A THESIS

ENTITLED

'STUDIES IN CYCLIC NITROXIDE RADICALS'

SUBMITTED TO THE UNIVERSITY OF STIRLING

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE DEPARTMENT OF CHEMISTRY

BY D. W. GILMOUR, B.Sc.

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TO MY PARENTS AND TRICIA

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A grant from the Science Research Council is gratefully acknowledged.

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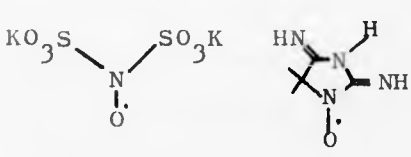
C O N T E N T S

INTRODUCTION

Interest in the chemistry of nitroxide radicals has intensified over the past twenty years resulting in an exponential growth in the study of nitroxides from several varied standpoints. These include the intrinsic theoretical, spectroscopic, chemical aspects and the broader application to allied sciences such as molecular biology, biophysics and polymer chemistry.

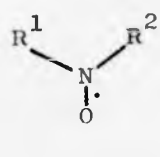
Several reviews[1-5] on nitroxide radical chemistry have been published and these serve to indicate the great diversity of structural types into which the nitroxide nucleus has been embedded. The principal objective of this introduction is, however, to highlight the progress made in aliphatic nitroxide radical chemistry. In particular, attention will be focused on the electronic and spectroscopic properties of this class of nitroxide. An attempt will also be made to describe the various synthetic methods which have been applied to prepare them.

The first nitroxide radical reported was made in 1845 by Fremy[6] who prepared the inorganic salt (1), but the first organic nitroxide, porphyrexide (2), was synthesised at the beginning of this century by Piloty and Schiverin[7]. Many years passed before a number of relatively stable diarylnitroxides of the type (3), R^1 and R^2 = aryl, were obtained[8]. However, it was not until 1959 that the first completely aliphatic nitroxide (4) was prepared by Lebedev[9].



(1)

(2)



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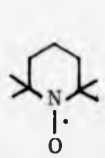
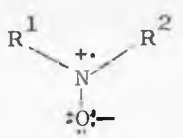


(4)

The intrinsic stability of the nitroxide molecule has been attributed to the arrangement of the electrons about the nitrogen and oxygen atoms. In valence bond terms, nitroxides of the general formula (3), where R^1 and R^2 are diaryl, dialkyl, or arylalkyl, can be represented by two contributing resonance structures (5) and (6). A detailed assessment of various spectroscopic parameters has enabled Hamilton and McConnell[10] to conclude that the unpaired electron is largely confined to the 2p atomic orbital on nitrogen corresponding to the canonical form (5). This simple picture of the bonding situation has been verified by Kikuchi[11] who has carried out LCAO-SCF-MO calculations using the CNDO/2 approximation.



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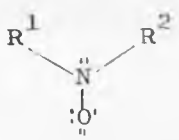


(6)

In a molecular orbital approach to the bonding in the nitroxide moiety, the nitrogen atom is considered to be sp^2 hybridised. Overlap by one of these hybrid orbitals with a p orbital of oxygen gives rise to a σ bonding and σ^* antibonding pair of orbitals, while overlap of the $2p_z$ orbitals of oxygen and nitrogen results in π bonding and π^* antibonding orbitals. As two of the electrons can occupy the π bonding orbital the unpaired electron is located in the π^* antibonding orbital. This results in a stabilised system which may be described as a two-centre three-electron bond. This bonding in nitroxide radicals can be represented by the molecular orbital energy diagram shown in Figure 1[12]. Figure 2 shows a similar representation for a carbonyl group.

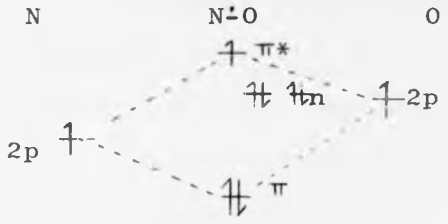


FIGURE 1

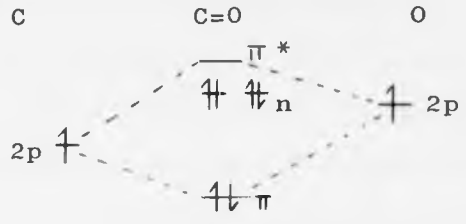
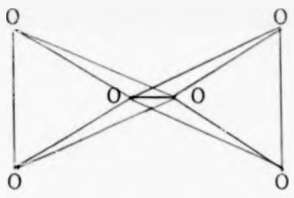


FIGURE 2

At first sight it is rather surprising that nitroxide radicals show no tendency to dimerise in solution. This behaviour is best explained by the double quartet hypothesis first proposed by Linnett[13], in which the six electrons of one spin are arranged as in (7) and the five of the other spin as in (8).



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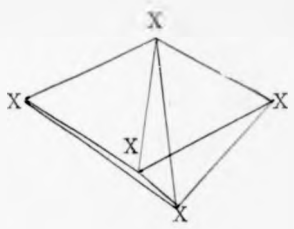


(8)

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

In contrast to the electronic stability, the chemical stability of nitroxide radicals is dependent upon the groups attached to the nitrogen atom. In general, stable aliphatic nitroxide radicals can only be isolated when the two carbon

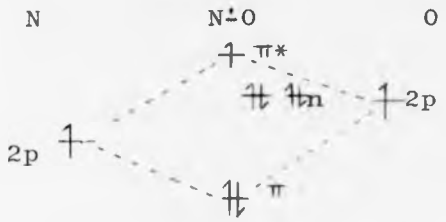
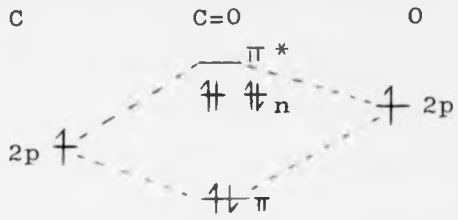


FIGURE 1



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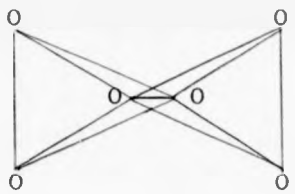

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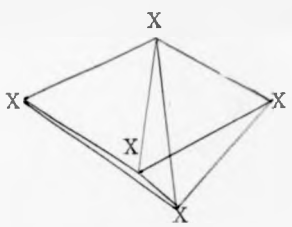

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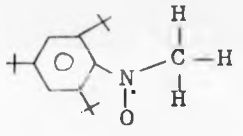
In contrast to the electronic stability, the chemical stability of nitroxide radicals is dependent upon the groups attached to the nitrogen atom. In general, stable aliphatic nitroxide radicals can only be isolated when the two carbon

atoms flanking the nitrogen atom are quaternary carbons whose substituents do not eliminate readily. When a β-hydrogen atom is present as in (9) a bimolecular decomposition occurs yielding the corresponding nitrone (10) and the hydroxylamine (11). The mechanism proposed for this reaction involves a diamagnetic dimer (12) as an intermediate[14-16]. A later study[17] on the decomposition of nitroxides using the labelled nitroxide (13) has shown that there is a deuterium isotope effect, $\frac{kH}{kD} = 9$ at 30°, for this decomposition. Thus the rate determining step involves the breaking of a C-H bond. In view of this fact a new mechanism has been proposed as outlined in Scheme 1, which is bimolecular, and does not involve a dimer of the type suggested earlier.



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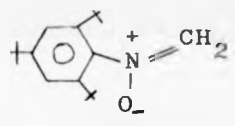

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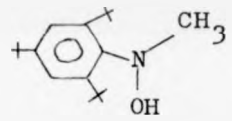

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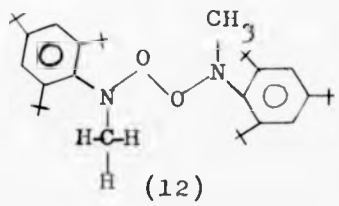

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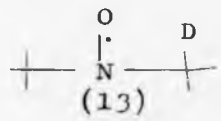

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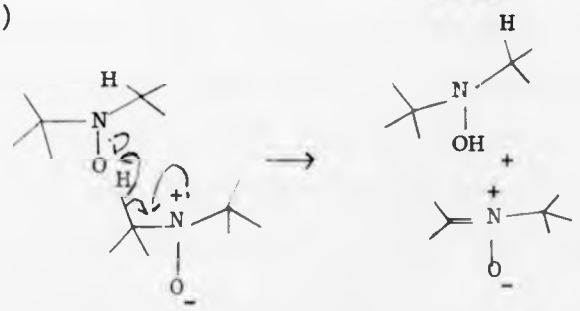
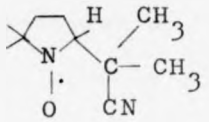


SCHEME 1

Nevertheless nitroxide radicals possessing a β-hydrogen have been isolated. These exceptions occur for two main reasons. First, the β-hydrogen may be very sterically

hindered as in (14)[18] and secondly, the orientation of the C-H bond with respect to the orbital on nitrogen containing the unpaired electron is not correctly aligned for a facile cleavage. The idealised geometry for homolytic scission of a β-hydrogen is seen in (15)[19-21]. With reference to the bicyclic nitroxide (16)[22] the C-H bond is practically orthogonal to the orbital containing the unpaired electron. The process of nitrone formation is also unfavourable in this bicyclic nitroxide due to Bredt's rule.



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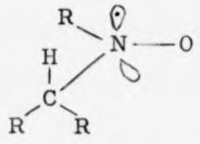

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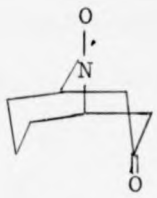
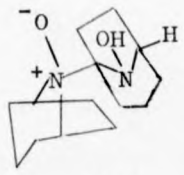


(16)

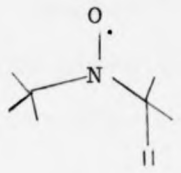
(17)



(18)

These bridgehead nitroxides have been found in some instances to decompose <u>via</u> a dimer though very slowly. Thus the nitroxide (17)[23] dimerises, not to give the expected compound, but rather to give the bridgehead dimer (18). In this context it has been found that 8-azabicyclo[3,2,1]-octane-N-oxyl (17) decompose much quicker than 9-azabicyclo-[3,3,1]nonane-N-oxyl (16).

The nitroxide radical (19)[24] is unusual from the point of chemical stability. Although the two carbons flanking the nitroxide are fully blocked, rapid decomposition to the trialkylhydroxylamine (20) occurs at room temperature.



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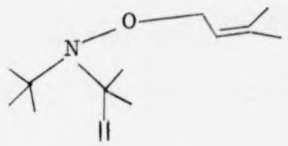
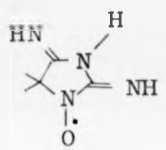


(20)

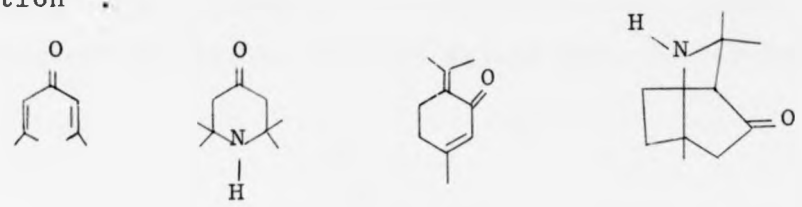
Nitroxides have been synthesised by a variety of methods. One of the most facile procedures involves the oxidation of an appropriately substituted hydroxylamine[3] by a variety of reagents which include silver oxide, lead oxide, potassium ferricyanide, oxygen, and sodium hypobromite. This method was used by Piloty and Schiverin in 1901 to prepare porphyrexide (2)[6].



(2)

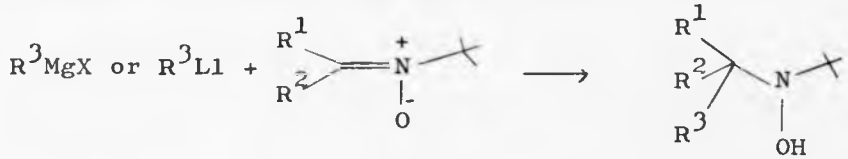
An obvious precursor for nitroxides is the corresponding amine and the development of suitable methods for the oxidation of an amine has led to the formation of many radicals, both stable and unstable. Di-t-alkylamines[25] can be oxidised to the corresponding nitroxide by treatment with hydrogen peroxide in the presence of a quaternary ammonium hydroxide and a salt of vanadium, molybdenum, or tungsten. Alternatively, hydrogen peroxide and phosphotungstic acid may be used[12]. The use of m-chloroperoxybenzoic acid also has been utilised for oxidising amines to nitroxides[1]. A major stumbling block in these two routes is the synthesis of the requisite amine or hydroxylamine precursor. A general method for the preparation of blocked amines is the double Michael addition of ammonia to a cross-conjugated

dienone. Thus phorone (21) gives triacetonamine (22) and piperitenone (23) gives the bicyclic amine (24)[26,27]. Bridged amines can also be prepared by the Robinson-Schopf reaction[28].



(21) (22) (23) (24)

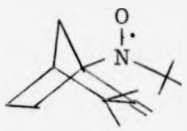
Blocked hydroxylamine precursors are generally prepared[29] by the addition of a Grignard or organo-lithium reagent to nitrones. This potentially attractive route is limited in the case of bridged bicyclic molecules by the difficulty of preparing suitable nitrone precursors.



The nitro group has also served as a precursor in the preparation of simple aliphatic nitroxides. Di-t-butyl nitroxide (25), for instance can be prepared by the reduction of t-nitrobutane with sodium metal[30]. The mechanism of this reaction has been shown[31] to proceed by the attack of a t-butyl radical derived from the collapse of the radical anion (26) on a second radical anion to form a diamagnetic salt $(^{t}C_4H_9)_2NO_2Na$. This salt upon hydrolysis affords di-t-butyl nitroxide. This method is not general as other t-nitroalkanes give radical anions which behave in a different fashion[1].

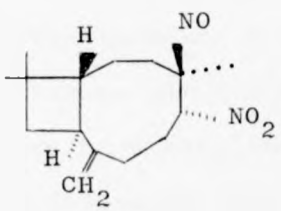
(25) (26)

Another procedure involves the addition of t-alkyl Grignard reagents to a nitro (or nitroso) alkane and is illustrated[32] by the reaction of 1-nitrocamphene with t-butylmagnesium chloride to give the nitroxide (27). Unfortunately the yields by this method are usually low.



(27)

An example of an intramolecular nitroxide formation is seen in the conversion of caryophyllene nitrosite (28) into the tricyclic nitroxide (29) by the reaction with iodine. This reaction has been envisaged as going <u>via</u> the radical (30)[33]. Later it was shown that this process can be used generally to yield five- and six-membered mono- and bicyclic-nitroxides[34,35].



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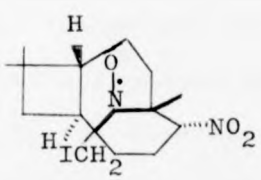

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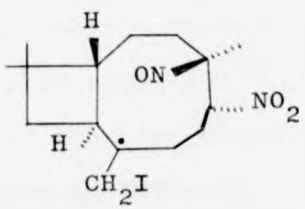
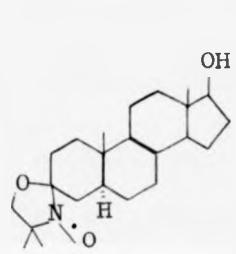


(30)

The ability of the nitroso group to scavenge short-lived radicals to produce nitroxides has been used in the so-called "spin trapping" experiments which have yielded structural information on various radicals appearing in polymerisation[36], radiolysis[37], photolysis[38], and various other chemical reactions[39,40]. This aspect of nitroxide radical chemistry has been reviewed by Perkins[41].

An interesting and easily accessible synthetic method for the production of nitroxides involves the condensation of a ketone with 2-amino-2-methylpropan-1-ol. A series of oxazolines can thus be generated and oxidised to the corresponding nitroxides by standard methods. This synthetic method has been used widely to form steroidal nitroxides which have been used as spin labels in biological membranes. An example of one of these is 17β-hydroxy-4',4'-dimethyl-spiro-(5 -androstane-3,2'-oxazolidine)-oxyl (31)[42].

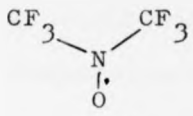


(31)

As well as the study of synthetic approaches to these radicals, nitroxides have also been examined by electron diffraction and x-ray techniques and recently a review of the molecular structure of nitroxides has been published[43]. These have resulted in the disclosure of the structural parameters of this moiety which are shown in Table 1.

TABLE 1

Compound	NO(Å)	CNC°	Angle between N-O bond and CNC plane°	Reference
(32)	1.26	121	22°	44
(33)	1.28	136	assumed planar	45
(34)	1.27	115	0°	46
(35)	1.27	117	0°	47
(36)	1.29	125	21°	48
(16)	1.29	114	30°	49
(29)	1.31	121	24°	50



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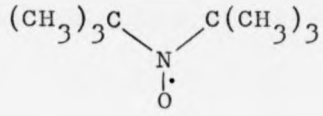
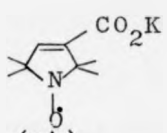


(33)



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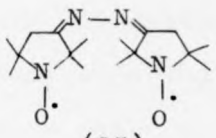

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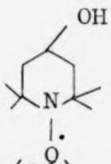

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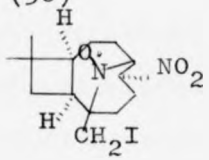


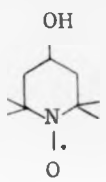
(29)

From Table 1 it can be seen that the average bond length of the nitrogen-oxygen bond of aliphatic nitroxides is 1.28Å. This value lies between the bond lengths of N-O (1.44Å) and N=O(1.20Å) and is consistent with a three-electron bond. The CNC bond angle of nitroxides is particularly sensitive to the geometry of the rest of the molecule. In di-t-butyl nitroxide (33) the CNC bond angle is 136° which can be explained as a widening of the angle to reduce non-bonded interactions. The opposite is seen in (34) and (35) where the CNC bond angle is reduced to 115° and 117° respectively due to the constraints of the five-membered ring. The angle between the N-O bond and the CNC plane varies between planar (0°) and slightly pyramidal (20°).

The fact that several nitroxides have pyramidal geometry at the radical centre leads to the interesting speculation that the ground state electronic configuration of the nitroxide radical bears a close resemblance to the excited state of the carbonyl group[51]. Thus, in the $^1n\rightarrow\pi^*$ and the $^3n\rightarrow\pi^*$ states of formaldehyde, the C=O axis subtends

an angle with the HCH plane of approximately 27^{o} and 35^{o} respectively[52].

