SYNTHETIC AND CONFORMATIONAL STUDIES

OF CYCLIC SYSTEMS

Thesis submitted for the Degree of Doctor of Philosophy

in the Faculty of Science, University of Glasgow

by Eric Cuthbertson, B.Sc.

Chemistry Department, October 1974.

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ERRATA

Page 1, line 1: for survey on read survey of.

Page 2, line 13: delete colon.

Page 9, line 19: read the deuterated cycloheptanone...

Page 10, line 15: read the presence of lone-pairs...

Page 23, line 4: read consistent with a non-planar...

Page 29, line 3: read has been briefly mentioned...

lines 4,5: delete first two commas.

line 19: for -70° read -60°.

Page 74, line 9: for (III) read (XI).

Page 87, line 11: for HBr read HCl.

Page 91, line 19: for (36) read (37).

Page 109, line 7: read of an element...

Page 119, line 24: read This did not lead...

Page 133, line 11: read absence of high-resolution...

Acknowledgments.

I wish to record my sincere thanks to Dr. D.D. MacNicol, whose helpful supervision during the past three years I have greatly appreciated. I thank the technical staff of the Chemistry Department, particularly Mr. J. Gall for excellent 100 MHz n.m.r. services, Mrs. F. Lawrie and her staff for infra-red and 60 MHz n.m.r. spectra, Mr. A. Ritchie for mass spectra, Miss F.G. Cowan and Mrs. W.W. Harkness for microanalyses, and Mr. D. Walker for g.l.c. services. I also acknowledge the invaluable contributions of Dr. R.K. Mackenzie to the n.m.r. studies, particularly in developing and modifying the necessary computer programs, and of Dr. A.D.U. Hardy for an X-ray analysis.

Finally, I wish to thank the University of Glasgow for a Research Scholarship.

CONTENTS

SUMMARY

Part I begins with a literature survey on the conformations of unfused seven-membered ring systems. The preparation of a series of seven-membered heterocycles containing a cis-azine grouping is then described. The reaction of a hindered diketosulphide with hydrazine led to the expected 2,7-dihydro-1,4,5-thiadiazepine or several other products one of which contains the novel 8-oxa-3-thia-6,7-diazabicyclo[3.2.1] octane ring system. The crystal-structure and reactivity of this compound are discussed.

The determination, by the kinetic ^{1}H n.m.r. method, of the barriers to ring-inversion in the cyclic azines is then described, values between 12.1 and 21.1 kcal/mole being found. The likely conformational equilibrium, and the electronic and steric effects influencing the relative magnitudes of the barriers, are considered. The free-energy barrier for eucarvone is found to be consistent with the greater conformational mobility expected for seven-membered carbocyclic 1,3-dienes. A few other related kinetic n.m.r. studies are also reported.

In Part II, after a review of the preparation and synthetic applications of 9-heterobicyclo[3.3.1] nonane derivatives, studies of the reactions of syn-3,7-dibromo-cis,cis-cycloocta-1,5-diene are described. These include routes to dioxaadamantane

and to several 9-heterobicyclo[3.3.1]nona-2,6-dienes, as well as a [3.3.1] carbocycle. The formation of the fluxional bicyclo[5.1.0]octa-2,5-diene by three different routes was discovered, including tellurium extrusion from 9-tellurabicyclo[3.3.1]nona- 2,6-diene; pyrolysis of other cyclic tellurides was also studied.

Attempts to prepare bicyclo[3.3.2] and [3.3.3] systems from the dibromo-cyclooctadiene were unsuccessful, but in two cases, the novel 8,10-dithiabicyclo[5.3.1]undeca-2,5-diene ring system was formed by a rearrangement.

The final sections describe: studies of the mass spectral fragmentation of some 9-heterobicyclo[3.3.1] nona-2,6-dienes, ^{1}H n.m.r. studies of such systems and their conformational implications, and lastly, ^{1}H n.m.r. studies of the 8,10-dithiabicyclo[5.3.1] undeca-2,5-diene system, from which its preferred conformation in solution is deduced.

PART I.

Synthesis, Reactivity, and Ring-inversion of Some Seven-membered Carbocycles and Heterocycles.

Introduction.

The Conformations of Seven-membered Rings.

This introduction surveys the literature on the conformations of unfused carbocyclic and heterocyclic seven-membered systems. Benzo-fused derivatives are only considered where they illustrate features not adequately studied elsewhere. The only comprehensive review to date is that of Tochtermann[1], although the reviews of Binsch[2] and Sutherland[3] contain useful, brief surveys of seven-membered cyclic systems.

Cycloheptanes.

Only in the last fifteen years has conformational analysis been extended to seven-membered rings. Yet, as early as 1922, Mohr[4] had suggested two possible three-dimensional representations of cycloheptane, a chair and a boat, both plane-symmetrical, and with bond angles of 109.5°. These he believed to be strain-free, since only Baeyer angle strain was considered. The factors which determine molecular

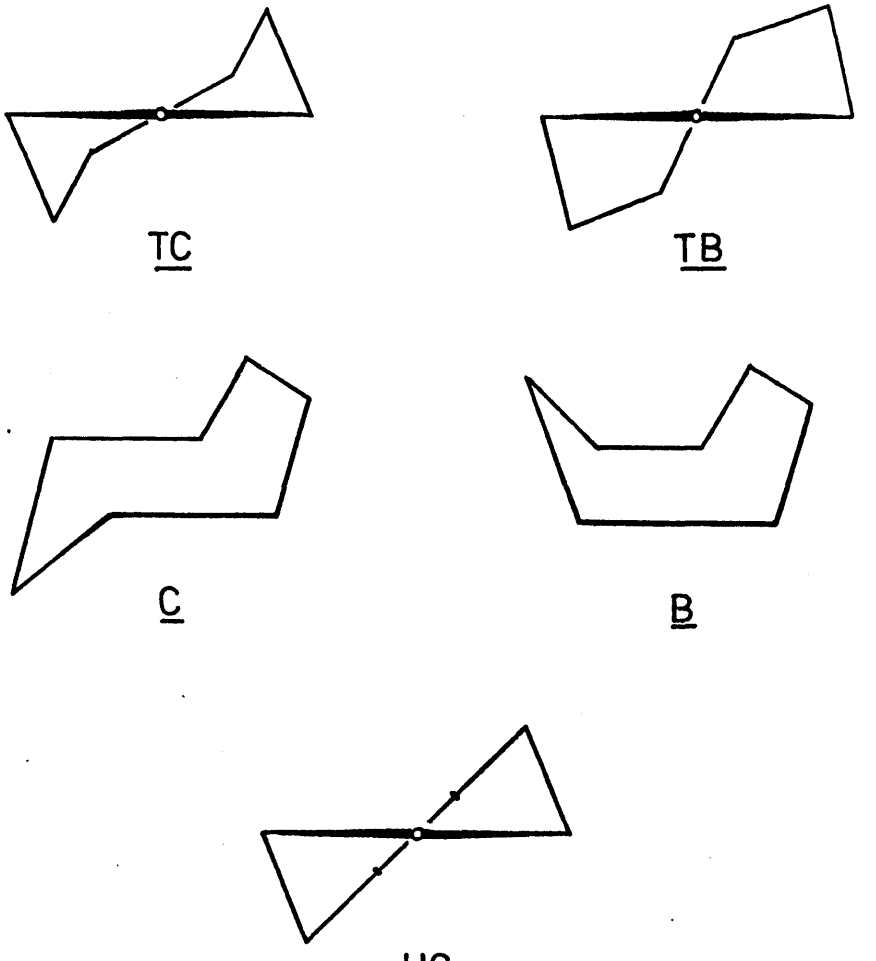


Fig 1

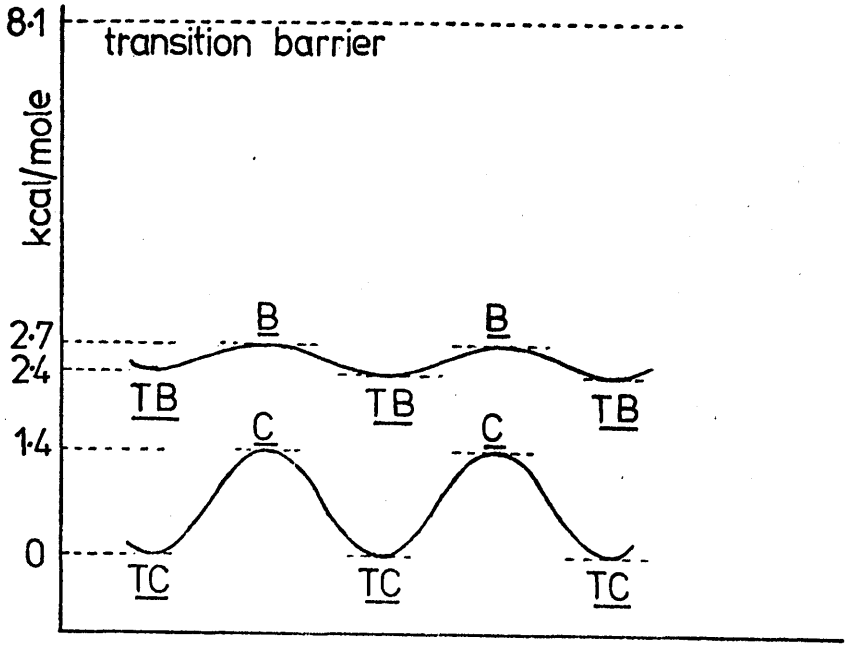


Fig 2 Cycloheptane energy profile

conformations are now much better understood, so that, in addition to bond-angle strain, there has to be consideration of torsional or eclipsing (Pitzer) strain, non-bond interactions (Van der Waals repulsion or attraction), and, to a much lesser extent, bond-length strain (bond stretching or compression).

Attempts were made to allow for some of these factors when the conformation of cycloheptane again came to be considered. Early approximate calculations by Allinger[5] and by Pauncz and Ginsburg[6] were soon superseded by the first of Hendrickson's papers[7] containing the results of detailed computer-assisted strain energy calculations, which have since been[8-10] extended and further refined. The lowest-energy conformation of cycloheptane was calculated to be a twist-chair with C_2 symmetry (TC in fig. 1), which can undergo a very facile pseudorotation process (barrier estimated[10] at 1.4 Kcal/mole) via the chair with C_s symmetry (C in fig. 1) to a second, equivalent TC conformation, which can then continue the pseudorotation cycle. Equivalent twist-boats with C_2 symmetry (TB in fig. 1) can also pseudorotate (barrier 0.3 kcal/mole) via the boat with C_s symmetry (B in fig. 1). Interconversion between C-TC and B-TB families, however, requires more severe angle deformation, and the activation barrier for this "ring-flip" process (via the half-chair HC) was estimated to be 8.1 Kcal/mole. The TC was calculated to be 2.4 Kcal/mole more stable than the TB. These results are represented in fig. 2.

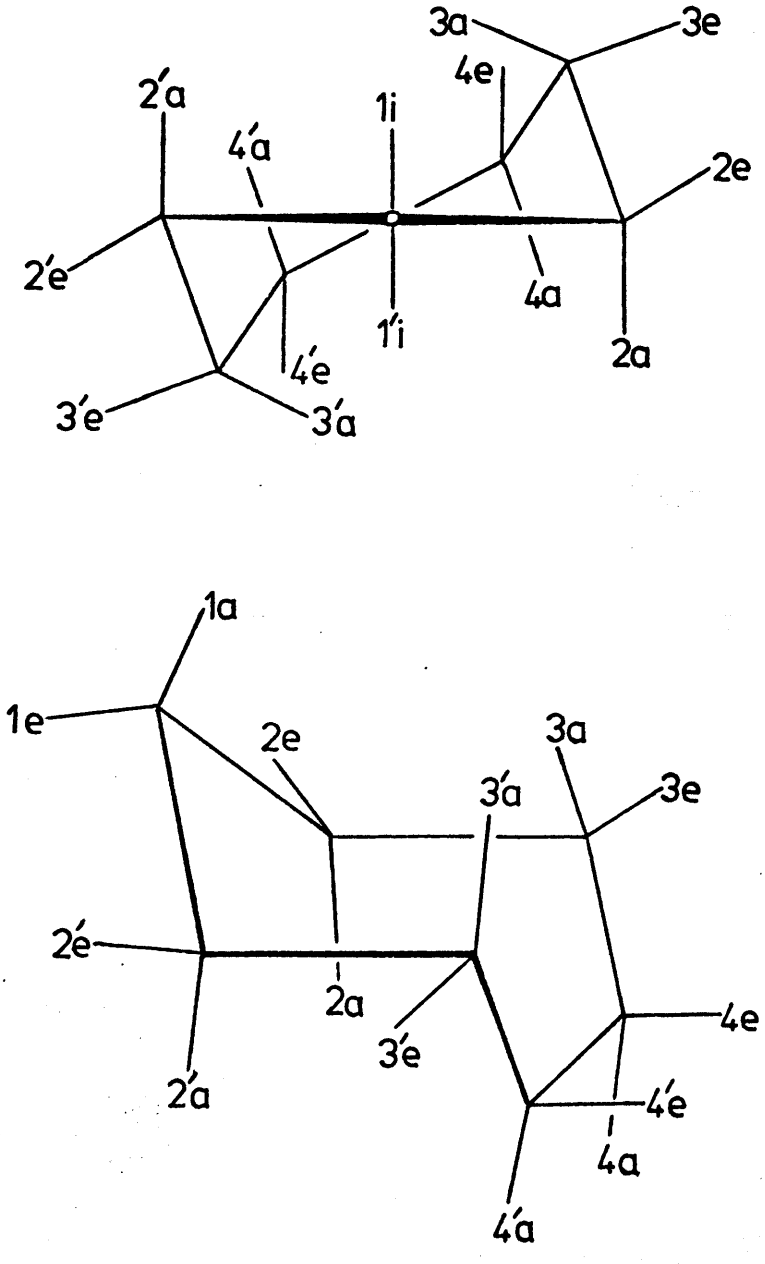

3a
3e
4e
2'a
1i
4'a
2e
2'e
4a
1'i
2a
4'e
3'e
3'a
1a
1e
2e
3a
3'a
3e
2'e
2a
4e
3'e
2'a
4'e
4a
4'a

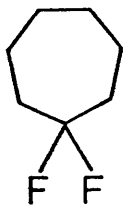
Fig 3

The TC conformation has endocyclic bond-angles which vary[10] between 113° and 116°, though this does not imply as much angle-opening as was once supposed, since the zero-strain C-C-C bond-angle is now known[9,10] to be about 112.5°, not 109.5°.

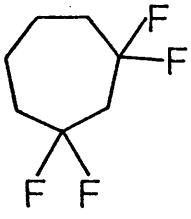
TC cycloheptane has 7 distinct substitution positions[7], which can be labelled axial (a), equatorial (e), or isoclinal (i) (fig. 3). The relative steric hindrance to substituents in these positions is: 2e, 3e, 4e < 1i < 4a < 2a, 3a. The C conformation has 8 distinct substitution positions of relative energies: 1e, 2e, 3e < 4e < 1a, 2a, 4a ≪ 3a. The conformational analysis of substituted cycloheptanes is dominated by the severe steric compression experienced by a substituent in the 3a (C) position owing to the proximity of the 3′a atom. Pseudorotation exchanges a substituent between each one of the TC and C positions, and for a large substituent, pseudorotation through the 3a (C) position may have such a high barrier that it may be energetically more favourable for the ring to flip into the B-TB series, undergo partial pseudorotation, and then reconvert to the C-TC family.

Experimental results obtained for cycloheptane derivatives have been readily interpretable on the basis of Hendrickson's conclusions. Roberts and coworkers have exploited the large chemical shifts characteristic of ^{19}F n.m.r. to investigate conformational processes[11].

The ^{1}H-decoupled ^{19}F resonances of 1,1-difluorocycloheptane (1) and 1,1,3,3-tetrafluorocycloheptane (2) showed no kinetic broadening at -170° and -150° respectively, indicating fast pseudorotation with an energy barrier of less than 5 Kcal/mole. By examining compounds with bulkier substituents, the conformational possibilities can be limited, since the larger groups will prefer the 2e, 3e, 4e, and 1i positions in the TC ground state[8,10]. Thus, 4,4-difluoro-1,1-dimethylcycloheptane (3) will prefer to have its methyl groups in the equivalent 1i positions



(1)



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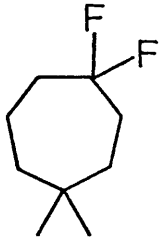


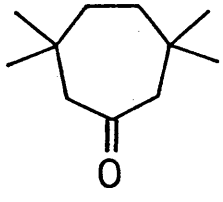
(3)

(fig. 3). ^{19}F n.m.r.[11] of (3) revealed a conformational equilibrium with a free energy of activation ($\Delta G^{\neq}$) of 5.0 Kcal/mole at -150°. This increased barrier probably derives from a 3a - 3'a methyl-fluorine interaction in one of the C conformers of the pseudorotation cycle.

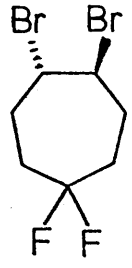
^{1}H n.m.r.[12] of 3,3,6,6-tetramethylcycloheptanone (4) gave a value for $\Delta G^{\neq}$ of 8.5 Kcal/mole at -85°. In this case, a complete pseudorotation cycle in the C-TC series involves a very severe 3a-3'a (C) methyl-methyl interaction. Approximate calculations[13] put the barrier at about 14 Kcal/mole, while steric

crowding in the ground state may reduce the barrier to the ring-flip process to about 6-7 Kcal/mole. It has therefore been suggested that the observed kinetic process is a composite one, consisting of partial pseudorotation in the C-TC series, ring flip, partial pseudorotation in the B-TB series, and ring-flip back to the C-TC series. The observed barrier in compound (3) may also be of such a composite nature[11,13].

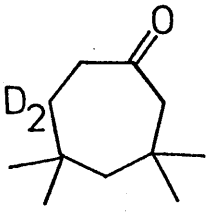
A further interesting example is 1,1-difluoro-trans-4,5-dibromocycloheptane (5), the low-temperature ^{19}F spectrum of which[11] corresponds to a mixture of two different TC conformers of nearly equal energies. Interconversion between them ($\Delta H^{\neq}$= 9.8 Kcal/mole) is again thought to proceed via the B-TB series.



(4)



(5)



(6)

The use of specific deuteration in conjunction with deuterium-decoupled ^{1}H n.m.r. has also been of value in the investigation of conformational processes; the deuterated dycloheptanone (6) was shown[14] to have a free-energy barrier of 6.3 Kcal/mole at -138°.

Christl and Roberts have applied ^{13}C n.m.r. to the study[15] of the conformations at ambient temperatures of a large number of methyl-substituted cycloheptanes,

cycloheptanols[16], and cycloheptanones. γ-effects, which depend mainly on steric interactions, are found to be useful in the detailed assignment of spectra, and the conformational preferences determined in this way are in good agreement with predictions derived from Hendrickson's results[10].

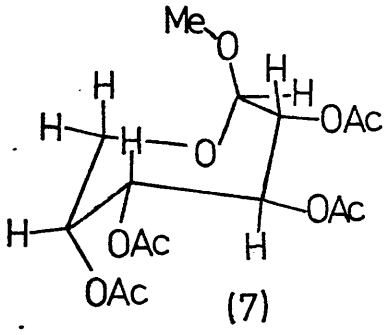
Heterocyclic analogues of cycloheptane.

The introduction of oxygen, nitrogen or sulphur atoms into a ring usually modifies somewhat its preferred conformation and its conformational mobility.[17,18] These changes can be attributed to the following:- the strain arising from angle deformation, torsion, and non-bonded interactions will all be subject to the different properties of the heteroatoms, particularly the presence of lone-paris; the bond-lengths will be changed, especially for sulphur; there may be dipolar effects which determine the orientation of polar substituents; if two (or more) adjacent heteroatoms are present there is usually a considerably increased barrier to rotation about the bond connecting them.

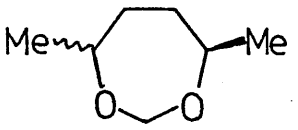
Saturated oxygen and nitrogen heteocycles.

X-ray crystal studies of septanoses[19], including (7), show that the oxepane ring adopts a conformation between a chair and a twist-chair, with the ring oxygen in the position labelled 3 in fig. 3, thus removing

the diaxial interaction in this position. The axial position of the methoxyl group may also result in a favourable dipolar interaction with the ring oxygen[17]. A study[20] by ^{1}H and ^{13}C n.m.r. of cis-and trans-4,7-dimethyl-1,3-dioxacycloheptanes (8) allows the most probable conformations to be assigned. It is considered that each isomer will consist of a rapidly pseudorotating mixture of chair (not twist) conformers.



(7)



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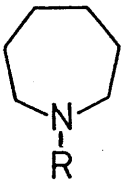


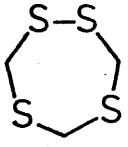
(9a):R=H
(9b):R=Me

The ^{1}H n.m.r. spectrum of azepane (9a) showed no kinetic broadening down to -150°, and in the case of the N-methyl compound (9b) the kinetic process observed was slow nitrogen inversion[21].

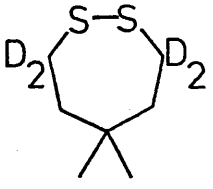
Saturated sulphur heterocycles.

The introduction of divalent sulphur (also sulphone, see later) into cyclic systems[18] is often accompanied by a considerable increase in ring-inversion barriers. This can usually be attributed to the smaller unstrained C-S-C bond-angle value (about 99-100°) as compared with C-C-C, C-O-C, C-N-C (about 110-114°), combined with a greater resistance to bond-angle opening. Conformational data on thiepanes does not seem to be available, but in the tetrathiepane (10) pseudorotation appeared[22] to be fast at -90°.

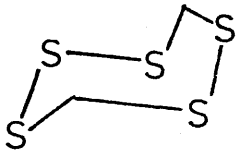
The ^1H n.m.r.[23] of the deuterated dimethyl dithiepane (11) at -48°, however, reveals the presence of a mixture of two slowly-interconverting conformers ($\Delta G^{\neq}$= 10.8 Kcal/mole): a chair form with hindered pseudorotation, and a rapidly-pseudorotating boat form of closely similar energy. At about -100°, a second kinetic effect ($\Delta G^{\neq}$= 8.0 Kcal/mole) can be discerned, believed to correspond to a slowing down of the boat pseudorotation.



(10)



(11)



(12)

The increased inversion barriers in rings containing S-S bonds are also reflected in a study of the naturally-occurring pentathiepane lenthionine (12). The X-ray crystal structure[24] shows a chair conformation, while from ^1H n.m.r. a barrier (E_a) to ring inversion of 12.9 Kcal/mole was obtained[22]. The appearance of its "frozen" spectrum (at -80°) as two sharp singlets (rather than AB quartets) may indicate that pseudorotation is fast at this temperature.

Cycloheptenes.

Cycloheptene can exist in either a rigid chair conformation or a flexible boat family of conformations.

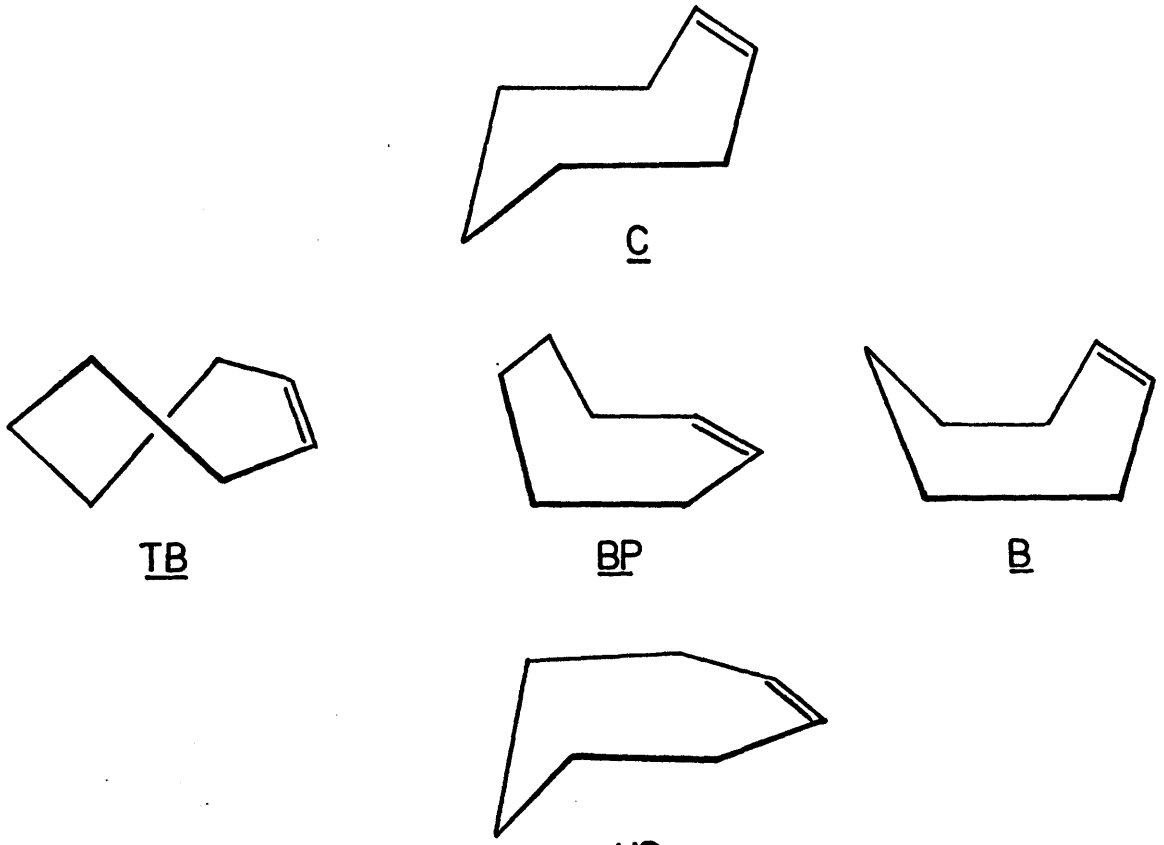


Fig 4

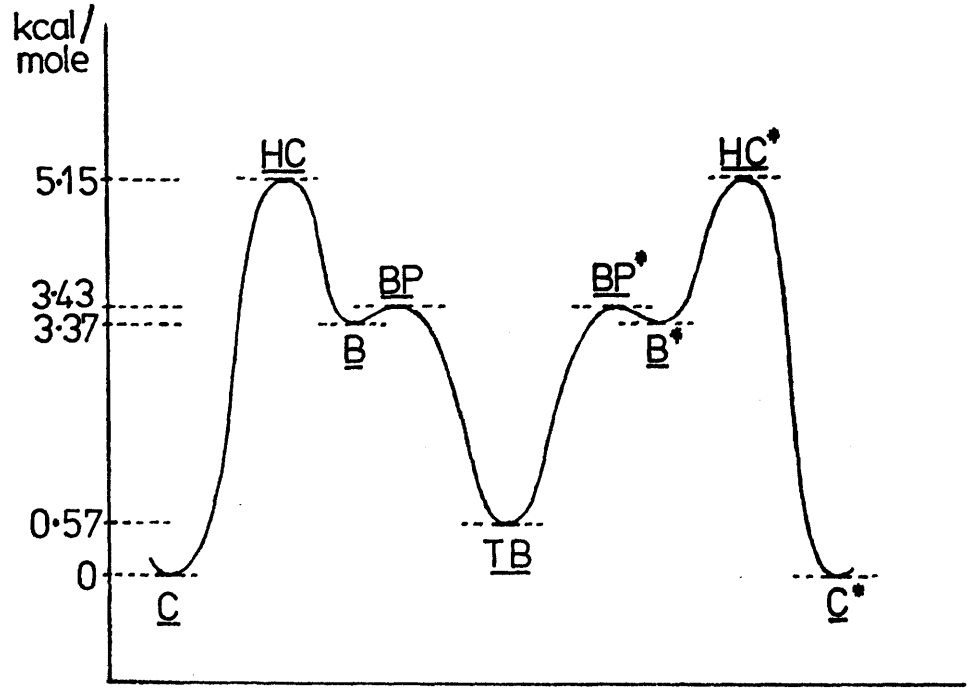
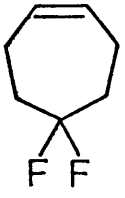
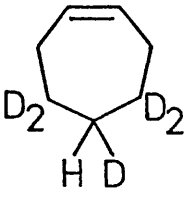


Fig 5 Energy profile for cycloheptene chair-chair inversion
[* denotes inverted conformation]

Attempts were made[6,25] to calculate the conformational energies, which appeared to favour the boat, while Favini and coworkers[26] preferred the chair. More recent molecular mechanics calculations by Allinger and Sprague[27] gave the chair with C_s symmetry (C in fig. 4) as the most stable conformation by 0.6 Kcal/mole. Pseudorotation in the boat family proceeds from the twist-boat with C_2 symmetry (TB) energy minimum, through the biplanar (BP) energy maximum ($\Delta H^{\neq}$ = 3.4 Kcal/mole) to the regular boat of C_s symmetry (B). Inversion of the chair requires ring-flip to B, pseudorotation, and ring-flip to the inverted chair conformer. The activation barrier for chair-chair inversion was calculated to be 5.2 Kcal/mole (see fig. 5). The transition-state for chair-boat interconversion is thought to be a form with six atoms in a plane (HC) - that is, the double-bond end of the ring is flattened.



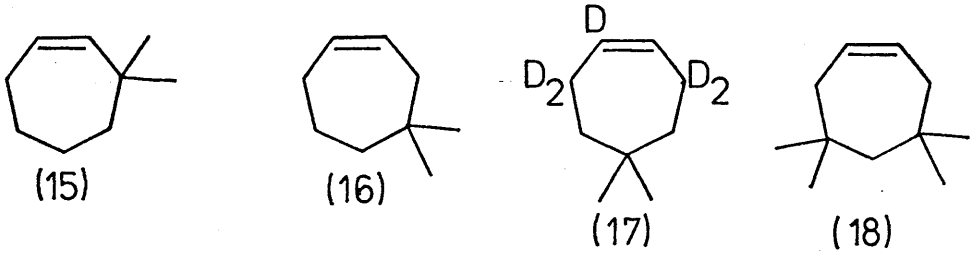
(13)



(14)

$\Delta H^{\neq}$ for 5,5-difluorocycloheptene (13) was found to be 7.4 Kcal/mole by ^{19}F n.m.r.[11] However, ^{1}H n.m.r. of the deuterated cycloheptene (14) by St-Jacques and Vaziri[28] gave an inversion barrier ($\Delta G^{\neq}$) of only 5.0 Kcal/mole, in good agreement with the calculated[27] barrier. These results indicate

that the effect of fluorine substitution on conformational barriers is by no means as negligible as Roberts has suggested[11].



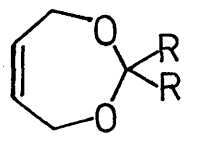
(15) (16) (17) (18)

A more recent study[29] of the methyl-substituted cycloheptenes (15) - (18) by ^1H n.m.r. gave barriers of: 5, 6.0, 6.2 and 7.7 Kcal/mole respectively. Comparison of the barrier in (18) with that in the corresponding benzo-fused compound[30] suggests that the rate-limiting step in the ring inversion of (18) may be a pseudorotation in the B-TB series.

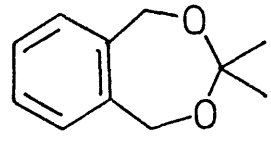
Oxygen and Nitrogen heterocycles with one double bond.

An ^1H n.m.r. examination[31] of the dioxacycloheptenes (19a and b) failed to reveal any kinetic broadening, while the benzo-derivative (20) had a $\Delta G^{\neq}$ barrier of 9.7 Kcal/mole, some 2 Kcal/mole lower than that of the corresponding carbocycle. ^{19}F n.m.r. indicated[32] that γ,γ -difluorocaprolactone and γ,γ -difluorocaprolactam (21a and b) had free-energy barriers of about 10 Kcal/mole, which seems surprisingly high. However, a barrier of only 6.7 Kcal/mole was obtained by an ultrasonic study of N-methylcaprolactam[33], and it appears that fluorine substitution again causes an increase in barrier,

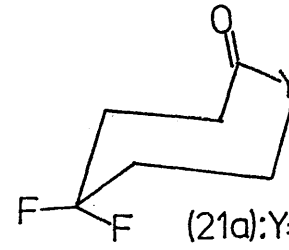
possibly by interaction across the ring.



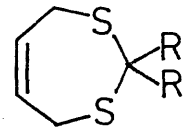
(19a):R=H
(19b):R=Me



(20)



(21a):Y=O
(2 b):Y=NH



(22a):R=H
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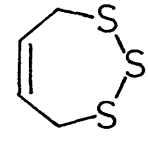


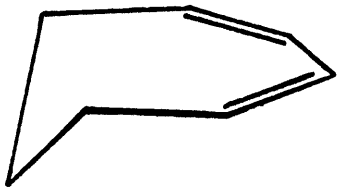
(23)

Sulphur heteocycles with one double bond.

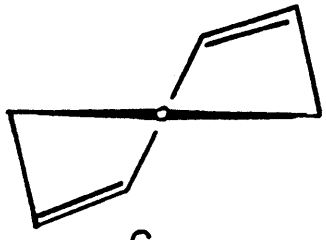
The tetrahydrodithiepines (22a and b) showed barriers[31] to ring inversion ($\Delta G^{\neq}$) of 8.5 and 8.2 Kcal/mole respectively at -100°. Interestingly also, (22b) exists at-120° as a 2 : 1 mixture of chair and boat conformations[34]. The tetrahydrotrithiepane[35] (23) has a comparable barrier ($\Delta G^{\neq}$) of 8.9 Kcal/mole at -90°.

Cycloheptadienes and hetero-analogues.

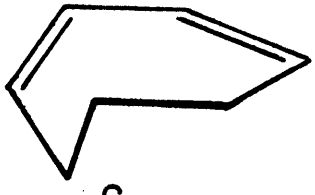
Very little conformational work has been carried out on unfused seven-membered rings containing two double bonds. The conformation of cyclohepta-1,3-diene itself remains a matter of some doubt. Its u.v. spectrum[36] resembles that of a conjugated diene, while electron-diffraction results[37,38] have also been interpreted in terms of a conformation of C_s symmetry with a planar butadiene moiety. Against



C_s



C_2

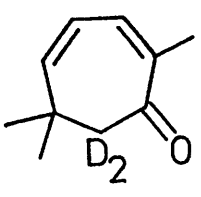


C_1

Fig 6

this must be set the analysis of its 300 MHz ^{1}H n.m.r. spectrum[39]; the value for the coupling constant J_{23} of 6.89 Hz indicates a non-coplanar arrangement of the double bonds, and a twisted boat conformation of C_2 symmetry (see fig. 6). The C_2 conformation was also favoured in the strain energy calculations of Favini and coworkers[40]. Allinger and Sprague's recent molecular mechanics calculations[41] provide a possible solution to the problem. The C_s, C_2 and a third C_1 conformation (with carbon atoms 2, 3, 4, 5 coplanar) are all estimated to be of almost identical energy, and to be interconvertible by very facile pseudorotation ($\Delta H^{\neq}$ barriers of 0 - 1 Kcal/mole). It may be possible to rationalise the electron-diffraction results [37,38] and the ^{1}H n.m.r. spectrum[39] by considering such a rapidly-pseudorotating mixture of conformers.

Computer analysis[42] of the room-temperature ^{1}H n.m.r. spectrum of α,α-dideuteroeucarvone (24) is believed to indicate flattening of the butadiene moiety (see later in this thesis).



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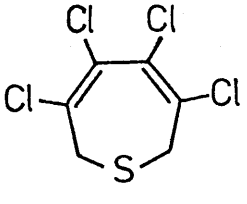

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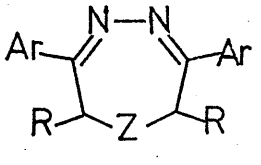


(26) R=Me or H
Z=S or SO_2

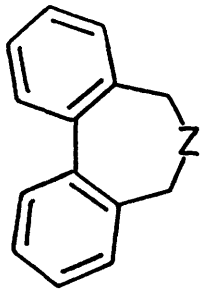
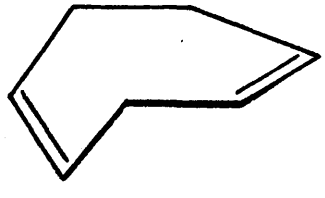
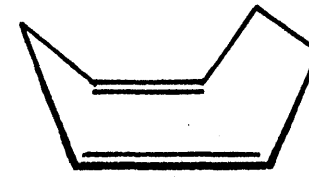


Table 1

Cpd.	Z	$\Delta G^{\neq}$	E_a	ref.
(27)	C=NOH	13·7		47
(28)	$C(CO_2Et)_2$	14·5		47
(29)	O	9·2	9·2	48 49
(30)	NCH_2Ph	10·1		49
(31)	S	15·5	16·1	47 48
(32)	SO_2	18·2		47



BP



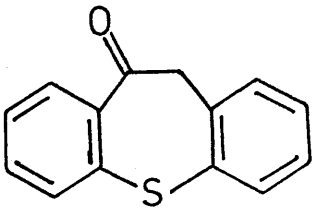
B

Fig 7

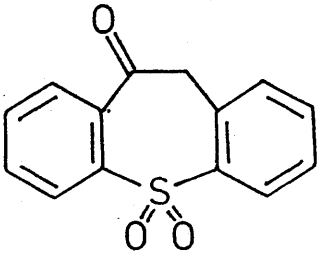
The tetrachlorodihydrothiepine (25) has an enthalpy barrier of 8.9 Kcal/mole[43], while dihydro-1,4,5-thiadiazepines of the type (26) are known[44,45] to have much higher barriers. Compounds of this type are discussed in full later in this thesis.

The 2,2'-bridged biphenyls which may be considered to be derived from cyclohepta-1,3-diene or its hetero-analogues have received considerable attention[1,46]. The extra rigidity imposed by the benzene rings makes a twisted boat the only likely conformation for the seven-membered ring. A selection of ring-inversion barriers in this series[47-49] (compounds (27) to (32)) is presented in table 1. It is evident that, in this system, replacement of the carbon by oxygen or nitrogen lowers the inversion barrier, while introduction of a sulphide or sulphone group considerably increases it, the effect of the sulphone group being the greater.

In the case of cyclohepta-1,4-diene, molecular models appear to indicate the biplanar form with no symmetry (BP in fig. 7) as the most likely conformation. However, calculations have been carried out[40] assuming a boat (B) conformation of C_s symmetry, which appears, at least by casual inspection, to have greater angle strain and eclipsing strain. No experimental results are available to clarify the picture.



