopy the product was established as being a 3:1 mixture of two isomeric diester-substituted vinylcyclohexene-sulpholane structures (432). Thus, the ^{13}C NMR spectrum displayed the presence of 14 carbon resonances for each isomer, with the close structural relationship between the two products evident from the large

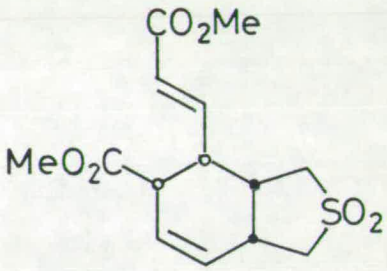
number of almost coincidental signals. Evidence for the vinylcyclohexene structure of each isomer was apparent from the olefinic region of the spectrum which contained four resonances for each isomer, with one of the four markedly deshielded compared to the remaining three as a consequence of allylic conjugation with the ester carbonyl group. In addition, the presence in each isomer of two dissimilar carbonyl chemical shift values, at ca δ 166 (typical of an α,β-unsaturated ester carbonyl chemical shift) and at ca δ 172 (typical of an isolated ester carbonyl chemical shift) are in agreement with the proposed general structure (432) for both isomeric products.



(432)



(432a)



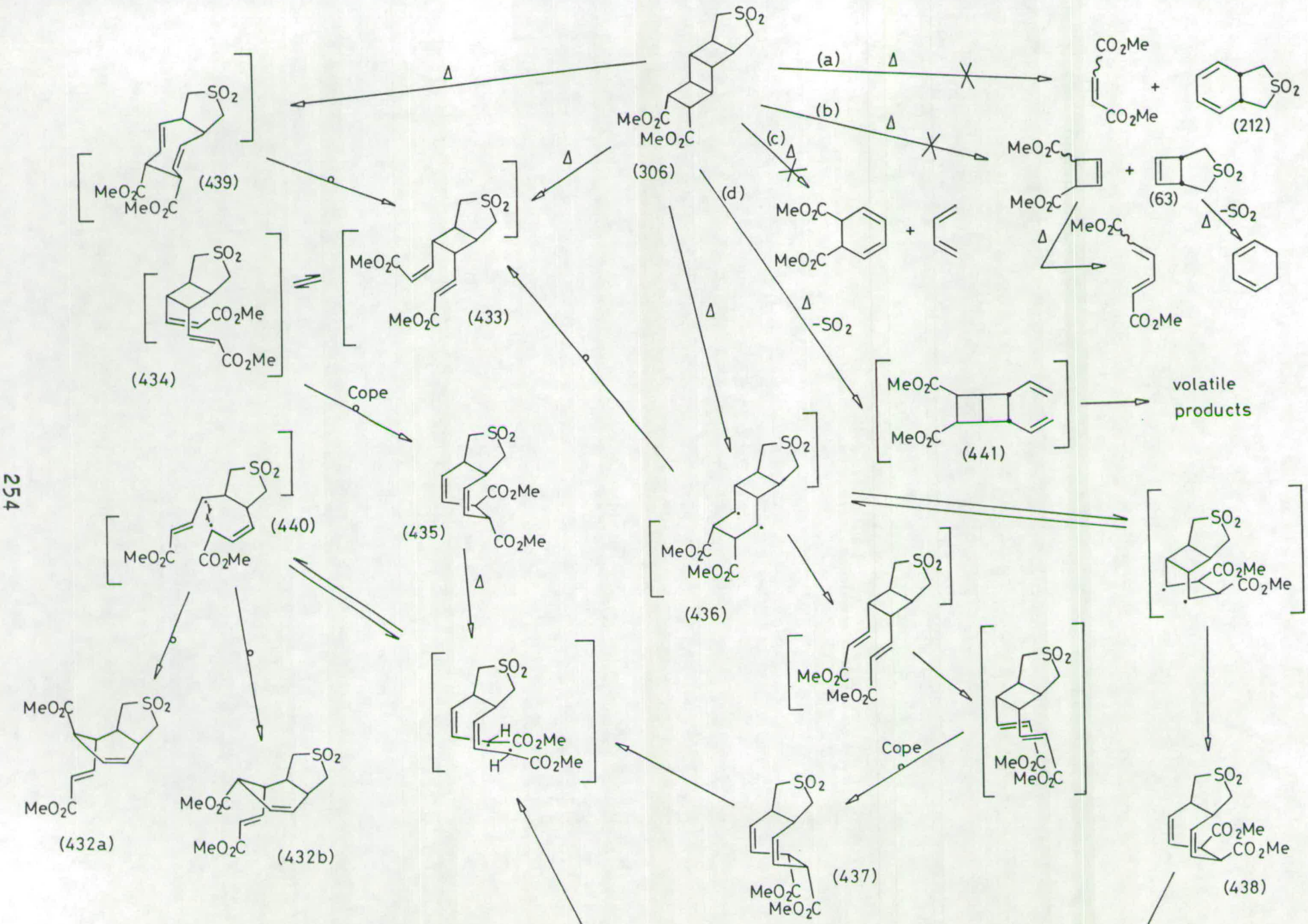
(432b)

A detailed examination of the ^{1}H NMR (and ^{1}H-2D COSY) spectrum of the mixture also confirmed the vinylcyclohexene nature of the two products. Thus, the major isomer exhibited a doublet of doublet signal at δ 6.59 - assigned to the allylically deshielded methine proton H_{10} - containing a trans vicinal olefinic coupling constant $J_{10,11}$ = 13 Hz (together with the vicinal coupling constant $J_{2,10}$ = 8 Hz) in accord with a trans vinyl stereochemistry. Similarly, the minor isomer displayed an almost identical signal at δ 6.83. In spite of the determination of a ^{1}H-2D COSY spectrum of the isomeric mixture, no definate assignments of the 2-vinyl and 3-methoxycarbonyl substituents could be made based upon the available information. However, tentative assignments of the major and minor isomers to structures (432a) and (432b) respectively appear reasonable since

such isomers, differing only in the stereochemistry of the 3-methoxycarbonyl substituent, would be expected to demonstrate the very similar ^{13}C NMR resonances which were found. Furthermore, these two structures, each with the bulky vinyl substituent disposed on the opposite face of the cyclohexene ring to that of the fused sulpholane ring, represent the two least sterically congested of the four possible isomers of system (432).

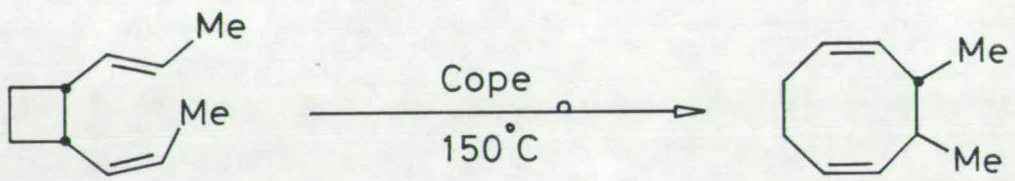
The two other sulphone-containing product fractions which were separated by preparative TLC were isolated as liquids in very low yield which restricted identification of these. Analysis of both fractions by ^{1}H NMR spectroscopy indicated these to possess similar spectra in accord with olefinically unsaturated sulpholane systems, possibly diester-substituted cycloocta-1,5-diene-sulpholane in nature. In addition, GLC analysis of the pyrolysate prior to chromatographic separation determined that twelve volatile components, including the seven found on FVP of (306) at 400°C, were present. Two of these predominated, but none of them were identified; comparison of GLC retention times with authentic samples of the volatile products which would be formed if the diester (306) fragmented *via* possible pathways (a), (b) and (c) (Scheme 51) confirmed that none of these options was operational in practice.

As outlined in Scheme 51, a number of alternative mechanisms may be proposed for the formation of the two vinylcyclohexene products (432a) and (432b) from the tetracyclic system (306). Concerted ($\sigma_{2s} + \sigma_{2a}$) fragmentation of the two terminal cyclobutane rings is a feasible low temperature pathway (operating at an FVP temperature of 400°C) to the intermediate (*E*,*Z*)-divinylcyclobutane (433). This species would be expected, under the pyrolysis conditions, to undergo a Cope rearrangement *via* a boat conformation. The chair conformation,


(306)
(a) Δ
(b) Δ
(c) Δ
(d)
(212)
(63)
(439)
(433)
(434)
(435)
(436)
(437)
(438)
(440)
(441)
Cope
Cope
-SO2
volatile products
(432a)
(432b)

Scheme 51

which is generally the lower energy route for the Cope rearrangement, cannot be adopted in this case due to the geometrical constraints imposed by cis-fusion of the vinyl groups to the cyclobutane template. This situation is therefore very similar to the Cope cyclisation of the (E,Z)-cis-dipropenylcyclobutane (442) which has been reported[195] as yielding trans-3,4-dimethyl (Z,Z)-cycloocta-1,5-diene (443) upon heating to 150°C. Thus, Cope cyclisation of the conformer (434) to form the trans-diester substituted (Z,Z)-cycloocta-1,5-diene (435) would be expected in preference to cyclisation of the alternative conformer (433) to a highly strained (E,E)-cycloocta-1,5-diene system. The former cyclooctadiene may be one of the unidentified products resulting from FVP of (306) at 400°C and 500°C.

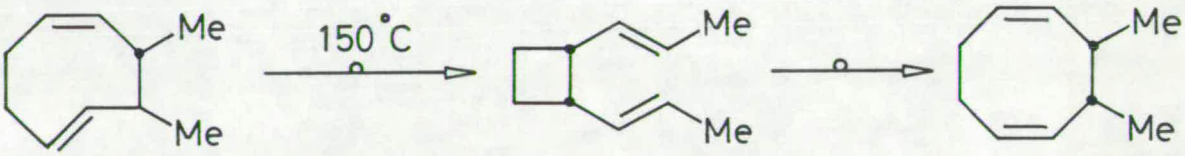


(442) (443)

An alternative route to the intermediate (433) and hence to cyclooctadiene (435) may be proposed. The diradical (436) may be formed from (306) in a similar homolytic cleavage process to that by which the diradical (404) was obtained from the related exo-cis diester-substituted bicyclo[2.2.0]hexane system (402)[31]. Since the diradical (404) then thermally rearranged via a chair-like conformation to the (E,Z)-diene product (405), a similar transformation of (436) to (433) may be in order. Consultation of a Dreiding model of the diradical (436) indicated that it could attain the necessary chair conformation required for rearrangement to the (E,Z)-divinylcyclobutane (433), and hence an alternative route from (306) to (435) appears possible.

Incidentally, the diradical (436) may also undergo the transformations depicted in Scheme 51 with formation of the two (Z,Z)-cycloocta-1,5-diene products (437) and (438), which may well be the unidentified unsaturated products obtained on FVP of (306) at both 400°C and 500°C.

One further mechanism by which the trans-diester substituted cyclooctadiene (435) may be constructed involves the concerted (σ_{2s} + σ_{2a}) fragmentation of the three cyclobutane rings of (306) to generate the intermediate (E,Z)-cyclooctadiene (439). Although the high strain inherent in (439) acts in disfavour of this mechanism, facile rearrangement of the intermediate to the trans-diester (435) via intermediates (433) and (434) is perfectly feasible as a means of relieving ring strain. Indeed, a precedent has already been established for such a rearrangement: the trans-dimethyl (E,Z)-cycloocta-1,5-diene (444) has been reported[196] as converting to the cis-dimethyl (Z,Z)-cycloocta-1,5-diene (445) via a cis-divinylcyclobutane species upon heating at moderate temperatures.



(444) (445)

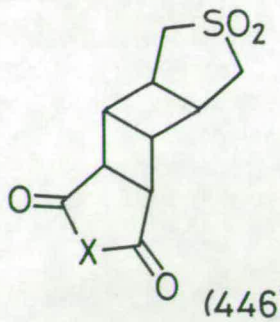
In practice, the two vinylcyclohexene structures (432a) and (432b) were not formed on FVP of (306) at 400°C, although at least two unsaturated sulphones, possibly two of the cyclooctadiene structures (435), (437) and (438), were detected. The decrease in yield of these unidentified products on FVP of (306) at 500°C coincides with the isolation of significant quantities of the two isomeric vinylcyclohexene products. This change in product distribution is in accord with a thermal homolytic fragmentation of the suspected cyclooctadiene

systems (435), (437) and (438) at the higher temperature with generation of the common bis-allylic radical (440). The conjugated, and hence long-lived, nature of diradical (440) should allow this intermediate to adopt a suitable conformation prior to radical coupling with formation of the two most thermodynamically stable vinylcyclohexene products (432a) and (432b).

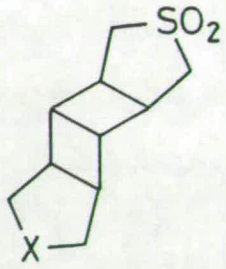
Formation of the twelve unidentified volatile products detected on FVP of (306) at 500°C may occur by direct extrusion of sulphur dioxide followed by rearrangement and fragmentation of the resultant divinylcyclobutane intermediate (441); similar extrusion processes operating on the miriad of sulphone systems shown in Scheme 51 may also account for the number of volatile products observed.

4. FVP of transoid, transoid-11-thiatetracyclo[7.3.0.$0^{2,8}$.$0^{3,7}$]-dodecane 11,11-dioxide based systems

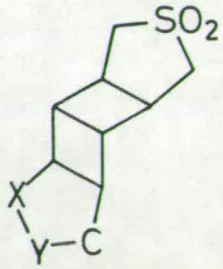
A large number of compounds belonging to the title compound class, which may be represented by structure (211; n = 3), were available for pyrolysis. In contradistinction to the thermal fragmentation behaviour of the tetracycles (211; n = 1, 2) which contain small, strained terminal rings, the comparatively strain-free five-membered terminal ring series (211; n = 3) would be predicted to undergo direct thermal extrusion of sulphur dioxide rather than to undergo thermal ring-opening reactions to isomeric unsaturated sulphone products. The tetracyclic compounds (211; n = 3) which were available for a study of thermal fragmentation behaviour were found to fall into three distinct sub-classes, represented by the general structures (446), (447) and (448). Each of these sub-classes is now considered in turn.



(446)



(447)



(448)

a. FVP of transoid-4-thiatricyclo[5.2.0.$0^{2,6}$]nonane-exo-cis-8,9-dicarboxylic heterocyclic systems (446)

The three members of the title class (446), the syntheses of which have been described previously, are the N-phenylimide (354), the anhydride (242a) and the thioanhydride (360).

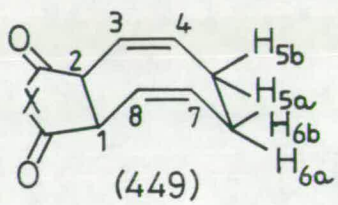
FVP of the N-phenylimide (354) at 650°C was found to be inefficient due to the thermal degradation of the bulk of the pyrolysis sample in the inlet upon application of the inlet oven temperature of 200°C found to be necessary to effect volatilisation. However, from the quantity of (354) which was volatilised (assumed unchanged) a high yield of sulphur dioxide extrusion products was realised. Analysis of this by ^{1}H NMR and GLC/ GC-MS determinations indicated the presence of three isomeric $C_{16}H_{15}NO_2$ (M^+ 253) structures in 85, 5 and 4% yields (in order of increasing GLC retention time).

In order to circumvent the problems of sample involatility, the imide (354) was submitted to vertical vacuum pyrolysis (VVP) [for a description of this technique see p.433] at 600°C. An almost quantitative yield of the same three products found upon FVP at 650°C was obtained, although the ratio of these was markedly different (67, 4 and 26% yield in order of increasing GLC retention time).

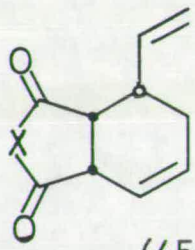
The presence of increased quantities of the product with the longest retention time in the pyrolysate (a light yellow oil) allowed separation of this as fine colourless needles (19% isolated

yield), m.p. 164-167°C following crystallisation from methylene chloride/ diisopropyl ether. Elemental composition and mass spectral analyses confirmed the earlier GC-MS findings that this product possessed a formula of $C_{16}H_{15}NO_2$, and the purity of the sample was proved following GLC analysis which indicated only the longest retained of the three isomers in the crude pyrolysate to be present.

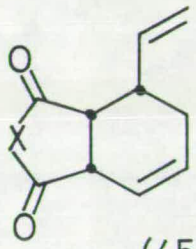
With a view to establishing the structure of this compound, examination of the infrared spectrum showed that the sulphone group was absent and that the imide functionality had been retained. Consultation of the ^1H and ^{13}C NMR spectra proved to be of most utility. As reproduced in Figure 25, the symmetric nature of the spectra taken in conjunction with the disposition of signals was in full accord with the cis-fused (Z,Z)-cycloocta-1,5-diene structure (449; X = NPh). Although the olefinic region of the ^1H NMR spectrum



(449)



(450)



(451)

was not first order, selective decoupling ^1H NMR studies allowed the identification of the cis-olefinic coupling constant $J_{3,4}$ ($J_{7,8}$) = 10.9 Hz together with the trans vicinal coupling constant $J_{1,8}$ ($J_{2,3}$) = 2.4 Hz. The overall geometry of the bicyclic system (449; X = NPh) was verified by NOE irradiation of the signal due to protons H_{5a},H_{6a} ($-\delta$ 2.5) which resulted in a 7% enhancement in the signal associated with protons H_1,H_2 (δ 4.14): the spacial proximity of these proton pairs is in agreement solely with structure (449; X = NPh) for the cyclooctadiene product.

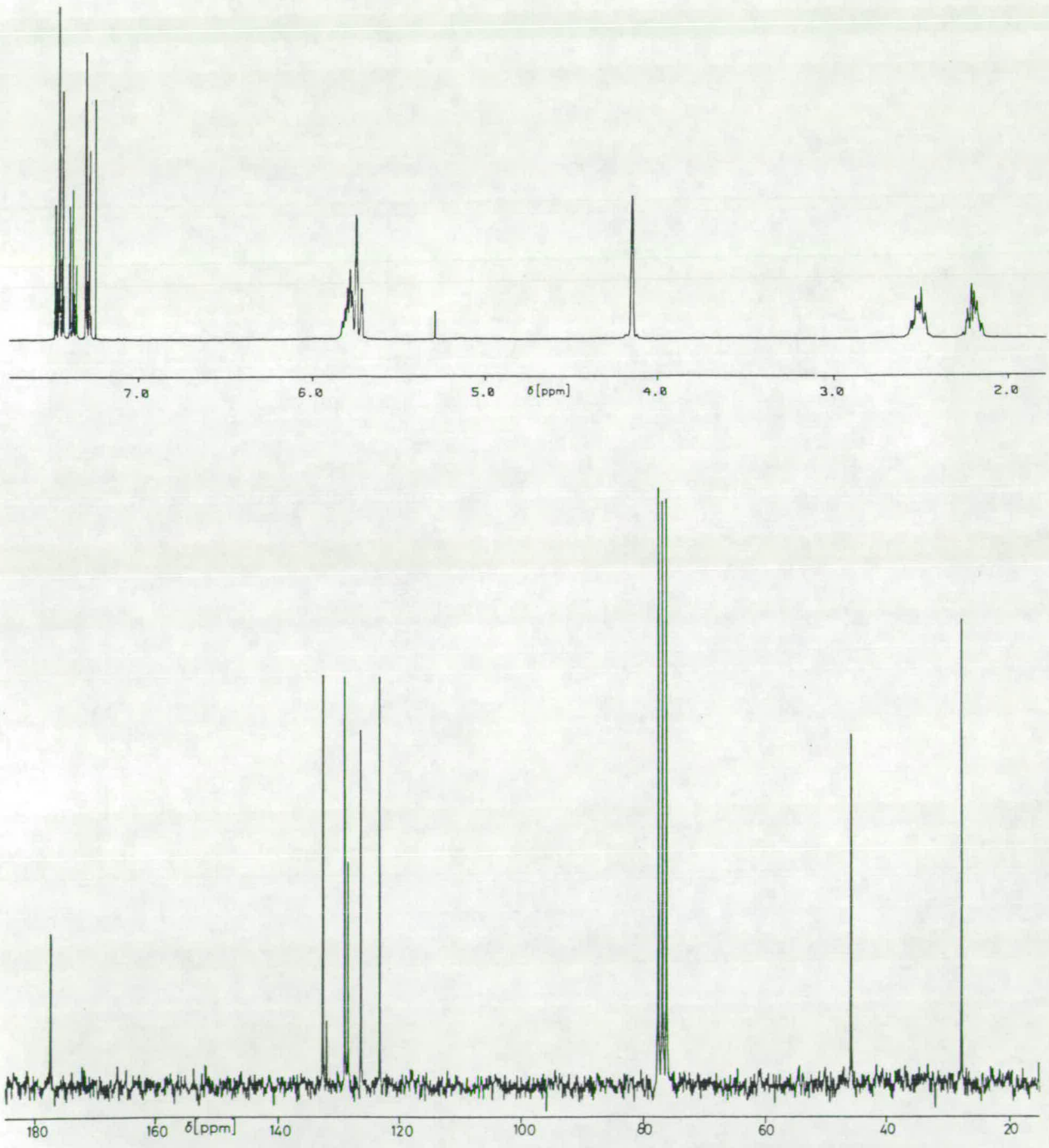


Figure 25 : ^{1}H and ^{13}C NMR spectra of (449; X = NPh)

Following the removal of the bulk of the product (449; X = NPh) from the crude VVP product mixture, the identification of the two remaining isomeric products was facilitated. Thus, examination of ^{13}C and ^{13}C DEPT spectra of the pyrolysate established that the two unidentified isomers possessed close structural features: each exhibited 14 carbon environments at similar chemical shift values in accord with unsymmetric C_{16} systems formed by extrusion of sulphur dioxide from (354). In detail, the ^{13}C NMR spectra demonstrated for each isomer the presence of two carbonyl resonances, the four resonances characteristic of the phenyl ring, and four olefinic (one methylene, three methine) and four saturated (one methylene, three methine) signals at positions characteristic of vinylcyclohexene structures.

Confirmation of this was achieved from examination of the ^{1}H NMR spectrum, shown in Figure 26. Thus, the characteristic presence of the vinyl-methylene multiplet at δ 5.05-5.34 together with the

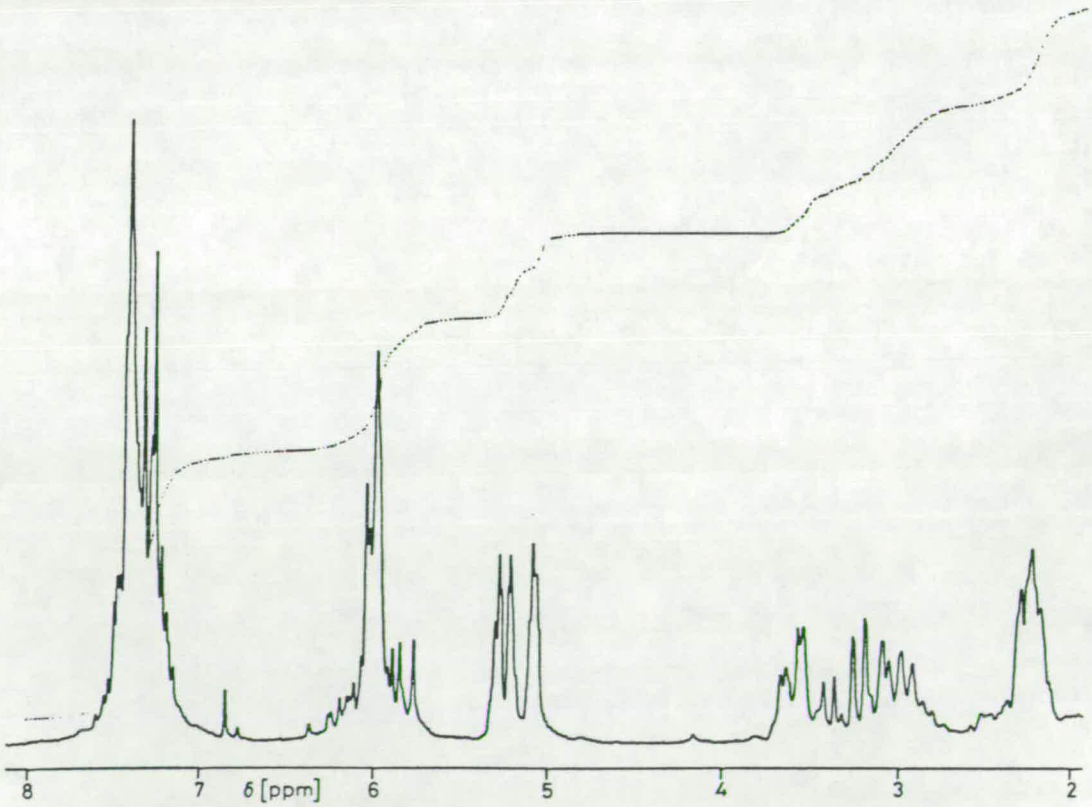


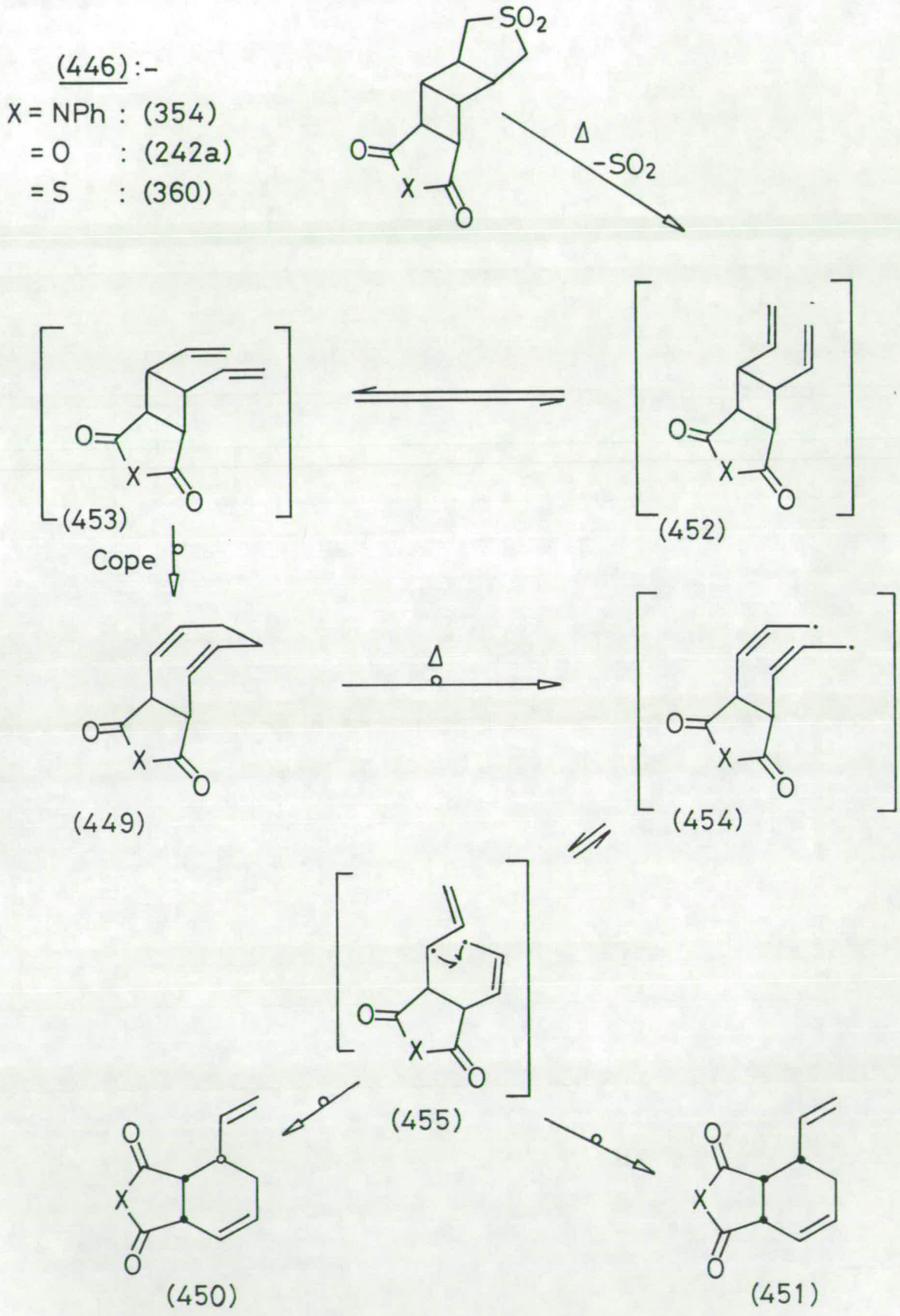
Figure 26 : ^{1}H NMR spectrum of (450; X = NPh) and (451; X = NPh)

vinyl-methine and two olefinic cyclohexene protons at δ 5.77-6.26 established the major isomer (and as a consequence of the similarity in carbon spectra, also the minor isomer) as vinylcyclohexene in nature. The major and minor vinylcyclohexene products were provisionally assigned structures (450; X = NPh) and (451; X = NPh) respectively. However, these two isomers could not be separated by TLC and an attempted separation by preparative GLC failed due to the involatility of the isomeric components, thus precluding final verification of the vinyl stereochemistry of each isomer. The mechanism of formation of the isomers (Scheme 52) and the analogy between these and the structurally-identified vinylcyclohexene products resulting from FVP of the related system (242a) (described later) vindicate these tentative assignments.

In order to obtain further information concerning the mechanism of formation of the three identified products resulting from pyrolysis of (354), both the pure cyclooctadiene imide-(449; X = NPh) and the mixture of vinylcyclohexene-imides (450; X = NPh) and (451; X = NPh) were repyrolysed. FVP of the cyclooctadiene (449; X = NPh) at 650°C gave a mixture of starting imide, (450; X = NPh) and (451; X = NPh) respectively in 7, 76 and 7% yields, a ratio not dissimilar to that found on FVP of the tetracyclic imide (354) at the same temperature. Pyrolysis of a mixture of the two vinylcyclohexene isomers (450; X = NPh) and (451; X = NPh) [together with some unseparated cyclooctadiene (449; X = NPh)] under identical conditions returned a ratio of vinylcyclohexene isomers which was unchanged within experimental error. These results indicate that the cyclooctadiene (449; X = NPh) is the primary extrusion product formed upon thermal fragmentation of tetracycle (354), and that this undergoes a partial rearrangement under

the pyrolysis conditions employed to generate both vinylcyclohexene products (450; X = NPh) and (451; X = NPh), with no significant isomerisation occurring between these last two.

The full mechanism for the conversion of tetracycle (354) to the three isolated products is detailed in Scheme 52. Thermal extrusion of sulphur dioxide from (354) occurs either *via* a concerted or diradical route with formation of an intermediate *cis*-divinylcyclobutane based system (452; X = NPh). Following the precedent of similar systems encountered during the pyrolysis of the tricyclic series (210) which have previously been mentioned, the *cis*-divinylcyclobutane structure would then be expected to undergo a facile Cope rearrangement from conformation (453; X = NPh) to generate the isolated (*Z*,*Z*)-cyclooctadiene product (449; X = NPh). Cope cyclisation directly from conformation (452; X = NPh) would be disfavoured due to the comparatively high ring strain inherent in the resultant (*E*,*E*)-cyclooctadiene. As in previous examples, the Cope cyclisation of such divinylcyclobutane systems is restricted to proceed only through the boat-like, rather than the chair-like, transition state due to the constraints placed upon the vinyl groups as a consequence of fusion directly to a cyclobutane ring. The fragmentation of the cyclooctadiene (449; X = NPh), which was determined experimentally to result in formation of the vinylcyclohexene products (450; X = NPh) and (451; X = NPh), would be expected to occur *via* homolytic fragmentation and intermediacy of a long-lived allylically-stabilised diradical (454; X = NPh). Cyclisation of this *via* the conformation (455; X = NPh) would then give rise to the isolated vinylcyclohexene products with formation of the thermodynamically more stable *trans*-vinyl isomer (450; X = NPh) predominating over the *cis*-vinyl structure (451; X = NPh).


(446):-
X = NPh : (354)
= O : (242a)
= S : (360)
SO2
Δ
-SO2
(453)
(452)
Cope
(449)
(454)
(455)
(450)
(451)

Scheme 52

An interesting point to emerge from pyrolysis of the tetracyclic imide (354) under both FVP and VVP conditions is the variation in ratio of the three isomeric products. The much higher yield of the cyclooctadiene (449; X = NPh) at the expense of primarily the major vinylcyclohexene isomer (450; X = NPh) under VVP conditions is at first sight peculiar. This technique, although carried out at a slightly lower temperature (600°C) than the FVP (650°C), by virtue of the longer contact time of the starting material and products with the hot zone might be expected to encourage secondary rearrangements - such as the thermal fragmentation of the cyclooctadiene (449; X = NPh) to the vinylcyclohexenes (450; X = NPh) and (451; X = NPh) - to a greater extent than expected under FVP conditions. That the converse is found in practice appears to result from the enhanced collisional deactivation of the primary product, the cyclooctadiene (449; X = NPh) [which is initially formed in a highly vibrationally excited state on extrusion of sulphur dioxide from (354)] under the lower vacuum conditions existing within the hot zone during the process of VVP. Thus, a greater yield of the primary product (449; X = NPh) was isolated than under FVP conditions in which the high vacuum conditions employed restrict the interactions between molecules so that loss of the vibrational energy within the primary extrusion product must occur by secondary rearrangements - in this case by rearrangement of (449; X = NPh) to the two vinylcyclohexene products (450; X = NPh) and (451; X = NPh).

Following FVP of the second member of the series (446), the anhydride (242a), the pyrolysis products and the mechanism of formation of these were found to be in accord with the general mechanism shown in Scheme 52. Thus, FVP of anhydride (242a) at 650°C resulted in an almost quantitative yield of three isomeric products, these being the

cyclooctadiene (449; X = O) (6%) and the two vinylcyclohexenes (450; X = O) (64%) and (451; X = O) (25%) as indicated by ^{1}H and ^{13}C NMR, and by GLC analyses.

On repeating the FVP of (242a) at lower temperature (500°C), a pyrolysate consisting of starting material (17%) together with the three extrusion products found on FVP at 650°C was obtained. The latter were easily separated from unchanged (242a) due to the difference in solubility in deuteriochloroform of the non-sulphone products - examination of the resultant solution by ^{1}H NMR spectroscopy indicated that while the ratio of the two vinylcyclohexene products (450; X = O) and (451; X = O) (combined 49% yield) was unchanged compared to the higher temperature FVP of (242a), the yield of the cyclooctadiene product (449; X = O) (35%) was much enhanced. This finding is in full accord with the mechanism depicted in Scheme 52 since the increase in the cyclooctadiene (449; X = O) yield would be expected at lower temperatures where there is less opportunity for thermal rearrangements of this primary extrusion product to the isomeric vinylcyclohexene systems.

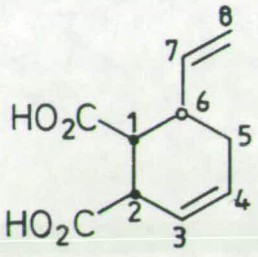
As no chromatographic means other than GLC could be found to separate the three isomeric anhydride products resulting from the pyrolysis of (242a), the assignments of stereochemistry made to the major and minor vinylcyclohexene products could not be positively verified. In order to effect this target, it was decided to convert the anhydride mixture to the corresponding dimethyl ester systems in the hope of more facile separation and characterisation of these. Treatment of the three component anhydride mixture obtained from FVP of (242a) at 650°C with boiling acidified methanol yielded an analytically pure sample of the corresponding dimethyl esters (392), (394) and (395) in approximately the same ratio as that of the starting

anhydrides. Unfortunately, no separation of the three diester products could be achieved by TLC; partial fragmentation of the mixture to the dienes (396) and (397) via a retro-Diels-Alder reaction was noted upon injection of a sample into a GLC inlet port, thus frustrating separation of the three diester isomers by preparative GLC. Nonetheless, the diester mixture was found to be useful in the investigation of the thermal fragmentation mechanism of the tricyclic diester (365; R = Me), as has been described earlier in this section.

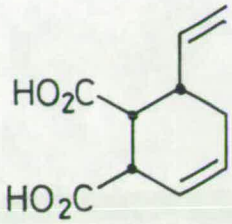
An alternative means of establishing the vinyl substituent stereochemistry of (450; X = O) and (451; X = O) was attempted. Since the anhydride mixture obtained on FVP of (242a) was found to be very hygroscopic - acting to prevent resolution of the anhydride components - hydrolysis of the mixture to the corresponding diacids, in the hope of achieving separation of these, was tried.

Heating of a 6:68:26 part mixture of the anhydrides (449; X = O), (450; X = O) and (451; X = O) in boiling water gave a colourless solution. On slow cooling, finger-shaped crystals (m.p. 156-159°C) were formed. Analysis of this material by standard elemental composition and spectral determinations established it to be a single vinylcyclohexene diacid compound, isolated in 25% yield. Evaporation of the aqueous filtrate revealed that the bulk of the diacid products were present in this fraction. Examination of the resultant crystalline solid indicated it to be an approximately 2:1 mixture respectively of the previously isolated diacid product and a vinylcyclohexene diacid isomer. It was therefore concluded that the pure compound initially isolated resulted from quantitative hydrolysis of the major anhydride isomer (450; X = O) and, in the reasonable assumption that no change in vinyl substituent occurred during this reaction, that the isolated diacid possessed the same trans-vinyl stereochemistry,

ie was of structure (456). Accordingly, the minor diacid isomer was assigned the cis-vinyl stereochemistry of (457).



(456)



(457)

As the assignment of vinyl-substituent stereochemistry for the vinylcyclohexene anhydride (450; X = O) had not been verified due to the difficulties of separation from the other two isomers with which it was formed, the isolation of the derived diacid (456) presented the opportunity to define the vinyl stereochemistry of this, and consequently of both the anhydrides (450; X = O) and (451; X = O). The method of choice for determination of vinyl disposition in (456) involved location of the signals due to H_1 and H_6 in the ^1H NMR spectrum followed by examination of these for signal enhancement upon NOE irradiation. After examination of a number of selectively decoupled proton spectra acquired at high field (360 MHz), the signals due to protons H_1 and H_6 were located. Unfortunately, these signals were coincidental precluding any NOE determination of vinyl-substituent stereochemistry.

It had been apparent from the ^1H NMR analysis of the three component anhydride mixture resulting from FVP of (242a) at 650°C that the major isomer (450; X = O) possessed fairly well separated saturated vinylcyclohexene proton signals which, upon removal of the overlapping resonances due to the alternative two isomers, could form the basis of a successful determination of vinyl-substituent geometry by means of NOE irradiation. Thus, the diacid (456) was dehydrated by stirring in acetic anhydride at 50°C for one hour to give a single

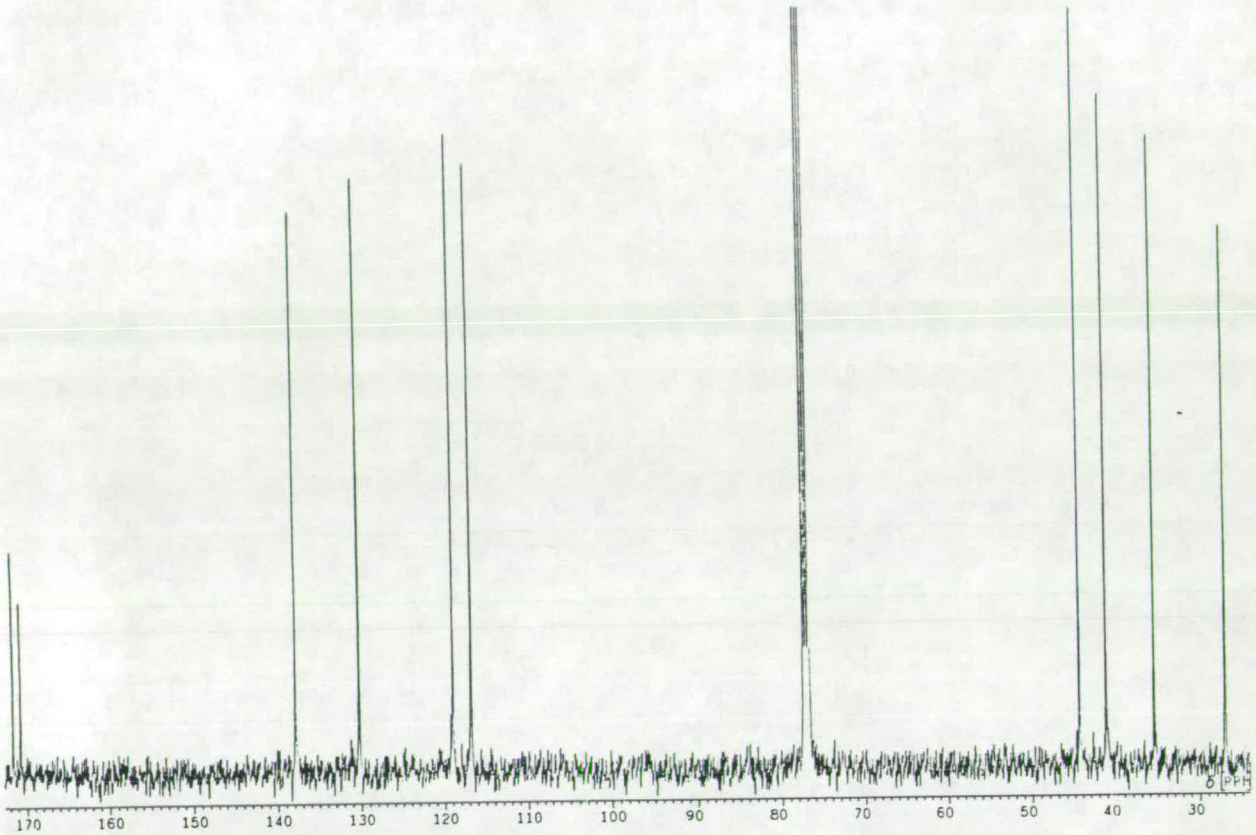
anhydride product (93%) which on comparison of ^{1}H and ^{13}C NMR spectra (Figure 27) with those of the mixture of (449; X = O), (450; X = O) and (451; X = O) was confirmed as being the major vinylcyclohexene anhydride isomer (450; X = O).