This parallel can be extended to encompass the chemical reactivity of the carbonyl and nitroxide group. The ground state nitroxide radical is a relatively poor hydrogen abstractor requiring labile bonds like the S-H group to demonstrate reactivity. However the $n\rightarrow\pi^*$ excited state of a nitroxide is an extremely efficient hydrogen abstractor[53,54] rivalling the $^3n\rightarrow\pi^*$ state of aliphatic ketones. On photolysis of the nitroxide (36) in toluene solution the hydroxylamines (37) and (38) are obtained in good yield.



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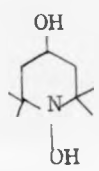

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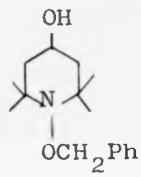


(38)

This analogy has also been used to explain the observed features in the ultraviolet spectra of nitroxide radicals. The distinctive red/orange colour of aliphatic nitroxides is due to a weak band in the 410-450 nm range ($\varepsilon \sim 5$-10) which has been ascribed to the $n\rightarrow\pi^*$ transition on the basis of solvent shift studies[12]. The intense band at 230 nm ($\varepsilon \sim 2500$) has been attributed to a $\pi\rightarrow\pi^*$ transition.

The absorption of plane-polarised light by the $n\rightarrow\pi^*$ transition of optically active ketones, measured by optical rotatory dispersion (o.r.d.) and circular dichroism (c.d.), is dependent upon the absolute stereochemistry of the molecule[55]. In view of the similarity between the $n\rightarrow\pi^*$ transitions of nitroxides and ketones some o.r.d. and c.d. studies on nitroxides have been undertaken[56-59]. These studies

suggest that nitroxides obey a similar rule to ketones in their absorption of plane-polarised light (see Discussion).

Electron paramagnetic resonance (e.p.r.) is another spectroscopic method which has been widely used to study nitroxides. The main feature of the e.p.r. spectra is the presence of a 1:1:1 triplet. This is due to the interaction of the unpaired electron with the nuclear spin of ^{14}N which has a nuclear spin quantum number of ± 1. In di-t-alkyl nitroxides this coupling, a_n, has a value of 1.6 x 10^{-4}T. The g value is of the order of 2.0060 and varies with solvent. The lower the polarity of the solvent the higher the g value[12]. There is also a solvent dependence on the a_n value[12,60] which may vary by almost 0.2 x 10^{-4}T on changing the solvent from benzene to 10M lithium chloride. This is a linear relationship with respect to Kosower's Constant K[61] (Figure 3). The largest a_n values are obtained with saturated aqueous lithium chloride as solvent

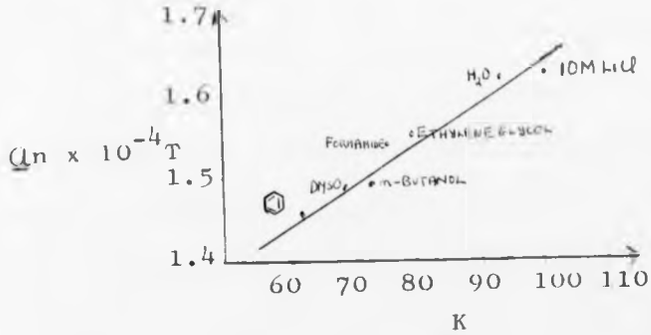


FIGURE 3

Under favourable conditions high resolution e.p.r. spectra exhibit additional splittings due to the nuclei ^{15}N, ^{13}C and ^{17}O present in their natural abundance[62] and to γ- and δ-hydrogen atoms.

The infrared spectra of nitroxides exhibit a weak band at about 1350 cm^{-1} which has been attributed to the stretching vibration of the N-O bond on the basis of labelling studies[63]. This value lies between that for a NO single bond of amine oxides (960 cm^{-1}) and a NO double bond of nitroso compounds (1600 cm^{-1}) which again would appear to be reasonable for a two-centred thre-electron bond. Unfortunately, this stretching mode is often masked in nitroxide radical i.r. spectra by the bending modes of the gem dimethyl group which appear at 1360 and 1380 cm^{-1}.

The unpaired electron has two major effects on the nuclear magnetic resonance (n.m.r.) spectra of nitroxides. First the spectral lines are broadened because the electron has a short spin lattice relaxation time and a short spin exchange time in dilute solutions. It has been demonstrated [64,65] that in extremely concentrated radical solutions, greater than 3 molar, well resolved spectra can be obtained. The use of solvents such as di-t-butyl nitroxide, as a paramagnetic solvent, appears to be a promising technique for observing nitroxide n.m.r. spectra without using a large quantity of material[66]. An alternative method of using n.m.r. to obtain information on nitroxides involves converting the nitroxide, <u>in situ</u>, into the corresponding hydroxylamine by the addition of hydrazobenzene[67] or phenylhydrazine[68]. Thus the n.m.r. spectrum of the corresponding hydroxylamine is obtained. The nitroxide is regenerated by stirring the mixture with silver oxide.

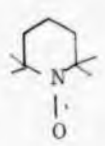
The second effect the unpaired electron has on the n.m.r. spectra of nitroxides is to cause a chemical shift displacement relative to what is expected for a similar non-

radical compound. This paramagnetic shift of a nucleus, H, is dependent upon the magnitude and sign of the hyperfine coupling constant $\underline{a}i$. This relationship is given by the equation

$$\underline{a}i = \frac{H}{\gamma_e/\gamma_n\ (g\beta H/4kT)}$$

where γ_e and γ_n are the gyromagnetic ratios of the electron and the nucleus respectively, k is Boltzmann's constant, T is the absolute temperature and β is the Bohr magneton.

The n.m.r. spectra of nitroxides have been used to determine the conformation of nitroxide radicals[69,70]. The n.m.r. spectrum of nitroxide (4) shows only one signal for the four methyl groups whereas two non-equivalent pairs of methyl groups are observed in the case of the nitroxide (36). The conclusion drawn from this is that the hydroxyl compound predominantly exists in the chair conformation (39).



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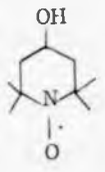

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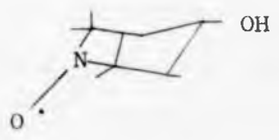

(39)

The use of the nitroxide moiety as a paramagnetic shift reagent[71] in n.m.r. spectroscopy has recently been reported[72]. A hydrogen bond is formed between the nitroxide and hydroxyl- or amino-protons of the donor molecule. This hydrogen bond induces a large upfield contact shift, accompanied by strong line broadening, for the hydroxyl- or amino-proton. The nitroxide also induces a downfield contact shift for the other C-H protons in the proton donor molecule. In addition, a downfield pseudocontact shift is exhibited by methyl protons in close spacial contact.

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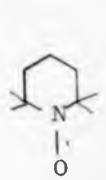

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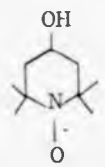

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A distinguishing feature of the mass spectra of nitroxides is the appearance of peaks at M+1 and M-14[73]. The M+1 peak has been assigned to the abstraction of a hydrogen atom by the radical from water in the mass spectrometer. The presence of the M-14 peak arises from the loss of a methyl radical from the M+1 ion. These M+1 and M-14 peaks are characteristic of nitroxide radicals.

The most significant use of the nitroxide moiety has occurred in the field of molecular biology where the spin labelling technique for probing biomolecular structures has been developed. This technique, which was first reported by Stone *et al*[74] in 1965, is extremely useful for monitoring the molecular changes which occur in biological systems and depends upon the fact that the shape of the nitroxide e.p.r. spectrum is extremely sensitive to its environment[75-77]. Thus a nitroxide which is either covalently or non-covalently incorporated into a biological system can report a considerable amount of information about its environment *via* the $\underline{a}_n$ value and the $\underline{g}$-factor both of which are anisotropic with respect to the way in which the radical is orientated relative to an applied field and with solvent polarity. Thus, analysis of the perturbed e.p.r. spectrum in terms of these parameters and the line shape can be correlated with such aspects as local polarity, viscosity and rates of molecular tumbling. In turn this information can be used to reveal such enzymatic parameters as polarity of binding sites, active site geometry, rotational correlation times and dynamic properties of biological membranes.

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DISCUSSION

1. Resumé of the Octant Rule

Since the object of this work was to examine the chir-optical properties of nitroxide radicals in terms of an octant rule a resumé will be given here of the use of the octant rule for the carbonyl group and also the evidence already reported for nitroxides. This preamble will set the scene for the subsequent discussion concerning the work embodied in this thesis.

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 disperson (o.r.d.) properties of a compound while the latter is responsible for its circular dichroism (c.d.) properties[1,2].

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[3]) 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 (1) in which ψ is the rotation of the plane of polarisation in radians per unit length, λ is the wavelength of the light and n_L and n_R are the refractive indices for left and right circularly polarised light respectively. Since n_L and n_R vary with wavelength, the rotation of place polarised light varies with wavelength

$$\psi = \frac{\pi}{\lambda}(n_L - n_R) \qquad (1)$$

Normally the experimentally measured rotation is expressed

as the specific rotation $[\alpha]_\lambda^T$, where λ is the wavelength of the incident light and T is the temperature of the measurement. Specific rotation is defined by equation (2) where α is the measured rotation of the plane of polarisation in degrees, l is the length of the cell path in decimeters and c is the concentration of the solution in gram per millilitre of solution.

$$[\alpha]_\lambda^T = \frac{\alpha}{lc} \qquad (2)$$

The molecular rotation $[\Phi]$ is another useful unit since allows the comparison of rotations on a mole for mole basis and is defined by equation (3)

$$[\Phi] = \frac{\text{specific rotation x molecular weight}}{100} \qquad (3)$$

A plot of the molecular rotation of a substance against the wavelength of the incident light is the o.r.d. curve of the substance.

Related to this is the phenomenon of c.d. This arises from the fact that a chiral medium has different molar extinction coefficients for left and right circularly polarised light. A plot of the differential dichroic absorption, $\Delta\varepsilon$ as defined by equation (4), against wavelength is known as a c.d. curve.

$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R \qquad (4)$$

Where ε_L and ε_R are the molar extinction coefficients of left and right circularly polarised light respectively. However, a generally accepted unit of c.d. is the molar ellipticity $[\theta]$ which is related to $\Delta\varepsilon$ by the relationship (5).

$$[\theta] = 3,300\Delta\varepsilon \qquad (5)$$

The most interesting and useful o.r.d. and c.d. curves are obtained in the vicinity of the electronic absorption

bands of the substance being examined. These give rise to Cotton effects in o.r.d. spectra and maxima in c.d. spectra. An immense body of data on the o.r.d. spectra of organic molecules was accumulated principally by the school of Djerassi[4]. In particular they studied the Cotton effects produced by the $n \rightarrow \pi^*$ electronic transition of carbonyl compounds.

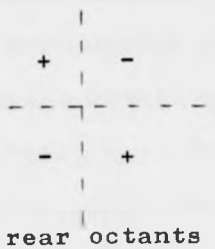
The empirical theories evolved by these workers were merged with the theoretical treatments of Moffitt and Moscowitz in the enanciation of the octant rule[5]. Since its establishment, as a rational basis for relating the o.r.d. and c.d. characteristics of chiral carbonyl compounds, the octant rule has been applied with a great deal of success to a broad spectrum of stereochemical and configurational problems.

In its simplest form the rule states that the space surrounding the carbonyl chromophore is divided into eight regions. These regions are formed by the two symmetry planes of the isolated (C_{2v}) chromophore and by a third surface perpendicular to and bisecting the C=O bond. If these three planes are taken to define a Cartesian co-ordinate system then the sign of the contribution made by an alkyl substituent to the observed c.d. of the $n \rightarrow \pi^*$ transition varies as the sign of the product of the atomic co-ordinates. An alkyl substituent symmetrically placed across the carbonyl symmetry plane exerts no effect on the c.d. due to cancellation.

The rudimentary proof of the octant rule involved the study of cyclohexanones of rigid geometry in which the perturbing atoms were carbon and hydrogen, neglecting the effect of the hydrogen atoms. When a cyclohexanone is

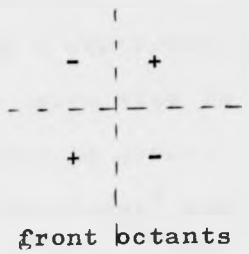
considered with respect to the co-ordinate system as shown in Figure 1, the presence of a perturbing atom in four octants gives rise to a positive contribution to the c.d. and o.r.d. spectra of the ketone while a negative contribution is obtained by an atom in the other four octants. For convenience the octants about the carbonyl have been divided into octants which are in front of or in the rear of the plane bisecting the C=O bond. The sign of the contribution an atom makes to the c.d. and o.r.d. of a carbonyl in each octant is shown in Figures 2 and 3.

FIGURE 1



rear octants

FIGURE 2



front octants

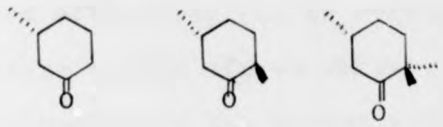
FIGURE 3

The values obtained from o.r.d. and c.d. measurements are interchangeable[6] as defined by equation (6), and for simplicity all values quoted will be in c.d. units, i.e.

$$\Delta\varepsilon = \frac{a}{40.28} \qquad (6)$$

Application of the octant rule to (+)-3-methylcyclohexanone (1), for example, is aided by drawing it as shown in Figure 4. It can be seen that the ring carbons cancel each other and the net contribution to the Cotton effect comes from the equatorial methyl which is in the rear upper left octant, i.e. a positive contribution. The c.d. curve of (1) has a $\Delta\varepsilon$ value of +0.62. The addition of a methyl group in one of the nodal planes, as in 2,5-dimethylcyclohexanone (2) does not change the amplitude of the Cotton effect as predicted. The further addition of a methyl group at C-2 (3)

results in a cyclohexanone with two substituents in positive octants and $\Delta\varepsilon$ increases to +2.01.



(1) (2) (3)

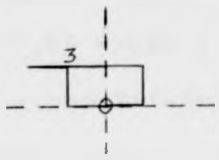


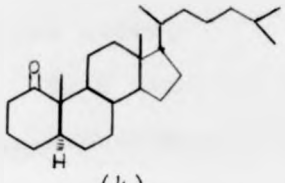
FIGURE 4

The behaviour of alkyl- and cycloalkyl-substituents appeared to be so regular that attempts were made to allot a fixed value to the contribution to $\Delta\varepsilon$ of various groups on the assumption that these contributions were additive. On this basis a 3-equatorial methyl group has a contribution of $\Delta\varepsilon$ =+0.62 and a 2-axial methyl group is calculated to be, $\Delta\varepsilon$ =+1.39. These analyses have been limited to groups of closely related compounds, e.g. the trans-decalones[7] and some of their alkylated derivatives, tricyclic analogues[7-9] and terpenes[10].

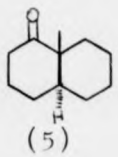
An observation in the derivation of the original octant rule concerned the existence and shape of the surface bisecting the carbonyl group. It has been shown[11,12] that a quadrant rule is the minimum sector rule required for the carbonyl chromophore and that the quadrants are defined by the intersecting symmetry planes.

One of the first compounds observed which exhibited front octant effects is 5α-cholestan-1-one (4)[13] which has a weak negative Cotton effect, $\Delta\varepsilon$ =0.62. The corresponding decalone (5) has a positive Cotton effect, $\Delta\varepsilon$ =+0.79. The difference between these two compounds is the C and D rings of the steroid. Carbons 12 and 17 and the side chain are in the front lower right octant which provides a negative contribution to the Cotton effect. Later the des-D-analogue

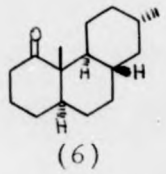
of 5 -androstan-7-one (6) and the D-homo-5α-androstan-7-one (7) were prepared[14] and their c.d. spectra compared. The Cotton effect for (6) is negative, $\Delta\varepsilon$=-0.85 while (7) has a positive Cotton effect, $\Delta\varepsilon$=+0.13. This constitutes a contribution to the Cotton effect by the D-homo-ring of $\Delta\varepsilon$=+0.98 due to the front octant contributions of carbons 15, 16 and 17. The front octant contribution of the D-ring to the observed $\Delta\varepsilon$ values for 5α-androstan-7-one (8) ($\Delta\varepsilon$= +0.23) and 5α-cholestan-7-one (9) ($\Delta\varepsilon$=+0.21) where only two carbons of the D-ring (C-15 and C-17) can be considered to be in the front octant.



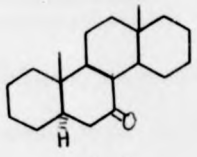
(4)



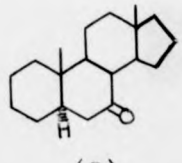
(5)



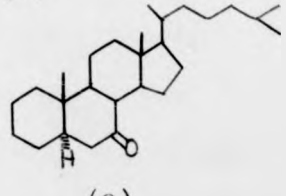
(6)



(7)

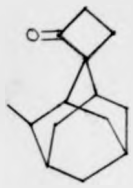


(8)



(9)

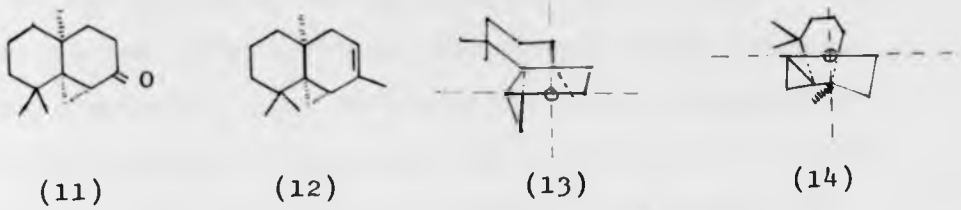
In the examples of front octant behaviour examined so far there have also been atoms in the rear octants the contributions of which have had to be subtracted from the overall $\Delta\varepsilon$ value. Recently however, the ketone (10) has been prepared[15] which has one methyl group in a front octant as the sole perturbing atom. The Cotton effect of (10) is strongly negative, derived from a methyl group in the lower right or upper left front octant and as such is strong evidence for the existence of front octants and the validity of the octant rule.



