A THESIS

ENTITLED

# ' STUDIES IN NITROXIDE RADICAL CHEMISTRY '

SUBMITTED TO THE UNIVERSITY OF GLASGOW

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE FACULTY OF SCIENCE

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CHEMISTRY DEPARTMENT

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To Jeanette.

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Finally I should like to thank my wife and my parents for their encouragement and for their patience in typing the manuscript.

## SUMMARY

A suitable synthetic route to trimethyldecahydroquinoline nitroxide radicals is described. The key step involves double Michael addition of ammonia to a cross-conjugated dienone which was itself constructed using an aliphatic Friedel-Crafts acylation. Convenient methods of resolving both *cis* and *trans* compounds in this series were discovered and a study of the chiroptical properties of the optically active nitroxide radicals thus obtained has provided useful information on the conformation of such molecules.

Some preliminary experiments to synthesise the related tetramethyldecahydroisoquinoline nitroxides are described.

THOMSON, C. (Dr. Roberts) 1968-1971 Ph.D.

Post-Graduate Lectures Attended.

1968/1969

Newer Aspects of N.M.R. Spectroscopy

Kinetics of Organic Reaction Mechanisms

The Year in Organic Chemistry

Organic Literature Seminars

1969/1970

Organic Photochemistry

Enzymically catalysed hydrolysis of esters and amides

The Year in Organic Chemistry

1970/1971

The use of semi-empirical theories in organic chemistry

Modern methods of protein structure investigation

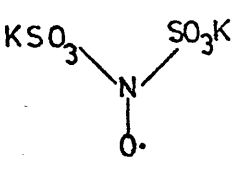
Operational research

The Year in Organic Chemistry

CONTENTS.

# INTRODUCTION.

The history of nitroxide radicals stems from the work of Fremy[1], who in 1845, prepared the inorganic salt (1). Over fifty years elapsed, however, before the first organic nitroxide, porphyrexide (2), was obtained by Piloty and Schwerin[2] in 1901 and subsequently Wieland and his co-workers[3] prepared a number of relatively stable diaryl nitroxides of the type (3, $R_1$ and $R_2$ = aryl). It was not until 1959 that Lebedev and Kazarnovskii[4] isolated the first completely aliphatic nitroxide (4) and shortly after this Hoffmann[5] described the synthesis of di-t-butyl nitroxide (3, $R_1$ and $R_2$ = t-butyl).

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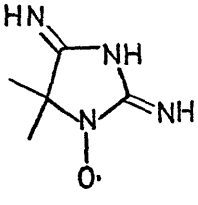


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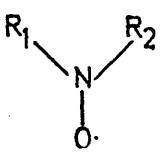


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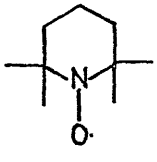
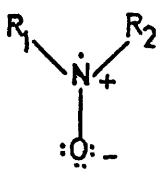



(4)

With the advent of electron paramagnetic resonance (e.p.r.) spectroscopy, intensive interest in various aspects of the chemistry of nitroxide radicals has been generated. This has culminated in a number of general synthetic methods which, in turn, have permitted the diversification of the study of nitroxide radicals into such fields as spin-labelling of bio-molecules[6], spin-trapping[7], anti-oxidant and polymerisation[8] and detailed spectroscopic analysis.

Over the last few years, several reviews[9,10,11,12] on nitroxide radicals have been published and thus it is deemed undesirable in this introduction to reiterate well-documented facts. Rather it is the intention to concentrate on the spectroscopic and physical properties of nitroxide radicals since these are more pertinent to the subject matter of this thesis. In particular, the main emphasis will be on aliphatic nitroxide radicals.

Nitroxide radicals of general formula (3) are formally quadricovalent compounds of nitrogen containing an unpaired electron. In valence-bond terms, two contributing resonance structures (5) and (6) may be written for nitroxide radicals. In (5) the unpaired electron occupies the $2p_z$ orbital of N and a pair of electrons occupies the $2p_z$ orbital of O. This places a formal positive charge on N and a unit negative charge on O. In (6) the situation is reversed, the unpaired electron occupying the $2p_z$ orbital of O while the pair of electrons is in the $2p_z$ orbital of N. There is no formal charge separation in this contributing structure. This valence-bond description explains the high dipole moment (3.14D.) which has been found experimentally for 2,2,6,6-tetramethylpiperidine-1-oxyl (4)[13].



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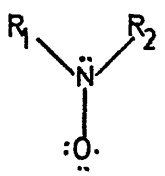
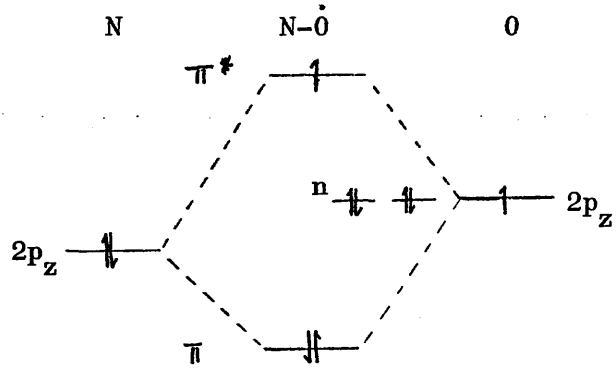


(6)

In molecular-orbital terms the bonding may be described as follows. The bonds at N are $sp^2$ hybridised. A $\sigma$ bond is formed by overlap of one of these with a p orbital on O and overlap of the $2p_z$ orbitals on N and O produces a pair of $\pi$-bonding and $\pi^*$-antibonding orbitals. Two electrons occupy the $\pi$-bonding orbital while the unpaired electron is in the $\pi^*$-antibonding orbital. Hence the following orbital-energy scheme can be drawn for the bonding in nitroxide radicals[14].

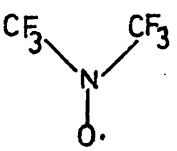



It can be seen from this diagram that there is an analogy between the electronic configuration of nitroxide radicals and the $n\rightarrow\pi^*$ excited state of carbonyl compounds. The only difference between these is that the latter has only one electron in one of the n orbitals on oxygen. This analogy does not extend to the chemical properties of these molecules since nitroxides are much poorer hydrogen abstractors than the $n\rightarrow\pi^*$ excited state of ketones. However, Keana[15] has recently shown that the $n\rightarrow\pi^*$ excited state of nitroxide radicals is an efficient hydrogen abstractor. In particular, the nitroxide (7) on photolysis in toluene solution

| Compound. | $r_{NO}(A^{o})$ | $\angle CNC$ | Angle between NO bond and CNC plane. | Reference. |
|---|---|---|---|---|
| 10* | 1.26 | 121° | 22° | 17 |
| 11* | 1.28 | 136° | assumed planar | 18 |
| 12 | 1.23 | 124° | 0 | 19 |
| 13 | 1.26 | 125° | 0 | 20 |
| 7 | 1.29 | 125° | 16° | 21 |
| 7** | 1.26 | 136° | 21° | 22 |
| 14 | 1.27 | 115° | 0 | 23 |
| 15 | 1.31 | 121° | 24° | 24 |

*Electron diffraction.

**Initially less accurate structure determination.

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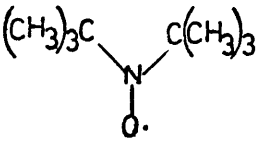


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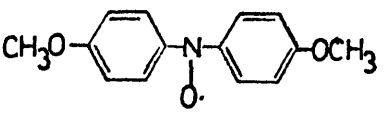


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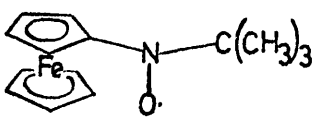


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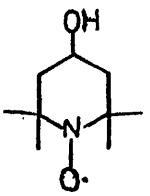


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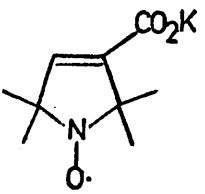


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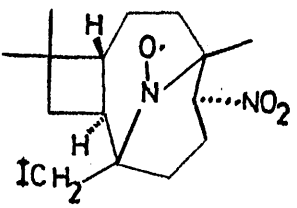
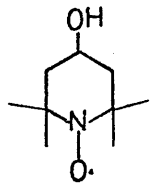


produces the compounds (8) and (9) in good yield.

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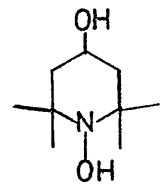


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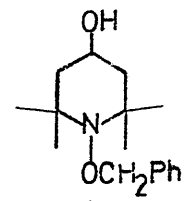



(9)

This qualitative description of the bonding in nitroxide radicals has been put on a more quantitative basis by Kikuchi[16] who has carried out LCAO-SCF-MO calculations using the CNDO/2 approximation and found that the above description is correct for the ground state of nitroxide radicals.

The structural parameters of several nitroxide radicals have now been determined by electron diffraction and X-ray diffraction techniques. Pertinent bond lengths and angles for the nitroxide moiety in these compounds are given in the accompanying table.

In the purely aliphatic nitroxide radicals the average bond length is 1.29A°, which is consistent with a three electron NO bond since the bond lengths of N-O and N=O are 1.44A° and 1.20A° respectively. Apart from di-t-butyl nitroxide (11) and the five membered ring nitroxide (14) the CNC bond angle is remarkably constant (121-125°). In (11) the bulky t-butyl groups may be causing a widening of the bond angle to reduce non-bonded interactions while in (14) the size of ring probably prevents any widening of this angle. It can be seen that the dihedral angle which the NO bond subtends with the CNC plane varies from 0° (planar) to 24° (pyramidal). The dialkyl compounds are normally pyramidal while those with an aromatic ring into which the unpaired electron is delocalised are planar.

It is not yet clear whether this grouping 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 $H_2NO$ and $(CF_3)_2NO$ is the more stable, although only slightly so, and that the rate of inversion of such molecules will be extremely fast. For most purposes it is usual to consider that the nitroxide moiety is planar.

The ultraviolet spectra[9] of di-t-alkyl nitroxides show two bands at about 230 nm ($\varepsilon$ = about 2,500) and 410-450 nm ($\varepsilon$ = 5-15). This latter band in the visible region of the spectrum is responsible for the characteristic orange/red colour of di-t-alkyl nitroxides. By considering the effect of solvent polarity on the position of these bands, Rassat and co-workers[27] have assigned the band at about 430 nm to an $n \rightarrow \pi^*$ transition and the 230 nm band to a $\pi - \pi^*$ transition.

By far the most important technique for the study of free radicals is e.p.r. spectroscopy. The e.p.r. spectra of many nitroxides, both stable and unstable, have been obtained and are now well documented[9]. The main feature of the spectra of di-t-alkyl nitroxides in solution is the presence of a 1:1:1 triplet due to coupling of the unpaired electron with the nuclear spin of nitrogen (I=1) and with a coupling constant, $a_N$, of about 14-17 gauss. The g-value is around 2.0060. Under favourable conditions, high resolution spectra of di-t-alkyl nitroxides show other couplings to the nuclei $^{15}N$ and $^{13}C$ present in natural abundance or to $\gamma$ and $\delta$ hydrogen atoms.

Increasing use is now being made of nuclear magnetic resonance (n.m.r.)spectroscopy in the study of free radicals. The presence of an unpaired electron has two main effects on the n.m.r. spectrum of a compound.

(a) The lines are broadened due to a decrease in the spin-lattice relaxation time.

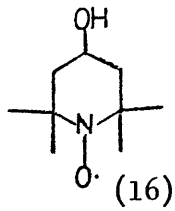
(b) The position of a line is shifted by an amount dependent on the sign and magnitude of the hyperfine coupling constant between the electron and the nucleus in question.

To obtain a well resolved spectrum, extremely concentrated solutions are required ($>3\underline{M}$ usually). A promising technique would appear to be the use of paramagnetic solvents such as di-t-butyl nitroxide (11).[28] These studies can lead to the determination of the sign and magnitude of small hyperfine coupling constants not normally obtainable from the e.p.r. spectrum, by use of the relationship;

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

where $a_i$ is the hyperfine coupling constant of the nucleus in question, $\gamma_e$ and $\gamma_N$ are the gyromagnetic ratios of the electron and the nucleus, k is Boltzmann's constant, T is the absolute temperature, $\beta$ is the Bohr magneton, and $\Delta H$ is the chemical shift of the nucleus in question relative to the same nucleus in a corresponding diamagnetic molecule. Conformational information can also be obtained from the n.m.r. spectra of radicals.[29,30] Since the nitroxide radical (16) shows two different types of methyl group in its n.m.r. spectrum it was concluded that the molecule existed

predominantly in the chair conformation (17).

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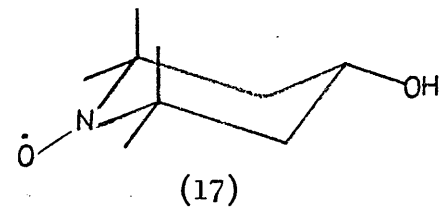


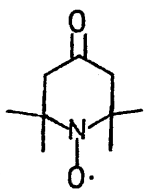

(17)

The infrared spectra [9] of nitroxide radicals usually show a band near 1350 $cm^{-1}$ due to the stretching vibration of the NO bond, but this is often masked by other absorptions such as the bending modes of gem-dimethyl groupings which usually appear at about 1360 and 1380 $cm^{-1}$. This frequency, however, seems reasonable for a three electron bond since the stretching frequency of the NO single bond in amine oxides occurs at about 960 $cm^{-1}$ whilst that of NO double bonds in monomeric nitroso compounds occurs at about 1600 $cm^{-1}$.

Little has been published on the mass spectra of nitroxide radicals. The distinguishing features of the published spectra [31] are the presence of peaks at P+1, much more intense than can be attributed to isotope abundances, and at P-14. The former arises by abstraction of a hydrogen atom from water in the spectrometer and the latter by loss of a methyl radical from the P+1 ion. Few other compounds show this P-14 peak and hence this is extremely characteristic of nitroxide radicals.

Other techniques which have been used to study nitroxides are dipole moment measurements [32] and optical rotatory dispersion (ORD)/ circular dichroism (CD)[33]. The former technique has been used to determine the preferred conformation of the keto-nitroxide (18). By comparing the experimental value with those calculated for the

chair (19), twist (20) and boat (21) forms it was concluded that this molecule exists in the twist conformation (20). CD spectra of the t-butyl camphenyl nitroxide (22) were recorded but little information was obtained from them and the value of this technique remains to be assessed.



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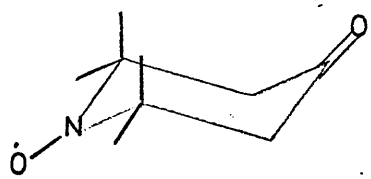

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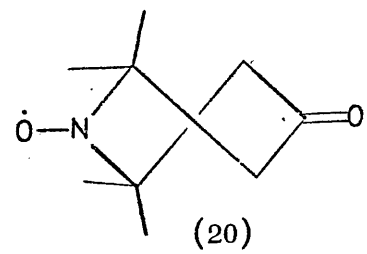

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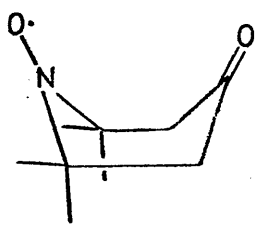

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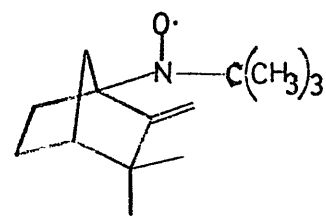
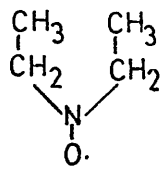


(22)

Since this thesis concentrates on stable di-t-alkyl nitroxides it is perhaps pertinent to mention what is known about the stability of aliphatic nitroxides. In general stable aliphatic nitroxides are only obtained if the two carbon atoms flanking the nitrogen atom are fully substituted, (e.g. 18,22). When β- hydrogen atoms are present as in (23) a bimolecular decomposition occurs to yield the corresponding nitrone (24) and hydroxylamine (25). Recent evidence [34] suggests that this may occur via the dimer (26).

Exceptions to this occur when the β-hydrogen is extremely hindered as in (27)[35] or at a bridgehead position as in (28)[36]. In (27) approach of a second molecule of nitroxide to abstract the β-hydrogen is prevented whilst in (28) the energy required to form a bridgehead nitrone is prohibitive.



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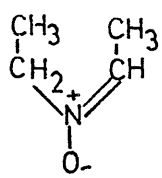

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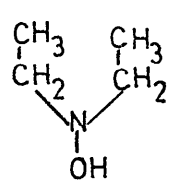

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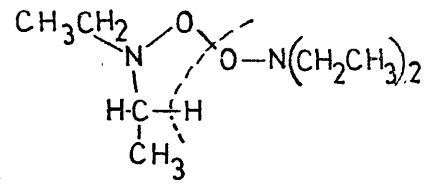

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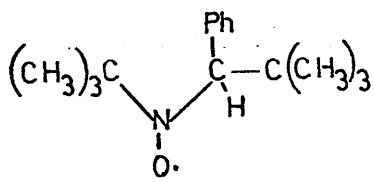

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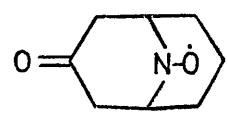
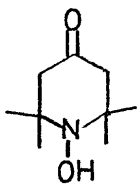


(28)

However, even di-t-alkyl nitroxides are not always stable and it has been shown[37] that the nitroxide (18) decomposes in refluxing benzene to yield the hydroxylamine (29) and phorone (30) although this may be a special case since the carbonyl group activates the hydrogen atom which is abstracted and the initial product (31) is a conjugated ketone. It also appears that di-t-alkyl nitroxides with reasonably long side chains such as (32) are unstable although complete details of the mode of decomposition have not yet been disclosed[38].



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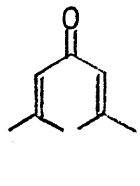

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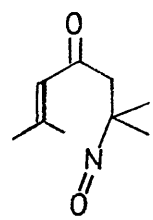

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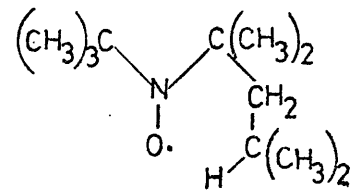

(32)

There is much work yet to be done to delineate the full range of structure, stability and chemistry of nitroxide radicals. The work described in this thesis is an attempt to help broaden our knowledge of nitroxide chemistry in the following ways.

(a) To extend the scope of existing synthetic methods to the production of new types of nitroxide radical.

(b) To examine the chiroptical properties of nitroxides and evaluate the utility of ORD and CD in studying these compounds.

(c) To gain information in the stereochemistry of cyclic nitroxides.

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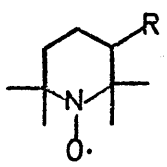
# DISCUSSION.

## 1. Synthetic studies leading to decahydroquinoline nitroxides.

In considering suitable types of nitroxide radical for an optical rotatory dispersion (ORD) and circular dichroism (CD) study, the most obvious candidates were of the monocyclic (1), bicyclic (2) and (3), and spiro (4) series. It was felt that ring inversion in the monocyclic system (1) would complicate interpretation of the spectra while the spiro system (4) would be associated with the problems of substituents in front octants. Since much information on ORD and CD has come from studies in the decalone series[1], e.g. 1-decalone (5) and 2-decalone (6), especially in the rigid trans-fused compounds, it was decided that the most suitable types of molecule were of the trimethyldecahydroquinoline (2) and tetramethyldecahydroisoquinoline (3) series.

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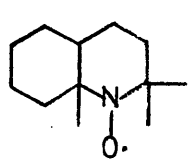


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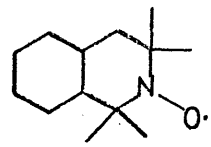


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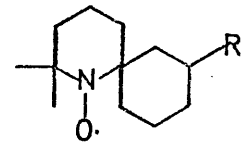


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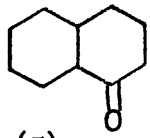


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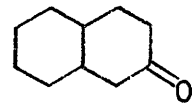
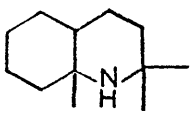



(6)

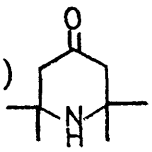
It was early recognised that a number of difficulties lay ahead on a project of this kind. There were no known compounds of either type reported in the literature and this necessitated the

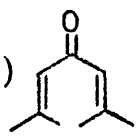
development of suitable synthetic routes to these molecules. Each of these compounds can exist in cis and trans forms which could create difficulties in separation and identification of isomers. The resolution of a compound has long been recognised to be an arduous task and once achieved creates the problem of determining the optical purity and absolute configuration of the chiral molecule obtained.

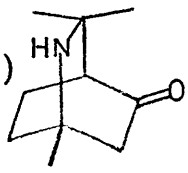
With these reservations in mind several possible synthetic routes to the decahydroquinoline nitroxide (2) were considered, one of which was put successfully into practice. Some approaches to the isoquinoline-type nitroxide (3) are described later in this thesis. Since most nitroxides are prepared by oxidation of the corresponding amine the obvious simplifying assumption is to attempt synthesis of the corresponding amine (7)

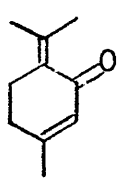
(7) 

The main difficulty in such a synthesis is production of the required amine flanked by two fully substituted carbon atoms. Consideration of the literature indicates that the most generally useful method of creating this synthon is a double Michael addition of ammonia to a cross-conjugated dienone. This method has been used to produce triacetonamine (8) from phorone (9)[2] and the bicyclic amine (10) from piperitenone (11).[3]

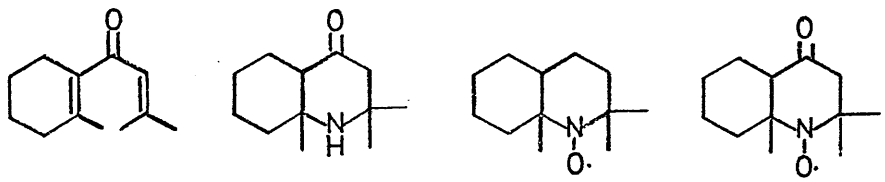
(8) 

(9) 

(10) 

(11) 

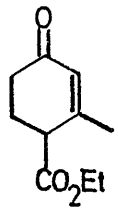
Thus it appeared that reaction of the cross-conjugated dienone (12) with ammonia would produce the bicyclic amino-ketone (13) probably as a mixture of cis and trans isomers. Hopefully these would be amenable to separation and resolution. Removal of the carbonyl group on position 4 would produce the amine (7) which on oxidation would lead to the desired nitroxide (2). The presence of a carbonyl group at position 4 in compound (13) was considered advantageous since the derived keto-nitroxide (14) would provide useful additional stereochemical information by examination of the carbonyl ORD and CD behaviour. This functionality also provides a handle for preparing other derivatives of this ring system.



(12) (13) (2) (14)

Two other routes were considered of some merit although the success enjoyed by the above approach precluded any experimental work on them. However, it is considered to be of some interest to mention them. Alkylation of the readily available enone-ester (15)[4] with the amino-bromide (16) should produce the amine (17). Hydrolysis of the ester, decarboxylation and ring closure should produce the amino-ketone (18) isomeric with (13), again as a cis,trans mixture.

It was anticipated that the amino-bromide (16) might have to be protected as the amide (19) to prevent ring closure to the azetidine (20).

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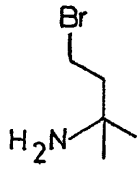


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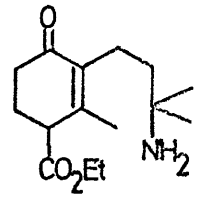


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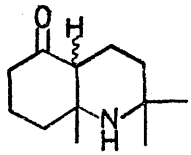


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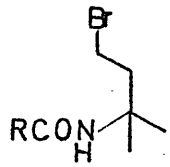


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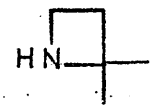
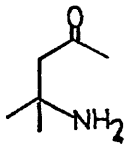



(20)

It has been shown[5] that treatment of diacetonamine (21) with acetone and calcium chloride produces triacetonamine (8). This suggested that 1-acetyl-2-methyl cyclohexene (22) might be converted to the β-amino-ketone (23) and thence by treatment with acetone and calcium chloride to the amino-ketone mixture (13).

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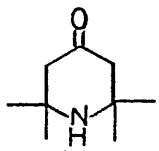


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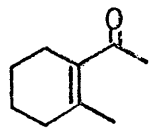


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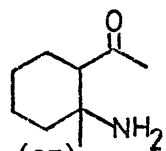


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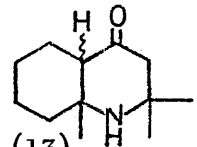
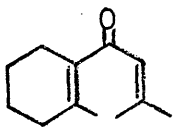



(13)

As mentioned above the successful route proceeded through the key cross-conjugated dienone (12) and will now be discussed. A plausible method for constructing this key intermediate involved Friedel-Crafts acylation of 1-methylcyclohexene (24) with β,β-dimethylacryloyl chloride (25). A study of the literature[6] on this type

of reaction showed that reaction of isobutene with (25) in the presence of stannic chloride produces phorone (9) in 48% yield[7]. This is also the standard method for preparing 1-acetyl-2-methylcyclohexene (22) from 1-methylcyclohexene (24).[8]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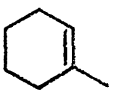
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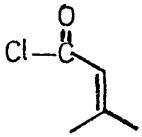

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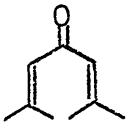
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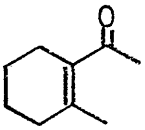
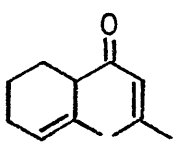
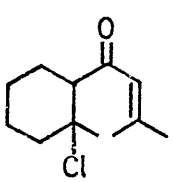

(22)

Accordingly, 1-methylcyclohexene (24) was prepared from cyclohexanone by reaction with methylmagnesium iodide to form 1-methylcyclohexanol followed by dehydration by distillation from anhydrous aluminium sulphate. $\beta,\beta$-Dimethylacryloyl chloride (24) was prepared from the corresponding acid by treatment with thionyl chloride.

Condensation of 1-methylcyclohexene with $\beta,\beta$-dimethylacryloyl chloride was carried out under the catalytic influence of stannic chloride by the method of Colonge and Dumont.[7]

The product composition varied from run to run, but usually contained little or no cross-conjugated dienone (12). The major product was the corresponding $\beta,\gamma$-unsaturated dienone (26) accompanied by smaller amounts of the $\beta$-chloro-enone (27) and a much less volatile product which was probably 1-chloro-1-methylcyclohexane. The latter arises simply by addition of hydrogen chloride, which is formed in the reaction, across the double bond of 1-methylcyclohexene.

(26) 



(27)

It was thought that elimination of hydrogen chloride from (27) followed by isomerisation of the non-conjugated double bond of (26) would produce the required dienone (12). To this end, the effect of a number of acids and bases on the Friedel-Crafts product was studied using analytical gas liquid chromatography (g.l.c.) to monitor the reaction (it had been found that (12), (26) and (27) were completely separated on a 5% QF-1 column at 100°C). These studies showed that refluxing the crude product in diethylaniline solution caused elimination of hydrogen chloride from (27) and partial isomerisation of the non-conjugated dienone (26). The mixture of dienones thus produced had a ratio of cross-conjugated to $\beta,\gamma$-unsaturated dienone of 1.8 : 1. This ratio could be raised to 2.5-3 : 1 by refluxing the mixture with p-toluenesulphonic acid in benzene.

The three compounds (12),(26) and (27) could be separated and purified by careful preparative thin layer chromatography (t.l.c.) and each gave analytical and spectral data commensurate with the assigned structures. However, on a preparative scale it was decided to carry on the synthesis using the mixture of dienones produced by treating the crude product successively with diethylaniline and p-toluenesulphonic acid in benzene.

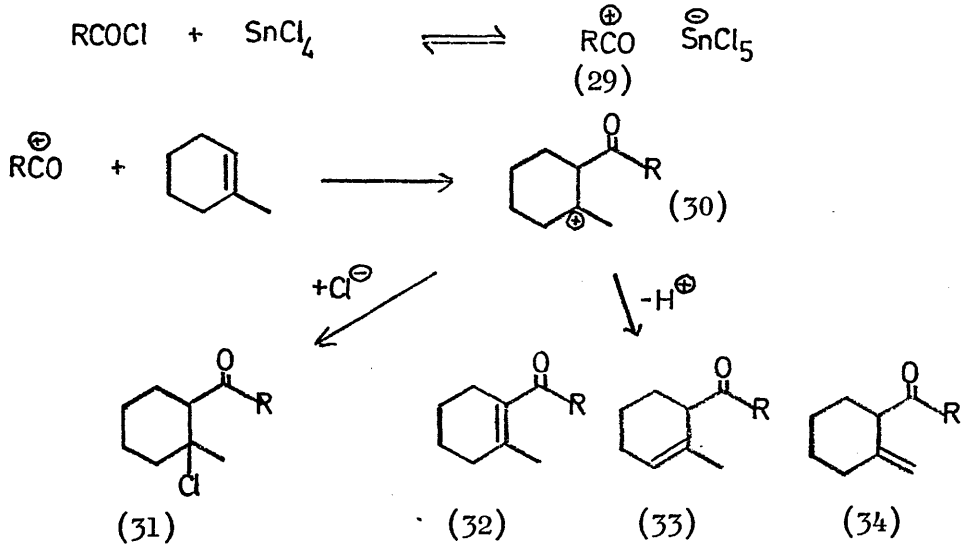
The production of substantial amounts of $\beta,\gamma$-unsaturated ketone in this reaction is not without precedent. Deno and Chafetz[8a] for instance, reacted 1-methylcyclohexene (24) with acetic anhydride in the presence of zinc chloride and obtained exclusively the

$\beta,\gamma$-unsaturated isomer (28).

(24) (28)

The first step in these reactions is undoubtedly reaction of the acid chloride with the Lewis acid to form an acyl cation (29, see Scheme I.). This cation then reacts with the olefin according to Markownikov's rule to yield the carbonium ion (30). This ion can then capture a chloride ion to form (31) or lose a proton to form the enones (32), (33) and (34), although often none of the latter is observed.

Scheme I.



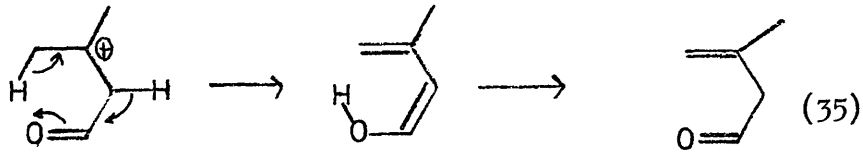

Three proposals have been made to account for the large proportion of $\beta,\gamma$-unsaturated isomer (33) found in some of these reactions.

(a)A cyclic transition state is involved in which the carbonyl oxygen abstracts the $\gamma$-proton and forms the enol of the $\beta,\gamma$-

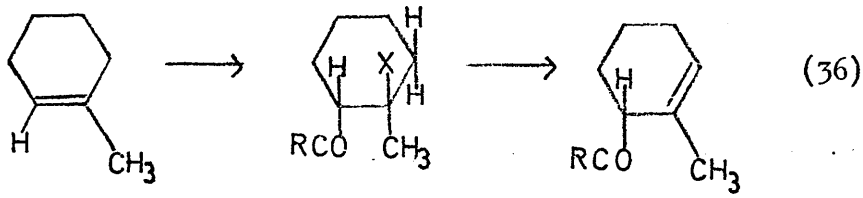
unsaturated ketone (35)[9].

