RADICAL REARRANGEMENTS OF UNSATURATED RING DERIVATIVES AND THE INVESTIGATION OF ROUTES TO POLYNITROXIDES

A thesis presented by **Finlay MacCorquodale, B.Sc.** to the University of St. Andrews in application for the degree of Doctor of Philosophy.

August 1989

DECLARATIONS

I, Finlay MacCorquodale, hereby certify that this thesis has been composed 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.

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I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No 12 on 1st October 1986 and as a candidate for the degree of Ph.D. on 1st October 1987.

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PUBLICATIONS

F. MacCorquodale and J.C. Walton, "Formation of Bicyclo[3.2.1]octane, Bicyclo[4.2.1]nonane and Bicyclo[3.3.1]nonane by Transannular Radical Cyclisations", *J. Chem. Soc., Chem. Commun.*, 1456, (1987).

F. MacCorquodale and J.C. Walton, "E.S.R. Studies of Cycles and Bicycles", *J. Chem. Soc., Farady Trans., I*, 3233, (1988).

F. MacCorquodale and J.C. Walton, "Cyclisation of 5-Bromomethyl-cycloheptene and - cyclo-octene: a New Route to Bicyclo[3.2.1]octanes and Bicyclo[4.2.1]nonanes", *J. Chem. Soc., Perkin Trans., II*, 347, (1989)

R. Gash, F. MacCorquodale and J.C. Walton, "Free Radical Cyclisation of Unsaturated Epoxides", *Tetrahedron*, Accepted for publication.

J.A. Crayston, F. MacCorquodale, J.C. Walton and D.J. Worsfold, "Synthesis and Electrochemical Characterisation of Poly(TEMPO-acrylate)", In Preparation.

P.N. Culshaw, M.J. Dalton, F. MacCorquodale and J.C. Walton, "Radical Rearrangements of the Cycloheptatriene System", In Preparation.

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LIST OF ABBREVIATIONS

n.m.r. - Nuclear magnetic resonance (in $CDCl_3$ unless otherwise stated).

m.s. - Mass spectrum.

i.r. - Infra - red.

u.v. - Ultra - violet.

e.s.r - Electron spin resonance.

h.f.s. - Hyper-fine splitting.

g.l.c. - Gas - Liquid Chromatography.

g.p.c. - Gel - Permeation Chromatography.

g.c.m.s. - Gas - Chromatography - Mass Spectroscopy.

c.v. - Cyclic voltamogram.

δ - δ relative to tetramethylsilane.

SOMO - Semi - occupied molecular orbital.

HOMO - Highest occupied molecular orbital.

LUMO - Lowest unoccupied molecular orbital.

POMO - Partially occupied molecular orbital.

ABSTRACT

In part 1, the radical rearrangements of some halomethyl substituted unsaturated rings are described. Cyclohept-4-enylmethyl bromide gave bicyclo[3.2.1]octane upon reduction with Bu_3SnH. Under the same conditions cyclo-oct-4-enylmethyl bromide gave bicyclo[4.2.1]nonane as the major product together with a small amount of bicyclo[3.3.1]nonane. 4,7-dihydro-1,3-dioxepin-2-ylmethyl bromide was reduced by Bu_3SnH to give 4,7-dihydro-2-methyl-1,3-dioxepin as the major product in addition to a trace of 2,7-dioxabicyclo[3.2.1]octane. 4,7-Dihydro-2-methyl-1,3-dioxepin-2-ylmethyl bromide was reduced to give 1-methyl-2,7-dioxabicyclo[3.2.1]octane in good yield. Cyclohepta-2,4,6-trien-1-ylmethyl chloride and 1-methylcyclohepta-2,4,6-trien-1-ylmethyl chloride were reduced to give styrene and α-methylstyrene respectively. The e.s.r. parameters for some 1,3-dioxan-5-ylmethyl radicals and for some substituted tropyl radicals have been determined. The conformational preferences of the former have been elucidated.

In part 2, the synthesis of poly(TEMPO-acrylate), a nitroxide homopolymer is described. The polymer was shown to have similar chemical properties to monomeric nitroxides and to act as an efficient catalyst for the oxidation of amines. Attempts to synthesise [3,2-b;2',3'-d]dithienopyrrole failed. [3,2-b]thienoindole was electropolymerised to give a polymer with a conductivity of $10^{-3}\ \Omega^{-1}cm^{-1}$. N-ethyl[3,2-b]thienoindole did not electropolymerise. [3,2-b]Thienoindoyl nitroxide could not be isolated and was unstable in high dielectric solvents.

To My Parents

"Just as one could not feel the pull of a magnet with one's skin, so one could not hope to grasp in cognate terms the nature of ultimate reality. It was a text written in invisible ink; and though one could not read it, the knowledge that it existed was sufficient to alter the texture of one's existence."[1]

PART ONE

RADICAL REARRANGEMENTS OF UNSATURATED RING DERIVATIVES

CHAPTER 1

RING FORMING RADICAL REARRANGEMENTS

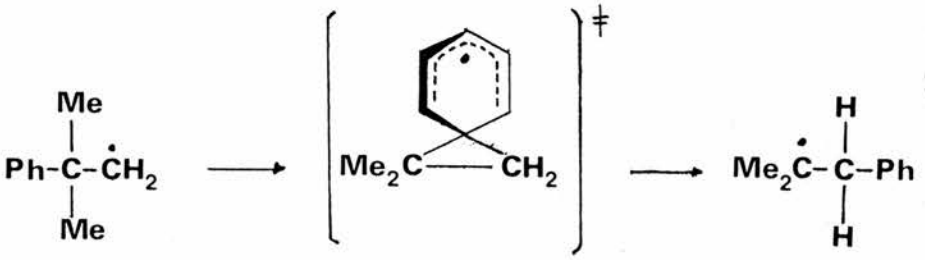
(An Introduction)

1.1 Introduction to Radical Rearrangements.

A rearrangement has been defined by De Mayo[2] as "any change in the atomic disposition in the molecule (with concomitant bond cleavage, σ or π, and reformation)." This definition was later extended by Beckwith and Ingold[3] to include processes in which no bonds are broken or formed but in which there is, nonetheless, a change in the disposition of the atoms of a molecule. An example they cite is the inversion of a radical formed from an optically active precursor.

We are left with a suitably general definition for a ubiquitous concept.

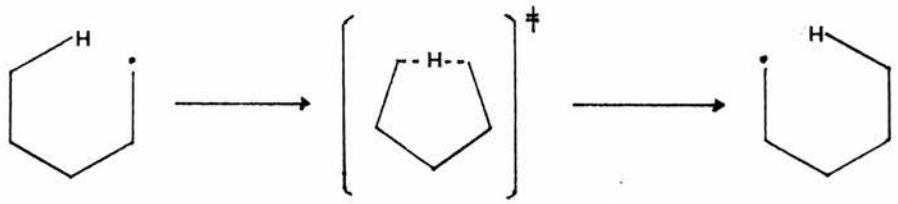
Most free radical rearrangements fall into four general categories: group transfers, atom transfers, ring opening and ring closure reactions. Our knowledge of these reactions has accumulated over some forty-five years. The first radical rearrangement to be identified was the neophyl rearrangement which was discovered in 1944 by Urry and Kharasch (**Scheme 1**).[4]



Scheme 1

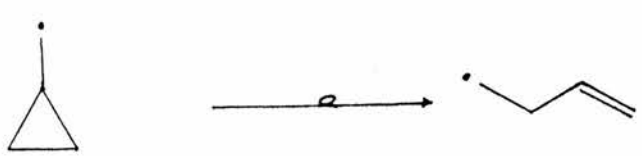
This is an example of the most common type of group transfer, involving a 1,2 shift. Other types of group transfer are known, including 1,4 and 1,5 shifts.

Hydrogen atom transfers most commonly involve a 1,5 shift which occurs via a six membered cyclic transition state (**Scheme 2**). Heteroatom transfers occur most often with halogens and involve a migration process, a 1,2 shift is common.



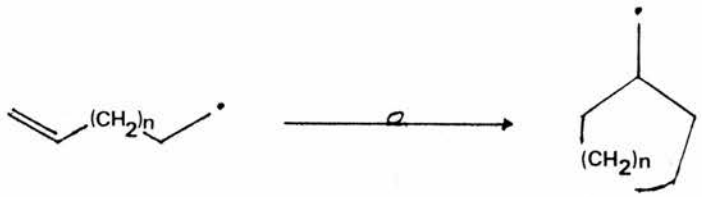
Scheme 2

Ring opening of a radical species is usually asociated with relief of strain and the formation of a more stable radical. e.g. β-scission of cyclopropylmethyl radicals (**Scheme 3**). The stereoelectronic requirements of the transition state are also important in determining the activation energy for the process.[5]



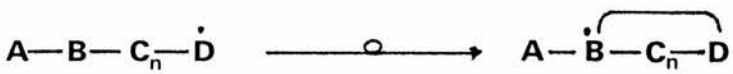
Scheme 3

Ring closure can be effected when there is intramolecular addition of a radical centre to an unsaturated function (**Scheme 4**).



Scheme 4

The addition can also be to a coordinatively unsaturated atom (**Scheme 5**) although there are relatively few examples of this.



Scheme 5

The very large number of all types of radical rearrangements which have by now been studied are the subject of a number of excellent and extensive reviews[2,3,6] and no further attention will be given to most of them here. Chapters 2 - 4 of this thesis are mainly concerned with the search for and investigation of transannular ring closure reactions. The remainder of this chapter will be devoted to describing our understanding of free radical ring closure reactions and the relatively recent upsurge of interest in finding applications for these types of cyclisation. The work which is described in subsequent chapters finds its motivation both in seeking to discover and understand new ring forming reactions and in a desire to contribute to the fund of new synthetic routes to cyclic, bicyclic and polycyclic molecules which involve free radical intermediates.

1.2 Radical Ring Closures

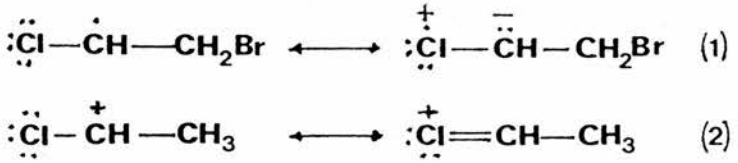
Radical rearrangements which result in the formation of a ring usually involve intramolecular addition of a radical centre to an unsaturated function, e.g. an olefin or a carbonyl group. When reviewing what is known about such reactions, it is instructive to begin by considering the intermolecular reactions of radicals with double bonds.

Radical Addition to Olefins - A Complex Problem.

Mayo and Walling[7] were the first to offer an explanation of the preferred orientation of radical addition in the "anti-Markownikov" addition of HBr to unsymmetrical alkenes. Kharasch[8] and Hey and Waters[9] had shown that the reaction involved the initial addition of a bromine atom (**Scheme 6**).

Scheme 6

The Mayo-Walling hypothesis was that the point of attack was determined by the relative stabilities of the two possible adduct radicals which could be formed. These authors defined stability strictly in terms of heat of formation. However, most workers in the three decades which followed tended to assign this stability to resonance stabilisation of the favoured adduct (1). This approach reflected the accepted explanation for normal Markownikov addition, i.e. that the intermediate carbocation (2) was resonance stabilised.



(1)

(2)

It has been observed since[10] that one canonical form of (1) involves separation of charge and is therefore unlikely to contribute much to the ground state of the adduct radical (1).

Some discussion of the possible importance of polar effects in the progress of this and related reactions took place subsequent to the publication of the Mayo-Walling hypothesis.[11] However, the work of Haszeldine[12] indicated that such considerations could not adequately explain the experimental observations which were available. The resonance theory persisted and was further extended by Haszeldine[13] who postulated that the stability of a radical decreased as the number of hydrogens attached to the carbon bearing the unpaired electron increased; and by Cadogan[14] who interpreted adduct radical stability in terms of hyperconjugation.

The resonance stabilisation theory is entirely consistent with many sets of experimental data and, indeed, at the time of publication of the original Mayo-Walling review, there was no experimental evidence which contradicted their hypothesis.

In 1976, Tedder and Walton[10] reviewed a large number of radical addition reactions. These authors drew attention to a number of examples of this type of reaction for which the resonance theory either fails or is not the only possible explanation for the progress of the reaction.

They contrast the behaviour of the most halogenated and the least halogenated methyl radicals in reaction with trifluoroethylene. The former add preferentially to the CHF end of the olefin whereas the latter add to the CF_2 end. This clearly shows that delocalisation of the odd electron is not the prime factor in determining the orientation of addition; rather, it seems as if polar forces play a significant role. The series of radicals $CF_3\cdot$, $CF_2Br\cdot$, $CFBr_2\cdot$ and $CBr_3\cdot$ would be expected to show a slight increase in the orientation ratio CHF:CF_2 as their polarity decreases across the series, if polarity was the dominant directive factor. In fact the opposite occurs, showing that steric repulsion introduced by the presence of bulky bromine atoms is also important.

This example, amongst others, vindicated the earlier ideas of Price[15], Waters[16], and Mayo and Walling[11] which had held that polar factors might be important in these reactions but which had been largely discounted or overlooked at the time.

The Tedder-Walton review[10] pointed to the danger of comparing orientation ratios in ignorance of the kinetics of the possible reactions. For example, radical addition to vinyl fluoride shows a preference for attack at the CH_2 end of the olefin which is in accordance with resonance theory. However, kinetic analysis of many such reactions showed that the rate of addition to CH_2 is in fact slower than the rate of addition to CHF. It follows that it is not resonance stabilisation of one adduct radical which determines the outcome of these reactions. It seemed instead that the fluorine substituent inhibits attack at its end of vinyl fluoride.

In more recent work, Giese has studied the importance of substituent effects and has shown that these effects can be described by FMO theory.[17] The SOMO of the radical interacts with the LUMO or the HOMO of the carbon - carbon double bond. Radicals with a high lying SOMO interact preferentially with the LUMO. Therefore, electron withdrawing groups on the alkene, which lower the LUMO energy increase the rate of radical addition by reducing the SOMO - LUMO difference. It has been shown, for example, that cyclohexyl radicals react 8,500 times faster with acrolein than with 1-hexene.[18] Likewise, increasing the SOMO energy also increases the rate of reaction. Thus t-butyl radical reacts faster with a given alkene than primary or secondary radicals do in spite of the fact that the bond formed in the former case is weaker. For radicals with electron withdrawing substituents the SOMO - HOMO interaction dominates and electron donating substituents on the alkenes increase the rate of the reaction. Thus the malonyl radical reacts 23 times faster with enamine than with acrylester.[19]

Subsequently, Fischer has shown that the rate of reaction and the activation energy for addition of t-butyl radicals to substituted alkenes depends approximately linearly on the electron affinity of the olefin.[20]

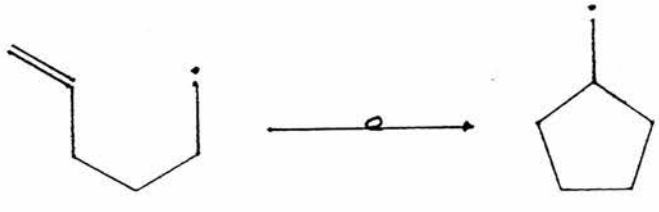
From these results we have a picture of a "complex interplay of steric, polar and bond strength terms"[10] governing the orientation of addition of radicals to double bonds, rather than the simple qualitative thermodynamic criteria which had been inferred from early experimental data.

This conclusion is particularly inescapable for more complex systems e.g. those involving intramolecular reactions. As will be discussed, thermodynamic criteria often fail quite dramatically to predict the outcome of these addition reactions.

The 5-hexenyl Cyclisation.

The 5-hexenyl radical cyclisation is probably the most studied and the most utilised intramolecular radical reaction in the literature. Its supremacy stems from the fact that it is a very fast reaction, which makes it useful as a synthetic and a kinetic tool, and also from its near complete rejection of thermodynamics as a rationale for its behaviour. The latter property has made it a favoured object of inquiry into the "complex interplay" of factors which govern radical addition to olefins.

It has been well and repeatedly established that the 5-hexenyl radical cyclises by intramolecular addition with high regiospecificity to give the cyclopentylcarbinyl radical (**Scheme 7**).

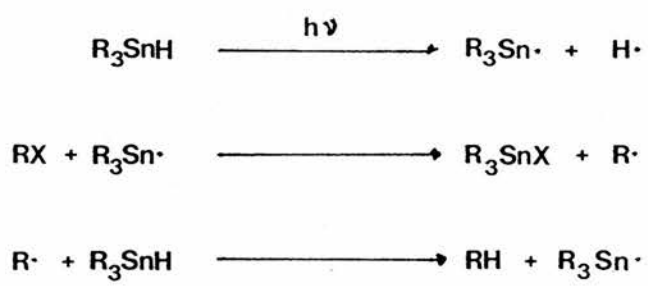


Scheme 7

This conclusion has been obtained from analysis of the products formed when the radical was generated from a variety of different precursors. In the early work the radical was generated

by thermolysis of di-6-heptenoylperoxide[21], by reaction of 6-mercapto-1-hexene with triethyl phosphite[22] and by Kolbe electrolysis of 6-heptenoic acid[23] In each of those cases at least 95% of the cyclised products observed were derived from the cyclopentylcarbinyl radical. In many of the experiments which have been done only 1,5 cyclisation products were observed.

Trialkyl- and triarylstannane reduction of alkyl halides has become a popular way of generating alkyl radicals and of determining the products of their reactions. Hydrogen abstraction from the tin hydride is sufficiently fast to sustain the chain reaction shown in **Scheme 8** but it is not so fast that it dominates any rearrangement of the alkyl radical which is formed.



Scheme 8

Also, if a rearrangement takes place, because the hydrogen transfer step is fast and quantitative, the relative proportions of the products derived from reduction of the rearranged and the unrearranged radicals reflect the relative rates of the rearrangement and the hydrogen abstraction reaction. Thus, if the rate of hydrogen abstraction is known, the rate of the rearrangement can be derived experimentally. Likewise, if more than one rearrangement is possible, the relative amounts of the

reduction products reflect the relative rates of the rearrangements.

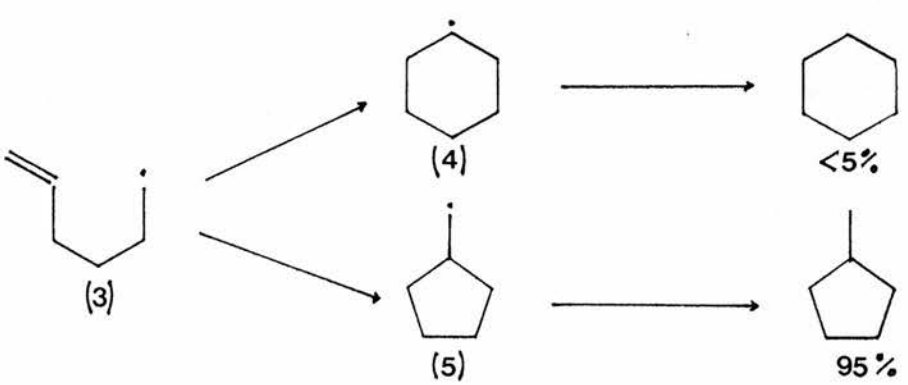
The rate constant for hydride abstraction from tributyltin hydride has been measured[24,25] and the more recent value of

$$\log k_H = 9.07 - 3.69/2.3RT$$

determined by Ingold et al.[25] is widely accepted and is used in this thesis.

A few other radical chain reducing agents, eg. (η^5 cyclopentadienyl) tricarbonylhydridovanadate[26] and tris(trimethylsilyl)silane[27] have been prepared and studied but none has yet been used as widely and become as cheaply available commercially as the tin hydrides have.

When 6-bromohexene was treated with tributyl tin hydride in an early study[28] the product identified was methylcyclopentane. However, more careful analysis of the products of the reaction[29] showed that cyclohexane was also a product albeit a very minor one (<5% at ordinary temperatures). It followed that 1,6 cyclisation of the 5-hexenyl radical is also an available pathway but that it is disfavoured relative to 1,5 cyclisation (**Scheme 9**)



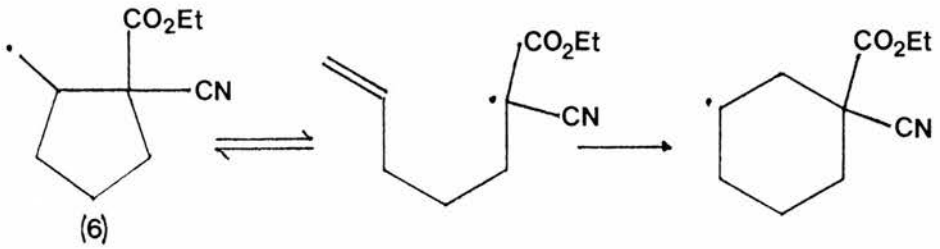
Scheme 9

Clearly, the value of $k_{1,5}$ is very much greater than $k_{1,6}$ and in fact the ratio $k_{1,6}/k_{1,5}$ has been determined to be 0.02 at 65°C.[30]

Further support for the reaction mechanism in **Scheme 9** has been obtained from experiments in which the cyclopentylcarbinyl and the cyclohexyl radicals were generated separately and which demonstrated the irreversibility of each mode of cyclisation under the tin hydride reaction conditions.[31-33] It was also shown that the radicals (3), (4) and (5) are discrete species and that a π-complex analogous to the intermediate in carbocationic addition to a double bond[34] was not involved.[31,33,35].

The temperature dependence of the populations of the 5-hexenyl and the cyclopentylcarbinyl radicals has also been observed directly by e.s.r.[36]

The intramolecular reaction of the 5-hexenyl radical leads to the formation of the thermodynamically less stable product. The accepted generalisation that primary radicals are less stable than secondary radicals indicates that the cyclohexyl radical should be more stable than the cyclopentylcarbinyl radical and this conclusion has been supported by quantitative thermochemical calculations.[21,37] There is also experimental evidence to support this. For example, cyclopentylcarbinyl radicals rearrange to cyclohexyl radicals in the gas phase at high temperatures (>298°C)[38] and substituted cyclopentylcarbinyl radicals e.g. (6) rearrange to cyclohexyl radicals in solution at ordinary temperatures (**Scheme 10**).[39]



Scheme 10

A number of explanations have been advanced for this remarkable regioselectivity. Capon and Rees[40] and Bischof[41] have drawn attention to the comparatively favourable entropy of activation which is associated with the 1,5 cyclisation. When the ring closure takes place the methylene groups incorporated into the ring lose some rotational freedom. The 1,5 cyclisation incorporates one fewer methylene into the ring than the 1,6 cyclisation and it is therefore entropically more favoured. While this contention is not disputed, it has been shown that the magnitude of this effect is not sufficient to account for the degree of regioselectivity observed.[29,42]

Steric arguments have also been invoked. It has been suggested that steric repulsion between the hydrogens on C2 and C6 disfavours the transition state for the 1,6 cyclisation (**Figure 1**).[43,44] This assertion has been supported by studies of substituted 5-hexenyl radicals.

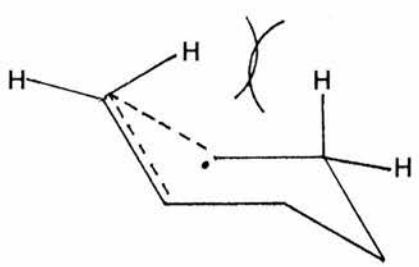
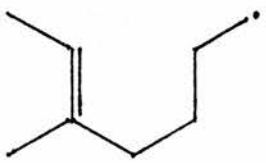
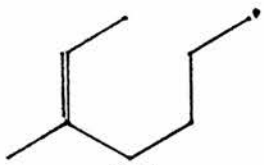


Figure 1

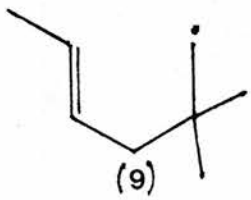
The E-alkenyl radical (7) cyclises in both the 1,5 and the 1,6 modes whereas the Z-isomer (8) gives only the 1,5 cyclisation product.[44] Complementarily, the 2,2-disubstituted radical (9) gives a reduced yield (<1 rel.%) of the 1,6 cyclisation product compared with the 5-hexenyl radical (ca. 5 rel.%).[45]



(7)



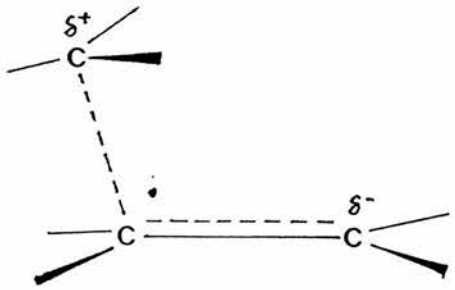
(8)



(9)

However, it has been determined that the contribution of such a steric effect to the transition state free energy of the 1,6 cyclisation is not sufficient to account for the experimental observations[45] and it has also been shown that alkenylaryl radicals which have no C2 proton also exhibit a strong preference for the 1,5 mode of cyclisation.[46,47]

The above arguments are all valid as far as they go but neither one nor all of them solve the problem. The hypothesis which has shed most light on the subject and which has evolved into the accepted theory of intramolecular radical additions was first mooted in 1968 by Beckwith et al.[48] It is based on a stereoelectronic approach. Theoretical studies have shown that the dominant mode of attack for a radical reacting with a double bond is overlap of the semi-occupied 2p orbital with one lobe of the π^* orbital of the double bond which gives rise to the transition state (10).[49]



(10)

It can be seen by inspection of models (**Figure 2**), and has also been shown by the less subjective methods of statistical calculation[50] and vector analysis[51], that this disposition of atoms can be accomodated with less distortion of the incipient ring for exo-cyclisation than for endo-cyclisation.

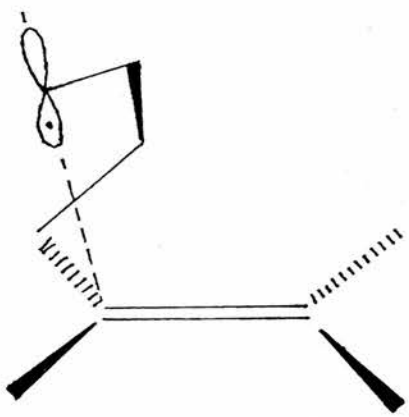


Figure 2

This stereoelectronic approach has culminated with theoretical studies in which variations of Allinger's MM2 force field[52] have been devised to predict the relative rates and the regio- and stereochemistry of ring closure of a number of alkenyl and related radicals.[53-55] These methods have enabled the calculation of transition state energies which are the crucial factors governing the course of these reactions.

1.3 Variations On A Theme.

The development of a satisfactory understanding of why ω-alkenyl radicals cyclise in the way that they do has allowed chemists to return down the mountain armed with the knowledge that "any structural feature which affects the ability of an unsaturated radical to accomodate the intimate transition complex for homolytic addition will necessarily also affect the rate and regioselectivity of ring closure".[42] We are thus able to predict the likely outcome of reactions on the basis of theoretical transition state energy or to use the experimentally determined course of a reaction to make statements about the geometry, and therefore the energy of the possible transition states.

It is not the case, however, that all recent work on this subject is rigorously physical in its outlook and approach. There has been a substantial groundswell of interest in intramolecular radical cyclisations during this decade which has carried the subject beyond the domain of the physical organic chemist and has established these reactions as very important synthetic tools.

The by now very large number of syntheses which involve radical cyclisations have been in part collected by Giese[56] in his book on radical synthesis and some of the earlier, less targeted examples have been reviewed by Beckwith and Ingold[3]. New examples continue to appear virtually every month. It will suffice here to discuss the types of radicals which have been looked at and no attempt will be made to review the subject comprehensively.

The Chain Length.

The rate constants for the ring closure of alkenyl radicals vary according to the entropy loss for ring formation which increases with chain length, the heat of formation of the ring which is greater for small, strained rings than for large ones and the statistical factor which is unfavourable for long chain lengths. The interplay of these factors results in rate constants at ordinary temperatures which are in the order hexenyl > butenyl > heptenyl > octenyl > pentenyl. Also, as the chain length increases and the rings which are formed become more flexible, the energy difference between the exo and endo transition states becomes less and so the reaction is less regiospecific. This generalisation can fail if some non-bonded interaction increases the energy of one transition state e.g. in the case of 7-octenyl radical.[42] The 5-hexenyl radical exo-cyclisation is an order of magnitude faster than its nearest rival along the series and it has the only chain length which has been employed widely in systhesis.

Recently, there has been some development of interest in certain types of longer chains. Porter has reported the cyclisation reactions of 14 - 20 membered polyenes which have a carbonyl function α to the double bond which is the initial point of radical attack. These cyclisations are synthetically useful.

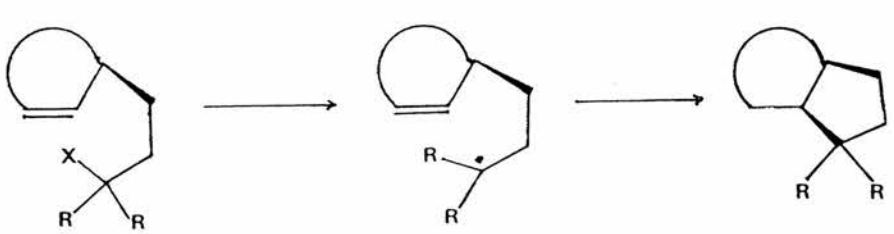
Substituents

As has been alluded to earlier, the introduction of substituents to the 5-hexenyl radical can alter the outcome of

its intramolecular reaction. Substituents, particularly on the double bond, disfavour one or other mode of cyclisation for steric reasons.[44] Gem dialkyl substituted radicals cyclise faster than their unsubstituted counterparts as there is a release of strain energy on formation of the ring.[45,57]

Substituents on the radical centre can have quite a profound effect on the course of the reaction. Electron withdrawing substituents stabilise the radical and therefore increase the rate of ring opening. Under certain conditions the cyclisation of such radicals is reversible and this favours the formation of the thermodynamically more stable six membered ring.[38] Conversely, a methyl substituent on the radical centre may interact with the fractional positive charge in the transition state (**10**), increasing its stability. It has been observed that a single methyl substituent on the radical centre does not reduce the rate of cyclisation to the extent which was expected for steric reasons[58] and it is thought that a favourable electronic interaction compensates for the unfavourable steric one.

If part of the 5-hexenyl chain is incorporated into a ring this can limit the stereochemical possibilities for the ring closure. There are now a number of reports in the literature of the synthesis and reaction of chiral radical precursors of the type shown in **Scheme 11**.



Scheme 11

The radical centre can only attack from the side of the ring above which it is positioned as it is only from this position that it can meet the stereoelectronic requirements of the transition state. This has proved useful in synthesising many chiral bicyclic molecules.[59]

If part of the chain is incorporated into a rigid ring the number of degrees of freedom of the chain is reduced and some conformations which the simple system can occupy become prohibitively strained. This may lead to one or both modes of cyclisation being disfavoured.

Heteroatoms in the Chain.

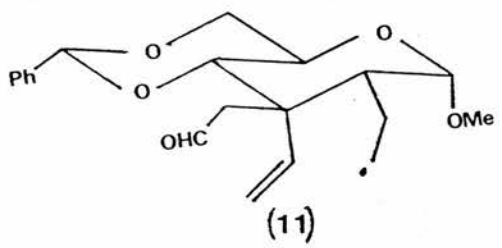
The introduction of a heteroatom into the 5-hexenyl chain alters the length of the chain and this may make the transition states for the cyclisations more or less easily attainable. For example, the substitution of an oxygen at the 3-position of 5-hexenyl reduces some bond lengths (C-O < C-C) and bond angles (C-O-C < C-C-C). Thus the minimum C1-C5 distance for an unstrained conformation of the heterosubstituted radical is less than it is for the alkenyl radical, but the C1-C6 distance is greater. 3-oxa-5-hexenyl radical therefore undergoes faster 1,5 cyclisation and slower 1,6 cyclisation than 5-hexenyl radical does.[26,60]

Variation Of The Unsaturated Function.

In principle any unsaturated function can participate in intramolecular cyclisation reactions and, to the author's

knowledge, alkynes, carbonyl groups and nitriles as well as alkenes have been used in this type of reaction. While kinetic data is scarce on the more exotic radicals, one can anticipate that the different bond lengths of these various functional groups have an effect on the energy of the transition state for cyclisation and that the polar character of some of them must also bear on the stability of the intimate transition state (**10**).

In this context, Fraser-Ried and Tsang[61] have reported an interesting radical (**11**) which has a choice of unsaturated groups with which to react; an olefin and a carbonyl. They found that cycloaddition to the carbonyl was the preferred pathway for (**11**) and a number of comparable radicals.



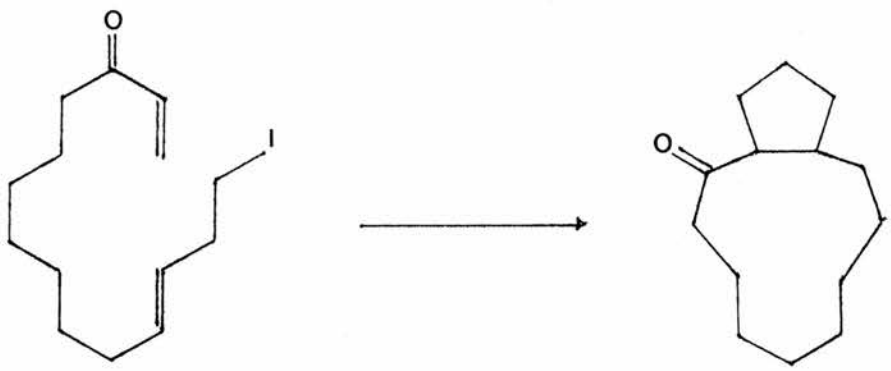
(11)

Variation Of The Radical Centre.

This is perhaps the most straightforward way of introducing a heteroatom into the product of a cyclisation reaction. Sulphur and oxygen centred radicals are prepared straightforwardly by the action of a peroxyl radical on an alcohol or a thiol. Recently, an efficient method of preparing nitrogen centred radicals has been reported.[62] Peroxyl radicals also can attack olefins and intramolecular alkenylperoxyl radical cyclisations have been reported[63] although they seem to be considerably slower processes than the 5-hexenyl radical cyclisation. Silyl and phosphoryl radical cyclisations have also been reported.[64,65]

More Convoluted Reaction Pathways.

The final class of 5-hexenyl type cyclisations which is receiving considerable attention involves multiple rearrangements. Molecules are designed with more than one reactive centre, a radical is generated from some functional group which then reacts with one unsaturated function to form an adduct radical which is placed so that it can react with another unsaturated group (Scheme 12).[66]



Scheme 12

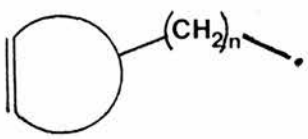
There are now a number of very elegant "serial" reactions which generate complex polyheterocyclic molecules from relatively simple precursors e.g. the total synthesis of capnellene, reported by Curran and Chen, the final stage of which is a double radical cyclisation.[67]

These reactions can involve additional complications. In the secondary cyclisation reactions the "5-hexenyl" unit is partially or wholly incorporated into the structure of one or more rings. The radical's ability to attain the transition state required for the second cyclisation is therefore intimately associated with the conformational behaviour of the rings it is part of.

1.4 Transannular Cyclisations.

It is the association between the properties of the 5-hexenyl radical and the properties of ring systems in which it can be contained which is the subject of the first part of this thesis.

The work described is a contribution to the relatively neglected field of transannular cycloaddition of a radical centre and a double bond which are located on opposite sides of a ring system (**12**).



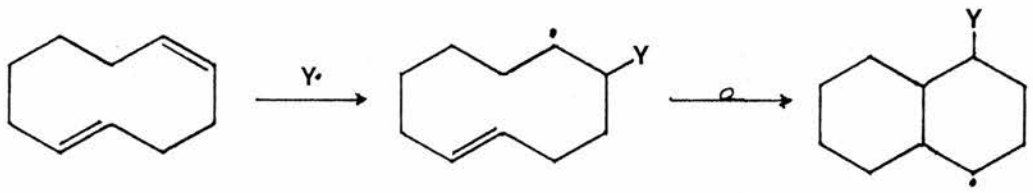
(**12**)

For a radical of this type (**12**) to cyclise it must, as always, be able to arrange the reactive centres in the correct disposition for the intimate transition state (**10**) without introducing substantial strain in the rest of the structure. Whether this is possible or not depends on the conformational freedom of the alkenyl unit. This in turn depends on the value of n and the conformational behaviour of the ring.

Cycloalkenylalkyl and cycloalkenyl radicals are more likely to cyclise like their open chain analogues if they have similar conformational freedom to the open chain or, within a more restricted conformational regime, they have access to a structure which can accomodate the stereoelectronic requirements for cyclisation.

Hence, for the cyclohexene ring which has access to a limited number of conformations, the 4-methyl radical (n=0) does not cyclise[68] whereas some longer chain (n>1) analogues do.[3] The cyclopentenylethyl radical, which consists of a conformationally almost rigid ring but which has n=1, also cyclises although yields of cyclised products are low, presumably because of the strain which is introduced on formation of the bicycloheptane ring.[69]

Transannular cyclisations for larger rings are known. Cycloalkenes with eight or more ring atoms show complex conformational behaviour which resembles open chain systems much more than the lower members of the series. 5-cyclodecyl radicals undergo transannular cyclisation to give decalyl radicals (**Scheme 13**).[70]

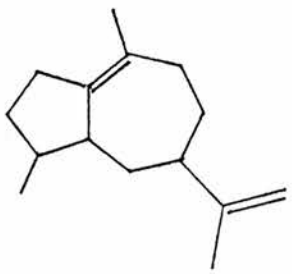


Scheme 13

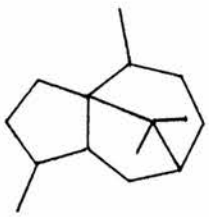
Cyclo-oct-4-enyloxyl radicals cyclise to give 9-oxabicyclo[4.2.1]nonanyl radicals.[71]

It seemed that the most interesting types of radicals to study with a view to discovering new cyclisation reactions were the more conformationally restricted ones which appeared to be capable of adopting a conformation which is suitable for a cyclisation rearrangement. Inspection of molecular models indicated that cyclohept-4-enylmethyl type radicals conformed to

this definition. There were also two early reports in the literature of similar radicals which had apparently afforded minor amounts of bicyclic products. Photolysis of α-bulnesene (13) with dimethylsulphide was reported to have led to a small amount of (14).[72] Also, the N-chloramines (15), n=1 or 2, gave low yields of the corresponding 8-azabicyclo-octane and 9-azabicyclononane in reactions which probably involved cycloalkenylaminyl radicals.[73]



(13)



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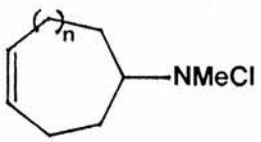


(15)

The cyclohept-4-enylmethyl radical was chosen for the starting point for this work. In parallel with the work which has been done on open chain systems, the effect of introducing different features to this basic system was subsequently investigated. The synthetic utility of such radicals is set in the context of the special stereoelectronic considerations which pertain to cyclic radicals. Some physical properties of other, related cyclic radicals have also been studied.

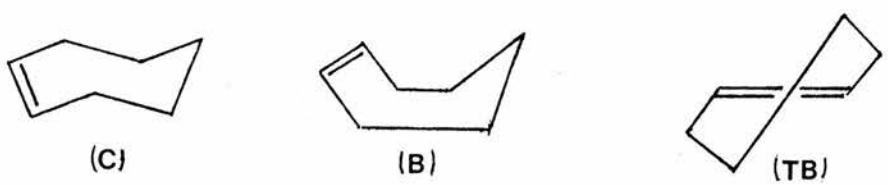
CHAPTER 2

CYCLOALKENYLMETHYL RADICALS

2.1 Cyclohept-4-enylmethyl radical.

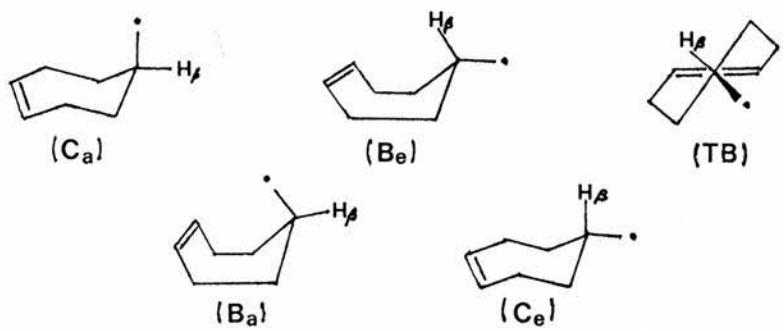
Structure and Reactivity.

The cycloheptene ring (1) is known[74,75] to have three important conformations: the chair (C), the boat (B) and the twist boat (TB).



(1)

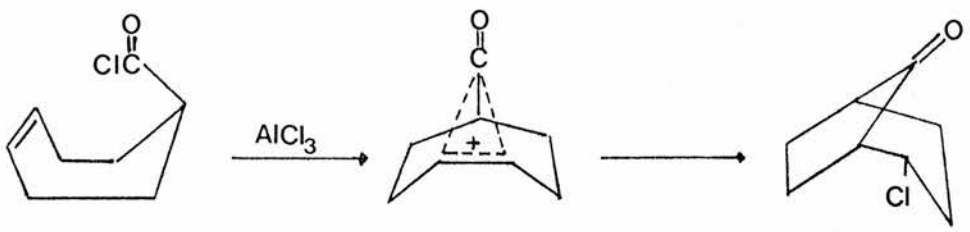
For cyclohept-4-enylmethyl radical (2), there are therefore five conformations: the chair axial (C_a), the boat equatorial (B_e), the twist boat (TB), the boat axial (B_a) and the chair equatorial (C_e).



(2)

Molecular models indicated that in the boat axial conformation, the radical centre could approach close to the double bond. Further, the radical centre and the double bond are contained within a hex-5-enyl unit within the larger molecule. These two observations indicated that the stereochemistry of the radical might allow a transannular cyclisation reaction to occur to give the bicyclo[3.2.1]octan-2-yl radical. However, such a reaction would only be favoured if the boat axial conformation of (2) was sufficiently highly populated at ordinary temperatures. Although the very limited amount of evidence in the literature of the occurence of similar reactions suggested that transannular cyclisation was a minor process[72,73], there were a number of indirect indications that it could be important in the case of (2).

Carbocationic transannular cyclisation reactions are known which involve the cycloheptene ring, presumably in the boat conformation (Scheme 1).[76]

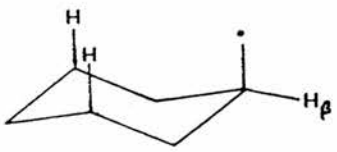


Scheme 1

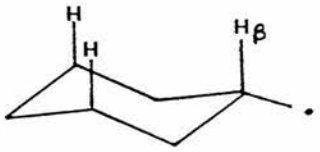
A low temperature proton n.m.r. study of 5-deuteriocycloheptene found that the signal for the 5-proton broadened and split into two peaks below 102K. These were assigned to the two chair conformations.[77] These workers calculated the barrier to chair inversion for cycloheptene to be

5.0 kcal mol^{-1}. Such a low barrier should allow rapid interconversion via the boats (**Figure** 3) at ambient temperature.

Further insight into this problem is obtained by looking at the e.s.r. of (2). Recently, e.s.r. has been used to probe both the ring conformations and the dynamic processes which occur in medium[78] and large[79] rings which are substituted by a CH_2 group. These studies rely on the assumption that the small planar radical group does not greatly perturb the adjacent ring. The e.s.r. spectra for radicals of this type are double triplets which in some cases also show small long range splittings. It has been shown that for a number of cycloalkylmethyl radicals the doublet splitting from the β-hydrogen is larger for axial or quasi-axial conformers than it is for equatorial or quasi-equatorial conformers. e.g. The β-h.f.s. for axial cyclohexylmethyl radical(3) is 41.2G at 140K whereas for the equatorial conformer (4) $a(H_\beta)$ = 30.4G at 140K.[80]



(3)



(4)

This effect has its origin in the different rotational energy functions of the C_β-C_α bonds in (3) and (4). In the axial radicals the barrier is much higher because of steric hindrance from the *syn*-axial hydrogens at C(3) and C(5). The axial radical therefore has a greater preference for the eclipsed conformation with respect to the C_β-H_β bond in which steric repulsion between the $C_\alpha H_2$ protons and the *syn*-axial protons is minimised (**Figure** 1.)

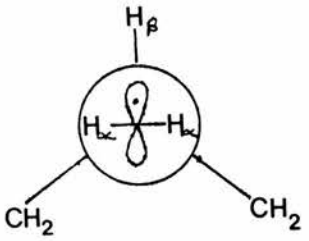
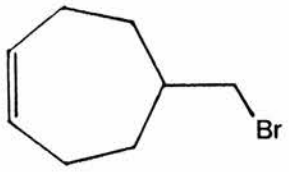


Figure 1

The radical was generated from the bromide (5), in t-butylbenzene or cyclopropane solution with hexamethylditin or triethylsilane and di-t-butylperoxide, by irradiation in the cavity of the e.s.r. spectrometer.



(5)

The spectrum obtained (**Figure 2**) consists of two double triplets. One double triplet, the major component, 79% at 270K, had $a(2H_\alpha)$ = 22.3G and $a(H_\beta)$ = 36.2G. The minor component, 21% at 270K had $a(2H_\alpha)$ = 22.3G and $a(H_\beta)$ = 45.6

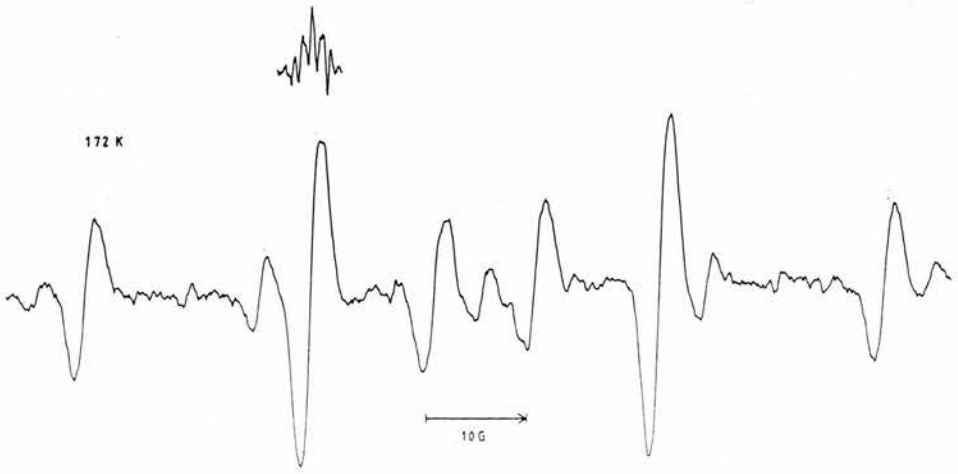


Figure 2: E.s.r. spectrum of cyclohept-4-enylmethyl radicals (2 at 172K in cyclopropane solvent.