(33a)

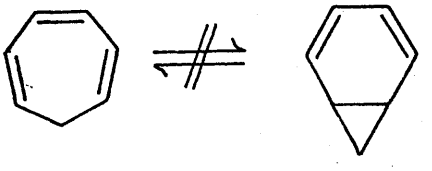


(33b)

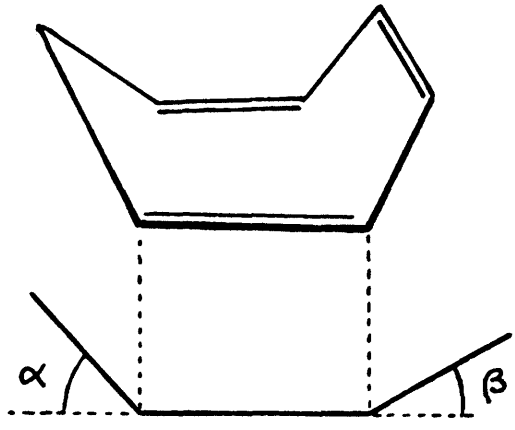
A few related fused systems have been investigated, for example the dihydro-dibenzo [b,f] thiepinones (33 a and b) have free-energy barriers to inversion of 9.3 and 10.7 Kcal/mole respectively[50]. Again it can be seen that the sulphone group increases the barrier relative to the corresponding sulphide.

Cycloheptatrienes.

Systems with three double bonds in a seven-membered ring have been extensively studied. Cycloheptatriene (34a) aroused interest because of possible relevance to theories of aromaticity, and also because of a potential valence-tautomerism to the norcaradiene[51] structure (34b). Early ^{1}H n.m.r. studies[52] showed that (34a) is the only detectable isomer at room temperature. Doering[53]



(34a) (34b)



Cycloheptatriene boat

Fig8 $\alpha \approx 50°$

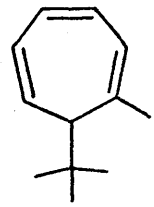
$\beta \approx 28°$

proposed that cycloheptatriene would have a planar structure with pseudo-aromatic properties. However, experimental observations of derivatives were consistent with non-planar, boat-shaped conformation[54,55].

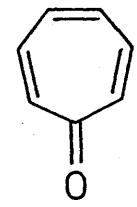
The situation in cycloheptatriene itself was clarified by the low-temperature ^{1}H n.m.r. studies carried out independently by Anet[56] and by Jensen and Smith[57]. These indicated a free-energy barrier to ring-inversion in the region of 6 Kcal/mole at -143^{o}, nor could any evidence be found for the existence of an equilibrium between (34a) and norcaradiene (34b). Results of electron-diffraction[58] and microwave[59] studies both gave a boat conformation, but showed rather large discrepancies in the detailed geometry. Analysis of the room-temperature ^{1}H n.m.r. spectrum[60] was consistent with the microwave results, and recent molecular mechanics calculations by Allinger and Sprague[61] have given a detailed geometry in good agreement with that obtained by microwave analysis (see fig. 8).

The ^{19}F n.m.r. of the bis-trifluoromethyl compound (35) showed no kinetic broadening down to -185^{o}, suggesting that here the ring is flattened, with consequent lowering of the inversion barrier[62]. Analysis of the room-temperature ^{1}H n.m.r. spectra of a series of 7-monosubstituted cycloheptatrienes[63] showed the preference of alkyl or aryl substituents

(35)



(36)



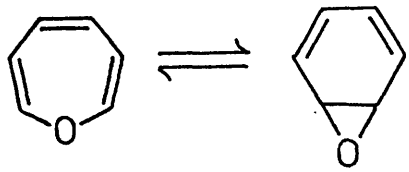
(37)

for an equatorial orientation. Interestingly, though, 1-methyl-7-t-butylcycloheptatriene (36) exists as a mixture of axial and equatorial conformers, with the axial t-butyl predominating. The ^{1}H n.m.r.[64] shows kinetic broadening at ambient temperatures, and variable-temperature studies give a free energy of activation of 14.8 Kcal/mole at 25° for the axial to equatorial conversion. The steric crowding present in the equatorial conformer is evidenced by the observation of slow t-butyl rotation below -104°.

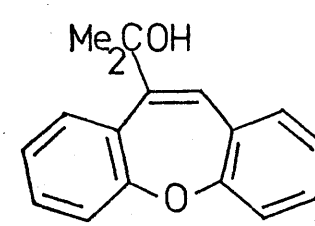
Unlike cycloheptatriene, tropone (37) is planar, though it is not now considered to be aromatic[65].

Oxepines.

In contrast to cycloheptatriene, oxepine (38a) exists in equilibrium with its valence tautomer



(38a) (38b)

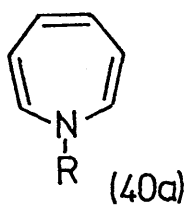


(39)

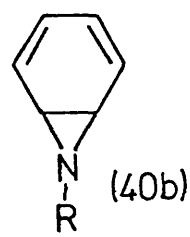
benzene oxide (38b)[51]. However, the introduction of fused aromatic rings prevents tautomerism since the process would entail dearomatisation. A study by ^{1}H n.m.r. of the dibenzoxazepine (39) revealed a barrier to ring-inversion ($\Delta G^{\neq}$) of 10.3 Kcal/mole at -69°, about 7 Kcal/mole lower than that for the corresponding carbocycle[66].

Azepines and diazepines.

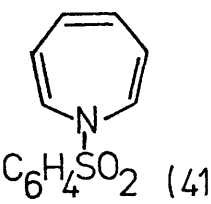
The rather unstable ^{1}H-azepines (40a) do not appear to be in equilibrium with significant amounts of the valence-tautomeric benzene imine structure (40b)[51]. An X-ray crystal-structure determination[67] of the 1H-azepine derivative (41) showed that the azepine ring is boat-shaped with alternating single and double bonds. The 3H-azepine (42) was shown by



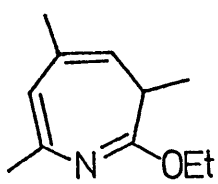
(40a)



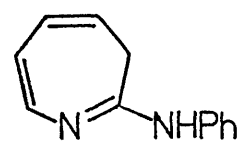
(40b)



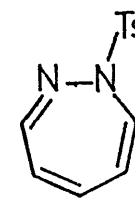
(41)



(42)



(43)

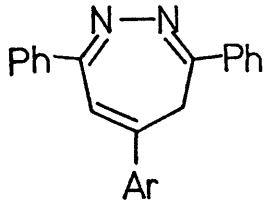


(44)

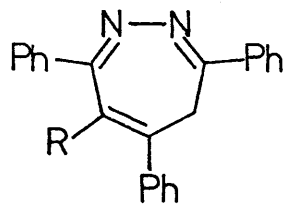
room-temperature n.m.r.[68] to exist in a boat conformation with the 3-methyl group equatorial, while low-temperature studies[69] of the 3H-azepine (43) gave a barrier to ring-inversion ($\Delta G^{\neq}$) of about

10 Kcal/mole at -55°.

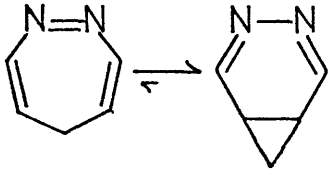
An X-ray diffraction study of the 1H-1,2-diazepine derivative (44) showed that it has a boat conformation in the crystal, in which there appeared to be little or no conjugation to the imine C=N, while, it was suggested, some conjugation may be present in the butadiene moiety[70]. ^{1}H n.m.r. investigations[71,72] of a series of triaryl-4H-1,2-diazepines (45) have revealed no evidence of valence tautomerism, but have shown the existence of high barriers to ring-inversion ($\Delta H^{\neq}$ varied from 18.95 to 20.16 Kcal/mole). Introduction of a methyl or phenyl group in the 6-position caused an increase in the barrier[72], and for both compounds (46a) and (46b), no collapse of the methylene signals was observed at 180° and 190° respectively, indicating minimum $\Delta G^{\neq}$ values of about 23 Kcal/mole.



(45)



(46a): R=Me
(46b): R=Ph



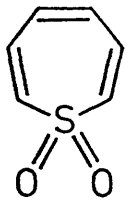
(47a) (47b)

Compounds expected to contain the 5H-1,2-diazepine ring system (47a) have been the subject of numerous investigations[51], and have been found to exist almost entirely in the valence-tautomeric bicyclo[4.1.0] form (47b). However, there is good

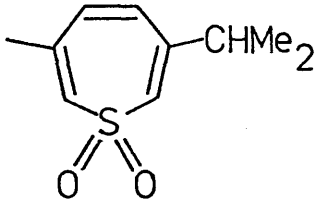
evidence for a very low equilibrium concentration of the diazepine at higher temperatures[51,73].

Thiepines.

The properties of the thiepine 1,1-dioxide system have been investigated by Mock and coworkers. The X-ray crystal structure of (48) was determined[74], it being found that the molecule adopts a somewhat flattened boat conformation, with some twisting of



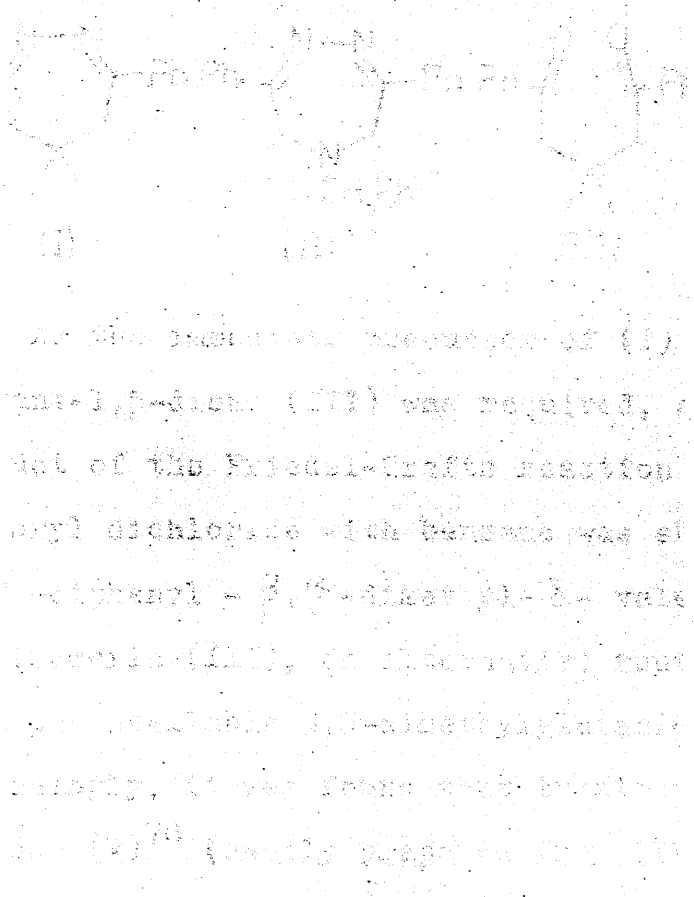
(48)



(49)

the double bonds and opening of the carbon valence angles. Analysis of the room-temperature ^{1}H n.m.r. spectrum[75] of (48) also indicates a flattened boat as the conformation in solution. The ring-inversion of the alkylated derivative (49) was also studied[76], using 250MHz ^{1}H n.m.r., a free-energy barrier of only 6.4 Kcal/mole at -150° being found, very close to that in cycloheptatriene. Since the presence of the sulphone group would be expected to raise the barrier considerably (longer C-S bonds and a small C-S-C bond angle), these results have been interpreted as implying the existence of significant delocalisation in the ring.

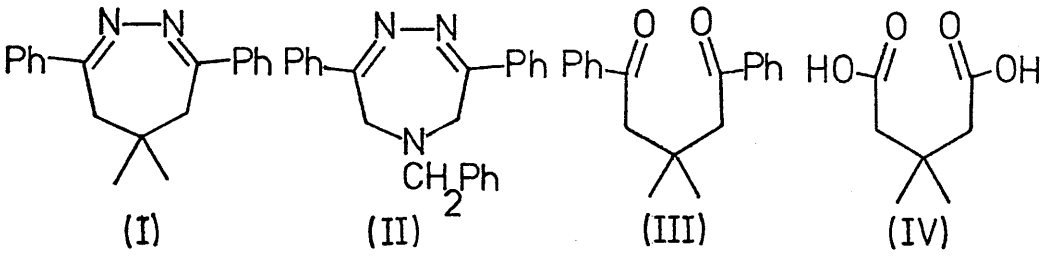
A large number of benzo-,dibenzo-, and tribenzo-fused analogues of cycloheptatriene and the corresponding heterocycles have been investigated[1]. Many have very high barriers to ring inversion, such that in some cases separation of enantiomers is possible. Detailed consideration of these compounds is outside the scope of this review.



RESULTS AND DISCUSSION.

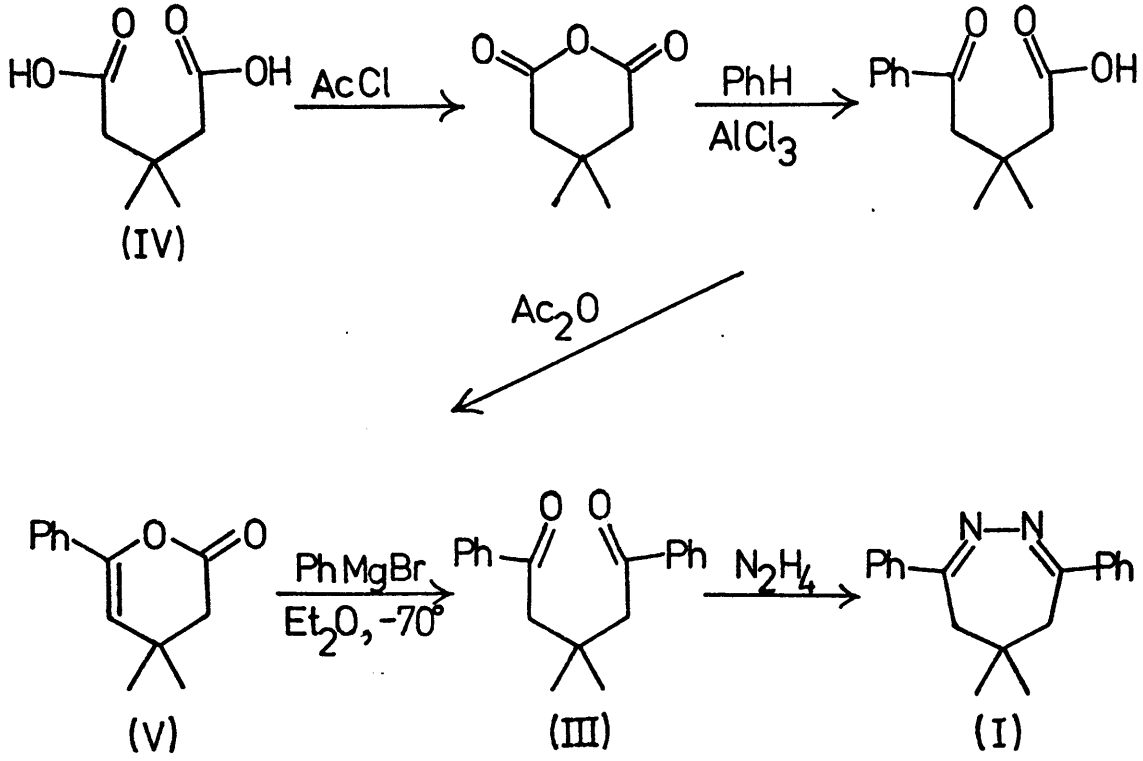
The existence of high barriers to ring-inversion in 3,6-diaryl-2,7-dihydro-1,4,5 thiadiazepines[44,45] has been briefly mention in the introduction. In order to study further this, and closely-related ring-systems, a series of compounds has been prepared, and studied by Kinetic ^{1}H n.m.r.

Preparation of 5,5-dimethyl-3,7-diphenyl-5,6-dihydro-4H-1,2-diazepine (I) and 5-benzyl-3,7-diphenyl-5,6-dihydro-4H-1,2,5-triazepine (II).

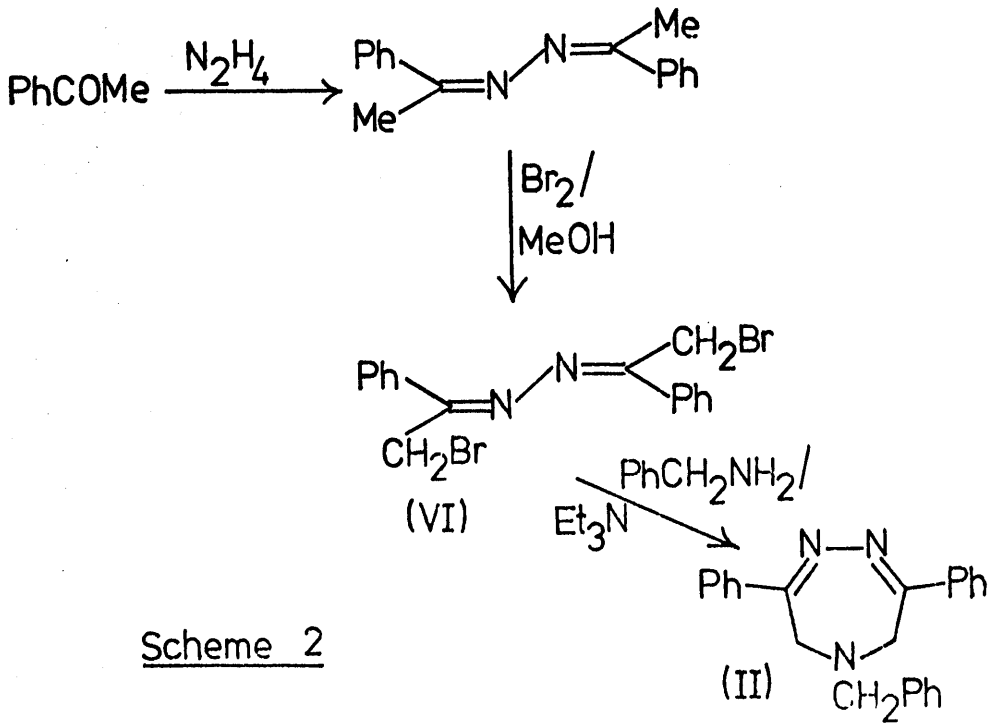


(I) (II) (III) (IV)

As the immediate precursor of (I) 1,5-diphenyl-pentane-1,5-dione (III) was required, and since the product of the Friedel-Crafts reaction of 3,3-dimethyl-glutaryl dichloride with benzene was shown[77] to be δ,δ-diphenyl - β,β-dimethyl- δ- valerolactone, not the isomeric (III), an alternative route was sought from the available 3,3-dimethylglutaric acid (IV). Accordingly, it was found that treatment of the enol lactone (V)[78] (easily prepared from (IV)), with phenylmagnesium bromide at -70° gave (III) directly in good yield[79]. Crude (III) was readily cyclised with hydrazine to give the required diazepine (I) (Scheme 1).



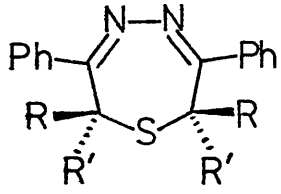
Scheme 1



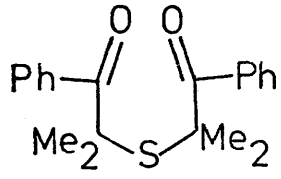
Scheme 2

Triazepine (II), the only example of its ring system so far reported, was prepared by the published method[80] which involves treatment of the dibromo-azine (VI) with benzylamine (Scheme 2).

Preparation of 3,6-diphenyl-2,2,7,7-tetramethyl-2,7-dihydro-1,4,5-thiadiazepine (VII); other products of the reaction of 2,2"-thiobis (isobutyrophenone) (VIII) with hydrazine.



(VII) :R=R′=Me
(IX) :R=R=H
(X) :R=Me,R′=H



(VIII)

By analogy with the preparation of the closely-related systems (IX) and (X) by the action of hydrazine on the appropriate diketosulphide[45,81,82], the reaction of (VIII) with hydrazine was studied. (VIII) itself was prepared in high yield by the action of anhydrous sodium sulphide on 2-bromoisobutyrophenone in DMF. When treated with anydrous hydrazine in benzene or pyridine for approximately three weeks, a highly crystalline compound $C_{20}H_{24}N_2OS$, m.p. 219-221°, was deposited. This compound was assigned structure (XI) on the basis of its molecular weight and the following spectroscopic data: its i.r. spectrum (KBr disc), which shows ν(N-H) absorption at 3303 and 3275 cm^{-1} and the absence of OH, C=O, or C=N absorption; its ^1H n.m.r. spectrum, which indicates the presence of two equivalent pairs

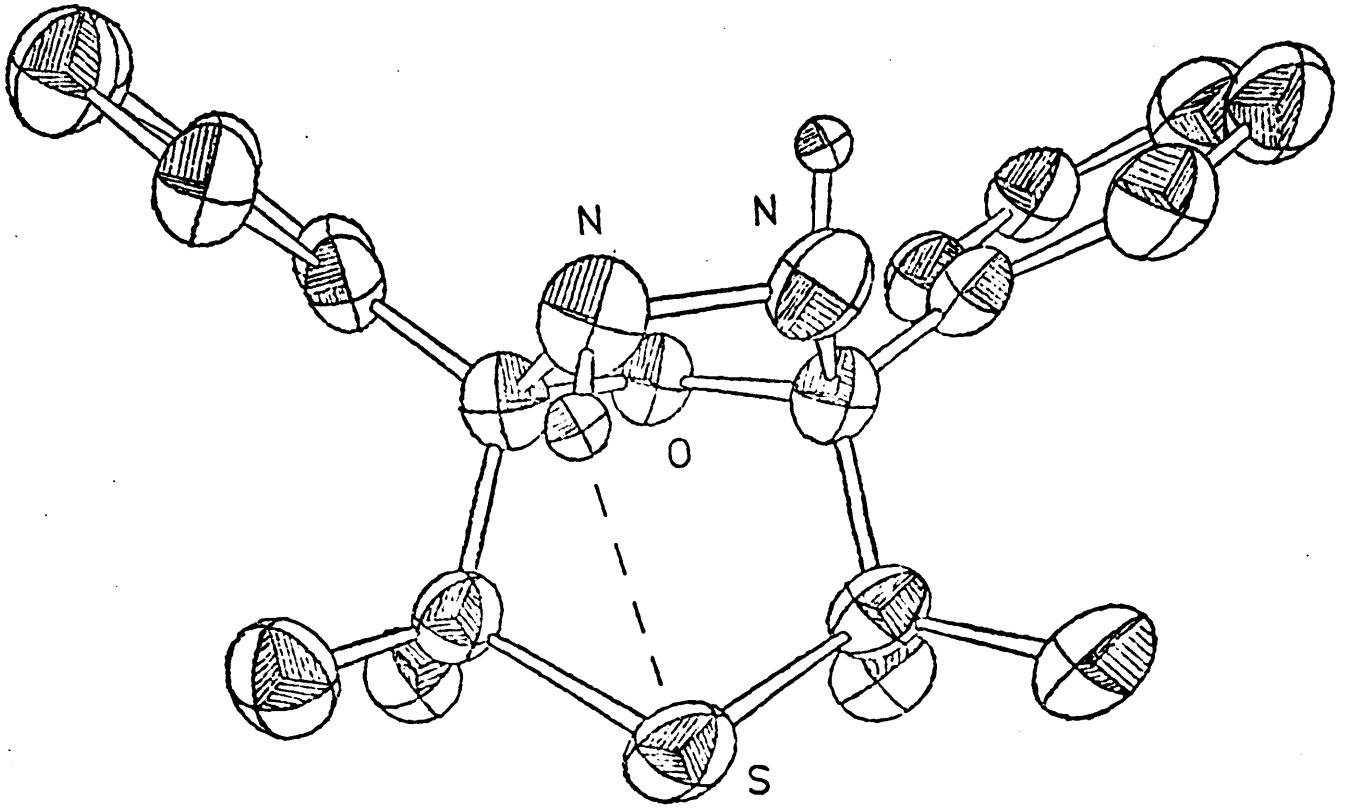
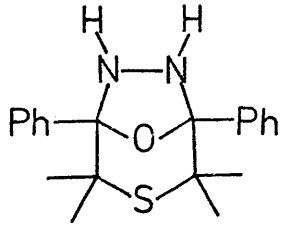


Fig 1 An ORTEP drawing showing a general view of the molecular structure of (XI) in the crystal. (Only the hydrogen atoms attached to nitrogen are included, and the intramolecular hydrogen bond involving one of these is denoted by a broken line.)

of diastereotopic geminal methyl groups*; and its u.v. spectrum, typical of a benzenoid chromophore having no further conjugation.



(XI)

Since (XI) embodies the first example of the 8-oxa-3-thia-6,7-diazabicyclo[3.2.1]octane ring-system, a single-crystal X-ray diffraction analysis was carried out.** The compound forms triclinic crystals of space-group $P\bar{1}$; a general view of the structure is shown in Fig. 1. The seven-membered thiadiazepane ring has a slightly-flattened boat conformation, and there is an intramolecular N-H...S hydrogen bond, involving one bridge nitrogen and its hydrogen. The six-membered 1,4-oxathiane ring exists as a chair with a pronounced flattening of its four

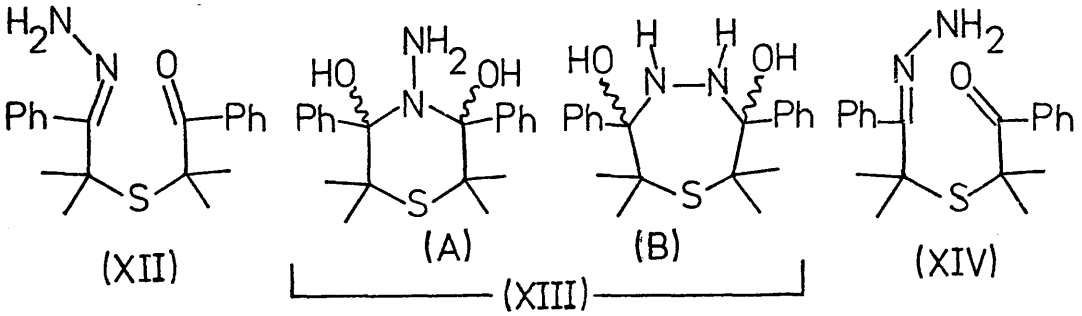
---

* A diagnostically useful weak coupling between diastereotopic methyl groups appears as a significant broadening of the resonances ($W_{\frac{1}{2}}$ ca. 1.3 Hz), and indicates the geminal non-equivalence. The origin of broadening, also observed for (VII), (XIII), (XV), (XVIII), and (XIX), was confirmed by decoupling in the case of (VII).

** The X-ray analysis was performed by Dr. A.D.U. Hardy, and is detailed in a forthcoming publication (ref. 83)

ring carbons and sulphur, indicating the presence of an inverse reflex effect[84] corresponding to that found in the bridged carbocycle.

Evaporation of the benzene solution remaining after isolation of (XI) gave, as the major product (60% isolated), an isomer of (XI) whose i.r. (ν(N-H) and ν (C=O))and ^{1}H n.m.r. showed it to be a monohydrazone of (VIII), the E structure (XII) being indicated by its resistance to cyclisation under a variety of conditions.

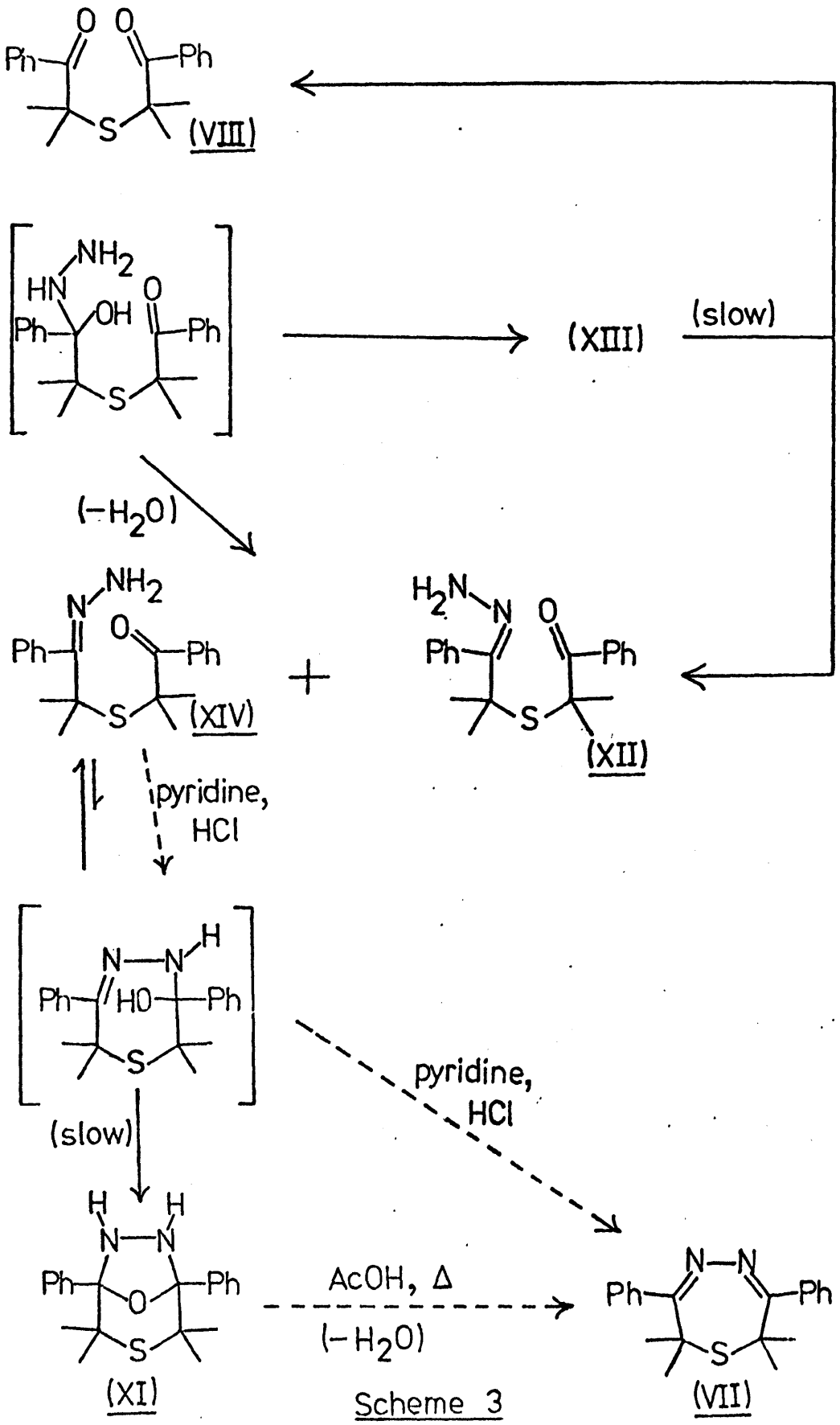


Carrying out the reaction in presence of molecular sieve 3A powder appeared to optimise the formation of another compound (XIII), isolable with difficulty, which analysed satisfactorily for $C_{20}H_{26}N_2O_2S$, the formulated alternative structures (A) and (B) being consistent with the available spectroscopic data. (XIII) is susceptible to facile thermal or hydrolytic breakdown leading to the monohydrazone (XII) and the diketosulphide (VIII).

In several runs the course of the reaction was monitored by ^{1}H n.m.r. and it was found that (XI) was only present in appreciable amounts after about one week. At times shorter than this, a pair of

narrow methyl resonances ($W_{\frac{1}{2}}$ *ca.* 0.8 Hz) was observed close to those of the E-hydrazone (XII). The disappearance of these signals in presence of traces of acid (in $CDCl_3$) is accompanied by the appearance of an equivalent amount of (XI); and in a separate experiment the addition of acetic acid catalysed the formation of (XI), which was isolated in *ca.* 10% yield. This behaviour is consistent with a tentative assignment of these resonances to the methyl groups of the Z-hydrazone (XIV), though a preliminary attempt to isolate this intermediate compound proved unsuccessful.

In a parallel series of experiments using the homogeneous pyridine-hydrazine system, the course of the reaction was followed by ^1H n.m.r. for 20 days. The results, given in the Experimental, show that the concentration of (XIV), the presumed intermediate in the formation of (XI), reached a maximum after about 3 days. Treatment of the pyridine solution at this time with excess acetic acid gave (XI) in 12% isolated yield. However, work-up with HCl in aqueous methanol gave instead a 9.5% yield of the originally-sought dihydrothiadiazepine (VII), m.p. 207-208°. The structure of (VII) was confirmed by its micro-analysis, osmometric M.W., and spectroscopic data: its i.r., which shows ν(C=N) and no ν(N-H); its mass spectrum, m/e 322 (M^+); its ^1H n.m.r., which corresponds to slow ring inversion, with widely-spaced



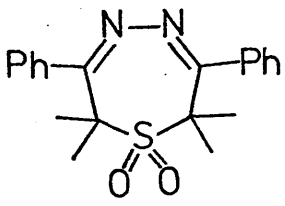
Scheme 3

Proposed major pathways for products derived from (VIII)

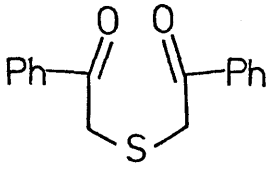
(Solid arrows indicate reactions occurring at room temp. in hydrazine-benzene or hydrazine-pyridine; dotted arrows indicate treatment with a further reagent.)

diastereotopic methyl resonances; and its u.v. spectrum, which shows some further conjugation of the aromatic rings.

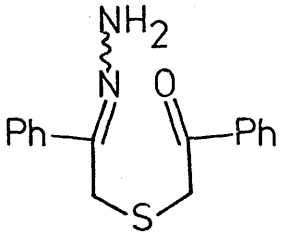
(VII) was not detected from HCl work-up of the earlier runs using benzene as solvent. (XI) in pyridine was precipitated unchanged on treatment with methanolic HCl, implicating another intermediate, possibly (XIV), in the formation of (VII). However, more prolonged treatment under reflux with glacial acetic acid effected dehydration of (XI) to (VII) in good yield. (VII) was also converted into its sulphone (XV). An outline of the above reactions is given in Scheme 3.



(XV)



(XVI)

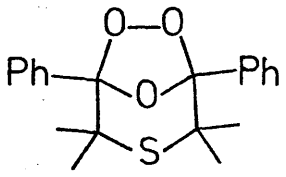


(XVII)

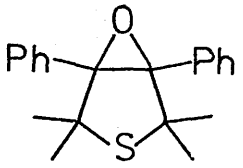
In order to determine whether the formation of the novel compound (XI) had any parallel in other systems we have reinvestigated the action of hydrazine on 2,2"-thiodiacetophenone (XVI)[81,82]. Under a variety of conditions the only products detected were the dihydrothiadiazepine (IX) and a single mono-hydrazone (XVII) m.p. 131-132°. No evidence could be found for an isomeric compound, m.p. 225°, previously reported[81]. This suggests the importance of gem-dimethyl substitution in the stabilisation of (XI).

Thermal Stability of (XI) and its Reactions with Molecular Oxygen.

(XI) in the crystal is stable indefinitely in air, and in solution, in the absence of air shows resistance to thermolysis at 200°. However, (XI) in solution in the presence of molecular oxygen undergoes facile oxidation. At room temperature in benzene solution (XI)was transformed cleanly in high yield to the ozonide (XVIII), m.p. 182-185° (decomp.), this structure being assigned on its osmometric

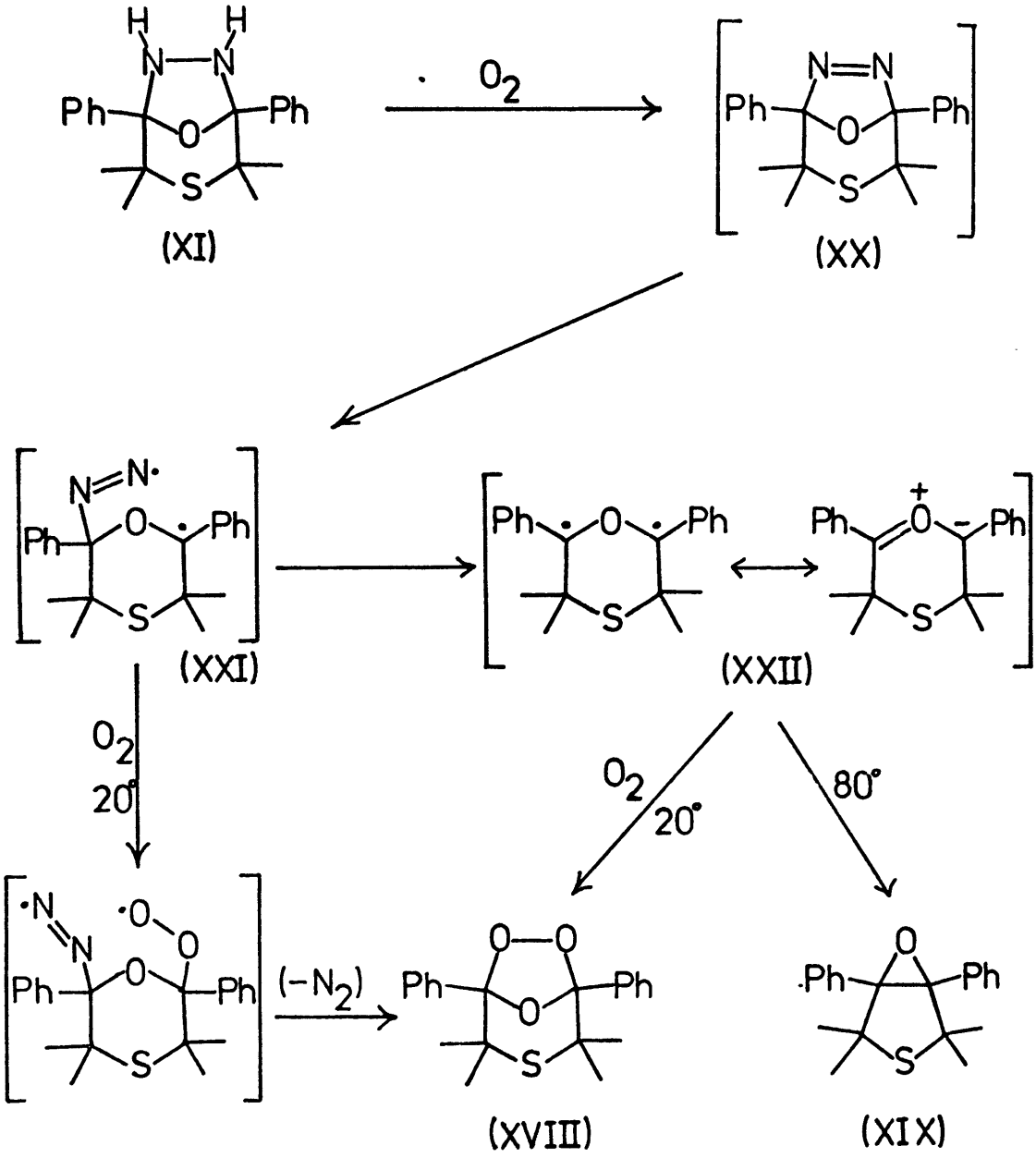


(XVIII)



(XIX)

molecular weight; its i.r. spectrum, which apart from the absence of (N-H) absorption resembles that of (XI) and shows no strong absorption attributable to γ(S=O); its ^{1}H n.m.r., and its u.v., which is similar to that of (XI). Further confirmation of this structure comes from its reduction by zinc and acetic acid to (VIII). On performing the air oxidation of (XI) in refluxing benzene, a quite distinct product can be isolated in good yield. This second oxidation product, m.p. 180-181°, which analyses for $C_{20}H_{22}OS$ has m/e 310 (M^+) and other spectroscopic properties completely consistent with the expoxide structure (XIX). This duality of oxidation behaviour, summarised in Scheme 4, may arise



Scheme 4

Suggested pathways for oxidation of (XI)

from differing concentrations of dissolved molecular oxygen. The initial oxidation step is almost certainly the formation of the azo compound (XX); this may then extrude nitrogen as shown, the nature of the eventual product being determined by the availability of molecular oxygen to add to either (XXI) or (XXII) before collapse to the epoxide (XIX). In keeping with these suggested pathways, (XIX) in benzene solution at room temperature does not react with oxygen, nor is any epoxide (XIX) observed on refluxing the ozonide (XVIII) in benzene. The possible addition of O_2 to the dipolar species (XXII) may have a parallel in the postulated formation of an ozonide, analogous to (XVIII), as an unisolated intermediate in the oxidation of a previously-reported carbonyl ylide[85].