(b)According to Taft's principle[10] the least acidic proton is eliminated and this is one of the γ protons.

(c)A trans addition followed by a trans elimination might occur (36).[11]

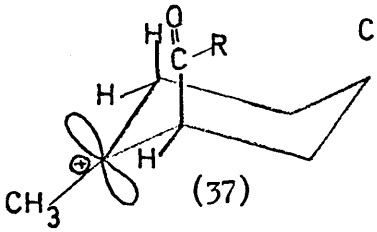


(35)

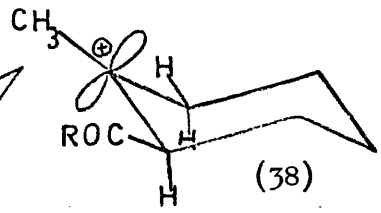


(36)

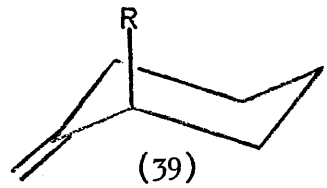
Another contributing factor is that approach of the acyl cation to the olefin must occur from an axial direction thus generating the carbonium ion in conformation (37). This conformation is probably favoured over (38) since in the latter the acyl and methyl groups are ecliped. This is similar to $A^{1,3}$ strain as proposed by Johnson[12] to explain the preferred conformation of 2-alkyl-1-methylenecyclohexanes which is (39).



(37)



(38)



(39)

In (37) only the axial γ-hydrogen is suitably oriented, with respect to the vacant p-orbital, for elimination and this is also the only one accessible to the carbonyl oxygen. The two equatorial

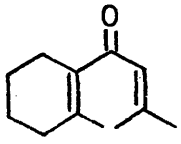
hydrogens adjacent to the carbonium ion are at right angles to the vacant p-orbital and hence are unsuited for elimination.

The fact that there is still as much as 25% of the $\beta,\gamma$-unsaturated dienone in the mixture after equilibration is also worthy of comment. It is thought that the cross-conjugated dienone is not substantially more stable than the $\beta,\gamma$ -unsaturated isomer for the following reasons.

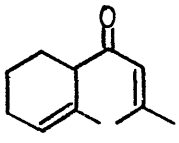
(a)Cross conjugation does not lead to such a large decrease in the electronic energy of a system as does linear conjugation.[13]

(b)The two bulky substituents on the tetrasubstituted double bond of (12) have a reasonably large steric interference. This effect has been used by Braude et.al.[14] to rationalise the fact that the extinction coefficients for the series of enones (40, R=H,Me,$Bu^n$) are 12,500, 6,500 and 4,000 respectively,indicating steric inhibition of resonance. There is less interference in the $\beta,\gamma$-unsaturated isomer (26) which will probably exist in conformation (41).[12]

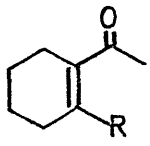
Some experimental evidence for this comes from the fact that (12) and (26) have very similar ultraviolet spectra ($\lambda$max.248 nm, $\varepsilon$=8,400 and $\lambda$max. 242 nm, $\varepsilon$ = 8,600 respectively).



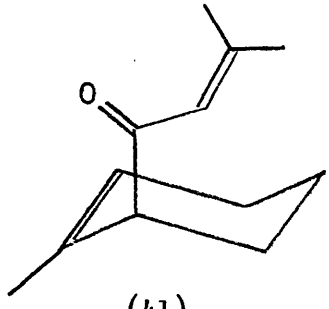

(12)




(26)

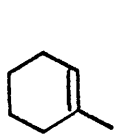



(40)

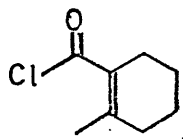



(41)

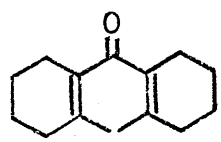
These results are in contrast to those of Kurland[15] who treated 1-methylcyclohexene (24) with the acid chloride (42) in the presence of stannic chloride, followed by treatment with methanolic potassium hydroxide. The product (43) thus obtained showed no trace of $\beta,\gamma$-unsaturated isomer. This discrepancy is difficult to explain even although different reagent quantities and base were used.



(24)

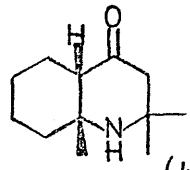


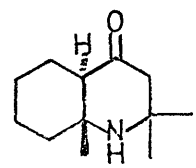

(42)



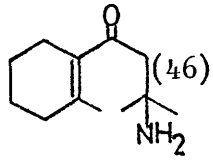

(43)

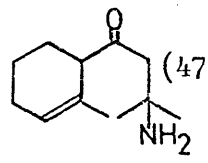
The mixture of dienones (12) and (26) was used directly for the next stage. Treatment of this mixture with concentrated aqueous ammonia solution for three days produced a complex mixture of basic and neutral material. The basic material was separated, by acid extraction, from the neutral material which proved to be largely unreacted dienone mixture. The basic material was then separated by preparative t.l.c. into two main bands. The less polar component had spectral data consistent with it being a mixture of the cis and trans bicyclic amino ketones (44) and (45). In addition, it showed two spots on t.l.c. and two peaks on g.l.c.

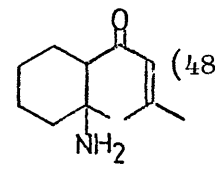

(44)

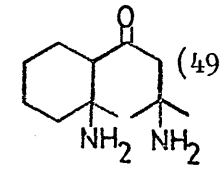

(45)

The more polar material showed peaks in its infrared spectrum at 3,450 (N-H stretch), 1705 (C=O stretch), 1680 (conjugated C=O stretch) and 1600 $cm^{-1}$ (C=C stretch). It is possible that this was a mixture of some or all of the uncyclised Michael adducts (46) to (49). This seems likely since on refluxing in ethanol solution it was converted to the dienone mixture in good yield. This proved a convenient procedure for removing this material from the reaction mixture.


(46)

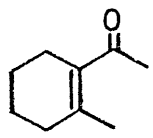

(47)


(48)

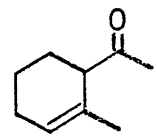

(49)

Since the yield of the desired amino-ketones was low (approximately 20%) attempts were made to increase this by using anhydrous ammonia, either neat or in organic solvents, and varying temperature. This led to no useful improvement of the yield. It was thought the recovered neutral material could be recycled to increase the yield. One cycle of isomerisation and Michael addition of ammonia was carried out giving some more amino-ketone mixture. However, careful examination of the neutral material recovered from this series of reactions showed the presence on g.l.c. of two peaks of much shorter retention times than the dienones. These could

be isolated by fractional distillation and shown to be a mixture of 1-acetyl-2-methylcyclohexene (22) and 3-acetyl-2-methylcyclohexene (28) by infrared and n.m.r. comparison with an authentic sample.[8] Hence a retro-aldol condensation must have occurred and this could be partly responsible for the low yield as well as the presence of substantial amounts of uncyclised material.



(22)

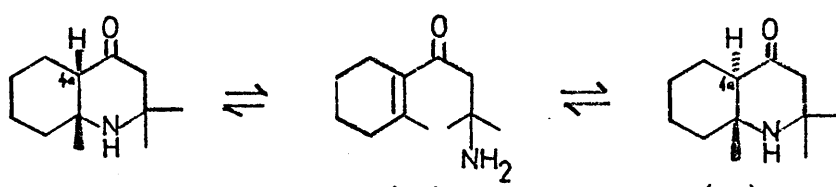


(28)

Although the cis and trans amino-ketones (44) and (45) ran as separate bands on preparative t.l.c. all attempts to separate these compounds were fruitless. After eluting the separated bands, examination by analytical t.l.c. and n.m.r. showed that each fraction contained the original mixture of amino-ketones. Two explanations of this behaviour are possible.

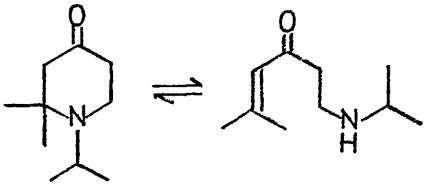
(a) Base catalysed epimerisation of the tertiary C4a position is occurring. The congested nature of the amino group would seem to make this unlikely.

(b) The cis and trans isomers are equilibrated via the open chain intermediate (50).



(44) (50) (45)

The second explanation is supported by the results of Mistryukov[16] who has shown by t.l.c. and ultraviolet analysis that the piperidone (51) is in equilibrium with the amino-enone (52). However, an attempt to observe either of these phenomena by deuterium incorporation at the α- positions was made by repeatedly scanning the n.m.r. spectrum of the mixture in the presence of deuterium oxide but this was unsuccessful.



(51) (52)

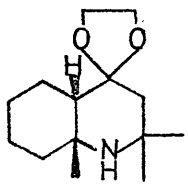
In order to circumvent this problem, two general courses of action were available.

(a) The ketonic functions must be changed into another grouping in which the retro-Michael or enolisation reactions are impossible. Suitable transformation products would be the corresponding alcohols, ketals or thioketals.

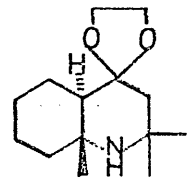
(b) The amino function must be converted into a non-basic function which is not amenable to the retro-Michael reaction. The only likely useful conversion is oxidation to the corresponding nitroxide since introduction of the normal amine protecting groups into such a hindered site is very difficult. All of these possibilities were tried with varying success.

Conversion of the mixture of amino-ketones (44) and (45) to the mixture of amino-ketals (53) and (54) was accomplished by heating with ethyl orthoformate, ethylene glycol and

*p*- toluenesulphonic acid.[17] Since this mixture was not amenable to chromatographic separation it was oxidised with m-chloroperbenzoic acid to the mixture of nitroxide-ketals (55) and (56). This mixture could be separated into its components by careful preparative t.l.c. These compounds gave mass spectra and infrared spectra compatible with the assigned structures although the less polar component was contaminated with ketonic material. Due to the low yield (28%) and difficulties in purification this route was not investigated further.



(53)



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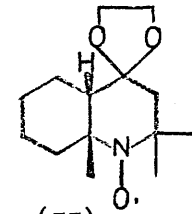
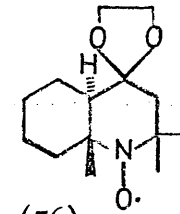
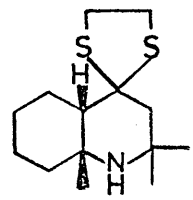


(55)



(56)

Treatment of the amino-ketone mixture with ethanedithiol and boron trifluoride etherate yielded a mixture of the thioketals (57) and (58) in good yield. Careful t.l.c. on basic silica gel separated this mixture into its components.



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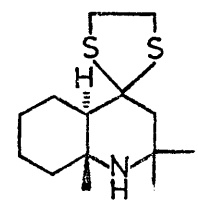
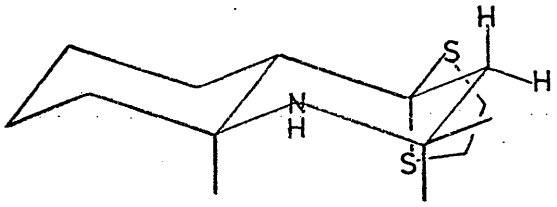


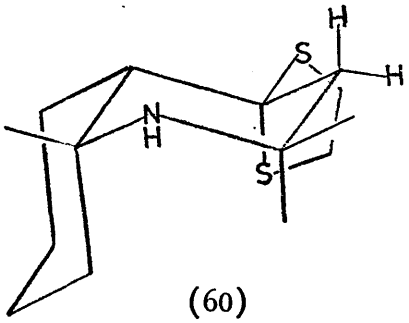
(58)

These two compounds gave analytical and spectral data fully consistent with structures (57) and (58). In its n.m.r. spectrum, the more polar component showed an AB quartet, J= 14 Hz, centred on 7.81 $\tau$. This signal must be associated with the methylene group at

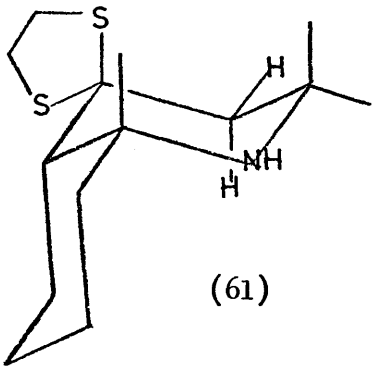
position 3 and allows us to assign the trans stereochemistry (58) to this compound. The trans compound must be in the rigid conformation (59) and the axial and equatorial protons on position 3 would be expected to show a geminal coupling constant of the order of 14 Hz.[18] The cis compound, on the other hand, is probably a mobile equilibrium of conformers (60) and (61) in which the hydrogen on position 3 would become almost equivalent and hence not show any coupling.




(59)

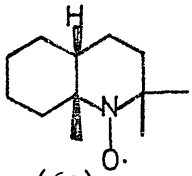



(60)




(61)

Raney nickel desulphurisation of the cis thioketal (57) yielded a product which was immediately oxidised with m-chloroperbenzoic acid to yield the cis nitroxide radical (62). This showed one spot on t.l.c., one peak on g.l.c. and gave analytical and spectral data in full accord with this structure.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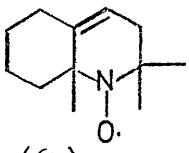
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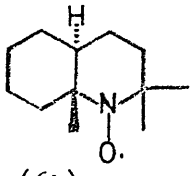
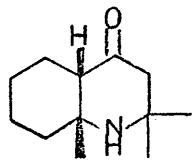

(64)

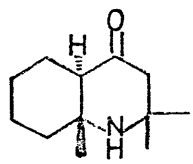
Similar treatment of the trans thioketal (58) yielded a red solid which showed one spot on t.l.c. but two peaks on g.l.c. (ratio 4 : 1). The less abundant component corresponded in retention time to either (62) or the tri-substituted olefin (63) which was prepared in an alternative fashion (vide infra) and had the same retention time as (62). It is felt that (63) is mechanistically the most likely contaminant. The major component was thought to be the trans nitroxide (64) and was obtained in extremely low yield free of the minor contaminant by chromatography on silica gel impregnated with silver nitrate. The low yields in this sequence led to its abandonment.

In both the routes investigated above, amino groups were oxidised to the corresponding nitroxide radicals because it was found that the amines had very poor chromatographic characteristics. Very polar solvent systems, often involving diethylamine had to be used. The staining of chromatoplates, especially non-destructively, was difficult and only low recovery yields were obtained. The nitroxide radicals were much less polar and staining methods were not required since on a preparative scale the nitroxide bands were clearly visible. This procedure was often used throughout this work.

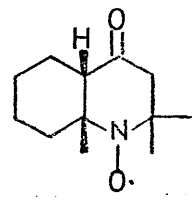
The mixture of amino-ketones (44) and (45) was oxidised using either hydrogen peroxide/sodium tungstate or m-chloroperbenzoic acid (the latter gave higher yields) to give a mixture of the nitroxide-ketones (65) and (66). This mixture could only be separated into its components with great difficulty using preparative t.l.c. Attempted separation by preparative g.l.c. failed because of thermal decomposition of the compounds.



(44)



(45)



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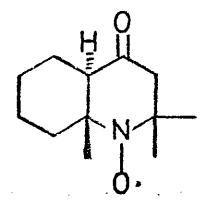
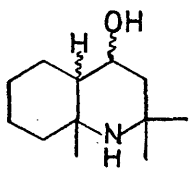
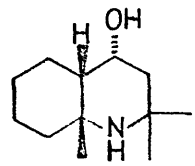


(66)

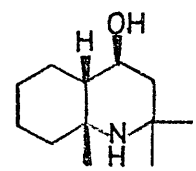
Lithium aluminium hydride reduction of the mixture of amino-ketones (44) and (45) led to a mixture of amino-alcohols (67) which showed three spots on t.l.c. and hence contained at least three of the four possible isomers. Column chromatography on alumina allowed the isolation of a small quantity of the least polar isomer whose n,m.r. spectrum showed it to be the cis, cis-isomer (68), vide infra.



(67)



(68)



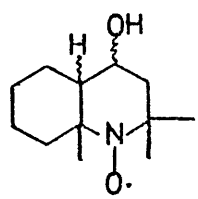
(69)

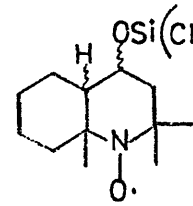
In order to increase the stereoselectivity of the reduction and hence perhaps reduce the number of stereoisomers formed, it was decided to try bulky reducing agents such as dicyclohexylborane [19] and lithium tri-t-butoxy aluminium hydride.[20] Reduction of the

amino-ketone mixture with dicyclohexylborane gave a low yield of amino-alcohol which showed only one spot on t.l.c. Since it was found that these amino-alcohols are appreciably water soluble it is thought that the bulk of the product was washed out with water which was necessitated to remove the diglyme solvent.

Lithium tri-t-butoxy aluminium hydride reduction of the amino-ketone mixture gave a product which showed two spots on t.l.c. The less polar component was isolated in low yield and from its n.m.r. spectrum was considered to be the cis, trans-isomer (69) as discussed later.

However, the chromatographic difficulties of amines, as noted above, were again proving troublesome and so the mixture of amino-alcohols (67), obtained by lithium tri-t-butoxy aluminium hydride reduction was oxidised with hydrogen peroxide/sodium tungstate to yield the mixture of nitroxide alcohols (70). This mixture showed only two spots on t.l.c. and two peaks on g.l.c. on a number of columns. However, conversion to the mixture of trimethylsilyl ethers (71) was carried out using trimethylsilyl chloride and hexamethyldisilazane in the presence of pyridine. This mixture showed three peaks on g.l.c. The same nitroxide-alcohol mixture (70) could also be obtained by reduction of the keto-nitroxide mixture (65) and (66) with lithium tri-t-butoxy aluminium hydride.

(70) 

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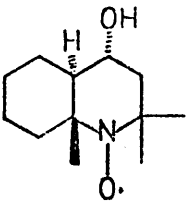


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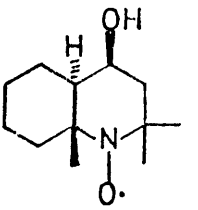


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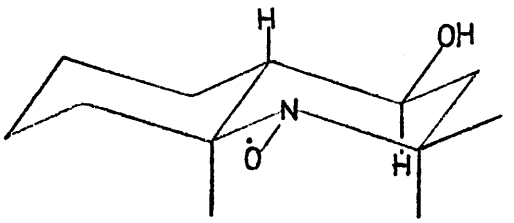


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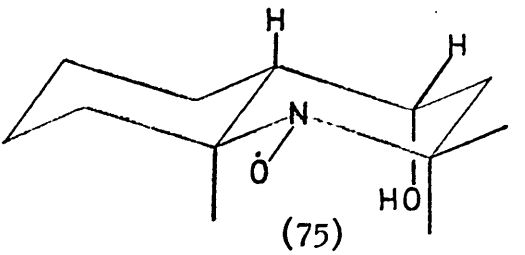


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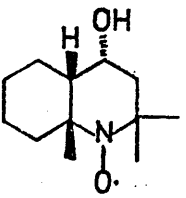
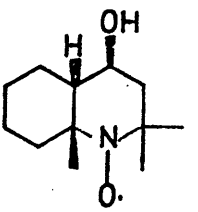



(76)

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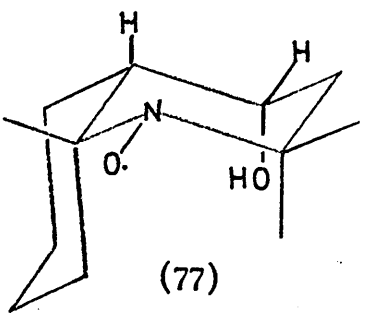


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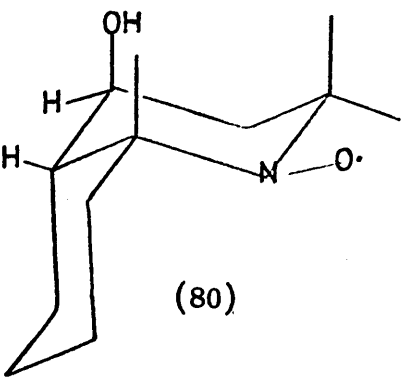


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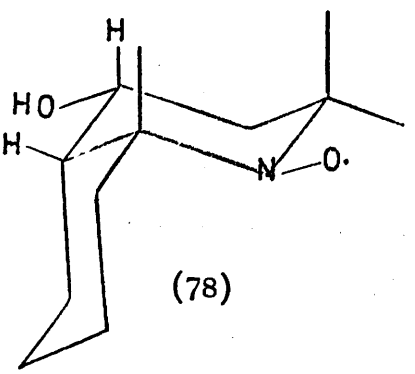
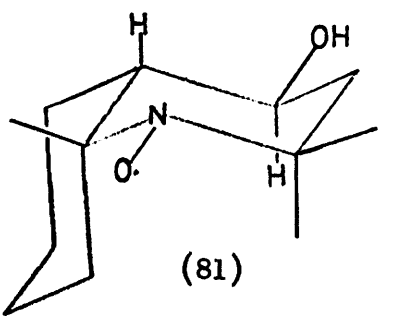



(78)




(81)

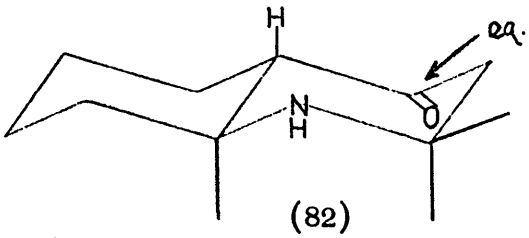
Having obtained a reasonable method of synthesising the mixture of nitroxide alcohols (70) the next problem was to separate the mixture into its constituents (probably three isomers) and determine their stereochemistry.

Preparative t.l.c. separated the mixture into two red bands. The less polar band yielded a red crystalline solid which after one crystallisation from benzene/petroleum ether had m.p. 116-118°C. The more polar band yielded a red oil which could be induced to crystallise from benzene/petroleum ether. Four crystallisations gave material with m.p. 104-106.5°C. This band was later shown to contain two compounds and hence a fortuitous fractional crystallisation had been carried out.

If we assume that both of the six-membered rings in these compounds are in chair conformations then the two possible trans-fused compounds (72) and (73) can be represented as (74) and (75). The cis-fused compound (76) can exist in conformations (77) and (78) while (79) can exist as (80) and (81). The preferred conformations of the cis compounds are expected to be the equatorial conformers (78) and (81).

At this time a paper[21] appeared in the literature which showed that selective trimethylsilylation of equatorial hydroxyl groups can be achieved using trimethylsilyldiethylamine in acetone. It was hoped that this might be of use in the present instance.

Treatment of the mixture of nitroxide-alcohols with excess trimethylsilyldiethylamine in acetone solution and monitoring the progress of the reaction by t.l.c. showed that the more polar

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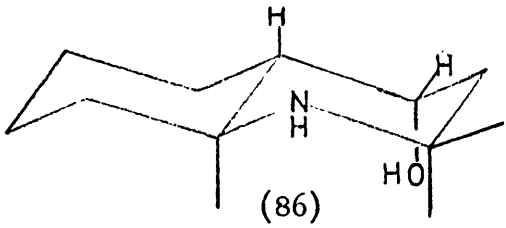


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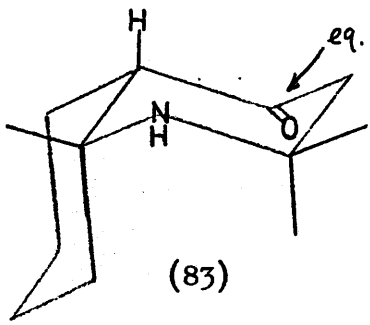
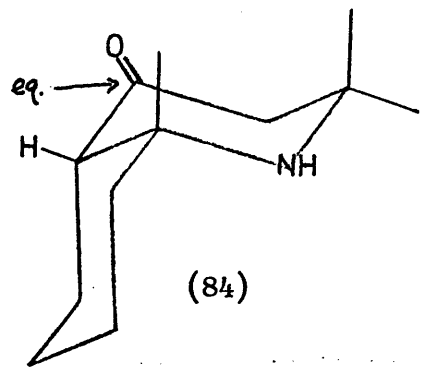



(83)

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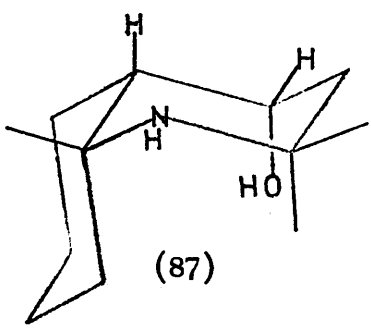


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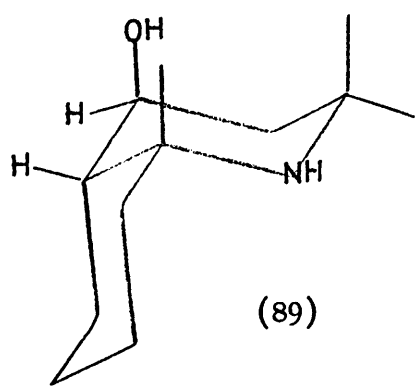
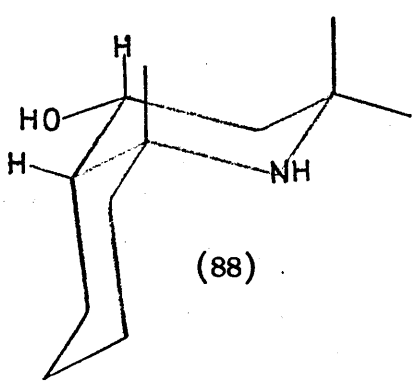
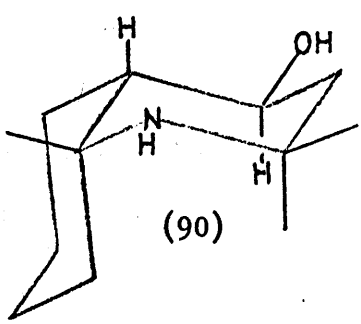



(89)




(88)



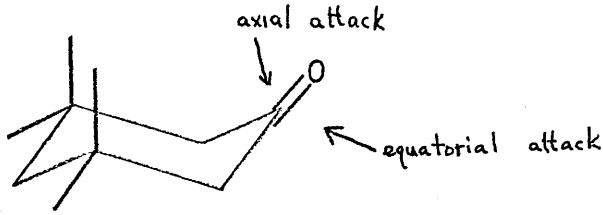

(90)

component had completely reacted in 5 hours with the production of two much less polar compounds, the trimethylsilyl ethers. The less polar alcohol was unreactive under these conditions, leading to the conclusion that this compound is probably the axial alcohol (73).

The resultant mixture of one alcohol and two trimethylsilyl ethers could be readily separated by a combination of column and thin layer chromatography. Better still, the bulk of the mixture could be separated into its components using dry-column chromatography.[22]

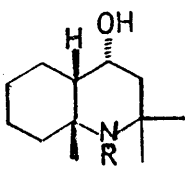
The unreactive alcohol obtained in this manner was identical by t.l.c. and m.p. comparison to the less polar alcohol obtained above (m.p.116-118°C). Each trimethylsilyl ether was hydrolysed to the corresponding nitroxide alcohol using dilute sodium hydroxide in methanol. The two alcohols had m.p. 104-106° and 81-84.5°C, the former being identical to the isomer obtained by fractional crystallisation of the more polar fraction obtained by t.l.c. In this manner it was possible to obtain three of the four possible isomers in high purity and reasonable yield. At no point was it possible to secure any evidence of the presence of the fourth isomer.

In retrospect, it is possible to rationalise the formation of only three isomers. If we consider the conformations of the bicyclic amino-ketones it is probable that the trans isomer is held rigidly in conformation (82) while the cis isomer is an equilibrium mixture of (83) and (84) which should not differ greatly in energy.

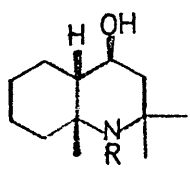



(85)

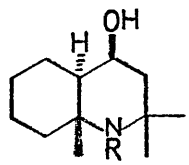
Eliel and Senda[23] have shown that in the lithium tri-t-butoxy aluminium hydride reduction of 3,3,5,5-tetra-methylcyclohexanone (85), the rate of equatorial attack of the reducing agent is greater than that of axial attack by a factor of 4,900. Since similar steric interactions are apparent in the bicyclic amino ketones it is expected that the products of reduction should be derived exclusively by equatorial attack of the hydride. Equatorial attack on (82) should produce (86) and thence nitroxide alcohol (75). Similarly, equatorial attack on conformer (83) of the cis ketone would produce (87) which can then flip into the more stable conformation (88). Equatorial attack of hydride on (84) would produce (89) and thence (90). These considerations would suggest that only the three alcohols (68), (69) and (91) would be produced by reduction of the amino-ketone mixture and then by oxidation, a mixture of the nitroxide alcohols (76), (79) and (73).




(68), R=H
(76), R=0




(69), R=H
(79), R=0

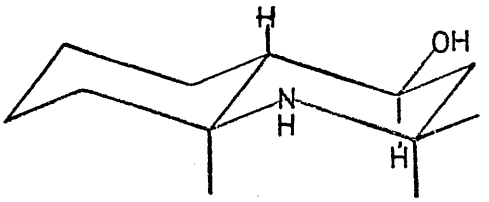



(91), R=H
(73), R=0

Each of the nitroxide alcohols was reduced to the corresponding amino-alcohol using hydrogen over a Raney nickel catalyst.[24] Reduction of the suspected axial isomer, m.p.116-118°C, produced an amino alcohol m.p. 126-127°C. The n.m.r. spectrum of this compound showed the carbinyl proton on position 4 as a multiplet centred on 5.97$\tau$ with a half-band width,[25] $W_{\frac{1}{2}}$ = 8 Hz. This implies that this proton is equatorial and hence the hydroxyl is axial, as suspected. In confirmation of this, two of the methyl groups appeared about 0.3 p.p.m. downfield from the third. This deshielding of methyl groups in a 1,3-diaxial relationship to a hydroxyl group is well established[26] and hence a confident assignment of structure (91) can be made for this compound. Thus the nitroxide-radical derived from this amino alcohol is the trans, cis - isomer (73).

Reduction of the isomer, m.p.104-106.5°C., gave rise to an amino alcohol m.p.89-91.5°C. The carbinyl proton of this compound appeared as a 1:1:2:2:1:1 sextet at 5.95 $\tau$ . As the X signal of an ABCX system, the following coupling constants were obtained, JAX= 11 Hz, JBX = 11 Hz and JCX = 4 Hz. This implies that this proton is axial and coupled diaxially with two protons and axial-equatorially with one proton.[27] Hence this compound can be assigned structure(68) The trans, trans-isomer (92) would also exhibit this type of spectrum but was considered unlikely to be produced in the reduction step.

