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

Contents

Contents(cont'd)

SUMMARY

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 SCl_2 in an identical regiospecific manner to produce the

unsymmetrical 1:1 adducts (307 and 305) while 1-benzoyloxycyclo-

hepta-3,5-diene (286) gave the expected symmetrical dichloride (295).

Cyclohepta-3,5-dienone (282) reacted with SCl_2 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[1] 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[2] 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[3-6] to give 1 in

yields ranging from 12% to 42%. The most recent modification[7]

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[8] 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[9-15] and has contributed to the steady

Figure 1
The Diamond Crystal Lattice
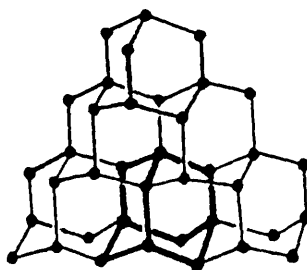
Scheme 1
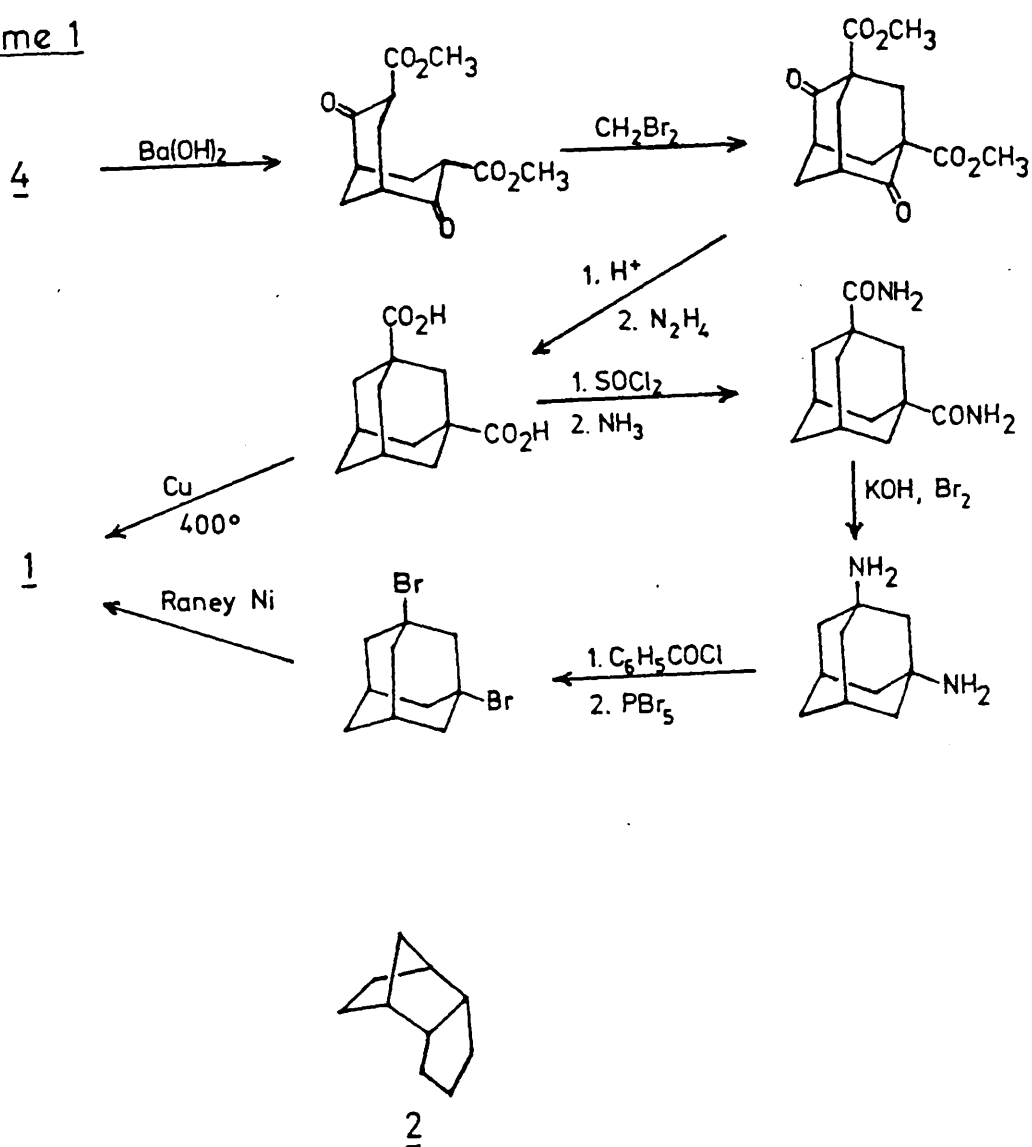
increase in the number of derivatives which have been prepared in
synthetic studies, in mechanistic and stereochemical investigations
and for biological testing. Like other saturated hydrocarbons
however, the utility of 1 as a synthetic intermediate is limited
and although bridgehead positions are readily 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 derivaties 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

3

Scheme 2

4 → (CH₂Br₂) → **5** → (Zn, HCl) → **6**

Scheme 3

4 → (H⁺) → **79** → (C₄H₉N) → **7** → (Br₂CHCO₂C₂H₅) → **8** → (1. H⁺ 2. Zn/HCl) → **9**

10
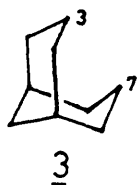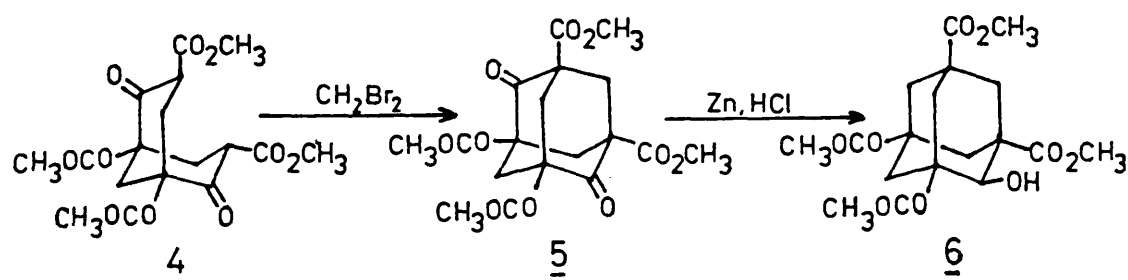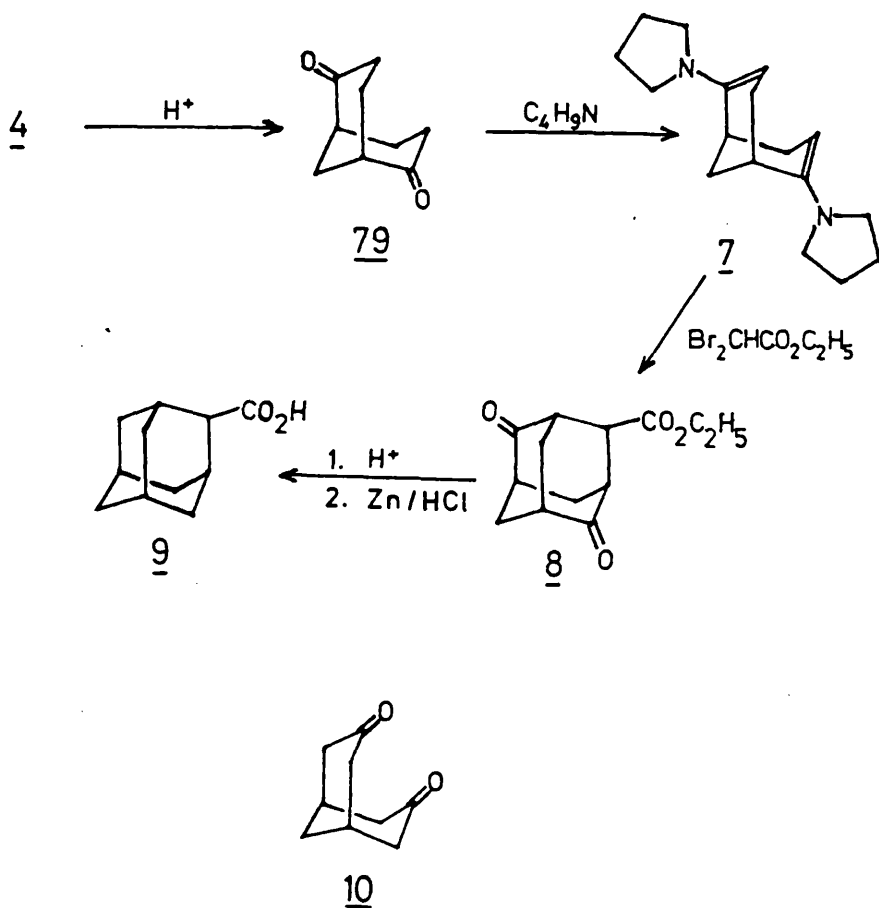
(Scheme 4) was condensed with nitromethane to give 12. Catalytic
reduction of this product yielded the substituted 2-aminoadamantane
(13). The high and varied functionality of products obtainable
in this way render them particularly suitable for further
functional group manipulation.

Photolysis of bicyclo[3.3.1]nonanes has also provided entry into
usefully substituted adamantanes. Thus irradiation[20] of epoxide
(14) has been used to produce 1,3-dihydroxyadamantane (15). Photo-
induced cyclisation[21] 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
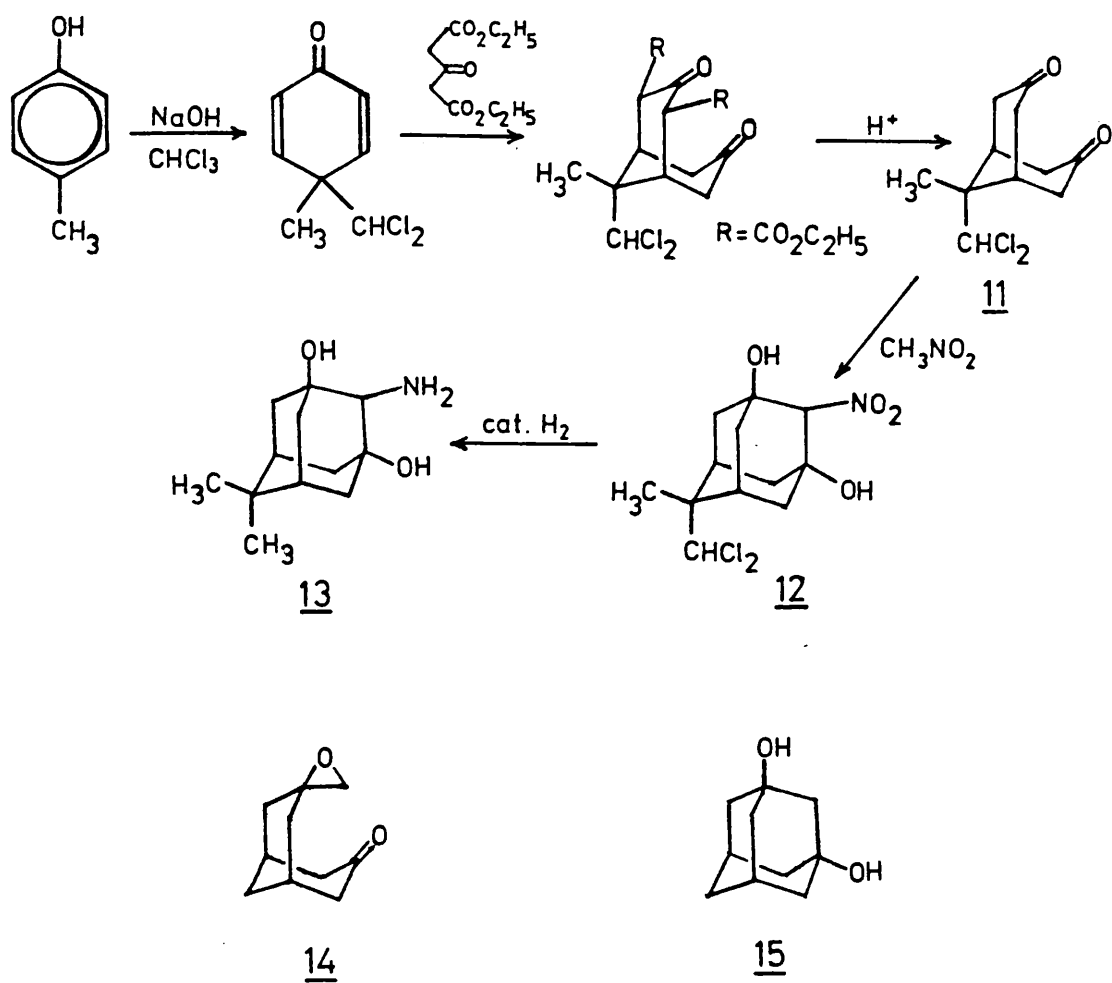
Scheme 5
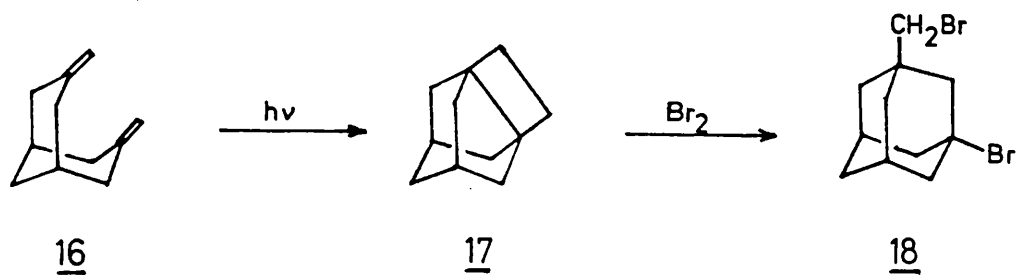
Scheme 6

R = H or $CO_2C_2H_5$
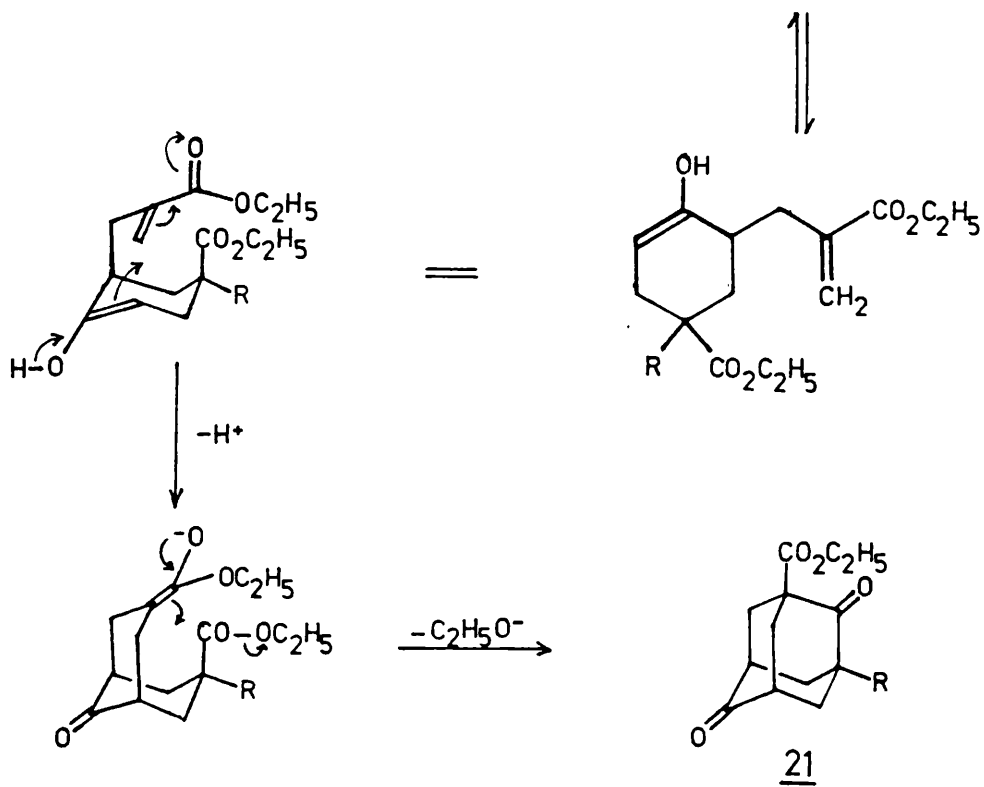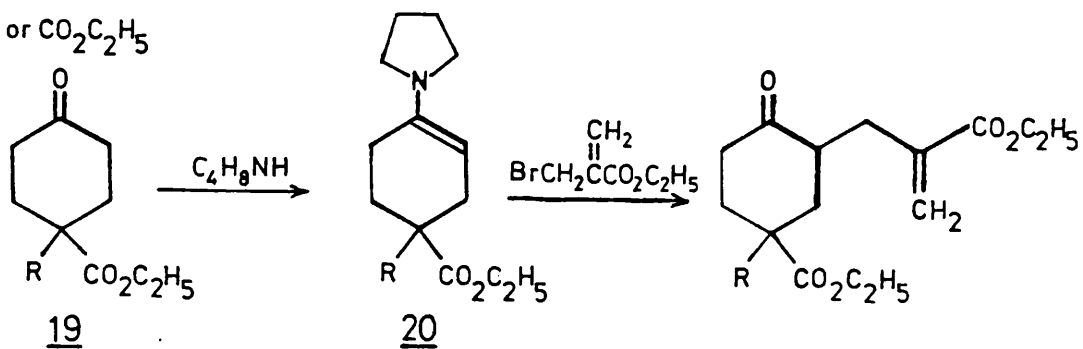
systems possessing skeletal oxygen, nitrogen and sulphur. For the same reasons, the preparation of mixed heteroadamantanes, such as oxathia- and azathiaadamantanes, has not been reviewed. Entry into these systems, however, follows the same basic strategies as those which are discussed.

Heteroadamantanes have been reported which contain non-metals such as arsenic[24], boron[25], phosphorus[26], selenium[27] and silicon[28] and a variety of metals such as calcium[29], copper[30], rhodium[31] and tin[32].
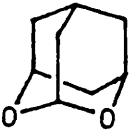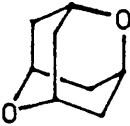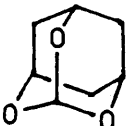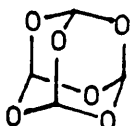
2-Oxaadamantane (Oxaadamantane, 23)

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[33] 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[19] 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,

<u>Table 1</u>   Oxaadamantanes.

Structure	Name	Number
	2-	<u>23</u>
	2,4-di-	<u>61</u>
	2,6-di-	<u>49</u>
	2,4,6-tri-	<u>65</u>
	2,4,9-tri-	<u>66</u>
	2,4,10-tri-	<u>67</u>
	2,4,6,8-tetra-	—
	2,4,6,9-tetra-	—
	penta-	—
	hexa-	—

22

Scheme 7

11 $\xrightarrow{\text{LiAlH}_4}$
(structure with OH, H₃C, CHCl₂) $\xrightarrow{\text{c.H}_2\text{SO}_4}$
(structure **25** with O, H₃C, CHCl₂) $\xrightarrow{\text{cat. H}_2}$
(structure **24** with O, H₃C, CH₃)

25

24

26

27

28

Scheme 8

(structure with ClHg, O, HgCl)

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

$\xleftarrow[\text{NaCl, H}_2\text{O}]{\text{Hg(OAc)}_2}$ **26**

23 $\xleftarrow{\text{c. H}_2\text{SO}_4}$ **26**

26 $\xrightarrow{\text{HCO}_3\text{H}}$ (structure with HO, O, OH)

26 $\xrightarrow[\text{H}_2\text{O}]{\text{Br}_2}$ (structure with Br, O, Br)

$\xrightarrow{\text{Raney Ni}}$ **23**
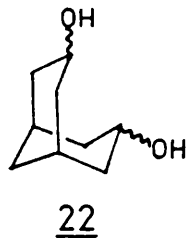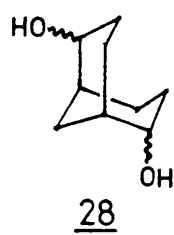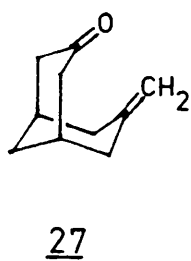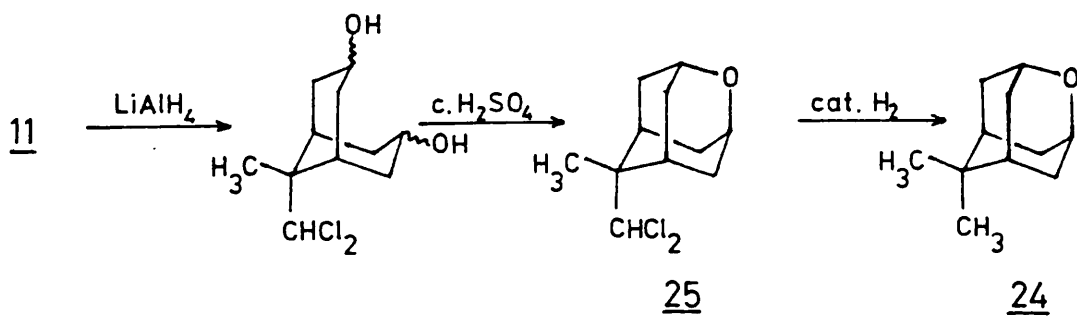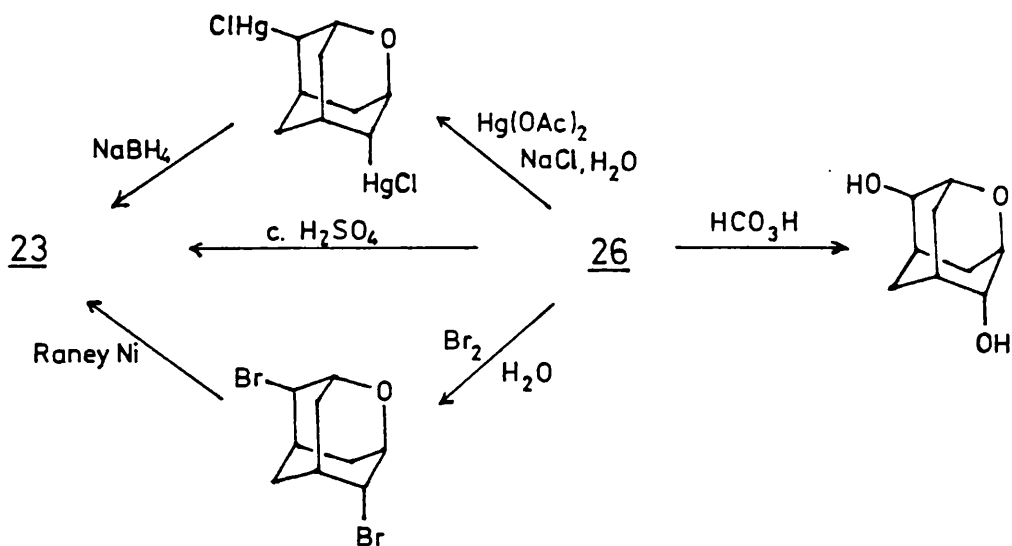
is readily available in quantity from Meerwein's tetraester (4) and has been converted to oxaadamantanes by a number of routes including oxymercuration[34,35], sulphuric acid hydrolysis[34], reaction with aqueous bromine or potassium triiodide[35,36], or peracid oxidation[36] (Scheme 8).

Dione (10) and its monomethylene relative (27) may both be prepared from 1,3-dihaloadamantanes[37,38] (Scheme 9) and provide potentially useful routes to simple oxaadamantanes. Reduction of 10 with hydrogen - Raney Nickel[39] or sodium borohydride[40], 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[39] (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[40] 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[41] with pyrollidine 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[38,42]. In particular this reaction is a key step in the synthesis[42] (Scheme 12) of the oxaadamantyl urea (34) which exhibits strong hypoglycemic properties

Scheme 9

X = Cl or Br
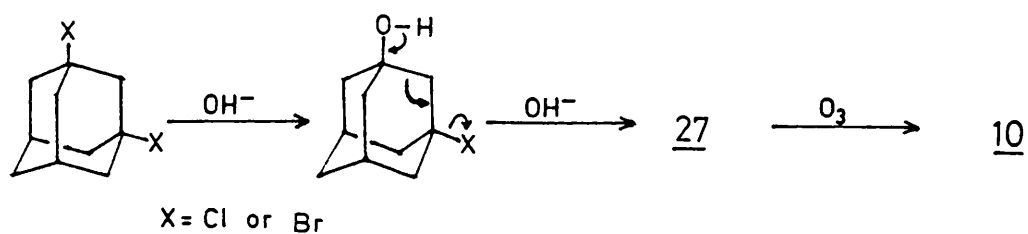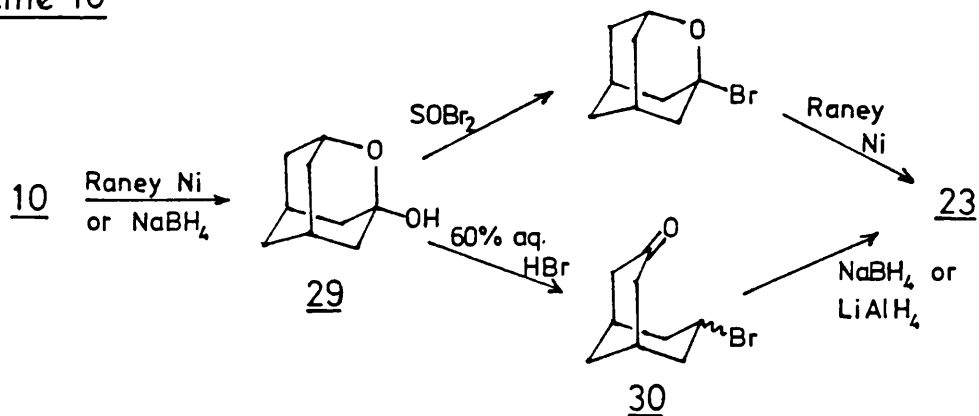
Scheme 10

Scheme 11

Scheme 12

Ar = ⬡—Cl
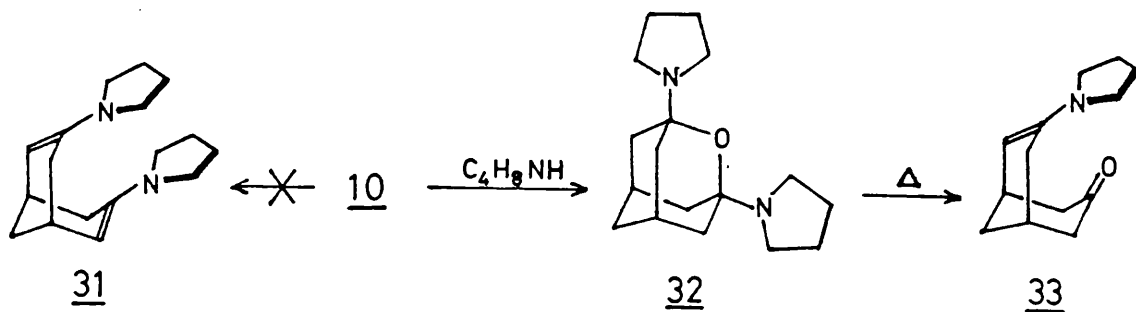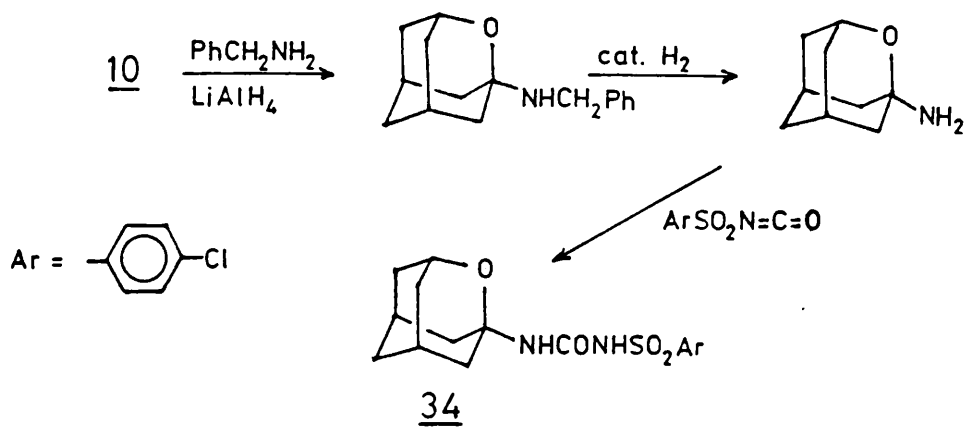
and is of potential use in the treatment of diabetes. The reaction

of 10 with Grignard or organolithium reagents[43] 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 LiAlH$_4$ (Scheme 13) yields endo-alcohol (37),

the stereochemistry of which is ideal for ring-closure under acid

conditions to 1-methyl-2-oxaadamantane (38)[43]. Moreover,

oxymercuration of 27 proceeds[43] 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[44] to occur with simultaneous cyclisation

furnishing 40 or 41, while dry hydrogen chloride has been used

by Stepanov and co-workers[45] to effect the conversion of 14 to the

related chloride (42) (Scheme 15). The same group has more

recently studied[46] 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[47] and by Averina and Zefirov[48,49]. 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.
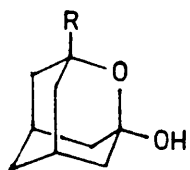
$\underline{35}$ R = CH$_3$
$\underline{36}$ R = Ph

Scheme 13
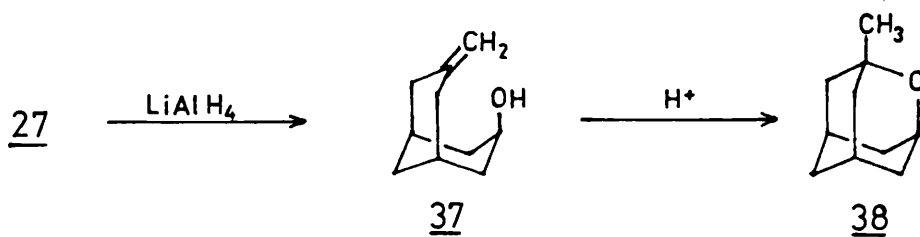
Scheme 14
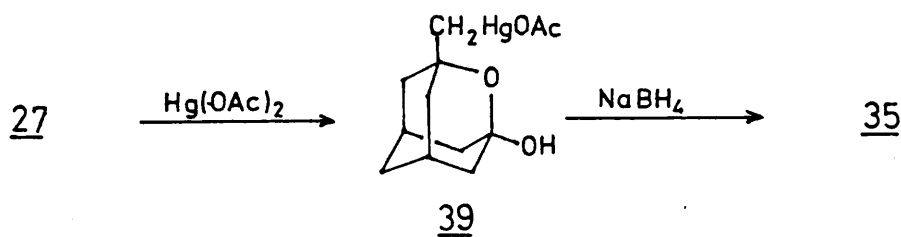
Scheme 15

$\underline{40}$ R = H
$\underline{41}$ R = CH$_3$ or C$_2$H$_5$
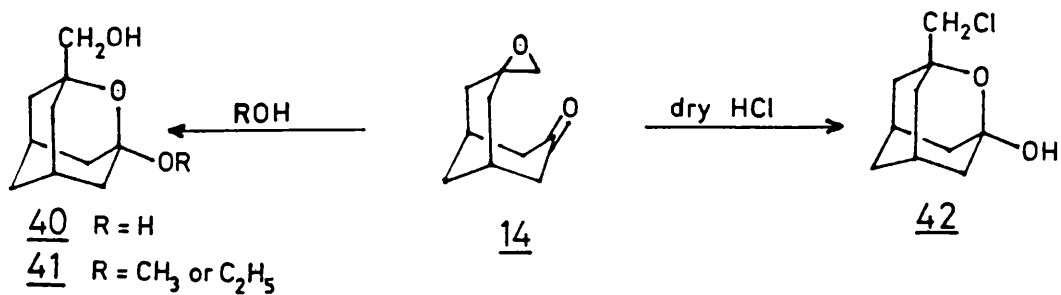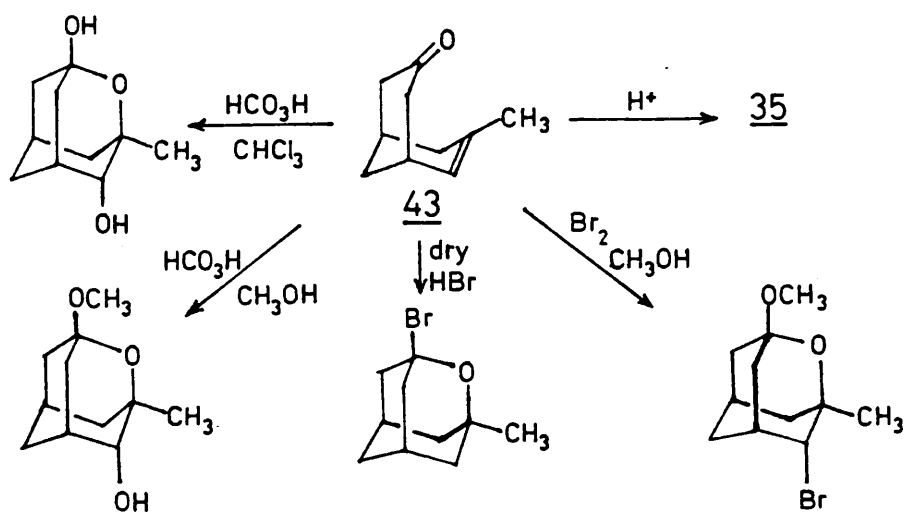
Scheme 16

Scheme 17
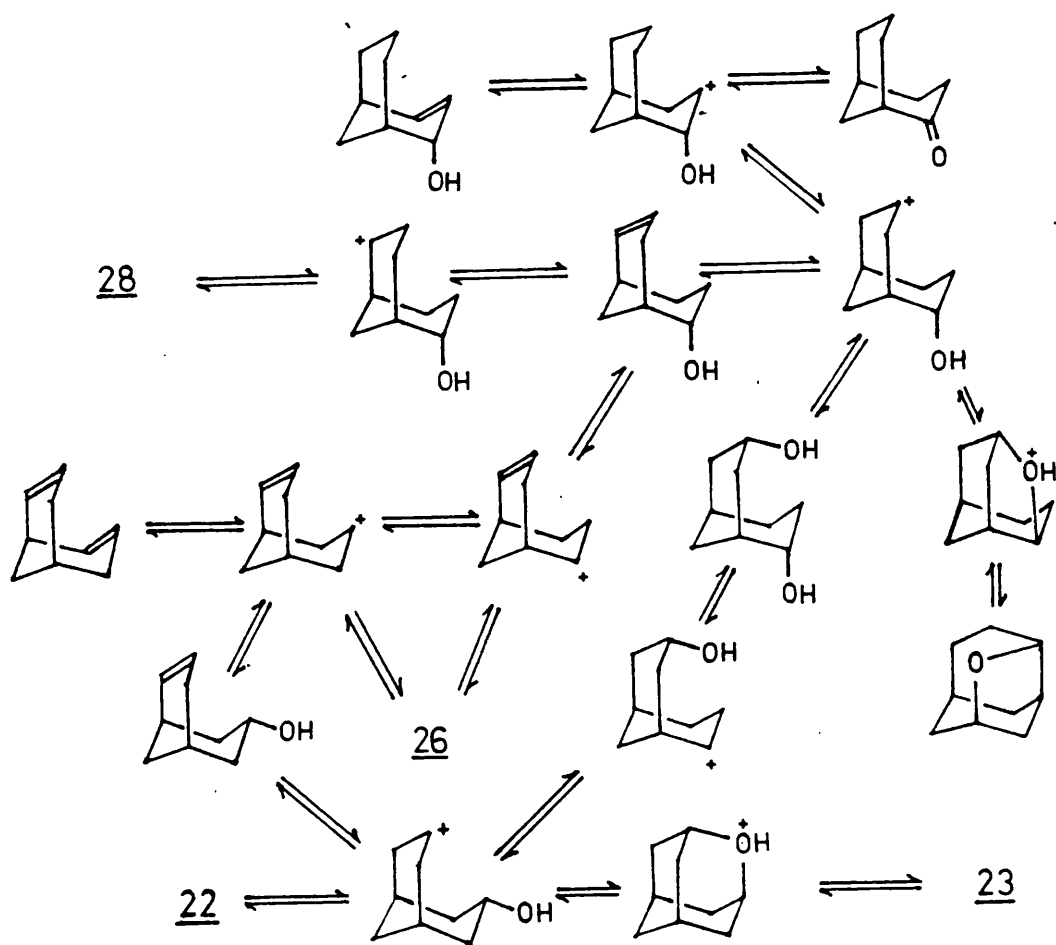
The reaction undoubtedly involves a large number of intra- and intermolecular hydride transfers and accordingly a complete mechanistic description of all processes taking place would be unduly involved. A simplified reaction pathway is however depicted in Scheme 17.