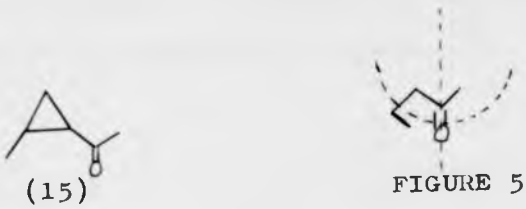
(10)

The shape of the third surface was taken to be planar and bisecting the carbonyl bond purely for convenience in the original paper and it was specifically cautioned that this surface was probably not a plane. Schellman[12] has stated that this surface is not planar because of the unsymmetrical distribution of the Π electrons on the carbon and oxygen atoms.

In a study of substituted cyclohexanones, cis- and trans-decalones, steroids and bicyclo [2,2,1] heptan-2-ones Coulombeau and Rassat[16] attempted to determine algebraicly the contribution of a methyl group to the Cotton effect. The values obtained agree with an octant rule with two perpendicular planes and a third surface curving backwards away from the carbonyl oxygen. A curved third surface has also been used to explain the anomalous Cotton effect of cyclopropane rings adjacent to a carbonyl group[17]. Thus the ketone[18] (11), a degradation product of thujopsene[19] (12), a compound of known absolute stereochemistry shows a positive Cotton effect. When (11) is drawn in the octant projections (13) and (14) it can be seen that the cyclopropane ring is in the lower left octant. If the cyclopropane ring is in a front octant then the octant rule is obeyed and the ketone (11) exhibits consignate behaviour[20]. This curved surface is shown for s-cis-methyl-2-cyclopropyl-1-(methyl)-ketone (15) in Figure 5.



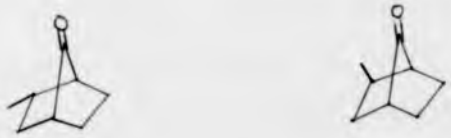
(11) (12) (13) (14)



(15)

FIGURE 5

A third surface has also been invoked to explain why endo-2-methylbicyclo[2,2,1]heptan-7-one (16) obeys the octant rule while exo-2-methylbicyclo[2,2,1]heptan-7-one (17) gives an apparently anti-octant effect[21], i.e. dissignate behaviour[20]. If the third surface curves such that the axial methyl group is in a front octant then this compound exhibits consignate behaviour. This seeming dissignate behaviour of a β-axial substituent has also been found by Snatzke and Eckhardt[22] in a series of β-substituted adamantanones.



(16) (17)

Another limitation to the scope of the original octant rule has been highlighted by the work of Hudec on the long range effect of hetero-substituents upon the $n \rightarrow \pi^*$ Cotton effect of ketones[23] and extended to include alkyl substituents [24,25]. Kirk and Klyne have also used this approach to include decalones and their analogues[26]. This approach proposes that interactions within the hydrocarbon chains

outside the carbonyl chromophore dominate the contributions to the Cotton effect, rather than direct action on the carbonyl moiety. They maintain that these through-bond interactions have a pronounced effect only when a "planar zig-zag" of bonds connects the carbonyl group with the perturbing group as illustrated in Figure 6[26].

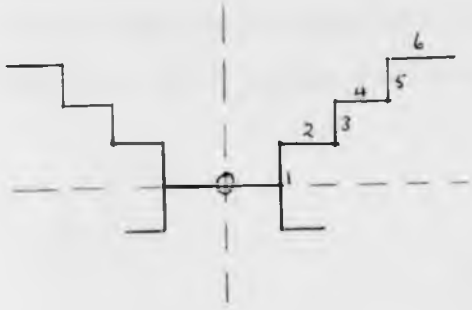
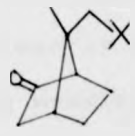


FIGURE 6

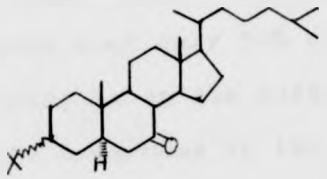
The planar zig-zag for ketones of the extended decalone class comprises one lobe of the p-orbital at the carbonyl carbon atom, the carbonyl-C bond, the C_α-C_β bond, the equatorial bond of the cyclohexanone ring and any other bonds which are alternatively parallel to the C_α-C_β bond and the β-equatorial bond. In ketones of other classes any connecting zig-zag of C-C bonds having essentially the same orientation in space, as the decalone class, with respect to the carbonyl group, will produce a similar effect.

The contribution of a group X on a planar zig-zag has been studied for zig-zags with substituents on β-, γ-, and δ- positions[22,24,25]. It was found that the group X could have two opposing contributions to the Cotton effect. First X may have an inductive effect which tends to withdraw electron density from the carbonyl group. Secondly an electromeric effect may be caused by X, if it has a lone pair of electrons, which allows electron donation to the carbonyl

group, provided the axis of the lone pair extends the planar zig-zag. From observations including π-camphor derivatives (18) and 3-substituted-7-oxo-5α-steroids (19) it was found that enhanced consignate behaviour was observed when a dominant electromeric effect occured while dissignate behaviour resulted from a dominant inductive effect. It was noted that these observations correlate in a qualitative sense with Hammett σ[27] and Taft σ^*[28] values for substituents.



(18)



(19)

The work of Kirk and Klyne[26] on decalones and their analogues adds support to this approach. Thus ketones of the all trans-decalone class which exhibit enhanced Cotton effects, when compared with their parent bicyclic ketones, are those in which the addition rings include bonds which add to the length of the planar zig-zag. Where the third and subsequent rings do not extend the planar zig-zag, e.g. most cis-decalones, there is no enhancement of the Cotton effect and it remains essentially that of the parent decalone. This study notes two different types of axial methyl substituents. An axial methyl group has a consignate effect if the group is on a planar zig-zag which extends beyond the first two C-C bonds, while dissignate behaviours is observed for an axial methyl substituent on the second C-C bond of the zig-zag.

The analysis of the octant rule has been, so far, purely empirical. The impediment to the theoretical

calculations of the octant rule is the determination of sufficiently good wave functions. Ab initio calculations have become available for molecules the size of methylcyclohexanone[29]. However, it is still necessary to resort to more approximate semiempirical calculations for comparative studies of the larger molecules found in the applications of the octant rule.

Recently a CNDO/S study of the rotatory strengths of the carbonyl $n \rightarrow \pi^*$ transition has been carried out[30]. From these calculations it has been determined that only 50% of the non-bonding n-orbital electron density is on the carbonyl group itself which rises to 85% when the α-carbons in the chromophore are included. The remainder of the orbital is delocalised over the rest of the molecule. Changes in the structure affect primarily the electron density on oxygen. The π^* orbital, on the other hand, is almost completely localised on the carbonyl group. Thus changes in the Cotton effect can be attributed to changes in the electron density of n-orbital. These changes in the electron density of the n-orbital arise from changes in the ground state stereochemistry of the molecule. In view of this it is consistent that the structural inferences concerning ketones, derived from the Cotton effect (by application of the octant rule), are dependent on the ground state stereochemistry.

The rotatory strengths for ketones have been calculated for a number of substituted cyclohexanones and decalones, including many of the molecules on which the octant rule was originally based. The calculated values of the rotatory strengths are in good qualitative agreement with experimental values.

Thus results for the four methylcyclohexanes (20)-(23) agree in sign and relative magnitude with experimental data. These compounds had been the subject of earlier calculations[29,31-34] all of which except one[32], predict dissignate behaviour for (23). The analysis of eleven cis- and trans-decalones adds support for the planar zig-zag hypothesis.

(20) (21) (22) (23)

The shape of the third surface of the octant rule has also been calculated, in this study, for aliphatic ketones with one more carbon atom on one side of the carbonyl than on the other. The molecule can then be twisted in such a way that the only source of chirality is the extra methyl group. Thus the rotatory strength could be calculated as a function of the position of the methyl group and a surface was constructed. It was found that the third surface was convex in the +Z- direction as shown in Figure 7. Although this surface is the opposite shape to the previously proposed third surface[16] it cuts just behind the 3-axial position placing a methyl group at this position in a front octant.

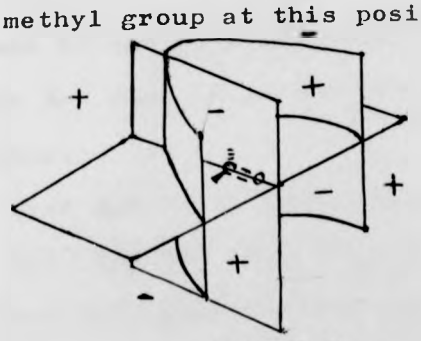


FIGURE 7

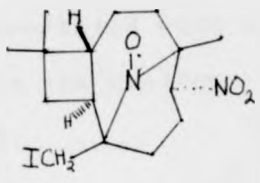
In view of the similarity in the electronic ground state and chemical reactivity between nitroxides and ketones it has been postulated that an octant rule may exist for nitroxides analogous to the rule for ketones.

Certain difficulties can be envisaged in searching for evidence to prove that nitroxides obey an octant rule. First, the extinction coefficient for the $n \rightarrow \pi^*$ transitions of nitroxides, in their ultra violet spectra, is smaller than the extinction coefficients for the $n \rightarrow \pi^*$ transition of ketones. If this is also true for the $\Delta\xi$ values in the c.d. measurements then one is searching for a very small value. Secondly, in general the two carbons adjacent to the nitrogen atom of a stable nitroxide are usually substituted, resulting in piperidine nitroxides having a deformed chair conformation. Additionally, this adjacent substitution is usually symmetrical and thus makes no contribution possible from α-substituents.

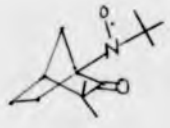
A further complication arises from the geometry of the nitroxide moiety. If the geometry of the nitroxide is the same as that of a carbonyl group then it has been proposed[35] that the sign and construction of the octants will be similar for both functional groups. Some nitroxides have pyramidal geometry, however, and in this instance the planes constructing the octants are not mutually perpendicular to each other. In this case it has been proposed[35] that the XY- plane passes through the N-O bond while the two remaining planes are as in the ketone.

The first optically active nitroxide recorded was the nitroxide (24) derived from caryophyllene nitrosite[36,37], but the first c.d. measurements were made on the camphenyl

nitroxide (25)[38]. Unfortunately, in this latter molecule the nitroxide moiety is not in a fixed geometry and thus it is difficult to interpret its c.d. spectrum in terms of an octant rule.



(24)



(25)

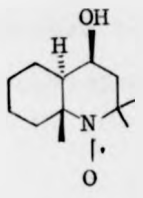
The bicyclic notroxides (27) and (28) of known absolute stereochemistry have been prepared[39]. The iodonitroxide (27) exhibits a small negative Cotton effect for the $n \rightarrow \pi^*$ transition of the nitroxide at 476 nm ($\Delta\epsilon = -0.05$) in agreement with the proposed octant rule. The nitroxide (28) shows no maximum for the nitroxide group which has been attributed to the high degree of symmetry in the vicinity of the nitroxide chromophore. It is interesting to note that the equatorial methyl group, which is the sole cause of dissymmetry in (28), is not on a primary zig-zag extending from the nitroxide and thus should have zero contribution to the Cotton effect of (28).

(27)

(28)

A series of decahydroquinoline nitroxides (29)-(33) have been synthesised[40]. The absolute stereochemistry of

the alcohols (29)-(31) was determined by Horeau's method[41] and two of these alcohols namely (29) and (30) were then converted into the corresponding ketones (32) and (33) whose absolute stereochemistry was now known. The evidence obtained from these nitroxides indicates that the signs of the rear octants associated with an octant rule for the nitroxide chromophore are analogous to those of the carbonyl group.



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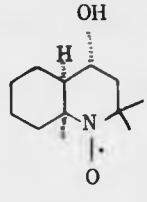
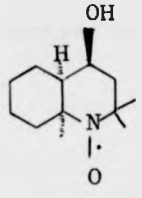


(30)



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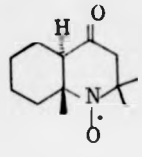
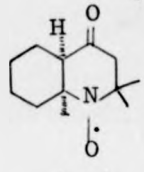
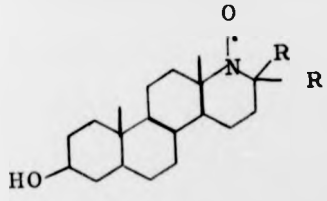


(32)

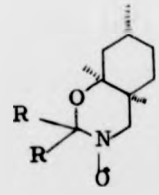


(33)

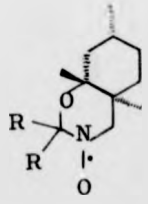
Additional support for an octant rule for nitroxides comes from a study[35] of two steroidal nitroxides (34), R=CH_2-$CH{=}CH_2$ or R=C_3H_7, and a series of isoxazoline nitroxides (35) and (36), of known absolute stereochemistry where R=CH_3 or $-(CH_2)_5-$. The sign of the c.d. spectra in all cases was the same as would be predicted by applying an octant rule similar to the rule for ketones.



(34)

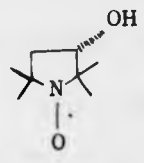


(35)



(36)

Five membered rings, in general, do not have fixed conformations as rapid ring inversion occurs. Due to this the application of an octant rule to pyrrolidine nitroxides is difficult in a quantative sense. The nitroxide (37), however, has been prepared and its c.d. spectrum has been compared with the two ketones (38) and (39)[42]. These three compounds have Cotton effects which agree with the sign predicted by an octant rule if they exist in the half chair conformation found in the crystal.



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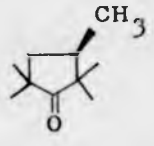

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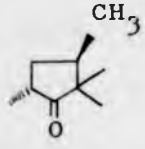

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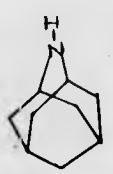
2. Synthesis, resolution and chiroptical properties of 2-aza-4,4-dimethyl-6-oxaadamantane-2oxyl

The studies in this thesis have been directed towards the synthesis of optically active nitroxide radicals of known enantiomeric purity and absolute stereochemistry which can be structurally related to known ketones of rigid geometry. In this way the c.d. spectra obtained can be compared both qualitatively and quantitatively with those of the corresponding ketones thus testing the validity of the postulated octant rule for nitroxides.

On considering a suitably rigid structure in which to imbed the nitroxide function for a c.d. study the most obvious candidate would appear to be the adamantane skeleton. A nitroxide prepared from a suitably functionalised optically active derivative of 2-azaadamantane (1) avoids the ambiguities associated with ring inversion and non-chair conformations and, in addition, the stereochemistry of any substituent is known and fixed. If the two 4-methyl-2-azaadamantanenitroxides (2)* and (3) are chosen, an additional bonus is gained in that the corresponding optically active adamantan-2-ones (4) and (5) have been synthesised[1] and thus a direct comparison of nitroxide with analogous ketone would be possible.

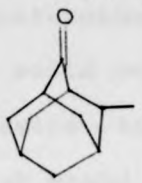


(1)

(2)

(3)

*FOOTNOTE: The stereochemistry depicted throughout is the 1R configuration assigned to the resolved material in this thesis.



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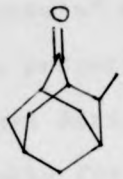
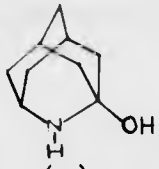


(5)

Initially, therefore, methods of preparing (1) which would enable the introduction of methyl groups at C-4 were considered. All previous syntheses of 2-azaadamantane have involved as a key step the insertion of nitrogen between the 3 and 7 positions of a bicyclo [3,3,1] nonane derivative. For instance the reaction of bicyclo [3,3,1] nonan-3,7-dione (6) with ammonia gave the 2-azaadamantan-1-ol (7)[2]. Treatment of this alcohol with thionyl chloride gave the chloro-compound (8) which was dehalogenated with Raney nickel to yield (1). A precursor of (6) is 3-methylene-bicyclo [3,3,1] nonan-7-one (9)[3,4]. Mono-methylation of the carbon adjacent to the carbonyl group of (9) followed by ozonolysis to the corresponding dione (10) would yield the desired starting material for conversion into a 4-methyl-2-azaadamantane. There are, however, several drawbacks in this approach. First the route to (6) from adamantane proceeds in less than 30% yield thus making this approach uneconomical. Secondly, while base equilibration would result in the equatorial methyl isomer being formed the axial methyl isomer would have to be separated from the mixture. Thirdly, resolution of these compounds would probably be best achieved with one of the amines (7)-(9) and this would make the determination of the absolute stereochemistry difficult. The absolute stereo-

chemistry could be determined by Horeau's[5] method, however, the secondary amine would need to be protected. By reacting (6) with methylamine the N-methyl derivative (11) can be obtained which would be suitable for a determination of its absolute stereochemistry however this would then have to be N-demethylated which would add an extra step to the synthetic pathway.


(6)



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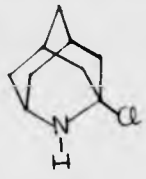

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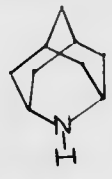
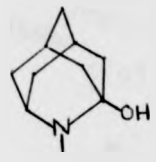

(1)

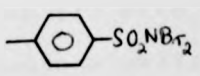

(9)


(10)



(11)

An alternative stratagem[6] involves the addition of N,N-dibromotoluene-4-sulphonamide (12) to bicyclo [3,3,1] nonan-2,6-diene (13) to yield the dibromo-2-azaadamantane (14) which yields the sulphonamide (15) on treatment with Raney nickel. Detosylation is achieved with sodium in liquid ammonia to yield (1). In this avenue of approach there is again the problem of low yield in the overall reaction sequence to prepare the vital intermediate (13) and in determining the absolute stereochemistry as resolution would probably be achieved with the 2-azaadamantane derivative.



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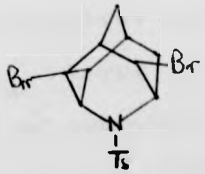
(13)



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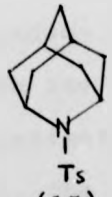
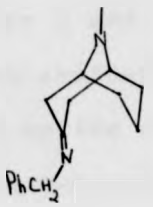


(15)

At this time a third approach to the synthesis of 2-azaadamantane derivatives appeared[7]. In this instance 2,6-diazaadamantane (16) was synthesised. Pseudopelletierine (17) was converted into its benzyl-imine (18) which was catylatically hydrogenated to give exclusively the endo isomer (19). Bromination yielded (20) which was converted into (21), by treatment with sulphuric acid, which in turn was transformed to (16).