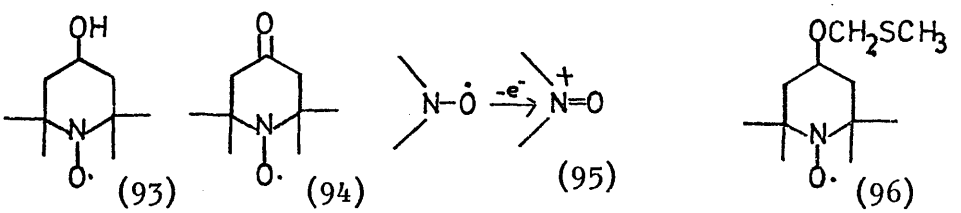
(92)



The third nitroxide alcohol, m.p. 81-84.5°C, gave an amino-alcohol, m.p. 81-83.5°C, on reduction. The carbinyl proton of this molecule appeared as a septet at 5.67$\tau$ with JAX = 11 Hz, JBX = 4 Hz and JCX = 4 Hz. This implies that this proton is axial, and coupled <u>trans</u> diaxially to one proton and axial-equatorially to two protons. Thus we can ascribe structure (69) to this compound.

The n.m.r. spectra of both the <u>cis</u> compounds also imply that the conformational equilibria (87)$\rightleftharpoons$(88) and (89)$\rightleftharpoons$(90) lie almost totally on the side of the equatorial isomers (88) and (90).

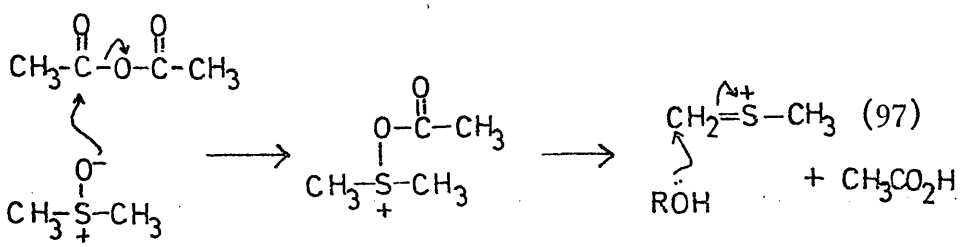
To proceed with the synthetic studies, a method was required for the oxidation of a hydroxy-nitroxide to a keto-nitroxide. To this end model studies were carried out with the readily available nitroxide-alcohol (93)[28] since the oxidation product (94)[28] was readily available for comparison. Attempts using oxidising agents based on chromium VI such as Jones reagent or chromium trioxide-pyridine[29] led to destruction of the nitroxide radical.
Since the oxidation potential for the nitroxide to oxammonium ion (95) conversion is only of the order of 0.5 volt[30] it was felt that strong one electron oxidising agents such as transition metal oxidants were to be avoided.




(93) (94) (95) (96)

Attention was next focussed on the reagent dimethylsulphoxide/

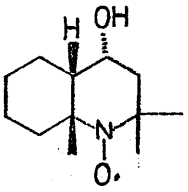
acetic anhydride.[31] This did indeed convert the alcohol (93) into a much less polar compound which had a different $R_f$ to (94). Isolation of this compound and examination of its infrared spectrum showed neither hydroxyl nor carbonyl absorption. A strong band at 1075 $cm^{-1}$ indicated that this compound might be the thioether (96). This product has often been noted[32] as a by-product in this reaction and is thought to arise by capture of the ion (97) formed from the dimethylsulphoxide and acetic anhydride as indicated.



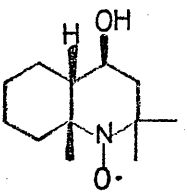

The Pfitzner-Moffatt reagent[33] (dimethylsulphoxide/dicyclohexylcarbodiimide/pyridinium trifluoroacetate) was therefore tried next. This reagent oxidised (93) to (94) as was shown by t.l.c. and infrared comparison with an authentic sample of (94).

Using this method, both the suspected cis-nitroxide alcohols (76) and (79) were oxidised to the same keto-nitroxide (65) as evidenced by t.l.c., g.l.c., and infrared comparison of the products. This serves as a final proof of structure for these alcohols.

The trans-nitroxide alcohol (73) was oxidised by this method to yield the trans-keto-nitroxide (66). Both ketones (65) and (66) gave analytical and spectral data in full accord with the assigned structures.



(76)



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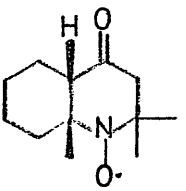

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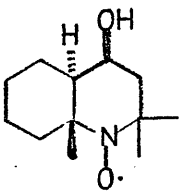

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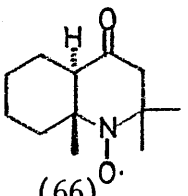
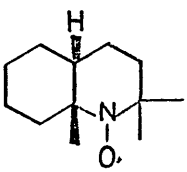
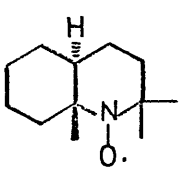


(66)

Having developed a reasonable synthetic route to the decahydroquinoline nitroxides shown above, the one remaining problem was to find a suitable method of removing the oxygen function at position 4 in these molecules to produce the parent unsubstituted nitroxides (62) and (64).



(62)



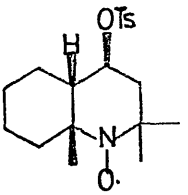
(64)

Any method of effecting this transformation must not involve epimerisation at the tertiary 4a position nor must it involve destruction of the nitroxide radical.

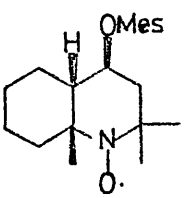
A promising method seemed to be sodium borohydride reduction of a tosylhydrazone [34] of one of the ketones. This method has been

shown not to involve epimerisation of the centres adjacent to the carbonyl group. However, when this method was applied to the trans-nitroxide ketone (66), no trace of the desired product was seen on t.l.c. analysis of the product.

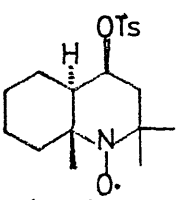
The next approach was conversion of a nitroxide alcohol to a tosylate or mesylate followed by hydride reduction.[35] The cis,trans-alcohol (79) was readily converted to the tosylate (98) and the mesylate (99) under the usual conditions whereas the trans, cis-isomer (73) was unreactive under these conditions. However, the trans, cis-tosylate (100) could be obtained by prior conversion of the alcohol (73) to the lithium alkoxide (101) followed by addition of p-toluenesulphonyl chloride.[36]



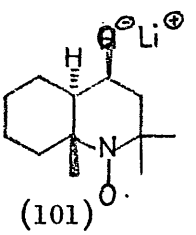
(98)



(99)



(100)

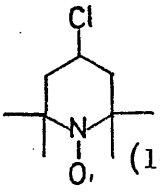


(101)

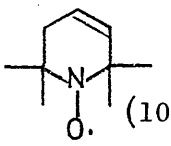
Attempts to reduce these compounds to the parent nitroxides produced only low yields of nitroxide containing material which was invariably contaminated with other products.

The last method was conversion of the alcohol to a halide followed by tri-n-butyltin hydride reduction.[37] To produce the required halide, model studies were performed with the monocyclic alcohol (93) since although Kosman and Piette[38] have suggested that this conversion may be brought about using triphenylphosphine in carbon tetrachloride, they did not give any examples of this as

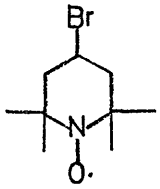
applied to nitroxides. The alcohol (93) was converted by carbon tetrachloride/triphenyl phosphine[39] into the chloride (102)[40] in low yield. The chloride was contaminated with what appeared to be the olefin (103) from which it was separated by crystallisation. Similarly the bromide (104)[40] was obtained using carbon tetrabromide/triphenylphosphine in toluene solution.



(102)

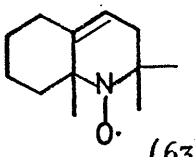


(103)

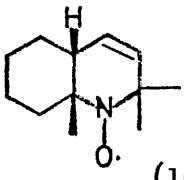


(104)

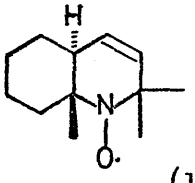
When the cis, trans-alcohol (79) was reacted with carbon tetrabromide and triphenylphosphine a product was obtained whose short retention time and mass spectrum suggested it must be an olefin formed by elimination of water from the alcohol. The cis,cis-alcohol (76) and the trans, cis-alcohol (73) gave olefinic products which were shown to be identical by t.l.c. and g.l.c. This can only be explained if this olefin is the trisubstituted isomer (63). Since the olefin obtained from the cis, trans-alcohol (79) is different from this compound it must be the disubstituted isomer (105). No evidence was obtained for the presence of (106) in the product from the trans-alcohol.



(63)

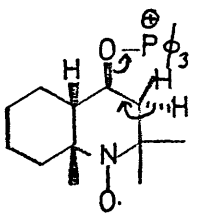


(105)

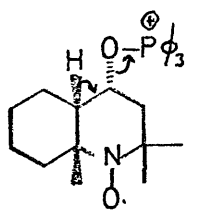


(106)

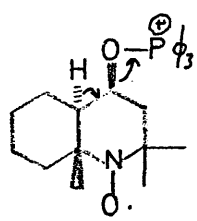
Lack of time prevented further development of this latter scheme which seems promising, since, even if the bicyclic nitroxide halides cannot be obtained, hydrogenation of the olefins should lead to the required saturated nitroxides. To explain why only one olefin, presumably the less-stable disubstituted isomer (105) is obtained from (79) it is necessary to assume that the intermediate in the reaction (107) undergoes an anti elimination rather than substitution by halide. This intermediate has only one trans hydrogen atom and elimination of this leads to the disubstituted isomer (105)



(107)



(108)



(109)

The intermediates from the other isomers (108) and (109) have a trans hydrogen at the ring junction and elimination of this leads to the trisubstituted isomer (63) in both cases.

## EXPERIMENTAL.

All melting points were recorded on a Kofler hot-stage and are uncorrected.

Infrared spectra were recorded on Perkin-Elmer 257 or Unicam S.P.200 instruments. Ultraviolet spectra were recorded on a Unicam S.P.800 instrument using either ethanol or methanol as solvent. Nuclear magnetic resonance (n.m.r.) spectra were recorded on Varian T-60 or Varian HA-100 spectrometers using tetramethylsilane as internal standard and deuterochloroform as solvent unless otherwise stated. Electron paramagnetic resonance spectra were recorded on a Decca X 3 instrument, operating in the X-band region at a frequency of 9270 MHz. Mass spectra were recorded on an AEI MS 12 instrument.

Gas liquid chromatography (g.l.c.) was performed on Pye Argon instruments using 4 feet packed columns and argon as carrier gas. Thin layer chromatography (t.l.c.) was carried out using Kieselgel silica while column chromatography was carried out with Woelm alumina. Petroleum ether refers to the fraction boiling in the range 60-80$^{o}$C.

1-Methylcyclohexanol.

This was prepared from cyclohexanone and methylmagnesium iodide by the method of Signaigo and Cramer.[41]

b.p. 54-57°C/10 mm. (lit.[41] 53-54°C/7 mm.)

1-Methylcyclohexene (24).

This was prepared by dehydration of 1-methylcyclohexanol by distillation from anhydrous aluminium sulphate.

b.p. 109-112°C. (lit.[41] 109-110°C)

β,β-Dimethylacryloyl chloride (25).

This was prepared from β,β-dimethylacrylic acid and thionyl chloride in the usual manner.

b.p. 52-54°C/17 mm.

1-Acetyl-2-methylcyclohexene (22).

This was prepared from 1-methylcyclohexene and acetyl chloride under the catalytic influence of stannic chloride.[8]

b.p. 90-95°C/17 mm. (lit.[8] 95-100°C/23 mm.).

1-(β,β-dimethylacryloyl)-2-methylcyclohexene (12).

To a stirred solution of 1 - methylcyclohexene (2.39 g.) and β,β-dimethylacryloyl chloride (2.15 g.) cooled in an ice-bath, was added dropwise stannic chloride (0.1 ml., 0.23 g.). The mixture was stirred at ambient temperature for 3 hours and then hydrolysed by pouring into 3N hydrochloric acid (10 ml.). The resultant mixture was extracted thoroughly with ether and

the organic extracts washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution and brine. After drying over magnesium sulphate the solvent was removed to yield a brown oil (3.3 g.) which was distilled yielding two main fractions.

Fraction 1 : b.p. 35-40°C/14 mm. - 0.76 g.

Fraction 2 : b.p. 118-128°C/14 mm. - 1.40 g.

Fraction 1 showed no infrared absorption in the hydroxyl or carbonyl regions and its simple n.m.r. spectrum, $\tau$ 7.8-8.6 (br) and 8.43 (s) suggested that it was 1-chloro-1-methylcyclohexane.

Fraction 2 showed two peaks on g.l.c. (Retention times 11.3 and 21.3 minutes on 5% QF-1 at 100°C and gas flow rate 70 ml.min.$^{-1}$), which corresponded to 3-($\beta$,$\beta$-dimethylacryloyl)-2-methylcyclohexene (26) and 1-chloro-2-($\beta$,$\beta$-dimethylacryloyl)-1-methylcyclohexane (27).

In another run a fraction was obtained which contained, in addition to the above two components, 1-($\beta$,$\beta$-dimethylacryloyl)-2-methylcyclohexene (12) (Retention time 18.6 minutes under the above conditions). This mixture was separated into its components by preparative t.l.c. developing three times with ethyl acetate/petroleum ether (1:49).

Least polar component : 1-chloro-2-($\beta$,$\beta$-dimethylacryloyl)-1-methylcyclohexane (27). $\nu$ max.(film) 1680 (s) and 1620 (vs) cm$^{-1}$, $\tau$ 3.84 (1H,m), 6.96 (1H,m), 7.86 (3H,d,J=1Hz), 8.10 (3H,d,J=1Hz), 8.36 (3H,s), 7.8-8.7 (8H,m).

Found : C, 67.20 ; H , 8.89 %

$C_{12}H_{19}OCl$ requires: C, 67.16 ; H, 8.86 %

Middle Component : 3- ($\beta,\beta$-dimethylacryloyl)-2-methylcyclohexene (26). $\nu$ max. ($CHCl_3$) 1682 (s) and 1617 (vs) $cm^{-1}$,

$\tau$ 3.87 (1H, m), 4.37 (1H,m) , 6.95 (1 H,m), 7.82 (3H,d, J = 1Hz), 8.08 (3 H,d, J = 1Hz), 8.37 (3H,m). 7.7-8.6 (6H,m).

$\lambda$ max. (ethanol) 242 nm. ($\varepsilon$ = 8,600).

Found : C, 80.57 ; H, 10.16%

$C_{12}H_{18}O$ requires : C, 80.85 ; H, 10.18%

Most polar component : 1-($\beta,\beta$ -dimethylacryloyl)-2-methyl cyclohexene (12) $\nu$ max. ($CHCl_3$) 1664 (s) and 1610 (vs) $cm^{-1}$,

$\tau$ 3.90 (1H,m), 7.90 (3H, d, J = 1Hz), 8.14 (3H, d, J= 1Hz), 7.7-8.5 (11H, m).

$\lambda$ max. (ethanol) 248 nm. ($\varepsilon$ = 8,400).

Found : C, 80.72 ; H , 10.09 %

$C_{12}H_{18}O$ requires : C, 80.85 ; H, 10.18 %

In order to maximise the yield of the desired cross-conjugated dienone, small samples of the crude Friedel-Crafts reaction product were treated with either acid or base under the conditions shown in the following table. On completion of the reaction, the mixtures were dissolved in ether, extracted successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, brine and dried over magnesium sulphate. The solvent was removed and a sample of the product (2-5 mg.)

was dissolved in ether (1 ml.) for analytical g.l.c. examination. The relative retention times were β,γunsaturated dienone 1.00, cross conjugated dienone 1.66 and β-chloroenone 1.92 using a 5%QF-1 column at a temperature of 100°C and gas flow rates of about 45 ml.min$^{-1}$. The product compositions are shown in the following table. This shows that the yield of the desired cross-conjugated dienone is maximised if the crude Friedel-Crafts product is treated successively with refluxing diethylaniline and then p - toluenesulphonic acid in refluxing benzene.

In a typical run the crude reaction product (95 g.) was refluxed in diethylaniline (100 ml.) for 1¼ hours, cooled and dissolved in ethyl acetate. The resultant solution was extracted with dilute hydrochloric acid, sodium bicarbonate solution and brine. After drying over magnesium sulphate and removal of the solvent a red oil was obtained which was dissolved in benzene (1.25 l.). p-Toluenesulphonic acid (10 g.) was added and the mixture refluxed for 3½ hours. After cooling and extracting with hydrochloric acid, sodium bicarbonate solution and brine, the mixture was dried over magnesium sulphate. Removal of the solvent yielded a red oil (53g.) which on distillation yielded a mixture of the cross-conjugated and β,γ unsaturated dienones in a 2.5 : 1 ratio, 37.0 g., b.p. 120-127°C/12 mm. This was used for subsequent experiments.

| Reaction Conditions | Proportion of α,β-Isomer(12) | Proportion of β,γ-Isomer(26) | Proportion of β-chloroenone(27) |
|---|---|---|---|
| Crude product | 0% * | 80% | 20% |
| Pyridine (Reflux 3 hr.) | 0% | 80% | 20% |
| Diethylaniline (Room temp. 20 hr.) | 0% | 80% | 20% |
| Diethylaniline (Reflux 1¼ hr.) | 64% | 36% | 0% |
| Hydrochloric/ acetic acid (1:5, reflux 1 hr.) | 69% ** | 28% | 3% |
| Sulphuric acid (50%, room temp. 2hr.) | 30% | 58% | 12% |
| Oxalic acid (10%, reflux 18 hr.) | 59% | 39% | 2% |
| p-Toluenesulphonic acid/benzene (Reflux 3 hr.) | 70% | 23% | 7% |

* This value varied from run to run but in most runs no cross-conjugated isomer was present at all.

** Extensive decomposition appeared to have occurred as shown by the large number of peaks of shorter retention time one of which corresponded to 1-acetyl-2-methylcyclohexene.

2,2,8a - Trimethyloctahydro-4-quinolone (13).

A mixture of the above dienones (35.0 g.), dioxane (50 ml.) and concentrated ammonia solution (150 ml., d = 0.880) was stirred vigorously in a securely stoppered flask for 3 days. The resultant mixture was acidified by addition of dilute hydrochloric acid and extracted with ether to remove any neutral material. The mixture was then basified and saturated with solid potassium carbonate. Extraction with ether, drying over magnesium sulphate and removal of the solvent yielded an orange oil (23.8 g.). This was refluxed in ethanol (250 ml.) for 4 hours and the basic material separated from the neutral as above to yield a brown oil (9.4 g.) which was a mixture of cis-and trans-2,2,8a-trimethyloctahydro-4-quinolones, (44) and (45). This material showed two closely running spots on analytical t.l.c. using petroleum ether/ethyl acetate/diethylamine (8: 2: 1) and two peaks on analytical g.l.c. (Retention times 5.8 and 8.6 minutes on 1% NGS at 100°C and carrier gas flow rate 60 ml.min.$^{-1}$) $\nu$ max.(film) 1702 cm$^{-1}$; $\tau$ 7.6-8.8 (br) 8.67 (s), 8.73 (s), 8.91 (s).

The following attempts were made to separate this mixture of isomers.

(a) Preparative t.l.c. using petroleum ether/ethyl acetate/diethylamine (25: 2: 1) as solvent system and developing twice gave two bands which stained negatively when the plate was sprayed with iodine vapour. These two bands were scraped off and eluted

with methanol/chloroform (1:9). On examination of these fractions by t.l.c. and n.m.r. it was observed that they contained the original mixture.

(b) Preparative t.l.c. on basic silica gel (prepared by using 2% potassium hydroxide to make up the plates) also gave two bands which on elution gave the same mixture by t.l.c. and n.m.r. analysis.

(c) Chromatography on sephadex LH-20 also failed to effect separation of these compounds.

The crude product from the addition of ammonia to the dienone mixture was observed to contain a much more polar component which was isolated by preparative t.l.c.

$\nu$max.(film) 3450 (m), 1705 (vs) 1680 (vs) and 1600 (s) $cm^{-1}$.

$\tau$ 4.35 (v.small peak), 7.0 - 8.6 (complex), 8.77 (sharp intense singlet). This would appear to be a mixture of the non-cyclised, mono- and di-adducts (46), (47), (48) and (49). This was confirmed by the fact that refluxing this component in ethanol solution for 4 hours regenerated the dienone mixture and this presented a useful method for removing this material from the mixture.

Lithium aluminium hydride reduction of mixture of cis and trans 2,2,8a - trimethyloctahydro-4-quinolone (44) and (45).

To a solution of lithium aluminium hydride (207 mg.) in dry tetrahydrofuran (15 ml.), cooled in an ice-bath, was added dropwise with stirring a solution of a mixture of cis- and trans- 2,2,8a-trimethyloctahydro-4-quinolone (590 mg.) in tetrahydrofuran (5 ml.). After stirring for three hours the mixture was decomposed by cautious addition of saturated sodium sulphate solution. The mixture was filtered, dried over sodium sulphate and the solvent removed to yield a yellow gummy oil (590 mg.) which was chromatographed on neutral alumina (grade III, 20 g.). Elution with benzene yielded a clear oil (30 mg.) which slowly solidified, identical by t.l.c. and n.m.r. to cis,cis - 2,2, 8a - trimethyldecahydro-4-quinolinol (68) (vide infra). Further elution with benzene and ether/benzene mixtures yielded a mixture of amino-alcohols (161 mg.) which showed three spots on analytical t.l.c.

Lithium tri-(t-butoxy)-aluminium hydride reduction of cis-and trans-2,2,8a-trimethyloctahydro-4-quinolone (44) and (45).

To a stirred solution of lithium tri-(t-butoxy)-aluminium hydride (290 mg.) in tetrahydrofuran (2 ml.), was added a mixture of the amino-ketones (86 mg.) in tetrahydrofuran (2 ml.). After stirring for four hours, the mixture was decomposed with saturated sodium sulphate solution and filtered. The solid residue was washed thoroughly with chloroform and the combined organic extracts dried over magnesium sulphate.

Removal of the solvent yielded a clear viscous oil (71 mg.). This showed two spots on t.l.c., the less polar compound being isolated by preparative t.l.c. on basic silica gel developing twice with hexane/ethanol/acetone (4:1:1). This proved to be identical to cis,trans-2,2,8a-trimethyldeca-hydro-4-quinolinol (69) (vide infra).

Dicylohexylborane reduction of cis and trans-2,2,8a-trimethyl-octahydro-4-quinolone.

To a stirred mixture of sodium borohydride (40 mg.), cyclohexene (217 mg.) and diglyme (1 ml.), cooled in an ice-bath, was added dropwise a solution of boron trifluoride etherate (150 mg.) in diglyme (1 ml.). Stirring was continued for 1½ hours at 0°C during which time a white precipitate formed. To this mixture was added dropwise a solution of cis-and trans-2,2,8a-trimethyloctahydro-4-quinolone (89 mg.) in diglyme (1 ml.). The mixture was stirred overnight at room temperature and five drops of water added. 3N Sodium hydroxide solution (0.17 ml.) and 30% hydrogen peroxide solution (0.17 ml.) were then added and the mixture stirred for a further 30 minutes. The mixture was then extracted thoroughly with ether. The basic material was extracted with dilute hydrochloric acid, which was then neutralised by addition of solid potassium carbonate and extracted with ether. After thoroughly washing this extract with brine, drying over magnesium sulphate and removal of the solvent, an oil (10 mg.)

was obtained which showed one spot on t.l.c. corresponding to the less polar component in the lithium tri-t-butoxy aluminium hydride reduction.

Oxidation of 2,2,8a-trimethyldecahydro-4-quinolinol mixture to 4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl mixture.

The mixture of amino-alcohols (67) (881 mg.) was dissolved in methanol (10 ml.). To this was added sodium tungstate (32 mg.), ethylenediamine tetraacetic acid (42 mg.), water (1 ml.) and 30% hydrogen peroxide solution (2 ml.). The mixture was stirred at room temperature for $3\frac{1}{2}$ days, filtered, most of the methanol removed under reduced pressure, saturated with potassium carbonate and thoroughly extracted with benzene. After drying over potassium carbonate, removal of the solvent yielded a red viscous oil (747 mg.). A portion of this (110 mg.) was separated into two components by preparative t.l.c. developing five times with ether/petroleum ether (1:2) and scraping off the red bands.

Less polar component: 24 mg. orange crystals, m.p. 116-118°C after one recrystallisation from benzene/petroleum ether. This was identical by m.p., t.l.c. and g.l.c. to trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (73) (vide infra).

More polar component: 56 mg. orange oil, a mixture of cis,cis- and cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl which after 4 crystallisations from benzene/petroleum ether gave pure cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (79), m.p. 104-106.5°C.

Attempts to separate these compounds by column chromatography on either neutral alumina or silica gel were unsuccessful.

Oxidation of cis-and trans-2,2,8a-trimethyloctahydro-4-quinolone to the corresponding nitroxide radicals (65) and (66).

A mixture of cis and trans- 2,2,8a-trimethyloctahydro-4-quinolone (1.1 g.) was dissolved in a mixture of water and methanol (1:1, 25 ml.). Sodium tungstate (27 mg.), the disodium salt of ethylenediamine-tetraacetic acid (38 mg.) and 30% hydrogen peroxide solution (1.5 ml.) were added. The mixture was stirred for 5 days, saturated with potassium carbonate and extracted with ether. The ethereal extracts were washed thoroughly with 1N sulphuric acid, saturated sodium bicarbonate solution and brine. Drying over magnesium sulphate and removal of the solvent yielded a red oil(415 mg. $\nu$ max.(film) 1712 $cm^{-1}$. This showed two closely running spots on t.l.c. and two peaks on g.l.c; retention times 24.8 and 34.7 minutes (1% NGS,100°C, flow rate 65 ml.$min^{-1}$.).

(b) To a stirred solution of the mixture of amino-ketones (13) (8.1 g.)in tetrahydrofuran (100 ml.) was added dropwise with ice-bath cooling a solution of m-chloroperbenzoic acid (10.0g.) in tetrahydrofuran (50 ml.). After the addition was complete (10 min.)the mixture was stirred for a further 20 minutes and then transferred to a separatory funnel. Ether was added and the solution extracted 4 times with saturated sodium bicarbonate solution (500 ml.) dried over magnesium sulphate and the solvent removed

to yield a red oil (8.2g.) which was dissolved in benzene and percolated through a short column of neutral alumina. T.l.c. showed the presence of the two keto-nitroxides and a less polar impurity, max.(film) 1770 (w) and 1712 (s) $am^{-1}$.

Separation by preparative t.l.c. of this mixture of keto-nitroxides was possible only if as little as 30 mg. of mixture was applied to a 20cm x 20cm x 0.5 mm silica gel plate, eluting three times with ether/petroleum ether (1:4) and allowing generously for overlap of the bands. That separation had been achieved was confirmed by analytical g.l.c.

An attempt was made to separate these isomers by preparative g.l.c.,but with the larger column it was necessary to raise the temperature to 160°C and extensive decomposition occurred.

Reduction of Keto-nitroxide mixture (14) to hydroxy-nitroxide mixture (70).

A solution of lithium tri-(t-butoxy)-aluminium hydride was prepared by adding dry t-butanol (20.9 g.) dropwise to a stirred solution of lithium aluminium hydride (3.98 g.) in dry tetrahydrofuran (150 ml.) over a period of 1 hour. To this was added, with ice-bath cooling, a solution of the keto-nitroxides (14) (7.1 g.) in tetrahydrofuran (50 ml.) over a period of 30 minutes and the mixture stirred at ambient temperatures for a further 3 hours. The complex was decomposed by dropwise addition of saturated sodium sulphate solution at 0°C. The resultant mixture was filtered, dried over magnesium sulphate and the

solvent removed to yield a dark red oil, (7.06 g.) $\nu$ max.(film) 3,500 $cm.^{-1}$. This showed two spots on t.l.c. and only two peaks on g.l.c. on a variety of columns. A small sample of this was converted to the trimethylsilyl ether derivatives by shaking with trimethylsilyl chloride and hexamethyldisilazane in pyridine solution for 5 minutes. Removal of the solvent, dissolution of the residue in ether, followed by filtration gave a solution suitable for g.l.c. analysis. This showed three peaks, retention times 13.3, 17.5 and 27.8 minutes, on a 5% QF.1 column at 125°C and a gas flow rate of 65 $ml.min.^{-1}$.

Selective trimethylsilylation of hydroxy-nitroxide mixture (70).

To a mixture of the hydroxy-nitroxides (70) (6 mg.) in acetone (0.1 ml.) was added two drops of trimethylsilyldiethylamine. The mixture was shaken and allowed to stand at room temperature. Aliquots were removed for analytical t.l.c. at $1\frac{1}{2}$, 3 and 5 hours. The more polar component of the alcohol mixture was removed and two much less polar components were observed due to the trimethylsilyl ethers being formed. The reaction was complete in 5 hours.

Separation of hydroxy-nitroxide mixture.

The alcohol mixture (70) (7.6 g.) was dissolved in acetone (12 ml.) and trimethylsilyldiethylamine (12 ml.) was added. The mixture was allowed to stand at room temperature for 5 hours and then all volatile materials were removed on a rotatory evaporator. The resultant red oil was chromatographed on neutral alumina

(grade III, 200g.) Fractions of 120 ml. were collected using the following solvent systems.

| | | |
|---|---|---|
| Fractions 1-8 | : | petroleum ether |
| " 9-23 | : | 2% ether/petroleum ether |
| " 24-31 | : | 5% ether/petroleum ether |
| " 32-39 | : | 10% ether/petroleum ether |
| " 40-47 | : | 25% ether/petroleum ether |
| " 48-56 | : | 50% ether/petroleum ether |
| " 57-60 | : | 75% ether/petroleum ether |

Each fraction was examined by analytical t.l.c. and combined as follows.

Fractions 2-16 : red oil (3.30 g.), a mixture of two trimethylsilyl ethers.

Fractions 17-36: red oil (1.17 g.). the more polar trimethylsilyl ether.

Fractions 50-60: orange solid (1.94 g.), the less polar nitroxide alcohol.

The trimethylsilyl ethers in fractions 2-16 were separated by preparative t.l.c. on 5 100 cm x 20 cm.. x 0.1 mm silica gel plates eluting with 12% ether/petroleum ether. Combination of pure components gave :

Less polar trimethylsilyl ether (1.31 g.) $\nu_{max}$ (film) 1250, 860 and 768 $cm^{-1}$.

More polar trimethylsilyl ether (2.82 g.) $\nu$max (film) 1250, 858 and 760 $cm^{-1}$.

Trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (73)

Recrystallisation of fractions 50-60 from benzene/petroleum ether gave pure trans,cis-4-hydroxy-2,2,8a trimethyldecahydroquinoline-1-oxyl (73) (1.69 g.); m.p.116-118°C; $\nu$ max. (Nujol) 3,440 (s) and 1,346 (m) $cm^{-1}$, $\nu$ max.($CCl_4$) at high dilution 3,630 $cm^{-1}$;

$a_N$ ($CHCl_3$) = 15.9 gauss, g = 2.0063;

$\lambda$ max. (ethanol) 440 nm ($\varepsilon$=9.9) and 243 nm ($\varepsilon$ = 2,600);

$M^+$ = 212, $C_{12}H_{22}NO_2$ = 212.3

Found : C,67.67 ; H , 10.63 ; N, 6.42 %

$C_{12}H_{22}NO_2$ requires : C, 67.89 ; H, 10.45 ; N, 6.60 %

Cis, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (76)

The less polar trimethylsilyl ether (1.31 g.), methanol (100 ml.), 4% potassium hydroxide solution (10 ml.) and benzene (25 ml.) was heated under gentle reflux for 8 hours. The methanol was removed on a rotatory evaporator and the aqueous residue thoroughly extracted with ether. The ethereal extracts were washed with brine, dried over magnesium sulphate and the solvent removed to yield a red oil (990 mg.) which slowly solidified on standing. This was pure cis, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (76); m.p. 81-84.5°C. $\nu$max.(Nujol) 3,480 $cm^{-1}$, $\nu$ max.($CCl_4$)

at high dilution 3,620 $cm^{-1}$., $a_N$ ($CHCl_3$) = 16.2 gauss, g= 2.0067.

$\lambda$ max.(ethanol) 442 nm ($\varepsilon$ = 13.6) and 243 nm ($\varepsilon$ = 1,840)

$M^+$ = 212, $C_{12}H_{22}NO_2$= 212.3

Found : C, 67.76 ; H, 10.38 ; N , 6.54 %

$C_{12}H_{22}NO_2$ requires : C, 67.89 ; H , 10.45 ; N. 6.60 %

Cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (79)

The more polar trimethylsilyl ether (2.82 g.) was hydrolysed as described above to yield a red solid (2.00 g.) which on recrystallisation from benzene/petroleum ether gave pure cis, trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl, (79), m.p. 104-106°C. $\nu$ max.(Nujol)3,450 $cm^{-1}$, $\nu$ max.($CCl_4$) at high dilution 3,630 amd 3,600 $cm^{-1}$ (no change on further dilution).

$a_N$= ($CHCl_3$) = 15.9 gauss , g = 2.0064.

$\lambda$ max. (ethanol) 432 nm ($\varepsilon$ = 14.5) and 245 nm ($\varepsilon$ = 1,800)

$M^+$ = 212 , $C_{12}H_{22}NO_2$ = 212.3

Found : C, 68.01 ; H, 10.33 ; N, 6.43 %

$C_{12}H_{22}NO_2$ requires : C, 67.89 ; H, 10.45 ; N, 6.60 %

Separation of trimethylsilyl ethers on dry-packed column.

The trimethylsilyl ethers had $R_f$ values of 0.21 and 0.29 when run on basic alumina plates (activity III) using benzene as solvent. Accordingly, some of the mixture (150 mg.) was adsorbed onto basic alumina (grade III, 0.75 g.) and placed on top of a dry-packed column of alumina (45 g.) The column was

developed with benzene, collecting 2.5 ml. fractions when red material was eluted. Combining like fractions yielded :

Less polar component : 54 mg.

Mixture : 28 mg.

More polar component : 52 mg.

Total recovery of material 89%.

Trans, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline.(91)

Trans, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (1.69 g.) was dissolved in methanol (100 ml.) and about one half-teaspoon of Raney nickel (W-2, approximately 1.5 g.)was added. The flask was attached to a hydrogenator and hydrogenation allowed to take place in the usual fashion. After $2\frac{1}{2}$ hours, hydrogen uptake had ceased (250 ml., 93% of theory). The catalyst was filtered off and washed thoroughly with methanol. Removal of the solvent yielded a slightly yellow oil (1.65 g.) which crystallised on standing. A sample of this was sublimed at 0.1 mm. (block temperature 120°C) to yield pure trans, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline (91) as a white solid, m.p.126-127°C.

$\nu$ max.(Nujol) 3,200 (br.)$cm^{-1}$, $\nu$ max.($CCl_4$) at high dilution 3,630 $cm^{-1}$.

$\tau$5.97 (1H,m,$W_{\frac{1}{2}}$ = 8 Hz),7.70 - 8.80 (13H,m)two disappear on $D_2O$ exchange, 8.54 (3H,s) 8.58 (3H,s) 8.87 (3H,s)

Found : C, 72.95 ; H , 11.65 ; N , 6.95 %

$C_{12}H_{23}NO$ requires : C, 73.04 , H , 11.75 ; N , 7.10 %

Cis, cis-4-hydroxy-2,2,8a-Trimethyldecahydroquinoline (68)

Hydrogenation of cis, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (105 mg.) over Raney nickel (W-2 ) as described above, gave pure cic,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline (68) (90 mg.),m.p. 81-83.5°C. after sublimation.

$\nu$ max.(Nujol) 3,430, 3,320 and 3,260 $bm^{-1}$,$\nu$max.($CCl_4$) at high dilution, 3,625 $cm^{-1}$.

$\tau$ 5.67 (1H, septet, JAX= 11 Hz, JBX= 6 Hz, JCX= 4 Hz), 8.0-9.0 (1 H, m) two disappear on $D_2O$ exchange, 8.77 (6H, s), 8.83 (3H, s).

Found : C , 73.10 ; H , 11.93 ; N , 6.95%

$C_{12}H_{23}NO$ requires : C , 73.04 ; H , 11.75 ; N , 7.10%

Cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline (69)

Hydrogenation of cis, trans-4-hydroxy-2,2,8a trimethyldecahydroquinoline-1-oxyl (90 mg.) over Raney nickel (W-2) as described above yielded pure cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline ( 69) as a white solid (86 mg.) m.p. 89-91.5°C after sublimation.

$\nu$ max.(Nujol) 3,100 (v.br.)$cm^{-1}$; $\nu$max. ($CCl_4$) at high dilution 3,630 and 3,605 $cm^{-1}$ unchanged on further dilution.

$\tau$ 5.95 (1H, sextet, JAX= 11 Hz, JBX = 11 Hz, JCX = 4 Hz), 7.7-8.9 (13H,m) two disappear on $D_2O$ exchange, 8.75 (3H,s) 8.82 (3H,s), 8.85 (3H,s)

Found : C , 73.14 ; H , 11.87 ; N , 6.97%

$C_{12}H_{23}NO$ requires : C , 73.04 ; H , 11.75 ; N , 7.10%

Attempted oxidations of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (93) to 2,2,6,6-tetramethyl-4-piperidone-1-oxyl (94).

(a) Using Cornforth's reagent.[29]

Chromium trioxide (200 mg.) was dissolved in water (0.2 ml.) and the resulting solution added with stirring to pyridine (2 ml.) with ice-bath cooling. To this mixture was added a solution of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (74 mg.) in pyridine (0.5 ml.). The flask was stoppered, shaken, and allowed to stand at room temperature for 4 days. The mixture was poured into water, filtered through celite and thoroughly extracted with ethyl acetate. The organic layer was filtered through celite, washed with 1N sulphuric acid, saturated sodium bicarbonate and brine. After drying over magnesium sulphate and removal of the solvent, a green oil (48 mg.) was obtained. This showed 4 spots on analytical t.l.c., none of which corresponded to starting material nor desired product.

(b) Dimethyl sulphoxide/acetic anhydride.[31]

Acetic anhydride (1 ml.) was added to a solution of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (78 mg.) in dry dimethyl sulphoxide (1.5 ml.) The mixture was allowed to stand at room temperature for 20 hours. Ethanol (3 ml.) was added and the mixture allowed to stand for 1 hour. The mixture was then dissolved in ether and washed thoroughly with brine. After drying over magnesium sulphate and removal of the solvent, a red oil (130 mg.) was obtained. The main component of this was much less polar than the desired ketone and was isolated by preparative t.l.c. as a red oil (61 mg.).

$\nu$ max.(film) 1075 $cm^{-1}$. This is thought to be the thioether (96).

(c) Pfitzner-Moffatt Oxidation.[33]

A mixture of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (43 mg.,0.25 mmole), dicyclohexylcarbodiimide (151 mg., 0.75 mmole ), pyridinium trifluoroacetate (24 mg.,0.125 mmole), dimethyl sulphoxide (1 ml.) and benzene (1 ml.) was stirred at room temperature for 18 hours, a white precipitate forming after a short time. Ethyl acetate (approximately 20 ml.) was added, the mixture filtered and transferred to a separatory funnel. The solution was washed thoroughly with water, dried over magnesium sulphate and the solvent removed to yield an orange oil (41 mg.). This was purified by preparative t.l.c. to yield an orange oil (19 mg.) which slowly crystallised. This was identical to 2,2,6,6-tetramethyl-4-piperidone-1-oxyl by t.l.c. and infrared comparison.

Trans-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl (66).

To a stirred mixture of trans, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (54 mg.,0.25 mmole), dicyclohexylcarbodiimide (150 mg.,0.25 mmole), dimethyl sulphoxide (1 ml.) benzene (1 ml.) was added pyridinium trifluoroacetate (24 mg., 0.125 mmole). A white precipitate formed within a few minutes and stirring was continued for 18 hours. The mixture was filtered to remove dicyclohexylurea, diluted with ethyl acetate and washed thoroughly with water. After drying over magnesium sulphate and removal of the solvent, a red oil (92 mg.) was obtained. Residual dicyclohexylurea was

removed by preparative t.l.c. (50% ether/petroleum ether) to yield a yellow crystalline solid which was sublimed at reduced pressure to yield trans-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl as a yellow solid, m.p. 64-67°C.

$\nu$ max. ($CCl_4$) 1722 and 1362 $cm^{-1}$.

$a_N$ ($CHCl_3$) = 15.1 gauss , g = 2,0071

$\lambda$ max. (methanol) 422 nm ($\varepsilon$ = 6.8) and 234 nm ($\varepsilon$ = 2,200)

$M^+$ = 210, $C_{12}H_{20}NO_2$ = 210.3

Found : C , 68.55 ; H , 9.31 ; N , 6.38 %

$C_{12}H_{20}NO_2$ requires: C , 68.55 ; H , 9.59 ; N , 6.66 %

Cis-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl (65)

(a) Oxidation of cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (58 mg.) by the above method yielded cis-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl (51 mg.) as a red oil after purification by t.l.c. and short-path distillation (b.p.90-95°C/0.2 mm).

$\nu$max. ($CCl_4$) 1719 and 1355 $cm^{-1}$.

$a_N$ ($CHCl_3$) = 15.2 gauss, g = 2.0064

$\lambda$max. (methanol) 430 nm ($\varepsilon$ = 6.8) and 239 nm ($\varepsilon$ = 2,050)

$M^+$ = 210, $C_{12}H_{20}NO_2$ = 210.3

Found : C , 68.51 ; H, 9.54 ; N , 6.56 %

$C_{12}H_{20}NO$ requires: C , 68.53 ; H, 9.59 ; N , 6.66 %

(b) Oxidation of cis,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl (54 mg.) by the usual procedure gave cis-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl (45 mg.), identical to that in (a) above by t.l.c.,g.l.c. and infrared comparison.

G.l.c. also showed that no epimerisation at position 4a had occurred during these oxidations.

Ethylene ketals of cis- and trans-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl (55) and (56).

A mixture of cis- and trans-2,2,8a-trimethyloctahydro-4-quinolone (721 mg.), ethyl orthoformate (3 ml.), ethylene glycol (1.5 ml.) and p-toluenesulphonic acid (900 mg.) was refluxed for $1\frac{1}{2}$ hours. After cooling, the mixture was poured into saturated sodium bicarbonate solution and ice. After thorough extraction with ether, the organic extracts were washed with sodium bicarbonate solution and brine. Drying over magnesium sulphate and removal of the solvent yielded a brown oil (1.05 g.). The infrared spectrum of this material showed a carbonyl band at 1720 $cm^{-1}$, but analytical t.l.c. (basic silica using hexane/ethanol/acetone in ratio 16:1:2) showed no trace of the starting ketones but two overlapping spots (the ketals (53) and (54)) and a much less polar spot. As this mixture did not appear amenable to chromatographic separation, it was oxidised to the corresponding nitroxide radical mixture as follows.

To a stirred solution of the above ketal-amine mixture (905 mg.) in tetrahydrofuran (10 ml.) was added dropwise a

solution of m-chloroperbenzoic acid (1.25 g.) in tetrahydrofuran (10 ml.). After stirring for 10 minutes, the mixture was diluted with ether, extracted thoroughly with sodium bicarbonate solution, dried over magnesium sulphate and the solvent removed to yield a red oil (1.01 g.) This was purified by preparative t.l.c. developing the plates twice with ether/petroleum ether (1:4) and scraping off the two red bands obtained.

More polar component : further chromatographic purification yielded a red solid (155 mg.), $\nu$ max ($CCl_4$) 1070, 1040 $cm^{-1}$, $M^+$ 254 , $C_{14}H_{24}NO_3$ requires 254.3

Less polar component : further chromatographic purification yielded a red oil (110 mg.), $\nu$ max. ($CCl_4$) 1730 (w) and 1090(s) $cm^{-1}$, $M^+$ 254. The carbonyl impurity could not be removed by further chromatography or short-path distillation.

Ethylenethioketals of cis and trans-2,2,8a-trimethyloctahydro quinolone, (57) and (58)

To a stirred solution of cis and trans-2,2,8a-trimethyloctahydro-4-quinolone (98 mg.) in ethane dithiol (0.3 ml.) was added borontrifluoride etherate (0.6 ml.). The mixture was placed under nitrogen and stirred overnight. After pouring onto water the mixture was basified with dilute sodium hydroxide solution and extracted with ether. The ethereal extracts were then washed several times with sodium hydroxide solution, brine, and dried over magnesium sulphate. Removal of the solvent yielded

a yellow oil (120 mg.) which could be separated into two components by preparative t.l.c. on basic silica.

Less polar component : cis-thioketal (57) 44 mg. oil

$\nu$ max. ($CCl_4$) 1380, 1370 $cm^{-1}$.

$\tau$ 6.50-6.90 (4H,m) , 8.58 (3H,s), 8.60(3H,s) , 8.83 (3H,s), 7.8-8.8 (12H, m) one disappears on $D_2O$ exchange.

Found : C, 62.02 ; H , 9.20 ; N , 5.01 %

$C_{14}H_{25}NS_2$ requires: C, 61.96 ; H , 9.29 ; N , 5.16 %

More polar component : trans-thioketal (58) 42 mg. yellow solid.

$\nu$ max. ($CCl_4$) 1380, 1370 $cm^{-1}$.

$\tau$ 6.57-6.97 (4H, m) , 7.81 (2H, AB quartet, JAB = 14 Hz), 8.57 (3H, s) , 8.72 (3H,s ) , 8.90 (3H,s ) 7.8-8.9 (10H , m) one disappears on $D_2O$ exchange.

Found : C, 62.21 ; H , 9.23 ; N, 5.04 %

$C_{14}H_{25}NS_2$ requires: C, 61.96 ; H , 9.29 ; N , 5.16 %

Cis-2,2,8a-trimethyldecahydroquinoline-1-oxyl.(62)

To a solution of the cis-thioketal (300 mg.) in ethanol (20 ml.) was added two heaped spatulas of Raney nickel (W-2) and the mixture stirred under nitrogen for 20 hours. The catalyst was filtered and the solvent evaporated to yield a clear oil (68 mg.) which was dissolved in tetrahydrofuran (6 ml.). To this solution was added m-chloroperbenzoic acid (160 mg.) in tetrahydrofuran (2 ml.). The mixture was stirred for 2 hours, diluted with ether and washed thoroughly with saturated sodium bi-

carbonate solution. After drying over magnesium sulphate and removal of the solvent a red oil (72 mg.) was obtained. This was purified by preparative t.l.c., developing twice with ether/petroleum ether (1:4), to yield a red oil (48 mg.) which showed one spot on t.l.c. and one peak on g.l.c. (Retention time 12 min. on 1% NGS at 100°C and gas flow rate of 35 ml.min$^{-1}$). This was cis-2,2,8a-trimethyldecahydroquinoline-1-oxyl (62).

$\nu$max. ($CCl_4$) 1355, 1340 cm$^{-1}$.

$a_N$ ($CHCl_3$) =16.0 gauss , g =2.0071

$\lambda$max. (methanol) 438 nm ($\varepsilon$=11.9) and 245 nm ($\varepsilon$=1,910).

$M^+$ = 196, $C_{12}H_{22}NO$ requires 196·3

Found : C, 73.40 ; H , 11.23 ; N , 7.05 %

$C_{12}H_{22}NO$ requires: C, 73.45 ; H , 11.30 ; N , 7.14 %

Trans-2,2,8a-trimethyldecahydroquinoline-1-oxyl (64).

To a solution of the trans-thioketal (113 mg.) in ethanol (10 ml.) was added one heaped spatula of Raney nickel (W-2) and the mixture refluxed under nitrogen for 5 hours. Filtration of the catalyst and removal of the solvent yielded a thick clear oil (44 mg.) which was dissolved in tetrahydrofuran (2.5 ml.). To this was added a solution of m-chloroperbenzoic acid (130 mg.) in tetrahydrofuran (2 ml.). the mixture stirred for 1 hour and worked up as above to yield a red oil (50 mg.) which was purified by preparative t.l.c. developing with ether/petroleum ether (1:4) to yield a red solid (24 mg.) which showed two peaks on

g.l.c. in the ratio of 1 : 4 (Retention times 12 minutes and 15 minutes, 1% NGS at 100°C and gas flow rate 35 ml.min.$^{-1}$.). The former peak corresponds in retention time to either the cis-nitroxide prepared above or, more likely, the trisubstituted olefinic nitroxide (63)

This material was dissolved in pentane and chromatographed on silica impregnated with silver nitrate (2g.) elution with 10% ether/pentane gave a red solid 2 mg.) which had a mass spectrum in accord with it being trans-2,2,8a-trimethyldecahydroquinoline-1-oxyl (64)

$M^+$ = 196, $C_{12}H_{22}NO$ requires 196.3

$a_N$ ($CHCl_3$) =16.4 gauss, g =2.0074

Attempted Caglioti reduction[34] of trans-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl(66).

A mixture of trans-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl (14 mg.)p-toluenesulphonylhydrazine (20 mg.) and methanol (2 ml.) was refluxed for 1½ hours. After cooling, sodium borohydride (20 mg.) was added and the mixture refluxed for 4 hours. The mixture was then cooled, diluted with ether, and washed successively with water, saturated sodium bicarbonate solution and brine. After drying over magnesium sulphate, removal of the solvent yielded a yellow oil (15 mg.) whose infrared spectrum showed a strong hydroxyl band at 3,500 $cm^{-1}$. This was dissolved in ether (20 ml.) and refluxed with silver oxide (100 mg.) for ½ hour. T.l.c. showed no trace of the unsubstituted nitroxide (64)

Conversion of trans, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl to the tosylate (100).

To a stirred solution of the trans, cis-nitroxide alcohol (55 mg.) in tetrahydrofuran (2 ml.) under nitrogen, cooled in an ice-bath, was added a solution of n-butyllithium in hexane (0.16 ml of 2.5 M, 0.4 mmole). After stirring for ½ hour, p-toluenesulphonyl chloride (80 mg.) was added and the mixture stirred at ambient temperature for 1½ hours. The mixture was then diluted with ether, washed with sodium bicarbonate solution and brine and finally dried over a mixture of potassium carbonate and sodium sulphate. Removal of the

solvent yielded a red oil (110 mg.). Infrared and t.l.c. indicated that not much alcohol was present, however two much less polar spots were observed. A portion of this oil (55 mg.) was purified by preparative t.l.c. using ether/petroleum ether (1:1) to yield a red oil (100) (21 mg.); $\nu$max.(film) 1600,1495, 1185,1175, 725 $cm^{-1}$.

Attempted lithium aluminium hydride reduction of the trans,cis-tosylate(100).

To a solution of the trans,cis-tosylate (20 mg.) in ether (2 ml.) was added lithium aluminium hydride (25 mg.) and the mixture stirred for 3 hours at room temperature. Saturated sodium sulphate solution was added until a white granular precipitate was obtained, the mixture filtered and the solvent evaporated to yield a red oil (12 mg.). This was further purified by preparative t.l.c. to yield a red oil (5 mg.) which corresponded in Rf to the desired unsubstituted nitroxide but contained an impurity of almost identical Rf .

Conversion of cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl to the tosylate (98)

A mixture of the cis,trans-nitroxide alcohol (54 mg.), p-toluenesulphonyl chloride (100 mg.) and pyridine (1 ml.) was allowed to stand in the refrigerator for 3 days. The mixture was poured onto a mixture of ice and water and stirred for 15 minutes.

The mixture was then extracted with ether, washed with saturated sodium bicarbonate solution, brine and dried over sodium sulphate and potassium carbonate. Removal of the solvent yielded an orange solid (91 mg.)which was purified by preparative t.l.c. in ether/petroleum ether (3:2) to yield an orange solid (69 mg.) which was recrystallised from ether/petroleum ether to yield pink needles, m.p. 124.5-126.5°C; $\nu$max.(Nujol) 3,030 (w), 1595 (m), 1185 (s), 1170 (s) $cm^{-1}$.

Conversion of trans, cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl to the mesylate (99) and reduction with lithium aluminium hydride.

To a solution of the trans, cis-nitroxide alcohol (55 mg.), triethylamine (40 mg.) and dry methylene chloride (1.5 ml.) cooled in an ice-bath was added redistilled methanesulphonyl chloride (50 mg.) in dry methylene chloride (0.5 ml.). The mixture was stirred for 15 minutes, transferred to a separatory funnel with ether and washed with ice-cold water, 1N hydrochloric acid, sodium bicarbonate solution and brine. After drying over sodium sulphate, the solvent was removed to yield a red oil (59 mg.) which was purified by preparative t.l.c. in ether/petroleum ether (1:1) to yield a red oil (59 mg.) which was purified by preparative t.l.c. in ether/petroleum ether (1:1) to yield a red oil (21 mg.), whose infrared spectrum showed no hydroxyl stretching bands and a strong band at 1174 $cm^{-1}$ ($-OSO_2-$ stretch) This material was dissolved

in ether (2 ml.) and lithium aluminium hydride (25 mg.) added. After stirring for 30 minutes the mixture was decomposed by the saturated sodium sulphate technique, and the solvent removed to yield an oil (12 mg.) which was chromatographed to yield a red oil (2 mg.) which showed 3 spots on t.l.c. one of which corresponded in $R_f$ to the desired ubsubstituted nitroxide.

4-Chloro-2,2,6,6-tetramethylpiperidine-1-oxyl (102)

A mixture of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (1.0 g.,6.4 mmoles), triphenylphosphine (1.71 g., 6.5 mmoles) and carbon tetrachloride (35 ml.) was refluxed under nitrogen for 9 hours during which black, oily globules formed on the side of the flask. The mixture was decanted, filtered and evaporated under reduced pressure to yield a red oil (2.8 g.) which was chromatographed on neutral alumina (grade III). Elution with pentane to 25% ether/pentane solvent systems yielded a red oil which contained unreacted triphenylphosphine, 4-chloro-2,2,6,6-tetramethylpiperidine-1-oxyl and 2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine-1-oxyl. Crystallisation from hexane yielded 4-chloro-2,2,6,6-tetramethylpiperidine-1-oxyl (126 mg.) as red prisms m.p.110.5 - 112°C (sealed tube), lit.[40] 111.5°C; $\nu$ max.(Nujol) 1360, 1340, 770, 650 $cm^{-1}$; Retention time 20.5 minutes on 1% NGS at 50°C and flow rate 50 ml.$min.^{-1}$. Preparative t.l.c. of the mother liquors using ether/petroleum ether (15:85) yielded a red oil (174 mg.) which appeared to consist mainly of 2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine -1-oxyl (103). Retention time 3 minutes on

1% NGS at 50°C and gas flow rate 50 ml.min.$^{-1}$; $\nu$max.(film) 3040 (w), 1660 (vw), 1360 (s), 1355 (s), and 720 (s) cm$^{-1}$; $\lambda$ max. 432 nm ($\varepsilon$ = 8.6).

4-Bromo-2,2,6,6-tetramethylpiperidine-1-oxyl (104).

A mixture of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (126 mg.), triphenylphosphine (197 mg.), carbon tetrabromide (299 mg.) and toluene (6 ml.) was heated in oil bath at 100°C for 1½ hours. The mixture was then filtered and evaporated at reduced pressure to yield a red semi-solid mass which was purified by preparative t.l.c. using ether/petroleum ether (1:9) to yield a red crystalline solid (55 mg.). g.l.c. showed the presence of some olefin. Recrystallisation from hexane gave red prisms of 4-bromo-2,2,6,6-tetramethylpiperidine-1-oxyl, m.p. 129-130°C (sealed tube), lit[40] 129°C. Retention time 7.5 min. on 1% NGS at 100°C and gas flow rate 30 ml.min.$^{-1}$; $\nu$max. (Nujol) 1360, 1328, 730, 630 cm$^{-1}$.

Attempted conversion of cis, trans-4-Hydroxy-2,2,8a trimethyl-decahydroquinoline-1-oxyl (79) to the bromide.

A mixture of the cis, trans-nitroxide alcohol (106 mg.), carbon tetrabromide (231 mg.), triphenylphosphine (133 mg.) and toluene (7 ml.) was heated at 80°C for 1 hour. The mixture was then cooled, filtered and evaporated to yield a red oil(380 mg.) which was purified by preparative t.l.c. in ether/petroleum ether (1:8) to yield a red oil (36 mg.). This was chromatographed on silica

gel impregnated with silver nitrate and eluted with 5% ether/pentane. The resultant red oil (16 mg.) had retention time 13.5 minutes on 1% NGS at 75°C and gas flow rate 45 ml. $min^{-1}$; $M^+$194 , $C_{12}H_{20}NO$ requires 194.3

$\nu$max.(film) 3040, 1360, 745 $cm^{-1}$; and is considered to be the olefin, cis-2,2,8a-trimethyl-1,2,4a,5,6,7,8,8a-octahydroquinoline-1-oxyl (105)

Attempted conversion of trans,cis-and cis,cis-nitroxide alcohols to the bromides.

(a) Treatment of the trans, cis alcohol (57 mg.) with triphenylphosphine (68 mg.) and carbon tetrabromide (193 mg.) gave after chromatography a red oil (9 mg.).

(b) Treatment of the cis,cis-alcohol (73 mg.) with triphenylphosphine (89 mg.) and carbon tetrabromide (262 mg.) gave after chromatography a red oil (17 mg.).

The products from (a) and (b) had identical $R_f$ and staining properties both on silica t.l.c. and silica/silver nitrate t.l.c. They also had the same retention time (20 minutes on 1% NGS at 75°C and flow rate 45 ml.$min.^{-1}$). The mass spectrum showed $M^+$= 194, $C_{12}H_{20}NO$ requires 194.3 . It is considered that these compounds are the same, i.e. 2,2,8a-trimethyl-1,2,3,5,6,7,8,8a-octahydroquinoline-1-oxyl (63 ).

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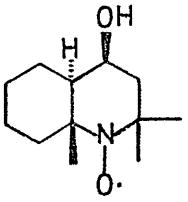
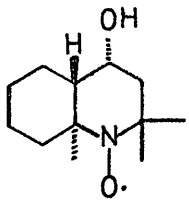
2. The resolution and chiroptical properties of some decahydroquinoline nitroxides.

Once a satisfactory route to decahydroquinoline nitroxides had been developed it was necessary to decide at what stage resolution should be attempted. Chromatographic methods of resolution, e.g. column chromatography on a dissymmetric adsorbent,[1] is becoming increasingly important although as yet only low optical yields are obtained. Still the most useful method appears to be conversion of the racemate into a diastereomeric mixture by reaction with an optically pure reagent followed by separation of the resultant diastereomers usually by crystallisation, sometimes by chromatography[2]. This method is very much one of trial and error. The only general guideline in planning a resolution was mentioned by Woodward[3]. This rule of thumb states that the chiral centres of both the racemate and the optically-active resolving agent should be as close as possible to the site of chemical combination.

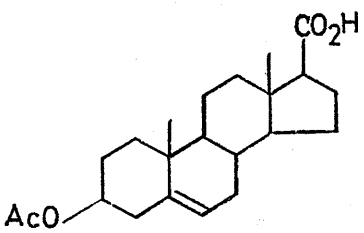
It is well known that carboxylic acids and amines are the most readily resolvable compounds. This arises from the fact that a wide range of crystalline salts are readily prepared and that recovery of the resolved compound is easily accomplished in good yield. The functional group which next seemed to offer almost as wide a range of possible resolutions was the hydroxyl group.


OH
H
N
O·

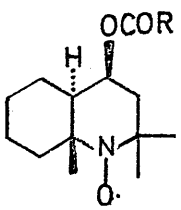
(3)


OH
H
N
O·

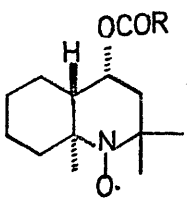
(4)


CO2H
AcO

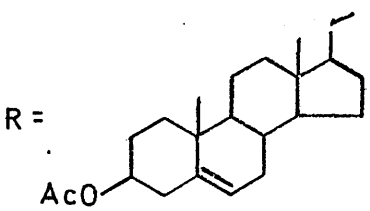
(5)

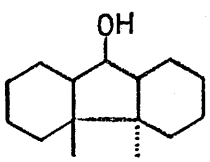

OCOR
H
N
O·

(6)

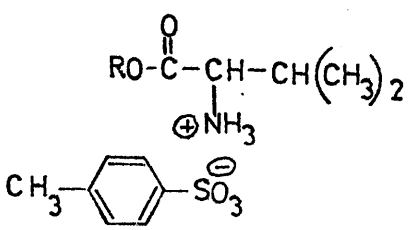

OCOR
H
N
O·

(7)


R =
AcO

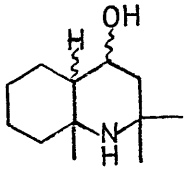

OH

(8)

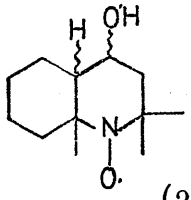

O
RO-C-CH-CH(CH3)2
⊕NH3
CH3
SO3⊖

(9)

This can be converted to a wide range of esters, urethanes, and salts (via half-phthalate esters). These general considerations led us to consider the amino-alcohols(1) or nitroxide alcohols (2) as the best candidates for resolution experiments.



(1)

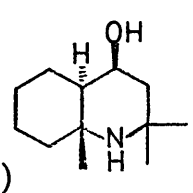


(2)

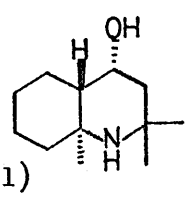
The first experiments were conducted with trans,cis-nitroxide alcohol (3) since this molecule should have a fairly rigid skeleton. The reagent which has had greatest success in resolving alcohols in the recent literature is a readily available steroid acid, 3β-acetoxy-$\Delta^5$-etienic acid (5)[4,5]. Accordingly the acid (5) was converted to the acid chloride with oxalyl chloride and allowed to react with the racemic alcohol (3) and (4) in pyridine solution. The resultant diasteromeric ester mixture (6) and (7) was obtained in moderate yield after chromatographic purification. Since Kurland[6] has shown that the diastereomeric etienate esters of the alcohol (8) can be separated by careful preparative t.l.c. it was decided to try this approach. However on analytical t.l.c. after multiple running the mixture appeared as a tight spot with no sign of streaking let alone separation. Combining this fact with the rather low yield in the esterification led to the abandonment of this approach.