A few oxaadamantanes have been prepared by the oxidation of bicyclic and tricyclic alcohols. Thus 2-hydroxyadamantane (44)[50] and 3-hydroxybicyclo[3.3.1]nonane (45)[51] 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 hypoiodite 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
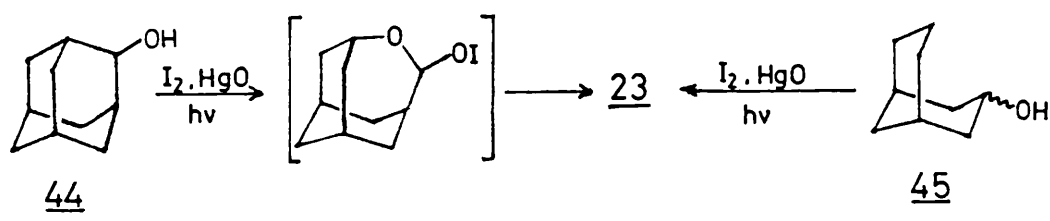
Scheme 19
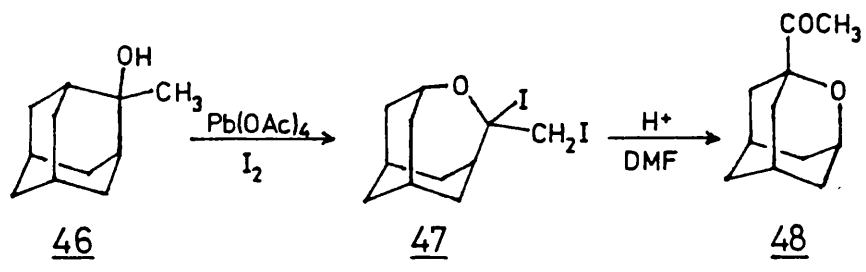
Scheme 20
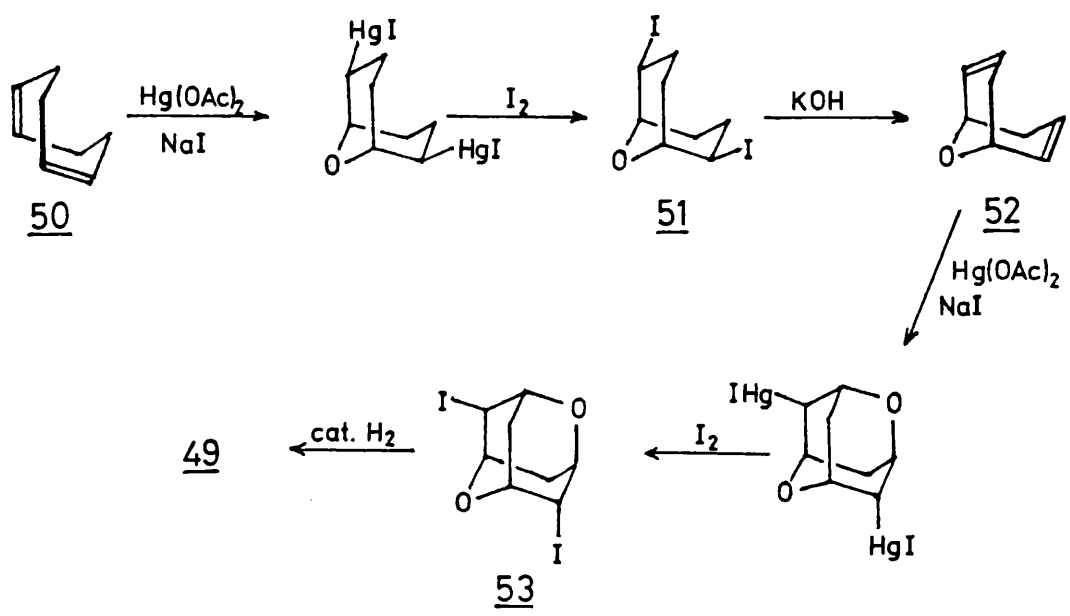
iodine cleavage of the organomercury complex formed gave diiodoether (51)[53]. Dehydroiodination of 51 yielded the versatile bicyclic diene (52) which by repeating the oxymercuration sequence was cyclised to diiodide (53). Catalytic reduction of 53 furnished the parent diether (49) in excellent overall yield (Scheme 20).

In a more recent, but closely related study[54], 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[55] 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[56] 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[57] 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[58] 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
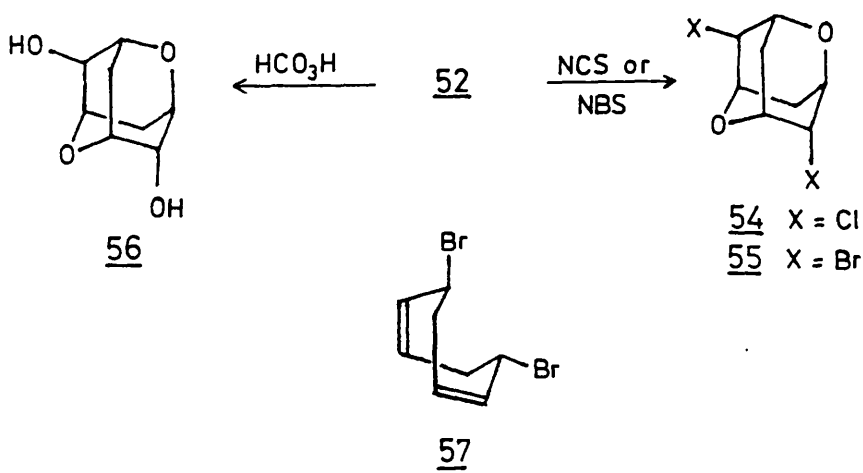
Scheme 22
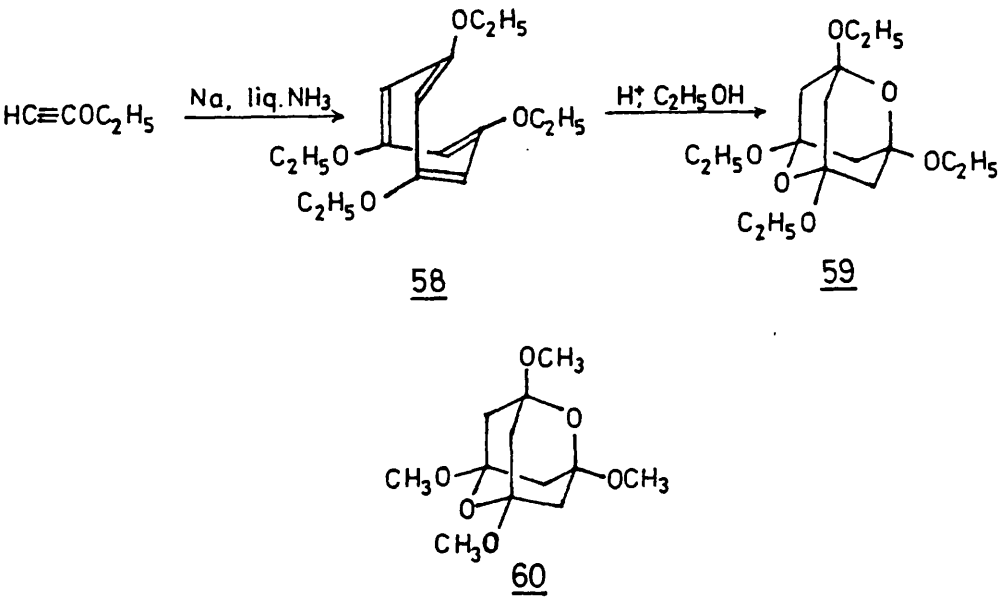
Scheme 23
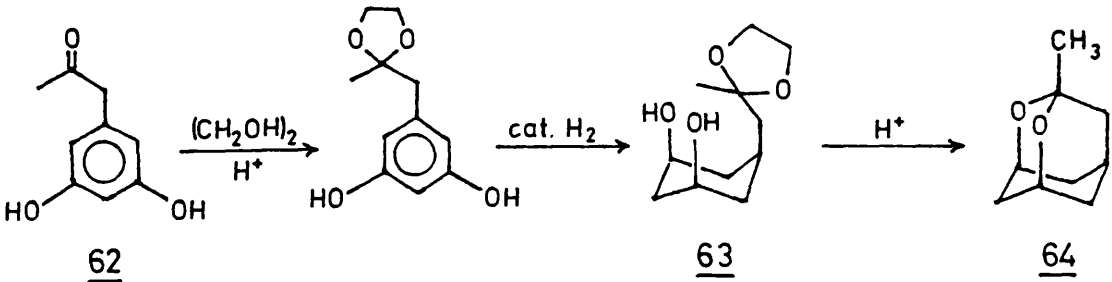
Miscellaneous Higher Polyoxaadamantanes

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-trioxaadamantane (67) being synthesised[59,60] in 75% yield by the condensation of 68 with ethyl or methyl orthoformate (Scheme 24). Construction of the 2,4,9-trioxaadamantane (66) nucleus generally involves an intermediate of the form $RC(CH_2COR')_3$ 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-trioxaadamantane (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-trioxaadamantane (76). The precise mode of cyclisation of 74 is unclear but most probably involves the intermediate formation of tetrahydropyran (75).

Scheme 24

cat. H₂ → ... ⇌ ... HC(OR)₃ / H⁺ → **67**

R = CH₃ or C₂H₅

68

Scheme 25

$CH_2=CHCH_2MgBr \xrightarrow{ClCO_2C_2H_5} (CH_2=CHCH_2)_3COH \xrightarrow{O_3} (O=CHCH_2)_3COH$

69 **70**

↓ CH₃OH / CaCl₂

71 ← H⁺ ← (methoxy acetal structure with OH)

72

Scheme 26

base → NaBH₄ →

73

↓ H⁺

76 ← H⁺ ← **75** ← H⁺ ← **74**
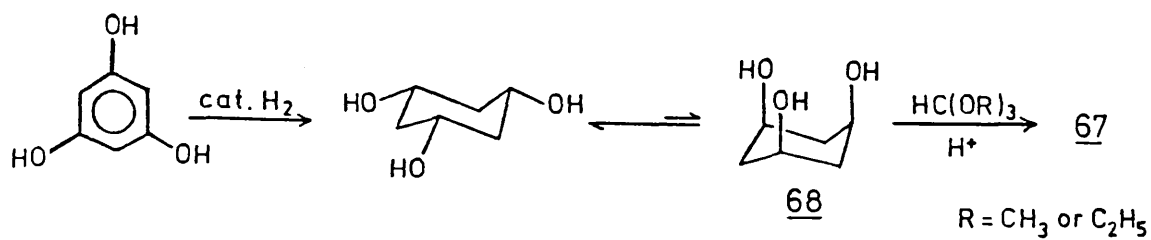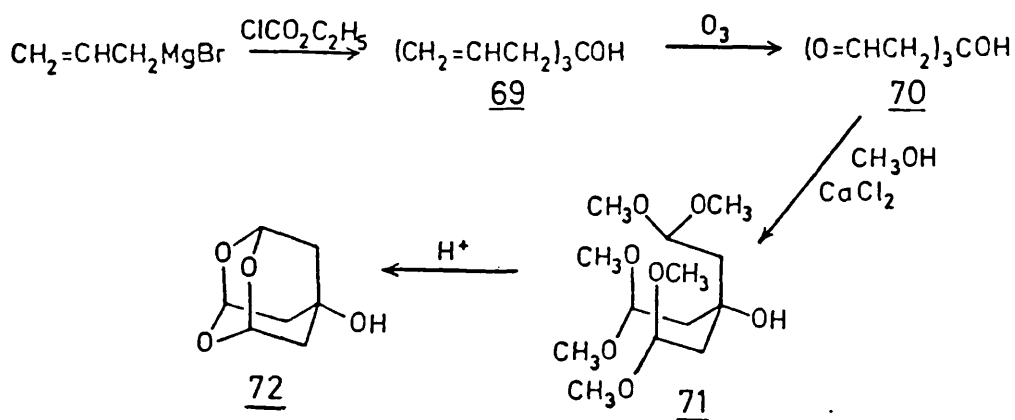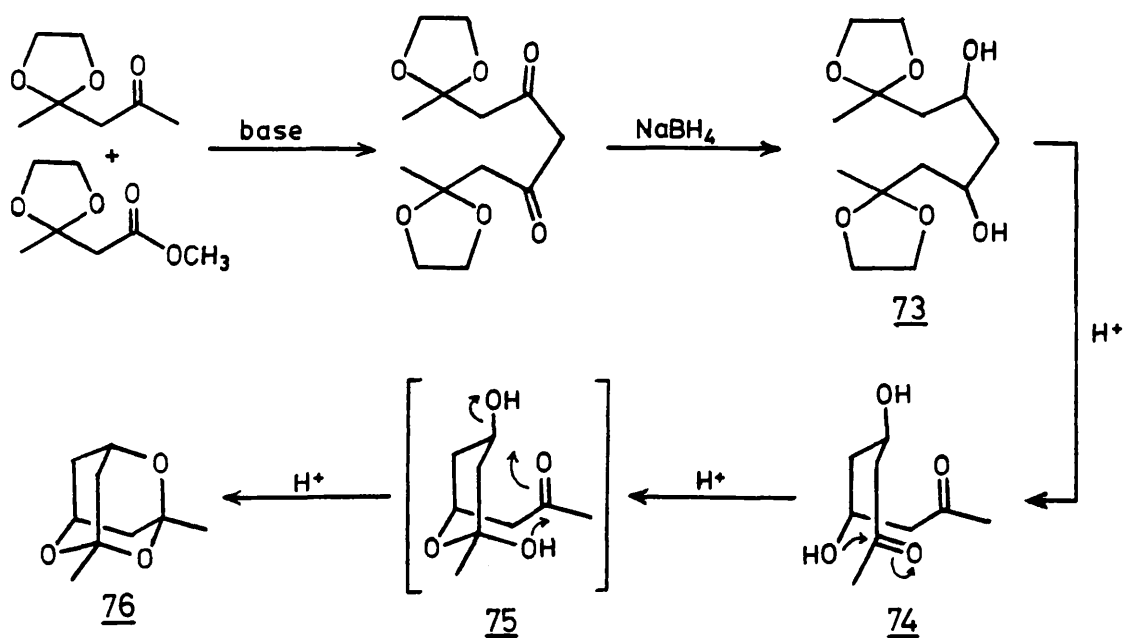
Polysubstituted 2,4,6,8-tetraoxaadamantanes such as 77 have been prepared[63,64] by dimerization of β-ketoaldehydes of the type R'COCR$_2$CHO under the influence of boron trifluoride etherate, cyclisation occurring by a similar mechanism to that already described for trioxaadamantanes (Scheme 27).

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[65,66] as a sweet smelling solid, m.p. 320°, 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, SOCl$_2$, and sulphuryl chloride, SO$_2$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[67,68] to its bisenamine (7) which reacted with SCl$_2$ to give the useful dione (80). Wolff-Kishner reduction of 80 which has been converted to a variety of other derivatives[69-71] provided the first laboratory synthesis of 78 (Scheme 28). Alternatively, 78 has been prepared[34] by LiAlH$_4$ reduction of 4,8-dichloro-2-thiaadamantane (81) which was obtained by the condensation of SCl$_2$ with diene (26).

Scheme 27

77 R = CH$_3$, R' = C$_6$H$_5$

78
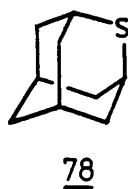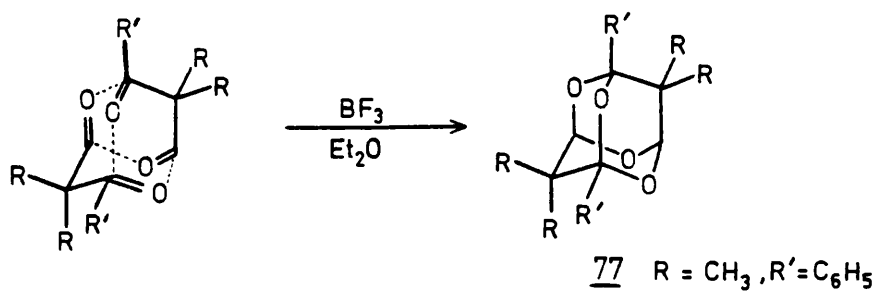
Scheme 28
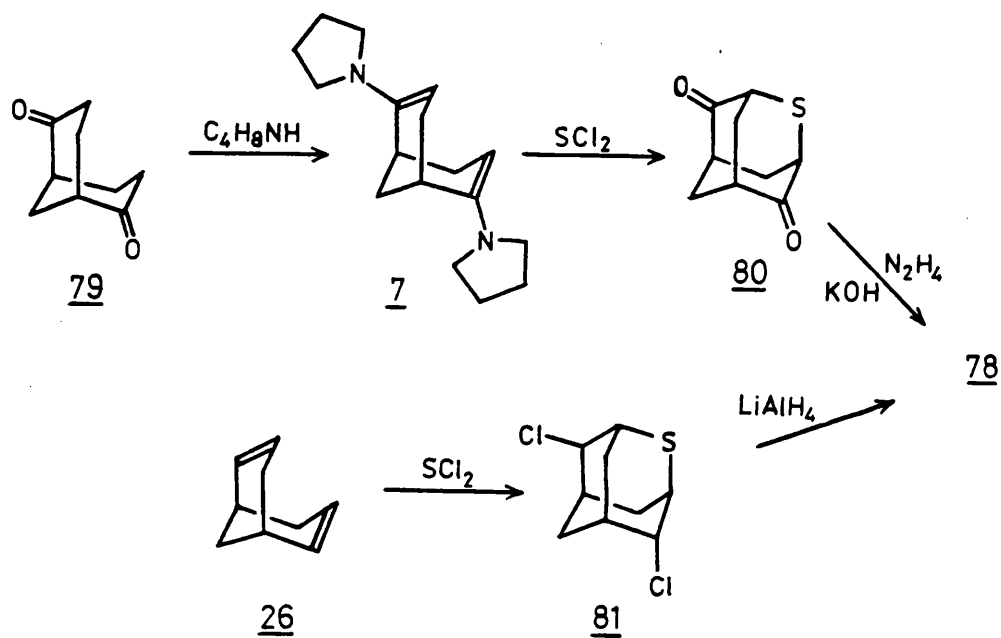
A novel thiaadamantane, which does not have a direct counterpart in the oxaadamantane field is the 1-thianiaadamantane cation (83). This species has been prepared as the bromide salt by the treatment[72] of mercaptan (82) with sodium carbonate (Scheme 29), but as yet has received little further attention.

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 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
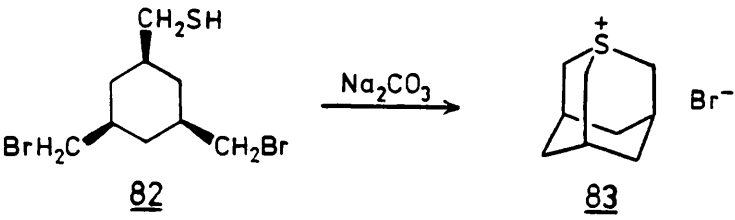
Scheme 30

Scheme 31

Scheme 32

90 → base → 91 + other products

92

Scheme 33

R
O

R
O

H₂S, HCl
C₂H₅OH

93

94

Scheme 34

95 → n-BuLi → 96 → D₂O → 97

Scheme 35

98 → 1. n-BuLi 2. CO₂ → 99
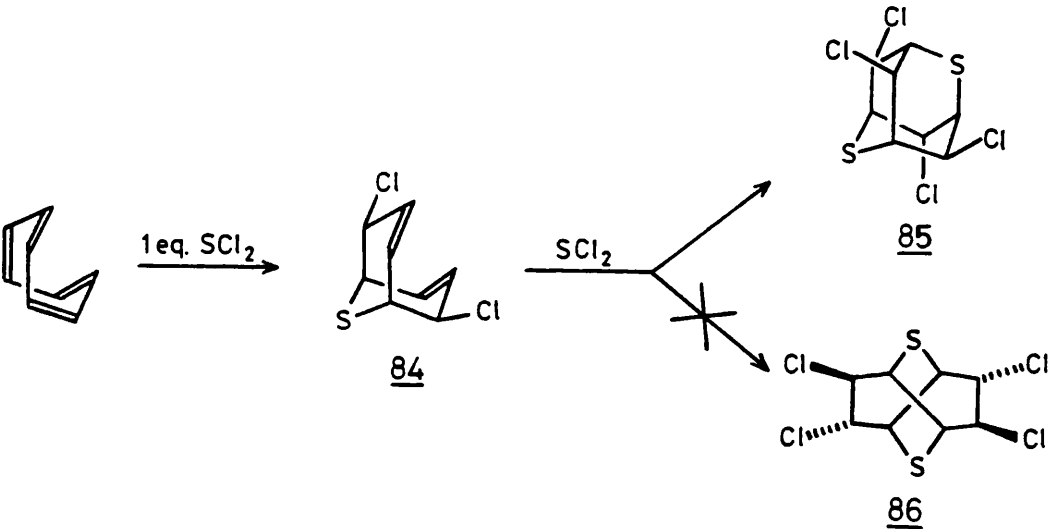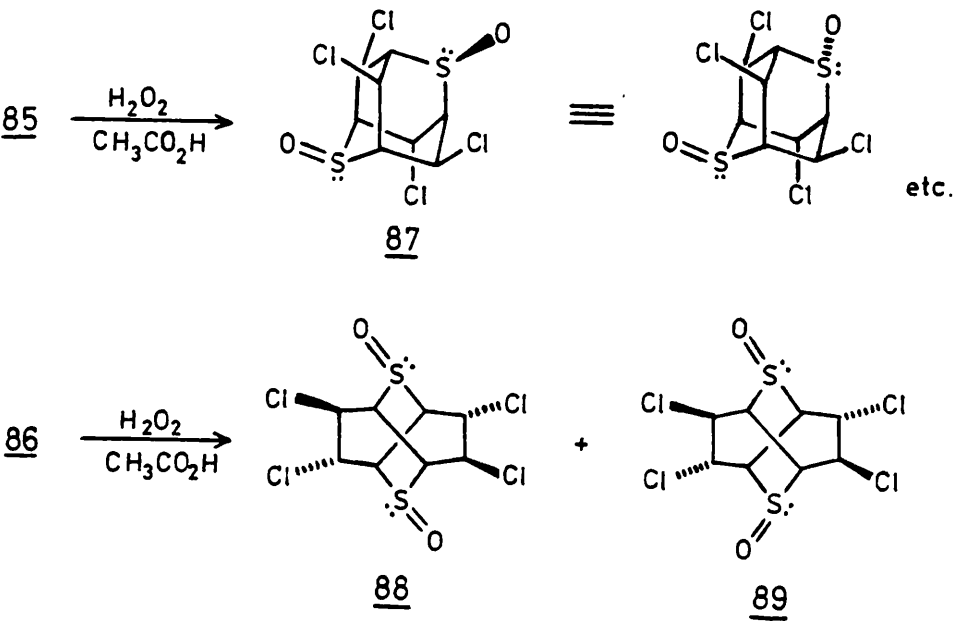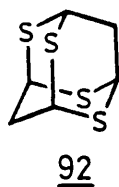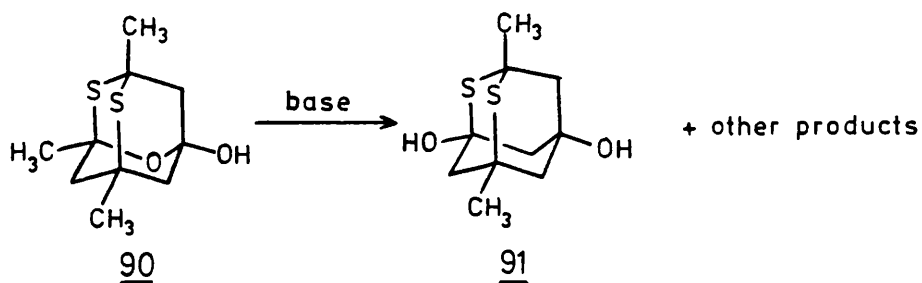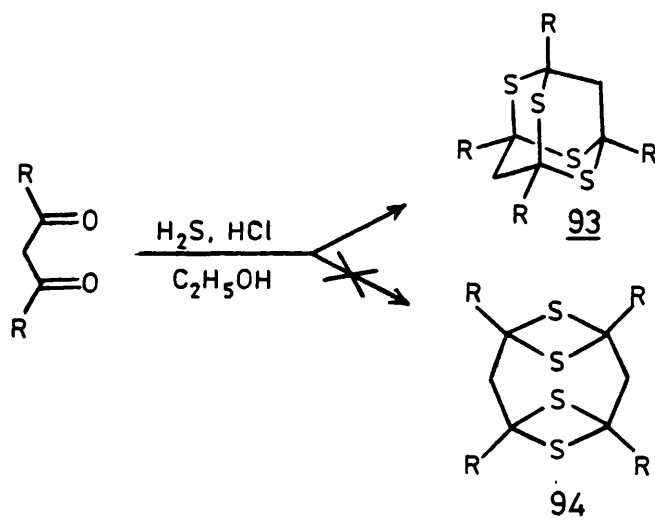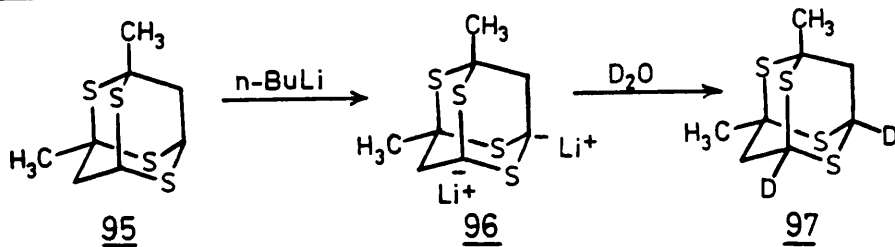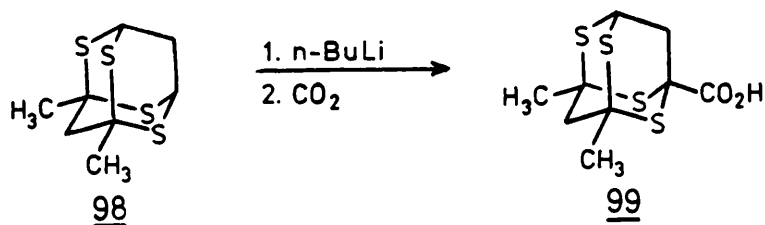
Miscellaneous Higher Polythiaadamantanes

At the present time no synthetically useful routes to trithia- or pentathiaadamantanes have been reported and of the two tetrathia- adamantanes 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 β-diketones (Scheme 33). Although this reaction has been known for many years[77], the structure of the dimerised β-dithioketone product was considered to be 94 and it was only relatively recently that the true tetrathiaadamantane formula was established[78].

More recently, the reaction of β-diketones with thiol acids has been reported[79], to yield 2,4,6,8-tetrathiaadamantanes. 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 β-dithioketones.

Functionalisation of unsubstituted bridgehead positions of the 2,4,6,8-tetrathiaadamantane nucleus has been accomplished by direct metallation using n-butyl lithium. Thus dimethyl derivative (95) forms the dilithium salt (96)[80] in which each negative charge is partly delocalised through sulphur. Addition of D_2O 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[81] of dimethyltetrathiaadamantane (98) with n-butyl lithium followed by carbonylation to give carboxylic acid (99) (Scheme 35).

Hexathiaadamantane (100) has been obtained[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[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[84], bromine with thioacetic acid[85] and acetyl chloride with

liquid hydrogen sulphide[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[87] in 1951.

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[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

$$HCO_2H \xrightarrow[C_6H_5NO_2]{H_2S, HCl} \underline{100}$$

$$\underline{101}$$

Scheme 37

$$\xrightarrow[\text{2. Ester}^n.]{\text{1. MnO}_4^-} \underline{103} \xrightarrow[\text{2. LiAlH}_4]{\text{1. cat. H}_2} \underline{104}$$

$$\underline{104} \xrightarrow[\text{glac. CH}_3\text{CO}_2\text{H}]{\text{HBr}} \underline{105}$$

$$\underline{105} \xrightarrow{\text{NH}_3} \underline{102}$$

Scheme 38

$$\text{(bromo ester)} + \text{(enamine)} \longrightarrow \underline{106} \xrightarrow[\text{BF}_3]{\substack{\text{SH} \\ \text{SH}}} \text{(dithiolane)}$$

$$R = CH_3\text{—}\langle\rangle\text{—}SO_2$$

$$\text{(dithiolane)} \xrightarrow{\substack{\text{Raney} \\ \text{Ni}}} \text{(CO}_2\text{Et)} \xrightarrow{\text{LiAlH}_4} \text{(CH}_2\text{OH)} \xrightarrow[\text{CH}_3\text{CO}_2\text{H}]{\text{HCl}} \underline{102}$$
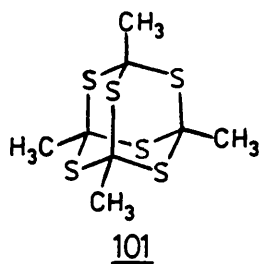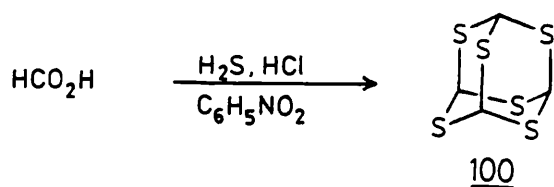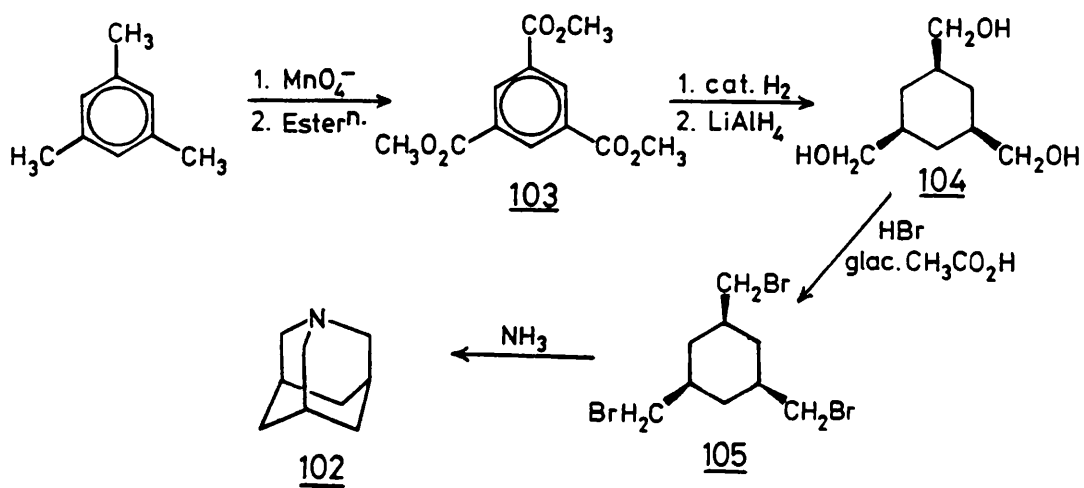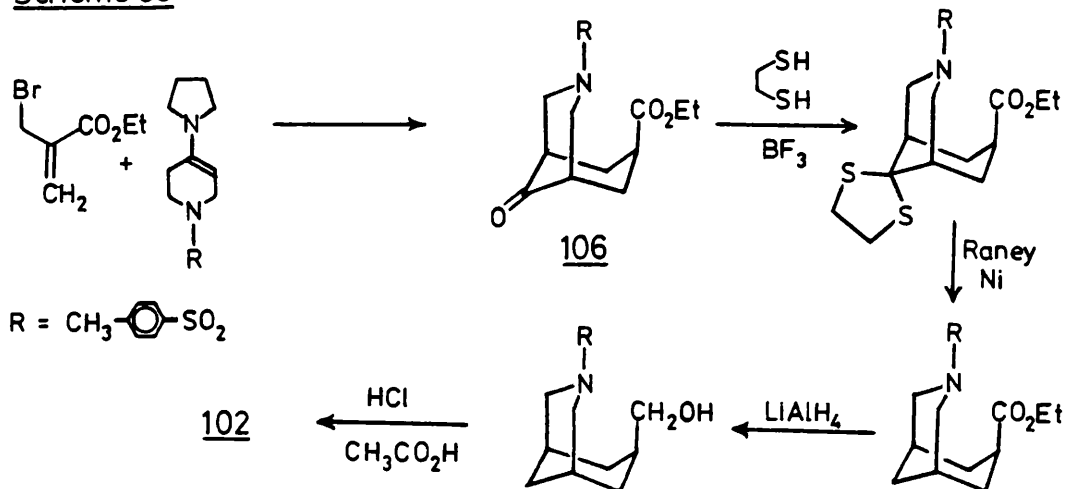
An alternative synthesis of 102 which has been recently reported

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]. α-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.
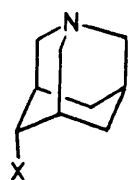
107 X = OH
108 X = NH$_2$

109

Scheme 39

10

R = CH$_3$—⟨benzene⟩—SO$_2$

26

110 Br

109

Scheme 40

79

112
+

111

113

R = H or CH$_3$
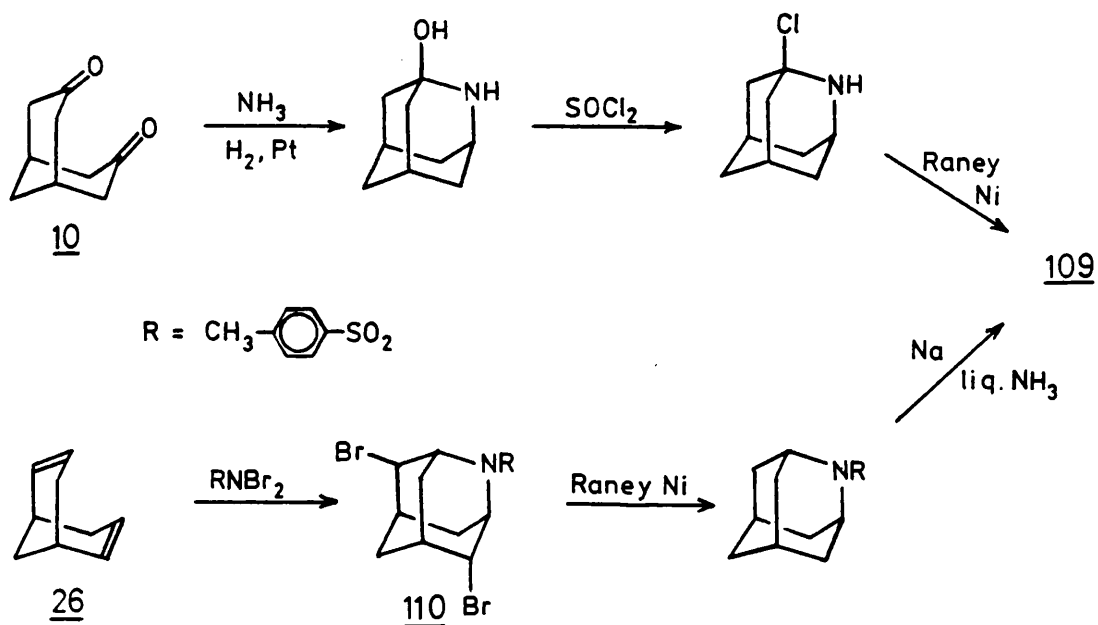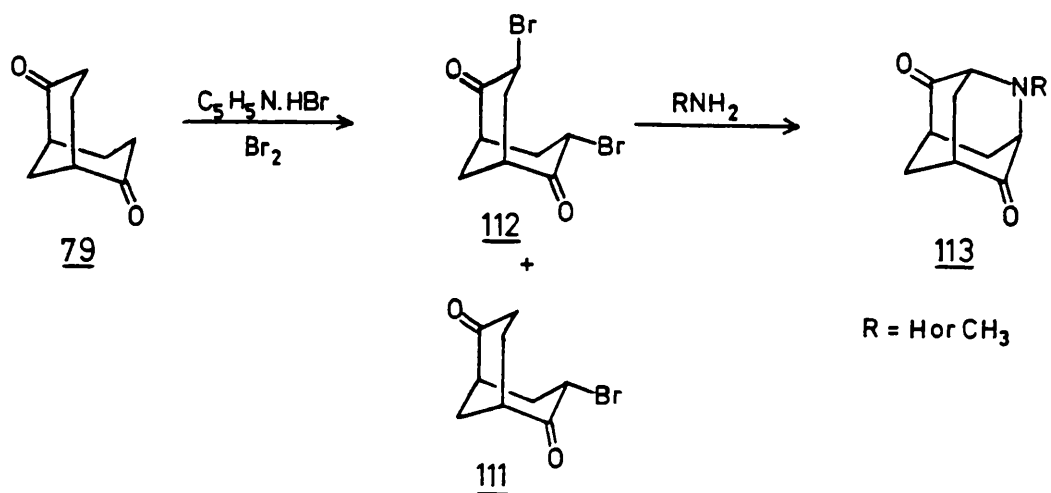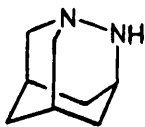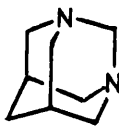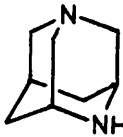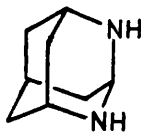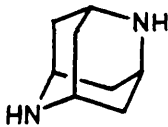
Diazaadamantanes

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[96,97] 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[98].

The synthesis of 2,6-diazaadamantanes has been reported by several
authors including Stetter[94,99], Portmann and Ganter[100] and
Dupeyre and Rassat[101]. The approach adopted by Stetter[94,99] 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 dehydro-
brominated 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 2   Diazaadamantanes.

Structure	Name	Number
	1,2 -	—
	1,3 -	114
	1,4 -	—
	2,4 -	—
	2,6 -	115

Scheme 41

116

$R^1, R^2, R^3, R^4 = H$ or Alkyl

Scheme 42

50

RNBr$_2$

Br

RN

Br

117

215°

RN

118

RNBr$_2$

Br

NR

RN

Br

119

Raney Ni

NR

RN

Na
liq. NH$_3$

115

$R = CH_3$—⬡—SO_2

Scheme 43

RN

120 R = C$_6$H$_5$SO$_2$

121 R = CHO

CH$_3$NH$_2$

HO

NCH$_3$

RN

OH

122 R = C$_6$H$_5$SO$_2$

123 R = CHO
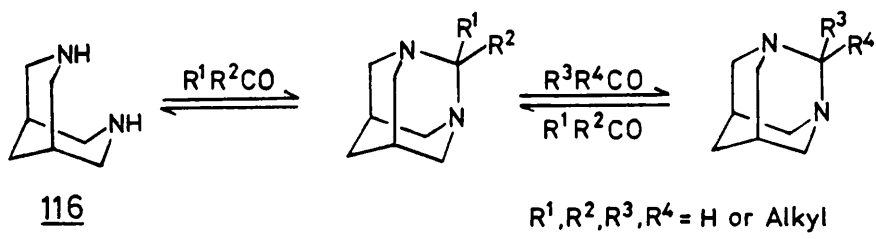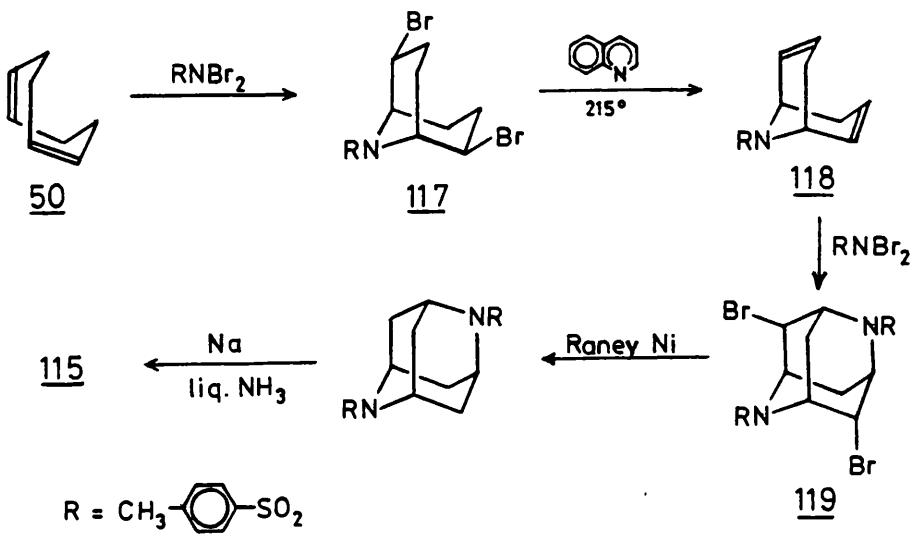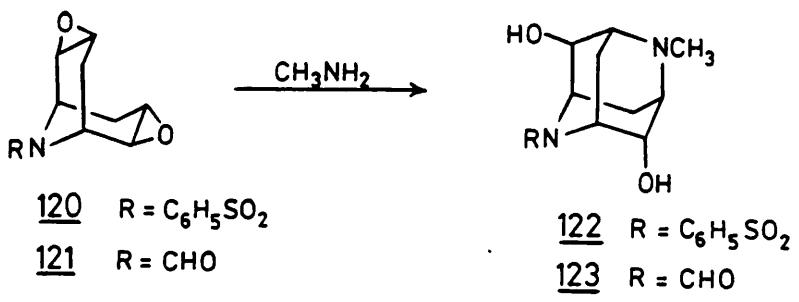
Following a related sequence (Scheme 43), Portmann and Ganter[100] have also synthesised a number of 4,8-disubstituted 2,6-diazaadamantanes. In their approach, entry into the diazaadamantane system was gained by the condensation of a primary amine (methylamine) with diepoxides (<u>120</u> and <u>121</u>). By virtue of their functionality at C(4) and C(8), the products of these condensations, diols (<u>122</u> and <u>123</u>) are particularly suitable as precursors for the synthesis of a number of diazaadmantanes which have potential pharmaceutical application.