(17)



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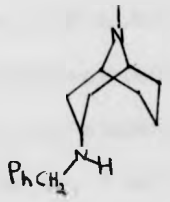

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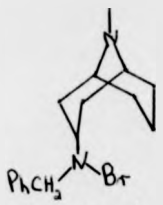

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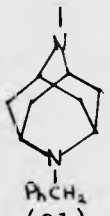

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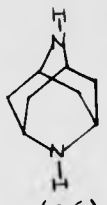


(16)

Thus if a suitable 2-methylbicyclo[3,3,1]nonan-3-one could be prepared the synthesis outlined for 2,6-diazaadamantane (16) could be utilised. The ring closure step in this synthesis only proceeds in 25% yield and as with the other syntheses the problems of separation of isomers, resolution and determination of absolute stereochemistry make this sequence unattractive.

It was at this point that alternatives to 2-azaadamantane (1) were considered. In an attempt to retain the adamantane skeleton the next class of compounds investigated were derivatives of 2-aza-6-oxaadamantanes (22), i.e. the

4-methyl-2-aza-6-oxaadamantane nitroxides (23) and (24)

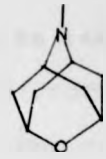
(22)

(23)

(24)

As with the syntheses directed towards 2-azaadamantanes a key step in approaches to 2-aza-6-oxaadamantane (22) is the ring closure between the 3 and 7 positions of a bicyclo-[3,3,1] nonane. The first synthesis of 2-aza-6-oxaadamantane (22) was accomplished by the elimination of ethanol from (25) to yield 2-methyl-2-aza-6-oxaadamantane (26)[8].

(25)

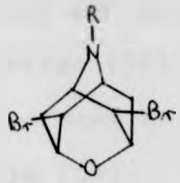


(26)

This skeleton has also been constructed, by analogy with a method for the preparation of 2-azaadamantane, using the reaction of N,N-dibromotoluene-4-sulphonamide (12) with 9-oxabicyclo[3,3,1]nonan-2,6-diene (27)[9]. In the same report (22) was synthesised by the action of aqueous N-bromosuccinamide on 9-azabicyclo[3,3,1]nonan-2,6-diene (28) via the 2,6-dibromo-2-aza-6-oxaadamantane (29). In both these approaches the problem of synthesising a suitable starting material with the appropriate methyl group and the difficulties in ascertaining the absolute stereochemistry of the molecule once resolved make these two approaches less than ideal.

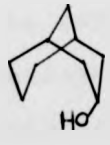
(27)

(28)



(29)

An alternative route reported by Kashman and Benary[10] involves the use of lead tetraacetate to effect the ring closure of an endo-bicyclo[3,3,1]nonan-3-ol. This reaction had already been used on endo-bicyclo[3,3,1]nonan-3-ol (30) itself to prepare 2-oxaadamantane (31)[11]. Kashman and Benary used endo 9-acetamido-9-azabicyclo[3,3,1]nonan-3-ol (32) which yielded (33) on treatment with lead tetraacetate. In this report no attempt was made to remove the acetamido-group. In this scheme a versatile route to endo 9-azabicyclo-[3,3,1]nonan-3-ols is essential. One of the most flexible routes to such substrates involves the Robinson-Schopf reaction[12] to prepare a 9-azabicyclo[3,3,1]nonan-3-one which is then reduced to the desired alcohol. In this manner endo-6,6-dimethyl-9-azabicyclo[3,3,1]-nonan-3-ol (34) had been prepared by Japanese workers[13].



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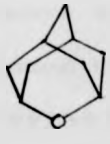

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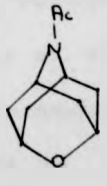
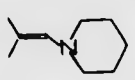


(33)

In this scheme the piperidine enamine of isobutral-dehyde (35) was converted to the dihydropyran (36) which in turn was treated with an acidic ion exchange resin to

yield 2,2-dimethylgluteraldehyde (37). This dialdehyde (37) was reacted with acetone dicarboxylic acid and methylamine to yield the 6,6-dimethylpseudopelletierine (38). Reduction of the ketone (38) with lithium aluminium hydride yielded (39) which was N-demethylated to yield (34).

(34)



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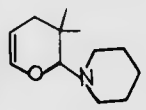

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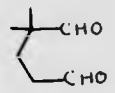


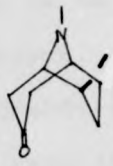
(37)

(38)

(39)

In this reaction sequence by starting with the enamine of prop ionaldehyde instead of butyraldehyde the desired mono-methyl 2-aza-6-oxaadamantanes (23) and (24) could be prepared. Again a major drawback in this approach is that a mixture of axial and equatorial methyl isomers would be obtained at the pseudopelletierine stage, i.e. (40) and (41). In favour of this approach it was felt that resolution of the separated isomers could be carried out on one of the 9-azabicyclo[3,3,1]nonan derivatives (40)-(45). In addition to this it was considered that the octant rule could be used on the resolved ketones (40) and (41) to ascertain their absolute stereochemistries. If this failed then Horeau's method[5] could be used on the resolved alcohols (42) and (43).

(40)



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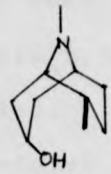

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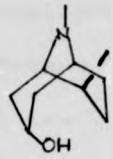
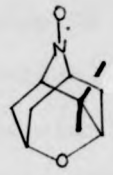


(43)

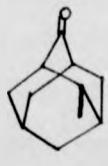
(44)

(45)



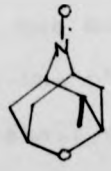
(46)

In view of the potential problem of separating the mixture of mono-methyl compounds (40)-(45) (see Discussion Part 3) it was felt that the dimethyl series should be prepared initially thus leading to the nitroxide (46) in an optically active form of known absolute stereochemistry. While direct comparison with the known optically active 4-methyladamantan-2-ones (4) and (5) would not be possible the proposed octant rule for nitroxides could be put to the test and knowledge might be gained which would be helpful in the preparation, separation, and structural assignment in the mono-methyl series. In addition it would permit the additivity of the octant rule to be checked when the two mono-methyl nitroxides (23) and (24) were prepared.

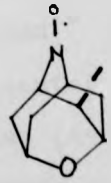


(4)

(5)



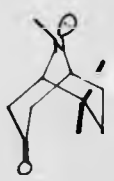
(23)



(24)

In view of the fact that the ketone (38) was intended

to be used in the determination of the absolute stereochemistry in this series it is essential that the conformation of the molecule is known. In bicyclo[3,3,1]nonan-3-ones the twin chair conformation is adopted. Additional information is gained from the ultra violet (u.v.) spectrum of this ketone. An extra absorption is present at 258 n.m. (ε=1456) for the n→π^* transition, in addition to the normal n-π^* transition for ketones at 220 n.m. (ε=1628). This extra transition has been found in other β-amino ketones and has been attributed to a coupling between the lone pair on nitrogen and the carbonyl through a σ bond interaction. It has been shown[14,15] that the conformation responsible for this transition is the one in which the lone pair of electrons of the nitrogen is trans-diaxial to the C_α-C_β bond as shown in (47)



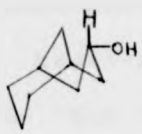
(47)

(39)

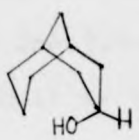
(34)

As stated earlier reduction of (46) with lithium aliminium hydride yielded (39) which was N-demethylated to give (34). It was noticed that in the nuclear magnetic resonance (n.m.r.) spectra of these two amino-alcohols the methine proton signal was different. The conformation of endo-bicyclo[3,3,1]nonan-3-ols has been discussed[16] and the preferred conformation is the chair-boat conformation (48) rather than the twin chair conformation (49). If the twin chair conformation was adopted this would lead

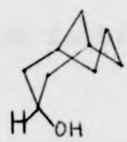
to an unfavourable transannular interaction between the OH at position 3 and the proton at position 7. The chair-boat conformation (50) has been ruled out by analysis of the signal for the C-3 proton in the n.m.r. spectrum. The signal for this proton is a triplet of triplets with coupling constants of 9Hz and 6Hz. This coupling is consistent with axial-axial coupling (9Hz) and axial-equatorial coupling (6Hz) between the C-3 proton and the two pairs of adjacent protons.



(48)

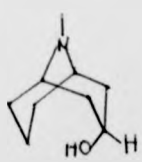


(49)

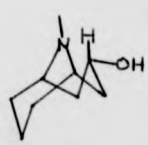


(50)

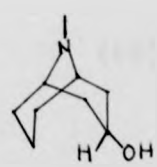
The n.m.r. spectrum of endo-9-methyl-9-azabicyclo [3,3,1]-nonan-3 -ol (51) has been recorded[17] and in this compound the signal for the 3-methine proton is a 1:4:6:4:1 quintet with a coupling constant of 6.8Hz for the coupling between the methine proton and the two pairs of adjacent protons. This has been attributed to a dynamic equilibration of the chair-boat conformations with the conformer (52) being present in 85%. Additional information to support this was obtained from a study of the ^{13}C n.m.r. spectrum of this compound and its epimeric alcohol (53)[18].



(51)



(52)

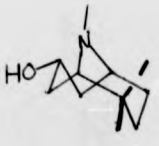


(53)

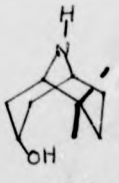
It has been shown[19] that gauche interactions between the C-7 proton and the C-2 and C-4 protons cause a downfield shift of about 5 ppm for the carbon at position 7 without concomitant downfield shift at the carbons at positions 2 and 4. The chemical shift for C-7 would be about 20 ppm. In compound (51) this signal is shifted to 14.5 ppm while the signal for C-7 in the n.m.r. spectrum of (52) comes at 19.8 ppm[18]. Thus it would appear that the transanular interaction between the hydroxyl and the C-7 proton in (51) is large enough to cause the conformation (52) to be adopted. However, in (53) the 3,7-interaction is between protons and thus the twin chair is adopted[18].

In the n.m.r. spectrum of (39) the signal for the C-3 methine proton is a narrow multiplet indicative of axial-equatorial and equatorial-axial couplings with the two pairs of adjacent protons. In this instance it would appear that the twin chair conformation (39) is adopted. If the chair-boat conformation (54) was adopted it would cause a severe 1,3-steric interaction between the N-methyl and the C-6 axial-methyl which must be less favourable than the 3,7-interaction between a hydroxyl and a proton.

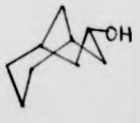
(39)



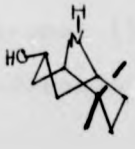
(54)



(34)



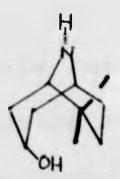
(48)



(55)

In contrast the n.m.r. spectrum of (34) has a signal for the C-3 methine proton which is a triplet of triplets with coupling constants of 9Hz and 6Hz similar to (48) thus implying that the chair-boat conformation (55) is adopted. The equilibrium seen in (51) between the possible chair-boat conformations[17] is not favourable here as the C-6 methyl groups would cause excessive steric strain.

Treatment of 6,6-dimethyl-9-azabicyclo[3,3,1]nonan-3-ol (34) with acetic anhydride in pyridine at room temperature gave a mixture of acetylated compounds while refluxing in pyridine with acetic anhydride gave the diacetylated derivative (56). Treatment of (56) with methanolic potassium hydroxide yielded the corresponding acetamide (57) in almost quantitative yield. It was found, however, that by treating (34) with one molar equivalent of acetyl chloride at -22° resulted in the formation of the desired acetamide (57) in one step.



(34)

(56)

(57)

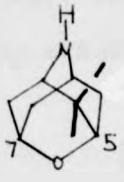
(58)

(59)

Conversion of the alcohol (57) into the desired 4,4-dimethyl-2-acetamido-2-aza-6-oxaadamantane (58) was

accomplished by the lead tetraacetate oxidation in benzene with iodine[10]. A major by-product from this reaction, the ketone (59) was reduced with sodium borohydride to the alcohol (57) and this was then separated from (58) by column chromatography.

Removal of the acetamido group proved to be difficult. Base hydrolysis failed, even though drastic conditions were used, e.g. the hydrolysis was attempted with potassium hydroxide in ethylene glycol at 160° for 2 days. Fortunately reaction of the amide with a Grignard reagent, methyl magnesium bromide, resulted in the removal of the acetamide to yield 4,4-dimethyl-2-aza-6-oxaadamantane (60) in almost quantitative yield.



(60)

(46)

The signals for the C-5 and C-7 methine protons in the n.m.r. spectra of (58) and (60) are narrow multiplets similar to the signal obtained for (39). As the adamantanes (58) and (60) are definitely in the twin chair conformation this is consistent with the assignment of a twin chair conformation for the alcohol (39).

The oxidation of (60) to 4,4-dimethyl-2-aza-6-oxa-adamantane-2-oxyl (46) was achieved using m-chloroperoxy-benzoic acid in methylene chloride at 0°C. Preparative thin layer chromatography gave the pure nitroxide as a pale yellow solid. The electron paramagnetic resonance (epr) spectrum

of (46) consists of a 1:1:1 triplet as expected due to ^{14}N coupling with the unpaired electron. There is no well defined hyperfine coupling between the unpaired electron and the hydrogens on adjacent carbons. The lines of the triplet are broad, however, suggesting that the lack of symmetry in the molecule may cause overlap of the small couplings. It is not uncommon, however, for the $\underline{A}_H$ values to be observed in this type of nitroxide. The magnitude of $\underline{A}_H$ for the 1,3-protons is related to the spin density on nitrogen and the C-H bond by equation (1)[20] where P_N is the density on nitrogen, B_o and B_2 are constants and θ is the dihedral angle as shown in Figure 1. This relationship has been refined for aliphatic nitroxides where B_o is almost zero and it can be shown that $\underline{A}_H = 26\text{Cos}^2\theta$.

$$\underline{A}_H = P_N(B_o + B_2\text{Cos}^2\theta) \qquad (1)$$

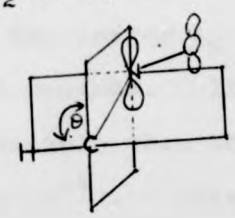
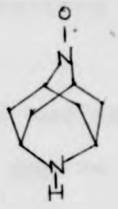


FIGURE 1

In the symmetric nitroxides (61) and (62), which have identical e.p.r. spectra, the $\underline{A}_H$ value for the 1,3-protons and the unpaired electron has been found[21] to be 0.28 x 10^{-4}T. Additional $\underline{A}_H$ values of 0.145 and 0.08 x 10^{-4}T have been reported for the remaining protons. Recently the e.p.r. spectrum of 2-azaadamantan-2-oxyl (63) has been reported[22] and the 1,3-protons have been found to have an $\underline{A}_H$ value of 0.285 x 10^{-4}T while the remaining protons have $\underline{A}_H$ values of 0.18, 0.095 and 0.19 x 10^{-4}T which have been

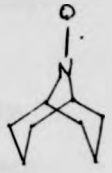
assigned to the β-axial, β-equatorial and δ protons respectively. These reports contrast with the reported e.p.r. spectrum of (64)[23] which did not produce a resolved spectrum even at -160° in pentane. From these results the value of $\underline{A}_H$ for the 1,3-protons of (46) and the unpaired electron would be expected to be in the order of 0.28×10^{-4}T.

(61)



(62)

(63)



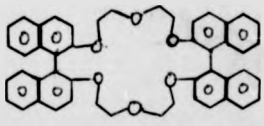
(64)

It has been shown[24] that the $\underline{A}_H$ value of a methylene hydrogen atom in a <u>trans</u> (zig-zag) coplanar arrangement of bonds with the unpaired electron is much larger than with other methylene hydrogen atoms. In the case of (61) these protons with the larger $\underline{A}_H$ values are C-4 equatorial and the C-5 and C-7 protons. If this coplanar arrangement of bonds was not possible then the $\underline{A}_H$ value would be in the order of 0.03×10^{-4}T. This would occur if the N-O bond was not planar with respect to the CNC plane. This coupled with the non-magnetic equivalence of the C-1 and C-3 protons could account for the lack of well defined hyperfine coupling between the unpaired electron and the protons of (46).

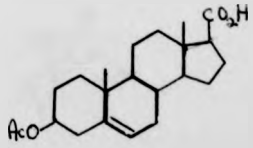
Upon the completion of a satisfactory route to 4,4-dimethyl-2-aza-6-oxaadamantane-2-oxyl (46) it was then necessary to decide at what stage resolution should be attempted. The problem of separating optical isomers has been tackled from a variety of different approaches and a timely review article on resolution has appeared recently[25].

Carboxylic acids and amines are the most readily resolvable compounds due to the fact that a wide range of crystalline salts are easily prepared and that the recovery of the resolved compound can be accomplished in good yield. Chromatographic methods of resolution, e.g. column chromatography on a dissymmetric absorbent are becoming increasingly important. Primary amine salts have been resolved by eluting the salt from a column with a solution of the optically active crown ether (65) in chloroform[26]. More recently an optically active crown ether bound to the column support has been used[27].

(46)



(65)



(66)

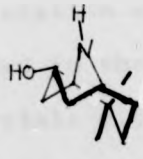
Latterly high pressure liquid chromatography (h.p.l.c.) has been used to separate amino acids by converting the amino acid into its N-d-10-camphorsulphonyl-p-nitrobenzyl ester and eluting this derivative on an h.p.l.c. column[28]. Amines and alcohols have been successfully separated as

amides and esters respectively by the use of 3-β-acetoxy-Δ^5-etienic acid (66)[29,30].

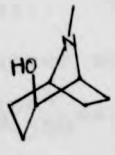
Still the most successful method appears to be the conversion of the racemate into a diastereomeric mixture by reaction with an optically pure reagent followed by separation of the resultant diastereomers, usually by crystallisation. This method is very much one of trial and error. One of the few guiding principles in planning a resolution has been mentioned by Woodward et al[31]. 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.

These general considerations led us to consider the amino-alcohols (39) and (55) as the best candidates for resolution experiments. A large scale resolution of the bicyclic amino-alcohol (67) by crystallisation of the diastereomic salts with (+)-tartaric acid[32] tends to support this approach.