Kinetic n.m.r. studies.

The 100 MHz ^1H n.m.r. spectrum of diazepine (I) in CD_2Cl_2 at +62° comprises, in addition to aromatic signals, sharp singlets at τ 7.55 (4H, methylene) and τ 8.87 (6H, methyl). On lowering the temperature, the methylene signal broadens, and below the coalescence temperature of approximately 7°, splits; at -35.6°, a frozen AA'BB' spectrum (approximately AB) was observed. Between -54.6° and -35.6°, the mild linear temperature-dependence of ν_{AB}, the chemical shift difference, gave an approximate

T(°C)	$k(s^{-1})$	$\Delta G^{\neq}$(kcal/mole)
−16·7	5·6	14·05
−9·9	13·7	13·97
−5·7	21·3	13·97
+0·4	39·5	13·97
+5·4	57·5	14·02
+12·1	117·5	13·97
+14·8	144·5	13·99

Table 1 Ring-inversion in (I).

extrapolated ν_{AB} (for T *ca.* 0°C) of 25 Hz. This, together with the values J_{AB} = 13.6 Hz, limiting $W_{\frac{1}{2}}$ = 2.5 Hz, allowed theoretical lineshapes for different rates to be computed using the program[86] DNMR 3, and thus the rates at several of the experimental temperatures were determined. The transformed Eyring equation[87]:

$$\Delta G^{\neq} = 2.303RT \left(\log \frac{\kappa k_B}{h} + \log T - \log k\right) \quad (1)$$

where R is the gas constant, T is the absolute temperature,
k_B is the Boltzmann constant, h is Planck's constant,
κ is the transmission coefficient (taken as 1.0), and
k is the rate constant,
gives the expression for the free-energy of activation:-

$$\Delta G^{\neq} = 4.576T \left(10.319 + \log T - \log k\right) \quad (2)$$

Application of equation (2) to the rates obtained for the diazepine (I) gave $\Delta G^{\neq}$ at each temperature; the results are given in Table 1. Further refinement of the computed spectra is necessary for an exact fit; in particular, allowance for the variation of ν_{AB} and $W_{\frac{1}{2}}$ with temperature*.

The value obtained for $\Delta G^{\neq}$, however, (13.99 ± 0.05 kcal/mole) showed remarkably little variation with temperature, suggesting that $\Delta S^{\neq}$ is very small or negligible.

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* $W_{\frac{1}{2}}$ for fast exchange (+ 62°) is 0.9 Hz. At -54.6°, viscosity broadening increases this to 2.75 Hz.

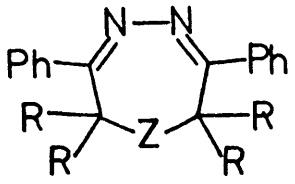


Table 2 Free-energy barriers to ring-inversion.

Cpd.	Z	R	freq. (MHz)	ν_{AB} (Hz)	J_{AB} (Hz)	T_c (°C)	k_c (s^{-1})	$\Delta G^{\neq}$ (kcal/mole)
(I)	CMe_2	H	100	25·0	13·6	(~7)	—	13·99±0·05
(II)	NCH_2Ph	H	100	43·0	12·9	−25±2	118	12·07±0·1
(IX)	S	H	60	10·8	12·8	97±?	73·6	18·6±0·2*
(XXIII)	SO_2	H	60	19·9	14·3	142±?	89·5	20·8±0·3*
(VII)	S	Me	60	56·0	—	154±4	124·4	21·2±0·3

* from ref. 45.

The methyl signal of (I) showed no kinetic broadening down to -60° in CD_2Cl_2, acetone-d_6, CS_2, or toluene-d_8, showing that the methyl groups remain chemically equivalent for slow exchange.

The 100 MHz spectrum of triazepine (II) in CD_2Cl_2 at 34°, comprises, in addition to aromatic resonances, singlets at, τ 6.18 (2H, benzyl methylene, and τ 6.44 (4H, ring methylene). The ring methylene signal gave the expected kinetic effect at lower temperatures, and in the frozen spectra between -82° and -60°, ν_{AB} was observed to be constant within the accuracy of the experiment. In this case, the rate of ring-inversion was calculated only at the coalescence temperature, using the equation:

$$k_c = \frac{\pi}{\sqrt{2}}(\nu^2 + 6\,J^2)^{\frac{1}{2}} \quad \text{——(3)}$$

which was derived [48] from Alexander's line-shape treatment[88]. $\Delta G^{\neq}$ was then calculated using equation (2). These results are given in table 2, along with, for comparison, the barrier calculated for (I), and the approximate values previously reported[45]. for thiadiazepine (IX) and its sulphone (XXIII). For rapid nitrogen inversion, the benzyl methylene protons of (II) should also become diastereotopic on slowing down of ring inversion, but no obvious kinetic broadening of this signal was observed down to -82°, presumably because of a very small chemical shift difference.

The 60 MHz spectrum of tetramethyl thiadiazepine

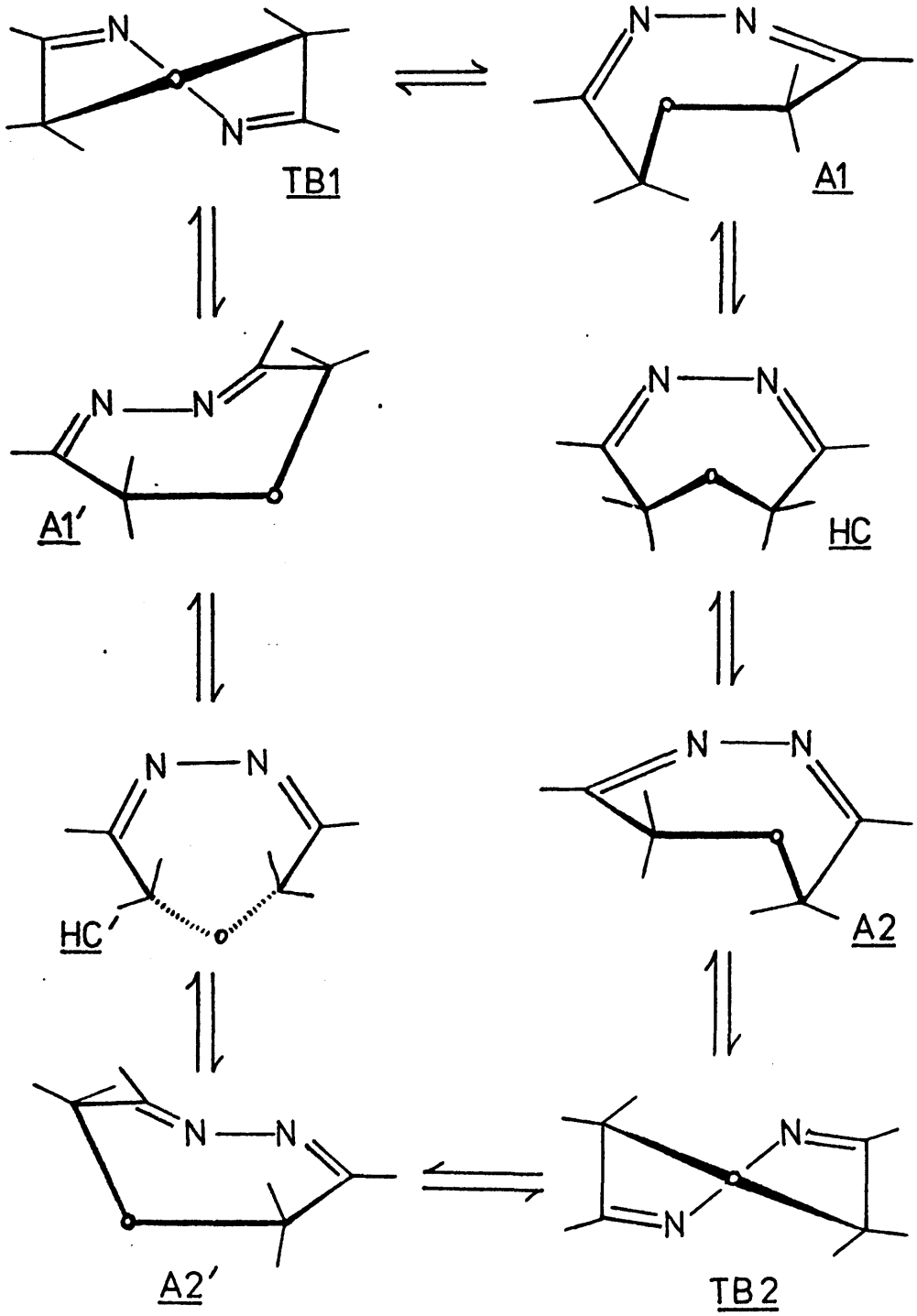


Fig 2 Conformations and course of ring-inversion for this series. [N.B. ' denotes identical conformer.]

(VII) in diphenyl ether at +90° consists of (aromatic resonances obscured) two methyl singlets at about τ 8.04 and 8.97, corresponding to slow ring-inversion. The chemical shift difference showed no significant temperature dependence, and $\Delta G^{\neq}$ was again calculated by means of the approximate coalescence method, using the equation (for negligible J):-

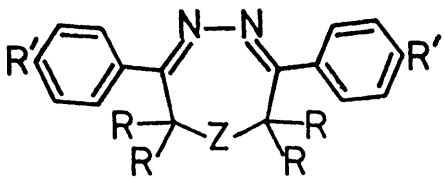
$$K_c = \frac{\pi \nu}{\sqrt{2}} \quad \text{——(4)},$$

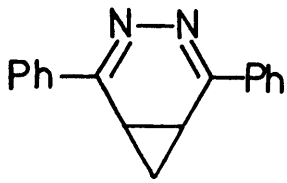
followed by equation (2). The results are included in Table 2. It is also intended to carry out a kinetic n.m.r. study of sulphone (XV).

The ground-state conformation of the dihydro-diazepine,-triazepine, or -thiadiazepine ring.

As was noted in the Introduction, the amount of experimental data on the conformations of unfused seven-membered rings, carbocyclic or heterocyclic, having two endocyclic double bonds is very meagre. Indeed, the conclusive establishment of the exact conformation of such a system has not appeared in the literature.

In the series of compounds listed in Table 2, each has a similar range of conformational possibilities, shown in Fig. 2 (see also the Introduction Fig. 6). The likely conformations fall into three categories: two enantiomeric twisted boats of C_2 symmetry (TB1 and TB2) with 3 atoms coplanar, a pair of identical half-chairs of C_S symmetry (HC and HC')





(XXIV)

Table 3 U.v. data (solvent EtOH)

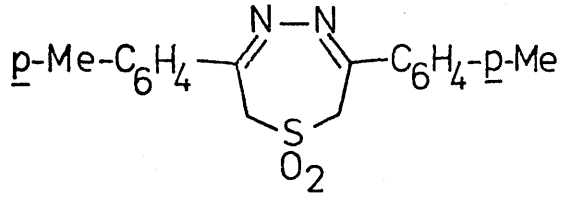
Cpd.	Z	R	R′	λ_{max}(log ε) (nm)	ref.
(I)	CMe_2	H	H	265(4·19), 274(4·20), 287(4·20)	—
(II)	NCH_2Ph	H	H	270(4·36)	—
(IX)	S	H	H	269(4·28)	—
(XXIII)	SO_2	H	H	280(4·36)	—
(XXV)	SO_2	H	Me	295(~4·3)	—
(VII)	S	Me	H	232(4·08), 275sh(3·68)	—
(XV)	SO_2	Me	H	247(4·01), 275sh(3·89)	—
PhCH=NMe	—	—	—	247(4·23)	90
(XXIV)	—	—	—	316(4·32)(MeOH)	89

with 6 atoms coplanar, and two enantiomeric pairs of an asymmetric form (A1, A1' and A2, A2') with 5 atoms coplanar.

For diazepine (I), the ground-state conformation must, for slow ring-inversion, give rise to two chemically-shifted methylene resonances, but with the methyl resonances remaining equivalent. Thus, the HC, in which the methyl groups are not symmetry-related is inconsistent with the n.m.r. evidence. U.v. data (Table 3) also implies non-planarity of the azine moiety, since the rigid cis-planar azine (XXIV) absorbs at considerably longer wavelength[89].

The TB conformation, with carbon-5 on the C_2 axis, appears to be consistent with the n.m.r. and u.v. spectra, but, although a single A conformer can be discounted on symmetry grounds, it is not possible to rule out the alternative possibility that (I) is present as a mixture of conformers pseudorotating rapidly between A1 and A1' or between A2 and A2'.

However, for the 2,7-dihydro-1,4,5-thiadiazepine system, an X-ray structure analysis has been carried out[91]. The compound studied was 3,6-bis(p-tolyl)-2,7-dihydro-1,4,5-thiadiazepine 1,1-dioxide (XXV). A general view of the structure is given in Fig. 3.



(XXV)

The thiadiazepine ring has a C_2 TB conformation with

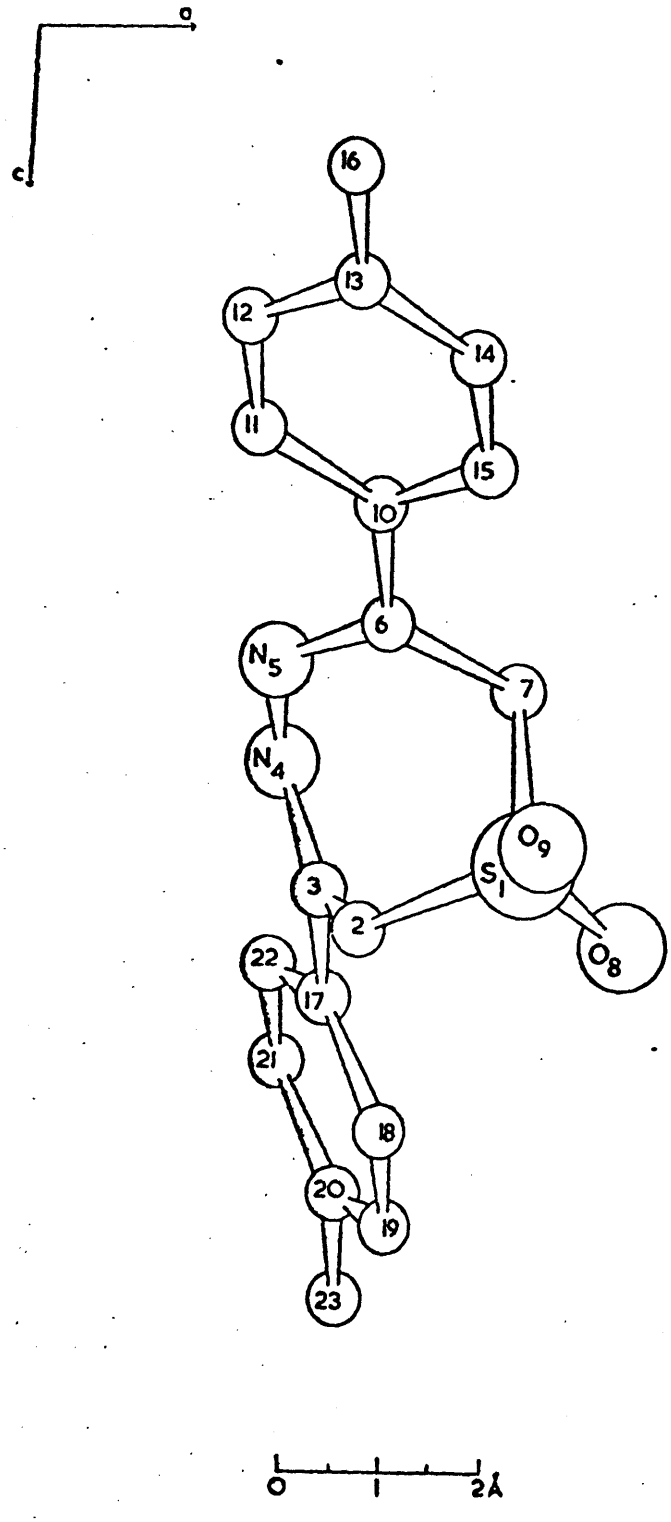


Fig 3 General view of the structure of (XXV) in the crystal showing only the non-hydrogen atoms.

a C-N-N-C dihedral angle of 61.8°, and a C-S-C bond angle of 101°.

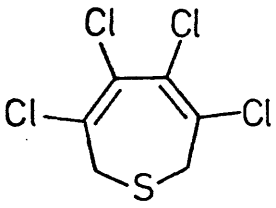
In the case of tetramethyl derivative (VII), consideration of models indicates that the HC can almost certainly be ruled out as the ground state conformation, since it would possess a very severe transannular methyl-methyl interaction, and here again, a TB appears to be by far the most likely conformation.

The conformational possibilities of triazepine (II) are likely to be very similar to those of (I).

Ring-inversion of the cyclic azines.

The ring-inversion process in the series of compounds may be considered to take place as shown in Fig. 2. and corresponds to the pseudorotation of cyclohepta-1,3-diene, proposed by Allinger and Sprague[41]. Since the near-zero barrier proposed by these workers is in sharp contrast to the present findings, a study of the low-temperature ^{1}H n.m.r. spectra of cyclohepta-1,3-diene was made. The results were inconclusive (see later section), but it is likely that any barrier present in this carbocycle is substantially lower than those measured for the heterocycles described here. In the diazepine (I), models appear to indicate that there would be no great steric interference to ring inversion from the phenyl groups, and it seems likely that the fairly high barrier is largely attributable to hindered rotation about the

N-N bond, possibly as a result of interaction between the N-1 and N-2 lone pairs in the HC transition state (cf. the preference of acyclic azines for a trans-planar stereochemistry[92]). Some support for this view may be indicated by a comparison of the barrier in thiadiazepine (IX) (18.6 kcal/mole)[45] with that in the tetrachlorothiepine (XXVI) (8.1 kcal/mole)[43]. It is unlikely that such a large difference could be brought about merely by the different substitution patterns.



(XXVI)

A comparison of the barriers in the series (I) (II), (IX), and (XXIII) provides a measure of the effect on ring-mobility of replacing carbon - 5 in (I) with nitrogen, sulphide and sulphone, respectively. The observed trend is comparable to that reported for the dibenzo-fused compounds[46] described in the Introduction (see Introduction, Table 1). The presence of a single nitrogen atom in place of carbon, as in (II), causes a slight lowering of the barrier to ring-inversion, while, as has been observed in several other examples(see Introduction), the replacement of carbon by sulphide or sulphone ((IX) and (XXIII) respectively) results in a substantially increased barrier.

The 'ring-stiffening' property of the sulphide and sulphone groups is almost certainly the result of increased bond-lengths and the decreased equilibrium C-S-C bond-angle. These factors probably increase greatly the strain in the HC transition-state (Fig. 2), and the bond-angle effect should be particularly important since this conformation already possesses considerable angle-strain. The further increase in barrier in sulphone (XXIII) may be the result of a greater resistance to C-S-C bond angle opening due to repulsion between the sulphone oxygen atoms.

A Dreiding model of the tetramethyl thiadiazepine (VII) indicates that, if the bond-angles are allowed to distort only enough to invert the ring, the HC transition-state requires two methyl groups (syn-2,7) to pass within ca. 1.7Å (carbon-carbon distance) of each other, thus suggesting, apparently, that ring-inversion would be impossible without severe bond-angle deformation. The observed free-energy barrier, however, is only about 1.5 kcal/mole higher than that for (IX), in which no such steric hindrance to ring-inversion is present. The explanation for the smallness of the effect very probably lies in the severe steric crowding which is already present in the ground-state of (VII), as can be readily appreciated on attempting to build a space-filling model of the structure. An approximate drawing of the likely

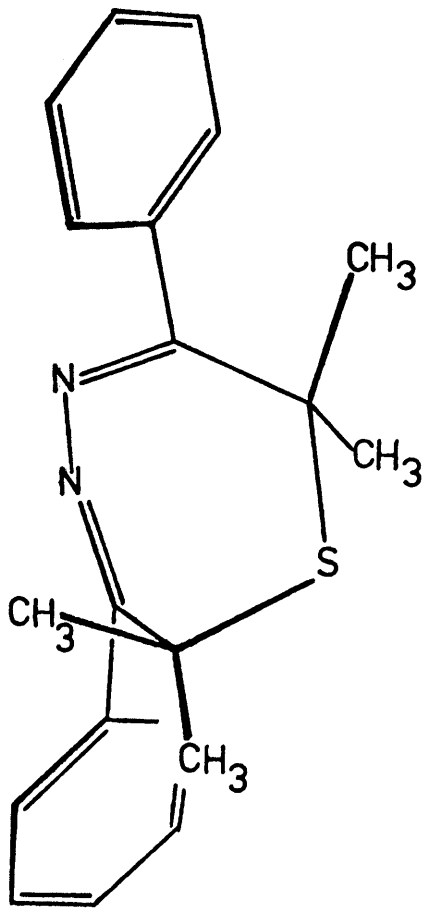
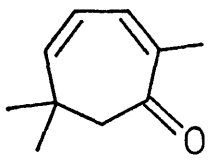


Fig 4 Probable conformation of (VII)

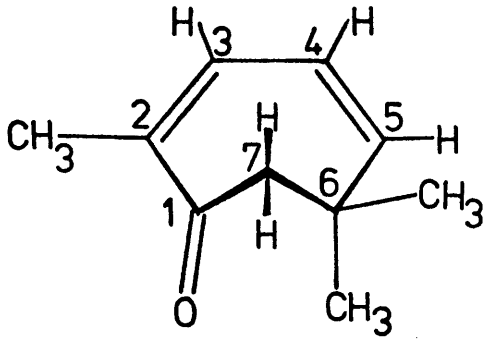
conformation of (VII) is shown in Fig. 4. Each benzene ring is twisted by at least ca. 60° from the plane of the adjacent C=N double bond, due to steric interaction with a methyl group, and the resulting loss of conjugation (contributing to increased ground-state energy) is confirmed by the strongly shifted and attenuated u.v. absorption (Table 3), and in the absence of any extra deshielding of the ortho protons in the n.m.r. spectrum (the aromatic protons appear as a narrow multiplet at τ 2.53 in $CDCl_3$; cf. (I), (II) and (IX) in Experimental). It appears, also, that slightly more effective conjugation of the Ph-C=N- moieties may be possible in the HC transition state. A further severe steric interaction in the ground state is the (2), (5) or (7), (4) methyl-nitrogen contact, and this would be relieved by some opening of the endocyclic bond angles resulting in a further increase in ground-state energy. The highly-hindered nature of (VII) is probably also the reason for the preferential formation of (XI) and (XII) under conditions which might reasonably have been expected to yield (VII) (see earlier).

Ring-inversion in related carbocycles.

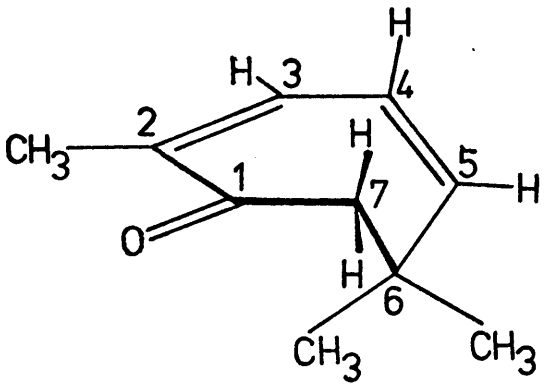


(XXVII)

The 100 MHz ^1H n.m.r. spectrum of eucarvone



(A)



(B)

Fig 5 Conformations of (XXVII)

(XXVII) in CF_2Cl_2 at -60° corresponds to rapid ring-inversion, and comprises, in addition to olefinic resonances, a singlet at τ 8.19 (6H) from the gem-dimethyl protons, a narrow multiplet centred at τ 8.09 (3H) from the methyl on C-2, and a closely spaced doublet at τ 7.37 (2H, $J_{5,7}$ ca. 1 Hz) from the methylene protons. Below ca. 80°, both the gem-dimethyl and methylene resonances are kinetically broadened, and by -130°, a frozen spectrum was observed, with non-equivalent methyl resonances 24.1 Hz apart, and an AB quartet structure for the methylene protons (ν_{AB} = 52.5 Hz, J_{AB} = 13.3 Hz). The methyl doublet coalescence (T_C = -105°) and the methylene coalescence (T_C = -100°) both gave $\Delta G^{\neq}$ = 8.3±0.1 kcal/mole, by application of equations (2) - (4).

The room-temperature spectrum of (XXVII) in $CDCl_3$ has $J_{3,4}$ = 7.6 Hz, indicating a fairly flat diene portion[39,42]. The i.r. spectrum in CCl_4 shows ν(C=O) at 1661 cm^{-1}, indicating strong conjugation, and thus implying near planarity of the enone portion. The equilibrium conformation of the molecule is probably, therefore, somewhere between the half-chair (A) with C-1 C-2, C-3, C-4, C-5 and C-6 coplanar, and the form (B), with the carbonyl oxygen, C-1, C-2, C-3, C-4, and C-7 coplanar (see Fig. 5).

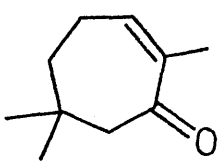
Eucarvone illustrates the lowering of the inversion barrier in a carbocyclic system (compared

with the heterocycles described above). However, it is not possible to draw a direct parallel with the conformation equilibrium in cyclohepta-1,3-diene because of the presence in (XXVII) of strong enone conjugation the loss of which in the transition state may be reflected to a considerable extent in the magnitude of the inversion barrier. In a study of cyclohepta-1,3-diene itself, no obvious kinetic changes could be detected in the methylene resonances down to -130° (100 MHz, CF_2Cl_2, or 3:1 CS_2- cyclopropane as solvent). It is not certain, however, whether this confirms the existence of only low pseudorotation barriers[41], or whether the frozen spectrum has very small or zero chemical shift differences. The spectrum of cyclohepta-1,3-diene itself is, in any case, too complex for accurate kinetic measurements and definitive results in this area probably require the preparation of suitable derivatives (such as deuterated analogues).

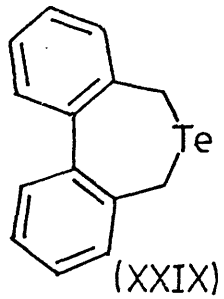
Other kinetic studies.

The increase in flexibility of the seven-membered ring on saturation of one double bond of eucarvone was shown by a low-temperature study of γ,δ-dihydro-eucarvone (XXVIII). At -120°, a temperature at which (XXVII) gives a frozen spectrum, (XXVIII) shows minimal kinetic broadening of its gem-dimethyl signal at τ8.97 (1:1 $CHClF_2$ - CF_3Cl as solvent). At -156°, pronounced broadening was observed ($W_{\frac{1}{2}}$ ca. 16 Hz), and allowing for some viscosity broadening, an upper limit

on $\Delta G^{\neq}$ could be set at about 6 kcal/mole (cf. 5.0 ± 0.3 for cycloheptene[28]).



(XXVIII)



(XXIX)

The preparation of 5,7-dihydrodibenzo[c,e] tellurepine (XXIX) (see Part II of this Thesis) prompted a study of its ring-inversion. The 60 MHz spectrum at 120° in toluene-d_8 shows a frozen AA' BB' (approximately AB) system consisting of doublets at about τ 6.25 and τ 7.15 (J 10.6 Hz). The spectrum is kinetically broadened at higher temperatures, but in this case the spectral quality was not adequate to determine the coalescence temperature (> 170°). By estimating the maximum linewidth at 140° as 4.2 Hz, a lower limit of 22 kcal/mole was set on the free-energy barrier.

Since a considerable amount of results exists on the conformational equilibria of related 2,2'-bridged biphenyls[46] (see Introduction), this further example presents an interesting comparison; for instance, the corresponding dibenzothiepine has a free-energy barrier of only 15.5 kcal/mole[47]. It appears that the greater length of the C-Te bond (ca. 2.2Å) compared with C-S (ca 1.8Å) greatly increases the strain present in the ring-inversion transition state.

EXPERIMENTAL

General details.

60 MHz ^{1}H n.m.r. spectra were measured on a Varian T-60 instrument, 100 MHz spectra on a Varian HA-100 instrument, and 220 MHz spectra on the P.C.M.U. Varian HR-220 instrument at Harwell. Tetramethylsilane was used as internal standard/lock except where detailed below. I.r. spectra were measured on Perkin-Elmer 225 or 257 instruments and u.v. spectra on a Pye-Unicam SP-800A instrument. Mass spectra were obtained on an A.E.I.-G.E.C. MS 12 instrument, and high-resolution mass measurements on an A.E.I.-G.E.C. MS 902 double-focusing instrument. Osmometric m.wts. were determined using a Mechrolab 301A vapour-pressure osmometer. M.ps. were determined on a Reichert apparatus and are uncorrected.

T.l.c. was carried out using Merck silica-gel G or GF_{254}. Petroleum spirit refers to the fraction boiling between 60° and 80° unless otherwise stated.

Low-temperature n.m.r. experiments. - These were carried out on the HA-100 using an improved version of the standard nitrogen-gas cooling system with continuous temperature monitoring by a carefully-calibrated thermocouple inserted below the sample. (The cooling and temperature-measuring equipment has been described previously[93]). Temperature stability was better than $\pm 0.2^{\circ}$ at -120°, and accuracy of

measurement of the actual sample temperature better than ±1°. Kinetic n.m.r. studies of (I), and (XXVII) used CH_2Cl_2 as internal lock signal, and for (XXVIII), $CHClF_2$ was used.

High-temperature n.m.r. experiments. - These employed a Jeol C-60HL 60 MHz instrument using the standard equipment, and with temperature calibration against propane-1,3-diol. Temperature stability appeared to be better than ±1° at 150°, and accuracy of measurement probably about ±2°. Hexamethyl disilane was used as internal standard in all experiments.

3,3-Dimethyl-4-benzoylbutyric acid. - This was prepared by a method similar to that of Blomquist and Jaffe[78]. The improved procedure was as detailed in ref. 94.

4,4-Dimethyl-3,4-dihydro-6-phenyl-2H-pyran-2-one (V). - A solution of the above ketoacid (35.9g ; 0.163 mole) in acetic anhydride (100ml) was refluxed 5 h, the acetic acid and excess acetic anhydride removed by azeotropic distillation with methylcyclohexane, and the crude enol lactone distilled under vacuum, giving pure (V) as a colourless oil, b.p. 96-98° at 0.015mm (yield 28.3g ; 83%).

1,5-Diphenyl-3,3-dimethylpentane-1,5-dione (III). - A solution of phenylmagnesium bromide [prepared from Mg (2.68g ; 0.11g. atom) and bromobenzene (18.0g ; 0.115 mole) in ether (170ml)] was added dropwise

during 2 h. to a stirred solution of (V) (20.2g ; 0.100 mole) in dry toluene (130ml) at -60° under N_2. The mixture was then allowed to warm up to room temperature during 16h, and, with stirring, a mixture of 6M hydrochloric acid (excess) and crushed ice added, the organic layer separated, and the aqueous layer extracted with ether (2 x 100ml). The combined organic phase was washed with water (50ml), saturated sodium bicarbonate until alkaline, and finally brine (100ml), dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The pale yellow oil obtained (29g) was by ^1H n.m.r. about 60% of diketone (III). Distillation (b.p. 142-152° at 0.03mm), did not significantly increase the purity, but gel-column chromatography (modified Sephadex, 9:1 methanol-petroleum spirit as eluant) gave nearly pure (III) as a viscous, colourless oil. (Found: C, 82.10; H, 7.32. $C_{19}H_{20}O_2$ requires C, 81.40; H, 7.19%), ν_{max} (film) 3050, 1667 (s); ($CDCl_3$) 1.9-2.2 (4H,m), 2.4-2.7 (6H,m), 6.73 (4H,s), 8.58 (6H,s).

3,7-Diphenyl-5,5-dimethyl-5,6-dihydro-4H-1,2-diazepine (I). - Crude diketone (III) (1.4g) was dissolved in glacial acetic acid (7ml), hydrazine hydrate (1ml) added, the mixture heated 2.5 h. at 100°, and allowed to cool overnight. Large crystals (0.15g) of (I) were deposited. Recrystallisation from petroleum spirit gave pure (I) as colourless needles, m.p. 101-102°. (Found: C, 82.56; H, 7.49; N, 9.63. $C_{19}H_{20}N_2$ requires C, 82.57; H, 7.29, N, 10.14%);

m/e 276 (M^+), ν_{max} (KBr) 3050, 2960; 1539 (C=N), 1532 (C=N), 1459, 1439, 1368, 1325, 766 (s), 747 (s), 688 (s) cm^{-1}; τ ($CDCl_3$) 1.9-2.15 (4H,m), 2.45-2.7 (6H,m), 7.53 (4H,s), 8.84 (6H,s).

5-Benzyl-3,7-diphenyl-5,6-dihydro-4H-1,2,5 triazepine (II). - This was prepared by the published method,* and obtained as fine, colourless needles from acetone, m.p. 110-112°; τ ($CDCl_3$), 1.95-2.2 (4H,m), 2.4-2.7 (11H,m), 6.18 (2H,s), 6.43 (4H,s).

2,2"-thiobis(isobutyrophenone) (VIII). - A stirred suspension of anhydrous**sodium sulphide (9.00g, 0.115 mole) in dry DMF (150ml) was treated with 2-bromoisobutyrophenone[95] (34.0g; 0.150 mole) in dry DMF (75ml). Some heat was evolved, and, after a few minutes, the mixture became deep orange in colour. After stirring at room temperature for 2 h. the mixture was poured into water (500ml), precipitating the product as a cream-coloured solid. Recrystallisation from methanol gave colourless plates of (VIII) (19.9g; 81%), m.p. 103-104°. (Found: C, 73.53; H, 6.88. $C_{20}H_{22}O_2S$ requires C, 73.60; H, 6.79%), m/e 326 (M^+), ν_{max} (KBr), 1667 cm^{-1} (C=O), τ ($CDCl_3$) 1.6-1.9 (4H,m), 2.4-2.8 (6H,m), 8.43 (12H,s).

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* Employs the potentially dangerous bromine-methanol combination, and should preferably be modified.

** The yield was greatly reduced by the presence of water.

Preparation of 1,5-diphenyl-2,2,4,4-tetramethyl-8-oxa-3-thia-6,7-diazabicyclo[3.2.1]octane (XI) and 2,2"-thiobis(isobutyrophenone) E-monohydrazone (XII) in benzene without acid catalysis. - A solution of diketosulphide (VIII) (3.26g ; 10.0 mole) in dry benzene (6ml) was stirred at room temperature with anhydrous hydrazine[96] (1.5ml). After 3 weeks, colourless crystals of (XI), had been deposited. These were filtered off, dried under vacuum and recrystallised from benzene-light petroleum giving colourless needles (0.32g), m.p. 219-221° (evacuated sealed tube). (Found: C, 70.31; H, 7.23; N, 8.79 . $C_{20}H_{24}N_2OS$ requires C, 70.56; H, 7.11; N, 8.23%), m/e 340 (15 eV, weak, M^+) (osmometric M.W. (toluene) 338; requires 340); ν_{max} (KBr) 3303 (N-H),3275 (N-H), 1107, 1053, 892; ν_{max} (CCl_4) 3301, 1049, 888 cm^{-1}, τ ($CDCl_3$) 2.3-2.8 (10H,m), 5.05 (2H,br), 8.45 (6H,s, $W_{\frac{1}{2}}$ ca. 1.3 Hz), 8.77 (6H, 2, $W_{\frac{1}{2}}$ ca. 1.3 Hz); no intense u.v. absorption at $\lambda > 230$ nm.

The filtrate from the reaction was washed with water (3 x 10ml), dried (Na_2SO_4), and concentrated in vacuo. Fractional crystallisation from light petroleum gave more (XI) (combined yield 0.44g; 13%), and mono-hydrazone (XII) (2.05g; 60%) as colourless tablets (from light petroleum), m.p. 86-87°. (Found: C, 70.44; H,7.24; N, 7.94. $C_{20}H_{24}N_2OS$. requires C, 70.56; H, 7.11; N, 8.23%); m/e 340 (M^+); ν_{max}

(KBr) 3430 (N-H), 1662 (C=O), ν_{max} (CCl_4) 3430, 1672 cm^{-1}; τ ($CDCl_3$) 1.6-1.8 (2H,m), 2.4-2.8 (8H,m), 5.0 (2H, br), 8.32 (6H,s, $W_{\frac{1}{2}}$ ca. 0.8 Hz), 8.55 (6H, s, $W_{\frac{1}{2}}$ ca. 0.8 Hz), λ_{max} (EtOH) 242 (ε= 16,000), 280 (sh) (ε = 3,500)nm.

Further studies of reaction of (VIII) with hydrazine in benzene. - A series of reactions was carried out by stirring mixtures of (VIII) (3.26g) and anhydrous hydrazine (1.5ml) in dry benzene (8ml) (a) without molecular sieve, (b) with Union Carbide molecular sieve of different types (3A pellets or powder, or 5A pellets or powder). The reactions were monitored at various stages by evaporation in vacuo of the benzene from a small sample followed by ^1H n.m.r. analysis (in $CDCl_3$). For reaction times of 2-6 days, the methyl region indicated, along with unreacted (VIII), the presence of (XII) and (XIII). Additional methyl signals ($W_{\frac{1}{2}}$ ca. 0.8 Hz) at τ 8.27 and 8.51 were tentatively assigned to Z-mono-hydrazone (XIV). The results of the different runs were rather variable, and, in general, the only consistent effect attributable to the presence of molecular sieves was a slight increase in the formation of (XIII) in the presence of type 3A powder.

