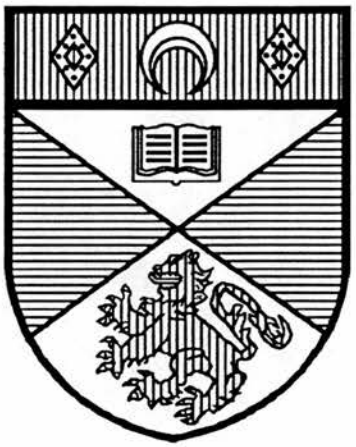


FREE RADICAL REARRANGEMENTS IN SYNTHESIS.

A thesis presented by Andrew Charles Hindson, BSc.,
to the University of St. Andrews, in application
for the Degree of Doctor of Philosophy

DECLARATION

I, Andrew Charles Hindson, hereby certify that this thesis has been compiled by myself, that it is a record of my own work and that it has not been accepted in partial or complete fulfilment of any other degree or professional qualification.

Signed____ ____Date 4th Nov 1992

I was admitted to the Faculty of Science of the University of St.Andrews, under Ordinance General No. 12 on 1st October 1988, and as a candidate for the Degree of Doctor of Philosophy on 29th September 1989.

Signed___ _____Date 4th Nov 1992.

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the Degree of Doctor of Philosophy.

Signature of Supervisor__ _____Date 4th Nov. 1992

Declaration

In submitting this thesis to the University of St. Andrews, I understand that I am giving permission for it to be made available for its use in accordance with the regulations of the University library for the time being in force, subject to any copyright vested in the work not being affected thereby. I also understand that the title and abstract will be published, and that a copy of the work may also be made and supplied to any *bona fide* library or research worker

CONTENTS

Chapter 4.

Acknowledgments

I would like to express my gratitude to Dr. J. C. Walton for his guidance and patience during the course of this work, and for always being accessible and encouraging when problems arose. I would also like to thank Dr. D. C. Nonhebel and co. workers for some of the radical precursors used for the work in Chapter 4. I am very grateful to the Department of Chemistry for awarding me a Soutar scholarship to enable this research to be carried out, and providing the finance to allow me to attend a conference at Arles in southern France. Thanks go to the technical staff in the department, particularly the services of GC / MS, and computing. Finally, thanks go to friends who have provided enjoyable times both on and off the golf course.

Postgraduate Lecture Courses

As part of the requirements of the Department of Chemistry, the following lecture courses were attended during the period of research;

Semi-conductor Growth Technology, (D.J. Cole-Hamilton); Naphthalene, Anthracene and other Polycyclic Compounds, (D.M.G. Lloyd); New Synthetic Methods Using Sulphur, Selenium and Phosphorus, (R.K. Mackie); Heavy Atom Multiply-Bonded Compounds, (R.A. Aitken); Naturally occurring Organosulphur Compounds, (R.A. Aitken); Industrial Chemistry, (F.D. Gunstone and C. Glidewell); Pharmaceutical Chemistry, (R.A. Aitken and A.R. Butler); Photochemistry, (J.A. Crayston); and Aspects of Materials Chemistry, (J.A. Crayston)

List of Abbreviations

NMR	Nuclear Magnetic Resonance, (in $CDCl_3$ unless otherwise stated)
g.l.c.	Gas-Liquid Chromatography.
GC / MS	Gas-Chromatography / Mass Spectrometry.
EPR	Electron Paramagnetic Resonance.
hfs	Hyper-fine splitting.
δ	Relative to Tetramethylsilane.
SOMO	Semi Occupied Molecular Orbital.
BOOB	Di-tert butyl peroxide.
AIBN	Azo-iso-butyronitrile.
I.R.	Infra-Red.
U.V.	Ultra-Violet.

Abstract

In chapter 1, the syntheses of a number of 2,2- disubstituted 4,7-dihydro-1,3-dioxepins are described, together with EPR studies on the radicals derived from these compounds. In the case of 2-bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin, bromine abstraction was achieved with tin radicals to yield a CH_2• rotor type radical. This radical was studied by EPR spectroscopy and an exchange broadening process was observed. The experimental spectra were computer simulated in order to obtain the best-fit rate constants and hence calculate the activation energy for rotation of the CH_2• group, which was found to be 7.7 kcal mol^{-1}. The transannular cyclisation of this compound was investigated, using the Bu_3SnH reduction method, the product proportions being measured by g.c. analysis. The rate constant and activation energy for the cyclisation were calculated to be $k_{c(298)} = 4.9 \times 10^5\ s^{-1}$, $E_a = 9.02$ kcal mol^{-1}. The hydrolysis reaction of the bicyclic ketal produced by cyclisation, 1-phenyl-2,7-dioxabicyclo[3.2.1]octane was investigated. EPR studies were carried out on the allyl type radicals formed by hydrogen abstraction from the C(4) or C(7) positions on the 1,3-dioxepin molecules. In the case of the 2,2-dimethyl-, and 2,2-diethyl-1,3-dioxepins, the exchange broadening process observed (due to conformational changes in the ring) was computer simulated and the activation energies for ring inversion were calculated to be 8.1 kcal mol^{-1}, and 6.1 kcal mol^{-1} respectively for the two compounds.

Chapter 2 reports the syntheses of some 2,2-disubstituted 4,7-dihydro-1.3-dithiepins. Several of these compounds were studied by EPR in the presence of t-BuO• radicals. The expected allyl type radical (analogous to that of the 1,3-dioxepins) was not observed. Instead another radical of a secondary nature was found to be present, formed either by rearrangement of the dithiepin molecule, or by some decomposition process. Some

photolysis / product analysis type reactions were carried out on the dithiepins using GC / MS to identify the fragmentation products of these molecules.

Chapter 3 describes the EPR, photolysis, and bromination studies on three cyclic epoxides - cyclopentene oxide, cyclohexene oxide, and cyclo-octene oxide. Photolysis reactions were performed in the presence of CCl_3Br and di-tert butyl peroxide, and brominations involved NBS and Br_2 / CCl_4. The products were analysed by GC / MS.

Chapter 4 describes the examination of " interior chain extension " type reactions, and the EPR study of a number of cyclopropane derivatives, together with the reactions of selected compounds with the radical precursors NBS and $(Me_3Si)_2NBr$.

To my Mam and Dad

" Both of you were right. "

Publication

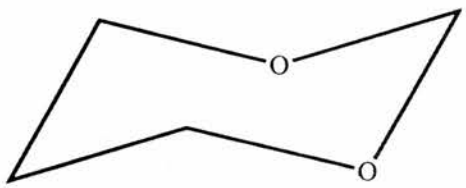
A. C. Hindson and J. C. Walton, " Cycloalkylmethyl Radicals - Part 7. - Electron Paramagnetic Resonance Characterisation of Axial and Equatorial Centres in Seven - Membered Alicyclic Molecules. " *J. Chem. Soc., Faraday Trans.*, 1990, **86**(19), 3237 - 3241.

CHAPTER ONE

1,3-DIOXEPINS

1.1 INTRODUCTION

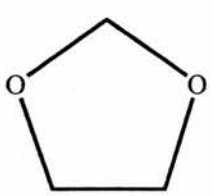
The conformational analyses of 1,3-dioxacycloalkanes has been quite extensively studied by many workers over the past thirty years.[1-5] The six-membered variety, namely 1,3-dioxanes (1,3-dioxacyclohexanes) **(1)**



(**1**)

have received most attention[6,7] and it appears that six-membered heterocyclic conformations, other than the chair , are comparatively unimportant.[8,9] An exception to this occurs however , when substituted derivatives show strong *syn*-1,3-diaxial interactions in the chair form. The changes in properties observed due to substitution on C(2), can be interpreted in terms of an axial-equatorial conformer equilibrium.

Derivatives of 1,3-dioxacyclopentanes[4,10] (1,3-dioxolanes) **(2)**, 1,3-dioxacycloheptanes[3,11,12] **(3)**, and, 1,3-dioxacyclo-octanes[13] **(4)**,



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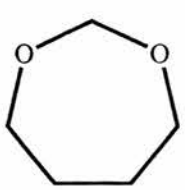

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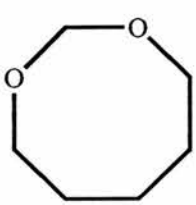
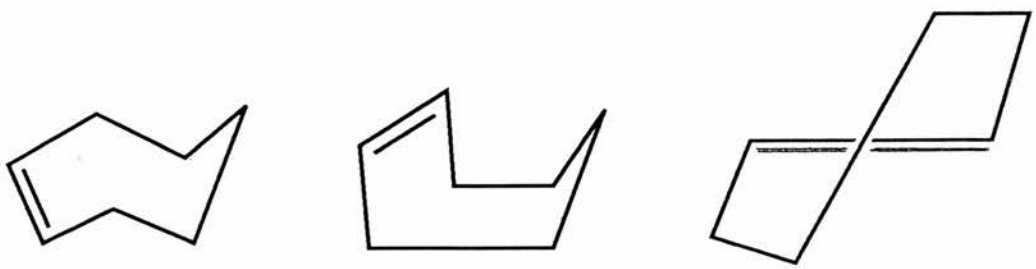


(**4**)

potentially exhibit more complex behaviour because of the possible existence of several low-energy ring conformations, which can interconvert by low-energy processes (pseudorotational or other). Obviously NMR studies have provided important information about the conformational changes in various ring systems. However it has been found that the methylenyl group, $CH_2^{\bullet}$, when attached to an alicyclic ring, can act as a useful " spin-probe " for conformations populated by that molecule.[14,15] EPR spectra of these transient radicals allow conformational analyses to be carried out, and in favourable cases, the activation energies of the ring inversion or pseudorotational processes can be investigated.[14] This method has been applied to six-membered rings, [16,17] and to some larger rings, particularly those with 9-15 carbon atoms.[15]

The work in this chapter is primarily concerned with 2-substituted-4,7-dihydro-1,3-dioxepins, and the " spin-probe " technique,[16] as applied to these molecules will be discussed later. Before considering 1,3-dioxepins in more detail , it is worth briefly considering work that has been done on the seven-membered ring without the presence of any oxygen atoms.

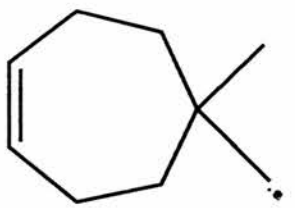
The cycloheptene ring is known to have three important conformations;[18,19] the chair **(C)**, the boat **(B)**, and the twist-boat **(TB)**.



C **B** **TB**

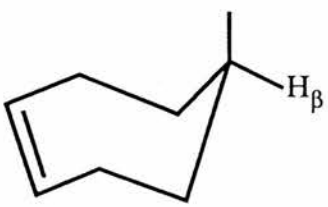
Force field calculations[20,21] have indicated that the chair form is predominant, being favoured by some 0.57 kcal mol^{-1} over the twist-boat form, and by 3.37 kcal mol^{-1} over the boat.[18]

By analogy with cycloheptene, there are therefore at least five possible conformations of the cyclohept-4-enylmethyl radical **(5)**.

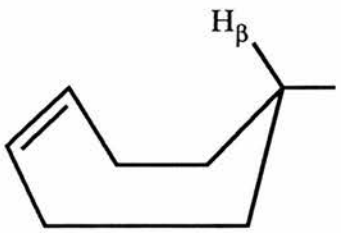


(5)

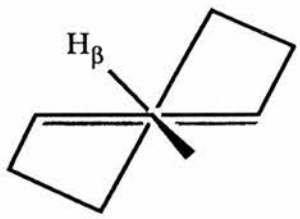
These conformations are the chair-axial **(Ca)**, boat-equatorial **(Be)**, twist-boat **(TB)**, the boat-axial **(Ba)**, and the chair-equatorial **(Ce)**.



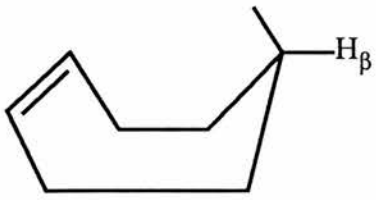
(Ca)



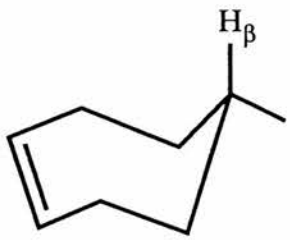
(Be)



(TB)

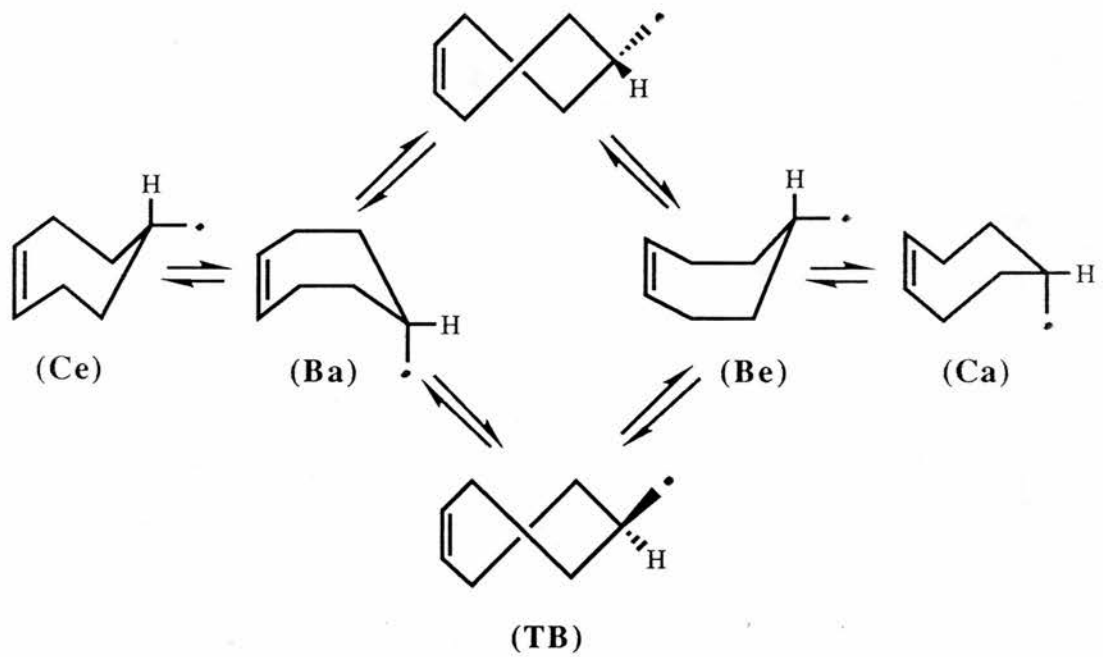


(Ba)



(Ce)

It is likely that these five conformations interconvert in the way shown by scheme 1.



Scheme 1.

The EPR spectral study of the cyclohept-4-enylmethyl radical will be considered later.

Generally cycloalkylmethyl radicals are formed from the corresponding parent cycloalkylmethyl bromide, by bromine abstraction with photochemically generated triethylsilyl or trimethyltin radicals, in t-butyl benzene as a solvent at temperatures above ca. 200 K, and in cyclopropane or n-propane at lower temperatures. The cycloheptylmethyl radical **(6)**, generated from the corresponding bromide,

(6)

was found to give the EPR spectrum shown in Fig 1.[22]

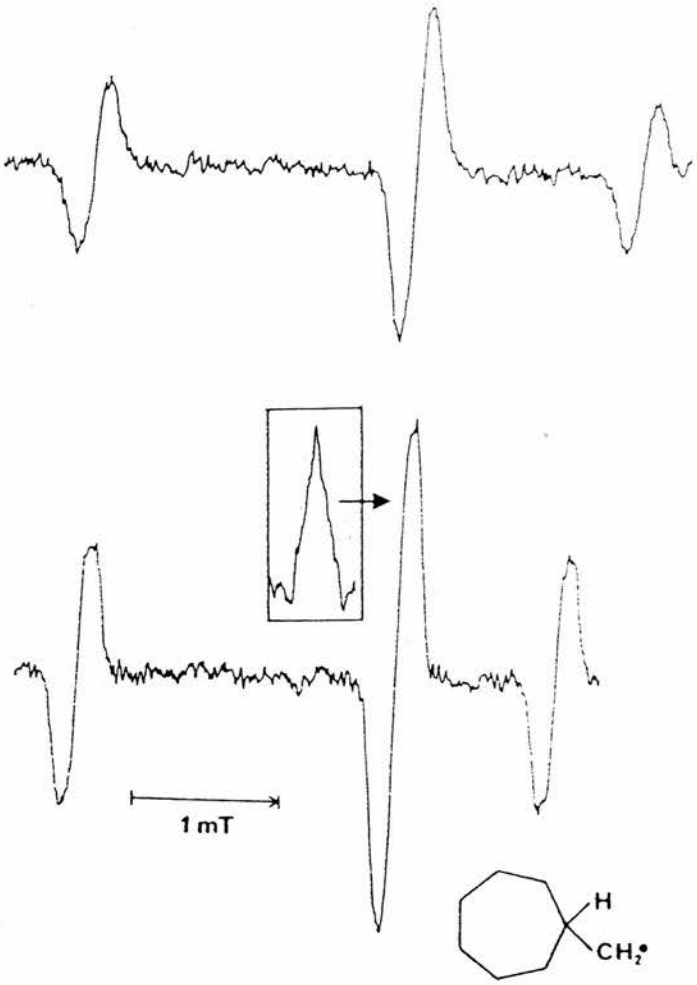


Fig 1. Low field half of the 9.2 GHz EPR spectrum of cycloheptylmethyl radicals (6) : upper trace, 140 K ; lower trace 250 K. The inset shows the $M_\alpha = 0$, $M_\beta = -1/2$ line on the same scale with second derivative presentation.

The spectrum consists of a double triplet from one β- and two α- hydrogens. The magnitude of $a(H_\beta) = 3.76$mT at 140 K, and its

negative temperature coefficient, indicate that **(6)** adopts an orientation about the C_β–C_α bond in which the H_β eclipses the p-orbital containing the unpaired electron.

Most cycloalkylmethyl radicals show well resolved long-range hyperfine splittings (hfs), but **(6)** did not. The inset in Fig 1. shows a poorly defined pentet obtained by a second derivative sweep. The spectra indicate the presence of only one species in the range of temperature 110-300 K. The cycloheptane ring conformers are known to interconvert very quickly by pseudorotation processes with very low energy barriers. Force-field calculations [23] have indicated that these barriers are approximately 1.4 kcal mol^{-1}. The dynamic effects in NMR spectra have not been observed[24] except for cycloheptanes with two pairs of geminal substituents.[25,26] It is likely therefore, that the EPR signal of **(6)** is the average over all populated conformations. The magnitude of the β–hfs of **(6)** supports this conclusion because it is intermediate between that of equatorial radicals (2.8-3.2mT) and that of axial radicals (3.8-4.1mT).

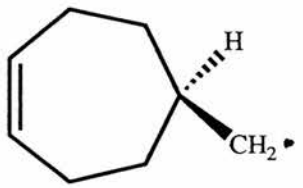
Table 1.

		hfs / mT			
Radical	T / K	a ($2H_\alpha$)	a ($2H_\beta$)	Other	Ref
6	140	2.21	3.76	--	15
7 major	140	2.22	3.67	0.09	27,22
7 minor	140	2.22	4.69	--	27,22
34 (Ce)	140	2.30	2.55	--	27
34 (TB)	140	2.30	2.30	--	27
35	161	2.32	--	0.28(3H), 0.04(4H)	27
36	239	1.98, 2.03	--	--	27
36	295	1.97	--	--	27

Table 1. EPR parameters for seven-membered cycloalkylmethyl radicals
All g factors 2.003 ± 0.001

The fact that the average spectrum is obtained at 110 K, shows that the barrier to ring pseudorotation must be ≤ 2.7 kcal mol^{-1}.

The EPR spectra of the cyclohept-4-enylmethyl radicals (**7**) have been reported.[28,29]

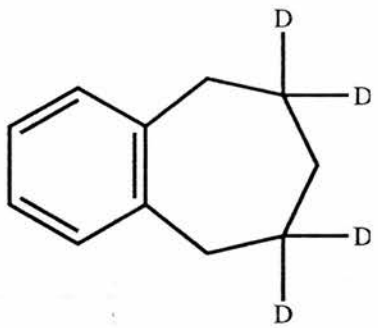


(**7**)

Two main sets of signals were observed (Table 1). Under high resolution, the major component indicated[22] that there were probably more than two conformations of (**7**) present. The five possible conformations of (**7**) and their interconversion were shown in scheme 1. It is probable that the major spectrum, with the smaller $a(H_\beta)$ consists of a superposition of the equatorial chair **(Ce)**, and the twist-boat **(TB)** conformations.[24,6] The latter is expected to have a β–hydrogen hfs not very different from the equatorial value. The minor spectrum with the larger $a(H_\beta)$ value, is probably due to the chair axial form **(Ca)** or boat axial form **(Ba)**, or possibly a mixture of both. Above ca. 240 K, the spectra of (**7**) weaken and broaden, probably because ring inversion becomes important. The average spectrum was not observed, the likely cause of this being that the radical simultaneously undergoes a transannular cyclisation to give the bicyclo[3.2.1]octan-2-yl radical, and the spectrum of this radical was observed at 340 K,[22] although it was weak. It was

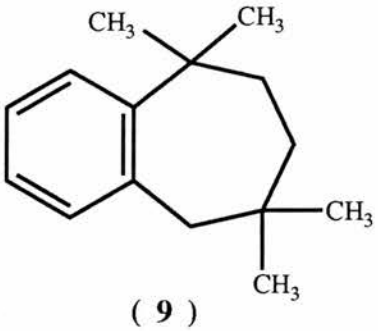
estimated that the ring inversion activation energy of (**7**) must be ≤ 5.0 kcal mol^{-1}, and this figure compares well with the $\Delta G^{\neq}$ value of 5.0 kcal mol^{-1} which was determined by NMR for the inversion of cycloheptene itself.[30]

The dipole moment of the benzene analogue of 4-cycloheptene-1-one[31] indicates a predominance of the chair form of approximately 95%. A ^{19}F NMR study of 5,5-difluorocycloheptene[25] also showed that it existed mainly in the chair form. A similar conclusion was reached for 4,4,6,6-tetradeuterio-1,2-benzocycloheptene[32] (**8**).



(**8**)

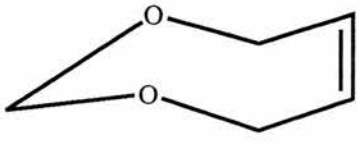
A number of di- and tetramethyl derivatives of benzocycloheptene have been studied, and it has been concluded that the chair form is dominant, with the activation energy to inversion ranging between 9.9 and 13.7 kcal mol^{-1}.[33] An NMR study of 1,1,4,4-tetramethyl-6,7-benzocycloheptene (**9**),[34] found that the chair and boat forms existed in a 2:1 equilibrium mixture.



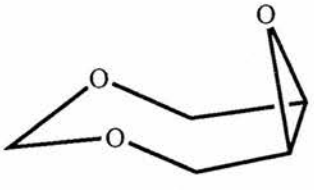
(**9**)

Dioxepins

Consideration of models of 1,3-dioxacycloheptanes reveals that when pseudorotation at C 5,6 is hindered, only one chair conformation is possible. The pseudorotation pathway of the chair form can be excluded by the introduction of a double bond at C 5,6 (**10**), or by the construction of a small ring containing C 5,6 (**11,12**).

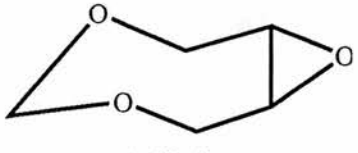


(**10**)



(**11**)

chair
conformations



(**12**)

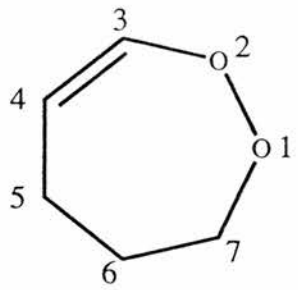
Studies on the conformation of compounds which contain a double bond at C 5,6, indicate that 2,2-dimethyl-1,3-dioxabenzocycloheptene,[32] *cis*- and *trans*-4,7-dimethyl-1,3-dioxacyclohept-5-ene and r-2-*tert*-butyl-c-4,t-7-dimethyl-1,3-dioxacyclohept-5-ene[5] exist in twist-boat conformations.

The construction of an epoxide ring at C 5,6, makes 1,3-dioxacyclohept-5-ene oxide more stable in the twist-boat conformation than in the chair. It is thought that a generalised anomeric effect and the strain imposed on the system by the double bond or the epoxide ring, results in higher energies for the chair form than for the twist-boat.[36] The geometry of the chair conformations for the 1,3-dioxacyclohept-5-enes **(10)**, is such that the C(4)-O and C(7)-O bonds are *syn* periplanar, and each of these bonds is in turn *syn* (and *anti*) periplanar to the p-orbitals of the π-bonds. In the twist-boat conformations, these bonds and p-orbitals are orientated gauche.[6] These orientations are predicted by the Wolfe rule[37] which states : " when electron pairs or polar bonds are placed on adjacent pyramidal atoms, *syn* or *anti*-periplanar orientations are disfavoured with respect to the structure which contains the maximum number of gauche interactions ".

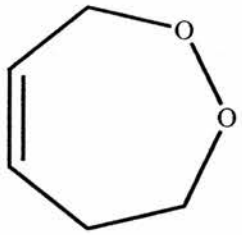
Reports that cycloheptene[30] and cycloheptene oxide are more stable in the chair than the twist-boat configurations, lead to the conclusion that the strain imposed by the double bond or epoxide ring is not sufficient to raise the energy of the chair above the twist boat. It appears that an additional amount of energy is required to do this as indicated by 1,3-dioxacyclohept-5-enes and 1,3-dioxacyclohept-5-ene oxides. The generalised anomeric effect[38] from the 1,3-oxygens alone is not enough to accomplish this ; in fact a more generalised anomeric effect is required.

Monocyclic Dioxepins

Three mono-unsaturated 7-membered ring systems containing two oxygen atoms are possible :- 1,2-dioxepins **(13 + 14)**; 1,3-dioxepins **(15 + 16)**; 1,4-dioxepins **(17 + 18)**.



(**13**)



(**14**)

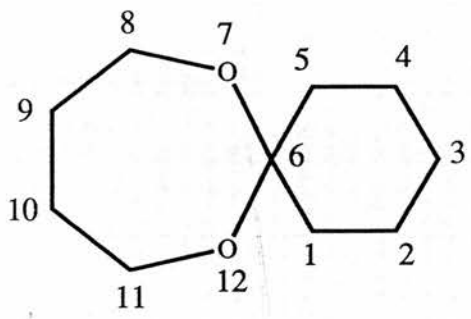
(**15**)

(**16**)

(**17**)

(**18**)

By far and away the largest group are the 1,3-dioxepins; in particular the 4,7-dihydro variety of type **(16)**. There are no known derivatives of 1,2-dioxepins, but there are some 1,4-dioxepins. Brannock and Lappin prepared the first dioxepins of type **(15)**.[39] Very little is known about 1,4-dioxepins,[40] and only derivatives of structure **(17)** are known.[41] The numbering of the rings is shown for structure **(13)**. Spiro-type compounds such as **(19)**, are named according to the length of the chain;



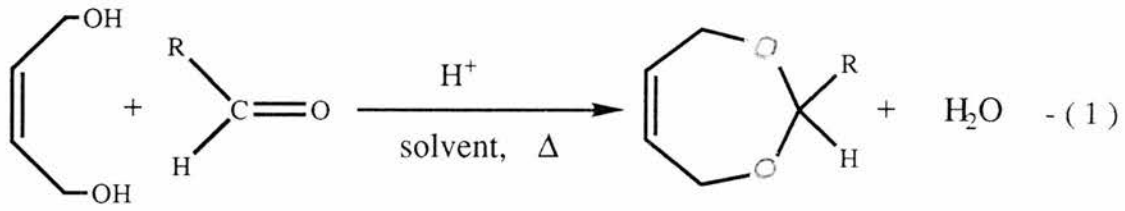
(**19**)

hence compound **(19)** is 7,12-dioxaspiro[5,6]dodec-9-ene and the numbering of the rings is indicated.

The work described in this chapter is concerned with preparative and EPR studies on 2-substituted-4,7-dihydro-1,3-dioxepins.

Methods of Preparation of 1,3-Dioxepins

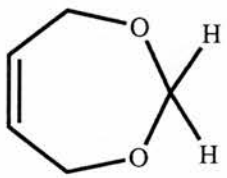
(1) Condensation of *cis*-2-Butene-1,4-diol with Aldehydes



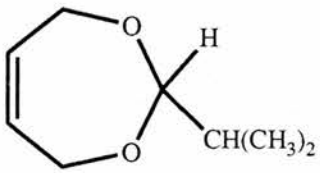
- (1)

Aldehydes react with *cis*-2-butene-1,4-diol as shown (equation 1). Strong acids , such as p-toluene sulphonic acid (toluene-4-sulphonic acid) or concentrated sulphuric acid can be employed as catalysts. The reaction is usually carried out in benzene or toluene, and this acts as an azeotroping agent for the removal of water during the reaction.[39] If a solvent is not used, the product distils from the reaction mixture along with water, and separation occurs on cooling. Distillation normally requires temperatures in excess 180°C, and in some cases , best results are achieved by neutralising the acid before distillation, although this is not always the case. An example of this is in the preparation of 4,7-dihydro-1,3-dioxepin from formaldehyde. Highest yields occur when the product is distilled from the acidic reaction. If the mixture is neutralised before distillation, only a 25% yield is obtained, together with a viscous, non-volatile polymer. It seems that a linear polymer is formed during the reaction, and under acidic conditions this is converted to a volatile acetal.[39]

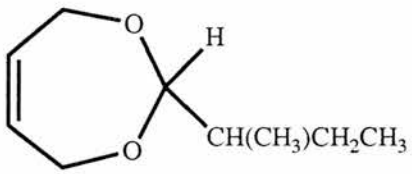
Generally, aldehydes such as formaldehyde, isobutyraldehyde (2-methyl propionaldehyde), 2-methyl butyraldehyde, benzaldehyde and crotonaldehyde give high yields of the the appropriate 1,3-dioxepin derivative as shown **(20-24)** respectively.



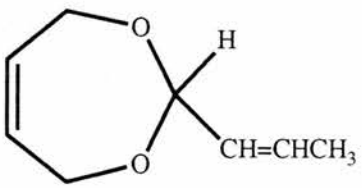
(**20**)



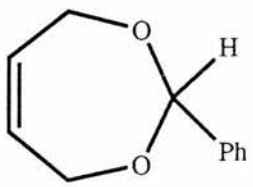
(**21**)



(**22**)



(**23**)



(**24**)

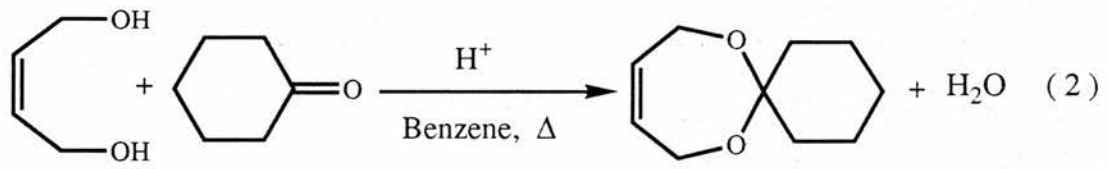
Some unsaturated aldehydes, such as acrolein, give mostly polymeric products.[42]

(2) Condensation of *cis*-2-Butene-1,4-diol with Ketones

Generally, alkyl ketones such as acetone, 4-methyl-2-pentanone, or 3-pentanone,[39] do not give the corresponding 1,3-dioxepin when combined with *cis*-2-butene-1,4-diol in the same way as aldehydes. The products obtained are the unreacted ketones, and a dehydration product of the diol; 2,5-dihydrofuran. Sometimes if a large excess of the ketone is used, a reasonable yield of the 1,3-dioxepin is obtained.[43] An example of this is in the treatment of the diol with a large excess of acetone with sodium sulphate and concentrated sulphuric acid as catalysts. The product obtained was 2,2-dimethyl-4,7-dihydro-1,3-dioxepin. Phenyl ketones such as

acetophenone, benzophenone, and p-chloroacetophenone give low yields of the 1,3-dioxepins.[42]

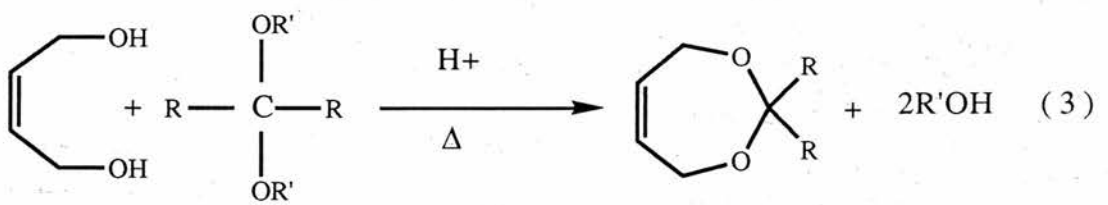
Cyclic ketones react fairly easily with *cis*-2-butene-1,4-diol to give good yields of spiro derivatives of 1,3-dioxepins. An example of this type of reaction is in the synthesis of 7,12-dioxaspiro[5,6]dodec-9-ene from cyclohexanone and the diol, in benzene with p-toluene sulphonic acid. This is represented by equation 2.



(2)

(3) Condensation of *cis*-2-Butene-1,4-diol with Acetals or Ketals.

This method involves an exchange reaction between *cis*-2-butene-1,4-diol and an acetal, in the presence of an acid catalyst[44] (equation 3)

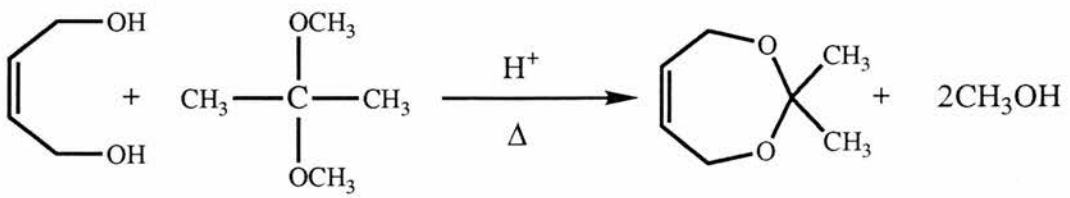


(3)

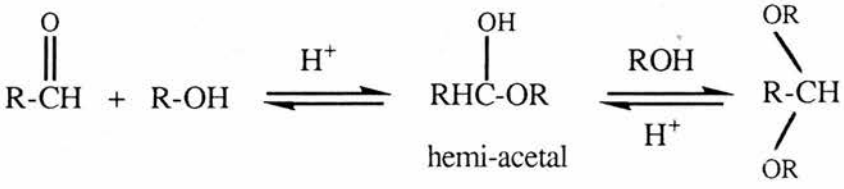
The alcohol formed in the exchange must be distilled out due to the reversibility of the reaction. This method was discovered and developed by Sterling, Watson, and Pawloski,[44] and gives good yields of substituted 1,3-dioxepins when molar excesses of the acetal are used. However, the

highest yields are achieved by using solvents such as benzene or ethyl acetate, instead of using excess acetal. Several non-oxidizing catalysts have been used, such as sulphuric acid, dichloroacetic acid, p-toluene sulphonic acid, or phosphoric acid. Once the alcohol is formed in the reaction, the mixture is sometimes neutralised before the product is purified further.

Acetals such as acetaldehyde dimethyl acetal, and benzaldehyde dimethyl acetal, or ketals such as acetone dimethyl ketal, acetone butyl methyl ketal, acetone dibutyl ketal, 2-butanone dimethyl ketal, 3-pentanone dimethyl ketal, cyclohexanone dimethyl ketal and bromo-2-propanone dimethyl ketal can be condensed with *cis*-2-butene-1,4-diol to give substituted 1,3-dioxepins in yields of at least 50%. However there are exceptions to this; dimethoxymethane gives only 3-5% of the desired product on condensation with the diol. Acetals of aldehydes and ketals of cyclic ketones have been found to give higher yields than ketals of alkyl ketones. Mixed acetals can also be used. This method is much better than methods (1) and (2), because dialkyl derivatives can be obtained in high yields. The reaction of the diol with acetone dimethyl ketal, (equation 3) for example, produces yields of at least 50% of the 2,2-dimethyl derivative, which is much better than that obtained by reaction of the diol with acetone itself.

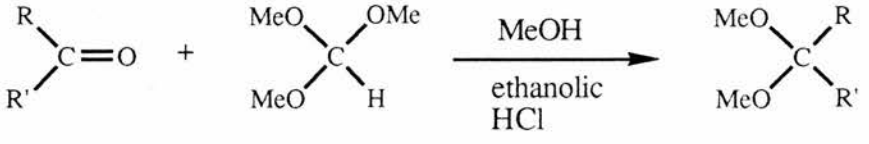


The acetals and ketals used in the preparation of 1,3-dioxepins, can be made by various methods. Alcohols react with aldehydes according to equation (4).



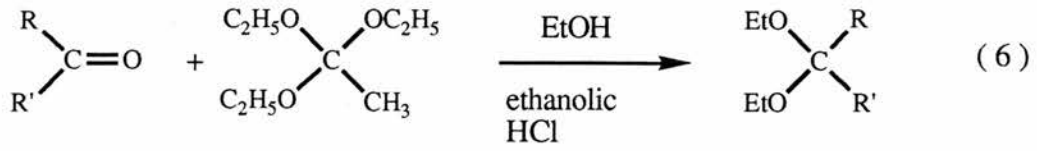
(4)

Another method is to treat the appropriate aldehyde or ketone, with a mixture of equimolar quantities of trimethyl orthoformate with absolute methanol, employing a few drops of ethanolic HCl as catalyst. (equation 5)



(5)

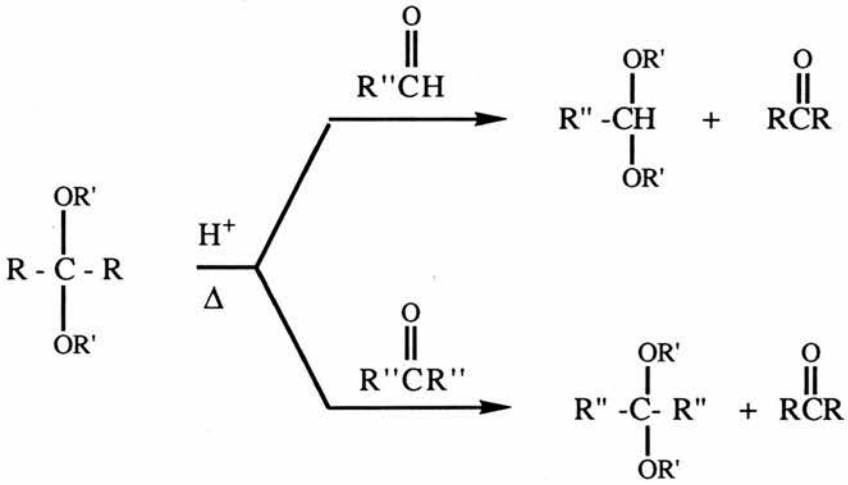
The use of orthoformates in the synthesis of ketals is very well established,[45] but very few of the methods used have employed orthoformates other than triethyl orthoformate, until the work of Fife and Hagiopan [46] who used trimethyl orthoformate. Post[47] has reported that the yields of ketals decrease with increasing size of the trialkyl part of the molecule. Dykstra[48] claimed good yields with tripropyl and tributyl orthoformates. Alternatively, triethyl orthoacetate in absolute ethanol can be used (equation 6)



(6)

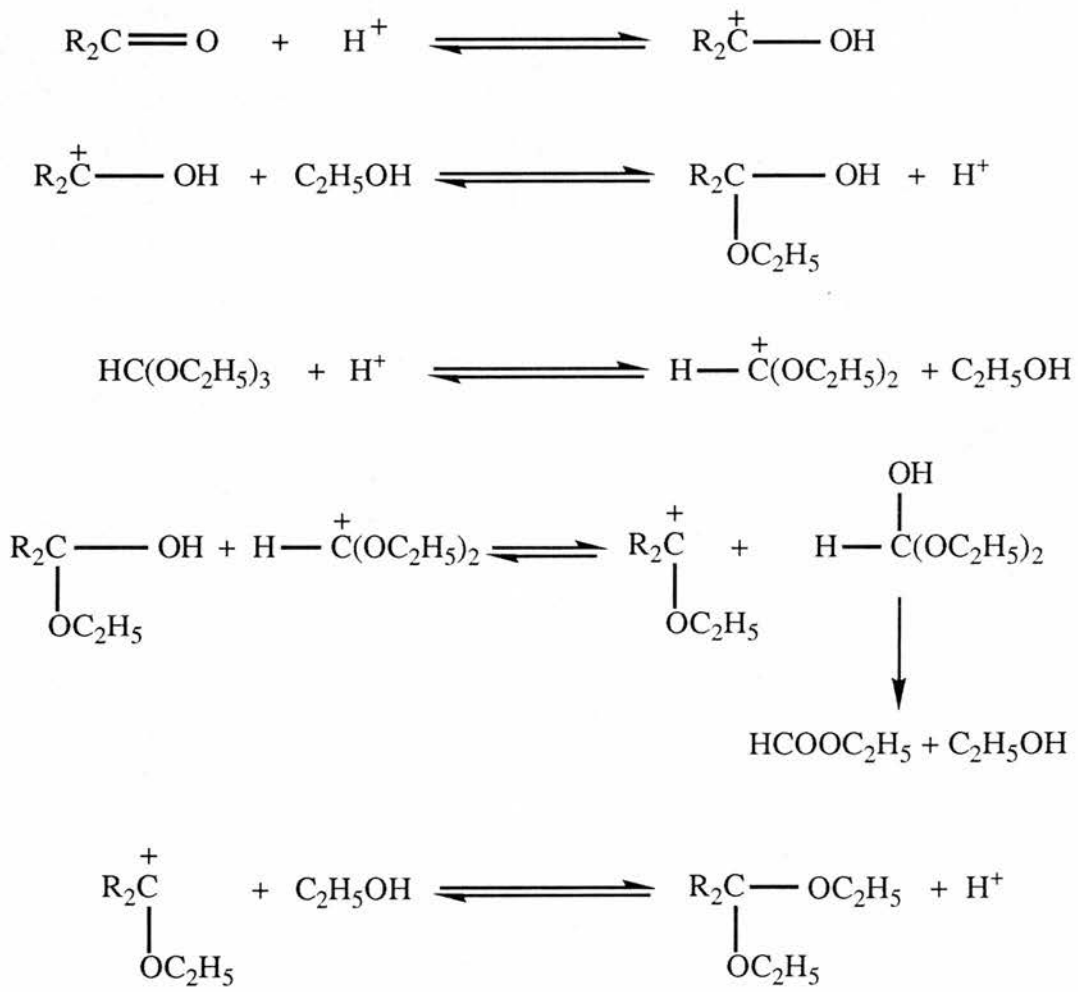
Reaction conditions vary, but allowing the mixture to stand at ambient temperature for ca. 24 hours is often sufficient to form the ketal. Anhydrous potassium carbonate is added to neutralise the excess acid, and the alcohol is evaporated off; the residual ketal being purified by distillation.

Acetals and ketals may also be prepared by condensing another acetal or ketal with a ketone or aldehyde.



Some examples of this type of reaction are :- acetone dimethyl ketal reacts with cyclohexanone in the presence of an acid catalyst to give 80% cyclohexanone dimethyl ketal. Benzaldehyde yields 75% benzaldehyde dimethyl acetal, and acrolein gives 60% acrolein dimethyl ketal.

Mechanisms for the preparation of ketals from orthoesters have been proposed by several groups of workers.[49,50] The mechanism outlined below was presented by Mackenzie *et. al.*[45]

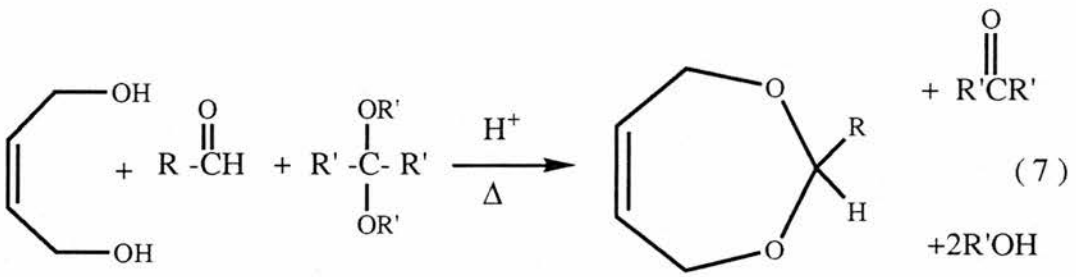


It can be seen that the catalyst acts as an activator of the carbonyl compound, rather than an activator of the orthoester.

(4) Condensation of *cis*-2-Butene-1,4-diol with an Aldehyde and an Acetal or Ketal

In this method, the reaction of an acetal or ketal with an aldehyde, followed by the reaction of the new acetal or ketal with *cis*-2-

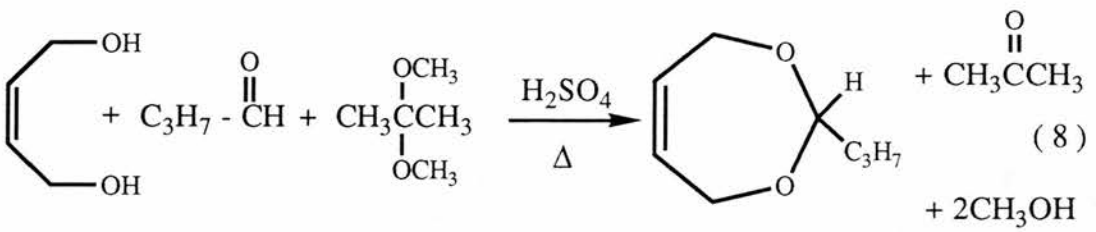
butene-1,4-diol, results in the formation of the 1,3-dioxepin formed from the aldehyde used in the reaction [44] (equation 7).



(7)

In this double exchange reaction, the acetal of the aldehyde is thought to form first, then it reacts with the diol ; the lower boiling products being distilled from the reaction mixture. It has been found that equimolar amounts of the diol, aldehyde, and acetal give good yields, but the best results are obtained with excesses of aldehyde and acetal, or when a solvent such as benzene or ethyl acetate are used instead of excess reactants.

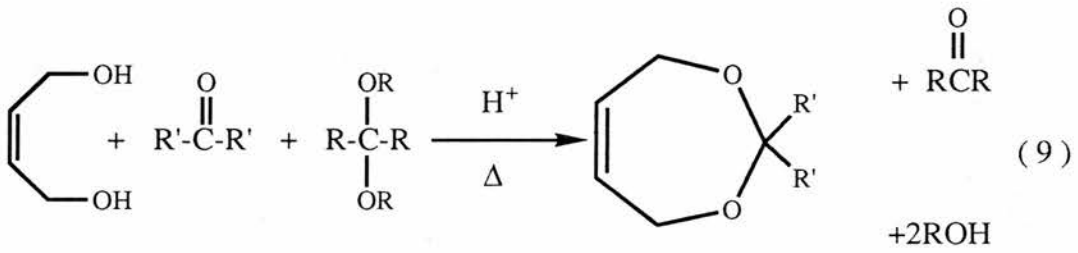
Care has to be taken when choosing the acetals or ketals used in the double exchange mechanism. Acetone dimethyl ketal or acetone diethyl ketal give the lowest yields of 1,3-dioxepins from aldehydes. The by-product, acetone, reacts slowly with the diol. A mixture of products is obtained when using aldehyde acetals, or ketones. Short-chain aldehydes tend to give an exothermic reaction initially, when combined with the acetal and diol, and so the reactants have to be cooled at this stage. Longer chain aldehydes e.g. butyraldehyde, give an endothermic reaction. Yields in excess of 80% are obtainable. The reaction of the diol with acetone dimethyl ketal and n-butyraldehyde, gives 2-propyl-4,7-dihydro-1,3-dioxepin in 97% yield (equation 8)



(8)

(5) Condensation of *cis*-2-Butene-1,4-diol with a Ketone and an Acetal or Ketal.

Di-substituted 1,3-dioxepins can be prepared in a double exchange reaction with the diol, acetal, and a ketone (equation 9) in the same manner as that described in **(3)** for the reaction with acetals and ketals.[44]



(9)

This reaction is not quite as simple as that described for the double exchange reaction with aldehydes. It has been found that acetone dimethyl ketal, 2-butanone, and *cis*-2-butene-1,4-diol give a 47% yield of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin from the ketal , and only a 36% yield of the 2-ethyl-2-methyl derivative from the ketone. Ketals of alkyl ketones give higher yields of the dioxepins than do acetals of aldehydes or ketals of cyclic ketones. An example of this is the reaction of acetaldehyde diethyl acetal, 2-butanone and the diol, which yields only 3% of the 2-

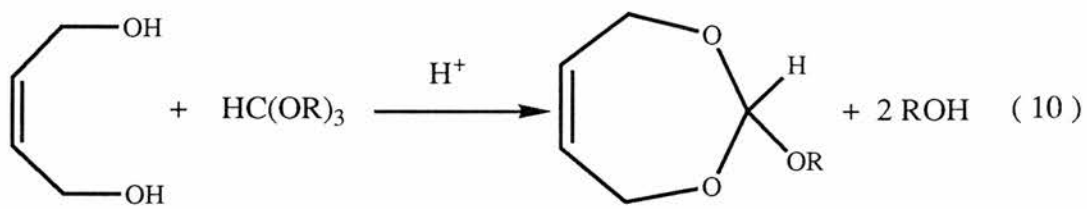
ethyl-2-methyl dioxepin, together with 78% of the 2-methyl dioxepin from the acetal.

Cyclic ketones like cyclohexanone give high yields of spiro dioxepins. Cyclohexanone , acetone dimethyl ketal, and the diol give 88% yield of 7,12-dioxaspiro[5,6]dodec-9-ene. Yields of 80% or better are obtained from other cyclic ketones.

Haloalkanes, such as bromoacetone, give high yields of the halo derivative of the 1,3-dioxepin. Bromoacetone itself gives an 88% yield of 2-bromomethyl-2-methyl-4,7-dihydro-1,3-dioxepin on reaction with a ketal and the diol.

The double exchange reaction with phenyl ketones gives low conversions: acetone dimethyl ketal and the diol give a 25% yield of 2-phenyl-2-methyl dioxepin, together with 45% of the 2,2-dimethyl dioxepin. Although the double exchange reaction does not produce very high yields, it is still superior to the direct reaction of the diol with ketones.

(6) Condensation of *cis*-2-Butene-1,4-diol with Trialkyl Orthoformates



(10)

The diol reacts with trialkyl orthoformates, such as trimethyl orthoformate, according to equation 10. Again, an acid catalyst is required, and good yields are obtained at ambient temperatures -- higher temperatures tend to produce decomposition products.

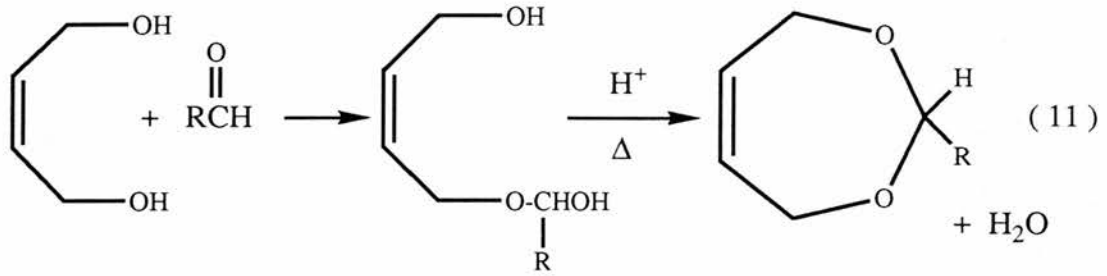
When trimethyl orthoformate, the diol, and a trace of concentrated sulphuric acid are mixed together and heated, the low boiling products being distilled out; then allowing the mixture to cool, followed by neutralisation, distillation affords only 10% of the 1,3-dioxepin. Alternatively, stirring the mixture at room temperature for *ca.* 2 hours, and then neutralising and distilling gives a 65% yield of 2-methoxy-4,7-dihydro-1,3-dioxepin.

Other trialkyl orthoesters, such as trimethyl orthoacetate, and triethyl orthopropionate react similarly.

(7) Dehydration of an Aldehyde 4-Hydroxy-2-Buten-1-yl Hemiacetal

cis-2-butene-1,4-diol reacts with an aldehyde at *ca.* 50°C, in the absence of a catalyst, to form the hemiacetal of the aldehyde,[51] e.g. formaldehyde yields formaldehyde 4-hydroxy-2-butene-1-yl hemiacetal; benzaldehyde forms benzaldehyde 4-hydroxy-2-butene-1-yl hemiacetal; and crotonaldehyde forms crotonaldehyde 4-hydroxy-2-butene-1-yl hemiacetal. Ketones react slowly with the diol, even when an acid catalyst is present, especially alkyl ketones such as acetone.

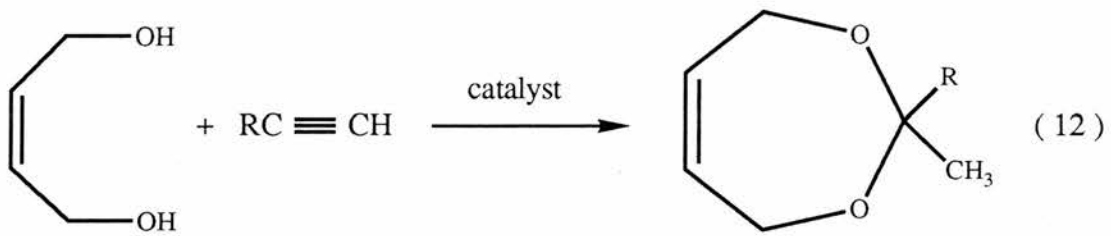
Typically, isobutyraldehyde for example, is added dropwise under nitrogen to the diol at *ca.* 30°C; the product obtained being isobutyraldehyde 4-hydroxy-2-butene-1-yl hemiacetal. The dioxepin is synthesized by adding the hemiacetal dropwise to refluxing benzene, containing a catalytic amount of p-toluene sulphonic acid. The rate of addition is controlled so that no more than 10% of the hemiacetal is unreacted at any one time. The water produced is azeotroped off and the mixture cooled. Once the catalyst has been neutralised, the product is distilled, to give in this case 2-isopropyl-4,7-dihydro-1,3-dioxepin. Equation 11. indicates the general scheme.



(11)

(8) Condensation of *cis*-2-Butene-1,4-diol with Acetylenes

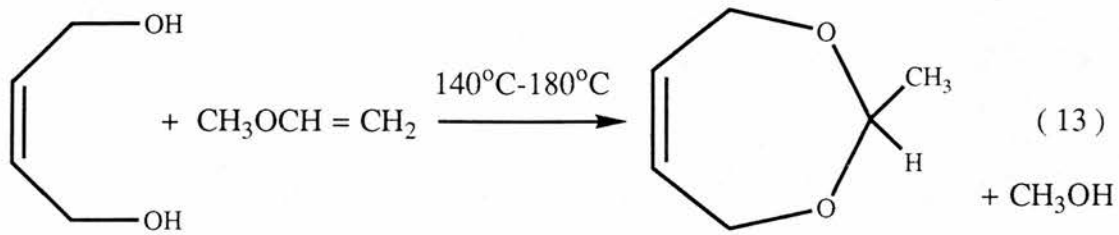
The diol reacts exothermically with an acetylene in the presence of red mercuric oxide, boron trifluoride etherate, and a trace of an acid (equation 12).



(12)

Reaction temperatures between 50°C and 100°C are achieved by controlling the addition of the acetylenic compound, and the mixtures are neutralised before purification. Unfortunately this is not a very good method for producing 1,3-dioxepins. Usually the main products are 2,5-divinyl-1.4-dioxane and a ketone. The 2,5-divinyl-1,4-dioxane is produced by the diol reacting with itself,[52] and the water formed in this reaction then combines with the acetylene to give a ketone.[53] It seems that ether formation is more rapid than the addition of the diol to the acetylene.

(9) Condensation of *cis*-2-Butene-1,4-diol with Vinyl Ethers



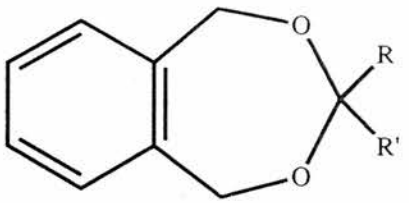
(13)

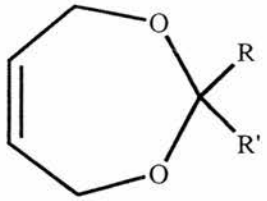
+ CH_3OH

cis-2-butene-1,4-diol reacts with methyl vinyl ether at 140°C-180°C to afford 2-methyl-4,7-dihydro-1,3-dioxepin [54] (equation 13). Although no other mention of this reaction appears in the literature, it would be expected that other vinyl ether compounds would give acceptable yields of 1,3-dioxepins.

NMR Studies on 2-Substituted 1,3-Dioxepins and Benzodioxepins

2-substituted derivatives of 1,3-dioxacyclohept-5-enes (4,7-dihydro-1,3-dioxepins) and 1,3-dioxa-5,6-benzocycloheptene have been studied by St. Jacques and co-workers[55] using ^{1}H and ^{13}C NMR spectroscopy. The compounds they studied are shown below :-





R = R' = H	**26a**	**26b**
R = R" = CH_3	**27a**	**27b**
R = CH_3, R' = H	**28a**	**28b**
R = OCH_3, R' = H	**29a**	**29b**
R = $C(CH_3)_3$, R' = H	**30a**	**30b**

NMR parameters obtained below the coalescence temperature were used to give direct information on the most stable conformation(s). This method was valid, provided that further averaging did not take place through conformational processes, involving low activation barriers. In the "**b**" series of compounds, only **27b** and **29b** fall within this area.

Compounds **26a-29a**, the 1,3-dioxabenzocycloheptenes, showed signals which indicated that the molecules existed in the chair and/or twist-boat forms. Increased amounts of the **TB** form were interpreted in terms of the effects associated with steric and electronic interactions of the 2-substituents.

^{1}H and ^{13}C spectral changes were observed for **27b**, **29b**, and **30b**. Part of the spectral change observed for **30b** was due to the slowing down of the internal rotation of the t-butyl group.[56] The rate constant, and hence the free activation energy for each compound (**27b**, **29b** :- TB $\leftrightarrow$ TB*; **30b** :- C $\leftrightarrow$ C*) at the coalescence temperature, T_c, was calculated. (Table 2)

R	R'	Compound	T_c / °C	Free activation energy / kcal mol^{-1}
CH_3	CH_3	**27b**	- 130	6.8 [57]
OCH_3	H	**29b**	- 163	5.2 [24]
$C(CH_3)_3$	H	**30b**	-136	6.1 [24]

Table 2

Conformations of the Seven-membered Ring

The substituent in 2-monosubstituted 1,3-dioxepins can either be axially or equatorially orientated in the chair (**C**), and the boat forms (**B**)- hence this leads to **C-a**, **B-a**, **C-e**, and **B-e** forms.

NMR data for compound **27b** ($R = R' = CH_3$) at low temperature, indicates that there are two non-equivalent methylene environments, and that the two allylic carbons are equivalent. Additionally, both methyl groups have the same environment, and this means that **27b** must be in the **TB** form, which has also been found to be the conformation for compound **27a**.[58]

Similarly compound **29b** ($R = OCH_3$, $R' = H$) was found to exist in the **TB** form, as had previously been established to be the case for compound **29a**.[58] The non-equivalence of the allylic carbons ruled out the **C-a**, **B-a**, **C-e** and **B-e** forms for **29b**, since they all contain equivalent allylic carbon atoms. Comparison of splitting patterns and ^{13}C shift data for **29a**, and **29b**, ruled out the possibility of a mixture of two of the above conformations for **29b**.

Direct information on the most stable conformations of compounds **26b**, **28b** and **30b**, was not available for these molecules because neither ring protons, nor ring carbons gave a spectral change. Three possibilities then exist for these compounds :-

(i) a single, non-averaging ring conformation exists.

(ii) a single, but rapidly averaging (via ring inversion) conformation exists.
(iii) a mixture of different, but rapidly interconverting conformations exists.

Previous work has established that **26a** exists as a mixture of the **C** (79%), and **TB** (21%), and that **27a** and **29a** exist in the **TB** forms.[58] Using this information as a reference, and by comparison of chemical shift data, it was concluded that **26b** existed predominantly in the **TB** form.

The C-4,7 chemical shifts of **28b** and **30b** are very different to that of **26b.** (Table 3).

Compound	T / °C	C - 5,6	C - 2	C - 4,7	Other ^{13}C atoms (substituted on C-2)
26b	25 -148	131.78 131.45	98.05 96.93	68.49 67.22	
27b	25 -148	131.72 130.58	103.46 103.21	62.63 61.97	24.59 (CH_3) 29.34 (CH_3)
28b	25 -148	131.56 130.94	103.17 102.40	66.07 65.54	20.63 (CH_3) 20.22 (CH_3)
29b	25 -163	130.83 130.21	115.90 114.23	62.78 64.08 60.29	54.00 (OCH_3) 54.23 (OCH_3)
30b	25 -148	130.65 129.29	113.44 112.92	69.92 70.02	37.37 (C) 25.38 (CH_3) 36.89 (C) 26.96 (CH_3)

Table 3

^{13}C chemical shifts for compounds in series **b** at room and low temperature [a]

a In ppm downfield from TMS for solutions in CHF_2Cl containing TMS and CD_2Cl_2 (15%) as lock signal.