Dupeyre and Rassat[101] produced <u>115</u> by the reaction pathway illustrated in Scheme 44. The Mannich condensation of methylamine, glutaraldehyde and acetone dicarboxylic acid yielded the pseudo-pelletierine derivative (<u>124</u>). 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 (<u>125</u>) was obtained as the exclusive product. N-bromination of <u>125</u> followed by ring-closure with concentrated sulphuric acid (Hofmann-Löffler-Freytag reaction) furnished 2,6-diazaadamantane (<u>126</u>) in 25% yield. <u>126</u> was converted by conventional methods to a number of other 2,6-diazaadamantanes including the parent compound (<u>115</u>).

Miscellaneous Higher Polyazaadamantanes

Of the many possible polyazaadamantanes containing three or more skeletal nitrogen atoms, derivatives of only three, 1,3,5-triaza-adamantane (<u>127</u>), 2,4,10-triazaadamantane (<u>135</u>) and 1,3,5,7-tetra-azaadamantane (<u>138</u>) are known.

Scheme 44

CH_3NH_2
+
$OHC(CH_2)_3CHO$
+
$HO_2CCH_2COCH_2CO_2H$

→ **124**

$\xrightarrow[\text{RaneyNi}]{C_6H_5CH_2NH_2}$ **125**

$\downarrow Br_2$

126 $\xleftarrow{c.\ H_2SO_4}$

126 $\downarrow H_2\ /\ Pd/C$

$\xrightarrow[\text{OH}^-]{KMnO_4}$ **115**

127

135

138
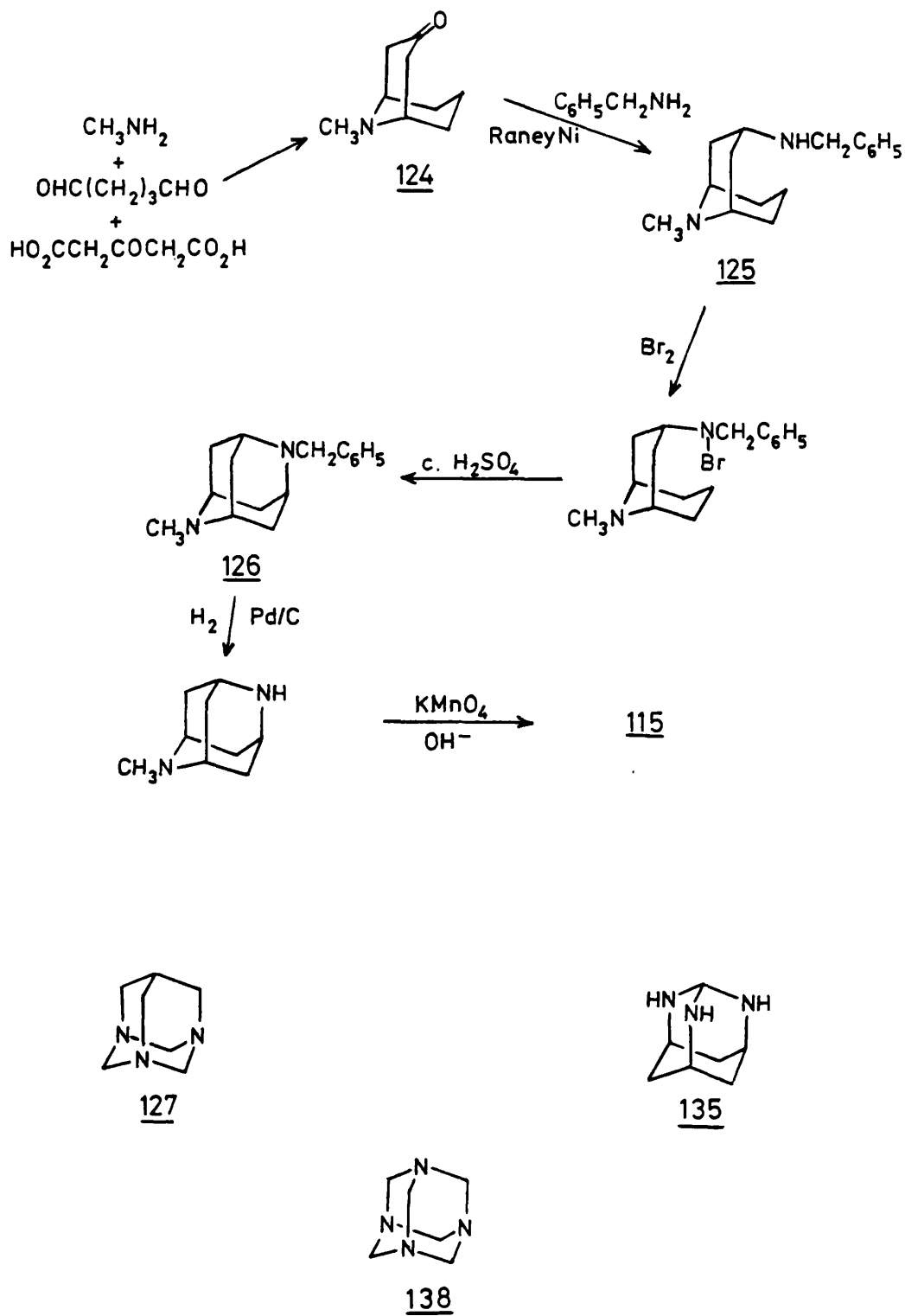
7-methyltriazaadamantane (128) has been prepared[102] by the route

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-nitro-

derivative (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-

triazaadamantane (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-tetraazaadamantane (138). Commonly known as hexamethylene-

tetramine 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 adamantanoid 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

$CH_3C(CH_2OH)_3$ $\xrightarrow{PBr_3}$ $CH_3C(CH_2Br)_3$ $\xrightarrow[\text{2. } H_3O^+]{\text{1. K(Phth)}}$ $CH_3C(CH_2NH_2)_3$

$\xrightarrow{CH_2O}$

Phth =

128

129 Py = 2-pyridyl

Scheme 46

$O_2NC(CH_2OH)_3$ $\xrightarrow[CH_2O]{NH_4OAc}$ **130** $\xleftarrow[CH_2O]{NH_4OAc}$ CH_3NO_2

130 $\xrightarrow{LiAlH_4}$ **131**

130 $\xrightarrow{Ac_2O}$ **132**

133 $\xleftarrow{Ac_2O}$ **131**

133 (NHCOCH$_3$ ... CH$_3$CON ... CH$_3$CON)

131 (NH$_2$)

132 (NO$_2$ ... CH$_3$CON ... CH$_3$CON)

$CH_3C(CH_2N=CH\text{-Py})_3$

134

Scheme 47

R = CH₂CH₂CH₃

Ts = CH₃—⟨benzene ring⟩—SO₂

H₂/Pd   Ac₂O
R₂O

H₂/Ni

HC(OC₂H₅)₃
H⁺

137

HC(OC₂H₅)₃
H⁺

136

HCl

TsCl
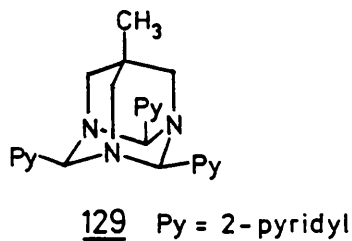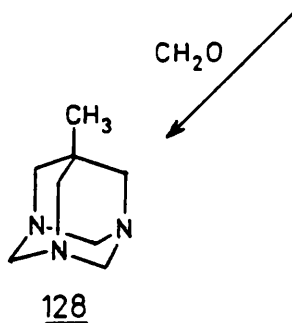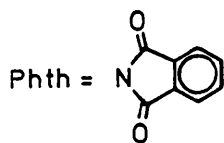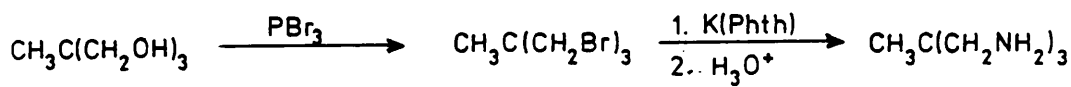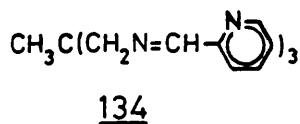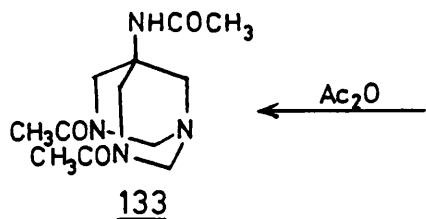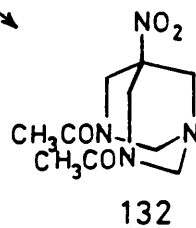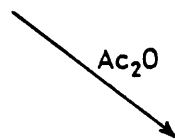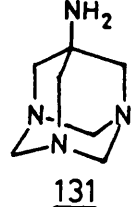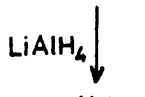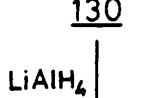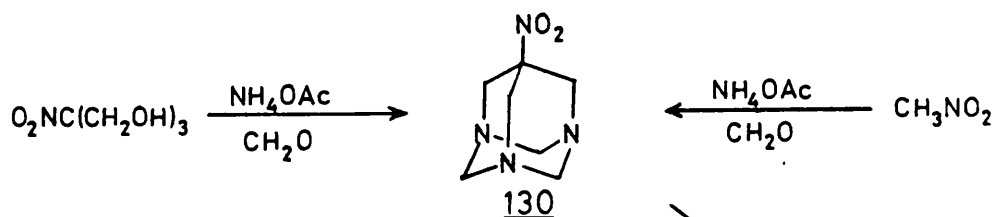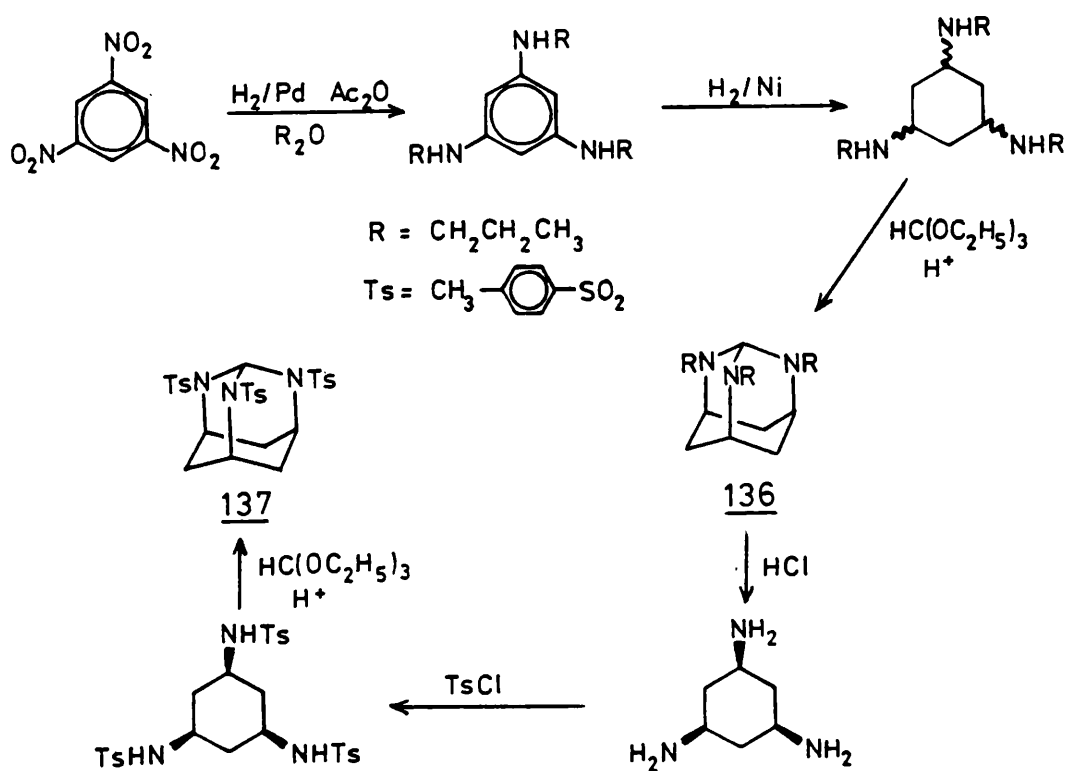
Part Two

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[108]. A class of
compounds which has been shown to have particular synthetic utility is
that of the β-ketosulphoxides, $RCOCH_2SOCH_3$, which may be readily
prepared[109] 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, α-keto
aldehydes, α-keto esters and glycols (Scheme 49) has been reviewed by
Russell and Ochrymowycz[110]. More complex β-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 β-keto
sulphoxides has been investigated by Ganter and Moser[111]. 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 (λ 2537Å) 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_α-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

$$CH_3SOCH_3 \xrightarrow{\text{KOBu}^t} {}^-CH_2SOCH_3 \xrightarrow{RCO_2R'} RCOCH_2SOCH_3$$
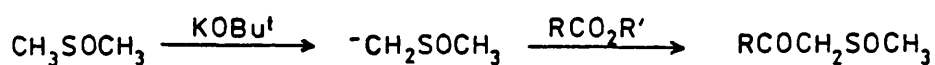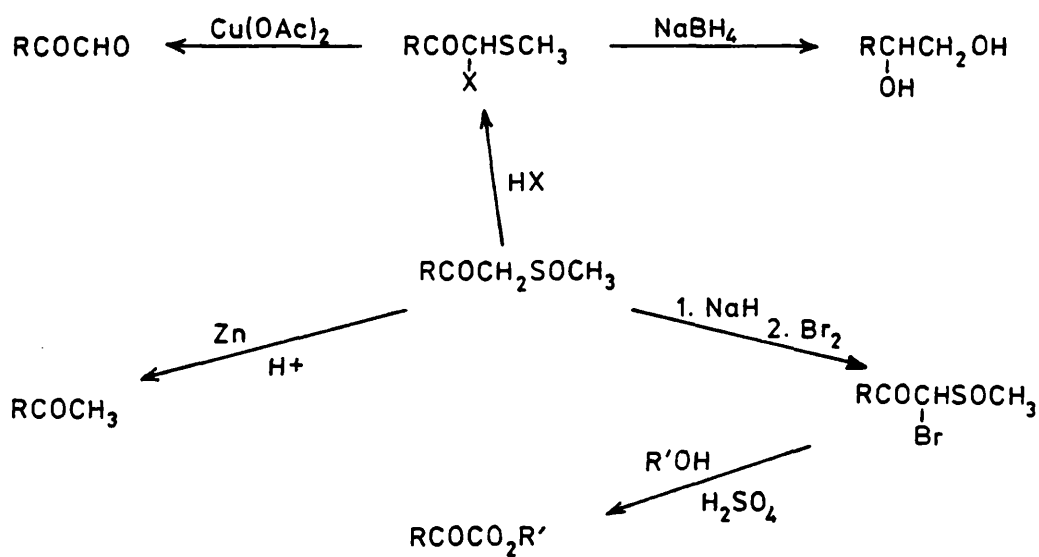
Scheme 49

Scheme 50
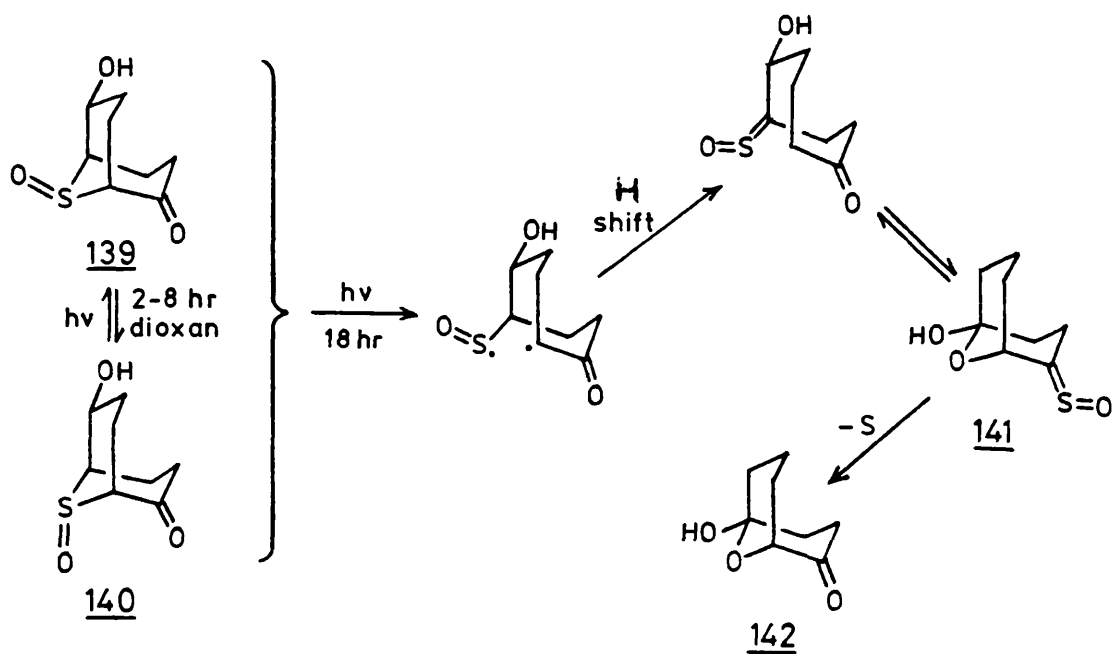
The same authors had previously studied[112] the photolytic rearrangement

of the related β-keto sulphides, (143 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 51

143 → (hν) → → (benzene) → **145**

→ (CH₃OH) → **146**

144 → (hν, CH₃OH) → **147**

Scheme 52

148 → (hν) → → (CH₃OH) → **149**

148 ⇌ → (hν) → → → **150**

Scheme 53

151   →   hν   →   152

Scheme 54

153   →   hν   →   154

155
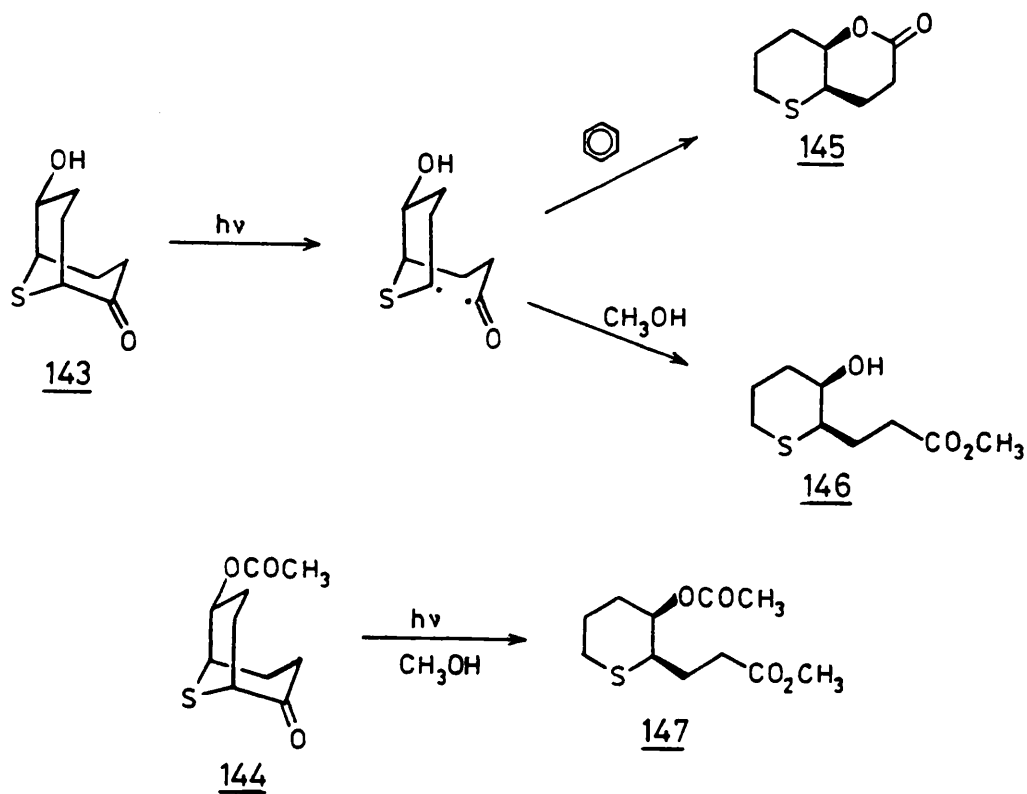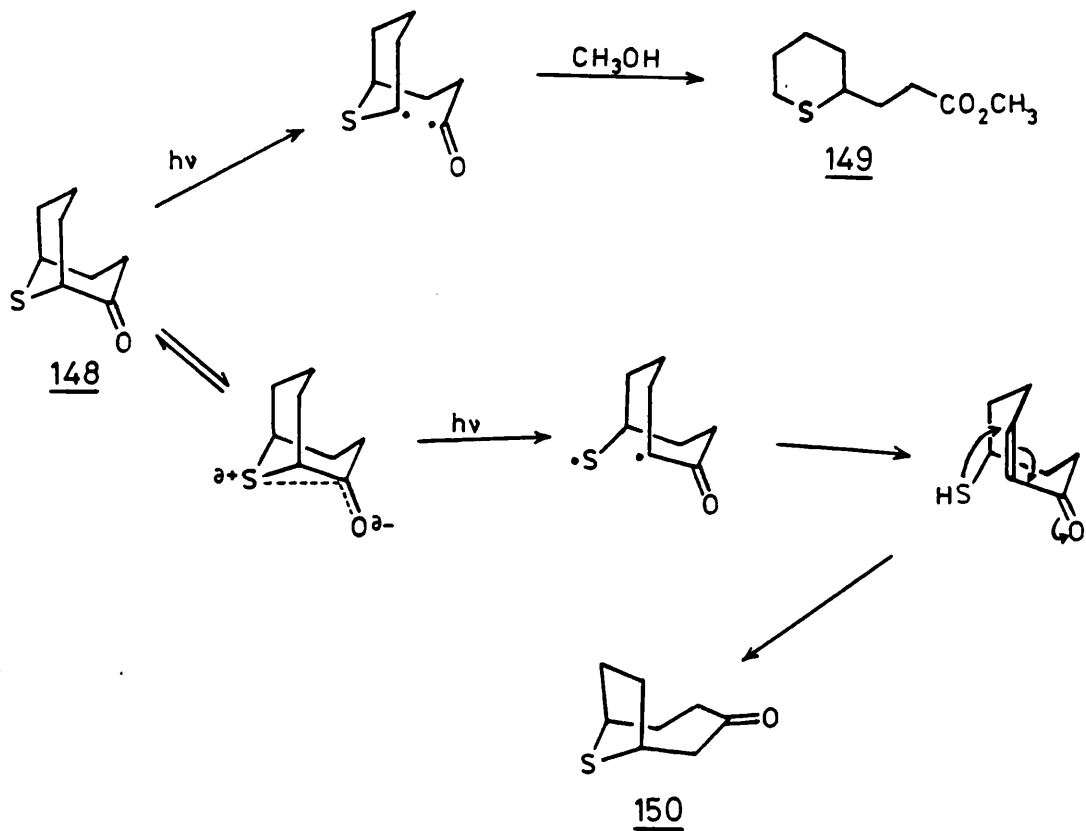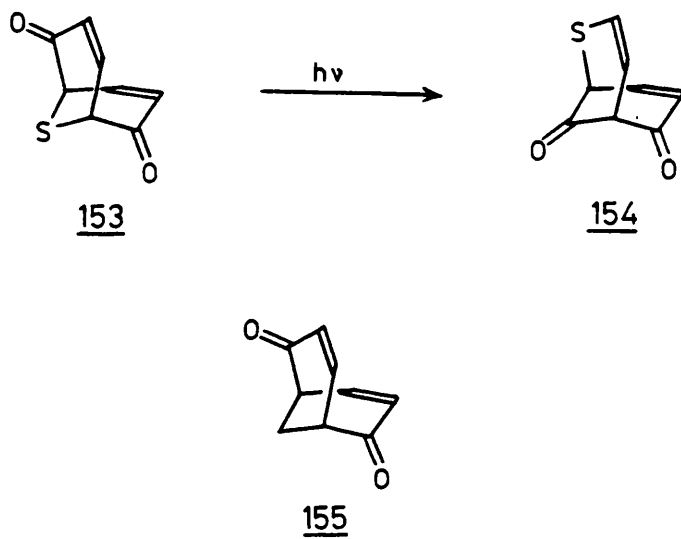
has been shown[115] to rearrange only by [1,5] and [1,2] sigmatropic

rearrangements, no such reactions have been observed during the

photolysis of 153, the formation of 154 being explained[114] 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 rearrange-

ment 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_2

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
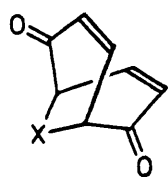
156 X = SO
157 X = SO₂

Scheme 55

156
or
157

hv
−SO or SO₂

158

159

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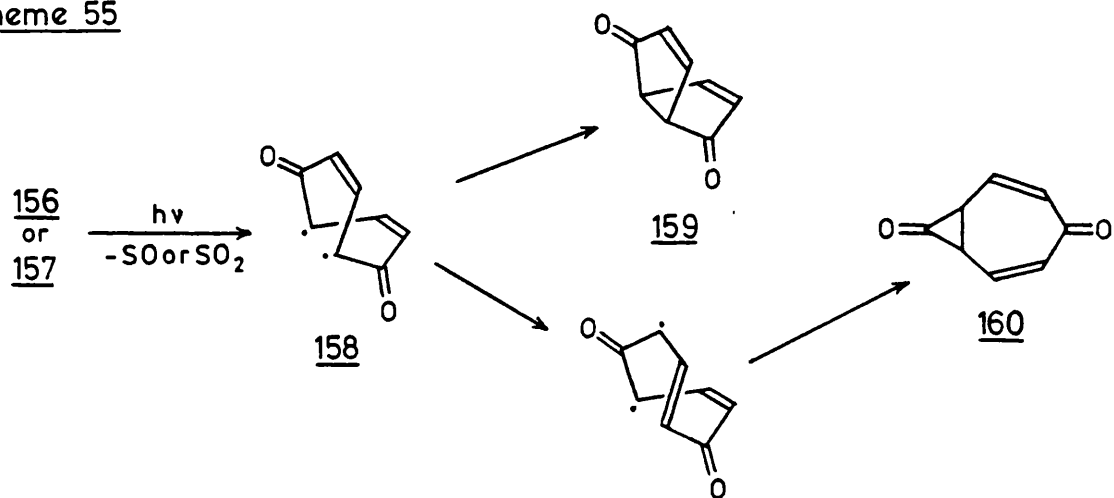
unsaturated bicyclooctandiones (159 and/or 160) (Scheme 55). In order to test these ideas 156 and 157, which had not previously appeared in the literature, had first to be synthesised.

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[116]. Of the two syntheses of 153 hitherto reported in the literature[114,117] (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)[118,119] 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[119]. 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.

Scheme 56
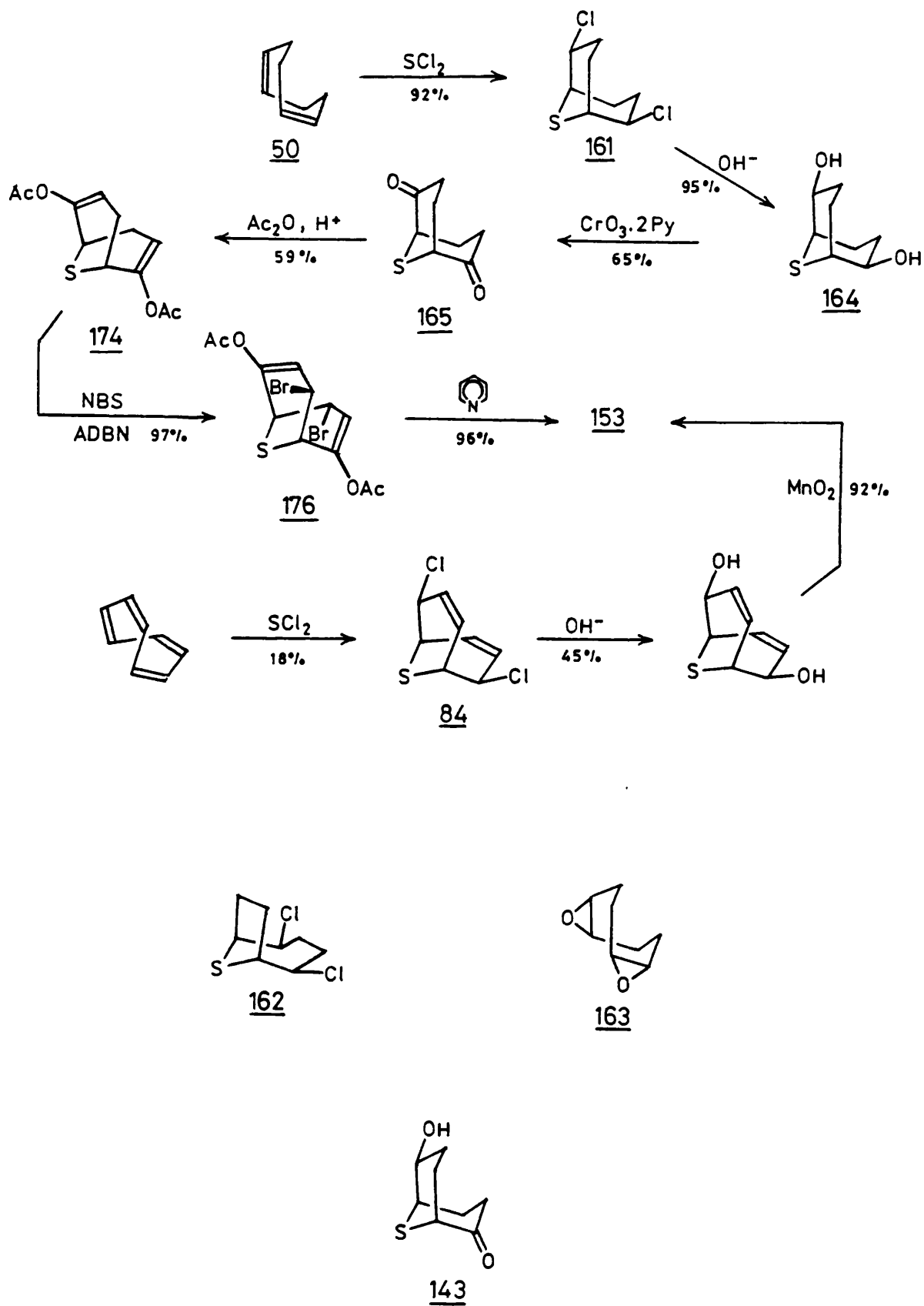
An interesting feature of this condensation reaction is that dichloride
(161) is produced completely unaccompanied by any isomeric 2,5-dichloro-
9-thiabicyclo[4.2.1]nonane (162), reflecting the greater thermodynamic
stability of the more symmetrical [3.3.1] framework. The high yield
and stereospecificity 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[120] a mixture of skeletal isomers).

Dichloride (161) was hydrolysed[119] 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[119] 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[117] by the use of chromium trioxide-
pyridine complex ($CrO_3.2C_5H_5N$) employing a modified Collins procedure[121].
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[117],
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[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)[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[112]. 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 O<u>H</u> doublet (J=4Hz) at ∂ 5.11 coupled to a complex <u>H</u>-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, $C_8H_{12}O_2S$, 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 <u>164</u> were attempted. The well known Jones oxidation procedure[122] 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[123] oxidation which has been developed by Albright and Goldman[124] 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 sulphoxide 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 $\delta 2.18$ and $\delta 4.70$ which integrated almost

exactly in the ratio of 3:2. In addition, multiplets at $\delta 2.80$ and

$\delta 4.17$ (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

CH$_3$SCH$_3$ ... $\xrightarrow{-\text{CH}_3\text{CO}_2^-}$ ... CH$_3$$\overset{+}{\text{S}}CH_3$ HOCHR^{1}R^2 $\xrightarrow{-\text{CH}_3\text{CO}_2\text{H}}$ CH$_3$$\overset{+}{\text{S}}CH_3$

CH$_3$C=O
  OCOCH$_3$

OCOCH$_3$

166

O=CR^{1}R^2
   H

167

$\xrightarrow{-\text{H}^+}$

CH$_3$SCH$_3$ + R^{1}R^{2}C=O

OR^1

OR^2

S
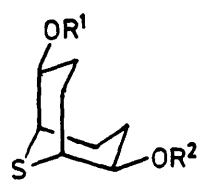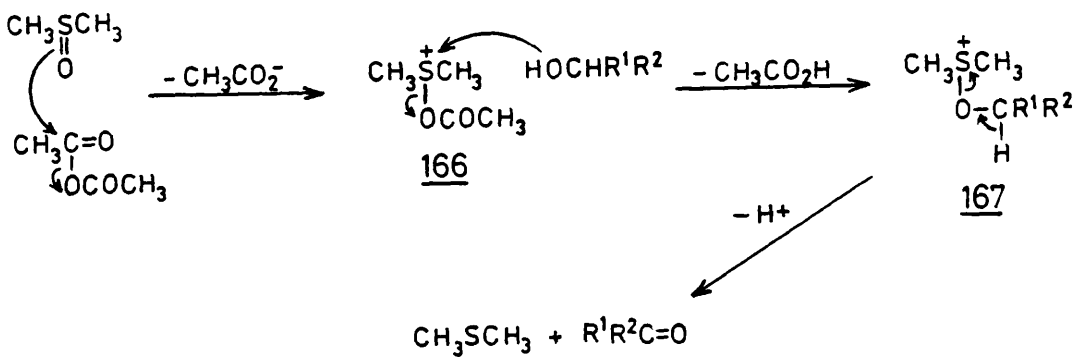
168 R^1 = R^2 = COCH$_3$
169 R^1 = R^2 = CH$_2$SCH$_3$
170 R^1 = COCH$_3$, R^2 = CH$_2$SCH$_3$

Scheme 58

H
CH$_3$$\overset{+}{\text{S}}$—CH$_2$ $\xrightarrow{-\text{CH}_3\text{CO}_2\text{H}}$ CH$_3$$\overset{+}{\text{S}}$=CH$_2$ HOCHR^{1}R^2
  OCOCH$_3$

166

171

$\xrightarrow{-\text{H}^+}$ R^{1}R^{2}HCOCH$_2$SCH$_3$
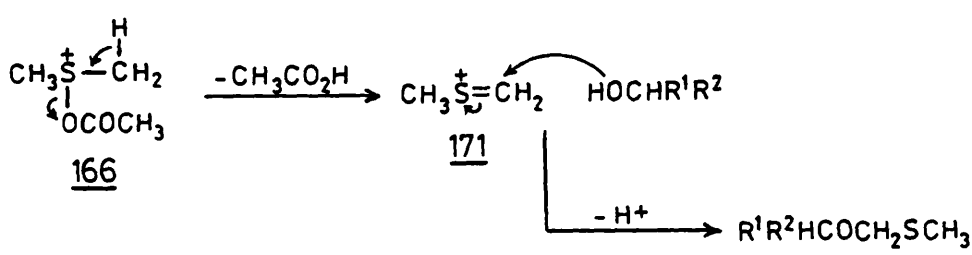
a low intensity peak at m/e 276 and established the identity of the

minor product as <u>170</u>. No peak at m/e 294, corresponding to <u>169</u>, was

observed.

The formation of Pummerer[125] type reaction products such as <u>170</u> during

dimethyl sulphoxide oxidations of alcohols is attributable to the

reaction of the substrate with <u>171</u> which is formed by elimination of

acetic acid from <u>167</u> (Scheme 58). It was not altogether clear why

even small amounts of oxidised product were not observed although it

has been claimed[124] that the reaction proceeds more efficiently with

sterically hindered alcohols, less hindered groups giving more of

the Pummerer product.

A second, alternative, oxidation procedure[126], which appeared to be

both powerful and selective utilised an acidic solution of chromium

trioxide in dimethyl formamide and several attempts to oxidise <u>164</u> were

made using this procedure. On a small scale, reaction of <u>164</u> with

6 molar equivalents of chromium trioxide - H_2SO_4 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 (<u>143</u>). 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 <u>143</u>.

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 <u>143</u>, no dione (<u>165</u>) being isolated.

A third approach was investigated and utilised the oxidative

cleavage of ethers by aqueous bromine. Deno and Potter[127] 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[119] in

quantitative yield by treatment of 161 with sodium methoxide in methanol

at 65°. Treatment of the distilled product (b.p. 157-165°, 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 = OCH$_3$
173 X = Br

$$\underset{\displaystyle 175}{(CH_3)_2 \overset{\displaystyle CN}{C} N = N \overset{\displaystyle CN}{C} (CH_3)_2}$$
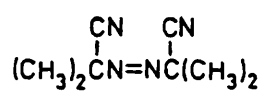
be highly resistant to bromine oxidation. It is of course possible

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[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)[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[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°, 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[129]. 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[130,131] to powerful proton acceptors such as sodium hydride[131,132]. Under the latter heading catalysts include toluene-p-sulphonic acid[133], boron trifluoride[134] and strong mineral acids[135].

Of the various procedures available, dione (165) was converted to its bisenol acetate (174) using a variation of the procedure adopted by Meerwein[136] who had prepared the analogous all-carbon bisenol acetate (177) from bicyclo[3.3.1]nonan-2,6-dione (79). 79 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 (177) contaminated with a little monoenol acetate (178), (Scheme 59), no C-acylated products being reported.