(39)



(55)



(67)

Small scale experiments were set up using four readily available optically active acids (see experimental section for details) and (39) to see if crystalline salts were formed and whether fractional crystallisation would provide a suitable method of separation of the diastereomeric

salt mixtures formed. In all attempts a clear oil was obtained which resisted all attempts to cause crystallisation. Similar experiments were set up simultaneously using the same optically active acids and (55). In this instance colourless crystals were obtained of the salt of (55) and (+)-tartaric acid, but a colourless oil was obtained with all other optically active acids and (55). The salt of (55) and (+)-tartaric acid was collected by filtration and dried to yield colourless crystals m.p. 165-179°, $[\alpha]_{589}^{24}$= +10.8°. The amine was liberated by dissolving the salt in water, making the resulting solution basic and extracting with methylene chloride. The recovered amine had a small positive rotation $[\alpha]_{589}^{24}$=+1.31°. The amine obtained from the mother liquors by this method had a small negative rotation $[\alpha]_{589}^{24}$=-0.7° and hence of lower optical purity. A repetition of this experiment on a much larger scale gave a crop of crystals which on recrystallisation, from 50% methanol/ether, gave colourless crystals m.p. 172-176°, $[\alpha]_{D}^{24}$=+11.9°. Further recrystallisation failed to alter the melting point or the rotation of this salt. The amino-alcohol (55) liberated in the above manner was obtained as colourless crystals m.p. 114° $[\alpha]_{589}^{24}$=+1.55°. It was decided to use this last material for the preparation of optically active 4,4-dimethyl-2-aza-6-oxaadamantane-2-oxyl (46).

On obtaining an optically active compound by resolution of synthetic material one of the many problems is knowing when a resolution is complete, or if not, how much of each enantiomer is present[33]. There are two terms which have

been defined to express this latter quantity and these are numerically equal.

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

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

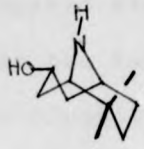
With synthetic material it is often not possible to determine the rotation of the pure enantiomer and thus the number of moles of each form present must be determined in another way. Techniques of determining this quantity based on isotopic dilution, g.l.c. and n.m.r. analyses have been developed and these have been reviewed[34].

The method chosen in this case was n.m.r. spectroscopy. Optically active solvents have been used as in an asymmetric solvent[35] the signals for the enantiomers may have different chemical shifts and thus the % enantiomeric purity can be calculated by integrating the signal, for each enantiomer, of a suitable group on the molecule. More recently lanthanide shift reagents, with optically active ligands, have been used to create a different chemical shift for the protons on the enantiomers[36]. Both these approaches were tried on the amino alcohols (39) and (55) however, as is the case with many compounds, no significant separation in the n.m.r. signals was obtained by either method.

The use of n.m.r. spectroscopy with diastereoisomeric esters has been applied to determine the optical purity of alcohols by Mislow and Raban[37]. This approach has been modified by Mosher *et al*[38] who used (+) methoxytri-

fluoromethylphenylacetic acid (68). This has been chosen because the trifluoromethyl signals are usually far apart (10-70H) and hence integration is uncomplicated.

(39)



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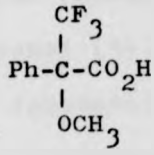
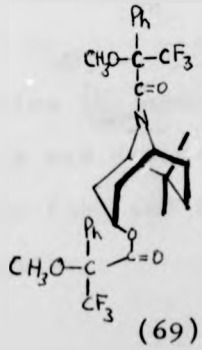
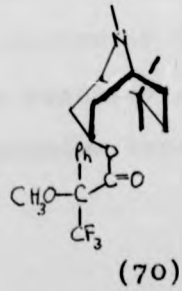


(68)

It was felt that if (54) was used to prepare the mixture of diastereomeric esters a complication would arise from the formation of the amide (69) which would be subject to hindered rotation and thus complicate the situation. Thus it was decided to use (39) for the preparation of the mixture of diasteriomeric esters (70). The normal method of preparation of this type of ester involves treatment of the alcohol in pyridine with the acid chloride prepared from (68). With the alcohol (39), however, it is in the twin chair conformation and thus the hydroxyl group is sterically hindered and the reaction did not yield the desired ester. Treatment of the alcohol (39) with one equivalent of methyl lithium followed by the addition of the acid chloride of (68) resulted in the formation of the desired ester (70) in quantitative yield.



(69)



(70)

Initially the ester (70) was formed with racemic alcohol (39) and (+)-acid (68). The proton n.m.r. spectrum of this ester showed no splitting of the methoxyl signals, but the ^{19}F n.m.r. spectrum of (70) showed two singlets in a ratio of 1:1 as expected starting from racemic material.

In a test experiment the racemic alcohol (54) was converted to the racemic alcohol (39) by treatment with formic acid and formaldehyde. The material obtained was identical with (39) prepared by reduction of (38) as already reported. Thus the resolved alcohol (55) was similarly converted into resolved (39) by treatment with formic acid and formaldehyde. The resolved alcohol (39) was then converted into the desired ester (70) using (+)-acid (68). This resolved ester again had two singlets in its ^{19}F n.m.r. spectrum, however, in this instance the ratio was 2:1. This gives a value of 33% for the enantiomeric purity.

(38)

(71)

The final remaining problem was to determine the absolute configuration of these compounds. The octant rule[39] for ketones is well established in its use for assigning the absolute configuration of molecules and thus it was decided to prepare resolved samples of the ketones (38) and (71) and to examine their optical properties.

Oxidation of the racemic alcohol (39) with chromium trioxide in pyridine gave the ketone (38) which was identical in every respect with the material prepared by the Robinson Schopf reaction. Similarly the ketone (71) was prepared by oxidation of the alcohol (54). These reactions were then repeated using resolved alcohols (39) and (54).

An interesting feature of the ultra violet (u.v.) spectrum of the ketone (38) was, in addition to the normal $n \rightarrow \pi^*$ transition for ketones, an absorption maximum at 258 nm. ($\varepsilon = 1456$). This is consistent with the (u.v.) spectra of β-amino-ketones where the lone pair on nitrogen interacts with the carbonyl through a σ bond interaction[40]. It has been shown that the configuration responsible for this coupled transition is the one in which the lone pair on nitrogen is equatorial. This extra transition is absent in the u.v. spectrum of the ketone (71) and thus in this compound the lone pair on nitrogen is axial.

This positioning of the lone pair on nitrogen in (38) and (71) suggests that the steric interaction with the axial methyl group is greatest for a methyl group and that the 1,3 interaction of the axial methyl group is greater for a lone pair than hydrogen. A great deal of work has been carried out to ascertain the most favourable conformation of the lone pair on nitrogen in piperidine rings. In general it has been shown that in piperidine the configuration with an equatorial N-H is favoured[41]. In a low temperature study[42] down to -174°C the n.m.r. spectrum of piperidine shows no axial coupling with the N-H and the -axial protons thus implying the nitrogen lone pair is

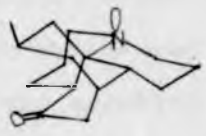
axial. In this study, and others, no compounds were studied which have a 1,3 interaction with an axial methyl group as is the case with (71) and thus it would appear that the lone pair interaction with the axial methyl group is sufficiently larger than the interaction between the axial methyl group and hydrogen to cause the piperidine ring without the gem dimethyl substituent to have the lone pair on nitrogen in the less favourable equatorial configuration (72). The ketone (38) has the choice of a 1,3 interaction between two methyl groups or a methyl group and a lone pair and from the u.v. evidence the latter is the preferred interaction and thus the piperidine ring without the gem dimethyl substituent has its lone pair on nitrogen in the favoured axial configuration (73).

(72)

(73)

As previously mentioned 6,6-dimethylpseudopelletierine adopts the conformation (73). Hudec has shown[14] that when the nitrogen lone pair is trans-diaxial to the C_α-C_β bond coupling through the σ bonds is possible and that these compounds will have a consignate effect. However, when the lone pair is not trans-diaxial to the C_α-C_β bond no coupling is possible and the electron withdrawing nature of nitrogen causes dissignate behaviour. This effect has been found in the lycopodium group of alkaloids. Lycopodine (74) has its nitrogen lone pair trans-diaxial to the C_α-C_β

bond adjacent to the carbonyl bond and thus obeying the octant rule in a consignate sense has a positive Cotton effect ($\Delta\varepsilon$=+4.39)[43]. Its C-12 epimer (75) however does not have its lone pair on nitrogen <u>trans</u>-diaxial to the $C_\alpha - C_\beta$ bond adjacent to the carbonyl and thus having dissignate behaviour shows a negative Cotton effect ($\Delta\varepsilon$=-1.09). From this it can be deduced that the ketone (73) will have consignate behaviour while the ketone (72) will have dissignate behaviour.

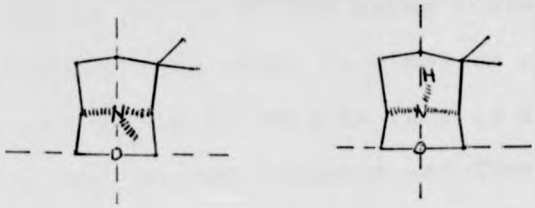


(74)

(75)

The resolved amino-ketone (73) has a negative Cotton effect at about 300 nm ($\Delta\varepsilon$ =-0.126) for its n→π^* transition of the ketone. From the octant projection (76) it can be seen that, as this ketone obeys the octant rule in a consignate manner a negative contribution to the Cotton effect will result if the dimethyl group is in the upper right rear octant. Thus the resolved material has the **1R** configuration. The ketone (72) must also have this configuration and thus can be represented by the octant projection (77) again with the dimethyl group in the upper right rear octant. As this ketone has dissignate behaviour a positive Cotton effect would be expected from this compound. In agreement with this the resolved ketone (72) has a positive Cotton effect at 286 nm ($\Delta\varepsilon$ =+0.342) and hence supports the assignment of the **1R** configuration to

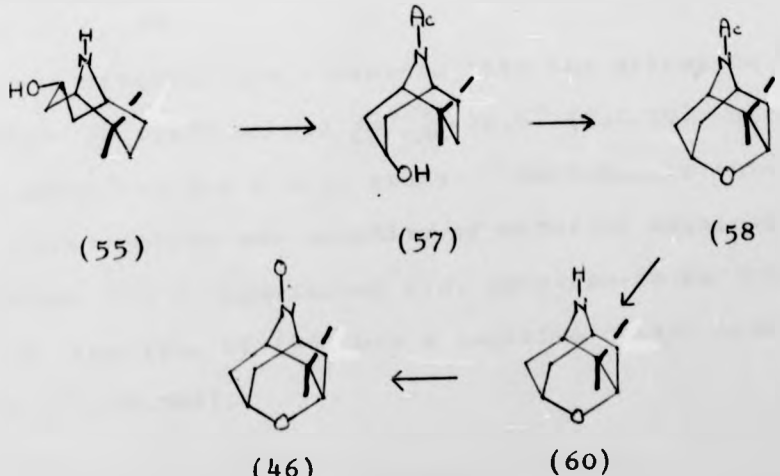
the resolved material.



(76) (77)

Using the route devised for the synthesis of (±)-4,4-dimethyl-2-aza-6-oxaadamantane-2-oxyl (46) as outlined in Scheme 1, the resolved amino alcohol (55) was converted into the optically active nitroxide (46). This nitroxide was purified as before and submitted for a c.d. study. Unfortunately the quantity of material obtained and the degree of enantiomeric purity was not sufficient to obtain a significant c.d. curve.

The two obvious approaches to surmount this problem were first to make more material, though how much would be required was not known. Secondly attempts could be made to increase the enantiomeric purity of the resolved material. It was decided to try and increase the enantiomeric purity of the material and if possible increase the quantity of (46) obtained.



(55) (57) (58)

(46) (60)

SCHEME 1

As attempts made to resolve (39) and (55) had resulted in an enantiomeric purity of 33% being achieved, it was felt that the amine (60) might be a better candidate for resolution. In favour of this is that it is only one step away from the desired compound and from its rotation the absolute stereochemistry and the optical purity can be calculated from the results obtained from the earlier resolution.

The resolving acid chosen for the first attempt was (+)-2-nitrotartranilio acid[44] as this compound has been reported as being successful in resolving amines which had resisted other commonly-used resolving acids. Thus the salt of the amine (60) and (+)-2-nitro-tartranilic acid was crystallised from methanol to yield colourless crystals m.p. 161-167°C $[\alpha]_{589}^{24}$ +63.65°(C=1.04). A further crystallisation from methanol yielded the desired salt m.p. 163-167°C $[\alpha]_{589}^{24}$ +68° (C=0.64). This salt was then dissolved in water, sodium carbonate was added and the resulting mixture extracted with methylene chloride. Removal of the solvent yielded the desired adamantane (60) as an oil $[\alpha]_{589}^{24}$ +51° (C=0.15) which represents an optical purity of 57.6%.

This material was converted into the nitroxide (46) as before to yield an oil $[\alpha]_{589}^{24}$ +26.6° (C=0.79) which was again submitted for a c.d. study. Fortunately this time the optical purity and quantity of material obtained was sufficient for a significant c.d. spectrum to be obtained. The c.d. spectrum of (46) has a negative Cotton effect at 416 nm ($\Delta\varepsilon$=-0.048).

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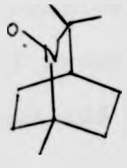
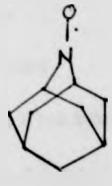
In attempting to interpret this Cotton effect it is necessary to know if the nitroxide is planar or pyramidal. Theoretical calculations and an e.p.r. study[45] of the bicyclo[3,2,1] nitroxide (78) suggest that the N-O bond is slightly pyramidal making an angle of 30° with the CNC plane. Similar calculations[46] have been carried out on the bicyclo [2,2,2]nitroxide (79) again suggest that the N-O bond is pyramidal but in this instance rapid inversion of the N-O bond occurs. This situation has also been postulated for 2,6-diazaadamantane bis-nitroxide (80)[21]. The nitroxide (81) has recently been reported[22] to dimerise in the solid state, however, in solution the N-O bond is pyramidal and rapidly inverting between two configurations of the same energy. This barrier to inversion has been calculated[46] for (79) and found to be 2-4 K cal mole^{-1}. This report states that this value probably overestimates this barrier to inversion and favours a value of 0.1 K cal mole^{-1} obtained by an <u>ab initito</u> calculation on H_2NO.

(78)



(79)

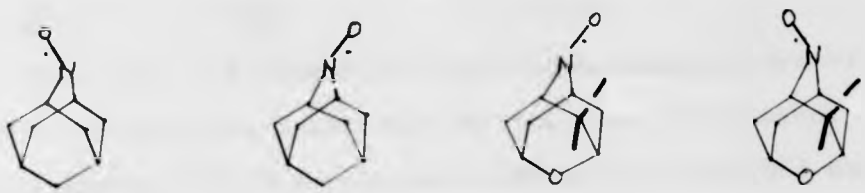
(80)



(81)

In view of this it would appear reasonable that the N-O bond in the nitroxide (46) will be pyramidal making an angle of about 30° with the CNC plane. The two configurations of (81) <u>i.e.</u> (82) and (83) have the same energy and thus will be equally populated. This is not the case with (46) where the two possible configurations (84) and

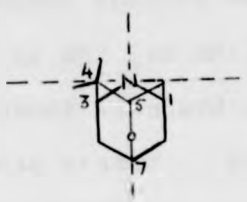
(85) do not have the same steric interactions. In the configuration (84) there is a 1,3 steric interaction between the oxygen of the nitroxide function and the axial methyl group. This 1,3 diaxial interaction has been shown[47], for methyl groups, to cause a decrease in favourability of 3.7 K cal mole^{-1}. Indeed it is this 1,3 diaxial interaction which is responsible for the ketones (38) and (71) adopting different configurations. There is no 1,3 diaxial interaction in the configuration (85) and thus this configuration will be the more favourable one.



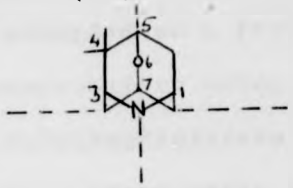
(82) (83) (84) (85)

If the nitroxide (85) is viewed in the octant projection (86) it can be seen that the axial methyl group is in the rear upper left octant and thus would be expected to have a positive contribution to the Cotton effect. The equatorial methyl group on the other hand is in the lower left rear octant and thus has a negative contribution to the Cotton effect. It is known that the contribution of a β-axial methyl group to the Cotton effect of a ketone is about 10% of the contribution a β-equatorial methyl group makes to the Cotton effect and thus the net contribution to the Cotton effect in (85) will be in the sign of the equatorial methyl group <u>i.e.</u> negative. If the nitroxide (84) is viewed in the octant projection (87) it can be seen that both methyl groups are in the upper left octant and

thus would be expected to have a positive contribution to the Cotton effect. The unfavourable 1,3 diaxial interaction in this configuration, however, suggests that the contribution of (84) to the Cotton effect of 4,4-dimethyl-2-aza-6-oxaadamantan-2-oxyl will be negligible compared to the contribution of configuration (85).

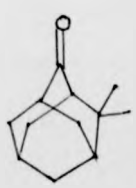


(86)



(87)

Thus (1R) 4,4-dimethyl-2-aza-6-oxaadamantan-2-oxyl (46) exhibits consignate behaviour for its n→π* transition. The corresponding (1S) 4,4-dimethyl-adamantan-2-one (88) has been synthesised[48] and its c.d. spectrum recorded. It has a positive Cotton effect at 303 nm ($\Delta\varepsilon = 0.61$) and exhibits consignate behaviour for its n→π* Transition of the carbonyl. Thus this work adds support to the hypothesis that the nitroxide group obeys an octant rule analogous to that for ketones.



(88)

EXPERIMENTAL

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

Infrared spectra were recorded on a Perkin-Elmer 457 instrument. Ultra-violet spectra were recorded on a Perkin-Elmer 402 instrument using ethanol as solvent. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-10 (60 MHz) or R32 (90 MHz) spectrometers using tetramethylsilane as internal standard and deuterochloroform as solvent unless otherwise stated. Electron paramagnetic resonance spectra were recorded on a Jeol JES-PE-IX instrument, operating in the X-band region at a frequency of 9270 MHz. Mass spectra were recorded at P.C.M.U., Harwell, Didcot, Berks.

Optical rotations were measured on a Perkin-Elmer 141 polarimeter using methanol as solvent. Circular dichroism curves were recorded at Westfield College, London, using methanol as solvent.

1-Isobutenylpiperidine (35)

Isobutyraldehyde (26.1 g) was added dropwise to a stirred solution of piperidine (44.4 ml) ptoluene sulphonic acid (100 mg) in dry benzene (300 ml). The water formed was azeotroped from the reaction mixture during refluxing over three hours. After the solution had cooled the benzene was removed under vacuum. The resulting pale yellow liquid was distilled, b.p. 52°C/10 mm (lit[49], 52°C/14 mm) to yield 1-isobutenylpiperidine (45.6 g, 91%); $\nu_{max.}$ (film) 1655 cm^{-1}; τ 4.7-4.9 (1H,m), 7.4-7.6(4H,m), and 8.2-8.7(12H,m).

