A THESIS

ENTITLED

'STUDIES IN NITROXIDE RADICAL CHEMISTRY'

presented to The University

of Glasgow for the degree of

Doctor of Philosophy

by

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1972

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To my parents

ACKNOWLEDGMENTS.

I would like to record my sincere thanks and appreciation to my supervisor, Dr. J.S. Roberts, for his helpful advice, friendly encouragement, and endless patience over the last three years.

My thanks are also due to Dr. A.L. Porte, for recording the e.p.r. spectra, to Dr. P.M. Scopes for running the c.d. spectra, and to Professor A.R. Katritzky and Dr. I.D. Blackburne for the dipole moment measurement.

In addition I would like to express my gratitude to the technical staff of this department for their able assistance.

Finally, I wish to acknowledge the receipt of a Scholarship from the Carnegie Trust for the Universities of Scotland.

SUMMARY.

The approach adopted in this study of nitroxide radical chemistry involves two closely interrelated themes. In the first section, attention is focused on the development of novel methods for nitroxide radical synthesis, while in the second section a more physico-chemical approach assumes the dominant role.

Thus, in Chapter 1, caryophyllene nitrosite is shown to react with caryophyllene by an intermolecular "ene" reaction to afford an unusually stable nitroxide adduct possessing a hydrogen atom on the α carbon. Some extensions of this method are discussed.

In Chapter 2, the successful elaboration of several suitably substituted δ-ϵ unsaturated nitro-olefins to a variety of pyrollidino nitroxide radicals by a bifurcated approach is presented.

In the second section, the previously developed synthetic methods are extended to encompass the synthesis of several bicyclo(3,3,1) nitroxide radicals and the conformational and chiroptical properties of these compounds are examined.

CONTENTS

INTRODUCTION.

The study of nitroxide radicals is of relatively recent vintage and over the past twelve years has witnessed an exponential growth from several varied standpoints. These include the intrinsic theoretical, spectroscopic and chemical aspects and the broader application to other allied sciences such as molecular biology, biophysics and polymer chemistry.

Several reviews, [1,2,3,4] on nitroxide radical chemistry have recently been published and these serve to indicate the great diversity of structural types into which the nitroxide nucleus has been embedded. The primary objective of this introduction is, however, to highlight the progress made in aliphatic nitroxide radical chemistry. In particular, attention will be focused on the electronic and spectroscopic properties of this class of nitroxide; and an attempt will be made to delineate the various synthetic methods which have been employed to prepare them. These aspects will act as a convenient springboard from which the results embodied in this thesis may be considered.

The inherent electronic stability of the nitroxide function accounts for the unusually long lifetimes of these radical species, and is readily appreciated by constructing the simple molecular orbital energy level diagram shown in Fig. 1.[5].

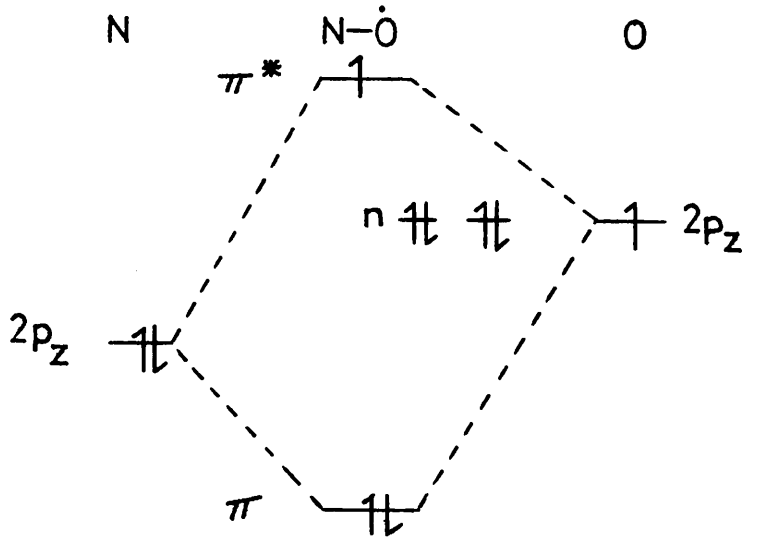
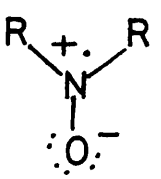


Fig. 1

The bonds to nitrogen are considered to be sp^2 hybrids and a σ bond is formed by the overlap of one of these hybrids with a p orbital on oxygen. Overlap of the $2p_z$ orbitals on nitrogen and oxygen results in a π bonding and a π^* antibonding orbital. Since two electrons occupy the π bonding orbital the unpaired electron resides in the π^* antibonding orbital, thus forming a stabilised π system which may be described as a two-centre three-electron bond.

In valence-bond terminology the nitroxide moeity can be represented by the two contributing resonance structures (1) and (2).



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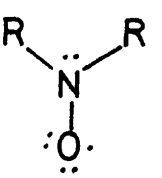

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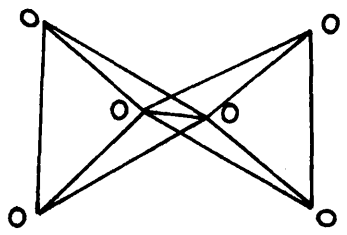
A detailed assessment of various spectroscopic parameters has enabled McConnell[6] to conclude that the unpaired electron is largely confined to the $2p\pi$ atomic orbital on nitrogen corresponding to the

canonical form (1). This simple picture of the bonding situation has been verified by Kikuchi [7] who has carried out LCAO - SCF - MO calculations using the CNDO/2 approximation.

At first sight, it may seem surprising that the nitroxide function is also a thermodynamically stable species, showing no tendancy to dimerise in solution. This behaviour is best explained by the double quartet hypothesis first proposed by Linnett, [8] in which the six electrons of one spin are arranged as in (3) and the five of the other spin as in (4).



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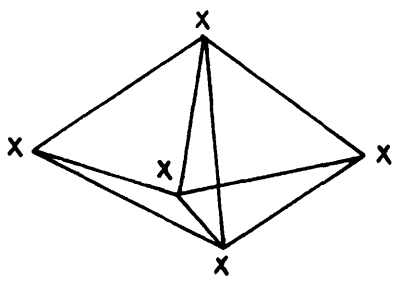

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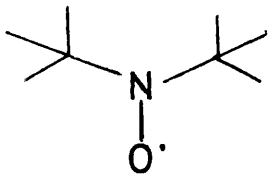
In this way, each atom obtains an octet of electrons, interelectronic repulsion is at a minimum, and there are five bonding electrons between the atoms. In consequence, dimerisation is an energetically unfavourable reaction, since it would lead to an increase in interelectronic repulsion without any corresponding increase in the number of bonding electrons.

Although this electronic stability is an intrinsic feature of the N-Ȯ bond the chemical stability of a nitroxide radical is markedly dependent on the nature of the groups attached to the nitrogen atom. In general, stable aliphatic nitroxide radicals can only be isolated when the two carbon atoms flanking the nitrogen atom are fully substituted. Thus, di-t-butyl nitroxide (5) is a stable red liquid with a camphoraceous odour.



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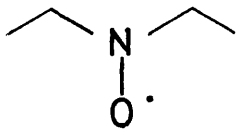

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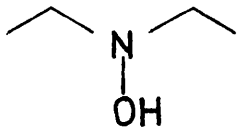

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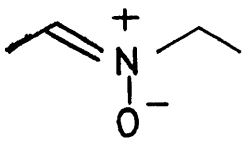

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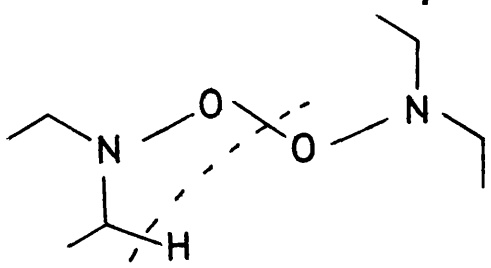

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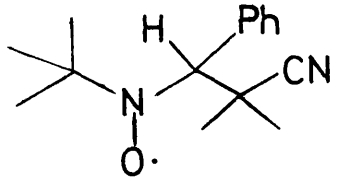
When the ∝ positions are not fully substituted, as in the case of diethyl nitroxide (6), rapid disproportionation to the corresponding hydroxylamine (7) and nitrone (8) occurs. The mechanism of this reaction has recently been investigated by Ingold et al.[9], who have shown that, despite the thermodynamic stability factor, a diamagnetic derivative for which the dimeric structure (9) is proposed, precedes the transition state in this disproportionation. This observation lends support to the hypothesis that steric factors may also be instrumental in contributing to thermodynamic stability by blocking dimerisation.

Nevertheless, within the last few years, several stable nitroxide radicals possessing hydrogen atoms on the ∝ carbon have been isolated. Thus Iwamura and Inamoto[10] have prepared the relatively stable nitroxides (10) and (11), and benzhydryl-t-butyl nitroxide (12) has been isolated, albeit in impure form, by Janzen.[11] The decreased reactivity of these nitroxides towards disproportionation has been attributed to spatial congestion around the β hydrogen atom.



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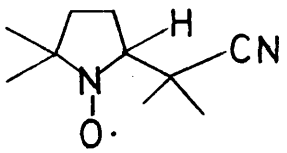

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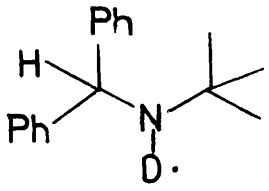

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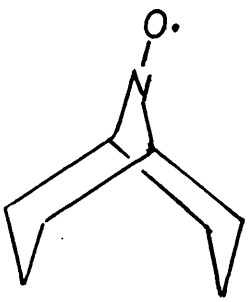
The bicyclic nitroxides (13)[12] and (14),[13] which also possess β hydrogens are special cases inasmuch as nitrone formation is prohibited by Bredt's rule.



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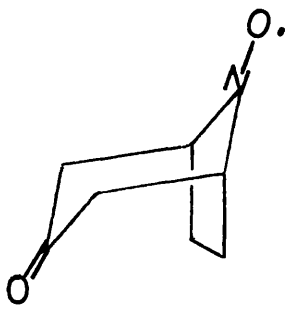

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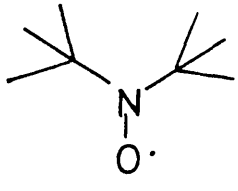
The nitroxide radical (15) which has recently been prepared in our laboratories[14] is perhaps one of the most unusual from the viewpoint of chemical stability. Although the two carbon atoms flanking the nitroxide are fully blocked, rapid decomposition to the trialkylhydroxylamine (16) occurs at room temperature. It would also appear that di-t-alkyl nitroxides with reasonably long side chains such as (17) and (18) are unstable. The complete details of the mode of decomposition have not yet been published[15].

Table 1.

Compound	r_{NO} Å	∠CNC °	Angle between NO bond and CNC plane	Ref.
19*	1.28	136	assumed planar	16
20*	1.26	121	22°	17
21	1.29	125	16°	18
22	1.27	115	0°	19
23	1.31	121	24°	20
24	1.29	114	30°	21
25	1.27	117	0°	22

* Electron diffraction



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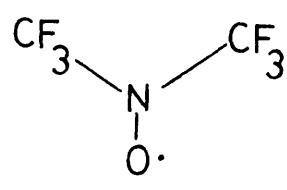

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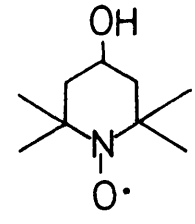

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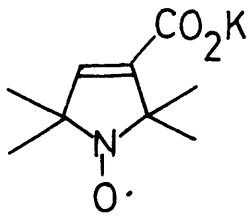

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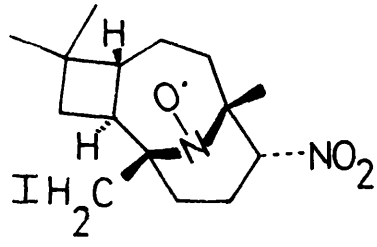

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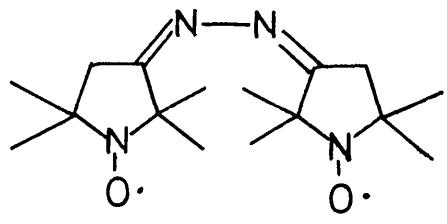

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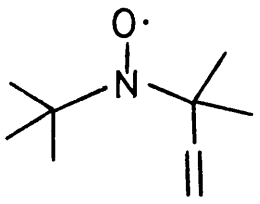

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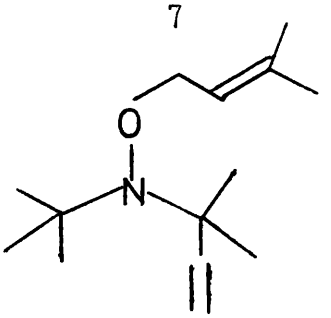

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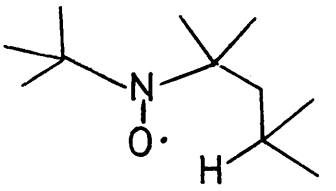

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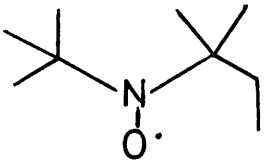

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Thus, the overall picture which emerges is that the nitroxide function is an exceptionally stable one from the electronic, thermodynamic and chemical standpoints. This factor has enabled a wide variety of spectroscopic and physical techniques to be employed in probing the nature of these radical species.

The structural parameters obtained by electron and X-Ray diffraction techniques for a number of nitroxide radicals are set out in Table 1.

The average bond length of 1.29Å is entirely consistent for a two-centre three-electron bond since the bond lengths for N-O and N=O are 1.44Å and 1.20Å respectively. The variation in the CNC bond angle seems to be a direct reflection of the degree of constraint imposed by the geometry of the molecule. Thus, in the pyrrolidine nitroxide (22) the angle is 115°, whereas in the more mobile di-t-butyl nitroxide (19) this angle can be widened to 136° to reduce non-bonding interactions.

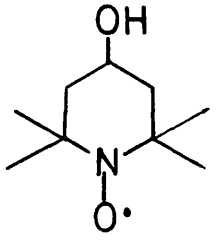
One of the most intriguing features from these analyses is that several of the nitroxides have a pyramidal geometry at the radical centre. This leads on to the interesting speculation first propounded by Rassat[23] that the ground state electronic configuration of the nitroxide radical bears a close resemblance to the excited state of the carbonyl group. Thus, in the $^1n \rightarrow \pi^*$ and $^3n \rightarrow \pi^*$

states of formaldehyde, the C-O axis subtends an angle with the HCH plane of approximately 27° and 35° respectively.[24]

It is not yet clear whether the nitroxide function is planar or pyramidal in solution as opposed to the solid state. Attempts to solve this by theoretical calculation [25,26] suggest that the pyramidal form of $H_2NO\cdot$ and $(CF_3)_2NO\cdot$ is the more stable, although only slightly so, and that the rate of inversion of such molecules will be extremely fast. Hence, for most purposes it is usual to consider that the nitroxide function is planar.

Recourse to the partial molecular orbital energy diagram of the nitroxide group (Fig.1) also illustrates that the basic electronic set-up is similar to that of the carbonyl group.

In addition, this parallel can be extended to encompass the chemical reactivity of the species in question. Thus the ground state nitroxide radical is a relatively poor hydrogen abstractor requiring labile bonds like the S-H group to demonstrate its reactivity. On the other hand, the $n\rightarrow\pi^*$ excited state of the nitroxide is an extremely efficient hydrogen abstractor rivalling if not exceeding the $^3n\rightarrow\pi^*$ state of aliphatic ketones, since Keana[27] has shown that photolysis of the nitroxide (26) in toluene solution produces the compounds (27) and (28) in good yield.



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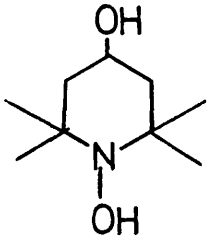

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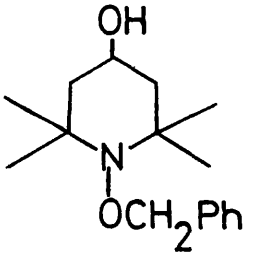

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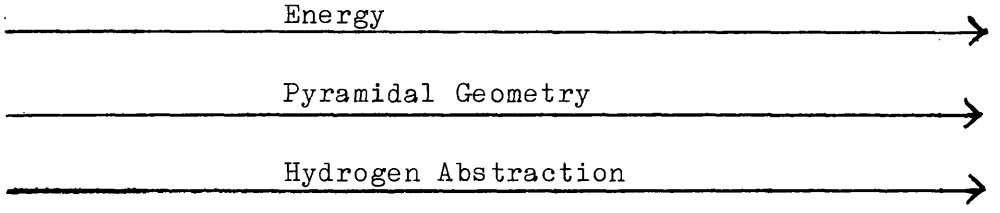
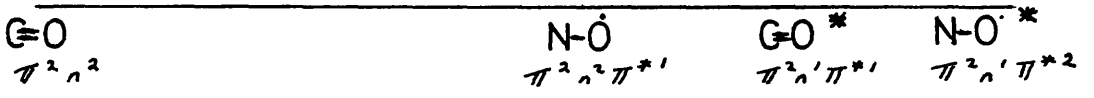
This closely interrelated spectrum of structure and reactivity relationships between the nitroxide and carbonyl groups can probably be

represented most easily by some form of convergent series as shown.





This 'analogy' has also been used to explain the observed features in the ultraviolet spectra of nitroxide radicals. The characteristic orange/red colour of aliphatic nitroxides, which is due to the presence of a very weak band in the 410-450nm range ($\varepsilon \sim 5$-10), has, in consequence, been described as the $n \rightarrow \pi^*$ transition on the basis of solvent shift studies.[28] The intense band at ca. 230nm. ($\varepsilon \sim 2500$) has been attributed to the $\pi \rightarrow \pi^*$ transition.

Many spectroscopic properties are however unique to the nitroxide function. By far the most commonly applied spectroscopic tool is electron paramagnetic resonance (e.p.r.). The e.p.r. spectrum of the nitroxide function in solution consists of three equally intense lines, due to the interaction of the unpaired electron with the magnetic nucleus of nitrogen (I=1). The nitrogen hyperfine splitting constant, a_N, which is a measure of the spacing of these lines is generally in the range 13-17 oersteds for aliphatic nitroxide radicals. Since a theoretical calculation[29] of the a_N value for an unpaired electron in a 2s orbital on nitrogen yields a value of 552 oersteds, and the observed hyperfine splitting is a relatively small fraction of this value, support is lent to a planar nitroxide structure with the unpaired electron occupying a π^* orbital on the nitrogen and oxygen atoms. Under favourable conditions, further hyperfine splitting from protons

on more remote carbon atoms can be detected. Since the possible mechanisms of this long range hyperfine coupling are a source of current controversy detailed discussion will be deferred until later.

The second spectroscopic parameter which is measured from the e.p.r. spectrum is the g value. For nitroxide radicals the g value is of the order 2.0060 which is larger than the free electron value (2.0023) in accordance with expectations[30] from the molecular orbital description. Thus the main contribution to the g value is derived from mixing of the $(\pi)^2(n)^2(\pi^*)^1$ ground state with the $(\pi)^2(n)^1(\pi^*)^2$ excited state and is expected to increase the g value since it promotes a paired electron.

The pioneering work of Kreilick[31] has served to demonstrate that the nuclear magnetic resonance (n.m.r.) spectrum of a paramagnetic species can be used to obtain valuable information. Favourable conditions for the observation of the n.m.r. spectrum are that the electron has a short spin-lattice relaxation time and/or a short spin exchange time. Unfortunately, these conditions only prevail in extremely concentrated radical solutions, although a promising technique would appear to be the use of paramagnetic solvents such a di-t-butyl nitroxide (19) itself.[32] An expensive alternative is the use of a 310 MHz n.m.r. spectrometer.

In the presence of rapid electron spin relaxation the n.m.r. spectrum consists of a single paramagnetic shifted line from each group of equivalent protons in the molecule. The relationship between the paramagnetic shift of the absorption relative to the same nucleus in a diamagnetic derivative, ΔH, and the hyperfine coupling constant, a_i, is given by :

$$a_i = \frac{\Delta H}{(\gamma_e/\gamma_n)(g\beta H/4kT)}$$

where γ_e, and γ_n are the gyromagnetic ratios of the electron and the nucleus, k is Boltzmann's constant, T is the absolute temperature, and β is the Bohr magneton. The importance of this equation lies in the fact that both the magnitude and the sign of extremely small hyperfine coupling constants can be calculated from the spectrum. These couplings are often unresolved in the e.p.r. spectrum.

The n.m.r. spectrum can also be used in a more direct fashion to obtain information on the conformation of nitroxide radicals[33,34]. For example, the n.m.r. spectrum of the nitroxide alcohol (26) shows separate peaks for the axial and equatorial methyl groups in addition to separate peaks for the axial and equatorial protons at C_3 and C_5, indicating that a chair conformation (29) is preferred.

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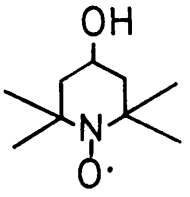

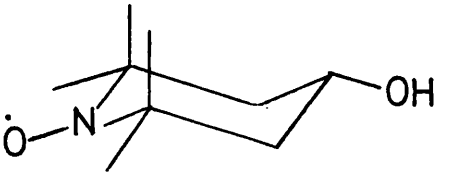

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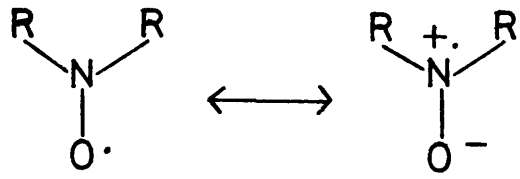
Furthermore, a variable temperature n.m.r. study of (26) has indicated that the enthalpy difference is only about 0.5k.cal/mole. This low value was attributed to a flattening of the chair due to 1,3-diaxial methyl-methyl interactions. This is also in accord with the X-Ray analysis[18].

The infrared spectra[1] of nitroxide radicals exhibit a weak band at ca.1350 $cm.^{-1}$ which has been attributed to the N-O stretching frequency on the basis of labelling studies[35]. Once again this would appear to be reasonable for a two-centre three-electron bond since the N-O stretching frequency in amine oxides occurs at 960$cm.^{-1}$ whilst that of monomeric aliphatic nitroso compounds is observed at 1600$cm.^{-1}$. The diagnostic utility of this band is considerably weakened however, since masking by the bending modes of the gem-dimethyl groups at 1360 and 1385$cm.^{-1}$ often occurs.

Examination of the mass spectral characteristics of nitroxides reveals that, in addition to the molecular ion, M^+, a significant peak appears at M^++1. This has been assigned to hydrogen atom abstraction by the radical from water in the mass spectrometer. A second distinguishing feature of the published[36] mass spectra of nitroxides is the presence of a peak at M^+-14 which arises by loss of a methyl radical from the M^++1 ion.



1 **2**

In agreement with the proposed hybrid structure (1↔2) the dipole moment of the nitroxide group[2] (3.14D) is larger than that of the corresponding hydroxylamine (about 1.0D). Dipole moment measurements can also yield valuable conformational information. Thus, the dipole moment of 1.36D which has been measured[37] for 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (30) is consistent with that calculated for the twist boat conformation (31). This conformation is also consonant with the results obtained by an e.p.r. study[38].

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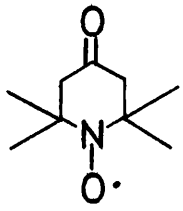

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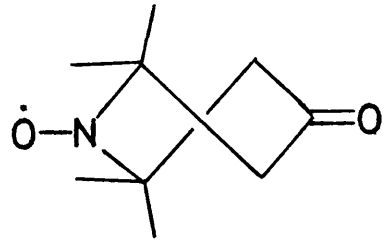
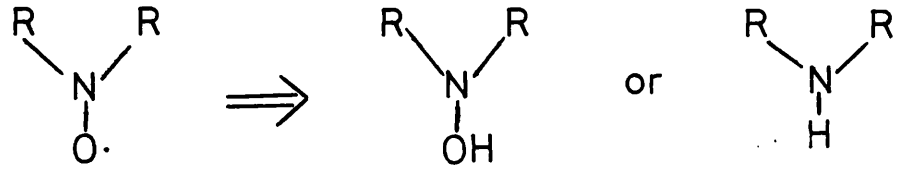


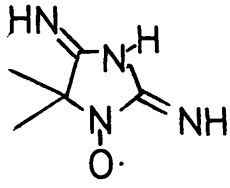
Before proceeding to the subject matter of this thesis, it is important to consider briefly the currently available methods for nitroxide radical synthesis.

The first 'antithetic' transformation which any practising nitroxide radical chemist would make is to replace the nitroxide with the

corresponding hydroxylamino or amino 'synthon'.[39]



The oxidation of hydroxylamines to nitroxides is extremely well-documented[3] and can be readily accomplished using a wide variety of reagents which include silver oxide, lead dioxide, potassium ferricyanide, permanganate, oxygen and sodium hypobromite. This method was used by Piloty and Schwerin[40] in 1901 to prepare porphyrexide (32), the first example of an organic nitroxide.



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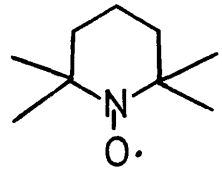

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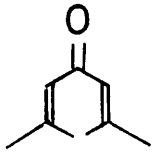
The development of suitable methods for the oxidation of an amine to the corresponding nitroxide was an extremely important advance and led to the documentation of many radicals, both stable and unstable particularly in the laboratories of Rassat in Grenoble and Rozantsev in Moscow. Di-t-alkylamines[41] can be oxidised to the corresponding nitroxides, generally in good yield, by treatment with hydrogen peroxide in the presence of a quaternary ammonium hydroxide and a salt of vanadium, molybdenum, or tungsten. Alternatively, hydrogen peroxide and phosphotungstic acid may be used.[42] This method was introduced by Lebedev[43] in 1959 and served to prepare the first totally aliphatic nitroxide (33). A valuable addend to these methods is the use of m-chloroperbenzoic acid.[1]

This formidable array of oxidative methods would appear, at first sight, to reduce the task of nitroxide radical synthesis to the trivial problem of functional group manipulation. On closer scrutiny, however, the dearth of synthetic methods which are presently available to produce the requisite blocked precursor, is seen to constitute a major stumbling block to this approach. With the exception of the Robinson - Schopf reaction[44], which has been used to prepare several bridged amines, the most generally useful method is the double Michael addition of ammonia to a cross conjugated dienone. Thus phorone (34) gives triacetonamine (35) and piperitenone (36) gives the bicyclic amine (37)[45].



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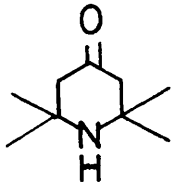

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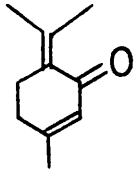

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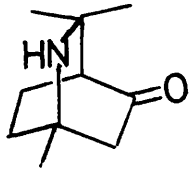

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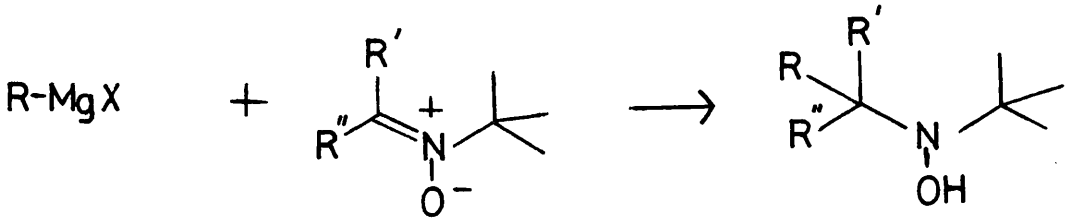
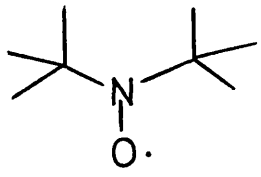
Blocked hydroxylamine precursors are generally available[46] by the addition of a Grignard reagent to a nitrone:



Once again, however, this potentially attractive route is limited in the case of cyclic and bridged bicyclic molecules by the inflexibility of the standard reductive cyclisation route to nitrones.

The nitro group has also served as a precursor in the preparation of simple aliphatic nitroxides. In 1961, Hoffmann[47] was able to prepare di-t-butyl nitroxide (19) by the reduction of t-nitrobutane

with sodium metal. The mechanism of this reaction was subsequently investigated in detail[48] and shown to proceed by the attack of a t-butyl radical, derived from the collapse of a t-butyl radical anion (38), on a second radical anion to form a diamagnetic salt : $(^{t}C_4H_9)_2NO_2\text{-}Na^{+}$. This salt, upon hydrolysis affords di-t-butyl nitroxide. This method is not general since other t-nitroalkanes give radical-anions which behave in a different fashion.[1]



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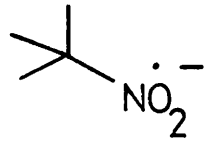

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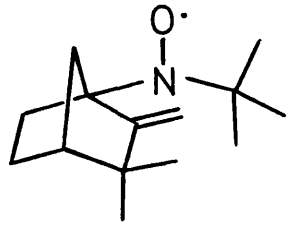

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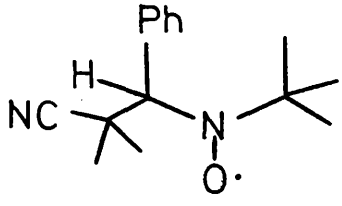
A second reductive approach involves the addition of a t-alkyl Grignard reagent to a nitro (or nitroso) alkane and is illustrated[49] by the reaction of 1-nitrocamphene with t-butyl magnesium chloride to give the nitroxide (39). The yields obtained by this method are usually low and the limitations self-evident.

The addition of cyanoisopropyl radicals to nitrones has been used to prepare the previously mentioned unstable nitroxides (10) and (11). The full potential of this method remains however to be assessed.



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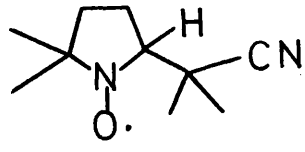
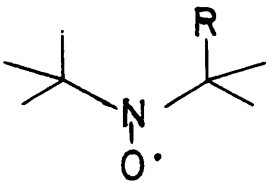


11

The ability of the nitroso group to scavenge reactive radicals makes it one of the most versatile progenitors of nitroxide radicals. By using this technique Hoffmann[50] was able to prepare a series of nitroxides e.g. (40; R = CN, CO_2Me) by the thermal decomposition of aliphatic azo compounds in the presence of monomeric nitrosoalkanes.



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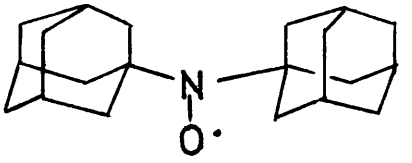
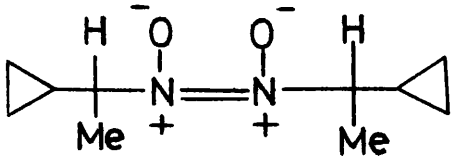


41

The photolysis of nitroso - dimers has also been employed as exemplified in the synthesis of di-adamantyl nitroxide (41) by de Boer and coworkers[51]. The Dutch group have also shown[52] that photolysis of the nitroso - dimer (43) gives rise to the unstable nitroxide (42), thus providing convincing evidence that this reaction proceeds <u>via</u> initial photodissociation of the C-NO bond, followed by trapping of the alkyl radical with a second nitroso-alkane.



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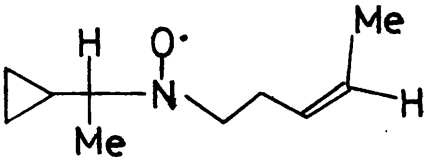
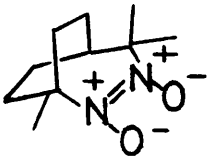


42

A particularly elegant intramolecular application of this reaction has recently been provided by Rassat and Rey[53] who have shown that photolysis of the nitroso-dimer (44) gives the bicyclic nitroxide (45) in good yield.

44



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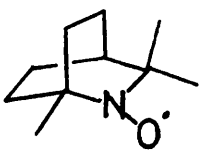
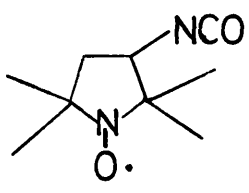


This synthetic method also represents the simplest application of nitroxide radicals in the so-called "spin trapping" method which has witnessed extensive use in recent years. By taking advantage of the relatively long-lived nitroxide formed by the reaction of an extremely short-lived radical with 2-methyl-2-nitrosopropane, structural information on various radicals appearing in polymerisation[54], radiolysis[55], photolysis[56], and various other chemical reactions [57,58] has been obtained. This aspect of nitroxide radical chemistry has been reviewed by Perkins[59].

By far the most important application of nitroxide radicals to date lies in their use as spin labels for probing biomolecular structure. This technique which was developed by McConnell and coworkers[6] in 1966, is extremely useful for monitoring the molecular changes which occur in biological systems and depends on the fact that the shape of the nitroxide radical e.p.r. spectrum is extremely sensitive to its environment and changes with the viscosity of the medium surrounding the radical. As this subject has been extensively reviewed[60,61] one example will suffice to show the power of the method in action.

The spectrum of bovine serum albumin, labelled by reaction with the nitroxide (46), shows three sharp lines, arising from freely moving spin labels, superimposed on a broad anisotropic signal arising from tightly bound labels. As the pH is lowered, the intensity of the sharp lines increases at the expense of the broad one, indicating that the protein is uncoiling and in the process releasing restricted nitroxide labels.



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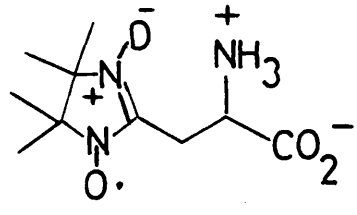

47

Arising out of these investigations has been the complementary synthesis of paramagnetic analogues and models of physiologically active compounds as exemplified by the free radical analogue of histidine[62](47).

In conclusion, it must be admitted that this introduction has not given an in-depth account of all aspects of nitroxide radical chemistry. For instance, the important areas of spin-labelling and spin-trapping have received but a cursory glance and several classes of both stable and unstable nitroxide radicals have barely been mentioned. Nevertheless, it is hoped that this bird's eye view has provided sufficient indication of the broad and exciting spectrum of interests which nitroxide radicals have thus far created. It is in keeping with this general theme that the studies described in this thesis have been pursued over a relatively broad front although two interrelated facets have emerged. Thus in the first section the major objective is the development of novel synthetic methods while in the second section a more physico-chemical approach assumes the dominant role.

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Section One

CHAPTER 1.

THE INTERMOLECULAR 'ENE' REACTION.

"Time and again the penetration of a new sector of the vast, often surprising and always beautiful panorama of natural products has led to new insights which could hardly have been achieved by more self-conscious fundamental investigations."

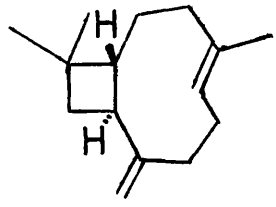
R.B. Woodward.[1]

The history of organic chemistry provides, in abudance, instances of the major role played by the study of natural products in revealing, extending, and shaping the fundamental bases of the science. In this respect, the study of caryophyllene (1), the major constituent of clove oil from Eugenia caryophylatta, is a particularly rewarding one.

The facility with which this molecular acrobat of the sesquiterpene field underwent deep-seated molecular rearrangements plagued the early investigators, and the now unanimously accepted structure (1) was only revealed in 1951, when Barton and coworkers[2] were able to reconstruct the molecular jig-saw. The synthetic challenge of the diene was then taken up by Corey[3], and successfully realised in 1963. This molecule was also instrumental in extending fundamental concepts of carbonium ion behaviour and transannular cyclisations in medium sized rings[4].

But the chemistry of caryophyllene had yet another contribution to make; in initiating the study of nitroxide radicals at Glasgow. In the course of a re-examination of the chemistry of caryophyllene nitrosite (2) which will be detailed in chapter 2, the chance observation was made that recrystallisation of crude samples of the nitrosite led to the isolation of minute quantities of a yellow

crystalline material.