Acylation of 165 under these conditions was found[117] 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 (174). As with the preparation of 177 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, 174 was accompanied by considerable amounts of partially reacted material, resin and other unidentified by-products. In an attempt to reduce the

Scheme 59

79 $\xrightarrow[\substack{\text{c. } H_2SO_4 \\ \text{(1 drop in 30 ml Ac}_2\text{O)}}]{Ac_2O}$ 177 + 178

179
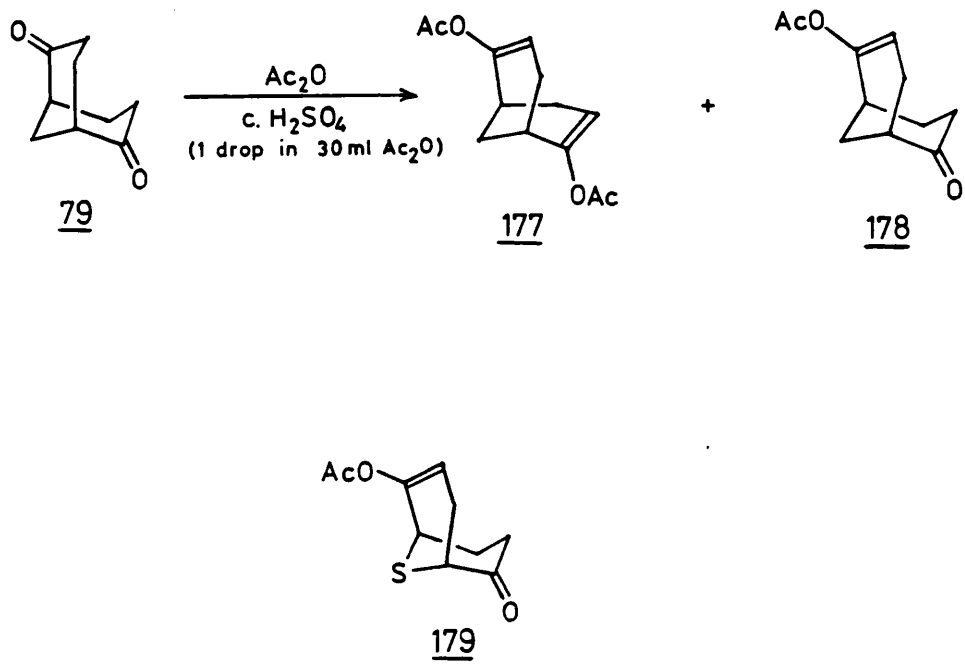
quantities of these undesirable by-products, especially the resinous

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 monoenol acetate (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[137] 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 H_2SO_4

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 $\partial 1.65$ and $\partial 2.00$, 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 suphuric 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 $\partial 4.95$ (vide infra).

Table 3   Products formed by the reaction of 165 with acetic anhydride–conc.
sulphuric acid mixtures. Yields refer to isolated material.

H_2SO_4 (drops per 30ml Ac_2O)	Reaction Time(h)	O–Acylated Products	C–Acylated Products
(3	6	174(56%), 179(18%)	180(7%))
12	6	174(13%)	180(32%), 182(8%)
18	6	174(3%)	180(30%), 182(16%)
24	6	—	182(26%)
30	6	—	182(10%)

Optimum isolable yields of the new product were obtained from the

acetylations containing 12 and 18 drops of sulphuric acid per 30 ml

Ac_2O. 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 $C_{12}H_{14}O_4S$.

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, $CH_2=C=O$, and acetic acid CH_3CO_2H,

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 (CCl_4) 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 n→π* carbonyl transition at 312 nm[138].

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 β- to a sulphur bridge and a methyl group which is geminal to an acetoxyl 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 β-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-acylation 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

165

180

Scheme 60

165 ⇌ H⁺ → $CH_3C=O$ ... $\overset{+}{O}H$ $=CCH_3$ ... Ac₂O / −AcOH → $COCH_3$ 181

H⁺ ⇌

180 ← Ac₂O / −AcOH ... CH_3 $C=O$ ... $CH_3C=O$ $\overset{+}{O}H$ CCH_3
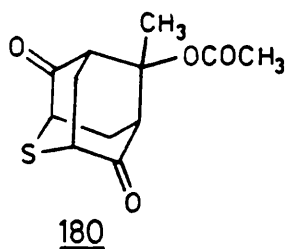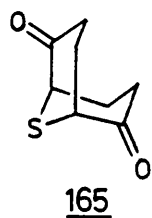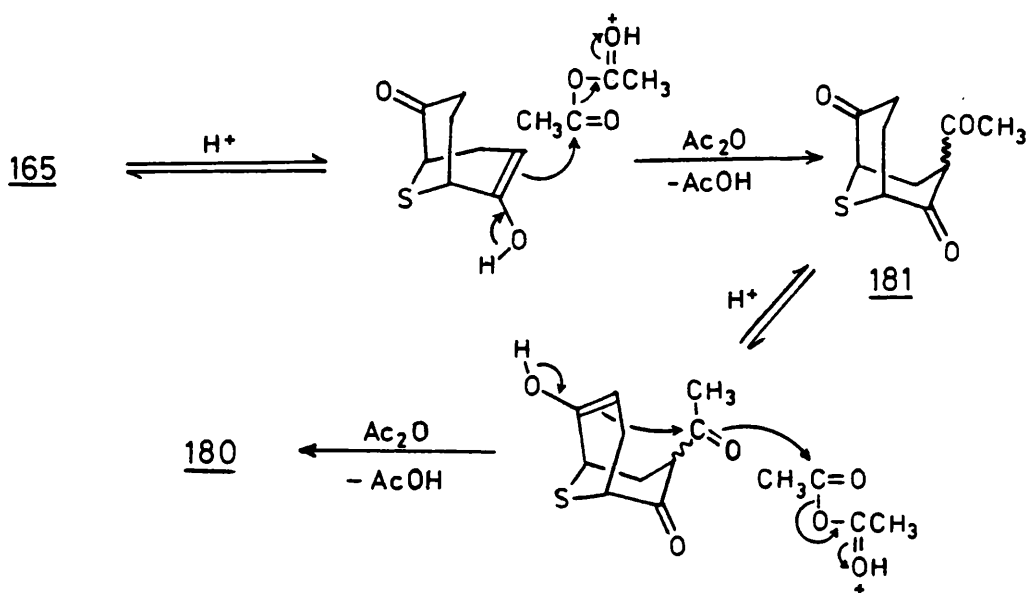
resonances in the product spectra) when highly acidic conditions were

employed. Indeed, compound B was found to be the only extractable

product when acid concentrations of greater than 24 drops per 30 ml

Ac_2O 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°. Microanalysis

of the compound was consistent with a molecular formula of

$C_{10}H_{10}O_2S$ 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 δ4.95.

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 C$_2$ 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[141] 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 $R^1 = R^2 = C(CH_3)_3$

184 $R^1 = C(CH_3)_3$, $R^2 = CF_2CF_2CF_3$
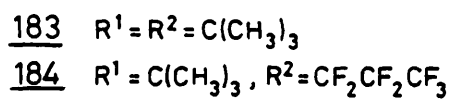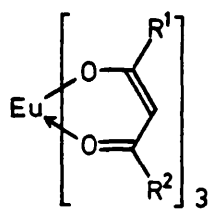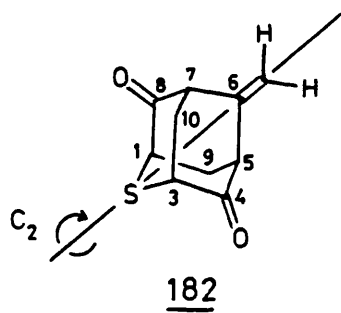
By virtue of their ability to expand their coordination shells by
acquiring ligands with lone pairs, the central metal atoms of these
complexes are able to form bonds to functional groups such as $-NH_2$,
$-OH$ and $\supset C=O$. In the p.m.r. spectrometer, ligand protons will
experience not only the external magnetic field, H^o, generated by the
instrument, but also a localised field, H^{Eu}, produced by the nearby
paramagnetic europium nucleus. Since the strength of H^{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 <u>182</u> 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 ∂ 5.23 which was least shifted (ca.
0.37 ∂ 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)<u>H</u> and C(5,7)<u>H</u>, 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).

$$R_{Eu} = \frac{\text{conc. of } Eu(fod)_3}{\text{conc. of } \underline{182}}$$
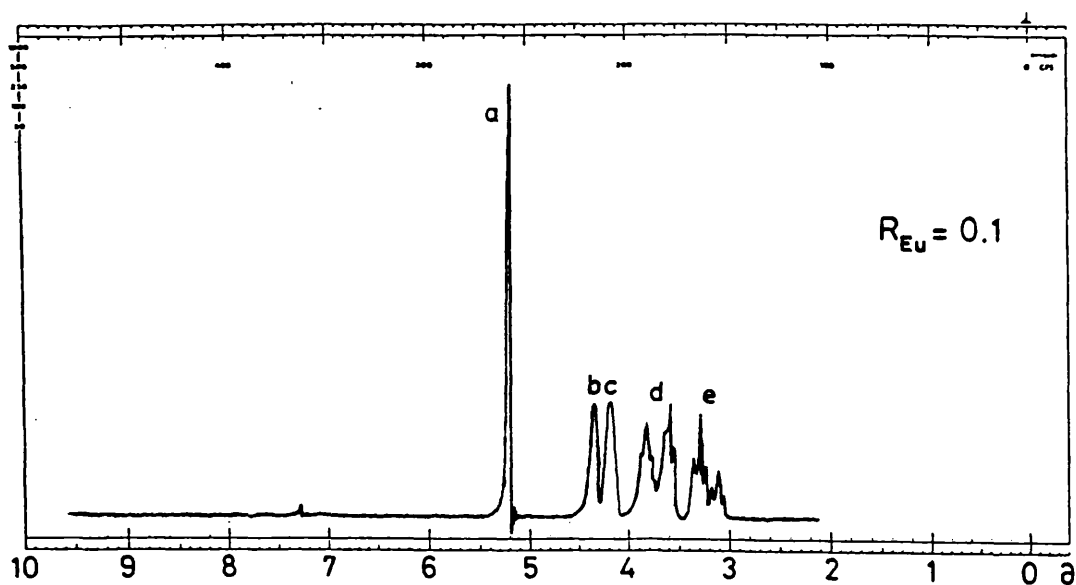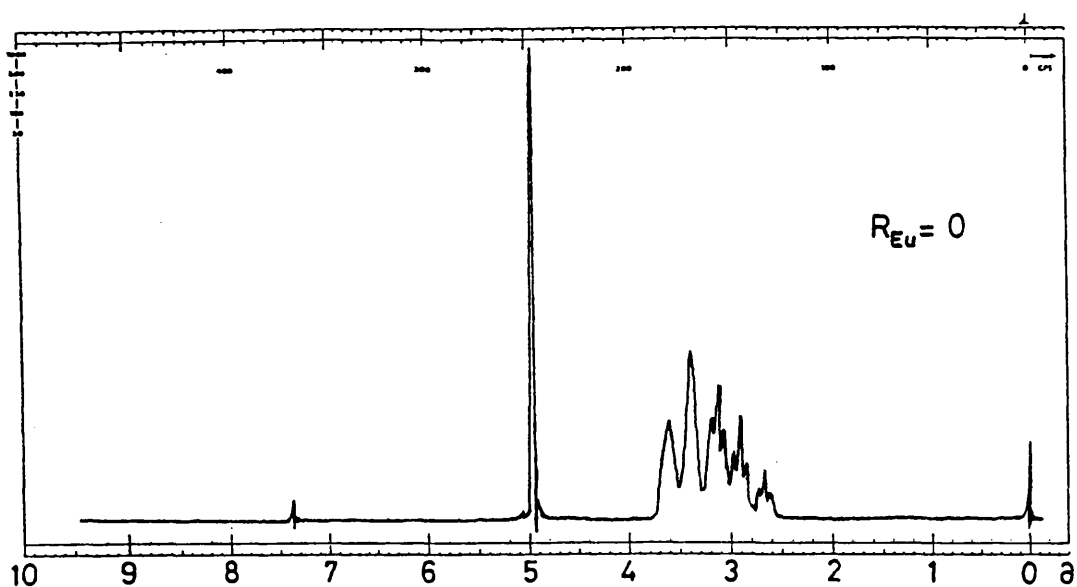
Figure 2 (Continued)
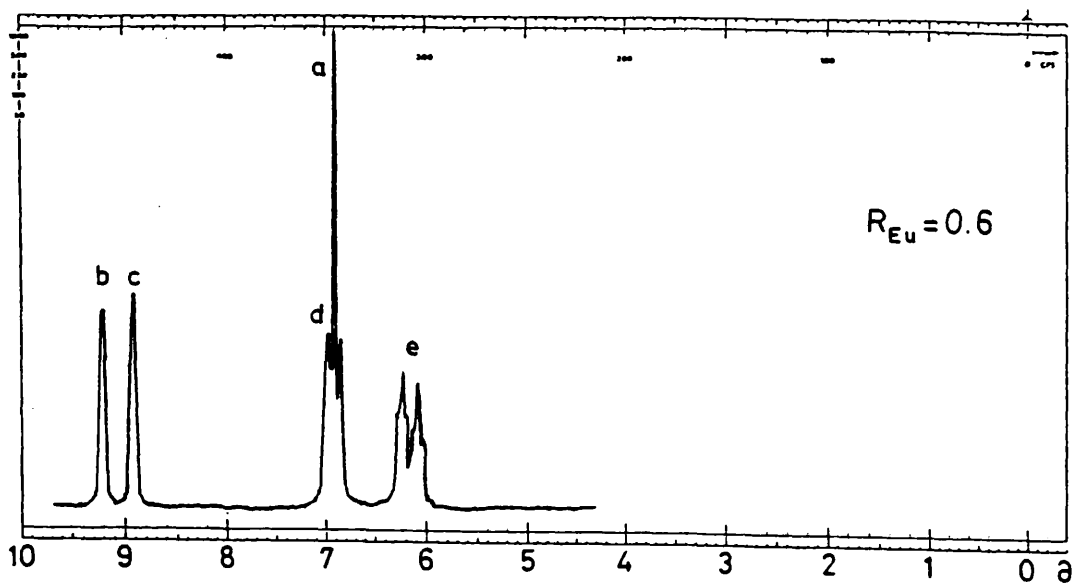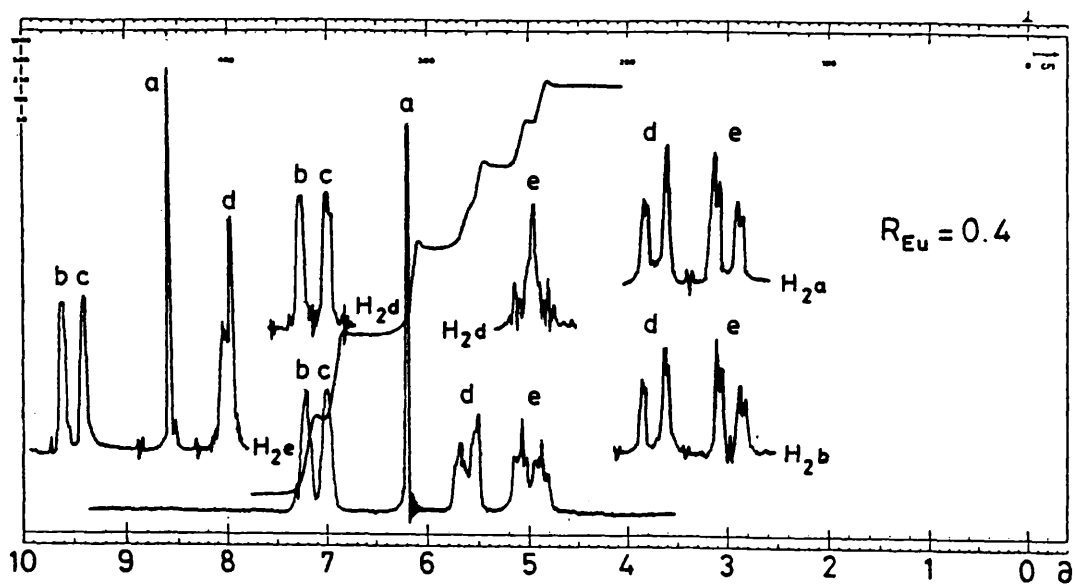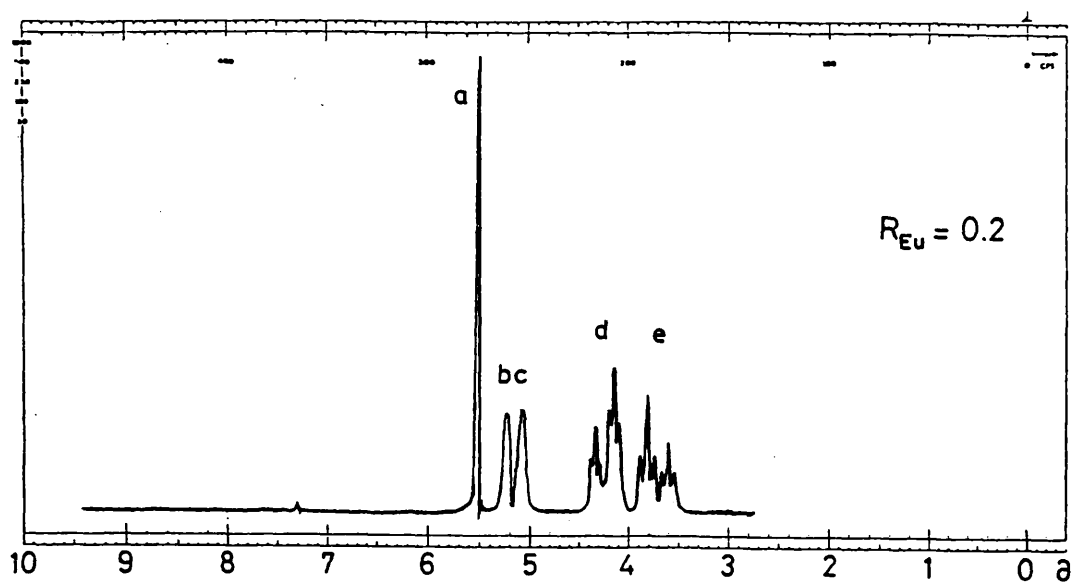
Table 4   Full assignment of the p.m.r. spectrum of 182 as derived from the Europium shifted spectra and decoupling experiments shown in Figure 2
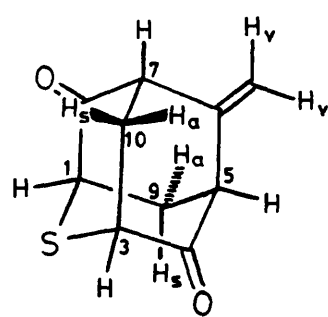
Signal	Chemical Shift a	Multiplicity	Assignment	Coupling
a	4.95	s	$\underline{H}_v$	—
b	3.50	m	$C(1,3)\underline{H}$	$J_{1,9s}(J_{3,10s}) = 2.5\,Hz$ $J_{1,9a}(J_{3,10a}) = 4.0\,Hz$
c	3.34	m	$C(5,7)\underline{H}$	$J_{5,9s}(J_{7,10s}) = 2.5\,Hz$ $J_{5,9a}(J_{7,10a}) = 4.0\,Hz$
d	3.16	dt	$C(9,10)\underline{H}_s$	$J_{9s,1}(J_{10s,3}) = 2.5\,Hz$ $J_{9s,5}(J_{10s,7}) = 2.5\,Hz$ $J_{gem} = 13\,Hz$
e	2.78	dt	$C(9,10)\underline{H}_a$	$J_{9a,1}(J_{10a,3}) = 4.0\,Hz$ $J_{9a,5}(J_{10a,7}) = 4.0\,Hz$ $J_{gem} = 13\,Hz$

pair of almost identical multiplets showing complex splitting, had

each been strongly pulled downfield by ca 0.9 ∂ 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 syn-(H_s) and those anti-(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°, while that between C(1)-H and C(9)-H_s is

simultaneously opened out to 65° (Figure 3).

An empirical relationship between vicinal coupling constants (J_{vic})

and dihedral angles (θ) has been developed by Karplus[144] and is

shown graphically in Figure 4. It may be seen that for $\theta < 90°$,

Figure 3

Comparison of the dihedral angles between the bridgehead and neighbouring methylene protons of (a) adamantane(<u>1</u>) and (b) alkene(<u>182</u>)

(a)   (b)
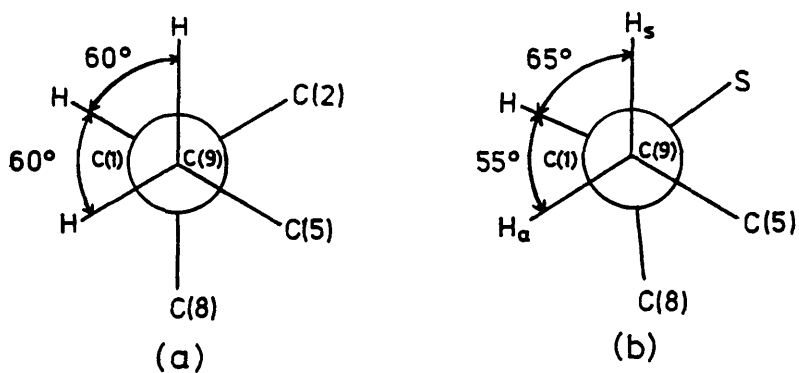
Figure 4

Variation of the vicinal coupling constant J_{vic} with the dihedral angle θ
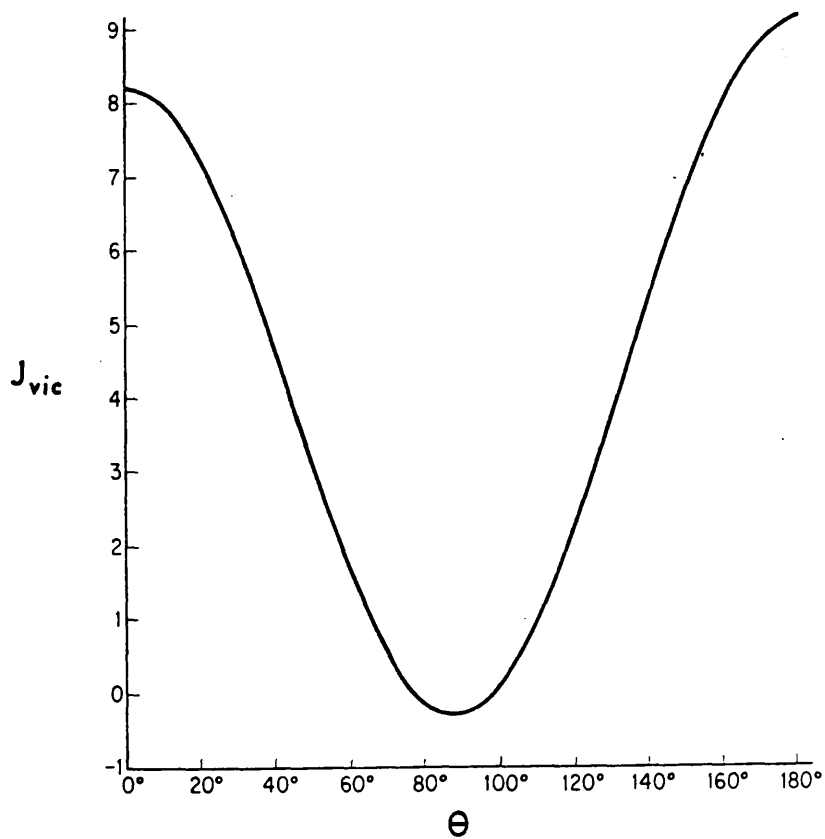
J_{vic} increases as θ decreases. Using this relationship, the
farther upfield of the two methylene resonances of 182, displaying
a minor splitting of 4Hz was assigned to $C(9,10)\underline{H}_a$ while the
remaining signal, exhibiting a minor splitting of only 2.5 Hz
was assigned to $C(9,10)\underline{H}_s$.

At a $Eu(fod)_3$ / alkene ratio of 0.6, the accidental equivalence
of signals arising from the exomethylene protons and $C(9,10)\underline{H}_s$
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 δ 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 $C_{10}H_{12}O_3S$ 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 β-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 hydrolyses 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 $\xrightarrow{\text{aq. NaOH} \atop \text{or KOH, CH}_3\text{OH}}$ ... **185** $\underset{\text{H}^+}{\overset{\text{OH}^-}{\rightleftharpoons}}$ **185a** $\xrightarrow{\text{KOH} \atop \text{CH}_3\text{OH}}$ ...

165 $\xleftarrow{\text{H}^+}$ ... $\xleftarrow[-\text{CH}_3\text{CO}_2\text{H}]{\text{OH}^-}$ **181**
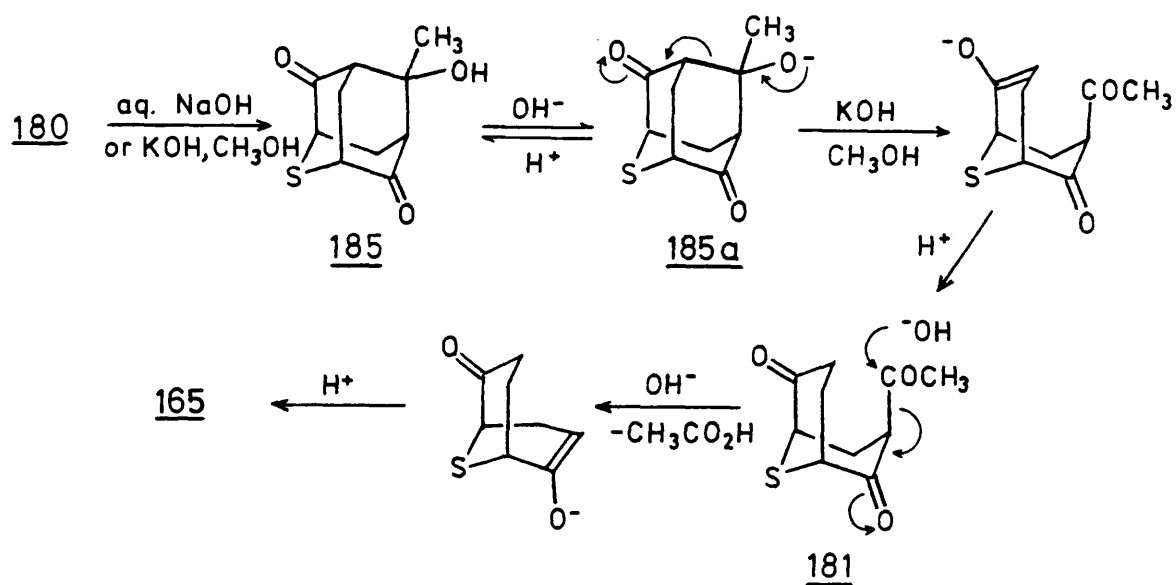
Table 5   Treatment of **180** with conc. H_2SO_4

Solvent	Reaction time (hours)	Product ratio 180:182
Ac_2O	4	1 : 4
$(CH_2OCH_3)_2$	2	9 : 1
1,4-Dioxan	4	4 : 1

Scheme 62

180 $\xrightarrow{\text{H}^+}$ ... $\xrightarrow{-\text{AcOH}}$ **186**

$\xrightarrow[\text{cis- elimin}^n]{-\text{AcOH}}$ $\overset{\Delta}{\times}$ ... $\xrightarrow{-\text{H}^+}$ **182**
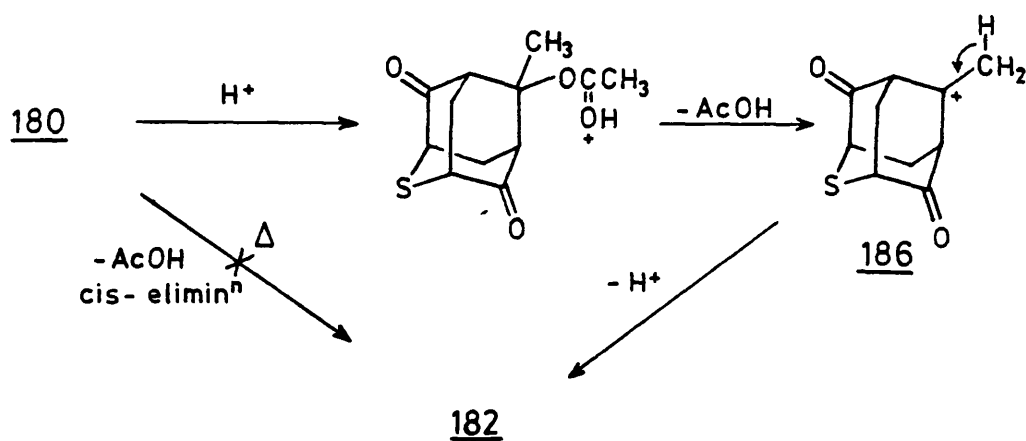
functionality at C(6).

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[142,145].

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)[142,145] but was unchanged after pyrolysis at 150-220°.

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[146], via the tertiary

carbonium ion (186)) rather than a pyrolytic cis-elimination which

was originally postulated[147].

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 (79, 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 bourne 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 Honig[47].

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

refluxing[17] 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}.

79   X = CH₂

187   X = O

188   X = NR
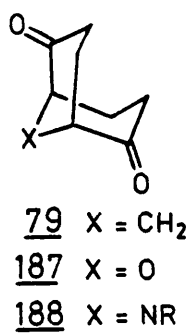
Scheme 63
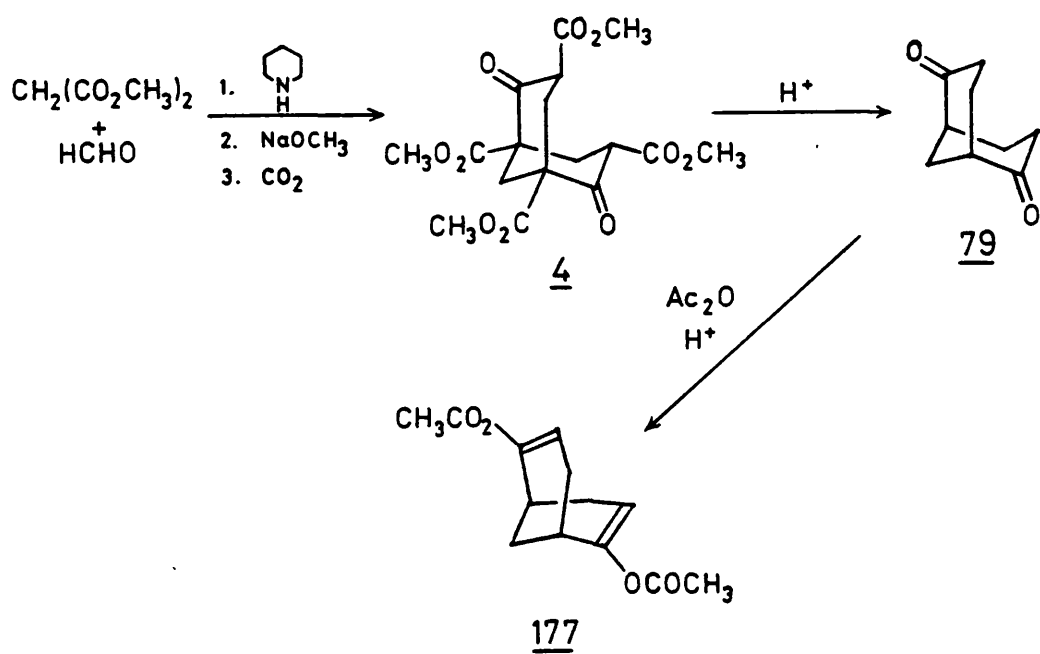
79 was refluxed in the usual manner with a mixture of acetic
anhydride and conc. sulphuric acid and furnished a tarry product,
the ether extract of which was separated into three components
by preparative t.l.c..

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 ∂2.12 confirmed
the presence of two acetoxyl groups while a deshielded two-proton
multiplet at ∂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 ∂1.92 (2H) and ∂2.28 (4H)
were attributed respectively to C(9)H_2 and C(4,8)H_2 while the
bridgehead protons, C(1,5)H, appeared as a multiplet at ∂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 ∂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 ∂ 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 ∂ 2.93 (2H) and ∂ 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[148] who had previously synthesised 189 in several stages from 79 (Scheme 64) and gave the melting point of the former as 163-164° in good agreement with the present value.

From the lowest band, a third crystalline product was isolated as colourless needles, m.p. 124-126°. 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

189

Scheme 64

79 → (C$_4$H$_8$NH) → 7 → (Br$_2$CHCO$_2$CH$_3$) → CO$_2$CH$_3$

H$^+$ | HC(OC$_2$H$_5$)$_3$

C$_2$H$_5$O, OC$_2$H$_5$, CO$_2$CH$_3$, OC$_2$H$_5$, OC$_2$H$_5$

1. LiAlH$_4$
2. H$^+$

CH$_2$OH

LiBr
120°

CH$_2$Br → C$_2$H$_5$N(C$_6$H$_{11}$)$_2$ → 189
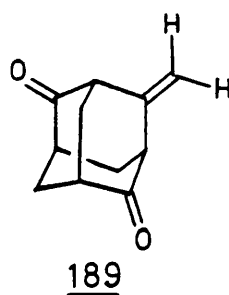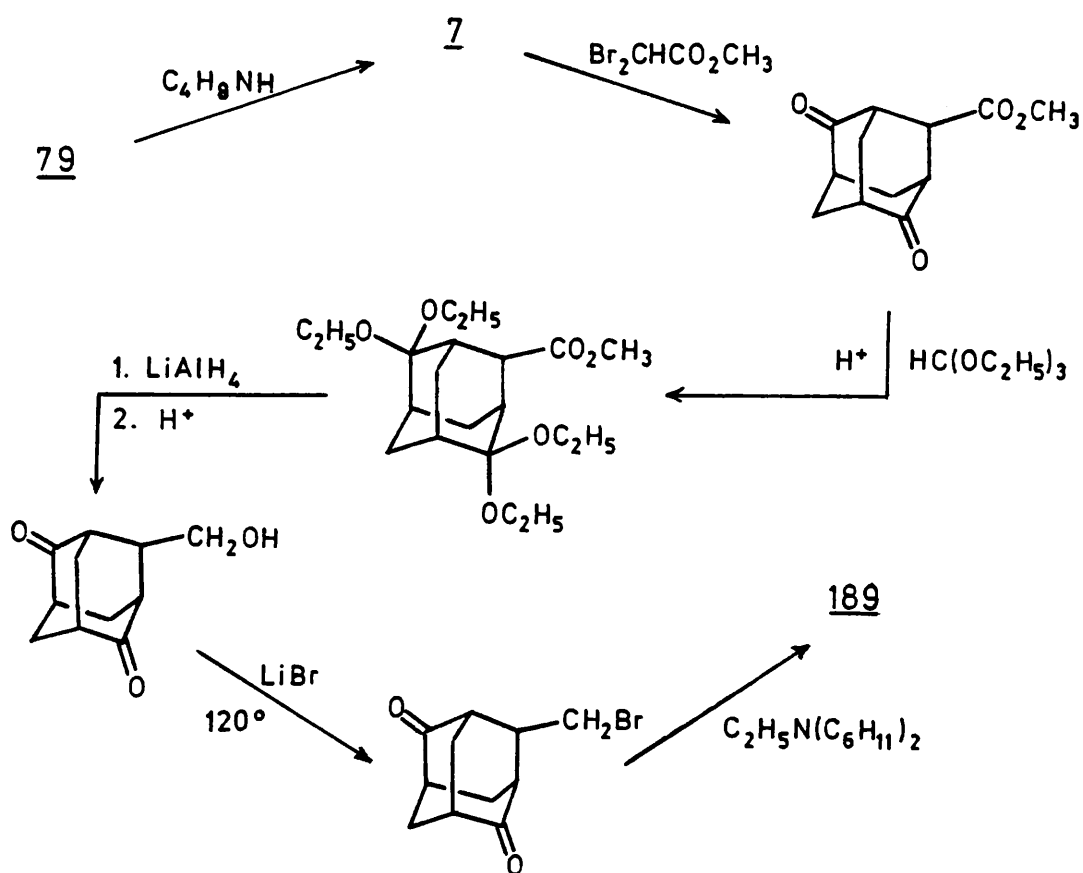
acetic acid, similar to that found in the spectrum of 180. The

infrared spectrum (CCl_4) 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 ∂ 1.62 and 2.04 in the p.m.r.

spectrum revealed the presence of a tertiary methyl group and an

acetoxyl 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 ∂ 1.80 and 2.60

which integrated for six protons, and a pair of two-proton methine

multiplets at ∂ 2.70 and 3.25.   From the spectroscopic evidence

it was clear that the product, obtained in 20% yield, was

4-acetoxy-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

190 R = H
191 R = CO₂CH₃

CH₃CO₂
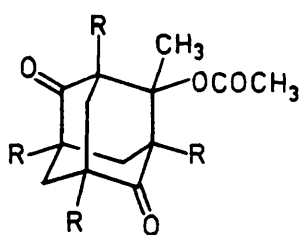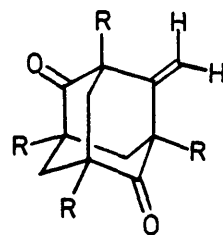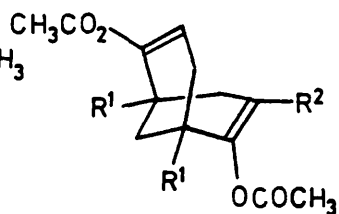
193 R¹ = CO₂CH₃, R² = H
194 R¹ = R² = CO₂CH₃

192 R = CO₂CH₃

Figure 5

The 100 MHz p.m.r. spectra of (a) 193 and (b) 194
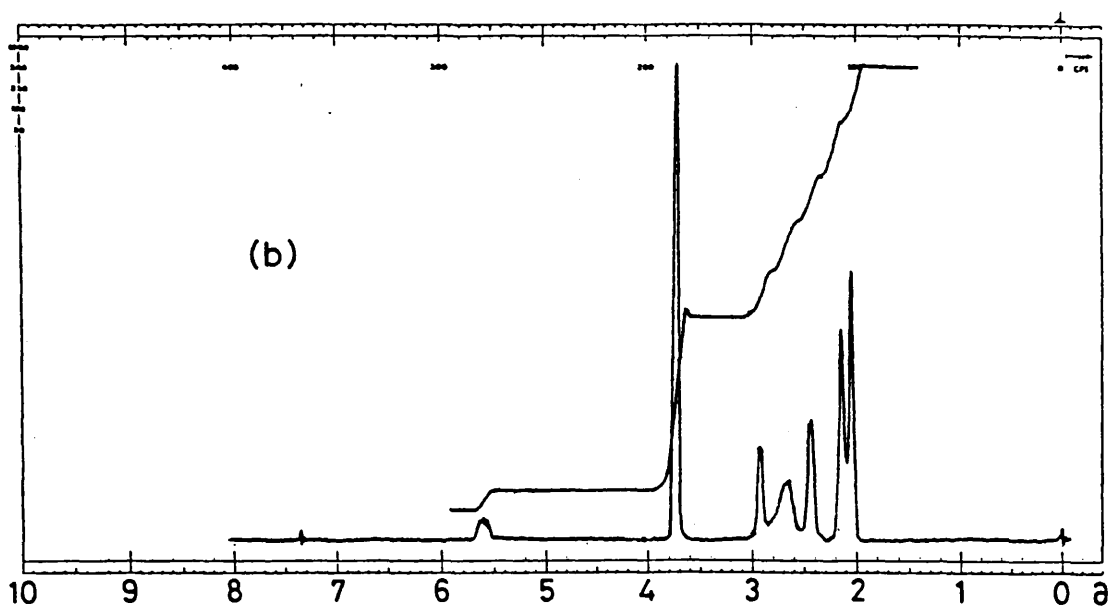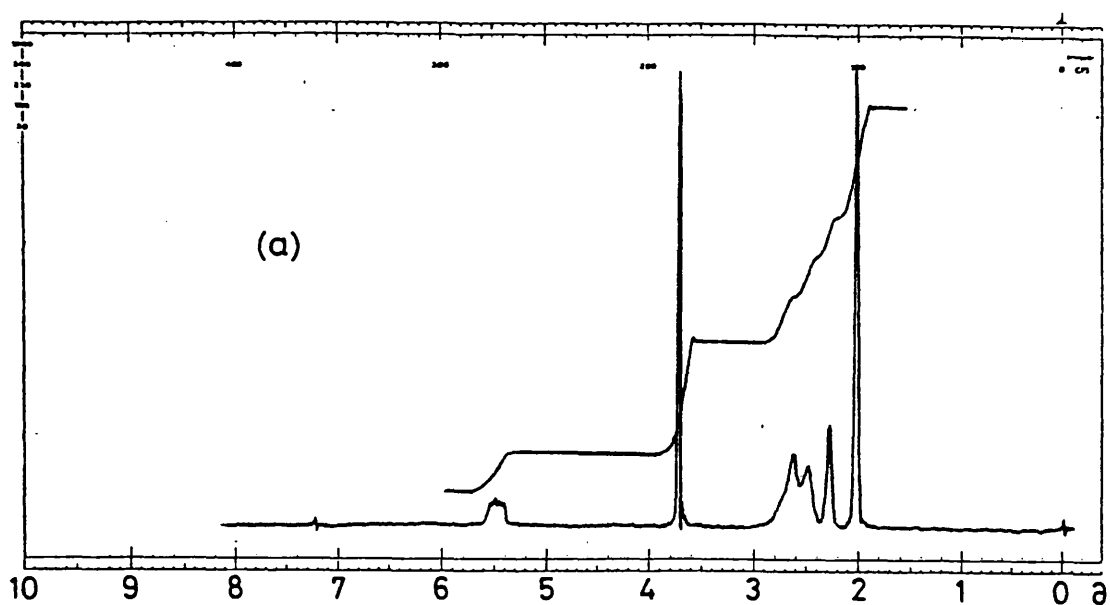
at ∂ 2.09 and 3.70. The former was diagnostic of two magnetically equivalent acetoxyl groups while the latter manifested the retention of two identical methyl ester functions from 4. A broad multiplet at ∂ 2.62 (4H) was assigned as two methylene groups while a neighbouring two-proton singlet at ∂ 2.36 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 ∂ 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 ∂ 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 CH_2 resonances were present in the ∂ 2.0 to 3.0 region. Slightly broadened singlets at ∂ 2.92 and 2.41 were assigned as two uncoupled methylene groups while a third signal at ∂ 2.67 showed a complex splitting pattern and was necessarily coupled to a one-proton vinyl multiplet at ∂ 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)[149] was synthesised in two
stages from 50 (Scheme 65) as a 2:1 mixture with 9-oxabicyclo-
[4.2.1]nonan-2,5-dione (195). Following the procedure of Zefirov[54,]
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 synthesis[54] 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
eg acid hydrolysis of 163[120] and oxymercuration of 50[53].