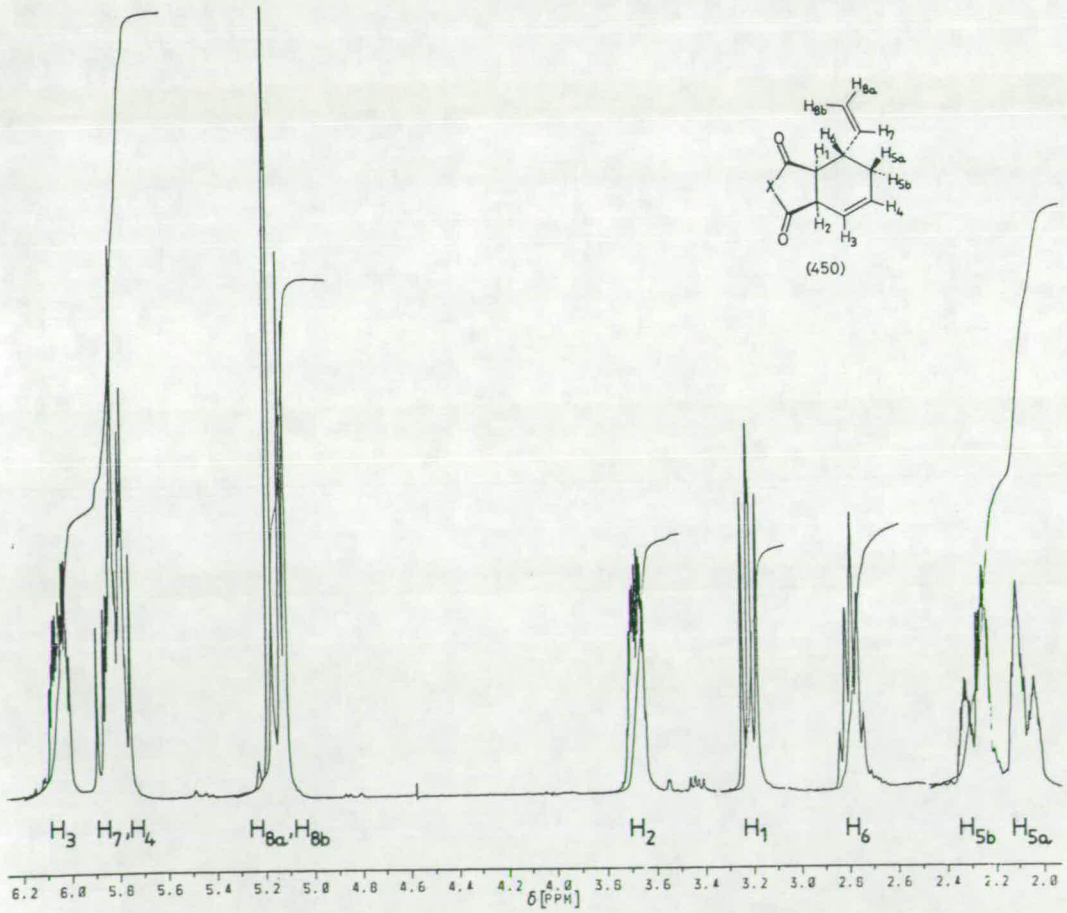
Within the ^{1}H NMR spectrum of (450; X = O), the assignments of the lowest field saturated signal at δ3.67 to proton H_2 (deshielded by conjugative interaction with the neighbouring olefin and carbonyl groups) and the signals at δ3.20 and δ2.78 to protons H_1 and H_6 respectively were fully confirmed by the results of homonuclear decoupling of each of these signals as demonstrated in Figure 28. In addition to permitting the complete signal to proton assignment shown in Figures 27 and 28, the decoupled spectra enabled full identification and quantification of all of the coupling constants present, which are shown in Table 1.

$J_{1,2}$ = 8.5 Hz	$J_{5a,5b}$ = 18.0 Hz
$J_{1,6}$ = 5.9 Hz	$J_{5a,6}$ = 5.9 Hz
$J_{2,3}$ = 2.3 Hz	$J_{5b,6}$ = 5.9 Hz
$J_{2,4}$ = 3.9 Hz	$J_{6,7}$ = 5.9 Hz
$J_{3,4}$ = 10.0 Hz	$J_{6,8b}$ = 0.5 Hz
$J_{3,5a}$ = 4.2 Hz	$J_{7,8a}$ = 10.3 Hz
$J_{3,5b}$ = 4.2 Hz	$J_{7,8b}$ = 17.5 Hz
$J_{4,5a}$ = 1.9 Hz	$J_{8a,8b}$ = 0.9 Hz
$J_{4,5b}$ = 1.9 Hz	

Table 1 : Coupling constants in the ^{1}H NMR spectrum of (450; X = O)

Consideration of these coupling constants furnishes confirmatory evidence for the vinylcyclohexene structure of the major anhydride isomer. The presence of a vinyl group is evident from the trans- and cis-olefinic coupling constants $J_{7,8b}$ = 17.5 Hz and $J_{7,8a}$ =





(450)

Figure 27 : ^{1}H and ^{13}C NMR spectra of (450; X = O)

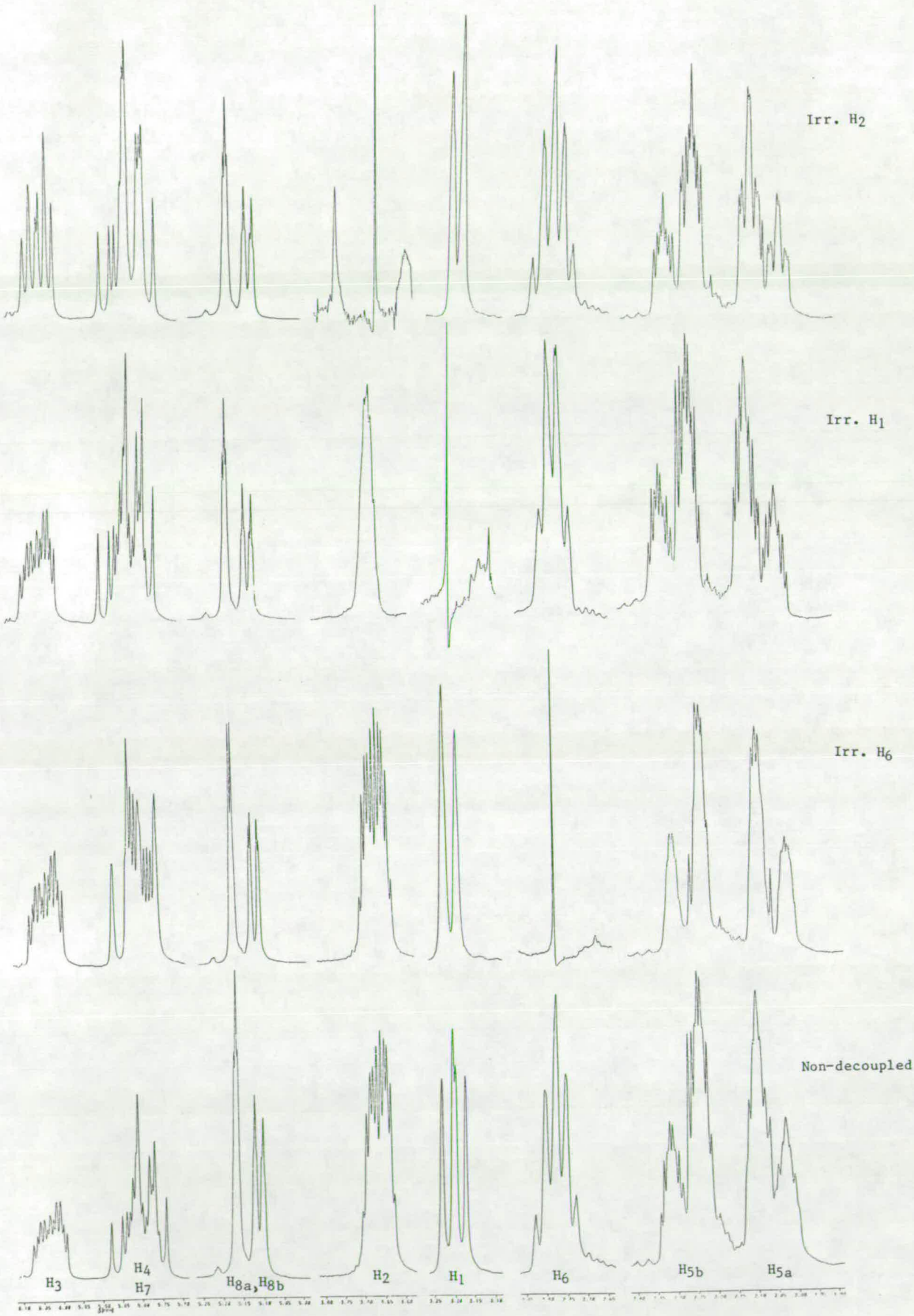


Figure 28 : Selectively decoupled ^1H NMR spectra of (450; X = O)

10.3 Hz respectively. In addition, the olefinic coupling constant $J_{3,4}$ = 10.0 Hz is in accord with expectation for a cyclohexene system.

Construction of Dreiding models of the two vinylcyclohexene anhydrides (450; X = O) and (451; X = O) and examination of these indicated that only the former system could adopt a conformation in which the dihedral angles between protons, and hence expected coupling constants were compatible with the observed coupling constants. This conformation, which represents an average of more extreme conformations within the NMR timescale, is an envelope-shaped structure in which the vinylcyclohexene carbons C2-C6 adopt a planar configuration and in which the apex of the envelope is formed by the ring-fusion carbon, C1. Thus, this conformation displays equal dihedral angles $\phi_{5a,6}$ = $\phi_{5b,6}$ = 58° in accord with the observed coupling constants $J_{5a,6}$ = $J_{5b,6}$ = 5.9 Hz. Similarly, the planar arrangement of C2-C6 explains the equivalence of the observed couplings between protons H_{5a},H_{5b} and protons H_3 and H_4. A dihedral angle $\phi_{1,2}$ = 42°, and $\phi_{1,6}$ = 55° is reflected by the coupling constants $J_{1,2}$ = 8.5 Hz (indicative of a cis-fused bicyclic system) and $J_{1,6}$ = 5.9 Hz.

Final and conclusive proof that the structure of the major anhydride isomer was indeed the trans-vinylcyclohexene system (450; X = O) was furnished by analysis of the ^{1}H-2D NOESY spectrum (Figure 29). This clearly indicates a close spacial relationship between the ring fusion proton H_1 and both protons H_7 and H_{8b} in agreement with the conformation of (450; X = O) described above. A large observed NOE effect between the cis-disposed ring fusion protons H_1 and H_2 is as expected, but interestingly a sizeable interaction between protons H_1 and H_6 is apparent. At first sight this might be taken as indicative of a cis arrangement of H_1 and H_6 and therefore in accord with the cis-vinyl substituted isomer (451; X = O). However, consultation of the Dreiding model of (450; X = O) in the aforementioned envelope

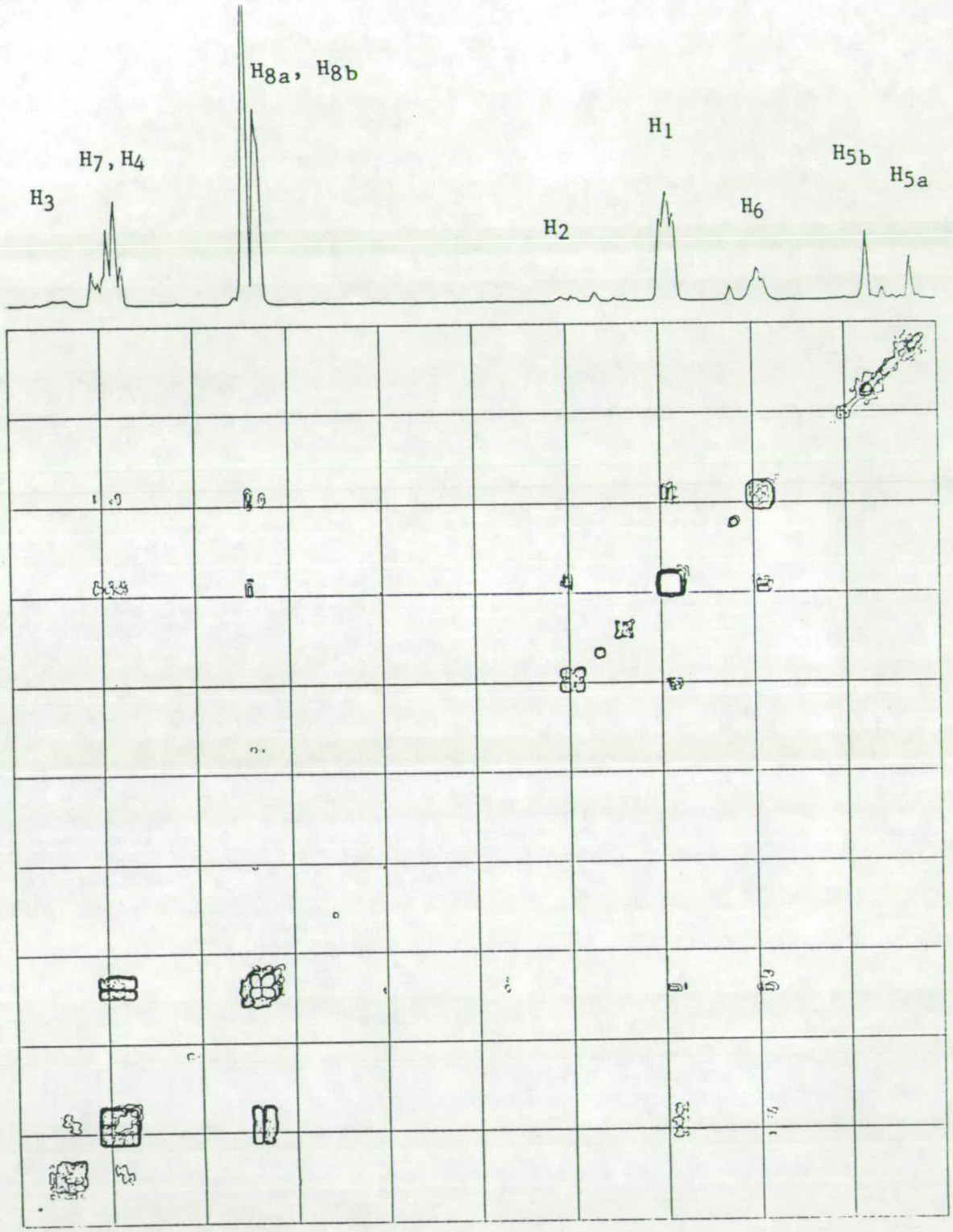


Figure 29 : ^{1}H-2D NOESY spectrum of (450; X = O)

conformation demonstrated that a close spacial disposition of these protons clearly exists: the danger of interpreting ^{1}H NMR spectral information without recourse to accurate models of the particular systems is thus ably demonstrated. In addition to unequivocally establishing the trans-vinyl stereochemistry of the major anhydride isomer (450; X = O) resulting from FVP of (242a), these findings also vindicate the cis-vinyl stereochemistry of (451; X = O) and the trans-vinyl stereochemistry of diacid (456); supporting evidence for the assignment of vinyl stereochemistries to the two analogous vinylcyclohexene-imide isomers (450; X = NPh) and (451; X = NPh) is also furnished.

Turning now to the pyrolysis of the third and final member of the class (446) - the thioanhydride (360) - a complicating factor in this case was that the thioanhydride could only be obtained in appreciable quantities as the major component in a 63:37 part mixture with the anhydride (242a). However, this inconvenience was offset to some extent by the fact that the pyrolysis products resulting from anhydride (242a) had previously been identified.

FVP of a 63:37 mixture of thioanhydride (360) and anhydride (242a) at 650°C resulted in formation of three thioanhydride isomers of formula $C_{10}H_{10}O_2S$ in 64, 18 and 5% yields as established by GC-MS and GLC analyses of the pyrolysate. Examination of this by ^{1}H and ^{13}C DEPT NMR spectroscopy established the vinylcyclohexene structure of the major isomer. By analogy to the pyrolyses of the related systems (354) and (242a), the major thioanhydride isomer was accorded structure (450; X = S), the product of intermediate yield, structure (451; X = S), and the lowest intensity product assigned structure (449; X = S). Although some evidence for the structures of the latter two products was observed in the proton spectrum, the complexity of this six component mixture [containing the three anhydride products (449; X = O), (450; X = O) and (451; X = O)] precluded identification of the minor thioanhydride compounds.

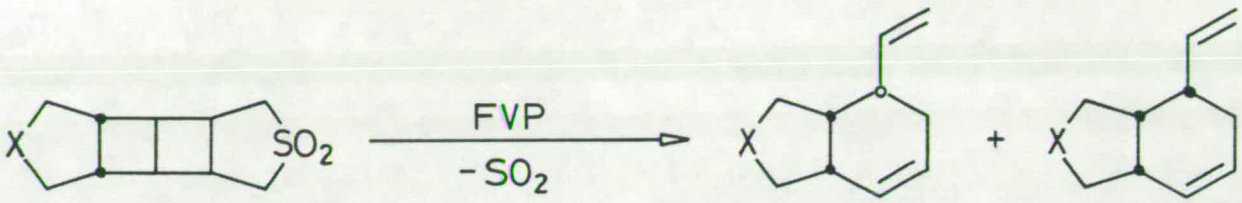
At the conclusion of the pyrolytic study of the series (446; X = NPh, O, S) it can be stated that firm evidence was found for fragmentation of these systems *via* the mechanism outlined in Scheme 52.

b. FVP of transoid, transoid-5-hetero-11-thiatetracyclo[7.3.0.$0^{2,8}$.$0^{3,7}$]dodecane 11,11-dioxide systems (447)

Five compounds belonging to the title class were available for a comparative study of thermal fragmentation behaviour, these being systems (447; X = O, S, NCH_2Ph, SO_2) and the tetradeuterated analogue of (447; X = O), the tetrahydrofuran (368). It was expected that thermal fragmentation of these compounds would mirror that found for pyrolysis of the related series (446).

FVP of the tetrahydrofuran system (367) at 650°C resulted in isolation of a mixture of colourless oil and polymeric solid. Dissolution of the oil in deuteriochloroform enabled examination of the pyrolysate by ^1H and ^{13}C NMR spectroscopy, and by GLC and GC-MS to be undertaken. No sulphone-containing compounds were detected, the products being identified as four $C_{10}H_{14}O$ isomers in 2, 58, 16 and 4% yields in order of increasing GLC retention times (10% carbowax, 150°C). By means of preparative GLC, the two most abundant isomers were separated and both were spectrally characterised as vinylcyclohexene-tetrahydrofuran structures. On the basis of the *trans*-vinyl stereochemistry of the major vinylcyclohexene product (450; X = O) arising from FVP of (242a) at 650°C, the major tetrahydrofuran isomer was initially assigned the *trans*-vinyl stereochemistry of structure (458; X = O) and the minor isomer assigned structure (459; X = O) pending confirmation of these stereochemistries by spectroscopic means.

High field (360 MHz) proton spectra for both of the separated isomers are displayed in Figure 30. The assignment of signals to protons shown, and the associated coupling constants displayed in Table 2, were made on the basis of results obtained following extensive



(447) (458) (459)

selective decoupling studies carried out on each isomer. Both isomers were clearly vinylcyclohexene systems - a fact which had been obvious from the ^1H NMR spectrum of the crude pyrolysate - and a detailed analysis of the proton spectra was undertaken in order to verify the initial stereochemical assignments of the vinyl substituents in each isomer.

In detail, the proton spectra of the isomers displayed trans- and cis-olefinic coupling constants $J_{10,11b} \simeq 17$ Hz and $J_{10,11a} \simeq 10$ Hz giving rise to the distinctive appearance of the vinyl-methylene signals at δ5.0-5.1 in each case. The remaining vinyl signal (due to methine proton H_{10}) in fashion typical of vinyl methine groups is located at lower field, and in both isomers occurs at similar positions to the olefinic cyclohexene signals (δ5.5-6.0). Both isomers demonstrate a cis-olefinic coupling constant $J_{4,5} = 10.0$ Hz for the interaction between the unsaturated cyclohexene protons - coupling of both protons H_4 and H_5 to the methylene protons H_{3a} and H_{3b} are indicative of the basic cyclohexene structure of both isomers.

Evidence for the presence of an intact tetrahydrofuran ring in each isomer was furnished from analysis of the signals corresponding to methylene proton pairs H_{7a},H_{7b} and H_{9a},H_{9b}. These signals demonstrated the presence of the geminal coupling constants $J_{7a,7b} \simeq$

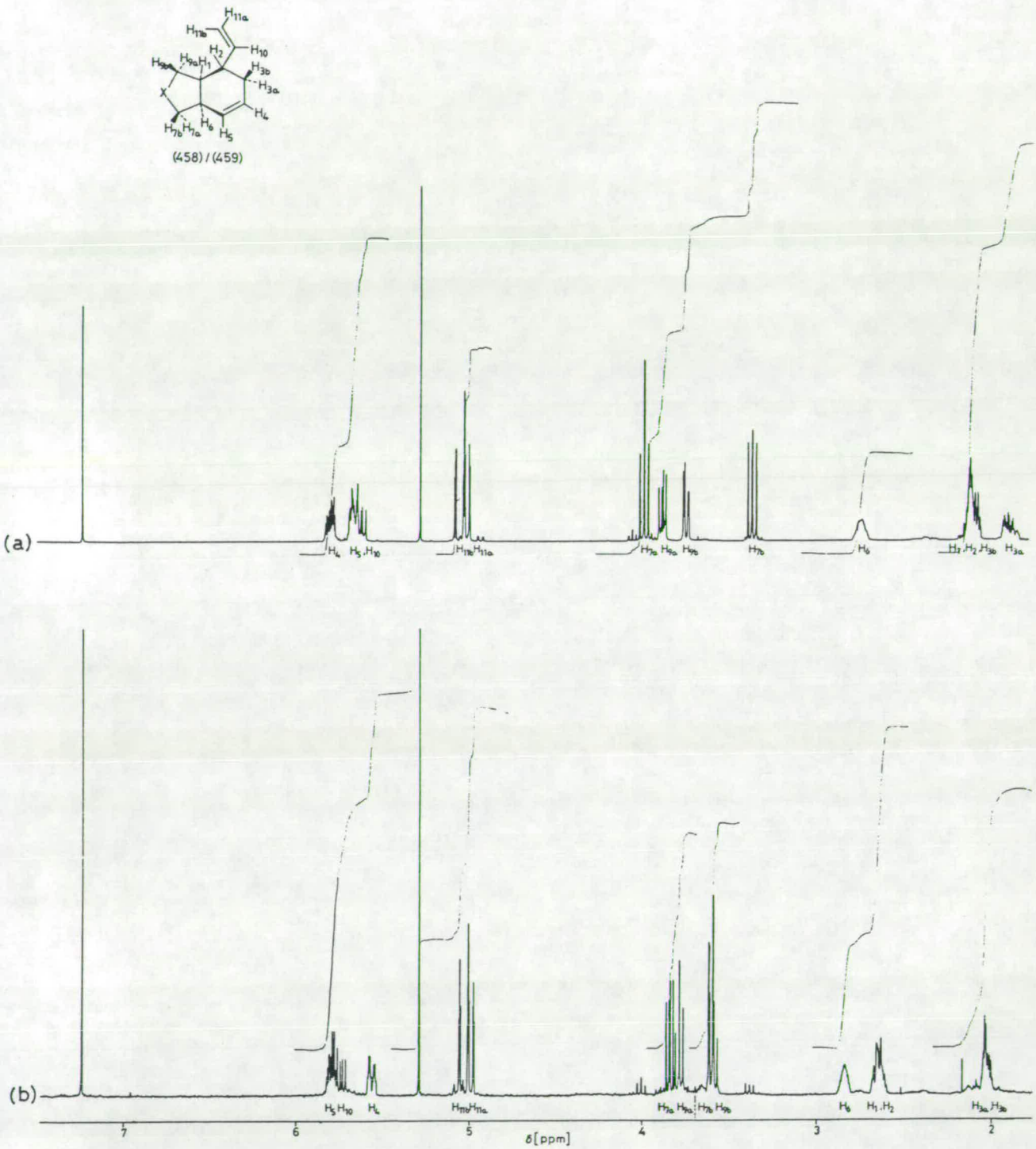


Figure 30 : (a) ^{1}H NMR spectrum (360 MHz) of major isomer (458; X = O)

(b) ^{1}H NMR spectrum (360 MHz) of minor isomer (459; X = O)

major isomer (458; X = O)	minor isomer (459; X = O)
$J_{1,9a}$ = 6.2 Hz	$J_{1,9a}$ = 8.4 Hz
$J_{1,9b}$ = 2.6 Hz	$J_{1,9b}$ = 8.4 Hz
$J_{2,3a}$ = 7.4 Hz	$J_{2,4}$ = 1.0 Hz
$J_{2,3b}$ = 1.1 Hz	$J_{2,10}$ = 6.1 Hz
$J_{2,10}$ = 7.5 Hz	$J_{2,11a}$ = 1.5 Hz
$J_{2,11a}$ = 0.3 Hz	$J_{2,11b}$ = 1.5 Hz
$J_{2,11b}$ = 0.8 Hz	$J_{3a,4}$ = 2.6 Hz
$J_{3a,3b}$ = 14.7 Hz	$J_{3a,5}$ = 2.4 Hz
$J_{3a,4}$ = 2.5 Hz	$J_{3b,4}$ = 2.6 Hz
$J_{3a,5}$ = 2.5 Hz	$J_{3b,5}$ = 2.4 Hz
$J_{3a,6}$ = 2.5 Hz	$J_{4,5}$ = 10.0 Hz
$J_{3b,4}$ = 5.1 Hz	$J_{4,6}$ = 2.6 Hz
$J_{3b,5}$ = 1.1 Hz	$J_{5,6}$ = 2.4 Hz
$J_{4,5}$ = 10.0 Hz	$J_{6,7a}$ = 6.1 Hz
$J_{4,6}$ = 2.5 Hz	$J_{6,7b}$ = 2.0 Hz
$J_{5,6}$ = 3.8 Hz	$J_{7a,7b}$ = 8.3 Hz
$J_{6,7a}$ = 8.1 Hz	$J_{9a,9b}$ = 8.4 Hz
$J_{6,7b}$ = 9.0 Hz	$J_{10,11a}$ = 10.5 Hz
$J_{7a,7b}$ = 8.1 Hz	$J_{10,11b}$ = 17.3 Hz
$J_{9a,9b}$ = 8.8 Hz	$J_{11a,11b}$ = 1.5 Hz
$J_{10,11a}$ = 10.3 Hz	
$J_{10,11b}$ = 17.2 Hz	
$J_{11a,11b}$ = 1.7 Hz	

Table 2 : Coupling constants in the ^1H NMR spectra of (458; X = O), (459; X =

$J_{9a,9b} \simeq 8.5$ Hz, and the observed coupling of H_{7a},H_{7b} with H_6, and of H_{9a},H_{9b} with H_1, is in accord with a bicyclic system containing a fused tetrahydrofuran ring for each isomer. Further confirmation of the vinylcyclohexene-tetrahydrofuran structure of both isomers was accorded upon inspection of the ^{13}C DEPT NMR spectra which consisted of four methylene and six methine carbon environments at expected chemical shift values.

A most unfortunate coincidence of the resonances corresponding to protons H_1 and H_2 in the proton spectra of both isomers prevented the verification, by ^1H NOE studies, of the vinyl group stereochemical assignments previously made. However, the acquisition of a ^1H-2D NOESY NMR spectrum of the major vinylcyclohexene isomer (458; X = O) did confirm the close spacial relationship between the two geminal protons of the C3, C7 and C9 methylene groups; apart from verifying these proton assignments little else of value was realised.

Comparison of the observed coupling constants for each isomer with those expected from an inspection of dihedral angles of the corresponding Dreiding models does indicate that the major product possesses structure (458; X = O), and the minor structure (459; X = O) as previously assigned. For both isomers, consultation of the models indicates that two extreme conformers exist in which the cyclohexene ring adopts an envelope-shaped structure. The apex of the envelope structure is the vinyl-substituted carbon, C2, for one conformer; for the alternative conformer, the apex is the methylene carbon, C3.

In consideration of the coupling constants $J_{2,3a} = 7.4$ Hz and $J_{2,3b} = 1.1$ Hz observed in the spectrum of the major vinylcyclohexene isomer, it is found from an inspection of the two Dreiding models that of the four possible conformers of (458; X = O) and (459; X = O), these couplings are most in accord with the former system in the

lowest energy conformer in which C2 forms the apex of the envelope structure. For this conformer the measured dihedral angles (available from a Dreiding model) of $\phi_{2,3a} \simeq 180°$ and $\phi_{2,3b} \simeq 60°$ are in agreement with those required to generate the magnitude of the observed coupling constants $J_{2,3a}$ and $J_{2,3b}$. Further evidence that this conformer predominates at room temperature may be derived from the chemical shifts and couplings associated with the tetrahydrofuran methylene protons. Thus, the similarity in magnitude of the observed coupling constants $J_{6,7a}$ and $J_{6,7b} \simeq 8-9$ Hz reflect the respective dihedral angles of 30° and 150° evident from the model in the conformation described above. Similarly, the observed coupling constants $J_{1,9a} = 6.2$ Hz and $J_{1,9b} = 2.6$ Hz mirror the distortion of the tetrahydrofuran ring in this conformation : dihedral angles $\phi_{1,9a} \simeq 10°$ and $\phi_{1,9b} \simeq 100°$ were apparent from inspection of the model, in accord with these coupling constants.

Incidentally, the reason for the large difference in chemical shift values for the H_{7a} and H_{7b} signals is obvious from inspection of the predominant conformer of the major isomer (458; X = O). In this, proton H_{7a} is disposed such that it is in line with the axis of the cyclohexene double bond and consequently deshielded (appearing at δ 4.00) by intrusion into the deshielding region associated with the olefin moiety, when compared with the chemical shifts of the unaffected protons H_{9a} and H_{9b}, found at δ 3.8-3.9. In contradistinction, the geminal partner H_{7b}, due to the geometry of this conformation, is located within the shielding region associated with the olefin group of the cyclohexene ring and is therefore located 0.4-0.5 δ to high field of the standard methylene protons H_{9a},H_{9b}.

Turning now to the less abundant vinylcyclohexene product, a comparison of the chemical shifts and coupling constants observed

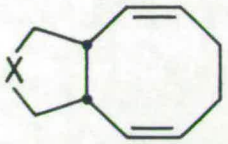
in the ^1H NMR spectrum (Figure 30) with those expected from inspection of a model of the time-averaged structure of the two extreme envelope conformers of the cis-vinyl substituted system (459; X = O) indicates that good agreement exists between the two. The rapid interconversion (compared to the NMR timescale) of the two envelope conformers giving rise to a ^1H NMR spectrum of an average conformation is indicated by the almost equal magnitude of $J_{3a,4}$ and $J_{3b,4}$ which is a consequence of the similarity in the corresponding dihedral angles $\phi_{3a,4}$ and $\phi_{3b,4} \simeq 65°$ associated with the near planar cyclohexene ring of the average conformation. A similarity in the size of $J_{1,9a}$ and $J_{1,9b}$, coupled with a large difference in the values of $J_{6,7a}$ and $J_{6,7b}$ is in direct opposition to the situation regarding the corresponding coupling constants in the alternative vinylcyclohexene isomer. These findings are a reflection of the distortion of the tetrahydrofuran ring by steric interaction of the vinyl substituent with the C9 methylene group as is clearly evident from inspection of the average conformation of a Dreiding model of the minor isomer (459; X = O). In addition, the range of chemical shifts over which the tetrahydrofuran methylene protons of the cis-vinyl isomer (459; X = O) are found is much smaller (0.25δ cf. 0.60δ) than for the trans-vinyl system (458; X = O). This observation is in keeping with a planar cyclohexene ring of the average conformation of the cis-vinyl isomer which prevents any shielding or deshielding effect operating on the tetrahydrofuran methylene protons, in contrast to the situation previously described in the trans-vinyl analogue.

One further point which reinforces the stereochemical assignments made to the two vinylcyclohexene structures may be deduced from the relative chemical shifts of the coincidental H_1 and H_2 signals of each isomer. For the less abundant isomer (459; X = O),

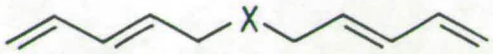
these resonances are observed at ca δ 2.62, some 0.5δ to lower field than the equivalent proton signals in the spectrum of the predominant vinylcyclohexene product (458; X = O). The observed relative downfield shift of the H_1 and H_2 signals in the minor isomer can be attributed to a mutually deshielding steric interaction between these protons as a consequence of their close spacial relationship within structure (459; X = O), a situation not present in the major isomer (458; X = O).

To summarise, detailed examination of the ^1H NMR spectra of the separated vinylcyclohexene-tetrahydrofuran products allowed complete assignment of signals to protons, and permitted identification and evaluation of the majority of coupling constants in each case. Although direct verification of the stereochemical assignments made to the two isomers on the basis of the analogy of (450; X = O) and (451; X = O) was not obtained, interpretation of the proton spectra in conjunction with inspection of Dreiding models furnished a substantial body of evidence in support of these. It was therefore concluded that the major isomer obtained from FVP of (367) at 650°C possessed trans-vinyl stereochemistry (458; X = O), and that the minor isomer possessed the cis-vinyl geometry of structure (459; X = O).

Having established the structures of the two major products resulting from FVP of (367), the two minor products remain to be identified. Due to the low yield of these components, no spectral information other than GC-MS data was available restricting any assignment of structure to the realm of speculation. On the basis of the formation of the two vinylcyclohexene-tetrahydrofuran products (458; X = O) and (459; X = O), and the analogy which therefore exists between the pyrolysis mechanisms of systems (446) and the tetrahydrofuran (367), the product at shortest retention time may be the cyclooctadiene-tetrahydrofuran (460; X = O). The fourth isomeric product, observed at



(460)



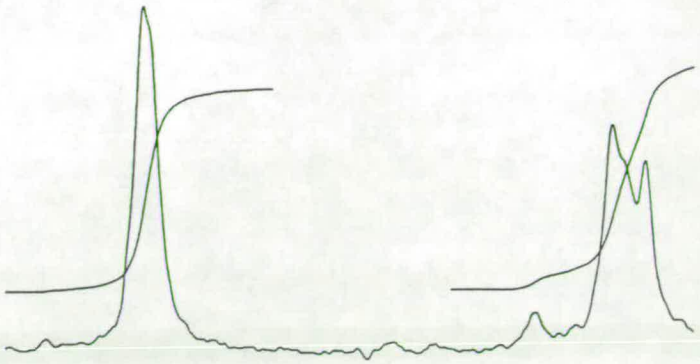
(461)

the longest retention time on GLC (10% carbowax) analysis, may well be the tetraolefin (461; X = O) which due to the extensive unsaturation present would be expected at longer retention times than the isomeric vinylcyclohexene- or cyclooctadiene-tetrahydrofuran structures. Formation of (461; X = O) is feasible via a retro-Diels-Alder fragmentation of the trans-vinylcyclohexene-tetrahydrofuran (458; X = O) under the pyrolysis conditions, in a reaction similar to the thermal fragmentation of the vinylcyclohexene-diester (394) described earlier.

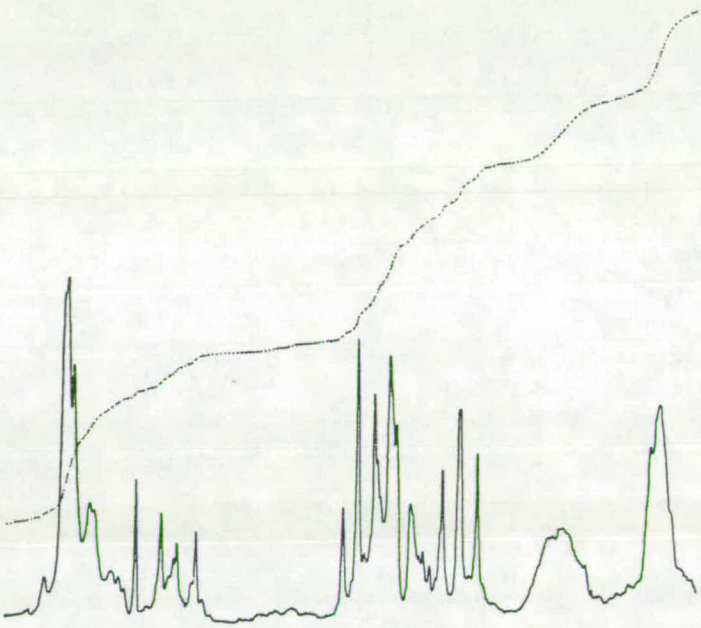
Flash vacuum pyrolysis of the tetradeuterated system (368) under identical conditions (650°C) to that used to effect thermal fragmentation of the parent tetracyclic tetrahydrofuran (367) resulted in formation of a mixture of colourless oil and polymeric solid. Analysis of the former product by GLC demonstrated that four products were present which displayed identical retention times and similar concentrations to the four components found on FVP of the parent system (367) at 650°C. Following the determination of GC-MS spectra of each of the four products resulting from FVP of (368) and comparison with those of the four isomers obtained from thermal fragmentation of (367), it was evident that the former systems were the tetradeuterated analogues of the latter products. Obviously the slight structural change between the tetracyclic sulphones (367) and (368) does not result in any noticeable alteration in the mechanism of thermal decomposition, resulting in a similar product distribution in each case.

As shown in Figure 31, a comparison of the ^{1}H NMR spectra of the crude pyrolysates resulting from FVP of (367) and (368) reveals

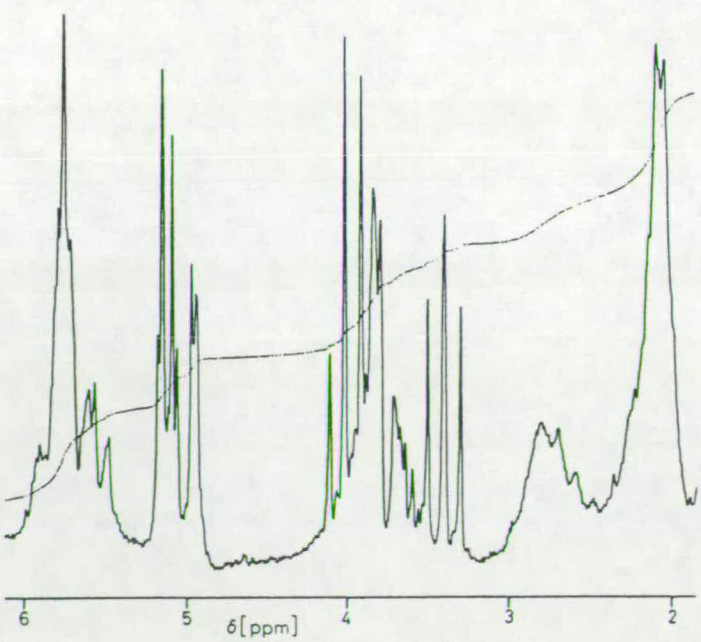
Figure 31 : ^{1}H and ^{2}H NMR spectra of pyrolysate of (368)



^{2}H NMR spectrum of pyrolysate of (368)



^{1}H NMR spectrum of pyrolysate of (368)



^{1}H NMR spectrum of pyrolysate of (367)

that significant differences are present. Since both spectra are dominated by the presence of the major trans-vinylcyclohexene products, the absence of certain signals in the ^1H NMR spectrum of the pyrolysate derived from (368) compared to that derived from (367) is indicative of occupation of these positions by deuterium rather than hydrogen. Thus, the signals for the protons H_{3a},H_{3b} and H_{11a},H_{11b} in the product (458; X = O) are absent in the ^1H NMR spectrum of the pyrolysate of (368), but signals for deuterium atoms occupying the equivalent positions are observed in the deuterium spectrum as shown in Figure 31. Therefore, not only does the results of FVP of (368) substantiate the vinylcyclohexene nature of the major product (458; X = O) resulting from pyrolysis of the parent system (367), it also furnishes evidence in support of the general mechanism outlined in Scheme 52 as being applicable to the thermal fragmentation of both tetracyclic series (446) and (447).