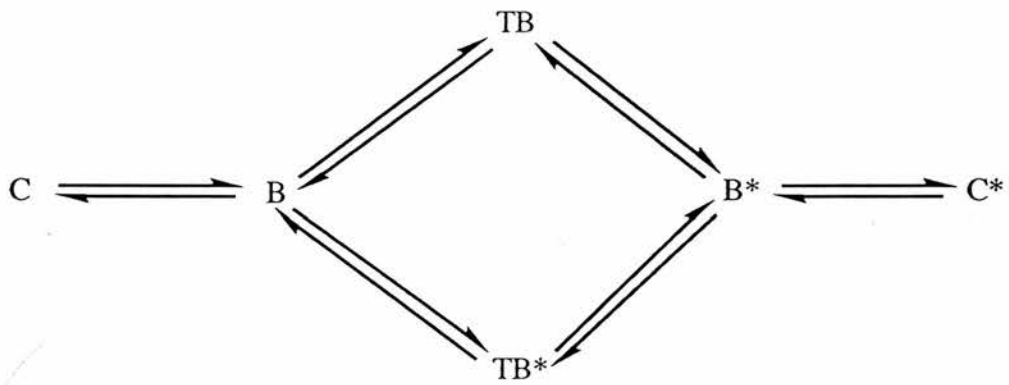
Data for **28b** and **30b** shows that the most stable conformations of these two molecules must be different, and because both **28a** and **30a** exist in the same **C-e** conformation, and have larger C-4,7 chemical

shifts than **26a (TB)**, then it can be deduced that **30b** exists in the **C-e** form as does **30a**, but **28b** is mainly in the **TB** form, unlike **28a**.

It is interesting to note that, although both the monosubstituted derivatives **28b** and **29b** exist mostly in the **TB** form, the activation barrier for **28b** is lower for pseudorotation, and rapid conformational averaging takes place.

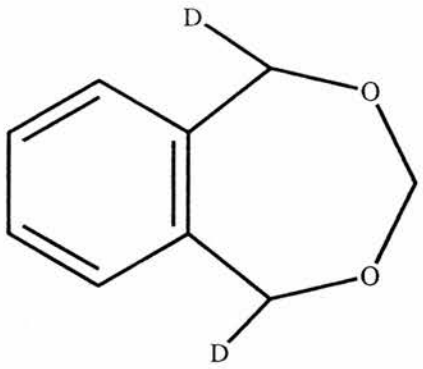
Conformational Averaging Processes

The conformational interconversion pathways of the cycloheptene ring are represented in scheme 2.[55]



Scheme 2.

The chair inversion process (**C--->B**) of cycloheptene and benzocycloheptene is the rate determining step, with free energy values of 5.0[30] and 10.9[32] kcal mol^{-1}. The corresponding energy barrier for **26a** (1,3-dioxa-5,6-benzocycloheptene) was reported as 8.0 kcal mol^{-1},[58] but these workers were unable to determine the free energy barrier to pseudorotation (**TB <----> B <----> TB***). Investigations into the dideuterated 1,3-dioxabenzocycloheptene **(31)**,



(**31**)

showed no spectral change for the signals of the **TB** conformation. This led to the conclusion that the pseudorotation barrier of **26a** is less than 5.0 kcal mol^{-1}. The absence of spectral changes for **26b** also indicate that the barrier to pseudorotation for this compound is less than 5.0 kcal mol^{-1}.

Dimethyl substitution on C(2), increases the pseudorotation barrier to 6.8 kcal mol^{-1} for **27b**.[58] A similar increase was found for **27a** ($\Delta G^{\neq}$ = 10.0 kcal mol^{-1}). Increased steric interactions in the transition state for pseudorotation are deemed responsible for the observed increase.

Compounds **28b** (2-CH_3), and **29b** (2-OCH_3), both exist predominantly in the **TB** form, and yet exhibit different dynamic behaviour. The methyl group is expected to exert greater steric compression than the methoxy group, and the barrier differences in this case are probably more due to electronic effects.

Table 4 summaries the conformational processes of several of the seven-membered cyclic molecules.

Compound	Stable Conformation(s)	ΔG C ↔ C* (kcal mol^{-1})	ΔG TB ↔ TB* (kcal mol^{-1})	Reference
Benzocycloheptene	C	10.9	--	32
Cycloheptene	C	5.0	--	30
26a	C (79%)[a], TB (21%)	8.0	< 5	55
26b	TB	--	< 5	55
27a	TB	--	10.0	58
27b	TB	--	6.8	55
29a	TB	--	6.7	58
29b	TB	--	5.2	55
32	C(50%)[b],TB(50%)[b]	8.9	6.6	59
33	TB	--	5.3	59

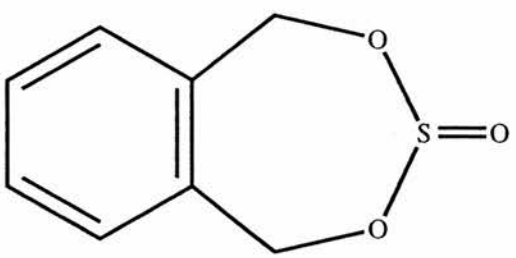
Table 4

Free energy barriers for the conformational processes of seven-membered cyclic molecules

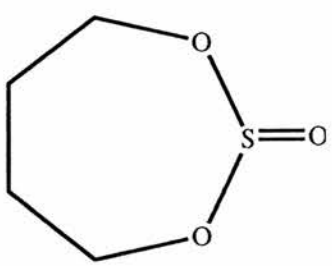
a In CHF_2Cl at -130°C

b In CHF_2Cl at -100°C

Comparison of data for compounds **29a**, **29b** (both R = OCH_3, R' = H) and structures **32** and **33** below[59] :-



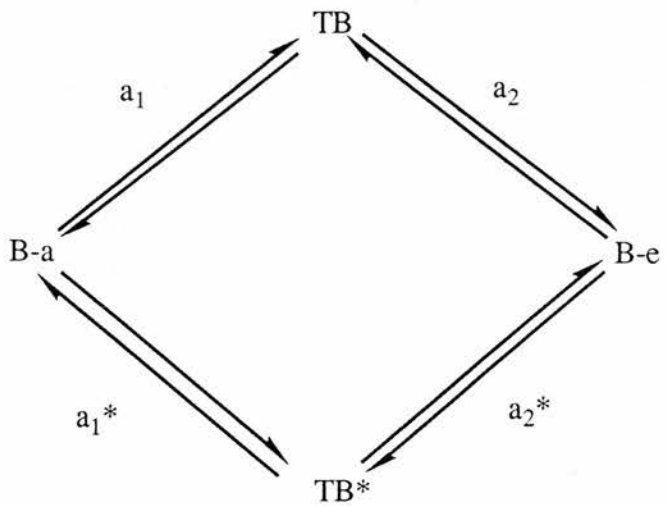
(**32**)



(**33**)

show that electronic effects are a major factor in the similarity of the free energy barriers to pseudorotation of the **TB** form of each compound. Anet and Yavari reported that the generalised anomeric effect increases the rotational barrier of chloromethyl methyl ether ($ClCH_2OCH_3$), [60] and it would seem most probable that stereoelectronic forces would be responsible for increased pseudorotation barriers in these four molecules.

When $R = CH_3$, $R' = H$ (**28b**) and $R = OCH_3$, $R' = H$ (**29b**), two pathways are possible for **TB** inversion (scheme 3).



Scheme 3

a_1 and a_2 represent forms of intermediate geometries, with five coplanar ring atoms; [18] the only difference being in the position of the substituent. The more favoured of the two pathways, whether it be through **B-a** or **B-e**, depends on the relative importance of the steric and electronic interactions in the ground state **TB** conformation and along each pathway.

Compound **27b** ($R = R' = CH_3$) possesses a methyl group at both the axial and equatorial positions in the boat form, and this can be used to model the energy requirement for pseudorotation through **B-a.** A model for the route through **B-e** is **26b** ($R = R' = H$). The fact that no

spectral change is observed for **28b** ($R = CH_3$, $R' = H$), means that the **TB** form of this compound inverts via a pathway closer to that of **26b** (i.e. **B-e**), rather than **27b**, which shows a spectral change consistent with the higher pseudorotation barrier for inversion through **B-a**.

The Conformational Effect of the Benzo- Group

The **TB** form of the dioxepin rings **26a**, and **26b** is found to be more stabilised than is the case for the analogous hydrocarbon rings, and this is due mainly to the electronic interactions connected with the anomeric effect in the acetal unit of the heterocycles.[58] Moreover, comparison of the results for pairs of molecules, **26a**, **26b** and **28a**, **28b**, taken in conjunction with the published results for the sulphites **32**, and **33**, shows that generally, replacement of the benzo group by a double bond, substantially stabilizes the **TB** conformer relative to the chair form.

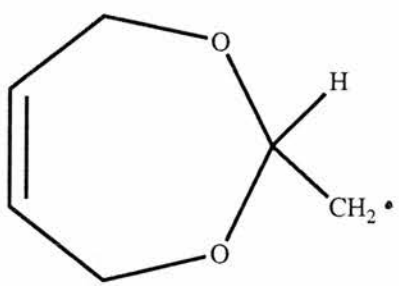
To understand this trend, one has to remember that the differences in torsional interactions at the allylic bonds (H / H eclipsing similar to that in propene whose rotational barrier is 1.98 kcal mol^{-1})[61] and benzylic bonds (H / Csp^2 eclipsing as in toluene whose rotational barrier is *ca.*. 0.5 kcal mol^{-1}),[62] influence conformational populations.[18] Hence, replacing the benzo group by a double bond stabilises the **TB** form relative to the **C** form, because higher torsional strain about the allylic bonds found in the **C** form , is reduced by the conformational change to the **TB** form, in which torsional angles reduce the reduced torsional energy.

Consideration of the values of the free energy barriers in Table 4, shows that the molecules **27a**, **29a**, and **32**, all possess slightly larger pseudorotation barriers than their counterparts **27b**, **29b**, and **33**, (i.e. the presence of the benzene ring at C 5,6 increases the barrier). Seemingly,

changes in the allylic and benzylic torsional strain during the pseudorotational cycle are partly responsible. The difference in the $\Delta G^{\neq}$ value for the 2,2-dimethyl substitution for compounds **27a** and **27b**, infer that other influences, perhaps electronic or of a solvation nature could play a part.

EPR Studies on Radicals derived from 1,3-Dioxepins

The EPR spectra of 1,3-dioxacyclohept-5-enylmethyl radicals **(34)** have been reported.[27]



(**34**)

Spectra obtained at 210 K, 170 K and 150 K are reproduced in Fig 2.

The spectrum at 150 K shows a pattern of lines resultant from two different conformations, with slightly different H_β hfs. As the temperature increases the spectra broaden, coalescing at *ca.*. 190 K, and sharpening up to give a single average spectrum at 210 K, with $a(H_\beta) = a(2H_\alpha)$ (see Table 1, page 6). Both low temperature ring conformations exhibit an $a(H_\beta)$ value that is lower than the free rotation average of *ca.* 2.7mT, and hence the preferred orientation about the C_α-C_β bond has H_β in the nodal plane of the p-orbital containing the unpaired election (SOMO). The magnitude of $a(H_\beta)$ eliminates the possibility of axial

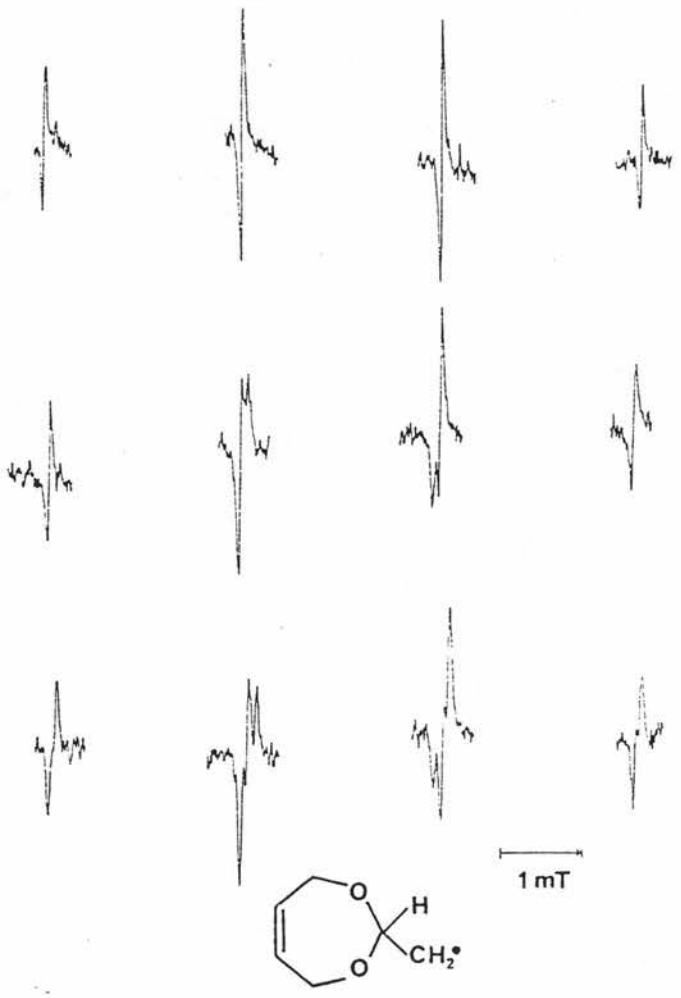
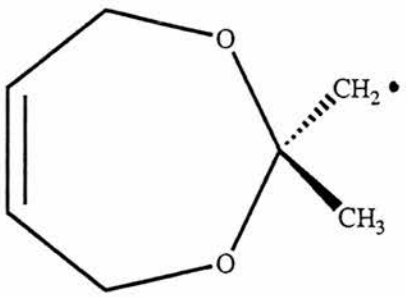


Fig. 2. 9.2 GHz EPR spectra of 1,3-dioxacyclohept-5-enylmethyl radicals (**34**) in cyclopropane solution; top, 210 K; centre, 170 K; bottom, 150 K.

conformations, and the spectrum at 150 K is almost certainly due to a mixture (c.a. 50:50) of the chair equatorial conformation, (**34 C-e**) [analogous to **C-e**, scheme 1, page 4] and the twist-boat conformation, **34 TB** [analogous to **TB**, scheme 1]. The spectrum with the larger H_β hfs has been assigned to the (**34 C-e**) conformer (Table 1), because models have indicated that there is least steric hindrance to rotation about the $C_\beta - C_\alpha$ bond in this conformation. This situation leads to the H_β hfs values being closest to the free rotation limit. The coalescence temperature, and the difference in the a (H_β) values, allowed the calculation of the Arrhenius activation energy for interconversion of the conformers, and this was found to be 5.0 kcal mol^{-1} (alternatively, the free energy of activation, $\Delta G^{\neq}$, at 190 K was 4.7 kcal mol^{-1}).[27] Radical (**34**), is structurally very similar to compound (**28b**), for which St. Jacques et. al. suggested a stable twist boat conformation with a minor chair contribution. In the radical (**34**), the free-energy barrier corresponds to the ring-inversion process that interconverts the chair and the twist boat conformers via the boat (see scheme 1). It would be expected that this ring inversion process would have a higher activation barrier than ring pseudorotation, but it appears that in the case of the 1,3-dioxacyclohept-5-ene ring, these barriers are roughly equal.

The EPR spectra of the 2-methyl substituted radical (**35**) have also been reported.[27]



(**35**)

The spectrum obtained at 161K is shown in Fig 3.

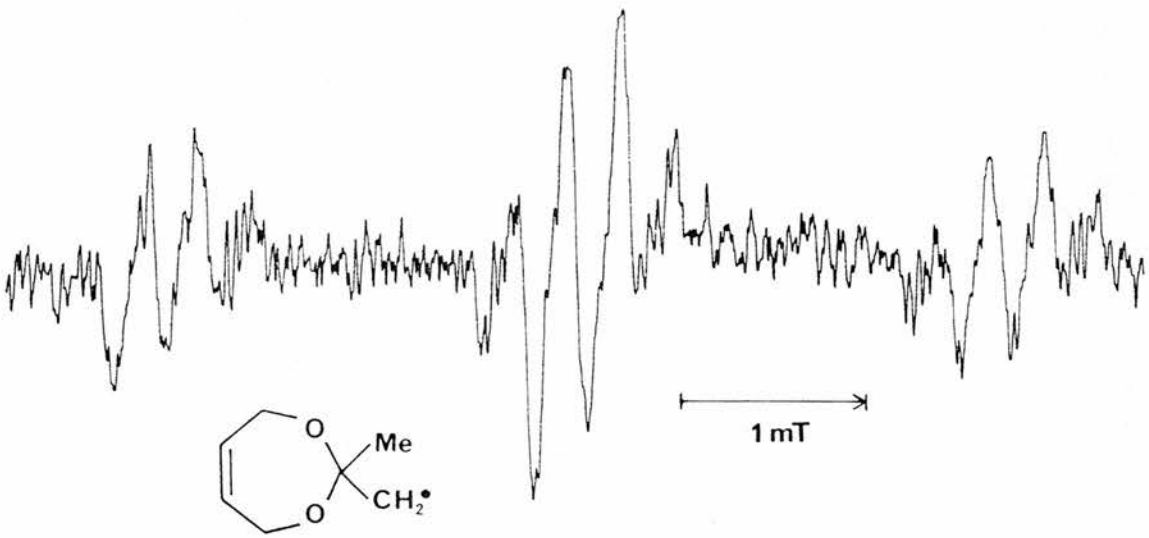
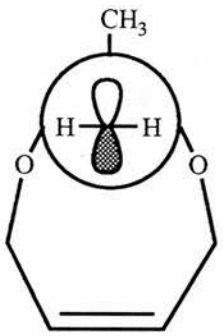


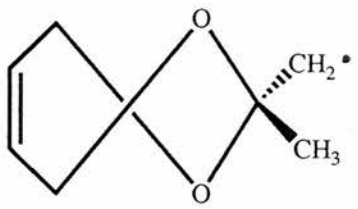
Fig 3. 9.2 GHz EPR spectrum of 2-methyl-1,3-dioxacyclohept-5-enylmethyl radical (**35**) in cyclopropane at 161 K.

The spectra were essentially unchanged in the temperature range 150-190 K, but were found to quickly weaken in intensity at lower temperatures. The only radical that was detected above this temperature range was an allyl type radical, formed by hydrogen abstraction from the C(4) or C(7) positions. This type of radical will be discussed at greater length later. The relatively clear resolution of Fig 3. indicates that only one conformation makes a significant contribution. The large quartet γ - H hfs (Table 1) of the methyl group points to a situation whereby the CH_3 group eclipses the SOMO,[63] (**35(i)**), and the rotation about the C_β-C_α bond must be slow. Further long-range splittings were not resolved, in contrast to the spectra obtained for (**34**). The splittings that

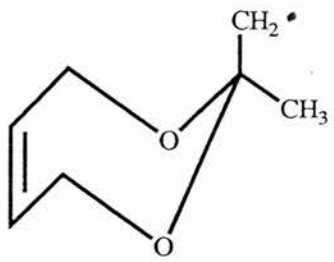
were obtained are shown in Table 1, page 6 . The data was not sufficient to precisely define the most stable ring conformation, but the twist boat (**35 TB**), or the chair axial (**35 C-a**) are the main possibilities.



35(i)



35(TB)

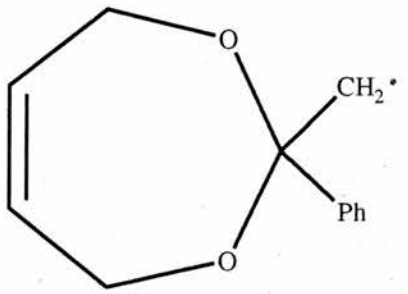


35(C-a)

In view of the contrast between the spectrum of (**35**), and that of the 2-phenyl radical (**36**), which follows, the twist boat conformation (**35 TB**) seems the most likely.[55] The 2,2-dimethyl-1,3-dioxacycloheptene molecule (**27b**), is structurally very similar to the 2-methyl-1,3-dioxacyclohept-5-enylmethyl radical (**35**). The former has been discussed previously in relation to NMR studies, from which it was concluded that the most stable conformation was the twist boat (with an activation energy to inversion of 6.8 kcal mol^{-1} (Table 4)).

EPR Study of the 2-Phenyl-1,3-Dioxacyclohept-5-enylmethyl Radical

The EPR spectra of the 2-phenyl radical (**36**)



(**36**)

at three different temperatures are shown in Fig 4. Solubility problems prevented us obtaining satisfactory spectra below *ca.* 200 K in cyclopropane.

The radical (**36**) was formed from 2-bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin by bromine abstraction with trimethyltin radicals, produced from hexamethylditin by interaction with photochemically generated $Bu^tO\cdot$ radicals.

$$Bu^tOOBu^t + h\upsilon \text{ ----------> } 2\ Bu^tO\cdot$$

$$(Me)_3SnSn(Me)_3 + Bu^tO\cdot \text{ ----------> } 2\ (Me)_3Sn\cdot$$

The spectra show only a single conformation; the fact that no long-range splittings could be detected, suggests that in (**36**), the orientation about the C_β-C_α bond is different from that in (**35**), or that the ring conformation is different, or both. The notable feature of these spectra is that at T < ca. 250 K, the two H_α show non-equivalent hfs. For example at 239 K, a (H_α) = 1.98mT, and a (H_α) = 2.03mT, whereas at 295 K a ($2H_\alpha$) = 1.97mT. (see Table 1, page 6) The exchange broadening process that is evident from the spectra, was simulated by assuming a two-jump model, and using Heinzer's program.[64] The best fit rate constants k, were then obtained by comparison of the computer

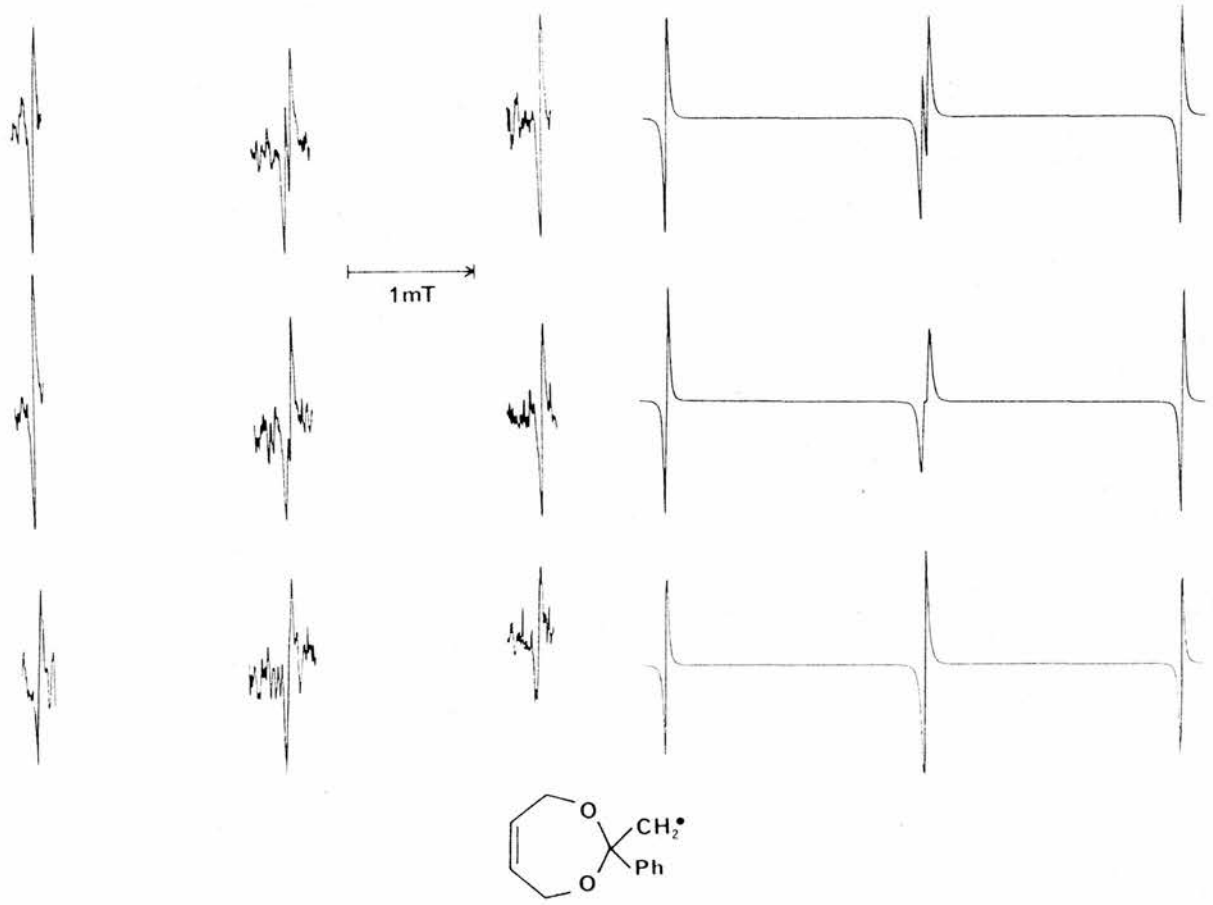


Fig. 4. 9.2 GHz EPR spectra of 2-phenyl-2-bromomethyl-4,7-dihydro-1,3-dioxepin radicals (**36**) in t-butylbenzene: left-hand side, experimental spectra at, from the top, 239, 262 and 295 K; right-hand side simulations with, from the top, ($/10^6 k\ s^{-1}$), 0.6, 1.7 and 10.0.

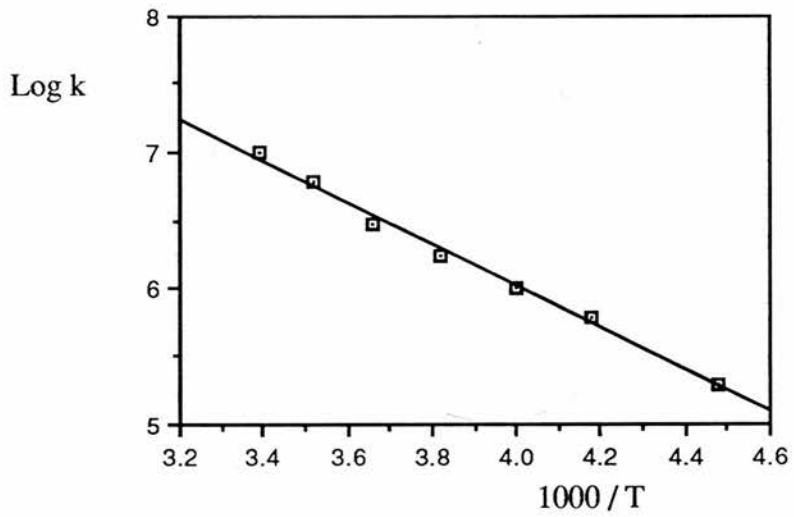
simulated spectra with those obtained experimentally. Table 5 shows the values (best fit) obtained.

Table 5

Best-fit rate constants for the spectra in Fig 4

T / K	228	239	250	262	273	284	295
10^6k / s-1	0.2	0.6	1.0	1.7	3.0	6.0	10.0

The rate equation for the " rotor " type motion was derived from a plot of log k vs 1000/T



This yielded the following Arrhenius parameters :-

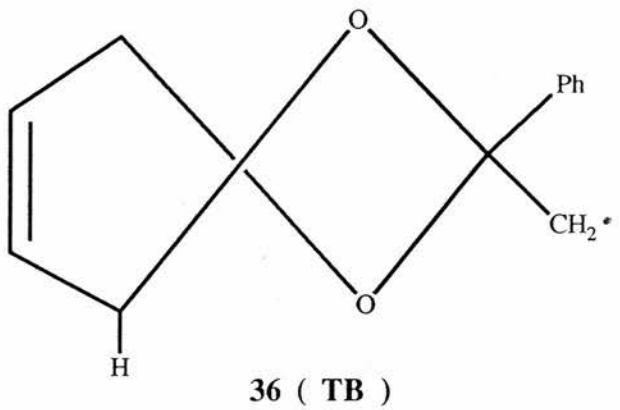
Log (A/s-1) = 12.5 ± 0.3

$E_a = 7.4 \pm 0.3$ kcal`mol^{-1}

(with $r^2 = 99.1\%$)

[alternatively $\Delta G^{\neq}$ (260K) = 7.7 kcal`mol^{-1}]

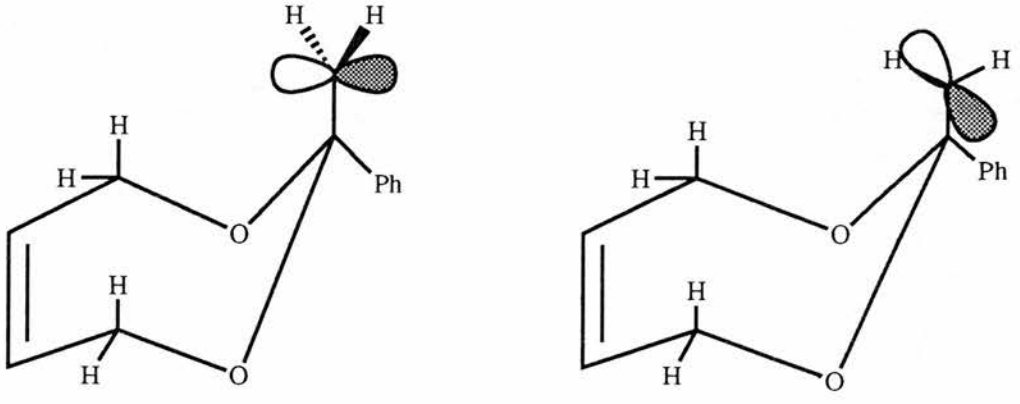
Clearly this is an exceptionally high barrier for a $CH_2^{\bullet}$ rotor. Considering firstly, the twist boat conformation of the radical (**36 TB**).



36 (TB)

In this case the two H_α are non-equivalent, whatever the preferred conformation about the C_β-C_α bond. This is consistent with the EPR result obtained, and so (**36 TB**) could be the correct arrangement. However, in this conformation, the large phenyl substituent is subject to greater steric strain from the hydrogens on C(7), than would be the case in an alternative chair conformation. In the twist boat conformation, the $CH_2^{\bullet}$ rotor experiences very little steric constraint because it is impeded in its motion by only one syn axial hydrogen on C(4). There is therefore no reason to expect a large barrier to $CH_2^{\bullet}$ rotation. By analogy with the radical (**35**), which almost certainly does exist in the twist boat conformation, resolved long-range hfs would be expected from (**36**), if it too adopted the twist boat conformation, but none were evident. It seems most likely therefore, that the 2-phenyl radical assumes a chair conformation, the $CH_2^{\bullet}$ group being in the axial position, and the phenyl group equatorial. The large phenyl group experiences less steric strain in this position, and the conformation is consequently " locked " on the EPR timescale. The NMR studies discussed earlier in connection with 1,3-dioxacycloheptenes and 1,3-dioxabenzocycloheptenes [58] showed that with

bulky 2-substituents, such as t-butyl, the chair conformation was preferred. In the case of the 2-phenyl radical, the chair conformation allows two possible minimum energy orientations of the CH_2· group about the C_β-C_α bond. (Fig 5)



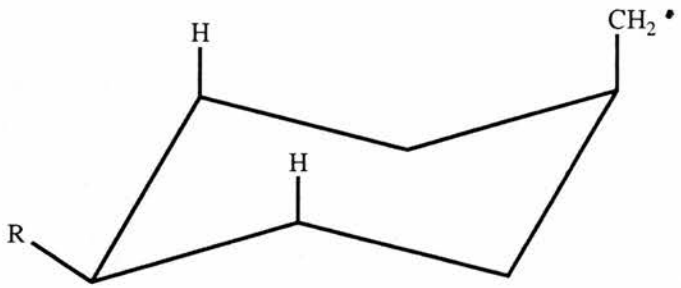
36' (**C-a**) **36** (**C-a**)

Fig 5

In the first of these chair conformations (**36' C-a**), the two α–hydrogens are always equivalent, and therefore this is not consistent with the observed EPR spectrum. In the second possible chair conformation (**36 C-a**), the phenyl substituent lies in the nodal plane of the SOMO. The two α–hydrogens can jump between two different sites, and so this structure fits the observation. Moreover in (**36 C-a**), the CH_2· rotor experiences steric interaction from two *syn* axial hydrogens, one on C(4) and one on C(7). A higher than normal barrier to rotation would therefore be expected. Structure (**36 C-a**) seems to be the one which best fits the experimental data.

The barriers to rotation of several radicals of the type R_2CHCH_2·, including cycloalkylmethyls, have been calculated from the variation in the a (H_β) with temperature,[65,29] and these were all found to be < 1.0 kcal mol^{-1}. However, a barrier as high as ca. 6.0 kcal mol^{-1} has been observed

for CH_2· rotation in the chair axial conformation of cyclohexylmethyl radicals (**37 C-a**).

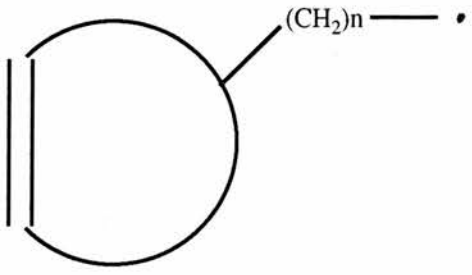


37 (C-a)

For this molecule, again the high rotation barrier is due to the CH_2· group experiencing steric hindrance from two *syn* axial hydrogens. The barrier height was deduced from the changes in long-range hfs with temperature. The two different approaches employed, show that axial radicals which have the CH_2· group sterically hindered by two *syn* axial hydrogens,[66] exhibit particularly high rotation barriers.

Transannular Radical Cyclisations

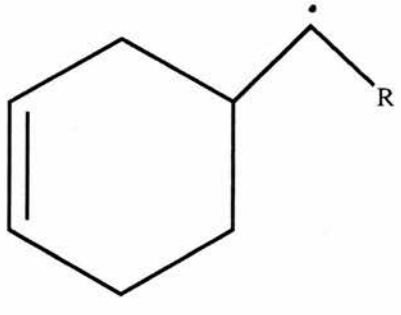
A number of useful syntheses involving bi- and poly- cyclic structures have been reported,[67,68] and the area involving free radical cyclisation is growing steadily. If we consider a transannular cyclisation of a radical of type (**38**).



(**38**)

The side chain must normally be at least two carbon atoms in length ($n \geq 1$) for appreciable bicyclisation to occur. An exception to this rule i.e. bicyclisation with a one-carbon side chain, occurs when the ring conformation is favourable. If the C_1 side chain ($CR_2\cdot$ group) occupies an axial, or quasi-axial position, then such a situation enables the radical centre to approach from above plane of the double bond. This is the stereochemically preferred orientation from which cyclisation is favoured, so long as additional excessive strain is not imposed on the rest of the ring structure. The conformational freedom of the alkenyl unit is very much a determining factor.

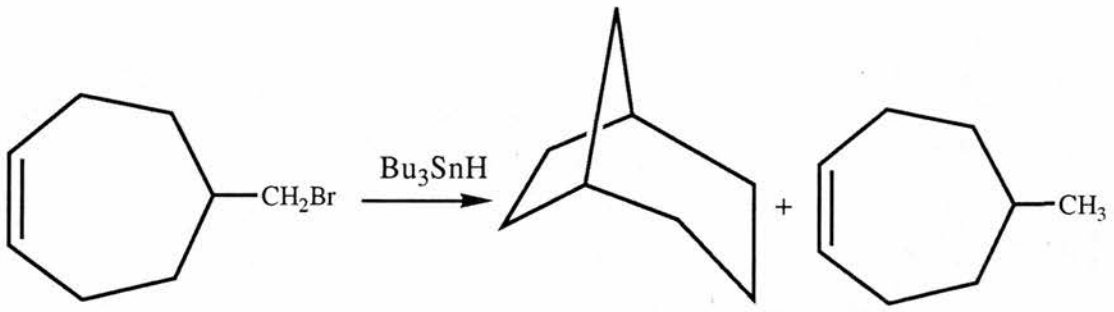
The side chain of the cyclohex-3-enylmethyl radical (**39**),



(**39**)

can occupy the quasi-axial position in the half-chair conformation, but cyclisation was found not to occur for either the parent radical (R = H), or for any derivatives. It has been found that transannular cyclisation occurs more readily for seven- and eight- membered

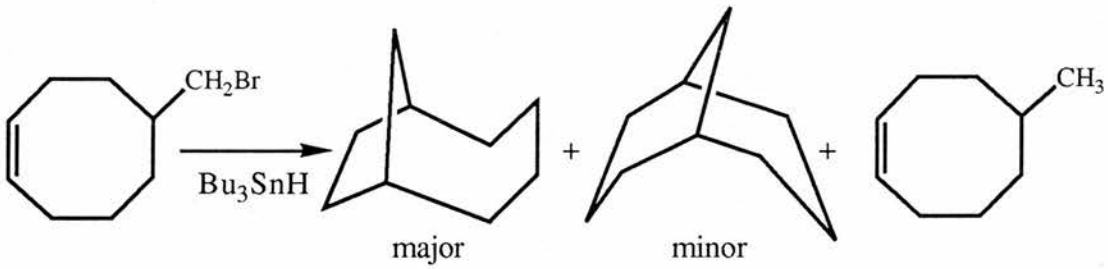
rings. Examples are shown in schemes 4. and 5.[69]



(**40**) (**41**)

Bicyclo[3.2.1]octane 5-methyl-cycloheptene

Scheme 4



major minor

(**42**) (**43**) (**44**)

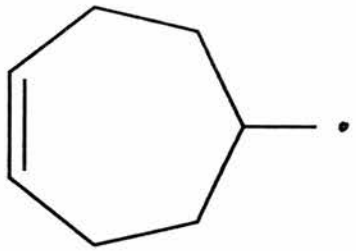
Bicyclo[4.2.1]nonane 5-Methyl -cyclo-octene

Bicyclo[3.3.1]nonane

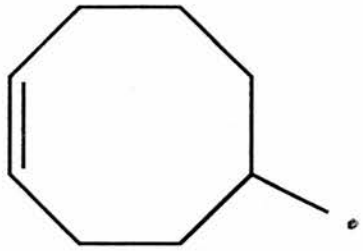
Scheme 5

The proportions of the cyclised products, bicyclo[3.2.1]octane (**40**) and bicyclo[4.2.1nonane (**42**), have been found to depend very much on temperature, and the concentration of tributyltin hydride, although yields of up to *ca.* 75% were obtainable.

The cyclisations described occur via the cycloheptenylmethyl radical (**7**) and the cyclooctenylmethyl radicals (**45**)

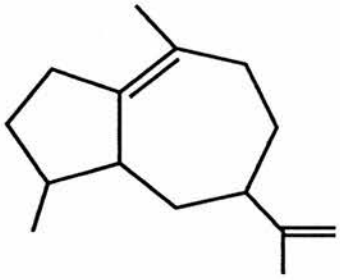


(7)

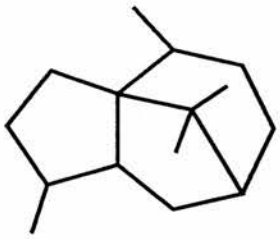


(45)

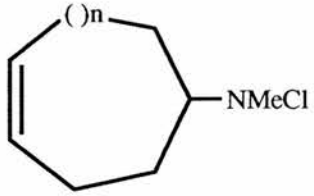
The most stable conformation of (**7**); the chair form with the CH_2• group equatorial (see previously, page 7), would put the CH_2• group too far removed from the double bond for intramolecular addition. It seems quite surprising then that high yields of the bicycloalkane (**40**) are achieved. One other example of a bicyclisation involving a cycloheptenylmethyl- type radical occurs when α–bulnesene (**46**) is photolysed in the presence of dimethyl sulphide.[70]



(**46**)



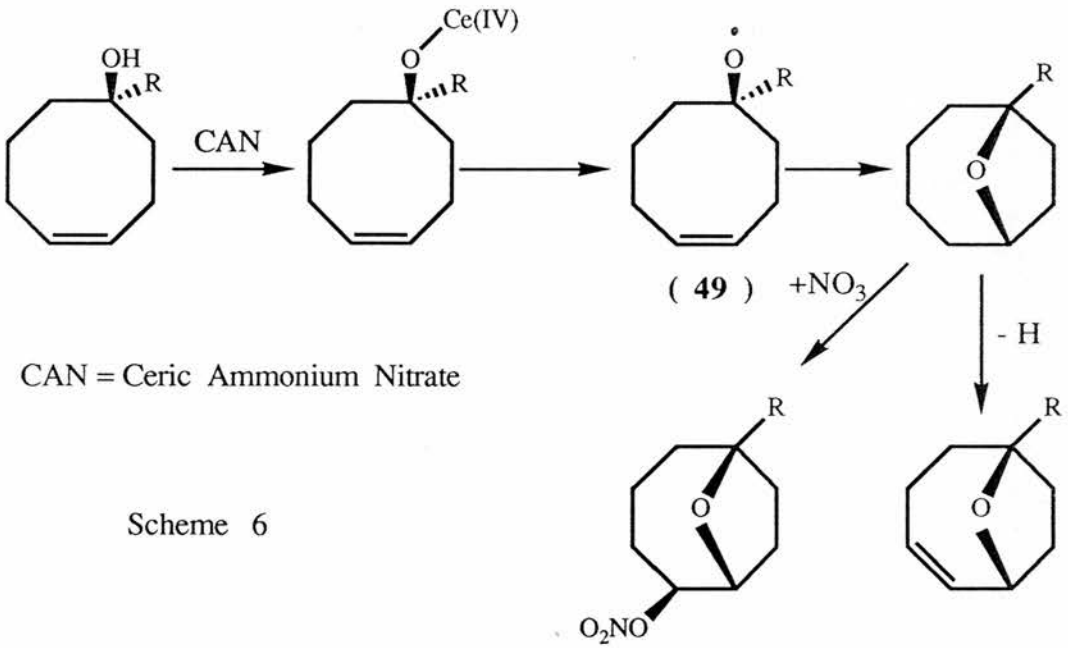
(**47**)



(**48**)

A complex mixture of products was obtained from this reaction, but desuphurisation afforded a small quantity of the cyclised material (**47**). Cycloalkenylaminyl radicals are thought to play a part in the transannular cyclisation of N-chloroamines. Compound (**48**) (n = 1) yields 8-azabicyclo-octane and compound (**48**) (n = 2) gives 9-azabicyclononane, both in low yield.[71]

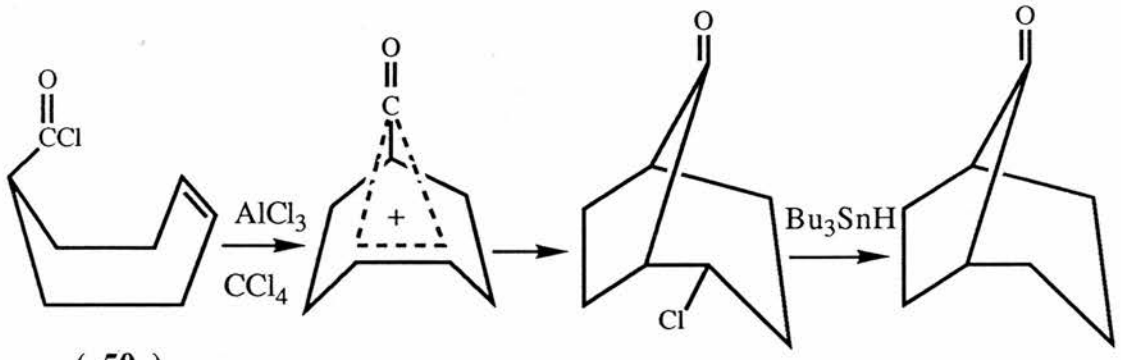
The transannular cyclisation of cyclo-octenyloxy radicals[72] (**49**) have also been reported recently. (Scheme 6)



CAN = Ceric Ammonium Nitrate

Scheme 6

In the presence of aluminium chloride, cyclohept-4-ene-1-carbonyl chloride (**50**), undergoes cyclisation[73] according to Scheme 7.



(**50**)

Scheme 7.

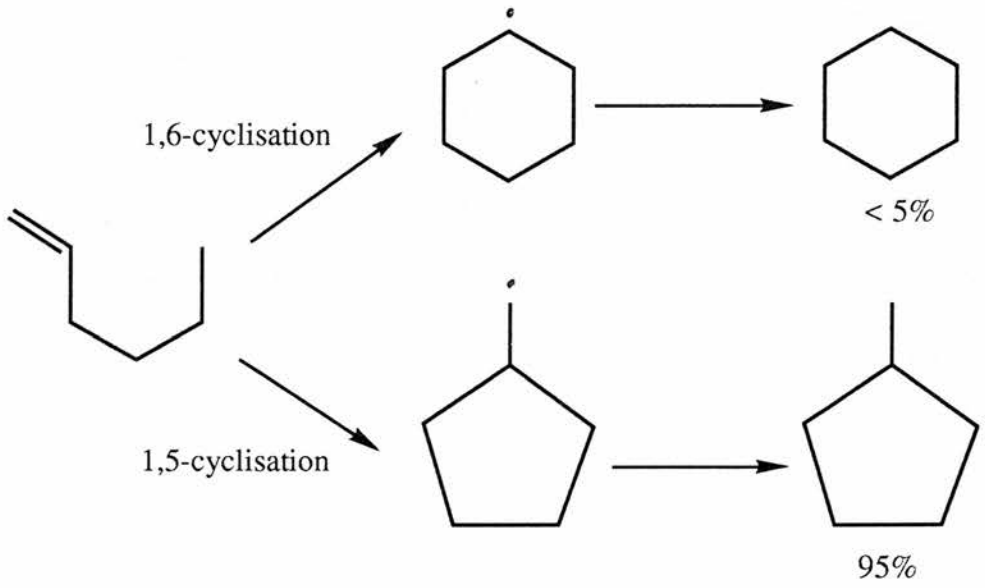
The conformation that allows cyclisation is the boat form and the mechanism is thought to involve a carbocationic intermediate.

The EPR spectra of the cycloheptenylmethyl radical (**7**) have been represented previously, and confirm that the radical has access to the axial

boat conformation that allows cyclisation - the CH_2· group being almost ideally placed for interaction with the double bond in this arrangement.

The expected conformation of the cyclo-octenylmethyl radical (**45**) is a quasi-equatorial form, and must be analogous to the axial boat of (**7**) for cyclisation to occur. The EPR spectrum of the cyclo-octenylmethyl radical (**45**) has been found to be insufficiently interpretable to prove the existence of more than one conformer.

The rate constant for the hex-5-enyl cyclisation is well known, the 1,5-cyclisation being the overwhelmingly preferred mode.[74-78] (Scheme 8)

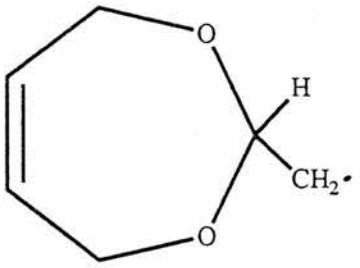


Scheme 8

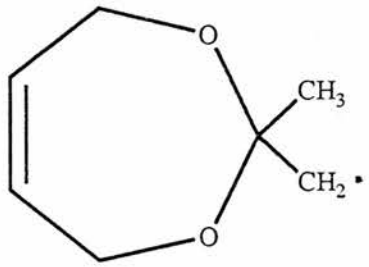
The rate constants and Arrhenius parameters for the cyclisation of (**7**) ----> (**40**), and, (**45**) ----> (**42**), are very similar, but slightly smaller than those for the hex-5-enyl. This is probably due to the fact that for both (**7**) and (**45**), several conformations are populated, and only one conformation contributes to cyclisation. The direct rate of cyclisation for the boat-axial conformation of (**7**) is not experimentally accessible, but it is thought to be actually faster than the hex-5-enyl cyclisation.

Transannular Radical Cyclisations of 1,3-Dioxepins

In this research, the transannular cyclisations of 1,3-dioxepins were of interest. Previous workers had investigated the 4,7-dihydro-1,3-dioxepin-2-yl methyl radical (**34**), and the 4,7-dihydro-2-methyl-1,3-dioxepin-2-yl methyl radical (**35**) :-

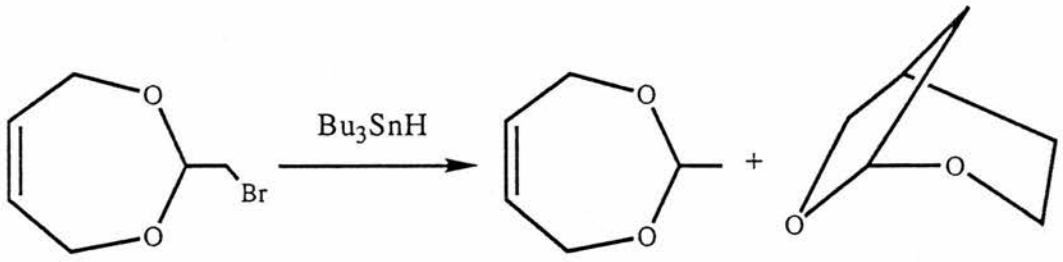


(**34**)



(**35**)

In the case of radical (**34**) treatment of the parent bromide with tributyltin hydride would lead to the formation of two possible products. (Scheme 9)



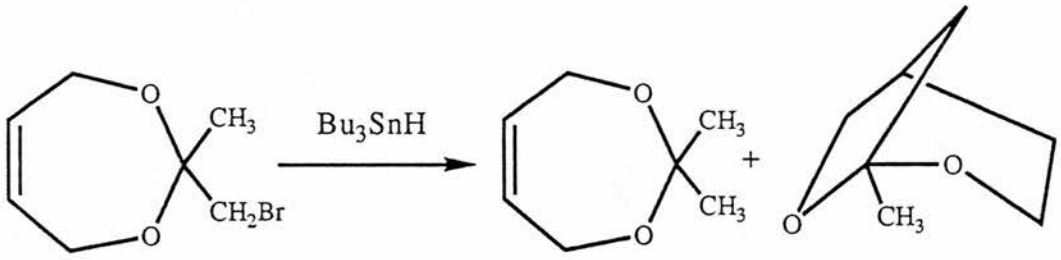
(**51**) (**52**)

Scheme 9

These workers found that over a range of temperatures, the rate of bicyclisation is low; the major product always being the unrearranged species (**51**), although traces of the bicyclic acetal were detected. It appears that although the boat axial conformation is populated, it is only to a minor degree, and hydrogen abstraction from the reducing agent is

the fastest mode of reaction. Theoretically, reducing the rate of hydrogen abstraction from the reducing agent should increase the fraction of cyclised product obtained. It has been found that tris (trimethylsilyl) silane[79] transfers hydrogen to carbon centred radicals between four and five times less readily than tributyltin hydride. However it was also discovered that using this compound did not significantly increase the amount of cyclised product (**52**). The rate of cyclisation of (**34**) was estimated to be $k_{c(298)} = 10^3 - 10^4\ s^{-1}$, by comparison of the proportions of the cyclised product with those obtained in other reactions

In the case of radical (**35**), reaction of the parent bromide with tributyltin hydride would lead to the formation of the two possible products shown in Scheme 10.



(**53**) (**54**)

Scheme 10

The proportions of (**53**) and (**54**) were found to vary considerably with temperature and tributyltin hydride concentration. The product concentrations for a variety of reaction conditions were obtained from g.l.c. analysis, the rate equation being derived from a plot of $\log k_c$ (k_c = rate of cyclisation) vs 1000 / T. The Arrhenius equation obtained was :-

$$\log k_c = 12.5 \pm 1{,}960 / T$$

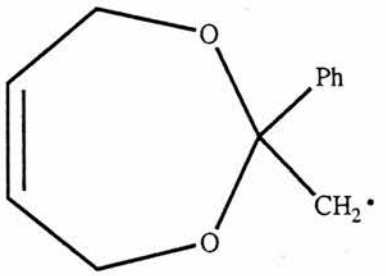
therefore $k_{c\,(298)} = 8.4 \times 10^5\ s^{-1}$

$A = 12.5 \pm 1.0$

and $E_a = 8.96 \pm 0.6$ kcal mol^{-1}

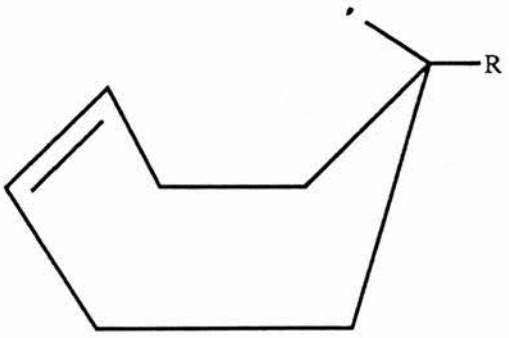
Transannular Cyclisation of the 2-Phenyl-1,3-Dioxacyclohept-5-enyl Methyl Radical (36)

It was decided to investigate in a similar way, the rate of cyclisation of the 2-phenyl radical (**36**).



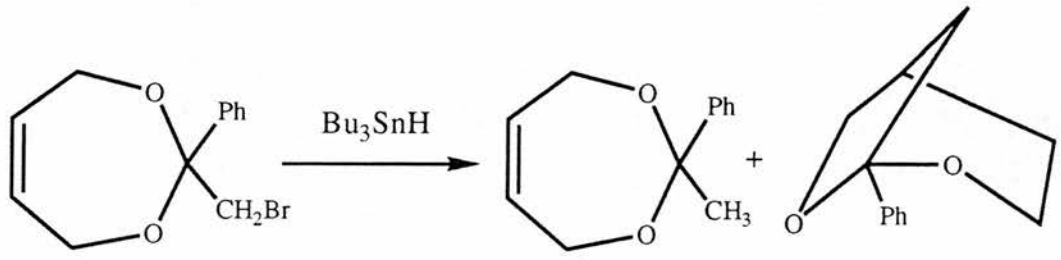
(**36**)

We know that the ideal conformation for cyclisation is the axial boat :-



and that the amount of cyclisation was more significant for $R = CH_3$, than for $R = H$. We postulated that perhaps, increasing the bulk of the R group would increase the rate of cyclisation, and hence a phenyl substituent might result in an increased yield of cyclised product. The two

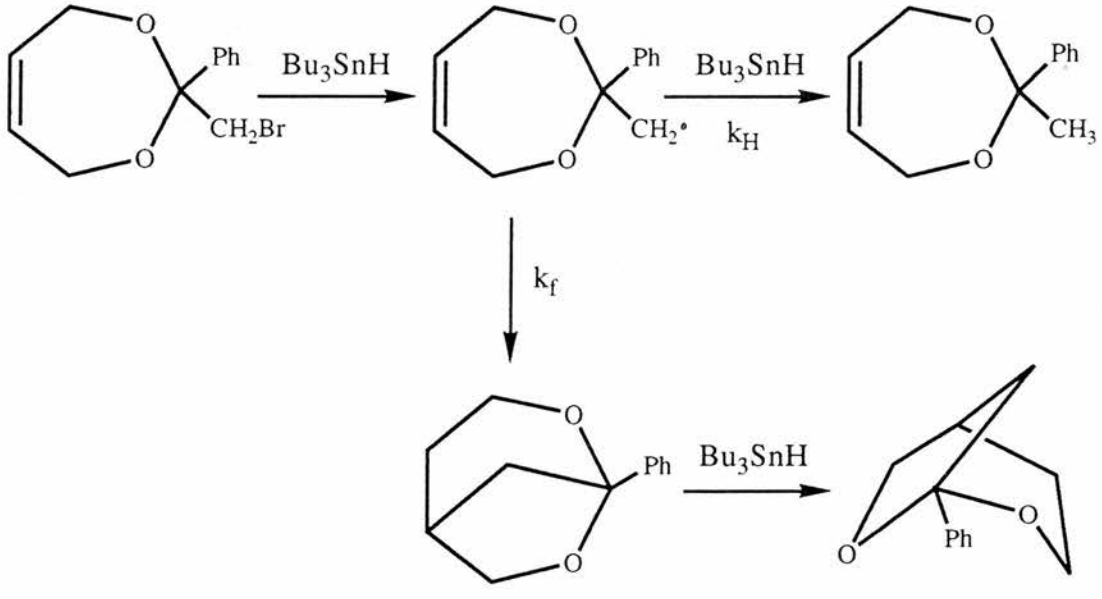
possible products are indicated in scheme 11, for the reaction with tributyltin hydride of the parent bromide.



(**55**) (**56**)

Scheme 11

Kinetics of the Cyclisation of (36)



Scheme 12

The rate constant for the cyclisation of (**36**) was determined by the quantitative analysis of the products of tin hydride reductions of the parent bromide. The photochemical reductions were performed in the temperature range 25 - 150°C, with *tert*-butylbenzene as a solvent and using

hexadecane as an internal standard. The area percentage of the cyclised and uncyclised products together with the standard, obtained from g.l.c. analysis are shown in Table 6.

Temperature °C	Area %		
	Uncyclised [RH]	Cyclised [SH]	Hexadecane
25	2.997	1.562	14.387
50	3.569	3.111	6.119
75	2.500	3.379	6.708
100	0.967	3.906	6.790
125	0.984	3.902	6.130
150	0.783	3.652	7.266

Table 6

If we allow the uncyclised product to be denoted by RH, and the cyclised product to be denoted by SH, and representing Bu_3SnH by MH, the overall process can be represented mathematically as described below :-

$$MH \xrightarrow{I_n} M\cdot \quad \text{initiation}$$

$$M\cdot + RBr \xrightarrow{k_I} MBr + R\cdot$$

$$R\cdot + MH \xrightarrow{K_H} RH + M\cdot$$

$$R\cdot \xrightarrow{K_f} S\cdot$$

$$S\cdot + MH \xrightarrow{K_H} SH + M\cdot$$

Assuming steady state conditions we then have :-

$$\frac{d[R]}{dt} = k_I [M][RBr] - k_H [R][MH] - k_f [R] = 0$$

$$\frac{d[S]}{dt} = k_f [R] - k_H [S][MH] = 0$$

$$\frac{d[RH]}{dt} = k_H [R][MH]$$

$$\frac{d[SH]}{dt} = k_H [S][MH] = k_f [R]$$

then

$$\frac{d[SH]}{dt} \Big/ \frac{d[RH]}{dt} = \frac{k_f [R]}{k_H [R][MH]} = \frac{k_f}{k_H [MH]}$$

and so :-

$$\frac{[SH]}{[RH]} \approx \frac{k_f}{k_H [MH]}$$

Hence using the values of k_H from Ingold et al.[80] and calculating [SH], [RH], and [MH], k_f, the rate constant of cyclisation can be obtained. (Table 7.)

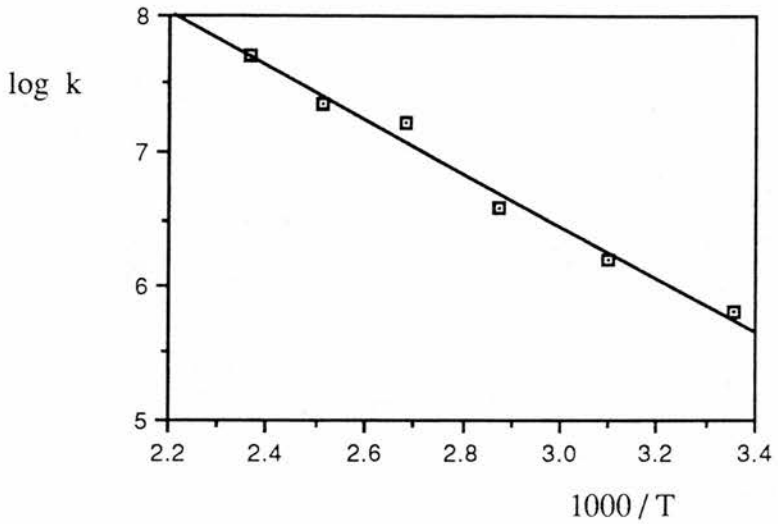
Temperature / K	[RH] mol dm^{-3}	[SH] mol dm^{-3}	a log k_H	k_f / s^{-1} x 10^5
298	0.021	0.011	6.362	6.33
323	0.058	0.051	6.572	15.98
348	0.037	0.050	6.751	37.93
373	0.014	0.057	6.906	166.07
398	0.016	0.064	7.042	221.08
423	0.011	0.078	7.162	512.16

Table 7

notes :- [MH] = 0.542 mol dm^{-3}

(a) equation $\log k_H = 9.07 - 0.807 / T$ employed to obtain k_H

The rate equation for cyclisation was obtained from an Arrhenius plot of log k_f vs 1000 / T.



The Arrhenius equation thus derived is :-

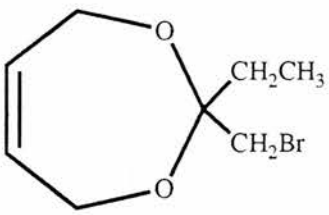
$$\log k_f = 12.3\ (\pm 0.36) - 1.97(10^3)\ (\pm 0.13) / T$$

This gives $k_{f(298)} = 4.9 \times 10^5\ s^{-1}$

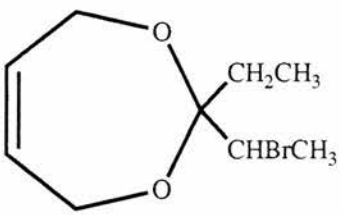
$A = 12.3 \pm 0.36$

$E_a = 9.02\ kcal\ mol^{-1}$

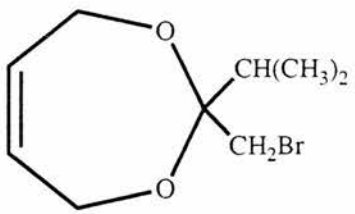
Attempts were made to prepare the di-substituted (on the 2-position) 4,7-dihydro-1,3-dioxepins shown below :-



(**57**)



(**58**)

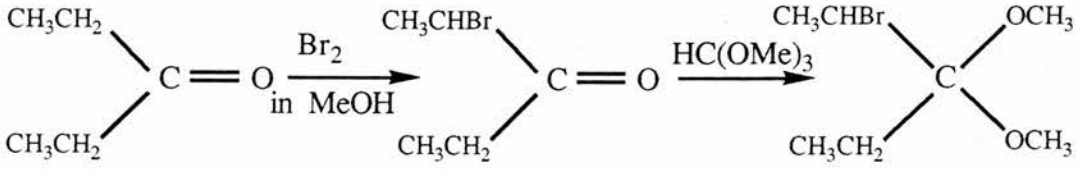


(**59**)

It was hoped to obtain more data about cyclisation rates from these compounds as a comparison to the information already obtained. However, in the case of (**57**), the starting ketone, 1-bromo-2-butanone, is commercially available and stabilised by 0.5% sodium carbonate, could not be condensed with the diol. The dimethyl ketal of the ketone was produced by reaction with trimethyl orthoformate, but this

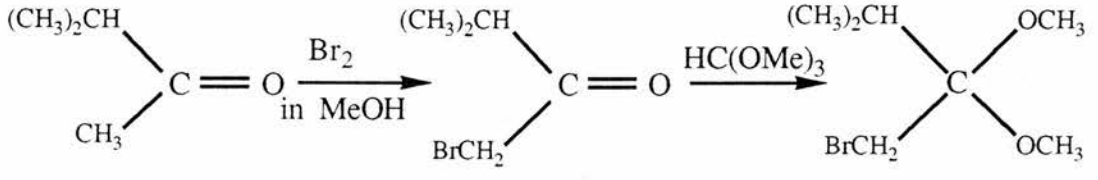
also failed to react with *cis*-2-butene-1,4-diol.