Another method which has shown considerable promise for the resolution of alcohols is to convert them to the p-toluenesulphonate salts of their valine esters (9)[7]. The procedure involves heating the alcohol with one half equivalent of amino acid and p-toluenesulphonic acid with azeotropic removal of water. The crystalline product obtained is greatly enriched with the enantiomer of the alcohol which forms the more stable of the two possible diastereomeric esters. One or two crystallisations then serve to produce the pure diastereomer. Application of this method to the trans,cis-alcohol (3) and (4) failed. A brown oil was obtained. It is thought that this long period of heating in a strongly acidic environment caused decomposition of the nitroxide.

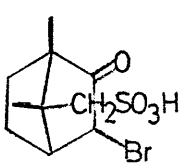
Since resolution via the hydroxyl group was proving difficult, it was decided to try to resolve the corresponding amino-alcohol (10) and (11). Small scale experiments were set up using seven readily available optically active acids (see experimental section for details) to see if crystalline salts were formed and whether fractional crystallisation would provide a suitable method of separation of the diastereomeric salt mixtures formed. (-)-α-Bromocamphor-π-sulphonic acid (12) gave the most promising results.




(10)

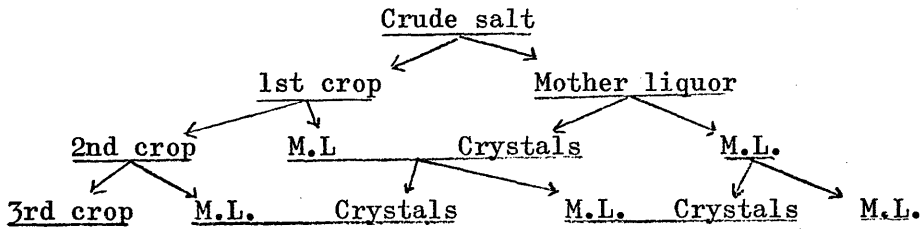



(11)




(12)

The crystalline salt mixture from the amino-alcohol (10) and (11) and the acid (12) was subjected to a systematic triangular recrystallisation procedure (from ethanol)[8]. This involves recrystallising the crystalline material from the first mother liquors from the mother liquors of the second crystallisation as indicated in the following diagram.

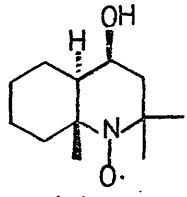



and so on

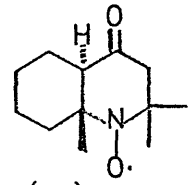
After five stages of this procedure the 'head' and 'tail' fractions were decomposed by percolating methanolic solutions of the salts through basic ion exchange columns. The amino-alcohol from the 'head' fraction had $[\alpha]_{589} = -5.6^{\circ}$ while that from the 'tail' fraction had $[\alpha]_{589} = +12.8^{\circ}$. Hence the mother liequors contained material of much higher optical purity. It was decided to use this latter material for the preparation of optically active nitroxide radicals of the trans series. This decision necessitated that the optical purity of these compounds be determined at some stage in order to quantify any ORD and CD data obtained. The absolute configuration of this compound was shown to be as indicated in

formula (10).

Oxidation of the (+)trans,cis-amino-alcohol(10), $[\alpha]_{589}$= +12.8°, with hydrogen peroxide and sodium tungstate produced the (-)trans, cis-nitroxide alcohol (3), $[\alpha]_{589}$= -39.6°. Oxidation of this latter compound by the Pfitzner-Moffatt procedure produced the (-)-trans- nitroxide ketone (13), $[\alpha]_{589}$= -105°.

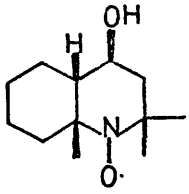



(3)

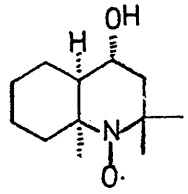



(13)

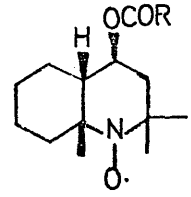
Having thus obtained a reasonable method of entry into optically active nitroxides of the trans-decahydroquinoline series an effort was made to resolve the cis,trans-nitroxide alcohol (14) and (15). Again the first experiments were directed at separating the mixture of diastereomeric etienate esters, (16) and (17), - this time successfully. The mixture of the etienates was prepared as before.



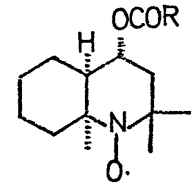

(14)



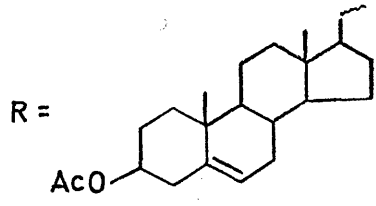

(15)




(16)




(17)

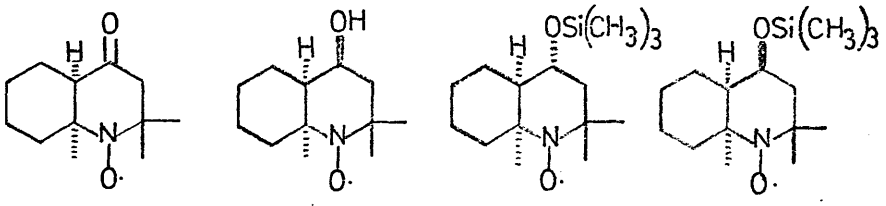


Preparative t.l.c. using continuous development with low polarity solvents in a Desaga chamber led to separation of the mixture into two closely running bands. These were scraped off making a generous allowance for overlap. The less polar ester (17) had $[\alpha]_{589} = +24.8^{\circ}$ while the more polar ester (16) had $[\alpha]_{589} = -46.8^{\circ}$ in one of these experiments. The more polar ester appeared to be highly crystalline and so the original mixture was crystallised from methanol. One crystallisation yielded material with $[\alpha]_{589} = -41.6^{\circ}$ while a second crystallisation produced material of $[\alpha]_{589} = -52.1^{\circ}$. Thus crystallisation seemed to be a very efficient method of separating the diastereomers.

Hydrolysis of the etienate (16) was accomplished by refluxing in aqueous ethanolic sodium hydroxide to give the (-)-cis,trans nitroxide alcohol (14), $[\alpha]_{589} = -98.5^{\circ}$: The ester recovered from the mother liquors was hydrolysed to yield the enantiomeric alcohol (15), $[\alpha]_{589} = +64.9^{\circ}$. This was used for preparation of the nitroxides (18) and (19).

Oxidation of the nitroxide alcohol (15) with dimethylsulphoxide/dicyclohexylcarbodiimide/pyridinium trifluoroacetate yielded the ketone (18), $[\alpha]_{589} = -50.4^{\circ}$.

To obtain the epimeric alcohol (19) the optically active ketone (18) was reduced to the mixture of (15) and (19) with lithium tri-t-butoxy aluminium hydride and separated *via* the trimethylsilyl ethers (20) and (21) as before. Hydrolysis of the ether (21) gave the alcohol (19), $[\alpha]_{589} = +11.8^{o}$.



(18) (19) (20) (21)

In an optically active compound obtained by resolution of synthetic material one of the main problems is knowing when a resolution is complete, or if not, how much of each enantiomer is present[9]. Two terms have been defined to express this latter quantity and these are numerically equal.

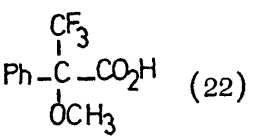
$$\% \text{ optical purity} = \frac{\text{specific rotation of enantiomeric mixture}}{\text{specific rotation of one pure enantiomer}} \times 100$$

$$\% \text{enantiomeric purity} = \frac{\text{no of moles of (-) form} - \text{no of moles of (+) form}}{\text{no of moles of (-) form} + \text{no of moles of (+) form}} \times 100$$

Since with synthetic material it is often not possible to determine the rotation of the pure enantiomer we must rely on other methods of determining the enantiomeric purity. In

the last ten years or so powerful techniques of determining this quantity based on isotopic dilution, g.l.c. and n.m.r. analyses have been developed. These have recently been reviewed by Mislow and Raban[10].

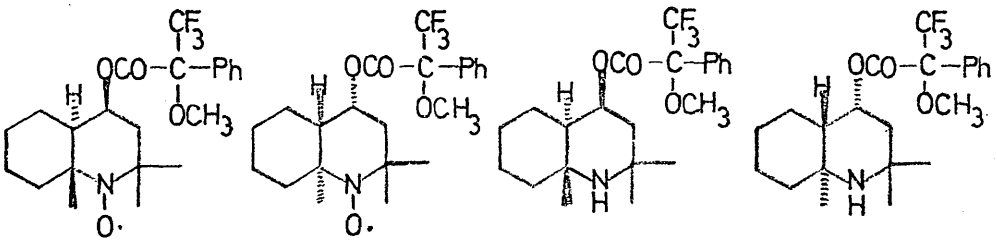
The method chosen in this case was that of Mislow and Raban[11] as modified by Mosher[12] in which a partially resolved alcohol is converted to a mixture of diastereomeric esters in which it is hoped that signals from the diastereomers will have sufficiently different chemical shifts to allow determination of the mixture composition by integration. In this particular method the acid used is (+)-methoxytrifluoromethylphenylacetic acid (22). This has been chosen because, although the methoxyl signals in the resultant esters are usually sufficiently separated for integration (0-8 Hz), the trifluoromethyl signals are usually far apart (10-70 Hz) and hence integration is uncomplicated. The fluorine spectra obtained here were misleading; however the proton magnetic resonance spectra gave the required information.



(22)

In order to test the applicability of the method and provide a standard the racemic trans,cis-alcohol mixture (3) and (4) was

reacted with the acid chloride of (22) in pyridine solution to yield the mixture of esters (23) and (24). To obtain an n.m.r. spectrum this mixture was reduced to the amino-ester mixture (25) and (26) by catalytic hydrogenation over Raney nickel.



(23) (24) (25) (26)

Expansion of the 100 MHz. n.m.r. spectrum of this mixture showed two methoxyl signals at 6.42 and 6.48 $\tau$. These were quartets (J=1.2Hz) caused by long-range coupling to the fluorine atoms. These two signals were in the expected 1 : 1 ratio. There were also two methyl singlets at 8.90 and 9.08 $\tau$ which were sufficiently clear of the rest of the spectrum to allow integration. Again these were in a 1 : 1 ratio (see figure 1.).

This procedure was repeated in the (-)-trans,cis-nitroxide alcohol (3), $[\alpha]_{589} = -39.6^{\circ}$. The n.m.r. spectrum of the resultant amino-ester mixture showed two methoxyl quartets at 6.41 and 6.47 $\tau$ in a ratio of 1 : 2.4. There were four methyl signals sufficiently upfield to allow integration. One pair at 8.93 and 8.99 $\tau$ were in a 1 : 2.4 ratio, while the second pair at 9.05 and 9.17 $\tau$ were in a 1 : 2.3 ratio (see figure 2). Averaging these gives a value of

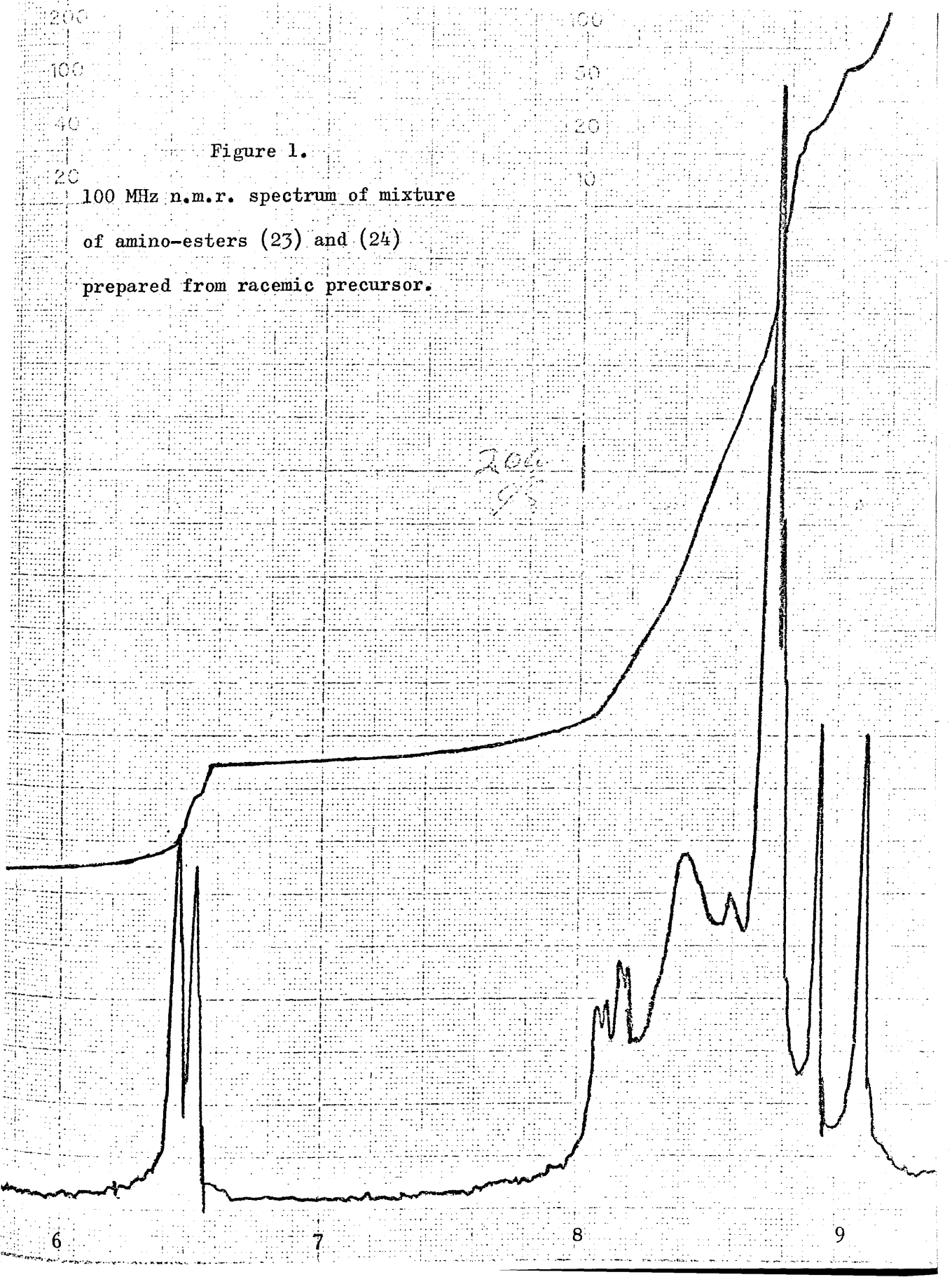
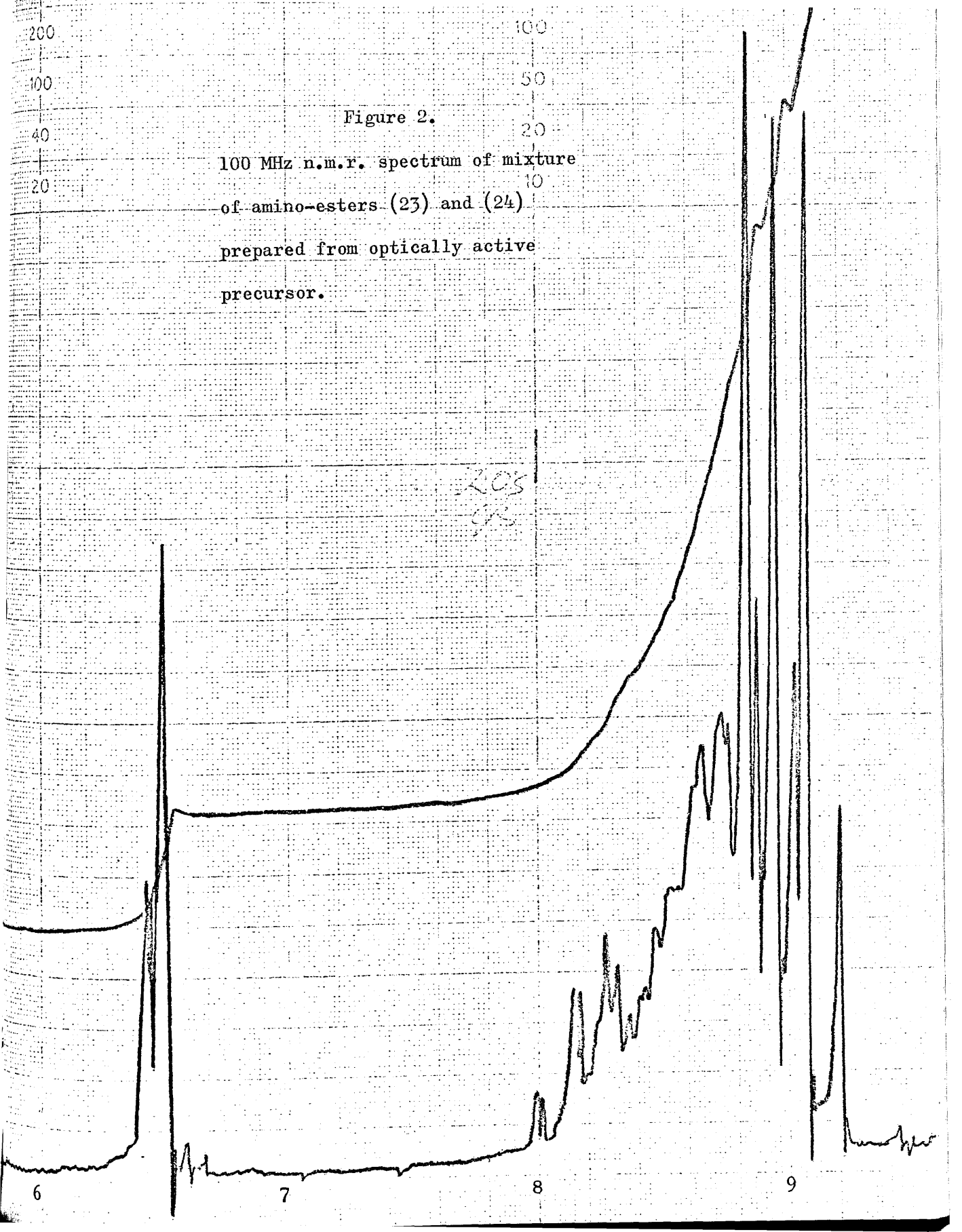



Figure 1.

100 MHz n.m.r. spectrum of mixture of amino-esters (23) and (24) prepared from racemic precursor.

Figure 2.

100 MHz n.m.r. spectrum of mixture of amino-esters (23) and (24) prepared from optically active precursor.

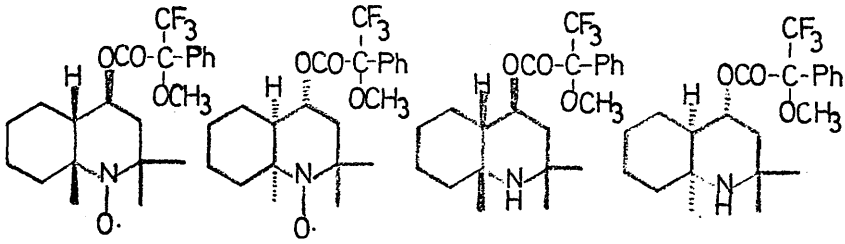


41% for the enantiomeric purity of this compound.

It is obvious from the chemical shifts quoted above that there are substantial shifts of the resonances between esters of the racemic material and esters of the optically active material. It is thought that the changes in the asymmetric environment of a given proton as caused by solute-solute interactions causes this effect.

An attempt to determine the enantiomeric purity from the $^{19}$F n.m.r. spectrum was unsuccessful. The esters from the racemic alcohol did indeed show two broad signals separated by12 Hz in a 1 : 1 ratio. However the material derived from the optically active alcohol showed only one peak. It is thought that the chemical shift changes noted above have this time caused accidential coincidence of the signals. This has not been noted in the literature and would appear to limit the reliability of the method if only one type of spectrum was obtained. In this case the proton n.m.r. spectrum gave three independent pieces of evidence that the material was only 41% optically pure and not 100% as would be adduced from the fluorine n.m.r. spectrum.

The racemic cis,trans-nitroxide alcohol (14) and (15) was likewise converted to the ester mixture (27) and (28) and then by reduction to the amino-ester mixture (29) and (30). Similarly the optically active alcohol (14), $[\alpha]_{589} = -98.5^{\circ}$, was converted to the ester (30).



(27) (28) (29) (30)

The amino-ester mixture from the racemic alcohol showed two methoxyl quartets at 6.41 and 6.45 $\tau$ in a 1 : 1 ratio, while the ester from the optically-active alcohol showed only one methoxyl quartet at 6.45 $\tau$ (see figures 3 and 4). This shows that the alcohol (14) is greater than 95% enantiomerically pure. Since most of the transformations described in the cis series were carried out on the enantiomeric alcohol (15) with $[\alpha]_{589} = -64.9^{\circ}$ an enantiomeric purity of 66% was used for this compound. These values were used to correct all ORD and CD curves obtained and are only held to be correct to $\pm$5%, a value which is often taken as the limit of accuracy on n.m.r. integration[13].

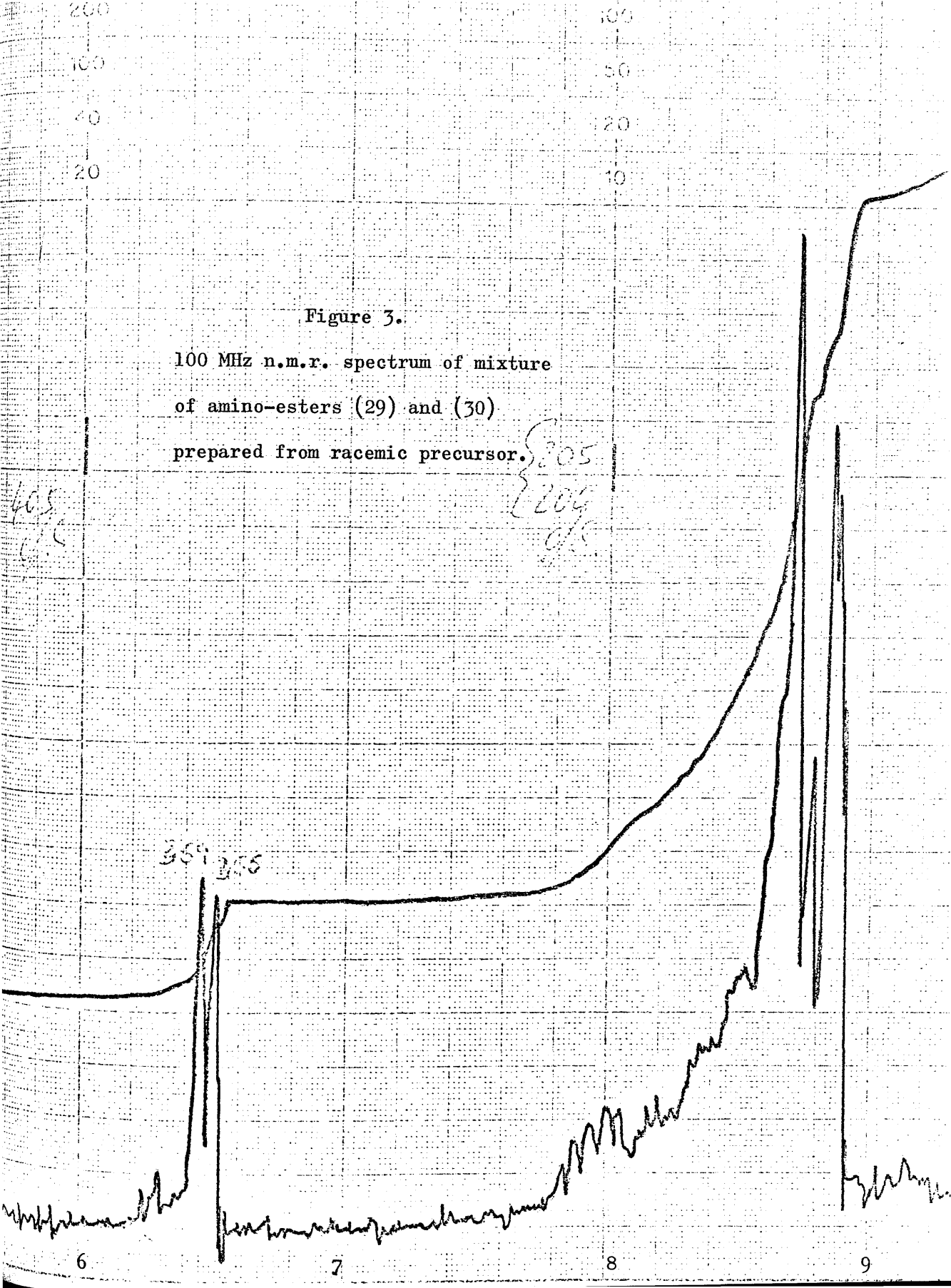



Figure 3.

100 MHz n.m.r. spectrum of mixture of amino-esters (29) and (30) prepared from racemic precursor.

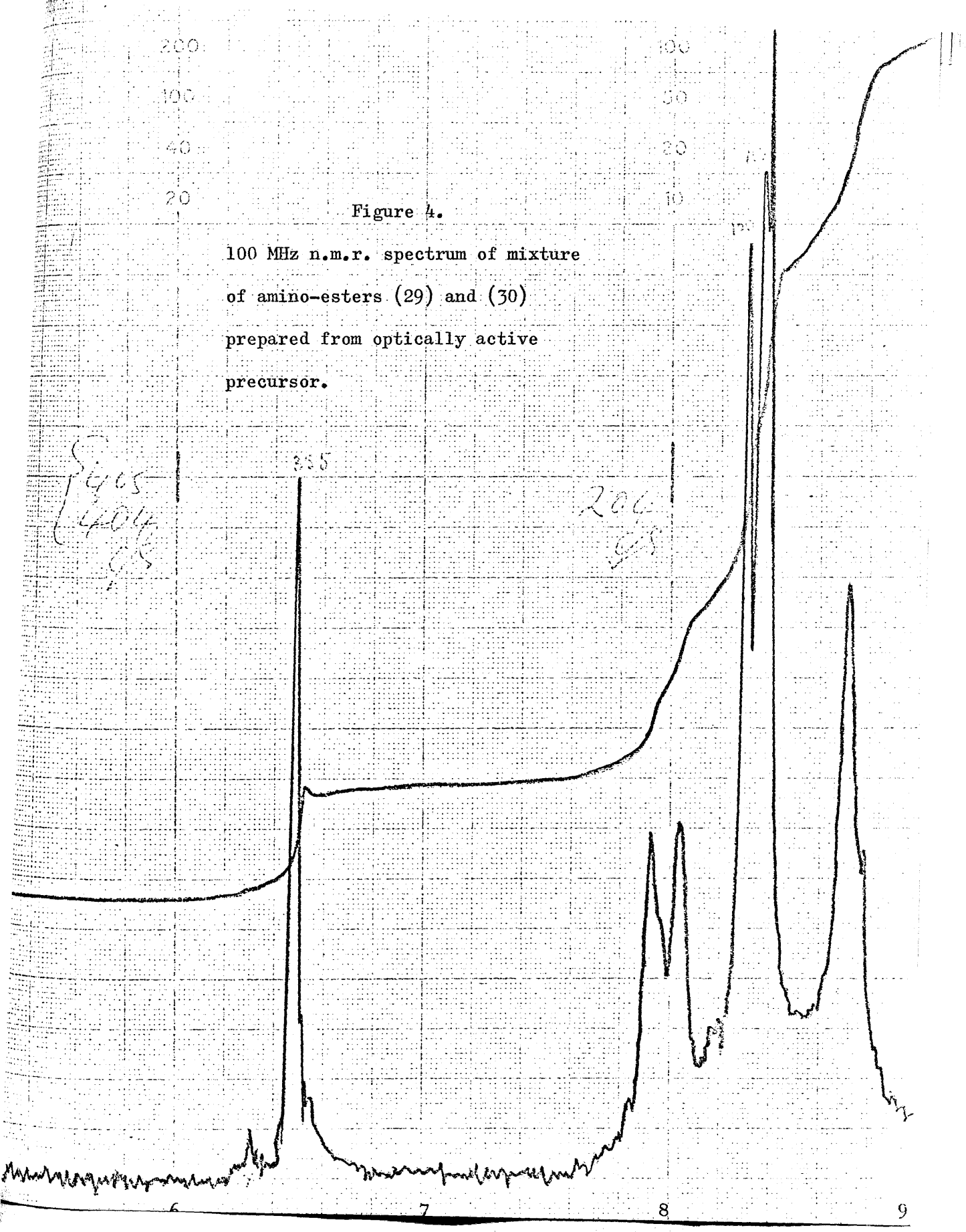



Figure 4.

100 MHz n.m.r. spectrum of mixture of amino-esters (29) and (30) prepared from optically active precursor.

The one remaining problem was to determine the absolute configuration of these compounds. It was thought that application of Horeau's method[14] of asymmetric esterification to the alcohols (3) or (4) and (14) or (15) would prove this point.

Accordingly (+)-cis,trans-nitroxide alcohol (14)or(15) $[\alpha]_{589}$= +64.9°, was reacted with an excess of α-phenylbutyric anhydride in pyridine solution[15]. The crude product showed no trace of starting alcohol by t.l.c. or infrared analysis. The excess α-phenylbutyric acid recovered after reaction had $[\alpha]_{589}$= +1.2°. This corresponded to an optical yield of 11% and allows a safe assignment of the R configuration to the 4 position of this compound. The complete absolute configuration is defined as 4R,4aR,8aS and is represented in formula (15). This has been assumed in the previous discussion.

Application of the method to (-)-trans,cis-nitroxide alcohol (3) or (4) was complicated by the fact that esterification was not complete. However by making allowances for unreacted alcohol it was possible to show that an optical yield of $>$ 20% was involved. The α-phenylbutyric acid recovered was laevorotatory and hence the configuration S could be assigned to position 4 of this compound and its absolute configuration designated 4S,4aR,8aR as represented in formula (3).

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.[16,17]

When a beam of polarised light (which can be considered to be the resultant of two circularly polarised light beams vibrating in-phase and at the same frequency[18]) traverses a chiral medium, the speed of the left circularly polarised component is different from that of the right circularly polarised component because the medium has different indices of refraction for left and right circularly polarised light. This is expressed in Fresnel's equation (31) in which $\psi$ is the rotation of the plane of polarisation in radians per unit length, $\lambda$ is the wavelength of the light and $n_L$ and $n_R$ are the refractive indices for left and right circularly polarised light. Since $n_L$ and $n_R$ vary with wavelength, the rotation of plane polarised light varies with wavelength.

$$\psi = \frac{\pi}{\lambda}(n_L - n_R) \qquad (31)$$

Normally the experimentally measured rotation is expressed as the specific rotation, $[\alpha]_\lambda^T$, where $\lambda$ is the wavelength of the incident light and T is the temperature of measurement. Specific rotation is defined by equation (32) where $\alpha$ is the measured rotation of the plane of polarisation in degrees, $\ell$ is the length of the cell path in decimetres and c is the concentration of the

solution in gram per millilitre of solution.