A third member of the series (447), the tetrahydrothiophene (371) was submitted to FVP at 650°C. Analysis of the pyrolysate by GLC, GC-MS and ^1H, ^{13}C DEPT NMR spectroscopy indicated that three $C_{10}H_{14}S$ products had been formed in 55, 11 and 5% yields. The major component was established as a vinylcyclohexene-tetrahydrothiophene compound - probably of structure (458; X = S) by analogy to the major product (458; X = O) found on FVP of (367) - following examination of the ^1H and ^{13}C DEPT NMR spectra of the pyrolysate. No spectral information other than GC-MS data was available to facilitate identification of the remaining two products. Similarities between the major isomer and the next most abundant product in terms of mass spectral fragmentation pattern and GLC retention times formed the basis of a very tentative assignment of this isomer to the cis-vinyl substituted system (459; X = S). This assignment is supported by analogy to the isomeric products (458; X = O) and (459; X = O) realised

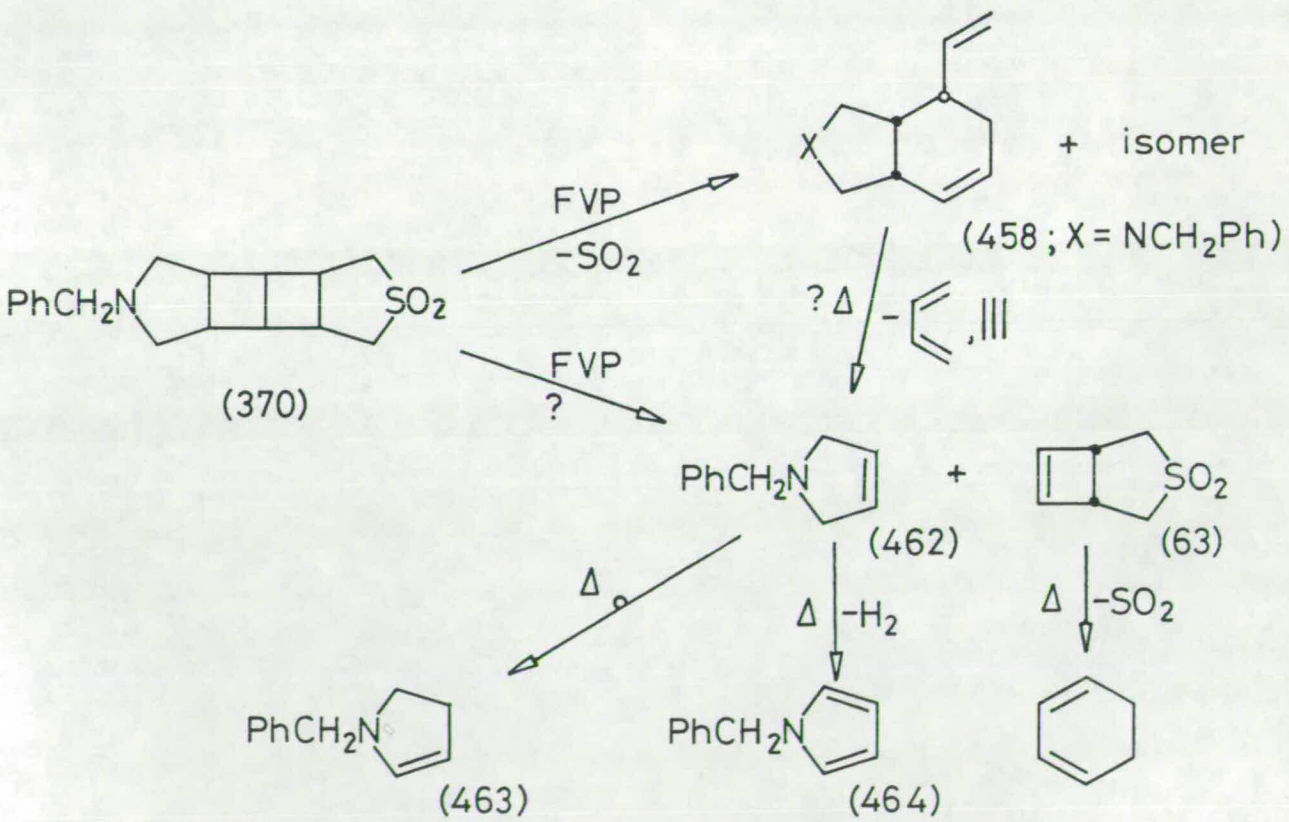
on FVP of (367). The third isomeric component displayed marked differences in retention time and mass spectral fragmentation pattern compared to the other two components. This is due to a fundamental structural difference, and a possible structure for the lowest intensity product is the acyclic sulphide (461; X = S).

Tertiary amine (370) was submitted to FVP at 650°C giving a pyrolysate comprising a yellow oil and polymeric solid. Examination of the oil demonstrated that no sulphone-containing compounds were present, and analysis by GLC indicated the presence of eight products. Following further analyses by ^{1}H and ^{13}C DEPT NMR, and by GC-MS determinations of the eight components, the major product was found to be a vinylcyclohexene system, believed to be the trans-vinyl compound (458; X = NCH_2Ph) (63% yield) by analogy to the major products (458) formed on pyrolysis of other members of the series (447). An isomeric product was located at longer retention time but due to the low yield (4%) no NMR spectral data could be found to indicate whether or not this was the cis-vinyl isomer (459; X = NCH_2Ph); GC-MS data indicated that this product displayed a markedly different fragmentation pattern from the major product (458; X = NCH_2Ph) and this may be evidence in favour of a product of a different structural type, such as the acyclic tertiary amine (461; X = NCH_2Ph).

In contrast to the pyrolysates obtained under identical conditions from the related tetracyclic compounds (367) and (371), the product mixture realised upon pyrolysis of (370) contained significant quantities of volatile products arising from fragmentation processes involving extrusion of fragments in addition to sulphur dioxide from the starting sulphone. Of the six volatile compounds detected in the pyrolysate which enter this category, the component present in the highest yield (9%) was found by GC-MS to be of formula $C_{11}H_{11}N$ and to display a fragmentation pattern similar to that

reported[197] for N-benzylpyrrole (464). Re-examination of the ^{1}H NMR spectrum of the pyrolysate confirmed the presence of this product since characteristic unsaturated signals [δ 6.02 (t, J = 2 Hz) and δ 6.52 (t, J = 2 Hz)] for the pyrrole ring protons were located which compared well with the reported[198] proton spectrum.

Two components of the pyrolysate which were present in low concentration (combined 1.5% yield) were found by GC-MS examination to be of formula $C_{11}H_{13}N$ and to demonstrate fragmentation patterns in accord with those expected of the isomeric N-benzylpyrrolines (462) and (463). The product (462) may be realised by thermal fragmentation of the major vinylcyclohexene product (458; X = NCH_2Ph) or from other isomeric systems possibly present in the pyrolysate such as (459; X = NCH_2Ph), or (460; X = NCH_2Ph). Alternatively, a thermal fragmentation of the parent system (370) with initial formation of (462) is feasible. Rearrangement of this product may occur to generate the isomeric system (463) and facile dehydrogenation to realise the resonance



stabilised product, N-benzylpyrrole (464), an identified pyrolysis product, would be a favoured thermodynamic pathway. Incidentally, the other cyclic system formed upon fragmentation of (370), the cyclobutene-sulpholane (63) would generate cyclohexa-1,3-diene under the pyrolysis conditions, as described earlier (p.22). The remaining unidentified products present in the pyrolysate may similarly be related to fragmentation processes other than extrusion of sulphur dioxide operating upon (370): a $C_{13}H_{13}N$ product evident in the pyrolysate may be formed by fragmentation of butadiene sulphone from (370) followed by dehydrogenation and rearrangement of the remaining fragment. It is not clear why structure (370) is more liable to such fragmentation processes which compete with extrusion of sulphur dioxide than the related systems (367), (368) and (371).

The fifth and final member of the tetracyclic series (447), the disulphone (372) was anticipated to deviate in thermal fragmentation behaviour from the other members of the series. This compound alone of the series (447) possesses the ability to undergo extrusion processes from both of the terminal five-membered rings. In practice, FVP of (372) at 650°C gave a pyrolysate of a colourless oil, dissolved in deuteriochloroform while still cold, together with a polymeric solid. Examination of the ^1H NMR spectrum indicated the absence of sulphone-containing compounds and the presence of largely olefinic products. Analysis of the pyrolysate by GLC indicated that at least 16 volatile products were present of which only benzene (2% yield) and toluene (1%) were identified. The large number of unsaturated products is not unexpected in light of the alternative thermal extrusion pathways open to the disulphone (372). Stepwise extrusion of both sulphur dioxide molecules appears to be most probable. Loss of the first unit of sulphur dioxide may occur to generate (460; X = SO_2),

(458; X = SO_2) and (459; X = SO_2). Loss of the second unit of sulphur dioxide from any of these, or from other intermediates *en route* to these species, would be expected to result in highly unsaturated hydrocarbons capable of extensive rearrangement processes under the pyrolysis conditions employed to give the large number of products observed.

In summary, for the members of the series (447) [excepting (447; X = SO_2)] it has been found that upon pyrolysis a thermal extrusion of sulphur dioxide occurred to generate the vinylcyclohexene systems (458) and (459) as the predominant products. Mechanistically, these products are expected to form by parallel processes to that shown in Scheme 52 for thermal fragmentation of the closely related series (446). Differences in the product distributions obtained upon pyrolysis of the various members of the two series (446) and (447) are apparent. Thus, much lower quantities (or none at all) of the cyclooctadiene product (460) were realised from (447); in contrast, the pyrolysis of (446) yielded substantial quantities of the cyclooctadiene product (449). In addition, a greater excess of the *trans*-vinylcyclohexene product (458) over the *cis*-isomer (459) was found for the pyrolysis of (447) compared to the corresponding products obtained from the series (446). This is exemplified in the case of FVP at 650°C of (367) where a ratio of (458; X = O) to (459; X = O) of 3.6:1 contrasts with a ratio of (450; X = O) to (451; X = O) of 2.6:1 on identical pyrolysis of (242a). It would appear that the variation in the ratio of the vinylcyclohexene products between the two series reflects the difference in the composition of the non-sulpholane heterocyclic ring. The presence of two methylene units rather than the carbonyl groups might reasonably be expected to sterically disfavour the *cis*-vinyl isomer (459) relative to the *trans*-vinyl isomer

(458) to a greater extent than in the corresponding isomeric pairs (451) and (450).

c. FVP of transoid, transoid-4,5-dihetero-11-thiatetracyclo-[7.3.0.$0^{2,8}$.$0^{3,7}$]dodecane/ene 11,11-dioxide systems (448)

The three systems available for pyrolysis which belong to the title class (448) were prepared by reaction of the relevant 1,3-dipole with the transoid tricyclic sulpholane (208) as has been previously described. Thus, the diazomethane adduct (272a), the diphenyl nitrone adduct (271a) and the p-anisonitrile oxide adduct (270a) were pyrolysed with the expectation that the presence of comparatively weak bonds within the diheterocyclic rings of these systems would present the opportunity for competing thermal fragmentation processes to those of extrusion of sulphur dioxide which predominate in the pyrolyses of the related systems (446) and (447).

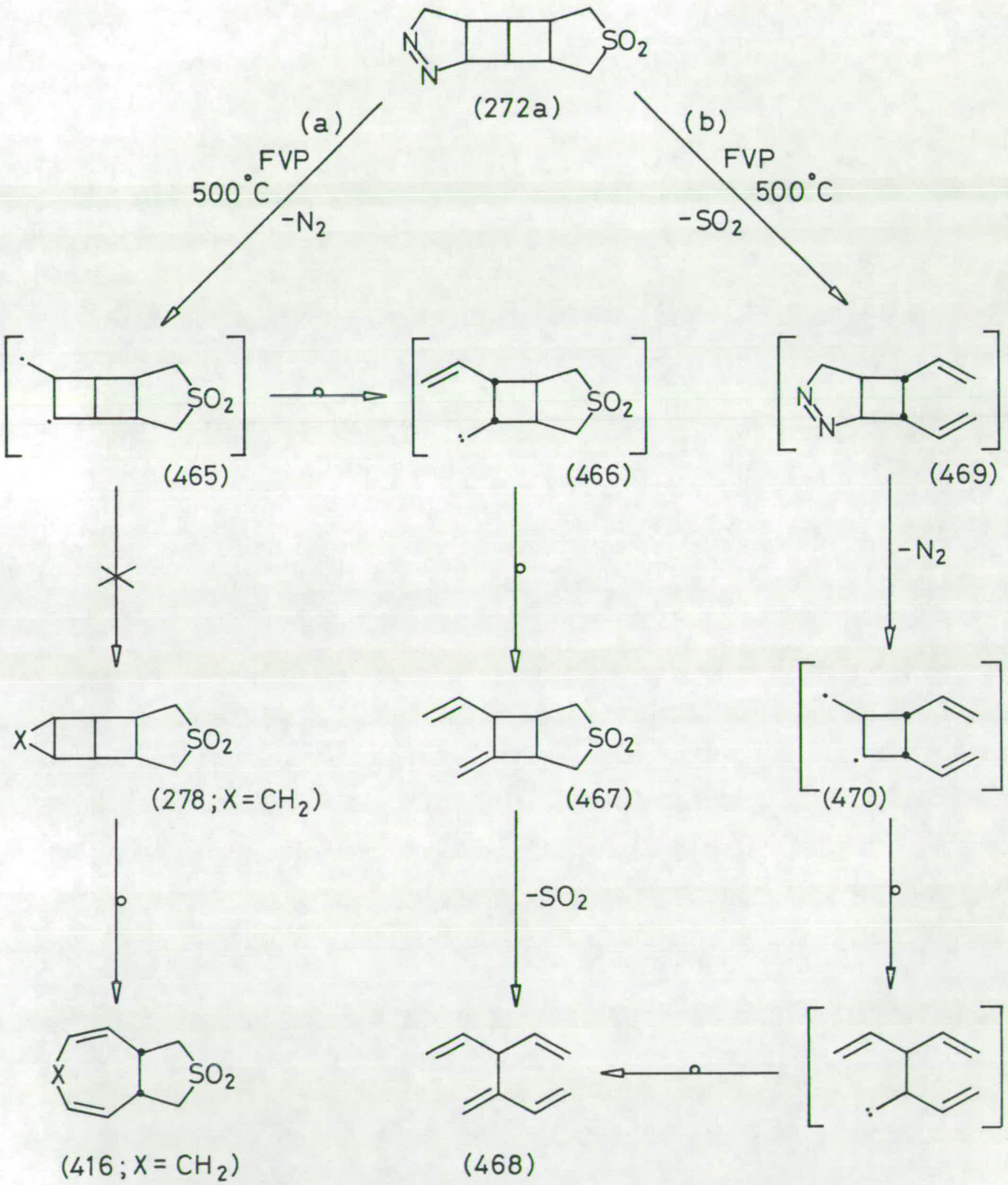
Prior to the pyrolysis of the diazomethane adduct (272a), it was considered feasible that the system would extrude both sulphur dioxide and nitrogen fragments in view of the ease of extrusion of these stable species. Upon FVP of (272a) at 500°C, a pyrolysate of light yellow oil was obtained. This was dissolved in deuteriochloroform while still cold and analysed by ^{1}H and ^{13}C DEPT NMR spectroscopy which indicated the absence of starting sulphone and presence of a sulpholane product in low yield (ca 5%). Examination of the pyrolysate by capillary GC-MS confirmed the presence of a sulpholane product of formula $C_9H_{12}O_2S$. In view of the structure of the main product (described shortly), the unsaturated sulpholane system (467) is a speculative but possible structure for this compound and is in accord with the exhibited GC-MS fragmentation pattern.

In addition to the sulphone product, GC-MS indicated that nine C_9H_{12} isomeric products at much shorter retention times. Eight

of these were present in approximately equal intensity accounting for ca 20% of the consumed sulphone (272a) although none were identified; the remaining isomer (65% yield) dominated the signals present in the ^{1}H and ^{13}C DEPT NMR spectra and analysis of these and the GC-MS fragmentation pattern allowed the tentative assignment of structure (468) to be made. In particular, the ^{13}C DEPT NMR spectrum was instructive : three unsaturated methylene and three methine (one saturated) signals were found at expected values and multiplicities in accord with structure (468). The pyrolysate was found to undergo polymerisation on standing at -20°C for several weeks, this observation being in agreement with the highly olefinic structure of the major product.

FVP of sulphone (272a) at 400°C resulted in isolation of starting sulphone (27% recovered) together with a product mixture largely unchanged from that obtained on pyrolysis at 500°C.

In terms of the mechanism of formation of the predominant product (468), two alternative pathways involving initial extrusion of nitrogen (pathway (a)) or sulphur dioxide (pathway (b)) may be proposed as outlined in Scheme 53. For systems such as (272a) where two fragments may be extruded from remote parts of the structure, a stepwise loss of these is expected. As described earlier (p.2), the thermal extrusion of nitrogen is known to occur more easily than that of sulphur dioxide, indicating that pathway (a) is the more likely process for decomposition of (272a). Thus, extrusion of nitrogen with formation of the intermediate diradical (465) may result in the formation of a carbene system (466), in relief of ring strain in the former system; insertion of the carbene moiety into the α C-H bond would generate the bicyclic unsaturated sulpholane (467) - possibly the sulpholane product detected in low yield on FVP of (272a) at 500°C.


(272a)
(a)
FVP
500°C
-N2
(b)
FVP
500°C
-SO2
(465)
(466)
(469)
-N2
(278; X = CH2)
(467)
(470)
-SO2
(416; X = CH2)
(468)

Scheme 53

As described in the Introduction (p.16), bicyclic systems of type (467) readily extrude sulphur dioxide with formation of divinyl products : under the pyrolysis conditions employed, sulpholane (467) would therefore be expected to expel sulphur dioxide with generation of the major isolated product (468).

An alternative rearrangement of the initially formed diradical to form the cyclopropane system (278; X = CH_2) would be energetically disfavoured in light of the high ring strain inherent in this structure. Comparison of the GC-MS fragmentation pattern and ^{13}C DEPT NMR data of the unidentified sulpholane product detected in the pyrolysate of (272a) at 500°C with those of (278; X = CH_2) or (416; X = CH_2) [the thermally stable product earlier shown to form on fragmentation of (278; X = CH_2) under these pyrolysis conditions] indicated that neither was present in the pyrolysate.

Although direct extrusion of sulphur dioxide (pathway (b) in Scheme 53) from the diazomethane adduct (272a) may account for the formation of the major product (468) by the fragmentation and rearrangement processes shown, such a mechanism is unlikely on three counts. Firstly, sulphur dioxide is generally much less easy to thermally extrude than nitrogen (favouring pathway (a)); secondly, the divinylcyclobutane system (469) if formed would be more likely to undergo Cope cyclisation to generate the corresponding (Z,Z)-cycloocta-1,5-diene product (and hence to vinylcyclohexene based products) in accord with the precedents described earlier in this section, than to directly extrude nitrogen with formation of the diradical intermediate (470). Incidentally, the extrusion of nitrogen from the cyclooctadiene or vinylcyclohexene based systems would not be expected to result in predominant formation of the observed major product (468). A third reason is the presence in the pyrolysate of a sulphone product -

indicative of operation of an alternative fragmentation pathway. Hence pathway (b) is certainly not the major extrusion route to (468), although it may operate to a limited extent and be the source of the minor C_9H_{12} components of the pyrolysate mixture.

FVP of the C,N-diphenyl nitrone adduct (271a) at 400°C was attempted, but at an inlet temperature of 160°C which was required for sample volatilisation the starting sulphone was found to decompose to give a dark coloured oil. Both the pyrolysate and the pyrolysis residue (which accounted for more than half of the initial sample) were analysed by ^1H NMR spectroscopy and TLC which indicated the absence of starting sulphone (271a) and the presence of an unidentified sulphone product together with more volatile (non sulphone-containing) aromatic products. Due to the extensive decomposition of (271a) in the FVP inlet upon heating, VVP of the sulphone was attempted in order to circumvent the involatility problem.

VVP of (271a) at 400°C resulted in isolation of a mixture of the sulphone-containing product (the major component) observed on FVP at 400°C and at least seven volatile components (detected by GLC) none of which were identified. Differences in the solubility and polarity characteristics of the sulphone permitted the separation of this from the other components to give slightly brown-coloured crystals, melting with decomposition at 242-244°C. From analysis of the mass spectrum, the sulphone product was found to be isomeric with the starting sulphone (271a), permitting calculation of the isolated yield as 54%. In addition, inspection of the infrared spectrum confirmed the retention of the sulphone group in the product although no other functionalities could be easily identified.

Comparison of the ^1H and ^{13}C NMR spectra of the unidentified sulphone product (Figure 32) with those of the starting sulphone (271a)

(Figures 4 and 5, p. 112) confirms the isomeric nature and highlights some striking differences in structure between the two. Thus, the three singlets at δ5.78, 4.46 and 3.95 in the proton spectrum of the product, which from consultation of the 2D ^{1}H-^{13}C correlated NMR spectrum (Figure 33) correspond to the three lowest field, non-aromatic carbon resonances, appear at significantly deshielded positions compared to the 'corresponding' proton and carbon resonances of the methine groups C(3)H, C(6)H and C(7)H located in the diheterocyclic ring of (271a). The lack of coupling between the three methine groups in the product is in contrast with the situation in starting sulphone (271a) and suggests that the diheterocyclic and cyclobutane ring fusion bond [C(3)-C(7)] of the latter has been cleaved in formation of the product. However, the ^{13}C NMR spectrum of the product is in accord with retention of the fused sulpholane-cyclobutane part of (271a) in the product.

Another feature of note in the proton spectrum of the thermally rearranged isomer is the shielded position of the aromatic signals in the region δ6.3-7.1. Analysis of the ^{1}H-2D COSY spectrum of the product (Figure 34) indicates that the five protons in this region are strongly coupled to each other and are therefore all present in one aromatic ring. The shielded positions of the signals for the two ortho protons (δ6.34) and para proton (δ6.69) are in contrast with the comparatively downfield aromatic resonances in starting sulphone (271a), and in all probability this shielding effect arises from a greater delocalisation of the lone pair on nitrogen into the bonded aromatic ring in the product. This implies that in the product the nitrogen atom is no longer bonded directly to oxygen as in the starting sulphone (271a) where delocalisation of the nitrogen lone pair into the bonded aromatic ring (acting to shield the o and p

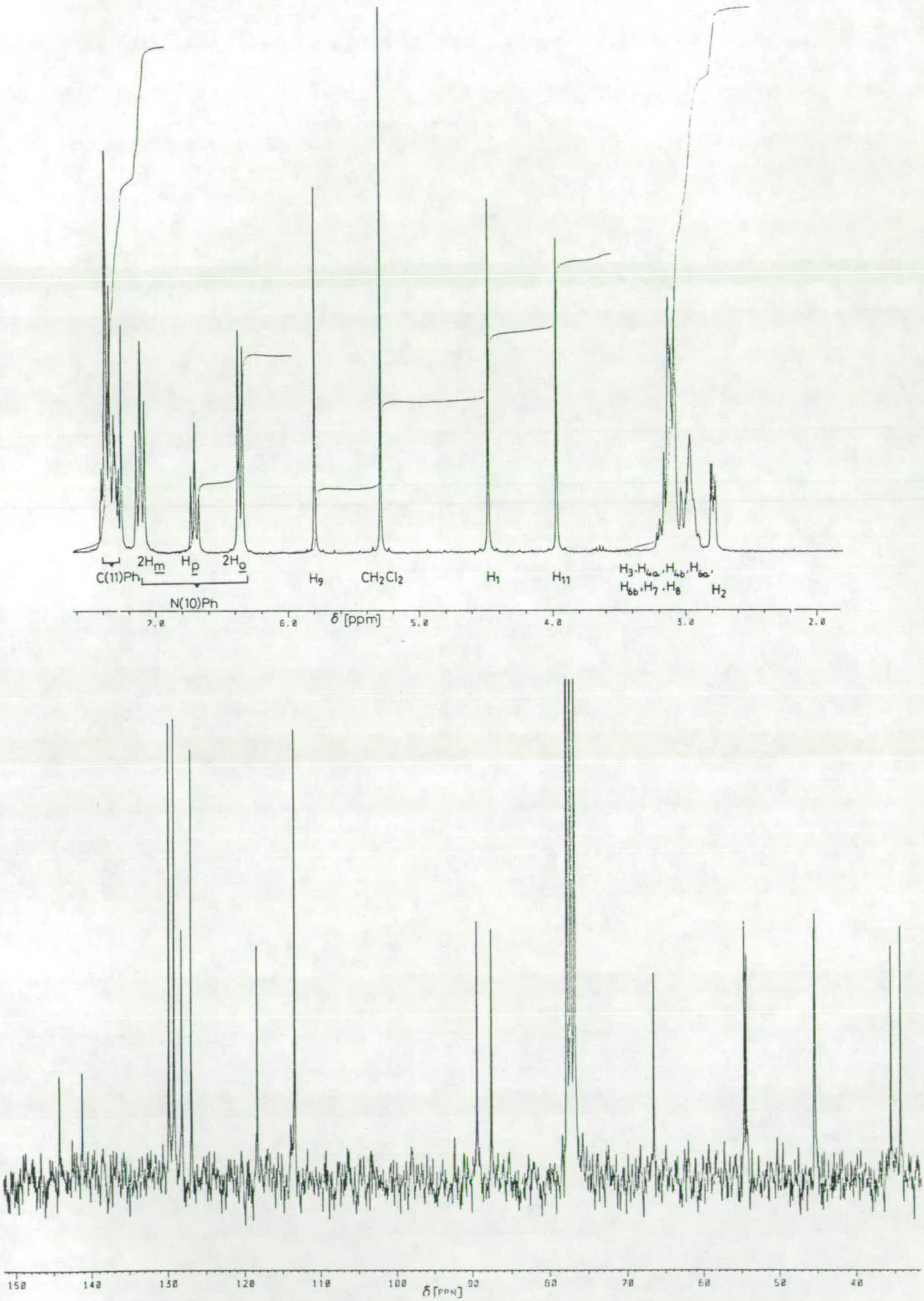


Figure 32 : ^{1}H and ^{13}C NMR spectra of (474)

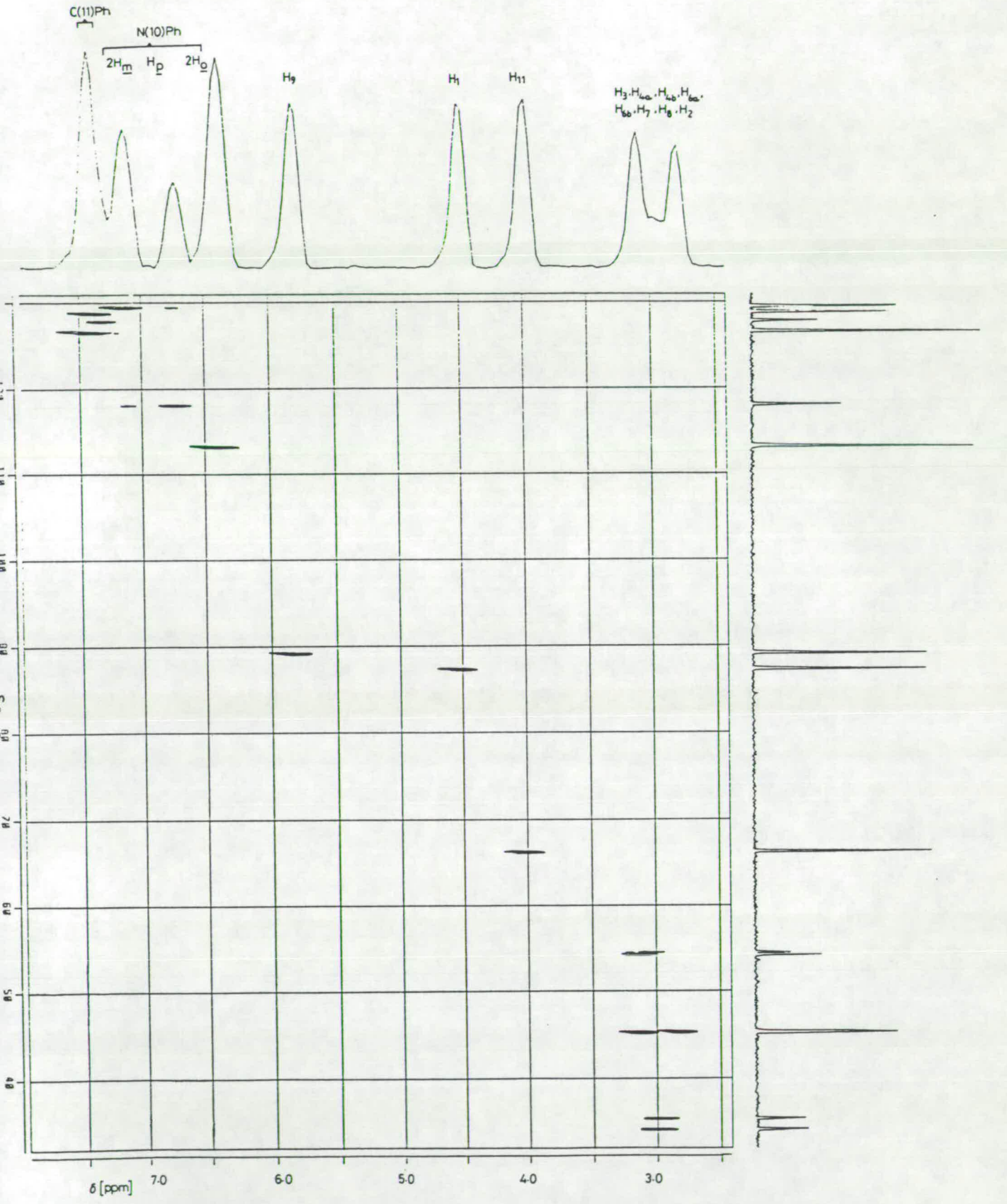


Figure 33 : ^{1}H-^{13}C 2D correlated NMR spectrum of (474)

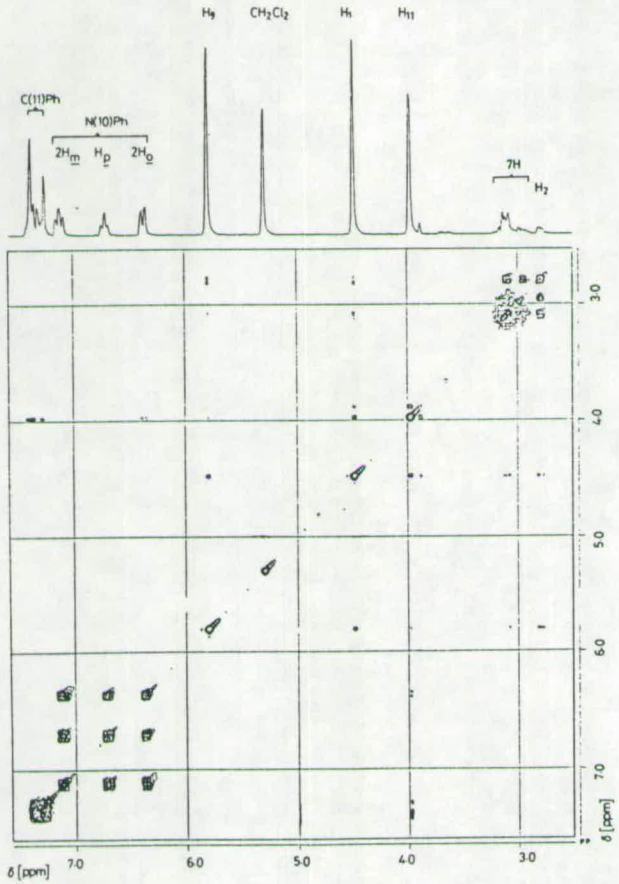


Figure 34 : ^{1}H-2D COSY spectrum of (474)

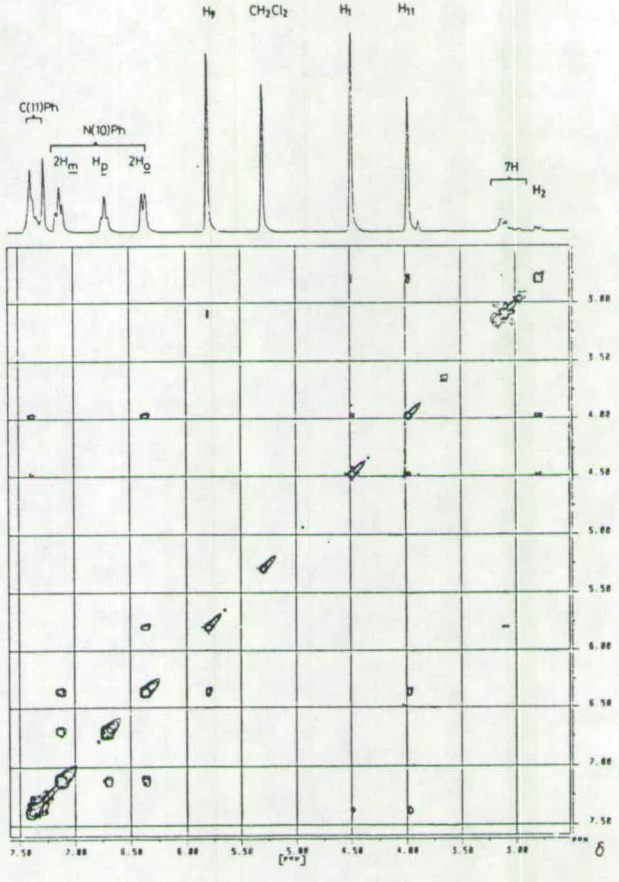


Figure 35 : ^{1}H-2D NOESY spectrum of (474)

positions) is limited by strong electron withdrawal by the adjacent oxygen atom.

The scission of the nitrogen-oxygen bond, and of the fusion bond between the dihetero-ring and the cyclobutane ring, taken in conjunction with the general deshielding of the diheterocyclic methine protons of (271a) upon thermal isomerisation implies that the product possesses structure (474). Re-examination of the NMR spectra fully vindicates this assignment of structure. Thus, the three methine groups C(1)H, C(9)H and C(11)H in (474) would be expected to display signals in the ^{1}H and ^{13}C NMR spectra at significantly different chemical shift values compared to those of the parent methines C(7)H, C(3)H and C(6)H in starting sulphone (271a). In detail, compared to the signal for proton H_3 in (271a), a deshielding (by 0.9δ) of the derived H_9 signal in the product (474) is apparent, this being due to the combined deshielding effects of the neighbouring oxygen and nitrogen ring elements for H_9, as opposed to only oxygen for H_3 in (271a). Similarly, the signal for proton H_1 of (474) is deshielded (by 0.9δ) due to the presence of an adjacent oxygen atom, on comparison with the parent H_7 signal in (271a). In contrast, the H_{11} resonance of (474) is shielded (by 0.5δ) compared to the parent H_6 signal in (271a) due principally to the intrusion of H_{11} into the shielding region associated with the N(10) aromatic ring. The proximity of H_{11} to this ring in product (474) is demonstrated by the strong interaction between H_{11} and the o-protons of the N(10)-phenyl system evident in the ^{1}H-2D NOESY spectrum (Figure 35).

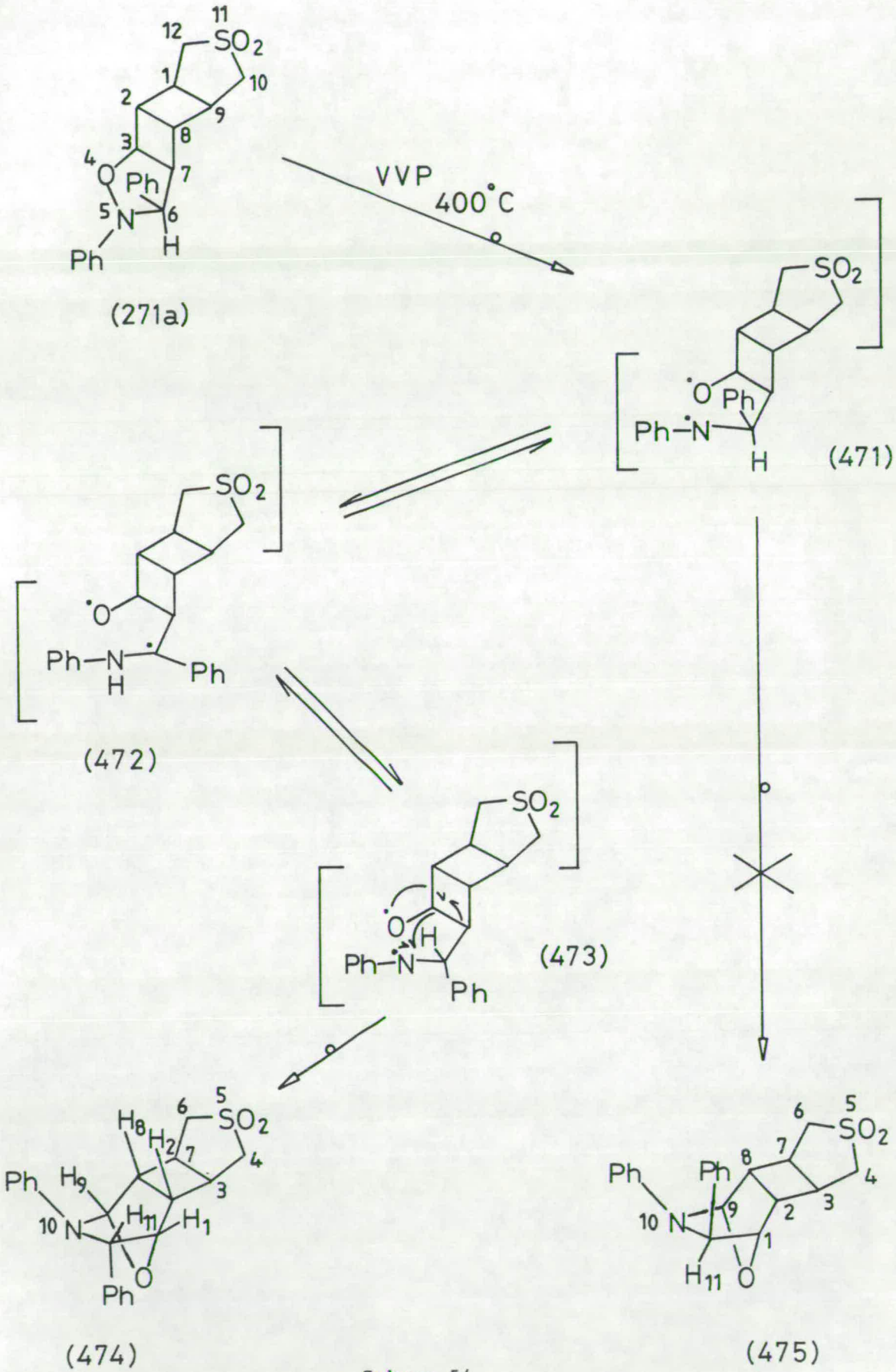
The differences in the isomeric structures is also reflected in the relative positions of the carbon resonances of the three methine groups in the diheterocyclic part of (474) compared to those of the dihetero-ring of (271a). Additionally, the almost equivalent

chemical shift values of C(2) and C(8) in (474) reflects the more evenly distributed deshielding effect of oxygen on these carbons compared to the substantial difference in chemical shifts of the corresponding C(2) and C(8) resonances (resulting from the asymmetric disposition of the ring oxygen element) in (271a).

Further evidence for the structure of the product (474) may be deduced from analysis of the ^{1}H-2D COSY spectrum (Figure 34). Long range couplings between the 'singlets' corresponding to H_1 and H_9, and also between H_1 and H_{11} are in accord with structure (474). Similarly weak couplings between H_{11} and both phenyl ring resonances, between H_1 and H_2 and between H_8 and H_9 were also observed. The almost zero coupling between the latter two pairs of protons which gives rise to the initially surprising singlet appearance of the signals due to H_1 and H_9 is a consequence of the near orthogonal dihedral angles $\phi_{1,2}$ and $\phi_{8,9}$. Coupling to H_1 and H_9 would also be reduced by the presence of the strongly electronegative oxa bridge to which both C(1)H and C(9)H methine groups are attached.

Conclusive evidence for the stereochemistry of the product as being that shown in structure (474) was furnished by examination of the ^{1}H-2D NOESY spectrum (Figure 35). This indicates that protons H_1, H_2 and H_{11} are all close in space, requiring the C(11)-phenyl substituent to be disposed on the same face of the system as the oxa bridge. In addition, a strong NOE interaction between the o-protons of the N(10)-phenyl ring and both protons H_9 and H_{11} is only in accord with the stereochemistry of structure (474).

Having established in some detail the structure of the thermally isomerised product (474), the question of the mechanism of formation of this from (271a) remains to be addressed. A curious feature which requires explanation is the inversion of configuration



Scheme 54

of C(6) in (271a) to give C(11) in the thermally rearranged product (474). The mechanism proposed in Scheme 54 to account for these observations involves an initial thermal homolytic scission of the weakest bond (nitrogen-oxygen) in the starting sulphone (271a) with generation of diradical intermediate (471). Intramolecular hydrogen abstraction by the anilino radical to form (472), followed by re-abstraction of the hydrogen atom with generation of the intermediate (473) would allow the 'correct' substituent configuration of C(11) to be realised on radical-induced cyclobutane ring opening to form the isolated product (474).

A parallel ring opening of diradical (471) would be expected to form structure (475), identical to the isolated product (474) in all respects save the configuration of the C(11) group. However no such alternative product was detected experimentally and it is feasible that formation of (475) is disfavoured due to a steric repulsion between the cyclobutane ring skeleton and the tolyl ring of (471) which prevents the anilino radical from attaining a close enough approach to the cyclobutane ring to induce ring opening. No such handicap exists in the radical-induced ring opening of the cyclobutane ring in (473) with resultant preparation of the isolated product (474).

In addition to the product (474) of the isomerisation process outlined in Scheme 54, seven volatile components were detected on VVP of (271a) at 400°C but due to the lack of information regarding the identity of these no mechanism can be proposed for their formation. However, the extrusion of sulphur dioxide (and possibly other fragments) from (271a) and (474), or from any of the diradical intermediates shown in Scheme 54, must be regarded as possible routes to the volatile products formed. It was found that VVP at 600°C of the VVP (400°C) pyrolysate obtained from (271a), which predominantly consisted of

sulphone (474), resulted in formation of a mixture containing 12 volatile components in approximately equal concentration, with no sulphone-containing compounds present. None of the volatile products were identified and although seven were initially present in the starting material the increase in number on VVP of (474) at 600°C indicates that this system fragments to give a complex array of products.