2-Piperidino-3.3-dimethyl-Δ^5-dihydropyran (36)

To a stirred solution of 1-isobutenylpiperidine (85.6 g) in anhydrous ether was added slowly acrolein (38 g) and the resulting solution refluxed for seventeen hours. When the solution had cooled the ether was removed under reduced pressure and the residue distilled to yield (36) (106 g, 87%) as a colourless oil, b.p. 83-87°C/3mm (lit.[13] 83-87°C/3 mm); τ 3.5-3.7 (1H, m), 5.3-5.6 (1H, m), 6.8-8.8 (12H, m), and 9.0 (6H, d, J=Hz).

6,6,9-Trimethyl-9-azabicyclo[3,3,1]nonan-3-one (38)

A mixture of the dihydropyran (36) (106 g), Amberlite resin IR120 (H^+) (450 ml) and 40% aqueous acetone (670 ml) was stirred vigorously at room temperature for one day. The resin was removed by filtration and washed with 50% aqueous acetone (500 ml). To these combined solutions were added methylamine hydrochloride (39.8 g) and acetone dicarboxylic acid (89.5 g). The resulting solution was adjusted to pH4 with sodium acetate and allowed to stand at room temperature for two days. The solution was then made

acidic with aqueous hydrochloric acid and the acetone removed under vacuum. The acidic solution was made basic with potassium hydroxide pellets and extracted with benzene (3 x 200 ml). The combined organic extracts were dried over potassium carbonate and the solvent removed under reduced pressure to yield a dark oil which was distilled to yield (38) (62.9 g, 63.5%) as a pale yellow oil, b.p. 93-95°C/ 1.5 mm. (lit.[13] 93-95°C/1.5 mm.). Recrystallisation from n-hexane gave colourless crystals, m.p. 66-68°C (lit.[13] 66-68°C), $\nu_{max.}$ ($CHCl_3$) 1695 cm^{-1}; λmax. (t OH); 214 nm (ε = 1628) and 257 nm (ε = 1455); τ 6.6-8.7 (1OH, m), 7.4 (3H,S), 8.85 (3H, S) and 9.1 (3H,S).

Endo-6,6,9-trimethyl-9-azabicyclo[3,3,1]nonan-3-ol (39)

To a suspension of lithium aluminium hydride (8.9 g) in anhydrous ether (250 ml) was slowly added a solution of (38) (44 g) in anhydrous ether (150 ml) and the mixture refluxed for two hours. After the mixture had cooled the excess hydride was destroyed with a solution of saturated sodium sulphate (10 ml). The resulting mixture was filtered, dried over sodium sulphate and the ether removed to yield a pale yellow oil (44 g, 99%), b.p. 95-97°C/1 mm. This product solidified on standing and crystallisation from n-hexane yielded (39) as colourless plates, m.p. 81-82°C (lit.[13] m.p. 81-82°C); $\nu_{max.}$ ($CHCl_3$) 3360 cm^{-1}; τ 5.65- 5.95 (1H, m), 7-8.8 (11H, m) one disappears on D_2O exchange, 7.5 (3H, s), 8.9 (3H, s) and 9.1 (3H, s).

Endo-6.6-dimethyl-9-azabicyclo[3.3.1]nonan-3-ol (34)

A solution of potassium permanganate (32 g) dissolved in water (1.6 l) was added dropwise to a stirred solution of potassium hydroxide (14.5 g) and the amine (39) (14.5 g) in

40% aqueous methanol (1.35 l) maintaining the temperature at 0-5°C throughout. After one hour at room temperature Celite (200 g) was added and the mixture filtered. The methanol was removed from the filtrate under vacuum and the aqueous layer extracted with methylene chloride (3 x 250 ml). The combined organic layers were dried over potassium carbonate and concentrated to yield (34) as a pale yellow oil (11.5 g, 85.3%). The manganese dioxide residue was extracted with methanol in a soxhlet apparatus for 6 hours and the methanol removed under vacuum to yield a further quantity of (34) (0.9 g, 6.7%). Crystallisation of the combined fractions from ethyl acetate afforded (34) as colourless crystals, m.p. 91°C (lit[13] m.p. 91°C); $\nu_{max.}$ ($CHCl_3$) 3620 and 3300 cm^{-1}; τ 5.8-6.2 (1H, m), 6.6-6.9 (1H, m), 7.2-7.4 (1H, m), 7.6-8.8 (10H, m) two disappear on D_2O exchange, 8.9 (3H, s) and 9.15 (3H, s); M^+ = 169.1470, $C_{10}H_{19}NO$, requires M^+ = 169.1467.

Endo-3-acetoxy-6,6-dimethyl-9-acetamido-9-azabicyclo[3,3,1]nonane (56)

Acetic anhydride (0.1 ml) was added to a solution of the amine (34) (120 mg) in pyridine (1.0 ml) and the resulting solution refluxed for one day. The solution was made acidic with 2N hydrochloric acid (10 ml) and extracted with chloroform (2 x 15 ml). The combined organic extracts were dried over potassium carbonate and the solvent evaporated to yield (56) as a brown oil (133 mg, 73%); $\nu_{max.}$ (film) 1730 and 1620 cm^{-1}; τ 4.8-5.3 (2H, m, $W_{\frac{1}{2}}$ = 15Hz), 5.4-6.0 (1H, m, $W_{\frac{1}{2}}$ = 16Hz), 7.4-8.8 (8H, m), 7.95 (3H, d, J = 3Hz), 7.98 (3H, s), 9.0 (6H, d, J = 3Hz).

Endo-6.6-dimethyl-9-acetamido-9-azabicyclo[3,3,1]nonan-3-ol (57)

(i) The acetate (56) (624 mg) was dissolved in 1% methanolic

potassium hydroxide solution (16 ml) and the resulting solution allowed to stand at room temperature overnight. The solution was neutralised with 10% methanolic hydrochloric acid (1.6 ml) and the solvent removed by evaporation. The residue was dissolved in chloroform (25 ml), washed with water (10 ml), dried and concentrated under reduced pressure to yield (57) (422 mg, 83%) as a pale yellow oil. Distillation afforded (57) as a colourless oil b.p. 140-145°C/ 0.1 mm; $\nu_{max.}$ (film) 3320 and 1605 cm^{-1}; τ 46-48 (3H, m), 7.5-8.9 (9H, m) one disappears on D_2O exchange, 7.9-7.95 (3H, d, J = 6Hz), 8.95 (3H, s) and 9.15 (3H, s); M^+ = 211.1573 $C_{12}H_{21}NO_2$ requires M^+ = 211.1572.

(ii) A solution of (34) (1 g) in dry pyridine (50 ml) was cooled to -22°C, in a carbon dioxide carbon tetrachloride slush bath, and acetyl chloride (0.5 ml) was added dropwise keeping the temperature below -20°C throughout. Water (2 ml) was added after two minutes and the resulting solution evaporated to dryness under reduced pressure. Water (5 ml) and chloroform (25 ml) were added and the aqueous layer extracted with chloroform (2 x 25 ml). The chloroform layers were combined, dried over sodium sulphate and the solvent removed to yield (57) (1.48 g, 98.5%) as a pale yellow oil which was identical in every respect with the material obtained earlier.

2-Acetamido-2-aza-4.4-dimethyl-6-oxaadamantane (58)

A mixture of dry benzene (85 ml), lead tetraacetate (8.6 g) and anhydrous calcium carbonate (4.32 g) was refluxed for fifteen minutes. The acetate (57) (1.44 g) in dry benzene (72 ml) and iodine (3.7 g) were added and the refluxing was continued for three hours. The cooled

solution was filtered and then washed with 20% sodium thiosulphate (100 ml) and distilled water (50 ml). The resulting benzene solution was dried over sodium sulphate and the solvent removed to yield a brown oil. This oil was dissolved in ethanol (25 ml) and sodium borohydride (800 mg) was added and the mixture stirred at room temperature for fifteen hours. Saturated sodium sulphate (10 ml) was added, the mixture was dried over sodium sulphate, filtered and the ethanol removed under reduced pressure. The resulting brown oil (1.4 g) was purified by column chromatography with silica (50 g). Elution with 1% methanol/methylene chloride yielded (58) as a pale yellow oil (700 mg, 48%); $\nu_{max.}$ ($CHCl_3$) 1620 cm^{-1}; τ 4.9-5.5 (2H, m), 5.6-6 (1H, m, $W_{\frac{1}{2}}$ = 12 Hz), 6.3-6.5 (1H, m, $W_{\frac{1}{2}}$ = 16Hz), 7.9 (3H, d, J = 2Hz), 8.75 (3H, d, J = 1Hz), 9.05 (3H, d, J = 5Hz); M^+= 209.1415, $C_{12}H_{19}NO_2$ requires M^+ = 209.1416.

Attempted preparation of 2-aza-4,4-dimethyl-6-oxaadamantane (60)

(i) The acetamide (58) (100 mg) in methanol (20 ml) and water (10 ml) was refluxed with sodium hydroxide (2 g) for twenty-four hours. The methanol was removed under vacuum and the aqueous layer was extracted with ether (3 x 10 ml). The starting acetamide (58) was obtained in quantative yield.

(ii) Potassium-t-butoxide (115 mg) was added to a solution of the acetamide (58) (50 mg) in dry tetrahydropuran (5 ml) and the solution was stirred for ninety minutes. After the solvent had been removed under reduced pressure, water (2.5 ml) and ether (25 ml) were added. The organic layer was washed with saturated brine (2.5 ml), dried over potassium carbonate and the solvent removed to yield starting material quantatively.

(iii) Sodium hydroxide (2 g), ethanol (20 ml), water (10 ml) and the acetamide (58) (100 mg) were refluxed for two days. The ethanol was removed under reduced pressure and the water layer extracted with ether (3 x 10 ml). The combined ether extracts were dried over potassium carbonate and removed to yield the starting material in quantative yield.

(iv) A mixture of diethyleneglycol (15 ml), the acetamide (58) (100 mg) and sodium hydroxide (2 g) was heated at 170°C for two days. After the solution had cooled, water (15 ml) was added and the resulting solution extracted with methylene chloride (3 x 25 ml). Tne methylene chloride extracts were combined and washed with 1.1 M hydrochloric acid (2 x 50 ml). The aqueous extracts were made basic with sodium hydroxide pellets and extracted with ether (2 x 50 ml). The combined ether extracts were dried over potassium carbonate and the solvent removed under vacuum to yield (58) (84 mg). No other compound was obtained.

2-Aza-4,4-dimethyl-6-oxaadamantane (60)

To a stirred solution of the acetamide (58) (280 mg) in anhydrous ether (10 ml) a ten molar excess of methyl magnesium bromide in ether was added. The resulting mixture was refluxed for sixteen hours after which time 1.1M hydrochloric acid (25 ml) was added. The aqueous layer was made basic with potassium hydroxide pellets and filtered. The aqueous layer was continuously extracted with chloroform for twenty-four hours. The solid obtained by filtration was extracted in a soxhlet apparatus for one day. The combined organic layers were reduced to dryness under vacuum and chloroform (50 ml) and water (5 ml) were added. The chloroform layer was separated, dried over potassium carbonate and

the solvent removed under reduced pressure to yield (60) (200 mg, 98%) as a colourless crystals m.p. 212°C; τ 5.7-6.0 (1H, m, $W_{\frac{1}{2}}$ = 11Hz), 6.0-6.2 (1H, m, $W_{\frac{1}{2}}$=12Hz)6.3-6.5 (1H, m, $W_{\frac{1}{2}}$ = 8Hz), 6.5-6.7 (1H, m, $W_{\frac{1}{2}}$ = 8Hz), 7.5-8.8 (7H, m) one disappears on D_2O exchange, 8.8 (3H, s) and 8.9 (3H, s); M^+ = 167.1307, $C_{10}H_{17}NO$ requires M^+ = 167.1310.

2-Aza-4.4-dimethyl-6-oxaadamantane-2-oxyl (46)

A solution of m-chloroperoxybenzoic acid (500 mg) in dry methylene chloride (20 ml) was added dropwise to a stirred solution of the amine (60) (80 mg) in methylene chloride (10 ml) at 0°C, buffered with disodium hydrogenphosphate (100 mg). The resulting mixture was stirred at 0°C for one hour and then at room temperature for two hours. The solution was washed with 10% sodium sulphite (25 ml), 10% sodium bicarbonate (25 ml), dried over potassium carbonate and the solvent removed under vacuum to yield a red oil (80 mg, 91%). Preparative thin-layer chromatography with silica yielded on elution with 5% chloroform/ether a red oil which was sublimed (160°C at 10 mm) to yield a pale yellow solid m.p. 81°C, A_N (pentane) 1.69 x 10^{-4}T, g = 2.0066; (in the presence of hydroxybenzene) 5.9-6.2 (1H, m, $W_{\frac{1}{2}}$ = 13Hz), 6.6-6.9 (2H, m, $W_{\frac{1}{2}}$ = 13Hz), 7.0-7.2 (1H, m, $W_{\frac{1}{2}}$ = 9Hz), 7.6-8.8 (7H, m), 8.85 (3H, s), and 8.95 (3H, s); $\lambda_{max.}$ (CH_3OH) 416(ε = 6.4), 245 (ε = 1620); M^+ = 182.1187, $C_{10}H_{16}NO_2$ requires M^+ = 182.1181.

6.6.9-Trimethyl-9-azabicyclo[3,3,1]nonan-3-one (38)

Chromium trioxide (0.15 g) was added to a stirred solution of freshly distilled pyridine (0.48 g) in anhydrous methylene chloride (3 ml). The solution was stirred for twenty minutes until a deep burgandy colour appeared. The alcohol (39) (80 mg) was added and the stirring continued for a further

fifteen minutes. Water (5 ml) and methylene chloride (10 ml) were added and the methylene chloride layer extracted with 1.1M hydrochloric acid (2 x 10 ml). The acidic solution was made basic with potassium hydroxide pellets and extracted with methylene chloride (3 x 25 ml). The combined organic extracts were dried over potassium carbonate and the solvent removed under vacuum to yield the ketone (38) (69 mg 87%). Recrystallisation from n-hexane gave colourless prisms, m.p. 66-68°C (lit[13] 66-68°C).

Endo-6,6,9-trimethyl-9-azabicyclo[3.3.1]nonan-3-ol (39)

A mixture of the amine (34) (100 mg), formalin (0.3 ml) and formic acid (0.1 ml) was refluxed for two hours. After the solution had cooled water (15 ml) was added and the pH of the solution adjucted to 14 with sodium hydroxide pellets. The resulting solution was extracted with methylene chloride (2 x 10 ml) and the organic extracts were dried over potassium carbonate and the solvent removed under vacuum to yield a pale yellow oil (105 mg, 97%) which solidified on standing. Crystallisation from n-hexane afforded colourless plates m.p. 81°C which were identical, by n.m.r., i.r. and mixed melting point, with (39) prepared earlier.

Resolution of endo-6,6-dimethyl-9-azabicyclo[3.3.1]nonan-3-ol (34)

The amino-alcohol (34) (169 mg) was dissolved in the minimum volume of hot dry methanol and (+)-tartaric acid (150 mg), dissolved in the minimum volume of hot methanol, was added. After maintaining the solution at room temperature for three days, anhydrous ether (1 ml) was added and the resulting precipitate redissolved by heating. The solution was allowed to cool whereupon crystals formed. The crystals were collected by filtration to yield the salt (120 mg) as

colourless crystals, m.p. 165-179°C, $[\alpha]_{589}^{24}$ = +10.8° (C = 12). The amine was liberated by dissolving the diastereoisomeric salt in water (5 ml), adjusting the pH to 14 and extracting with methylene chloride (2 x 25 ml). The organic layer was dried over sodium sulphate and the solvent removed under vacuum to yield (34) (60 mg) $[\alpha]_{589}^{24}$ = +1.32° (C = 2.1).

Large scale resolution

The amino-alcohol (34) (13 g) was dissolved in hot methanol (10 ml) and (+)-tartaric acid (11.4 g) in hot methanol (10 ml) was added. Ether (30 ml) was added and a white precipitate appeared which redissolved on heating. The solution was cooled to 0°C and kept at this temperature overnight. The resulting colourless crystals were collected by filtration and dried under reduced pressure to yield the desired salt (14.36 g), m.p. 167-170°C. These crystals were redissolved in hot 50% methanol/ether (250 ml). On standing at 0°C overnight the crystals which had formed were collected by filtration to yield a colourless solid; m.p. 172-176°C, $[\alpha]_{589}^{24}$ = +11.9° (C = 4.21). Further recrystallisation failed to alter the melting point or the optical rotation of the salt. The amino-alcohol (34) was obtained by dissolving the salt in water (50 ml), adjusting the pH to 14 with potassium hydroxide pellets and extracting the resulting mixture with methylene chloride (2 x 200 ml). The organic fraction was dried over sodium sulphate and the solvent removed to yield (34) as colourless crystals m.p. = 114°C, $[\alpha]_{589}^{24}$ = +1.55° (C = 1.22). This material was spectroscopically identical with racemic (34).

Attempted preparation of endo-(±)-3-/-methoxy- -trifluromethylphenylacetoxy/-6,6,9-trimethyl-9-azabicyclo/3,3,1/nonane (70)

(i) (±)- -Methoxy- -trifluromethylphenylacetic acid (68) (100 mg)

in freshly distilled thionyl chloride (5 ml) was refluxed for four and a half hours. The excess thionyl chloride was removed under vacuum to yield a colourless oil. Pyridine (5 ml) and the amino-alcohol (39) (78 mg) were added and the solution allowed to stand at room temperature for 17 hours. The pyridine was removed under reduced pressure, then chloroform (20 ml) and saturated sodium bicarbonate solution (20 ml) were added. The chloroform layer was removed and the aqueous phase extracted with chloroform (3 x 20 ml). The combined chloroform layers were dried over potassium carbonate and the solvent removed under vacuum to yield the starting amine (39) quantatively.

(ii) A solution of (±) - -methoxy- -trifluromethylphenylacetyl chloride (115 mg) in anhydrous pyridine (5 ml) was added to a solution of (39) (78 mg) in pyridine (5 ml) and the resulting solution refluxed for seventeen hours. The solvent was removed under vacuum and chloroform (20 ml) and saturated sodium bicarbonate solution (20 ml) were added. The chloroform layer was separated and the aqueous phase extracted with chloroform (3 x 20 ml). The chloroform extracts were dried over potassium carbonate and the solvent removed to yield an oil which appeared to contain a small amount of the desired ester (70); $\nu_{max.}$ ($CHCl_3$), 3360 and 1735cm^{-1}.