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l.c} \qquad (32)$$

The molecular rotation $[\phi]$ is another useful unit since it allows the comparison of rotations on a mole-for-mole basis and is defined by equation (33).

$$[\phi] = \frac{\text{specific rotation x molecular weight}}{100} \qquad (33)$$

$$[\phi] = \frac{\text{specific rotation x molecular weight}}{100} \qquad (33)$$

A plot of molecular rotation of a substance against the wavelength of the incident light is the optical rotatory dispersion (ORD) curve of the substance.

Related to this is the phenomenon of circular dichroism (CD). This arises from the fact that a chiral medium has different molecular extinction coefficients for left and right circularly polarised light. A plot of the differential dichroic absorption, $\Delta\varepsilon$ as defined by equation (34), against wavelength is known as a CD curve.

$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R \qquad (34)$$

Where $\varepsilon_L$ and $\varepsilon_R$ are the molecular extinction coefficients of left and right circularly polarised light respectively. However, the more generally accepted unit of CD is the molecular ellipticity $[\theta]$ which is related to $\Delta\varepsilon$ by the relationship (35).

$$[\theta] = 3{,}300\,\Delta\varepsilon \qquad (35)$$

The most interesting and useful ORD and CD curves are obtained

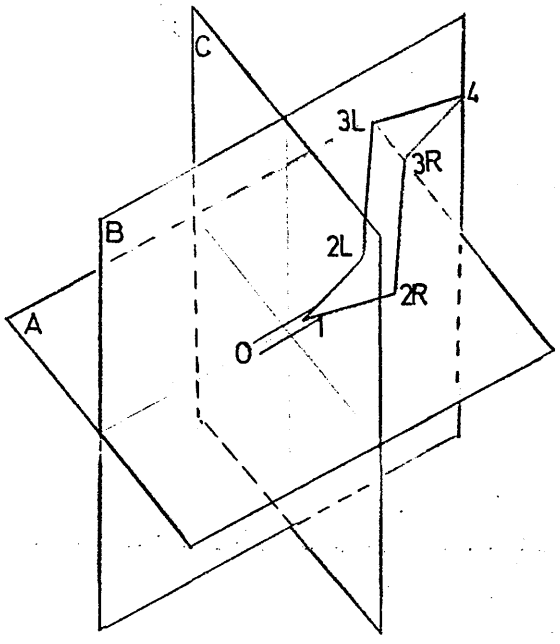



Figure 5.

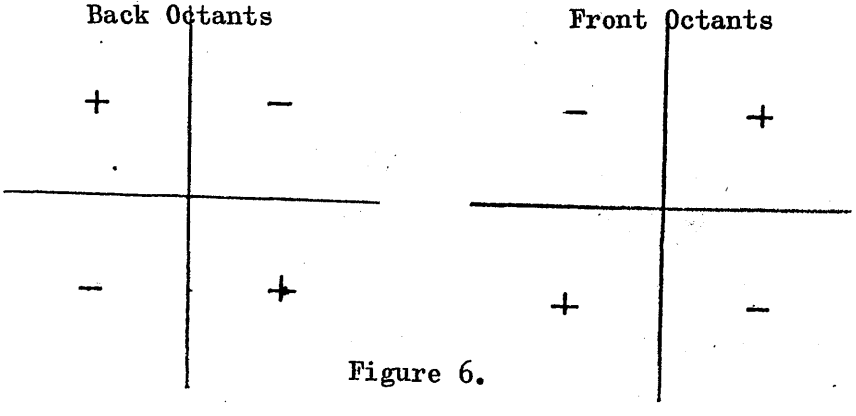



Figure 6.

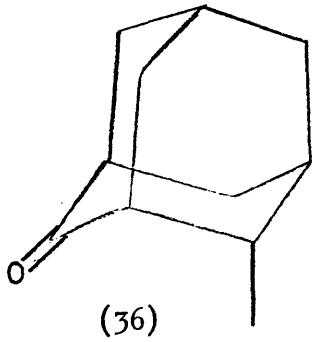
in the vicinity of the electronic absorption bands of the substance being examined. These give rise to Cotton effects in ORD spectra and maxima in CD spectra. An immense body of data on the ORD spectra of organic molecules was accumulated principally by the school of Djerassi.[19] In particular they studied the Cotton effects produced by the $n \rightarrow \pi^*$ electronic transition of carbonyl compounds.

The empirical theories evolved by these workers were merged with the theoretical treatments of Moffitt and Moscowitz in the enunciation of the Octant Rule in 1961.[20] Since it is the purpose of this work to discuss the chiroptical properties of nitroxide radicals in terms of the Octant Rule, a brief resume will be given here.

Three perpendicular planes bisecting the carbonyl group divide the space surrounding this group into eight octants (figure 5). 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 Cotton effect of a ketone depends on the nature and position of the asymmetrically located groups in the compound. Groups in the top left and bottom right of the back four octants as viewed along the O=C band make a positive contribution whereas those in the top right and bottom left octants make a negative contribution (figure 6). The situation is reversed in the front four octants although these octants are rarely occupied.

This rule has served admirably over the years and has provided

much configurational and conformational information. Recently, however, self-consistent field molecular orbital calculations[21] suggested that 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(36) and (37).[22] These calculations, as well as some recently reported experimental findings[23], also suggest that the third plane C is not straight as shown but is curved and following the contours of the molecule. However, with these reservations in mind the Octant Rule is still extremely useful in explaining the chiroptical properties of ketones.

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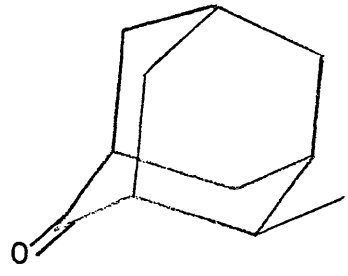
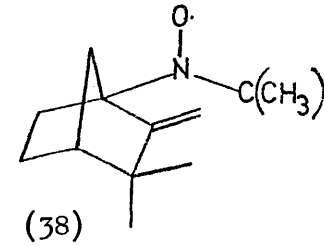



(37)




(38)

Only one report has appeared on the chiroptical properties of a nitroxide radical, the t-butyl camphenyl nitroxide (38).[24] This compound shows a negative maximum in its CD curve at $\lambda$= 465 nm ($[\theta]$ = -462) in cyclohexane and at $\lambda$= 447 nm ($[\theta]$ = - 231) in methanol. However, due to free rotation about both CN bonds little or no structural information could be gleaned from this spectrum.

Table 1. $n-\pi^*$ transitions of N–$\dot{O}$.

| Compound | Ultraviolet $\lambda_{max.}$ | Ultraviolet $\varepsilon$ | Circular Dichroism $\lambda_{max.}$ | Circular Dichroism $[\theta]$ | Optical Rotatory Dispersion $\lambda$ | Optical Rotatory Dispersion a |
|---|---|---|---|---|---|---|
| (13) | 422 | 6.8 | 425 | -1240 | 430 | -6.4 |
| (18) | 430 | 6.8 | 432 | +370 | N.O. | N.O. |
| (3) | 440 | 9.9 | 423 | -950 | 425 | -10.9 |
| (15) | 442 | 13.6 | 445 | +1070 | 440 | +15.7 |
| (19) | 432 | 14.5 | N.O. | N.O. | N.O. | N.O. |

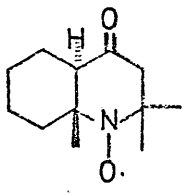
Table 2. $n-\pi^*$ transitions of C=O.

| | | | | | |
|---|---|---|---|---|---|
| (13) | N.O. | N.O. | 296 | -7600 | First extremum |
| (18) | N.O. | N.O. | 299 | -3100 | only observed. |

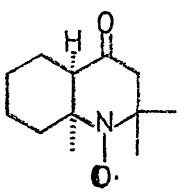
Table 3. Other transitions.

| | | | | | | |
|---|---|---|---|---|---|---|
| (13) | 234 | 2200 | N.O. | N.O. | N.O. | N.O. |
| (18) | 239 | 2050 | N.O. | N.O. | N.O. | N.O. |
| (3) | 243 | 2600 | N.O. | N.O. | N.O. | N.O. |
| (15) | 245 | 1800 | 254 | -2590 | First extremum only observed. | |
| (19) | 243 | 1840 | 252<br>216 | +3550<br>-1570 | 252 | +55.9 |

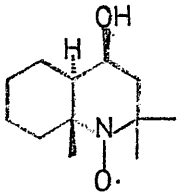
The CD curves of the decahydroquinoline nitroxides (13), (18), (3), (15) and (19) are shown in figures 7 and 8 and the corresponding ORD curves in figures 9 and 10 (all run in methanol solution). The ultraviolet, CD and ORD data on these compounds are collated in tables 1-3.



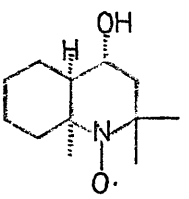
(13)



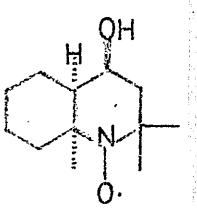
(18)



(3)



(15)



(19)

Compounds (13), (18), (3) and (15) all show CD maxima in the region 420-450 nm due to the $n \rightarrow \overline{\pi}^*$ transition of the nitroxide function. At the concentration used in the experiment the cis, cis-alcohol (19) did not show any absorption in this region. This implies that this compound (in terms of the groups surrounding the nitroxide) must be 'symmetrical'. In addition to this band, the two keto-nitroxides show maxima at about 300 nm caused by the $n \rightarrow \pi^*$ transition of the carbonyl group. The spectra of the two cis-alcohols were obtained down to almost 200 nm showing maxima at 252 and 254 nm most likely due to the $\pi \rightarrow \pi^*$ transition of the nitroxide. Most interesting is the observation that the alcohol (19) shows another maximum in this region at 216 nm while (15) seems to show the beginning of a maximum at about this wavelength. If this is so, then it seems that these compounds have another electronic transition in this region which is not resolved in the ultraviolet spectra. This might reasonably be expected to be a $\pi^* \rightarrow \sigma^*$

Figure 7.

CD curves of keto-nitroxides (13) and (18) in methanol.

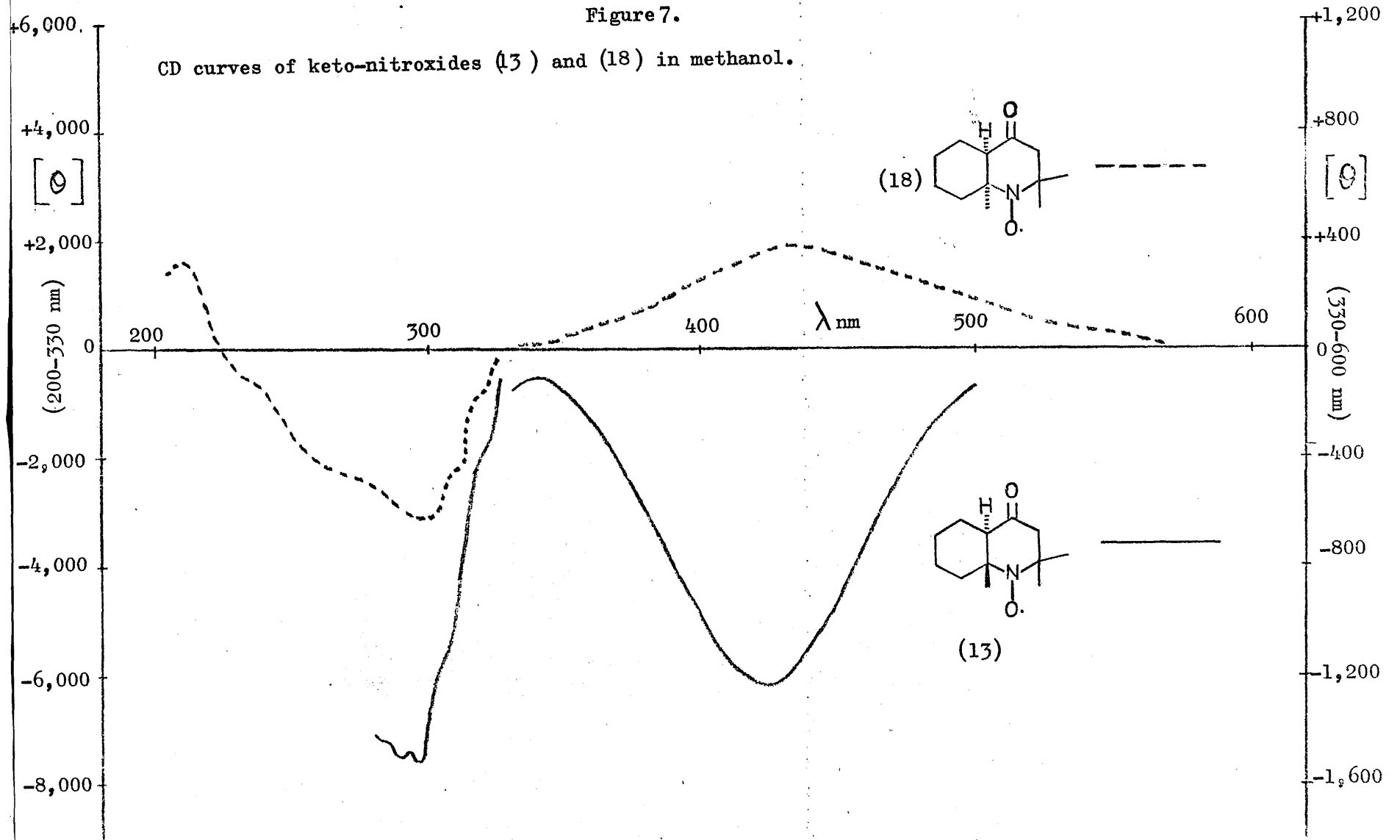


Figure 8.

CD curves of hydroxy-nitroxides ( 3), (15), (19) in methanol.

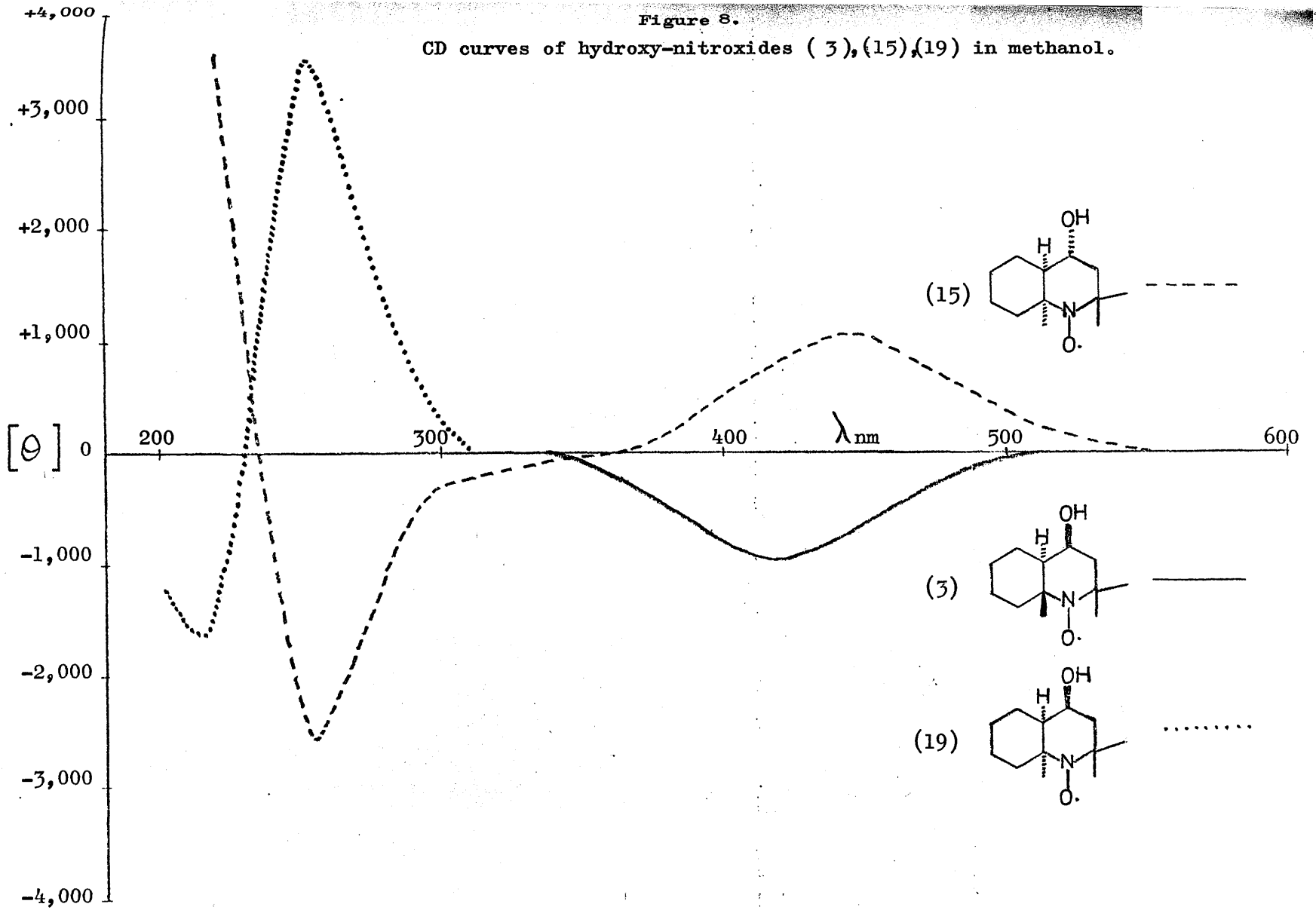
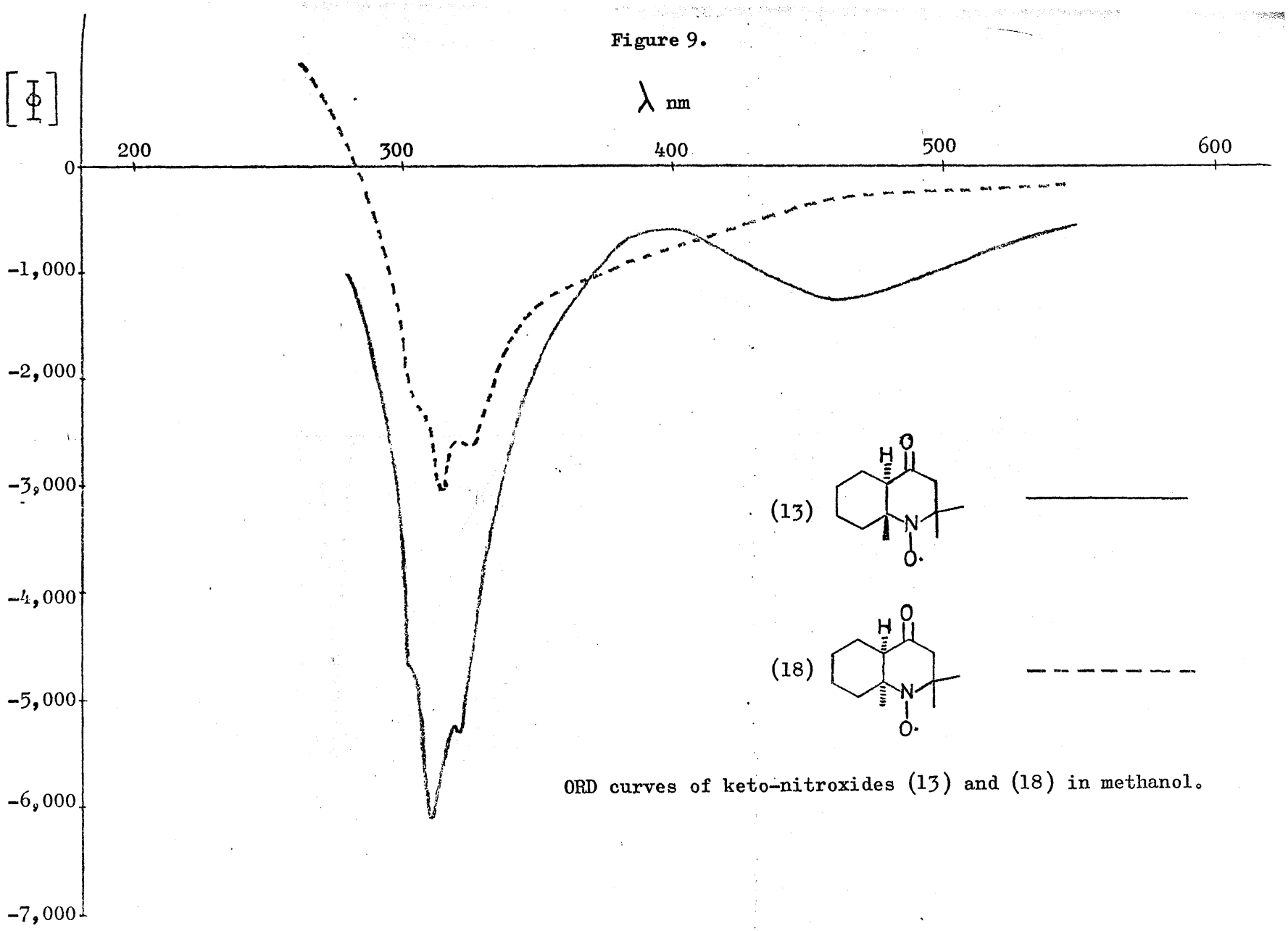


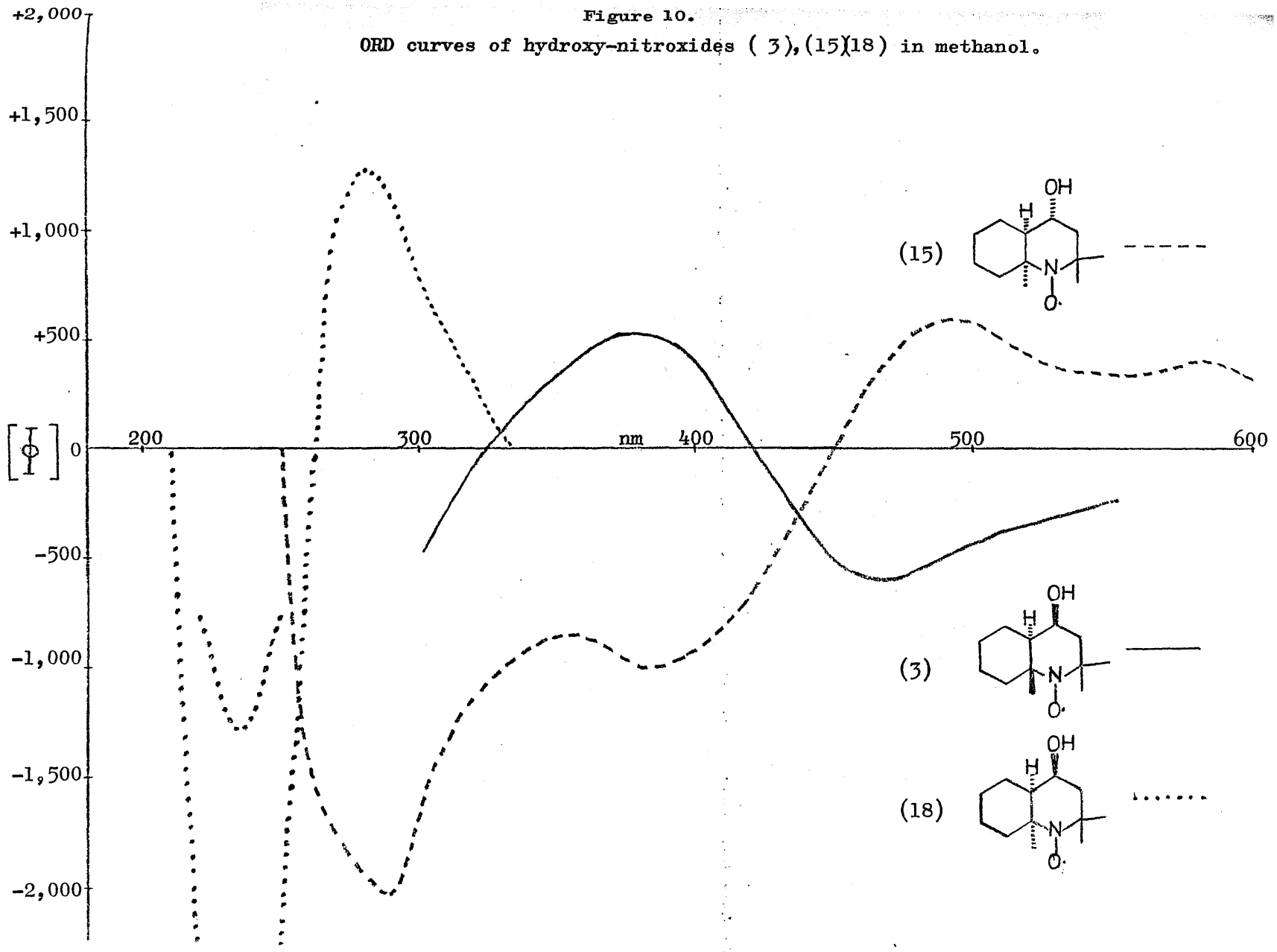
Figure 9.

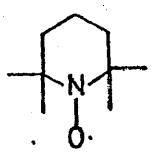



ORD curves of keto-nitroxides (13) and (18) in methanol.

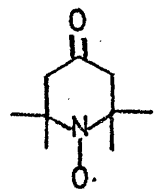
Figure 10.

ORD curves of hydroxy-nitroxides ( 3), (15) (18) in methanol.






(39)

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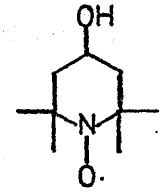
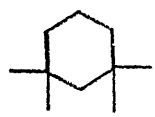
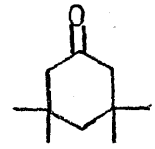



(41)



(42)



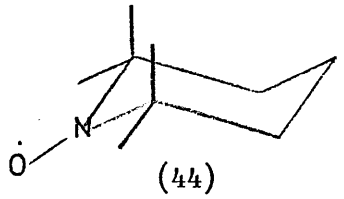

(43)

transition which is probably the next lowest energy transition after $\pi \rightarrow \pi^*$ This ability of CD spectra to unmask hidden transitions in the ultraviolet spectra of a molecule is well known.[25] This conclusion, however, can only be regarded as tentative at present.

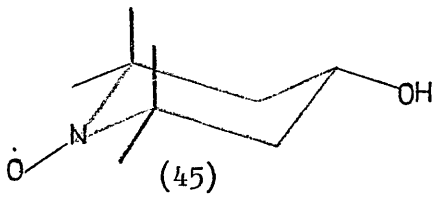
Consideration of the ORD curves shows that similar features are present in these, although complicated by the background curves of these molecules. Indeed, the carbonyl Cotton effect and background curve of the cis-keto-nitroxide (18) so dominates the spectrum that the Cotton effect of the nitroxide is not observable. Thus we can see clearly the Cotton effects of the nitroxide function of compounds (13), (3) and (15) and the first extrema of the carbonyl Cotton effects of (13) and (18). However, the greater selectivity of the CD curves, in that a particular electronic transition is observed without complicating effects of background, is obvious.

Since the absolute configurations of the nitroxide radicals (13), (3), (18) and (19) have been determined, it should be possible to deduce conformational information from these spectra. However, before attempting this, it is advisable to consider what is known about the conformations of the simple monocyclic nitroxides (39), (40) and (41) and polyalkylated cyclohexanes such as (42) and (43). This should provide some insight into the factors which affect the conformational preferences of such molecules.

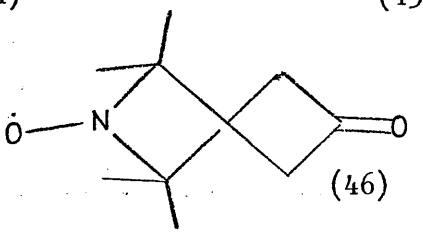
Considering first the monocyclic nitroxides it is believed that (39) and (41) exist in the chair conformations (44) and (45) respectively, probably considerably flattened, while the keto-nitroxide (40) is thought to exist in the twist conformation (46).




(44)




(45)




(46)

The evidence that has been adduced in favour of these proposals is as follows. The hyperfine splittings of the high resolution e.p.r. spectra of these compounds can sometimes be analysed in terms of the unpaired electron coupling with the nuclei $^{13}C$ and $^{15}N$ isotopes present in natural abundance.[26] The size of the coupling constant between the unpaired electron and the $\beta$-carbon, $a_c$, depends on the dihedral angle between the $C_\alpha - C_\beta$ bond and the $p$-orbital on nitrogen, $\theta$, according to the relationship.

$$a_c = \left[B_0 + B_1 \left\langle \cos^2\theta \right\rangle\right] \rho_N^{\pi}$$

Where $B_0$ and $B_1$ are constants and $\rho_N^{\pi}$ is the electron spin density on nitrogen.

The coupling constant, $a_c$=5.6 gauss, observed for the radical (40) is best explained in terms of a rapid pseudorotation between

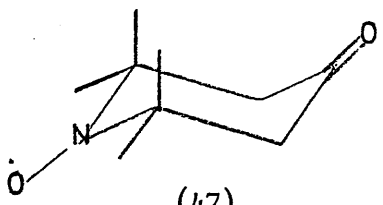
two twist conformations of equal energy. Unfortunately, the high resolution spectra of (39) and (41) showed only splitting due to remote hydrogens and not to the $\beta$-carbons.

Rassat[26] has shown that the alcohol (41) does not show an intramolecular hydrogen bond despite an earlier report of Rozantsev[27] that it did. Taken with the n.m.r. evidence[28] which clearly shows separate signals for axial and equatorial methyls and methylene hydrogens, it would appear that (41) exists predominantly in the chair conformation (45) with the hydroxyl group equatorial. This has been shown to be definitely true in the solid state by X-ray crystallography.[29]

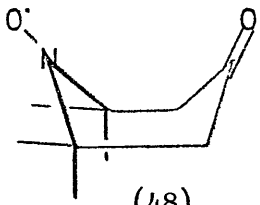
In the same n.m.r. study it was shown that only one methyl peak and one methylene peak could be observed for the keto-nitroxide (40). These did not, however, have diamagnetic shifts corresponding to the average of those observed for the axial and equatorial groups in (41). Hence, it is unlikely that this radical exists in the chair conformation (rapidly flipping). The unsubstituted nitroxide (39) again shows only one methyl peak and one $\beta$-methylene peak which this time have the average of the values found for (41). This suggests that this molecule is undergoing a rapid inversion between two chair forms of equal energy. These considerations also suggest that the keto-nitroxide nust be in a twist conformation such as (46) and undergoing a rapid interconversion to another twist conformation which would make the methyl groups equivalent.

A dipole moment study[30] of the keto-nitroxide (40) gave fairly

definitive evidence for a twist conformation. The dipole moment calculated for the chair conformation (47) is 0.4 D.,while for the boat (48) it is 4.0 D. The observed value of 1.36 D. correlates best with the twist conformation (46) which has a calculated dipole moment of 1.4 D. with an angle of 152° between the NO and CO dipoles.