Flash vacuum pyrolysis of the third and final member of the dihetero series (448), the p-anisonitrile oxide adduct (270a), was undertaken at 450°C. Unchanged starting material (15%) was easily separated from the much more chloroform-soluble pyrolysis products. Analysis of the pyrolysate by ^{1}H NMR spectroscopy established that no sulphone-containing products were present, and of the complex unsaturated resonances observed only those of 3-(p-methoxyphenyl)isoxazole (476) [24% yield on consumed (270a)] were identified by comparison with the reported[182] proton spectrum.

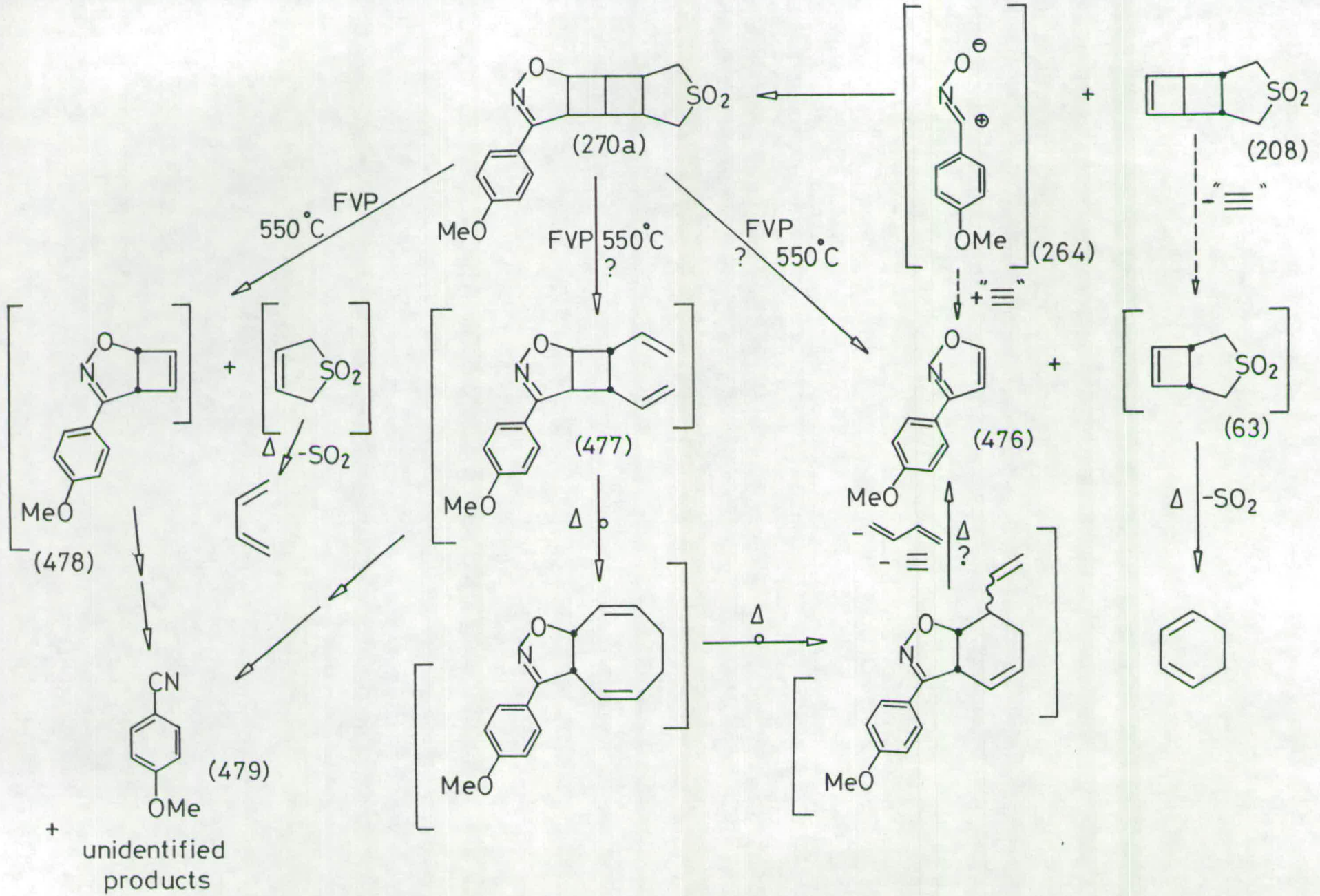
On conducting the FVP of (270a) at the higher temperature of 550°C, complete consumption of starting sulphone was achieved to give a pyrolysate found by ^{1}H NMR spectroscopy to be similar to that obtained at 450°C. In addition to the isoxazole (476) (20% yield), the proton signals characteristic of p-methoxybenzonitrile (479) (8% yield) were recognised. Separation of three distinct bands by preparative TLC of the pyrolysate did not assist in the identification of other aromatic products due to the presence in each band of a number of compounds.

A discussion of the thermal fragmentation mechanisms operational in the case of (270a) is severely restricted in view of the large number of unidentified products which account for the majority of the consumed sulphone. However, with regard to the identified products it would appear that a possible thermal fragmentation

pathway is the forbidden retro [2 π + 2 π] cyclisation to generate the isoxazole (476), as shown in Scheme 55. This process is favoured by the formation of the resonance stabilised heterocycle (476) and the relief of ring strain in the precursor sulphone (270a). Although the isoxazole (476) is known[182] to be stable to the pyrolysis conditions which were used, the other compound expected to be formed by this fragmentation pathway, the cyclobutene-sulpholane (63), extrudes sulphur dioxide with generation of the volatile (hence undetected) hydrocarbon, cyclohexa-1,3-diene[34].

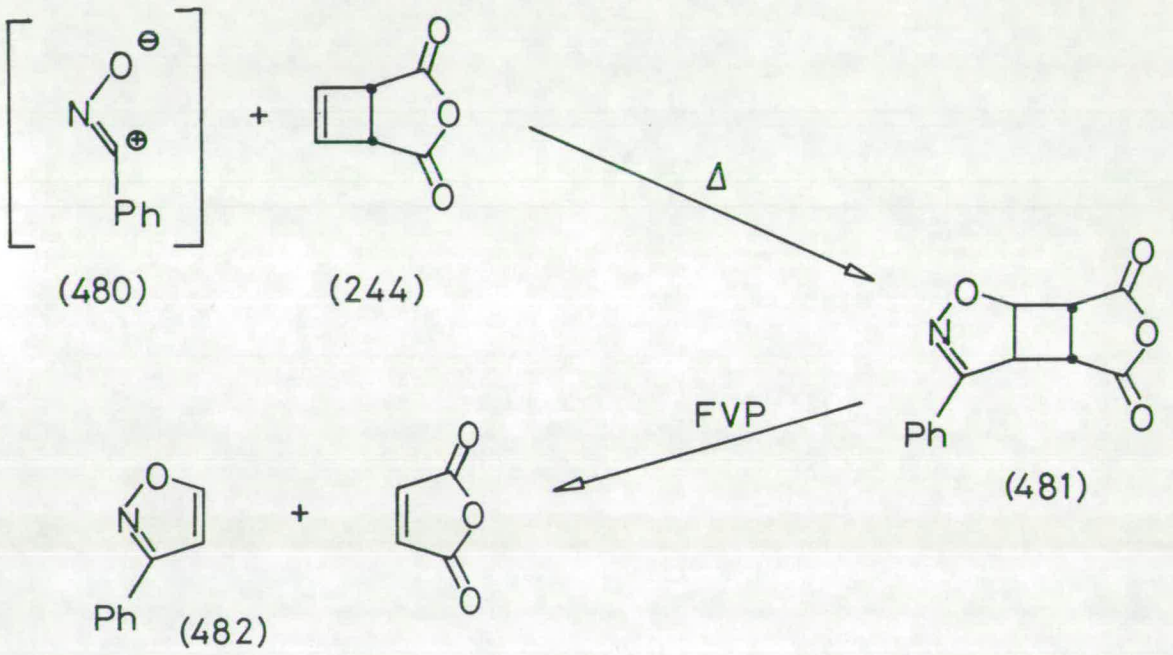
An alternative route to the isoxazole (476) is possible *via* initial extrusion of sulphur dioxide from (270a), with Cope cyclisation of the *cis*-divinylcyclobutane intermediate (477) leading to a cyclooctadiene system (Scheme 55). As in related examples described previously, rearrangement of the latter to isomeric vinylcyclohexene structures is feasible - thermal extrusion of buta-1,3-diene and ethylene fragments from these would generate the stable heterocycle (476). The presence of signals in the olefinic region of the proton spectrum of the pyrolysates obtained on FVP of (270a) may be related to the presence of the cyclooctadiene and/ or vinylcyclohexene based structures implicated in this route to (476). Incidentally, the presence of the heterocycle (476) in the pyrolysate derived from (270a) is analogous to the formation of (462) on thermal fragmentation of the related tetracyclic system (370), though in the latter case a vinylcyclohexene product (the possible source of (462) by extrusion of buta-1,3-diene and ethylene) was positively identified.

As outlined in Scheme 55, the conversion of *p*-anisonitrile oxide (264) to isoxazole (476) is achieved by reaction with sulphone (208) and pyrolysis of the resultant adduct (270a). As the net result


(270a)
FVP 550°C
FVP 550°C ?
FVP ? 550°C
MeO
OMe
(264)
(208)
(478)
(477)
(476)
(63)
(479)
CN
OMe
unidentified products

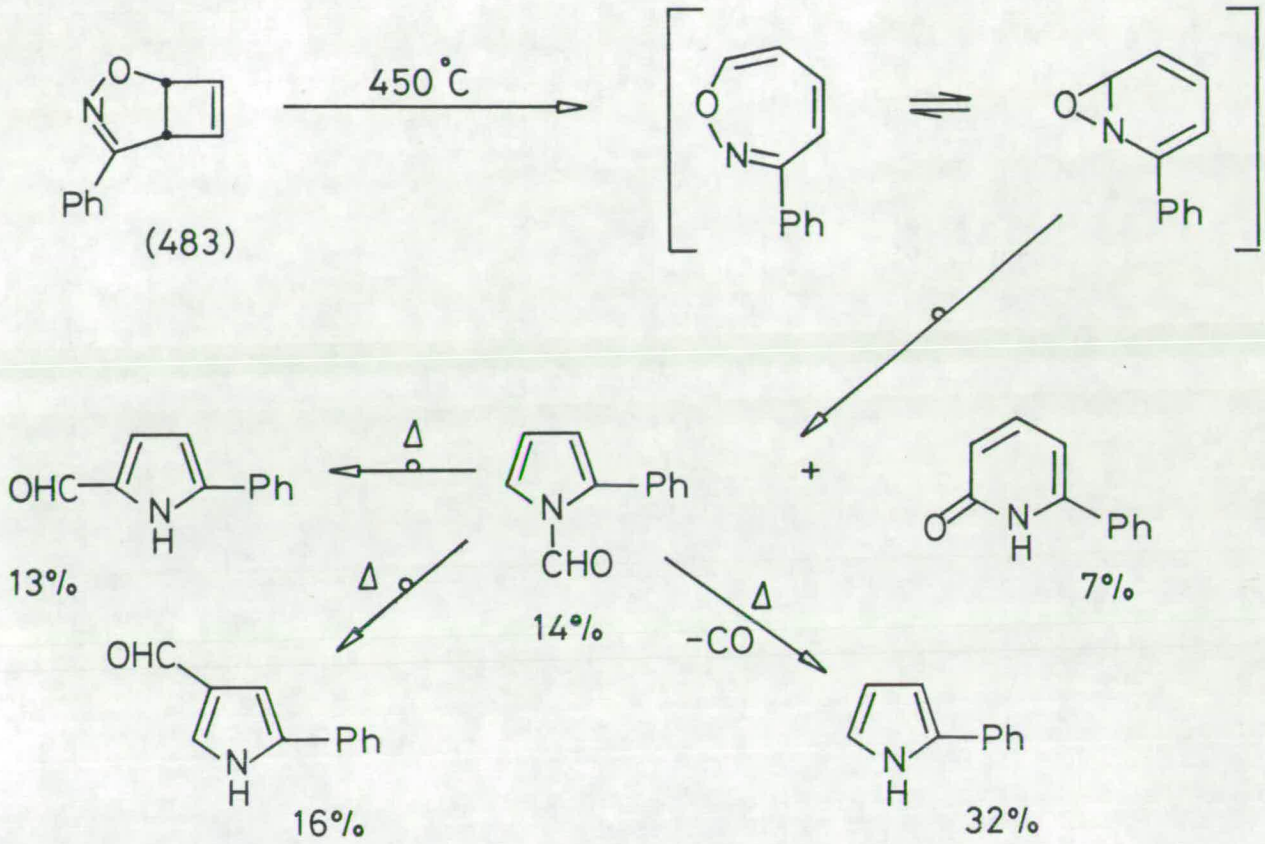
Scheme 55

of this reaction sequence is the transfer of an acetylene unit from sulphone (208) to p-anisonitrile oxide (264), the sulphone acts as an acetylene synthon. In this respect, the cyclobutene (208) parallels the behaviour of the cyclobutene anhydride (244) which has been found[199] to yield the isoxazole (482) in 71% yield following FVP of the adduct (481) formed by reaction of (244) with benzonitrile oxide (480).



(480) (244) (481) (482)

A further fragmentation route which may operate on pyrolysis of (270a) involves the cleavage of the alternative cyclobutane ring with generation of butadiene sulphone (known to decompose to buta-1,3-diene and sulphur dioxide even under comparatively mild thermal conditions - see p.33) and the cyclobutene (478). Although no direct evidence for the formation of (478) was apparent, this compound would not be expected to survive the pyrolysis conditions employed. It has been reported[200] by Mukai et al that vapour phase pyrolysis (450°C) of the related cyclobutene system (483) resulted in formation of the five products shown in Scheme 56. A similar fragmentation of cyclobutene (478) would therefore be expected on FVP at 450°C or 550°C,



Scheme 56

and a parallel series of products to those shown in Scheme 56 would be in accord with the number of unsaturated products present in these pyrolysates which, incidentally, displayed aldehydic and possibly amino resonances in the proton spectra.

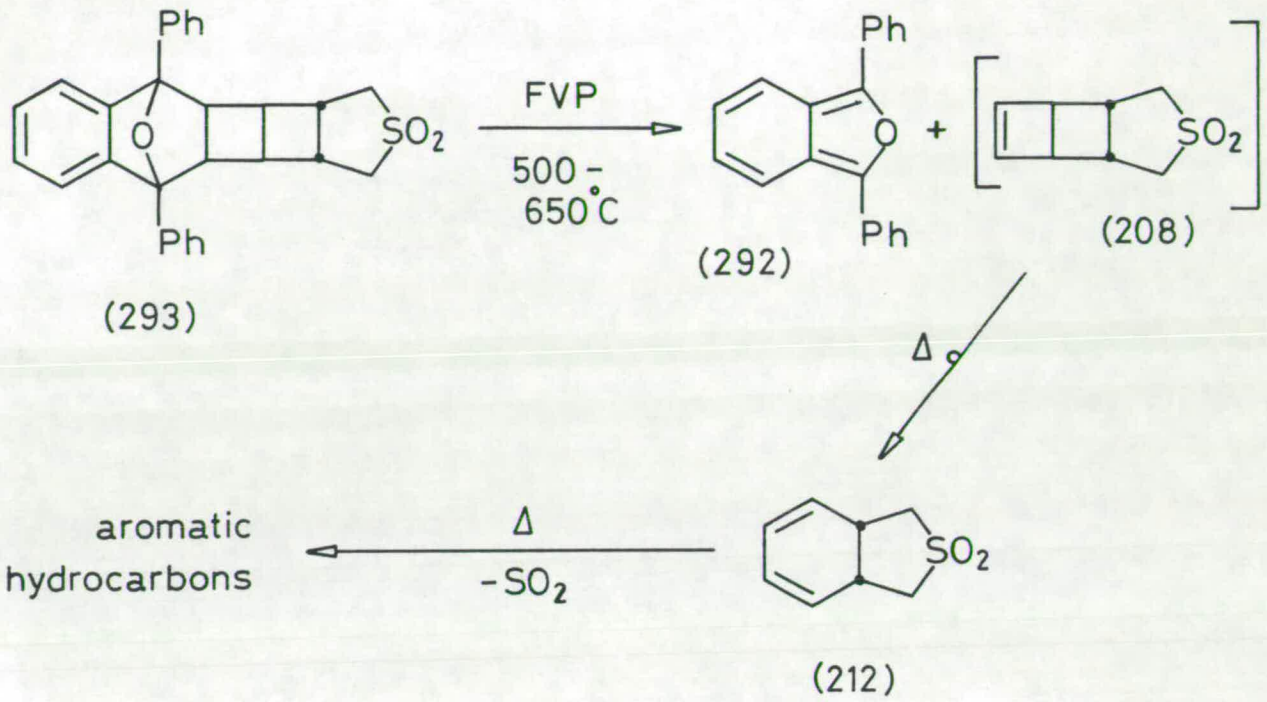
In summary, the results of pyrolysis of the three members of the series (448) show significant deviations from those obtained upon thermal fragmentation of the related series (446) and (447). Whilst in the latter two series direct extrusion of sulphur dioxide predominated with generation of a cis-1,2-divinylcyclobutane intermediate which then underwent rearrangement processes to yield isolated (mainly) cyclooctadiene- and vinylcyclohexene-based products, thermal fragmentation of the members of series (448) occurred principally at the diheterocyclic ring in which comparatively fragile bonds were present, or within the tetracyclic ring structure, prior to extrusion of sulphur dioxide.

5. FVP of 14-bridged-6-thiapentacyclo[9.2.1.$0^{2,10}$.$0^{3,9}$.$0^{4,8}$]tetradec-12-ene 6,6-dioxide systems

The title compounds conform to the series (211; n = 4) in which the six-membered ring is bridged. As described previously, the Diels-Alder reaction of the transoid tricyclic sulphone (208) with tetracyclone (294) and 1,3-diphenylisobenzofuran (292) resulted in formation of the isomeric tetracyclone adducts (295a) and (295b), and bridged system (293) respectively. The pyrolysis of these title systems was undertaken in completion of the thermal fragmentation study of the series (211; n = 1-4), and it was noted that alone of all the tetracyclic systems available for pyrolysis, the bridged compounds possessed the ability to undergo a retro-Diels-Alder fragmentation in competition to sulphur dioxide extrusion.

FVP of the oxa-bridged system (293) at 500°C resulted in formation of a yellow/ green solid. Analysis of this by ^{1}H NMR spectroscopy and by TLC demonstrated that starting sulphone (293) (42%) was present, together with 1,3-diphenylisobenzofuran (292) [95% yield on consumed sulphone (293)] and the cyclohexadiene-sulpholane (212) [82% yield]. A low total yield of nine volatile products, mainly the aromatic hydrocarbons associated with extrusion of sulphur dioxide from (212), was detected by GLC. Upon FVP of the bridged system (293) at higher temperature (650°C) complete conversion of the sulphone was achieved. Again the products were 1,3-diphenylisobenzofuran (292) (95%), bicyclic sulpholane (212) (12%) and the volatile products (ca 45%) found on FVP at 500°C.

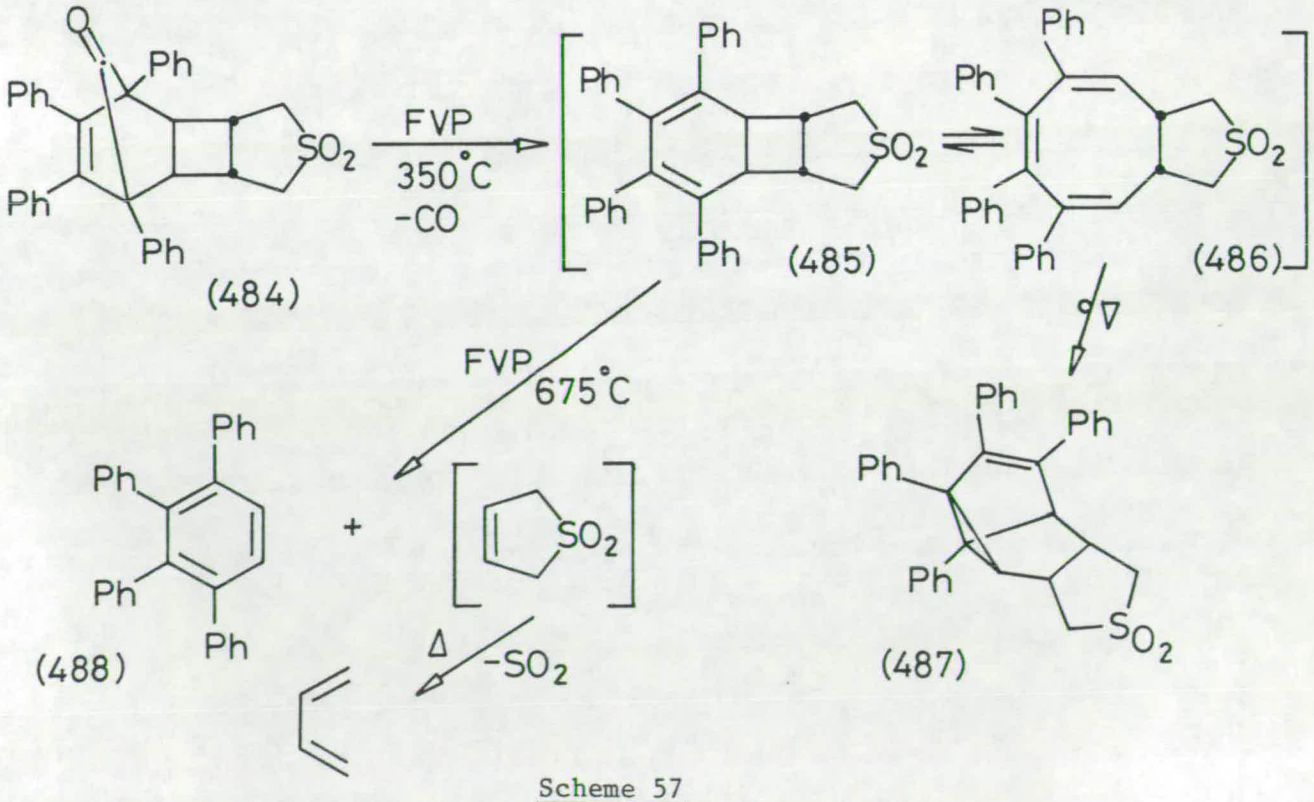
For pyrolysis of (293) it is clear that only the retro-Diels-Alder fragmentation process is operational, giving rise to the materials from which the system was constructed, namely 1,3-diphenylisobenzofuran (292) and the transoid tricyclic sulpholane (208).



Although the furan is known[182] to be stable to FVP at 650°C [further evidenced by the high recovered yield of (292) here], the sulphone has previously been shown to undergo complete ring opening on FVP at 600°C to generate the diene (212) [p. 231]. That (212) then undergoes extrusion of sulphur dioxide - with generation of the characteristic range of aromatic hydrocarbons - to a significant extent even at the relatively mild pyrolysis temperature of 500°C is a reflection of the vibrationally excited condition of the _in situ_ generated species. As is detailed in a later section, the thermal fragmentation of unexcited or 'cold' diene (212) to an equivalent extent to that observed on FVP of (293) at 500°C would require an FVP temperature of _ca_ 750°C. Interestingly, analysis of the mass spectrum of (293) reveals a further example of the close links between mass spectral (electron-impact) and pyrolytic fragmentation pathways which is frequently encountered : electron-impact fragmentation of (293) generates an intense signal at m/e 270 [corresponding to 1,3-diphenylisobenzofuran

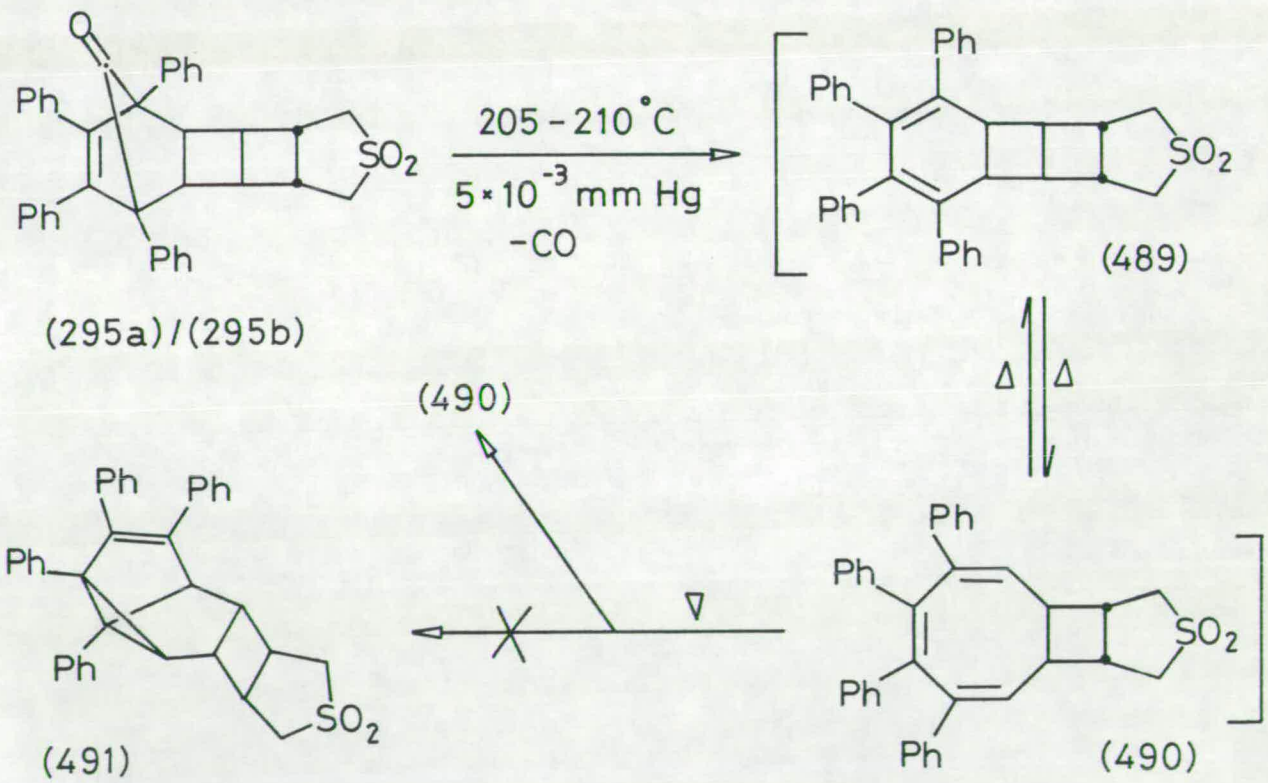
(292)] and also a peak of significant intensity at m/e 105 [corresponding to loss of $HSO_2^{\bullet}$ from diene (212)].

The thermal fragmentation behaviour of the remaining bridged systems, the tetracyclone adducts (295a) and (295b), was of especial interest in view of the unusual rearrangement associated with pyrolysis of the smaller ring analogue (484). This was found[182] to extrude carbon monoxide on FVP at 350°C to give, as an isolated product, the dihydrosemibullvalene (487). As outlined in Scheme 57, this product was rationalised as being formed by ring opening of the carbon monoxide - extrusion product (485) to the cycloocta-1,3,5-triene intermediate (486), followed by a precedented[201] thermal intramolecular [π_{4a} + π_{2a}] cycloaddition to (487). Although this system appears rather strained at first sight, it is actually more thermodynamically stable than the cyclohexadiene (485) or cyclooctatriene (486) precursors. Incidentally, FVP of (484) at an elevated temperature (675°C) resulted only in isolation of 1,2,3,4-tetraphenylbenzene (488) via the proposed intermediacy of diene (485)[182].



Scheme 57

Strict application of these findings to the low temperature pyrolysis (extruding carbon monoxide only) of (295a) and (295b) predicts the formation of the pentacyclic dihydrosemibullvalene system (491). In practice, on heating of a 2:1 mixture of the isomeric tetracyclone adducts (295a) and (295b) at 205-210°C and at a pressure of 5×10^{-3} mm Hg the sample was observed to melt with evolution of gas and formation of a crystalline product. Examination of this material by infrared spectroscopy indicated that while the sulphone group had been retained, the carbonyl group was absent. Mass spectral and elemental composition determinations established that the sulphone product resulted from simple loss of carbon monoxide from the starting adducts. However, ^{1}H and ^{13}C NMR spectra indicated the product not to be the expected dihydrosemibullvalene (491) but a single structure possessing two-fold symmetry, the cyclooctatriene (490).



Scheme 58

As outlined in Scheme 58, this product is considered to arise by thermal extrusion of carbon monoxide from the bridged isomers (295a) and (295b) followed by concerted ring opening of the resultant cyclohexadiene tetracycle (489). It would appear that at elevated temperatures a delicate balance exists between the isomeric cyclohexadiene, cyclooctatriene and dihydrosemibullvalene structures which is dependent primarily on ring strain/ steric repulsion factors. Structure (490) appears to be the most thermodynamically stable of the three isomers, explaining the sole isolation of this product at ambient temperature. An equilibrium between (489), (490) and (491) may exist at elevated temperatures, and the melting behaviour displayed by a pure specimen of (490) is perhaps indicative of such a situation. It was found that (490) underwent a partial melting process at 155-160°C; upon further heating partial crystallisation occurred until complete melting was observed at 237-242°C.

6. Summary of pyrolysis results

A brief summary can now be made of the main features emerging from the FVP of the series (211; n = 0, 1, 2, 3, 4). The saturated tricyclic systems (211; n = 0), which are equivalent to the class of compounds (69; n = 2), underwent extrusion of sulphur dioxide on FVP at ca 650°C. In accord with the thermal fragmentation behaviour of other members of the series (69) for which n = 0, 1, 3, 4, 5 (see p.25), a cis-1,2-divinyl compound (70; n = 2) was produced and this was found to undergo Cope cyclisation under the pyrolysis conditions in similar fashion to the intermediate divinyl species (70; n = 0, 1) afforded by pyrolysis of systems (69; n = 0, 1).

FVP of systems (211; n = 1, 2) at ca 500°C resulted in ring opening of the tetracyclic systems (in relief of ring strain) to generate

isomeric, unsaturated bicyclic products. Systems (211; n = 3) possessing stable five-membered, non-sulpholane rings were found to extrude sulphur dioxide on FVP at ca 650°C to generate intermediate cis-1,2-divinylcyclobutane-cyclopentane species which thermally rearranged principally to cycloocta-1,5-diene and 4-vinylcyclohex-1-ene based products. The comparative lack of ring strain associated with the terminal ring of compounds (211; n = 3) appeared to be the cause of the alteration in thermal fragmentation mechanism from that operating with the smaller ring systems (211; n = 1, 2).

Finally, FVP at ca 600°C of two bridged examples of the class (211; n = 4) was found to result in operation of ring fragmentation processes other than that of direct extrusion of sulphur dioxide. However, in both cases the presence of olefinic unsaturation influenced the fragmentation mechanism precluding effective comparison with the saturated series (211; n = 0, 1, 2, 3).

G. Preparation, Diene Reactivity and FVP of cis- and trans-8-Thiabicyclo[4.3.0]nona-2,4-diene 8,8-dioxides (212), (235)

1. Preparation and diene reactivity of cis-8-thiabicyclo[4.3.0]-nona-2,4-diene 8,8-dioxide (212)

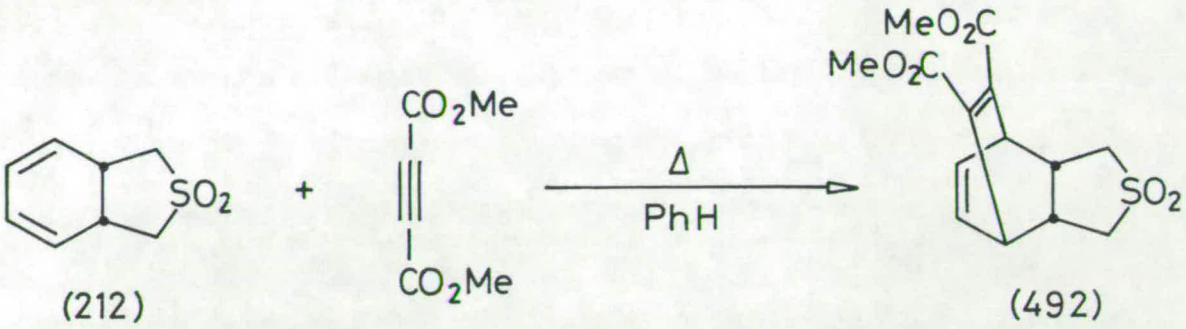
The cis-fused cyclohexadiene-sulpholane (212) has been previously prepared by bromination of the olefin (65), followed by base-induced bis-dehydrobromination of the resultant dibromide (229) [see p. 80]. Although the 2,4-diene (212) had to be separated from minor amounts of the isomeric 1,3-diene (230) which concomitantly formed in the second stage of this reaction sequence, this route was the preferred one for the preparation of (212) in the quantities required for a study of diene reactivity. Three alternative routes to (212) have also been described, these being the FVP of both the transoid (208) and cisoid (209) tricyclic isomers [p.231], and the FVP of the dibromide (229) [p. 81]. Although all three routes generated (212) in good-to-fair yields and purity, the relative scarcity of tricyclic systems (208) and (209) - compared to the olefin (65) - and the difficulties of scale-up procedures with respect to the FVP of dibromide (229) rendered these routes less viable than the bromination/ basic bis-dehydrobromination route described above.

The reactivity of the diene moiety of (212) towards photochemical ring closure has previously been detailed [p.83]. In summary, the desired formation of the transoid (208) and cisoid (209) tricyclic isomers was not observed under any of the range of photolysis conditions which were employed. However, under specific photolysis conditions a cis-fused to trans-fused isomerisation process was operational which gave rise to the trans-fused diene (235). In addition, under a variety of irradiation conditions, dehydrogenation of (212) to the benzo-fused sulpholene (110) occurred.

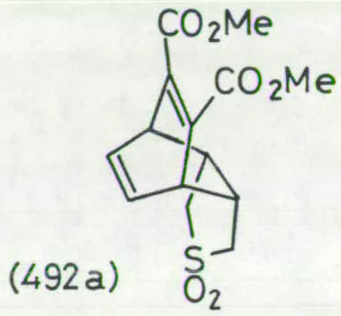
In view of this, facile dehydrogenation of (212) may be expected to occur under standard dehydrogenating conditions. Thus, treatment of a solution of (212) in boiling benzene under nitrogen with 10% palladium-on-charcoal gave the aromatic system (110) in fair yield as colourless rhombs, m.p. 149-150°C (lit.[202] m.p. 150-152°C).

The principal interest in an examination of the olefin reactivity of (212) lay in the Diels-Alder reactions of this reasonably electron-rich diene with symmetrical electron-deficient dienophiles giving rise to adducts (213). Such novel tricyclic systems would be of interest not only with regard to their pyrolytic fragmentation behaviour, but also with respect to a possible through-space interaction between the proximate olefin and sulphone groups in the endo isomers of adducts (213). In addition to the effect upon olefin reactivity in the endo isomers of (213), the manifestation of such a through-space interaction should also be apparent from a comparison of olefin ionisation potentials (πIp) of these systems and appropriate standard, unsaturated systems lacking such an interaction (such as the exo-isomers of (213)). With a view to the preparation of the tricyclic Diels-Alder adducts (213) - possibly in both endo and exo stereochemistries - the reactivity of cis-fused cyclohexadienesulpholane (212) towards the electron-deficient dienophiles, dimethyl acetylenedicarboxylate (DMAD), maleic anhydride, and butadiene sulphone were examined.

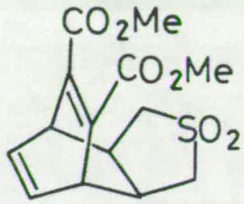
Treatment of diene (212) with a slight excess of DMAD in boiling benzene for 56 hours led to isolation of a crystalline adduct (492) of the two starting materials in 33% yield. Characterisation of the product by elemental composition and spectroscopic analyses confirmed it to be a single one of the two possible isomers (492a) and (492b). No trace of the alternative isomer was detected in the crude reaction product. Although the structural information available from



(212) (492)



(492a)

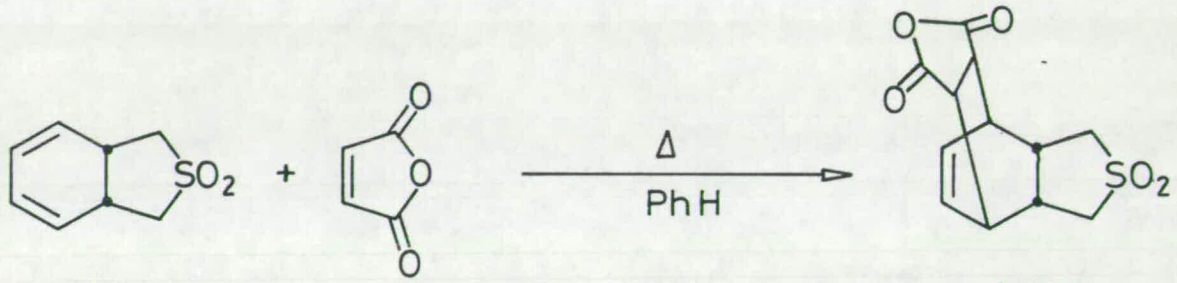


(492b)

the spectroscopic examination of the adduct (492) was not sufficient to differentiate between isomers (492a) and (492b), it was later unambiguously established to be the exo-isomer (492a) (see p.345).

The formation of solely the exo-isomer (492a) in the Diels-Alder reaction of (212) and DMAD is likely to be a reflection of the operation of steric and secondary orbital factors. Approach of the DMAD molecule to the least hindered face of the diene (212), ie from the face opposite to that containing the cis-fused sulpholane ring, would suffer less steric repulsion than the alternative approach pathway and therefore result in preferential formation of the exo-adduct (492a). In addition, the transition state which is favoured on steric considerations is also expected to be in receipt of a stabilising intramolecular secondary orbital interaction between the spacially proximate orbitals of the sulphone group and the forming olefinic double bond. In practice, these two factors acting in favour of the formation of the exo-isomer (492a) are sufficient to exclude appreciable amounts of the endo-isomer (492b) from being obtained.

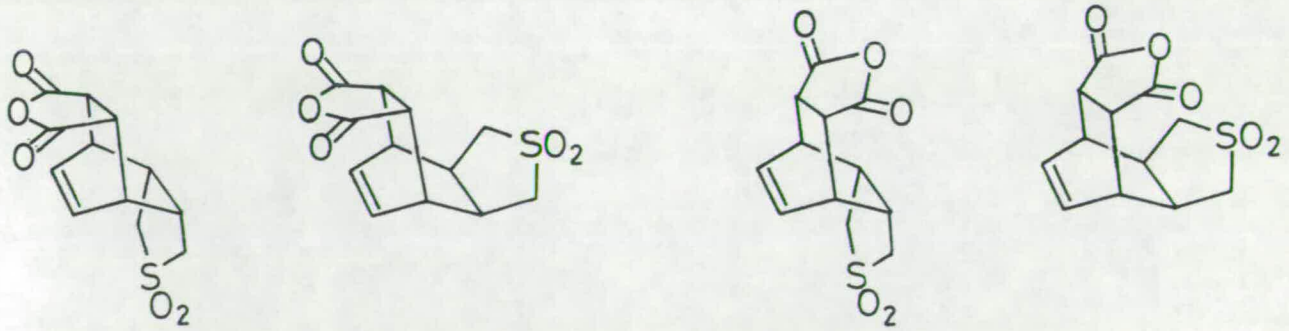
Turning to the reaction of diene (212) with maleic anhydride, it was found that under similar conditions to those employed in the reaction of (212) with DMAD, adduct formation occurred much more readily. Thus, after 20 hours of heating of (212) and maleic anhydride in boiling benzene, a 62% yield of insoluble colourless crystals of the adduct (493) was obtained. This product was fully characterised by



(212) (493)

elemental composition and standard spectroscopic determinations as a single compound possessing two-fold symmetry as expected for a structure of type (493). Four stereoisomers (493a)-(493d) may feasibly result from this reaction; recourse to ^{1}H-2D COSY and ^{1}H-2D NOESY NMR analyses permitted the unambiguous assignment of the product to one of these four structures.

