Aspects of the Synthesis of Polycyclic Thianes and Related Systems

A Thesis presented to the University of Glasgow for the Degree of Doctor of Philosophy by William Routledge 1978
To my loving wife
and parents
ACKNOWLEDGEMENT

I should like to express my gratitude to Dr P H McCabe for his advice, guidance and enthusiasm throughout the duration of this work. For the opportunity to pursue this line of research, I wish to thank Professors R A Raphael (Cambridge) and G W Kirby. I am indebted to the technical staff of the University of Glasgow Chemistry Department for the provision of routine spectroscopic and analytical data and to the departmental librarians for their efficient service. Finally I want to express my appreciation to the Science Research Council for financial support.
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The acid-catalysed acetylation of bicyclo[3.3.1]nonan-2,6-dione (79) and its 9-thia and 9-oxa analogues (165 and 187) is described. In the presence of toluene-p-sulphonic acid or low concentrations of concentrated sulphuric acid, O-acetylation occurred to produce mixtures of the corresponding mono- and bisenol acetates. At higher sulphuric acid levels, C-acetylation was favoured, 79 and 165 producing adamantane and 2-thiaadamantane derivatives respectively while 187 yielded the doubly C-acetylated species (202).

The attempted dehydrochlorination of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane (161) with pyridine failed to produce an olefinic product but yielded instead the bispyridinium salt (215). Reaction of chloroalkene (213) with pyridine at room temperature gave monopyridinium salt (216) which underwent facile structural rearrangement at elevated temperatures (>50°) to give a mixture of 216 and 225. Pyrolytic elimination of pyridine hydrochloride from 215 and 216 proceeded with structural rearrangement furnishing 9-thiabicyclo[4.2.1]nona-2,4-diene (229).

In order to prepare 8-thiabicyclo[3.2.1]octane derivatives as potential precursors to thia- analogues of biologically active tropane alkaloids, the condensation of sulphur dichloride with cycloheptadienes (238, 282, 286 and 292) was investigated. Cyclohepta-2,6-dienone (238) and its ethylene ketal (292) reacted with SCl₂ in an identical regiospecific manner to produce the unsymmetrical 1:1 adducts (307 and 305) while 1-benzoyloxycyclohepta-3,5-diene (286) gave the expected symmetrical dichloride (295). Cyclohepta-3,5-dienone (282) reacted with SCl₂ with the elimination of
one equivalent of hydrogen chloride furnishing the photosensitive allylic chloride \((301)\) which was further dehydrochlorinated to 8-thiabicyclo[3.2.1]octa-3,6-dien-2-one \((303)\).
Part One

The Synthesis of Adamantanes and Heteroadamantanes

A Review
The highly symmetrical tricyclodecane, adamantane (1) was first isolated in 1933 by Landa and Macháček from a high-boiling petroleum fraction originating in the Hodonin field of Czechoslovakia. Although found only in trace quantities the unusually high melting point (269°) and exceptional crystallinity of the compound facilitated its separation. Eight years later Prelog and Seiwerth published an elegant laboratory synthesis of the hydrocarbon (Scheme 1) and clearly demonstrated the close relationship of its carbon framework to the spatial arrangement of atoms in the diamond crystal lattice (Figure 1).

A suitable high-yield route to 1 nevertheless remained to be discovered and for many years the compound was no more than a curiosity. However, in the late 1950's, the isomerisation of the readily obtainable tetrahydrodicyclopentadiene (2) in the presence of various Lewis acid catalysts was reported to give 1 in yields ranging from 12% to 42%. The most recent modification of this approach, employing aluminium halides accompanied by alkyl halide co-catalysts has furnished yields in excess of 80% making it the current method of choice for the preparation of adamantane. Although this type of rearrangement was at first thought to be limited only to C_{10} tricyclics, later work showed that such diverse materials as Nujol, cholesterol, cyclohexene and dodecane also yield small amounts of adamantane and alkyladamantanes when subjected to Lewis acids, reflecting the high thermodynamic stability of the strain-free tricyclo[3.3.1.1^{3,7}] decane nucleus.

The availability of the parent hydrocarbon in recent years has been one of the principal reasons for the current rapid growth of adamantane chemistry and has contributed to the steady
Figure 1
The Diamond Crystal Lattice

Scheme 1

1. Raney Ni
2. Raney Ni

4. Ba(OH)₂ → CO₂CH₃ → CH₂Br₂ → KOH, Br₂

1. H⁺ → 2. N₂H₄ → 1. SOCl₂ → 2. NH₃ → CONH₂ → KOH, Br₂

1. C₅H₆COCl → 2. PBr₅ → NH₂
increase in the number of derivatives which have been prepared in synthetic studies, in mechanistic and stereochemical investigations and for biological testing. Like other saturated hydrocarbons however, the utility of \( \mathbf{1} \) as a synthetic intermediate is limited and although bridgehead positions are readily halogenated, alkylated, acylated and carboxylated\(^{14} \), the controlled functionalisation of the methylene groups is less easily achieved.

An alternative and potentially more flexible approach to the synthesis of adamantanes is by their construction from simpler fragments. Although a variety of such schemes have been postulated\(^{11} \), only one pathway - the insertion of a one-carbon fragment between the C(3) and C(7) positions of an appropriately substituted bicyclo[3.3.1]nonane (3) precursor - has been followed up with notable success. Exemplifying this approach the first reported synthesis\(^{16} \) of adamantane derivatives utilised the condensation of Meerwein's tetraester (4)\(^{17} \) with methylene bromide to give 5 which on Clemmensen reduction yielded alcohol (6) (Scheme 2). The earliest preparation\(^{2} \) of the parent hydrocarbon, already mentioned (Scheme 1), appeared soon after and followed the same basic strategy furnishing 1 in 3% overall yield based on tetraester (4).

Adamantane-2-carboxylic acid (9) which is difficult to prepare by other means, has been obtained by Stetter,\(^{18} \) from 4 by a five-stage synthesis (Scheme 3), which included the condensation of bisenamine (7) with ethyl dibromoacetate yielding diketoester (8). The same author has shown\(^{19} \) that the condensation of bicyclo[3.3.1]-nonan-3,7-dione (10) derivatives with carbanions may also be used for the production of highly functionalised adamantanes. In particular, dione (11), prepared in three stages from p-cresol
(Scheme 4) was condensed with nitromethane to give 12. Catalytic reduction of this product yielded the substituted 2-aminoadamantane (13). The high and varied functionality of products obtainable in this way render them particularly suitable for further functional group manipulation.

Photolysis of bicyclo[3.3.1]nonanes has also provided entry into usefully substituted adamantanes. Thus irradiation of epoxide (14) has been used to produce 1,3-dihydroxyadamantane (15). Photo-induced cyclisation of diene (16) furnished the fused noradamantane (17) which, unlike other cyclobutanes was found to be reactive towards bromine giving 18 as the major product (Scheme 5).

Although of limited synthetic utility because of inconvenient starting materials and poor overall yields the work of Owen and Robins\(^ {22} \) and Kutsuma and Sugasawa\(^ {23} \) illustrates an ingenious direct synthesis of an adamantane from a cyclohexane derivative. Thus cyclohexanone (19) was converted to enamine (20) which reacted with ethyl 2-bromomethyl acrylate by a sequence of alkylation, Michael addition and Claisen condensation (Scheme 6) to produce the novel adamantandione (21).

**Heterocyclic Analogues of Adamantane**

In addition to advances made in the carbocyclic field, much attention in the last twenty years has been devoted to the synthesis and study of heterocyclic analogues of adamantane. The scope of the subject has become so great that an exhaustive literature survey cannot be adequately dealt with in a brief review of this type, and the following discussion will of necessity be restricted only to those
Scheme 4

1. OH
2. CHCl₃
3. NaOH
4. CH₃
5. CH₂CHCl₂
6. CO₂C₂H₅
7. H₃C
8. CH₂Cl
9. CH₂Cl
10. R = CO₂C₂H₅
11. H⁺
12. CH₃NO₂
13. H₃C
14. CH₃
15. OH

Scheme 5

16. hv
17. Br₂
18. CH₂Br
Scheme 6

$R = H$ or $CO_2C_2H_5$

19

$C_6H_8NH$ → 20

$BrCH_2CO_2C_2H_5$ → 21

$HO^-$ → $C_2H_5O^-$
systems possessing skeletal oxygen, nitrogen and sulphur. For the same reasons, the preparation of mixed heteroadamantanes, such as oxathia- and azathiaadamantanes, has not been reviewed. Entry into these systems, however, follows the same basic strategies as those which are discussed.

Heteroadamantanes have been reported which contain non-metals such as arsenic, boron, phosphorus, selenium and silicon and a variety of metals such as calcium, copper, rhodium and tin.

2-Oxaadamantane (Oxaadamantane, 23)

By virtue of its divalent nature, oxygen may replace one or more of the methylene groups of the adamantane skeleton, and thus ten different oxaadamantanes are theoretically possible. These compounds are shown in Table 1, and derivatives of many of them are known.

The synthesis of 2-oxaadamantanes has been achieved by several different pathways, most of which involve a bicyclo[3,3,1]nonane intermediate. In particular the parent compound (23), a volatile solid with a penetrating camphor-like odour, was first isolated in 1962 by the dehydration of bicyclo[3,3,1]nonan-3,7-diol (22) with concentrated sulphuric acid using the same approach as had been employed three years earlier for the preparation of its 6,6-dimethyl and 6-dichloromethyl-6-methyl derivatives (24 and 25) (Scheme 7).

Other oxaadamantane precursors are diene (26), dione (10), ketoalkene (27) and diol (28). The first of these compounds, 26,
Table 1  Oxaadamantanes.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>2-</td>
<td>23</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>2,4-di-</td>
<td>61</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>2,6-di-</td>
<td>49</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>2,4,6-tri-</td>
<td>65</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure" /></td>
<td>2,4,9-tri-</td>
<td>66</td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure" /></td>
<td>2,4,10-tri-</td>
<td>67</td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure" /></td>
<td>2,4,6,8-tetra-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image8.png" alt="Structure" /></td>
<td>2,4,6,9-tetra-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image9.png" alt="Structure" /></td>
<td>penta-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image10.png" alt="Structure" /></td>
<td>hexa-</td>
<td>-</td>
</tr>
</tbody>
</table>
Scheme 7

11 $\xrightarrow{\text{LiAlH}_4}$ 11

$\xrightarrow{\text{c. H}_2\text{SO}_4}$ 25

$\xrightarrow{\text{cat. H}_2}$ 24

Scheme 8

23 $\xrightarrow{\text{NaBH}_4}$ 23

$\xrightarrow{\text{Hg(OAc)}_2, \text{NaCl, H}_2\text{O}}$ 26

$\xrightarrow{\text{c. H}_2\text{SO}_4}$ 26

$\xrightarrow{\text{Raney Ni}}$ 26

$\xrightarrow{\text{HCO}_3\text{H}}$ 26

$\xrightarrow{\text{Br}_2, \text{H}_2\text{O}}$ 26
is readily available in quantity from Meerwein's tetraester (4) and has been converted to oxaadamantanes by a number of routes including oxymercuration\(^3_4,3_5\), sulphuric acid hydrolysis\(^3_4\), reaction with aqueous bromine or potassium triiodide\(^3_5,3_6\), or peracid oxidation\(^3_6\) (Scheme 8).

Dione (10) and its monomethylene relative (27) may both be prepared from 1,3-dihaloadamantanes\(^3_7,3_8\) (Scheme 9) and provide potentially useful routes to simple oxaadamantanes. Reduction of 10 with hydrogen - Raney Nickel\(^3_9\) or sodium borohydride\(^4_0\), for example, gave the cyclised hemiketal (29) which cannot undergo further reduction. Removal of the hydroxyl group of 29 by successive treatment with thionyl bromide and hydrogen - Raney Nickel\(^3_9\) (Scheme 10) proceeded without ring-opening to furnish the parent ether (23). Reaction of 29 with 60% aqueous hydrogen bromide, on the other hand yielded\(^4_0\) the bicyclic bromoketone 30 which recyclised to 23 on reduction with NaBH\(_4\) or LiAlH\(_4\).

Instead of forming the expected bisenamine (31), dione (10) condensed\(^4_1\) with pyrrolidine to produce 32 (Scheme 11). This demonstrates the ease of ring-closure to produce oxaadamantane species. Diamines of this type are of low stability however and rapidly decompose on heating to the ring-opened ketoenamine (33).

Reduction of 10 with LiAlH\(_4\) in the presence of primary amines affords a useful route to 1-amino-2-oxaadamantane\(^3_8,4_2\). In particular this reaction is a key step in the synthesis\(^4_2\) (Scheme 12) of the oxaadamantyl urea (34) which exhibits strong hypoglycemic properties.
Scheme 9

\[
\begin{align*}
X &= \text{Cl or Br} \\
X &= \text{Cl or Br} \\
X &= \text{Cl or Br}
\end{align*}
\]

Scheme 10

10 Raney Ni
or NaBH₄

\[
\begin{align*}
\text{SOBr}_2 &\rightarrow 29 \\
\text{Raney Ni} &\rightarrow 23 \\
\text{NaBH}_4 &\text{or LiAlH}_4
\end{align*}
\]

Scheme 11

\[
\begin{align*}
\text{C}_4\text{H}_8\text{NH} &\rightarrow 32 \\
\Delta &\rightarrow 33
\end{align*}
\]

Scheme 12

\[
\begin{align*}
10 &\text{PhCH}_2\text{NH} \\
\text{LiAlH}_4 &\rightarrow 34
\end{align*}
\]
and is of potential use in the treatment of diabetes. The reaction of 10 with Grignard or organolithium reagents provides a potentially useful route to alkyl or aryl hemiketals such as 35 and 36 which may in turn be dehydroxylated as already described.

Ketoalkene (27), which is an intermediate in the preparation of 10 from adamantane (vide supra), has also been converted to oxaadamantanes under a variety of conditions. For example, reduction of 27 with LiAlH₄ (Scheme 13) yields endo-alcohol (37), the stereochemistry of which is ideal for ring-closure under acid conditions to 1-methyl-2-oxaadamantane (38). Moreover, oxymercuration of 27 proceeds with direct cyclisation yielding 39 which may be converted by conventional methods to hemiketal (35) (Scheme 14).

Hydrolysis or alcoholysis of 14, the epoxide derived from 27, has also been shown to occur with simultaneous cyclisation furnishing 40 or 41, while dry hydrogen chloride has been used by Stepanov and co-workers to effect the conversion of 14 to the related chloride (42) (Scheme 15). The same group has more recently studied the reactions of ketoalkene (43) and have prepared oxaadamantanes from it by several methods (Scheme 16).

The acid-catalysed dehydration and rearrangement of diol (28) to oxaadamantane (23) has been reported independently by Shaefer and Honig and by Averina and Zefirov. Although of interest because of the complex nature of the rearrangements observed the reaction is of little synthetic importance due to the low yield of 23 (<10%) and the formation of a large number of coproducts.
Scheme 13

27 \xrightarrow{\text{LiAlH}_4} 37 \xrightarrow{\text{H}^+} 38

Scheme 14

27 \xrightarrow{\text{Hg(OAc)}_2} 39 \xrightarrow{\text{NaBH}_4} 35

Scheme 15

40 \xrightarrow{\text{ROH}} 14 \xrightarrow{\text{dry HCl}} 42
The reaction undoubtedly involves a large number of intra- and intermolecular hydride transfers and accordingly a complete mechanistic description of all processes taking place would be unduly involved. A simplified reaction pathway is however depicted in Scheme 17.

A few oxaadamantanes have been prepared by the oxidation of bicyclic and tricyclic alcohols. Thus 2-hydroxyadamantane \( (44) \) and 3-hydroxybicyclo[3.3.1]nonane \( (45) \) both give \( 23 \) in good yield on treatment with mercuric oxide and iodine under irradiation by a tungsten lamp. While the latter reaction appears to be a relatively simple oxidative coupling, the course of the former is not clearly understood, but has been suggested\(^{50} \) to involve a hypoiodate intermediate which decomposes with loss of carbon monoxide (Scheme 18). Lead tetraacetate - iodine has also been used\(^{51} \) to effect the cyclisation of \( 45 \) to \( 23 \) but treatment of 2-hydroxy-2-methyladamantane \( (46) \) with this reagent has been found\(^{52} \) to give homooxaadamantane \( (47) \) (Scheme 19). Acid hydrolysis of \( 47 \) induces ring contraction with deiodination yielding a useful route to 1-acetyl-2-oxaadamantane \( (48) \).

**Dioxaadamantanes**

Two possible isomeric dioxaadamantanes are possible (Table 1) and although derivatives of both are known, only one parent, 2,6-dioxaadamantane \( (49) \) has been isolated (vide infra). In general, \( 49 \) and its derivatives are most readily synthesised from cyclooctadienes and cyclooctatetraenes. For example, oxymercuration of cycloocta-1,5-diene \( (50) \) followed by sodium iodide work-up and
Scheme 18

\[ \text{HOH} \xrightarrow{I_2, HgO \text{ hv}} [\text{hydroxy compound}] \xrightarrow{} 23 \xleftarrow{I_2, HgO \text{ hv}} \text{OH} \]

Scheme 19

\[ \text{OH} \xrightarrow{\text{CH}_3 \ Pbi(OAc)_4 \ I_2} \xrightarrow{\text{DMF}} \text{COCH}_3 \]

Scheme 20

\[ \text{Hg(OAc)}_2 \xrightarrow{\text{NaI}} \text{HgI} \xrightarrow{I_2} \text{I} \xrightarrow{\text{KOH}} \text{52} \xrightarrow{\text{Hg(OAc)}_2 \ NaI} \]

\[ \text{cat. H}_2 \xrightarrow{} \text{53} \xrightarrow{I_2} \]

\[ \text{I}_9 \text{Hg} \xrightarrow{} \text{51} \xrightarrow{} \]

\[ \text{50} \xrightarrow{} \text{51} \xrightarrow{} \text{52} \xrightarrow{} \text{53} \]
iodine cleavage of the organomercury complex formed gave diiodoether (51). Dehydroiodination of 51 yielded the versatile bicyclic diene (52) which by repeating the oxymercuration sequence was cyclised to diiodide (53). Catalytic reduction of 53 furnished the parent diether (49) in excellent overall yield (Scheme 20).

In a more recent, but closely related study, 52 has been converted to dichloride (54) and dibromide (55) by reaction with N-chloro- and N-bromosuccinimide respectively while diol (56) has been obtained by the oxidation of 52 with performic acid (Scheme 21). About the same time, 55 was reported to be formed by the oxidation of dibromodiene (57) with sodium dichromate in HMPT.

One of the earliest reported dioxaadamantanes was produced from a substituted cyclooctatetraene. Thus 58, readily obtained from ethoxyacetylene (Scheme 22), was converted to 1,3,5,7-tetraethoxy-2,6-dioxaadamantane (59) by the action of absolute ethanol containing a little hydrochloric acid. The analogous tetramethoxy compound (60) was also prepared and the crystal and molecular structure of this compound has been studied by x-ray diffraction.

Although 2,4-dioxaadamantane (61) has not been prepared, its 3-methyl derivative (64) has been synthesised from the substituted resorcinol (62) as shown in Scheme 23. After protection of the carbonyl group by ketalisation, catalytic reduction of the aromatic system gave 1,3-dihydroxycyclohexane (63). Treatment of 63 with dilute mineral acid promoted the one-step deprotection and ring-closure to dioxaadamantane (64).
Scheme 21

\[
\text{HO} \quad \begin{array}{c}
\text{56} \\
\text{OH}
\end{array} \xleftarrow{\text{HCO}_2\text{H}} \quad \begin{array}{c}
\text{52} \\
\rightarrow
\end{array} \quad \begin{array}{c}
\text{X} \\
\text{O}
\end{array} \xrightarrow{\text{NCS or NBS}} \quad \begin{array}{c}
\text{54} \\
\text{X} = \text{Cl}
\end{array} \quad \begin{array}{c}
\text{55} \\
\text{X} = \text{Br}
\end{array} \quad \begin{array}{c}
\text{57}
\end{array}
\]

Scheme 22

\[
\text{HC} \equiv \text{CO}_2\text{H} \quad \xrightarrow{\text{Na, liq.NH}_3} \quad \begin{array}{c}
\text{58} \\
\text{OC}_2\text{H}_5
\end{array} \xrightarrow{\text{H}^+ \text{C}_2\text{H}_5\text{OH}} \quad \begin{array}{c}
\text{59} \\
\text{OC}_2\text{H}_5
\end{array}
\]

Scheme 23

\[
\begin{array}{c}
\text{62} \\
\text{HO} \quad \text{H}_2\text{O}
\end{array} \xrightarrow{\text{[CH}_2\text{OH}]_2} \quad \begin{array}{c}
\text{63} \\
\text{HO} \quad \text{H}_2\text{O}
\end{array} \xrightarrow{\text{cat. H}_2} \quad \begin{array}{c}
\text{64} \\
\text{CH}_3
\end{array}
\]
Miscellaneous Higher Polyoxaadamantanes

Derivatives of all three trioxaadamantanes (65, 66, and 67) have been prepared by Stetter, but only in one case has the parent compound been isolated, 2,4,10-trioxadamantane (67) being synthesised\(^ {59,60}\) in 75\% yield by the condensation of \(\text{68}\) with ethyl or methyl orthoformate (Scheme 24). Construction of the 2,4,9-trioxadamantane (66) nucleus generally involves an intermediate of the form \(\text{RC(CH\(_2\)COR\(_1\))}\) and is illustrated by the synthesis\(^ {61}\) of alcohol (72) (Scheme 25). Thus triallylcarbinol (69), prepared from ethyl chloroformate and allylmagnesium chloride, was cleaved with ozone to give trialdehyde (70). Cyclisation of 70 was accomplished by conversion to triacetal (71) which reverted to 72 on standing at room temperature in acetic acid. Interestingly, none of the above trioxaadamantanes, which embody acetal or orthoester functional groups, show any tendency to exist as non-tricyclic carbonyl forms even at elevated temperatures. Moreover they do not react with Grignard or organolithium reagents underlining the high stability of the adamantane framework.

The preparation of a 2,4,6-trioxadamantane (65) derivative was accomplished by Stetter\(^ {62}\) by the elegant synthetic pathway depicted in Scheme 26. Using classical methods, Stetter obtained diol (73) which on acid hydrolysis to the free dihydroxydione (74), spontaneously cyclised to 3,5-dimethyl-2,4,6-trioxadamantane (76). The precise mode of cyclisation of 74 is unclear but most probably involves the intermediate formation of tetrahydropyran (75).
Scheme 24

\[
\begin{align*}
\text{cat. H}_2 & \quad \text{Scheme 24} \\
\text{HO} & \quad \text{HO}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 25} \\
\text{CH}_2=\text{CHCH}_2\text{MgBr} & \quad \text{Cl} \text{CO}_2\text{C}_2\text{H}_5 \\
\text{O}_3 & \quad \text{(CH}_2=\text{CHCH}_2)_3\text{COH} \\
\text{CH}_3\text{OH} & \quad \text{CaCl}_2
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 26} \\
\text{base} & \quad \text{NaBH}_4 \\
\text{H}^+ & \quad \text{H}^+
\end{align*}
\]
Polysubstituted 2,4,6,8-tetraoxadamantanes such as 77 have been prepared by dimerization of \( \beta \)-ketoaldehydes of the type \( \text{R'CO}_2\text{CHO} \) under the influence of boron trifluoride etherate, cyclisation occurring by a similar mechanism to that already described for trioxadamantanes (Scheme 27).

2-Thiaadamantane (78)

Sulphur, like oxygen, may take the place of the methylene groups in the adamantane molecule. The simplest thioether produced in this way, 2-thiaadamantane (78) is the only naturally occurring simple heteroadamantane and was first isolated as a sweet smelling solid, m.p. 320\(^\circ\), from the kerosene fraction of petroleum obtained from the Agha Jari field of Southern Iran.

Synthetic entry into the 2-thiaadamantane system has thus far been restricted to the reaction of bicyclo[3.3.1]nona-2,6-dienes with sulphur dichloride. The corresponding sulphoxides and sulphones may also be prepared directly by reaction of these dienes with thionyl chloride, \( \text{SOCl}_2 \), and sulphuryl chloride, \( \text{SO}_2\text{Cl}_2 \), respectively. Several variations of the procedure have been used by Stetter and co-workers for the synthesis of a number of 2-thiaadamantanes including the parent compound (78). Thus dione (79) was converted to its bisenamine (7) which reacted with \( \text{SCl}_2 \) to give the useful dione (80). Wolff-Kishner reduction of 80 which has been converted to a variety of other derivatives provided the first laboratory synthesis of 78 (Scheme 28). Alternatively, 78 has been prepared by LiAlH\(_4\) reduction of 4,8-dichloro-2-thiaadamantane (81) which was obtained by the condensation of \( \text{SCl}_2 \) with diene (26).
Scheme 27

\[
\begin{align*}
\text{R} & \quad \text{BF}_3 \\
\text{Et}_2\text{O} & \quad \rightarrow \\
\text{R} & \quad \text{R'} \\
\text{R} & \quad \text{R'} \\
\text{R} & \quad \text{R'} \\
\end{align*}
\]

77 \quad R = \text{CH}_3, R' = \text{C}_6\text{H}_5

Scheme 28

79 \quad \xrightarrow{\text{C}_4\text{H}_6\text{NH}} 7 \quad \xrightarrow{\text{SCl}_2} 80 \quad \xrightarrow{\text{KOH}, \text{N}_2\text{H}_4} 78

26 \quad \xrightarrow{\text{SCl}_2} 81
A novel thiaadamantane, which does not have a direct counterpart in the oxaadamantane field is the 1-thiaadamantane cation (83). This species has been prepared as the bromide salt by the treatment\(^72\) of mercaptan (82) with sodium carbonate (Scheme 29), but as yet has received little further attention.

**Dithiaadamantanes**

Only one example of each of the two isomeric dithiaadamantanes is known. The addition of sulphur dichloride to cyclooctatetraene has been shown\(^73,74\) to proceed in two stages (Scheme 30). The initial 1:1 adduct, which may be isolated as an unstable solid is bisallylic chloride (84). In the presence of excess \(\text{SCl}_2\), however, this compound reacts further to produce highly crystalline tetrachlorodithiaadamantane (85). The structure of the product has been distinguished from the isomeric dithiatwistane (86) by p.m.r. spectroscopy\(^74\) and by oxidation of the product to the corresponding disulphoxide (Scheme 31). By virtue of its symmetry 85 can produce only one enantiomeric disulphoxide (87) whereas 86 may produce two (88 and 89). Isolation of only one disulphoxide confirmed the dithiaadamantane skeleton. Further structural proof was obtained from an independent x-ray crystallographic examination\(^75\) of the product.

By virtue of its exceptional crystallinity 2,4-dithiaadamantane (91) was obtained\(^76\) as the only easily separable product of the base catalysed rearrangement of 2-oxa-4,6-dithiaadamantanol (90) (Scheme 32). Obtained in ca 25% yield, 91 was identified by ultraviolet and mass spectroscopy and by a complete analysis of its p.m.r. spectrum.
Scheme 29

\[
\begin{align*}
\text{CH}_2\text{SH} & \quad \text{BrH}_2\text{C} \quad \text{CH}_2\text{Br} \\
& \xrightarrow{\text{Na}_2\text{CO}_3} \\
\text{82} & \quad \text{83}
\end{align*}
\]

Scheme 30

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
& \xrightarrow{1\text{eq. SCl}_2} \\
\text{84} & \quad \text{85}
\end{align*}
\]

Scheme 31

\[
\begin{align*}
\text{85} & \xrightarrow{\text{H}_2\text{O}_2 / \text{CH}_3\text{CO}_2\text{H}} \\
& \equiv \\
\text{86} & \quad \text{88} + \text{89}
\end{align*}
\]
Miscellaneous Higher Polythiaadamantanes

At the present time no synthetically useful routes to trithia- or pentathiaadamantanes have been reported and of the two tetrathiaadamantanes possible, only one system, the 2,4,6,8-isomer (92) and its derivatives have been studied. 92 and its bridgehead substituted derivatives (93) are readily prepared by the action of hydrogen sulphide on \( \beta \)-diketones (Scheme 33). Although this reaction has been known for many years\(^7\), the structure of the dimerised \( \beta \)-dithioketone product was considered to be 94 and it was only relatively recently that the true tetrathiaadamantane formula was established\(^7\).

More recently, the reaction of \( \beta \)-diketones with thiol acids has been reported\(^7\), to yield 2,4,6,8-tetraphthiaadamantanes. However, like the previous reaction, the product mixture was complex and was found to contain significant quantities of pentathiaadamantanes, hexathiaadamantanes (vide infra) and various oxathiaadamantanes making the isolation of products extremely difficult. A much cleaner product was obtained by the use of \( \beta \)-dithioketones.