The β-h.f.s. values suggest[79] that the major component is an equatorial radical and the minor component is an axial radical. Under high resolution conditions (**Figure** 2, inset) the major component shows additional fine structure which suggests that it is actually a mixture of two overlapping conformations. It is likely that the major component is a mixture of the C_e and B_e forms. The minor component could be either or both of the axial conformers. The e.s.r. parameters for radicals in the **T.B.** conformation are not known. The **T.B.** could contribute to either the major or the minor signal or it could be present at a concentration which is below the limit of detection.

The e.s.r. results confirm that conformations other than (2,C_e), the lowest energy form, are populated at ambient temperature. While the e.s.r. does not itself confirm the presence of both axial conformers, it follows from the presence of both equatorial conformers and at least one axial conformer that both B_a and B_e will be populated. The five possible conformations interconvert along the reaction pathway shown (**Figure** 3).

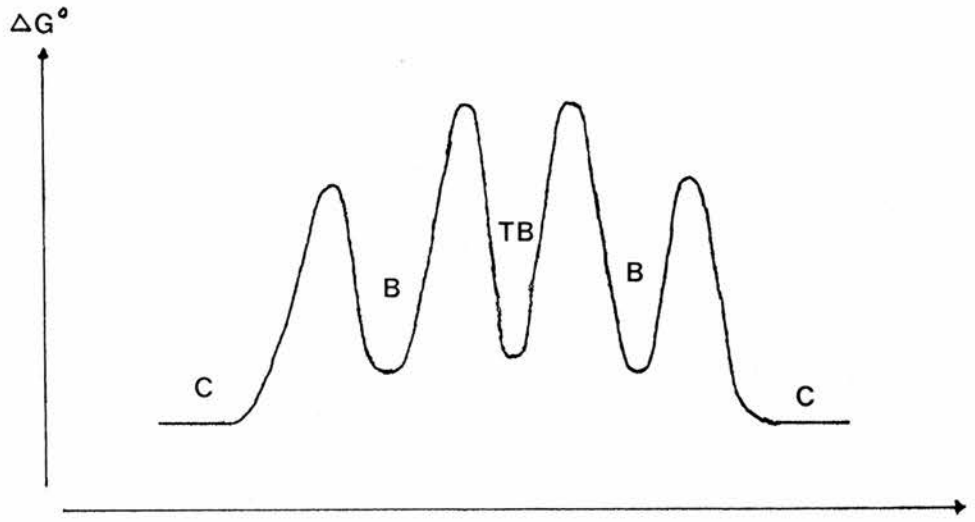


Figure 3: The reaction coordinate for cycloheptene inversion.

The equilibria between the conformations are fast[77], so the radical has access to the boat axial conformation which is apparently ideally placed for cyclisation.

As the temperature is increased, the spectrum of radical (2) (**Figure 2**) gradually weakens and at 340K is replaced by a new spectrum (**Figure 4**).

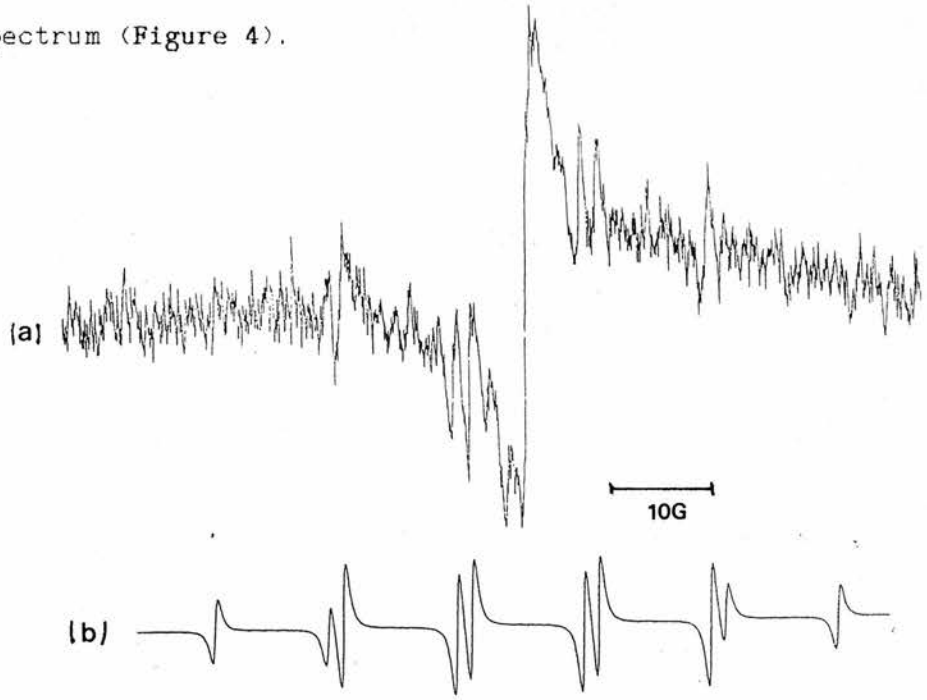


Figure 4: (a) E.s.r. spectrum attributed to (**6**) generated in t-butylbenzene at 340K; (b) Simulated spectrum for a(1H) 22.0G, a(2H) 25.0, a(1H) 50.0G.

This rather weak spectrum appears to show the presence of more than one radical. The major part of it analyses quite well for a(1H) = 22.0G, a(2H) = 25.0G and a(1H) = 50.0G and it can probably be attributed to the bicyclo[3.2.1]octan-2-yl radical (6).

(6)

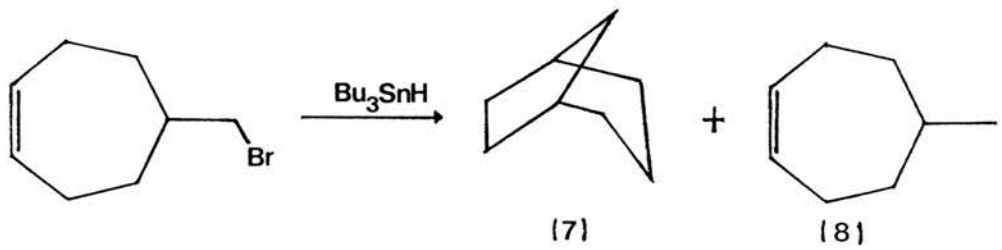
The value of 50.0G for the h.f.s. from the C(3) exo hydrogen seemed rather high in comparison with the comparable splitting in other bicyclic radicals which have been reported in the literature (**Table 1**). Such large h.f.s. values are known for very rigid molecules in which the radical SOMO almost perfectly eclipses a neighbouring C-H bond, e.g. the 2-adamantyl radical.[81] Models indicate that this is likely to be the situation for (6).

Table 1

Radical	h.f.s.	Reference
2-Norbornyl	H(3, *exo*) 35.1G	82
2-Bicyclo[2.2.2]octyl	H(3, *exo*) 37.0G	83
2-Bicyclo[2.2.2]oct-7-enyl	H(3, *exo*) 36.6G	84
2-Adamantyl	H(1)=H(3) 50.0G	81

Synthesis of Bicyclo[3.2.1]octane.

The bromide (5) was reduced by irradiating it in the presence of tributyltin hydride in oxygen-free conditions. G.l.c. analysis showed that there were two products which were separated by preparative g.l.c. and identified as bicyclo[3.2.1]octane (7) and 5-methylcycloheptene (8) (**Scheme 2**).



Scheme 2

The proportion of (7) was found to vary strongly with temperature and tributyltin hydride concentration. The relative proportions of (7) and (8) under a variety of reaction conditions are given in **Table 2**. With equimolar amounts of the two reagents a yield of 75% of (7) was obtained by slow addition of the hydride at 165°C. Slow addition minimises the rate of reduction of the radicals formed in the halogen abstraction stage of the reaction.

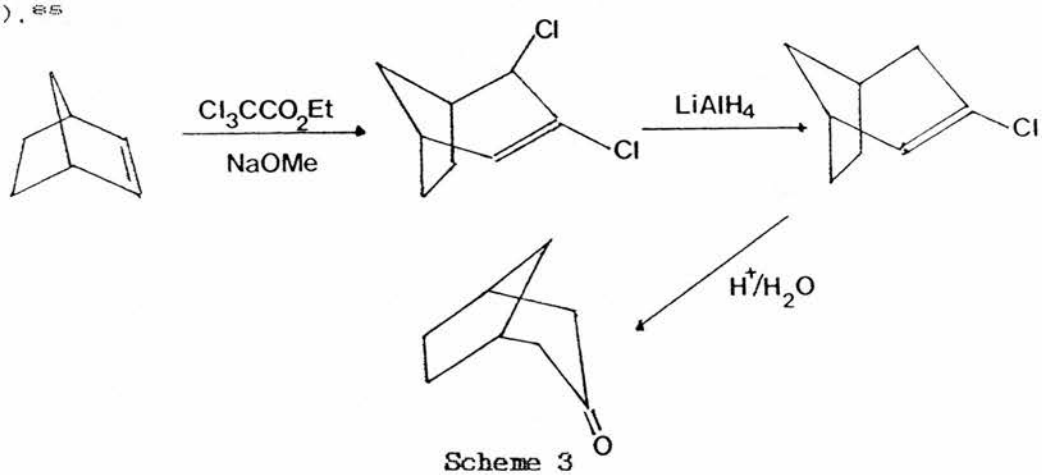
Table 2

Reductions of (5)[a] with Bu_3SnH in t-BuPh.

Temp/K	$[Bu_3SnH]$/mol dm^{-3}	(7)/rel.%	(8)/rel.%	(k_c/k_H)[g]/mol dm^{-3}
273	0.576	5	95	0.026
294	0.576	7	93	0.040
316[b]	0.646	14	86	0.086
321[c]	0.244	34	66	0.087
323[d]	0.814	12	88	0.094
328	0.576	13	87	0.080
337[e]	0.457	20	80	0.091
346	0.576	17	83	0.106
346	0.576	18	82	0.114
367	0.576	22	78	0.146
386	0.576	33	67	0.247
417[f]	0.576	38	62	0.315
450[f]	0.576	51	49	0.533

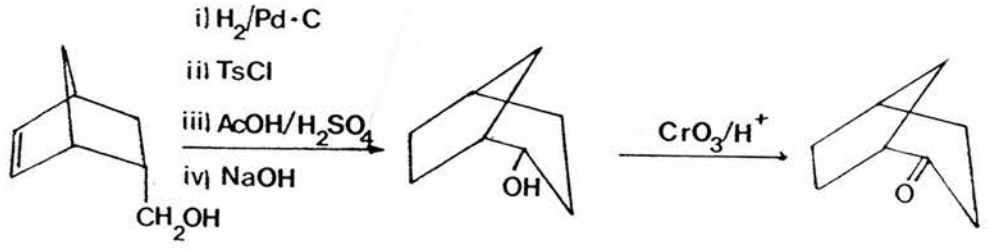
[a][(5)]=0.129M, [b][(5)]=0.243M, [c][(5)]=0.275M, [d][(5)]=0.229M, [e][(5)]=0.258M, [f]in hexadecane as solvent, [g]the ratio of the cyclisation rate constant to the rate constant for hydrogen abstraction from Bu_3SnH.

In addition to the route described earlier (**Scheme 1**), bicyclo[3.2.1]octane derivatives have previously been synthesised by ring expansion of a suitable norbornene derivative, e.g. treatment of norbornene with dichlorocarbene and subsequent reduction and hydrolysis gives bicyclo[3.2.1]octan-3-one (**Scheme 3**).[85]



Scheme 3

5-Hydroxymethylnorbornene has been converted into bicyclo[3.2.1]octan-2-one (**Scheme 4**).[86]



Scheme 4

The ready availability of the bromide (5) from the corresponding carboxylic acid[87], which in turn is straightforwardly synthesised from the dimethylamine enamine of cyclopentanone[88], makes the route in **Scheme 2** an attractive alternative.

Kinetics of the Cyclisation.

The rate of the cyclisation was determined by quantitative g.l.c. analysis of the products of tin hydride reductions of the

bromide (5). Reductions were carried out over the temperature range 0 - 170°C in t-butylbenzene or hexadecane as solvent. The product analysis is given in **Table** 2. The ratio of the cyclisation rate constant, k_c, to the rate constant for hydrogen abstraction from Bu_3SnH by radicals (2), k_H was evaluated at each temperature using the method of Beckwith.[29,69] The k_H value of Ingold and co-workers[25] was used to derive the absolute rate constant at each temperature (**Table** 3). The Arrhenius equation for the cyclisation was derived from a plot of log k_c against 1000/T (**Figure** 5).

Table 3

Temp/K	273	294	328	346	346	367	386	417	450
$k_c/10^5 s^{-1}$	0.3	0.8	3.3	5.8	6.3	10.8	23.6	43.5	94.8

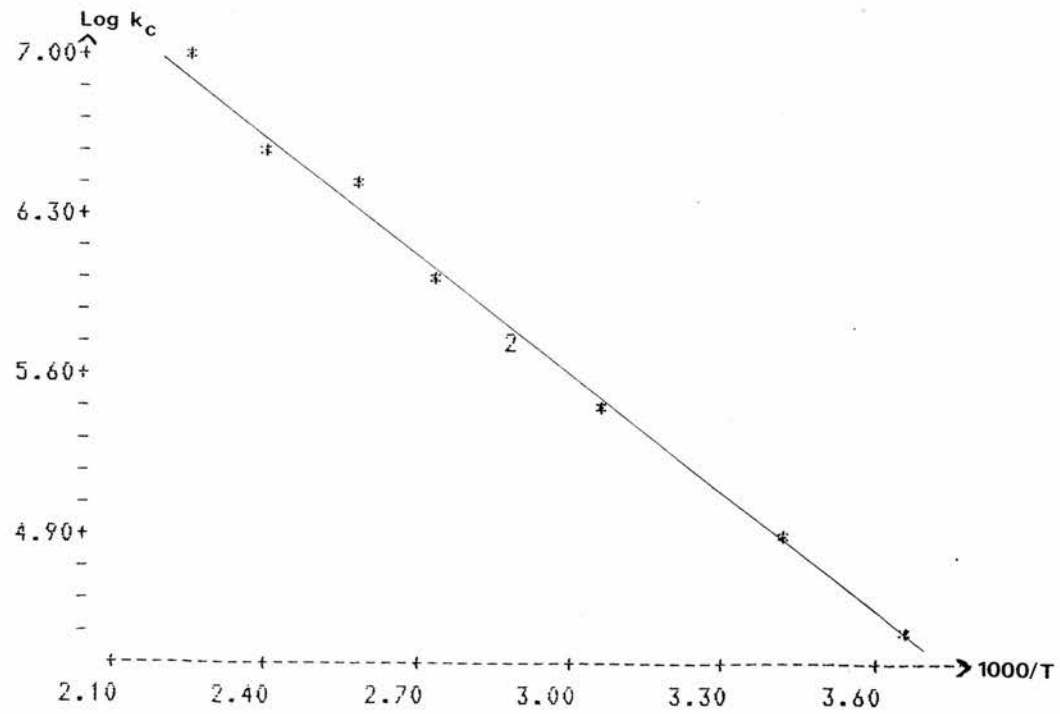


Figure 5: Arrhenius plot for the cyclisation of radical (2).

The Arrhenius equation thus derived is:

$$\log k_c = 10.9 - 1\ 720/T$$

which gives:

$$\text{Log } (A/s^{-1}) = 10.9 \pm 1;\ E_a = 7.9 \pm 0.3 \text{ kcal mol}^{-1}$$

$$\text{and } k_{c(298)} = 1.0 \times 10^{5\pm1}\ s^{-1}.$$

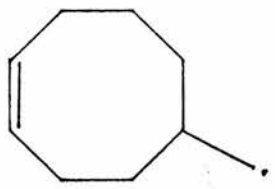
The corresponding values for the free 5-hexenyl radical are 10.4, 6.8 kcal mol^{-1} and 2.5×10^5 s^{-1} respectively.[25] The higher A factor for the cycloheptenylmethyl cyclisation is understandable in terms of the reduction in the number of degrees of freedom of the hex-5-enyl unit when contained within the cycloheptenylmethyl system. The radical centre can occupy relatively few points in space relative to the double bond and so, statistically, the number of "collisions" must be greater. It should be noted that although this interpretation of the difference in the A factors for (2) and 5-hexenyl is what one might have expected, the magnitude of the difference is not very significant. Both numbers are subject to an experimental error which is probably greater than the difference between them. Any such increment is overcompensated for in the rate equation by a comparatively high activation energy for the rearrangement of (2). This may be associated with the fact that the radical cannot cyclise in its lowest energy conformations, the chairs. In order to attain a conformation from which it can cyclise, it must cross an energy barrier of ca. 5 kcal mol^{-1}, a substantially higher barrier than is involved in the rotational motions of the open chain analogue. More importantly, the 1,5 cyclisation of (2) is also a 1,6 cyclisation, when viewed from the other side of the ring, the transition state for cyclisation is therefore likely to be more strained than it is for 5-hexenyl.

2.2 Cyclo-oct-4-enylmethyl Radicals

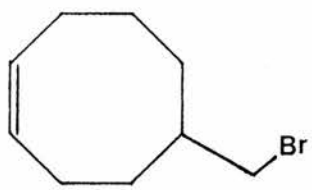
Structure and Reactivity

Both theoretical and experimental studies have indicated that *cis*-cyclo-octene does not have a single favoured conformation.[90,91] It exists as a rapidly interconverting mixture of conformers which are energetically similar and which are separated by very low energy barriers associated with various pseudorotational motions.

This conclusion was supported by an e.s.r. study of cyclo-oct-4-enylmethyl radical (**9**). The radical was generated from the corresponding bromide (**10**) by photolysis with hexamethylditin or triethylsilane and di-t-butylperoxide in solution in t-butylbenzene or cyclopropane in the cavity of the e.s.r. spectrometer. Over the temperature range 150 - 240K, only one broad double triplet was observed with $a(2H_{\alpha}) = 22.0G$ and $a(H_{\beta}) = 38.7G$ at 150K(**Figure 6**). No fine structure could be resolved even under high resolution conditions.



(9)



(10)

The observation of an averaged spectrum implies that the contributing conformers are rapidly interconverting, even at low temperatures and that therefore the barriers to inversion between them are very low.

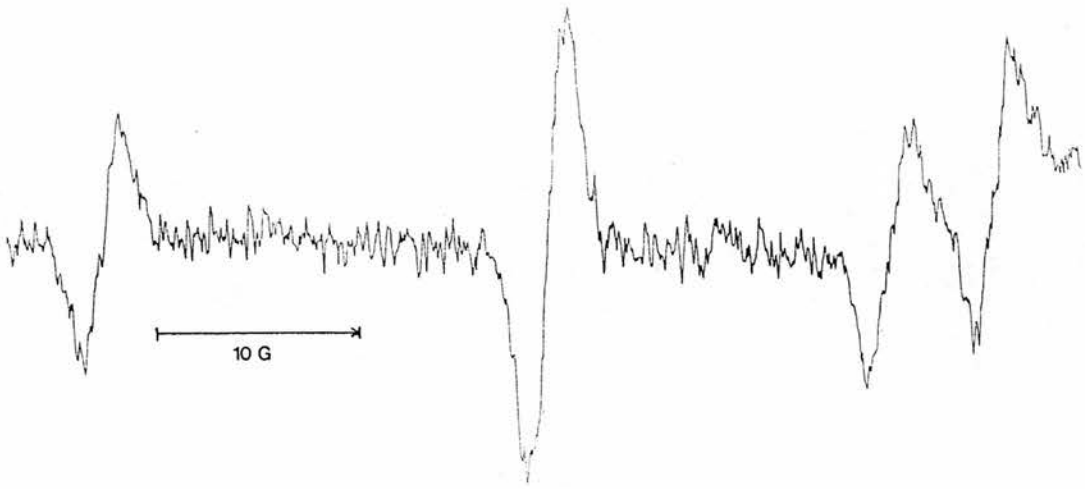


Figure 6: The low field half of the e.s.r. spectrum of (9) generated from (10) in cyclopropane at 150K.

The β-h.f.s. of the radical decreases with increasing temperature indicating that the radical has a preference for the eclipsed conformation with respect to the C_β-H_β bond (**Figure 7**).[80]

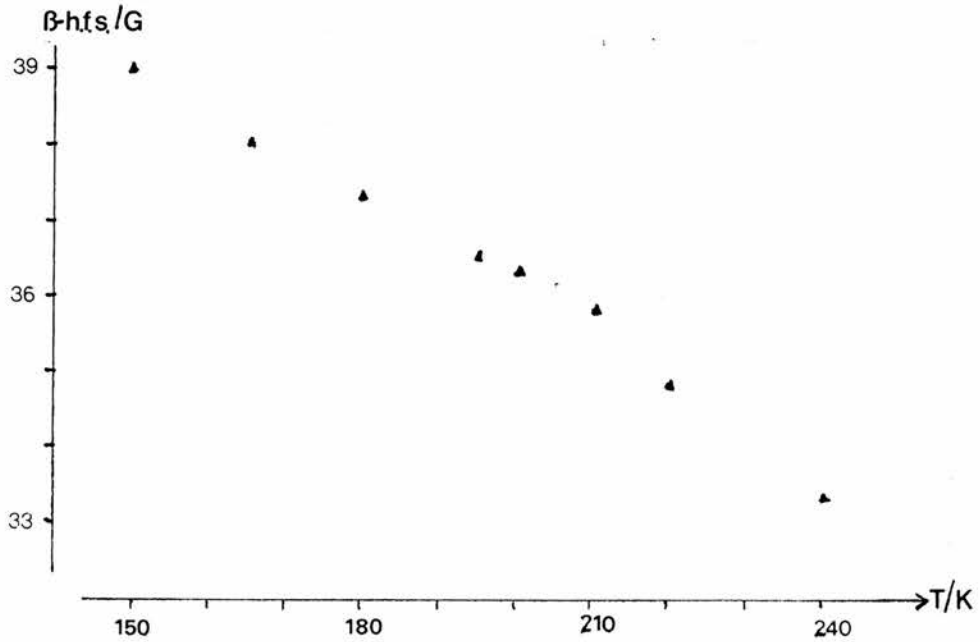
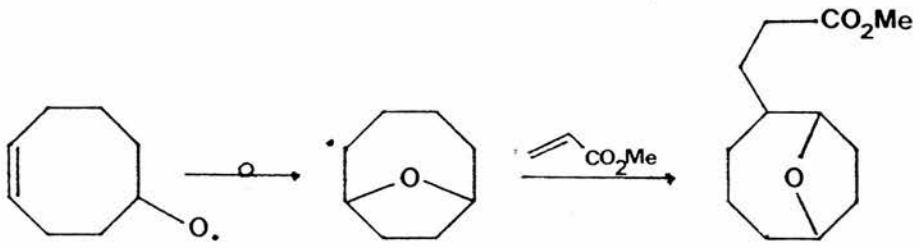


Figure 7: Variation of the β-h.f.s. of (9) with temperature.

At temperatures above 240K, the e.s.r. spectrum of (**9**) weakened and disappeared. It was not possible to observe bicyclononanyl radicals at higher temperatures.

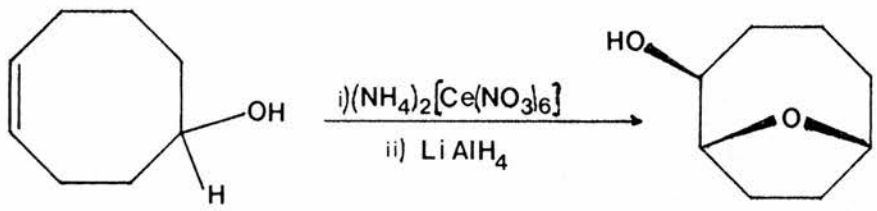
It follows that *cis*-cyclo-octene is more like an open chain hydrocarbon than cycloheptene. Transannular cyclisation of the cyclo-oct-4-enylmethyl radical (**9**), in which the radical centre and the double bond are contained in a 5-hexenyl unit within the molecule was expected to be a favoured process. It was anticipated that the activation energy for the rearrangement would be lower than in the case of cyclohept-4-enylmethyl radical because of the lower barrier to the ring attaining a suitable conformation and because the transition state for the 1,5 cyclisation of (**9**) would not incorporate a strained six-membered ring.

There was also precedent in the literature for the transannular cyclisation of related radicals. The cyclo-oct-4-enyloxyl radical cyclises to give 9-oxabicyclo[4.2.1]nonan-2-yl radicals (**Scheme 5**).[71]



Scheme 5

Recently, another reaction was reported[92] which probably involves transannular cyclisation of cyclo-oct-4-enyloxyl radicals (**Scheme 6**).

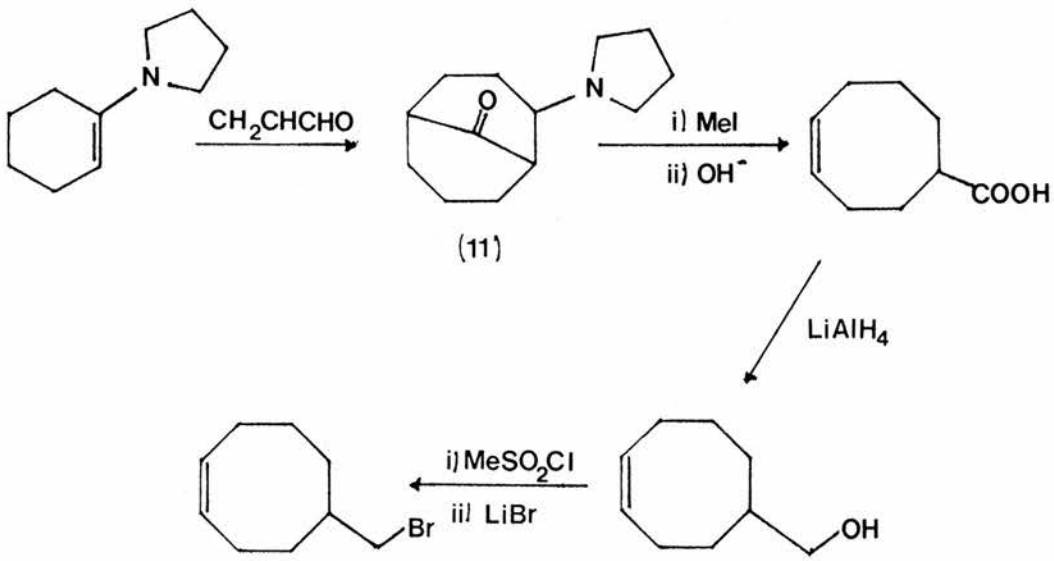


Scheme 6

Cyclo-oct-4-enylmethyl radical is non - symmetrical and therefore both a 1,5 and a 1,6 radical cyclisation are possible. It was hoped that this study would allow a comparison between the relative rates of these competing processes in this system compared with the open chain 5-hexenyl radical.

Synthesis of Bicyclo[4.2.1]nonane.

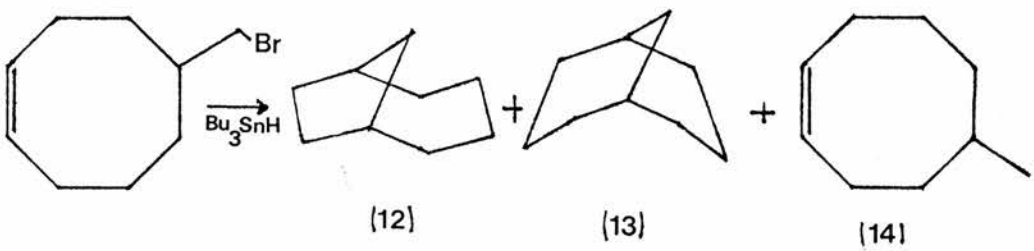
Cyclo-oct-4-enylmethyl bromide (**10**) was synthesised from cyclo-oct-4-ene carboxylic acid which in turn was prepared by the method of Stork and Landesman[99] according to **Scheme 7**.



Scheme 7

The overall yield of the bromide (**10**) was rather low, this was mainly due to the poor yield of the condensation product (**11**). Recently, a new variation on the Stork-Landesman synthesis of cyclohept-4-ene carboxylic acid was published in which the dimethylamine, rather than the pyrrolidine, enamine of cyclopentanone is converted to the acid using the Stork-Landesman reagents in a one pot procedure in acetonitrile solution.[88] If this synthesis can be adapted to the production of cyclo-oct-4-ene carboxylic acid, the bromide (**10**) can be prepared in a way which gives a more acceptable overall yield.

The bromide (**10**) was reduced with tributyltin hydride at 135°C. G.l.c. analysis of the product mixture showed that there were three components. The components were identified as bicyclo[4.2.1]nonane (**12**), bicyclo[3.3.1]nonane (**13**) and 5-methylcyclo-octene (**14**) (**Scheme 8**). The relative proportion of cyclised products was found to vary strongly with temperature and tributyltin hydride concentration. Yields of up to 70% of (**12**) could be obtained (**Table 4**).



Scheme 8

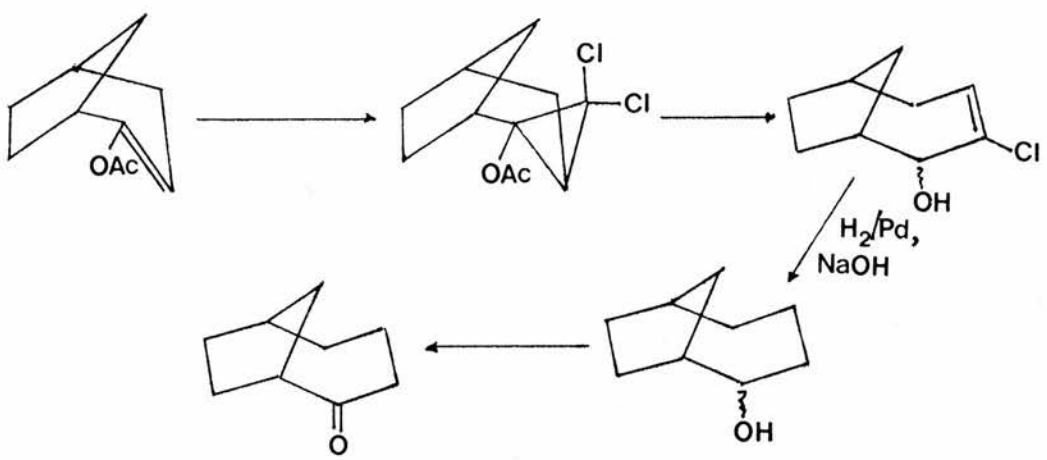
Table 4

Reduction of (10)[a] with Bu_3SnH in hexadecane.

Temp/ K	$[Bu_3SnH]$/ mol dm^{-3}	(12)/ rel.%	(13)/ rel.%	(14)/ rel.%	$(k_c(12)/k_H)$/ mol dm^{-3}	$(k_c(13)/k_H)$/ mol dm^{-3}
280[b]	0.255	20	3	77	0.031	0.005
314	0.255	50	7	43	0.130	0.030
368	0.255	64	9	27	0.249	0.064
371[c]	0.668	38	6	56	0.289	0.050
375[d]	0.472	51	7	42		0.051
377[e]	0.842	31	5	64	0.298	0.048
409	0.255	58	9	33	0.242	0.056
425	0.255	72	11	17	0.326	0.129
463	0.255	70	13	17	0.431	0.156

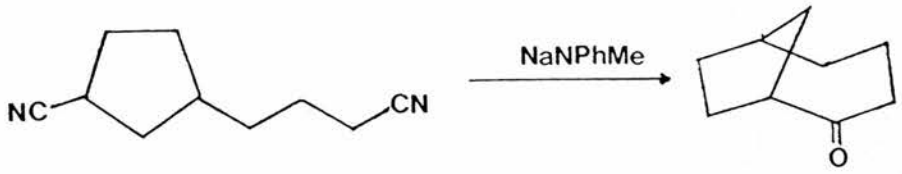
[a][(10)]=0.255M, [b]in cyclopentane as solvent, [c][(10)]=0.225M, [d][(10)]=0.239M, [e][(10)]=0.212M.

Other routes which have been reported to the bicyclo[4.2.1]nonane system are comparatively tedious. Treatment of bicyclo[3.2.1]octene derivatives with dichlorocarbene and subsequent ring expansion, reduction and hydrolysis gives the 2-ketone (Scheme 9).[94]

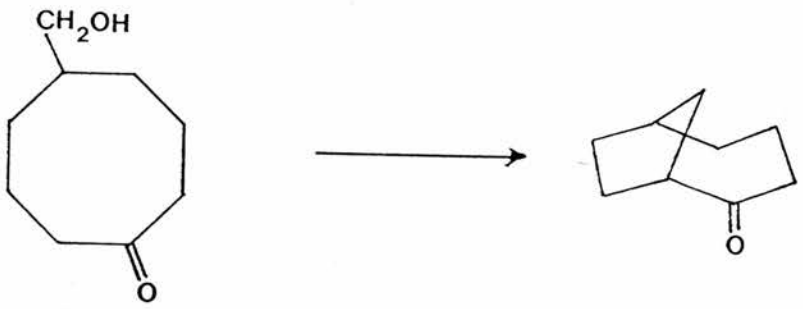


Scheme 9

Cyclisation of *cis*-4-(3-cyanocyclopentyl)-butyronitrile (**Scheme 10**)[95] and of 5-(tosyloxymethyl)cyclo-octanone (**Scheme 11**)[96] have been reported.



Scheme 10



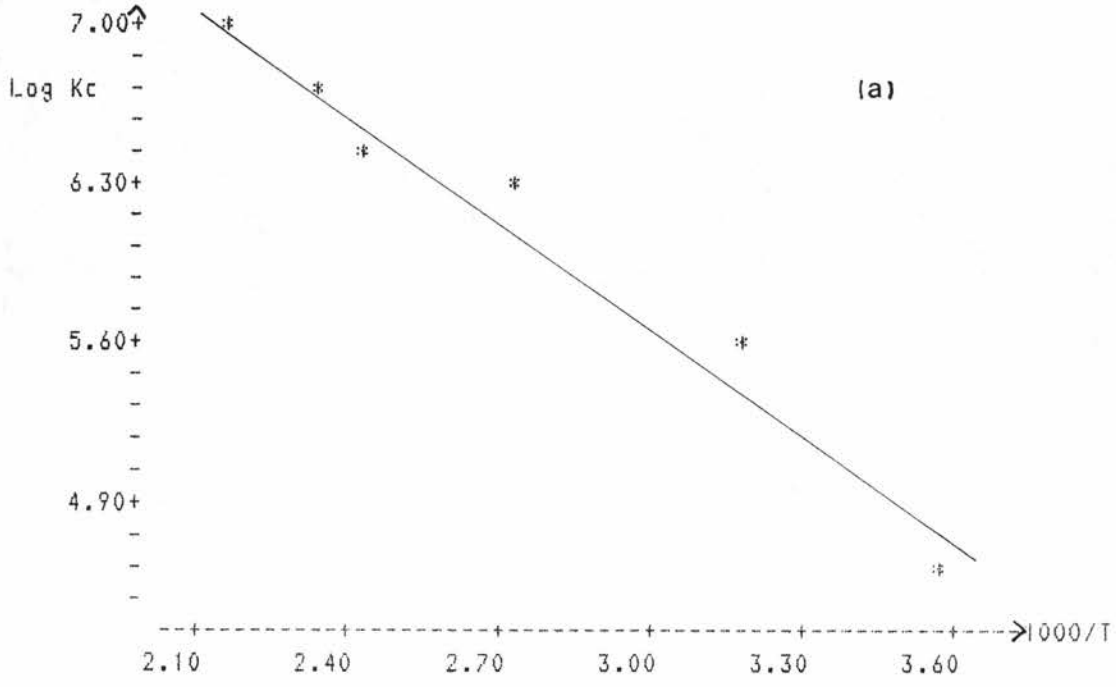
Scheme 11

Kinetics of the cyclisations.

The values of k_c for each case in **Table 4** were determined in the manner described before[25,29,69] and are listed in **Table 5**. The rate equations for both the 1,5 and 1,6 cyclisations of radical (**9**) were derived from a plot of log k_c against 1000/T (**Figure 8**).

Table 5

Temp/K	280	314	368	409	425	463
k_c(**12**)/$10^5 s^{-1}$	0.5	4.1	18.7	30.2	48.3	91.4
k_c(**13**)/$10^5 s^{-1}$	0.08	0.9	4.8	6.9	19.1	33.0



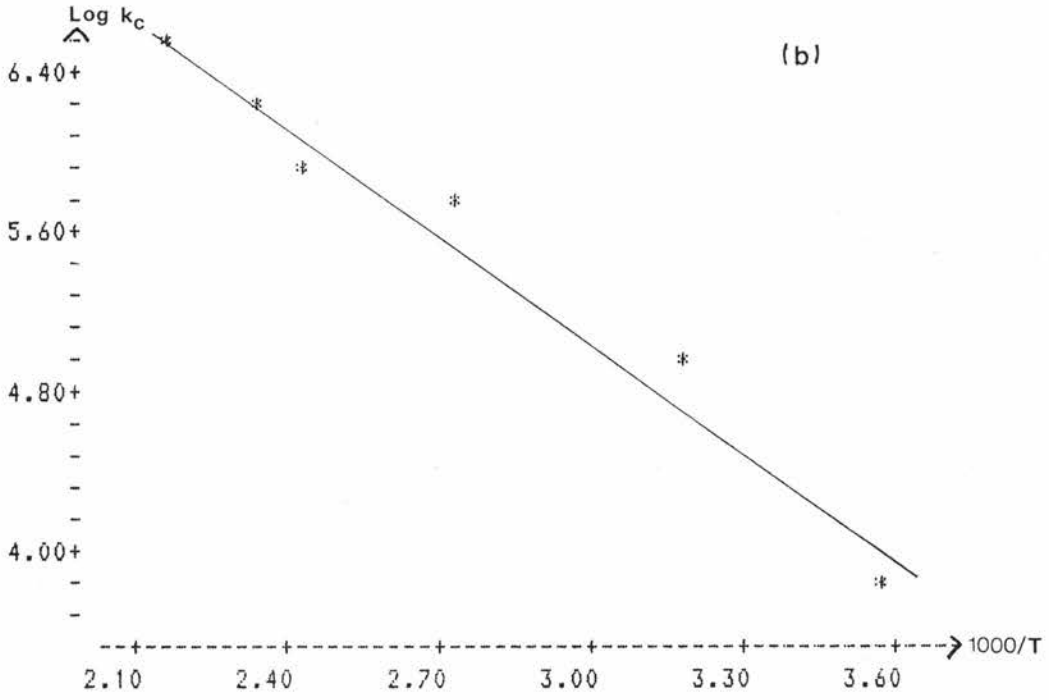


Figure 8: Arrhenius plots for the cyclisation of (9) (a) to give (12) and (b) to give (13).

From **Figure** 8(a) the Arrhenius equation for the 1,5 cyclisation of (9) is

$$\text{Log } k_c = 10.3 - 1\,530/T$$

which gives Log A = 10.3 ± 1 s^{-1}, E_a = 7.0 ± 1.0 kcal mol^{-1} and $k_{c(298)} = 1.5 \times 10^{5\pm1}\ s^{-1}$

From **Figure** 8(b) the Arrhenius equation for the 1,6 cyclisation of (9) is

$$\text{Log } k_c = 10.3 - 1\,740/T$$

which gives Log A = 10.3 ± 1 s^{-1}, E_a = 8.0 ± 1.3 kcal mol^{-1} and $k_{c(298)} = 2.9 \times 10^{4\pm1}\ s^{-1}$

The frequency factors for both these cyclisations are the same and are essentially equal to the value obtained for the 5-hexenyl radical cyclisation.[25] This was expected and reflects the conformational freedom of the cyclo-octene ring. The activation energy for the 1,5 cyclisation of (9) is close to that for the 1,5 5-hexenyl cyclisation. E_a for the 1,6 cyclisation is 1 kcal mol^{-1} higher. This difference was expected from the data on the 5-hexenyl radical but the magnitude of the difference was less than was anticipated. The ratio $k_{1,6(298)}/k_{1,5(298)}$ for (9) was 0.19. This compares with a ratio of 0.02 for the 5-hexenyl cyclisations.[30] It follows that either the transition state for the 1,6 cyclisation is stabilised, or that the transition state for the 1,5 cyclisation is destabilised by factors which operate in (9) but which do not operate in 5-hexenyl.

The 1,6 cyclisation forms the less strained of the two bicyclononyl rings. Bicyclo[3.3.1]nonane can be thought of as a fragment of the better known adamantane which consists of three

fused undistorted C6 chairs and has low strain energy. The calculated steric energy and the calculated and theoretical heats of formation of the two molecules have been found to be essentially the same.[97] This may have a bearing on the relative energies of the transition states.

More specifically, models indicate that in the case of the 1,6 cyclisation, the torsional angle between the hydrogen on C1 and the *exo* hydrogen on C8 in cyclo-oct-4-enylmethyl radical as the radical centre approaches the double bond is close to the ideal of 60° whereas in the same situation for the 1,5 cyclisation the same angle is very much less and appears to be almost zero when the atoms are disposed as they are expected to be in the transition state (**Figure 9**). This effect would be expected to destabilise the 1,5 transition state relative to the 1,6 transition state.

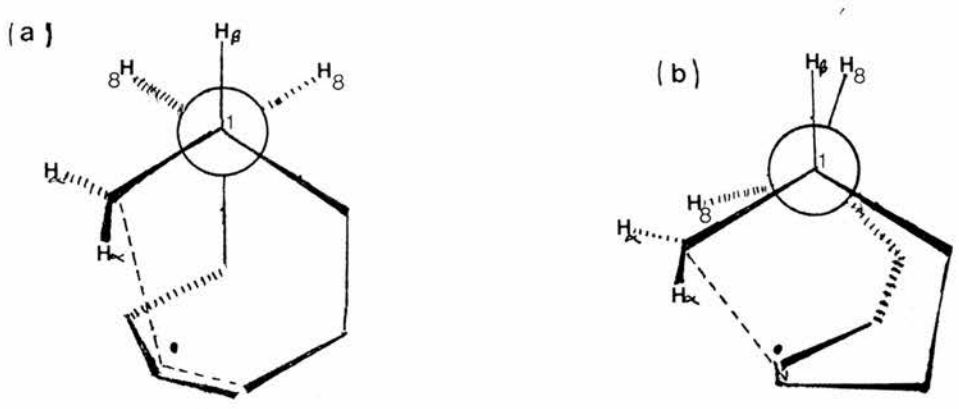
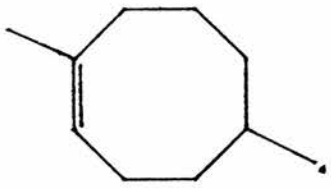


Figure 9: A schematic diagram of (a) the transition state for the 1,6 cyclisation of (9) and (b) for the 1,5 cyclisation of (9).

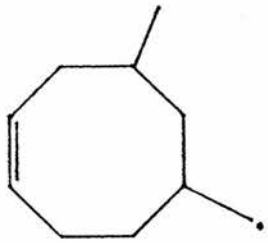
2.3 Attempted Preparation of Substituted Cyclo-oct-4-enylmethyl Radical Precursors.

It was considered that an investigation of the rearrangements of simple derivatives of the cyclo-oct-4-enylmethyl radical would be interesting. It was anticipated that the introduction of substituent methyl groups on the ring would have some interesting effects on the rates and relative rates of the cyclisations previously described. Such effects have been observed for the 5-hexenyl radical.[3]

It was therefore proposed to study the 5- and 7-methyl substituted radicals (15) and (16). The same synthetic approach as before was used to make the corresponding bromide precursors.

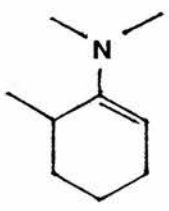


(15)

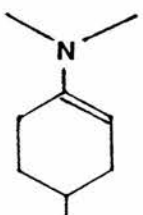


(16)

It was envisaged that it would be possible to make the required carboxylic acids from the appropriate substituted enamine of cyclohexanone using the newly reported Newcomb[88] variation of the Stork-Landesman procedure[93] using the dimethylamine enamines of the appropriate substituted cyclohexanones (17) and (18).



(17)



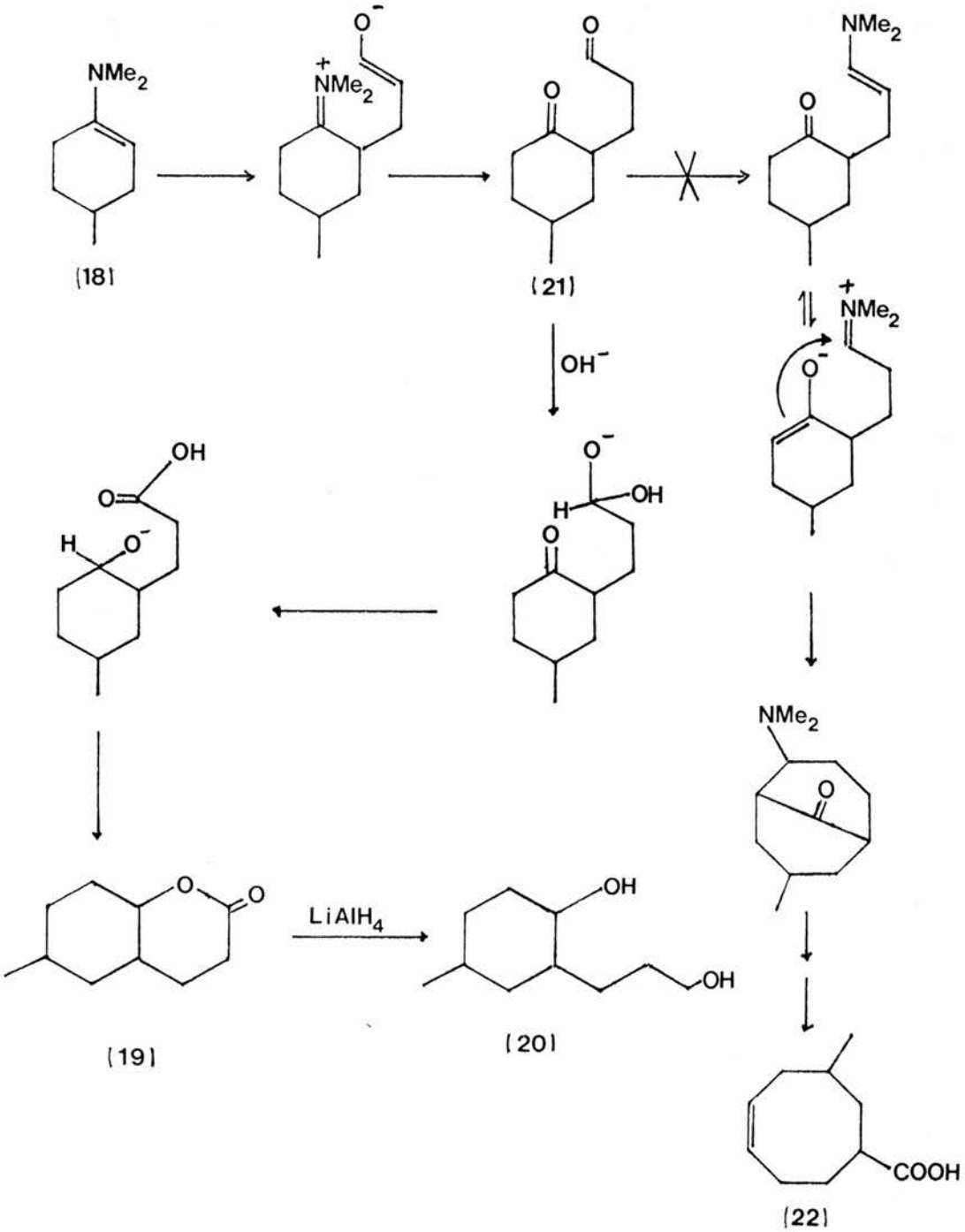
(18)

Attempts to synthesise the dimethylamine enamine of 2-methylcyclohexanone (17) proved unsuccessful. It was not possible to heat the reaction mixture greatly in a conventional Dean-Stark apparatus as refluxing dimethylamine acted as a coolant. After prolonged (18 months) reaction at ambient temperature no enamine was formed. While the pyrrolidine enamine of 2-methylcyclohexanone was known to be accessible[93] it was considered that the product formed in the reaction of this enamine with acrolein would probably be harder to isolate than (11); the crude product was expected to be more viscous, higher boiling and more vulnerable to decomposition during distillation. That was the combination of factors which led to the low yield of (11). The synthesis using the pyrrolidine enamine was therefore not attempted.