Separation of the skeletal isomers was not attempted at this stage.
Instead, a portion of the mixture was oxidised, as described by
Ganter[149] 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**

$\xrightarrow[\text{H}^+]{\text{CrO}_4^{2-}}$

187 (31%) + **195** (16%)
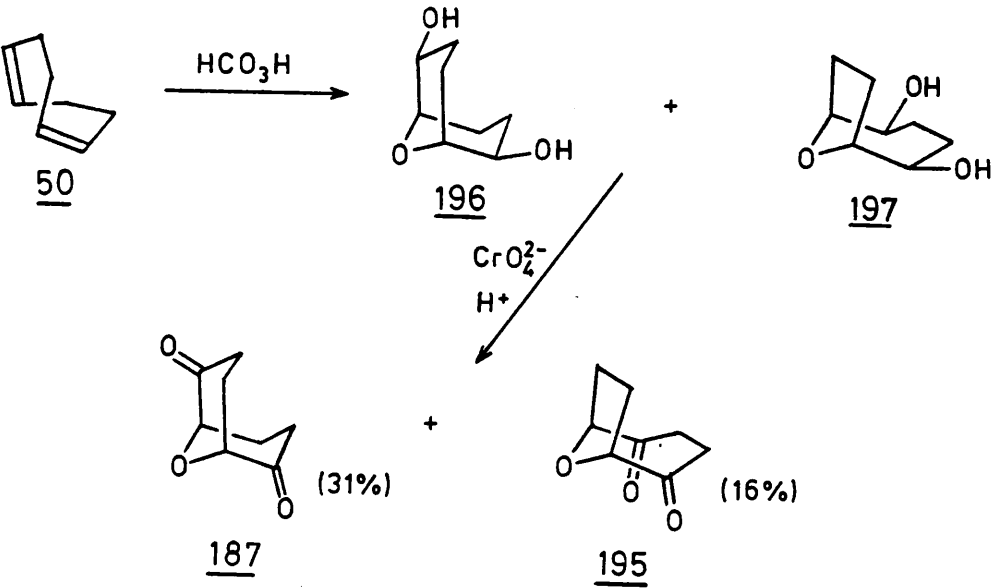
presence of only one compound. Moreover, the infrared spectrum

of the oil envinced 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 ∂ 4.44 (lit.[149] ∂ 4.40), the spectrum exhibited a second

bridgehead multiplet of lower intensity at ∂ 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 acetoxyl resonance at ∂ 2.11, a

methylene envelope (4H) at ∂ 2.51 and a vinyl multiplet (2H) at

∂ 5.52. The spectrum differed notably however in the position

of the bridgehead proton signal, which at ∂ 4.39 was consistent

with a 9-oxabicyclo[3.3.1]nonane skeleton[149].

The infrared spectrum (CCl_4) of the product exhibited a strong

ester carbonyl band at 1765 cm^{-1} (ε^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

$C_{12}H_{14}O_5$, 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, CH_2=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 acetoxyl 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[149]

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

198

199

Scheme 66

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

thin layer chromatography

$$\xrightarrow[\text{H}_2\text{O}]{\text{H}^+} 187$$

198

199

+ other products

Scheme 67

$$50 \quad \xrightarrow{\text{peracid}} \quad \underset{163}{\text{(structure)}} \quad \xrightarrow[\text{H}_2\text{O}]{\text{H}^+} \quad 196 \quad + \quad 197$$

AcCl

200

+

201

187

$$\xrightarrow[\text{H}^+]{\text{CrO}_4^{2-}}$$

196

$$\xleftarrow[\text{H}_2\text{O}]{\text{H}^+}$$

200

fractional crystal$^{\text{n}}$

201
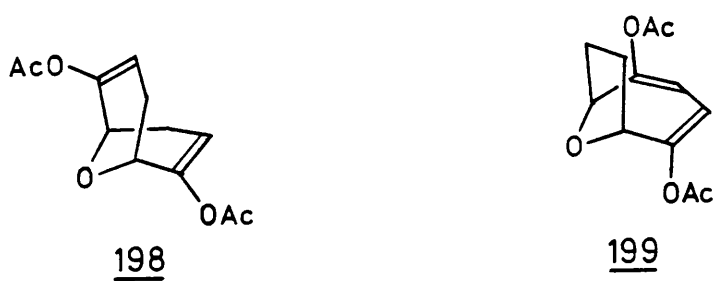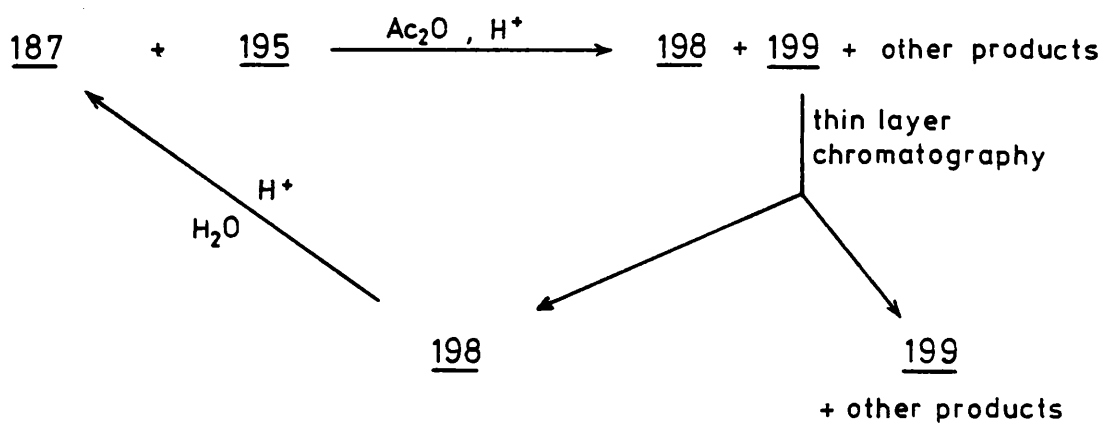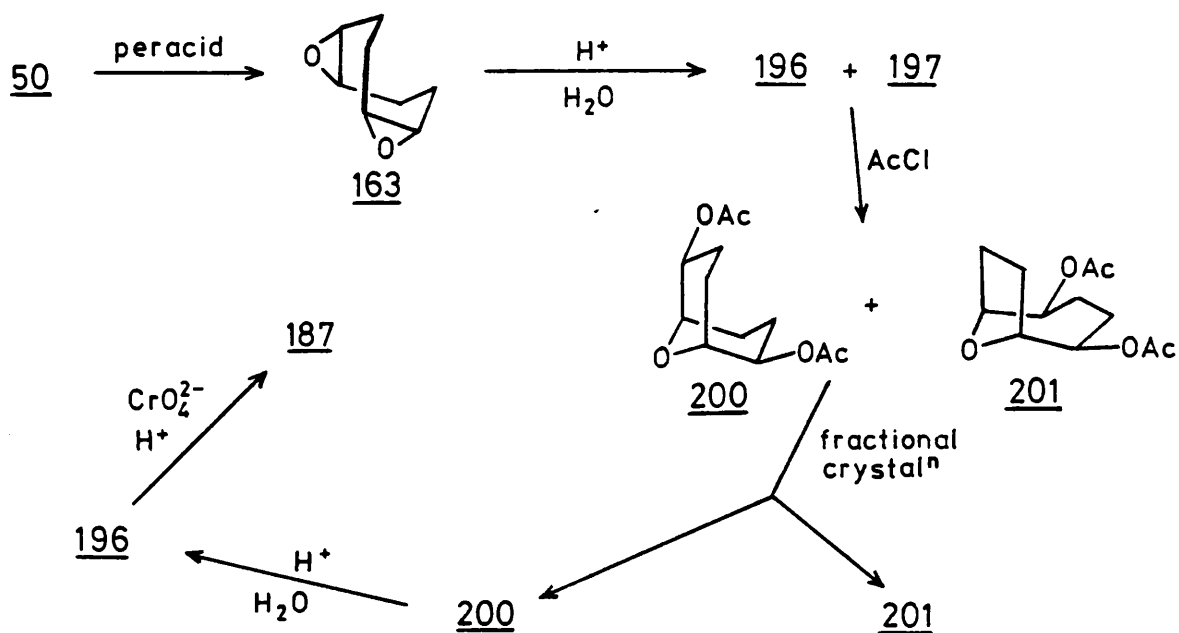
by its p.m.r. spectrum which, in contrast to that of the mixture, possessed only one bridgehead proton signal at ∂ 4.44.

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[149] in 1972. The method used by the Swiss group (Scheme 67) involved the acid hydrolysis[120] 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), R_f 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 ∂ 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[150], each signal integrating

for two protons. The farthest downfield multiplet of the spectrum,

at ∂ 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 ∂ 2.35,

which disappeared on addition of D_2O was assigned to weakly-bonded

enolic hydrogens. This compound was thus 3,7-diacetyl-9-oxabicyclo-

[3.3.1]nonan-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 acetoxyl 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

202 ⇌ 202a
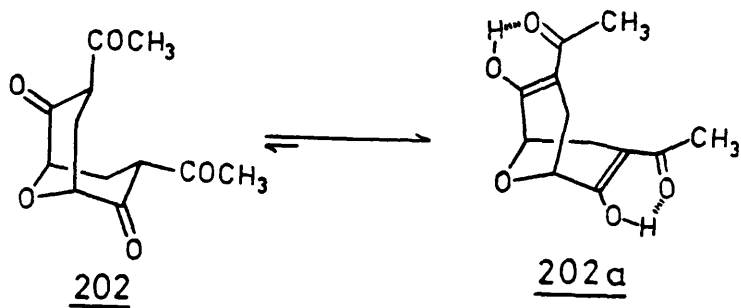
Figure 6

The 60 MHz p.m.r. spectrum of 202

203   204
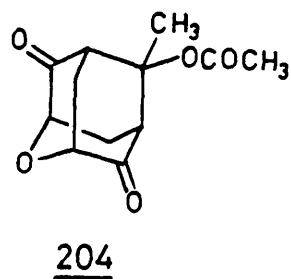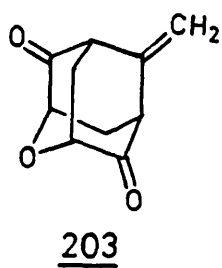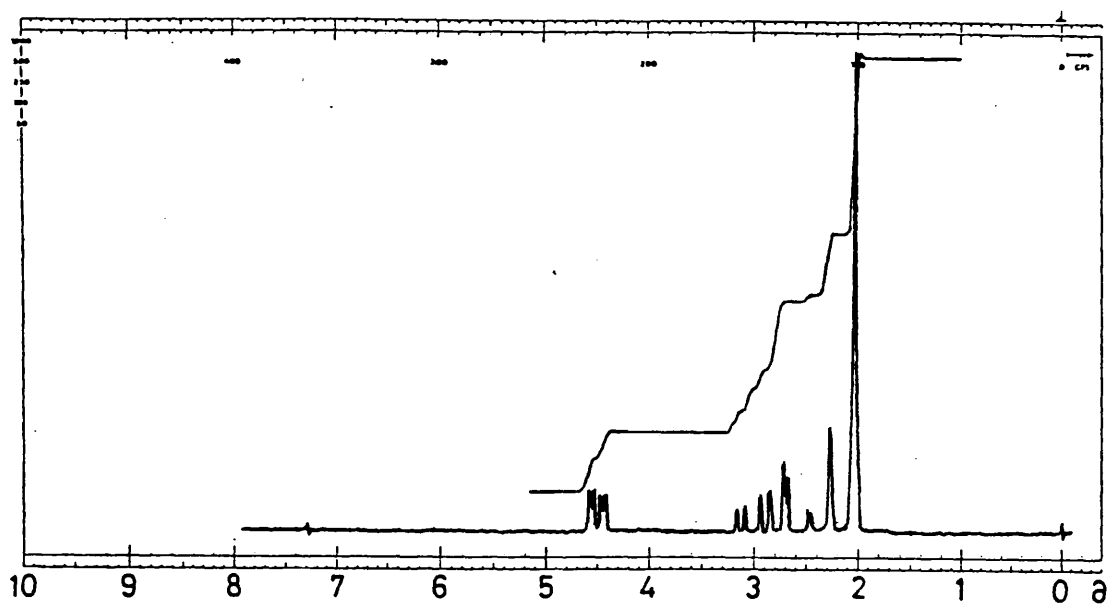
one would have expected. Moreover, the spectrum of Band 3 also
contained a pair of relatively low intensity singlets at ∂ 1.60
and 2.02 which could possibly be the non-equivalent methyl
resonances of tricyclic acetate (204) (Cf 180 and 190).

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[122,149] (Scheme 68).

Cycloocta-1,5-diene (50) was converted to 163 by treatment with m-chloroperbenzoic acid[151]. 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.[120] m.p. 25-27°) and by p.m.r. spectrum which possessed two multiplets at ∂ 1.93 (8H, CH_2) and ∂ 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 ∂ 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-O 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 ∂ 2.90 region of the p.m.r. spectrum (Cf. 163). The hydroxyl function gave a one-proton deuterium-exchangable signal at ∂ 2.34 while four protons bonded to carbon-bearing-oxygen

appeared as multiplets at ∂ 3.94 (2H), 4.52 (1H) and 5.32 (1H).
Four methylene groups gave rise to a broad envelope (8H) centred
at ∂ 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
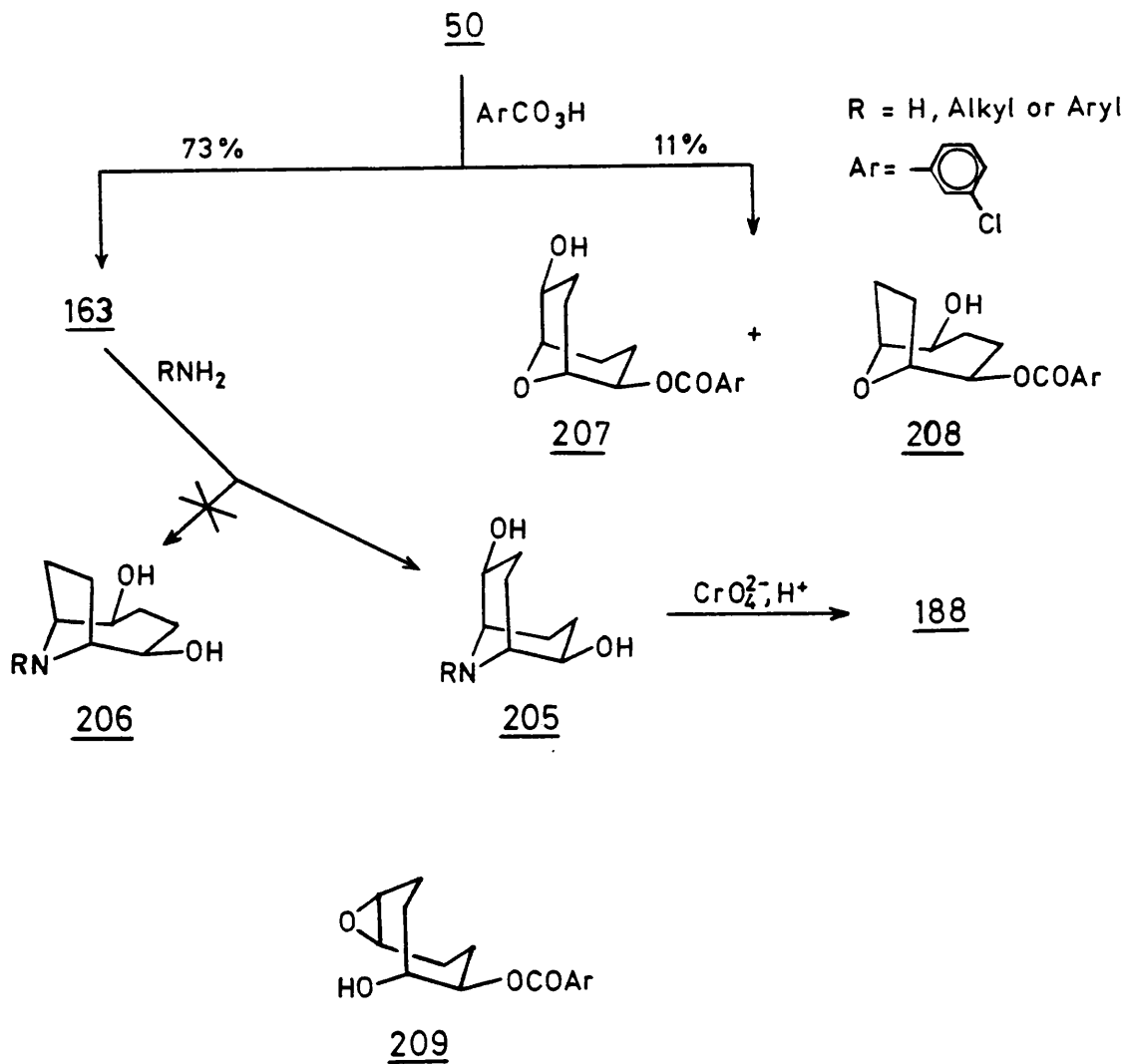
Scheme 69
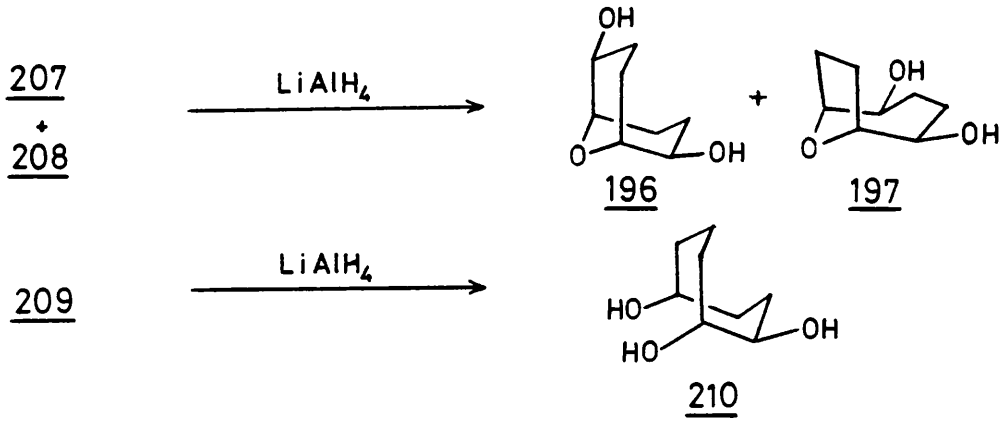
spectrometry were in accord with a molecular formula of $C_{14}H_{19}NO_2$ (m.w. 233) and confirmed the formation of the expected 1:1 adduct. The infrared spectrum of the product endorsed the presence of at least one hydroxyl function, having a broad intense band centred at 3365 cm^{-1}. Moreover the 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 ∂ 4.12. Being coupled to the neighbouring methine groups, the hydroxyl protons predictably took the form of a narrow doublet (J=4Hz) at ∂ 4.62, which was completely removed by the addition of D_2O to the p.m.r. tube. The remainder of the spectrum consisted of a five-proton aromatic multiplet at ∂ 6.33-7.29 and a complex methylene envelope (8H) between ∂ 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-azabicyco-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 acertain the course of acetylation of 9-azabicyclo[3.3.1.]-nonan-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 sulphoxide
solutions on Varian T-60 and HA-100 instruments. Band positions
are reported in parts per million (p.p.m.) downfield from either
tetramethylsilane, TMS, (for samples in $CDCl_3$ and d_6-DMSO) or
sodium 2,2-dimethyl-2-silapentane-5-sulphonate, DSS, (for D_2O
solutions) as internal reference (∂ scale).

Ultraviolet spectra were recorded in ethanol on a Unicam SP800
grating spectrophotometer. Routine mass spectra were obtained on
an AEI MS12 spectometer 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°, 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 (λ 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 fresly 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.

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.[119] m.p. 100-101°); ν_{max}^{KBr} 2933, 1485, 1160, 950 and 689 cm^{-1}; ∂ (CDCl$_3$) 2.09 - 2.65 (br env, 8H, methylene groups), 2.82 (m, 2H, bridgehead protons) and 4.71 (m, 2H, H-C-Cl).

2,6-Dihydroxy-9-thiabicyclo[3.3.1]nonane (164)[119]

Dichloride (161) (633 g, 3 mol) was dissolved in a mixture of 3 1 dimethyoxyethane and 3 1 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.[119] m.p. 240-241°); ν_{max}^{KBr} 3346, 2909, 1430, 1021, 989 and 880 cm^{-1}; ∂ (d$_6$-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)[117] and 6-hydroxy-9-thiabicyclo[3.3.1]nonan-2-one (143)[112]

(a)   AnalaR 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 165

(4.57 g, 0.027 mol, 39%), m.p. 141-142° (lit.[117] m.p. 141-142°);

ν_{max}^{KBr} 2965, 1693, 1445, 1209 and 889 cm^{-1}; ∂ (CDCl$_3$) 2.30-3.15

(m, 8H, methylene groups) and 3.39 (m, 2H, bridgehead protons).

(b)   Diol (164) (12 g, 0.07 mol) was allowed to react with

chromium trioxide-pyridine complex prepared from CrO$_3$ (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 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 Al$_2$O$_3$

eluted with chloroform-petroleum spirit and ethyl acetate-chloroform

mixtures of gradually increasing polarity). The first component to be

eluted was dione (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 (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° (lit.[112] m.p. 180-182°); ν_{max}^{KBr} 3404,

2921, 1686, 1462, 1230, 1034 and 900 cm^{-1}; ∂ (d$_6$-DMSO) 1.24-3.42

(br. env., 10H, methylene groups and bridgehead protons), 3.92

(m, 1H, H-C-OH) and 5.11 (d, 4Hz, 1H, -OH);   m/e 172(M$^+$), 154, 139,

126, 116, 100, 97 and 85; λ_{max}^{EtOH} 249 (log ε^a 2.43) and 303 nm

(2.31).

The third and most polar compound was unreacted 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[124]

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 Al_2O_3, 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_{max}^{KBr} 2931, 1746, 1491, 1443,

1376, 1240, 1055, 1039 and 879 cm^{-1}; ∂ (CDCl$_3$) 2.02 (s, 6H,

acetoxyl C$\underline{H}_3$), 1.73-2.25 (br env, 8H, methylene groups), 2.70 (m,

2H, bridgehead protons) and 5.20 (m, 2H, $\underline{H}$-C-OAc); m/e 258(M$^+$),

199, 155 and 138.

The minor component (34%) was not isolated but was tentatively

assigned as monoacetate (170); ∂ (CDCl$_3$) 1.80-2.60 (br env, 8H,

skeletal methylene groups), 2.09 (s, 3H, acetoxyl C$\underline{H}_3$), 2.18

(s, 3H, C$\underline{H}_3$-S), 2.80 (m, 2H, bridgehead protons), 4.17 (m, 1H,

$\underline{H}$-C-OCH$_2$SCH$_3$), 4.70 (s, 2H, -OC$\underline{H}_2$S-) and 5.31 (m, 1H, $\underline{H}$-C-OAc).

No oxidised products were identified.

(b)   Oxidation of <u>164</u> using chromium trioxide in dimethyl

         formamide[126]

<u>164</u> (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 (<u>143</u>).

Further attempts to prepare <u>165</u> 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 (<u>172</u>)

         with aqueous bromine[127]

Dimethoxide (<u>172</u>), 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 (<u>161</u>).

Bromine (129.6 g, 0.81 mol) was added dropwise over 30 min. to a

mixture of <u>172</u>, (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°); ν_{max}^{KBr} 2902, 2821, 1749, 1678, 1364, 1211, 1086, 898
and 683 cm^{-1}; ∂ (CDCl$_3$) 2.17 (s, 6H, acetoxyl C$\underline{H}_3$), 2.64 (m, 4H,
allylic C$\underline{H}_2$), 3.46 (m, 2H, bridgehead C$\underline{H}$) and 5.46 (m, 2H, olefinic
C$\underline{H}$). 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°)

ν_{max}^{KBr} 2942, 1751, 1696, 1420, 1380, 1210, 1094, 884 and 681 cm^{-1};

∂ (CDCl$_3$) 2.18 (s, 3H, acetoxyl C$\underline{H}_3$), 2.29-2.95 (br env, 6H,

methylene C$\underline{H}_2$), 3.22 (m, 1H, C(5)$\underline{H}$), 3.50 (m, 1H, C(1)$\underline{H}$) and 5.64

(m, 1H, olefinic C$\underline{H}$).

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

anhydride-sulphuric acid[117]

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%; $\nu_{max}^{CCl_4}$ 1752 (ϵ^a 710,

$\Delta\nu_{\frac{1}{2}}^a$ 17 cm^{-1}), 1729 (ϵ^a 560, $\Delta\nu_{\frac{1}{2}}^a$ 20 cm^{-1}) and 1719 (ϵ^a 480,

$\Delta\nu_{\frac{1}{2}}^a$ 13 cm^{-1}); ν_{max}^{KBr} 2985, 2942, 1740, 1712, 1238, 1102, 988 and

971 cm^{-1}; ∂ (CDCl$_3$) 1.65 (s, 3H, tertiary C$\underline{H}_3$), 2.00 (s, 3H, acetoxyl

C$\underline{H}_3$) and 2.51-3.64 (complex m, 8H, C(1,3,5,7)$\underline{H}$ and C(9,10)$\underline{H}_2$); m/e

254 (M$^+$), 212, 194, 179, 166, 133, 55 and 43; λ_{max}^{EtOH} 239 (log ϵ 2.62),

260 (2.47), 312 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.H_2SO_4 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.H_2SO_4 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.H_2SO_4 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 $C_{10}H_{10}O_2S$: C 61.85, H 5.19%. Found:

C 61.94, H 5.23%; $v_{max}^{CCl_4}$ 1723 cm^{-1} (ε^a 740, $\Delta v_{\frac{1}{2}}^a$ 34 cm^{-1}); v_{max}^{KBr} 2998,

2924, 2860, 1718, 1651, 1446, 1334, 1286, 1225, 1155, 1076, 990, 968,

907 and 766 cm^{-1}; ∂ (CDCl$_3$) 2.50-3.50 (complex m, 8H, C(1,3,5,7)$\underline{H}$

and C(9,10)$\underline{H}_2$) and 4.95 (s, 2H, olefinic C$\underline{H}_2$); m/e 194 (M$^+$), 166,

138, 123, 111, 105, 91 and 77; λ_{max}^{EtOH} 261 (log ε 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° 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° (decomp.); Anal. calc. for $C_{10}H_{12}O_3S$: C 56.60 H 5.70%. Found: C 56.76, H 5.79%; $v_{max}^{CCl_4}$ 3606, 1729 and 1723 cm^{-1}; v_{max}^{KBr} 3399, 2942, 1711, 1450, 1388, 1295, 1156, 1109, 971 and 944 cm^{-1}; ∂ (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; λ_{max}^{EtOH} 238 (log ε^a 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)[17]

Tetraester (4) was prepared by the method of Schaefer and Honig[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° (lit.[47] m.p. 163-164°); ν_{max}^{KBr} 2956, 1743, 1664, 1624, 1445, 1328, 1266, 1039, 997 and 836 cm^{-1}; ∂ (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)[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°, 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° (lit.[17] m.p. 141°); ν_{max}^{KBr} 2937, 1689, 1441, 1325, 1234, 995, 861 and 762 cm^{-1}; ∂ (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 prisims of

2,6-diacetoxybicyclo[3.3.1]nona-2,6-diene (<u>177</u>) (142 mg, 0.6 mmol, 18%),

m.p. 77-79° (lit.[136] m.p. 78-79°); ν_{max}^{KBr} 2939, 1743, 1438, 1368, 1214,

1104 and 908 cm^{-1}; ∂ (CDCl$_3$) 1.92 (m, 2H, C(9)$\underline{H}_2$), 2.12 (s, 6H, C$\underline{H}_3$),

2.28 (m, 4H, allylic C$\underline{H}_2$), 2.56 (m, 2H, C(1,5)$\underline{H}$) and 5.37 (m, 2H,

C(3,7)$\underline{H}$); m/e 236 (M$^+$) 194, 152. The middle band furnished

4-methyleneadamantan-2,6-dione (<u>189</u>) (183 mg, 1.04 mmol, 31% from

chloroform-hexane), m.p. (sealed tube) 160-162° (lit.[148] m.p. 163-164°);

$\nu_{max}^{CHCl_3}$ 1727 (ε^a 735) and 1715 cm^{-1} (910); ν_{max}^{KBr} 2941, 2869, 1723,

1708, 1647, 1457, 1296, 1229, 991 and 907 cm^{-1}; ∂ (CDCl$_3$) 2.00-2.53

(br env, 6H, C(8,9,10)$\underline{H}_2$), 2.93 (m, 2H, C(1,7)$\underline{H}$), 3.37 (m, 2H, C(3,5)$\underline{H}$)

and 4.86 (s, 2H, olefinic C$\underline{H}_2$); 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 (<u>190</u>) (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%; $\nu_{max}^{CCl_4}$ 1750 (ε^a 560, $\Delta\nu_{\frac{1}{2}}^a$ 24 cm^{-1}), 1724 cm^{-1}

(ε^a 820, $\Delta\nu_{\frac{1}{2}}^a$ 28 cm^{-1}); ν_{max}^{KBr} 2940, 1720, 1446, 1380, 1238, 1221,

1101, 1015, 985 and 760 cm^{-1}; ∂ (CDCl$_3$) 1.62 (s, 3H, tertiary C$\underline{H}_3$),

2.04 (s, 3H, acetoxyl C$\underline{H}_3$), 1.80-2.60 (br env, 6H, C$\underline{H}_2$), 2.70 (m, 2H,

C(1,7)$\underline{H}$) and 3.25 (m, 2H, C(3,5)$\underline{H}$); m/e 236 (M$^+$), 194, 176, 148, 120,

108, 99, 55 and 43.

Reaction of Meerwein's Tetraester (<u>4</u>)[17] with acetic anhydride-

conc. sulphuric acid.

Tetraester (<u>4</u>) (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%), ∂ (CDCl$_3$) 2.09 (s, 6H, acetoxyl CH$_3$), 2.36 (s, 2H, C(9)H$_2$), 2.62 (m, 4H, C(4,8)H$_2$), 3.70 (s, 6H, OCH$_3$) and 5.59 (m, 2H, 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%); ∂ (CDCl$_3$) 2.10 (s, 3H, acetoxyl CH$_3$), 2.18 (s, 3H, acetoxyl CH$_3$), 2.41 (s, 2H, C(9)H$_2$), 2.67 (m, 2H, C(8)H$_2$), 2.92 (s, 2H, C(4)H$_2$), 3.73 (s, 9H, OCH$_3$) and 5.61 (m, 1H, 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)[54,120,149]

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°) ν$_{max}^{KBr}$ 3420, 2911, 1665, 1482, 1350, 1230, 1049, 974 and 873 cm^{-1}.

9-oxabicyclo[3.3.1]nonan-2,6-dione (187) and 9-oxabicyclo[4.2.1]nonan-

2,5-dione (195)[149]

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; ν_{max}^{KBr} 2954, 1716, 1421, 1316, 1254, 1086, 960 and

870 cm^{-1}; ∂ (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%; $\nu_{max}^{CCl_4}$ 1765 cm^{-1} (ε^a 440, $\Delta\nu_{\frac{1}{2}}^a$ 31 cm^{-1});

ν_{max}^{KBr} 2941, 2841, 1758, 1690, 1431, 1368, 1208, 1114, 1042, 979,

940 and 897 cm^{-1}; ∂ (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 <u>198</u>

A mixture of <u>198</u> (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 (<u>187</u>) (437 mg, 2.84 mmol, 84%), m.p. 53-56° (lit.[149] m.p. 54-55°); ν_{max}^{KBr} 2950, 1720, 1441, 1244, 1080, 956 and 865 cm^{-1}; ∂ (CDCl$_3$) 1.73-3.24 (br env, 8H, C$\underline{H}_2$) and 4.44 (m, 2H, C(1,5)$\underline{H}$).

Acetylation of <u>187</u> using acetic anhydride - conc. sulphuric acid

Dione (<u>187</u>) (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 <u>198</u> (78 mg, 0.33 mmol, 23%) and, from the uppermost band, 3,7-diacetyl-9-oxabicyclo[3.3.1]nonan-2,6-dione (<u>202</u>) (54 mg, 0.23 mmol, 16%) which sublimed (110°, 0.03 mm Hg) as colourless needles, m.p. 154-156°; Anal. calc. for C$_{12}$H$_{14}$O$_5$: C 60.50, H 5.92%. Found: C 60.25, H 5.93%; ν_{max}^{KBr} 2940, 2849, 1600 (br complex) 1413, 1359, 1292, 1231, 1105, 1010, 924 and 723 cm^{-1}; ∂ (CDCl$_3$) 2.05 (s, 6H, C$\underline{H}_3$), 2.35 (s, 2H, enol O$\underline{H}$), 2.66 (dd, J=15 and 1.5 Hz, 2H, C(4,8)$\underline{H}$), 3.01 (dd, J=15 and 6 Hz, 2H, C(4,8)$\underline{H}$) and 4.53 (dd, J=6 and 1.5 Hz, 2H, C(1,5)$\underline{H}$); m/e 238 (M$^+$), 164, 121, 93, 65 and 43.

Epoxidation of 50[120,151]

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°); $\nu_{max}^{CCl_4}$ 2945, 2851, 1468,

1447, 1021, 919, 869 and 776 cm^{-1}; ∂(CDCl$_3$) 1.93 (m, 8H, C$\underline{H}_2$) and

2.93 (m, 4H, C$\underline{H}$).

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%), ν_{max}^{KBr} 3448, 3067, 2940,

1724, 1426, 1286, 1255, 1127, 1054, 975, 896 and 746 cm^{-1};

   ∂(CDCl$_3$) 1.60-2.31 (br env, 8H, C$\underline{H}_2$), 2.34 (m, 1H, O$\underline{H}$), 3.94 (m,

2H, bridgehead C$\underline{H}$), 4.52 (m, 1H, C$\underline{H}$OH), 5.32 (m, 1H, C$\underline{H}$OCOAr) 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[152]

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%;
ν_{max}^{KBr} 3365, 2940, 1599, 1507, 1385, 1316, 1048, 993, 879, 749
and 690 cm^{-1}; ∂ (d_6-DMSO) 1.08-2.42 (m, 8H, C$\underline{H}_2$), 4.12 (m, 4H,
C(1,5)$\underline{H}$ and C$\underline{H}$OH), 4.62 (d, J=4 Hz, 2H, O$\underline{H}$) and 6.33-7.29 (br env,
5H, aromatic C$\underline{H}$); m/e 233 (M$^+$), 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[154] in 1971 to be produced by the pyrolytic decomposition of adipate ester (313) (Scheme 70), subsequent attempts[158] 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[155] 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[118,119] 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[156,164]. 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[119] 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[119], instead, diol (164) and diether (214) respectively as a result of the sulphur-assisted nucleophilic displacement of chloride ion.