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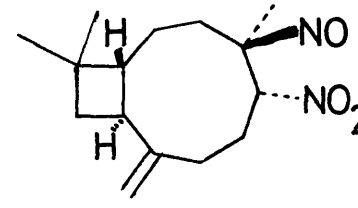
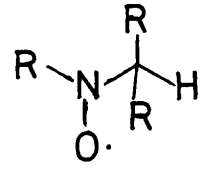


2

The n.m.r. spectrum of this compound over the range $0 \leq \tau \leq 10$ exhibited only two broad humps in the $4 \leq \tau \leq 6$ and $7.5 \leq \tau \leq 9.5$ regions with no visible fine structure, indicating that a paramagnetic species was present.

The e.p.r. spectrum consisted of a 1:1:1 triplet, (a_N=14.2 Oe, g=2.0061) with an additional hyperfine splitting of 2.3 Oe. The form of this spectrum and its magnetic parameters generated considerable interest because they uniquely defined this molecule as a stable nitroxide radical possessing a hydrogen atom on the α carbon i.e. of the type (3).



3

As already mentioned, such species are relatively rare in nitroxide radical chemistry in view of their ready disproportionation to the corresponding hydroxylamine and nitrone. It was felt, therefore, that some attempt to determine the structure of this yellow radical should be made, in the hope that, armed with this knowledge, some reasonable postulate could be advanced to account for its mode of formation. In the event, the mechanistic flash

of insight preceded the structural confirmation by several months.

A combination of mass-spectral and analytical data readily established the molecular formula, $C_{30}H_{47}N_2O_3$. The i.r. and u.v. spectra were of little diagnostic value and merely served to confirm that the molecule possessed one nitro group, ($\nu_{max.}$=216nm, ϵ=4,830) and olefinic double bonds of the exomethylene type. ($\nu_{max.}$=3080, 1644, 1560 and 901cm.$^{-1}$).

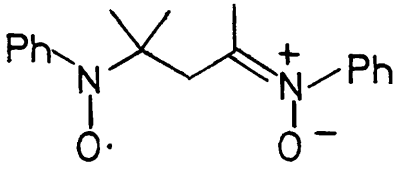
If the reasonable assumption is made that the nitroxide radical is derived by aerial oxidation of the corresponding hydroxylamine, then the yellow radical may be formulated as an adduct of caryophyllene nitrosite and caryophyllene. However, without the aid of a diamagnetic derivative suitable for n.m.r. analysis, it could always be possible, and especially so in caryophyllene chemistry, that some gross skeletal transformation had occurred. Our efforts were, therefore, directed towards the deceptively simple task of adding one hydrogen atom to the yellow radical to form the corresponding hydroxylamine.

In general, nitroxides are converted into the corresponding amines by treatment with strong reducing agents and to the hydroxylamine with mild ones. Thus reduction with stannous chloride in acid solution[5], or hydrogenation over Raney nickel[6] gives the amine, while hydrogenation over platinum[7], or reduction with phenylhydrazine[8], zinc in alkaline solution[9], or lithium aluminium hydride[10] gives the hydroxylamine.

Since the yellow radical contained a nitro group and a number of double bonds, it was apparent that, in principle, none of these methods was suitable. A carefully harvested crop of the radical was however subjected to hydride reduction in the hope that the desired hydroxylamine might be the kinetically controlled product.

As aliquot monitoring of the reaction mixture by analytical t.l.c. served to indicate that concomitant formation of six products was occurring, this approach was discontinued. Hydrazine and phenylhydrazine were also employed with singularly unsuccessful results.

A more promising technique appeared to be the conversion of the nitroxide function directly into the corresponding hydroxylamino - acetate. This reaction, which was reported by Banfield and Kenyon[9] in 1926, would appear to be of dubious merit in view of the fact that the original structure (4) proposed by these workers has subsequently been modified[11] to (5). Moreover, acetylation of the nitroxide (6) gives rise to the expected acetate (7).



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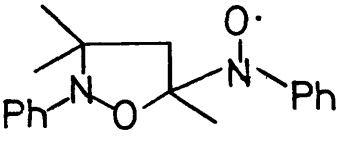

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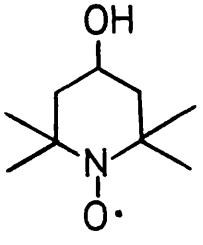

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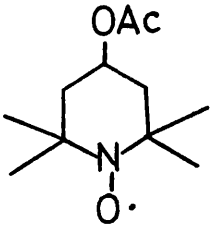

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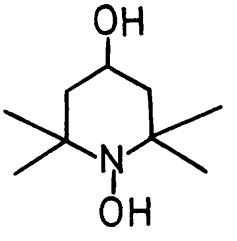
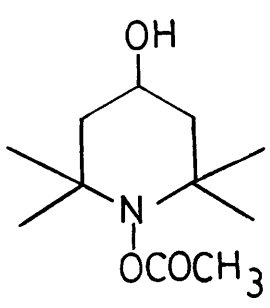


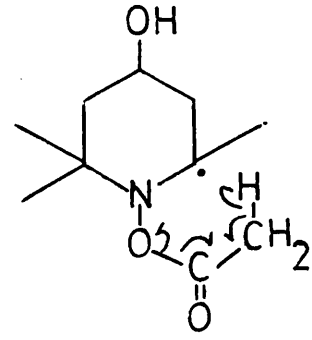
8

In our hands, acetylation of the yellow radical under a variety of standard conditions led to extensive decomposition.

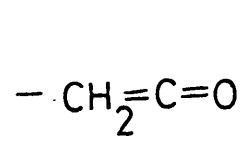
At this stage, no alternative methods of reduction were

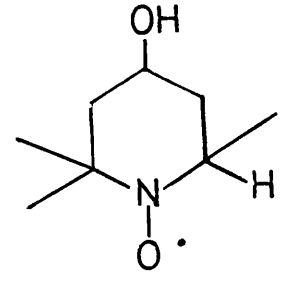


m/e 215

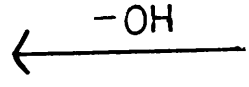


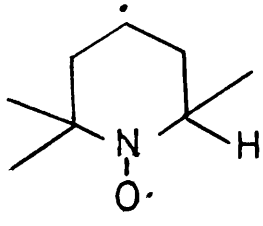
m/e 200





m/e 158
m/e 159



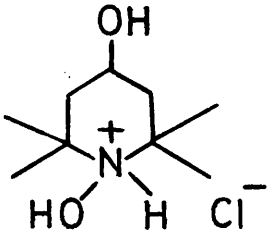


m/e 141

available, and model studies employing the nitroxide (6) were therefore undertaken. Samples of the hydroxylamine (8) were readily prepared by hydrazine reduction.

The first and most obvious method was to use the radical reducing agent, tri-n-butyl tin hydride[12]. Unfortunately, rapid aerial oxidation of the reaction product occurred and prevented the isolation of the hydroxylamine (8) by chromatographic techniques. This compound could nevertheless be trapped as its crystalline hydrochloride salt (9) by the action of gaseous hydrogen chloride. Alternatively, acetylation of the crude reaction mixture followed by preparative t.l.c. led to the isolation of a white crystalline solid, whose infrared spectrum exhibited ν_{OH}=3500, and $\nu_{C=O}$=1755 cm.$^{-1}$. The mass spectral cracking pattern shown opposite allowed the assignment of structure (10) to this compound. The n.m.r. spectrum is also in accord with the hydroxylamino-acetate (10). It is interesting to note that selective acetylation was achieved in this reaction.

9



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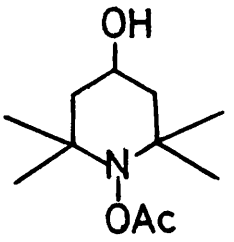
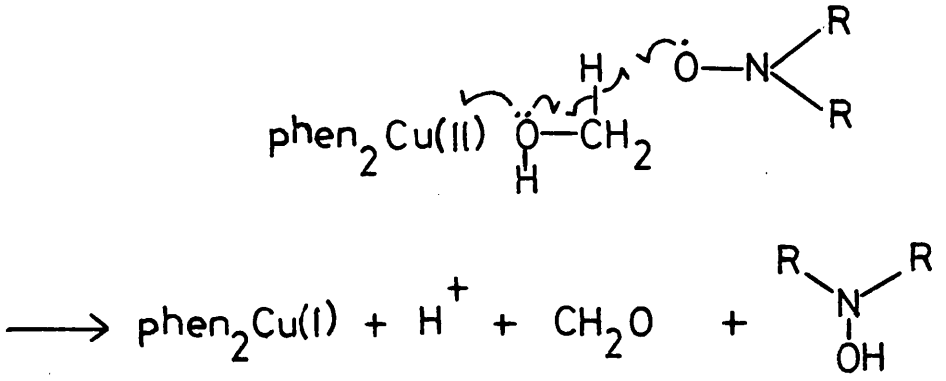


The reaction of caryophyllene nitrosite with tri-n-butyl tin hydride was also studies as a convenient model. In this case, a plethora of products was obtained and so it was deemed undesirable to effect reduction of the yellow radical by this technique.

The second method which was developed involved considerable experimental adaptation of a recent observation by Brackman and Gaasbeek[13]. These workers have recommended the use of di-t-butyl

nitroxide as a promoter in the autooxidation of methanol to formaldehyde, catalysed by cupric-phenanthroline complexes. The essential step is thought to involve the simultaneous abstraction of a hydrogen atom by the nitroxide, and an electron by cupric ion from coordinated methanol as shown.



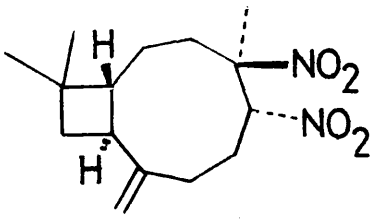
The nitroxide is regenerated by oxidation with copper (11) or air. By working in a completely inert atmosphere and removing the cuprous-phenanthroline complex by precipitation with ferricyanide it was possible, under rigorously controlled experimental conditions to achieve a reproducible conversion of the nitroxide (6) to the hydroxylamine (8) in acceptable yield. The yellow radical was however completely inert under these conditions, indicating that the nitroxide function was sterically inaccessible.

A related technique, which is also believed[14] to involve hydrogen abstraction, consisted of the reaction of the nitroxide (6) with hydrazobenzene. When this reaction was performed in an n.m.r. tube, a sharp spectrum of the hydroxylamine (8) was obtained. The yellow radical likewise gave a sharp spectrum with this reagent, but, in both cases, attempted isolation of the hydroxylamine by preparative t.l.c. was thwarted because of aerial re-oxidation. Although the spectrum confirmed our suspicions regarding the structure of the yellow radical, the presence of hydrazobenzene and azobenzene might possibly have obscured some low field signal.

Fortunately, this stumbling block was eventually rolled aside when a totally successful technique was discovered. This reaction, which proceeded smoothly and in virtually quantitative yield, allowed the isolation of the desired hydroxylamine as a relatively unstable white crystalline solid. It was perhaps a shot in the dark, but it did have the considerable advantage over all the other methods which were developed, in that it worked! The reaction of choice proved to be a simple hydrogenation over Lindlar catalyst.

The i.r. spectrum showed ν_{OH}=3560 cm.$^{-1}$ and ν_{NO_2}=1548 cm.$^{-1}$ and the mass spectrum gave the correct molecular ion at m/e 484, confirming that the desired conversion had been realised.

The n.m.r. spectrum showed 2 singlets at 9.02τ(12H) and 8.77τ(3H). The former signal is attributed to two gem-dimethyl groups while the latter is assigned to a methyl group on the carbon α to the hydroxylamine. The β hydrogen atom which is responsible for the additional hyperfine coupling in the e.p.r. spectrum appeared as a broadened triplet (J=6Hz.) at 6.78τ. Eight hydrogen atoms were located in the 4.9-5.3τ region as three singlets, overlying a broad base. These protons may be ascribed to three exomethylene groups, one hydrogen α to the nitro group, and the hydroxyl group of the hydroxylamine which is exchangeable with deuterium oxide. A reasonable analogy for the proton α to the nitro group may be found in dinitrocaryophyllene (11) where an asymmetric triplet is found at 4.82τ. Very little else can be deduced from the n.m.r. spectrum since the methylene region appears as a broad envelope, integrating for 24 protons, between 7.2 and 8.9τ.



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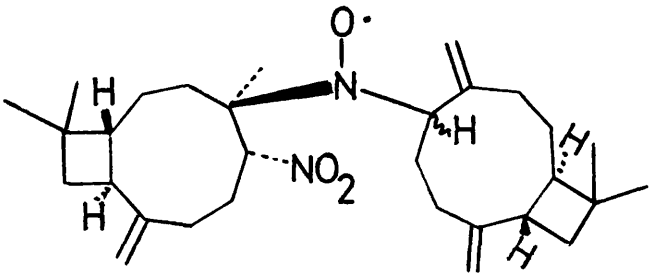
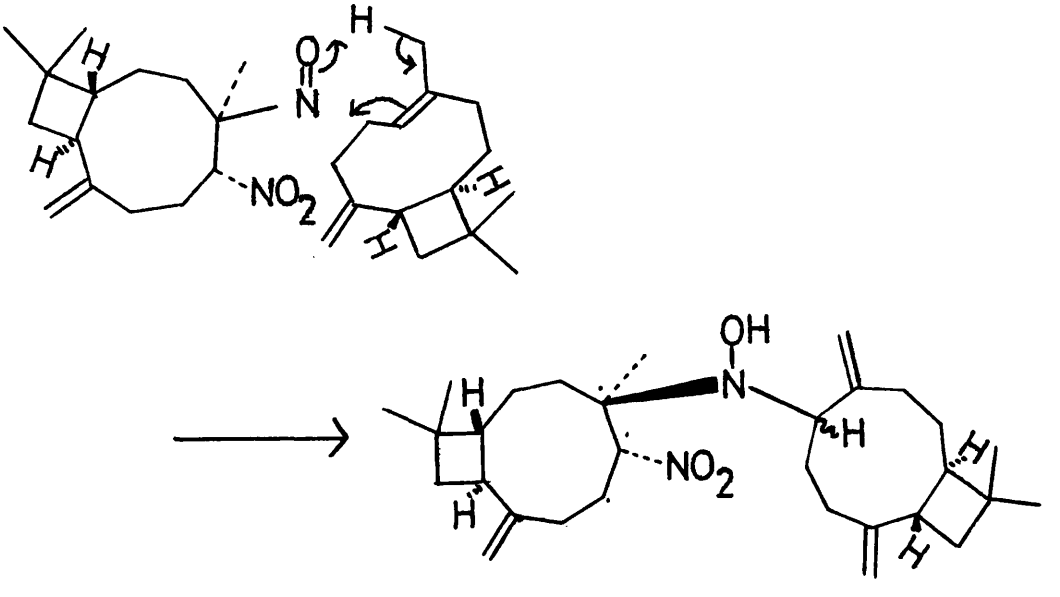


12

This data allowed the yellow radical to be formulated as N-4(4,11,11-trimethyl-5-nitro-7-methylenebicyclo (7,2,0) undecyl), N-4(11,11-dimethyl-3,8-dimethylenebicyclo (7,2,0) undecyl) -N-oxyl (12). In our laboratories, the less cumbersome name "yellow radical" is still however preferred.

The mode of formation of the radical (12) can be most readily envisaged in terms of an "ene" reaction between caryophyllene and caryophyllene nitrosite as shown, followed by oxidation of the intermediate hydroxylamine (13).

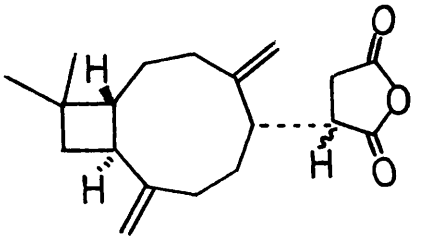


13

The 'ene' reaction, which has been the subject of a comprehensive review by Hoffmann[15], is, as its name implies, formally analogous to its more famous counterpart; the Diels-Alder reaction. Mechanistically however, this reaction is more closely related to the (1,5) sigmatropic shift.

The compelling evidence in favour of this mechanism derives from the fact that the yellow radical (12) can be obtained in high yield from the reaction of caryophyllene with caryophyllene nitrosite in chloroform solution in the dark. In point of fact, the latter stages of the investigation into the selective reduction of (12) were rendered considerably easier by the ready availability of material by this process, since, as already indicated, a reasonable mechanistic postulate preceded the confirmation of the molecular structure.

Nor is the 'ene' reaction without precendent in caryophyllene chemistry since Nickon[16] has shown that reaction with maleic anhydride as the enophile gives rise to the adduct (14).



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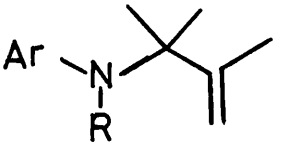


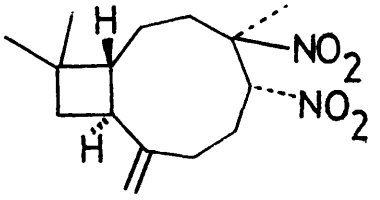
15 R= OH

16 R=—O·

At the time this work was in progress, the only previous report of an 'ene' reaction between an olefin and a nitroso compound was that of Sullivan[17], who succeeded in observing, by e.p.r. spectroscopy, the formation of several unstable alkenyl-aryl nitroxides (16) by the reaction of various nitrosobenzenes with

2,3-dimethylbut-2-ene. This work has been the subject of a recent investigation by Knight[18] who has vindicated the 'ene' mechanism by isolating the intermediate hydroxylamine (15). Haszeldine and coworkers[19] have also examined the reaction of pentafluoronitrosobenzene with various olefins and isolated the hydroxylamine adducts.

At this point, it is appropriate to mention that some attempt was also made in our studies to isolate the intermediate hydroxylamine (13). This consisted of reacting caryophyllene with caryophyllene nitrosite under a static nitrogen atmosphere in a deoxygenated pentane solution, since the hydroxylamine was known to be insoluble in this solvent. It was anticipated that this solvent change would not affect the course of the reaction, since, by analogy with other "no mechanism" reactions the 'ene' reaction is known[20] to be little affected by this change. It was therefore very gratifying to observe that, over a two week period, a white crystalline solid was deposited from the reaction. The i.r. spectrum and t.l.c. characteristics of this solid were not however identical with the expected hydroxylamine. Moreover, the same solid was obtained when the experiment was repeated in the absence of caryophyllene! This compound was ultimately identified as dinitrocaryophyllene (11) by rigorous comparison with an authentic sample. This unexpected disproportionation precluded any further attempts to isolate the intermediate hydroxylamine (13).



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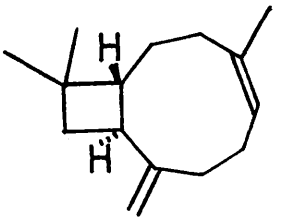
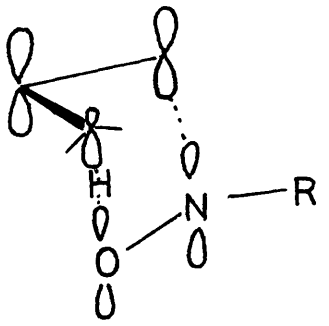


17

Another facet of this investigation involved the reaction of caryophyllene nitrosite with isocaryophyllene (17). Although the e.p.r. spectrum of the reaction mixture was identical to that obtained from the yellow radical, the reaction proceeded much more slowly and no crystalline paramagnetic species was ever isolated. This result would seem to indicate that the relief of strain in the trans trisubstituted double bond of caryophyllene constitutes the major driving force for the reaction.

One further point of stereochemical detail remains before the structure of the yellow radical can be completely delineated; this being the absolute configuration of the β hydrogen atom which is responsible for the additional hyperfine splitting in the e.p.r. spectrum. Some support for our belief that only one diastereoisomer is formed in the 'ene' reaction comes from the following observations. The yellow radical is a sharp-melting crystalline solid whose analytical t.l.c. shows one homogeneous spot in several solvent systems. Moreover, the n.m.r. spectrum of the corresponding hydroxylamine displays only one triplet for the β hydrogen atom.

Initially, it was felt that some useful prediction might be made by examining the steric requirements of the transition state. The optimum geometry for the concerted 'ene' reaction maximizes allylic resonance by turning the axis of the breaking carbon-hydrogen bond parallel to the p orbitals of the neighbouring double



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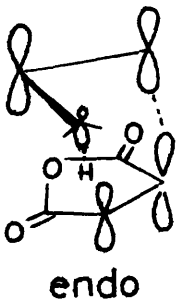

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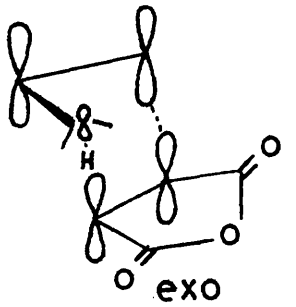

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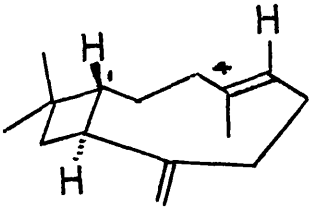

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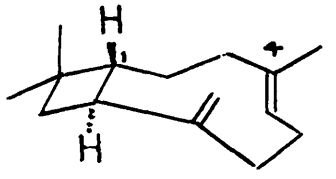

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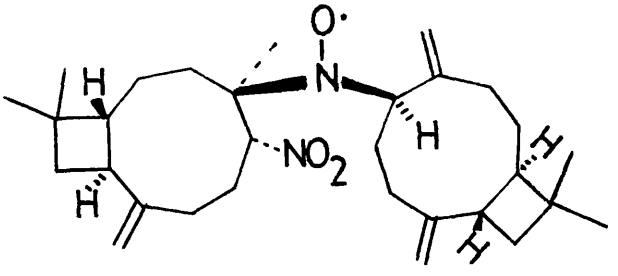

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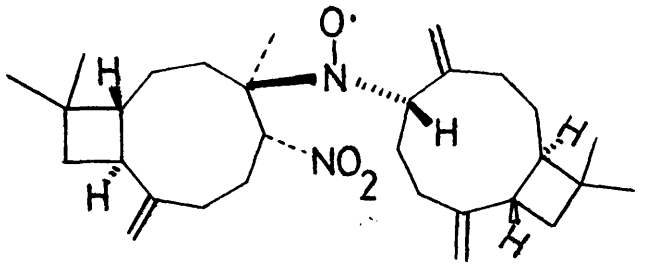


24

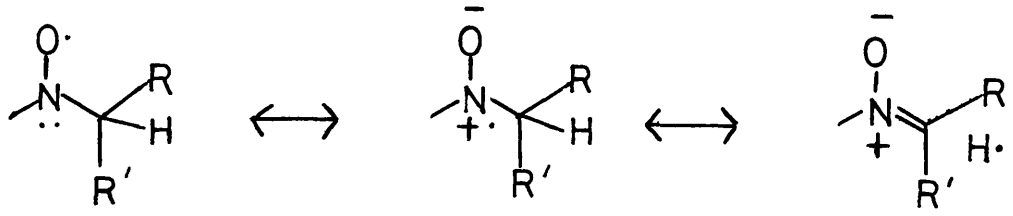
Caryophyllene Conformation	Transition State	Adduct
21	exo	(23)
22	exo	(24)
21	endo	(23)
22	endo	(24)

bond as in (18). The distinction between endo and exo transition states, which is illustrated for maleic anhydride in (19) and (20), is however much more difficult than in the Diels-Alder reaction since cyclic adducts are not formed. By considering the reaction of cis-and trans-but-2-ene with maleic anhydride Berson and his collaborators[21] have concluded that the endo selectivity is not particularly striking and is extremely sensitive to steric effects.

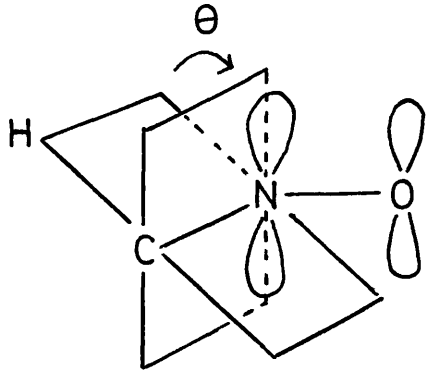
Another complicating factor in the case at hand is the suggestion by Barton[22] that the acid-catalysed reactions of caryophyllene may be rationalised in terms of two distinct conformations (21) and (22) in which the methyl group at C_4 is allowed to project upwards (22) or downwards (21) with respect to the hydrogen atom on C_1.

These considerations led to the predictions which are tabulated opposite. It is extremely interesting to note that, in this case, the absolute configuration of the yellow radical is determined solely by the conformation of caryophyllene which is chosen and the outcome is entirely unaffected by the exo or endo nature of the transition state. Thus it would appear that this reaction proceeds through only one conformation of caryophyllene. Unfortunately, no distinction can be made between the steric requirements of the transition state for the two possible conformations. It may however be important to note that the caryophyllene-maleic anhydride adduct arises from a transition state involving conformation (21).

A second theoretically-based approach embodying steric requirements was then made by considering the β-hydrogen hyperfine splitting constant in the e.p.r. spectrum. The mechanism of this hyperfine coupling is most readily (but not necessarily most accurately) ascribed to hyperconjugation.



The magnitude of this coupling depends both on the spin density on nitrogen (ρN) and the dihedral angle (θ) between the p orbital on nitrogen and the C-H bond which is defined as shown.



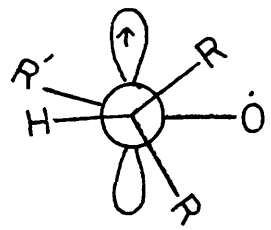
The relationship

$$A_H = \rho N(Bo + B_2 \cos^2\theta)$$

where Bo and B_2 are constants has much support in e.p.r. spectroscopy[23] and in the case of aliphatic nitroxides reduces to

$$A_H = 26 \cos^2\theta$$

By using this equation it will be apparent that the small hyperfine splitting constant of 2.3 Oe. for the methine hydrogen of the yellow radical can be attributed to the dominance of a conformation in which the average dihedral angle is close to 90° (A_H=0 at θ=90°). Two such conformations (25) and (26) are possible, although (25) is more probable since it minimises non bonding interactions.



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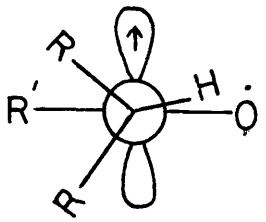
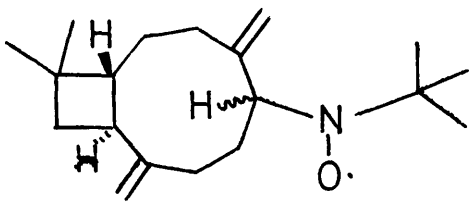


26

The four possible conformations corresponding to the calculated dihedral angles of 72° and 108° were examined for each of the two possible absolute configurations (23) and (24) of the yellow radical. Once again, however, no conclusive result could be reached in favour of either structure.

In order to examine the stereochemical outcome of a closely related analogue, the preparation of the radical (27) was undertaken.



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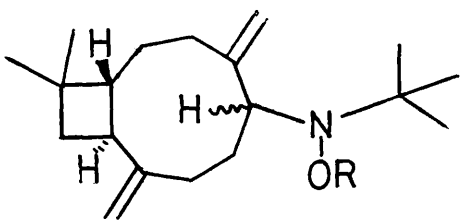


28 R = H
29 R = Ac

The reaction of caryophyllene with 2-methyl-2-nitrosopropane proceeded readily in chloroform solution and the radical (27) was isolated by preparative t.l.c. as a relatively unstable orange oil.

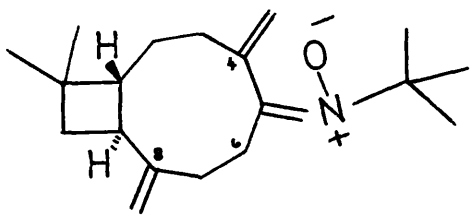
Once again, the e.p.r. spectrum in chloroform solution displayed a triplet of doublets, with a_N=14.90e. and a_H=2.30e;

and the mass spectrum showed, in addition to the molecular ion at $^{m}/e$ 290, a substantial $M^{+}+1$ peak at m/e 291. These observations confirmed the gross structure.

Nevertheless, this reaction deserves comment in a number of directions. Firstly, the instability of this nitroxide radical is attributed to the enhanced ease of hydrogen abstraction relative to the yellow radical (12) since the steric situation is much less crowded for a bimolecular disproportionation. Of greater moment is the n.m.r. spectrum of the corresponding hydroxylamine (28) which was obtained by the previously-developed Lindlar reduction technique as an extremely viscous clear oil. In sharp contrast to the n.m.r. spectrum of the yellow radical hydroxylamine (13), the β hydrogen atom appeared as an extremely broad signal at 6.60τ in which no triplet structure was discernable. Since this spectrum was generally subject to paramagnetic broadening due to aerial oxidation, the hydroxylamine (28) was treated with acetic anhydride/pyridine to afford the hydroxylamino-acetate (29). This compound, likewise, give an extremely broad multiplet at 6.50 τ for the β hydrogen atom.

These observations tend to support the hypothesis that an inseparable mixture of diastereoisomers is formed in the 'ene' reaction of caryophyllene with 2-methyl-2-nitrosopropane.

Furthermore, as evidenced by analytical t.l.c., the decomposition of the nitroxide (27) proceeds through the intermediacy of the corresponding hydroxylamine, to afford one primary decomposition product, which was isolated by preparative t.l.c. as an unstable white crystalline solid.



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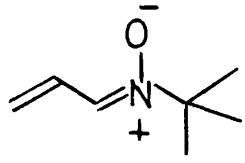
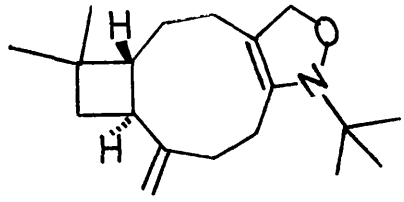


31

The structure (30) was assigned to this compound on the basis of its n.m.r. spectrum which showed a nine hydrogen singlet at 8.54 τ for the t-butyl group. In addition, the methylene group at C_6 appeared as a multiplet centred at 6.45 τ, and the olefinic region comprised two signals each integrating for two hydrogens at 5.08 τ and 4.66 τ, which correspond to the exomethylene group at C_8 and the exomethylene group conjugated to the nitrone at C_4, respectively. The overall complexity of the splitting pattern suggests that a mixture of the <u>cis</u> and <u>trans</u> isomers around the C=N bond is probably formed. Nevertheless, the chemical shift values are in reasonable accord with those reported recently by Baldwin[24] for the conjugated nitrone (31). One possible explanation for the observed instability of the conjugated nitrone may lie in the fact that an intramolecular electrocyclic reaction to give (32) is formally possible. Alternatively, decomposition may proceed in an intermolecular sense by 1,3 dipolar cycloaddition of the nitrone to the exomethylene group at C_4 or C_8. No further experiments were however performed to unravel this problem or confirm the suspicions outlined above.



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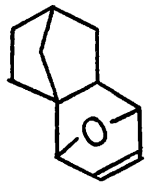
The isolation of the conjugated nitrone (30) as a crystalline solid; whereas the nitroxide (27), hydroxylamine (28), and acetate (29) were all obtained as viscous oils, lends some additional though tenuous support to the statement that a mixture of diastereoisomers is formed in the initial 'ene' reaction.

At this stage, our attention was directed to the intriguing possibility that the 'ene' reaction might be of value as a sensitive probe to distinguish between a twisted double bond and a biradical in the field of anti-Bredt olefins.

The principles involved are best illustrated by an example of particularly current research interest. Keese and Krebs[25] have shown that reaction of 1,2-dihalobicyclo (2,2,1) heptanes of the type (33) with n-butyllithium affords an extremely reactive intermediate which may be trapped as the "Diels-Alder" adduct (34). If this intermediate was the anti-Bredt olefin (35) as claimed, then reaction with 2-methyl-2-nitrosopropane as the enophile should give the nitroxide (36). On the other hand, if this intermediate was a biradical then 2-methyl-2-nitrosopropane should function as a "spin trap" through the intermediacy of (37). In this way, it can be seen that 2-methyl-2-nitrosopropane can serve as a bifunctional probe.

33 X=Cl, Br



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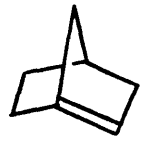

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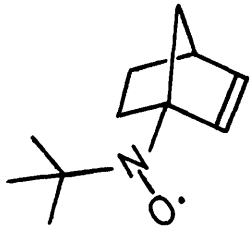

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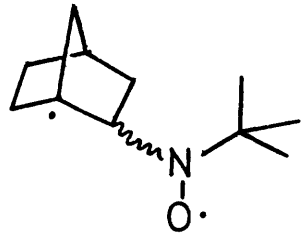

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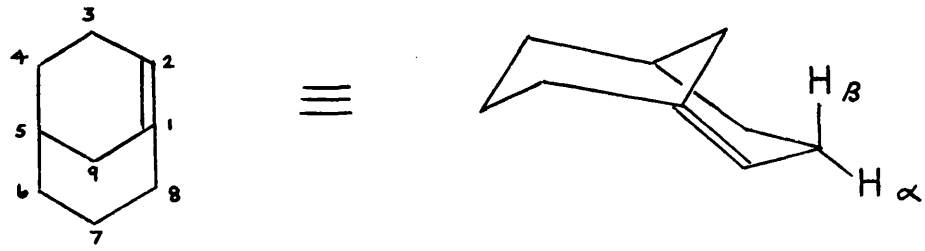
The only conceivable drawback to this plan is that the 'ene' reaction is Janus-faced inasmuch as both concerted and stepwise routes may be followed. A concerted course is generally preferred, but the stepwise process may occur if the optimum geometry of the transition state is inaccessible.

In consequence, it was decided to initiate this study by examining the reaction of 2-methyl-2-nitrosopropane with the known[26] anti-Bredt olefin, bicyclo(3,3,1)non-1-ene (38). Before undertaking the fifteen stage literature preparation, several theoretical considerations were evinced which seemed to assure success. First, examination of a molecular model of the olefin reveals that, of the six allylic hydrogen atoms, only the β hydrogen atom at C_3 is suitably disposed to enter into the favoured transition state discussed earlier. Moreover, if any of the hydrogen atoms at C_8 or C_9 were to react, the product would again be an anti-Bredt olefin. Hoffmann[15] has pointed out the particularly intriguing possibility that the anti-anti transition state (39), although less likely for steric reasons, is symmetry-allowed and thus remains a possibility for ene components containing



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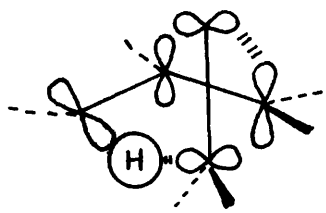

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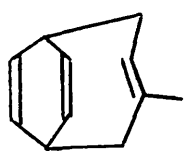

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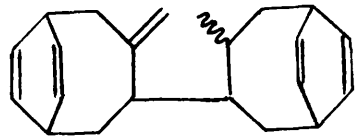

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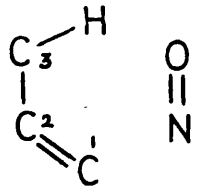
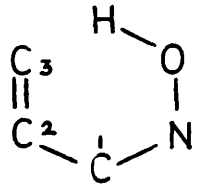


Bond Energy Expended

D $(C_3\text{-}H)$

$D_\pi (N{=}O)$

$D_\pi (C_2{=}C_1)$



Bond Energy Gained

D $(O\text{-}H)$

D $(C_1\text{-}N)$

$D_\pi (C_2{=}C_3)$

twisted double bonds. Secondly, olefins with strained double bonds seem particularly prone to enter into 'ene' reactions. Thus the photoadduct (40) of benzene and isoprene dimerises to (41) well below room temperature[27]. This example is particularly pertinent since bicyclo (3,3,1) non-1-ene may also be considered as a trans-cyclooctene possessing a twisted double bond. Finally, some mention should be made of the changes in bond energy during the 'ene' reaction. In the generalised scheme shown opposite, energy is expended by breaking the C_3-H σ bond and the N=O π bond while energy is gained by making the O-H and C_1-N bonds; the last items are particularly important for the energy in breaking the C_1=C_2 π bond of bicyclo (3,3,1) non-1-ene will be considerably less than that gained by forming the C_2=C_3 π bond.