The ^{1}H NMR spectrum is reproduced in Figure 36. Analysis of this indicated the methylene resonances (α- to the sulphone group) to occur at δ2.27 and δ3.08, each signal exhibiting a geminal coupling constant, $J_{3a,3b}$ ($J_{5a,5b}$) = 9.5 Hz, and coupling to the sulpholane ring fusion protons H_2,H_6 (δ2.57). Determination of the



(493a) (493b) (493c) (493d)

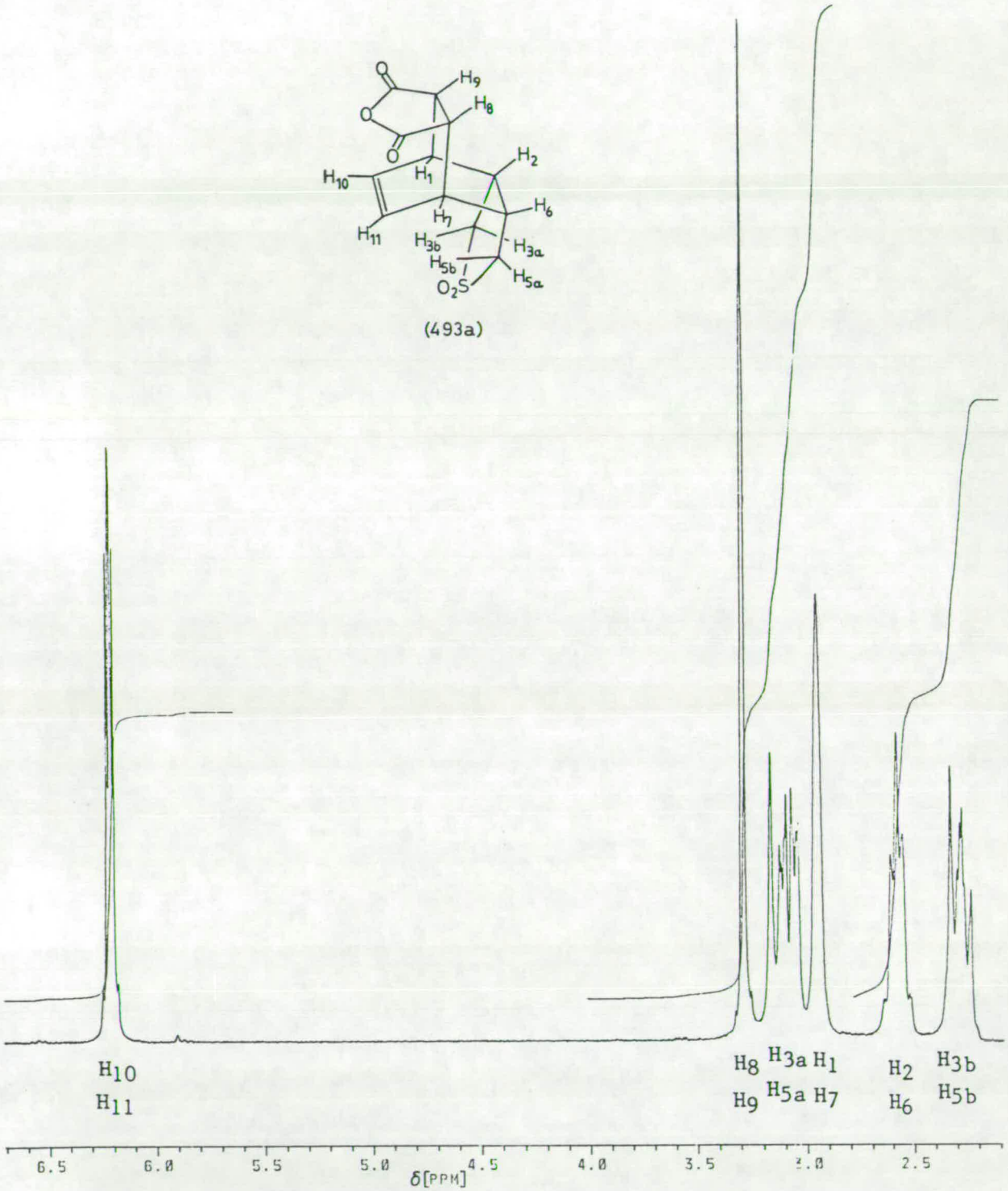


Figure 36 : ^{1}H NMR spectrum (250 MHz) of (493a)

^{1}H-2D COSY NMR spectrum, the saturated region of which is shown in Figure 37, confirmed these assignments. In addition, coupling between the signal (δ6.20) for the olefinic protons H_{10},H_{11} and the broad 'singlet' at δ2.94 enabled identification of the latter as being due to protons H_1,H_7; in turn, coupling of these to the most deshielded saturated signal at δ3.29 - evident in the ^{1}H-2D COSY NMR spectrum - allowed assignment of the latter to the anhydride ring-fusion protons H_8,H_9.

Inspection of the ^{1}H-2D NOESY NMR spectrum (Figure 38) indicated the presence of a strong NOE enhancement between the sulpholane methylene protons, as expected, and also a large interaction between protons H_2,H_6 and H_8,H_9. Such a close proximity of the sulpholane ring-fusion and anhydride ring-fusion protons is in accord only with structure (493a) of the four possible isomers (493a)-(493d) as that of the isolated product. Incidentally, the shielded position (by some 0.8δ) of the H_{3b},H_{5b} methylene protons compared to the H_{3a},H_{5a} methylene protons may be explained by the positioning of the former within the shielding region associated with the olefinic double bond[157].

The spectrally determined structure of the isolated product (493a) is in accord with that expected from consideration of the relative strengths of the secondary orbital overlaps operating within each of the transition states leading to formation of the four possible isomeric products (493a)-(493d). Only for the transition state leading to (493a) do stabilising secondary orbital overlaps exist between the proximate olefin and both carbonyl and sulphone groups, making this transition state the lowest energy one of the four alternatives, and resulting in (493a) being the kinetically preferred product. In addition, structure (493a) is favoured on steric grounds

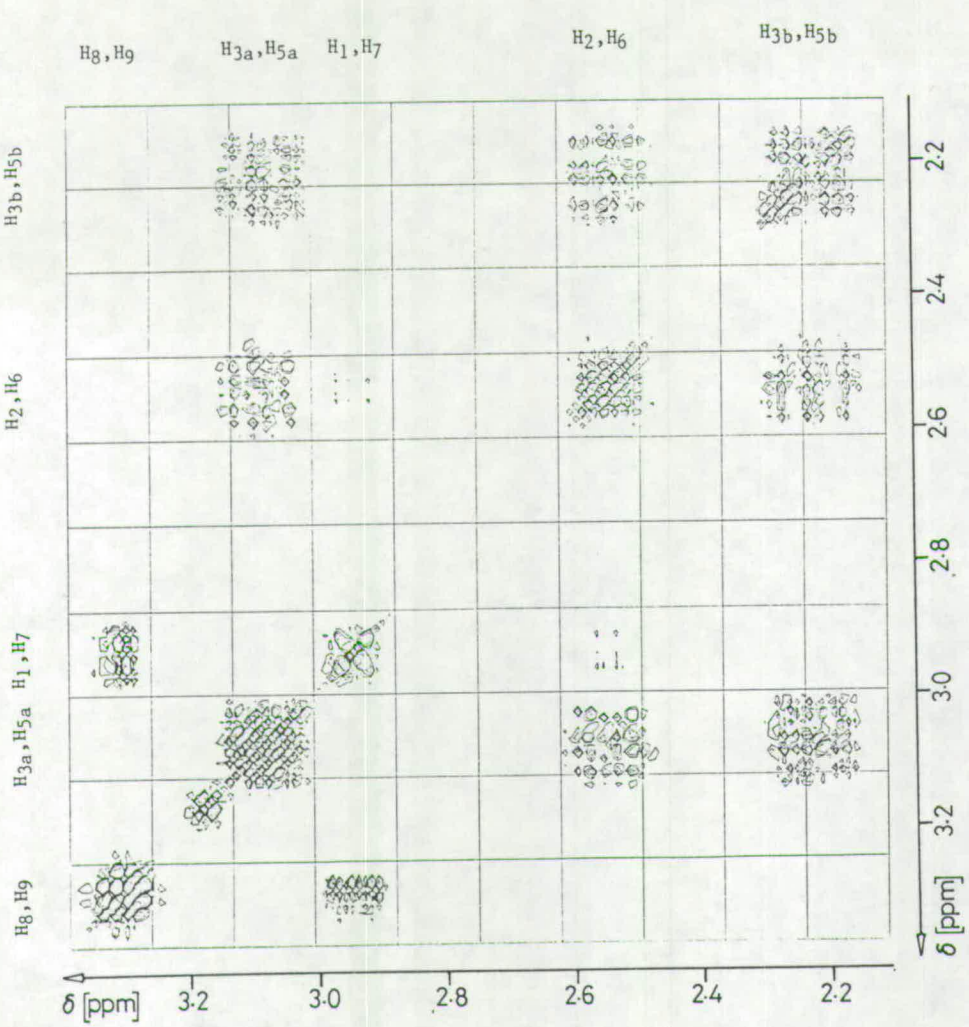


Figure 37 : ^{1}H-2D COSY NMR spectrum of (493a)

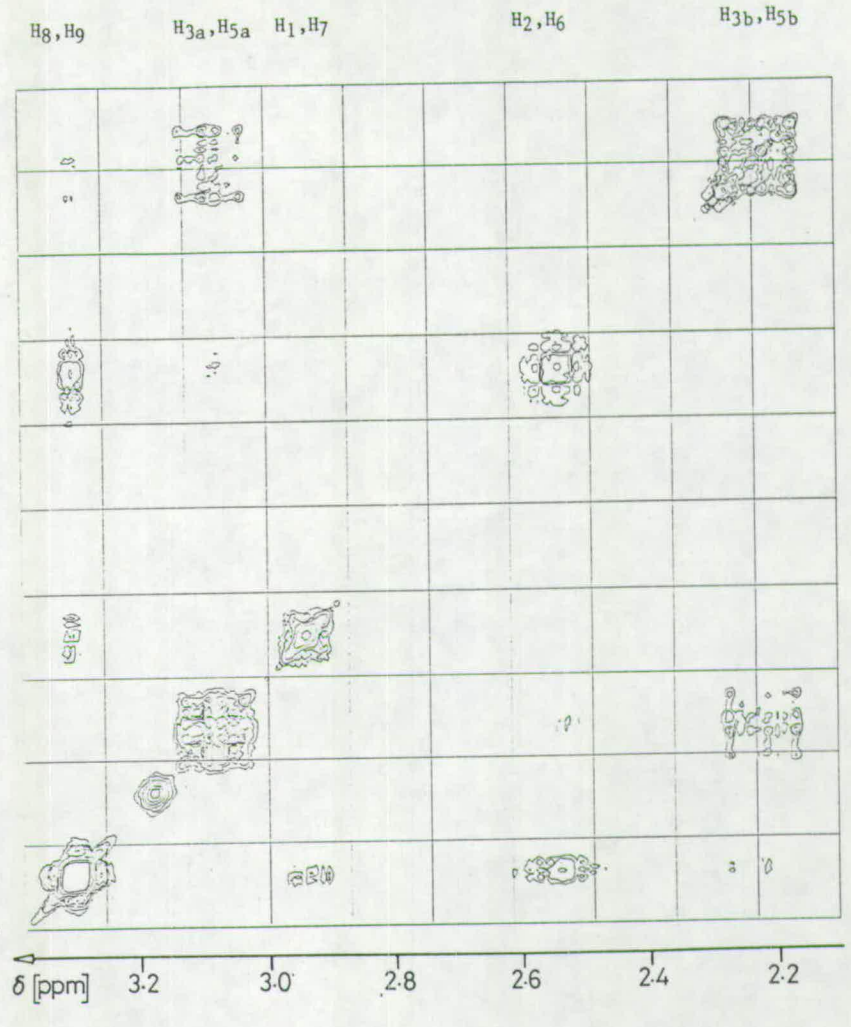


Figure 38 : ^{1}H-2D NOESY NMR spectrum of (493a)

as it results from addition of maleic anhydride to the less hindered face of the bicyclic diene system (212).

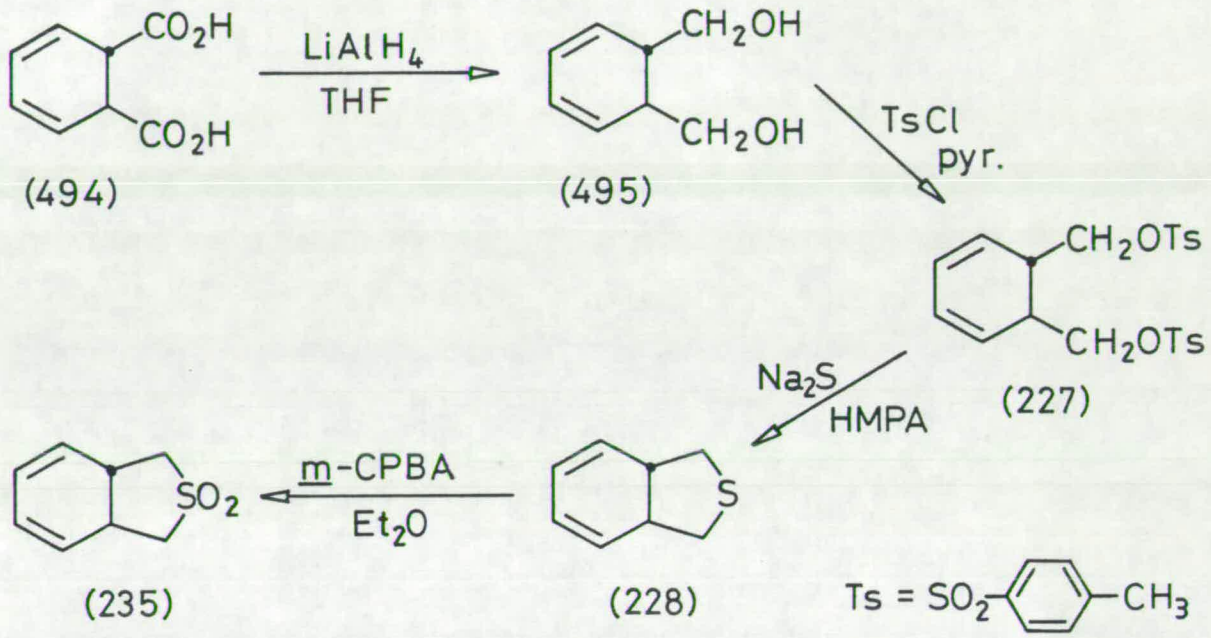
A third attempted Diels-Alder reaction was carried out by heating a solution of diene (212) and butadiene sulphone in benzene under reflux for 56 hours. However, both starting materials were recovered in quantitative yield. In light of the facile thermal decomposition of butadiene sulphone at temperature ca 125°C (see p. 33), the reaction was not re-attempted using a higher-boiling solvent. The lack of reactivity of butadiene sulphone (compared to DMAD and maleic anhydride) with the electron-rich diene (212) appears to result from the relative electron-richness of this dienophile.

2. Preparation and diene reactivity of trans-8-thiabicyclo[4.3.0]-nona-2,4-diene 8,8-dioxide (235)

The preparation of the trans-fused bicyclic system (235) was required to permit a comparison of thermal fragmentation and Diels-Alder reactivity to be made with the cis-fused isomer (212). As has been described previously (p. 84), the trans-fused isomer was realised by irradiation at 254 nm of a concentrated solution of the cis-fused isomer (212) in ether. However, the limitations of scale inherent in the available photochemical apparatus coupled with the inconvenience of separation of the two isomers - the irradiation could not be induced to go to completion - necessitated the preparation of (235) by an alternative route in order to furnish the diene in sufficient quantities and purity for these studies.

Synthesis of the trans-fused system (235) was attempted via the sequence of reactions outlined in Scheme 59, a route which parallels that by which the cis-fused isomer (212) was initially prepared (Scheme 30). Thus, reduction of trans-1,2-dihydrophthalic

acid (494) was effected by the use of lithium aluminium hydride in tetrahydrofuran giving the corresponding trans-diol (495) as a light



Scheme 59

yellow oil in 75% yield. Conversion of the trans-diol (495) to the ditosylate (227) in 52% yield was achieved by reaction with p-toluene sulphonyl chloride in pyridine solution at 0°C. Comparison of the ^{1}H and ^{13}C NMR spectra of the trans (227) and cis (222) ditosylate isomers indicated there to be close spectral similarities which reflect the close structural relationship between the two. This similarity is continued in the electron-impact mass spectra of the two ditosylate isomers, both being found to undergo extensive fragmentation during sample volatilisation with subsequently only comparatively low m/e fragment ions being detected. In addition, both isomers are found to decompose to black tars on exposure to atmosphere for several weeks. However, a sizeable difference in melting behaviour clearly distinguishes between the two isomers : the trans-ditosylate (227) melts at a substantially higher temperature [101-101.5°C] than the cis-ditosylate (222) [m.p. 68.5-70°C], presumably due to the

presence of stronger intermolecular forces between trans-ditosylate molecules within the crystal lattice.

Treatment of the trans-ditosylate (227) with anhydrous sodium sulphide in hexamethylphosphoramide for 23 hours at room temperature was successful in the preparation of the trans-fused cyclohexadiene-tetrahydrothiophene (228), albeit as a mixture containing 25% of the isomeric ring-opened product, benzyl methyl sulphide. This contrasts with the much poorer yield and purity of the corresponding cis-fused isomer (223) resulting from reaction of the cis-ditosylate (222) with sodium sulphide under similar conditions, as discussed earlier (p. 78).

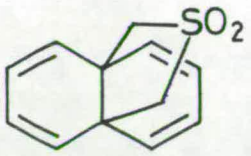
Due to the difficulties of separation of the trans-fused tetrahydrothiophene (228) from the benzyl methyl sulphide impurity, the unresolved mixture was oxidised by reaction with m-chloroperoxybenzoic acid in ether solution. The corresponding two sulphone products were separated by preparative TLC giving the desired trans-fused cyclohexadiene-sulpholane (235) in 27% yield from starting ditosylate (227). This product was fully characterised by standard means, and comparison of NMR spectral characteristics confirmed that it was identical to the product independently obtained upon irradiation of the cis-fused system (212) (p. 84), thus clearly establishing the isomeric cis/ trans-fused nature of these two isomers. Significant differences in the ^{1}H and ^{13}C NMR spectra of the trans-fused (235) and cis-fused (212) isomers are apparent, although the electron-impact mass spectra, being relatively insensitive to slightly structural changes in isomeric systems, are very similar. In common with the precedent of the trans-fused (418; X = O) [m.p. 125-126°C] and cis-fused (416; X = O) [m.p. 78-78.5°C] dihydrooxepin-sulpholanes, the trans-fused isomer (235) [m.p. 129-132°C] melts at a higher temperature

and is less polar (as measured by a higher R_f value on TLC (silica; ether) analysis) than the cis-fused isomer (212) [m.p. 35-36.5°C]. These two examples may reflect a general trend in the melting point and polarity characteristics of cis- and trans-fused cyclodiene-sulpholane systems, though many more examples would be required to fully establish this claim.

Having established an accessible route to the trans-fused system (235), a limited study of the reactivity of the electron-rich diene moiety was undertaken. Irradiation of a dilute solution of (235) in ether at 254 nm (previously described, p. 86) failed to produce isomerisation to the cis-fused isomer (212), in contrast to the observed isomerisation of (212) to (235) under identical photolysis conditions; only a slow polymerisation process was observed.

An attempted Diels-Alder reaction of diene (235) with maleic anhydride was undertaken by heating of the two in boiling benzene for 45 hours. Following work-up, a high recovered yield of the two starting materials together with a minor amount of an unidentified polymeric solid was realised. No Diels-Alder adduct was detected.

The reasons for the lack of reactivity of the trans-fused diene (235) towards maleic anhydride, under conditions identical to those employed in the preparation of the adduct (493a) from the cis-fused diene (212), are not clear. In terms of electron availability, the cis-fused isomer (212) would be expected to be significantly less electron-rich than the corresponding trans-fused diene (235) as a consequence of the difference in strength of the through-space orbital interaction between the sulphone and diene groups in each of the isomers. A stabilisation of the diene moiety in the cis-fused system (212) would be expected due to overlap with the proximate sulphone group by analogy to the related system (496), found to possess a high



(496)

diene ionisation potential (π Ip = 8.7 eV [203]) compared to the reference hydrocarbon, cyclohexa-1,3-diene (π Ip = 8.25 eV [162]). In contrast, the constraints imposed by the trans-fused geometry in (235) prevent any significant through-space overlap of sulphone and diene orbitals, so that the diene group in (235) is electron-rich compared to the diene moiety of (212), and hence should participate more readily in Diels-Alder cycloadditions with electron-deficient dienophiles such as maleic anhydride. However, the opposite order of reactivity is found experimentally.

Consideration of steric hinderance factors does not explain these findings : the trans-fused diene (235) is expected to undergo reaction with maleic anhydride more quickly since both (equivalent) faces of the diene system are accessible to the dienophile in contrast to the situation involving the cis-fused diene (212) in which only one face of the diene (that not containing the cis-fused sulpholane ring) is accessible.

However, in terms of ring strain it is apparent that a trans-fused sulpholane adduct of (235) and maleic anhydride would be thermodynamically less stable than the corresponding cis-fused isomeric adduct (493a). Whether this factor alone is sufficient to completely prevent isolation of a Diels-Alder adduct of (235) and maleic anhydride remains questionable. In light of the failure to react with the electron-deficient dienophile, maleic anhydride, no further Diels-Alder reactions involving the electron-rich diene (235) were attempted.

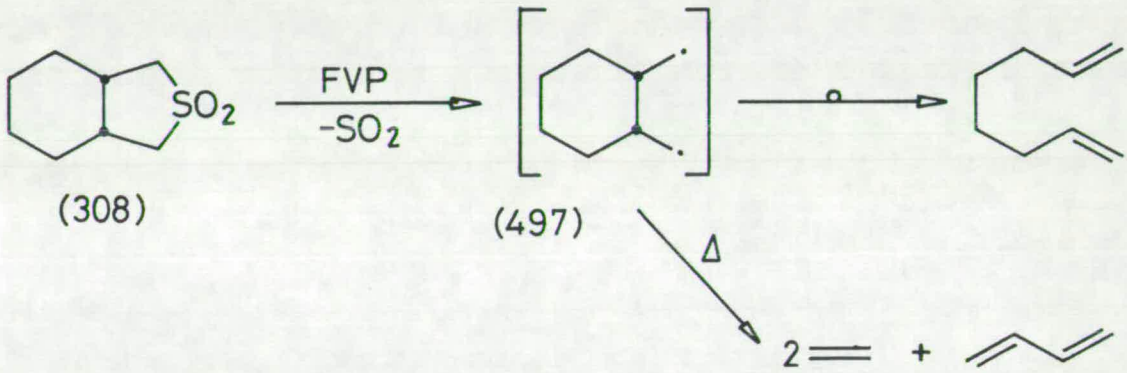
3. FVP of cis-8-thiabicyclo[4.3.0]nona-2,4-diene 8,8-dioxide (212) and hydro/dehydro derivatives

Following from the preparative work related in this and earlier sections, a number of related 8-thiabicyclo[4.3.0]nonapolyene 8,8-dioxide compounds were available for a comparative study of the effect of position and level of unsaturation upon the course of flash vacuum pyrolytic fragmentation. These compounds range from the fully saturated cyclohexane-sulpholane (308), through the three novel isomeric cyclohexadiene-sulpholanes (212), (235) and (230), to the benzo-fused sulpholene (110). The pyrolysis of the last compound has previously been studied[51], but is re-examined here under FVP conditions; the results of FVP of the cyclohexene-sulpholane (65), previously undertaken[33] by a colleague in these laboratories, is relevant to the pyrolysis behaviour of the series as a whole and is therefore included in the discussion.

FVP at 650°C of the first member of the series, the fully saturated bicycle (308), resulted in isolation of pure starting sulphone in high yield. The high thermal stability of this unstrained bicyclic system was evident upon analysis of the pyrolysate obtained at the considerably higher furnace temperature of 850°C : starting material (308) was recovered in 13% (unseparated) yield as shown by ^{1}H NMR spectroscopy. In combination with ^{1}H NMR spectroscopy, analysis by GLC and comparison with authentic samples allowed identification of the major volatile pyrolysate components as octa-1,7-diene (41% yield on consumed sulphone), benzene (2% yield) and buta-1,3-diene (not quantified). Two very minor components were not identified. On increasing the pyrolysis temperature to 925°C, the sulphone (308) was completely consumed with formation of a sizeable quantity of an unidentified polymeric solid, together with octa-1,7-

diene (20% yield), benzene (3%) and increased quantities (compared to the 850°C pyrolysate) of buta-1,3-diene and the two unidentified volatile products.

Mechanistically, the extreme conditions required to effect complete extrusion of sulphur dioxide from the saturated bicyclic system (308) points to the operation of a homolytic fragmentation process, possibly involving the intermediacy of diradical (497).



Rearrangement of this would be expected, particularly at the lower temperatures, to generate the observed major product, octa-1,7-diene. At the higher temperatures (ca 925°C) required for complete extrusion of sulphur dioxide, the diradical (497) may be expected to undergo competing thermal fragmentation processes to a greater extent, with formation of ethylene and buta-1,3-diene a likely major fragmentation pathway. This is in accord with the greater quantity of buta-1,3-diene detected and with the greater mass imbalance between starting sulphone and detected products (due to the formation of very volatile, hence undetected, products such as ethylene) found with increasing pyrolysis temperature. The decrease in yield of octa-1,7-diene at the higher pyrolysis temperature may reflect this more extensive fragmentation or diradical (497). Alternatively, this may be due to greater thermal fragmentation of octa-1,7-diene (to the other volatile products detected) or increased (radical-induced) polymerisation of

the diene in the FVP trap - in accord with the increased quantity of polymeric solid isolated.

FVP of the mono-unsaturated system (65) has previously been described[33] (see p.23). In common with (308), the cyclohexene analogue (65) was found to be very thermally stable, completely resisting fragmentation on FVP at 750°C. As shown in Scheme 10, FVP at 850°C resulted in partial fragmentation to give principally two aromatic species, benzene (33% yield) and toluene (29%); starting sulphone (65) was recovered in 11% yield and a considerable quantity of polymeric material was isolated[33]. A diradical intermediate (66), analogous to the intermediate (497) which is suspected to form during FVP of (308), appears likely although no evidence was reported for the presence of the ring-opened product, triene (67). Nonetheless, this compound may be present as an intermediate with the presence of increased unsaturation rendering the system more liable to thermal dehydrogenation/ rearrangement processes than the related octa-1,7-diene product obtained upon pyrolysis of (308) under identical conditions.

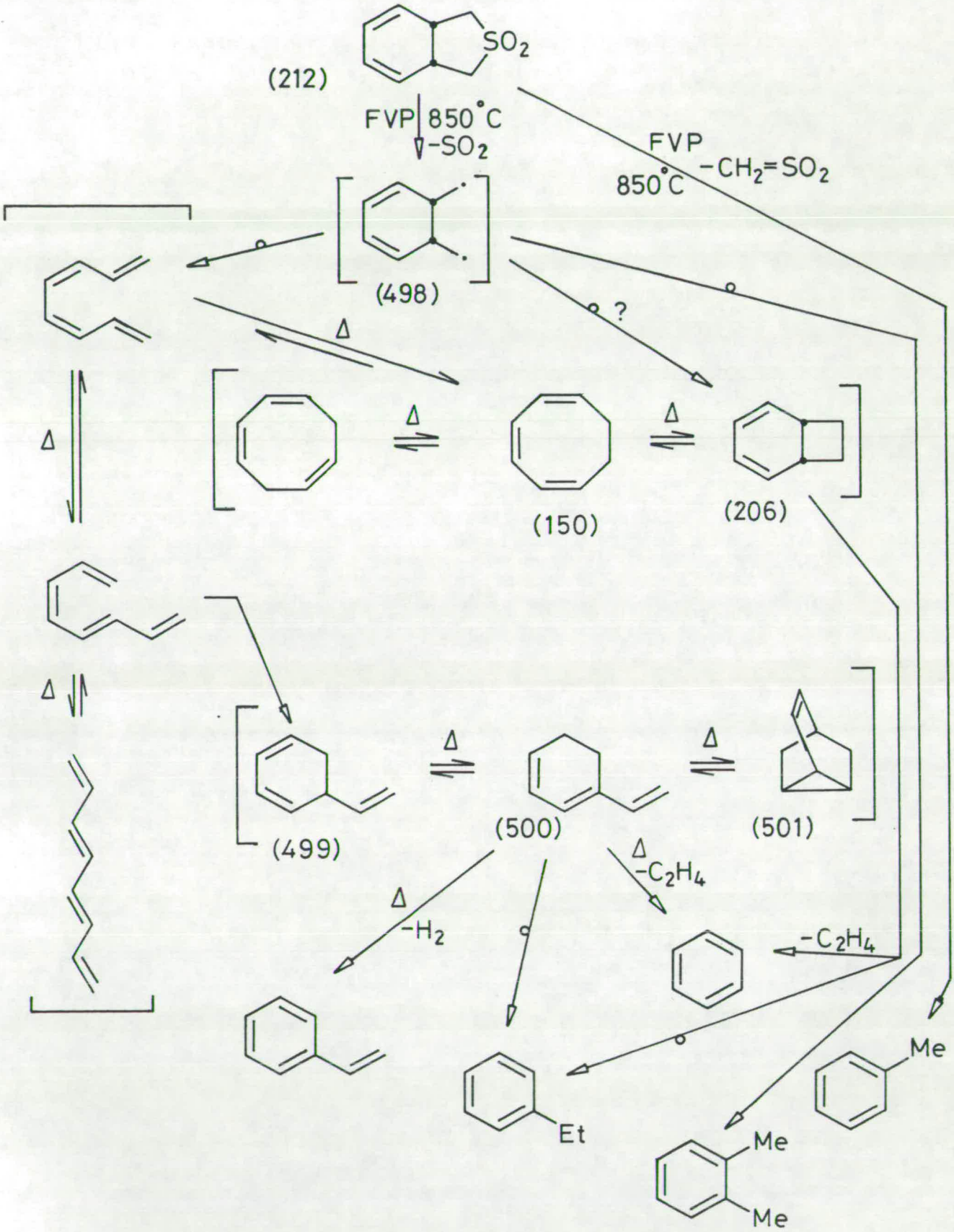
Turning to the three isomeric diene members of the 8-thia-bicyclo[4.3.0]nonapolyene 8,8-dioxide series, the results of the FVP of these at various temperatures are presented in Table 3. The first of these, the cis-fused diene (212) was quantitatively recovered following FVP at 625°C, and significant quantities of (212) were evident in the 850°C pyrolysate, emphasising the thermodynamic stability of this unstrained bicyclic system. A range of aromatic hydrocarbon products, comprising chiefly benzene, styrene and ethylbenzene, was identified and quantified by comparison of ^{1}H NMR and GLC analyses of the pyrolysate with those of standard solutions of authentic compounds.

Table 3 : Pyrolysis products [% yield] obtained on FVP of dienes (212), (235) and (230) at various temperatures

Diene / Temp.	(212)	(235)	(230)
625°C	(212) [100%]	-	-
650°C	-	C_8H_{10}((Z,Z,Z)-cyclo-octa-1,3,5-triene(150)/ bicyclo[4.2.0]octa-2,4-diene (206)?) [65%] o-xylene [14%] benzocyclobutene (112) [4%] styrene [2%]	-
850°C	(212) [15%] benzene [50%] toluene [3%] ethylbenzene [8%] o-xylene [5%] styrene [11%] 2 others [2%]	-	(230) [52%] benzene [0.5%] toluene [7%] ethylbenzene [1.5%] o-xylene [1.5%] styrene [21%] 2 others [4%]
950°C	-	-	(230) [2%] benzene [11%] toluene [35%] ethylbenzene [5%] o-xylene [0.5%] styrene [37%] 2 others [2%]

In consideration of the forcing conditions required to effect extrusion of sulphur dioxide from (212), it is probable that cleavage of the sulpholane ring occurs by a homolytic process. The intermediacy of diradical (498) is in accord with the intermediates suspected in the fragmentation of the related bicyclic structures (308) and (65), and a number of rearrangement/ fragmentation pathways may be proposed for conversion of (498) to the observed aromatic hydrocarbon products (Scheme 60). Thus, formation of the minor amounts of o-xylene present in the 850°C pyrolysate may be attributed to an intramolecular hydrogen abstraction process operating in diradical (498). However, the principal rearrangement pathway for (498) is likely to be that of ring cleavage to (Z,Z)-octatetraene, in consideration of the formation of octa-1,7-diene on FVP of the analogous saturated system (308) and in view of the conjugative stability of the tetraene system.

The cyclisation of (Z,Z)-octatetraene to (Z,Z,Z)-cycloocta-1,3,5-triene (150) has been reported by Ziegenbein[204] as occurring quickly, even at room temperature; related studies[205] on terminally substituted (Z,Z)-octatetraenes has established that the electrocyclisation of these systems occurs *via* a facile, thermally-allowed conrotatory process. Thus, the expected primary product of rearrangement of diradical (498), (Z,Z)-octatetraene, would undergo facile cyclisation under the pyrolysis conditions to (Z,Z,Z)-cycloocta-1,3,5-triene (150), a species known[206] to be in equilibrium with bicyclo[4.2.0]-octa-2,4-diene (206) and (Z,Z,Z)-cycloocta-1,3,6-triene at temperatures in excess of 225°C. The direct ring closure of diradical (498) would also allow entry into this three component equilibrium *via* initial formation of bicyclo[4.2.0]octa-2,4-diene (206). Fragmentation of the bicyclic diene would account for the formation of the observed products,


(212)
SO2
FVP 850°C
-SO2
FVP
850°C
-CH2=SO2
(498)
Δ
?
Δ
Δ
Δ
(150)
(206)
Δ
Δ
(499)
Δ
Δ
(500)
(501)
Δ
-C2H4
Δ
-H2
-C2H4
Et
Me
Me
Me

Scheme 60

ethylbenzene and benzene. Similarly, the styrene detected in the pyrolysate could be accounted for by dehydrogenation of diene (206) followed by the precedented[51] vacuum pyrolytic (770°C, 2 mm Hg of nitrogen) ring opening of the resultant benzocyclobutene (112) [see p.39]. However, as described later in this section, no fragmentation of *in situ* generated benzocyclobutene (112) occurs under true FVP conditions at 850°C, discounting this route as the source of styrene.

Formation of styrene, benzene and ethylbenzene may occur *via* an alternative rearrangement pathway open to (*Z*,*Z*)-octatetraene, that of thermal *cis*-*trans* isomerisation to (*E*,*Z*)-octatetraene, followed by precedented[206] cyclisation of the latter to the vinylcyclohexadiene (499). This compound is known[206] to exist in equilibrium with (500) and (501) at elevated temperatures, and double bond migration from either intermediate (499) or (500) under the forcing pyrolysis conditions would result in formation of ethylbenzene. Similarly, extrusion of ethylene from any of the three compounds in equilibrium would yield the principal pyrolysis product, benzene; the known[207] dehydrogenation of 1-vinylcyclohexa-1,3-diene (500) to give styrene on gas-phase pyrolysis (500°C, 20 mm Hg) furnishes a reasonable mechanism for the formation of this product on FVP of (212) at 850°C.

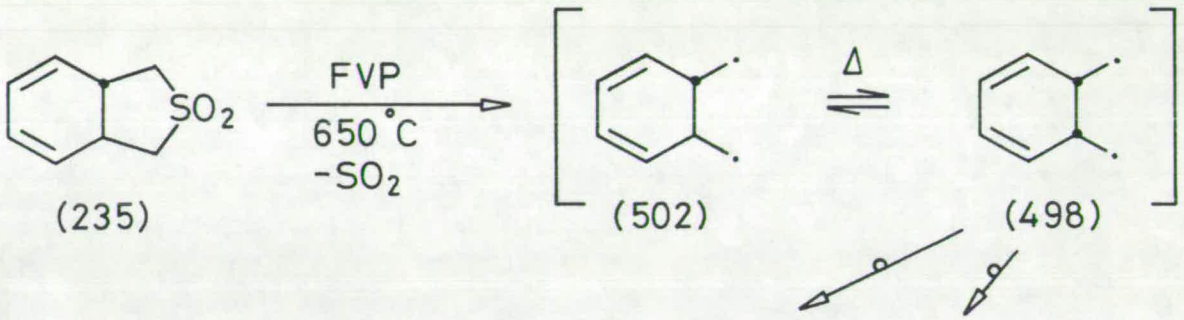
The only product arising from fragmentation of (212) which has not been mechanistically accounted for is toluene. By the nature of the FVP technique, toluene must be formed by a thermally-induced unimolecular fragmentation process and if it is formed *via* an intermediate itself obtained by extrusion of sulphur dioxide only from (212), the subsequent extrusion of the high energy species, methylene, from the intermediate would be required. This is very unlikely even under the harsh pyrolysis conditions employed, and the formation of toluene is more reasonably explained by direct thermal extrusion of sulphene from (212).

FVP of the second of the diene isomers, the trans-fused system (235) was carried out at 650°C. The resultant pyrolysate was devoid of starting material, and four volatile hydrocarbon products were present (Table 3). Comparison of the results of FVP of the cis-fused (212) and trans-fused (235) isomers clearly demonstrates that the greater strain present in the latter system encourages fragmentation of the sulpholane ring at lower temperatures; in fact, to match the consumption of the trans-fused bicyclic system (235) found on FVP at 650°C, the cis-fused isomer (212) would require a furnace temperature well in excess of 850°C. The greater ease of thermal fragmentation of the trans-fused cyclohexadiene-sulpholane system over the corresponding cis-fused isomer is in accord with the suspected thermal instability of the related trans-fused dihydrooxepin-sulpholane (418; X = O) over the cis-fused isomer (416; X = O), described earlier (p.240).

Comparison of ^{1}H NMR and GLC analytical data with those of authentic materials allowed identification of the three minor hydrocarbon components of the (235) pyrolysate as o-xylene, benzocyclobutene (112) and styrene. GC-MS analysis of the pyrolysate confirmed these assignments and established that the major product, formed in 65% yield, was a C_8H_{10} hydrocarbon. Although not confirmed, this major product was suspected to be an 85:15 equilibrium mixture of (Z,Z,Z)-cycloocta-1,3,5-triene (150) and bicyclo[4.2.0]octa-2,4-diene (206) on the basis of the distribution of olefinic and saturated resonances in the ^{1}H NMR spectrum of the pyrolysate. Cope et al have described[208] the formation of an 85:15 mixture of (150) : (206) on heating of pure (Z,Z,Z)-cycloocta-1,3,5-triene (150) to 80-100°C followed by cooling to room temperature. Although the proton spectrum of this mixture has not been reported (frustrating direct comparison with the spectrum of the pyrolysate derived from (235)), circumstantial

evidence exists for the formation of these hydrocarbons on pyrolysis of (235), as discussed below.

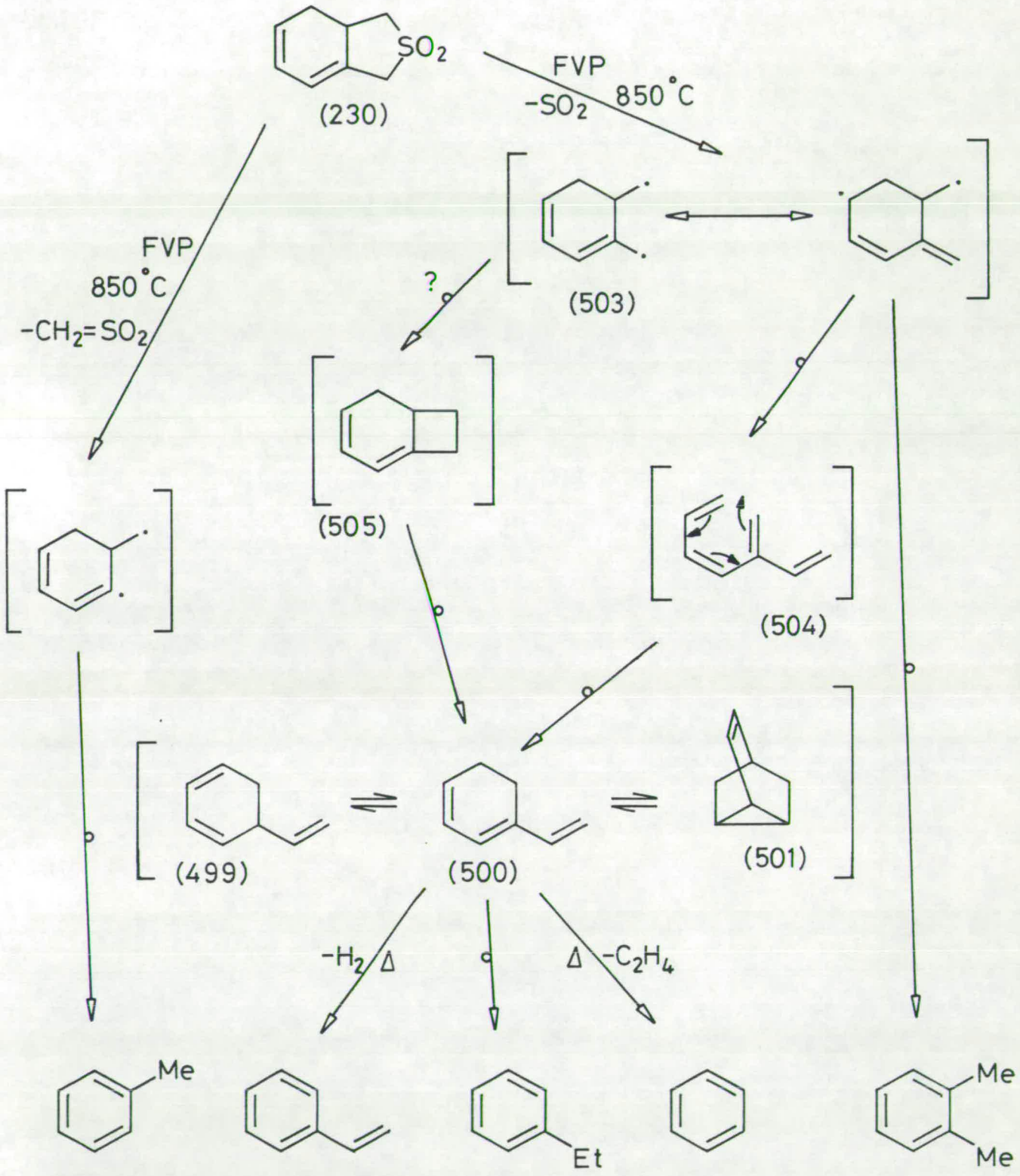
The formation of o-xylene and styrene on pyrolysis of both (212) and (235), coupled with the close structural relationship between the two isomeric sulphones, points to a parallel mechanism for thermal fragmentation of the two. Thus, homolytic fragmentation of the strained trans-fused sulpholane ring of (235) may generate the diradical intermediate (502), the counterpart of (498), the intermediate proposed in the fragmentation of (212). Under the pyrolysis conditions,



the isomeric diradicals may be in equilibrium, with rearrangements from (498) largely accounting for the observed products. Due to the comparatively mild FVP conditions used to effect fragmentation of (235), extensive secondary rearrangement/ fragmentation processes operating on (498) and subsequent intermediates - which lead to the formation of benzene and ethylbenzene in the pyrolysis of (212) at 850°C - are suppressed. Thus, the primary rearrangement of (498) [and (502)] to o-xylene is enhanced, and the (suspected) major products (Z,Z,Z)-cycloocta-1,3,5-triene (150) and bicyclo[4.2.0]octa-2,4-diene (206), formed by the rearrangements of (498) outlined in Scheme 60, are isolated rather than subjected to further rearrangement/ fragmentation processes. The formation of minor quantities of benzocyclobutene (112)

from (235) is supporting evidence for the intermediacy/ isolation of (150) and (206) since it may reasonably form by dehydrogenation of the latter under the pyrolysis conditions. Formation of styrene may be explained by the rearrangement of diradical (498) to the vinylcyclohexadienes (499) and (500), followed by dehydrogenation of either of these, as shown in Scheme 60; however, comparison of the reported ^1H NMR spectra of (499)[209] and (500)[206] with that of the pyrolysate of (235) indicated that neither of these compounds was isolated. The results of pyrolysis of the remaining diene, possessing structure (230), are shown in Table 3. This compound was found to be the most thermally stable of the three dienes whose pyrolysis was undertaken : over half (52%) of the sulphone (230) was recovered unchanged on FVP at 850°C, 17% was recovered on FVP at 900°C (not detailed in Table 3), and a small amount (2%) survived FVP at the extreme temperature of 950°C. The greater thermal stability of diene (230) is likely to result from the presence of less ring strain in the system, as a consequence of location of one of the olefin groups at a ring-fusion junction, compared to the isomeric dienes (212) and (235).