Functionalisation of unsubstituted bridgehead positions of the 2,4,6,8-tetraphthiaadamantane nucleus has been accomplished by direct metallation using n-butyl lithium. Thus dimethyl derivative (95) forms the dilithium salt (96)\(^8\) in which each negative charge is partly delocalised through sulphur. Addition of D\(_2\)O to this salt produced the dideutero- derivative (97) confirming the nature of the dianion (Scheme 34). Of greater synthetic importance, however, has been the treatment\(^8\) of dimethyltetraphthiaadamantane (98) with n-butyl lithium followed by carbonylation to give carboxylic acid (99) (Scheme 35).
Hexathiaadamantane (100) has been obtained\textsuperscript{82} by the acid-catalysed condensation of formic acid and hydrogen sulphide (Scheme 36), and was found to be practically insoluble in all common solvents. Structural confirmation has been obtained by x-ray diffraction studies\textsuperscript{83} which have in addition revealed a strong interaction between individual molecules of the compound. Due to this interaction, the intermolecular distances between adjacent sulphur atoms are 3.55 Å which is considerably less than the recognised van der Waals diameter of 3.7 Å.

Tetramethylhexathiaadamantane (101) has been obtained by a number of routes including the reactions of zinc chloride with thioacetic acid\textsuperscript{84}, bromine with thioacetic acid\textsuperscript{85} and acetyl chloride with liquid hydrogen sulphide\textsuperscript{86}. Like the tetrathiaadamantanes already discussed, however, the structural assignment of the compound thus produced, remained in error until it was correctly identified as 101 by Fredga\textsuperscript{87} in 1951.

\textbf{Azaadamantane}

Two isomeric azaadamantanes are possible and routes to both have been developed. The synthesis of 1-azaadamantane (102) has received attention from a number of workers, several of whom\textsuperscript{88-91} have followed the same basic strategy (Scheme 37). The starting material for this synthesis, mesitylene, was converted by conventional methods to triester (103) which was reduced in two stages to triol (104). Reaction of 104 with HBr in glacial acetic acid furnished 105 which condensed with ammonia to give 102 in low overall yield.
Scheme 36

\[
\text{HCO}_2\text{H} \xrightarrow{\text{H}_2\text{S, HCl}} \text{C}_6\text{H}_5\text{NO}_2 \rightarrow \begin{array}{c}
\text{100}
\end{array}
\]

Scheme 37

\[
\text{CH}_3
\]

1. \(\text{MnO}_4^-\)
2. Ester

\[
\begin{array}{c}
\text{CO}_2\text{CH}_3
\end{array}
\]

1. cat. \(\text{H}_2\)
2. LiAlH_4

\[
\begin{array}{c}
\text{103}
\end{array}
\]

\[
\begin{array}{c}
\text{CO}_2\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{104}
\end{array}
\]

\[
\begin{array}{c}
\text{H}_2\text{Br}
\end{array}
\]

\[
\begin{array}{c}
\text{glac. } \text{CH}_3\text{CO}_2\text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{105}
\end{array}
\]

\[
\begin{array}{c}
\text{NH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{BrH}_2\text{C}
\end{array}
\]

\[
\begin{array}{c}
\text{102}
\end{array}
\]

Scheme 38

\[
\begin{array}{c}
\text{BrCO}_2\text{Et}
\end{array}
\]

\[
\begin{array}{c}
\text{102}
\end{array}
\]

\[
\begin{array}{c}
\text{HCl}
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3\text{CO}_2\text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{102}
\end{array}
\]

\[
\begin{array}{c}
\text{R} = \text{CH}_3\text{CH} = \text{SO}_2
\end{array}
\]

\[
\begin{array}{c}
\text{102}
\end{array}
\]

\[
\begin{array}{c}
\text{R} = \text{CH}_3\text{O} = \text{SO}_2
\end{array}
\]
An alternative synthesis of 102 which has been recently reported by Speckamp et al.\(^92\) is outlined in Scheme 38. An important aspect of this reaction sequence is the presence of a carbonyl group in azabicyclononane (106). While elimination of this group leads to the preparation of the parent amine (102), its retention and modification allow the synthesis of a number of C(4) functionalised derivatives such as 107 and 108\(^93\).

2-azaadamantane (109) and its derivatives have been synthesised from bicyclo[3.3.1]nonanes employing reactions similar to those used for the preparation of 2-oxaadamantanes. For example, 109 was formed\(^39\) from dione (10) by the reaction sequence shown in Scheme 39 (cf the synthesis of 2-oxaadamantane from the same starting material). Similarly, diene (26) which may also be used for the preparation of 2-oxa- and 2-thiaadamantanes, has been converted\(^94\) to 4,8-dibromo-2-azaadamantane (110) by reaction with N,N-dibromo-p-toluenesulphonamide (Scheme 39). Catalytic reduction of 110 followed by treatment with sodium in liquid ammonia provided a convenient synthesis of 109.

2-azaadamantanes have been prepared from dione (79) by the reaction sequence shown in Scheme 40\(^95\). \(\alpha\)-Bromination of 79 with pyridine hydrobromide perbromide yielded a mixture of mono- and dibromodiketones (111 and 112) and reaction of the latter with ammonia or methylamine gave diketoazaadamantanes (113). This is a particularly attractive synthetic route to 2-azaadamantanes because of the availability of 79, the simplicity of the reactions involved and the presence of carbonyl groups at C(4) and C(8) of the product which allows facile modification of functionality.
Scheme 39

10

\[ \text{NH}_3 \quad \text{H}_2, \text{Pt} \]

\[ \text{R} = \text{CH}_3\text{-SO}_2 \]

26

\[ \text{RNBr}_2 \]

\[ \text{Raney Ni} \]

109

Scheme 40

79

\[ \text{C}_5\text{H}_5\text{N.HBr} \]

\[ \text{Br}_2 \]

112

\[ \text{RNH}_2 \]

113

\[ \text{R} = \text{Hor CH}_3 \]
**Diazaadamantanes**

Five isomers of diazaadamantane are possible and are shown in Table 2. However, only two of these, the 1,3- and 2,6-isomers (114 and 115) have been synthesised. The principal route to 1,3-diazaadamantanes, which are of interest due to their extreme toxicity, is the condensation of bispidine (116) with aldehydes or ketones (Scheme 41) and this approach was used (with formaldehyde as the carbonyl species) in two independent syntheses of the parent diamine (114) in 1955. An interesting feature of this reaction is that it is reversible, enabling one diazaadamantane to be converted to another by treatment with an aldehyde or ketone.

The synthesis of 2,6-diazaadamantanes has been reported by several authors including Stetter, Portmann and Ganter and Dupeyre and Rassat. The approach adopted by Stetter was essentially analogous to that used for the preparation of dioxaadamantanes (vide supra) and utilised cycloocta-1,5-diene (50) as starting material. Electrophilic addition of N,N-dibromo-p-toluenesulphonamide across the double bonds of 50 yielded 2,6-dibromo-9-azabicyclo[3.3.1]nonane (117) which was dehydrobrominated with quinoline at 215° to produce diene (118) (Scheme 42). Addition of the same dibromosulphonamide to this diene yielded 2,6-diazaadamantane (119) which was converted to the parent diamine (115) by catalytic reduction followed by detosylation with sodium in liquid ammonia.
<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>1.2-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>1.3-</td>
<td>114</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>1.4-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image4" alt="Structure" /></td>
<td>2.4-</td>
<td>-</td>
</tr>
<tr>
<td><img src="image5" alt="Structure" /></td>
<td>2.6-</td>
<td>115</td>
</tr>
</tbody>
</table>
Scheme 41

\[
\begin{align*}
\text{116} & \quad \xrightarrow{R^1R^2CO} \quad \text{R}^1\text{R}^2\text{CO} \\
& \quad \xrightarrow{R^3R^4\text{CO}} \quad \text{R}^1\text{R}^2\text{CO} \\
& \quad \text{R}^1,\text{R}^2,\text{R}^3,\text{R}^4 = \text{H or Alkyl}
\end{align*}
\]

Scheme 42

\[
\begin{align*}
\text{50} & \quad \xrightarrow{\text{RNBr}_2} \quad \text{RNBr} \\
\text{117} & \quad \xrightarrow{215^\circ} \quad \text{118} \\
\text{115} & \quad \xrightarrow{\text{Raney Ni}} \quad \text{119}
\end{align*}
\]

R = CH₃-SO₂

Scheme 43

\[
\begin{align*}
\text{120} & \quad \text{R} = \text{C}_6\text{H}_5\text{SO}_2 \\
\text{121} & \quad \text{R} = \text{CHO} \\
\text{122} & \quad \text{R} = \text{C}_6\text{H}_5\text{SO}_2 \\
\text{123} & \quad \text{R} = \text{CHO}
\end{align*}
\]
Following a related sequence (Scheme 43), Portmann and Ganter have also synthesised a number of 4,8-disubstituted 2,6-diazaadamantanes. In their approach, entry into the diazaadamantane system was gained by the condensation of a primary amine (methylamine) with diepoxides (120 and 121). By virtue of their functionality at C(4) and C(8), the products of these condensations, diols (122 and 123) are particularly suitable as precursors for the synthesis of a number of diazaadamantanes which have potential pharmaceutical application.

Dupeyre and Rassat produced 115 by the reaction pathway illustrated in Scheme 44. The Mannich condensation of methylamine, glutaraldehyde and acetone dicarboxylic acid yielded the pseudo-pelletierine derivative (124). This compound possesses a carbonyl group at C(3) which enabled the facile introduction of a second nitrogen atom into the molecule by reductive amination. Thus, in the presence of benzylamine, 3α-benzylamino-9-methylgranatinine (125) was obtained as the exclusive product. N-bromination of 125 followed by ring-closure with concentrated sulphuric acid (Hofmann-Löffler-Freytag reaction) furnished 2,6-diazaadamantane (126) in 25% yield. 126 was converted by conventional methods to a number of other 2,6-diazaadamantanes including the parent compound (115).

Miscellaneous Higher Polyazaadamantanes

Of the many possible polyazaadamantanes containing three or more skeletal nitrogen atoms, derivatives of only three, 1,3,5-triazaadamantane (127), 2,4,10-triazaadamantane (135) and 1,3,5,7-tetraazaadamantane (138) are known.
Scheme 44

\[
\begin{align*}
&\text{CH}_3\text{NH}_2 + \text{OHC(CH}_2\text{)}_3\text{CHO} + \text{HO}_2\text{CCH}_2\text{COCH}_2\text{CO}_2\text{H} \\
&\text{CH}_3\text{N}\\n&\text{124} \quad \text{RaneyNi} \\
&\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2 \quad \text{NHCH}_2\text{C}_6\text{H}_5 \\
&\text{125} \\
&\text{Br}_2 \quad \text{c. H}_2\text{SO}_4 \\
&\text{Br} \\
&\text{126} \\
&\text{H}_2 / \text{Pd/C} \\
&\text{N} \\
&\text{127} \quad \text{KMnO}_4 \quad \text{OH}^- \\
&\text{135} \\
&\text{138}
\end{align*}
\]
7-methyltriazaadamantane (128) has been prepared\(^{102}\) by the route shown in Scheme 45. This reaction proceeds equally well with a variety of aldehydes and has been used\(^{103}\) to produce 2,4,9-trisubstituted derivatives such as 129. The 7-nitroderivative (130) has been obtained\(^{103}\) by a related approach (Scheme 46) and by the more convenient condensation\(^{104}\) of nitromethane with formaldehyde in the presence of ammonium acetate. Lithium aluminium hydride reduction of 130 gave 7-amino-1,3,5-triazadaman-tane (131). In general, compounds of this type are relatively delicate species and are readily ring-opened to bicyclic or simpler products. For example, 130 and 131 react\(^{105}\) with acetic anhydride to give 1,3,7-triazabicyclo[3.3.1]nonanes (132 and 133) while 129 is rapidly cleaved\(^{103}\) by aqueous ferrous ion to produce complexes of 134.

2,4,10-triazaadamantanes (136 and 137) have been synthesised\(^{106}\) from 1,3,5-trinitrobenzene (Scheme 47) by a route similar to that used for the preparation of the corresponding trioxaadamantane system (vide supra). No attempt was made however to convert either 136 or 137 into the parent compound (135).

This review would be incomplete without a final mention of the ultimate condensation product of ammonia and formaldehyde, 1,3,5,7-tetrazaadamantane (138). Commonly known as hexamethylenetetramine or urotropine, 138 has been known\(^{107}\) since 1895 and is of historic interest as the first compound to be correctly identified as having an adamantanoïd structure. This ring system is however rather unstable and, like triazaadamantanes, readily reacts in the presence of acetic anhydride or mineral acids, with the formation of ring-opened products, a property which severely limits its synthetic importance.
Scheme 45

\[ \text{CH}_3\text{C(CH}_2\text{OH)}_3 \xrightarrow{\text{PBr}_3} \text{CH}_3\text{C(CH}_2\text{Br)}_3 \xrightarrow{1. \text{K(Phth)}} \xrightarrow{2. \text{H}_3\text{O}^+} \text{CH}_3\text{C(CH}_2\text{NH}_2)_3 \]

\[ \text{CH}_2\text{O} \xrightarrow{\text{Phth}} \]

\[ \text{Phth} = \begin{array}{c} \\
\end{array} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{V} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{Py} \]

\[ \text{Py} \]

\[ \text{Py} \]

\[ \text{Py} \]

\[ \text{Py} = 2\text{-pyridyl} \]

Scheme 46

\[ \text{O}_2\text{NC(CH}_2\text{OH)}_3 \xrightarrow{\text{NH}_4\text{OAc}} \xrightarrow{\text{CH}_2\text{O}} \text{CH}_3\text{NO}_2 \]

\[ \text{CH}_3\text{CON} \xrightarrow{\text{LiAlH}_4} \xrightarrow{\text{Ac}_2\text{O}} \text{CH}_3\text{CON} \]

\[ \text{NHCOCH}_3 \]

\[ \text{CH}_3\text{CON} \]

\[ \text{CH}_3\text{CON} \]

\[ \text{CH}_3\text{CON} \]

\[ \text{CH}_3\text{C(CH}_2\text{N=CH} \text{N)}_3 \]
Scheme 47

\[
\text{Scheme 47}
\]

\[
\begin{align*}
&\text{NO}_2 \quad \text{NO}_2 \\
\text{H}_2/\text{Pd} \quad \text{Ac}_2\text{O} \\
\text{R}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
&\text{RHN} \quad \text{NHR} \\
\text{R} = \text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{Ts} = \text{CH}_3-\text{SO}_2
\end{align*}
\]

\[
\begin{align*}
&\text{H}_2/\text{Ni} \\
&\text{HCl(OC}_2\text{H}_5\text{)}_3 \\
&\text{H}^+ \\
\end{align*}
\]

\[
\begin{align*}
&\text{Ts}\text{H} \quad \text{N} \quad \text{Ts} \quad \text{Ts} \\
&\text{N} \quad \text{Ts} \quad \text{Ts} \\
&\text{TsH} \quad \text{N} \quad \text{Ts} \\
&\text{H}_2\text{N} \quad \text{NH}_2 \\
&\text{X} \quad \text{1} \\
\end{align*}
\]

\[
\begin{align*}
&\text{TsCl} \\
&\text{HC(OC}_2\text{H}_5\text{)}_3 \\
&\text{H}^+ \\
&\text{137} \\
&\text{136}
\end{align*}
\]
Part Two

The Acetylation of Bicyclo[3.3.1]nonan-2,6-diones — a Novel Route to Adamantanes and Heteroadamantanes
INTRODUCTION

In recent years, considerable effort has been directed towards the preparation and study of organo-sulphur compounds and to their applications as intermediates in chemical synthesis. A class of compounds which has been shown to have particular synthetic utility is that of the $\beta$-ketosulphoxides, $\text{RCOCH}_2\text{SOCH}_3$, which may be readily prepared in high yields by the condensation of dimethyl sulphoxide with esters under basic conditions (Scheme 48). The conversion of such intermediates into a variety of products including methyl ketones, $\alpha$-keto aldehydes, $\alpha$-keto esters and glycols (Scheme 49) has been reviewed by Russell and Ochrymowycz. More complex $\beta$-keto sulphoxides which have also attracted attention as synthetic intermediates are often most conveniently prepared by selective oxidation of the corresponding sulphide.

The photochemical behaviour of saturated aliphatic and bicyclic $\beta$-keto sulphoxides has been investigated by Ganter and Moser. Of particular relevance to the present work was a study of the photolysis of the epimeric bicyclic sulphoxides (139 and 140). During short-period irradiations (2 to 8 hr) of dioxan solutions of 139 and 140 using a 0.9 watt low pressure mercury lamp ($\lambda$ 2537\AA) photostereomutation (light-induced inversion of configuration) of the sulphoxide grouping was found to be the predominant reaction. Longer irradiation (16 hr), on the other hand, of either compound, resulted in the formation of an additional desulphurised rearrangement product in approximately 30% yield. This moderately photostable product was identified as 1-hydroxy-9-oxabicyclo[3.3.1]nonan-4-one (142), the formation of which was explained by an initial $C_\alpha$-S cleavage, a subsequent transannular proton shift forming sulphine (141), and a final spontaneous loss of sulphur to give the observed product (Scheme 50).
Scheme 48

\[
\begin{align*}
\text{CH}_3\text{SOCH}_3 & \xrightarrow{\text{KOBu}^-} -\text{CH}_2\text{SOCH}_3 & \text{RCO}_2\text{R}' & \rightarrow \text{RCOCH}_2\text{SOCH}_3 \\
\end{align*}
\]

Scheme 49

\[
\begin{align*}
\text{RCOCHO} & \xrightarrow{\text{Cu(0Ac)}_2} \text{RCOCHSCH}_3 & \xrightarrow{\text{NaBH}_4} \text{RCHCH}_2\text{OH} \\
\text{RCOCH}_3 & \xrightarrow{\text{Zn}} \text{RCOCH}_2\text{SOCH}_3 & \xrightarrow{1. \text{NaH} \ 2. \text{Br}_2} \text{RCOCHSOCH}_3 \\
\text{RCO}_2\text{R}' & \xrightarrow{\text{R'OH}} \text{RCOCO}_2\text{R}' \\
\end{align*}
\]

Scheme 50

\[
\begin{align*}
\text{139} & \xrightarrow{2-8 \text{ hr} \text{ hv dioxan}} \text{139} \\
\text{140} & \xrightarrow{18 \text{ hr} \text{ hv}} \text{141} \\
\text{141} & \rightarrow \text{142} \\
\end{align*}
\]
The same authors had previously studied the photolytic rearrangement of the related β-keto sulphides, \((143\text{ and }144)\), and had shown that in this case products arose from ketene intermediates formed by an initial C(1)-C(2) bond cleavage (α-cleavage). Thus in a non-nucleophilic solvent such as benzene, irradiation of \(143\) gave lactone \((145)\), while in methanolic solution, the monocyclic ester \((146)\) was the main product. Analogously ester \((144)\) gave, in methanol, the ring-opened compound \((147)\) (Scheme 51).

As part of a more general photochemical study, the reactivities of some ketones in the 9-thiabicyclo[3.3.1]nonane field have been investigated by Padwa and Battisti\(^{113}\). In addition to the expected ring-opened product \((149)\) these authors have observed the formation of the skeletally rearranged product \((150)\), during the photolysis of 9-thiabicyclo[3.3.1]nonan-2-one \((148)\) (Scheme 52) and have suggested that intramolecular charge transfer between lone pairs on sulphur and the neighbouring carbonyl group is one of the principal factors controlling the course of this reaction. Similarly, the rearrangement of the unsaturated ketone \((151)\) to the strained 2-thiabicyclo[6.1.0]nonane derivative \((152)\) was also considered to proceed via the formation of a zwitterionic excited state (Scheme 53).

A cognate charge transfer interaction has been reported by Mellor and Webb\(^{114}\) to occur both in the ground state and in an excited electronic state of the more complex bisenone \((153)\), and has been recognised as being of primary importance during the photorearrangement of that compound to the 2-thiabicyclo[3.3.1]nonane derivative \((154)\) (Scheme 54). This observation is supported by the striking contrast in rearrangement behaviour between \(153\) and its 9-methano analogue \((155)\). While \(155\)
Scheme 53

\[ \text{151} \xrightarrow{hv} \text{152} \]

Scheme 54

\[ \text{153} \xrightarrow{hv} \text{154} \]

\[ \text{155} \]
has been shown to rearrange only by [1,5] and [1,2] sigmatropic rearrangements, no such reactions have been observed during the photolysis of 153, the formation of 154 being explained instead by a [1,3] sigmatropic shift.

**DISCUSSION**

An interesting extension of the work of Mellor which had become apparent and which had prompted the subsequently described work, was an investigation into the photolytic behaviour of 9-thiabicyclo[3.3.1]-nonan-3,7-dien-2,6-dione-9-oxide (156) and the related sulphone (157). Oxidation of the sulphur bridge of 153 to the corresponding sulphoxide and sulphone functions has the effect of involving the formerly non-bonding S-electrons in the formation of sulphur-oxygen covalent bonds. The availability of these electrons for intramolecular charge transfer to nearby unsaturated chromophores may therefore be expected to be diminished or, in the case of 157, completely nullified. In the absence of any other complicating factors, the photochemical rearrangement of 157 may therefore be expected to be reflective of the alicyclic bisenone (155), while sulphoxide (156) may be expected to exhibit properties intermediate between 155 and 153.

An additional reaction mode, however, becomes increasingly more plausible due to the improved leaving group ability of the SO and SO functions. The possible consequences of this reaction pathway, a photo-induced extrusion of sulphur monoxide from 156 or sulphur dioxide from 157 to produce the unsaturated diradical (158), has aroused some interest. Of the various ways in which the undoubtedly labile 158 might rearrange to achieve stability, the most likely method was considered to be by transannular radical coupling creating the
Scheme 55

156 or 157 $\xrightarrow{hv}$ -SO or SO$_2$

156 $x = SO$
157 $x = SO_2$

158

159

160
unsaturated bicyclooctandiones (159 and/or 160) (Scheme 55). In order to test these ideas 156 and 157, which had not previously appeared in the literature, had first to be synthesised.

The most convenient preparation of these compounds is by the oxidation of the corresponding sulphide (153), using respectively one and two equivalents of m-chloroperbenzoic acid. Of the two syntheses of 153 hitherto reported in the literature (Scheme 56) that of Raphael et al was the more attractive due to the use of a less expensive starting material, the greater stability and ease of purification of intermediates and, above all, a higher overall yield of product.

The starting material for the synthesis of 153 is E,E-cycloocta-1,5-diene (50). As normally supplied, 50 possesses a faint yellow colour which darkens on standing but which may be removed by distillation, if desired. In practice, distillation was not normally required since the presence of small amounts of impurities did not significantly affect the yield or quality of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane (161) prepared from it. Dichloride (161) was prepared by the simultaneous dropwise addition of 50 and an equimolar quantity of freshly distilled sulphur dichloride into excess methylene chloride, a modification of the procedure adopted by Weil. The technique of simultaneous dropwise addition is employed such that at any given instant, the concentration of either reactant is extremely low. This has the twofold advantage of slowing down the overall reaction rate, thereby aiding in the dissipation of evolved heat, and reducing the amount of polymeric by-products formed since the chance encounter of one molecule of cyclooctadiene with more than one molecule of sulphur dichloride is extremely unlikely.
An interesting feature of this condensation reaction is that dichloride (161) is produced completely unaccompanied by any isomeric 2,5-dichloro-9-thiabicyclo[4.2.1]nonane (162), reflecting the greater thermodynamic stability of the more symmetrical [3.3.1] framework. The high yield and stereospecificity of this condensation makes it an extremely attractive starting point for the preparation of other 9-thiabicyclo-[3.3.1]nonane derivatives (compare, for example, the condensation of cycloocta-1,5-diene diepoxide (163) with sodium sulphide which produces a mixture of skeletal isomers).

Dichloride (161) was hydrolysed in 86% yield by sodium hydroxide in dimethoxyethane to 2,6-dihydroxy-9-thiabicyclo[3.3.1]nonane (164). The cream-coloured amorphous product which precipitated during removal of solvent was recrystallised from methanol-ethyl acetate to give colourless prisms which melted over a rather wide range viz 235-240° (lit 241-242°) but which appeared spectroscopically to be of high purity.

Oxidation of diol (164)

Selective oxidation of 164 to 9-thiabicyclo[3.3.1]nonan-2,6-dione (165) was most conveniently accomplished by the use of chromium trioxide-pyridine complex (CrO₃·2C₅H₅N) employing a modified Collins procedure. Thus 165 was prepared in 39% yield by treating 164 with 6 molar equivalent of freshly prepared complex in methylene chloride. The crude product, containing mainly 165, together with a little (<5%) incompletely oxidised material, was recrystallised to give pure dione (165) which melted sharply at 141-142°C in concurrence with the literature value, and whose structure was verified by infrared and p.m.r. spectroscopy.

Of the four steps involved in preparing bisenone sulphide (153) starting
from cycloocta-1,5-diene, the oxidation of 164 to 165 proved to be the most troublesome and inefficient. While Raphael and coworkers\textsuperscript{117} have reported their yield for this reaction to be 65\%, several attempts to emulate their results gave, on average, recoveries of dione (165) no better than 40\%. Best yields were consistently obtained on small scale preparations, while batches of 20 g or more gave disappointingly low recoveries. In addition, an increase in the scale of the reaction was found to increase the proportions of partially oxidised material and starting diol (164) in the isolated product.

It was felt that a major contributory factor to poor recoveries in large scale oxidation attempts, was the inadequacy of the overhead electric stirring employed during the addition of 164 to the reaction vessel. As a more efficient stirring mechanism was not available, a chemical solution to the problem was sought.

As the problem seemed to lie in the formation of insoluble chromium complexes, it was decided to reduce the chromium trioxide:substrate molar ratio from 6:1 to 3:1. In the event, this resulted in no significant change in overall reaction yields. It did however have the undesirable effect of increasing the quantities of unreacted and partially reacted materials in the final product, such that crystallisation of dione (165) became more difficult. The mixture was nevertheless found to be readily separable into its components by the use of column chromatography, giving 165 in 22\% yield, hydroxy-ketone (143)\textsuperscript{112}, 7.5\%, and unreacted diol (164), 8.4\%.

The identity of 6-hydroxy-9-thiabicyclo[3.3.1]nonan-2-one (143) was
confirmed by its melting point (184-186°) and infrared spectrum (KBr) which showed a diagnostic O-H stretching vibration at 3404 cm\(^{-1}\) accompanied by a strong carbonyl absorption at 1686 cm\(^{-1}\) in good agreement with the literature values. The rather complex p.m.r. spectrum of the product in d\(_6\)-DMSO solution could not be used for an unambiguous structural ratification, but did possess a one-proton OH doublet (J=4Hz) at 3.511 coupled to a complex H-C=O resonance at 3.92.

More useful was the product's mass spectrum which showed a parent ion at m/e 172, corresponding to the formula, C\(_8\)H\(_{12}\)O\(_2\)S, accompanied by daughter ions at m/e 154 (M\(^+\)-H\(_2\)O), 139 (M\(^+\)-SH) and 126 (M\(^+\)-H\(_2\)O-CO).

It was clear that a reduction in the oxidant:substrate ratio did not offer any advantage over the original procedure. Moreover, an increase in the ratio to 12:1 was also found to have no marked advantage over the existing method.

These modifications of the Collins procedure having proved ineffective, several alternative methods of oxidising were attempted. The well known Jones oxidation procedure using chromium trioxide in acetone is unsuitable in this instance due to the vulnerability of the sulphur bridge to oxidation under these conditions, and prompted the examination of milder techniques.

The first procedure investigated was a modification of the efficient and widely used Pfitzner-Moffat oxidation which has been developed by Albright and Goldman and which employs a mixture of acetic anhydride and dimethyl sulphoxide as the oxidising species. The mechanism of the reaction is still not fully understood but is believed to proceed by an initial nucleophilic attack by dimethyl
sulphoxide on acetic anhydride, with displacement of acetate forming the reactive sulphonium intermediate (166) (Scheme 57). This species reacts with an alcohol molecule, with elimination of acetic acid giving 167 which deprotonates and dissociates into dimethyl sulphide and product ketone (or aldehyde).

Heating diol (164) to 50° for 72 hr in the presence of acetic anhydride-dimethyl sulfoxide yielded, on extraction of the unpleasantly smelling reaction mixture (reminiscent of rotting vegetable matter), a dark brown syrup-like residue which refused to crystallise from a variety of solvent mixtures. Column chromatography over alumina succeeded only in decolourising the product which at this stage could not be identified with certainty by p.m.r. as a single substance. Distillation of the viscous oil at 0.06 mm Hg gave a major fraction boiling between 140° and 144° which on standing overnight in a refrigerator deposited colourless crystals which melted in the range 97-100°. These crystals were recognised as 2,6-diacetoxy-9-thiabicyclo[3.3.1]nonane (168), (lit. 119 m.p. 100-101°) by comparison of infrared and p.m.r. spectra with those of an authentic sample. A mixed melting point which showed no significant depression confirmed the structural assignment.