Dimethyl ketals were synthesized as precursors to (**58**), and (**59**). Schemes 13. and 14. outline the method.



pentan-3-one (**60**) (**61**)

Scheme 13



(**62**) (**63**)

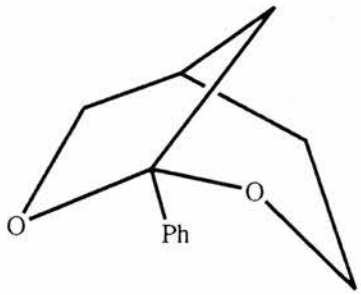
Scheme 14

It proved impossible, even under a variety of reactions, to couple either of the ketals with the diol. The presence of the bromine atom seemed to induce the production of involatile tarry residues.

The 2-bromomethyl-2-naphthyl-4,7-dihydro-1,3-dioxepin was prepared in a 2-stage synthesis. Firstly, 2-bromo-2-acetonaphthone dimethyl ketal was formed by reaction of 2-bromo-2-acetonaphthone with trimethyl orthoformate. This was then condensed with *cis*-2-butene-1,4-diol to form the desired 1,3-dioxepin. A CH_2· rotor radical was not observed for this compound, however an allyl type radical was evident (see later). This compound

proved to be quite unstable and difficult to synthesize, and we were unable to carry out cyclisation studies with it.

Synthesis of 1-Phenyl-2,7-Dioxabicyclo[3.2.1]octane (56)



(56)

Two methods were used to synthesize 1-phenyl-2,7-dioxabicyclo[3.2.1]octane. The first of these involved the photolysis of 2-bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin in the presence of tributyltin hydride and a small amount of t-butylbenzene (just sufficient to get the reaction mixture into solution). On completion of the photolysis the mixture was found to contain two major components. These were separated on a silica gel column using a mixture of ether and petroleum ether as eluent. The major fraction was found to be the unreacted bromide, and the minor fraction separated (16mg) was the cyclised product

A second method was attempted to try to increase the yield of the cyclised product. Organotin hydrides (such as tributyltin hydride) react with many types of organic compounds by radical chain mechanisms, but they are toxic and often awkward to separate from reaction products. The general chain mechanism is indicated by equations 14. and 15.

$$Bu_3Sn^{\bullet} + RHal \xrightarrow{\text{Fast}} Bu_3SnHal + R^{\bullet} \qquad (14)$$

$$R^{\bullet} + Bu_3SnH \xrightarrow{\text{Fast}} RH + Bu_3Sn^{\bullet} \qquad (15)$$

Organosilicon hydrides are preferred in many cases, but the Si-H bond is much stronger than the Sn-H bond and this prohibits much wider use. Triethylsilane gives poor results under similar conditions, because the reaction of the corresponding propagation step (equation 17) is too slow to maintain the chain

$$Et_3Si^{\bullet} + RHal \xrightarrow{\text{Fast}} Et_3SiHal + R^{\bullet} \qquad (16)$$

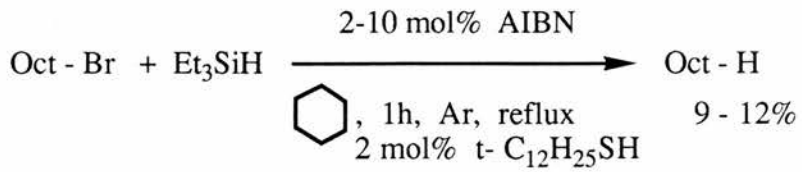
$$R^{\bullet} + Et_3SiH \xrightarrow{\text{Slow}} RH + Et_3Si^{\bullet} \qquad (17)$$

Tris(trimethylsilyl)silane is an effective reducing agent for alkyl halides because the Si-H bond in $(Me_3Si)_3SiH$ is much weaker than in Et_3SiH (331 kJ mol^{-1} and 377 kJ mol^{-1} respectively). Reaction 17. is slow probably due to unfavourable polar factors, and can be subject to polarity reversal catalysis (PRC). The strength of the S-H bond (384 kJ mol^{-1} in MeSH) means that thiols are suitable " acceptor " catalysts. Thiyl radicals are electrophilic, and reaction 17, in the presence of thiol, is replaced by reactions 18. and 19, both of which are enhanced by favourable polar effects.

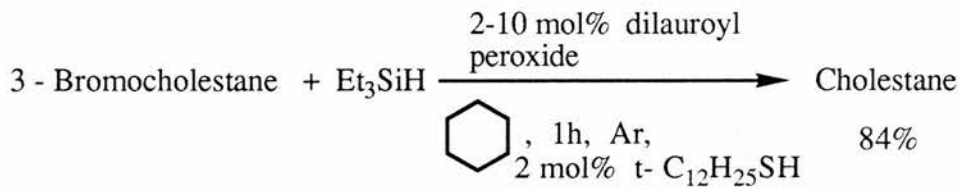
$$R^{\bullet} + XSH \xrightarrow{\text{Fast}} RH + XS^{\bullet} \qquad (18)$$

$$XS^{\bullet} + Et_3SiH \xrightarrow{\text{Fast}} XSH + Et_3Si^{\bullet} \qquad (19)$$

The following reaction is known to occur[81] :-

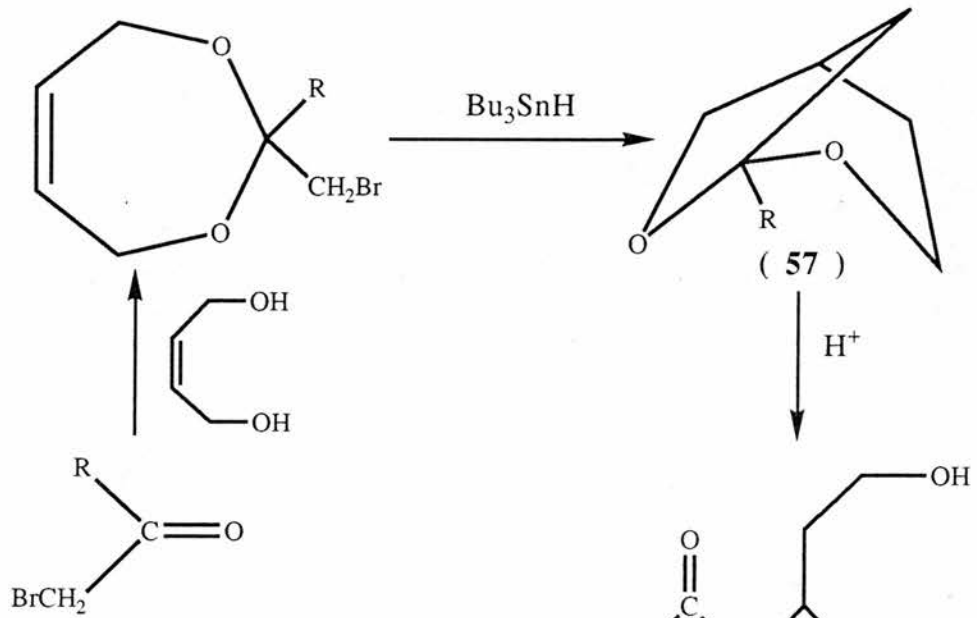


In this case AIBN is found to be a poor initiator, and by using dilauroyl peroxide increased yields are obtained.[82]



This type of reaction was attempted with 2-bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin using various percentages of dilauroyl peroxide and varying reaction times. However it was found that the parent bromide did not react, and none of the cyclised product was isolated. The original tributyltin hydride method produced a 65% yield of 1-phenyl-2,7-dioxabicyclo[3.2.1]octane after photolysis at 130°C for 2 hours.

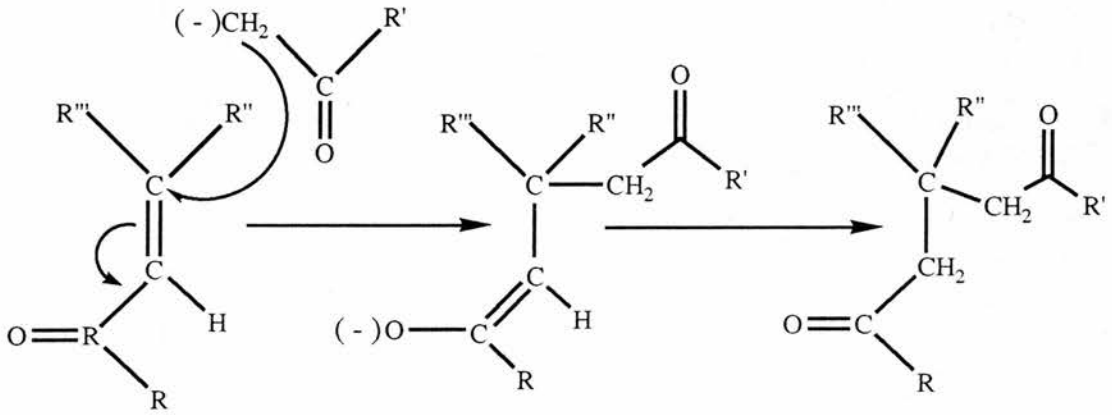
Hydrolysis of Bicyclic Ketals



Scheme 13

The bicyclic ketal with R = Ph, was hydrolysed to give the diol (**58**). Previous workers had achieved the same result with R = CH_3. The overall result achieved is the addition of the starting carbonyl compound to the double bond of *cis*-2-butene-1,4-diol. This method is novel and potentially useful because earlier approaches to the problem of the addition of carbonyl compounds to alkenes involved producing a radical from a double bond. e.g. by formation of an oxyl radical and addition of this to a reactive centre on the carbonyl compound. It was felt that more options were available with the carbonylmethyl group when compounds of type (**57**) were hydrolysed, and it was not necessary for the starting ketone to have a functional group which can react with alkyl radicals. A similar result could probably be obtained by a Michael

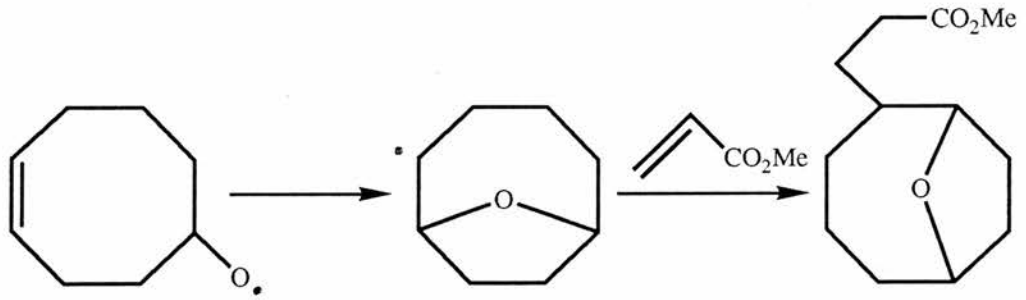
addition type of reaction. This involves the base catalysed conjugate addition of a nucleophile to an α,β–unsaturated system. (Scheme 14)



Scheme 14

The Michael addition requires that the carbon-carbon double bond be conjugated to a carbonyl group, or some other activating group.

A related type of reaction has been reported involving the cyclo-oct-4-enyloxyl radical.[83] (Scheme 15)



cyclo-oct-4-enyloxyl radical

9-oxabicyclo[4.2.1]non-2-yl radical

Scheme 15

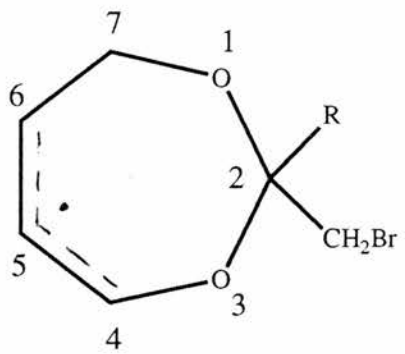
Table 8. summarises the best yields obtained for compounds (**57**), and (**58**) with various R groups in scheme 13.

R ($R'=CH_2Br$)	Compound Type (**57**) Yield (%)	Compound Type (**58**) Yield (%)
H	1 (121°C)	--
CH_3	50 (125°C)	63
Ph	65 (130°C)	70

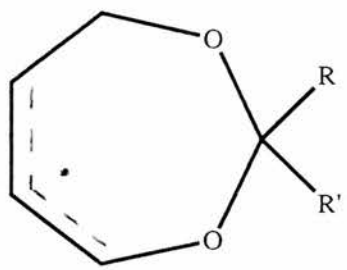
Table 8.

In the case of R = naphthyl, no cyclised product was obtained. The bulk of the naphthyl group appeared to make the molecule quite unstable, and susceptible to reverting back to the diol and ketal.

Allyl Radicals



(**59**)



(**60**)

The EPR spectra obtained from the CH_2• " rotor " type radicals obtained from compounds of type (**59**) have been discussed previously. It was found that the hydrogens situated in the 4- and 7-positions are particularly susceptible to abstraction by *tert*-butoxy radicals. EPR spectra of these allyl type radicals have been obtained for all of the substituted 1,3-dioxepins that we have synthesized. It has been discovered that where R = CH_2Br, and the competing reaction is bromine abstraction by hexamethylditin, allyl radicals are still easily detected. Careful

control of the proportions of $^{t}BuOOBu^{t}$ and hexamethylditin enables one or other of the radicals to predominate and hence be detected by EPR. A previous worker found that the $CH_2\cdot$ " rotor " radicals themselves were capable of hydrogen abstraction from the C(4) or C(7) positions on other dioxepin molecules, since allyl radicals were detected even in the absence of di-*tert* butyl peroxide.

Some examples of allyl radical EPR spectra obtained by photolysis of the appropriate disubstituted 1,3-dioxepin, in t-butyl benzene with di *tert*-butyl peroxide are set out in the following pages, Figs 6-10.

Tables 9 summarises the hfs for the allyl radicals of 1,3-dioxepins that we have observed, and table 10 shows the hfs for a selection of other allyl and cyclic allyl radicals for comparison.

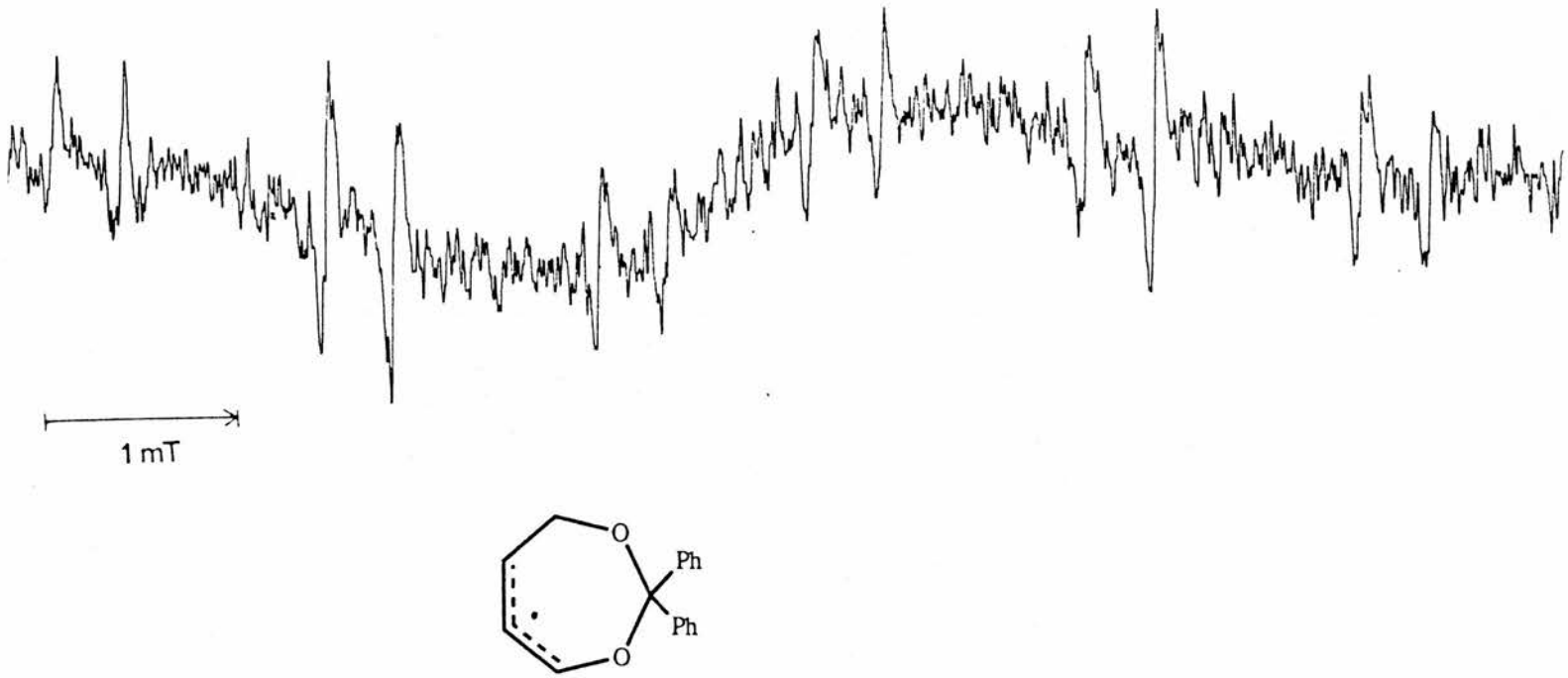
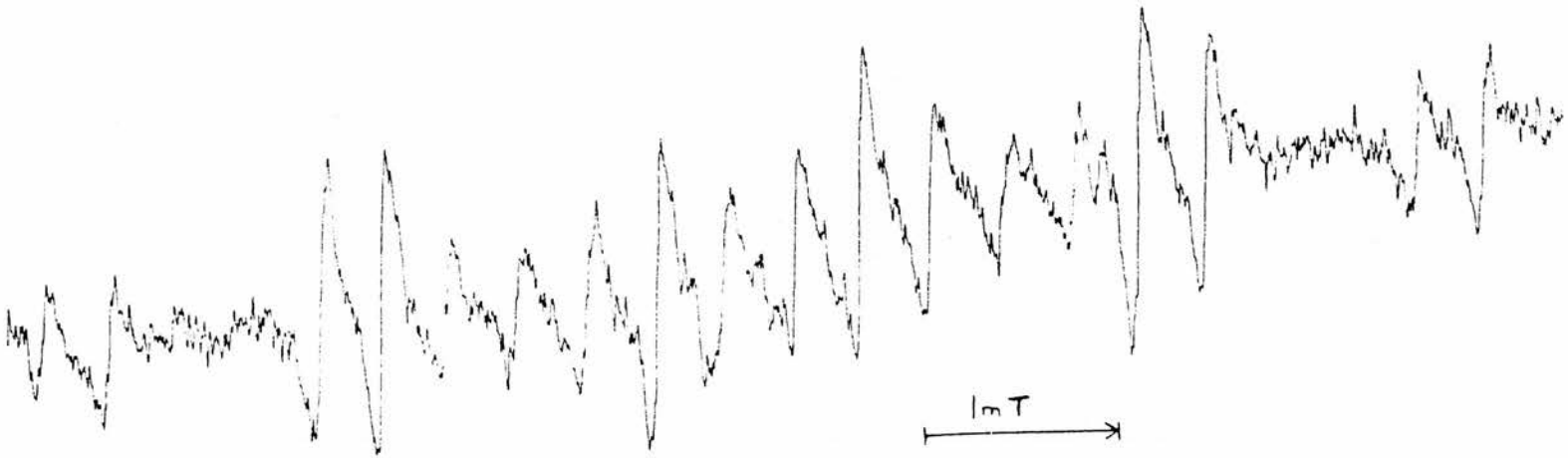


Fig. 6. 9.2 GHz EPR spectrum of the allyl radical derived from 2,2-diphenyl-4,7-dihydro-1,3-dioxepin in *tert*-butylbenzene at 210 K.



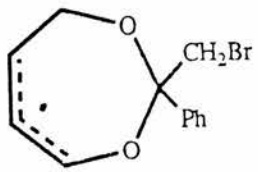


Fig. 7. 9.2 GHz EPR spectrum of the allyl radical derived from 2-bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin in *tert*-butylbenzene at 225 K, with a (1H) = 3.5 G, a (2H) = 14.2 G, a (1H) = 17.5 G and a (1H) = 24.5 G.

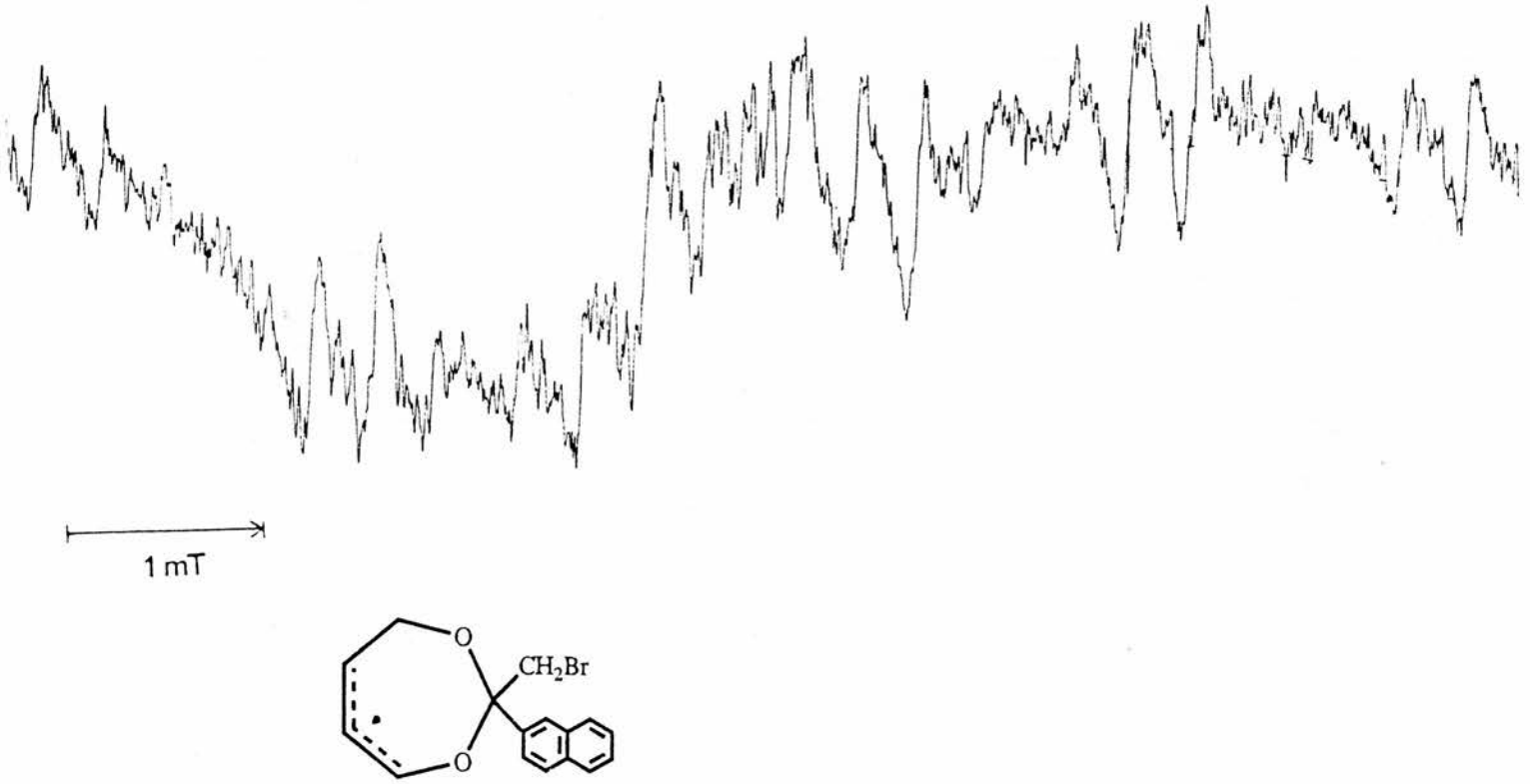


Fig. 8. 9.2 GHz EPR spectrum of the allyl radical derived from 2-bromomethyl-2-naphthyl-4,7-dihydro-1,3-dioxepin in *tert*-butylbenzene at 225 K.

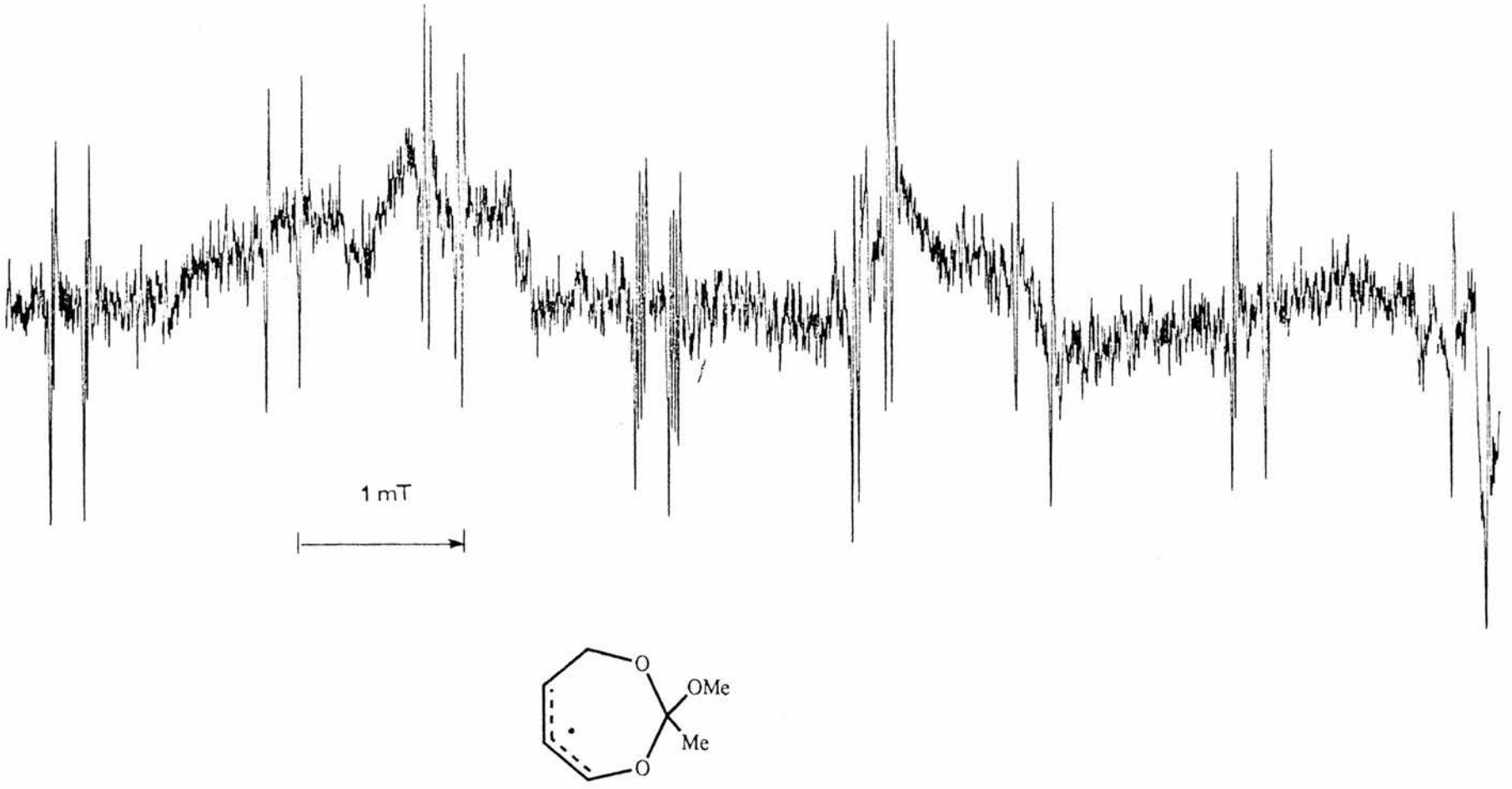
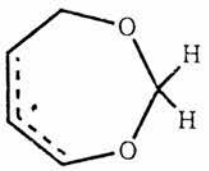


Fig. 9. 9.2 GHz EPR spectrum of the allyl radical derived from 2-methoxy-2-methyl-4,7-dihydro-1,3-dioxepin in *tert*-butylbenzene at 220 K.



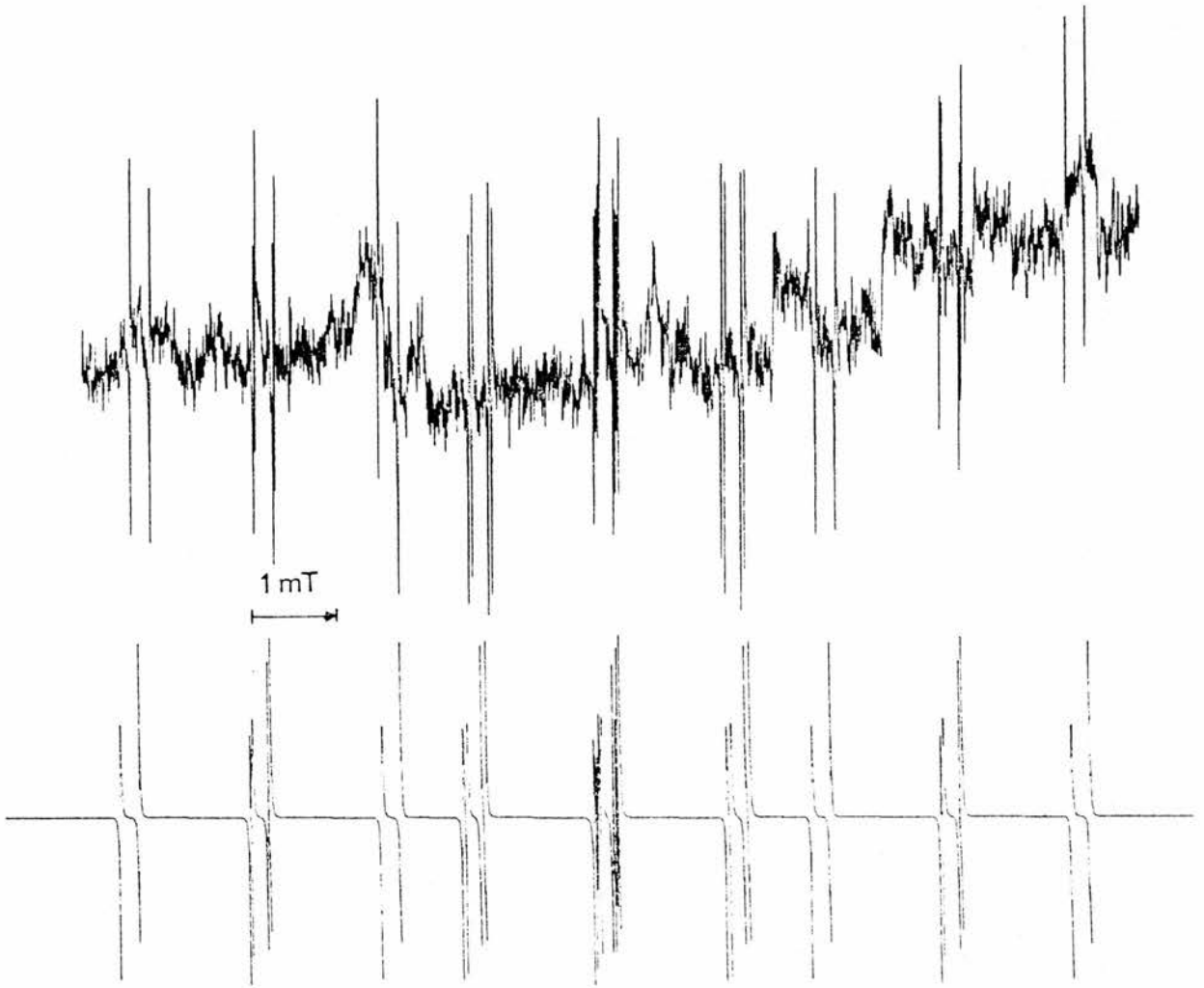


Fig. 10. 9.2 GHz EPR spectrum of the allyl radical derived from 4,7-dihydro-1,3-dioxepin (**26b**) in *tert*-butylbenzene; upper trace, experimental spectrum at 220 K, (200 G wide); lower trace, simulation with a (1H) = 1.95 G, a (1H) = 13.7 G, a (1H) = 14.0 G, a (1H) = 36.3 G and a (1H) = 36.8 G.

R	R'	T / K	hfs / G
Ph	Ph	210	a(1H) = 0.0, a(1H) = 3.4, a(2H) = 14.1, a(1H) = 42.9
Ph	CH_2Br	225	a(1H) = 3.5, a(2H) = 13.5, a(1H) = 17.5, a(1H) =24.5
Naphthyl	CH_2Br	225	a(1H) = 3.5, a(2H) = 13.5, a(1H) = 17.2, a(1H) =25.0
OMe	Me	220	a(1H) = 2.1, a(1H) = 13.1, a(1H) = 13.3, a(1H) =36.1, a(1H) = 36.4.
H	H	220	a(1H) = 2.0, a(1H) = 13.4, a(1H) = 13.6, a(1H) = 36.3, a(1H) = 36.7.

Table 9.

hfs for the 2,2-disubstituted 4,7-dihydro-1,3-dioxepins (allyl radicals) in Figs. 6-10.

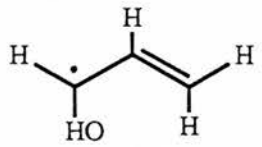
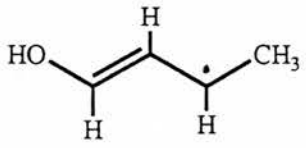
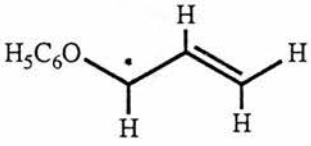
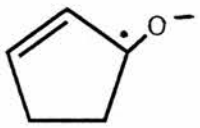
Radical	T / K	hfs / G	Reference
	231 302	a(1H) = 0.9, a(1H) = 3.0. a(1H) =0.5, a(1H) = 3.16 a(1H) = 13.3, a(1H) = 13.9	198
	231	a(1H) =0.7, a(1H) = 3.7, a(1H) =13.1, a(1H) =13.4, a(1H) = 15.8.	199
	223	a(1H) = 3.8, a(3H) = 14.0.	112
	220	a(1H) = 0.3, a(2H) = 11.3, a(1H) = 12.7, a(2H) = 17.2.	200

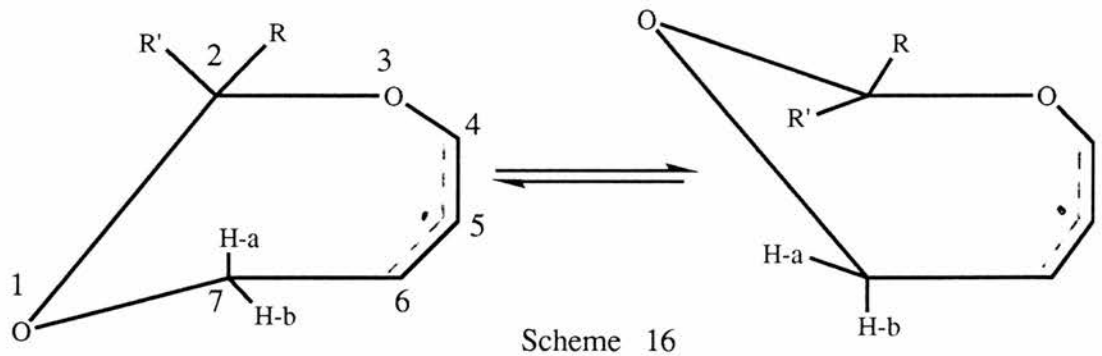
Table 10.

hfs for some allyl and cyclic allyl radicals

Particularly clear spectra were obtained for both 2,2-diethyl-4,7-dihydro-1,3-dioxepin and 2,2-dimethyl-4,7-dihydro-1,3-dioxepin.

The 2,2-diethyl derivative was photolysed in the cavity of the EPR spectrometer over the temperature range 200-340 K in t-butylbenzene with di-*tert*-butyl peroxide. The experimental spectrum and computer simulation for 215 K are shown in Fig 11.

An exchange broadening process was observed over the temperature range covered, which is due to conformational changes in the ring that make the pseudo axial and pseudo equatorial hydrogens, H-a and H-b, on C(4) or C(7) (i.e. the hydrogens on the site where abstraction has not occurred) equivalent in the limit of fast exchange (Scheme 16)



Scheme 16

The 9.2 GHz, half-field EPR spectra for 2,2-diethyl-4,7-dihydro-1,3-dioxepin at 200 K, 225 K, 270 K and 300 K are shown in Fig 12.

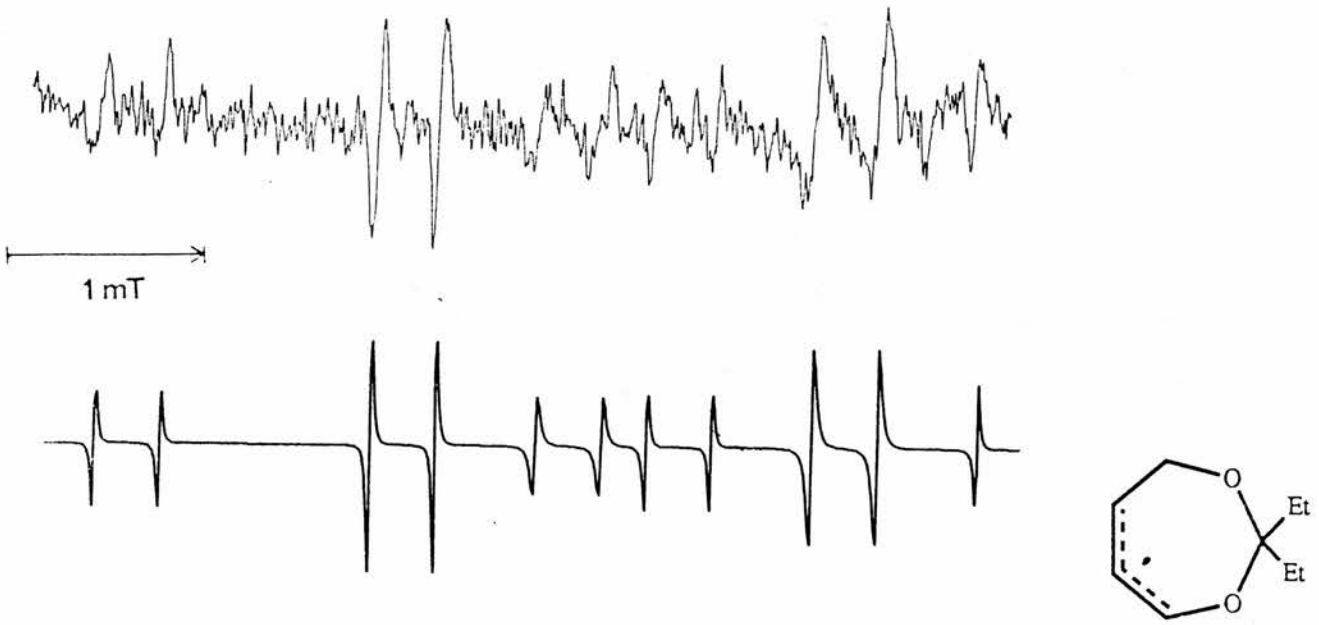


Fig. 11. 9.2 GHz, 1 / 2 field EPR spectrum of 2,2-diethyl-4,7-dihydro-1,3-dioxepin (allyl radicals) in t-butylbenzene. Upper trace, experimental spectrum at 285 K; lower trace, computer simulation with a(1H) = 3.3 G, a(2H) = 13.9 G, a(1H) = 19.7 G and a(1H) = 24.8 G.

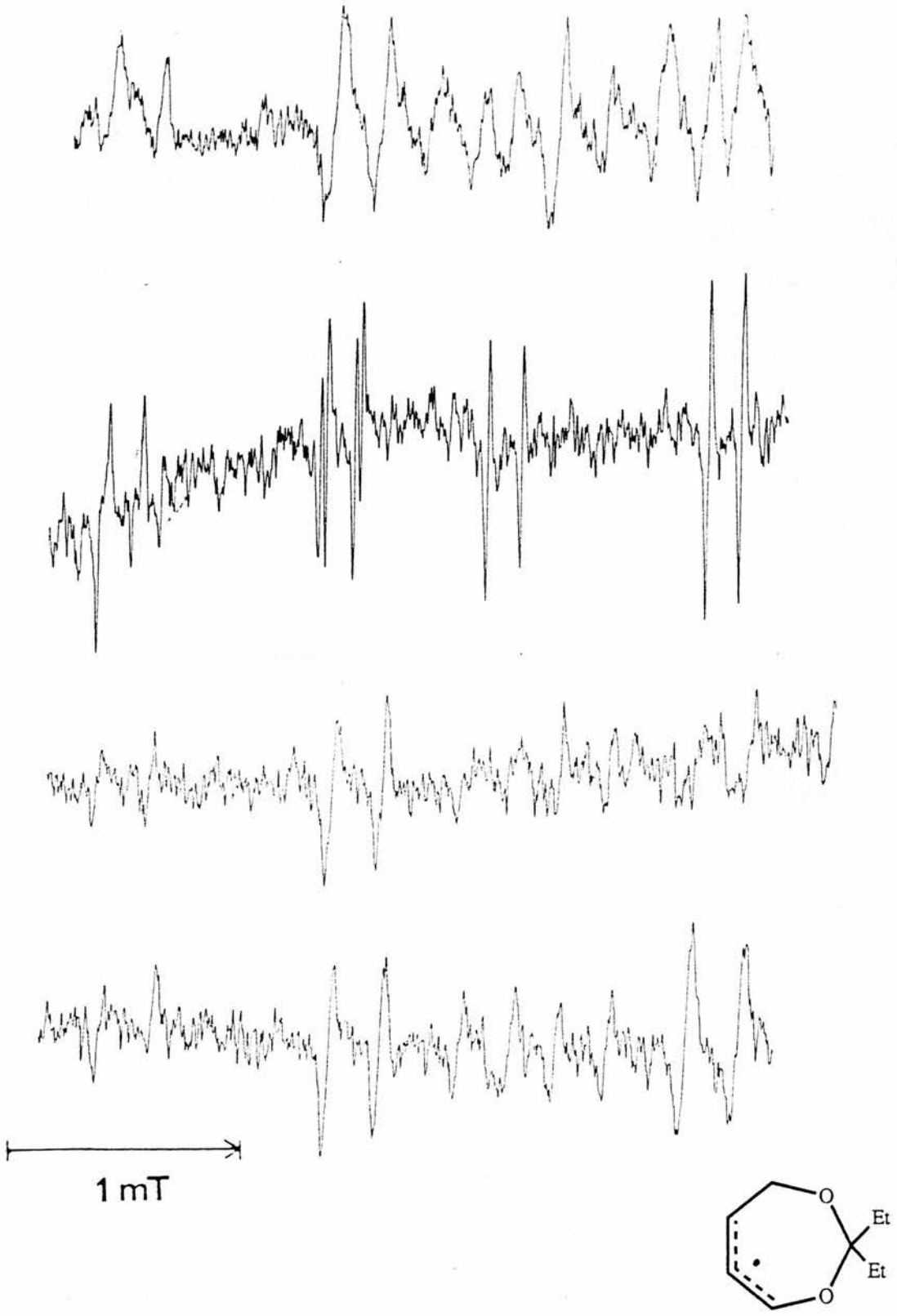


Fig. 12. 9.2 GHz 1 / 2 field EPR spectra of 2,2-diethyl-4,7-dihydro-1,3-dioxepin (allyl radicals) in t-butylbenzene at, from the top, 200 K, 225 K, 270K and 300 K.

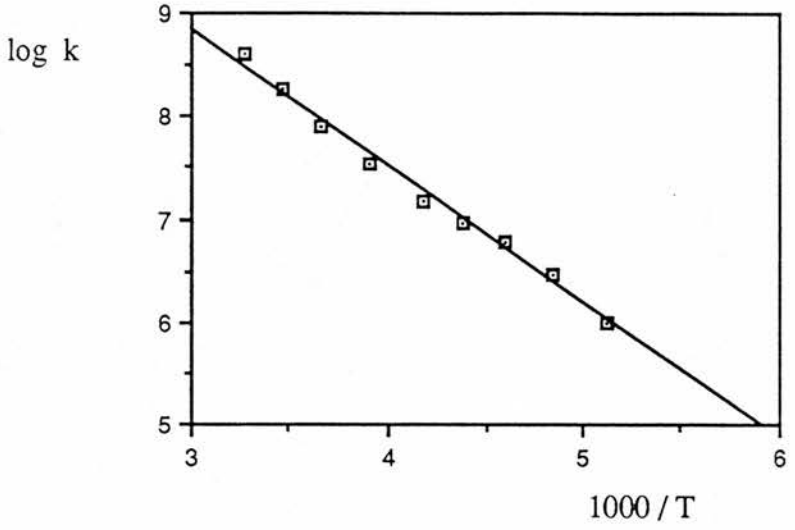
The experimental spectra were computer simulated in order to obtain the best fit rate constants (see Table 11)

T / K	Final k / s^{-1}	10^3 / T	log k
195	1.0×10^6	5.128	6.000
206	3.0×10^6	4.854	6.477
217	6.0×10^6	4.608	6.778
228	9.0×10^6	4.386	6.954
239	1.5×10^7	4.184	7.176
256	3.5×10^7	3.906	7.544
273	8.0×10^7	3.663	7.903
289	1.8×10^8	3.460	8.225
306	4.0×10^8	3.268	8.602

Table 11

T / K = corrected dial temperature for EPR cavity

In order to obtain the activation energy for ring flipping (ring inversion), an Arrhenius plot of log k vs 1000 / T was made.



The regression equation obtained was :-

$$\log k = 12.8 \pm 1.33\ (1000)/T$$

predictor	coeff	st-dev	t-ratio	P
constant	12.8207	0.2009	63.81	0.000
103 / T	-1.32677	0.04778	-27.77	0.000

s = 0.08637 R-sq = 99.1% R-sq (adj) = 99.0%

Hence $\log A / s^{-1} = 12.8 \pm 0.2$

and $E / 2.3R = 1.33 \pm 0.05$ $R = 1.9872$ cal K^{-1} mol^{-1}

$Ea = 6.1 \pm 0.3$ kcal mol^{-1} (R = R' = Et)

Similarly the 2,2-dimethyl derivative was photolysed in the cavity of the EPR spectrometer over the temperature range 150-360 K, in t-butyl benzene or cyclopropane as a solvent, with di - tert butyl peroxide. The experimental spectrum and computer simulation at 150 K are shown in Fig 13.

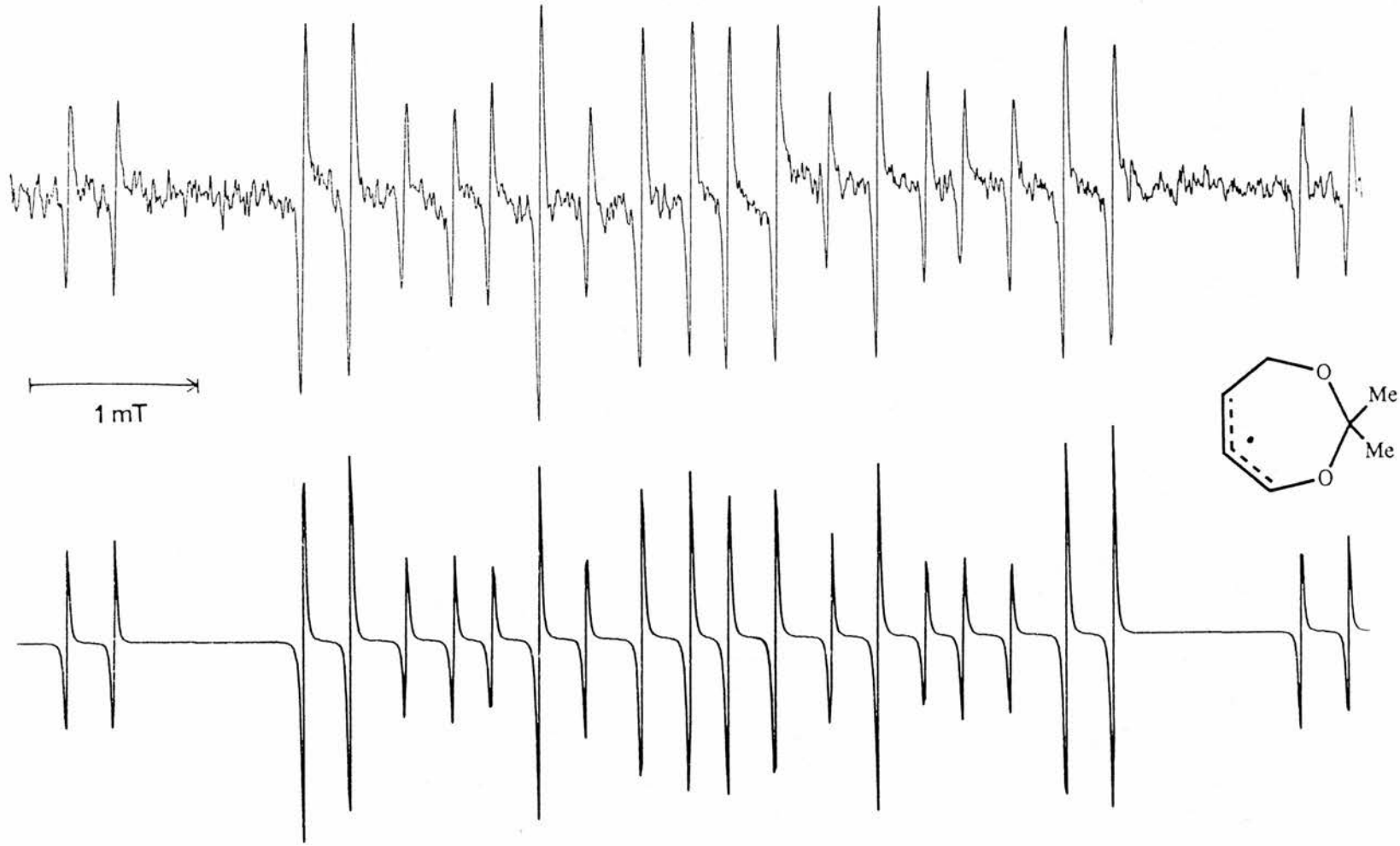


Fig. 13. 9.2 GHz EPR spectrum of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin (allyl radical) in t-butylbenzene . Upper trace, experimental spectrum at 150 K; lower trace computer simulation with a(1H) = 2.8 G, a(2H) = 13.9 G, a(1H) = 20.0 G and a(1H) = 25.05 G.

The exchange broadening process was again observed and the 9.2 GHz, half-field EPR spectra of 2,2-dimethyl dioxepin at 210 K, 255 K and 320 K are shown in Fig 14.

Again the experimental EPR spectra were computer simulated to obtain the best fit rate constants for ring inversion (Table 12).

T / K	Final k / s^{-1}	10^3 / T	log k
206	6.0 x 10^5	4.85	5.78
226	2.0 x 10^6	4.42	6.30
234	4.0 x 10^6	4.27	6.60
256	2.0 x 10^7	3.91	7.30
295	2.0 x 10^8	3.39	8.30
312	4.5 x 10^8	3.21	8.65
328	8.0 x 10^8	3.05	8.90
351	1.2 x 10^9	2.85	9.08
373	6.0 x 10^9	2.68	9.78

Table 12

T / K = corrected dial temperature for EPR cavity.

An Arrhenius plot of log k vs 1000 / T was made in order to calculate the activation energy for ring inversion.

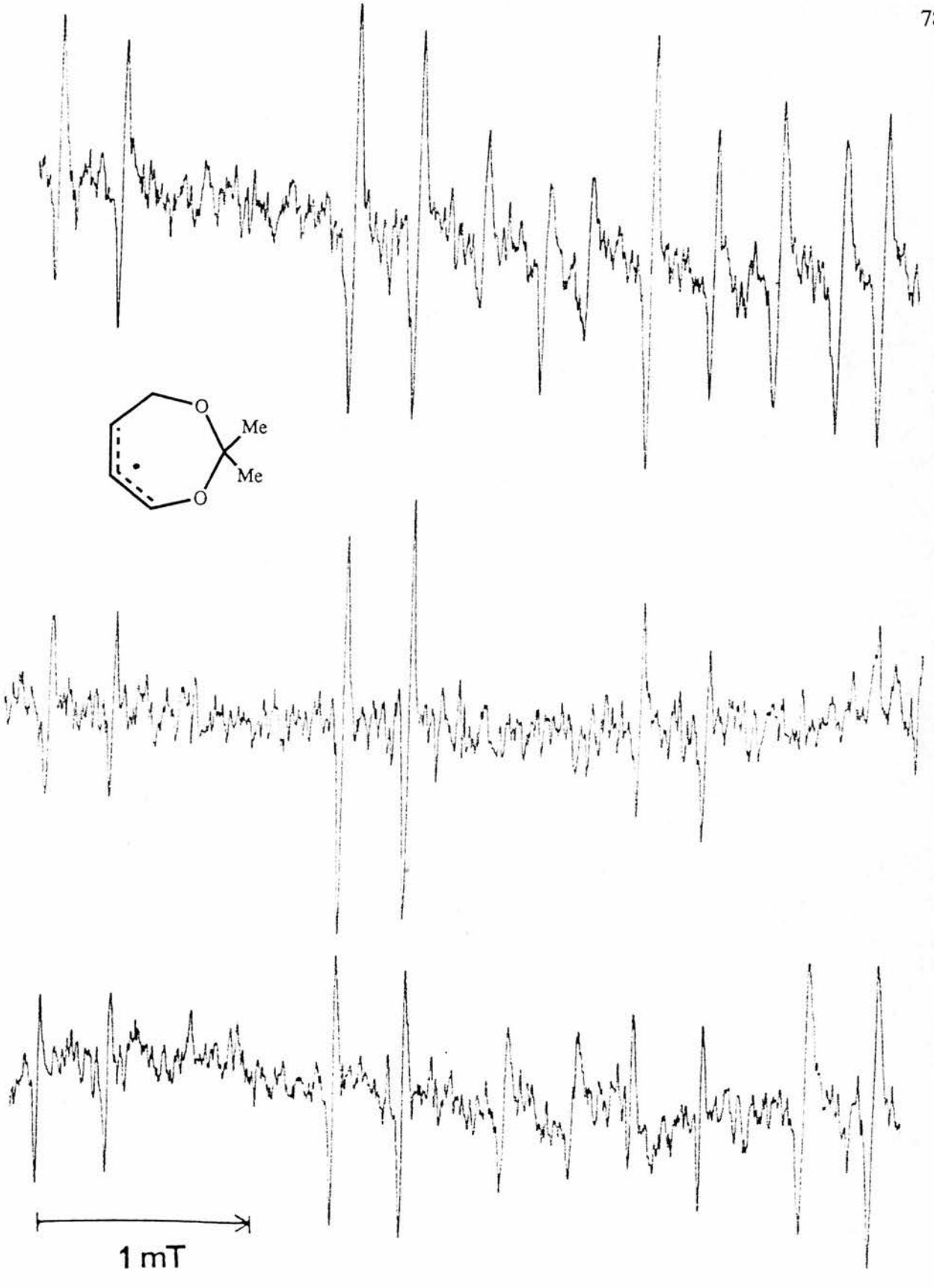
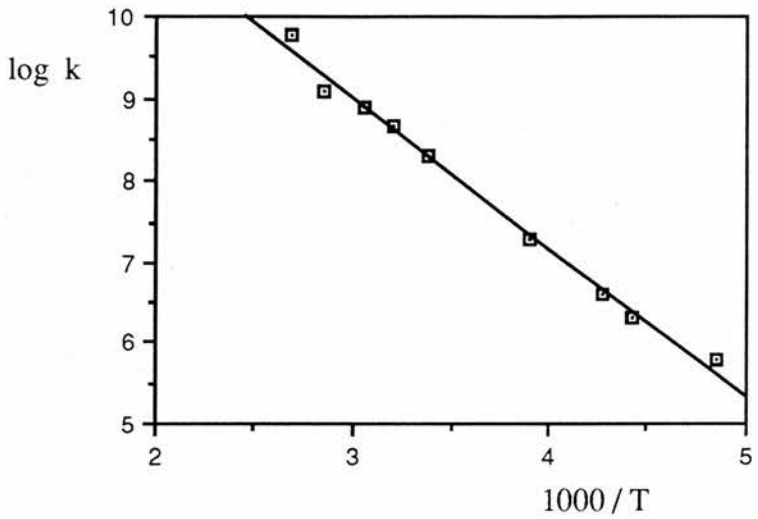


Fig. 14. 9.2 GHz 1 / 2 field EPR spectra of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin (allyl radicals) in t-butylbenzene, at, from the top, 210 K, 255 K and 320 K.



The regression equation obtained was :-

$\log k = 14.235 - 1.77\ (1000)\ /\ T$

($r^2 = 99.4\%$)

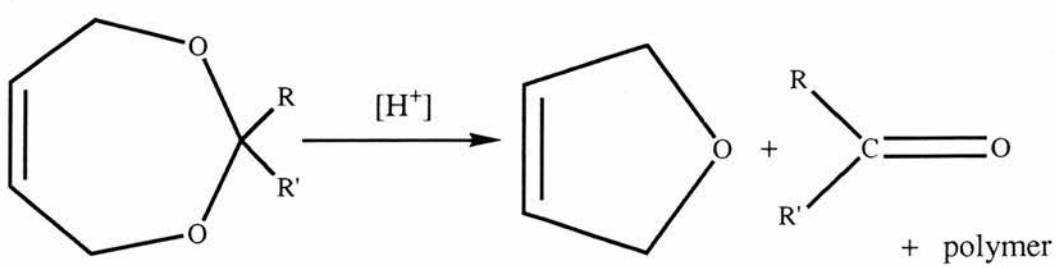
Hence $\log A / s^{-1} = 14.2$

and $E / 2.3R = 1.77$ $\quad R = 1.9872$ cal K^{-1} mol^{-1}

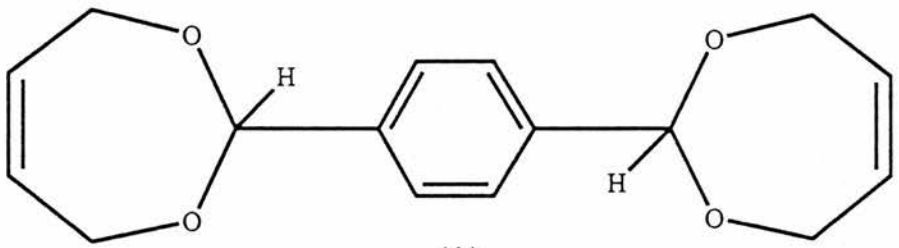
$E_a = 8.1$ kcalmol^{-1} (R = R' = Me)

Discussion and Conclusions

4,7-Dihydro-1,3-dioxepins are very useful compounds synthetically. They are stable to alkaline conditions, but acids cause the formation of 2,5-dihydrofuran, a carbonyl compound and some polymer.

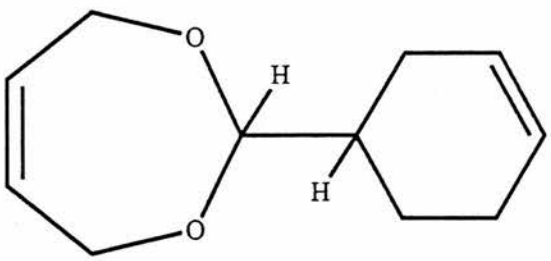


The dioxepins are also quite stable to heat,[84] for example 2-isopropyl-4,7-dihydro-1,3-dioxepin has been found to be unchanged when heated to 400°C over pumice. The two main uses of 1,3-dioxepins are in polymerisation reactions, and in the production of pesticides. They can be also used for breaking down emulsions of crude petroleum and aqueous liquids. Bis (1.3-dioxepins) such as (i)



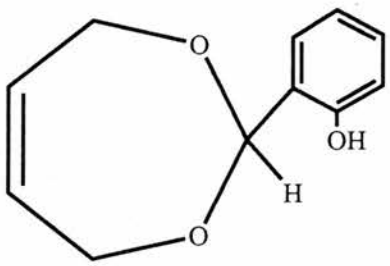
(i)

are useful as chain transfer agents[85] during the polymerisation of vinyl monomers. Several dioxepins such as 2-(cyclohexen-1-yl)-4,7-dihydro-1,3-dioxepins (ii),

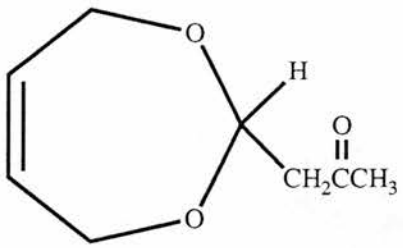


(ii)

spiro derivatives, x-(4,7-dihydro-1,3-dioxepin-2-yl) phenols (iii), keto substituted 1,3-dioxepins (iv),

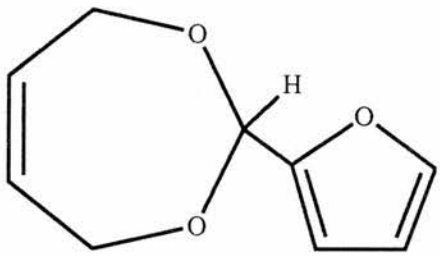


(iii)



(iv)

2-furyl (v) and 2-pyranyl dioxepins,



(v)

can all be copolymerised with butadiene, or other dienes to give latex polymers and vinyl rubber products, [86] often with improved tensile, soft, lubricant or elastic properties. Dioxepins have also been used as herbicides and paraciticides for the control of insects, worms, ticks and bacterial or fungal organisms. It can be seen that the 1,3-dioxepin class of compounds are important for study in their own right.