When the dimethylamine enamine of 4-methylcyclohexanone (18) was treated with acrolein and the product subsequently treated with methyl iodide followed by base and the final product mixture worked up in a manner suitable for the isolation of an acid the sole isolated product was identified as *trans*-6-methyloctahydrocoumarin (19) The *trans*- ring junction was confirmed by the δ value of 3-H compared with other *trans*-octahydrocoumarins.[97,98] Further confirmation of the identity of (18) was obtained by its reduction to the diol (20).

(19) is a novel product from the reaction of an enamine with an α,β unsaturated carbonyl compound and its formation was surprising. It is likely that enamine (18) condenses with acrolein via intermediate (21). Dicarbonyl compounds have been obtained from a number of similar reactions.[99,100] It appears

that the aldehyde enamine which is required for the next stage in the formation of acid (22) fails to form. The dicarbonyl compound (21) then undergoes a hydride transfer, probably when the base is added in the final stage to give the coumarin (19), possibly via the intermediates shown in Scheme 12 .



Scheme 12

The enamine (**18**) does not therefore provide a straightforward route to the cyclo-oct-4-enyl series whereas the dimethylamine enamine of cyclopentanone does provide a straightworward route to the cyclohept-4-enyl series.[66]

It is unlikely that the methyl substituent has any steric or electronic influence on the course of the reaction as it is well removed from the reactive sites. The most likely source of an explanation is the physical properties of the reagents and products present in the first stage of the reaction. The reaction mixture is more viscous when enamine (**18**) is used than it is in the case of the cyclopentanone enamine. It may be that the greater viscosity substantially reduces the rate of enamine formation and reformation in solution. Also, the "longer chain" ketones, and enamines such as (**21**) and (**18**) are likely to be poorer solvents for dimethylamine than their lower homologues. It may be that loss of dimethylamine from the reaction mixture prevented the reaction from proceeding as expected.

2.4 Experimental

Silica for column chromatography was Sorbsil M60. Light petroleum refers to the fraction which boils in the range 40 - 60°C. Ether refers to diethyl ether. Cyclohept-4-enylmethyl bromide was supplied by Dr. J. C. Walton. All other starting materials were obtained commercially. ^{1}H n.m.r. spectra were determined on Varian EM360 and Bruker WP80 and AM300 instruments. ^{13}C n.m.r. spectra were determined on Varian CFT20 and Bruker AM300 and AM400 instruments. Mass spectra were obtained on an AEI MS902 spectrometer. E.s.r. spectra were run on a Bruker ER 200D instrument; samples were made up in spectrosil tubes, degassed by several freeze-pump-thaw cycles or by bubbling nitrogen for ca. 15 minutes and photolysed in the cavity of the spectrometer with light from a 500W super-pressure Hg arc. Where distillations have been carried out using a Büchi Kugelrohr, the boiling temperatures given are dial temperatures and are uncorrected.

Reduction of Cyclohept-4-enylmethyl Bromide (5) with Tributyltin Hydride. Bromide (5) (1.5g, 8mmol) and Bu_3SnH (2.1g, 8mmol) were placed in a quartz tube, degassed by bubbling nitrogen for ca. 15 minutes, heated to 80°C and photolysed with light from a 250W medium pressure Hg arc for 2 hours. The products were distilled out on a vacuum line (0.75g). G.l.c. analysis showed two components together with a trace of unchanged bromide (5). The mixture was separated by preparative g.l.c. on a 3m × 1cm column packed with 10% MS200/50 on chromosorb WAW at 110°C. The first eluted component (80 rel.%) was, 5-methylcycloheptene, a clear liquid; δ_H(80MHz) 0.95(3H, d, J=7), 1.0 - 2.1(9H, m), 5.75(2H, m); δ_C(20MHz) 24.3(q), 28.0(t),

36.2(t), 38.2(d), 133.1(d); m/z 110(m^+, 40%), 95(60), 82(90), 81(70), 68(60), 67(100), 54(90) and 41(70). The second eluted component was bicyclo[3.2.1]octane (20 rel.%), a white solid; m.p. (sealed tube) 137 - 141°C (lit.[101] 139 - 141°C); δ_H(80MHz) 1.2 - 17(12H, m), 2.10(2H, br s); δ_C(20MHz)[102] 19.2(1C), 29.0(2C), 33.0(2C), 35.3(2C), 39.8(1C); m/z 110(m^+, 35%), 95(19), 82(100), 67(96), 54(46) and 41(54).

The bromide (5) (150mg, 0.79mmol) in hexadecane (0.5ml) was degassed and warmed to 165°C. This solution was photolysed with light from a 250W Hg arc while a solution of Bu_3SnH (250mg, 0.85mmol) in hexadecane (0.5ml) was added over 32 minutes. Photolysis was continued for a further 5 minutes. The mixture was cooled and the products were distilled directly out of the solution on the high vacuum line and identified as 5-methylcycloheptene (25 rel.%) and bicyclo[3.2.1]octane (75 rel.%)

Cyclo-oct-4-enecarboxylic acid.[93] The pyrrolidine enamine of cyclohexanone was prepared by condensation of cyclohexanone and pyrrolidine in refluxing toluene in a Dean-Stark apparatus. The enamine (46.0g, 0.30mol) was dissolved in dry benzene (250ml) and cooled in ice. Freshly distilled acrolein (28ml) in dry benzene (50ml) was added dropwise. The solution was warmed to room temperature and stirred for 2 hours. Dilute HCl (100ml) was added and stirring continued for 0.5 hours. The aqueous layer was separated, made alkaline with dilute NaOH (200ml) and extracted with ether (3 x 100ml). The extracts were combined with the benzene layer, dried (Na_2SO_4), and evaporated. The residue was distilled to give 2-pyrrolidinobicyclo[3.3.1]nonan-9-one (12.3g,

20%) as a viscous yellow oil; b.p. 82°C/0.3Torr (lit.[99] 125 - 127°C/0.5Torr; δ_C(20MHz) 21.2(1C), 23.2(2C), 27.6(1C), 27.9(1C), 30.5(1C), 34.1(1C), 45.7(1C), 51.1(1C), 52.0(2C), 68.8(1C) and 173.0(1C). 2-pyrrolidinobicyclo[3.3.1]nonan-9-one (12.0g, 58mmol) and methyl iodide (8.5g, 59mmol) were dissolved in tetrahydrofuran (80ml) and stirred at room temperature for 16 hours. The solution was decanted from the residue which was treated with acetone to dissolve some tarry material leaving a white powder. A further 1ml of methyl iodide was added to the solution which was then periodically refluxed and decanted until no more solid was formed. A total of 11.9g was obtained. This solid (7.0g) was dissolved in 50% NaOH solution and refluxed for 10 hours. The solution was cooled, acidified and extracted with ether (3 × 100ml). The extracts were dried (Na_2SO_4 and evaporated. The residue was distilled on a Büchi Kugelrohr to give cyclo-oct-4-enecarboxylic acid (4.4g, 49%) as an off white solid; b.p. 155°C/1.0Torr; δ_H(60MHz) 1.4 - 2.6(11H, m), 5.8(2H, m), 8,9(1H, br s).

Cyclo-oct-4-enylmethyl bromide (10). A solution of cyclo-oct-4-enecarboxylic acid (1.0g, 6.5mmol) in dry ether (10ml) was added slowly to ice cold $LiAlH_4$ (0.2g, 5.2mmol) in dry ether (20ml). The suspension was refluxed for 5 hours, cooled, water was added and the ether layer was decanted. Dilute sulphuric acid was added to the aqueous layer which was then extracted with ether (2 × 30ml). The ether layers were combined, washed with water and dried over Na_2SO_4. The ether was evaporated and the residue distilled on a Büchi kugelrohr to give the alcohol as an oil (0.73g, 80%); b.p. 126°C/0.5Torr; δ_H(80MHz) 1.0 - 1.9(8H, m), 2.2 - 2.4(4H, m), 3.4(2H, d, J=6), 5.5 - 5.9(2H, m). A solution

of the alcohol (1.30g, 9.4mmol) and triethylamine (1.4ml) in dry CH_2Cl_2 (50ml) was cooled and stirred in an ice bath under nitrogen. Methanesulphonyl chloride (1.25g) was added over 10 minutes. The solution was stirred and gradually warmed to room temperature over 30 minutes. Water (80ml) was added and the organic layer was washed successively with 2M HCl, brine and saturated bicarbonate solution then dried over Na_2SO_4. The solvent was evaporated at room temperature. The crude mesyl ester was added to LiBr (2.9g) in refluxing, dry acetone (40ml). Reflux was continued for 16 hours. The solution was cooled, filtered, the acetone was evaporated off and water added to the residue. The mixture was extracted with ether (2 × 50ml), the extract dried (Na_2SO_4) and the solvent evaporated to leave an oil which was chromatographed on silica (light petroleum) then distilled on a Büchi Kugelrohr to give the title bromide (**10**) as an oil (1.0g, 53%); b.p.87°C/1Torr, δ_H(80MHz) 1.1 - 2.0(7H, m), 2.0 - 2.3(4H, m), 3.3(2H, dd, J_1=6, J_2=2), 5.5 - 5.8(2H, m); δ_C(75MHz) 24.6(1C), 25.9(1C), 27.7(1C), 32.1(1C), 34.0(1C), 39.8(1C), 43.1(1C), 129.9(1C), 130.3(1C); m/z 204(m^+, 8%), 202(8), 176(8), 174(8), 123(80), 95(96), 81(100) and 79(100).

Reduction of Cyclo-oct-4-enylmethyl Bromide (10) with Tributyltin Hydride. Bromide (**10**) (0.5g, 2.5mmol) and Bu_3SnH (0.74g, 2.5mmol) were placed in a quartz tube, degassed by bubbling nitrogen for ca. 15 minutes then photolysed with light from a 250W medium pressure Hg arc for 2.5 hours at 135°C. The products were distilled out on a vacuum line (0.24g, 78mol.%). G.l.c. analysis showed three components. The mixture was separated by preparative g.l.c. on a 6m × 1cm carbowax 20M column at 70°C. The first eluted component was 5-methylcyclo-octene (62

rel.%); δ_H(300MHz) 0.9(3H, d, J=7), 1.1 - 1.2(1H, m), 1.4(3H, br s), 1.5 - 1.7(3H, m), 2.0 - 2.3(4H, m), 5.6 - 5.7(2H, m); δ_C(75MHz) 25.2, 25.4, 26.0, 27.8, 32.4, 34.9, 37.7, 129.8, 130.3; m/z 124(m^+, 11%), 109(16), 96(100), 81(74), 67(75) and 54(63). The second eluted component was bicyclo[3.3.1]nonane (6 rel.%); δ_H(300MHz) 1.5(6H, br s), 1.6 - 1.7(7H, m), 1.8 - 2.0(3H, m); δ_C(75MHz)[103] 23.2(C-3), 28.6(C-1), 32.3(C-2), 35.7(C-9); m/z 124(m^+, 85%), 82(51) and 81(100). The third eluted component was bicyclo[4.2.1]nonane (32 rel.%); δ_H(300MHz) 1.3 - 1.6(12H, m), 1.8 - 1.9(2H, m), 2.3(2H, br s); δ_C(75MHz)[103] 25.5(C-3), 32.9(C-7), 35.4(C-9), 35.7(C-2), 37.2(C-1); m/z 124(m^+, 29%), 96(75), 81(52) and 67(100)

1-Dimethylamino-4-methylcyclohexene (18). $Me_2NH.HCl$ (40g) was dissolved in the minimum amount of water and the solution added dropwise to NaOH (40g). The dimethylamine liberated was collected over CO_2-acetone and dissolved in dry ether (250ml). $CaCl_2$ (30g) was added followed by 4-methylcyclohexanone (12.6g, 113mmol). The mixture was kept at ambient temperature for 80 hours, filtered, the solvent evaporated and the residue distilled under reduced pressure to give the enamine (**18**) (12.8g, 83%), b.p. 66°C/15Torr; δ_H(60MHz) 1.0(3H, d, J=4), 1.0 - 2.5(7H, m), 2.6(6H, s), 4.6(1H, br s).

Attempted Preparation of 1-Dimethylamino-6-methylcyclohexene. 2-methylcyclohexanone (12.6g, 113mmol) was added to a solution of dimethylamine in ether over calcium chloride. After standing at ambient temperature for 18 months the solvent was evaporated. The residue was found to be unchanged 2-methylcyclohexanone.

Reaction of Enamine (18) with Acrolein, followed by Methyl Iodide and Base.[88] Enamine (18) (11.7g, 84mmol) was cooled to 0°C under dry nitrogen. Freshly distilled acrolein (5.6ml) was added dropwise during 1 hour. The mixture was warmed to room temperature and stirred for 16 hours. Anhydrous acetonitrile (20ml) was purged with nitrogen and added to the yellow oil. The solution was cooled to 0°C, MeI (5.3ml) was added dropwise and the mixture was warmed to room temperature and stirred for 2 hours. 20% aq. NaOH (80ml) was added and the mixture was refluxed for 16 hours. The solution was cooled, the aqueous layer removed, extracted with ether (2 × 100ml); the ether extract was dried over Na_2SO_4 and evaporated. Recrystallisation of the crude product from light petroleum gave white needles (1.2g, 9%) identified as 6-methyloctahydrocoumarin (**19**), m.p. 83 - 85°C; δ_H(300MHz) 1.0(3H, d, J=8), 1.2 - 2.1(10H, m), 2.5 - 2.8(2H, m), 3.8(1H, dt, J_t=9, J_d=4); δ_C(75MHz) 17.9(CH_3), 26.7(CH_2), 26.7(CH_2), 26.8(CH), 29.4(CH_2), 30.0(CH_2), 32.8(CH), 36.8(CH_2), 84.0(CH), 171.6(C=O); m/z 168(m^+, 6%), 124(5), 111(12), 96(33), 81(100), 67(36), 55(58); ν 1740cm^{-1} (C=O). (Found: C, 71.2; H, 9.7 Calc. for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6%)

Reduction of Lactone (19) with Lithium Aluminium Hydride. A solution of 6-methyloctahydrocoumarin (**19**) (1.30g, 7.7mmol) in dry ether (20ml) was added to ice-cold $LiAlH_4$ (0.30g, 7.9mmol) in dry ether (20ml). The suspension was refluxed for 3.5 hours then stirred at ambient temperature for 16 hours. Water was added and the ether layer decanted. Dilute sulphuric acid was added to the aqueous layer which was then extracted with ether (2 × 50ml). The ether layers were combined, dried over Na_2SO_4, the solvent was evaporated off and the residue was distilled on a Büchi Kugelrohr

to give a thick oil (1.17g, 88%), identified as 2-(3-hydroxypropyl)-4-methylcyclohexanol (**20**); δ_H(300MHz) 0.9(3H, d, J=8), 1.2 - 1.3(2H, m), 1.4 - 1.8(10H, m), 2.1(2H, br s), 3.4(1H, q, J=2), 3.6(2H, t, J=6); δ_C(75MHz) 19.9, 26.7, 27.9, 29.4, 29.6, 30.0, 35.0, 39.4, 62.9, 73.2; m/z 172(m^+, 1%), 154(3), 136(10), 115(20), 103(18), 97(49), 95(62), 81(49), 67(34), 61(27), 55(100); v 3,330 cm^{-1} (OH).

Kinetics of Tributyltin Hydride Reductions. The solvent, t-butylbenzene or hexadecane (0.5ml), was placed in a pyrex tube, heated to the desired temperature and degassed by bubbling nitrogen for ca. 15 minutes. To this was added the bromide (20μl), Bu_3SnH (see **Tables 2 and 4**) and octane (20μl) as an internal standard. The solution was photolysed for 1 hour with light from a 250W medium pressure Hg arc and then analysed by g.l.c. on a PYE UNICAM PU 4800 chromatograph. The values of k_c/k_H were obtained at each temperature from the initial Bu_3SnH concentration and the final product concentrations (**Tables 2 and 4**) using an integrated rate equation.[29,69] The best values of k_c/k_H were located with an iterative computer program based on NAG routine C05AXF.

CHAPTER 3

OXYGEN CONTAINING RINGS

3.1 Introduction.

In this chapter, the work described in the previous chapter is extended by applying the same rationale and methods to some oxygen containing rings.

Rings containing oxygen atoms have the same number of degrees of freedom as their hydrocarbon analogues (if only the ring skeleton is considered and not the substituent hydrogens). In principle, therefore, the same geometrical dispositions are available to corresponding types of rings. However, the introduction of heteroatoms alters bond lengths and angles, reduces or increases steric interactions and creates possibilities for types of interatomic interaction, e.g. hydrogen bonding, which do not exist in hydrocarbons. Consequently, rings which have the same number of atoms and the same bond orders but different patterns of heteroatom substitution often have markedly different conformational preferences and different free energy barriers to conformational transformations.[104]

As will be discussed later, 4,7-dihydro-1.3-dioxepin (1) is believed to have a preference for the twist-boat conformation.[105]

This preference has been ascribed[104] to the tendency of the oxygen containing end of the ring to get as close as possible to the *gauche* - *gauche* arrangement of bonds required for C-O-C-O-C fragments by the anomeric effect.[106]

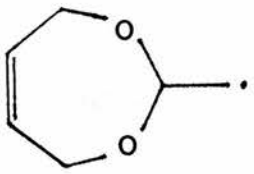
(1)

The twist boat inverts by a pseudorotation process along a low energy pathway through the boat conformation[105]. In the case of cyclohept-4-enylmethyl radical it was proposed that the boat axial conformation underwent transannular cyclisation and that this reaction was important at easily accesible temperatures, although the chair equatorial conformation was the favoured one. It appeared that 4,7-dihydro-1,3-dioxepin-2-ylmethyl radical would have access to boat conformations from its preferred conformation along a lower energy pathway than was the case for cyclohept-4-enylmethyl radical and that transannular cyclisation should be favoured, provided that the boat axial conformation was sufficiently highly populated.

In this study, the transannular cyclisations of 4,7-dihydro-1,3-dioxepin-2-ylmethyl radical and 4,7-dihydro-2-methyl-1,3-dioxepin-2-ylmethyl radical were investigated. In a supplementary study, the spin probe[78-80] technique for conformational analysis by e.s.r. was applied to the related six-membered ring 1,3-dioxan.

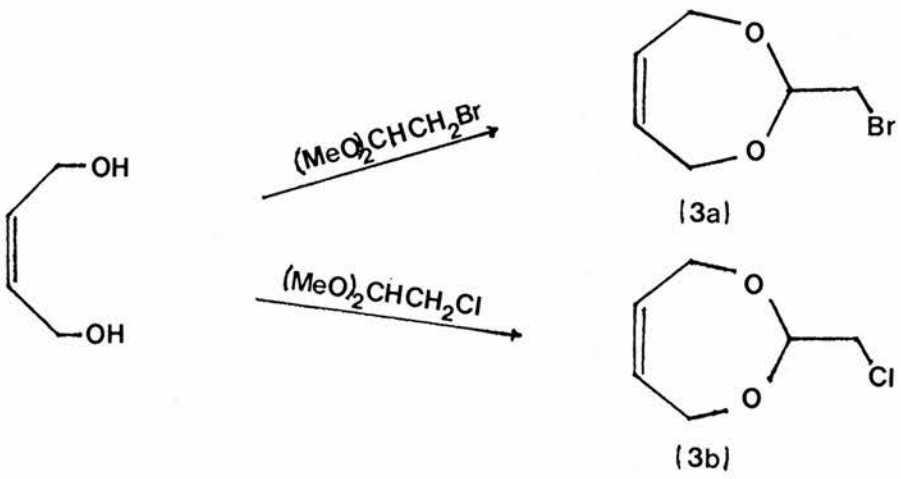
3.2 Radical Cyclisation of 4,7-dihydro-1,3-dioxepin Derivatives.

4,7-Dihydro-1,3-dioxepin-2-ylmethyl radical (2).



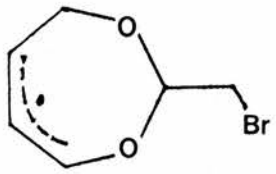
(2)

A suitable precursor for the radical (2) was the bromide (3a) which was synthesised straightforwardly by condensation of the appropriate diol and haloacetal (**Scheme 1**).



Scheme 1

In order to assess the likely importance of transannular cyclisation in (2) an e.s.r. study was carried out to investigate whether or not axial conformations were populated. The bromide (3a) was dissolved in t-butylbenzene with hexamethylditin and di-t-butylperoxide and the sample was photolysed in the cavity of the e.s.r. spectrometer at low temperatures. The spectrum obtained at 220K (**Figure 1**) analyses well for a(2H) = 3.1G, a(H) = 18.1G, a(H) = 24.2G, a(2H) = 14.2G and can be assigned to the allyl radical (4).



(4)

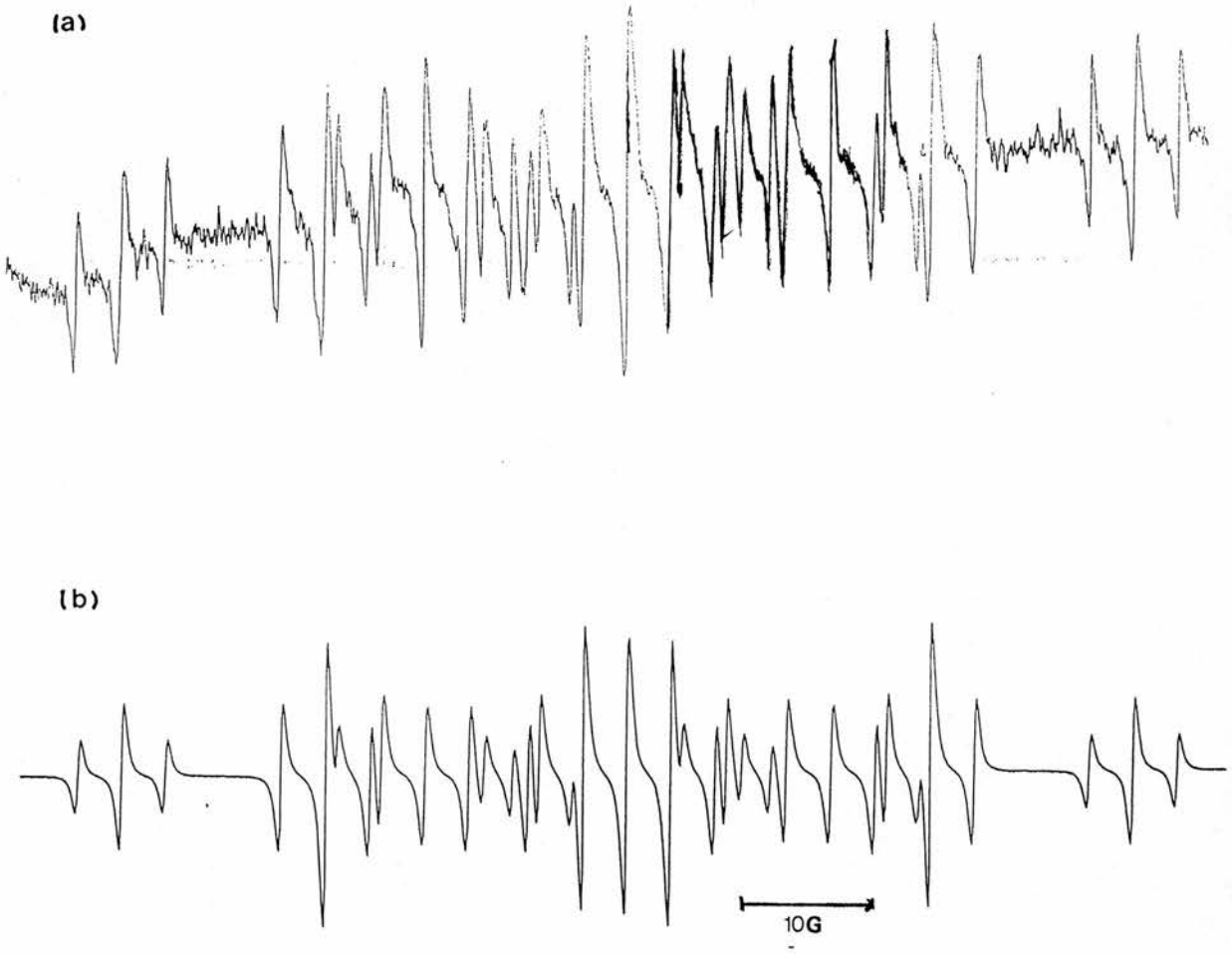


Figure 1: (a) The e.s.r. spectrum of (**4**) derived from (**3a**) at 220K in t-BuPh and (b) the simulated spectrum for a(2H)=3.1G, a(H)=18.1G, a(H)=24.2G and a(2H)=14.2G

It would appear that the hydrogens in the 4 and 7 positions on the ring are sufficiently labile to be abstracted by the t-butoxyl radical and that this reaction dominates the abstraction of halogen by tin radicals. A similar result was obtained when the chloride (**3b**) was treated in the same way. At 210K part of a second spectrum can be discerned (**Figure 2**). It is likely that this is the double triplet associated with radical (2). It was not possible to derive the β hyperfine splitting unambiguously but one triplet is clearly visible with an α-h.f.s. of 23.0G.

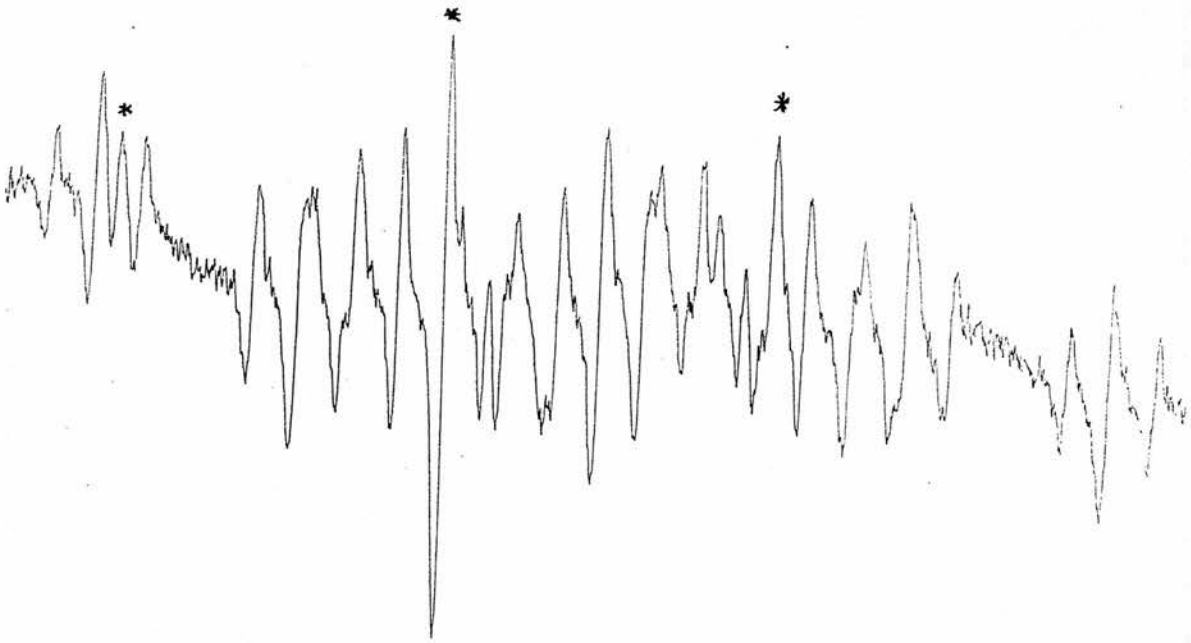


Figure 2: The e.s.r. spectrum derived from irradiation of (**3a**), Me_6Sn_2 and di-t-butylperoxide in t-BuPh at 210K with the peaks tentatively assigned to (2) marked *.

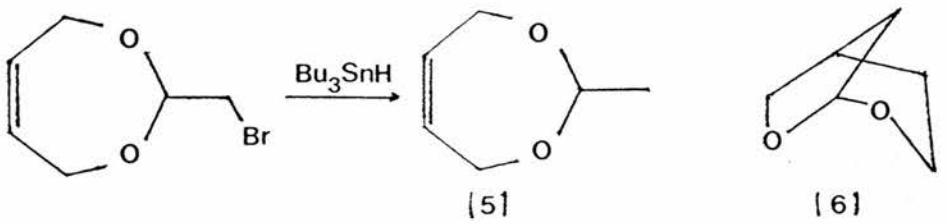
No peaks were observed at higher field than the limit of the major spectrum in Figure 2 and it follows that the width of the minor spectrum (*) does not exceed 73G which in turn implies that the β-h.f.s. of the minor spectrum does not exceed 27G and is therefore probably below the free rotation limit of 26.8G[107] which indicates that the radical prefers the bisected conformation with respect to the C_{β}-H_{β} bond (**Figure 3a**). It would be expected that steric interaction between the $CH_{2\alpha}$ protons and the olefinic protons in the boat axial conformation of (2) would give rise to a preference for the eclipsed conformation (**Figure 3b**). Therefore, the spectrum is not that of the boat axial conformer of the radical. On the basis of n.m.r. studies of the parent ring (1)[105] it seems likely that this is either an averaged spectrum or that of the twist - boat conformer. It cannot be concluded from this that no boat axial conformers are present. The limit of detection is around 20% of the minor radical (2) concentration.

(a) **Figure 3** (b)

In the absence of the butoxyl radical a weak spectrum was observed which was the same as that in figure 3. It follows that H abstraction from the 4 and 7 position is also effected by radicals of type (2). It was not possible to obtain a clearer spectrum of (2) by this approach.

When the bromide (3a) was reduced with one molar equivalent of tributyltin hydride at 80°C the major product was the acetal

(5) (Scheme 2). A trace of another product was formed which was almost certainly the bicyclic acetal (6).



[5] [6]

Scheme 2

The formation of a small amount of the expected product from transannular cyclisation of (2) is good evidence that the boat axial conformation of (2) is populated, but that other conformations are preferred. Consequently, the rate of bicyclisation is low and the process is not competitive with hydrogen abstraction from the reducing agent. The e.s.r. results might have led one to expect products derived from the allyl radical (4), these were not observed which implies that hydrogen abstraction by radicals (2) from (3a) is slower and not competitive with hydrogen abstraction from Bu_3SnH.

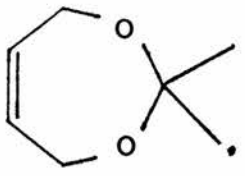
Increasing the temperature at which the reaction was carried out (up to 160°C), and therefore the rate of conformational transformations had a negligable effect on the proportion of transannular cyclisation. The increase in the proportion of (6) formed was within the measurement error and it was not possible to ascertain beyond doubt that there was an increase although that is what one would have predicted.

Decreasing the rate of hydrogen abstraction from the reducing agent would also be expected to increase the proportion of (6) formed. Tris(trimethylsilyl)silane has been pioneered as a

reducing agent by Chatgilialoglu et al[27] and it has been estimated that the rate of H abstraction from this compound by carbon centred radicals is a factor of 4 or 5 less than that for tributyltin hydride. Unfortunately, the use of this reducing agent did not lead to the formation of an unambiguously higher proportion of (6) than in the previous experiments.

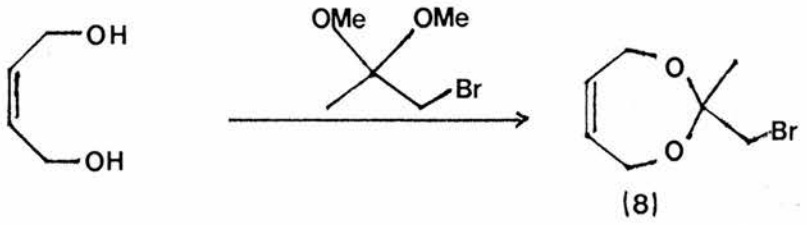
As the variation in the proportions of (5) and (6) with temperature could not be measured accurately, because in all cases the ratio of (5):(6) was very high it was not possible to determine the rate of the bicyclisation accurately. By comparing the proportion of (6) formed with Bu_3SnH at ca 100°C with the proportion of bicyclised product formed in reactions which are described elsewhere in this thesis, for which the rate equation is known at a similar temperature, it can be roughly estimated that for the bicyclisation of (2) $k_{c(298)}$ is between 10^3 and $10^4 s^{-1}$.

4,7-dihydro-2-methyl-1,3-dioxan-2-ylmethyl radical (7).



(7)

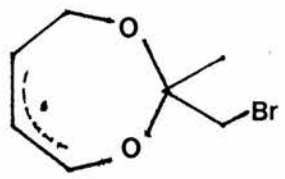
As before, a suitable precursor for this radical was prepared by condensing the appropriate bromoketal and diol (**Scheme 3**).



(8)

Scheme 3

The e.s.r spectrum of radicals derived from the bromide (8) was obtained although no conformational information was expected in the abscence of a β-hydrogen. The bromide (8), hexamethylditin and di-t-butylperoxide in t-butylbenzene were photolysed in the cavity of the e.s.r. spectrometer. The spectrum obtained (**Figure 4**) analyses quite straightforwardly for a(H) 24.5G, a(H) 17.2G, a(2H) 14.2G and a(H) 3.1G. and can be attributed to the allyl radical (9). Again, H abstraction from the 4 and 7 positions on the ring seems to be the most important type of reaction in this system. It was not possible to observe the triplet expected for radical (7) either in the presence or absence of peroxide.



(9)

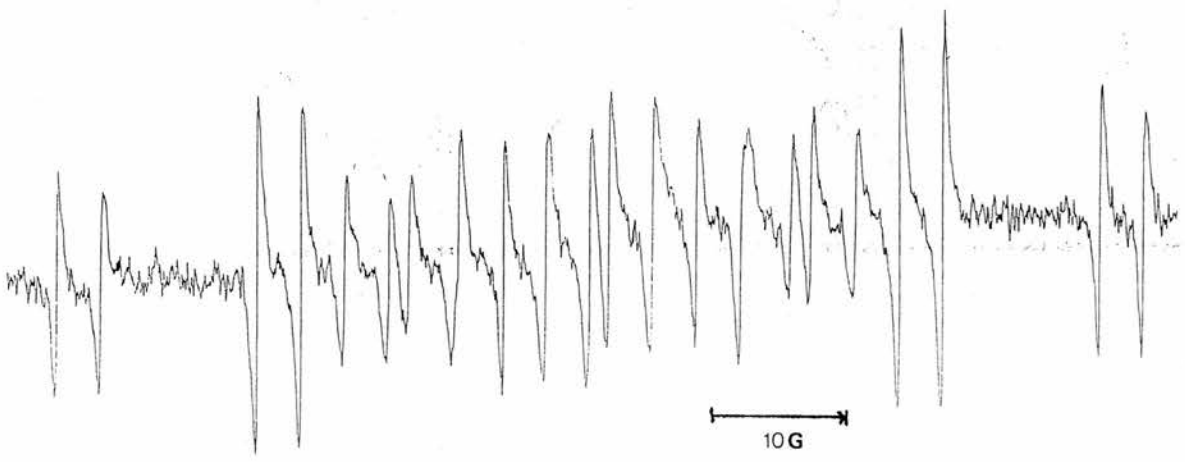
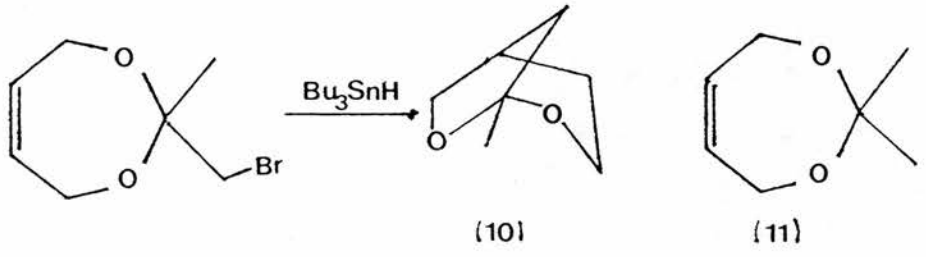


Figure 4: E.s.r. spectrum of (9) derived from (8) at 220K in t-BuPh

Reduction of the bromide (8) with tributyltin hydride gave two products which were identified as the ketals (10) and (11) (Scheme 4).



(10) (11)

Scheme 4

The proportions of (10) and (11) were found to vary strongly with temperature and tributyltin hydride concentration. The absolute product concentrations for a variety of reaction conditions were obtained by g.l.c. using an internal standard (Table 1) and the ratio of $k_c/k_{H(SnH)}$ in each case was determined using the methods noted in Chapter 2.29,89

Table 1

Reduction of (8)[a] with Bu_3SnH in hexadecane.

Temp/K	$[Bu_3SnH]$/mol dm^{-3}	(10)/rel.%	(11)/rel.%	(k_c/k_H)/mol dm^{-3}
272[b]	0.271	39	61	0.160
305	0.271	67	33	0.451
307[c]	0.467	62	38	[e]
307[d]	0.652	45	55	[e]
336	0.271	80	20	0.847
364	0.271	88	12	1.607
394	0.271	94	6	3.690

[a][(8)]=0.247M, [b]in cyclopentane solvent, [c][(8)]=0.233M, [d][(8)]=0.220M, [e]not measured.

This synthesis of 1-methyl-2,7-dioxabicyclo[3.2.1]octane gave a yield of 50% in a small preparative scale experiment at 125°C. The product was very easily purified by conventional column chromatography.

Kinetics of the Cyclisation of (7).

The rate constant for the cyclisation of (7) at each temperature was derived from the k_c/k_H values which are shown in **Table 1** using the k_H value of Ingold et al (**Table 2**).[25] The rate equation for the reaction was derived from a plot of log k_c vs 1000/T (**Figure 5**).

Table 2

Temp./K	272	305	336	364	393
$k_c/10^5$ s^{-1}	2.0	11.9	39.3	114.3	381.4

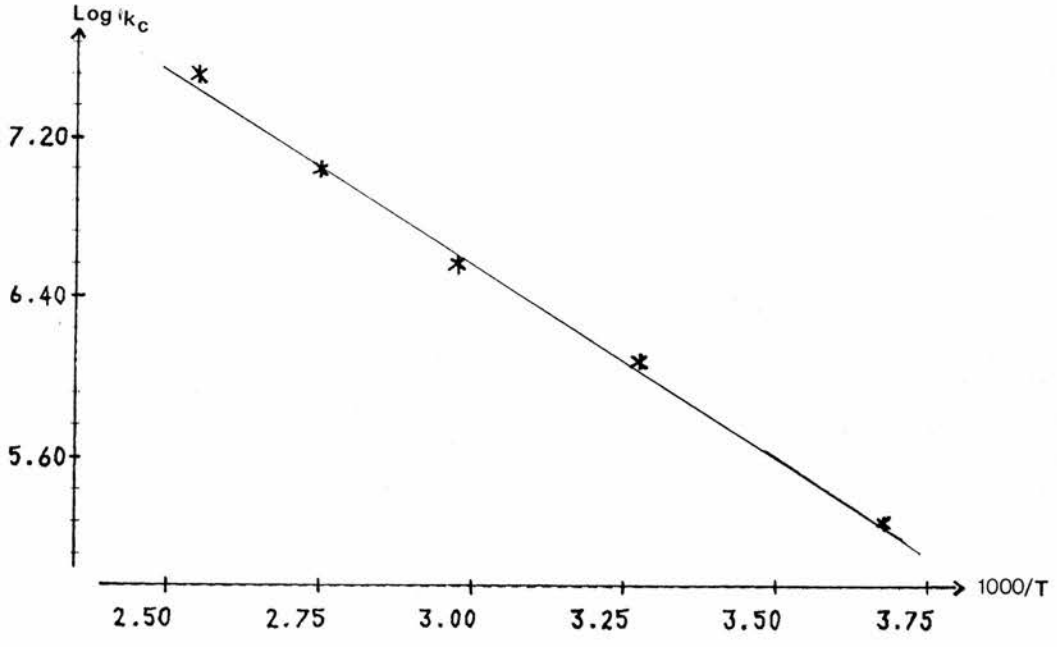
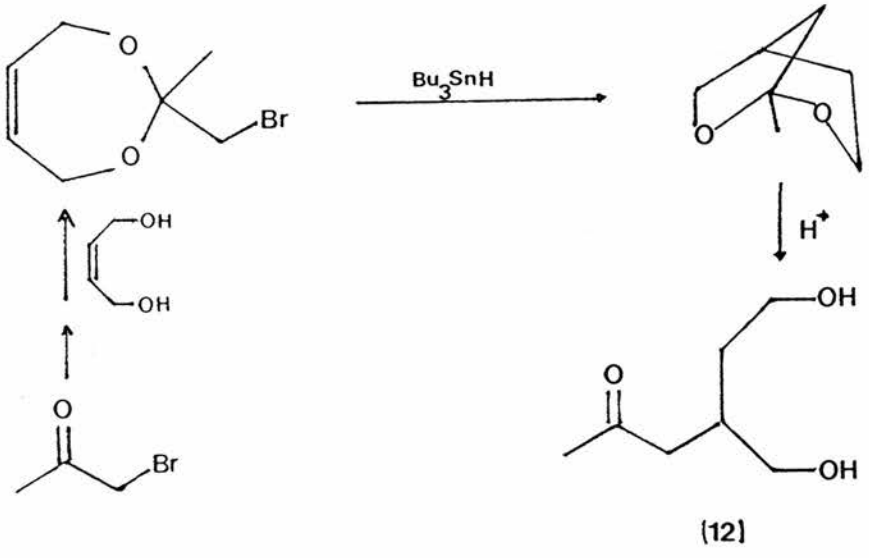


Figure 5: Arrhenius plot for the cyclisation of (7).

The Arrhenius equation thus derived is log k_c = 12.5 - 1,960/T. This gives $k_{c(298)}$ = 8.4 x $10^{5\pm1}$ s^{-1}, A = 12.5 ± 1.0 and E = 8.96 ± 0.6 kcal mol^{-1}

Hydrolysis of (10)

The bicyclic ketal (**10**) was hydrolysed to give the diol (12) The net reaction thus completed is the addition of the starting carbonyl compound to the double bond of *cis*-but-2-ene-1,4-diol (Scheme 5).



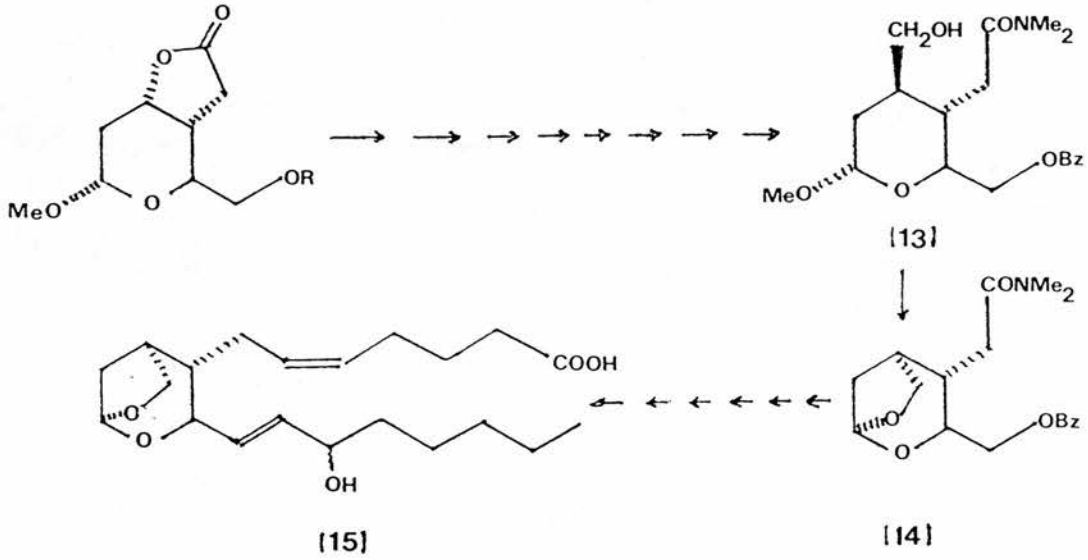
Scheme 5

Discussion and Conclusions.

The two synthetic achievements of this study are the preparation of 1-methyl-2,7-dioxabicyclo[3.2.1]octane and the addition of acetone to *cis*-but-2-ene-1,4-diol.

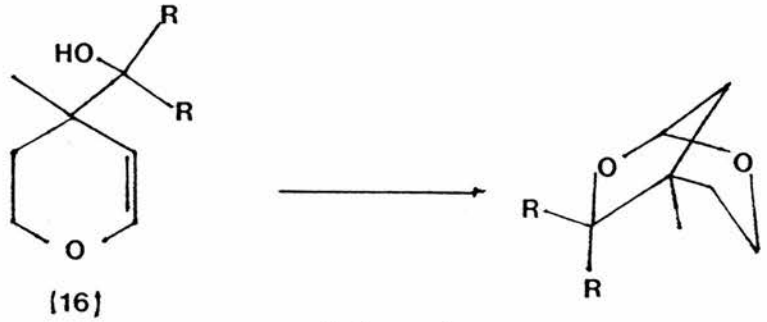
2,7-Dioxabicyclo[3.2.1]octane has been reported in the synthesis of a pharmaceutically active analogue of thromboxane A_2

(15). The ring forming reaction in this 15-stage preparation (**Scheme 6**) is the acid catalysed condensation of (13) to give (14).[108]



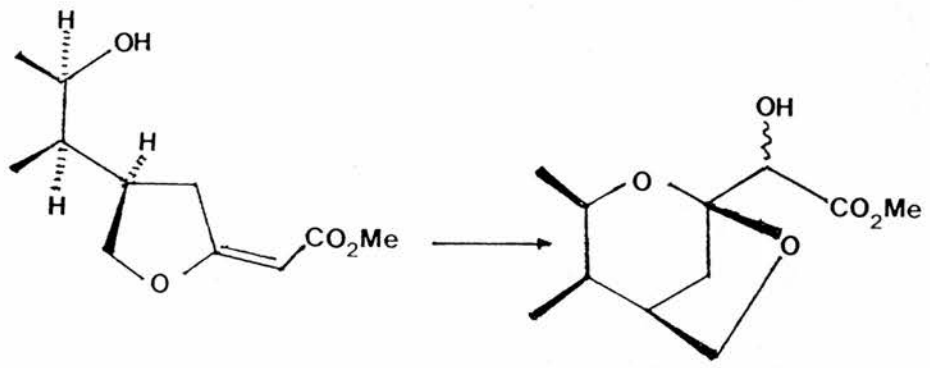
Scheme 6

Simpler derivatives of (10) have been prepared by the acid catalysed cyclisation of tertiary alcohol substituted dihydro-2H-pyrans such as (16), (**Scheme 7**).[109].



