21

CONFORMATIONAL STUDIES ON SOME NITROGEN CONTAINING COMPOUNDS

A thesis submitted to the University of Stirling

for the degree of

Doctor of Philosophy

David A.R. Williams

Department of Chemistry

April 1971

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

ABSTRACT

CONFORMATIONAL STUDIES ON SOME NITROGEN CONTAINING COMPOUNDS

An abstract of a thesis submitted to the

University of Stirling

for the degree of

Doctor of Philosophy

David A. R. Williams

Department of Chemistry

April 1971

ABSTRACT

Some N.M.R. techniques used in conformational analysis, the principal factors peculiar to heterocyclic conformational analysis, and the background to conformational effects in alkyl substituted hydroxylamines are reviewed.

The synthesis of N-carbethoxy- and N-methyl-tetrahydro-1,2-oxazines is discussed. The mechanism of formation of N-carbethoxy-tetrahydro-1,2-oxazines from the condensation of 1,4 dibromo-alkanes with N-hydroxyurethan under basic conditions is found to proceed by initial attack of the oxy-anion tautomer, formed from N-hydroxyurethane, on the more reactive bromo-substituted carbon.

The preferred conformations of several N-methyl-tetrahydro-1,2-oxazines are deduced from their N.M.R. spectra, and a measure of the free energy difference between the equatorial and axial positions for a methyl group substituted on any one of the four ring carbon atoms is estimated. A qualitative rationalisation of the variation in free energy difference with the point of substitution is given. The N-methyl group is found to strongly prefer the equatorial position.

The stereochemistry of the B/C ring junction of the alkaloid geneserine is deduced from its N.M.R. spectra, and is found to be cis.

The conformational equilibrium at nitrogen in some N,N-dimethyl-hexahydropyrimidines is studied by N.M.R. For N,N-dimethyl-hexahydropyrimidine and 1,3,5-trimethyl-hexahydropyrimidine a free energy difference between an equatorial and axial N-methyl group of ca. 0.5 kcal./mol. is found.

A new method of measuring rate constants by N.M.R. using a small digital computer is tested by studying the barriers to internal rotation in the N,N-dimethyl amides of the three pyridine carboxylic acids. The method is found to be satisfactory, and the free energies of activation for the rotational process at 25°C are 17.9 kcal./mol. for N,N-dimethyl picolinamide, 15.9 kcal./mol. for N,N-dimethyl nicotinamide, and 16.6 kcal./mol. for N,N-dimethyl isonicotinamide. The error on these values is considered to be less than 0.1 kcal./mol.

ACKNOWLEDGEMENTS

My thanks are due to:

Dr. F. G. Riddell for two and a half years of patient help, guidance and criticism;

Mr. G. M. Kellie, B.Sc. and Mr. L. G. Jacks for many helpful discussions;

Mr. J. Cameron (University of Glasgow) for his analytical service;

my fiancee, Jackie, my parents, and to several friends for helping read proofs;

Mr. W. McAdam and the technical and secretarial staff of the Chemistry Department, University of Stirling;

and the S.R.C. for providing the maintenance grant and running 220 M.Hz spectra.

CONTENTS

SECTION ONE

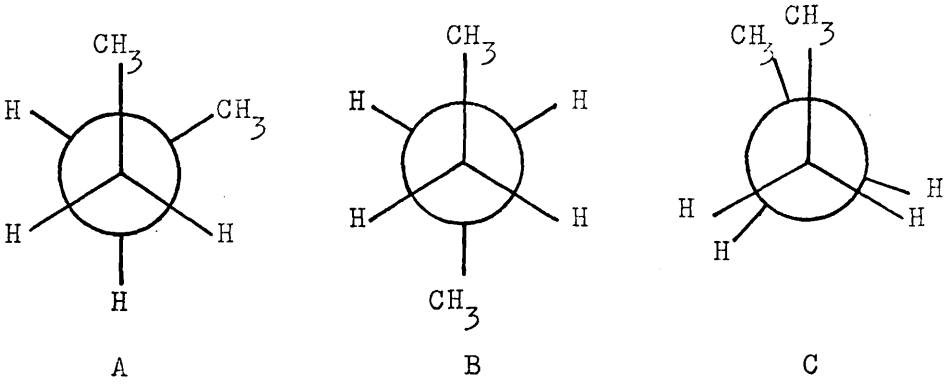
INTRODUCTION

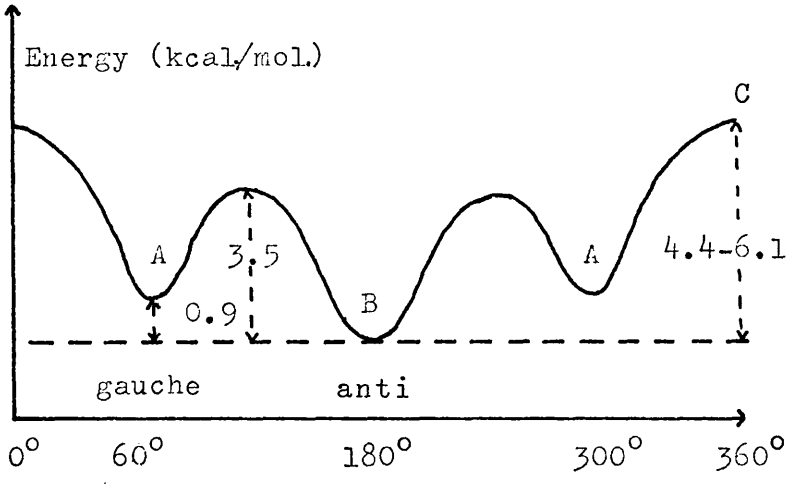
INTRODUCTION

Since this thesis is concerned with the study of the molecular conformations of some nitrogen containing compounds, in particular some tetrahydro-1,2-oxazines, the aim of this introduction is to review briefly those factors pertaining to their heterocyclic conformational analysis, and to show how the nuclear magnetic resonance method (N.M.R.) can give information about the systems and help elucidate the particular problems encountered. In general the discussion will be centred on six-membered cyclic compounds.

Conformation and Carbocyclic Systems

The term ' conformation' has been defined in several ways.[1] One of the most commonly accepted definitions is that proposed by Eliel[2]: "The term 'conformation' is used to denote any one of the infinite number of momentary arrangements of the atoms in space that result from rotation about single bonds." This definition applies to any arrangement of atoms in a molecule. However, in conformational analysis one is usually interested only in those states of a molecule that have a finite existence (i.e. are in the minimum of a potential energy well) and in this context the definition of a conformation as given by Dauben and Pitzer seems more appropriate: "By 'conformation' is meant any arrangement in space of the atoms of a molecule that can arise by rotation about a single bond and that is capable of finite existence."[1,3] Since in this thesis it is in general the ground state





Dihedral Angle in Degrees

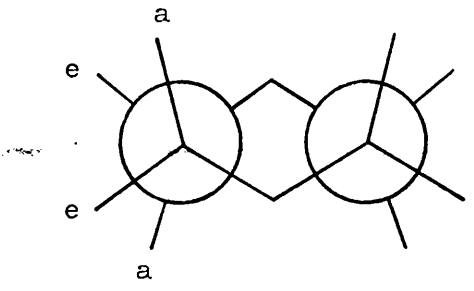
Figure 1.1 Potential Energy of n-Butane as a Function of Dihedral Angle

of molecules that is being considered, the latter definition of conformation is the one adopted throughout.

Thus, considering the potential energy of n-butane as a function of dihedral angle, Figure 1.1, there are three conformations which correspond to 'staggered' arrangements of the atoms. Two of these (A), the skew, gauche, or syn-clinal conformations (an enantiomeric pair), are less stable than the third (B), the anti-periplanar or trans conformation. Estimates of the energy differences between the conformations and the barriers to interconversion have been made from thermodynamic properties,[2] and are shown in Figure 1.1. The 'eclipsed' or syn-periplanar arrangement (C) corresponds to an energy maximum.

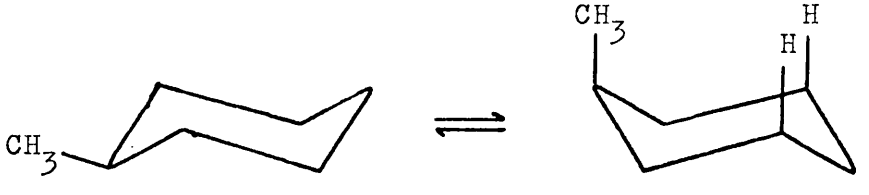
Since the ideas of Sachse, Mohr, and Huckel[4] were put forward, the concept of the chair and boat conformations of six-membered rings has become generally accepted. From electron diffraction studies Hassel and Davis[5] found that the chair conformation of cyclohexane is slightly flattened, Figure 1.2, compared to the classical model with a tetrahedral angle of 109.5°. These results were substantiated by Pierce and Nelson's microwave studies on fluorocyclohexane,[6] which was shown to have an angle of 55° between alternate carbon-carbon bonds.

At room temperature cyclohexane can be considered to exist in two equivalent chair conformations, rapidly interconverting by a ring inversion process.[7] The barrier for this process has been found by N.M.R.[8] to be 10-11 kcal./mol. Substitution of a methyl group on the ring lifts the degeneracy of the two forms, such that



Dihedral Angle	
aa	174.4
ae	54.5
ee	65.1

Figure 1.2 Conformation of Cyclohexane

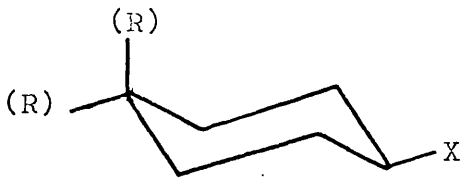


1.3a 1.3b

Figure 1.3 Conformations of Methylcyclohexane

methylcyclohexane exists in an equilibrium as in Figure 1.3. However, the axial methyl conformation, 1.3b, has two repulsive 1,3 non-bonded interactions arising from the two extra syn-clinal interactions present as in 'gauche' n-butane, and so conformation 1.3a is preferred. A free energy difference of 1.8 kcal./mol. has been found[9] (twice that of the energy difference in n-butane) corresponding to ca. 95% in the equatorial form and 5% in the axial form. For t-butyl cyclohexane, where in the axial conformation there would be even larger repulsive interactions, a free energy difference of 5.4 kcal./mol. is found[10] (i.e. there are ca. 0.01% of t-butyl-cyclohexane molecules that do not have an equatorial t-butyl group). Thus the free energy difference can be a measure of the conformational bias in a system.

Substitution of a group on the ring also affects the ring shape as illustrated in recent work by Booth.[11] A series of cis and trans 1,4 disubstituted cyclohexanes, Figure 1.4 where R = methyl, ethyl, isopropyl, and t-butyl and X = phthalimido, were studied by the change in vicinal coupling constants. The phthalimido group was found to prefer the equatorial position, and in the trans series, as R was increased in size, no change in ring shape was detected at the phthalimido end. However, in the cis series, as R increased in size, a significant flattening of the ring at the phthalimido end was observed. These results can be understood in terms of Figure 1.2, where axial substitution would tend to encourage ring flattening and equatorial substitution would discourage it.



R = Me, Et, iso Pr, t-Bu

X =

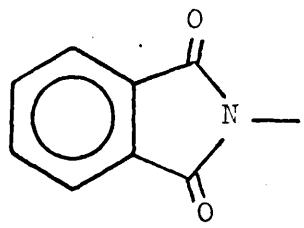


Figure 1.4 Phthalimido Cyclohexanes

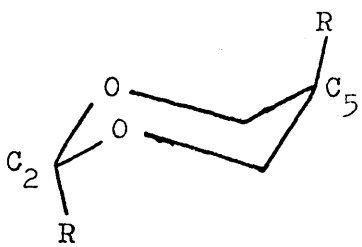
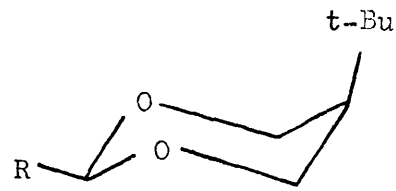


Figure 1.5 Ring Deformation in 1,3-Dioxan



R = Me, Et, iso Pr, t-Bu

Figure 1.6 Conformation of some cis 2,5-Disubstituted Dioxans

Although the above considerations can all apply to heterocyclic systems, some other factors must also be taken into account in heterocyclic conformational analysis.

Conformational Effects in Heterocycles

Many six-membered heterocyclic systems have been shown by a variety of physical methods, such as I.R. and Raman spectroscopy,[12] electron diffraction,[5,13] and dipole moments,[14] to prefer chair conformations with equatorial substituents.[15] However, there are two fundamental sources of difference between heterocyclic and carbocyclic conformational analysis. Firstly a change in the geometry of the ring is expected from the different bond angles and lengths involved, and secondly the substitution of a heteroatom has several electronic effects, including for nitrogen containing compounds the phenomenon of nitrogen inversion.

Often several of these effects are present in a ring system and gauging their relative importance and even distinguishing between them is sometimes difficult if not impossible.

1. Geometrical Effects

The bond length and angle changes, Table 1.1, that occur in heterocycles alter the shape of the chair conformation. A more puckered or a flattened chair form can result with a consequent variation in the effect of non-bonded interactions. For example, in the 1,3 dioxans it has been shown[16] that the shorter carbon-oxygen bond length leads to a smaller ring, flattened at the

TABLE 1.1 BOND LENGTHS, ANGLES, AND ROTATIONAL BARRIERS[15,75]

Bond	Length Å	Rotational Barrier kcal./mol.	Source	Bond Angle	
C-C	1.54	3.0	Ethane	-	
	1.54	-	Propane	C - C - C	111.5°
C-O	1.43	1.1	Methanol	-	
	1.43	2.7	Dimethyl Ether	C - O - C	111°
C-N	1.47	2.0	Methylamine	-	
	1.47	4.4	Trimethylamine	C - N - C	108°
N-N	1.47	11.5	Hydrazine	H - N - N	112°
O-O	1.47[33]	7.0	Hydrogen Peroxide	H - O - O	109° [33]
N-O	1.41[76]	10-12[a]	Hydroxylamine	N - O - H	103° [76]
	1.37	-	Methoxyamine	C - O - N	111°

a) Calculated, see refs. 28, 29.

C_4-C_5-C_6 end. Consequently the 5-axial bond leans out from the ring and the 2-axial bond leans into the ring, with the effect that the non-bonded interactions between 2-axial substituents and the 4 and 6 axial positions are increased, while those between a 5-axial group and the oxygen lone pairs are lessened (Figure 1.5). This latter effect may explain in part the preference of a 5-axial t-butyl group in some cis-2,5-dialkyl-1,3-dioxans[17] (Figure 1.6).

2. Electronic Effects

These arise from differences in electronegativity and from the lone pairs of electrons associated with the heteroatoms. In principle several effects can be distinguished, four of which will be considered: (a) changes in non-bonded interactions associated with the 'size' of the lone pair; (b) torsional barriers arising from hetero-hetero atom bonds; (c) dipolar effects; and (d) hydrogen-bonding effects.

(a) Non-Bonded Interactions

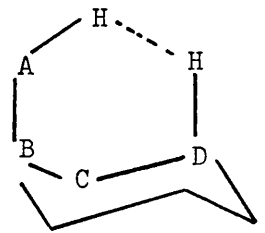
In heterocycles these can arise from interaction of lone pairs with β-axial substituents. The word 'size' is often used when referring to the spatial requirement of lone pairs; however, in a strict sense, this word should not be applied to any group or atom since its electron density is only zero at infinite distance. Using the word in context with lone pairs can be even more ambiguous since lone pair orbitals are more polarisable than a carbon-hydrogen bond, and both inter- and intra-molecular effects,

such as hydrogen bonding and distortion from neighbouring polar groups, will affect lone pair dimensions.

Nevertheless the spatial requirement of a lone pair has significant effects on equilibria and ring shapes, e.g. oxygen lone pairs appear to have a smaller interaction than a covalently bonded hydrogen[18] and this is probably the principal reason for the preference of the 5-axial t-butyl group over a 2-axial group mentioned above.[17]

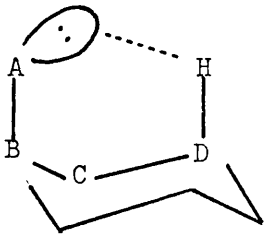
There appears to be more controversy over the nitrogen lone pair. Evidence for both axial and equatorial lone pairs in a variety of systems has been put forward by several research groups and is reviewed by Riddell.[15] The results appear to depend on which system is being studied and the method of measurement used. In the case of piperidine most reliable evidence at that time (1967) suggested that the N-H proton preferred an axial position, implying a large steric requirement for the lone pair. One piece of evidence came from microwave studies by Costain et al.,[19] but, lately[20] they have found the reverse to be true, i.e. the N-H proton prefers the equatorial position, by 0.25 ± 0.15 kcal./mol. at $25^{\circ}C$. Katritzky et al.[21] have shown by I.R. studies that the N-H proton prefers the equatorial position with an enthalpy difference of 0.5 ± 0.1 kcal./mol., and also that N-methyl-piperidine exists preferentially with an equatorial N-methyl group, a free energy difference of ca. 0.5 kcal./mol. having been calculated from dipole moments.[22]

Figure 1.7 "Standard Intramolecular Interactions"[23]



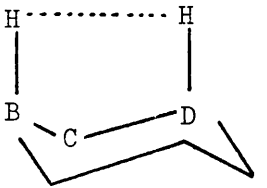
gauche-butane

b



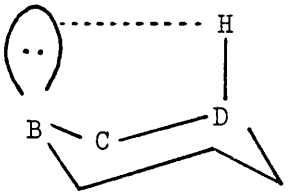
gauche-propylamine

pa



propane

p



ethylamine

e

Relationships: b - 2p = 0.85 kcal/mol

b - pa = 0.70 "

p - e = 0.20 "

Katritzky and his coworkers have also put forward an empirical method for determining conformational equilibria, based on the concept of 'standard intramolecular interactions'.[23] Figure 1.7 shows these four interactions, where A, B, C, and D are carbon, oxygen, or nitrogen, and lists the relationships found by Katritzky from experimental data. Although this method assumes the magnitude of each interaction to be constant and not to depend on the nature of the atom A, B, C, or D, and that all bonds are sp^3 hybridised with tetrahedral geometry, it appears to give a reasonable measure of equilibria in some systems,[23] and can perhaps be applied as a rough guide in other systems.

(b) Torsional Barriers

The torsional barriers for carbon-oxygen and carbon-nitrogen bonds (Table 1.1) are of similar magnitude to that for the carbon-carbon bond, and so relief of molecular strains by torsional deformations would be expected to be similar to carbocyclic systems. However, in molecules with two hetero atoms bonded together, there appear to be much higher rotational barriers which are likely to contribute to the high ring inversion barriers observed in, for example, certain tetrahydro-piperazines[24] and diacetone peroxide.[25] In some nitrogen containing compounds such barriers are of the same magnitude as nitrogen inversion barriers. For example Sutherland and Fletcher[26,27] have shown that the temperature dependence of the N.M.R. spectra of a number of hydrazine derivatives can be interpreted in terms of a high rotational barrier (ca. 12 kcal./mol.) while observations on analogous hydroxylamine derivatives suggest a similar barrier to nitrogen inversion

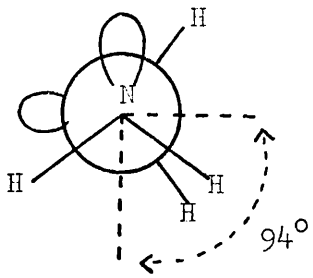


Figure 1.8 Newman Projection Formula of "Equilibrium" Conformation of Hydrazine

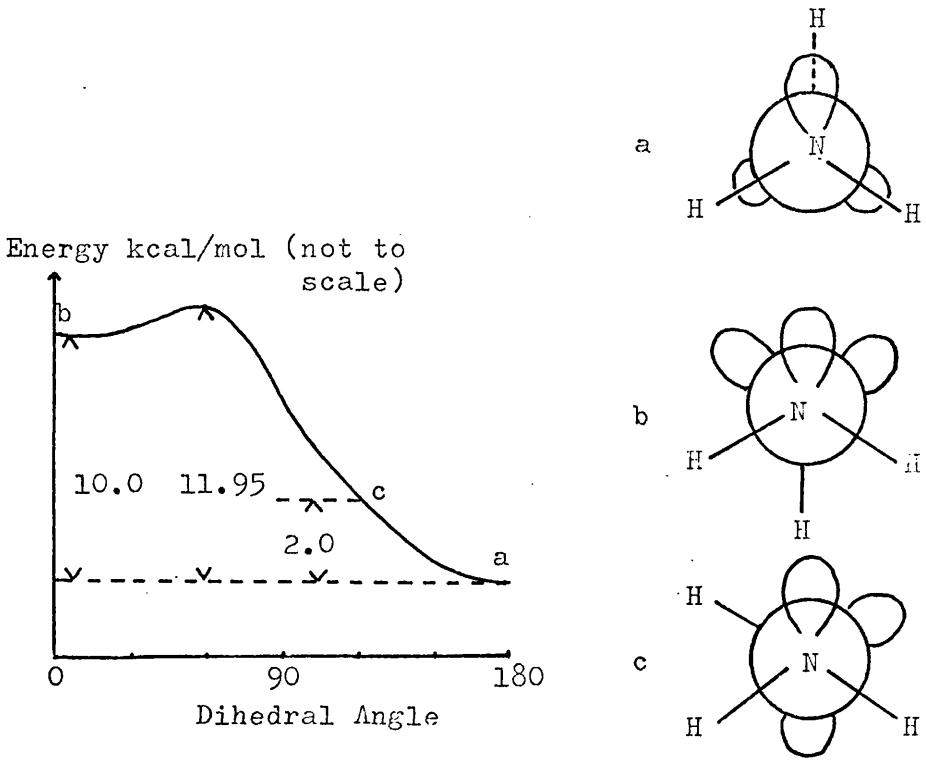
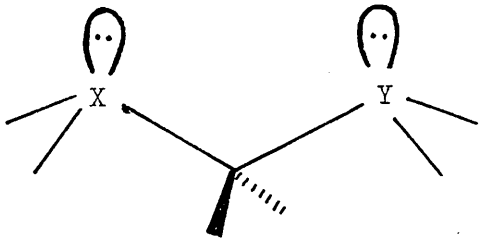


Figure 1.9 Potential Energy Curve and Equilibrium Conformations for Hydroxylamine

Calculations[28,29,30] and experimental results[31,32] have shown that for hydrazine and hydrogen peroxide, the most stable or preferred conformations are not necessarily 'staggered' ones. For example, Veillard[30] has calculated that hydrazine has the preferred conformation shown in Figure 1.8 - an almost eclipsed arrangement of atoms - which agrees well with experimentally determined parameters.[32] No experimental rotational barrier for hydroxylamine is known, but Figure 1.9 shows the potential energy of hydroxylamine as a function of rotational angle as determined from L.C.A.O. - M.O. - S.C.F. calculations (Linear Combination of Atomic Orbitals - Molecular Orbital - Self-Consistent Field) by Fink, Pan and Allen.[28] Pederson and Morukama[29] have obtained similar results. It can be seen that the energy difference between the predicted preferred conformation (a), with the O-H bond trans to the NH_2 bisector, and the perfectly "staggered" cis conformation (b) is ca. 10 kcal./mol. Pople and Gordon,[33] however, using the semi-empirical I.N.D.O. - S.C.F. technique (Intermediate Neglect of Differential Overlap) suggest the cis conformation to be preferred, but they have not calculated any rotational barriers. If the assumption is made that alkyl substitution does not markedly alter the shape or height of the potential energy function in Figure 1.9, or the preferred conformation, then conformation (b), which is the less stable, has the same conformation as the substituted hydroxylamine part of a tetrahydro-1,2-oxazine molecule in a chair conformation with an axial N-alkyl group. Rotation around the N-O bond in conformation (a) by ca. 60° gives



X and Y heteroatoms

Figure 1.10 The "Rabbit Ear" Effect

conformation (c) which has a much lower potential energy than (b) and corresponds to a tetrahydro-1,2-oxazine in the chair conformation with an equatorial N-alkyl group. From Figure 1.9 an energy difference between (b) and (c) of about 8 kcal./mol. can be found, suggesting that there would be a strong preference for an equatorial N-alkyl group in the tetrahydro-1,2-oxazines. From models it can be seen that the ring strain of ca. 2 kcal./mol. that is induced by the deformation of the preferred conformation (a) of hydroxylamine may lead to a puckering of the ring at the C_3-N-O-C_6 part of the tetrahydro-1,2-oxazine molecule.

(c) Dipolar Effects

The presence of more than one heteroatom in a system gives rise to interactions between the dipoles of the heteroatomic lone pairs. The interaction resulting from the conformation in Figure 1.10, which has two syn-axial lone pairs, the "rabbit ear effect",[34] is unfavoured. Eliel suggests the principal cause of this effect to be electrostatic dipole-dipole interactions,[34] but this view has been questioned by Wolfe et al.[35] who say "analyses of the phenomenon in terms of "dipole-dipole" repulsive interactions are without theoretical justification", and consider such phenomena in terms of the total potential energy of the system.

Manifestations of this effect are found in the anomeric effect in glycosides,[36] some 1,3-hexahydropyrimidines,[37,38] and tetrahydro-1,3-oxazines.[39] Recently Booth has shown[40] the preferred conformation of tetrahydro-1,3-oxazine itself to be that with an axial N-H proton.

The dipole moment of a molecule can also provide information about its conformation.[41] For example, Katritzky et al.[22] have studied the conformations of N-methyl-piperidine and its 4-(p-chloro-phenyl) derivative by dipole measurements in an attempt to assess the N-methyl equatorial-axial equilibrium in piperidines. Dipoles were measured by the method of Halverstadt and Kummler,[42] involving the change in dielectric constant with concentration, and calculations assumed the vectorial additivity of the p-chloro-phenyl group dipole moment and the piperidine ring moment. The results indicated a free energy difference between the equatorial and axial conformations of the N-methyl group of ca. 0.5 kcal./mol., or about 71% of the molecules had an axial lone pair. However, the quantitative significance of such methods has to be treated with caution since, firstly, molecular dipole moments are rarely the product of point charges and their separation, making calculation of interactions difficult; secondly, interactions of the dipoles may cause molecular distortions which will render standard geometrical parameters less reliable, and consequently will make further calculations susceptible to significant errors; and thirdly dipoles may not act wholly in the direction assigned to them from models or drawings.

(d) Hydrogen-Bonding Effects

An opportunity for hydrogen-bonding between solvent and solute occurs with the presence of a nitrogen lone pair in a molecule. The ability of a hydroxylic solvent to hydrogen-bond will depend on the spatial distribution of other groups around the lone pair. Thus

with an axial lone pair hydrogen-bonding will be sterically hindered by the degree of syn-axial substitution, while with an equatorial lone pair, inspection of models shows that the relative position (axial or equatorial) of an adjacent substituent will not affect the degree of hydrogen bonding.

Hydrogen-bonding might also be expected to increase nitrogen inversion barriers, since during the inversion process this hydrogen-bond must be broken, an event that need not occur with ring inversion. Although this effect has been used to distinguish between ring and nitrogen inversion,[43,44] recent work on some hydroxylamines[26] has shown that with the presence of a hydroxyl group bonded to nitrogen this criterion must be used with caution. Presumably a strong hydrogen-bonding effect will occur between the hydroxyl on nitrogen and the solvent, disrupting any hydrogen-bonding to the nitrogen. It is known that the boiling point of ammonia is considerably less than that of water, suggesting N-H---N hydrogen-bonds are weaker than O-H---O ones; and also that the hydrogen-bonds in hydrogen peroxide are stronger than those in water,[45] suggesting that in hydroxylamine derivatives strong hydrogen-bonds should be formed with the hydroxyl group rather than nitrogen.

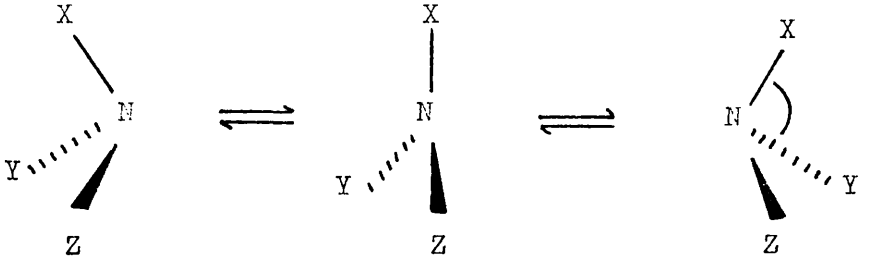


Figure 1.11 "Classical" Nitrogen Inversion

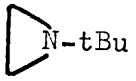
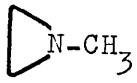
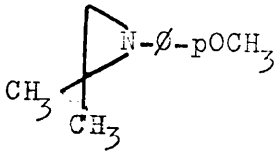
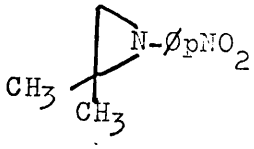
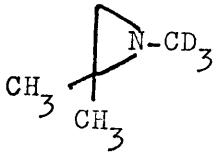
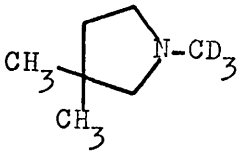
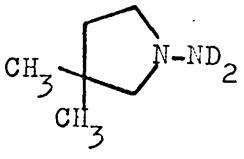
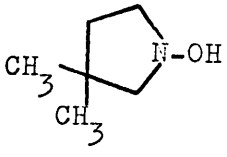
3. Nitrogen Inversion

A tricoordinate atom such as nitrogen can exist in two types of ground state geometry; either pyramidal with sp^3 type hybridisation (amines etc.), or planar with sp^2 hybridisation (imines etc.). Considering only the pyramidal type, although most of the following discussion can be applied to the planar form, interconversion through a planar transition state to an enantiomeric form is possible (Fig.1.11). This process is known as nitrogen inversion, and can be considered as an extension of the normal vibrational bending mode.

For ammonia and the primary amines quantum mechanical tunneling contributes to the overall rate of inversion, but as the reduced mass of the substituents increases this mechanism becomes of little importance.[46]

The magnitude of nitrogen inversion barriers have a wide range (Table 1.2), and have been measured by a variety of techniques. With a barrier of ca. 25 kcal./mol. or more, separate 'invertomers' can be isolated and their rate of interconversion followed by, for example, spectroscopic techniques. Very low barriers (0 - 5 kcal./mol.) can be studied by microwave spectroscopy e.g. ammonia has been found to have a barrier of 5.77 kcal./mol. by this method.[47] Vibrational spectroscopy is important over a wide range (5 to 30 kcal./mole), and the N.M.R. method involving line shape changes with temperature has provided a great deal of information[48,55] on inversion barriers in the 6 - 25 kcal./mol. range.

Table 1.2 Some Nitrogen Inversion Barriers[48]

Compound	No.	Barrier (kcal/mol.)
NH_2CHO	-	1.1
NH_3	-	5.77
	1.13	17.0
	1.14	22.3
	1.15	12.5
	1.16	8.2
	1.17	18.5
	1.18	7.4
	1.19	8.5
	1.20	13.0

Barriers have also been calculated by a number of approaches ranging from the empirical spectroscopic models proposed by Kincaid and Henriques,[49] and Costain and Sutherland,[50] through semi-empirical treatments such as MINDO (Modified Intermediate Neglect of Differential Overlap) which produce barriers similar to those observed,[48,51] to non-empirical methods such as those used by Lehn et al.[52] These last authors calculated values for aziridine (18.3 kcal/mol.) and oxaziridine (32.4 kcal/mol.) which not only compare very well with observed values, but also give some insight into the origin of the barrier and factors affecting it. In general these 'ab initio' calculations lead to results in agreement with experimental trends.