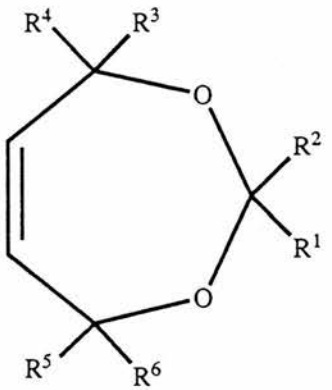
We have been able to observe a series of allyl radicals produced by hydrogen abstraction from either the C(4) or C(7) positions, and measure the hfs. It was then possible to use the EPR spectra computer simulations to obtain the rate of ring inversion at various temperatures, and hence calculate the activation energy for the process of ring inversion. This type of approach provides an alternative to the low temperature NMR technique that has been used by previous workers. We have also used this EPR method to measure the activation energy for

$CH_2\cdot$ rotation, in a " rotor " type radical. The $CH_2\cdot$ group acts as a useful spin probe for the conformations populated by the molecule.

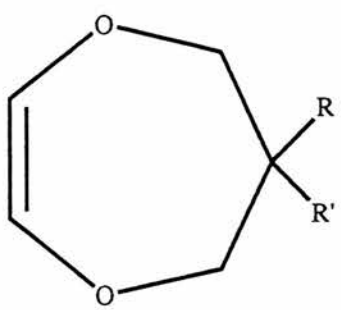
1-Phenyl-2,7-dioxabicyclo[3.2.1]octane has been successfully prepared. This class of bicyclic compounds are also of biochemical importance. The unsubstituted parent compound of the series has been used in the synthesis of insect poisons, and in the preparation of the pharmaceutical compound thromboxane. Substituted versions of these bicyclic compounds are obviously of interest from the point of view that different substituents can bring a number of changes to the properties of pharmaceuticals. The syntheses that we have described are attractive because they are relatively straightforward, and it is comparatively easy to introduce substituents at the bridgehead position.

The rate constants for the cyclisations of 2-bromomethyl-4,7-dihydro-1,3-dioxepin, 2-bromomethyl-2-methyl-4,7-dihydro-1,3-dioxepin and 2-bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin, have been found to be $k_{c(298)} = 10^3 - 10^4\ s^{-1}$ (estimate), $k_{c(298)} = 8.4 \times 10^5\ s^{-1}$, and $k_{c(298)} = 4.9 \times 10^5\ s^{-1}$ respectively. The cyclisation rate increases approximately 100 fold when a hydrogen at the two position is replaced by a methyl group. However replacement of the methyl group by a phenyl group, results in about the same cyclisation rate (within experimental error). So it seems that, although we thought that increasing the bulk of the 2-sustituent would increase the cyclisation rate, this does not in actual fact seem to be the case, as long as the substituent possesses more bulk than a hydrogen. It would also seem possible that there is an upper limit to the bulk of the 2-substituent which can be tolerated for cyclisation to occur. The reason for stating this is that we were unable to isolate any cyclised product when the 2-substituent was a naphthyl group. The molecule appeared to fragment back to a ketal.

There is plenty of scope for future workers investigating the reactions of 1,3-dioxepins with various substituents on the 4- and / or 7-positions.



It would be interesting to see what effects these substituents would have on the cyclisation reactions, and on the EPR spectra that would be obtained from these compounds. An alternative avenue of exploration would be to look at 1,4-dioxepins.



Very little has been done on these compounds, and they have the added advantage that there are no α–hydrogens to hinder cyclisation.

Experimental

^{1}H NMR spectra were recorded on a Varian EM - 360 NMR spectrometer (60 MHz), a Bruker AM 300 NMR spectrometer (300 MHz), and a Varian Gemini NMR spectrometer (200 MHz). ^{13}C NMR spectra were recorded using a Varian Gemini NMR spectrometer (50 MHz) or a Bruker AM300 NMR spectrometer (75 MHz), occasionally using DEPT - 135 pulse techniques to assign peaks where necessary. Samples were normally run in $CDCl_3$ using tetramethylsilane as an internal standard, the NMR data being expressed as shifts downfield from TMS in parts per million.

EPR spectra were recorded using a Bruker ER 200 D EPR Spectrometer, with photolysis from a 500W super-pressure Hg arc lamp. Samples were normally run in *tert*-butylbenzene and degassed by bubbling nitrogen through them for *ca.* 10 minutes. Some samples were run in cyclopropane using spectrosil tubes, and degassed by several freeze-pump-thaw cycles.

GC / MS were run on a Finnigan Incos 50 Quadrupole Mass Spectrometer, using a Hewlett-Packard HP5890 Gas Chromatograph. Preparative GLC experiments were carried out on a Pye-Unicam Series 105 Chromatograph, linked to a Pye Automatic Preparative Chromatograph.

GC analyses of the products for the determination of kinetic parameters were performed on a Philips Pye-Unicam PU 4500 Chromatograph, using a 3% OV101 column, linked up to a JJ Instruments CR 650A chart recorder, or a Spectra-Physics 4920 computing integrator.

Where distillations have been carried out using a Buchi Kugelrohr, the boiling temperatures are given as dial temperatures and are uncorrected. Melting points were determined using a Buchi melting point apparatus and

are also uncorrected. All starting materials were obtained commercially unless otherwise stated.

Phenacyl Bromide Dimethyl Acetal 2-bromoacetophenone (phenacyl bromide) (12.0g, 0.06mol) and trimethyl orthoformate (7.2g, 0.06mol) were mixed together in methanol (7.3ml, 0.18mol). 2 drops of ethanolic HCl were added and the mixture stirred at room temperature for *ca.* 24 hours. The solution was neutralised with potassium carbonate (tested with full-range pH paper), and then filtered. The methanol was removed under reduced pressure to leave the title compound as a green-brown solid. No further purification was undertaken (12.81g, 86.7%), m.p. 57-58°C. δ_H (60MHz) 3.0 (6H, s), 3.4 (2H, s), 7.0-7.4 (5H, m).

2-Bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin *cis*-2-Butene-1,4-diol (2.64g, 0.03mol), phenacyl bromide dimethyl acetal (7.3g, 0.03mol), toluene-4-sulphonic acid (0.28g, 1.5×10^{-3} mol, 5mol%) and methanol (40ml) were mixed together. The mixture was refluxed for 90 minutes and then the apparatus rearranged to allow the methanol to distil off over a period of 1 hour approx. The residual grey-green solid was obtained as the title 1,3-dioxepin, (4.61g, 57.1%), m.p. 59-60°C. δ_H (60MHz) 3.5 (2H, bs), 4.1 (4H, m), 5.55 (2H, m), 7.1-7.6 (5H, m). m/z (%) 106(8), 105(100), 91(19), 77(65), 65(12), 51(74), 50(36), 42(11) and 39(18).

1-Bromo-2-butanone A solution of 1-hydroxy-2-butanone (20.0g, 0.23mol) and pyridine (3.59g, 0.046mol (1/5 mol eq)) in ether (100ml) was cooled on an ice-salt bath. Phosphorus tribromide (24.58g, 1.092mol (2/5 mol eq)) was added dropwise, keeping the temperature at 0°C

approx. Upon completion of the addition, the mixture was stirred for a further 20 mins, and then ice-water was added (100ml). The ether layer was removed and the aqueous layer further extracted with ether (2 x 100ml). The combined extracts were washed with water (150ml), saturated $NaHCO_3$ (150ml), saturated NaCl (150ml) and then dried (Na_2SO_4). The solvent was evaporated to leave the crude product as a brown liquid (9.57g). The title compound was purified by distillation under reduced pressure to give a pale brown liquid (8.78g, 25.6%) b.p. 70-72°C / 20Torr (lit[87] 105°C / 150Torr). δ_H (60MHz) 0.8-1.2 (3H, t, J = 4Hz), 2.35 (2H, q, J = 6Hz), 3.8 (2H, bs).

1-Bromo-2-butanone Dimethyl Acetal 1-Bromo-2-butanone (2.0g, 0.01mol), trimethyl orthoformate (1.40g, 0.01mol) and methanol (0.32g, 0.03mol) were mixed together. 2 drops of ethanolic HCl were added and the mixture was stirred at room temperature under N_2 for *ca.* 18 hours. The excess methanol was removed by warming under reduced pressure, the residual liquid being distilled on a Buchi Kugelrohr to give the title acetal as a pale brown liquid (0.62g, 31.7%), b.p. 117-119°C / 20Torr . δ_H (60MHz) 1.6-1.9 (3H, t, J = 4Hz), 2.4 (6H, m), 3.5 (2H, bs), 4.2-4.6 (2H, q, J = 6Hz).

2-Bromo-pentan-3-one Pentan-3-one (15.0g, 0.174mol) and methanol (200ml) were mixed together and cooled (ice-salt bath). Bromine (13.92g, 0.174ml) was added dropwise to the stirred solution, keeping the temperature below 10°C. After the addition was complete, the mixture was stirred for a further *ca.* 1.5 hours. Water was added and the mixture was stirred at room temperature for 12 hours. Water was added (200ml)

and ether extracts were taken (5 x 100ml), the combined extracts were washed with 10% aqueous potassium carbonate (200ml), water (2 x 150ml), and dried ($CaCl_2$). The solvent was removed by flash evaporation to leave the crude product as an orange-brown liquid (5.94g). Distillation under reduced pressure on a Buchi Kugelrohr gave the title compound as a pale orange liquid (5.20g, 18.1%), bp. 117-120°C / 20Torr. δ_H (60MHz) 0.9-1.3 (3H, t, J = 7Hz), 1.7-1.85 (3H, d, J = 7Hz), 2.2-3.0 (2H, m), 4.2-4.6 (1H, q, J = 6Hz).

2-Bromo-pentan-3-one Dimethyl Acetal 2-Bromo-pentan-3-one (2.0g, 0.012mol), trimethyl orthoformate (1.29g, 0.012mol) and methanol (1.16g, 0.036mol)were mixed together. 2 drops of ethanolic HCl were added and the solution stirred at room temperature for *ca.* 24 hours. The excess methanol was removed on a rotary evaporator to leave the crude product as a brown liquid. This was distilled on a Buchi Kugelrohr to give the title acetal as a pale brown liquid (1.19g, 47.4%), b.p. 148-150°C / 20Torr . δ_H (60MHz) 1.0-1.3 (3H, t, J = 7Hz), 1.6-1.9 (3H, d, J = 7Hz), 2.2-3.0 (2H, m), 3.6 (6H, bs), 4.35-4.8 (1H, q, J = 8Hz).

1-Bromo-3-methyl-2-butanone 3-Methyl-2-butanone (methyl isopropyl ketone) (17.23g, 0.20mol) and methanol (200ml) were mixed together and cooled (ice-salt bath). Bromine (15.98g, 0.2mol) was added to the stirred solution, keeping the temperature below 10°C, and the mixture was stirred for a further *ca.* 1.5 hours (0-10°C). Water (100ml) was added (the colour changed from red to colourless) and the solution was stirred at room temperature for 12 hours. Water was added (200ml) and the mixture was extracted with ether (5 x 100ml), the combined ether extracts

were washed with aqueous 10% potassium carbonate (200ml), water (2 x 150ml), and dried ($CaCl_2$). The solvent was removed under reduced pressure to leave the crude product as an orange-brown liquid (15.28g). Further purification was achieved by distillation on a Buchi Kugelrohr, giving the title compound as a pale yellow liquid (13.98g, 42.3%), b.p. 110-113°C / 20Torr. δ_H (60MHz) 1.0-1.5 (6H, m), 1.8 (1H, m), 4.0 (2H, bs).

1-Bromo-3-methyl-2-butanone Dimethyl Acetal 1-Bromo-3-methyl-2-butanone (2.0g, 0.012mol), trimethyl orthoformate (1.29g, 0.012mol) and methanol (1.16g, 0,036mol, 3mol eq) were mixed together. 2 drops of ethanolic HCl were added and the mixture was stirred at room temperature. Initially the solution was pale yellow in colour but turned pale blue after 5 mins (approx). Potassium carbonate was added to neutralise the catalyst, once again causing the solution to turn pale yellow. Methanol (10ml) was added and the potassium carbonate was filtered off. The solvent methanol was removed under reduced pressure to leave a residual brown liquid, the ^1H NMR of which was inconsistent with the desired product.

2-Bromomethyl-2-naphthyl Dimethyl Acetal 2-Bromo-2-acetonaphthone (bromomethyl 2-naphthyl ketone) (5.0g, 0.02mol) and trimethyl orthoformate (2.13g, 0.02mol) were mixed together in methanol (2.44ml, 0.06mol). 2 drops of ethanolic HCl were added and the mixture was stirred at room temperature for *ca.* 19 hours. 2 further drops of ethanolic HCl were added, and the mixture stirred for a further 5 hours. The methanol was removed under reduced pressure (without neutralisation of the catalyst) to

leave the residue as the title compound (brown / dark green solid) (4.18g, 81.0%), m.p. 80-82°C. No further purification was undertaken. δ_H (60MHz) 3.2 (6H, s), 3.7 (2H, s), 7.3-8.1 (7H, m).

2-Bromomethyl-2-naphthyl-4,7-dihydro-1,3-dioxepin 2-Bromomethyl-2-naphthyl dimethyl acetal (5.21g, 0.018mol), *cis*-2-butene-1,4-diol (1.55g, 0.08mol) and toluene-4-sulphonic acid (0.17g, 9×10^{-4}mol, 5mol%) were mixed together and warmed up to 80°C on a water bath for *ca.* 1 hour. The methanol produced was removed under reduced pressure, during which time the dark brown solution turned pale brown in colour. The residual solid was purified by recrystallisation from petroleum ether (40:60) and ethyl acetate. The title dioxepin was obtained as a dark brown solid (0.64g, 11%), m.p. 86-87°C. δ_H (60MHz) 3.65 (2H, s), 4.1-4.2 (4H, bs), 5.5-5.6 (2H, bs), 7.2-8.0 (7H, m).

Reduction of 2-Bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin with Tributyltin Hydride (to form 1-phenyl-2,7-dioxabicyclo[3.2.1]octane) 2-Bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin (1.0g, 37mmol) was placed in a pyrex tube, degassed by bubbling nitrogen, heated to 130°C and irradiated with light from a 250W medium pressure Hg arc, while Bu_3SnH (1.08g, 37mmol) was added over 10 minutes. Photolysis was continued for a further 2 hours. The reaction mixture was extracted with 10ml of ether. The ether extract was washed with 5ml of dilute KF solution, dried (Na_2SO_4), and evaporated. The residual liquid (2.4g) was put onto a 15 x 2 cm column of neutral alumina eluted with 100ml of 5% ether in petroleum ether, 100ml of 10% ether in petroleum ether, and 100ml of 50% ether in petroleum ether. Two major components were

separated. The first component eluted in the second fraction was 2-methyl-2-phenyl-4,7-dihydro-1,3-dioxepin (35 mol%), m.p. 49-50°C, (lit[44] b.p 104°C / 2Torr); δ_H (300MHz) 1.58 (1H, s), 4.20 (4H, m), 5.61 (2H, t, J = 2Hz), 7.28 (3H, m), 7.55 (2H, m); δ_C (75MHz) 26.20 (2C), 62.13 (2C), 103.60 (1C), 125.89 (2C), 127.58 (1C), 128.01 (2C), 129.42 (1C) , 143.31 (2C). The second component, eluted in the third fraction was 1-phenyl-2,7-dioxabicyclo[3.2.1]octane (65 mol%), m.p. 52-53°C; δ_H (300MHz) 1.5-1.7 (2H, m), 1.9-2.1 (2H, m), 2.73 (1H, bs), 3.9-4.25 (4H, m), 7.3 (3H, m), 7.55 (2H, m); δ_C (75MHz) 29.65 (1C), 34.71 (1C), 44.13 (1C), 60.86 (1C), 73.49 (1C), 106.01 (1C), 125.46 (1C), 128.05 (2C), 128.12 (1C), 128.64 (1C).

Kinetics of the Tributyltin Hydride Reduction of 2-Bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin 2-Bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin (50mg, 1.87 x 10^{-4}mol), *tert*-butylbenzene (0.25ml) and hexadecane (10µl, as an internal standard) were heated to the desired temperature (in the range 25-150°C) and degassed by bubbling nitrogen for *ca.* 10 minutes. Bu_3SnH (50µl, 1.87 x 10^{-4}mol) was added to the solutions which were irradiated with light from a 250 W medium pressure Hg arc for a further 2 hours. The solutions were analysed by g.l.c. and the values of k_c / k_H were obtained at each temperature from the initial Bu_3SnH concentration and the final product concentrations, using the k_H values of Ingold *et al.*[20] Hence the value of k_c at each temperature was established

Attempted Preparation of 1-Phenyl-2,7-dioxabicyclo[3.2.1]octane

2-Bromomethyl-2-phenyl-4,7-dihydro-1,3-dioxepin (1.34g, 5mmol), triethylsilane (1.16g, 10mmol), dilauroyl peroxide (0.1g, 2.5 x 10-4 mol, 5mol%), dodecane thiol (0.02g, 10-4 mol, 2mol%) and cyclohexane (ml) were mixed together and heated at reflux under N_2 for *ca.* 1 hour. The mixture was then allowed to cool and diluted with a further 50ml of cyclohexane and washed successively with water (100ml), 6M NaOH (100ml) and water again (100ml) and dried ($MgSO_4$). After filtration and removal of the solvent under reduced pressure, the crude product appeared as a green / yellow solid (0.66g). This was found to be the unchanged starting bromide.

The same result was obtained using 10mol% dilauroyl peroxide and heating the mixture at reflux for *ca.* 6 hours.

Hydrolysis of 1-Phenyl-2,7-dioxabicyclo[3.2.1]octane (57)

(16.3mg, 85µmol) of the octane (**57**) was mixed with 5ml of 3.5% aqueous HCl and refluxed for 1 hour. The solution was neutralised with aqueous $NaHCO_3$ and evaporated. The residue was extracted with ether (20ml), which was dried and evaporated to leave an off-white solid residue (12mg, 70%) identified as 5-hydroxy-3-(hydroxymethyl)-1-phenyl-pentan-1-one. δ_H (300MHz) 2.15-2.25 (2H, m), 2.77-2.90 (1H, m), 3.05-3.2 (2H, m), 3.46 (2H, dd), 4.05 (2H, dd), 7.3-7.6 (3H, m), 7.9-8.0 (2H, m); δ_C(75MHz) 30.1 (CH), 32.1 (CH_2), 47.4 (CH_2), 67.6 (CH_2), 70.3 (CH_2), 125.5 (2C), 128.0 (2C), 128.2 (1C), 128.6 (1C), 207.6 (CO).

Benzophenone Dimethyl Ketal (Dimethoxydiphenylmethane)

Benzophenone (15.0g, 0.08mol), trimethyl orthoformate (8.73g, 0.01mol) and methanol (7.91g, 0.24mol) were mixed together. Two drops of ethanolic HCl were added and the mixture was stirred at room

temperature for *ca.* 24 hours. The excess methanol was removed under reduced pressure (without neutralisation of the catalyst) to leave the crude ketal as an off-white solid. This was purified by low temperature recrystallisation (ice-water bath) from petroleum ether (40:60) and ethyl acetate. The title ketal was obtained as a very light brown solid (16.73g, 89%), m.p. 102-104°C (lit[88] m.p. 97-99.5°C). δ_H (60MHz) 3.05 (6H, s), 7.1-7.9 (10H, m).

2,2-Diphenyl-4,7-dihydro-1,3-dioxepin *cis*-2-Butene-1,4-diol (5.45g, 0.06mol), benzophenone dimethyl ketal (14.12g, 0.06mol) and toluene-4-sulphonic acid (0.58g, 3 x 10^{-3}mol, 5mol%) were mixed together. Methanol (40ml) was added and the mixture was refluxed for 1 hour. The methanol was then allowed to distil off during a further 1 hour (approx) to leave the title compound as a faint yellow liquid (3.04g, 20.1%), b.p. 205°C / 22Torr (lit[89] 157°C / 1.2Torr). Further purification was achieved by preparative t.l.c. using a solvent mixture of 10% ether in petroleum ether (40:60), to get the compound sufficiently pure to allow EPR work to be carried out on it. δ_H (60MHz) 4.15-4.30 (4H, m), 5.6-5.8 (2H, m), 7.0-7.8 (10H, m).

2-Methoxy-2-methyl-4,7-dihydro-1,3-dioxepin *cis*-2-Butene-1,4-diol (15.0g, 0.17mol) and trimethyl orthoacetate (20.4g, 0.17mol) were mixed together with toluene-4-sulphonic acid (p-toluene sulphonic acid) (1.6g, 5mol%). The mixture was warmed to 40°C for 0.5 hour. The methanol produced and excess trimethyl orthoacetate were removed by flash evaporation and the residual liquid was distilled to give the 2,2-disubstituted title dioxepin as a colourless liquid (3.12g, 13%), bp. 80°C

/ 20Torr (lit[89] 44°C / 2.8Torr). δ_H (60MHz) 2.1 (3H, s), 3.35 3H, s), 4.65 (4H, m), and 5.8-6.0 (2H, m).

4,7-Dihydro-1,3-dioxepin *cis*-2-Butene-1,4-diol (20.0g, 0.23mol) and dimethoxymethane (17.3g, 0.23mol) were mixed with toluene-4-sulphonic acid (2.15g, 5mol%). The mixture was warmed to *ca.* 45°C for 0.5 hour. Methanol and unreacted dimethoxymethane were distilled out and the residue was purified by distillation to give the title dioxepin as a clear liquid (5.69g, 22.4%), b.p. 74°C / 20Torr (lit[89] bp. 126°C / 760torr) δ_H (300MHz) 4.3 (4H, m), 4.85 (2H, s), and 5.75 (2H, t, J = 1Hz); δ_C (75MHz) 16.6 (2C), 45.9 (1C), and 79.6 (2C).

Pentan-3-one Dimethyl Acetal (3,3-Dimethoxypentane) Pentan-3-one (4.0g, 0.046mol), trimethyl orthoformate (4.93g, 5.0ml, 0.046mol) and methanol (5.64ml, 0.138mol) were mixed together and 2 drops of ethanolic HCl were added. The mixture was stirred at room temperature for ca. 0.5 hour. The solution was then neutralised with potassium carbonate (tested with full-range pH paper), and then filtered. The methanol was evaporated under reduced pressure and the residual liquid purified by distillation, to give the title acetal as a colourless liquid (2.12g, 34.5%), bp. 127°C / 760Torr. δ_H (60MHz) 1.8 (6H, t, J = 7Hz), 1.4-1.85 (4H, q, J = 8Hz), 3.1 (6H, bs).

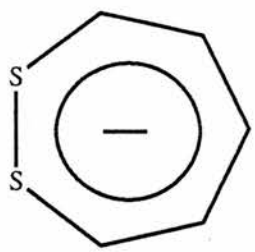
2,2-Diethyl-4,7-dihydro-1,3-dioxepin *cis*-2-Butene-1,4-diol (6.67g, 0.08mol) and pentan-3-one dimethyl acetal (3,3-dimeyhoxypentane (10.0g, 0.08mol) were mixed with toluene-4-sulphonic acid (0.72g, 5mol%). The

mixture was warmed to *ca.* 60°C for 0.5 hour and the excess methanol formed was distilled off. The residual liquid was distilled to yield 2,2-diethyl-4,7-dihydro-1,3-dioxepin as a colourless liquid (4.87g, 41%), bp. 86°C / 12Torr (lit[89] 108°C / 57Torr). δ_H (300MHz) 0.7 (6H, t, J = 6Hz), 1.7 (4H, q, J = 6Hz), 4.2 (4H, m), and 5.65 (2H, m); δ_C (75MHz) 8.1 (2C), 24.3 (2C), 60.9 (2C), 101.1 (1C), and 129.7 (2C).

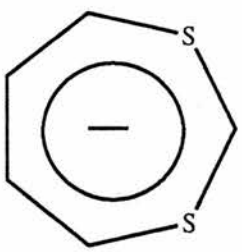
2,2-Dimethyl-4,7-dihydro-1,3-dioxepin *cis*-2-Butene-1,4-diol (15.2g, 0.17mol) and 2,2-dimethoxypropane (18.0g, 0.17mol) were mixed with toluene-4-sulphonic acid (1.64g, 5mol%). The mixture was warmed to *ca.* 50°C for 1 hour. Methanol and excess 2,2-dimethoxypropane were removed by distillation. The residue was purified by distillation on a Buchi Kugelrohr to give the title compound as a very pale yellow liquid (7.37g, 33.0%), bp. 90°C / 24Torr (lit[89] 41°C / 6Torr) δ_H (60MHz) 1.3-1.5 (6H, bs), 4.2 (4H, m), and 5.6 (2H, m)

CHAPTER TWO
1,3-Dithiepins

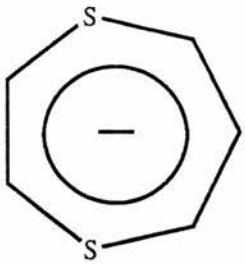
There are three possible arrangements of two sulphur atoms in a seven-membered ring, these being 1,2-, 1,3- , and 1,4-, and they are analogous to those described for the dioxepins. The sulphur atom is isoteric with a carbon-carbon double bond[90] and can participate in resonance delocalisation.[91] Hence, anions with two double bonds in the seven-membered ring are analogous to the cyclononatetraenide anion, which is a stable delocalised system.[92]



(**61**)



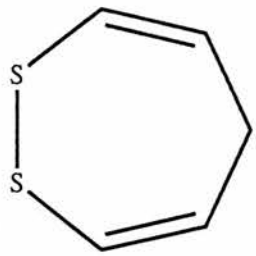
(**62**)



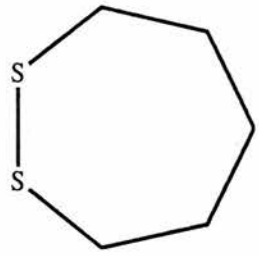
(**63**)

Molecular orbital calculations, using the Huckel approximation of the LCAO method[93] suggested however that all three of the anions (**61**), (**62**) , and (**63**) would be unstable and difficult to synthesize.

1,2-Dithiepins

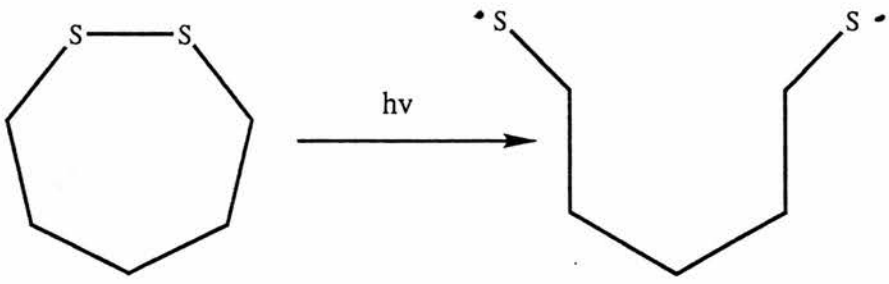


(**64**)



(**65**)

Compound (**64**), 5H-1,2-dithiepin, which has also been called 1,2-dithia-3,6-cycloheptadiene, has not been synthesized, although the literature does make reference to the isomeric product, 3H-1,2-dithiepin. 1,2-dithiepane (**65**), the fully reduced form of (**64**), also known as 1,2-dithiacycloheptene or pentamethylene disulphide has been prepared as a colourless, water-insoluble liquid, stable over a period of several months. Interestingly, 1,2-dithiepane gives thiyl radicals[94] (**66**) when photolysed with unfiltered UV light.



(**66**)

1,4-Dithiepins

(**67**)

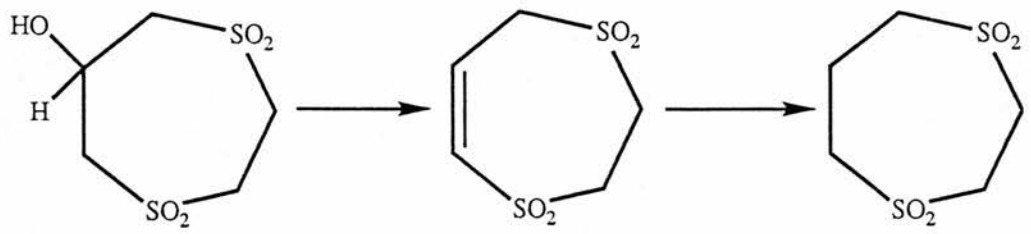
The parent compound of the series is 5H-1,4-dithiepin (**67**), but no monocyclic structures containing this 1,4-dithiepin ring are known.[95]

Dihydro-1,4-Dithiepins

(**68**)

(**69**)

The two possible structures of dihydro-1,4-dithiepins are 2,3-dihydro-5H-1,4-dithiepin (**68**), and 6,7-dihydro-5H-1,4-dithiepin (**69**), although neither of these compounds are known to exist. One monocyclic 2,3-dihydro derivative has been prepared by dehydration of 6-hydroxy-1,4-dithiepane 1,1,4,4-tetraoxide (**70**), (equation 20).



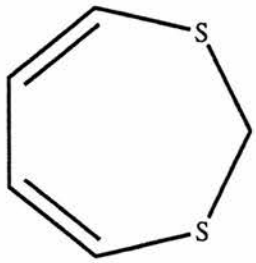
(**70**) (**71**) (**72**)

Equation 20

The product of the reaction, namely, 2,3-dihydro-5H-1,4-dithiepin 1,1,4,4-tetraoxide (**71**) was formed in 74% yield and its structure was conformed by reaction with aqueous potassium permanganate and by hydrogenation to the already known saturated disulphone[96] (**72**).

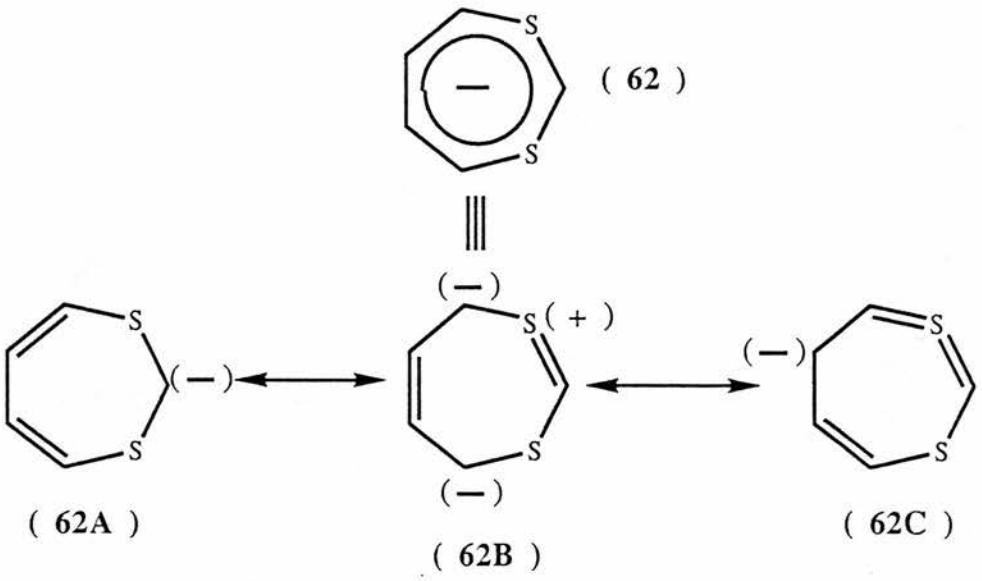
1,3-Dithiepins

No monocyclic compounds containing two double bonds in the 1,3-dithiepin ring are known (**73**).



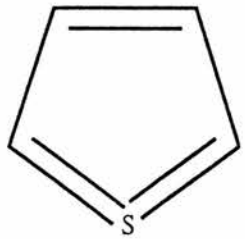
(**73**)

The anion derived from (**73**) (i.e. structure (**62**)) has the potential to be an aromatic substance, and from that point of view it is of theoretical interest. Three possible valence bond structures are indicated in scheme 17.



Scheme 17

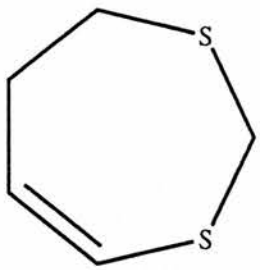
The 1,3-dithiepinide anion (**62**) is analogous to the cyclononatetraenide anion, and it contains ten π-electrons which satisfies Huckel's (4n + 2) rule for aromaticity. The valence bond structures of the 1,3-dithiepinide anion represented as only involving p-orbitals are thought to contribute only a small amount in the description of the anion, because of charge separation factors. Representation (**62c**) can be considered as a contributing structure, because the sulphur atoms can use both an electron-donating p-orbital and an electron-accepting d-orbital. In this case, d-orbital participation can stabilise the structure and increase aromatic character, provided that planarity can be achieved without causing excess steric strain.[97] Structure (**74**)



(**74**)

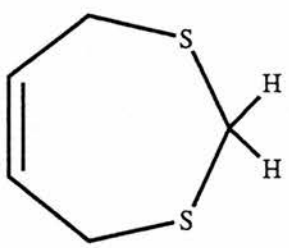
which has been employed to explain the aromaticity of thiophene,[98,91] is analogous to the canonical form (**62c**) of the 1,3-dithiepinide anion.

Dihydro-1,3-dithiepins

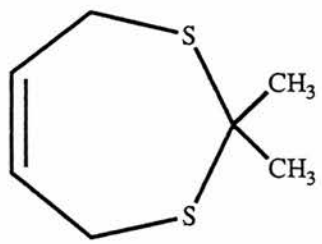


(**75**)

The 4,5-dihydro-1,3-dithiepin ring (**75**) is not known to exist. Friebolin et al. have synthesized 4,7-dihydro-1,3-dithiepin (**76**) and 2,2-dimethyl-4,7-dihydro-1,3-dithiepin (**77**) and investigated them using low temperature NMR techniques.[99]

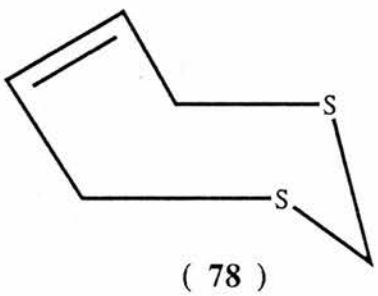


(**76**)

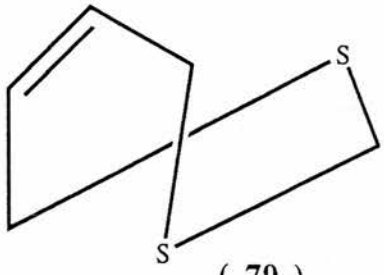


(**77**)

The low temperature NMR spectra of both (**76**) and (**77**), suggest that the preferred conformation of the 4,7-dihydro-1,3-dithiepin ring is the chair form (**78**), as opposed to the twist boat arrangement (**79**).



(**78**)
chair

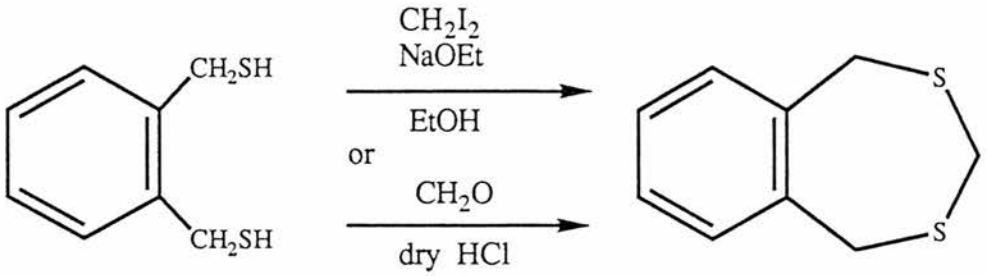


(**79**)
twist-boat

In the twist-boat form, substituents on C(2) occupy essentially equivalent positions. However in the chair form they can either be quasi-axial or quasi-equatorial. The separation of the chemical shifts of the AB doublet of doublets of the protons for (**76**), and the singlets corresponding to the non-equivalent methyl substituents of 2,2-dimethyl-4,7-dihydro-1,3-dithiepin (**77**) at the coalescence temperature, make it possible to calculate the activation energy for chair interconversion for these compounds. These were found to be 8.5 kcal mol^{-1} for 4,7-dihydro-1,3-dithiepin and 8.2 kcal mol^{-1} for 2,2-dimethyl-4,7-dihydro-1,3-dithiepin.[99]

Benzodithiepins

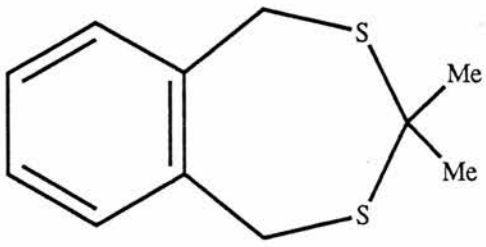
The compound in the series that has received most attention is 1,5-dihydro-3H-2,4-benzodithiepin (**81**).



(**80**) (**81**)

Scheme 17

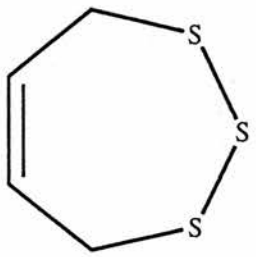
Scheme 17 outlines two methods that have been employed to synthesize 1,5-dihydro-3H-2,4-benzodithiepin. The compound was initially isolated by Kotz[100] in 1900 by reaction of the dithiol (**80**) with methylene iodide and sodium ethoxide in ethanol. A more general method was developed by Autenreith and Hennings[101,102] in which the dithiol (**80**) was mixed with a carbonyl compound, in the presence of dry HCl. The introduction of this fused benzene ring increases the barrier to ring inversion to 10.2 kcal mol^{-1} for 1,5-dihydro-3H-2,4-benzodithiepin (**81**),[99] as compared with 8.2 kcal mol^{-1} for 4,7-dihydrodithiepin (**78**). Variable temperature NMR studies on both 1,5-dihydro-3H-2,4-benzodithiepin (**81**) and its 3,3-dimethyl derivative (**82**),[99]



(**82**)

indicated that both compounds had a preference for the chair conformation.[99] The energy of activation for (**82**), the dimethyl substituted compound was found to be 12.1 kcal mol^{-1}.

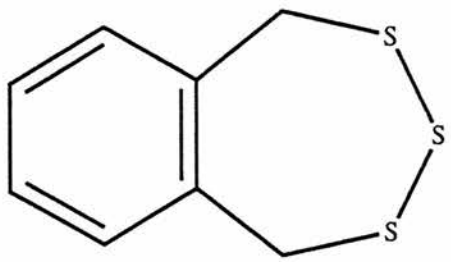
When the C(2) carbon on 4,7-dihydro-1,3-dithiepin is replaced by a sulphur atom to produce 4,7-dihydro-1,2,3-trithiepin (**83**), an increased barrier for ring inversion is observed. This was calculated to be 8.9 kcal mol^{-1}.



(**83**)

This is attributed to an increase in rigidity, or stiffening of the ring brought about by the addition of the third sulphur atom.[103]

Introduction of a fused benzene ring at the C(5) and C(6) position of the trithiepin (**83**), results in a particularly high activation energy for ring inversion of 17.4 kcal mol^{-1} for the benzo dihydro trithiepin (**84**).



(**84**)

Table 13. summarises the activation energies for ring inversion for the compounds discussed

Compound	Activation Energy $\Delta G^{\neq}$ / kcal mol^{-1}	Ref
(**76**) 4,7-dihydro-1,3-dithiepin	8.5	99
(**77**) 2,2-dimethyl-4,7-dihydro-1,3-dithiepin	8.2	99
(**81**) 1,5-dihydro-3H-2,4-benzodithiepin	10.2	99
(**82**) 3,3-dimethyl-1,5-dihydro-2,4-benzodithiepin	12.1	99
(**83**) 4,7-dihydro-1,2,3-trithiepin	8.9	99
(**84**) 1,5-dihydro-2,3,4-benzotrithiepin	17.4	103,104

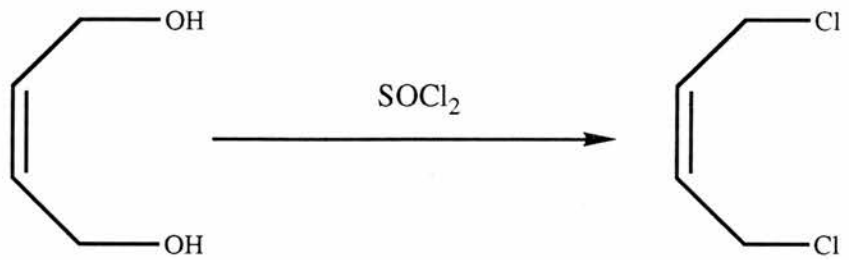
Table 13.

Methods of Preparation of 1,3-Dithiepins

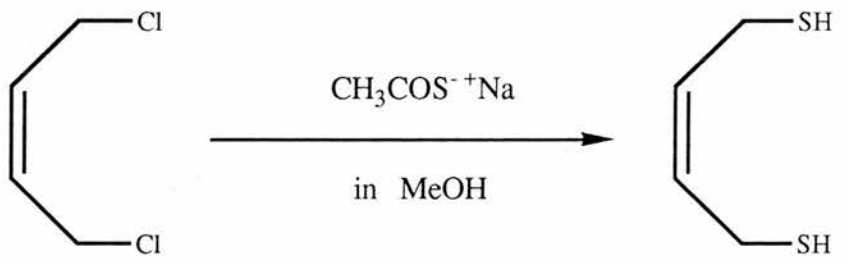
Only two 1,3-dithiepin derivatives have been synthesized previously, but their methods of preparation have never been published. It was envisaged that they could be prepared by methods analogous to those used to obtain 1,3-dioxepins. It was necessary to prepare cis-2-butene-1,4-dithiol, the sulphur analogue of cis-2-butene-1,4-diol. Several methods were attempted to produce the dithiol in acceptable yield and purity before a satisfactory method was obtained.

Synthesis of Cis-2-Butene-1,4-Dithiol

The first method attempted involved the conversion of cis-2-butene-1,4-diol to cis-1,4-dichloro-but-2-ene[105] by reaction with thionyl chloride.

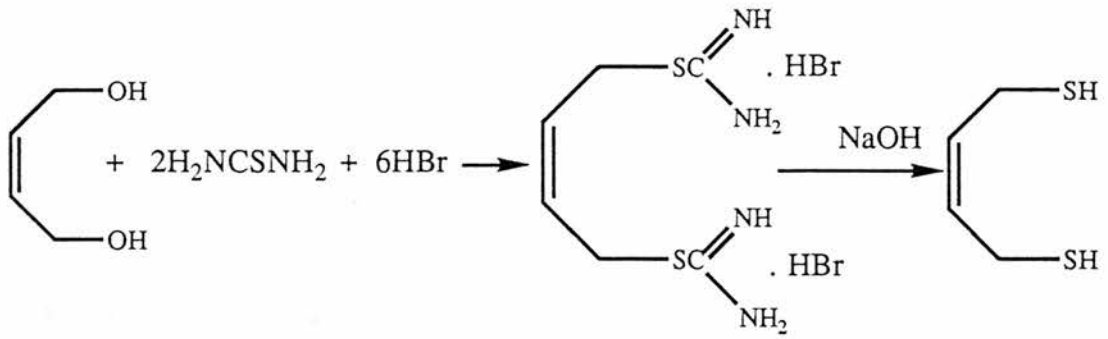


The reaction was carried out in pyridine as a solvent, and the reaction mixture was maintained as close to 0°C as possible during the addition of the thionyl chloride, to minimize the production of tarry residues. The *cis*-1,4-dichloro-but-2-ene so produced was purified by distillation, and then added to a solution of sodium thioacetate (prepared from thiolacetic acid and sodium) in methanol.[106]



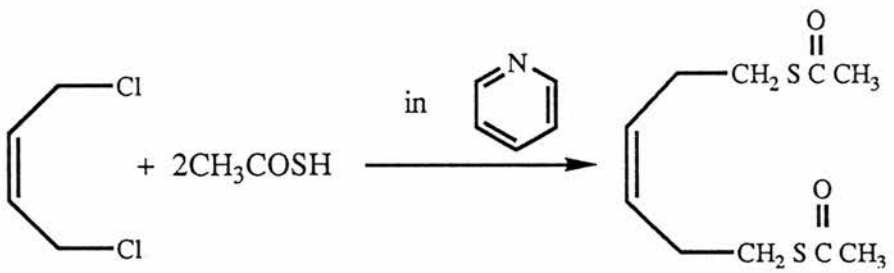
This method failed to produce the dithiol in good yield or purity. Various other solvents were used in place of methanol, such as benzene, toluene and dry ether, and the reaction time varied from a few hours to a few days, and although the dithiol was produced, the yields were extremely poor and the product was severely contaminated with by-products and almost impossible to purify.

A second method was attempted,[107] and this involved reacting *cis*-2-butene-1,4-diol with thiourea and hydrobromic acid

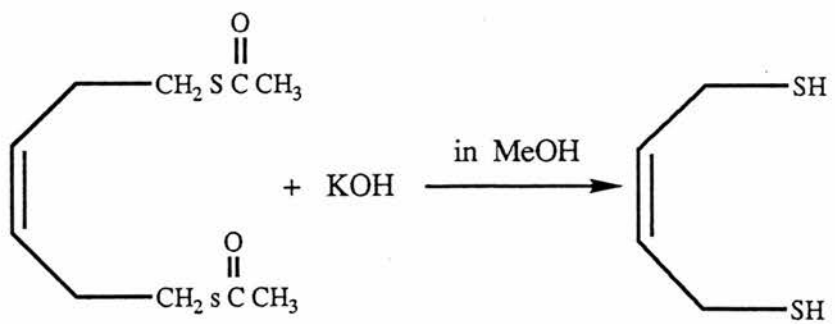


However this alternative method again did not produce a viable route to the dithiol. Increasing the length of time that the mixture was allowed to reflux did not have a significant effect on the poor yield of the dithiol or its quality.

A third and very much more successful method was implemented. Cis-1,4-dichloro-but-2-ene was mixed with thiolacetic acid, employing pyridine as a solvent and absorbent for the hydrogen chloride released. Good yields of cis-2-butene-1,4-dithiol diacetate were obtained.[108]

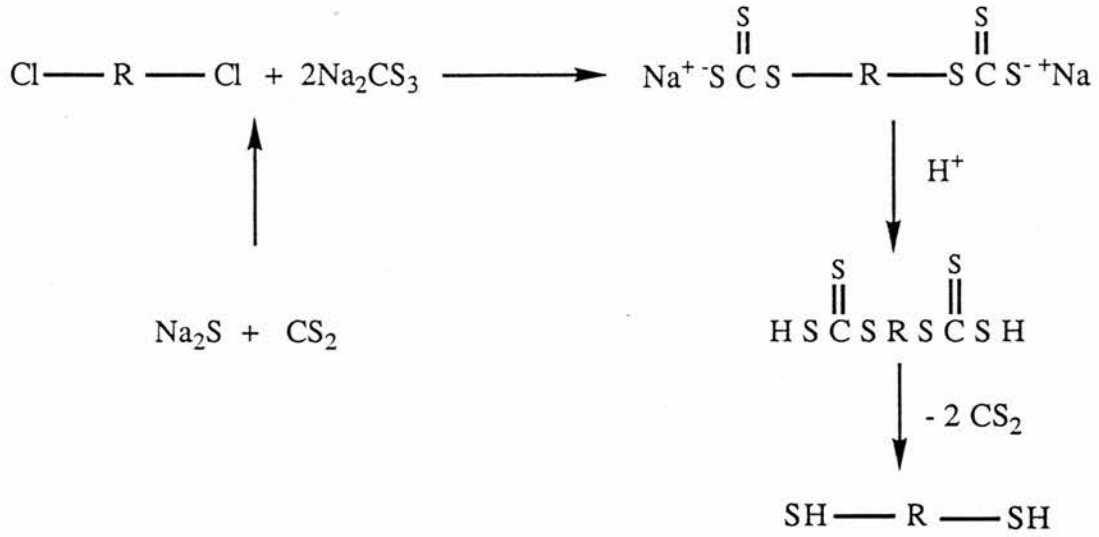


The cis-2-butene-1,4-dithiol diacetate was then converted to cis-2-butene-1,4-dithiol by reaction with potassium hydroxide in methanol.[108]

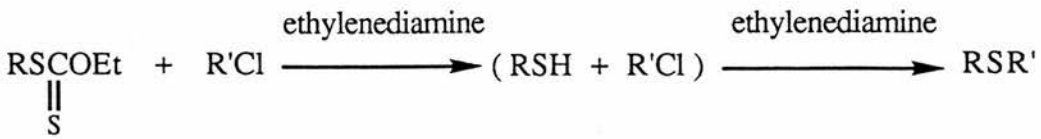


The dithiol obtained was in good yield and reasonable purity, and further purification was provided by distillation under reduced pressure, to produce a pale yellow foul-smelling liquid

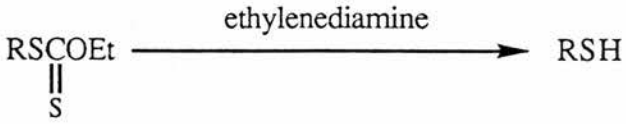
Two further methods have appeared in the literature that could probably have been used to synthesize the cis-2-butene-1,4-dithiol. The first method requires the preparation of sodium trithiocarbonate by reaction of sodium sulphide with carbon disulphide in water. This would then be mixed with cis-1,4-dichloro-but-2-ene, the product being washed with acid to recover carbon disulphide and yield the dithiol.[110]



The second possible method would be to produce the dithiol from a xanthogenic acid ester.[111]

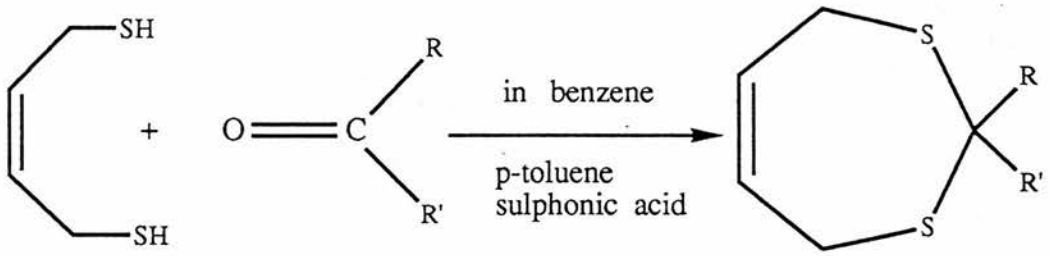


or more appropriately to produce a thiol :-



To form cis-2-butene-1,4-dithiol, the xanthogenic acid ester would be produced by mixing cis-1,4-dichloro-but-2-ene with potassium ethylxanthogenate in acetone. The diol would then be formed from the xanthogenic acid ester by reaction with ethylenediamine. The crude dithiol could then be purified by distillation under reduced pressure.

General Preparation of 1,3-Dithiepins

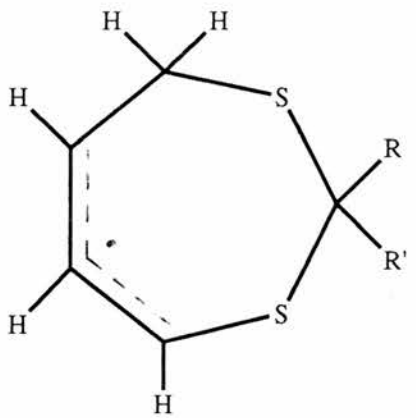


Cis-2- butene-1,4-dithiol is mixed with the appropriate carbonyl compound in benzene, together with a few milligrams of toluene-4-sulphonic acid as a catalyst. The mixture is heated under reflux for ca. 18 hours while the water formed from the reaction is removed by a Dean and Stark trap. Once this process is complete, the mixture is allowed to cool and then washed successively with 10% aqueous sodium hydroxide solution, to remove the unreacted dithiol and neutralise the catalyst, then with water. The mixture is dried over magnesium sulphate,

and the solvent is removed under reduced pressure. The product can be purified either by column chromatography on silica or by distillation, followed by fractional recrystallisation from pentane at low temperature (dry ice-ethanol).

Hydrogen Abstraction from 4,7-Dihydro-1,3-Dithiepins

By analogy with the results obtained for the 4,7-dihydro-1,3-dioxepins, it was anticipated that free radicals, in particular the *tert*-butoxy radical, $Bu^tO^{\bullet}$, would be able to abstract a hydrogen from either the C(4) or C(7) positions on the seven-membered dithiepin ring, to produce an allyl type radical (**85**)



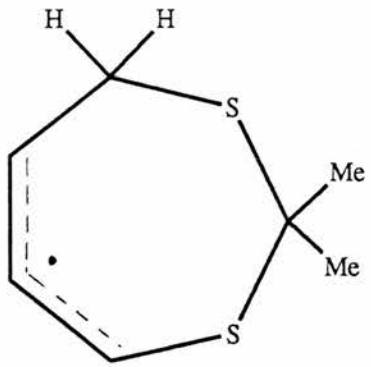
(**85**)

Several 4,7-dihydro-1,3-dithiepins with substituents on the C(2) position were prepared. Photolysis reactions were then carried out with these compounds in the presence of di-*tert* butyl peroxide, and the products were analysed by GC / MS. The compounds were also dissolved in *tert*-butyl benzene, and photolysed in the cavity of the EPR spectrometer in the presence of *tert*-butoxy radicals generated from di-*tert* butyl peroxide.

EPR Studies on 4,7-Dihydro-1,3-dithiepins

The parent compound of the series, namely 4,7-dihydro-1,3-dithiepin (**76**), was prepared by condensation of cis-2-butene-1,4-dithiol and dimethoxymethane. This dithiepin was examined by EPR over the temperature range 225 - 285 K, but failed to provide any interpretable signal, even after repeated purification of the compound by passage over activated alumina.

2,2-dimethyl-4,7-dihydro-1,3-dithiepin (**77**) was made by reaction of the dithiol with acetone and purified by low-temperature recrystallisation from pentane. Investigation by EPR over the temperature range 205-215 K gave a weak complex spectrum of total width 45 G. This was thought to consist of a mixture of at least two radicals, but neither could be attributed to the expected allyl type radical (**86**).



(**86**)

The absence of this allyl type radical was established from the fact that no large hfs associated with the two hydrogens that remain on C(4) or C(7) (i.e. the site where abstraction has not occurred) were present.

At higher temperatures, the spectra simplified and sharpened up to show a sixteen line pattern. The spectrum obtained at 275 K is shown in Fig 15.

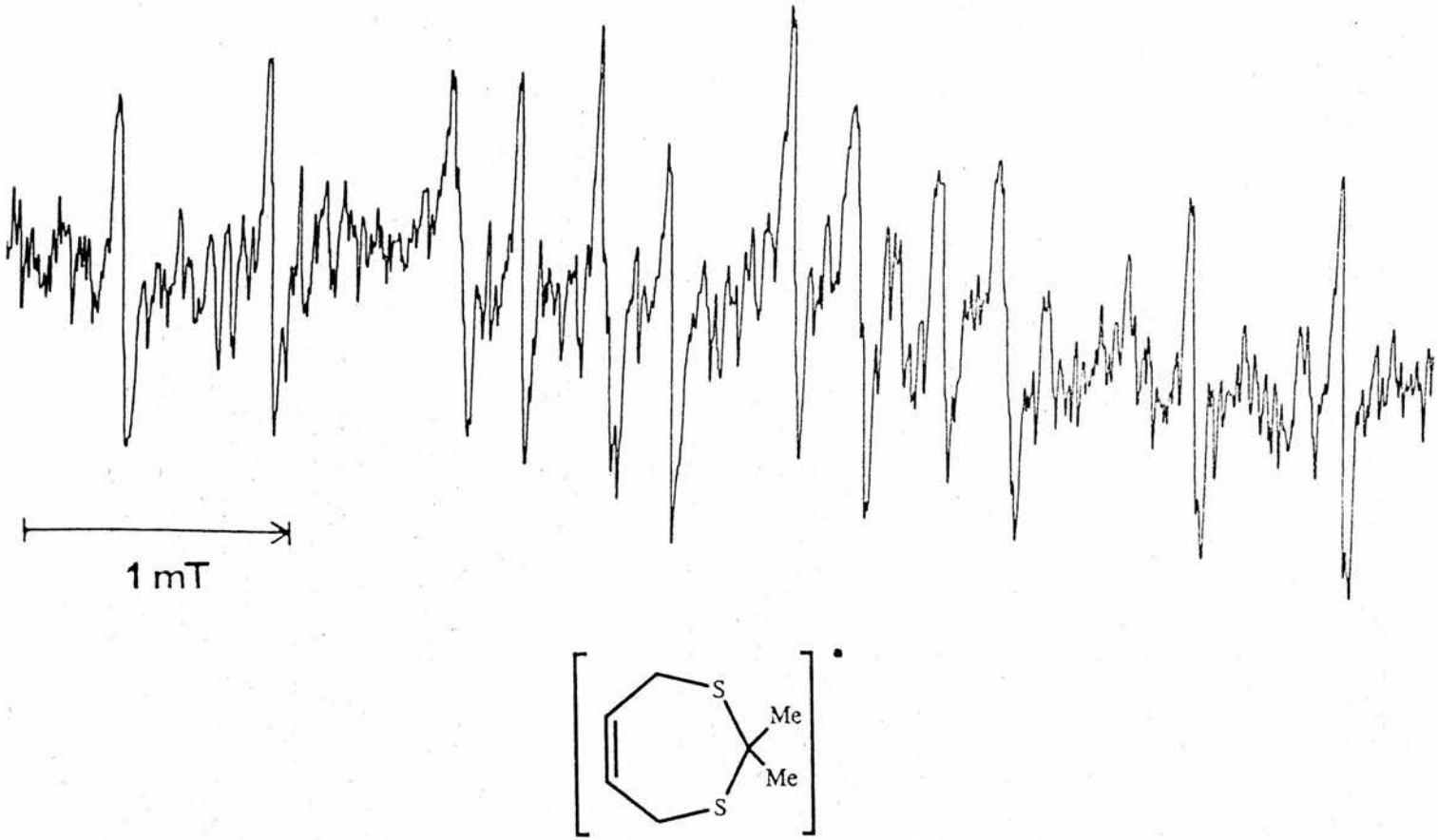
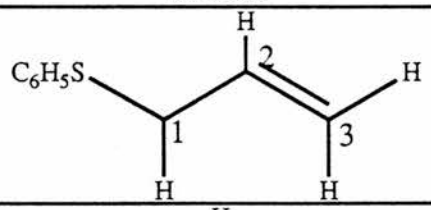
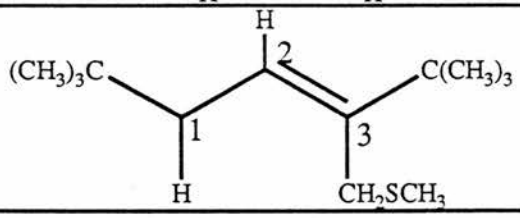


Fig. 15. 9.2 GHz EPR spectrum of the radical formed from 2,2-dimethyl-4,7-dihydro 1,3-dithiepin in t-butylbenzene at 275 K.

This was readily simulated on the computer with hfs for four hydrogens of a (1H) = 5.5 G, a (2H) = 12.3 G and a (1H) = 15.3 G. Fig 16.

Unexpectedly, this radical shows splittings from only four hydrogens, and not the five that would have been evident for the allyl radical. More importantly, the small doublet hfs of 5.5 G for its central hydrogen if an allyl system, is unusually large, and a search of the literature did not reveal any cyclic , linear or any other radicals with hydrogens having hfs of this magnitude.

Few allyl radicals with thiyl substituents have been observed by EPR, and consequently there is some doubt as to the magnitude of the hfs that would be obtained for such thiyl substituted allyls. Table 14. shows some values of hfs for cyclic allyls and some straight chain allyls.