Scheme 7

A substituted 2,7-dioxabicyclo[3.2.1]octane has been employed as an intermediate in the total synthesis of the insect poison dl-pederamide, the cyclisation step was also acid catalysed (**Scheme 8**).[110]



Scheme 8

The examples given above suggest that the 2,7-dioxabicyclo[3.2.1]octane system is of some biochemical importance and that new synthetic routes to it should be of some interest. The synthesis described in this thesis requires precursors which are relatively simple to construct. It is more amenable to the introduction of substituents, particularly in the 1-bridgehead position where substitution is achieved by starting with the appropriate bromoketone, many of which are commercially available, and converting it into the ketal.

Previous approaches to the addition of carbonyl compounds to alkenes have involved generating a radical from a double bond, e.g. by addition of an oxyl radical, and addition of that radical to a reactive site on the carbonyl containing molecule. An example[71] was given in chapter 2 (p.38). It would seem that greater flexibility in the type of carbonylmethyl group which can be introduced is offered by hydrolysis of compounds of type (**10**). It is not necessary for the starting ketone to have a functional group which can react with alkyl radicals.

The observation that the 4,7-dihydro-1,3-dioxepin-2-ylmethyl radical (**2**) cyclises very much more slowly than its cyclohept-4-enylmethyl counterpart could lead us to two possible conclusions.

Either the radical (2) boat axial conformation is relatively unpopulated or the boat axial conformation is less favourable for cyclisation. If the latter argument were important we would have to conclude that the distance between the radical centre and the olefinic π-bond is greater in the case of (2). While no work has been done on bond distances in dioxacycloheptenes, analogy with other related simple ring systems eg. 1,3-dioxan[104] would lead us to expect that the ring would be more compact than cycloheptene and that the C-O-C bond angles would be less than the corresponding C-C-C angles in cycloheptene. 1,3-Dioxan is significantly more puckered about the oxygen atoms where the dihedral angles are 60 - 63° than about the alicyclic part of the ring where the dihedral angles are 53 - 55°, similar to cyclohexane. The C-C bond lengths in 1,3-dioxan are 1.49 - 1.51Å, shorter than in cyclohexane (1.53Å). The reduction in C1-C5 distance relative to 5-hexenyl due to these two factors was asserted to be the explanation for the faster cyclisation of 3-oxahex-5-enyl radical compared to 5-hexenyl radical.[26,60] Both factors should favour cyclisation of the boat axial conformer of (2).

If the boat axial conformer is not favoured this could be due to the boat conformers having a high free energy value, or due to one particular inversion pathway, via the boat equatorial, being favoured. The accepted inversion pathway for cycloheptene type rings is shown (**Figure 6**). It has been established that this molecule exists predominantly in the chair conformation and that the rate determining step for the chair inversion process is the chair → boat transformation for which a free energy value of 5 kcal mol^{-1} has been determined.[77]

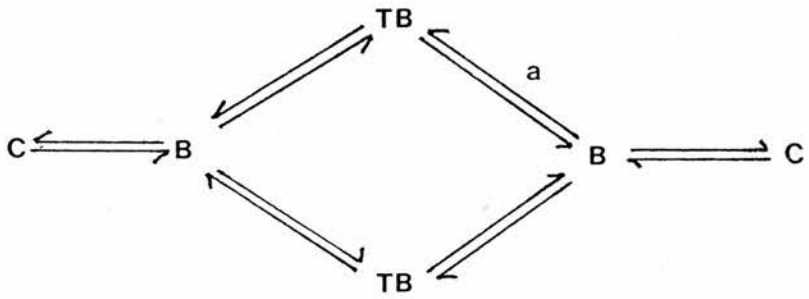
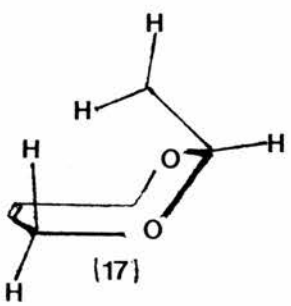


Figure 6

St. Amour and St. Jacques[105] have shown by n.m.r. methods that 4,7-dihydro-1,3-dioxepin exists predominantly in the twist-boat conformation and therefore that the pseudorotation process by which the twist-boat inverts is important. These workers could not calculate an energy barrier for this process but they concluded that it must be less than 5 kcal mol^{-1}. [There is also indirect evidence that the chair inversion barrier is greater in cycloheptene than in dioxacycloheptene.[111]] However, the same workers report that 2,2-dimethyl substitution raises the energy barrier for the pseudorotation to 6.8kcal mol^{-1}. Such an increase has been attributed to greater steric interaction in the transition state for pseudorotation,[105,111] i.e. between the methyl group and the olefinic protons in the boat conformation and/or between the methyl group and the C-4 proton in the intermediate conformation (17) located at **a** on **Figure 6**.



(17)

In the case of the 2-methyl monosubstituted dioxacycloheptene, no barrier could be measured.[105] The monosubstituted ring evidently inverts principally along the path which places the methyl group equatorial in the boat conformation.

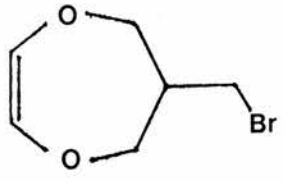
It follows that the radical (2) also has a significant preference for the pseudorotation pathway which goes through the boat equatorial conformer. In the case of the substituted radical (7) the pathway through the boat with the methyl equatorial is favoured because of the methyl's greater size compared to CH_2 . This pathway places the CH_2 group axial, i.e. favourable for cyclisation.

The fact that that steric interactions are more important in (2) than in cycloheptenylmethyl radical is consistent with the predictions about bond lengths and angles made earlier.

The rate of cyclisation of the substituted radical (7) exceeds that of cyclohept-4-enylmethyl radical by a factor of 8.4. This difference is associated with a higher A factor and a higher activation energy for the process. The higher A factor is consistent with the argument that the twist boat → boat → twist boat pseudorotation is the most important transformation of this ring and that the chairs contribute less. The radical centre has more frequent access to the boat axial conformation in (7) than in cyclohept-4-enylmethyl. This is to some extent compensated for by steric crowding in both the boat axial conformation and in the intermediate (17) which results in the pseudorotation of (7) - twist - boat to (7) - boat - axial having a higher energy barrier

than the chair → boat transformation of cyclohept-4-enylmethyl radical. The other possible contribution to the high activation energy for the cyclisation of (7) stems from the fact that as with cyclohept-4-enylmethyl radical, the 1,5 cyclisation is also a 1,6 cyclisation and the transition state for the 1,5 cyclisation has to incorporate a strained 6-membered ring. In the case of (7) most of the bond distances are likely to be shorter and so this strain factor will be greater.

Any future worker interested in gaining further insight into the explanation for the high activation energy for the cyclisation of (7) might consider preparing the 1,5-dioxacyclohept-6-en-3-ylmethyl bromide (18) and studying its radical reactions. In this system there are no hydrogens α - to the double bond which eliminates the possibility of steric crowding in the "sofa" intermediate (17). If the cyclisation of (18) also has a high activation energy then that will be good evidence that it is ring strain in the transition state which is the important factor in the case of (7).

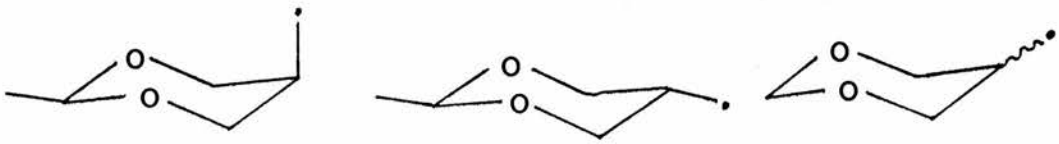


(18)

The synthesis of (18) will be more challenging than the trivial procedures which were used to prepare (3a) and (8). However, the basic ring is reported in the literature[11,12] and so a route to (18) should be accessible.

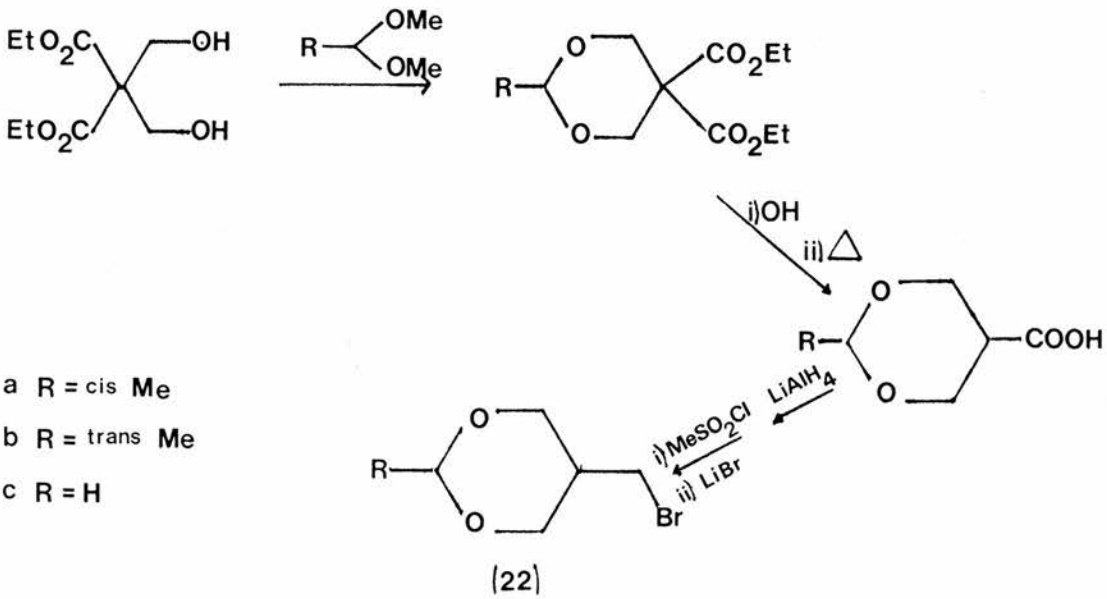
3.3. An E.S.R. Study of 1,3-dioxan-5-ylmethyl Radicals.

The use of the small planar CH_2• group as a spin probe to investigate the conformational behaviour of rings has been discussed in the previous chapter and elsewhere.[3] In this study the radicals (19), (20) and (21) were examined by e.s.r. spectroscopy over a range of temperatures and it was hoped that it would be possible to observe the dynamic behaviour of these radicals and thus determine the barrier to inversion of 1,3-dioxan by the e.s.r. method.



(19) (20) (21)

The radicals were generated from the corresponding bromides which were synthesised according to literature procedures as shown (**Scheme 9**).[113-115]



a R = cis Me
b R = trans Me
c R = H

(22)

Scheme 9

The bromides were dissolved in t-butylbenzene or cyclopropane with hexamethylditin or triethylsilane and di-t-butylperoxide and were irradiated in the cavity of the e.s.r. spectrometer.

In the case of *cis*- 2-methyl-1,3-dioxan-5-ylmethyl radical (**19**), only one conformation was observed (**Figure 7**) over the temperature range 203 - 273K above which the spectrum was too weak to observe. This was identified as the 5-axial conformation by analogy with the *cis*-2-t-butyl-1,3-dioxan-5-ylmethyl radical[116] which must occupy the conformation in which the CH_2 is axial because of the considerable steric crowding between the t-butyl and the axial hydrogens on C4 and C6 which would be introduced if the t-butyl group was placed axial.

For the *trans*-2-methyl-1,3-dioxan-5-ylmethyl radical (**20**), only the equatorial conformer was observed (**Figure 7**) over the temperature range 203 -293K. This was identified by analogy with *trans*-2-t-butyl-1,3-dioxan-5-ylmethyl radical[116] which must be diequatorial, again for steric reasons.

The unsubstituted 1,3-dioxan-5-ylmethyl radical (**21**) was observed to be in the equatorial conformation over the temperature range 143 - 333K, no axial conformer could be detected (**Figure 8**).

The hyperfine splittings are given in **Table 3**. The small β-h.f.s. values, which are below the free rotation limit[107], indicate that the radicals prefer the bisected conformation with respect to the C_β-H_β bond. The increase of the β-h.f.s. with temperature (**Figure 9**) also supports this interpretation.

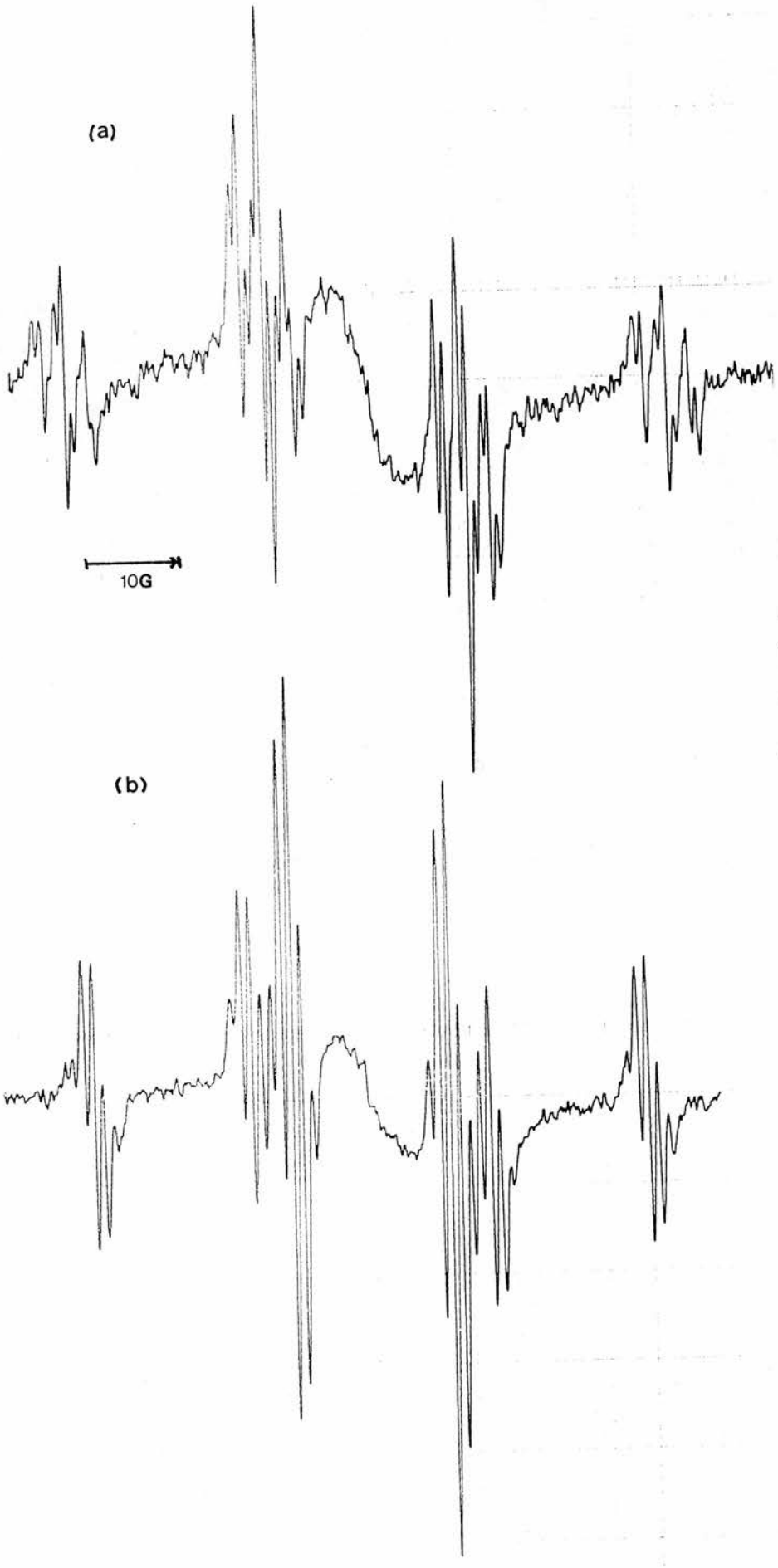


Figure 7: E.s.r. spectra of (a) (**19**) and (b) (**20**) derived from the corresponding bromides at 200K in t-BuPh.

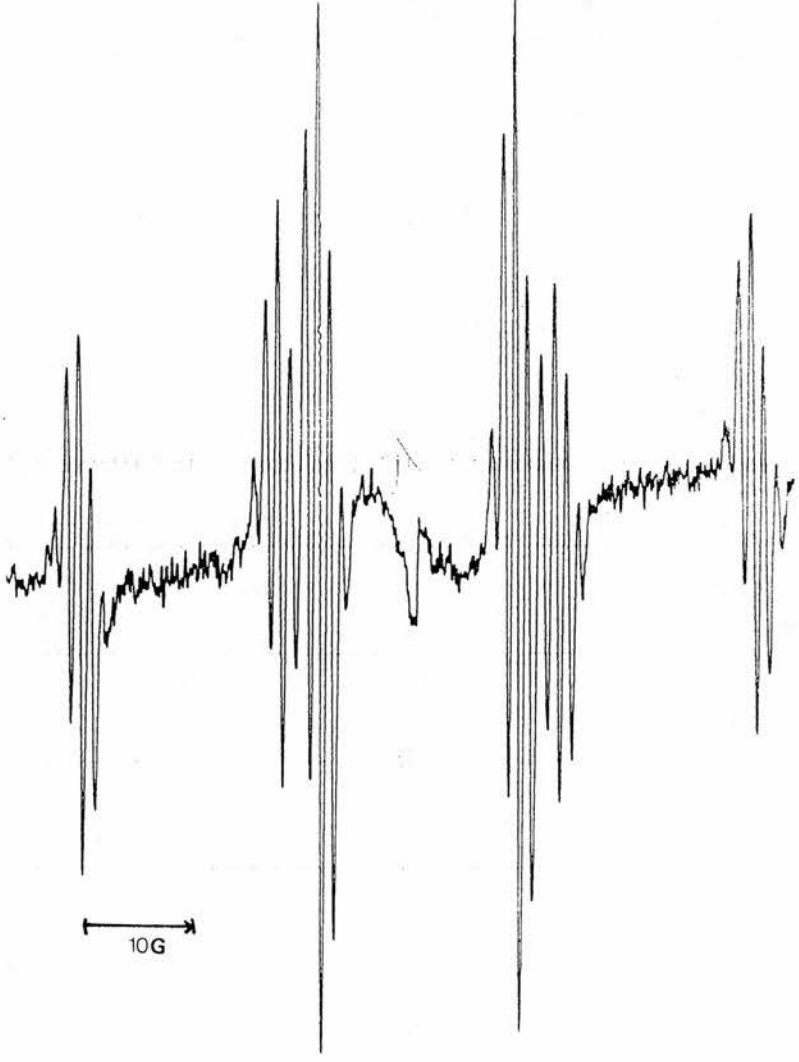
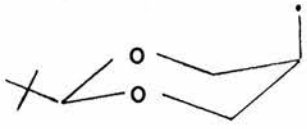
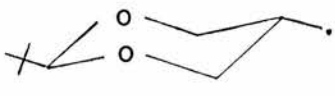


Figure 8: E.s.r. spectrum of (21) derived from the corresponding bromide at 215K in t-BuPh.

Table 3

Radical	Hyperfine Splittings	Temperature
(19)	$a(2H_\alpha)=22.2G$, $a(H_\beta)=22.0G$, $a(2H_\gamma)=2.8G$, $a(2H_\gamma)=0.8G$.	200K
(20)	$a(2H_\alpha)=22.1G$, $a(H_\beta)=17.7G$, $a(4H_\gamma)=1.1G$.	200K
(21)	$a(2H_\alpha)=22.0G$, $a(H_\beta)=18.0G$, $a(4H_\gamma)=1.1G$	200K
	$a(2H_\alpha)=22.2G$, $a(H_\beta)=19.8G$ $a(2H_\gamma)=2.8G$, $a(2H_\gamma)=0.8G$.[a]	140K
	$a(2H_\alpha)=22.2G$, $a(H_\beta)=16.5G$ $a(4H_\gamma)=1.15G$.[a]	140K

[a] Data from reference 116.

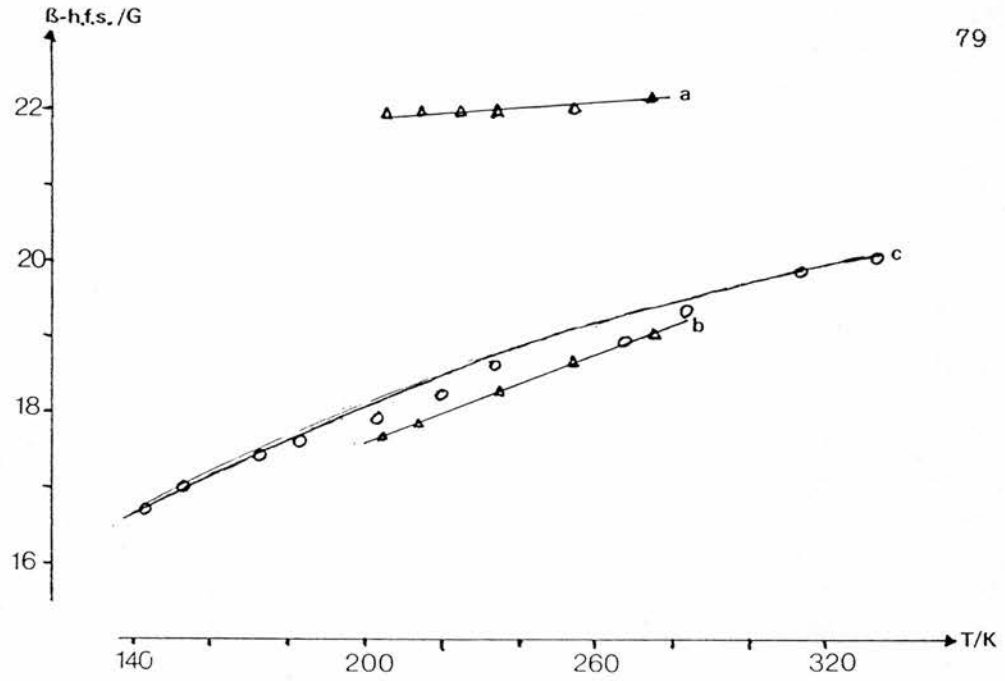


Figure 9: Variation of ß-h.f.s. with temperature for solutions of (a) (**19**), (b) (**20**) and (c) (**21**) in t-BuPh or cyclopropane

The axial radical (**20**) has both a large and a small γ-h.f.s. This is in line with the observation made for axial 2-t-butyl-1,3-dioxan-5-ylmethyl radical[116] and the larger of the two splittings can be attributed to the H_x pair which are in an all *trans* (W-plan) arrangement with respect to the SOMO.

When interpreting the results it is useful to examine n.m.r. data on the starting bromides (**Table 4**). It is fairly clear that the bromomethyl group in *cis*-5-bromomethyl-2-methyl-1,3-dioxan (**22a**) has a pronounced axial preference. Also, the *trans*-isomer (**22b**) has, as would be expected, a strong preference for the diequatorial conformation. These results can be interpreted as being dominated by steric considerations, with the 2-methyl group having a strong equatorial tendency; the equatorial preference of 2-methyl-1,3-dioxan has been calculated to be 3.98 kcal mol^{-1}.[117] It follows that the observed conformational preferences of the corresponding radicals (**19**) and (**20**), whether in equilibrium or not, are not surprising.

Table 3

N.m.r. Data for 2-Substituted 5-Bromomethyl-1,3-dioxans.

2-substituent	δ(H-5)	δ(CH_2Br)	Solvent	Reference
CH_3 - *cis*	1.62	3.64	CS_2	115
CH_3 - *trans*	2.20	3.02	CS_2	115
H	1.93	3.41	CS_2	115
CH_3 - *cis*	1.73	3.77	$CDCl_3$	
CH_3 - *trans*	2.34	3.10	$CDCl_3$	
H	2.04	3.40	$CDCl_3$	
t-Bu - *cis*	1.72	3.73	$CDCl_3$	116
t-Bu - *trans*	2.28	3.10	$CDCl_3$	116

Observation of only the equatorial conformer of 1,3-dioxan-5-ylmethyl radical over a wide range of temperatures is more puzzling. It is quite possible that at equilibrium the radical (**22**) may have a substantial preference for the equatorial conformation. 5-methyl-1,3-dioxan has been found by equilibration studies to have an equatorial preference of ca. 0.8 kcal mol^{-1} at 298K.[118] The source of disquiet is the axial preference of 0.085 kcal mol^{-1} assigned to the bromide (**22c**) by n.m.r. studies.[115] It should follow that at low temperatures, where the rate of radical destruction exceeds the rate of chair - chair inversion, the proportion of axial radicals should more closely reflect the equilibrium condition of the precursor bromide and should at least be of observable magnitude.

The temperature below which the rate of radical destruction exceeds the rate of inversion can be approximated. The rate of radical termination can be approximated after correction for the

viscosity of cyclopropane[119] by the Arrhenius equation given by Fischer[120] for t-butyl radicals in n-heptane:

$$\log(2k_t/dm^{-3}mol^{-1}s^{-1}) = 11.63 - (2.3\ kcal\ mol^{-1}/2.3RT)$$

The concentration of photochemically generated alkyl radicals is normally[121] ca. 10^{-7} mol dm^{-3}. The ring inversion is expected to have an activation energy of between 9.0 and 10.0 kcal mol^{-1} and a pre-exponential factor of 10^{13} which is normal for unimolecular reactions.

From this, the temperature below which the rate of termination exceeds the rate of inversion lies in the range 200 - 210K. On this basis, if the n.m.r interpretation is correct we would expect to see the axial conformer in the e.s.r. below this temperature range.

The n.m.r. study uses *cis*-2-methyl-5-bromomethyl-1,3-dioxan as its source of a δ value for axial bromomethyl. Inspection of the data from reference 115 (**Table 3**) does indeed lead one to the conclusion that (22c) has a slight axial preference. However, when these figures are compared with the n.m.r. data obtained for the same compounds in a different solvent, the picture becomes less clear, this is also the case when the data for the 2-t-butyl substituted 5-bromomethyl-1,3-dioxanes from reference 116 are considered. Either the solvent effect on the axial preference, or the error in the n.m.r. study, is greater than 0.085 kcal mol^{-1} and the bromomethyl group in (22c) has a slight equatorial preference in cyclopropane as the e.s.r. study has indicated.

3.4 Experimental

E.s.r. spectra were recorded on Bruker ER 200 D and Varian E104 instruments. Samples were made up in spectrosil tubes and degassed by several freeze-pump-thaw cycles. They were irradiated in the cavity of the spectrometer with light from a 500W super-pressure Hg arc or a 1000W high pressure Hg arc. Starting materials were obtained commercially unless otherwise indicated. Otherwise basic experimental procedures were performed using the instruments and methods described at the beginning of Section 2.4.

2-bromomethyl-4,7-dihydro-1,3-dioxepin (3a). 2-butene-1,4-diol (8.8g, 100 mmol) and bromoacetaldehyde dimethyl acetal (33.8g, 200mmol) were mixed with ca. 2mg of *p*-toluene sulphonic acid. The mixture was warmed in a distillation apparatus. Methanol and the excess of bromoacetaldehyde dimethyl acetal were removed by distillation. The residue was purified by distillation on a Büchi Kugelrohr to give the title acetal (**3a**) as a colourless oil (13.8g, 72%), b.p. 75°C/1 Torr; δ_H(80MHz) 3.4(2H, d, J=6), 4.0 - 4.7(4H, m), 5.0(1H, t, J=6), 5.7(2H, t, J=2); δ_C(75MHz) 31.4(1C), 65.7(2C), 102.2(1C), 129.2(2C); m/z(%) 125(21), 123(25), 99(29), 69(30), 53(10) and 41(100).

2-chloromethyl-4,7-dihydro-1,3-dioxepin (3b). 2-butene-1,4-diol (9.4g, 100 mmol) and chloroacetaldehyde dimethyl acetal (13.7g, 110 mmol) were mixed with ca. 2mg of *p*-toluene sulphonic

acid. The mixture was warmed in a distillation apparatus. Methanol and unreacted chloroacetaldehyde dimethyl acetal were distilled out. The residue was purified by distillation on a Büchi Kugelrohr to give the title acetal (**3b**) as a colourless liquid (8.3g, 56%), b.p. 58°C/1 Torr (lit[11a], 63°C/12Torr); δ_H(80MHz) 3.5(2H, d, J=5), 4.0 - 4.6(4H, m), 4.9(1H, t, J=5), 5.7(2H, t, J=2); δ_C(75MHz) 43.6(1C), 65.9(2C), 102.5(1C), 129.3(2C); m/z(%) 150(2), 148(6), 99(15), 81(38), 69(93) and 41(100).

2-bromomethyl-4,7-dihydro-2-methyl-1,3-dioxepin ***(8).*** 2-butene-1,4-diol (1.7g, 19mmol) and 1-bromo-2,2'-dimethoxy propane (4.8g, 26mmol) were mixed with a small amount of *p*-toluene sulphonic acid. The mixture was warmed in a distillation apparatus. Methanol and unreacted 1-bromo-2,2'-dimethoxy propane were distilled out. The residue was purified by distillation on a Büchi Kugelrohr to give the title ketal (**8**) (3.6g, 91%), b.p. 84°C/1Torr (lit[22], 116°C/10Torr); δ_H(80MHz) 1.55(3H, s), 3.5(2H, s), 4.3(4H, d, J=2), 5.65(2H, t, J=2); δ_C(75MHz) 20.9(1C), 34.7(1C), 62.0(2C), 101.7(1C), 129.1(2C); m/z(%) 139(7), 137(9), 123(2), 121(3), 113(55), 95(2), 93(3), 69(9), 57(10) and 43(100).

Reduction of 2-bromomethyl-4,7-dihydro-1,3-dioxepin (3a) with Tri-n-butyltin Hydride. Bromide (**3a**) (1.0g, 52mmol) was placed in a pyrex tube, degassed by bubbling nitrogen, heated to 97°C and irradiated with light from a 250W medium pressure Hg arc while Bu_3SnH (1.6g, 55mmol) was added dropwise over 20 minutes. Photolysis was continued for a further 100 minutes at 95 - 97°C. The products of the reaction were distilled directly out of the

reaction mixture at atmospheric pressure on a Büchi Kugelrohr (0.30g, 51 mol%). The mixture was analysed by g.l.c. which showed four components.The components were separated by preparative g.l.c. on a 4.5m × 1cm carbowax 20M column at 150°C. The first eluted component (<1 rel%) was not identified. The second eluted component (97 rel%) was 4,7-dihydro-2-methyldioxepin (**5**); δ_H(300MHz) 1.4(3H, d, J=6), 4.1(2H, d, J=14), 4.4(2H, d, J=14), 5.0(1H, q, J=6), 5.7(2H, m); δ_C(75MHz) 20.0(1C), 64.7(2C), 101.2(1C), 129.9(2C); m/z(%) 73(3), 69(18), 53(6), 45(100), 41(77) and 39(97). The third eluted component was bromoacetaldehyde dimethyl acetal (1 rel%) δ_H(300MHz) 3.4(2H, d, J=6), 3.4(6H, s), 4.6(1H, t, J=6). The fourth eluted component (1 rel%) was 2,7-dioxabicyclo[3.2.1]octane (**6**) ; δ_H(300MHz) 1.4 - 2.0(4H, m), 2.6(1H, bs), 3.4 - 4.0(4H, m), 5.0(1H, m); δ_C(75MHz) 30.0, 32.4, 38.5, 59.4, 72.4, 99.3; m/z(%) 114(m^+, 15), 84(25), 67(79), 55(100) and 41(78).

Reduction of 2-bromomethyl-4,7-dihydro-1,3-dioxepin (3a) with Triphenyltin Hydride. Bromide (**3a**) (0.5g, 26mmol) was placed in a pyrex tube, degassed by bubbling nitrogen, heated to 155°C and irradiated with light from a 250W, medium pressure Hg arc while Ph_3SnH (1.0g, 28mmol) was added over 30 minutes. Photolysis was continued for a further 1.5 hours. The reaction mixture was analysed by g.l.c. and g.c.m.s. The major product component (>95 mol%) was identified as 4,7-dihydro-2-methyldioxepin (**5**) by comparison with an authentic sample.

Reduction of 2-bromomethyl-4,7-dihydro-1,3-dioxepin (3a) with Tris(trimethylsilyl)silane[27,123]. Bromide (**3a**) (0.5g, 26mmol) and tris(trimethylsilyl) silane (0.7g, 28mmol) were dissolved in 2ml

of hexadecane in a pyrex tube, degassed by bubbling nitrogen, heated to 80°C and irradiated with light from a 250W, medium pressure Hg arc for 45 minutes. By the end of this time a quantity of a black oil had separated from the solution. G.lc. analysis of the reaction mixture indicated that most of the bromide (**3a**) was unreacted. The major product component (>95 rel.%) was identified as 4,7-dihydro-2-methyl-1,3-dioxepin (**5**) by comparison of its retention time with that of an authentic sample.

Reduction of 2-bromomethyl-2-methyl-4,7-dihydro-1,3-dioxepin (8) with Tributyltin Hydride. Bromide (8) (1.0g, 48mmol) was placed in a pyrex tube, degassed by bubbling nitrogen, heated to 125°C and irradiated with light from a 250W medium pressure Hg arc while Bu_3SnH (1.54g, 53mmol) was added over 10 minutes. Photolysis was continued for a further hour. The reaction mixture was extracted with 10ml of ether. The ether solution was washed with 5ml dilute aqueous KF solution, dried (Na_2SO_4) and evaporated. The residue was distilled on a Büchi Kugelrohr to give a colourless liquid (0.36g, 58%) which boiled over the range 85 - 110°C/15Torr. G.l.c. analysis showed two major components. The components were separated on a 15 × 2 cm neutral alumina column eluted with 120ml of 2% ether in pentane, 100ml 10% ether in pentane and 50ml ether. The first component (20 mol%), eluted in the second fraction, was 4,7-dihydro-2,2-dimethyl-1,3-dioxepin (**11**); δ_H(300MHz) 1.4(6H, s), 4.2(4H, m), 5.8(2H, m) (lit(60MHz)[124]; δ_C[4](75MHz) 24.0(2C), 61.4(2C), 101.9(1C), 129.5(2C); m/z(%) 113(8), 69(25), 59(100), 43(72). The second eluted component (80 mol%), eluted in the third fraction was 1-methyl-2,7-dioxabicyclo[3.2.1]octane (**10**); δ_H(300MHz) 1.4(3H, s),

1.4(1H, bs), 1.6 - 1.9(3H, m), 2.6(1H, bs), 3.7 - 4.0(4H, m); δ_C(75MHz) 23.8(CH_3), 29.6(CH_2), 34.5(CH), 42.5(CH_2), 60.4(CH_2), 72.9(CH_2), 105.1(C); m/z(%) 128(m^+, 8), 97(15), 83(32), 67(20), 55(17) and 43(100).

Hydrolysis of 1-methyl-2,7-dioxabicyclo[3.2.1]octane (10). (**10**) (70mg, 547μmol) 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 20ml ether which was dried and evaporated to leave a clear liquid residue (50mg, 63%) identified as 6-hydroxy-4-(hydroxymethyl) hexan-2-one (**12**); δ_H(300Hz) 1.8(1H, bs, absent in presence of D_2O), 2.2(6H, m), 2.6(3H, m), 3.3(1H, dd, J_1=8, J_2=6), 3.7 - 4.9(2H, m), 4.9(1H, dd, J_1=8, J_2=6); δ_C(75MHz) 30.1(CH), 32.1(CH_2), 34.3(CH_3), 47.4(CH_2), 67.6(CH_2), 73.0(CH_2), 207.6(CO); m/z(%) 111(1), 97(1), 83(3), 70(71), 58(5), 55(17) and 43(100); ν(OH) = 3370cm^{-1}, broad.

Kinetics of the Tributyltin Hydride Reduction of 2-bromomethyl-4,7-dihydro-2-methyl-1,3-dioxepin (8). Hexadecane (500μl) was placed in a pyrex tube, heated to the desired temperature and degassed by bubbling nitrogen for ca. 10 minutes. To this was added the bromide (**8**) (20μl), octane (23μl) as an internal standard and Bu_3SnH (see **Table 1**). The solution was irradiated with light from a 250W medium pressure Hg arc for one hour. The solutions were analysed by g.l.c. The values of k_c/k_H were obtained at each temperature from the initial Bu_3SnH concentration and the final product concentrations using an integrated rate equation[29,89]. The best values of k_c/k_H were

located with an iterative computer program based on NAG routine C05AXF.

5-bromomethyl-1,3-dioxan (22c). Diethyl bis(hydroxymethyl) malonate (22.02g, 0.1mol), paraformaldehyde (9.60g, 0.3mol) and *p*-toluene sulphonic acid (0.2g) were disolved in ethanol (50ml) and benzene (250ml). The solution was refluxed for 1 hour. The water produced was removed azeotropically by distilling out the benzene and ethanol. The residue was distilled on a Büchi Kugelrohr to give 5,5-dicarbethoxy-1,3-dioxan (18.5g, 80%); δ_H(300MHz) 1.3(6H, t, J=8), 4.2(4H, q, J=8), 4.3(4H, s), 4.8(2H, s). 5,5-Dicarbethoxy-1,3-dioxan (18.4g, 79mmol) was added to KOH (25.1g) in ethanol (210ml) and the solution refluxed for 1 hour. Successive 30ml portions of ethanol were distilled out and replaced with water. When about 210ml of distillate had been collected, the remaining solution was cooled in ice and conc. HCl added dropwise with stirring until it was acidic. The solution was extracted with 3 x 100ml ether, the extracts were combined, dried (Na_2SO_4), decolourised (charcoal) and the solvent evaporated to give 1,3-dioxan-5,5-dicarboxylic acid (8.5g, 60%); δ_H(80MHz) 4.2(4H, s), 4.8(2H, s), 4.9(2H, bs). 1,3-dioxan-5,5-dicarboxylic acid (8.35g, 47mmol) was refluxed in anhydrous pyridine for 90 minutes. The solution was cooled over ice/salt while 20% HCl (50ml) was added dropwise. The acidic solution was extracted with ether (3 x 50ml). The extracts were combined and washed with 10% HCl (30ml) then saturated NaCl (30ml), dried ($MgSO_4$) and evaporated to give 1,3-dioxan-5-carboxylic acid (4.20g, 68%); δ_H(80MHz) 2.7(1H, m), 3.7 -4.2(4H, ABX, δ_A3.8, δ_B4.0, J_{AX}=7, J_{BX}=5, J_{AB}=12), 4.6(1H, d, J=7), 4.8(1H, d, J=7), 3.2 - 5.0(bs). 1,3-Dioxan-5-carboxylic acid (2.64g, 20mmol) in

the minimum volume of ether was added to ice-cold $LiAlH_4$ (2.00g) in dry ether (20ml). The suspension was then refluxed for 3 hours, cooled, water was added and the ether layer decanted. Dilute sulphuric acid was added to the aqueous layer which was then extracted several times with ether. The ether fractions were combined, dried (Na_2SO_4) and evaporated. The residual oil was distilled on a Büchi Kugelrohr to give 5-hydroxymethyl-1,3-dioxan (1.14g, 48%) as a colourless oil; δ_H(80MHz) 1.9(1H, m), 2.9(1H, bs), 3.7(2H, d, J=7), 3.6 - 4.1(4H, ABX, δ_A3.7, δ_B4.0, J_{AX}=6, J_{BX}=4, J_{AB}=11), 4.8(2H, AB, degenerate) (lit.[115]). 5-hydroxymethyl-1,3-dioxan (1.70g, 14mmol) and carbon tetrabromide (4.78g, 14mmol) were dissolved in benzene (7ml), heated to 60°C and stirred while triphenyl phosphine (3.77g, 14mmol) was added in small portions. The solvent was evaporated and the product was distilled directly out of the residue on a Büchi Kugelrohr to give 5-bromomethyl-1,3-dioxan (1.82g, 72%); δ_H(60MHz) 2.1(1H, m), 3.5(2H, d, J=7), 3.6 - 4.2(4H, ABX, δ_A3.8, δ_B4.1, J_{AX}=5, J_{BX}=4, J_{AB}=12) (lit.[115]).

Cis- and trans- 5-bromomethyl-2-methyl-1,3-dioxan (22a) and (22b). Diethyl bis(hydroxymethyl) malonate (22.02g, 100mmol), acetal (23.6g, 200mmol) and *p*-toluene sulphonic acid (0.2g) were mixed and heated to 80°C in a distillation apparatus. The ethanol formed and the excess acetal were removed by distillation. The residue was distilled under reduced pressure to give 5,5-dicarbethoxy-2-methyl-1,3-dioxan (22.47g, 91%), b.p. 146°C/15Torr; δ_H(80MHz) 1.2(3H, t, J=7), 1.3(3H, t, J=7), 1.3(3H, d, J=2), 3.8(1H, t, J=1), 4.0(1H, t, J=1), 4.2(2H, q, J=7), 4.3(2H, q, J=7), 4.6(2H, m), 4.7(1H, t, J=1). 5,5-Dicarbethoxy-2-methyl-1,3-dioxan (22.40g, 91mmol) was added to NaOH (21.8g) in

ethanol (180ml). The solution was refluxed for 1hour. Ethanol was removed by distillation in 30ml portions and was progressively replaced with water. When virtually all the ethanol had been removed, the aqueous solution was cooled in ice and acidified with conc. HCl. The acidic solution was extracted with ether (3 × 100ml). The extracts were combined, dried ($MgSO_4$), decolourised (charcoal) and evaporated to give 2-methyl-1,3-dioxan-5,5-dicarboxylic acid (12.6g, 73%); δ_H(300MHz) 1.2(3H, d, J=4), 3.9(2H, d, J=12), 4.4(2H, d, J=12), 4.7(1H, q, J=4), 13.3(2H, bs). 2-Methyl-1,3-dioxan-5,5-dicarboxylic acid (13.00g, 68mmol) was stirred and refluxed in anhydrous pyridine (15ml) for 1 hour. The solution was cooled in ice - salt and 20% aqueous HCl (75ml) was added dropwise. The acidic solution was extracted with ether (3 × 100ml), the ether layers were combined, dried ($MgSO_4$), decolourised (charcoal) and evaporated to give a mixture of *cis*- and *trans*- 2-methyl-1,3-dioxan-5-carboxylic acid (3.46g, 35%). N.m.r. analysis indicated that the mixture was ca. 70% trans isomer; δ_H(300MHz) 1.2(3H, d, J=5), 2.5(1H, m), 3.5(1H, bs), 3.6 - 4.2 (ABX, δ_A4.1, δ_B3.7, J_{AX}=5, J_{BX}=11, JAB=11), 4.6(1H, q, J=5) and 30% *cis* isomer; δ_H(300MHz) 1.1(3H, d, J=5), 2.3(1H, m), 3.3(1H, bs), 3.8(2H, d, J=11), 4.3(2H, d, J=11), 4.6(1H, q, J=5). The mixture of 2-methyl-1,3-dioxan-5-carboxylic acids (3.40g, 23mmol) was dissolved in dry ether (20ml) and added to ice cold $LiAlH_4$ in dry ether (40ml) the suspension was then refluxed for 3 hours, water was added and the ether layer decanted. Dilute sulphuric acid was added to the aqueous layer which was then extracted several times with ether. The ether layers were combined, dried (Na_2SO_4) and evaporated to leave an oil (2.91g after distillation on a Büchi Kugelrohr). This oil and carbon tetrabromide (7.30g) were dissolved in benzene (11ml) and heated

to 60°C when triphenylphosphine (5.76g) was added slowly. The solvent was evaporated and *cis* and *trans* 5-bromomethyl-2-methyl-1,3-dioxane were distilled directly out of the residue (1.8g, 40%). G.l.c. and n.m.r analysis indicated that the mixture was 58% *cis*-5-bromomethyl-2-methyl-1,3-dioxan; δ_H(80MHz) 1.3(3H, d, J=5), 1.6 - 1.9(1H, m), 3.8(2H, d, J=8), 4.0(2H, m), 4.1(2H, m), 4.7(1H, q, J=5), (lit.[115]) and 42% *trans*-5-bromomethyl-2-methyl-1,3-dioxane; δ_H(80MHz) 1.3(3H, d, J=5), 2.1 - 2.6(1H, m), 3.1(2H, d, J=7), 3.3 - 4.3(4H, ABX, δ_A4.2, δ_B3.4, J_{AX}=5, J_{BX}=11, J_{AB}=11), 4.6(1H, q, J=5), (lit.[115]). The two isomers were separated by preparative g.l.c. on a 3m × 1cm FFAP column at 110°C

CHAPTER 4

CYCLOHEPTATRIENE

4.1. Introduction.

It has now been well established that the boat axial conformation of cyclohept-4-enylmethyl type radicals allows transannular cyclisation of the radical to occur.

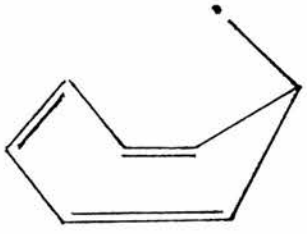
It seemed that an appropriate ring system to examine in this context was cycloheptatriene. This molecule is known to exist in a boat conformation (**Scheme 1**)). It inverts via a planar intermediate and the free energy barrier associated with this transformation has been determined to be 6.1 kcal mol^{-1}.[125] This is of the same order as the chair inversion barrier in cycloheptene and certainly allows rapid interconversion at room temperature.

Scheme 1

As with 4,7-dihydrodioxepin, the introduction of different features to the 7 - membered ring, in this case the alteration of bond orders, brings with it changes in bond lengths and angles. Unlike the case of 4,7-dihydrodioxepin, the nature of these changes is documented in the literature and the data for cycloheptatriene[126] are compared with the data for the cycloheptene boat conformer, which were obtained from an MM2 treatment of cycloheptene, in **Figure 1.**

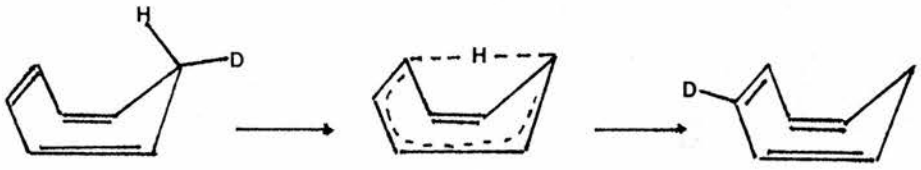
Figure 1

Although the cycloheptatriene ring is slightly flatter than the cycloheptene boat, the more compact size of the ring compensates for this and it appears that, in terms of the proximity of the radical centre to the double bond in the boat axial conformation of cyclohepta-2,4,6-trien-1-ylmethyl radical (1), transannular cyclisation is as feasible as it is in cyclohept-4-enylmethyl radical.