Reexamination of the p.m.r. spectrum of the crude product revealed that, in addition to resonances arising from 168, a pair of sharp singlets could be seen at δ2.18 and δ4.70 which integrated almost exactly in the ratio of 3:2. In addition, multiplets at δ2.80 and δ4.17 (1:1) were consistent with bridgehead and H-C-O protons respectively. On this basis, the minor component of the mixture was assigned as either bis(methyl thiomethyl ether) (169) or mono(methyl thiomethyl ether) (170). The mass spectrum of the crude product showed
Scheme 57

\[
\begin{align*}
\text{CH}_3\text{SCH}_3 & \xrightarrow{\text{CH}_3\text{CO}_2^-} \text{CH}_3\text{CH}_3^+\text{SCH}_3^\text{O} \xrightarrow{\text{HOCHR}^1\text{R}^2} \text{CH}_3\text{SCH}_3^\text{O} \xrightarrow{\text{H}^+} \text{CH}_3\text{SCH}_3 + \text{R}^1\text{R}^2\text{C}=\text{O} \\
\text{CH}_2\text{C}=\text{O} & \xrightarrow{\text{4OCOCH}_3} \text{CH}_3\text{SCH}_3^\text{O} \xrightarrow{\text{CH}_3\text{CO}_2^-} \text{CH}_3\text{CH}_3^+\text{SCH}_3^\text{O} \xrightarrow{\text{HOCHR}^1\text{R}^2} \text{CH}_3\text{SCH}_3^\text{O} \xrightarrow{\text{H}^+} \text{CH}_3\text{SCH}_3 + \text{R}^1\text{R}^2\text{C}=\text{O}
\end{align*}
\]

\[\text{OR}^1, \text{OR}^2, \text{R}^1 = \text{COCH}_3, \text{R}^2 = \text{CH}_2\text{SCH}_3\]

Scheme 58

\[
\begin{align*}
\text{CH}_3\text{S}^\text{H} & \xrightarrow{\text{CH}_3\text{CO}_2^-} \text{CH}_3\text{SCH}_3 \xrightarrow{\text{H}^+} \text{R}^1\text{R}^2\text{HCOCH}_2\text{SCH}_3
\end{align*}
\]

\[\text{CH}_3\text{S}^\text{H}, \text{R}^1 = \text{COCH}_3, \text{R}^2 = \text{CH}_2\text{SCH}_3\]
a low intensity peak at m/e 276 and established the identity of the minor product as 170. No peak at m/e 294, corresponding to 169, was observed.

The formation of Pummerer type reaction products such as 170 during dimethyl sulphoxide oxidations of alcohols is attributable to the reaction of the substrate with 171 which is formed by elimination of acetic acid from 167 (Scheme 58). It was not altogether clear why even small amounts of oxidised product were not observed although it has been claimed that the reaction proceeds more efficiently with sterically hindered alcohols, less hindered groups giving more of the Pummerer product.

A second, alternative, oxidation procedure, which appeared to be both powerful and selective utilised an acidic solution of chromium trioxide in dimethyl formamide and several attempts to oxidise 164 were made using this procedure. On a small scale, reaction of 164 with 6 molar equivalents of chromium trioxide - H₂SO₄ gave a disappointingly low yield (18%) of a brown solid which was shown by thin layer chromatography and p.m.r. spectroscopy to be almost entirely hydroxy-ketone (143). Despite the low yield, the ease of isolation of product was encouraging and further attempts were made to increase the overall recovery and promote further oxidation of 143.

The reaction, repeated at higher temperature (90°), gave no appreciable increase in yield and once again no dione was observed. A final attempt was made using 11 molar equivalents of chromium trioxide and heating the reaction mixture at 95° for 24 hr. These conditions were in the event found to be rather severe, and resulted in an extremely low recovery (<10%) of 143, no dione (165) being isolated.
A third approach was investigated and utilised the oxidative cleavage of ethers by aqueous bromine. Deno and Potter have described the oxidation of a wide variety of aliphatic ethers using aqueous bromine in a sodium acetate-acetic acid buffer solution at pH 4.6. Under these conditions, primary alkyl groups are converted to carboxylic acids and secondary alkyl groups to ketones in yields ranging between 30 and 100%. For example, diisopropyl ether gives acetone in 90% yield and isopropyl methyl ether is oxidised to acetone in 70% yield, the methyl group being converted to carbon dioxide.

The authors found it necessary to maintain the pH of the reaction medium around 5. Increase of acidity inevitably resulted in the formation of undesirable bromination products while at high pH, the reaction rate was reduced due to the formation of HOBr. In most cases the oxidation step was performed in the dark. Only in one instance, that of benzyl isopropyl ether was the reaction investigated in the presence of light, and was reported to result in a two-fold increase in the yield of oxidation product (benzaldehyde).

A potential ether precursor of dione (165) was 2,6-dimethoxy-9-thiabicyclo[3.3.1]nonane (172), which was conveniently prepared in quantitative yield by treatment of 161 with sodium methoxide in methanol at 65°C. Treatment of the distilled product (b.p. 157-165°C, 15 mm Hg) with an eight-fold molar excess of bromine gave a brown viscous oil, which was shown by p.m.r. spectroscopy to consist of unreacted dimethyl ether (172), contaminated by a trace of dibromide (173).

By comparison with the ethers studied by Deno and Potter, 172 appeared to
172 \[ X = \text{OCH}_3 \]
173 \[ X = \text{Br} \]

\[
\text{CN} \quad \text{CN}
\]

\[
(\text{CH}_3)_2\text{CN} = \text{NC}(\text{CH}_3)_2
\]

175
be highly resistant to bromine oxidation. It is of course possible that the reaction of 172 with bromine possesses a long induction period and that oxidation would be observed if the mixture was allowed to stand for a longer period. However this was considered unlikely and the reaction was not pursued.

Indeed, the method of Raphael et al\(^\text{117}\) remained the most efficient synthesis of 165 and was employed in small scale (20 mmol) in subsequent preparations of this compound.

**Acid catalysed acetylation of dione (165)**

The final steps in the synthesis of bisenone (153) using the route of Raphael (Scheme 56)\(^\text{117}\) involve the initial conversion of 165 to its bisenol acetate (174). Allylic bromination of this diene with N-bromosuccinimide in carbon tetrachloride (Wohl-Ziegler method\(^\text{128}\)), using azodiisobutyronitrile (175) as radical initiator, furnishes a good yield of dibromodiacetate (176). If required 176 may be isolated as a highly crystalline solid, m.p. 168-170\(^\circ\), but in practice may be employed in an impure state for the preparation of bisenone (153). Thus, the crude bromination product, normally obtained as a colourless oil containing greater than 95% dibromide (176), is treated with refluxing pyridine which promotes smooth dehydrobromination and de-esterification yielding 153.

The above sequence of reactions, is not in itself novel and does not merit particular comment. Nevertheless, a modification of the first step in the sequence, the acetylation of dione (165), has provided a basis for a major topic of this thesis. It is therefore perhaps, worthwhile considering briefly the history of this reaction.
Numerous methods have been reported for acylation, at oxygen and carbon, of active methylene compounds and have been reviewed by House. These reactions fall into two main categories namely (a) base-catalysed and (b) acid-catalysed acylations. In the former category, catalysts employed range from relatively weak bases such as sodium alkoxides to powerful proton acceptors such as sodium hydride. Under the latter heading catalysts include toluene-p-sulphonic acid, boron trifluoride and strong mineral acids.

Of the various procedures available, dione was converted to its bisenol acetate using a variation of the procedure adopted by Meerwein who had prepared the analogous all-carbon bisenol acetate from bicyclo[3.3.1]nonan-2,6-dione. reacted readily when refluxed with acetic anhydride containing a catalytic quantity of conc. sulphuric acid (1 drop conc. \( H_2SO_4 \) in 30 ml \( Ac_2O \)) to give bisenol acetate contaminated with a little mono-enol acetate, (Scheme 59), no C-acylated products being reported.

Acylation of under these conditions was found to be much less facile. By refluxing for 10 hr employing a more strongly acidic acetylation medium (10 drops conc. \( H_2SO_4 \) in 30 ml \( Ac_2O \)) and by continuously distilling out acetic acid formed during the reaction (replenishing \( Ac_2O \) as necessary), Raphael et al obtained a 59% yield of bisenol acetate. As with the preparation of no C-acylated products were identified.

Repeating the preparation for the present project, the above results were consistently duplicated. In all cases the desired product, was accompanied by considerable amounts of partially reacted material, resin and other unidentified by-products. In an attempt to reduce the
Scheme 59

\[ 79 \xrightarrow{\text{Ac}_2\text{O}, \text{c. H}_2\text{SO}_4, (1 \text{ drop in 30 ml Ac}_2\text{O})} \text{177} + \text{178} \]
quantities of these undesirable by-products, especially the resinous material thought to arise due to the harshly acidic conditions, various modifications to the above procedure were investigated.

The theory that a weaker acid catalyst would produce a cleaner reaction product was borne out empirically when dione (165) was treated in the usual way with acetic anhydride containing a trace of toluene-p-sulphonic acid. While the overall yield of 60%, was found to be almost identical to that observed with sulphuric acid, the desired product was found to be much cleaner and more easily separable from its impurities by crystallisation and thin layer chromatography. Moreover, the sole by-product, of note, is monoenoacetate (179), which may be isolated in 13% yield.

Using even milder reaction conditions, the yield of 179 may, in fact, be increased until it becomes the predominant product. Thus 165 has been refluxed for 20 hr with 2-acetoxypropene, employing toluene-p-sulphonic acid as catalyst, furnishing a tar-free product which contained 179 in 82% yield. Prolonged heating under these conditions (ca 25 hr) favours the formation of bisenol acetate (174). It is concluded therefore, from the above results, that in any future preparation of 174 and 179, the use of sulphuric acid should be avoided and that where possible, toluene-p-sulphonic acid should be the catalyst of choice.

However, several hitherto unrecognised advantages of using conc. sulphuric acid in this acetylation have also become apparent. In an investigation into the effect of varying the concentration of H₂SO₄ on reaction yields and product distribution, examination of the p.m.r. spectra of the petroleum spirit extracts revealed an interesting
feature. Common to almost all the spectra, were a pair of low-intensity singlets at 31.65 and 32.00, which invariably integrated in the ratio of 1:1. These signals were strongest when relatively high concentrations of acid had been employed, and were completely absent at low concentrations. In addition, an examination of the spectra of earlier reaction products revealed similar features, and suggested the presence of a compound not previously isolated, the rate of formation of which was dependent on the pH of the acetylation medium.

To test this hypothesis, 165 was treated with acetic anhydride containing an even higher concentration of catalyst than had been previously employed. Several concentrations of sulfuric acid were used ranging from 12 to 30 drops in 30 ml reaction mixture and replenishment of acetic anhydride was delayed as long as possible, because the resultant increase in acid concentration would, it was hoped, favour the formation of the new product. The results are summarised in Table 3.

As expected the higher acid concentration resulted in severe charring of the reaction mixture and overall yields of petroleum spirit - extractable material were greatly reduced, the lowest (ca 10%) being obtained from the most acidic batch. However, in all cases, the p.m.r. spectra of samples taken from the reaction mixtures after 6 hr showed that a significant enhancement in the relative yield of the unknown compound had been obtained. The new product was accompanied by bisenol acetate (174), monoenol acetate (179), and small amounts of other compounds, one of which displayed a sharp singlet at 34.95 (vide infra).
Table 3  Products formed by the reaction of 165 with acetic anhydride–conc.
sulphuric acid mixtures. Yields refer to isolated material.

<table>
<thead>
<tr>
<th>$\text{H}_2\text{SO}_4$ (drops per 30ml Ac$_2$O)</th>
<th>Reaction Time (h)</th>
<th>O-Acylated Products</th>
<th>C-Acylated Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>6</td>
<td>$174(56%)$, $179(18%)$</td>
<td>$180(7%)$</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>$174(13%)$</td>
<td>$180(32%)$, $182(8%)$</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>$174(3%)$</td>
<td>$180(30%)$, $182(16%)$</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>—</td>
<td>$182(26%)$</td>
</tr>
<tr>
<td>30</td>
<td>6</td>
<td>—</td>
<td>$182(10%)$</td>
</tr>
</tbody>
</table>
Optimum isolable yields of the new product were obtained from the acetylations containing 12 and 18 drops of sulphuric acid per 30 ml Ac₂O. By several crystallisations of the crude reaction products from ether-petroleum spirit the compound was obtained free of acetates (174 and 179) as stable colourless needles which melted sharply with sublimation at 172-172.5°. Micro-analytical data obtained from a sample, which had been further purified by vacuum sublimation, indicated this compound, A, to be an isomer of 174 having the molecular formula C₁₂H₁₄O₄S.

This was supported by mass spectral evidence which indicated a parent ion at m/e 254. Mass spectroscopy also provided some information as to the molecular structure of A. Major daughter ions at m/e 212 and 194 arising from loss of ketene, CH₂=C=O, and acetic acid CH₃CO₂H, respectively from the parent suggested that A contained at least one acetoxyl group. Moreover, the presence of an ion at m/e 166 (194 - CO) confirmed the occurrence of a ketonic carbonyl in the molecule.

The infrared spectrum (CCl₄) showed three overlapping carbonyl absorptions. The band at 1752 cm⁻¹ was assigned as an ester carbonyl stretching mode but was considered too low in frequency to be a vinyl acetate (cf. 174 and 179, the solution spectra of which show carbonyl absorptions at 1761 and 1763 cm⁻¹ respectively). The presence of this absorption and the sharp three proton singlet already referred to at δ₂.00 in the p.m.r. spectrum confirmed the presence of an acetoxyl group bonded to saturated carbon. The other two carbonyl absorptions at 1729 and 1719 cm⁻¹ were consistent with the occurrence of two alicyclic ketones while the three proton singlet at δ1.65 in the p.m.r. spectrum was indicative of the presence of a methyl group attached to tertiary carbon. The remainder of this spectrum,
consisted of poorly resolved methylene and methine envelopes extending from 2.51 to 3.64 and integrating for eight protons and was of little utility in structure elucidation.

Ultraviolet spectroscopy confirmed a close similarity between the structures of A and its parent dione (165). The proximity of a carbonyl group and a sulphur bridge in A was corroborated by the existence of a band at 239 nm arising from sulphur lone pair excitation, a sulphur-carbonyl charge transfer absorption at 260 nm and a perturbed \( \pi \rightarrow \pi^* \) carbonyl transition at 312 nm.

Compound A, was accordingly assigned structure (180), 6-acetoxy-6-methyl-2-thiaadamantan-4,8-dione. This structure incorporates into a tricyclic framework two carbonyl functions which are para to a sulphur bridge and a methyl group which is geminal to an acetoxy function.

The formation of 180 (Scheme 60) is considered to arise by two sequential condensation reactions, the first of which is a novel acetylation at C(3) of 165 to give \( \beta \)-diketone (181). Positive proof of the existence of this intermediate was not obtainable since the compound could not be isolated and its presence in the reaction mixture could not be inferred from spectroscopic studies. The elusiveness of 181 may be attributed however to its rapid rearrangement by intramolecular aldol condensation followed by instantaneous O-acetylation to give the observed product.

As mentioned briefly above, several of the acetylation products contained a compound, B, which gave rise to a sharp p.m.r. singlet at 4.95. This signal which had not been previously observed during acetylation reactions was found to be most intense (relative to other
Scheme 60

\[ 165 \xrightarrow{H^+} \] 165

\[ 165 \xrightarrow{\text{Ac}_2\text{O}, -\text{AcOH}} \xrightarrow{H^+} \xrightarrow{181} \] 180

\[ 180 \xrightarrow{\text{Ac}_2\text{O}, -\text{AcOH}} \] 180

\[ 180 \xrightarrow{\text{Ac}_2\text{O}, -\text{AcOH}} \] 180
resonances in the product spectra) when highly acidic conditions were employed. Indeed, compound B was found to be the only extractable product when acid concentrations of greater than 24 drops per 30 ml \( \text{Ac}_2\text{O} \) were used. Although p.m.r. examination of such reaction mixtures also revealed the presence of both 174 and 180 these compounds could not be separated from resinous material.

The crude petroleum spirit extract, comprising mainly B, was decolourised with activated charcoal, and recrystallised to give colourless needles which melted sharply at 169-170\(^\circ\). Microanalysis of the compound was consistent with a molecular formula of \( \text{C}_{10}\text{H}_{10}\text{O}_2 \) and was in agreement with its mass spectrum which indicated a molecular weight of 194.

By comparison with the complex mass spectrum of 180, that of B possessed relatively few intense signals. The major mode of fragmentation of the molecular ion was by two sequential losses of carbon monoxide, giving rise to ions of m/e 166 and 138, suggesting the presence of two ketone functions in the molecule. No evidence of ketene or acetic acid loss was detected, showing that B did not possess an acetoxyl function. Moreover, the infrared spectrum possessed only one absorption in the 1800-1700 cm\(^{-1}\) region, at 1723 cm\(^{-1}\), which was consistent with the presence of an alicyclic ketone rather than an ester function.

Other significant aspects of the infrared spectrum were a medium-intensity band at 1651 cm\(^{-1}\) and a strong absorption at 907 cm\(^{-1}\). While not diagnostic, these features suggested\(^{139}\) the presence of a 1,1-disubstituted ethylene moiety in the molecule and were supported by the already mentioned two-proton p.m.r. singlet at 84.95.
The remainder of the p.m.r. spectrum consisted of a series of highly split multiplets which were poorly resolved but which integrated for eight protons. The ultraviolet spectrum of B, which bore a close resemblance to that of 165 showed sulphur-carbonyl interaction bands at 261 and 309 nm, the latter possessing shoulders at 303 and 324 nm.

From the above spectroscopic evidence, and from the likelihood that the product possessed a close structural relationship to 165 and 180 and possibly had been formed from 180 by elimination of acetic acid, compound B was assigned as 6-methylene-2-thiaadamantan-4,8-dione (182).

This structure possesses as its only symmetry element (apart from the identity element, E) a two-fold axis through sulphur and C(6) and thus belongs to the C2 point group \(^{140}\). By virtue of this property, the ten hydrogen atoms in the molecule may be grouped into only five magnetically distinct types, each giving rise to its own p.m.r. signal integrating for two protons. As already discussed, however, four of these groups show very similar chemical shifts and lose their identity through mutual overlap.

A technique which has been used successfully to simplify p.m.r. spectra by removing accidental equivalence is the complexation of the compound under study with a paramagnetic shift inducing reagent. These reagents are air-stable, organic coordination compounds of elements from the Lanthanide series, the most commonly used complexes being tris(dipivalomethanato)europium(III) (Eu(dpm)_3, 183) and tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)-europium(III) (Eu(fod)_3, 184) which both show high solubility in organic solvents.
182

183 \( R^1 = R^2 = \text{C(CH}_3\text{)}_3 \)

184 \( R^1 = \text{C(CH}_3\text{)}_3, R^2 = \text{CF}_2\text{CF}_2\text{CF}_3 \)
By virtue of their ability to expand their coordination shells by acquiring ligands with lone pairs, the central metal atoms of these complexes are able to form bonds to functional groups such as -NH₂, -OH and -C=O. In the p.m.r. spectrometer, ligand protons will experience not only the external magnetic field, H⁰, generated by the instrument, but also a localised field, H⁰_{Eu}, produced by the nearby paramagnetic europium nucleus. Since the strength of H⁰_{Eu} falls off rapidly as the distance from the europium nucleus increases, those protons which are closest to the site of complexation will experience the greatest paramagnetic influences and as a consequence their p.m.r. signals will be shifted by the greatest distance to lower field.

The potential simplicity of the p.m.r. spectrum of 182 and the presence of lone-pair-bearing functions (two carbonyl groups and a sulphur atom) in the molecule suggested that this alkene would be an appropriate subject for decoupling studies on shifted spectra. Eu(fod)₃ was chosen as the complexing reagent in preference to Eu(dpm)₃ because of its superior solubility in deuterochloroform.

A number of concentrations were employed ranging from 0.1 to 0.6 mmol of shift reagent per mmol of substrate. The resultant shifted spectra are compared with the normal spectrum in Figure 2.

With only 0.1 mmol shift reagent per mmol alkene the spectrum became resolved into five distinct two-proton signals consistent with the ascribed structure. At this stage the lowest field absorption was the exomethylene singlet at δ 5.23 which was least shifted (ca. 0.37 δ units) reflecting the remoteness of these protons from the complexation centre. In contrast, the signals due to the two types of bridgehead protons, C(1,3)H and C(5,7)H, which consisted of a
Figure 2
The normal and Europium-shifted 100 MHz proton magnetic resonance spectra of 6-methylene-2-thiaadamantan-4,8-dione (182).

\[ R_{Eu} = \frac{\text{conc. of Eu(fod)}_3}{\text{conc. of 182}} \]

\[ R_{Eu} = 0 \]

\[ R_{Eu} = 0.1 \]

Continued...
Figure 2 (Continued)

$R_{\text{Eu}} = 0.2$

$R_{\text{Eu}} = 0.4$

$R_{\text{Eu}} = 0.6$
Table 4  Full assignment of the p.m.r. spectrum of 182 as derived from the Europium shifted spectra and decoupling experiments shown in Figure 2

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Signal</th>
<th>Chemical Shift $\delta$</th>
<th>Multiplicity</th>
<th>Assignment</th>
<th>Coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4.95</td>
<td>s</td>
<td>H$_v$</td>
<td></td>
</tr>
</tbody>
</table>
| b      | 3.50                    | m            | C(1,3)H    | $J_{1,9a}(J_{3,10a}) = 2.5$ Hz  
$J_{1,9a}(J_{3,10a}) = 4.0$ Hz |
| c      | 3.34                    | m            | C(5,7)H    | $J_{5,9a}(J_{7,10a}) = 2.5$ Hz  
$J_{5,9a}(J_{7,10a}) = 4.0$ Hz |
| d      | 3.16                    | dt           | C(9,10)H$_s$ | $J_{9s,1}(J_{10s,3}) = 2.5$ Hz  
$J_{9s,5}(J_{10s,7}) = 2.5$ Hz  
$J_{gem} = 13$ Hz |
| e      | 2.78                    | dt           | C(9,10)H$_a$ | $J_{9a,1}(J_{10a,3}) = 4.0$ Hz  
$J_{9a,5}(J_{10a,7}) = 4.0$ Hz  
$J_{gem} = 13$ Hz |
pair of almost identical multiplets showing complex splitting, had each been strongly pulled downfield by ca 0.9 \( \delta \) units, indicative of the close proximity of those protons to the europium nucleus. Although, from these spectra, no direct information could be obtained as to which methine protons gave rise to each signal, an unambiguous assignment has been obtained\(^{142,143}\) from \(^{13}\)C magnetic resonance studies indicating that the lower field multiplet originated from protons bonded to C(1) and C(3) (Table 4).

The true benefit of using shift reagent was however best seen on examination of the pair of resonances arising from protons attached to C(9) and C(10). These protons may be divided into two magnetically distinct types viz. those \( \text{syn-} (\text{H}_s) \) and those \( \text{anti-} (\text{H}_a) \) to the sulphur bridge and consequently give rise to two p.m.r. signals. Each of these signals could be clearly identified as being a doublet of triplets, having a major splitting of 13Hz attributable to mutual geminal coupling. Moreover by examination of molecular models and by measurement of minor coupling constants, it was possible to assign each multiplet with reasonable certainty.

Due primarily to the presence of the bulky sulphur atom, the molecular framework of 182 experiences a distortion away from the highly symmetrical geometry of adamantane (1). A direct effect of this deformation is to diminish the dihedral angle between the C(1)-H and C(9)-H\(_a\) bonds from 60 to 55\(^\circ\), while that between C(1)-H and C(9)-H\(_s\) is simultaneously opened out to 65\(^\circ\) (Figure 3).

An empirical relationship between vicinal coupling constants \( J_{\text{vic}} \) and dihedral angles (\( \Theta \)) has been developed by Karplus\(^{144}\) and is shown graphically in Figure 4. It may be seen that for \( \Theta < 90^\circ \),
**Figure 3**
Comparison of the dihedral angles between the bridgehead and neighbouring methylene protons of (a) adamantane(1) and (b) alkene(182)

![Diagram](image)

**Figure 4**
Variation of the vicinal coupling constant $J_{\text{vic}}$ with the dihedral angle $\theta$

![Graph](image)
increases as $\theta$ decreases. Using this relationship, the farther upfield of the two methylene resonances of 182, displaying a minor splitting of 4 Hz was assigned to C(9,10)$_a$ while the remaining signal, exhibiting a minor splitting of only 2.5 Hz was assigned to C(9,10)$_s$.

At a Eu(fod)$_3$ / alkene ratio of 0.6, the accidental equivalence of signals arising from the exomethylene protons and C(9,10)$_s$ made this concentration unsuitable for decoupling studies. Instead double irradiation experiments were carried out at a molar concentration ratio of 0.4, since the shifted signals produced were exceptionally well separated and were of almost first order appearance. The results of these experiments were in complete accord with the previous assignments and aided in the precise measurement of coupling constants. The results are summarised in Table 4.

Having arrived at incontravertible evidence for the structure of 182, its preparation from the supposedly related acetate (180) became apparent as a potentially simple structural proof of the latter.

In order to reduce the possibility of structural rearrangement, it was necessary to employ relatively mild conditions to effect the transformation and hence a pyrolytic deacetylation was not considered.

Instead, 180 was hydrolysed at room temperature with dilute aqueous sodium hydroxide and yielded a single product, the p.m.r. spectrum of which closely resembled that of the parent ester except for the absence of a characteristic three-proton acetoxyl singlet at $\delta$ 2.0. Moreover, the infrared spectrum of the colourless, needle-like, crystalline solid possessed no ester carbonyl absorption, but
instead showed a characteristic free hydroxyl stretching vibration at 3606 cm\(^{-1}\).

The most prominent feature of the spectrum was however a strong double carbonyl stretching absorption at 1729 and 1723 cm\(^{-1}\) which indicated the retention of both ketone functions in the molecule. The occurrence of the molecular ion at m/e 212 in the mass spectrum taken with microanalytical data supported a molecular formula of C\(_{10}\)H\(_{16}\)O\(_3\)S and was consistent with the product being the expected alcohol, 6-hydroxy-6-methyl-2-thiaadamantan-4,8-dione (185).

Although 185 is itself apparently unaffected by dilute aqueous alkali, it is unstable in the presence of methanolic potassium hydroxide, a property common to \(\beta\)-keto alcohols (aldols). When an attempt was made to hydrolyse 180 with KOH in aqueous methanol a mixture of two products was obtained. The minor component was 185 and was isolated in only 13\% yield. The major product (65\%) was dione (165) the formation of which was rationalised by the sequence of reactions depicted in Scheme 61. 180 hydrolysed in the normal way to give 185 which in the alkaline medium exists partially as alkoxide ion (185a). Retro-aldol cleavage of 185a with protonation of the resultant enolate anion gives the C-acylated bicyclic dione (181) already referred to as an intermediate in the formation of 180. 181 is unstable in the presence of strong base and hydrolysies with loss of acetic acid yielding 165.

Dehydration of 185 with excess phosphorous oxychloride in pyridine gave a crystalline product which was identical in all respects to alkene (182). Thus 185 and consequently acetate (180) possess the same skeletal structure as 182 and differ only in the nature of the
Scheme 61

\[
180 \xrightarrow{\text{aq. NaOH or KOH, CH}_3\text{OH}} 185 \xrightarrow{\text{OH}^-} 185a \xrightarrow{\text{KOH, CH}_3\text{OH}} 181 \xrightarrow{\text{H}^+} 182 \xrightarrow{\text{AcOH}} 186
\]

Table 5  Treatment of 180 with conc. H\textsubscript{2}SO\textsubscript{4}

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Reaction time (hours)</th>
<th>Product ratio 180:182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac\textsubscript{2}O</td>
<td>4</td>
<td>1:4</td>
</tr>
<tr>
<td>(CH\textsubscript{2}OCH\textsubscript{3})\textsubscript{2}</td>
<td>2</td>
<td>9:1</td>
</tr>
<tr>
<td>1,4-Dioxan</td>
<td>4</td>
<td>4:1</td>
</tr>
</tbody>
</table>

Scheme 62
functionality at C(6).

Further investigation into the acetylation of 165 has confirmed that the proportions of 174 and 180 produced are thermodynamically controlled. On treatment with acetic anhydride - sulphuric acid at 160°C, bisenol acetate (174) was partially converted to a mixture of 179, 180 and 182 (trace), showing the reversibility of the enol acetylation process. In contrast, the cyclisation of C-acylated intermediate (181) is irreversible since subjection of 180 to the acetylation conditions produced 182 but no bicyclic products.