Radical	hfs / G	Ref
	a (3H) = 11.3 (1,3,3) a (1H) = 3.8 (2)	112
	a (1H) = 12.5 (2) a (1H) = 3.9 (2) a (2H) = 6.3 (CH_2)	113

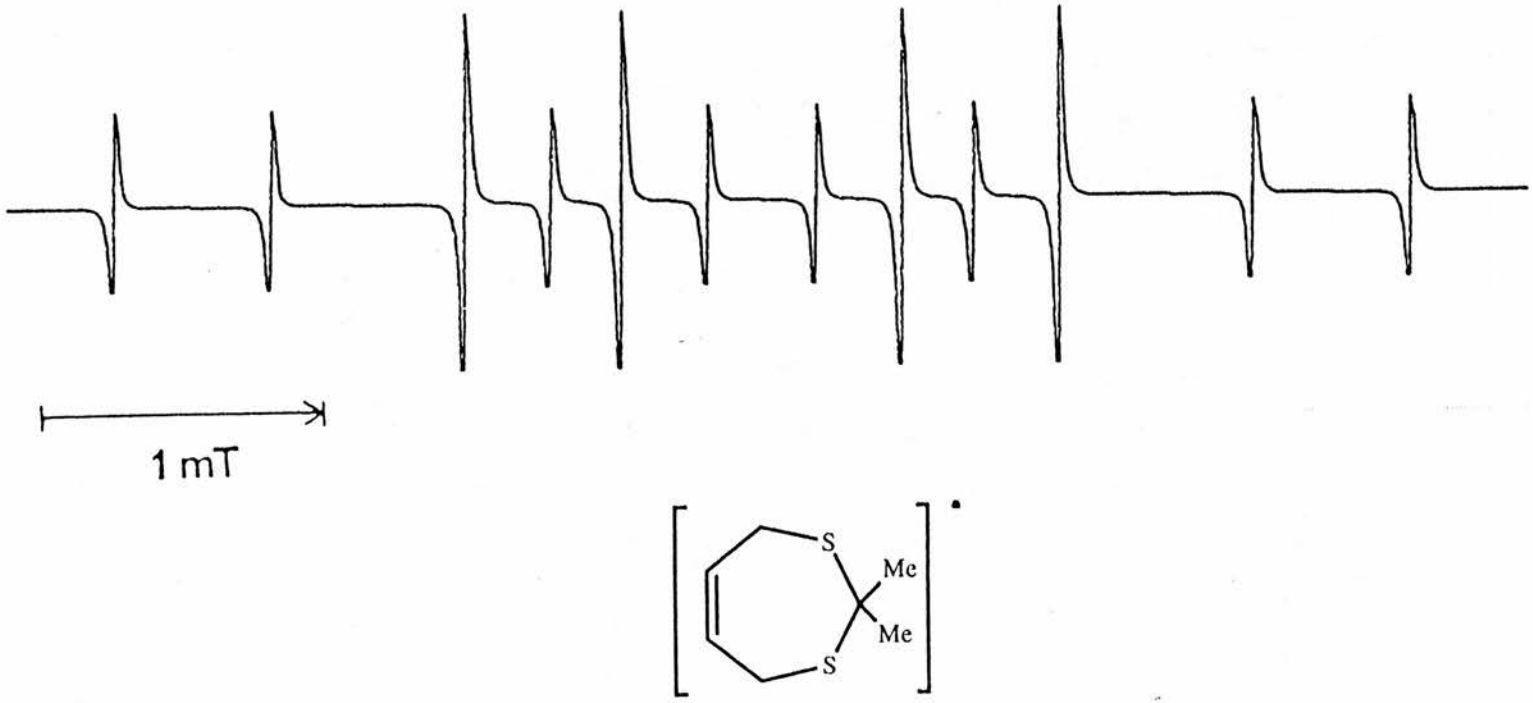


Fig. 16. Computer simulation of the EPR spectrum obtained from 2,2-dimethyl-4,7-dihydro-1,3-dithiepin at 275 K with a(1H) = 5.5 G, a(2H) = 12.3 G and a(1H) = 15.3 G.

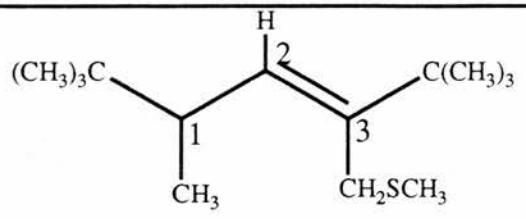
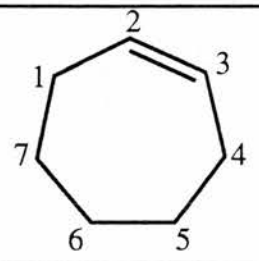
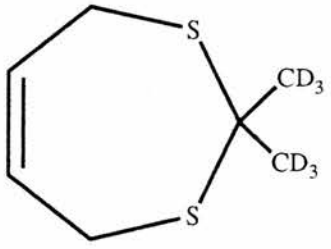
	a (1H) = 6.4 (2) a (3H) = 12.3 (1, CH_3) a (2H) = 6.4 (3, CH_2) a (18H) = 0.25 (1, 3, $C(CH_3)_3$)	113
	a (2H) = 13.8 (1, 3) a (1H) = 4.6 (2) a (2H) = 13.8 (4, 7 eq) a (2H) = 27.5 (4, 7 ax)	114

Table 14

A hexa-deuterated version (**87**) of the 4,4-dihydro-1,3-dithiepin was prepared by condensation of the dithiol with d_6-acetone

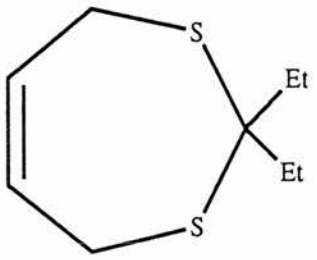


(**87**)

The purpose of preparing this compound was to try to confirm that the hydrogens observed for the radical from the 2,2-dimethyl dithiepin originated in the dithiol portion of the molecule, and not from the substituents on the C(2) position. The hexa-deuterated compound was dissolved up in *tert*-butylbenzene, and photolysed in the presence of *tert*-butoxy radicals, EPR spectra being recorded over a variety of temperatures. Difficulty was experienced in obtaining any sort of spectrum, and the compound was repeatedly purified by low temperature

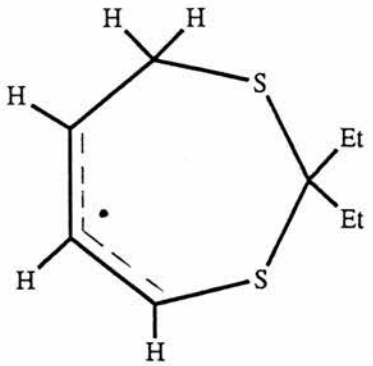
recrystallisations from pentane, and by passing it over a plug of activated alumina. Extremely weak spectra were observed at ca. 275 K, which was almost certainly the same as the unidentified radical obtained for the 2,2-dimethyl substituted dithiepin, but the spectra were not clear enough for definite identification.

2,2-diethyl-4,7-dihydro-1,3-dithiepin (**88**) was prepared by condensation of cis-2-butene-1,4-diol with pentan-3-one, resulting in a white crystalline solid after recrystallisation from pentane.



(**88**)

EPR spectra were recorded over the temperature range 210-320 K in tert-butyl benzene and 170-210 K in cyclopropane, in both cases using tert-butoxyl radicals as the initiator. At low temperatures, the spectra appeared as a broad complex mixture of lines, again none of which could be attributed to the expected allyl type radical (**89**)

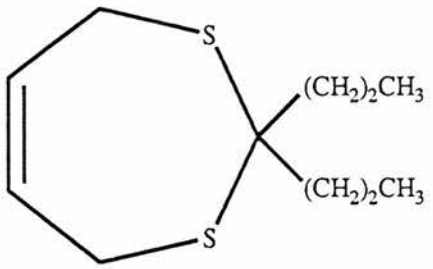


(**89**)

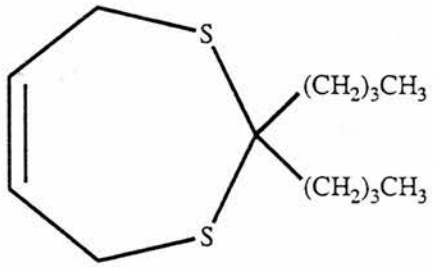
At higher temperatures, the spectrum obtained was identical to that observed for the 2,2-dimethyl dithiepin.

The spectrum detected at 300 K is shown in Fig 17.

Attempts were made to condense cis-2-butene-1,4-diol with 4-heptanone and 5-nonanone (di-n-butyl ketone) to produce compounds (**90**) and (**91**) respectively.



(**90**)



(**91**)

However neither of these compounds could be sufficiently purified either by recrystallisation from pentane, or by vacuum-line distillation, to allow EPR work to be carried out on them.

It appears that the same type of radical, although not clearly identifiable, but possessing four hydrogens, is produced from the dimethyl-, diethyl-, and hexadeuterated 2-substituted dithiepins. The fact that this radical is only observed at higher temperatures and after a significant amount of photolysis, together with the unusual magnitude of the hfs measured from the hydrogens, all suggest that it is a secondary radical, formed either by further rearrangement of the compounds, or by some form of decomposition process.

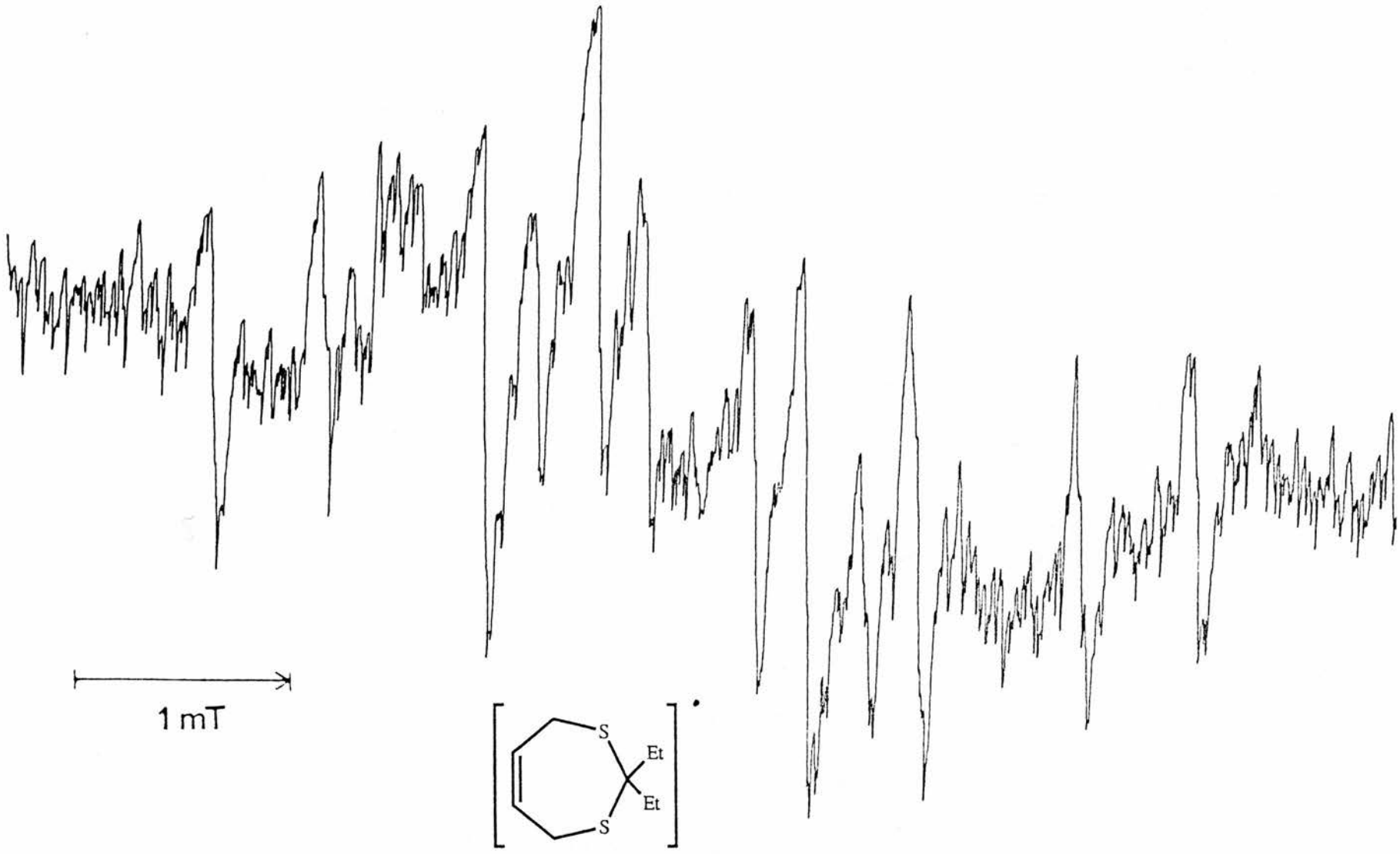
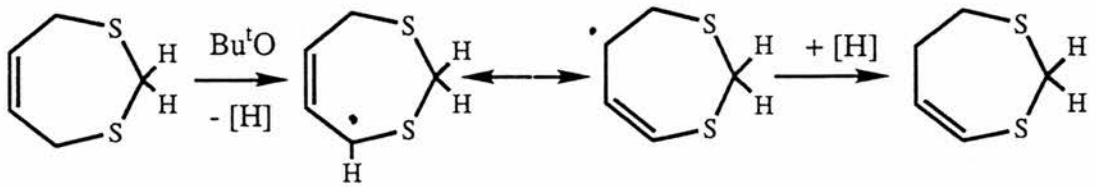


Fig. 17. 9.2 GHz EPR spectrum of the radical formed from 2,2-diethyl-4,7-dihydro-1,3-dioxepin at 300 K, in *tert*-butylbenzene.

Product Analysis from Photolysis Reactions Involving 1,3-Dithiepins

Several of the 2,2-disubstituted dithiepins were subjected to room temperature photolysis reactions in the presence of di-tert-butyl peroxide, and the products were analysed by GC / MS. The purpose of this was to try to asses how the dithiepins fragmented and hence shed some light on the curious EPR results obtained with them. A standard set of GC / MS conditions of 50°C for 5 minutes followed by a temperature increase of 10°C / min upto a final temperature of 200°C was used for all the investigations of the photolysis products of the dithiepins.

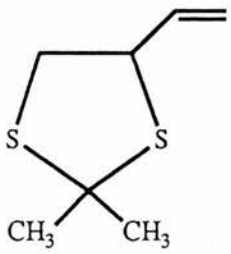
In the case of the parent compound of the series, 4,7-dihydro-1,3-dithiepin (**76**), two photolysis reactions were carried out, one for 20 hours and one for 4 days. Upon completion of both reactions, each mixture exhibited two main product peaks, separated by ca. 2 minutes. The second and larger peak in both instances was assigned to the unrearranged and intact starting dithiepin. This was confirmed by retention time comparisons with the unreacted starting material. The former, and smaller product peak was thought to be an isomeric product, since both peaks exhibited a parent molecular ion of mass 132. It seemed possible that this isomer could be the result of the rearrangement shown in scheme 18.



(**92**)

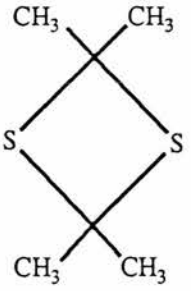
Scheme 18

Overall, compound (**92**) is the result of a shift of the double bond from its position in the starting material 4,7-dihydro-1,3-dithiepin. However this explanation seems unlikely on two counts : firstly compounds of type (**92**), which are 4,5-dihydro-1,3-dioxepins are not known to exist. Secondly, results published by Kohrman et al[108] show an alternative type of product which could have a parent molecular ion of mass 132, compound (**93**). These workers examined the products from an irradiation experiment on 2,2-dimethyl-4,7-dihydro-1,3-dithiepin (**77**). The photolysis was carried out over a period of 18 hours, and the products identified, together with their yields are shown below.



25%

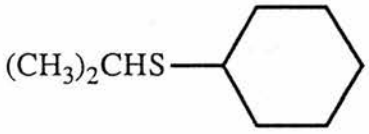
(**93**)



4%

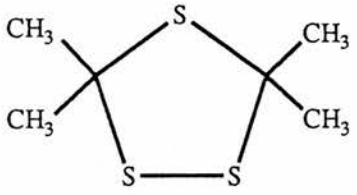
(**94**)

Unreacted Starting Material
11%



4%

(**95**)



8%

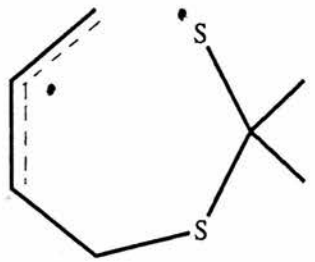
(**96**)

$(CH_3)_2CHSSCH(CH_3)_2$

3%

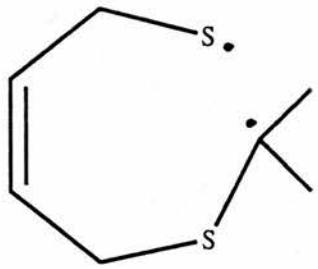
(**97**)

It was suggested that the formation of the major product (**93**) involved the diradical (**98**) shown below.



(**98**)

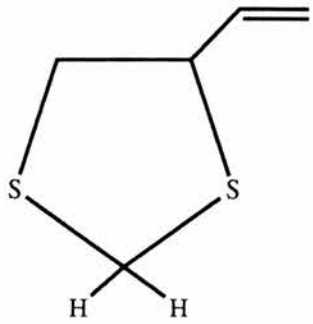
Products (**94**), (**95**) and (**96**) were thought to arise from acetone thione which could be formed from the diradical shown above, or by cleavage of the starting material at another position to form the diradical (**99**).



(**99**)

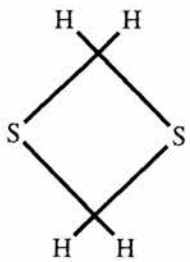
Product (**97**) probably arose from reaction of the diradical (**98**), or thione, with the solvent that they used which was cyclohexane.

In the light of these results, and by analogy, it seems most likely that the isomeric product observed in the photolysis of 4,7-dihydro-1,3-dithiepin (**78**), is compound (**100**).



(**100**)

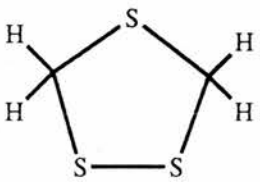
The analogous set of minor products (**101 - 104**)



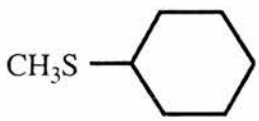
(**101**)

CH_3SSCH_3

(**102**)



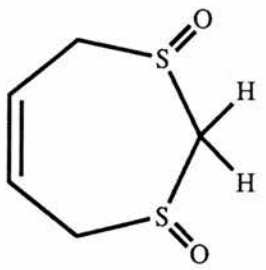
(**103**)



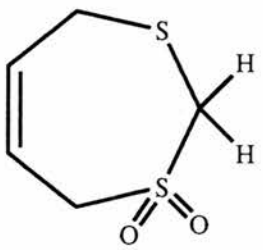
(**104**)

may well have been formed, but we were unable to identify them from GC / MS data.

The product mixture from photolysis over 4 days also showed additional peaks with longer retention times than for the starting dithiepin or its isomer. The largest of these peaks was thought to be due to either a bis-sulphoxide (**105**), or a sulphone (**106**), formed by oxidation, since a molecular M^+ ion of mass 164 was present, indicating the addition of two oxygens to the dithiepin ring.



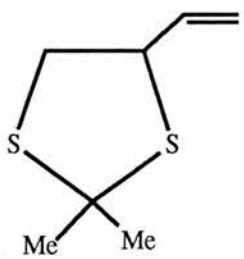
(**105**)



(**106**)

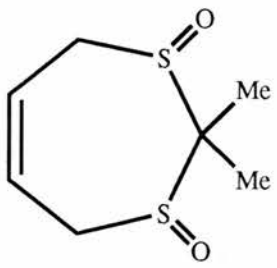
Tables (15) and (16) on page 136 , show the GC / MS data on the products from the photolysis reactions over 20 hours and 4 days respectively.

In a similar manner, 2,2-dimethyl-4,7-dihydro-1,3-dithiepin (**77**) was photolysed over 20 hours in the presence of peroxide and the products analysed by GC / MS. The main pattern of products was analogous to that obtained with the parent compound of the series (**76**). The first main product was again thought to be the isomer of 2,2-dimethyl dithiepin, being compound (**107**).

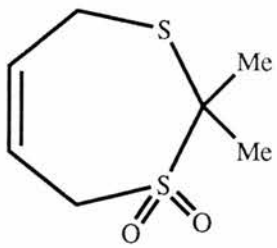


(**107**)

The largest peak which followed this was the unreacted 2,2-dimethyl dithiepin itself, followed by a smaller peak that was either a bis-sulphoxide (**108**), or a sulphone (**109**).



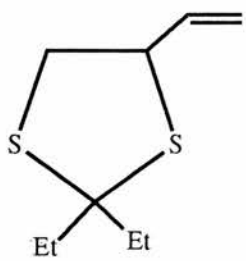
(**108**)



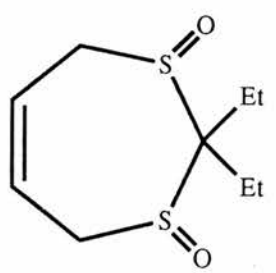
(**109**)

Table (17) on page 137 shows the GC / MS data obtained for the products of photolysis of the 2,2-dimethyl dithiepin over 20 hours. Minor components such as CH_3COCH_3 and C_4H_8S and $C_4H_{10}S$ fragments were also detected in the spectrum with fairly low retention times.

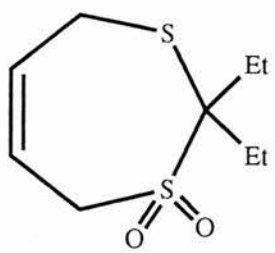
2,2-diethyl-4,7-dihydro-1,3-dithiepin was also photolysed with peroxide in two experiments, one for 20 hours and one for 4 days. Tables (18) and (19) on pages 137-138 summarise the GC / MS data obtained in both of these experiments. Minor components with short retention times which were detected were pentan-3-ol and pentan-3-one. Once again the main products were the isomer (**110**) of the starting dithiepin, the dithiepin itself and either the bis-sulphoxide (**111**) or the sulphone (**112**).



(**110**)



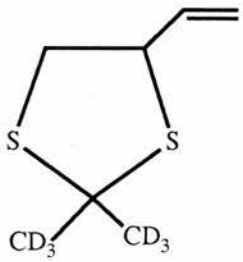
(**111**)



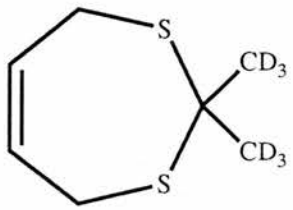
(**112**)

Finally 2,2-di (trideuteriomethyl)-4,7-dihydro-1,3-dithiepin was photolysed with peroxide in an experiment over 20 hours. Table (20) on page 138 gives the GC / MS data on the main products detected. Once

again the main components were the isomer of the parent dithiepin (**113**), and the unreacted dithiepin itself.



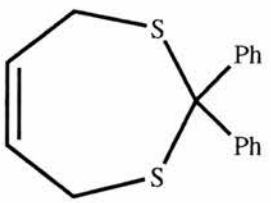
(**113**)



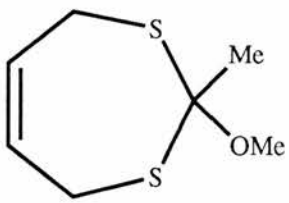
(**87**)

Attempted Preparations of some 1,3-Dithiepins

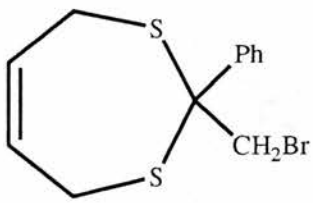
Some 2,2-disubstituted 1,3-dithiepins such as 2,2-diphenyl-4,7-dihydro-1,3-dithiepin (**114**), 2-methoxy-2-methyl-4,7-dihydro-1,3-dithiepin (**115**), 2-bromomethyl-2-phenyl-4,7-dihydro-1,3-dithiepin (**116**), 2-chloromethyl-2-phenyl-4,7-dihydro-1,3-dioxepin (**117**), and 2-bromomethyl-4,7-dihydro-1,3-dithiepin (**118**),



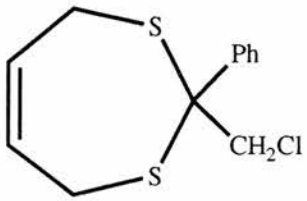
(**114**)



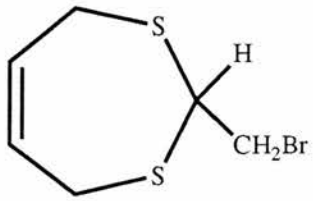
(**115**)



(**116**)



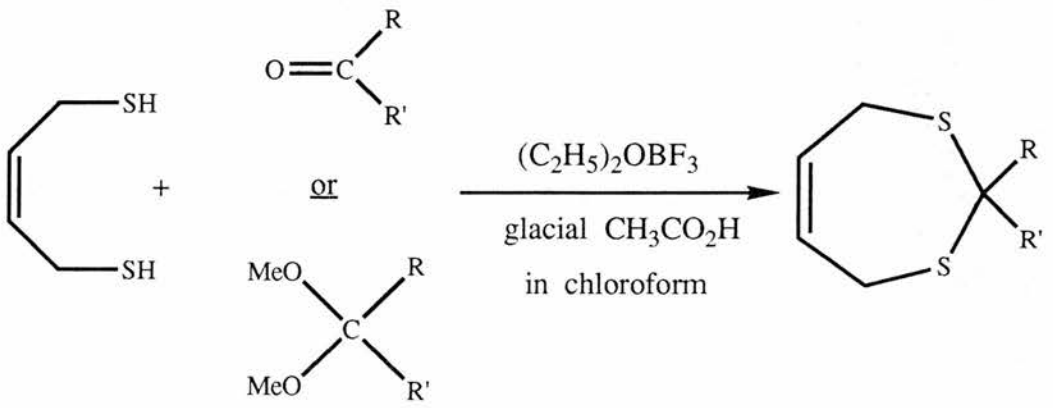
(**117**)



(**118**)

could not be prepared by the same standard method used for the other dithiepins. An alternative method was employed, analogous to that used in the formation of 1,3-dithianes,[115] in an

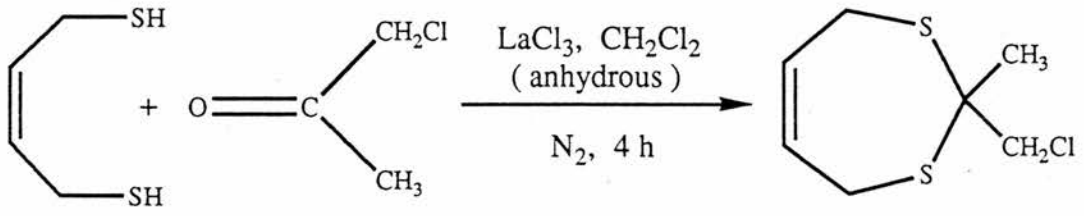
attempt to condense *cis*-2-butene-1,4-dithiol with the appropriately substituted carbonyl compound, or dimethyl ketal. (scheme 19).



Scheme 19

This method involved adding a mixture of the dithiol and carbonyl compound or dimethyl ketal in chloroform, to a refluxing mixture of $(C_2H_5)_2OBF_3$ (boron trifluoride etherate), glacial acetic acid and chloroform. The addition was performed at a constant rate over *ca.* 8 hours. Upon completion, the mixture was allowed to cool and then washed with 10% aqueous potassium hydroxide and water. The residual chloroform solution was dried over potassium carbonate and then the chloroform was evaporated off; purification of the product was then attempted either by reduced pressure distillation, or recrystalisation. This type of procedure produced very poor results. In some cases the ^1H NMR spectrum of the crude product was inconsistent with the desired compound, or the compound was present in very small amounts which could not be separated from major impurities either by recrystallisation or by distillation (the latter method in particular being prone to cause the formation of polymeric products).

A further method, analogous to that used in the preparation of 1,3-dithiolanes,[116] was employed in an attempted synthesis of 2-chloromethyl-2-methyl-4,7-dihydro-1,3-dithiepin. This involved the successive addition of $LaCl_3$ (anhydrous) and cis-2-butene-1,4-dithiol to a stirred solution of chloroacetone in CH_2Cl_2 (anhydrous), with agitation, under nitrogen.



However after washing the reaction mixture with 10% aqueous NaOH, saturated NaCl, water and drying ($MgSO_4$), the crude product obtained after solvent removal showed no evidence of the hydrogens in the ring by ^1H NMR. No further preparations of 1,3-dithiepins were undertaken with this method.

Discussion and Conclusions

It is clear from the results that we have obtained with the 2,2-disubstituted 4,7-dihydro-1,3-dithiepins that much more work needs to be done on the nature of the fragmentation products of these compounds. This is necessary in order to shed some light on the unusual EPR results obtained, whereby the expected allyl type radical (c.f. 1,3-dioxepins) was not observed. The spectra of the 2,2-dimethyl-, 2,2-diethyl- and 2,2-di (trideuteriomethyl) 1,3-dithiepins all indicate splittings from four hydrogens instead of the five that would be consistent with an allyl radical formed by hydrogen abstraction from

C(4) or C(7) in the ring. However it is evident that the radical centre is situated in the butene-thiol part of the molecule, and not connected with the substituents on the 2-position. The fact that hfs of four hydrogens are observed at relatively high temperature, and after significant photolysis, point to their origin being in a secondary radical resulting from further rearrangement, or from a decomposition process. It seems unlikely that an adduct is responsible for the observations, since any such adduct would have to result in a planar centred radical with associated splittings of 20-22 G. No splittings of this magnitude were measured.

Obviously further work is necessary to characterise the radical. When the precise origin of the observations is determined, it may then be possible to employ the " spin-probe " and EPR methods described in Chapter 1, to calculate the activation energies of ring inversion processes and the conformations populated by these molecules. This should prove more challenging than was the case for the 1,3-dioxepins, since the 1,3-dithiepins seem to behave in a different manner, and do not appear to be as robust. EPR methods would serve as an interesting comparison to the low temperature NMR techniques used by other workers.

Experimental

***cis*-1,4-Dichlorobut-2-ene** *cis*-2-Butene-1,4-diol (101ml, 108g, 1.23mol) in 200ml of pyridine was cooled in an ice-water bath, and thionyl chloride (250ml, 3.43mol) was added dropwise during 1.5 h, care being taken to keep the temperature of the mixture at *ca.* 0-5°C. The mixture was stirred for a further 16 h and gradually allowed to warm upto room temperature during this period, and then poured onto cracked ice. The whole mixture was extracted with ether (3 x 150ml); the ether extract was washed successively with saturated aqueous $NaHCO_3$ and water, and dried over Na_2SO_4. Flash evaporation of the solvent and purification of the residual liquid by distillation under reduced pressure gave *cis*-1,4-dichlorobut-2-ene as a colourless liquid (54.3g, 35.3%), b.p. 49°C / 15 Torr (lit[105] ,22.5°C / 3Torr, lit [105], 152.5°C / 758Torr); δ_H (200MHz) 4.15 (4H , d, J = 6Hz), 5.8-6.0 (2H, m); δ_C (50MHz) 38.6 (2C), 130.1 (2C).

(Attempted) Preparation of *cis*-2-Butene-1,4-dithiol[106] *cis*-1,4-Dichlorobut-2-ene (10.0g, 0.08mol) was added dropwise to a degassed solution of sodium thioacetate (0.2mol prepared from 14ml of thiolacetic acid and 4.5g of sodium) in methanol (300ml). The reaction mixture was refluxed under N_2 for 5 h. Concentrated hydrochloric acid (21ml, 0.21mol) was then added and the mixture was refluxed for a further 4 h. Methanol and methyl acetate were removed under reduced pressure, leaving NaCl, H_2O and a yellow oil. The oil was extracted with CH_2Cl_2 (25ml), washed with 0.1M HCl (2 x 20ml) and water (2 x 20ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residual liquid distilled to produce a pale orange liquid (4.6g, 48.1%), b.p. 110-113°C / 15Torr; δ_H (300MHz) 1.5-1.6 (2H, t) 3.1-3.3 (4H, t) and 5.6-5.7 (2H, t); δ_C (75MHz) 20.6 (2C), 129.4 (2C). The NMR

spectrum showed that the product was highly contaminated and it proved impossible to purify further by repeated distillations.

(Attempted) Preparation of *cis*-2-Butene-1,4-dithiol *cis*-2-Butene-1,4-diol (20.0g, 0.23mol), thiourea (34.6g, 0.45mol) and hydrobromic acid (48%, 229.6g, 1.36mol) were mixed together, and refluxed for 9 h with stirring.[107] NaOH (18.2g, 0.45mol) in water (200ml) was added and a stream of N_2 passed over the liquid which was refluxed for a further 2 h. The resulting mixture was extracted with ether (3 x 100ml), and the combined extracts washed with water (2 x 100ml) and dried over $MgSO_4$. Flash evaporation of the solvent, followed by reduced pressure distillation of the residue afforded a colourless liquid (3.7g, 19.3%), b.p. 80°C / 0.6Torr. The δ_H (60MHz) signals once again confirmed the presence of the product, *cis*-2-butene-1,4-dithiol, but showed the presence of a large amount of impurity between δ1.5 and δ3.8. This made it impossible to purify the dithiol.

***cis*-2-Butene-1,4-dithiol diacetate**[108] *cis*-1,4-Dichlorobut-2-ene (40.0g, 0.32mol) was added dropwise during 2 h to thiolacetic acid (48.7g, 0.64mol) in pyridine (250ml). Upon completion of the addition, the mixture was stirred for a further 0.5 h. Excess pyridine was then distilled out under reduced pressure (water pump *ca.* 15Torr) and the residue was added to water (150ml). The mixture was extracted with ether (4 x 150ml); the ether extracts were combined and dried over Na_2SO_4. The solvent was evaporated off and the title compound distilled out as an orange liquid (60.1g, 92,8%), b.p. 141°C / 1.5Torr. (lit[108] 91-92°C / 0.08Torr, lit[101] , 81-83°C / 0.1Torr). δ_H (200MHz) 2.35 (6H, s), 3.64 (4H, d, J = 2Hz) and 5.5-5.7 (2H, m); δ_C (50MHz) 26.3 (2C), 30.8 (2C), 127.9 (2C), 195.5 (2C).

***cis*-2-Butene-1,4-dithiol**[108] KOH (5.9g, 0.10mol) was dissolved in methanol (100ml), and added dropwise during 0.5 h to *cis*-2-butene-1,4-dithiol diacetate (10.7g, 0.05mol) also dissolved in methanol (100ml). Upon completion of the addition, 2M HCl was added until the mixture was neutral (pH paper - full range). Water (100ml) was added, and the whole mixture was extracted with ether (3 x 150ml) and the combined ether extracts were dried over $MgSO_4$. Evaporation of the solvent gave the residual liquid *cis*-2-butene-1,4-dithiol, as a pale yellow liquid, (4.7g, 78.2%). Further purification was deemed unecessary. (lit[108] , b.p. 55-56°C / 0.2Torr, lit[109] , b.p. 80-81°C / 11Torr). δ_H (200MHz) 1.5-1.6 (2H, t, J = 3Hz), 3.1-3.3 (4H, m) and 5.5-5.7 (2H, m); δ_C (50MHz) 21.2 (2C) and 130.0 (2C).

4,7-Dihydro-1,3-dithiepin To a solution of dimethoxymethane (1.90g, 0.025mol) in benzene (100ml) containing 5mg of toluene-4-sulphonic acid (p-toluene sulphonic acid), was added *cis*-2-butene-1,4-dithiol (3.0g, 0.025mol). The mixture was heated at *ca.* 45°C for 18 h, then a Dean-Stark trap was attached and the mixture refluxed for a further 3 h, the methanol produced being separated off. The solution remaining was allowed to cool and then washed with 10% aqueous NaOH (2 x 100ml), water (2 x 100ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure, to leave the product, 4,7-dihydro-1,3-dithiepin as a pale yellow liquid (2.39g, 72.4%). The product did not require further purification and solidified at ca. 20°C. (lit[106] m.p.= 26-27°C. δ_H (200MHz) 3.45 (4H, d, J = 3Hz), 4.0 (2H, s), 5.95 (2H, t, J = 3Hz); δ_C (50MHz) 29.3 (2C), 38.0 (1C), 129.3 (2C). m / z (%) (m^+)132(12), 85(100), 78(25), 45(67), 39(27), 27(34).

2,2-Dimethyl-4,7-dihydro-1,3-dithiepin To a solution of acetone (1.45g, 0.025mol) in benzene (70ml), containing 5mg of toluene-4-sulphonic acid, was added *cis*-2-butene-1,4-dithiol (3.0g, 0.025mol). The mixture was heated under reflux for 18 h while the water formed was removed by a Dean-Stark trap. The mixture was cooled and washed successively with 10% aqueous NaOH solution (2 x 75ml), water (2 x 100ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure on a Buchi Rotavapor to leave the crude product as a yellow / orange liquid (3.46g). The product was further purified by distillation on a Kugelrohr to give a pale yellow liquid (1.11g, 27.8%), b.p. 79°C / 0.7Torr. The 2,2-dimethyl-4,7-dihydro-1,3-dithiepin was dissolved up in boiling pentane and recrystallised at low temperature (dry ice-ethanol bath). The crystals were filtered through pre-chilled apparatus, however when the product warmed up to ambient temperature it reverted to being a pale yellow liquid. (lit[108] b.p. 58-61°C / 0.4Torr). δ_H (200MHz) 1.70 (6H, s), 3.3-3.5 (4H, m), 5.8-6.0 (2H, m); δ_C (50MHz) 27.2 (2C), 32.0 (2C), 54.6 (1C), 130.8 (2C). (lit [108] ir (CCl_4) 3015, 2960, 2910, 2855, 1650, 1438, 1380, 1362, 1162, 1150, and 1112 cm^{-1} ; uv (max) cyclohexane 227nm (ε 840) and 257 (398)); m / z (%) (m^+)160(9), 106(42), 95(13), 85(32), 74(27), 57(100), 45(48), 41(51), 39(44), 27(32).

2,2-Diethyl-4,7-dihydro-1,3-dithiepin To a solution of pentan-3-one (2.15g, 0.025mol) in benzene (100ml), containing 5mg of toluene-4-sulphonic acid, was added *cis*-2-butene-1,4-dithiol (3.0g, 0.025mol). The mixture was heated under reflux for 18 h, during which time the water formed was collected in a Dean-Stark trap. The mixture was allowed to cool, and then washed with 10% aqueous NaOH solution (2 x 100ml) and water (2 x 100ml), and then dried over $MgSO_4$. The solvent benzene was removed under reduced pressure to leave the crude product as a

yellow liquid (3.12g). The crude liquid was distilled on a Buchi Kugelrohr to give a very pale yellow liquid (1.25g, 26.6%), b.p. 98°C / 0.7Torr. The 2,2-diethyl-4,7-dihydro-1,3-dithiepin was dissolved in boiling pentane and recrystallised at low temperature (dry ice-ethanol bath). The crystalline compound was filtered through pre-chilled glassware to afford the 2,2-diethyl dithiepin as a white crystalline compound m.p. 27-28°C. δ_H (200MHz) 0.9-1.1 (6H, t, J = 7Hz), 1.8-2.0 (4H, q, J = 7Hz), 3.3 (4H, d, J = 2Hz), 5.8-5.9 (2H, m); δ_C (50MHz) 9.7 (2C), 26.8 (2C), 31.4 (2C), 63.9 (1C), 130.5 (2C). m / z (%) (m^+)188(5), 134(15), 102(18), 85(17), 73(80), 69(100), 45(64), 41(52), 39(33), 27(41).

2,2-Di-(trideuteriomethyl)-4,7-dihydro-1,3-dithiepin To a mixture of d_6-acetone (1.60g, 0.025mol) in benzene (100ml), containing 5mg of toluene-4-sulphonic acid, was added *cis*-2-butene-1,4-dithiol (3.0g, 0.025mol). The mixture was refluxed for 18 h over a Dean-Stark trap, allowing the water formed by the reaction to be removed. Once the reaction mixture had been allowed to cool down, it was washed with 10% aqueous NaOH (2 x 100ml) and water (2 x 100ml), and then dried over $MgSO_4$. The solvent benzene was removed on a Buchi Rotavapor after filtration of the drying agent, to leave the product as a pink-orange liquid (3.17g). The crude liquid was dissolved in a minimum volume of boiling pentane and recrystallised at low temperature. The crystals were filtered through pre-chilled glassware. The crystals reverted back to the liquid state at room temperature to yield (1.3g, 31.3%) of a brown-orange liquid. δ_H (200MHz) 3.3-3.4 (4H, m), 5.9-6.0 (2H, m); δ_C (50MHz) 26.7 (2C), 31.1 (2C), 53.8 (1C), 130.2 (2C); m / z (%) 166(7), 110(27), 85(49), 61(87), 45(100), 39(42), 27(47).

(Attempted) Preparation of 2,2-Di-n-propyl-4.7-dihydro-1,3-dithiepin

cis-2-Butene-1,4-dithiol (3.0g, 0.025mol), 4-heptanone (dipropyl ketone) (2.85g, 0.025mol), and 5mg of toluene-4-sulphonic acid were mixed together in benzene (100ml). The reaction mixture was heated under reflux for 18 h, the water formed during the reaction being removed by a Dean-Stark trap. Once the reaction mixture had cooled down, it was washed with 10% aqueous NaOH solution (2 x 100ml) and water (2 x 100ml), then dried over $MgSO_4$. The solvent benzene was removed on a rotavapor, leaving the crude product as a pink liquid (4.47g, 82.6%). Low temperature recrystallisation from pentane failed to produce the product as a crystalline solid. GC / MS analysis indicated that the product contained many impurities which could not be separated off by distillation on a vacuum line. δ_H (200MHz) 0.8-1.0 (6H, t, J = 6Hz), 1.7-1.9 (4H, m), 2.2-2.4 (4H, m), 3.3 (4H, d, J = 6Hz), 5.7-5.9 (2H, m); δ_C (50MHz) 14.1 (2C), 17.9 (2C), 20.5 (2C), 41.2 (2C), 62.2 (2C), 129.9 (2C). m / z (%) 216(3), 183(4), 162(9), 129(11), 102(12), 97(41), 87(46), 55(100), 45(69), 41(60), 39(39), 29(33), 27(46).

(Attempted) Preparation of 2,2-Di-n-butyl-4,7-dihydro-1,3-dithiepin

cis-2-Butene-1,4-dithiol (2.0g, 0.017mol), 5-nonanone (di-n-butyl ketone) (2.37g, 0.017mol), and 5mg of toluene-4-sulphonic acid were mixed together in benzene (100ml). The mixture was refluxed for 18 h while the water formed was removed by a Dean-Stark trap. The mixture was cooled, washed with 10% aqueous NaOH solution (2 x 100ml), and water (2 x 100ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure leaving the crude product as a pink liquid (3.85g, 92.7%). Low temperature recrystallisation from pentane failed to produce the product as a crystalline solid. GC / MS analysis indicated that the

product contained many impurities which could not be separated off by vacuum line distillation. δ_H (200MHz) 0.9-1.0 (6H, t, J = 6Hz), 1.2-1.4 (4H, m), 1.5-1.7 (4H, m) 2.35-2.45 (4H, m), 3.3 (4H, d, J = 6Hz), 5.8 (2H, m); δ_C (50MHz) 13.8 (2C), 22.7 (2C), 26.1 (2C), 38.5 (2C), 62.0 (1C), 129.9 (2C).

(Attempted) Preparation of 2,2-Diphenyl-4,7-dihydro-1,3-dithiepin

Boron trifluoride etherate (3.55g, 0,025mol), glacial acetic acid (6.2ml) and chloroform (50ml) were mixed together and heated at reflux with stirring.[116] *cis*-2-Butene-1,4-dithiol (3.0g, 0.025mol), benzophenone dimethyl acetal (6.28g, 0.028mol) and chloroform (50ml) were combined and added to the refluxing mixture over a period of 8 hours. The mixture was allowed to cool to room temperature and washed successively with water (2 x 100ml), 10% aqueous potassium hydroxide (2 x 100ml), and water (2 x 100ml) The chloroform solution was dried over anhydrous potassium carbonate. Evaporation of the solvent under reduced pressure yielded a brown / yellow solid residue, the ^{1}H NMR of which was inconsistent with the desired product. Further purification was not undertaken.

This method was also used to try to synthesize the 2-methoxy-2-methyl-..., 2-bromomethyl-2-phenyl-..., 2-chloromethyl-2-phenyl-..., and 2-bromomethyl-... 4,7-dihydro-1,3-dithiepins. Poor results were obtained, with products either showing ^{1}H NMR spectra inconsistent with the desired compound, or small amounts of the expected material that was awkward to separate from major amounts of impurity.

(Attempted) Preparation of 2-Chloromethyl-2-methyl-4,7-dihydro-1,3-dithiepin Lanthanum chloride ($LaCl_3$, anhydrous) (1.02g, 4.2 x 10^{-3} mol, 2mol eq) and *cis*-2-butene-1,4-dithiol (1.0g, 0.008mol, 4mol eq)

were successively added to a stirred solution of chloroacetone (0.19g, 2.1 x 10^{-3}mol, 1mol eq) in anhydrous CH_2Cl_2 (20ml) under N_2.[115] The mixture was stirred at room temperature for 4 hours and then diluted with pentane (20 ml), and filtered. Successive washings with 10% aqueous NaOH (40ml) (to remove the unreacted dithiol), water (60ml), saturated NaCl (60ml) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent removed on a rotary evaporator, leaving a dark brown liquid. The ^1H and ^{13}C NMR spectra of this crude material were inconsistent with the desired product (no evidence of the double bond hydrogens in the ring). Further purification was not attempted.

Table (15)

GC / MS data on the products of the photolysis of (**76**) for 20 hours

Retention Time	m+ and fragment ions (%)	Prob. molecular formula
1 : 15 min.	59(100), 57(15), 43(43), 41(46), 39(22), 31(90), 29(31), 27(28), 15(33).	$C_4H_{10}O$ m+ absent
1 : 56 min.	146(4), 57(100), 43(60), 41(56), 29(39).	$C_8H_{18}O_2$ (Bu^tOOBu^t)
8 : 48 min.	132(2), 87(41), 85(100), 45(80), 39(32), 27(47).	$C_5H_8S_2$
10 : 44 min.	132(12), 85(100), 78(25), 45(67), 39(27), 27(34).	$C_5H_8S_2$

Table (16)

GC / MS data on the products of the photolysis of (**76**) for 4 days

Retention Time	m+ and fragment ions (%)	Prob. molecular formula
1 : 55 min.	146(4), 57(100), 43(41), 41(43), 29(30), 15(25).	$C_8H_{18}O_2$ (Bu^tOOBu^t)
8 : 43 min.	132(4), 86(41), 85(100), 45(80), 39(32), 27(47).	$C_5H_8S_2$
10 : 49 min.	132(10), 85(100), 78(29), 45(83), 39(35), 27(41).	$C_5H_8S_2$
15 : 45 min.	163(2), 130(5), 85(17), 45(100), 29(12), 15(10).	$C_5H_8S_2O_2$

Table (17)

GC / MS data on the products of the photolysis of (**77**) for 20 hours

Retention Time	m+ and fragment ions (%)	Prob. molecular formula
1 : 10 min	58(12), 43(100), 42(16), 27(14), 15(59), 14(17).	CH_3COCH_3
1 : 32 min	90(34), 84(48), 75(45), 58(63), 48(43), 45(81), 43(70), 41(100), 39(81), 27(46).	$C_4H_{10}S$
1 : 38 min	88(35), 73(25), 55(38), 48(37), 45(89), 41(54), 39(100), 27(12), 15(17).	C_4H_8S
1 : 44 min	104(12), 89(5), 57(66), 41(100), 39(31), 29(66) 27(25), 15(9).	$C_5H_{12}S$
1 : 50 min	146(4), 73(7), 57(100), 43(32), 41(30), 29(38), 15(28).	$C_8H_{18}O_2$ (Bu^tOOBu^t)
9 : 08 min	160(1), 145(5), 106(20), 86(38), 59(100), 45(42), 41(37), 39(38), 27(29).	$C_7H_{12}S_2$
11 : 39 min	160(7), 106(39), 85(28), 74(25), 59(100), 41(76).	$C_7H_{12}S_2$
13 : 35 min	192(4), 118(15), 85(12), 74(100), 59(73), 39(33).	$C_7H_{12}S_2O_2$

Table (18)

GC / MS data on the products of photolysis of (**88**) for 20 hours

Retention Time	m+ amd fragment ions (%)	Prob. Molecular Formula
1 : 10 min	88(1), 59(87), 43(29), 41(46), 31(100), 29(35).	$C_5H_{12}O$
1 : 35 min	86(7), 57(57), 29(100).	$C_5H_{10}O$
12 : 55 min	188(1), 159(11), 103(11), 86(20), 73(100), 45(47).	$C_9H_{16}S_2$

15 : 00 min	188(2), 134(8), 102(14), 73(65), 69(100), 45(67), 41(66), 39(35), 27(32).	$C_9H_{16}S_2$

Table (19)

GC / MS data on the products of photolysis of (**88**) for 4 days

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
1 : 35 min	86(8), 57(62), 29(100), 28(34), 27(39), 26(10).	$C_5H_{10}O$
1 : 51 min	146(3), 73(7), 57(100), 43(60), 41(56), 29(42).	$C_8H_{18}O_2$ (Bu^tOOBu^t)
12 : 54 min	188(1), 159(23), 103(12), 86(23), 73(100), 69(24), 45(52), 41(35), 27(35).	$C_9H_{16}S_2$
14 : 45 min	188(3), 134(12), 102(20), 85(20), 73(87), 69(100), 45(75), 41(62), 27(48).	$C_9H_{16}S_2$
19 : 02 min	219(3), 218(16), 185(9), 154(15), 141(13), 109(100), 65(80), 39(65), 18(47).	$C_9H_{16}S_2O_2$

Table (20)

GC / MS data on the products of photolysis of (**87**) for 20 hours

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
1 : 55 min	146(4), 73(10), 57(100), 43(27), 41(20), 29(23), 27(22), 15(54).	$C_8H_{18}O_2$ (Bu^tOOBu^t)
11 : 34 min	165(1), 147(4), 111(19), 86(81), 62(100), 61(86), 45(73), 27(40).	$C_7H_6S_2D_6$

14 : 20 min	166(4), 165(6), 111(32), 85(45), 62(100), 61(87), 45(83), 27(51)	$C_7H_6S_2D_6$
20 : 43 min	162(2), 160(15), 128(18), 99(25), 87(42), 62(62), 45(100), 28(76).	m+ absent

CHAPTER 3

Radical Rearrangements in Cyclic Epoxides

Introduction To Free-Radical Rearrangements

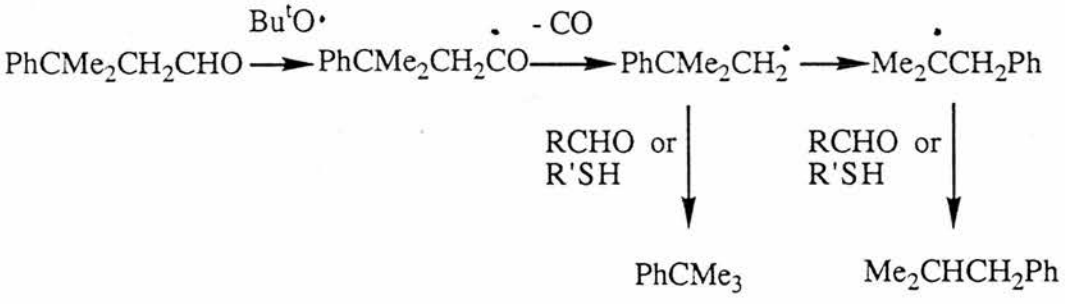
Free-radical rearrangements have been discussed in many papers and reviews, such as those by Walling,[117] Friedlina [118] and Wilt.[119] A practical but broad definition of the term " free-radical rearrangement " was put forward by De Mayo[120] in 1963 in his foreword to " Molecular Rearrangements ". He suggested that a rearrangement could be defined as " a change in the atomic disposition within a molecule (with accompanying bond cleavage, σ, or p, and reformation) ". Beckwith and Ingold[121] in 1980 extended this definition to encompass processes that did not involve the breaking and reforming of bonds, but which did however exhibit a change in the disposition of atoms within the molecule. The inversion of a radical formed from an optically active precursor provides an example of this type of rearrangement.

Although extensive work has been carried out over the past thirty or so years,[122-125] there are still far fewer examples of rearrangements involving radicals, than there are for carbo-cations or other electron deficient species. This is due in part to the very much smaller energy difference between primary and tertiary radicals, than between corresponding carbo-cations. A further reason for the comparative lack of radical rearrangements is the absence of low energy pathways for the 1,2-migration of alkyl groups.

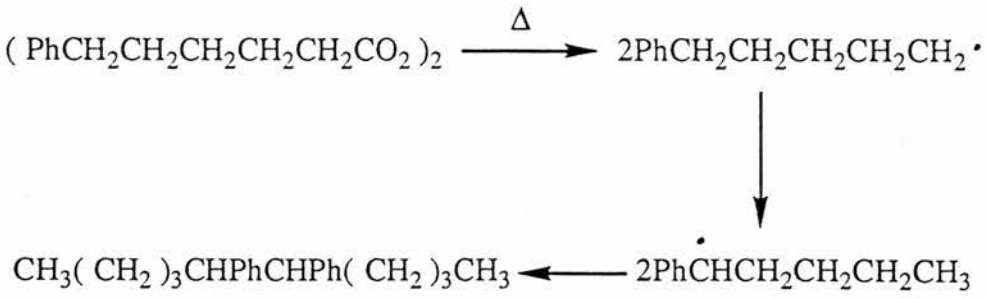
The majority of free-radical rearrangements have been classified into one of four main categories, either by the overall structural change or by

the nature of the individual steps involved. These categories are : atom transfers, group transfers, ring closure and ring opening processes. This latter area of ring opening reactions is the main subject of this chapter.

The first free-radical rearrangement to be reported was described in 1944 by Urry and Kharasch,[126] and it was that of the primary neophyl radical ($PhCMe_2CH_2\cdot$) to the tertiary radical ($PhCH_2\dot{C}Me_2$). Decarbonylation of 3-methyl-3-phenylbutanal yields isobutylbenzene and tert-butyl benzene, and the rearrangement is greatest under conditions where chain transfer with the aldehyde is reduced, i.e. in dilute solution. Suppression of all rearrangement is achieved by the addition of a thiol to the reaction mixture (thiols are good chain transfer agents).



The neophyl rearrangement is an example of the most common type of group transfer involving the 1,2-shift. Radical rearrangements involving the 1,2-migration of vinyl groups are also well known, as well as 1,4- and 1,5- shifts of various groups. The most common type of hydrogen migration from carbon to carbon is the 1,5- shift.[127] (Scheme 1)

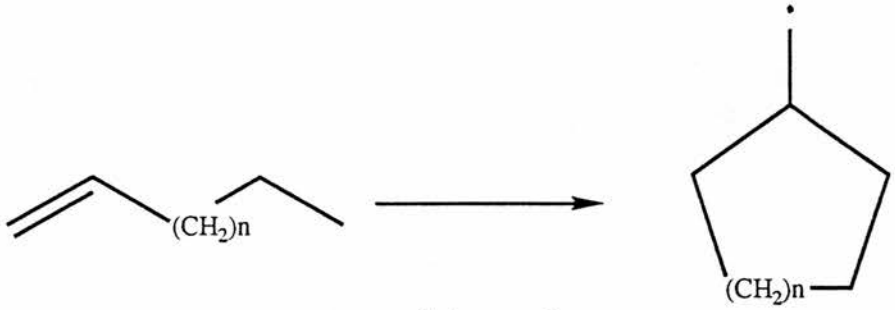


Scheme 1

Other examples involving 1,3- , 1,4-, 1,6-, 1,10-, and 1,11-hydrogen transfers are also documented

Heteroatom transfers are common with halogen atoms, and also involve a migratory process.

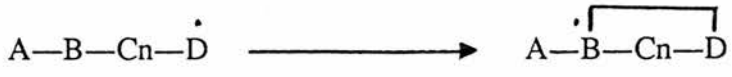
Ring closure processes are found to occur where intramolecular addition is possible between a radical centre and an unsaturated centre (Scheme 2).



Scheme 2

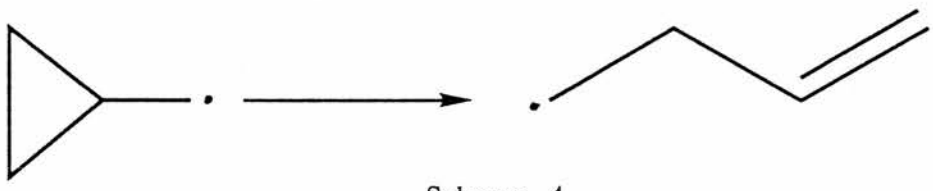
The cyclisation of the 5-hexenyl radical is an example of this type of process.

Although not as common, cyclisation can be achieved by addition to a coordinatively unsaturated atom (Scheme 3)



Scheme 3.

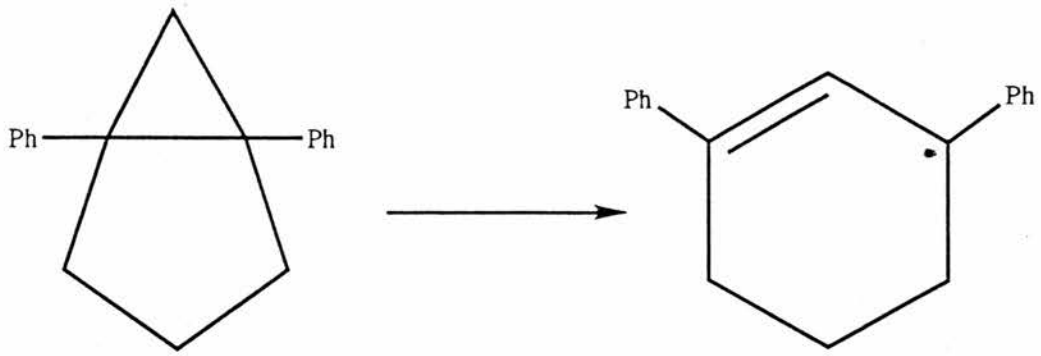
Ring opening processes of radical species are often a result of a relief of strain to produce a more stable radical. In the particular case of cycloalkyl ring opening, fission occurs at a β–γ bond (β–scission). Scheme 4 , shows this process for the cyclopropylmethyl radical.[128,129]



Scheme 4

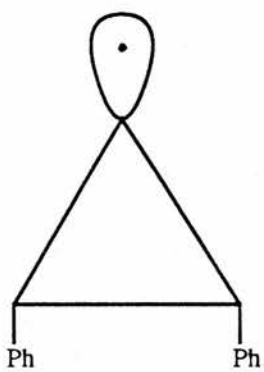
Many investigations have been carried out on the preferred mode of opening of cyclopropyl radicals.[130,131] The rules of orbital symmetry suggest that the preferred mode of ring opening of cyclopropyl cations is disrotary, and for cyclopropyl anions it is conrotary. Molecular orbital considerations are not as helpful for the ring opening of cyclopropyl radicals. Calculations indicate that ring opening is formally forbidden in both the disrotary and conrotary modes, but that a near disrotary mode is favoured for a distorted radical

Experimental evidence also points to a disrotary ring-opening mechanism in the case of the radical. In the particular case of the bicyclic radical (**1**), steric considerations preclude conrotary opening but allow disrotary ring- opening, hence the products are derived from the rearranged radical (**2**).[127]



(1) (2)

The amount of ring opening however is less than would be expected by comparison with cis-2,3-diphenylcyclopropyl radicals (3), which are able to undergo both types of ring opening.[127]



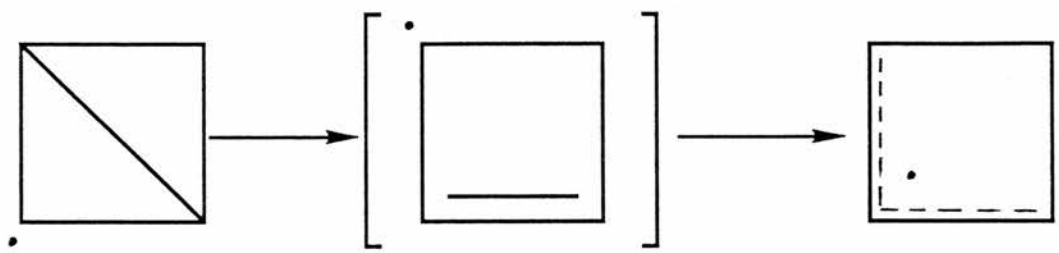
(3)

Therefore it appears that although a disrotary mode is more likely, conrotary processes can also occur.

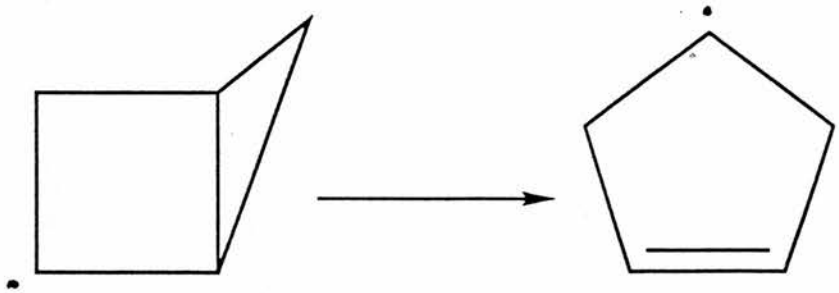
Rearrangement of radical species usually occurs because the product radical is thermodynamically more stable than the initial unrearranged species of radical.. Generally this holds true, particularly for those reactions involving group transfer. The neophyl rearrangement involves a primary radical rearranging to give a tertiary radical (the order of stability being :- tertiary > secondary > primary). Some produce rearranged products which are thermodynamically less favourable. The explanation for this lies in the fact that thermodynamic control does not take into

account any polar or steric effects that may influence the course of a reaction. It was stated previously that ring closure processes can be thought of as the attack on an unsaturated centre by a radical, and so conversely, ring opening can be seen as the disruption of a radical species, such that an unsaturated centre is developed, together with the formation of a new radical centre. Hence ring opening and ring closing reactions are essentially opposite reactions progressing through the same transition state. Beckwith et. al.[132] suggested that for a ring closure process, there must be maximum overlap of the SOMO and π^* orbital in the initial state of the rearrangement. Also, in the final state of the process, there must be overlap of the newly formed σ^* orbital and SOMO. Consequently it can be seen that ring fission requires maximized interaction of the SOMO and σ^* initially, and then overlap of the newly generated π^* and SOMO at the stage following the transition state. These sets of statements covering both ring closure and ring fission of radical species are collectively known as the " stereoelectronic effect ".[132,133]

There do exist examples of radicals undergoing β–scission in a contrasterioelectronic manner (Schemes (5) and (6)).