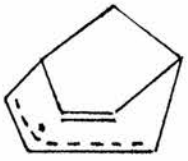
(1)

Further, it is known[127] that cycloheptatriene undergoes a 1,5 hydrogen transfer (Scheme 2) The transition state for which requires a reasonable proximity of the 4,5 and 7 carbons.



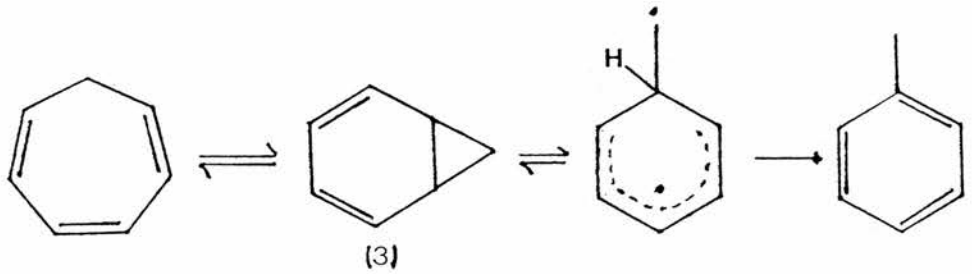
Scheme 2

If the radical (1) were to cyclise, the product radical would be an allyl type radical (2), if the C2-C3-C4 portion of the bicycle was sufficiently planar. It would therefore be stabilised relative to bicyclo[3.2.1]octan-2-yl radical. If the radical addition is concerted such product stabilisation should enhance the rate of cyclisation relative to that for the cyclohept-4-enyl methyl radical.[128]



(2)

There are also very important differences in the reactivity of cycloheptatriene compared to cycloheptene. Most importantly, cycloheptatriene is believed to be in equilibrium with norcaradiene (3)[129] which can isomerise to toluene (Scheme 3).



(3)

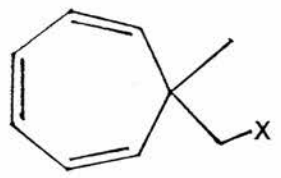
Scheme 3

The norcaradiene structure is known to be stabilised by electron withdrawing substituents, hence it has been possible to isolate 7,7-dicyanonorcaradiene.[130] The energy difference between cycloheptatriene and norcaradiene has been estimated as 11 ± 4 kcal mol^{-1} or 4.0 - 4.5 kcal mol^{-1}.[131,132] It follows from these earlier results that any rearrangement of the cyclohepta-2,4,6-trien-1-ylmethyl radical is expected to be in competition with rearrangements of the corresponding norcaradienyl radical.

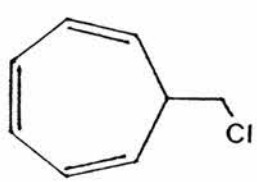
4.2 The Cyclohepta-2,4,6-trien-1-ylmethyl radical.

Synthesis of a suitable precursor.

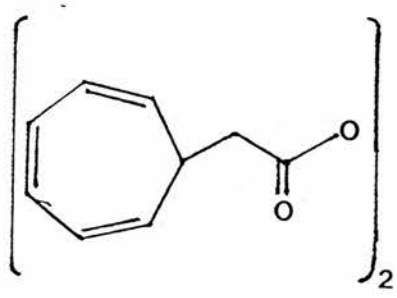
Three precursors for the radicals of type (**1**) were considered, the alkyl halides (**4**) and (**5**) and the diacylperoxide (6).



(4)
a) X = Br
b) X = Cl

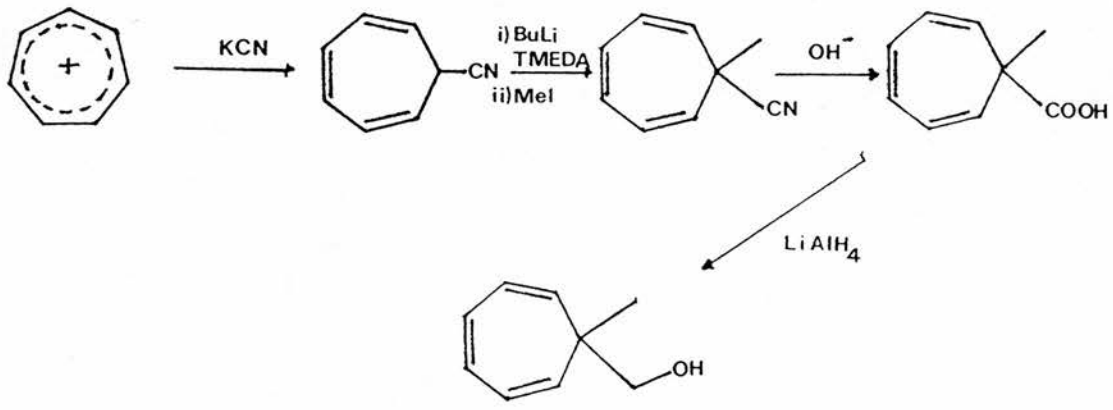


(5)



(6)

In pursuit of the alkyl halides (**4a**) and (**4b**), the alcohol (**7**) was synthesised straightforwardly according to familiar procedures (**Scheme 4**).

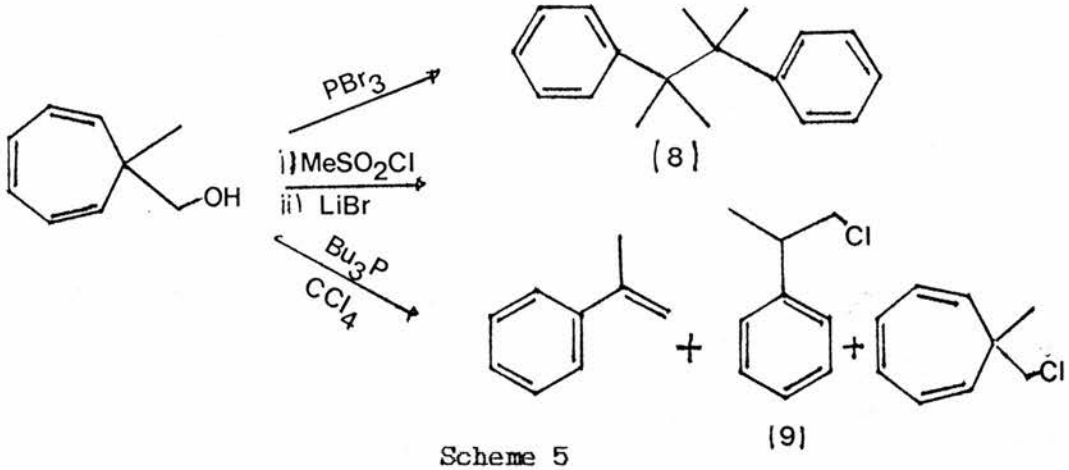


(7)

Scheme 4

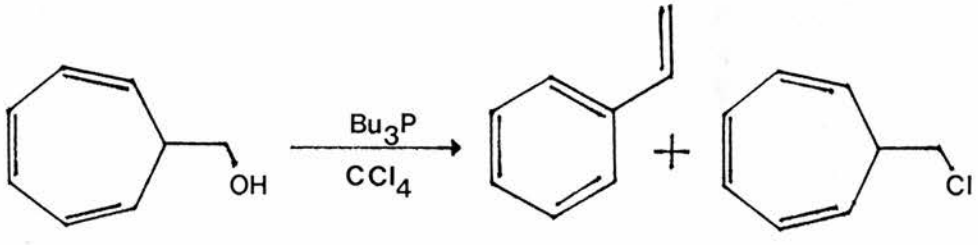
The synthesis of the bromide (**4a**) was attempted in two different ways (**Scheme 5**). In both cases aromatic compounds were obtained. It was only possible to identify the product of the reaction with PBr_3 which was a dimer of α-methylstyrene (**8**). The $MeSO_2Cl/LiBr$ reaction gave a mixture of products which could not be identified. N.m.r. and mass spectra revealed that the mixture contained compounds with m^+/z = 236 which were probably other dimers of α-methylstyrene and a compound which was probably a derivative of α-methylstyrene. α-methylstyrene itself was not present, nor was there any evidence of cycloheptatriene derivatives.

Preparation of the corresponding chloride (**4b**) by reaction of the alcohol with a phosphine in CCl_4[136] was more successful although it was found that the preparation had to be carried out under the mildest conditions or an isomeric product, tentatively identified as β-chlorocumene (**9**) was formed (**Scheme 5**). A substantial amount of α-methylstyrene was formed during both procedures. An attempt to prepare this chloride by reaction of (**7**) with thionyl chloride was less successful.



Scheme 5

The unsubstituted chloride (**5**) was sysnthesised in the same way (**Scheme 6**).

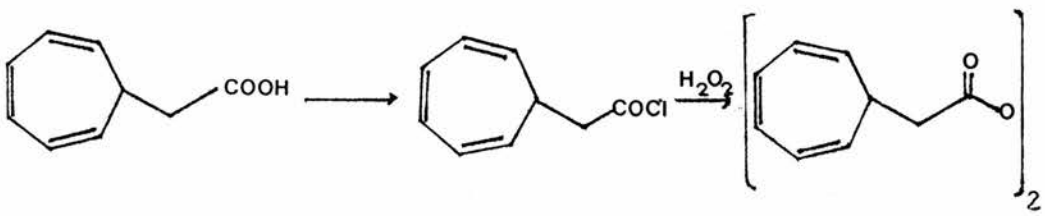


Scheme 6

The mixtures of chlorides and styrenes which were obtained were found to be impossible to separate using available techniques. Preparative g.l.c. of the mixture of (**4b**) and α-

methylstyrene gave α-methylstyrene as the only identifiable eluted product, even when the column was maintained as close to room temperature as the instrument would permit. It seems likely that the chloride decomposed or rearranged in the outlet tube of the chromatograph which was neccessarily at a temperature of 150°C or above. Distillation which involved heating was out of the question because of the instability of the chloride although distillation at room or very slightly elevated temperatures at low pressure did produce mixtures which were enriched in chloride, with the styrenes being more volatile. Conventional column chromatography of the mixtures on silica also destroyed the chloride and only the styrene was eluted.

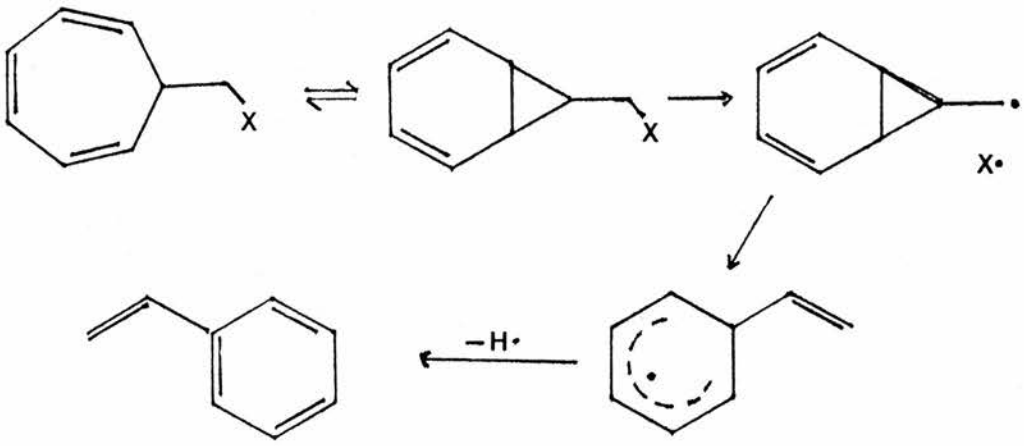
The diacylperoxide (6) was synthesised according to literature procedures (**Scheme 7**).[134]



Scheme 7

The formation of styrenes in the syntheses of the alkyl halides can be understood in terms of opening of the 3 - membered ring in the norcaradiene isomer of the target molecules. It is possible that this arises from instability of the transition states for the reactions. However, a simpler explanation is that ring opening is a result of homolysis of the carbon - halogen bond (**Scheme 8**). This is a more favoured process for C-Br bonds than for C-Cl bonds and the results noted above reflect this. The

mixtures of chlorides and styrenes which were prepared were found to be quite stable at 4°C. The formation of styrenes in the reactions with Bu_3P, which were carried out at ice - temperature, seemed at first to contradict the theory that simple homolysis was the reason for their formation; why did styrene formation not continue after the reaction was completed? The reaction of the alcohol with Bu_3P was highly exothermic and although the reaction mixture was immersed in an ice/salt bath, it seemed quite probable that local heating in the solution was responsible for the decomposition of the newly formed chloride.



Scheme 8

The formation of an isomer of the chloride in the reaction with triphenylphosphine suggests that another ring opening pathway is available which is presumably exactly analogous to the norcaradiene - toluene rearrangement shown in **Scheme 3**. A trace of this isomer was also formed in the tributylphosphine reactions. The rearrangement of unsubstituted cycloheptatriene to toluene is very slow at room temperature - reflecting the stability of the cyclopropane ring in the norcaradiene isomer. If the tentative identification of the isomeric chloride is correct

then that implies that the substituents on (**4b**) increase the rate of ring opening in the norcaradienyl form.

Generation of the radicals - Results and Discussion.

The mixture of the methyl substituted chloride (**4b**) and α-methylstyrene was reduced at room temperature with tributyltin hydride in a photochemically initiated reaction. Analysis of the product mixture by g.c.m.s. revealed a large number of components. Many of these components have not been properly characterised as they could not be satisfactorily separated by preparative g.l.c. The data obtained and tentative interpretations are given at the end of the experimental section of this chapter (**Table 2**). There were at least five different chlorides present in the mixture which had the molecular formula $C_9H_{11}Cl$, i.e. the same as the parent chloride, this indicated that the chloride was rearranging under these conditions. It is possible that some of these isomers arise from the formation of chlorine atoms as a result of photolysis of the starting material and readdition of chlorine to the various unsaturated functions present in the reaction mixture. Cycloheptatriene is also known to photolytically rearrange to bicyclo[3.2.0]hepta-2,6-dienes.[135]

At least three non - halogenated species were also present in the product mixture. When an attempt was made to separate the mixture by preparative g.l.c., the only component which could be positively identified was α-methylstyrene. As the proportion of this relative to the rest of the mixture was greater than in the starting material and as it was expected that some α-methylstyrene polymerisation would have occured during the

photolysis, it was concluded that α-methylstyrene was a product of the reaction. In fact, it is very likely that α-methylstyrene was very much the major product of the reaction. The g.c.m.s. analysis suggests that non - halogenated products account for only about 75 - 80% of the product mixture. Tin hydride reductions do not normally proceed so inefficiently and this apparent inefficiency can be explained by suggesting that poly(α-methylstyrene) is also a product of the reaction. All the other eluted fractions were contaminated with this compound which may indicate that some of the other constituents rearranged to α-methylstyrene in the outlet of the chromatograph. No component had a significant proportion of olefinic signal (other than the styrenes) and it was concluded that transannular cyclisation had not occured.

When the mixture of the unsubstituted chloride (5) and styrene was reduced in the same way the product mixture was found by g.c.m.s. to contain at least three chlorides with molecular formula C_8H_9Cl, including the starting material, some styrene and some minor products. The chlorides and minor products were not fully characterised and the data obtained on them is given at the end of the experimental section (**Table 3**). On this occasion it was not clear from the relative amount of styrene whether it was a product of the reduction or not although for the same reasons that were mentioned above, the low proportion of non - halogenated products which was observed by g.c.m.s. suggested that polystyrene was probably the major product of the reaction. Again it was concluded that transannular cyclisation had not taken place to any significant extent.

The diacylperoxide (**6**) was decomposed in refluxing toluene and in irradiated pentane at room temperature. Toluene was used as a solvent for the thermal decomposition as its benzylic hydrogens are readily abstracted by radicals and it was hoped that it would be possible to observe the reduced products of any radical rearrangement. In both cases styrene was formed. This added support to the conclusion that styrene is a product of radical (1) formation. In this experiment there was no styrene in the starting material and (1) is very likely to be the initial product from peroxide decomposition. At least three compounds with fragment or molecular ions with m/z > 200 were also observed by g.c.m.s., these were probably dimers of styrene and/or the various other possible radicals. Unfortunately their retention times were such that it was not possible to obtain tolerably separated peaks on any available preparative g.l.c. column without simultaneously broadening the signals beyond recognition. Mass spectral details are given at the end of the experimental section (**Table 4**)

When a solution of the chloride (**4b**)/α-methylstyrene mixture with hexamethylditin and di-t-butylperoxide in t-butylbenzene was irradiated in the cavity of the e.s.r. spectrometer no spectrum could be observed over the temperature range 205 - 240K. It seems likely that the explanation for this is simply that there are too many different radicals in the system, the spectra from which cancel each other out. Irradiation of a solution of the peroxide (**6**) in pentane in the cavity of the e.s.r. spectrometer did not result in the observation of a spectrum over the temperature range 170 - 290K, though the formation of bubbles indicated that the decomposition was proceeding.

The Arrhenius equation for the thermal rearrangement of cycloheptatriene to toluene (Figure 5.) has been determined to be $\log k = 13.9 - 52{,}200/2.3RT$[136] which gives $k_{298} = 3.7 \times 10^{-25}$ This is not going to be competitive with chlorine abstraction and formation of the radical (**1**). It seems likely that aromatisation occurs via ring opening of the cyclopropylmethyl radical in the norcaradienyl form of (**1**) according to the mechanism which was shown in **Scheme 6.**

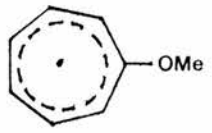
Cyclopropylmethyl radicals ring open with low activation energies and high rate constants compared with cyclopropyl radicals.[3] k is typically around 10^8 s^{-1}.

The fact that this process apparently outcompetes transannular cyclisation of (**1**) indicates that the rate constant for the isomerisation of (**1**) to norcaradienylmethyl radical is also faster than the expected transannular cyclisation rate of $10^5 - 10^6 s^{-1}$ at 298K.

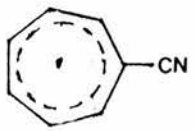
It appears that this rearrangement of (**1**) combines with photochemical and thermal rearrangements of the precursors (**4**) - (**6**) under the reaction conditions which have been applied in this study to create a tangled web of reaction pathways leading to complicated mixtures of products. It is clear that transannular cyclisation of (**1**) is not a favoured process. This contrast with the other 7 - membered ring substituted radicals is a result of the more diverse chemistry of cycloheptatriene rather than its conformational properties.

4.3. E.S.R. of Substituted Cycloheptatrienyl Radicals.

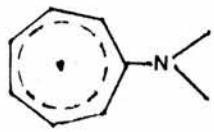
1-substituted cyclohepta-2,4,6-trienes have a labile tertiary hydrogen at the 1-position on the ring. It was expected that such a hydrogen could be readily abstracted by butoxy radicals. The e.s.r. spectra of radicals (**10**), (**11**) and (**12**) were obtained by photolysing solutions of the corresponding cycloheptatriene derivatives and di-t-butylperoxide in t-butylbenzene in the cavity of the e.s.r. spectrometer. The spectra (**Figures 2 and 3**) and the hyperfine splitting values are compared with those of related radicals which have been reported in the literature (**Table 1**).



(10)



(11)



(12)

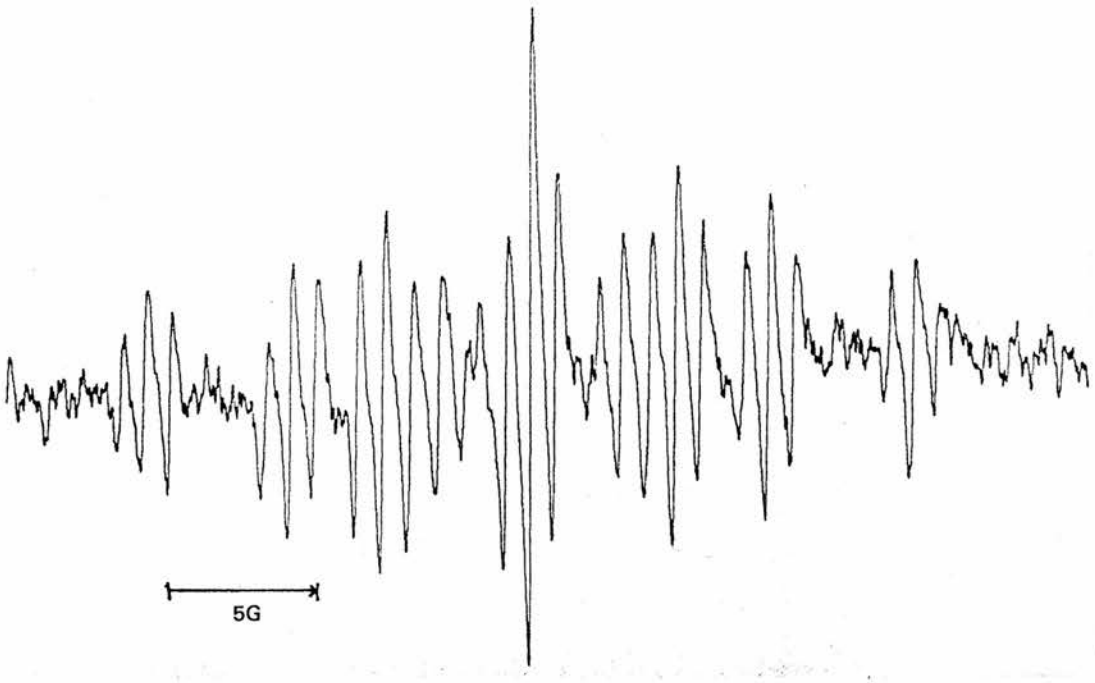


Figure 2: E.s.r. spectrum of (**10**) in t-BuPh at 260K with a(2H)=8.2G, a(2H)=5.0G and a(2H)=0.9G.

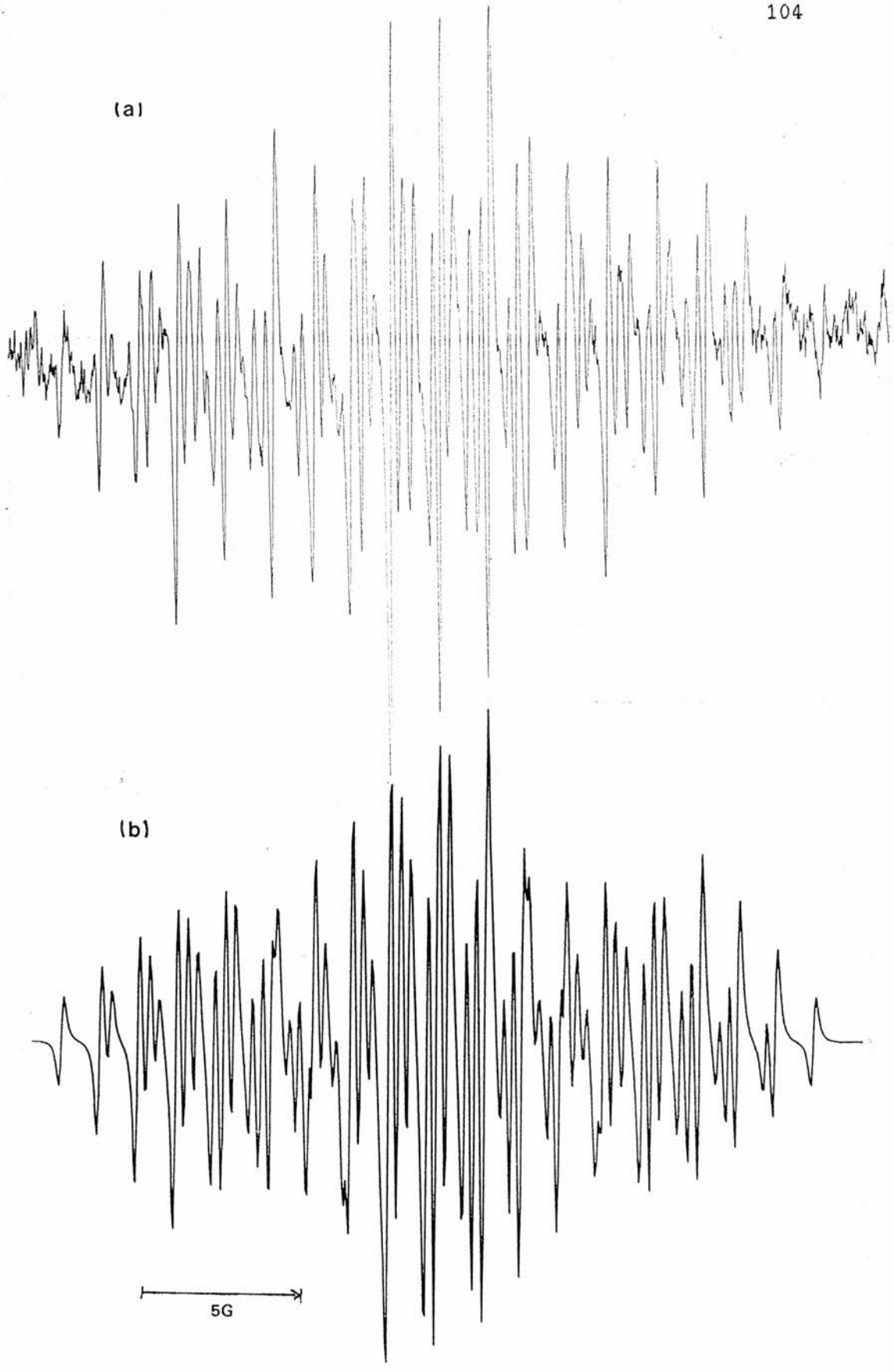


Figure 3: (a) E.s.r. spectrum of (11) in t-BuPh at 220K and (b) simulated spectrum for a(2H)=1.20G, a(N)=1.53G, a(2H)=2.40G, a(2H)=6.79G

Table 1

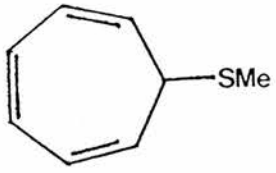
E.S.R. Hyperfine Splitting values (in Gauss) for substituted cycloheptatrienyl radicals

Substituent	Temp/K	H(2,7)	H(3,6)	H(4,5)	Other	Reference
H	212	3.91	3.91	3.91		137
CH_3	463	5.76	1.92	3.84	CH_3:1.92	138
Bu^t	295	4.91	2.77	4.18		139
C≡CMe	443	0.92	5.72	2.26	CH_3:4.48	140
$C_7H_7^-$	153	8.22	<0.3	5.02		141
O^-	300	8.58	0.10	5.05		142
OMe	260	8.2	0.9	5.0		This work
CN	220	1.20	6.79	2.40	N:1.53	This work
NMe_2	230	9.1	1.0	5.0	N:1.8	This work

By analogy with the acetylene in **Table 1** the splittings for the nitrile (**11**) can probably be assigned as a(H2,7)=1.20G, a(H3,6)=6.79G, a(H4,5)=2.40G and a(N)=1.53G. The OMe group is expected to be electron donating and the splittings can be assigned as a(H2,7)=8.2G, a(H3,6)=0.9G and a(H4,5)=5.0G.

Only very weak spectra could be obtained for the amine (**12**). This was apparently due to the amine's very pale yellow colour which intensified upon photolysis and which probably absorbed much of the incident light from the lamp. It was difficult to assign h.f.s. values to this spectrum as it was barely visible under high resolution conditions. The tentative assignments made were a(2H)=9.1G, a(2H)=5.0G, a(N)=1.8G and a(2H)=1.0G. This would be reasonably consistent with the results for the strongly electron donating substituents which are listed in **Table 1**.

The precursors for these radicals were synthesised by nucleophilic substitution on tropylium bromide. As detailed in the experimental section, it proved impossible to make some derivatives by this method. A clue as to why this may be the case was obtained by studying 1-thiomethoxycyclohepta-2,4,6-triene (13) in an e.s.r. experiment of the type described above. The spectrum obtained was a regular octet with a(7H) = 3.9G at 200K and was identified[137] as the C_7H_7 radical.



(13)

When (13), in t-butylbenzene solution, was irradiated in the absence of peroxide the same spectrum was observed. When the same solution was warmed, in the absence of light to 330K, again the C_7H_7 octet was clearly visible. It was weakly visible at temperatures as low as 330K and could not be observed above 350K.

It follows that (13) thermolyses and photolyses homolytically and is therefore both a thermal and photochemical source of thiomethoxyl radicals.

The observation of the tropylium radical at temperatures just above the ambient makes it likely that (13) slowly thermolyses at room temperature. The difficulty in obtaining some other cycloheptatriene derivatives may be associated with a similar thermal instability.

4.4 Experimental

Basic procedures were carried out as described in Chapter 2.

Tropylium Bromide. Cycloheptatriene (46.0g) in carbon tetrachloride (400ml) was cooled in an ice bath. Bromine (80.0g) in carbon tetrachloride (250ml) was added dropwise over a period of 4 hours. The solvent was removed in vacuo at room temperature. The residual dibromotropylidine was heated under water pump pressure at 50 - 70°C for 72 hours. The green solid formed was ground under CCl_4 and the mixture filtered under nitrogen and the solid dried under vacuum. The crude tropylium bromide was recrystallised from boiling ethanol (425ml) in a flask which had been flushed with nitrogen. Ethanol of crystallisation was removed in vacuo to leave pure tropylium bromide (27.9g, 32%), m.p. 208-210°C (lit.[143] 211°C); δ_H(60MHz) 9.4(7H, s).

1-cyanocyclohepta-2,4,6-triene. KCN (6.60g, 102mmol) in water (25ml) was added to tropylium bromide (10.00g, 58mmol) in water (25ml). The dark oil which separated was extracted with ether (3 x 25ml). The ether layers were combined, dried (Na_2SO_4) and evaporated. The residual oil was distilled on a Büchi Kugelrohr to give the title nitrile (5.52g, 81%), b.p. 132°C/15Torr[144]; δ_H(80MHz) 3.0(1H, t, J=6), 5.4(2H, dd, J_1=9, J_2=6)), 6.3(2H, m), 6.7(2H, dd, J_1=4, J_2=3).

1-cyano-1-methylcyclohepta-2,4,6-triene. 1-cyanocyclohepta-2,4,6-triene (5.0g, 43mmol) and N,N,N',N'-tetramethylethylene diamine (5.0g) were dissolved in THF (60ml), stirred and cooled to -78°C under nitrogen. 1.39M nBuLi in hexane (34ml) was added

slowly. The solution was stirred at -78°C for 30 minutes. MeI (9.0g) was added and the solution stirred for a further 2hours at low temperature then poured into water (300ml). The mixture was extracted with ether (3 × 100ml), the ether layers combined, dried (Na_2SO_4) and evaporated. The residue was distilled on a Büchi Kugelrohr to give the title compound as an off-white solid (4.0g, 71%), b.p. 92°C/1Torr; δ_H(80MHz)[145] 1.7(3H, s), 4.9(2H, d, J=9), 6.3(2H, m), 6.8(2H, m).

1-methylcyclohepta-2,4,6-trienyl-1-carboxylic acid. 1-cyano-1-methylcyclohepta-2,4,6-triene (7.5g, 57mmol) and NaOH (7.5g) were dissolved in a mixture of water (12ml) and methanol (40ml). The solution was refluxed for 5 hours, cooled, poured into water (100ml), the solution acidified with conc. HCl and extracted with ether (2 × 50ml). The ether layers were combined, dried (Na_2SO_4) and evaporated. The residue was recrystallised from a 1:1 mixture of light petroleum and ether to give white plates of the title compound (5.8g, 68%); δ_H(80MHz)[145] 1.0(3H, s), 3.9(2H, m), 6.0 - 6.5(4H, m).

1-hydroxymethyl-1-methylcyclohepta-2,4,6-triene ***(7).*** 1-methylcyclohepta-2,4,6-trienyl-1-carboxylic acid (7.5g, 50mmol) in dry ether (75ml) was added to $LiAlH_4$ (2.0g) in dry ether (100ml). The suspension was refluxed for 5.5 hours, cooled, water added, the ether layer decanted and dilute sulphuric acid added to the aqueous layer which was then extracted several times with ether. The ether layers were combined, dried (Na_2SO_4) and evaporated. The residual oil was distilled on a Büchi Kugelrohr to give the title compound (5.1g, 75%), b.p. 110°C/1Torr; δ_H(80MHz) 1.1(3H, s), 1.9(1H, bs), 3.3(2H, s), 5.1(2H, m), 6.1 -

6.6(4H, m); δ_C(75MHz) 21.2(1C), 41.3(1C), 65.7(1C), 125.2(2C), 129.5(2C), 130.1(2C); m/z 136(m^+, 2%), 117(15), 105(100), 91(16), 77(56), 65(15), 51(25) and 40(14).

Reaction of 1-hydroxymethyl-1-methylcyclohepta-2,4,6-triene (7) with methane sulphonyl chloride followed by lithium bromide. The alcohol (7) (3.0g, 22mmol) and triethylamine (3.1ml) were dissolved in dry methylene chloride (130ml) and cooled in ice. Methane sulphonyl chloride (2.0ml) was added over 10 minutes. The solution was warmed to room temperature over 1 hour, water was added, the methylene chloride layer was separated, washed with dilute HCl, brine and dilute bicarbonate solution, dried (Na_2SO_4) and evaporated at room temperature. The residual oil was added to LiBr (6.92g) in refluxing analar acetone (90ml), reflux was continued for 16 hours. The solution was cooled, filtered and the solvent evaporated. The residue was chromatographed on silica (25 x 2cm) with light petroleum (200ml) as the eluent. Petroleum was evaporated from the eluted material which was subsequently distilled on a Büchi Kugelrohr to give a colourless oil (2.1g). n.m.r. and mass spectral analysis indicated that this was a mixture of compounds but it was not possible to unambiguously identify any of them. The ^1H n.m.r. spectrum of the mixture contained an AB pattern at δ_A5.1 and δ_B4.8, J_{AB}=2, characteristic of compounds of the type PhC(X):CH_2. The mass spectrum of the mixture showed a peak at 236(82%) indicating that dimers of molecular formula $(C_9H_{10})_2$ were present.

Reaction of 1-hydroxymethyl-1-methylcyclohepta-2,4,6-triene (7) with Phosphorous Tribromide. The alcohol (7) (1.0g, 7.4mmol) and pyridine (0.12g, 1.4mmol) were dissolved in cyclopentane

(2.0ml) and cooled to -70°C. PBr_3 (0.81g, 2.3mmol) was added dropwise. The solution was stirred at -70°C for 2 hours then warmed to room temperature. Ice/water was added. The organic layer was washed with water, sodium carbonate solution then water, dried (Na_2SO_4), evaporated and the residue distilled on a Büchi Kugelrohr to give a clear oil (0.24g) which was identified as 2,3-dimethyl-2,3-diphenylbutane; δ_H(80MHz) 2.2(12H, s), 7.2 - 7.7(10H, m); δ_C(20MHz) 35.5(CH_3), 64.0(C), 125.7(CH), 127.7(CH), 128.3(CH), 146.8(C); m/z 236(60%), 221(40), 143(40), 118(100), 103(100), 91(100, 77(80), 63(20) and 51(50).

Reaction of 1-hydroxymethyl-1-methylcyclohepta-2,4,6-triene (7) with Triphenylphosphine in Carbon Tetrachloride. The alcohol (7) (1.00g, 6.5mmol) and triphenylphosphine (1.82g, 6.9mmol) were dissolved in carbon tetrachloride (13ml) and stirred under nitrogen at ca. 50°C for 5 hours. The solvent was evaporated and the volatile components of the residue were distilled out at between 20 and 60°C on the high vacuum line. G.c.m.s. analysis of the distillate showed it to contain three main components. It was attempted to separate these by preparative g.l.c. using a 4.5m × 1cm carbowax 20M column at 45°C. The first eluted component was identified as α-methylstyrene; δ_H(300MHz)[4] 2.1(3H, m), 5.0(1H, m), 5.3(1H, m), 7.1 - 7.3(3H, m), 7.4 - 7.5(2H, m). The second eluted component could not be collected; it apparently decomposed in the outlet of the chromatograph. Its mass spectrum is consistant with β-chlorocumene[146]; m/z 156(m^+,1%), 155(2), 154(m^+, 4%), 153(6), 140(1), 138(3), 118(82), 102(22), 90(63), 76(36), 61(11) and 50(100). The third eluted component was identified as the alcohol (7) by comparison of the data obtained with that obtained above. It was attempted to separate the three

components using conventional column chromatography on silica with light petroleum as the initial eluant followed by successively more polar mixtures of ether in light petroleum. Only α-methylstyrene was eluted.

Reaction of 1-hydroxymethyl-1-methylcyclohepta-2,4,6-triene (7) with Tributylphosphine in Carbon Tetrachloride. The alcohol (7) (0.40g, 7.4mmol) was dissolved in CCl_4 (5ml). The solution was cooled in ice while tributylphosphine (0.56g) was added slowly. The solution was then warmed to room temperature and stirred for 3 hours, decanted and the solvent evaporated at room temperature. The residue was distilled at room temperature on a high vacuum line to give a clear liquid (0.12g) which was identified as a mixture of α-methylstyrene (67 rel.%) and 1-chloromethyl-1-methylcyclohepta-2,4,6-triene (33 rel.%); δ_H(80MHz) 1.3(3H, s), 3.3(2H, s), 5.1 - 5.3(2H, m), 6.1 - 6.6(4H, m); m/z 156(m^+, 1%), 154(m^+, 3%), 141(2), 139(6), 117(33), 105(100), 91(35), 77(58), 63(11), 52(28) and 40(36). A trace of the compound previously identified as β-chlorocumene was also found to be present by g.c.m.s.

Reaction of 1-hydroxymethyl-1-methylcyclohepta-2,4,6-triene (7) with thionyl chloride. The alcohol (7) (2.0g, 13mmol) and anhydrous pyridine (1.0ml) were dissolved in anhydrous ether (30ml) and cooled to -10°C. Thionyl chloride (0.9ml) was added over 20 minutes. The solution was stirred at -10°C for 3.5 hours then warmed to room temperature over a further hour. The solution was filtered, washed with 10% $NaHCO_3$ (30ml), water (20ml) and saturated NaCl solution (15ml), dried ($MgSO_4$) and evaporated.

G.c.m.s. analysis of the crude product indicated that it was mainly α-methylstyrene by comparison with an authentic sample.

Reduction of a mixture of the chloride (4b) (33 rel.%) and α-methylstyrene (67 rel.%) with tributyltin hydride. The mixture (68mg) was dissolved in cyclopentane (0.5ml) and degassed by bubbling nitrogen. Bu_3^nSnH (43mg) was added and the solution was photolysed at room temperature with light from a 250W medium pressure Hg arc for 6 hours. The mixture was then analysed by g.c.m.s. and separation of its components by preparative g.l.c. on a 4.5m × 1cm carbowax 20M column at ca. 40°C. The major component of the mixture was α-methylstyrene and this was the only component which could be satisfactorally collected. G.c.m.s. data on the other components observed are given in **Table 2.**

Reaction of 1-hydroxymethylcyclohepta-2,4,6-triene with tributylphosphine in carbon tetrachloride. 1-hydroxymethylcyclohepta-2,4,6-triene (prepared by Mr. I.W. Harvey) (1.0g, 7.1mmol) was dissolved in carbon tetrachloride (10ml) and stirred in ice under nitrogen while tributylphosphine (1.7g) was added slowly. The solution was warmed to room temperature and stirred for three hours. The solution was decanted, the solvent evaporated and the residue distilled at room temperature on the high vacuum line to give a clear liquid (190mg) which was identified as a mixture of styrene (60 rel.%); δ_H(60MHz) 5.1 - 5.8(2H, ddd), 6.5 - 7.0(1H, dd), 7.2 - 7.5(5H, m) and 1-chloromethylcyclohepta-2,4,6-triene (5) (40 rel.%); δ_H(80MHz) 2.1 - 2.4(1H, m), 3.7(2H, d, J=6), 5.2 - 5.4(2H, m), 6.1 - 6.4(2H, m), 6.6 - 6.7(2H, m); m/z 142(m^+, 1%), 140(m^+, 3%), 103(18), 91(100), 77(33), 65(22), 51(20) and 39(29).

Reduction of a mixture of the chloride (5) (40 rel.%) and styrene (60 rel.%) with tributyltin hydride. The mixture (60mg) was dissolved in cyclopentane (100μl) and degassed by bubbling nitrogen. Tributyltin hydride (210mg) was added and the mixture was photolysed with light from a 250W medium pressure Hg arc at room temperature for 1 hour. All volatile material was distilled out of the reaction mixture at room temperature on the high vacuum line. The product mixture was analysed by g.c.m.s. Details are given in Table 3. The major components appeared to be isomers of the chloride (5).

Preparation of Di-(cyclohepta-2,4,6-triene-1-acetyl)peroxide (6). Oxalyl chloride (2.1g) was added to cyclohepta-2,4,6-triene-1-acetic acid (1.0g). After 30 minutes of gas evolution the mixture was refluxed for 5 hours. The excess oxalyl chloride was evaporated and the dark reaction mixture was extracted several times with dry n-pentane. The pentane solution was evaporated to leave a light orange oil. This oil (1.05g) was dissolved in n-pentane (3ml) and the solution stirred at -10°C. 30% hydrogen peroxide (0.7ml) was added at such a rate that the temperature of the reaction mixture did not exceed 10°C. Pyridine (0.5ml) was added dropwise and stirring continued for 2 hours at 0°C. The solution was neutralised with cold dilute sulphuric acid and the peroxide extracted with pentane (2 × 5ml). The extracts were combined, washed with cold dilute sulphuric acid, bicarbonate solution and water then dried (Na_2SO_4). A small amount of the solution was evaporated and redissolved in $CDCl_3$ to determine the ^1H n.m.r. of the product: δ_H(300MHz) 2.4(2H, quin, J=6), 2.7(4H, d, J=8), 5.3(4H, dd, J_1=8, J_2=6), 6.2(4H, m), 6.6(4H, m).

Decomposition of Di-(cyclohepta-2,4,6-triene-1-acteyl)peroxide (6). Decomposition was carried out thermally and photochemically. In the former case, a pentane solution of the peroxide (6) was mixed with an equal volume of toluene and the pentane evaporated. The toluene solution was then refluxed for 30 minutes. In the latter case the pentane solution was photolysed with light from a 250W medium pressure Hg arc for 30 minutes. In both cases the major isolable and identifiable product was styrene. G.c.m.s. data on other products is given in **Table 4**.

Preparation of 1-substituted-cyclohepta-2,4,6-trienes. Tropylium bromide (2.0g, 12mmol) was dissolved in water (20ml) and stirred while a solution of NaOMe, NaSMe or NMe_2, (12mmol) in water (20ml) was added. The solution was extracted with ether (2 × 30ml), the extracts were combined, dried (Na_2SO_4), evaporated and the residue distilled on a Büchi Kugelrohr. The following compounds were prepared: *1-(dimethylamino)cyclohepta-2,4,6-triene (1.1g, 68%);* δ_H(80MHz) 1.9(1H, m), 2.4(6H, s), 5.5 - 5.8(2H, m), 6.2 - 6.4(2H, m), 6.8 - 6.9(2H, m). *1-thiomethoxycyclohepta-2,4,6-triene (0.4g, 24%);* δ_H(300MHz) 2.1(3H, s), 3.4(1H, t, J=6), 5.5(2H, dd, J_1=8, J_2=6), 6.2(2H, m), 6.5(2H, m); δ_C(75MHz) 13.4(1C), 44.1(1C), 124.6(2C), 126.6(2C), 131.1(2C). *1-methoxycyclohepta-2,4,6-triene (0.6g, 41%)* ; δ_H(60MHz) , 3.4(4H, s), 5.4 - 5.7(2H, m), 6.1 - 6.4(2H, m), 6.7 - 6.8(2H, m). Attempts to prepare 1-hydroxycyclohepta-2,4,6-triene, 1-isopropoxycyclohepta-2,4,6-triene and 1-t-butoxycyclohepta-2,4,6-triene in this way were not successful.

Table 2

G.c.m.s. Data on the Products of the Reduction of (**4b**)

Retention time	m^+ and fragment ions (%)	Prob. molecular formula
3:14 min.	118(67), 117(100), 103(98) 91(41),77(71), 52(72).	α-methylstyrene
3:45 min.*	120(2), 119(20), 105(100), 91(22), 77(33).	C_9H_{12}
3:58 min.	120(24), 105(87), 77(100), 51(57), 43(32)	C_9H_{12}
4:07 min.	156,154(<1,1), 141,139(2,6) 118(13), 105(100), 91(31), 77(45), 51(36)	$C_9H_{11}Cl$
4:13 min.	121(38),77(13), 51(18), 43(100)	C_9H_{14}?
4:38 min.*	156,154(2,6), 132(42), 117(100), 103(22), 91(91), 77(38), 65(19), 52(24)	$C_9H_{11}Cl$
5:01 min.	156,154(<1,2), 141,139(2,6), 118(22), 105(100), 91(37), 77(39), 63(19),52(16), 41(25).	"
5:19 min.*	156,154(3,8), 141,139(11,34), 119(55), 106(71), 91(100), 77(49) 65(20), 51(41), 40(33).	$C_9H_{11}Cl$

Table 2 (Continued)

5:30 min.	156,154(1,4), 119(11), 105(100), 91(15), 77(22), 51(16), 40(10).	$C_9H_{11}Cl$

Table 3

G.c.m.s. Data on the Products of Reduction of (5)

Retention time	m^+ and fragment ions (%)	Prob. molecular formula
1:01 min.*	106(24), 105(25), 91(100), 77(22), 65(18), 51(13).	C_8H_{10}
3:01 min.	142,140((1,3), 103(13), 91(100), 77(31), 65(22), 51(20), 39(20).	C_8H_9Cl
3:12 min.	144,142(2,7), 107(24), 91(85), 77(100), 65(48), 51(32), 39(67)	$C_8H_{11}Cl$
3:19 min.	144,142(6,19), 107(20), 91(94), 77(100), 65(52), 51(36), 39(78).	"

Table 4

G.c.m.s. Data on the Products of Decomposition of (6)

Retention time	m^+ and fragment ions (%)	Prob. molecular formula
1:06 min.*	104(64), 103(100), 77(50), 63(18), 51(53).	styrene
2:11 min.*	120(14), 91(100), 65(32), 51(10, 40(8).	C_9H_{12}

Table 4 (Continued)

9:41 min.	205(5), 179(33), 161(6), 149(14), m^+ absent. 137(72), 123(30), 107(9), 95(100), 80(28), 65(11), 57(33).
10:42 min.	203(1), 189(22), 176(5), 162(14), " 147(19), 134(12), 120(33), 105(6), 92(100), 78(71), 63(21) 55(14).
11:04 min	218(5), 203(1), 189(27), 176(8), m^+ absent. 162(20), 147(21), 134(33), 120(35), 105(10), 92(100), 78(74), 63(39), 55(29), 49(10).

*Minor components; peak height is less than 10% of the maximum.

CONCLUSIONS TO PART ONE

The work which has been described in the first part of this thesis has established that 5-hexenyl radical cyclisations can proceed efficiently even when the radical is incorporated into a ring system which has limited conformational freedom.