Both steric and electronic factors influence nitrogen inversion barriers. Steric effects stem mainly from non-bonded interactions and angular strain. For example, the t-butyl group in compound 1.13 (Table 1.2) has greater repulsive interactions with the ring protons than the methyl group in 1.14. Consequently a decrease in the barrier is observed since the ground state is destabilised with respect to the transition state. On the other hand angular strain increases the inversion barrier (compounds 1.14 and 1.18). Since the inversion process has a planar transition state the angle, , in Figure 1.12 must span to 120°, but in the 3-membered aziridine such opening is hindered, whereas in the 5-membered ring it is not.

The principal electronic factors influencing barrier

heights are conjugation and heteroatom substitution, although separation of individual effects may be optimistic. Both (p-p) π conjugation of, for example, a carbonyl or aromatic system, or (p-d) π conjugation of a second row element having low lying d orbitals, with the nitrogen atom lowers the inversion barrier, since the p orbital of the transition state can overlap with such systems to a greater extent than an sp^3 hybridised lone pair. Examples of this are the extremely low barrier found for formamide[53] (1.1 kcal./mole), and change in barrier in compounds 1.15 and 1.16,[54] where the barrier decreases with the increase in electron withdrawing power of the substituent.

Heteroatom substitution gives rise to electronegativity and electron repulsion effects, both of which can increase the barrier (compounds 1.18, 1.19, and 1.20). If the substituent is more electronegative than nitrogen an increase in the s character of the nitrogen lone pair results from a negative inductive effect, and since the lone pair passes through a p orbital in the transition state, a barrier increase occurs. Similarly an electropositive substituent leads to a barrier decrease.

Electron repulsions from substituent lone pairs and the nitrogen lone pair are also greater in the transition state than ground state. Consequently a barrier increase results. However, increases may be modified by a lessening of dipolar interactions in the transition state, since the nitrogen lone pair becomes a p orbital with no dipole moment.

N.M.R. and Conformational Analysis

The application of N.M.R. to conformational problems is extensive, many books and reviews having been written.[56] The two basic N.M.R. parameters, the chemical shift and coupling constant are extremely sensitive to the spatial arrangement of atoms in a molecule, and by correlating known systems with these parameters some empirical relationships between N.M.R. phenomena and structure have been found. Such relationships include the effects of diamagnetic anisotropy, the variation in chemical shift with electronegativity of adjacent groups, and, of particular importance in this work, the variation of vicinal coupling constant (J) with dihedral angle.

From valence bond calculations[57] on ethane Karplus showed that J was related to the dihedral angle, ϕ, as in equation 1.1, where A and B are constants

$$J = A + B \cos^2 \phi \qquad 1.1$$

for any particular system. A more refined theoretical treatment[58] led to equation 1.2.

$$J = A + B \cos \phi + C \cos 2\phi \qquad 1.2$$

Although other factors such as bond length and angles, and the nature and spatial orientation of substituent groups can influence the vicinal coupling constant,[59] the applicability of equation 1.1 in determining approximate dihedral angles is probably still valid,

i.e. trans coupling constants tend to be large while gauche coupling constants are much smaller.

In terms of a six-membered ring (Figure 1.2), for $\phi = 0^{\circ}$ or 180°, corresponding to a totally eclipsed and an axial-axial coupling respectively, the vicinal constant is large, 12 Hz. being a typical value; while for $\phi = 50\text{-}70^{\circ}$, corresponding to axial-equatorial couplings the constant is small, and, because of the nature of the $\cos^2$ function, can vary markedly with small changes in ϕ. Typical values may be in the range 2-8 Hz. For $\phi = 90^{\circ}$ the constant is predicted to be equal to A which is in general very small (< 1 Hz.).

^{13}C Chemical Shifts

Recently use of ^{13}C N.M.R. has been made in conformational studies.[60,61,62,63] Dalling and Grant have studied the ^{13}C chemical shifts of cyclohexanes,[60] and have correlated chemical shift changes with substitution patterns. For example, the introduction of an equatorial methyl group shifts the C_1 resonance - 5.6 p.p.m. (i.e. downfield) and the C_2 resonance by - 8.9 p.p.m., while the effects on C_3 and C_4 are less than 1 p.p.m. Introduction of an axial methyl group causes a smaller shift of - 1.1 p.p.m. at C_1 and - 5.2 p.p.m. at C_2, while C_3 experiences an upfield shift of + 5.4 p.p.m., and C_4 of ca. + 0.1 p.p.m. Riddell and Kellie[62] have studied the ^{13}C spectra of some 1,3 dioxans and have found similar chemical shift correlations for some substitution patterns, but not for others.

For example, although introduction of an equatorial methyl group produces a shift of the ring carbon of about - 5 p.p.m., and an axial methyl group a shift of ca. - 1 p.p.m., introduction of a gem-dimethyl group at C_2 or C_5 deshields those atoms by 4.3 p.p.m. compared to a shielding of 3.4 p.p.m. observed in cyclohexane.[60] Thus two conclusions can be drawn from these results: firstly, that substituent stereochemistry can have a large effect on ring carbon chemical shifts, and correlations of these shifts can be of use in conformational assignments, and secondly that correlations from cyclohexanes need not be the same as those in heterocycles.

Free Energy Differences

Not only can N.M.R. techniques provide structural information but they can also be used to study the energetics of a system. If in a given system there are two interconvertible chair forms, the free energy difference, $\Delta G_{diff.}$, between the conformations is given by equation 1.3,[64] where K, the equilibrium constant, can be expressed as in equation 1.4,[65] where P_a and P_e are the magnitudes of a

$$\Delta G_{diff} = -RT \ln K \qquad 1.3$$

$$K = \frac{P_a - P}{P - P_e} \qquad 1.4$$

spectral property associated with a molecule having a group in an axial position and a molecule having the same group in the appropriate equatorial position respectively, and P is the value of this property in the conformational equilibrium.

Three such properties are commonly used to determine K : signal areas, chemical shifts, and coupling constants. If in the given system the equilibrium is "frozen out", by say cooling, the axial and equatorial groups of the two conformations may resonate at different points, making integration of the signal areas possible, and so leading to calculation of the equilibrium constant. The limitation of this method is that it cannot be applied if there is poor separation of the peaks.

The use of chemical shifts and coupling constants to determine the equilibrium constant involves the concept of the model compound of locked or 'frozen' conformation, whose spectral parameters can be correlated with this exact conformation and then compared to those in the equilibrium system. The underlying assumption is that the parameters derived for the model systems still hold for the equilibrium system, and the value of these methods of determining K depend on the choice of good model systems.

Energies of Activation

The lineshape of the N.M.R. signal of a group undergoing exchange between two or more sites varies with among other things the rate of exchange between the sites.[66] This phenomenon has been used to calculate the rates of particular processes such as restricted rotation and ring and nitrogen inversion. Rate constants (k) can be obtained at different temperatures and so thermodynamic parameters can be obtained from either the Arrhenius

equation,[64] 1.5, where E_A is the activation energy and A the frequency factor, or from the Eyring equation,[68] 1.6, where $\bar{K}$ is the transmission coefficient

$$k = A \exp \frac{-E_A}{RT} \qquad 1.5$$

$$k = \bar{K} \frac{k_B T}{h} \exp \frac{-\Delta G^{\ddagger}}{RT} \qquad 1.6$$

and $\Delta G^{\ddagger}$ the free energy of activation. If $\bar{K}$ is unity and giving the Planck and Boltzmann constants their numerical values equation 1.6 becomes equation 1.7 in terms of decimal logarithms. Since $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, where $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$

$$\Delta G^{\ddagger} = 4.57T[10.32 - \log(k/T)] \qquad 1.7$$

are the enthalpy and entropy of activation respectively, equation 1.7 can be written as equation 1.8. Thus all the activation parameters can be obtained easily. However,

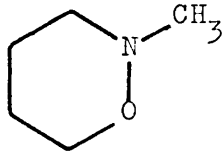
$$\log(k/T) = 10.32 - \frac{\Delta H^{\ddagger}}{4.57T} + \frac{\Delta S^{\ddagger}}{4.57} \qquad 1.8$$

$\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ tend to have greater systematic errors[69] than $\Delta G^{\ddagger}$, and so although $\Delta G^{\ddagger}$ varies with temperature, it is the parameter often quoted with the least inaccuracy.

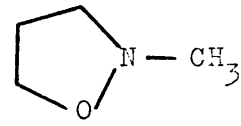
An estimate of k and hence $\Delta G^{\ddagger}$ at the coalescence temperature (T_c) is given by equation 1.9 in the case of simple

$$k = \frac{\pi \Delta \upsilon}{\sqrt{2}} \qquad 1.9$$

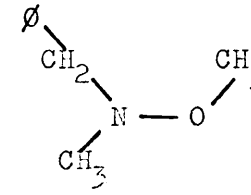
two site exchange, where $\Delta\nu$ is the chemical shift difference at final separation of the two signals. Results often quote this parameter ($\Delta G_c^{\neq}$) although as pointed out by Binsch[70] comparison with values at different temperatures may involve large errors.



1.21



1.22



1.23

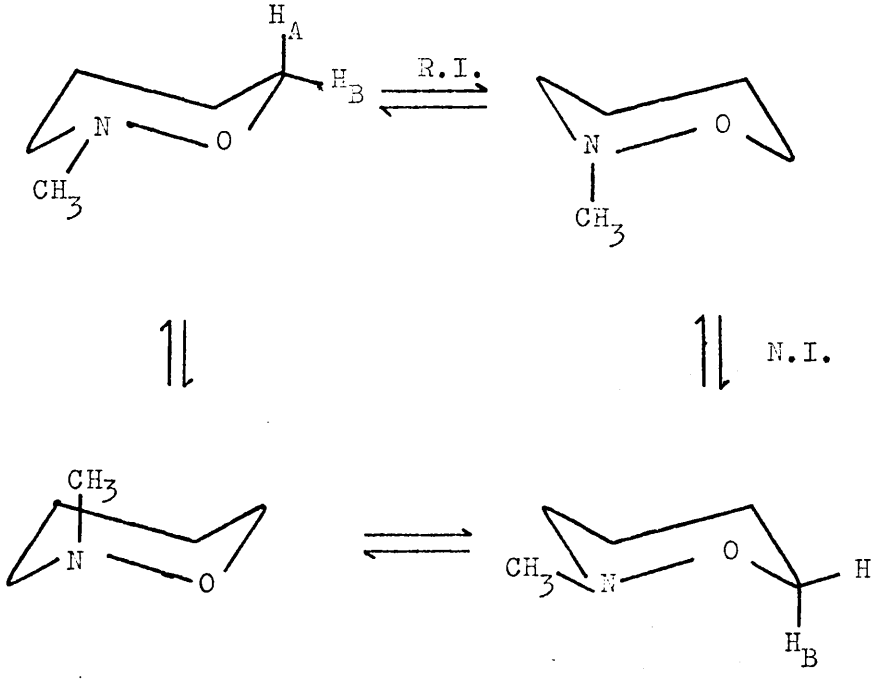


Figure 1.24 Ring and Nitrogen Inversions in N-Methyl-Tetrahydro-1,2-Oxazine

Conformational Studies on Hydroxylamines

Riddell, Lehn, and Wagner[44] found the N.M.R. spectra of N-methyl-tetrahydro-1,2-oxazine (1.21) and N-methyl-1,2-oxazolidine (1.22) to be temperature dependent. The oxazine can undergo ring and nitrogen inversions, Figure 1.24, whereas the oxazolidine can only have a nitrogen inversion process. Assuming a preference for an equatorial N-methyl group, although the following argument also holds for an axial preference, 'freezing out' of either process in the oxazine will lead to protons A and B in Figure 1.24 being anisochronous, and hence to the spectral changes.

The barriers to the observed process in both compounds 1.21 and 1.22, as calculated from coalescence temperatures (Table 1.3), show a marked hydrogen-bonding effect of 1.3 kcal./mol., strongly suggesting the observed process for the oxazine to be that of slow nitrogen inversion.

The conformational preference of the N-methyl group cannot be determined from this work, but it appears to be almost exclusively axialor equatorial since at - 100°C, where both ring and nitrogen inversion might be expected to be slow, only one N-methyl signal is observed.

There appears to be some controversy whether the observed process in alkyl substituted hydroxylamines is attributable to slow nitrogen inversion or a high torsional barrier. For hydrazine derivatives the observed process has been shown to be a high torsional

TABLE 1.3 FREE ENERGIES AND COALESCENCE TEMPERATURES FOR COMPOUNDS 1.21 and 1.22

Compound	Solvent	$T_c \pm 5^{\circ}$	$G_c \pm 0.5$ kcal./mol.
1.21	-	5	13.7
1.21	Hexane	3	13.7
1.21	CH_2Cl_2	5	13.7
1.21	D_2O/CD_3OD (4:1)	33	15.0
1.22	$CDCl_3$	42	15.6
1.22	D_2O	62	16.9

barrier,[71,26,27] ca. 11 kcal./mol. for tetra-alkyl substituted hydrazines, and ca. 20 kcal./mol. for diacyl, dialkyl hydrazines. For N-benzyl O,N-dimethyl hydroxylamine (1.23), the observed process (with a barrier of ca. 12 kcal./mol.) was attributed to slow nitrogen inversion by Griffiths and Roberts;[72] but the observation by Raban and Kenney[73] of small increases in the barrier (ca. 0.5 kcal./mol.) when either the N or O-methyl group in compound 1.23 was replaced by an isopropyl group suggested a torsional origin to the barrier. Sutherland and Fletcher think this latter view unlikely from their studies of similar hydroxylamine systems. They found a lower torsional barrier for N,O-diacyl hydroxylamines[26,27] than for analogous hydrazines, suggesting a lower torsional barrier in alkyl hydroxylamines, and they also found no significant steric effect associated with the O-alkyl substituent. Griffiths and Olsen[74] also support the idea of the slow process in alkyl hydroxylamines being nitrogen inversion.

At the start of the present work a study of some alkyl substituted tetrahydro-1,2-oxazines seemed justified for two reasons: firstly to gain insight into the geometry of the ring, to determine whether an axial or equatorial N-methyl group is preferred, and to investigate the non-bonded interactions that can arise; and secondly to further investigate the nature of the observed process in such ring systems.

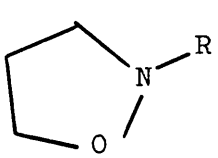
SECTION TWO

TETRAHYDRO-1,2-OXAZINES

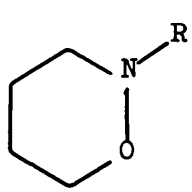
1. Synthesis

THE SYNTHESIS OF TETRAHYDRO-1,2-OXAZINES

The first synthesis of a tetrahydro-1,2-oxazine was accomplished by King[77] in 1942. It had been shown that alkyl halides in the presence of a strong base reacted with N-hydroxy-urethane to give O-alkyl hydroxyurethanes, which upon acid hydrolysis gave the corresponding O-alkyl hydroxylamines.[78] In an attempt to prepare 1,3-trimethylene-bis-oxyurethane and 1,4-tetramethylene-bis-oxyurethane from the respective 1,3 and 1,4-dibromides King isolated the cyclic compounds N-carbethoxy-iso-oxazolidine (2.1, R = CO_2Et) and N-carbethoxy-tetrahydro-1,2-oxazine (2.3, R = CO_2Et). Hydrolysis with hydrochloric acid and subsequent basification yielded the free bases (2.1 and 2.3, R = H), which showed typical amine behaviour in forming crystalline derivatives with hydrochloric and hydrobromic acids, methyl iodide, dinitrobenzoyl chloride, and picric acid.



2.1



2.3

In 1948 Arbuzov[79] reacted 1,3-butadiene with nitroso-benzene and obtained 2-phenyl-3,6-dihydro-1,2-oxazine in 90% yield. Wichterle and his coworkers confirmed this result and showed that upon catalytic

hydrogenation tetrahydro-1,2-oxazines could be obtained, although continued hydrogenation cleaved the nitrogen-oxygen bond to give amino alcohols.[80]

The pyrolysis of certain N-oxides are also known to give tetrahydro-1,2-oxazines,[81] and the mechanistic implications of this method are discussed in Section 2.3. No other work has been published to date on the synthesis of these oxazines, although some compounds are mentioned in papers concerned with nitrogen inversion.[74]

The present work required the preparation of several methyl substituted N-methyl-tetrahydro-1,2-oxazines. Since the required precursors are readily synthesised, and the reduction of N-carbethoxy compounds with lithium aluminium hydride is known to give N-methyl groups,[82] King's method of preparing the N-carbethoxy-tetrahydro-1,2-oxazines, from treatment of 1,4-dibromides with a strongly basic ethanolic solution of N-hydroxyurethane, was adopted.

Results and Discussion

The dibromides used in the preparation of the N-carbethoxy compounds were all prepared from the appropriate diols which were synthesised by standard procedures. Except for the preparation by hydroboration of 2,3-dimethyl-butane-1,4-diol required in the synthesis of 4,5,N-trimethyl-tetrahydro-1,2-oxazine, these procedures do not require discussion, and are outlined in the Experimental section.

The principal points of discussion are the stereochemical and mechanistic implications of the condensation of N-hydroxyurethane with the dibromides; the lithium aluminium hydride reductions of the N-carbethoxy compounds; and the physical properties of the N-methyl-tetrahydro-1,2-oxazines.

Table 2.1 shows the N-carbethoxy and N-methyl-tetrahydro-1,2-oxazines that have been prepared and each is assigned a number for reference.

The Reaction of N-hydroxyurethane with 1,4-Dibromides

Although King quotes a yield of over 80% for this reaction, yields of only 35% were obtained in this work using his method. In order to optimise the yield, several experimental conditions were varied. Neither the time of reaction, the base used, nor the water content of the solvent, ethanol, significantly affected the yield. However, addition of a trace of potassium iodide to the reaction of 1,4-dibromobutane and N-hydroxyurethane increased the yield to 45%, while the use of 1,4-di-iodo-butane instead of 1,4-dibromobutane gave 60% yield. When the ditosylate of cis-hexahydrophthalyl alcohol was used as the precursor for the decalin type compound 2.25 no product was obtained. Finally, using a 3:1 molar ratio of N-hydroxyurethane and base to dibromide was found to give consistent yields of between 60 and 70%. This method, given in detail in the Experimental section, was used in all subsequent preparations.

Table 2.1 Compounds Prepared and Reference Numbers

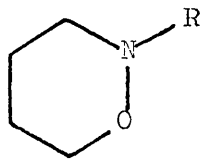
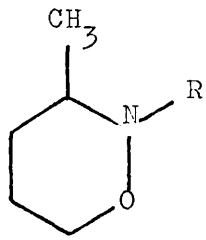
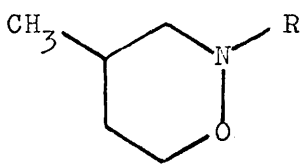
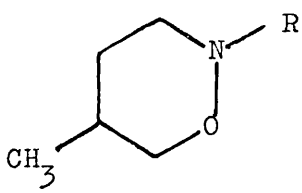
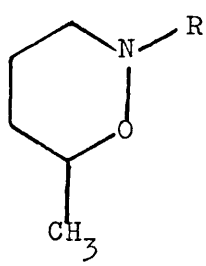
Compound	R = CO_2Et No.	R = CH_3 No.
	2.3	2.4
	2.5	2.6
	2.7	2.8
	2.9	2.10
	2.11	2.12

Table 2.1 (continued)

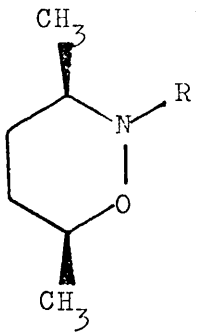
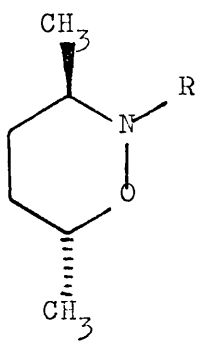
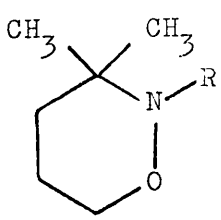
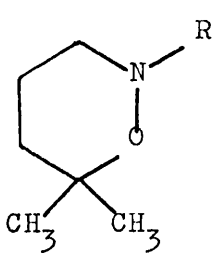
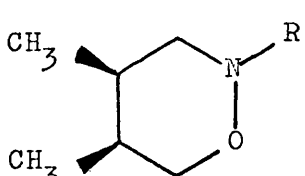
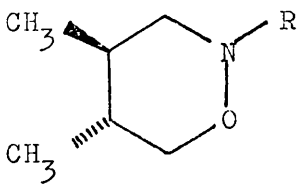
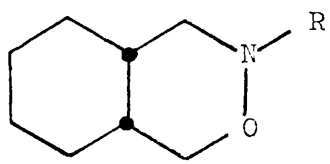
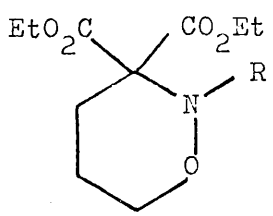
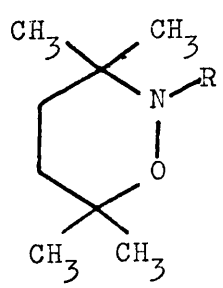
	R = CO_2Et No.	R = CH_3 No.
	2.13	2.14
	2.15	2.16
	2.17	2.18
	2.19	2.20
	2.21	2.22

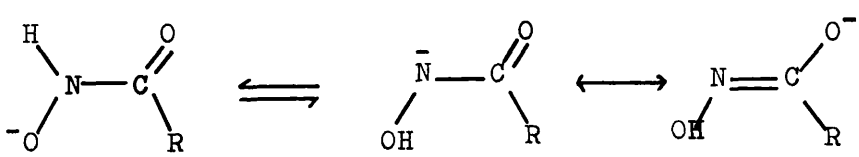
Table 2.1 (continued)

	R = CO_2Et No.	R = CH_3 No.
	2.23	2.24
	2.25	2.26
	2.27	-
	2.28	-

In several of the condensations two structural isomers can be formed as products, e.g. both 3 and 6 methyl, N-carbethoxy tetrahydro-1,2-oxazines (Compounds 2.5 and 2.11) are formed from 1,4-dibromopentane and N-hydroxyurethane. The relative amounts of each isomer formed, both in the condensation and reduction stages, can be conveniently found by G.L.C. analysis, and are shown for several cases in Table 2.2.

The first point arising from the results in Table 2.2 is the retention of configuration in the 3,6-dimethyl oxazines (2.13 and 2.15). In both the reaction with the meso and racemic dibromides the stereochemistry is maintained to give almost exclusively the cis and trans products respectively. The small amount of apparent loss of configuration could also be caused by imperfect separation of the meso and racemic dibromides.

The results also suggest a possible mechanism of ring formation. It seems reasonable that in the strongly basic conditions used, (sodium hydroxide in ethanol) that N-hydroxyurethane loses a proton from one of the two possible sites to give tautomers 2.2a and 2.2b (R = OEt). The mechanism for



2.2a 2.2b

TABLE 2.2

STRUCTURAL ISOMER PRODUCT RATIOS

Dibromide	Proportions of N-carbethoxy compounds
1,4-dibromopentane	2.5 : 2.11 = 3:1
2-methyl-1,4-dibromo-butane	2.7 : 2.9 = 3:2
2,5-dibromohexane (meso)	2.13 : 2.15 > 10:1
2,5-dibromohexane (racemic)	2.15 : 2.13 > 10:1
4-methyl-1,4-dibromo-pentane	2.17 : 2.19 = 7:1

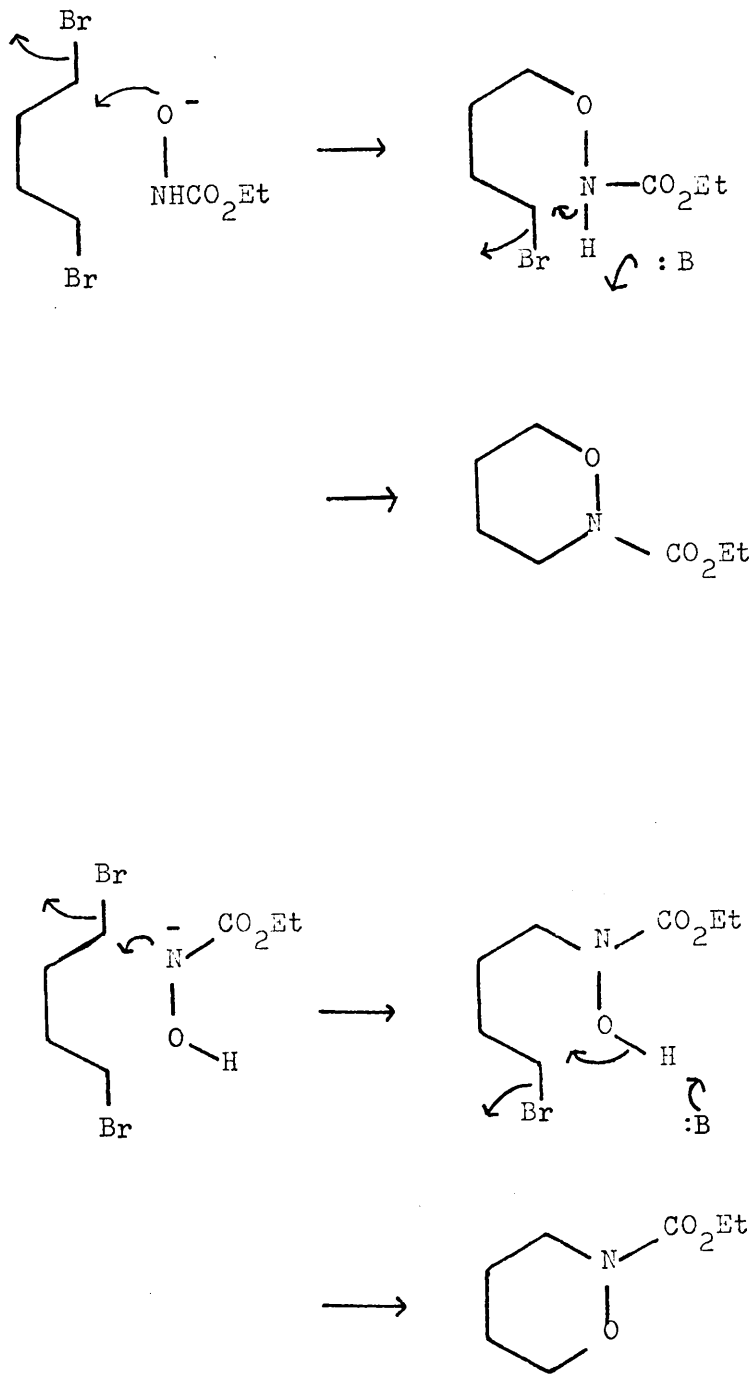


Figure 2.2 Possible Routes to Ring Closure.

ring formation could proceed by the two routes shown in Figure 2.2: initial attack by either oxygen or nitrogen. For an unsymmetrically substituted dibromide two isomers might be expected to form by either route. In fact, assuming the same molecularity, SN2 or SN1, and a similar rate of reaction at both reacting centres, it might be expected that the two isomers would be formed in roughly equal amounts. This is the case for the 4-and 5-methyl oxazines 2.7 and 2.9, where both centres are primary and are likely to react via an SN2 type of mechanism.

The retention of stereochemistry in the 3,6-dimethyl substituted case above implies that for a secondary centre the SN2 assumption still holds, and since the idea of a secondary centre reacting more slowly than a primary one under SN2 conditions is widely held,[83] the 3:1 bias in compounds 2.5 and 2.11 suggests the initial step in ring formation to be attack by the oxygen of tautomer 2.2a at the primary centre. Whether the lesser isomer is formed from slower attack by the oxygen at the secondary centre, or by the nitrogen of tautomer 2.2b attacking at the primary centre, is difficult to determine. Probably both mechanisms contribute.

Several pieces of evidence corroborate this idea of initial attack by oxygen. Jones and his coworkers,[78] while studying the reaction of alkyl halides with N-hydroxyurethane, found only O-alkylated products. Steinberg and Swidler[84] studied the dissociation of benzohydroxamic acid (2.2a and 2.2b, R = phenyl) in base and found

that, although the two tautomers appeared to exist in approximately equal concentrations, the nucleophilicity of 2.2a was far greater than 2.2b.

The 7:1 bias in the 3,3 and 6,6-dimethyl oxazines (2.17 and 2.19) also supports the proposed scheme of the initial SN2 displacement by oxygen at the primary centre followed by a slower SN1 attack at the tertiary centre. The small bias of 3:2 in compounds 2.7 and 2.9 may arise from the β substituent effect in nucleophilic reactions.[83]

A steric hindrance effect appears to be important in these reactions since repeated attempts to obtain compound 2.28 from 2,5-dimethyl-2,5-dibromo-hexane and N-hydroxyurethane failed; 2,5-dimethylhexane-2,5-diol, as well as the dibromide, was recovered in low yield from the reaction mixtures.

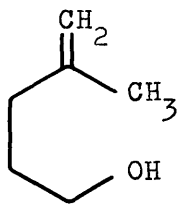
Reductions with Lithium Aluminium Hydride[82]

With the exception of compounds 2.17 and 2.19, the reduction of the N-carbethoxy compounds with lithium aluminium hydride proceeded smoothly giving around 60% yields once a satisfactory work-up technique had been evolved.

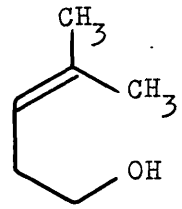
The reduction of the 3,3 and 6,6-dimethyl oxazines, 2.17 and 2.19, as a 7:1 mixture gave a very low yield of the N-methyl compounds 2.18 and 2.19 in a 1:5 ratio. Presumably the reduction of the carbethoxy group is hindered by the gem dimethyl group in compound 2.17 giving rise to the change in product ratio. However,

in an attempted reduction of compound 2.27 with lithium aluminium hydride, N.M.R. evidence suggested only the N-carbethoxy group had been reduced.

In a second attempted preparation of compounds 2.18 and 2.20 under more vigorous conditions a mixture of the isomeric alkene-ols 2.29 and 2.30 was isolated.[86] To form these compounds from the N-carbethoxy compounds requires that the nitrogen-oxygen bond be broken. Only one other case of a hydroxylamine bond being cleaved by lithium aluminium hydride is recorded and that is the conversion of N-(β-phenylisopropyl)hydroxylamine to β-phenylisopropylamine.[87]



2.29

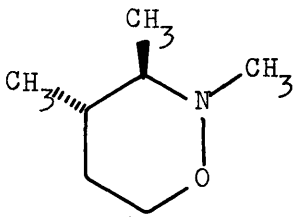


2.30

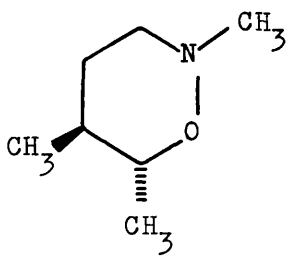
An explanation of the present case is not attempted since clearly this type of system requires further study.