Scheme 5

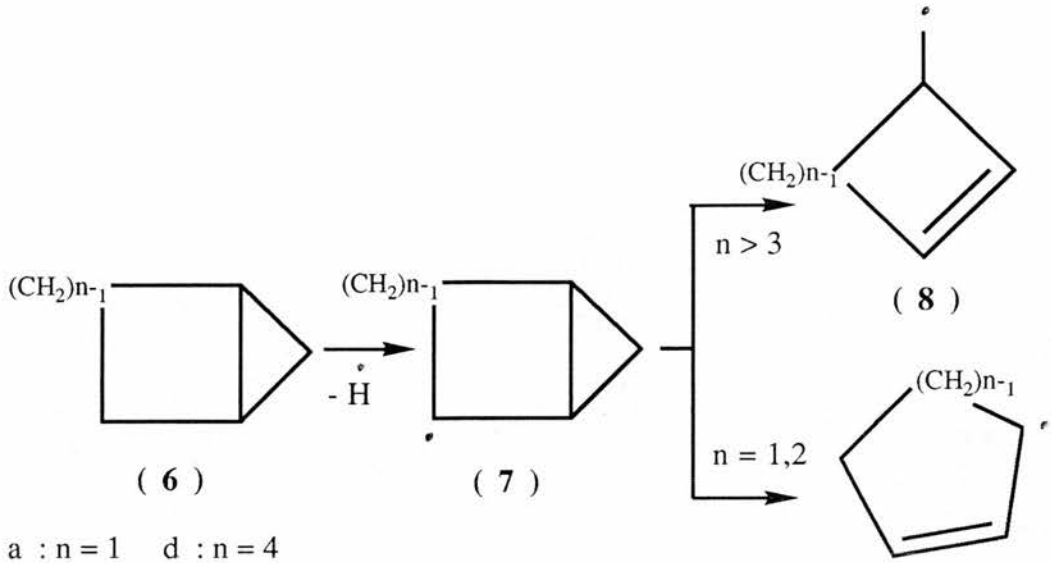


Scheme 6

Bicyclo[1.1.0]but-2-yl radicals (**4**), and bicyclo[2.1.0]pent-2-yl radicals (**5**) undergo β–scission of the β–γ bond which is orthogonal to the SOMO (i.e. the internal cyclopropane bond).[134-136] The probable reason for this contrastereoelectronic effect is that ring strain factors overcome the favourable stereoelectronic effect of external cyclopropane bond fission.

Ring Opening of Bicyclo[n.1.0]alkanes

^{1}H abstraction from the series of bicyclo[n.1.0]alkanes (**6**) produces the corresponding series of bicyclo[n.1.0]alk-2-yl radicals (**7**). These radicals are capable of undergoing β–scission at one of two different bonds (see Scheme 7)



a : n = 1 d : n = 4

b : n = 2 e : n = 5

c : n = 3 f : n = 6

Scheme 7.

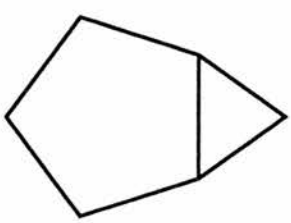
Many studies have been carried out on the bicyclo[n.1.0]alk-2-yl radicals, particularly with n = 3 and n = 4. These have been largely product analysis type studies.[137]

It has been found that chlorination of **6c**, yields products which exhibit little if any rearrangement. However radical chloroformylation of **6c** gives substantial amounts of rearranged products,[138] with approximately equal amounts of product from β–scission of both the internal and external cyclopropane bonds. Generation of radicals **7c** and **7d** by the tri-n-butyltin hydride reduction of the corresponding bicyclo[n.1.0]alkyl chlorides gave products that were mostly a result of external cyclopropane bond fission. A study of the photoreduction of bicyclo[n.1.0]alkan-2-ones (n = 3,4) discovered no trace of any product that resulted from internal cyclopropane bond fission. Instead they found that β–scission was confined exclusively to the external cyclopropane bond.

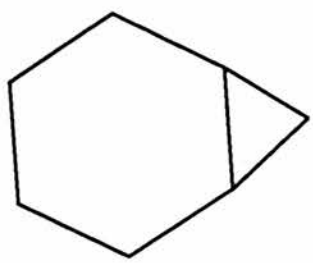
The bicyclo[n.1.0] radicals with n > 3 rearrange by β–scission, to produce the corresponding cycloalkenylmethyl radicals (**8**), but in the case of n = 3 i.e. **7c**, bond fission is observed from both the internal and

external cyclopropane bonds giving **9c** and **8c** respectively. It is likely that radical **9c** formation is favoured with increasing temperature. The species with n = 1,2 (**7a,b**) both undergo β–scission of the internal cyclopropane bond to afford cycloalkenyl radicals.[139] It appears therefore that there is a sharp contrast in the behaviour of the radicals for n = 2 and n = 3, as to which β–γ bond is broken in the ring opening process. For both the bicyclo[n.1.0]alkanes and the bicyclo[n.1.0]alk-2-yl radicals, both ring strain and the degree of overlap of the SOMO changes as n varies (and hence the stereoelectronic effects change with n.). The rate of homolytic ring scission is dependent on both factors. In the first two members of the series (n = 1,2), relief of ring strain outweighs any favourable overlap of the SOMO with the orbitals of the inner-ring bond, and so this bond is cleaved to yield a cycloalkenyl radical.[140-142] For higher members (n > 2) stereoelectronic control predominates i.e. the favourable overlap of the SOMO with the outer cyclopropane bond orbitals ensures that this bond breaks to give cycloalkenylmethyl radicals.

Previous workers have studied the photobromination reactions of both (**10**) and (**11**), by reaction with molecular bromine at *ca.* room



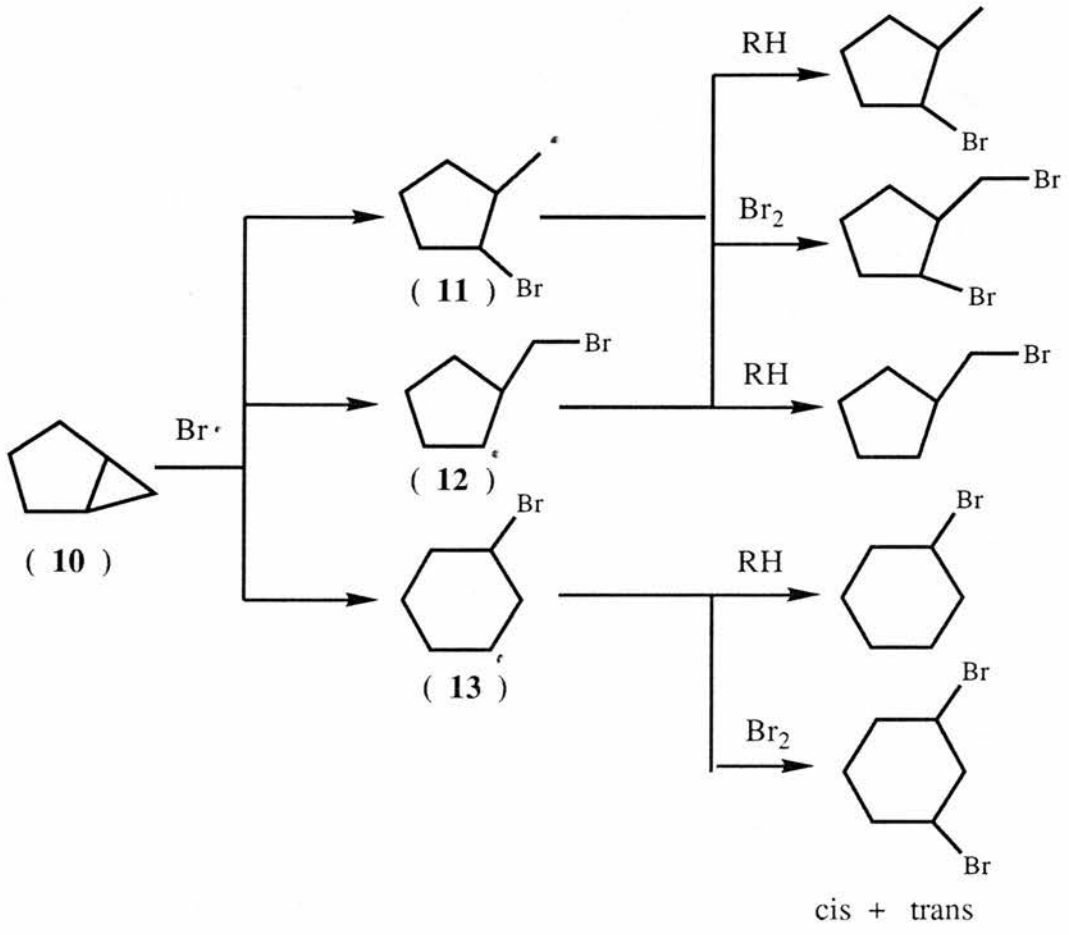
(**10**)



(**10***)

temperature in CCl_4. In the case of (**10**), reaction was completed in 1-2 mins approximately,[143] but for (**10***) a longer reaction time of *ca.* 20 mins was required. The major products for both compounds were largely a result of bimolecular homolytic substitution processes (S_H2).

The appropriate mechanisms for the reactions of (**10**) are indicated in Scheme 8.[29,144]

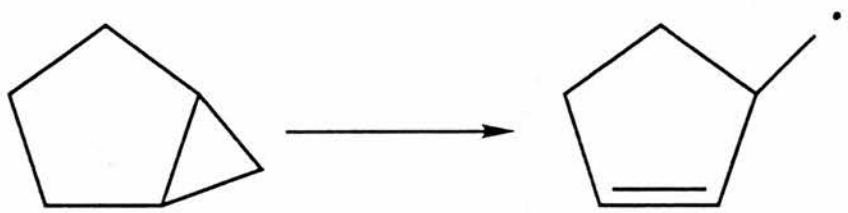


Scheme 8

Analogous products were obtained with bicyclo[4.1.0]heptane (**10***). Radical (**11**) was obtained as a result of bromine attack on the methylene carbon of the ring. Radical (**12**) was the result of bromine attack in the bridgehead carbon, followed by external cyclopropane bond fission, whereas radical (**13**) was the result of internal cyclopropane bond fission, preceded by bromine attack on the bridgehead carbon. Once any of these radicals has been formed, the possibility then exists either for further bromine abstraction or abstraction of hydrogen (from HBr

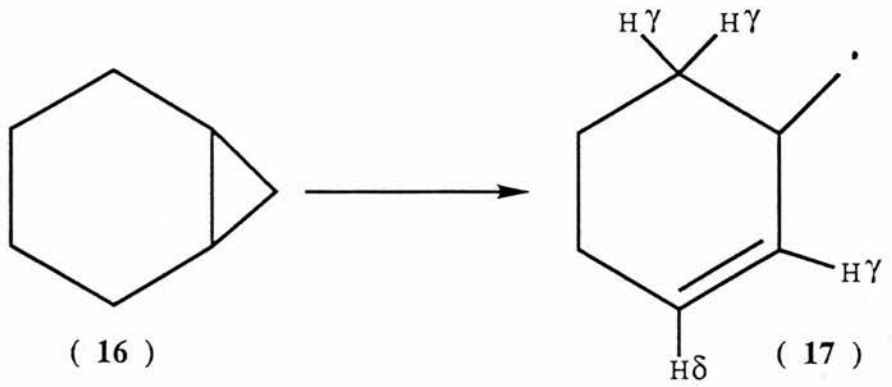
formed in solution or from the substrate itself), to yield the mixture of mono- and di-bromides. Chlorination experiments also performed on bicyclo[4.1.0]heptane (**10***) gave products entirely analogous to those obtained with the bromination reactions.[138]

The same workers performed a series of experiments investigating the EPR spectra obtained on ^1H abstraction from bicyclo[n.1.0]alkanes, using either di-tert butyl peroxide. ^1H abstraction from bicyclo[3.1.0]hexane (**10**) was found to produce a spectrum consisting of a doublet of triplets from two α–hydrogens and one β–hydrogen. Further fine structure was observed but not resolved and the spectrum was attributed to the cyclopentylmethyl radical (**15**).



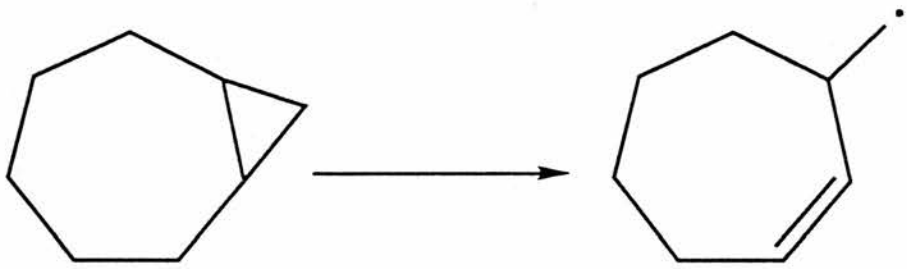
(**14**) (**15**)

Similarly, ^1H abstraction from bicyclo[4.1.0]heptane (**10***) produced a spectrum once again consisting of a doublet of triplets from two α–hydrogens and a single β–hydrogen. Low temperature spectra obtained enabled these workers to assign fine structure to the coupling of γ– and σ– hydrogens. The spectrum was assigned to the cyclohexenylmethyl radical (**17**).

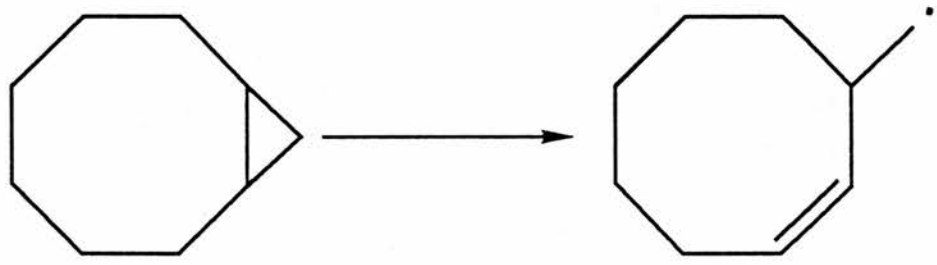


(**16**) (**17**)

The higher members of the series, bicyclo[5.1.0]octane (**18**), and bicyclo[6.1.0]nonane (**20**) produced EPR spectra that were due to the cycloheptenylmethyl- (**19**) and cyclo-octenylmethyl- (**21**) radicals respectively.

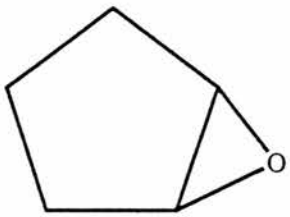


(**18**) (**19**)

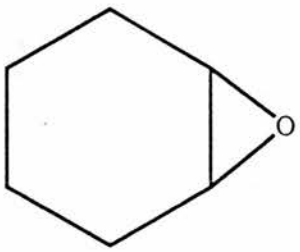


(**20**) (**21**)

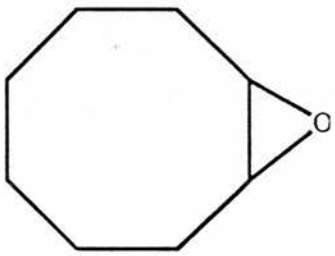
The remainder of this chapter is devoted to reporting the results of a study on some cyclic epoxides. Three epoxides in particular were examined; these were cyclopentene oxide (**22**), cyclohexene oxide (**23**), and cyclo-octene oxide (**24**).



(**22**)



(**23**)



(**24**)

These compounds were of interest because they are analogous to the bicyclo[n.1.0]alkanes that have been previously discussed. The effect of the oxygen atom in the three-membered ring on the mode of bond cleavage of these compounds was particularly intriguing. Various photobromination and EPR studies were carried out on each compound; the products were examined by GC / MS.

EPR and Photobromination Studies on Cyclopentene Oxide

Cyclopentene oxide was dissolved in tert-butyl benzene and a small amount of di-tert butyl peroxide added, and the mixture photolysed in the cavity of the EPR spectrometer over the temperature range 210-320 K. The spectrum obtained at 240 K is shown in Fig 1.

The spectrum analyses for a (1H) = 2.3 G, a (1H) = 15.0 G and a (2H) = 19.7 G, and is attributed to the allyl type radical shown below (**25**).

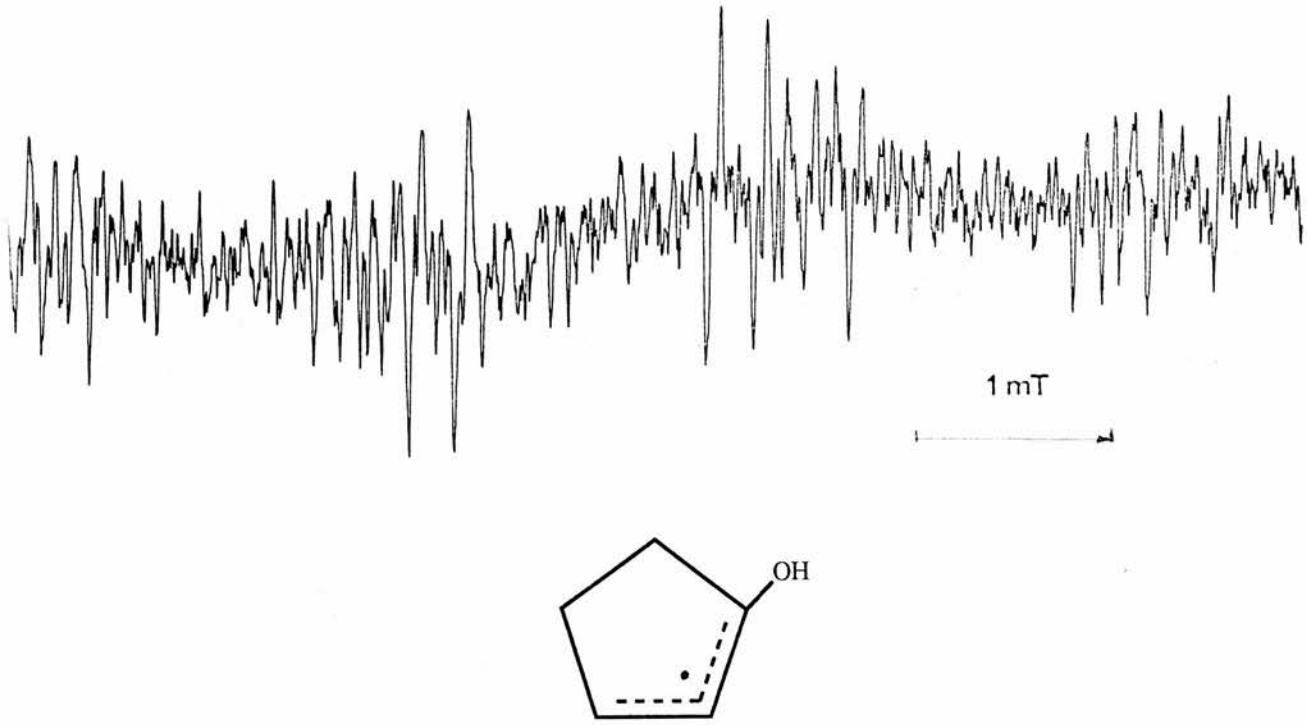
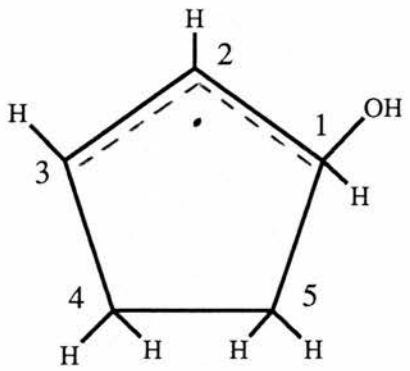


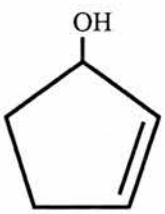
Fig. 1. 9.2 GHz EPR spectrum of the radical derived from cyclopentene oxide, at 240 K, in *tert*-butylbenzene.



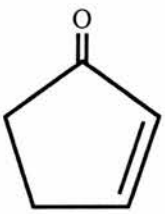
(**25**)

The hyperfine splittings for the hydrogens on C(4) were not detected, but it is thought that these would appear on the outer parts of the spectrum which was not recorded. This type of radical has been detected previously by Gilbert et al.[145] In that instance the allyl radical was prepared by the reaction of 2-cyclopentenyl hydroperoxide with $TiCl_3 / H_2O$. They reported hfs of a (1H) = 2.3 G, a (1H) = 14.9 G, a (2H) = 20.0 G, and a (2H) = 19.2 G for the hydrogens on C(2), C(3), C(4), and C(5) respectively at 300 K. These figures are in good agreement with the values that we have obtained.

The photolysed mixture from the EPR experiment was then analysed by GC / MS. Table 1 on page 173 summarises the GC / MS data for the major product components. The main products appear to be (**26**) and (**27**).

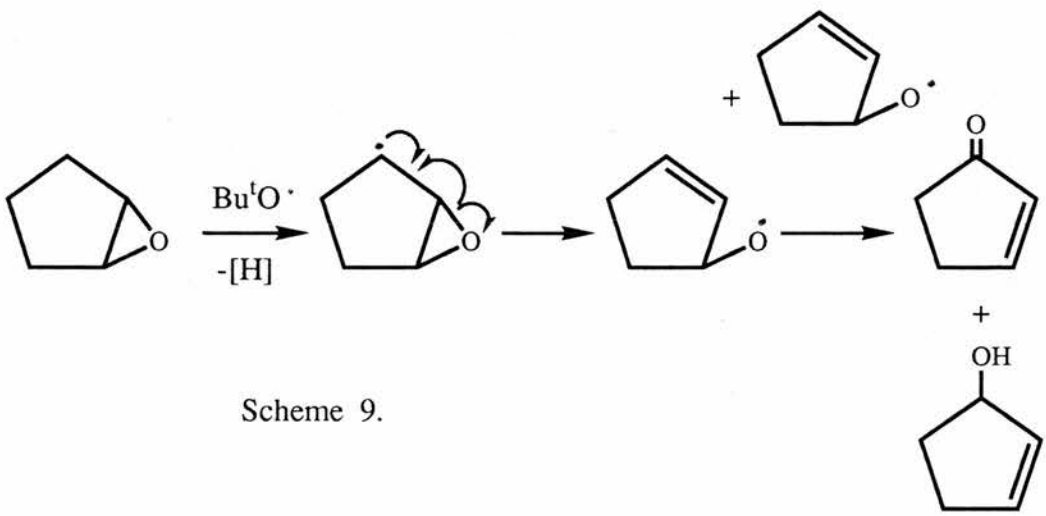


(**26**)



(**27**)

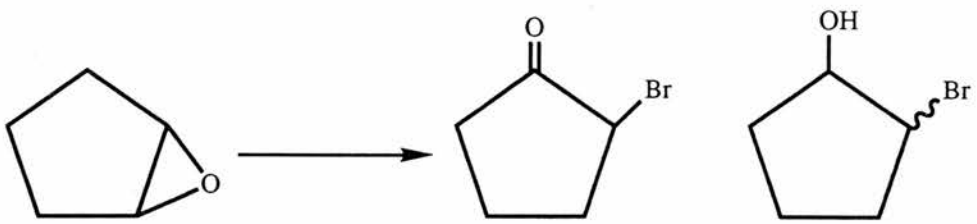
These are thought to occur by a disproportionation type of reaction as opposed to a bimolecular homolytic substitution reaction (S_H2). Scheme 9. indicates a likely mechanism for this process.



Scheme 9.

The GC / MS trace also showed the presence of Bu^{t}OH, BOOB, Bu^{t}Ph and unreacted cyclopentene oxide.

Two bromination experiments were performed with cyclopentene oxide, the first involving the reaction with NBS and 5mol% benzoyl peroxide. The mixture was refluxed in CCl_4 for ca. 60 hours, followed by filtration of the succinimide and removal of the solvent under reduced pressure. In the second experiment, bromine in deaerated CCl_4 was added to a deaerated mixture of cyclopentene oxide in CCl_4, with photolysis from an Hg arc lamp for 2 hours. Tables 2 and 3 on pages 173-4 , summarise the GC / MS data obtained from these experiments. In the case of the experiment with NBS, only two major products were detected; 2-bromocyclopentanone and 2-bromocyclopentanol (*cis* and / or *trans*).



4.2 : 1

Area calculations from the GC / MS spectra gave an approximate ratio of these products of 4.2 : 1. The second bromination experiment yielded only one major product : 2-bromocyclopentanol (*cis* or *trans*).

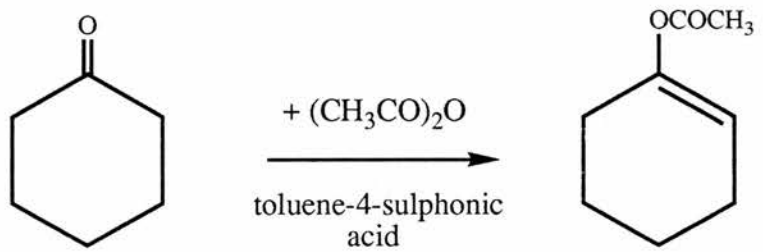
Cyclopentene oxide was mixed with CCl_3Br and photolysed with light from a 250 W Hg arc lamp for 8 hours. Table 4. on page 174 summarises the GC / MS data obtained from this experiment. A highly complex mixture of components was obtained, but the main products detected were :- 2-chlorocyclopentanol (*cis* and *trans*) and 2-bromocyclopentanol (*cis* and *trans*). Other species present on the scan were CCl_3Br, C_2Cl_6, $C_5H_7OCCl_3$ and dibrominated compounds of molecular formula $C_5H_9OBr_2$. Area calculations from the GC / MS spectra gave an approximate ratio of the two 2-chlorocyclopentanol compounds as approximately 1.2 : 1; and the two 2-bromocyclopentanol compounds as approximately 2.7 : 1. No further work was done to establish whether these ratios were *cis* : *trans* or *trans* : *cis*, as only the nature of the opening of the epoxide ring was of interest.

EPR and Bromination Studies on Cyclohexene Oxide

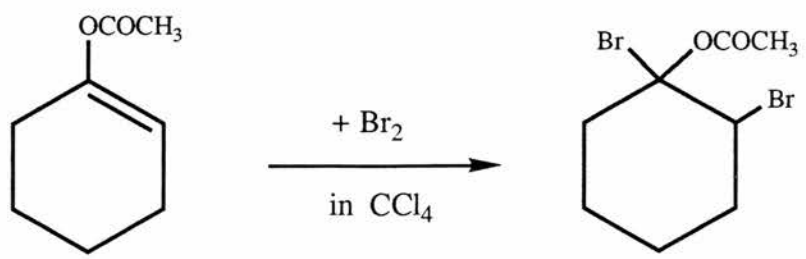
A number of compounds were synthesized that were anticipated to be possible products from the bromination reactions on cyclohexene oxide. This was necessary in order to assist in identifying the products from

retention time comparisons and fragmentation patterns of authentic compounds.

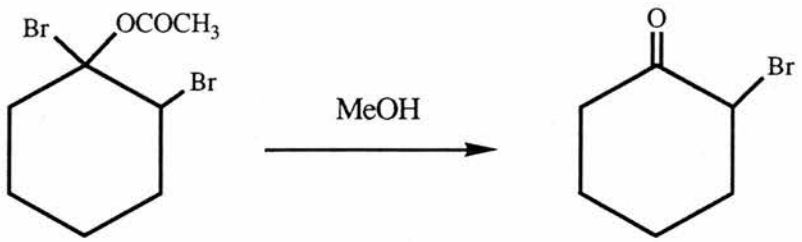
2-bromocyclohexanone was prepared by three routes. The first method[146] involved the addition of bromine to a mixture of cyclohexanone and chalk (calcium carbonate), the rate being controlled so that the temperature of the reaction remained at approximately 50°C. The mixture was then stirred for varying periods of time. This method produced unpredictable results, the reaction mixture having a tendency to explode (probably due to the presence of the chalk) even upto 1 hour after the bromine addition was complete and when the reaction appeared stable. A second, alternative method was used,[147] which required a three stage synthesis. Initally cyclohexanone enol acetate was formed by the reaction of cyclohexanone with acetic anhydride employing p-toluene sulphonic acid as a catalyst.



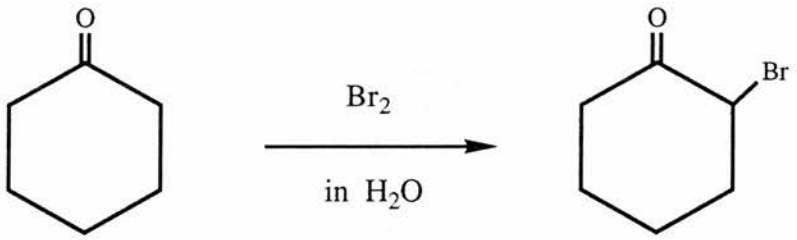
The enol acetate was brominated by reaction with liquid bromine in CCl_4.



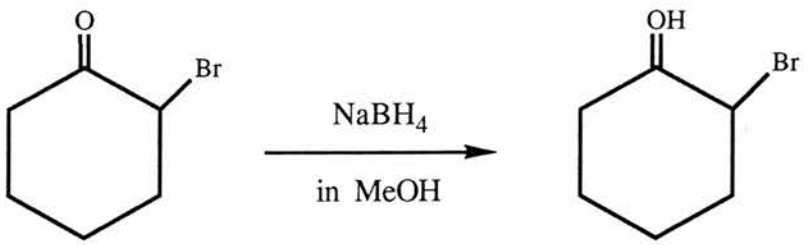
The final stage of the preparation, formation of the α–bromoketone (2-bromocyclohexanone), required the reaction of the brominated enol acetate with methanol, the mixture being allowed to stand for ca. 48 hours.



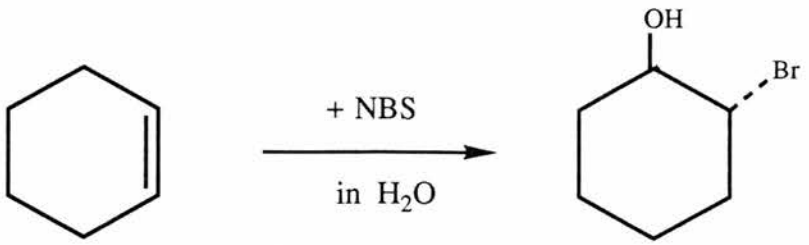
This method produced acceptable results. A third and simpler method[148] was also used wherby 2-bromocyclohexanone was formed by the reaction of cyclohexanone and bromine in water



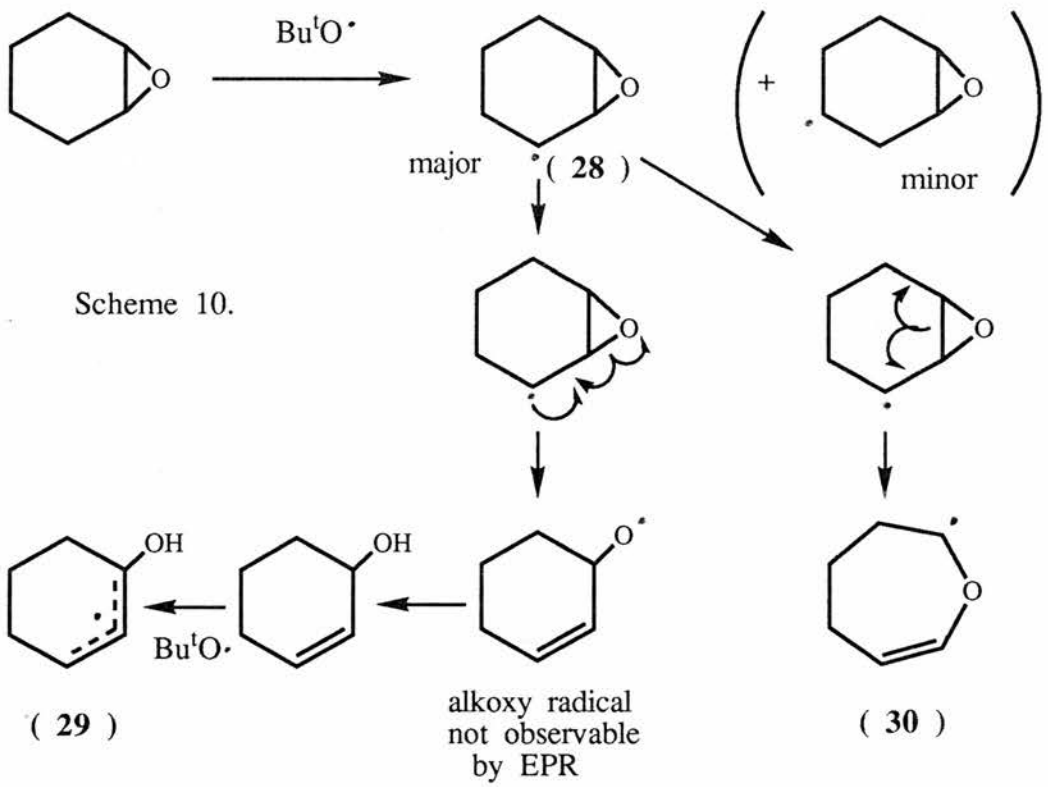
cis-2-Bromocyclohexanol was synthesized by the reaction of 2-bromocyclohexanone with sodium borohydride in methanol.[149]



The formation of *trans*-2-bromocyclohexanol involved the reaction of cyclohexene with NBS in water.[150]



Cyclohexene oxide was dissolved in *tert*-butylbenzene, and a small amount of BOOB added. The mixture was photolysed in the cavity of the EPR spectrometer and spectra were recorded over the temperature range 205-260 K. It was anticipated that there could be three possible major radicals produced, according to scheme 10 .

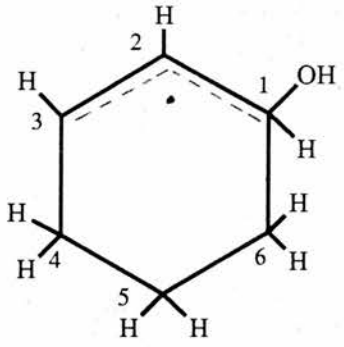


Scheme 10.

Radical (**29**) is the result of fission of an internal bond of the epoxide ring, radical (**30**) being the product of internal fission, both caused by the rearrangement of the major radical (**28**). Unfortunately no radicals were detected over the temperature range covered. The experiment

was repeated, this time in neat BOOB, but once again no radicals were detected over the extended temperature range 205-345 K.

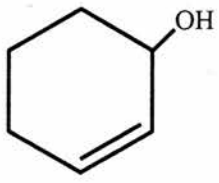
By analogy with the EPR results obtained with cyclopentene oxide, it would be expected that signals would have been observed from an allyl type radical (**31**).



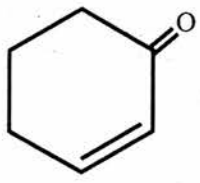
(**31**)

This radical has been reported by Gilbert et al,[145] and was made by the reaction of 2-cyclohexenyl hydroperoxide with $TiCl_3$ in water, using a pH 1-2 flow system. The assignments for the hfs that they reported were as follows :- H (2) = 3.50 G, H (3) = 15.0 G, H (4) = 31.5 G, H (6) = 30.0 G(note :- the assignments for both H (4) and H (6) were doublet splittings, probably representing the sum of two proton splittings; and the assignments for H (4) and H (6) may be reversed).

The photolysed mixture from the EPR experiment containing t-butyl benzene was analysed by GC / MS. Table (5) on page 175 summarises the GC / MS data for the major product components. The main products appear to be (**32**) and (**33**).



(**32**)



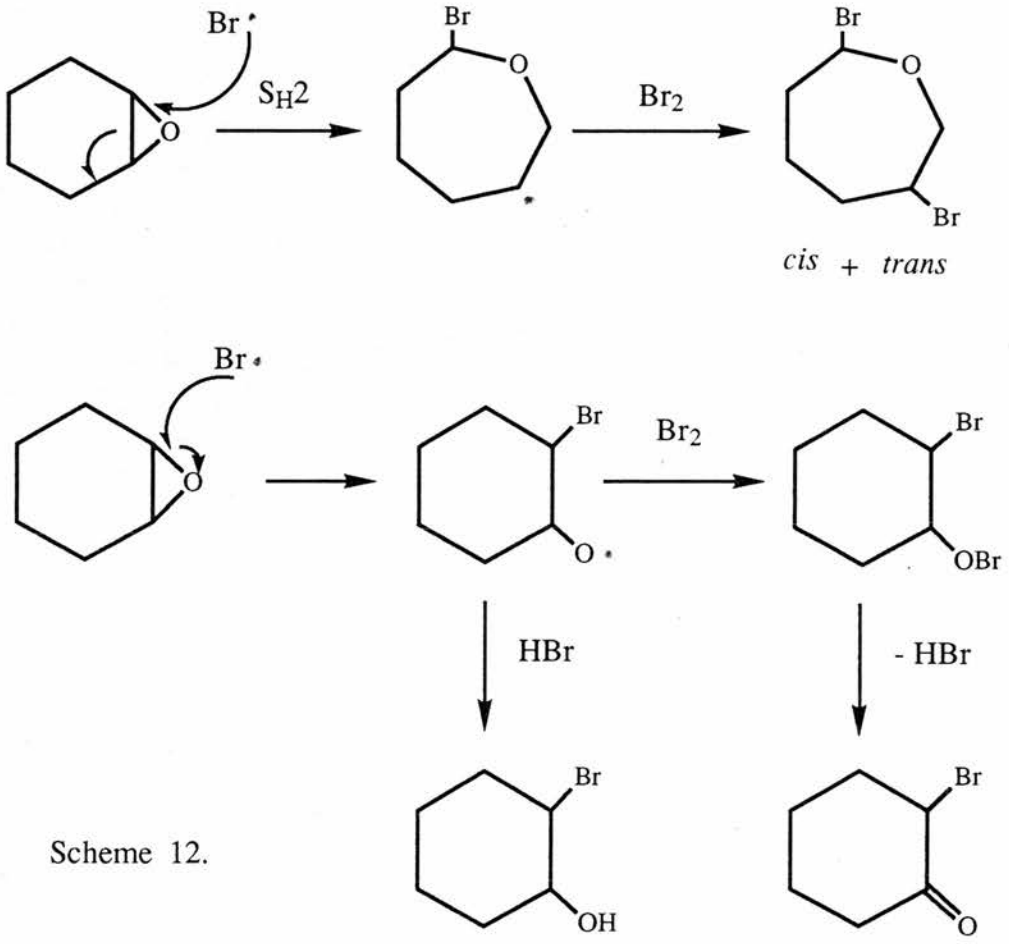
(**33**)

It is suggested that these could have occured by the disproportionation of two alkoxy radicals shown in scheme 11.

Scheme 11.

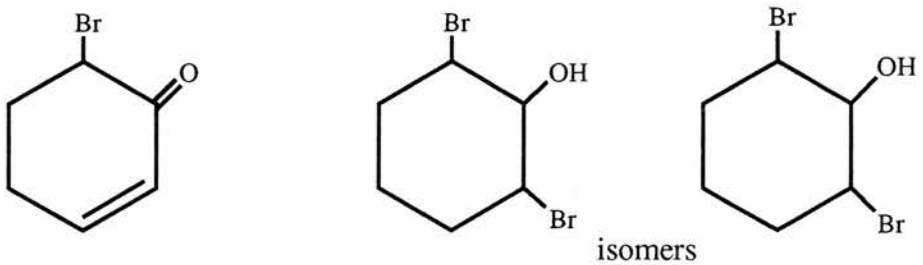
A minor amount of cyclohexanone was detected in the spectrum, together with the unreacted starting material, BOOB and *tert*-butylbenzene.

Two bromination experiments were carried out with cyclohexene oxide, one involving the reaction with NBS and 5mol% benzoyl peroxide, the mixture being refluxed in CCl_4 for ca. 60 hours. The crude reaction mixture was purified by distillation under reduced pressure. In the second experiment, bromine in deaerated CCl_4 was added dropwise to a deaerated mixture of cyclohexene oxide in CCl_4, with photolysis for ca. 2 hours from a tungsten lamp. Tables (6) and (7) on page 176 summarise the GC / MS data obtained from these experiments. In both cases, a number of possible products could result from both internal and external bond fission of the epoxide ring. Scheme (12) indicates the probable routes by reaction with bromine radicals



Scheme 12.

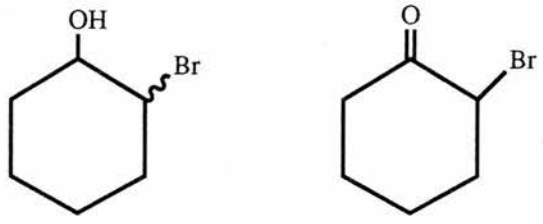
The main product from the bromination reaction with NBS was 2-bromocyclohexanone, together with smaller amounts of the three compounds shown below (**34-36**)



(**34**) (**35**) (**36**)

In the case of the reaction of cyclohexene oxide with Br_2, the major products were 2-bromocyclohexanol and 2-bromocyclohexanone. Area calculations from the GC / MS analysis gave an approximate ratio of

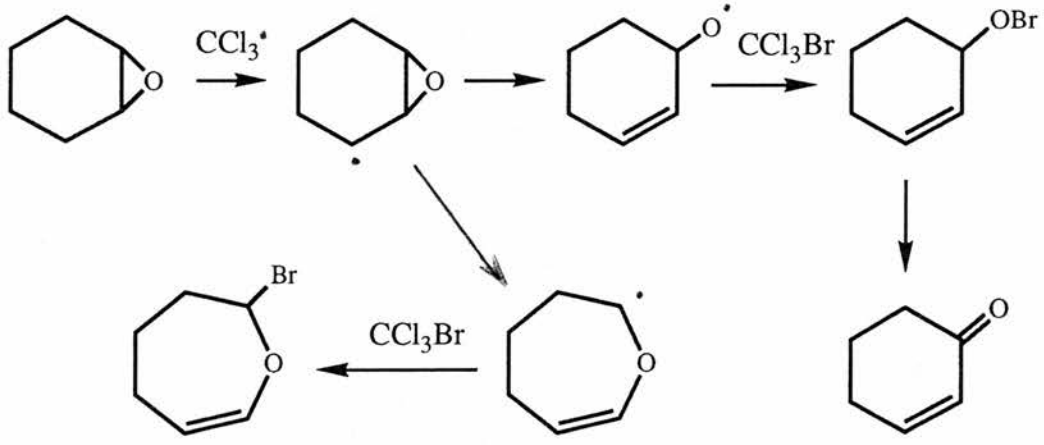
calculations from the GC / MS analysis gave an approximate ratio of these products of 3.5 : 1 respectively.



3.5 : 1

Compound (**34**) was also present, together with some dibrominated species.

Cyclohexene oxide was mixed with CCl_3Br and photolysed with light from a 250 W Hg arc lamp lamp for 12 hours. Table (8) on page 177 , summarises the GC / MS data obtained from this experiment. Once again two major reaction routes can be envisaged. (Scheme 13.)



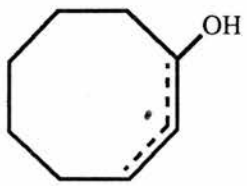
Scheme 13.

A complex mixture of products was obtained, but the main component was 2-bromocyclohexanol.

EPR and Bromination Studies on Cyclo-octene Oxide.

Cyclo-octene oxide was dissolved in *tert*-butylbenzene, and a small amount of BOOB added. The mixture was photolysed in the cavity of the

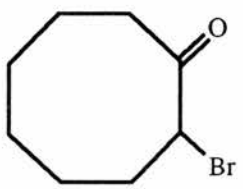
EPR spectrometer over the temperature range 220-320 K. Unfortunately no radicals were detected, even after repeated purification of the mixture through a plug of activated alumina. Once again it was anticipated that an allyl type radical (**37**) would have been observed.



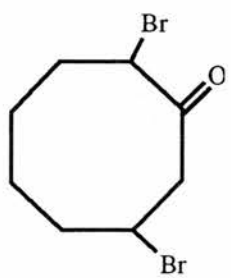
(**37**)

The photolysed mixture from the EPR experiment was analysed by GC / MS (Table 9, page 178). Three components were present ; *tert*-butylbenzene, BOOB, and the unreacted cyclo-octene oxide.

Two bromination experiments were undertaken with cyclo-octene oxide. The first involved the dropwise addition of bromine in deaerated CCl_4, to a deaerated mixture of cyclo-octene oxide in CCl_4. The mixture was photolysed with light from a 250 W medium pressure Hg arc lamp for two hours. The reaction mixture was analysed by GC / MS after removal of the CCl_4 under reduced pressure (Table 10, page 178) The two main products were (**38**) and (**39**).



(**38**)



(**39**)

These are thought to have been formed by similar mechanisms to those proposed for cyclopentene oxide and cyclohexene oxide.

In the second bromination experiment, cyclo-octene oxide was mixed with CCl_3Br, and photolysed with light from a 250 W medium pressure Hg arc lamp for 12 hours. An extremely complex mixture of products was produced, but GC / MS data (Table 11, page 179) indicated that the largest component 2-bromo-cyclo-octanone (**38**).

Conclusions

The study of the three cyclic epoxides, cyclopentene oxide, cyclohexene oxide and cyclo-octene oxide, has revealed that for a ring size of 5, 6 and 8 carbon atoms in length, the preferred mode of scission is β-scission of the external epoxide bond. The EPR result for cyclopentene oxide, and the compounds produced from the bromination reactions with Br_2, NBS and CCl_3Br are all consistent with this mode of ring opening. These observations are analogous to the results quoted for the bicyclo[n.1.0.] alkanes, and it would appear therefore, that for the three members of the series that we have studied at least, that the presence of the oxygen atom, does not influence the mode of ring opening to an appreciable degree.

Experimental

(Attempted) Preparation of 2-Bromocyclohexanone[159] Cyclohexanone (60g, 0.61mol), water (40ml) and chalk (calcium carbonate) (30.0g, 0.3mol) were mixed together and stirred on a water bath. Bromine (32ml, 1.24mol) was added dropwise at such a rate that the temperature of the reaction mixture remained at approximately 50°C. The resulting brown solution was stirred for a further 30 minutes without heating. Approximately 1 hour after the addition of the bromine was complete the reaction mixture spontaneously heated up causing an explosive release of the contents. Subsequent attempts using this method resulted in the same observation. It appears that the presence of the chalk provides nucleation sites for a highly exothermic reaction to take place. Alternative methods outlined below were used to synthesize 2-bromocyclohexanone.

2-Bromocyclohexanone (3-stage synthesis)[147]

(i) **Cyclohexanone Enol Acetate** Cyclohexanone (15.0g, 0.153mol), acetic anhydride (31.24g, 0.306mol) and p-toluene sulphonic acid (0.153g, 8×10^{-4} mol) (i.e. 1g per mol of cyclohexanone), were heated for *ca.* 4 hours. During this time acetic acid together with some acetic anhydride were allowed to distil off, care being taken not to allow the temperature of the reaction mixture to rise above 125°C (to avoid excessive losses of acetic anhydride). The residue was added to water (100ml) and the whole mixture extracted with ether (3 x 150ml). The combined ether extracts were washed with water (2 x 200ml) and 5% sodium carbonate solution (2 x 200ml) (to remove any acid present), and dried ($MgSO_4$). The drying agent was filtered off and the solvent removed under reduced pressure to leave a brown-orange liquid. This was purified by distillation on a Buchi Kugelrohr to give the title compound as a colourless liquid

(14.0g, 65.4%), bp. 95°C / 22Torr (lit[147] yield 68%, b 74-76°C / 17Torr). δ_H (200MHz) 1.4-1.85 (5H, m), 2.0 (5H, bs), 2.25 (1H, t, J = 2Hz), 5.25 (1H, bs); δ_C (50MHz) 21.4 (1C), 22.1 (1C), 23.0 (1C), 24.0 (1C), 27.2 (1C), 114.4 (1C), 148.8 (1C), 169.8 (1C).

(ii) **Bromination of Cyclohexanone Enol Acetate** Cyclohexanone enol acetate (12.0g, 0.086mol) was dissolved in twice its volume of CCl_4 and cooled on an ice bath. Bromine (6.85g, 0.086mol) was dissolved in an equal volume of CCl_4, and then slowly added to the above mixture with constant agitation, care being taken not to allow the temperature of the mixture to rise above 10°C. No further purification of the product was necessary before the next stage of the synthesis, formation of the α–bromoketone, 2-bromocyclohexanone

(iii) **Formation of the α–Bromoketone, 2-Bromocyclohexanone** The brominated cyclohexanone enol acetate formed above was added to an equal volume of methanol (Analar), with cooling on an ice bath. The mixture was allowed to stand for 2 days, during which time the solution turned from clear to pale pink. The mixture was then diluted with an equal volume of water, and the separated oil washed with 5% aqueous sodium carbonate solution to remove any acid present. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure, the residual liquid being distilled under reduced pressure to yield the α–bromoketone (2-bromocyclohexanone) (7.28g, 48.0%), bp. 105°C / 22Torr. (lit[147], yield 46%, bp. 112-113°C / 20Torr). δ_H (200MHz) 1.6-1.9 (6H, m), 2.2-2.35 (2H, m), 3.10-3.25 (1H, m); δ_C (75MHz) 20.6 (1C), 22.4 (1C), 27.5 (1C), 32.3 (1C), 54.0 (1C), 205.0 (1C).

2-Bromocyclohexanone[148] Cyclohexanone (10.0g, 0.1mol) was mixed with water (30ml), and bromine was added dropwise to the stirred heterogeneous mixture during 1 hour, while the temperature was maintained at ca. 5°C (ice-water bath). The mixture was stirred for a further 12 hours and allowed to warm upto room temperature during this period, forming a white solution of two layers. The organic layer was separated off and the aqueous layer extracted with ether (3 x 150ml). These extracts were combined with the organic layer and the whole solution washed with water (150ml) and saturated NaCl solution (200ml) and dried (Na_2SO_4). After removal of the drying agent by filtration and evaporation of the solvent, the crude product was distilled on a Buchi Kugelrohr to give the desired 2-bromocyclohexanone as a very pale orange liquid (12.94g, 71.3%), bp. 95°C / 12Torr (lit[148] 112-113°C / 20Torr) δ_H (200MHz). 1.3-1.95 (5H, m), 2.0-2.4 (2H, m), 2.7-2.9 (1H, m), 4.3-4.4 (1H, m); δ_C (50MHz) 25.2 (1C), 27.2 (1C), 37.3 (1C), 38.5 (1C), 54.2 (1C), 203.6 (1C).

Cis-2-Bromocyclohexanol[149] 2-bromocyclohexanone (8.0g, 0.045mol) was mixed with methanol (20ml), and 1.5mol eq of sodium borohydride (2.55g, 0.068mol) was added portionwise. During this addition the purple solution turned pale yellow in colour and heat was evolved. Stirring was continued for a further 2 hours. 100ml of water was added to the mixture which was then extracted with ether (3 x 150ml). The combined ether extracts were dried (Na_2SO_4). The drying agent was filtered off and the solvent removed under reduced pressure leaving 5.89g of a pale yellow liquid as the crude product. This was further purified by distillation on a Buchi Kugelrohr to yield the title compound as a colourless liquid (3.71g, 46.1%), bp. 65°C / 1Torr (lit[149] M.p. 28.5-29.0°C, ν_{max}(liquid film) 3450cm^{-1} (OH)) δ_H (200MHz) 1.2 (2H, t, J =

2Hz), 2.05 (2H, s), 2.35 (2H, t, J = 4Hz), 3.44 (2H, s), 3.67 (1H, s), 4.95 (1H, bs); δ_C (50MHz) 20.2 (1C), 22.0 (1C), 27.1 (1C), 32.0 (1C), 62.0 (1C), 70.4 (1C).

Trans-2-Bromocyclohexanol[150] Cyclohexene (8.22g, 0.1mol) was mixed with water (50ml) and NBS (17.80g, 0.1mol) was added. The mixture was stirred vigorously at room temperature for 48 hours, during which time the solution turned from pale orange in colour, to a clear solution with the white succinimide floating on the top. The organic layer was separated and combined with ether extracts of the aqueous layer (3 x 100ml). The combined organic phase was washed with water (150ml) and saturated NaCl solution (150ml), and then dried over $MgSO_4$. After removal of the drying agent and evaporation of the solvent, the crude product was obtained as a pale yellow liquid (16.15g). The product was purified by distillation on a Buchi Kugelrohr to give trans-2-bromocyclohexanol as a colourless liquid (12.91g, 73%), bp. 154°C / 25Torr (lit[150] b.p. 87-87.5°C, M.p. 26.5-26.7°C, ν_{max} (liquid film) 3400cm^{-1} (OH)). δ_H (200MHz) 1.2-1.5 (2H, m), 1.6-1.95 (3H, m), 2.05-2.20 (1H, m), 2.25-2.40 (1H, m), 3.55-3.70 (1H, m), 3.72 (1H, bs), 3.85-4.0 (1H, m); δ_C (50MHz) 24.0 (1C), 26.4 (1C), 33.7 (1C), 61.0 (1C), 75.0 (1C).

Bromination of Cyclopentene Oxide with NBS Cyclopentene oxide (1.0g, 0.012mol), NBS (2.49g, 0.014mol) and CCl_4 (25ml) were mixed together. Benzoyl peroxide (5mg) was added and the mixture was refluxed for 60 hours. During this time the NBS was converted to succinimide which floated to the top of the reaction mixture. The solution was allowed to cool down to room temperature and the succinimide was filtered off leaving a pale orange liquid. The CCl_4 was removed under

reduced pressure to leave an orange liquid. GC / MS analysis showed this liquid to consist of a number of components. Table (2) on page 173 , summarises the data for these products.

Bromination of Cyclopentene Oxide with Br_2 Bromine (1.0g, 0.013mol) in deaerated CCl_4 (10ml) was added dropwise to a deaerated solution of cyclopentene oxide (1.0g, 0.012mol) in deaerated CCl_4 (10ml). The solution was stirred at room temperature for 24 hours, during which time the solution turned from orange to almost colourless. The CCl_4 was evaporated off under reduced pressure to leave a pale yellow liquid. GC / MS analysis showed that this liquid consisted of several components; table (3) on page 174 , gives the data for these products.

Bromination of Cyclopentene Oxide with CCl_3Br Cyclopentene oxide (200mg, 2.4 x 10-3 mol) and CCl_3Br (1ml) were placed in an NMR tube. The mixture was photolysed with light from a 250 W medium pressure Hg arc lamp for 3 days. During this time turned from almost colourless to deep brown. GC / MS analysis showed an extremely complex mixture of products and table (4) on page 174, gives the data on the main components.

Bromination of Cyclohexene Oxide with NBS Cyclohexene Oxide (5.0g, 0.05mol), NBS (10.68g, 0.06mol) and CCl_4 (50ml) were mixed together . Benzoyl peroxide (0.1g, 5mol%) was added and the mixture was refluxed for ca. 60 hours. During this time the NBS was converted to succinimide, and this floated to the top of the reaction mixture. The solution was allowed to cool down to room temperature and the succinimide was filtered off leaving an orange/brown liquid, after

removal of the solvent, CCl_4, under reduced pressure. Table (6) on page 176 summarises the GC/MS data for the component mixture.

Bromination of Cyclohexene Oxide with Br_2 Bromine (4.5g, 0.06mol) in deaerated CCl_4 (50ml) was added dropwise to a deaerated solution of cyclohexene oxide (5.0g, 0.05mol) in CCl_4 (50ml). The solution was stirred at room temperature for 2 hours with photolysis from a 250 W medium pressure Hg arc lamp. During this time the colour of the solution turned from deep orange to pale orange in colour. The CCl_4 was evaporated off under reduced pressure to leave an orange liquid. GC/MS analysis showed that this liquid consisted of several components and table (7) on page 176, gives the data on these.

Bromination of Cyclohexene Oxide with CCl_3Br Cyclohexene oxide (200mg, 2.04 x 10-3mol) and CCl_3Br (1ml) were placed in an NMR tube. The mixture was photolysed with light from a 250 W medium pressure Hg arc lamp for 3 days. During this time the mixture turned from almost colourless to dark brown in colour. GC / MS analysis indicated the presence of many component products; table (8) on page 177, gives the data on the major ones of interest.

Bromination of Cyclo-octene Oxide with Br_2 Bromine (0.3g, 4 x 10^{-3}mol) in CCl_4 (10ml) was added to a deaerated solution of cyclo-octene oxide (0.5g, 4 x 10^{-3}mol) in CCl_4 (10ml). The solution was stirred for 2 hours at room temperature with photolysis from a 250 W Hg arc lamp. During this time the mixture turned from deep orange in colour to faint yellow. The CCl_4 was evaporated off under reduced pressure to leave an orange/yellow liquid. Table (10) on page 178, provides the GC/MS data on the component products.

Bromination of Cyclo-octene Oxide with CCl_3Br Cyclo-octene oxide (200mg, 1.6 x 10^{-4}mol) and CCl_3Br (1ml) were placed in an NMR tube. The mixture was photolysed with light from a 250 W medium pressure Hg arc lamp for 3 days. Over this period the solution turned from almost colourless to dark brown. GC / MS analysis indicated the presence of many components and table (11) on page 179 , gives the data on some of these.