(±)-Endo-3-/-methoxy- -triflurophenylacetoxy7-6,6,9-trimethyl-9-azabicyclo/3,3,1/nonane (70)

Methyl lithium (0.9 m.mol) in ether (300 µl) was added to a stirred solution of (39) (110 mg) in anhydrous ether. The acid chloride of (68) in ether (5 ml) was added dropwise to the solution and the resulting mixture stirred for sixteen hours. Chloroform (20 ml) was added and the resulting solution extracted with saturated sodium bicarbonate (20 ml).

The chloroform layer was dried over potassium carbonate and the solvent removed to yield the desired ester (70) as a pale yellow oil in quantative yield. $\nu_{max.}$ ($CHCl_3$) 1735 cm^{-1}; τ2.1-2.7 (5H, m), 4.5-4.8 (1H, m, $W_{\frac{1}{2}}$ =8Hz) 6.4-6.5 (3H, qJ = 2Hz), 7-8.7 (10H, m), 7.55 (3H, s), 8.7 (3H, s) and 8.9 (3H, s).

6,6-Dimethyl-9-azabicyclo[3,3,1]nonan-3-one (71)

A mixture of chromium trioxide (0.15 g), freshly distilled pyridine (0.48 ml) and anhydrous methylene chloride (10 ml) was stirred at room temperature for twenty minutes when a deep burgundy colour had appeared. The alcohol (34) (80 mg) was added and the stirring continued for a further fifteen minutes. Water (5 ml) and methylene chloride (10 ml) were added and the methylene chloride layer extracted with 1.5M hydrochloric acid (2 x 10 ml). The acidic extract was made basic with potassium hydroxide pellets and extracted with methylene chloride (3 x 25 ml). The resulting organic extracts were combined, dried over potassium carbonate and the solvent removed to yield the desired ketone (71) (70 mg). $\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1}; λmax. (EtOH) 214 nm (ε = 1533); 6.6-8.7 (11H, m) one disappears on D_2O exchange, 8.85 (3H, s) and 9.1 (3H, s).

Partially resolved (+)-endo-6,6,9-trimethyl-9-azabicyclo[3,3,1]-nonan-3-ol (39)

Acetyl chloride (0.5 ml) was added dropwise to a stirred solution of the (+)-amine (34) (1.59 g) in pyridine (50 ml) cooled to -22°C. After two minutes the reaction was quenched with 1.1M hydrochloric acid (10 ml) and the mixture extracted with chloroform (2 x 25 ml). The combined chloroform layers were dried over potassium carbonate and the solvent removed under vacuum to yield (+)- (39) as a colourless oil (1.8 g,

90%), $[\alpha]_{589}^{24}$ = +5.75° (C = 2.26). This material was spectroscopically identical with the reacemic material prepared earlier.

Partially resolved (+)-2-acetamido-2-aza-4,4-dimethyl-6-oxaadamantane (58)

A mixture of lead tetraacetate (8.6 g), anhydrous calcium carbonate (4.3 g) and dry benzene (85 ml) was refluxed for fifteen minutes. A solution of (+) (57) (1.44 g) in anhydrous benzene (70 ml) and iodine (3.7 g) were added and the refluxing continued for a further three hours. The resulting mixture was cooled in an ice bath and then filtered. The benzene solution was washed with 20% sodium thiosulphate (100 ml), followed by distilled water (50 ml) and then dried over sodium sulphate. Removal of the solvent yielded a brown oil (1.7 g). This oil was dissolved in ethanol, sodium borohydride (1 g) was added and the resulting solution allowed to stand at room temperature for seventeen hours. Water (5 ml) was added slowly and the resulting mixture filtered. The ethanol solution was concentrated under reduced pressure and chromatographed on silica (60 g). Elution with 2% methanol/methylene chloride (1000 ml) yielded the desired (+)-2-aza-6-oxaadamantane (58) (720 mg), $[\alpha]_{589}^{24}$ = +30.87 (C = 2.53). This material was spectroscopically identical with the reacemic mixture (58).

Partially resolved (+)-4,4-dimethyl-2-aza-6-oxaadamantane (60)

The (+) acetamide (58) (720 mg) was dissolved in anhydrous ether (30 ml) and a ten molar excess of methyl magnesium bromide in ether was added. This mixture was refluxed for sixteen hours, cooled, and then 1.1M hydrochloric acid (20 ml) was added. The ether layer was discarded and the aqueous layer was made basic with potassium hydroxide pellets and

filtered. The resulting solid was extracted for twenty-four hours in a soxhlet apparatus with methanol while the aqueous layer was saturated with sodium chloride and extracted continuously for twenty-four hours. The combined organic extracts were evaporated to dryness and chloroform (50 ml) and water (5 ml) were added. The organic layer was dried over potassium carbonate and the chloroform removed under vacuum to yield (+)-(60) (470 mg), $[\alpha]_{589}^{24}$ = +29.32° (c = 6.14). This material was identical spectroscopically with the racemic mixture (60).

Partially resolved (+)-4,4-dimethyl-2-aza-6-oxaadamantan-2-oxyl (46)

A solution of the (+)-amine (60) (80 mg) in dry methylene chloride (10 ml) was cooled to 0°C and a solution of m-chloroperoxybenzoic acid (500 mg) in dry methylene chloride (10 ml) was added using disodium hydrogenphosphate as buffer. The resulting mixture was stirred at 0°C for one hour and then at room temperature for two hours. The mixture was filtered and the organic layer washed with 10% sodium sulphite (25 ml), 10% sodium bicarbonate (25 ml), dried over potassium carbonate and the solvent removed to yield a red oil (75 mg, 86%). Preparative thin layer chromatography with silica yielded, on elution with 5% chloroform/ether, a yellow oil (20 mg) which was sublimed (160°C, 10 mm) to give the desired nitroxide (9.3 mg) as a pale yellow oil, $[\alpha]_{589}^{24}$ = +15.4° (c = 0.93), which was identical with the racemic mixture spectroscopically.

Partially resolved (-)-6,6,9-trimethyl-9-azabicyclo[3,3,1]-nonan-3-one (38)

Freshly distilled pyridine (0.48 ml), anhydrous methylene chloride (10 ml) and chromium trioxide (0.15 g) were stirred

at room temperature for twenty minutes during which time a deep burgundy colour appeared. The (+)-amino-alcohol (39) (80 mg) was added and the stirring continued for fifteen minutes. Water (5 ml) and methylene chloride (10 ml) were added. The organic layer was separated and extracted with 1.1M hydrochloric acid (2 x 20 ml). The acidic layer was made basic with potassium hydroxide pellets and extracted with methylene chloride (3 x 25 ml). The organic extracts were dried over potassium carbonate and the solvent removed to yield as a colourless solid (-) (38) (70 mg, 88%), m.p. 44°C, which was identical with the racemic mixture (38) spectroscopically; $[\alpha]_{589}^{24}$ = -1.0° (c = 1.1).

Partially resolved (+)-6,6-dimethyl-9-azabicyclo[3,3,1]nonan-3-one (71)

The alcohol (34) (80 mg) was added to a solution of pyridine (0.48 ml), anhydrous methylene chloride (10 ml) and chromium trioxide (0.15 g) and the resulting solution stirred for fifteen minutes at room temperature. Water (5 ml) and methylene chloride (10 ml) were added and the resulting two layers separated. The organic layer was washed with 1M hydrochloric acid (2 x 20 ml) and the acidic aqueous layer was made basic with potassium hydroxide pellets and extracted with methylene chloride. These organic extracts were dried over potassium carbonate and the solvent removed under vacuum to yield an oil (65 mg, 82%) which was identical spectroscopically with the racemic mixture; $[\alpha]_{589}^{24}$ = +5.5° (c = 1.13).

Partially resolved (+)-endo-3-[-methyl- -trifluromethyl-phenylacetoxy-]-6,6,9-trimethyl-9-azabicyclo[3,3,1]nonane (70)

To the lithium salt prepared from (39) (110 mg), by treatment with methyl lithium (0.9 m.mol) in ether (300 µl),

a solution of the acid chloride of (68) (180 mg) in ether (5 ml) was added, while stirring, and the resulting mixture stirred at room temperature for sixteen hours. Chloroform (20 ml) was added and the resulting solution extracted with saturated sodium bicarbonate (20 ml). The organic layer was dried over potassium carbonate and the solvent was removed under reduced pressure to yield the ester (71) as a pale yellow oil (240 mg, quantative). This material was spectroscopically identical with its racemate.

(+)-2,3-Diacetoxysuccinic anhydride

A solution of concentrated sulphuric acid (12 ml) in acetic anhydride (136 g) was added to (+)-tartaric acid (40 g) and the resulting mixture gently heated until all the (+)-tartaric acid had dissolved. The solution was then gently refluxed for ten minutes, cooled in ice for one hour and the resulting crystals collected by filtration and washed with benzene. These crystals were stirred with cold anhydrous ether, filtered, and dried to yield colourless crystals (41.1 g, 71%), m.p. 133-134°C (lit.[50] = 133-134°C).

(+)-2-Nitrotartranilic acid

A mixture of freshly prepared (+)-2,3-diacetoxysuccinic anhydride (41.1 g), 2-nitroaniline (29 g) and methylene chloride (380 ml) was refluxed for twenty hours. The resulting solution was extracted with 1.6% potassium hydroxide (380 ml) and water (200 ml). The combined aqueous extracts were stirred for two hours at room temperature, filtered and acidified with concentrated hydrochloric acid (67 ml). This mixture was cooled in an ice-bath and the resulting crystals collected by filtration (44 g). Recrystallisation from water followed by washing with ether yielded (+)-2-

nitrotartranilic acid (22.6 g) as pale yellow crystals, m.p. 196-198°C (lit.[44] = 196-198°C); $[\alpha]_{589}^{30}$ = +89.8° (c = 0.44) (lit.[44] $[\alpha]_D$ = +90.0° (c = 0.44)).

Resolution of 4,4-dimethyl-2-aza-6-oxaadamantane (60)

A solution of (+)-2-nitrotartranilic acid (140 mg) in the minimum volume of hot methanol was added to 4,4-dimethyl-2-aza-6-oxaadamantane (60) (137 mg) in hot methanol. The solution was allowed to stand at room temperature for two days and the crystals which had formed were collected by filtration to yield colourless crystals (131.2 mg), m.p. 105-112°C, $[\alpha]_{589}^{30}$ = +40.04° (c = 4.37). This salt (43.7 mg) was dissolved in distilled water (10 ml) made basic with potassium hydroxide pellets and extracted with methylene chloride (2 x 20 ml). The organic layer was dried over potassium carbonate and the solvent removed under vacuum to yield (60) (15.8 mg) $[\alpha]_{589}^{30}$ = +29.9° (c = 1.58). The amine (60) (15.8mg) and (+)-2-nitrotartranilic acid (25.5 mg) in methanol were added to the remainder of the crystals collected and this mixture was recrystallised from methanol to yield colourless crystals (97 mg), m.p. 161-167°C $[\alpha]_{589}^{30}$ = +63.65° (c = 1.04). A further recrystallisation from methanol afforded the salt (43.9 mg), m.p. 163-167°C $[\alpha]_{589}^{30}$ = +68.0° (c = 0.64). This salt was dissolved in distilled water (10 ml) and saturated with sodium carbonate. The resulting solution was extracted with methylene chloride (2 x 20 ml) and after drying over potassium carbonate the solvent was removed under reduced pressure to yield (60) (15.1 mg), $[\alpha]_{589}^{30}$ = +51° (c = 1.51) as a colourless oil identical spectroscopically with racemic (60).

(+)-4,4-Dimethyl-2-aza-6-oxaadamantane-2-oxyl (46)

A solution of m-chloroperoxybenzoic acid (128 mg) in methylene chloride (3 ml) was added dropwise to a stirred mixture of the amine (60) (15.1 mg) in methylene chloride (3 ml) at 0°C buffered with sodium dihydrogen phosphate. The resulting mixture was stirred at room temperature for two hours and then allowed to stand for sixteen hours at 0°C. The solution was then washed with 10% sodium sulphite (10 ml), sodium bicarbonate (10 ml), dried over potassium carbonate and the solvent evaporated under vacuum to yield a pale orange oil (20.7 mg). Sublimation at 160°C/10 mm yielded as a pale orange oil (46) (7.9 mg) $[\alpha]_{589}^{24}$ = +26.6° (c = 0.79); A_n(pentane) = 16.9 G, g = 2.0066; $\Delta\varepsilon$ = -0.28.

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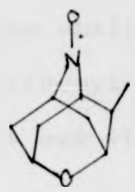
3. Synthetic approaches to 2-aza-4(e)-and 4(a)-6-oxaadamantane-2-oxyl

In an effort to extend the scope of this work and to test the validity of the conclusions deduced from it, an attempt was made to synthesise the corresponding 4-methyl-adamantane nitroxides (1) and (2). These compounds, in addition to substantiating the conclusions drawn earlier in a qualitative sense, should also give information on the additivity of the contribution made by the methyl substituent to the Cotton effect in a quantitative sense.

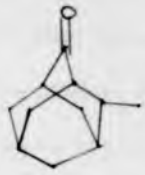
(1)



(2)

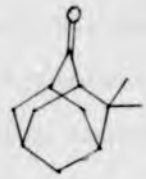
A number of optically active 4-substituted adamantan-2-ones have been prepared and their c.d. spectra recorded. The 4-methyladamantan-2-ones (3) and (4) have been prepared[1] and thus a direct comparison of the Cotton effects of ketones and nitroxides would be possible. In addition, 4,4-dimethyl-adamantan-2-one (5) has been synthesised[2] with an optical purity of 77±3%. The c.d. spectra of these three ketones (3), (4) and (5) have been recorded having $\Delta\varepsilon$ = +0.78, +0.09 and +0.61* respectively. If the reported value $\Delta\varepsilon$ = +0.61 for (5) is modified to take account of the optical purity of 77±3% then for optically pure material the Cotton effect for (5) will have a value of $\Delta\varepsilon$ = +0.78. This value is the same as the value of $\Delta\varepsilon$ for the 4(a)-methyladamantan-2-on (3) and thus appears to contradict the additivity of the octant rule.

*It is not clear from ref.[2] whether this value has been modified to take into account the optical purity of 77± 3%.



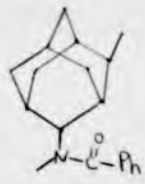
(3)

(4)

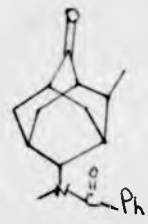


(5)

The 4-axial position in adamantan-2-ones, however, appears to have a variable contribution, to the Cotton effect, for methyl substituents. The biological hydroxylation and subsequent oxidation of the adamantane (6)[3] gave the adamantan-2-one (7). This ketone while having the same absolute stereochemistry about the carbonyl as (4) has a value of $\Delta\varepsilon$ = -0.09 i.e. the same magnitude but the opposite sign as (4).



(6)

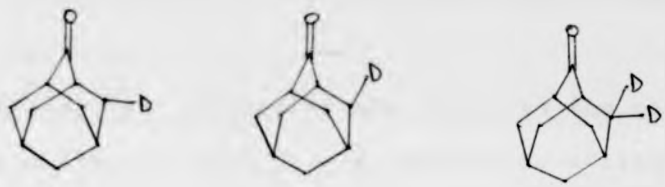


(7)

Recently the three optically active deuterioadamantan-2-ones (8), (9) and (10) have been reported[4] with an optical purity of 84±3%. In all three cases the deuterium substitution causes a dissignate contribution to the Cotton effect. In this series the Cotton effect of 1(s)-4(r)-deuterioadamantan-2-one (8) has a value of $\Delta\varepsilon$= -0.090* which, analogous with the corresponding methyl-adamantan-2-ones (3) and (4), is much larger than the Cotton effect of 1(S)-4(a)-deuterioadamantan-2-one (9) which has a value of $\Delta\varepsilon$ = -0.017. The corresponding 1(S)-4,4-dideuterioadamantan-2-one (10) has a recorded

*This value has not been modified to take into account the optical purity of 84±3%.

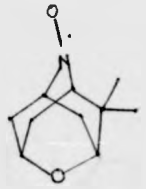
value of $\Delta\varepsilon$ = -0.088. It has been estimated that the magnitude of the possible error introduced into the c.d. of (8) by the presence of 5% of (9) is 1%. A further possible error arises from the fact that deuterium incorporation into (8) was 97%. In addition to these errors there remains the possibility that optical fractionation of the intermediates and of (8) during purification may have taken place. In the dideuteriocompound (10) the deuterium incorporation was 98% and optical fractionation may have occurred to introduce errors to the observed c.d. However, unless these errors are greater than 20% again it would appear that the octant rule is not additive for the 4-position of adamantan-2-ones.



(8) (9) (10)

An obvious feature which arises from the comparison of the Cotton effects of (5) and the corresponding oxaaza-adamantane nitroxide (11) is that while both exhibit consignate behaviour for their n - π^* transition the $\Delta\varepsilon$ value for the nitroxide (11), $\Delta\varepsilon$ = -0.048, is an order of magnitude smaller than for the ketone (5), $\Delta\varepsilon$ = 0.61. This suggests that the value of $\Delta\varepsilon$ for (1) and (2) will be an order of magnitude smaller than (3) and (4) respectively. Thus, as with (11), it may be necessary to prepare (1) and (2) in a state of high optical purity which may prove difficult. In the case of (2) as it would appear a 4-axial substituent has a contribution to the Cotton effect which is only about one tenth the contribution of a 4-equatorial substituent, this

fact becomes even more important.



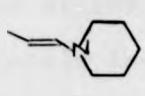
(11)

In the case of nitroxide (1) it is interesting to speculate on the effect of the removal of the steric interaction between the axial methyl group and the oxygen of the nitroxide. This should probably permit rapid inversion of the two configurations of the nitroxide moiety which might produce h.f.s.c., for the β-equatorial protons, which are large enough to observe as is normally found in this class of nitroxide.

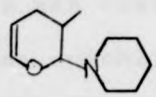
In view of the success of the route to the dimethyl-adamantane nitroxide (11) it was decided to utilise a similar synthetic pathway in an attempt to prepare the nitroxides (1) and (2). An obstacle in this approach is that the two-mono-methyl derivatives will be obtained as a mixture of isomers which will require separation at some stage in the synthesis. There is an additional problem in that once separated some means will then have to be found to assign the stereochemistry of each methyl group.

Initial attempts to prepare the piperidine enamine of proprionaldehyde (12) using the conventional method of removing the water azeotropically from a refluxing benzene solution proved to be unsuccessful due to the volatility of the aldehyde. This problem was overcome by adding slowly the aldehyde to a stirred mixture of excess piperidine and anhydrous potassium carbonate. An exothermic reaction ensued

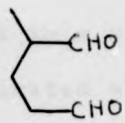
and the desired enamine (12) was obtained in high yield after thirty minutes.