Isolation of (XIII). - (VIII) (3.26g) was reacted with hydrazine in the presence of 3A sieve powder (as above). After 6 days, the mixture was filtered, and the filtrate concentrated in vacuo. The resulting oil

(3.2g) deposited some crystals on standing. This material was triturated with light petroleum and filtered with suction. ^{1}H n.m.r. of the resulting white solid showed it to be a mixture of (XIII) and (XII) (ca. 3:1). Boiling this material with light petroleum resulted in complete decomposition of (XIII), as did attempted sublimation (70° at 0.05 nm), giving a mixture (ca. 3:1) of (XII) and (VIII). (XIII) was purified, with considerable loss, by rapid crystallisation from light petroleum (b.p. 40-60°), followed by low-temperature (ca. -10°) crystallisation from anhydrous ether. Colourless needles of (XIII) (ca. 100mg) were obtained, m.p. 110-115° (decomp.). (Found: C, 67.21; H, 7.54; N, 7.98. $C_{20}H_{26}N_2O_2S$ requires C, 67.02; H, 7.31; N, 7.82%), m/e 340 (no M^+) ν_{max} (KBr) 3440 (O-H), 3350 (N-H), 3285 (N-H), 1139, 1056, 991 cm^{-1}, τ ($CDCl_3$) 2.2-2.8 (10H,m), 7.0 (4H,br), 8.52 (6H, s, $W_{\frac{1}{2}}$ ca. 1.3 Hz), 8.77 (6H, s, $W_{\frac{1}{2}}$ ca. 1.3 Hz), no intense u.v. absorption at $\lambda > 230$nm.

Preparation of (XI) using acid catalysis. - (VIII) (3.26g) was reacted with hydrazine in the presence of type 3A sieve pellets (as above). After 4 days, the mixture was filtered, the sieve washed with ether, the combined filtrate washed with water (4 x 25ml) and dried (Na_2SO_4). Evaporation of the solvent gave an oil (3.2g), whose ^{1}H n.m.r. showed the presence of (VIII), (XII) (major component) and (XIV), but not (XIII), owing to the aqueous work-up.

When a small sample of this mixture, dissolved in $CDCl_3$, was left for 1 day, the n.m.r. spectrum indicated complete disappearance of (XIV) and appearance of an equivalent amount of (XI) as estimated from the peak areas.

The remainder of the crude product mixture was dissolved in methanol (25ml). Addition of a crystal of (XI) resulted in precipitation of only a very small amount (ca. 1mg) of (XI). Acetic acid (3 drops) was added, causing colourless needles (0.33g; 10%) to separate out, identical by i.r. and ^1H n.m.r. to authentic (XI).

Reaction of (VIII) with hydrazine in benzene: work-up with hydrogen chloride. - (VIII) (3.26g) was reacted with anhydrous hydrazine without sieve (as above). After 4 days, the benzene solution was divided into two equal portions which were treated as follows:-

(a) The benzene solution was diluted with chloroform (40ml), and the solution treated with excess dry HCl.

(b) The benzene solution was diluted with methanol (40ml) and the solution treated with excess dry HCl. For both (a) and (b), work-up and crystallisation from methanol gave (XI). Dihydrothiadiazepine (VII) could not be detected in either case by ^1H n.m.r.

Methyl chemical shifts of (VIII), and (XI) - (XIV) in pyridine-hydrazine (ca. 9:1). - (VIII): τ 8.43; (XI): τ 8.45, 8.77; (XII): τ 8.27, 8.45; (XIII) τ 8.42, 8.67; (XIV): τ 8.26, 8.44.

Reaction of VIII) with hydrazine in pyridine. - (a) A solution of (VIII) (0.163g; 0.50 m mole) and anhydrous hydrazine (0.016ml; 0.5 m mole) in dry pyridine (0.4ml) was left at room temperature and its ^{1}H n.m.r. spectrum (in pyridine) monitored at intervals. After 7 days, a large amount of unreacted (VIII) remained.

(b) The experiment was repeated, using hydrazine in excess 0.045ml, 1.4 m mole). The reaction was followed to completion (20 days), and the variation in the concentration of the components is represented qualitatively as follows:—

(VIII): concentration decreased steadily, being undetectable after 5 days.

(XI): a trace present after 3 days; increased slowly to limit (ca. 15%) at 15-20 days.

(XII): formed rapidly in early stages; increased steadily to limit (ca. 70%) at 15-20 days.

(XIII): formed in early stages, reaching maximum (ca. 20%) after 2-3 days; then decreased slowly reaching ca. zero after 15-20 days.

(XIV): formed in early stages, reaching maximum (ca. 20%) after 3 days; then decreasing slowly, reaching ca. zero after 15-20 days.

After 20 days, crystals had formed in the solution.

Addition of a little water and filtration gave (XI) (24mg, 14%).

A solution of (VIII) (3.26g, 10 m mole) and hydrazine (0.90ml) in dry pyridine (8ml) was left at room temperature for 3 days. Work-up was carried out in one of (a) - (c) detailed below.

(a) Attempted isolation of (XIV). - The pyridine solution was diluted with ether (25ml), washed with water (6 x 25ml), dried (K_2CO_3) and concentrated in vacuo. An attempted fractional crystallisation from ether-light petroleum gave only E-hydrazone (XII) (total yield from 3 crops 2.2g, 65%). ^1H n.m.r. of the oil obtained after concentration of the mother liquors indicated the presence of (XIV) along with residual (XII), some unreacted (VIII), and other unidentified material. Crystals were not obtained from this mixture.

(b) Preparation of (XI) in pyridine. - The pyridine solution (see above) was poured into methanol (20ml), and, with stirring, the solution made slightly acid by addition of an excess of glacial acetic acid. Needles of (XI) slowly separated. Precipitation of (XI) was completed by addition of a little water, the crystals filtered off and washed with aqueous methanol. Recrystallisation from ethanol have pure (XI) (0.660g, 12%).

(c) Preparation of 3,6-diphenyl-2,2,7,7-tetramethyl-2,7-dihydro-1,4,5-thiadiazepine (VII). - The pyridine solution (see above) was added dropwise

with stirring, during 20 min, to a solution of 10M hydrochloric acid (22ml) in methanol (25ml), with cooling to 5-10°. The precipitated white powdery solid which was filtered off, washed with methanol and then with water to neutrality, was almost pure (VII) (0.305g, 9.5%). Recrystallisation from benzene-light petroleum gave colourless needles m.p. 207-208°. (Found: C, 74.83; H, 7.06; N, 8.26. $C_{20}H_{22}N_2S$ requires C, 74.51; H, 6.88; N, 8.69%), m/e 322 (M^+), (osmometric M.W. (toluene) 316; requires 322), ν_{max} (KBr) 1576 (C=N), 1570 (C=N), 1286, 1109, 1007, 985 cm^{-1}, τ ($CDCl_3$) 2.53 (10H,m), 8.02 (6H, s, $W_{\frac{1}{2}}$ ca. 1.4 Hz), 8.90 (6H, s, $W_{\frac{1}{2}}$ ca. 1.7 Hz; decoupling at τ 8.02, $W_{\frac{1}{2}}$ becomes ca. 1.2 Hz).

Treatment of (XI) with pyridine/HCl/methanol. - A solution of (III) (200mg) in pyridine (15ml) was subjected to the methanolic HCl work-up conditions described above. Recovery of the precipitated white solid and ^1H n.m.r. analysis showed it to be unchanged (XI).

Conversion of (XI) to (VII). - A solution of (XI) (0.068g, 0.20 m mole) in nitrogen-purged glacial acetic acid (2ml) was refluxed for 16 h, in a static nitrogen atmosphere. The solution was then cooled, diluted with chloroform (5ml), washed with saturated sodium bicarbonate solution (3 x 10ml) and water (2 x 5ml), dried (Na_2SO_4), and the solvent removed under reduced

pressure. The residual white solid was recrystallised from benzene-light petroleum, giving colourless needles (0.036g, 56%) m.p. 206-207°, identical by i.r. to authentic (VII).

Effect of heat and acids on E-mono-hydrazone (XII). - (a) A solution of (XII) (50mg) in dry benzene (10ml) was refluxed for 16h.

(b) A solution of (XII) (57mg) in benzene (100ml) containing glacial acetic acid (3 drops) was refluxed for 2 h.

(c) A solution of (XII) in $CDCl_3$ (0.4ml) containing a trace of p-toluenesulphonic acid was left at room temperature for 3 days.

In all cases, ^1H n.m.r. showed that (IV) remained substantially unchanged. No cyclised products (VII) or (XI), nor Z-hydrazone (XIV) could be detected.

3,6-diphenyl-2,2,7,7-tetramethyl-2,7-dihydro-1,4,5-thiadiazepine-1,1-dioxide (XV). - To a stirred solution of (VII) (0.208g, 0.646 m mole) in methylene chloride (3ml) was added dropwise during 10 min. at 0° a solution of 76% m-chloroperbenzoic acid (0.294g, 1.29 m mole) in methylene chloride (5ml). Stirring was continued for a further 30 min, after which the mixture was filtered, the filtrate washed with sodium metabisulphite solution (5ml), saturated sodium bicarbonate solution (10ml) and water (2 x 5ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. Recrystallisation of the resulting white

solid (244mg) from benzene gave sulphone (XV) as colourless plates m.p. 197-199° (decomp.). (Found: C, 67.80; H, 6.28; N, 8.16. $C_{20}H_{22}N_2O_2S$ requires C, 67.78; H, 6.26; N, 7.90%), ν_{max} (KBr) 1560 (C=N), 1298 (S=O), 1285 (S=O), 1154 (S=O), 1105, 1011 cm^{-1} τ($CDCl_3$) 2.3-2.7 (10H,m), 8.13 (6H, s, $W_{\frac{1}{2}}$ ca. 1.4 Hz), 8.46 (6H, s, $W_{\frac{1}{2}}$ ca. 1.6 Hz).

Reactions of 2,2"-thiodiacetophenone (XVI) with hydrazine[81]. - (a) A solution of diketosulphide (XVI) (0.540g, 2.0 m mole) (prepared similarly to (VIII)) and hydrazine hydrate (0.10ml, 2.0 m mole) in ethanol (3ml) was refluxed for 4 h. On cooling, the solution deposited crystals of dihydrothiadiazepine (IX) (0.25g), m.p. 176-178° (lit[81] 175°), ν_{max} (KBr) 1565, 1017 cm^{-1} τ($CDCl_3$) 1.9-2.3 (4H,m), 2.3-2.8 (6H,m), 6.37 (2H, d, J=12 Hz), 6.67 (2H, d, J=12 Hz).

(b) Hydrazine hydrate (0.28ml. 5.6 m mole) was added to a boiling solution of (XVI) (1.53g, 5.67 m mole) in ethanol (10ml). The mixture was refluxed for 10 min, cooled quickly in ice, and the precipitated crystals (0.53g) filtered off. Recrystallisation from ethanol gave colourless plates (0.355g) of a pure hydrazone (XVII) m.p. 131-132° (lit 128°), ν_{max} (KBr) 3365 (N-H), 3300 (N-H), 3205 (N-H), 1687 (C=O), 1682 (C=O), 1198, ν_{max} (CCl_4) 3420, 3305, 3220, 1693, 1678 cm^{-1}. τ($CDCl_3$) 1.9-2.8 (10H,m), 3.9 (2H,br), 6.10 (2H,s), 6.19 (2H,s).

(c) A solution of (XVI) (1.35g, 5.0 m mole) and

anhydrous hydrazine (0.5ml, 15 m mole) in dry pyridine (5ml) was left at room temperature for 3 h. Work-up with acetic acid (as for preparation of (XI) in pyridine) gave, as the only detectable product, the dihydrothiadiazepine (IX) (ca. 1.0g) identical by i.r. and ^{1}H n.m.r. to genuine material.

Reaction of hydrazone (XVII) with acetic acid[81]. - (a) (XVII) (10mg) was dissolved in hot (100°) glacial acetic acid. Fine colourless needles began to separate immediately. The mixture was rapidly cooled and diluted with water. The solid obtained was identical by i.r. with dihydrothiadiazepine (IX). No (N-H) absorption could be detected.

(b) To a solution of (XVII) (40mg) in $CDCl_3$ in an n.m.r. tube was added glacial acetic acid (2 drops), and the ^{1}H spectrum run immediately. New signals (corresponding to ca. 10% of the mixture had appeared at positions identical to those for the methylene protons of (IX). The spectrum was scanned repeatedly, and the concentration of (IX) was seen to increase until, after 30 min, no hydrazone (XVII) could be detected and the spectrum was identical to that of pure (IX). No intermediate compounds were detected during the reaction.

Attempted hydrolysis[81] of dihydrothiadiazepine (IX). - Samples of (IX) (0.270g, 1.0 m mole) were treated as follows: (a) refluxed 3 days with water (0.2ml) in ethanol (5ml); (b) refluxed 1 day with water (0.2ml) and glacial acetic acid (1 drop) in ethanol (5ml),

(c) refluxed 1 day with water (0.2ml) and a trace of sodium hydroxide in ethanol (5ml). In all cases, (IX) was recovered unchanged.

Thermal stability of (XI). - A degassed solution of (XI) (100mg) in dry, peroxide-free tetrahydropyran (2ml) in a sealed tube was heated for 20 min at 200°. The material obtained after removal of solvent was, by ^{1}H n.m.r. and i.r. unchanged (XI).

1,5-diphenyl-2,2,4,4-tetramethyl-6,7,8-trioxa -3-thiabicyclo[3.2.1]octane (XVIII). - A solution of (XI) (0.170g, 0.50 m mole) in benzene (10ml) was stirred vigorously for 1 day at room temperature, with free access of air. Removal of the benzene under reduced pressure gave almost pure ozonide (XVIII), uncontaminated with (XIX). Recrystallisation from ethanol gave pure (XVIII) (0.137g, 80%), as colourless needles, m.p. 182-185° (decomp.). (Found: C, 69.82; H, 6.68; N, 0.0. $C_{20}H_{22}O_3S$ requires C, 70.16; H, 6.48%), m/e 252 (no M^+), (osmometric M.W. (toluene) 347; requires 342), ν_{max} (KBr) 1132, 1074, 1043, τ ($CDCl_3$) 2.4-2.8 (10H,m), 8.41 (6H, s, $W_{\frac{1}{2}}$ ca. 1.3 Hz), 8.73 (6H, s, $W_{\frac{1}{2}}$ ca. 1.3 Hz), no intense u.v. absorption at $\lambda > 230$nm.

Identical results to the above were obtained by carrying out the reaction in an atmosphere of pure oxygen, whether or not light was excluded.

Reduction of ozonide (XVlll) by zinc in acetic acid. - A solution of (XVIII) (14.3mg) in acetic acid (1ml)

was stirred with an excess of zinc dust at room temperature for 2 days. The reaction mixture was centrifuged, the clear solution diluted with water and the precipitated solid recrystallised from methanol giving colourless plates (10mg), m.p. 102-104°, whose i.r. and ^{1}H n.m.r. were identical to those of diketosulphide (VIII).

1,5-diphenyl-2,2,4,4-tetramethyl-6-oxa-3-thiabicyclo [3.1.0]hexane (XIX). - A solution of (III) (0.450g, 1.32 m mole) in benzene (10ml) was stirred and refluxed for 1 day with free access of air. The yellow solution obtained was concentrated in vacuo and crude epoxide (XIX) obtained, ^{1}H n.m.r. showing the presence of only a trace of ozonide (XVIII). Minor impurities were removed by a short silicic acid column (Mallinckrodt, methylene chloride as eluant) followed by recrystallisation from ethanol, giving colourless needles of (XIX) (0.180g, 44%),m.p. 180-181° (Found: C, 77.53; H, 7.27; N, 0.0. $C_{20}H_{22}OS$ requires C, 77.39; H, 7.14%), m/e 310 (M^+), (Osmometric M.W. (chloroform) 317; requires 310), ν_{max} (KBr) 1129, 950 cm^{-1}, τ ($CDCl_3$) 2.4-3.0 (10H,m), 8.35 (6H, s, $W_{\frac{1}{2}}$ ca. 1.3 Hz), 8.63 (6H, s, $W_{\frac{1}{2}}$ ca. 1.3 Hz), no intense u.v. absorption at λ > 230nm.

Treatment of epoxide (XIX) with molecular oxygen. - (XIX) (150mg) was stirred in benzene solution in air at room temperature, using conditions identical to those used for preparing ozonide (XVIII). Recovery of the

material after 1 day and ^{1}H n.m.r. analysis showed it to be completely unchanged (XIX).

Effect of heat on ozonide (XVIII). - Ozonide (XVIII) (150mg) was heated under reflux in benzene for one day. ^{1}H n.m.r. of the solid obtained after evaporation of benzene showed it to be mainly unchanged (XVIII), though some decomposition to unidentified products has occurred; no trace of epoxide (XIX) could be detected.

Eucarvone (XXVII). - This was prepared from (-)carvone by the method of Corey and Burke[97].

γ,δ-Dihydroeucarvone (XXVIII). - A sample of the compound was available in this Department[98].

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PART II

Studies of Simple and Bridged Eight-membered Systems.

Introduction.

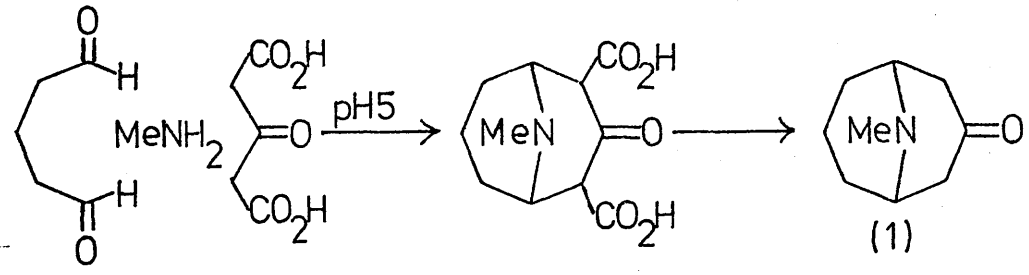
9-Heterobicyclo[3.3.1]nonane Ring Systems : Preparation and Some Synthetic Applications.

Compounds containing the bicyclo[3.3.1]nonane ring system[1], and heterocyclic analogues[2], are of considerable interest, particularly for conformational studies[3-7], and as intermediates in the synthesis of tricyclic compounds, such as heteroadamantanes[8]; there has also been some interest in the pharmacological activity of heterocyclic derivatives[2]. In this introduction, only the 9-hetero-systems, which are of particular current interest, will be considered.

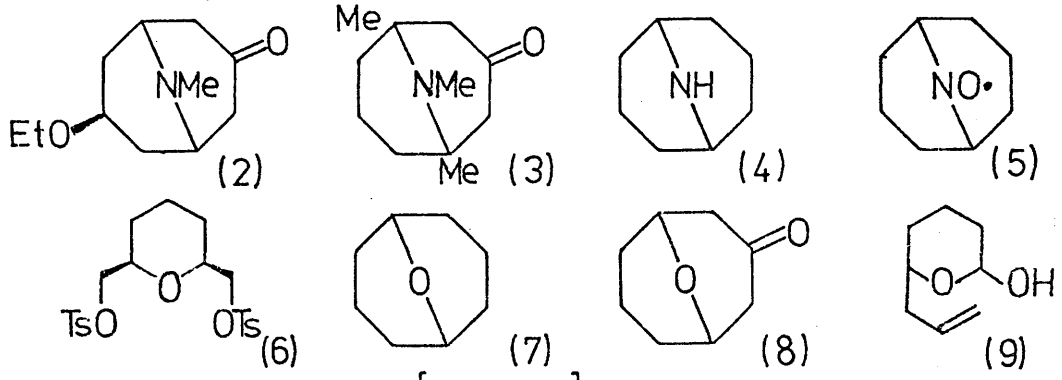
Preparation.

From acyclic or six-membered cyclic precursors.

In 1879, Tanret[9] reported the isolation of an alkaloid, which he named pseudopelletierine, from the pomegranate root-bark, and the 9-azabicyclo[3.3.1]nonan-3-one structure (1) was eventually assigned to it by Piccinini[10]. Historically also, pseudopelletierine was the starting-point for Willstätter's original isolation of cyclooctatetraene[11] in 1911, which he prepared by reduction of the ketone function, followed by an exhaustive methylation-elimination procedure.



In 1924, Robinson published an extension of his elegant tropinone synthesis to the homologous pseudopelletierine[12]. The synthesis, modified in detail by Schöpf[13], involves the Mannich condensation of glutaraldehyde and methylamine with acetonedicarboxylic acid at ambient temperature, in the presence of an acetate buffer. The Robinson-Schöpf synthesis was probably the first which mirrored a possible biosynthetic pathway and took place under conditions similar to those present in biological systems. The reaction has been used for the preparation of many similar compounds, including (2) from 3-ethoxy-glutaraldehyde[14], and the 1,5-dimethyl compound (3) from heptane 2,6-dione[15]. Similarly, by using ammonia as the amine component, and Wolff-Kishner reduction of the product, the unsubstituted 9-azabicyclo[3.3.1]nonane was prepared, and by oxidation with hydrogen peroxide, in the presence of phosphotungstic acid, the red, crystalline nitroxide radical (5) obtained[16].

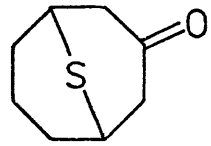


The 9-oxabicyclo[3.3.1]nonane ring system was

first prepared in 1957 by a laborious multi-step route, employing the cyclisation of the ditosylate (6) with diethyl malonate[17], the unsubstituted ether (7) eventually being obtained. A slightly shorter route to the ketone (8) was subsequently reported[18], using acid-catalysed cyclisation of the hemiacetal-olefin (9).

9-Thiabicyclo[3.3.1]nonane (10) was originally isolated from the sulphide fraction of Iranean petroleum[19], and the ring-system was synthesised[20] by treatment of the methiodide of (1) with aqueous sodium sulphide to give 9-thiabicyclo[3.3.1]nonan-3-one (11).

(10)



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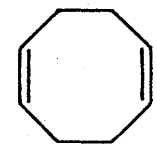
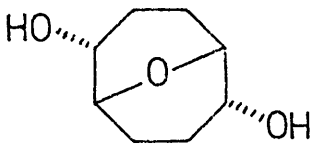


(12)

From cyclooctane derivatives.

Eight-membered carbocyclic compounds, which until fairly recently were rather difficult to synthesise, are now commercially-available in large quantities via metal-catalysed olefin cyclo-oligomerisation reactions. Direct bridging of eight-membered carbocycles is therefore an attractive route to 9-heterobicyclo[3.3.1]nonane derivatives.

Electrophilic additions to cis,cis-cycloocta-1,5-diene (12) often lead to bridged products. In the reactions of (12) with peracids a useful degree of selectivity is possible:



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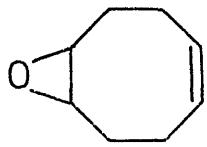

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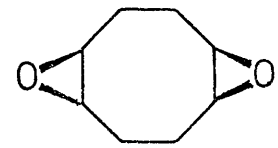
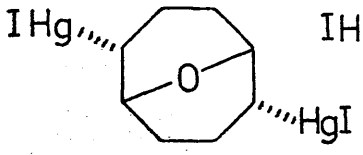


(15)

aqueous performic acid[21] gave a good yield of the [3.3.1] diol (13), peracetic acid[22] gave mainly the monoepoxide (14), and perbenzoic acid[22] the syn-diepoxide (15). A reaction which has been extensively applied in this area is olefin oxymercuration. Treatment of (12) with mercuric acetate in an aqueous medium, followed by potassium iodide, yielded a mixture of the mercuri-iodides (16) and (17). Iodine demercuration of this mixture led to varying proportions of six isomeric di-iodides from which the exo,exo isomer (18) could be crystallised[23]. A variation on the oxymercuration reaction was recently



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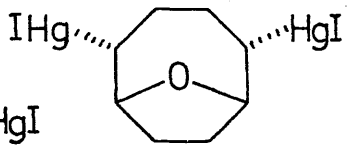

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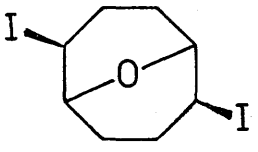
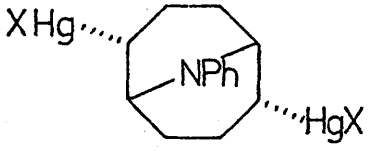


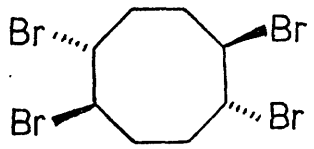
(18)



(19) X=Cl,Br

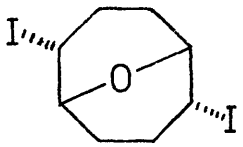
described[24] in which cyclooctadiene (12) was treated with aniline, mercuric acetate and a potassium halide to give the mercurihalide (19), reducible to 9-phenyl-9-azabicyclo [3.3.1] nonane. No [4.2.1] isomers were detected in this instance.

Reactions of (12) with halogens and pseudohalogens are also synthetically very useful. (12) with bromine in hexane[25] gave a mixture of two tetrabromides, from which isomer (20), on heating under pressure with ammonia formed 9-azabicyclo[3.3.1]nona-2,6-diene (21).



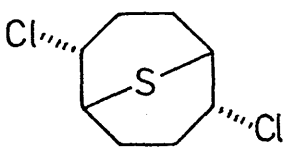
(20)

(21)

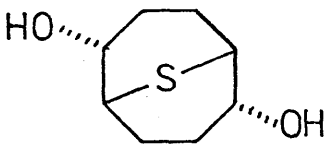


(22)

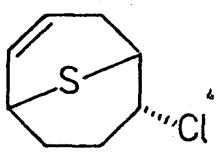
On the other hand, reaction of (12) with iodine in methanol[26] led directly to the endo,endo-di-iodo-9-oxabicyclo[3.3.1]compound (22). Addition of sulphur dichloride to (12) gave endo,endo-dichloro-sulphide (23) in high yield[27,28]. The reactions of the chlorine atoms of (23) show participation by sulphur[28], for example hydrolysis occurs very readily with retention of configuration, to give the endo, endo-diol (24). Rapid lithium aluminium hydride reduction to 9-thiabicyclo [3.3.1]nonane (10) also occurs, as does thermal elimin-



(23)



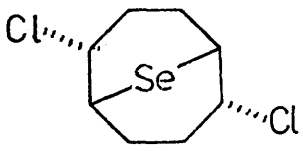
(24)



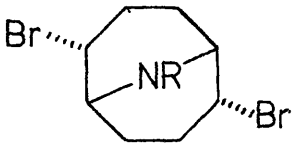
(25)

ation of one mole of HBr with formation of the chloro-olefin (25). Treatment of diene (12) with selenium monochloride (Se_2Cl_2) resulted[29] in deposition of elemental selenium, with formation of the endo,endo-dichloroselenide (26). The selenium bridge, however, is readily removable; for example, treatment of (26) with potassium cyanide gave, instead of the expected dicyanoselenide, cyclooctadiene (12), the same product, rather than the 9-selenabicyclo-nonane, being recovered on lithium aluminium hydride

reduction of (26). A further similar addition to (12) is that of N,N-dibromo-p-toluenesulphonamide, in this case the product[30] being the endo,endo-dibromo-9-azabicyclo[3.3.1]nonane (27).

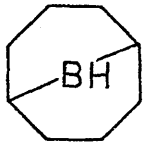


(26)



(27)

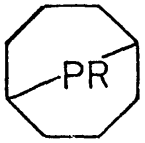
R=SO$_2$-C$_6$H$_4$-Me



(28)

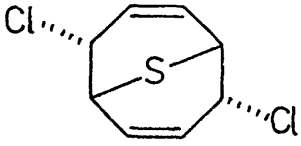
An important electrophilic addition reaction with (12) is hydroboration with diborane, which was found[31] to give 9-borabicyclo[3.3.1]nonane (28). Brown and coworkers have reinvestigated this compound '9-BBN', which exists as a crystalline, air-stable dimer, and have found it to be a useful, selective hydroboration reagent, as well as a versatile synthetic intermediate[32-34].

The preparation of the 9-phosphabicyclo[3.3.1]nonane ring system from (12) has also been reported[35]; this reaction, which is probably of a free-radical nature, takes place when (12) is heated with a primary phosphine in the presence of dibutyl peroxide, forming a mixture of the [3.3.1] compound (29) and its [4.2.1] isomer.

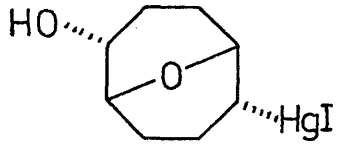


(29)

R=H,Ph,$C_{20}H_{42}$



(30)

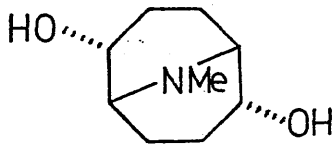


(31)

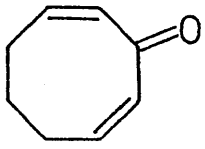
Bridging reactions of cyclooctatetraene have not been much used in synthesis of bicyclo[3.3.1] compounds.

However, it was found[36] that the dichlorodiene sulphide (30) could be obtained by addition of sulphur dichloride to the tetraene.

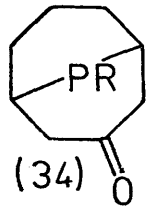
The epoxides of (12) have also been used in bridging reactions. Monoepoxide (14) was reacted with mercuric acetate, followed by potassium iodide, the hydroxy-mercuri-iodide (31) being obtained.[37] The diepoxide (15) was hydrolysed[22] by dilute aqueous acid to the diol (13), and also underwent nucleophilic attack by sodium sulphide[22] to give dihydroxysulphide (24), and by methylamine[38] to give dihydroxyamine (32), the corresponding [4.2.1] isomer also being obtained in each case.



(32)



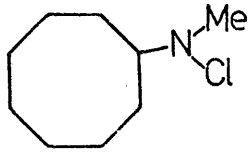
(33)



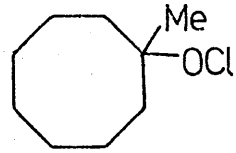
(34)

R=Ph,CH_2Ph

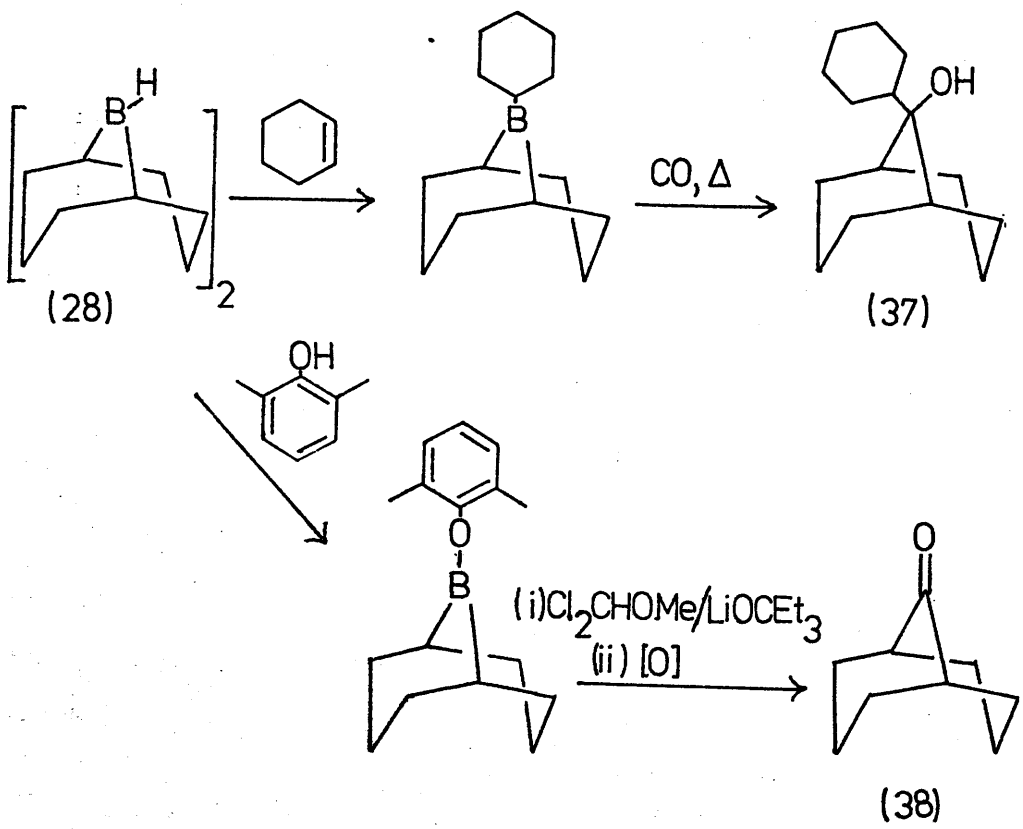
The formation of mixtures of isomers in bridging reactions is obviated by the use of cycloocta-2,7-dienone (33) as the eight-membered precursor. (33) was prepared[39] in good yield from cyclooctanone by a ketalisation-bromination-dehydrobromination-ketal hydrolysis sequence, and was found to undergo Michael additions in high yields; for example with methylamine, pseudopelletierine (1) is formed[40], while primary phosphines[41], such as benzyl phosphine, give the 9-phosphabicyclo[3.33.3.1]alogues (34).



(35)



(36)


H
B
2
(28)
B
CO, Δ
OH
(37)
OH
O
B
(i)Cl2CHOMe/LiOCEt3
(ii) [O]
O
(38)

Among other reactions which have been used in the preparation of 9-heterobicyclo[3.3.1]nonanes are the photolytic cyclisation of the chloro-amine (35), giving 9-methyl-9-azabicyclo[3.3.1]nonane[42], and of the hypochlorite (36), giving 1-methyl-9-oxabicyclo[3.3.1] nonane, and it[4.2.1] isomer[43].

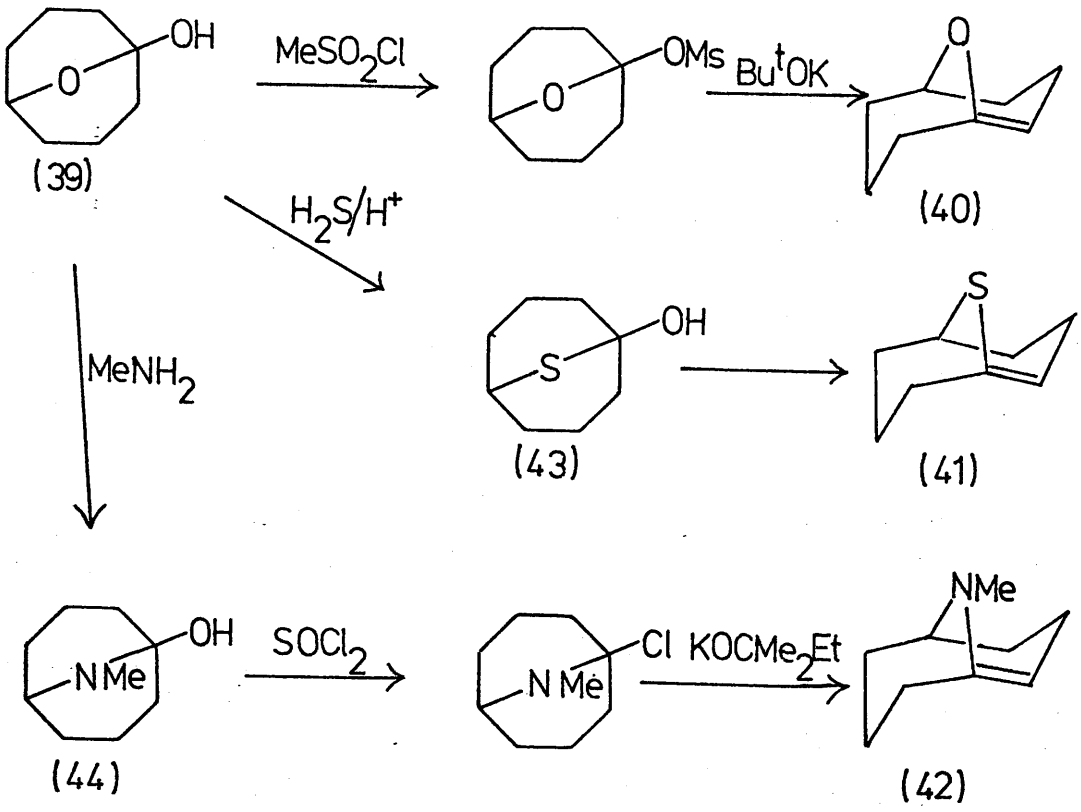
Synthetic Applications.

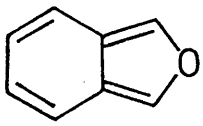
Reactions of 9-BBN (28).

As well as its use as a hydroboration reagent, and its conversion in the normal way to cyclooctane-*cis*-1,5-diol and cyclooctane-1,5-dione in high yield, a variety of other reactions of (28) and 9-substituted derivatives has been investigated, and are well-described elsewhere.[31,32] However, it is interesting to note here that (28) is a good source of carbocyclic bicyclo[3.3.1]nonane derivatives; for example, hydroboration of a suitable olefin with (28) gives a 9-alkyl derivative, which on heating with carbon monoxide forms the [3.3.1] alcohol (36) in near quantitative yield[44]. (27) also, on treatment with a hindered phenol, followed by base-promoted reaction of the resulting borinic acid with α,α-dichloromethyl ether, gives[45] an excellent yield of the difficultly accessible bicyclo[3.3.1]nonan-3-one (38).

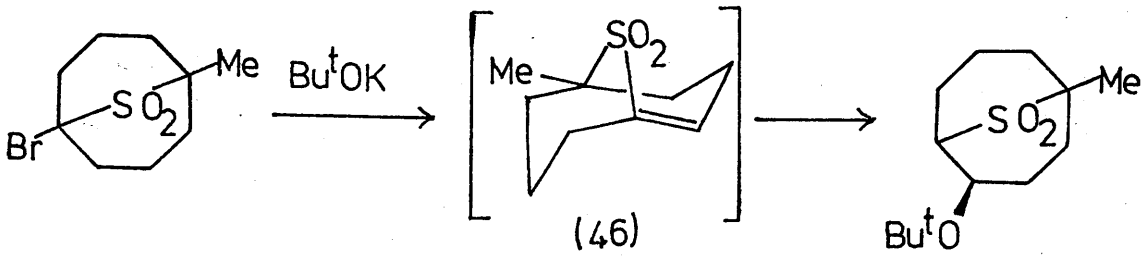
Formation of bridgehead olefins.

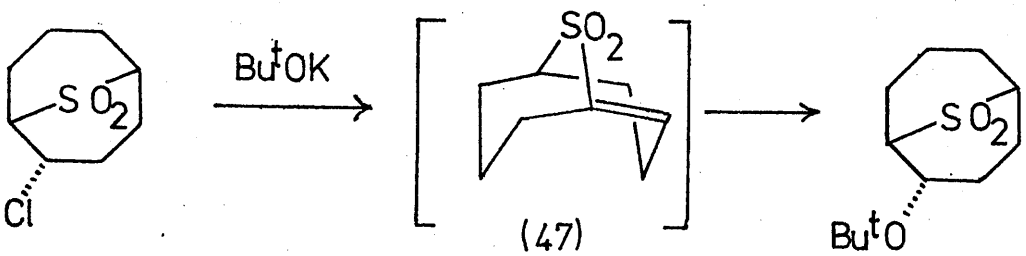
Recently Wiseman and his coworkers have prepared a series of bicyclo[3.3.1] compounds with a double-bond at the bridgehead. These highly-strained systems violate Bredt's rule[46], and have unusual reactivity.