In light of the extreme conditions required to effect fragmentation of (230), the principal mechanism for this is likely to involve homolytic cleavage of the sulpholane ring (in accord with the proposed fragmentation mechanisms of the related dienes (212) and (235)) with formation of the delocalised diradical intermediate (503). In contrast to the counterpart diradicals (498) and (502), this intermediate may rearrange *via* the highly conjugated hydrocarbon (504) to form the main isolated product, styrene, together with minor quantities of benzene and ethylbenzene, by the processes outlined in Scheme 61. Formation of all these products may also occur *via* ring closure of (503) to (505) followed by rearrangement of the latter.


SO2
(230)
FVP
850°C
-SO2
FVP
850°C
-CH2=SO2
?
(503)
(505)
(504)
(499)
(500)
(501)
-H2 Δ
Δ -C2H4
Me
Et
Me
Me

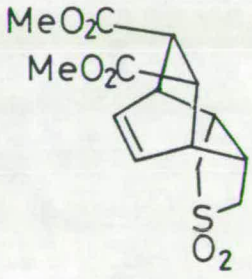
Scheme 61

A minor competing rearrangement of diradical (503) accounts for the formation of o-xylene. An alternative fragmentation pathway open to sulphone (230) involves thermal extrusion of sulphene and accounts for the isolation of toluene. In accord with the high-energy requirement of this extrusion process, it assumes greater importance with increasing pyrolysis temperature as evidenced by the enhanced yield of toluene at 950°C compared with that formed at 850°C.

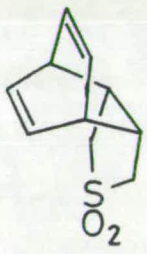
FVP of the final member of the 8-thiabicyclo[4.3.0]nonapolyene 8,8-dioxide series, the benzo-fused system (110), was undertaken. As described earlier (p. 39), (110) has been found[51] to extrude sulphur dioxide on vacuum pyrolysis at 770°C, 2 mm Hg to give benzocyclobutene (112) and a small quantity of styrene; on FVP at 500°C, 10^{-3} mm Hg, dideuterated derivatives of (110) gave $>95\%$ yield of the corresponding dideuteriobenzocyclobutenes[52]. However, in these laboratories FVP of (110) at 500°C, 6×10^{-3} mm Hg resulted in incomplete extrusion of sulphur dioxide giving a mixture of starting sulphone (25% recovered) and benzocyclobutene (112) (quantitative yield on consumed sulphone); following FVP at 850°C, 5×10^{-3} mm Hg only benzocyclobutene (112) (92% yield) was obtained. In contrast to the other members of the bicyclic series considered in this section, extrusion of sulphur dioxide from (110) occurs at moderate pyrolysis temperatures, in accord with a concerted extrusion pathway [via o-xylylene (111)[52]] only for fragmentation of this system.

H. Preparation, Olefin Reactivity and FVP of 4-Thiatricyclo-[5.2.2.$0^{2,6}$]undec-8-ene/undeca-8,10-diene 4,4-dioxide Systems

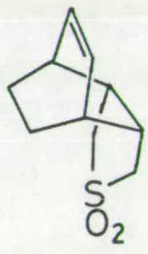
This section describes the preparation of the three unsaturated sulpholane compounds (506), (507) and (508) which share a common basic tricyclic structure. As for the related diene (492a), all of these novel bridged structures can be realised directly or indirectly from the Diels-Alder adducts of diene (212) and an appropriate dienophile. A limited study (especially in the cases of compounds (507) and (508)) of olefin reactivity of these four related bridged structures was undertaken with the aim of chemically detecting the presence or absence of through-space interactions between the sulphone and olefin groups. In addition, the novel sulpholane products arising from these studies were of interest with respect to their thermal fragmentation behaviour under FVP conditions.



(506)



(507)



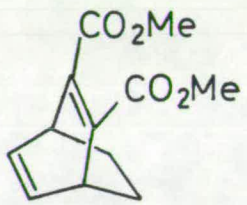
(508)

1. Olefin reactivity of dimethyl exo-4-thiatricyclo[5.2.2.$0^{2,6}$]-undeca-8,10-diene-8,9-dicarboxylate 4,4-dioxide (492a)

The title compound (492a) was prepared by the reaction of diene (212) and DMAD, as described in the preceeding section (p.315). Of the four unsaturated bridged systems considered in this section, the diene-diester (492a) is the most complicated in terms of through-space interactions between spacially proximate groups. This structure

possesses two pairs of through-space interactions to the unsubstituted (endo) olefin group : one between this olefin and the spacially-proximate diester-substituted (hence relatively electron-deficient) olefin, and the other to the spacially-close sulphone group. The through-space interactions are complimented by attendant through-bond (inductive) interactions between the three groups, thus creating a complicated multi-interactional system.

A simpler related system, dimethylbicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate (509), has been described[210] in the chemical



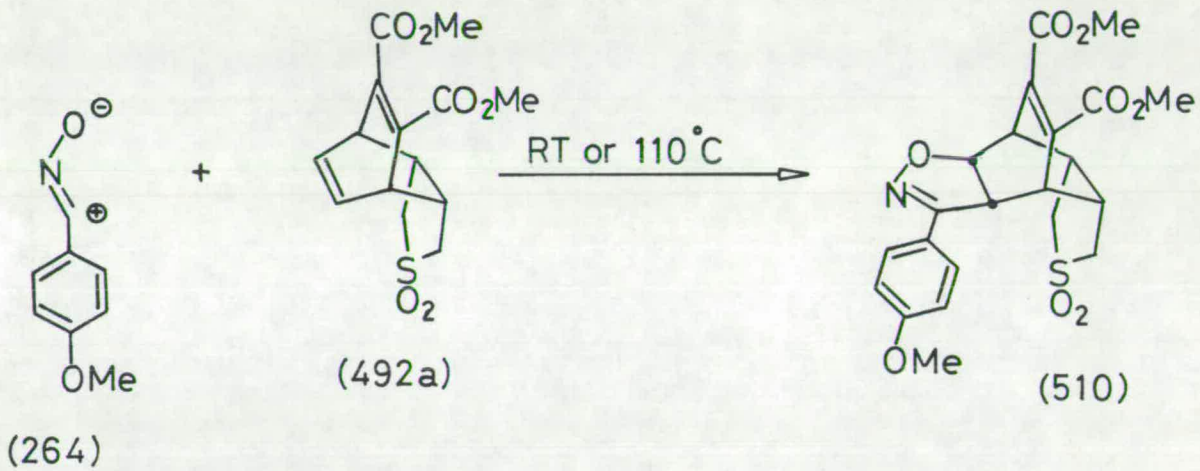
(509)

literature and some parallels may be drawn between the reactions of this compound and those undergone by the sulphone system (492a), which are now described.

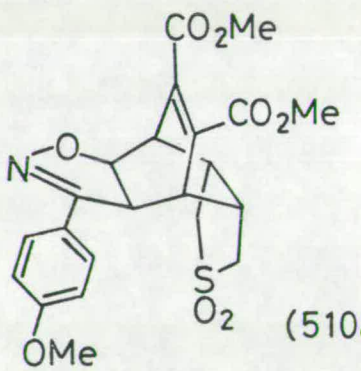
a. With 1,3-dipoles

The reactions of (492a) with p-anisonitrile oxide (264) and with diazomethane (266) were investigated. Treatment of a solution of the diene (492a) in benzene with three molar equivalents of p-anisonitrile oxide (264) [generated in situ by base-induced dehydrochlorination of p-anisohydroxamic chloride (269)] at room temperature resulted in isolation of a crystalline product, m.p. (decomp.) 275.5-277°C, established as a monoadduct (56% yield) of the 1,3-dipole (264) and sulpholane (492a) following examination of elemental composition and mass spectral data. This compound was found to be identical to that realised in 21% yield on thermal

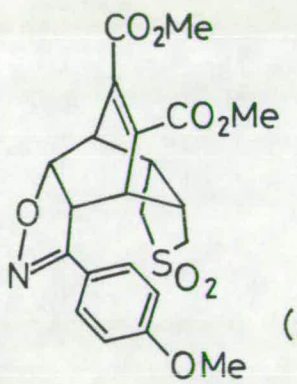
generation of p-anisonitrile oxide (264) in a solution of (492a) in boiling toluene. Although four alternative monoadducts may be visualised from the reaction of (264) and (492a), consultation of the ^{1}H and ^{13}C NMR spectra indicated that no olefinic methine group was present which therefore limited the structure of the single compound formed to either (510a) or (510b).



(264) (492a) (510)



(510a)

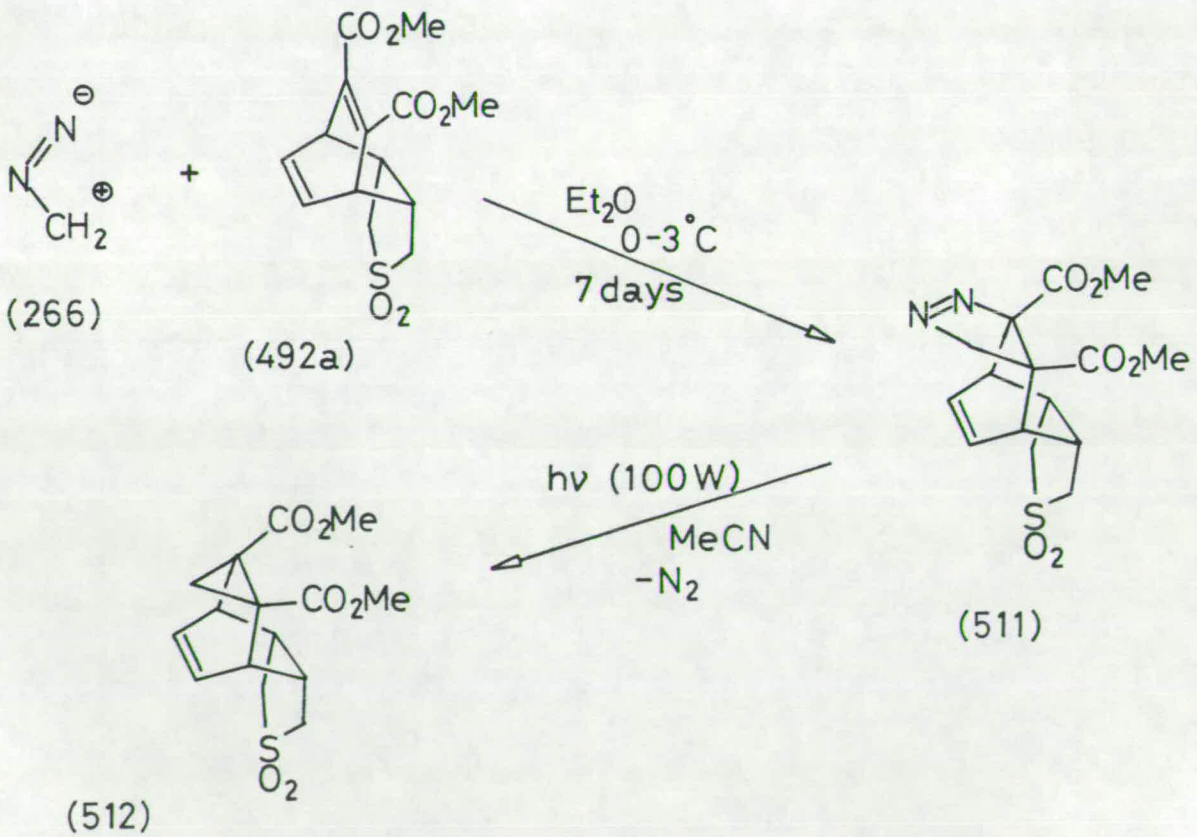


(510b)

Reaction of (264) with the unsubstituted olefin group in (492a) might reasonably be expected to result in formation of structure (510a) since, in the absence of any overriding steric factors, the transition state leading to formation of (510a) would benefit from a stabilising secondary orbital interaction with the spacially close disubstituted olefin group, an interaction which is not available in the transition state leading to formation of the alternative structure

(510b). Although this reasoning is not conclusive, the formation of a sole adduct from the reaction does indicate that a substantial directing influence - such as a secondary orbital interaction within the transition state - is in operation.

Reaction of the diene (492a) with diazomethane (266) was next attempted. Treatment of (492a) with a large excess of ethereal diazomethane (266) solution at 0-3°C resulted in slow formation of a high-yielding product as insoluble colourless flakes, m.p. (decomp.) 216-219°C. Again, elemental composition and mass spectral determinations of this were in accord with a monoadduct of the two reactants; in contradistinction to the previously related reaction of diene (492a) with p-anisonitrile oxide (264), examination of the ^{1}H and ^{13}C NMR spectra revealed that in the single diazomethane adduct formed, the 1,3-dipole had cyclised with the disubstituted olefin moiety as shown by the retention of the olefinic methine group in the product. Two



alternative structures for this adduct are feasible, though secondary orbital stabilisation factors in the reaction transition states would favour the formation of structure (511) over the alternative isomer. In order to ascertain if this suspected stereochemistry was actually present in the product, photochemical extrusion of nitrogen was attempted in the hope of preparing a symmetric cyclopropyl derivative, expected to be more amenable to ^1H NMR structural determinations than the precursor diazomethane adduct.

Irradiation (100W) through quartz of a solution of the diazomethane adduct in acetonitrile for five days resulted in complete consumption of starting material. A single crystalline product was isolated which was fully characterised as the expected cyclopropyl derivative of the starting diazomethane adduct; in particular, the ^1H NMR spectrum (Figure 39) was helpful in this assignment as it demonstrated the anticipated 'AB' pattern at high field characteristic of the cyclopropyl protons, H_{9a} and H_{9b}.

Further structural information was obtained by a combination of ^1H selective decoupling and NOE enhancement NMR studies. Thus, irradiation of the doublet of doublet (two proton) signal at δ 2.50 resulted in removal of a 12.5 Hz (geminal) coupling to the doublet of doublet signal at δ3.11, and also removal of a 10.5 Hz (cis-vicinal) coupling to the multiplet ca δ3.4. It is therefore apparent that each of these signals represents one of the two methylene proton pairs, H_{3a},H_{5a} and H_{3b},H_{5b} ; coupling of the methylene proton signal at δ2.50 to the multiplet at δ3.4 enables the latter to be assigned to the sulpholane ring-fusion protons H_2,H_6 , with the broad singlet at δ3.25 assigned to the bridgehead protons H_1,H_7 by default.

Completion and verification of the proton assignments, and consequently of the stereochemistry of the cyclopropyl product as a

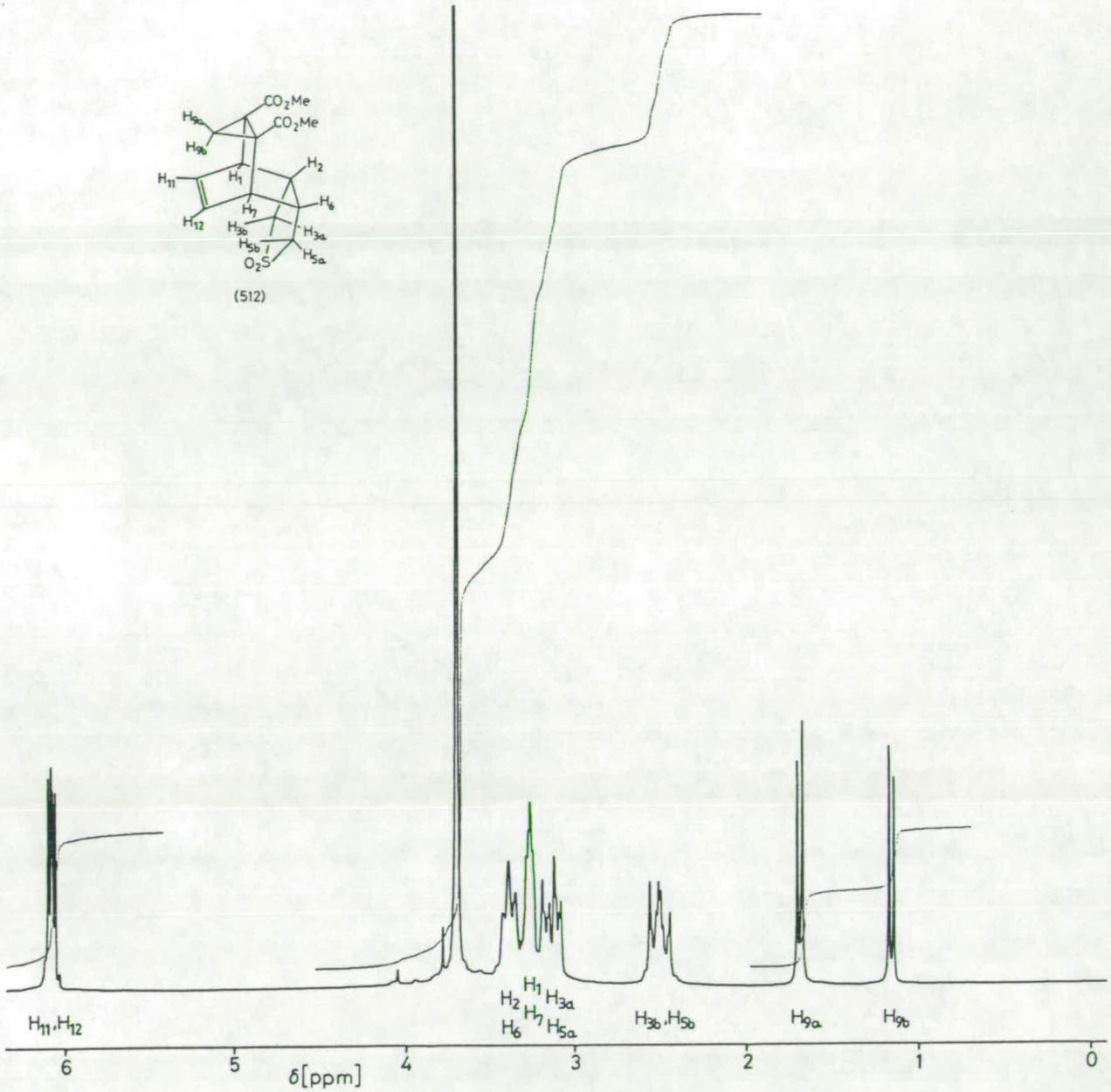


Figure 39 : ^{1}H NMR spectrum (200 MHz) of (512)

whole, was afforded following ^{1}H NOE enhancement studies. Thus, irradiation of the signal at δ1.15 resulted in a large enhancement (23%) in the signal at δ1.68 as expected for such geminally-disposed cyclopropyl protons. Additionally, an enhancement (3%) in the olefinic proton signal at δ6.07 was observed. In order to achieve the indicated close spacial arrangement between the olefinic protons and the cyclopropyl proton at δ1.15, it follows that the cyclopropyl ring must be disposed towards the cycloolefin portion of the system and that the product must therefore possess structure (512).

Confirmation of this stereochemical assignment was achieved following the reciprocal enhancement (3%) in the signal for cyclopropyl proton H_{9b} (δ1.15) upon irradiation of the olefinic protons H_{11},H_{12}. Enhancements of the signals due to bridgehead protons H_1,H_7 at δ3.25 (7%) and the methylene protons at δ2.50 (1.5%) were also observed, allowing assignment of the latter to protons H_{3b},H_{5b} (and therefore the signal at δ3.11 to protons H_{3a},H_{5a}) and verifying the geometry of the system (512) in which the sulpholane ring is <u>endo</u> to the cycloolefin moiety. Following the complete assignment of signals to protons for (512), the shielded position (by <u>ca</u> 0.6δ) of the methylene protons H_{3b},H_{5b} compared to their geminal partners H_{3a},H_{5a} (found within the typical sulpholane-methylene chemical shift range) appears peculiar; this is explained by the protrusion of H_{3b},H_{5b} into the shielding region[157] associated with the olefin group.

The unambiguous determination of the stereochemistry of (512) has a bearing on the assignment of stereochemistries to the precursor diazomethane adduct and diene systems. Since the reaction sequence leading from the diene (212)-DMAD adduct to (512) involves two transformations precluding any change in basic ring geometry, the known stereochemistry of (512) leads to assignment of structure (511)

to the diazomethane adduct (as expected in consideration of secondary orbital factors in the possible reaction transition states) and of exo-stereochemistry (492a) to the diene (212)-DMAD adduct (described earlier, p.315).

Having established the (partial) stereochemistries of the adducts obtained on reaction of the two 1,3-dipoles with the diene (492a), the alternate regiospecificities demonstrated in the two reactions requires rationalisation. The addition of p-anisonitrile oxide (264) solely to the unsubstituted double bond of (492a), and the contrasting addition of diazomethane (266) solely to the diester-substituted olefin group of (492a) cannot be adequately explained by invocation of steric factors. However, consideration of the relevant frontier molecular orbital interactions involved in each reaction does account for the observed regiospecificities.

An orbital correlation diagram incorporating approximate highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbital energies for the two dipoles and for the two localised olefin groups (considered for reasons of simplification not to interact through-bond or through-space with one another), constructed as described by Houk et al[129,132], is displayed in Figure 40. The HOMO and LUMO energy values for the electron-deficient diester-substituted olefin group in (492a) have been assigned lower values than those of the comparatively electron-rich unsubstituted olefin group[133]. As described earlier (p.107), the HOMO-LUMO interaction between the dipole and either of the two available olefin groups which possesses the smallest orbital energy difference (ΔE) will be the dominant frontier orbital interaction; the smaller the value of ΔE, then the faster will be the rate of reaction between the dipole and the relevant olefin group.

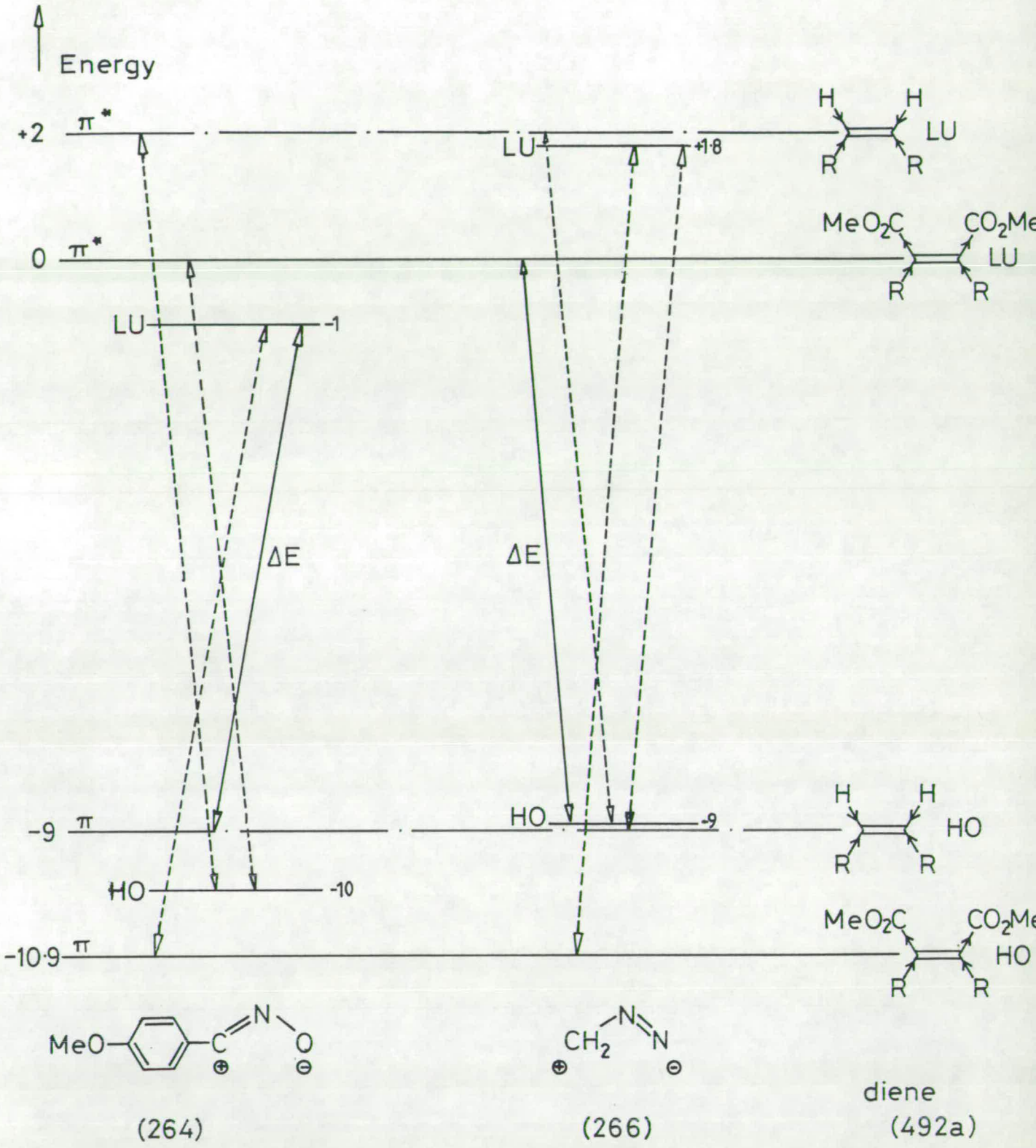


Figure 40 : Orbital correlation diagram for the reaction of diene (492a) with 1,3-dipoles (264) and (266)

For the reaction of (492a) and p-anisonitrile oxide (264), the orbital correlation diagram (Figure 40) indicates that the smallest ΔE value (8 eV) exists between the LUMO of the dipole and the HOMO of the unsubstituted olefin group. This reaction is therefore under dipole LUMO control (Type III according to Sustmann terminology[129,133]) with p-anisonitrile oxide (264) predicted to add across the unsubstituted cycloolefin group of (492a). The smallest ΔE (9.9 eV) for interaction of the dipole (264) with the diester-substituted cycloolefin moiety of (492a) is sufficiently larger than 8 eV to disfavour this addition completely, and therefore the prediction of regiospecific addition of (264) to the unsubstituted cycloolefin moiety of (492a) which may be derived from the orbital correlation diagram is in agreement with the experimental findings.

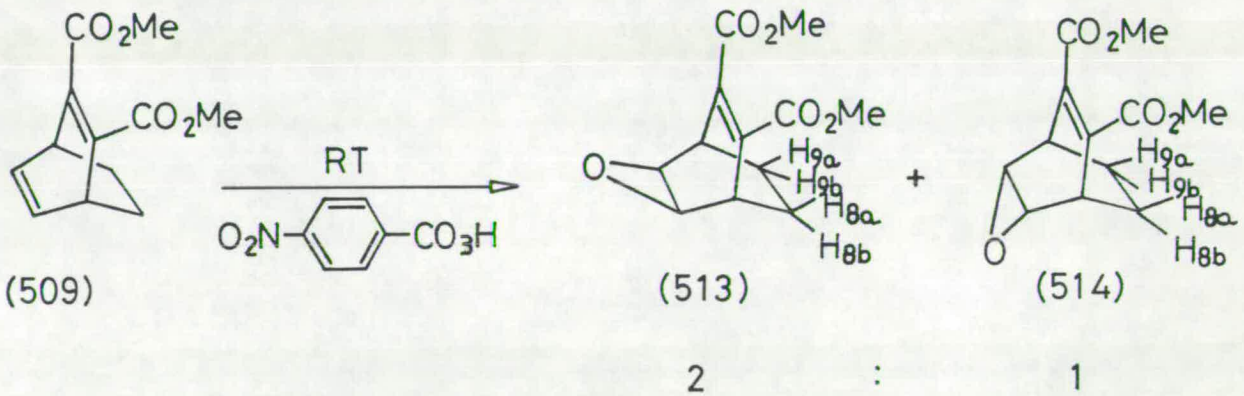
For the addition of diazomethane (266) to diene (492a), the dominant frontier molecular orbital interaction is shown by Figure 40 to exist between the diazomethane HOMO and the disubstituted olefin moiety of (492a) LUMO (Type I interaction[129,133]) for which $\Delta E = 9$ eV. As this ΔE value is considerably smaller than the smaller of the two orbital interaction difference energies between the unsubstituted cycloolefin group in (492a) and diazomethane, for which $\Delta E = 10.8$ eV, diazomethane (266) is predicted to add regiospecifically to the disubstituted double bond of (492a), as found in practice.

Thus, the application of frontier molecular orbital considerations to the reaction of diene (492a) with the two dipoles (264) and (266) allows explanation of the experimental findings. Although the simple orbital correlation diagram shown in Figure 40 neglects to take account of the presence of through-bond and through-space interactions between the two olefin groups and the sulphone group in system (492a), the effects of these in determining the

relative energies of the two pairs of olefin frontier orbitals is expected to be minimal in comparison to that of direct bonding of the strongly electronegative methoxycarbonyl groups to only one of the olefin moieties. Thus, the qualitative implications concerning reactivity of (492a) derived from the orbital correlation diagram are not affected by omission of these through-bond and through-space factors.

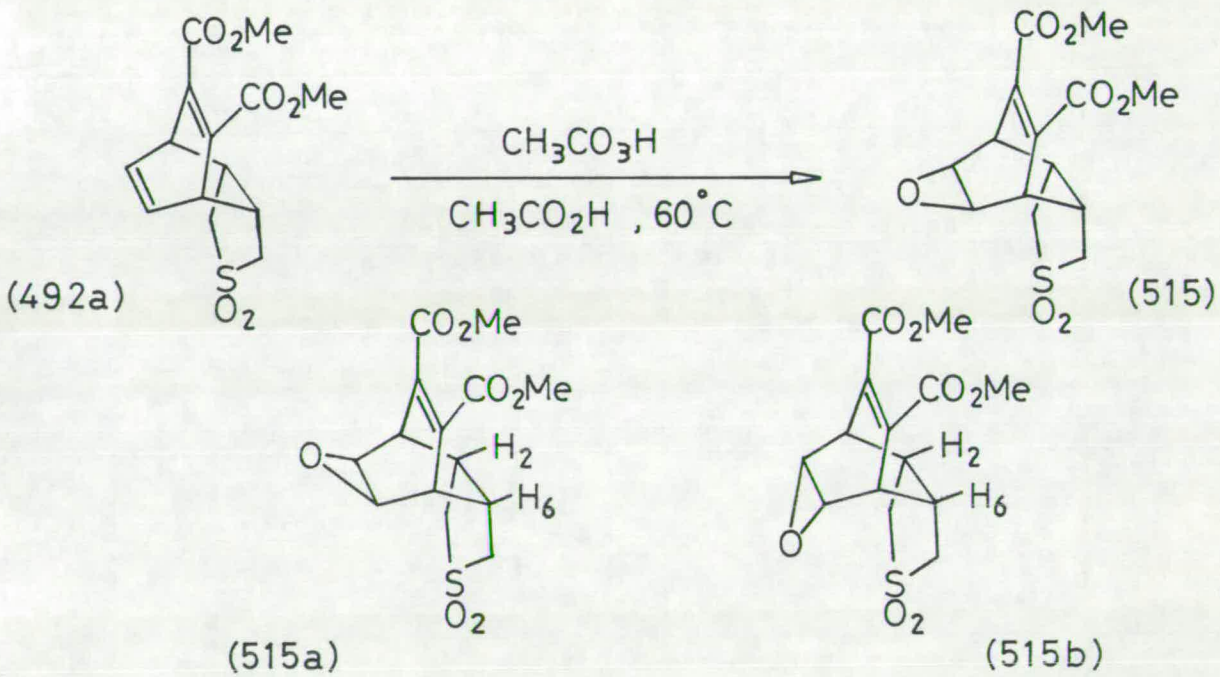
b. Epoxidation

The epoxidation of the related bicyclic system (509) has been reported by Plenat et al[210] who found that treatment of (509) with one molar equivalent of p-nitroperoxybenzoic acid at room temperature gave a quantitative yield of a ca 2:1 mixture of the isomeric epoxides (513) and (514). Treatment of (492a) with a large excess of peracetic

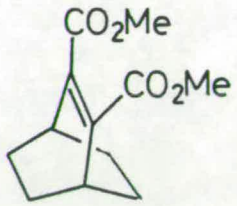


acid (generated in situ by reaction of hydrogen peroxide with acetic acid) in acetic acid at 60°C for 24 hours resulted in recovery of starting sulphone (492a) (30%) together with isolation of a comparatively methylene chloride-insoluble colourless solid product, m.p. 260-262°C. On the basis of elemental composition and mass spectral analyses this was determined to be a monoepoxide of (492a), formed in 51% yield from consumed starting sulphone. Examination of the ^{1}H and ^{13}C NMR

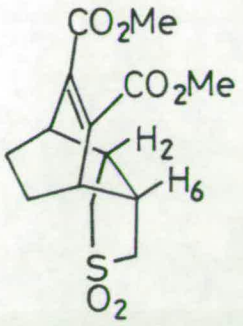
spectra indicated that the product was a single one of the four possible isomeric structures, and further that it resulted from epoxidation of the comparatively electron-rich, unsubstituted cycloolefin group of diene (492a), striking a parallel with the epoxidation of the analogous diene (509), previously described. Therefore, the two structures (515a) and (515b) remain as possibilities for the epoxidation product. However, final assignment of the epoxide to one of these could not be achieved by use of ^{1}H NMR spectroscopy, in contrast to the situation found for the related epoxide structures (513) and (514).



The exo epoxide (514) is known[210] to exhibit a signal in the ^{1}H NMR spectrum for protons H_{8a},H_{9a} which is shielded (by 0.5 δ), and a signal for protons H_{8b},H_{9b} which is deshielded (by 0.4 δ) relative to the chemical shifts of the signals due to the corresponding protons in the standard bridged system (516). No such effect is observed in the proton spectrum of the isomeric endo epoxide (513).



(516)



(517)

As this difference in the ^1H NMR spectra of the exo (514) and endo (513) epoxides reflects a general trend in the spectra of 6,7-disubstituted-3-oxatricyclo[3.2.2.$0^{2,4}$]nonane systems, assignment of exo or endo epoxide stereochemistry can generally be readily made to such systems on examination of proton spectra[210].

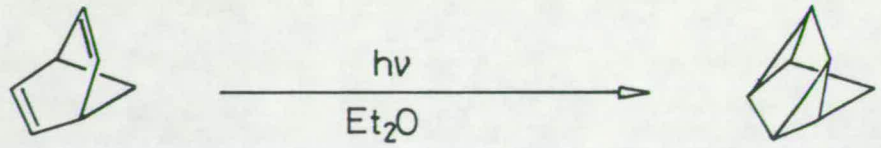
Extending these general observations to the more complex, related tetracyclic epoxides (515a) and (515b), it would be expected that in (515b), protons H_2,H_6 would resonate at a markedly shielded position in the proton spectrum relative to that of the corresponding H_2,H_6 protons in the standard tetracyclic system (517) [the synthesis of which is described later - see p.354]. In the case of epoxide (515a), the signal due to the H_2,H_6 protons would be observed at a comparable chemical shift value in the proton spectrum to that of the corresponding protons in (517). Thus, a ready assignment of structure (515a) or (515b) to the monoepoxide derived from diene (492a) should be feasible upon comparison of the proton spectra of this and the standard sulphone (517). Unfortunately, the ^1H NMR spectra of both sulphones could not be adequately resolved to permit identification and hence comparison of the H_2,H_6 resonances, frustrating a conceptually attractive means of stereochemical assignment of the epoxide product.

However, in consideration of the predominant formation (for steric reasons) of the endo (513) over the exo (514) epoxide on

treatment of diene (509) with the bulky oxidising agent, p-nitro-peroxybenzoic acid[210], it is reasonable to expect that the increased bias against formation of the 'exo' epoxide (515b) furnished by the disposition of the sulpholane ring in (492a) will result in sole formation of the 'endo' epoxide (515a), in spite of the use of a smaller oxidising agent (peracetic acid) in the latter case. Thus, consideration of steric factors does account for one half of the observed stereospecificity of the epoxidation of (492a); the lack of epoxidation of the disubstituted cycloolefin group of (492a) is likely to result from the electron-deficient nature of this double bond (compared to the unsubstituted cycloolefin group also present in the system) which completely discourages attack of the electrophilic oxidising species, peracetic acid, at this position. The absence of any diepoxide product in spite of the large (theoretical) excess of peracetic acid present is not surprising in view of the regiospecificity of the reaction and the fact that some of the starting diene (492a) was recovered at the termination of the reaction.

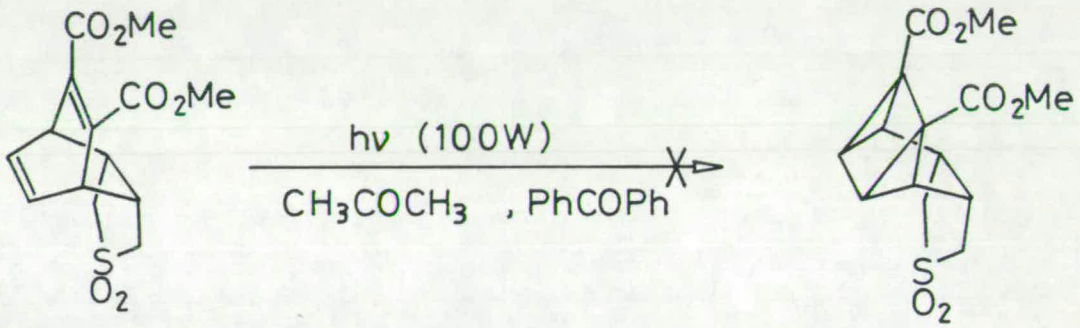
c. Photochemical reactivity

It was noted that the diene (492a) possessed a similar structure to norbornadiene (518), a system which is known[211] to undergo a facile intramolecular [2 π + 2 π] photocyclisation to quadricyclene (519). The photolysis of diene (492a) was undertaken



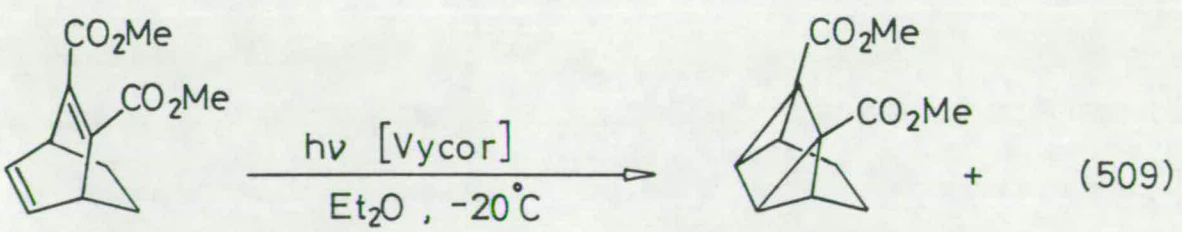
(518) (519)

in order to effect a parallel transformation to the novel prismane (520). Irradiation (100W) through quartz glassware of a very dilute solution of (492a) in acetone for 21 hours resulted only in quantitative recovery of the starting diene. Additional photolyses carried out using benzophenone as photosensitiser and acetone or chloroform as solvent gave, on irradiation as before for 32 hours, the starting diene (492a) in reduced quantity (ca 60% recovered); no products were observed.