Table (1)

GC / MS data on the products of the photolysis of Cyclopentene Oxide with BOOB

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
1 : 22min	72, 59(32), 43(100), 31(39), 27(30), 15(57).	$C_4H_{10}O$ (Bu^tOH)
1 : 57 min	83(15), 55(67), 41(78), 39(56), 29(72), 28(59), 27(100), 26(38).	C_5H_8O
2 : 17 min	146(3), 85(5), 73(7), 57(100), 41(61), 29(55), 27(90), 15(35).	$C_8H_{18}O_2$ (Bu^tOOBu^t)
2 : 58 min	82(61), 81(19), 54(37), 53(88), 39(100), 27(66), 26(49).	C_5H_6O

Table (2)

GC / MS data on the products of the reaction of Cyclopentene Oxide with NBS

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
7 : 57 min	164(4), 162(5), 134(2), 121(1), 108(12), 106(11), 83(49), 55(100), 27(82).	C_5H_7OBr
8 : 19min	166(2), 164(2), 146(1), 85(18), 67(22), 57(100), 41(38), 29(49).	C_5H_9OBr

Table (3)

GC / MS data on the products of the reaction of Cyclopentene Oxide with Br_2

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
9 : 09 min	164(4), 166(4), 147(4), 85(14), 67(65), 57(100), 41(34), 29(35).	C_5H_9OBr
17 : 20 min	151(4), 149(6), 147(4), 68(26), 67(100), 41(41), 27(18).	$C_5H_8OBr_2$ m+ absent

Table (4)

GC / MS data on the products of the reaction of Cyclopentene Oxide with CCl_3Br

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
2 : 17 min	163(32), 121(94), 117(100), 82(42), 81(35), 47(94), 35(93).	CCl_3Br
6 : 59 min	120(4), 103(6), 102(5), 71(6), 67(61), 57(100), 41(34), 27(29).	C_5H_9OCl
8 : 10 min	120(3), 102(4), 71(7), 67(12), 57(100), 41(18), 29(14), 27(22).	C_5H_9OCl
9 : 00 min	203(33), 201(56), 199(35), 166(34), 121(93), 117(100), 94(30), 57(82).	C_2Cl_6
9 : 42 min	166(4), 164(4), 146(2), 136(3), 85(26), 67(25), 57(100), 29(35).	C_5H_9OBr
13 : 19 min	200(5), 172(4), 165(4), 137(9), 109(28), 101(24), 83(50), 55(100)	$C_5H_7OCCl_3$ m+ absent

17 : 32 min	166(5), 164(4), 149(5), 69(29), 67(100), 41(28), 27(18).	$C_5H_9OBr_2$ m+ absent
21 : 00 min	209, 164, 147(6), 85(4), 67(100), 41(20), 27(12).	$C_5H_9OBr_2$

Table (5)

GC / MS data on the products of the photolysis of Cyclohexene Oxide with BOOB

Retention Time	m+ and fragment ions (%)	Prob Molecular Formula
2 : 12 min	146(4), 73(6), 57(100), 43(39), 41(29), 29(22), 15(23).	$C_8H_{18}O_2$ (Bu^tOOBu^t)
3 : 57 min	103(1), 98(2), 97(6), 83(39), 69(13), 54(25), 42(61), 41(100).	$C_6H_{10}O$
4 : 09 min	99(2), 98(36), 70(18), 69(27), 55(82), 42(100), 39(57), 27(66).	$C_6H_{10}O$
4 : 17 min	99(3), 98(41), 97(55), 83(71), 79(31), 70(100) 69(59), 27(96).	$C_6H_{10}O$
4 : 51 min	97(1), 96(26), 68(100), 53(6), 39(38), 27(21).	C_6H_9O
6 : 55 min	135(3), 134(25), 119(100), 115(5), 103(6), 91(67).	$C_{10}H_{14}$

Table (6)

GC / MS data on the products of the reaction of Cyclohexene Oxide with NBS

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
3 : 11 min	98(4), 97(11), 83(70), 69(17), 57(20), 54(35), 42(72), 41(100), 27(100).	$C_6H_{10}O$
4 : 43 min	158(43), 156(43), 77(100), 74(15), 51(38), 50(41).	C_6H_5Br
10 :46 min	178(14), 176(15), 134(8), 132(8), 97(54).	$C_6H_{10}OBr$
11 : 09 min	174(2), 176(2), 148(2), 146(2), 97(59), 79(21), 67(28), 41(100).	C_6H_9OBr
12 : 04 min	177(2), 176(33), 174(32), 148(38), 146(37), 133(11), 120(18), 67(49), 39(100).	C_6H_8OBr
14 : 00 min	260(1), 258(3), 266(2), 179(25), 161(16), 97(75), 79(77), 41(100).	$C_6H_{10}OBr_2$
15 : 12 min	177(1), 151(7), 149(8), 137(49), 135(51), 69(28), 57(65), 43(99), 41(100).	$C_6H_{10}OBr_2$ m+ absent

Table (7)

GC / MS data on the products of the reaction of Cyclohexene Oxide with Br_2

Retention Time	m+ and fragment ions (%)	Prob Molecular Formula
2 : 15 min	167(3), 165(14), 163(33), 161(21), 121(33), 119(100), 117(50), 82(38).	CCl_3Br m+ absent

3 : 15 min	98(5), 97(12), 83(77), 69(19), 54(42), 42(82), 41(100), 27(83).	$C_6H_{10}O$
3 : 45 min	99(3), 98(38), 97(5), 83(10), 70(23), 69(33), 55(100), 42(98).	$C_6H_{10}O$
10 : 05 min	180(4), 178(11), 176(9), 134(9), 132(10), 99(37), 97(26), 81(100).	$C_6H_{11}OBr$
10 : 20 min	178(24), 176(25), 134(17), 132(16), 97(75), 69(36), 55(100), 41(100)	C_6H_9OBr
10 : 51 min	176(8), 174(7), 95(4), 94(5), 68(100), 40(20), 39(27), 27(17).	C_6H_7OBr
12 : 56 min	214(5), 212(21), 210(15), 177(4), 175(3), 131(26), 88(43), 67(85), 41(100).	C_6H_8OBrCl
14 : 15 min	258(5), 256(13), 254(7), 177(18), 175(22), 134(31), 132(30), 67(58), 41(100).	$C_6H_8OBr_2$

Table (8)

GC / MS data on the products of the reaction of Cyclohexene Oxide with CCl_3Br

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
7 : 17 min	136(2), 134(4), 118(1), 98(7), 88(9), 80(23), 57(100), 27(30).	$C_6H_{11}OCl$
8 : 38 min	205(8), 203(22), 201(34), 199(21), 166(30), 164(23), 131(12), 129(12), 121(32), 119(98), 117(100).	C_2Cl_6 m+ absent
9 : 14 min	180(1), 178(1), 134(3), 132(3), 99(26), 81(100), 57(79).	$C_6H_{11}OBr$
10 : 00min	196(1), 125, 119(2), 117(7), 81(100), 79(15), 41(11), 39(12).	$C_6H_{10}BrCl$

11 : 29 min	242, 163(7), 161(9), 81(100), 79(18), 67(4), 53(11), 41(20).	$C_6H_{10}Br_2$

Table (9)

GC / MS data on the products of the reaction of Cyclo-octene Oxide with BOOB

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
1 : 41 min	146(3), 131, 90, 73(6), 57(100), 43(61), 41(52).	$C_8H_{18}O_2$ Bu^tOOBu^t
7 : 57 min	136(1), 134(15), 121(7), 119(80), 103(7), 91(100), 79(21), 77(28).	$C_{10}H_{18}$ t-butyl benzene
11 : 14 min	125, 111(3), 97(6), 83(12), 67(31), 57(29), 55(75), 41(100).	$C_8H_{14}O$

Table (10)

GC / MS data on the products of the reaction of Cyclo-octene Oxide with Br_2

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
11: 33 min	126(3), 98(24), 84(23), 83(27), 82(12), 69(15), 55(80), 41(100).	$C_8H_{14}O$
15 : 57 min	204(1), 160(1), 125(2), 98(63), 81(10), 69(11), 55(100), 41(78).	$C_8H_{13}OBr$
19 : 58 min	284(1), 205(2), 176(5), 97(20), 95(24), 67(27), 55(100), 41(88).	$C_8H_{12}OBr_2$

Table (11)

GC / MS data on the products of the reaction of Cyclo-octene Oxide with CCl_3Br

Retention Time	m+ and fragment ions (%)	Prob. Molecular Formula
9 : 46 min	126(5), 98(33), 84(19), 83(22), 82(100), 67(36), 55(85), 41(100).	$C_8H_{14}O$
13 : 49 min	204(1), 160(2), 125(2), 98(53), 81(16), 69(11), 55(100), 41(45).	$C_8H_{13}OBr$

CHAPTER 4

Cyclopropanes and Interior Chain Extension Reactions

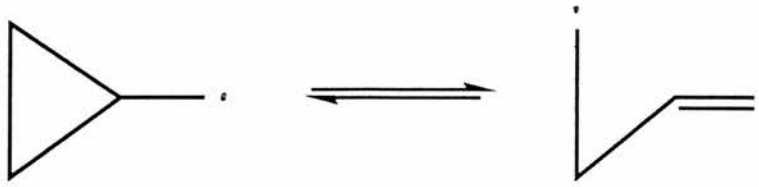
Introduction

Many workers have carried out quite extensive investigations in the area of radical cyclisation reactions.[151] However the synthetic possibilities of the reverse process (i.e. radical ring opening) have not been studied in great detail, although it is true to say that the physical organic chemistry[121,152] of these ring-opening reactions have been well explored. They have sometimes been used as mechanistic probes[153-157] and chronometric devices[158-160] in the detection and study of radical intermediates.

The work of this chapter is concerned with the possible synthetic uses of compounds containing the cyclopropyl ring, in terms of their ring-opening possibilities.

The simplest radical in this class of compounds is the cyclopropylmethyl radical, which has been generated in various ways e.g. photolytic, thermolytic or electron transfer reactions, from a variety of precursor molecules. The parent cyclopropylmethyl radical has been found to have a ring strain energy of ca. 115 kJ mol^{-1}.

Homolytic cleavage of the C_β–C_γ bond (β–scission) yields the but-3-enyl radical (Scheme 1). The process occurs quite rapidly and in an exothermic manner, despite the fact that the rearranged species is an unstabilised primary radical.

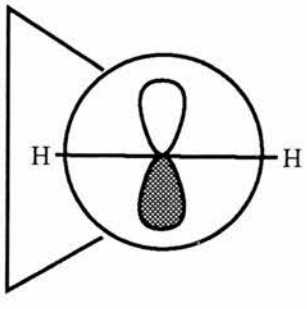


Scheme 1

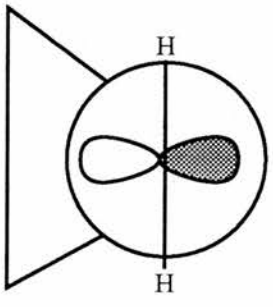
The rate constants for this type of process have been determined, as have some of the stereoelectronic and conformational characteristics.[128,161] The cyclopropylmethyl radical displays no non-classical, or fluxional characteristics, unlike the cyclopropylmethyl cation, and it does not rearrange to give any cyclobutane derivatives.

The rate of formation of the cyclopropylmethyl is higher from diazenes, peroxides and other precursors, than from model acyclic radicals,[162] indicating that there is a small amount of thermodynamic stabilisation involved in its formation.

EPR studies have also indicated that there is restricted rotation of the methylenyl group carrying the unpaired electron, and that the preferred conformation is bisected rather than perpendicular.



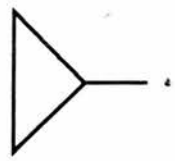
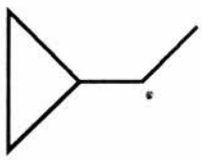
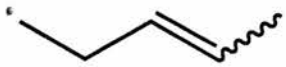
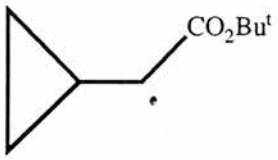
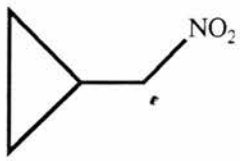
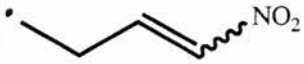
Bisected



Perpedicular

Cyclopropylmethyl radical reactions in solution, normally give rearranged products solely, resulting from the rapidity of the ring cleavage.

Exceptions to this norm do however present themselves when reaction species are present that are capable of trapping the unrearranged radical extremely quickly, or when the radical possesses substituents which retard the β–scission step. Rate constants have been measured for a number of free radical reaction types, and these have become helpful in judging the feasibilty of synthetic procedures. Some kinetic data for the ring cleavage of cyclopropylmethyl radicals with different substituents is shown below (Table 1).

...Cyclopropylmethyl radical-	Rearranged radical	10^{-8} $k_r[s^{-1}]$ 37°C	log $[A/s^{-1}]$	E [kJ mol^{-1}]	Ref
 Cyclopropyl methyl	 But-3-enyl	1.2	13.15	29.5	129 163 164 165 166
 α–Methyl....	 (E) + (Z)-Pent-3-enyl	0.7	13.15	31.4	167
 α–tert-butoxy-carbonyl...	 4-tert-Butoxy-carbonylbut-3-enyl	ca.10^{-4}	--	--	168
 α–Nitro...	 4-Nitrobut-3-enyl	≤10^{-4}	--	--	169

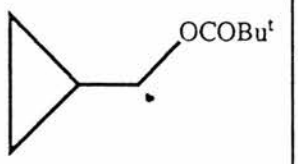
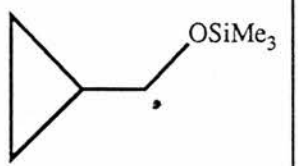
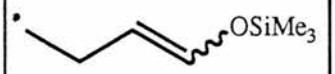
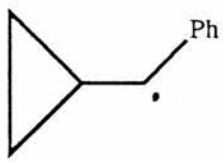
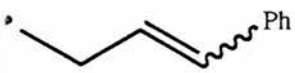
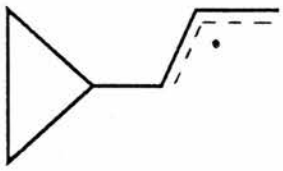
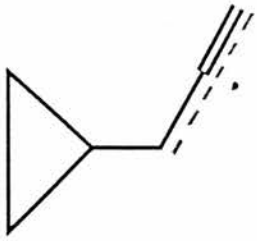
 α–(2,2-Dimethyl propanoyloxy).....	 4-(2,2-Dimethylprop-anoyloxy)but-3-enyl	1.0	--	--	168
 α–(Trimethylsilyl oxy)....	 (E) + (Z)-4-(Trimethyl silyloxy)but-3-enyl	0.2	--	--	170
 α–phenyl...	 4-Phenylbut-3-enyl	2.7 x10^{-3}	--	--	171

Table 1. Kinetic Data for Cyclopropylmethyl to But-3-enyl type Rearrangements.

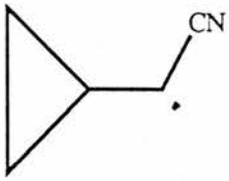
A determining factor in the rate of rearrangement for cyclopropylmethyl type radicals, is the degree of overlap of the SOMO and the bond to be broken. In conformationally mobile radicals, rotation about the C_α–C_β bond can maximize this. Particular substituents at the radical centre that are capable of withdrawing electron density e.g. tert-butoxycarbonyl or nitro, decrease the rate of cleavage, almost certainly due to a reduction in the amount of overlap. Also the rate of cleavage is reduced in 1-(cyclopropyl) allyl, 1-(cyclopropyl)prop-2-ynyl and α–cyanocyclopropylmethyl radicals, where resonance delocalisation pulls electron density away from the α–carbon atom.



1- (cyclopropyl) allyl



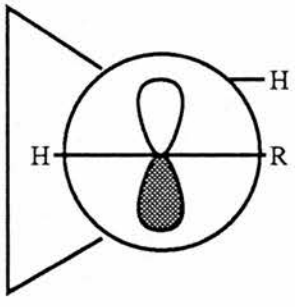
1- (cyclopropyl) prop-2-ynyl



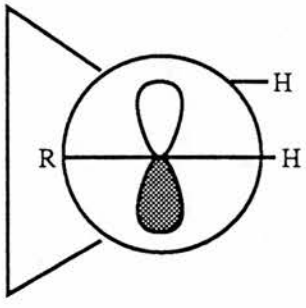
α–cyanocyclopropylmethyl

Equally, electron releasing substituents at the radical centre e.g. methyl, trimethylsilyloxy and 2,2-dimethyl-propanoyloxy also decrease the rate of rearrangement probably because they suppress the amount of unpaired spin available for overlap at the radical centre.

The rearrangements of α–substitued cyclopropylmethyl radicals give a mixture of (E)- and (Z)- butenyl radicals; the (E)- isomer usually being the major product.



Anti-conformer

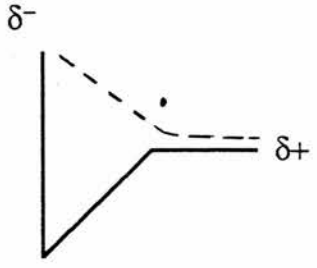


Syn-conformer

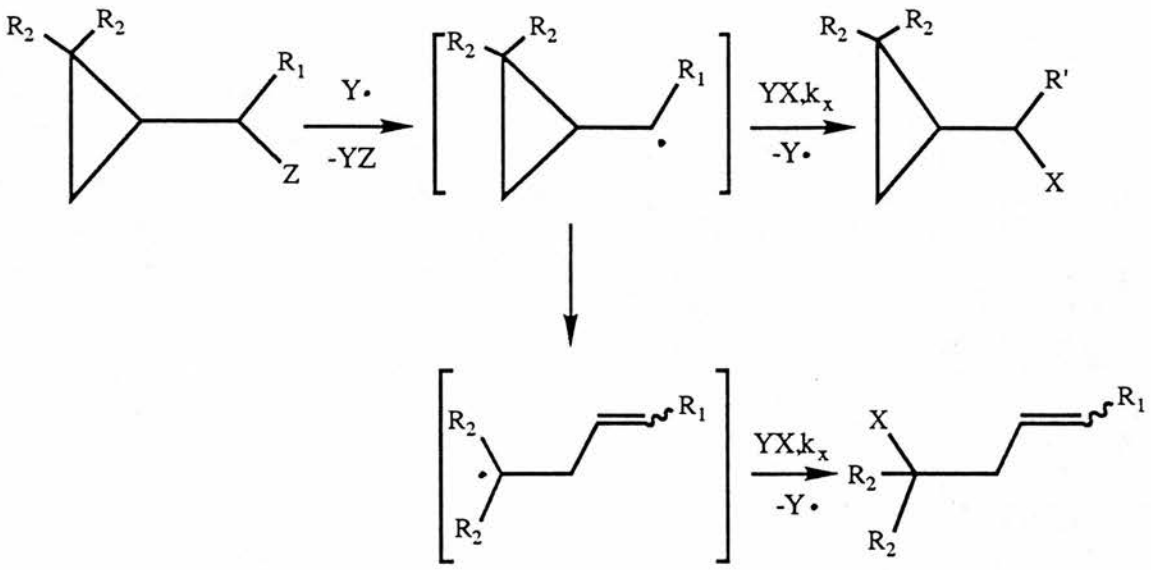
This stereoelectronic result is probably caused by the higher proportion of the anti-conformer compared to the syn-conformer. The anti-conformer is lower in energy for steric reasons. (i.e. non-bonded interactions between the substituent and the ring hydrogen atoms is less

important. The (E)-alkene is also thermodynamically more stable than the (Z)-alkene.[121]

Alkyl substituents at the C(1) position have only a minimal influence on the degree of ring opening, but substituents at the C(2) position, that allow stabilisation of the rearranged radical e.g. 1,2,2-trimethyl- or 1,2,2,3,3-pentamethyl-cyclopropylmethyl radicals, give higher rates of β–scission. Substituents in C(2) that delocalise electron density in the rearranged radical e.g. 2-ethoxycarbonyl- or 2-phenyl-, display substantial increases in the rate of rearrangement. The rearrangement of the trans-2-phenylcyclopropylmethyl radical is one of the fastest known unimolecular reactions in solution (note :- the decay of a transition state is thought to be only about thirty times faster).[172] The rearrangement of trans-2,trans-3-diphenylcyclopropylmethyl is also particularly fast.[80] The stereoelectronic influences dictate to a large degree the rate of β–scission. There is evidence that the transition state is polar in nature, (see structure below) and substituents that can contribute to this, lower the activation energy of rearrangement.[173]

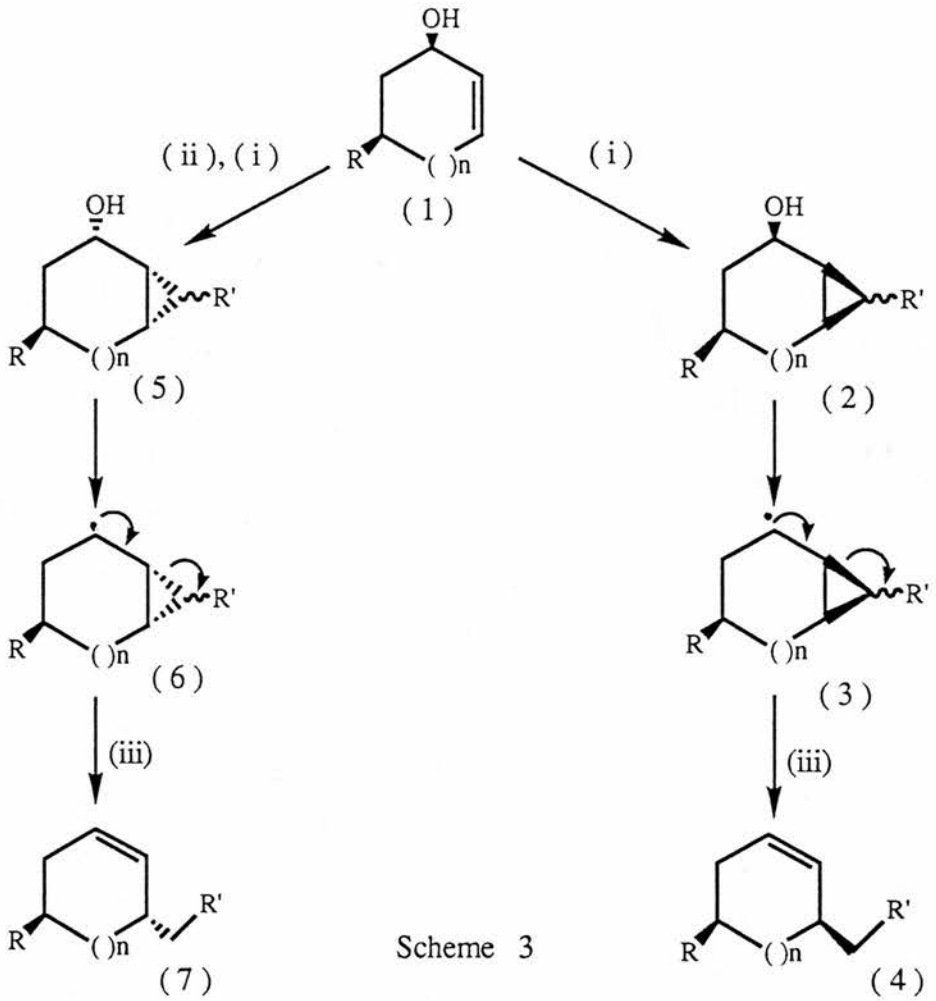


Synthetically, ring opening rearrangements can be incorporated into a chain sequence. (Scheme 2)



Scheme 2

Similarly Clive et. al.[174] have reported the preparation and ring opening of cyclopropylmethyl radicals as a general synthetic method for attachment of alkyl and substituted alkyl groups to cyclic structures. (see Scheme 3)



Scheme 3

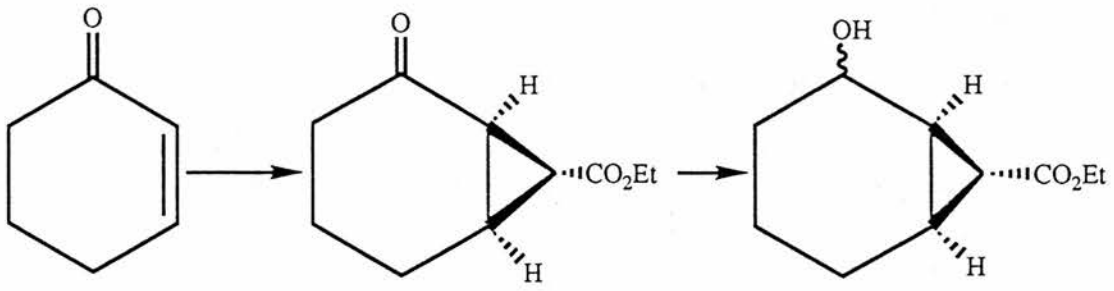
(i) cyclopropanation, (ii) Mitsunobu inversion, (iii) stannane
R' = H, alkyl group, electron-withdrawing group

(ii) ref 176, (iii) ref 175.

These procedures incorporate facilities to enable stereochemistry to be controlled. (cf (1) ------> (4) and (1) ------> (7), Scheme 3)

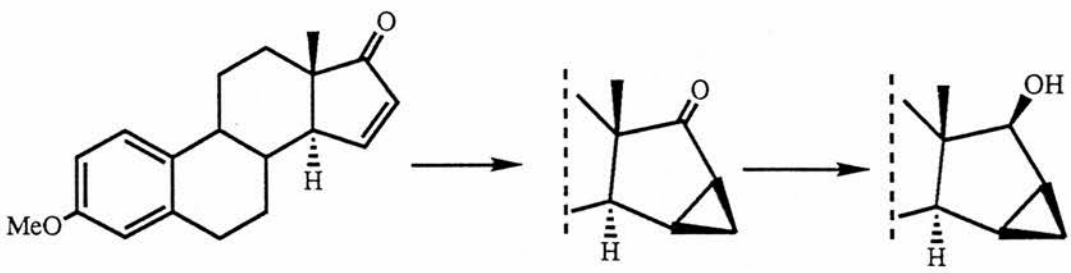
These workers produced cyclopropanes from allylic alcohols or enones, using variations in the classical Simmons-Smith[176] reaction. In the case of the alcohols, the cyclopropanation was directed by the hydroxy group. A phase-transfer method[177] was employed to produce a geminal dichloride. It was observed that when the initial substrate was an enone, the stereochemistry could not be directed absolutely,[178] and the

cyclopropanated enone had to be reduced to the corresponding alcohol.(see Scheme 4).

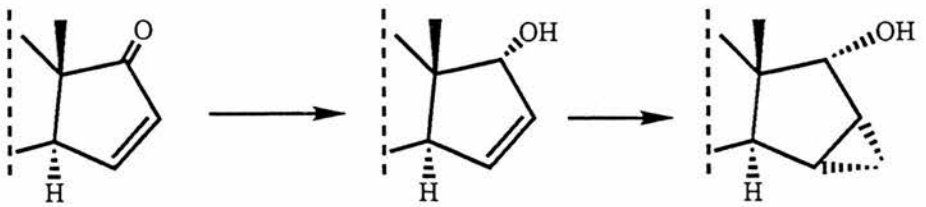


Scheme 4.

However, if the enone was initially reduced to an allylic alcohol, the stereochemistry could be more precisely controlled. Schemes 5 and 6 show how two isomeric cyclopropanes could be formed from the same starting material.

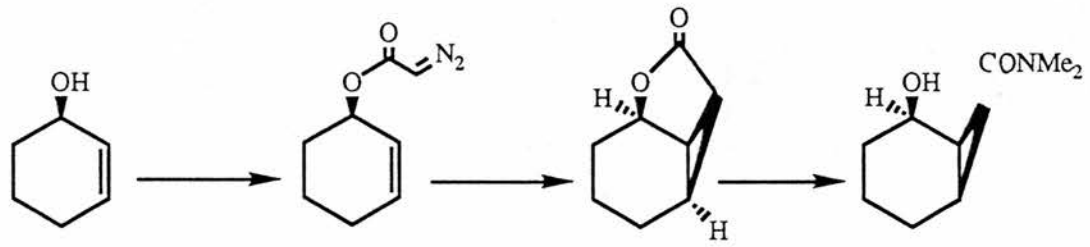


Scheme 5



Scheme 6

It was also found that internal cyclopropanation was suitable for the methods of Scheme 6. This has the advantage that there is inherent stereocontrol [179] (Scheme 7).

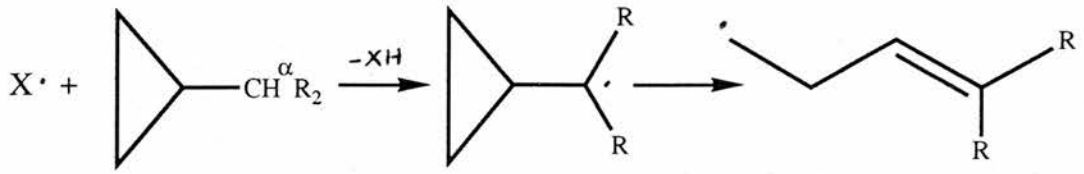


Scheme 7

Generation of the initial radical in Scheme 3 (step (2) -----> (3)) was achieved in two steps: firstly the hydroxy group was replaced by a benzeneseleno group, then this was treated with stannane.[180] All of the selenides that Clive et. al.[174] produced underwent homolysis in the presence of stannane, but the best conditions for ring opening were influenced by the pattern of substituents on the cyclopropane ring.

The advantages of the method that these workers used are that the benzeneseleno group is tolerant to a wide range of reaction conditions, both before and during the homolysis step. Also functional groups can be present that would not normally be stable to organometallic reagents.

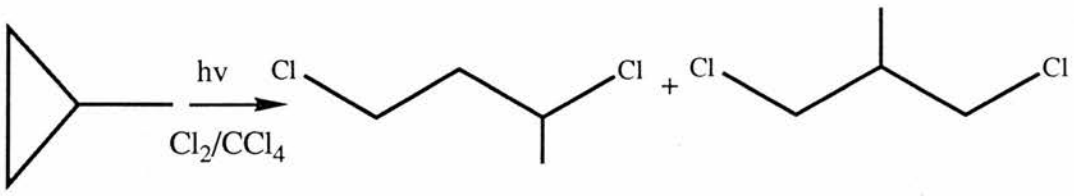
Cyclopropylmethyl radicals can easily be formed by abstraction of hydrogen atoms from sites adjacent to the three-membered ring (i.e. the α–hydrogens) in alkylcyclopropanes. (Scheme 8)



Scheme 8

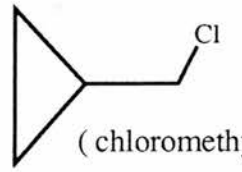
The attacking radical is unable to abstract any of the hydrogens from the cyclopropane ring itself since they are all too strongly bound. Additionally, the α–hydrogens are activated by being next to the three-membered ring. These factors combined, indicate that the sequence may have possible synthetic uses. A negating factor however is that most chain propagating radicals X·, are not sufficiently discriminating in their selection of hydrogen atoms, and a mixture of products is usually formed.

Molecular halogens are commonly used in photochemically initiated reactions with hydrocarbons of the general type outlined above. The reaction scheme for the alkylcyclopropane / halogen rearrangement is complicated by the fact that homolytic substitution (S_H2) at a ring carbon atom, together with ring opening, occurs at a competitive rate with hydrogen abstraction from the alkyl side chain.[181,182] An example of this is provided by the photochlorination of methylcyclopropane (Scheme 9); the products comprise of a mixture of 1,3-dichlorides from the S_H2 reaction, and monochlorides produced by hydrogen abstraction from the side chain.[181,183]



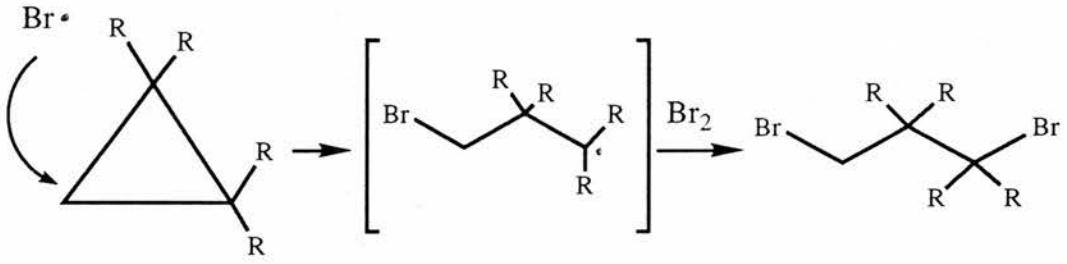
methylcyclopropane 1,3-dichlorobutane 1,3-dichloro-2-methyl propane

Scheme 9



(chloromethyl)-cyclopropane

Photolysis reactions of alkylcyclopropanes carried out in the presence of Br_2, in CCl_4, yield cleaner reaction mixtures, with the products almost solely 1,3-dibromides from substitution reactions.[144,184] (Scheme 10).

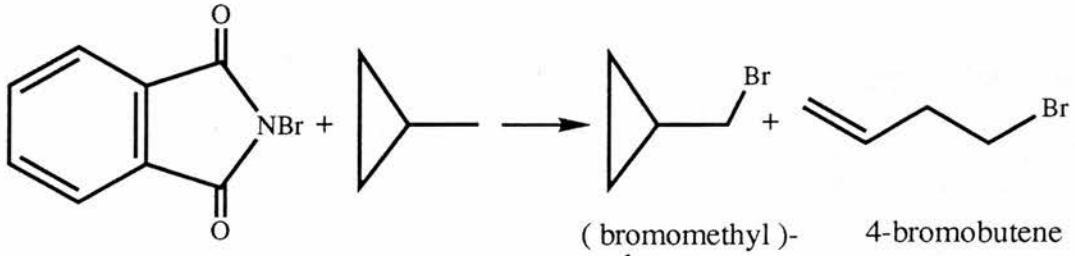


R = H or alkyl

Scheme 10

Halogenating agents such as N-bromosuccinimide (NBS) attack mostly at side chain sites when the conditions are controlled so that the radical chain propagating species is the succinimidyl radical rather than the bromine atom. It has been observed that bromine abstraction from NBS is much more rapid than β–bond scission, and so unrearranged products predominate.[185] This type of reasoning also explains why in the reaction of methylcyclopropane with either N-bromo-3,3-dimethyl

glutarimide, or N-bromopthalimide, only unrearranged products have been isolated.[184] (Scheme 11).



N-bromopthalimide

(bromomethyl)-cyclopropane

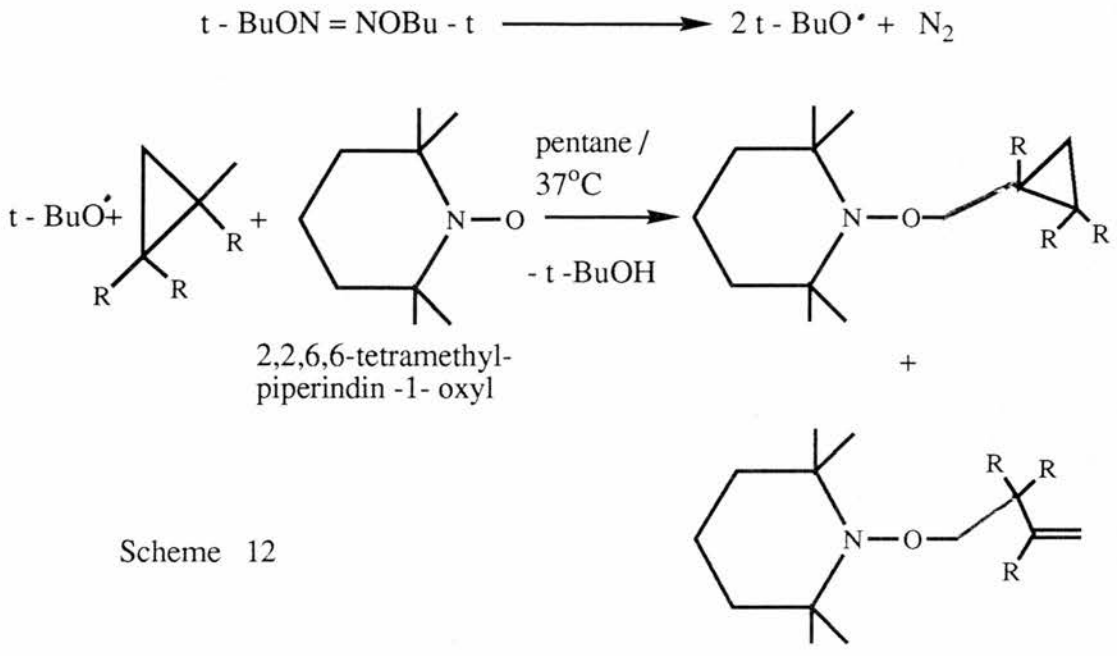
36%

4-bromobutene

c.a. 2%

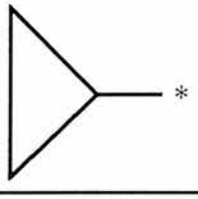
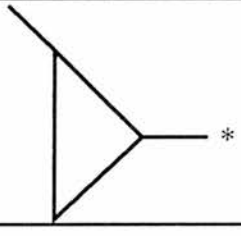
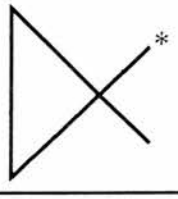
Scheme 11

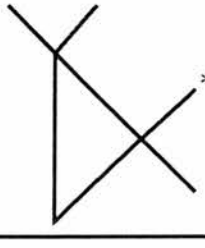
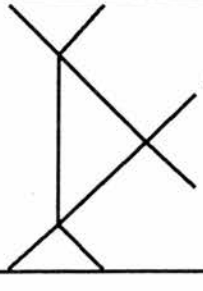
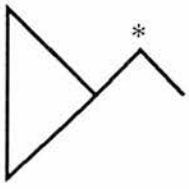
Tert-butoxy radicals preferentially abstract α–hydrogens from compounds, and this factor is often used to obtain spectroscopic data in cyclopropylmethyl type radicals and their rearrangements.[128,170,186,187] *Tert*-butyl hyponitrite has been found to react with alkylcyclopropanes, in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) to yield a mixture of trialkylhydroxylamines. The relative yields of these have been used to measure the per bond rates of hydrogen abstraction from the α–positions of various compounds, relative to the rate of hydrogen abstraction from cyclopentane.[167] (Scheme 12).



Scheme 12

The relative rates of hydrogen abstraction from some alkylcyclopropanes by tert-butoxyl radicals at 37°C are shown in Table 2.

Entry	1	2	3
Substrate [a]			
k_{rel} (37°C) [b]	0.34	0.48	0.28

Entry	4	5	6
Substrate [a]			
k_{rel} (37°C) [b]	0.24	0.16	1.6

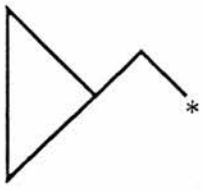
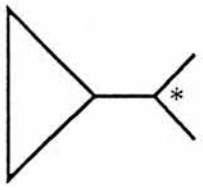
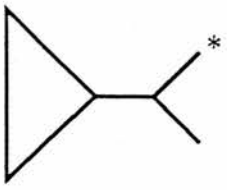
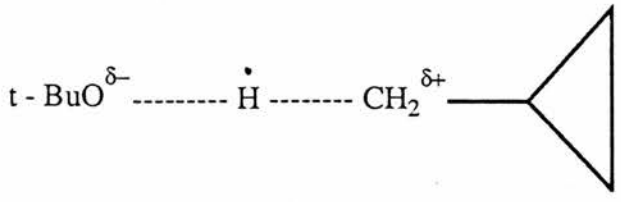
Entry	7	8	9
Substrate [a]			
k_{rel} (37°C) [b]	0.053	3.9	0.056

Table 2.

(a) The * indicates the site of H-atom abstraction

(b) Relative rates per identical bond

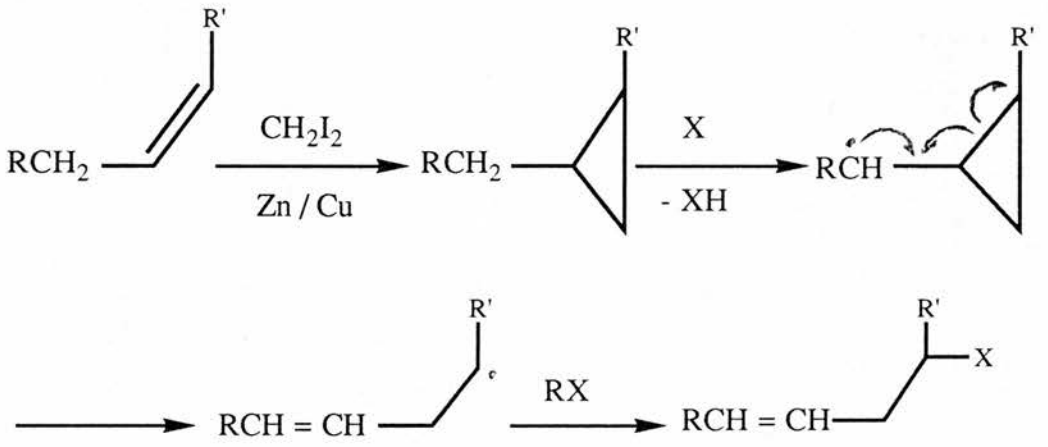
These figures show that α–hydrogens are much more easily abstracted than ordinary methyl hydrogens. A probable explanation for this can be found in an enhanced polar effect i.e. stabilisation of the transition state by structures such as[167] :-



An additional factor is likely to be stabilisation of the cyclopropylmethyl radicals by overlap of the SOMO with the pseudo- π-orbital system of the cyclopropane ring. The comparatively low activity of gem-dialkylcyclopropanes is thought to be due to the steric inaccessibility of the α–hydrogen atoms caused by eclipsing neighbouring substituents. The most effective tert-butoxyl radical precursor which is used in chain sequences, is tert-butyl hypochlorite, however chlorinations of alkylcyclopropanes with this reagent tend to form complicated mixtures of products, mainly of the unrearranged variety.[183]

" Interior Chain Extension " Sequences.

Based on the information above, it was decided to carry out an investigation into " interior chain extension " reactions on alkenes. Consider the following reaction. Scheme 13 .



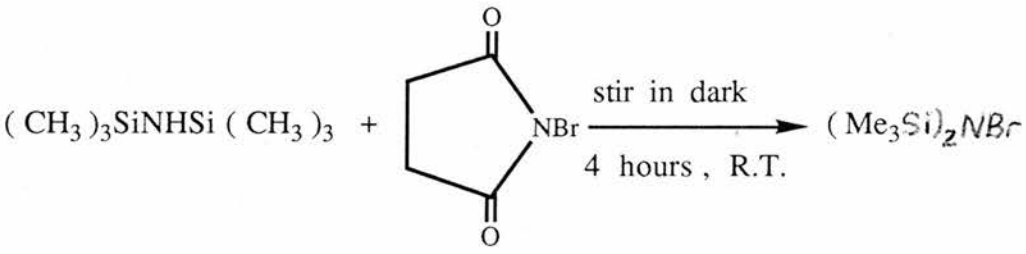
Scheme 13

Examination of entries 6, and 8, in Table 2, pages 193/4, indicates that the cyclopropane ring itself has the capability of activating the adjacent α–hydrogen atoms, thus making Scheme (13) a potentially useful synthetic process.

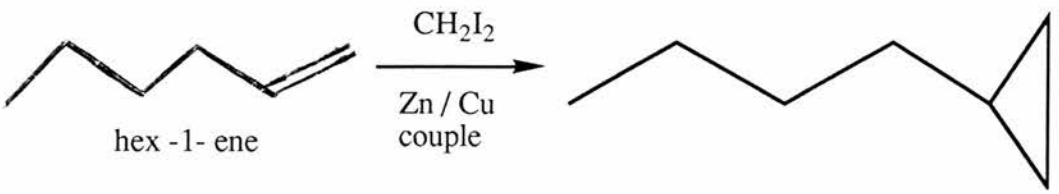
Beginning with an alkene, the Simmons-Smith reaction with chloroform and a zinc-copper couple converts the double bond of the alkene into a cyclopropane ring.[188] Hydrogen abstraction from the carbon adjacent to the ring results in a cyclopropylmethyl to butenyl type rearrangement. The overall effect of the sequence is to extend the chain length of the alkene by one carbon atom. This extra carbon is " effectively " introduced into the middle of the double bond, hence the description " interior chain extension ". The potential advantage of this

approach is that no specific R group is required and on the surface it would appear that less functional group manipulation is necessary to produce similar results obtained by Clive *et. al.*[174]

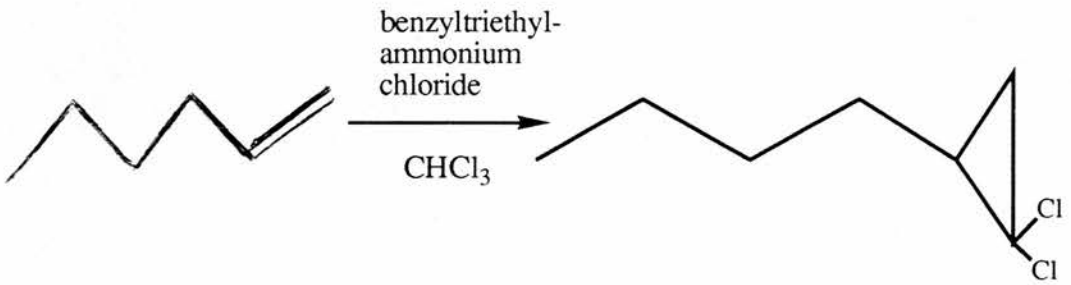
It was decided to explore this system using two different radical precursors, RX. These were N-bromosuccinimide (NBS), and bis (trimethylsilyl) N-bromoamine, which is formed by reaction of NBS with 1,1,1,3,3,3-hexamethyldisilazane.[190]



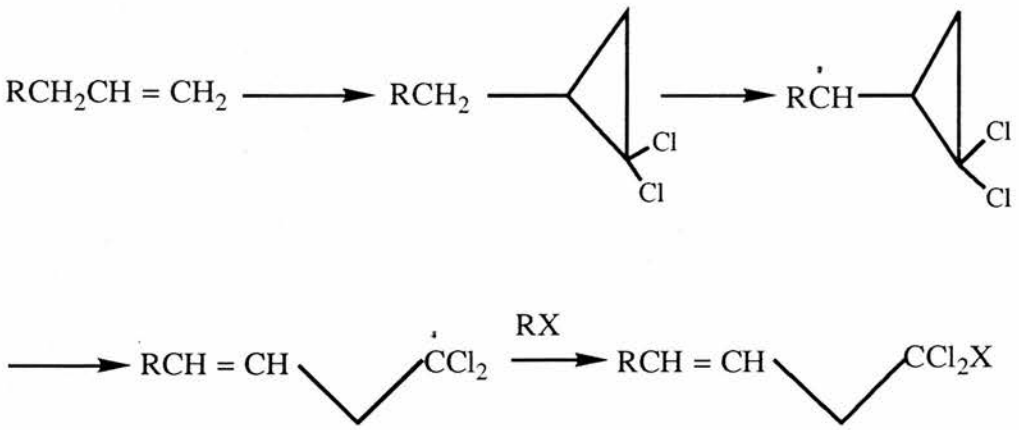
Several methods are available for producing zinc-copper couples,[191] e.g. Simmons / Smith,[176,192] Shank / Shechter,[192,193] Rawson / Harrison,[194] and Conia / Denis / Girad.[195] The method of LeGoff[196] was employed using cupric acetate monohydrate, glacial acetic acid and zinc dust. The Simmons-Smith[176] reaction was attempted using hex-1-ene, yielding butylcyclopropane.



A dichlorinated butylcyclopropane was also prepared in a phase-transfer catalysis type reaction.



In this case chloroform was acting as source of dichlorocarbene, and benzyltriethylammonium chloride was the phase-transfer catalyst. Thus, with the dichlorinated butylcyclopropane the overall. reaction sequence would be :-

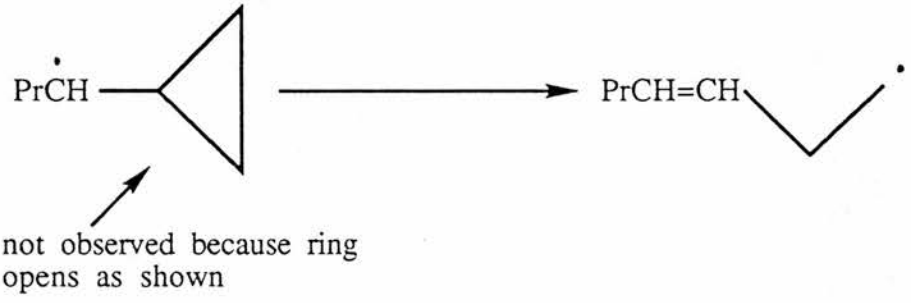


The successes and failures encountered with these interior chain extension reactions will be discussed simultaneously with the EPR studies of some cyclopropane derivatives in the following section.

EPR Study of Cyclopropane Derivatives

Hydrogen abstraction from butylcyclopropane and the dichlorinated butylcyclopropane was examined by EPR spectroscopy to determine if both ring closed and ring opened radicals could be observed.

EPR spectra of butylcyclopropane were recorded at a variety of temperatures between 150 - 250 K. The samples were prepared in t-butyl benzene or cyclopropane with di-tert butyl peroxide. Examination of the spectra revealed that the ring opened species was present.



The spectrum obtained at 220 K is shown in Fig 1.

The spectrum analyses for consists of a double triplet and analyses for :- a(1H) = 0.7 G, a(2H) = 22.5 G and a(2H) = 28.9 G, plus additional small doublet splittings. The radical is fully ring opened at 150 K, and this is consistent with the known rates of ring opening for comparable compounds. Some exchange broadening was observed, but the low temperature exchange limit could not be reached

The unrearranged radical (i.e. cyclopropyl ring intact) was not detected even at temperatures as low as 145 K in cyclopropane

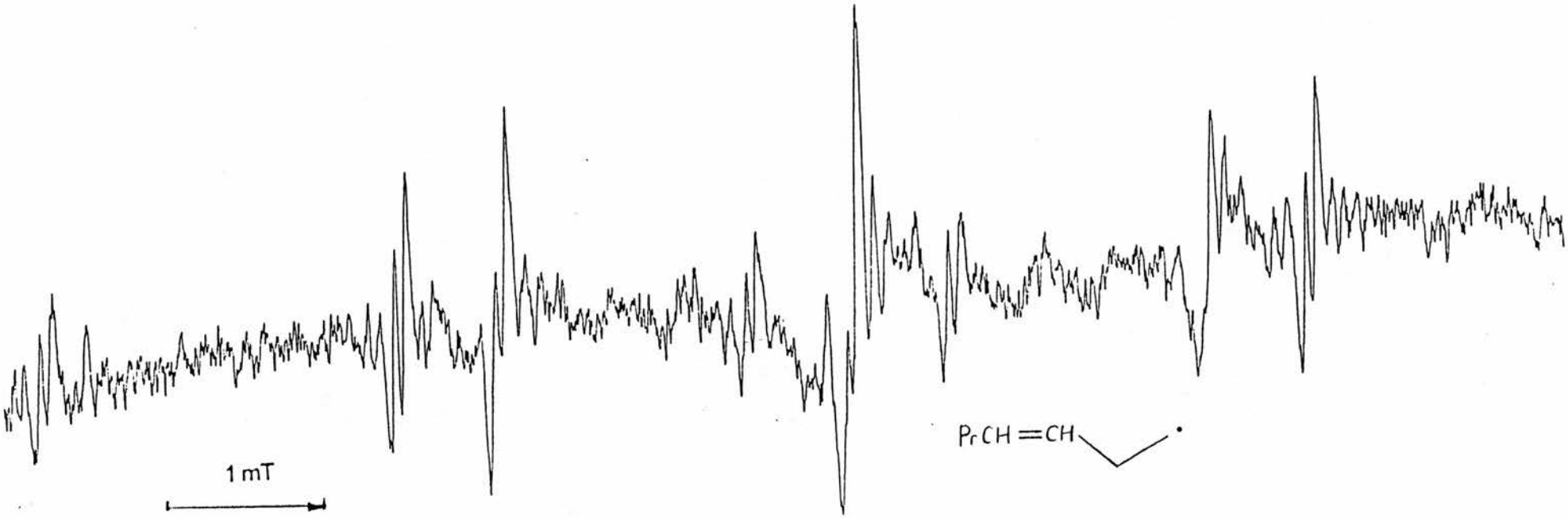
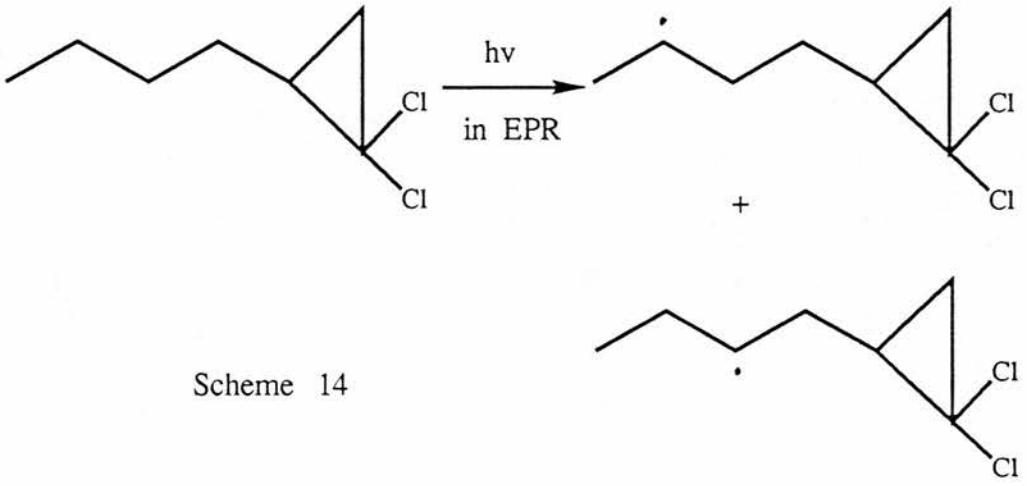


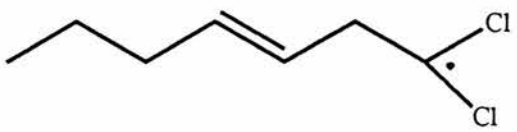
Fig. 1 9.2 GHz EPR spectrum of Butylcyclopropane, in cyclopropane at 220 K

The dichlorinated butylcyclopropane was also examined by EPR spectroscopy over the temperature range 150-250 K.



Scheme 14

A mixture of two radicals was observed (scheme 14) produced by abstraction at various positions along the chain. The ring opened radical shown below was not observed, but it may well have been present and would have been difficult to detect by EPR due to the presence and position of the chlorine atoms relative to the radical centre.



The spectrum obtained at 200 K is shown in Fig 2.

The spectrum analyses for two radicals; the former and major radical having hfs of a(1H) = 22.2 G and a(3H) = 26.0 G, the latter and minor radical exhibiting hfs of a(1H) = 22.0 G and a(4H) = 26.0 G.

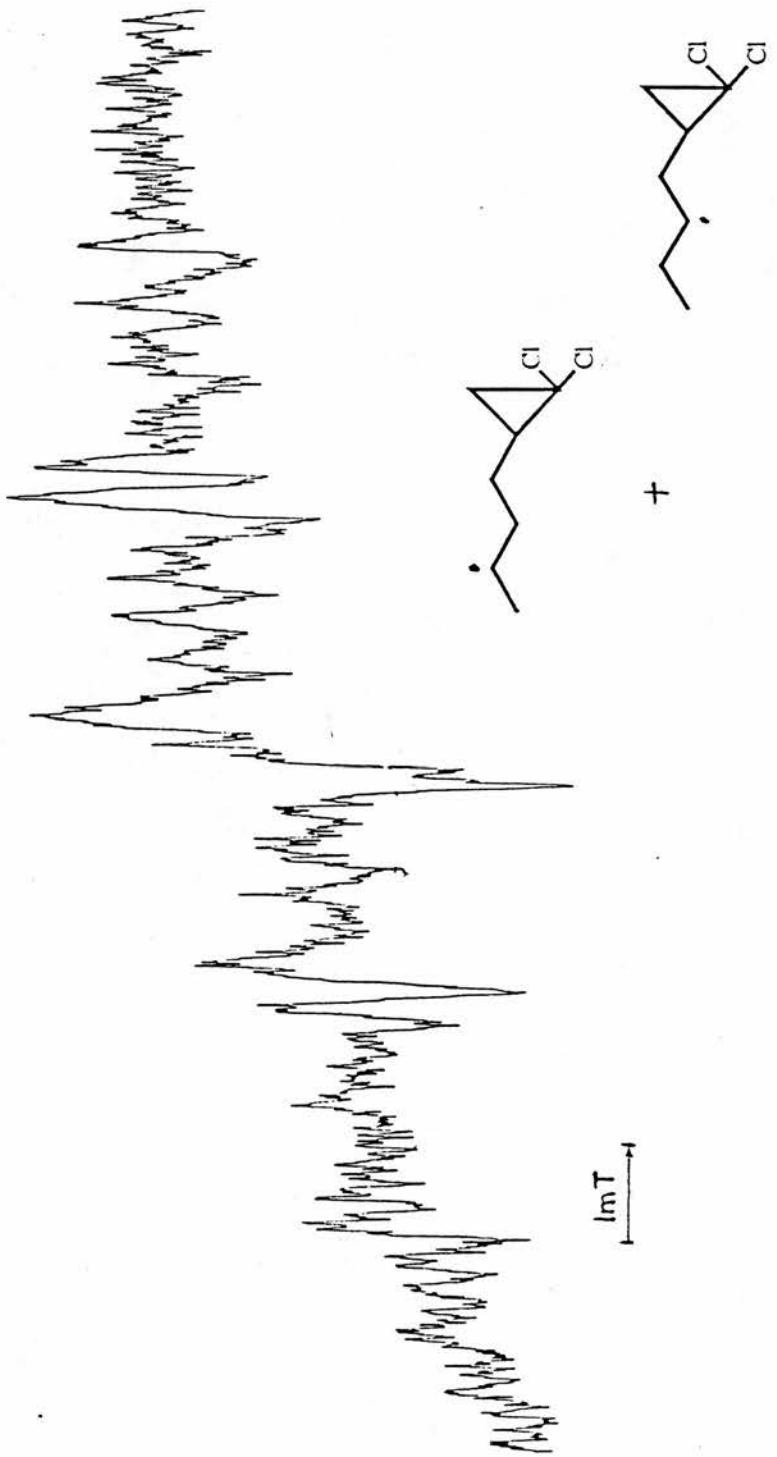
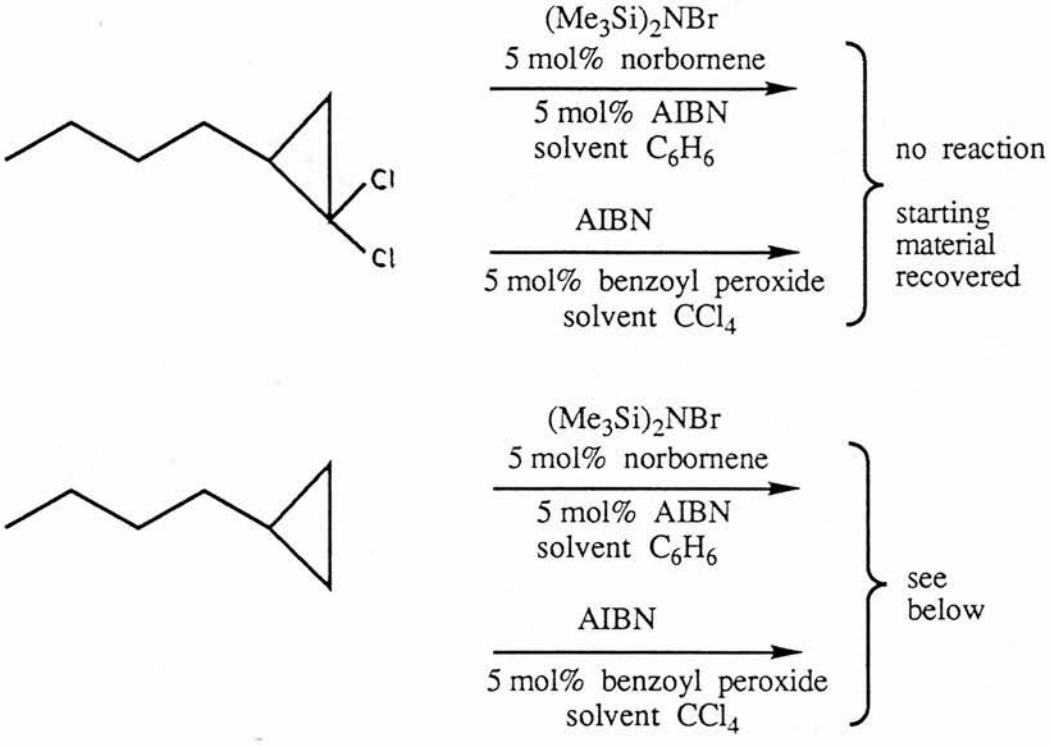
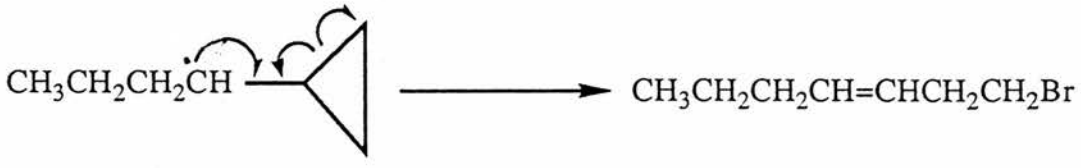


Fig. 2. 9.2 GHz EPR spectrum of 1-butyl-2,2-dichlorocyclopropane, in cyclopropane, at 200 K (200 G wide)

Bromination reactions were carried out on both the butylcyclopropanes, using NBS and bis (trimethylsilyl) N-bromoamine.

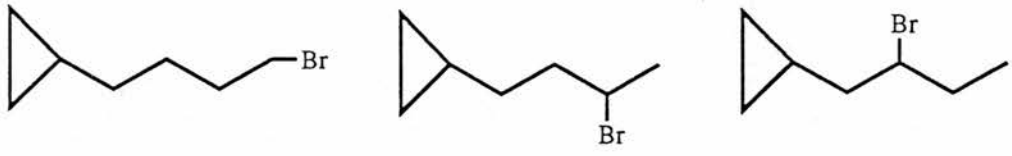


The reaction of butylcyclopropane with both (Me_3Si)$_2$ NBr and NBS would have been expected to form 1-bromo-hept-3-ene according to Scheme 15.

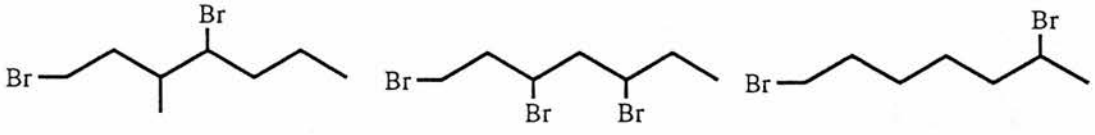


Scheme 15

However in both cases, a mixture of mono-brominated and poly-brominated compounds was obtained. Some of these were separated by preparative g.c. and identified



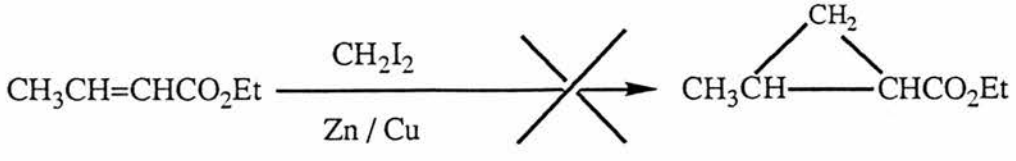
Mono-brominated



Poly-brominated

The reaction times of butylcyclopropane with NBS and $(Me_3Si)_2NBr$ were shortened and the reaction temperatures reduced to try to control the site of hydrogen abstraction, but it was found that poly-brominated products were still obtained.

These results indicated that the cyclopropyl group alone was not sufficient to direct the hydrogen abstraction to the α–position. It was evident that a certain amount of functionality was required both to aid the α–hydrogen abstraction and to reduce the number of possible other positions for abstraction. A number of possible starting materials were selected with these objectives in mind. The first of these was ethyl crotonate.



It proved impossible to isolate sufficient cyclopropanated product in this instance. A possible explanation for this lies in the fact that it has been found that in general, " the presence of electronegative groups near to the point of olefinic unsaturation leads to much reduced yield of cyclopropanes ".[197] However, " when electronegative groups are removed from the site of unsaturation, the yields of cyclopropanated products are not lowered ". With this in mind ethyl vinylacetate was chosen as a suitable starting compound. This was prepared in two steps,[198] firstly vinyl acetic acid was treated with thionyl chloride to form the corresponding acid chloride, vinyl acetyl chloride.

$$CH_2{=}CHCH_2CO_2H + SOCl_2 \longrightarrow CH_2{=}CHCH_2COCl$$

Vinyl acetyl chloride was then mixed with ethanol to form the required ethyl vinylacetate.

$$CH_2{=}CHCH_2COCl + EtOH \longrightarrow CH_2{=}CHCH_2CO_2Et$$

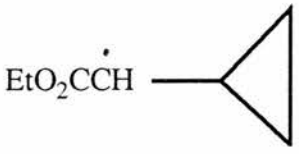
Cyclopropanation was carried out by the Simmons-Smith method to form ethyl cyclopropylacetate.

$$CH_2{=}CHCH_2CO_2Et \xrightarrow[Zn/Cu]{CH_2I_2} \begin{array}{c} CH_2 \\ CH_2 \quad CHCH_2CO_2Et \end{array}$$

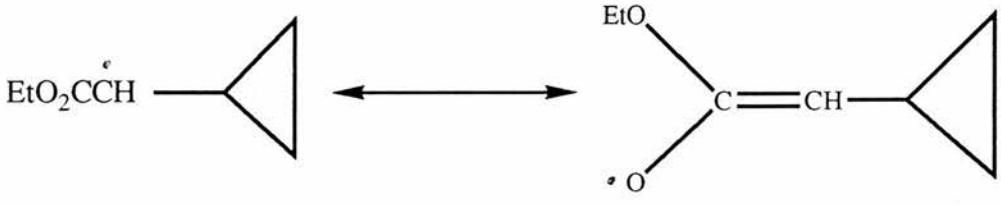
Cyclopropanation proved to be difficult with poor yields, but small amounts of ethyl cyclopropylacetate were produced and separated by preparative g.c. EPR spectra of this compound were recorded in the

range 150-230 K in cyclopropane with di-*tert*-butyl peroxide. The spectrum obtained at 230 K is shown in Fig 3.