This latter observation also indicated that 182 probably does not arise directly from a bicyclic precursor, but is in fact the product of elimination of acetic acid from 180. Indeed, 180 was slowly converted to 182 when heated with a catalytic quantity of sulphuric acid in an inert solvent (1,2-dimethoxyethane or 1,4-dioxan) (Table 5) but was unchanged after pyrolysis at 150-220°C. These observations, taken with the fact that alkene (182) was itself inert to acetic anhydride - sulphuric acid, indicated that the elimination step, 180 → 182 (Scheme 62) is an irreversible, acid-catalysed process (most probably E1, via the tertiary carbonium ion (186)) rather than a pyrolytic cis-elimination which was originally postulated.

**Acetylation of Diones (79 and 187)**

The reaction of 165 with acetic anhydride - sulphuric acid to produce 180 and 182, provides a novel and potentially important
synthetic route to 2-thiaadamantane derivatives from a bicyclic precursor. The possibility that similar behaviour would be exhibited by other bicyclo[3.3.1]nonan-2,6-diones prompted an investigation into the utility of acetylation as a general route to adamantanes and 2-heteroadamantanes. Consequently the synthesis and acetylation of diones (179, 187 and 188, R=Ph) viz. the 9-methano, 9-oxa and N-phenyl-9-aza analogues of 165, were attempted.

Although a shortage of time prevented the completion of this study, the generality of this acylation approach to adamantane derivatives was partly borne out.

Although Meerwein had already synthesised 17 bicyclo[3.3.1]nonan-2,6-dione (79) (Scheme 63) and had treated it with acetic anhydride to obtain bisenol acetate (177),136 no reference was made to other acylation products. It was considered, however, that tricyclic products may in fact have been present, but were not detected using the techniques available at that time. In order to reinvestigate the reaction, 79 was synthesised via tetraester (4) using a modification of Meerwein's original procedure developed by Schaefer and Honig47. The intermediate, m.p. 159-162° (lit.47 m.p. 163-164°), possessed spectroscopic characteristics which were concurrent with the desired structure.

Hydrolysis and decarboxylation of 4 were easily accomplished by refluxing17 with dilute hydrochloric acid, giving 79 as the only product. 79 was characterised by melting point, 138-142° (lit.17 m.p. 141°), and infrared spectrum which exhibited a strong carbonyl band at 1689 cm⁻¹.
Scheme 63

\[
\begin{align*}
&\text{CH}_2(\text{CO}_2\text{CH}_3)_2 + \text{HCHO} \\
&\quad \xrightarrow{1. \text{H^+}} \xrightarrow{2. \text{NaOCH}_3} \xrightarrow{3. \text{CO}_2} \text{CH}_3O_2C\xrightarrow{\text{CO}_2}\xrightarrow{\text{CO}_2}\xrightarrow{\text{H^+}} \text{CH}_3O_2C\xrightarrow{\text{Ac}_2\text{O}} \text{Ac}_2\text{O} \\
&\quad \xrightarrow{\text{H^+}} \text{CH}_3\text{CO}_2\xrightarrow{\text{Ac}_2\text{O}} \text{Ac}_2\text{O} \\
&\quad \xrightarrow{\text{H^+}} \text{CH}_3\text{CO}_2\xrightarrow{\text{Ac}_2\text{O}} \text{Ac}_2\text{O} \\
&\quad \xrightarrow{\text{H^+}} \text{CH}_3\text{CO}_2\xrightarrow{\text{Ac}_2\text{O}} \text{Ac}_2\text{O} \\
&\text{79} \quad X = \text{CH}_2 \\
&\text{187} \quad X = \text{O} \\
&\text{188} \quad X = \text{NR}
\end{align*}
\]
79 was refluxed in the usual manner with a mixture of acetic anhydride and conc. sulphuric acid and furnished a tarry product, the ether extract of which was separated into three components by preparative t.l.c.

The uppermost band gave a colourless solid which crystallised from ether-petroleum spirit as prisms of 177, m.p. 77-79° (lit. 136 m.p. 78-79°) the identity of which was confirmed by infrared and p.m.r. spectroscopy. The infrared spectrum showed an intense ester carbonyl absorption at 1743 cm⁻¹ but the absence of an absorption in the 1700 cm⁻¹ region indicated that the ketonic functions of the original dione were no longer present.

The p.m.r. spectrum showed all the features which would be expected of bisenol acetate (177). A six-proton singlet at δ 2.12 confirmed the presence of two acetoxy groups while a deshielded two-proton multiplet at δ 5.37, typical of olefinic hydrogen, was attributed to C(3,7)H. The remainder of the spectrum consisted of methylene and methine envelopes. Absorptions at δ 1.92 (2H) and δ 2.28 (4H) were attributed respectively to C(9)H₂ and C(4,8)H₂ while the bridgehead protons, C(1,5)H, appeared as a multiplet at δ 2.56 (2H).

177 was isolated in 18% yield and was the least abundant of the three reaction products.

Extraction of the middle band yielded another colourless solid which crystallised from chloroform-hexane as prisms, m.p. (sealed tube) 160-162°. The p.m.r. spectrum of this compound bore a close resemblance to that of alkene (182). In particular, a sharp two-proton singlet at δ 4.86 revealed the presence of a terminal methylene group.
The existence of a geminally substituted carbon-carbon double bond was supported by the infrared spectrum (KBr disc) which possessed a classical medium-intensity stretching absorption at 1647 cm$^{-1}$ accompanied by a carbon-hydrogen out-of-plane deformation at 907 cm$^{-1}$. An intense carbonyl band, having maxima at 1727 and 1715 cm$^{-1}$ showed that the ketonic functions of 79 had been retained in the product.

A broad six-proton envelope at $\delta$ 2.00-2.53, in the p.m.r. spectrum was attributed to the composite signals of three methylene groups and two poorly resolved multiplets at $\delta$ 2.93 (2H) and $\delta$ 3.37 (2H) were assigned as bridgehead methine resonances. The mass spectral molecular ion at m/e 176 was in accord with the molecular formula, C$_{11}$H$_{12}$O$_2$. Moreover, the major fragmentation pathway involved a double loss of 28 (carbon monoxide) and supported the existence of two ketone groups in the molecule.

On the basis of the above evidence, this product which was isolated in 31% yield was identified as 4-methyleneadamantan-2,6-dione (189), and was corroborated by the work of Stetter and Thomas who had previously synthesised 189 in several stages from 79 (Scheme 64) and gave the melting point of the former as 163-164$^\circ$ in good agreement with the present value.

From the lowest band, a third crystalline product was isolated as colourless needles, m.p. 124-126$^\circ$. Microanalysis of the material corresponded to a molecular formula of C$_{13}$H$_{16}$O$_4$ and indicated that the product was a structural isomer of 177 (cf. 174 and 180). The mass spectrum showed a parent ion at m/e 236 accompanied by daughter ions at 194 and 176 corresponding to respective losses of ketene and
acetic acid, similar to that found in the spectrum of 180. The infrared spectrum (CCl₄) of the product possessed, as its major feature, a strong ester carbonyl absorption at 1750 cm⁻¹ overlapping an even stronger ketonic carbonyl band at 1724 cm⁻¹.

Sharp three-proton singlets at δ 1.62 and 2.04 in the p.m.r. spectrum revealed the presence of a tertiary methyl group and an acetoxy moiety in the molecule (cf. the p.m.r. spectrum of 180). In its other aspects, the spectrum closely resembled that of 189 and featured a broad methylene envelope between δ 1.80 and 2.60 which integrated for six protons, and a pair of two-proton methine multiplets at δ 2.70 and 3.25. From the spectroscopic evidence it was clear that the product, obtained in 20% yield, was 4-acetoxyl-4-methyladamantan-2,6-dione (190). Thus 79 reacts in an analogous manner to 165 with an acetic anhydride - sulphuric acid mixture, to give adamantanes in yields of synthetic utility.

The availability of 4 prompted an investigation into its behaviour under acetylation conditions. In the event, cyclisation to produce the highly substituted acetate (191) and alkene (192) did not take place. Instead, the crude reaction product yielded two bicyclic compounds which were only partially separable by t.l.c. and were not fully characterised.

Extraction of the uppermost band gave a colourless oil which resisted crystallisation from a variety of solvents. The compound was nevertheless pure enough to provide a p.m.r. spectrum of sufficient resolution to enable a structural identification. A major aspect of the spectrum (Figure 5) was a pair of sharp six-proton singlets
Figure 5
The 100 MHz p.m.r. spectra of (a) 193 and (b) 194
at δ 2.09 and 3.70. The former was diagnostic of two magnetically equivalent acetoxyl groups while the latter manifested the retention of two identical methyl ester functions from 4. A broad multiplet at δ 2.62 (4H) was assigned as two methylene groups while a neighbouring two-proton singlet at δ 2.36 was considered to arise from a methylene group sandwiched between two fully substituted carbons. The remaining feature of the spectrum was a two-proton multiplet at δ 5.59, closely similar in multiplicity and chemical shift to the vinyl protons of enol acetates (174, 177 and 179). From this evidence the product was identified as 2,6-diacetoxy-1,5-di(methoxycarbonyl)bicyclo[3.3.1]nona-2,6-diene (193).

The other, more polar, reaction product was obtained as an impure colourless oil which also would not crystallise. The compound possessed a relatively simple p.m.r. spectrum (Figure 5) which closely resembled that of 193 and allowed positive structural elucidation. This spectrum was dominated by methyl ester and acetate methyl resonances. The sharp singlets at δ 3.73, 2.18 and 2.10 integrating in the ratio 3:1:1 evinced the presence of three methoxycarbonyl functions and two magnetically distinct acetoxyl groups. Three separate CH₂ resonances were present in the δ 2.0 to 3.0 region. Slightly broadened singlets at δ 2.92 and 2.41 were assigned as two uncoupled methylene groups while a third signal at δ 2.67 showed a complex splitting pattern and was necessarily coupled to a one-proton vinyl multiplet at δ 5.61. These spectroscopic features identified the product as 2,6-diacetoxy-1,3,5-tri(methoxycarbonyl)bicyclo[3.3.1]nona-2,6-diene (194).
193 and 194, which were isolated in 26% and 35% yields respectively, were formed by acid-catalysed enol acetylation, solvolysis and decarboxylation of tetraester (4) although the precise order of events, during the complex reaction sequence is unknown. No C-acylated or tricyclic products were detected, their formation possibly being suppressed due to steric interference by the C(3) and C(7) ester functions.

9-oxabicyclo[3.3.1]nonan-2,6-dione (187) was synthesised in two stages from 50 (Scheme65 ) as a 2:1 mixture with 9-oxabicyclo-[4.2.1]nonan-2,5-dione (195). Following the procedure of Zefirov54, 50 was oxidised by hydrogen peroxide in the presence of formic acid to give, after hydrolysis of intermediate formate esters, a colourless highly crystalline product which melted at 56-66°. Although in the original synthesis54 diol (196), lit.54,149 m.p. 82-83°, was reported to be formed unaccompanied by isomeric diol (197), the broad and depressed melting range of the material obtained suggested that an isomeric mixture was present. This inconsistency with the literature could not be satisfactorily explained but the formation of an isomeric impurity was not entirely unexpected since mixtures are invariably obtained during syntheses of 9-oxabicyclo[3.3.1]nonanes e.g acid hydrolysis of 163120 and oxymercuration of 5053.

Separation of the skeletal isomers was not attempted at this stage. Instead, a portion of the mixture was oxidised, as described by Canter149 using Jones reagent to give a mixture of diones (187 and 195). The oxidation product which was obtained in 47% yield as a colourless oil gave a single spot on t.l.c., suggesting the
Scheme 65

\[ 50 \xrightarrow{\text{HCO}_3\text{H}} 196 + 197 + 187 (31\%) + 195 (16\%) \]
presence of only one compound. Moreover, the infrared spectrum of the oil enivenced a single carbonyl stretching band at 1716 cm\(^{-1}\) which was sharp and devoid of shoulders. However, p.m.r. spectroscopy clearly identified the product as being a binary mixture. In addition to the expected bridgehead signal of 187 at \(\delta 4.44\) (lit. \(\delta 4.40\)), the spectrum exhibited a second bridgehead multiplet of lower intensity at \(\delta 4.68\), indicating the presence of 195. The relative intensities of these signals showed that the mixture contained 66\% of the desired dione (187) and 34\% of the unwanted isomer (195).

Like their parent diols, 187 and 195 were too alike in physical properties to be separable by conventional methods. However, conversion of the mixture to bisenol acetate derivatives (198 and 199) furnished compounds which differed sufficiently in polarity as to be easily separable on silica-gel plates. Enol acetylation was accomplished in the usual way using a mixture of acetic anhydride and toluene-p-sulphonic acid, the latter being employed in preference to conc. sulphuric acid to avoid charring and to minimise the formation of by-products. Even so, preparative t.l.c. (Benzene-ethyl acetate 3:1) separated the ether-extractable product into at least five distinct bands.

Extraction of the major band (R\(_f\) 0.53) with ethyl acetate yielded a yellow oil which sublimed in vacuo as colourless needles, m.p. 89-91°. The p.m.r. spectrum of this solid closely resembled that of 174, having a six-proton acetoxy resonance at \(\delta 2.11\), a methylene envelope (4H) at \(\delta 2.51\) and a vinyl multiplet (2H) at \(\delta 5.52\). The spectrum differed notably however in the position
of the bridgehead proton signal, which at δ 4.39 was consistent with a 9-oxabicyclo[3.3.1]nonane skeleton.  

The infrared spectrum (CCl₄) of the product exhibited a strong ester carbonyl band at 1765 cm⁻¹ (ν a 440) accompanied by a medium intensity C-C double bond stretching absorption at 1690 cm⁻¹. Microanalytical figures were in accord with a molecular formula of C₁₂H₁₄O₅, and were supported by the mass spectrum which possessed a parent ion at m/e 238. Daughter ions at m/e 196 and 154 showed fragmentation by two successive losses of ketene, CH₂=C=O, a feature common to enol acetates. The above evidence confirmed that the solid, isolated in 52% yield, was 2,6-diacetoxy-9-oxabicyclo[3.3.1]nona-2,6-diene (198).  

Extraction of several of the remaining bands yielded colourless oils, all of which evinced acetoxy signals in their p.m.r. spectra. However, none of these materials could be positively identified as 199 and, as a result of their rapid decomposition on standing (as shown by t.l.c.), their characterisation was not attempted.  

Dione 187 was recovered in high yield from 198 by smooth hydrolysis with refluxing dilute hydrochloric acid. Crystallisation of the crude product from ether-petroleum spirit gave colourless prisms which melted at 53-56° in good agreement with the literature value (54-55°). The infrared spectrum of pure 187 was remarkably similar to that of the dione mixture already described, possessing an intense carbonyl absorption at 1720 cm⁻¹ and a strong carbon-oxygen single bond stretching band at 1080 cm⁻¹. The isomeric purity of the product was however clearly demonstrated.
Scheme 66

\[ 187 + 195 \xrightarrow{\text{Ac}_2\text{O}, \text{H}^+} 198 + 199 + \text{other products} \]

thin layer chromatography

+ other products

Scheme 67

\[ \text{peracid} \xrightarrow{} 163 \xrightarrow{\text{H}^+} 196 + 197 \]

\[ 187 + 196 \xrightarrow{\text{H}^+, \text{H}_2\text{O}} 200 + 201 \]

fractional crystal
by its p.m.r. spectrum which, in contrast to that of the mixture, possessed only one bridgehead proton signal at δ 4.44.

This preparation (Scheme 66) of 9-oxabicyclo[3.3.1]nonan-2,6-dione (187), free of any isomeric impurity, is an alternative to the original procedure devised by Ganter in 1972. The method used by the Swiss group (Scheme 67) involved the acid hydrolysis of cycloocta-1,5-diene diepoxide (163) which, as already mentioned, gave a mixture of isomeric diols (196 and 197). The mixed diols were converted to their acetates (200 and 201) which could be separated by multiple fractional crystallisation. Hydrolysis of 200 and Jones oxidation of the product gave pure dione (187) in low overall yield from 50. The enol acetate route, however, is comprised of fewer stages and also obviates the need for tedious repeated fractional crystallisation.

Acetylation of 187 was carried out, as before, using 19 drops of concentrated sulphuric acid per 30 ml acetic anhydride. Analytical thin layer chromatography of the crude product revealed at least six different reaction products, most of which were not well differentiated. Nevertheless, by the use of a preparative thin layer chromatogram, which showed four major bands when inspected under ultraviolet light, two of these products were isolated and fully characterised.

Extraction of the uppermost band (Band 1), Rf 0.75, yielded an off-white crystalline solid which sublimed under vacuum as colourless needles, m.p. 154-156°. Microanalysis of the product suggested
that it was isomeric with bisenol acetate (198) having a molecular formula of C_{12}H_{14}O_{5}, and this was confirmed by mass spectrometry which indicated a molecular weight of 238. Ester groups were clearly not present in the structure as shown by the absence from the mass spectrum of daughter ions at m/e 196 and 178 (loss of ketene and acetic acid respectively) and by the absence of a carbonyl absorption in the 1750 cm^{-1} region of the infrared spectrum. Moreover, the absence of an alicyclic ketone band at ca 1700 cm^{-1} was evidence that the carbonyl groups of the parent dione (187) were no longer present in their original form. The most intense absorption in the infrared spectrum, and an important clue to the structure of the compound, was however a broad complex absorption centred at 1600 cm^{-1} which had no precedence in the present work. This was considered to arise from an enolised β-diketone system.

The profile of the p.m.r. spectrum (Figure 6) also excluded the compound from any class of acetylation products previously observed. The major feature of this spectrum was a sharp six-proton singlet at δ 2.05 which was assigned as coincident methyl resonances of two acetoxyl groups. The presence of acetoxyl functions was precluded by the infrared and mass-spectral evidence presented above. The skeletal resonances appeared as three mutually-coupled double doublets, typical of an AMX spin system, each signal integrating for two protons. The farthest downfield multiplet of the spectrum, at δ 4.53, was assigned as a pair of equivalent bridgehead protons, which were coupled to each of the more shielded resonances at
3.01 and 2.57 by 6 and 1.5 Hz respectively. These higher-field signals were attributed to two coincident allylic methylene groups, the protons of which possessed different chemical shifts and showed a geminal coupling of 15 Hz. A two-proton singlet at 3.35, which disappeared on addition of D_{2}O was assigned to weakly-bonded enolic hydrogens. This compound was thus 3,7-diacetyl-9-oxabicyclo-[3.3.1]non-2,6-dione (202) which must exist predominantly in the intramolecularly hydrogen-bonded enol form (202a).

Extraction of Band 2 (R_f ca 0.5) yielded, after crystallisation, bisenol acetate (198) in 23% yield, the product being identified by its characteristic p.m.r. and infrared spectra (vide supra). Bands 3 and 4 furnished yellowish oils which could not be induced to crystallise and which rapidly darkened on standing. Both oils gave rise to multiple acetoxy and/or acetyl signals in their complex p.m.r. spectra and appeared to be polyacetylated. Attempts at further purification by t.l.c. failed to resolve the mixtures into compounds which were pure enough to be characterised. In fact, using the same eluent (ethyl acetate-benzene, 1:3) as was used in the original separation, a range of overlapping bands were obtained between R_f 0.1 and 0.8 suggesting that rapid decomposition was occurring on contact with the stationary phase (silica gel), thus prohibiting the isolation of desired products.

Although the major component of Bands 3 and 4 could not be isolated, their p.m.r. spectra exhibited several features of interest. In particular, both bands possessed a sharp, medium-intensity singlet at 4.32 which may be attributable to the presence of tricyclic alkene (203), although the signal is fractionally more shielded than
Figure 6
The 60 MHz p.m.r. spectrum of 202
one would have expected. Moreover, the spectrum of Band 3 also contained a pair of relatively low intensity singlets at 31.60 and 2.02 which could possibly be the non-equivalent methyl resonances of tricyclic acetate (204) (Cf 180 and 190).

Regrettably, these speculative assignments could not be confirmed since a shortage of time prevented a further study of the reaction. Although some evidence has been observed to suggest the formation of 2-oxaadamantane derivatives, it is clear that 9-oxabicyclo[3.3.1]nonan-2,6-dione (187) does not react with acetic anhydride - sulphuric acid in an identical manner to its 9-thia and 9-methano relatives (165 and 79). For some, as yet, inexplicable reason 187 shows an increased susceptibility to multiple acetylation as is indicated by the unpredicted formation of a doubly C-acylated bicyclic derivative (202). Moreover the acetylation products obtained with the exception of 198 and 202 appear to decompose rapidly at ambient temperatures and are thus completely different in character to the stable crystalline bicyclic and adamantanoid compounds previously encountered. It is hoped that future investigation of this reaction will confirm the formation of 2-oxaadamantane derivatives and that it will be possible, by manipulation of the reaction parameters, to optimise the yields of these products to a synthetically useful degree.

An Approach to the Synthesis of 2-azaadamantanes

The synthesis of 9-azabicyclo[3.3.1]nonan-2,6-dione (188, R=H) or an N-substituted derivative (188, R=Alkyl or Aryl) was not expected to pose any difficulty since the diol precursor (205) may be readily
prepared by condensing 163 with ammonia or the appropriate primary amine. Under the reaction conditions, the product is obtained completely free of isomeric [4.2.1] diol (206) and is potentially convertible to 188 by Jones oxidation (Scheme 68).

Cycloocta-1,5-diene (50) was converted to 163 by treatment with m-chloroperbenzoic acid. Analytical t.l.c. comparison of the reaction mixture with an authentic sample of 163 revealed that the required product was accompanied by another more polar compound. Column chromatography readily separated the mixture into its components and furnished 163 as the major product in 73% yield. This compound was isolated as a highly crystalline, colourless solid, characterised by melting point, 24-25° (lit. m.p. 25-27°) and by p.m.r. spectrum which possessed two multiplets at δ 1.93 (8H, CH₂) and δ 2.93 (4H, CH).

The minor reaction product, an extremely viscous, colourless oil showing a molecular ion at m/e 296 in the mass spectrum, was identified as a m-chlorobenzoate ester by virtue of its carbonyl stretching vibration at 1724 cm⁻¹ and aromatic proton resonances at δ 7.18 - 7.95 (4H) which closely resembled those of the parent acid. Other significant infrared features included a strong hydroxyl band at 3448 cm⁻¹ and a very intense C-0 stretching vibration at 1255 cm⁻¹. Although the latter absorption is a characteristic of both epoxide and benzoate ester groupings, it was ascribed to the latter due to the absence of an epoxide methine signal in the δ 2.90 region of the p.m.r. spectrum (Cf. 163). The hydroxyl function gave a one-proton deuterium-exchangable signal at δ 2.34 while four protons bonded to carbon-bearing-oxygen
appeared as multiplets at $\delta$ 3.94 (2H), 4.52 (1H) and 5.32 (1H).
Four methylene groups gave rise to a broad envelope (8H) centred at $\delta$ 2.00.

By analogy with the alcoholic products formed during acid hydrolysis of 163, this oily product was considered most likely to be a mixture of isomeric bicyclic hydroxyesters (207 and 208). The alternative structure, monoepoxide (209), was discounted on the basis of the p.m.r. evidence already cited. It is, in theory, possible to test this structural proposal by reducing the product with lithium aluminium hydride (Scheme 69). Isolation of a mixture of the already prepared isomeric diols (196 and 197) would favour the assigned structures. On the other hand, isolation of triol (210) could be considered unambiguous confirmation of the epoxide structure (209).

163 was converted to a 9-azabicyclo[3.3.1]nonane by condensation with aniline, this amine being chosen on account of its ease of purification and its lower volatility than simple aliphatic amines and because the aromatic substituent was likely to impart stability to the product without blocking reactivity of the bicyclic skeleton or hampering structure elucidation.

Condensation was carried out in a sealed pyrolysis tube, optimum yields being obtained when the temperature was kept around 105° and when reactants were diluted with methanol. The crude crystalline product recrystallised from ethyl acetate-ether to give colourless prisms which melted sharply at 176-178°. Microanalysis and mass
Scheme 68

\[
\begin{align*}
50 & \quad \text{ArCO}_2\text{H} \\
& \quad \text{R} = \text{H, Alkyl or Aryl} \\
& \quad \text{Ar} = \text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
73\% & \quad \text{ArOH} \\
& \quad \text{OH} \\
& \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
163 & \quad \text{RNH}_2 \\
& \quad \text{OH} \\
& \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
206 & \quad \text{RNH}_2 \\
& \quad \text{OH} \\
& \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
205 & \quad \text{CrO}_2\text{H}^+ \\
& \quad \text{RNH}_2 \\
& \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
188 & \\
\end{align*}
\]

Scheme 69

\[
\begin{align*}
207 & \quad \text{LiAlH}_4 \\
& \quad \text{OH} \\
& \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
208 & \quad \text{LiAlH}_4 \\
& \quad \text{OH} \\
& \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
209 & \quad \text{LiAlH}_4 \\
& \quad \text{OH} \\
& \quad \text{OH} \\
\end{align*}
\]
spectrometry were in accord with a molecular formula of $C_{14}H_{19}NO_2$ (m.w. 233) and confirmed the formation of the expected 1:1 adduct. The infrared spectrum of the product endorsed the presence of at least one hydroxyl function, having a broad intense band centred at 3365 cm$^{-1}$. Moreover the presence of a phenyl group was supported by a pair of sharp peaks at 1599 and 1507 cm$^{-1}$.

The p.m.r. spectrum ($d_6$-DMSO) of the product possessed only four regions of absorption instead of the expected five. However, the anomaly could be satisfactorily explained by assuming accidental equivalence of the bridgehead protons and those bonded to carbon-bearing-oxygen, the combined signal appearing as a four-proton multiplet at $\delta$ 4.12. Being coupled to the neighbouring methine groups, the hydroxyl protons predictably took the form of a narrow doublet ($J$=4Hz) at $\delta$ 4.62, which was completely removed by the addition of D$_2$O to the p.m.r. tube. The remainder of the spectrum consisted of a five-proton aromatic multiplet at $\delta$ 6.33-7.29 and a complex methylene envelope (8H) between $\delta$ 1.08 and 2.42.

Although the high crystallinity and narrow melting range of the product taken with its sharp spectral characteristics were indicative of an isomerically pure compound, the analytical and spectroscopic information available was insufficient in itself to differentiate between skeletal isomers. However the material was assigned as 205 (R=Ph) by analogy with previous syntheses$^{94,99,100,152}$ of 9-azabicyclo-nonanes in which [3.3.1] ringsystems have been obtained as the sole product.

Oxidation of 205 (R=Ph) to the corresponding dione (188, R=Ph) was not attempted.
These preliminary results show that the acetylation of bicyclo[3.3.1]-
nonan-2,6-diones does not proceed by a unique pathway. For the
9-methano and 9-thia cases (79 and 165) acetylation at high acidity
furnishes adamantane derivatives in synthetically useful yields;
however, the formation of a C-acetylated product without ring closure
for the 9-oxa analogue (187) cannot be satisfactorily rationalised.
In future work, an attempt should be made to resolve this disparity
and should ascertain the course of acetylation of 9-azabicyclo[3.3.1]-
onan-2,6-dione (188).

It was decided at this juncture not to return to the objective of
synthesising 156 and 157 in view of Mellor's publications 114,115 in
this field which considerably overlapped with our research interests.
However, the photochemical behaviour of 156 and 157 has been
subsequently studied by C.R.Nelson 142 who found that the extrusion
of sulphur monoxide and sulphur dioxide does not occur by a simple
process. A complete appreciation of the photochemistry of these
systems must await further investigation.
Experimental Section
General

Melting points were determined on microscope slides using coverslips on a Kofler hot-stage apparatus and are uncorrected. Qualitative infrared spectra were obtained on ca. 1-2 mg samples dispersed in pressed potassium bromide discs (300 mg) on a Perkin Elmer 257 spectrometer, calibrated with the 1603 cm\(^{-1}\) absorption of polystyrene. Quantitative infrared spectra were obtained in carbon tetrachloride or chloroform on a Perkin Elmer 225 instrument and were calibrated with the 1669, 1717.5 and 1740 cm\(^{-1}\) bands of water vapour.

Proton magnetic resonance (p.m.r.) spectra were recorded in deuterochloroform, deuterium oxide or d\(_6\)-dimethyl sulfoxide solutions on Varian T-60 and HA-100 instruments. Band positions are reported in parts per million (p.p.m.) downfield from either tetramethyilsilane, TMS, (for samples in CDCl\(_3\) and d\(_6\)-DMSO) or sodium 2,2-dimethyl-2-silapentane-5-sulphonate, DSS, (for D\(_2\)O solutions) as internal reference (\(\delta\) scale).

Ultraviolet spectra were recorded in ethanol on a Unicam SP800 grating spectrophotometer. Routine mass spectra were obtained on an AEI MS12 spectrometer while high resolution mass determinations were carried out on an AEI MS9 instrument.