211

212

Scheme 70

229

50

265°

NBS

313

Δ

Na₂S

57

212

213

161 X = Cl
164 X = OH
214 X = OC₂H₅
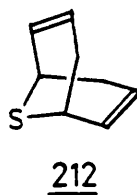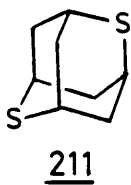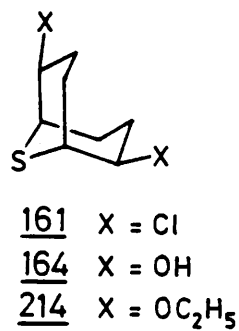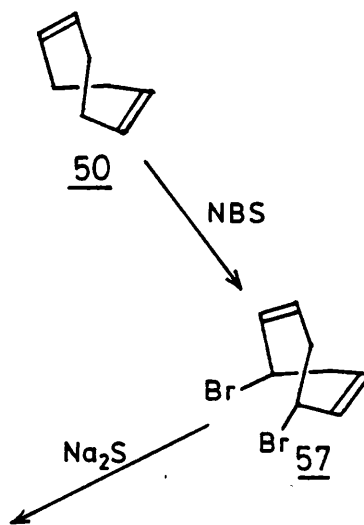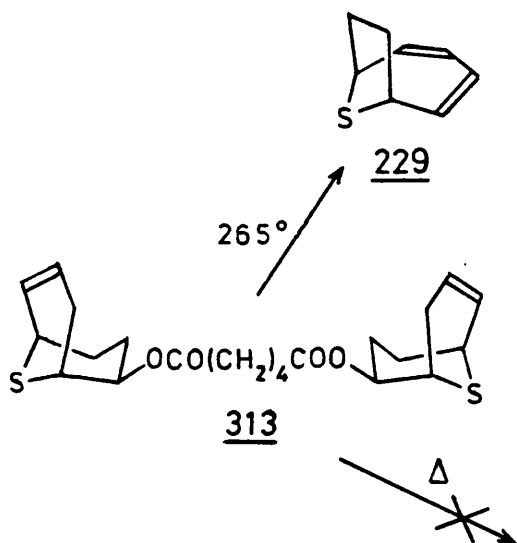
A third alternative, yet to be investigated, was the treatment of 161

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 ∂ 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 ∂3.48 together with a methylene envelope between

∂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 ∂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 ∂4.65 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 ∂5.80 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.

215   216

Scheme 71

$$161 \xrightarrow[\text{-HCl}]{168°} 213 \rightleftharpoons \quad 219$$

218    $\xleftarrow[\text{-HCl}]{219}$ 217

H_2O -HCl

216
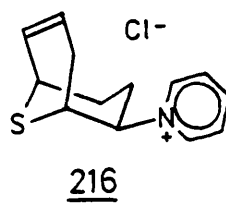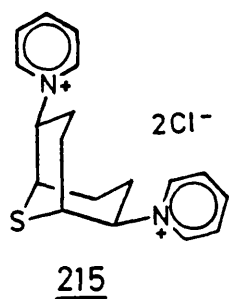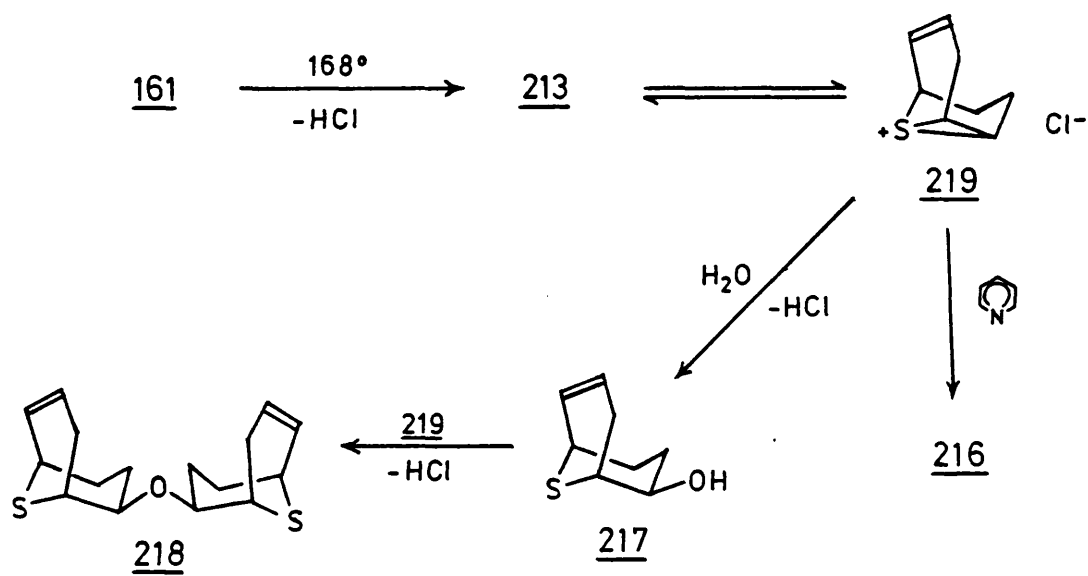
172   X = Y = OCH$_3$
173   X = Y = Br
220   X = Y = I
221   X = Cl, Y = OH
222   X = Cl, Y = OCH$_3$

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[119] (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 nucleo-
philic displacement is clearly demonstrated by the two intersting
by-products which are invariably formed[158] 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 anchimerically 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[119,158] for several years although
their existence has not been directly proved.

An interesting development of the concept has however recently
been published by Vincent[159], 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 FSO_3H and liquid SO_2. Based on ^{13}C magnetic resonance

results in was reported that dichloride (161) at -60° exists

predominantly as the twistanoid sulphonium (chloronium) ion (223)

which on warming to -30° 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 $90-93^\circ$ 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 ∂ 8.00 -

9.14 region and were accompanied by both sharp (∂ 6.09) and broad

(∂ 5.88 and 6.34) signals in the olefinic region. Medium intensity

envelopes attributable to bridgehead protons (∂ 3.46) and hydrogen

on carbon bearing pyridinium (∂ 5.45) were also of an unexpectedly

complex nature and it was concluded, in accord with the micro-

Scheme 72

223   161   224

164   X = Y = OH
172   X = Y = OCH₃
221   X = OH, Y = Cl
222   X = OCH₃, Y = Cl

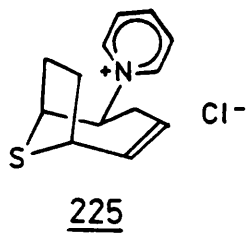225
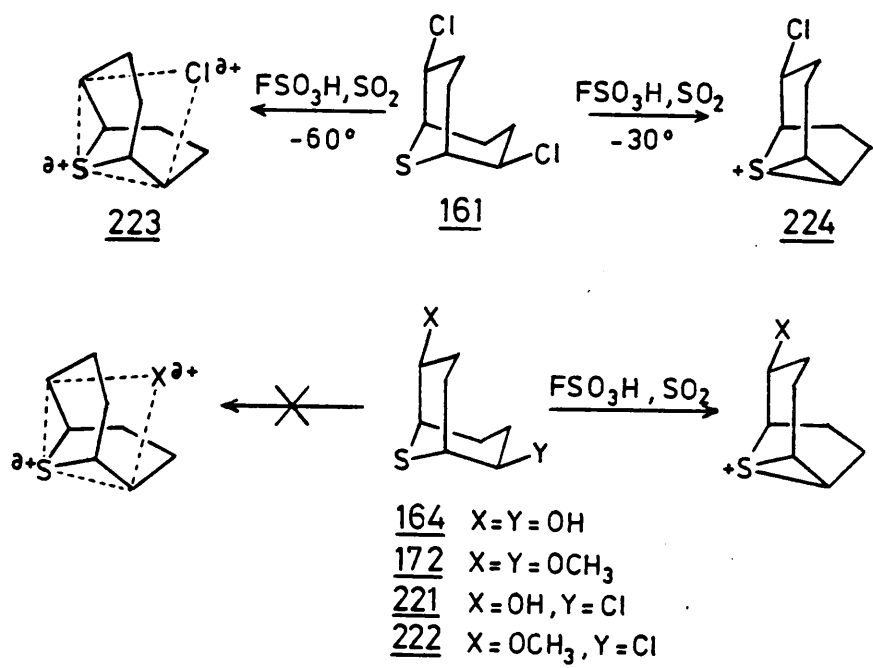
Figure 7

The 100 MHz p.m.r. spectra of (a) <u>215</u>, (b) <u>216</u> and (c) a 2:1 mixture of <u>216</u> and <u>225</u>.
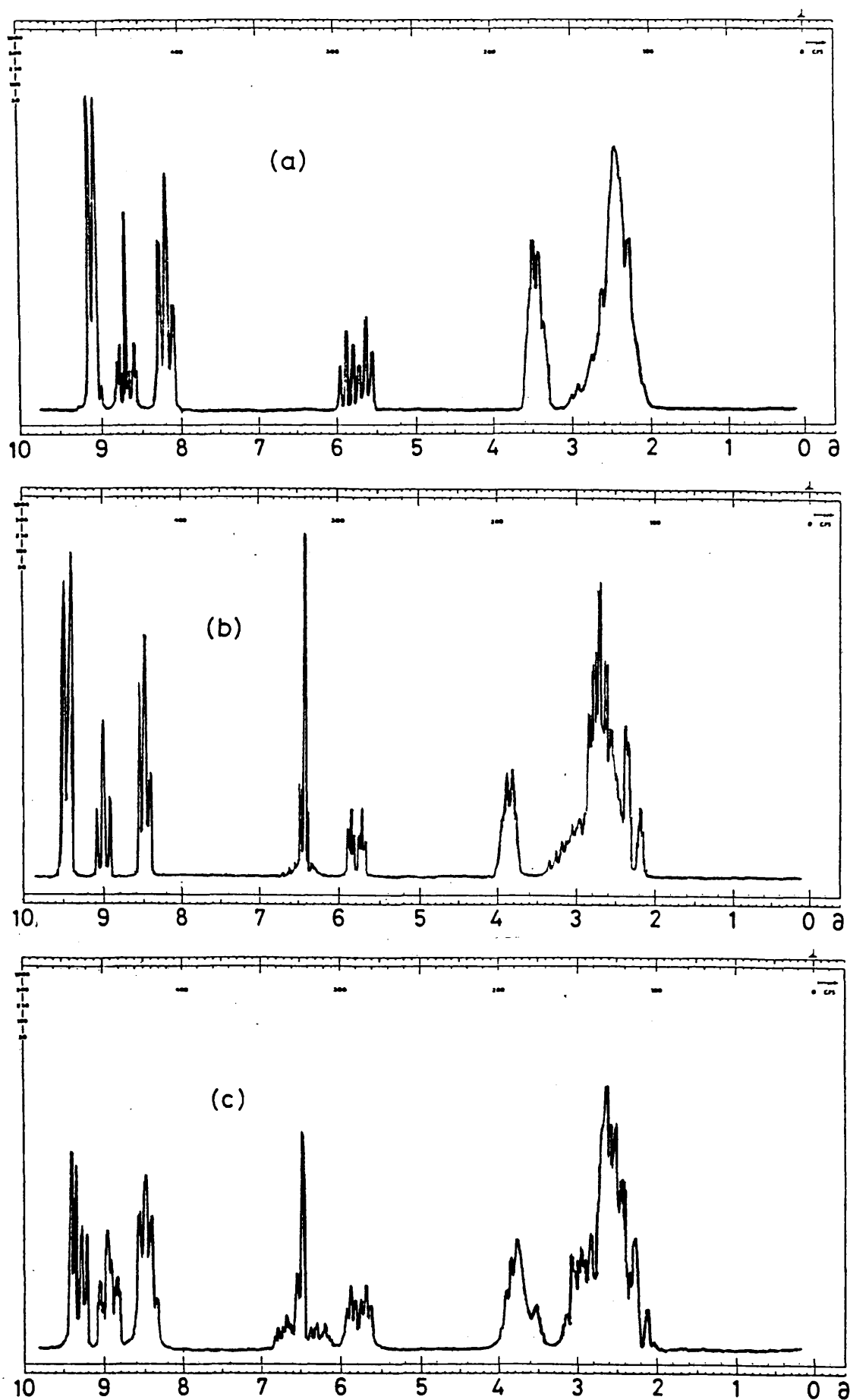
analytical data, that the observed product was a mixture of skeletal

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 $C_{13}H_{16}ClNS$. The p.m.r. spectrum of the product

exhibited sharp pyridinium resonances at ∂ 8.12 (2H), 8.60 (1H)

and 9.01 (2H), a crisp one-proton $\underline{H}$-C-$\overset{+}{N}$ signal at ∂ 5.45, a

complex bridgehead multiplet (2H) at ∂ 3.46 and a broad methylene

envelope between ∂ 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 ∂ 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 ∂ 5.45

($\underline{H}$-C-$\overset{+}{N}$) sharpened only the bridgehead (∂ 3.46) and upfield

methylene (∂ 2.34) signals while irradiation at ∂ 2.72 (allylic

methylene) collapsed both bridgehead and vinyl multiplets. Double

irradiation of the bridgehead multiplet (∂ 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 ∂ 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 $(C_{13}H_{16}ClNS)_2 \cdot 3H_2O$.

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

Scheme 73
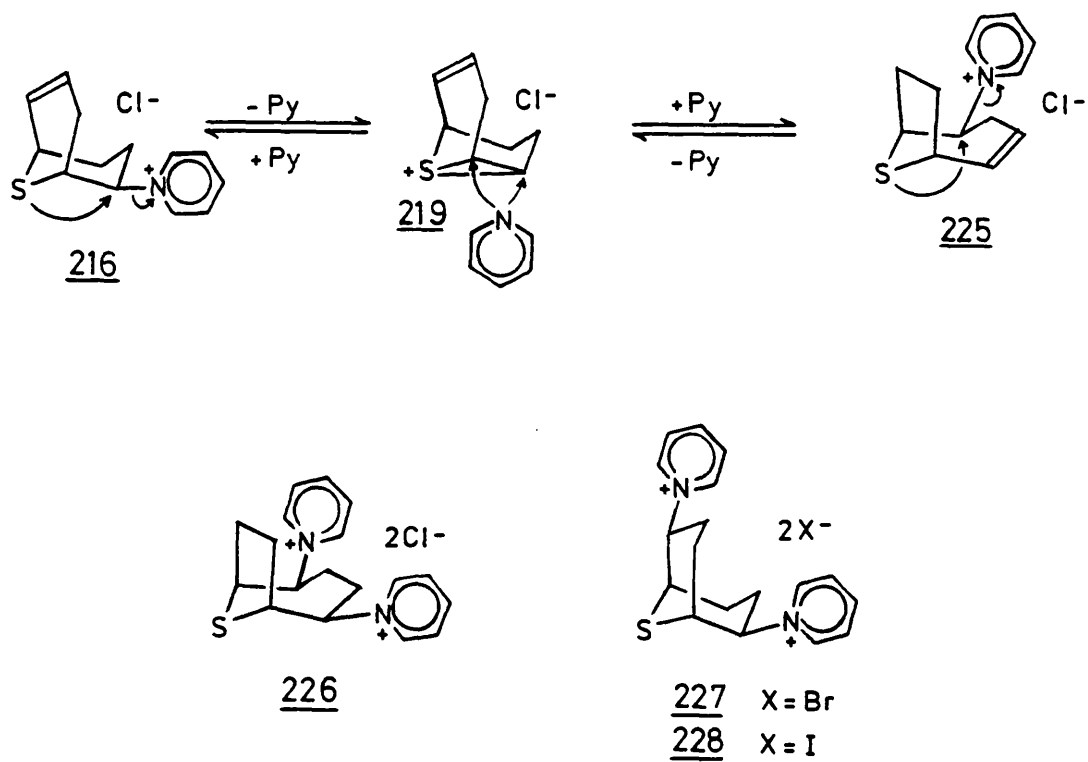
Figure 8

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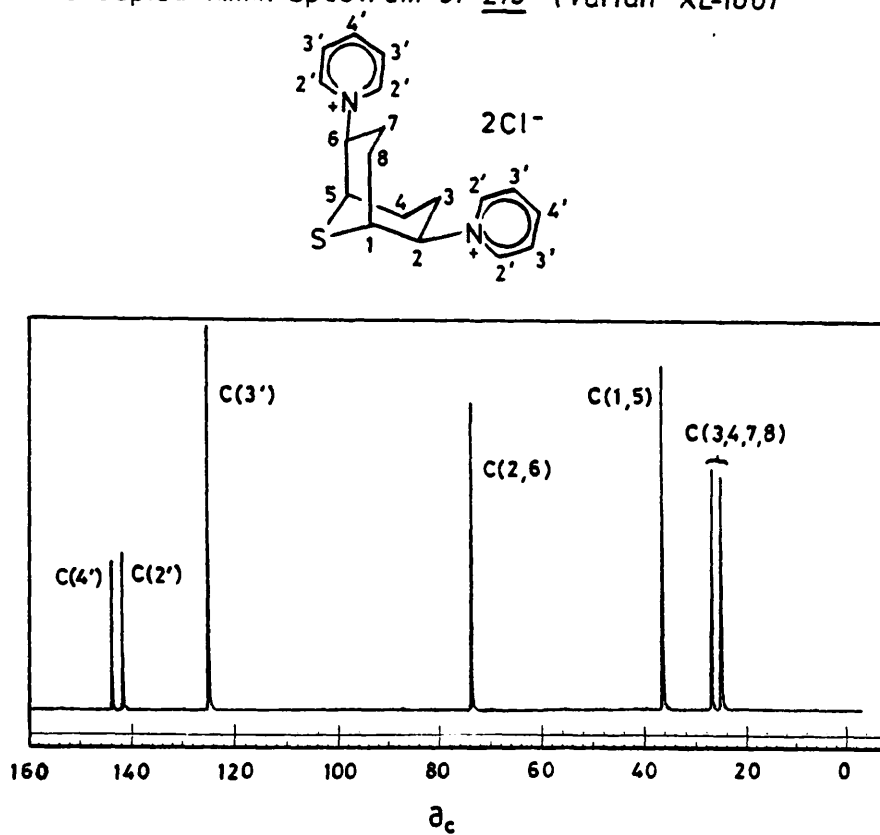
overlapping triplets (2H) at ∂ 5.80 bore a close resemblance, in profile and chemical shift, to the corresponding signal of 216.

The position of the two proton bridgehead signal (∂ 3.48) was consistent[160] 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[119] 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 ^{13}C 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 $C_{18}H_{28}Cl_2N_2O_3S$ 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[161] 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 ∂ 2.21, 4.00, 5.81 and 6.40 showing the major component to be

the skeletally rearranged diene (229)[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[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

Scheme 74

215 $\xrightarrow[250°]{-Py}$

2 Cl⁻

H¹ H²

$\xrightarrow{-H^2Cl}$

$\xrightarrow{-H^1Cl}$

Cl⁻

216

$\xrightarrow[\times]{}$

212

$\xrightarrow[250°]{-Py.HCl}$ 229 $\xleftarrow[250°]{-Py.HCl}$

Cl⁻

225

$\xrightarrow[\times]{}$

212

229

230

CH_3

H_3C CH_3

Scheme 75

161 $\xrightarrow[-Col.HCl]{230}$ 213 $\xrightarrow[-Col.HCl]{230}$ 229

231 X = Br

232 X = I

2X⁻
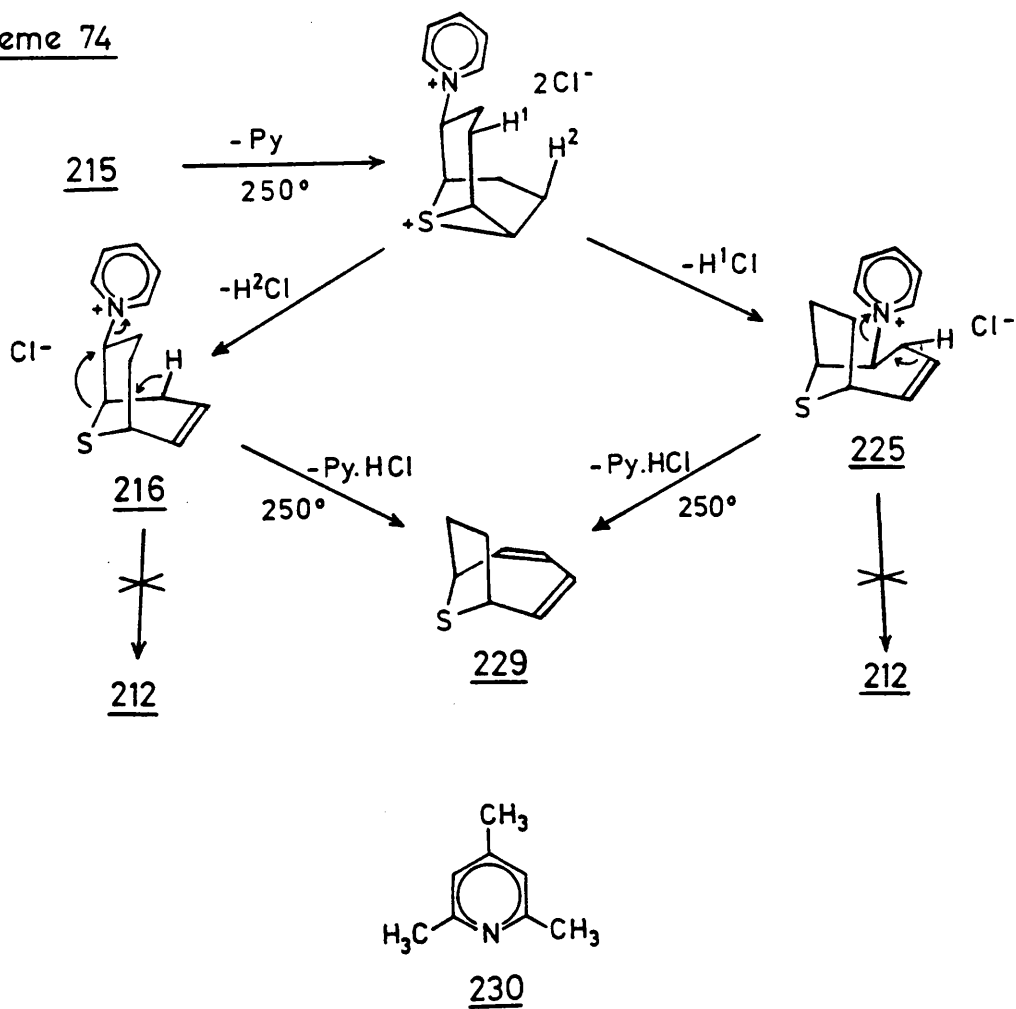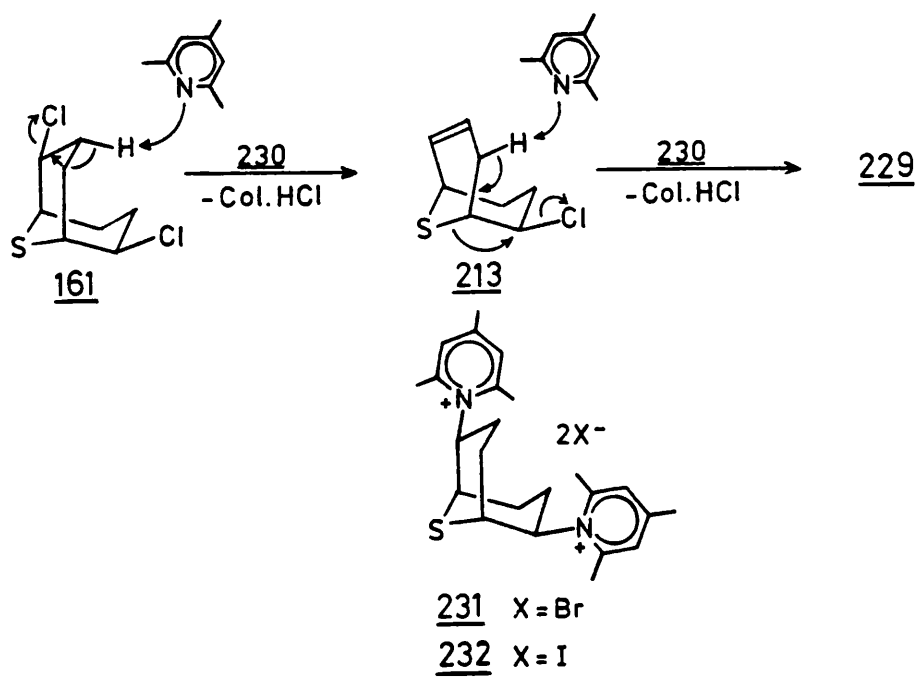
217 and 218 (Scheme 74).

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)[158]

Treatment of 161 with refluxing 2,4,6-collidine (230) has been shown[158] 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[162] 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[163]

Potassium t-butoxide has been widely used[164,165] to dehydro-halogenate 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[165]. Because of its strongly basic character,

KOBu[t] has also been used[166] 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[163] was

the highly rearranged episulphide (233)[167,182]. 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[155] 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 suit-

ability of which as a precursor of tricyclic systems remains

to be established.

Scheme 76

$$161 \xrightarrow[\text{DMSO}]{\text{KOBu}^t} \quad \underline{224} \quad \longrightarrow \quad \underline{233}$$

B⁻ = (CH₃)₃CO⁻ or CH₃SOCH₂⁻

Scheme 76

$161 \xrightarrow[\text{DMSO}]{\text{KOBu}^t}$ **224** $\longrightarrow$ **233**

$B^- = (CH_3)_3CO^-$ or $CH_3SOCH_2^-$
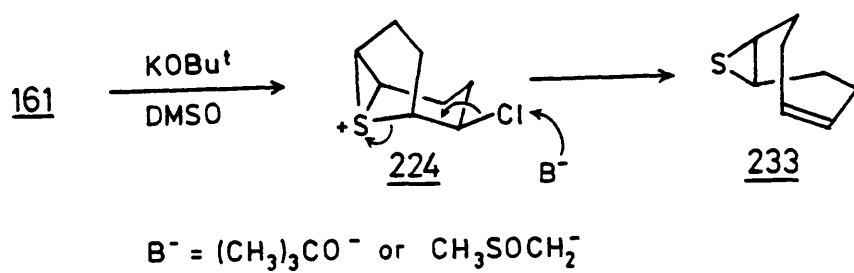
Experimental Section

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 $C_{18}H_{28}Cl_2N_2O_3S$: C 51.06,
H 6.67, N 6.62%. Found: C 51.40, H 6.56, N 6.58%; ν_{max}^{KBr} 3387,
3130, 3056, 2939, 2856, 1630, 1575, 1480, 1340, 1140, 1026, 868, 770,
721 and 682 cm^{-1}; ∂ (D$_2$O) 2.30-2.64 (m, 8H, C$\underline{H}_2$), 3.48 (m, 2H,
C(1,5)$\underline{H}$), 5.80 (m, 2H, C(2,6)$\underline{H}$), 8.22 (t, 4H, C(3',5')$\underline{H}$), 8.71 (t,
2H, C(4')$\underline{H}$) and 9.15 (d, 4H, C(2',6')$\underline{H}$); λ_{max}^{EtOH} 256 (sh, logϵ 3.90),
2.62 (3.99) and 269 nm (sh, 3.90).

Pyrolytic dehydrochlorination of 161[119]

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); $\nu_{max}^{CCl_4}$ 3027, 2937,
2846, 1651, 1452, 1208, 1077, 876, 688 and 659 cm^{-1}; ∂ (CDCl$_3$) 2.04
(m, 4H, C(7,8)$\underline{H}_2$), 2.58 (m, 2H, C(4)$\underline{H}_2$), 3.10 (m, 2H, C(1,5)$\underline{H}$),
4.56 (m, 1H, $\underline{H}$-C-Cl) and 5.84 (m, 2H, olefinic C$\underline{H}$).

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 $C_{13}H_{16}ClNS$: C 61.47, H 6.35,

N 5.52%. Found: C 61.20, H 6.8, N 5.4%; ν_{max}^{KBr} 3010, 1635, 1477,

1132 and 680 cm^{-1}; ∂ (D_2O) 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_{max}^{EtOH} 249 (sh, log ε 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 $C_{13}H_{16}ClNS$: 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_{max}^{KBr} 3020, 1630, 1478, 1137 and 682 cm^{-1}; ∂ (D_2O) 1.87-2.90

(complex m, 6H, C$\underline{H}_2$), 3.46 (br m, 2H, C(1,5)$\underline{H}$), 5.45 (m, 1H,

C(6)$\underline{H}$), 6.09 (m, 2H, olefinic C$\underline{H}$), 8.12 (t, 2H, C(3')$\underline{H}$),

8.60 (t, 1H, C(4')$\underline{H}$) and 9.01 (d, 2H, C(2')$\underline{H}$); λ_{max}^{EtOH} 256 (sh,

logϵ 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 (CDCl$_3$) of the crude product

showed the major component to be diene (229)[158], ∂ 2.21 (m, 4H, C$\underline{H}_2$),

4.00 (m, 2H, bridgehead C$\underline{H}$), 5.81 (m, 2H, C(2,5)$\underline{H}$) and 6.40 (m, 2H,

C(3,4)$\underline{H}$), accompanied by small amounts (< 5%) of 217 and 218[158].

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[158]. 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.
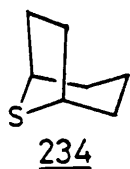
Part Four

The Synthesis
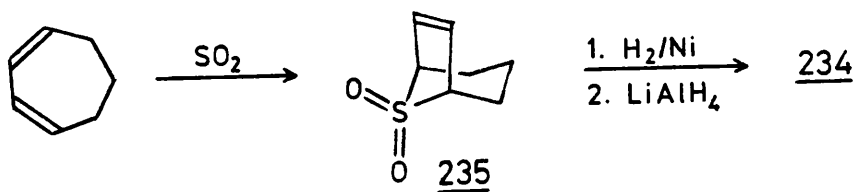of Polysubstituted
8-Thiabicyclo[3.2.1]octanes

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[168] in 1955 when the
parent thioether was isolated from Iranian kerosene and a
subsequent laboratory synthesis (Scheme 77)[169] 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[170] of sodium sulphide
with tropinone methiodide (237) and by the Michael addition[171]
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[172] or lithium aluminium hydride[173] and their
aromatic esters (241, 242 and 243) have been prepared for biological
testing[173]. Conversion of 236 to its tosyl hydrazone (244) followed
by pyrolysis has given[174] alkene (245) (Scheme 79) while Claisen
condensation with aromatic aldehydes yielded 2,4-dibenzylidine
derivatives (246) which exhibit fungistatic activity[175]. Beckmann
rearrangement of oxime (247) to 248 is a step in the synthesis
(Scheme 80)[176] of 3-aza-9-thiabicyclo[4.2.1]nonane derivatives, such
as 249, which are effective in the treatment of hypertension.

234

Scheme 77

235

1. H$_2$/Ni
2. LiAlH$_4$

234

Scheme 78

237

Na$_2$S

236

H$_2$S

238

239 R^1 = H , R^2 = OH
240 R^1 = OH , R^2 = H

241 R = Ph
242 R = CH(Ph)$_2$
243 R = CHPh

Scheme 79

236

TsNNH$_2$
H$^+$

244

Δ

245

1. NaH
2. ArCHO

246

Scheme 80

247 → (H⁺) → 248 → (cat. H₂) →

249

Scheme 81

250 → (n-BuLi) → → (SO₂Cl₂) → 251 → (Δ, –SO₂) → 252

Scheme 82

234 → (1. SO₂Cl₂, 2. ArCO₃H) → 253 + 254

234 → (SO₂Cl₂) → 255 → (–H⁺) → 256 → 257 → ([O]) → 253
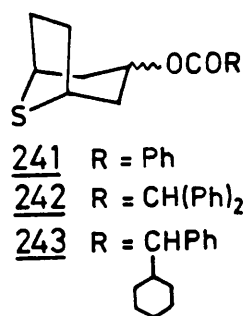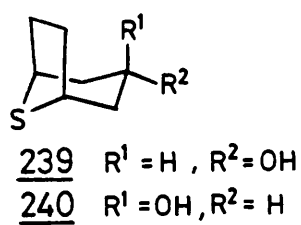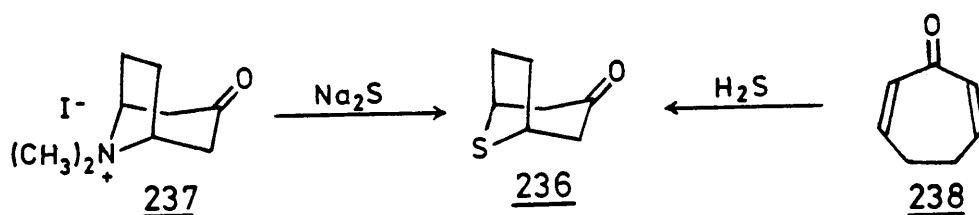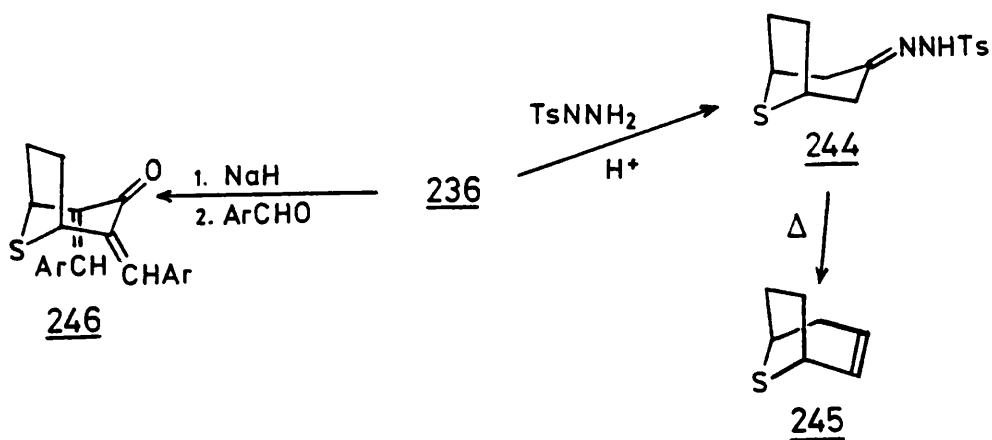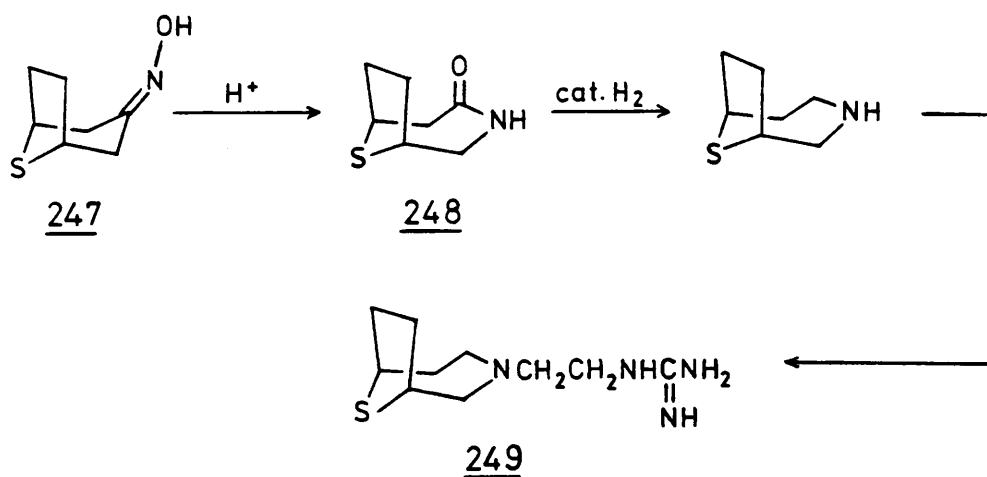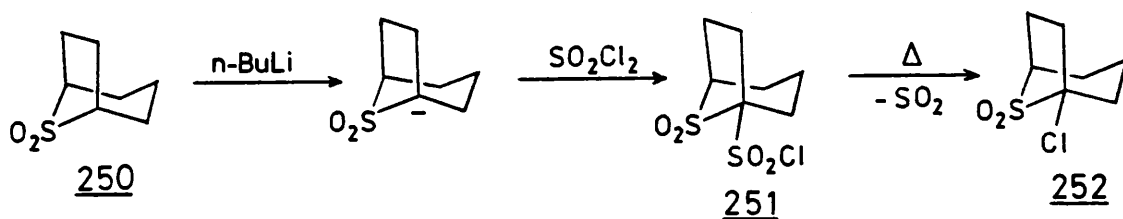
Bridgehead substitution of the 8-thiabicyclo[3.2.1]octane nucleus has been achieved[177] by treatment of sulphone (250) with n-butyl lithium and sulphuryl chloride, SO_2Cl_2 to give sulphonyl chloride (251). On heating, 251 decomposes with evolution of SO_2 furnishing α-chlorosulphone (252) (Scheme 81). In contrast, the reaction of 234 with SO_2Cl_2, followed by oxidation of the crude product by monoperphthalic acid produced[177] a mixture of β-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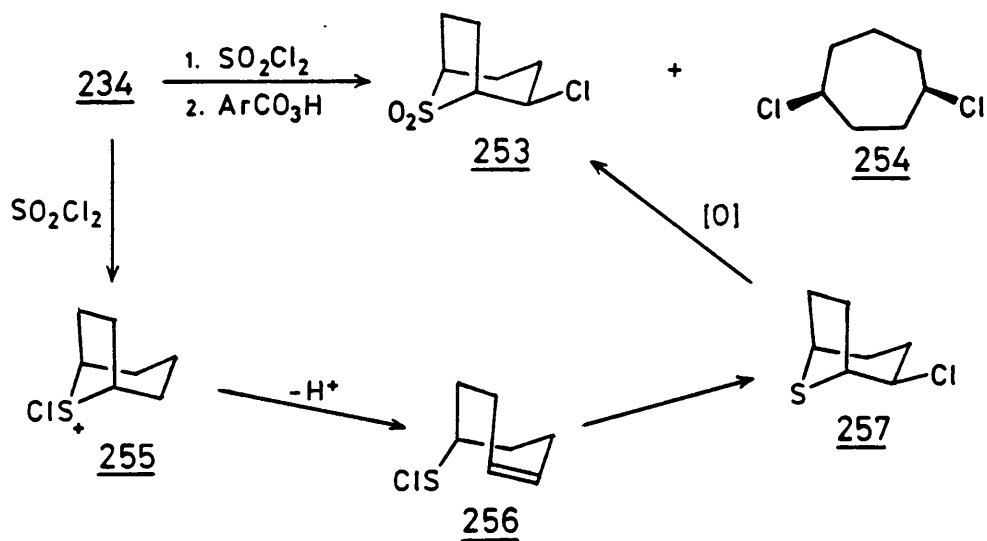] of 260 by sodium carbonate yielded both 261 and 262, and the latter has been oxidised[179] to dione (263) (Scheme 83).

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.