(492a) (520)

The failure to obtain the photoproduct (520) from (492a) is not surprising in the subsequent light of the photochemical behaviour demonstrated by the analogous bicyclic system (509) under similar photolysis conditions. Prinzbach et al have described[212] the failure of (509) to photocyclise to the prismane (521) under sensitised irradiation conditions. Application of low temperature (-20°C) to the direct irradiation (through a Vycor filter) of a very dilute solution of (509) in ether was found to result in formation of a 2:3 mixture



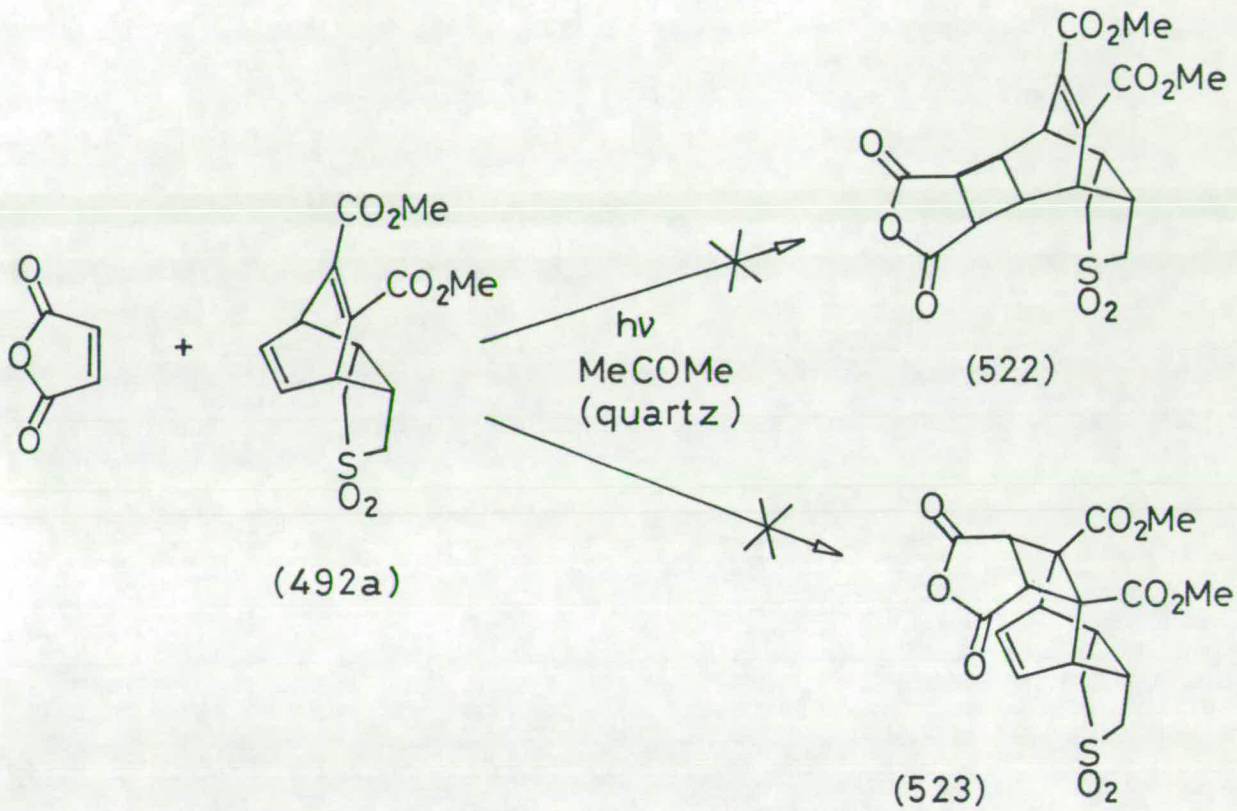
(509) (521)

2 : 3

of the prismane (521) and starting diene (509). In contrast to quadricyclene (519), the prismane (521) was found[212] to undergo facile (symmetry-forbidden) thermal cycloreversion ($t_{\frac{1}{2}}$ = 12 minutes at 19°C) with regeneration of the starting diene. In consideration of the similar structures of (509) and (492a), the failure to isolate the photocyclised product (520) under the photolysis conditions employed with (492a) is understandable, since the product (520) may well undergo thermal cycloreversion to the starting diene more quickly than it can be photochemically assembled. This expected thermal instability of (520), rather than the alternative reason of electron-deficiency of the unsubstituted cycloolefin group in (492a) effected by the suspected through-space interaction with the spacially proximate sulphone group, forms the most reasonable explanation for the observed lack of isolation of the desired photoproduct.

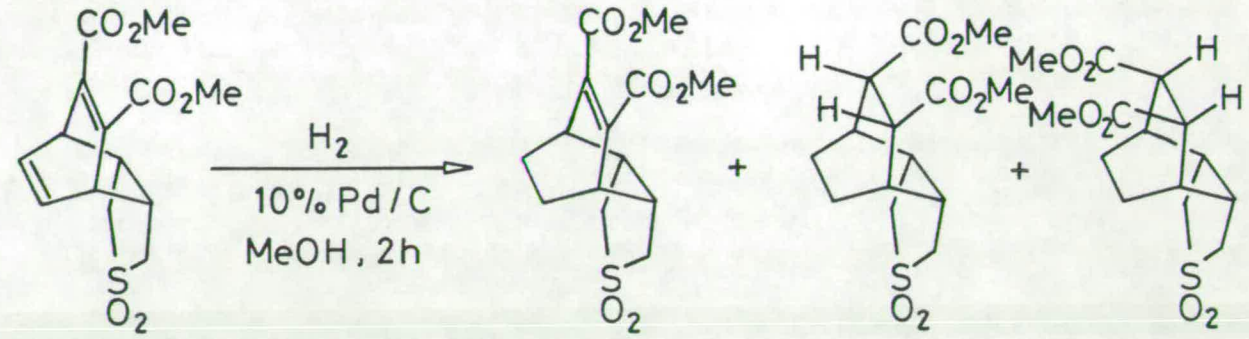
An intermolecular [2 π + 2 π] photocyclisation of (492a) and maleic anhydride with a view to preparation of the pentacyclic adducts (522) and/ or (523) [or isomers] was next attempted. Photolysis (100W) through quartz of a solution containing approximately equimolar quantities of (492a) and maleic anhydride in acetone was carried out for a period of 17 hours. Evaporation of the resultant diene (492a)-free solution gave a colourless solid, the infrared spectrum of which indicated the presence of anhydride and ester carbonyl absorptions, and also sulphone bands. Following the failure of this material to undergo vacuum sublimation, and after examination of ^{1}H and ^{13}C DEPT NMR spectra - found to be complex, and to contain negligible amounts of olefinic methine signals - the photoproduct was identified as a copolymer of (492a) and maleic anhydride. No evidence for the presence of discrete photoadducts such as (522) or (523) was observed; however,

these may have formed at some stage and thereafter been incorporated into the isolated polymeric product.



d. Hydrogenation

Catalytic hydrogenation (10% palladium-on-charcoal, one atmosphere pressure of hydrogen) of a methanolic solution of the diene (492a) was conducted for two hours, giving a three-component mixture of products in high yield. Analysis of this by ^{1}H and ^{13}C NMR spectroscopy indicated it not to contain starting diene (492a) or any product containing olefinic methine groups; it was found to be in accord with a mixture of a monohydrogenated product (ca 50%) and a 2:1 ratio of two bishydrogenated products (total ca 35%). The predominant (monohydrogenated) product was isolated following separation by MPLC and recrystallisation from methanol to give colourless flakes, m.p. 199-201°C, which were fully characterised as the α,β-unsaturated diester system (517) (29% yield). A repeat hydrogenation of (492a) under similar conditions but for an extended period (six hours) resulted



(492a) (517) (524) (525)

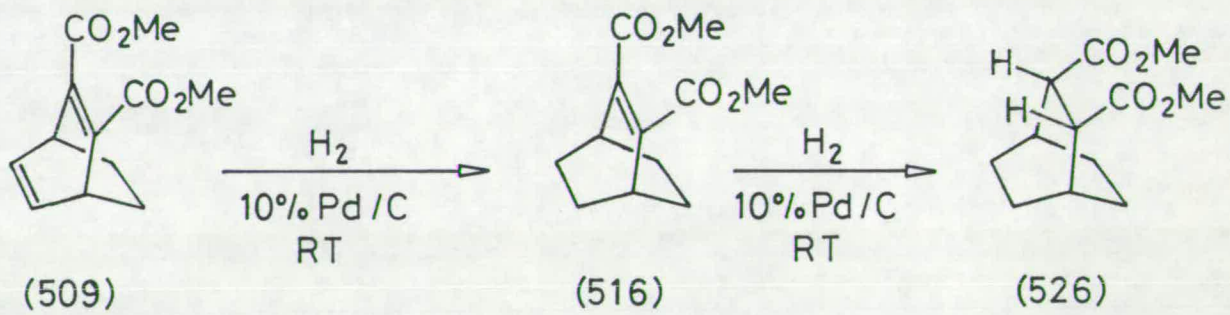
48% 24% 11%

in formation only of the two bishydrogenated isomers (89% yield) detected previously in a near identical 2:1 ratio. Although the two products could not be separated by means of column chromatography or preferential crystallisation, they were accorded structures (524) and (525) on the basis of their ^{1}H and ^{13}C DEPT NMR spectra. These indicated both isomers to possess saturated, two-fold-symmetric structures in accord with the two possible products resulting from cis-addition of hydrogen to the olefin group of the monohydrogenated system (517). The assignment of structure (525) to the minor isomer was made following the observed enhancement of the ^{13}C NMR signals for only the less abundant product upon addition of an authentic sample of (525) [the synthesis of which is described later - see p.362] to the mixture; the major isomer was therefore assigned structure (524) in view of its spectral similarities to (525) and the common formation of both from diene (492a).

In terms of the mechanism of hydrogenation of diene (492a), it would appear from the experimental findings that the principal pathway involves initial addition of hydrogen to the unsubstituted cycloolefin moiety to give the monohydrogenated product (517). A slower reduction of the disubstituted cycloolefin system of (517) -

in accord with general findings[146] on the ease of hydrogenation of substituted olefins with palladium catalysts - then occurs to give (524) and (525) as the final hydrogenated products. As expected for hydrogenation in a neutral medium using palladium-on-charcoal as catalyst[213], solely cis addition of hydrogen to the olefin (517) occurs to give both of the possible cis-diester products (524) and (525). The observed excess of the endo-cis-diester product (524) over the corresponding exo-cis-diester (525) is an indication of the greater accessibility of the face of olefin (517) not containing the fused sulpholane ring to the catalyst surface.

These findings mirror those reported[213] for the hydrogenation of the related bicyclic diene (509) using 10% palladium-on-charcoal and one atmosphere pressure of hydrogen : the monohydrogenated product (516) was initially formed, and continued hydrogenation under the same conditions effected transformation to the only possible cis-hydrogenated product (526) in greater than 98% selectivity.



(509) (516) (526)

2. Preparation and olefin reactivity of dimethyl exo-4-thiatricyclo[5.2.2.$0^{2,6}$]undec-10-ene-exo-cis-8,9-dicarboxylate 4,4-dioxide (506)

The title compound (506) was prepared by treatment of the anhydride (493a) with boiling acidified methanol. A high yield of the diester - obtained as colourless flakes, m.p. 182-183°C - was

realised and this product was fully characterised as (506) by standard analytical means. In accord with the geometry of diester (506), the proximity of sulphone and olefin groups is expected to result in a strong through-space interaction between the two. This interaction should render the olefin moiety appreciably electron-deficient compared to that of the standard system, bicyclo[2.2.2]oct-2-ene (πIp = 9.05 eV [214]). A provisional series of reactions was carried out on the olefin group of (506) and is now described. These reactions parallel the reactions carried out on the diene (492a) which have been described above; a comparison of the reactivity of the olefin group of (506) with that of the corresponding unsubstituted cycloolefin system of (492a) was considered of interest. However, a potential problem facing such a comparison results from the probable greater steric hinderance of the olefin system of (506) - due to the presence and disposition of the ester substituents - compared to the unsubstituted olefin group of diene (492a).

a. With 1,3-dipoles

Treatment of the diester (506) with an excess of p-anisonitrile oxide (264), generated in situ by the thermal elimination (boiling toluene) of hydrogen chloride from p-anisohydroxamic chloride (269), failed to produce any sulphone-containing products with the starting olefin being recovered in high yield. Similarly, no reaction was observed between the diester (506) and diazomethane (266) in methanol/ether solution on standing at 0-3°C for 30 days; starting sulphone (506) was recovered in 88% yield. A repeat reaction using a mixture of ether, ethanol and methylene chloride (otherwise identical to the above) gave similar results.

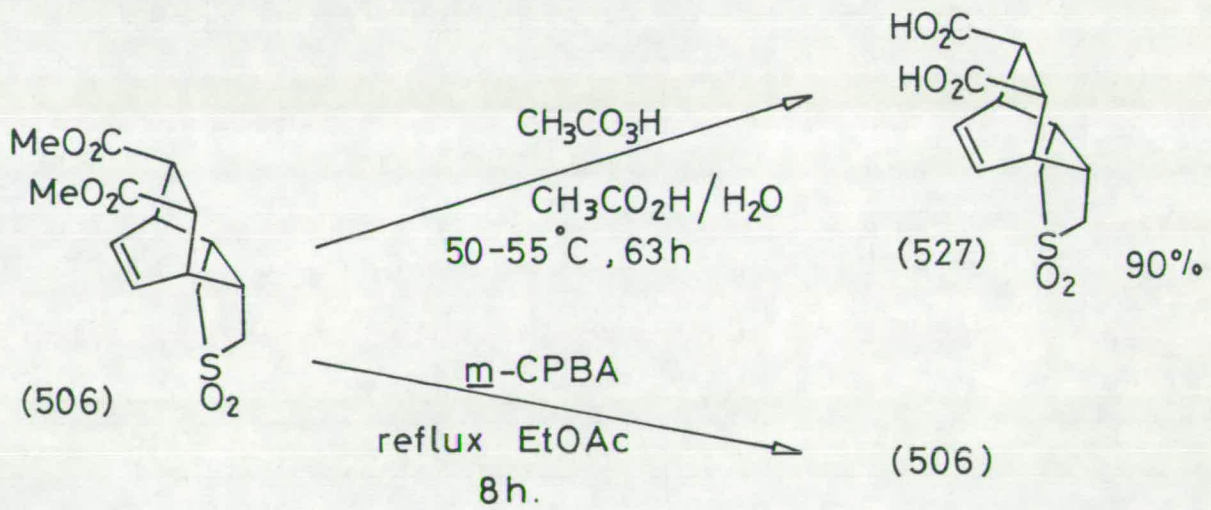
The lack of reaction with p-anisonitrile oxide (264) or diazomethane (266) is surprising in consideration of the π-electron availability of the olefin system of (506). For this compound, the olefin group should be no more electron-deficient than the unsubstituted cycloolefin equivalent in diene (492a) [both expected to be stabilised by through-space interaction with the proximate sulphone group] but should be much more electron-deficient than the olefin group of the transoid system (208). Yet while both (492a) and (208) readily undergo addition of p-anisonitrile oxide (264) by dipole LUMO controlled processes, under similar reaction conditions the diester (506) does not. Similarly, both the electron-deficient diester-substituted olefin group of (492a) and the electron-rich cyclobutene π-system of (208) react with diazomethane (266) via processes with sizeable dipole HOMO contributions. The olefin group of (506), expectedly of intermediate electron-availability compared to the reactive π-systems of (492a) and (208), should also undergo addition of diazomethane (266) by a dipole HOMO controlled process. As no electronic reason for the observed lack of reaction of (506) with the two dipoles (264) and (266) is apparent, it is reasonable to assume that the steric barrier imposed by the enveloping ester groups and the sulpholane ring on either face of the olefin π-system in (506) is sufficiently great to completely prevent reaction even with the smaller of the two dipoles, diazomethane (266).

b. Epoxidation

Treatment of the diester (506) with an excess of peracetic acid, generated in situ by reaction of aqueous hydrogen peroxide solution and acetic acid at 50-55°C, resulted in precipitation of a colourless solid product from the reaction solution, a process which

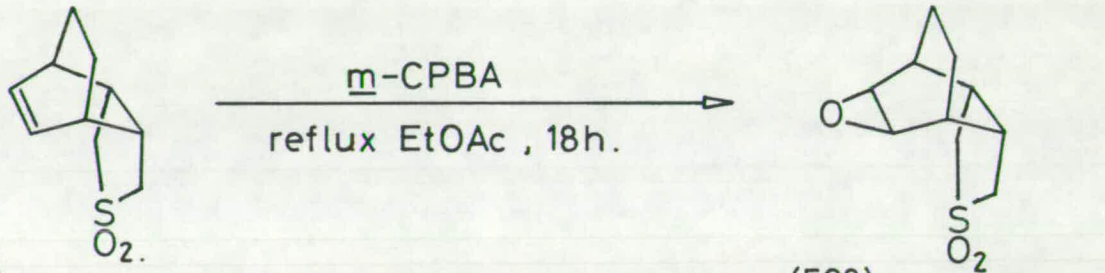
appeared complete after a reaction period of 63 hours. Detailed examination of this high-yielding product revealed that it was not an epoxide product, but rather that it was the cis-diacid derivative (527) of the starting diester (506), as shown by the identical spectral (^{1}H, ^{13}C NMR and IR) and melting point characteristics of this and an authentic sample of (527) [synthesis described later - see p.364]. No evidence was obtained for the formation of an epoxide product either of (506) or of (527); a repeat reaction furnished identical results.

It would appear that both (506) and (527) are stable to epoxidation using peracetic acid under the reaction conditions; the diacid (527) was presumably formed via an acid-catalysed ester hydrolysis process operating on (506), with the requisite water



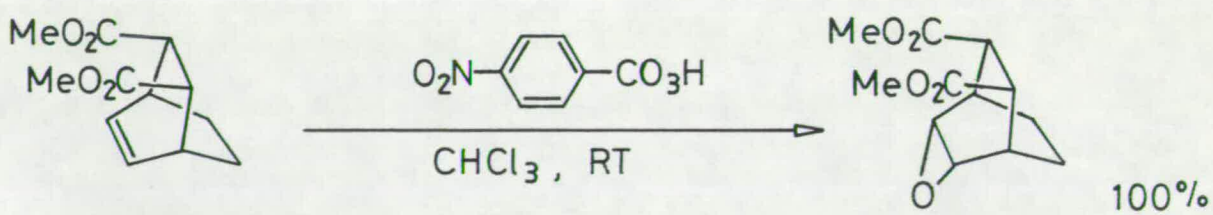
available from the aqueous solution of hydrogen peroxide used to generate the peracetic acid. In order to circumvent any complicating hydrolysis reactions, the epoxidation of (506) was next attempted by treatment with the powerful oxidising agent, m-chloroperoxybenzoic acid in boiling ethyl acetate for a period of eight hours. However, starting olefin (506) was quantitatively recovered.

The lack of epoxidation of (506) with strong oxidising agents is unlikely to be solely the result of electron-deficiency of the olefin group due to orbital overlap through-space with the sulphone group: epoxidation of the closely related tricyclic system (329) has been found[95] to proceed in 52% yield to generate a single product (528)



(329) (528) 52%

of undefined epoxide stereochemistry, using m-chloroperoxybenzoic acid and similar reaction conditions to those which failed to result in epoxidation of (506). Since (329) possesses an olefin group (πIp = 9.75 eV [95]) in receipt of a stabilising through-space interaction with the spacially close sulphone group of a similar magnitude to that expected to operate in the disubstituted analogue (506), the lack of epoxidation of the latter is liable to reflect the operation of steric hinderance rather than electronic factors. Further circumstantial evidence for this view is furnished by the formation of solely the exo-epoxide (530) upon treatment of the bicyclic



(529) (530) 100%

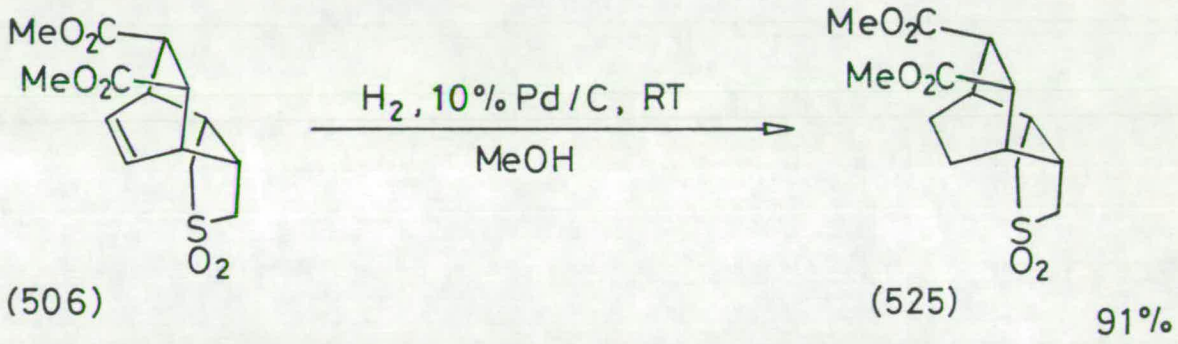
system (529) with p-nitroperoxybenzoic acid at room temperature[210]. Formation of the analogous epoxide with the oxirane ring exo to the diester-substituted bridge from (506) would be sterically inhibited by the presence of the sulpholane ring.

c. Photolysis with maleic anhydride

Irradiation (100W) through quartz of a solution of the olefin (506) and an excess of maleic anhydride in acetone failed to result in formation of a [2π + 2π] photoadduct of the two: monitoring of the course of the photolysis by ^{1}H NMR spectroscopy indicated that all of the maleic anhydride was consumed after six hours, although (506) was present in unchanged amount after this time. Further additions of maleic anhydride to the photolysis solution followed by continued irradiation for a total of 40 hours gave a quantitative recovery of starting sulphone (506). A small quantity of an insoluble crystalline product was obtained which was identified as the transoid tricyclic photodimer of maleic anhydride[108] following comparison with an authentic sample prepared under similar photolysis conditions. The experimentally observed dimerisation of maleic anhydride in preference to the photoaddition of maleic anhydride to the olefin (506) may be rationalised as resulting from the steric barrier to the latter process imposed by the overcrowded environment of the olefin system of (506). Certainly the electron-deficient character of this moiety is an unlikely source of the observed photochemical unreactivity of (506) : maleic anhydride is recognised as being an active olefin with regard to cyclobutane formation with cyclic olefins possessing a wide range of electron availabilities[108,215].

d. Hydrogenation

Catalytic hydrogenation of the olefin (506) was conducted in methanol using 10% palladium-on-charcoal as catalyst under one atmosphere pressure of hydrogen. Uptake of gas ceased after four hours and work-up resulted in isolation of a high yield of a fully saturated product, characterised as the tricyclic diester (525). In this case, the steric hinderance of the olefin group of (506) - demonstrated by its



(506) (525) 91%

previously described unreactivity towards various reagents - is insufficient to prevent adsorption and hydrogenation of the π-system on the catalyst surface.

As stated previously (p.355), the saturated diester (525) was detected as a minor component of the product mixture resulting from hydrogenation of the diene (492a). Since the diester (525) can be approached by chemical manipulation (without any change in basic ring structure) of both of the Diels-Alder adducts (492a) and (493a), the spectrally previously-established structural relationship between the adducts (the sulpholane ring being disposed towards the unsubstituted cycloolefin group in each system) is confirmed; similarly, the parallel in mechanism of formation of the adducts by secondary orbital stabilised addition of the dienophile (DMAD or maleic anhydride) to the least-hindered face of the diene (212) is reinforced.

e. Bromination

In light of the similarities in disposition of the sulpholane ring and olefin group of the diester (506) and the cisoid tricyclic system (209), with both systems expected to exhibit strong deactivations of the olefin group towards electrophilic reactions due to through-space interaction with the proximate sulphone group, a deviation in bromination behaviour from the norm was expected upon addition of bromine to (506), bearing in mind the unusual bromination pathway undergone by (209) [see p.183]. In the event, the addition of bromine to a solution of (506) in methylene chloride at 0°C resulted in no observed decolourisation after a 15 minute period; monitoring of the reaction visually [to detect formation of an insoluble salt product analogous to (336) which was obtained on bromination of (209)] and by TLC during the heating of the reaction solution under reflux for a 48 hour period failed to detect any bromination products. Starting olefin (506) was quantitatively recovered on termination of the reaction.

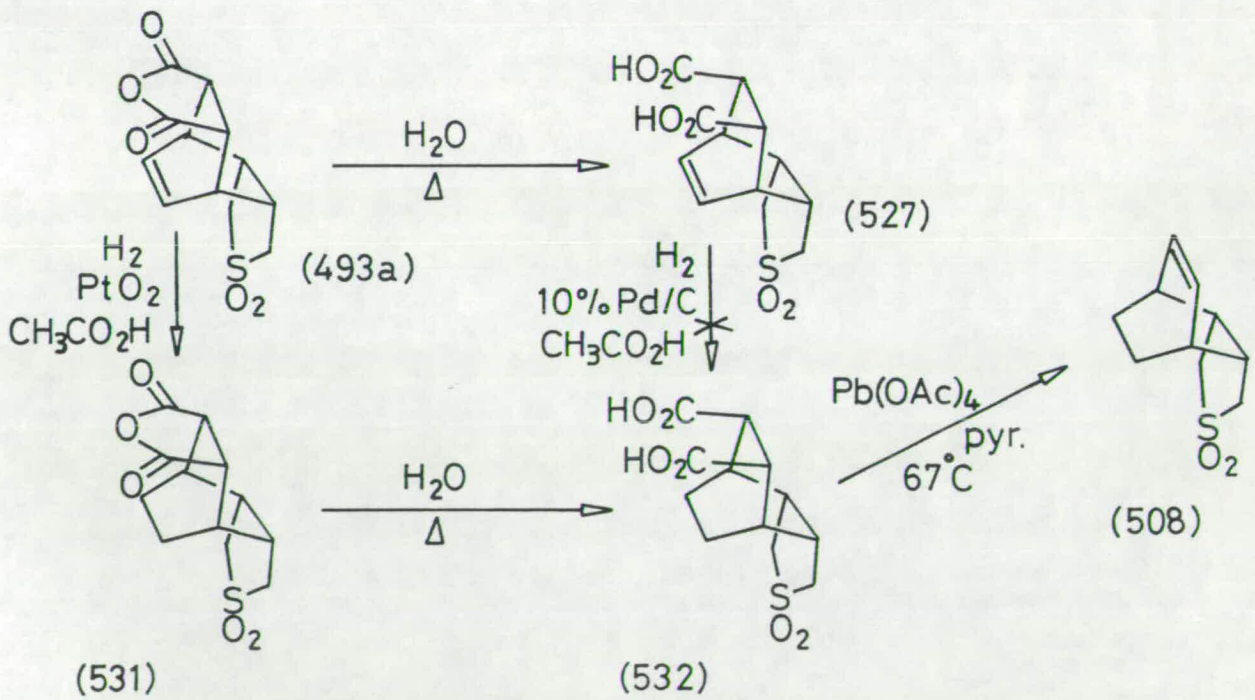
Taking the previously-related failures of other reactions attempted with the olefin system of (506) into account, it is obvious that the primary reason for the lack of bromination is steric in origin, although the deactivation of the olefin group due to a through-space interaction with the sulphone group also contributes to this. The last point is emphasised by the difficulty experienced in brominating the analogous unsubstituted olefin (329) under similarly forcing reaction conditions, as described later (p.368).

3. Preparation and olefin reactivity (towards bromine) of exo-4-thiatricyclo[5.2.2.$0^{2,6}$]undec-8-ene 4,4-dioxide (508)

Following the identification of structure (493a) for the adduct of diene (212) and maleic anhydride, it was recognised that

chemical manipulation of this system (Scheme 62) would permit synthesis of the exo olefin (508) enabling a comparison to be made with the known[95] endo isomer (329). The numerical value (0.70 eV) of the combined through-space and through-bond interactions in the endo isomer (329) can be estimated by comparison of the olefin ionisation potentials of (329) [πIp = 9.75 eV [95]] and the standard hydrocarbon, bicyclo[2.2.2]oct-2-ene [πIp = 9.05 eV [214]] by the reasoning described earlier (p.171). Preparation of the exo isomer (508) followed by determination of its UV-PES spectrum (from which the πIp value may be measured) would permit quantification of both the through-space and through-bond interactions in the endo isomer (329), enabling a direct comparison to be made of the numerical value and the chemical consequences (towards an electrophilic process such as bromination) of the through-space interaction in the endo isomer.

The first stage in the initially attempted route to the exo olefin (508) (Scheme 62) involved hydrolysis of the anhydride (493a) to the cis-diacid (527), a transformation effected in quantitative



Scheme 62

yield simply by treatment of the anhydride with boiling water for 2.5 hours. In the following stage, hydrogenation of a solution of the diacid (527) in acetic acid was attempted using 10% palladium-on-charcoal as catalyst at one atmosphere pressure of hydrogen. After uptake of hydrogen had almost ceased (three hours), work-up gave a crystalline product which was found not to be the expected saturated diacid product (532), but which was identified as being purely the anhydride (493a), obtained in 83% yield. As dehydration of (527) back to the precursor anhydride (493a) under the reaction conditions constituted an unwelcome complication in this synthetic route to the olefin (508), the alternative route involving direct hydrogenation of (493a) followed by hydrolysis of the resultant saturated anhydride (531) was attempted in order to circumvent this problem.

Reduction of a solution of the anhydride (493a) in acetic acid using platinum oxide (Adam's catalyst) and one atmosphere pressure of hydrogen at room temperature appeared complete after agitation for five hours. Analysis of the crude product by ^{1}H NMR and IR spectroscopy indicated this to be an 85:15 part mixture of the desired saturated anhydride (531) and starting anhydride (493a). This mixture was hydrolysed by heating in boiling water for one hour to give the corresponding 85:15 mixture of diacid products (532) and (527). However, the hope that the major component of the mixture could be isolated in pure form by recrystallisation from water was not realised, a mixture identical in composition - fully characterised as an 85:15 part mixture of (532) and (527) - being obtained. The unseparated diacid mixture was used directly in the next (bisdecarboxylation) reaction step *en route* to the *exo* olefin (508) (Scheme 62).

Treatment of the diacid mixture of (532) and (527) with an excess of lead tetraacetate in oxygenated pyridine at 67°C resulted in evolution of gas which ceased after a few minutes. After work-up, a semi-crystalline product was isolated; recrystallisation from ethanol gave colourless, finger-shaped crystals, m.p. 111-113°C. Elemental composition and mass spectral data were in accord with a molecular formula of $C_{10}H_{14}O_2S$ for this product, as required for a compound of structure (508). However, examination of the proton spectrum of this material indicated it to be almost identical to that of the endo olefin (329) which is known[33] to possess an almost identical melting point (112-113°C) to the isolated bisdecarboxylation product.

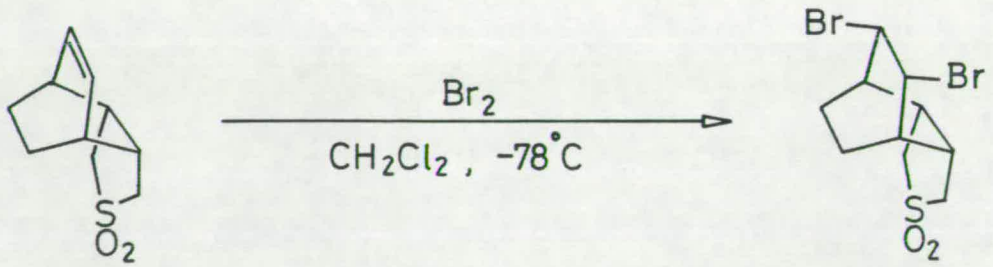
Fears that the initial assignment of stereochemistry to the anhydride (493a) was incorrect, and that the endo (329) rather than the exo (508) olefin had been prepared by the reaction sequence outlined in Scheme 62 were allayed following determination of the mixed (equimolar) melting point of the endo isomer (329) and the isolated bisdecarboxylation product : a value of 77-84°C for this clearly demonstrated the dissimilar structures of the two compounds. In addition, the five line ^{13}C DEPT NMR spectrum of the bisdecarboxylation product was found to be similar, but not identical, to that of the endo olefin (329). Thus, exo geometry (508) was assigned to the isolated product, verifying the assignment of stereochemistry previously given to the starting anhydride (493a) following ^1H NMR studies of the system (p.317), and also confirming the stereochemistries of the products derived from this anhydride which have also been described.

Incidentally, ^1H NMR spectroscopic and TLC analyses of the recrystallisation filtrate derived from decarboxylation of the 85:15 mixture of diacids (532) and (527) indicated that further exo olefin

(508) was present, together with a minor quantity of the diene (507). This diene results from bisdecarboxylation of (527) and was identified by comparison with an authentic sample prepared by this route (see p.370).

Having obtained the desired exo olefin (508), the determination of its UV-PES spectrum was desired to enable a comparison of π Ip values to be made with the endo isomer (329) and hence establish a numerical value for the through-space interaction in the latter system. Unfortunately, access could not be gained to a spectrometer capable of recording the UV-PES spectrum of (508), frustrating the acquisition of ionisation potential data not only for (508), but also for a number of other interesting unsaturated sulphone systems described in this thesis. Nonetheless, the chemical consequences of the through-space interaction in the endo olefin (329) was hoped to be demonstrated by the differing reactivity of the exo and endo isomeric olefins towards an electrophilic reaction, namely bromination.

For the exo olefin (508), a mechanism involving anti addition of bromine, with facile formation of the trans-dibromide (533), would be expected as in the bromination of any isolated cycloolefin group which is not significantly sterically hindered. Addition of bromine to a solution of the exo olefin (508) in methylene chloride at -78°C was observed to result in instant decolourisation until greater than one molar equivalent had been added. The expected trans-dibromide



(508) (533)

(533) was isolated in 72% yield as colourless rhombic crystals, m.p. 192-195°C. Characterisation of this product was facilitated by a ^{13}C DEPT NMR spectrum which displayed ten carbon resonances (four methylene and six methine) at expected chemical shift values for the asymmetric dibromide structure (533).

In contradistinction, addition of a small quantity of bromine to a solution of the endo isomer (329)[33] [kindly supplied by Dr R.A. Aitken, University of Edinburgh] in chloroform at 0°C resulted in no decolourisation of the reagent after a period of 15 minutes. Following the addition of an excess of bromine, the reaction solution was heated under reflux for 1.5 hours; the residue obtained on evaporation of the reaction solution was examined by ^{1}H NMR spectroscopic and TLC analyses which indicated that only starting olefin (329) was present. However, continued heating of the olefin (329) with excess of bromine in boiling chloroform for a total of 24 hours resulted in complete consumption of the starting sulphone. Several broad bands were evident on TLC analysis of the resultant complex mixture of brominated products : separation of these was effected by chromatographic means but analysis by ^{1}H and ^{13}C NMR spectroscopy indicated that several products (some of which were olefinically unsaturated) were present in each band, precluding identification of any of the many products formed.

Although the lack of identification of the products derived from bromination of (329) prevents any fruitful discussion of the mechanisms involved, the overall conclusion is that this olefin is extremely deactivated to addition of bromine compared to the exo isomer (508). This effect appears to be at least partially due to a reduced electron-availability of the olefin π-system of (329) resulting from orbital interaction through space with the proximate

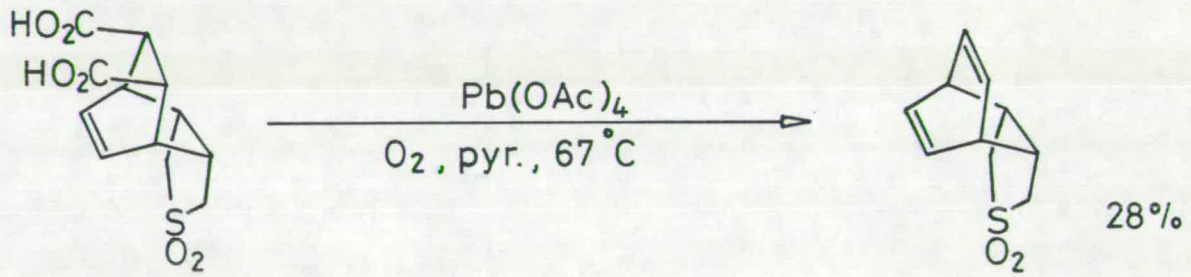
sulphone group. However, on consideration that the even more electron-deficient olefin group of the cyclobutene-sulpholane (63) [πIp = 10.25 eV cf. 9.75 eV for (329)[95]] does undergo a sluggish bromination (see p. 182) in which relief of ring strain may be a facilitating factor, it would appear that a significant steric hinderance of the olefin group of (329) is also operating to prevent bromination. Justification for this reasoning is furnished by the analogous diester-substituted system (506) which is expected to possess a similar deactivating through-space interaction to that present in (329), and in addition to possess greater steric hinderance of the olefin system by virtue of the disposition of the ester substituents, and which was found to be completely stable to bromination under extreme conditions (see p.363).

4. Preparation and olefin reactivity of 4-thiatricyclo[5.2.2.$0^{2,6}$]-undeca-8,10-diene 4,4-dioxide (507)

The preparation of the diene (507) was of interest with respect to a comparison of reactivity of the two olefin groups present with the corresponding groups in the related disubstituted system (492a), the olefin reactivity of which has been discussed at some length earlier in this section. In similar fashion to (492a), the two olefin groups of (507) are expected to display a dichotomy of reactivity : the endo olefin group is spacially close to the sulphone group and should be comparatively electron-deficient (as a consequence of the resultant through-space interaction) compared to the exo olefin group, which is not in receipt of such an effect. Complicating through-bond and through-space interactions between the two olefin groups of (507) should not detract from the overall electron-deficiency of the endo olefin group relative to the exo olefin moiety. This is, incidentally, a reversal of the situation found in the related system

(492a) where electron-withdrawal by the ester substituents effected a greater stabilisation of the exo olefin group than did the through-space interaction (with the proximate sulphone group) exert upon the endo olefin group. Thus, the effect of the through-space orbital overlap between the endo olefin and the sulphone group should be more obviously apparent from the πIp data (available from the UV-PE spectrum) and by the regioselectivity of reactions of the olefin groups for (507) than for the analogous disubstituted system (492a).

The synthesis of diene (507) was achieved by bisdecarboxylation of the diacid (527) using lead tetraacetate in oxygenated pyridine at 67°C giving the desired diene in 28% yield as colourless flakes, m.p. 147-150°C, which fully satisfied elemental composition and spectral expectations. Examination of the proton spectrum indicated that the



(527) (507)

signals due to the two non-equivalent olefin groups of (507) closely overlapped; a chemical shift difference of only 0.31 δ between the resonances of the olefinic methine groups in the ^{13}C NMR spectrum was more surprising. Evidently any difference in the electron-availabilities of the two olefin groups (due to a through-space interaction of only one of these with the sulphone group) is not reflected in a noticeable dichotomy of the corresponding proton or carbon resonance chemical shift values. This behaviour parallels that found for the transoid

(208) and cisoid (209) tricyclic isomers which displayed very similar olefinic methine proton and carbon resonance chemical shift values, and the reasons expounded for this similarity between the tricyclic isomers (see p. 181) may apply also to the intramolecular situation regarding the exo/ endo olefin groups of (507).

As for the other unsaturated sulphone systems discussed earlier, the UV-PE spectrum of (507) could not be obtained due to the unavailability of a suitable spectrometer. The expected dichotomy in electron availability of the exo and endo olefin groups could not therefore be established by physical means, leaving a study of the chemical reactivity of each olefin group as the remaining means of investigating this. Although system (507) warrants a study of olefin reactivity of at least the same scale as that previously detailed for the related disubstituted structure (492a), temporal restrictions were such as to limit this study merely to photolysis and bromination reactions.

Irradiation (400W) of a dilute solution of (507) in deuteriochloroform through quartz for 11.5 hours gave a dark-coloured photolysate. Analysis of this by ^{1}H and ^{13}C NMR spectroscopy indicated that only 10% of the starting diene (507) remained; no discrete products could be detected and the diene (507) appeared to have largely undergone a polymerisation process with incorporation of the solvent in the polymeric product. A repeat photolysis differing only in the use of a Vycor filter gave similar results. Photolysis through pyrex (rather than quartz) but otherwise as above for a period of 70 hours gave a quantitative recovery of starting diene (507).

In common with the disubstituted system (492a), no intramolecular [2 π + 2 π] photocyclised product was isolated and this would appear to be principally due to the strain inherent in such a prismane structure which, by analogy to the prismane system

(521) [212], would be expected to undergo a facile thermal ring-opening process under the prevailing conditions. Certainly the electron-deficient nature of the *endo* olefin group of (507) (expected to result from an orbital interaction through space with the sulphone group) should present no significant handicap to the intramolecular photocyclisation process.

The dichotomy of electron availabilities of the two olefin groups of (507) was expected to be highlighted by the different reactivities of these towards an electrophilic reaction process. In this respect, the reaction of (507) with bromine was attempted. Thus, the addition of slightly less than one molar equivalent of bromine to a solution of the diene (507) in chloroform at -60°C was observed to result in no decolourisation of the added bromine. On stirring at room temperature for 4.5 days, an almost colourless solution was obtained. Evaporation of this to dryness gave a crystalline residue, found on ^{1}H and ^{13}C NMR spectroscopic analyses to contain no starting diene (507), and to be consistent with a mixture of a major saturated dibromide product (*ca* 75% yield on available bromine) together with at least three other products, one (or more) of which was olefinically unsaturated.