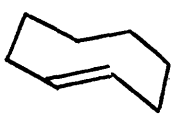
In short, these considerations sustained the investigator during the long months of functional group manipulation which were required to produce the olefin.

It was mildly distrubing to observe that when solutions of bicyclo (3,3,1) non-1-ene and 2-methyl-2-nitrosopropane were mixed in an inert atmosphere no instantaneous decolourisation of the reaction mixture occurred. Greater surprise was occasioned however when the blue solution persisted for one week, and analytical t.l c. served to indicate that no reaction was occurring! Since the 'ene' reaction is known to be facilitated by increase in pressure, recourse was made to a sealed tube reaction. Over a four day period at 100°C, the blue colour was slowly discharged and the reaction mixture assumed a straw colouration. In this case, analytical t.l.c. showed that extensive transmogrification had occurred and no useful products were ever isolated from this reaction.

It is, at times, difficult to discern the silver lining, but,

in retrospect, this is an extremely fascinating non-reaction. The electronic and thermodynamic parameters for this reaction would appear to be totally satisfied since the 'ene' reaction of caryophyllene with 2-methyl-2-nitrosopropane presented no problem. The only conceivable doubt in this respect is that the twisted nature of the double bond minimises the allylic assistance given to the breaking of the C_3-H σ bond. Notwithstanding this, it should be borne in mind that the initial rate-limiting abstraction of an allylic hydrogen is the exception rather than the rule in the 'ene' reaction.

This leads to the inescapable conclusion that the correct transition state cannot be achieved because of steric factors. In this respect a recent paper by Mock[28] deserves some comment. This author has submitted that the torsional strain of the twisted double bond in <u>trans</u>-cyclooctene (42) might be relieved and a better overlap attained if the double bond undergoes modest rehybridisation with the incorporation of some s character into the lobes of the π bond as in (43). Attention is drawn to the fact that the lobes on the same face of the double bond are expanded in this situation.



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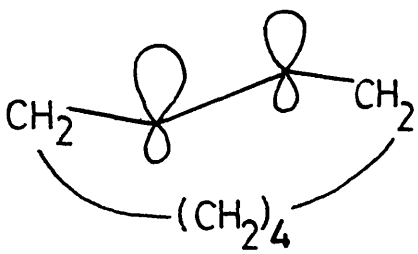

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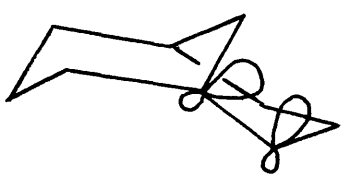


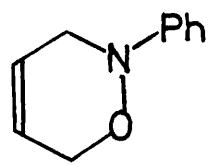
44

If this concept can be extended to bridged <u>trans</u>-cyclooctenes then bicyclo (3,3,1) non-1-ene may be represented as shown (44), and the approach of the enophile is effectively blocked by the

bridgehead hydrogen atoms.

At this juncture, it was decided to step outwith the bounds of aliphatic nitroxide radical chemistry, and react the olefin with nitrosobenzene. This reagent was chosen, not only because it might create a less hindered transition state, but principally for its enhanced reactivity over aliphatic nitroso compounds in the 1,4 cycloaddition reaction[29]. Thus nitrosobenzene readily yields Diels-Alder adducts of the type (45)

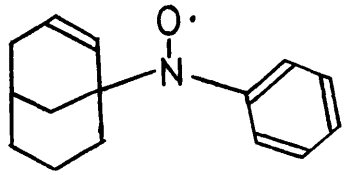
45



The reaction of nitrosobenzene with bicyclo (3,3,1) non-1-ene proceeded readily in benzene solution at room temperature, and the greenish blue colour of the nitroso monomer was completely discharged in two hours. Analytical t.l.c. showed the presence of one major component which was contaminated by small traces of a yellow-coloured compound. When the chromatoplate was developed with an alkaline 2,3,5-triphenyltetrazolium spray the major component was stained to a brilliant red colour. The reaction of hydroxylamines with this reagent is known to form red formazans. All attempts to isolate this hydroxylamine were totally unsuccessful since rapid oxidation took place with the formation of a deep red solution which gave an intense signal in the e.p.r. spectrometer. This signal consisted of a 1:1:1 triplet whose low a_N value of 12.40e., which compares favourably with those previously reported[30] for alkylaryl nitroxide radicals, is a result of spin delocalisation.

These observations may be placed on the credit side and lend considerable support to the idea that the desired nitroxide (46)

was formed in this reaction.



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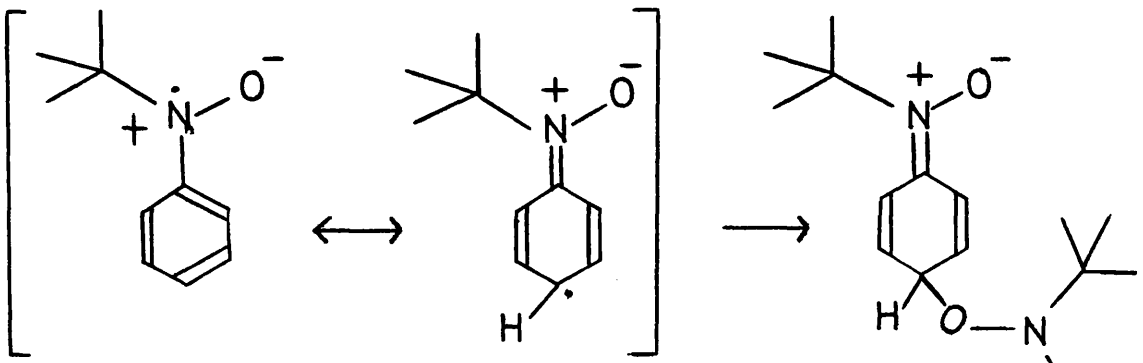
Unfortunately this radical is not sufficiently stable to be isolated by preparative t.l.c. This was not altogether unexpected since Forrester et al.[31] have shown that t-butylphenyl nitroxide (47) decomposes rapidly in concentrated solution to give N-t-butylaniline (48) and N-t-butyl-p-benzoquinonimine N-oxide (49) as shown.



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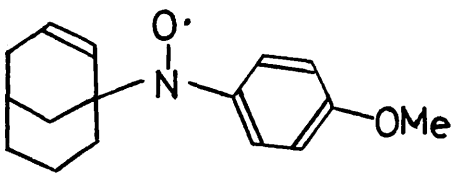

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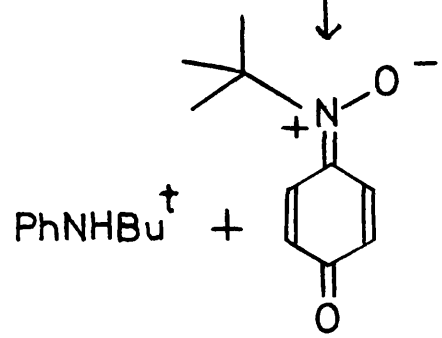

48 **49**

On the debit side is the fact that when this reaction was conducted in an n.m.r. tube a vigorous exothermic reaction occurred and the olefinic triplet of bicyclo(3,3,1)non-1-ene completely disappeared. No trace of olefinic protons corresponding to those at C_2 and C_3 could however be detected in the range 3.5 - 4.5τ.

The experiment was repeated using p-methoxynitrosobenzene, which was expected to stabilise the product nitroxide (50) by preventing disproportionation at the *para* position. Yet again the isolation of products was impossible because of rapid decomposition. A well-resolved e.p.r. spectrum was however obtained which showed, in addition to the 1:1:1 triplet (a_N = 13.90e) a further triplet splitting of 1.1 Oe. due to the two *ortho* protons.

At this stage, these investigations were peremptorily cut short because of lack of time, and even more critically because of paucity of material.

Nevertheless, these preliminary investigations, inconclusive though they may be, do show some promise, and would appear to justify future work. With this in mind it is suggested that trifluoronitrosomethane might prove to be the bifunctional probe for anti-Bredt olefins which is sought. This compound combines the advantages of small steric bulk with the enhanced reactivity which permits it to react as a dienophile in the Diels-Alder reaction. Moreover, the work of Haszeldine and his collaborators[19] have shown that trifluoroalkylhydroxylamines are less susceptible to oxidation.

In conclusion, further work is needed before the claim to understand the 'ene' reaction of nitroso compounds with olefins is made. Although this approach has provided a useful entry to the study of nitroxides with β hydrogen atoms, it would appear to be limited, on the preparative scale at least, to olefins with relatively strained π bonds.

EXPERIMENTAL PROCEDURE.

All melting points were recorded on a Kofler hot-stage and are uncorrected; boiling points are not corrected.

Analytical gas liquid chromatography (g.l.c.) was carried out on Pye-Argon instruments employing 4^{1}x4mm. packed glass columns and argon as the carrier gas. Thin (0.25mm.) and thick (1.00mm.) layer chromatoplates were prepared from Merck's 'Kieselgel G' and were developed with ceric ammonium sulphate and/or iodine. The adsorbent used in column chromatography was Woelm alumina.

Where necessary, solvents were purified and dried in the recommended manner, and reagents were either distilled or recrystallised. Petroleum ether refers to the fraction boiling in the range 40-60^{o}C and all organic extracts were dried over anhydrous magnesium sulphate unless otherwise stated.

Routine infra-red spectra were recorded on Perkin-Elmer 257 or Unicam S.P. 200 instruments and high resolution spectra were obtained using the Unicam S.P. 100 double-beam infra-red spectrophotometer equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum. Ultraviolet absorption spectra were measured using an automatic Unicam S.P. 800 instrument. Nuclear magnetic resonance (n.m.r.) spectra were recorded on Varian T-60 or Varian HA-100 spectrometers using tetramethylsilane as internal reference as solutions in deuterochloroform. Benzene was also used during the studies on solvent shifts and the spectra obtained with this solvent are indicated in the text. The n.m.r. spectra of hydroxylamines susceptible to aerial oxidation were recorded in the presence of the reducing agent hydrazobenzene. Electron paramagnetic resonance (e.p.r.) spectra were measured on a Decca X3 instrument,

operating in the X-band region at a frequency of 9270MHz. Mass spectra were determined on an AEI MS12 instrument and high resolution mass measurements were made using an AEI MS9 instrument.

EXPERIMENTAL.

PURIFICATION OF CARYOPHLLENE (1)

The following purification procedure yields caryophyllene in greater than 99% purity.

Commercial grade caryophyllene supplied by Koch-Light (300g.), dissolved in petroleum ether (300ml.), was thoroughly washed with sodium hydroxide (2M, 3x300ml.), followed by repeated washing with distilled water until the aqueous layer was neutral. The organic layer was then washed with aqueous silver nitrate solution (50%; 3x200ml.) to remove humulene. After washing with distilled water (3x300ml.), the petroleum extract was dried and the solvent removed to afford a colourless oil which, on fractional distillation, gave pure caryophyllene (1); b.p. 124-125°/21mm.; $\nu_{max.}$ (liquid film) = 3070, 1670, 1635, 890, 825 and 815cm.$^{-1}$.

CARYOPHYLLENE NITROSITE. (2)

A solution of caryophyllene (100g.) in petroleum ether (110ml.) was charged into a 500ml. conical flask wrapped in silver paper and cooled to 0°C in the dark. Saturated aqueous sodium nitrite (65g.) was added to this solution, and then, with vigorous shaking, glacial acetic acid (40ml.) was added slowly over a 45 minute period. After a further 15 minutes the light blue crystals were collected by filtration, washed with ice-cold distilled water (40ml.), ice-cold ethanol (60ml.), and allowed to dry at room temperature protected from the light. Recrystallisation from ethanol gave light blue needles (14g.) m.p. 112-113°C (lit.[32] 113°C).

$\nu_{max.}$ (nujol) = 1642, 1575, 1548, 914 and 884cm.$^{-1}$.

τ = 8.96, (6H, singlet, gem-dimethyl), 8.76, (3H, singlet, $\underline{CH_3}$-CNO), 4.71, (2H, singlet, =$\underline{CH_2}$), 3.96, (1H, triplet, $\underline{H}$-C-NO_2).

ISOLATION OF THE YELLOW RADICAL (12) DERIVED FROM CRUDE CARYOPHYLLENE NITROSITE (2) : N-(4,11,11-TRIMETHYL-5-NITRO-8-METHYLENEBICYCLO[7,2,0]UNDECAN-4-YL),N-(11,11-DIMETHYL-4,8-DIMETHYLENEBICYCLO[7,2,0]UNDECAN-5-YL), N-OXYL.

Samples of the crude nitrosite, prepared by the above procedure, were allowed to stand in the dark for two weeks. The greenish blue solid was then dissolved in warm methanol and slowly cooled when a crop of yellow crystals was deposited. This material was collected by filtration, washed with cold methanol, and dried at room temperature. In this manner, 20mg. of material (m.p. 167°C.) could be obtained from 2g. of the nitrosite.

$\nu_{max.}$ (CCl_4) = 3080, 1644, 1560 and 901cm.$^{-1}$.

e.p.r. ($CHCl_3$), triplet of doublets, a_N = 14.2 and a_h = 2.30$_e$, g = 2.0061.

$\lambda_{max.}$ (C_6H_{12}) = 216nm. (ϵ = 4,830).

M^++1 = 484; M^+ = 483.

Found: C, 74.32; H, 9.85; N, 5.62%

$C_{30}H_{47}N_2O_3$ requires: C,74.49; H, 9.79; N, 5.79%

ATTEMPTED CONVERSION OF THE YELLOW RADICAL (12) TO A DIAMAGNETIC DERIVATIVE.

(a) ACETYLATION.

Method (i):- The radical (20mg.) was dissolved in acetic anhydride (2.0ml.) and heated on a steam bath for 1 hour. The solution was then poured on to crushed ice and the precipitate, collected by filtration, was recrystallised from methanol to give pale yellow needles (16mg.), m.p. 167-168°C, readily identified as unreacted starting material.

Method (ii):- The radical (24.1mg.) was dissolved in dry pyridine (3.0ml.) and acetic anhydride (16μl.) was added *via* a syringe. The solution was then refluxed for 0.5 hr, when the initially yellow solution became dark brown. Analytical t.l.c. served to indicate that extensive decomposition had occurred.

Method (iii):- The radical (25mg.) was dissolved in acetic anhydride (3.0ml.). Sodium acetate (13mg.) was added and the solution was maintained at reflux for 0.5hr. Once again, extensive decomposition occurred.

(b) LITHIUM ALUMINIUM HYDRIDE REDUCTION.

A solution of the radical (20mg.) in anhydrous ether (5ml.) was treated with lithium aluminium hydride (28mg.). The reaction was magnetically stirred for 48 hours. Normal work-up procedure for hydride reductions gave a thick colourless oil (18.5mg.). Analytical t.l.c. indicated the presence of at least seven products from this reaction.

(c) PHENYLHYDRAZINE REDUCTION.

Redistilled phenylhydrazine (12μl.) was added *via* a syringe to a solution of the radical (50mg.) in dry methanol (10ml.) and the reaction mixture was maintained at 50°C overnight with magnetic stirring. Extensive transmogrification occurred with the formation of no less than sixteen spots on analytical t.l.c.

MODEL STUDIES:- THE REDUCTION OF 4 - HYDROXY - 2,2,6,6 - TETRAMETHYLPIPERIDINE - 1 - OXYL (6) TO THE CORRESPONDING HYDROXYLAMINE (7).

4 - HYDROXY - 2,2,6,6 - TETRAMETHYLPIPERDINE - 1 - OXYL. (6)

This compound was prepared in 60% yield by oxidation of the corresponding amine as described by Rassat *et. al.*,[33] m.p. 72°C. lit. 71.5°C.

(a) HYDRAZINE REDUCTION.

Hydrazine hydrate (90%, 0.05ml.) was added to a solution of the radical (6) (172mg.) in ethanol (10ml.). The orange solution was heated on a steam bath for 1.5 hours. Removal of solvent from the now colourless solution gave a white crystalline material (168mg.) m.p. 162°C. lit.[34] 158°C. This compound gave a positive test with alkaline 2,3,5 - triphenyltetrazolium chloride.

$\nu_{max.}$ (Nujol) = 2490, 1170, 1033 and 958cm.$^{-1}$

(d_6 MeSOMe) = 8.94, (12H, singlet, 4x$\underline{CH_3}$ - C - NOH), 8.06 - 8.80, (4H, multiplet), 5.9 - 6.8, (1H, broad multiplet, $\underline{H}$C - OH), 5.66, (1H, broad, exchangeable with D_2O, O$\underline{H}$), 2.07, (1H, broad, exchangeable with D_2O, O$\underline{H}$).

(b) REDUCTION BY HYDROGEN ABSTRACTION FROM METHANOL.

A phenanthroline - cupric complex waa prepared by the addition of phenanthroline (436mg.) to a solution of cupric nitrate (241.6mg.) dissolved in methanol (20ml.) and water (5ml.). This solution was added dropwise under nitrogen over 0.75hr. to a well-stirred solution of the nitroxide (6) (173.8mg.) in methanol (10ml.) maintained at 45°C in an oil bath, and allowed to react for 2 hours. Potassium ferrocyanide (423mg.) in water (10ml.) was then added dropwise over a 5 minute period to precipitate the cuprous salts. Rapid filtration, dilution with water and extraction with ether (3x30ml.) gave a clear colourless solution, which, after drying and removal of solvent afforded a white crystalline solid (75mg.) identical to that described in (a) above.

(c) TRI-N-BUTYL TIN HYDRIDE REDUCTION.

Tri-n-butyl tin hydride was prepared by lithium aluminium hydride reduction of the corresponding chloride as described by Kuivila and Beurnal[35]. b.p. 68-76°C a) 0.3mm. $\nu_{max.}$ (Liquid film) = 1804cm.$^{-1}$.

The radical (6) (162mg.), dissolved in freshly distilled tetrahydrofuran (10ml.), was treaded with tri-n-butyl tin hydride (290mg.) in tetrahydrofuran (5ml.) and the initially orange solution was refluxed until colourless (1 hour).

Attempted isolation of the hydroxylamine (7) at this stage proved to be abortive since ready aerial oxidation to the starting nitroxide occurred on the chromatoplate.

The clear solution was accordingly treated in one of two ways. Dry gaseous hydrogen chloride was bubbled into the clear solution which immediately became milky. The solution was allowed to stand overnight, diluted with ether, and the white crystalline hydroxylammonium hydrochloride (137mg.) isolated by filtration m.p. 263°C. lit.[34] 264-265°C.

Alternatively the clear solution was treated with acetic anhydride (210mg.) and refluxed for a further 2 hours. Preparative t.l.c. afforded a clear oil (137mg.) which solidified to long clear needles on standing, m.p. 71-73°C.

The following data served to establish this compound as N-acetoxy-4-hydroxy-2,2,6,6-tetramethylpiperidine. (10).

$\nu_{max.}$ (nujol) = 3,500, 1755, 1200, 1066 and 780cm.$^{-1}$.

τ = 8.79, 8.90, (12H, 2 singlets, $\underline{CH_3}$ - C - NOAc), 8.0 - 8.75, (5H, multiplet, 1H exchangeable with D_2O), 7.92, (3H, singlet, NOCO$\underline{CH_3}$), 4.00, (1H, broad multiplet, $\underline{H}$ - C - OH).

M^+ = 215, Peaks at $^m/_e$ 200, 159, 158, 124, and 43. m* at 124.8.

Found : C, 61.26; H, 9.67; N, 6.43%

$C_{11}H_{21}NO_3$ Requires : C, 61.36; H, 9.83; N, 6.51%.

(d) HYDRAZOBENZENE REDUCTION.

Hydrazobenzene (50mg.) was added to a solution of the nitroxide (6) (43.5mg.) in deuterochloroform. After 0.5.hours the reaction mixture was examined in the n.m.r. spectrometer.

A sharp spectrum of the hydroxylamine (7) was obtained, but attempts to isolate this compound by preparative t.l.c. led only to recovery of the starting nitroxide.

(e) HYDROGENATION OF 4 - HYDROXY - 2,2,6,6 - TETRAMETHYLPIPERIDINE - 1 - OXYL OVER LINDLAR CATALYST.

Hydrogenation of the nitroxide (6) (177mg.) in methanol (10ml.) over a Lindlar catalyst[36] (47mg.) in the usual manner afforded, after filtration of the catalyst through a glass filter paper and removal of solvent, an essentially quantitative yield of the desired hydroxylamine (7) (175mg.). The spectroscopic and chromatographic properties of this material were identical in all respects to those described above.

ATTEMPTED HYDRAZINE REDUCTION OF THE YELLOW RADICAL (12).

Hydrazine hydrate (90% 10µl) was added *via* a syringe to a solution of the radical (12) (52mg.) in ethanol (10ml.). After refluxing the reaction mixture on a steam bath for 45 minutes, hydrazine hydrate (40µl) was added and heating continued for a further 2 hours, when the solution had become colourless. Aliquot monitoring of the reaction by t.l.c. revealed that concomitant formation of six products was occurring.

ATTEMPTED REDUCTION OF THE YELLOW RADICAL (12) BY HYDROGEN ABSTRACTION FROM METHANOL.

The application of this method exactly as described in (b) above led only to the recovery of unreacted starting material. The reaction was also performed under more forcing conditions (50°C for 20 hours) with similar results.

ATTEMPTED TRI-N-BUTYL TIN HYDRIDE REDUCTION OF CARYOPHYLLENE NITROSITE (2).

Tri-n-butyl tin hydride (1.2g) was added to a solution of caryophyllene nitrosite (280mg.) in tetrahydrofuran (12ml.) and the

reaction was heated under reflux until the blue colour of caryophyllene nitrosite had disappeared (1.5hours). Analytical t.l.c. examination of the reaction mixture revealed the presence of at least six products and served to indicate that this method of reduction was inapplicable to the yellow radical (12).

HYDRAZOBENZENE REDUCTION OF THE YELLOW RADICAL (12).

Hydrazobenzene (25mg.) was added to a solution of the radical (12) (48.3mg.) in chloroform (10ml.) and the reaction was magnetically stirred for 24 hours under a nitrogen atmosphere. Analytical t.l.c. of an aliquot showed that the starting material had been cleanly consumed. The solvent was removed, and replaced by deuterochloroform and the reaction mixture was examined in the n.m.r. spectrometer. The n.m.r. spectrum thus obtained was identical, save for aromatic protons, to that obtained by hydrogenation over Lindlar catalyst. (vide infra).

HYDROGENATION OF THE YELLOW RADICAL (12) TO THE CORRESPONDING HYDROXYLAMINE (13).

The radical (12) (49.1mg.) was dissolved in ethyl acetate (10ml.). Lindlar catalyst (24.4mg.) was added and the magnetically stirred solution was hydrogenated at atmospheric pressure for 19 hours. The catalyst was removed by filtration through a celite pad under nitrogen and solvent was evaporated under reduced pressure to afford the crystalline hydroxylamine (13) (48.3mg.) m.p. 134-136°C. This compound formed a brilliant claret-red formazan with alkaline 2,3,5-triphenyltetrazolium chloride.

$\nu_{max.}$ (Nujol) = 3560, 1636, 1548, 925, 900 and 884cm.$^{-1}$.

τ = 9.02, (12H, singlet, 2 gem-dimethyls), 9.77, (3H, singlet, Me-C-NOH), 6.78, (1H, broadened triplet, CH-NOH), 5.02-5.26, (7H, multiplet, CH+NO_2 and 3x=CH_2), 5.02-5.26, (1H, exchangeable with D_2ONOH).

M^+ = 484. $C_{30}H_{48}N_2O_3$ requires 484.

SYNTHESIS OF THE YELLOW RADICAL (12).

Freshly purified caryophyllene (8.16g) was dissolved in chloroform (25ml.) and added to a solution of caryophyllene nitrosite (2.8g) in chloroform (25ml.). This solution was allowed to stand in the dark in the presence of air for 11 days, with occasional replenishment of solvent. The dark green oil which remained on removal of chloroform was dissolved in petroleum ether (10ml) and methanol was added to precipitate a yellow solid, (2.05g.) which was collected by filtration, and thoroughly washed with cold methanol. Recrystallisation of this solid from petroleum ether afforded the yellow radical (12) (1.86g., 39%).

ISOCARYOPHYLLENE (17).

Caryophyllene nitrosite (1.0g) was dissolved in the minimum amount of ethanol and refluxed in the presence of an electric light bulb for 4 hours, during which time the initially dark blue colour was replaced by a straw colouration. The reaction mixture was poured into an excess of water, thoroughly extracted with petroleum ether (4x50ml.), dried, and the solvent removed to yield a clear oil (710mg.) which g.l.c. analysis showed to be pure isocaryophyllene (>99%).

REACTION OF CARYOPHYLLENE NITROSITE (2) WITH ISOCARYOPHYLLENE (17).

To a solution of caryophyllene nitrosite (280mg.) in chloroform (2ml.) Isocaryophyllene (710mg.) in chloroform (2ml.) was added. Examination of the reaction mixture in the cavity of the e.p.r. spectrometer revealed the presence of a paramagnetic species whose spectroscopic parameters (a_N=14.2 and a_H=2.3 Oe; g=2.0061) were identical to those described for the yellow radical (12). This reaction appears to be slower than that described

for caryophyllene inasmuch as the characteristic green colour develops much more slowly. Aliquot monitoring of the reaction by t.l.c. failed to indicate the presence of the nitroxide which also defied isolation after four weeks by the technique described above.

ATTEMPTED ISOLATION OF THE INTERMEDIATE HYDROXYLAMINE (13) IN THE REACTION OF CARYOPHYLLENE NITROSITE (2) WITH CARYOPHYLLENE (1).

A carefully deoxygenated solution of caryophyllene nitrosite (284.5mg.) and caryophyllene (414mg.) in pentane (25ml.) was prepared. The solution was then magnetically stirred in complete darkness under a positive pressure of nitrogen for 17 days during which time the blue colour of the solution largely disappeared and a white solid was precipitated. The pentane solution was decanted and the white solid was washed with pentane. Removal of solvent from the pentane extracts gave a thick oil (597.8mg.). The white solid (95mg.) was recrystallised from petroleum ether, (100-120°), m.p. 131-132°C. T.l.c. comparison of the reaction products with an authentic sample of the hydroxylamine (13) established the non-identity of the white solid with this material. In addition, only traces of the desired hydroxylamine (13) were detected by t.l.c. The white solid was readily identified as dinitrocaryophyllene (11) by comparison of the spectral (i.r. and n.m.r.) and chromatographic properties with an authentic sample.

DINITROCARYOPHYLLENE (11).

Dinitrocaryophyllene was prepared as described by Deussen[37] or alternatively by oxidation of caryophyllene nitrosite with Fenton's reagent, m.p. 131.5-132.5°C.

$\nu_{max.}$(Nujol) = 1644, 1558 and 921cm.$^{-1}$.

τ = 8.95, (6H, singlet, gemdimethyl), 8.04, (3H, singlet, $\underline{CH_3}$-C-NO_2), 4.78, (2H, singlet, = $\underline{CH_2}$), 4.82, (1H, broad, $\underline{HC}$-NO_2). M^+ = 296.

DISPROPORTIONATION OF CARYOPHYLLENE NITROSITE (2).

Caryophyllene nitrosite (100mg.) was dissolved in pentane (12ml.) and magnetically stirred in the dark under nitrogen as previously described. After 17 days removal of solvent and preparative t.l.c. afforded dinitrocaryophyllene (11) (23.3mg.) together with unreacted nitrosite (35mg.).

2 - METHYL - 2 - NITROPROPANE.

This compound was prepared by oxidation of t-butylamine as described by Kornblum[38]. b.p. 126°C.

2 - METHYL - 2 - NITROSOPROPANE

Reduction of 2-methyl-2-nitropropane with aluminium amalgam and subsequent oxidation according to the method of Forrester[39], furnished this compound as the white crystalline dimer, m.p.83°C. lit. 83-84°C.

REACTION OF CARYOPHYLLENE (1) WITH 2 - METHYL - 2 - NITROSOPROPANE. N - (t - BUTYL), N - (11, 11 - DIMETHYL - 4,8 - DIMETHYLENE-BICYCLO (7,2,0) UNDECAN - 5 - YL), - N - OXYL. (27).

Freshly purified caryophyllene (409mg.) in chloroform (10ml.) was added to solid 2-methyl-2-nitrosopropane (87mg.). The blue solution turned green on being allowed to stand in the dark for 14 days, care being taken to ensure that complete evaporation of the solution did not occur. The major product of the reaction was isolated by preparative t.l.c. as a relatively unstable reddish oil (130mg.) (44%).

$\nu_{max.}$ (Liquid Film) = 3070, 1642, 1361, and 885cm.$^{-1}$.

e.p.r. ($CHCl_3$), triplet of doublets, a_N=14.9, and a_H=2.30e. g=2.0067.

M^++1 = 291; M^+ = 290 $C_{19}H_{32}NO$ requires 290.

HYDROGENATION OF THE NITROXIDE RADICAL (27) TO THE CORRESPONDING HYDROXYLAMINE. (28).

Hydrogenation of a freshly prepared sample of the nitroxide radical (27) (136.2mg.) in ethyl acetate (10ml.) with Lindlar catalyst (54mg.) for 17 hours and work up as previously described gave the corresponding hydroxylamine (28) (134.4mg.) as a clear viscous oil which gave a positive test with alkaline 2,3,5 - triphenyltetrazolium chloride.

$\nu_{max.}$(Liquid Film) = 3500, 3082, 1638 and 890cm.$^{-1}$.

τ = 9.00, (6H, singlet, gem-dimethyl), 8.84, (9H, singlet, t-butyl), 7.2-8.6, (12H, multiplet), 6.58, (1H, broad, HC-NOH), 5.83, (1H, broad, exchangeable with D_2O), 5.07, (4H, broad singlet, 2x = CH_2).

ACETYLATION OF THE HYDROXYLAMINE (28).

A freshly prepared sample of the hydroxylamine (130mg.), acetic anhydride (250mg.), and pyridine, (100mg.) in dry tetrahydrofuran (20ml.) was allowed to react at room temperature, under nitrogen, for 7 days. The hydroxylamino - acetate (29) (50mg.) was isolated by preparative t.l.c. as an extremely viscous oil.

$\nu_{max.}$(liquid film) = 3090, 1770, 1635, 1368, 1195, 1002, 895, and 905cm.$^{-1}$.

τ = 9.02, (6H, singlet, gem-dimethyl), 8.87, (9H, singlet, t-butyl), 7.4-8.8, (12H, multiplet), 7.98 (3H, singlet, CH_3-CON), 6.52, (1H, very broad, H-C-NOAc), 5.08, (4H, broad multiplet, 2x = CH_2).

DECOMPOSITION OF THE NITROXIDE (27).

The decomposition of the nitroxide (27) was monitored by analytical tlc. which, by comparison with an authentic sample, demonstrated the intermediacy of the hydroxylamine (28). A

sample of the major primary decomposition product was isolated by preparative t.l.c. as an unstable poorly crystalline solid. The spectroscopic properties of this compound are in accord with structure (30).

$\nu_{max.}$ (liquid film) = 3070, 1705, 1630, and 905 $cm.^{-1}$

τ = 9.03, (6H, singlet, gem-dimethyl), 8.54 (9H, singlet, $(CH_3)_3$-C=N-O), 6.9-8.8 (12H, complex), 6.16-6.66 (2H, multiplet, CH_2-C=N-O), 5.08 (2H, broad, exomethylene), 5.66 (2H, broadened multiplet, exomethylene conjugated to nitrone).

1-CARBETHOXYBICYCLO(3,3,1)NONAN-9-ONE.

This compound was prepared as described by Colvin and Parker.[40]

BICYCLO(3,3,1)NON-1-ENE (38).

This compound was prepared in nine stages from 1-carbethoxybicyclo(3,3,1)non-1-ene as described by Wiseman et al.[26]

τ = 4.15 (1H, triplet, J = 7Hz).

ATTEMPTED REACTION OF BICYCLO(3,3,1)NON-1-ENE WITH 2-METHYL-2-NITROSOPROPANE.

(a) AT ROOM TEMPERATURE.

A solution of 2-methyl-2-nitrosopropane (60mg.) in pentane (2ml.) was added under a nitrogen atmosphere to a solution of bicyclo(3,3,1)non-1-ene (ca. 60mg. from 0.5g. of the corresponding methiodide precursor) in pentane (2ml.). After 2 days in the dark at room temperature the solution was still blue, and analytical t.l.c. indicated that no reaction had occurred. After this time, the pentane and 2-methyl-2-nitrosopropane (60mg.) in rigorously acid-free chloroform (10ml.) was added. This solution was allowed to stand in the dark under nitrogen for 7 days when t.l.c. evidence once again demonstrated that no reaction had occurred.

(b) IN A SEALED TUBE AT 100°C.

2-Methyl-2-nitrosopropane (100mg.) and bicyclo (3,3,1) non-1-ene (ca. 110mg. from 1g. of the methiodide precursor) were dissolved in benzene (15ml.) and heated in a sealed tube under a nitrogen atmosphere for 4 days in an oil bath maintained at 100°C. During this time the initially blue solution gradually became greenish and eventually assumed a straw colour. The tube was then cooled, opened, and the contents transferred to a small round-bottomed flask where the solvent was removed under vacuum through a vigreux column. As analytical t.l.c. indicated that a plethora of products were formed in the reaction this approach was discontinued.

NITROSOBENZENE.

Nitrosobenzene was prepared as described by Vogel[41] and purified by sublimation at 80°C. into a trap maintained at -40°C. m.p. 68° (lit, 68°).

REACTION OF NITROSOBENZENE WITH BICYCLO (3,3,1) NON-1-ENE (38).

A solution of nitrosobenzene (120mg) in benzene (5ml.) was added under a nitrogen atmosphere to a freshly-prepared solution of bicyclo (3,3,1) non-1-ene (ca. 110mg. from 1 g. of the methiodide precursor) in benzene (5ml.). The greenish blue colour was discharged over a 2 hour period and the solution was allowed to stand for 16 hours at room temperature in the dark. Analytical t.l.c. showed the presence of one major product which was contaminated by trace ammounts of a yellow coloured material. This major component gave a positive test on an analytical chromatoplate by spraying with alkaline 2,3,5-triphenyltetrazolium chloride solution. Attempts to isolate the major product by preparative t.l.c. were singularly unsuccessful; since rapid

aerial oxidation occurred to provide a deep red solution which gave an intense signal in the e.p.r. spectrometer comprising a broadened triplet a_N=12.40e.; g=2.0060. (C_6H_6) when this reaction was performed in an n.m.r. tube a vigorous exothermic reaction ensued and the olefinic triplet of bicyclo (3,3,1) non-1-ene disappeared. No olefinic protons corresponding to those at C_2 and C_3 in the expected product (46) could be detected in this spectrum. Radical broadening was also observed.

p-METHOXYNITROSOBENZENE.

This compound was prepared by etherification of p-nitrosophenol as described by Hays, de Butts and Young, and was obtained as a dark blue-green low melting solid. lit. [42] m.p. 25°C.

REACTION OF p-METHOXYNITROSOBENZENE WITH BICYCLO (3,3,1) NON-1-ENE.(38).

The experiment described above was repeated using p-methoxynitrosobenzene (150mg.). Similar observations were recorded and once again product isolation at the hydroxylamine and nitroxide stages proved unsuccessful. In this case however, a well resolved e.p.r. spectrum was obtained which showed, in addition to the 1:1:1 triplet a_N=13.90e, further triplet splitting due to the two ortho hydrogen atoms a_H=1.1 0e.; g = 2.0061 (CCl_4).