A third attempted preparation of compounds 2.18 and 2.20 using sodium dihydro-bis-(2-methoxy-ethoxy)aluminate (S.D.A.) as a reducing agent gave a low yield of a base with an N.M.R. spectrum consistent with an N-methyl oxazine structure, but different from the previously obtained sample of compounds 2.18 and 2.20. The temperature independence of the N.M.R. spectrum, and the presence of

two C-methyl doublets suggests this unknown compound may be 2.31 or 2.32. However, further study is again indicated.



2.31



2.32

Physical Properties of the N-Methyl-Tetrahydro-1,2-Oxazines

Table 2.3 shows the boiling points of the N-methyl oxazines and the melting points of their picrate derivatives. There is the expected increase in boiling point with molecular weight, and in the two cases of diastereoisomerism, the cis and trans 3,6,N-trimethyl compounds (2.14 and 2.16) and the cis and trans 4,5,N-trimethyl compounds (2.22 and 2.24), the higher boiling point is associated with the cis isomer. This may be explained in terms of the 'Von Auwers-Skita' rule,[88] the cis isomer having the smaller molecular volume and consequently the higher enthalpy and higher boiling point. However, this rule is usually applied to alicyclic systems with no appreciable intermolecular interactions other than dispersion forces, so agreement in this case where intermolecular dipolar forces are present may be fortuitous.

Hydroboration[89]

In the preparation of the cis and trans 4,5-dimethyl

TABLE 2.3

PHYSICAL DATA FOR N-METHYL-TETRAHYDRO-1,2-OXAZINES

Compound	Boiling Point °C	Melting Point of Picrate °C
2.4	94	-
2.6) 2.12)	104 - 105	177 -
2.8 and 2.10	98	110 - 113
2.14	138 - 140	147 - 148
2.16	128	133 - 134
2.22	143	154 - 155
2.24	138	135 - 136
2.26	68 at 5 mm	134

oxazines, 2.21 and 2.23, 2,3-dimethyl-butane-1,4-diol is required. A convenient synthesis of this diol is by hydroboration and subsequent oxidation of 2,3-dimethyl-buta-1,3-diene. Brown suggests that only the meso diol is formed in this reaction,[90] but a subsequent 3:2 product mixture of the N-methyl oxazines 2.22 and 2.24 does not confirm this suggestion.

Carcinogenic Activity

Hydroxylamine is commonly known to have a harmful character and N-hydroxyurethane has been found to be a carcinogen.[91] Some of the compounds synthesised in this work were, therefore, tested at the Imperial Cancer Research Fund for possible carcinogenic activity. The compounds tested were 2.3, 2.4, 2.25, and the oxazine formed from the pyrolysis of nicotine N-oxide (2.41 see Section 2.3). The method used in an initial test for carcinogenic activity was the increase in uptake or otherwise of ^{3}H thymidine into D.N.A.[92] Only compound 2.25 had any effect on the system and this occurred at high dosage levels. However, further tests on the nicotine derivative (2.41) are being carried out.

Conclusions

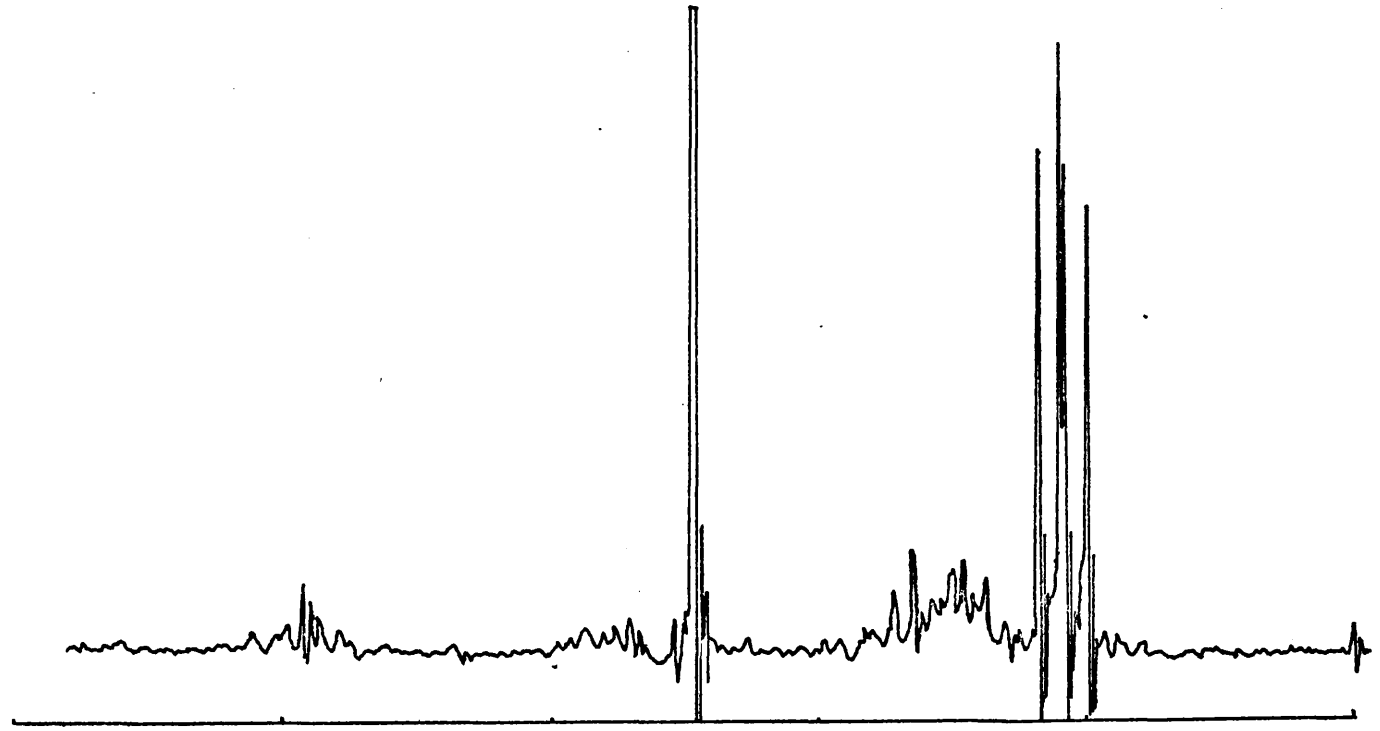
Preparative methods giving yields of 30-35% over two stages have been found for the N-methyl-tetrahydro-1,2-oxazines starting from 1,4-dibromides. The ring formation reaction of the dibromides with N-hydroxyurethane appears to go by way of the oxy-anion tautomer, 2.2a; and the lithium aluminium hydride reduction of an N-carbethoxy group to methyl is hindered by adjacent gem dimethyl groupings.

SECTION TWO

TETRAHYDRO-1,2-OXAZINES

2. N.M.R. Spectra and Conformations

Figure 2.3 Proton N.M.R. Spectrum of Cis-3,6,N-Trimethyl-Tetrahydro-1,2-Oxazine (Compound 2.14).



Temperature +30° Solvent CH_2Cl_2 Reference T.M.S.

THE N.M.R. SPECTRA AND CONFORMATIONS OF THE N-METHYL TETRAHYDRO-1,2-OXAZINES

General Points

This chapter presents firstly a general picture of the N.M.R. spectra of the N-methyl-tetrahydro-1,2-oxazines, and then discusses in some detail the elucidation of the preferred conformations of the oxazines.

The N.M.R. spectra have several general characteristics, as shown in Figure 2.3 by the spectrum of cis-3,6,N-trimethyl-tetrahydro-1,2-oxazine (compound 2.14). Four resonance regions can be distinguished. Starting at low field the resonance of the C_6 protons occurs around 6.2 τ, a typical position for protons deshielded by an adjacent oxygen. These resonances are in general broad multiplets arising from couplings to adjacent protons on C_5 and to substituent methyl groups. Analysis of such splitting patterns has been attempted in a number of cases and the results are given in context.

The C_3 proton resonances, which are also multiplets from couplings to C_4 protons and substituent methyl groups, occur around 7.2 τ. Analysis of these signals is hampered by the N-methyl signal (ca. 7.5 τ) which, although a singlet, overlaps and obscures parts of the C_3 resonances.

The C_4 and C_5 proton resonances form the third general region around 8.5 τ. The coupling between C_4 and C_5 as well as that to C_3 and C_6 and substituent methyl groups makes this region the most

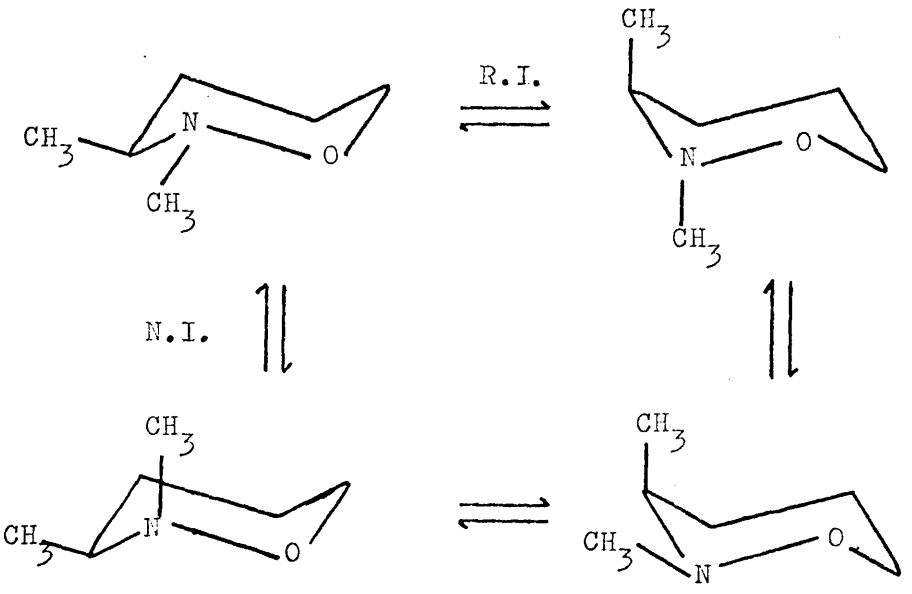


Figure 2.4 Equilibrium Scheme for 3,N-Dimethyl-Tetrahydro-1,2-oxazine

difficult to analyse. No attempts have been made in this work.

The final region is the C-methyl resonances centred around 9.0 τ. Except for compounds 2.18 and 2.20 which have gem dimethyl groups, the methyl resonances are doublets with a coupling constant of about 6.0 Hz. This constant appears to be insensitive to the methyl group's point of substitution and to whether the group is axial or equatorial. However, the chemical shift of these groups is found to vary with temperature, solvent, and position in the ring.

The Dimethyl-Tetrahydro-1,2-Oxazines

As was shown in the introduction the different conformations of N-methyl-tetrahydro-1,2-oxazine (compound 2.4 and 1.22) are in equilibrium through a series of ring and nitrogen inversions (Figure 1.24). The same idea can be applied to the 3, 4, 5, and 6 methyl, N-methyl oxazines (2.6, 2.8, 2.10, and 2.12), and a representative equilibrium scheme, for compound 2.6, is shown in Figure 2.4. Since one of these processes, probably nitrogen inversion, was shown to be slow at low temperatures (ca. -40°)[44] for compound 2.4 it might be expected that by observing the low temperature N.M.R. spectra of these compounds, some idea of their conformational preferences might be gained. In fact for all four of these compounds there is no change in their spectra even as low as -70°C in methylene chloride, except for a small amount of line broadening.

This observation does not mean there are no inversion processes occurring, but rather that the equilibrium for all these compounds is so far displaced to the most stable conformation that any other cannot be detected by N.M.R. The assumption is now made that the most stable conformation is the one with both methyl groups equatorial. This seems reasonable on two counts: firstly as was shown in the introduction an equatorial N-methyl group is predicted to be more stable than an axial one in the tetrahydro-1,2-oxazines and in, for example, N-methyl piperidine the conformation with an equatorial N-methyl has been found to be preferred;[22] secondly an axial C-methyl has two syn-axial interactions not present in the equatorial conformation. The observation of only one N-methyl signal at very low temperatures (- 100°C) in N-methyl-tetrahydro-1,2-oxazine itself also supports this assumption.

An upper limit to the proportion of a second conformation can be set by the noise level of the spectrum. Since the noise was in general less than 5% of the magnitude of the N-methyl signal of the major conformation there is probably less than 5% of any minor conformation present. A lower limit to the free energy difference between the major conformation and any other of 1.1 ± 0.1 kcal./mol. at -70°C can then be calculated.

Cis-4,5,N-Trimethyl-Tetrahydro-1,2-Oxazine (2.22)

Since the cis-4,5,N-trimethyl oxazine (2.22) and the cis-2-oxa-3-aza-3-methyl-decalin (2.26) are similar in structure

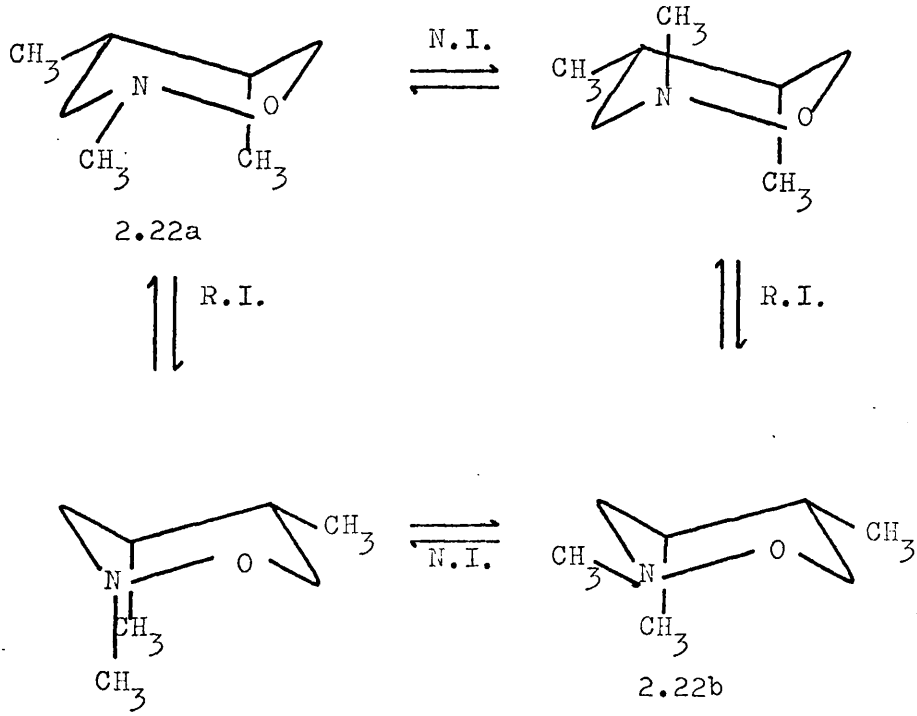


Figure 2.5 Equilibrium Conformations of cis-4,5,N-Trimethyl-Tetrahydro-1,2-oxazines

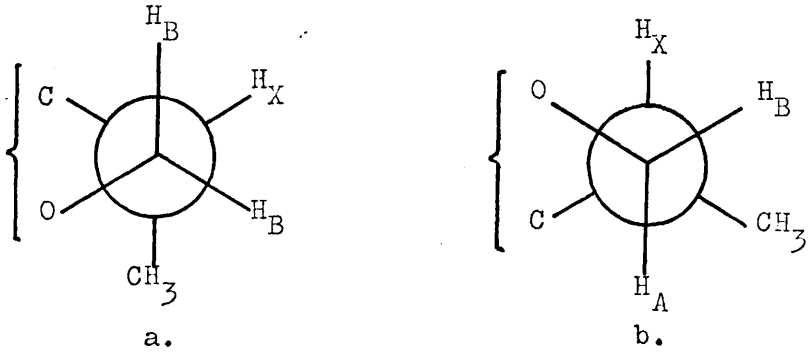


Figure 2.6 Newman Projection Formulae along C_6-C_5 for Conformations 2.22a and 2.22b.

and give rise to the same qualitative results, the following discussion of compound 2.22 is also applicable to compound 2.26.

The N.M.R. spectrum of compound 2.22 changes markedly with temperature. At -35°C an unequal doublet is observed for the N-methyl resonance, while both the C_6 and C_3 protons give rise to fairly well defined splitting patterns. At +60°C a single N-methyl resonance occurs and the C_6 and C_3 proton patterns have altered. Although 60 MHz. spectra showed these changes in a variety of solvents, 100 MHz spectra of compound 2.22 and 220 MHz spectra of compound 2.26, using deuteriomethanol as solvent, were found to be more easily interpreted.

The possible conformations of compound 2.22 arising from ring and nitrogen inversions are shown in Figure 2.5. The temperature dependence of the N.M.R. spectrum clearly shows that one of these processes is being 'frozen out' at low temperatures. Again assuming a preference for an equatorial N-methyl group, the equilibrium scheme reduces to a virtual equilibrium between conformations 2.22a and 2.22b. Because of the angular dependence of vicinal coupling constants, conformations 2.22a and b should give rise to different ABX spectra for the C_5 - C_6 protons, and the C_3 - C_4 protons (Figure 2.6). When the observed process is slow it might be expected that both ABX systems would be observed, but the conformational bias, as shown by the difference in intensities of the N-methyl signals at -35°C, leads to one predominant pattern. For

compound 2.22 an AB quartet with the low field signals partially split is the major pattern observed for the C_6 protons. This can be accounted for by the AB portion of an ABX system having two small vicinal couplings; which implies two gauche couplings as in conformation 2.22a.

Since the ratio of the two conformations is ca. 3:1 in deuteriomethanol as found by integration of the N-methyl signals, conformation 2.22a is preferred by 0.52 $\pm$ 0.1 kcal./mol. over conformation 2.22b at -35°C. This also holds for the corresponding conformations of compound 2.26.

At +60°C, when both ring and nitrogen inversion are fast the AB portion of an ABX system is again observed for the C_6 protons of compound 2.22, the coupling constants being the weighted means of those for conformations 2.22a and 2.22b. If the equilibrium constant is known then the coupling constants for the minor conformation, 2.22b, can be calculated.

Complete analyses of the ABX systems are not possible since the X portions (C_5 and C_4 protons) are further coupled to the C_5 and C_4 methyls and to each other, but the geminal (J_{AB}), and vicinal (J_{AX}, J_{BX}) coupling constants, and the chemical shift between protons A and B ($\Delta\upsilon_{AB}$) can be obtained from the AB portion by standard procedures.[66] The results of the analyses of compounds 2.22 and 2.26 are shown in Tables 2.4 and 2.5. Analysis of the C_3 protons is possible for compound 2.26 both at -35°C and +60°C, and,

although the C_6 resonances are broad at +60°C, the patterns belonging to both the major and minor conformations are observable at -35°C. The tables also show the assignments of the various vicinal couplings to specific protons. This is discussed below.

As a check, spectra were computed by the ABX procedure, using the results of the analyses, and in all cases in Tables 2.4 and 2.5 a good fit in both line position and intensity was obtained.

On thermodynamic grounds a decrease from the 3:1 equilibrium ratio of the conformations of compounds 2.22 and 2.26 could be expected with an increase in temperature and it was found that a 2:1 ratio gave plausible predictions for the coupling constants of the minor conformations. However, large errors must necessarily be associated with such predictions.

The ABX analysis results for compounds 2.22 and 2.26 agree quantitatively with the preference of conformation 2.22a (and the corresponding one for compound 2.26). The expected magnitudes for the various vicinal couplings arising in conformations 2.22a and b are both observed and predicted.

The large trans axial-axial couplings are found to be associated with the low field proton of the ABX system in compounds 2.22 and 2.26. This is an unusual effect, equatorial protons generally coming to low field since they are usually less shielded than axial ones.[93] If the assumption that the axial protons at C_3 and C_6 always come to low field in compounds 2.22 and 2.26 is made,

TABLE 2.4

COUPLING CONSTANTS, ASSIGNMENTS, AND CHEMICAL SHIFTS FOR THE C_6 PROTONS OF COMPOUND 2.22

Temperature	- 35°	- 35°	+ 60°
Conformation	Major (2.22a)	Minor (2.22a)*	Average
$\Delta\upsilon_{AB}$ p.p.m	0.28	0.16	0.17
J_{AB} Hz	11.4	11.4	11.2
J_{AX} "	0 ($J_{5e,6e}$)	14.7 ($J_{5a,6a}$)	4.9
J_{BX} "	2.4 ($J_{5e,6a}$)	5.7 ($J_{5a,6e}$)	3.5

* Predicted values solvent deuteriomethanol

Errors: J $\pm$ 0.2 Hz on observed results; $\pm$ 3.0 Hz on predicted values

$\pm$ 0.01 p.p.m. on observed results

The errors also apply to Table 2.5.

TABLE 2.5

COUPLING CONSTANTS, ASSIGNMENTS AND CHEMICAL SHIFTS FOR THE C_3 and C_6 PROTONS OF COMPOUND 2.26

Temperature		- 30°		+ 60°
Conformation		Major (2.26a)	Minor (2.26b)	Average
Region		C_3 protons		
$\Delta\upsilon_{AB}$	p.p.m	0.16	0.12	0.15
J_{AB}	Hz	12.0	12.0 *	12.0
J_{AX}	"	13.3 ($J_{4a,3a}$)	ca. 0.0 ($J_{4e,3e}$)*	8.7
J_{BX}	"	4.7 ($J_{4a,3e}$)	7.5 ($J_{4e,3a}$) *	3.3
Region		C_6 protons		
$\Delta\upsilon_{AB}$	p.p.m.	0.38	0.59	-
J_{AB}	Hz	11.5	11.5	-
J_{AX}	"	-0.7 ($J_{5e,6e}$)	12.3 ($J_{5a,6a}$)	-
J_{BX}	"	2.2 ($J_{5e,6a}$)	7.7 ($J_{5a,6e}$)	-

* Predicted values solvent deuteriomethanol

then the assignment of the other coupling constants to the appropriate equatorial-equatorial, and equatorial-axial proton couplings in compounds 2.22 and 2.26 can be made from a study of the splitting of the low and high field AB resonances. If the assumption is invalid then the assignments must be reversed.

The 5-axial protons in some 1,3 dioxans have also been found to come at low field relative to the 5-equatorial protons.[94] Explanations in terms of electrostatic fields of the oxygen lone pairs,[95] and overlap of the anti-bonding orbitals of the 5-equatorial proton-carbon bond with the anti-bonding orbitals of the oxygen atoms,[94] have been put forward. A similar effect might be expected for trans-4,5,N-trimethyl-tetrahydro-1,2-oxazine, compound 2.24, where the same spatial arrangement of both nitrogen and oxygen lone pairs and the C_3 and C_6 axial protons exists as in the major and minor conformations of compound 2.22. Table 2.6 shows the results of the ABX analyses of compound 2.24. The large axial-axial coupling occurs in the high field portion of the AB system implying the equatorial proton to be at low field. This suggests that the observed reversal in compounds 2.22 and 2.26 arises through some influence of an axial methyl group across the ring.

A small increase in the preferred conformations of compounds 2.22 and 2.26 occurs on changing from non-polar solvents to deuteriomethanol. This effect, presumably due to hydrogen-bonding, substantiates the assignment of conformation 2.22a as the preferred one in compound 2.22, since hydrogen-bonding is hindered by the

4-axial methyl group in conformation 2.22b, but not in conformation 2.22a. (Similarly for compound 2.26). A second implication of this effect is that an equatorial N-methyl group is preferred since with an equatorial lone pair on nitrogen hydrogen-bonding would be equally facile in both conformations.

TABLE 2.6

COUPLING CONSTANTS, ASSIGNMENTS, AND CHEMICAL SHIFTS FOR THE C_3 and C_6 PROTONS OF COMPOUND 2.24

Region	C_3 protons	C_6 protons
$\Delta\upsilon_{AB}$ p.p.m.	0.78	0.38
J_{AB} Hz.	11.5	11.5
J_{AX} "	11.1 ($J_{3a,4a}$)	10.3 ($J_{5a,6a}$)
J_{BX} "	3.9 ($J_{3e,4a}$)	4.7 ($J_{5a,6e}$)

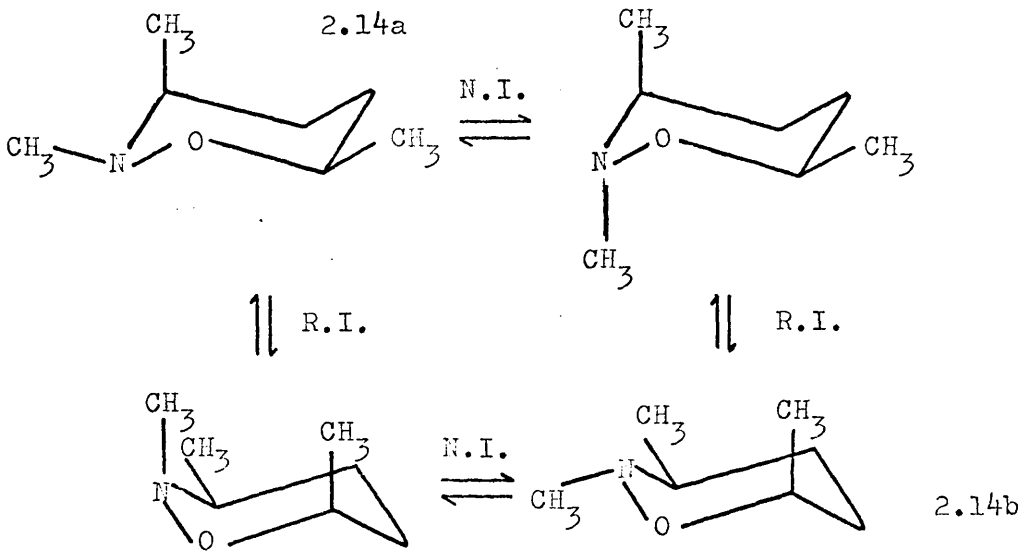


Figure 2.7 Equilibrium Scheme for cis-3,6-N-Trimethyl-Tetrahydro-1,2-Oxazine

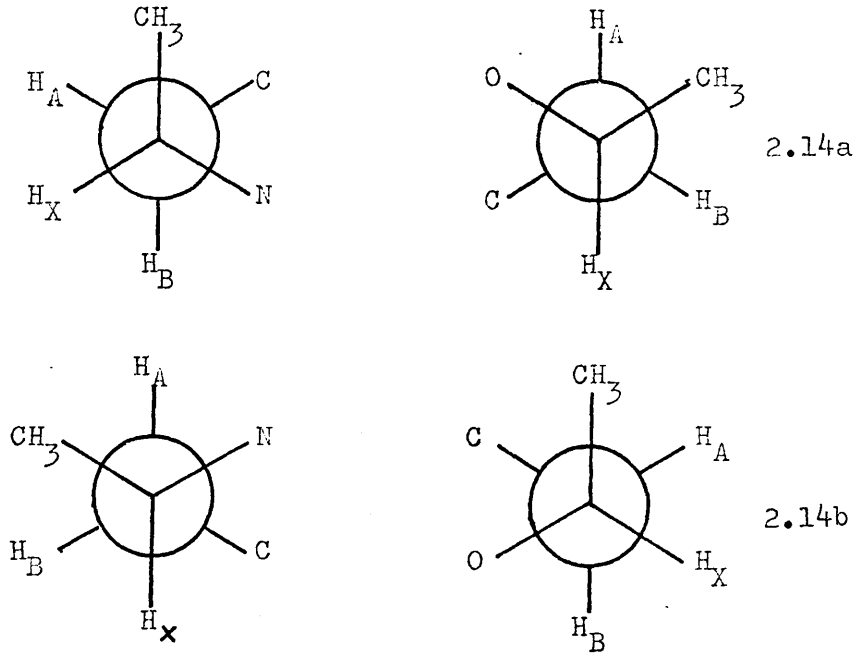


Figure 2.8 Newman Projection Formulae for cis-3,6 N-Trimethyl-Tetrahydro-1,2-Oxazine

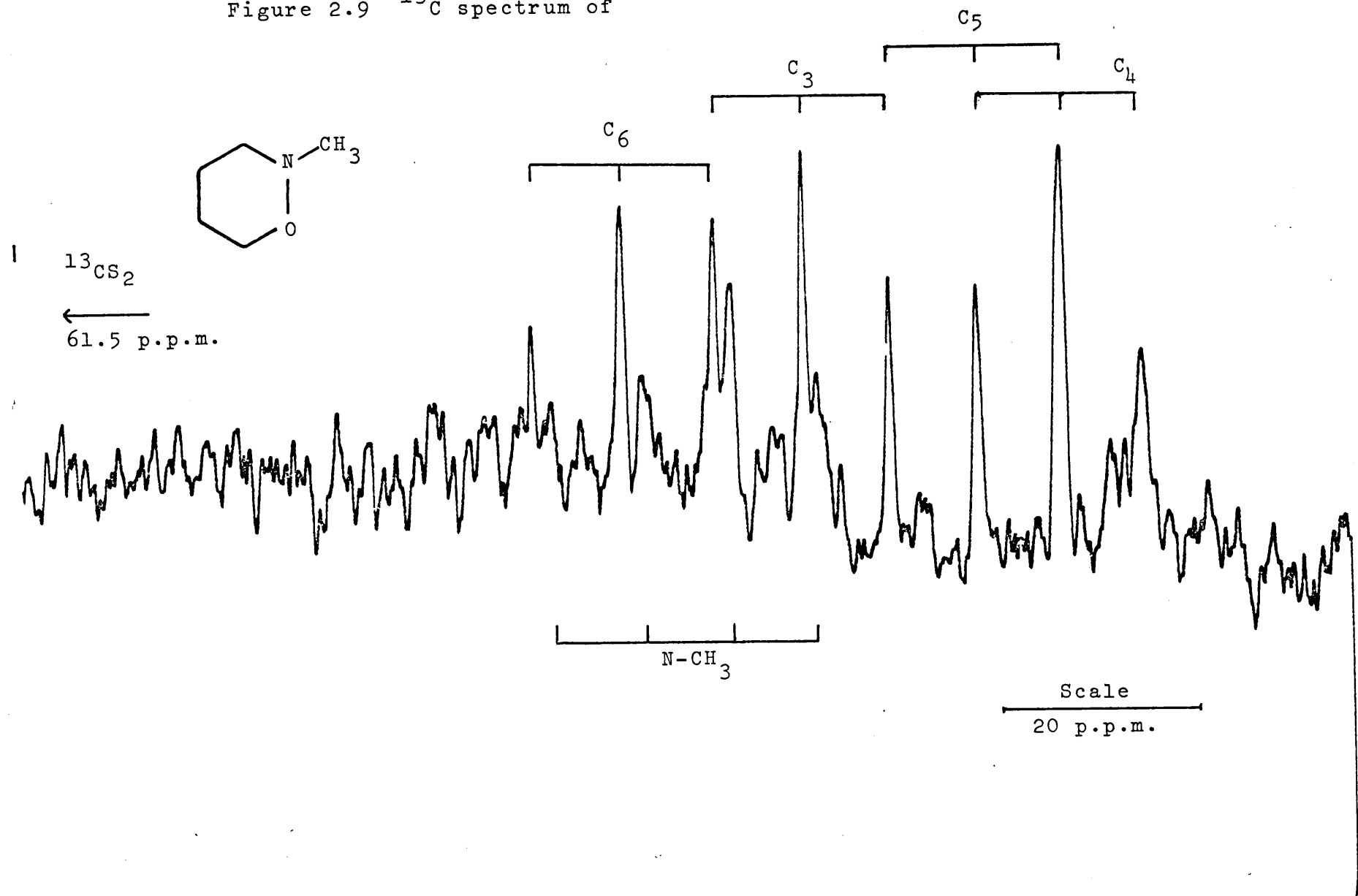
Cis-3,6,N-Trimethyl-Tetrahydro-1,2-Oxazine (2.14)

The N.M.R. spectrum of this compound (2.14) also shows temperature dependence. The higher field C-methyl doublet, shown by spin decoupling experiments to be the C_3 methyl, broadens as the temperature is lowered, but resharpens at -50°C. The N-methyl signal remains as a singlet, but both the C_3 and C_6 proton resonances collapse and at -50°C the C_3 proton signal has a different splitting pattern than at room temperature.