Analytical thin layer chromatography (t.l.c.) was performed using layers of Merck Kieselgel G (0.25 mm) on microscope slides. Chromatograms were visualised by spraying either with ceric sulphate solution followed by heating to 120\(^\circ\), or with iodine vapour. Preparative t.l.c. was carried out using 1 mm layers of Merck Kieselgel HF\(_{254}\) silica on 20 cm x 20 cm or 20 cm x 100 cm plates and were viewed under ultraviolet light (\(\lambda\) 254 nm).
Alumina employed in column chromatography was Woelm Grade 1 (neutral) unless otherwise stated.

Petroleum spirit used was previously distilled and was of boiling range 60-80°. Other common solvents employed in preparative work were either of AnalaR grade or were distilled prior to use. Redistilled pyridine was dried over potassium hydroxide pellets and dimethyl sulphoxide was stored over 4A molecular sieves\(^{153}\). Methylene chloride was purified by passage through Woelm basic alumina (Grade 0) and was also stored over 4A molecular sieves.

Aqueous sodium hydroxide, hydrochloric acid and sodium carbonate solutions used were approximately 2N. Sodium bicarbonate and sodium chloride solutions were saturated. Solutions in organic solvents were dried over anhydrous magnesium sulphate before being stripped of solvent using a Buchi rotary evaporator in conjunction with a water aspirator.

Sulphur dichloride was freshly distilled, prior to use, from a small amount of phosphorus trichloride, the fraction boiling between 58 and 61° being retained\(^{153}\).

8N Jones reagent was prepared\(^{122,149}\) by dissolving 26.72 g AnalaR chromium trioxide in 23 ml concentrated sulphuric acid and diluting to 100 ml with distilled water.

\[ \text{2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (161)}^{118,119} \]

E,E-cycloocta-1,5-diene (50) (1944 g, 18 mol) and freshly distilled sulphur dichloride (1854 g, 18 mol) were simultaneously added dropwise over 3 hr to 2.5 l methylene chloride which was vigorously stirred
and maintained at -5°. After concentrating the mother liquors, the crystalline product was collected and recrystallised from benzene to give 161 (3207g, 15.2 mol, 84%), m.p. 99-101° (lit. 100-101°); ν\textsubscript{KBr}\text{max} 2933, 1485, 1160, 950 and 689 cm\textsuperscript{-1}; δ (CDCl\textsubscript{3}) 2.09 - 2.65 (br env, 8H, methylene groups), 2.82 (m, 2H, bridgehead protons) and 4.71 (m, 2H, H-C-Cl).

Dichloride (161) (633 g, 3 mol) was dissolved in a mixture of 31 dimethoxyethane and 31 10% aqueous sodium hydroxide solution and the mixture refluxed for 21 h under an atmosphere of nitrogen. The reaction mixture was further concentrated and the resultant precipitate filtered off. Recrystallisation from ethyl acetate-methanol gave 164 (448g, 2.6 mol, 86%), m.p. 235-240° (lit. 240-241°); ν\textsubscript{KBr}\text{max} 3346, 2909, 1430, 1021, 989 and 880 cm\textsuperscript{-1}; δ (d\textsubscript{6}-DMSO) 1.46-2.30 (br env, 8H, methylene groups), 2.46 (m, 2H, bridgehead protons), 3.99 (m, 2H, H-C-OH) and 4.91 (d, 5Hz, 2H, -OH).

9-Thiabicyclo[3.3.1]nonan-2,6-dione (165)\textsuperscript{117} and 6-hydroxy-9-thiabicyclo[3.3.1]nonan-2-one (143)\textsuperscript{112}

(a) AnalR chromium trioxide (42 g, 0.42 mol) was added in small portions to a mechanically stirred solution of 65 ml pyridine in 100 ml methylene chloride maintained at room temperature. After 15 min a solution of diol (164) (12 g, 0.07 mol) dissolved in a further 90 ml pyridine was slowly added and vigorous stirring continued for a further 30 min. The supernatant liquor was decanted off the residues extracted with boiling ethyl acetate. The combined supernatants and extracts were evaporated to small volume and residual pyridine removed by codistillation with benzene. The
residues were dissolved in ethyl acetate and washed in turn with hydrochloric acid, sodium hydroxide and water to neutrality. Drying and evaporation of solvent gave a viscous oil which was crystallised from chloroform-petroleum spirit to give \textit{165} (4.57 g, 0.027 mol, 39\%), m.p. 141-142° \textit{(lit. 117 m.p. 141-142°);} £max  2965, 1693, 1445, 1209 and 889 cm⁻¹; \(\delta\) (CDCl₃)  2.30-3.15 (m, 8H, methylene groups) and 3.39 (m, 2H, bridgehead protons).

(b) Diol \textit{(164)} (12 g, 0.07 mol) was allowed to react with chromium trioxide-pyridine complex prepared from \textit{CrO₃} (21 g, 0.21 mol) as described above. After extraction and work-up, a yellow oil (4.71 g) was obtained which was shown by \textit{t.l.c.} (chloroform-petroleum spirit, 9:1) to be a mixture of at least three components. Separation of the components was achieved by column chromatography through alumina (120 cm x 3.5 cm i.d. column containing 900 g \textit{Al₂O₃} eluted with chloroform-petroleum spirit and ethyl acetate-chloroform mixtures of gradually increasing polarity). The first component to be eluted was dione \textit{(165)} (2.61 g, 0.015 mol, 22\%) which recrystallised as above from chloroform-petroleum spirit. The second was 6-hydroxy-9-thiabicyclo[3.3.1]nonan-2-one \textit{(143)} (0.91 g, 0.005 mol, 7.5\%) and was purified by sublimation (110°, 0.05 mm Hg) to give a waxy solid, m.p. 184-186° \textit{(lit. 112 m.p. 180-182°);} £max  3404, 2921, 1686, 1462, 1230, 1034 and 900 cm⁻¹; \(\delta\) (d₆-DMSO)  1.24-3.42 (br. env., 10H, methylene groups and bridgehead protons), 3.92 (m, 1H, 
\(\text{H-C-OH}\)) and 5.11 (d, 4Hz, 1H, \(-\text{OH}\)); \textit{m/e} 172(M⁺), 154, 139, 126, 116, 100, 97 and 85; \(\lambda_{\text{max}}^{\text{EtOH}}\) 249 (log \(\varepsilon\) 2.43) and 303 nm (2.31).

The third and most polar compound was unreacted \textit{164} (1.02 g, 0.006 mol, 8.4\%).
Additional attempts to prepare 9-thiabicyclo[3.3.1]nonan-2,6-dione (165)

(a) Reaction of 164 with acetic anhydride – dimethyl sulphoxide

Diol (164) (3.2 g, 19 mmol) was dissolved in 23 ml dimethyl sulphoxide and 13 ml acetic anhydride. The solution was heated to 50° and maintained at that temperature with stirring for 72 hr. On cooling, the reaction mixture was dissolved in 100 ml methylene chloride and washed with water (12 times), aqueous sodium bicarbonate (5 times) and again with water to neutrality. Drying over anhydrous sodium sulphate followed by evaporation of solvent left a brown syrup (1.53 g). Partial purification was achieved by column chromatography (40 cm x 1.4 cm i.d. column, 40 g Al₂O₃, ether) and fractional distillation (140-144°, 0.06 mm Hg) giving a colourless oil (1.08 g) which crystallised on standing. The major component (66%) of this oil was identified as 2,6-diacetoxy-9-thiabicyclo[3.3.1]nonane (168), m.p. 97-100° (lit. 119 m.p. 100-101°); ν\textsubscript{max}\textsuperscript{KBr} 2931, 1746, 1491, 1443, 1376, 1240, 1055, 1039 and 879 cm\(^{-1}\); δ (CDCl₃) 2.02 (s, 6H, acetoxy CH₃), 1.73-2.25 (br env, 8H, methylene groups), 2.70 (m, 2H, bridgehead protons) and 5.20 (m, 2H, H-C-OAc); m/e 258(M⁺), 199, 155 and 138.

The minor component (34%) was not isolated but was tentatively assigned as monoacetate (170); δ (CDCl₃) 1.80-2.60 (br env, 8H, skeletal methylene groups), 2.09 (s, 3H, acetoxy CH₃), 2.18 (s, 3H, CH₃-S), 2.80 (m, 2H, bridgehead protons), 4.17 (m, 1H, H-C-CH₂SCH₃), 4.70 (s, 2H, -OCH₂S-) and 5.31 (m, 1H, H-C-OAc).

No oxidised products were identified.
(b) Oxidation of 164 using chromium trioxide in dimethyl formamide

164 (720 mg, 4.2 mmol) was dissolved in 50 ml dimethyl formamide. Chromium trioxide (2.52 g, 25.2 mmol) and 8 drops conc. sulphuric acid were added gradually, and the solution allowed to stir at room temperature for 24 hr. 250 ml ethyl acetate was added and the mixture washed with saturated sodium metabisulphite solution. The metabisulphite washings were back extracted with a little ethyl acetate and the combined organic solutions washed with acidified sodium metabisulphite, sodium bicarbonate and water in sequence, dried and stripped of solvent under vacuum. The residue (140 mg) was identified by its p.m.r. spectrum and by t.l.c. comparison to be mainly hydroxyketone (143).

Further attempts to prepare 165 by this method using increased amounts of oxidant and elevated temperatures (90°) also proved unsuccessful.

(c) Reaction of 2,6-dimethoxy-9-thiabicyclo[3.3.1]nonane (172) with aqueous bromine

Dimethoxide (172), b.p. 157-165° at 15 mm Hg (lit. 119 b.p. 156-160°, 18 mm Hg), was prepared in quantitative yield by the action of sodium methoxide on dichloride (161).

Bromine (129.6 g, 0.81 mol) was added dropwise over 30 min. to a mixture of 172, (20.2 g, 0.1 mol), 250 ml 0.5N aqueous sodium acetate and 250 ml acetic acid (pH 4.6). The resultant solution was stirred continuously at room temperature for 48 hr. A saturated solution of sodium sulphide was added until all excess
bromine had been removed. After concentration under reduced pressure, the residues were extracted with chloroform. The extracts were dried and stripped of solvent leaving a brown oil which was shown by p.m.r. spectroscopy to be largely unreacted starting material. On standing, brownish crystals were deposited from the crude product and were identified as dibromide (173), m.p. 131-133° (lit.119 m.p. 134.5-135.5).

No oxidised material was isolated.

Reaction of 9-thiabicyclo[3.3.1]nonan-2,6-dione (165) with acetic anhydride-toluene-p-sulphonic acid 137

Dione (165) (2.14 g, 12.6 mmol) was dissolved in 25 ml acetic anhydride, 10 mg toluene-p-sulphonic acid added and the mixture heated to reflux for 3 hr. During the following 3 hr acetic acid and acetic anhydride were allowed to distil out of the reaction mixture, fresh acetic anhydride being added occasionally to maintain a suitable level of solvent. Finally the reaction mixture was taken down to dryness and any traces of acetic anhydride removed by codistillation with benzene. The residual brown tar was extracted with boiling petroleum spirit and the combined extracts evaporated to dryness leaving a yellowish gum (2.41 g) which solidified on standing. Fractional crystallisation from ether-petroleum spirit gave 2,6-diacetoxy-9-thiabicyclo[3.3.1]-nona-2,6-diene (174) (1.46 g, 5.7 mmol, 46%), m.p. 105-107° (lit.117 m.p. 107-108°); υKBr max 2902, 2821, 1749, 1678, 1364, 1211, 1086, 898 and 683 cm⁻¹; δ(CDCl₃) 2.17 (s, 6H, acetoxyl CH₃), 2.64 (m, 4H, allylic CH₂), 3.46 (m, 2H, bridgehead CH) and 5.46 (m, 2H, olefinic CH). Thin layer chromatography (chloroform-petroleum spirit 4:1) of the residual material yielded a further 0.44 g (1.7 mmol, 14%)
bisenolacetate (174) and 2-acetoxy-9-thiabicyclo[3.3.1]non-2-en-6-one (179) (0.34 g, 1.6 mmol, 13%), m.p. 88-91° (lit.137 m.p. 88-90.5°)

\[
\begin{align*}
\text{v}_{\max}^{\text{KBr}} &= 2942, 1751, 1696, 1420, 1380, 1210, 1094, 884 \text{ and } 681 \text{ cm}^{-1}; \\
\sigma (\text{CDCl}_3) &= 2.18 (s, 3H, acetoxyl CH_3), 2.29-2.95 (br env, 6H, methylene CH_2), 3.22 (m, 1H, C(5)H), 3.50 (m, 1H, C(1)H) \text{ and } 5.64 (m, 1H, olefinic CH).
\end{align*}
\]

Reaction of 9-thiabicyclo[3.3.1]nonan-2,6-dione (165) with acetic anhydride-sulphuric acid

Dione (165) (1.70 g, 10 mmol), 25 ml acetic anhydride and 10 drops AnalaR conc. sulphuric acid were refluxed for 2 hr. Solvent was allowed to distil out over a further 3 hr, as above, leaving a black tarry residue (2.07 g) which was extracted with boiling petroleum spirit yielding, on evaporation, a yellow-green semi-solid (1.34 g). Recrystallisation of the crude product from ether-petroleum spirit gave 6-acetoxy-6-methyl-2-thiaadamantan-4,8-dione (180) (824 mg, 3.24 mmol, 32.4%), m.p. 172-172.5°; Anal. calc. for C_{12}H_{14}O_4S:

C 56.69, H 5.55%. Found: C 56.62, H 5.49%; \(v_{\max}^{\text{CCl}_4} 1752 (\epsilon^a 710, \Delta \nu^a_{\pm} 17 \text{ cm}^{-1}), 1729 (\epsilon^a 560, \Delta \nu^a_{\pm} 20 \text{ cm}^{-1}) \text{ and } 1719 (\epsilon^a 480, \Delta \nu^a_{\pm} 13 \text{ cm}^{-1}); \text{v}_{\max}^{\text{KBr}} 2985, 2942, 1740, 1712, 1238, 1102, 988 \text{ and } 971 \text{ cm}^{-1}; \sigma (\text{CDCl}_3) 1.65 (s, 3H, tertiary CH_3), 2.00 (s, 3H, acetoxyl CH_3) \text{ and } 2.51-3.64 (\text{complex m, } 8H, \text{C}(1,3,5,7)\text{H and C}(9,10)\text{H}_2); \ m/e 254 (M^+), 212, 194, 179, 166, 133, 55 \text{ and } 43; \lambda_{\text{EtOH}}^{\max} 239 (\log \epsilon 2.62), 260 (2.47), 312 \text{ nm (2.63)}.

Preparative thin layer chromatography of the mother liquors (ethyl acetate-petroleum spirit, 1:4) provided from the upper band, 174 (329 mg, 1.3 mmol, 13%) and from the lower band, 6-methylene-2-thiaadamantan-4,8-dione (182) (1.55 mg, 0.8 mmol, 8%) which
Addendum 1

The Effect of changes in sulphuric acid concentration on the reaction of 165 with acetic anhydride.

Following a similar procedure to that described on p.63, a mixture of dione (165) (1.70 g, 10 mmol) and acetic anhydride (30 ml) was reacted in the presence of varying amounts of concentrated sulphuric acid. Products were isolated by extraction of the crude reaction residues with petroleum spirit followed by preparative thin layer chromatography of the extract. Products were identified by p.m.r. spectroscopy.

(a) 18 drops c.H₂SO₄ in 30 ml acetic anhydride gave 174 (0.076 g, 0.3 mmol, 3%), 180 (0.762 g, 3.0 mmol, 30%) and 182 (0.310 g, 1.6 mmol, 16%).

(b) 24 drops c.H₂SO₄ in 30 ml acetic anhydride gave 182 (0.504 g, 2.6 mmol, 26%). No bisenol acetate (174) or diketoacetate (180) were isolated.

(c) 30 drops c.H₂SO₄ in 30 ml acetic anhydride gave 182 (0.194 g, 1.0 mmol, 10%). No 174 or 180 were isolated.
recrystallised from chloroform-petroleum spirit as colourless needles, m.p. 169-170°C; Anal. calc. for C_{10}H_{10}O_{2}S: C 61.85, H 5.19%. Found: C 61.94, H 5.23%; $\nu_{\text{max}}^{\text{CCl}_4}$ 1723 cm$^{-1}$ ($\varepsilon^a$ 740, $\Delta \nu^a_2$ 34 cm$^{-1}$); $\nu_{\text{max}}^{\text{KBr}}$ 2998, 2924, 2860, 1718, 1651, 1446, 1334, 1286, 1225, 1155, 1076, 990, 968, 907 and 766 cm$^{-1}$; $\delta$ (CDCl$_3$) 2.50-3.50 (complex m, 8H, C(1,3,5,7)H and C(9,10)H$_2$) and 4.95 (s, 2H, olefinic CH$_2$); m/e 194 (M$^+$), 166, 138, 123, 111, 105, 91 and 77; $\lambda_{\text{max}}^{\text{EtOH}}$ 261 (log $\varepsilon$ 2.42), 303 (2.21), 309 (2.22), 324 nm (2.03).

Addendum 1

Acid catalysed isomerisation of 2,6-diacetoxy-9-thiabicyclo[3.3.1]nona-2,6-diene (174)

Bisenol acetate (174) (100 mg, 0.39 mmol) and 0.1 ml of a mixture prepared from 24 drops AnalaR conc. sulphuric acid in 30 ml acetic anhydride, were maintained at 160°C for 5 hr in a sealed pyrolysis tube. On cooling and removal of solvent by codistillation with benzene, a black tarry residue was obtained which on preparative thin layer chromatography (chloroform-petroleum spirit 4:1) yielded monoenol acetate (179) (26 mg, 0.12 mmol, 31%), unreacted bisenol acetate (174) (28 mg, 0.11 mmol, 28%) and diketoacetate (180) (15 mg, 0.06 mmol, 15%). All materials were identified by p.m.r. spectroscopy and were not further purified.

Hydrolysis of 6-acetoxy-6-methyl-2-thiaadamantan-4,8-dione (180)

(a) Acetate (180) (66 mg, 0.26 mmol) and 25 ml 2N aqueous sodium hydroxide were allowed to stir at room temperature for 34 hr. After neutralisation with dilute hydrochloric acid, extraction with ethyl acetate, drying and evaporation of solvent under reduced pressure, a brown crystalline solid (51 mg) was obtained. Decolourisation with activated charcoal, followed by crystallisation from chloroform-
petroleum spirit gave colourless needles of 6-hydroxy-6-methyl-2-thiaadamantan-4,8-dione (185) (46 mg, 0.22 mmol, 83%), m.p. (sealed tube) 265-267\degree (decomp.); Anal. calc. for C_{10}H_{14}O_{3}S: C 56.60 H 5.70%. Found: C 56.76, H 5.79%; $\nu_{\text{CCL}_{4}}$ max 3606, 1729 and 1723 cm\(^{-1}\); $\nu_{\text{KBr}}$ max 3399, 2942, 1711, 1450, 1388, 1295, 1156, 1109, 971 and 944 cm\(^{-1}\); $\delta$ (CDCl\(_3\)) 1.43 (s, 3H, CH\(_{3}\)), 2.59-3.43 (br env, 9H, C(1,3,5,7)H, C(9,10)H\(_{2}\) and OH); m/e 212 (M\(^{+}\)), 179, 151, 137, 126, 113, 97 and 85; $\lambda_{\text{EtOH}}$ max 238 (log $\varepsilon$ 2.80), 268 (2.90) and 297 nm (3.17).

(b) A mixture of 180 (672 mg, 2.6 mmol), potassium hydroxide (1.4 g, 25 mmol), 10 ml methanol and 10 ml water was stirred for 65 hr. at room temperature. After neutralisation and extraction as in (a) above, preparative t.l.c. of the resultant oily product (393 mg) was carried out using ethyl acetate-chloroform (1:9). Extraction of the upper band with boiling ethyl acetate gave dione (165) (288 mg, 1.7 mmol, 65%) while the lower band gave alcohol (185) (74 mg, 0.3 mmol, 13%) each product being identified by their infrared and p.m.r. spectra.

Dehydration of 6-hydroxy-6-methyl-2-thiaadamantan-4,8-dione (185)

To a solution of 185 (171 mg, 0.81 mmol) in 15 ml dry pyridine was added 5 ml phosphorus oxychloride and the mixture refluxed for 6 hr. On cooling the reaction mixture was poured on to crushed ice, extracted with chloroform and the combined extracts washed with dilute hydrochloric acid (twice) and water to neutrality. Drying over anhydrous sodium sulphate and evaporation of solvent left a colourless semi-solid which was crystallised from chloroform-petroleum spirit to give alkene (182) (58 mg, 0.3 mmol, 37%) identical in all aspects to an authentic sample.
Preparation of Meerwein's Tetraester-1,3,5,7-tetra(methoxycarbonyl)-bicyclo[3.3.1]nonan-2,6-dione (4)\textsuperscript{17}

Tetraester (4) was prepared by the method of Schaefer and Honig,\textsuperscript{47} from dimethyl malonate (61 g, 0.5 mol) and 95% paraformaldehyde (12 g, 0.38 mol) using 2 ml piperidine as catalyst. Crystallisation of the crude product from benzene gave 4 (29.76 g, 0.078 mol, 62%) m.p. 159-162\degree (lit.\textsuperscript{47} m.p. 163-164\degree); $\nu_{\text{max}}^{\text{KBr}}$ 2956, 1743, 1664, 1624, 1445, 1328, 1266, 1039, 997 and 836 cm$^{-1}$; $\delta$ (CDCl$_3$) 2.32 (s, 2H, C(9)H$_2$), 2.86 (s, 4H, C(4,8)H$_2$) 3.76 (s, 12H, CH$_3$) and 3.80 (s, 2H, C(3,7)H).

Decarboxylation of tetraester (4) to bicyclo[3.3.1]nonan-2,6-dione (79)\textsuperscript{17,136}

A mixture of 4 (10 g, 26 mmol), 50 ml conc. hydrochloric acid and 35 ml water were refluxed for 17 hr. Removal of solvent under vacuum left a brownish residue which was sublimed (140\degree, 0.5 mm Hg) to give a colourless solid. Recrystallisation from benzene gave prismatic dione (79) (2.48 g, 16.3 mmol, 63%), m.p. 138-142\degree (lit.\textsuperscript{17} m.p. 141\degree); $\nu_{\text{max}}^{\text{KBr}}$ 2937, 1689, 1441, 1325, 1234, 995, 861 and 762 cm$^{-1}$; $\delta$ (CDCl$_3$) 1.81-2.57 (m, 10H, CH$_2$) and 2.85 (m, 2H, CH).

Reaction of bicyclo[3.3.1]nonan-2,6-dione (79) with acetic anhydride-conc. sulphuric acid

To a solution of diketone (79) (510 mg, 3.35 mmol) in 8 ml acetic anhydride was added 4 drops concentrated sulphuric acid and the mixture refluxed for 3 hr. Solvent was allowed to distil out as in the acetylation of 165 and the residue extracted with ether. Evaporation of the combined extracts gave a yellow oily solid (559 mg) which on preparative t.l.c. (ethyl acetate-hexane 3:7) yielded three major products. Extraction of the uppermost band gave a colourless solid
which crystallised from ether-petroleum spirit as prisms of
2,6-diacetoxybicyclo[3.3.1]nona-2,6-diene (177) (142 mg, 0.6 mmol, 18%),
m.p. 77-79° (lit. 136 m.p. 78-79°); \( \nu_{\text{KBr}}^{\text{max}} \) 2939, 1743, 1438, 1368, 1214,
1104 and 908 cm\(^{-1}\); \( \delta \) (CDCl\(_3\)) 1.92 (m, 2H, C(9)\_H\(_2\)), 2.12 (s, 6H, CH\(_3\)),
2.28 (m, 4H, allylic CH\(_2\)), 2.56 (m, 2H, C(1,5)\_H) and 5.37 (m, 2H,
C(3,7)\_H); m/e 236 (M\(^+\)) 194, 152. The middle band furnished
4-methyleneadamantan-2,6-dione (189) (183 mg, 1.04 mmol, 31% from
chloroform-hexane), m.p. (sealed tube) 160-162° (lit. 148 m.p. 163-164°);
\( \nu_{\text{CHCl}_3}^{\text{max}} \) 1727 (\( \varepsilon \) 735) and 1715 cm\(^{-1}\) (910); \( \nu_{\text{KBr}}^{\text{max}} \) 2941, 2869, 1723,
1708, 1647, 1457, 1296, 1229, 991 and 907 cm\(^{-1}\); \( \delta \) (CDCl\(_3\)) 2.00-2.53
(br env, 6H, C(8,9,10)\_H\(_2\)), 2.93 (m, 2H, C(1,7)\_H), 3.37 (m, 2H, C(3,5)\_H)
and 4.86 (s, 2H, olefinic CH\(_2\)); m/e 176 (M\(^+\)), 148, 133, 120 and 105.
Recrystallisation from ether-petroleum spirit of the solid obtained
by extracting the lowest band gave colourless needles of 4-acetoxy-4-
methyladamantan-2,6-dione (190) (159 mg, 0.67 mmol, 20%), m.p. (sealed
tube) 124-126°; Anal. calc. for C\(_{13}\)H\(_{16}\)O\(_4\): C 66.08, H 6.83%. Found:
C 66.32, H 6.81%; \( \nu_{\text{CCl}_4}^{\text{max}} \) 1750 (\( \varepsilon \) 560, \( \Delta \nu^{\text{a}} \)) 24 cm\(^{-1}\), 1724 cm\(^{-1}\)
(\( \varepsilon \) 820, \( \Delta \nu^{\text{a}} \)) 28 cm\(^{-1}\); \( \nu_{\text{KBr}}^{\text{max}} \) 2940, 1720, 1466, 1380, 1238, 1221,
1101, 1015, 985 and 760 cm\(^{-1}\); \( \delta \) (CDCl\(_3\)) 1.62 (s, 3H, tertiary CH\(_3\)),
2.04 (s, 3H, acetoxyl CH\(_3\)), 1.80-2.60 (br env, 6H, CH\(_2\)), 2.70 (m, 2H,
C(1,7)\_H) and 3.25 (m, 2H, C(3,5)\_H); m/e 236 (M\(^+\)), 194, 176, 148, 120,
108, 99, 55 and 43.

Reaction of Meerwein's Tetraester (4)\(^{17}\) with acetic anhydride-
c onc. sulphuric acid.

Tetraester (4) (1.0 g, 2.62 mmol), 8 ml acetic anhydride and 3 drops
concentrated sulphuric acid were refluxed for 65 hr. Removal of
solvent and extraction of the residue with ether gave a yellow oily
product (608 mg). Preparative t.l.c. of the product showed two major
bands. Extraction of the upper band gave, as a colourless oil, 2,6-diacetoxy-1,5-di(methoxycarbonyl)bicyclo[3.3.1]nona-2,6-diene (193) (236 mg, 0.67 mmol, 26%), \[\delta (\text{CDCl}_3) 2.09 \ (s, \ 6\text{H, acetoxyl CH}_3), 2.36 \ (s, \ 2\text{H, C(9)H}_2), 2.62 \ (m, \ 4\text{H, C(4,8)H}_2), 3.70 \ (s, \ 6\text{H, OCH}_3) \text{ and } 5.59 \ (m, \ 2\text{H, C(3,6)H}).\] Isolated from the lower band, also as a colourless oil, was 2,6-diacetoxy-1,3,5-tri(methoxy-carbonyl)bicyclo[3.3.1]nona-2,6-diene (194) (372 mg, 0.91 mmol, 35%); \[\delta (\text{CDCl}_3) 2.10 \ (s, \ 3\text{H, acetoxyl CH}_3), 2.18 \ (s, \ 3\text{H, acetoxyl CH}_3), 2.41 \ (s, \ 2\text{H, C(9)H}_2), 2.67 \ (m, \ 2\text{H, C(8)H}_2), 2.92 \ (s, \ 2\text{H, C(4)H}_2), 3.73 \ (s, \ 9\text{H, OCH}_3) \text{ and } 5.61 \ (m, \ 1\text{H, C(7)H}).\] Attempts at purification by recrystallisation and chromatography proved unsuccessful, and were not pursued.