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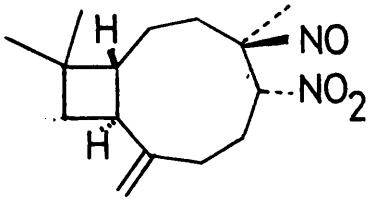
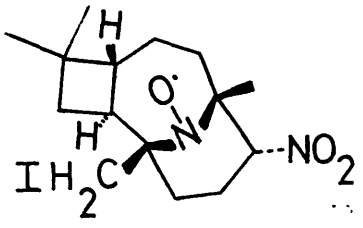
CHAPTER 2.

INTRAMOLECULAR RADICAL CYCLISATION REACTIONS.

Some time ago, in the course of a reinvestigation of the chemistry of caryophyllene nitrosite (1), a stable crystalline "iodo-nitrosite" was prepared in 50% yield by treatment of the nitrosite with iodine in chloroform solution at room temperature, using the procedure originally described by Deussen[1]. The structure of this compound was unambiguously estiblished as the iodo-nitroxide radical (2) by a single crystal X-ray analysis[2].



1

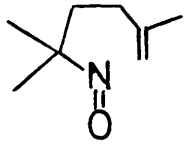


2

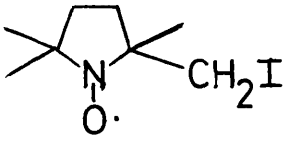
While this reaction demonstrated, once again, the remarkable propensity of the caryophyllene skeleton to undergo transannular cyclisation, it was considered that even greater significance lay in the synthetic potential of this approach to nitroxide radicals. Thus, it was decided to initiate an investigation into the cyclisation of suitably substituted nitroso-olefins.

A detailed examination of the literature revealed a dearth of such nitroso-olefins or their immediate precursors, particularly so in the case of those required for intramolecular cyclisation to nitroxide radicals of the piperidino class. Our attention was therefore initially directed to a study of $\delta\ \varepsilon$ - unsaturated

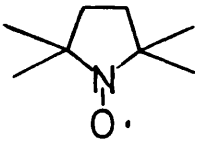
nitroso olefins, and, in particular, to the synthesis of the simplest example, viz. the nitroso-olefin (3), since on analogous cyclisation would lead to the iodo-nitroxide (4) and further chemical transformations would enable a direct comparison to be made with the known pyrrolidino nitroxide radical (5).



3

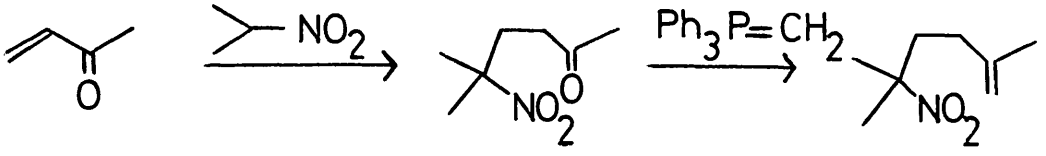


4

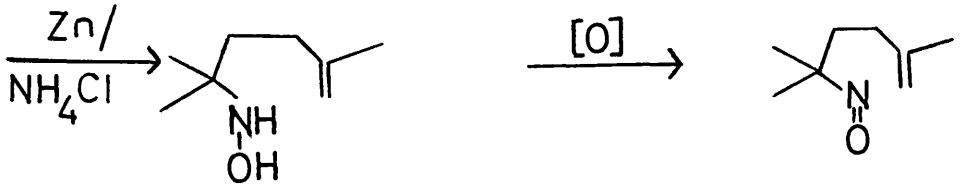


5

The decision to examine $\delta\,\varepsilon$ - unsaturated nitroso olefins was also dictated, to a large extent, by the simplicity of the intended synthetic strategy. Although this is illustrated in Scheme 1 for the particular case of the nitroso-olefin (3), it can be seen that this route constitutes a general approach to the desired system.



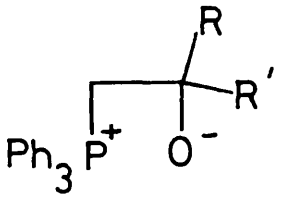
6 **7**



8 **3**

Scheme 1

In the first instance, the required nitroketone (6) was readily available by Michael addition of 2-nitropropane to methyl vinyl ketone as described by Schechter and coworkers[3]. The Wittig reaction, however, deserves some comment. Initially, when phenyllithium was used as the base to generate the ylid from the phosphonium salt, the nitro-olefin (7) was invariably obtained in low yield. In consequence, the discovery that much higher yields were obtained when potassium t-butoxide was employed, represented a considerable advance. The mechanistic rationale for this observation undoubtedly lies in the ability of the intermediate betaine (9) to form a lithio complex (10) which is much more resistant to breakdown by syn elimination[4].



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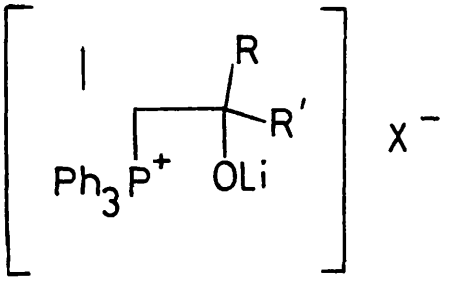
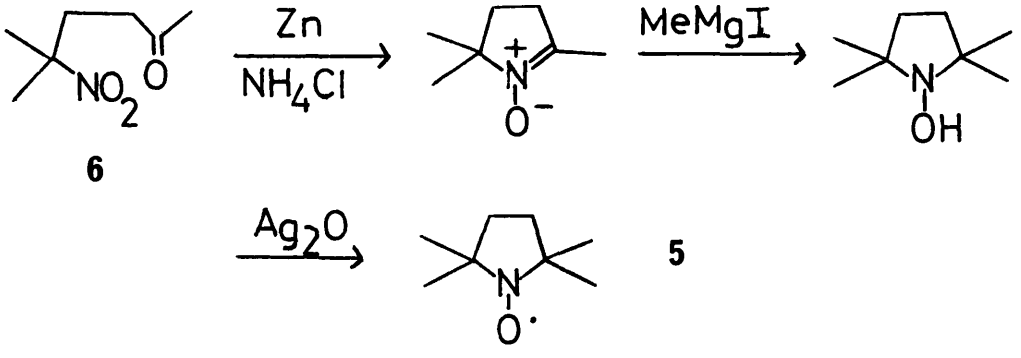


10

Selective reduction of the nitro-olefin (7) with zinc and ammonium chloride proceeded smoothly to give the hydroxylamino-olefin (8) as a clear oil which gave a positive test with alkaline 2,3,5 - triphenyltetrazolium chloride solution, and showed $\nu_{OH}^{'}$=3,300cm.$^{-1}$. It was interesting to note that the n.m.r. spectrum, which exhibited the anticipated absorption at 5.32 τ for the exomethylene group, also displayed some paramagnetic line broadening on standing.

And so the stage was set for the penultimate step to give the nitroso-olefin (3). Accordingly, the hydroxylamino-olefin (8) was dissolved in ether and shaken with excess silver oxide. The

only indication of the desired nitroso-olefin (3), however, was the appearance and subsequent disappearance of the characteristic blue colour which is associated with the $n \rightarrow \pi^*$ transition of the nitroso chromophore! Nevertheless, an even greater surprise was in store, in the sense that the only material to be isolated from this reaction was a mobile red oil, which gave an intense paramagnetic triplet signal in the e.p.r. spectrometer! The identity of this compound was unambiguously established as 2,2,5,5 - tetramethyl - pyrrolidine - 1 - oxyl (5) by a detailed comparison of the spectral and g.l.c. properties with an authentic sample which was prepared as shown in Scheme 2.

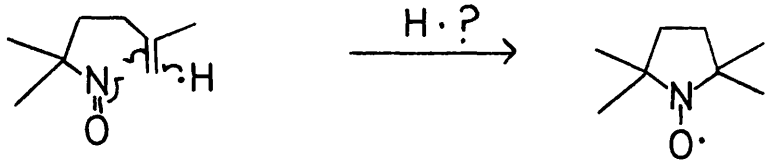


Scheme 2

The formation of the nitroxide (5) was now seen to explain the paramagnetic line broadening in the n.m.r. spectrum of the hydroxylamino-olefin (8) since aerial oxidation also led to radical formation. Similar observations were also recorded when sodium metaperiodate was used as oxidant. Although the yield of the pyrrolidino-nitroxide (5) was only 15% from the nitro-olefin (7), this was not altogether surprising in view of its extreme volatility.

Any mechanistic speculation as to the intermediacy of the

nitroso-olefin (3) in the formation of the nitroxide (5) was realistically untenable, inasmuch as some form of reductive ring closure was required:

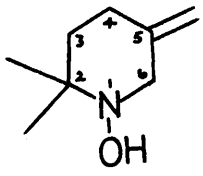


3 **5**

Hence, it was recognised that two distinct problems had to be solved; viz. the fate of the nitroso-olefin (3) and the mode of formation of the nitroxide radical (5).

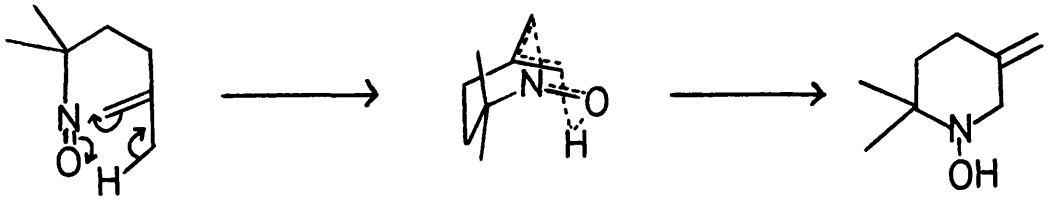
Fortunately, at this time, Maassen and de Boer[5] published a short paper advocating the use of the Fetizon reagent (silver carbonate on celite) as an extremely quick and efficient oxidant for the conversion of hydroxylamines to nitroso compounds. With the hydroxylamino-olefin (8), this reagent gave a deep blue solution, whose analytical t.l.c. showed, in addition to the pyrrolidino-nitroxide (5), a less polar blue spot, which was presumed to be the elusive nitroso-olefin (3). Within forty-five minutes at room temperature in the dark however, the blue colour had completely disappeared and analytical t.l.c. showed the presence of a new component. This compound, which was isolated by preparative t.l.c. as a colourless oil, gave a positive tetrazolium test and showed hydroxyl and olefinic absorption in the i.r. spectrum. ($\nu_{max.}$ = 3280, 3090, 1658 and 903cm.$^{-1}$). The n.m.r. spectrum proved to be particularly informative, and the data set out below, led to the assignment of the cyclic hydroxylamine structure (11).

τ	H	Multiplicity	Assignment
8.80	6	singlet	$(C\underline{H}_3)_2C$-NOH
8.42	2	multiplet	C-3 $\underline{H}_2$
7.85	2	multiplet	C-4 $\underline{H}_2$
6.50	2	singlet	$C\underline{H}_2$-NOH
5.24	2	singlet	$=C\underline{H}_2$
3-3.5	1	broad (exchangeable with D_2O)	NO$\underline{H}$



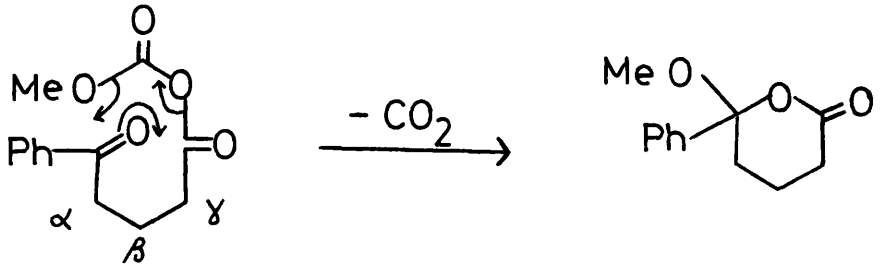
11

All too often in organic chemistry, the historian is forced to replace his <u>a priori</u> assumptions by <u>a posteriori</u> rationalisations. In this case, it is simple, in retrospect, to see that the nitroso-olefin (3) is beautifully set up for an unprecedented intramolecular 'ene' reaction via the bicyclo (3,3,1) transition state as shown in Scheme 3.



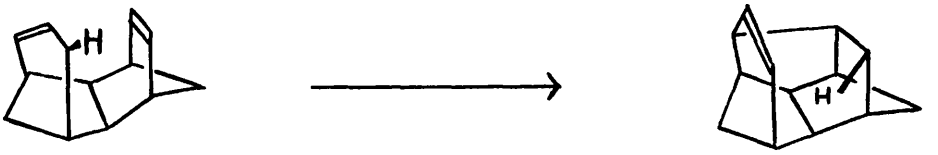
Scheme 3

This observation requires amplification in several directions. In particular, the concept of an intramolecular reaction proceeding by a bicyclic mechanism was first proposed by Newman[6] who showed that pyrolysis of the mixed anhydride (12) gave the pseudo ester (13).



12 **13**

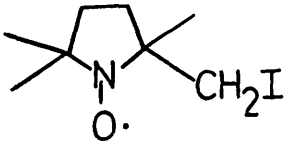
The American group have also provided several examples of reactions involving (3,2,1) and (4,2,2) pathways, although, in each case, and in contrast to the 'ene' reaction above, some molecular fragment is always expelled. In a further extension, mixed anhydrides of the type (12) have been prepared with gem-dimethyl substituents on the α, β, and γ positions. It is interesting to note that, unlike their acyclic counterparts, where the gem-dimethyl effect usually facilitates ring closure reactions involving the formation of five and /or six membered rings, these bicyclic intermediates show no enhancement of reactivity. Examination of the literature[7] reveals that almost all of the observed intramolecular 'ene' reactions have only proceeded at elevated temperatures. The sole exception appears to be the birdcage homologue (14) which has been found[8] to cyclize to (15) with a half-life of about six hours at 45°C.



14 **15**

In this case, the two π bonds are held rigidly in almost parallel planes and separated by only 2Å. Although no quantitative measurements have been made, the intramolecular 'ene' reaction of the nitroso-olefin (3) is undoubtedly even more facile. In addition to the obvious entropic factors, this is probably a reflection of an almost perfect transition-state geometry.

While this rather ironic divertissement was ceratinly worthy of further study in its own right, it did not help to solve the initial aim of the investigation. Nevertheless, it was very encouraging to observe that, despite its extreme instability, the nitroso-olefin (3) did undergo reaction with iodine in methylene chloride solution at -40°C to afford the long-awaited iodo-nitroxide radical (4).

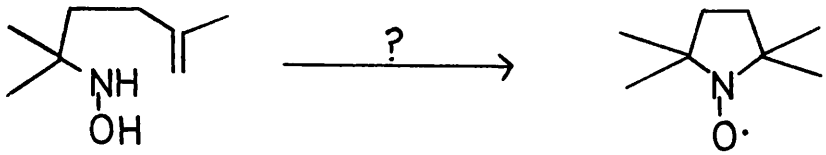


4

This compound, which could be separated from the parent nitroxide (5) by careful column chromatography, was isolated in low yield as an unstable yellow oil, and the structural

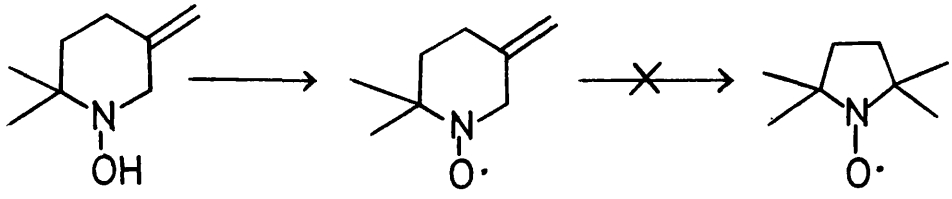
assignment is based on e.p.r. and mass spectral evidence.

When these facets of this multifarious reaction had been satisfactorily unravelled, it was now possible to return to the second and most intriguing problem of all; viz. the formation of the parent pyrrolidino-nitroxide (5) from the acyclic hydroxylamino-olefin (8).



8 **5**

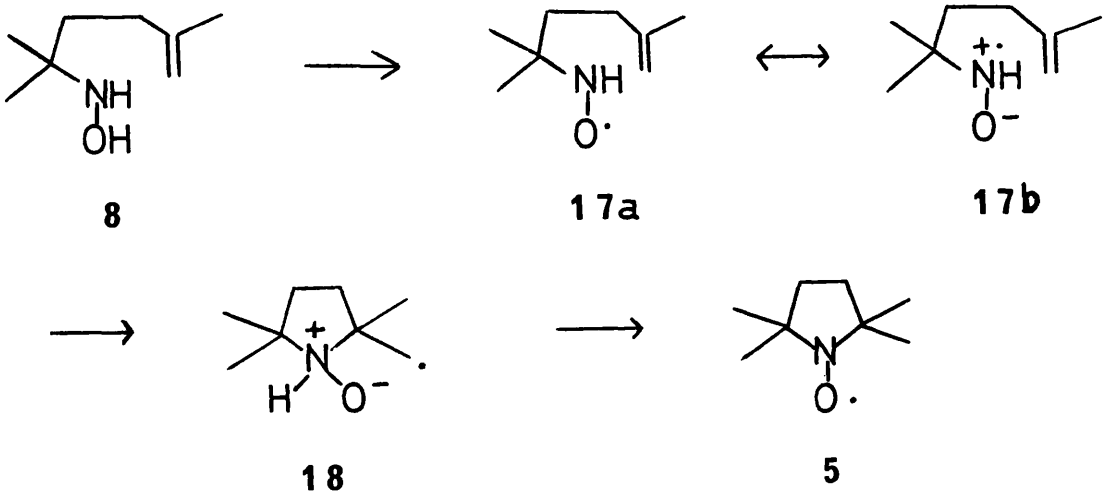
Although it seemed to be highly improbable that the cyclic hydroxylamine (11) could undergo some form of bizarre rearrangement to the nitroxide (5), this possibility was rigorously excluded by oxidising the hydroxylamine (11) in the cavity of the e.p.r. spectrometer and observing the growth and subsequent decay of the unstable nitroxide radical (16), without any enhancement of the signal due to trace impurities of the pyrrolidino-nitroxide (5) (Scheme 4).



11 **16** **5**

Scheme 4

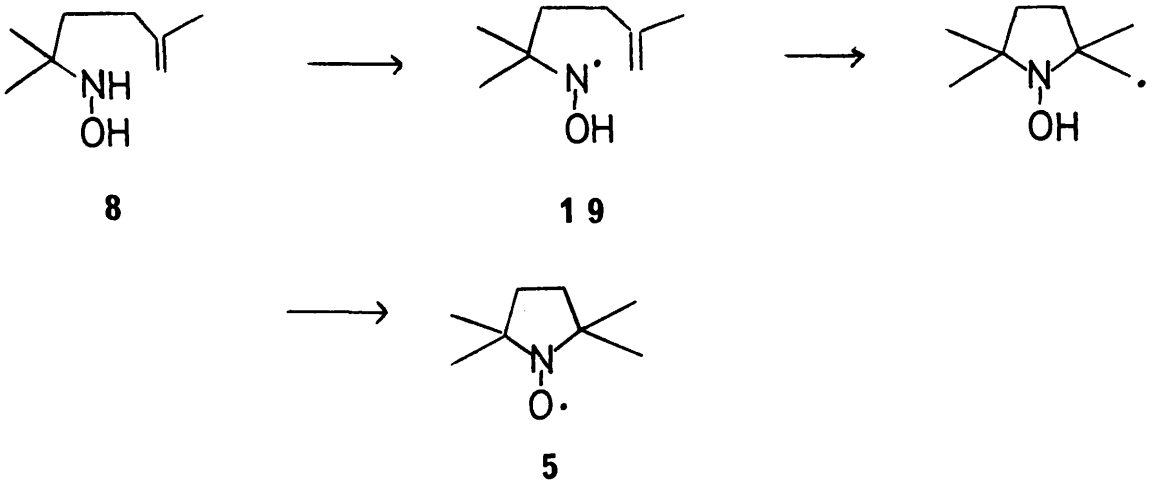
In consequence, it was necessary at this juncture to formulate a mechanism which did not involve the intermediacy of the nitroso-olefin (3) or its rearranged 'ene' product (11). In principle, two related mechanisms are possible.



Scheme 5

The first of these is shown in Scheme 5 and involves, as the initial step, a one-electron oxidation of the olefinic-hydroxylamine (8) to the monoalkyl nitroxide radical (17). This is followed by intramolecular radical cyclisation to give the inter-mediate (18), which should be a very reactive primary radical capable of hydrogen atom abstraction by an intermolecular or an intramolecular process, to give the observed nitroxide (5).

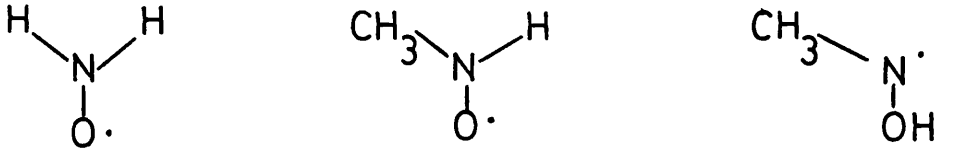
A feasible alternative to the monoalkyl nitroxide radical (17) is the hydroxylamino radical (19) which could also undergo subsequent cyclisation and hydrogen atom abstraction to give the nitroxide (5) as shown in Scheme 6.



8 19 5

Scheme 6

At the present time, there would appear to be some controversy in the literature regarding the exact nature of the primary intermediate in the one-electron oxidation of hydroxylamines.



20 21 22

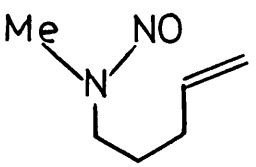
Gutch and Waters[9] have examined the oxidation of hydroxylamine and N-methylhydroxylamine with ceric ammonium nitrate and ferricyanide using e.p.r. flow techniques. In the case of hydroxylamine itself a 1:3:4:3:1 quintet was observed. This is consistent with the formulation of the radical intermediate as the nitroxide (20) where $a_n \simeq a_h$. The N-methylhydroxylamine radical showed a 1:5:11:14:11:5:1 septet which could be attributable to either the nitroxide radical (21) or to the hydroxylamino radical (22) since hyperfine splitting due to hydroxyl protons is usually very

small. However, the fact that oxidation of O-methylhydroxylamine occurred very slowly and that no radical signal could be detected, led these authors to favour the nitroxide radical structure (21). On the other hand, by using the technique of pulse radiolysis, Simic and Hayon[10] have recently shown that one-electron oxidation of hydroxylamine and O-methylhydroxylamine with hydroxyl radicals gives rise to similar intermediates, thus favouring the hydroxylamino radical structure (22). A feasible explanation might be that the nature of the radical is controlled by its method of production, or alternatively that the two species might undergo rapid equilibration.

Nevertheless, in our own case, it was possible to adduce partial support for the hypothesis that the nitroxide (5) was formed as a result of intramolecular radical trapping of a discrete intermediate in the oxidation of the acyclic hydroxylamino-olefin (8). Thus when the oxidation of the hydroxylamine (8) was accomplished with diethylazodicarboxylate[11], a reaction which converts a hydroxylamine to a nitroso compound by a presumed concerted process, only trace amounts of the radical (5) were produced as evidenced by analytical t.l.c.

The second step in each of the two proposed mechanisms, which involves intramolecular radical cyclisation, is strongly supported by literature analogy. Two distinct cases must however be recognised.

In the first case, the olefinic aminium radical cation, $R_2\overset{+\cdot}{N}H$, would seem to be a reasonable model for the dipolar form of the monoalkyl nitroxide (17b). This intermediate has been proposed by Chow, Menon, and Perry[12] to account for their specific intramolecular nitrosamine photoaddition under acidic conditions,



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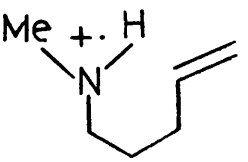

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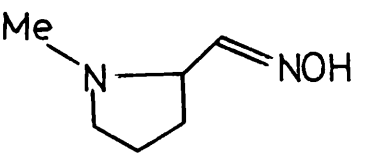

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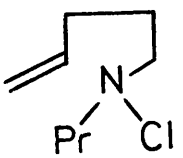

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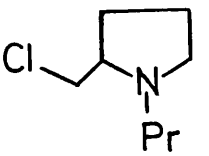

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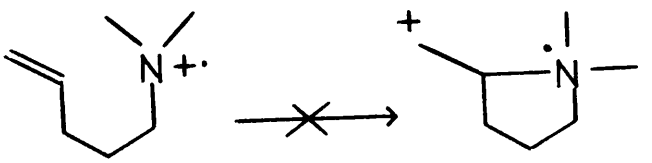

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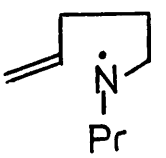
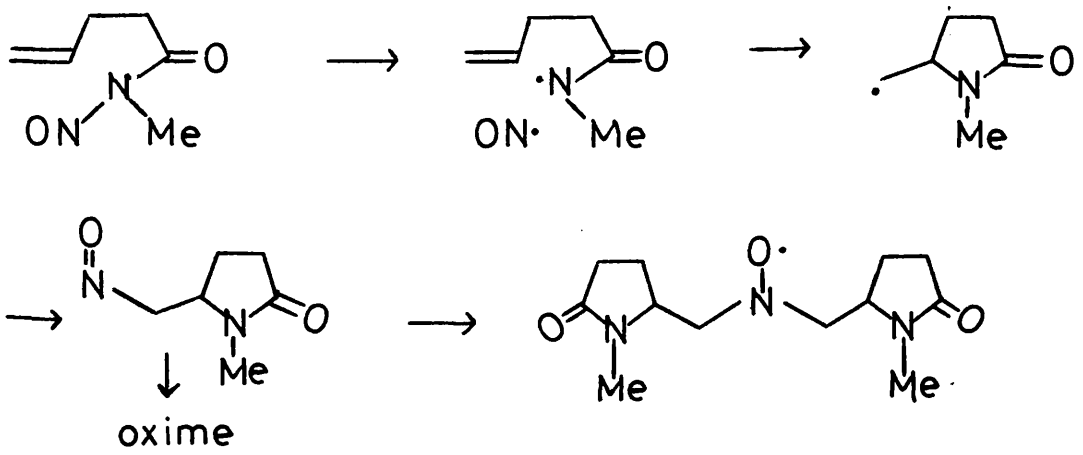


30

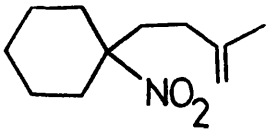
as exemplified by the conversion of (23) to (24) via (25). The olefinic aminium radical cation is also proposed as an intermediate by Surzur and coworkers[13] in the conversion of the chloro-amine (26) to the pyrrolidine (27) under acidic conditions. It is interesting to note that the radical cation is constrained to react by a purely radical pathway since electrophilic addition e.g. (28)→(29) leads to a violation of the Octet rule at the nitrogen centre. Nevertheless, electrostatic interaction between the positive charge on nitrogen and the π cloud of the double bond may be important in setting up the correct geometry for reaction.

In the second case, a neutral aminium radical is involved and serves as a model for the hydroxylamino radical (19). Thus photolysis of the chloro-amine (26) has been shown by Surzur et. al.[14] to produce the neutral aminium radical (30) which once again cyclises to the pyrrolidine (27). This author has also provided evidence for the intermediacy of the primary radical by the use of the spin trapping method as shown in Scheme 7.[15]



Scheme 7

Irrespective of the exact nature of the intermediates involved, this reaction was of obvious synthetic interest; and so it was decided to extend its scope by examining a closely-related compound.



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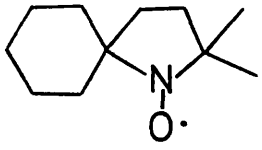
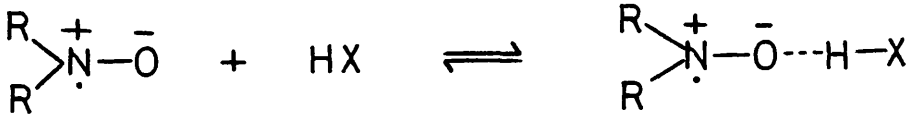
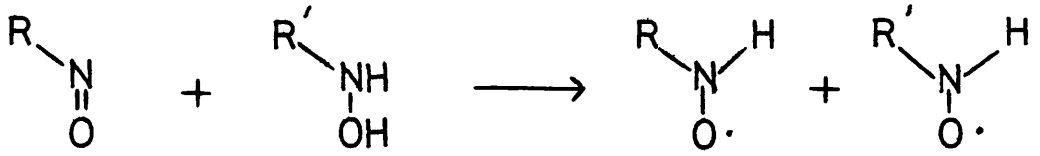


32

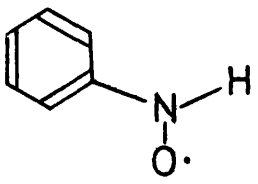
The nitro-olefin (31) was accordingly prepared by a similar sequence starting from 1-nitrocyclohexane, and the corresponding hydroxylamine was subjected to oxidation with silver oxide. In this case the spiro-nitroxide radical (32) proved to be considerably less volatile than the pyrrolidino-nitroxide (5), and was therefore isolated as a low melting orange solid in 30% overall yield from the nitro-olefin (31). While this yield represented a significant improvement, some attempt was nevertheless made to find optimum conditions. The first experiment towards this end consisted of performing the oxidation of the hydroxylamino-olefin in isopropanol. Two separate reasons influenced this choice of solvent. Firstly, if the reaction proceeded through a monoalkyl nitroxide radical, then hydrogen bonding between the radical and solvent as shown is known[16] from e.p.r. studies to increase the spin density on nitrogen. This was expected to facilitate ring closure.



Secondly, it was anticipated that the primary radical generated by the intramolecular radical cyclisation would be capable of abstracting a hydrogen atom from isopropanol. In the event, however, no improved yield resulted by this approach. A second experiment with an underlying current of mechanistic interest was then attempted. This consisted of reacting the hydroxylamino-olefin with 2-methyl-2-nitrosopropane since de Boer and coworkers[17] have shown that an interesting disproportionation takes place to form two monoalkyl nitroxide radicals:



Although this reaction proceeded very smoothly, the spiro-nitroxide radical (32) was isolated in exactly the same yield. Nevertheless, this method of cyclisation might prove to be a valuable addend if other sensitive functional groups are present in the molecule. The third approach was a reductive one, based on the observation by Rassat et. al.[18], that lithium aluminium hydride reduction of nitrobenzene gives rise to monophenyl nitroxide (33) and diphenyl nitroxide (34) in the e.p.r. spectrum.



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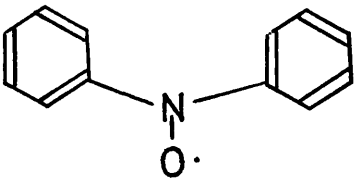


34

When this reaction was applied to the nitro-olefin (7) no pyrrolidino-nitroxide (5) was detected by analytical t.l.c.

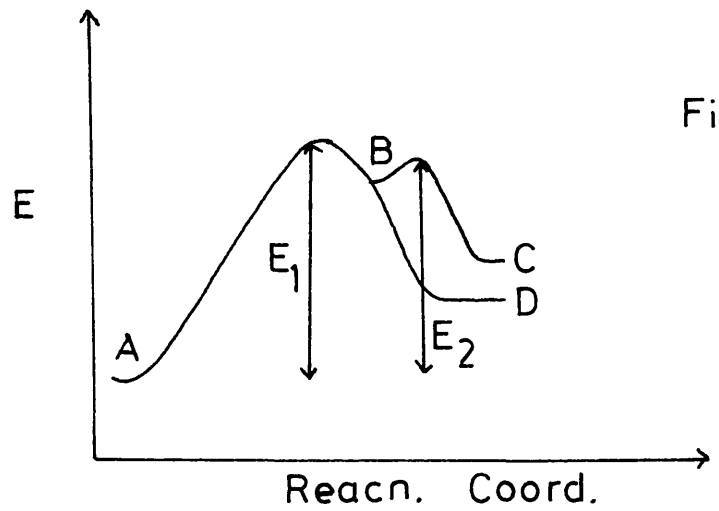


Fig. 1

$E_1 > E_2$

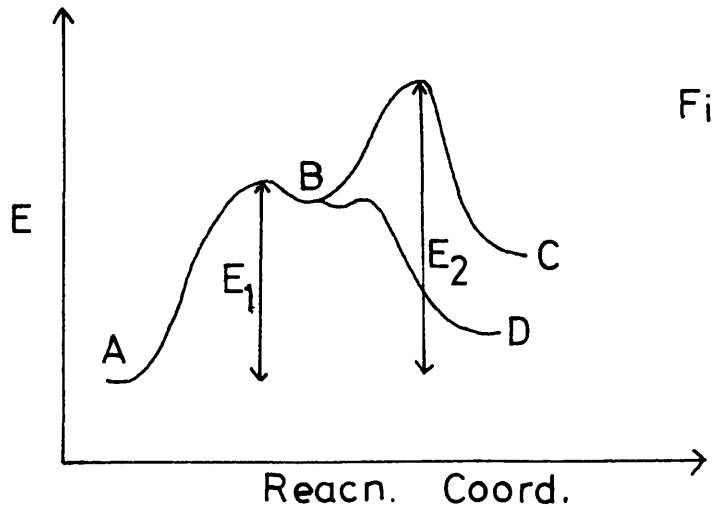
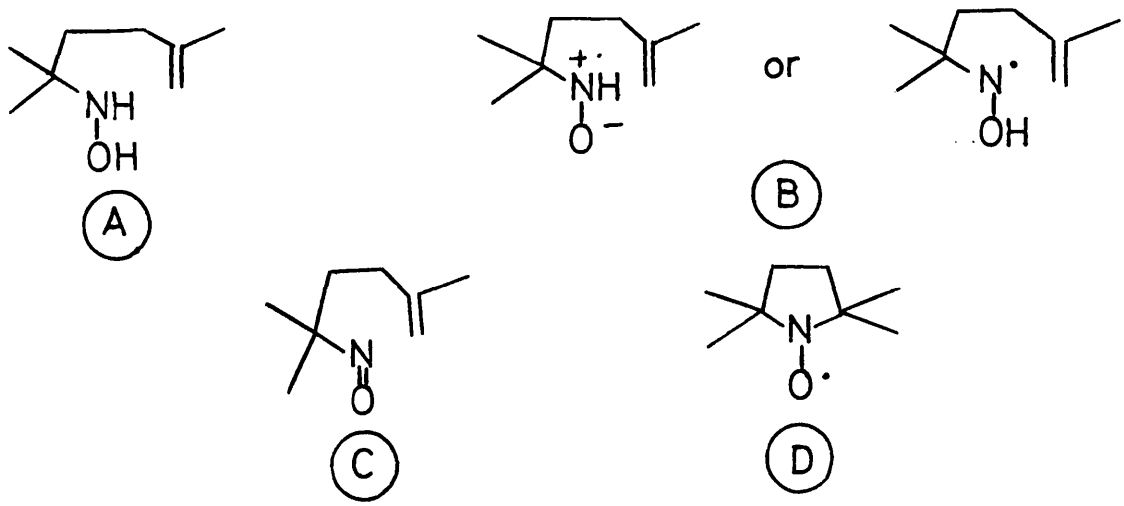


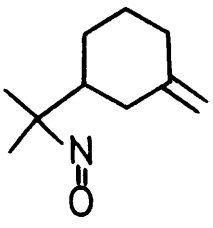
Fig. 2

$E_1 < E_2$



The only remaining experimental alternative was to examine a large number of transition metal ions of varying oxidation potential. Even this formidable task could not be assured of success as consideration of the two representative energy level profiles will show. The reaction can only be channelled through the desired intramolecular radical cyclisation pathway ABD if the oxidation potential for the step AB is less than that for the step BC as in Figure 2, or alternatively if the transformation of A to B is much faster than that of B to C. Since oxidation potentials and the kinetics of each step could be obtained by cyclic voltammetry, the undertaking of such a study is strongly recommended. Controlled electrochemical oxidation might also prove to be the most efficient method for nitroxide radical formation.

At this stage, it was felt that some study should be given once again to the initial aim of this investigation. Our attention was therefore directed towards the synthesis of a nitroso-olefin which could not possibly undergo any complicating intramolecular 'ene' reaction. Such a molecule is the nitroso-olefin (35) where the 'ene' reaction is prohibited by Bredt's rule.