The ring and nitrogen inversions which compound 2.14 can undergo are shown in Figure 2.7, and, assuming a preference for an equatorial N-methyl group, the equilibrium reduces to that between conformations 2.14a and 2.14b which are shown in Figure 2.8.

The splitting patterns for the C_3 and C_6 protons should be the X portion of an ABX system, but with each resonance line further split into a quartet by the respective C-methyl protons. The X portion of an ABX system consists of six lines the outer two of which are the least intense and often not discernable. However, a measure of $|J_{AX} + J_{BX}|$ can be obtained from the separation of the two most intense spectral lines. The 60 MHz spectrum of compound 2.14 at room temperature in methylene chloride shows for the C_6 proton resonance a quartet of quartets with a coupling of 6.3 Hz to the C_6 methyl and a $|J_{AX} + J_{BX}|$ of ca. 10 Hz. At -50°C the C_3 protons also give a quartet of quartets with a C_3-methyl proton coupling of 6.9 Hz. and a $|J_{AX} + J_{BX}|$ of ca. 6.5 Hz. The C_6 proton resonance, however, gives essentially the same pattern as at room temperature. At 60 MHz. no other splitting patterns could be interpreted. These results

Figure 2.9 ^{13}C spectrum of

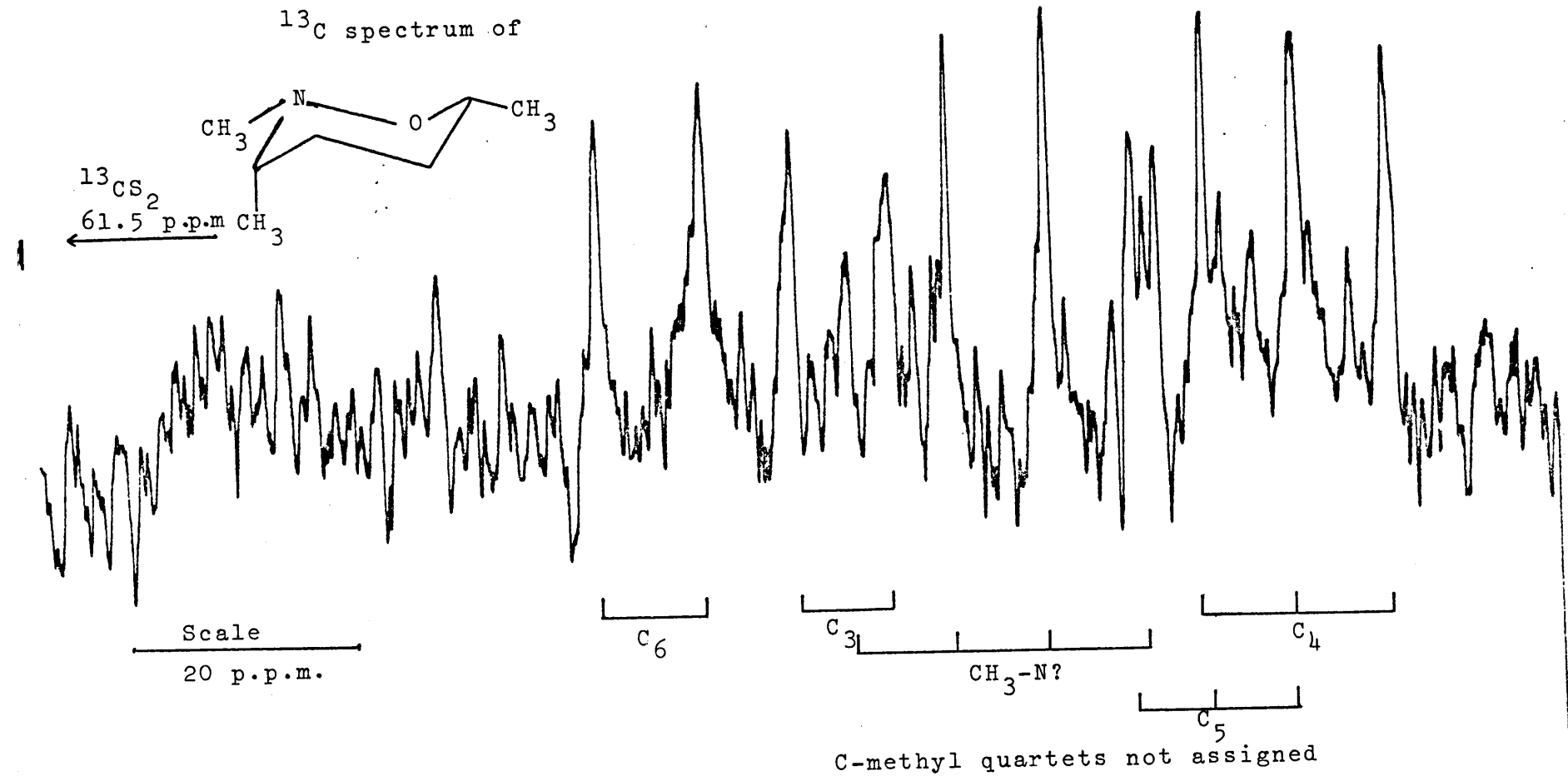


suggest two small gauche couplings to the C_3 proton of compound 2.14, and a small and large vicinal coupling to the C_6 proton, i.e. conformation 2.14a with an equatorial C_6 methyl group is possibly the preferred one.

The N.M.R. spectrum of trans-3,6,N-trimethyl-tetrahydro-1,2-oxazine (2.16) tends to confirm this assignment of the preferred conformation, because a similar pattern is observed for the C_6 proton at room temperature and -50°C as is observed for the C_6 proton in the cis compound 2.14, but a different pattern is observed for the C_3 proton in compound 2.16 than is seen for the C_3 proton in compound 2.14.

More conclusive evidence of which conformation is preferred comes from a comparison of the ^{13}C spectra of N-methyl-tetrahydro-1,2-oxazine (2.4) and the cis-3,6,N-trimethyl oxazine (2.14), Figures 2.9 and 2.10 respectively. The peaks are assigned on the basis of previous ^{13}C work on the dioxans and cyclohexanes,[60-63] and on the observed splitting patterns. The expected quartet of the N-methyl groups is difficult to determine and is only tentatively assigned. Nevertheless, the C_6 resonance is found to have shifted by 3 p.p.m. downfield in compound 2.14 compared to the same resonance in compound 2.4, while the C_3 resonance in both compounds has the same chemical shift. These results suggest the presence of an equatorial C-methyl group at C_6, i.e. conformation 2.14a is preferred. However, further work on the ^{13}C spectra of the tetrahydro-1,2-oxazines seems to be indicated before a rigorous assignment can be made.

Figure 2.10



C-methyl quartets not assigned

Since the N-methyl proton resonance remained a singlet at low temperatures there is some difficulty in determining the relative amounts of the two conformations 2.14a and 2.14b. However, 100 MHz. spectra of the C-methyl region at -35°C shows two sets of two doublets in the approximate ratio of 3:1, which leads to a free energy difference of 0.5 ± 0.1 kcal./mol. at -35°C.

6,6,N-Trimethyl-Tetrahydro-1,2-Oxazine (2.20)

The room temperature N.M.R. spectrum of the products from the lithium aluminium hydride reduction of the mixture of the N-carbethoxy compounds 2.17 and 2.19 shows two N-methyl peaks in the ratio 5:1, C_3 proton resonances around 7.4τ, a singlet C-methyl resonance at 8.8τ, C_4 and C_5 proton resonances, but only a weak signal in the C_6 proton region. This evidence implies compound 2.20 with the C_6 gem dimethyl group to be the major isomer present, and the singlet C-methyl peak suggests rapid ring and nitrogen inversion at room temperature.

At low temperatures (-45°C) the C-methyl resonance has split into a doublet with a chemical shift difference of 10.2 Hz. A coalescence temperature of -10 ± 5°C was found for the collapse of this doublet, corresponding to a free energy of activation for the observed process of 13.7 ± 0.5 kcal./mol. at -10°C. with methylene chloride as solvent. This value is the same as that found for N-methyl-tetrahydro-1,2-oxazine (2.4), Table 1.3.[44] The lack of any

increase in the barrier on increasing the size of the substituent on the oxygen atom suggests the observed process is probably not of torsional origin as postulated by Raban and Kenney,[73] and is thus a slow nitrogen inversion. The lack of a barrier decrease suggests that introduction of a gem dimethyl group at C_6 does not alter the geometry at nitrogen sufficiently to cause a change in the nitrogen inversion barrier.

Conclusion Discussion

The above results for the tetrahydro-1,2-oxazine system can be summarised as follows.

(a) There is a strong preference for the N-methyl group to be equatorial. This is in agreement with Fink, Pan, and Allen's calculations[28] on the preferred conformation of hydroxylamine.

(b) With a single C-methyl substituent in the oxazine ring the preferred conformation is that with both the C- and N-methyl groups equatorial, and there is a free energy difference between the C-axial and C-equatorial conformations of at least 1.1 kcal./mol. at -70°C.

(c) With two C-methyl groups substituted either on the C_3 and C_6 carbons or on the C_4 and C_5 carbons and such that one group must be axial the preferred conformation by 0.5 ± 0.1 kcal./mol. is that which does not have a C-methyl group syn axial to the nitrogen lone pair.

(d) Slow nitrogen inversion rather than ring inversion is probably the observed process in the N-methyl-tetrahydro-1,2-oxazines.

Results (b) and (c) can be expressed in the following manner, where C_{ne} and C_{na} are carbon atoms in the oxazine ring upon which there is respectively an equatorial or axial methyl group, and where > means preferred over.

$C_{ne} > C_{na}$ by at least 1.1 kcal./mol.

where n = 3, 4, 5, 6.

$C_{3a} > C_{6a}$ by 0.5 kcal./mol.

$C_{5a} > C_{4a}$ " " " "

Riddell has studied the 3,5,N-trimethyl-tetrahydro-1,2-oxazine (2.33) and found from coupling constant measurements that conformation 2.33a with an axial C_5 methyl group is preferred over conformation 2.33b, and from low temperature N.M.R. studies that the free energy difference between the conformations is 0.6 kcal./mol.[96]

i.e. $C_{5a} > C_{3a}$ by 0.6 kcal./mol.

From these expressions it follows that

$C_{5a} > C_{6a}$ by 1.1 kcal./mol.

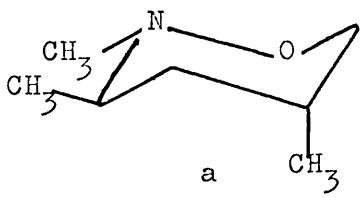
If any one of the free energy differences between axial and equatorial C-methyl groups can be found exactly then the rest follow from the above relationships. If it is assumed that:

$C_{5e} > C_{5a}$ by 1.1 kcal./mol.

then $C_{4e} > C_{4a}$ " 1.6 " "

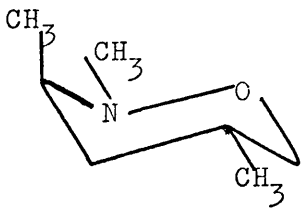
$C_{3e} > C_{3a}$ " 1.7 " "

$C_{6e} > C_{6a}$ " 2.2 " "

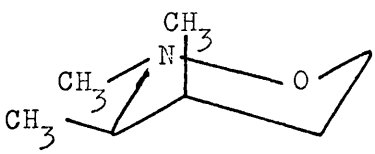


a

2.33

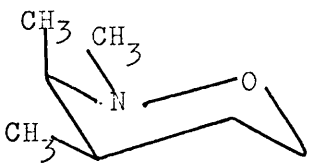


b

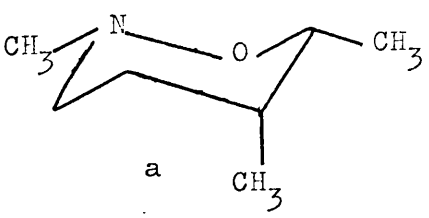


a

2.34

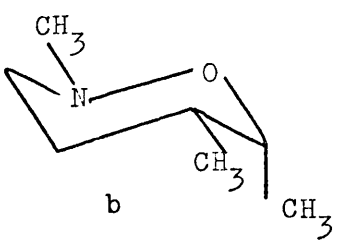


b

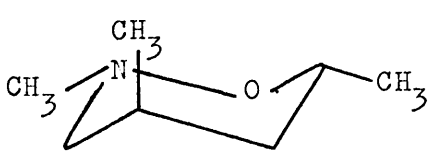


a

2.35

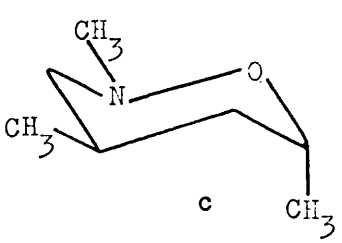


b



a

2.36



c

These relationships can then be used to predict the preferred conformations in the other possible C, C' dimethyl substituted N-methyl oxazines where one C-methyl group is necessarily axial. Thus in cis-3,4,N-trimethyl-tetrahydro-1,2-oxazine (2.34) conformations 2.34a and 2.34b should be almost equally favoured, but with a slight preference for conformation 2.34a. In cis-5,6,N-trimethyl-tetrahydro-1,2-oxazine (2.35) conformation 2.35a should be very much preferred over conformation 2.35b (by ca. 1.1 kcal./mol.); and in trans-4,6,N-trimethyl-tetrahydro-1,2-oxazine (2.36) conformation 2.36a should be preferred by ca. 0.6 kcal./mol.

These free energy differences depend on the relative size of the two gauche n-butane type interactions that an axial C-methyl group experiences, and, summarising what was discussed in the introduction, the size of these interactions depends on the geometry of the ring system and the nature of the groups with which the axial methyl group is interacting. In, for example, the axial conformation of methylcyclohexane, a measure of the gauche interaction is the distance between the protons of the axial methyl group and the syn axial protons of the ring. However, with lone pairs instead of protons interacting with an axial methyl as in the oxazine ring there is some difficulty in applying this method. Thus in the following discussion the distance between the axial methyl carbon and the gauche ring atom is taken as a measure of the gauche type of interaction. For the axial conformation of methylcyclohexane, measuring from a

Dreiding model, this distance is 3.0 ± 0.05 Å for both of the two gauche interactions each of which is 0.8 - 0.9 kcal./mol.[9]

Table 2.7 shows the different distances involved for the four possible axial methyl substituents on the tetrahydro-1,2-oxazine ring as measured from Dreiding models, and also the free energy difference between the axial and equatorial conformation ΔG_{diff} for each position.

TABLE 2.7

SOME INTERATOMIC DISTANCES IN THE TETRAHYDRO-1,2-OXAZINE RING

Axial Methyl Group on:	Distance to gauche N or gauche O(Å)		Distance to gauche Carbon (Å)	ΔG_{diff} kcal./mol.
C_3	-	2.7	3.1	1.7
C_4	3.05	-	3.2	1.6
C_5	-	3.0	3.2	1.1
C_6	2.6	-	3.15	2.2

The axial C-methyl to gauche carbon distance are all about the same and suggest a similar if not slightly smaller gauche interaction than in methylcyclohexane. However, the axial C_6 methyl is predicted on this geometrical basis to have a larger interaction because of the shorter interatomic distance (2.6 Å), and this is reflected in the large free energy difference, 2.2 kcal./mol. The axial C_3 methyl is predicted to have a similar interaction, but as this interaction is with an oxygen lone pair, which, as shown in the introduction, tends to be smaller than a covalently bonded hydrogen and consequently has smaller interactions,[15] a lesser free energy difference than in the C_6 axial methyl case might be expected. This is in fact found (1.7 kcal./mol.). On the geometrical basis the C_4 and C_5 axial methyls are predicted to have similar interactions to each other and to that in the axial conformation in cyclohexane. For the C_4 axial methyl which interacts with a nitrogen lone pair there is a similar free energy difference to that in methylcyclohexane (1.6 kcal./mol.), but for the C_5 axial methyl which interacts with an oxygen lone pair there is a smaller free energy difference (1.1 kcal./mol.).

This rationalisation of the observed energy differences with molecular structure is subject to several assumptions. It depends on the choice of a good molecular model system and Dreiding models are perhaps the best available for accurate representation of bond lengths and angles. A more important aspect is whether ring

deformation through torsional or angular strains alters the ring geometry to a significant extent from that observed with a model, and if it does whether the deformation enhances or refutes the above arguments.

The assumption that the free energy difference between the axial and equatorial C_5-methyl group is 1.1 kcal./mol. has also been made. This seems a reasonable value based on the present experimental evidence since it was shown above that the value is probably not less than 1.1 kcal./mol., and if it were much greater it would lead to a rather large value for the C_6 axial methyl. (c.f. isopropylcyclohexane which has been found to have a free energy difference between axial and equatorial conformations of 2.1 kcal./mol.[9]).

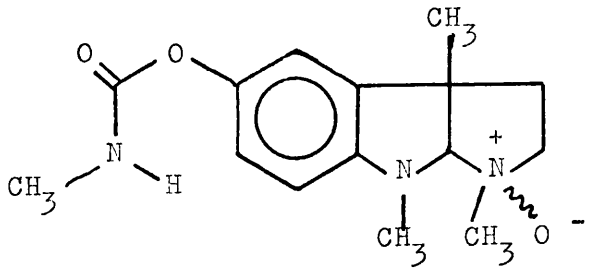
It has also been assumed that the interactions of the four different C-equatorial groups are all equivalent, and that the various free energy differences observed can be accounted for solely by differences in the axial group interactions.

Clearly further research is required to investigate the free energy differences in the other C, C' dimethyl tetrahydro-1,2-oxazines, and to obtain a more accurate idea of the oxazine ring shape.

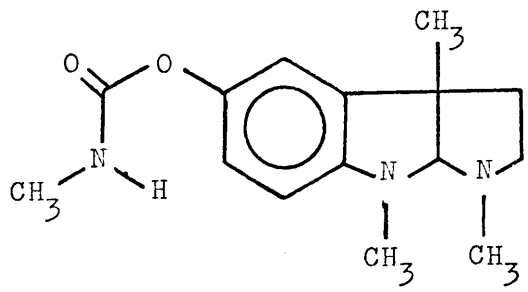
SECTION TWO

TETRAHYDRO-1,2-OXAZINES

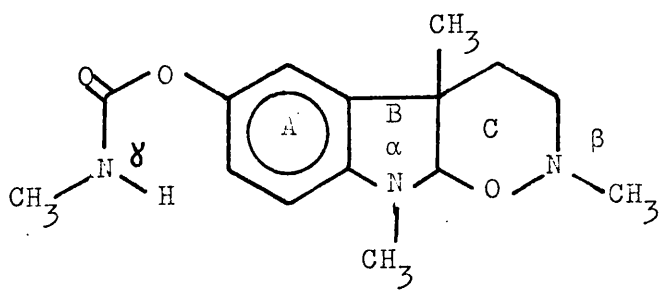
3. The Stereochemistry of Geneserine



2.37



2.38



2.39

THE STEREOCHEMISTRY OF GENESERINE

Introduction

Geneserine, formerly thought to be the N-oxide (compound 2.37) of physostigmine (compound 2.38), an indole alkaloid from Calabar beans,[97] has recently been shown by Hootele[98] from mass spectral and N.M.R. studies to have the structure 2.39. The only feature of this structure remaining undetermined was that of the stereochemistry of the B/C ring junction, and since this system contains a tetrahydro-1,2-oxazine ring it was felt that some information could be obtained by further N.M.R. studies.

Results and Discussion

The N.M.R. spectrum of geneserine at 33.5°C shows four singlet resonances at 5.24 τ for the bridgehead methine proton, 7.12 τ for the α N-methyl group, 7.44 τ for the β N-methyl group, and 8.79 τ for the bridgehead methyl; a complex multiplet centred around 3.2 τ for the aromatic protons; a doublet with coupling constant of 6.0 Hz centred at 7.10 τ for the γ N-methyl; and two broad multiplets at 7.5 τ and 7.9 τ for the protons in the oxazine ring.

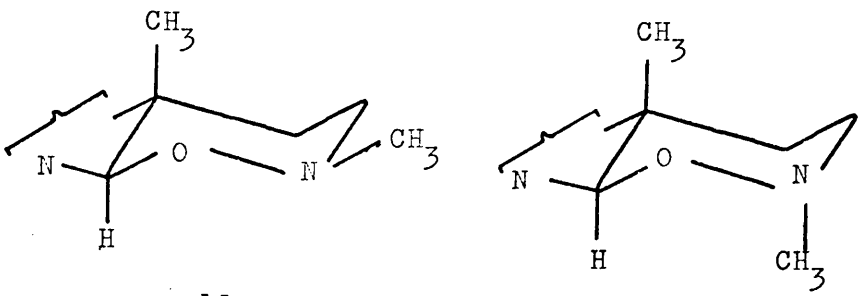
The four singlet resonances are found to split into unequal doublets at low temperature, with the bridgehead methyl and methine protons being the most convenient to study as they are well separated from other resonances. Table 2.8 shows these resonances and their changes with temperature.

TABLE 2.8

N.M.R. DATA FOR GENESERINE

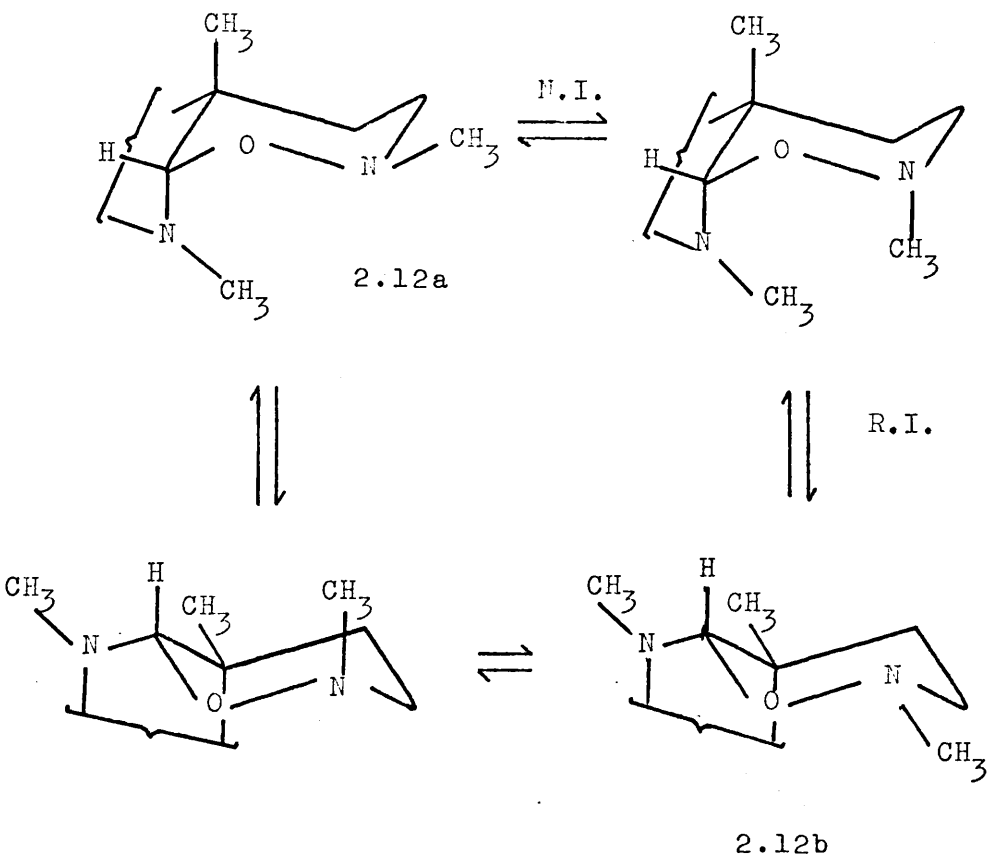
Temperature °C	Solvent	Bridgehead Methyl (τ)		Bridgehead Methine (τ)	
		Major	Minor	Major	Minor
33.5	$CDCl_3$	8.79		5.24	
-43.5	"	8.85	8.62	5.15	5.49
33.5	CD_3OD	8.86		5.26	
-40	"	8.92	8.70	5.22	5.59
33.5	$CDCl_3/CD_3OD$	8.82		5.26	
-41	"	8.85	8.62	5.16	5.52

In deuteriochloroform the integrated intensity of the two peaks was found to be 2:1 and the coalescence temperature -22 ± 3°. This leads to a free energy of activation for the observed process of 12.8 ± 0.5 kcal./mol. In an attempt to measure a hydrogen bonding effect on the rate process, spectra were obtained in deuteriomethanol, but this change of solvent altered the conformational proportions to ca. 10:1 in favour of the major conformation, making an estimate of the coalescence temperature impossible. However, with a 3:1 v/v mixture of deuteriochloroform and deuteriomethanol the conformational ratio was found to be 3:1 and the coalescence temperature -18 ± 3°.



2.11a 2.11b

Figure 2.11 Trans Ring Fusion in Geneserine



2.12b

Figure 2.12 Cis Ring Fusion in Geneserine

The measurement of an accurate coalescence temperature is difficult with peaks of unequal intensity, and this small change from -22° to -18° with solvent merely indicates a hydrogen bonding effect such as might be expected for slow nitrogen inversion.

If the stereochemistry at the ring junction were trans, the hydrindane-type portion of the molecule would not be able to ring invert[99] and so the observed process must be assigned to an axial equatorial nitrogen inversion process (Figure 2.11) (2.11a $\rightleftharpoons$ 2.11b). However, on the basis of the results of Section 2.2, it seems unlikely that a conformation with an axial N-methyl group would contribute as much as 10 - 30% to the equilibrium.

The results can be more readily explained in terms of a cis ring fusion. In this case a ring inversion as well as nitrogen inversion is possible and an equilibrium scheme as in Figure 2.12 can be constructed. Assuming a preference for equatorial N-methyl groups, conformations 2.12a and 2.12b are then the ones to be considered at low temperature. Examination of models shows that non-bonded interactions are similar in both conformations, accounting for the near 50:50 equilibrium in deuterochloroform. However, hydrogen bonding to the axial lone pair in 2.12a is hindered by the syn axial N-methyl group and the aromatic ring, whereas in 2.12b it is not. Thus the change in equilibrium from 2:1 to 10:1 on going from deuteriochloroform to deuteriomethanol is also consistent with a cis ring junction, and suggests the preferred conformation of geneserine to be 2.12b.

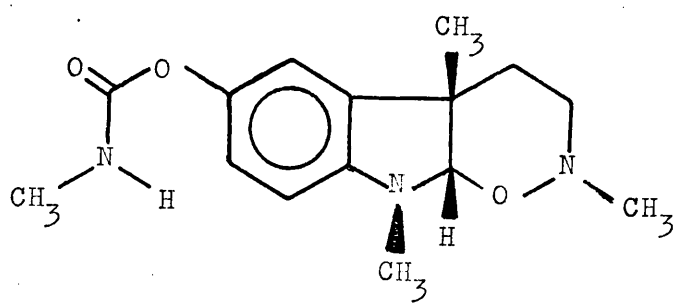


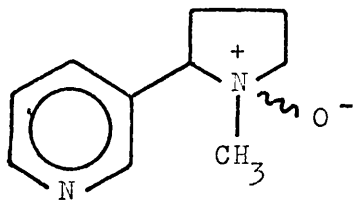
Figure 2.13 Stereochemistry of Geneserine

Such a ring fusion might be expected to show a significant nuclear Overhauser effect. This was attempted as part of this work, but an inconclusive result of 10% ± 10% was observed. However, Robinson and Moorcroft[100] found a 15% increase in the integrated intensity of the bridgehead methine proton by irradiating at the bridgehead methyl, and also a 10% increase in the methine signal by irradiation of the α N-methyl signal. (No estimation of error was given). From this they conclude that as well as a cis ring fusion, the geneserine molecule has a predominate cis relationship between the α N-methyl and the bridgehead methine (Figure 2.13).

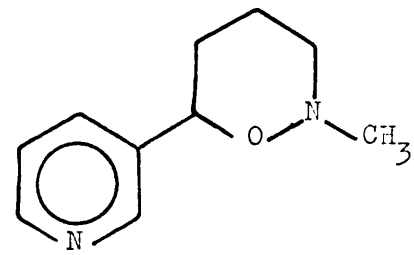
It may be argued that the observed spectral changes could be caused by restricted rotation around the carbon-nitrogen bond in the urethane portion of the molecule but this seems unlikely on a number of counts. Firstly the urethane group is remote from the centres showing the largest changes, and the doublet observed for the urethane N-methyl does not change in shape from -40 to +60°C; secondly the observed solvent effect would be difficult to explain; and finally it is found that in some amide systems with a mono-substituted nitrogen one conformation, that of the N-substituent cis to the carbonyl, is strongly preferred i.e. there is no observed rate process.[101,102]

Mechanistic Implications

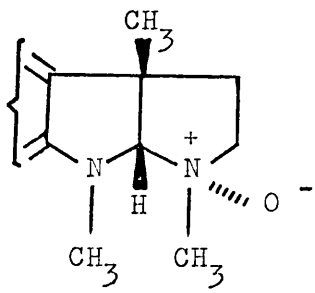
Carruthers and Johnstone[103] showed the conversion by pyrolysis of the nicotine N-oxide (Compound 2.40) to the



2.40



2.41



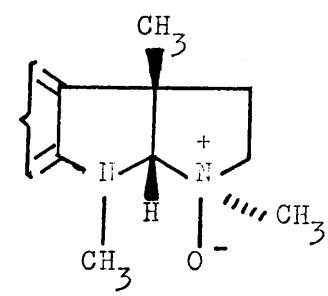


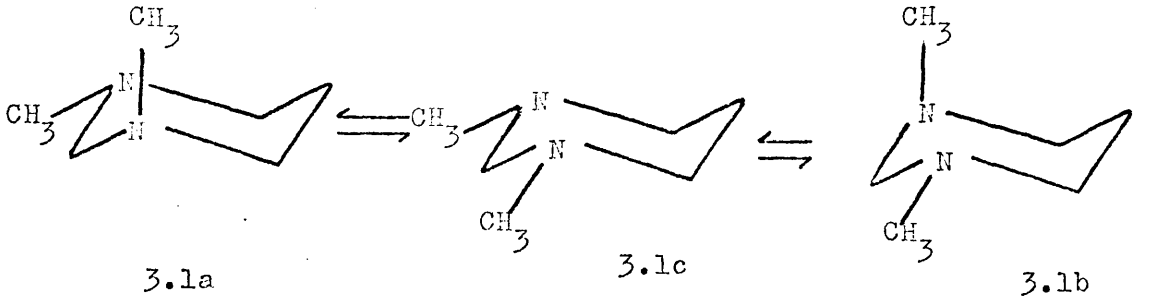
Figure 2.14 Diastereomer β-N-oxides of Physostigmine

1,2-oxazine (Compound 2.41) to be stereoselective and suggested a concerted intramolecular mechanism without inversion resembling the Meisenhemer rearrangement[104,105] to account for it. Since geneserine is formed by the N-oxidation of physostigmine[97] it seems reasonable to suggest an analogous ring forming reaction. Newkome and Bhacca have shown physostigmine to have a cis ring fusion[106] and inspection of models of the two possible diastereomic β N-oxides (Figure 2.14) shows that in both an intramolecular mechanism could lead to the cis ring fusion in geneserine.