OH
O
MeSO2Cl
OMs
Bu^tOK
O
(39)
(40)
H2S/H+
MeNH2
OH
S
S
(43)
(41)
OH
NMe
SOCl2
Cl
NMe
KOCMe2Et
NMe
(44)
(42)


O

(45)


Me
SO2
Br
Bu^tOK
Me
SO2
(46)
Me
SO2
Bu^tO

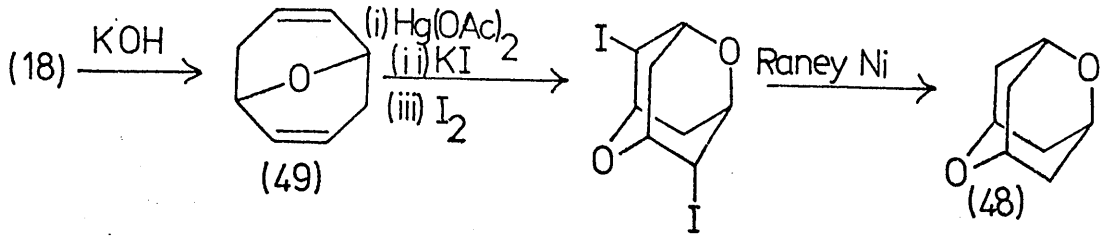

SO2
Cl
Bu^tOK
SO2
(47)
SO2
Bu^tO

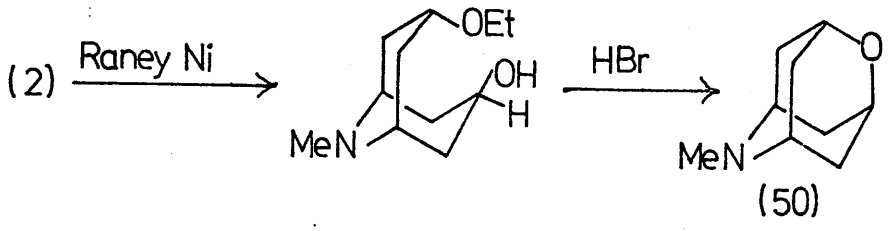
Starting from 5-hydroxycyclooctanone (which exists entirely in the hemiacetal form (39)), the stable anti-Bredt 9-hetero-bicyclo[3.3.1]non-1-enes (40) to (42) were prepared. Formation of the mesylate of (39), followed by base-induced elimination[47], gave (40); reaction of (39) with hydrogen sulphide gave hydroxy-sulphide (43), which was converted to (41) via the mesylate[48]; and the hydroxy-amine (44), formed from (39) and methylamine, was converted to (42) by chlorination followed by elimination[49]. All these anti-Bredt compounds readily form Diels-Alder adducts with 1,3-diphenylisobenzofuran (45), showing their activated nature. However, severe distortion of the alkene system prevents effective conjugation with the heteroatom. Consequently, (40) is much more slowly hydrolysed than a normal enol ether[47], while (42) alkylates at nitrogen, not at carbon, as would a normal enamine[49]. The formation of two sulphones, trapped as their Diels-Alder adducts, has also been reported, (46) with the Z-configuration, and more surprisingly, (47) with the very strained E configuration[50].

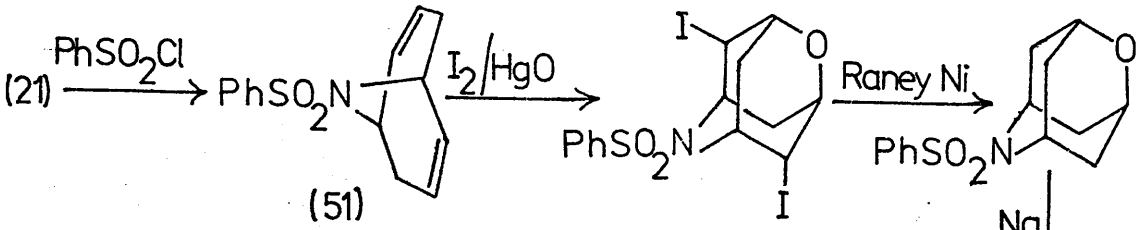
Synthesis of tricyclic systems.

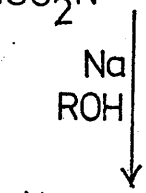
Much of the work in this field has been carried out by the groups of Stetter et al. and Ganter et al. Ganter[8] has also published a short summary of the preparations of compounds of this type.

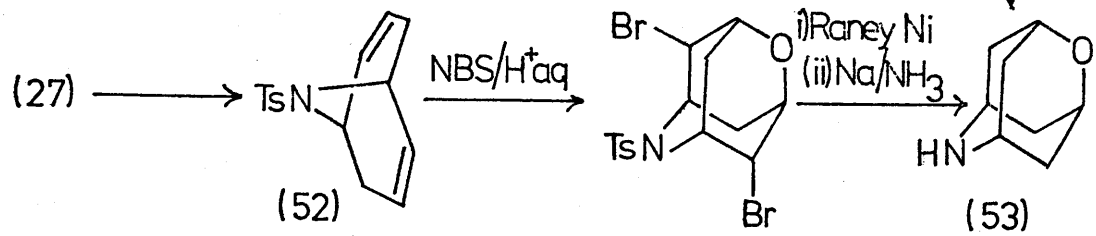
2,6-Diheteroadamantanes - The extremely high stability of adamantanoid compounds often results in their exclusive

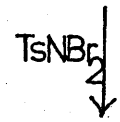

(18)
KOH
(i) Hg(OAc)2
(ii) KI
(iii) I2
Raney Ni
(49)
(48)

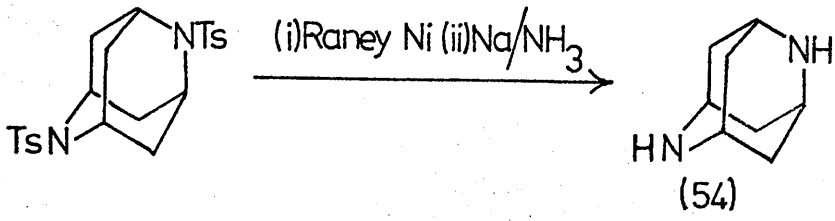

(2)
Raney Ni
OEt
OH
H
MeN
HBr
MeN
(50)

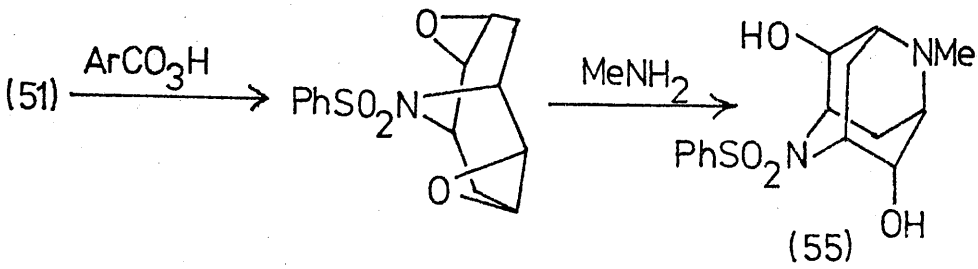

(21)
PhSO2Cl
PhSO2N
(51)
I2/HgO
PhSO2N
I
Raney Ni
PhSO2N


Na
ROH


(27)
TsN
(52)
NBS/H+aq
Br
TsN
Br
i)Raney Ni
(ii)Na/NH3
HN
(53)


TsNBr2

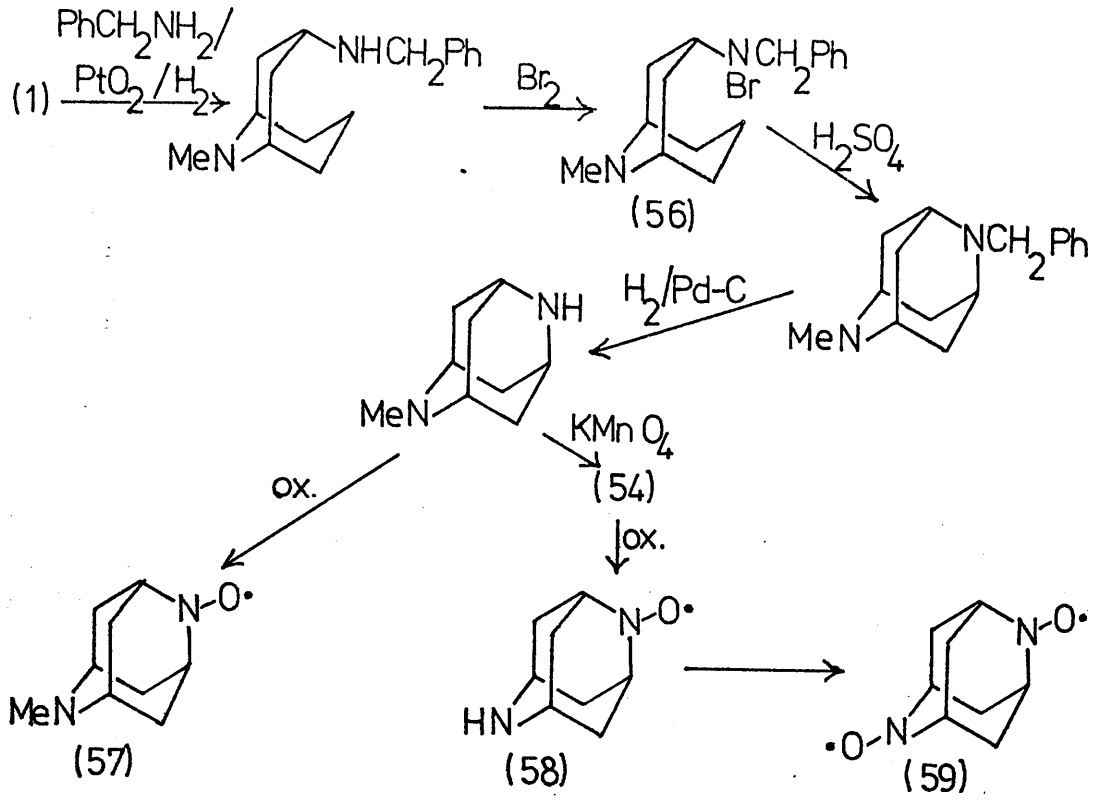

NTs
TsN
(i)Raney Ni (ii)Na/NH3
NH
HN
(54)

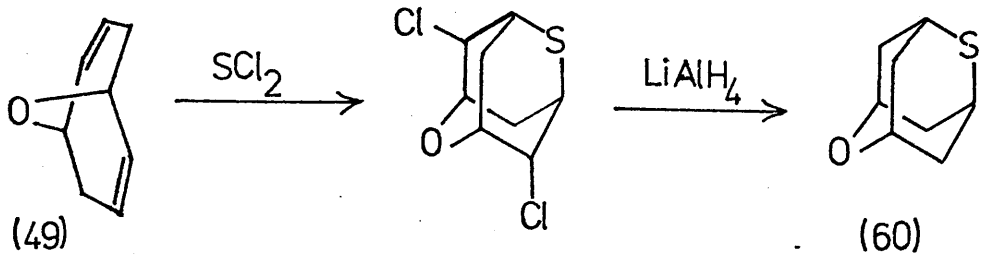

(51)
ArCO3H
PhSO2N
MeNH2
HO
NMe
PhSO2N
OH
(55)

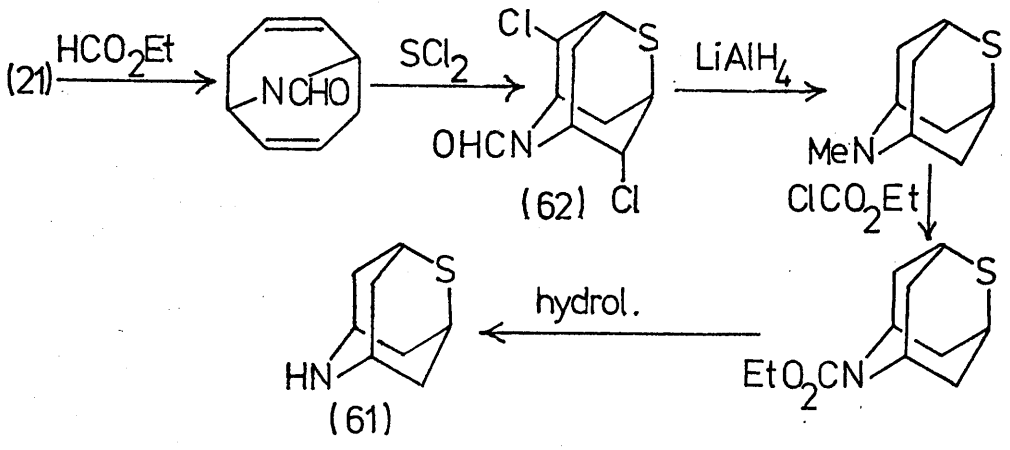
formation in a cyclisation reaction which might be expected to give several isomeric products. 2,6-Dioxaadamantane (48) was prepared[51] from the di-iodide (18). Base-induced elimination to the diene ether (49) was followed by oxymercuration-demercuration which inserted a second oxygen bridge, and the resulting di-iodo-compound could be readily reduced to (48).

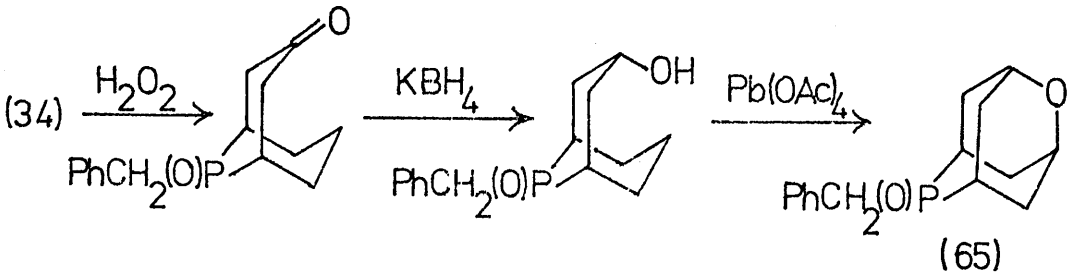
The original preparation of the 2-oxa-6-azaadamantane skeleton[14] employed the ethoxy-ketoamine (2). Reduction of the carbonyl group to hydroxyl, followed by acid-catalysed ether-exchange, gave the 6-methyl compound (50). Several other routes to this ring-system have since been reported, one of which used a simple one-step oxymercuration-demercuration procedure on the diene sulphonamide (51), with mercuric oxide and iodine[52]. Another method[30] began with the 9-tosyl dibromide (27). Elimination, followed by treatment of the resulting diene (52) with N-bromosuccinimide in aqueous acidic medium, gave a dibromo oxaazaadamantane, reducible to the parent compound (53).

The unsubstituted 2,6-diazaadamantane (54) was made[53] by treatment of diene sulphonamide (52) with a further equivalent of N,N-dibromo-p-toluenesulphonamide, followed by reduction. A different route was also devised[38] in which diene sulphonamide (51) was converted to its diepoxide, which was reacted with methylamine to give the substituted diazaadamantane (55). Nitroxide radicals derived from 2,6-diazaadamantane have also been prepared[54] from pseudopelletierine (1), in a route involving


PhCH2NH2/
(1) PtO2/H2
NHCH2Ph
MeN
Br2
NCH2Ph
Br
MeN
(56)
H2SO4
NCH2Ph
MeN
H2/Pd-C
NH
MeN
KMnO4
(54)
ox.
ox.
N-O•
MeN
(57)
N-O•
HN
(58)
N-O•
•O-N
(59)


O
(49)
SCl2
Cl
S
O
Cl
LiAlH4
S
O
(60)

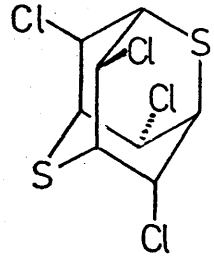

(21) HCO2Et
NCHO
SCl2
Cl
S
OHCN
(62) Cl
LiAlH4
S
MeN
ClCO2Et
S
EtO2CN
hydrol.
S
HN
(61)


(34) H2O2
O
PhCH2(O)P
KBH4
OH
PhCH2(O)P
Pb(OAc)4
O
PhCH2(O)P
(65)

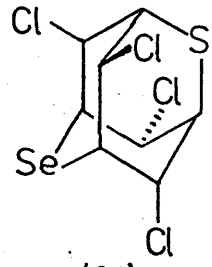
Hofmann-Löffler cyclisation of the N-bromoamine (56) with sulphuric acid, followed by dealkylation. The radicals (57), (58) and (59) are all high-melting crystalline solids.

2-Oxa-6-thiaadamantane (60) was prepared[55], very simply, by reduction of the sulphur dichloride adduct of the diene ether (49). The synthesis[25] of 2-thia-6-azaadamantane (61) used the diene amine (21), which was formylated, the product treated with sulphur dichloride to give the dichloro-thia-azaadamantane (62), which on reduction and demethylation gave (61).

Neither the unsubstituted 2,6-dithiaadamantane nor 2-thia-6-selenaadamantane has been reported, though the tetrachloro-derivatives (63)[36] and (64)[29] were isolated



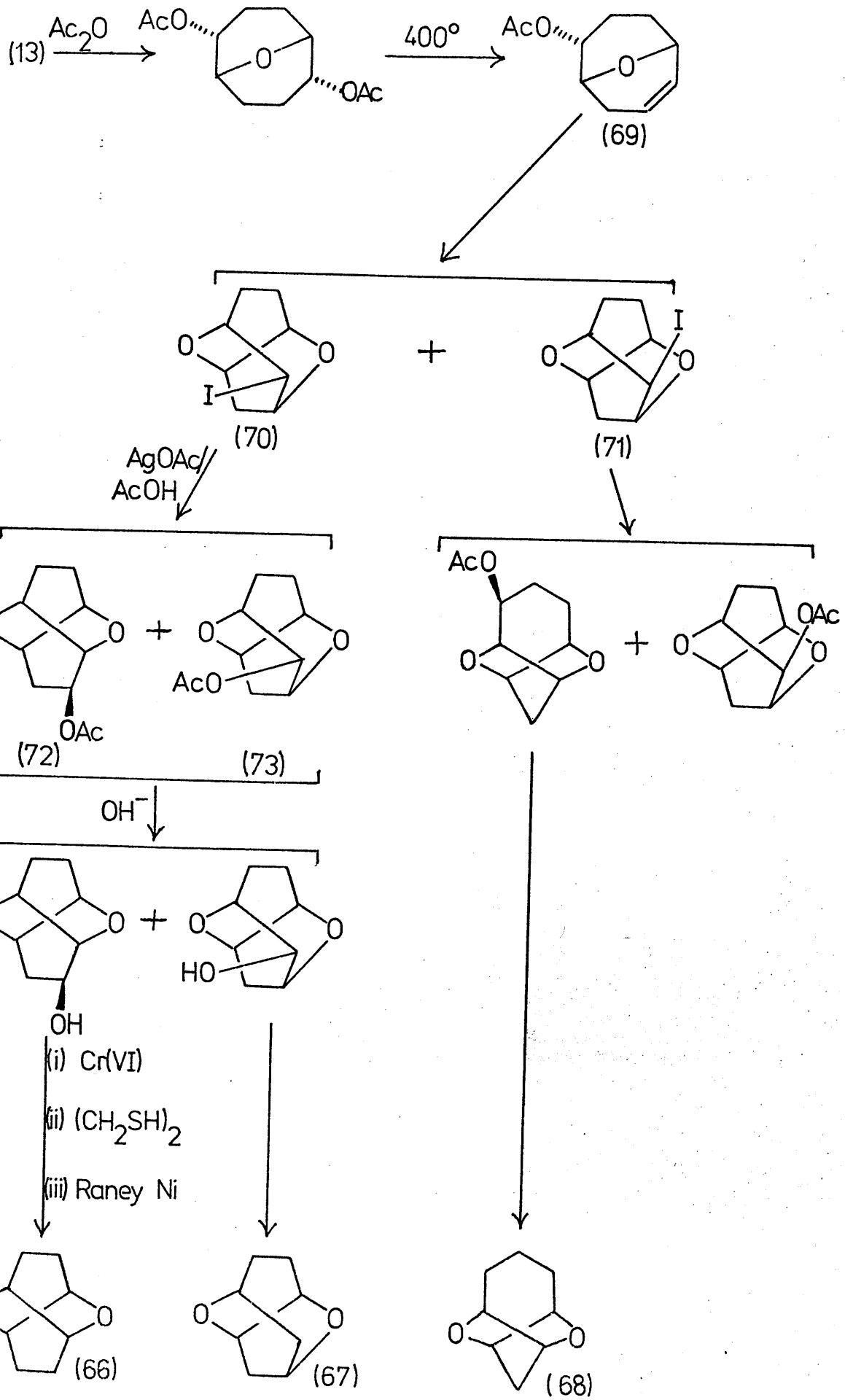
(63)



(64)

after reaction of the dichlorodiene-sulphide (30) with sulphur dichloride and selenium monochloride respectively.

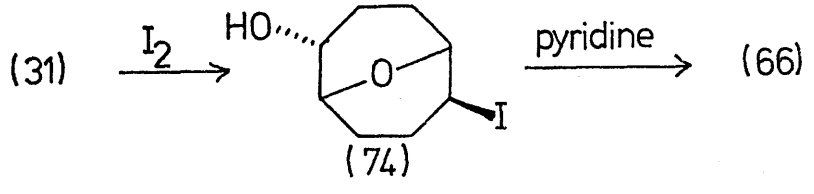
The 2-oxa-6-phosphaadamantane derivative (65) was made from the tertiary phosphine (34). Oxidation to the phosphine oxide and reduction of the carbonyl group to hydroxyl were followed by free-radical oxidation-cyclisation with lead tetraacetate[41].

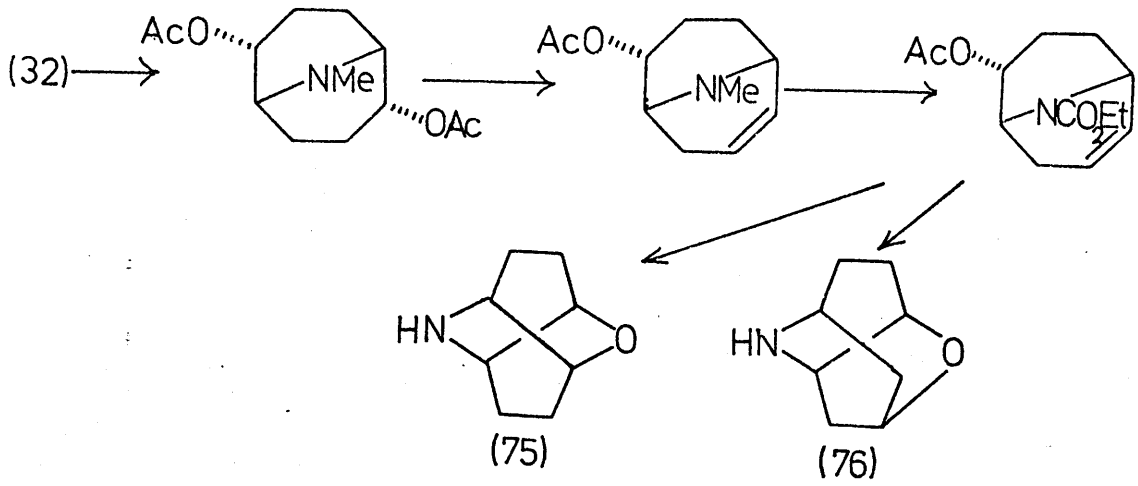

(13)
Ac_2O
AcO
OAc
400°
(69)
(70)
(71)
AgOAc/
AcOH
(72)
(73)
OH^-
OH
HO
(i) Cr(VI)
(ii) $(CH_2SH)_2$
(iii) Raney Ni
(66)
(67)
(68)

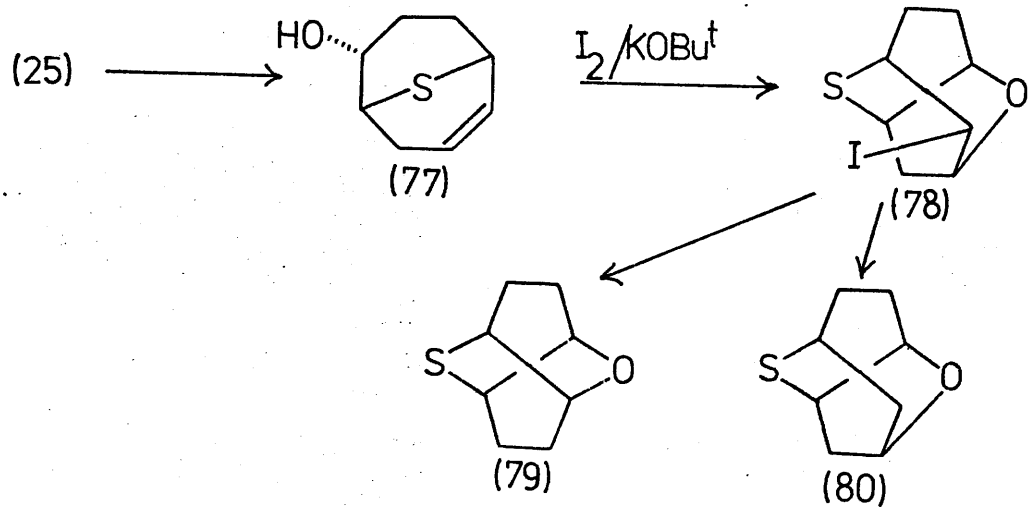
2,7-Diheterotwistanes, 2,7-diheteroisotwistanes, and 2,8-diheterohomotwistbrendanes - These more strained ring systems have been investigated in some detail by Ganter and coworkers.

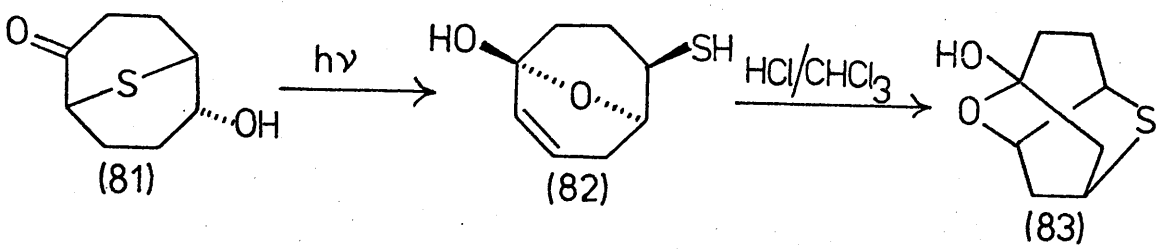
2,7-Dioxatwistane (66), 2,7-dioxaisotwistane (67), and 2,8-dioxahomotwistbrendane (68) were obtained[56-58] from the diol (13) by the following route:- The diacetate of (13) was pyrolysed to give, among other products, the enol acetate (69), which was hydrolysed, and by oxymercuration-demercuration afforded a mixture of the isomeric iododioxaisotwistanes (70) and (71). (70) was treated[56] with silver acetate, which by a partial (about 50%) skeletal rearrangement, yielded a mixture of the acetoxydioxatwistane (72) and the unrearranged isotwistane derivative (73), which were hydrolysed to the corresponding alcohols, and separated chromatographically. Jones oxidation, thioketalisation, and Raney-nickel reduction provided (66) and (67). When the iodide isomer (71) was similarly treated[58] with silver acetate, only 4% rearrangement to the highly-strained dioxahomotwistbrendane skeleton took place. The parent (68) was isolated in a similar way to (66) and (67).

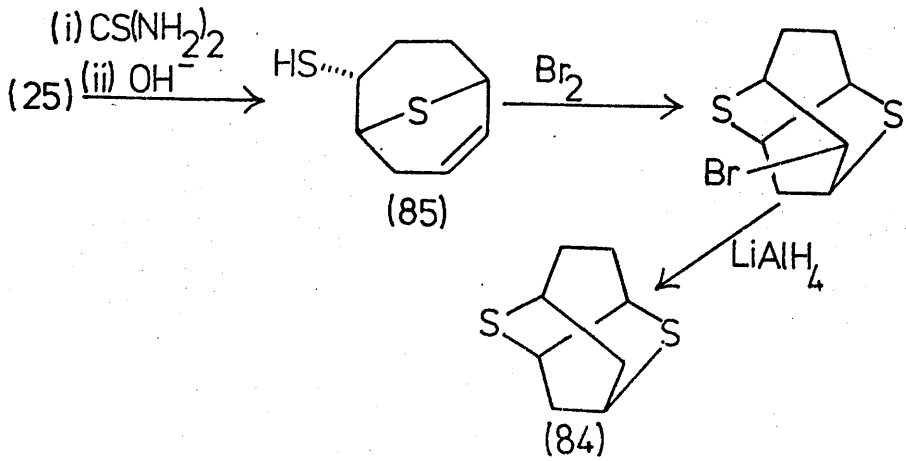
A more direct synthesis of dioxatwistane (66) used the hydroxymercuri-iodide (31) as precursor[37].




(32)
AcO
NMe
OAc
AcO
NMe
AcO
NCO2Et
HN
O
(75)
HN
O
(76)


(25)
HO
S
(77)
I2/KOBut
S
O
I
(78)
S
O
(79)
S
O
(80)


O
S
OH
(81)
hν
HO
O
SH
(82)
HCl/CHCl3
HO
O
S
(83)


(i) CS(NH2)2
(25)
(ii) OH−
HS
S
(85)
Br2
S
S
Br
LiAlH4
S
S
(84)

Demercuration gave a mixture of isomeric hydroxy-iodides, from which (74) was obtained. (74), on heating in pyridine afforded, in good yield, 2,7-dioxa-twistane (66). It is interesting to note that, unlike dioxaadamantane, dioxatwistane and dioxaisotwistane are chiral molecules, which have been isolated optically pure[57].

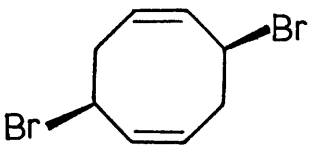
2-Oxa-7-azatwistane (75) and 2-oxa-7-azaisotwistane (76) were made from the dihydroxyamine (32) by a sequence of reactions[38] analogous to those for the corresponding dioxa-compounds.

Hydrolysis of the chloro-olefin (25) gave the enol sulphide (77), which was cyclised directly to the iodo-2-oxa-7-thiaisotwistane (78) by treatment with iodine and base[59]. Silver acetate isomerisation, followed by a series of reactions comparable to those for the dioxa- and oxa-aza- systems, provided 2-oxa-7-thiatwistane (79) and 2-oxa-7-thiaisotwistane (80). Another route to the oxathiaisotwistane skeleton employed[60] photolysis of the ketol sulphide (81) in methanol, to give, amongst other products, the hydroxythiol (82), which could be cyclised almost quantitatively with acid to the hydroxy-2-oxa-7-thiaisotwistane (83).

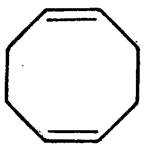
Attempts to isolate 2,7-dithiatwistane have not so far been successful[8]. However, 2,7-dithiaisotwistane (84) was prepared[61] by treatment of chloro-olefin (25) with thiourea, and hydrolysis of the thiouronium salt to the ene-thiol (85), which by cyclisation with bromine and reduction of the resulting bromide gave the isotwistane (84).

RESULTS AND DISCUSSION

A variety of methods for the preparation of 9-heterobicyclo[3.3.1]nonane systems has been outlined in the Introduction. It would, however, be of considerable interest to devise a flexible synthesis of derivatives having functionality in both three-carbon bridges, such molecules being of utility for further synthetic steps, and also as model compounds in n.m.r. conformational studies. In developing a route to such doubly-functionalised compounds, it would be desirable to include the following features:- applicability to a variety of 9-heteroatoms and possibly also to carbon itself; avoidance of formation of isomers such as bicyclo[4.2.1] compounds; and possibility of extension to other bridged systems, such as bicyclo[3.3.2]decane and bicyclo[3.3.3] undecane analogues.



(I)



(II)

The dibromo-cis,cis-cycloocta-1,5-diene (I), whose structure and detailed conformation were recently determined[62] (see Fig. 1), appeared, therefore, to be

an especially appropriate precursor for such syntheses, owing to the syn-3,7 arrangement of its allylic bromine atoms, as well as its remarkable crystallinity and stability.

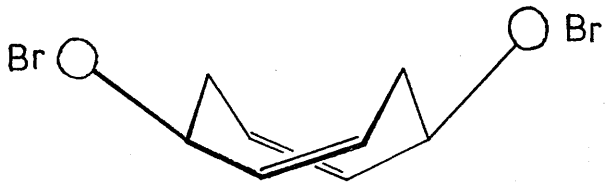


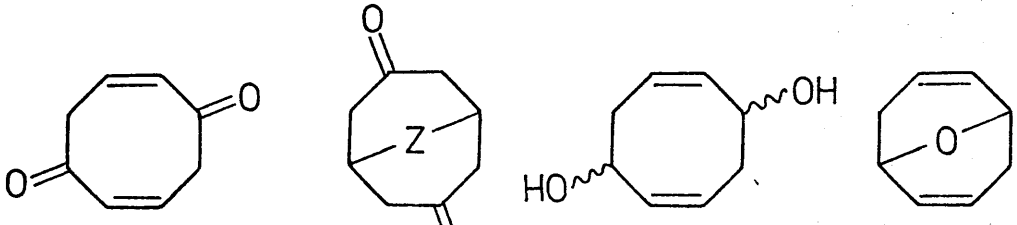
Fig. 1 The conformation of (I) in the crystal and in solution.

The main initial difficulty in attempting to study the reactions of (I) was its preparation in reasonable quantities. The previously-described method[62], in which cis,cis-cycloocta-1,5-diene (II) was reacted with N-bromosuccinimide, gave a very low isolated yield and entailed an inconvenient chromatographic separation in order to free (I) from the main reaction product[63], the isomeric 5,8-dibromo-cis,cis-cycloocta-1,3-diene. A preliminary attempt was therefore made to increase the specificity of the allylic bromination reaction by complexing diene (II) to a transition metal (in this case copper [I]), but when the copper complex was reacted with NBS, none of dibromide (I) could be isolated. Some progress may be possible in this direction by the use of different transition metals and milder reagents, but it was decided not to pursue this further. A considerable

improvement in the direct cyclooctadiene bromination method was made, however, by slight modification of reaction conditions, including careful drying of reagents, and the isolation of pure (I) by a straightforward crystallisation procedure; in consequence, the isolated yield of (I) was increased threefold. This improved method allowed production of (I) on a large scale, thus compensating for the rather modest yield.

Attempts to convert (I) to cycloocta-2,6-diene-1,5-dione (III).

In order to provide a route to interesting bridged systems possessing dual carbonyl functionality, as indicated by the general structure (A), methods were investigated whereby dibromide (I) might first be converted into the diene-dione (III), which would be expected to undergo bridging reactions very readily by means of a double Michael addition process*.



(III) (A): (IV) (V)

Z = 1, 2, 3, ... atom bridge

One approach to the preparation of (III) was to hydrolyse dibromide (I) to the corresponding diol (IV), which should be convertible to (III) by a suitable oxidation reaction. (I) was found to be

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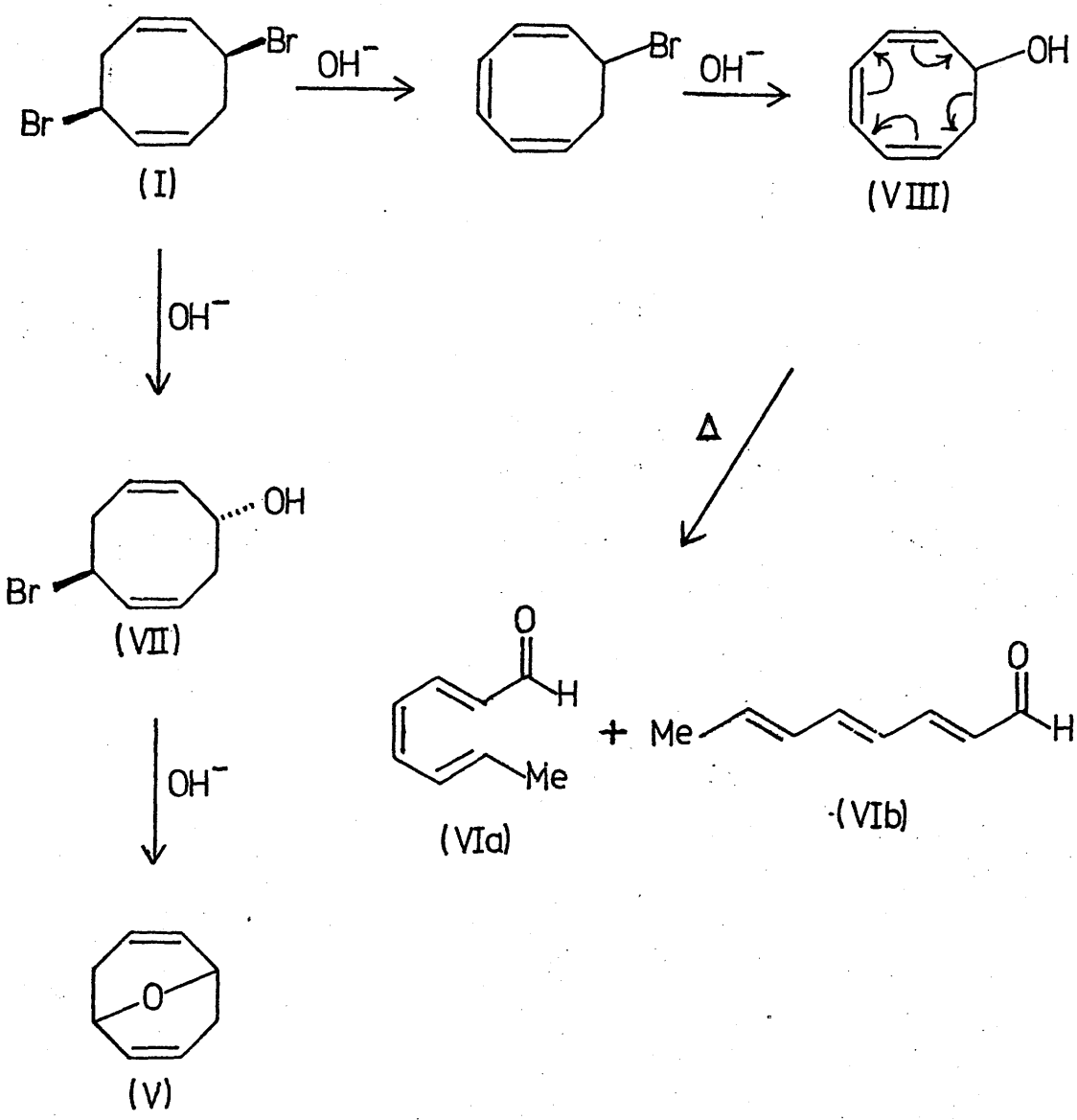
* For such an approach in the preparation of 9-hetero-bicyclo[3.3.1]nonanes, cf. refs. 40, 41.