235 X=SO$_2$
258 X=S

Scheme 83
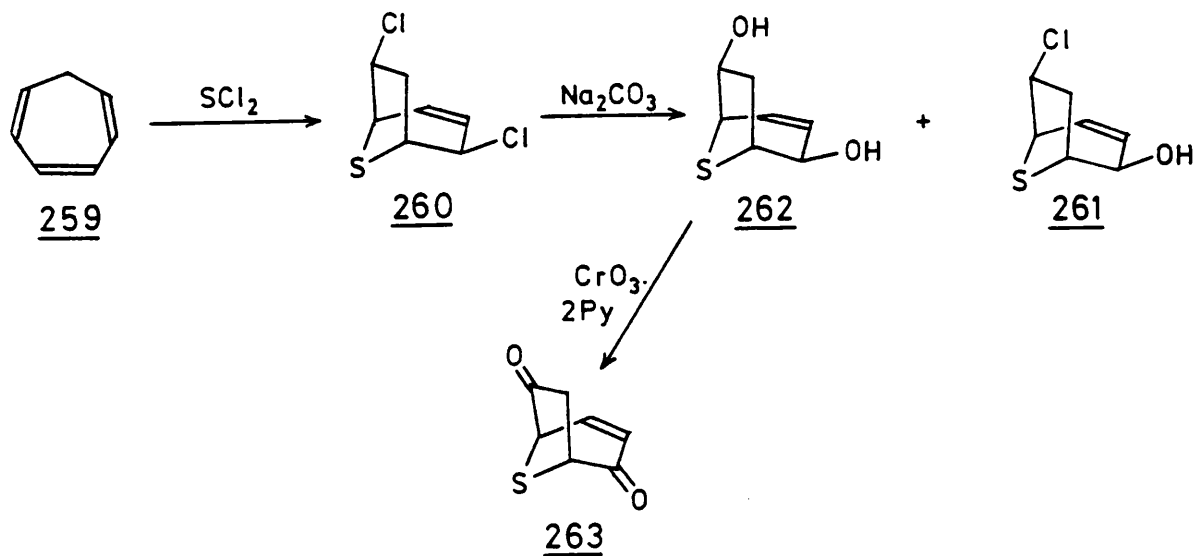
Scheme 84
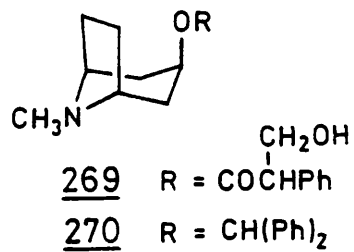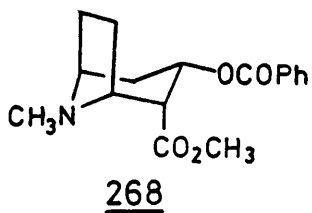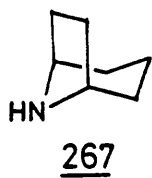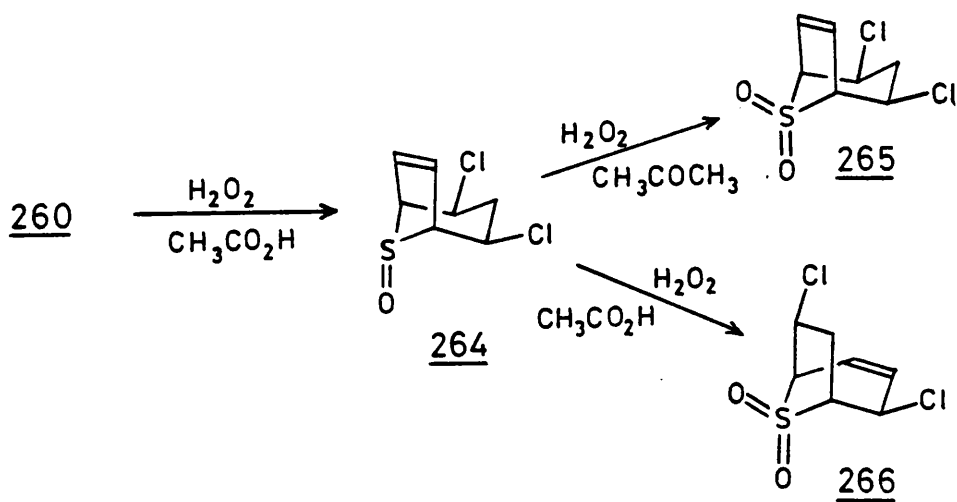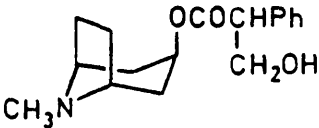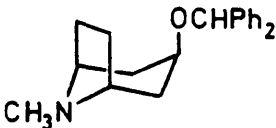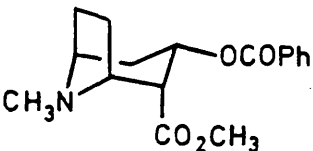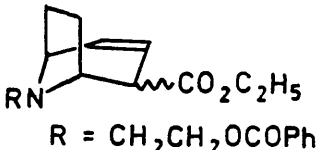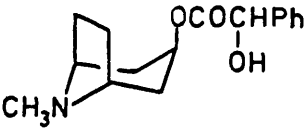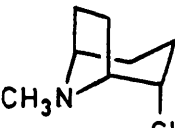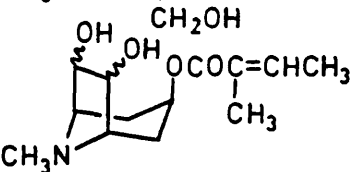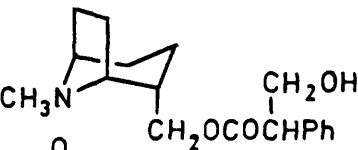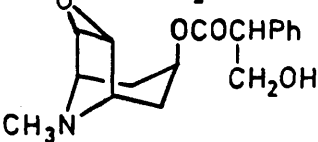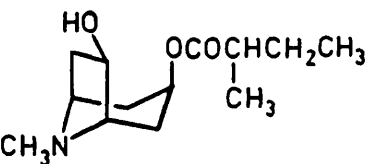
Closely related in structure to these compounds are the numerous
naturally-occurring derivatives of 8-azabicyclo[3.2.1]octane (267),
collectively known as the tropane alkaloids. Many of these
compounds possess powerful physiological activity and have found
use as pharmaceuticals. Possibly the best known members of the
series are β-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 antihistamine 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
pharmacalogically 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.

Structure	Name	Properties
OCOCHPh / CH₂OH / CH₃N	Atropine (±Hyoscyamine)	antispasmodic, analgesic, anaesthetic, parasympatholytic
OCHPh₂ / CH₃N	Benztropine	antispasmodic, antihistamine, parasympatholytic, used in treatment of Parkinsonian syndrome
OCOPh / CH₃N / CO₂CH₃	β-Cocaine	narcotic, analgesic, local anaesthetic
RN ∿CO₂C₂H₅, R = CH₂CH₂OCOPh	Eccaine	non-toxic anaesthetic
OCOCHPh / OH / CH₃N	Homatropine	cycloplegic parasympatholytic mydriatic
CH₃N	Homotropine	local anaesthetic mydriatic
OH OH CH₂OH OCOC=CHCH₃ / CH₃ / CH₃N	Meteloidine	found in _Datura meteloides_
CH₃N CH₂OH / CH₂OCOCHPh	Mydriasin	powerful mydriatic
O OCOCHPh / CH₂OH / CH₃N	Scopolamine	antispasmodic
HO OCOCHCH₂CH₃ / CH₃ / CH₃N	Valeroidine	found in _Duboisia myoporoides_

DISCUSSION

The reaction of sulphur dichloride, 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[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 SCl_2 to carbon-carbon double bonds is now
believed[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[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[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[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

271

272

Scheme 85

273

274

275
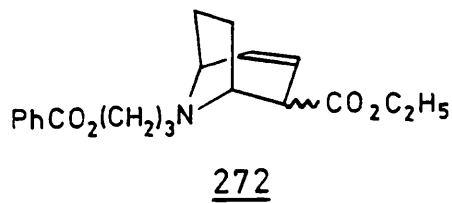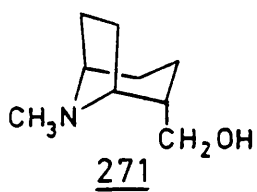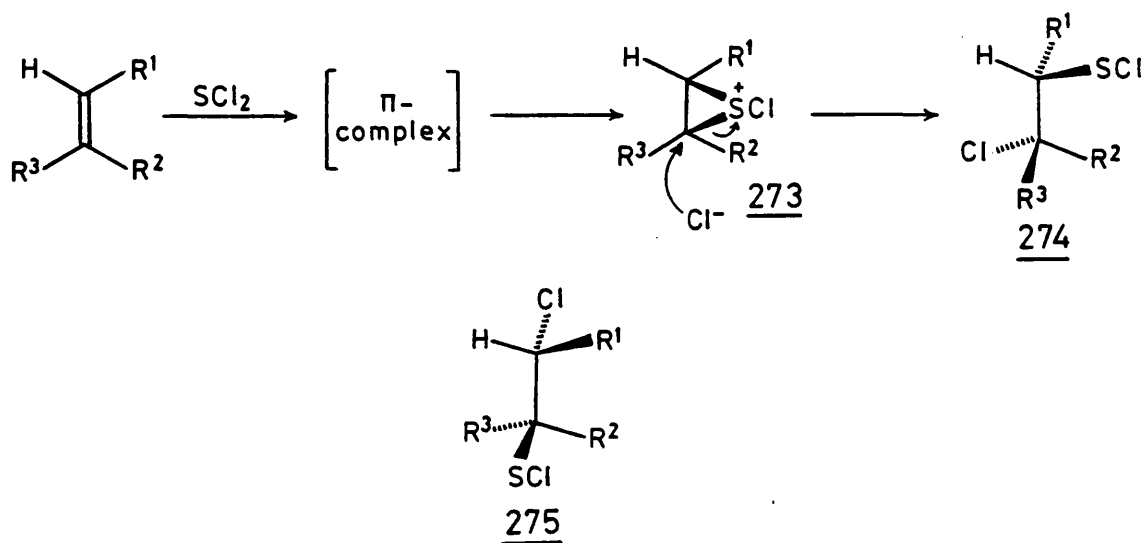
Scheme 86

276
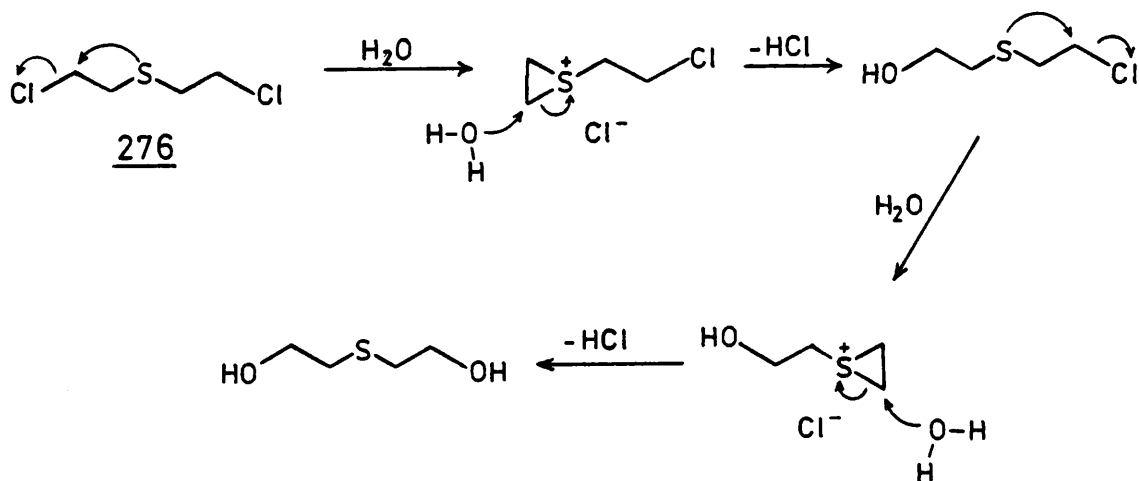
variety of unsaturated systems including dienes[181-183,186],

acetylenes[187], enol ethers and enamines[188], oximes[189] and nitriles[190]

have yielded novel sulphur-containing products. In particular, the

addition of SCl_2 to cyclic polyolefins has been widely used

for the preparation of thiabicyclic systems.

Prompted by the stereospecific formation[74] of allylic chloride

(260) from cycloheptatriene (259), the reaction of SCl_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[170] from tropinone

methiodide (237) by reaction with sodium sulphide, the corresponding

methiodides of tropine (277), pseudotropine (278)[191] and β-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 β-cocaine (268),

the synthesis of 281 was of particlar interest. In absence of a

direct route from 268 (vide supra) it was proposed to convert 236

into β-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

277 R¹ = OH, R² = H

278 R¹ = H, R² = OH

Scheme 87

236 →
1. NaH or n-BuLi
2. ClCO₂CH₃ or (CH₃O)₂CO

279 → NaBH₄ → 280

PhCOCl

281

Scheme 88

259 → SeO₂ → 284 → LiAlH₄, ether or NaBH₄, CH₃OH → 285

284 → H₂O or CH₃OH → 282

285 → LiAlH₄ ether → no reaction

282 → NaBH₄ → 283
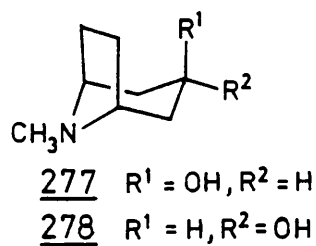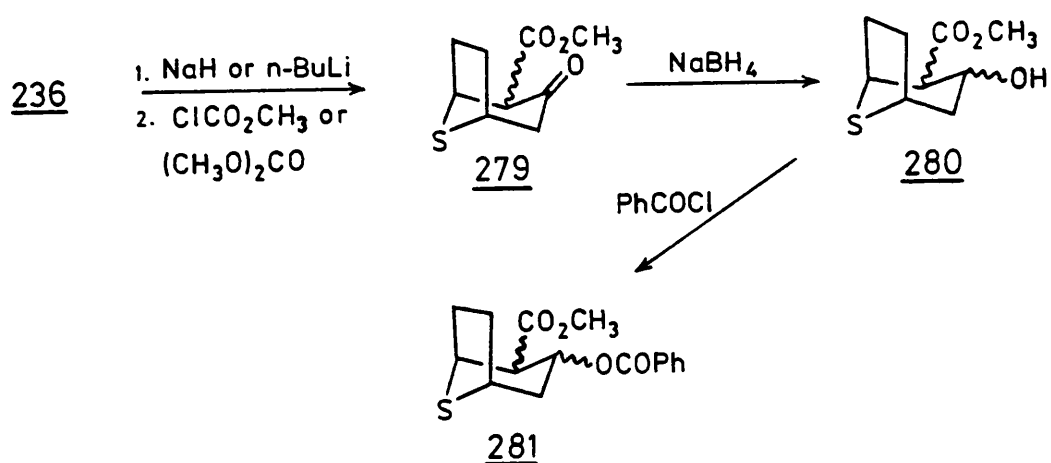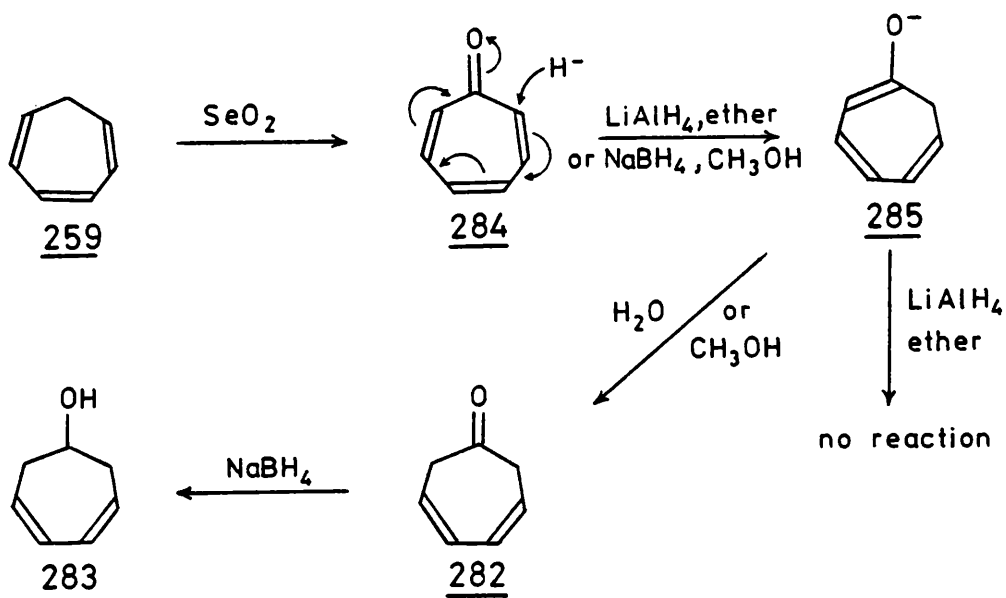
diastereoisomers (Scheme 87). In the event, however, all

attempts to prepare 279 by treatment of 236 with sodium hydride-

dimethyl carbonate[192] or n-butyl lithium - methyl chloroformate[193]

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)[194,195] was prepared in two steps from

cycloheptatriene (259). Allylic oxidation[196] 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 LiAlH$_4$ is used. This may be rationalised[195] 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[197,198] 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[197].

Cycloalk-2-enones (287) are readily prepared by a number of

methods[199].   The synthesis of $\alpha, \beta, \alpha', \beta'$-cycloalkadienones

(289) is less common but has been accomplished[200] by α, α'-di-

bromination 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 $C_{14}H_{14}Cl_2O_2S$.

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 ∂ 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 ∂ 3.66, taken with a sharp H-C-Cl multiplet

at ∂ 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).

286 OCOPh

287

Scheme 89

(CH₂OH)₂ / H⁺

288

Br₂

NaOH

H⁺

289

290 X = H
291 X = Br

292
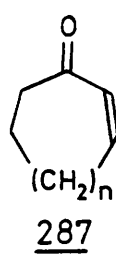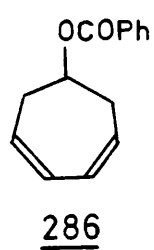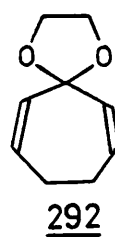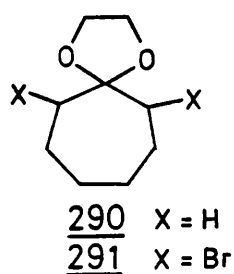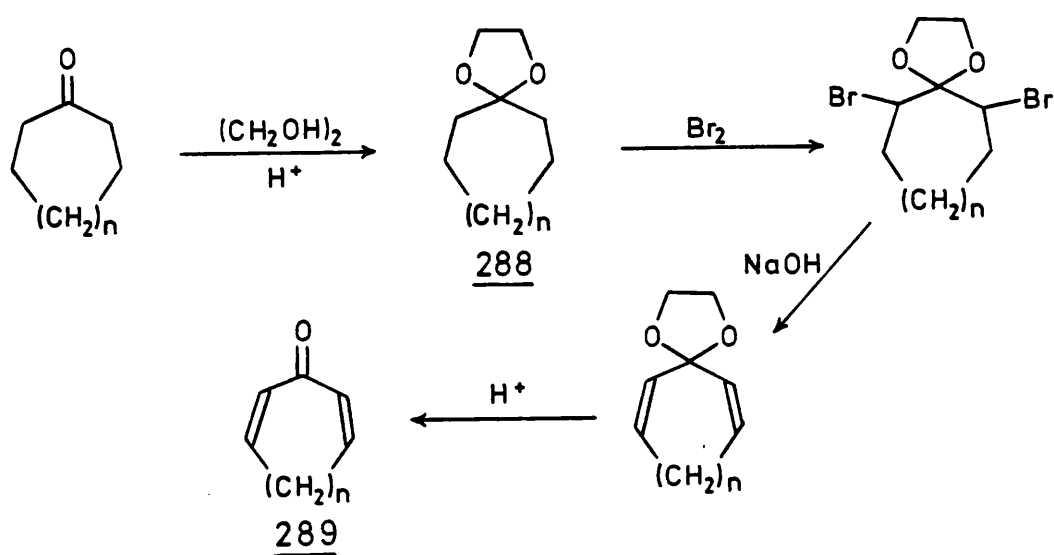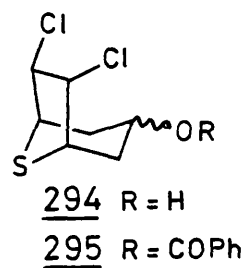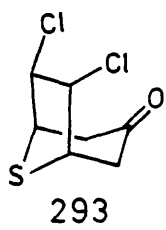
Figure 9

The 100 MHz p.m.r. spectra of (a) 295 and (b) 296.
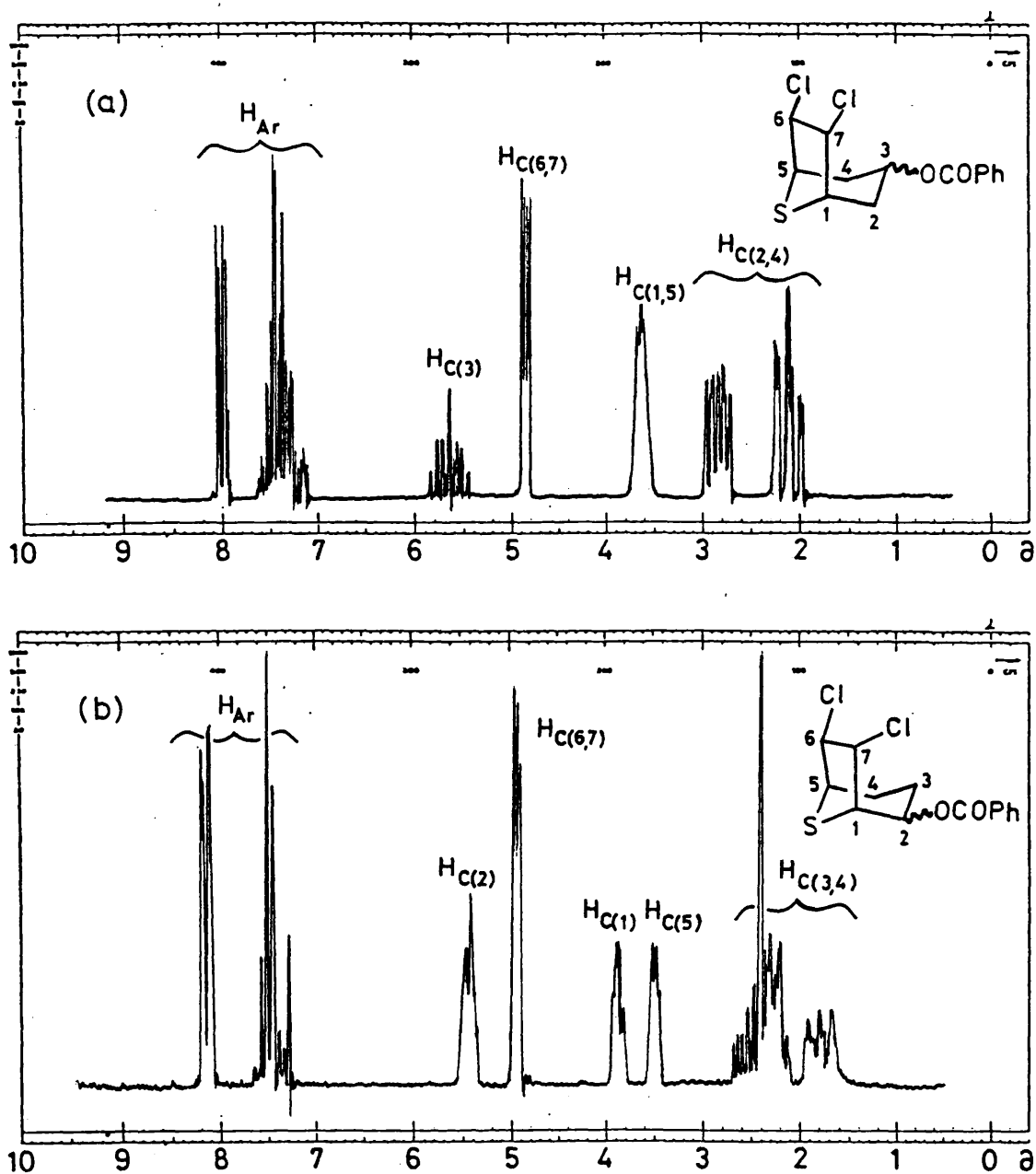
By thin layer chromatography of the liquors remaining after
crystallisation of 295, an additional minor reaction product was
isolated as colourless crystals, m.p. 117-118°. Although
possessing similar aromatic features at ∂ 7.50 (m, 3H) and 8.08
(m, 2H), the p.m.r. spectrum differed from that of 295 by having
two bridgehead signals at ∂ 3.49 and 3.90, each of which integrated
for one proton (Figure 9). Moreover, the hydrogen-on-carbon-bearing-
oxygen resonance at ∂ 5.48 was coupled to a lesser degree than the
corresponding signal of 295. Double irradiation of this multiplet
sharpened the bridgehead resonance at ∂ 3.90 and indicated a vicinal
relationship between the corresponding protons. More comprehensive
decoupling studies, a high resolution mass measurement (indicating a
formula of $C_{14}H_{14}Cl_2O_2S$) 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 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
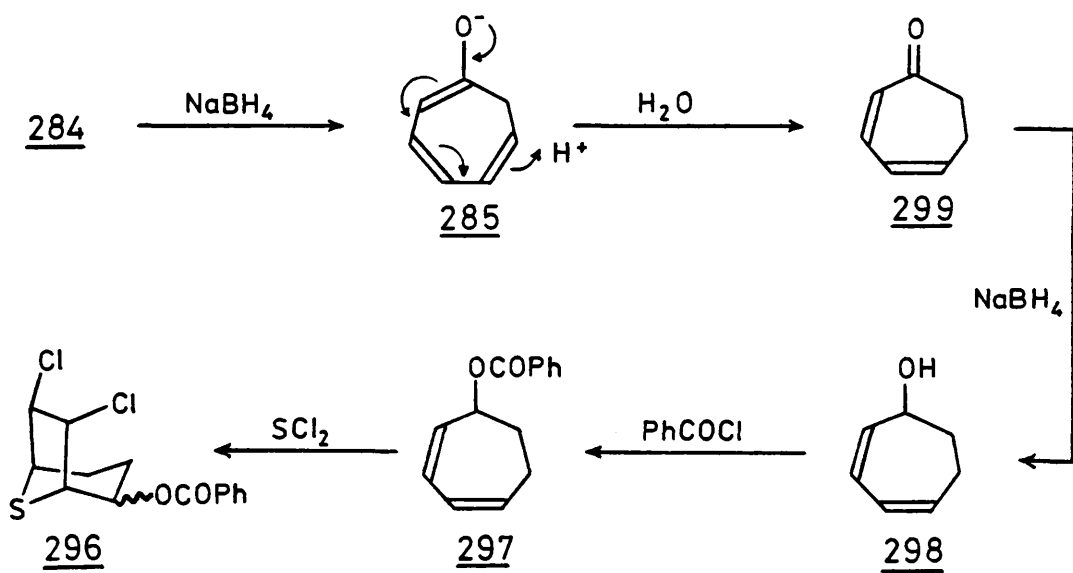
Scheme 91
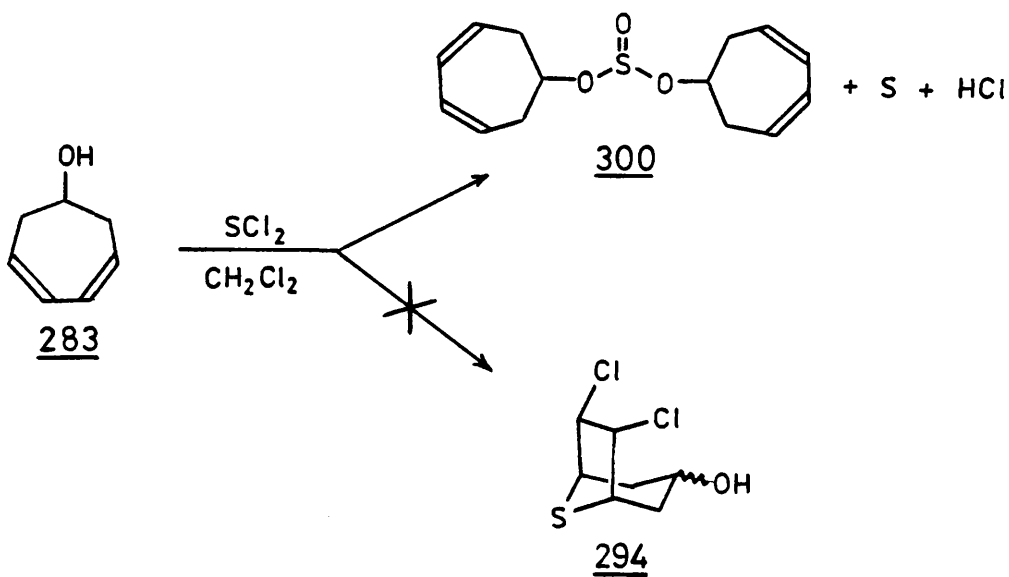
8-thiabicyclo[3.2.1]octane system. These results suggested that,
rather than adding across the double bonds of 283, SCl_2 had reacted
preferentially with the hydroxyl function yielding dialkyl
sulphite (300) as the possible product (Scheme 91). Rigorous
structural confirmation of 300 was not however undertaken and the
reaction was not further investigated. The crude product from
the reaction of dienone (282) with SCl_2 was unstable and continuously
darkened on standing. While it decolourised somewhat when passed
through neutral alumina and appeared as one spot (R_f 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, C_7H_7ClOS 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.

Figure 10

The 60 MHz p.m.r. spectra of (a) <u>301</u> and (b) <u>303</u>
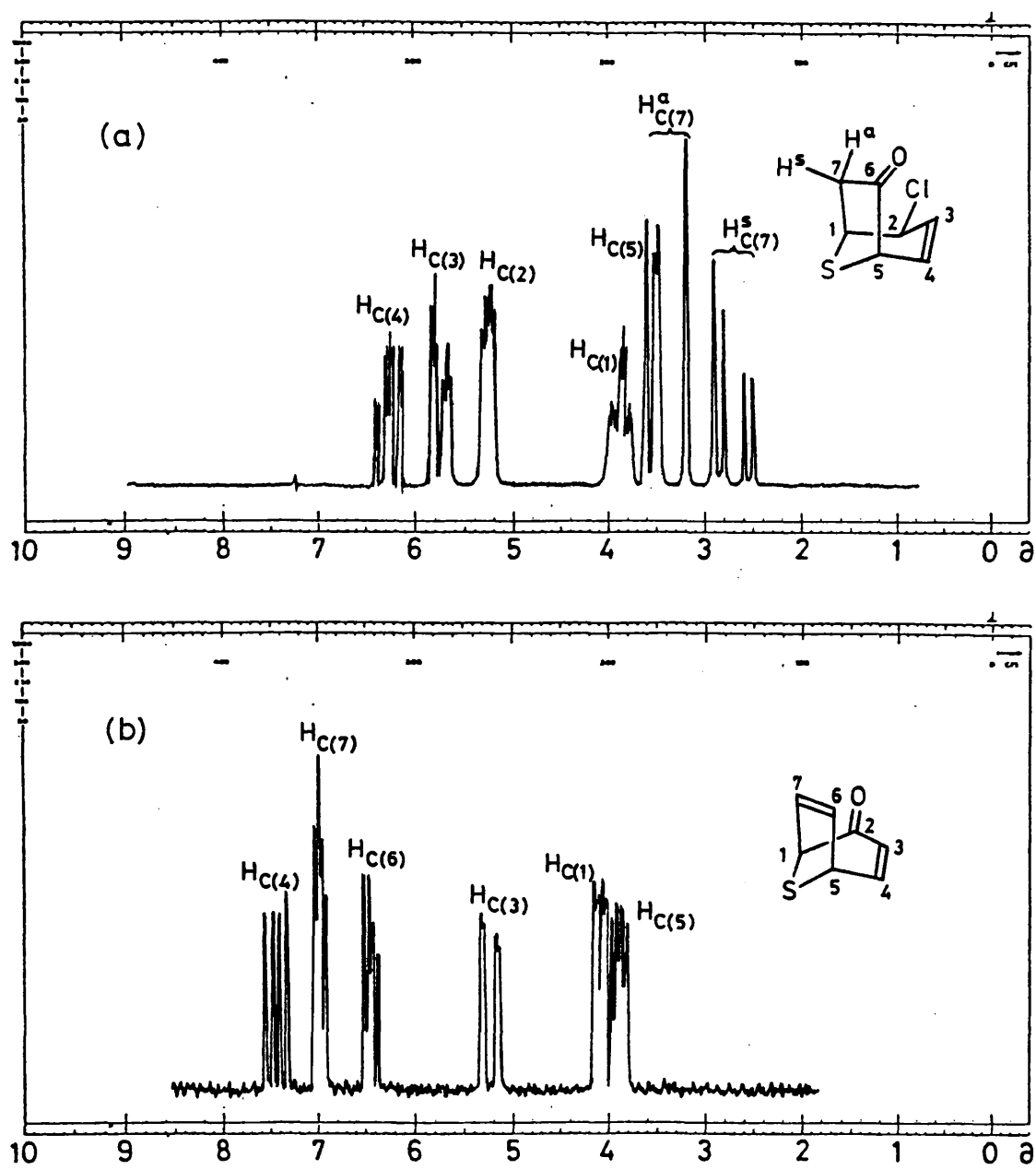
Double resonance experiments showed that a doublet at ∂ 3.33 and a
double doublet at ∂ 2.75 were mutually coupled by 18 Hz and these
were attributed to geminally situated methylene protons which were
slightly deshielded. The higher-field signal was coupled by 7Hz to
a bridgehead multiplet at ∂ 3.86 which also interacted with a complex
H̲-C-Cl resonance at ∂ 5.24. Olefinic signals at ∂ 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 (∂ 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)[201] and thioketones (1:1 adduct)[202]. Thus 301
results from a conventional trans-addition of 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

Scheme 92

282 $\xrightarrow{\text{SCl}_2}$ 302 $\rightleftharpoons$

$\downarrow$ -HCl

303 $\equiv$ $\xleftarrow[\text{-HCl}]{\text{Al}_2\text{O}_3}$ 301

304

305

306

307
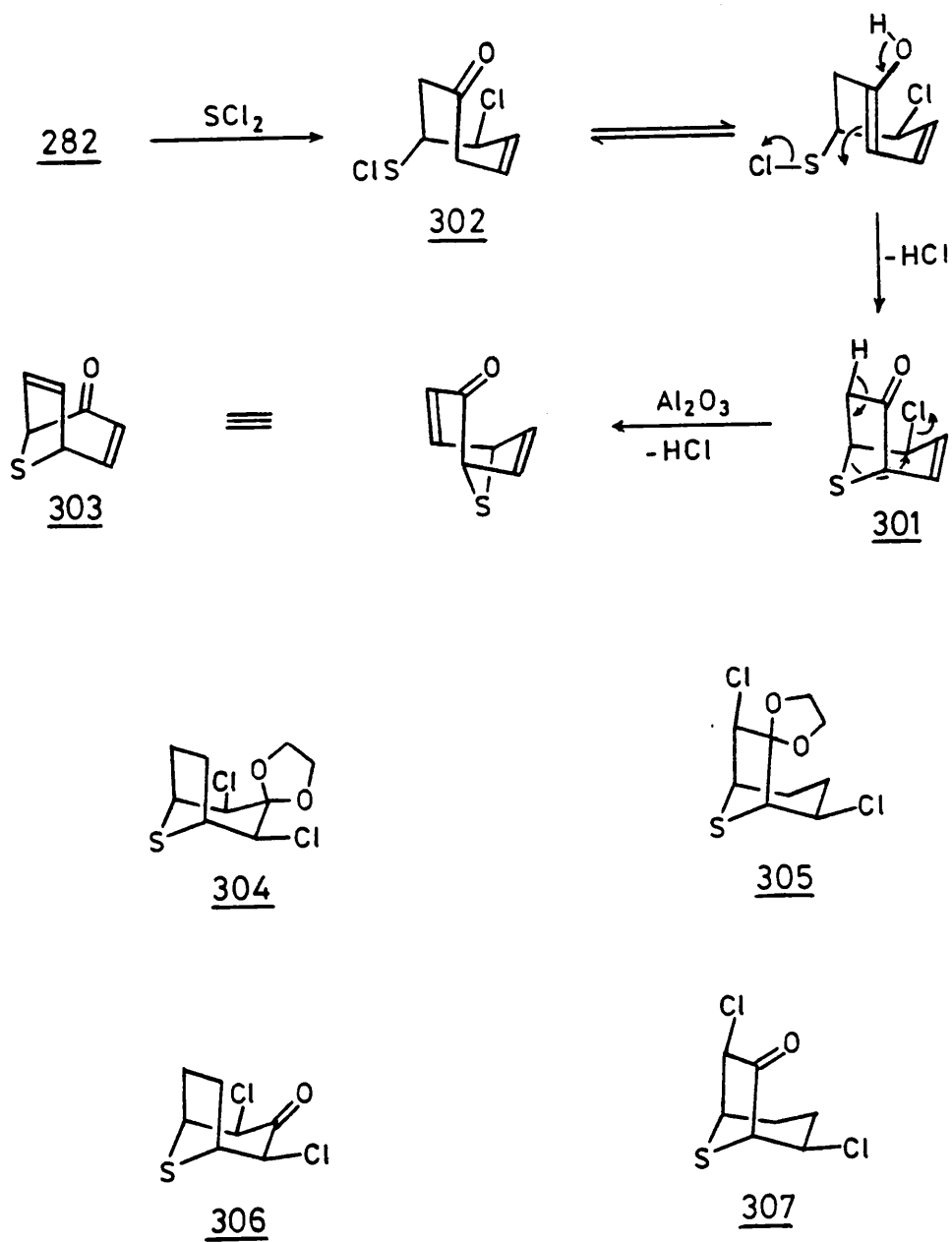
Addendum 2

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 ∂ 5.26 (C(3)H̲), coupled (11 Hz) to another
deshielded multiplet at ∂ 7.42 (1H, C(4)H̲). The remainder of
the p.m.r. spectrum consisted of two H̲-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 ∂ 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°. Microanalysis confirmed the product as a 1:1
adduct, C$_9$H$_{12}$Cl$_2$O$_2$S, 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 ∂ 3.80-4.32 in the p.m.r. spectrum. This

contrasted with the appearance as a sharp singlet (∂ 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 $C_9H_{13}ClO_3S$, 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

Scheme 93
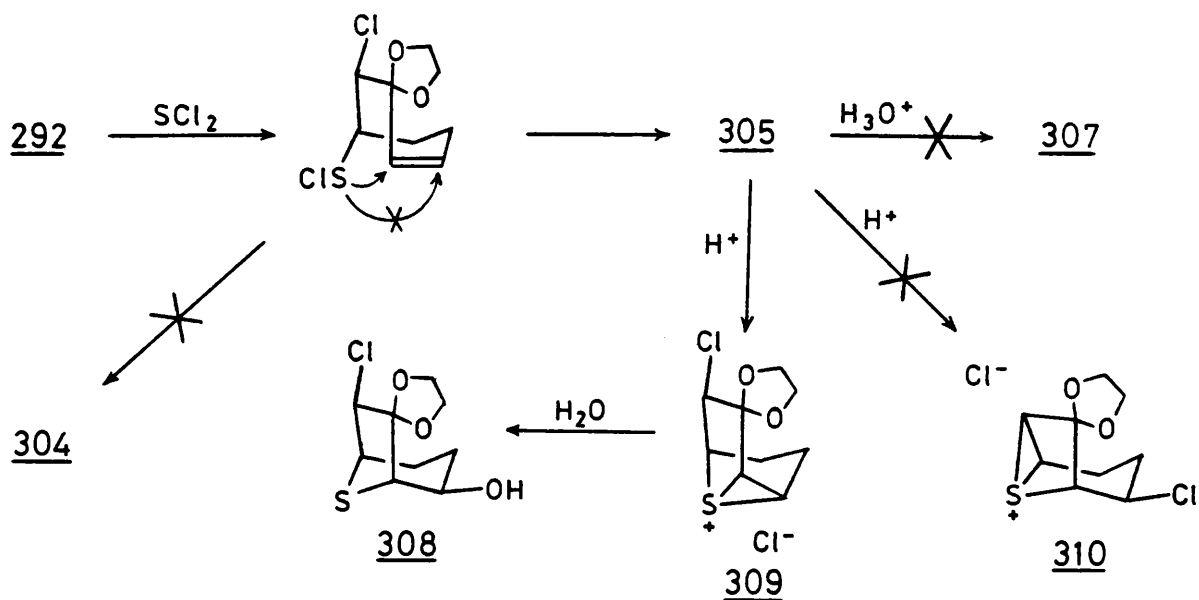
Scheme 94
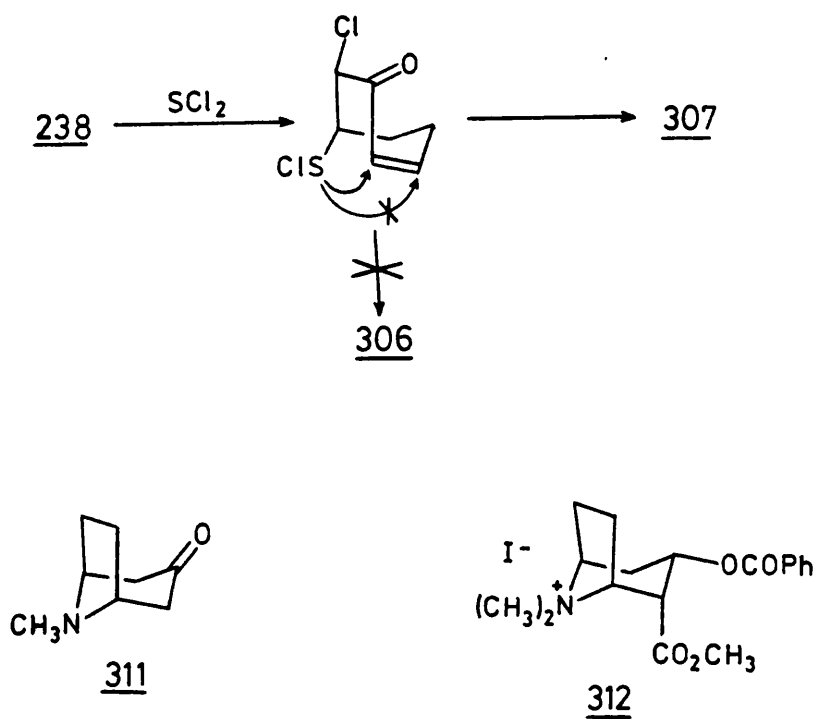
at ∂ 4.59 (J=6 Hz) showed that hydrolysis had not occurred at C(6)

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 β- to the thioether

function, hydrolysis is anchimerically assisted and proceeds through

the episulphonium intermediate (309) as in the mechanism proposed

for hydrolysis of 161[119]. Although C(6)-Cl is also β- 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_N1 mechanism.