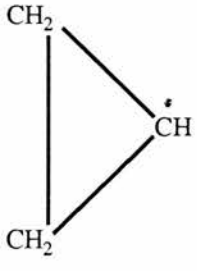
The spectrum analyses for :- a(1H) = 1.7 G, a(2H) = 3.2 G and a large doublet splitting of a(1H) = 18.2 G. Several other long range splittings were also present. This can be attributed to the radical shown below with the cyclopropyl ring unopened.



The ring opened species was not observed, and this was thought to be due to the possibility of spin delocalisation into the carbonyl system.



This would account for the retarded degree of ring opening of the radical because of the stabilizing effect of delocalisation. The cyclopropyl radical was also observed from the solvent



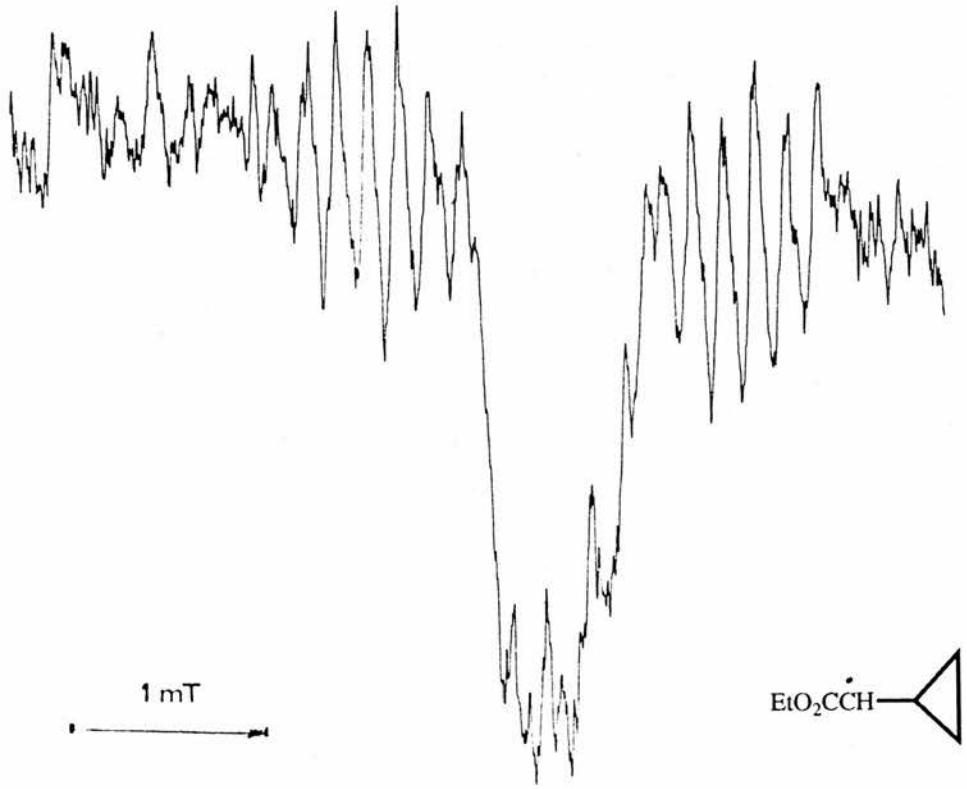
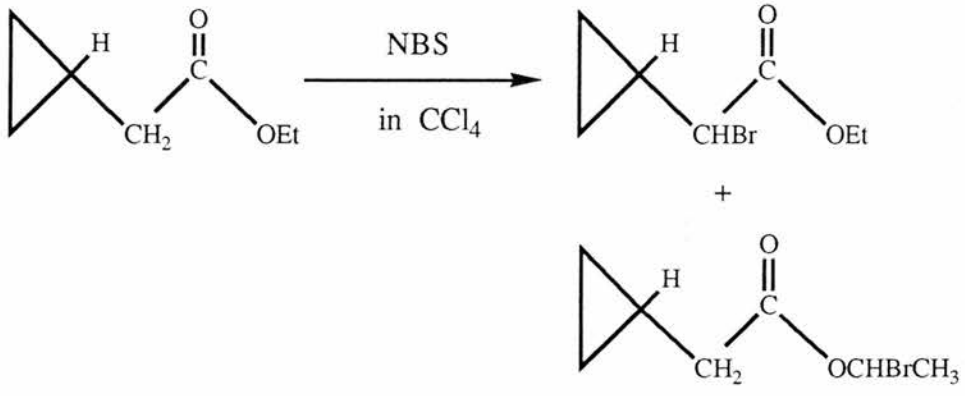


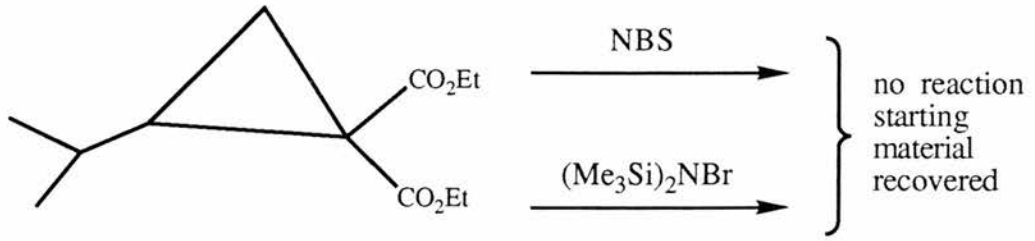
Fig. 3. 9.2 GHz EPR spectrum of ethyl cyclopropylacetate at 230 K, in *tert*-butylbenzene

The values in Table 1 on pages 182/3 show a slightly retarded rate of ring opening for the α-trimethylsilyloxy cyclopropylmethyl radical and a much reduced rate for the α–*tert*-butoxycarbonyl cyclopropylmethyl radical compared to the parent cyclopropylmethyl radical. These results are also due to a delocalisation effect.

An experiment was carried out with ethyl cyclopropylacetate and NBS in CCl_4. A fairly complex mixture of products was produced, but GC / MS and ^1H NMR spectra were consistent with the two products shown below (ethyl α-bromocyclopropylacetate and 1-bromoethyl cyclopropylacetate).



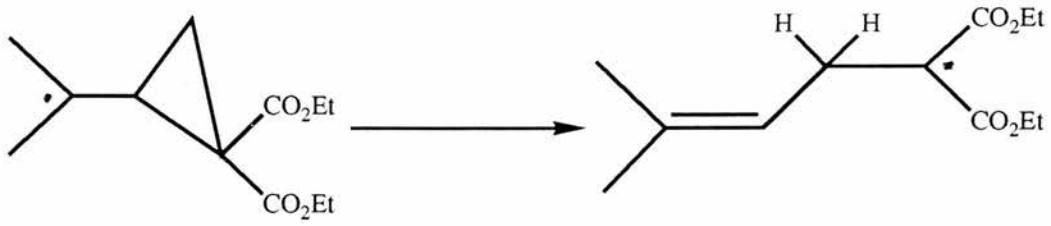
The EPR results for ethyl cyclopropylacetate made it seem likely that it would not be useful in the overall chain extension scheme. It was decided to investigate a compound with two acetate groups, but much further removed from a possible site of hydrogen abstraction. To this end diethyl 2-isopropylcyclopropyldicarboxylate was selected. This compound appeared to have only one possible site for hydrogen abstraction.



In experiments with NBS and ($Me_3Si)_2NBr$ the starting material only was recovered with no ring opened products being isolated. This compound was examined by EPR spectroscopy over the temperature range 220-320 K, in *tert*-butyl benzene with di-*tert*-butyl peroxide. The spectrum obtained at 220 K is shown in Fig 4.

The spectrum analyses for :- a(4H) = 0.7 G and a(1H) = 23.5 G.

It is apparent that even at 220 K, the cyclopropane ring has opened to give the radical shown below, which is consistent with the hfs measured.



Ring opening appears to proceed very rapidly, even at low temperatures. As the temperature increased, the signal from this radical gradually weakened and was replaced by the spectrum of a second radical, the hfs of which at 260 K were measured as a (3H) = 24.3 G, a (1H) = 20.1G. This is the result of hydrogen abstraction from the ethoxycarbonyl portion of the molecule. (see Fig. 5.)

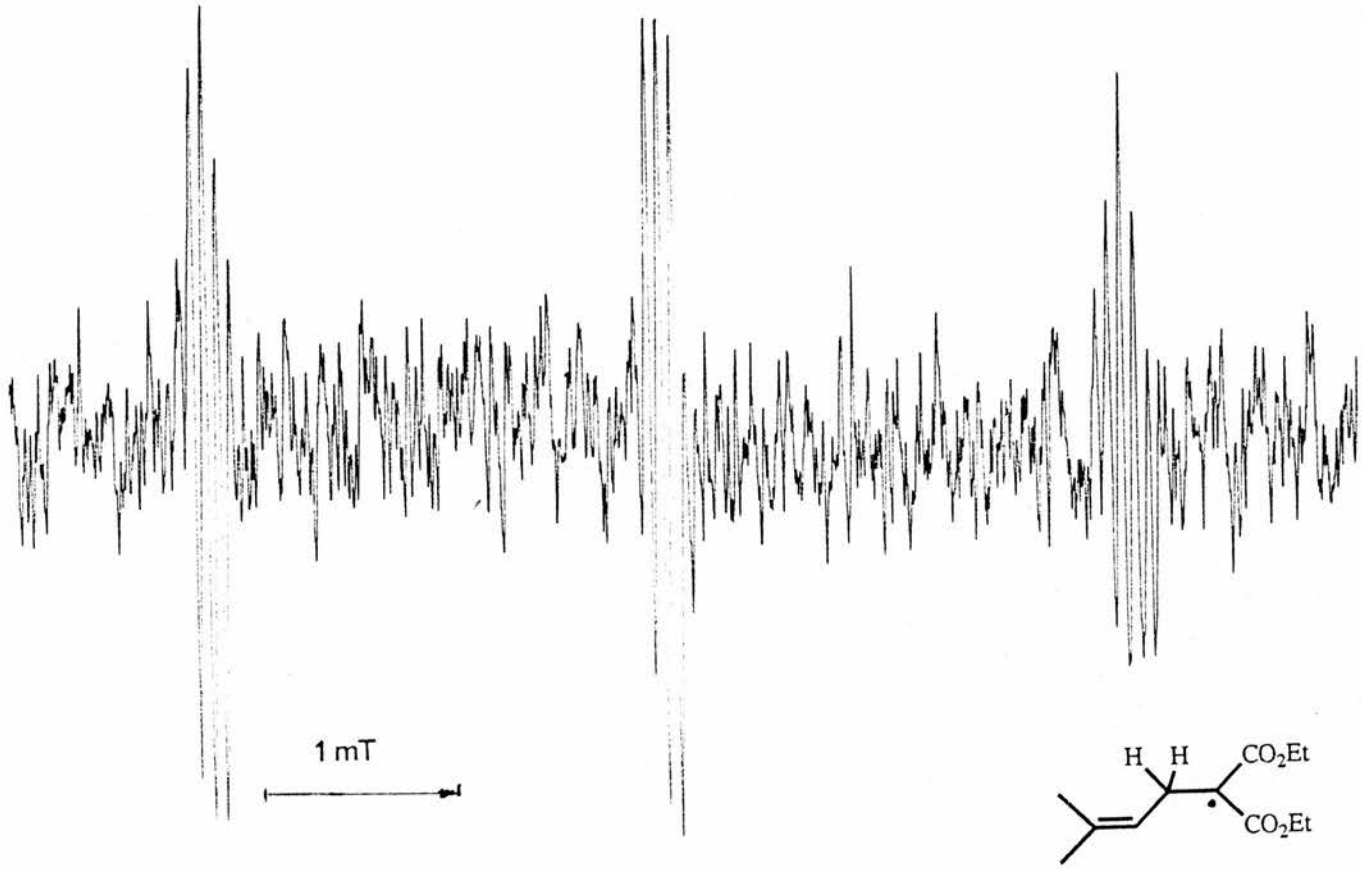


Fig. 4. 9.2 GHz EPR spectrum of 1-isopropyl-2,2-diethoxycarbonyl cyclopropane, at 220 K, *tert*-butylbenzene

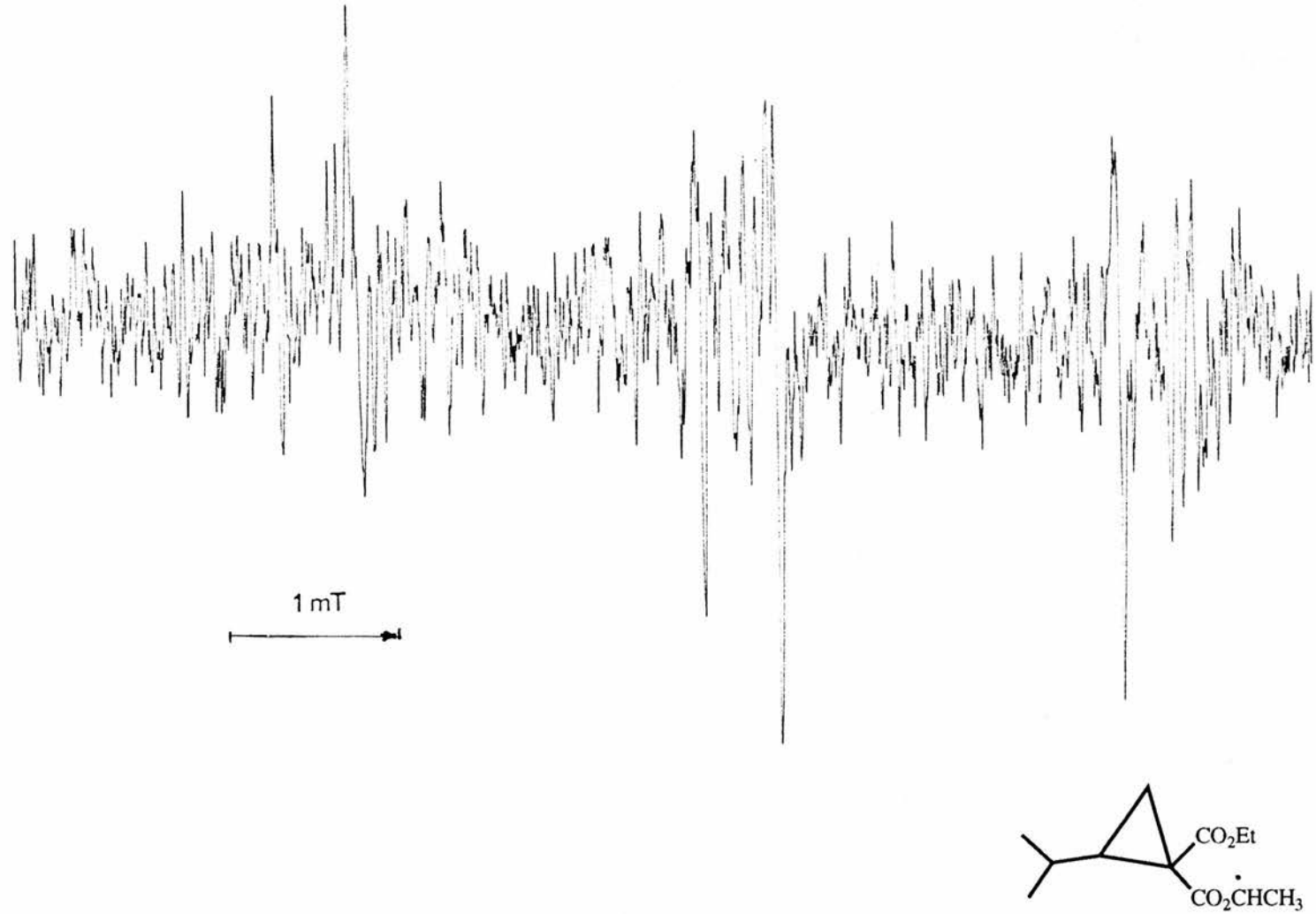
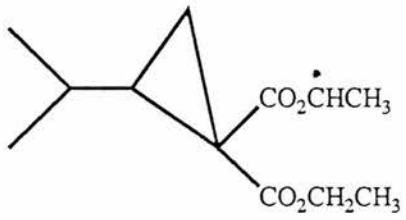
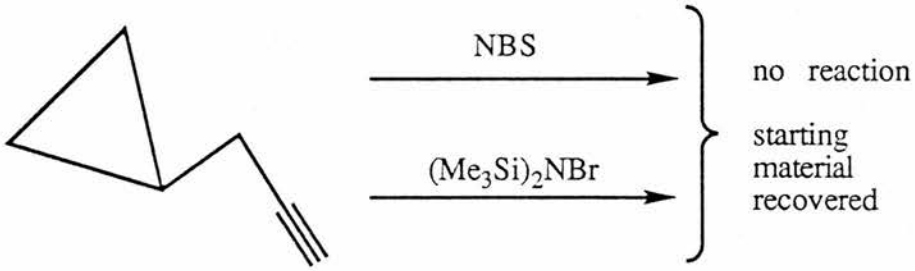


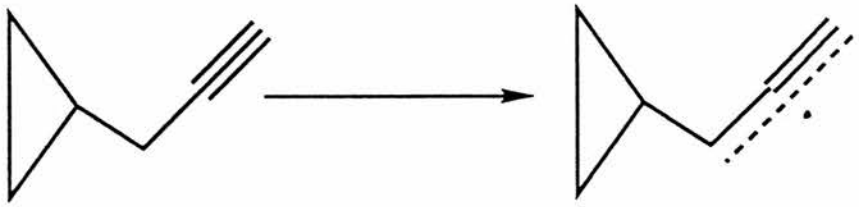
Fig. 5. 9.2 GHz EPR spectrum of diethyl 2-isopropylcyclopropyldicarboxylate at 260 K, in *tert*-butylbenzene.



It was becoming increasingly evident that the overall interior chain extension process was severely hindered by the fact that α–hydrogen was extremely difficult to direct without other hydrogens being removed as well. One final compound was tested for feasibility : cyclopropyl propyne. Experiments with both NBS and $(Me_3Si)_2NBr$ were carried out.



Once again only the starting material was recovered. EPR spectra were recorded in BOOB (neat) and in cyclopropane with BOOB. A good spectrum was obtained at 150 K which analysed for a (2H) = 1.52 G, a (1H) = 1.72 G, a (2H) = 2.15 G, a (1H) = 10.9 G, and a (1H) = 17.7 G, attributable to the radical shown below.

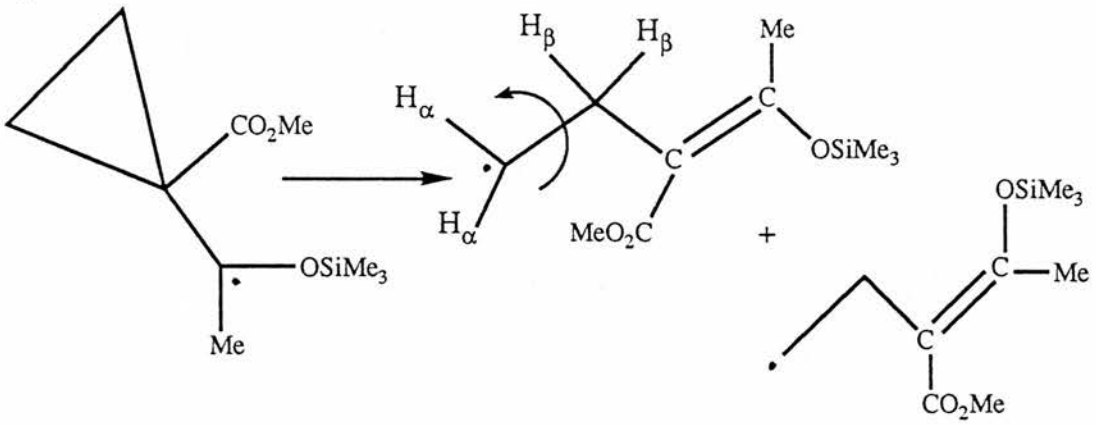


Above 290 K, a sudden loss of intensity was observed, which was probably due to some sort of rearrangement, but the ring opened radical was not observed Once again, resonance delocalisation is thought to be

responsible for the lack of ring opened products obtained (c.f. 1-(cyclopropyl)prop-2-ynyl radical).

Evidently the relatively simple approach that we wanted to adopt with regard to radical ring opening of cyclopropyl compounds and incorporation into synthetic pathways would not produce satisfactory or predictable results. A greater degree of functional group manipulation was required which was not really the object of this project.

The factors influencing the ring opening obviously needed further study. Some useful precursors were provided by Nonhebel.[201] Among these compounds was 1-acetyl-α–(trimethylsilyloxy)-cyclopropane which was studied by EPR spectroscopy in the temperature range 120-270 K in CF_2Cl_2, cyclopropane or tert-butyl benzene with di-tert-butyl peroxide. From the appearance of the spectra it was apparent that the ring unopened radical was not present , even at 120 K, hence the ring must open rapidly to exhibit the rearranged species, scheme 16



Scheme 16.

The spectrum obtained at 140 K in CF_2Cl_2 with BOOB is shown in Fig 6.

The spectrum analyses for a (2H) = 22.6 G, a (1H) = 31.2 G, and a (1H) = 32.2 G. A minor component was detected with hfs of a (3H) = 19.5 G

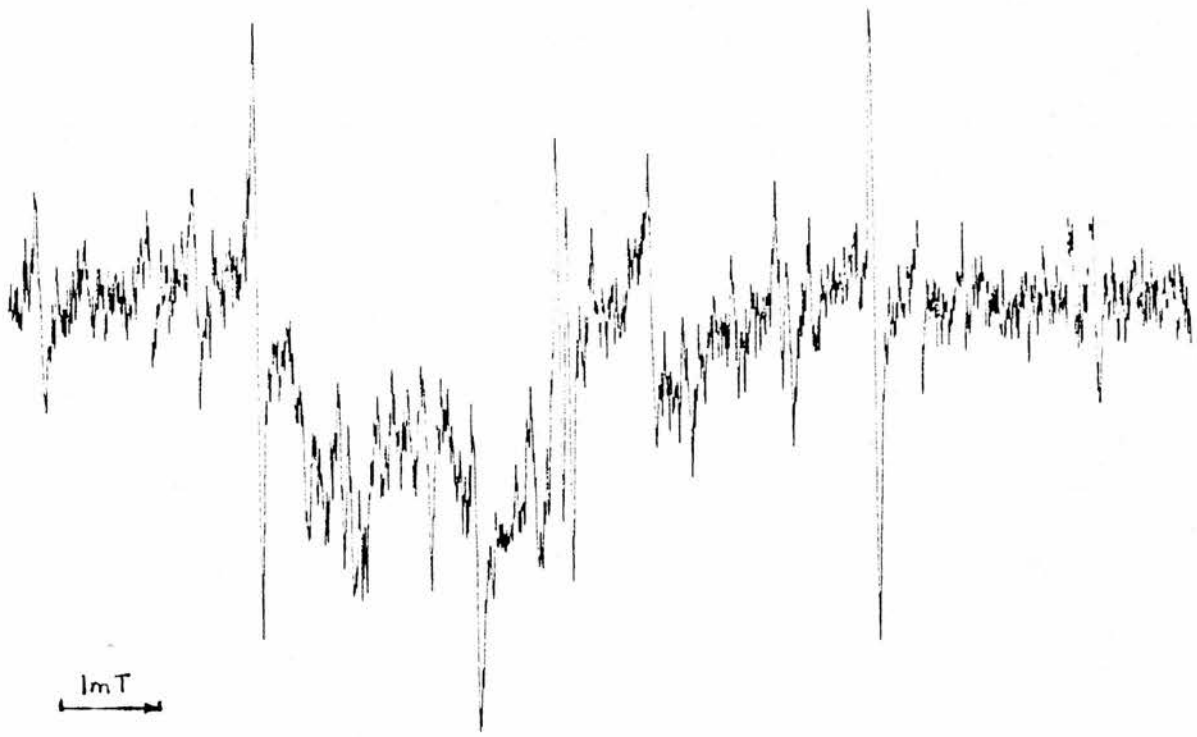
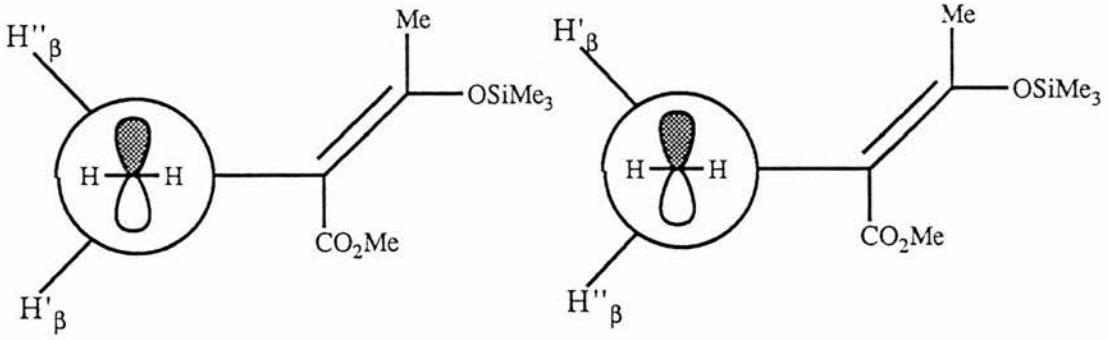


Fig. 6. 9.2 GHz EPR spectrum of the radical from 1-acetyl-α-(trimethylsilyloxy) cyclopropane, in cyclopropane, at 140 K (200 G wide).

that could be resolved. The minor component could not be identified but it was unlike the ring unopened radical. It is possible that the alternative isomer with the $OSiMe_3$ and Me groups interchanged could contribute to this spectrum. The spectra exhibited an exchange broadening type of process due to rotation about the C_α–C_β bond. At low temperature a doublet appears in the central region of the spectrum. As the temperature increases, the spin rates about the C_α–C_β and C_β–C_γ bonds increase. and the doublet sharpens up and coalesces to a single line at ca. 200 K. By 265 K free rotation is occuring. The half-field spectra (the full spectra are 200 G wide) obtained at 150 K, 200 K and 265 K illustrate this process (Fig 7)



The Newman projections (above) show how rotation of the hydrogens about C_β, gives rise to them being able to occupy two different sites relative to the SOMO at the radical centre. Hence this explains the exchange broadening process observed in the spectra. At low temperatures the two H_β are non-equivalent, exhibiting a central doublet in the EPR spectrum. As the temperature increases, the H_β atoms rotate more rapidly, effectively becoming equivalent. At ca. 190 K, the central doublet has coalesced to a broad single line as a result of this equivalence, and

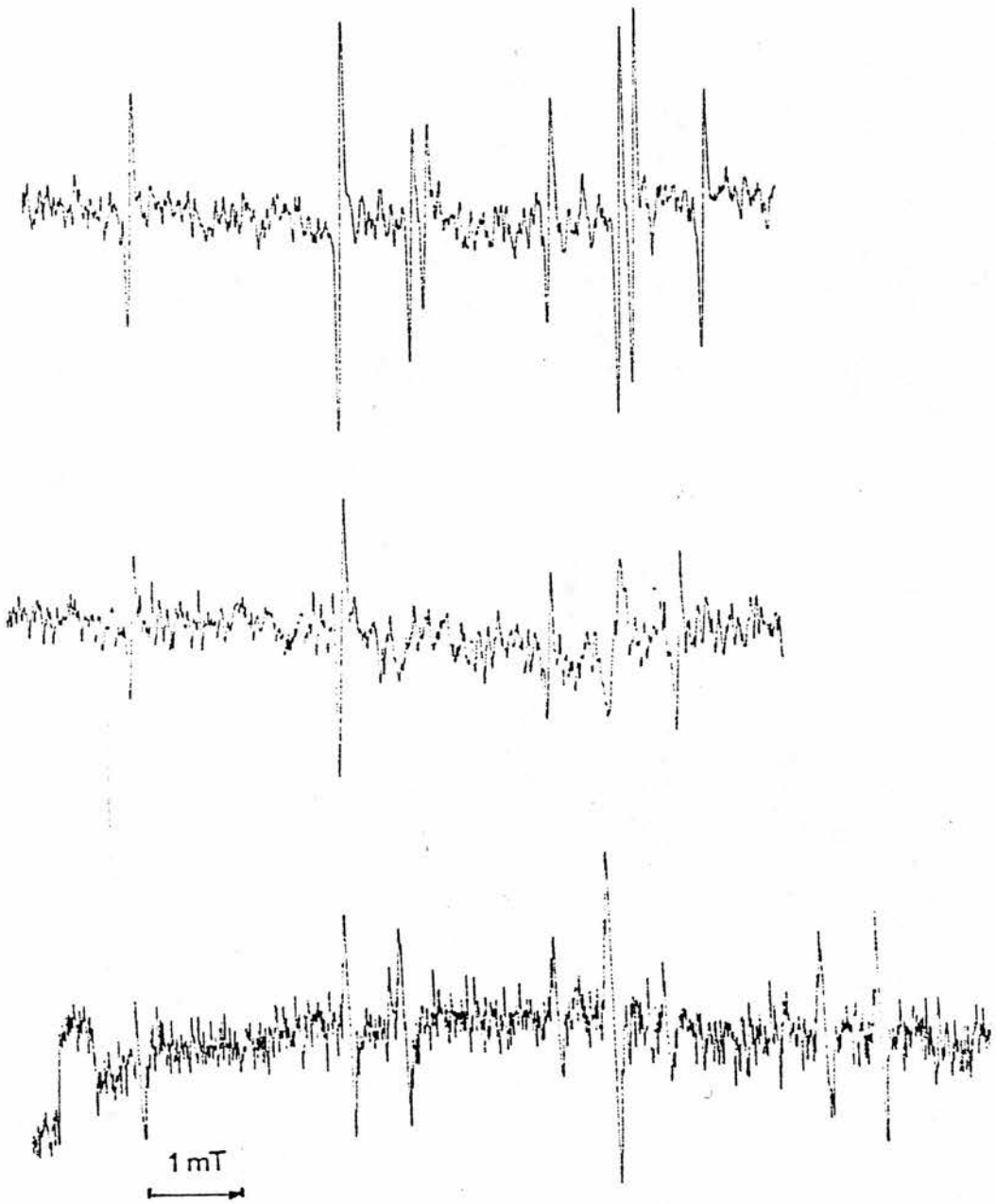


Fig. 7. 9.2 GHz 1 / 2 field EPR spectra of 1-acetyl-∝-(trimethylsilyloxy) cyclopropane, at, from the top, 150 K; centre, 200 K; bottom 265 K, (full spectra 200 G wide)

above 190 K this broad single line sharpens up as the free rotation limit is reached.

In these laboratories we have established a linear correlation between the rate of β-scission, k, for cyclopropylmethyl and cyclobutylmethyl radicals, and the temperature T_f; wherby T_f is the temperature at which the proportions of the rearranged and unrearranged radicals are equal. Thus, under EPR conditions, we have

$$\text{Log } k = \text{Log } A - E / 2.3RT$$

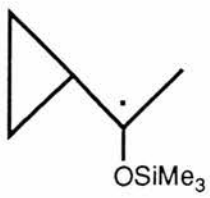
Log A = 13.0 for all the radicals that have been studied, and, hence from this expression we can approximately calculate the rate of ring opening for a cyclopropyl or cyclobutyl radical at any temperature. In the case of 1-acetyl-α-(trimethylsilyloxy) cyclopropane the EPR spectra show that the radical is fully ring opened at 120 K. Hence from our linear correlation, it follows that the activation energy for β-scission must be < 6.0 kcal mol^{-1}. The rate constant at 298 K can then be calculated to be

$$\text{Log } k = \text{Log } A - E / 2.3RT$$

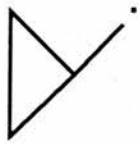
$$\text{Log } k = 13 - 6000 / (298)\,(2.3)\,(1.987) = 8.594$$

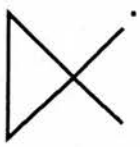
$$\therefore\ k_{298} \geq 4 \times 10^8\ s^{-1}\ .$$

The rate constant of $k_{298} \geq 4 \times 10^8\ s^{-1}$ for the β-scission of 1-acetyl-α-(trimethylsilyloxy) cyclopropane is somewhat larger than might have been expected. In fact it is about one order of magnitude larger than the radical derived from α-methyl-α-(trimethylsilyloxy) cyclopropane. (shown below)



Consider the relative rates of β-scission of the cyclopropylmethyl radicals shown below :-





Relative rates of β-scission	0.34	0.28

It is evident from these figures that the addition of another substituent (in this case a methyl group) at the 1-position does not substantially alter the rate of β-scission. Therefore it seems unusual that 1-acetyl-α-(trimethylsilyloxy) cyclopropane has a much higher rate of β-scission. The methoxycarbonyl group on the 1-position neither stabilises the rearranged radical, nor provides any destabilisation of the unrearranged radical. This anomalous result merits further investigation.

1-(pent-3-yl)-2,2-diethoxycarbonyl cyclopropane was also supplied by Nonhebel and co-workers.[201] This compound was also examined by EPR spectroscopy over the temperature range 150-160 K, in cyclopropane with BOOB, and 225-310 K in tert-butyl benzene with BOOB. The spectrum obtained at 245 K is shown in Fig 8.

The spectrum analyses for :- a(1H) = 0.7 G and a(2H) = 23.5 G

The same spectrum was observed at 150 K and is consistent with the ring opened radical shown below

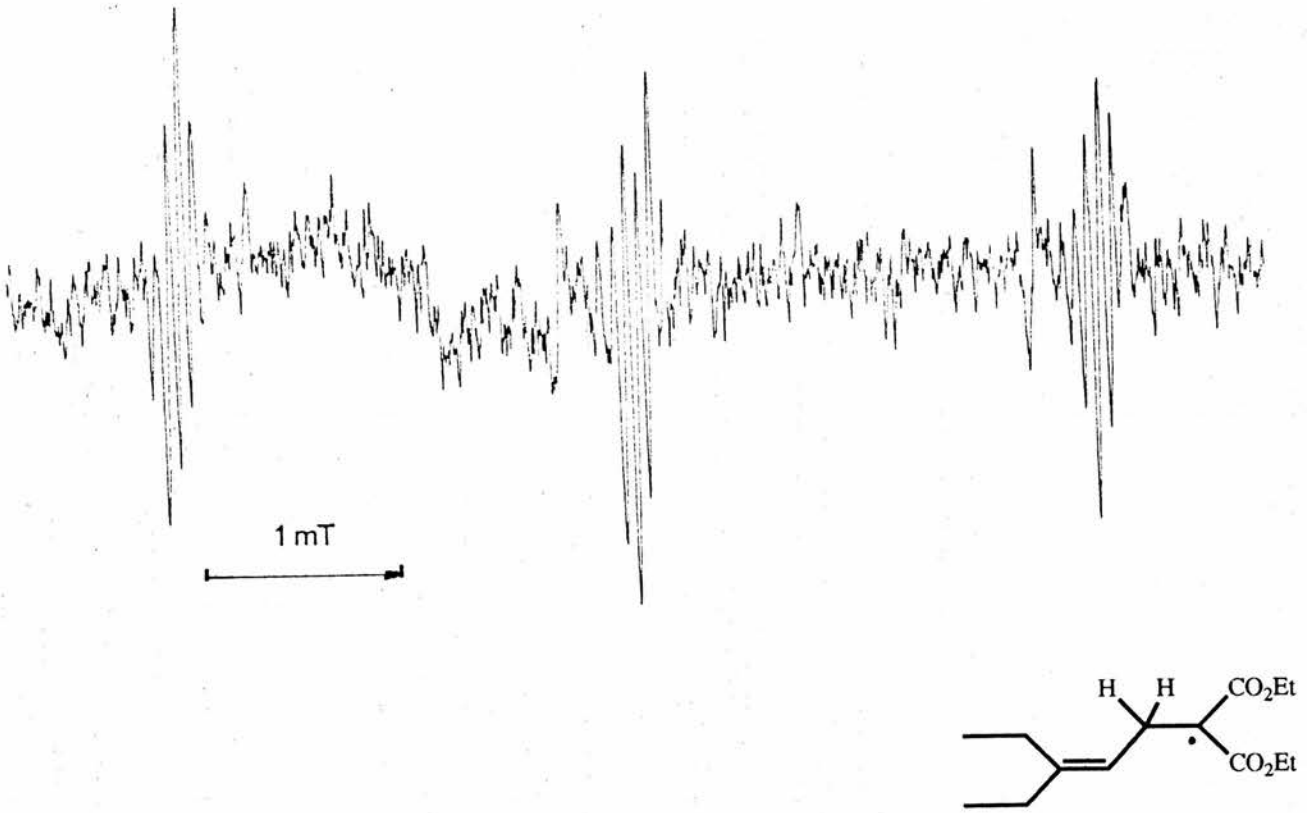


Fig. 8. 9.2 GHz EPR spectrum of the radical from 1-(pent-3-yl)-2,2-diethoxycarbonyl cyclopropane, in *tert*-butylbenzene, at 245 K.

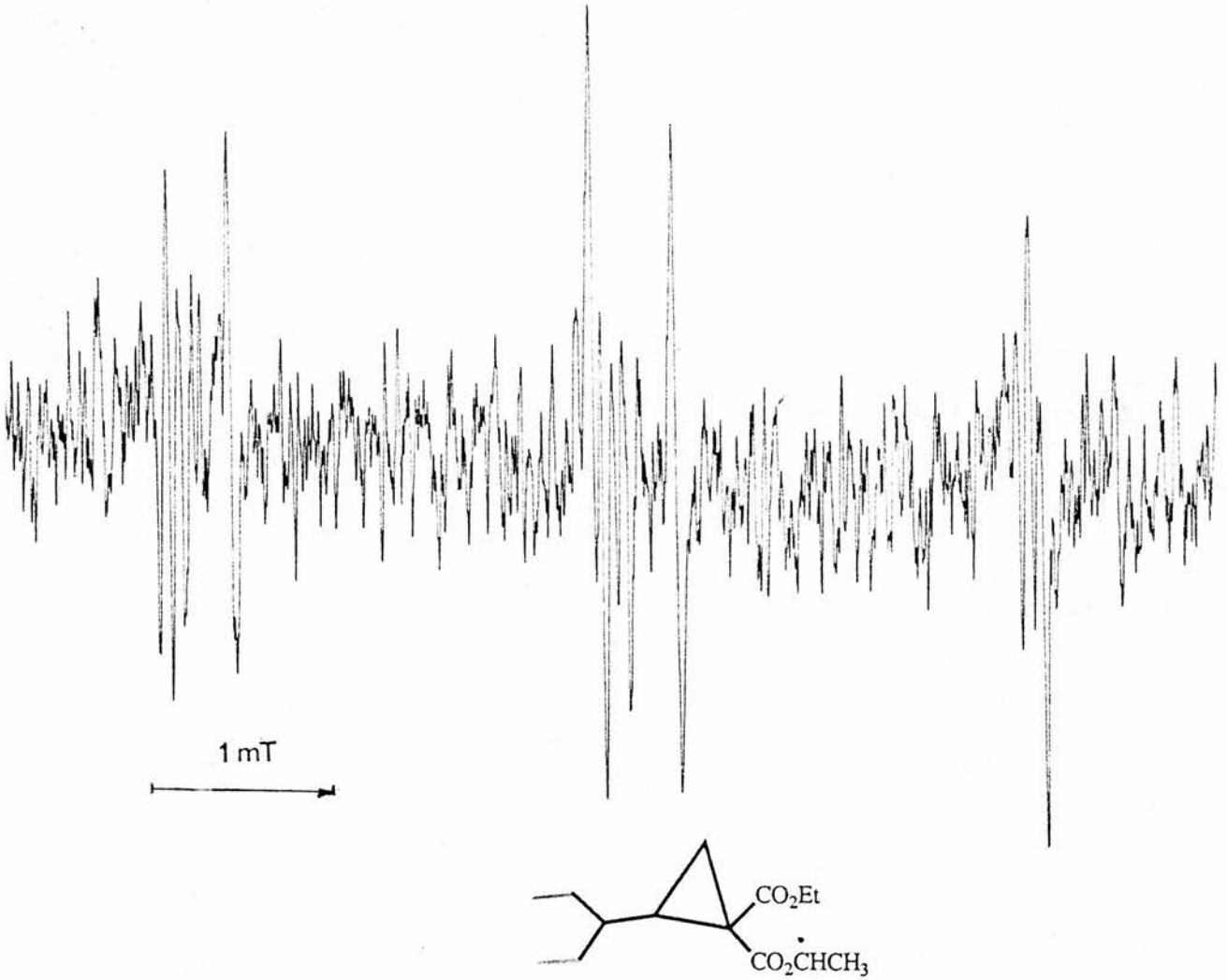


Fig. 9. 9 GHz EPR spectrum of 1-(pent-3-yl)-2,2-diethoxycarbonyl cyclopropane, at 240 K, in *tert*-butylbenzene .

Once again, using the linear correlation that has been established between the rate of β-scission and temperature, for cyclopropylmethyl and cyclobutylmethyl radicals, it is possible to estimate the rate of ring opening of the radical derived from 1-(pent-3-yl)-2,2-diethoxycarbonyl cyclopropane.

Since the radical is fully ring opened at 150 K, our linear correlation indicates that the activation energy for β-scission must be ≤ 7.0 kcalmol^{-1}. The rate constant at 298 K can then be calculated, using the value Log A = 13.0.

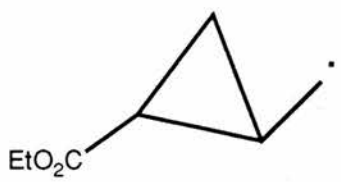
$$\text{Log } k = 13 - 7000 / (298) (2.3) (1.987)$$

$$\text{Log } k = 7.860$$

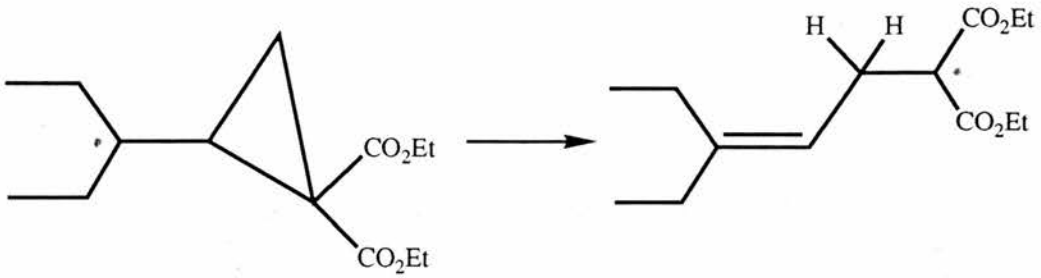
$$\text{then } k_{298} \geq 7 \times 10^{7} s^{-1}$$

since the activation energy for β-scission ≤ 7.0 kcalmol^{-1} .

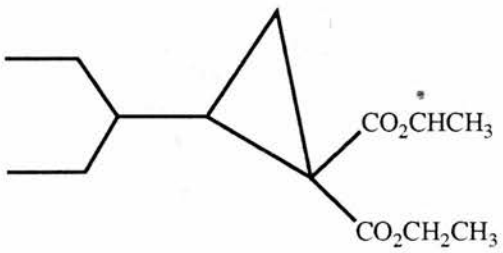
[note:- this value is of the same order of magnitude as the rate of ring opening for the ethoxycarbonyl cyclopropylmethyl radical shown below



for which $k_{298} \geq 10^{8} s^{-1}$].



Evidently ring opening appears to proceed in a very rapid manner, and entirely analogously to that described for diethyl 2-isopropylcyclopropyl-dicarboxylate. Similarly at higher temperatures the signal from this radical gradually weakens and the spectrum of a second radical becomes predominant, the hfs of which at 240 K were measured as a (1H) = 20.1 G, a (3H) = 24.3 G (Fig 9.). This radical is also the result of hydrogen abstraction from the ethoxycarbonyl portion of the molecule.



Tables 3 and 4. summarises the proportions of the rearranged radical and the radical from the ethoxycarbonyl portion of the molecule for both diethyl 2-isopropylcyclopropyldicarboxylate and 1-(pent-3-yl)-2,2-diethoxycarbonyl-cyclopropane

diethyl 2-isopropylcyclopropyldicarboxylate

T / K	Solvent	$RCO_2\dot{C}HCH_3$	Rearranged Radical
150-270	cyclopropane	100%	0
220	Bu^{t}Ph	Minor	Major
290	Bu^{t}Ph	Major	Minor

Table 3.

1-(pent-3-yl) -2,2-diethoxycarbonyl cyclopropane

T / K	Solvent	$RCO_2\dot{C}HCH_3$	Rearranged Radical
150-160	cyclopropane	0	100%
225	Bu^{t}Ph	Minor	Major
285	Bu^{t}Ph	Major	Minor

Table 4.

Experimental

Bis(Trimethylsilyl) N-Bromoamine 1,1,1,3,3,3-Hexamethyldisilazane (10.3g, 0.06mol) and N-bromosuccinimide (11.4g, 0.06mol) were dissolved in chloroform (50ml), and stirred in the dark at room temperature for 4 hours. During this time the succinimide floated to the top of the reaction mixture. This was filtered off and the residual liquid was distilled on a Vigreux column under reduced pressure to yield bis(trimethylsilyl) N-bromoamine as an orange liquid (9.45g, 55.7%), bp. 60-62°C / 15Torr (lit[190] 63°C / 20Torr). δ_H (60MHz) 0.00 (6H, s).

Zinc / Copper Couple To a hot, rapidly stirred solution of cupric acetate monohydrate (2.0g, 0.01mol) in glacial acetic acid (50ml) was added zinc filings (35g, 0.54mol). After about 5 minutes all of the copper had deposited on the zinc. The couple was allowed to settle for *ca.* 1.5 minutes, then as much of the acetic acid as possible was decanted off, care being taken not to lose the silt-like couple. The dark reddish-grey couple was then washed with one 50ml portion of acetic acid, followed by three 100ml portions of ether. The moist couple was then ready for use.

Butylcyclopropane To the zinc / copper couple previously prepared was added dry ether (50ml) and approximately 3ml of methylene iodide (CH_2I_2). The mixture was warmed gently on an oil bath until bubbles began to rise from the couple. Hex-1-ene (15g, 0.178mol) and methylene iodide (66.74g, 0.249mol) (ratio of alkene : CH_2I_2 = 0.25 : 0.35) were added to the refluxing mixture. The mixture was stirred under reflux for *ca.* 21 hours, during which time the Zn / Cu couple almost entirely decomposed forming a purple precipitate in solution. The reaction

mixture was decanted off and poured onto cracked ice containing HCl (1M, 250ml). The ethereal layer was washed successively with HCl (1M, 200ml), water (3 x 200ml), and dried over K_2CO_3. The ether was evaporated off and the residual liquid distilled on a Vigreux column under reduced pressure. The title compound distilled over as a faint yellow liquid (3.62g, 20.7%), bp. 69-71°C / 15Torr. δ_H (300MHz) 0.00 (2H, m), 0.35-0.45 (2H, m), 0.6-0.7 (1H, m), 0.9 (3H, t, J = 6Hz), 1.2 (2H, m), 1.3-1.45 (4H, m); δ_C (75MHz) 4.4 (2C), 11.0 (1C), 14.2 (1C), 22.8 (1C), 32.1 (1C), 34.7 (1C).

1-Butyl-2,2-dichlorocyclopropane Hex-1-ene (8.41g, 0.1mol), chloroform (36g, 24ml, 0.3mol) and benzyltriethylammonium chloride (0.5g) were mixed together and stirred vigorously at 40°C (water bath). 30ml of 50% w / w aqueous NaOH (i.e. 15g of NaOH, 30ml of water) was added to the solution over 30 minutes. The mixture was stirred at 40°C for a further 4 hours and then allowed to cool and poured onto saturated aqueous sodium chloride solution (200ml). The resulting mixture was extracted with ether (2 x 150ml), and dried over Na_2SO_4. The solvent ether was removed on a Rotavapor and the residual liquid was purified by fractional distillation on a Vigreux column under reduced pressure. 1-Butyl-2,2-dichlorocyclopropane was afforded as a colourless liquid (2.97g, 17.8%), bp. 72-73°C / 15Torr. δ_H (300MHz) 0.95 (2H, m), 1.05 (1H, m), 1.3-1.7 (9H, m). δ_C (75MHz) 14.0 (1C), 22.4 (1C), 26.8 (1C), 30.0 (1C), 30.8 (1C), 30.9 (1C), 61.7 (1C).

Bromination of 1-Butyl-2,2-dichlorocyclopropane with $(Me_3Si)_2NBr$ 1-Butyl-2,2-dichlorocyclopropane (2.00g, 0.012mol), $(Me_3Si)_2NBr$ (2.88g, 0.012mol), norbornene (norbornylene) (0.06g, 6 x 10^{-4}mol, 5mol%), α,α'-azoisobutyronitrile (AIBN) (0.1g, 6 x 10^{-4}mol, 5mol%) and benzene (10ml)

were mixed together and stirred at 60°C approx. for 60 hours. The resulting mixture was shaken successively with dilute HCl solution (5M, 20ml) and sodium bicarbonate solution (20ml). The benzene solution was dried over Na_2SO_4. After filtration of the drying agent and removal of the solvent on a Rotavapor, the residual liquid was distilled on a Buchi Kugelrohr. The product was found to be the unchanged starting material, 1-butyl-2,2-dichlorocyclopropane.

Bromination of 1-Butyl-2,2-Dichlorocyclopropane with NBS

1-butyl-2,2-dichlorocyclopropane (2.00g, 0.012mol), NBS (2.14g, 0.012mol), and CCl_4 (20ml) were mixed together. Benzoyl peroxide (0.15g 6 x 10^{-4}mol, 5mol%) was added and the mixture was refluxed for 24 hours. Once the mixture had cooled down to room temperature the solid components were filtered off. The solvent , CCl_4, was removed under reduced pressure to leave a pale brown liquid, which was found to be the unreacted starting material, 1-butyl-2,2-dichlorocyclopropane.

Bromination of Butylcyclopropane with $(Me_3Si)_2NBr$

Butylcyclopropane (2.00g, 0.02mol), $(Me_3Si)_2NBr$ (4.90g, 0.02mol), norbornylene (0.1g, 1.02 x 10^{-3}mol, 5mol%), AIBN (0.17g, 1.02 x 10^{-3}mol, 5mol%), and benzene (10ml) were mixed together and stirred at 60°C for 24 hours approx. After this time, a second 5mol% batch of AIBN was added and the mixture stirred for a further 24 hours at 60°C. The resulting orange solution was added to twice its volume of dilute HCl solution (5M, 20ml). The aqueous layer was run off after shaking and sodium bicarbonate solution added (20ml). The organic layer was separated off and dried (Na_2SO_4). After filtration of the drying agent and removal of the solvent under reduced pressure, the residual pale orange / yellow liquid was found to consist of a number of components, some of which

were separated in small amounts by prep g.c. using a 12 ft 10% FFAP column with Chromosorb as a solid support (80-100 mesh), operated at 150°C. Milligram amounts of products were separated, two of which had ^{1}H NMR spectra consistent with; 3-bromo-1-cyclopropylbutane, δ_H(300MHz) 0.13 (3H, m), 0.65 (2H, m), 0.45 (2H, m), 0.9 (1H, m), 1.45 (2H, m), 1.9 (2H, m) and 4.2 (1H, m); 2-bromo-1-cyclopropylbutane, δ_H(300MHz) 0.13 (3H, m), 0.43 (2H, m), 0.55 (2H, m), 0.57 (1H, m), 1.45 (2H, m), 1.9 (2H, m) and 4.1 (1H, m).

Bromination of Butylcyclopropane with NBS Butylcyclopropane (2.0g, 0.02mol), NBS (3.63g, 0.02mol) and CCl_4 (20ml) were mixed together. Benzoyl peroxide (0.25g, 2 x 10^{-3}mol, 5mol%) was added and the mixture was refluxed for 24 hours. Once the mixture had cooled, the white succinimide was filtered off. The solvent CCl_4 was removed under reduced pressure to leave an orange / yellow liquid. The liquid was allowed to stand for a while during which time white crystals formed. These were filtered off and ^{1}H NMR examination indicated that they were benzoic acid. The residual orange / yellow liquid was subjected to prep g.c. under the same conditions as those described for the bromination reaction of butyl cyclopropane with $(Me_3Si)_2NBr$. A few milligrams of product was separated which had the ^{1}H NMR consistent with 4-bromo-1-cyclopropylbutane, δ_H(300MHz) 0.05 (2H, m), 0.41 (2H, m), 0.65 (1H, m), 1.25 (2H, m), 1.55 (2H, m), 1.9 (2H, m), and 3.45 (2H, m).

(Attempted) Cyclopropanation of Ethyl crotonate To the Zn / Cu couple previously prepared was added dry ether (50ml) and methylene iodide (CH_2I_2) (3ml). The mixture was warmed gently on an oil bath until bubbles began to rise from the couple. Ethyl crotonate (20.0g, 0.175mol) and CH_2I_2 (65.62g, 0.25mol) (ratio of alkene : CH_2I_2 = 0.25

: 0.35) were added and the mixture was stirred at reflux for 21 hours approx. The reaction mixture was decanted off and poured onto cracked ice containing HCl (1M, 250ml). The organic layer was separated off and washed successively with HCl (1M, 200ml) and water (3 x 200ml), and dried over K_2CO_3. The solvent was evaporated after removal of the drying agent to leave a brown residue which was found to be the unchanged ethyl crotonate with δ_H (60MHz) 1.13 (3H, t, J = 7Hz), 1.7 (3H, d, J = 7Hz), 4.05 (2H, q, J = 7Hz), 5.5-5.95 (1H, m), 6.55-7.2(1H, m).

But-3-enoyl chloride (Vinyl acetyl chloride) Thionyl chloride (16.65g,0.14mol) was warmed gently on a water bath and but-3-enoic acid (10.0g, 0.12mol) was added dropwise to the stirred solution during 40 minutes. Upon completion of the addition, the mixture was heated for a further 30 minutes. The apparatus was rearranged and the crude acid chloride was distilled out from the reaction mixture. Further distillation was required to purify the but-3-enoyl chloride which was formed as a colourless liquid (10.14g, 83.5%), bp. 94-95°C / 760Torr (lit[198] yield 74.2%, bp. 98-99°C / 760Torr).

Ethyl but-3-enoate (Ethyl vinyl acetate) Absolute ethanol (4.5g, 0.095mol) was stirred and cooled on an ice-water bath, in a flask equipped with a calcium chloride guard tube. But-3-enoyl chloride (10.0g, 0.095mol) was added dropwise to the ethanol over a period of about 40 minutes. The ice-water bath was removed and the reaction mixture allowed to stand for 1 hour, before being poured into water (100ml). The mixture was washed with sodium hydrogen carbonate solution (50ml), followed by water (100ml). The organic layer was separated off and dried over $CaCl_2$. After filtration of the drying agent, the crude product was distilled through a short fractionating column at atmospheric pressure to yield ethyl vinyl acetate as a colourless liquid (8.55g, 76.2%) bp.

125-127°C / 760Torr, (lit[198] yield 75%, bp. 125-127°C / 760Torr). δ_H (60MHz) 1.0 (3H, t, J = 8Hz), 2.85 (2H, d, J = 7Hz), 3.7-4.2 (2H, q,), 4.7-4.95 (1H, m), 5.05 (1H, bs), 5.4-6.2 (1H, m).

Cyclopropanation of Ethyl but-3-enoate To the Zn / Cu couple previously prepared was added dry ether (50ml) and 3ml of methylene iodide (CH_2I_2). The mixture was warmed gently on an oil bath until bubbles began to rise from the couple. Ethyl but-3-enoate (5.0g, 0.04mol) and methylene iodide (16.44g, 0.06mol) (ratio of alkene : CH_2I_2 = 0.25 : 0.35) were added to the mixture which was stirred under reflux for 21 hours. The reaction mixture was decanted and poured onto cracked ice containing HCl (1M, 250ml). The organic layer was separated and washed successively with HCl (1M, 200ml), and H_2O (3 x 200ml), and dried over K_2CO_3. After filtration of the drying agent and removal of the solvent, small scale t.l.c. of the residual liquid in 5% ether in petroleum ether 40 : 60, showed the presence of several components. Ethyl cyclopropylacetate was separated by preparative g.c. using a 12 ft 10% FFAP column using Chromosorb as a solid support (80-100 mesh), operated at 150°C. The title compound was obtained as a colourless liquid (0.06g, 1.3%). δ_H (300MHz) 0.15 (2H, m), 0.55 (2H, m), 1.28 (3H, t, J = 2Hz), 2.2 (3H, m), 4.17 (2H, q); δ_C (75MHz) 4.4 (1C), 6.9 (1C), 14.3 (1C), 30.9 (1C), 35.9 (1C), 60.3 (1C), 173.3 (1C).

Bromination of Ethyl Cyclopropylacetate with NBS Ethyl cyclopropylacetate (0.03g, 2.3 x 10^{-4}mol), NBS (0.04g, 2.3 x 10^{-4}mol) and CCl_4 (15ml) were mixed together. Benzoyl peroxide (3mg, 1.2 x 10^{-5}mol, 5mol%) was added and the mixture was refluxed for 48 hours. Upon cooling down to room temperature the white succinimide was filtered off and the resulting solution washed with dilute HCl (5M, 30ml), and then

dried (Na_2SO_4). Removal of the drying agent and evaporation of the solvent yielded a few milligrams of a faint yellow solid. ^1H NMR and GC / MS analysis indicated the presence of two identifiable components; ethyl α-bromocyclopropylacetate, δ_H (300MHz) 0.15 (2H, m), 0.53 (2H, m), 1.05 (1H, m), 1.28 (3H, t, J = 2Hz), 3.2 (1H, m), 4.15 (2H, q, J = 3Hz); and 1-bromoethyl cyclopropylacetate δ_H (300MHz) 0.15 (2H, m), 0.53 (2H, m), 1.05 (1H, m), 1.3 (3H, d, J = 3Hz), 2.35 (2H, m), 3.6 (1H, m).

(Attempted) Bromination of Diethyl 2-isopropylcyclopropyl-dicarboxylate with NBS Diethyl 2-isopropylcyclopropyldicarboxylate (0.5g, 2.2 x 10^{-3}mol), NBS (0.39g, 2.2 x 10^{-3}mol) and CCl_4 (10ml) were mixed together. Benzoyl peroxide (0.03g, 1.1 x 10^{-4}mol, 5mol%) was added and the mixture was refluxed for 60 hours. After cooling down to room temperature the solid components were removed by filtration. The solvent was removed under reduced pressure to yield 0.61g of a fairly viscous yellow liquid. GC / MS analysis showed only one major component which was found to be the unreacted starting material with δ_H(300MHz) 0.95-1.1 (7H, m), 1.2-1.4 (8H, m), 1.6-1.8 (1H, m) and 4.05-4.3 (4H, m); δ_C(75MHz) 14.0 (CH_3), 14.1 (CH_3), 20.1 (CH_2), 21.8 (CH_3), 22.5 (CH_3), 28.6 (CH), 34.8 (1C), 36.2 (CH), 61.2 (CH_2), 61.3 (CH_2), 168.5 (CO) and 170.6 (CO) (assigned with DEPT-135); m / z (%) 228, 199(2), 183(23), 173(48), 138(25), 136(100), 128(52) and 127(93).

(Attempted) Bromination of Diethyl 2-isopropyl-cyclopropyldicarboxylate with $(Me_3Si)_2NBr$ Diethyl 2-isopropylcyclo-propyldicarboxylate (0.4g, 1.8 x 10^{-3}mol), $(Me_3Si)_2NBr$ (0.42g, 1.8 x 10^{-3}mol), norbornene (8mg, 5mol%), AIBN (14mg, 5mol%) and benzene (10ml)

were mixed together and stirred at 60°C for 60 hours. The resulting mixture was shaken successively with dilute HCl solution (5M, 20ml) and sodium bicarbonate solution (20ml). The benzene solution was dried over Na_2SO_4. After filtration of the drying agent and removal of the solvent benzene on a Rotavapor, 0.54g of an orange liquid remained. This was found to be the unreacted starting material

(Attempted) Bromination of Cyclopropylpropyne with NBS. Cyclopropylpropyne (0.21g, 2.6 x 10^{-3}mol), NBS (0.47g, 2.6 x 10^{-3}mol) and CCl_4 (10ml) were mixed together. Benzoyl peroxide (0.03g, 1.3 x 10^{-4}mol) was added and the mixture was stirred at 60°C for 24 hours. Upon cooling, the solid components were removed by filtration, and the solvent CCl_4 evaporated under reduced pressure. The residue was distilled at atmospheric pressure to give 0.44g of a colourless liquid. ^{1}H NMR and GC / MS analysis of this material did not reveal any evidence of bromination of the starting material.

(Attempted) Bromination of Cyclopropylpropyne with $(Me_3Si)_2NBr$ Cyclopropylpropyne (0.16g, 2 x 10^{-3}mol), $(Me_3Si)_2NBr$ (0.48g, 2 x 10^{-3}mol) and benzene (10ml) were mixed together. Norbornylene (9mg, 10^{-4}mol, 5mol%) and AIBN (16mg, 10^{-4}mol, 5mol%) were added and the mixture heated at 60°C for 40 hours approx. The resulting mixture was shaken successively with dilute HCl (5M, 5ml) and sodium bicarbonate solution, and dried (Na_2SO_4). After filtration of the drying agent and removal of the solvent under reduced pressure, ^{1}H NMR and GC / MS analysis of the residue showed it to be inconsistent with bromination of the starting material.

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