9-oxabicyclo[3.3.1]nonan-2,6-diol (196) and 9-oxabicyclo[4.2.1]-
nonan-2,5-diol (197)

To 90% formic acid (100 ml) at 0°, was added 30% hydrogen peroxide (70 ml), maintaining vigorous stirring. Cycloocta-1,5-diene (50) (48.4 g, 0.45 mol) was added to the mixture over a period of 30 min. The mixture was stirred for 2 hours at 0° and allowed to come to room temperature overnight. After evaporation of volatiles under reduced pressure, 5N sodium hydroxide (30 ml) was added and the mixture heated to 100° for 45 min. On cooling a colourless, highly crystalline solid (26.3 g) separated out. Recrystallisation from ether gave colourless needles of a mixture of diols 196 and 197 (19.3 g, 0.12 mol, 27%) m.p. 56-66° (lit. 54 m.p. of 196 is 82-83°) \(v_{\text{KBr}}^\text{max} 3420, 2911, 1665, 1482, 1350, 1230, 1049, 974 \text{ and } 873 \text{ cm}^{-1}.\)
A mixture of diols (196 and 197) (4.74 g, 30.8 mmol), obtained as above was dissolved in acetone (100 ml), 8N Jones reagent (18 ml) added and the mixture stirred at room temperature for 30 min. After neutralisation with saturated sodium bicarbonate solution, the reaction mixture was continuously extracted with ethyl acetate for 2 days. Thin layer chromatography (ethyl acetate-benzene 1:2) of the ethyl acetate extracts gave a mixture of diketones (187 and 195) (2.21 g, 14.4 mmol, 46.6%) as a colourless oil which could not be made to solidify; $\nu_{\text{KBr}}^{\text{max}}$ 2954, 1716, 1421, 1316, 1254, 1086, 960 and 870 cm$^{-1}$; $\delta$(CDCl$_3$) 1.66-3.29 (br env), 4.44 (m) and 4.68 (m).

Acetylation of 187 and 195

A portion (1.04 g, 6.76 mmol) of the mixture of 187 and 195 obtained above was dissolved in acetic anhydride (25 ml), toluene-p-sulphonic acid (20 mg) added and the mixture refluxed for 42 hr. Evaporation to dryness and extraction of the residue with ether gave a brown oil (1.39 g). Thin layer chromatography (ethyl acetate-benzene 1:3) gave 2,6-diacetoxy-9-oxabicyclo[3.3.1]nona-2,6-diene (198) (830 mg, 3.5 mmol, 52%) which was sublimed (85°, 0.03 mm Hg) to give colourless needles, m.p. 89-91°; Anal. calc. for $C_{12}H_{14}O_5$: C 60.50, H 5.92%. Found: C 60.34, H 5.77%; $\nu_{\text{CCl}_4}^{\text{CCl}_4}$ 1765 cm$^{-1}$ ($\varepsilon$ 440, $\Delta\nu^a_2$ 31 cm$^{-1}$); $\nu_{\text{KBr}}^{\text{max}}$ 2941, 2841, 1758, 1690, 1431, 1368, 1208, 1114, 1042, 979, 940 and 897 cm$^{-1}$; $\delta$(CDCl$_3$) 2.11 (s, 6H, CH$_3$), 2.51 (m, 4H, CH$_2$), 4.39 (m, 2H, C(1,5)H) and 5.52 (m, 2H, C(3,7)H); m/e 238 (M$^+$), 196, 154, 136, 126, 97, 83, 70, 55 and 43.

2,5-diacetoxy-9-oxabicyclo[4.2.1]nona-2,4-diene (199) was not isolated.
Acid-catalysed hydrolysis of 198

A mixture of 198 (800 mg, 3.36 mmol) and 2N hydrochloric acid (25 ml) was refluxed for 16 hrs. On cooling and neutralisation with saturated sodium bicarbonate, the reaction mixture was continuously extracted with ethyl acetate for 6 hr. The extract was dried and evaporated, and the solid residue recrystallised from ether-petroleum spirit to give 9-oxabicyclo[3.3.1]nonan-2,6-dione (187) (437 mg, 2.84 mmol, 84%), m.p. 53-56° (lit. 149 m.p. 54-55°); ν<sub>max</sub> KBr 2950, 1720, 1441, 1244, 1080, 956 and 865 cm<sup>-1</sup>; δ (CDCl<sub>3</sub>) 1.73-3.24 (br env, 8H, CH<sub>2</sub>) and 4.44 (m, 2H, C(1,5)H).

Acetylation of 187 using acetic anhydride - conc. sulphuric acid

Dione (187) (220 mg, 1.43 mmol), acetic anhydride (8 ml) and concentrated sulphuric acid (5 drops) were refluxed for 4 hr. The reaction mixture was stripped of solvent and extracted with ether as already described. Preparative thin layer chromatography of the yellow oily extract (180 mg) employing ethyl acetate-benzene (1:3) yielded 198 (78 mg, 0.33 mmol, 23%) and, from the uppermost band, 3,7-diacetyl-9-oxabicyclo[3.3.1]nonan-2,6-dione (202) (54 mg, 0.23 mmol, 16%) which sublimed (110°, 0.03 mm Hg) as colourless needles, m.p. 154-156°; Anal. calc. for C<sub>12</sub>H<sub>14</sub>O<sub>5</sub>; C 60.50, H 5.92%. Found: C 60.25, H 5.93%; ν<sub>max</sub> KBr 2940, 2849, 1600 (br complex) 1413, 1359, 1292, 1231, 1105, 1010, 924 and 723 cm<sup>-1</sup>; δ (CDCl<sub>3</sub>) 2.05 (s, 6H, CH<sub>3</sub>), 2.35 (s, 2H, enol OH), 2.66 (dd, J=15 and 1.5 Hz, 2H, C(4,8)H<sub>2</sub>) 3.01 (dd, J=15 and 6 Hz, 2H, C(4,8)H<sub>2</sub>) and 4.53 (dd, J=6 and 1.5 Hz, 2H, C(1,5)H); m/e 238 (M<sup>+</sup>), 164, 121, 93, 65 and 43.
Epoxidation of 50

Cycloocta-1,5-diene (50) (13.0 g, 0.12 mol) was added dropwise to a solution of m-chloroperbenzoic acid (62.0 g, 0.32 mol) in 500 ml chloroform which was magnetically stirred and cooled to 0°. Stirring was continued for a further 18 hr at room temperature, the solution filtered to remove m-chlorobenzoic acid and the filtrate washed with 2N sodium hydroxide (twice) and water to neutrality. Drying and evaporation gave a yellow oil (20.3 g) which was chromatographed over basic alumina (Woelm Grade 0, 150 g, ether-petroleum spirit). Fractions eluted with ether-petroleum spirit, 1:1 gave colourless needles of cycloocta-1,5-diene diepoxide (163), (12.32 g, 0.088 mol, 73%), m.p. 24-25° (lit. 120 m.p. 25-27°); \( \nu_{\text{max}}^\text{CCl}_4 \) 2945, 2851, 1468, 1447, 1021, 919, 869 and 776 cm\(^{-1}\); \( \delta(\text{CDCl}_3) \) 1.93 (m, 8H, CH\(_2\)) and 2.93 (m, 4H, CH).

Later fractions (ether-petroleum spirit 4:1) were combined to give a mixture of m-chlorobenzoate esters, (207 and 208) as a viscous colourless oil (4.03 g, 0.014 mol, 11%), \( \nu_{\text{KBr}}^\text{max} \) 3448, 3067, 2940, 1724, 1426, 1286, 1255, 1127, 1054, 975, 896 and 746 cm\(^{-1}\); \( \delta(\text{CDCl}_3) \) 1.60-2.31 (br env, 8H, CH\(_2\)), 2.34 (m, 1H, OH), 3.94 (m, 2H, bridgehead CH), 4.52 (m, 1H, CHO\(_{\text{OH}}\)), 5.32 (m, 1H, CHO\(_{\text{COAr}}\)) and 7.18-7.95 (br env, 4H, aromatic protons); m/e 296 (M\(^+\)), 278, 239, 157, 139 and 122.

Condensation of aniline with 163

163 (1.00 g, 7.14 mmol), aniline (660 mg, 4.62 mmol) and 2 ml AnalAr methanol was heated to 105° for 14 hr in a sealed pyrolysis tube. On cooling the mixture was evaporated to dryness leaving a
pale brown crystalline solid, which was recrystallised from ethyl acetate-ether to give colourless prisms of 2,6-dihydroxy-N-phenyl-9-azabicyclo[3.3.1]nonane (205, R=Ph), m.p. 176-178°; Anal. calc. for C_{14}H_{19}NO_2: C 72.07, H 8.21%. Found: C 72.20, H 8.38%;

\[ \nu_{\text{KBr}} \text{ cm}^{-1}: 3365, 2940, 1599, 1507, 1385, 1316, 1048, 993, 879, 749 \] and 690 cm\(^{-1}\);

\[ \delta_{\text{d}_{6}-\text{DMSO}} \text{ (m, 8H, CH}_2\text{), 4.12 (m, 4H, C(1,5)H and CHO)} \text{H}, 4.62 (d, J=4 Hz, 2H, OH) and 6.33-7.29 (br env, 5H, aromatic CH); m/e 233 (M^+) \text{, 216, 174, 146, 145, 144, 119 and 104.} \]
Part Three

The Preparation, Rearrangement and Pyrolytic Decomposition of \(N\)-(9-Thiabicyclo[3.3.1]nonyl)-Pyridinium Salts
As part of a proposed synthetic pathway to 2,6-dithiaadamantane (211) derivatives, it was necessary to prepare 9-thiabicyclo[3.3.1]nona-2,6-diene (212). Although this compound was first reported in 1971 to be produced by the pyrolytic decomposition of adipate ester (313) (Scheme 70), subsequent attempts to repeat the preparation, yielded, instead, the rearranged diene (229) and it thus became apparent that the original structural assignment had been in error. In 1974, however, McNicol showed that monocyclic dibromodiene (57), which is obtained by the capricious allylic bromination of cycloocta-1,5-diene (50), reacted with sodium sulphide to produce 212 in moderate yield (22%). Nevertheless, there seemed to be no obvious reason why 212 could not be obtained by a simple dehydrochlorination of dichloride (161), which had been prepared in abundance by the quantitative condensation of sulphur dichloride with 50. The following paragraphs, however, illustrate that double dehydrochlorination of 161 is not a straightforward process.

A number of methods for the dehydrohalogenation of alkyl halides have been described in the literature. Several of these, unfortunately, had already been shown to be unsuitable for the preparation of diene (212). In particular, the pyrolysis of 161 has been demonstrated to effect only partial loss of hydrogen chloride, the major product being chloroalkene (213). Also inapplicable was the use of strong bases such as sodium hydroxide and sodium ethoxide which furnish, instead, diol (164) and diether (214) respectively as a result of the sulphur-assisted nucleophilic displacement of chloride ion.
Scheme 70

265°

229

211

212

313

50

NBS

Br

57

Na₂S

212

213

161  x = Cl

164  x = OH

214  x = OC₂H₅
A third alternative, yet to be investigated, was the treatment of 161 with an organic base such as pyridine or triethylamine. Accordingly dichloride (161) was refluxed in an excess of dried pyridine. A fine colourless precipitate, thought to be pyridine hydrochloride, appeared almost immediately, and continued to accumulate as the reaction proceeded. After removal of this solid by filtration, work-up of the ether-soluble residues was notable in its failure to produce any of the expected diene (212).

P.m.r. examination of the recrystallised water-soluble precipitate, which proved to be the only reaction product, established the presence of several functional groups. As expected, the farthest downfield signals, appearing at δ 8.22 (triplet), 8.71 (triplet) and 9.15 (doublet), and integrating in the ratios 2:1:2, confirmed the existence of pyridinium moieties. These signals were accompanied by a typical 9-thiabicyclo[3.3.1]nonane bridgehead resonance at δ 3.48 together with a methylene envelope between δ 2.30 and 2.64 which was in profile rather more complex than that of the parent dichloride (161). The most interesting feature of the spectrum was what appeared to be a pair of small partially overlapping triplets centred around δ 5.80, the unambiguous assignment of which could not be made from the information available at the time. It seemed probable, however, that these multiplets arose from either hydrogen on olefinic carbon, suggesting a certain degree of dehydrochlorination, or hydrogen on carbon bearing cationic nitrogen 157 , formed through nucleophilic displacement of chloride by pyridine.
Unfortunately, a full structural identification was hampered by the presence of an intense water signal at 94.65 which persisted despite several attempts to dry the precipitate by heating in vacuo. Considered to arise from water of crystallisation in the ionic product, the signal caused base-line distortion and prevented accurate integration of several of the less intense but structurally more important spectral features. Moreover, it was impossible to tell if any additional product resonances were concealed under this signal.

Based on the alternative assignments of the multiplets in the 95.80 region (vide supra) and barring structural isomerisation, two possibilities for the nature of the product were envisaged. If these signals were indeed due to hydrogen on positive nitrogen, and no other resonances were present in the same region (ie under the water singlet), it followed that the product was bispyridinium salt (215). On the other hand, if the pair of triplets arose from protons attached to a carbon-carbon double bond, the product had to be a mixture of pyridine hydrochloride and the monopyridinium salt (216). There seemed little prospect of obtaining the latter in a pure state from this mixture.

Because of their close structural similarity, it was impossible to distinguish with certainty, either spectroscopically or microanalytically, between the two possible product compositions. It was concluded, therefore, that the problem could most easily be resolved by comparison of the product spectra with those of an authentic sample of pure monopyridinium salt (216), prepared by an independent route.
Scheme 71

161 $\xrightarrow{168^\circ}$ -HCl $\rightarrow$ 213 $\xleftrightarrow{\text{H}_2\text{O}}$ -HCl $\rightarrow$

218 $\xrightarrow{219}$ -HCl $\rightarrow$ 217 $\xrightarrow{\text{N}}$ 216

172 $X=Y=\text{OCH}_3$
173 $X=Y=\text{Br}$
220 $X=Y=\text{I}$
221 $X=\text{Cl}, Y=\text{OH}$
222 $X=\text{Cl}, Y=\text{OCH}_3$
In order to prepare 216, the simplest approach appeared to be an initial elimination of hydrogen chloride from 161 forming chloroalkene (213), which could then be converted to the desired product by reaction with pyridine (Scheme 71). The first stage of this synthesis was achieved by pyrolysis of 161 at 168° in sealed tubes (vide supra). Distillation of the crude product yielded 213 as a colourless liquid which had spectroscopic properties consistent with the assigned structure. The susceptibility of the remaining chlorine substituent to nucleophilic displacement is clearly demonstrated by the two interesting by-products which are invariably formed during this reaction. The major impurity, hydroxyalkene (217), is believed to arise by reaction of 213 with water adhering to the walls of the pyrolysis tube and its yield may be suppressed by flame drying the glassware prior to use. Once formed, however, 217 may react further with another molecule of 213 to give the other less abundant impurity, di(9-thiabicyclo[3.3.1]non-2-en-6-yl)ether (218).

During the formation of these compounds the departure of chloride is without doubt anichmerically assisted by sulphur and proceeds via the episulphonium ion (219) (Scheme 71). The occurrence of episulphonium intermediates in the reactions of 9-thiabicyclo[3.3.1]-nonane derivatives has been accepted for several years although their existence has not been directly proved.

An interesting development of the concept has however recently been published by Vincent, who has studied the behaviour of compounds (161, 164, 172, 173, 220, 221 and 222).
at low temperatures in a variety of highly acidic media such as a mixture of $\text{FSO}_3\text{H}$ and liquid $\text{SO}_2$. Based on $^{13}\text{C}$ magnetic resonance results it was reported that dichloride (161) at $-60^\circ$ exists predominantly as the twistanoid sulphonium (chloronium) ion (223) which on warming to $-30^\circ$ reverts to the more conventional episulphonium species (224) (Scheme 72), and that these intermediates are possibly present during the solvolysis of 161 in methanol or aqueous dioxane. Although analogous results have been obtained for dibromide (173) and diiodide (220), related compounds such as diol (164), dimethoxide (172) and chlorides (221 and 222) have been observed only in the simpler episulphonium form inferring that oxygen is unable to participate in the same manner as chlorine in the formation of twistanoid intermediates.

Dehydrochlorination of chloroalkene (213) was not as clear-cut as at first believed. During the initial attempts to prepare 216 by refluxing 213 with an excess of pyridine, the expected ionic precipitate either failed to appear or took the form of an impure, highly coloured solid which eventually deposited on standing. Recrystallisation of the product furnished crystals which melted at 90-93° and which gave microanalytical figures in good agreement with those expected of monopyridinium salt (216). However, the p.m.r. spectrum of the product was extremely complex and could not be completely explained by the presence of 216 alone. Two partly distinct sets of pyridinium resonances were visible in the $\delta$ 8.00 - 9.14 region and were accompanied by both sharp ($\delta$ 6.09) and broad ($\delta$ 5.88 and 6.34) signals in the olefinic region. Medium intensity envelopes attributable to bridgehead protons ($\delta$ 3.46) and hydrogen on carbon bearing pyridinium ($\delta$ 5.45) were also of an unexpectedly complex nature and it was concluded, in accord with the micro-
Scheme 72

\[ \text{Scheme 72} \]

\[ \begin{align*}
223 & \xrightarrow{\text{FSO}_3\text{H}, \text{SO}_2, -60^\circ} \text{Cl}^+ \\
161 & \xrightarrow{\text{FSO}_3\text{H}, \text{SO}_2, -30^\circ} 224 \\
\end{align*} \]

\[ \begin{align*}
164 & \quad X=\text{OH} \\
172 & \quad X=\text{OCH}_3 \\
221 & \quad X=\text{OH}, Y=\text{Cl} \\
222 & \quad X=\text{OCH}_3, Y=\text{Cl} \\
\end{align*} \]
Figure 7

The 100 MHz p.m.r. spectra of (a) 215, (b) 216 and (c) a 2:1 mixture of 216 and 225.
analytical data, that the observed product was a mixture of skeletal isomers 216 and 225 (in the approximate ratio of 2:1 as estimated by integration of the pyridinium signals). The p.m.r. spectra of the isomeric mixture and pure 216 are compared in Figure 7.

As the formation of 9-thiabicyclo[4.2.1]nonyl salt (225) was thought to be favoured by elevated temperatures further attempts to prepare 216 were carried out below 40°. Under these conditions a colourless precipitate was formed on standing for several days. Melting at 215 - 217°, the microcrystalline solid gave, without further purification, satisfactory analytical figures for a formula of C_{13}H_{16}CINS. The p.m.r. spectrum of the product exhibited sharp pyridinium resonances at δ 8.12 (2H), 8.60 (1H) and 9.01 (2H), a crisp one-proton H-C-N signal at δ 5.45, a complex bridgehead multiplet (2H) at δ 3.46 and a broad methylene envelope between δ 1.87 and 2.90 integrating for six protons. The presence of a carbon-carbon double bond was supported by a sharp multiplet (2H) at δ 6.09 and a medium intensity absorption at 1630 cm⁻¹ in the infrared spectrum.

The arrangement of functional groups and the presence of a bicyclo-[3.3.1]nonane skeleton was established by double irradiation experiments on the p.m.r. sample. Thus secondary irradiation at δ 5.45 (H-C-N⁺) sharpened only the bridgehead (δ 3.46) and upfield methylene (δ 2.34) signals while irradiation at δ 2.72 (allylic methylene) collapsed both bridgehead and vinyl multiplets. Double irradiation of the bridgehead multiplet (δ 3.46) effected a sharpening of all other skeletal absorptions. The above evidence eliminates 225 and confirms 216 as the true structure of the product.
Subsequent attempts to purify the crude precipitate obtained above, using hot solvents, resulted in the recovery of low-melting (110-121°) isomeric mixtures of 216 and 225 similar to those previously described. In rationalisation, it appears that, on heating, the proximity of a good leaving group (pyridine) to the electron-rich sulphur bridge of 216 promotes anchimERICALLY assisted fission of the C-N bond yielding the episulphonium species (219) (Scheme 73). Recombination of this ion with nucleophilic pyridine may occur at either C(5) or C(6) resulting in the observed product mixture.

Interestingly recrystallisation of the crude product from cold chloroform-ether also resulted in the recovery of crystals possessing an unexpectedly low melting point (111-113°). Although p.m.r. spectroscopy confirmed that no structural rearrangement had taken place, an intense signal at δ 4.70 revealed the presence of water of crystallisation in the sample. Subsequent microanalytical results were in accord with the hydrated salt having the formula \((C_{13}H_{16}C1NS)_2\cdot3H_2O\).

The structure of monopyridinium salt (216) being firmly established, it was clear by spectral comparison that this compound was not formed during the reaction of 161 with pyridine, but rather that the ionic precipitate isolated was indeed bispyridinium salt (215). The p.m.r. spectrum (Figure 7) of a twice recrystallised sample of the product, showed improved resolution over earlier spectra, and was in good agreement with this structure, each band integrating for the requisite number of protons. Moreover, in support of their resultant assignment as hydrogen on carbon bearing pyridinium, the
Figure 8

$^{13}$C noise-decoupled n.m.r. spectrum of 215 (Varian XL-100)
overlapping triplets (2H) at δ 5.80 bore a close resemblance, in profile and chemical shift, to the corresponding signal of 216.

The position of the two proton bridgehead signal (δ 3.48) was consistent with a bicyclo[3.3.1]nonane skeleton and was strongly supported by the appearance in the infrared spectrum of an anomalously high carbon-hydrogen bending mode at 1485 cm⁻¹ which was attributable to the non-bonded interaction of endo-protons attached to C(3) and C(7).

The overall sharpness of the p.m.r. spectrum, particularly the aromatic resonances, reflected the purity of the product. That 215 was not contaminated by structural isomer 226 was further shown by the ¹³C n.m.r. spectrum (Figure 8) which revealed the presence of only seven magnetically distinct carbon atoms whose signals possessed the expected multiplicity when recorded with off resonance decoupling.

Microanalysis agreed most closely with a molecular formula of C₁₈H₂₈Cl₂N₂O₅S and indicated that the recrystallised salt existed as the trihydrate. An attempt to obtain additional structural information by mass spectrometry was however unsuccessful due, most probably, to the involatility of the ionic solid the spectrum showing only signals which were attributed to a trace quantity of 161 in the sample.

Treatment of dibromide (173) and diiodide (220) with pyridine resulted in the formation of bispyridinium salts (227 and 228) which were identical to 215 in spectroscopic properties but differed by the nature of the anion present.
Pyrolysis of salts (215 and 216)

It has been shown above that the pyridinium substituent of 216 is extremely labile and that the C-N bond is readily cleaved by warming in solvent. It was thus felt that pyrolysis of 215 and 216, in the absence of nucleophiles, could lead to the formation of olefins by Hofmann elimination of pyridine hydrochloride.

Normally, Hofmann eliminations are performed on aqueous solutions of quaternary ammonium hydroxides, obtained from the corresponding halides by treatment with moist silver oxide. However, the use of standard Hofmann conditions for the pyrolysis of 215 and 216 were considered inappropriate due to the strong possibility of forming ethers and/or hydroxylated products similar to those obtained during the pyrolysis of 213 (vide supra).

The pyrolysis of 215 was carried out at 250° on a sample of the crude product obtained by reacting 161 with pyridine under strictly anhydrous conditions. The p.m.r. spectrum of the ether soluble fraction of the pyrolysis product exhibited prominent multiplets at δ 2.21, 4.00, 5.81 and 6.40 showing the major component to be the skeletally rearranged diene (229)\textsuperscript{158}. 229 was accompanied by small amounts of 217 and 218 (<5%) but no signals arising from diene (212) were detected.

At 104°, monopyridinium salt (216) was stable to decomposition and was thus unlike the quaternary ammonium hydroxides used in Hofmann eliminations\textsuperscript{161}. However, at higher temperature (250°), 216 behaved in an analogous manner to 215, by eliminating pyridine hydrochloride to give diene (229), contaminated by small amounts of
Related attempts to dehydrochlorinate 161

Two alternative methods for converting 161 into diene (212) have been investigated

(a) Reaction with 2,4,6-collidine (230)

Treatment of 161 with refluxing 2,4,6-collidine (230) has been shown to promote smooth dehydrochlorination with structural rearrangement to give the thermodynamically more stable diene (229) (Scheme 75) in a reaction which is mechanistically related to the pyrolytic decomposition of 215 (vide supra). Although of comparable basicity, 230 is a much poorer nucleophile than pyridine due to steric hindrance by methyl groups in the 2- and 6- positions and, as a result, a collidinium analogue of 215 has not been observed. In contrast, the reaction of collidine with dibromide (173) and diiodide (220) has resulted in the isolation of biscollidinium salts (231 and 232), the formation of which has been facilitated by the increased leaving group ability of bromide and iodide.

(b) Reaction with potassium t-butoxide in DMSO or t-Butanol

Potassium t-butoxide has been widely used to dehydrohalogenate alkyl halides because of its strong basicity combined with poor nucleophilicity. In the reaction of
t-butoxide with secondary or tertiary alkyl halides, where a number of isomeric alkenes may be formed, the observed product often arises by anti-Saytzeff elimination following the preferential abstraction of the least sterically hindered proton. Because of its strongly basic character, KOBu has also been used to accelerate the prototropic isomerisation of olefins.

The reaction of 161 with potassium t-butoxide in t-butanol or DMSO failed to produce either of the expected dienes (212 or 229). Instead the major product of the reaction was the highly rearranged episulphide (233). This novel dechlorination - rearrangement is rationalised (Scheme 76) by the sulphur-assisted expulsion of chloride followed by nucleophilic attack of t-butoxide (or dimsyl anion) on chlorine. The formation of 233 is strong evidence for the intermediacy of episulphonium ion (224) since the three-membered ring of 224 is retained in the product. Dibromide (173) and diiodide (220) react with potassium t-butoxide in the same manner as 161.

During the above attempts to prepare diene (212) MacNicol described his synthesis of this compound. He privately communicated to Dr. P.H. McCabe that the condensation of 212 with sulphur dichloride furnished a mixture in which the presence of dithiaadamantanes was not definitely ascertained. With this prior knowledge, no attempt was made to repeat MacNicol's synthesis nor to explore alternative routes to 212, the suitability of which as a precursor of tricyclic systems remains to be established.
Scheme 76

161 $\xrightarrow{\text{KOBu}^+ \quad \text{DMSO}}$ 224 $\xrightarrow{\text{B}^-}$ 233

$B^- = (\text{CH}_3)_3\text{CO}^-$ or $\text{CH}_3\text{SOCH}_2^-$
Experimental Section
Attempted dehydrochlorination of 161

A solution of 161 (1.13 g, 5.4 mmol) in dried pyridine (5 ml) was refluxed for 3 hr. On cooling, the colourless precipitate was removed by filtration, washed with a little ethanol, dried and collected. Recrystallisation from aqueous methanol gave highly crystalline N,N'-(9-thiabicyclo[3.3.1]non-2,6-diyl)bispyridinium dichloride (215), trihydrate (1.57 g, 3.71 mmol, 69%), m.p. 238-240° (decomp.); Anal. calc. for C_{18}H_{28}Cl_{2}N_{2}O_{3}: C 51.06, H 6.67, N 6.62%. Found: C 51.40, H 6.56, N 6.58%; v_{max}^{KBr} 3387, 3130, 3056, 2939, 2856, 1630, 1575, 1480, 1340, 1140, 1026, 868, 770, 721 and 682 cm^{-1}; θ (D_{2}O) 2.30-2.64 (m, 8H, CH_{2}), 3.48 (m, 2H, C(1,5)H), 5.80 (m, 2H, C(2,6)H), 8.22 (t, 4H, C(3',5')H), 8.71 (t, 2H, C(4')H) and 9.15 (d, 4H, C(2',6')H); λ_{max}^{EtOH} 256 (sh, log ε 3.90), 2.62 (3.99) and 269 nm (sh, 3.90).

Pyrolytic dehydrochlorination of 161

161 (12.0 g, 56.9 mmol) was vacuum sealed in four flame-dried Pyrex pyrolysis tubes (50 cm x 1.5 cm i.d.) and heated at 168° for 19 hr. On cooling, the brown viscous liquid product was extracted with ether and the extract, after removal of solvent, distilled in vacuo to give chloroalkene (213) (7.22 g, 41.4 mmol, 73%), b.p. 84-90°, 0.8 mm Hg (lit. 119 b.p. 64-69°, 0.3 mm Hg); v_{max}^{CCL_{4}} 3027, 2937, 2846, 1651, 1452, 1208, 1077, 876, 688 and 659 cm^{-1}; θ (CDCl_{3}) 2.04 (m, 4H, C(7,8)H_{2}), 2.58 (m, 2H, C(4)H_{2}), 3.10 (m, 2H, C(1,5)H), 4.56 (m, 1H, H-C-Cl) and 5.84 (m, 2H, olefinic CH).

Later fractions boiling at 90-98°, 98-105° and 105-107° contained 213 contaminated by increasing amounts of 217 and 218.158.
Reaction of 213 with pyridine

(a) 213 (350 mg, 2.0 mmol) dissolved in anhydrous pyridine (5 ml) was refluxed for 3 hr. On cooling, pyridine was removed by codistillation with benzene under reduced pressure. The residue was dissolved in water and extracted with ether to give, on removal of solvent, a mixture (127 mg) of 217 and 218. Evaporation of the aqueous layer furnished a brown oil from which no crystalline product was obtained.