A trans isomer of geneserine might be expected to exist, but it has been shown that acidification, which opens the molecule at the bridgehead, followed by basification gives a quantitative recovery of geneserine.[107] This can be accounted for by the cis form being either the thermodynamically more stable isomer, or being the kinetically controlled work up product of acid solution.

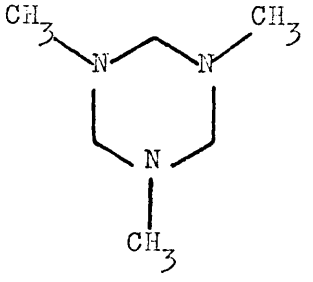
SECTION THREE

CONFORMATIONAL EQUILIBRIA IN HEXAHYDROPYRIMIDINES

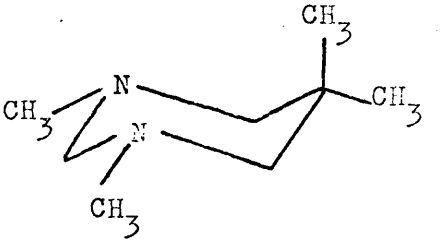


3.1a 3.1c 3.1b

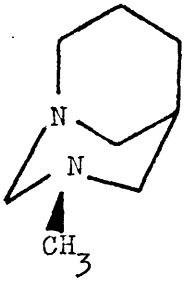
Figure 3.1 Conformational Equilibrium at Nitrogen



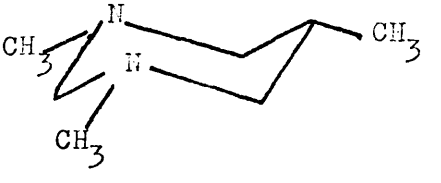
3.2



3.3



3.4



3.5

CONFORMATIONAL EQUILIBRIA IN HEXAHYDROPYRIMIDINES

Introduction

The hexahydropyrimidine system, which can undergo ring and nitrogen inversion, has been studied by Riddell[108] and Hamer and Farmer.[109] For the N,N-dimethyl compound (3.1) a free energy of activation of 11.3 ± 0.4 kcal./mol. to ring inversion has been found from N.M.R. studies. For the N,N-diethyl compound, the free energy is found to decrease by 0.4 kcal./mol.[108] A similar effect is found in the sym-tri-alkyl-triazines (3.2),[110] where as R changes from methyl to ethyl to isopropyl to t-butyl the barrier to ring inversion drops by ca. 0.7 kcal./mol. at each step, i.e. each time a proton on an N-methyl group is replaced by a methyl group there is a barrier decrease of ca. 0.2 kcal./mol. This effect can be explained in terms of the ring becoming more planar as the non-bonded interactions from the larger substituents increase.

A second feature of the hexahydropyrimidine system is the possibility of conformational equilibria at nitrogen (Figure 3.1). The position of the equilibrium will depend on the relative sizes of the non-bonded and dipolar interactions in conformations 3.1a and 3.1c. A qualitative N.M.R. study by Eliel[111] on several alkyl substituted hexahydropyrimidines suggested that a substantial proportion of the molecules exist with one N-methyl group axial. Katritzky et. al. have found by dipole measurements a free energy difference between 3.1a and 3.1c of 0.54 ± 0.08 kcal./mol.[112] It, therefore, seemed of interest to attempt a quantitative measurement of this equilibrium by N.M.R. methods.

The chemical shift difference between axial and equatorial protons, Δ ae, in cyclohexane has been shown to be 0.4 - 0.5 p.p.m.,[113] with the axial proton to higher field, i.e. shielded to a greater extent. Introduction of a nitrogen atom increases Δ ae of the adjacent methylene group to as much as 1.7 p.p.m.[114] in six-membered rings, the shielding of the axial proton, and hence the magnitude of Δ ae, depending on the stereochemistry at nitrogen. An equatorial N-alkyl group and/or an axial lone pair shields the axial proton more and so Δ ae is smaller with an axial nitrogen substituent than with an equatorial one.[115]

The geminal coupling constant, J_{AB}, between protons of a methylene group adjacent to oxygen or nitrogen is also found to vary with the spatial orientation of the adjacent lone pairs.[116,117,118] The geminal coupling constants of protons on an sp^3 hybridised carbon are generally negative,[119] but it has been found that they become less negative if adjacent lone pairs are parallel to the carbon-hydrogen bonds.

These two effects are possible criteria for the measurement of conformational equilibria as in Figure 3.1. Study of model compounds constrained in conformations with a) di-equatorial N-methyl groups and b) axial/equatorial N-methyl groups will give limits to Δae and J_{AB}. Comparison of these with the equilibrium system should provide some measure of the equilibrium constant, and hence the free energy difference between the conformations. These criteria have been applied by Riddell and Lehn to the tetrahydro-1,3-oxazine system,[118]

but lately criticism of such methods, especially the use of Δ ae, has been made on the basis of dipole measurements.[120]

Results and Discussion

As models compounds 3.3 and 3.4 were synthesised as in the experimental section. Compound 3.3 was considered to be a fair model for both N-methyl groups being equatorial, since the presence of a 5-axial methyl group would present very unfavourable non-bonded interactions to an axial N-methyl group. At room temperature the C_2 methylene protons of compound 3.3 are magnetically equivalent due to rapid ring and nitrogen inversion, but at low temperatures (ca. -60°) an AB quartet is observed, Δ ae and J_{AB} being obtained by standard procedures.

The structure of the diaza-bicyclo-[3,3,1]-nonane, 3.4, necessitates one alkyl group being axial, but it may not be an ideal model compound since the bicyclo-[3,3,1]-nonane system has been shown to exist as two flattened chairs,[121] and 3-aza-bicyclo-[3,3,1]-nonane hydrobromide has been found to have a similar conformation.[122] Since in compound 3.4 ring inversion is not possible, the C_2 protons show an AB quartet at room temperature.

1,3,5-trimethyl-hexahydropyrimidine, compound 3.5, was also included in this study, the Δ ae and J_{AB} parameters again being obtained at room temperature since the 5-methyl group, preferring the equatorial position, biases the ring inversion equilibrium to predominantly one conformation. However, a similar equilibria to compound 3.1 at the nitrogen atom is still possible.

In all these compounds the low field lines of the AB quartet are broader than the upfield lines; a triplet (J = 1.5 Hz) being observed for compound 3.5. These observations lead to the assignment of the low field lines to the equatorial proton in each case, since long range coupling through the "W plan" arrangement of bonds is possible to the C_4 protons.[123]

The Δ ae and J_{AB} results are presented in Table 3.1. It can be seen that the conformations of compounds 3.1 and 3.5 lie between the diequatorial and axial-equatorial extremes. Equilibrium constants, K , can be calculated and are presented in Table 3.2.

Considering the results for compound 3.5, the J_{AB} results appear more consistent than the Δ ae ones. This perhaps confirms the unreliability of using Δ ae as a measure of conformational equilibria. It might be expected that solvent effects, temperature, and anisotropic effects of remote groups would influence chemical shifts more than coupling constants.

Taking 0.7 $\pm$ 0.15 as an average equilibrium constant from the J_{AB} results for compound 3.4 a free energy difference between the di-equatorial and axial-equatorial conformations of 0.22 $\pm$ 0.1 kcal./mol. can be calculated. An entropy factor of $T\Delta S = RT\ln 2$ must be added to this value since there are two axial-equatorial conformations. The final free energy difference is then 0.6 $\pm$ 0.1 kcal./mol. at 33.5°C.

The equilibrium constants of 0.56 and 0.77 for 1,3-dimethyl-hexahydropyrimidine involve the assumption that Δ ae and J_{AB} for

TABLE 3.1 N.M.R. DATA FOR THE HEXAHYDROPYRIMIDINES

Temperature 33.5° except where stated

Compound	Solvent	Δae ± 0.01 p.p.m.	J_{AB} ± 0.2 Hz
3.1	$CDCl_3$ (-73°)	1.26	8.9
3.3	CH_2Cl_2 (-60°)	1.68	7.9
	CH_2Cl_2 (-75°)	1.65	7.9
3.4	$CDCl_3$	0.52	11.2
	CCl_4	0.52	11.0
	CH_2Cl_2	0.51	10.9
	CD_3OD	0.53	11.0
3.5	$CDCl_3$	1.04	9.1
	CCl_4	0.84	9.3
	CH_2Cl_2	1.00	9.1
	CD_3OD	1.17	9.2

TABLE 3.2 EQUILIBRIUM CONSTANTS (K) FOR EQUILIBRIA AT NITROGEN IN COMPOUNDS 3.1 and 3.4

Compound	Solvent	K from Δae	K from J_{AB}
3.1	$CDCl_3$	0.56*	0.77*
3.5	$CDCl_3$	1.23	0.57
	CCl_4	2.62	0.82
	CH_2Cl_2	1.39	0.67
	CD_3OD	0.80	0.72

* At -73°C, otherwise at 33.5°C

compound 3.4 do not alter with temperature - a condition which may not be met. Nevertheless a free energy difference of 0.4 ± 0.1 kcal./mol. at -73°C can be estimated as above from the J_{AB} result.

Another possible method of estimating the conformational equilibria involves the change in chemical shift, τ, of the axial C_2 proton in the 2-p-nitro-phenyl analogues of compounds 3.1 to 3.4. Introduction of this substituent in the 2 position should not change the conformation of the hexahydropyrimidine ring, but will lock it in the chair form with the 2-substituent in the more stable equatorial position. The results of this study are shown in Table 3.3. Although this method gave apparently consistent results in the tetrahydro-1,3-oxazine case,[118] the introduction of the p-nitrophenyl group in this case appears to have markedly altered the equilibrium in favour of the di-equatorial conformation. The origin of this change is not easily seen, and no explanation is put forward. Clearly more study of this type of system is required.

TABLE 3.3

CHEMICAL SHIFTS IN p-NITROPHENYL SUBSTITUTED HEXAHYDROPYRIMIDINES AT 33.5° (SOLVENT $CDCl_3$)

Compound with p-nitrophenyl in 2-equatorial position	C_2 axial Chemical Shift (τ value)	Equilibrium constant
3.1	6.95	0.13
3.3	7.11	-
3.4	5.71	-
3.5	7.00	0.03

The conclusions to be drawn from this work are that (a) in the 1,3-hexahydropyrimidines, 3.1 and 3.4, at least 40% of the molecules have an axial N-methyl group at room temperature, an observation that can be explained in terms of Eliel's "rabbit ear" effect;[34] and that (b) the free energy differences of ca. 0.5 kcal./mol. from coupling constants appear more reliable than those calculated from chemical shift differences, and agree well with that found by dipole measurements.[112] Eliel et.al. have recently synthesised and studied the above compounds by N.M.R. and agree with the results presented here.[124]

SECTION FOUR

RESTRICTED ROTATION IN PYRIDINE CARBOXYLIC ACID AMIDES

RESTRICTED ROTATION IN PYRIDINE CARBOXYLIC ACID AMIDES

Introduction

The N.M.R. method has been used to study the barriers to rotation in a variety of systems having partial double bonds.[125,126] Even from the earliest studies on dimethyl formamide[127] it was apparent that the method was subject to large errors, one source of which was the use of approximate formulae, such as the "peak height to valley" ratio method,[128] to determine rate and consequently thermodynamic parameters. Recently, however, fast large store computers have facilitated the use of the full line shape expression[129] needed for the calculation of accurate rate parameters. Such methods usually rely on the visual matching of a computed spectrum with the experimental one.

The present work was initially undertaken to test the potential of a slightly different approach to rate measurements[130] by N.M.R. The use of small digital computers on line to N.M.R. spectrometers is fairly widespread, their main application being the enhancement of signal-to-noise ratio. However, the digitised form of the spectrum also makes it easy to transfer to a large computer, programmed for spectral analysis. This digitised spectrum can then be compared by a least squares analysis to a calculated spectrum - thus avoiding visual comparison errors.

In this work the rotational barriers of the N,N-dimethyl amides of benzoic, picolinic, nicotinic, and isonicotinic acids were obtained by this method.

The N.M.R. Method

Although the following arguments are considered in terms of N,N-dimethyl amides, they can also be applied to any exchange broadened doublet.

Rotation about the carbon-nitrogen bond in amides can be considered as a first order equilibrium reaction with a rate constant, k, which is inversely related to the mean lifetime, τ, of the ground state. Assuming the time spent in the transition state is negligible compared to τ, when τ is small, i.e. there is fast rotation, a singlet is observed for the N-methyl signal. As increases the singlet broadens and then splits into two signals, corresponding to the now anisochronous N-methyl groups.

This change in lineshape depends not only on τ, but also on the transverse or spin-spin relaxation time, T_2, and on the final chemical shift difference, $\delta\omega$, between the N-methyl signals. A measure of T_2, which is assumed to remain constant with temperature, is obtained from the reciprocal of the half-width of the peaks after complete separation. $\delta\omega$, which is sometimes found to vary with temperature, is found by observing the separation of the peaks at several temperatures well below the coalescence phenomenon (at least 30° in the present work) and extrapolating in a linear manner to the appropriate temperatures.

The Computational Method

Experimental spectra are output on paper tape, via a small on-line computer, as a series of integers representing the height of the spectrum at small frequency intervals (ca. 0.03 Hz). A typical spectral output may be around 1200 points. Calculation in a large computer using this spectrum and $\delta\omega$ and T_2 as data proceeds as follows. The baseline of the spectrum is approximated to a straight line from a given number of points at the beginning and end of the data tape. After the baseline has been subtracted from the spectrum, the spectral area is obtained by integration and a preliminary line shape is calculated. The normalising constant of the line shape expression is varied until the areas of the calculated and experimental spectra are similar. The lifetime parameter, τ, is then allowed to change incrementally and a least squares analysis of the calculated and experimental spectra for each τ value is performed. This iterative procedure continues until the best fit, i.e. that with the least error, is found.

The output data consists of matched calculated and experimental spectra, together with all the τ values, and associated errors, used in a particular run. A typical time for such a run is around 11 minutes. For any one compound six or seven spectra would be treated in this manner. The rate constants, obtained from the τ values, are then used in the construction of Arrhenius plots.

Errors

Three different sources of error can be important in the above method. Firstly, a major instrumental source of error is that of temperature measurement. In the present work a thermocouple placed close to the sample in the coil was used. Although the use of an external standard which varies with temperature (e.g. the chemical shift difference between the methyl and hydroxyl proton signals of methanol for low temperature work) may give more accurate absolute temperatures, the temperatures in this study were internally consistent to at least $\pm$ 1°C ($\pm$ 0.02 units on the $1/T \times 10^3$ scale in Figure 4.2).

Secondly the phasing of the N.M.R. signals must be as good as possible, and must be checked at each temperature at which a spectrum is obtained. In a preliminary study of N,N-dimethyl nicotinamide a small discrepancy in the phasing of ca. 5°, barely noticeable to the eye, led to an energy of activation for the rotational barrier of about 2 kcal./mol. less than that now found. The free energy of activation of 14.7 kcal./mol. found in this work for N,N-dimethyl benzamide is significantly lower than that found by Mannschreck[131] (15.3 kcal./mol.): a phasing error may account for this.

A third source of error is in the measurement of T_2. Measuring a line width on a narrow peak is not an accurate procedure, an error of at least 10% being incurred. However, it has been shown[132]

that around coalescence calculated line shapes are insensitive to changes in T_2. The serious errors arising from this source are likely to come at the fast and slow exchange limits.

Results and Discussion

Figures 4.1 and 4.2 show the chemical shift variation with temperature and the Arrhenius plots for the pyridine carboxylic acid amides and N,N-dimethyl benzamide. Figure 4.3 gives some examples of the curve fitting obtained by the above method for N,N-dimethyl isonicotinamide. All fitted curves were of at least this standard. Table 4.1 gives the activation parameters associated with the rotational barriers. Since the principal source of error is probably in temperature measurement, and since these parameters are determined over a fairly small range of temperatures there are significant errors associated with enthalpies and entropies. Thus discussion is in terms of the free energy parameter $\Delta G^{\ddagger}$ at 25°C.

A linear regression coefficient of better than 0.99 was found for all the Arrhenius plots, while the use of standard statistical methods suggested the error on $\Delta G^{\ddagger}_{298}$ values was less than 0.1 kcal./mol.

Chemical Shift Variation with Temperature

Figure 4.1 shows that there is a slight linear variation in chemical shift difference with temperature. The origin of this effect may lie in either a solvent effect[133] or in a variation in the

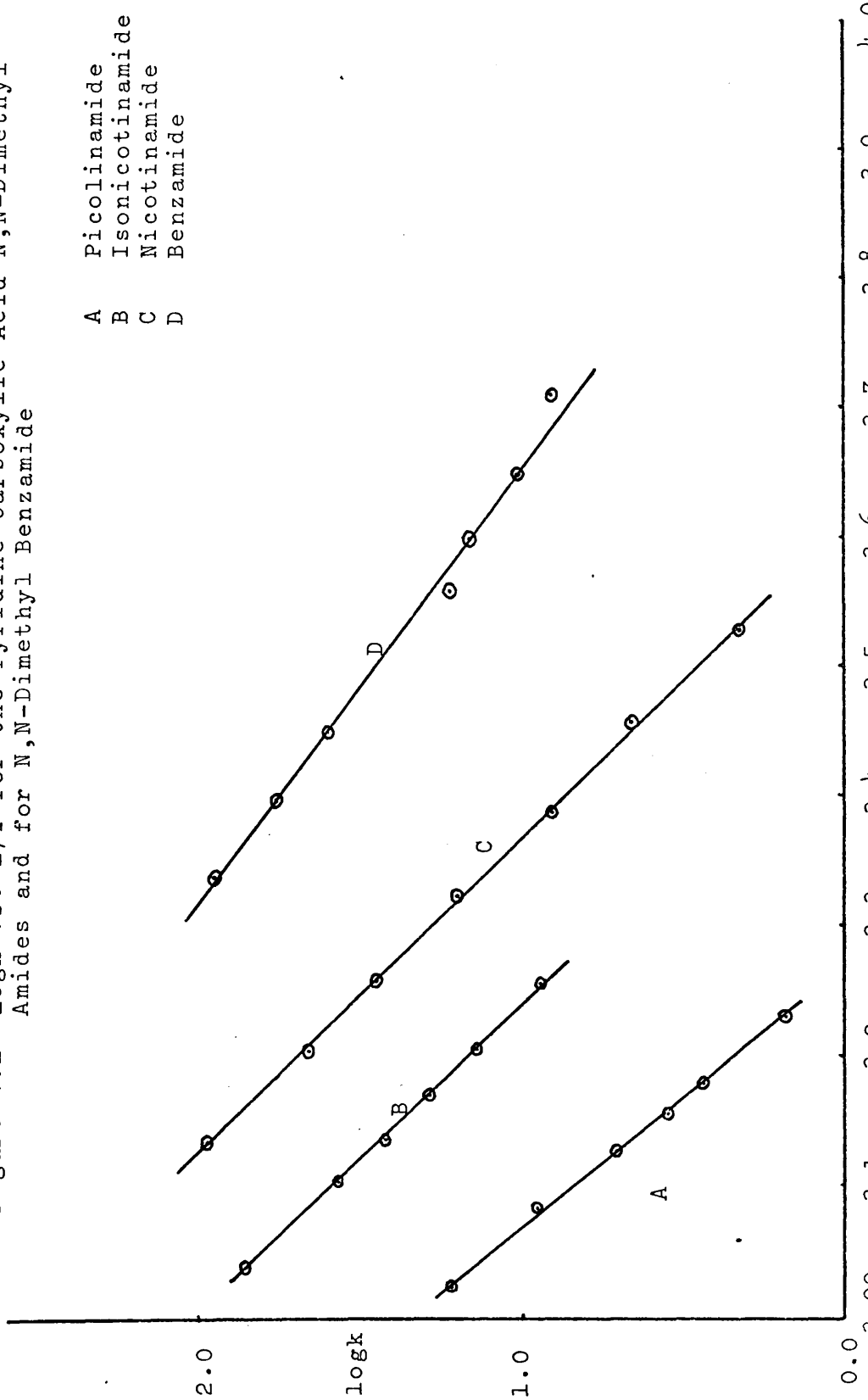
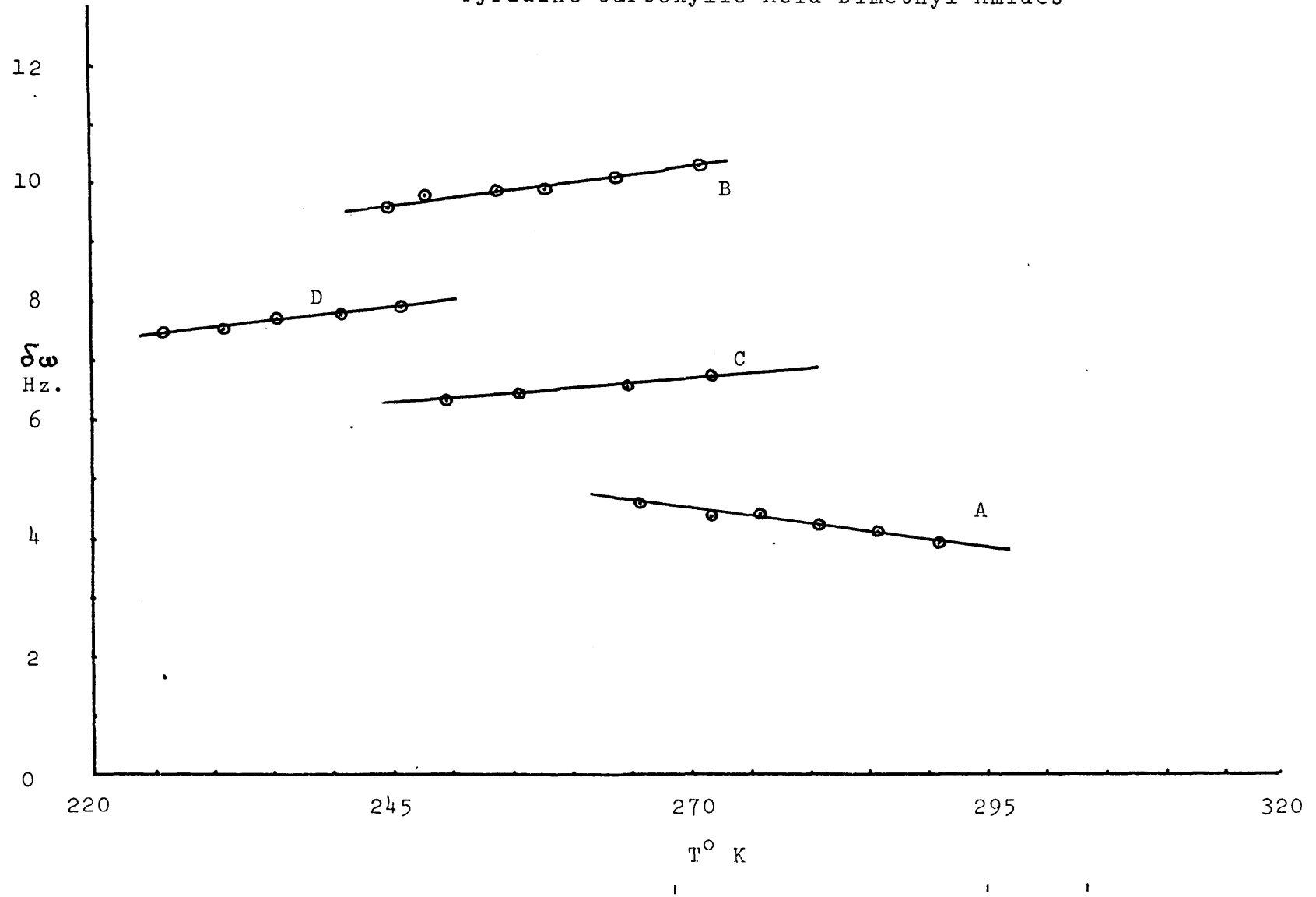


Figure 4.1 logk vs. 1/T for the Pyridine Carboxylic Acid N,N-Dimethyl Amides and for N,N-Dimethyl Benzamide

Figure 4.2 Chemical Shift Difference vs. Temperature for Pyridine Carboxylic Acid Dimethyl Amides



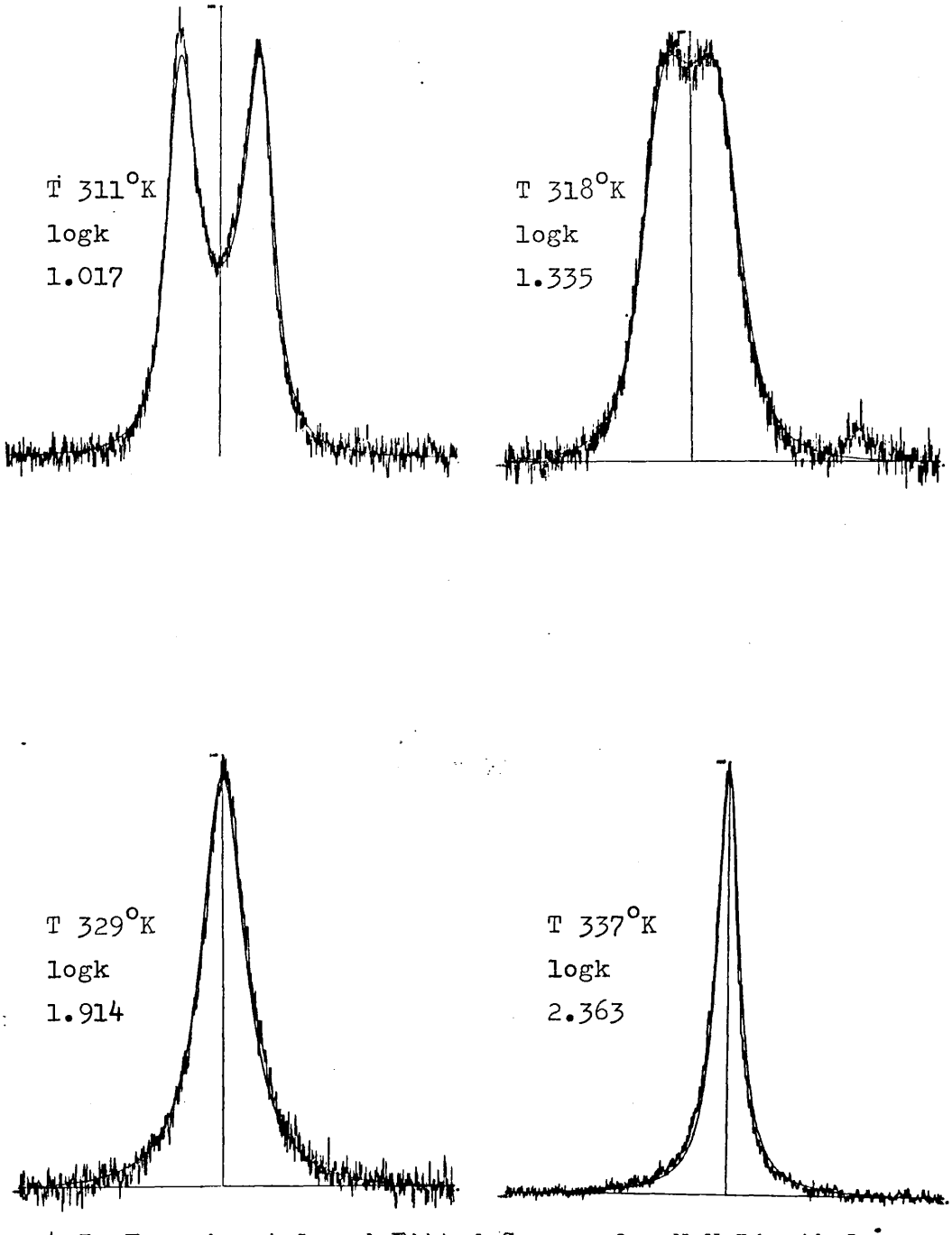


Figure 4.3 Experimental and Fitted Curves for N,N-Dimethyl Isonicotinamide

TABLE 4.1

THERMODYNAMIC DATA FOR THE PYRIDINE CARBOXYLIC ACID DIMETHYL AMIDES

N,N-dimethyl amide	E_A kcal./mol (a)	log γ (a)	$\Delta G^{\ddagger}_{298}$ kcal./mole (b)	T_c (c)
Benzamide	15.3	13.2	14.7 (d)	283
Picolinamide	22.2	15.9	17.9	319
Nicotinamide	18.9	14.9	15.9	298
Isonicotinamide	18.8	14.4	16.6	318

(a) Energy of activation and frequency factor from Arrhenius plots Figure 4.2

(b) Free energy of activation calculated using equation 1.7, $\pm$ 0.1 kcal./mol.

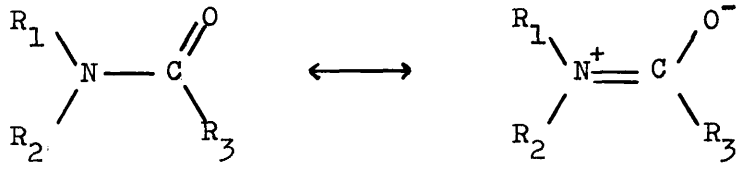
(c) Coalescence temperature ^{o}K

(d) c.f. Mannschreck's value of 15.3 kcal./mol. at 25^{o}C. [131]

population of the vibrational and rotational states with temperature.[134] Since the temperature range is small and since both the solvent, deuteriochloroform, and the amides are polar molecules, a variation in solvation is the more likely explanation. However, Jackman et.al.[135] found the chemical shifts did not vary in general in their study of some benzamides using a very polar solvent - acetonitrile.

Rotational Barriers

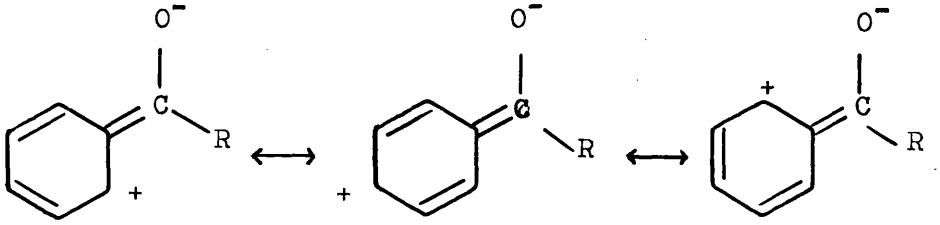
The barrier to rotation in amides is considered to arise from the partial double bond character of the carbon-nitrogen bond; the amide structure may be described as a resonance hybrid of 4.1a and 4.1b, with the dipolar form contributing about 40%.[136] In energy terms the barrier should be ca. 20 kcal./mole.