Scheme 1

Proposed mechanism for the hydrolysis of dibromocyclooctadiene (I) by aqueous bicarbonate in acetonitrile.

resistant to conditions known to effect hydrolysis of allylic halides (sodium bicarbonate in refluxing aqueous THF[64]); this relatively low reactivity may be the result of some steric hindrance in the S_N2 transition state, as suggested by consideration of space-filling molecular models. However, refluxing of (I) with aqueous bicarbonate in the more polar solvent acetonitrile did result in displacement of bromide, giving, in addition to water-soluble material, 9-oxabicyclo[3.3.1]nona-2,6-diene (V), together with a small, but significant, amount of an aldehyde (not isolated pure) the available data for which (u.v., i.r. and ^1H n.m.r) are in accord with the octatrienal structures (VI a or b)[65-67]. The considerable amount of water-soluble material obtained from the hydrolysis of (I) may possibly include the diol (IV), but an attempt at isolation gave only an intractable gum.

The isolated yield of the highly-volatile (V) was rather low (ca 14%) since no attempt was made, in this instance, to optimise conditions for its formation or isolation. Its structure was assigned from its m.s. and its ^1H n.m.r. spectrum (see later sections of Discussion) by comparison with an authentic sample, independently prepared[68]. Its formation in this experiment is readily rationalised in terms of an S_N2 displacement of one bromide ion from (I) by hydroxide, followed by base-catalysed, transannular cyclisation of the intermediate anti-bromoalcohol (VII).

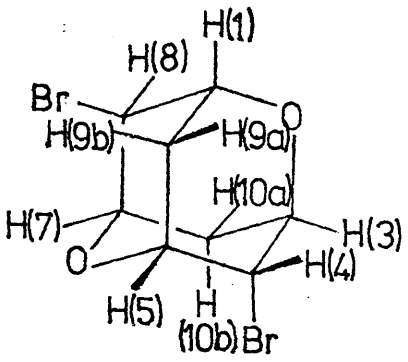
The formation of the aldehyde (VI) can be explained as proceeding from (I) by elimination hydrolysis in the basic reaction medium, to give the cycloocta-trienol (VIII), whose thermal electrocyclic ring-opening, in refluxing acetonitrile, to give (VI a and b) has previously been reported[65]. These reactions of (I) are outlined in Scheme 1.

In view of the reported[69] conversion of an allylic chloride to an enone by aqueous dichromate, the use of Cr(VI) as an oxidant for dibromide (I) was investigated. In a preliminary experiment, (I) was recovered unchanged after treatment with the CrO_3.2 pyridine complex in methylene chloride. Next, with the aim of effecting attack by dichromate ion on the dibromide, a solution of (I) was stirred with sodium dichromate dihydrate in hexamethylphosphoric triamide (HMPT), a solvent well-known to enhance greatly the nucleophilicity of anions. After 3 days, workup with dilute mineral acid gave no carbonyl compounds, but instead about 40% (later optimised to 65%, see experimental) of a highly-crystalline colourless compound, $C_8H_{10}Br_2O_2$, having i.r. and n.m.r. spectra indicative of a dibromo-diether structure.

Attempts to effect dehydrobromination, even under very severe conditions (such as potassium t-butoxide in HMPT at 100°, or lithium dicyclohexylamide in refluxing THF) led to recovery of the dibromo diether in high yield. This appeared to render unlikely any structure in which a CH_2 group was bonded to a CH-Br

Table 1

^{1}H n.m.r. data for (IX)



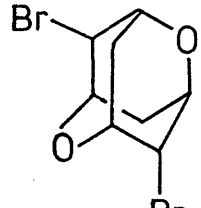
Normal Spectrum

τ(CDCl$_3$)	J(Hz)	assignments
5·5–5·9 (m)		H(1),(3);(4),(8);(5),(7)
6·97 (dxd)	13, 5	H(9b),(10b)
7·93 (dxm)	13	H(9a), (10a)

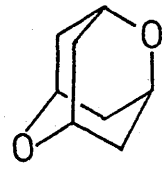
Eu(DPM)$_3$ shifted spectrum (qualitative) in CDCl$_3$ (100 MHz)

Approx downfield shift from TMS (Hz)	assignment	J (Hz)
698	H(1),(3)	$J_{1,8}, J_{3,4} \sim 1$; $J_{1,9a}, J_{3,10a} \sim 1$; $J_{1,9b}, J_{3,10b} \sim 5$
892	H(4),(8)	$J_{4,5}, J_{7,8} \sim 4$; $J_{4,10a}, J_{8,9a} \sim 1.5$
1343	H(5),(7)	$J_{5,9a}, J_{7,10a} \sim 4$; $J_{5,9b}, J_{7,10b} \sim 1$
650	H(9a),(10a)	$J_{9a,9b}, J_{10a,10b} \sim 13$
596	H(9b),(10b)	

group. Use of Eu $(DPM)_3$ shift reagent was of considerable help in interpreting the ^1H n.m.r. spectrum (the unshifted spectrum showed a complex absorption containing 3 overlapping methine multiplets), the observation of only 5 distinct chemically-shifted positions indicating the presence of an lement of symmetry in the molecule. Comparison of the observed coupling constants (Table 1) with those reported[52] for substituted diheteroadamantanes indicated the most likely structure to be syn-4,8-dibromo-2,6-dioxaadamantane (IX), and this was finally confirmed by lithium aluminium hydride reduction to 2,6-dioxaadamantane (X) itself, identical to a sample prepared independently.

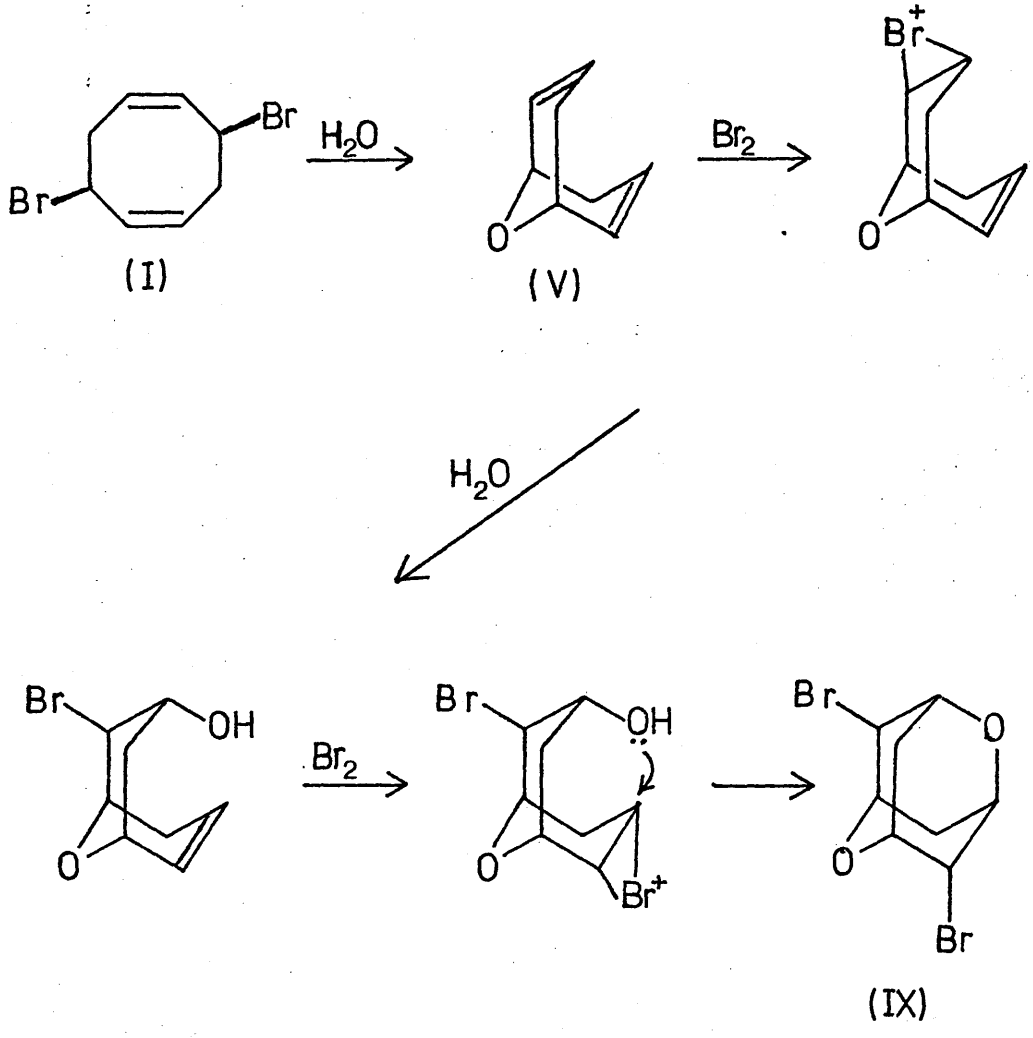


(IX)



(X)

The conversion of (I) to (IX) was found to be a two-step process, the second bridging reaction occurring only on addition of acid. When the reaction mixture was worked up under neutral conditions, no (IX) was obtained, and, instead, 9-oxabicyclo[3.3.1] nona-2,6-diene (V) could be isolated in up to 75% yield. It was also found that (V) could be converted to (IX) by treatment with a solution of bromine in aqueous potassium bromide, similarly to a previously-described preparation of 2-oxaadamantane[70]. The

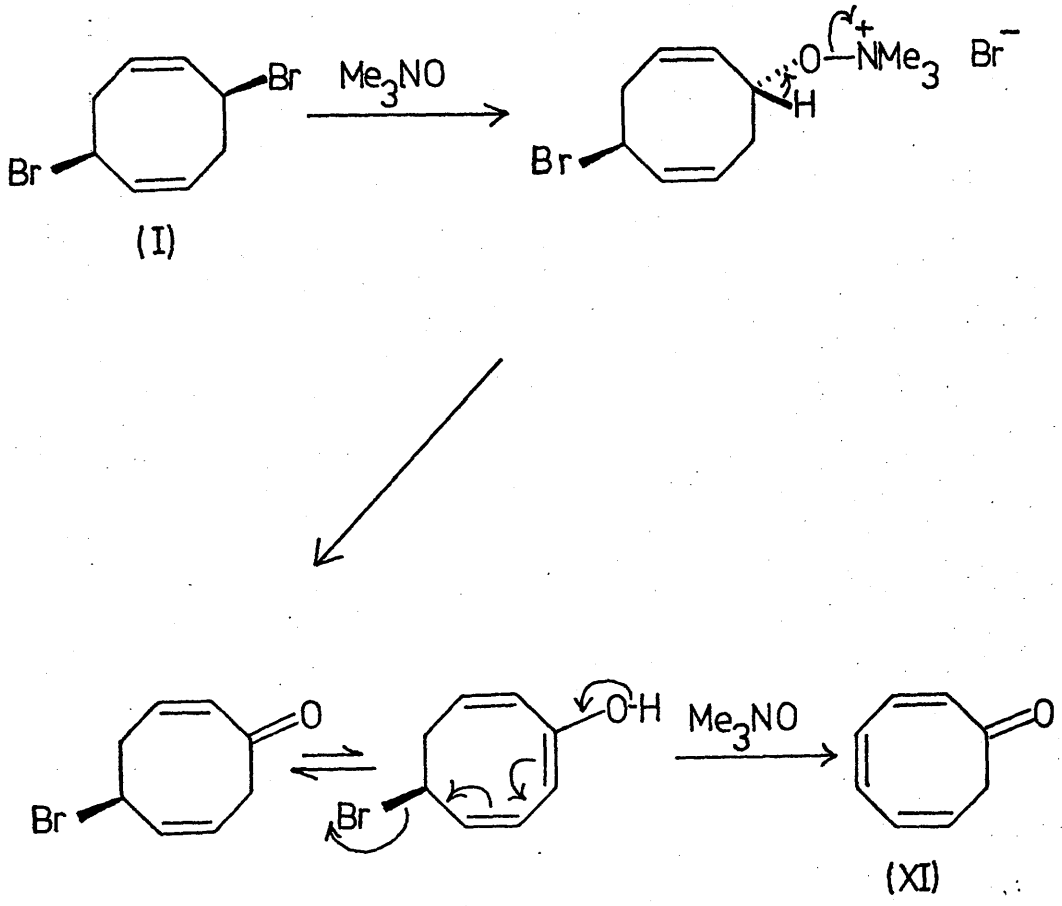


Scheme 2

Proposed mechanism for formation of 4,8-dibromo-2,6-dioxaadamantane (IX) from (V) with $Br^-/Cr_2O_7^{2-}$/acid.

course of the formation of (IX) from (I) (outlined in Scheme 2) is therefore:- (i) nucleophilic displacement of Br^- by water, promoted by HMPT; (ii) oxidation of liberated Br^- by Cr(VI) in the presence of acid to form Br_2 in situ, which is then available for the second bridging step. Apparently the presence of sodium dichromate in the reaction medium increases the rate of step (i), perhaps by consuming liberated HBr, as evidenced by the incompleteness of the conversion of (I) to (V) in aqueous HMPT in the absence of dichromate. As a method for preparing the useful diene ether (V), treatment of (I) with water/HMPT/dichromate compares favourably with previously published routes[51,68], which entail more steps, and give an impure product, requiring fractional distillation.

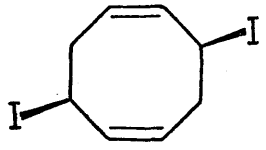
A reagent for conversion of alkyl halides to ketones without intermediate alcohol formation is trimethylamine oxide[71]. Treatment of dibromocyclooctadiene (I) with the anhydrous amine oxide in chloroform gave, in good yield, an oil whose i.r. was consistent with a conjugated enone structure. However, its ^1H n.m.r. spectrum had an olefinic : methylene proton ratio of 3:1, not consistent with the structure (III), and a comparison of this spectrum with the published spectrum[72] of cycloocta-2,4,6-trienone (XI) showed them to be identical. Apparently the replacement of one bromine by a carbonyl facilitates the elimination of HBr, even in presence of the weakly-basic amine oxide (Scheme 3).



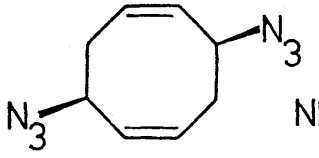
Scheme 3

Probable mechanism of oxidation of (I) to cyclooctatrienone (XI).

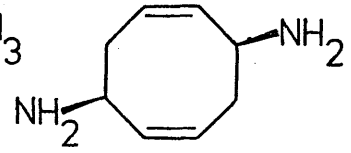
Attempts to convert (I) to (III) by treatment with the sodium salt of 2-nitropropane[73] were unsuccessful, as was similar treatment of the diiodide (XII), prepared by reaction of (I) with potassium iodide in acetone; the dihalide (I) or (XII) being recovered unchanged in either case.



(XII)



(XIII)



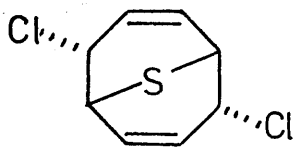
(XIV)

Finally, a more indirect approach to the ketone (III) was tried in which (I) was converted to the diazide (XIII) with sodium azide in DMF; lithium aluminium hydride reduction of (XIII) gave the corresponding diamine (XIV), but an attempted oxidation of this compound with 3,5-di-t-butyl-1,2-benzoquinone gave an unidentified mixture of products in which significant amounts of (III) could not be detected.

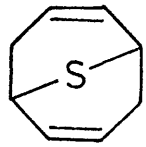
Formation of new 9-heterobicyclo[3.3.1]nona-2,6-dienes.

The foregoing investigations, though not providing a route to (III), have given useful information about the reactivity of (I) towards nucleophiles. Although less reactive than an allylic bromide such as 3-bromocyclohexene[64], dibromide (I) under suitable conditions will readily undergo nucleophilic substitution, as shown by the ease of formation of 9-oxabicyclo[3.3.1] nona-2,6-diene (V). This bridging with oxygen is

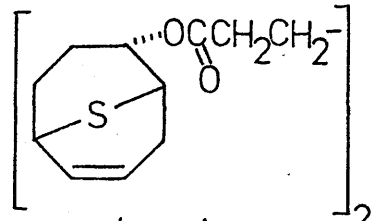
paralleled in investigations which have been carried out using other ambident nucleophiles.



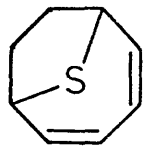
(XV)



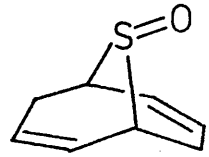
(XVI)



(XVII)



(XVIII)

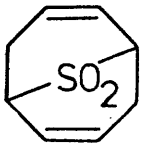


(XIX)

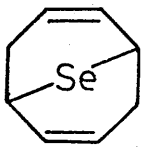
$LiAlH_4$ reduction of the dichlorodiene (XV) was reported[36] to give a liquid assigned the 9-thiabicyclo [3.3.1] nona-2,6-diene structure (XVI), but the apparent lack of crystallinity of this material (see below) suggests the presence, wholly or partly, of isomers of (XVI). The only other reported preparation of (XVI)[74], by pyrolysis of the ester (XVII), has recently been shown to be in error, the sole product being the isomeric 9-thiabicyclo[4.2.1]nona-2,4-diene (XVIII).[75]

Treatment of (I) with anhydrous sodium sulphide in DMF gave, in moderate yield, the highly-crystalline, volatile (XVI), m.p. 41-41.5°, whose structure was assigned on the basis of its diimide reduction to the known 9-thiabicyclo[3.3.1]non-2-ene, the formation of a single sulphoxide (XIX) (ν_{max} (KBr) 1049 cm^{-1}), and the analysis of its ^1H n.m.r. spectrum described later in this Discussion. (XVI), unlike the isomeric (XVIII), possesses high thermal stability, showing no

noticeable decomposition (^{1}H n.m.r. monitoring) after being heated in a sealed tube for 16 h. at 200°, with toluene-d_8 as solvent. Oxidation of (XVI) with m-chloroperbenzoic acid was found to give a good yield of either the sulphoxide (XIX) or the sulphone (XX), depending on the quantity of reagent used. (XIX) shows the expected chemical non-equivalence of all the protons in its ^{1}H n.m.r. spectrum (described later).



(XX)



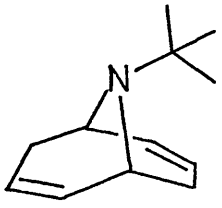
(XXI)

9-Selenabicyclo[3.3.1]nona-2,6-diene (XXI), which has not previously been reported in the literature, was readily prepared in an analogous way to (XVI), by the action of Na_2Se on (I). (XXI) is also a volatile crystalline solid, m.p. 54-55°, with spectroscopic properties, particularly its ^{1}H n.m.r., closely resembling those of (XVI).

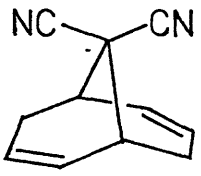
Direct introduction of a nitrogen bridge into the eight-membered ring results from treatment of (I) with the primary amine t-butylamine, which in refluxing acetonitrile gave, in about 45% yield, 9-t-butyl-9-azabicyclo[3.3.1]nona-2,6-diene (XXII), the structure being confirmed by spectroscopic data. The ^{1}H n.m.r. spectrum of (XXII) at room temperature (see later),

as expected, is consistent with rapid nitrogen inversion and rapid t-butyl rotation. The effective C_2 symmetry axis of the free amine is lost on protonation; the spectrum of the hydrochloride in $CDCl_3$ is more complex, corresponding to slow inversion about protonated nitrogen. This preparation of the 9-azabicyclo[3.3.1]nona-2,6-diene system is an alternative to the previously-described methods of Ganter[25] and Stetter[30] (see Introduction).

It was also of interest to investigate the possibility of extending the single-atom bridging reaction to a carbon nucleophile. Accordingly, reaction of (I) in DMSO with malononitrile in the presence of sodium hydride gave a good yield of crystalline 9,9-dicyanobicyclo[3.3.1]nona-2,6-diene



(XXII)



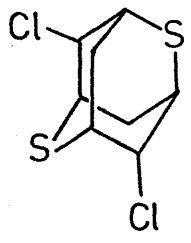
(XXIII)

(XXIII), assigned the formulated structure on the basis of its spectroscopic data. The ^1H n.m.r. spectrum of (XXIII), (see later) despite fairly large solvent shifts between $CDCl_3$ and C_6D_6, shows equivalence of the bridgeheads in both solvents.

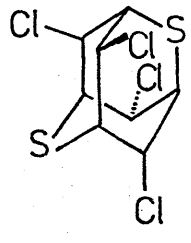
It was expected that cyclisation of bicyclo[3.3.1] nona-2,6-dienes and 9-hetero-analogues with electrophilic reagents such as sulphur dichloride would readily lead

to the corresponding heteroadamantane skeleton, reactions of this type having many parallels[8], as indicated in the Introduction. Surprisingly, however, treatment of diene sulphide (XVI) with sulphur dichloride under a variety of conditions, including low temperature (-70^{o}) and high dilution, led in all cases to amorphous, apparently polymeric material, m.s. of which may indicate the presence of a very minor proportion of the expected syn-4,8-dichloro-2,6-dithiaadamantane (XXIV), but separation attempts were not considered worthwhile.

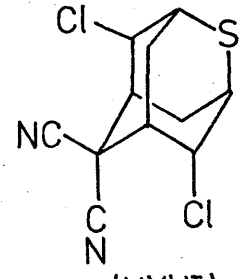
It would appear from this result that the 9-sulphur atom of (XVI) directs electrophilic addition of the SCl_2 sulphur on to the exo face of the molecule of (XVI), perhaps by the formation of a transient complex with a chlorine atom. The resulting



(XXIV)



(XXV)



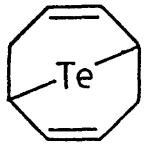
(XXVI)

exo-sulphenyl chloride can only react intermolecularly, forming polymer. This reaction stands in marked contrast to the previously described[36] preparation of the tetrachlorodithiaadamantane (XXV) by SCl_2 addition to (XV); here the presence of chlorine substituents appears to direct SCl_2 addition on to the endo-face.

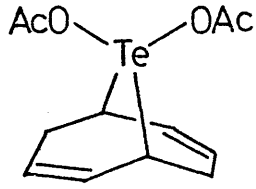
Addition of SCl_2 to the dicyano-diene (XXIII) did, however, give a crystalline product, very insoluble in common solvents, the available data for which (m.s., i.r, m.p.) are consistent with the 6,6-dicyano-2-thiaadamantane structure (XXVI).

Studies of cyclic tellurides.

When attempts were made to extend further the scope of the single-atom bridging with double nucleophilic displacement, by reacting dibromide (I) with Na_2Te in DMF, a product was obtained whose ^1H n.m.r. showed not only resonances corresponding to the expected 9-tellurabicyclo[3.3.1]nona-2,6-diene (XXVII), but also indicated the presence of additional olefinic protons, as well as a very broad absorption extending from approximately τ 5-10. Column chromatography allowed separation of the pure (XXVII)

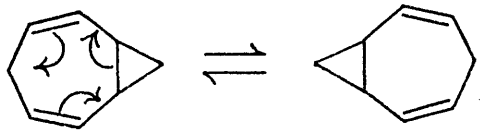


(XXVII)



(XXVIII)

(18% isolated yield), m.p. 69-71°, which was characterised by its m.s. (see later section of Discussion), formation of the highly-crystalline bis-acetoxy derivative (XXVIII) on treatment with lead tetra-acetate[76], and its ^1H n.m.r. spectrum (described later).



(XXIX)

The chromatographic purification of (XXVII) also provided as the only other detectable volatile product (22% yield) a liquid hydrocarbon, further purified by g.l.p.c., whose room-temperature ^1H n.m.r. spectrum showed the enormous kinetic broadening effect previously observed in the spectrum of the product mixture. At low temperature (-52^o), a 'frozen' spectrum could be observed, the spectra at both temperatures corresponding very closely to the published spectra[77] of bicyclo[5.1.0]octa-2,5-diene ('3,4-homotropylidene') (XXIX). This interesting fluxional molecule undergoes a degenerate Cope rearrangement which exchanges cyclopropane methylenes with allylic methylenes, and vinyl hydrogen positions with allylic cyclopropane positions. The very large chemical shift differences between exchanging sites results in the extremely broad appearance of the spectrum in the kinetic region.*

In order to establish the origin of hydrocarbon (XXIX) as a product of reaction of (I) with Na_2Te, a control experiment was carried out in which pure telluride (XXVII) was subjected to similar aqueous workup conditions to those employed in its preparation. This did no lead to detectable amounts of (XXIX) (g.l.c. analysis), showing that formation of (XXIX), in this instance, was not a result of breakdown of (XXVII).

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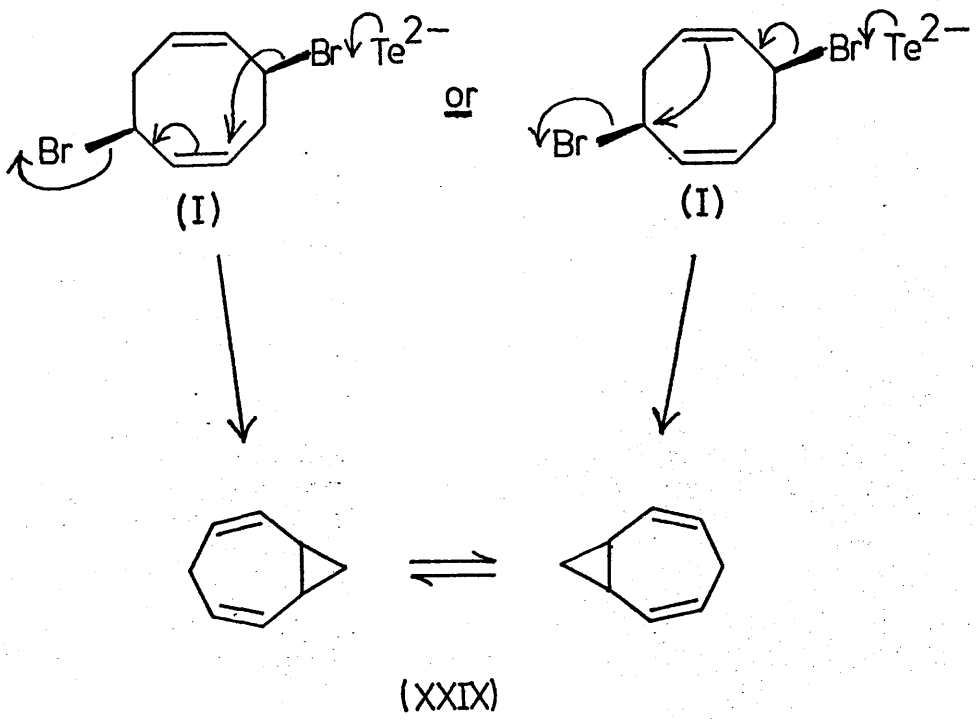
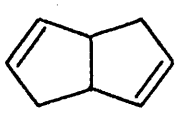
* A kinetic n.m.r. study of an octadeutero-derivative of (XXIX) showed $\Delta H^{\neq}$ for the valence-tautomerism to be 11.8 ± 0.2 K cal/mole (ref. 78).



Scheme 4

Possible mechanism of formation of '3,4-homotropylidene' (XXIX) from (I) with Te^{2-}.



(XXX)

The action of the highly-nucleophilic Te^{2-} anion on (I) may, therefore, involve, as well as simple S_N2 displacement of Br^-, a competing attack of Te^{2-} on a bromine atom itself (Scheme 4). This type of reductive elimination, long known[79] for the isoelectronic I^-, has not previously been reported for Te^{2-}. *

A mechanistically-distinct mode of formation of (XXIX) was discovered while investigating the thermal stability of (XXVII). While stable indefinitely under nitrogen in the dark, (XXVII), on heating in a degassed inert solvent (toluene - d_8), was found to extrude elemental tellurium. After 8 h. at 175°, ^1H n.m.r. analysis showed complete disappearance of (XXVII), with formation, as the only detectable organic product, of (XXIX), characterised by the temperature-dependence of its ^1H n.m.r. spectrum. Interestingly, (XXIX), and not its isomer bicyclo[3.3.0]octa-2,6-diene (XXX), reported to be thermodynamically more stable[77], is formed in both these reactions. It is also interesting to note the much greater ease of thermal tellurium extrusion compared with sulphur, since sulphide (XVI) is extremely stable thermally (see above).

In his preliminary studies of the dibromide (I), Zabkiewicz[81] reported that reduction of (I) with zinc in ethanol gave a single hydrocarbon, whose nature was

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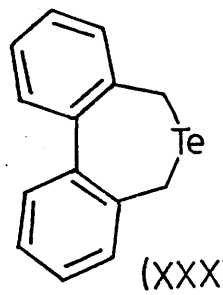
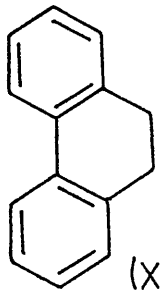
* But for the use of Te^{2-} to reduce vinylic halides see ref. 80.

unknown. In view of the unexpected nature of the product obtained with Na_2Te, it was of considerable interest to reinvestigate this reduction, and so, using the conditions previously described[81], again a single hydrocarbon, pure by g.l.c., was obtained. Comparison of g.l.c. retention times and ^1H n.m.r. spectra showed that this hydrocarbon was also bicyclo [5.1.0] octa-2,5-diene (XXIX), formed in high yield. This probably, therefore, represents the best method to date for its preparation.

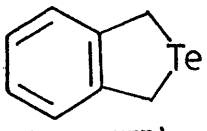
With a view to determining whether telluride pyrolysis had any applicability to the formation of carbon-carbon bonds in other, dissimilar cyclic systems, sodium telluride was reacted with 2,2'-bis-(bromomethyl) biphenyl to give mainly 5,7-dihydrodibenzo [c,e] tellurepine (XXXI), along with some 9,10-dihydrophenanthrene (XXXII) (ca 25% of isolated product), formed by direct attack of Te^{2-} on a bromine atom. 1,3-Dihydrobenzo[c] tellurophene (XXXIII) was also prepared, but in this case no direct hydrocarbon



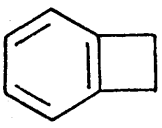
(XXXI)



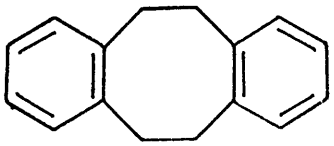
(XXXII)



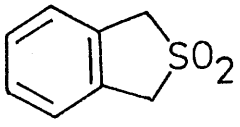
(XXXIII)



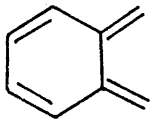
(XXXIV)



(XXXV)



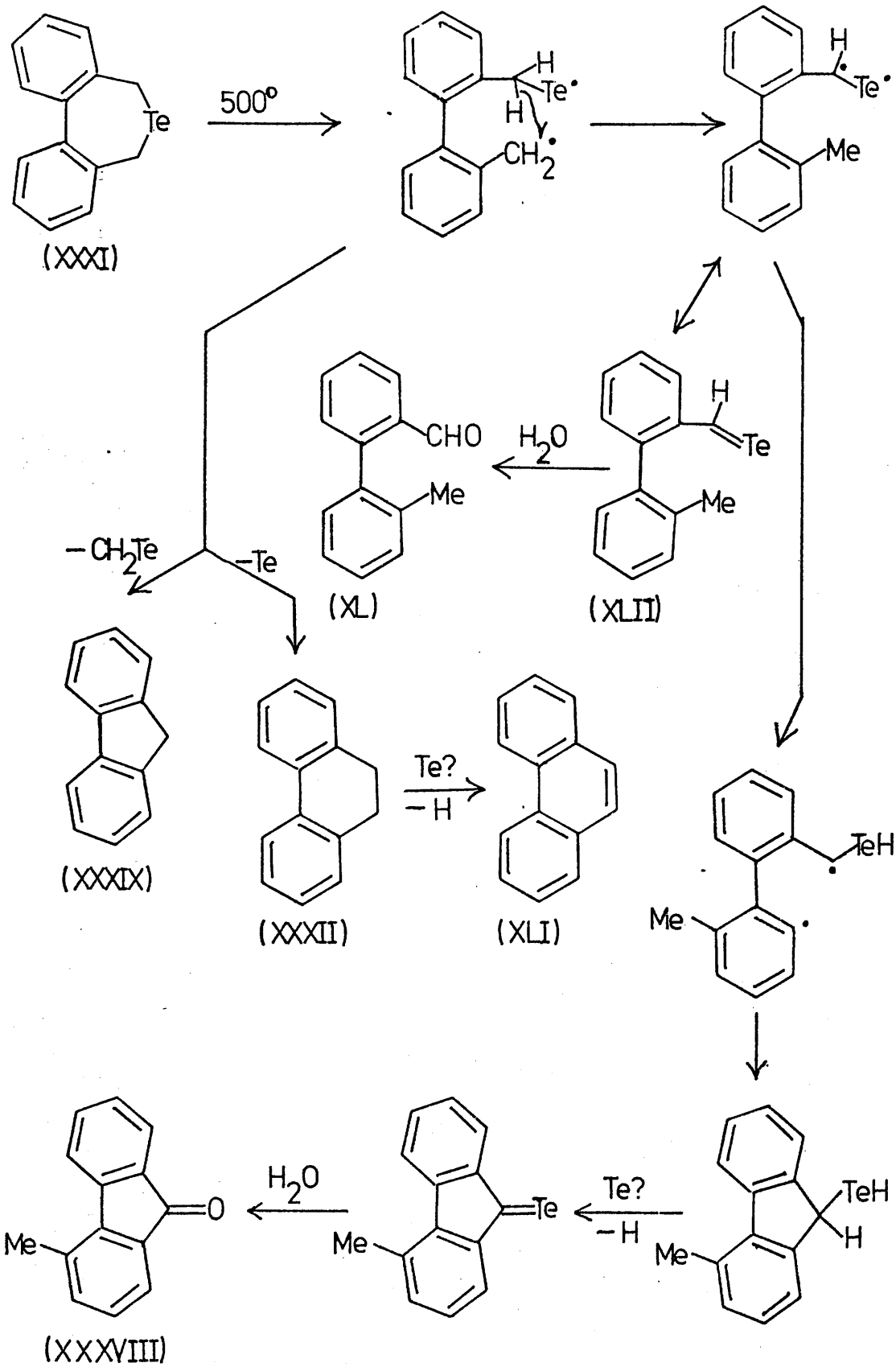
(XXXVI)



(XXXVII)

formation could be detected by ^{1}H n.m.r. of the crude product. Pyrolysis of (XXXIII) over quartz wool in the vapour phase at 500° gave a good yield of benzocyclobutene (XXXIV), isolable in high purity, and probably also a minor amount of tetrahydrodibenzo [a,e] cyclooctene (XXXV). This pyrolysis closely parallels that of the sulphone (XXXVI), which has been found[82] to give, initially, the reactive o-xylylene (XXXVII), which can cyclise to (XXXIV) or to (XXXV), depending on the temperature.

Pyrolysis of tellurepine (XXXI) over quartz wool also led to loss of tellurium, but in this case giving a rather complex mixture of products. The only material isolated in a reasonably pure state was a yellow, crystalline ketone, whose properties closely resemble those reported[83,84] for 4-methyl fluoren-9-one (XXXVIII). By partial separation on prep. t.l.c., and comparison of ^{1}H n.m.r. spectra, the following tentative assignments of the product mixture were made:- fluorene (XXXIX) ca 32%, 2-formyl-2'-methylbiphenyl (XL) ca 22%, 4-methylfluoren-9-one (XXXVIII) ca 18%, phenanthrene (XLI) 10-15%, dihydrophenanthrene (XXXII) ca 8%. Despite attempts to drive all adsorbed water from the quartz wool by preheating the pyrolysis apparatus for 16h, a small amount of water was collected along with the products of pyrolysis, and its presence may explain the formation of oxygen-containing products.



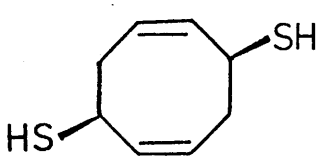
Scheme 5

Suggested products and mechanism of pyrolysis of (XXXI).

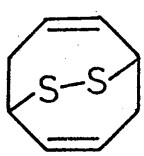
The nature of the products obtained, subject to complete confirmation of their structural assignments, strongly implies a non-concerted, radical mechanism for this extrusion of Te, and a suggested mechanism for the pyrolysis, involving as a possible transient intermediate the telluro-aldehyde species (XLII), is outlined in Scheme 5.

Attempts to introduce 2- and 3-atom bridges into dibromide (I).

The straightforward preparation of a variety of bicyclo[3.3.1] systems from the dibromide (I) prompted attempts to extend the reaction to bridges with more than one atom. Attempts to form a two-atom bridge have not met with success. Direct reaction of (I) with Na_2S_2 led to a low yield of monosulphide (XVI), along with much amorphous material of low solubility, presumably polymeric. An alternative approach, by which (I) was converted to the corresponding dithiol (XLIII) (with acetylthiourea in ethanol[85]) which was then oxidised with iodine, gave in low yield, as the only identifiable product, a compound which again,



(XLIII)



(XLIV)

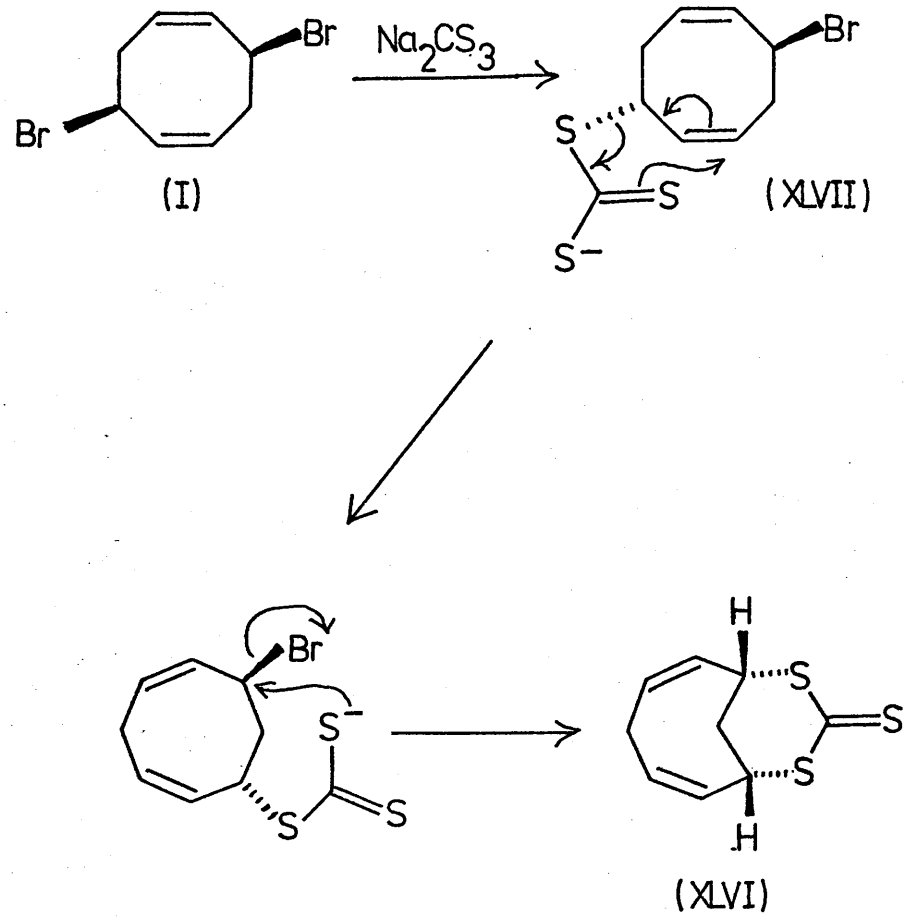
from ^1H n.m.r., appeared to be the monosulphide (XVI).