(b) 213 (993 mg, 5.70 mmol) dissolved in pyridine (15 ml) was refluxed for 3 hr as in (a) above. On standing at room temperature for 16 hr, the reaction mixture deposited a red solid (1.0 g) which was removed by filtration. The solid product was washed with ether and recrystallised twice from chloroform-ether giving a mixture of pyridinium salts (216 and 225) (526 mg, 2.08 mmol, 36%), m.p. 90-93°; Anal. calc. for C₁₃H₁₆ClNS: C 61.47, H 6.35, N 5.52%. Found: C 61.20, H 6.8, N 5.4%. ν<sub>max</sub><sup>KBr</sup> 3010, 1635, 1477, 1132 and 680 cm⁻¹; ¹H (D₂O) 1.87-2.91 (m), 3.46 (m), 5.45 (m), 5.88 (m), 6.09 (m), 6.34 (m), 8.12 (t), 8.60 (t), 8.85 (d) and 9.01 (d); λ<sub>max</sub><sup>EtOH</sup> 249 (sh, log E 3.49), 256 (sh, 3.59), 262 (3.64) and 268 nm (sh, 3.54).

(c) 213 (1.098 g, 6.29 mmol) and pyridine (15 ml) were stirred at room temperature for 64 hr. The colourless precipitate formed, was filtered off and washed with ether, giving N-(9-thiabicyclo-[3.3.1]non-2-en-6-yl)pyridinium chloride (216) (295 mg, 1.16 mmol, 18.5%), m.p. 215-217°; Anal. calc. for C₁₃H₁₆ClNS: C 61.47, H 6.35, N 5.52, S 12.63%. Found: C 60.9, H 6.5, N 5.7, S 12.4%; ν<sub>max</sub><sup>KBr</sup> 3020, 1630, 1478, 1137 and 682 cm⁻¹; ¹H (D₂O) 1.87-2.90
(complex m, 6H, CH₂), 3.46 (br m, 2H, C(1,5)H), 5.45 (m, 1H, C(6)H, 6.09 (m, 2H, olefinic CH), 8.12 (t, 2H, C(3')H), 8.60 (t, 1H, C(4')H) and 9.01 (d, 2H, C(2')H); \( \lambda_{\text{max}} \) EtOH 256 (sh, log \( \varepsilon \) 3.53), 262 (3.58), 2.68 (sh, 3.51) and 296 nm (2.86).

Recrystallisation of the product from chloroform-ether gave the hydrated salt \((C_{13}H_{16}ClNS)_2 \cdot 3H_2O\), m.p. 111-113°; Anal. calc. for \( C_{26}H_{38}Cl_2N_2O_3S_2 \): C 55.60, H 6.82, N 4.99%. Found: C 55.60, H 6.46, N 4.80%.

**Pyrolytic decomposition of 215**

Anhydrous bispyridinium salt (215) (128 mg, 0.35 mmol) was pyrolysed in a flame dried sealed pyrolysis tube (17 cm x 0.5 cm i.d., Pyrex) at 250° for 1 hr. The dark brown liquid product was extracted with ether and the extract filtered and evaporated under suction. The p.m.r. spectrum (CDCl₃) of the crude product showed the major component to be diene (229)\(^1^{58}\), \( \delta \) 2.21 (m, 4H, CH₂), 4.00 (m, 2H, bridgehead CH), 5.81 (m, 2H, C(2,5)H) and 6.40 (m, 2H, C(3,4)H), accompanied by small amounts (< 5%) of 217 and 218\(^1^{58}\).

**Pyrolysis of monopyridinium salt (216)**

(a) 216 (108 mg, 0.43 mmol) was pyrolysed, as above, at 104° for 5 hr. On cooling, the product was extracted with ether, and the extract filtered and stripped of solvent under suction. P.m.r. spectroscopy of the residue (ca 10 mg) showed the presence of 217 and 218\(^1^{58}\). No diene resonances were observed.

(b) 216 (118 mg, 0.46 mmol) was pyrolysed, as above at 250° for 1 hr. Ether extraction of the product, followed by evaporation of
solvent gave a yellow oil (54 mg), which was shown by p.m.r. spectroscopy to be predominantly diene (229)_{158} accompanied by traces of 217 and 218.
Part Four

The Synthesis of Polysubstituted 8-Thiabicyclo[3.2.1]octanes
INTRODUCTION

In contrast to 9-thiabicyclononanes, the related 8-thiabicyclo[3.2.1]octane (234) field has received little attention. The system was first reported in 1955 when the parent thioether was isolated from Iranian kerosene and a subsequent laboratory synthesis (Scheme 77) of 234 by reduction of the Diels-Alder adduct (235) of cyclohepta-1,3-diene and sulphur dioxide confirmed the structural assignment.

Ketone (236) was one of the first derivatives of 234 to be prepared and has been obtained by the reaction of sodium sulphide with tropinone methiodide (237) and by the Michael addition of hydrogen sulphide to cyclohepta-2,6-dienone (238). (Scheme 78). As one of the principal intermediates for the preparation of other 8-thiabicyclo[3.2.1]octane derivatives, 236 has been used to introduce functionality at C(2), C(3) and C(4) of the bicyclic framework.

Epimeric alcohols (239 and 240) were obtained by reducing 236 with sodium borohydride or lithium aluminium hydride and their aromatic esters (241, 242 and 243) have been prepared for biological testing. Conversion of 236 to its tosyl hydrazone (244) followed by pyrolysis has given alkene (245) (Scheme 79) while Claisen condensation with aromatic aldehydes yielded 2,4-dibenzylidine derivatives (246) which exhibit fungistatic activity. Beckmann rearrangement of oxime (247) to 248 is a step in the synthesis (Scheme 80) of 3-aza-9-thiabicyclo[4.2.1]nonane derivatives, such as 249, which are effective in the treatment of hypertension.
Scheme 77

\[
\text{Scheme 77}
\]

\[
\text{SO}_2 \rightarrow \text{235} \rightarrow 1. \text{H}_2/\text{Ni} \rightarrow 2. \text{LiAlH}_4 \rightarrow 234
\]

Scheme 78

\[
\text{I}^- \quad \text{(CH}_3 \text{)}_2\text{N} \quad \text{237} \quad \rightarrow \quad \text{Na}_2\text{S} \quad \rightarrow \quad \text{236} \quad \rightarrow \quad \text{H}_2\text{S} \quad \rightarrow \quad \text{238}
\]

\[
\text{239} \quad \text{R}^1 = \text{H}, \text{R}^2 = \text{OH}
\]

\[
\text{240} \quad \text{R}^1 = \text{OH}, \text{R}^2 = \text{H}
\]

Scheme 79

\[
\text{ArCH} \quad \text{CHAr} \quad \rightarrow \quad 1. \text{NaH} \quad \rightarrow \quad 2. \text{ArCHO} \quad \rightarrow \quad 236
\]

\[
\text{TsNNH}_2 \quad \rightarrow \quad \text{244} \quad \rightarrow \quad \Delta \rightarrow \quad \text{245}
\]
Bridgehead substitution of the 8-thiabicyclo[3.2.1]octane nucleus has been achieved\(^{177}\) by treatment of sulphone (250) with \(\text{n-butyl lithium}\) and sulphuryl chloride, \(\text{SO}_2\text{Cl}_2\) to give sulphonyl chloride (251). On heating, 251 decomposes with evolution of \(\text{SO}_2\) furnishing \(\alpha\)-chlorosulphone (252) (Scheme 81). In contrast, the reaction of 234 with \(\text{SO}_2\text{Cl}_2\), followed by oxidation of the crude product by monoperphthalic acid produced\(^ {177}\) a mixture of \(\beta\)-chlorosulphone (253) and 1,4-dichlorocycloheptane (254). The formation of 253 has been rationalised by deprotonation and C-S cleavage of chlorosulphonium species (255) to give sulphenyl chloride (256) which recombines intramolecularly to chlorosulphide (257) prior to oxidation (Scheme 82).

Apart from the preparation\(^ {169,178}\) of alkenes (235 and 258), only one method for the introduction of C(6) and C(7) functionality has been reported. Thus condensation of cycloheptatriene (259) with sulphur dichloride furnished\(^ {74}\) 260 as the only isolable product. Hydrolysis\(^ {74}\) of 260 by sodium carbonate yielded both 261 and 262, and the latter has been oxidised\(^ {179}\) to dione (263) (Scheme 83).

Oxidation\(^ {74}\) of 260 with hydrogen peroxide in glacial acetic acid led to the rearranged sulphoxide (264) (Scheme 84) in which the repulsive interaction of the electronegative sulphoxide group with the electron rich chlorine atoms and carbon-carbon double bond has been minimised. Further oxidation of 264 by hydrogen peroxide in acetone gave 265, while in acetic acid, rearrangement again occurred to give sulphone (266) which possesses the same allylic chloride structure as the original sulphide.
Scheme 83

\[ \text{259} \xrightarrow{\text{SCl}_2} \text{260} \xrightarrow{\text{Na}_2\text{CO}_3} \text{260} \xrightarrow{\text{CrO}_3, 2\text{Py}} \text{262} + \text{261} \]

Scheme 84

\[ \text{260} \xrightarrow{\text{H}_2\text{O}_2, \text{CH}_3\text{CO}_2\text{H}} \text{264} \xrightarrow{\text{H}_2\text{O}_2} \text{265} \]

Chemical structures and reactions are depicted in the diagram, with reactions and products labeled accordingly.
Closely related in structure to these compounds are the numerous naturally-occurring derivatives of 8-azabicyclo[3.2.1]octane (267), collectively known as the tropane alkaloids. Many of these compounds possess powerful physiological activity and have found use as pharmaceuticals. Possibly the best known members of the series are \(\beta\)-cocaine (268) and atropine (269) which are potent narcotics but which, in controlled doses, act as analgesics and anaesthetics.

A large number of synthetic tropanes has been prepared and many have exhibited properties superior to their natural counterparts. In particular 3-tropyl benzhydryl ether (benztropine, 270) possesses antihistaminic and antispasmodic characters while homotropine (271) and eccaine (272) are valuable non-toxic anaesthetics. These compounds are listed with a number of other natural and synthetic tropanes in Table 6.

The biological activity shown by tropane alkaloids and several 8-thiabicyclo[3.2.1]octanes (vide supra) suggests that other appropriately substituted derivatives of 234 might also possess pharmacologically useful properties. This section describes the preparation of potential precursors to a few of these sulphur bridged compounds.
Table 6  A selection of naturally occurring and synthetic tropane alkaloids.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Atropine (±Hyoscyamine)</td>
<td>antispasmodic, analgesic, anaesthetic, parasympatholytic</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Benztropine</td>
<td>antispasmodic, antihistamine, parasympatholytic, used in treatment of Parkinsonian syndrome</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>p-Cocaine</td>
<td>narcotic, analgesic, local anaesthetic</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>Eccaine</td>
<td>non-toxic anaesthetic</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure" /></td>
<td>Homatropine</td>
<td>cycloplegic, parasympatholytic, mydriatic</td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure" /></td>
<td>Homotropine</td>
<td>local anaesthetic, mydriatic</td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure" /></td>
<td>Meteloidine</td>
<td>found in Datura meteloides</td>
</tr>
<tr>
<td><img src="image8.png" alt="Structure" /></td>
<td>Mydriasin</td>
<td>powerful mydriatic</td>
</tr>
<tr>
<td><img src="image9.png" alt="Structure" /></td>
<td>Scopolamine</td>
<td>antispasmodic</td>
</tr>
<tr>
<td><img src="image10.png" alt="Structure" /></td>
<td>Valeroidine</td>
<td>found in Duboisia myoporoides</td>
</tr>
</tbody>
</table>


DISCUSSION

The reaction of sulphur dichloride, $\text{SCl}_2$, with olefins has been known for over a century, mineral oils and other organic materials being subjected to the reagent as a qualitative thermal test for unsaturation\textsuperscript{180}. Nevertheless, very little was known about the nature of the reaction and it was some time before the synthetic utility of the reagent was fully realised.

The trans-addition of $\text{SCl}_2$ to carbon-carbon double bonds is now believed\textsuperscript{181} to proceed by formation of a π-complex and a cyclic episulphonium cation (273), the latter of which is opened by chloride to give the Markovnikov adduct (274) (Scheme 85). However, several investigations\textsuperscript{182,183} on the reaction of terminal olefins have indicated that steric factors often control the direction of ring-opening of 273 resulting in the anti-Markovnikov addition product (275).

One of the earliest and most important synthetic uses of sulphur dichloride was in the preparation\textsuperscript{184} of its highly toxic ethylene adduct, bis(2-chloroethyl)sulphide (276) which was used extensively in chemical warfare during World War I and was commonly known as 'Mustard Gas'. The extreme toxicity of 276 has been attributed\textsuperscript{185} to its ease of penetration through the body tissue (due to its high lipid solubility) combined with subsequent intracellular evolution of hydrogen chloride by facile sulphur-assisted hydrolysis (Scheme 86).

More recently, the reactions of sulphur dichloride with a wide
Scheme 85

\[
\begin{align*}
&\text{H} & & \text{R}^1 & & \text{R}^2 \\
&\text{R}^3 & & \text{R}^2 & & \text{R}^3 \\
&\text{SCl}_2 & & \text{H-} & & \text{complex} \\
\end{align*}
\]

Scheme 86

\[
\begin{align*}
&\text{Cl} & & \text{Cl} & & \text{H}_2\text{O} & & \text{HCl} \\
&\text{C} & & \text{C} & & \text{Cl}^- & & \text{H}_2\text{O} \\
\end{align*}
\]
variety of unsaturated systems including dienes\textsuperscript{181-183,186}, acetylenes\textsuperscript{187}, enol ethers and enamines\textsuperscript{188}, oximes\textsuperscript{189} and nitriles\textsuperscript{190} have yielded novel sulphur-containing products. In particular, the addition of SCl\textsubscript{2} to cyclic polyolefins has been widely used for the preparation of thiabicyclic systems.

Prompted by the stereospecific formation\textsuperscript{74} of allylic chloride (260) from cycloheptatriene (259), the reaction of SCl\textsubscript{2} with several substituted cycloheptadienes has been investigated in order to synthesise suitably functionalised 8-thiabicyclo[3.2.1]-octanes as precursors to thia-analogues of biologically active tropane alkaloids. Using this approach, chloride, ester and carbonyl groups and unsaturation have been introduced at potentially useful positions of the bicyclic framework.

Concurrent with this investigation, the direct preparation of several derivatives of 234 from their tropanoid analogues were studied. Although 236 is readily synthesised\textsuperscript{170} from tropinone methiodide (237) by reaction with sodium sulphide, the corresponding methiodides of tropine (277), pseudotropine (278)\textsuperscript{191} and \(\beta\)-cocaine (268) under identical conditions, failed to produce sulphur bridged products. Although steric interactions may have an effect, the reasons for the inertness of these compounds is unknown.

Because of its significance as a sulphur analogue of \(\beta\)-cocaine (268), the synthesis of 281 was of particular interest. In absence of a direct route from 268 (vide supra) it was proposed to convert 236 into \(\beta\)-ketoester (279). Reduction of the carbonyl function of 279 followed by benzoylation of the resulting thiatropine derivative (280) would yield the desired product (281) as a mixture of
Scheme 87

1. NaH or n-BuLi
2. ClCO₂CH₃ or (CH₃O)₂CO

Scheme 88

SeO₂

LiAlH₄, ether or NaBH₄, CH₃OH

H₂O or CH₃OH

no reaction
diastereoisomers (Scheme 87). In the event, however, all attempts to prepare 279 by treatment of 236 with sodium hydride-dimethyl carbonate or n-butyl lithium - methyl chloroformate proved unsuccessful and were not further investigated.

The preparation of substituted cycloheptadienes

A number of substituted cycloheptadienes have appeared in the literature. Because of their ease of preparation, dienones (238 and 282) and dienol (283) were particularly attractive as precursors to 8-thiabicyclo[3.2.1]octanes. Moreover the positions of oxygen functionality in these dienes were ideally suited to the formation of sulphur-bridged alcohols and ketones having substitution patterns similar to known tropane alkaloids.

Cyclohepta-3,5-dienone (282) was prepared in two steps from cycloheptatriene (259). Allylic oxidation of 259 using selenium dioxide furnished tropone (284) which was reduced to 282 with lithium aluminium hydride. Interestingly, under these conditions, only small amounts of dienol (283) are formed, even if a large excess of LiAlH₄ is used. This may be rationalised by nucleophilic attack of hydride ion at C(2) of 284 followed by electronic reorganisation to give enolate ion (285). Under the aprotic conditions employed, 285 is unable to react further and, on hydrolysis, tautomerises to ketone (282) (Scheme 88).

Dienol (283) may however be prepared from 284 by reduction with sodium borohydride in aqueous methanol. In this case the intermediate enolate ion (285) is protonated in situ by solvent
yielding 282 which is susceptible to further reduction by borohydride ion (Scheme 88). 283 was converted to its benzoate ester (286) by treatment with benzoyl chloride and pyridine.

Cycloalk-2-enones (287) are readily prepared by a number of methods. The synthesis of α,β,α',β'-cycloalkadienones (289) is less common but has been accomplished by α,α'- dibromination of the corresponding cycloalkanone ketal (288) followed by dehydrobromination and hydrolysis of the ketal function (Scheme 89). Using this approach cycloheptanone was converted through 290 and 291 to 292 and was hydrolysed by dilute mineral acid to dienone (238).

The synthesis of chlorinated 8-thiabicyclo[3.2.1]octanes

The reaction of dienes (282, 283 and 286) with sulphur dichloride was expected to proceed as for reported 1,3-dienes and produce the 6,7-dichlorinated products (293, 294 and 295) respectively. In the event, 286 reacted predictably in methylene chloride at -70° to produce in almost quantitative yield, a colourless crystalline solid, m.p. 160-161°, which analysed for C_{14}H_{14}Cl_{2}O_{2}S. The mass spectrum showed a molecular ion triplet at m/e 316, 318 and 320 (intensity 9:6:1) confirming the presence of two chlorine atoms, while p.m.r. signals at δ 7.29-8.31 (pair of multiplets, 5H) and an intense infrared band at 1721 cm⁻¹ showed that the benzoate ester function of 286 had remained intact. A narrow, two-proton bridgehead singlet at δ 3.66, taken with a sharp H-C-Cl multiplet at δ 4.89 (Figure 9) was evidence of a plane of symmetry through sulphur and C(3), and identified the product as the expected benzoate ester (295).
Scheme 89

\[
\text{Ketone} \xrightarrow{(\text{CH}_2\text{OH})_2 \text{H}^+} \overset{288}{\text{Ether}} \xrightarrow{\text{Br}_2} \overset{289}{\text{Dibromide}} \xrightarrow{\text{NaOH}} \overset{288}{\text{Ether}} \xrightarrow{\text{H}^+} \overset{289}{\text{Diketone}}
\]

\[
\overset{290}{\text{Ether}} \quad X = \text{H} \\
\overset{291}{\text{Ether}} \quad X = \text{Br}
\]

\[
\overset{286}{\text{Phenylcyclopentadiene}} \quad \overset{287}{\text{Cyclopentadiene}}
\]
Figure 9

The 100 MHz p.m.r. spectra of (a) 295 and (b) 296.
By thin layer chromatography of the liquors remaining after crystallisation of 295, an additional minor reaction product was isolated as colourless crystals, m.p. 117-118°. Although possessing similar aromatic features at δ 7.50 (m, 3H) and 8.08 (m, 2H), the p.m.r. spectrum differed from that of 295 by having two bridgehead signals at δ 3.49 and 3.90, each of which integrated for one proton (Figure 9). Moreover, the hydrogen-on-carbon-bearing-oxygen resonance at δ 5.48 was coupled to a lesser degree than the corresponding signal of 295. Double irradiation of this multiplet sharpened the bridgehead resonance at δ 3.90 and indicated a vicinal relationship between the corresponding protons. More comprehensive decoupling studies, a high resolution mass measurement (indicating a formula of $\text{C}_{14}\text{H}_{14}\text{Cl}_{2}\text{O}_{2}\text{S}$) and infrared information gave unambiguous proof that the minor product (2.4%) was the isomeric benzoate ester (296).

The formation of 296 may be rationalised by the reaction of sulphur dichloride with 297 which was present in 286 as a trace impurity due to the formation of dienol (298) during the reduction of tropone (284). Thus instead of forming 282 by protonation at C(2), enolate ion (285) rearranged with protonation at C(6) to give the conjugated dienone (299) which led to 298 on further reduction (Scheme 90).

In contrast to 286, dienol (283) and dienone (282) did not behave as expected and evolved hydrogen chloride on reaction with $\text{SCl}_2$. In addition, 283 formed an amorphous cream precipitate which was identified as elemental sulphur, while the p.m.r. spectrum of its crude product possessed none of the characteristics of an
Scheme 90

284 $\xrightarrow{\text{NaBH}_4}$ 285 $\xrightarrow{\text{H}_2\text{O}}$ 299

296 $\xrightarrow{\text{SCl}_2}$ 297 $\xrightarrow{\text{PhCOCl}}$ 298

Scheme 91

283 $\xrightarrow{\text{SCl}_2, \text{CH}_2\text{Cl}_2}$ 294

$\text{OH}$ $\xrightarrow{\text{H}_2\text{O}}$ 300

$\text{OH}$ $\xrightarrow{\text{NaBH}_4}$ 299

$\text{OH}$ $\xrightarrow{\text{H}_2\text{O}}$ 300

$\text{OH}$ $\xrightarrow{\text{NaBH}_4}$ 299
8-thiabicyclo[3.2.1]octane system. These results suggested that, rather than adding across the double bonds of 283, SCl₂ had reacted preferentially with the hydroxyl function yielding dialkyl sulphite (300) as the possible product (Scheme 91). Rigorous structural confirmation of 300 was not however undertaken and the reaction was not further investigated. The crude product from the reaction of dienone (282) with SCl₂ was unstable and continuously darkened on standing. While it decolourised somewhat when passed through neutral alumina and appeared as one spot (Rf 0.68, chloroform-petroleum spirit 7:3) on t.l.c. it showed no tendency to crystallise and failed to give reproducible microanalytical data. However, a high resolution mass measurement on the molecular ion of the mass spectrum was in close agreement with the molecular formula, C₇H₇ClO₅ and the presence of only one chlorine atom was supported by a molecular ion pair at m/e 174 and 176 of intensity ratio 3:1.

The infrared spectrum possessed prominent bands at 1736 and 1631 cm⁻¹ which revealed the presence of an alicyclic ketone and a carbon-carbon double bond which were not in conjugation. The unusually high frequency of the former absorption was taken to indicate that the carbonyl group was situated in a five membered or otherwise strained ring.

The p.m.r. spectrum of the product (Figure 10) was complex and consisted of seven distinct one-proton signals, the sharpness and well-defined splitting patterns of which implied a rigid molecular framework.
The 60 MHz p.m.r. spectra of (a) 301 and (b) 303

(a)

(b)
Double resonance experiments showed that a doublet at $\delta$ 3.33 and a double doublet at $\delta$ 2.75 were mutually coupled by 18 Hz and these were attributed to geminally situated methylene protons which were slightly deshielded. The higher-field signal was coupled by 7 Hz to a bridgehead multiplet at $\delta$ 3.86 which also interacted with a complex H-C-Cl resonance at $\delta$ 5.24. Olefinic signals at $\delta$ 5.75 and 6.18 were mutually coupled by 10 Hz in accord with the presence of a cis-double bond while further coupling of the lower-field hydrogen to a second bridgehead proton ($\delta$ 3.57, d, $J$=7 Hz) indicated the sulphur bridge to be allylic.

Based on this information the product was assigned as 2-chloro-8-thiabicyclo[3.2.1]oct-3-en-6-one (301) which embodies a five-membered ring ketone and an allyl chloride into a rigid bicyclic framework. The formation of 301 is an example of the condensation of sulphur dichloride with an active methylene group which has been previously used for the preparation of thioethers (1:2 adduct)\textsuperscript{201} and thioketones (1:1 adduct)\textsuperscript{202}. Thus 301 results from a conventional trans-addition of $\text{SCl}_2$ across one double bond of 282 producing sulphenyl chloride (302) which reacts intramolecularly as its enol tautomer to form a sulphur bridge with elimination of HCl (Scheme 92).

On a single occasion which could not be repeated column chromatography of crude 301 produced an abnormally highly coloured product. T.l.c. analysis (chloroform-petroleum spirit 7:3) of the yellow oil showed that, in addition to 301, a more polar ($R_f$ 0.50), intensely coloured compound was present. Isolation of the impurity by preparative t.l.c. gave a photolabile canary yellow semi-solid which could not be fully characterised because of its low yield. Strong bands at
Addendum 2

Several attempts were made at preparing 303 by the dehydrochlorination of 301. Treatment of 301 with chromatographic alumina (Woelm Grade 0, basic) in refluxing benzene, 2,4,6-collidine (230) at 105° or sodium methoxide in methanol at room temperature failed to produce a reaction. Reaction of 301 with potassium t-butoxide in dimethyl sulphoxide at room temperature gave a complex mixture of products, none of which were identified as dienone (303). Characterisation of these products was not attempted.
1690 (C=O) and 1589 cm$^{-1}$ (C=C) in the infrared spectrum, however, identified the compound as a conjugated enone and were supported by the presence, in the p.m.r. spectrum, of a shielded one-proton vinyl doublet at $\delta$ 5.26 (C(3)H), coupled (11 Hz) to another deshielded multiplet at $\delta$ 7.42 (1H, C(4)H). The remainder of the p.m.r. spectrum consisted of two H-C-S (bridgehead) multiplets each of which integrated for one proton, and a pair of complex mutually coupled (J=6 Hz) vinyl multiplets (each 1H) at $\delta$ 6.50 and 7.02 (Figure 10). On the basis of these spectra, mechanistic considerations and its close physical similarity to bisenone (153), the product was tentatively assigned as dienone (303), formed by dehydrochlorination and skeletal rearrangement of 301 (Scheme 92) similar to that already observed in 9-thiabicyclo[3.3.1]nonyl systems 158.

Addendum 2

The addition of sulphur dichloride to ketal (292) was expected to produce a mixture of isomeric dichlorides (304 and 305) while 238 was a potential precursor of the related ketones (306 and 307). On reaction, however, 292 yielded a single product which was purified by t.l.c. and recrystallised as colourless needles, m.p. 112-114$^\circ$. Microanalysis confirmed the product as a 1:1 adduct, $C_9H_{12}Cl_2O_2S$, a molecular formula which was in accord with the mass spectral molecular ions at m/e 254, 256 and 258 (9:6:1). The absence of bands in the 1500-1800 cm$^{-1}$ region of the infrared spectrum proved that both carbon-carbon double bonds of 292 had reacted and that the dioxolane moiety had remained intact.

The methylene protons of this latter group gave rise to a broad four-proton envelope at $\delta$ 3.80-4.32 in the p.m.r. spectrum. This
contrasted with the appearance as a sharp singlet (at 3.88) of the dioxolane methylene protons of 292 and indicated that the insertion of a sulphur bridge resulted in the loss of magnetic equivalence within this group. The presence of two distinct bridgehead multiplets at 3.26 and 3.40 each integrating for one proton disfavoured the more symmetrical adduct (304) and was supported by the existence of two separate one-proton H-C-Cl resonances at 4.49 and 4.68, the latter of which was a 6 Hz doublet. The remainder of the spectrum consisted of a four-proton methylene envelope at 1.91-2.83 and was in accord with the compound being bicyclic dichloride (305) in which a ketal function is spiro to a five-membered ring.

Examination of molecular models clearly demonstrated that steric interactions between bulky substituents were much less severe in 305 than in 304 and satisfactorily explained the exclusive formation of the less symmetrical dichloride (Scheme 93).

An attempted acid hydrolysis of the dioxolane function failed to give a ketonic product. Instead, a colourless crystalline solid, m.p. 85.5-87°, was obtained which possessed a hydroxyl stretching absorption at 3380 cm⁻¹ in its infrared spectrum. Mass spectrometry, showing molecular ions at m/e 236 and 238 (3:1), and microanalysis, indicating a molecular formula C₉H₁₅ClO₃S, confirmed that one chlorine atom of 305 had been replaced by a hydroxyl group.

The p.m.r. spectrum was similar to that of 305. However the H-C-Cl resonance of 305 at 4.49 had been replaced by a one-proton H-C-O multiplet at 4.11 and a deuterium oxide exchangeable OH doublet (1H, J=12 Hz) at 2.93. Retention of a one-proton H-C-Cl doublet
at $\Delta 4.59$ ($J=6$ Hz) showed that hydrolysis had not occurred at C(6) and confirmed the product as 308 (Scheme 93).

The formation of 308 suggests that chlorine at C(2) is much more easily displaced by nucleophiles than chlorine at C(6). For the C(2)-Cl, bonded to a six-membered ring and $\beta$- to the thioether function, hydrolysis is anichimerically assisted and proceeds through the episulphonium intermediate (309) as in the mechanism proposed for hydrolysis of 161 119. Although C(6)-Cl is also $\beta$- to the bridging sulphur atom, the strain engendered in forming an episulphonium intermediate (310) within the five-membered ring prevents facile replacement at C(6) by an $S^1$ mechanism.