As is the case with all reactions of radicals with unsaturated functions, many factors have to be taken into account in order to predict or interpret the outcome of a transannular cyclisation reaction. Because the systems which have been studied have all involved carbinyl radicals reacting with an olefin, polar effects have not contributed to the observed divergence in their reactivity. The most important influences on the course of each reaction have been judged to be of the stereochemical type.

Studies of derivatives of the 5-hexenyl radical have shown that altering bond distances in the chain, by introducing a heteroatom, increased the rate of the 1,5-cyclisation. The study of dihydrodioxepinylmethyl radicals in Chapter 3 has shown that this also holds true for transannular cyclisations unless the shorter bond distances lead to steric crowding in the conformation of the radical which is favourable for cyclisation. This is a more important consideration for cyclic radicals than for open chain radicals because the methylene groups in the ring are not freely rotating. It has also been shown that a small steric effect of this type can be overcome by introducing a

larger compensating effect which forces the radical into the conformation in which it can cyclise. Hence, although the 4,7-dihydro-1,3-dioxepin-2-ylmethyl radical cyclises slowly, the 2-methyl derivative cyclises at least 100 times faster.

The 5-hexenyl radical cyclises preferentially in the 1,5 (exo) mode because the disposition of atoms required for the transition state can be accommodated with less distortion of the incipient ring in this mode than in the 1,6-mode. In a transannular cyclisation there are two incipient rings in the transition state. It has been shown in the study of cyclo-oct-4-enylmethyl radical in chapter two that the transition state which incorporates a 5-membered ring is more favourable but that the steric energy of the other ring which is being formed is an important consideration. In this particular case, the degree of selectivity was reduced, probably largely as a result of torsional strain in the 7-membered ring in the transition state for 1,5-cyclisation.

Further evidence of the importance of considering the steric requirements of both rings in a cyclisation transition state was obtained from the relatively slow rate of cyclohept-4-enylmethyl radical compared to 5-hexenyl radical. It was suggested that this was most likely to be due to the transition state having to accomodate both a 5- and a 6-membered ring. Also, the high activation energy for the cyclisation of 4,7-dihydro-2-methyl-1,3-dioxepin-2-ylmethyl radical can probably not be adequately accounted for in terms of steric crowding and it was suggested that the inclusion of a strained oxepane ring in the transition state could be the explanation for this observation.

The study of cycloheptatriene derivatives highlighted the fact that the chemical properties of a ring can dominate its physical properties. Conformationally, the cyclohepta-2,4,6-trien-1-ylmethyl radical appeared to be well adapted for intramolecular reaction. It only has two low energy conformations and one of them seemed to meet the requirements for cyclisation. Both statistically and geometrically it seemed a likely candidate to undergo fast rearrangement. In fact it did undergo fast rearrangement but not in the desired direction. Another radical reaction which the ring allowed supervened.

Such considerations will no doubt be important if transannular radical cyclisations are incorporated into more elaborate synthetic schemes. Three of the reactions which have been reported here are synthetically viable routes to bicyclo[3.2.1]octane, bicyclo[4.2.1]nonane and 1-methyl-2,7-dioxabicyclo[3.2.1]octane. High yields were obtained under the optimum conditions. New routes to bicyclic molecules are likely to be of considerable interest because of their utility in the construction of biologically active molecules.

With this in mind the syntheses in this work have two defects which may prompt further study. One is that the reducing agent used is a tin compound which, because of its toxicity, may be incompatible with the purpose of synthesising some biochemicals. The usefulness of other reducing agents should be investigated. This work has not investigated the possibility of stereospecific transannular cyclisations which might find wider application than those which have been discussed. Directive substituents are the tools which have been most studied in attempts to influence the

stereospecificity of radical addition and for the 5-hexenyl system this has had some success.

Also with biochemicals in view, this work should be further extended to other heterocyclic systems. This will include using heterocyclic rings and heteroatom centred radicals. Since the work in Chapter 2 was published, Newcomb has extended it to the synthesis of 8-azabicyclo[3.2.1]octane.[147] The use of other ring systems will also lead to further interesting information about the stereochemical influences on the course of these reactions.

A considerable amount of further work can therefore be envisaged as the transannular radical cyclisations of unsaturated ring derivatives play their part in the ever expanding field of radical synthesis.

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PART TWO

THE INVESTIGATION OF ROUTES TO POLYNITROXIDES

CHAPTER 5

POLYRADICALS

(An Introduction)

5.1 Stable Free Radicals.

Most of free radical chemistry is associated with highly reactive, transient species. Most of the radical reactions which have been studied would not be viable were this not the case. The very fast rates of the rearrangements which are described in Part 1 are crucial to their synthetic utility and it was pointed out in Chapter 1 that reducing the reactivity or increasing the stability of a particular type of radical can have a significant effect on the course of a particular reaction.

There are a number of types of radical which can be described as stabilised and which persist for long periods, in some cases indefinitely under certain conditions. What exactly is meant by the term "stable" has been rather ambiguous. Griller and Ingold[1] began an account of the problem of what constituted a stable carbon centred radical by quoting, apparently in exasperation, Lewis Carol's Wonderland character Humpty Dumpty's views on precision of speech: *"When I use a word it means just what I want it to mean - neither more nor less"*. They suggest that the liberty of the adjective should be curtailed and that it should

be confined to describing only those radicals which are so unreactive in a normal laboratory atmosphere that no special precautions are required in their handling and storage. All other stabilised radicals should be described as persistent, the degree of persistence being an interpretation of some kinetic parameter of the processes by which the radical decays.

On this basis the radicals which are investigated in the work described in chapters 6 and 7 can be described as stable or highly persistent under the appropriate conditions.

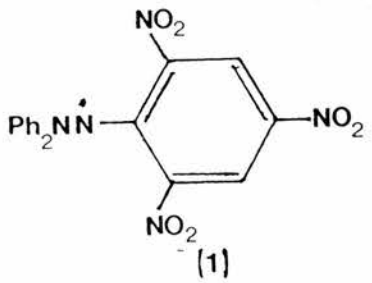
As will be more fully discussed later, the uses which have been envisaged for polyradicals require that they should be stable and reasonably easily handled. When discussing how they can be constructed and reviewing the work which has been done on the subject, it is necessary to begin by describing the types of compound which could be incorporated into a suitable monomer unit.

The highly stabilised organic radicals which are known derive their stability from a combination of delocalisation of the unpaired electron coupled with a sterically hindered radical centre which reduces the rate of possible intermolecular reactions. The absence of any reactive group, e.g. a labile hydrogen atom, proximal to the radical centre is also an important consideration.

Free radical chemistry began with the discovery of the first persistent organic free radical, the triphenylmethyl radical, by Gomberg in 1900.[2] Since then many other carbon centred radicals

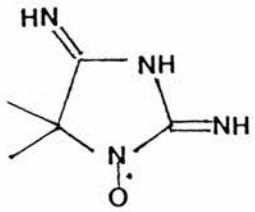
and radical ions have been prepared and characterised. The stability of triphenylmethyl stems mainly from the delocalisation of the unpaired electron into the aromatic ring systems and steric hindrance to reactivity at the radical centre. Triphenylmethyl is only stable in solution in the absence of oxygen and is therefore of litle interest to those who seek stable rather than persistent radicals. The introduction of features which increase the extent of the delocalisation and decrease the ability of the radical to dimerise have led to isolable carbon centred radicals. For example the perchlorotriphenylmethyl radical is completely inert to oxygen[3] and the replacement of the phenyl groups in triphenylmethyl with diarylvinyl groups to give tetraphenylallyl radical etc. has been shown to lead to radicals which can be isolated as green crystals.[4,5]

A number of aryl substituted amino radicals are also known. Like their carbon analogues the stability of these radicals is related to unpaired electron delocalisation and steric considerations and most are persistent in solution but are not isolable. More stable, however are certain hydrazyl radicals particularly the sterically hindered 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) (1) which was first prepared by Goldschmidt.[6,7] The crucial factor which gives this radical its remarkable stability in both the solid state and solution is the presence of the two nitro groups *ortho* to the radical centre which sterically inhibit dimerisation.[8,9]



(1)

The first organic radical which was successfully isolated was the nitroxide porphyrexide (2) which was prepared in 1901 by Piloty and Schwerin.[10] It was found that such radicals did not have the same tendency to dimerise as those mentioned above[10] although they do dimerise at very low temperatures.[11]

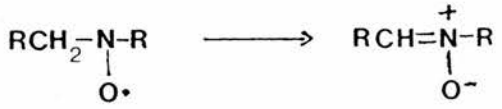


(2)

The stability of the nitroxyl group has been attributed[12] to its hybrid structure (3) which gives the radical an intrinsic stability.

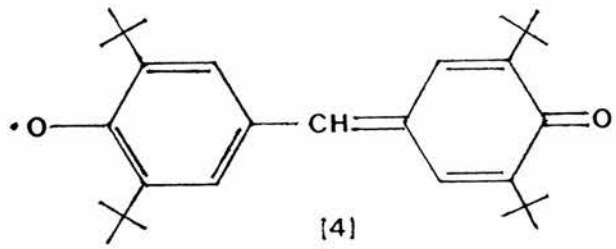
(3)

The attachment of groups, eg. phenyl, which cause the odd electron to be delocalised over the aromatic system play little or no part in preventing such radicals from dimerising. This delocalisation may in fact have a destabilising effect if it allows the molecule to undergo some other sort of self reaction. Stable nitroxides are formed if the groups attached to the N-O group do not enable it to participate in self reactions. It is not a requirement that these groups be bulky or highly conjugated. For example, dialky nitroxides which have a hydrogen attached to the α-carbon disproportionate to give nitrones (**Scheme 1**) whereas t-alkyl nitroxides are very stable in both the solid state and in solution.[13,14]



Scheme 1

The final major class of stable radicals are derived from hindered phenols by hydrogen abstraction or by oxidation of the corresponding phenoxy anion. Indirect routes from cyclohexadienones have also been employed. The best known of these aryloxyl radicals is galvinoxyl radical (**4**) which is isolable as a blue crystalline solid and is stable to oxygen in the solid state[15,16] although it absorbs oxygen slowly in solution. Most aryloxyl radicals do react with oxygen, the rate of reaction, i.e. the stability of the radical, is determined by the same considerations which dominate the behaviour of the carbinyl and aminyl radicals described earlier.



[4]

The glance at the range of persistent free radicals which has just been provided indicates that nitroxides offer some superiority over the others in terms of stability and variety. It is nitroxides which have been selected as the materials for the work described in the final two chapters of this thesis and, as will now be discussed, it is nitroxides which have proved most popular with other workers who have synthesised polyradicals.

5.2 The Synthesis of Polyradicals -A Short History.

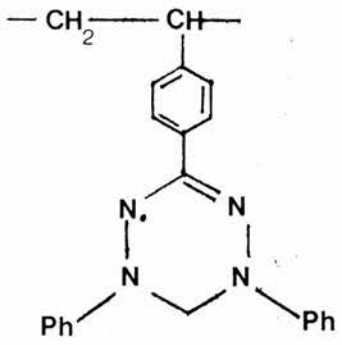
The first report of the synthesis of polyradicals appeared in 1956. Henglein and Boysen[17] reported the modification of polymers by their irradiation with gamma rays in the presence of DPPH. They claimed that hydrazine groups were thereby incorporated into the polymer via one of the free phenyl groups of DPPH and that subsequent oxidation led to polymers with hydrazyl side groups.

A more conventional method for preparing similar materials was reported by Braun et al.[18] in 1962. Poly-*m,m*-dinitro-*p*-fluorostyrene was reacted with N,N-diphenylhydrazine and subsequently oxidised to form a polymer containing DPPH groups which was reported to be stable to air.

The same group[19,20] also reported the synthesis of poly(triarylmethyl) radicals by polymerisation of *p*-diarylhydroxymethylstyrenes which were converted to the corresponding chlorides by treatment with acetyl chloride and then treated with zinc-potassium to form the radicals. They calculated that the number of radical sites per repeat unit (of polystyrene) was between 0.1 and 0.2.

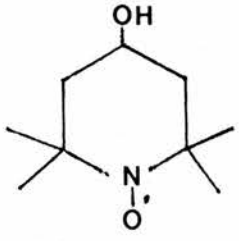
Some polymeric radical ions were also prepared by modification of polystyrenes during the early 1960s.[21,22]

The preparation of polyverdazyls (5) by similar polystyrene modification strategies was reported by Kurusu et al.[23] in 1967 and by Kinoshita and Schultz[24] in 1968.



(5)

It was in the late 1960s that the first reports of direct polymerisation of free radicals appeared. Griffith et al.[25] described the anionic polymerisation of the methacrylate ester of 2,2,6,6-tetramethylpiperidin-4-ol (TEMPOL) (**6**).



(6)

This polymer had a molecular weight of between 1050 and 1950 depending on the conditions used in its preparation. These workers also reported the reaction of commercial maleic anhydride - methyl vinyl ether (1:1) copolymer with TEMPOL to form a polymer in which approximately one half of the anhydride units had reacted with the nitroxide alcohol to form the corresponding half ester.

Direct polymerisation of a polyverdazyl by polyaddition or polycondensation was described by Neugebauer and Trischmann in 1968.[26] The biradical 1,4-bis[1,5-diphenyl-3-(4-aminophenyl)verdazyl-6-yl]butane added in solution to diisocyanates to form green insoluble polyureas. In this case the

existence of free radicals in the polymer was inferred only from its chemical behaviour; no physical measurements were reported.

Anionic polymerisation of vinyl-verdazyl was reported in 1971 by Kinoshita et al.[27] The polymerisation is rather unusual however in that it apparently did not proceed to more than a few percent conversion unless more than 1 molar equivalent of initiator (n-BuLi) was used. This suggests that the radical was in some way strongly inhibiting the anionic polymerisation reaction. Given this level of initiation it is not surprising that only low molecular weight polymers (2750) were reported. The radical content was estimated to be 24.5%. It is debatable whether this material should be referred to as a polyradical as the results imply 2 radical centres per macromolecule. Polymerisation with sodium naphthalene as an initiator gave materials with a higher radical content but lower molecular weight. The conversion rates were between 30 - 50%. Some copolymers which had radical contents of between 1 and 31% were also prepared.

N-(4-diphenylamino)acrylamide and the analogous methacrylamide were polymerised by a free radical method by Braun and Hauge (1971)[28] Oxidation of the resulting polymer with lead dioxide unexpectedly produced a polynitroxide instead of the expected diphenylnitrogen radical polymer. The e.s.r. spectrum of this polymer is reported to be quite well resolved which indicates that the nitroxide units are well separated along the chains. If the polymer had a high spin density, spin - spin interactions would be expected to lead to a single broad line spectrum.

Two related new routes to polymers incorporating the 2,2,6,6-tetramethylpiperidinyl nitroxide (TEMPO) unit were investigated by Kurosaki et al. (1972 - 4).[29,30] These involved free radical polymerisations and copolymerisations of the methacrylate esters of TEMPOL and 4-aminoTEMPO (TEMPAMINE) and also the corresponding hydroxylamine hydrochlorides and hydrosulphates. The precursor polymers which were formed then underwent simple chemical modifications to form the polynitroxides. Polymers with molecular weights of over 100,000 and high spin density were thus obtained.

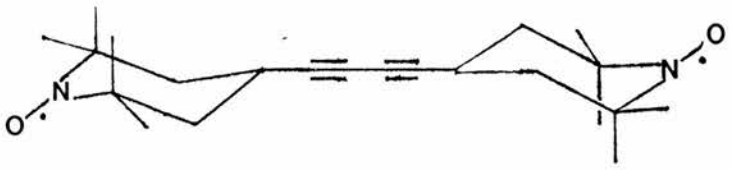
Kato and Nakano (1972)[31] reported the surprising result that the hindered phenol β-vinyloxy(3,5-di-t-butyl-4-hydroxy)benzoate could be copolymerised with styrene and maleic anhydride in spite of its known radical scavenging properties. No attempt was made, however, to convert these polymers into the corresponding polyradicals. A wider range of polymers formed from hindered phenols by cationic as well as free radical polymerisation has been synthesised by Kato et al.[32]

In 1982 Kamachi et al.[33] polymerised the methacrylate ester of TEMPOL using the same technique as Griffith et al[25] but reported that much higher molecular weights were obtained (over 140,000).

Recent syntheses of polyradicals have all involved nitroxides as the radical unit. Miyazawa et al.[34] have prepared polymers of 4-O-vinylbenzylTEMPO by a similar strategy to that used by Kurosaki et al.[29] whereby the amine is polymerised by a free radical technique and subsequently oxidised to give the polynitroxide. The N-protonated cation of TEMPAMINE has been

incorporated into films of naffion for electrochemical study by Kaifer and Bard.[35]

Also for electrochemical studies, a 2,2,5,5-tetramethyl-3-pyrrolinyl nitroxide derivative of pyrrole has been electropolymerised on platinum and glassy carbon electrodes by controlled potential oxidation of solutions in acetonitrile.[36] In another preparation which incorporates nitroxide functions into an unsaturated polymer, two groups have reported topochemical polymerisation of the diacetylene diradical (7).[37,38]



(7)

Another approach to TEMPO derivatives of polyacrylates was reported last year by Osa et al.[39] TEMPAMINE was reacted with polyacrylic acid to form a polymer in which 71% of the acrylyl units are substituted by TEMPO.

From the above chronology, which although not all - inclusive, is representative, one can see that the techniques which have been employed in polyradical syntheses can be divided into direct and indirect strategies. The ideal synthesis, for a homopolymer, is one which leads to a polymer of reasonably high molecular weight and a high percentge of incorporation of the radical. It is unfortunate that not all authors report the latter statistic but it does appear that direct polymerisation of nitroxides is currently supreme.

5.3 Applications and Prospects.

Chemical Properties of Polyradicals.

When the first investigations into polyradicals were undertaken the principal motive for the work was that stable free radicals were known to be excellent radical scavengers. They were therefore useful as antioxidants. Piperidyl species have been incorporated into polymers by diffusion techniques with a view to stabilising the material as well as by the copolymerisation techniques which were described in the previous section.[40]

There are a number of other chemical reactions which stable radicals participate in. Nitroxides react with a number of persistent as well as reactive radicals. For example, 4,4-dinitrophenyl nitroxide reacts with triphenylmethyl radical to form the 1:1 adduct.[7] Reaction of nitroxides with acids leads to the formation of hydroxylamines and oxoammonium salts.[41] Nitroxides and other stable radicals abstract certain types of reactive hydrogen. For example, porphyrexide oxidises phenols to quinones[42]. Radicals which have the highest redox potential are the most reactive in these types of reactions. Nitroxides have also been shown to promote the dissociation of weak bonds in other systems. The triphenylmethyl radical has been generated from triphenylmethyl bromide by dissolution of the bromide in di-t-butyl nitroxide.[43,44] Likewise, the nitroxides also catalyse the decomposition of certain acyl halides and peroxides.[45]

The use of a polyradical in the chemical reactions of monomeric stable radicals has two main possible advantages and

one possible disadvantage. A radical homopolymer can be prepared which is heavily if not entirely substituted with radical side groups. It seems possible that such high local concentrations could have an effect on the rate or efficiency of a one electron transfer reaction. If the reaction is performed in solution, the product polymer is much easier to isolate from the other products because of its low solubility in many solvents. It can simply be precipitated out. This observation implies the main likely disadvantage which is that most polymers are soluble in only a few solvents, simple aromatics, e.g. toluene, are the most commonly employed. One electron transfer reactions in heterogeneous systems are only efficient if the nitroxide polymer surface is well solvated allowing efficient diffusion of the reagent species to the reactive sites on the polymer. The scope for a particular reaction may be limited by this consideration. For example, it is often undesirable to use aromatic solvents in radical reactions as they can trap reactive radicals to form unwanted side products.

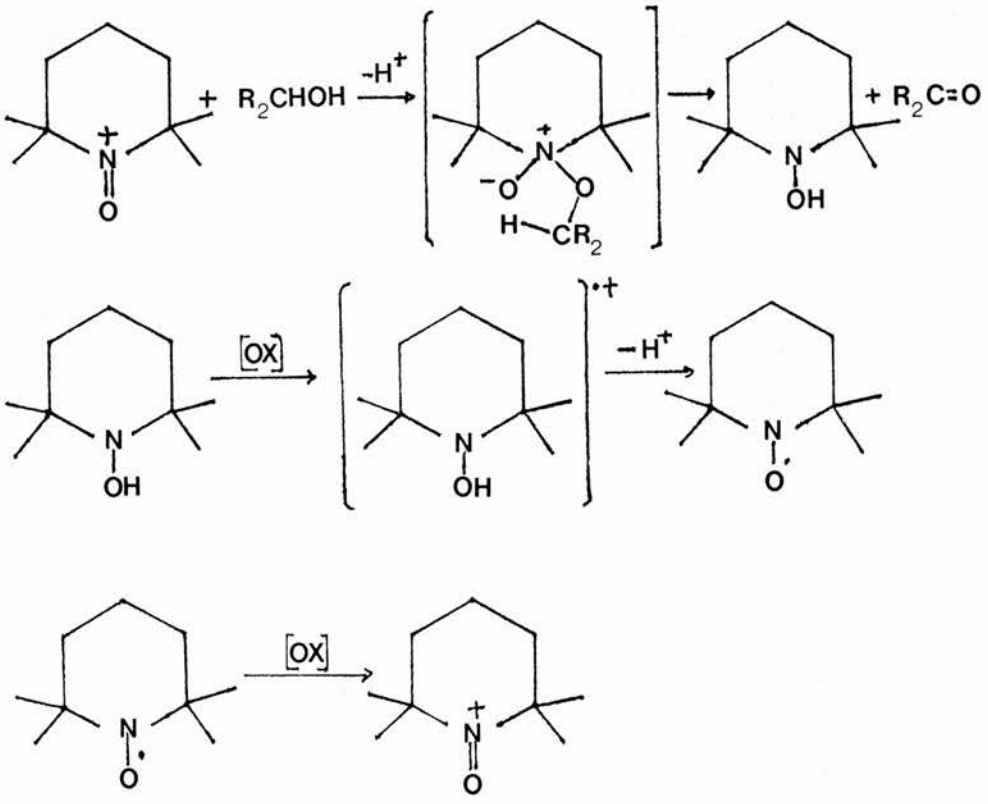
Most of the interest in chemical uses of polyradicals, particularly polynitroxides, in recent years has focussed not on the reactions of the radical itself but of its oxidised form the oxoammonium cation.

These salts have been known for some time[45] and have been shown to be oxidising agents of hydroxide anion to hydrogen peroxide[47], of alcohols to the corresponding carbonyl compounds[46,48] and of amines to nitriles and aldehydes via imines.[49] The oxoammonium cation is converted to the hydroxylamine in these reactions and this can be recycled back to

the cation via the nitroxide by chemical or electrochemical oxidation.[50,51] The piperidine skeleton can therefore be used repeatedly.

Because the oxoammonium salt is formed by a one electron oxidation of the nitroxide and this salt readily oxidises other materials it can be said that oxoammonium salts mediate oxidation reactions. Because the product of reduction of the oxoammonium salt can be recycled, catalytic amounts of it can be used.

Semmelhack et al. have made several studies of oxoammonium mediated electrochemical oxidation of alcohols and amines.[49,50b] and have proposed the mechanism shown in **Scheme 2.**[52]



Scheme 2.

Because of the success of this type of reaction there has been some upsurge of interest in examining the utility of polymeric nitroxides in the same context.

Miyazawa and Endo[34] have used a polymeric nitroxide to mediate the chemical oxidation of benzyl alcohol with Fe(III) and have obtained quantitative yields of benzaldehyde.

Other groups[36,39] have used nitroxide polymers in the electrocatalytic oxidation of nerol[39] and a number of benzylic alcohols. In these studies the polynitroxide is in some way imobilised on the working electrode. It has been shown that this type of system is also a useful synthetic tool although the yields of aldehyde or ketone were quite variable.

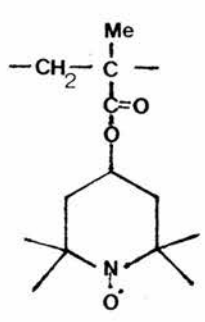
Chapter 6 of this thesis is concerned with the chemical utility of polynitroxides. A polyacrylic nitroxide was synthesised and some one electron transfer reactions were investigated. The existing work on the electrocatalytic oxidation of alcohols using polymer modified electrodes was extended to a series of amines.

Physical Properties of Polyradicals.

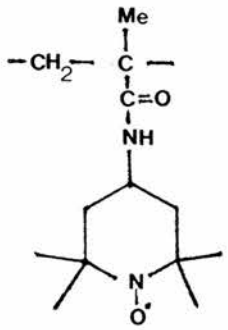
Since the early syntheses of polyradicals there has been persistent speculation on the subject of possible cooperative interactions between the unpaired spins leading to ferro, ferri or antiferromagnetism.

Some stable radicals exhibit ferromagnetic or antiferromagnetic intermolecular exchange under certain conditions in the solid state. For example galvinoxyl radical exhibits ferromagnetic exchange in the solid state above 85K. Its paramagnetic susceptibilty follows the Curie - Weiss law [$\chi_M = c/(T-\theta)$] with a Weiss constant θ = 19K. At 85K it undergoes a phase transition and most of the paramagnetic susceptibility disappears below this temperature.[53] Below 85K the interaction becomes antiferromagnetic and this has been assigned to dimerisation associated with the phase transition.[54] It has been shown that mixed crystals of 4% galvinoxyl in hydrogalvinoxyl remain ferromagnetically coupled down to 77K, the lowest temperature studied.[54]

It has been considered that electron exchange phenomena might be better facilitated in a polymeric rather than in a monomeric crystalline radical. Some e.s.r. studies have supported this view.[55] Kamachi et al[33] have reported magnetic susceptibility measurements on two nitroxide substituted methacrylate polymers (8) and (9).



(8)



(9)

χ_M^{-1} vs T plots indicated that the observed χ_M in both cases followed the Curie - Weiss law with $\theta_{(8)}$ = -3.3 indicating antiferromagnetic exchange interaction between unpaired

electrons. Magnetic moment calculations showed that μ decreased gradually down to 20K and below that somewhat more sharply showing that the antiferromagnetic interaction overwhelms the thermal energy at about that temperature. This transition was not observed in the relationship between χ_M^{-1} and T and it was concluded from this that the transition was very weak. By contrast, however the equivalent measurements on the monomers from which (8) and (9) were prepared showed that above 6K the interaction between unpaired electrons was negligible. Interestingly, the μ vs T plot for the methacrylate ester of TEMPOL indicates a weak ferromagnetic interaction below 6K but these authors do not offer an explanation for this phenomenon.

Recently Ovchinnikov et al[37] reported the thermal, photochemical and glow discharge treatment of the α-phase of the diradical (7) which gave a black polymer, some samples of which exhibited field dependant magnetisation corresponding to an "insignificant amount" (0.1%) of a ferromagnet. A similar study was reported by Miller et al[38] who prepared a black amorphous substance by heating the β-phase of the same radical to 90°C. These workers report a substantial loss of magnetic moment as a result of the conversion but they do not report any ferromagnetism.

The most exciting class of compounds with spin S = ½ and which exhibit cooperative magnetic phenomena which have been investigated to date are charge transfer complexes which consist of linear chains of alternating cation radical donors and anion radical acceptors. This work culminated in the preparation of $[Fe(C_5Me_5)_2]\cdot^+[TCNE]\cdot^-$ where TCNE is tetracyanoethylene.[56] This

complex shows spontaneous magnetisation in the absence of an applied magnetic field below 4.8K and was the first molecular based ferromagnet to be developed.

The preparation of this complex was the outcome of persistent modification of steric and electronic features to find the combination which stabilised ferromagnetic coupling as well as bulk ferromagnetic behaviour. The primary tactic in this case was to use a small radical anion to try to avoid spin pairing bond formation.

Miller et al. have used the solid experimental data they have obtained on hexamethylferricinium and related salts to devise some tentative guidelines for the preparation of other magnetic materials.[57,58] They have developed a model based on the admixture of the lowest charge transfer excited state with the ground state. This model holds that stabilisation of ferromagnetic coupling is consistent only with forward, ie (A←D), charge transfer. They assume that excitation arises from the highest energy POMO. It follows from their model that if ferromagnetic coupling is to be achieved via the McConnell mechanism[59] a stable radical must posess a non - half - filled degenerate POMO and the lowest excited state which is formed by virtual charge transfer must have the same multiplicity and mixes with the ground state.

Such ferricinium complexes are important because they show that ferromagnetism is achievable in organic based systems. Although Fe is present, it has been shown that a radical anion containing an unpaired electron in a totally organic p-based

orbital is essential for achieving the bulk ferromagnetism which is observed.

Matga[60] suggested that large planar hydrocarbons comprised of meta-substituted triplet diphenylcarbenes should have a ferromagnetically coupled ground state, but, recent preparation of such materials by Iwamura et al[61] and measurement of their paramagnetic susceptibility has indicated only independent spin or antiferromagnetic behaviour.

Charge transfer complexes in which the donor and acceptor molecules form separate stacks rather than alternate along chains are noted for their very high electrical conductivity.[62] The only known organic superconductors are complexes of this type derived from tetramethyltetraselenafulvalene (TMTSF) and bis(ethylenedithiolo)tetrathiofulvalene (BEDT-TTF). The cation stacks in these systems have a zig-zag configuration which allows overlap of adjacent sulphur or selenium orbitals to form a conduction band. The origins of superconductivity in these systems remain somewhat obscure. There is no reason to doubt that the basic theory of superconductivity in metals, ie. that it is based on highly coordinated motion of electron pairs[63] also applies to these systems. But the reasons for its onset in particular systems in particular conditions are a source of debate. It is clear, however, that structural aspects are important.

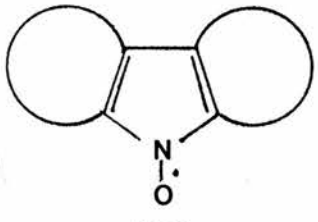
It was considered that it would be interesting to examine polyradicals in which there was more than one type of spin in the

context of looking for electronic interactions of the type which could give rise to superconductivity and ferromagnetism.

Conducting polymers such as polythiophene or polypyrrole in their oxidised state are a sort of polyradical. They generally have one electron defficiency, i.e. one unpaired electron, for every 3 - 10 repeat units,[64] stabilised by a counter anion. The strategy envisaged was to build a nitroxide function into such polymers. There would therefore be two different types of unpaired electron in the system. If the polycation was stabilised by a radical anion there would be three. Provided the structure was such that bonding interactions were at least partly avoided there seemed the prospect of making some interesting observations.

The polypyrrole derivative prepared by Deronzier et al[36] conforms to this general type but they have not studied it from any other than the electrocatalytic point of view.

The strategy adopted for this work was to attempt to make and polymerise condensed pyrrole nitroxides of type (**10**).



(10)

Chapter 7 of this thesis describes work towards the preparation of such polymers. At this time their synthesis is still elusive, but the work reported here has identified some problems and helped to clarify the path for future work.

CHAPTER 6

POLY(TEMPO-ACRYLATE)

6.1 Introduction

In this chapter some contributions to what might be called the mainstream of polynitroxide research are discussed. The results described have been obtained by investigating a polymer which is a simple homopolymer of a 2,2,6,6-tetramethylpiperidinyl nitroxide (TEMPO) derivative and therefore of the type which has been the subject of much of the limited amount of work which has been done on polyradicals hitherto.

As was indicated in Chapter 5, a number of homopolymers and co-polymers of TEMPO derivatives have been reported in the literature. The strategies which have been employed for preparing these materials can be divided into two groups, those in which the polynitroxide has been prepared by modification of another polymer and those where a nitroxide monomer unit has been polymerised directly.

It seemed to the author that the latter method was the better of the two. There are likely to be problems involved in the oxidation of, particularly, high molecular weight polyamines.

Generally, solvent systems which are good oxidising media and good solvents for the commonly used oxidising agents, e.g. water, alcohols and acetonitrile, are poor solvents for polymers. Indeed, methanol is commonly used for precipitating the product in polymer synthesis. Also it seemed doubtful whether all the amine sites would be easily oxidised on a polymer chain. For this to happen is the equivalent of achieving a quantitative yield in the reaction in spite of the fact that the probability of successful "colisions" between the oxidising agent and the substrate is reduced as a result of the amine groups being bunched together rather than randomly distributed in the solution. It is also known that many polymers are susceptible to oxidative degradation and it is generally safer to prepare them in oxygen free conditions.

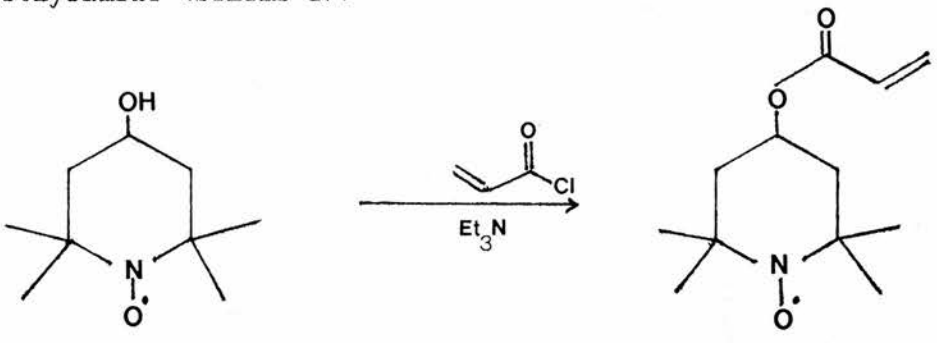
Of the various nitroxide homopolymerisations which have been carried out, the one which has been most successful in terms of the degree of polymerisation achieved was the anionic polymerisation of the methacrylate ester of 2,2,6,6-tetramethyl-4-piperidinol (TEMPOL) and the corresponding amino ester.[33]

In order to contribute something new to the synthetic pool, it was decided to investigate whether the acrylate ester of TEMPOL would also polymerise readily. Generally, acrylates polymerise less well than their methacrylate counterparts because the tertiary hydrogen can participate in various termination processes.[65]

The polymerisation turned out to be satisfactory and some properties of the resulting polymer have been investigated.

6.2 Preparation and Polymerisation of TEMPO-acrylate.

The acrylate ester of 2,2,6,6-tetramethyl-4-piperidinol (TEMPO-acrylate) was prepared quite straightforwardly by reacting the alcohol with acrylic acid chloride in the presence of triethylamine (Scheme 1).



Scheme 1

The polymerisation was carried out anionically using high vacuum techniques.[65] 1,1-diphenylethylene dimer di-potassium salt (DPE) and n-butyl lithium were employed as initiators for the reaction. Different methods for the introduction of the initiator, different amounts of initiator and different reaction times were employed in order to find the optimum conditions for the polymerisation. The product polymers were analysed for molecular weight and purity by gel permeation chromatography. The experiments and results are summarised in **Figure 1** and **Table 1**.

Table 1

Polymerisation of TEMPO-acrylate.

Initiator, Rel. %	Addition Method	Temp./K	Time	Weight Average Mol. Weight.	Conversion Ratio
DPE, 1%	Break Seal	195-213	3h	- (g.p.c. 1)	16%
n-BuLi, 1%	Syringe	195	2h	57,390 (g.p.c. 2)	60%
n-BuLi, 1%	Fragile Bulb	195	2h	22,960 (g.p.c. 3)	60%
n-BuLi, 3%	Fragile Bulb	195	2h	9,433 (g.p.c. 4)	60%
n-BuLi, 1%	Fragile Bulb	195	20h	40,700 (g.p.c. 5)	80%

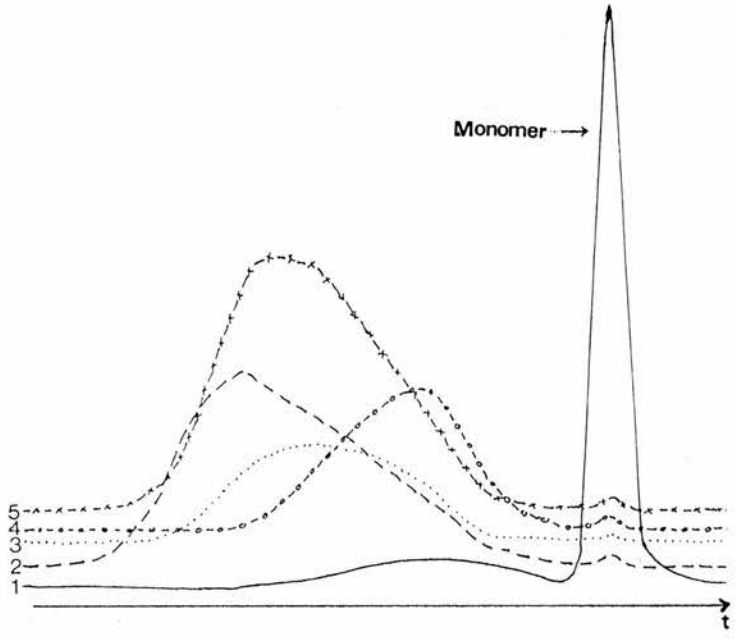


Figure 1: G.p.c. traces for the polymers formed in the reactions in **Table 1**. The numbers correspond to the numbers given in **Table 1**.

As can be seen from Table 1, a reasonably high molecular weight polymer was obtained in high yield using butyl lithium added from a fragile bulb in the reactor to initiate the polymerisation. Although the injection technique gave a polymer with a higher average molecular weight, the distribution (**Figure**

1) is broader and therefore, there is a considerable contribution from low molecular weight material.

The high conversion ratio which could be obtained was very gratifying as much lower conversion ratios are common for acrylate polymerisations.[65]

The polymer was a pale pink material which showed absorptions in the infra-red for the carbonyl (1724 cm^{-1}) and nitroxide (1360 cm^{-1}) functions. There was a weak absorption at just above 1600 cm^{-1} which may have been due to some residual alkene function, possibly due to a trace of monomer. The polymer gives a single broad line in its e.s.r. spectrum, $g = 2.0045$, $\Delta H_{pp} = 12.5G$ (**Figure** 2) which was independent of molecular weight and temperature. The lack of structure is also observed for concentrated solutions of nitroxyl radicals and is associated with spin-spin interactions of proximal unpaired electrons.[33] Integration of the e.s.r. of a polymer solution of known concentration (in terms of monomer units) and comparison with a standard DPPH solution indicated that all the nitroxide functions were intact and active on the polymer.

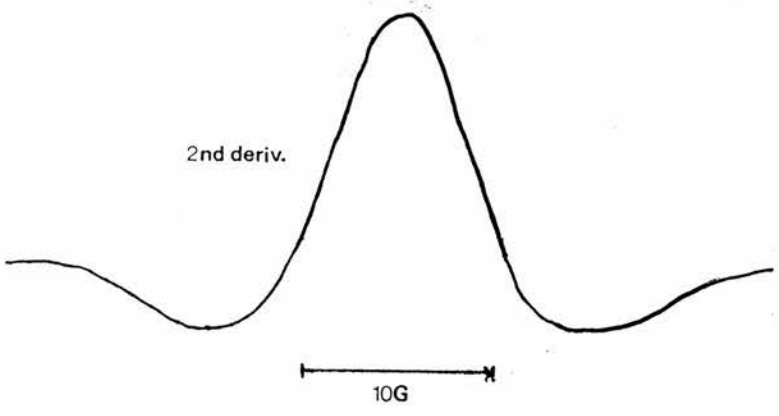


Figure 2: E.s.r. spectrum of poly(TEMPO-acrylate) in CH_2Cl_2 at 293K

Magnetic susceptibility measurements did not reveal a transition to antiferromagnetic coupling down to 4.2K. It is possible that a very weak transition could have been obscured by the background level generated by the rather crude equipment which was employed for this purpose.[66]

Some Chemical Properties.

One of the ambitions for this type of polymer has always been its possible use as an anti-oxidant. Some simple experiments were employed to test the radical scavenging ability of the polymer and to investigate whether it could be incorporated into another polymer.

Phenyldiazonium tetrafluoroborate was used as a source of phenyl radicals to investigate the radical scavenging ability of the polymer. The experiment was caried out in two ways. In an e.s.r. experiment, a drop of a 0.1M diazonium solution was added to a degassed solution of the polymer in benzene (10^{-4}M) in a soda-glass capillary in the cavity of the e.s.r. spectrometer at room temperature. The signal from the polynitroxide disappeared over a period of 1 hour indicating that it had reacted with the radicals produced by the slow rooom temperature decomposition of the diazonium ion.

Phenyl radical may also be generated from the diazonium salt electrochemically by reduction at -0.7V relative to Ag/Ag^{+}. An equimolar solution of the polynitroxide and phenyldiazonium tetrafluoroborate (10mM) in acetonitrile containing tetrabutylammonium tetrafluoroborate (TBAT) (0.1M) as electrolyte

was prepared and placed in a standard electrochemical cell with a Pt microelectrode as the working electrode. When the potential was scanned positively the cyclic voltamogram showed a reversible oxidation at +0.85V vs Ag/Ag^{+} (see section 6.3), corresponding to the oxidation of the nitroxide function to the oxoammonium cation and re-reduction. When the potential was held at the diazonium salt reduction potential for two minutes and the positive wave was rescanned, a different voltammogram was observed (**Figure 3**). This indicates that the nitroxide functions have reacted, presumably with phenyl radicals to form a new polymer which has two oxidation peaks and a reduction peak. This electroactivity is most likely to be associated with the phenyl group attached to the product polymer.

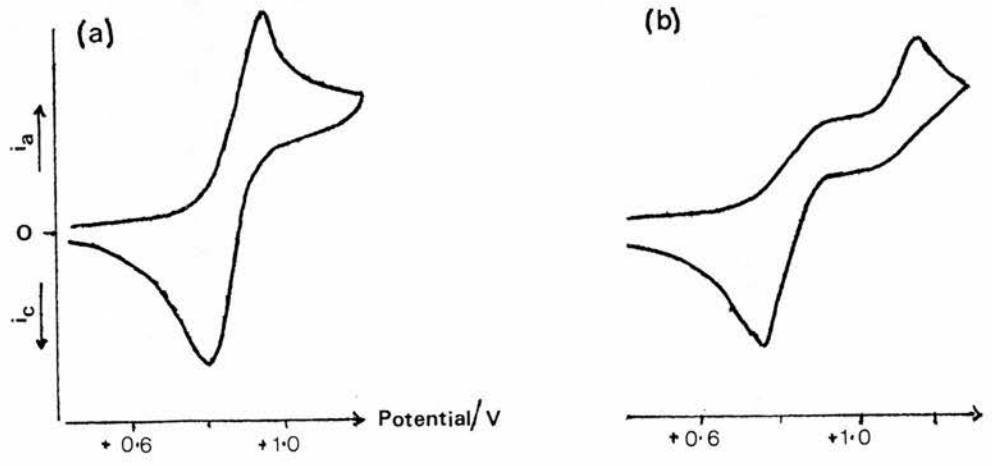


Figure 3: (a) The c.v. of poly(TEMPO-acrylate) and (b) after the generation of phenyl radicals.

It seems, however, that it will be very problematic to incorporate this material into another polymer. Two common methods of compounding materials with polymers are melt compounding and diffusion[40]. This polymer was found to be stable

in an inert atmosphere up to ca. 120°C but it did not melt or become plastic at this temperature. Above this temperature the polymer darkened and began to flow at ca. 190°C. However, all samples which were heated above 120°C were found on cooling to be e.s.r. inactive. A film of commercial polypropylene was immersed in a solution of the lowest molecular weight nitroxide polymer which was available (weight average molecular weight = 9,433) in toluene for 5 days. After this period the film was washed in clean toluene and its i.r. was examined. It was found to exhibit none of the absorptions which are characteristic of the nitroxide polymer and it was concluded that none of the nitroxide had been absorbed into the polypropylene.

The polynitroxide was found to catalyse the decomposition of acetyl chloride but not with benzoyl chloride, methane sulphonyl chloride or acryloyl chloride.

In the reaction with acetyl chloride a new, white polymer was formed which was insoluble in methylene chloride but was soluble in water and methanol. This was presumably the polymer nitroxide halide $(R_2NOCl)_n$. The n.m.r. of this polymer shows three signals in the region δ3.5 -4.5 which is downfield of the value normally expected for protons α to a carbonyl and may indicate that there are some ether linkages in the polymer.

In similar experiments the polynitroxide was found to catalyse the decomposition of diacetylperoxide to give a brown, e.s.r. inactive, product polymer which is likely to be the methyl derivative $(R_2NOMe)_n$. It did not decompose dibenzoyl peroxide. It

did not appear to decompose hydrogen peroxide either. This was deduced from the fact that the reaction of the polymer with H_2O_2 in *p*-dichlorobenzene did not lead to the formation of any *p*-dichlorohydroxybenzene as would have been expected from trapping of HO radicals by the solvent if the decomposition had proceeded.

The polymer was treated with a 10-fold excess of benzyl bromide, bromodiphenylmethane or bromotriphenylmethane in methylene chloride in the cavity of the e.s.r. spectrometer. The decay of the polymer signal was monitored. It was found that the polymer reacted with Ph_3CBr and Ph_2CHBr but not with $PhCH_2Br$ to give a white precipitate, presumably of the polymer nitroxide bromide. A plot of the log of the nitroxide signal integral vs time (**Figure 4**) indicated first order kinetics with $t_{½}$ values of 23 minutes and 49 minutes for Ph_3CBr and Ph_2CHBr respectively.