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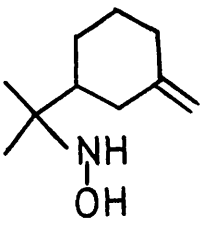

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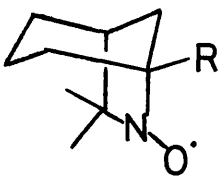
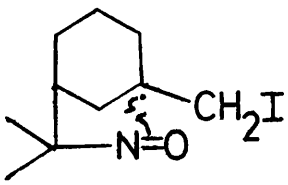


37 R = CH_3

38 R = CH_2I

The synthesis of the hydroxylamino-olefin (36) by the standard three-step sequence occasioned no difficulty. It was surprising however that the oxidation of this compound proceeded very cleanly and allowed the direct isolation of the nitroso-olefin (35) as its white crystalline dimer. No trace of the bicyclo(3,2,1)nitroxide (37), which could have arisen in principle by the aminium radical or hydroxylamino radical route, was detected in this reaction. Nevertheless, it was very gratifying to obeserve that treatment of the nitroso-olefin (35) with iodine in chloroform solution at room temperature led to the formation of the iodo-nitroxide radical (38). The compound could be isolated in the form of beautiful golden-yellow needles in 20% overall yield from the nitro-olefin without any purification at the intermediate reduction or oxidation stages.

The simplest mechanism for the iodine cyclisation reaction involves the addition of an iodine atom to the exomethylene double bond to generate the tertiary alkyl radical (39) which is then trapped by the nitroso group. Barton et al.[19] have also recently postulated radical intermediates in the reaction of pinene (40) with iodine to give the di-iodide (41).



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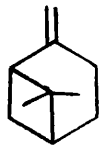

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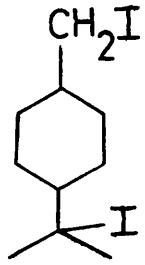


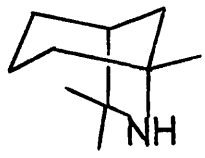
41

Having developed a reasonable route to the bicyclo(3,2,1) iodo-nitroxide (38) it was of synthetic interest to find a suitable method of removing the iodine atom to produce the parent nitroxide (37).

A promising method appeared to be tri-n-butyl tin hydride reduction[20]. However, when this method was applied to the iodo-nitroxide radical (38) a reaction mixture whose analytical t.l.c. showed five spots was obtained.

The next approach was reduction of the iodo-nitroxide (38) with sodium borohydride in hexamethylphosphoramide[21]. Although this method afforded the desired parent nitroxide (37) the reaction product was invariably contaminated with several other compounds.

The successful method involved hydrogenation of the iodo-nitroxide (38) over a Raney nickel catalyst. In addition to the expected amine (42) the corresponding hydroiodide was also formed and so the crude product from the reduction was stirred with ion exchange resin to afford the free amine.



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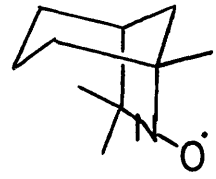
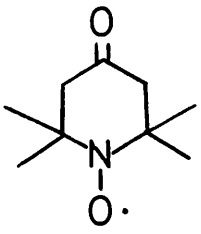


37

Oxidation of the amine (42) with m-chloroperbenzoic acid proceeded without incident and the parent nitroxide radical (37) was isolated by preparative t.l.c. as an extremely volatile red oil with a camphoraceous odour.

The nitroso-olefin (35) was also used in some unsuccessful attempts to augment the overall versatility of the cyclisation reaction by employing other radical initiators. Thus, diphenyl disulphide and dimethyl disulphide in the presence of dibenzoyl peroxide as radical initiator reacted very slowly indeed.

Analytical t.l.c. revealed trace amounts of several products, which it is thought might be derived by subsequent reactions of the nitroxide, since Murayama and Yoshioka[22] have shown that reaction of triacetonamine nitroxide (43) with PhS. radicals leads to the formation of the corresponding hydroxylamine (44), amine (45), and amide (46).



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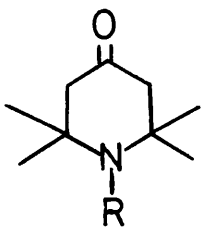
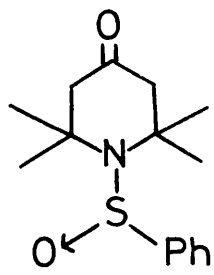


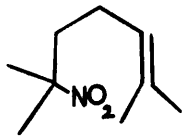
44 R=OH
45 R = H



46

The slow rate of this reaction prevented any attempts to confirm these suspicions. In consequence, it is felt that the best method of obtaining diverse functionality would be to use nucleophilic displacement reactions at the primary iodomethyl group of the nitroxide. Alternatively, a functionalised Wittig reagent could be used at the intermediate nitro-ketone stage.

In view of the success enjoyed in the formation of five-membered ring nitroxide radicals, it was decided to try and prepare a nitroxide of the piperidino class from the nitro-olefin (47).



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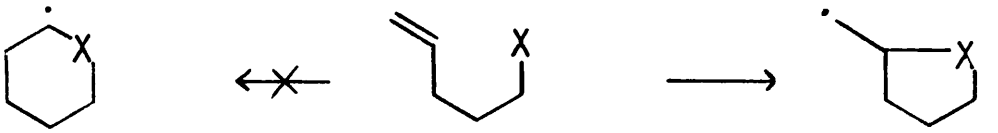
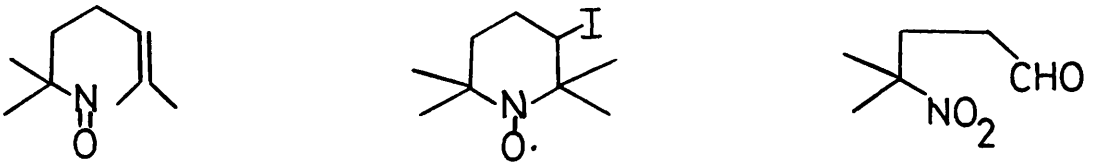


50 **48** **49**



51 **52** **53**

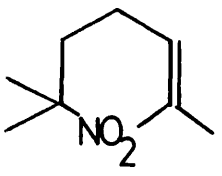
It must be admitted that the possibility of effecting cyclisation to a stable nitroxide radical by the aminium radical route was not considered to be favourable, since radical initiated intramolecular addition is known[23,24] to favour the formation of five-membered rings (48→49) over those possessing six members, even in cases where the radical intermediate of the former (49) is less stable than that of the latter (50). Nevertheless, it was felt that reaction of the nitroso-olefin (51) might lead to formation of the iodo-nitroxide radical (52).

Unfortunately, these plans were shelved at an early stage since the Wittig reaction of the nitro-aldehyde (53) with isopropylidenetriphenyl-phosphorane gave only trace amounts of the desired nitro-olefin (47). A possible explanation, based on the extremely poor mass balance for this reaction, may be that under the basic conditions of the Wittig reaction, a facile retro-Michael reaction of the nitro-aldehyde (53) to 2-nitropropane and acrolein occurs.

In conclusion, the essence of this work is that it constitutes a bifurcated approach to the synthesis of pyrrolidino nitroxide radicals; viz. oxidation of a suitably substituted hydroxylamino-olefin yields either a nitroso compound capable of cyclisation with iodine, or a nitroxide radical directly by intramolecular trapping of the radical intermediate in the one-electron oxidation of hydroxylamines.

Perhaps the most important contribution of this preliminary investigation lies in the legacy of work which has yet to be done.

In particular, the influence of ring size and substitution pattern of the double bond remain to be assessed, and the exact mechanism and limitations of the 'aminium radical' type pathway have yet to be determined. For these reasons, it is suggested that the nitro-olefins (47), (54) and (55) would make an interesting series for comparison purposes.



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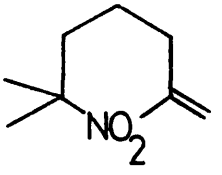

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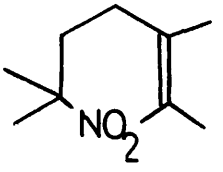


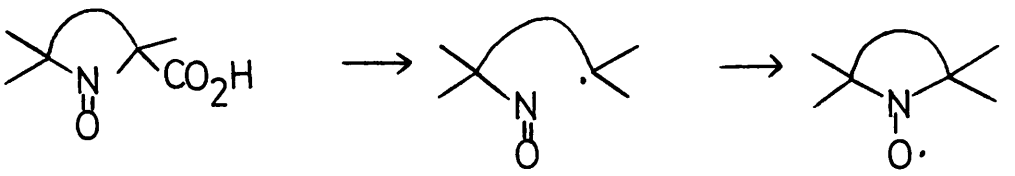
55

From the synthetic standpoint, the task of alicyclic nitroxide radical synthesis has been reduced to the formation of an acyclic nitro or nitroso olefin, and hence new routes which bypass the limitations of the initial Michael reaction must be found.

It is also wothwhile, on some occasions, and especially so in synthetic organic chemistry, to indicate some areas of research which were not particularly fruitful. For this reason, another

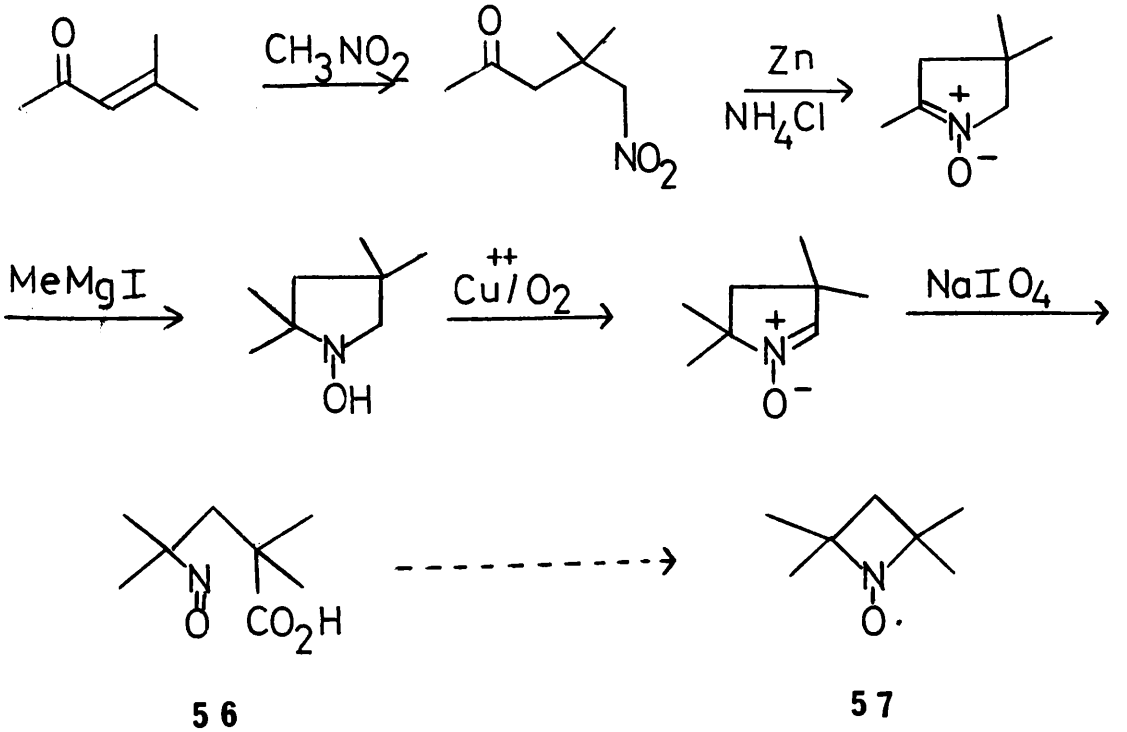
facet of intramolecular radical cyclisation, which occupied our attention for some time prior to the previously described studies, will now be presented.

In this case, the underlying principle was to generate a tertiary alkyl radical by decarboxylation of a suitably substituted nitroso-acid, inthe hope that this would undergo subsequent cyclisation to a nitroxide radical as shown in Scheme 8.



Scheme 8

The ready availibility of the nitroso-acid (56), which was prepared as shown in Scheme 9, dictated that the ultimate goal was the hitherto unknown four-membered ring nitroxide radical (57).



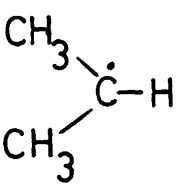
Scheme 9

The general procedure which was followed involved e.p.r. examination of the crude reaction mixtures from decarboxylation experiments which were known to pass through radical intermediates. The method was not subjected to any further scrutiny if no radical signal was detected. Some model experiments were also performed which utilised the intermolecular reaction of pivalic acid with 2-methyl-2-nitrosopropane. In this way a relatively rapid screening of several reactions was achieved.

The first reaction to be attempted was the electrochemical decarboxylation of the nitroso-acid (56), which gave rise to eleven discrete spots on analytical t.l.c. and no signal in the e.p.r. spectrometer.

A second approach entailed examination of the Cristol-Firth modification of the Hunsdiecker reaction. In this case the alkyl radical is considered to arise from breakdown of an intermediate acyl hypohalite: RCO_2Br. This reaction was also unsuccessful.

It was anticipated that photolysis of the nitroso-acid (56) in the presence of lead tetraacetate might be attended by greater success since Lagercrantz and coworkers [25] had shown, in a spin trapping experiment, that the intermediate alkyl radical (58) from decarboxylation of isobutyric acid could be effectively scavenged by 2-methyl-2-nitrosobutan-3-one to give the nitroxide radical (59).



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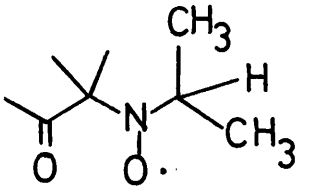


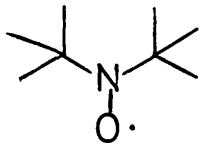
59

With the nitroso acid (56), a complex radical signal was obtained in the e.p.r. spectrometer. This proved to be quite unstable however and so the desired nitroxide (57) could not have been formed in this reaction.

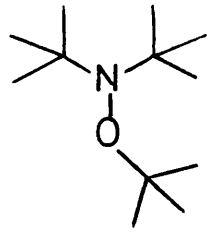
The last method to be investigated, which involved photolysis of thallium carboxylates, had been shown by Kochi et al.[26] to proceed by the radical mechanism illustrated :

$$Tl(OOCR)_3 \xrightarrow{h\nu} Tl(OOCR)_2 + R\cdot + CO_2$$

Furthermore, Torsell[27] has recently demonstrated that the alkyl radicals from the above decarboxylation can be trapped with 2-methyl-2-nitrosopropane. The use of this method led to encouraging preliminary results. Thus photolysis of thallium pivalate in the presence of 2-methyl-2-nitrosopropane gave rise to an e.p.r. spectrum consistent with the formation of di-t-butyl nitroxide (60) in the reaction; and photolysis of the thallium carboxylate of the nitroso-acid (56) likewise gave rise to a stable triplet signal in the e.p.r. spectrometer. A detailed product analysis of these two reactions revealed however that the nitroxide radicals were present in minute concentration. The sole product to be detected from the intermolecular reaction was shown by g.l.c. comparison with an authentic sample[28] to be tri-t-butyl hydroxylamine (61). No di-t-butyl nitroxide (60) was present from g.l.c. analysis.

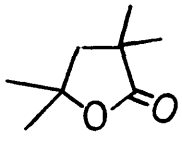


60



61

Only one product was in evidence by t.l.c. and g.l.c. examination of the intramolecular photoylsis reaction. This was isolated by preparative t.l.c. as a low-melting, volatile, white crystalline solid whose i.r. spectrum showed $\nu_{c=o}$ at 1760cm.$^{-1}$. Mass spectral and n.m.r. data allowed the compound to be formulated as 2,2,4,4-tetramethyl-γ-butyrolactone (62). These spectral properties are consistent with those previously reported[29] for this compound.



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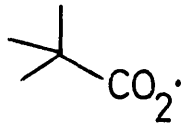

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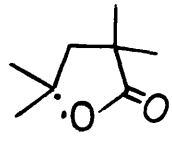
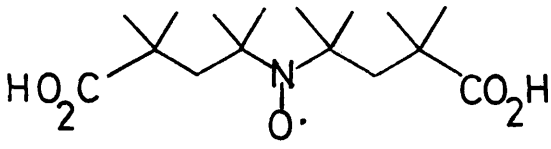


64

The formation of these two products makes an interesting comparison. In the intermolecular reaction, the intermediate carboxylate radical (63) is probably generated in a solvent cage, and sufficient time elapses to enable loss of carbon dioxide. Subsequent reaction with 2-methyl-2-nitrosopropane forms the nitroxide radical (60), which also appears to be an efficient spin trap and effectively scavenges another t-butyl radical to form the trialkylhydroxylamine (61). In the

intramolecular reaction homolysis of the $C_\gamma NO$ bond is competitive with radical decarboxylation and an intermediate biradical of the type (64) is presumably formed. This undergoes ring closure to the γ lactone (62) before loss of carbon dioxide can occur.

From the viewpoint of nitroxide radical synthesis, no rigorous claim can be made for the formation of the four-membered ring nitroxide (57), since other compounds e.g. (65) and (66) could also give rise to a stable triplet signal in the e.p.r. spectrum.



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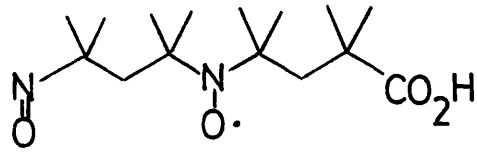

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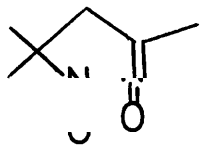

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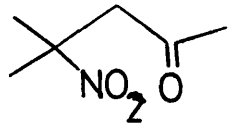

68

Some time after the completion of these unsuccessful investigations, the formation of several four-membered ring nitroxide radical derivatives was reported by Rassat et. al.[30]. Nevertheless, it would still be interesting to approach the synthetic problem by intramolecular radical cyclisation from the nitroso-olefin (67), by analogy with our previous work. This would appear to be possible since the corresponding nitro-ketone (68) is a known compound[31]. Unfortunately time did not permit an attempted synthesis by this method.

EXPERIMENTAL.

5-METHYL-5-NITROHEXAN-2-ONE (6)

This was prepared by Michael addition of 2-nitropropane to methyl vinyl ketone by the method of Lunt,[30] and was obtained in 80% yield as a clear yellow liquid, b.p. 134-138°C/20mm. lit. 124°C/12mm. $\nu_{max.}$ (liquid film) = 1720 and 1540 $cm.^{-1}$

2,5-DIMETHYL-5-NITROHEX-1-ENE (7).

(a) Wittig Reaction using phenyllithium as base.

A canary yellow solution of methylenetriphenyl-phosphorane was prepared by the addition, via a syringe, of phenyllithium in hexane solution (3ml.) to a suspension of triphenylmethylphosphonium bromide (2.142g., 6mmoles) in freshly distilled dry tetrahydrofuran (15ml.) under a nitrogen atmosphere and stirring for 3.5 hours. A solution of 5-methyl-5-nitrohexan-2-one (6) (318mg., 2 mmoles) in tetrahydrofuran (10ml.) was added with the immediate formation of a light brown precipitate, which was stirred for 1 hour. The solution was then refluxed by heating in an oil bath maintained at 80°C for 2.5 hours and allowed to come to room temperature over a 10 hour period. Tetrahydrofuran was removed on the rotary evaporator and the residue was taken up in ether, filtered, and concentrated. Preparative t.l.c. afforded the title compound (97.8mg., 28%) as a clear colourless oil.

$\nu_{max.}$ (liquid film) = 3070, 1645, 1538, 1340, 1368, 1390, and 885 $cm.^{-1}$

τ = 8.38 (6H, singlet, $(CH_3)_2$-C-NO_2), 7.99 (3H, singlet, vinylic methyl), 5.28 (2H, broad singlet, exomethylene).

Short path distillation gave an analytical sample.

	Found :	C, 61.16 ; H, 9.43 ; N, 8.64%
$C_8H_{15}NO_2$	requires	C, 61.12 ; H, 9.62 ; N, 8.91%.

(b) Using potassium-t-butoxide as base.

Ylid formation was accomplished by the dropwise addition of a solution of potassium t-butoxide (6.72g., 60 mmoles) in tetrahydrofuran (30ml.) to a well-stirred suspension of triphenylmethylphosphonium bromide (21.4g., 60 mmoles) in dry tetrahydrofuran (100ml.) under nitrogen. The reaction was stirred for 2 hours to give a clear yellow solution. 5-methyl-5-nitrohexan-2-one (4.77g., 30 mmoles.) in tetrahydrofuran (20ml.) was added and the precipitated betaine was stirred for 1 hour at room temperature, then refluxed in an oil bath maintained at 80°C for 3.5. hours, and allowed to come to room temperature overnight. Work up as previously described and column chromatography furnished 2,5-dimethyl-5-nitro-hex-1-ene (2.45g., 53%).

2, 5 - DIMETHYL - 5 - HYDROXYLAMINOHEX - 1 - ENE (8)

Freshly-activated zinc dust (1.40g.) was added portionwise, over a 5 minute period, to a well-stirred mixture of ammonium chloride (250mg.) and 2,5-dimethyl-5-nitrohex-1-ene (320mg.) in ethanol (3ml.) and water (2ml.) with cooling in an ice bath. The reaction was stirred for a further 25 minutes at 0°C, and then filtered through a celite column which was thoroughly washed with ether (75ml.). The ethereal filtrate was diluted with water (20ml.), separated, extracted and dried in the usual manner and the solvent removed to furnish the pure hydroxylamino-olefin (8) (249.5mg., 76%) as an unstable clear viscous oil, which gave a positive test with alkaline 2,3,5-triphenyltetrazolium chloride.

$\nu_{max.}$ (liquid film) = 3300, 1646 and 880cm.$^{-1}$.

τ = 8.74, 8.56, (6H, 2 singlets, $(CH_3)_2$-C-NOH), 8.3, (3H, singlet, CH_3-C=C), 7.8-8.2, (4H, multiplet), 5.32, (2H, singlet, = CH_2).

2,2,5,5 - TETRAMETHYLPYRROLIDINE - 1 - OXYL (5)

Zinc/ammonium chloride reduction of 5-methyl-5-nitrohexan-2-one and subsequent reaction with methylmagnesium iodide by the method of Lunt[30] gave 1-Hydroxy-2,2,5,5-tetramethylpyrrolidine, bp 78-80°C/20mm. Oxidation of the hydroxylamine with silver oxide as described later and column chromatography yielded the parent nitroxide (5) in 15% overall yield as an extremely volatile red oil.

$\nu_{max.}$ (liquid film) = 2980, 1463, 1378, 1365, 1326, 1260, 1124, 1088 and 668cm.$^{-1}$.

$a_n(Et_2O)$ = 15.0 Oe. , g = 2.0052.

M^++1 = 143 ; M^+ = 142.

ATTEMPTED PREPARATION OF 2,5 - DIMETHYL -5 - NITROSOHEX - 1 - ENE (3) BY OXIDATION OF 2,5 - DIMETHYL - 5 - HYDROXYLAMINOHEX - 1 - ENE (8)

(a) With Silver Oxide.

A freshly-prepared solution of the hydroxylamino-olefin (240mg.) in ether (25ml.) was shaken with an excess of freshly-prepared silver oxide (4g.) for 18 hours. Filtration through glass filter paper, careful removal of the solvent by using a vigreux column, and column chromatography, gave, as the only isolable product, a very volatile red oil. (27.8mg. 13%). The identity of this compound was established as 2,2,5,5-tetramethyl-pyrrolidine-1-oxyl by spectral comparison of the properties described above, by t.l.c. comparison in several solvent systems, and by g.l.c. injection and coinjection on a 5% QF1 column at 75°C and 45ml./min. (Rt = 5.88 min).

(b) With Sodium Periodate.

To a well-stirred solution of sodium periodate (600mg.) in water (3ml.) was added a solution of the hydroxylamino-olefin (8) (249mg.) in ethanol; the immediate precipitation of sodium iodate

occurred at this point. Stirring was continued for 1 hour and the precipitate was then filtered, washed with water (6ml.) and thoroughly extracted with chloroform to give a green solution. After drying, and removal of solvent, a yellow oil (107.1mg.) was obtained whose analytical t.l.c. showed the presence of 2,2,5,5-tetramethylpyrrolidine-1-oxyl, and possibly (11).

(c) With Silver Carbonate/Celite (Fetizon's Reagent[5])

2,5 Dimethyl-5-hydroxylaminohex-1-ene (218.8mg.) was dissolved in dry methylene chloride (25ml.) and shaken vigorously with a suspension of the Fetizon reagent (3g.) at room temperature for 10-15 minutes. Filtration through celite afforded an intensely dark-blue solution whose analytical t.l.c. showed 2 components. The more polar of these was shown by t.l.c. comparison to be the nitroxide (5), while the less polar, being a blue compound was presumed to be the elusive nitroso-olefin (3). Attempts to effect isolation of 2,5-dimethyl-5-nitroso-hex-1-ene (3) by preparative t.l.c. were thwarted because of the extreme instability of this compound, the blue solution being completely decolourised in 45 minutes at room temperature in the dark. Analytical t.l.c. at this stage indicated the appearance of a new hydroxylamine (positive tetrazolium test) which was isolated by preparative t.l.c. as a colourless oil (85mg.) and shown to be 1-Hydroxy-2,2-dimethyl-5-exomethylene-piperidine (11).

$\nu_{max.}$ (liquid film) = 3280, 3090, 1658, 1383, 1368 and 903cm.$^{-1}$.

τ = 8.80. (6H, singlet, $(CH_3)_2C$-NOH), 8.42, (2H, multiplet), 7.85, (2H, multiplet, CH_2-C=C), 6.50, (2H, broadened singlet, CH_2-NOH), 5.24, (2H, broadened singlet, $=CH_2$), 3.0-3.5, (1H, broad, exchangeable with D_2O, NOH).

2,5,5 - TRIMETHYL - 2 - IODO- METHYLPYRROLIDINE - 1 - OXYL (4).

Immediate addition of a freshly-prepared solution of 2,5-dimethyl-5-nitrosohex-1-ene (from 285mg. of the nitro-olefin) to an excess of iodine (1g.) in methylene chloride at - 40°C for 2 hours and overnight at room temperature, resulted, after extraction with sodium thiosulphate solution, washing with water, drying and removal of solvent, in the production of a coloured oil whose analytical t.l.c. showed in addition to polymer, 2 spots. Column chromatography, (Grade III Alumina, 10g., packed in pentane, and elution with 2% ether/pentane) furnished the iodonitroxide (4) (22.4mg.) and the parent nitroxide (5) (10mg.). The iodonitroxide (4) is a yellowish-orange oil which undergoes rapid decomposition at room temperature over a 24 hour period.

$\nu_{max.}$ (liquid film) = 1468, 1376 and 1332cm.$^{-1}$.

a_N ($CHCl_3$) = 13.60e, g = 2.0064, broad.

M^++1 = 269; M^+ = 268. $C_8H_{15}NOI$ requires 268.

1 - NITRO - 1 - (3-OXOBUTYL) - CYCLOHEXANE

Michael addition of nitrocyclohexane to methyl vinyl ketone using 'Triton B' catalyst as described by Lunt[30] gave the nitro-ketone in 60% yield as a dark yellow oil, b.p. 170°C/1mm. (lit. 176°C/15mm.) $\nu_{max.}$ (liquid film) = 1720 and 1540cm.$^{-1}$.

1 - NITRO - 1 - (3-METHYLBUT-3-ENYL) CYCLOHEXANE (31)

A solution of methylenetriphenylphosphorane was prepared under nitrogen as previously described, from triphenylmethylphosphonium bromide (1.4g.) and phenyllithium in hexane solution (30ml., 2.1M) and stirred at room temperature for 3 hours. The nitro-ketone, (4.7g.) in freshly-distilled tetrahydrofuran (30ml.), was added and the precipitated betaine was stirred at room temperature for 0.5

hours. The reaction mixture was then refluxed for 4.5 hours in an oil bath maintained at 80°C, and allowed to come to room temperature overnight. Work up involving filtration. solvent removal, and column chromatography, furnished the desired nitro-olefin (31) as a clear mobile liquid (2.75g. 58%).

$\nu_{max.}$ (liquid film) = 3120, 3000, 2910, 1655, 1540, 1380, 1352, 898, and 850cm.$^{-1}$.

τ = 8.08, (3H, singlet, vinylic methyl), 5.33, (2H, broadered singlet, exomethylene).

An analytical sample was prepared by short path distillation.

Found : C, 66.91; H, 9.48; N, 6.95%.

$C_{11}H_{19}NO_2$ Requires : C, 66.97; H, 9.71; N, 7.10%.

1 - AZA - 2,2 - DIMETHYLSPIRO (5,4) DECANE - 1 - OXYL (32).

Reduction of the nitro-olefin (31) (350mg.) with zinc (1.4g.) and ammonium chloride (252mg.) in aqueous ethanol (2:3, 5ml.) at 0-5°C for 30 minutes and work up as previously described gave the hydroxylamino-olefin as a viscous oil which was not characterised. Oxidation of the hydroxylamine in ether (30ml.) with an excess of silver oxide (4g.) was accomplished by shaking vigorously at room temperature for 30 minutes. Filtration of the reaction mixture through a glass filter paper gave a clear blue solution whose analytical t.l.c. showed 3 spots. The least polar compound was blue while the middle component appeared as a yellow spot. The most polar spot gave a positive test with an alkaline 2,3,5-triphenyltetrazolium chloride spray. On standing for 1 hour at room temperature the blue colour was completely discharged from the solution and analytical t.l.c. showed only .2 components. The spiro-nitroxide (32) was isolated by preparative t.l.c. as an orange-yellow oil (92mg., 28%) which slowly crystallised on

standing m.p. 29-31.5°C.

$\nu_{max.}$ (liquid film) = 3040, 3000, 2925, 1465, 1382, 1365 and 1335cm^{-1}.

a_N (Et_2O) = 13.8 Oe., g = 2.0070.

M^++1, 183; M^+, 182.

$\lambda_{max.}$ (hexane) = 212nm. (ε1,222), 235nm. (ε 1,534) and 418nm. (ε 3.7).

High resolution mass measurement M^+ = 182.1538

Calculated for $C_{11}H_{20}NO$ = 182.1544.

4 - METHYL - 4 - NITROPENTANAL (53).

Reaction of 2-nitropropane with acrolein by the method of Schechter[3] gave the desired nitro-aldehyde in 48% yield. b.p. 60°C/1m.m. lit. 89°C/3mm. $\nu_{max.}$ (liquid film) 2740, 1724, 1545, 1402, 1380 and 1362cm.$^{-1}$.

2,6 - DIMETHYL - 6 - NITROHEPT - 2 - ENE (47).

Potassium-t-butoxide (672mg.) in dry tetrahydrofuran (10ml.) was added dropwise to a well-stirred suspension of isopropyltriphenylphosphonium iodide (2.592g.) in tetrahydrofuran (10ml.) under a nitrogen atmosphere. The mixture was stirred for 2 hours at room temperature to give a blood-red solution of isopropylidenetriphenylphosphorane. 4-Nitro-4-methyl-pentanal (290mg.) in tetrahydrofuran (10ml.) was added and the reaction was stirred for 2 hours at room temperature, refluxed in an oil bath maintained at 70°C for 1.5 hours, and allowed to reach room temperature over a 10 hour period. Work up involving dilution with ether, washing with water, drying, solvent removal, and preparative t.l.c. gave 2,6-dimethyl-6-nitrohept-2-ene as a colourless oil (16mg.)

$\nu_{max.}$ (liquid film) = 1540, 1400, 1378, 1352, 862 and 852cm.$^{-1}$.

τ = 8.39, (12H, broadened singlet, $(\underline{CH_3})_2$-C-NO_2 and $(\underline{CH_3})_2$-C=C), 8.08, (4H, multiplet), 4.9, (1H, broad, $\underline{H}$-C=C).

All attempts to scale up this reaction or to improve the yield proved singularly unsuccessful.

3 - (1-METHYL-1-NITROETHYL) - CYCLOHEXANONE.

The Michael addition of 2-nitropropane to cyclohex-2-ene-1-one proceeded smoothly to give the nitro-ketone as a clear oil, b.p. 180°C/12mm., which solidified in the receiver.

$\nu_{max.}$ (Nujol Mull) = 1712 and 1535cm.$^{-1}$.

1 - (1-METHYL-1-NITROETHYL) - 3 - EXOMETHYLENE CYCLOHEXANE.

The nitro-ketone (5g.) in tetrahydrofuran (20ml.) was added with magnetic stirring under nitrogen to a solution of methylenetriphenylphosphorane, prepared in the usual manner from the phosphonium bromide (21.4g), and potassium-t-butoxide (6.72g) in tetrahydrofuran (150ml.). After stirring for 1.5 hours at room temperature the reaction was heated at 80°C for 4.5 hours and allowed to reach room temperature overnight. Work up as described earlier and column chromatography gave a colourless mobile oil (2.76g., 55%) which was shown to be

1-(1-methyl-1-nitroethyl)-3-exomethylenecyclohexane.

$\nu_{max.}$ (liquid film) = 3125, 3080, 1668, 1555, 1415, 1391, 1364, 912 and 867cm.$^{-1}$.

τ = 8.48, (6H, singlet, $(\underline{CH_3})_2$, 7.7-9.2, (8H, multiplet), 5.33, (2H, broadened singlet, = $\underline{CH_2}$).

An analytical sample was prepared by short path distillation.

Found : C, 65.62; H, 9.15; N, 7.46%.

$C_{10}H_{17}NO_2$ Requires : C, 65.54; H, 9.35; N, 7.64%.

1-(1-METHYL-1-NITROSOETHYL)-3-EXOMETHYLENECYCLOHEXANE (35).

Zinc dust (1.4g.) was added to a stirred mixture of ammonium chloride (250mg.) and 1-(1-methyl-1-nitrosoethyl)-3-exomethylenecylohexane (362mg.) in aqueous ethanol (1:2, 6ml.) with cooling in an ice bath. Stirring was continued for 25 minutes and the solution was then filtered through a celite column, diluted with water, and thoroughly extracted with ether. The combined ethereal extracts were dried, concentrated to ca. 30ml., and then shaken vigorously at room temperature for 20 minutes with freshly prepared silver oxide (2g.). The reaction mixture was filtered through a glass filter paper and the blue ethereal filtrate was dried and concentrated. The nitroso-olefin (35) was purified by preparative t.l.c. and obtained as a blue oil (177.4mg., 53%) which slowly crystallised to a white solid m.p. 77-79°C. on standing.

$\nu_{max.}$ (Nujol Mull) = 3080, 1654, 1269, 1259, 1229, and 892cm.$^{-1}$.

$\nu_{max.}$ ($CHCl_3$) = 1662 and 1640cm.$^{-1}$.

τ = 9.03, (6H, singlet, $(CH_3)_2$-C-NO), 5.33, (2H, broadened singlet, $=CH_2$).

$\lambda_{max.}$ ($CHCl_3$) = 687nm. (ϵ = 7.8).

Found : C, 70.36; H, 9.75; N, 8.24%.

$C_{10}H_{17}NO$ Requires : C, 71.81; H, 10.25; N, 8.38%.

6,6 - DIMETHYL - 1 - IODOMETHYL - 7 - AZABICYCLO (3,2,1) OCTAN - 7 - OXYL (38).

To a solution of 1-(1-methyl-1-nitrosoethyl)-3-exomethylenecyclohexane (177.4mg.) in Analar chloroform (30ml.) was added dropwise a solution of iodine (127mg.) in chloroform (30ml.) and allowed to stand in the dark for 18 hours. Removal of solvent

gave an oil which was chromatographed on alumina (Grade III, 6g., packed in pentane) eluting with 5% ether-pentane and collecting 10ml. fractions. Fractions 1-3 contained unreacted starting material (40mg.) while fractions 9-20 were combined and the solvent removed to give golden yellow microcrystalline needles (105mg., 43%) m.p. 96°C which was shown to be the desired iodo-nitroxide (38).