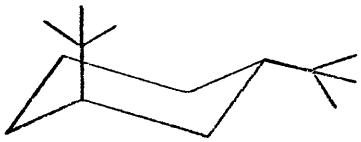

(47)




(48)

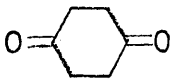
In terms of alicyclic chemistry the following facts are thought to be of importance. Few cyclohexane rings containing no $sp^2$ centres are in boat conformations.[31] One of the few known examples is trans-1,3 -di-t-butylcyclohexane (49) which would have a prohibitive axial t-butyl group in the chair (50).[32]

(49)



(50)

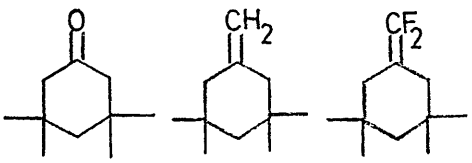
The presence of one $sp^2$ centre lowers the energy difference between chair and boat forms from 5.5 kcal./mole to around 3 kcal./mole.[33] The presence of another $sp^2$ centre lowers this energy gap even more and cyclohexane-1,4-dione (51) exists almost exclusively in the twist form (52).[34,35] Presumably this also minimises dipole interactions in non-polar solvents and the gas phase.



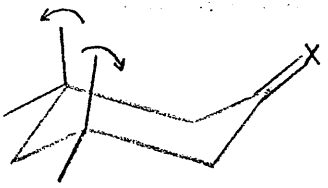
(51)

(52)

It might be expected that a combination of non-bonded interactions and one $sp^2$ centre would be enough to produce a favourable twist conformation in the tetramethylcyclohexane (43). However, the available chemical[36] and n.m.r. evidence[37,38] and the conformational calculations of Allinger[39] suggest that this molecule and the related exomethylene compounds (53) and (54) exist in flattened chair conformations (55).

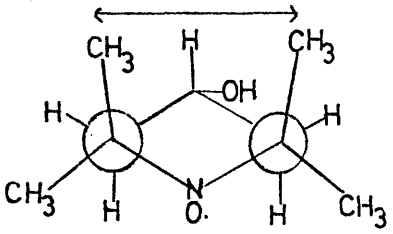


(43) (53) (54)

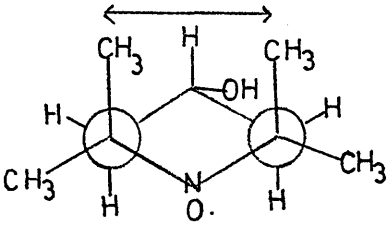


(55)

The flattened chair conformation (56) is very clearly shown in the X-ray structure of (41).[29] In this molecule the axial methyl groups are pushed almost 0.7 $A^{o}$ further apart than they would be in a perfect chair conformation (57).



(56)



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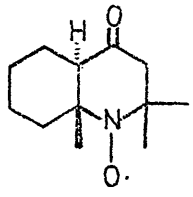

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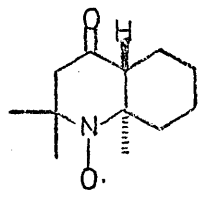
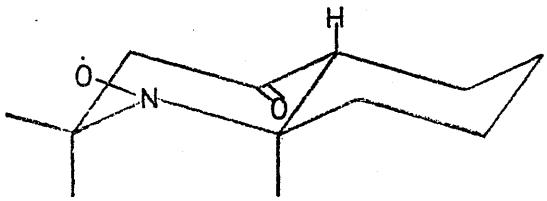
(13)





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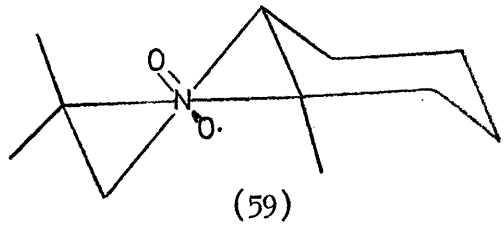

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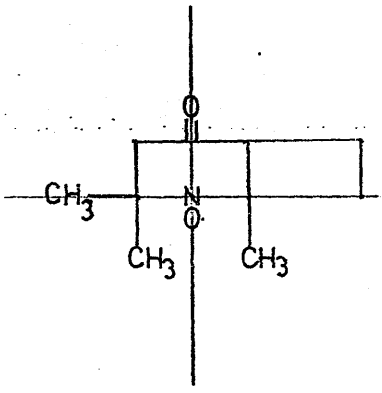

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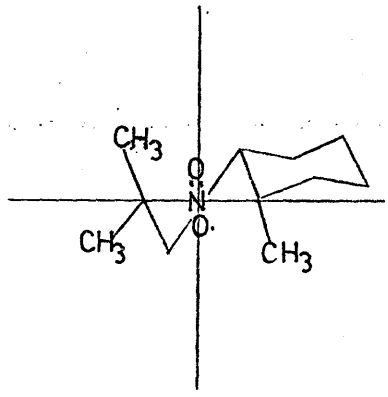
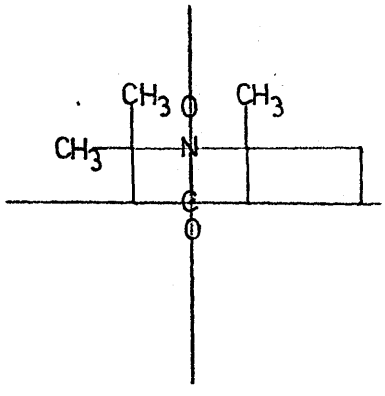
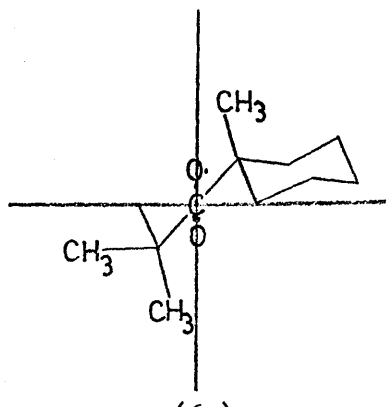


(62)



(61)



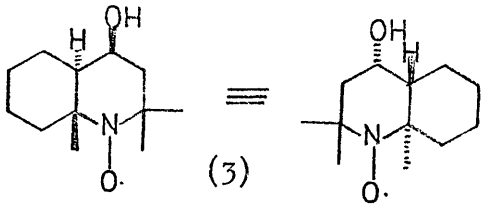
(63)

To sum up, it would appear that in the monocyclic nitroxides with no additional $sp^2$ centres the preferred conformation is a flattened chair whereas the presence of a $sp^2$ centre in the 4 position favours a twist conformation.

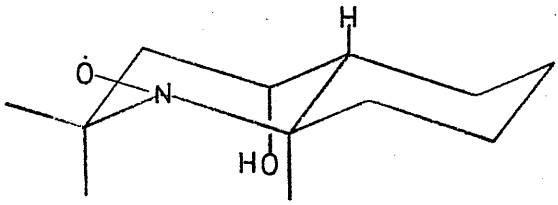
The compounds most likely to be amenable to conformational analysis are the trans-fused compounds (13) and (3). The two most likely conformations for the keto-nitroxide (13) are the all-chair conformation (58) and the chair-twist conformation (59). The former conformation has a severe 1,3-diaxial interaction between the methyl groups on C2 and C8a. This amounts to about 3 kcal./mole[33] and would probably mean that in such a conformation the piperidinooxy ring would be considerably flattened. In the chair-twist conformation (59) this interaction is reduced to practically zero.

The CD curve of this compound shows a negative maximum at 425 nm, $[\theta]$ = -1,230, due to the $n\rightarrow\pi^*$ transition of the nitroxide function and a negative maximum at 297 nm, $[\theta]$ = - 7,640, caused by the $n\rightarrow\pi^*$ excitation of the carbonyl group. Likewise the ORD curve shows a negative Cotton effect centred on 428 nm, a =-6.4 and the first extremum of a negative Cotton effect at 311 nm, $[\phi]$ = -6,090.

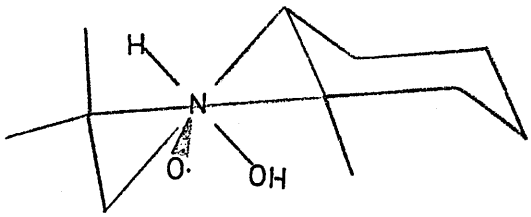
The octant projections for the all-chair form (58) are as shown in (60) for the NO group and in (61) for the CO group. It can be seen that in (60) the contributions of the axial C2 and C8a methyl groups cancel one another as do the contributions from C3 and C4a. The equatorial C2 methyl, C2, C4, C7, C8 and C8a all lie on symmetry



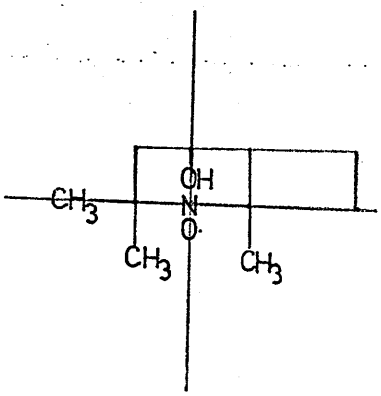

(3)




(64)




(65)

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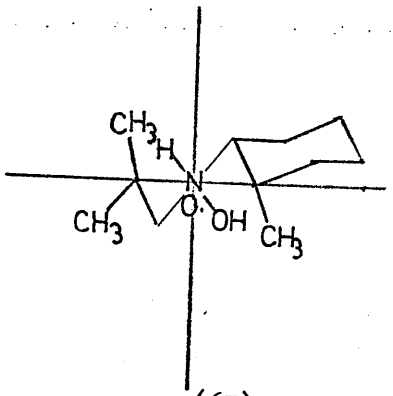



(67)

planes and hence have no effect. The only groups contributing to the rotatory power are the C5 and C6 methylene groups which lie in a negative octant. This conformation is therefore predicted to have a small negative CD maximum due to the nitroxide.

The octant projection (61) shows that only the equatorial C2 methyl and the C7 and C8 methylene contribute to the rotatory power of the carbonyl group. Since these are of opposite sign with the former probably predominating[23], a weak positive maximum is expected for the carbonyl CD.

The octant projections for the twist form (59) are shown in (62) and (63). The nitroxide projection (62) shows that a weak negative CD would be expected for this group while the carbonyl projection (63) suggests that a very strong negative CD maximum is expected for this group. Thus it is seen that the chair-twist conformation (59) best explains the observed CD and ORD curves.

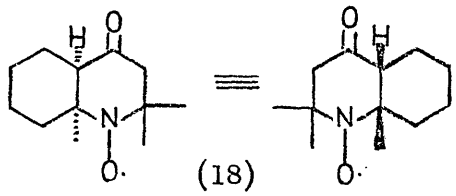
The trans, cis-alcohol (3) shows a negative maximum at 423 nm, $[\theta] = -977$, in its CD curve and a negative Cotton effect centred on 421 nm, a = -10.9 in its ORD curve. The all-chair conformation (64) has an octant projection (66) suggestive of a negative CD maximum. The chair-twist conformation (65) also has an octant projection (67) suggestive of a negative CD maximum.

The similarity of the spectra to those of the ketone (13) perhaps suggests that conformation (65) is preferred. This is

reasonable since in the all-chair conformation (64) there exist extremely bad interactions between the methyl groups and the hydroxyl group. This syn-triaxial interaction would total about 8.5 kcal./mole[40] in a perfect chair conformation and hence this would be unlikely to be preferred. However, the chemical evidence (lack of reaction with trimethylsilyldiethylamine) suggests that hydroxyl group in the molecule, if not in an axial position, must be reasonably hindered.

If the energy differences between the different possible conformations are reasonably small then it is expected that more than one conformer would be appreciably populated. The observed CD and ORD curves in this case would be the weighted sum of those of the individual conformers. In this case the observed spectrum is usually dominated by the conformer with the strongest rotatory power and not necessarily the most abundant[41]. This limitation must be borne in mind in the above and subsequent arguments.

A reasonable analogy for these compounds is provided by the D-homosteroids (68) and (69) which were studied by Allinger[42]. Using the generally accepted values for non-bonded and torsional energies, the author deduced that a twist conformation for ring D in these compounds would be preferred. This was supported by ORD and dipole moment measurements. This paper also indicates that regular boat conformations such as (70) and (71) are not



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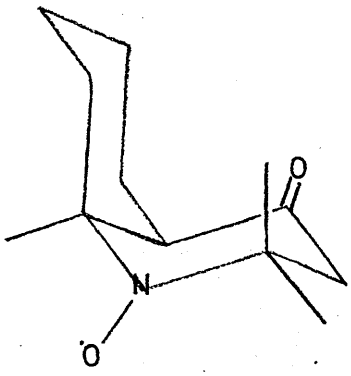
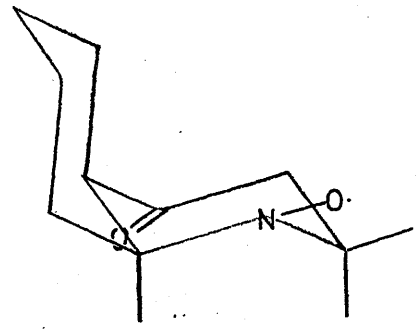
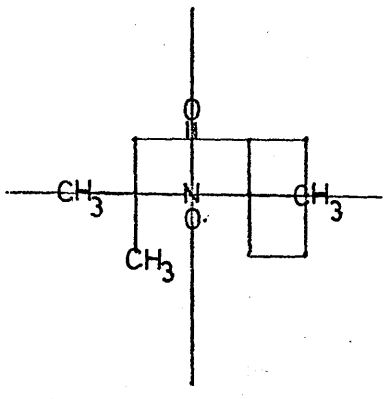


(72)



(73)



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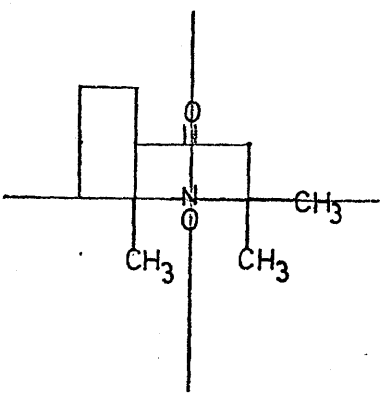

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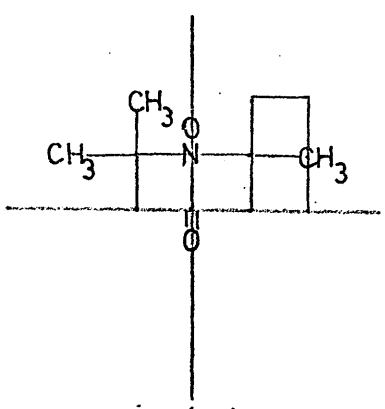

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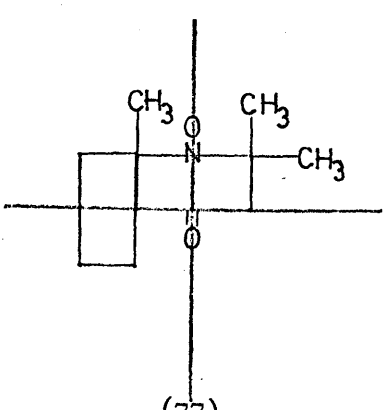
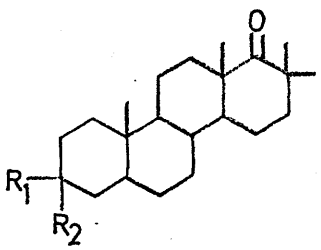


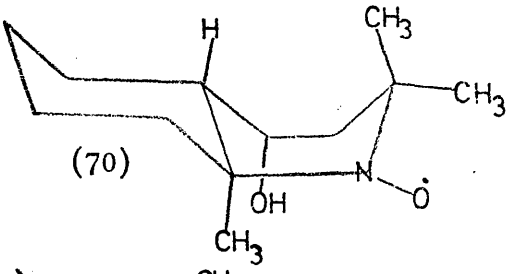
(77)

very probable since the bow-sprit interaction between a methyl and a hydrogen is of the order of 6 kcal./mole. The twist form (65), in fact, lies halfway between these extremes.

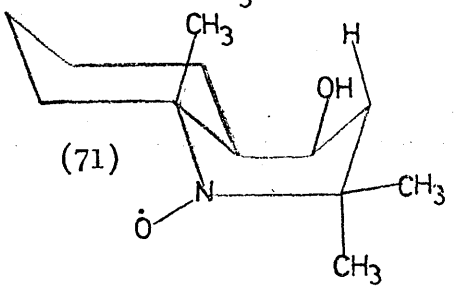


(68), $R_1 = R_2 = H$

(69), $R_1 = R_2 = O$

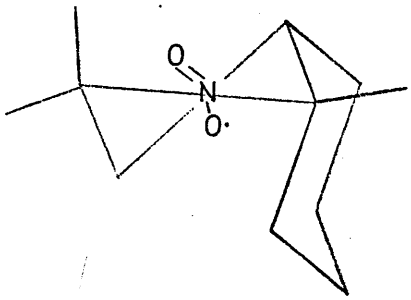


(70)

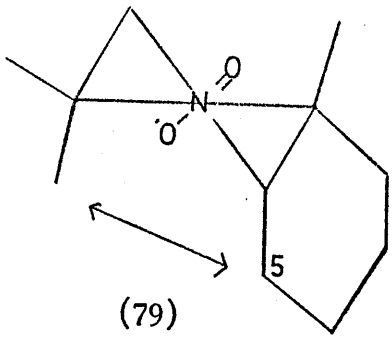


(71)

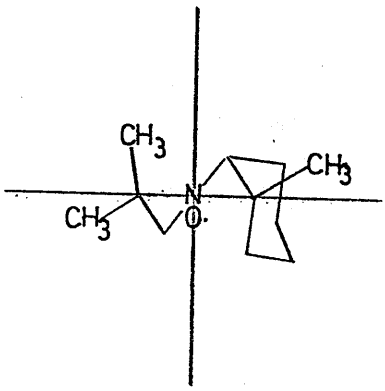
It is now appropriate to consider the stereochemistry of the conformationally more mobile cis-fused compounds. The cis-ketone (18) has available to it four possible conformations (neglecting regular boats). Of the two all-chair conformations (72) and (73) it is not possible to say, a priori, which would be the more suitable since (72) has two axial substituents in the heterocyclic ring and two in the alicyclic ring while (73) has three axial substituents in the heterocyclic ring and but one in the alicyclic portion.



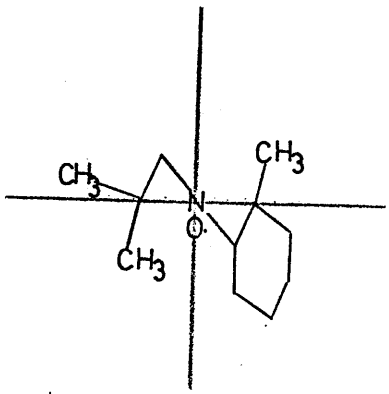

(78)



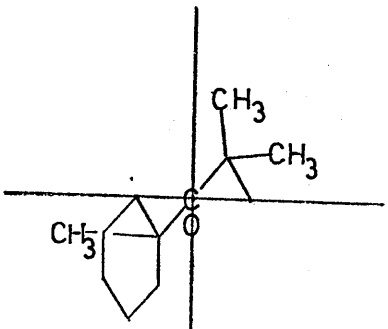

(79)



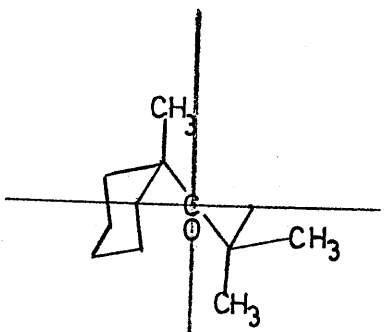

(80)




(82)




(81)



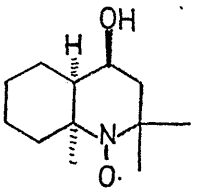

(83)

Table 4.

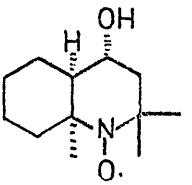
| Conformation. | Predicted sign of N–O Cotton effect. | Predicted sign of C=O Cotton effect. |
|---|---|---|
| (72) | – | – |
| (73) | + | – |
| (78) | ? | –– |
| (79) | + | + |
| Observed | + | –– |

Of the two chair-twist forms (78) and (79) the latter has a bad interaction between one of the methyls on C2 and the C5 methylene group. This interaction would be expected to be at least as large as a methyl-hydrogen bow-sprit interaction (6 kcal./mole[42]) and would be expected to be unfavourable.

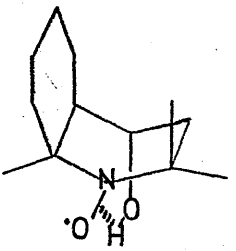
Consideration of the octant projections for these conformations allows the construction of the following table of predicted signs for the Cotton effects (table 4). The CD spectrum of this compound shows a positive maximum at 435 nm, $[\theta]$ = +360 and a negative maximum at 299 nm, $[\theta]$ = -3,100. Thus conformations (72) and (79) are not favoured or at most, make very little contribution to the CD curve. However, it is difficult to estimate what sign the nitroxide function in the chair-twist conformation (78) will have since in the octant projection (80) there are substituents in all four octants which do not readily cancel one another out. However, in the ketone projection (81) all contributing substituents are in negative quadrants, as was the case with the trans-keto-nitroxide (13), and a strong negative CD maximum is expected and observed. This may be tempered to some extent by the presence of other conformers of lesser rotatory power and thus be not as strong as the trans-compound. A reasonable explanation is that this compound is an equilibrium mixture of conformers (73) and (78) although the presence of small proportions of the conformers (72) and (79) cannot be excluded.



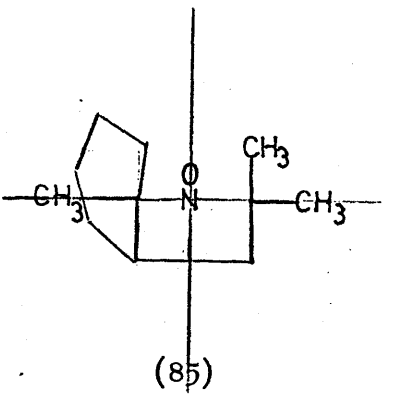

(19)



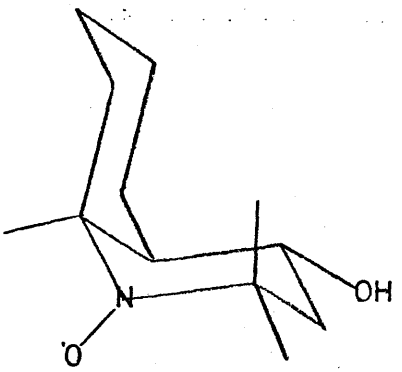

(15)



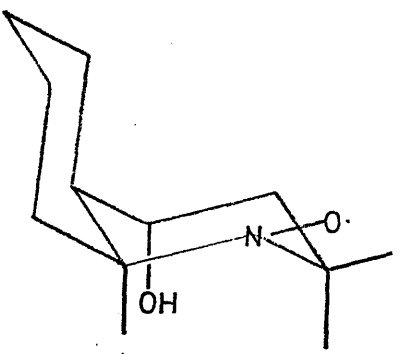

(84)



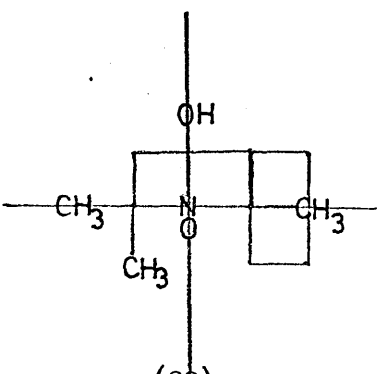

(85)



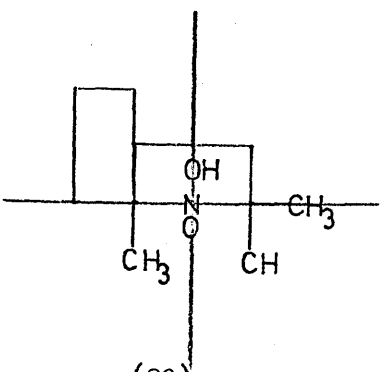

(86)




(87)



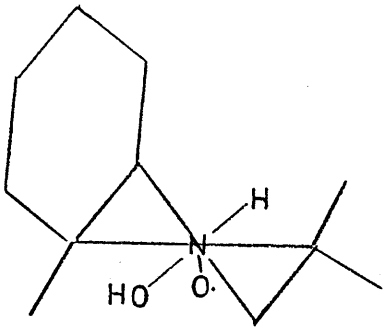

(88)



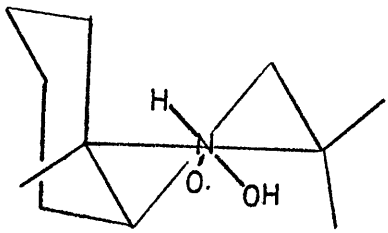

(89)

The remaining cis-alcohols also present a vexing problem. The cis-cis-isomer (19), as noted before, does not show a CD maximum in the 400-450 nm region, or at least the Cotton effect was too weak to be observable at the concentration used (which was approximately the same as used for the other cis compounds). This means that, in the octant projections of the preferred conformer, the contributions from substituents in the negative octants must exactly balance out the contributions from the substituents occupying positive octants. Alternatively, the conformational equilibrium must be such that the rotatory power of one conformer balances exactly the rotatory power of the other. This may be more likely since it is difficult to draw an octant diagram in which contributions cancel out.

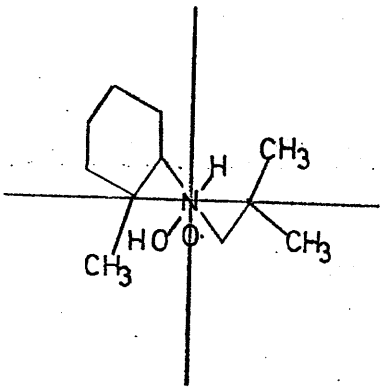
The cis, trans-isomer (15) shows a positive CD maximum at 447 nm, $[\theta] = +1070$, and a positive Cotton effect at 446 nm, $a = +15.7$ in its ORD spectrum. In addition, it is significant than in its infrared spectrum this compound shows two hydroxyl bands at 3,630 and 3,600 $cm^{-1}$. These do not change on dilution and hence are indicative of a weak hydrogen-bond[43] between the hydroxyl group and the nitroxide function. This can only be realised in the boat conformation (84) which would indeed be predicted to show a positive CD maximum (projection 85). However, the chemical behaviour of this compound (fast reaction



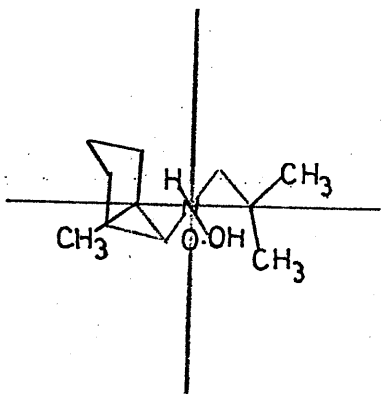

(90)




(91)




(92)




(93)

with trimethylsilyldiethylamine) indicate that other conformations in which the hydroxyl is much more exposed than in (84) must be present. Also, some of the other conformations, (87) and (90), would be expected to show positive CD maxima and hence cannot be discounted.

The above analysis of the conformations of the nitroxide alcohols shows that the argument, based on all-chair conformations, which led to the choice of trimethylsilyldiethylamine to aid the separation of these isomers was wrong. The result, however, was right.

It can be seen from this work that ORD and CD spectra can give very useful information on the electronic transitions and stereochemistry of nitroxides. Although not unambiguous, this information is only difficultly obtained by other methods. To extend the utility of the method it is thought that the effect of solvent and temperature on the CD spectra of these compounds would be worthwhile studying as this should give better information regarding any conformational equilibria[44]. It is also believed that some independent verification of the conclusions drawn in this thesis, e.g. n.m.r. or dipole moment studies are required.

## EXPERIMENTAL.

The same general experimental details apply here as outlined on page 41. In addition all rotations were measured at room temperature on a Perkin-Elmer 141 polarimeter. The ORD and CD curves were measured in methanol solution using a Carey-60 spectropolarimeter.

Attempted resolution of trans,cis-4-hydroxy-2,2,8a-trimethyl-decahydroquinoline-1-oxyl.(3) and (4)

(a) as 3β-acetoxy-$\Delta^5$-etienate ester.[5]

A mixture of 3β-acetoxy-$\Delta^5$-etienic acid (5) (100 mg.), benzene (2.75 ml.) and oxalyl chloride (0.1 ml.) was allowed to stand at room temperature for 23 hours. The solvent and excess oxalyl chloride were removed on a rotatory evaporator. To the crude acid chloride was added pyridine (2 ml.) followed by a solution of the trans,cis-nitroxide alcohol (3)and(4) (40 mg.) in pyridine (1 ml.). After standing at room temperature for two days, water (5 ml.) was added and the orange precipitate collected by filtration. The precipitate was washed with ether (3β-acetoxy-$\Delta^5$-etienic acid is fairly insoluble in ether) and the washings purified by preparative t.l.c. developing with ether/petroleum ether (5:1) to yield a light fluffy foam (53 mg.), $\nu$max.($CCl_4$) 1730 $cm^{-1}$. Analytical t.l.c. developing 16 times in ethyl acetate/petroleum ether (1:9) or 8 times in ethyl acetate/petroleum ether (1:3) did not produce streaking of the spot let alone separation of the diastereomers (6) and (7).

(b) as p-toluenesulphonate salt of valine ester.(9)[7]

A mixture of L-valine (27 mg.), trans,cis-nitroxide alcohol (109 mg.) and p-toluenesulphonic acid (52 mg.) in a mixture of benzene and toluene (70:30,5 ml.) was refluxed in a Dean and Stark water separator for 30 hours. The mixture was cooled, filtered, and the solvents evaporated under reduced pressure. A brown oil was obtained with no trace of crystalline material. Probably extensive decomposition of the nitroxide in the strong acid medium at elevated temperatures had occurred.

Resolution of trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline.

Small scale attempts were made to form crystalline salts of the following optically active acids with the indicated results.

(-)-malic acid : oil obtained.

L-(-)-tartaric acid : oil obtained.

L-(-)-2-pyrrolidone-5-carboxylic acid : oil obtained.

(-)-dibenzoyltartaric acid : oil which slowly crystallised.

(+)-di-p-toluoyltartaric acid : oil which slowly crystallised.

D-(+)-camphor-10-sulphonic acid : white crystalline solid.

(-)-α-bromocamphor-π-sulphonic acid : white crystalline solid.

The salt from D-(+)-camphor-10-sulphonic acid was crystallised from isopropanol with the following results :

1st. crystallisation : m.p. 268-276°C, $[\alpha]_{589}$=+23.3° (c=1.0,methanol)

2nd. crystallisation : m.p. 268-273°C, $[\alpha]_{589}$=+23.5° (c=2.0,methanol)

3rd. crystallisation : m.p. 267-270°C, $[\alpha]_{589}$=+23.5° (c=1.9,methanol)

The material from the third crystallisation was dissolved in 4N sodium hydroxide solution and extracted continuously with ether for 24 hours. After removal of the solvent a brown solid was obtained which on sublimation at 0.4 mm. yielded the trans,cis-amino alcohol as a slightly yellow solid which showed no rotation at either 589 or 365 nm in methanol solution.