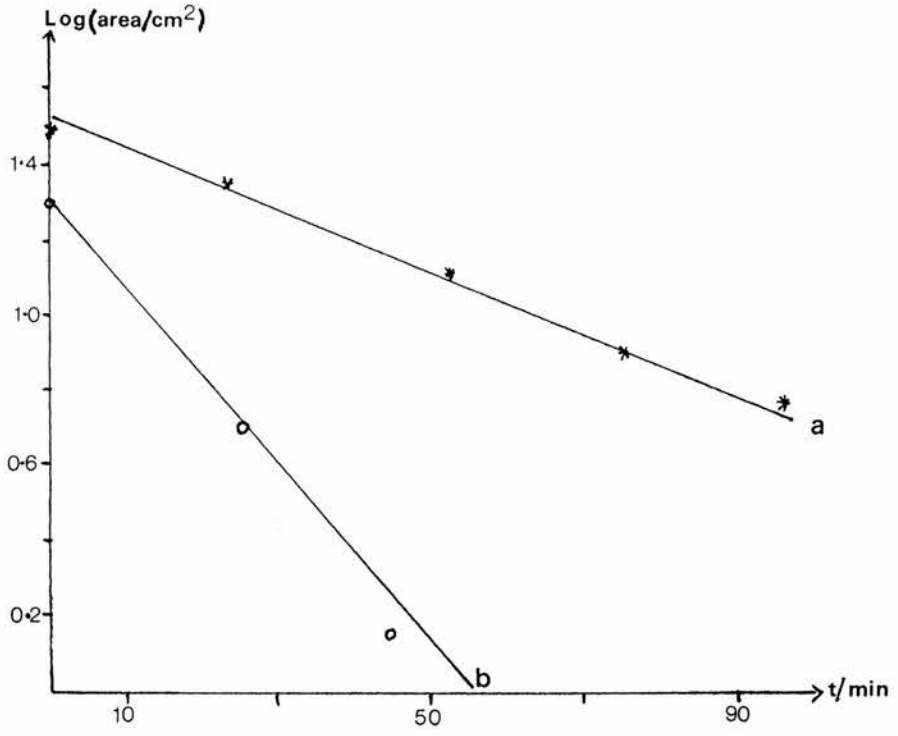


Figure 4: Decay of poly(TEMPO-acrylate) e.s.r. signal intensity with time in the presence of (a)Ph_2CHBr and (b) Ph_3CBr

It can be concluded from these experimental observations that poly(TEMPO-acrylate) behaves, chemically, in a very similar way to monomeric nitroxides which have a similar redox potential.[43-45]

6.3 Cyclic Voltametry and Electrocatalysis of Amine Oxidations with Poly(TEMPO-acrylate).

Cyclic voltametry of Poly(TEMPO-acrylate) dissolved in acetonitrile (1mM) with TBAT (0.1M) as the supporting electrolyte revealed a one electron, reversible oxidation wave with $E^{\circ\prime}$ = +0.85V relative to Ag/Ag^{+}. [$E^{\circ\prime}$ refers to measurements at 18°C rather than 25°C; $E^{\circ\prime}$(Ferrocene) = +0.48V] This value is marginally higher than that obtained for the monomer; $E^{\circ\prime}$ = 0.80V.[67] In methylene chloride the redox potential shifts slightly to +0.81V vs Ag/Ag^{+} and the wave is less symmetrical, probably due to poorer solvation of the oxidised form. A similar observation was made in the case of polyvinylferrocene.[68]

It was established that the polymer in solution had a tendency to adsorb onto the working electrode (a phenomenon which was not reported for the analogous methacrylate polymer in DMF solution[33]). This was established by removing the electrode from a solution of the polymer in acetonitrile or methylene chloride and placing it in fresh acetonitrile/TBAT (0.1M). In this system the redox wave shown in **Figure 5** was observed. The wave is typical of a surface confined redox couple with peak separation (ΔE_{pp}) close to zero and peak height (i_p) vs scan rate (v) proportionality. It follows from this proportionality that the total quantity of electroactive sites (Γ) is given by the

relationship $\Gamma = Q/nFA$, where Q is the charge under the current-potential (time) curve and A is the area of the working electrode.[69]

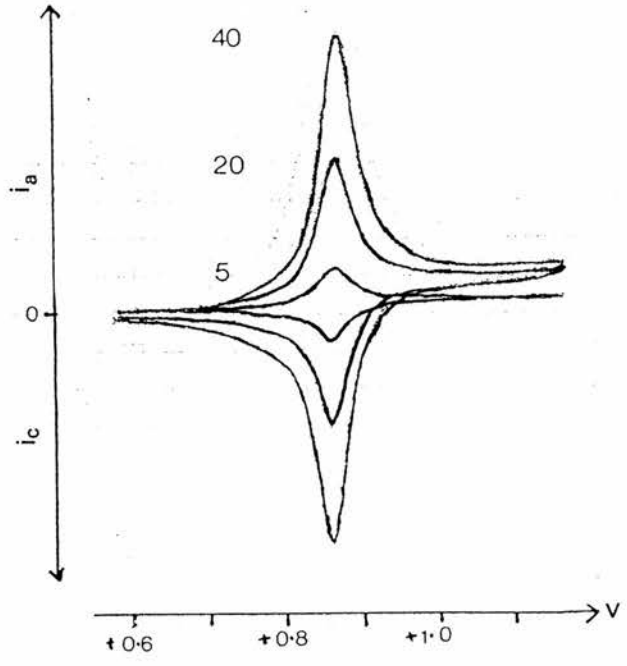


Figure 5: Variation of i_p with v/mV s^{-1} for electrode confined poly(TEMPO-acrylate).

It was found that the concentration of electroactive sites on the electrode was typically 10^{-9} - 10^{-10} mols cm^{-2}. 10^{-10} mols cm^{-2} is indicative of monolayer coverage.

The stability of the electrode adsorbed film to electrochemical cycling in various solvents was investigated. The decline in i_{pa} was monitored over time and the results are illustrated in **Figure 6**. The greater instability of the film in methylene chloride than in other solvents reflects the greater solubility of the polymer in that solvent. The film was somewhat more stable in water but not as stable as one might have expected considering only the solubility of the polymer in water. The explanation for this is almost certainly that the oxidised form of the polymer which is likely to be very similar in character to

the polymer halides described in section 6.2 is expected to be more soluble in water than in other solvents.

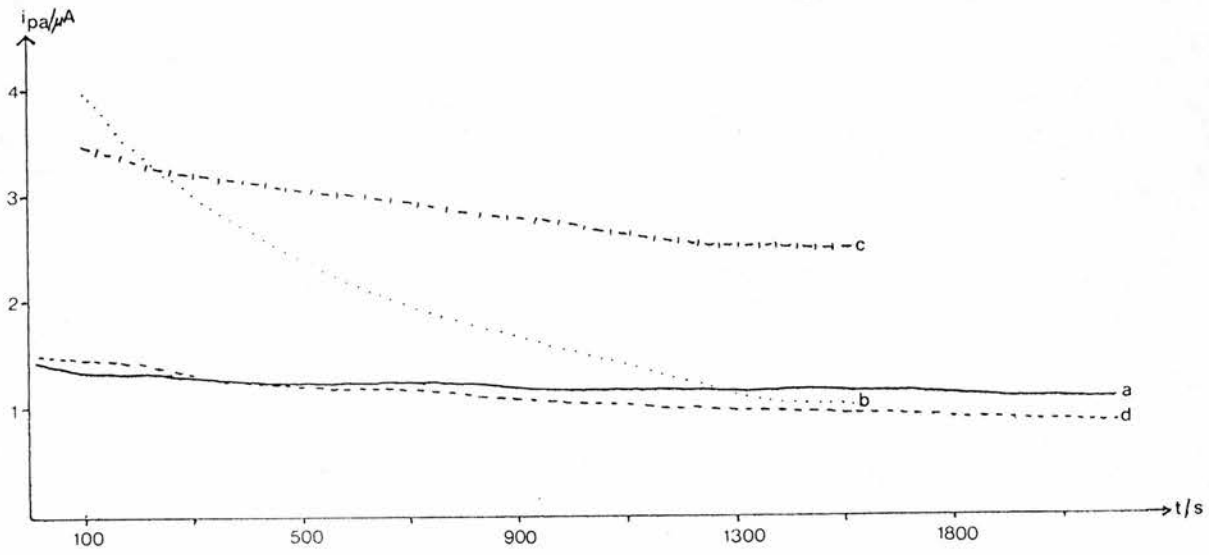


Figure 6: Decay of i_{pa} with time for electrode confined poly(TEMPO-acrylate) in (a) acetonitrile, (b) methylene chloride, (c) methanol and (d) water.

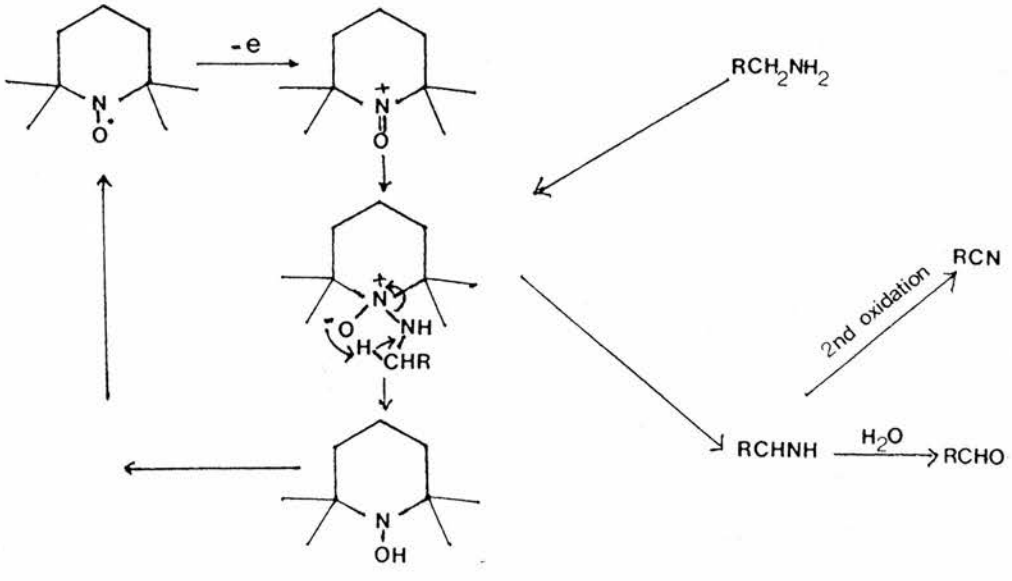
In all cases the i_{pA} values tended to plateau after a time. This implies that solubility is not the only factor responsible for the confinement of the film on the electrode. There must also be some chemical explanation which is likely to be coordination of the Pt electrode to the carbonyl function of the polymer. If this were the case then it would be expected that the layer which is in contact with the electrode surface would be resistant to dissolution.

Electrocatalysis of Amine Oxidation.

It was initially intended to examine the usefulness of poly(TEMPO-acrylate) as a mediator in the electrocatalytic oxidation of amines in solution. This would have allowed direct

comparisons to be made with the work of Semmelhack et al who used monomeric nitroxides for the same purpose.[50b] However, the tendency for the polymer to adsorb onto the working electrode would have rendered such comparisons meaningless. The electrocatalytic oxidation of amines was therefore investigated using poly(TEMPO-acrylate) modified electrodes prepared by dip-coating of the electrode in a saturated solution of polymer (weight average molecular weight = 40,700) in methylene chloride.

A film of the polymer deposited on a Pt microelectrode was cycled in acetonitrile/TBAT (0.1M) and the cyclic voltamogram recorded. The amine to be oxidised was added to the solution (10mM) which was then cycled repeatedly. An increase in the anodic current due to polymer oxidation and the disappearance of the reduction peak were observed. It seems likely that this behaviour results from the catalytic oxidation of the amine regenerating the nitroxide at the electrode (**Scheme 2**) by analogy with the results of Semmelhack and others.[49-52]



Scheme 2

The magnitude of the increase in anodic current, the definition of the catalytic wave and the stability of the catalytic wave, were found to vary for different amines. Two contrasting examples are illustrated in **Figure 7**.

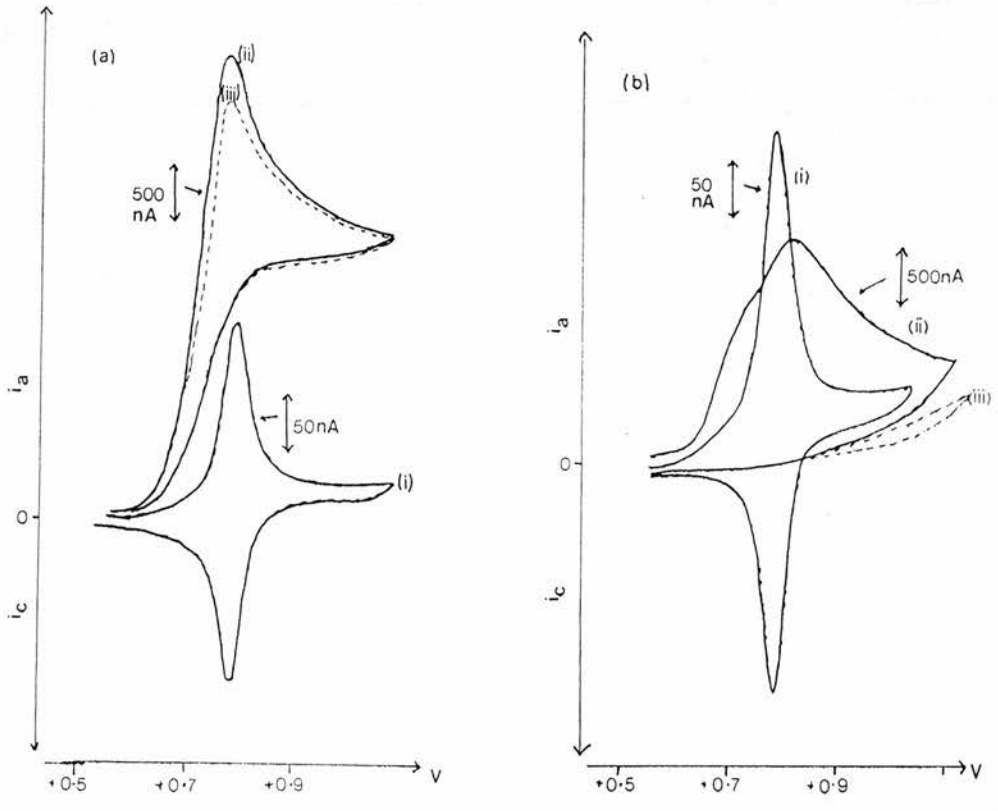


Figure 7: Catalytic waves for (a) benzylamine and (b) cyclopentylamine oxidation; (i) before addition of amine, (ii) first cycle, (iii) 3rd cycle.

The observation of the catalytic current enables the rate constant k_{cat} to be calculated from the relationship $i_{cat} = (nFA\Gamma_{cat})k_{cat}C$ where n is the number of electrons transferred (assumed to be 1), A is the area of the electrode, Γ is the surface excess of the catalyst and C is the concentration of the substrate. The quantity $nFA\Gamma_{cat} = Q_{cat}$, the charge associated with the redox process. Full data for the amines studied are given in **Table 2**.

Table 2

Data[a] for the electrocatalytic oxidation of amines by electrode-confined poly(TEMPO-acrylate) monolayer.

Amine	1st cycle k/s^{-1}	$E^{\circ\prime}$/V	E_p/V	$E_p-E_{p/2}$	% i_{cat}
	$i_{cat}/\mu A$	polymer[b]		/mV	3rd cycle
NH_3	6.6	1.65	0.78	0.96	80	15
$BzNH_2$	4.4	1.10	0.79	0.78	60	89
Et_2NH	19.0	4.75	0.80	1.35	200	19
$Ph(CH_2)_3NH_2$	3.5	0.88	0.80	0.84	60	69
p-TolNHEt	3.6	0.90	0.79	0.74	60	100
$cycloC_5H_9NH_2$	2.3	0.58	0.80	0.84	120	6
$C_5H_{11}NH_2$	4.3	1.08	0.77	0.80	60	100

[a]All 40 mV s^{-1} scan rate and 10mM substrate concentration in 0.1M TBAT in MeCN. [b]In the absence of substrate.

It is likely that the results which are listed in **Table 2** are the outcome of a number of different influences.

The factors which are expected to be most important when interpreting the data on a particular reaction are: the difference between the redox potential of the substrate and that of the mediator; the ease of proton abstraction (**Scheme 2**) which will be related to the stability of the product thus formed; the stability of the mediator in a particular system and steric hindrance to the formation of the initial R_2NONR adduct (**Scheme 2**).

It has been established from the results of Semmelhack[50] and Deronzier[36] that the presence of a weak base in the oxoammonium mediated oxidation of amines and alcohols enhances the rate of

the reaction. However, it has also been shown that although the rate of the reaction is greater in the presence of stronger bases, the rate of decomposition of the mediator is greater under these conditions too. It has been found that for synthetic electrocatalysis it was often more satisfactory to use a system with a low catalytic rate in which the mediator had a long lifetime rather than one which gave a fast rate but in which the mediator had a relatively short lifetime.[36]

It is likely that the rapid decline in i_{pa} values for ammonia, diethylamine and cyclopentylamine are due to decomposition of the mediator. When the polymer films which were used in these reactions were removed from the solution of substrate and placed in fresh MeCN/TBAT they did not show any electroactivity. The high initial catalytic current due to the oxidation of dimethylamine is probably due mainly to its basic strength which makes it an effective proton scavenger. This effect is compensated for in the case of ammonia, probably by the unfavourable nature of the deprotonation step and in the case of cyclopentylamine, probably, by steric hindrance to the formation of the initial adduct.

The oxidation potentials for ammonia and dimethylamine are significantly higher than that of the polymer. As this would be expected to drive the rate of the reaction in the opposite direction to that observed, it seems that any effect from this is compensated for by other factors.

The other results in **Table 2** can also be explained in terms of several interacting considerations. It seems that a weak base

which reacts rapidly is the ideal substrate. Nonylamine and N-ethyl-*p*-toluamine cause the mediator to deteriorate less rapidly than benzylamine and 3-phenylpropylamine.

Where comparisons are available, this work has confirmed the trends which have been observed for oxoammonium mediated electrocatalytic preparative oxidations of amines using monomeric nitroxides.[50]

The electrocatalytic oxidation of benzylamine was carried out on a preparative scale in MeCN/H_2O (24:1) solution with lithium perchlorate as supporting electrolyte and 2,6-lutidine as an auxilliary base.

In order to have the maximum amount of surface confined polymer available in the system, and therefore to maximise the longevity of the modified electrode, the electrode used was a piece of carbon fibre which had been painted with a saturated solution of the polymer in methylene chloride and subsequently washed in acetonitrile to remove any excess.

The electrolysis was performed in a standard two compartment cell and was continued at +0.8V for 220 minutes at the end of which the benzylamine had been consumed and some nitroxide functions were still intact. The product mixture was analysed by g.c.m.s. and found to contain benzaldehyde (78 rel. %) and benzonitrile (22 rel. %). This compares with 86 rel. % benzaldehyde and 14 rel. % benzonitrile reported by Semmelhack[50] for a comparable experiment using a monomeric nitroxide in solution.

Conclusions

Poly(TEMPO-acrylate) has been shown to be an easily synthesised polymeric nitroxide. It has also been shown that the polymerisation process does not result in significant destruction of the nitroxide functions. The polymer is therefore useful for any application which requires a high density of unpaired spins.

The polymer has been shown to behave chemically in a very similar way to monomeric nitroxides. There does not appear to be any steric impediment to the reactions of polymer bound TEMPO units.

Platinum and carbon fibre electrodes modified with films of the polymer are stable to electrochemical cycling in acetonitrile and are reasonably so in water. This has enabled the application of these electrodes to the electrocatalysed oxidation of amines in solution. The instability of the polymer or its derivatives to strong bases has limited the scope of this technique. However it has been shown that some catalyses proceed without such destruction of the polymer and the results in this work nicely complement those of Deronzier[36] and Osa[39]who have reported similar experiments with alcohols as the substrate.

The increase in anodic current which is observed upon the oxidation of a substrate by these modified electrodes and the fact that this can be observed directly suggests that it may be possible to develop such modified electrodes as sensors for amines and alcohols. It is likely that future work will proceed in this direction.

6.4 Experimental

Basic techniques for the determination of spectra etc. were the same as described for chapter 2 except that the e.s.r. spectra of radicals in polar solvents were determined in soda - glass capillaries.

2,2,6,6-tetramethylpiperidinyl-4-acrylate Nitroxide. 4-hydroxy-2,2,6,6-tetramethylpiperidine (18.4g, 117mmol), sodium tungstate (1.80g) and ethylenediamine tetra-acetic acid (1.80g) were dissolved in water (80ml). 30% hydrogen peroxide solution (35ml) was added and the mixture stirred at ambient temperature for 5 hours. The solution was saturated with potassium carbonate then extracted with ether (3 x 50ml). The extracts were combined, dried (Na_2SO_4) and evaporated. The residual orange mass was recrystallised from a 50/50 mixture of ether and light petroleum to give 4-hydroxy-2,2,6,6-tetramethylpiperidinyl nitroxide (17.5g, 87%) as orange needles; a(N) (CH_2Cl_2) = 16.2G (270K); m/z 172(m^+, 13%), 157(5), 142(4), 127(3), 124(6), 116(9), 112(1), 109(8), 98(8), 85(31), 71(100), 57(64). 4-hydroxy-2,2,6,6-tetramethylpiperidinyl nitroxide (12.0g, 70mmol) and triethylamine (10.7ml) were dissolved in CH_2Cl_2 (50ml) and cooled over ice. The solution was vigorously stirred while a solution of freshly distilled acrylic acid chloride (7.8ml) in methylene chloride (20ml) was added dropwise. The solution was allowed to warm gradually to room temperature and stirring was continued for 2 hours. The precipitate was removed by filtration and the solution was washed with dilute hydrochloric acid (5ml) and water (10m), dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica with light petroleum as the eluant. The

eluted material was recrystallised from light petroleum to give the title nitroxide as deep red sweet smelling needles (10.1g, 64%); a(N) (CH_2Cl_2) = 16.2G (270K); m/z 226(m^+, 20%), 194(4), 154(14), 139(28), 124(82), 109(100), 81(19), 67(13), 55(67), 41(19); v (C=O) 1715cm^{-1}, (N-O) 1360cm-1.

Polymerisation of 2,2,6,6-Tetramethylpiperidinyl-4-acrylate nitroxide.

Materials. The solvent, tetrahydrofuran (500ml), was dried by refluxing over potassium metal for 20 hours and was then distilled, with the first 100ml and the last 100ml being discarded. The distillate was redistilled into a flask coated with Na/K amalgam on the high vacuum line. The anticipated blue colouration was observed. Dipotassium diphenylethylene dimer dianion was prepared as follows. 1,1-diphenylethylene (20µl) was placed in a tube containing a break-seal and pumped at ambient temperature for 2 seconds and then at -78°C for several minutes. This tube was sealed and blown onto a 50ml flask with attachments as shown (Figure 8)

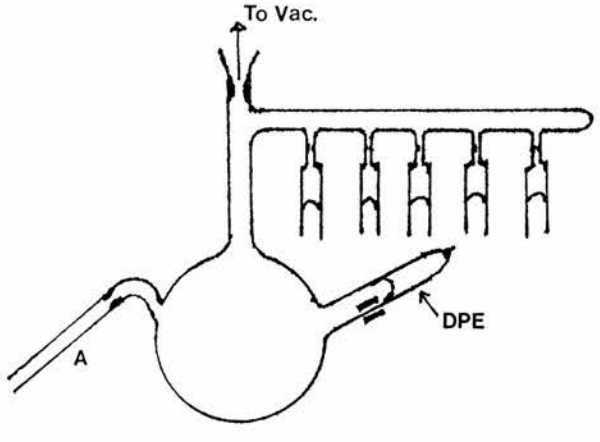


Figure 8

A small piece of potassium was placed in tube A which was sealed. The apparatus was attached to the vacuum line and pumped out. The potassium metal was distilled into the flask and tube A was removed. THF (25ml) was distilled into the apparatus which was then sealed. The seal in the tube containing the diphenylethylene was broken, the contents were mixed intermittantly for 1 hour and distributed evenly between each of 5 break-seal tubes which were then sealed off, each tube therefore contained ca. 2×10^{-5} mols of the dianion. n-Butyllithium was used as supplied (Aldrich).

Polymerisation using Diphenylethylene dianion. The monomer (0.5g, 2.2mmol) was placed in a tube to which a vial of the dianion solution had been attached. This apparatus was attached to the high vacuum line and pumped out. THF (2ml) was distilled into the tube which was then sealed off. The monomer was allowed to dissolve then the apparatus was cooled to -78°C and the initiator was added. Cooling was continued for 80 minutes after which it was found that some of the monomer had reprecipitated so the temperature was raised to ca. -60°C and maintained for a further 100 minutes. The reactor was opened and the contents poured into vigorously stirred methanol (200ml). No polymer precipitated. Analysis of the methanolic solution by g.p.c. indicated that 16% of the monomer had been converted to polymer. The weight average molecular weight could not be computed because of the very broad nature of the distribution curve (**Figure 1**).

Polymerisation using n-butylithium 1. The monomer (0.5g, 2.2mmol) was placed in a tube with a side arm sealed with a rubber serum cap. The tube was attached to the vacuum line and

pumped out. THF (13ml) was distilled into the tube and the monomer allowed to dissolve. 1.6M BuLi solution in hexane (87µl, 1 rel%) was added, the side arm was removed, the reactor sealed, cooled to -78°C and shaken. Cooling was continued for 170 minutes after which the vessel was opened and the contents poured into vigorously stirring light petroleum. The precipitated material was separated by centrifuging the mixture for 10 minutes at 2000 rpm. The polymer (0.3g) was analysed by g.p.c. and found to have a weight average molecular weight of 57,390 (**Figure 1, Table 1**). ν (C=O) 1724 cm^{-1}, ν (N-O) 1360 cm^{-1}.

Polymerisation using n-Butylithium 2. 1.6M n-BuLi (**Table 3**) was syringed into apparatus A (**Figure 9**) under nitrogen in a dry box. The apparatus was then attached to the vacuum line, pumped at room temperature for 2 seconds then cooled and pumped further so that only a little of the solvent remained. The fragile bulb was sealed off and placed in apparatus B (**Figure 9**) which was constructed as shown. The monomer (**Table 3**) was placed in

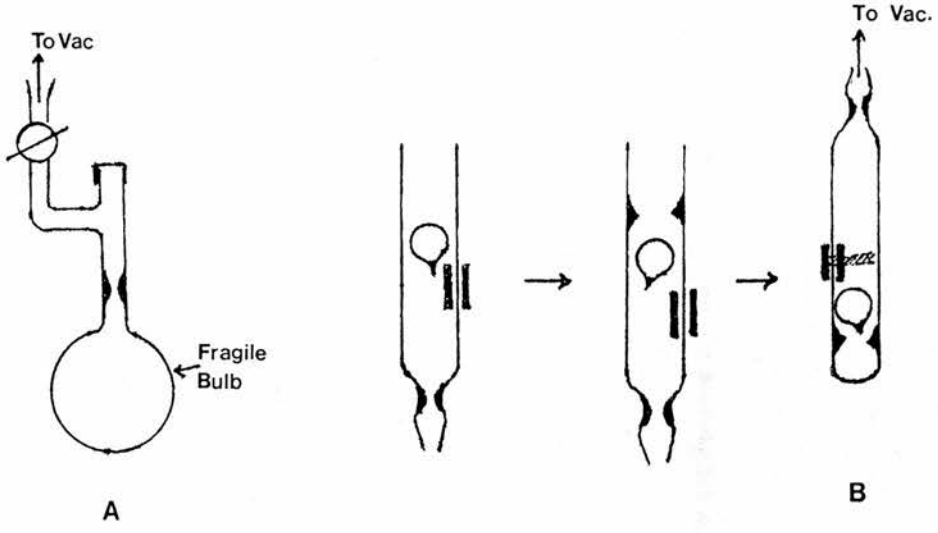


Figure 9

apparatus B which was pumped out on the vacuum line. THF (**Table 3**) was distilled into the reactor and the vessel was sealed. The monomer was dissolved up and the reactor cooled to -78°C. The fragile bulb containing the initiator was broken and the contents mixed with the monomer solution. Cooling was maintained for the periods specified in **Table 3** at the end of which the reactor was opened and the contents poured into rapidly stirring light petroleum. The precipitated polymer (**Table 3**) was isolated by centrifuging the mixture for 10 minutes at 2000 rpm. The polymer was further purified from a residual trace of monomer by dissolution in methylene chloride and reprecipitation from light petroleum.

Table 3

n-Butyl lithium initiated polymerisations of poly(TEMPO-acrylate)

Monomer/g	1.6M n-BuLi/μl	Solvent	Reaction time	Polymer yield
0.5	80	15ml	2h	0.3g, 60%
0.5	240	15ml	2h	0.3g, 60%
2.4g	380	60ml	20h	1.9g, 80%

Reaction of Polytempoacrylate with Acid Chlorides. The polymer (30mg, 0.13mmol N-O·) was dissolved in methylene chloride (1ml) and a large excess of the acid chloride was added. The precipitate which formed was filtered off. The product polymer was water soluble; δ_H(300MHz) 1.4 - 2.0(ca. 12H, m), 2.2 - 2.8(ca. 7H, bs) 3.5(<1H, bs), 3.7(<1H, bs), 4.1(<1H, bs), 5.4(<1H, bs), 5.7(<1H, bs).

Reaction of Polytempoacrylate with diacylperoxides. The polymer (30mg, 0.13mmol N-O·) was dissolved in methylene chloride

(1ml) and a solution containing an excess of the peroxide was added. Any product polymer was precipitated by adding light petroleum and isolated by filtration. The product polymer from the reaction with diacetyl peroxide was found to be e.s.r. inactive.

Reaction of Polytempoacrylate with Hydrogen Peroxide. The Polymer (30mg, 0.13mmol N-O) was added to a solution of *p*-dichlorobenzene in 30% hydrogen peroxide (2ml) and ethanol (10ml). The solution was stirred at room temperature for 2 hours then dried (Na_2SO_4) over 4 hours and analysed by g.c.m.s. which showed that no hydroxy derivatives of the dichlorobenzene had been formed or that they were present below the limit of detection.

Reaction of Polytempoacrylate with Benzyl Bromides. A solution of the polymer (0.1mM) and the bromide (1.0mM) in methylene chloride was prepared, placed in a soda glass capilary and degassed by bubbling nitrogen for 30 seconds. The capillary was placed in the cavity of the e.s.r. spectrometer and the disappearance of the polymer signal was monitored (**Figure 6**).

Preparative electrocatalysis of Benzylamine. The solution which was electrolysed in a standard two compartment cell was made up with lithium perchlorate (1.3g, 12.2mmol), lutidine (1.43g, 13.2mmol) and benzylamine (19.4mg, 0.18mmol) in MeCN (24ml) and water (1ml). The anode was a 3cm × 15cm piece of woven carbon fibre. The products of the electrolysis were identified as benzaldehyde (78 rel.%) and benzonitrile (22 rel.%) by comparison of their mass spectra with those of authentic samples.

CHAPTER 7

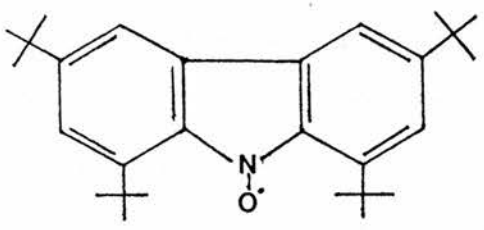
TOWARDS POLYARYL NITROXIDES

7.1 Synthesis.

Introduction

There are many pyrrole derived nitroxides which have been reported in the literature. For the most part, these have only been prepared under e.s.r. conditions and there is therefore no indication of the applicability of the methods used to bulk synthesis.

The e.s.r. spectra of pyrrole nitroxide derivatives show splittings from all the H and N atoms in the ring system indicating that there is substantial delocalisation of the unpaired electron. This delocalisation renders these radicals much more reactive than their tetramethylpiperidine counterparts. In terms of the definitions in chapter 5, most are persistent rather than stable radicals. Many persist in solution for several days but few have been isolated. The most stable are the heavily substituted radicals such as the tetra-t-butyl carbazole (1) which has been isolated as red crystals.[70] The most reactive are those with α-hydrogens, e.g. pyrrole nitroxide itself.



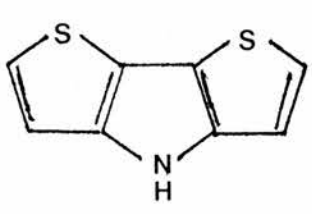
[1]

It is a requirement of the ultimate goals of this work that the pyrrole derivative which is to be polymerised to form a polyaryl nitroxide is capable of forming a polymer which is conductive. Unfortunately, aromatic compounds which have bulky substituents can be difficult to polymerise oxidatively, either for straightforward steric reasons or because the substituents block the most reactive sites on the cation or cation radical which is formed in the initial oxidation. Also, polymers formed from compounds with bulky substituents tend to be poor conductors as the substituents prevent the rings becomming co-planar in the polymer.[71] Hence, the conductivity of poly-N-isobutylpyrrole is an order of magnitude less than that of poly-N-n-butylpyrrole.[72] It has been pointed out that electronic effects from the substituents can also play an important role.[73]

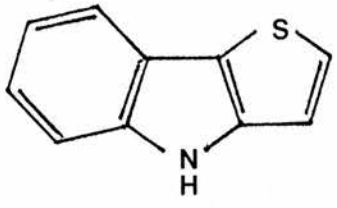
So, while it may seem attractively straightforward to prepare and polymerise a stable aryl nitroxide for study, it is unlikely that this would be satisfactory. Efforts were directed instead towards nitroxides of intermediate stability which it was hoped would be stable in their polymeric form where the ring systems would be substituted by each other.

The amines (2) and (3) were chosen as suitable building blocks. Both [3,2-b]thienoindole and [3,2-b;2',3'-d]dithienopyrrole were reported in the literature[74,75] and so

synthetic routes to obtain them were already described. However, as will be described, the preparation of [3,2-b;2',3'-d]dithienopyrrole presented unexpected difficulties. The polymerisation of neither amine had been reported but analogy with similar compounds suggested that the polymers should be conductive. Polyindole has a conductivity of $5 \times 10^{-3} - 10^{-2}$ $\Omega^{-1}cm^{-1}$.[76] Poly-[3,4-b;3',4'-d]dithienothiophene has a conductivity of 1.0 Ω^{-1} cm^{-1}.[77]



(2)

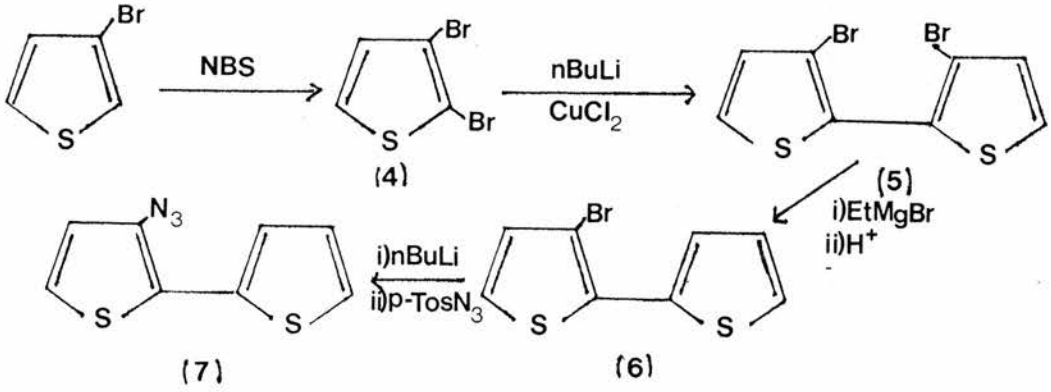


(3)

The nitroxide of (3) had been prepared in an e.s.r. experiment[78] and had been observed to persist in thiophene solution.

Attempted Synthesis of [3,2-b;2',3'-d]Dithienopyrrole (2).

Zanirato et al[75] have reported the synthesis of (2) by thermal decomposition of the azide (7) which they had prepared according to methods which are described in the literature and are outlined in Scheme 1.[79-81]



Scheme 1

This author found that the coupling of (4) to form (5) proceeded in poor yield and that purification of (5) formed in this organolithium coupling reaction was rather tedious, involving careful chromatography and repeated recrystallisations before analytically satisfactory material could be obtained. It was decided therefore to look at the possibility of performing this coupling reaction in a different way.

Coupling of thiophene rings has been achieved by Ullmann type reactions of substituted thienyl bromides using copper as a catalyst[82], using catalytic or stoichiometric amounts of Ni(0) complexes or activated nickel to couple halothiophenes[83] and there are numerous examples of coupling reactions which proceed via other types of thienylmetallic compounds, e.g. Grignard reagents and thienylcopper reagents[84]. There is also a report of replacement of the diazonium group in 2-nitro-3-thiophenediazonium ion by a 2-thienyl group under Gomberg[85] conditions but this proceeded in low yield.

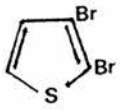
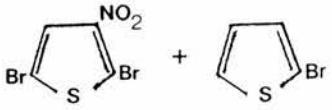
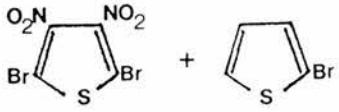
The possibility of building a useful coupled dithiophene by the use of the Ullmann procedure[82] was investigated. The Ullmann coupling of bromothiophenes and bromoselenophenes was known to proceed satisfactorily when there are electron withdrawing groups on the ring, e.g. NO_2 or RCOO.[82] Simple iodothiophenes have also been shown to couple although in the case of 2-iodothiophene only oligomeric products are obtained when the reaction is carried out in the absence of solvent. This was attributed to the thermal decomposition of the formed cupric iodide which lead to the iodination of the initially formed 2,2'-dithiophene and continuation of the reaction.[86]

Mixed coupling reactions of bromothiophenes and bromonitrothiophenes were attempted, with and without solvent and using heat or ultrasound to promote the reaction. The latter technique has been shown to work for a number of heterogeneous reactions.[87] It was anticipated that mixtures of coupled products might be obtained but that it should not be too difficult to separate the useful ones.

2,5-Dibromo-3-nitrothiophene and 2,5-dibromo-3,4-dinitrothiophene were prepared by nitrating 2,5-dibromothiophene.[88] The former product is very much a minor product of this reaction. It can also be prepared by bromination of 3-nitrothiophene which is easily prepared together with 2-nitrothiophene by nitration and hydrolysis of thiophene-2-sulphonylchloride.[89] The nitro-substituted compounds were selected because some similar compounds had been successfully coupled and because a 3-nitro-2,2'-dithiophene can be converted into the corresponding azide for use in the Zanirato[75] synthesis. There are also a number of examples of converting *o*-arylnitroaryl compounds directly to fused tricyclic amines by treatment with triethylphosphite.[90]

All these coupling reactions which are summarised in Table 1 were unsuccessful. It appears that the bromo and dibromothiophenes are simply not reactive in the conditions used. The nitro-substituted dibromothiophenes appear to be reactive but they proceed to form dark polymeric materials and no lower coupled products, dimers or trimers were identified. Monohalogenated nitrothiophenes might be more useful but such compounds would be tortuous to prepare.

Table 1

Reagents	Conditions	Product
	DMF, 5h reflux.	None
〃	No solvent, 17h sonication.	None
	DMF, 5h reflux.	Tar
〃 〃	DMF, 17h sonication.	None
	DMF, 2h at 120°C.	Tar
〃 〃	DMF, 4h at room temperature.	None
〃 〃	No solvent, 17h sonication.	Tar
〃 〃	DMF, 17h sonication.	Tar

Returning to Scheme 1, the 3,3'-dibromo-2,2'-bithiophene (5) was debrominated by the preparation and decomposition of the 3-Grignard reagent to give the monobromide (6). This bromide was also difficult to purify and it was used as an oil.

Debromination of 3,3'-dibromo-2,2'dithiophene was also attempted using 1 molar equivalent and 1.5 molar equivalents of tributyltin hydride. G.c.m.s. analysis of the resulting solutions showed that in addition to the starting material and a trace of bithiophene the major product was a tin compound which was not identified but from the presence of a cluster of isotopic peaks corresponding to SnS^+ it was inferred that attack on sulphur by

the tin radicals was more important than attack on bromine in this compound. A small amount of (6) was formed when an excess of tributyltin hydride was used but the "tin sulphide" was again the major product.

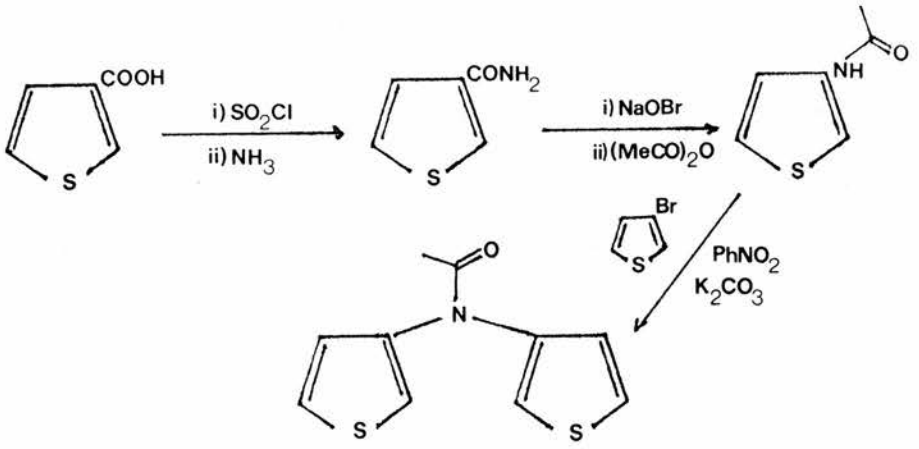
Conversion of this bromide to the corresponding azide (7), by reaction with *p*-toluenesulphonyl azide and decomposition of (7) in refluxing chlorobenzene according to Zanirato's method in an inert atmosphere gave a black intractable solid.

While there is no reason to doubt the authenticity of Zanirato's results, it was not possible, using the described procedure, to repeat them for this particular system. They report several different related thienyl azide decompositions and for the 2-thienylazides they also report the formation of polymeric material. It seems likely that in the case of the experiments described here that a minor impurity in one of the reagents has initiated a polymerisation reaction but whether the source of this was the undeniably slightly impure bromide (6) or the solvent was not determined.

It was decided to abandon this line of attack and to approach the problem from the other direction, i.e. to form the amine linkage first.

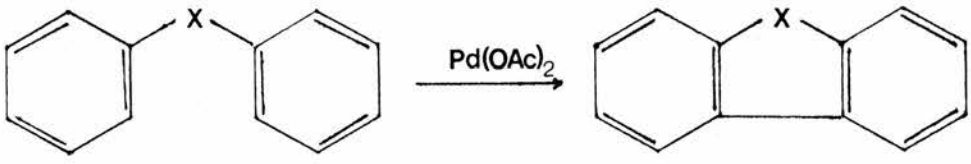
N,N-di(3-thienyl)acetamide was prepared according to the method of Grol[91] as shown in **Scheme** 2. Oxidative coupling reactions of the type shown in **Scheme** 3 have been carried out successfully for a number of diaryl substituted amines and amides as well as for diaryl ethers and ketones.[92] Although the

reactions of dithienyl compounds with Palladium Acetate had not been reported, it seemed that this might be a good route to the tricycle (2) required for the polymerisation study.



(8)

Scheme 2

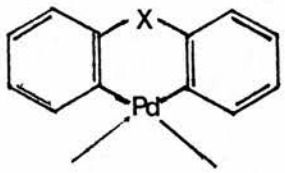


Scheme 3

Unfortunately, when N,N-di(3-thienyl)acetamide (8) was reacted with palladium acetate in refluxing acetic acid, the reagent was consumed but only black intractable material was formed.

From the data in Akermark's paper[92] it appears that the palladium acetate reaction proceeds most effectively for the diaryl compounds which are linked by an electron donating substituent. i.e. the more electron rich the rings are, the more readily the coupling proceeds. Thiophene rings, because of their smaller size have a higher electron density than benzene This

fact is reflected in the instability of thienylamines.[93] The problem may be that they are too reactive. An intermediate of type (9) has been proposed[92] for the reaction of a palladium complex with diphenyl compounds.



(9)

It seems possible that because the thiophene ring is expected to be more reactive, the geometry of the intermediate palladium complex may be less specific and consequently reaction pathways other than intramolecular cyclisation, e.g. intermolecular coupling are also favoured.

Another interesting piece of information comes from the ^{13}C n.m.r. of the amide (8) in which the signals for the ring carbons are broadened, indicating that their rotation is restricted and that they are not quite equivalent (**Figure 1**)

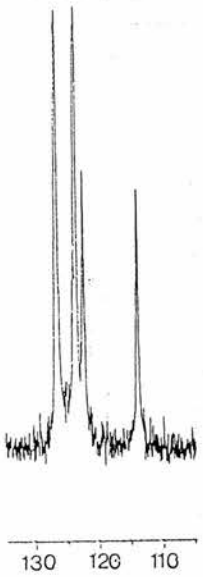


Figure 1: Room temperature ^{13}C n.m.r. of N,N-di(3-thienyl)acetamide (8).

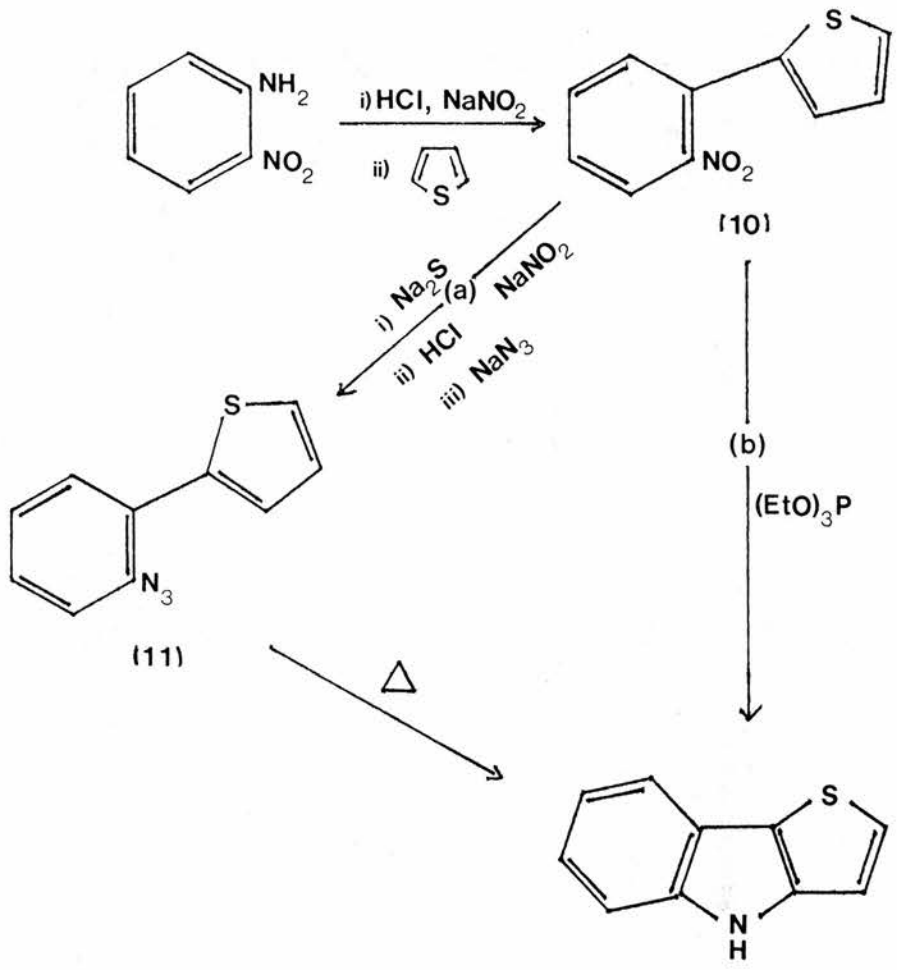
This restricted rotation could also affect the efficiency of the formation of the intermediate of type (9), although whether this effect is important at refluxing acetic acid temperature has not been investigated.

This experiment concluded the author's attempts to synthesise [3,2-b;2',3'-d]dithienopyrrole. Future workers may wish to investigate the failure of the thermolysis of 3-azido-2,2'-dithiophene or to turn to another method. The phosphite reduction of 3-nitro-2,2'-dithiophene is an attractive possibility. This will require the coupling of a 2-halo-3-nitrothiophene with a 2-halothiophene via one of the organometallic methods. This may involve a risk of the metal coordinating to the nitro group but the fact that 2,5'-dinitroselenophene has been prepared in an Ullmann coupling reaction is encouraging.[82] An alternative method would be Gomberg treatment of 3-nitro-2-thienyldiazonium ion with thiophene. The 3-thienyldiazonium ion has been reacted in this way to give a low yield of product.[85] 2-Thienylamines, from which the 2-thienyldiazonium would be prepared are less stable than their 3-thienyl counterparts and the synthesis might be problematic.