Recrystallisation of the complex mixture from ethanol resulted in isolation of the major product as colourless flakes, m.p. 190-193°C. Following satisfactory elemental composition and mass spectral analyses, this was confirmed to be a dibromide product of the diene (507). The retention of the sulphone group was apparent upon examination of the infrared spectrum, and the ^{1}H and ^{13}C DEPT NMR spectra (Figure 41) demonstrated the saturated nature of the dibromide product. A basic tetracyclic structure for this product was proposed in light of the reported[216] bromination of norbornadiene

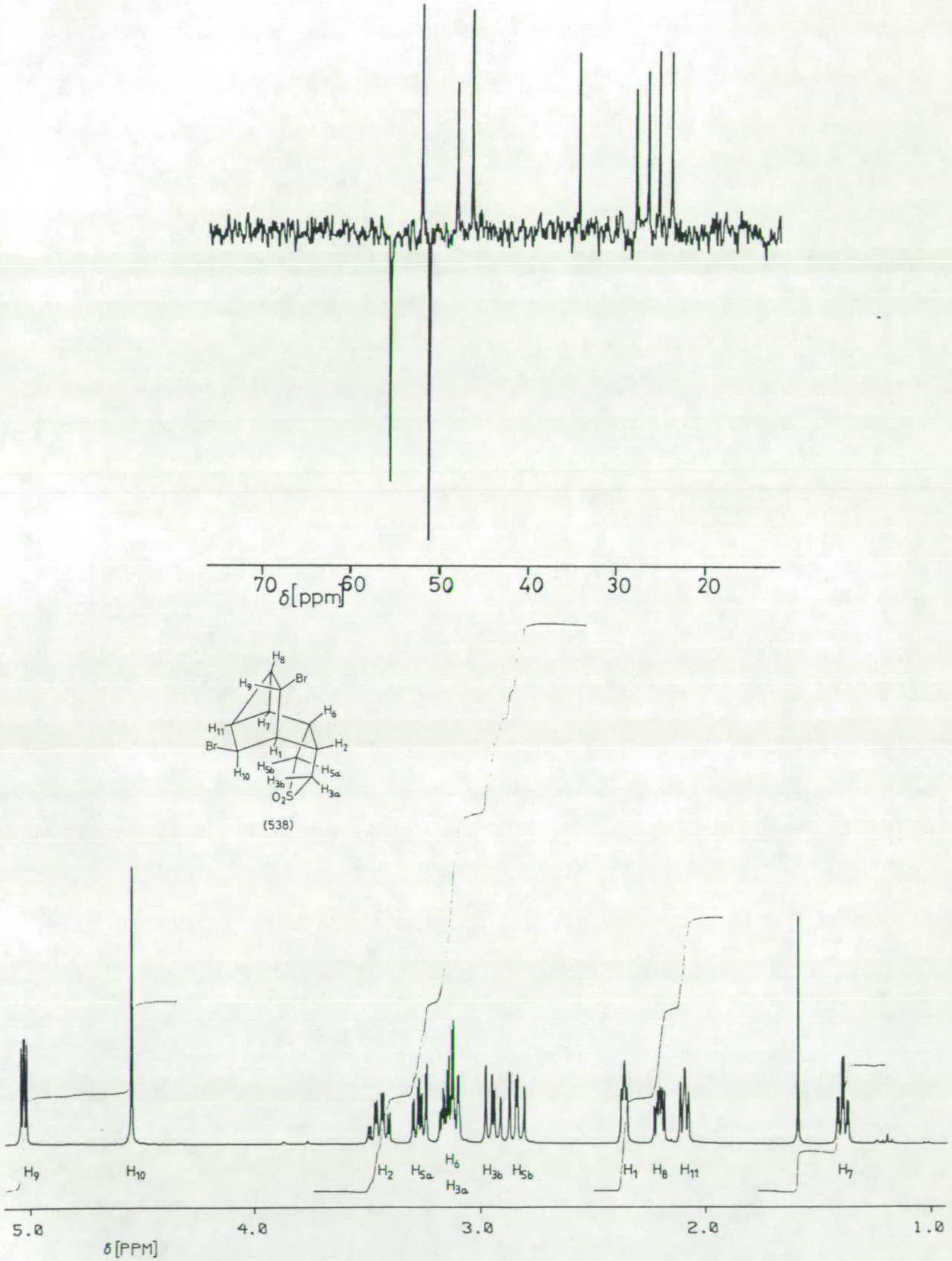
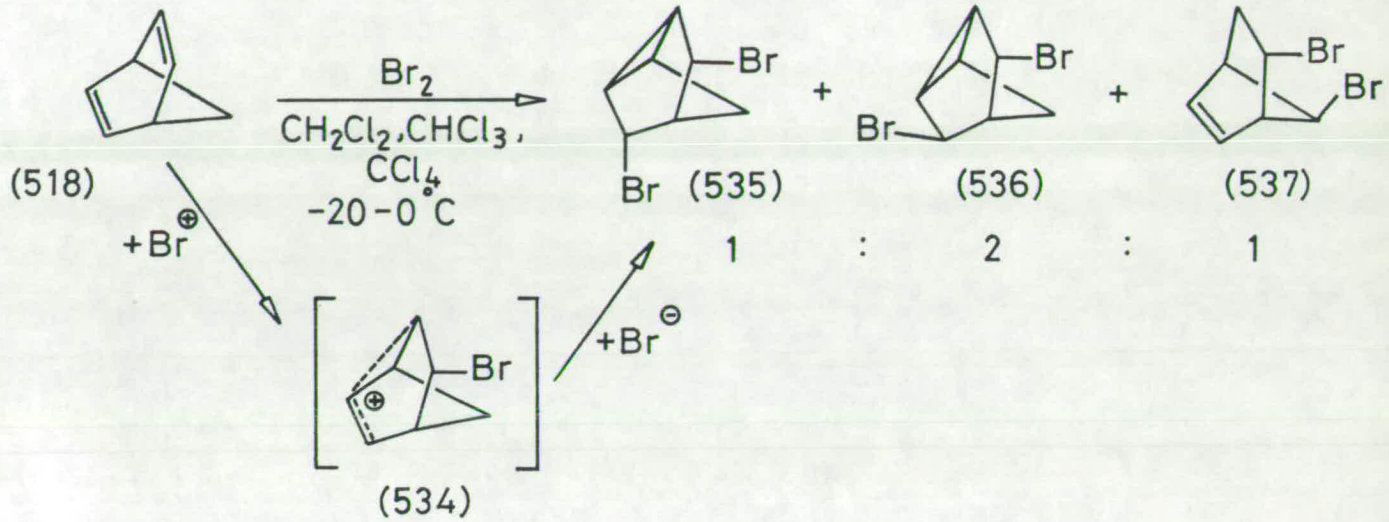


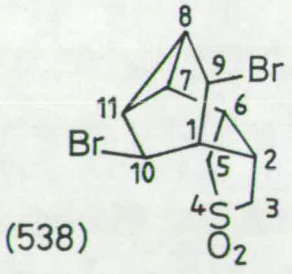
Figure 41 : ^{1}H NMR spectrum (360 MHz) and ^{13}C DEPT NMR spectrum of dibromide (538)

(518) with one molar equivalent of bromine to give the cis (535) and trans (536) isomeric 3,5-dibromonortricyclenes and, by a skeletal

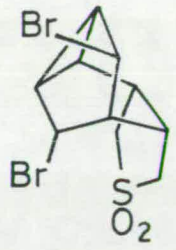


rearrangement process, the unsaturated dibromide (537) in a ca 1:2:1 ratio.

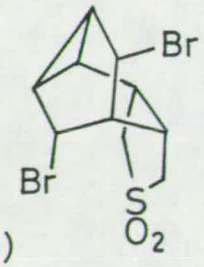
Four tetracyclic structures for the major dibromide product derived from (507) are possible, these being the trans-dibromide structures (538) and (539), and the cis-dibromide counterparts (540) and (541). Since mono-addition of bromine to bicyclo[2.2.2]octa-



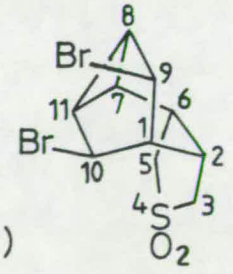
(538)



(539)

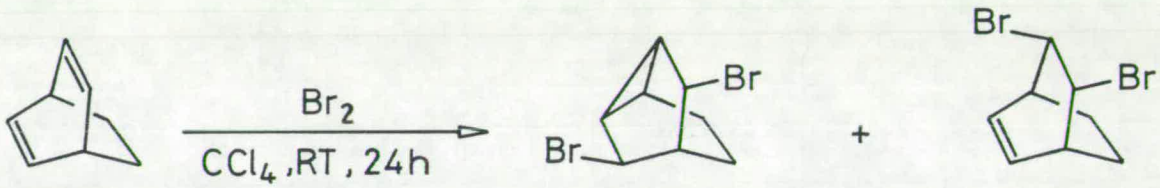


(540)



(541)

2,5-diene (542) has been described[217] as resulting in formation of only the trans-dibromotricycle (543) and the unsaturated dibromide (544), and in consideration of the predominant formation of the trans-dibromide (536) on mono-addition of bromine to norbornadiene (518), it would appear that of the four tetracyclic dibromides (538)-(541), one of the trans-isomers (538) or (539) is the most likely structure for the isolated product derived from (507). This being the case, the least sterically congested isomer (538) is the more probable of the two trans-dibromides.



(542) (543) (544)

3 : 7

Using a combination of ^{1}H selective decoupling and NOE enhancement NMR studies the structure of the major dibromide product was unambiguously identified. Thus, starting from the reasonable assumption that the two most deshielded signals at δ 5.03 and δ 4.54 were due to the two bromomethine protons, the NOE irradiation of each of these (shown in Figure 42) was performed in order to elucidate the product structure. Irradiation of the signal at δ 4.54 resulted in enhancements in the signals at δ 2.94 (7.5%) and δ 2.83 (2.5%), both of which were assigned to non-geminally-related sulpholane methylene protons on the basis of their exhibited geminal constants of 14.2 Hz and 13.2 Hz respectively. This information restricted the possible structure of the product to either (538) or (541) since only these isomers possess the close spacial relationship of the bromomethine

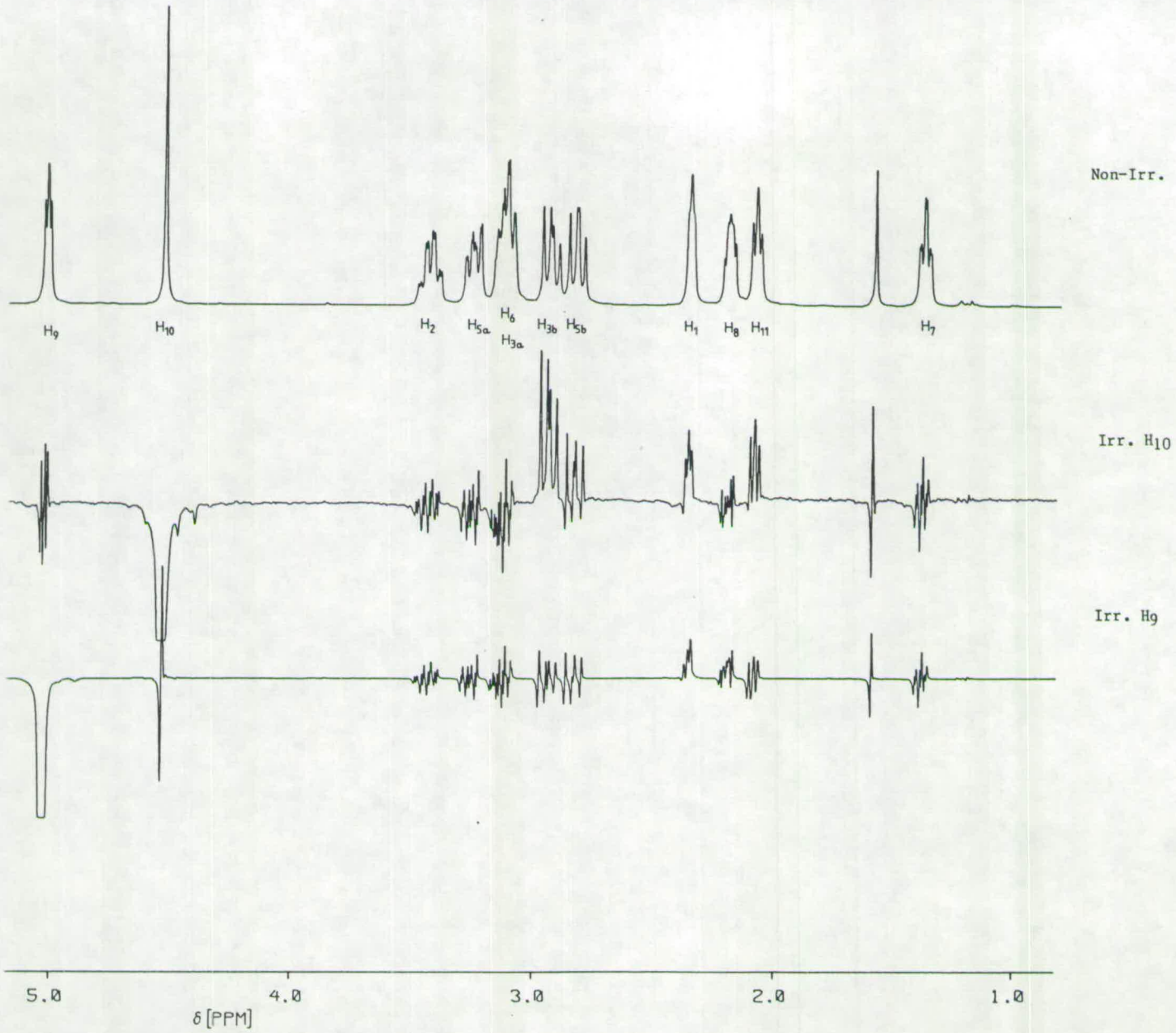


Figure 42 : NOE enhancement ^{1}H NOE spectra of dibromide (538)

proton, H_{10} (at δ 4.54) and the sulpholane protons, H_{3b} and H_{5b}, which was established by the observed NOE enhancements. In addition, NOE irradiation of H_{10} (δ 4.54) resulted in significant enhancements in the signals at δ 2.36 and δ 2.09, which were respectively assigned to the neighbouring (spacially proximate) protons H_1 and H_{11} in structure (538)/(541). The singlet signal for H_{10} must therefore reflect near orthogonal dihedral angles between this and the H_1 and H_{11} protons.

Following NOE irradiation of the remaining bromomethine proton (H_9) at δ 5.03, observed enhancements in the signals at δ 2.36 (assigned to H_1) and δ 2.20 (assigned to H_8) - both of which display coupling to H_9 - were in accord with the neighbouring disposition of the three protons in the dibromide structure (538) or (541). The presence of sizeable couplings to bromomethine proton H_9 is in contrast to the lack of coupling observed to the other bromomethine proton, H_{10}. Thus, the magnitude of the dihedral angles $\phi_{1,9}$ and $\phi_{8,9}$ must be very different from those of $\phi_{1,10}$ and $\phi_{10,11}$ (expected to be ca 90°), and these dihedral angles are therefore more in agreement with the trans-dibromide structure (538) than the cis-dibromide isomer (541). Indirect evidence for the assignment of structure (538) to the major dibromide product derived from diene (507) is furnished by the observed lack of enhancement of the H_2 signal (later established to be at δ 3.44) on NOE irradiation of the H_9 signal (δ 5.03); the only alternative structure, the cis-dibromide system (541), would be expected to demonstrate such an effect.

The spectra derived from selective decoupling of each discrete, coupled proton resonance in the ^1H NMR spectrum of the major dibromide product are shown in Figure 43. Detailed analysis of these, considered together with the results of the ^1H NOE enhancement

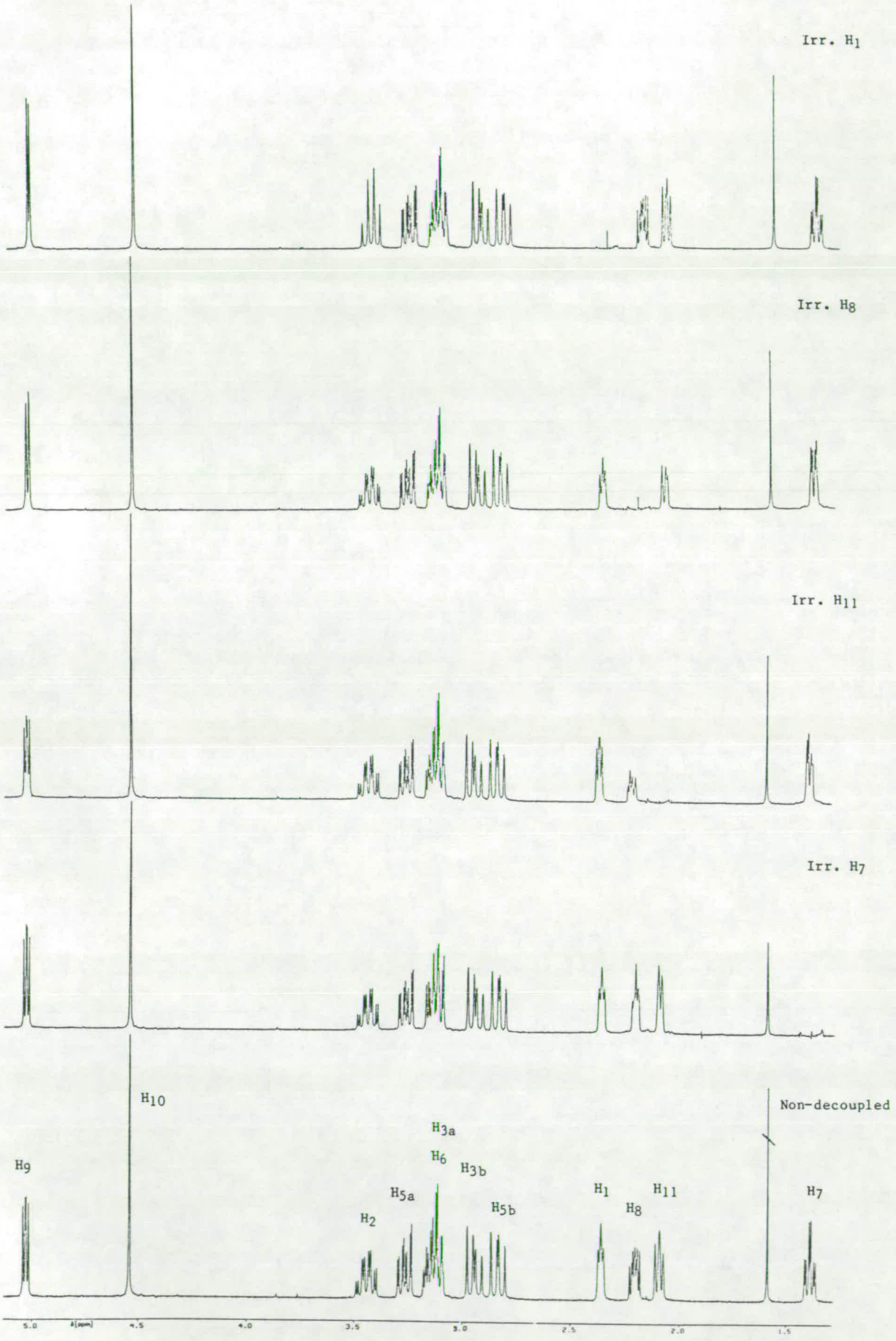


Figure 43 : Selectively decoupled ^{1}H NMR spectra of dibromide (538)

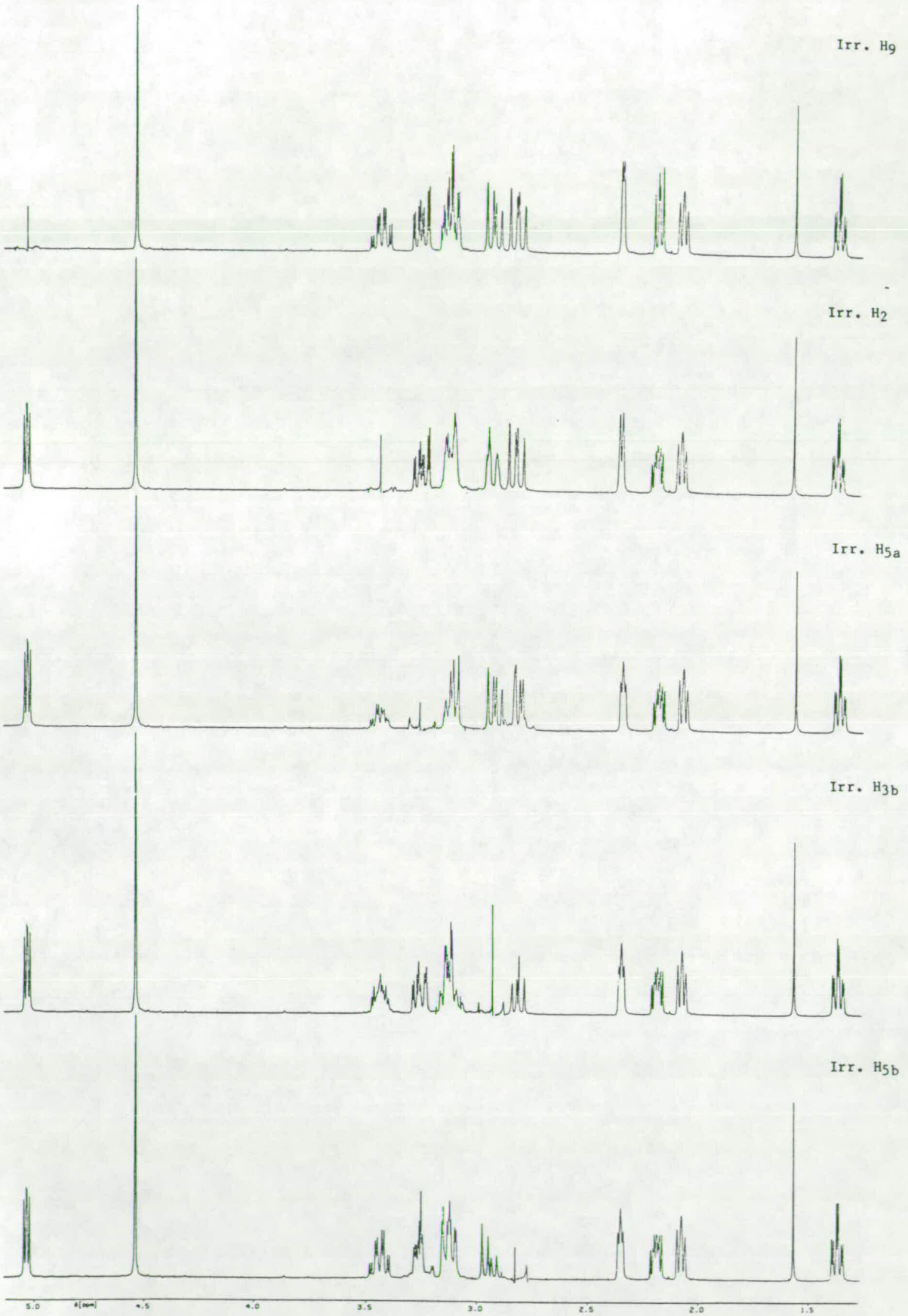
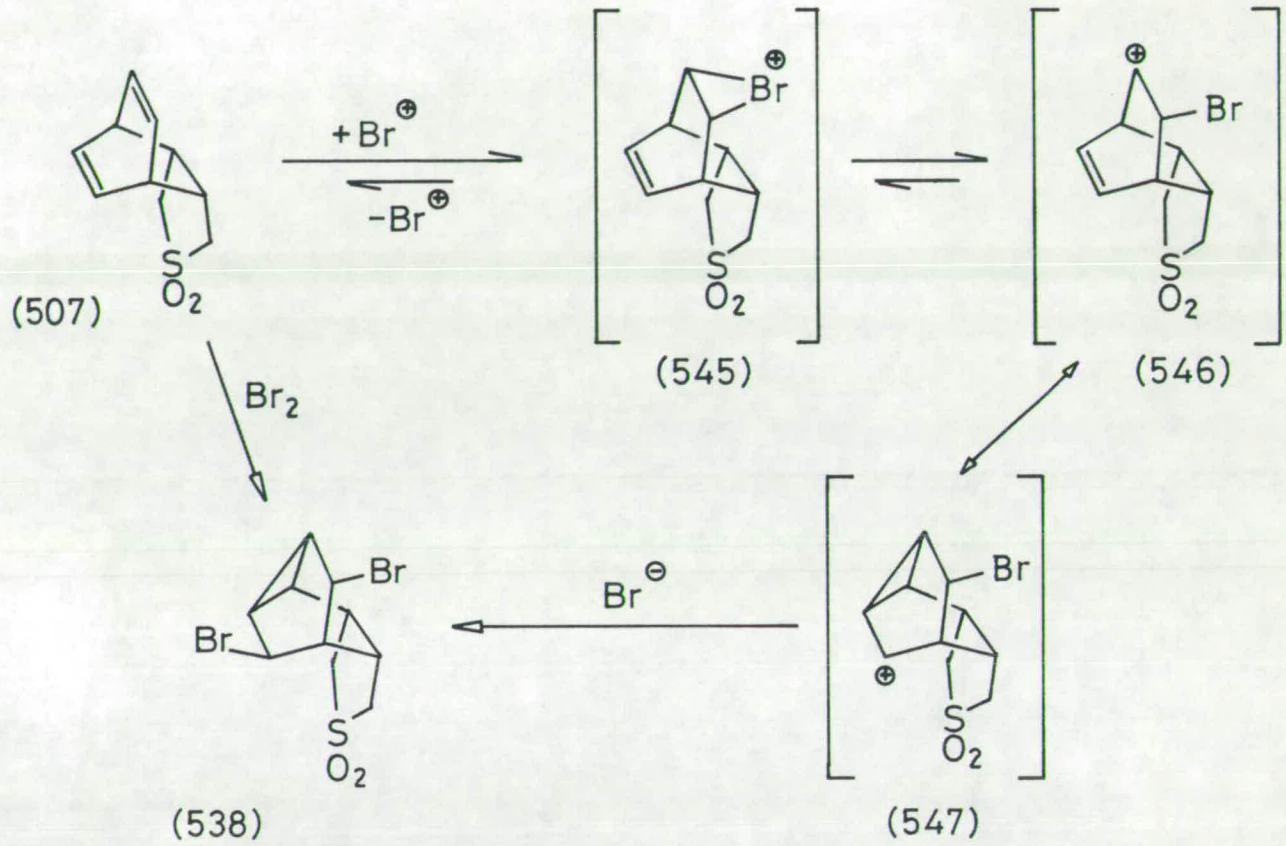


Figure 43 (cont.) : Selectively decoupled ^{1}H NMR spectra of dibromide (538)

studies are sufficient to enable the complete and unambiguous assignment of signals to protons shown in Figures 41, 42 and 43 to be made. Furthermore, the assignment of every coupling constant present in the proton spectrum was achieved, and the magnitude of these were found to agree well with those expected for (538) allowing final verification of this as the structure of the isolated dibromide product derived from the diene (507). An interesting feature to emerge from consideration of the coupling constants is the magnitude of $J_{3a,5a}$ = 2.3 Hz and $J_{3b,5b}$ = 0.7 Hz which appear too large for ^{5}J couplings and would therefore appear to result from ^{4}J coupling of these protons through the relaying sulphone group.

Having identified the major product resulting from mono-addition of bromine to the diene (507), the identity of the minor bromination products remains to be established. However, none of these components could be adequately separated using preparative TLC, precluding identification and hence any sensible discussion of their mechanism of formation.

With regard to the mechanism of formation of the dominant product (538), it would appear most probable that the diene (507) undergoes initial electrophilic attack at the least hindered face of the more electron-rich <u>exo</u> olefin group with generation of the cyclic bromonium ion intermediate (545) (Scheme 63). Ring opening of this to generate a homoallylic cation, the resonance hybrid of (546) and (547), may be proposed in view of the suspected intermediacy of the related cation (534) in the bromination of norbornadiene (518)[216]. The stabilisation of the positive charge effected by ring opening of (545) to the homoallylic cation is expectedly largely a result of the contribution of canonical form (547) : a through-space coulomb interaction between the localised carbonium ion and the sulphone group



Scheme 63

exists in this form, a feature not present in the other contributing canonical form (546). As a consequence of the greater contribution of (547) to the cationic resonance hybrid, attack of bromide ion from the least hindered face of the cation would result predominantly in formation of the isolated trans-dibromide product (538). Thus, the participation of the remote (in through-bond terms) sulphone group in the bromination of diene (507) results in the formation of a saturated trans-dibromide as the major product, in contrast to the bromination of the related hydrocarbon, bicyclo[2.2.2]octa-2,5-diene (542) which yielded[217] largely the unsaturated trans-dibromide (544), as discussed earlier (p. 375).

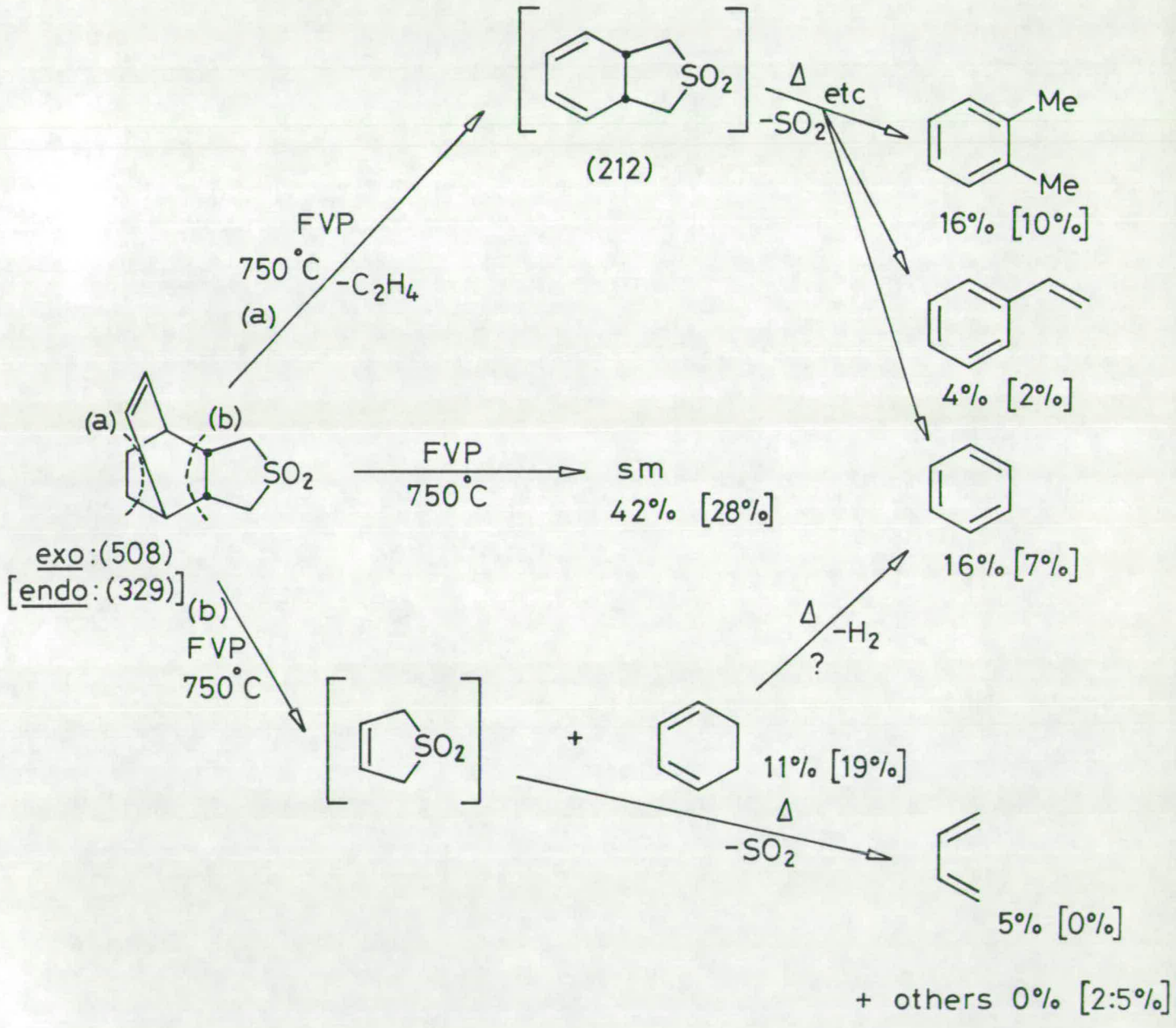
With respect to the three (or more) minor unidentified products formed on bromination of the diene (507), obviously a large number of bromination pathways are potentially open to the diene including initial formation of alternative cyclic bromonium ion intermediates to (545) each with a number of possible skeletal rearrangements prior to addition of bromide ion and consequent product formation.

5. FVP of 4-thiatricyclo[5.2.2.$0^{2,6}$]undec-8-ene 4,4-dioxide based systems

The thermal fragmentation behaviour under FVP conditions of a series of six related olefinically-unsaturated bridged compounds is now considered. The members of the series, which consists of the adducts (492a) and (493a) and derived systems prepared by previously-detailed synthetic procedures, are expected to display fragmentation pathways strongly influenced by the level and position of unsaturation.

Pyrolysis of the first two members of the bridged series, the exo (508) and endo (329) isomeric olefins was undertaken to establish if the presence of a through-space interaction between the olefin and sulphone groups in the endo system (329) influences the ease and direction of thermal fragmentation relative to that of the exo (508) isomer. The FVP of each isomer was carried out under identical conditions at a furnace temperature of 750°C. Analysis of the two pyrolysates by ^{1}H NMR spectroscopy and GLC indicated each to contain a similar spectrum of hydrocarbon products, as detailed in Scheme 64. The major products resulting from FVP of the endo olefin (329) were similar to those described[33] for a previous pyrolytic study of this system by an associate in these laboratories.

Mechanistically, the formation of the observed aromatic products from the two isomers (508) and (329) can be rationalised by consideration of the two competing retro-Diels-Alder fragmentation pathways outlined in Scheme 64. The driving force governing these fragmentation processes is the formation of conjugatively-stabilised extrusion fragments, these being the diene (212) [pathway (a)] and

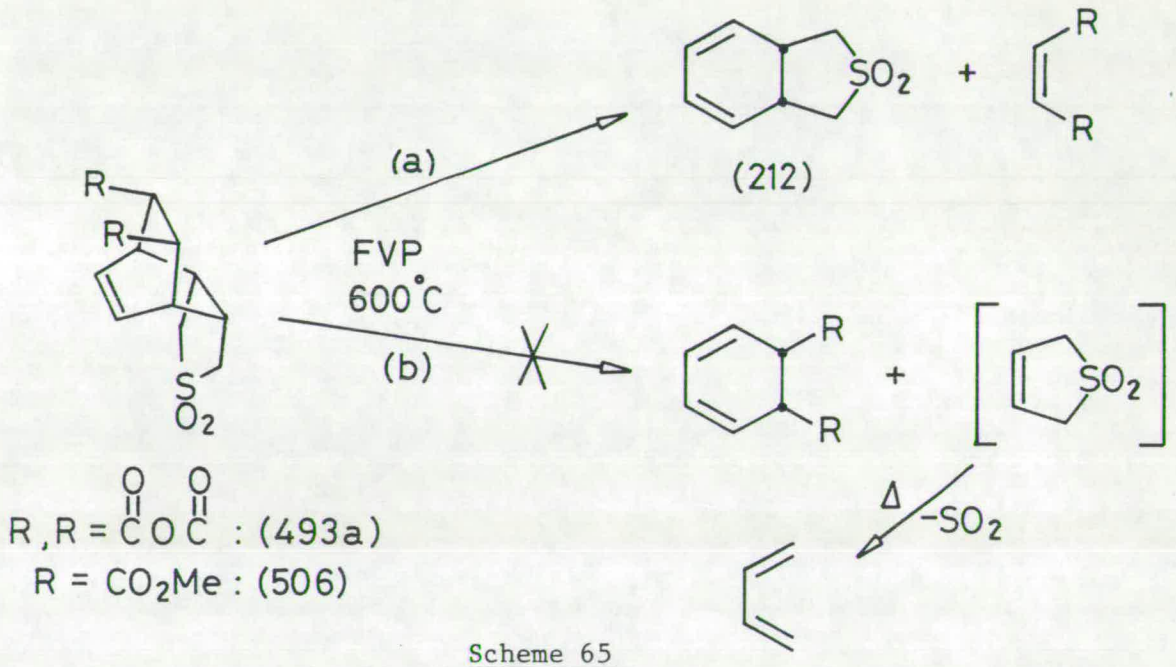


Scheme 64

cyclohexa-1,3-diene [pathway (b)], formed by extrusion of ethylene and butadiene sulphone respectively. Although both fragmentation pathways (a) and (b) operate for each of the exo (508) and endo (329) isomers, detailed examination of the ratios of the pyrolysis products obtained from the two sulphones indicate that the presence of a through-space interaction in the endo isomer does result in a slight difference in the ease and modes of fragmentation of this system compared to the exo isomer.

The observed thermal instability of the endo olefin (329) relative to the exo isomer (508) (indicated by the lower yield of recovered starting sulphone for pyrolysis of the endo system) may be taken as an indication that the activation energy barriers to the retro-Diels-Alder processes of pathways (a) and (b) (Scheme 64) are lower for the endo isomer as a result of participation of the proximate sulphone group in secondary orbital stabilisation of the two fragmentation transition states. No such effect can operate within the exo olefin (508), imparting a greater thermal stability to this system compared to the corresponding endo isomer (329). Interestingly, the ratio of operation of pathway (b) to pathway (a) is slightly greater for fragmentation of the endo olefin (329) than for the corresponding exo isomer (508), as evident from the differing ratio of cyclohexa-1,3-diene to aromatic products in the two pyrolysates. An enhanced secondary orbital stabilisation of the transition state leading to the formation of the more electron-rich diene (cyclohexa-1,3-diene) and electron-deficient olefin (butadiene sulphone) [pathway (b)] over that leading to formation of the comparatively electron-deficient diene (212) and electron-rich olefin (ethylene) [pathway (a)] in the endo isomer (329) would account for the observed product distribution.

Two disubstituted analogues of the endo olefin (329), the anhydride (493a) and the derived dimethyl ester (506), were available for a study of thermal fragmentation behaviour. FVP at 600°C of the anhydride (493a) resulted solely in a retro-Diels-Alder fragmentation to give the diene (212) and maleic anhydride, the materials from which the system had originally been constructed via a Diels-Alder reaction.



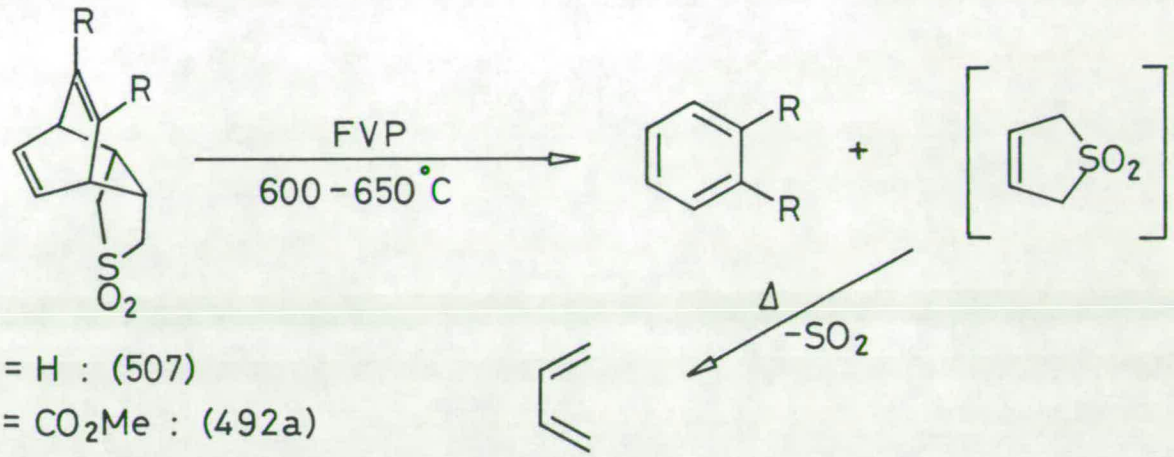
Scheme 65

FVP at 600°C of the dimethyl ester (506) resulted largely in recovery of the starting olefin (61%), with the consumed material being accounted for by a retro-Diels-Alder fragmentation to the diene (212) and dimethyl maleate (Scheme 65). Increasing the furnace temperature to 700°C resulted in complete fragmentation of the starting olefin (506) on FVP, the detected products being the diene (212) (31% yield) and a mixture of dimethyl maleate (61%) and dimethyl fumarate (31%). The presence of dimethyl fumarate only at the elevated pyrolysis temperature of 700°C presumably reflects the operation of a cis-trans thermal isomerisation process on the initially formed dimethyl maleate; the low isolated yield of the diene (212) compared

to the combined yield of diester products found on FVP at 700°C is due to the operation of secondary thermal extrusion processes upon the *in situ* generated (hence vibrationally excited) diene (212), resulting in formation of volatile aromatic hydrocarbons (see p.328).

In contrast to the two competing retro-Diels-Alder processes operating in the thermal fragmentations of the related *exo* (508) and *endo* (329) systems (Scheme 64), no evidence was found for the operation of two such pathways in the thermal dissociation of the disubstituted systems (493a) and (506) (Scheme 65). The presence of the carbonyl-bearing substituents in the latter two systems directs the retro-Diels-Alder process solely towards the formation of the thermodynamically stable α,β-unsaturated olefin (maleic anhydride or dimethyl maleate) and the diene (212) [pathway (a)] at the expense of the higher energy extrusion process [pathway (b)] shown in Scheme 65.

Two bridged diene systems, the parent structure (507) and its 8,9-diester-substituted analogue (492a), complete the series of related bridged systems whose pyrolysis was undertaken. FVP of (507) at 600°C resulted in clean fragmentation to benzene (90% yield), together with a minor amount of styrene (3% yield); FVP of the related diester (492a) at 650°C generated an almost quantitative yield of dimethyl phthalate. The fragmentation behaviour of (492a) mirrors that of the related bicyclic diester-diene system (509) which has been reported[218] as undergoing dissociation to dimethyl phthalate and ethylene on thermolysis at 170°C. Mechanistically, both dienes (507) and (492a) undergo facile, thermal retro-Diels-Alder fragmentations with generation of the isolated thermodynamically stable aromatic products (the driving force for the fragmentation) and the olefin, butadiene sulphone which is known[41] to undergo secondary fragmentation to buta-1,3-diene and sulphur dioxide under the pyrolysis conditions.



R = H : (507)

R = CO_2Me : (492a)

The comparatively low pyrolysis temperatures required to effect complete thermal fragmentation of the dienes (507) and (492a) is in contrast with those required for complete dissociation of the four mono-olefins discussed immediately previously, and is a reflection of the influence of the two olefin groups in determining the ease and direction of fragmentation in the diene systems.

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