4.1a 4.1b

For a majority of symmetrically substituted amides, the most reliable results show the barrier to be in the 15 - 25 kcal./mol range, the exact figure depending on steric and electronic effects.

For example there is a marked difference in barrier between N,N-dimethyl benzamide, 15.3 kcal./mol.,[131] and N,N-dimethyl acetamide, 22.0 kcal./mol. This can be attributed to the mesomeric influence of the aromatic ring, the resonance form 4.2 competing with the nitrogen p electrons for conjugation with the carbonyl group. A reduction in the double bond character of the carbon-nitrogen bond results in a lower barrier. The stability of this resonance form will be affected by substituent groups.



$R = N(CH_3)_2$

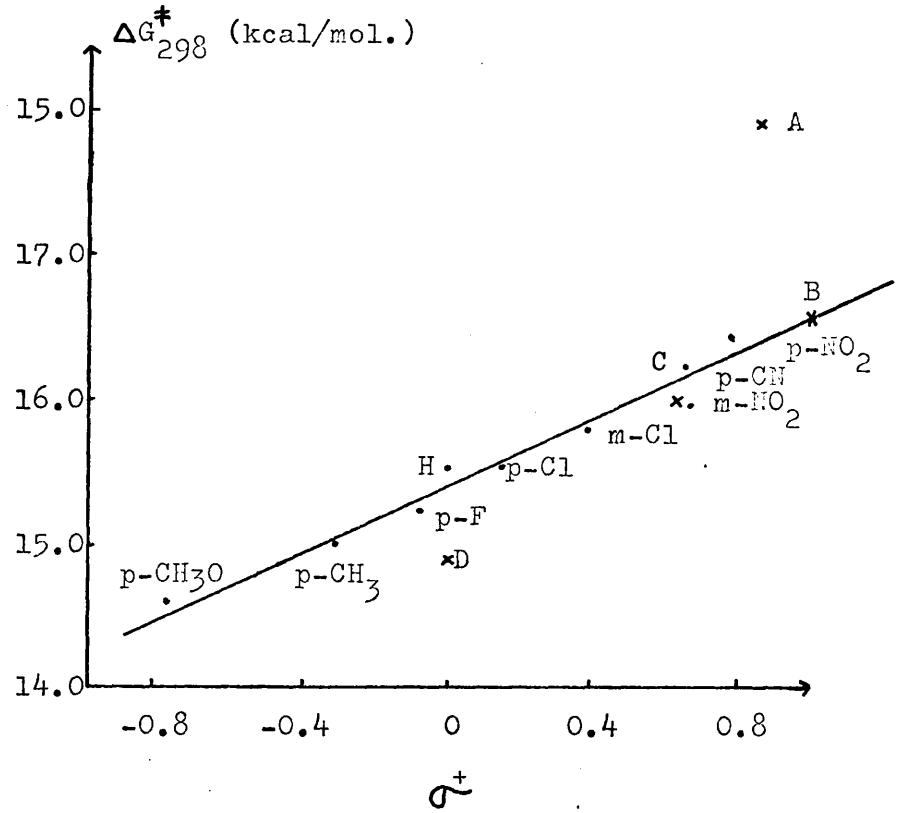
4.2

Considering the nitrogen atom of pyridine as a group with a positive inductive effect, the presence of the nitrogen in the ortho or para position with respect to the amide group decreases the stability of form 4.2 and the barrier increases over that for benzamide (Table 4.1). With nitrogen in the meta position the stability is not affected so much and the barrier increases to a lesser extent.

Jackman et. al.[135] have found a linear relationship between the free energies of activation in a series of meta and para substituted benzamides and the corresponding σ^+ substituent constants.[137] Considering nitrogen as a substituent in pyridine Jaffe found the σ values for aza substitution being ortho, meta, and para to a group on the ring to be 0.81, 0.62, and 0.93 respectively.[138] Favini and Simonetta[139] did not find good agreement either theoretically or empirically with these values when they studied the alkaline hydrolysis of the pyridine carboxylic acid esters, but they did find reasonable agreement when studying the hydrolysis of the corresponding amides. Thus using these parameters, the observed barriers for N,N-dimethyl isonicotinamide and nicotinamide fall on the Jackman line (Figure 4.4), correlating these results with his. A positive ρ^+ value (1.13) was found and confirms the idea of a barrier increase with increasing electron withdrawal and shows the barrier to be dependent on conjugation between the carbonyl and aromatic functions.

Using Jaffe's σ value for nitrogen in the ortho position for N,N-dimethyl picolinamide a large deviation from the line is observed, showing the presence of an ortho 'proximity' effect. Such effects are usually explained in terms of (a) steric effects, e.g. the rotational barrier in o-nitro-N,N-dimethyl benzamide (18.5 kcal./mol.)[135] is very much greater than that for N,N-dimethyl benzamide because the planarity of the ring-carbonyl

Figure 4.4 $\Delta G^{\ddagger}$ vs. σ^{+} for N,N-dimethylbenzamides and the Pyridine Carboxylic Acid Dimethyl Amides



Only some of the values found by Jackman et.al. are shown.

A Picolinamide

B Isonicotinamide

C Nicotinamide

D Benzamide

overlap is disturbed by the steric interactions of the nitro and amide group;[125] or (b) by an electronic interaction between the groups which could stabilise or destabilise the ground state.

Either type of interaction in this case seems unlikely since the nitrogen lone pair is not as large as a nitro group and would not appear to have any direct polar interaction with the amide function. A possible explanation may lie with a solvation effect: the lone pair of the nitrogen associating with a solvent molecule and thereby increasing its spatial requirement.

SECTION FIVE

EXPERIMENTAL

EXPERIMENTAL

N.M.R. Spectra

The 60 MHz spectra were all run in ca. 15% w/v solutions at 33.5°C, except where stated, on a Perkin-Elmer R10 instrument fitted with the standard variable temperature device.

^{13}C spectra were also run on the R10 at 33.5°C using an 8.5 mm probe and neat liquids as samples.

100 MHz spectra were obtained from a Varian HA100 instrument and 220 MHz spectra from the S.R.C. instrument at Runcorn.

Computing

All programs, written in Fortran IV or Algol, were processed by an Elliot 4100, while spectral accumulations and digitised spectral output were done by a Digiac computer on line to the N.M.R. spectrometer.

G.L.C.

Perkin-Elmer F11 gas chromatographs were used for analytical samples, while a Varian Aerograph 700 were used for preparative work. A Carbowax 20M + KOH on chromosorb W column was found suitable for the separation of N-methyl tetrahydro-1,2-oxazines, and both a 1½% fluorosilicone oil on AW DMCS chromosorb W column and a 15% silicone grease on chromosorb P column were used for N-carbethoxy-oxazines. Typical retention times with a temperature of 180°C for the N-carbethoxy compounds and 90°C for

the N-methyl compounds were ca. 10-20 min., using a carrier gas (N_2) pressure of 5 p.s.i.

Synthetic Routes to the N-Methyl-Tetrahydro-1,2-Oxazines

The experimental procedures in the synthesis of the tetrahydro-1,2-oxazines are illustrated in Figures 5.1 to 5.8. Each reaction stage is numbered and the experimental details are recorded in numerical order. Similar preparations are recorded under the same number and a typical example is given.

1. N-hydroxyurethane[141]

Finely powdered hydroxylamine hydrochloride (292.5g., 4.5 mol.) and anhydrous potassium carbonate (570g., 4.1 mol.) were added to diethyl ether (2.3 l.) and water (30 ml.). This mixture was stirred vigorously while ethyl chloroformate (450g., 4.2 mol.) was added dropwise over ca. 3 hr. Heat and carbon dioxide were evolved during the addition, and the mixture turned slightly yellow over 48 hr. The ether layer was decanted and the remaining sludge washed with ether (4 x 500 ml.). The combined extracts were dried over magnesium sulphate and evaporated. Distillation gave N-hydroxyurethane (290g., 2.8 mol., 66%) b.p. 108-110°/3 mm, (literature b.p. 113-116°/3 mm).

2. Condensation of N-hydroxyurethane with 1,4-dibromo-alkanes

The following general procedure, illustrated by the reaction of 1,4-dibromobutane with N-hydroxyurethane, was finally adopted.

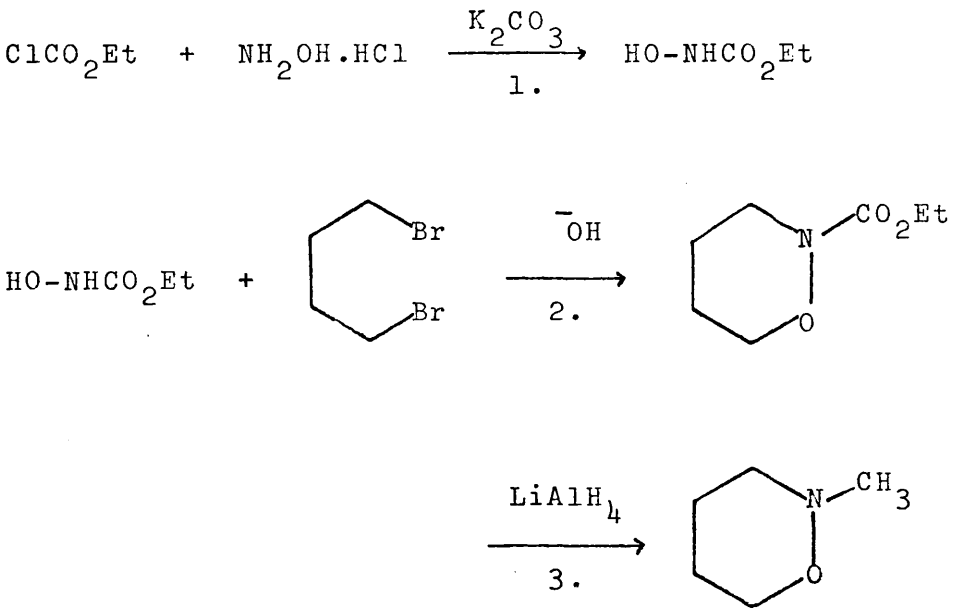


Figure 5.1 Preparation of N-Methyl-Tetrahydro-1,2-Oxazine

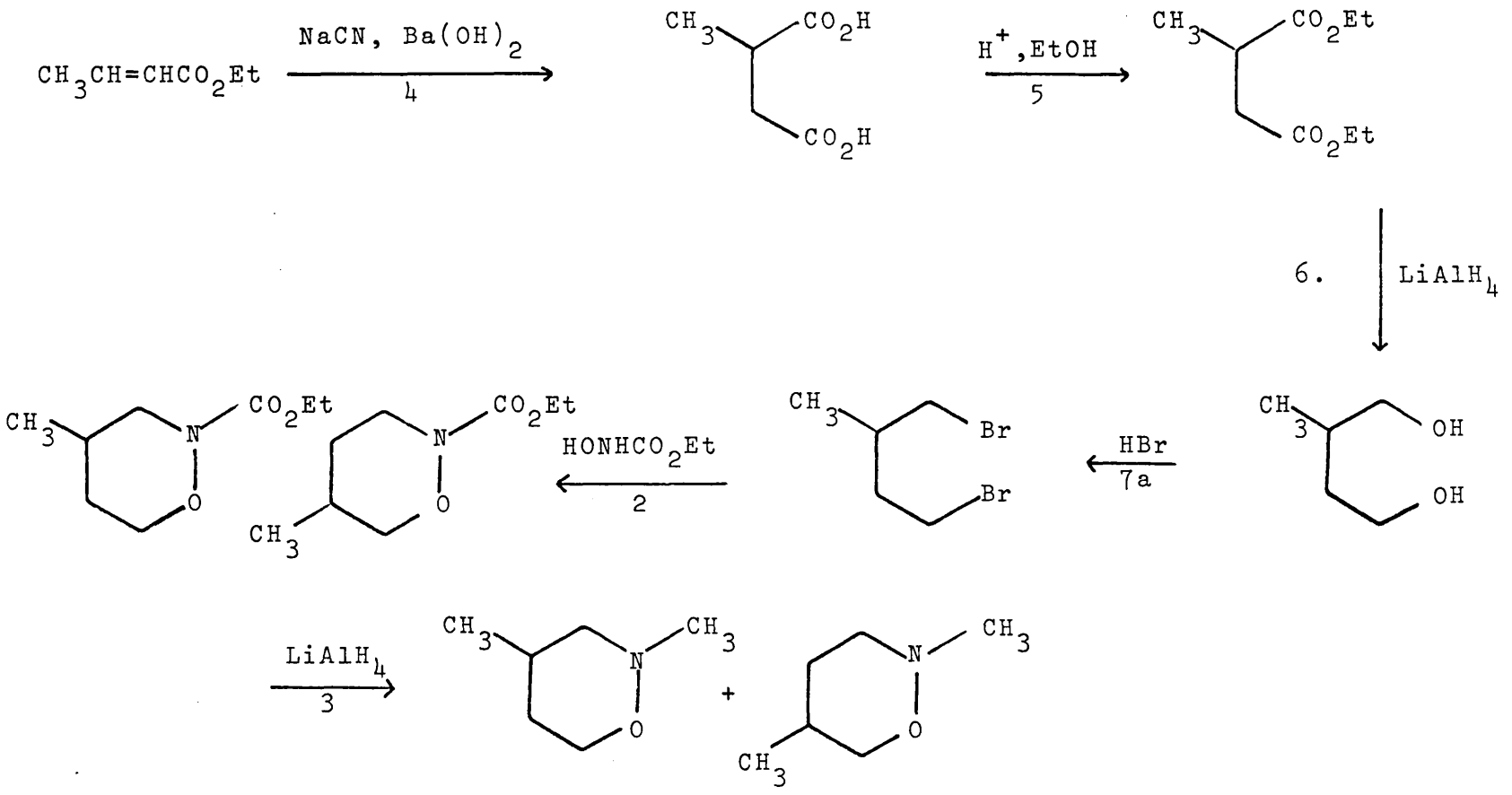
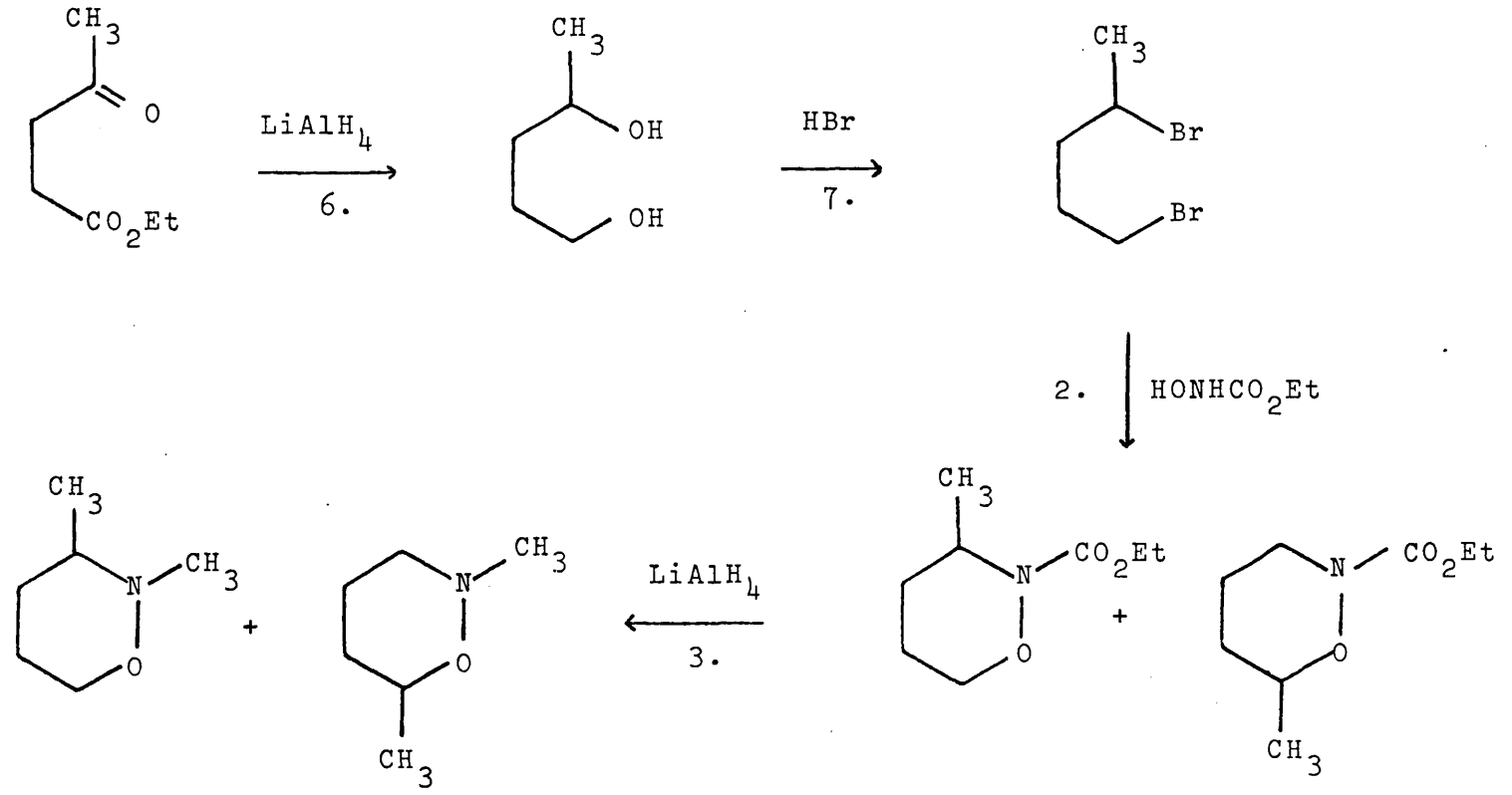


Figure 5.2 Preparation of 4 and 5,N-Dimethyl-Tetrahydro-1,2-Oxazines



Separated G.L.C.