Moreover, in S_N2 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} (ε 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 ∂ 3.63 (1H) was ascribed to C(5)H while a simpler one-proton signal at ∂ 3.70 due to C(1)H was deshielded by its proximity to a carbonyl group. Similarly, a highly split resonance at ∂ 4.47 was attributable to C(2)H while that at ∂ 4.81 resulted from C(6)H. The remainder of the spectrum consisted of a methylene envelope at ∂ 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 [204] 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)[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.[203]
m.p. 278°); ν_{max}^{KBr} 3028, 1725, 1449, 1316, 1199, 1110, 980
and 921 cm^{-1}.

8-thiabicyclo[3.2.1]octan-3-one (236)[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 O, basic).
Recrystallisation from aqueous methanol gave 236 (1.57 g, 11 mmol,
55%) m.p. 155-157° (lit.[170] m.p. 155-156°), ν_{max}^{KBr} 2940, 1707, 1460,
1398, 1327, 1200, 1039, 976 and 881 cm^{-1}; ∂ (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[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)   n-Butyl lithium-methyl chloroformate[193]

2.1 M 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.

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
(53.0g, 0.48 mol) and cycloheptatriene (259) (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); $\nu_{max}^{liq. film}$ 3010,
1710, 1633, 1576, 1520, 1470, 1247, 1210, 895, 830 and 780 cm^{-1};
∂ (CDCl$_3$) 7.13 (complex m).

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

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); $\nu_{max}^{liq. film}$ 3025, 2898, 1710, 1649, 1596, 1424, 1238, 1211,

1050, 831 and 681 cm^{-1}; ∂ (CDCl$_3$) 3.05 (d, J=6 Hz, 4H, C$\underline{H}_2$),

5.87 (m, 2H, C(4,5)$\underline{H}$) and 6.32 (m, 2H, C(3,6)$\underline{H}$).

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);

$\nu_{max}^{liq. film}$ 3354, 3012, 1892, 1615, 1439, 1048, 1012, 832 and 671 cm^{-1}

∂ (CDCl$_3$) 2.50 (m, 4H, C$\underline{H}_2$), 3.61 (m, 1H, O$\underline{H}$), 4.11 (m, 1H, C$\underline{H}$OH)

and 5.75 (m, 4H, olefinic C$\underline{H}$).

1-benzoyloxycyclohepta-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);

$\nu_{max}^{liq.\ film}$ 3005, 2940, 1712, 1600, 1446, 1267, 1104, 1015, 700

and 655 cm^{-1}; ∂ (CDCl$_3$) 1.82-3.10 (br m, 4H, C$\underline{H}_2$), 5.36 (m, 1H,

C$\underline{H}$OCOPh), 5.82 (m, 4H, olefinic C$\underline{H}$) and 7.10-8.30 (complex m, 5H,

aromatic C$\underline{H}$).

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%)

b.p. 46-49°, 0.15 mm Hg; $\nu_{max}^{liq.\ film}$ 2925, 2859, 1450, 1366, 1210,

1115, 1094, 1026, 941, 876 and 774 cm^{-1}; ∂ (CDCl$_3$) 1.30-2.07

(complex m, 12H, cycloheptane C$\underline{H}_2$) and 3.86 (s, 4H, dioxolane C$\underline{H}_2$).

Cyclohepta-2,6-dienone ethylene ketal (292)[200]

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); $\nu_{max}^{liq. film}$ 3020, 2935, 2872, 1661, 1399,

1211, 1090, 1006, 963, 820 and 791 cm^{-1}; ∂ (CDCl$_3$) 2.29 (m, 4H,

allylic C$\underline{H}_2$), 3.88 (s, 4H, dioxolane C$\underline{H}_2$), 5.60 (d, J=12 Hz, 2H,

C(2,7)$\underline{H}$) and 5.91 (m, 2H, C(3,6)$\underline{H}$).

Cyclohepta-2,6-dienone (238)[200]

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. 50.5-51°, 1.0 mm Hg); $\nu_{max}^{liq. film}$ 3011, 2932, 2898, 1646, 1608,

1426, 1404, 1360, 1286, 1253, 1185, 1158 and 843 cm^{-1}; ∂ (CDCl$_3$)

2.47 (m, 4H, C$\underline{H}_2$), 6.03 (d, J=12 Hz, C(2,7)$\underline{H}$) and 6.67 (pr m, 2H,

C(3,6)$\underline{H}$).

Reaction of cyclic dienes with sulphur dichloride[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_7H_7ClOS: 173.99062. Found: 173.99021; $\nu_{max}^{CCl_4}$ 1749 cm^{-1}; ν_{max}^{KBr} 3040, 2925, 1736, 1631, 1401, 1187, 1122, 1075, 971, 878, 770, 710 and 664 cm^{-1}; ∂ (CDCl$_3$) 2.75 (dd, J=18 and 7 Hz, 1H, C(7)$\underline{H}^s$), 3.33 (d, J= 18 Hz, 1H, C(7)$\underline{H}^a$), 3.57 (d, J=7 Hz, 1H, C(5)$\underline{H}$), 3.86 (m, J=7 Hz, 1H, C(1)$\underline{H}$), 5.24 (m, J=7 and 2 Hz, 1H, C(2)$\underline{H}$Cl), 5.75 (dt, J=10 and 2 Hz, 1H, C(3)$\underline{H}$ and 6.18 (m, J=10,7 and 2 Hz, 1H, C(4)$\underline{H}$); m/e [176 and 174] (M$^+$), 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);

v_{max}^{KBr} 1690, 1589, 1371, 1310, 1220, 1130, 918, 854, 717 and 671 cm^{-1};

∂ (CDCl$_3$) 3.95 (dd, J=7 and 4 Hz, 1H, C(5)$\underline{H}$), 4.14 (d, J=4 Hz, 1H,

C(1)$\underline{H}$), 5.26 (d, J=11 Hz, 1H, C(3)$\underline{H}$), 6.50 (dd, J=6 and 4 Hz, 1H,

C(6)$\underline{H}$), 7.02 (dd, J=6 and 4 Hz, 1H, C(7)$\underline{H}$) and 7.42 (dd, J= 11 and

7 Hz, 1H, C(4)$\underline{H}$).

2 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 $C_{14}H_{14}Cl_2O_2S$:

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%; $v_{max}^{CCl_4}$ 1726 cm^{-1} (ε 474); v_{max}^{KBr} 3028, 2940,

2920, 1721, 1600, 1275, 1111, 984, 885 and 702 cm^{-1}; ∂ (CDCl$_3$) 2.10

(m, 2H, C(2,4)$\underline{H}_2$), 2.87 (m, 2H, C(2,4)$\underline{H}_2$), 3.66 (m, 2H, C(1,5)$\underline{H}$),

4.89 (m, 2H, C(6,7)$\underline{H}$), 5.75 (m, 1H, C(3)$\underline{H}$) and 7.29-8.31 (pr m, 5H,

aromatic C$\underline{H}$); m/e [320, 318 and 316] (M^+), [283 and 281],

[198, 196 and 194], [161 and 159], [178 and 176], 141, 105, 97

and 77; $\lambda_{max}^{CH_3CN}$ 230 (log ε 4.13), 274 (2.95) and 281 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 $C_{14}H_{14}Cl_2O_2S$:

316.00913. Found: 316.00878; ν_{max}^{KBr} 3057, 2940, 2920, 2845, 1714,

1603, 1584, 1493, 1449, 1344, 1315, 1271, 1110, 941, 884, 773 and

710 cm^{-1}; ∂ (CDCl$_3$) 1.70-2.46 (m, 4H, C$\underline{H}_2$), 3.49 (m, 1H, bridgehead

C$\underline{H}$), 3.90 (m, 1H, bridgehead C$\underline{H}$), 4.94 (m, 2H, C(6,7)$\underline{H}$), 5.48 (m, 1H,

C(2)$\underline{H}$) and 7.50-8.08 (pr m, 5H, aromatic C$\underline{H}$); 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 $C_9H_{12}Cl_2O_2S$: C 42.36, H 4.74%. Found: C 42.59, H 4.70%;

ν_{max}^{KBr} 2979, 2930, 2852, 1460, 1335, 1204, 1097, 1036, 994, 950,

881, 817, 725 and 634 cm^{-1}; ∂ (CDCl$_3$) 1.91-2.83 (br env, 4H,

C(3,4)$\underline{H}_2$), 3.26 (m, 1H, C(1)$\underline{H}$), 3.40 (m, 1H, C(5)$\underline{H}$), 3.80-4.32 (m,

4H, dioxolane C$\underline{H}_2$), 4.49 (m, 1H, C(2)$\underline{H}$Cl) and 4.68 (d, J=6 Hz, 1H,

C(6)$\underline{H}$Cl); 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 $C_7H_8Cl_2OS$:

C 39.83, H 3.82%. Found: C 40.02, H 3.78%; $\nu_{max}^{CCl_4}$ 1761 cm^{-1}

(ε 480); ν_{max}^{KBr} 2990, 2949, 2878, 1750, 1439, 1346, 1223, 1120, 1006, 984, 883, 805, 744, 706 and 642 cm^{-1}; ∂ (CDCl$_3$) 1.74-2.67 (br env, 4H, C(3,4)$\underline{H}_2$), 3.63 (m, 1H, C(5)$\underline{H}$), 3.70 (m, J=6 Hz, 1H, C(1)$\underline{H}$), 4.47 (m, 1H, C(2)$\underline{H}$Cl), 4.81 (d, J=6 Hz, 1H, C(6)$\underline{H}$Cl); 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 (CHCl$_3$-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 (CHCl$_3$ - 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 C$_9$H$_{13}$ClO$_3$S: C 45.66, H 5.54%. Found: C 45.45, H 5.47%; $\nu_{max}^{CCl_4}$ 3559 (ϵ 65); ν_{max}^{KBr} 3380, 2945, 2880, 1469, 1390, 1292, 1197, 1130, 1053, 1036, 980, 950, 864, 749 and 650 cm^{-1}; ∂ (CDCl$_3$) 1.83-2.60 (br env, 4H, C(3,4)$\underline{H}_2$),

2.93 (d, J=12 Hz, 1H, O$\underline{\text{H}}$), 3.19 (m, 1H, C(1)$\underline{\text{H}}$), 3.36 (m, J=6 and

4 Hz, 1H, C(5)$\underline{\text{H}}$), 3.94 (m, J=12 and 4Hz, 1H, C(2)$\underline{\text{H}}$OH), 4.11 (m,

4H, dioxolane C$\underline{\text{H}}_2$) and 4.59 (d, J=6 Hz, 1H, C(6)$\underline{\text{H}}$Cl);

m/e [238 and 236] (M$^+$), [220 and 218], 201, 183, 149, 125, 118

and 105.

References

1   S. Landa and V. Macháček, Coll. Czech. Chem. Commun.,

       1933, 5, 1.

2   V. Prelog and R. Seiwerth, Ber., 1941, 74, 1644 and 1769.

3   P. von R. Schleyer, J. Amer. Chem. Soc., 1957, 79, 3292.

4   P. von R. Schleyer and M. M. Donaldson, ibid., 1960, 82, 4645.

5   E. I. Du Pont de Nemours & Co., Belgian Pat. 583,519 (1959).

6   H. Koch and J. Franken, Brennstoff-Chemie, 1961, 42, 90.

7   H. Hoffmann and C. H. Trottier, U.S. Pat. 3,457,317 (1969).

8   M. Nomura, P. von R. Schleyer and A. A. Arz, J. Amer. Chem.

       Soc., 1967, 89, 3657.

9   R. C. Fort Jnr. and P. von R. Schleyer, Chem. Rev., 1964, 277.

10   V. V. Sevost'yanova, M. M. Krayuskin and A. G. Yurchenko,

       Russ. Chem. Rev., 1970, 39, 817.

11   H. Stetter, Angew. Chem., 1954, 66, 217.

12   Idem, ibid., 1962, 74, 361.

13   A. Fredga, Svensk. Kem. Tidskr., 1960, 72, 151.

14   R. C. Bingham and P. von R. Schleyer, Fortschr. Chem. Forsch.,

       1971, 18.

15   "Adamantane - The Chemistry of Diamond Molecules", Studies in

       Organic Chemistry Vol. 5, R. C. Fort Jnr., Ed. P. G. Gassman,

       Marcel Dekker Inc., New York, 1976.

16   O. Böttger, Ber., 1937, 70, 314.

17   H. Meerwein and W. Schürmann, Ann., 1913, 398, 196.

18   H. Stetter, H. Held and J. Mayer, ibid., 1962, 658, 151.

19   H. Stetter and J. Mayer, Angew. Chem., 1959, 71, 430.

20   T. Mori, K. H. Yang, K. Kimoto and H. Nozaki, Tet. Lett., 1970,

       2419.

21   A. G. Yurchenko, A. T. Voroschenko and F. N. Stepanov,

       Zh. Org. Khim., 1970, 6, 189.

22   L. N. Owen and P. A. Robins, J. Chem. Soc., 1949, 327.

23   T. Kutsuma and S. Sugasawa, Tet., 1958, 3, 175.

24   H. -J. Vetter, H. Noth and W. Jahn, Z. Anorg. Allg. Chem.,
      1964, 328, 144.

25   A. Weissbach, J. Org. Chem., 1958, 23, 329.

26   Y. Kashman and E. Benary, Tet., 1972, 28, 4091.

27   F. Lautenschlaeger, J. Org. Chem., 1969, 34, 4002.

28   A. L. Smith and H. A. Clark, J. Amer. Chem. Soc., 1961, 83,
      3345.

29   H. Stetter and K. Dieminger, Ber., 1959, 92, 2658.

30   A. Domenicano, R. Spagna and A. Vaciago, Chem. Commun., 1970,
      1146.

31   F. Lions and K. V. Martin, J. Amer. Chem. Soc., 1957, 79, 1572.

32   M. Komura and R. Okawara, Inorg. Nucl. Chem. Lett., 1966, 2, 93.

33   H. Stetter and P. Tacke, Angew. Chem., 1962, 74, 354.

34   H. Stetter and E. F. Schwarz, Ber., 1968, 101, 2464.

35   N. S. Zefirov and N. V. Averina, Zh. Org. Khim., 1969, 5,
      190, 1936 and 1991.

36   N. S. Zefirov, V. A. Tartakovskii and N. V. Averina, ibid.,
      1971, 7, 504.

37   A. Hamill, A. Karim and M. A. McKervey, Tet., 1971, 27, 4317.

38   A. R. Gagneux and R. Meier, Tet. Lett., 1969, 1365.

39   H. Stetter, P. Tacke and J. Gärtner, Ber., 1964, 97, 3480.

40   J. Cable and J. K. MacLeod, Austral. J. Chem., 1973, 26, 2147.

41   H. Stetter and K. Komorowski, Ber., 1971, 104, 75.

42   H. Dietrich (J. R. Geigy A.-G.), S. Afr. Pat. 6,803,012 (1968).

43   H. Stetter, J. Gärtner and P. Tacke, Ber., 1966, 99, 1435.

44   K. Gerzon and D. Kau, J. Med. Chem., 1967, 10, 189.

45   F. N. Stepanov, T. N. Utochka, and A. G. Yurchenko,
     Zh. Org. Khim., 1972, 8, 1183.

46   T. N Utochka, A. G. Yurchenko, S. D. Isaev and F. N Stepanov,
     ibid., 1974, 10, 59.

47   J. P. Schaefer and L. M. Honig, J. Org. Chem., 1968, 33, 2655.

48   N. V. Averina and N. S. Zefirov, Chem. Commun., 1973, 197.

49   N. S. Zefirov, Zh. Org. Khim., 1975, 11, 77.

50   R. M. Black, G. B. Gill and D. Hands, Chem Commun., 1972, 311.

51   M. Fisch, S. Smallcombe, J. C. Gramaine, M. A. McKervey and
     J. E. Anderson, J. Org. Chem., 1970, 35, 1886.

52   G. B. Gill and R. M. Black, Chem Commun., 1971, 172.

53   H. Stetter, H. -J. Meissner and W. D. Last, Ber., 1968, 101,
     2889.

54   N. V. Averina, N. S. Zefirov, P. Kadzyauskas, S. V. Rogozina,
     N. K. Sadovaya and N. M. Soldatov, Zh. Org. Khim., 1974, 10,
     1442.

55   E. Cuthbertson and D. D. McNicol, Tet. Lett., 1974, 2367.

56   J. F. H. Braams, H. J. T. Bos and F. Arens, Rec. Trav. Chim.,
     1968, 87, 193.

57   J. A. Kanters and J. B. Hulscher, ibid., 1968, 87, 201.

58   H. Stetter and R. Hesse, Monatsh., 1967, 98, 755.

59   H. Stetter and K. H. Steinacker, Ber., 1953, 86, 790.

60   Idem, ibid., 1954, 87, 205.

61   H. Stetter and M. Dohr, ibid., 1953, 86 589.

62   H. Stetter and S. Vestner, ibid., 1964, 97, 169.

63   L. Dolesj and Z. Arnold, Coll. Czech. Chem. Commun., 1966,
     31, 4187.

64   S. -O. Almqvist, Acta Chem. Scand., 1968, 22, 1367.

65   S. F. Birch, T. V. Cullum, R. A. Dean and R. L. Denyer,

      Nature, 1952, 170, 629.

66   S. F. Birch, J. Inst. Petrol., 1953, 39, 185.

67   H. Stetter and H. Held, Angew. Chem., 1961, 73, 114.

68   H. Stetter, H. Held and A. Schulte-Oestrich, Ber., 1962, 95,

      1687.

69   S. Landa and J. Janků, Coll. Czech. Chem. Commun., 1969, 34,

      2014.

70   Idem, ibid., 1972, 37, 2269.

71   G. Snatzke and B. Wolfram, Tet., 1972, 28, 655.

72   F. Klages and H. Schmidt, Ber., 1963, 96, 2063.

73   P. Y. Blanc, P. Diehl, H. Fritz and P. Schläpfler,

      Experientia, 1967, 23, 896.

74   F. Lautenschlaeger, J. Org. Chem., 1968, 33, 2627.

75   T. Higuchi and W. Nowacki, Z. Kristallogr., Kristallgeom.,

      Kristallphys., Kristallchem., 1972, 135, 56.

76   S. -O. Almqvist and K. Olsson, Chemica Scripta, 1971, 1, 30.

77   E. Fromm and P. Ziersh, Ber., 1906, 39, 3599.

78   A. Fredga and A. Brandstrom, Ark. Kemi., 1950, 1, 197.

79   K. Olsson, ibid., 1966, 26, 465; idem, ibid., 1967, 28, 53;

      A Brandstrom, ibid., 1952, 3, 41.

80   D. L. Coffen, Rec. Chem. Prog., 1969, 30, 275.

81   K. Olsson, Acta Chem. Scand., 1968, 22, 2390.

82   A. Fredga and K. Olsson, Ark. Kemi., 1956, 9, 163.

83   E. K. Andersen and I. Lindqvist, ibid., 1956, 9, 169.

84   J. Bongartz, Ber., 1886, 19, 2182.

85 P. Candiani, Gazz. Chim. Ital., 1895, 25, 81.

86 R. W. Borgeson and J. A. Wilkinson, J. Amer. Chem. Soc.,

    1929, 51, 1455.

87 A. Fredga and H. Bauer, Ark. Kemi., 1951, 2, 113.

88 R. Fusco and G. Bianchetti, Gazz. Chim. Ital., 1956, 86, 500.

89 M. S. Newman and H. S. Lowrie, J. Amer. Chem. Soc., 1954,

    76, 4598.

90 R. Lukes and V. Galik, Coll. Czech. Chem. Commun., 1954,

    19, 712.

91 V. Galik, Z. Kafka, M. Safar and S. Landa, ibid., 1974, 39,

    895.

92 W. N. Speckamp, J. Dijkink and H. O. Huisman, Chem. Commun.,

    1970, 196; A. W. J. D. Dekkers, W. N. Speckamp and

    H. O Huisman, Tet. Lett., 1971, 489; W. N. Speckamp,

    J. Dijkink, A. W. J. D. Dekkers and H. O. Huisman, Tet.,

    1971, 27, 3143.

93 H. Stetter and W. Reinartz, Ber., 1972, 105, 2773.

94 H. Stetter and K. Heckel, Tet. Lett., 1972, 1907.

95 G. Snatzke and H. Seidler, ibid., 1969, 5135.

96 H. Stetter and H. Hennig, Ber., 1955, 88, 789.

97 F. Galvinosky and H. Langer, Monatsh., 1955, 86, 449.

98 R. L. Vittory, G. Settimj, F. Gatta, N. Sarti and

    S. Chiavarelli, Gazz. Chim. Ital., 1967, 97, 1294.

99 H. Stetter and K. Heckel, Tet. Lett., 1972, 801; idem,

    Ber., 1973, 106, 339.

100 R. E. Portmann and C. Ganter, Helv. Chim. Acta, 1973, 56, 1962.

101 R. -M. Dupeyre and A. Rassat, Tet. Lett., 1973, 2699.

102 H. Stetter and W. Böckmann, Ber., 1951, 84, 834.

103 D. A. Durham, F. A. Hart and D. Shaw, J. Inorg. Nucl. Chem.,

    1967, 29, 509.

104   N. W. Gabel, U.S. Pat. 3,301,854 (1967).

105   E. B. Hodge, J. Org. Chem., 1972, 37, 320.

106   H. Stetter, D. Theisen and G. J. Steffens, Ber., 1970, 103, 200.

107   P. Duden and M. Scharff, Ann., 1895, 288, 218.

108   L. Field, Synthesis, 1972, 101.

109   H. -D. Becker, G. J. Mikol and G. A. Russell, J. Amer. Chem. Soc., 1963, 85, 3410; E. J. Corey and M. Chaykovsky, ibid., 1965, 87, 1345.

110   G. A. Russell and L. A. Ochrymowycz, J. Org. Chem., 1969, 34, 764.

111   C. Ganter and J. -F. Moser, Helv. Chim. Acta, 1971, 54, 2228.

112   Idem, ibid., 1968, 51, 300.

113   A. Padwa and A. Battisti, J. Amer. Chem. Soc., 1971, 93, 1304.

114   J. M. Mellor and C. F. Webb, J. Chem. Soc. Perkin 1, 1972, 211.

115   P. A. Knott and J. M. Mellor, Tet. Lett., 1970, 1829.

116   R. Curci, A. Giovine and G. Modena, Tet., 1966, 22, 1235; G. A. Russell and L. A. Ochrymowycz, J. Org. Chem., 1970, 35, 2106.

117   D. D. MacNicol, P. H. McCabe and R. A. Raphael, Synth. Commun., 1972, 2, 185.

118   E. J. Corey and E. Block, J. Org. Chem., 1966, 31, 1663.

119   E. D. Weil, K. J. Smith and R. J. Gruber, ibid., 1966, 31, 1669.

120   A. C. Cope, B. S. Fisher, W. Funke, J. M. McIntosh and M. A. McKervey, ibid., 1969, 34, 2231.

121   R. Ratcliffe and R. Rodehorst, ibid., 1970, 35, 4000.

122   K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 1946, 39.

123   K. E. Pfitzner and J. G. Moffatt, J. Amer. Chem. Soc., 1963, 85, 3027.

124   J. D. Albright and L. Goldman, ibid., 1965, 87, 4214.

125   R. Pummerer, Ber., 1909, 42, 2282; idem, ibid., 1910, 43, 1401.

126   G. Snatzke, ibid., 1961, 94, 729.

127   N. C. Deno and N. H. Potter, J. Amer. Chem. Soc., 1967, 89,
       3550.

128   C. Djerassi, Chem. Rev., 1948, 43, 271.

129   H. O. House, "Modern Synthetic Reactions, 2nd Edn.", Benjamin,
       Menlo Park, California, 1972, pp 772-782.

130   E. E. Royals, J. Amer. Chem. Soc., 1948, 70, 489;   E. E. Royals,
       J. C. Hoppe, A. D. Jordan Jnr. and A. G. Robinson III, ibid.,
       1951, 73, 5857.

131   E. E. Royals and D. G. Turpin, ibid., 1954, 76, 5452.

132   N. Green and F. B. LaForge, ibid., 1948, 70, 2287;   J. D. Hobson,
       J. Raines and R. J. Whiteoak, J. Chem. Soc., 1963, 3495.

133   P. Z. Bedoukian, J. Amer. Chem. Soc., 1945, 67, 1430.

134   C. R. Hauser and J. T. Adams, ibid., 1944, 66, 345;   idem,
       ibid., 1945, 67, 284;   H. S. Booth and D. R. Martin,
       "Boron Trifluoride and its Derivatives", Wiley, New York,
       1949;   C. R. Hauser, F. C. Frostick Jnr. and E. H. Man,
       J. Amer. Chem. Soc., 1952, 74, 3231;   R. M. Manyik,
       F. C. Frostick Jnr., J. J. Sanderson and C. R. Hauser, ibid.,
       1953, 75, 5030;   C. R. Hauser, F. W. Swamer and J. T. Adams,
       Org. Reactions, 1954, 8, 59.

135   L. F. Fieser and E. B. Hershberg, J. Amer. Chem. Soc., 1939,
       61, 1272;   idem, ibid., 1940, 62, 49;   W. S. Johnson, Org.
       Reactions, 1944, 2, 114.

136   H. Meerwein, F. Kiel, G. Klosgen and S. Schoch, J. Prakt.
       Chem., 1922, 104, 161.

137   P. H. McCabe, unpublished.

138   L. A. Paquette and L. D. Wise, J. Amer. Chem. Soc., 1967, 89, 6659.

139   J. R. Dyer, "Applications of Absorption Spectroscopy of

Organic Compounds", Prentice Hall, Englewood Cliffs,

New Jersey, 1965.

140   G. M. Barrow, "Introduction to Molecular Spectroscopy",

McGraw-Hill, New York, 1962.

141   For a recent review of the uses of Lanthanide shift reagents,

see M. I. Foreman in Specialist Periodical Reports of The

Chemical Society, "Nuclear Magnetic Resonance", Vols. 1-6,

1972-1977.

142   C. R. Nelson, Ph.D. Thesis, Univ. of Glasgow, 1977.

143   P. H. McCabe and C. R. Nelson, J. Mag. Res., 1976, 22, 183.

144   D. H. Williams and I. Fleming, "Spectroscopic Methods in

Organic Chemistry", McGraw-Hill, London, 1966.

145   P. H. McCabe, C. R. Nelson and W. Routledge, Tetrahedron,

1977, 33, 1749 and 1755.

146   D. V. Banthorpe, "Elimination Reactions", Elsevier, London,

1963, p 145.

147   P. H. McCabe and W. Routledge, Tet. Lett., 1973, 3919.

148   H. Stetter and H. G. Thomas, Ber., 1966, 99, 920.

149   R. O. Duthaler, K. Wicker, P. Ackermann and C. Ganter, Helv.

Chim. Acta, 1972, 55, 1809.

150   D. J. Pasto and C. R. Johnson, "Organic Structure Determination",

Prentice-Hall, Englewood Cliffs, New Jersey, 1969.

151   D. J. Pasto and C. C. Cumbo, J. Org. Chem., 1965, 30, 1271.

152   R. E. Portmann and C. Ganter, Helv. Chim. Acta, 1973, 56, 1991.

153   D. D. Perrin, W. L. F. Armarego and D. R. Perrin,

"Purification of Laboratory Chemicals", Pergamon, Oxford, 1966.

154   E. D. Weil (Hooker Chemicals Corp.), U.S. Pat. 3,574,233 (1971).

155   E. Cuthbertson and D. D. MacNicol, J. Chem. Soc. Perkin I,

        1974, 1893.

156   W. S. Johnson, W. A. Vredenburgh and J. E. Pike, J. Amer. Chem.

        Soc., 1960, $\underline{82}$, 3409; E. R. H. Jones, G. Eglinton,

        M. C. Whiting and B. L. Shaw, Org. Synth. Coll. Vol. IV,

        404; E. W. Warnhoff, D. G. Martin and W. S. Johnson, ibid.,

        162; J. P. Schaefer and L. Endres, Org. Synth., 1967,

        $\underline{47}$, 31.

157   H. M. Gilow and J. H. Ridd,   J. Org. Chem., 1974, $\underline{39}$, 3481.

158   P. H. McCabe and C. M. Livingston, Tet. Lett., 1973, 3029;

        C. M. Livingston, Ph.D. Thesis, Univ. of Glasgow, 1975.

159   J. A. J. M. Vincent, P. Schipper, Ae. de Groot and H. M. Buck,

        Tet. Lett., 1975, 1989; J. A. J. M. Vincent, F. P. M. Vereyken,

        B. G. M. Wauben and H. M. Buck, J. Royal Neth. Chem. Soc.,

        1976, $\underline{95}$, 236.

160   H. Franz, H Höbold, R. Höhn, G. Müller-Hagen, R. Müller,

        W. Prtizkow and H. Schmidt, J. Prakt. Chem., 1970, $\underline{312}$, 622.

161   A. C. Cope and R. D. Bach, Org. Synth. Coll. Vol. V, 315.

162   A. Stewart, Ph.D. Thesis, Univ. of Glasgow, unpublished.

163   P. H. McCabe, C. M. Livingston and A. Stewart, J. Chem. Soc.

        Chem. Commun., 1977, 661.

164   H. C. Brown and I. Moritani, J. Amer. Chem. Soc., 1953, $\underline{75}$,

        4112.

165   M. S. Newman, "Steric Effects in Organic Chemistry",

        John Wiley and Sons, New York, 1956, p. 338.

166   C. C. Price and W. H. Snyder, J. Amer. Chem. Soc., 1961, $\underline{83}$,

        1773; J. Cunningham, R. Gigg and C. D. Warren, Tet. Lett.,

        1964, 1191; L. F. Fieser and M. Fieser, "Reagents for

        Organic Synthesis", John Wiley and Sons, New York, 1967, p. 300.

167 Dunlop Rubber Co. Ltd., French Pat. 1,428,686 (1965).

168 S. F. Birch, T. V. Callum, R. A. Dean, and R. L. Denyer,
     Ind. Eng. Chem., 1955, $\underline{47}$, 240.

169 S. F. Birch, R. A. Dean, N. J. Hunter and E. V. Whitehead,
     J. Org. Chem., 1957, $\underline{22}$, 1590; S. F. Birch, T. V. Callum
     and R. A. Dean, Chem. Data Ser., 1958, $\underline{3}$, 359.

170 V. Horák, J. Závada and A. Piskala, Chem. and Ind., 1958,
     1113; idem, Acta Chim. Acad. Sci. Hung., 1959, $\underline{21}$, 97;
     V. Horák, Czech. Pat. 91,154 (1959).

171 V. Horák and P. Zuman, Tet. Lett., 1961, 746; V. Horak,
     Coll. Czech. Chem. Commun., 1963, $\underline{28}$, 1614.

172 R. E. Ireland and H. A. Smith, Chem. and Ind., 1959, 1252.

173 V. Horák and J. Závada, Coll. Czech. Chem. Commun., 1962,
     $\underline{27}$, 1224.

174 P. Y. Johnson, E. Koza and R. E. Kohrman, J. Org. Chem., 1973,
     $\underline{38}$, 2967.

175 M. R. Bell (Sterling Drug Inc.), U.S. Pat. 3,396,162 (1968).

176 L. D. Wise and G. C. Morrison, U.S. Pat. 3,763,185 (1973);
     L. D. Wise, G. C. Morrison, K. Egan, M. A. Commarato,
     G. Kopia and E. C. LaHime, J. Med. Chem., 1974, $\underline{17}$, 1232.

177 L. A. Paquette and R. W. Houser, J. Amer. Chem. Soc., 1969,
     $\underline{91}$, 3870.

178 T. Yamaguchi, K. Nagai and O. Itabashi, Kobunshi Kagaku, 1973,
     $\underline{30}$, 464.

179 H. Tsuruta, M. Ogasawara and T. Mukai, Chem. Lett., 1974, 887.

180 F. Guthrie, Quart. J. Chem. Soc., 1860, $\underline{12}$, 109; idem, ibid.,
     1861, $\underline{13}$, 129.

181 F. Lautenschlaeger, J. Org. Chem., 1966, 31, 1679; idem,

The Princeton University Conference on the Chemistry of

Sulphides, 1966, 73.

182 Idem, J. Org. Chem., 1968, 33, 2620.

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

184 J. B. Conant, E. B. Hartshorn and G. O Richardson, J. Amer.

Chem. Soc., 1920, 42, 585.

185 E. K. Marshall Jnr., J. Amer. Med. Assoc., 1919, 73, 684.

186 H. J. Backer and J. Strating, Rec. Trav. Chim., 1935, 54, 52.

187 K. E. Schulte, H. Walker and L. Rolf, Tet. Lett., 1967, 4819;

T. J. Barton and R. G. Zika, J. Org. Chem., 1970, 35, 1729.

188 M. Mühlstädt, P. Schneider and D. Martinetz, J. Prakt. Chem.,

1973, 315, 935.

189 K. Pilgram, J. Org. Chem., 1970, 35, 1165.

190 A. Kristinsson, Tet. Lett., 1973, 4489.

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

192 E. J. Corey, R. B. Mitra and H. Uda, J. Amer. Chem. Soc.,

1964, 86, 485.

193 A. Michael and N. Weiner, J. Org. Chem., 1938, 3, 372.

194 O. L. Chapman, D. J. Pasto and A. A. Griswold, J. Amer. Chem.

Soc., 1962, 84, 1213.

195 D. I. Schuster, J. M. Palmer and S. C. Dickerman, J. Org. Chem.,

1966, 31, 4281; D. I. Schuster, B. R. Sckolnick and

F. -T. H. Lee, J. Amer. Chem. Soc., 1968, 90, 1300.

196 P. Radlick, J. Org. Chem., 1964, 29, 960.

197 W. W. Flood, Ph.D. Thesis, Univ. of Glasgow, 1971.

198 J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, J. Amer.

Chem. Soc., 1955, 77, 4401.

199   A. C. Cope, M. R. Kinter and R. T. Keller, J. Amer. Chem.

      Soc., 1954, 76, 2757;   E. A. Brande and E. A. Evans, J. Chem.

      Soc., 1954, 607;   H. Adler and F. H. Flock, Ber., 1956, 89,

      1732;   W. F. Gannon and H. O. House, Org. Synth., 1960, 40,

      14;   K. L. Williamson, R. T. Keller, G. S. Fonken,

      J. Szmuszkovicz and W. S. Johnson, J. Org. Chem., 1962,

      27, 1612.

200   E. W. Garbisch Jnr., J. Org. Chem., 1965, 30, 2109.

201   A. Delisle, Ber., 1887, 20, 2008.

202   K. G. Naik and S. A. Vaishnav, J. Ind. Chem. Soc., 1936, 13,

      25 and 28.

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

204   P.H. McCabe and W. Routledge, Tet. Lett., 1976, 85.