$\nu_{max.}$ (Nujol Mull) = 1398, 1385, 1328, 1298, 1247, 966, 855, 837, 798 and 693cm.$^{-1}$.

a_N ($CHCl_3$) = 14.4 Oe, g = 2.0072.

M^++1, = 295; M^+, = 294; Significant Peaks at $^m/_e$; 280, 264, 252, 236, 221, 168, and 95.

$\lambda_{max.}$ (hexane) = 224nm. (ϵ = 1,918) and 239nm. (ϵ = 2,065).

Found : C, 41.08; H, 5.86; N, 4.86%.

$C_{10}H_{17}NOI$ Requires : C, 40.83; H, 5.83; N, 4.76%.

In larger scale runs this compound can be prepared in ca. 20% overall yield from the nitro-olefin without purification at the intermediate reduction and oxidation stages.

ATTEMPTED TRI-N-BUTYL TIN HYDRIDE REDUCTION OF 6,6 - DIMETHYL - 1 - IODOMETHYL - 7 - AZABICYCLO (3,2,1) OCTAN - 7 - OXYL (38).

To a solution of the iodonitroxide (38) (138mg.) in diethyl ether (5ml.) under nitrogen was added a solution of tri-n-butyl tin hydride (350mg.) in diethyl ether (5ml.) and the mixture was magnetically-stirred for 2 days, when the initially yellow solution had become colourless, and gave a positive test with alkaline 2,3,5-triphenyltetrazolium chloride. Excess silver oxide was added and the mixture was shaken at room temperature for 20 minutes, filtered, and examined by t.l.c. which showed, in addition to hexa-n-butyl-di-tin, at least 5 spots.

ATTEMPTED MICRO-SCALE REDUCTION OF 6,6 - DIMETHYL - 1 - IODOMETHYL - 7 - AZABICYCLO (3,2,1) OCTAN - 7 - OXYL (38).

Sodium borohydride (10mg.) was added to a solution of the iodo-nitroxide (38) (5.4mg.) in hexamethylphosphoramide (0.4ml.) and allowed to stand at room temperature for 20 hours. Brine was added and the solution was thoroughly extracted with ether, dried, and a small portion was tested with alkaline 2,3,5 - triphenyl-tetrazolium chloride. Since a positive test was obtained the bulk of the ethereal solution was shaken with silver oxide, filtered, and the solvent removed. Analytical t.l.c. showed 6 spots one of which was readily identified as the starting material. The major product was later shown by t.l.c. comparison in several solvent systems to be the parent nitroxide (37).

1,6,6-TRIMETHYL - 7 AZABICYCLO (3,2,1) OCTAN - 7 - OXYL (37).

6,6-Dimethyl-1-iodomethyl-7-azabicyclo (3,2,1)-octan-7-oxyl (147mg.) was dissolved in ethanol (15ml.) and about one teaspoon of Raney-nickel (W-2, approximately 2.5g.) was added. The flask was attached to a hydrogenator and hydrogenation allowed to take place in the usual fashion. After 3.5 hours, the catalyst was filtered off and washed thoroughly with warm ethanol. In an earlier experiment solvent removal on the rotary evaporator led to the loss of the amine (42) and the isolation of a white, ether-insoluble solid which was shown to be the amine hydroiodide.

m.p. $>230^{\circ}C$ (decomp.)

$\nu_{max.}$ (Nujol Mull) = $1604cm.^{-1}$.

τ = 8.36, (9H, singlet), 7.4-8.8, (9H, multiplet), 1.5-2, (2H, broad).

The ethanolic filtrate was, in consequence, stirred with basic

Amberlite IRA-400 (OH^-) ion exchange resin for 2 hours. Filtration of the resin and careful removal of the solvent in vacuo through a Vigreux column yielded the crude amine (46.2mg.) as a yellow oil.

$\nu_{max.}$ (liquid film) = 3450-3350, 1382 and 1368cm.$^{-1}$.

τ = 8.84, (6H, singlet), 8.76, (3H, singlet).

The amine, without further purification was dissolved in methylene chloride, (6ml.) and a solution of m-chloroperbenzoic acid (120mg.) in methylene chloride (2ml.) was added. The mixture was stirred for 2 hours, diluted with methylene chloride, and washed thoroughly with saturated sodium bicarbonate solution. After drying and removal of solvent, a red oil (31mg.) was obtained. This was purified by preparative t.l.c. to yield 1,6,6-trimethyl-7-azabicyclo (3,2,1) octan-7-oxyl as an extremely volatile red oil (20mg.) with a camphoraceous odour.

$\nu_{max.}$ (CCl_4) = 1462, 1376, 1370 and 1360cm.$^{-1}$.

a_N ($CHCl_3$) = 15.60e., g = 2.0071.

M^++1 = 169; M^+ = 168; significant ions at $^m/_e$ at 126, 110 and 94.

$\lambda_{max.}$ (hexane) = 214nm. (ε= 4,139) and 232nm. (ε= 5,083).

High resulution mass measurement M^+=168.1375.

Calculated for $C_{10}H_{18}NO$ 168.1386.

ATTEMPTED ADDITIONS OF DIPHENYL DISULPHIDE AND DIMETHYL DISULPHIDE TO 1-(1-METHYL-1-NITROSOETHYL)-3- EXOMETHYLENECYCLOHEXANE (35)

To a solution of the nitroso-olefin (35) (140mg.) in carbon tetrachloride (5ml.) containing dibenzoylperoxide (10mg.) was added a solution of diphenyl disulphide (91mg.) in carbon tetrachloride (5ml.) The solution was allowed to stand in the dark at room temperature for 5 days. No colour change was

detected in the blue solution during this time. Analytical t.l.c. revealed, in addition to unreacted starting materials concomitant formation of four compounds and served to indicate that the rate of cyclisation was not competitive with the anticipated reaction of the nitroxide with sulphur radicals.

The above experiment was repeated using an equivalent weight of dimethyl disulphide and led to similar observations.

OXIDATION OF - 1 - HYDROXY - 2,2 - DIMETHYL - 5 - EXOMETHYLENEPIPERIDINE (11).

Repeated attempts to prepare a pure sample of 1-hydroxy-2,2-dimethyl-5-exomethylenepiperidine were unsuccessful since trace amounts of 2,2,5,5-tetramethylpyrollidine-1-oxyl were always detected by e.p.r. Useful information could, nevertheless, be obtained by dissolving a sample of the hydroxylamine (11) in methylene chloride, adding excess m-chloroperbenzoic acid, and monitoring the progress of the reaction in the cavity of the e.p.r. spectrometer. The growth and decay of an unstable radical species was followed with time. No enhancement in the intensity of the triplet from 2,2,5,5-tetramethylpyrollidine-1-oxyl was detected, indicating that oxidative rearrangement of the hydroxylamine (11) to this nitroxide did not occur.

OXIDATION OF 2,5 - DIMETHYL - 5 - HYDROXYLAMINOHEX - 1 - ENE (8) WITH DIETHYL AZODICARBOXYLATE.

A freshly prepared solution of 2,5-dimethyl-5-hydroxylaminohex-1-ene (243mg.) in diethyl ether (10ml.) was added slowly to a flask maintained at 0°C, with simultaneous dropwise addition of an ethereal solution of diethyl azodicarboxylate (295mg.). The solution became green and stirring was maintained at 0°C for 1.5 hours. Aliquot monitoring of the reaction by

analytical t.l.c. revealed that only trace amounts of 2,2,5,5-tetramethylpyrrolidine-1-oxyl were formed in this reaction. Removal of the precipitated diethyl hydrazodicarboxylate by filtration and preparative t.l.c. isolated 1-hydroxy-2,2-dimethyl-5-exomethylenepiperidine (61.4mg.), whose spectral properties were identical to those described earlier for the compound.

DISPROPORTIONATION OF 1 - HYDROXYLAMINO - 1 - (3-METHYL-BUT-3-ENEYL) - CYCLOHEXANE WITH 2 - METHYL - 2 - NITROSOPROPANE.

A solution of the hydroxylamino-olefin freshly-prepared from 1-nitro-1-(3-methylbut-3-enyl)-cyclohexane (350mg.), in ethanol (10ml.), was added to solid 2-methyl-2-nitrosopropane dimer (153mg.) and the mixture was warmed on a steam bath for 3 minutes to obtain a blue solution of the monomer. The flask was then sealed under nitrogen and allowed to stand in the dark for 20 hours, after which time the green solution was heated under nitrogen in an oil bath maintained at 65°C for 2 hours to ensure complete reaction. Removal of solvent *in vacuo*, followed by preparative t.l.c. gave 1-aza-2,2-dimethylspiro (5,4) decane-1-oxyl (32) (82.5mg.), m.p. 29-31°C, whose spectral and chromatographic properties were identical to an authentic sample.

OXIDATION OF - 1 - HYDROXYLAMINO - 1 - (3-METHYL-BUT-3-ENYL) - CYCLOHEXANE IN ISOPROPANOL.

Zinc/ammonium chloride reduction of 1-nitro-1-(3-methylbut-3-enyl)-cyclohexane (350mg.) in the usual manner furnished a sample of the hydroxylamino-olefin which was immediately dissolved in pure isopropanol (25ml.) and shaken with an excess (9g.) of silver oxide at room temperature for 30 minutes. Filtration through a

glass filter paper followed by solvent removal and preparative t.l.c. gave the spiro-nitroxide (32) (29.7mg.).

The experiment was repeated using reagent quantities as above, but oxidation was accomplished using the Fetizon reagent (4g.) for 40 minutes at room temperature. The mixture was filtered through celite, washed with ether (200ml.) and the combined ethereal extracts were thoroughly washed with water (3x150ml.), dried, and the solvent removed. Preparative t.l.c. afforded the spiro-nitroxide (32) (51.6mg.).

LITHIUM ALUMINIUM HYDRIDE REDUCTION OS 2,5 - DIMETHYL - 5 - NITROHEX - 1 - ENE (7).

A stirred suspension of lithium aluminium hydride (19mg.) in anhydrous ether (15ml.) was added over a 15 minute period to a solution of 2,5-dimethyl-5-nitrohex-1-ene (157mg.) in ether (7ml.) with cooling in an ice bath and magnetically stirred for 16 hours.

The progress of the reaction was monitored throughout by analytical t.l.c. which indicated that no detectable quantity of 2,2,5,5-tetramethyl pyrrolidine-1-oxyl (5) was formed in this reaction.

4,4 - DIMETHYL - 5 - NITROPENTAN - 2 - ONE.

This was prepared as described by Klotzel[31] from nitromethane (10moles) and mesityl oxide (1mole) b.p. 110-114°/14mm. (lit. 112-113.5°/14mm.) $\nu_{max.}$ (liquid film) = 1706 and 1552cm.$^{-1}$.

3,3,5,5 - TETRAMETHYL - Δ^1 - PYRROLINE - 1 - OXIDE.

Reductive cyclisation of 4,4-dimethyl-5-nitro-pentan-2-one with zinc and ammonium chloride gave 2,4,4-trimethyl-Δ^1-pyrroline -1-oxide. Treatment of this nitrone with methylmagnesium iodide

and subsequent copper-catalysed aerial oxidation of the hydroxylamine gave the title compound. b.p. 73°C/1m.m. lit.[32] 73°C/1mm. $\nu_{max.}$ (liquid film) = 1583, 1460, 1368, 1254, 1176 and 772cm.$^{-1}$.

2,2,4 - TRIMETHYL - 4 - NITROSOPENTANOIC ACID (56).

Oxidative cleavage of 3,3,5,5-tetramethyl-Δ^{1}-pyrroline-1-oxide with sodium metaperiodate by the method of Qureshi and Sklarz[33] gave the nitroso-acid (56) m.p. 107°C lit. 104-106°C as a white crystalline dimer.

$\nu_{max.}$ (Nujol Mull) = 1715cm.$^{-1}$ (melt in chloroform) = 1708 and 1565cm^{-1}

DI - t - BUTYLNITROXIDE (60) AND TRI - t - BUTYLHYDROXYLAMINE (61).

These two compounds were prepared as a mixture by the method of Hoffmann, et. al.[28], involving reduction of t-nitrobutane with sodium metal. Samples of the pure compounds were isolated by preparative t.l.c.

Di-t-butylnitroxide : $\nu_{max.}$ (liquid film) = 1483, 1392, 1368 and 1345cm.$^{-1}$. a_n = 15.5 Oe., g = 2.0063.

Tri-t-butylhydroxylamine : τ = 8.75 (18H, singlet) and 8.83 (9H singlet).

MODEL STUDIES:- THE DECARBOXYLATION OF PIVALIC ACID IN THE PRESENCE OF 2-METHYL-2-NITROSOPROPANE.

The following reactions were performed with the intention of devising an efficient method for the trapping of the intermediate alkyl radical with 2-methyl-2-nitrosopropane. Accordingly, crude reaction mixtures were examined in the cavity of the e.p.r. spectrometer and the method was not subjected to further scrutiny if no radical signal was detected.

(a) HUNSDIECKER REACTION: - CRISTOL - FIRTH MODIFICATION.[34]

To a mixture of 2-methyl-2-nitrosopropane, (670mg.) and pivalic acid (1.02g.) in carbon tetrachloride (50ml.) was added red mercuric oxide (4.40g.). The stirred reaction was heated in an oil bath maintained at 80°C and bromine (806mg.) in carbon tetrachloride (20ml.) was added over a 45 minute period. The temperature was then raised to 100°C and the solution was refluxed for 5 hours. The cooled solution was filtered, washed with 5% sodium hydroxide solution, water, and then dried to give a clear solution which gave no signal in the e.p.r. spectrometer. The reaction was repeated using iodine as the halogen with similar results.

(b) PHOTOLYSIS OF THALLIUM (111) - PIVALATE IN THE PRESENCE OF 2 - METHYL - 2 - NITROSOPROPANE.

2-methyl-2-nitrosopropane (23.6mg.), pivalic acid (26mg.) and thallium (111) acetate (20mg.) were dissolved in benzene (20ml.) and the mixture was photolysed with a medium-pressure mercury arc lamp for 16 hours. Removal of solvent, dilution with ether, and filtration to remove the precipitated thallium salts, gave a greenish oil (30mg.) which showed the characteristic triplet of nitroxide radicals in the e.p.r. spectrometer; a_n=15.4 Oe., g=2.0062. Detailed g.l.c. examination of the product was then carried out using a 10% 20M P.E.G. column at 75°C and 36ml/minute flow rate. The major product (Rt=4.64min.) was shown by injection and coinjection with an authentic sample to be tri-t-butylhydroxylamine. No di-t-butyl-nitroxide (Rt=6.12min) was detected in this way.

The experiment was repeated using thallium (111)-pivalate (prepared by metathesis of pivalic acid with thallium (111) acetate) and similar results were obtained.

DECARBOXYLATION OF 2,4,4 - TRIMETHYL - 4 - NITROSO PENTANOIC ACID (56).

(a) Electrolytic Method.

A solution of the monomeric nitroso-acid (398mg.) in 10% aqueous pyridine was prepared and triethylamine (1.25ml.) was added. The reaction was electrolysed with platinum cage electrodes at a potential of 50 volts (0.8A) for 2 hours by which time no more gas evolution was observed. The current was stopped and the dark brown solution was diluted with water (300ml.) and extracted thoroughly with ether (3x300ml.). The ethereal extract was washed with water (3x300ml.), dilute hydrochloric acid (2N 3x 300ml.), sodium bicarbonate (300ml.) and water (2x300ml.). The extract was then dried and the solution concentrated to give a dark red oil (284mg.) which showed 11 distinct spots on analytical t.l.c. and gave no signal in the e.p.r. spectrometer.

(b) Photolysis in the presence of Lead Tetraacetate.

2,2,4-trimethyl-4-nitrosopentanoic acid (611mg.) and lead tetraacetate (1g.) were dissolved in methylene chloride (15ml.) and the solution was photolysed with a medium-pressure mercury arc lamp at room temperature for 30 minutes. No stable radical signal was detected in the e.p.r. spectrometer.

(c) Hunsdiecker Reaction:- Cristol - Firth Modification[34].

A solution of the monomeric nitroso-acid (56) (86.8mg.) in carbon tetrachloride (20ml.) was prepared by adding the solvent to a melt of the acid. Red mercuric oxide (280.6mg.) was added and the stirred solution was heated to reflux temperature in an oil bath. Bromine (40mg.) in carbon tetrachloride was added slowly over a 10 minute interval and the mixture was refluxed for 1 hour.

The cooled solution was filtered, and the solvent removed to give a solid residue which was taken up in ether and washed successively with 5% sodium hydroxide solution and water. Drying and removal of solvent gave a blue oil (44.6mg.) which gave no signal in the e.p.r. spectrometer.

(d) PHOTOLYSIS OF 2,2,4 ; TRIMETHYL - 4 - NITROSOPENTANOIC ACID IN THE PRESENCE OF THALLIUM (111) ACETATE.

Thallium (111) acetate (76mg.) was added to amelt of the nitroso-acid (309mg.) in an oil bath at 150°C. After 15 minutes the flask was removed and benzene (20ml.) was added. The solution was photolysed for 16 hours with a medium-pressure mercury arc lamp and the crude reaction mixture was examined in the e.p.r. spectrometer when the triplet spectrum of a stable nitroxide radical was observed: a_n=15.1 Oe., g=2.0042. Benzene was removed *in vacuo* using a vigreux column and ether was added to precipitate thallium salts. Only one compound however could be detected by g.l.c. and t.l.c. analyses. This compound was isolated by preparative t.l.c. as an extremely volatile white crystalline solid. (66mg.) m.p. 24-32°C.

$\nu_{max.}$ (melt) = 1760 and 1106cm.$^{-1}$.

τ = 8.68, (6H, singlet $(CH_3)_2$-CO-O), 8.57, (6H, singlet, $(CH_3)_2$-O-CO(, 7.96, (2H, singlet).

M^+-15=127; also m/e 98. M^+ not observed.

The spectroscopic data are in accord with those reported by Turro[29] for 2,2,4,4-tetramethyl-γ- butyrolactone (62).

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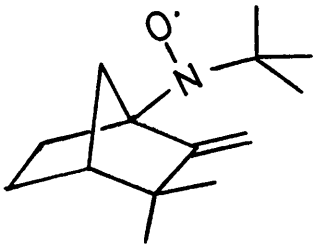
Section Two

THE SYNTHESES AND CHIROPTICAL PROPERTIES OF SOME 3 - AZABICYCLO (3,3,1) NONAN - 7 - ONE NITROXIDE RADICALS.

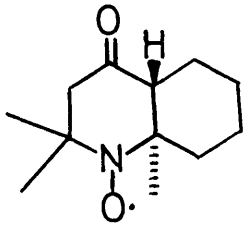
In view of the marked similarity between the nitroxide function and the carbonyl group vis. a vis. electronic configuration, geometry, and chemical reactivity, it is somewhat surprising to find that the chiroptical properties of nitroxide radicals have received little attention. At the present time, very few optically active nitroxide radicals have been prepared, and of those, only the camphenyl nitroxide (1) has been examined by circular dichroism[1].



1

The first steps to rectify this situation have already been taken in our laboratories as part of a long-term investigation whose ulitmate aim is to ascertain if the Cotton effect associated with the nitroxide chromophore can be interpreted in terms of an octant rule similar to that of the carbonyl chromophore[2]. If such a rule can be developed for nitroxide radicals, then this technique will prove to be a fruitful source of information on the conformational preferences of these species. Additional interest also centres on the ability of c.d. spectra to unmask hidden transitions in the ultraviolet spectra of a molecule[3].

The results[4] of a preliminary investigation of some decahydroquinoline nitroxide radicals were most encouraging in this respect.



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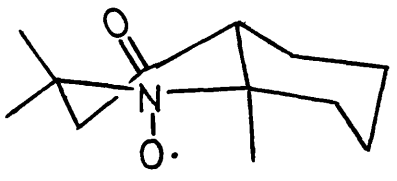
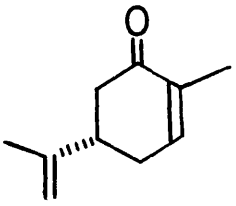


3

For example, by using the carbonyl group in the rigid trans-fused nitroxide (2) as an 'internal chiroptical handle', it was possible to deduce that the chair-twist form (3) was favoured. On the premise that the nitroxide group could be treated empirically in terms of the carbonyl octant rule it was predicted that the $n \rightarrow \pi^*$ transition of the nitroxide chromophore would give rise to a sizeable negative c.d. maximum for this conformation. This was indeed observed.

It was therefore of interest to extend the scope of these studies by examining other optically-active nitroxide radicals of known absolute configuration and conformation. From the synthetic standpoint, the preparation of the nitroxide (2) entailed the arduous and time-consuming tasks of resolution, and determinations of optical purity and absolute configuration. In the present study however, a much more direct approach was adopted by using an optically-active substrate in the form of the sweet-smelling monoterpene, (+) - carvone (4).



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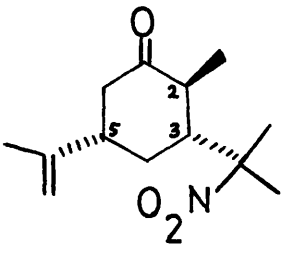

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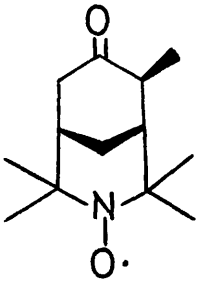


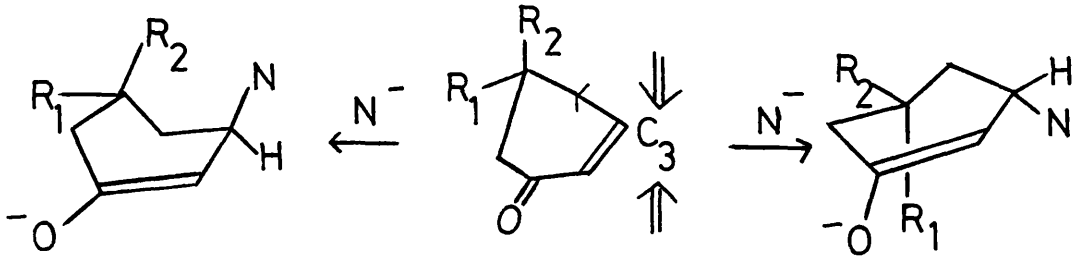
6

The synthetic strategy was to employ the Michael reaction of 2-nitropropane with (+) - carvone to generate the nitro-olefin (5), which was considered to be an apposite progenitor of the bicyclic nitroxide radical (6) through one of the two possible methods developed earlier.

This reaction sequence deserves some comment from two important standpoints. In the first place, the successful elaboration of the nitro-olefin (5) to the nitroxide (6) would provide a valuable extension of the previously developed synthetic methods to a nitroxide radical of the piperidino class. Secondly, the stereochemistry of the desired Michael adduct (5) is worthy of detailed examination. The configuration of the methyl group α to the carbonyl at C_2 occasioned little cause for concern since it was assumed that, under equilibrating conditions, the thermodynamically more stable equatorial isomer would be formed. Furthermore, under non- epimerising cyclisation conditions, this would be translated to the configuration shown in the nitroxide radical (6) in which the methyl group is axial in a cyclohexanone chair. The crucial factor, on which the success of the whole project hinged, was that the two side chains at C_3 and C_5 must be <u>cis</u> for any cyclisation to take place. Although the stereochemistry of the Michael reaction has not been extensively

investigated the available literature did not offer any hopeful augury in this respect.

Thus, Allinger and Riew[5] have shown that the related 1,4 Grignard addition to an α,β unsaturated ketone occurs in a product like transition state in which the incoming nucleophile approaches C_3 orthogonal to the plane of the double bond as shown in Figure 1.



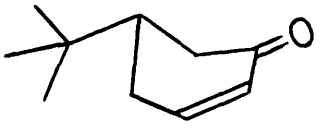
half-chair half-boat

trans ..... R_1= isopropenyl, R_2= H .....cis

cis ..... R_1= H, R_2 = isopropenyl .....trans

Figure 1

In consequence, there are four transition states leading to two different products cis and trans, and the stereochemical outcome of the reaction is dictated by the relative energies of these transition states. From the Figure it can be seen that the trans product is generally favoured since it results from an approach of the nucleophile to C_3 avoiding steric interference from the existing isopropenyl substituent on C_5. The desired cis product can only be obtained from a half-boat or a half-chair transition state in which the approach of the nucleophile is blocked by a pseudo-axial isopropenyl group.



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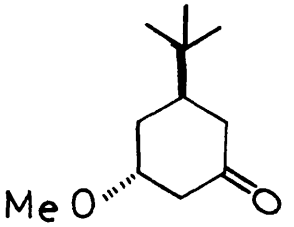
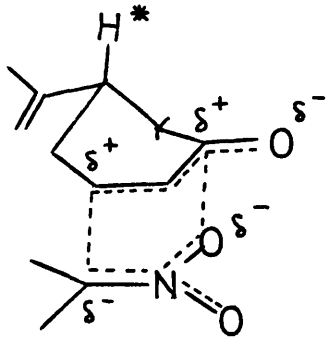


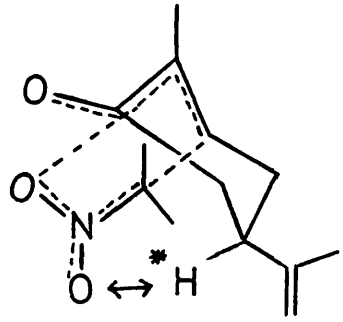
8

An even less hopeful observation has been recorded by Chamberlain and Whitham[6], who have examined the base catalysed addition of methanol to 5-t-butycyclohex-2-ene-1-one (7) and shown that the trans-3-methoxy-5-t-butylcyclohexanone (8) with an axial methoxy group is not only the kinetically controlled product, but also predominates at equilibrium.

In the case at hand however, it is important to realise that an ambident anion is involved. This led to the speculation that a stabilising electronic interaction between the 2-nitropropane anion and the electropositive carbon atom of the enone system might give rise to a pseudo bicyclo (3,3,1) transition state. Examination of the two possible transition states (9a) and (9b) which lead to the cis and trans products respectively reveals that the latter has an unfavourable interaction between the axial hydrogen atom on C_5 (H^*) and the oxygen atom of the incoming nucleophile. Similar electrostatic interactions have been employed by Marshall et al.[7] in an analysis of a Michael reaction involving the ambident anion from 2-carbethoxycyclohexanone.



9a



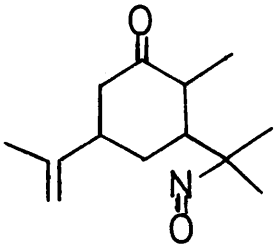
9b

In the event however, this reaction did engender some experimental difficulty. Initially, benzyltrimethylammonium hydroxide was chosen as the basic catalyst, since this reagent had been employed successfully in the preparation of all the previously-required nitroketones. In this particular case however, even after prolonged reaction times, no observable change took place. Nevertheless, by using sodium methoxide in methanol, and employing an eight day reflux, the required nitroketone could be obtained in 12% yield as a very viscous pale-yellow oil which gave the correct molecular ion at $^{m}/_{e}$ 239 in the mass spectrum and showed ν_{NO_2} = 1545cm.$^{-1}$ and $\nu_{C=O}$ = 1712cm.$^{-1}$. Other basic conditions, which were examined in an attempt to improve this yield, included the use of potassium t-butoxide in tetrahydrofuran and calcium hydride in methanol. This latter combination, which has been recommended[8] for Michael additions involving nitro compounds proved to be the most successful and gave a 17% yield.

The overall complexity of the n.m.r. spectra of the products obtained from these varied experimental conditions, coupled with differences in the relative intensities of several peaks, lends considerable support to the hypothesis that a diastereoisomeric mixture is formed in this reaction. Although some partial

separation on preparative t.l.c. could be achieved by the technique of multiple running, no concrete conclusions could be reached as to the number and relative proportions of the various possible stereoisomers. From the synthetic viewpoint however, such a separation was unnecessary, and so it was decided to continue the reaction sequence with the isomeric mixture. Moreover, the best criterion for assessing the presence of the required cis-nitro olefin (5) would be the ultimate obtention of cyclised nitroxide material.

In consequence, the nitro-olefin mixture was reduced with zinc and ammonium chloride, and the hydroxylamino-olefin mixture thus obtained was then subjected, without further scrutiny, to silver oxide oxidation. The end product of this reaction sequence was a mixture of the nitroso-olefins (10), which could be isolated, after purification by preparative t.l.c., as a viscous blue oil.



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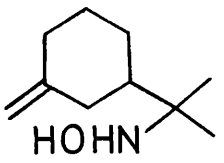
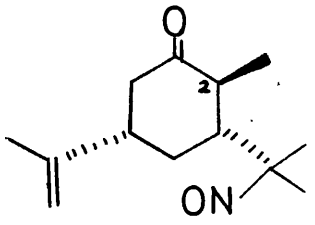


11

It is interesting to note that no trace of the nitroxide radical (6), which could, in principle, have arisen by the "aminium radical type" closure, was detected on oxidation. Indeed, as in the case of the hydroxylamino-olefin (11), deliberate attempts to induce this pathway by disproportionation with 2-methyl-2-nitrosopropane, were singularly unsuccessful, leading only to the recovery of unreacted starting material and trace amounts of the nitroso-olefin (10).

Fortunately, however, the second limb of the bifurcated approach proved to be in a much more receptive mood. Treatment of the nitroso-olefin mixture (10) with iodine in chloroform at room temperature in the dark for two days, led to the isolation of a dark oil which was easily separated by preparative t.l.c. into two coloured bands.

The less polar blue band, which comprised the unreacted nitroso-olefin, was of significant value inasmuch as subtractive comparison of its n.m.r. spectrum with that of the initial mixture allowed some assignments to be made as to the nature of the reactive nitroso-olefin (12).



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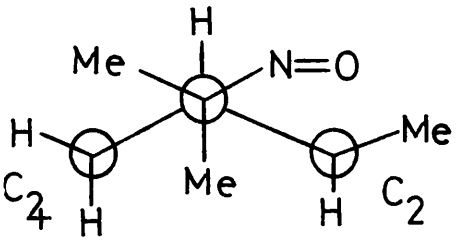

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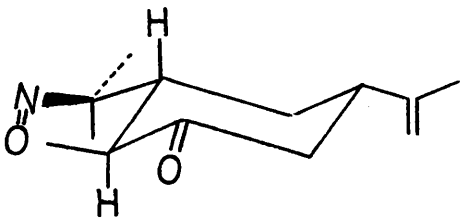
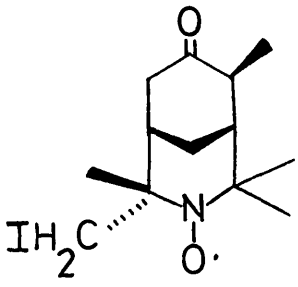


13

In particular, it was intriguing to note that the methyl doublet at C_2 was located at the unusually high value of 9.53τ, and that the two methyl groups of the gem-dimethyl nitroso moeity absorbed at 9.20 and 8.74 τ. These observations are best explained by the existence of a preferred rotamer (13), whose Newman projection is shown in (14). In this staggered conformation, the methyl group at C_2 would lie in the shielding zone of the nitroso group, and the two methyl groups attached to the nitroso group would be in magnetically different environments.



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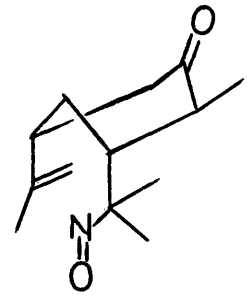

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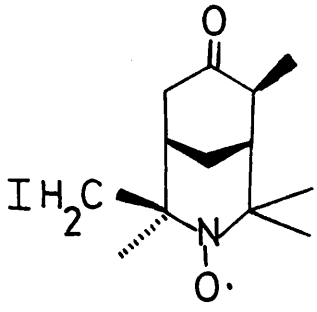

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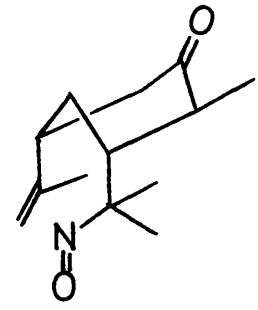


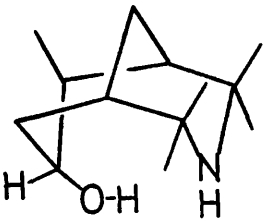
18

Examination of the red nitroxide band by multiple running on analytical t.l.c. revealed as expected, the presence of two closely running components. Thus the two nitroxide radicals (15) and (16) can be derived from the probable boat-like transition states (17) and (18) respectively, which differ only in the orientation of the isopropenyl group. Molecular models indicate that (17) and (18) are both equally probable, and lead moreover to a tertiary alkyl radical in which rotation is severely restricted.

Although pure samples of the two iodo-nitroxide radicals could only be obtained by arduous chromatography involving sacrificial cuts, it was decided to convert each one to the same parent nitroxide (6), as an additional check that these two compounds differed only in the configuration of the iodomethyl group.

Initially, it was felt that the most successful dehalogenation method would be hydrogenation over a Raney nickel catalyst. In the case of both iodo-nitroxide radicals however, this led to the

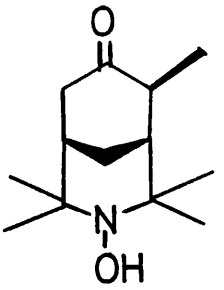
formation of the same amino-alcohol (19), thus necessitating an additional oxidation step in the synthetic sequence. Moreover, despite the use of freshly-prepared batches of Raney-nickel, the product was invariably contaminated, to a greater or lesser extent, by the presence of partially reduced ketonic and hydroxylamine material.



19

The assignment of the mechanistically favoured endo configuration to the amino-alcohol (19) is based upon the presence of a strong intramolecular hydrogen bond ($\nu_{max.}$ =3,120cm.$^{-1}$; unaffected by dilution), and on the half-band width of 8Hz. for the carbinyl proton in the n.m.r. spectrum, which is entirely consistent[9] with coupling to two equatorial and one axial protons.

Greater success was attendant upon a second method of effecting dehalogenation. Thus, hydrogenolysis of the non-polar iodo-nitroxide radical in basic methanol solution over a 5% palladium-charcoal catalyst gave the hydroxylamine (20) and subsequent oxidation with silver oxide gave the desired parent nitroxide radical (6).



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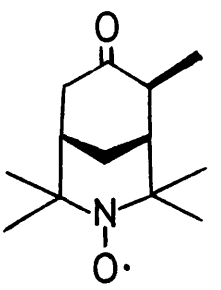
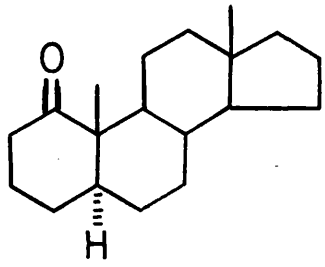


6

The polar iodo-nitroxide radical likewise gave the same hydroxylamine (20) on reduction as evidenced by n.m.r. comparison, and the same parent nitroxide (6) as indicated by i.r., t.l.c., m.p., and mass spectral cracking pattern.

The assignment of the predicted configuration of the methyl group at C_6 was initially based on n.m.r. solvent shift studies. The empirical rule which has been formulated[10,11] may be stated as follows: if a reference plane P is drawn through the carbon atom of the carbonyl group at right angles to the carbon-oxygen bond, then protons close to and in front of P show very small downfield shifts, while protons behind P are considerably shielded. Thus, in 5α-androstan-1-one (21), which possesses an axial methyl group adjacent to the carbonyl function, the methyl resonance suffers an appreciable upfield shift ($\Delta = \delta^{obs.}_{CDCl_3} - \delta_{C_6H_6} = 0.2\text{-}0.3$ppm) on passing from deuterochloroform to benzene solution[12].