Figure 5.3 Preparation of 3 and 6,N-Dimethyl-Tetrahydro-1,2-Oxazines

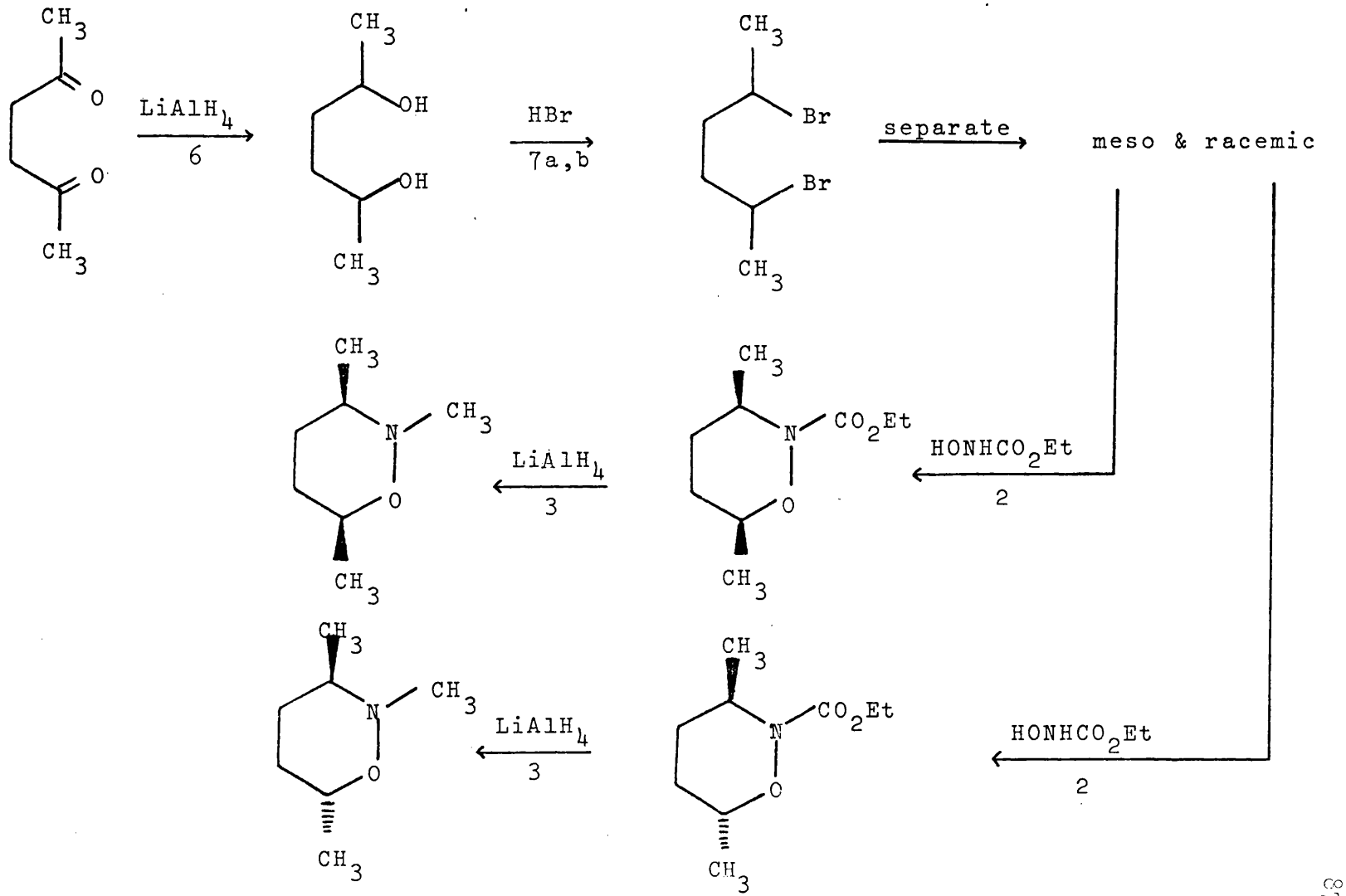


Figure 5.4 Preparation of cis and trans 3,6,N-Trimethyl-Tetrahydro-1,2-Oxazines

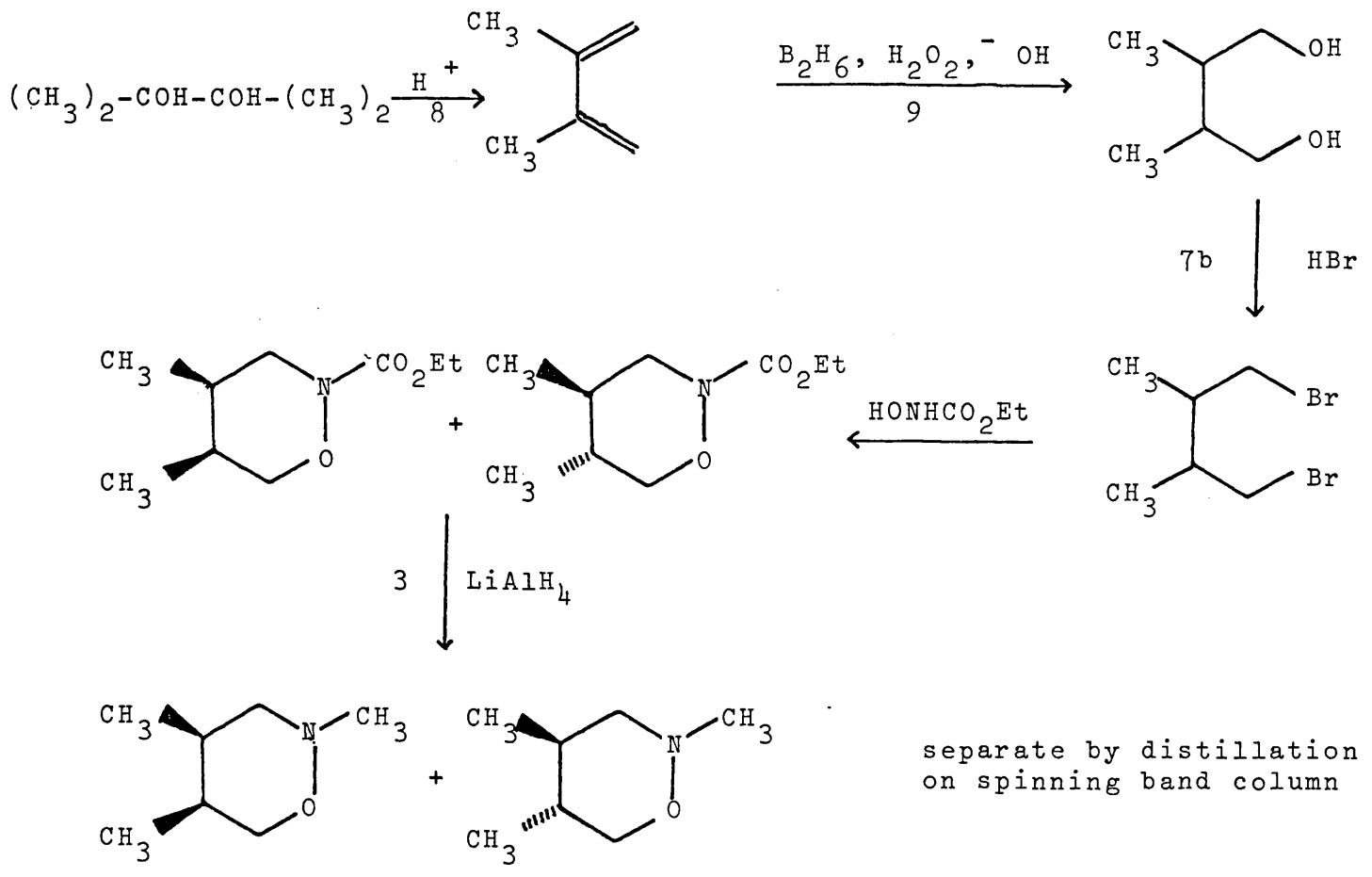


Figure 5.5 Preparation of cis and trans 4,5,N-Trimethyl-Tetrahydro-1,2-Oxazines

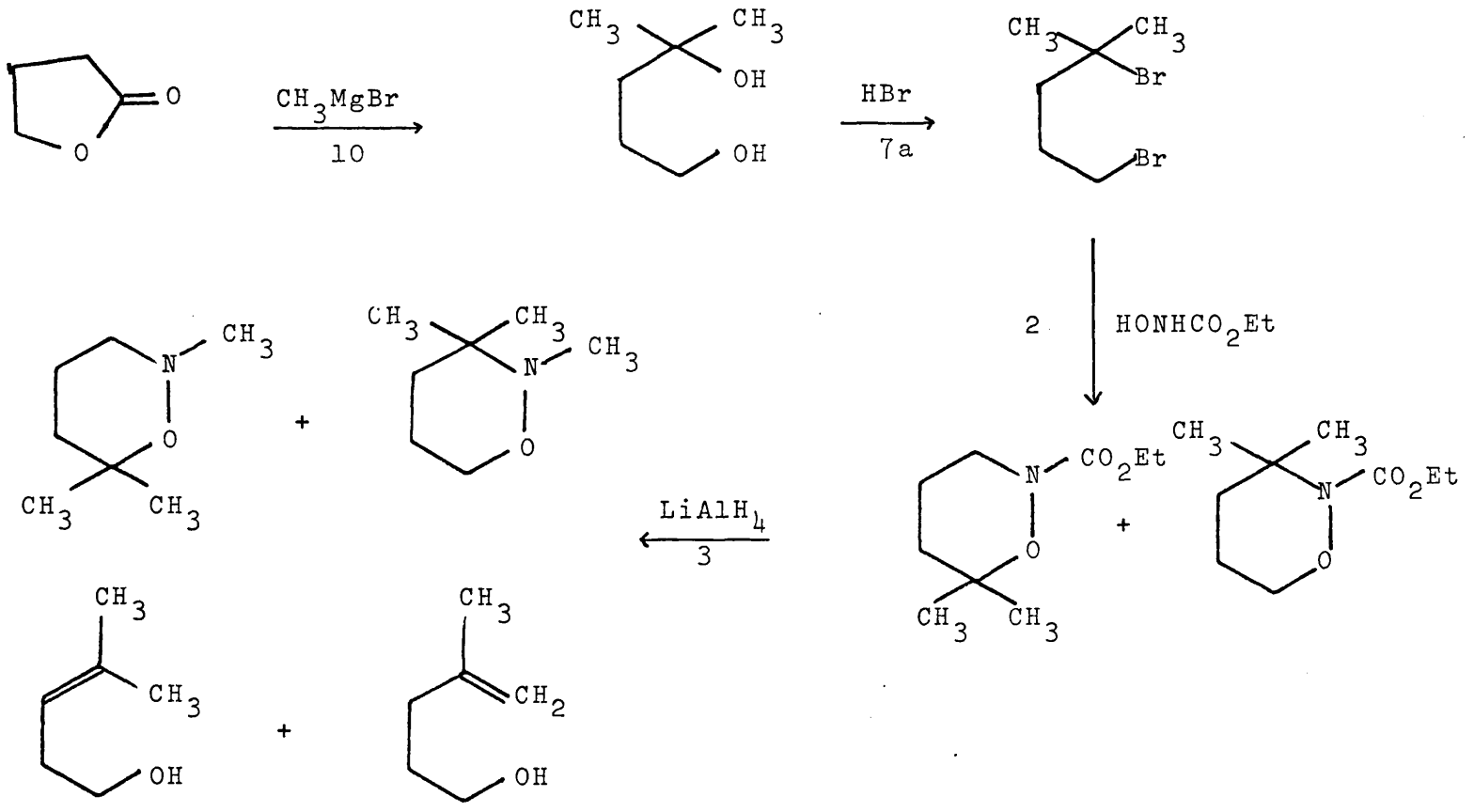


Figure 5.6 Preparation of 3,3,N and 6,6,N Trimethyl-Tetrahydro-1,2-Oxazines

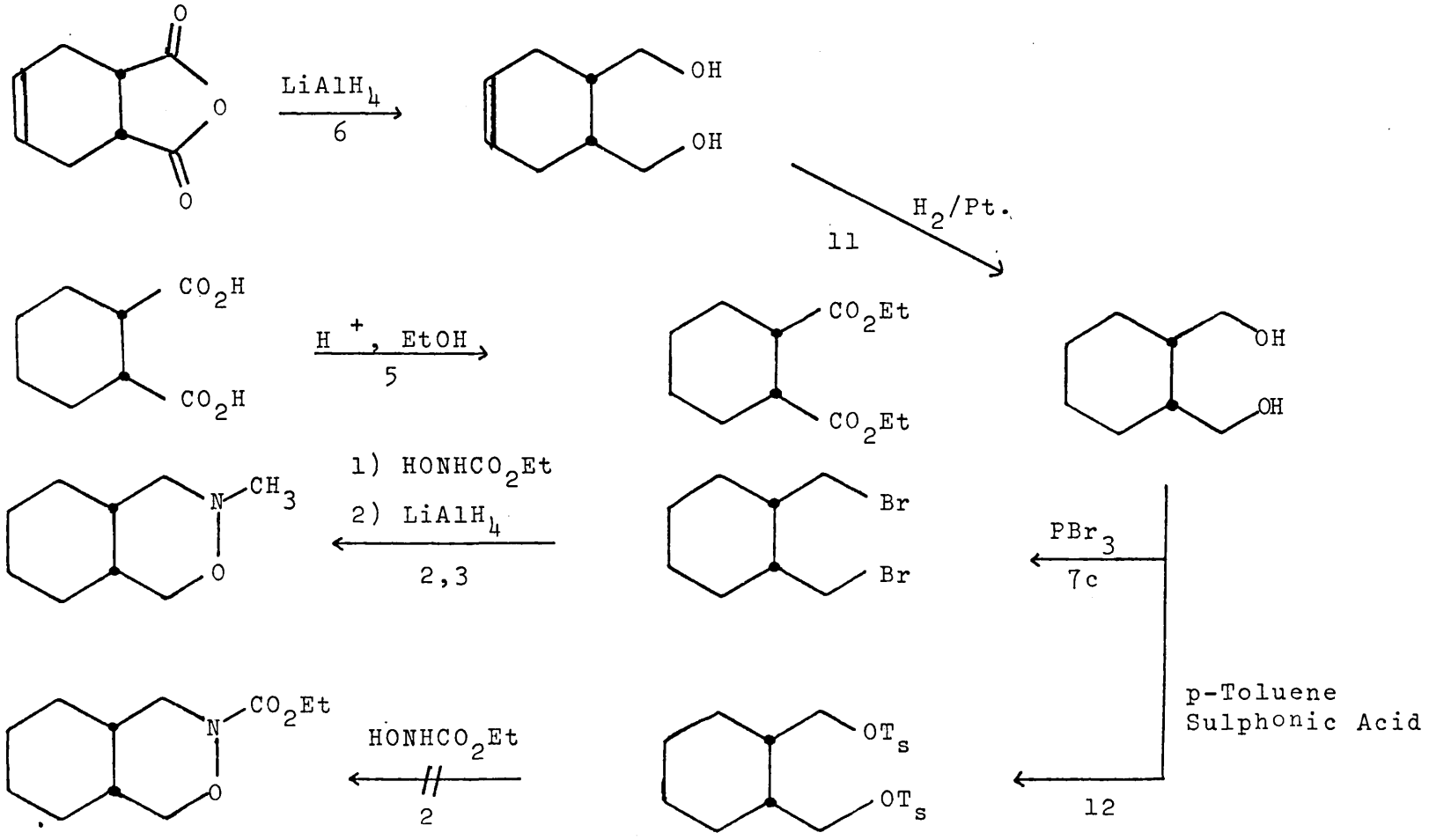


Figure 5.7 Preparation of 2-oxa-3-aza-3-methyl-cis-decalin

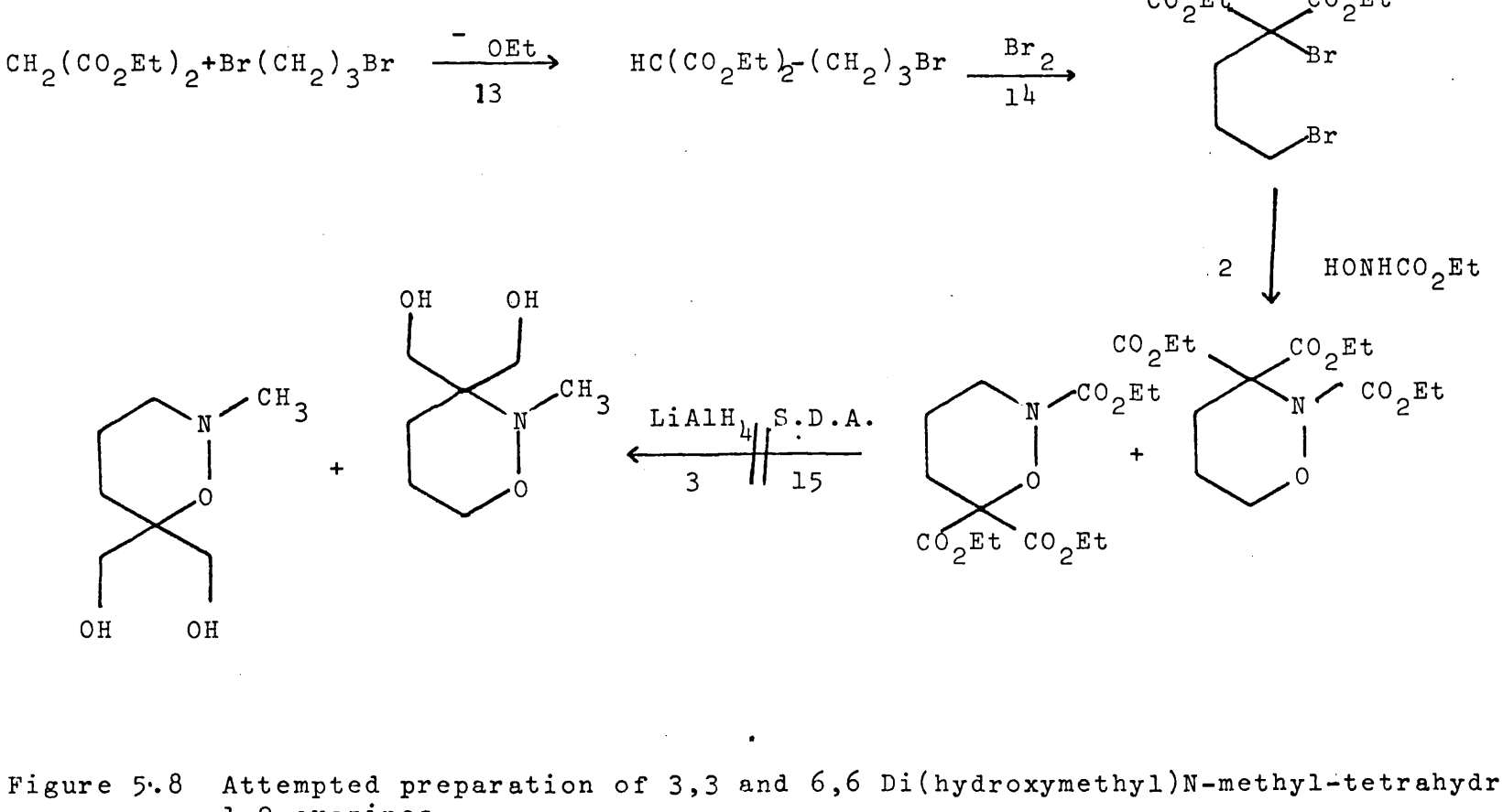


Figure 5.8 Attempted preparation of 3,3 and 6,6 Di(hydroxymethyl)N-methyl-tetrahydro-1,2-oxazines

N-hydroxyurethane (63g., 0.6 mol.), potassium hydroxide (33.6g., 0.6 mol.), and 1,4-dibromobutane (43.2g., 0.2 mol.) in absolute ethanol (300 ml.) were refluxed on a water bath for 6 hr. The solution was decanted from the pale yellow residue which was washed with ethanol (3 x 50 ml.), and the combined extracts were evaporated to leave a crude mixture of N-hydroxyurethane and product. To this oil was added an equal volume of water, and this mixture was shaken vigorously. The two resulting layers were separated and the aqueous layer washed once with an equal volume of ether. The ether extract and organic layer were combined, dried over magnesium sulphate and evaporated. Distillation gave N-carbethoxy-tetrahydro-1,2-oxazine (23g., 0.14 mol., 72%) b.p. 58-62°/0.25 mm, (literature 113-116°/12 mm).[76]

In some preparations a 2:1 ratio of base and N-hydroxyurethane to dibromide was used, but yields were lower (ca. 30%). Table 5.1 gives the boiling points and yields for several of the N-carbethoxy-tetrahydro-1,2-oxazines that were prepared.

3. Lithium Aluminium Hydride Reductions of N-carbethoxy-tetrahydro-1,2-oxazines

The following general procedure was finally adopted. This illustration is the preparation of 2-oxa-3-aza-3-methyl-cis-decalin (Compound 2.26).

The N-carbethoxy-oxazine, 2.23, (7g., 0.03 mol.) in dry ether (10 ml.) was added cautiously to a solution of lithium aluminium hydride (2.7g., 0.07 mol.) in dry ether (20 ml.). After stirring for 1 hr. water (3 ml.), 50% sodium hydroxide solution (3 ml.)

TABLE 5.1

BOILING POINTS AND YIELDS FOR N-CARBETHOXY-TETRAHYDRO-1,2-OXAZINES

Compound	b.p. °C	Yield %	Ratio[a]
2.3	58-62°/0.25 mm	30	2:1
		70	3:1
2.5 and 2.11[c]	b	30	2:1
2.7 and 2.9[c]	-	29	2:1
2.13	-	58	3:1
2.17 and 2.19[c]	122°/4 mm	41	2:1
2.21 and 2.23[c]	135°/2 mm	71	3:1
2.25	114°/1.5 mm	26	2:1
2.27	185°/6 mm	10	2:1

a: Ratio of base and N-hydroxyurethane to dibromide

b: Separated by G.L.C.

c: Mixtures

and water (10 ml.) were added to the mixture, and the ether decanted. The residual sludge was washed with ether (3 x 30 ml.), and the extracts were combined and dried over magnesium sulphate. The ether was distilled off through a 25 cm. Vigreux column; a small amount of ethanol also distilled after the ether. The residue yielded on distillation the oxazine 2.26 (3.0g., 0.019 mol., 64%), b.p. 68°/5 mm.

Initially these preparations were worked up as follows: the ether extracts were washed with dilute hydrochloric acid, the acid layer evaporated to dryness, and the residue taken up in a minimum volume of water. Sodium hydroxide pellets were then added until the solution was strongly basic. At this point the oxazines would form a separate layer which was taken off and distilled. This procedure, however, gave only 20-30% yields.

4. Methyl Succinic Acid

This was prepared by a literature method.[142] Starting from ethyl crotonate (92.1g., 0.8 mol.), methyl succinic acid (68g., 0.5 mol., 64%) was obtained, m.p. 108-111° (literature 110-111°).

5. Esterification Procedure[143]

The following general procedure, illustrated by the preparation of diethyl-cis-hexahydrophthalate, was used.

Commercial cis-hexahydrophthalic acid (100g., 0.58 mol.) was added to dry ethanol (300 ml.), dry benzene (600 ml.), and concentrated sulphuric acid (2 ml.). After refluxing for 30 hr., the mixture was poured into water (1 l.), the benzene layer separated,

TABLE 5.2 ANALYTICAL DATA FOR THE PICRATES OF THE N-METHYL-TETRAHYDRO-1,2-OXAZINES

Compound	Picrate Formula	Found %			Formula Requires %		
		C	H	N	C	H	N
2.26	$C_{12}H_{16}N_4O_8$	41.85	4.65	16.21	41.86	4.68	16.27
2.8 and 2.10[a]	"	41.70	4.50	16.31	"	"	"
2.14	$C_{13}H_{18}N_4O_8$	43.68	5.08	15.80	43.57	5.07	15.63
2.16	"	43.42	5.07	15.78	"	"	"
2.22	"	43.71	5.06	15.75	"	"	"
2.24	"	43.70	5.08	15.82	"	"	"
2.26	$C_{15}H_{20}N_4O_8$	46.72	5.20	14.40	46.88	5.25	14.58

a: Analysed as a mixture

and the aqueous layer washed with ether (3 x 100 ml.). The benzene and ether extracts were combined, dried over magnesium sulphate, and evaporated. Distillation of the residue gave diethyl-cis-hexahydrophthalate (84g., 0.36 mol., 64%) b.p. 122°/5 mm. (literature 133°/10 mm.)

Other esters prepared in this manner were:

ethyl levulate b.p. 107-109°/12 mm. (literature 205-206°/760 mm) yield 65%

diethyl methylsuccinate b.p. 120-124°/4 mm. (literature 121-123°/4 mm) yield 60%

6. Lithium Aluminium Hydride Reductions of Esters and Ketones

These preparations were carried out in essentially the same manner as the reductions of the N-carbethoxy compounds (para.3 above). Table 5.3 shows the diols prepared, the starting materials, boiling points, molar ratio of hydride to starting material, and yields.

7. 1,4-Dibromides

These compounds were prepared from the corresponding 1,4 diols by one of the following three methods:

(a) Hydrobromic Acid and Hydrogen Bromide[144]

This method is illustrated by the preparation of 2-methyl-1,4-dibromobutane.

2-methyl-butane-1,4-diol (7g., 0.07 mol.) and 48% hydrobromic acid (35 ml.) were mixed, left to stand overnight, and then refluxed for 2 hr. Two layers were observed at this point - the

TABLE 5.3 DIOLS FROM LITHIUM ALUMINIUM HYDRIDE REDUCTIONS

Starting compound	Diol	Hydride:Substrate Ratio	Observed b.p. °C	Literature b.p. °C	Yield %
Methyl succinic acid	2-methyl butane-1,4-diol	3:2	96-100°/2 mm	98°/2 mm	50
Ethyl laevulate	Pentane-1,4-diol	3:4	107-108°/4 mm	95-96°/1.5 mm	47
Hexane-2,5-dione	Hexane-2,5-diol	1:2	-	85-87°/1 mm	75
Tetrahydro-phthalic anhydride	tetrahydro-cis-Δ3-phthalyl alcohol	1:1	-	130-137°/1.0 mm 1.5 mm	78
Diethyl-cis-hexa-hydrophthalate	cis-hexahydro-phthalyl alcohol	1:1	-	138-141°/1.5 mm	90

lower dark brown, the upper almost colourless. Hydrogen bromide gas, generated by the action of concentrated sulphuric acid on hydrobromic acid, was passed into the solution for ca. 15 min. until saturation of the solution was considered complete. The mixture was refluxed for a further 2 hr. After cooling, the reaction was poured on to ice (ca. 25g.), and extracted with chloroform (3 x 30 ml.). The chloroform extracts were combined, washed with water (1 x 50 ml.), dried over magnesium sulphate, and evaporated. The residue gave on distillation 2-methyl-1,4-dibromobutane (9g., 0.04 mol., 58%) b.p. 36°/0.1 mm (literature 63-64°/3 mm.)

(b) Anhydrous Hydrogen Bromide[145]

This procedure is illustrated by the preparation of 2,3-dimethyl-1,4-dibromobutane.

2,3-dimethyl-1,4-dibromobutane (49g., 0.4 mol.) was heated on a boiling water bath while anhydrous hydrogen bromide was passed in for 5 hr. The resulting mixture was cooled and poured into ether (200 ml.) and water (500 ml.). The ether phase was separated, and washed with ice-cold concentrated sulphuric acid (10 ml.), water (50 ml.), 10% sodium carbonate solution (ca. 100 ml.), and finally twice more with water (100 ml.) After drying over magnesium sulphate and evaporating the ether, the crude product was distilled to give 2,3-dimethyl-1,4-dibromobutane (70g., 0.28 mol., 68%) b.p. 96-100°/11 mm. (literature 106-8°/22 mm).

(c) Phosphorous Tribromide[146]

The example chosen to illustrate this method is the preparation of cis-hexahydrophthalyl-dibromide.

Phosphorous tribromide (85g., 30 ml., 0.3 mol.) was added to cis-hexahydrophthalyl alcohol (44g., 0.3 mol.) cooled to ca. -10° in an ice/salt bath. The mixture was stirred and allowed to come to room temperature. Hydrogen bromide was given off at this point. The mixture was heated until no further hydrogen bromide was liberated. Water (100 ml.) was added, and the product extracted with methylene chloride (3 x 100 ml.). The extracts were washed with 10% sodium carbonate solution (100 ml.) and water (200 ml.) before being dried over magnesium sulphate. The solvent was evaporated to give cis-hexahydrophthalyl-dibromide (48g., 0.18 mol., 59%). No further purification was attempted since both I.R. and N.M.R. spectra suggested greater than 90% purity. (literature b.p. 112-3°/2.5 mm.)

Table 5.4 shows the dibromides prepared, the method of preparation, boiling points, and yields.

The meso and racemic 2,5-dibromohexanes were separated by freezing the crude mixture in liquid nitrogen, and then filtering off the solid meso compound as the mixture warmed up. The meso isomer was then recrystallised from benzene.

8. 2,3-Dimethyl-1,3-Butadiene

This was prepared by the standard method[147] of dehydrating pinacol. From pinacol (400g., 3.3 mol.) 2,3-dimethyl-1,3-butadiene (157g., 1.9 mol.) was obtained (58%) b.p. 69-71° (literature 69-71°).

TABLE 5.4 PHYSICAL DATA FOR 1,4-DIBROMIDES

Dibromide	Preparative Method	Observed b.p. °C	Literature b.p. °C	Yield %
2-methyl-1,4-dibromo butane	a	36°/0.1 mm	63-64°/3 mm	58
1,4-dibromo-pentane	a	64°/4 mm	99°/4 mm	58
2,5-dibromo-hexane				
meso)	a	m.p. 37°	m.p. 38°	71
racemic)	a	-	94°/13 mm	
"	b	-	"	89
2,3-dimethyl-1,4-dibromo butane	b	96-100°/11 mm	106-8°/22 mm	
2,5-dimethyl-2,5-dibromo hexane	c	m.p. 68°	m.p. 65°	90
cis-hexahydro-phthalyl dibromide	c	-	112-3°/2.5 mm	59

9. Hydroboration of 2,3-Dimethyl-1,3-Butadiene[89,90]

Because of the reactivity of diborane with air and water, solvents were carefully dried before use, and the whole procedure was done under nitrogen.

Diborane was prepared by the addition of boron trifluoride diethyl etherate (71g., 0.5 mol.) to sodium borohydride (19g., 0.5 mol.). The diborane, which was evolved rapidly at room temperature, was passed into a stirred solution of 2,3-dimethyl-1,3-butadiene (11.5g., 16 ml., 0.2 mol.) in tetrahydrofuran (200 ml.), cooled to ca. 0° in an ice/salt bath. When the evolution of diborane had stopped (ca. 1 hr.) the solution was allowed to stir for 0.5 hr. at room temperature. Excess diborane in the solution was destroyed by cautious addition of water. 3M sodium hydroxide solution (48 ml.) was added, followed by 30% hydrogen peroxide (48 ml.). The reaction was allowed to stand for 1 hr. before potassium carbonate (150g.) was added. The tetrahydrofuran layer was separated, the aqueous layer washed with ether (3 x 100 ml.), and the extracts and tetrahydrofuran combined and dried over anhydrous potassium carbonate. Evaporation and distillation gave 2,3-dimethyl-1,4-butane diol (10g., 0.09 mol., 43%). b.p. $102\text{-}3^{\circ}/1$ mm. n_D^{25} 1.4518.

10. 4-Methyl-1,4-Pentane diol[148]

Methyl bromide, prepared by a standard method,[149] was passed into dry ether (700 ml.) containing dry magnesium turnings (65g., 2.7 mol.). The solution was stirred until all the magnesium had reacted (ca. 2 hr.), and then the methyl bromide supply was

stopped. Freshly distilled butyrolactone (80g., 0.93 mol.) in dry ether (100 ml.) was added over 1 hr. After stirring for a further hour and standing overnight, the mixture was hydrolysed with saturated ammonium chloride solution, and the product was isolated by continuous ether extraction for 100 hr. Distillation gave 4-methyl-1,4-pentane diol (40g., 0.34 mol., 38%) b.p. 122°/10 mm. (literature 126-7°/16 mm.)

2,5-Dimethyl-2,5-hexane diol was prepared in the same manner yield 40% m.p. 86-88° (literature 87-88°).

11. Catalytic Hydrogenation

The reduction of cis-tetrahydro-Δ3-phthalyl alcohol was carried out in the standard manner[150] using Adam's catalyst in an atmospheric pressure hydrogenator.

12. cis-Hexahydrophthalyl Alcohol Ditosylate[151]

cis-Hexahydrophthalyl alcohol (7g., 0.05 mol.) was added slowly to a solution of p-toluene sulphonic acid (19g., 0.1 mol.) in pyridine (25 ml.). A yellow colouration was noted, and the mixture became warm. On evaporation of the pyridine a yellow oil (20g.) remained. N.M.R. suggested this to be the desired product, but the literature suggested[151] the product should be a crystalline solid, m.p. 80-82°. No attempt at purification was made.

13. 3-Bromopropyl-Diethylmalonate[152]

Diethylmalonate (80g., 0.5 mol.) was heated at 50° for 1 hr. with a solution of sodium ethoxide (17g., 0.26 mol.) in ethanol (80 ml.). On cooling, this solution was added dropwise to

1,3-dibromopropane (54g., 0.27 mol.) in ether (75 ml.). After stirring and refluxing for 48 hr. the mixture was poured into water (200 ml.); the organic layer was separated, washed with water, and dried over magnesium sulphate. After evaporation, the residue was distilled to give 3-bromopropyl-diethylmalonate (10g., 0.04 mol., 14%) b.p. 170°/15 mm. (literature 167°/15 mm.).

1,1,5,5-tetracarbethoxy-pentane is a major side product, but since its boiling point is 192°/3 mm, the malonate is easily separated by distillation.

14. (3-Bromopropyl)-Bromodiethylmalonate[153]

Bromine (5g., 0.03 mol.) was added to a solution of 3-bromopropyl diethylmalonate (8g., 0.03 mol.) in carbon tetrachloride (20 ml.). After refluxing for 2 hr. and standing overnight, the mixture was washed with sodium carbonate solution (5 x 20 ml.), and the solvent evaporated after drying over magnesium sulphate. Distillation gave (3-bromopropyl)-bromodiethylmalonate (8g., 0.02 mol., 66%) b.p. 154°/3 mm. This material showed signs of decomposition upon standing for 12 hr.

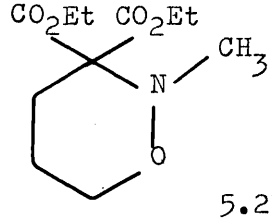
15. Reduction of 3,3,N-tricarbethoxytetrahydro-1,2-oxazine

This reduction was attempted using sodium dihydro-bis-(2-methoxy-ethoxy)-aluminate (S.D.A. 5.1) as a 70% solution in

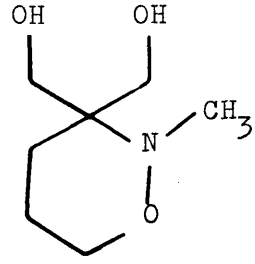
$$NaAlH_2[OCH_2CH_2OCH_3]_2 \qquad 5.1$$

benzene.

3,3,N-tricarbethoxy-tetrahydro-1,2-oxazine (5g., 0.015 mol.) in dry ether (50 ml.) was added to 70% SDA solution (16.2 mls.) in ether (50 ml.). After stirring overnight, 2M sodium hydroxide solution was added to the mixture until all reaction had stopped. The organic layer was decanted, and the white residue washed with ether (3 x 50 ml.). The ether extracts were combined, and, after drying over magnesium sulphate, were evaporated to give ca. 1.5g of a brown, viscous oil. T.L.C. on silica gel using chloroform as the elutant showed several spots, while NMR suggested the principal product to be Compound 5.2 not Compound 5.3 as was desired.



5.2



5.3

Reduction of 3,3,N-tricarbethoxy-tetrahydro-1,2-oxazine with lithium aluminium hydride also failed to give the desired product.

Reduction of 3,3-dimethyl-N-carbethoxy-tetrahydro-1,2-oxazine (Compound 2.17) using S.D.A. in a similar manner gave an unidentified product.

Synthetic Routes to the Hexahydropyrimidines

The reaction schemes followed to the hexahydropyrimidines are shown below in Figures 5.9 to 5.12. Again each reaction is numbered.