(12)



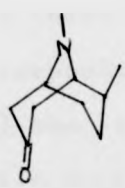
(13)



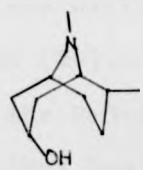
(14)

This enamine was treated with acrolein as before to yield the dihydropyran (13) which was immediately hydrolysed to gluteraldehyde (14) with an acidic resin. Without isolation, (14) was converted into a mixture of the 6-methyl-9-azabicyclo-[3,3,1]nonan-3-ones (15) and (16) by the use of the Robinson Schopf reaction. This mixture of ketones was converted into the corresponding alcohols (17) and (18) by reduction with lithium aliminium hydride.

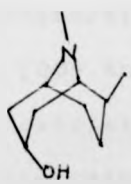
(15)



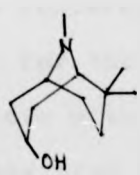
(16)



(17)



(18)

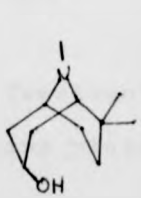


(19)

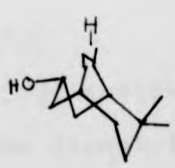
It was at this stage in the synthesis that it was decided to make the first attempt to separate the isomers. Distillation of the dimethyl-analogue (19) yielded pure material and there was no obvious decomposition caused by heating during the distillation. Thus the mixture of alcohols

(17) and (18) was distilled under vacuum using a spinning band column. The first fraction collected from the column appeared, by n.m.r. spectroscopy to be only one isomer and thus the remainder of the sample was distilled in this manner. The more volatile isomer was quickly contaminated with small amounts of the less volatile isomer and thus the pure more volatile isomer was obtained in a low yield, based on the percentage present in the mixture calculated to be about 40% from the n.m.r. spectrum of the mixture. The pure less volatile isomer was obtained in quite good yield, after all the more volatile isomer had been distilled off, by this method.

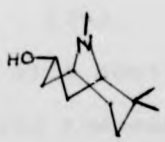
It was also at this point in the synthetic sequence that the first information was obtained which indicated the configuration of the 6-methyl group in each isomer. It had been noted earlier that there was a marked difference in the n.m.r. spectra of the compounds (19) and (20). In the n.m.r. spectrum of (19) the signal for the C-3 methine proton is not well resolved with $W_{\frac{1}{2}}$ = 8Hz and this has been ascribed to the twin chair conformation being adopted due to the unfavourable interaction in the conformation (21). However, in the case of (20) this signal for the C-3 methine proton is a nine line triplet of triplets with coupling constants of 9 and 6Hz respectively. This type of signal has been reported for the endo-bicyclo[3,3,1]nonan-3-ol (22) and this has been attributed to the molecule adopting the conformation depicted[5].



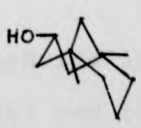
(19)



(20)



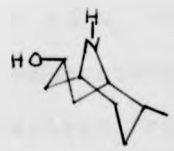
(21)

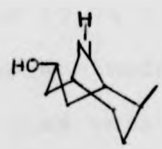


(22)

In the case of the mono-methyl alcohols (17) and (18) the more volatile isomer has a signal for the C-3 methine proton, in its n.m.r. spectrum, which is a triplet of triplets with coupling constants of 9 and 6Hz suggesting that the chair-boat conformation is adopted. This suggests that there is no 1,3-methyl-methyl interaction in this molecule and hence that the methyl group has the equatorial configuration. In the n.m.r. spectrum of the less volatile isomer the signal due to the C-3 methine proton is a quintet with a coupling constant of 6.6Hz. This signal could arise if the molecule was in the twin-chair conformation and the protons on the adjacent carbons were magnetically equivalent. This suggests that the methyl group has the axial configuration and the twin-chair conformation is adopted to avoid a 1,3 steric interaction between the methyl groups.

The two alcohols (17) and (18) were separately N-demethylated selectively by the action of basic potassium permanganate to give the corresponding amines (23) and (24). In both these secondary amines the signal for the C-3 methine proton in their n.m.r. spectra is a nine line triplet of triplets with coupling constants of 9Hz and 6Hz respectively, suggesting that the chair boat conformations (23) and (24) are adopted.

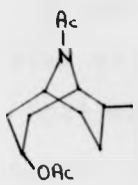




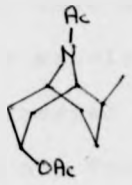
(23) (24)

Treatment of (23) and (24) with acetic anhydride in pyridine yielded the diacetylated compounds (25) and (26)

It has been hoped that the 6-axial methyl compound (24) would acetylate slower, at nitrogen, than its 6-equatorial isomer due to increased steric hinderance about nitrogen. Unfortunately both isomers appeared to acetylate at the same rate when monitored by t.l.c. and i.r. spectroscopy. Hydrolysis of the 3-acetoxy group was accomplished with methanolic potassium hydroxide on (25) and (26) in individual reactions to yield the acetamides (27) and (28) in quantitative yield.

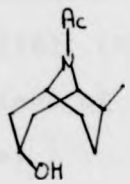


(25)



(26)

(27)



(28)

The n.m.r. spectra of (25)-(28) again proved useful in helping to assign the stereochemistry at C-6. In all four cases the n.m.r. spectra of these compounds had a signal for the C-3 methine proton which was a broadunresolved peak $W_{\frac{1}{2}}$ = 16Hz. This tends to suggest that the twin-chair conformations (25)-(28) were adopted. In a variable temperature study carried out on the acetamide prepared from the more volatile endo-6,9-dimethyl-9-azabicyclo[3,3,1]nonan-3-ol, by the route outlined, it was found that the coalescence temperature for the acetamido signal occurred at 80°C. This corresponds to a ΔG_c value[6] of 19.74 K cal mole^{-1}. The coalescence temperature of the acetamido signal for the derivative prepared from the less volatile endo-6,9-dimethyl-9-azabicyclo[3,3,1]nonan-3-ol was found to be 101°C and ΔG_c calculated[6] from this was calculated to be 20.35 Kcal mole^{-1}.

Hindered rotation of acetamides is a well-known phenomenon and it is recognised that the energy barrier to rotation

increases with increasing electronic factors and steric hindrance[7,8]. In the case of the acetamides (27) and (28) the major difference is a steric factor. Thus the axial methyl compound will exert a greater steric hindrance than the equatorial methyl isomer and therefore have the larger energy barrier. This evidence again suggests that the more volatile isomer has the 6-methyl group in an equatorial configuration.

It was decided that at this stage in the synthesis the initial attempts at resolving the amines (17), (18), (23) and (24) would be carried out. Unfortunately lack of time prevented this and any further work in this area.

The same general experimental details apply here as outlined on page 69. In addition variable temperation nuclear magnetic resonance studies were carried out in nitrobenzene.

Microanalyses were carried out at Dr. F. B. Strauss Microanalytical Laboratory, 10 Carlton Road, Oxford.

1-Proprionylpiperidine (12)

Prop ionaldehyde (100 ml) was added dropwise to a stirred mixture of piperidine (256 ml) and anhydrous potassium carbonate (216 g). This mixture was stirred for twenty minutes, filtered and the resulting solution distilled under reduced pressure to yield (12) (73 g, 42%), b.p. 49°C/9 mm (lit.[9] 61-63°C/15 mm); $\nu_{max.}$ film 1655 cm^{-1}.

2-Piperidino-3-methyl-Δ^5-dihydropyran (13)

Acrolein (52.4 g) was added dropwise to a solution of (12) (106.8 g) in anhydrous ether (100 ml) and the resulting solution refluxed for seventeen hours. The ether was removed under vacuum and the product distilled to give (13) as an oil (61 g, 40%), b.p. 83-85°C/3 mm.

6,9-Dimethyl-9-azabicyclo[3,3,1]nonan-3-one (15, 16)

A solution of (13) (61 g) in 40% aqueous acetone (420 ml) was stirred vigorously with Amberlite resin IR 120 (H^+) (280 ml) at room temperature for sixteen hours. The resin was removed by filtration and washed with 50% aqueous acetone (320 ml). The solutions were combined and methylamine hydrochloride (24.8 g) and acetone dicarboxylic acid (56 g) were added. Sodium acetate was added until the solution was pH4 and the resulting mixture allowed to stand for two days at room temperature. This solution was then made acidic with concentrated hydrochloric acid and the acetone removed under reduced pressure. Potassium hydroxide pellets were added until the solution was basic and then it was extracted with benzene (3 x 100 ml). The organic extracts were dried over potassium carbonate and the benzene removed under vacuum to yield (40, 41) (38 g, 67.5%) as a pale brown

oil; $\nu_{max.}$ film 1695 cm^{-1}.

Endo-6,9-dimethyl-9-azabicyclo[3,3,1]nonan-3-ol (17,18)

A solution of the ketones (15, 16) (38 g) in ether (140 ml) was added dropwise to a suspension of lithium aluminium hydride (8.3 g) in ether (230 ml) and the resulting mixture refluxed for two hours. The mixture was cooled and the excess hydride destroyed by the addition of saturated sodium sulphate (10 ml). This mixture was filtered, dried over sodium sulphate and the ether removed under vacuum to yield a pale yellow oil (36.6 g), 97%), b.p. 76-80°C/0.1 mm. Distillation on a spinning bandcolumn afforded the two isomers b.p. 105/1 mm and b.p. 126°/2 mm. Anal. Found: C, 70.68; H, 11.18; N 8.35% and C, 70.31; H, 11.44; N, 8.22% respectively. $C_{10}H_{19}NO$ requires C, 70.96; H 11.31; N 8.27%; τ 5.6-5.9 (1H, m, $W_{\frac{1}{2}}$ = 16Hz), 7.55 (3H, S), 6.8-8.6 (12H, m) one disappears on D_2O exchange, and 8.85 (3H, d, J = 8Hz), and 5.7-6.1 (1H, p, J = 8Hz), 6.8-8.9 (12H, m) one disappears on D_2O exchange, and 9.2 (3H, d, J = 6Hz) respectively.

Endo-6(e)-methyl-9-azabicyclo[3,3,1]nonan-3-ol (23)

The amine (17) (240 mg) was dissolved in water (15 ml) and methanol (9 ml), potassium hydroxide (240 mg) was added and the solution cooled to 0°C. A solution of potassium permanganate (0.57 g) in water (20 ml) was added to this stirred solution keeping the temperature between 0-5°C throughout the resulting mixture stirred at 0°C for one hour. Celite was added and the mixture filtered. The methanol was removed under reduced pressure and the resulting aqueous layer extracted with methylene chloride (3 x 15 ml). The combined organic layers were dried over potassium carbonate and concentrated under vacuum to yield a pale yellow oil

(210 mg, 95.5%) which solidified on standing. Crystallisation from ethyl acetate afforded (23) as colourless crystals, m.p. 98-99°C; $\nu_{max.}$ ($CHCl_3$) 3360 cm^{-1}; τ 5.9-6.3 (1H, t of t, JAX =9Hz, JBX =6Hz), 6.7-8.8 (13H, m) two disappear on D_2O exchange, and 8.85 (3H, d, J = 8Hz).

Endo-3-acetoxy-6(ε)-methyl-9-acetamido-9-azabicyclo[3.3.1]-nonane (25)

Acetic anhydride (0.2 ml) was added to a solution of the amine (23) (210 mg) in pyridine (2 ml) and the solution allowed to stand at room temperature overnight. The solution was made acidic with 2N hydrochloric acid and extracted with chloroform (2 x 25 ml). The combined organic layers were dried over potassium carbonate and the solvent removed under vacuum to yield (25) as a pale yellow oil (300 mg, 93%); $\nu_{max.}$ (film) 1720 and 1620 cm^{-1}; τ 4.9-5.4 (2H, m, $W_{\frac{1}{2}}$ = 16Hz), 5.7-6.3 (1H, m, $W_{\frac{1}{2}}$ = 16Hz), 7.3-8.8 (9H, m), 7.94 (3H, d, J = 3Hz), 7.97 (3H, s) and 9.0 (3H,q, J = 3Hz); M^+ = 239.1520, $C_{13}H_{21}NO_3$ requires M^+=239.1521.

Endo-6(ε)-methyl-9-acetamido-9-azabicyclo[3.3.1]nonan-3-ol (27)

A solution of (25) (220 mg) in 1% methanolic potassium hydroxide (5 ml) was allowed to stand at room temperature overnight. After neutralisation with 10% methanolic hydrochloric acid (0.5 ml) the solvent was removed by evaporation. The residue dissolved in chloroform (10 ml), and the chloroform washed with water (10 ml), dried over potassium carbonate and concentrated under vacuum to yield (27) as a pale yellow oil (180 mg, 99%); $\nu_{max.}$ (film) 3320 and 1615 cm^{-1}; τ 4.8-5.4 (1H, m, $W_{\frac{1}{2}}$=24 Hz), 5.5-6.7 (3H, m) one disappears on D_2O exchange, 7.2-8.8 (9H, m), 7.85 (3H, d, J = 3Hz), and 9.0 (3H, d, J = 8Hz); M^+ = 197.1416, $C_{11}H_{19}NO_2$ requires M^+ 197.1414.

Endo-6(a)-methyl-9-azabicyclo[3,3,1]nonan-3-ol (24)

A solution of potassium permanganate (0.28 g) in water (15 ml) was added to a stirred solution of (18) (120 mg), water (7.5 ml), methanol (4.5 ml) and potassium hydroxide (120 mg) maintaining the temperature between 0-5°C throughout. This mixture was stirred at 0°C for one hour then celite was added and the mixture filtered. The methanol was removed under reduced pressure and the aqueous layer extracted with methylene chloride (3 x 10 ml). The combined organic layers were dried over potassium carbonate and the solvent evaporated to yield (45) as a pale yellow oil (120 mg, 93.5%); $\nu_{max.}$ (film) 3360 cm^{-1}; τ 5.8-6.2 (1H, t of t, JAX = 9Hz, JBX = 6Hz), 6.4-7.0 (2H, m, $W_{\frac{1}{2}}$ = 30Hz), 7.5-8.95 (11H, m) two disappear on D_2O exchange, and 9.2 (3H, d, J = 6Hz).

Endo-3-acetoxy-6(a)-methyl-9-acetamido-9-azabicyclo[3,3,1]-nonane (26)

To the amine (24) (120 mg) in anhydrous pyridine (1 ml), acetic anhydride (0.1 ml) was added and the resulting solution left at room temperature overnight. The solution was then made acidic with 2N hydrochloric acid and extracted with chloroform (2 x 15 ml). The combined organic extracts were dried over potassium carbonate and the solvent evaporated to yield (26) (170 mg, 92%) as a pale yellow oil; $\nu_{max.}$ (film) 1720 and 1615 cm^{-1}; τ 5.0-5.4 (2H, m), 5.7-6.2 (1H, m), 7.5-8.8 (9H, m), 7.92 (3H, d, J = 3Hz), 7.95 (3H, s), 9.1 (3H, d of d, J = 3Hz); M^+ = 239.1519, $C_{13}H_{21}NO_3$ requires M^+ = 239.1521.

Endo-6(a)-methyl-9-acetamido-9-azabicyclo[3,3,1]nonan-3-ol (28)

The acetate (26) (170 mg) was dissolved in 1% methanolic potassium hydroxide (5 ml) and the resulting solution allowed to stand at room temperature overnight. The solution was

Endo-6(a)-methyl-9-azabicyclo[3,3,1]nonan-3-ol (24)

A solution of potassium permanganate (0.28 g) in water (15 ml) was added to a stirred solution of (18) (120 mg), water (7.5 ml), methanol (4.5 ml) and potassium hydroxide (120 mg) maintaining the temperature between 0-5°C throughout. This mixture was stirred at 0°C for one hour then celite was added and the mixture filtered. The methanol was removed under reduced pressure and the aqueous layer extracted with methylene chloride (3 x 10 ml). The combined organic layers were dried over potassium carbonate and the solvent evaporated to yield (45) as a pale yellow oil (120 mg, 93.5%); $\nu_{max.}$ (film) 3360 cm^{-1}; τ 5.8-6.2 (1H, t of t, JAX = 9Hz, JBX = 6Hz), 6.4-7.0 (2H, m, $W_{\frac{1}{2}}$ = 30Hz), 7.5-8.95 (11H, m) two disappear on D_2O exchange, and 9.2 (3H, d, J = 6Hz).

Endo-3-acetoxy-6(a)-methyl-9-acetamido-9-azabicyclo[3,3,1]-nonane (26)

To the amine (24) (120 mg) in anhydrous pyridine (1 ml), acetic anhydride (0.1 ml) was added and the resulting solution left at room temperature overnight. The solution was then made acidic with 2N hydrochloric acid and extracted with chloroform (2 x 15 ml). The combined organic extracts were dried over potassium carbonate and the solvent evaporated to yield (26) (170 mg, 92%) as a pale yellow oil; $\nu_{max.}$ (film) 1720 and 1615 cm^{-1}; τ 5.0-5.4 (2H, m), 5.7-6.2 (1H, m), 7.5-8.8 (9H, m), 7.92 (3H, d, J = 3Hz), 7.95 (3H, s), 9.1 (3H, d of d, J = 3Hz); M^+ = 239.1519, $C_{13}H_{21}NO_3$ requires M^+ = 239.1521.

Endo-6(a)-methyl-9-acetamido-9-azabicyclo[3,3,1]nonan-3-ol (28)

The acetate (26) (170 mg) was dissolved in 1% methanolic potassium hydroxide (5 ml) and the resulting solution allowed to stand at room temperature overnight. The solution was

neutralised with 10% methanolic hydrochloric acid (0.5 ml) and the solvent was removed by evaporation. The residue was dissolved in chloroform (10 ml) and the chloroform washed with water (10 ml), dried, and concentrated under reduced pressure to yield (28) (140 mg, quantitative) as a pale yellow oil; $\nu_{max.}$ (film) 3320 and 1610 cm^{-1}; τ 5.0-5.4 (2H, m) one disappears on D_2O exchange, 5.7-6.4 (2H, m, $W_{\frac{1}{2}}$ = 6Hz), 7.4-8.9 (9H, m), 7.9 (3H, d, J = 3Hz), and 9.2 (3H, q, J = 3Hz); M^+ = 197.1418, $C_{11}H_{19}NO_2$ requires M^+ = 197.1414.

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