Possibly the high strain inherent in 9,10-dithia-bicyclo [3.3.2]deca-2,6-diene (XLIV) may result in spontaneous loss of sulphur to give the very stable (XVI).

Introduction of a three-atom bridge across (I) might be a possible route to analogues of bicyclo [3.3.3]undecane ('manxane'). Such systems are particularly difficult to synthesise[86], and the formation of manxanes with functionality on all three bridges has not so far been achieved.

The reaction between (I) and the disodium salt of di-t-butyl acetonedicarboxylate gave an oily product whose ^{1}H n.m.r. indicated the presence of t-butyl groups, but was otherwise uninformative; t.l.c. indicated a number of components, and the material was not further investigated.

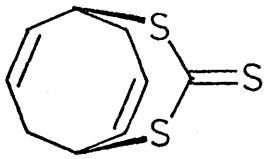
However, when (I) was treated with the highly-nucleophilic trithiocarbonate anion in acetonitrile, a bright-yellow, highly-crystalline product $C_9H_{10}S_3$ could be isolated in moderate yield. Analysis of its ^{1}H n.m.r. spectrum revealed the presence of equivalent bridgehead protons along with four chemically non-equivalent methylene protons, not consistent with the bicyclo [3.3.3] structure (XLV). The detailed analysis of its 100 and 220 MHz spectra (see later) allowed the assignment of the structure 9-thiono-8,10-



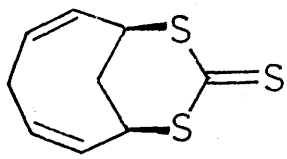
Scheme 6

Probable course of formation of the rearranged trithiocarbonate (XLVI).

dithiabicyclo[5.3.1]undeca-2,5-diene (XLVI). The



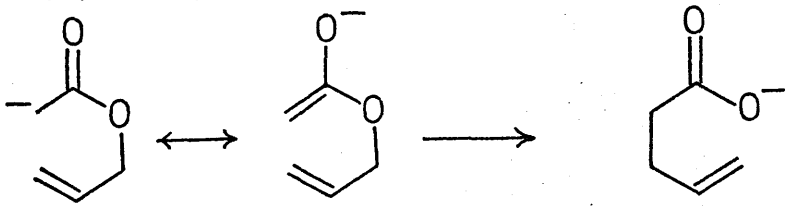
(XLV)



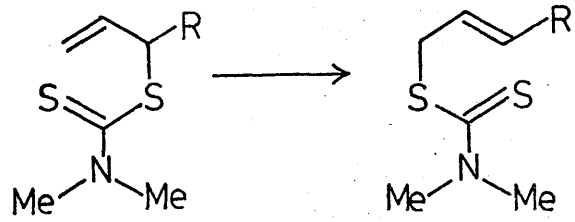
(XLVI)

formation of (XLVI) rather than (XLV) is probably an indication of the highly-strained nature of bicyclo[3.3.3] systems.

In the formation of (XLVI), the initial S_N2 displacement of bromide may well be followed by a [3,3] sigmatropic rearrangement of the intermediate anion (XLVII) (Scheme 6) in the symmetry-allowed suprafacial mode, which then leads to cyclisation by a second nucleophilic displacement. Parallels to the rearrangement of (XLVII) may be seen in the facile [3,3] sigmatropic rearrangement of the allyl ester enolate anion (XLVIII) to (XLIX)[87], and also in the somewhat similar, though non-ionic, dithiocarbamate system (L)→(LI)[88].



(XLVIII) (XLIX)

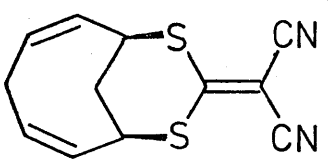


(L) (LI)

An alternative approach to the synthesis of the

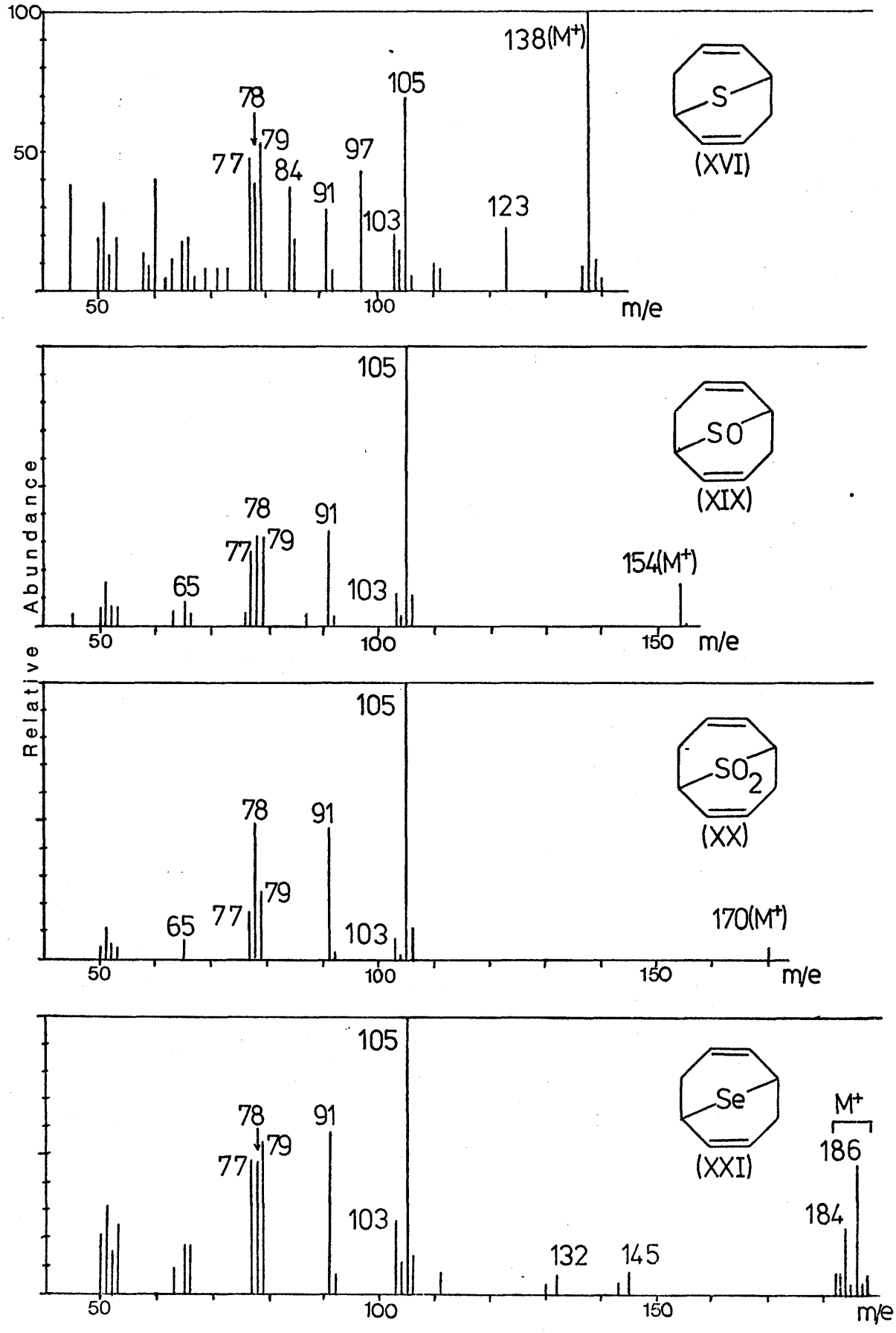
bicyclo [3.3.3] structure (XLV) was tried in which dithiol (XLIII) was treated with thiophosgene in the presence of pyridine. A mixture of products was obtained, but it was evident that a side-reaction between thiophosgene and pyridine had occurred, and better results may be possible by modified reaction conditions.

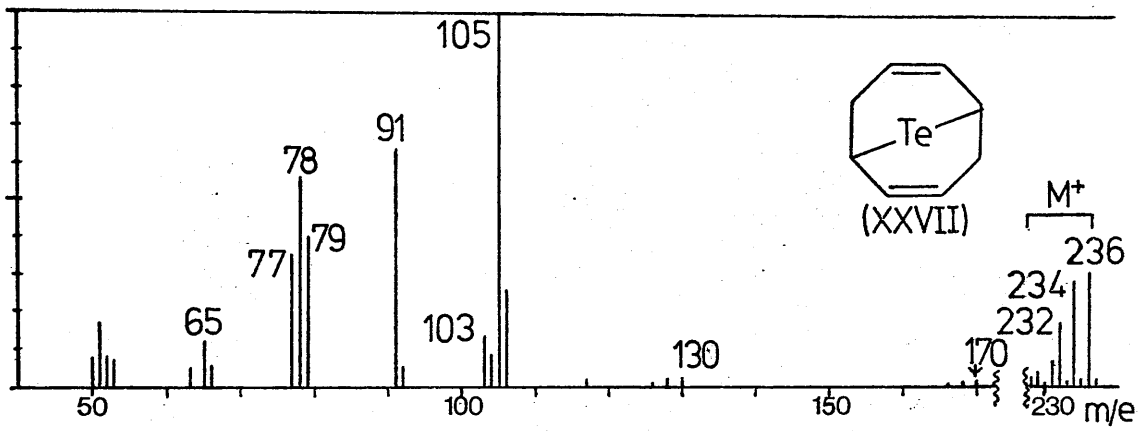
A second example of a displacement reaction involving rearrangement was discovered when (I) was treated with the dithiomethylenemalononitrile ion $[S_2C = C(CN)_2]^{2-}$. The triethylamine salt reacted with (I) in acetonitrile to give a good yield of a colourless, crystalline solid, whose spectroscopic properties were consistent with the structure (LII), and, in particular, its ^1H n.m.r. spectrum at 220 MHz,

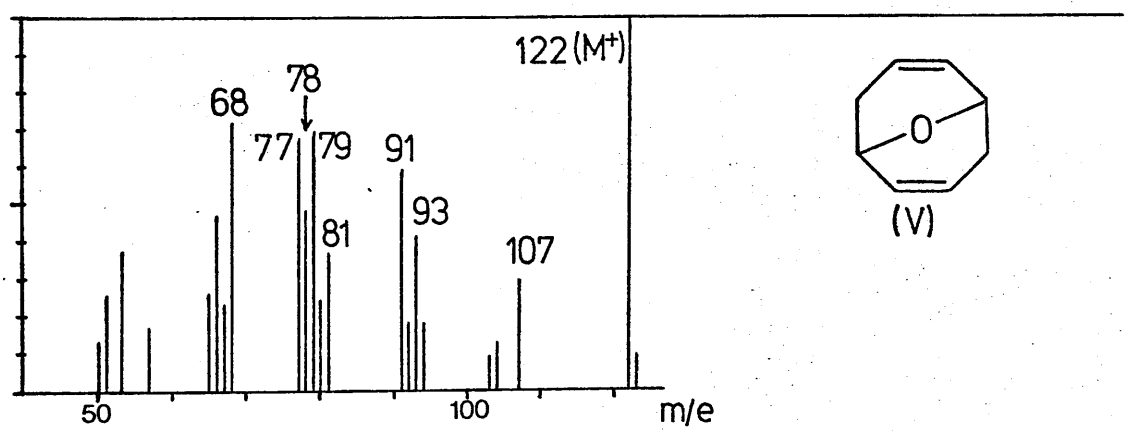


(LII)

despite a different solvent, showed a close similarity to that of the trithiocarbonate (XLVI) (see later). Interesting features of the i.r. spectrum of (LII) are the intense conjugated C = N absorptions at 2220 and 2210 cm^{-1}, and also a very strong absorption at 1426 cm^{-1}, which may be assignable to the exocyclic C = C stretching vibration, greatly shifted and intensified by conjugation with the nitrile and sulphide groups.


100
50
138(M+)
105
78
79
77
84
97
91
103
123
50
100
m/e
S
(XVI)
Abundance
105
78
91
77
79
65
103
154(M+)
50
100
150
m/e
SO
(XIX)
Relative
105
78
91
79
77
65
103
170(M+)
50
100
150
m/e
SO2
(XX)
105
78
91
79
77
103
132
145
184
186
M+
50
100
150
m/e
Se
(XXI)





Figs 2-7

Line diagrams for 9-heterobicyclo[3.3.1]nona-2,6-dienes

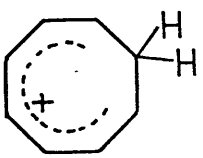
Table 2 Metastable Peaks

Cpd	m*	Possible	Fragmentation
(XVI)	109·6	138→123	$-CH_3^{\bullet}$
	101	105→103	$-H_2$
	78	105→91	$-CH_2$
	59·4	105→79	$-C_2H_2$
	57·5	103→77	$-C_2H_2$
	56·5	105→77	$-C_2H_4$
	46·4	91→65	$-C_2H_2$
(XIX)	101	105→103	$-H_2$
	78	105→91	$-CH_2$
	71·7	154→105	$-\underline{SOH}^{\bullet}$
	59·5	105→79	$-C_2H_2$
	57·6	103→77	$-C_2H_2$
	56·5	105→77	$-C_2H_4$
	46·5	91→65	$-C_2H_2$
(XX)	101	105→103	$-H_2$
	78	105→91	$-CH_2$
	65	170→105	$-\underline{SO_2H}^{\bullet}$
	59·5	105→79	$-C_2H_2$
	57·5	103→77	$-C_2H_2$
	56·5	105→77	$-C_2H_4$
	46·6	91→65	$-C_2H_2$
(XXI)	101	105→103	$-H_2$
	59·4	105→79 or 186→105	$-C_2H_2$ or $-\underline{SeH}^{\bullet}$
(XXVII)	101	105→103	$-H_2$
	78	105→91	$-CH_2$
	59·4	105→79	$-C_2H_2$
	57·4	103→77	$-C_2H_2$
	56·5	105→77	$-C_2H_4$
	46–49 (complex)	236→105 / 234→105	$-\underline{TeH}^{\bullet}$
		91→65	$-C_2H_2$

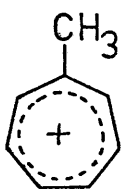
Mass spectra of group (VI) 9-heterobicyclo[3.3.1] nona-2,6-dienes.

The 70 eV mass spectra of compounds (XVI), (XIX), (XX), (XXI), and (XXVII) were found to have many similarities (Figs. 2 6), with common peaks at m/e 105, 103, 91, 79, 78, 77, and 65, as well as similar patterns of metastable peaks (Table 2). These features point to a common fragmentation mechanism for all five compounds, and the above fragment ions were tentatively identified, in the absence of high-resoltuion data, as follows:-

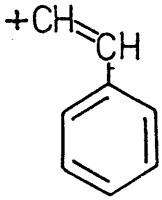
m/e 105 (C_8H_9): This fragment has been recognised in previous m.s. studies[89,90], being formulated as either the homotropylium ion (LIII)[91] or the methyltropylium ion (LIV). The ion was reported[89] to fragment by loss of acetylene to give $C_6H_7^+$.



(LIII)



(LIV)



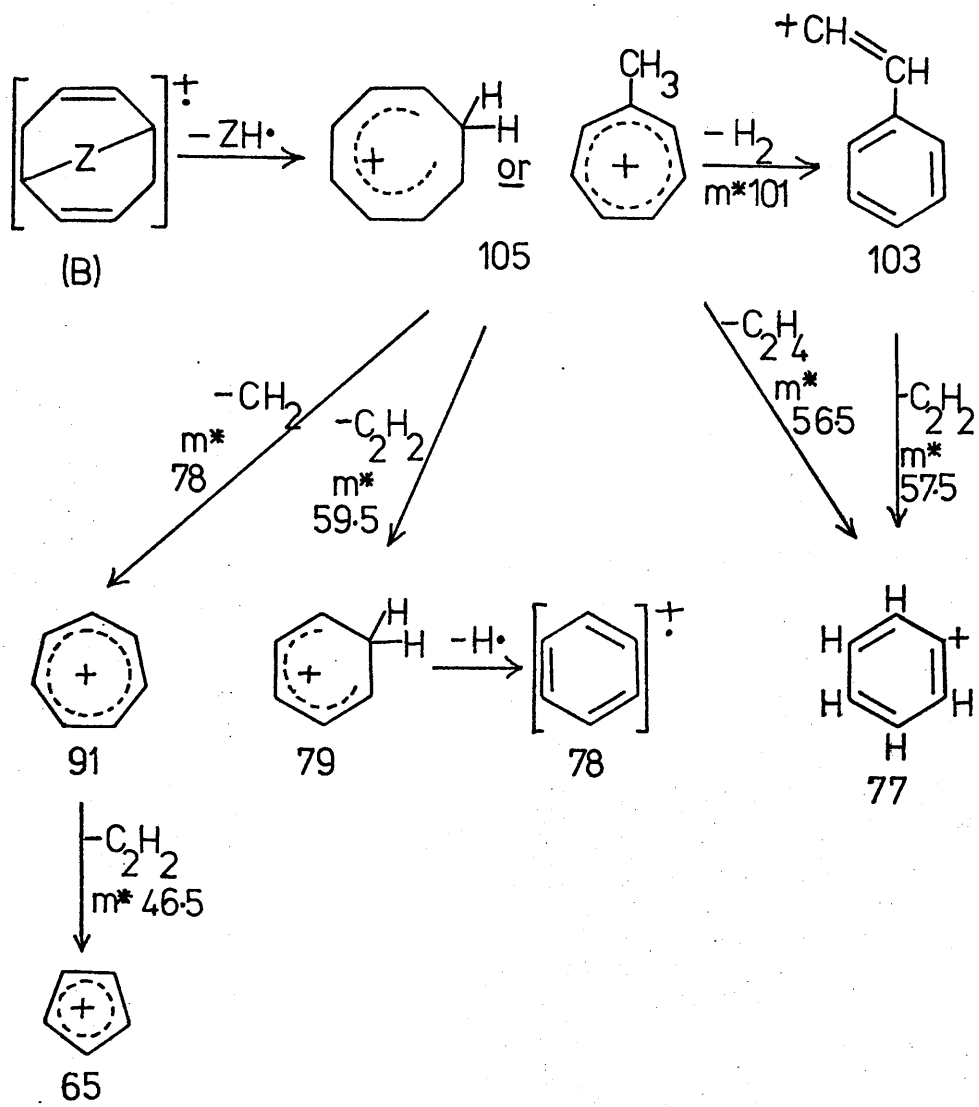
(LV)

(LVI)

m/e 103 ($C_8H_7^+$): This may be the styryl ion (LV), which was reported[92] to fragment by loss of acetylene to give $C_6H_5^+$.

m/e 91,79, 78, 77: These are the well-known $C_7H_7^+$, $C_6H_7^+$, $C_6H_6^{+\cdot}$, and $C_6H_5^+$ aromatic ions.

m/e 65 ($C_5H_5^+$): This can probably be formulated as (LVI).



Scheme 7

Suggested major m.s. fragmentation of dienes (B):

Z = S, SO, SO_2, Se, Te.

The presence of these ions, together with the metastable peaks (Table 2), can be rationalised in terms of the fragmentation outlined in Scheme 7. A notable feature of this proposed breakdown mechanism is the initial loss of the fragment ZH· confirmed by metastables in (XIX), (XX), and (XXVII). Such a fragmentation, for which there are parallels in the previously reported m.s. data of simple[93] and bridged[94] heterocycles, may also be comparable with the thermal breakdown of the [3.3.1] dienes. Thus, for example, the decrease in intensity of the molecular ion in the series (XVI) > (XXI) > (XXVII) probably parallels their thermal stability (cf. earlier section on pyrolysis of (XXVII)), and reflects the decreasing strength of the C-heteroatom bond. The low intensity of the molecular ions of (XIX) and (XX) may similarly imply a ready thermal extrusion of SO or SO_2 respectively.

Several other ions in the m.s. of (XVI), (XXI), and (XXVII) are of interest. (XVI), in particular shows quite intense peaks at m/e 123, 97, 84, and 45. These probably correspond to alternative breakdown patterns in which sulphur is retained in the charged fragment, and may have the following compositions: m/e 123, $C_7H_7S^+$; m/e 97, $C_5H_5S^+$ (thiopyrylium); m/e 84, $C_4H_4S^{\cdot+}$ (thiophene radical ion); m/e 45, possibly $CH{=}S^+$ (cf. ref. 95). In (XXI) and (XXVII) very weak ions corresponding to $C_5H_5\,Se^+$ (145, ^{80}Se), $C_4H_4Se^{\cdot+}$ (132, ^{80}Se), $C_3H_4Te^{\cdot+}$ (170, ^{130}Te) are

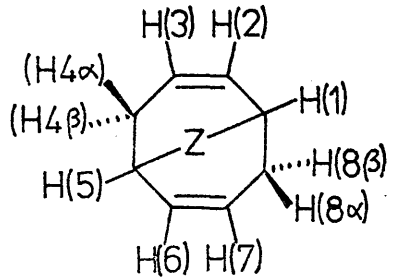


Table 3

100 MHz ^{1}H n.m.r. data for 9-Heterobicyclo[3.3.1]nona-2,6-dienes

Cpd.	Z	τ ppm H(1),(5)	H(2),(6)	H(3),(7)	H(4α),(8α)	H(4β),(8β)	|J|(Hz)	solvent
(V)	O	5·52(d×m J~6)	4·19(narrow m)		7·47(d×d, J~17, 6) 8·12(d×d, J~17, 4)		$J_{4\alpha,4\beta}$, $J_{8\alpha,8\beta}$ ~17	$CDCl_3$
(XXII)	NBu^t	6·29(d×m J~6)	4·22(narrow m)		7·70(d×d, J~17, 6) 8·21(d×d, J~17, 4)		τ 8·86(s) Bu^t; $J_{4\alpha,4\beta}$, $J_{8\alpha,8\beta}$ ~17	$CDCl_3$
(XXIII)	$C(CN)_2$	6·90(sym. m)	4·20(narrow m)		7·31(d×m, J~18, 5)	7·81(d×d, J~18, 4)	$J_{1,8\alpha}$, $J_{4\alpha,5}$ ~5; $J_{2,3}$, $J_{6,7}$ ~10 $J_{3,4\beta}$, $J_{7,8\beta}$ ~4; $J_{3,4\alpha}$, $J_{7,8\alpha}$ ~2	$CDCl_3$
		7·75(sym. m)	4·8-5·1(m, J~10)	4·55-4·8(m, J~10,4,2	7·82(d×m, J~18)	8·60(d×d, J~18, 4)	$J_{4\alpha,4\beta}$, $J_{8\alpha,8\beta}$ ~18	C_6D_6
(XX)	SO_2	6·52(sym.m)	4·24(narrow m)		6·93(d×m, J~18) 7·45(d×m, J~18)		$J_{4\alpha,4\beta}$, $J_{8\alpha,8\beta}$ ~18	$CDCl_3$

(XVI)	S	6·54	3·98	4·24	7·42	7·85	$J_{1,2}, J_{5,6}$ +6·7; $J_{1,8\alpha}, J_{4\alpha,5}$ +5·0; $J_{1,8\beta}, J_{4\beta,5}$ +2·0; $J_{2,3}, J_{6,7}$ +10·5; $J_{2,4\alpha}, J_{6,8\alpha}$ 1·4; $J_{2,4\beta}, J_{6,8}$ 2·0; $J_{3,4\alpha}, J_{7,8\alpha}$ +2·0; $J_{3,4\beta}, J_{7,8\beta}$ +4·9; $J_{4\alpha,4\beta}, J_{8\alpha,8\beta}$ −18·4	$CDCl_3$
(XIX)	SO	6·33 / 6·39 (overlapping)	4·3 (narrow m)	4·01 (m, J 10·5, 5, 2) 4·22 (m, J 10·5, 5, 2)	7·15 (d×m, J~18) 7·31 (d×m, J~18) 7·58 (d×m, J~18) 7·89 (d×m, J~18)		$J_{2,3}$ 10·5; $J_{6,7}$ 10·5; $J_{3,4\alpha}$ 2; $J_{7,8\alpha}$ 2; $J_{3,4\beta}$ 5; $J_{7,8\beta}$ 5; $J_{4\alpha,4\beta}$ ~18; $J_{8\alpha,8\beta}$ ~18	$CDCl_3$ [220 MHz]
(XXI)	Se	6·32 (sym. m)	3·75–4·1 (m, J~10·5, 6)	4·1–4·4 (m, J~10·5, 4·5, 2)	7·33 (d×m, J~18) 7·81 (d×m, J~18)		$J_{1,2}, J_{5,6}$ ~6; $J_{2,3}, J_{6,7}$ ~10·5 $J_{3,4\alpha}, J_{7,8\alpha}$ ~2; $J_{3,4\beta}, J_{7,8\beta}$ ~5; $J_{4\alpha,4\beta}, J_{8\alpha,8\beta}$ ~18	$CDCl_3$
(XXVII)	Te	6·21 (sym. m)	3·95–4·2 (m, J~11, 7, 2, 1)	4·2–4·45 (m, J 11·0, 4·6, 2·2)	7·38 (d×m, J 19·0) 8·22 (d×m, J 19·0)		$J_{1,2}, J_{5,6}$ ~7; $J_{2,3}, J_{6,7}$ 11·0; $J_{3,4\alpha}, J_{7,8\alpha}$ 2·2; $J_{3,4\beta}, J_{7,8\beta}$ 4·6; $J_{4\alpha,4\beta}, J_{8\alpha,8\beta}$ 19·0	$CDCl_3$

observed, as is a weak Te^+ series at m/e 130, 128, 126.

The oxygen-containing analogue (V) has a very different m.s. from the above series (Fig. 7). The m/e 105 peak is completely absent, and many of the major ions probably correspond to oxygen-containing fragments such as: m/e 107, $C_7H_7O^+$; m/e 93 $C_6H_5O^+$; m/e 81, $C_5H_5O^+$; m/e 68, $C_4H_4O^+$.

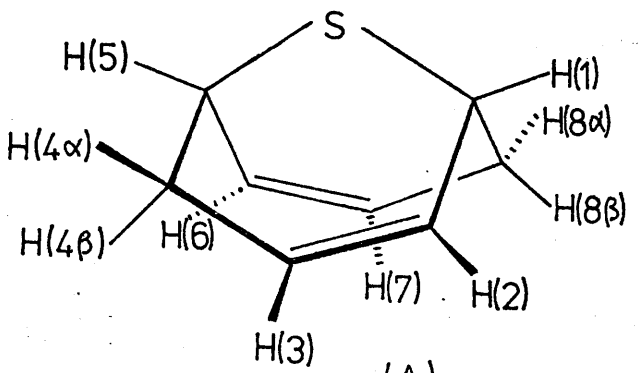
^{1}H n.m.r. spectra and conformation of 9-heterobicyclo [3.3.1]nona-2,6-dienes.

Spectral parameters for a series of the compounds previously prepared are listed, in varying detail, in Table 3. The data for most of the compounds are approximate estimates, but in the case of sulphide (XVI), the values and assignments have been determined by spin-decoupling and comparison of experimental and calculated spectra using an expanded version[96] of the line-shape program[97] UEAITR. The spin system can be described as AA' BB' MM' XX' YY', and the main coupling constants have been determined to an accuracy of probably about ±0.2 Hz; some small (ca. 1 Hz or less) long-range coupling constants have still to be determined.

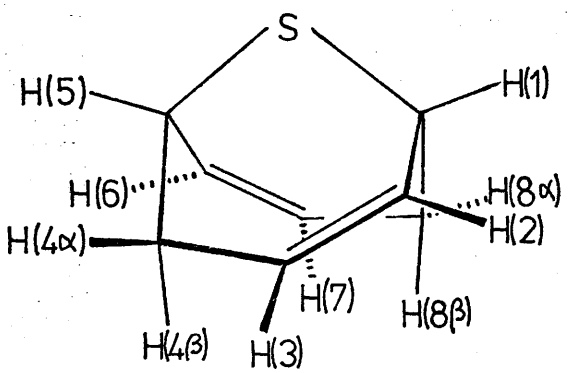
Application of an approximate Karplus-type relationship[98] of the form:

$$J_{vic} = a + b\cos\theta + c\cos 2\theta \quad \text{---(1)}$$

allowed a rough estimate to be made of the dihedral angles around (C(4) (or C(8)), the constants a, b,



(A)



(B)

Fig 8 Conformations of (XVI)

Table 4

(XVI)	J_{obs} (Hz)	Dihedral angle		
		θ_{calcd}	θ_{estd}	
			(A)	(B)
H(3),(4α)	+2·0	65° or 110°	65°	30°
H(3),(4β)	4·9	48° or 128°	55°	90°
H(4α),(5)	5·0	47° or 127°	50°	10°
H(4β),(5)	2·0	65° or 110°	70°	110°

and c being set at a = 6.1, b= -1, c = 5.8, by analogy with published calculations[99-102]; the values calculated for these angles are given in Table 4, along with those estimated from Dreiding models of the conformations (A) and (B) in Fig. 8. The results thus indicate (allowing for the approximate nature of the method) that the predominant conformer in solution is (A) in which the cycloocta-1,5-diene ring adopts a slightly-twisted boat conformation[103], rather than (B), which represents a different twisted-boat conformation. Microwave studies* have, in fact, shown that the molecule undergoes rapid flexing in the vapour phase. The large geminal coupling constant observed (-18.4 Hz) is also consistent with a conformation, such as (A) with $\theta_{3,4\alpha}$ and $\theta_{3,4\beta}$ near 60° [104].

For sulphoxide (XIX), selenide (XXI), telluride (XXVII), and dinitrile (XXIII), the available coupling constants appear to be close to those measured for (XVI), implying no marked change in their preferred conformation. In (XVI), (XXI) and (XXVII), a noticeable trend is a downfield shift in the position of the bridgehead multiplet in the series S → Se → Te.

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* Microwave analysis of (XVI) was carried out by Dr. J.K. Tyler.

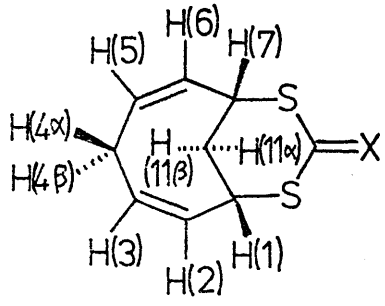


Table 5

220MHz ^{1}H nmr data for (XLVI) and (LII)

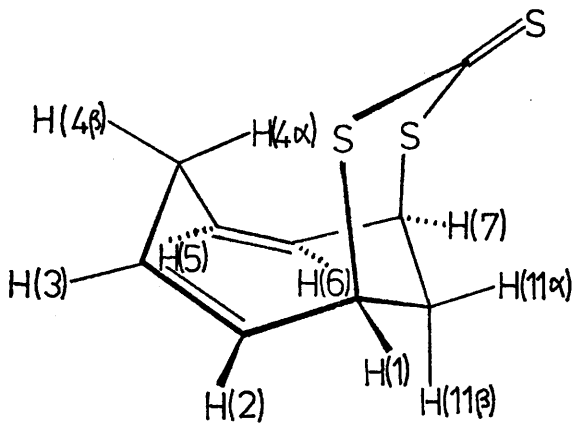
Cpd	X	τ ppm H(1),(7)	H(2),(6)	H(3),(5)	H(4α)	H(4β)	H(11α)	H(11β)	J (Hz)	solvent
(XLVI)	S	5·677	4·327	4·219	6·778	7·316	7·297	6·540	$J_{1,2}, J_{6,7}$ 3·9; $J_{1,3}, J_{5,7}$ 1·5; $J_{1,4\alpha}, J_{4\alpha,7} \sim 1$; $J_{1,11\alpha}, J_{7,11\alpha}$ 5·6; $J_{1,11\beta}, J_{7,11\beta}$ 3·2; $J_{2,3}, J_{5,6}$ 11·3; $J_{2,4\alpha}, J_{4\alpha,6} \sim 1.5$; $J_{2,4\beta}, J_{4\beta,6} < 1$; $J_{2,11\alpha}, J_{6,11\alpha} \leq 1$; $J_{3,4\alpha}, J_{4\alpha,5}$ 6·2; $J_{3,4\beta}, J_{4\beta,5}$ 9·0; $J_{4\alpha,4\beta} -14.8$; $J_{11\alpha,11\beta} -15.3$	CS_2
(LII)	$C(CN)_2$	5·50	4·25	4·15	6·78	7·26	7·39	6·58	$J_{1,2}, J_{6,7}$ 3·3; $J_{1,3}, J_{5,7}$ 1·5; $J_{1,11\alpha}, J_{7,11\alpha}$ 5·8 $J_{1,11\beta}, J_{7,11\beta}$ 3·3; $J_{2,3}, J_{5,6}$ 11·2; $J_{3,4\alpha}, J_{4\alpha,5}$ 5·4; $J_{3,4\beta}, J_{4\beta,5}$ 8·8; $J_{4\alpha,4\beta} -15.4$; $J_{11\alpha,11\beta} -15.6$	$CDCl_3$

This effect, which is opposite to that expected on a simple electronegativity basis, has previously been observed[105] in the shifts of vinylic protons α to S, Se or Te. In other respects, the spectrum of selenide (XXI) appears to be almost identical to that of (XVI). The spectrum of telluride (XXVII), however, while still showing a close general similarity, has some other noticeable differences: ^{125}Te sidebands[106] can be observed on either side of the bridgehead multiplet ($|J|_{Te-H}$ ca. 55 Hz), while one of the methylene resonances (probably corresponding to β in Fig. 8) shows a significant upfield shift compared with the sulphide or selenide, possibly due to a long-range effect of the large Te atom. Some of the coupling constants in (XXVII) also appear to have slightly altered values. Unfortunately, the literature for comparison of the properties of organotellurium compounds is very sparse.

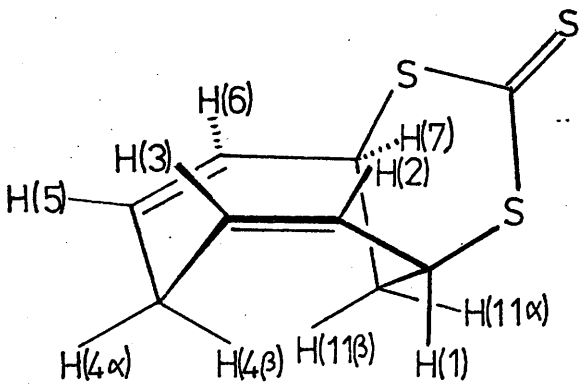
Accidental near-equivalence of the olefinic protons of (V), (XXII), and (XX) makes detailed analysis of their spectra difficult.

^{1}H n.m.r. and conformation of 8,10-dithiabicyclo [5.3.1]undeca-2,5-dienes.

Spectral parameters for (XLVI) and (LII) are listed in Table 5. The data for trithiocarbonate (XLVI) were obtained from 100 and 220 MHz spectra



(A)



(B)

Fig 9 Conformations of (XLVI)

by decoupling, and were checked by a preliminary computer plotting. The spin system can be described as AB FG MM' XX' YY' and the main coupling constants have been determined to an accuracy of about ± 0.3 Hz. Final refinement has still to be carried out. From consideration of a Dreiding model of (XLVI), it is clear that there are two possible families of conformations, corresponding to crown or boat forms of cycloocta-1,4-diene[107]. The crown conformation (Fig. 9 (A)) possesses little flexibility, while the boat conformation (Fig. 9 (B)) can undergo a degenerate flexing of the 3-atom bridge. In estimating the dihedral angles in conformation (B), it is therefore necessary to consider both possible forms. For conformation (A), the dihedral angle between H(1) and H(2) was measured from a model to be about 5°, while the two possible forms of conformation (B) give values of about 25° and 95°. Comparison with a model compound[108], in which a near-eclipsing situation gives rise to a vicinal coupling of 8.5 Hz, rules out (A) as the major conformer (observed J_{12} = 3.9 Hz). Approximate calculations using a Karplus-type relationship (equation (1)) for the vicinal couplings to the H(11) protons also gave values consistent with conformation (B). In keeping with this, the i.r. spectrum of (XLVI) has its methylene scissoring band at 1473 (solution) or 1467 cm^{-1} (KBr disc), implying a moderate degree of

steric interaction between H(4β) and H (11β) (cf. refs. 3, 62), and thus indicating that the conformation is of the boat type (B) in the solid as well as in solution. Two distinct crystalline modifications of (XLVI) have been found, an orthorhombic, and a rare monoclinic form. Both forms have i.r. absorptions at 1467 cm^{-1}, and an X-ray analysis of the monoclinic form (space group $P2_1/n$) is currently under way.

In order to determine whether or not the 'bridge flexing' motion of the molecule had a substantial barrier, the ^1H n.m.r. spectrum of (XLVI) was measured at -50° in CD_2Cl_2. No kinetic changes could be detected at this temperature. Investigations at lower temperatures were hampered by lack of solubility. However, by setting a limiting rate of 10 s^{-1} for the conformational process, it was estimated that the free-energy barrier was less than about 12 kcal/mole.

The spectral parameters for the related dinitrile (LII) have been estimated from 220 MHz spectra. The close similarity of the corresponding coupling constants for (XLVI) and (LII) indicates that the predominant conformation for both compounds is virtually the same.

EXPERIMENTAL.

For general experimental details see Part I Experimental section.

Analytical g.l.c. was performed on a Perkin-Elmer F-11 chromatograph with a 1% APL column and N_2 as carrier gas. Preparative g.l.c. was performed on a Pye Series 105 automatic preparative chromatograph.

syn-3,7-Dibromo-cis,cis-cycloocta-1,5-diene (I). To a stirred suspension of dry NBS (712g ; 4.0 mole) and α-azo-isobutyronitrile (7.5g) in dry, redistilled carbon tetrachloride (2.5 l) was added cis,cis-cycloocta-1,5-diene (II) (216g ; 2.0 mole) and the mixture heated to boiling with efficient stirring. When the initially vigorous reaction had moderated, the mixture was refluxed gently with stirring for a further 1.5 h., cooled, filtered, the filtrate concentrated in vacuo and the residual yellow oil dissolved in 95% ethanol (1.4 l). Some crystals separated immediately, and the bulk of the required dibromide crystallised out on cooling overnight at -30^{0}. The crystals were filtered off cold, washed with methanol and finally with a 2:1 mixture of methanol and ether. Concentration of the mother liquors and cooling for several weeks at -30^{0} gave more (I), the total yield being 39.5g. The

material obtained in this way was sufficiently pure for further use but, if necessary, could be recrystallised from ethanol as long, colourless needles, m.p. 122-123°.

Reaction of cuprous chloride complex of (II) with NBS. - To a stirred suspension of NBS (3.56g, 20.0 m mole) in refluxing carbon tetrachloride (10ml) was added α-azo-isobutyronitrile (40mg), followed by a slurry of the copper complex[109] (2.07g ; 5.0 m mole) in carbon tetrachloride (15ml), and the mixture refluxed 1.5 h. after which time the initially white suspension had become dark green. After cooling and filtration, the yellow solution was concentrated in vacuo. No dibromide (I) could be detected in the ^{1}H n.m.r. of the residual oil, nor could crystallisation be induced.