Moreover, in $S^2$ displacement the approach of the nucleophile ($H_2O$) towards C(6) is sterically hindered by both sulphur and dioxolane oxygen and explains the inertness of the chlorine, bonded to this carbon, under hydrolytic conditions.

Although it could not be prepared by acid hydrolysis of 305, 307 was obtained in high yield (82%) as the only product of $SCl_2$ addition to 238 (Scheme 94). In support of the structural assignment, micro-analysis of the crystalline product, m.p. 139-141°, was in accord with a molecular formula of $C_7H_8Cl_2OS$ and was confirmed by parent ions at m/e 210, 212 and 214 (9:6:1) in the mass spectrum. Fragmentation of the molecular ion by loss of carbon monoxide indicated the presence of a ketonic carbonyl group and was supported by the infrared spectrum ($CCl_4$) which possessed a strong band at 1761 cm$^{-1}$ ($\delta 480$).
In confirmation of the asymmetrical structure (307), the p.m.r. spectrum of the product possessed two distinct bridgehead signals and two separate one-proton H-C-Cl resonances. A complex multiplet at δ 3.63 (1H) was ascribed to C(5)H while a simpler one-proton signal at δ 3.70 due to C(1)H was deshielded by its proximity to a carbonyl group. Similarly, a highly split resonance at δ 4.47 was attributable to C(2)H while that at δ 4.81 resulted from C(6)H. The remainder of the spectrum consisted of a methylene envelope at δ 1.74-2.67 (4H) arising from protons attached to C(3) and C(4).

Although relatively few examples have been studied, the addition of sulphur dichloride to substituted cycloheptadienes has thus been shown to be highly regio- and stereoselective and produces chlorinated derivatives of 234 in high yield. By appropriate choice of monocyclic precursors a variety of substitution patterns are possible making this reaction the most flexible synthesis of 8-thiabicyclo[3.2.1]octanes available and providing a route to compounds of potential biological activity.
Experimental Section
Tropinone Methiodide (237)\textsuperscript{203}

Tropinone (311) (4.06 g, 29.2 mmol) was dissolved in abs. ethanol (25 ml) and methyl iodide (5.5 g, 38.7 mmol) added dropwise with stirring. Stirring was continued for 2 hr and ether (75 ml) added. The precipitated product was filtered and washed with ether. Recrystallisation from aqueous methanol gave methiodide (237) (7.51 g, 26.7 mmol, 91\%), m.p. 276-279° (decomp.) (lit.\textsuperscript{203} m.p. 278°); \(\nu_{\text{KBr}}^\text{max}\) 3028, 1725, 1449, 1316, 1199, 1110, 980 and 921 cm\(^{-1}\).

8-thiabicyclo[3.2.1]octan-3-one (236)\textsuperscript{170}

A mixture of 237 (5.60 g, 20 mmol) and sodium sulphide nonahydrate (5.60 g, 23.3 mmol) was dissolved in water (50 ml) and stirred at 85° for 2 hr under nitrogen. On cooling the solution was extracted four times with ether and the combined extracts washed with dilute hydrochloric acid, and brine to neutrality. Drying and evaporation of solvent gave a brown solid which was decolourised by passing through a short column of alumina (Woelm Grade 0, basic).

Recrystallisation from aqueous methanol gave 236 (1.57 g, 11 mmol, 55\%) m.p. 155-157° (lit.\textsuperscript{170} m.p. 155-156°), \(\nu_{\text{KBr}}^\text{max}\) 2940, 1707, 1460, 1398, 1327, 1200, 1039, 976 and 881 cm\(^{-1}\); \(\delta\) (CDCl\(_3\)) 2.06 (m, 4H, C(6,7)H\(_2\)), 2.68 (m, 4H, C(2,4)H\(_2\)) and 3.81 (m, 2H, C(1,5)H).

Attempted synthesis of 2-methoxycarbonyl-8-thiabicyclo[3.2.1]octan-3-one (279)

(a) Sodium hydride-dimethyl carbonate\textsuperscript{192}

A solution of 236 (142 mg, 1 mmol) in dry dioxan (5 ml) was added dropwise over 5 min to a mixture of a 54\% mineral oil dispersion of sodium hydride (90 mg, 2 mmol) and freshly distilled dimethyl
carbonate (500 mg, 5.6 mmol) in dioxan (10 ml). The mixture was stirred under nitrogen at 96° for 3½ hr. The yellow solution was allowed to cool, acidified with 50% v/v aqueous acetic acid (9 ml), and evaporated to dryness. The residue was dissolved in water and extracted with ether. The combined extracts were washed with a little sodium bicarbonate, dried and evaporated, yielding a colourless solid (151 mg) identified by p.m.r. spectroscopy and t.l.c. as unreacted 236.

(b) \textit{n-Butyl lithium-methyl chloroformate}^{193}

2.1 M \textit{n}-butyl lithium in hexane (1 ml) was added dropwise to a stirred solution of 236 (284 mg, 2 mmol) in hexane (10 ml), causing the immediate formation of a colourless precipitate. Stirring was continued under nitrogen for a further 5 min and methyl chloroformate (189 mg, 2 mmol), dissolved in hexane (2 ml), added. The solution was stirred at room temperature for 16 hr, a further 5 ml hexane added and the mixture washed three times with water. Drying and evaporation of solvent gave a colourless oil (339 mg) which slowly crystallised on standing. T.l.c. and p.m.r. analysis showed the material to be unreacted 236.

\textbf{Attempted synthesis of 2-methoxycarbonyl-3-benzoyloxy-8-thiabicyclo-[3.2.1]octane (281)}

Cocaine (268) (303 mg, 1 mmol) was dissolved in absolute ethanol (4 ml) and methylene iodide (1 ml) added. The mixture was stirred at room temperature for 21 hr and ether (5 ml) added. The precipitated methiodide (312) (429 mg, 0.96 mmol, 96%) was collected, dissolved in water (20 ml) and sodium sulphide nonahydrate (300 mg,
1.2 mmol) added. The mixture was stirred for 20 hr at 90°, allowed to cool and extracted with ether. Drying and evaporation of the ether extracts gave a yellow oil (9 mg) which could not be characterised.

Cycloheptatrienone (Tropone, 284)\(^{196}\)

To a solution of potassium dihydrogen phosphate (13.5 g) in distilled water (33 ml) was added 1,4-dioxan (330 ml), selenium dioxide (53.0 g, 0.48 mol) and cycloheptatriene (285) (43.0 g, 0.46 mol). The mixture was stirred at 90° for 15 hr, filtered and the filtrate poured into water (750 ml). The mixture was extracted three times with methylene chloride and the extract washed with saturated sodium bicarbonate solution, dried and evaporated leaving a dark brown oily product (15.3 g). Distillation of this residue under reduced pressure (3 mm Hg) gave tropone (284), (11.19 g, 0.11 mol, 23%), b.p. 80-85° (lit.\(^{196}\) b.p. 91-92°, 4 mm Hg); \(\nu\)\(^{\text{lq. film}}\) 3010, 1710, 1633, 1576, 1520, 1470, 1247, 1210, 895, 830 and 780 cm\(^{-1}\); \(\delta\) (CDCl\(_3\)) 7.13 (complex m).

The product contained ca 5% benzaldehyde (\(\nu\)\(^{\text{max}}\) 1705 cm\(^{-1}\)) due to oxidation of toluene which was present in the original cycloheptatriene.

Cyclohepta-3,5-dienone (282)\(^{194,195,197}\)

A solution of tropone, (284) (2.51 g, 23.7 mmol) in anhydrous ether (50 ml) was added dropwise to a vigorously stirred suspension of lithium aluminium hydride (0.71 g, 17.85 mmol) in anhydrous ether (100 ml). Rapid stirring was continued at room temperature for a further 2 hr and excess lithium aluminium hydride destroyed by the
addition of glacial acetic acid (25 ml). The mixture was allowed
to stand for 10 min and then neutralised with saturated sodium
bicarbonate solution. The organic layer which had separated was
washed with a further portion of sodium bicarbonate, dried, and
stripped of solvent. Distillation of the residue in vacuo gave 282
(1.00 g, 9.25 mmol, 39%), b.p. 40-45°, 4 mm Hg (lit.195 b.p. 40-45°,
4 mm Hg); \( \nu_{\text{liq. film}}^{\text{max}} \) 3025, 2898, 1710, 1649, 1596, 1424, 1238, 1211,
1050, 831 and 681 cm\(^{-1}\); \( \delta \) (CDCl\(_3\)) 3.05 (d, J=6 Hz, 4H, CH\(_2\)),
5.87 (m, 2H, C(4,5)H) and 6.32 (m, 2H, C(3,6)H).

Cyclohepta-3,5-dienol (283)\(^{195,197,198}\)

Sodium borohydride (1.401 g, 38.9 mmol) was added slowly to a
solution of tropone (284) (2.10 g, 19.8 mmol) in a mixture of
methanol (50 ml) and water (7 ml), causing immediate evolution of
hydrogen. The mixture was stirred for 2 hr at room temperature
and residual sodium borohydride was decomposed by the dropwise
addition of glacial acetic acid (7 ml). The mixture was
neutralised with saturated sodium carbonate solution and extracted
with ether. The combined extracts were washed with brine, dried
and evaporated. The brown oily residue was distilled in vacuo to
give as a colourless oil, cyclohepta-3,5-dienol (283) (1.42 g,
12.9 mmol, 65%), b.p. 60-65°, 18 mm Hg (lit.\(^{198}\) b.p. 45-52°, 6 mm Hg);
\( \nu_{\text{liq. film}}^{\text{max}} \) 3354, 3012, 1892, 1615, 1439, 1048, 1012, 832 and 671 cm\(^{-1}\)
\( \delta \) (CDCl\(_3\)) 2.50 (m, 4H, CH\(_2\)), 3.61 (m, 1H, OH), 4.11 (m, 1H, CHOH)
and 5.75 (m, 4H, olefinic CH).

l-benzyloxy cyclohepta-3,5-diene (286)\(^{197}\)

To a solution of 283 (4.18 g, 38 mmol) in anhydrous pyridine (5 ml)
was added redistilled benzoyl chloride (6.19 g, 44.1 mmol) and the solution refluxed for 2 hr. On cooling the mixture was taken up in ethyl acetate and washed with 2N hydrochloric acid to remove excess pyridine. Further washing with saturated sodium bicarbonate and brine to neutrality was followed by drying and evaporation of solvent to leave a brown sweet smelling liquid (7.92 g). Distillation gave 286 (5.85 g 27.3 mmol, 72%), b.p. 134-138°, 0.7 mm Hg, (lit. 197 b.p. 120-124°, 0.25 mm Hg);

\[ \nu_{\text{max}} \text{film} \quad 3005, 2940, 1712, 1600, 1446, 1267, 1104, 1015, 700 \text{ and } 655 \text{ cm}^{-1}; \quad \delta (\text{CDCl}_3) 1.82-3.10 (\text{br m, } 4\text{H, } \text{CH}_2), \quad 5.36 (\text{m, } 1\text{H, } \text{CHOCOPh}), \quad 5.82 (\text{m, } 4\text{H, olefinic } \text{CH}) \text{ and } 7.10-8.30 (\text{complex m, } 5\text{H, aromatic } \text{CH}).

Cycloheptanone ethylene ketal (290)

A mixture of cycloheptanone (113.5 g, 1.01 mol), ethylene glycol (108.4 g, 1.75 mol), benzene (150 ml) and toluene-p-sulphonic acid (75 mg) was refluxed for 21 hr using a Dean and Stark trap containing silica gel as drying agent. The mixture was allowed to cool, poured into ether (250 ml), washed with saturated sodium bicarbonate solution (100 ml), and brine (3 x 150 ml), dried over anhydrous sodium sulphate and stripped of solvent. The crude product was purified by distillation giving 290 (132.5 g, 0.85 mmol, 84%)

\[ \text{b.p. } 46-49°, \quad 0.15 \text{ mm Hg} \quad \nu_{\text{max}} \text{film} \quad 2925, 2859, 1450, 1366, 1210, 1115, 1094, 1026, 941, 876 \text{ and } 774 \text{ cm}^{-1}; \quad \delta (\text{CDCl}_3) 1.30-2.07 \text{ (complex m, } 12\text{H, cycloheptane } \text{CH}_2) \text{ and } 3.86 (\text{s, } 4\text{H, dioxolane } \text{CH}_2).

Cyclohepta-2,6-dienone ethylene ketal (292)

Bromine (128 g, 0.8 mol) was added to a solution of 290 (62.4 g,
0.4 mol) in ether (500 ml) at such a rate as to maintain a gentle reflux. Further bromine was added dropwise until the brown colour persisted. A solution of monosodium ethylene glycolate, prepared from sodium (20 g, 0.87 mol) and ethylene glycol (300 ml), was added slowly with vigorous stirring and the resultant mixture poured into water. The ether layer was separated, washed with brine and dried over anhydrous sodium sulphate. Evaporation of solvent gave, as a yellow oil (125.5 g) crude dibromoketal (291). The unpurified product was added to a mixture of sodium hydroxide (88 g, 2.2 mol) and methanol (100 ml), and was refluxed for a further 48 hr. The reaction mixture was poured into brine and extracted twice with 400 ml pentane. The extracts were combined and dried, and solvent evaporated at atmospheric pressure. Distillation of the residue at reduced pressure gave 292 (40.7 g, 0.27 mol, 67%), b.p. 63-68°, 1.2 mm Hg (lit. 200 b.p. 58°, 0.75 mm Hg); \( \nu_{\text{max}} \) 3020, 2935, 2872, 1661, 1399, 1211, 1090, 1006, 963, 820 and 791 cm\(^{-1}\); \( \delta \) (CDC\(_3\)) 2.29 (m, 4H, allylic CH\(_2\)), 3.88 (s, 4H, dioxolane CH\(_2\)), 5.60 (d, J=12 Hz, 2H, C(2,7)H) and 5.91 (m, 2H, C(3,6)H).

Cyclohepta-2,6-dienone (238)

Ketal (292) (1.52 g, 10 mmol) was shaken at room temperature with 0.5N sulphuric acid (5 ml) for 5 min. The mixture was extracted with ether and the extracts washed with saturated sodium bicarbonate and brine, and stripped of solvent. Distillation of the residue gave 238 (0.86 g, 7.96 mmol, 80%), b.p. 40-46°, 0.5 mm Hg (lit. 200 b.p. 50-51°, 1.0 mm Hg); \( \nu_{\text{max}} \) 3011, 2932, 2898, 1646, 1608, 1426, 1404, 1360, 1286, 1253, 1185, 1158 and 843 cm\(^{-1}\); \( \delta \) (CDC\(_3\)) 2.47 (m, 4H, CH\(_2\)), 6.03 (d, J=12 Hz, C(2,7)H) and 6.67 (pr m, 2H, C(3,6)H).
Reaction of cyclic dienes with sulphur dichloride\textsuperscript{74} - general procedure

Cyclic diene (10 mmol) and sulphur dichloride (1.03 g, 10 mmol), each dissolved in methylene chloride (10 ml), were added simultaneously over 2 min to methylene chloride (25 ml) which was vigorously stirred at -70°. The stirred mixture was maintained at -70° for 30 min and was allowed to come to room temperature. The solution was washed in turn with saturated sodium bicarbonate and brine, dried and solvent removed at reduced pressure. The crude product was purified by thin layer or column chromatography.

1  Addition of sulphur dichloride to dienone (282)

282 and sulphur dichloride were allowed to react as in the general procedure. Due to evolution of hydrogen chloride during the reaction, several bicarbonate washings were required. Evaporation of solvent gave a yellow oil which darkened on standing. The crude product was dissolved in chloroform and chromatographed over alumina (Woelm Grade I, neutral, 25 g) furnishing, on removal of solvents, chloroketone (301) (1.68 g, 9.62 mmol, 96\%) as a pale yellow oil which could not be crystallised. Mass calc. for C\textsubscript{7}H\textsubscript{7}ClO\textsubscript{5}: 173.99062. Found: 173.99021; $\nu_{\text{KBr}}$ max 3040, 2925, 1736, 1631, 1401, 1187, 1122, 1075, 971, 878, 770, 710 and 664 cm\textsuperscript{-1};

$\delta$ (CDCl\textsubscript{3}) 2.75 (dd, J=18 and 7 Hz, 1H, C(7)H\textsuperscript{S}), 3.33 (d, J= 18 Hz, 1H, C(7)H\textsuperscript{a}), 3.57 (d, J=7 Hz, 1H, C(5)H), 3.86 (m, J=7 Hz, 1H, C(1)H), 5.24 (m, J=7 and 2 Hz, 1H, C(2)HCl), 5.75 (dt, J=10 and 2 Hz, 1H, C(3)H) and 6.18 (m, J=10,7 and 2 Hz, 1H, C(4)H); m/e [176 and 174] (M\textsuperscript{+}), 155, 139, 111, 110, 97, 84, 78 and 77.

On one occasion, an additional compound was obtained during column
chromatography of the crude reaction product. This compound, which was purified by thin layer chromatography (chloroform-petroleum spirit, 7:3) was isolated as an unstable canary yellow semi-solid (53 mg) identified as 8-thiabicyclo[3.2.1]octa-3,6-dien-2-one (303);

\[ \text{KBr}_{\text{max}} 1690, 1589, 1371, 1310, 1220, 1130, 918, 854, 717 \text{ and } 671 \text{ cm}^{-1}; \]

\[ \text{a (CDCl}_3\text{)} 3.95 \text{ (dd, } J=7 \text{ and } 4 \text{ Hz, } 1\text{H, C(5)H)}, 4.14 \text{ (d, } J=4 \text{ Hz, } 1\text{H, C(1)H)}, 5.26 \text{ (d, } J=11 \text{ Hz, } 1\text{H, C(3)H)} \]

Addition of sulphur dichloride to ester (286)

Following the general procedure, 286 and sulphur dichloride were reacted to give an almost colourless crystalline solid (3.08 g) as crude product. Recrystallisation from benzene furnished needles of 3-benzoyloxy-6,7-dichloro-8-thiabicyclo[3.2.1]octane (295) (2.66 g, 8.4 mmol, 84%), m.p. 160-161°. Anal. calc. for C\textsubscript{14}H\textsubscript{14}Cl\textsubscript{2}O,S:

C 52.98, H 4.46, Cl 22.36, S 10.11%. Found: C 52.86, H 4.57, Cl 22.73, S 10.54%; \[ \text{KBr}_{\text{max}} 1726 \text{ cm}^{-1}(\epsilon 474); \text{CCl}_4_{\text{max}} 3028, 2940, 2920, 1721, 1600, 1275, 1111, 984, 885 \text{ and } 702 \text{ cm}^{-1}; \text{a (CDCl}_3\text{)} 2.10 \text{ (m, } 2\text{H, C(2,4)H}_2\text{)}, 2.87 \text{ (m, } 2\text{H, C(2,4)H}_2\text{)}, 3.66 \text{ (m, } 2\text{H, C(1,5)H)}, 4.89 \text{ (m, } 2\text{H, C(6,7)H)}, 5.75 \text{ (m, } 1\text{H, C(3)H)} \text{ and } 7.29-8.31 \text{ (pr m, } 5\text{H, aromatic CH)}; \text{m/e} \text{ [320, 318 and 316]} (M^+), [283 and 281], [198, 196 and 194], [161 and 159], [178 and 176], [141], [105], [97] \text{ and } 77; \lambda_{\text{max}}^{\text{CH}_{3}\text{CN}} 230 (\log \epsilon 4.13), 274 (2.95) \text{ and } 281 \text{ nm (2.86).}

Thin layer chromatography (ether-petroleum spirit, 1:4) of the remaining liquors gave additional benzoate (295) (285 mg, 0.9 mmol, 9%) and 2-benzoyloxy-6,7-dichloro-8-thiabicyclo[3.2.1]octane (296),...
which was sublimed (110°, 0.03 mm Hg) as colourless needles (75 mg, 0.24 mmol, 2%), m.p. 117-118°. Mass calc. for $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{O}_2\text{S}$: 316.00913. Found: 316.00878; $\nu^\text{KBr max} 3057, 2940, 2920, 2845, 1714, 1603, 1584, 1493, 1449, 1344, 1315, 1271, 1110, 884, 773 and 710 cm$^{-1}; \Delta (\text{CDCl}_3) 1.70-2.46 (m, 4H, CH$_2$), 3.49 (m, 1H, bridgehead CH), 3.90 (m, 1H, bridgehead CH), 4.94 (m, 2H, C(6,7)H), 5.48 (m, 1H, C(2)H) and 7.50-8.08 (pr m, 5H, aromatic CH); m/e [320, 318 and 316] (M$^+$), [283 and 281], 246, [198, 196 and 194], [178 and 176], [161 and 159], 141, 105, 97, 91, 77.

3 Addition of sulphur dichloride to ketal (292)

292 and sulphur dichloride were reacted following the general procedure. Evaporation of methylene chloride yielded a yellow solid (2.55 g) which darkened slightly on standing at room temperature overnight. Preparative t.l.c. (ether-petroleum spirit, 3:7) gave 305 (2.21 g, 8.7 mmol, 87%), m.p. 112-114°. Anal. calc. for $\text{C}_{9}\text{H}_{12}\text{Cl}_2\text{O}_2\text{S}$: C 42.36, H 4.74%. Found: C 42.59, H 4.70%; $\nu^\text{KBr max} 2979, 2930, 2852, 1460, 1335, 1204, 1097, 1036, 994, 950, 881, 817, 725 and 634 cm$^{-1}; \Delta (\text{CDCl}_3) 1.91-2.83 (br env, 4H, C(3,4)H$_2$), 3.26 (m, 1H, C(1)H), 3.40 (m, 1H, C(5)H), 3.80-4.32 (m, 4H, dioxolane CH$_2$), 4.49 (m, 1H, C(2)HCl) and 4.68 (d, J=6 Hz, 1H, C(6)HCl); m/e [258, 256 and 254] (M$^+$), [222, 220 and 218], 183, 146, 120 and 99.

4 Addition of sulphur dichloride to dienone (238)

Following the general procedure 238 and sulphur dichloride condensed to give a yellow crystalline solid (2.12 g) which recrystallised from ethyl acetate - hexane furnishing dichloroketone (307) (1.73 g, 8.2 mmol, 82%), m.p. 139-141°. Anal. calc. for $\text{C}_{7}\text{H}_8\text{Cl}_2\text{OS}$:

C 39.83, H 3.82%. Found: C 40.02, H 3.78%; $\nu^\text{CCl}_4 1761$ cm$^{-1}$
\[ \varepsilon_{480}; \, \nu_{\text{max}} \, 2990, \, 2949, \, 2878, \, 1750, \, 1439, \, 1346, \, 1223, \, 1120, \, 1006, \, 984, \, 883, \, 805, \, 744, \, 706 \, \text{and} \, 642 \, \text{cm}^{-1}; \, \text{a} \, (\text{CDCl}_3) \, 1.74-2.67 \]

(br env, 4H, C(3,4)H₂), 3.63 (m, 1H, C(5)H), 3.70 (m, J=6 Hz, 1H, C(1)H), 4.47 (m, 1H, C(2)HCl), 4.81 (d, J=6 Hz, 1H, C(6)HCl);

m/e [214, 212 and 210] (M⁺), [186, 184 and 182], [177 and 175], [149 and 147], 113, 111, 99, 94 and 88.

Attempted dehydrochlorination of 301

(a) Chromatographic alumina (Woelm Grade 0, basic, 2 g) was added to a solution of 301 (450 mg, 2.58 mmol) in AnalaR benzene (5 ml). The mixture was refluxed with stirring for 65 hr. The alumina was filtered off, washed with ethyl acetate and the combined filtrates and washings evaporated to dryness leaving a yellow oil (430 mg) identified by t.l.c. comparison (CHCl₃-petroleum spirit, 7:3) and p.m.r. spectroscopy to be unreacted starting material.

(b) A solution of 301 (96 mg, 0.55 mmol) in 2,4,6-collidine (230) (1 ml) was warmed to 105° for 2 hr. On cooling, the mixture was taken up in ether and washed twice with 2N hydrochloric acid, water to neutrality and brine. Drying and evaporation of ether gave a dark yellow oil (53 mg), identified as in (a) to be mainly unreacted starting material.

(c) To a solution of 301 (480 mg, 2.75 mmol) in AnalaR methanol (15 ml), was added sodium (63 mg, 2.75 mmol), with vigorous stirring. The solution which immediately assumed a deep red colour was stirred at room temperature for 3 hr, stripped of solvent, 10 mls water added and the aqueous solution extracted with ether. The ether
layer was washed with brine, dried and evaporated leaving a dark red oily residue (207 mg), which proved to be unreacted starting material.

(d) A solution of 301 (349 mg, 2 mmol) in dimethyl sulphoxide (2 ml) was added dropwise to a solution of potassium t-butoxide (224 mg, 2 mmol) in dimethyl sulphoxide (3 ml) and the mixture stirred at room temperature for 2 hr under nitrogen. The deep red solution was poured on to crushed ice and extracted with ether. The combined extracts were washed four times with brine and dried. Evaporation left a dark brown semi-solid (197 mg). Thin layer chromatography (CHCl₃ - petroleum spirit, 7:3) showed that no starting material remained and that the product contained many components, none of which were identified as 303.

Acid catalysed hydrolysis of ketal (305)

A mixture of 305 (182 mg, 0.71 mmol), chloroform (10 ml) and 2N sulphuric acid (10 ml) was stirred at room temperature for 65 hr, after which time t.l.c. (ethyl acetate - petroleum spirit, 1:4) showed that the reaction had gone to completion. The organic layer was separated and washed with aqueous sodium bicarbonate and water to neutrality, dried and solvent removed under suction. Preparative t.l.c. (ethyl acetate - petroleum spirit, 1:4) and recrystallisation (ether-hexane) gave colourless prisms of 308 (147 mg, 0.62 mmol, 87%), m.p. 85.5-87°. Anal. calc. for C₉H₁₃ClO₃S: C 45.66, H 5.54%. Found: C 45.45, H 5.47%; ν₅₅₅₉ (CCl₄) 3559, ν₅₅₃₈ (KBr) 3380, 2945, 2880, 1469, 1390, 1292, 1197, 1130, 1053, 1036, 980, 950, 864, 749 and 650 cm⁻¹; δ (CDCl₃) 1.83-2.60 (br env, 4H, C(3,4)H₂).
2.93 (d, J=12 Hz, 1H, O\text{H}), 3.19 (m, 1H, C(1)\text{H}), 3.36 (m, J=6 and 4 Hz, 1H, C(5)\text{H}), 3.94 (m, J=12 and 4 Hz, 1H, C(2)\text{HOH}), 4.11 (m, 4H, dioxolane \text{CH}_2) and 4.59 (d, J=6 Hz, 1H, C(6)\text{HCl}); m/e [238 and 236] (\text{M}^+), [220 and 218], 201, 183, 149, 125, 118 and 105.
2 V. Prelog and R. Seiwerth, Ber., 1941, 74, 1644 and 1769.
12 Idem, ibid., 1962, 74, 361.
16 O. Bottger, Ber., 1937, 70, 314.
26 Y. Kashman and E. Benary, Tet., 1972, 28, 4091.
29 H. Stetter and K. Dieminger, Ber., 1959, 92, 2658.
41 H. Stetter and K. Komorowski, Ber., 1971, 104, 75.
60 Idem, ibid., 1954, 87, 205.
61 H. Stetter and M. Dohr, ibid., 1953, 86 589.
70 Idem, ibid., 1972, 37, 2269.
77 E. Fromm and P. Ziersh, Ber., 1906, 39, 3599.
84 J. Bongartz, Ber., 1886, 19, 2182.
G. Snatzke and H. Seidler, ibid., 1969, 5135.
H. Stetter and W. Böckmann, Ber., 1951, 84, 834.
104 N. W. Gabel, U.S. Pat. 3,301,854 (1967).
112 Idem, ibid., 1968, 51, 300.
120 A. C. Cope, B. S. Fisher, W. Funke, J. M. McIntosh and M. A. McKervey, ibid., 1969, 34, 2231.
125 R. Pummerer, Ber., 1909, 42, 2282; idem, ibid., 1910, 43, 1401.
131 E. E. Royals and D. G. Turpin, ibid., 1954, 76, 5452.
137 P. H. McCabe, unpublished.
148 H. Stetter and H. G. Thomas, Ber., 1966, 99, 920.
172 R. E. Ireland and H. A. Smith, Chem. and Ind., 1959, 1252.
175 M. R. Bell (Sterling Drug Inc.), U.S. Pat. 3,396,162 (1968).
180 F. Guthrie, Quart. J. Chem. Soc., 1860, 12, 109; idem, ibid., 1861, 13, 129.


183 T. J. Barton and R. C. Kippenham Jnr., ibid., 1972, 37, 4194.


191 R. Willstätter, Ber., 1901, 34, 3165.


203 R. Willstätter, Ber., 1896, 29, 393.