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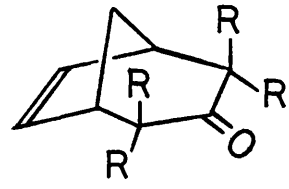
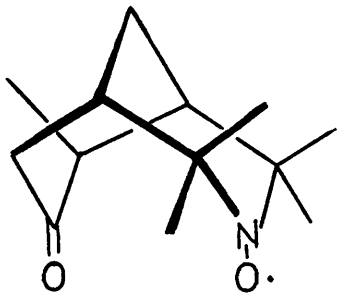


22 R= H or Me

In the case of the hydroxylamine (20), the resonance of the methyl doublet is shifted upfield by 0.26p.p.m. lending credence to the predicted axial configuration. Further support in favour of this configuration may be adduced from the recent results of Hoffmann[13], who has studied a series of polymethylated bicyclo (3,2,1) oct-6-en-3 ones (22) and concluded that the axial methyl groups absorb in the 8.70-8.85τ region and the equatorial methyl groups in the 9.00-9.15τ region. The hydroxylamine (20) shows a



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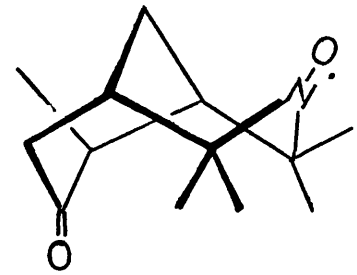

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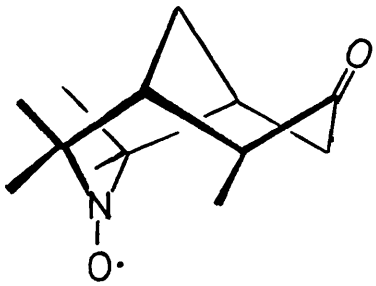

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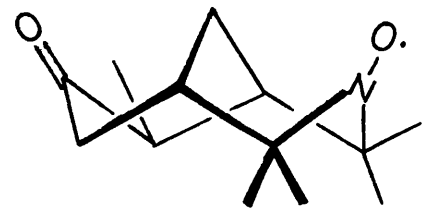


27

Conformation	Intervector angle α	μ calc.
24	0^{o}	5.8
25	120^{o}	3.0
26	120^{o}	3.0
27	150^{o}	1.5
μ obs. = 5.2 D	α calc. = 54^{o}	

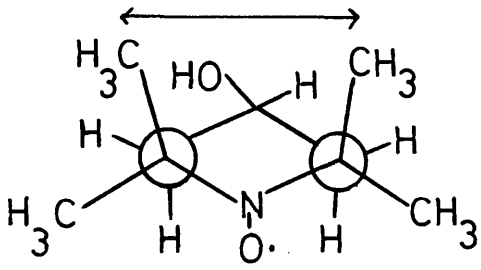
methyl doublet at 8.78τ. This conclusion was ultimately verified from the c.d. spectrum (vide infra).

At first sight, it may seem surprising that under the base-catalysed hydrogenolysis conditions, this methyl group did not suffer epimerisation to the equatorial configuration. On closer scrutiny however, it is apparent that such a process would introduce a severe 1,3 diaxial interaction between the methyl groups on C_4 and C_6; this would amount to 3k cal./mole.[14] in the twin chair conformation (23).

23

Having developed a satisfactory synthetic route to an optically-active nitroxide radical of known absolute configuration, it was now necessary to determine the conformation. This problem was simply solved by measuring the dipole moment of the keto-nitroxide (6), and comparing the observed value with those calculated for the conformations shown opposite on the assumption that the dipole moments of the nitroxide and carbonyl moeities may be taken as 3.14D.[15] and 2.66D.[16] respectively. The measured value of 5.2D. is most reasonably accommodated in terms of the chair-chair conformation (24), but the deviation from the perfect value of 5.8D may be attributed to a flattening of the piperidinoxy ring to relieve 1,3 diaxial methyl interactions. The flattened chair conformation is not without precedent in nitroxide radical chemistry. Thus the X-ray structure[17] of the nitroxide alcohol reveals a

flattened chair conformation (28) in which the axial methyl groups are pushed almost 0.7Å further apart than they would be in the perfect chair conformation (29). This deformation can also be extrapolated to the solution chemistry of the nitroxide alcohol since a variable temperature n.m.r. study has indicated[18] that the enthalpy difference between the two chair forms is only about 0.5k cal./mole. An alternative explanation is that the nitroxide grouping adopts an equatorial configuration in the piperidinoxy ring .



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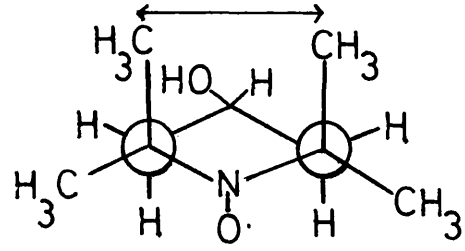


29

At this stage, it is now appropriate to provide a brief introduction to chiroptical phenomena. The most distinctive feature of a chiral substance is its ability to refract and absorb right and left circularly-polarised light to different extents. The former phenomenon gives rise to the optical rotatory dispersion properties of a compound, while the latter is responsible for its circular dichroism properties[3,19].

Since a chiral medium has different molecular extinction coefficients for left and right circularly polarised light, (ε_L and ε_R respectively), it is possible to plot the differential dichroic absorption, $\Delta\varepsilon$, against the wavelength as defined by equation [30], The curve so obtained is known as a c.d. curve.

$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R \qquad [30]$$

However, the more generally accepted unit of c.d. is the molecular ellipticity $[\theta]$, which is related to $\Delta\varepsilon$ by equation [31]:

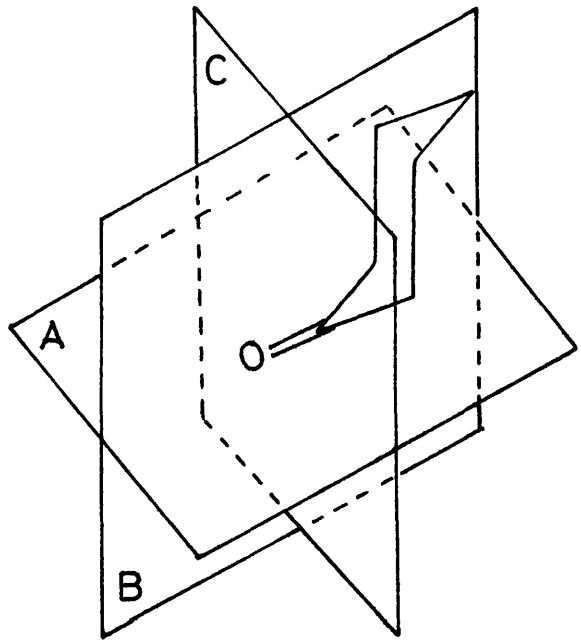


Figure 2

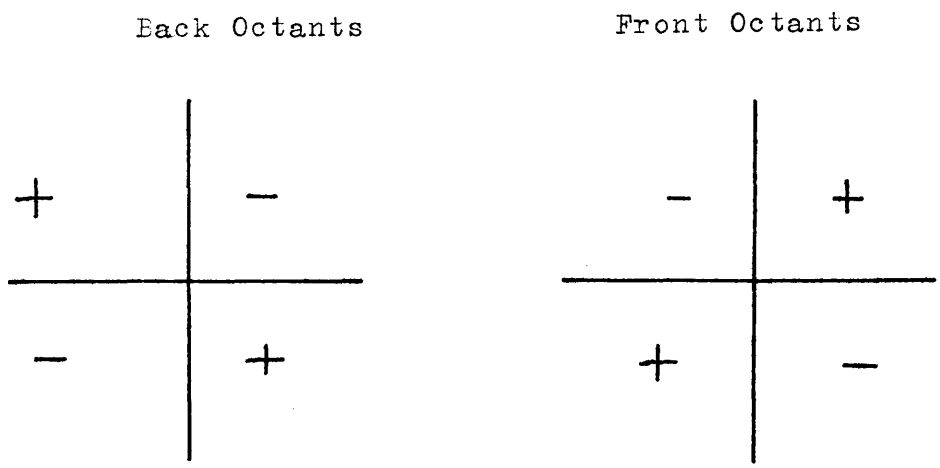


Figure 3

$$[\theta] = 3,300\ \Delta\varepsilon \quad [31]$$

The most interesting o.r.d. and c.d. curves are obtained in the vicinity of the electronic absorption bands of the substance being examined. These give rise to Cotton effects in o.r.d. spectra and maxima in c.d. spectra.

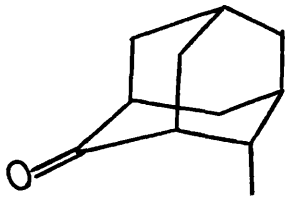
In this work, it was decided to concentrate on circular dichroism since this technique is free from the background effects often associated with o.r.d. spectra. On occasion however, it was necessary to relate the observed features in the c.d. spectrum to published o.r.d data. In this case, use was made of an important corollary of the Kronig-Kramers transform[20] in which the molecular amplitude, a, of the o.r.d. curve is related to $\Delta\varepsilon$, by the relationship [32].

$$a = 40.28\ \Delta\varepsilon \quad [32]$$

An immense body of data on the o.r.d. spectra of organic molecules has been accumulated principally by the schools of Djerassi and Klyne[21]. In particular, these groups studied the Cotton effect associated with the $n \rightarrow \pi^*$ electronic transition of the carbonyl chromophore. The empirical theories evolved by these workers were merged with the theoretical treatments of Moffit and Moscowitz in the enunciation of the Octant Rule in 1961[2]. This rule may be summarised as follows. Three perpendicular planes bisecting the carbonyl group divide the space surrounding this group into eight octants as shown in Figure 2. These planes are to a first approximation, the nodal and symmetry planes of the orbitals involved in the $n \rightarrow \pi^*$ transition. The sign and magnitude of the c.d. maximum of a ketone depends on the nature and position of the asymmetrically located groups in the compounds. Groups in the top left and bottom right of the back four octants as viewed along the O=C bond make a positive contribution whereas those in

the top right and bottom left octants make a negative contribution (Figure 3). The situation is reversed in the front four octants which are rarely occupied.

This rule has provided much configurational and conformational information over the years. Recently, however, self-consistent field molecular orbital calculations[22] have suggested than an axial 3-methyl group makes a contribution of opposite sign to that predicted by the Octant Rule. This has since been verified in the rigid, optically-active adamantanones (33) and (34)[23]. These observations suggest that the third plane C is not straight as shown but is curved and follows the contours of the molecule. Nevertheless, with this reservation in mind, the Octant Rule is still extremely useful in interpreting the chiroptical properties of ketones.



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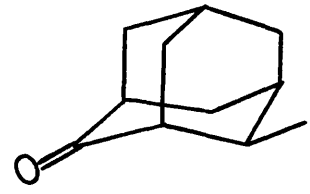


34

The c.d. spectrum of the keto-nitroxide radical (6), which was obtained in hexane solution is shown in Figure 4. A similar spectrum, but with less fine structure, was also observed in methanol solution. The relevant data are collated in Table 1.

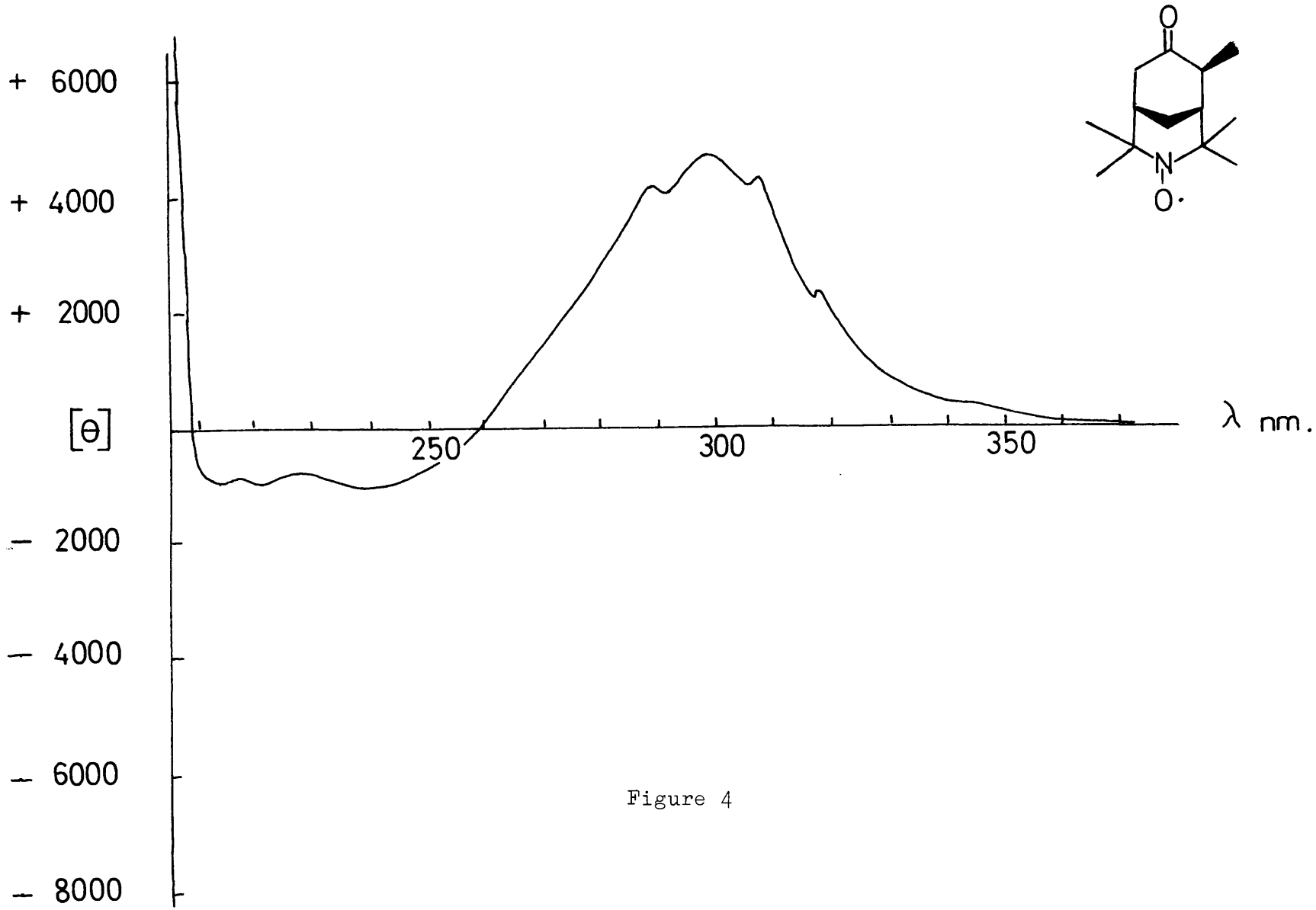
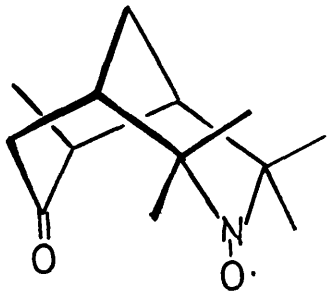


Figure 4

Table 1

Solvent	$\lambda_{max.}$ nm.	$\Delta\varepsilon$	$[\theta]$	a	Assignment
Hexane	340	+0.16	+528		
	318	+0.72	+2376		
	307	+1.30	+4290		
	298	+1.43	+4719	+57.6	$n \rightarrow \pi^*$ C=O
	289	+1.25	+4125		
	244	-0.29	-957		$\pi - \pi^*$ N-O
	221	-0.29	-957		
	214	-0.29	-957		
	194	+3.44	+11352		
Methanol	336	+0.21	+693		
	295	+1.56	+5148	+62.8	$n \rightarrow \pi^*$ C=O
	251	-0.23	-759		$\pi - \pi^*$ N-O
	216	-0.55	-1815		

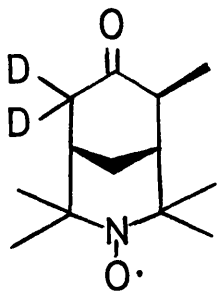


24

Analysis of the twin chair conformation (24) in terms of the octant rule leads to the prediction of a large positive c.d. maximum for the $n \rightarrow \pi^*$ transition of the carbonyl group and a small but positive c.d. maximum for the $n \rightarrow \pi^*$ transition of the nitroxide chromophore. In the event however, no maximum was observed for the $n \rightarrow \pi^*$ transition of the nitroxide group. This unfortunate result can only mean that the asymmetrically perturbing influence of the axial methyl group adjacent to the carbonyl is extremely weak at this remote distance, and, in consequence, the nitroxide chromophore behaves as a 'symmetrical' group. The $n \rightarrow \pi^*$ transition of the carbonyl group however does provide definitive evidence for the presence of an axial methyl group in a cyclohexanone chair. In particular, the values of +58 and +63 for the molecular amplitudes in hexane and in methanol, which were calculated from equation [32], are very close indeed to the value of -67 which has been derived by Djerassi et al.[24]. for (-) 2-axial methylcyclohexanone. Our result also lends additional support to the theoretical calculations of Tai and Allinger[25] who have predicted a value of -71 for the molecular amplitude of (-) -2-axial methylcyclohexanone.

Our understandable disappointment in the failure of the keto-nitroxide radical (6) to confirm or deny the validity of an octant rule for nitroxide radicals was, however, partly offset by an

additional bonus of theoretical interest in the form of a well-resolved e.p.r. spectrum. This showed a nitrogen hyperfine splitting of 15.30e. and additional long range hyperfine coupling to three protons. This was manifested in a doublet splitting of 0.52 Oe. and a triplet splitting of 0.99 Oe., due to the interaction of the unpaired electron with one and two protons respectively. Although it seemed unlikely that either of these couplings arose from the three protons adjacent to the carbonyl group, this possibility was tested by deuteration studies. From the experimental viewpoint this did occasion some difficulty since the keto-nitroxide radical proved to be very unstable in basic media. However, by employing a short reaction time it was possible to isolate small quantities of the nitroxide which showed a high incorporation of two deuterium atoms by mass spectral analysis. Quantitative measurement of the deuterium incorporation proved to be impossible because of an apparent variation in the relative intensities of the characteristic M^+ and M^++1 peaks. It is thought that this may be due to inter/intramolecular deuterium abstraction from the activated positions adjacent to the carbonyl.



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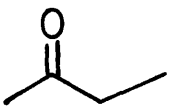


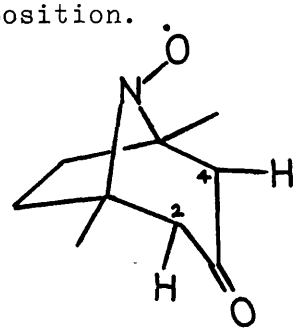
36

Two reasons influence our belief that the dominant d_2 species is as shown in (35). The first of these is that axial deuteration of cyclohexanone is known[26] to be faster than equatorial deuteration, while the second is that deuteration of methyl-ethyl ketone (36)

proceeds faster at the less substituted carbon atom.[27]

Since the e.p.r. spectrum of the deuterated species was unchanged, it was possible, on symmetry grounds, to assign the triplet splitting of 0.99 Oe to the bridgehead γ protons at C_1 and C_5, and the doublet splitting of 0.52 Oe to one of the two δ protons at C_9.

A detailed theoretical analysis of these long-range hyperfine couplings, in terms of the two currently-held spin polarisation mechanisms,[28,29] will only be possible after the signs of the coupling constants have been determined by n.m.r. analysis. In addition, it is desirable to know the exact geometry of the molecule. To this end, an X-ray analysis of the nitroxide (6) by direct methods is currently being performed. Nevertheless, it is interesting to speculate that the γ coupling may arise from the W-plan description first recognised by Russell.[30] This is possible if the nitroxide group adopts a pyramidal configuration with the N-O bond in an axial situation. W-coupling has recently been proposed by Rassat and Ronzaud[31] to account for the long-range γ coupling to the equatorial protons at C_2 and C_4 in the bicyclic nitroxide (37). In this case the nitroxide bond must also adopt an axial position.



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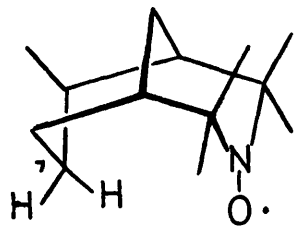
38

The observed δ coupling in the nitroxide (6) probably arises from coupling to the proton at C_9 which is equatorial in the piperidinoxy ring, since Windle et al.[32] have shown from a study of

substituted piperidines (38) that δ coupling is only observed when R=H. Since the exact mechanism and the possible angular and conformational dependance of long range γ and δ hyperfine coupling is not well understood at the present time, the rigorous theoretical analysis should prove to be a rewarding study.

The observation of long range hyperfine coupling in the e.p.r. spectrum of the keto-nitroxide (6) prompted the synthesis of the nor-keto analogue (39) to test the possibility of through-space coupling with the axial proton at C_7.



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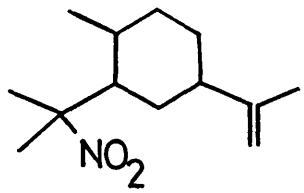
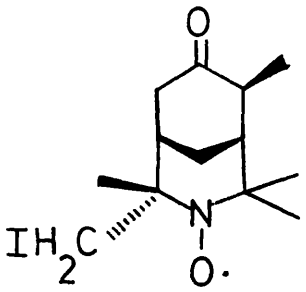


40

Efforts were initially directed towards the obtention of the nitro-olefin (40). The Wolf-Kishner and Cagliotti reactions were not however crowned with success and any attempts to remove the ketonic function at a later stage in the synthetic sequence were abandoned because of the startling events now to be unfolded.

The reader may have paused to contemplate on the alacrity with which the two iodo-nitroxide radicals (15) and (16) were dismissed; particularly since the asymmetric environment around the nitroxide chromophore should make these optically active synthetic intermediates especially suitable for c.d. study.



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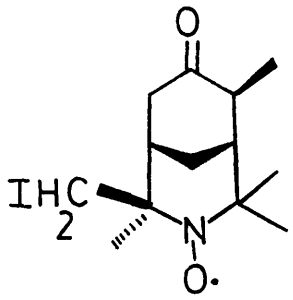

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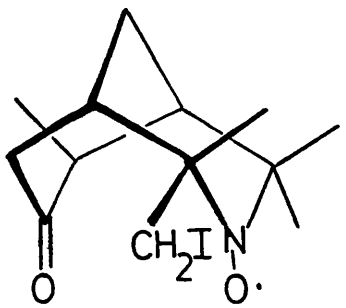


41

Thus, analysis of the twin chair conformation (41) of the iodo-nitroxide radical (15), in terms of the octant rule, leads to the prediction of a large positive c.d. maximum for the $n \rightarrow \pi^*$ transition of the carbonyl group and a negligible effect from the equatorial iodomethyl group on the $n \rightarrow \pi^*$ transition of the nitroxide chromophore.

Such a spectrum was indeed obtained from the less-polar of the two iodo-nitroxide radicals. This is reproduced in Figure 5 for hexane solution and the data and assignments for hexane and methanol solutions are collated in Table 2. Once again, the calculated molecular amplitude value of +69 for the $n \rightarrow \pi^*$ transition of the carbonyl chromophore at 296nm. in methanol lends firm support for the presence of a 2-axial methyl group in a cyclohexanone chair conformation, and indicates moreover that the contribution

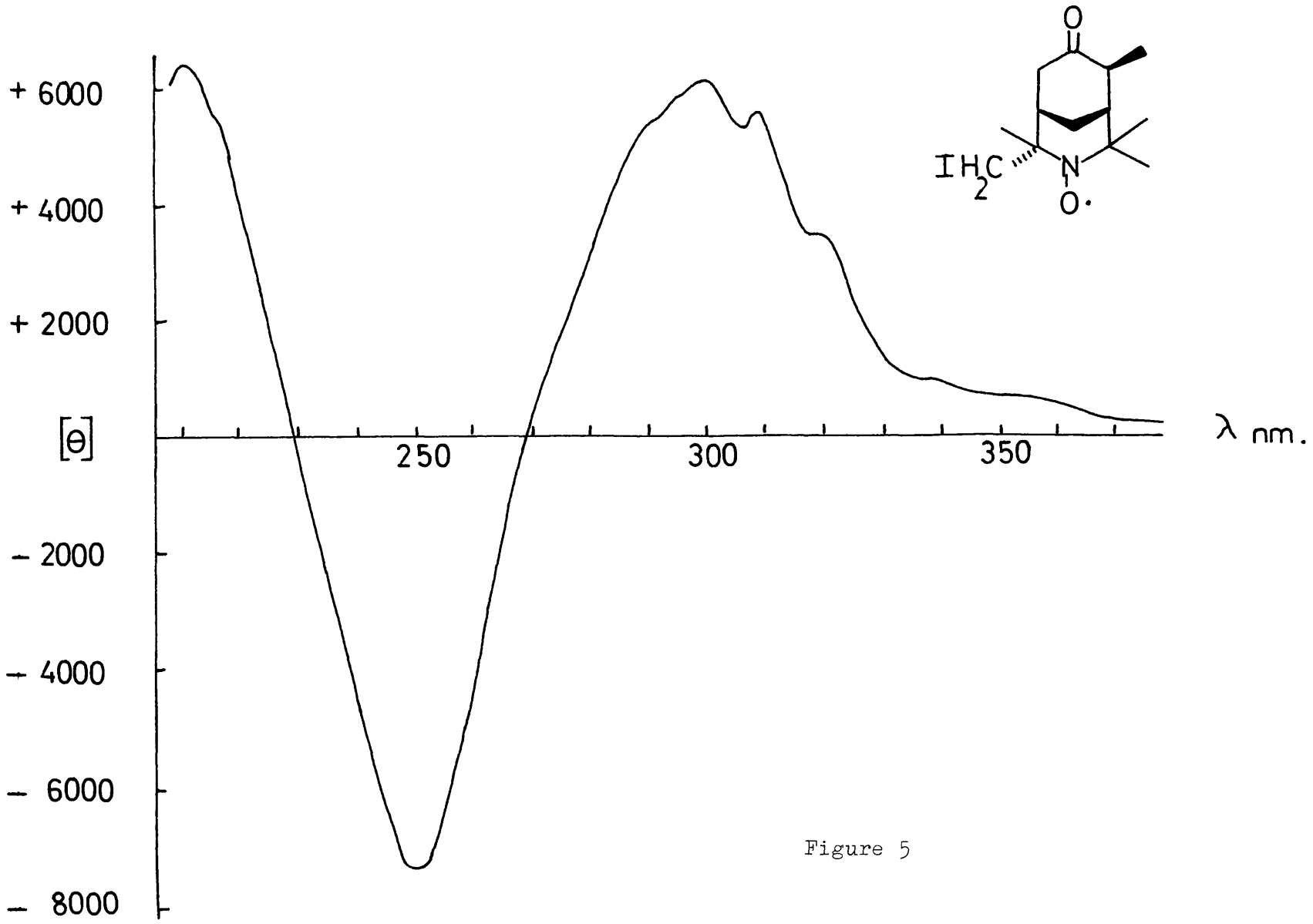


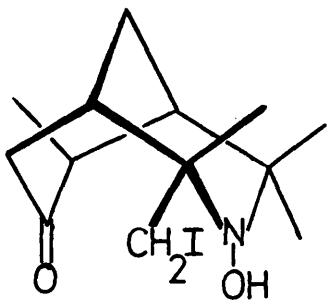
Figure 5

Table 2

Solvent	λ max. nm.	$\Delta\varepsilon$	$[\theta]$	a	Assignment
Hexane	337	+0.25	+825		
	318	+1.04	+3432		
	308	+1.70	+5610		
	299	+1.90	+6270	+76.5	$n \rightarrow \pi^*$ C=O
	247	-2.32	-7656		$n \rightarrow \sigma^*$ I
	209	+2.00	+6600		
Methanol	330	+0.30	+990		
	296	+1.72	+5676	+69.3	$n \rightarrow \pi^*$ C=O
	248	-1.91	-6303		$n \rightarrow \sigma^*$ I
	215	+1.27	+4191		
	476	-0.05	-165	-2.0	$n \rightarrow \pi^*$ N-$\dot{O}$

from the remote iodomethyl group is very weak. The large negative maximum at 248nm. is attributed to the $n \rightarrow \sigma^*$ electronic transition associated with the iodine atom on the basis of recently reported findings[33,34]. More interesting is the presence of a very small negative c.d. maximum at 476nm. in methanol for the $n \rightarrow \pi^*$ transition of the nitroxide. This is totally absent in hexane solution. The sign of this maximum is contrary to prediction since a quantitative study[35] of the Cotton effect associated with α-equatorial alkyl cyclohexanones has indicated that the equatorial methyl, isopropyl, and t-butyl groups do not lie exactly in the nodal plane but make a small positive contribution to the Cotton effect in a similar absolute configuration. A possible explanation for this observation may lie in the fact that the iodomethyl group can intrude into a front octant and hence give an opposite sign. In any event, the molecular amplitude of this transition is extremely small. (a = 2.0).

These configurational and conformational assignments are also consonant with the n.m.r. spectrum of the corresponding hydroxylamine (42) which was obtained by hydrogenation of the less-polar iodo-nitroxide radical (15) over a Lindlar catalyst.



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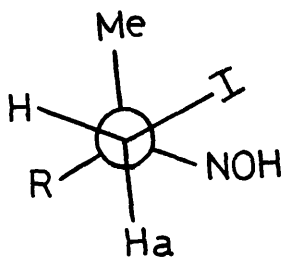
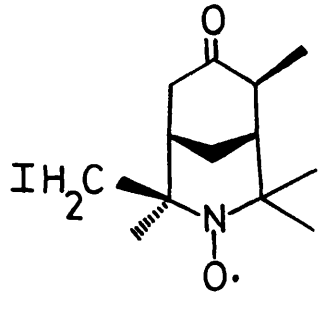


43

Thus the spectrum in benzene shows three well-resolved methyl

groups and a methyl doublet shifted upfield by 0.36p.p.m. In addition, the iodomethyl group appears as an AB quartet (J=10Hz) located at 6.72 and 6.32τ in $CDCl_3$, whose upper limb is further split. This can be rationalised in terms of a preferred, staggered rotamer whose Newman projection is shown in (43). In this situation W-coupling is possible between H_a and the appositely located protons of the adjacent methyl group. If this rotamer can also be extended to the corresponding iodo-nitroxide radical (41), then the iodomethyl group does intrude into a front octant.

Last in order of presentation, but certainly not least in order of importanee, is the more-polar of the two iodo-nitroxide radicals, which is without doubt, the most unusual nitroxide to be studied in the course of this work. By a process of elimination, based on the evolution of the overall synthetic sequence and the assignments already made, the only logical structure should be as shown in (16). However, the spectral properties of this compound are so unique that even a tentative structural assignment must be approached with the utmost caution!



16

In the beginning, was a high resolution mass measurement which vindicated the molecular formula $C_{13}H_{21}NO_2I$; and an infrared spectrum which displayed carbonyl absorption at 1718cm.$^{-1}$.

The e.p.r. spectrum however provided the first indication of abnormal behaviour. In sharp contrast to the simple triplet

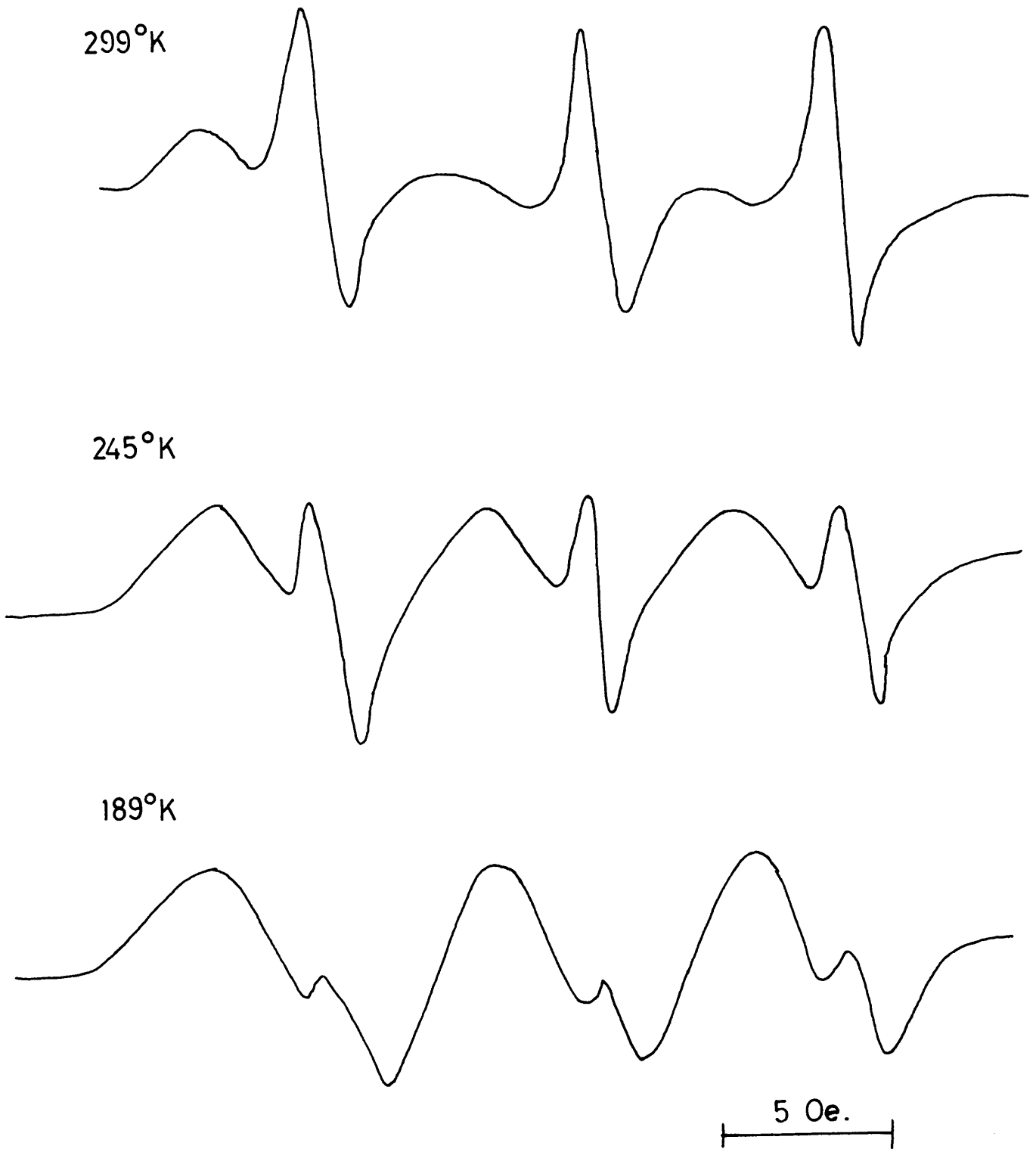


Figure 6

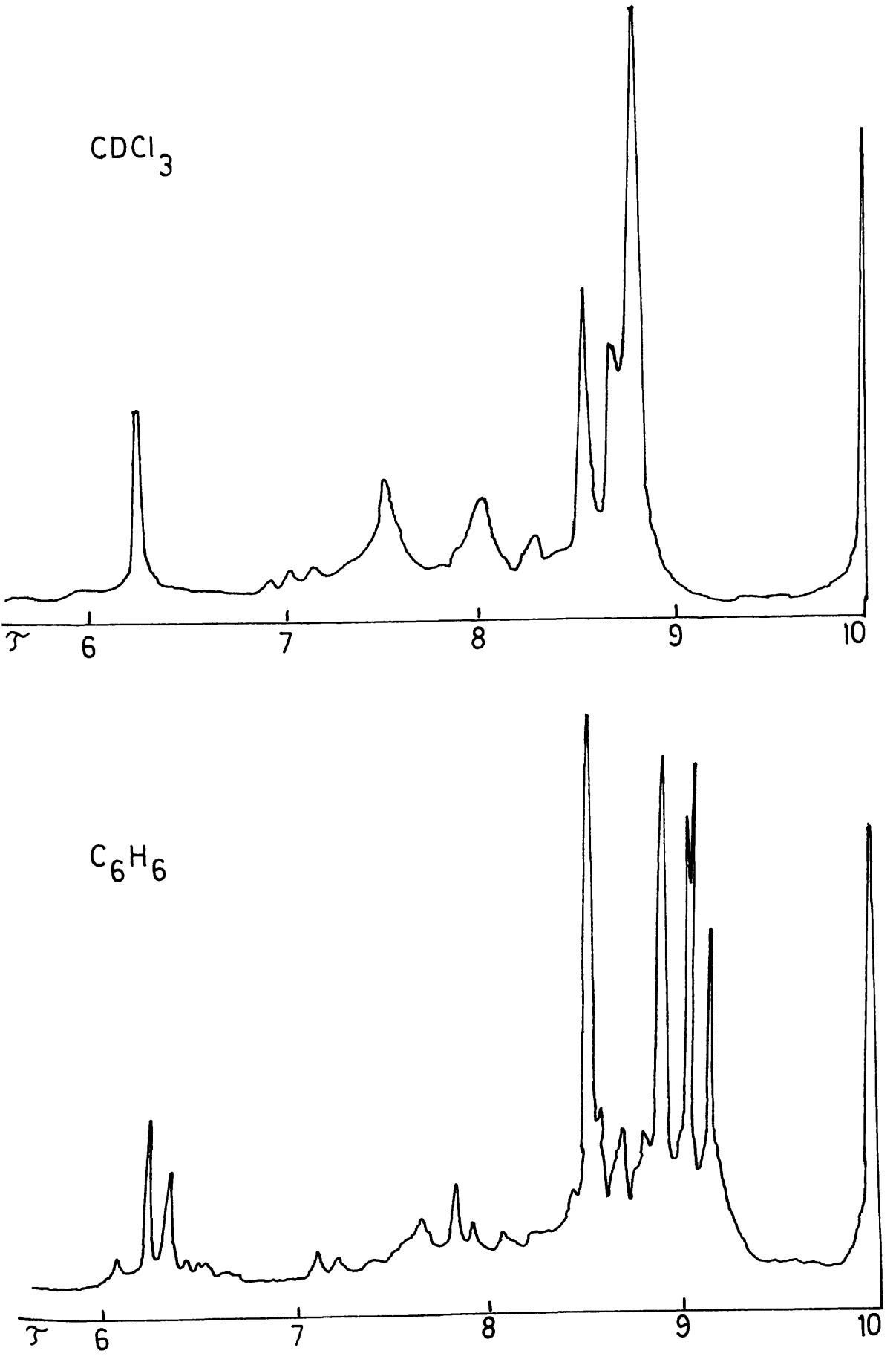
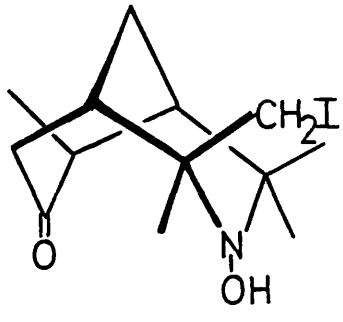


Figure 7

spectrum of the less-polar iodo-nitroxide (15), the observed signal was comprised of one sharp triplet (a_N=15.5 Oe; g=2.0071) and one very broad triplet (a_N=15.2 Oe.) whose g value of 2.0090 is unusually high. Moreover, as examination of Figure 6 will show, the relative intensities of these two triplets are markedly and reversibily temperature dependent. The only conclusion to be drawn from this spectrum is that the nitroxide is undergoing some form of conformational or tautomeric change, and that the two species involved have totally different electronic environments in the vicinity of the nitroxide group. It is nevertheless difficult to explain the breadth and the high g value of the second triplet.