The salt from (-)-α-bromocamphor-π-sulphonic acid was recrystallised twice from ethanol. The amino alcohol was regenerated in quantitative yield by percolating a methanol solution of the salt through an ion exchange column of basic Amberlite IRA-400($OH^-$). After sublimation, the amino alcohol had the following specific rotations.

$[\alpha]_{589}$=-3.4°, $[\alpha]_{365}$=-10.6° (c=0.83,methanol).

Large scale resolution of trans,cis-amino alcohol.(10)

A solution of the trans,cis-amino alcohol (3.19 g.,16.2 mmole) and (-)-α-bromocamphor-π-sulphonic acid ammonium salt (5.31 g., 16.2 mmole) in methanol (250 ml.) was heated on a steam bath until no more ammonia was evolved. The solvent was removed on a rotatory evaporator to yield a white crystalline solid which was systematically recrystallised from ethanol with the results shown below.

1st. crystallisation : 5.4 g., m.p. 235-263°C, $[\alpha]_{589}$= -62.0° (c=2.1,methanol.)

2nd. crystallisation : 3.3 g., m.p. 246-269°C, $[\alpha]_{589}$= -59.6° (c=1.8,methanol.)

3rd. crystallisation : 1.8 g., m.p. 246-263°C, $[\alpha]_{589}$= -63.5° (c=1.9,methanol.)

4th. crystallisation : 1.2 g., m.p. 250-264°C, $[\alpha]_{589}$= -61.6° (c=2.0,methanol.)

5th. crystallisation : 0.5 g., m.p. 251-265°C, $[\alpha]_{589}$= -63.9° (c=2.1,methanol.)

A portion of this 5th. crop (100 mg.) was decomposed on a basic ion-exchange column and sublimed to yield the amino alcohol (33 mg.), $[\alpha]_{589}$= -5.6°, $[\alpha]_{365}$= -18,3°(c=1.4,methanol.)

The 'tail' mother liquor fractions after 5 rounds of recrystallisation were also decomposed to yield the crystalline amino alcohol (396 mg.), $[\alpha]_{589}$= +12.8°, $[\alpha]_{365}$= +38.6°(c=0.9,methanol.) This material was used for preparation of optically active nitroxide radicals.

Resolution of cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl as the 3 β- acetoxy- $\Delta^5$-etienate ester

3 β-Acetoxy- $\Delta^5$-etienic acid (134 mg.) was dissolved in thionyl chloride (2 ml.) and allowed to stand at room temperature for 4 hours. The thionyl chloride was removed under reduced pressure to yield a pale yellow solid (143 mg.), $\nu$max (Nujol) 1790 and 1730 $cm^{-1}$. To this was added pyridine (2 ml.) followed by a solution of the cis, trans-nitroxide alcohol (45 mg.) in pyridine (1 ml.). After standing overnight at room temperature the mixture was diluted with ethyl acetate and transferred to a separatory funnel. The organic layer was washed with 1N hydrochloric acid and saturated sodium bicarbonate solution. After drying over magnesium sulphate and removal of the solvent a red oil (125 mg.) was obtained. This was purified by preparative t.l.c. using ether/petroleum ether (1:1) as solvent to yield a red oil (75 mg.), $\nu$ max.($CCl_4$) 1731 $cm^{-1}$.

A sample of this ester (27 mg.) was streaked on a preparative t.l.c. plate (20 cm x 20 cm x 0.5 mm) and continuously developed using a Desaga chamber with ether/petroleum ether (1:9) for 6 hours. Two closely running bands were observed which were cut out, allowing generously for overlap. The two components had the following rotations.

Top band : $[\alpha]_{589} = +24.8^{\circ}$, $[\alpha]_{365} = -210^{\circ}$ (c=0.42, tetrahydrofuran).

Bottom band : $[\alpha]_{589} = -46.8^{\circ}$, $[\alpha]_{365} = +131^{\circ}$ (c=0.44, tetrahydrofuran).

Another sample (25 mg.) was separated by t.l.c. using continuous elution with ethyl acetate/petroleum ether (1:19) to yield components with the following rotations.

Top band : $[\alpha]_{589}$= +22.9°, $[\alpha]_{365}$= -203°(c=0.38, tetrahydrofuran).

Bottom band : $[\alpha]_{589}$= -48,1°, $[\alpha]_{365}$= +138°(c=0.32, tetrahydrofuran).

One crystallisation of the rest of the material from methanol gave an orange solid with the following properties :

$[\alpha]_{589}$= -41.6°, $[\alpha]_{365}$= +104° (c=0.12 tetrahydrofuran), m.p. 204-225°C.

Large scale resolution of cis,trans-nitroxide alcohol.(14)and(15)

From 3β-acetoxy-$\Delta^5$-etienic acid (4.3 g.) and the cis,trans-nitroxide alcohol (2.1 g.) was prepared the etienate ester which was chromatographed on neutral alumina (grade III, 200 g.). Elution with solvent systems ether/petroleum ether (1:9) to ether/petroleum ether (1:6) gave the etienate ester (4.5 g.) as a red solid.

Two recrystallisations of this material from methanol gave red needles (1.1 g.), m.p. 202-216°c, $[\alpha]_{589}$= -52.1°(c=0.1, tetrahydrofuran). The combined mother liquors were concentrated and crystallised to yield needles (1.1 g.) m.p. 160-195°C. The mother liquors from this fraction were evaporated to dryness to yield a red solid (1.9 g.), m.p. 120-150°C.

Hydrolysis of etienate ester. (17)

The etienate ester (1.9 g., m.p. 120-150°C) was dissolved in ethanol (100 ml.) and to this was added a solution of sodium hydroxide in water (3 g. in 20 ml.). The mixture was refluxed for 16 hours, cooled and most of the ethanol removed on a rotatory evaporator. The resultant mixture was extracted thoroughly with ether, the ethereal layer washed with dilute sodium hydroxide solution, brine and dried over magnesium sulphate. Removal of the solvent yielded a red oil (536 mg.) which slowly solidified. This was chromatographed on neutral alumina (grade III, 20 g.) eluting with ether/petroleum ether (30:70) to yield (+)cis,trans-4-hydroxy-2,2,8a trimethyldecahydroquinoline-1-oxyl as a red solid, $[\alpha]_{589}$= +64.9°(c= 0.98,methanol.) (15)

Hydrolysis of the etienate ester (m.p. 202-216°C) gave the enantiomeric nitroxide alcohol, $[\alpha]_{589}$= -98.5°(c=0.39,methanol).(14)

(-)Cis-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl. (18)

Oxidation of the (+)cis,trans-nitroxide alcohol ( $[\alpha]_{589}$= +64.9°) using dimethylsuphoxide, dicyclohexyl carbodiimide and pyridinium trifluoroacetate in the usual fashion gave (-)cis-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl as a red oil, $[\alpha]_{589}$= - 50.4° (c=0.27,methanol).

(+)-Ciscis-4-hydroxy-2.2.8a-trimethyldecahydroquinoline-1-oxyl.(19)

To a stirred mixture of tetrahydrofuran (2 ml.) and lithium aluminium hydride (45 mg.) was added t-butanol (236 mg.) in tetrahydrofuran (2 ml.) followed by (-)-cis-ketone(18)(80 mg., $[\alpha]_{589} = -50.4^{o}$) in tetrahydrofuran (0.6 ml.). The mixture was stirred at room temperature for 16 hours and decomposed by the sodium sulphate technique. The red oil thus obtained (78 mg.) was dissolved in acetone (0.5 ml.) and trimethylsilyldiethylamine (0.3 ml.) added. The mixture was allowed to stand at room temperature for 5 hours, the solvent removed and the red oil obtained separated by preparative t.l.c. into components.

Top band : 38 mg. red oil, cis,cis-trimethylsilyl ether (21).

Bottom band : 34 mg. red oil, cis,trans-trimethylsilyl ether (20 ).

The material from the top band was hydrolysed by refluxing with 4% sodium hydroxide solution (0.5 ml.) in a mixture of methanol (5 ml.) and benzene (0.5 ml.) for 12 hours. The usual work-up followed by preparative t.l.c. yielded (+)-cis,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl as a red oil, $[\alpha]_{589} = +11.8^{o}$ (c= 0.48,methanol).

(-)-Trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl. (3)

A mixture of (+)-trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline (298 mg., $[\alpha]_{589}$= +12.8°), sodium tungstate (19 mg.), the disodium salt of ethylenediaminetetraacetic (28 mg.), 30% hydrogen peroxide solution (1,5 ml.), water (7.5 ml.) and methanol (7.5 ml.) was stirred at room temperature for 6 days. The mixture was then extracted with ether, washed with sodium bicarbonate solution and brine, dried over magnesium sulphate and the solvent removed to yield a red solid (243 mg.) which was purified by preparative t.l.c. Sublimation then yielded the trans,cis-nitroxide alcohol ( 3 ) as a red solid (204 mg.), $[\alpha]_{589}$= -39.6° (c=0.73,methanol).

(-)Trans-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl.(13)

Oxidation of the (-)-trans,cis-nitroxide alcohol (27 mg. $[\alpha]_{589}$= -39.6°) by the usual method gave (-)-trans-2,2,8a trimethyloctahydro-4-quinolone-1-oxyl (13 ) as a yellow solid (21 mg.), $[\alpha]_{589}$= -105° (c=0.72, methanol).

Determination of the absolute configuration of (-)-Trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxylby Horeau's method.[14]

α-Phenylbutyric anhydride was prepared by refluxing α-phenylbutyric acid (1.2.g.) in acetic anhydride (12 ml.)for 16 hours. Removal of the solvent, azeotroping several times with toluene yielded a clear, slightly yellow oil, $\nu$max(film) 1810 and 1740 $cm^{-1}$, which was used without further purification.

A solution of the above anhydride (121 mg.,0.27 mmole), (-)-trans,cis-nitroxide alcohol (25 mg.,0.12 mmole) and pyridine (2.5 ml.) was allowed to stand at room temperature overnight. Water

(1 ml.) was added, the mixture allowed to stand for 5 hours and then diluted with ether. The organic layer was extracted three times with saturated sodium bicarbonatesolution. This bicarbonate extract was acidified with sulphuric acid and thoroughly extracted with chloroform. The chloroform extracts were washed with water, dried over magnesium sulphate and the solvent removed to yield $\alpha$-phenylbutyric acid as a slightly yellow oil which slowly solidified. This was shown to be pure by NMR analysis.

The neutral ethereal extracts were washed thoroughly with 1N hydrochloric acid, water and dried over magnesium sulphate. Removal of the solvent yielded a red oil (36 mg.) which was separated by preparative t.l.c. into two components. The more polar component was the starting alcohol (8 mg.) and the less polar was the $\alpha$-phenylbutyrate ester (18 mg.), $\upsilon$ max ($CCl_4$) 1740 $cm^{-1}$.

The $\alpha$-phenylbutyric acid was dissolved in benzene (2 ml.) and its rotation measured,

$$[\alpha]_{589} = -1.46^{\circ} (c=3.5, \text{benzene}).$$

Based on the amount of ester isolated (18 mg., 0.051 mmole) and an optical purity of 43% for the nitroxide alcohol, we can calculate that for 100% induction of asymmetry the rotation of the $\alpha$-phenylbutyric acid would have been $-9.96^{\circ}$.

$$\text{Hence optical yield} = \frac{1.46}{9.96} \times \frac{100}{0.43} = \underline{35\%}$$

Based on the maximum amount of alcohol that might have reacted (17 mg.), the optical yield is calculated to be $\underline{20\%}$

It is generally assumed that for optical yields $>10\%$ this method gives correct predictions of absolute configuration. We can assign the absolute configuration S to position 4 in (-)trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl.

Hence the total absolute configuration of this compound is 4S,4aR,8aR. (3)

The absolute configuration of (-)trans-2,2,8a-trimethyloctahydro-4-quinolone-1-oxyl is therefore 4aR,8aR (13)

Determination of absolute configuration of (+)cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl.

$\alpha$-Phenylbutyric anhydride (113 mg., 0.25 mmole), (+) cis,trans-nitroxide alcohol (21 mg., 0.098 mmole, $[\alpha]_{589} = +64.9^{\circ}$) and pyridine (2.5 ml.) was allowed to stand at room temperature for 18 hours. Water (1 ml.) was added and the mixture allowed to stand for 3 hours. Work up as above gave $\alpha$-phenylbutyric acid (90 mg.) and a red oily ester (30 mg.) which showed no trace of unreacted alcohol by t.l.c. or infrared analysis ($\nu$ max (film) = 1740 $cm^{-1}$).

The $\alpha$-phenylbutyric acid was dissolved in benzene (2 ml.) and its rotation measured.

$[\alpha]_{589} = +1.2^{\circ}$ (c=4.5, benzene).

Optical yield = 11%

Configuration at position 4 is R.

Hence the absolute configuration of this compound is designated 4R,4aR,8aS. (15)

Hence the absolute configuration of (-)cis-2,2,8a-trimethyl-octahydro-4-quinolone-1-oxyl is 4aR,8aS; and the absolute configuration of (+)-cis,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl is 4S,4aR,8aS.

Determination of optical purity of (-)trans,cis-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl.(3)

A solution of (+)-methoxytrifluoromethylphenylacetic acid (100 mg.) in thionyl chloride (4 ml.) was refluxed for $4\frac{1}{2}$ hours. Excess thionyl chloride was removed at the water pump, the last traces being removed by azeotroping with benzene. The resultant acid chloride was dissolved in pyridine (1.5 ml.) and to this was added a solution of the racemic trans,cis-nitroxide alcohol (3)and(4) (49 mg.) in pyridine (1.5 ml.) with stirring and ice-bath cooling. The mixture was stirred at ambient temperature for 22 hours, then diluted with ether, washed thoroughly with 1N hydrochloric acid, saturated sodium bicarbonate solution and brine, and dried over magnesium sulphate. Removal of the solvent yielded a red oil which was purified by preparative t.l.c., using ether/petroleum ether (1:1) as solvent, to yield a red oil (73 mg.), $\nu$ max ($CCl_4$) 1750 $cm^{-1}$. A sample of this ester (65 mg) was dissolved in methanol (10 ml.) and Raney nickel added. Hydrogenation in the usual manner, filtration and removal of the solvent yielded a clear oil (64 mg.), $\nu$ max (film) 1740 $cm^{-1}$, $\tau$ 2.4-2.6 (5H,m), 4.70(1H,m), 5.40 (1H,br, disappears on $D_2O$ exchange),6.45 (3H,m), 8.0-9.2 (20H, complex multiplet).

The spectrum was run at 100 MHz with scale expansions in the 6.4-6.5 $\tau$ region (methoxyl) and 8.9-9.2 $\tau$ region (methyl). The methoxyl region showed two quartets centred at 6.42 and 6.48 $\tau$ (J= 1.2Hz) which were almost completely separated and in a 1 : 1 ratio. In the methyl region two singlets were observed at 8.90 and 9.08 $\tau$ sufficiently separated from the rest of the spectrum to allow the areas under them to be measured. These were again in 1 : 1 ratio. Hence this is a 1 : 1 mixture of diastereomers as expected.

The same procedure was repeated on a sample of (-)trans,cis-nitroxide alcohol ($[\alpha]_{589} = -39.6^{0}$). The amino-ester thus obtained had in general terms a very similar NMR spectrum to that above but there were significant differences in the chemicals shifts of individual peaks.

$\tau$ 2.35-2.60(5H,m),4.68(1H,m),6.44(3H,m), 8.0-9.2 (21H,complex multplet).

The methoxyl region showed two quartets at 6.41 and 6.47 $\tau$ in a ratio of 1 : 2.4. The methyl region showed 4 peaks far enough upfield from the rest of the spectrum to allow the areas under them to be measured at 8.93 , 8.99 , 9.05 and 9.17 $\tau$; in ratios of 2.4 : 1 and 2.3 : 1. The average of these gives an optical purity of 43% for this compound.

Determination of optical purity of (-)-cis,trans-4-hydroxy-2,2,8a-trimethyldecahydroquinoline-1-oxyl.(14)

The above procedure was carried out with samples of racemic and optically active cis,trans-nitroxide alcohols ($[\alpha]_{589} = -98.5^{\circ}$) and the NMR spectra of the (+) methoxytrifluoromethylphenylacetate esters obtained after reduction of the nitroxide to the amine were recorded. Racemic amino-esters : $\tau$ 2.4-2.7(5H,m)4.48(1H,m),6.43(3H,m), 7.8-8.9(21H,complex multiplet). Expansion of the methoxyl region showed two quartets at 6.41 and 6.45 $\tau$(J=1.1Hz) in a ratio of 1 : 1. Optically active amino ester : $\tau$ 2.4-2.7(5H,m),4.51(1H,m) 6.45(3H,m), 7.8-8.8 (complex multiplet,21H). Expansion of the methoxyl region showed only one quartet at 6.45 $\tau$ and hence we may conclude that this compound is 95% optically pure.

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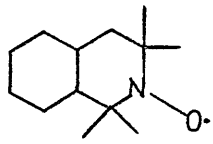
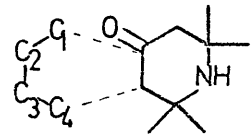
## 3. Synthetic approaches to decahydroisoquinoline nitroxides.

The other type of bicyclic nitroxide radical which was considered worthy of study was the tetramethyldecahydroisoquinoline nitroxide (1) or its derivatives. Bearing in mind that the greatest synthetic difficulty is production of the blocked amine this might at first sight seem a fairly difficult problem. However, when it is realised that this compound could be derived by annelation of triacetonamine (2) the task appears deceptively simple. A few of the abhorrtive exploratory experiments performed with this end in mind will now be described.



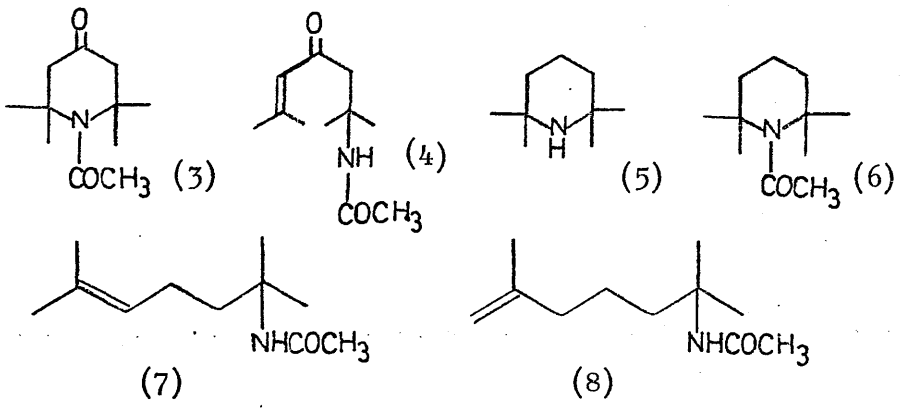

(1)




(2)

A number of attempts were made to protect the amino function of triacetonamine with conventional acylating and alkylating reagents. The difficulty of causing reaction at such a hindered site has been noted before[1]. Refluxing triacetonamine (2) in a mixture of acetic anhydride and sodium acetate produced a mixture of two compounds which could be separated by preparative t.l.c. The less polar component appeared to be N-acetyl triacetonamine (3)[2] while the more polar component appeared to be the ring opened

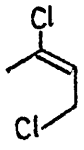
product (4). Ring opening has also been observed [3] on attempted acetylation of the tetramethylpiperidine (5) when as well as the expected product (6) the ring opened products (7) and (8) were obtained.



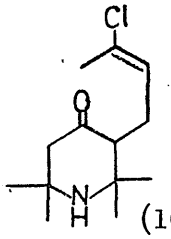

It was decided, therefore, to use triacetonamine itself in attempted annelations in the hope that the hindered nature of the amine would prevent this group interfering in any of the reactions. However, attempted annelation of triacetonamine with methyl vinyl ketone[4] was unsuccessful, only unreacted starting material being recovered.

Stork[5] has described a number of methyl vinyl ketone equivalents which have been used with varying success as methyl vinyl ketone synthons. It was decided to try the most readily available of these, 1,3-dichlorobut-2-ene (9)[6]. Triacetonamine was refluxed with sodamide in benzene to produce the enolate ion which was then treated with 1,3-dichlorobut-2-ene[7]. A product

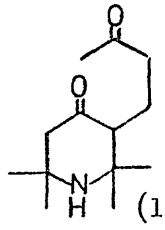
could be isolated in low yield by preparative t.l.c. whose n.m.r. spectrum seemed consistent with the monoalkylated product (10). Unreacted triacetonamine was also obtained. The low yield can reasonably be explained by the gem-dimethyl groups preventing access of the alkylating reagent to the α-methylene groups of the ketone. Treatment of this product (10) with concentrated sulphuric acid[6] produced a compound which was thought to be the diketone (11). Normally the product obtained from this acid treatment is cyclised material such as (12) or (13). In order to obtain either of these, the suspected diketone (11) was treated with ethanolic potassium hydroxide to yield a product which showed three spots on t.l.c. and bands at 1715 and 1670 $cm^{-1}$ in its infrared spectrum. This could mean that both the fused (12) and bridged (13) amines were produced in this reaction. However, because of the low yields and complexity of the mixture obtained this approach was not investigated further.



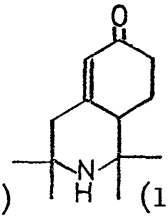

(9)




(10)




(11)

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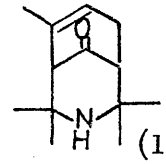
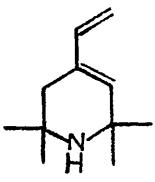



(13)

Another approach which was investigated involved conversion of triacetonamine to the diene (14) which on Diels-Alder addition

to a suitable dienophile (15) should produce the compound (16) with the required isoquinoline ring system. The standard method for producing such dienes involves conversion of a ketone to the corresponding ethynyl carbinol, reduction of the acetylene to the olefin and dehydration of the resultant vinyl carbinol[8]. Conversion of triacetonamine to the ethynyl carbinol (17) was accomplished using lithium acetylide ethylenediamine complex[9] in benzene solution. This compound was insoluble in every organic solvent tried except hot ethylene glycol monomethyl ether. This thwarted all attempts to reduce it to the vinyl carbinol (18) using lithium aluminium hydride[10]. This latter compound (18), however, could be produced in high yield by Grignard addition of vinyl magnesium bromide solution[11].

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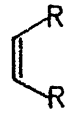


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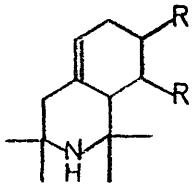


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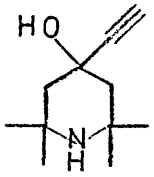


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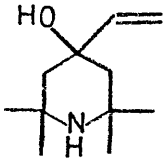


(18)

All attempts to dehydrate this compound have proved fruitless. However, no attempts have been made to utilise the corresponding nitroxide which might be a better candidate for elimination experiments. Lack of time prevented any further work in this direction.

## EXPERIMENTAL.

### Triacetonamine (2).

This was prepared from phorone and concentrated ammonia solution by the method of Sandris and Ourisson [2]. In order to obtain anhydrous material an ethereal solution was dried over anhydrous magnesium sulphate and distilled to yield triacetonamine, b.p. 90°C/10 mm., which slowly solidified, m.p. 35°C.

### Acetylation of triacetonamine.

A mixture of triacetonamine (91 mg.), sodium acetate (108 mg.) and acetic anhydride (2 ml.) was refluxed for seven hours and then allowed to stand at room temperature for 48 hours. Water (7.5 ml.) was added and the mixture heated on the steam-bath. The solution was basified with solid potassium carbonate and extracted thoroughly with ether. The organic extracts were washed successively with saturated sodium bicarbonate solution and brine. After drying over magnesium sulphate and removal of the solvent, a yellow oil was obtained which was separated by preparative t.l.c. into two components (developed twice with petroleum ether/ethyl acetate/diethylamine, 70:15:10).

Less polar component (3) : 22 mg., $\nu_{max.}(CHCl_3)$ 1730 (s), 1630 (s) and 1370 (s) $cm^{-1}$, $\tau$ 7.4(4H,s), 7.8(3H,s), 8.5(12H,s).

More polar component (4) : 20 mg., $\nu_{max.}(CHCl_3)$ 3440 (m), 3380 (br), 1670 (s), and 1615 (s) $cm^{-1}$, $\tau$ 3.95(2H,m), 7.20(3H,s),

7.85(3H,d), 8.10(3H,s), 8.12(3H,d), 8.58(6H,s). Peak at 3.95$\tau$ integrates for only one proton when a few drops of $D_2O$ and trifluoroacetic acid were added.

Attempted annelation of triacetonamine with methyl vinyl ketone.

To a solution of triacetonamine (3.3 g.) in ether (90 ml.) to which had been added ethanolic potassium hydroxide (1.5 ml. of 2M ) was added dropwise over a period of one hour a solution of methyl vinyl ketone (1.5 g.) in ether (25 ml.) with stirring and ice-bath cooling. After addition was complete the mixture was stirred at room temperature for 3 hours. The mixture was then poured onto ice and dilute hydrochloric acid was added until the pH was 6. The layers were separated, the aqueous layer being extracted several times with ether. The aqueous extracts were then basified, extracted with ether and the ethereal layer dried over magnesium sulphate. Removal of the solvent under reduced pressure yielded a mobile yellow oil (2.95 g.)which showed a broad band at 3450 $cm^{-1}$ and a band at 1705 $cm^{-1}$in its infrared spectrum. Distillation gave an unidentified low boiling fraction and a fraction boiling at 79-82$^{o}$C/10 mm. This was identical by n.m.r. and infrared comparison to triacetonamine.

Attempted annelation of triacetonamine with 1,3-dichlorobut-2-ene.

Triacetonamine (1.66 g.) was refluxed with powdered sodamide (0.42 g.) in benzene (11 ml.) for 6 hours and then allowed to cool

overnight under nitrogen. 1,3-Dichlorobut-2-ene (1.69 g.) in benzene (5 ml.) was added dropwise followed by another portion of benzene (5 ml.). The mixture was refluxed for 4 hours, cooled and poured into hydrochloric acid solution (50%). The layers were separated and the aqueous layer basified. Extraction with ether, drying over magnesium sulphate and removal of the solvent yielded a yellow oil (700 mg.). This showed two spots on t.l.c. which corresponded to triacetonamine and a less polar component. Preparative t.l.c. separation of a sample of this mixture (250 mg.) using petroleum ether/ethyl acetate/diethylamine (25:4:1) as solvent system and eluting three times yielded the less polar material as an oil (58 mg.) and triacetonamine (97 mg.).

Less polar component (10) : $\tau$ 7.70(4H,m), 7.97(3H,s), 8.48(2H,s), 8.70(3H,s), 8.77(3H,s), 8.85(3H,s), 8.96(3H,s), 4.50(1H,s).

Treatment of this material with sulphuric acid (90%) at 0°C for 30 minutes, followed by basification, ether extraction, drying over magnesium sulphate and removal of the solvent yielded a yellow oil (40 mg.). Preparative t.l.c. yielded an oil (24 mg.), $\tau$ 7.70(2H,s), 7.90(3H,s), 8.70(3H,s), 8.75(3H,s), 8.85(3H,s), 8.97(3H,s), 7.50-8.50(6H).

Treatment of this material (11) with ethanolic potassium hydroxide (0.2 ml., 3M) for 2 hours, dilution with water and extraction with ether yielded solid material (12 mg.) which showed 3 spots on t.l.c. and bands at 1715 and 1670 $cm^{-1}$ in its infrared spectrum.

4-Ethynyl-2,2,6,6-tetramethyl-4-piperidinol (17).

A mixture of lithium acetylide ethylenediamine complex (1.18 g.) and benzene (20 ml.) was stirred under nitrogen at 35°C. To this was added dropwise over 15 minutes a solution of triacetonamine (1.01 g.) in benzene (4 ml.). Stirring was continued for 3 hours, water (5 ml.) added and the mixture refluxed for 1 hour. After cooling the mixture was filtered and the white solid obtained extracted with ethylene glycol monomethyl ether in a Soxhlet apparatus. Removal of the solvent and crystallisation from the same solvent yielded a white powdery solid (314 mg.), m.p. 209-214°C (lit.[12] 214-215°C), $\nu_{max.}$ (Nujol) 3210 (s), 3200-2700 (br), and 2100 (w) $cm^{-1}$.

Attempted reduction of ethynyl carbinol (17) to vinyl carbinol (18).

The ethynyl carbinol (84 mg.) was placed in a Soxhlet thimble which was situated above a refluxing mixture of tetrahydrofuran (25 ml.) and lithium aluminium hydride (40 mg.). After 3 hours reflux the mixture was decomposed by addition of saturated sodium sulphate solution. Filtration and removal of the solvent yielded a white solid whose infrared spectrum was identical to that of the starting material.

4-vinyl-2,2,6,6-tetramethyl-4-piperidinol (18).

Magnesium turnings (1.14g.) were flame dried in a stream of nitrogen. Dry tetrahydrofuran (15 ml.) was added followed by a few drops of vinyl bromide in tetrahydrofuran (6.3 g. in 15 ml.). A few drops of ethylene dibromide were added to initiate the reaction and then, with stirring, the remainder of the vinyl

bromide solution was added at such a rate that the temperature was maintained at 45-50°C. On completion of the addition the mixture was refluxed for 1 hour and then cooled in an ice-bath. The dry-ice condenser which had been used until this point was replaced by a reflux condenser. Triacetonamine (3.28 g.) in tetrahydrofuran (6 ml.) was added dropwise over 20 minutes, the mixture stirred at ambient temperature for 19 hours, and then refluxed for 1 hour. After cooling the mixture was decomposed by pouring into an ice-cold saturated solution of ammonium chloride. Extraction with ether, drying over magnesium sulphate and removal of the solvent yielded a yellow oil (0.75 g.) which showed 4 spots on t.l.c. The aqueous extracts were continuously extracted with ether for 18 hours to yield a yellowish-white solid (2.68 g., 71%) which was the desired vinyl carbinol (18), m.p.54-56.5°C (after sublimation), $\nu_{max.}$(Nujol) 3300 (br), 1640 (w), 1000 (s), 925 (s) $cm^{-1}$, $\tau$ 4.06(1H,q,JAB=17Hz,JAC=10Hz), 4.80(1H,q,JBA=17Hz,JBC=1.5Hz), 5.05(1H,q,JCA=10Hz,JCB=1.5Hz), 8.2-8.8(6H,two disappear on $D_2O$ exchange), 8.60(6H,s), 8.87(6H,s).

Found : C,71.91 ; H,11.42 ; N,7.37%,

$C_{11}H_{21}NO$ requires: C,72.08 ; H,11.55 ; N,7.64%.

Attempted dehydrations of the vinyl carbinol (18).

The following reagents have been tried with no success: Iodine, distillation from potassium bisulphate, p-toluenesulphonic acid and perchloric acid : starting material recovered unchanged. Thionyl chloride/pyridine : no isolable product.

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