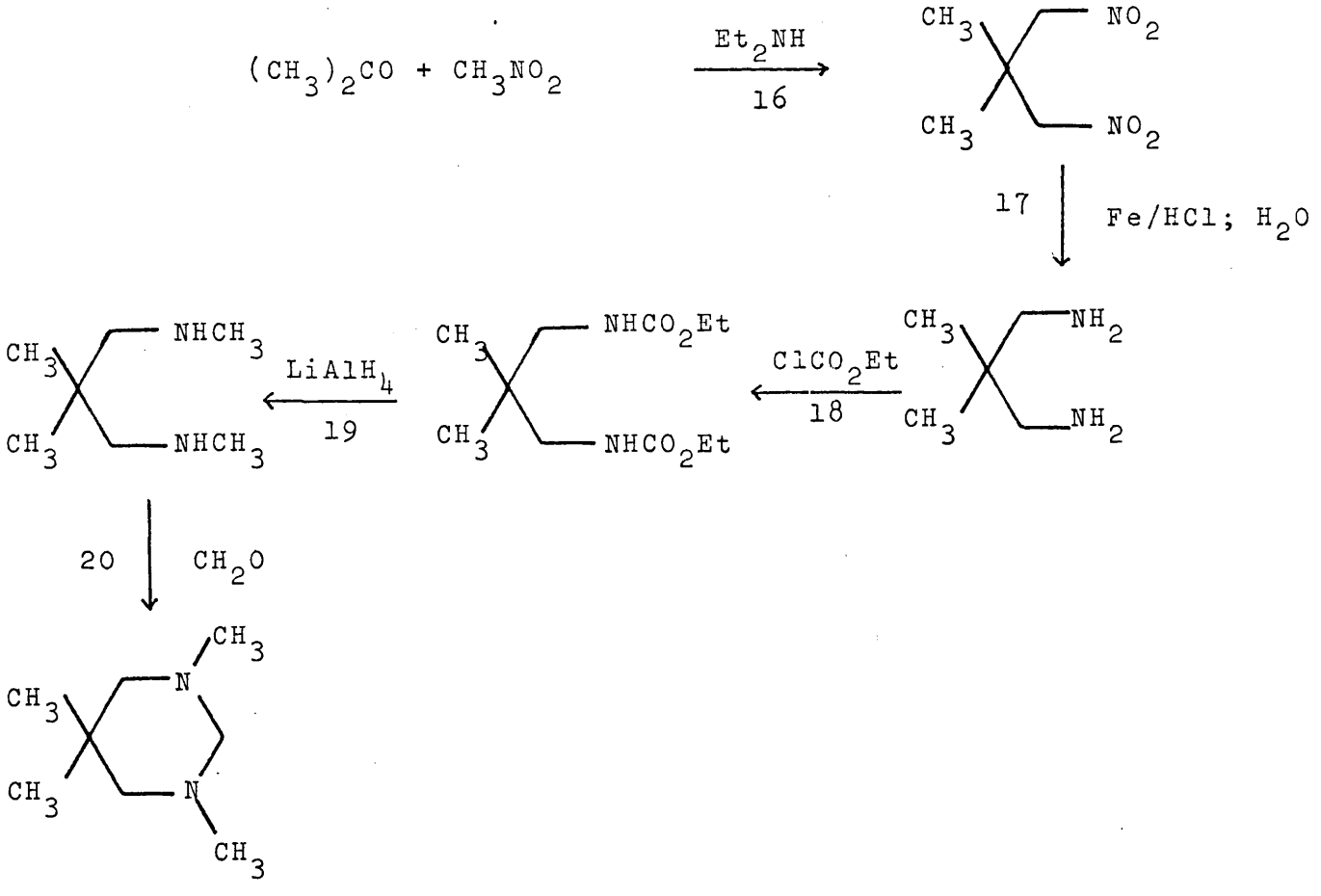


Figure 5.9 Preparation of 5,5,N,N-Tetramethyl-hexahydropyrimidine

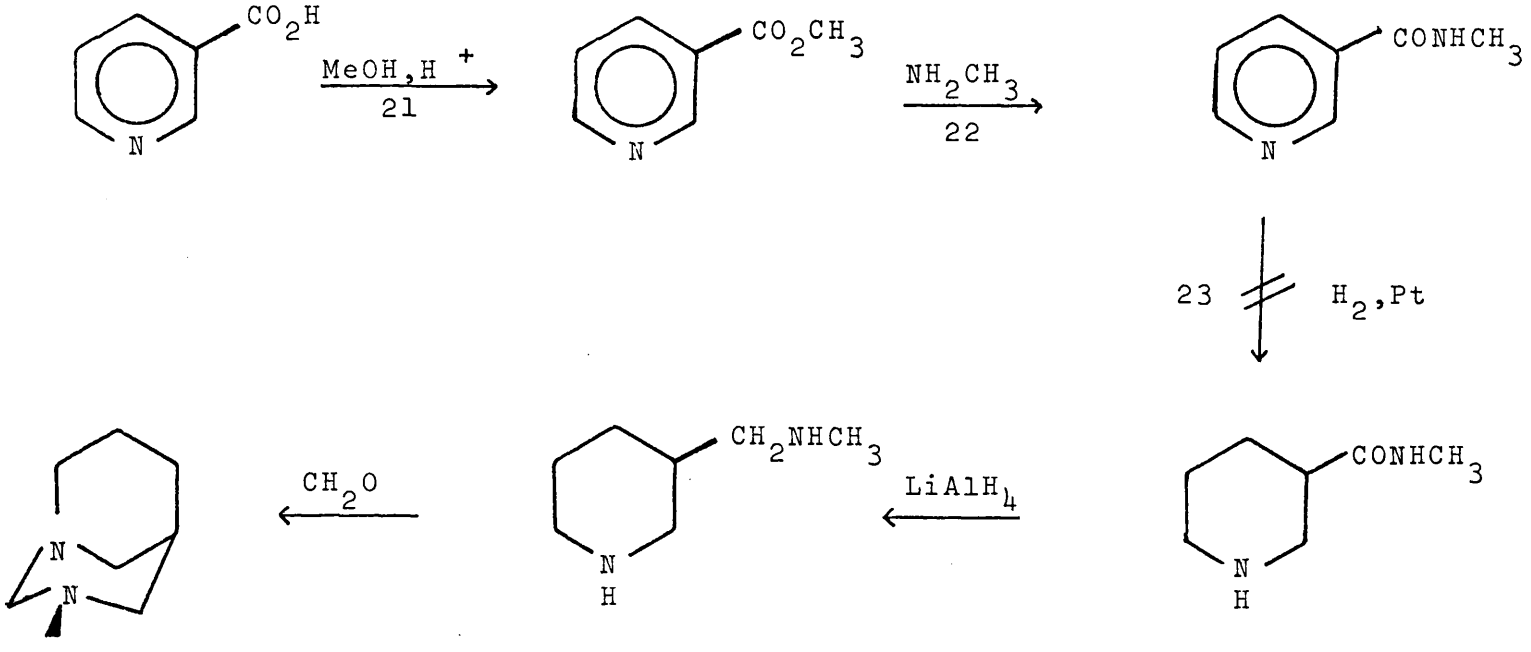


Figure 5.10 First Proposed Route to 1,3-Diaza-3-Methyl-Bicyclo-[3,3,1]-Nonane

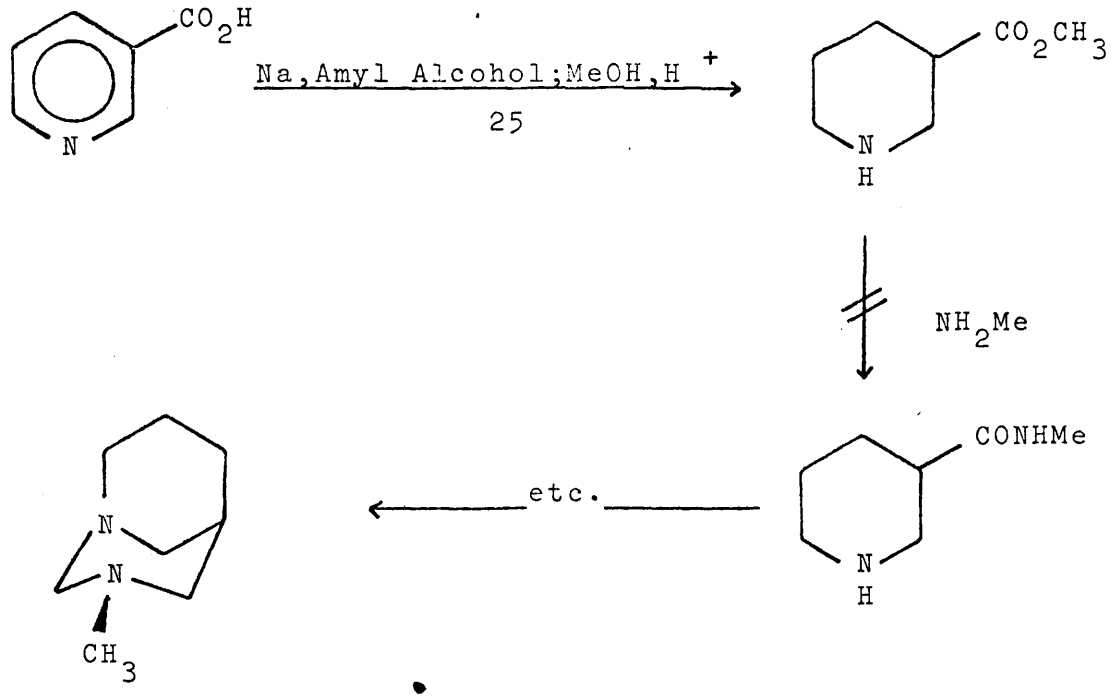


Figure 5.11 Second Proposed Route to 1,3-Diaza-3-Methyl-Bicyclo-[3,3,1]-Nonane

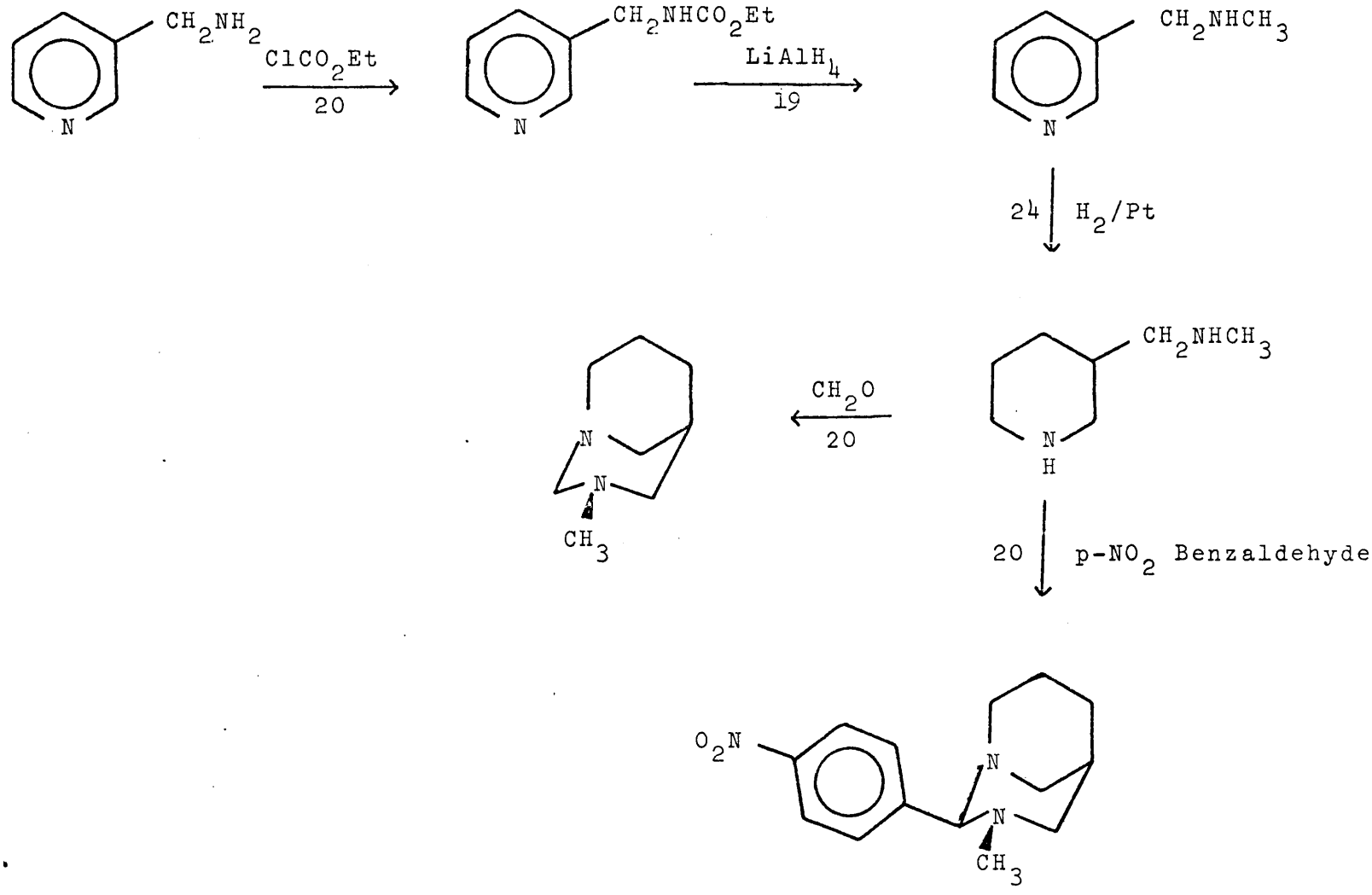


Figure 5.12 Final Route to 1,3-Diaza-3-Methyl-Bicyclo-[3,3,1]-Nonane

16. 2,2-Dimethyl-1,3-Dinitropropane[154]

A mixture of nitromethane (183g., 160 ml., 3 mol.), diethylamine (21.5g., 30 ml., 0.3 mol.), and acetone (60g., 75 ml., 1 mol.) was refluxed for 4 days, after which it was poured into water (1 l.) and acidified with concentrated hydrochloric acid. The product was extracted with chloroform (4 x 200 ml.); the combined extracts were dried over magnesium sulphate and evaporated. Distillation of the residue, through a heated air condenser, gave 2,2-dimethyl-1,3-dinitropropane (80g., 0.5 mol., 50%) b.p. 102-104°/2 mm., m.p. ca. 80° (literature b.p. 130-132°/10 mm., m.p. 75-80°).

17. 2,2-Dimethyl-1,3-propanediamine[155,156]

To a refluxing mixture of iron filings (149g., 2.6 mol.), water (223 ml.), and concentrated hydrochloric acid (23 ml.) was added alternately 2,2-dimethyl-1,3-dinitropropane (66.7g., 0.4 mol.) and concentrated hydrochloric acid (66.7 ml.) in such a way as to keep the mixture refluxing without external heating. After this addition was complete, ca. 1 hr., the mixture was stirred for 3 hr., and then the residual solid was filtered off and washed well with water. The combined green filtrate and water washings were refiltered to remove residual iron filings, and were evaporated to a brownish-green residue. This material was treated with sodium hydroxide (66.7g.) in water (66.7 ml.), and the free diamine was extracted with ether (6 x 50 ml.). After drying over magnesium

sulphate, the ether was evaporated and the residue distilled to give 2,2-dimethyl-1,3-propane-diamine. (10g., 0.1 mol., 25%) b.p. 158-162°.

18. 2,2-dimethyl-N,N'-dicarbethoxy-1,2-propane diamine[156]

Ethyl chloroformate (23.4g., 0.22 mol.) was added slowly to an ice cold mixture of 2,2-dimethyl-1,3-propane diamine (10g., 0.09 mol.), ether (70 ml.), and water (50 ml.). After this addition was complete, ca. 0.5 hr., 50% sodium hydroxide solution (8.7 ml.) was added over 0.5 hr. After stirring for 8 hr. at room temperature, the ether layer was isolated, and the aqueous layer washed with ether (3 x 50 ml.). The ether extracts were combined, washed with water, and dried over magnesium sulphate. Evaporation gave a clear yellow liquid. This material was taken up in chloroform (20 ml.), washed with water, and redried over magnesium sulphate. Evaporation gave white crystals of 2,2-dimethyl-N,N'-dicarbethoxy-1,3-propane diamine (14.8g., 0.06 mol., 60%) which were washed with hexane and air dried.

3-(N-carbethoxy-amino-methyl)-pyridine was prepared in an analogous manner from 3-aminomethylpyridine. The yield was 55% b.p. 182°/5 mm.

19. 2,2,N,N'-tetramethyl-1,3-propane diamine, and 3-(N-methyl-amino-methyl)pyridine

These two compounds were prepared from the respective N-carbethoxy compounds by reductions with lithium aluminium hydride as in para.3 above.

The propane-diamine was obtained in 50% yield b.p. 145-6°/550 mm, while the pyridine derivative was obtained in 15% yield b.p. 154-160°.

20. Condensation of Diamines with Aldehydes

This is illustrated by the preparation of 2-p-nitrophenyl-3-methyl-bicyclo-1,3-diaza-[3,3,1]-nonane.

3-(N-methyl-amino-methyl)-piperidine (1g., 0.007 mol.) was dissolved in a solution of p-nitrobenzaldehyde (1.05g., 0.007 mol.) in dry benzene (10 ml.). The mixture was refluxed in a Dean and Stark apparatus until no further water came off (ca. 1 hr.). Evaporation yielded a viscous oil which solidified on standing. Recrystallisation from low boiling petroleum ether gave colourless crystals of 2-p-nitrophenyl-bicyclo-1,3-diaza[3,3,1]-nonane. (0.05g., 25%) m.p. 87-88°. (Found: C, 62.39; H, 7.48; N, 16.58. Calc. for $C_{14}H_{19}N_3O_2$ C, 62.63; H, 7.68; N, 16.85).

A similar method was used for the condensation of diamines with formaldehyde, using either 40% aqueous formaldehyde solution, or paraformaldehyde. Other compounds prepared in this manner were: 5,5,N,N'-tetramethyl-hexahydropyrimidine (b.p. 80°/120 mm.) and its p-nitro-phenyl analogue; and 3-methyl bicyclo-1,3-diaza-[3,3,1]-nonane. This structure was confirmed by N.M.R. and mass spectral evidence.

21. Esterification of Nicotinic Acid[157]

Nicotinic acid (12.3g., 0.1 mol.) was added to a solution of concentrated sulphuric acid (20g., 11 ml.) in dry methanol (50 ml.). The mixture was refluxed for 4 hr., cooled, poured onto ice (50g.)

and made alkaline with concentrated ammonia solution. The product was extracted with ether (3 x 25 ml.) and was distilled to give a quantitative yield of methyl-nicotinate b.p. 214° m.p. 38° (literature b.p. 204°).

22. N-methyl-nicotinamide[158]

Methyl nicotinate (4g., 0.03 mol.) was dissolved in 33% aqueous methylamine solution (6 ml.) and the mixture was left to stand overnight. The solution was evaporated to dryness, and the residue extracted with boiling toluene. The amide crystallised from the toluene, and after recrystallisation from toluene N-methyl-nicotinamide (2g., 0.015 mol. 50%) was obtained, m.p. 105-6°.

A similar method was used in the attempted preparation of N-methyl nipecotamide from methyl nipecotinate, however, no identifiable product was obtained.

23. Attempted Catalytic Reduction of N-methyl Nicotinamide[150]

This was attempted in the same way as in paragraph 11 above, using glacial acetic acid as the solvent to avoid poisoning of the platinum catalyst by the free base. No identifiable product was obtained.

24. Reduction of 3-(N-methyl-amino-methyl)-pyridine

Using dilute hydrochloric acid as the solvent and Adam's catalyst, 3-(N-methyl-amino-methyl)-pyridine (4.0g., 0.03 mol.) was reduced to 3-(N-methyl-amino-methyl)-piperidine (3.8g., 0.03 mol.) 95% at 3 atmospheres of hydrogen in a rocking autoclave. The product was extracted with ether from the basified reaction mixture.

25. Piperidine-3-methyl carboxylate[159]

Nicotinic acid (30g., 0.25 mol.) was heated and stirred with dry amyl alcohol (1.2 l.) while sodium metal (96g., 4.1 mol.) was added in small pieces. When all the sodium had dissolved, ca. 4 hr., the mixture was poured into water (1.2 l.), and the alcohol separated and washed with water (1.0 l.). The aqueous extracts were combined, acidified with concentrated hydrochloric acid, and evaporated to dryness. The residue was extracted with methanol (600 ml.). This solvent was evaporated, and the residue refluxed with methanol (150 ml.) and concentrated sulphuric acid (30 ml.) for 10 hr. The alcohol was evaporated, the acid almost neutralised with 15% sodium hydroxide solution, and the solution saturated with potassium carbonate. The neutral solution was extracted with ether (200 ml.) which upon evaporation gave 1 ml. of material whose I.R. spectrum did not correspond to the desired ester. The solution was then made strongly basic with sodium hydroxide, and re-extracted with chloroform. After drying and evaporating this extract, the residue was distilled to give piperidine-3-methyl-carboxylate (8g., 0.06 mol., 23%) b.p. ca. 120°/20 mm.

The N,N-Dimethyl Amides of Benzoic and Pyridine Carboxylic Acids

These were all prepared by an analogous method to N-methyl nicotinamide (paragraph 22 above). Table 5.5 lists their physical data.

TABLE 5.5

PHYSICAL DATA FOR THE DIMETHYL AMIDES

Compound (N,N Dimethyl)	Melting Point Observed °C	Literature °C
Benzamide	42° (b.p. 86-88°/ 0.5 mm	43° 132-133°/ 15 mm).
Picolinamide	102°	-
Nicotinamide	45°	50°
Isonicotinamide	54-56°	59°

SECTION SIX

BIBLIOGRAPHY

BIBLIOGRAPHY

1. M. Hanack, 'Conformation Theory', Academic Press, 1965, p.23.

2. E. L. Eliel, 'Stereochemistry of Carbon Compounds', McGraw-Hill, 1962, p.124.

3. W. G. Dauben and K. S. Pitzer, in 'Steric Effects in Organic Chemistry', ed. M. S. Newman, Wiley, 1956, Chapter 1.

4. a) H. Sachse, Ber., 1890, 23, 1363; Z.Physik.Chem. (Leipzig), 1892, 10, 203.

   b) E. Mohr, J.Prakt.Chem., 1918, [2], 98, 315.

   c) W. Huckel, Ann., 1925, 441, 42.

5. M. Davis and O. Hassel, Acta Chem.Scand., 1963, 17, 1181.

6. L. Pierce and R. Nelson, J.Amer.Chem.Soc., 1966, 88, 216.

7. J. E. Anderson, Quart.Rev., 1965, 14, 426.

8. a) F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, J.Amer.Chem.Soc., 1962, 84, 386.

   b) F.A.L. Anet and A.J.R. Bourn, J.Amer.Chem.Soc., 1967, 89, 760.

9. a) A. H. Lewin and S. Winstein, J.Amer.Chem.Soc., 1962, 84, 2464.

   b) M. Hanack, ref.1, p.92.

10. G. H. Whitham, 'Alicyclic Chemistry', Oldbourne, 1963, Chap.4.

11. H. Booth, personal communication.

12. F. E. Malherbe and H. J. Bernstein, J.Amer.Chem.Soc., 1952, 74, 4408.

13. L. E. Sutton and L. O. Brockway, J.Amer.Chem.Soc., 1935, 57, 473.

14. K. E. Calderbank and R.J.W. Le Fevre, J.Chem.Soc., 1949, 189.

15. F. G. Riddell, Quart.Rev., 1967, 21, 364.

16. A. J. De Kok and C. Romers, Recueil, 1970, 89, 313.

17. a) F. G. Riddell and M.J.T. Robinson, Tetrahedron, 1967, 23, 3417.

b) E. L. Eliel and M. C. Knoeber, J.Amer.Chem.Soc., 1966, 88, 5347.

18. Ref.15, p.377.

19. C. C. Costain, P. J. Buckley, and J. E. Parkin, personal communication to F. G. Riddell (1967).

20. P. J. Buckley, C. C. Costain, and J. E. Parkin, Chem.Comm., 1968, 668.

21. R. W. Baldock and A. R. Katritzky, J.Chem.Soc.(B), 1968, 1470.

22. R. J. Bishop, L. E. Sutton, D. Dineen, R.A.Y. Jones, A. R. Katritzky, and R. J. Wyatt, J.Chem.Soc.(B), 1967, 493.

23. P. J. Brignell, K. Brown, and A. R. Katritzky, J.Chem.Soc.(B), 1968, 1462.

24. J. C. Brelière and J. M. Lehn, Chem.Comm., 1965, 426.

25. R. W. Murray, P. R. Story, and M. L. Kaplan, J.Amer.Chem.Soc., 1966, 88, 526.

26. J. R. Fletcher and I. O. Sutherland, Chem.Comm., 1970, 687.

27. a) J. R. Fletcher and I. O. Sutherland, Chem.Comm., 1969, 706.

b) B. J. Price and I. O. Sutherland, Chem.Comm., 1967, 1032.

28. W. H. Fink, D. C. Pan, and L. C. Allen, J.Chem.Phys., 1967, 47, 895.

29. L. Pedersen and K. Morukama, J.Chem.Phys., 1967, 46, 3941.

30. A. Veillard, Theoret.Chim.Acta, 1966, 5, 413.

31. R. H. Hunt, R. A. Leacock, C. W. Peters, K. T. Hecht, J.Chem.Phys., 1965, 42, 1931.

32. A. Yamaguchi, I. Ichishima, T. Shimanoushi, and S. Mizushima, J.Chem.Phys., 1959, 31, 843.

33. M. S. Gordon and J. A. Pople, J.Chem.Phys., 1968, 49, 4643.

34. E. L. Eliel, Kemisk Tidskrift, 1969, NR/6-7, 22.

35. S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, J.Chem.Soc.(B), 1970, 142.

36. J. T. Edward, Chem. and Ind., 1955, 1102.

37. E. L. Eliel, R. O. Hutchins, and L. D. Kopp, J.Amer.Chem.Soc., 1968, 90, 7174.

38. R.A.Y. Jones, A. R. Katritzky, and M. Snarey, J.Chem.Soc.(B), 1970, 131.

39. J. M. Lehn and F. G. Riddell, J.Chem.Soc.(B), 1968, 1224.

40. H. Booth, personal communication.

41. R.J.W. Le Fevre, 'Dipole Moments', Methuen, 1953.

42. I. F. Halverstadt and W. D. Kumler, J.Amer.Chem.Soc., 1942, 64, 2988.

43. J. M. Lehn, B. J. Price, F. G. Riddell, and I. O. Sutherland, J.Chem.Soc.(B), 1967, 387.

44. J. M. Lehn, F. G. Riddell, and J. Wagner, Chem.Comm., 1968, 1403.

45. F. A. Cotton and G. Wilkinson, 'Advanced Inorganic Chemistry', Interscience, 1966, p.373.

46. G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules", Van Nostrand Co., 1945.

47. J. D. Swalen and J. A. Ibers, J.Chem.Phys., 1962, 36, 1914.

48. J. M. Lehn, Fortschr.Chem.Forsch., 1970, 15, 313.

49. J. F. Kincaid and F. C. Henriques Jr., J.Amer.Chem.Soc., 1940, 62, 1474.

50. C. C. Costain and G.B.B.M. Sutherland, J.Phys.Chem., 1952, 56, 321.

51. M.J.S. Dewar and M. Shanshal, J.Amer.Chem.Soc., 1969, 91, 3654.

52. J. M. Lehn, B. Munsch, Ph. Millie, and A. Veillard, Theoret.Chim.Acta., 1969, 13, 313.

53. C. C. Costain and J. M. Dowling, J.Chem.Phys., 1960, 32, 158.

54. J. M. Lehn, unpublished results.

55. A. Rauk, L. C. Allen, K. Mislow, Angew.Chem.Internat.Edn., 1970, 9, 400.

56. See for example the reference section of ref.66a.

57. M. Karplus, J.Chem.Phys., 1959, 30, 11.

58. M. Karplus, J.Amer.Chem.Soc., 1963, 85, 2870.

59. H. Booth, in 'Progress in N.M.R. Spectroscopy', ed. J. W. Emsley, J. Feeny, L. H. Sutcliffe, Pergamon, 1969, Vol.5, Chap.4.

60. D. K. Dalling and D. M. Grant, J.Amer.Chem.Soc., 1967, 89, 6612.

61. D. K. Dalling and D. M. Grant, ibid., 5313, and references therein.

62. a) F. G. Riddell, J.Chem.Soc.(B), 1970, 331.

b) F. G. Riddell and G. M. Kellie, in press.

63. a) G. W. Buchanan, D. A. Ross, and J. B. Stothers, J.Amer.Chem.Soc., 1966, 88, 4301.

b) H. J. Reich, M. Joutelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, J.Amer.Chem.Soc., 1969, 91, 7445.

64. W. J. Moore, 'Physical Chemistry', Longmans, 1965, 4th ed.

65. N. C. Franklin and H. Feltkamp, Angew.Chem.Internat.Ed., 1965, 4, 774.

66. a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High-resolution Nuclear Magnetic Resonance', McGraw-Hill, 1959, Chap.10.

b) J. W. Emsley, J. Feeny, L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy', Pergamon, 1965, Chap.9.

68. S. Glasstone, K. J. Laidler, and H. Eyring, 'The Theory of Rate Processes', McGraw-Hill, 1941, Chap.1.

69. a) A. Allerhand, F. Chen, and H. S. Gutowsky, J.Chem.Phys., 1965, 42, 3040.

b) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, J.Amer.Chem.Soc., 1966, 88, 3185.

70. G. Binsch in 'Topics in Stereochemistry', ed. E. L. Eliel and N. L. Allinger, Interscience, 1968.

71. M.J.S. Dewar and B. Jennings, J.Amer.Chem.Soc., 1969, 91, 3655.

72. D. L. Griffiths and J. D. Roberts, J.Amer.Chem.Soc., 1965, 87, 4089.

73. M. Raban and G.W.J. Kenney, Tetrahedron Letters, 1969, 17, 1295.

74. D. L. Griffith and B. L. Olsen, Chem.Comm., 1968, 1682.

75. 'Interatomic Distances', J.Chem.Soc., special publication No. 11, 1958.

76. P. A. Giguire and I. D. Liu, Canad.J.Chem., 1952, 30, 948.

77. H. King, J.Chem.Soc., 1942, 432.

78. a) L. W. Jones and R. Oesper, J.Amer.Chem.Soc., 1914, 36, 730.

b) L. W. Jones and L. Neuffer, ibid., 2208.

c) C. Hecker, Amer.Chem.J., 1913, 50, 457.

d) L. Neuffer and A. L. Hoffmann, J.Amer.Chem.Soc., 1925, 47, 1685.

79. Yu. A. Arbuzov, Doklady Akad.Nauk.S.S.S.R., 1948, 60, 993-6.

80. O. Wichterle and S. Svastal, Coll.Czec.Chem.Comm., 1951, 16, 33.

81. a) C. H. Rayburn, W. R. Harlan, H. R. Hanmer, J.Amer.Chem.Soc., 1950, 72, 1721.

b) W. Carruthers and R.A.W. Johnstone, J.Chem.Soc., 1965, 1653.

82. N. G. Gaylord, 'Reduction with Complex Metal Hydrides', Interscience, 1956.

83. P. Sykes, 'A Guidebook to Mechanism in Organic Chemistry', Longmans, 1965.

84. R. Swidler and G. M. Steinberg, J.Org.Chem., 1965, 30, 2362.

86. R. S. Bly and R. T. Swindell, J.Org.Chem., 1965, 30, 10.

87. R. T. Gilsdorf and F. F. Nord, J.Amer.Chem.Soc., 1952, 74, 1837.

88. E. L. Eliel, ref.2, p.216.

89. H. C. Brown, 'Hydroboration', Benjamin, 1962.

90. G. Zweifel, K. Nagase, and H. C. Brown, J.Amer.Chem.Soc., 1962, 84, 183.

91. A. M. Creighton, Imperial Cancer Research Fund, personal communication.

92. See for example, A. M. Creighton and G. D. Birnie, Int.J.Cancer, 1970, 5, 47.

93. a) F. A. Bovey, ref. 119, p.77.
b) R. F. Zürcher, Helv.Chim.Acta., 1961, 44, 1755.

94. A. Anteunis, D. Tavernier, and F. Borremans, Bull.Soc.Chim.Belg., 1966, 75, 396.

95. H. Booth, unpublished work.

96. F. G. Riddell, personal communication.

97. M. and M. Polonovski, Bull.Soc.Chim., 1925, 37, 744.

98. C. Hootelé, Tetrahedron Letters, 1969, 32, 2713.

99. M. Hanack, ref.1, p.172.

100. B. Robinson and D. Moorcroft, J.Chem.Soc.(C), 1970, 2077.

101. H. Kessler, Angew.Chem.Internat.Ed., 1970, 9, 219.

102. T. H. Siddal III and W. E. Stewart, Chem.Rev., 1970, 70, 517.

103. See ref.81b.

104. J. Meisenheimer, Ber., 1919, 52, 1667.

105. A. C. Cope, T. T. Foster, and P. H. Towle, J.Amer.Chem.Soc., 1949, 71, 3929, and references therein.

106. G. R. Newkome and N. S. Bhacca, Chem.Comm., 1969, 385.

107. F. G. Riddell, D.A.R. Williams, C. Hootelé, and (in part) N. Reid, J.Chem.Soc.(B), 1970, 1739.

108. F. G. Riddell, J.Chem.Soc. (B), 1967, 560.

109. R. F. Farmer and J. Hamer, Tetrahedron, 1968, 24, 829.

110. J. M. Lehn, F. G. Riddell, B. J. Price, and I. O. Sutherland, J.Chem.Soc.(B), 1967, 387.

111. See ref.37.

112. See ref.38.

113. a) F. R. Jensen, D. S. Noyce, C. H. Sederholm, A. J. Berlin, J.Amer.Chem.Soc., 1960, 82, 1256.

b) See ref.8a.

114. a) A. R. Katritzky, unpublished results.

b) F. G. Riddell and D.A.R. Williams, Tetrahedron Letters, in press.

115. H. Booth and J. H. Little, Tetrahedron, 1967, 23, 291.

116. For example, T. A. Crabb and R. F. Newton, Chem. and Ind., 1966, 339.

117. M. Anteunis, Bull.Soc.Chim.Belg., 1966, 75, 413.

118. J. M. Lehn and F. G. Riddell, J.Chem.Soc.(B), 1968, 1224, and refs. therein.

119. F. A. Bovey, 'Nuclear Magnetic Resonance Spectroscopy', Academic Press, 1969, Chap.5.

120. A. R. Katritzky, personal communication.

121. W.A.C. Brown, J. Martin, and G. A. Sim, J.Chem.Soc., 1965, 1844.

122. M. Dobler and J. D. Dunitz, Helv.Chim.Acta, 1964, 47, 695.

123. A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, Tetrahedron Letters, 1964, 233.

124. E. L. Eliel, personal communication.

125. T. H. Siddall and W. E. Stewart, in 'Progress in N.M.R. Spectroscopy', Vol.5, ed. J. W. Emsley, J. Feeny, L. H. Sutcliffe, Pergamon, 1969, Chap.2.

126. See ref.102.

127. H. S. Gutowsky and C. H. Holm, J.Chem.Phys., 1956, 25, 1228.

128. a) ref.69b.

b) C. W. Fryer, F. Conti, C. Franconi, Ricerca Sci., Rend.Sez.A, 1965, 35(2), 788.

129. See ref.66.

130. B. G. Cox, F. G. Riddell, and D.A.R. Williams, J.Chem.Soc.(B), 1970, 859.

131. A. Mannschreck, Tetrahedron Letters, 1965, 1341.

132. Ref.69b.

133. P. Laszlo, in 'Progress in N.M.R. Spectroscopy', Vol.3, ed. J. W. Emsley, J. Feeny, L. H. Sutcliffe, Pergamon Press, 1967, p.231.

134. A. D. Buckingham, J.Chem.Phys., 1962, 36, 3096.

135. L. M. Jackman, T. E. Kavanagh, R. C. Haddon, Org.Mag.Resonance, 1969, 1, 109.

136. L. Pauling, 'The Nature of the Chemical Bond', Cornell U.P., 1963.

137. a) J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions', John Wiley, 1963, Chaps. 6, 7, and 8.

b) P. R. Wells, 'Linear Free Energy Relationships', Academic Press, 1968.

c) K. B. Wiberg, 'Physical Organic Chemistry', Wiley, 1964.

138. a) H. H. Jaffé, Chem.Rev., 1953, 53, 191.

b) H. H. Jaffé, J.Chem.Phys., 1952, 20, 1554.

139. a) Favini and Simonetta, Gazz.Chim.Ital., 1954, 84, 566.

b) Favini and Simonetta, Gazz.Chim.Ital., 1955, 85, 1026.

c) H. H. Jaffé and H. L. Jones in 'Advances in Heterocyclic Chemistry', ed. A. R. Katritzky and A. J. Boulton, Academic Press, 1961, Vol.3, p.209.

141. R. T. Major, F. Dürsch, and H. J. Hess, J.Org.Chem., 1959, 24, 431.

142. G. B. Brown, Org.Synth., Coll. Vol.3, 613.

143. A. I. Vogel, 'Practical Organic Chemistry', Longmans, 3rd ed. 1956, p.386.

144. E. M. Van Heyningen, U.S.P. 2,621,183/1952.

145. G. E. McCasland and S. Proskow, J.Amer.Chem.Soc., 1956, 78, 5646.

146. A. T. Blomquist and J. A. Verdol, J.Amer.Chem.Soc., 1955, 77, 1806.

147. C.F.H. Allen and A. Bell, Org.Synth., Coll. Vol.3, 312.

148. I. K. Sarycheva, N. G. Morozova, V. A. Abramovich, S. A. Breitburt, L. F. Sergienko, and N. A. Preobrazhenshii, Zur.Obshchei.Kim., 1955, 25, 2001.

149. N. Weiner, Org.Synth., Coll. Vol.2, 280.

150. a) V. I. Komarewsky, C. H. Riesz, and F. L. Morritz, in 'Technique of Organic Chemistry', ed. A. Weissberger, Interscience, 1956, Vol.II, p.1.

151. J. F. Bussert, K. W. Greenlee, J. M. Derfer, and C. E. Boord, J.Amer.Chem.Soc., 1956, 6076.

152. A. C. Knipe, Ph.D. Thesis, King's College, London, 1967.

153. C. S. Palmer and P. W. McWherter, Org.Synth., Coll. Vol.1, 245.

154. A. Lambert and A. Lowe, J.Chem.Soc., 1947, 1517.

155. M. Senkus, Ind. and Eng.Chem., 1948, 40, 506.

156. E. L. Eliel, personal communication.

157. A. I. Vogel, ref.143, p.849.

158. B. Prijs, R. Gall, R. Hinderling, and H. Erlenmeyer, Helv.Chim.Acta, 1954, 37, 90.

159. G. R. Clemo, J. Ormston, and G. R. Ramage, J.Chem.Soc., 1931, 3187.