In the hope of obtaining some structural information, the corresponding iodo-hydroxylamine was prepared by hydrogenation over Lindlar catalyst. The n.m.r. spectra of this compound which are reproduced in Figure 7 for $CDCl_3$ and benzene solutions did not permit definitive interpretation. The most intriguing feature of these spectra is the presence of a low field methyl singlet at 8.56τ which is unaffected by change of solvent. If this observation is to be reconciled in terms of structure (16), then it is necessary to postulate that the iodomethyl group is capable of desheilding a methyl group in the 1,3-diaxial situation (44).



44

Although this would appear to be possible no literature precedent can be found. Other features of note in these spectra

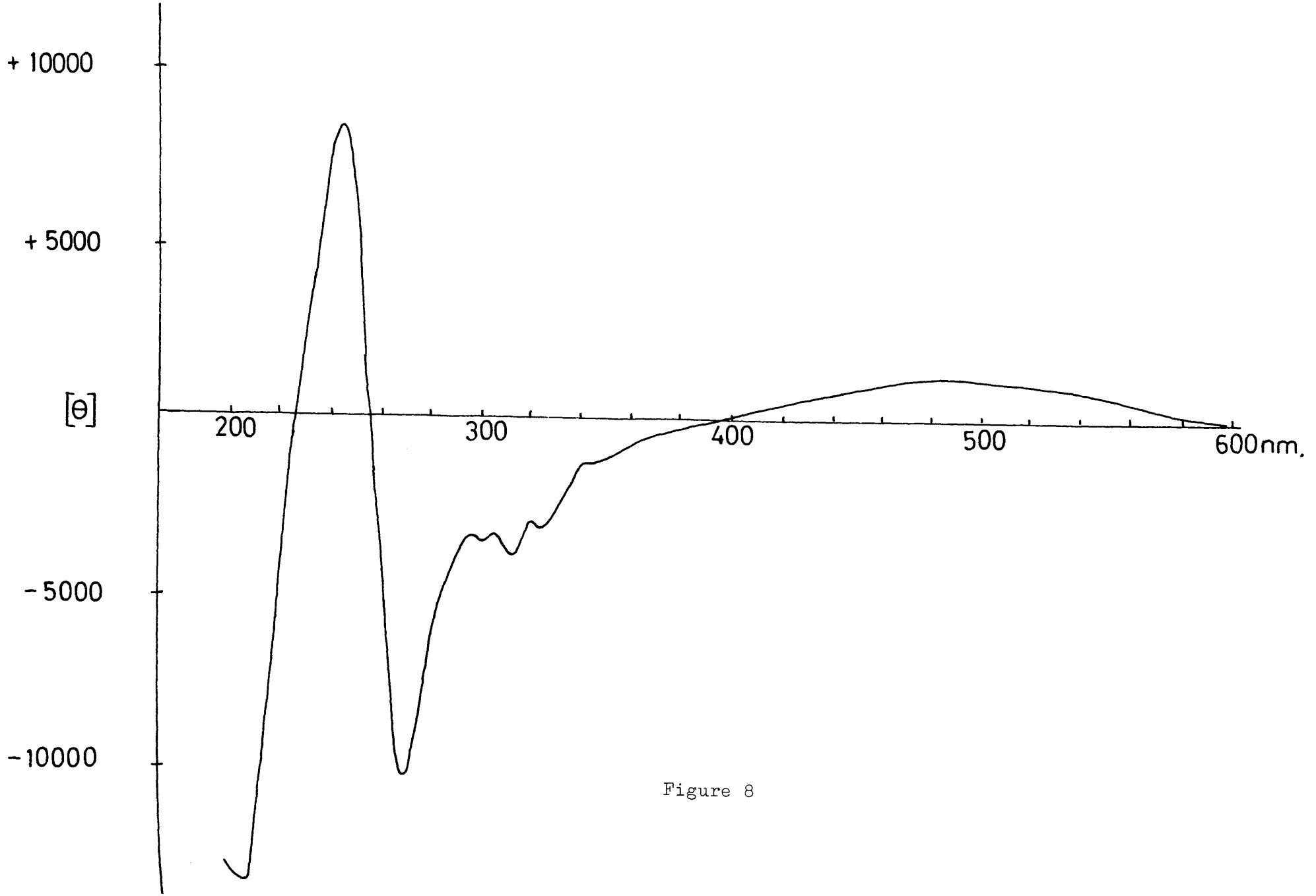


Figure 8

Table 3

Solvent	$\lambda_{max.}$ nm.	$\Delta\varepsilon$	$[\theta]$	Assignment
Hexane	490	+0.47	+1551	$n \rightarrow \pi^*$ N-O
	315	-1.26	-4158	
	274	-3.28	-10824	$n \rightarrow \pi^*$ C=O ?
	242	+2.48	+8184	
	209	-4.03	-13299	
Methanol	470	+0.40	+1320	$n \rightarrow \pi^*$ N-O
	321	-0.62	-2046	
	272	-2.78	-9174	$n \rightarrow \pi^*$ C=O ?
	242	+2.03	+6699	
	208	-4.78	-15744	

are that the iodomethyl group appears an an A_2 system centred at 6.25τ in $CDCl_3$ and as an AB system at 6.46τ in benzene. Because of overlapping signals it is more difficult to pick out the methyl doublet, although an upfield shift has certainly occurred. This problem was not encountered in the cases of the less-polar iodo-hydroxylamine (42) and the parent hydroxylamine (20) where the methyl doublet was cleanly resolved.

The most mysterious phenomenon of all however, is the c.d. spectrum of the more-polar iodo-nitroxide, which is reproduced in Figure 8. This spectrum is not upside down nor have the molecular ellipticity and wavelength scales been distorted in any way! Comparison of the data in Table 3 with the values already assigned to the nitroxides (6) and (15) in Tables 1 and 2 merely serves to highlight this anomalous behaviour. In the absence of definite structural knowledge, only negative conclusions can be drawn. Thus, it would appear that this molecule does not possess an axial methyl group α to the carbonyl in a cyclohexanone chair conformation. Furthermore, the values of molecular ellipticity and molecular amplitude would suggest that the contribution of the iodomethyl group to the $n \rightarrow \pi^*$ transition of the carbonyl chromophore is considerable. The assignment of the positive maxima at 470nm. and 490nm. in methanol and hexane respectively to the $n \rightarrow \pi^*$ electronic transition of the nitroxide is supported by the ultraviolet spectrum. This shows absorption at 470nm. in methanol with an ε value of 29. Since the normal nitroxide values for the $n \rightarrow \pi^*$ transition lie in the 410-450n.m. range with an ε value of about $5\text{-}10^{36}$, it is apparent that for some reason, this particular transition is energetically more favourable.

The problem has been presented; but the solution is yet to be found. The discussion which this bizarre molecule has engendered,

and the various structures which have been proposed, scrutinised, and rejected, would require another volume and would serve no useful purpose. From the emotional viewpoint, this traumatic experience can only be likened to the Wagner-Meerwein shifts which plagued the early investigators in the terpene field.

Fortunately however, the screen of mystery which has enshrouded the more-polar iodo-nitroxide radical is soon to be penetrated. Recourse has been made to the court of last appeal, and the nitroxide has obligingly crystallised in the orthorhombic space group $P2_12_12_1$. The presence of the iodine atom is an additional source of comfort since this will enable the powerful heavy atom method of X-ray crystallographic analysis to be employed. The result of this structure determination is eagerly awaited at the present time.

In the final analysis, it must be admitted that once again in the course of this work, some problems have been generated and others have been solved. Nevertheless, the overall synthetic sequence affords striking testimony to the power of the iodine cyclisation reaction and the physico-chemical measurements have advanced our knowledge of nitroxide radical chemistry.

EXPERIMENTAL

The same general experimental details already outlined apply in this section. In addition all rotations were measured using a Perkin-Elmer 141 polarimeter at a room temperature of 25°C. The c.d. curves were obtained by using a Carey 60 spectropolarimeter.

ATTEMPTED MICHAEL ADDITIONS OF 2 - NITROPROPANE TO (+) - CARVONE (4).

(a). A solution of carvone (8g.) and 2-nitropropane (17g.) in ether (150ml.) containing benzyl-trimethylammonium hydroxide (40% aqueous soln; 1ml, "Triton B") was heated under reflux for 7 days. The cooled solution was washed with dilute hydrochloric acid, sodium bicarbonate and finally with water. Drying and solvent removal afforded only unreacted starting material as evidenced by analytical t.l.c. and i.r. examination.

(b) The above experiment was repeated using anhydrous Triton B (700mg.) prepared by azeotropic removal of water in a Dean and Stark apparatus. Dry ethanol (150ml.) was used as solvent and the reaction mixture was refluxed for 20 days, with similar results to those described in (a) above.

2 - METHYL - 3 - (1-METHYL-1-NITROETHYL)- 5 - ISOPROPENYL CYCLOHEXANONE (5).

Carvone (15g.) and 2-nitropropane (40g.) were added to a solution of sodium methoxide (5.4g.) in dry methanol (150ml.) and the mixture was heated under reflux for 8 days. The reaction mixture was then concentrated by solvent removal and ether (400ml.) and dilute hydrochloric acid were added. The green solution was transferred to a separatory funnel, and the ethereal extract was washed with brine until neutral. Drying and removal of solvent gave a dark brown oil (20g). which was fractionally distilled to give a dark yellow oil (2.9g.), b.p. 128-130°C/ 4mm. This oil was purified by short column chromatography to give a pale yellow oil. (2.3g.).

$\nu_{max.}$ (liquid film) = 3080, 2980, 1712, 1644, 1545 and 894cm.$^{-1}$.

M^{+} = 239.

High resolution mass measurement M^+ = 239.1510.

calculated for $C_{13}H_{21}NO_3$ = 239.1521.

This reaction was also performed under the following variety of basic conditions in an attempt to optimise the yield.

a). Using potassium-t-butoxide as base.

To a solution of potassium-t-butoxide (5g.) in dry tetrahydrofuran (110ml.) was added 2-nitropropane (80g.) with the immediate formation of a white precipitate. Carvone (36g.) was added dropwise over a 10 minute period and the mixture was magnetically stirred at room temperature for 16 hours when analytical t.l.c. indicated that no reaction had occurred. Accordingly the reaction mixture was heated in an oil bath maintained at 80°C for 7 days. Work up as previously described gave a dark yellow oil (2.7g.), b.p. 127-130°C/0.4mm.

b). Using Calcium hydride as base.

A mixture of carvone (15g.) and 2-nitropropane (88g.) in dry methanol (80ml.) containing calcium hydride (4g.) was refluxed for 7 days. The usual work up afforded, after distillation a yellow oil (4.03g.).

The overall complexity of the n.m.r. spectra obtained from the various experimental conditions employed, coupled with a difference in the relative intensity of several peaks, lend support to the hypothesis that different proportions of an isomeric mixture are formed.

Attempts to separate this isomeric mixture by multiple running on preparative t.l.c. led to the production of two partially-merged zones which were barely separated. Sacrificial cuts were taken and the n.m.r. spectra of the two enriched fractions were

examined, allowing the following assignments:

Compound A: τ = 8.95, (3H, doublet, J=7Hz., $\underline{CH_3}$-CH-CO), 8.36 and 8.41, (6H, 2 singlets, $(\underline{CH_3})_2$-C-NO_2), 8.23, (3H, broadened singlet, $\underline{CH_3}$-C=C), 5.13, (2H, broadened singlet, exomethylene).

Compound B: = 8.91, 8.82, 8.71, (singlets), 8.23, (broadened singlet), 5.14, (broadened singlet).

Both A and B have $\nu_{max.}$ (liquid film) = 1712 and 1645cm.$^{-1}$.

No assignment can be made to fraction B on the basis of its n.m.r. spectrum.

2 - METHYL - 3 - (1-METHYL-1-HYDROXYLAMINOETHYL) - 5 - ISOPROPENYL CYCLOHEXANONE.

Zinc dust (1.4g.) was added portionwise, over a 5 minute period, to a well-stirred mixture of ammonium chloride (250mg.) and the isomeric nitro ketone mixture (360mg.) in aqueous ethanol (2:3, 5ml.) with cooling in an ice bath. The reaction was magnetically stirred for 35 minutes at 0°C, and then filtered through a celite column which was thoroughly washed with ether (75ml.). The ethereal filtrate was diluted with water (20ml.), separated, extracted and dried in the usual manner. Removal of solvent gave the hydroxylamino olefin as a colourless viscous oil (320mg.) which was subjected to the following oxidation step.

2 - METHYL - 3 - (1-METHYL-1-NITROSOETHYL) - 5 - ISOPROPENYL CYCLOHEXANONE (10).

The hydroxylamino-olefin (320mg.) in ether (25ml.) was shaken with excess freshly-prepared silver oxide (3g.) at room temperature for 30 minutes. Filtration through glass filter paper, and solvent removal gave a blue oil (260mg.). Preparative t.l.c. was undertaken and the blue band was isolated as a viscous

oil (96mg.).

$\nu_{max.}$ (liquid film) = 1710, 1646, 1550 and 904cm.$^{-1}$.

$\lambda_{max.}$ ($CHCl_3$) = 686nm. (ε = 8.6).

Subtractive comparison of the n.m.r. spectrum of the nitroso-olefin mixture with that of the nitroso-olefin unreacted in the iodine cyclisation (vide infra) allows the following assignments to be made for the reactive stereoisomer.

τ = 9.53, (3H, doublet, J=7Hz, CH_3-CH-CO), 9.20, (3H, singlet, CH_3-C-NO), 8.74, (3H, singlet, CH_3-C-NO), 8.21, (3H, broadened singlet, CH_3-C=C), 5.16, (2H, broadened singlet, 1x=CH_2).

2,4,4,6 - TETRAMETHYL - 2 - IODOMETHYL - 3 - AZABICYCLO [3,3,1] NONAN - 7 - ONE - 3 - OXYL (15)and (16).

A solution of iodine (340mg.) in Analar chloroform (25ml.) was added dropwise to a freshly-prepared solution of 2-methyl-3-(1-methyl-1-nitrosoethyl)-5-isopropenylcyclohexanone (from 1.09g. of the corresponding nitro-ketone) in chloroform (25ml.), and the reaction was allowed to stand in the dark for 2 days at room temperature. Unreacted iodine was removed by shaking with sodium thiosulphate solution, followed by water. Drying and removal of solvent gave a dark oil. Preparative t.l.c. served to separate the unreacted nitroso-olefin from the iodo-nitroxide (235mg.) which was obtained as a dark red oil. Analytical t.l.c. showed that the iodo-nitroxide band was a mixture of 2 compounds. Multiple running of the nitroxide band (4x40% ether-petrol) enabled pure samples of the two components to be obtained. This engendered considerable loss of material, however, since sacrificial cuts had to be taken.

NON - POLAR IODO - NITROXIDE (15).

$\nu_{max.}$ (CCl_4) = 1712cm.$^{-1}$

a_n (CCl_4) = 15.2 Oe., g = 2.0071.

M^++1 = 351; M^+ = 350, M^+-14 = 336

$\lambda_{max.}$ ($CHCl_3$) = 248nm. (ε = 3,255), 474nm. (ε = 6.4).

High resolution mass measurement M^+ = 350.0618

calculated for $C_{13}H_{21}NO_2I$ = 350.0619

$[\alpha]_D^{25}$ = -28° (c = 0.175 C_6H_{12})

Rose-pink needles mp. 124-127°C (decomp.)

Polar Iodonitroxide (16)

$\nu_{max.}$ (CCl_4) = 1718cm.$^{-1}$.

a_{n1} (CCl_4) = 15.5 Oe. g_1 = 2.0071 (sharp)

a_{n2} (CCl_4) = 15.2 Oe. g_2 = 2.0090 (broad)

M^++1 = 351; M^+ = 350, M^+-14 = 336, significant ion at $^m/_e$ 210.

$\lambda_{max.}$ ($CHCl_3$) = 268n.m. (ε = 3,159)

$\lambda_{max.}$ (MeOH) = 470n.m. (ε = 29)

High resolution mass measurement M^+ = 350.0614

calculated for $C_{13}H_{21}NO_2I$ = 350.0619

$[\alpha]_D^{25}$ = +98° (c = 0.156 C_6H_{12})

Peachy-Pink needles m.p. 118-122.5°C.(decomp.)

HYDROGENATION OF THE NON - POLAR IODO - NITROXIDE (15) TO THE CORRESPONDING HYDROXYLAMINE (42)

The non-polar iodo-nitroxide (15) (145.6mg.) was dissolved in ethyl acetate (10ml.). Lindlar catalyst (53.8mg.) was added and the magnetically-stirred solution was hydrogenated at atmospheric pressure for 19 hours. The catalyst was removed by filtration through a celite pad under nitrogen and the solvent was removed *in vacuo* to give a clear viscous oil (142mg.) which gave a slow

Positive test with alkaline 2,3,5-triphenyltetrazolium chloride.

This compound appeared as one clean spot on analytical t.l.c.

$\nu_{max.}$ (liquid film) = 3380, 2978, 1704 and 1114cm.$^{-1}$.

τ = 8.79, (6H, singlet, $\underline{CH_3}$-C-NOH), 8.78, (3H, doublet, J=7Hz, $\underline{CH_3}$-CH-CO), 8.68, (3H, broadened singlet, $\underline{CH_3}$-C-NOH), 7.4-8.6, (7H, multiplet), 6.72, (1H, doublet, Jgem = 10Hz., broadened by further coupling $\underline{CH_2}$-I), 6.32, (1H, doublet, Jgem = 10Hz., $\underline{CH_2}$-I), 4.88, (1H, broad, exchangeable with D_2O, NO$\underline{H}$).

$\tau(C_6H_6)$ = 9.14, (3H, doublet, J = 7c.p.s., $\underline{CH_3}$-CHCO), 8.98, (3H, singlet, $\underline{CH_3}$-C-NOH), 8.88, (3H, Singlet, $\underline{CH_3}$-C-NOH), 8.74, (3H, singlet, $\underline{CH_3}$-C-NOH), 7-8.6, (7H, multiplet), 6.72, (1H, Doublet, Jgem. = 10Hz., broadened by further coupling $\underline{CH_2}$-I), 6.32, (1H, doublet, Jgem. = 10Hz., $\underline{CH_2}$-I).

High resolution i.r. dilution studies revealed no intramolecular I $\cdots$H-O hydrogen bond.

Oxidation of the hydroxylamine with silver oxide in the usual manner afforded the starting non-polar iodo-nitroxide (15).

HYDROGENATION OF THE POLAR IODO - NITROXIDE (16) TO THE CORRESPONDING HYDROXYLAMINE.

The polar iodo-nitroxide (16) (30.6mg.) was dissolved in ethyl acetate (10ml.) and Lindlar catalyst (52.6mg.) was added. Hydrogenation at atmospheric pressure for 19 hours and work up as described above gave a colourless oil (28mg.), which gave a positive test with alkaline 2,3,5-triphenyltetrazolium chloride.

$\nu_{max.}$ (liquid film) = 3420, 2978, 2705, and 1108cm.$^{-1}$.

τ = 8.80, (6H, singlet, $\underline{CH_3}$-C-NOH), 8.76, (3H, doublet, mashed by 6H singlet, $\underline{CH_3}$-CH- CO), 8.56, (3H, singlet, $\underline{CH_3}$-C-NOH), 6.8-8.4, (7H, multiplet), 6.25, (2H, singlet, $\underline{CH_2}$-I), 5.08, (1H, broad exchangeable with D_2O, NO$\underline{H}$).

$\tau(C_6H_6)$ = 9.14, (3H, doublet, J=7c.p.s., $\underline{CH_3}$-CH-CO), 9.12, (3H, singlet, $\underline{CH_3}$-C-NOH), 8.98, (3H, singlet, $\underline{CH_3}$-C-NOH), 8.58, (3H, singlet, $\underline{CH_3}$-C-NOH), 7-8.8, (7H, multiplet), 6.46, (1H, doublet, Jgem. = 10Hz. $\underline{CH_2}$-I), 6.21, (1H, doublet, Jgem.=10Hz, $\underline{CH_2}$-I).

Oxidation of the hydroxylamine with silver oxide furnished the starting polar iodo-nitroxide.

2,2,4,4,6 - PENTAMETHYL - 7 - HYDROXY - 3 - AZABICYCLO [3,3,1] - NONANE (19)

(a) By hydrogenation of the non-polar iodo-nitroxide (15) over Raney Nickel.

The non-polar iodo-nitroxide (175mg.) was dissolved in methanol (10ml.) and about 1 level teaspoonful of Raney Nickel (W-2) was added. The magnetically-stirred solution was hydrogenated at atmospheric pressure for 3.5 hours. The catalyst was then removed by filtration through a glass filter paper and thoroughly washed with warm methanol. The combined washings were stirred at room temperature for 1.5 hours with excess Amberlite ion exchange resin (IRB 400 OH^-). Removal of the resin by filtration, and concentration of the solvent afforded a yellow solid (72mg.) which was sublimed (120°C/0.4mm) to give a white solid.

$\nu_{max.}$ (Nujol Mull) = 3220, 1500 and 1254cm.$^{-1}$.

$\nu_{max.}$ (CCl_4) = 3120cm.$^{-1}$ (unaffected by dilution).

τ = 8.95, (3H, doublet, J=7Hz. $\underline{CH_3}$-C-C-OH), 8.75, (6H, broad singlet, ($\underline{CH_3}$)$_2$-C-NH), 8.66, (6H, singlet, ($\underline{CH_3}$)$_2$-C-NH), 7.5-8.6, (8H, multiplet), 6.58, (1H, multiplet, $W_{\frac{1}{2}}$ = 8Hz $\underline{H}$-C-OH).

M^+ = 211.

High resolution mass measurement: M^+ = 211.1936.

calculated for $C_{13}H_{25}NO$ = 211.1936.

(b) by hydrogenation of the polar iodo-nitroxide (16) over Raney-Nickel

Hydrogenation of the polar iodo-nitroxide (16) (449mg.) in methanol (10ml.) over a Raney-nickel catalyst (W-2) and work up as described above led to the isolation of oily crystalline material (16mg.) whose n.m.r. spectrum was similar to that described in (a) above. The i.r. spectrum, however, showed absorption at 1730cm.$^{-1}$, indicating the presence of ketonic material.

Despite the preparation of fresh batches of Raney nickel, this reaction proved to be irreproducible, with respect to both iodo-nitroxide radicals, and led to the abandonment of the amino-alcohol (19) as a viable comparison product.

2,2,4,4,6 - PENTAMETHYL - 3 - AZABICYCLO [3,3,1] NONAN - 7 - ONE - 3 - OXYL (6).

(a) by hydrogenolysis of the non-polar iodo-nitroxide (15)

The non-polar iodo-nitroxide (15) (170mg.) was dissolved in methanol (10ml.) containing sodium hydroxide (50mg.) 5% Palladium-charcoal catalyst (62mg.) was added and the magnetically-stirred solution was hydrogenated at atmospheric pressure for 2.5 hours. The catalyst was removed by filtration through a glass filter paper and the methanol was removed on the rotary evaporator. The residue was taken up in ether, washed with water, dried, and the solvent removed to afford a clear colourless oil.

$\nu_{max.}$ (liquid film) = 3380 and 1695cm.$^{-1}$.

τ = 8.80, (12H, singlet CH_3-C-NOH), 8.78, (3H, doublet J=7Hz. CH_3-CH-CO), 6.8-8.6, (7H, multiplet) 5.37, (1H, broad, exchangeable with D_2O NOH).

$\tau(C_6H_6)$ = 9.04, (3H, doublet, J=7Hz., CH_3-CH-CO), 8.88, (12H, singlet, CH_3-C-NOH), 6.8-8.8, (7H, multiplet).

The hydroxylamine (20) was dissolved in ether (30ml.) and shaken with excess silver oxide (2g.) at room temperature for 25 minutes. Filtration through glass filter paper and solvent removal gave a red oil which was purified by preparative t.l.c. and isolated as pale rose-pink microcrystalline needles (52.1mg.), m.p. 106.5-108.5°C.

$\nu_{max.}$ (Nujol Mull) = 1703, 1490, 1321, 1080 and 794cm.$^{-1}$.

a_n (CCl_4): = 15.30e. g = 2.0070

a_H (doublet)= 0.520e a_H (triplet) = 0.99 0e.

M^++1 = 225, M^+ = 224, M^+-14 = 210

$\lambda_{max.}$ (CH_3OH) = 241nm. (ε = 2,143) and 460nm. (ε = 12.3).

High resolution mass measurement: M^+ = 224.1649.

calculated for $C_{13}H_{22}NO_2$: M^+ = 224.1650.

$[\alpha]_D^{25}$ = +32.1°, (C = 0.28 hexane)

(b) by hydrogenolysis of the polar iodo-nitroxide (16).

The polar iodo-nitroxide (16) (25mg.) was dissolved in methanol (10ml.) containing sodium hydroxide (8mg.) 5% Palladium-charcoal catalyst (50mg.) was added and hydrogenation allowed to proceed for 2.5 hours. Work up as previously described gave the keto-hydroxylamine (20) whose n.m.r. spectra in $CDCl_3$ and in C_6H_6 were identical to those described in (a) above. Oxidation of the keto-hydroxylamine (20) with silver oxide in the usual manner furnished the keto-nitroxide (6) (4.2mg.), m.p. 103-104.5°C. The infrared spectrum and the mass spectral cracking pattern were identical to those described in (a) above. The chromatographic properties in several solvent systems were also identical.

DIPOLE MOMENT MEASUREMENT OF 2,2,4,4,6 - PENTAMETHYL - 3 - AZABICYCLO 3,3,1 NONAN - 7 - ONE - 3 - OXYL (6)

These measurements were performed at the University of East Anglia by Dr. I.D. Blackburne.

The method involved calculation of the total molar polarisation ($T^P_{2\infty}$) of the solute from measurements of the specific volume and dielectric constant of dilute solutions. The following measurements were recorded at 25°C in benzene solution.

$10^6 w$	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(\nu_1 - \nu_{12})$
661	7988	153
1057	12957	249
1622	20395	379
2121	27075	500

where: ε_1 = dielectric constant of benzene

ε_{12} = dielectric constant of solution.

V_1 = specific volume of benzene.

V_{12} = specific volume of solution.

W = weight fraction of solute.

The limiting values for zero solute concentrations were determined and the total molar polarization evaluated using the Halverstadt-Kummler equation[37]. Atom polarization was neglected and the electron polarization (P_E) was estimated from tables.

$\frac{d\varepsilon}{dw}$	$\frac{-dv}{dw}$	$T^P_{2\infty}$	P_E
13.095 $\pm$0.114	0.237 $\pm$0.002	612.86	60.842.

Calculation of the dipole moment (μ) using the expression:

$$\mu = 0.01282 \sqrt{(T^P - P_E)T}$$

gives a value of 5.2D for the dipole moment of the keto-nitroxide (6).

DEUTERATION OF 2,2,4,4,6 - PENTAMETHYL - 3 - AZABICYCLO [3,3,1] NONAN - 7 - ONE - 3 - OXYL (6).

A solution of sodium deuteroxide was prepared by the careful addition of sodium metal (109mg.) to a solution of dry, freshly-distilled dioxan (5ml.) and deuterium oxide (5ml.).

A small portion of this solution (0.5ml.) was added, under nitrogen, to the keto-nitroxide (6) (20mg.) and allowed to stand for 1 hour at room temperature, after which a further 0.5ml. of the basic solution was added. After 2 hours the reaction mixture was poured into ice-cold deuterium oxide (5ml.) and thoroughly extracted with pentane. The pentane extracts were combined, washed with ice-cold water, dried over sodium sulphate, and the solvent was then removed to give a reddish brown oil (6mg.). The deuterated keto nitroxide (1.2mg.) was isolated by preparative t.l.c. as a nicely crystalline compound.

Mass spectral analysis indicated a high incorporation of 2 deuterium atoms into the molecule. The e.p.r. spectrum was unchanged from that reported earlier for the non-deuterated keto-nitroxide (6).

ATTEMPTED DISPROPORTIONATION OF 2 - METHYL - 3 - (1-METHYL-1-HYDROXYLAMINOETHYL) - 5 - ISOPROPENYL CYCLOHEXANONE WITH 2 - METHYL - 2 - NITROSOPROPANE.

A freshly-prepared solution of the hydroxylamino-olefin (225mg.) in ethanol (10ml.) was added to solid 2-methyl-2-nitrosopropane dimer (92mg.) and the mixture was gently warmed on a steam bath for 5 minutes to obtain a deep-blue solution of the

monomer. The flask was then sealed under nitrogen and allowed to stand in the dark for 3 days, after which time the solution was still deep blue in colour. Analytical t.l.c. examination of the reaction mixture at this stage showed only unreacted hydroxylamino-olefin together with a trace of the corresponding nitroso-olefin (10), and no trace of 2,2,4,4,6-pentamethyl-3-azabicyclo [3,3,1] nonan-7-one-3-oxyl (6) as evidenced by t.l.c. comparison with an authentic sample.

2,2,4,4,6 - PENTAMETHYL - 3 - AZABICYCLO [3,3,1]NONAN - 7 - ONE - 3 - OXYL (6).

The general synthetic sequence developed above was used to prepare batches of the parent keto-nitroxide (6). The zinc/ammonium chloride reduction, silver oxide oxidation, and iodine cyclisation can be scaled up without difficulty to obtain a mixture of the iodo-nitroxides (740mg.) from the nitro-olefin (5) (3.0g.). The heterogeneous hydrogenolysis, however, proved to be extremely sensitive, and the serendipitous conditions which led to reproducible yields are therefore described below.

The mixture of iodo-nitroxides (740mg.) was dissolved in methanol (40ml.) containing sodium hydroxide (240mg.). 5% Palladium-charcoal catalyst (200mg.) was added and the mixture was hydrogenated at atmospheric pressure with vigorous stirring for 2.5 hours. The catalyst was removed by filtration through a glass filter paper and the methanol was concentrated to about 2-3ml. in vacuo. Water (15ml.) was added, and the aqueous solution was thoroughly extracted with ether (3x50ml.), dried over sodium sulphate, and the solvent removed. Oxidation of the hydroxylamine in ether (50ml.) with silver oxide (1g.) at room temperature for 25 minutes, followed by filtration, solvent removal, and preparative t.l.c. furnished the parent keto-nitroxide (6) (158.4mg.).

ATTEMPTED WOLFF - KISHNER[38] REDUCTION OF 2 - METHYL - 3 - (1-METHYL -1 - NITROETHYL - 5 - ISOPROPENYL CYCLOHEXANONE (5).

The nitro-olefin (5) (482mg.) was refluxed in ethanol (10ml.) with a 10 fold excess of anhydrous hydrazine (330mg.) for 22 hours. Ethanol was removed on the rotary evaporator, and the residue was taken up in ether, washed with water, dried, and the solvent removed to give the hydrazone as a clear viscous oil: $\nu_{max.}$(liquid film) = 3300, 1645, 1542, 1400, 1378, 1348 and 892cm.$^{-1}$.

The crude hydrazone in anhydrous dimethylsulphoxide (3ml.) was added *via* a syringe over a 4 hour period to a stirred solution of potassium-t-butoxide (400mg.) in dimethylsulphoxide (2ml.). The reaction mixture turned dark brown. Methylene chloride and water were added and the organic layer was extracted, washed with water, dried, and the solvent removed to give a dark-brown oil (500mg.), whose i.r. spectrum showed bands at 3380, 1644, 1535 and 890cm.$^{-1}$. No product of this reaction, whose R_f value was less than or equal to that of the starting material could be detected by analytical t.l.c.

ATTEMPTED CAGLIOTTI REACTION[39] OF 2 - METHYL - 3 - (1-METHYL-1-NITROETHYL) - 5 - ISOPROPENYL CYCLOHEXANONE (5).

A solution of the nitro-ketone (5) (478mg.) in dry methanol (5ml.) was added to a solution of tosylhydrazine (372mg.) in methanol (5ml.) and the mixture was refluxed for 24 hours. Removal of solvent gave a yellow oil (855mg.) whose i.r. spectrum displayed no carbonyl absorption. $\nu_{max.}$ (liquid film) = 3360, 1644, 1600, 1542, 1168, 1024 and 810cm.$^{-1}$.

To the crude tosylhydrazone (320mg.) in dry dioxan (15ml.) was added excess sodium borohydride (1g.). The mixture was heated in an oil bath maintained at 90°C for 8 hours, and the cooled solution

was diluted with water, acidified with dilute hydrochloric acid, and thoroughly extracted with ether. The ethereal extract was dried and the solvent removed to furnish a clear oil (180mg.) whose i.r. spectrum displayed carbonyl absorption at 1720cm.$^{-1}$.

No useful product could be isolated from the reaction by preparative t.l.c. The reaction was also repeated using methanol as solvent with similar results.

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