Synthesis of [3,2-b]Thienoindole.

[3,2-b]Thienoindole (3) was synthesised by Smith and Boyer[74] according to route (a) in **Scheme 4**. The initial stage is a Gomberg[85b] type reaction of *o*-nitrophenyldiazonium ion followed by conversion of the *o*-nitro(2-thienyl)benzene (10) to the azide (11) and thermolysis. It seemed that the latter stages could be simplified by treating the *o*-nitro(2-thienyl)benzene with

triethylphosphite according to the method of Cadogan et al,[90] route (b) in Scheme 4, and this turned out to be the case. [3,2-b]thienoindole was thus obtained from (10) in 71% yield.



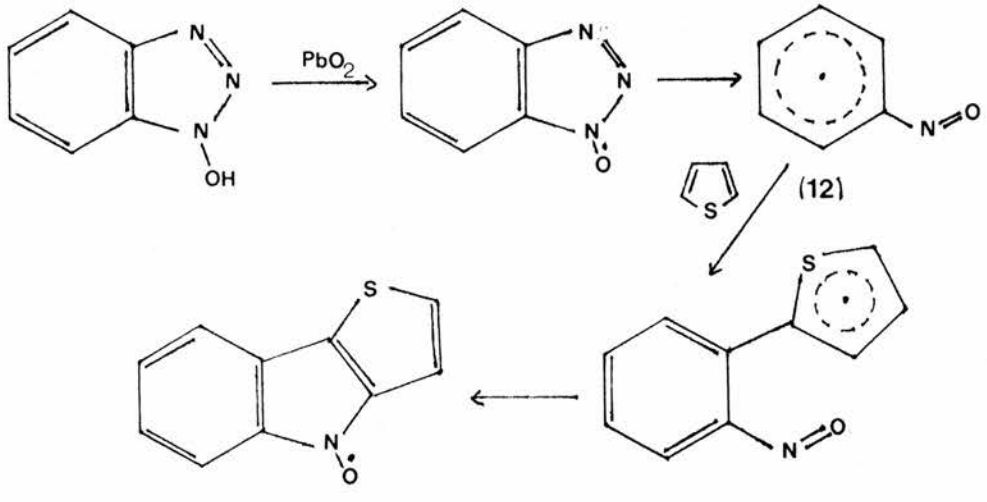
Scheme 4

Synthesis of [3,2-b]Thienoindoyl nitroxide.

Direct methods for the oxidation of [3,2-b]thienoindole failed. Hydrogen peroxide with and without the commonly used pertungstate catalyst[95], di-t-butyl peroxide and air were used as oxidising agents in various solvents (Table 2 in section 7.3). In the case of air no reaction was observed. In all other cases

highly coloured products, red or purple were formed but these were not e.s.r. active. Other workers have observed highly coloured polymeric products upon oxidation of pyrrole derivatives and they are believed to have been formed as a result of oxidation of the ring carbons rather than the nitrogen although they have never been properly characterised.[95]

Most aryl nitroxides which have been observed have been generated in e.s.r. experiments by the action of lead dioxide on hydroxylamines. Aurich and Weiss have reported the formation of [3,2-b]thienoindoyl nitroxide from the reaction of 1-hydroxybenzotriazole with lead dioxide in thiophene solution.[78] They propose the mechanism shown in Scheme 5.



Scheme 5

This procedure was repeated and the radical with the reported e.s.r. parameters, a(N)=6.45G, a(H)=2.05G, a(H)=1.81G, a(H)=1.05G, a(H)=0.45G and a(H)=0.24G was observed. The radical (13) was observed to persist in thiophene solution, under nitrogen, for 3 days. However, when the thiophene solvent was

evaporated the red-black tarry residue was found to be e.s.r. inactive in the solid state and when redissolved in solution.

The observation that the radical (13) was not isolable led to attempts to transfer it to solution in a solvent in which its electrochemistry could be studied and not be swamped by that of thiophene. Alliquots of the thiophene solution were added to a high boiling high dielectric solvent, dimethylformamide or propylene carbonate, and the thiophene was pumped off. When the resulting solutions were examined by e.s.r. spectroscopy they were found to be inactive. The suggestion that these highly polar solvents incresed the rate of radical termination was confirmed by preparing a solution of the radical (13) in thiophene as before and observing its e.s.r. spectrum after two drops of propylene carbonate were added to the solution. The e.s.r. signal disappeared over a period of two minutes.

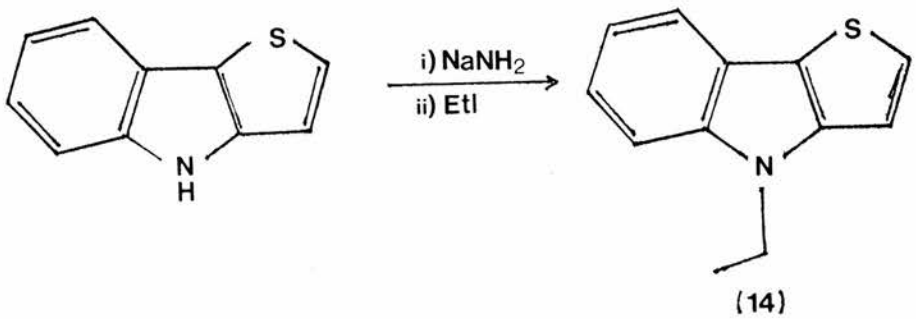
Whether these polar solvents promote bond cleavage in the radical or whether they are directly attacked by the radical is not clear as no analysis of the solutions was carried out.

An attempt was also made to prepare the radical in a solvent which is suitable for electrochemistry. One molar equivalent of 1-hydroxybenzotriazole and of thiophene were reacted with an excess of lead dioxide in acetonitrile. The solution was examined by e.s.r. and a single broad line was observed. No resolution on this line could be obtained to enable the radical to be identified. The most likely cause of this previously unobserved spectrum is a reaction involving the intermediate radical (12) in

Scheme 5 and acetonitrile as the solvent is the only different feature which has been introduced.

In a parallel effort, the synthesis of the [3,2-b]thienoindole hydroxylamine was attempted. Indole hydroxylamines have been prepared indirectly by cyclisation of a suitable derivative of benzene but has not been prepared directly from the amine.[96] It was decided to try to prepare the desired compound via decomposition of the tertiary amine oxide. This method has been used in the preparation of many aliphatic hydroxylamines[97] but not, to the author's knowledge for the preparation of aromatic hydroxylamines.

The N-ethyl tertiary amine (14) was prepared straightforwardly by treatment of [3,2-b]thienoindole with sodamide followed by ethyl iodide (Scheme 6). By contrast an attempt to form a tertiary amine by reaction of thienoindole with methyl 3-bromopropanoate in the presence of an inorganic base (sodium bicarbonate) was unsuccessful.



(14)

Scheme 6

Reaction of the tertiary amine (14) with hydrogen peroxide in ethanol/water and in acetic acid, according to the methods

prescribed for aliphatic amines,[98] gave intractable products rather than the hoped for tertiary N-oxide. Presumably the reasons for the failure of this experiment are similar to the reasons for the failure of the direct oxidation of the secondary amine which was described earlier, i.e. that the ring is being oxidised at sites other than the nitrogen.

Attempts to prepare the [3,2-b]thienoindoyl nitroxide in a form in which electropolymerisation experiments can be carried out were concluded at this point. It may be that a chemical polymerisation using Fe(III) as the oxidant could be attempted in a two phase system in which the radical is contained in solution in a solvent with which neither the radical nor the oxidant reacts readily. Substituted benzene compounds might be suitable (e.g. t-butylbenzene) and this is a possibility which future workers might investigate.

7.2 Polymerisation of [3,2-b]Thienoindole and N-Ethyl [3,2-b]Thienoindole.

In order to establish the value of future work on the preparation of [3,2-b]thienoindoyl nitroxide, it was considered neccessary to investigate the chemical and electropolymerisation of the free amine. As the N-ethyl derivative was available from the above noted work, its polymerisation was also investigated. It was considered important to establish the polymerisability of the amines, the mode of polymerisation and the conductivity of any polymer.

Poly-[3,2-b]thienoindole.

Electrochemical cycling of 5mM solutions of [3,2-b]thienoindole (3), using a Pt microelectrode as the working electrode, gave cyclic voltamograms which had an oxidation peak at +1.1V relative to Ag/Ag^{+}, a much smaller reduction peak at +0.1V with peak current (i_p) values in the ratio ca. 6:1 on the first cycle. There was also at least one other minor reduction peak at +0.7V. Upon repeated cycling the value of i_{pa} was found to increase (Figure 2) and after a number of cycles a dark deposit could be seen forming on the electrode.

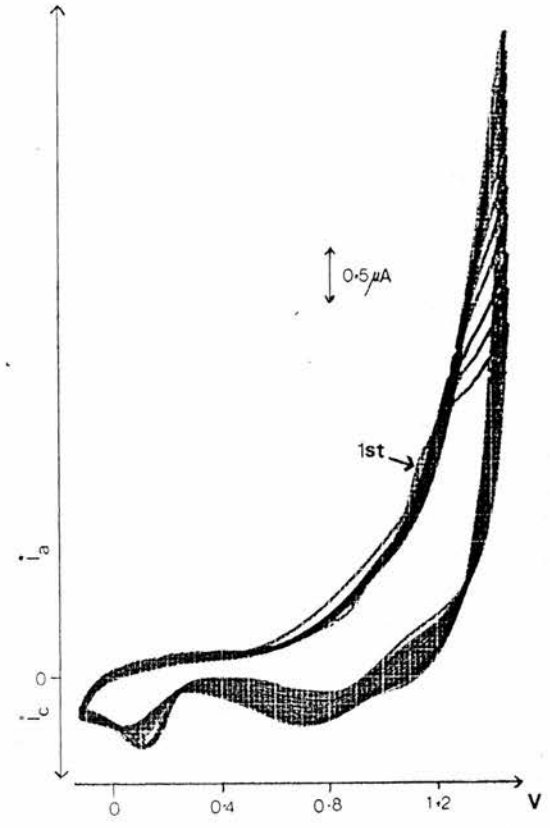


Figure 2: Development of c.v. upon repeated cycling of a solution of (3) in MeCN.

These observations are consistent with the growth of a conducting polymer on the electrode. As the polymer grows, the effective area of the electrode increases, the number of moles of substrate oxidised during each cycle and therefore the charge passed also increase giving a larger current. If the polymer formed were insulating, there would be no redox activity once the Pt electrode became coated unless the polymer were also permeable. The reduction wave at +0.1V probably corresponds to partial reduction of the oxidised species which is formed at +1.1V. The minor peak at +0.7V will be shown to be a reduction of the polymer which was formed.

When the solution was electrolysed at +1.1V, a red colouration was observed at the electrode, this was initially assumed to be the radical cation which was expected to be formed by the initial oxidation at the electrode.

It was found that films of the polymer could be grown on an Au/acetate working electrode in both methylene chloride and acetonitrile solvents with tetrabutylammonium hexafluorophosphate or tetrafluoroborate as the electrolyte. There was a greater amount of dissolution of the polymer in methylene chloride.

The conductivity of the polymer films was measured using a linear four point probe technique[96] whereby current is impressed on the two outer probes and the resistivity of the material is calculated from the potential difference between the two inner probes. The conductivity was found to be 10^{-3} $\Omega^{-1}cm^{-1}$. This is slighty poorer than that reported for polyindole[76] but is still sufficiently good for the material to be termed conductive and

potentially of value as the conducting backbone in the envisaged polynitroxides.

An electrode coated with the polymer film was cycled repeatedly in a clean solution of electrolyte and was found to be quite stable under these conditions. The cyclic voltamogram shows a reversible oxidation which presumably corresponds to cycling between the oxidised and neutral states of the polymer (**Figure 3**). When the scan rate (v) was varied it was found that i_p was proportional to v and that therefore charge transport across the film is fast and that all the electroactive sites in the film are in equilibrium with the electrode potential.

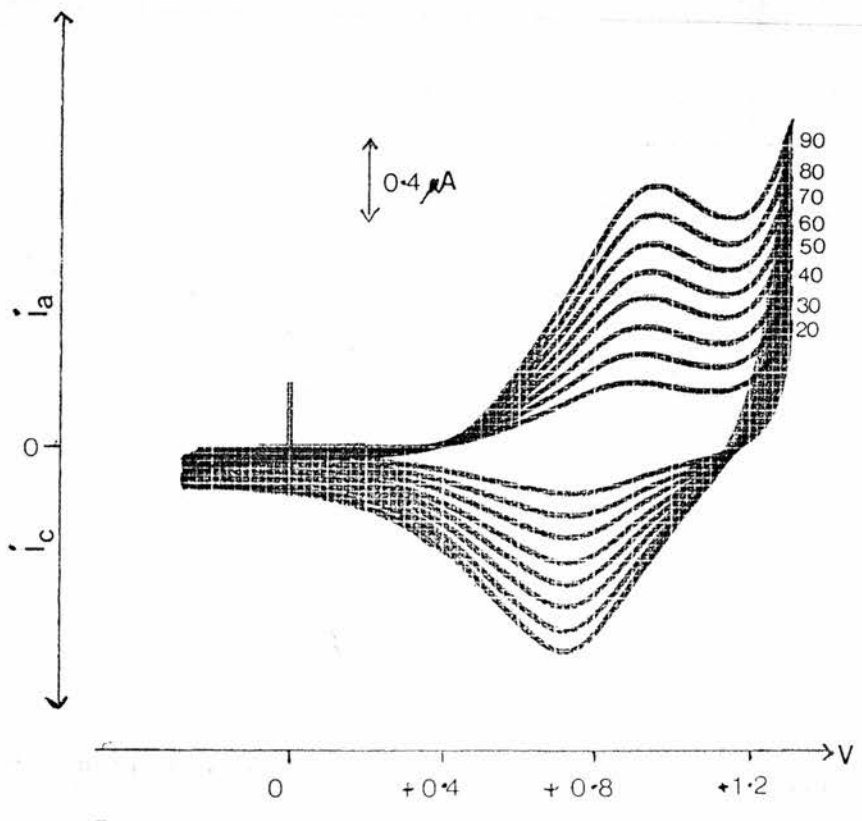


Figure 3: C.v. of polythienoindole with variable v/mv s^{-1}.

The electrolysis of a 1mM solution of [3,2-b]thienoindole in methylene chloride with tetrabutylammonium hexafluorophosphate as the electrolyte at +1.1V vs Ag wire in a quartz cell in the cavity of the e.s.r. spectrometer did not generate any e.s.r. active species, although the red colouration previously noted was observed in the vicinity of the working electrode. This strongly suggested that the initial oxidation which initiates the polymerisation is a two electron transfer. It would follow that the oxidised form of the polymer is a polydication and not a polyradical cation. This was supported by the observation that the polymer itself is not e.s.r. active unlike, for example, polypyrrole which has a strong e.s.r. signal with g = 2.0026.[99]

This observation and conclusion casts doubt on the prediction that the corresponding polynitroxide would offer the possibility of cooperative interactions between the unpaired electrons from the nitroxide function and those in the conjugated π-system. It is not, of course, possible to draw a firm conclusion from this; the oxidation potentials for electrons in the nitroxide may well be quite different.

Another result from this polymerisation which casts doubt on the value of polymerising thienoindoyl nitroxide is the absence of an N-H stretch absorption in the infra -red of poly-[3,2-b]thienoindole. This implies that the polymer is linked via the nitrogen atoms. A similar conclusion was put forward in the case of polyindole[100] which also does not have an N-H stretching absorption. It is a more surprising observation in this case. Polyindole is believed to polymerise predominantly in the mode shown in **Figure 4**.

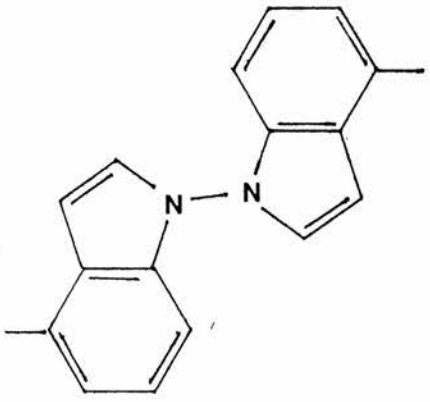


Figure 4

When the N position is blocked, indole does not electropolymerise. The thienoindole, however has an additional site, α to the sulphur which was expected to be very reactive. (Pyrrole and thiophene are known to polymerise predominantly through the α-carbons.) This polymer presumably polymerises through the nitrogen and the carbon α to the sulphur; it is rather surprising that the benzene ring does not participate.

The polymerisation of (3) was also attempted in a chemical experiment in a two phase system with $Fe(NO_3)_3$ as the oxidant. A dark solid formed at the interface which can be considered as being analogous to "pyrrole black"[191] a chemically prepared form of polypyrrole. This material which was reddish brown when dry was found by elemental analysis to have the approximate empirical formula $C_{10}H_5NS(NO_3)_{0.9}$. If the 'polymer' is in a dicationic form this implies that it is 45% oxidised. This is rather high. The oxidised form of electrochemically prepared polypyrrole is generally between 25 and 30% oxidised and many other polymers are oxidised to a lesser extent than that.[64] Pyrrole black formed by oxidation of pyrrole by hydrogen peroxide incorporates a stoichiometric amount of oxygen and it is thought that the pyrrole units are linked by oxygen in this material.

The chemically prepared 'polymer' of [3,2-b]thienoindole was found to have a conductivity lower than the limit of the measurement technique, i.e. $<10^{-10}\Omega^{-1}cm^{-1}$. The material was very brittle, however, and the difficulty of obtaining good probe - sample contacts may mean that this result is misleading. The material, like the electrochemically prepared films, was e.s.r. inactive and had no N-H stretching absorption in its infra-red.

Polymerisation of N-Ethyl [3,2-b]Thienoindole.

A solution of N-ethyl [3,2-b]thienoindole in acetonitrile with tetrabutylammonium tetrafluoroborate as the electrolyte was electrochemically cycled using a Pt microelectrode as the working electrode. The cyclic voltamogram obtained is shown (**Figure 5**)

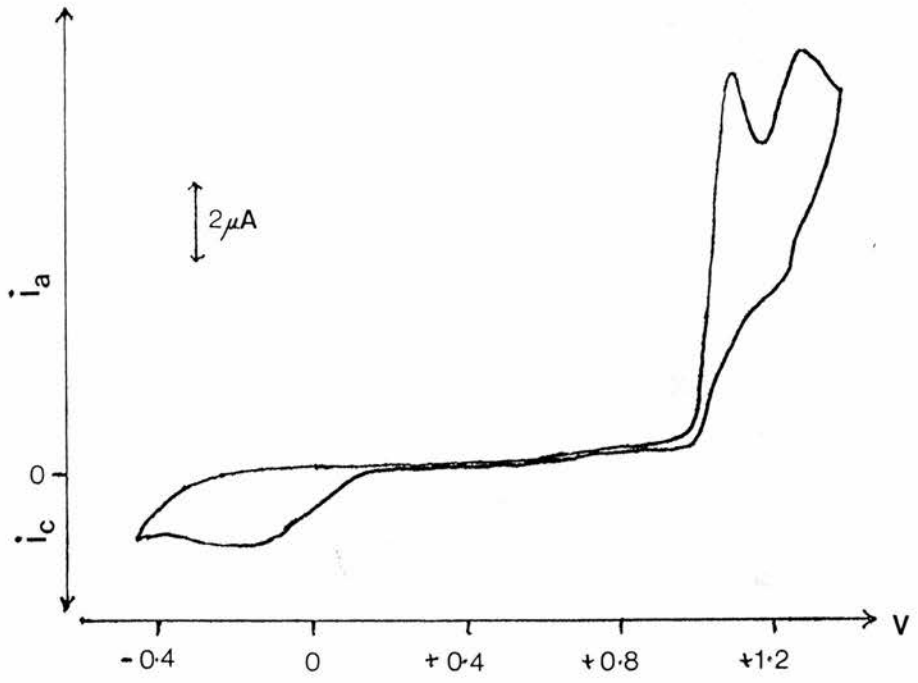


Figure 5: C.v. recorded upon cycling of a solution of (**14**) in MeCN.

The voltamogram shows two oxidations at +1.07V and +1.25V relative to the standard calomel electrode (s.c.e.) and two smaller reduction peaks at +1.2V and -0.15V. There was no change in i_p values with repeated cycling. This indicated that there was no growth of conducting polymer. After several cycles a metallic gold coloured deposit was observed on the working electrode. It is likely that this was the tetrafluoroborate salt of the dication formed by the observed oxidations. The precipitation of such a salt would explain why the oxidations are not observed to be fully reversible.

These observations back up some of the conclusions drawn from the experiments with the secondary amine. Firstly, the fact that the tertiary amine does not polymerise supports the view that thienoindole polymerisation proceeds through the nitrogen and is in line with the results obtained for N-substituted indole. Secondly, the unambiguous observation that there are two oxidation peaks close together in the c.v. of the tertiary amine lends credence to the suggestion that this is also the case for the secondary amine. It is unlikely that either oxidation is associated with the ethyl group.

The chemical polymerisation of N-ethyl [3,2-b]thienoindole was attempted using a similar system to that used for the secondary amine. A blue - black solid formed at the interface but its formation was very much slower than the material formed in the secondary amine polymerisation. The material was found by elemental analysis to have the approximate empirical formula $C_{12}H_{11}NS(NO_3)_{0.6}$ which suggested that it was a low molecular

weight salt, rather than a partially oxidised polymer. It was e.s.r. inactive and had a conductivity less than 10^{-10} $\Omega^{-1}cm^{-1}$.

General Conclusions.

The conclusion that thienoindole polymerises through the nitrogen suggests that it is not a suitable system on which to base a polynitroxide. If the nitroxide also polymerised through the nitrogen the polymer would not be a polynitroxide but most likely a poly(amine oxide) which might decompose to give ring opened systems under certain conditions. Alternatively the nitroxide may just not polymerise.

There are, of course, subsidiary and more general questions to be answered concerning the likely effect on polymerisation of formation of the oxoammonium ion if that occurs at a lower potential than any other oxidation of the nitroxide molecule. The answer to this question will have to await the outcome of further experimentation.

From the limited amount of work which has been done here it would seem that the use of a nitroxide based on the dithienopyrrole, which was the other target of the synthetic part of this work, would avoid at least one of the problems which have been identified in the thienoindole system. It has two reactive thiophene α sites available for polymerisation and is therefore unlikely to polymerise through the nitrogen.

7.3 Experimental

3,3'-Dibromo-2,2'-dithiophene (5). 2,3-Dibromothiophene (prepared by reacting 3-bromothiophene with N-bromosuccinimide[79]) (20.0g, 62mmol) was dissolved in 50ml of dry ether and cooled under nitrogen to -70°C. 2.5M n-butyllithium in hexane (64ml, 160mmol) was added with stirring over 3 hours. The solution was maintained at -70°C for a further 30 minutes. Anhydrous $CuCl_2$ (22.0g, 163mmol) was added slowly with vigorous stirring and the mixture was then allowed to warm to room temperature over 16 hours. The solution was decanted and the solid residue was washed with ether (100ml). The ethereal solutions were combined and washed with dilute HCl (4 x 100ml) and water (100ml) then dried (Na_2SO_4) and evaporated. The residue was purified on a silica column (2 x 15cm) with light petroleum as the eluant. The eluted pale yellow solid was purified further by repeated recrystallisation from light petroleum to give white prisims of the title compound (3.34g, 33%); δ_H(60MHz) 7.1 - 7.6 (4H, AB, δ_A7.5, δ_B7.1, J_{AB}=5); δ_C(75MHz) 112.6(C), 127.5(CH), 128.9(C), 130.6(CH); m/z 326(m^+, 58%), 324(100), 322(52), 245(18), 243(18), 201(15), 199(15), 164(45), 120(12), 82(9); Calc. 29.63 %C, 1.23 %H, found 29.59 %C, 1.07 %H.

2,5-Dibromo-3-nitrothiophene and 2,5-Dibromo-3,4-dinitrothiophene. 2,5-dibromothiophene (10.0g, 41mmol) and concentrated sulphuric acid (40ml) were mixed and cooled in ice. concentrated nitric acid (20ml) was added dropwise with stirring such that the temperature in the reaction vessel did not exceed 30°C. The reaction mixture was poured into ice. The precipitate of 2,5-dibromo-3,4-dinitrothiophene (3.2g, 86 rel.%, 24 abs.%)

was filtered off and recrystallised from light petroleum; m.p. 133 - 135°C. The filtrant was extracted repeatedly with ether, the extracts were combined and washed with bicarbonate solution, the bicarbonate washings were re-extracted with ether, the ether layers were combined, dried (Na_2SO_4) and evaporated. The residue was distilled on a Büchi Kugelrohr to give 2,5-dibromo-3-nitrothiophene as an oily mass of yellow crystals (0.45g, 14 rel%, 3.8 abs%); δ_H(60MHz) 8.3(1H, s) which was not purified further.

Attempted Ullmann Coupling of Bromothiophenes. The catalyst used in the coupling reactions was copper bronze which had been activated by washing with a weak solution of iodine in acetone. The reactions which were attempted and the reaction conditions are listed below.

2,3-Dibromothiophene (3.0g, 12mmol) was dissolved in DMF (10ml), catalyst (3.5g) was added and the mixture was refluxed for 5 hours. The liquid was decanted, the solvent was removed and the residue identified as unreacted dibromothiophene by comparison of its ^{1}H n.m.r. with that of an authentic sample.

2,3-Dibromothiophene (1.5g, 6mmol) was mixed with catalyst (1.8g) and the mixture sonicated in an ultrasound cleaning bath for 17 hours. The mixture was then diluted with ether, the ethereal solution was filtered and the ether was evaporated. The residue was identified as unreacted dibromothiophene by comparison of its ^{1}H n.m.r. with that of an authentic sample.

2,5-dibromo-3-nitrothiophene (200mg, 0.7mmol) and 2-bromothiophene (114mg, 0.7mmol) were dissolved in DMF (2.0ml) and catalyst (50mg) was added. The mixture was refluxed for 5 hours. The residue was diluted with ether, the ethereal solution filtered and evaporated. The dark residual material was not identified.

2,5-dibromo-3-nitrothiophene (0.5g, 1.7mmol) and 2-bromothiophene (2.0ml) were dissolved in DMF (2.0ml), catalyst (1.8g) was added and the mixture was sonicated for 17 hours in an ultrasound cleaning bath. The mixture was diluted with ether and the ethereal solution filtered and evaporated. ^{1}H n.m.r. analysis of the residue indicated that it was a mixture of the two reactants.

2,5-dibromo-3,4-dinitrothiophene (3.32g, 10mmol) and 2-bromothiophene (3.26g, 20mmol) were dissolved in DMF (20ml) and heated at 120°C for 2 hours. The mixture was cooled, diluted with ether, the ethereal solution filtered and evaporated. The dark residue was not identified.

2,5-dibromo-3,4-dinitrothiophene (1.0g, 3mmol) and 2-bromothiophene (2ml) were dissolved in DMF (5ml),mixed with catalyst (1.2g) and stirred for 4 hours at room temperature. The mixture was then diluted with ether, the ethereal solution was filtered and evaporated. The residue was found to be a mixture of the reactants by ^{1}H n.m.r.

2,5-dibromo-3,4-dinitrothiophene (1.0g, 3mmol) and 2-bromothiophene (2ml) were mixed with catalyst (1.2g) and

sonnicated for 17 hours. The mixture was diluted with ether, the ethereal solution was filtered and evaporated. The residue was found to be mainly the reagents by ^{1}H n.m.r., together with some tarry material which was not identified. The experiment was repeated in DMF (5ml) and this resulted in the formation of a larger proportion of the tarry material which had δ_H 6.7 -7.7(bs) and was not characterised further.

3-Bromo-2,2'-bithiophene: Grignard Method. 3,3'-Dibromo-2,2'-dithiophene (5.0g, 15mmol) and magnesium turnings were covered with dry ether and stirred while ethyl bromide (14.6g, 13mmol) was added slowly such that the solution refluxed gently. The mixture was stirred at room temperature for 16 hours then refluxed for a further 5 hours. The mixture was cooled, decomposed with 2N HCl, the ether layer was washed with bicarbonate solution and water then dried (Na_2SO_4) and evaporated. The residue was distilled on a Büchi Kugelrohr to give 3-bromo-2,2'-dithiophene (1.85g, 49%) as an oil which was not purified further; b.p. 140-150°C/1 Torr; δ_H(80MHz) 6.9 - 7.5(5H, m); m/z 246(m^+, 23%), 244(23), 166(52), 121(60), 69(40), 57(32), 45(100).

3-Bromo-2,2'-bithiophene: Attempted Radical Reduction Method. 3,3'-dibromo-2,2'dithiophene (68mg, 0.2mmol) was dissolved in dry ether (0.5ml) and the solution degassed by bubbling nitrogen for ca. 2 minutes. Tributyltin hydride (52mg, 0.2mmol) was added and the solution was photolysed for 1 hour with light from a 250W medium pressure Hg arc. The solution was diluted with ether (10ml) and washed with dilute aqueous KF (10ml), dried (Na_2SO_4) and concentrated. The concentrated solution was analysed by

g.c.m.s. and found to consist of 3 components. The first eluted component (ca. 5 rel.%) was bithiophene by comparison with an authentic spectrum; m/z 166(m^+, 100%), 121(16), 69(7) and 45(12). The second eluted component was not identified but had isotopic groups characteristic of tin compounds at m/z 311(5%), 269(64), 257(5), 213(32), 177(43), 155(66), 120(34) and also peaks at m/z 57(97) and 41(100). The third eluted component was identified as 3,3'-dibromo-2,2'-dithiophene by comparison of its spectrum with that of an authentic sample.

3-Bromo-2,2'-bithiophene: Attempted Radical Reduction Method - Excess of Hydride. 3,3'-dibromo-2,2'-dithiophene (32mg, 0.1mmol) was dissolved in ether (0.6ml) and the solution was degassed by bubbling nitrogen for ca. 2 minutes. Tributyltin hydride (43mg, 0.15mmol) was added and the solution was irradiated with light from a 250W medium pressure Hg arc for 260 minutes. The mixture was diluted with ether (10ml) and washed with aqueous ammonia, dried (Na_2SO_4) and evaporated. The product was analysed by mass spectroscopy and was found to be a mixture of 3,3'-dibromo-2,2'-dithiophene, 3-bromo-2,2'-dithiophene, 2,2'-dithiophene and the unidentified tin compound noted above by analogy with authentic spectra and those already described. The mixture had δ_C(75MHz) 107.9, 112.7, 123.7, 124.3, 124.4, 126.1, 126.8, 127.2, 127.5, 127.8, 130.8, 131.8, 132.3, 134.3, 137.4. and δ_H(80MHz) 6.9 - 7.5(m).

Attempted Preparation of [3,2-b;2',3'-d]Dithienopyrrole (2). A solution of 3-bromo-2,2'-dithiophene (1.66g, 6.8mmol) in dry ether (2.7ml) was added dropwise to a stirred solution of 2.5M n-butyllithium in hexanes (3.0ml) at -70°C. Stirring was continued

for 45 minutes then an ethereal solution of *p*-toluenesulphonyl azide (1.48g, 7.5mmol) was added dropwise and the solution was stirred at -70°C for 5 hours. The yellow triazine salt which formed was rapidly filtered off and washed several times with dry ether. The salt was then suspended in dry ether (20ml) at 0°C, when a solution of tetrasodium pyrophosphate decahydrate (3.1g) in water (34ml) was added. The mixture was stirred at room temperature for 16 hours. The ether layer was separated and the aqueous layer was extracted with pentane (2 × 20ml). The combined organic layers were washed with water (20ml) and dried (Na_2SO_4). The solution was reduced in volume to ca. 3ml and transferred to a silica column (15 × 2cm) which was eluted with light petroleum (150ml). The eluted solution was evaporated at room temperature and the residue was dissolved in chlorobenzene (5ml). This solution was added dropwise to refluxing chlorobenzene (10ml) under nitrogen. Reflux was continued for 30 minutes at the end of which the solution had turned black. The solvent was removed by distillation to leave a black tarry residue which had δ_H(60MHz) 7.0 - 7.7(bs) and 7.7 - 8.5(bs) and was not characterised further.

***N*-(3-thienyl)acetamide.** Thiophene-3-carboxylic acid (5.0g, 39mmol) was dissolved in thionyl chloride (10ml) and refluxed for 6 hours. The excess of thionyl chloride was removed by distillation with benzene then the residue was cooled and poured slowly into a large excess of 10% aqueous ammonia. The precipitate was filtered off and recrystallised from a 50:50 methanol/water mixture to give 3-thienylamide (4.7g, 95%); m.p. 174 - 178°C (with decomposition), lit.[102] 178-179°C . A sodium hypobromite solution was prepared by adding bromine (2.7ml) to an

ice cold solution of NaOH (8.0g) in water (70ml) under nitrogen. 3-thienylamide (4.7g, 37mmol) was added slowly to the cold solution. Stirring was continued at ice temperature for 1 hour then the solution was gradually warmed to 70°C and maintained at this temperature for 45 minutes. The temperature was not allowed to rise above 75°C. The now dark red solution was cooled over ice and acetic anhydride (7ml) was added slowly with vigorous stirring. The precipitate was filtered off and recrystallised from methanol to give the title compound as white plates (2.5g, 48%); δ_H(300MHz) 6.9(1H, d, J=6), 7.2(1H, dd, J_1=6, J_2=4), 7.5(1H, d, J=4), 7.8(1H, bs); δ_C 23.9(CH_3), 110.3(CH), 121.0(CH), 124.5(CH), 135.6(C), 167.7(C); m/z 141(m^+, 28%), 99(100), 71(20), 54(16), 45(38), 43(57).

N,N-Di(3-thienyl)acetamide (8). N-(3-thienyl)acetamide (450mg, 3.2mmol) and 3-bromothiophene (2.5ml) were dissolved in nitrobenzene (10ml). Potassium carbonate (450mg) and copper bronze (50mg) were added and the mixture was refluxed for 4 hours. The solvent and excess 3-bromothiophene were removed by distillation under water pump pressure. The last traces of nitrobenzene were removed by distillation in steam. The residue was distilled on a Büchi Kugelrohr to give the title compound as an off-white solid (580mg, 81%); b.p. 205°C/1Torr; δ_H(80MHz) 2.1(3H, s), 7.0 - 7.2(2H, m), 7.3 - 7.5(4H, m); δ_C(75MHz) (**Figure 1**) 23.8, 113.9, 122.4, 123.5, 126.6, 169.7; m/z 223(m^+, 25%), 181(100), 136(77), 110(16), 97(8), 83(12), 69(8), 57(7), 45(78), 43(89), 39(59) and 28(19).

Reaction of N,N-Di(3-thienyl)acetamide (8) with Palladium (II) Acetate. N,N-di(3-thienyl)acetamide (140mg, 0.6mmol) was

dissolved in glacial acetic acid (2ml). Palladium (II) acetate (140mg, 0.6mmol) was added and the mixture was stirred and monitored by t.l.c on alumina with ether as the eluant. After 2 hours no reaction had taken place. The mixture was then refluxed for 3 hours at the end of which t.l.c. indicated that there was only one mobile component in the mixture. The solvent was removed under reduced pressure and the, mostly intractable, black residue was washed with methanol (30ml). The washings were decolourised by passing through charcoal and were evaporated to leave a residue (30mg) which was identified as N,N-di(3-thienyl)acetamide by comparison of its mass spectrum with that described earlier.

o-Thienylnitrobenzene. *o*-Nitroaniline (28.0g, 200mmol) was mixed with water (80ml) and concentrated HCl (45ml) and cooled over ice - salt. A solution of sodium nitrite (14.5g) in water (50ml) was added dropwise with stirring. Stirring was continued for a further hour then the diazonium solution was filtered, thiophene (100g) was added and the mixture cooled to 0 - 5°C. A solution of hydrated sodium acetate (80.0g) in water (200ml) was added dropwise with stirring. The mixture was stirred and maintained at ice - temperature for 3 hours then warmed to room temperature and stirred for 48 hours. The mixture was filtered and the thiophene layer separated. The aqueous layer was extracted with ether (2 x 200ml) and all the organic layers were combined, dried (Na_2SO_4) and the ether and the excess thiophene were removed under reduced pressure to leave a dark red tar. The residue was distilled under reduced pressure (b.p. 115 - 122°C/0.1Torr) to give a golden yellow oil which partially crystallised on standing. This material was recrystallised from methanol to give the title compound as bright yellow needles

(8.6g, 21%); m.p. 50 - 52°C (lit.[74] 51 - 52°C); δ_H(80MHz) 6.9 - 7.2(2H, m), 7.4 - 7.8(3H, m), 8.0 - 8.3(2H, m).

[3,2-b]Thienoindole (3). *o*-Thienylnitrobenzene (2.0g, 9.8mmol) was mixed with triethylphosphite (10ml) and refluxed for 2 hours. The excess triethylphosphite and the triethylphosphate which had formed were removed by distillation under reduced pressure. The dark residue was distilled on a Büchi Kugelrohr at oil pump pressure to give an off - white solid which was subsequently recrystallised from methanol to give the title compound as white plates (1.2g, 71%); m.p. 173 - 175°C (lit.[74] 175°C); δ_H(300MHz) 7.0(1H, d, J=6), 7.1 - 7.4(4H, m), 7.7(1H, dd, J_1=8, J_2=2), 8.0(1H, bs); δ_C(75MHz) 111.4(CH), 111.9(CH), 117.9(C), 118.8(CH), 119.8(CH), 122.1(C), 122.8(CH), 126.9(CH), 141.2(C), 143.0(C); ν (N-H) 3390 cm^{-1}.

N-Ethylthienoindole (14). A suspension of sodamide was prepared by slowly dissolving sodium metal (1.1g) in liquid ammonia (125ml) to which ferric nitrate (ca. 10mg) had been added. To this solution, (3,2b) thienoindole (2.45g, 14mmol) in dry ether (100ml) was added slowly. The mixture was stirred for 1 hour then a solution of ethyl iodide (6.7g, 43mmol) in dry ether (5ml) was added. The mixture was stirred for 16 hours while the remaining ammonia evaporated. The residue was washed into a separator with a mixture of ether and water. The ether layer was separated and the aqueous layer extracted with ether. The ether layers were combined, dried (Na_2SO_4) and evaporated. The residue was distilled on a Büchi Kugelrohr to give the title compound (**14**) as a thick colourless oil (1.7g, 60%) which discoloured on standing; b.p. 185 - 190°C/2Torr; δ_H(300MHz) 1.4(3H, t, J=7),

4.3(2H, q, J=7), 7.0(1H, d, J=6), 7.1(1H, t, J=7), 7.2 - 7.4(3H, m), 7.7(1H, dd, J_1=8, J_2=2); δ_C(75MHz) 14.7(CH_3), 39.7(CH_2), 109.6(CH), 110.1(CH), 116.0(C), 118.9(CH), 118.9(CH), 121.8(C), 122.3(CH), 126.7(CH), 140.8(C), 144.8(C); m/z 201(m^+, 54%), 186(100), 172(13), 128(13), 115(18), 101(9), 93(5), 87(4), 75(4), 69(5), 45(7).

Attempted Preparation of N-(methyl-n-propanoate)-thienoindole. [3,2-b]Thienoindole (0.4g, 2.3mmol) was dissolved in toluene (5ml) and this solution was mixed with a solution of $NaHCO_3$ (0.24g) in water (1ml). The mixture was stirred and heated to ca. 90°C when methyl-3-bromopropanoate (0.4g, 2.4mmol) was added dropwise. The mixture was maintained at ca. 90°C for 3 hours then cooled, filtered, the organic layer was separated and washed with brine (2ml), dried (Na_2SO_4) and evaporated. The residue was analysed by ^1H n.m.r. and found to be [3,2-b]thienoindole by analogy with the spectrum described above.

Attempted Preparation of N-Ethyl[3,2-b]thienoindole N-oxide. N-Ethyl[3,2-b]thienoindole (240mg, 1.2mmol) and 30% aqueous hydrogen peroxide (150µl, 1.3mmol) were dissolved in the minimum amount of ethanol and refluxed for 10 hours then stirred at room temperature for 40 hours (until the solution tested negative for peroxide). The solvent was evaporated to leave a reddish - black residue which was mostly intractable. Part of this material was taken up in methanol which on evaporation of the methanolic solution and ^1H n.m.r. analysis of the residue was shown to be mainly N-ethyl[3,2-b]thienoindole by comparison of its spectrum with that described above. The same result was obtained for reaction times of 7 hours reflux and 2 hours at room temperature.

N-Ethyl[3,2-b]thienoindole (500mg, 2.5mmol) was dissolved in glacial acetic acid (2ml) and this solution was degassed by bubbling nitrogen. 30% Hydrogen peroxide (300μl) was added and the solution was heated to ca. 120°C. After 45 minutes a violent reaction occured. The solvent was removed to leave a black solid which was entirely intractable.

Electropolymerisation of [3,2-b]Thienoindole (3). A solution of [3,2-b]thienoindole (5mM) and tetrabutylammonium hexafluorophosphate (100mM) in methylene chloride was electrolysed at +1.0V vs Ag/Ag^{+}; the working electrode was a $1cm^{2}$ gold film on polyacetate, the counter electrode was Pt wire. Potentiostating was continued for ca. 30 minutes after which a dark film had coated the working electrode; u.v/vis. λ_{max}=480nm; i.r. ν (N-H) absent.

Chemical Polymerisation of [3,2-b]Thienoindole. [3,2-b]Thienoindole (300mg, 1.7mmol) was dissolved in methylene chloride (2ml) and the solution was placed in a tube over saturated aqueous ferric nitrate (2ml) and stood for 24 hours. The dark solid which formed at the interface was removed by filtration and washed repeatedly with water and dried in vacuo over $CaCl_2$. The reddish brown material thus obtained (160mg) analysed for 52.68 %C, 2.38 %H, 11.29 %N; i.r. ν (N-H) absent, ν/cm-1 1620, 1510, 1450, 1390, 1330, 1290, 745.

Attempted Electrochemical Polymerisation of N-Ethyl[3,2-b]thienoindole (14). A solution of the title compound (**14**) (50mM) and tetrabutylammonium tetrafluoroborate (100mM) in acetonitrile was electrolysed at +1.1V vs s.c.e.; the working electrode was a

Pt microelectrode, the counter electrode was Pt wire. The electrode current did not increase with potentiostating and after 5 minutes a metallic gold coloured deposit could be observed on the working electrode. This deposit was not characterised.

Chemical polymerisation of N-Ethy[3,2-b]thienoindole (14). A solution of the amine (**14**) (200mg, 1.0mmol) was dissolved in light petroleum (2ml) and this solution was placed in a tube over saturated aqueous ferric nitrate (2ml) and stood for 72 hours. The dark solid which formed was removed by filtration and washed repeatedly with water and light petroleum then dried in vacuo over $CaCl_2$ to give a blue - black solid (70mg) which analysed for 61.18 %C, 4.81 %H, 7.19 %N; i.r. v/cm-1 2930, 1730, 1610, 1510, 1450, 1390, 1295, 745.

Solutions of [3,2-b]Thienoindoyl nitroxide in Thiophene. 1-Hydroxybenzotriazole (1.0g, 7.4 mmol) was mixed with thiophene (25ml) and the suspension was degassed by bubbling nitrogen for ca. 15 minutes. The suspension was kept under nitrogen and lead dioxide (4g, 16.7mmol) was added and the mixture stirred for 30 minutes. The solution was filtered and analysed by e.s.r. The e.s.r. parameters for the observed radical were in agreement with those described in the literature[7e] for the title radical (**13**).

Attempted Preparation of [3,2-b]Thienoindinoyl Nitroxide in Acetonitrile. 1-Hydroxybenzotriazole (0.5g, 3.7mmol) and thiophene (0.3g, 3.6mmol) were mixed in acetonitrile (5ml) and the mixture was degassed by bubbling nitrogen for ca. 15 minutes. Lead dioxide (4.0g) was added and the mixture stirred under nitrogen for 24 hours. Aliquots of the solution were analysed by

e.s.r. from time to time. A single broad line persisted in the e.s.r. for the duration of the experiment. The title radical (13) was not observed.

Attempted Preparation of [3,2-b]Thienoindinoyl Nitroxide by Direct Oxidation of the Amine. In each experiment a 2.5% solution of the amine (3) (2ml) in the appropriate solvent was degassed by bubbling nitrogen for ca. 5 minutes and an excess of the oxidant was added. The solution was then shaken or stirred for ca. 1 hour. In each case listed (**Table 1**) highly coloured (red or purple) solutions resulted which were not e.s.r. active and were not characterised further.

Table 2

Oxidant	Solvent
Hydrogen Peroxide	Water/Ethanol (1:1)
H_2O_2 + NaOH	Water/Ethanol (1:1)
Hydrogen Peroxide	Ethanol
Hydrogen Peroxide	1,4-Dioxan
$H_2O_2/NaWO_4$/EDTA	Methanol/Water (4:1)
Di-t-butylperoxide[a]	t-Butylbenzene
Air	Acetonitrile

a. A weak, broad, single line, was observed in the e.s.r. but the line width was incompatible with a poorly resolved spectrum of [3,2-b]thienoindoyl nitroxide.

In situ Electrolysis of a Solution of [3,2-b]Thienoindole in the Cavity of the E.S.R. Spectrometer. A solution of [3,2-b]thienoindole (1mM) and tetrabutylammonium hexafluorophosphate (100mM) was electrolysed in a 1.5 × 10 × 25mm quartz flat cell in

the cavity of the e.s.r. spectrometer (**Figure 6**). The working electrode was Pt gauze, the counter electrode was a W loop, the reference was Ag wire. The solution was potentiostated at +1.0V. No e.s.r. signal was observed in the region g = 2.002 - 2.003 or in any other region examined.

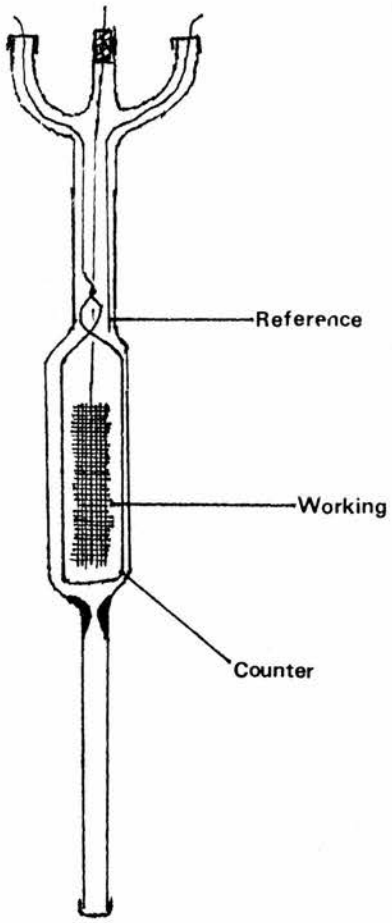


Figure 6. Electrochemical e.s.r. apparatus.

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