Hydrolysis of (I). - (a) A solution of (I) (50mg) in acetone (5ml) containing water (0.1ml) was left at room temperature. After 4 d., (I) was recovered unchanged.
(b) (Cf. ref. 64). To a solution of (I) (0.532g ; 2.0m mole) in THF (5ml) was added a solution of sodium bicarbonate (0.50g) in water (1ml) and the mixture stirred and refluxed. After 3 d., only unchanged (I) could be detected by ^{1}H n.m.r.
(c) A mixture of (I) (2.00g ; 7.52 m mole) and sodium bicarbonate (5.0g) in acetonitrile (60ml) and water (3ml) was stirred and refluxed 16 h. under N_2. The

brown mixture was poured into water (100ml), and extracted with pentane (4 x 40ml), the combined extracts washed with brine (3 x 25ml), dried (Na_2SO_4), and the pentane evaporated at room temperature under reduced pressure. The orange residue (ca 400mg) appeared from ^1H n.m.r. to be mainly diene ether (V) together with an aldehyde, and other unidentified material. Two short-path distillations at 10mm gave (V) (ca 130mg, 14%), m.s. and ^1H n.m.r. (see Discussion for details) were identical to those of an authentic sample of (V), independently synthesised[68]. The crude aldehyde had the following spectral properties (lit. values for cyclooctatrienal (VI b) in parenthesis) : λ_{max} (EtOH) 317 nm (lit.[66] 316), ν_{max} (film) ca 1680, 1615 cm^{-1} (lit.[67] ($CHCl_3$) 1674, 1615 cm^{-1}); τ ($CDCl_3$) ca 0.45 (d, J ca 8 Hz), ca 2.7-3.5 (complex), 8.1 (d, J ca 6 Hz).

The water was removed from the aqueous layer (remaining after pentane extraction above) by azeotroping with benzene. Concentration of the resulting benzene solution gave an oil which darkened and resinified on standing. ^1H n.m.r. was very complex; m.s. complex but had fairly strong ion at m/e 122 [possibly $C_8H_{10}(OH)_2 - H_2O$].

Attempted oxidation of (I) with CrO_3.2pyridine. - The method was similar to that described in ref. 110

After 2 h. at room temperature, workup gave only unchanged (I).

syn-4,8-Dibromo-2,6-dioxaadamantane (IX). - A mixture of dibromide (I) (1.24g ; 4.66 m mole) and powdered $Na_2Cr_2O_7.2H_2O$ (1.5g) in HMPT (15ml) and water (0.5ml) was stirred 3 d. at room temperature. The mixture was then poured into 2.5M sulphuric acid (60ml), and stirred 1 h., with gradual addition of further dichromate (ca 3g). The green solution was extracted with ether-methylene chloride (4:1) (3 x 20ml), the extracts washed with water (4 x 25ml), dried (Na_2SO_4), and the solvent evaporated. The partly-crystalline residue was washed with a little petroleum spirit, and sublimed (110° at 0.05mm) to give the colourless, crystalline (IX) (0.902g ; 65%), m.p. 136-137°. (Found: C, 32.39; H, 3.43. $C_8H_{10}Br_2O_2$ requires C, 32.25; H, 3.38%), m/e 300, 298, 296 (ca 1:2:1), ν_{max} (KBr) 2971, 1438, 1324, 1291, 1240, 1212, 1166, 1088, 1057 (s), 1042, 1020 (s) 977 (s)., 839, 804, 799, 790, 729, 720 (s), 652 cm^{-1}, ^1H n.m.r. see DISCUSSION.

9-Oxabicyclo[3.3.1]nona-2,6-diene (V) from (I) with water/HMPT/dichromate. - A mixture of dibromide (I) (1.24g ; 4.66 m mole) and powdered $Na_2Cr_2O_7.2H_2O$ (1.5g) in HMPT (15ml) and water (0.5ml) was stirred 3 d. at room temperature. The mixture was poured into satd. brine (50ml) and extracted with pentane (4 x 20ml),

the combined extracts washed with water (20ml) and satd. brine (3 x 20ml), dried (Na_2SO_4) and the pentane evaporated under reduced pressure without heating. The resulting colourless oil was almost pure (V) (0.43g ; 75%), low-temperature sublimation giving crystalline (V), m.p. 32-34° (lit.[51] 35-36°), ^1H n.m.r. identical to authentic sample. (No (IX) could be detected by ^1H n.m.r. of the crude product.)

(IX) from diene ether (V) and aqueous Br_2-KBr. - Application of the method of Zefirov et al.[70] to (V) (0.0106g, 0.87m mole) yielded an impure product, separated on prep t.l.c. (silica gel, Merck, methylene chloride as solvent), giving as the major component (IX) (ca 100mg, about 40% yield), m.p. 133-136°, undepressed on addition of authentic (IX), and with identical ^1H n.m.r.

(V) from (I) and water/HMPT. - To a solution of (I) (0.150g) in HMPT (2ml) was added water (0.1ml). After 5 d. at room temperature, the solution was strongly acid (universal indicator). Dilution with water and extraction with ether gave material which by ^1H n.m.r. was a mixture (ca 4 : 1) of (V) and unreacted (I).

Treatment of (IX) with bases. - The following conditions were applied to (IX):- (a) DBN in THF, 16 h at room temperature; (b) potassium t-butoxide in THF, 16 h at room temperature; (c) potassium t-butoxide in

HMPT, 30 min. at 100°; (d) lithium dicyclohexylamide in THF, 2 h. reflux. In all cases, (IX) was recovered in 85-100% yield. ^{1}H n.m.r. revealed no trace of olefinic material.

2,6-Dioxaadamantane (X) from dibromo-compound (IX). - A solution of (IX) (0.087g ; 0.29 m mole) in THF (3ml) was treated with excess $LiAlH_4$, and the solution refluxed 16 h. With cooling to 0°, satd. ammonium sulphate solution was added dropwise, the mixture filtered through glass-fibre paper, the solid washed with ether, the combined filtrate dried (K_2CO_3), and the solvent evaporated to give a white solid (40mg), which on sublimation (75° at 10mm) gave colourless crystals, m.p. 180-182° (sealed tube), undepressed on addition of authentic (X), ^{1}H n.m.r. identical to authentic (X) (prepared from diiodo-2,6-dioxaadamantane).

syn-4,8-Diiodo-2,6-dioxaadamantane. - This was prepared from diene ether (V) by treatment with mercuric oxide and iodine in chloroform by the method of Portmann and Ganter[52] and had m.p. 150-152°, τ ($CDCl_3$) 5.3-5.5 (2H,m), 5.5-5.9 (4H,m), 6.7-7.0 (2H, complex d, J ca 13 Hz), 7.6-7.9 (2H, complex d, J ca 13 Hz), spectrum rather similar to that of (IX).

2,6-Dioxaadamantane (X) from diiodo-derivative. - A solution of the diiodo-compound (100mg) in ether

(3ml) was stirred 1d. with excess $LiAlH_4$ at room temperature. Workup in the usual way, and sublimation of the product gave (X), m.p. 179-181°, τ ($CDCl_3$) 5.65-5.85 (4H,m), 7.95-8.05 (8H,m, becomes s on double irradiation at τ 5.75) (shifts in agreement with lit.[51] values).

Reaction[71] of (I) with trimethylamine oxide. - A solution of anhydrous trimethylamine oxide[111] (0.564g ; 7.52 m mole) in chloroform (5ml) was added dropwise during 10 min. to a solution of (I) (0.484g ; 1.82 m mole) in refluxing chloroform (5ml), and the mixture refluxed a further 1.5 h. The chloroform solution was washed with water (2 x 10ml), dried (Na_2SO_4), and the solvent evaporated, giving a pale yellow oil (ca 200mg), ν max (film) 1660, 1625 cm^{-1}; τ ($CDCl_3$) 3.1-4.4 (6H, complex), 6.92 (2H, d, J ca 8Hz), identical with the published spectrum[72] of cycloocta-2,4,6-trienone (XI).

Attempted reaction of (I) with 2-nitropropane[73]. - A solution of 2-nitropropane (0.246g ; 2.77 m mole) in dry acetonitrile (3ml) under N_2 was treated with sodium hydride (0.100g of 60% dispersion; 2.5 m mole) and the mixture stirred 30 min. A solution of (I) (0.300g ; 1.13 m mole) in acetonitrile (5ml) was then added and the mixture stirred 5 h at room temperature. Workup gave only unchanged (I). No ketonic material

could be detected (t.l.c. 2,4-DNP spray).

syn-3,7-Diiodo-cis,cis-cycloocta-1,5-diene (XII). - A solution of (I) (0.684g ; 2.57 m mole) in acetone (12ml) was stirred 16 h with potassium iodide (1.8g). The mixture was filtered, the filtrate concentrated and the resulting solid washed with methanol. The yellow crystalline material thus obtained (which decomposed over a few weeks, releasing iodine) weighed 0.536g; 58%; τ ($CDCl_3$) 3.9-4.8 (4H,m), 5.0-5.5 (2H, m), 6.0-6.6 (2H,m), 6.9-7.4 (2H,m), very close similarity to published spectrum of (I)[62], ν max (KBr) 3020, 1485, 1114, 770, 751, 709 cm^{-1}.

Attempted reaction of (XII) with 2-nitropropane. - Repetition of the above method using (XII) led to recovery of starting material.

Diazide (XIII). - To a solution of (I) (1.34g ; 5.04 m mole) in DMF (20ml) was added a solution of sodium azide (1.3g ; 20 m mole) in water (6ml) and the mixture left 1 h at room temperature, poured into water (50ml), extracted with ether (3 x 25ml), the ether extracts washed with water (4 x 25ml), dried (Na_2SO_4), and the solvent evaporated, giving a pale yellow oil, single spot on t.l.c. (silica gel, 15% ethyl acetate-petroleum spirit), ν_{max} (film) 3020, 2090 (vs), 1655, 1480, 1430, 1250 (s), 930, 745 cm^{-1}; τ ($CDCl_3$) 4.0-4.7 (4H,m),

5.4-5.9 (2H, approx. symmetric m), 7.1-7.7 (4H,m).

Diamine (XIV). - A solution of diazide (XIII) (0.173g ; 0.91 m mole) in THF (3ml) was added dropwise to a stirred solution of $LiAlH_4$ (0.120g) in THF (5ml) during 10 min. The mixture was refluxed 2 h., and worked up in the usual way to give, after drying by azeotroping with benzene, a crude oil (125mg), ν_{max} (film) 3350 (s,br), 3260 (s,br) cm^{-1}; τ ($CDCl_3$) 4.3-4.9 (4H,m), 5.8-6.2 (2H, quintet-like m), 7.2-8.2 (4H,m). 8.3 (4H,br).

Attempted oxidation of (XIV). - The crude (XIV) (125mg) was treated with 2 equivalents of 3,5-di-t-butyl-1,2-benzoquinone, using the method of Corey and Achiwa[112] I.r. of the product showed only a weak carbonyl absorption (ca 1660 cm^{-1}), and ^1H n.m.r. was complex, but showed no methylene doublet attributable to the required diene-dione (III).

9 -Thiabicyclo[3.3.1]nona-2,6-diene (XVI). - A solution of (I) (1.33g ; 5.0 m mole) in dry DMF (15ml) was added to a stirred suspension of anhydrous sodium sulphide (4.55g ; 5.84 m mole) in dry DMF (25ml). The mixture turned an intense yellow colour, and, after stirring for 3 h. at room temperature, was poured into saturated brine (50ml), extracted with n-pentane (3 x 20ml) and the combined extracts washed in turn with water (10ml) and brine (25ml). The pentane solution was dried (Na_2SO_4) and the pentane carefully removed at room temperature under reduced pressure.

The residual pale yellow oil (0.53g) was chromatographed on silicic acid (Mallinckrodt; 25% CH_2Cl_2-petroleum spirit b.p. 40-50° as eluant), giving the crystalline, highly volatile (XVI), (150mg, 22%) which was further purified by low-temperature sublimation. The pure compound crystallised in colourless prisms, m.p. 41-41.5°. (Found: C, 69.55; H, 7.32. $C_8H_{10}S$ requires C, 69.51; H, 7.30%), ν_{max} (KBr) 3017, 2880, 1644, 1413, 1378, 1190, 833, 790, 697(s), 656 cm^{-1}; ^1H n.m.r., m.s. see DISCUSSION.

Diimide reduction of (XVI). - The method was based on the work of Hamersma and Snyder[113] using potassium azodicarboxylate as diimide generator.

Using anhydrous pyridine as solvent, the potassium azodicarboxylate was not noticeably decomposed by excess acetic acid, and (XVI) was recovered unchanged after a reaction time of 3 days. Dioxan was then used as solvent. Glacial acetic acid (0.16ml) was added with stirring to a mixture of (IIa) (113.5mg ; 0.823 m mole) and potassium azodicarboxylate (640mg ; 3.3 m mole) in pure, dry dioxan (6ml). An immediate brisk effervescence ensued, and the yellow colour had been discharged within 30 minutes. The mixture was stirred for a further 30 minutes, and left overnight at room temperature. It was then poured into water (15ml), extracted with methylene chloride (3 x 5ml), the combined extracts washed with water (10ml) and brine

(2 x 10ml). The solution was dried (Na_2SO_4), and the solvent evaporated, giving a colourless, waxy solid (113mg) which was sublimed at 80°, 760mm, m.p. 126-131°, ν_{max} (CCl_4) in complete agreement with literature[28] values for 9-thiabicyclo[3.3.1]non-2-ene containing a minor amount of 9-thiabicyclo[3.3.1] nonane. Use of a 15-fold excess of potassium azodicarboxylate increased the relative proportion of the saturated compound.

Effect of heat on (XVI). - A solution of (XVI) in toluene-d_8 was heated at 200° in a sealed n.m.r. tube, and the ^1H spectrum monitored periodically. After a total of 16 hours, the spectrum showed no significant alteration, τ 3.9-4.7 (4H,m), 6.75-7.05 (2H,m), 7.3-8.5 (4H,m).

9-Thiabicyclo[3.3.1]nona-2,6-diene-9-oxide (XIX). - To a stirred solution of (XVI) (84.3mg ; 0.610 m mole) in methylene chloride (2ml) at -10° was added dropwise a solution of 85% m-chloroper-benzoic acid (113mg ; 0.56 m mole) in methylene chloride (2ml), and the mixture allowed to warm up to room temperature during 1 hour. The solution was washed with saturated sodium carbonate solution (5ml), and saturated brine (2 x 5ml), dried (Na_2SO_4) and the solvent and excess (XVI) evaporated under reduced pressure. The colourless, crystalline sulphoxide (XIX) (88mg) thus obtained was purified by sublimation at 95°, 0.1mm, m.p. 120-122°

(Found: C, 62.57; H, 6.52. $C_8H_{10}OS$ requires C, 62.33; H, 6.54%), ν_{max} (KBr) 3021, 2904, 1644, 1428, 1381, 1207, 1049 (vs), 830, 800, 712 (s), 683 (s) cm^{-1}; ^1H n.m.r. see DISCUSSION.

9-Thiabicyclo[3.3.1]nona-2,6-diene-9,9-dioxide (XX). - To a stirred solution of (XVI) (82.9mg ; 0.60 m mole) in methylene chloride (2ml) was added 85% m-chloroperbenzoic acid (245mg ; 1.21 m mole) methylene chloride (5ml) and the mixture left 1 hour at room temperature. Workup as for (XIX) gave the sulphone (102mg), containing a small amount of sulphoxide. Sublimation at 110° (0.1mm) gave colourless crystals m.p. 165-167° (Found: C, 56.74; H, 5.89. $C_8H_{10}O_2S$ requires C, 56.45; H, 5.92%), ν_{max} (KBr) 3029, 2907 (m), 1641, 1421, 1300 (vs), 1194, 1119 (vs), 821, 793, 712, 692 cm^{-1}; ^1H n.m.r. see DISCUSSION.

9-Selenabicyclo[3.3.1]nona-2,6-diene (XXI). - Anhydrous sodium selenide (2.04g ; 16.3 m mole) was added in portions in an atmosphere of nitrogen to a stirred solution of (I) (2.77g ; 10.4 m mole) in dry, nitrogen purged DMF (60ml). The mixture became warm, and darkened in colour, and after stirring for 3 hours at room temperature, was worked up as for (XVI), giving an orange-coloured oil (0.322g). This was passed through a short column of silicic acid (Mallinckrodt; 25% CH_2Cl_2-petroleum spirit b.p. 40-50° as eluant) to give a yellow oil (0.252g ; 1.36 m mole, 13%) which crystallised on slight cooling. Sublimation at 45°,

0.1mm gave colourless, highly volatile (XXI) (m.p. 54-55°). (Found: m/e 185.9944. $C_8H_{10}{}^{80}Se$ requires 185.9947), ν_{max} (CCl_4) 3016, 2876, 1644, 1412, 1382, 1339, 1216, 906, 694 (s), 629 cm^{-1}; ^1H n.m.r. see DISCUSSION.

9-t-Butyl-9-azabicyclo[3.3.1]nona-2,6-diene (XXII). - A mixture of (I) (0.744g ; 2.80 m mole) t-butyl amine (0.4ml) and powdered calcium carbonate (1g) in dry acetonitrile (25ml) was stirred and refluxed for 16 hours in a static nitrogen atmosphere. The dark solution was filtered, and the solven evaporated under reduced pressure. The residue was dissolved in methanol (10ml), basified with 5M aqueous sodium hydroxide solution, and the resulting solution extracted with 1 : 1 ether-petrol (b.p. 40-60°) (3 x 7ml). The combined extracts were washed with brine (3 x 10ml), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The crude amine weighed 0.486g. Chromatography on alumina (Woelm basic, grade II),) eluting with 10% chloroform-petrol (b.p. 40-60°) gave (XXII) (223mg ; 1.26 m mole, 45% overall yield) as an almost colourless liquid, m/e 177, ν_{max} (CCl_4) 3020, 2968, 2890, 1650, 1474, 1463, 1425, 1391, 1361 (s), 1221 (s), 1185 (s), 1171, 1101, 1072, 882 (s), 699 (s), 612 cm^{-1}; ^1H n.m.r. see DISCUSSION.

(XXII) Hydrochloride. - A solution of (XXII) (100mg)

in anhydrous ether (5ml) was treated with dry hydrogen chloride, precipitating quantitatively the hydrochloride as a white solid. This was filtered off and washed with anhydrous ether. Recrystallisation three times from a 4 : 1 mixture of diisopropyl ether and ethanol gave an analytical sample (Found: C, 67.35; H, 9.76; N, 7.1. $C_{12}H_{20}ClN$ required C, 67.43; H, 9.43; N, 6.6%), ν_{max} (KBr) 3020, 2975, 2910, 2735 (br), 2530 (vs,br), 1655, 1183 (s), 725 (vs) cm^{-1}; τ ($CDCl_3$) 3.9-4.4 (4H,m), 5.5-6.0 (2H,br.d), 6.50-8.10 (4H,m), 8.38 (9H,s).

9,9-Dicyanobicyclo[3.3.1]nona-2,6-diene (XXIII). - The method is based on that of Bloomfield.[114] To a stirred suspension of powdered sodium hydride (1.00g ; 25 m mole of 60% benzene dispersion) in dry DMSO (30ml) was added malononitrile (0.715g ; 11 m mole) dry DMSO (15ml). After evolution of hydrogen had ceased, a solution of (I) (2.66g ; 10 m mole) in a mixture of benzene (20ml) and DMSO (20ml) was added with stirring during 10 minutes, and stirring continued for 3 hours. The mixture was then poured into saturated brine (250ml), extracted with ether (4 x 50ml), the combined extracts washed with water (25ml) and brine (3 x 50ml) and dried over anhydrous sodium sulphate. Evaporation of the ether under reduced pressure gave a light brown oil (1.33g) which crystallised on cooling. Sublimation (70°, 0.01mm) followed by recrystallisation from aqueous ethanol gave colourless needles of (XXIII) m.p. 119-120°,

(0,99g ; 58%). (Found: m/e 170.0839. $C_{11}H_{10}N_2$ requires 170.0849), ν_{max} (KBr) 3045, 2930, 2905, 2245, 2240, 1649, 1429, 1425, 1381 (m) 1256 (m), 920, 879, 844, 794, 717 (s), 700 (s), cm^{-1}; ^1H n.m.r. see DISCUSSION.

Addition of SCl_2 to sulphide (XVI). - A solution of (XVI) (0.090g ; 0.65 m mole) in methylene chloride (50ml), and a solution of freshly-distilled SCl_2 (0.041ml ; 0.65 m mole) in methylene chloride (50ml) were added dropwise at equal rates with stirring to methylene chloride (200ml) cooled to -10°, during 4 h. After the addition was complete, the solution was allowed to warm up to room temperature (1 h), and the solvent evaporated, yielding an amorphous, pale-yellow solid (150mg), which did not melt sharply but fused into a glassy material (ca 70-120°), which gradually darkened and became mobile on further heating (up to 300°). ^1H n.m.r. showed three overlapping complex absorptions (ratio ca 1 : 2 : 2), τ 5.1-5.9, 5.9-6.8, 6.8-7.8. The m.s. had the following m/e above 200: 298, 294, 255, 242, 241, 240, 227, 207, 205 (all weak; no obvious Cl isotope pattern; expected for compound (XXIV) m/e 205, 207 ca 3:2).

Similar results obtained on performing the reaction at -70°.

Reaction of dinitrile (XXIII) with SCl_2. - A solution of freshly-distilled SCl_2 (0.19ml, 3.0 m mole) in

methylene chloride (30ml) was added dropwise with stirring to a solution of dinitrile (XXIII) (0.498, 2.93 m mole) in methylene chloride (120ml) at -5°. The mixture was left at room temperature for 16 h., and then the solvent evaporated under reduced pressure, giving a semi-solid mass. This material was stirred with ether (15ml), filtered, and the solid washed with a little chloroform, giving the white microcrystalline (XXVI) (105mg ; 13%), m.p. (dec) ca 267-270°, m/e 272, 274 (ca 3:2), 237, 239 (ca 3:1), ν_{max} (KBr) 2930, 2238, 1443, 1049, 955, 847, 774 cm^{-1}; solubility too low for n.m.r.

9-Tellurabicyclo[3.3.1]nona-2,6-diene (XXVII) and bicyclo[5.1.0]octa-2,5-diene (XXIX). - Anhydrous sodium telluride (5.7g) was added in a nitrogen atmosphere to a stirred solution of dibromide (I) (4.23g ; 15.9 m mole) in dry, nitrogen-purged DMF (60ml), the mixture stirred 1 h. at room temperature in the dark and then poured into nitrogen-purged water (60ml) and extracted with pentane (3 x 30ml). The black solid material was stirred with 50ml pentane, filtered, and the filtrate and pentane extracts combined, washed with water (2 x 25ml), and dried (Na_2SO_4). This solution was chromatographed on silicic acid (Mallinckrodt); elution with pentane gave a solution of the hydrocarbon (XXIX), while further elution with 15% methylene chloride petroleum spirit (b.p.40-50°) gave a pale yellow solution of the pure telluride (XXVII).

Concentration of the telluride solution gave (XXVII) (0.67g ; 18%) as light-sensitive yellow crystals m.p. 69-71°. (Found: m/e 235.98 56. $C_8H_{10}{}^{130}Te$ requires 235.9859), ν_{max} (KBr) 3006, 2952, 2873, 1639, 1409, 1380, 1215, 889, 814, 777, 700 (s), 685 cm^{-1}; ^1H n.m.r. and m.s. see DISCUSSION.

The pentane solution of (XXIX) was concentrated by careful distillation of the solvent through a Vigreux column. The resulting solution was separated from remaining solvent by g.l.p.c. (retn. time 6 minutes on 15% APL at 148°, N_2 30 lb/in^2), and diene (XXIX) (ca 0.37g ; 22%) obtained as a colourless liquid, m/e 105, 91, 79, 78, 77, ν_{max} (CCl_4) 3008, 1660 cm^{-1}; τ ($CDCl_3$) (34°) 3.9-4.5 (2H,br), ca 4-10 (8H,v.br); (-52°) broadened resonances at τ 4.1-4.9 (4H), 7.0-7.8 (2H), 8.4-8.7 (2H), 8.8-9.2 (1H), 10.1-10.3 (1H), very similar to published spectrum[77].

Treatment of (XXVII) with aqueous DMF. - A pentane solution of telluride (XXVII) was shaken with aqueous DMF in the presence of atmospheric oxygen. The pentane layer was separated, washed through a short column of silicic acid with pentane, and the eluate analysed by g.l.c. No trace of (XXIX) could be detected.

Pyrolysis of telluride (XXVII). - A solution of (XXVII) (30mg) in degassed toluene-d_8 (0.4ml) was sealed in an n.m.r. tube and heated in an oven. The tube was removed periodically, allowed to cool, and the room-

temperature ^{1}H n.m.r. spectrum of the solution recorded. The reaction was extremely slow at temperatures below about 150°. At 175°, Te was extruded at a convenient rate, being deposited as a grey metallic mass. The presence of (XXIX) (very broad resonances at 34°) in the spectrum could be detected after ca 30 minutes at 175°, telluride (XXVII) being undetectable after 4 h. The tube was heated a further 4 h. to ensure completion of the reaction. ^{1}H n.m.r. (+160°) τ (C_7D_8) broadened resonances at ca 4.4 (2H), 6.7 (4H), 8.2 (2H), 8.7 (2H); (-66°) τ (C_7D_8) 4.25 (2H,complex d, J = 10.5 Hz), 4.6 (2H,m), 7.1-7.4 (1H,complex d, J ca 20 Hz), 7.6-8.0 (1H,d x t, J ca 20 Hz, 7 Hz), 8.6-8.9 (2H,m), 9.1-9.4 (1H.m), [>10 (1H) not recorded].

9,9-Bis-acetoxy-9-tellurabicyclo[3.3.1]nona-2,6-diene (XXVIII). - Reaction of telluride (XXVII) (0.171g ; 0.732 m mole) with lead tetraacetate (0.319g ; 0.72 m mole) by the method of Pant[76] gave crude (XXVIII), (199mg ; 87%), as almost colourless crystals. The bis-acetoxy-compound was recrystallised, with some decomposition, from benzene, giving colourless, transparent prisms, which blackened above 110° and had m.p. about 152-155°(decomp.; evac. sealed tube); m/e 354, 352, 350, 349, 348, 346 (ca 13:12:8:3:2:1), 295, 293, 291, 290, 289, 287 (ca 13:12:8:3:2:1), 236, 234, 232, 231, 230, 228 (ca 13:12:8:3:2:1), ν_{max} (KBr) 3020, 2920, 1640 (s), 1620 (vs), 1424, 1357 (s), 1286 (vs), 1223, 1006, 920, 816, 700, 659 (s) cm^{-1}; τ (C_7D_8)

4.5-5.0 (4H,m), 6.1-6.3 (2H,m), 7.5-7.9 (2H, complex d, J ca 18 Hz), 8.32 (6H,s), 8.3-8.8 (2H,complex d, J ca 18 Hz).

Bicyclo[5.1.0]octa-2,5-diene (XXIX) from (I) and zinc[81]. - To a solution of dibromide (I) (0.266g ; 1.0 m mole) in ethanol (20ml) was added zinc powder (300mg) and the mixture stirred and refluxed 2 h, then cooled, diluted with water (30ml), extracted with n-pentane (3 x 10ml), the combined extracts washed with water (4 x 10ml), dried (Na_2SO_4), and the solvent removed by distillation (Vigreux column). The colourless liquid thus obtained (ca 80mg) gave a single peak on g.l.c., and was identical by g.l.c. and ^1H n.m.r. to diene (XXIX) previously prepared.

5,7-Dihydrodibenzo[c,e]tellurepine (XXXI) and 9,10-dihydrophenanthrene (XXXII). - To a stirred solution of 2,2′-bis (bromomethyl)biphenyl[115] (2.72g ; 8.00 m mole) in dry, N_2-purged DMF (40ml) was added dry Na_2Te (2.12g ; 12.2 m mole), the mixture stirred under N_2 16 h at room temperature, poured into water (40ml) and extracted with ether (3 x 30ml), the combined extracts washed with water (5 x 25ml), dried (Na_2SO_4), and the solvent evaporated giving an orange oil (1.8g) which crystallised on cooling. Chromatography of the crude material on silicic acid (30% methylene chloride-petroleum spirit as eluant) gave 9,10-dihydrophenanthrene (XXXII) (ca 110mg ; 8%) followed by (XXXI)

(570mg ; 24%) as yellow needles (from petroleum spirit), m.p. 90-92°. (XXXI) could also be obtained directly by crystallisation of the crude product. (XXXI): m/e 310,308, 306, 305, 304, 302 (ca 13:12: 8:3:2:1), τ ($CDCl_3$) 2.5-3.0 (8H,m), 5.91 (2H, d, J ca 10.5 Hz), 6.58 (2H, d, J ca 10.5 Hz).

(XXXII): m/e 180, 179, 178, τ ($CDCl_3$) 2.1-2.9 (8H,m), 7.13 (4H,s), identical to published spectrum.[116]

1,3-Dihydrobenzo[c]tellurophene (XXXIII). - This compound was prepared by treatment of α,α-dibromo-o-xylene (2.59g ; 9.81 m mole) with Na_2Te (2.59g ; 14.9 m mole) by the method detailed for compound (XXXI). Because of its rapid decomposition in solution in contact with air, the isolated yield of pure (XXXIII) was greatly reduced. Low-temperature crystallisation from petroleum spirit (b.p. 40-60°) gave (XXXIII) as pale-yellow plates, (ca 200mg), m.p. 44-46° (evac. sealed tube). (Found: m/e 233.9694. C_8H_8Te requires 233.9693); τ ($CDCl_3$) 2.4-3.0 (4H,m), 5.41 (4H,s).

No hydrocarbon signals could be indentified in the ^1H n.m.r. of the crude product.

Pyrolysis of (XXXIII). - Tellurophene (XXXIII) was heated to ca 150° in a low-pressure stream of He (0.4-0.5mm), and the vapours passed through a silica tube loosely packed with quartz wool and heated to approx. 500°. The product, collected in a receiver cooled in liquid N_2, was benzocyclobutene (XXXIV) (0.028g,74%),

pure apart from a trace of water; m/e 104 (M^+), 78, 77, τ ($CDCl_3$) 2.90 (centre; 4H,m), 6.83 (4H,s); n.m.r. identical to authentic sample independently prepared.[117]

From the tube connecting the pyrolysis tube and the cold trap was collected, in addition, a yellow, partly solid material (ca 15mg), which by ^1H n.m.r. appeared to be a mixture (ca 8:4:1 mole ratio) of unreacted (XXXIII) with benzocyclobutene (XXXIV) and tetrahydro-dibenzo[a,e]cyclooctene (XXXV)[82].

Pyrolysis of (XXXI). - Tellurepine (XXXI) (59mg) was pyrolysed in the same way as (XXXIII), giving, along with a trace of water, a mixture of products, partially separated on prep. t.l.c. (silica gel, 50% methylene chloride-petroleum spirit as solvent), yielding three major bands: (a) (Least polar) mixture of hydrocarbons, τ ($CDCl_3$) 1.32 (m) (similar m for sample of phenanthrene (XLI)); 2.1-2.9 (complex); 6.11 (s) (identical for sample of fluorene (XXXIX)); 7.13 (s) (9,10-dihydrophenanthrene (XXXII) lit.[116] 7.14); 7.27 (s), unidentified; (b) Colourless oil, ($CDCl_3$) 0.20 (s), 1.8-2.9 (complex), 7.91 (s), absorption in ratio ca 1:12:3, corresponding to an aldehyde, possibly (XL) + impurity; (c) Most polar band, yellow crystalline solid (from petroleum spirit), m.p. 83-85°, m/e 194, τ ($CDCl_3$) 2.2-2.9 (7H,m), 7.41 (3H,s); ν_{max} (KBr) 1705, 1607 cm^{-1}, λ_{max} (EtOH) 249, 258

nm; (4-methyl fluoren-9-one (XXXVIII) lit[83]. m.p. 91-93°, lit.[84] τ ($CDCl_3$) 7.41; fluoren-9-one λ_{max} (EtOH) 249, 257.5 from authentic sample). Rough estimates (from ^1H n.m.r. integration) of the proportions of these compounds in the product mixture given in Discussion.

Reaction of (I) with Na_2S_2. - Sodium disulphide (0.357 ; 3.24 m mole), prepared by heating anhydrous Na_2S with sulphur,[118] was dissolved in water (2ml). To this was added with stirring a solution of (I) (0.532g ; 2.00 m mole) in acetonitrile (15ml) and the mixture stirred 16 h. at room temperature. Addition of water (50ml) and extraction with methylene chloride gave a viscous, pale-yellow material (0.235g), which after chromatography on silicic acid (Mallinckrodt, 30% methylene chloride-petroleum spirit b.p. 40-50° as eluant), gave a small amount of a poorly crystalline solid (ca 25mg ; 9%), whose ^1H n.m.r. spectrum comprised peaks identical to those of monosulphide (XVI), along with other minor, unidentified resonances. The other amorphous products of this reaction appear to be polymeric in nature.

Dimercaptocycloocta-1,5-diene (XLIII); (cf. ref. 85). - A mixture of dibromide (I) (5.71g ; 21.4 m mole) and N-acetyl-thiourea (7.19g ; 61 m mole) in ethanol (50ml) was refluxed 2 h. under N_2. The precipitated acetylurea was filtered off, and the filtrate concentrated in vacuo. The dithiol (XLII) was purified by chromatography

over silicic acid (Mallinckrodt, methylene chloride as eluant), giving (XLIII) as a colourless, foul-smelling oil (1.64g ; 45%), ν_{max} (film) 3015, 2530 (S-H), 1480; τ ($CDCl_3$) 3.9-4.6 (4H,m), 5.9-6.7 (2H, symm.m), 6.7-7.8 (m), 8.19 (2H, d, J ca 8 Hz; thiol).

Iodine oxidation of dithiol (XLIII). - A solution of NaOH (0.53ml of N/1 aqueous) in methanol (5ml) was treated with dithiol (XLIII) (0.045g ; 0.264 m mole) under N_2. With stirring, a 10% solution of I_2 in methanol was added dropwise. After stirring a further 30 min., the cloudy mixture was treated with pentane (10ml) and water (5ml), the pentane layer separated, washed with water to neutrality, dried (Na_2SO_4), and the pentane evaporated in vacuo. The material obtained (ca 10mg) had ^1H n.m.r. closely resembling that of authentic (XVI).

Reaction of (I) with di-t-butyl acetonedicarboxylate. - A solution of the di-t-butyl ester[119] (1.59g ; 6.16 m mole) in dry THF (40ml) under N_2 was treated with sodium hydride-benzene dispersion (2 equivalents), and stirred 30 min. at room temperature. A solution of dibromide (I) (1.638g ; 6.16 m mole) in THF (20ml) was then added gradually, the mixture refluxed 1 h. then left a further 16 h. at room temperature, poured into water (150ml), extracted with ether, the aqueous layer carefully neutralised with dilute HCl, and re-extracted.

The combined extracts were washed with water, dried and the solvent evaporated giving a partly-crystalline material. Recovery of crystalline unreacted (I) (0.2g) left a red-coloured oil, t.l.c. of which (silica, 20% ethyl acetate-petroleum spirit as solvent) showed several components including baseline material (Ce (IV) spray); τ ($CDCl_3$) 3.6-4.8 (br), 6.0-9.0 (br, complex), 8.50 (strong s).

9-Thiono-8,10-dithiabicyclo[5.3.1]undeca-2,5-diene (XLVI). - A solution of (I) (2.60g ; 9.80 m mole) in acetonitrile (100ml) was treated, with stirring, with an aqueous solution of sodium trithiocarbonate (5ml of conc. soln. prepared as in ref.120 diluted to 8ml ; ca 15 m mole), dropwise during 15 min. The mixture was stirred at room temperature during a further 1.5 h., poured into water (300ml), the precipitated yellow solid filtered off, washed with water, dried, dissolved in warm carbon disulphide, the solution filtered, and cooled to -20°, depositing large bright-yellow plates of (XLVI) (0.69g ; 33%) m.p. 132-134°. (Found: C, 50.58; H, 4.81: $C_9H_{10}S_3$ requires C, 50.43; H, 4.70%); m/e 214 (M^+), 138, 105, λ_{max} ($CHCl_3$) 302 (log ε 3.84), 344 (log ε 4.09) nm ; ν_{max} (KBr) 3010, 2870, 1467, 1210, 1000 (s), 971, 920 (s), 788, 745, 722, 600 cm^{-1}; ν_{max} (CCl_4) 1473, 1020 (s) cm^{-1}; ^1H n.m.r. see DISCUSSION. (Osmometric m.w. (benzene) 208; requires 214).

Reaction of dithiol (XLIII) with thiophosgene and pyridine. - To a solution of (XLIII) (0.34g ; 1.98 m

mole) and pyridine (0.32ml ; 4.0 m mole) in benzene (20ml), was added dropwise with stirring under N_2 a solution of thiophosgene (0.15ml ; 2 m mole) in benzene (5ml). After 1.5 h. at room temperature, workup gave a mixture of at least 4 components (t.l.c.; silica, 20% ethyl acetate-petroleum spirit as solvent). Chromatography of the crude mixture on silicic acid gave a yellow oil (50mg), whose ^1H n.m.r. showed a complex pattern of absorption in the ranges 1.4-1.6, 2.6-3.7, 3.7-4.5, 6.4-8.1; m.s. showed m/e 203, 201 (ca 1:3), 166, 127, 125, 122, consistent with a component of molecular formula $C_7H_4ClNS_2$.

9-(Dicyanomethylene)-8,10-dithiabicyclo[5.3.1]undeca-2,5-diene (LII). - A solution of bis (triethylammoniothio) methylenemalononitrile[121] (4.0g ; 12.7 m mole) in acetonitrile (20ml) was added dropwise during 20 min. to a stirred solution of dibromide (I) (2.66g ; 10.0 m mole) in acetonitrile (100ml). The mixture was stirred at room temperature a further 1.5 h., poured into water (100ml), extracted with methylene chloride (2 x 40ml), the extracts washed with water (3 x 25ml), dried (Na_2SO_4), passed through a short column of silicic acid to remove residual salts, giving a pale-yellow solid, followed by a deep-yellow semisolid material which was rechromatographed, to give a total yield of the dinitrile (LII) of 1.34g (55%). Recrystallisation from methanol gave almost colourless needles, m.p. 158-159°. (Found: C, 58.5; H, 4.21; N, 11.14.

$C_{12}H_{10}N_2S_2$ requires C, 58.54; H, 4.09; N, 11.38%); m/e 246 (M^+), 138, 105, λ_{max} ($CHCl_3$) 294 (log ε 3.87), 343 (log ε 4.26) nm ; ν_{max} (KBr) 3032, 3020, 2955, 2903, 2220 (s), 2210 (s), 1468, 1426 (vs), 1028, 971, 940, 859, 785, 750 cm^{-1}; ^1H n.m.r. see DISCUSSION.

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